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REVIEW ARTICLE

Insulin-Like Growth Factor (IGF) Pathway Targeting in Cancer: Role of the IGF Axis and Opportunities for Future Combination Studies

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Abstract Despite a strong preclinical rationale for targeting the insulin-like growth factor (IGF) axis in cancer, clinical studies of IGF-1 receptor (IGF-1R)-targeted monotherapies have been largely disappointing, and any potential success has been limited by the lack of validated predictive biomarkers for patient enrichment. A large body of preclinical evidence suggests that the key role of the IGF axis in cancer is in driving treatment resistance, via general proliferative/survival mechanisms, interactions with other mitogenic signaling networks, and class-specific mechanisms such as DNA damage repair. Consequently, combining IGF-targeted agents with standard cytotoxic agents, other targeted agents, endocrine therapies, or immunotherapies represents an attractive therapeutic approach. Anti-IGF-1R monoclonal antibodies (mAbs) do not inhibit IGF ligand 2 (IGF-2) activation of the insulin receptor isoform-A (INSR-A), which may limit their anti-proliferative activity. In addition, due to their lack of specificity, IGF-1R tyrosine kinase inhibitors are associated with hyperglycemia as a result of interference with signaling through the classical metabolic INSR-B isoform; this may preclude their use at clinically effective doses. Conversely, IGF-1/IGF-2 ligand-neutralizing mAbs inhibit proliferative/anti-apoptotic signaling via IGF-1R and INSR-A, without compromising the metabolic function of INSR-B. Therefore, combination regimens that include these agents may be more efficacious and tolerable versus IGF-1R-targeted combinations. Herein, we review the preclinical and clinical experience with IGF-targeted therapies to-date, and discuss the rationale for future combination approaches as a means to overcome treatment resistance.

Key Points

Therapeutic targeting of insulin-like growth factor (IGF) signaling has been investigated in many types of human cancer.

Interactions between the IGF axis and other signaling networks can result in resistance to therapies that target individual signaling pathways.

IGF-targeted combination therapy represents a promising approach to anti-cancer therapy, as supported by a large body of preclinical evidence.

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1 The IGF Axis and Its Role in Tumor Biology

1.1 IGF: Dramatis Moleculae

Insulin-like growth factor (IGF) signaling plays an important role in regulating growth and development in normal human tissues by promoting cellular proliferation and differentiation

and preventing apoptosis [1, 2]. The IGF axis comprises insu-
lin and two related ligands, IGF ligands 1 and 2 (IGF-1 and
IGF-2) that regulate cellular processes by interacting with spe-
cific cell-surface receptors (Fig. 1) [1, 5]. The IGF-1 receptor
(IGF-1R) is a heterotetrameric receptor with two extracellular,
ligand-binding domains (alpha subunits) and two transmem-
brane beta subunits that contain the kinase domain; the alpha
and beta domains are linked by disulfide bonds [6]. Along
with the insulin receptor (INSR), IGF-1R is a member of the
receptor tyrosine kinase (RTK) class 2 family of receptors
(insulin receptor family) [1, 3]. IGF-1R binds the IGF ligands
with varying affinities depending on the cell type and exper-
imental conditions, both IGFs binding with higher affinity
than insulin. IGF-2 also binds to INSR-A, a fetal isoform that
is overexpressed in some tumors, and to IGF-2 receptor (IGF-
2R), a structurally unrelated receptor that lacks tyrosine kinase
activity and serves as a scavenger for circulating IGF-2 [7].

In addition to INSR-A, which binds insulin and IGF-2 with
equal affinity and transmits proliferative/survival signals,
INSR exists in the classical metabolic isoform, INSR-B,
which binds insulin [1] and regulates glucose uptake [5, 7].
Among these components, the IGF axis includes hybrid re-
ceptors composed of IGF-1R and INSR isoforms; these IGF-
1R/INSR heterodimers contain predominantly INSR-A in ma-
lignant cells, and bind IGF-1, IGF-2, and insulin [7].

The IGF system also encompasses various IGF-binding
proteins (IGFBPs), IGFBP-specific proteases, and IGFBP-
related peptides, which bind to and modify the activity of
IGF ligands (Fig. 1) [1, 5]. Aside from their endocrine role
in IGF transport, IGFBPs have many additional, IGF-
independent biological functions that modulate cellular
growth and survival [8]. For example, in breast cancer,
IGFBP3 has been shown to interact with the epidermal growth
factor receptor (EGFR) and can influence the response to
DNA damage [9]. A comprehensive assessment of IGFBP
biology is beyond the scope of this review. However, for more
details, please refer to a 2014 review paper by Baxter [8].

1.2 The IGF Axis in Cancer

Increased expression of IGF-1R and/or circulating levels of
IGF ligands has been observed in various cancers, including
Ewing sarcoma, breast cancer, prostate cancer, pancreatic can-
cer, melanoma, and many other tumor types; this overexpres-
sion is associated with faster disease progression and a poor
prognosis in some tumors [10–12]. Moreover, the presence of
a functional IGF-1R has been shown to be essential for ma-
lignant transformation [13]. IGF-1R overexpression can result
from the loss of tumor suppressors, including p53, breast can-
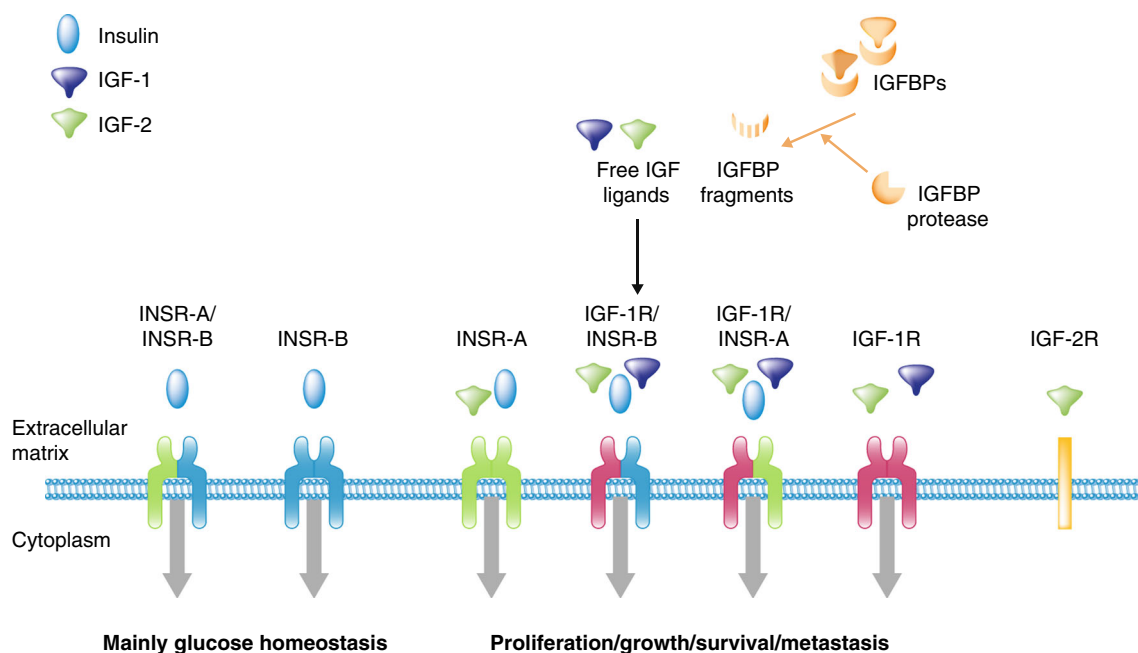cer gene-1 (BRCA1), von Hippel-Lindau protein and Wilms's

Fig. 1 Components of the insulin/IGF axis. The IGF axis consists of
ligands (insulin, IGF-1, and IGF-2), receptors (INSR, IGF-1R, IGF-2R,
and IGF-1R/INSR hybrid receptors), IGFBPs 1 to 7, and IGFBP
proteases. The IGF ligands bind their receptors and binding proteins
with high affinity. IGFBPs bind tightly to IGF ligands, influencing
binding to their receptors; IGFBP proteases cleave the IGFBPs into
fragments with lower affinity for the IGF ligands, thereby increasing
free IGF-1 and IGF-2 bioavailability. IGF-1/IGF-2 and insulin can
cross-bind to each other's receptor, albeit with much weaker affinity than
that for the preferred ligand. Activation of the INSR-B isoform regulates
glucose metabolism, while activation of IGF-1R, INSR-A, and IGF-1R/
INSR hybrid receptors promotes cellular growth, proliferation, survival,
and metastasis. IGF-2R is an unrelated monomeric receptor that acts as a
scavenger for circulating IGF-2 [1, 3, 4]. *IGF-1/–2* insulin-like growth
factor ligand 1/2, *IGFBP* IGF binding protein, *IGF-1R/IGF-2R* type 1/
type 2 IGF receptor, *INSR* insulin receptor

tumor suppressor WT1 [14–16]. However, IGF signaling in tumor cells is driven by the presence of the ligands rather than receptor aberrations [14], and there is evidence that a low circulating IGF-1 concentration can protect against tumorigenesis [17, 18]. IGF ligands can be delivered to the IGF-1R from distant (endocrine) or nearby (paracrine) sources, with circulating free-ligand levels regulated by the different IGFBPs [2]. In addition, autocrine production of IGF ligands in some tumor cells which themselves express IGF-1R can also contribute to tumor proliferation [19, 20].

In addition to IGF-1 and IGF-1R, overexpression of IGF-2 and INSR-A is reported in a wide range of human cancers, including breast, colorectal, prostate, and lung cancers, and is also associated with a poor prognosis [21–23]. In preclinical studies, direct upregulation of IGF-2 in response to chemotherapy was shown to enhance the aggressive properties of castration-resistant prostate cancer (CRPC) models by activating INSR-A and/or IGF-1R/INSR-A hybrid receptors; thus, both IGF ligands can function as part of an adaptive mechanism that promotes resistance and tumorigenicity in certain cancers, during or after treatment [23, 24]. Furthermore, in tumor cells where IGF-1R and INSR are co-expressed, upregulated INSR can compensate for IGF-1R inhibition, thereby limiting sustained inhibition of downstream signaling and contributing to resistance to IGF-1R-targeted therapy [25, 26].

Recently, Josep Llovet and co-workers [27] showed that, in hepatocellular carcinoma (HCC), IGF-2 expression can be upregulated through epigenetic mechanisms, whereby increased IGF-2 mRNA and protein levels in human HCC tissues were associated with reduced methylation at the fetal *IGF-2* promoters [27]. Furthermore, in mice with HCC xenografts, treatment with xentuzumab (an IGF-neutralizing monoclonal Ab [mAb]) either as a single agent or in combination with sorafenib (which is routinely used in the treatment of liver cancer) reduced tumor growth rate and improved survival compared with vehicle-treated or sorafenib-treated controls. Thus, IGF-2 appears to be an actionable oncogene target for drugs that inhibit both IGF ligands [27].

The IGF axis potentially contributes to and sustains the acquisition of several hallmarks of cancer [28]. For example, dysregulated IGF signaling is thought to contribute to an imbalance between cancer stem-cell self-renewal and differentiation, resulting in the development of non-differentiated cells with stem cell-like properties, and subsequent malignant transformation [29]. Activated IGF-1R can stabilize integrins and promote epithelial mesenchymal transition (EMT), which, in cancer, can contribute to subsequent progression to metastatic disease [30]. In addition, the IGF pathway has been implicated in DNA damage repair processes [9, 31–33]. Exposure to R-1507, a mAb directed against IGF-1R, downregulated the nucleotide excision repair pathway in human small cell lung cancer (SCLC) cell lines and induced chemo- and radio-sensitization to cisplatin/ionizing radiation in selected SCLC models [32]. Similarly,

IGF-1R depletion or inhibition has been shown to attenuate repair of radiation-induced double strand breaks (DSBs) in prostate cancer cell lines [31, 33].

On activation of IGF-1R or IGF-1R/INSR hybrid receptors, downstream signal transduction occurs via two major pathways (Fig. 2) [5, 34]. Activation of the RAS/mitogen-activated protein kinase (MAPK) cascade results in the transcription of genes that drive cellular proliferation, such as the D-type cyclins. Activation of cyclin D/cyclin-dependent kinase 4 (CDK4) complexes leads to increased E2F-dependent transcription, via liberation of the E2F transcription factor from sequestration by the retinoblastoma protein, so driving passage through the G_1/S-phase transition during cell-cycle progression [35–37]. In parallel, signaling via the phosphatidylinositol 3-kinase/protein kinase-B (PI3K/Akt) pathway confers protection from apoptosis [5]. In addition, Akt acts on cell-cycle regulatory proteins, inducing inhibitory phosphorylation of glycogen synthase kinase-3 beta, p21, and p27, to stabilize type-D cyclins and promote cell-cycle progression [38–40]. Akt also promotes cyclin D function via induction of the mammalian target of rapamycin complex 1 (mTORC1), by preventing its inhibition by tuberous sclerosis complex (TSC) proteins. This ultimately leads to ribosomal biogenesis and more efficient translation of cell-cycle progression-specific mRNAs, which are essential for cellular growth and subsequent cellular proliferation [41, 42]. Hence, both the MAPK and PI3K/Akt pathways contribute to cell-cycle progression and proliferation mediated by IGF-1R or IGF-1R/INSR hybrid receptors.

In addition to this canonical signaling from the plasma membrane, IGF-1R can be modified by the addition of small ubiquitin-like modifier proteins (sumoylation) that enable it to translocate to the nucleus, where it can interact with chromatin and regulate gene transcription [43–46]. Nuclear IGF-1R has been shown to bind to *IGF-1R* promoter DNA and stimulate *IGF-1R* gene expression in estrogen receptor (ER)-positive breast cancer cells [47]. Finally, as well as the two main signal transduction pathways and post-translational modifications such as sumoylation, IGF-1R signaling is affected by alternative downstream mechanisms, through interactions with other plasma-membrane molecules, such as integrins and G-protein-coupled receptors [48].

Overall, it is clear that IGF signaling has the capacity to influence many of the underlying phenotypes of cancer. However, the IGF axis is only one component within a complex system of signaling networks, all of which play a part in promoting the invasive properties of cancer [49]. A large body of preclinical evidence suggests that the main function of IGF signaling in cancer is in conferring resistance to other types of anti-cancer therapy [2, 49, 50]. This is supported by the very rare occurrence of mutations in IGF-axis genes in common cancers, implying that the IGF axis is seldom the primary driver of tumorigenesis [51, 52].
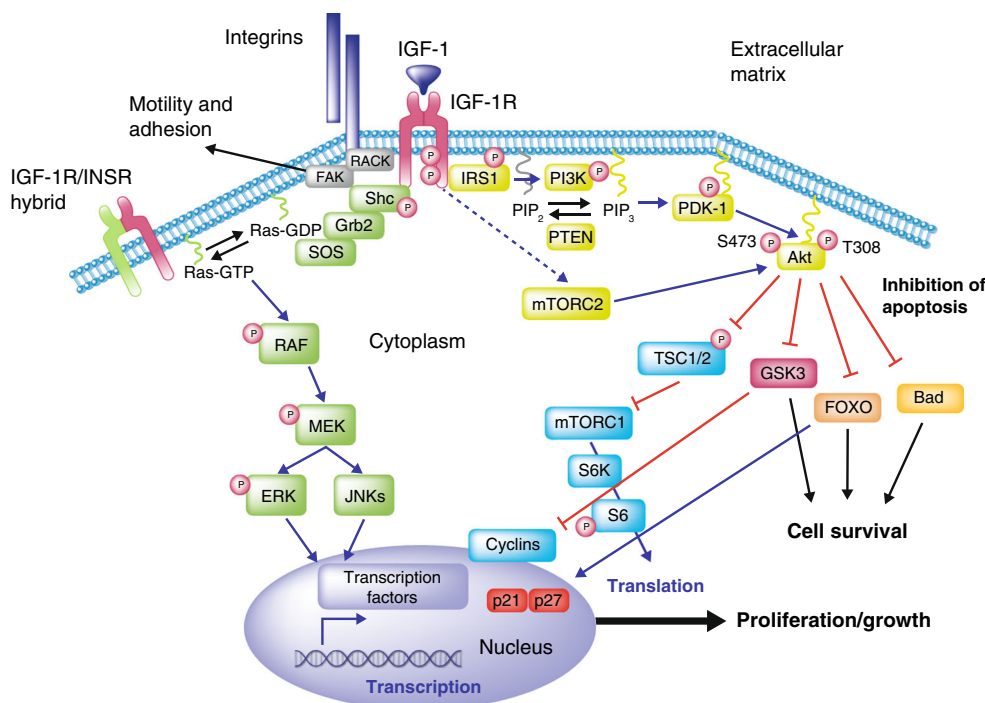
Fig. 2 IGF-1R downstream signaling. Ligand binding to IGF-1R or IGF-1R/INSR hybrid receptors leads to phosphorylation of tyrosines that create binding sites for docking proteins including IRS 1–6 and Shc. Recruitment of IRS and Shc activates signaling via the PI3K/Akt and Ras/Raf/MAPK pathways, which regulate cellular proliferation, survival, migration, and metabolism. In addition to these pathways, interactions between IGF-1R and integrins, via scaffolding with RACK1 and FAK proteins, regulate cellular adhesion and motility [5]. Blue arrows indicate activation. Red arrows indicate inhibition. P indicates major sites of phosphorylation. *Akt* protein kinase B, *ERK* extracellular-signal-regulated kinase, *IGF-1R* type 1 insulin-like growth factor receptor, *INSR* insulin receptor, *IRS* INSR substrate, *MAPK* mitogen-activated protein kinase, *MEK* mitogen-activated protein kinase/Erk kinase, *mTORC1* mammalian target of rapamycin complex 1, *PI3K* phosphatidylinositol-3-kinase, *PTEN* phosphatase and tensin homolog, *Shc* Src homology and collagen domain protein

In this review, we will summarize the clinical experience with different therapeutic strategies that target the IGF axis, including discussion of why dual IGF-1/IGF-2-targeting approaches and how the use of predictive biomarkers for patient enrichment might potentially improve clinical benefit. Finally, we will discuss the rationale for future combination approaches as a means to overcome treatment resistance.

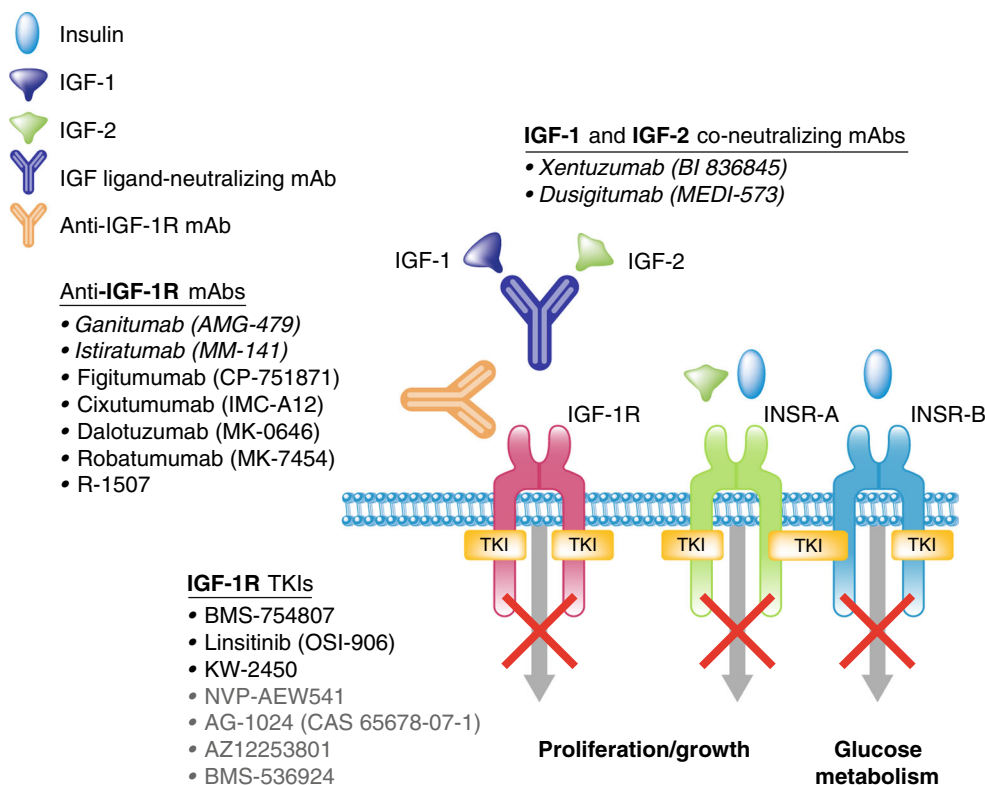## 2 Strategies to Target the IGF System in Cancer

2.1 IGF-1R mAbs

A number of therapeutic strategies that target the IGF system have been tested in a wide range of cancer types. These approaches fall into three major categories (Fig. 3). The initial strategy was to use anti-IGF-1R mAbs in order to block ligand–receptor interactions, and induce receptor internalization and subsequent degradation [21]. Many therapeutic mAbs directed against IGF-1R have been developed, and encouraging preclinical activity has been observed with ganitumab [53], figitumumab [54], dalotuzumab [67], R-1507 [55], robatumumab [56], and istiratumab, a tetravalent bispecific mAb that inhibits both IGF-1R and ErbB3 [57], in a

wide range of tumor models [1]. Although IGF-1R specific, some of these agents can also induce downregulation of INSR-A or -B in IGF-1R/INSR hybrid receptors, potentially through receptor endocytosis [68]. However, these agents do not inhibit IGF-2 activation of INSR-A homodimers [65, 69].

2.2 IGF-1R Tyrosine Kinase Inhibitors (TKIs)

An alternative approach to targeting IGF-1R signaling has been to use TKIs that inhibit RTKs. Therapeutic TKIs were developed initially as IGF-1R-specific inhibitors; however, a high level of homology in the kinase domains of IGF-1R, INSR-A, and INSR-B means that, in intact cells and in vivo, IGF-1R TKIs can affect all three [6, 70]; thus, linsitinib, BMS-754807 and KW-2450 are often described as dual IGF-1R/INSR inhibitors [60–62]. Each of these agents has shown promising activity in preclinical models; for example, linsitinib demonstrated superior anti-tumor activity compared with the selective anti-IGF-1R mAb MAB391 in mice bearing human tumor xenografts [25]. However, cross-reactivity with INSR-B can modulate glucose metabolism in vivo, leading to insulin resistance and hyperglycemia [21, 71, 72]. In addition, there are other known off-target effects with IGF-1R TKIs,

Fig. 3 Examples of IGF-targeted agents. Anti-IGF-1R mAbs block ligand–receptor interactions and induce receptor internalization and degradation [53–59]. Small molecule TKIs bind to the receptor tyrosine kinase domain and block signaling downstream of IGF-1R and INSR [60–64]. IGF ligand-neutralizing mAbs bind to and neutralize both IGF ligands, thereby blocking the activation of IGF-1R and INSR-A [65, 66]. Agents shown in gray have only been evaluated preclinically. Agents in italics are in ongoing clinical trials as monotherapy or in combination with other anti-cancer treatments. Clinical development of all other agents shown has been terminated. *IGF-1/−2* insulin-like growth factor ligand 1/2, *IGF-1R* type 1 IGF receptor, *INSR* insulin receptor, *mAb* monoclonal antibody, *TKI* tyrosine kinase inhibitor

Insulin
IGF-1
IGF-2
IGF ligand-neutralizing mAb
Anti-IGF-1R mAb

IGF-1 and **IGF-2** co-neutralizing mAbs
• *Xentuzumab (BI 836845)*
• *Dusigitumab (MEDI-573)*

Anti-IGF-1R mAbs
• *Ganitumab (AMG-479)*
• *Istiratumab (MM-141)*
• Figitumumab (CP-751871)
• Cixutumumab (IMC-A12)
• Dalotuzumab (MK-0646)
• Robatumumab (MK-7454)
• R-1507

IGF-1R TKIs
• BMS-754807
• Linsitinib (OSI-906)
• KW-2450
• NVP-AEW541
• AG-1024 (CAS 65678-07-1)
• AZ12253801
• BMS-536924

IGF-1, IGF-2, IGF-1R, INSR-A, INSR-B, TKI

Proliferation/growth   **Glucose metabolism**

e.g. inhibition of TrkA, TrkB, and aurora kinases by BMS-754807 [60], which may influence their therapeutic use.

2.3 IGF-1/−2 Blocking mAbs

A third therapeutic approach is to target the IGF-1 and IGF-2 ligands directly, thereby inhibiting proliferative/anti-apoptotic signaling via IGF-1R and INSR-A and their hybrid receptors, without compromising the function of INSR-B or affecting insulin action [65, 66, 73]. Thus, these agents demonstrate a lower potential for hyperglycemia compared with IGF-1R TKIs [65, 66]. In contrast with IGF-1R-specific mAbs, which can show reduced anti-proliferative activity in heterogeneous cell populations that contain a high percentage of INSR-A-expressing cells, IGF-1/IGF-2-neutralizing mAbs should also have greater anti-tumor activity in tumors that express both IGF-1R and INSR-A, or INSR-A alone [65].

Two IGF-1/IGF-2 co-neutralizing mAbs, dusigitumab (MEDI-573) [65] and xentuzumab (BI 836845) [66], have been developed. Dusigitumab shows stronger binding affinity for IGF-2 than IGF-1, while xentuzumab binds with higher affinity to IGF-1 [65, 66]. Both dusigitumab and xentuzumab have demonstrated encouraging anti-proliferative activity in vitro and in vivo in preclinical models [65, 66, 74]. Xentuzumab also binds rat and mouse IGF-1 and IGF-2, which has allowed a comprehensive characterization of its in vivo pharmacodynamic properties in both species. In rats,

there was no significant toxicity following long-term exposure to xentuzumab at levels sufficient to attenuate serum IGF bioactivity and somatic growth [66].

Dusigitumab and xentuzumab are in ongoing clinical development in early-phase trials, either as monotherapy or in combination with other treatments, in metastatic hormone receptor-positive breast cancer, CRPC, and non-small cell lung cancer (NSCLC). Phase I clinical data for dusigitumab in US patients with advanced solid tumors have shown preliminary anti-tumor activity, with 13 of 39 patients in the dose-escalation cohort achieving stable disease. Dusigitumab demonstrated a favorable toxicity profile, the most common adverse events (AEs; of any cause) being decreased appetite and fatigue [75]. Similarly, dusigitumab was well tolerated in a phase I dose-escalation study in Japanese patients with advanced solid tumors, in which the best response was stable disease in four out of 10 patients [76]. Xentuzumab has also demonstrated good tolerability in three phase I dose-escalation studies using weekly or 3-weekly dosing, in patients with advanced solid tumors in the UK, Asia, and Japan. Similar to dusigitumab, the most common AEs in these trials included decreased appetite, gastrointestinal disorders and fatigue [77–79]. In addition, encouraging anti-tumor activity has been observed with xentuzumab, whereby two out of 48 (4%) patients in the Asian study had a partial response and a further 15 (31%) patients had stable disease [78]. In the Japanese study, there was a confirmed partial response in one of nine patients

(patient with desmoid tumor) treated at the recommended phase II dose (RP2D; 1000 mg weekly), and two patients had confirmed stable disease [77].

3 Clinical Experience with IGF-Targeted Agents As Monotherapy

3.1 First Conundrum: The Absence of Meaningful Monotherapy Activity with IGF-1R-Targeted Agents

Despite a strong preclinical rationale, targeting the IGF axis has provided distinct challenges, and, with the exception of IGF-ligand-blocking mAbs, clinical development programs for most IGF-targeted agents have been compromised by failures in the clinical trial setting [80]. To date, clinical trials of single-agent anti-IGF-1R mAbs and IGF-1R TKIs have been disappointing, reporting low objective response rates and with only minor responses and disease stabilization in most tumor types (Table 1) [58, 59, 62, 81–96]. Exceptions include Ewing sarcoma, with evidence of activity in approximately 10% of patients, and soft-tissue sarcomas [81–85]. Recently published phase II data showed that a subset of patients with Ewing sarcoma achieved durable (>4 years) responses to the IGF-1R mAb robatumumab [97]. So far, there has been insufficient evidence of single-agent activity in common cancers, and as a result, clinical development has been terminated for most IGF-1R-targeted mAbs and TKIs.

Potential reasons for these negative clinical data with anti-IGF-1R mAbs may include an inability to sustain inhibition of proliferative/survival signaling in vivo, since these agents fail to suppress IGF-2-induced INSR-A signaling in tumor cells [73]. For IGF-1R TKIs, the risk of hyperglycemia due to co-inhibition of INSR-B may limit their ability to achieve clinically relevant IGF-1R blockade in tumor tissue [1]. Notably, neither of these limitations would be expected to apply to dusigitumab or xentuzumab based on their IGF-ligand-blocking mechanism of action [65, 66].

In addition to these limitations, resistance to IGF-targeted agents can arise from redundancy and crosstalk with other RTK signaling pathways, including EGFR, human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor receptor (VEGFR), mesenchymal epithelial transition factor (cMET), platelet-derived growth factor receptor (PDGFR), and anaplastic lymphoma kinase (ALK), as well as with steroid hormone receptors such as the androgen receptor (AR), ER, and progesterone receptor (PR) [49, 50, 63, 98–107] (Fig. 4). Furthermore, preclinical data in breast cancer suggest that inhibition of IGF-1R upregulates INSR-A, leading to IGF-2-induced amplification of Wnt and Notch signaling, which results in the expansion of stem/progenitor populations; this may lead to the development of tumors with high self-renewal potential and confer resistance to other types of anti-cancer treatment [108, 109].

3.2 Second Conundrum: The Absence of a Bona Fide Predictive Biomarker

A notable challenge has been the lack of a bona fide predictive biomarker to allow selection of patients who are most likely to benefit from IGF-targeted therapy. Although there is near-ubiquitous expression of IGF-1R in human cancers, mutations in IGF-1R are rarely reported [51, 52]. IGF-1R is, therefore, considered an "epi-driver" gene, that is, one that is expressed aberrantly in tumors, but is not the main driver of tumor development [110]. For this reason, other predictive biomarkers may be needed for patient selection in clinical trials of IGF-targeted therapies [21].

Although the IGF axis appears to be relatively unperturbed by somatic mutations, genetic studies suggest that the risk of cancer may be influenced by IGF and/or insulin gene variants. For example, non-synonymous polymorphisms in the IGF-2R gene appear to contribute to the risks of esophageal and gastric cancers [111]. Moreover, single-nucleotide polymorphisms (SNPs) in IGF-axis genes were associated with improved progression-free survival (PFS) and overall survival (OS) outcomes with chemotherapy in patients with gastric cancer [112]. A polymorphism in the 3′ untranslated region of IGF-1 was also found to be significantly associated with improved survival in patients with NSCLC [113]. In a pooled analysis that included more than 3000 cancer specimens, cancer-associated somatic copy number variations (CNVs) were detected in the IGF-1R gene region [114]. In addition, high polysomy in the IGF-1R gene was found to predict improved survival in operable NSCLC [115], suggesting that, similar to polymorphisms, CNVs could have a prognostic value in cancer. Further investigation is needed to determine whether molecular markers such as these could also serve as potential predictive biomarkers for response to IGF-targeted therapies.

A number of clinical studies have investigated possible associations of circulating free or total IGF-1 with clinical benefit of IGF-targeted agents, using serum and/or plasma-based assays, albeit with mixed results (Table 2) [116–125]. Similar to molecular markers, further research to confirm circulating free or total IGF-1 as a predictive biomarker, along with robust validation of any assay procedure(s) used, is a prerequisite for use in randomized clinical trials.

Other candidate biomarkers, either within the IGF axis or in other pathways that influence response to IGF-targeted therapies, have been investigated using various IGF-1R-targeted agents [21]. For example, preclinical and clinical evidence suggests that high expression of IGF-2 and insulin receptor substrates, and differential expression of different IGFBPs may be associated with increased sensitivity to anti-IGF-1R mAbs [122, 126, 127]. In colorectal cancer (CRC) cell lines,

Table 1 Examples of single-agent clinical trials of IGF-1R-targeted agents

Indication	IGF-targeted agent	MoA	Phase	Key efficacy results	Key safety results	Current stage of development	References
Ewing sarcoma and refractory solid tumors	Cixutumumab	Anti-IGF-1R mAb	I/II (pediatric)	• Limited activity in Ewing sarcoma	• Well tolerated	Discontinued	[81]
Ewing sarcoma, soft-tissue sarcomas	Cixutumumab	Anti-IGF-1R mAb	II	• Clinical benefit in adipocytic sarcoma	• Generally well tolerated; hyperglycemia was among the most common AEs	Discontinued	[82]
Ewing sarcoma and other sarcomas	Figitumumab	Anti-IGF-1R mAb	I	• Two patients with Ewing sarcoma had objective responses (one complete response and one partial response) • Eight patients had stable disease (six with Ewing sarcoma, one with synovial sarcoma, and one with fibrosarcoma) lasting ≥4 months	• Well tolerated; AEs were mostly mild-to-moderate	Discontinued	[83]
Ewing sarcoma, other solid tumors, and NHL	Ganitumab	Anti-IGF-1R mAb	I	• Preliminary efficacy in Ewing sarcoma	• Manageable tolerability	Phase III in Ewing sarcoma (combination); discontinued in most other indications	[84]
Bone and soft-tissue sarcomas	R-1507	Anti-IGF-1R mAb	II	• Limited efficacy (ORR 2.5%)	• Well tolerated	Discontinued	[85]
Neuroendocrine tumors	Dalotuzumab	Anti-IGF-1R mAb	II	• No single-agent activity	• Grade 3/4 hyperglycemia in 32% of patients	Discontinued	[58]
SCLC	Linsitinib	IGF-1R/INSR TKI	II	• No evidence of clinical activity; one of 29 patients had stable disease	• Well tolerated	Discontinued	[86]
Head and neck SCC	Figitumumab	Anti-IGF-1R mAb	II	• No clinically significant activity in unselected patients	• Hyperglycemia in 41% of patients	Discontinued	[87]
Head and neck SCC	Cixutumumab	Anti-IGF-1R mAb	II	• No PFS improvement vs. historical data with cetuximab	• Tolerable safety profile	Discontinued	[88]
HCC	Cixutumumab	Anti-IGF-1R mAb	II	• No clinically meaningful activity in unselected patients	• Grade 3/4 hyperglycemia in 46% of patients	Discontinued	[59]
HCC	Istiratumab	Dual IGF-1R/ErbB3 mAb	I	• Pharmacodynamic analysis suggested appropriate target engagement; IGF-1R levels decreased after istiratumab exposure	• Well tolerated	Phase II in metastatic pancreatic cancer (combination)	[89]
CRC	Figitumumab	Anti-IGF-1R mAb	II	• No objective responses • Survival data did not support further study at the tested doses (20 or 30 mg/kg)	• Most common grade 3/4 non-hematologic AEs were hyperglycemia and asthenia	Discontinued	[90]
Adrenocortical carcinoma	Figitumumab	Anti-IGF-1R mAb	I; dose expansion	• Eight of 14 patients had stable disease; no objective responses	• Generally well tolerated; hyperglycemia was the most common AE	Discontinued	[91]
Breast cancer (progressed after endocrine therapy)	Cixutumumab	Anti-IGF-1R mAb	II	• No objective responses with cixutumumab monotherapy	• Acceptable safety profile	Discontinued	[92]
Ovarian cancer	Ganitumab	Anti-IGF-1R mAb	II	• Modest single-agent activity in unselected patients • Four of 61 patients had an objective response	• Well tolerated	Phase III in Ewing sarcoma (combination); discontinued in most other indications	[93]

Table 1 (continued)

Indication	IGF-targeted agent	MoA	Phase	Key efficacy results	Key safety results	Current stage of development	References
Solid tumors	BMS-754807	IGF-1R/INSR TKI	I	• Radiologic responses and prolonged stable disease suggested anti-tumor activity	• Well tolerated at dose exceeding preclinical minimum effective exposures	Discontinued	[94]
Refractory solid tumors	Figitumumab	Anti-IGF-1R mAb	I	• 10 of 15 patients treated at maximal feasible dose (20 mg/kg) had stable disease; no objective responses	• Well tolerated	Discontinued	[95]
Advanced solid tumors	Linsitinib	IGF-1R/INSR TKI	I	• Preliminary efficacy in adrenocortical carcinoma	• Manageable tolerability	Discontinued	[96]
Advanced solid tumors	KW-2450	IGF-1R/INSR TKI	I	• Four of 10 evaluable patients had stable disease	• MTD was 37.5 mg QD • DLTs in two of six patients at 50 mg/day (grade 3 hyperglycemia) and one of seven patients at 37.5 mg/day (grade 3 rash)	Discontinued	[62]

AE adverse event, *CRC* colorectal cancer, *DLT* dose-limiting toxicities, *HCC* hepatocellular carcinoma, *IGF-1R* insulin-like growth factor receptor 1, *INSR* insulin receptor, *mAb* monoclonal antibody, *MoA* mechanism of action, *MTD* maximum tolerated dose, *NHL* non-Hodgkin lymphoma, *ORR* objective response rate, *PFS* progression-free survival, *QD* once daily, *SCC* squamous cell carcinoma, *SCLC* small-cell lung cancer, *TKI* tyrosine kinase inhibitor

dusigitumab neutralized IGF-2 and induced significant tumor growth inhibition in mouse models that overexpressed IGF-2, a finding that supports evaluation of dusigitumab in CRC patients whose tumors overexpress IGF-2 [128]. Pavlicek et al. investigated correlations between genomic characteristics of cancer cell lines and figitumumab anti-proliferative activity, and found that components of the IGF pathway, including insulin receptor substrate 2 (IRS2) and IGFBP5, played a pivotal role in determining the sensitivity of tumors to single-agent figitumumab. In addition, alteration or expression of the *MYB* oncogene was reported to be associated with sensitivity to IGF-1R inhibitors [126]. In preclinical models of SCLC, low levels of phosphorylated extracellular-signal-regulated kinase (ERK) prior to treatment appeared to be predictive of resistance to IGF-1R inhibition [129]. With regard to clinical studies, exclusive nuclear IGF-1R was associated with response to various IGF-1R Abs in patients with sarcoma, shown by improved PFS and OS, suggesting IGF-1R nuclear translocation could also be a biomarker of IGF pathway activation [130]. However, despite these findings, there is currently a lack of any validated predictive biomarkers for patient enrichment in clinical trials of IGF-targeted agents [21].

4 Rationale for Combination Studies Using IGF-Targeted Agents

4.1 Mechanisms of Resistance

The extensive interactions between the IGF axis and other signaling networks/cellular processes inevitably lead to signaling redundancy and the potential for development of primary resistance to anti-cancer therapies. IGF-1R signaling can contribute to treatment resistance via general mechanisms that promote tumorigenesis, through crosstalk/redundancy with other RTK signaling networks that drive cellular proliferation and upregulation of anti-apoptotic proteins [49]. In addition, the IGF axis has specific effects relevant to individual classes of anti-cancer treatment. For example, IGF-1R signaling is thought to upregulate the activity of efflux pumps such as multidrug-resistance-associated protein 2, which can reduce the intracellular concentration of cytotoxic drugs [131]. IGF-1R signaling may also promote DSB repair following treatment with DNA-damaging agents, thereby reducing the efficacy of standard cytotoxic treatments [31, 32, 132]. Finally, crosstalk between the IGF axis and signaling via the ER [133] or AR [134] can promote treatment resistance by stimulating hormone-receptor-dependent transcriptional pathways.

In addition to primary treatment resistance, IGF signaling plays a key role in the development of acquired resistance to chemotherapeutic or targeted agents via feedback relief responses, which lead to compensatory activation of IGF
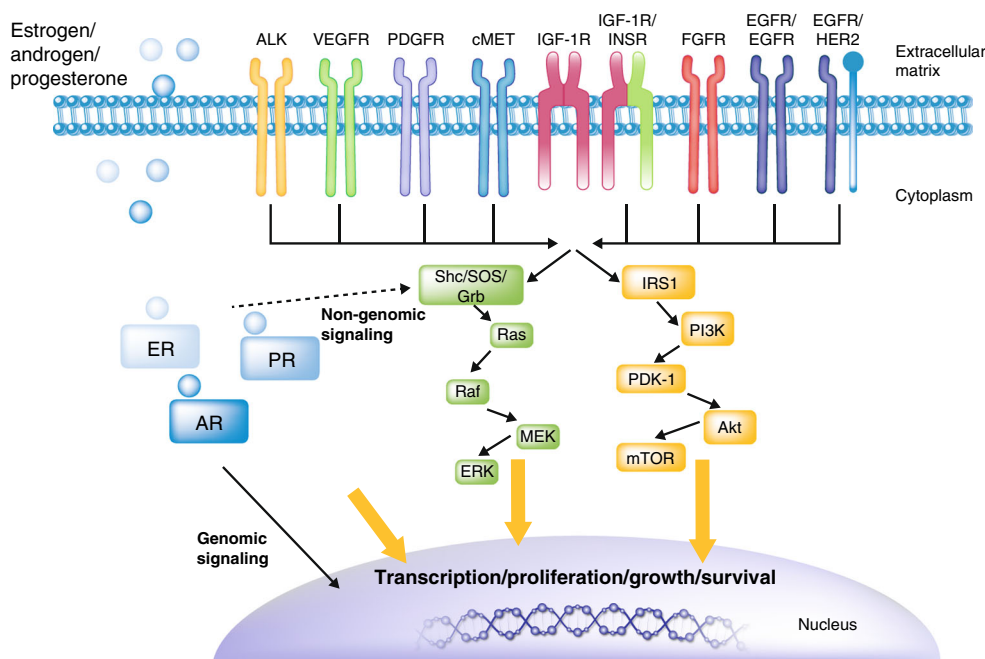
Fig. 4 Crosstalk between IGF-1R and other RTKs/steroid hormone receptors. Crosstalk between IGF-1R and other RTKs (including ALK, VEGFR, PDGFR, cMET, FGFR, EGFR, and HER2) and steroid hormone receptors (ER, AR, and PR), and compensatory activation of the MAPK and PI3K/Akt signaling pathways downstream of IGF-1R signaling can confer resistance to targeted therapies [2, 49]. *Akt* protein kinase B, *AR* androgen receptor, *ALK* anaplastic lymphoma kinase, *cMET* mesenchymal epithelial transition factor, *EGFR* epithelial growth factor receptor, *ER* estrogen receptor, *ERK* extracellular-signal-regulated kinase, *FGFR* fibroblast growth factor receptor, *HER2* human epidermal growth factor receptor 2, *IGF-1R* type 1 insulin-like growth factor receptor, *INSR* insulin receptor, *MEK* mitogen-activated protein kinase/Erk kinase, *mTOR* mammalian target of rapamycin, *PDGFR* platelet-derived growth factor receptor, *PI3K* phosphatidylinositol-3-kinase, *PR* progesterone receptor, *Shc* Src homology and collagen domain protein, *VEGFR* vascular endothelial growth factor

survival signaling [135]. For example, acquired resistance to EGFR TKIs in lung squamous cell carcinoma and adenocarcinoma can result from IGF-1R activation, via the loss of the negative regulator IGFBP3 [135–137].

Given these mechanisms, IGF-targeted therapy lends itself as an attractive backbone to novel combination regimens as a strategy to prevent or overcome treatment resistance, and combinations that incorporate IGF-targeted agents with standard cytotoxic agents and/or other targeted therapies have been investigated preclinically in many human cancers (Table 3). The remainder of this review will summarize the current evidence to support various combination approaches and discuss potential opportunities for future clinical trials.

4.2 Combination with DNA-Damaging Agents

Preclinical evidence suggests that IGF signaling can protect tumor cells from chemotherapy- or radiotherapy-induced cell death [24, 31, 32, 138–144]. For example, in models of CRPC, upregulation of IGF-2 via the transcription factor GATA2 strongly contributed to chemotherapy resistance after docetaxel and cabazitaxel treatment, by activating numerous downstream kinases including IGF-1R and INSR. Moreover, dual IGF-1R/INSR inhibition restored the efficacy of both chemotherapy drugs and improved in vitro and in vivo

survival [24]. In another study, exposure of murine glioma stem cells to fractionated radiation induced an increase in IGF-1 secretion and upregulation of IGF-1R, which together conferred resistance by protecting cells from subsequent radiation therapy [143].

Some studies support the importance of the scheduling of IGF-1R inhibition and chemotherapy, in order to achieve an optimal therapeutic response, suggesting that treatment sequencing approaches should be considered in future combination clinical trials incorporating these two treatment modalities [140, 141]. In contrast, combination with IGF-targeted therapies may increase radio-sensitivity without regard to scheduling of radiation and IGF-1R inhibition [142].

Inhibition of IGF-1R signaling is thought to enhance the effects of chemotherapy or radiotherapy primarily through suppression of DNA damage repair [5, 31, 32]. For example, addition of the anti-IGF-1R mAb R-1507 increased the anti-tumor activity of a standard cisplatin/ionizing radiation couplet in in vitro and in vivo models of SCLC. Moreover, genomic and functional analyses identified downregulation of the nucleotide excision repair pathway in SCLC cells treated with the R-1507/cis-IR combination [32].

With regard to clinical evidence to support the use of IGF-1R-targeted/cytotoxic drug combinations, IGF-1R overexpression in tumor tissue samples was found to be associated

Table 2 Summary results of total/free IGF-1 as a biomarker of clinical benefit

Indication/phase	Study treatment	Assay	Specimen	Total IGF-1	Total IGF-1 clinical effect	Free IGF-1	Free IGF-1 clinical effect	Reference
Ewing sarcoma; other sarcomas; phase I	Figitumumab	NA	Serum	Yes	• 60–130 ng/mL range associated with significantly longer OS • Total IGF-1 <110 ng/mL vs ≥110 ng/mL: OS 4.4 vs 10.6 months ($p < 0.001$)	Yes	• Higher free serum IGF-1 associated with longer OS; significant in the 0.4–0.85 range • Free IGF-1 <65 ng/mL vs ≥65 ng/mL: OS 3.65 vs 10.4 months ($p < 0.001$) • Late PFS improvement in patients with high free IGF-1 but only minor effects on median PFS	[116]
Ewing sarcoma; phase II	R-1507	ELISA	Serum	Yes	• Total IGF-1 ≥110 ng/mL (pretreatment and Week 6) and a higher % increase of total IGF-1 from baseline to Week 6 predicted improved OS	No	• NA	[117]
Ewing sarcoma or desmoplastic small round cell tumors; phase II	Ganitumab	Radioimmunoassay	Serum	Yes	• No relationship between response and IGF-1 levels or EWS gene translocations	No	• NA	[118]
NSCLC; phase I	Figitumumab	Radioimmunoassay	Serum	Yes	• Higher serum total IGF-1 concentration–time profile and baseline total IGF-1 in patients with a PR vs those with stable disease	No	• NA	[119]
NSCLC; phase I/II	Cixutumumab	ELISA	Serum/plasma	No	• NA	Yes	• Non-significant trend for better PFS in highest quartile of free IGF-1	[120]
Pancreatic adenocarcinoma; phase II	Dalotuzumab	ELISA	Serum	Yes	• Addition of dalotuzumab to gemcitabine plus erlotinib improved PFS in patients with high total IGF-1 (>median; $p = 0.016$)	No	• NA	[121]
Pancreatic adenocarcinoma; phase II	Ganitumab + gemcitabine	ELISA	Serum/plasma	Yes	• Improvement in OS with the addition of ganitumab was enhanced in patients with higher baseline total IGF-1 (>105 ng/mL), but not significantly so ($p = 0.27$)	Yes	• Not included in correlation analysis due to high frequency of patients with undetectable free IGF-1	[122]
Pancreatic adenocarcinoma; phase III	Ganitumab	Radioimmunoassay	Serum	Yes	• No significant interaction with OS or PFS treatment effect with ganitumab	No	• NA	[123]
Solid tumors (breast cancer arm); phase I	Istiratumab	ELISA	Serum	No	• NA	Yes	• Patients with elevated free IGF-1 remained on study longer and received a greater number of doses	[124]
Advanced solid tumors; phase I	R-1507 + erlotinib	ELISA	Serum	Yes	• None	Yes	• Significantly higher PFS rate at 12 weeks in patients with high free serum IGF-1 (>median)	[125]

ELISA enzyme-linked immunosorbent assay, *NA* not applicable, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PR* partial response, *PFS* progression-free survival

with shorter survival and a less favorable response to temozolomide chemotherapy in patients with glioblastoma multiforme (GBM) [167]. However, the results of combination trials with IGF-1R inhibitory drugs and chemotherapy have been disappointing. In a phase III trial in unselected patients with metastatic pancreatic cancer, a combination of ganitumab plus gemcitabine had manageable toxicity but did not improve OS compared with gemcitabine alone [123]. Similarly, addition of figitumumab to paclitaxel plus carboplatin failed to increase OS in patients with advanced nonadenocarcinoma NSCLC; this phase III study was closed early due to futility and an increased incidence of serious AEs and deaths in the figitumumab arm [168]. Furthermore, a phase II/III study of the IGF-1R mAb dalotuzumab in combination with cetuximab and irinotecan was discontinued prematurely due to lack of overall benefit with the addition of dalotuzumab, although there was a trend towards longer PFS and OS with this combination in patients with higher tumor IGF-1 mRNA [169]. Notably, none of these studies incorporated the sequential schedule of administration that was found to be optimal in preclinical studies [140, 141]. Based on these findings, and despite a convincing preclinical rationale, we suggest that factors contributing to failure of these clinical trials are likely to include toxicity, suboptimal treatment scheduling, and the lack of a predictive biomarker.

Regarding IGF-1R TKIs, three separate phase I/II clinical studies have evaluated the safety and efficacy of BMS-754807 in combination with paclitaxel plus carboplatin in patients with advanced solid tumors (NCT00793897), and with either trastuzumab (an HER-targeted mAb) or letrozole in patients with breast cancer (NCT00788333; NCT01225172); however, no results have been published, to-date. A phase II trial is investigating the efficacy and safety of istiratumab in combination with gemcitabine plus nab-paclitaxel in patients with metastatic pancreatic cancer, on the basis of preclinical evidence that istiratumab can induce significant tumor regression, including durable complete responses [57, 170].

4.3 Combination with Inhibitors of Other RTKs and Downstream Effectors

4.3.1 RTK Inhibitors

Crosstalk between the IGF axis and other RTK signaling pathways (including EGFR, HER2, VEGFR, PGDFR, cMET, and ALK) results in reciprocal compensatory mechanisms that limit response and/or mediate acquired resistance to treatments that target an individual pathway (Fig. 4) [49, 50, 63, 98–107, 137, 146, 171, 172].

This crosstalk is particularly apparent with regard to IGF and EGFR. In GBM, both of these pathways mediate activation of PI3K/Akt signaling [145]. Administration of AG1478, an EGFR TKI, resulted in IGF-1R upregulation in GBM cell

lines, leading to sustained compensatory signaling through the PI3K pathway which produced potent anti-apoptotic and pro-invasion effects [145]. In another preclinical GBM study, the EGFR TKI gefitinib was effective in attenuating downstream MAPK/MEK/ERK activity, but concurrent inhibition of EGFR and IGF-1R/INSR was required to suppress Akt and induce apoptosis [105]. Similarly, in pediatric GBM, IGF-1R inhibition reduced signaling through the PI3K pathway, while targeting PDGFR resulted in parallel inhibition of signaling via the MAPK pathway. Targeting both receptors together resulted in enhanced anti-tumor activity compared with inhibition of either receptor alone [147].

Phospho-RTK array analysis in lung cancer models identified increased IGF-1R phosphorylation in erlotinib-resistant adenocarcinoma cells with wild-type *EGFR* [106]. In another study, NSCLC cell lines resistant to irreversible (e.g. PF299804) or mutant-selective (WZ4002) EGFR TKIs demonstrated activated IGF signaling due to loss of IGFBP3 expression, and combination of PF299804 or WZ4002 with the IGF-1R inhibitor BMS-536924 prevented the emergence of drug-resistant clones [137]. The sensitivity of NSCLC cells with acquired resistance to WZ4002 was also restored by AG-1024 (a small-molecule IGF-1R TKI) or xentuzumab [63]. IGF-1R knockdown sensitized resistant NSCLC cells to afatinib, another irreversible EGFR TKI, with combined treatment resulting in more than additive effects on tumor growth inhibition in vivo [103]. Inhibition of IGF-1R signaling using microRNAs has also been shown to partially reverse acquired resistance to erlotinib in NSCLC models, and sensitize *HER2*-positive breast cancer cells to HER-targeted drugs [100, 101]. Finally, IGF-2 overexpression has been observed in CRC patients whose tumors lacked resistance-conferring *KRAS* mutations but who responded to the EGFR mAb cetuximab with stable disease rather than an objective response. Furthermore, inhibition of IGF-1R/INSR signaling with BMS-754807 potentiated the anti-tumor effects of cetuximab in IGF2-over-expressing xenografts [107].

Based on this preclinical evidence with EGFR and IGF-1R inhibitors, together with the potential for better tolerability of IGF-ligand blockers, xentuzumab is under clinical investigation in combination with afatinib in a phase Ib trial in patients with NSCLC (NCT02191891). This combination demonstrated a manageable safety profile and encouraging activity; at the RP2D, one of 12 patients had a partial response and 10 patients had stable disease [173].

Activation of IGF-1R signaling has also been demonstrated in models of ALK TKI resistance, supporting the use of combined treatment with IGF-targeted therapies and ALK inhibitors, or second-generation ALK TKIs such as ceritinib (LDK-378), which simultaneously inhibits ALK and IGF-1R phosphorylation [104].

Table 3 Preclinical evidence for rational combination approaches

Combination treatment modality	Combination partner(s)	IGF-targeted agent(s)/ intervention	MoA	Indication	Key results	References
DNA-damaging agents						
Chemotherapy	Docetaxel; cabazitaxel	Linsitinib	Dual IGF-1R/INSR TKI	CRPC	• Upregulation of IGF-2 via GATA2 strongly contributed to chemo-resistance • Dual IGF-1R/INSR inhibition restored the efficacy of chemotherapy	[24]
	Gemcitabine	BMS-754807	Dual IGF-1R/INSR TKI	Pancreatic cancer	• Improved net tumor growth inhibition (94% vs. 35%) with combination vs gemcitabine alone	[138]
	Gemcitabine	Xentuzumab	IGF-1/IGF-2-neutralizing Ab	Pancreatic cancer	• Combination with xentuzumab and gemcitabine synergistically inhibited tumor growth and increased tumor cell death • Phosphorylation of INSR and IGF-1R was decreased in tumors treated with xentuzumab	[139]
	Doxorubicin	scFv-Fc; EM164	Anti-IGF-1R mAb	Breast cancer	• Chemotherapy followed by IGF-1R inhibition was more effective than the reverse sequence • Cell cycle arrest in response to pre-IGF-1R prevented cellular apoptosis	[140]
	Temozolomide	Linsitinib; AZ3801	IGF-1R TKIs	Melanoma	• Synergistic anti-tumor effects were greatest when temozolomide administered before IGF-1R inhibition	[141]
Radiation	Fractionated radiation	Ganitumab	Anti-IGF-1 mAb	Head and neck cancer	• Combination potentiated tumor growth delay without regard to treatment scheduling	[142]
	Fractionated radiation	Not specified	IGF-1-neutralizing Ab	Glioma	• Increased IGF-1 secretion and IGF-1R upregulation protected cells from subsequent radiation therapy • IGF-1 neutralizing Ab markedly reduced radio-resistance	[143]
	Ionizing radiation	BMS-754807; caloric restriction	IGF-1R/INSR TKI	Breast cancer	• IGF-1R/INSR inhibition or caloric restriction, in combination with radiation therapy, decreased metastatic burden to a similar extent • Caloric restriction plus radiotherapy decreased proliferation and increased apoptosis, partly through downregulation of the IGF-1R signaling pathway	[144]
	Acute radiation	AZ12253801	IGF-1R TKI	Prostate cancer	• AZ12253801 enhanced radio-sensitivity and delayed DSB repair	[31]
	Cisplatin/ ionizing radiation	R-1507	Anti-IGF-1R mAb	SCLC	• Increased anti-tumor activity with combination vs cisplatin/ionizing radiation alone • Downregulation of nucleotide excision repair pathway with IGF-1R inhibition	[32]
Targeted therapies – RTK inhibitors						
ErbB family blocker	Afatinib	NVP-AEW541	IGF-1R TKI	Pancreatic cancer	• Combination treatment induced synergistic growth inhibition	[102]
ErbB family blocker	Afatinib	Linsitinib	Dual IGF-1R/INSR TKI	NSCLC	• Combination treatment had additive anti-tumor effects and led to sensitization of afatinib-resistant cells	[103]
EGFR TKI	Erlotinib	miR-223 overexpression	IGF-1R inhibition	NSCLC	• miR-223 overexpression partially reversed acquired resistance to erlotinib by inhibiting IGF-1R/PI3K/Akt signaling	[101]

Table 3 (continued)

Combination treatment modality	Combination partner(s)	IGF-targeted agent(s)/ intervention	MoA	Indication	Key results	References
EGFR TKI	Gefitinib	Linsitinib	Dual IGF-1R/INSR TKI	GBM	• Concurrent inhibition of EGFR and IGF-1R/INSR required to suppress Akt and induce apoptosis	[105]
EGFR TKI	AG-1478	AG-1024	IGF-1R TKI	GBM	• Co-inhibition of IGF-1R and EGFR greatly enhanced spontaneous and radiation-induced apoptosis and reduced invasive potential of GBM cells	[145]
EGFR TKI	WZ4002; PF299804	BMS-536924; linsitinib	IGF-1R TKI		• Combination of WZ4002 or PF299804 with IGF-1R inhibition restored sensitivity to EGFR TKIs	[137]
EGFR TKI	WZ4002	Xentuzumab; AG-1024	IGF-1/IGF-2-neutralizing Ab; IGF-1R TKI; IGF-1R shRNA	NSCLC	• Combined treatment with xentuzumab, AG-1024 or IGF-1R shRNA restored sensitivity to WZ4002 in EGFR TKI-resistant cells	[63]
EGFR mAb	Cetuximab	BMS-754807	Dual IGF-1R/INSR TKI	CRC	• IGF-2 overexpression or IGF-1R/INSR inhibition reduced or potentiated the anti-tumor effects of cetuximab, respectively	[107]
HER-targeted drug	Lapatinib; neratinib; afatinib	miR-630 overexpression	IGF-1R inhibition	HER2+ breast cancer	• miR-630 overexpression reduced resistance/insensitivity to HER-targeted drugs • miR-630 inhibition induced a more aggressive cellular phenotype	[100]
HER-targeted drug	Trastuzumab	IGF-1R siRNA; NVP-AEW541	IGF-1R knockdown; IGF-1R TKI	HER2+ breast cancer	• IGF-1R siRNA or NVP-AEW541 enhanced anti-tumor responses to trastuzumab	[98]
HER-targeted drug	HER1/HER2 peptide mimics/ vaccine Abs	IGF-1R peptide mimics/vaccine Abs	–	Esophageal cancer; triple-negative breast cancer	• Combination treatment increased inhibition of receptor phosphorylation and induced significantly higher levels of apoptosis vs single-agent treatment	[146]
Bcr-Abl/ PDGFR/cKit inhibitor	Imatinib	NVP-AEW541	IGF-1R TKI	Pediatric GBM	• Co-targeting of IGF-1R and PDGFRα/β resulted in synergistic inhibition of tumor growth in vitro and in vivo vs single-agent treatments	[147]
Bcr-Abl/Src family TKI	Dasatinib	BMS-754807; Linsitinib	Dual IGF-1R/INSR TKI	Prostate cancer; NSCLC	• Greater inhibition of tumor growth observed with combination vs single agents	[148, 149]
Bcr-Abl/Src family TKI	Dasatinib	R-1507; BMS-754807	Anti-IGF-1R mAb; Dual IGF-1R/INSR TKI	Rhabdomyosarcoma	• Dasatinib and IGF-1R TKIs had synergistic effects on tumor cell growth inhibition	[150]
ALK TKI[a]	Ceritinib; crizotinib	Linsitinib	Dual IGF-1R/ALK inhibitor	ALK fusion positive lung cancer	• Combined treatment with linsitinib and crizotinib resulted in reduced proliferation and increased levels of apoptosis versus single-agent treatments • The dual IGF-1R/ALK inhibitor ceritinib improved anti-tumor activity vs. crizotinib	[104]
Targeted therapies – PI3K/Akt/mTOR and MAPK pathway inhibitors						
MEK/ERK inhibitor	Selumetinib	R-1507	Anti-IGF-1R mAb	CRC	• Combination had synergistic apoptotic effects in vitro and anti-tumor effects in vivo in KRAS-mutant CRC models	[151]
MEK/ERK inhibitor	U0126; selumetinib	Linsitinib	Dual IGF-1R/INSR TKI	CRC	• Combination of linsitinib and MEK/ERK inhibitors synergistically inhibited tumor growth in vitro (U0126) and in vivo (selumetinib)	[152]
MEK/ERK inhibitor	U0126	Figitumumab	Anti-IGF-1 mAb	SCLC	• MEK/ERK inhibition enhanced the anti-tumor effects of figitumumab in SCLC cells; high IGF-1R expression was correlated with reduced patient survival	[22]

Table 3 (continued)

Combination treatment modality	Combination partner(s)	IGF-targeted agent(s)/intervention	MoA	Indication	Key results	References
MEK inhibitor	Trametinib; PD-0325901	Linsitinib; NVP-AEW541	Dual IGF-1R/INSR TKI; IGF-1R TKI	KRAS-mutant NSCLC	• Combination treatments had synergistic effects in reducing KRAS-mutant cell viability • PI3K stimulation by KRAS was dependent upon IGF-1R kinase activity	[153]
Akt inhibitor	Akti-1/2; MK-2206	NA	NA	Various tumor types	• Akt inhibition induced the expression of HER, IGF-1R and INSR in solid tumor cell lines; this induction was markedly attenuated by FOXO knockdown • Combined inhibition Akt and HER kinases led to in vivo tumor regressions in a breast cancer model	[99]
mTOR inhibitor	Temsirolimus	hR1	Anti-IGF-1R mAb	Renal cell carcinoma	• IGF-1R and mTOR targeting synergistically inhibited tumor growth	[154]
mTOR inhibitor	Rapamycin	Xentuzumab	IGF-1/IGF-2-neutralizing Ab	Ewing sarcoma	• Synergistic effects in inhibiting tumor cell proliferation • Reduction of serum IGF bioactivity in the absence of hyperglycemia	[66]
mTOR inhibitor	Rapamycin; AZD2014	Dusigitumab	IGF-1/IGF-2-neutralizing Ab	Ewing sarcoma; other sarcomas	• Synergistic anti-proliferative effects, particularly in Ewing sarcoma • Preclinical responses were correlated with the level of inhibition of Akt/mTOR signaling	[74]
mTOR inhibitor	Everolimus	NVP-AEW541	IGF-1R TKI	Prostate cancer	• Combination treatment with everolimus and NVP-AEW541 significantly inhibited cell proliferation more than either drug alone	[155]
mTOR inhibitor	Ridaforolimus	Dalotuzumab	Anti-IGF-1R mAb	Breast cancer; NSCLC	• Combined inhibition of mTOR and IGF-1R potentiated anti-tumor activity in breast and lung cancer cells and in a NSCLC xenograft model	[156]
PI3Kβ inhibitor	Ac-KIN-193; TGX-221	NVP-AEW541	IGF-1R TKI	Melanoma	• Addition of NVP-AEW541 enhanced the anti-proliferative effects of PI3Kβ inhibition in $PTEN^{LOF}$/$BRAF^{MUT}$ melanoma cell lines, prevented PI3K/mTOR signaling rebound and blocked tumor growth	[157]
STAT3 inhibitor[b]	NT157	NA	Dual IGF-1R/ALK inhibitor	Melanoma; colorectal cancer	• Co-inhibition of IGF-1R and STAT3 resulted in potent anti-tumor activity	[158, 159]
Other targeted agents						
CDK4/6 inhibitor	PD-0332991	BMS-754807	Dual IGF-1R/INSR TKI	Pancreatic cancer	• Synergistic anti-proliferative effects on pancreatic ductal adenocarcinoma cells in vitro and in vivo • Sensitivity to combination correlated with reduced activity of mTORC1	[160]
CDK4/6 inhibitor	PD-0332991	R-1507; NVP-AEW541	Anti-IGF-1R mAb; IGF-1R TKI	Dedifferentiated liposarcoma	• Combined treatment had synergistic effects in reducing tumor cell viability	[161]
PARP inhibitor	Olaparib	BMS-536924	IGF-1R TKI	Ovarian cancer; breast cancer	• Impairment of homologous recombination provoked by IGF-1R inhibition conferred increased sensitivity to PARP inhibition • Combination decreased cell survival more potently than single agents	[162]
	Metformin	Figitumumab	Anti-IGF-1R mAb	SCLC; NSCLC	• Metformin enhanced the anti-tumor effects of figitumumab	[22, 163]

Table 3 (continued)

Combination treatment modality	Combination partner(s)	IGF-targeted agent(s)/ intervention	MoA	Indication	Key results	References
	Metformin	Figitumumab	Anti-IGF-1R mAb	NSCLC	• Metformin enhanced the anti-tumor effects of figitumumab • High IGF-1R expression was negatively correlated with survival	[22]
ATR kinase inhibitor	VE-821	BMS-754807; Linsitinib	Dual IGF-1R/INSR TKIs	Breast cancer	• IGF-1R TKIs potentiated the effects of ATR kinase inhibition or cisplatin in breast cancer cells	[164]
Endocrine therapies						
Estrogen inhibitor; Aromatase inhibitor	Tamoxifen; letrozole	BMS-754807	Dual IGF-1R/INSR TKI	Breast cancer	• IGF-1R inhibition enhanced anti-tumor activity and overcame resistance to tamoxifen and letrozole	[133]
Androgen inhibition	Castration	Cixutumumab	Anti-IGF-1R mAb	Prostate cancer	• Androgen stimulation induced IGF-1 upregulation in AR+ cells and enhanced proliferation and invasiveness • IGF-1R inhibition enhanced tumor regression and delayed tumor regrowth after castration	[134]
Androgen inhibition	Abiraterone	Figitumumab	Anti-IGF-1R mAb	Prostate cancer	• Co-administration of figitumumab and abiraterone had synergistic anti-proliferative effects in prostate cancer cells expressing the androgen-regulated fusion protein TMPRSS2-ERG	[165]
Immune therapies						
CSF-1R inhibition	BLZ945	Linsitinib; BKM120	Dual IGF-1R/INSR TKI; PI3K inhibitor	GBM	• Combining IGF-1R or PI3K blockade with continuous CSF-1R inhibition significantly improved OS in genetic mouse models; IGF-1R- or PI3K-inhibitor monotherapy was less effective	[166]

[a] Ceritinib is a single-agent treatment that inhibits both ALK and IGF-1R, whereas crizotinib inhibits ALK only; [b] Single-agent treatment that inhibits both STAT3 and IGF-1R

Ab antibody, *Akt* protein kinase-B, *ALK* anaplastic lymphoma kinase, *AR* androgen receptor, *CDK4/6* cyclin-dependent kinase 4/6, *CRC* colorectal cancer, *CRPC* castration-resistant prostate cancer, *CSF-1R* colony stimulating factor 1 receptor, *DSB* double strand break, *EGFR* epidermal growth factor receptor, *ERK* extracellular-signal-regulated kinase, *GBM* glioblastoma multiforme, *HER* human epidermal growth factor receptor, *IGF* insulin-like growth factor, *IGF-1R* insulin-like growth factor receptor 1, *INSR* insulin receptor, *KRAS* Kirsten rat sarcoma viral oncogene homolog, *MAPK* mitogen-activated protein kinase, *mAb* monoclonal antibody, *MEK* mitogen-activated protein kinase/Erk kinase, *miR* microRNA, *MoA* mechanism of action, *mTOR* mammalian target of rapamycin, *mTORC1* mTOR complex 1, *NA* not applicable, *NSCLC* non-small cell lung cancer, *OS* overall survival, *PARP* poly(ADP-ribose) polymerase, *PI3K* phosphatidylinositol 3-kinase, *PTEN* phosphatase and tensin homolog, *PTEN*^LOF/*BRAF*^MUT BRAF-mutated melanoma cell lines with PTEN loss of function, *RTK* receptor tyrosine kinase, *SCLC* small cell lung cancer, *shRNA* short hairpin RNA, *siRNA* small interfering RNA, *TKI* tyrosine kinase inhibitor

4.3.2 PI3K/Akt/mTOR and MAPK Pathway Inhibitors

With regard to downstream effector pathways, reciprocal interactions between Src and IGF-1R signaling have been shown to promote treatment resistance in prostate and lung cancer models; thus, combining IGF-targeted agents with drugs that target Src may be more effective than targeting either signaling component alone [148, 149]. Indeed, there is evidence that co-targeting IGF-1R and Src family kinases by combining anti-IGF-1R mAbs/IGF-1R TKIs with dasatinib resulted in more effective growth inhibition than single-agent treatments in rhabdomyosarcoma cell lines [150].

Extensive preclinical evidence suggests that IGF-1R activation can also mediate acquired resistance to inhibitors of the PI3K/Akt/mTOR and MAPK signaling pathways [22, 66, 74, 99, 151–154, 157, 174], not least because drugs that target individual components of mitogenic signaling pathways can relieve feedback inhibition of other signaling components. For example, Akt inhibition can lead, via activation of FOXO transcription factors, to reciprocal upregulation of IGF-1R, INSR, and other RTKs to reactivate the PI3K/Akt/mTOR pathway. In an equivalent process, inhibition of mTORC1 activates Akt and ERK signaling by blocking S6K-dependent feedback and activating IGF-1R and HER kinases [99]. Thus, combined inhibition of multiple mitogenic signaling pathways that are reciprocally reactivated by feedback relief may show enhanced anti-tumor activity. In one preclinical study, combination of xentuzumab with mTORC1 inhibitor rapamycin significantly enhanced its anti-tumor activity in Ewing sarcoma, and responses were associated with effective neutralization of circulating bioactive IGF-1/IGF-2 and with suppression of Akt activity in tumor tissue [66]. Also in Ewing sarcoma, dusigitumab in combination with rapamycin or mTORC1/2 kinase inhibitor AZD2014 was more effective than single-agent dusigitumab in inhibiting in vivo tumor growth [74]. Several studies support the use of triple therapies that incorporate IGF-targeted agents and mTOR inhibitors with other drugs. For example, this concept is supported by a study of dalotuzumab, the mTORC1 inhibitor ridaforolimus, and letrozole in hormone-sensitive breast cancer, in which the greatest anti-tumor effects were observed when all three drugs were combined [175]. In addition, a recent preclinical study of IGF-1R/mTOR inhibition in Ewing sarcoma identified several potential bypass pathways leading to resistance, including upregulation of IRS1, PI3K, and STAT3; these signaling proteins represent additional targets that could be incorporated into future studies of combined IGF-1R/mTOR inhibitors [176]. Indeed, promising data have been reported using the novel agent NT157, which inhibits both IGF-1R-IRS1/2 and STAT3 signaling in tumor and stromal cells, and has potent anti-tumor effects in preclinical models of melanoma and colorectal cancer [158, 159].

In one preclinical study that aimed to identify potential combination partners for MAPK pathway inhibitors, a large-scale short hairpin RNA screen revealed an adaptive response involving the IGF-1R/PI3Kα network in BRAF-mutated melanoma cell lines with phosphatase and tensin homolog (PTEN) loss of function. Co-inhibition of the MAPK pathway, PI3Kβ, and either PI3Kα or IGF-1R synergistically sustained PI3K signaling blockade, induced apoptosis, and suppressed in vivo tumor growth [157]. Simultaneous inhibition of the PI3K/Akt and MAPK signaling pathways has also demonstrated clinical activity in patients with some human cancers, albeit at the expense of increased toxicity [177, 178]. However, KRAS can directly activate the MEK/ERK and PI3K/Akt signaling pathways, which may underlie the resistance of KRAS mutant cancers to TKIs [151, 179, 180]. Ebi et al. showed that RTKs, particularly IGF-1R, regulated PI3K signaling in KRAS mutant cell lines, suggesting that targeting IGF-1R in combination with MAPK pathway inhibition could be an effective treatment strategy in KRAS mutant cancers [151].

4.3.3 Other Targeted Agents

Disruption of the CDK4/6 axis can contribute to unscheduled proliferation and tumorigenesis in a variety of cancers that show particular genomic features, such as mutations in CDKN2A [181]. For this reason, selective CDK4/6 inhibitors have been developed as potential anti-cancer therapies. In addition, emerging evidence from drug screening studies suggests that IGF- and CDK4/6-targeted agents can have synergistic anti-tumor effects in models of pancreatic cancer and soft tissue sarcoma by co-operatively suppressing Akt signaling [160, 161]. Combined inhibition of IGF-1R and poly(ADP-ribose) polymerase (PARP) may also improve clinical efficacy by interfering with DNA damage repair, specifically in cancers with defective homologous recombination (HR) deficiency, found in approximately 50% of breast and ovarian cancers [162]. Moreover, BMS-754807 has been shown to sensitize MCF7 breast cancer cells to inhibitors of ataxia telangiectasia-mutated and RAD3-related kinase (ATR), both of which mediate DNA damage repair, and to potentiate the effects of cisplatin in some cell lines [164].

Finally, INSR signaling can contribute to tumor proliferation and survival, primarily through the INSR-A isoform [182]. Indeed, insulin-driven proliferative signaling through INSR-A is reported to be a compensatory mechanism after endocrine therapy in breast cancer [183]. Drugs such as the anti-diabetic drug metformin that improve insulin sensitivity and lower insulin levels could counteract these effects; thus, such treatments represent potential combination partners for therapies targeting the IGF axis. In support of this hypothesis, metformin enhanced the anti-tumor effects of figitumumab in SCLC and NSCLC cell lines. As metformin has both hypoglycemic and anti-cancer effects, this treatment may also offset some of the adverse effects observed with anti-IGF-1R

mAbs and IGF-1R TKIs [22, 163]. Clinical data from ongoing trials combining IGF-targeting drugs such as ganitumab with metformin (I-SPY 2 trial; NCT01042379) are eagerly awaited.

4.3.4 Clinical Combination Studies with Targeted Agents

Clinical studies to-date have demonstrated feasibility of several targeted combination approaches, with a focus on inhibitors of EGFR and mTOR. Most studies involving anti-IGF-1R mAbs have identified only known class-effect toxicities and no new relevant side effects [155, 184–187]. However, similar to monotherapy studies, the majority of clinical trials evaluating regimens that incorporate IGF-1R-targeted agents with other targeted therapies have, so far, shown limited clinical benefit. In a phase I trial in patients with advanced solid tumors, treatment with the IGF-1R/INSR TKI linsitinib in combination with erlotinib was well tolerated, with preliminary evidence of clinical activity, particularly in patients with NSCLC. Moreover, durable responses were observed in patients unlikely to respond to erlotinib monotherapy [188]. However, a phase II study of the same combination in patients with NSCLC harboring activating *EGFR* mutations was terminated early due to inferiority in the linsitinib arm, together with increased toxicity that necessitated erlotinib dose reductions and discontinuations [189]. Addition of ganitumab to the EGFR Ab panitumumab failed to improve clinical outcomes in a randomized phase Ib/II trial in patients with CRC [190].

Outcomes have been similarly negative in trials testing combined IGF-1R/mTOR inhibition. There was no evidence of clinical activity in a phase Ib study in patients with metastatic CRC who received linsitinib in combination with the mTORC1 inhibitor everolimus [191]. Treatment with cixutumumab plus temsirolimus, another mTORC1 inhibitor, produced no objective responses in a phase II trial in children and young adults with refractory sarcoma [192], even though, in an earlier phase I study in adult cancer patients, this treatment induced objective responses in two of three patients with Ewing sarcoma and four of 10 patients with adrenocortical carcinoma [186]. In a phase I study in patients with neuroendocrine tumors, cixutumumab was assessed in combination with everolimus plus octreotide, a long-acting somatostatin analog, but was associated with adverse effects, including hyperglycemia, that may limit its long-term tolerance [193]. Recruitment to a phase II trial of dalotuzumab plus ridaforolimus in patients with ER-positive breast cancer was suspended due to a higher than expected rate of stomatitis in the combination arm, although the combination was shown to be tolerable with lower doses of ridaforolimus [194]. In a phase I trial in 87 patients with advanced cancers, the same combination resulted in six confirmed partial responses, including three patients with breast cancer. In total, 10 of 23 patients with breast cancer and six of 11 patients with ER-positive/high-proliferative breast cancer showed evidence of anti-tumor activity, based on objective responses, PFS, and tumor metabolic rates/biomarkers [156].

So far, clinical benefit with targeted combination therapies has been observed in only a minority of cases, which re-emphasizes the importance of better selection of patients who are most likely to benefit from combinatorial IGF-targeted therapy. This process could be aided by future research into the identification of biomarkers for IGF therapy response.

4.4 Combination with Endocrine Therapies

Interactions identified between the IGF axis and endocrine pathways provide a mechanistic rationale for investigating IGF-targeted therapies in combination with hormone therapy in breast and prostate cancers [133, 134, 164, 195–197]. In preclinical breast cancer models, inhibition of IGF-1R signaling with BMS-754807 was shown to overcome resistance to tamoxifen, a partial estrogen agonist, and letrozole, a non-steroidal aromatase inhibitor (AI), in ER-positive MCF-7 cells [133]. In prostate cancer, androgen stimulation induced IGF-1 upregulation in AR-positive cells and enhanced their proliferation and invasiveness [196]. Furthermore, inhibition of IGF-1R potentiated regression of prostate cancer xenografts and delayed recurrence following castration [134]. Of note, different AR splice variants may differentially alter IGF-axis components, as stimulation of full-length AR (AR^{fl}) or AR^{v567es} (a constitutively active variant that skips exons 5, 6, and 7) has been shown to enhance or suppress IGF-1R expression, respectively [198]. In PTEN-mutated prostate cancer, inhibition of PI3Kβ relieved feedback inhibition of IGF-1R and other RTKs, leading to activation of PI3Kα and downstream signaling pathways. Combined inhibition of PI3Kα and PI3Kβ suppressed this feedback relief, but resulted in potent AR activation; therefore, combined inhibition of both PI3K isoforms and AR may be required to maximize tumor regression [174]. In studies performed to better understand the molecular determinants of IGF-1R overexpression in prostate cancer, expression of TMPRSS2-ERG (T2E), an androgen-regulated oncogenic fusion protein, was shown to upregulate IGF-1R mRNA and protein expression, whilst overexpression of truncated ERG increased the sensitivity of prostate cancer cells to the IGF-1R TKI NVP-AEW541 and to anti-IGF-1R mAbs figitumumab and AVE1642 [165, 199]. Furthermore, co-administration of figitumumab and abiraterone, an irreversible inhibitor of cytochrome P450 17A1 that prevents androgen synthesis, resulted in synergistic anti-proliferative activity in T2E-expressing cell lines [165].

Despite the preclinical evidence supporting evaluation of IGF-targeted and endocrine therapy combinations, treatment with ganitumab plus the AI exemestane or ER antagonist fulvestrant did not improve PFS in women with previously

treated hormone receptor-positive breast cancer, and OS was lower in the combination group versus endocrine treatment alone [197, 200]. Furthermore, planned biomarker analyses, including *PI3KCA* mutations, could not identify any patient subgroups that benefited from ganitumab [197]. The IGF-1R TKI KW-2450 has shown modest single-agent clinical activity in phase I, with dose-limiting toxicities of hyperglycemia and rash [62]. However, another phase I study of this agent, in combination with lapatinib and letrozole in *HER2*-positive breast cancer (NCT01199367), was terminated and no results have been made available.

Several current studies are testing IGF ligand-neutralizing Abs with endocrine therapy. Dusigitumab is in phase II development in combination with an AI, for the first-line treatment of metastatic breast cancer (NCT01446159); however, data are not yet available. A phase Ib/II trial is also investigating the safety and efficacy of xentuzumab in combination with exemestane and everolimus in the same setting. At the RP2D (xentuzumab 1000 mg/week plus exemestane 25 mg/day and everolimus 10 mg/day), this triple combination had a manageable safety profile and encouraging preliminary anti-tumor activity, with 62% of patients achieving disease control and 24% of patients achieving a partial response [201].

In a prospective neoadjuvant study in prostate cancer, treatment with cixutumumab in combination with androgen-deprivation therapy (ADT) resulted in significant changes in serum components of the IGF and glucose homeostasis pathways (growth hormone, IGF-1, IGF-2, IGFBP3, and insulin) versus ADT alone, albeit only in overweight or obese patients. This finding further highlights the need for appropriate patient selection in clinical trials of IGF-targeted therapies [195]. For patients with CRPC, clinical practice guidelines recommend the use of chemotherapy and/or targeted agents in addition to continued hormone therapy. These treatments, examples of which include abiraterone and enzalutamide (an AR antagonist) [202, 203], could also be considered as combination partners for IGF-targeted therapies. A phase Ib/II study is currently recruiting patients with metastatic CRPC following progression on docetaxel, to evaluate treatment with xentuzumab in combination with enzalutamide, versus enzalutamide alone (NCT02204072).

4.5 Combination with Immune Therapy

Abs that inhibit immune checkpoints, particularly those directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1, have shown very encouraging efficacy in melanoma and NSCLC [204–209]. However, although immunotherapies are associated with durable tumor control, objective response rates are relatively low. In an attempt to improve response rates, combination regimens that incorporate both targeted agents and immunotherapies are currently undergoing clinical evaluation in a wide range of cancers [210].

Several lines of evidence provide a rationale for combining IGF-signaling inhibitors and immune therapies. The contribution of the IGF axis in regulating immune function was first highlighted in a series of studies reporting that downregulating IGF-1 or IGF-1R enhanced the immunogenicity of GBM models in rats, as well as in a small clinical study in astrocytoma [211–213]. Subsequent studies revealed that IGF-1 alleviates a number of autoimmune conditions, including autoimmune diabetes and contact dermatitis, and that its protective effect appears to be correlated with increased infiltration by regulatory T cells in affected tissues [214–216]. IGF-1 has also been implicated in the expression of immunosuppressive cytokines including interleukin-10 [217, 218], as well as induction of the M2 phenotype of macrophages [219]. In preclinical models of HCC, expression of IGF-1 by M2 macrophages increased hepatoma growth. Furthermore, sorafenib treatment reduced macrophage IGF-1 expression and IGF-1-driven cell proliferation, associated with altered macrophage polarization [220].

A recent study in pancreatic ductal adenocarcinoma suggested a role for IGF signaling in tumor infiltration of tumor-associated macrophages (TAMs). A positive correlation was identified between activated insulin and IGF receptors, which were expressed in tumor biopsies from 72% of patients, and infiltration of TAMs. Furthermore, the data indicated that TAMs and tumor stromal myofibroblasts can directly support chemo-resistance, by secreting IGF-1 and IGF-2 [139]. In addition to these findings, inhibition of IGF-1/IGF-2 with xentuzumab sensitized tumors to gemcitabine in a murine pancreatic cancer model [139]. Activation of IGF-1R signaling through stimulation by TAM-derived IGF-1 has also been shown to mediate acquired resistance to colony stimulating factor 1 receptor (CSF-1R) inhibitors in glioma. Moreover, in genetic mouse models of GBM, combined CSF-1R and IGF-1R inhibition significantly improved survival outcomes [166].

Finally, cell death induced by IGF-1R inhibition may lead to the release of tumor-specific antigens (TSAs) that help to initiate and potentiate immune responses facilitated by immunotherapeutic agents. Compared with circulating B cells, tumor-infiltrating B cells in melanoma patients show increased expression of inflammatory cytokines and growth factors, including IGF-1, which could reduce TSA release within the tumor microenvironment, potentially leading to resistance to immune checkpoint inhibitors such as anti-CTLA-4 and anti-PD-1 mAbs [221].

5 Conclusions and Future Perspectives

Dysregulation of the IGF axis can contribute to many of the hallmarks of cancer and is implicated in the development of resistance to a number of standard-of-care therapies. Thus, the IGF axis is an attractive therapeutic target. Despite this, the lack of a bona fide predictive biomarker for patient enrichment has impeded the clinical development of IGF-targeted therapies. Pre-treatment circulating or tumor IGF levels have been proposed as a potential candidate by several groups [116–123, 125, 169], although such hypotheses will need to be tested and confirmed in randomized, stratified clinical trials. There is clearly meaningful activity and long-term benefit from IGF-targeted monotherapies in patients with Ewing sarcoma and soft-tissue sarcoma [81–83]. In common cancers, the key to success will be to develop mechanistically rational combination therapies, reflecting the role of the IGF axis as an epi-driver and bypass pathway [52, 80, 110].

Given that IGF-neutralizing Abs inhibit signaling through both IGF-1R and INSR-A, without impacting insulin and glucose metabolism [66, 75], combination of these agents with other types of anti-cancer treatment could represent a more clinically effective and tolerable approach compared with combinations that include IGF-1R mAbs or TKIs. Based on preclinical and clinical evidence to date, we suggest that the key priorities for future studies should focus on the following combination approaches/partners for IGF ligand-neutralizing Abs: (1) EGFR family inhibitors, such as afatinib, particularly in the context of resistance to third-generation EGFR TKIs; (2) CDK inhibitors, given that IGF-1R has been identified in screening studies as having a role in mediating resistance to these drugs; (3) endocrine therapy, since sensitivity to IGF-targeted agents has been observed in ER-positive breast cancer models; (4) immune checkpoint inhibitors, based on the roles of IGF ligands in promoting an immunosuppressive environment; and (5) radiotherapy, although no clinical trial has tested this hypothesis yet, despite the supportive preclinical data.

Future clinical research of IGF-targeted therapies may also be improved by incorporating Adaptive Design Clinical Trials, which include prospectively planned opportunities for modification of the study design based on analysis during the study [222]. Coupled with precise measurement of IGF ligands in the circulation, and IGFs and receptors in clinical tumor tissue, this approach could potentially reveal effective combination regimens and help to identify predictive biomarkers for better selection of patients most likely to derive clinical benefit.

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