![cancers logo]

Review

The IGF-II–Insulin Receptor Isoform-A Autocrine Signal in Cancer: *Actionable Perspectives*

Pierluigi Scalia [1,2,*], **Antonio Giordano** [1,3] and **Stephen J. Williams** [1,4]

1   Sbarro Institute for Cancer Research and Molecular Medicine and Center for Biotechnology, Biology Department, Temple University, Philadelphia, PA 19122, USA; giordano@temple.edu (A.G.); sjwilliamspa@comcast.net (S.J.W.)
2   Istituto Somatogene per la Ricerca Onco-Genomica, ISOPROG, 93100 Caltanissetta, Italy
3   Department of Medical Biotechnology, University of Siena, 53100 Siena, Italy
4   Somatolink Foundation, Inc., Philadelphia, PA 19102, USA
*   Correspondence: plscalia@isoprog.org

![check for updates]

Abstract: Insulin receptor overexpression is a common event in human cancer. Its overexpression is associated with a relative increase in the expression of its isoform A (IR^A), a shorter variant lacking 11 aa in the extracellular domain, conferring high affinity for the binding of IGF-II along with added intracellular signaling specificity for this ligand. Since IGF-II is secreted by the vast majority of malignant solid cancers, where it establishes autocrine stimuli, the co-expression of IGF-II and IR^A in cancer provides specific advantages such as apoptosis escape, growth, and proliferation to those cancers bearing such a co-expression pattern. However, little is known about the exact role of this autocrine ligand–receptor system in sustaining cancer malignant features such as angiogenesis, invasion, and metastasis. The recent finding that the overexpression of angiogenic receptor kinase EphB4 along with VEGF-A is tightly dependent on the IGF-II/IR^A autocrine system independently of IGF1R provided new perspectives for all malignant IGF2omas (those aggressive solid cancers secreting IGF-II). The present review provides an updated view of the IGF system in cancer, focusing on the biology of the autocrine IGF-II/IR^A ligand–receptor axis and supporting its underscored role as a malignant-switch checkpoint target.

Keywords: IGF(I/II/1R), Insulin-like Growth factor (1 or 2 or receptor); IR^A/IR-A; insulin receptor isoform A; IGFBP; IGF binding protein; ITN; integrin; M6PR; mannose 6 phosphate receptor; TF; Transferrin; VTN; vitronectin; HIF; hypoxia-inducible factor; VHL; Von Hippel-Landau gene product; OCT; off-context targeting

1. The Insulin–IGF Ligand and Receptor System in Cancer

The family of the insulin and IGF ligands and receptors are known for their central metabolic and growth-related functions spanning throughout phylogenetically distant organisms [1,2]. Up to the late 90s, the working model for the role of insulin, IGFs, and their receptors in cancer was based on a scenario dominated by two cousin receptors (the IGF-IR and the insulin receptor) used by their own ligands (IGF-I for the IGF-I receptor and insulin for the insulin receptor), with the IGF-I receptor being considered the sole active mediator of the IGF-I and IGF-II effects, making the latter a favorite target for halting the actions of IGFs in cancer [3,4]. This paradigm (the IGF1R mandatory transducer hypothesis) has undergone many changes over time with the realization, first, that the IGFIR is able to form hybrid variants with the insulin receptor [5,6] and, second, that the insulin receptor (IR) could mediate IGF-specific effects. Indeed, genetic evidence of the permissive role of the insulin receptor in a number of developmental and body-size effects mediated by IGF-II had been shown in genetic

studies conducted both in null mice [7] and in transgenic mouse models [8]. However, cellular studies were not able to reproduce such a result in vitro until a specific isoform of the insulin receptor, lacking 12 aa in the extracellular portion corresponding to exon 11 (IR$^\mathbf{A}$), was shown to be the high-affinity receptor for IGF-II in both fetal and cancer cells [9]. This finding, besides changing a long-rooted view, also presented a distinct role for the insulin receptor far beyond defining it as a pure metabolic and growth permissive mediator. A number of subsequent studies have also demonstrated insulin and IGF ligand-specific differences in their activation of the IR$^\mathbf{A}$. In particular, such differences have been demonstrated at the gene expression level [10] and at the signaling level [11,12]. In this regard, it is worth noting that IGF-II has been found to be able to bind and transduce signals via both the homo-tetrameric, high-affinity RTKs (IGF1R and IR$^\mathbf{A}$) and via its hetero-tetrameric (IGF1R/IR$^\mathbf{A}$) hybrid receptor in cancer [13]. This amplifies the range of cancer-promoting autocrine signals exerted by IGF-II at the cellular level. The ultimate demonstration of the potential of the autocrine IGF-II/IR$^\mathbf{A}$ axis in cancer came from the recent finding that, when activated by IGF-II, the IR$^\mathbf{A}$ variant is able to acutely and reversibly activate a post-translational, ubiquitin-dependent, and IGF1R-independent degradation rescue signal, causing EphB4 ectopic expression in malignant mesothelioma cell lines [14]. Altogether, these reports fully disprove the old concept of purely redundant biological roles between IGF ligands and RTKs, and point at their contextual co-expression patterns as key indicators of the predominant and/or parallel effects exerted in cancer cells according to the pre-existing permissive or inhibiting signaling network. These contextual ligand–receptor interactions exerted by autocrine IGF-II and the contributions of paracrine IGF signals in cancer are summarized in Figure 1.
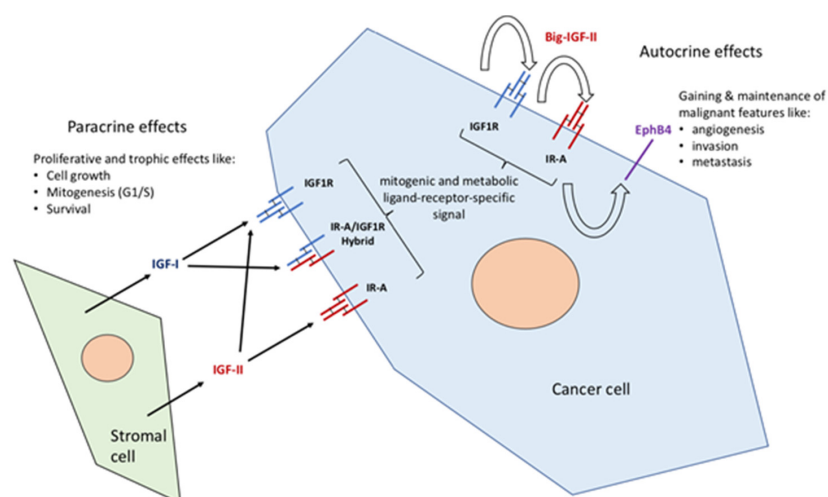

Figure 1. The family of insulin/IGF ligands and receptors in cancer: an updated functional overview. New contextual evidence points at a differential rather than overlapping role of IGFs and their TK receptors. In particular, the role of IGF-II and its cancer-secreted variant (Big-IGF2), as the most commonly expressed IGF ligand in malignant cancer cells, along with the A variant (exon 11) of the insulin receptor (IR$^\mathbf{A}$), an almost ubiquitously expressed variant of the IR in cancer binding IGF-II (and its high molecular form expressed in cancer) with high affinity, has gained additional interest on the basis of its ligand-receptor-specific (and IGF1R-independent) ability to tightly control the protein expression of an angiogenic invasion metastatic factor such as EphB4 [14]. This type of effect fully differentiates the outcome and relevance of the autocrine IGF-II/IR$^\mathbf{A}$ signal towards gaining and/or maintaining malignant features. It also allows new anti-target scenarios within the IGF family to be envisioned and provides a mechanistic explanation for the observed failure of single therapy blockade of the IGF-I receptor in clinical trials.

2. IGF-II is a Bona Fide Oncogenic Ligand Tightly Regulated Under Development and a Commonly Selected Self-Stimulatory Signal in Cancer

In comparison to IGF-I (the main growth-hormone-induced ligand and physiological effect mediator) and as discussed below, IGF-II undergoes different and extensive regulation at the genetic,

epigenetic, and post-transcriptional levels. Interestingly, the escape from such tight regulation, as observed in cancer, offers IGF-II distinctive advantages over IGF-I, mainly linked to its ability to activate specific developmental, cellular, and cancer-promoting signals via Insulin receptor A. Overall, IGF-II (a) has a wider possibility of transcriptional regulation and control at the gene promoter level via its four promoters and 10 exons [15,16], all of which produce a pre-pro-hormone and four isoform variants; (b) is epigenetically regulated via DNA-methylation-dependent and -methylation-independent mechanisms [17–23] with a paternal-restricted expression pattern which is typically lost in cancer (loss of imprinting), causing increased/biallelic expression and bloodstream secretion levels [24–30]; (c) displays post-translational variants derived via differential processing of its pre-pro-hormone leading, to an O-glycosylated high molecular weight form (also known as Big-IGF2) [31,32] retaining its binding and signaling activity for IR^A [33] but with acquired capability to elude physiological binders such as the high-affinity scavenging receptor also known as igf2R (binding mannose 6-phosphate as well) and IGFBP3 [34]. This and the potential clinical implications have also been reviewed in References [35,36]. Finally, (d) additional types of regulation of the igf2 transcript linked to non-coding RNA products have also been demonstrated, adding a layer of additional regulation for the igf2 gene [37–43]. The escape from any of these regulatory mechanisms make IGF-II and, more so, its cancer-secreted variant (Big)IGF-II, an ideal autocrine signal for highly demanding cellular requirements such as those found throughout the tumorigenic process [33,34,44]. No less important, (e) IGF-II binds to the IGF1R, the Insulin receptor isoform A, and their hybrid tetra-dimeric forms under different physiological and pathological contexts to exert ligand-receptor-specific cellular effects [7,9,14,45]. The contextual roles mentioned above for IGF-I and IGF-II ligands in cancer are graphically summarized in Figure 2.
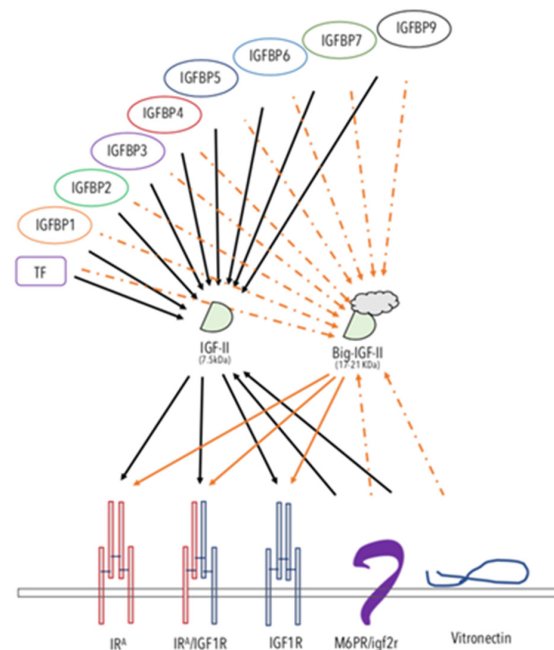
Figure 2. The IGF-II-binding/-neutralizing and -transducing system. The schematic figure summarizes the interactions reported in the literature for IGF-II. The known soluble, extracellular and/or membrane-bound IGF-II-binding proteins are displayed. The solid arrows represent experimentally supported interactions. The dashed arrows represent interactions that have been shown to either be impaired or not yet experimentally confirmed. Arrows from a ligand to its RTKs indicate activating–transducing properties. Arrows towards IGF-II indicate a binding–neutralizing effect. The overview of the comprehensive IGF ligands system role in cancer is shown in Figure 2.

3. The IGF-II Binders: A Fine-Tuned System for the Control of IGF-II Levels in the Extracellular and Tumor Microenvironment

Igf2R/m6pR. The non-transducing/scavenger high-affinity-binding membrane-bound protein known as igf2 receptor (reviewed in Reference [46]), initially thought to be an IGF-II biological mediator, exerts, indeed, most of its IGF-related effects by neutralizing IGF-II and subtracting it from other transducing interactions (namely from the IR[A] and the IGF1R receptor tyrosine kinases). The key evidence for such a view comes from the demonstration of the absence of a TK domain in its cloned structure [47] and from the oncogenic effect shown by null mutation of igf2rR/m6pR in mice [48]. Indeed, the tumor-suppressing effect of the igf2R/m6pR can be interpreted as further demonstration of the oncogenic potential of IGF-II when present in high levels in vertebrates either at focal tissue levels and/or in the whole organism bloodstream.

The IGFBPs 1-7 and 9. Insulin-like growth factor-II has been shown to bind to most of the soluble extracellular proteins of the IGFBP family, as reviewed elsewhere [49–51]. The cumulative effect of IGF-II binding proteins towards the IGF-II levels in the bloodstream might mitigate its increased exposure to local tissues. As a result, some authors have to proposed the use of recombinant fragments of IGFBPs as tools to counteract IGF-II oncogenicity. However, the fact that cancer-secreted IGF-II has been found to interact poorly with IGFBPs [34,52,53] might be seen as an escape mechanism for all those cancers using IGF-II as an autocrine growth factor to sustain/maintain their malignant growth features. These potential limits should be taken into consideration.

Transferrin (TF). TF has been shown to be a constitutive component of the 150kDa trimeric IGF binding protein complex found in the bloodstream [51]. Its binding to IGFs (I and II) is less strong than other IGF–IGFBP interactions (where the highest affinity is shown with IGFBP3), and its physiological role is still to be determined.

Vitronectin (VTN). VTN is a constitutive component of the extracellular matrix, involved in cell-to-cell interactions [54,55]. VTN has been known to bind integrin (ITN) alpha5beta3 and, as such, has been also referred as to integrin receptor [56]. Interestingly, VTN, which bears a somatomedin-like domain, binds IGF-II with high affinity [57,58]. Although the physiological and pathological roles of VTN interaction with IGF-II are still to be determined, some evidence points at a suppressing role of VTN on IGF-II-induced proliferation and migration via interference with the IGF-II mitogenic signaling (Scalia et al., manuscript in preparation).

Overall, the studies on IGF-II physiological binders are in agreement with the genetic studies supporting a distinctive cancer-promoting role for this IGF, differentiating it from its related cousin, IGF-1. The finding that cancer-secreted IGF-II (big-IGF-II) skips the binding control exerted on mature IGF-II by the IGFBPs (as graphically summarized in Figure 2) suggests that more specific targeting strategies should be considered in order to target this factor in its cancer-specific context.

4. Autocrine IGFII and the IR[A] Isoform Co-Expression in Cancer: At the Root of IGF-I Receptor Block Resistance

A number of historical results obtained in igf1r null murine fibroblasts (r-cells) both in absence or presence (r+) of human IGFIR expression abundantly demonstrated the isolated mitogenic and growth-linked effects of the IGF-I receptor as a key permissive signal for most of the non-IGF RTKs already targeted in therapy [59,60]. This triggered the development of a number of IGF-IR specific MAbs [61–64] and small molecules [65,66]) by the pharma industry in the first decade of the new millennium [67]. Although the experimental evidence showing a functional role for the IGF-II/IR[A] both in embryonal fibroblasts and in cancer has been available since the late 90a, these findings did not seem to affect the rush of drug developers to bring IGF-IR specific blockers to clinical trials. The specific single blocking of IGFIR in phase II clinical studies failed [68,69]; the extent of the negative impact of anti-IGF1R monotherapy drugs in clinical studies because of the underscoring of the IGF-II/IR[A] role could have been easily avoided by including IGF-II/IR[A] testing in the associated companion diagnostics required for the selection of responsive patients [70]. Interestingly, in 2006, a human anti-IGF-II MAb

with pan-IGF-II blocking capabilities (neutralizing both the mature and high molecular weight IGF-II variant) was developed [71] as an alternative blocking strategy to IGFIR [72], clearly underestimating the advantages and the differential biological roles of the two therapeutic approaches. Unfortunately, the IGFIR blockers results have delayed the opportunity to test the effectiveness of molecular anti-IGF system targets based upon existing and new evidence revisiting the "IGF1R mandatory transducer hypothesis". This trend should be reversed based on the cumulative validated biological knowledge of this system (with regards to the IGF-II/IR[A] axis role), which is supported by mechanistic explanation and scientific strength, ultimately disclosing the biological differences among IGF ligands and their TK receptors (IR[A], IGF1R, and their hybrid variants) in mediating specific and contextual cancer-actionable effects that are now exploitable in the genomic-driven age [9,11,13].

5. The Autocrine IGF-II/IR[A] System and the Malignant Switch in Solid Tumors: Hints from the Hypoxic Network

Hypoxia is an intrinsic feature of solid cancers' tridimensional growth, affecting the inner core of the growing tumor tissue at the pre-vascular stage and clearly affecting the extracellular tumoral microenvironment. Under these circumstances, a tight sequential relationship is established between hypoxia and the expression of hypoxia-induced genes, in which HIF isoforms and VHL have been shown to play a major role [73,74]. Among the factors that have been shown to be induced or upregulated under hypoxic conditions are VEGF, EphB4, and IGF-II [75–83]. However, if for VEGF and EphB4 a solid base of supporting evidence has established their role in angiogenesis and cancer blood vessel formation, in the case of IGF-II, its angiogenic role in the literature has been variably and interchangeably associated with the angiogenic role of IGF-I. Indeed, as mentioned before, there is evidence supporting the notion that IGF-I and IGF-II are all but interchangeable molecules under both physiological and pathological conditions, as shown by their differential affinity and signaling properties via the known IGF1R/IR RTKs. All these structural and ligand–receptor interaction differences provide plenty of biological opportunity for their diversified use by the cell under hypoxic conditions (typical of early-stage and overtly malignant cancers). As for the association of IGF-II with the hypoxic tumor microenvironment, what we know from the published literature is that (1) IGF-II, but not IGF-I, is responsible for the hypoglycemic paraneoplastic effects observed in a number of patients affected by aggressive solid cancers (IGF2omas) [35,36]; (2) that IGF-II (as well as VEGF-A and EphB4) can be upregulated by HIF and hypoxia [83–85]; (3) that VEGF, which also exerts autocrine signals [86], can be upregulated via the IGF-IR and the IR[A] [87–89] and is under the control of IGF-II and its autocrine loop under hypoxic experimental conditions [14,84,90]. Interestingly, (4) Hypoxia-induced HIF2alpha can regulate IGF-II [91] and (5) IGF-II can upregulate HIF1alpha, which is an inducer of VEGF [14,90]. All these functional links observed in solid cancers can determine a number of coordinated local events towards the acquisition and/or maintenance of angiogenic, invasive, and metastatic potential, and are compatible with an underscored role of IGF-II in the angiogenic switch, supporting its validation as an anti-angiogenic target. It is worth noting the effects that autocrine IGF-II exerts exclusively via the IR[A] independently of the IGF1R, such as in regards to EphB4 acute protein level regulation in certain cancers such as malignant mesothelioma [14], making the IGF-II/IR[A] signal in these cancers a distinctive, non-redundant ligand–receptor loop with targetable value. This has been observed in vitro and ex vivo using cancer cells exposed to their conditioned media (pH ~6.9–7.2), a feature common to the extracellular conditions found in solid cancer microenvironments in vivo.

6. Learning from the IGF System Targeting in Cancer: Not All Ligand–Receptor Interactions are Created Equal (Context is "All You Need")

As in a chess game, any winning move or strategy comes from failure. In the case of the realization of the importance of the IGF system in cancer, the biological relevance of some of its family components, namely the IGF1R as the supposed sole mediator of the IGF-I and IGF-II effects, came early in the drug industry game, although experimental data related to atypical variants [92,93] and hybrid

receptors with its related cousin, the insulin receptor (IR) [94–96], were already known. Indeed, the overexpression of the IR in cancer, first reported in breast tumors and related cell lines [97,98], has not been interpreted as relevant by the supporters of the "IGF1R mandatory-transducer" hypothesis, based on the assumption that the IR serves solely as a purely metabolic transducer, of which overexpression in cancer cells merely provides metabolic advantages over normal tissues with regards to nutrient consumption [12]. This scenario, reproducible but incomplete, began to be revealed as a fallacy when the short isoform of the IR (not expressing its exon 11 on the extracellular domain) was shown to be an onco-fetal high-IGF-II-affinity receptor. In this context, the failure of the clinical trials (and the many compounds which have not passed the preclinical stage) for all those drugs directed against the IGF1R (reviewed in Table 1A,B) did not come as a surprise, in contrast to the main supporters of its direct targeting [68]. Even the strategy of a double block of the IGF1R and the IR would have the same limits (and counter-effects) as shown by the clinical trials of linsitinib [99–103], a small molecule inhibiting both RTK receptors. This led to a recent approach conveyed in the development of xentuzumab and disigitumab (double anti-IGF1/IGF2 MAbs), targeting the known IGF ligands rather than their RTKs [104–106], currently in phase I testing. Although this approach (that of targeting the IGF ligands rather than their RTKs) may gain more leverage in phase II trials, the risk at phase III remains, since the growth-related, trophic, and protective effects of IGF-I on muscle tissue, bone, and other organs' cellular components (such as the physiological stem cell compartments) may induce systemic effects opposite to those intended (especially in pediatric patients). These observed and potential off-target effects linked to the targeting of the individual as well as combined IGF family components can be explained in terms of "off-context targeting" ("OCT" effect), since each of these ligands and receptors plays a central role in physiological growth and metabolism from the embryonal stage to adulthood. An exploitable alternative to the approaches reviewed herein is the targeting of their known cancer variants in their pathological context. This could include, for example, the targeting of a context-selected IGF/RTK complex with agents discriminating their individual physiological components from their pathological variants. Specifically, the view supported by our groups and others [9,14,45,107,108] that the autocrine IGF-II/IR^A ligand–receptor complex in cancer bears the required biological relevance and contextual pathological value would justify such a therapeutic strategy. Contextual conditions that would benefit by this ligand–receptor targeting are further discussed below.

Table 1. (**A**) IGF system targeting drugs tested in clinical trials. (**B**) IGF System targeting drugs and target strategies in preclinical development.

IGF Targeting Drug Type/Name	Malignancy	Clinical Phase Achieved	Refs.
(A)			
Small Molecules			
IGF1R specific TK inhibitor(s)			
BMS-754807	Solid tumors	I	[109]
	hormone resist. breast cancer	II	[110]
KW-2450	advanced solid	I	[111,112]
IGF1R/IR dual TK inhibitor			
Linsitinib (OSI-906)	Solid tumors	I	[99–101]
	Adrenal Carc.	III	[101,102]
	colorectal	I	[100,103]
Immunological approaches for present (NK-mediated) and foreseeable (T-Cell-mediated) targeting of the IGF-system			
First generation target Rx (single IGF targeting Mabs proposed as monotherapy):			
MAbs anti-IGF1R			
Dalotuzumab (MK-0646)	Solid tumors	I	[113,114]
	Neuroendocrine	I	[115]
	Colorectal	I	[116]
	SCLC	I	[117]
	NSCLC	I/II	
Figitumumab (CP-751871)	Sarcoma	I	[118]
	Solid tumors	I	[119]
	Adren. Carc.	I	[120]
	Ewing	I/II	[118]
	Prostate	II	[121,122]
	Colorectal	II	[123]
	NSCLC [a]	I/II/III	[124–126]
	Mult. myeloma	I	[127]

Table 1. *Cont.*

Ganitumab (AMG-479)	Solid tumor	II	[128,129]
	Pancreatic	I, II, III	[130–132]
	Ewing	II	[133]
	breast	II	[134]
	colorectal	II	[135]
Cixutumumab (IMC-A12)	hepatic	I/II	[136]
	pancreas	I	[137]
	thymus	II	[138]
Robatumumab (MK-7454)	sarcoma	II	[139]
	colorectal	II	[140]
Istiratumab (MM-141)	pancreatic	II	[141,142]
R1507	solid tumor	I	[143]
Second generation target Rx (multiple RTKs or ligands targeting MAbs)			
MAbs co-targeting of IGF1-IGF2 ligands			
Xentuzumab(BI-836845)	NSCLC	I	[104]
Dusigitumab (MEDI-573)	solid tumors	I	[105,106]

Table 1. *Cont.*

(B)				
Small Molecules				
IGF targeting Drug Type/Name	**Tumor Models Tested**	**Preclinical Assessment**	**Clinical?**	**Refs.**
IGF1R specific TK inhibitor(s)				
NVP-AEW541	Multiple myeloma Musculoskeletal, Ewings fibrosarcoma	In vitro In vitro, xenografts In vitro, xenografts	No	[144] [145] [146]
Tyrphostin AG-1024	breast cancer cells osteosarcoma cell lines pancreatic cancer cell lines	In vitro In vitro	No	[147] [148] [149]
BMS-536924	ovarian cancer cell lines	Increases radiosensistivity		[150]
IGF1R/IR dual TK inhibitor				
AZ12253801	NSCLC Colon adenoma	In vitro cytotoxicity, soft agar APC min +/− mouse model	No	[151] [152]
LL28	Lung cancer	In vitro cytotoxicity, xenograft, KRAS lung murine model	No	[153]
Immunological approaches for present (NK-mediated) and foreseeable (T-Cell-mediated) targeting of the IGF-system				
Second generation target Rx (multiple RTKs or ligands targeting MAbs)				
MAbs co-targeting of IGF1-IGF2 ligands				
m67 {bispecific scFv combining m610.27+m708.5}cc		Pharmacokinetic study in macaques		[154]
M708.5 {bispecific scFV to IGF-I/IGF-II}	Various tumor cell lines Neuroblastoma	In vitro anti-tumor activity In-vivo xenograft antitumor		[155] [156]

7. Targeting the Autocrine IGFII/IR^A Loop in Cancer: A Further Treatment Co-Target for Current Checkpoint Therapies?

It has become increasingly evident how tumor-microenvironment-linked autocrine ligand–receptorial systems can play a distinctive biological role in escaping the effects of targeted monotherapies [157–160]. For example, VEGF-A and ADAM9 have been linked to resistance to dabrafenib as a result of downregulation of miR-126-3p [161]. This type of resistance could share autocrine IGF-II/IR^A block sensitivity, these factors being actual (VEGF-A) or potential (ADAM-9) autocrine IGF-II-signaling-regulated targets. In other cases, IGF-II has been found to be directly responsible for the acquired resistance to targeted drugs [162]. Other studies have highlighted the relationship between RTKs and resistance to immune checkpoint inhibitors [163,164]. Even though the concept that an increase in RTK ligands acting in a paracrine or autocrine manner is responsible for native and/or acquired drug resistance in not new [165], no study so far has directly addressed the role of autocrine IGF-II through its RTKs (IR^A and IGFIR) under these circumstances. Altogether, the evidence that IGF-II is also used by cancer stem cells, besides being commonly expressed in solid cancers [166–169], supported by the findings already obtained using genetic, molecular, and cellular approaches, suggests further new hypotheses. In particular, the observation that the presence of autocrine IGF-II loops is associated with overtly malignant cancer cell lines [14,45,94,170–173] and that IGF-II over-expression overlaps with those cancer types currently poorly responsive to immune checkpoint therapy (such as malignant mesothelioma [174–176], glioblastoma [177,178], and pancreatic carcinoma [179,180]) along with certain BRAF-inhibitor-treated recurring cancers [181,182] suggest that the autocrine IGF-II/IR^A axis role under these circumstances should be investigated and its targeting potential experimentally vetted. Importantly, a sufficient amount of scientific evidence differentiating the biological and contextual pathological roles of the two IGF-II receptor tyrosine kinase signal transducers, namely the IGFIR and the IR^A, has been produced to clear out the doubts and unmet past expectations linked to the failed strategy of IGFIR blocking [68,69]. In summary, the autocrine IGF-II/IR^A ligand–receptor axis plays a key role in mediating IGF cancer-promoting effects, which have only recently begun to be revealed in terms of their distinctive and IGF-IR-independent signaling patterns. Specific preclinical studies are needed to address the full potential of this self-stimulatory axis and its specific molecular regulatory network in current precision oncology strategies. In particular, regarding the autocrine circuits, the receptorial machinery, and the signaling network active under hypoxic conditions, and potentially conditioning the benign vs malignant phenotypic switch, it is worth noting the recent demonstration of the receptor-specific effect that the IGF-II autocrine loop exerts via the IR^A in regards to the acute protein level regulation of the angiogenic kinase EphB4 [14]. This was observed in vitro using cancer-cell-conditioned media (pH ~6.9–7.2), this hypoxia with low pH being a common feature to the extracellular conditions found in solid cancer microenvironments in vivo.

8. Conclusions and Future Perspectives

Cumulative evidence on the autocrine IGF-II biology, further strengthened by our recent findings on the role of the IGF-II/IR^A signal [14], support a growing targetable value of this cancer-secreted ligand in order to block or revert its effects during malignant progression in a variety of solid cancers. In summary, the autocrine IGF-II/IR^A ligand–receptor axis plays a key role in mediating IGF cancer-promoting effects, which have only recently begun to be revealed in terms of their distinctive and IGF1R-independent signaling patterns. Selective targeting strategies and new translational studies aiming to pinpoint patient response and validate the therapeutic value of cancer-secreted IGF-II and its non-overlapping RTK effects (such the IGF-II/IR^A-dependent expression of EphB4 in malignant mesothelioma [14]) will prove essential in positioning the block of this established cancer-driving axis among the already validated precision oncology therapeutic agents. Specific preclinical studies are needed to weigh the full potential of this self-stimulatory axis and its specific molecular regulatory network in current personalized strategies.

References

1. LeRoith, D.; Kavsan, V.M.; Koval, A.P.; Roberts, C.T., Jr. Phylogeny of the insulin-like growth factors (IGFs) and receptors: A molecular approach. *Mol. Reprod. Dev.* **1993**, *35*, 332–336. [CrossRef]

2. Chan, S.J.; Steiner, D.F. Insulin Through the Ages: Phylogeny of a Growth Promoting and Metabolic Regulatory Hormone. *Integr. Comp. Biol.* **2000**, *40*, 213–222. [CrossRef]

3. Avnet, S.; Sciacca, L.; Salerno, M.; Gancitano, G.; Cassarino, M.F.; Longhi, A.; Zakikhani, M.; Carboni, J.M.; Gottardis, M.; Giunti, A.; et al. Insulin receptor isoform A and insulin-like growth factor II as additional treatment targets in human osteosarcoma. *Cancer Res.* **2009**, *69*, 2443–2452. [CrossRef]

4. Ulanet, D.B.; Ludwig, D.L.; Kahn, C.R.; Hanahan, D. Insulin receptor functionally enhances multistage tumor progression and conveys intrinsic resistance to IGF-1R targeted therapy. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 10791–10798. [CrossRef]

5. Benyoucef, S.; Surinya, K.H.; Hadaschik, D.; Siddle, K. Characterization of insulin/IGF hybrid receptors: Contributions of the insulin receptor L2 and Fn1 domains and the alternatively spliced exon 11 sequence to ligand binding and receptor activation. *Biochem. J.* **2007**, *403*, 603–613. [CrossRef]

6. Blanquart, C.; Achi, J.; Issad, T. Characterization of IRA/IRB hybrid insulin receptors using bioluminescence resonance energy transfer. *Biochem. Pharmacol.* **2008**, *76*, 873–883. [CrossRef]

7. Louvi, A.; Accili, D.; Efstratiadis, A. Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. *Dev. Biol.* **1997**, *189*, 33–48. [CrossRef]

8. Nakae, J.; Kido, Y.; Accili, D. Distinct and overlapping functions of insulin and IGF-I receptors. *Endocr. Rev.* **2001**, *22*, 818–835. [CrossRef]

9. Frasca, F.; Pandini, G.; Scalia, P.; Sciacca, L.; Mineo, R.; Costantino, A.; Goldfine, I.D.; Belfiore, A.; Vigneri, R. Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. *Mol. Cell. Biol.* **1999**, *19*, 3278–3288. [CrossRef]

10. Pandini, G.; Conte, E.; Medico, E.; Sciacca, L.; Vigneri, R.; Belfiore, A. IGF-II binding to insulin receptor isoform A induces a partially different gene expression profile from insulin binding. *Ann. N. Y. Acad. Sci.* **2004**, *1028*, 450–456. [CrossRef]

11. Sacco, A.; Morcavallo, A.; Pandini, G.; Vigneri, R.; Belfiore, A. Differential signaling activation by insulin and insulin-like growth factors I and II upon binding to insulin receptor isoform A. *Endocrinology* **2009**, *150*, 3594–3602. [CrossRef] [PubMed]

12. Vella, V.; Nicolosi, M.L.; Giuliano, M.; Morrione, A.; Malaguarnera, R.; Belfiore, A. Insulin Receptor Isoform A Modulates Metabolic Reprogramming of Breast Cancer Cells in Response to IGF2 and Insulin Stimulation. *Cells* **2019**, *8*, 1017. [CrossRef] [PubMed]

13. Belfiore, A.; Malaguarnera, R.; Vella, V.; Lawrence, M.C.; Sciacca, L.; Frasca, F.; Morrione, A.; Vigneri, R. Insulin Receptor Isoforms in Physiology and Disease: An Updated View. *Endocr. Rev.* **2017**, *38*, 379–431. [CrossRef]

14. Scalia, P.; Pandini, G.; Carnevale, V.; Giordano, A.; Williams, S.J. Identification of a novel EphB4 phosphodegron regulated by the autocrine IGFII/IR(A) axis in malignant mesothelioma. *Oncogene* **2019**, *38*, 5987–6001. [CrossRef]

15. Mineo, R.; Fichera, E.; Liang, S.J.; Fujita-Yamaguchi, Y. Promoter usage for insulin-like growth factor-II in cancerous and benign human breast, prostate, and bladder tissues, and confirmation of a 10th exon. *Biochem. Biophys. Res. Commun.* **2000**, *268*, 886–892. [CrossRef]

16. Brouwer-Visser, J.; Huang, G.S. IGF2 signaling and regulation in cancer. *Cytokine Growth Factor Rev.* **2015**, *26*, 371–377. [CrossRef]

17. Frost, J.M.; Monk, D.; Stojilkovic-Mikic, T.; Woodfine, K.; Chitty, L.S.; Murrell, A.; Stanier, P.; Moore, G.E. Evaluation of allelic expression of imprinted genes in adult human blood. *PLoS ONE* **2010**, *5*, e13556. [CrossRef]

18. Reik, W.; Constancia, M.; Dean, W.; Davies, K.; Bowden, L.; Murrell, A.; Feil, R.; Walter, J.; Kelsey, G. Igf2 imprinting in development and disease. *Int. J. Dev. Biol.* **2000**, *44*, 145–150.

19. Zheng, Q.F.; Xu, B.; Wang, H.M.; Ding, L.H.; Liu, J.Y.; Zhu, L.Y.; Qiu, H.; Zhang, L.; Ni, G.Y.; Ye, J.; et al. Epigenetic alterations contribute to promoter activity of imprinting gene IGF2. *Biochim. Biophys. Acta Gene Regul. Mech.* **2018**, *1861*, 117–124. [CrossRef]

20. Hu, J.F.; Oruganti, H.; Vu, T.H.; Hoffman, A.R. The role of histone acetylation in the allelic expression of the imprinted human insulin-like growth factor II gene. *Biochem. Biophys. Res. Commun.* **1998**, *251*, 403–408. [CrossRef]

21. Li, T.; Chen, H.; Li, W.; Cui, J.; Wang, G.; Hu, X.; Hoffman, A.R.; Hu, J. Promoter histone H3K27 methylation in the control of IGF2 imprinting in human tumor cell lines. *Hum. Mol. Genet.* **2014**, *23*, 117–128. [CrossRef]

22. Ishizaki, T.; Yoshie, M.; Yaginuma, Y.; Tanaka, T.; Ogawa, K. Loss of Igf2 imprinting in monoclonal mouse hepatic tumor cells is not associated with abnormal methylation patterns for the H19, Igf2, and Kvlqt1 differentially methylated regions. *J. Biol. Chem.* **2003**, *278*, 6222–6228. [CrossRef]

23. Wolffe, A.P. Transcriptional control: Imprinting insulation. *Curr. Biol.* **2000**, *10*, R463–R465. [CrossRef]

24. Cui, H. Loss of imprinting of IGF2 as an epigenetic marker for the risk of human cancer. *Dis. Markers* **2007**, *23*, 105–112. [CrossRef]

25. Christofori, G.; Naik, P.; Hanahan, D. Deregulation of both imprinted and expressed alleles of the insulin-like growth factor 2 gene during beta-cell tumorigenesis. *Nat. Genet.* **1995**, *10*, 196–201. [CrossRef]

26. Uchida, K.; Kondo, M.; Takeda, S.; Osada, H.; Takahashi, T.; Nakao, A. Altered transcriptional regulation of the insulin-like growth factor 2 gene in human hepatocellular carcinoma. *Mol. Carcinog.* **1997**, *18*, 193–198. [CrossRef]

27. Nakagawa, H.; Chadwick, R.B.; Peltomaki, P.; Plass, C.; Nakamura, Y.; de La Chapelle, A. Loss of imprinting of the insulin-like growth factor II gene occurs by biallelic methylation in a core region of H19-associated CTCF-binding sites in colorectal cancer. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 591–596. [CrossRef]

28. Cui, H.; Cruz-Correa, M.; Giardiello, F.M.; Hutcheon, D.F.; Kafonek, D.R.; Brandenburg, S.; Wu, Y.; He, X.; Powe, N.R.; Feinberg, A.P. Loss of IGF2 imprinting: A potential marker of colorectal cancer risk. *Science* **2003**, *299*, 1753–1755. [CrossRef]

29. Kaneda, A.; Feinberg, A.P. Loss of imprinting of IGF2: A common epigenetic modifier of intestinal tumor risk. *Cancer Res.* **2005**, *65*, 11236–11240. [CrossRef]

30. Kaneda, A.; Wang, C.J.; Cheong, R.; Timp, W.; Onyango, P.; Wen, B.; Iacobuzio-Donahue, C.A.; Ohlsson, R.; Andraos, R.; Pearson, M.A.; et al. Enhanced sensitivity to IGF-II signaling links loss of imprinting of IGF2 to increased cell proliferation and tumor risk. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20926–20931. [CrossRef]

31. Gowan, L.K.; Hampton, B.; Hill, D.J.; Schlueter, R.J.; Perdue, J.F. Purification and characterization of a unique high molecular weight form of insulin-like growth factor II. *Endocrinology* **1987**, *121*, 449–458. [CrossRef]

32. Daughaday, W.H.; Trivedi, B.; Baxter, R.C. Abnormal serum IGF-II transport in non-islet cell tumor hypoglycemia results from abnormalities of both IGF binding protein-3 and acid labile subunit and leads to elevation of serum free IGF-II. *Endocrine* **1995**, *3*, 425–428. [CrossRef]

33. Marks, A.G.; Carroll, J.M.; Purnell, J.Q.; Roberts, C.T., Jr. Plasma distribution and signaling activities of IGF-II precursors. *Endocrinology* **2011**, *152*, 922–930. [CrossRef]

34. Greenall, S.A.; Bentley, J.D.; Pearce, L.A.; Scoble, J.A.; Sparrow, L.G.; Bartone, N.A.; Xiao, X.; Baxter, R.C.; Cosgrove, L.J.; Adams, T.E. Biochemical characterization of individual human glycosylated pro-insulin-like growth factor (IGF)-II and big-IGF-II isoforms associated with cancer. *J. Biol. Chem.* **2013**, *288*, 59–68. [CrossRef]

35. Dynkevich, Y.; Rother, K.I.; Whitford, I.; Qureshi, S.; Galiveeti, S.; Szulc, A.L.; Danoff, A.; Breen, T.L.; Kaviani, N.; Shanik, M.H.; et al. Tumors, IGF-2, and hypoglycemia: Insights from the clinic, the laboratory, and the historical archive. *Endocr. Rev.* **2013**, *34*, 798–826. [CrossRef]

36. Livingstone, C. IGF2 and cancer. *Endocr. Relat. Cancer* **2013**, *20*, R321–R339. [CrossRef]

37. Polesskaya, A.; Cuvellier, S.; Naguibneva, I.; Duquet, A.; Moss, E.G.; Harel-Bellan, A. Lin-28 binds IGF-2 mRNA and participates in skeletal myogenesis by increasing translation efficiency. *Genes Dev.* **2007**, *21*, 1125–1138. [CrossRef]

38. Dai, N.; Rapley, J.; Angel, M.; Yanik, M.F.; Blower, M.D.; Avruch, J. mTOR phosphorylates IMP2 to promote IGF2 mRNA translation by internal ribosomal entry. *Genes Dev.* **2011**, *25*, 1159–1172. [CrossRef]

39. Dai, N.; Christiansen, J.; Nielsen, F.C.; Avruch, J. mTOR complex 2 phosphorylates IMP1 cotranslationally to promote IGF2 production and the proliferation of mouse embryonic fibroblasts. *Genes Dev.* **2013**, *27*, 301–312. [CrossRef]

40. Gao, W.; Gu, Y.; Li, Z.; Cai, H.; Peng, Q.; Tu, M.; Kondo, Y.; Shinjo, K.; Zhu, Y.; Zhang, J.; et al. miR-615-5p is epigenetically inactivated and functions as a tumor suppressor in pancreatic ductal adenocarcinoma. *Oncogene* **2015**, *34*, 1629–1640. [CrossRef]

41. Dai, N.; Ji, F.; Wright, J.; Minichiello, L.; Sadreyev, R.; Avruch, J. IGF2 mRNA binding protein-2 is a tumor promoter that drives cancer proliferation through its client mRNAs IGF2 and HMGA1. *Elife* **2017**, *6*, e27155. [CrossRef] [PubMed]

42. Balzeau, J.; Menezes, M.R.; Cao, S.; Hagan, J.P. The LIN28/let-7 Pathway in Cancer. *Front Genet* **2017**, *8*, 31. [CrossRef] [PubMed]

43. Gailhouste, L.; Liew, L.C.; Yasukawa, K.; Hatada, I.; Tanaka, Y.; Kato, T.; Nakagama, H.; Ochiya, T. MEG3-derived miR-493-5p overcomes the oncogenic feature of IGF2-miR-483 loss of imprinting in hepatic cancer cells. *Cell Death Dis.* **2019**, *10*, 553. [CrossRef] [PubMed]

44. Gallagher, E.J.; LeRoith, D. The proliferating role of insulin and insulin-like growth factors in cancer. *Trends Endocrinol. Metab.* **2010**, *21*, 610–618. [CrossRef] [PubMed]

45. Sciacca, L.; Costantino, A.; Pandini, G.; Mineo, R.; Frasca, F.; Scalia, P.; Sbraccia, P.; Goldfine, I.D.; Vigneri, R.; Belfiore, A. Insulin receptor activation by IGF-II in breast cancers: Evidence for a new autocrine/paracrine mechanism. *Oncogene* **1999**, *18*, 2471–2479. [CrossRef]

46. Martin-Kleiner, I.; Gall Troselj, K. Mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) in carcinogenesis. *Cancer Lett.* **2010**, *289*, 11–22. [CrossRef]

47. Oshima, A.; Nolan, C.M.; Kyle, J.W.; Grubb, J.H.; Sly, W.S. The human cation-independent mannose 6-phosphate receptor. Cloning and sequence of the full-length cDNA and expression of functional receptor in COS cells. *J. Biol. Chem.* **1988**, *263*, 2553–2562.

48. Wise, T.L.; Pravtcheva, D.D. Delayed onset of Igf2-induced mammary tumors in Igf2r transgenic mice. *Cancer Res.* **2006**, *66*, 1327–1336. [CrossRef]

49. Sitar, T.; Popowicz, G.M.; Siwanowicz, I.; Huber, R.; Holak, T.A. Structural basis for the inhibition of insulin-like growth factors by insulin-like growth factor-binding proteins. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 13028–13033. [CrossRef]

50. Daughaday, W.H.; Trivedi, B.; Baxter, R.C. Serum "big insulin-like growth factor II" from patients with tumor hypoglycemia lacks normal E-domain O-linked glycosylation, a possible determinant of normal propeptide processing. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5823–5827. [CrossRef]

51. Oesterreicher, S.; Blum, W.F.; Schmidt, B.; Braulke, T.; Kubler, B. Interaction of insulin-like growth factor II (IGF-II) with multiple plasma proteins: High affinity binding of plasminogen to IGF-II and IGF-binding protein-3. *J. Biol. Chem.* **2005**, *280*, 9994–10000. [CrossRef] [PubMed]

52. Daughaday, W.H.; Kapadia, M. Significance of abnormal serum binding of insulin-like growth factor II in the development of hypoglycemia in patients with non-islet-cell tumors. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 6778–6782. [CrossRef] [PubMed]

53. Baxter, R.C.; Daughaday, W.H. Impaired formation of the ternary insulin-like growth factor-binding protein complex in patients with hypoglycemia due to nonislet cell tumors. *J. Clin. Endocrinol. Metab.* **1991**, *73*, 696–702. [CrossRef] [PubMed]

54. Hayman, E.G.; Pierschbacher, M.D.; Ohgren, Y.; Ruoslahti, E. Serum spreading factor (vitronectin) is present at the cell surface and in tissues. *Proc. Natl. Acad. Sci. USA* **1983**, *80*, 4003–4007. [CrossRef]

55. Hayman, E.G.; Pierschbacher, M.D.; Suzuki, S.; Ruoslahti, E. Vitronectin–a major cell attachment-promoting protein in fetal bovine serum. *Exp. Cell Res. Suppl.* **1985**, *160*, 245–258. [CrossRef]

56. Wang, L.; Zhang, X.; Pang, N.; Xiao, L.; Li, Y.; Chen, N.; Ren, M.; Deng, X.; Wu, J. Glycation of vitronectin inhibits VEGF-induced angiogenesis by uncoupling VEGF receptor-2-alphavbeta3 integrin cross-talk. *Cell Death Dis.* **2015**, *6*, e1796. [CrossRef]

57. Upton, Z.; Cuttle, L.; Noble, A.; Kempf, M.; Topping, G.; Malda, J.; Xie, Y.; Mill, J.; Harkin, D.G.; Kravchuk, O.; et al. Vitronectin: Growth factor complexes hold potential as a wound therapy approach. *J. Investig. Dermatol.* **2008**, *128*, 1535–1544. [CrossRef]

58. Arciniegas, E.; Neves, Y.C.; Carrillo, L.M. Potential role for insulin-like growth factor II and vitronectin in the endothelial-mesenchymal transition process. *Differentiation* **2006**, *74*, 277–292. [CrossRef]

59. Coppola, D.; Ferber, A.; Miura, M.; Sell, C.; D'Ambrosio, C.; Rubin, R.; Baserga, R. A functional insulin-like growth factor I receptor is required for the mitogenic and transforming activities of the epidermal growth factor receptor. *Mol. Cell. Biol.* **1994**, *14*, 4588–4595. [CrossRef]

60. Sell, C.; Dumenil, G.; Deveaud, C.; Miura, M.; Coppola, D.; DeAngelis, T.; Rubin, R.; Efstratiadis, A.; Baserga, R. Effect of a null mutation of the insulin-like growth factor I receptor gene on growth and transformation of mouse embryo fibroblasts. *Mol. Cell. Biol.* **1994**, *14*, 3604–3612. [CrossRef]

61. Haluska, P.; Shaw, H.M.; Batzel, G.N.; Yin, D.; Molina, J.R.; Molife, L.R.; Yap, T.A.; Roberts, M.L.; Sharma, A.; Gualberto, A.; et al. Phase I dose escalation study of the anti insulin-like growth factor-I receptor monoclonal antibody CP-751,871 in patients with refractory solid tumors. *Clin. Cancer Res.* **2007**, *13*, 5834–5840. [CrossRef] [PubMed]

62. Karp, D.D.; Paz-Ares, L.G.; Novello, S.; Haluska, P.; Garland, L.; Cardenal, F.; Blakely, L.J.; Eisenberg, P.D.; Langer, C.J.; Blumenschein, G., Jr.; et al. Phase II study of the anti-insulin-like growth factor type 1 receptor antibody CP-751,871 in combination with paclitaxel and carboplatin in previously untreated, locally advanced, or metastatic non-small-cell lung cancer. *J. Clin. Oncol.* **2009**, *27*, 2516–2522. [CrossRef] [PubMed]

63. Golan, T.; Javle, M. Targeting the insulin growth factor pathway in gastrointestinal cancers. *Oncology (Williston Park)* **2011**, *25*, 518–526, 529. [PubMed]

64. Brana, I.; Berger, R.; Golan, T.; Haluska, P.; Edenfield, J.; Fiorica, J.; Stephenson, J.; Martin, L.P.; Westin, S.; Hanjani, P.; et al. A parallel-arm phase I trial of the humanised anti-IGF-1R antibody dalotuzumab in combination with the AKT inhibitor MK-2206, the mTOR inhibitor ridaforolimus, or the NOTCH inhibitor MK-0752, in patients with advanced solid tumours. *Br. J. Cancer* **2014**, *111*, 1932–1944. [CrossRef] [PubMed]

65. Haluska, P.; Carboni, J.M.; Loegering, D.A.; Lee, F.Y.; Wittman, M.; Saulnier, M.G.; Frennesson, D.B.; Kalli, K.R.; Conover, C.A.; Attar, R.M.; et al. In vitro and in vivo antitumor effects of the dual insulin-like growth factor-I/insulin receptor inhibitor, BMS-554417. *Cancer Res.* **2006**, *66*, 362–371. [CrossRef]

66. Bitelman, C.; Sarfstein, R.; Sarig, M.; Attias-Geva, Z.; Fishman, A.; Werner, H.; Bruchim, I. IGF1R-directed targeted therapy enhances the cytotoxic effect of chemotherapy in endometrial cancer. *Cancer Lett.* **2013**, *335*, 153–159. [CrossRef]

67. Gariboldi, M.B.; Ravizza, R.; Monti, E. The IGFR1 inhibitor NVP-AEW541 disrupts a pro-survival and pro-angiogenic IGF-STAT3-HIF1 pathway in human glioblastoma cells. *Biochem. Pharmacol.* **2010**, *80*, 455–462. [CrossRef]

68. Baserga, R. The decline and fall of the IGF-I receptor. *J. Cell. Physiol.* **2013**, *228*, 675–679. [CrossRef]

69. Beckwith, H.; Yee, D. Minireview: Were the IGF Signaling Inhibitors All Bad? *Mol. Endocrinol.* **2015**, *29*, 1549–1557. [CrossRef]

70. Buck, E.; Gokhale, P.C.; Koujak, S.; Brown, E.; Eyzaguirre, A.; Tao, N.; Rosenfeld-Franklin, M.; Lerner, L.; Chiu, M.I.; Wild, R.; et al. Compensatory insulin receptor (IR) activation on inhibition of insulin-like growth factor-1 receptor (IGF-1R): Rationale for cotargeting IGF-1R and IR in cancer. *Mol. Cancer Ther.* **2010**, *9*, 2652–2664. [CrossRef]

71. Feng, Y.; Zhu, Z.; Xiao, X.; Choudhry, V.; Barrett, J.C.; Dimitrov, D.S. Novel human monoclonal antibodies to insulin-like growth factor (IGF)-II that potently inhibit the IGF receptor type I signal transduction function. *Mol. Cancer Ther.* **2006**, *5*, 114–120. [CrossRef] [PubMed]

72. Feng, Y.; Dimitrov, D.S. Monoclonal antibodies against components of the IGF system for cancer treatment. *Curr. Opin. Drug Discov. Devel.* **2008**, *11*, 178–185. [PubMed]

73. Maina, E.N.; Morris, M.R.; Zatyka, M.; Raval, R.R.; Banks, R.E.; Richards, F.M.; Johnson, C.M.; Maher, E.R. Identification of novel VHL target genes and relationship to hypoxic response pathways. *Oncogene* **2005**, *24*, 4549–4558. [CrossRef] [PubMed]

74. Pezzuto, A.; Carico, E. Role of HIF-1 in Cancer Progression: Novel Insights. A Review. *Curr. Mol. Med.* **2018**, *18*, 343–351. [CrossRef]

75. Senger, D.R.; Galli, S.J.; Dvorak, A.M.; Perruzzi, C.A.; Harvey, V.S.; Dvorak, H.F. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science* **1983**, *219*, 983–985. [CrossRef]

76. Hanahan, D.; Folkman, J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell* **1996**, *86*, 353–364. [CrossRef]

77. Sinha, U.K.; Kundra, A.; Scalia, P.; Smith, D.L.; Parsa, B.; Masood, R.; Gill, P.S. Expression of EphB4 in head and neck squamous cell carcinoma. *Ear Nose Throat J.* **2003**, *82*, 866, 869–870, 887. [CrossRef]

78. Xia, G.; Kumar, S.R.; Masood, R.; Zhu, S.; Reddy, R.; Krasnoperov, V.; Quinn, D.I.; Henshall, S.M.; Sutherland, R.L.; Pinski, J.K.; et al. EphB4 expression and biological significance in prostate cancer. *Cancer Res.* **2005**, *65*, 4623–4632. [CrossRef]

79. Huang, X.; Yamada, Y.; Kidoya, H.; Naito, H.; Nagahama, Y.; Kong, L.; Katoh, S.Y.; Li, W.L.; Ueno, M.; Takakura, N. EphB4 overexpression in B16 melanoma cells affects arterial-venous patterning in tumor angiogenesis. *Cancer Res.* **2007**, *67*, 9800–9808. [CrossRef]

80. Kumar, S.R.; Scehnet, J.S.; Ley, E.J.; Singh, J.; Krasnoperov, V.; Liu, R.; Manchanda, P.K.; Ladner, R.D.; Hawes, D.; Weaver, F.A.; et al. Preferential induction of EphB4 over EphB2 and its implication in colorectal cancer progression. *Cancer Res.* **2009**, *69*, 3736–3745. [CrossRef]

81. Brantley-Sieders, D.M.; Jiang, A.; Sarma, K.; Badu-Nkansah, A.; Walter, D.L.; Shyr, Y.; Chen, J. Eph/ephrin profiling in human breast cancer reveals significant associations between expression level and clinical outcome. *PLoS ONE* **2011**, *6*, e24426. [CrossRef] [PubMed]

82. Becerikli, M.; Merwart, B.; Lam, M.C.; Suppelna, P.; Rittig, A.; Mirmohammedsadegh, A.; Stricker, I.; Theiss, C.; Singer, B.B.; Jacobsen, F.; et al. EPHB4 tyrosine-kinase receptor expression and biological significance in soft tissue sarcoma. *Int. J. Cancer* **2015**, *136*, 1781–1791. [CrossRef] [PubMed]

83. Furlan, D.; Sahnane, N.; Carnevali, I.; Cerutti, R.; Bertoni, F.; Kwee, I.; Uccella, S.; Bertolini, V.; Chiaravalli, A.M.; Capella, C. Up-regulation of the hypoxia-inducible factor-1 transcriptional pathway in colorectal carcinomas. *Hum. Pathol.* **2008**, *39*, 1483–1494. [CrossRef] [PubMed]

84. Kim, K.W.; Bae, S.K.; Lee, O.H.; Bae, M.H.; Lee, M.J.; Park, B.C. Insulin-like growth factor II induced by hypoxia may contribute to angiogenesis of human hepatocellular carcinoma. *Cancer Res.* **1998**, *58*, 348–351. [PubMed]

85. Vihanto, M.M.; Plock, J.; Erni, D.; Frey, B.M.; Frey, F.J.; Huynh-Do, U. Hypoxia up-regulates expression of Eph receptors and ephrins in mouse skin. *FASEB J.* **2005**, *19*, 1689–1691. [CrossRef] [PubMed]

86. Masood, R.; Kundra, A.; Zhu, S.; Xia, G.; Scalia, P.; Smith, D.L.; Gill, P.S. Malignant mesothelioma growth inhibition by agents that target the VEGF and VEGF-C autocrine loops. *Int. J. Cancer* **2003**, *104*, 603–610. [CrossRef]

87. Stoeltzing, O.; Liu, W.; Reinmuth, N.; Fan, F.; Parikh, A.A.; Bucana, C.D.; Evans, D.B.; Semenza, G.L.; Ellis, L.M. Regulation of hypoxia-inducible factor-1alpha, vascular endothelial growth factor, and angiogenesis by an insulin-like growth factor-I receptor autocrine loop in human pancreatic cancer. *Am. J. Pathol.* **2003**, *163*, 1001–1011. [CrossRef]

88. Reinmuth, N.; Fan, F.; Liu, W.; Parikh, A.A.; Stoeltzing, O.; Jung, Y.D.; Bucana, C.D.; Radinsky, R.; Gallick, G.E.; Ellis, L.M. Impact of insulin-like growth factor receptor-I function on angiogenesis, growth, and metastasis of colon cancer. *Lab. Investig.* **2002**, *82*, 1377–1389. [CrossRef]

89. Reinmuth, N.; Liu, W.; Fan, F.; Jung, Y.D.; Ahmad, S.A.; Stoeltzing, O.; Bucana, C.D.; Radinsky, R.; Ellis, L.M. Blockade of insulin-like growth factor I receptor function inhibits growth and angiogenesis of colon cancer. *Clin. Cancer Res.* **2002**, *8*, 3259–3269.

90. Kwon, Y.W.; Kwon, K.S.; Moon, H.E.; Park, J.A.; Choi, K.S.; Kim, Y.S.; Jang, H.S.; Oh, C.K.; Lee, Y.M.; Kwon, Y.G.; et al. Insulin-like growth factor-II regulates the expression of vascular endothelial growth factor by the human keratinocyte cell line HaCaT. *J. Investig. Dermatol.* **2004**, *123*, 152–158. [CrossRef]

91. Mohlin, S.; Hamidian, A.; Pahlman, S. HIF2A and IGF2 expression correlates in human neuroblastoma cells and normal immature sympathetic neuroblasts. *Neoplasia* **2013**, *15*, 328–334. [CrossRef] [PubMed]

92. Milazzo, G.; Yip, C.C.; Maddux, B.A.; Vigneri, R.; Goldfine, I.D. High-affinity insulin binding to an atypical insulin-like growth factor-I receptor in human breast cancer cells. *J. Clin. Investig.* **1992**, *89*, 899–908. [CrossRef]

93. Zhang, B.; Roth, R.A. The insulin receptor-related receptor. Tissue expression, ligand binding specificity, and signaling capabilities. *J. Biol. Chem.* **1992**, *267*, 18320–18328. [PubMed]

94. Pandini, G.; Frasca, F.; Mineo, R.; Sciacca, L.; Vigneri, R.; Belfiore, A. Insulin/insulin-like growth factor I hybrid receptors have different biological characteristics depending on the insulin receptor isoform involved. *J. Biol. Chem.* **2002**, *277*, 39684–39695. [CrossRef] [PubMed]

95. Pandini, G.; Vigneri, R.; Costantino, A.; Frasca, F.; Ippolito, A.; Fujita-Yamaguchi, Y.; Siddle, K.; Goldfine, I.D.; Belfiore, A. Insulin and insulin-like growth factor-I (IGF-I) receptor overexpression in breast cancers leads to insulin/IGF-I hybrid receptor overexpression: Evidence for a second mechanism of IGF-I signaling. *Clin. Cancer Res.* **1999**, *5*, 1935–1944.

96. Bailyes, E.M.; Nave, B.T.; Soos, M.A.; Orr, S.R.; Hayward, A.C.; Siddle, K. Insulin receptor/IGF-I receptor hybrids are widely distributed in mammalian tissues: Quantification of individual receptor species by selective immunoprecipitation and immunoblotting. *Biochem. J.* **1997**, *327*, 209–215. [CrossRef]

97. Milazzo, G.; Giorgino, F.; Damante, G.; Sung, C.; Stampfer, M.R.; Vigneri, R.; Goldfine, I.D.; Belfiore, A. Insulin receptor expression and function in human breast cancer cell lines. *Cancer Res.* **1992**, *52*, 3924–3930.

98. Papa, V.; Pezzino, V.; Costantino, A.; Belfiore, A.; Giuffrida, D.; Frittitta, L.; Vannelli, G.B.; Brand, R.; Goldfine, I.D.; Vigneri, R. Elevated insulin receptor content in human breast cancer. *J. Clin. Investig.* **1990**, *86*, 1503–1510. [CrossRef]

99. Puzanov, I.; Lindsay, C.R.; Goff, L.; Sosman, J.; Gilbert, J.; Berlin, J.; Poondru, S.; Simantov, R.; Gedrich, R.; Stephens, A.; et al. A phase I study of continuous oral dosing of OSI-906, a dual inhibitor of insulin-like growth factor-1 and insulin receptors, in patients with advanced solid tumors. *Clin. Cancer Res.* **2015**, *21*, 701–711. [CrossRef]

100. Bendell, J.C.; Jones, S.F.; Hart, L.; Spigel, D.R.; Lane, C.M.; Earwood, C.; Infante, J.R.; Barton, J.; Burris, H.A. A phase Ib study of linsitinib (OSI-906), a dual inhibitor of IGF-1R and IR tyrosine kinase, in combination with everolimus as treatment for patients with refractory metastatic colorectal cancer. *Investig. New Drugs* **2015**, *33*, 187–193. [CrossRef]

101. Jones, R.L.; Kim, E.S.; Nava-Parada, P.; Alam, S.; Johnson, F.M.; Stephens, A.W.; Simantov, R.; Poondru, S.; Gedrich, R.; Lippman, S.M.; et al. Phase I study of intermittent oral dosing of the insulin-like growth factor-1 and insulin receptors inhibitor OSI-906 in patients with advanced solid tumors. *Clin. Cancer Res.* **2015**, *21*, 693–700. [CrossRef] [PubMed]

102. Fassnacht, M.; Berruti, A.; Baudin, E.; Demeure, M.J.; Gilbert, J.; Haak, H.; Kroiss, M.; Quinn, D.I.; Hesseltine, E.; Ronchi, C.L.; et al. Linsitinib (OSI-906) versus placebo for patients with locally advanced or metastatic adrenocortical carcinoma: A double-blind, randomised, phase 3 study. *Lancet Oncol.* **2015**, *16*, 426–435. [CrossRef]

103. Davis, S.L.; Eckhardt, S.G.; Diamond, J.R.; Messersmith, W.A.; Dasari, A.; Weekes, C.D.; Lieu, C.H.; Kane, M.; Choon Tan, A.; Pitts, T.M.; et al. A Phase I Dose-Escalation Study of Linsitinib (OSI-906), a Small-Molecule Dual Insulin-Like Growth Factor-1 Receptor/Insulin Receptor Kinase Inhibitor, in Combination with Irinotecan in Patients with Advanced Cancer. *Oncologist* **2018**, *23*, 1409. [CrossRef] [PubMed]

104. Parra-Guillen, Z.P.; Schmid, U.; Janda, A.; Freiwald, M.; Troconiz, I.F. Model-Informed Dose Selection for Xentuzumab, a Dual Insulin-Like Growth Factor-I/II-Neutralizing Antibody. *Clin. Pharmacol. Ther.* **2019**. [CrossRef]

105. Murakami, H.; Ikeda, M.; Okusaka, T.; Inaba, Y.; Iguchi, H.; Yagawa, K.; Yamamoto, N. A Phase I study of MEDI-575, a PDGFRalpha monoclonal antibody, in Japanese patients with advanced solid tumors. *Cancer Chemother. Pharmacol.* **2015**, *76*, 631–639. [CrossRef]

106. Iguchi, H.; Nishina, T.; Nogami, N.; Kozuki, T.; Yamagiwa, Y.; Yagawa, K. Phase I dose-escalation study evaluating safety, tolerability and pharmacokinetics of MEDI-573, a dual IGF-I/II neutralizing antibody, in Japanese patients with advanced solid tumours. *Invest. New Drugs* **2015**, *33*, 194–200. [CrossRef]

107. Scalia, P.; Heart, E.; Comai, L.; Vigneri, R.; Sung, C.K. Regulation of the Akt/Glycogen synthase kinase-3 axis by insulin-like growth factor-II via activation of the human insulin receptor isoform-A. *J. Cell. Biochem.* **2001**, *82*, 610–618. [CrossRef]

108. Belfiore, A.; Malaguarnera, R. Insulin receptor and cancer. *Endocr. Relat. Cancer* **2011**, *18*, R125–R147. [CrossRef]

109. Desai, J.; Solomon, B.J.; Davis, I.D.; Lipton, L.R.; Hicks, R.; Scott, A.M.; Park, J.; Clemens, P.L.; Gestone, T.A.; Finckenstein, F.G. Phase I dose-escalation study of daily BMS-754807, an oral, dual IGF-1R/insulin receptor (IR) inhibitor in subjects with solid tumors. *J. Clin. Oncol.* **2010**, *28*, 3104. [CrossRef]

110. Haluska, P.; Dhar, A.; Hou, X.; Huang, F.; Nuyten, D.S.A.; Park, J.; Brodie, A.H.; Ingle, J.N.; Carboni, J.M.; Gottardis, M.M.; et al. Phase II trial of the dual IGF-1R/IR inhibitor BMS-754807 with or without letrozole in aromatase inhibitor-resistant breast cancer. *J. Clin. Oncol.* **2011**, *29*, TPS111. [CrossRef]

111. Umehara, H.; Maekawa, Y.; Koizumi, F.; Shimizu, M.; Ota, T.; Fouad, T.M.; Willey, J.; Kaito, H.; Shiraishi, N.; Nakashima, D.; et al. Preclinical and phase I clinical studies of KW-2450, a dual IGF-1R/IR tyrosine kinase inhibitor, in combination with lapatinib and letrozole. *Ther. Adv. Med. Oncol.* **2018**, *10*, 1758835918786858. [CrossRef] [PubMed]

112. Schwartz, G.K.; Dickson, M.A.; LoRusso, P.M.; Sausville, E.A.; Maekawa, Y.; Watanabe, Y.; Kashima, N.; Nakashima, D.; Akinaga, S. Preclinical and first-in-human phase I studies of KW-2450, an oral tyrosine kinase inhibitor with insulin-like growth factor receptor-1/insulin receptor selectivity. *Cancer Sci.* **2016**, *107*, 499–506. [CrossRef] [PubMed]

113. Atzori, F.; Tabernero, J.; Cervantes, A.; Prudkin, L.; Andreu, J.; Rodriguez-Braun, E.; Domingo, A.; Guijarro, J.; Gamez, C.; Rodon, J.; et al. A phase I pharmacokinetic and pharmacodynamic study of dalotuzumab (MK-0646), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in patients with advanced solid tumors. *Clin. Cancer Res.* **2011**, *17*, 6304–6312. [CrossRef] [PubMed]

114. Di Cosimo, S.; Sathyanarayanan, S.; Bendell, J.C.; Cervantes, A.; Stein, M.N.; Brana, I.; Roda, D.; Haines, B.B.; Zhang, T.; Winter, C.G.; et al. Combination of the mTOR inhibitor ridaforolimus and the anti-IGF1R monoclonal antibody dalotuzumab: Preclinical characterization and phase I clinical trial. *Clin. Cancer Res.* **2015**, *21*, 49–59. [CrossRef]

115. Doi, T.; Muro, K.; Yoshino, T.; Fuse, N.; Ura, T.; Takahari, D.; Feng, H.P.; Shimamoto, T.; Noguchi, K.; Ohtsu, A. Phase 1 pharmacokinetic study of MK-0646 (dalotuzumab), an anti-insulin-like growth factor-1 receptor monoclonal antibody, in combination with cetuximab and irinotecan in Japanese patients with advanced colorectal cancer. *Cancer Chemother. Pharmacol.* **2013**, *72*, 643–652. [CrossRef]

116. Ellis, P.M.; Shepherd, F.A.; Laurie, S.A.; Goss, G.D.; Olivo, M.; Powers, J.; Seymour, L.; Bradbury, P.A. NCIC CTG IND.190 phase I trial of dalotuzumab (MK-0646) in combination with cisplatin and etoposide in extensive-stage small-cell lung cancer. *J. Thorac. Oncol.* **2014**, *9*, 410–413. [CrossRef]

117. Moran, T.; Felip, E.; Keedy, V.; Borghaei, H.; Shepherd, F.A.; Insa, A.; Brown, H.; Fitzgerald, T.; Sathyanarayanan, S.; Reilly, J.F.; et al. Activity of dalotuzumab, a selective anti-IGF1R antibody, in combination with erlotinib in unselected patients with Non-small-cell lung cancer: A phase I/II randomized trial. *Exp. Hematol. Oncol.* **2014**, *3*, 26. [CrossRef]

118. Olmos, D.; Postel-Vinay, S.; Molife, L.R.; Okuno, S.H.; Schuetze, S.M.; Paccagnella, M.L.; Batzel, G.N.; Yin, D.; Pritchard-Jones, K.; Judson, I.; et al. Safety, pharmacokinetics, and preliminary activity of the anti-IGF-1R antibody figitumumab (CP-751,871) in patients with sarcoma and Ewing's sarcoma: A phase 1 expansion cohort study. *Lancet Oncol.* **2010**, *11*, 129–135. [CrossRef]

119. Molife, L.R.; Fong, P.C.; Paccagnella, L.; Reid, A.H.; Shaw, H.M.; Vidal, L.; Arkenau, H.T.; Karavasilis, V.; Yap, T.A.; Olmos, D.; et al. The insulin-like growth factor-I receptor inhibitor figitumumab (CP-751,871) in combination with docetaxel in patients with advanced solid tumours: Results of a phase Ib dose-escalation, open-label study. *Br. J. Cancer* **2010**, *103*, 332–339. [CrossRef]

120. Haluska, P.; Worden, F.; Olmos, D.; Yin, D.; Schteingart, D.; Batzel, G.N.; Paccagnella, M.L.; de Bono, J.S.; Gualberto, A.; Hammer, G.D. Safety, tolerability, and pharmacokinetics of the anti-IGF-1R monoclonal antibody figitumumab in patients with refractory adrenocortical carcinoma. *Cancer Chemother. Pharmacol.* **2010**, *65*, 765–773. [CrossRef]

121. de Bono, J.S.; Piulats, J.M.; Pandha, H.S.; Petrylak, D.P.; Saad, F.; Aparicio, L.M.; Sandhu, S.K.; Fong, P.; Gillessen, S.; Hudes, G.R.; et al. Phase II randomized study of figitumumab plus docetaxel and docetaxel alone with crossover for metastatic castration-resistant prostate cancer. *Clin. Cancer Res.* **2014**, *20*, 1925–1934. [CrossRef] [PubMed]

122. Chi, K.N.; Gleave, M.E.; Fazli, L.; Goldenberg, S.L.; So, A.; Kollmannsberger, C.; Murray, N.; Tinker, A.; Pollak, M. A phase II pharmacodynamic study of preoperative figitumumab in patients with localized prostate cancer. *Clin. Cancer Res.* **2012**, *18*, 3407–3413. [CrossRef]

123. Becerra, C.R.; Salazar, R.; Garcia-Carbonero, R.; Thomas, A.L.; Vazquez-Mazon, F.J.; Cassidy, J.; Maughan, T.; Castillo, M.G.; Iveson, T.; Yin, D.; et al. Figitumumab in patients with refractory metastatic colorectal cancer previously treated with standard therapies: A nonrandomized, open-label, phase II trial. *Cancer Chemother. Pharmacol.* **2014**, *73*, 695–702. [CrossRef] [PubMed]

124. Goto, Y.; Sekine, I.; Tanioka, M.; Shibata, T.; Tanai, C.; Asahina, H.; Nokihara, H.; Yamamoto, N.; Kunitoh, H.; Ohe, Y.; et al. Figitumumab combined with carboplatin and paclitaxel in treatment-naive Japanese patients with advanced non-small cell lung cancer. *Investig. New Drugs* **2012**, *30*, 1548–1556. [CrossRef]

125. Langer, C.J.; Novello, S.; Park, K.; Krzakowski, M.; Karp, D.D.; Mok, T.; Benner, R.J.; Scranton, J.R.; Olszanski, A.J.; Jassem, J. Randomized, phase III trial of first-line figitumumab in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone in patients with advanced non-small-cell lung cancer. *J. Clin. Oncol.* **2014**, *32*, 2059–2066. [CrossRef] [PubMed]

126. Scagliotti, G.V.; Bondarenko, I.; Blackhall, F.; Barlesi, F.; Hsia, T.C.; Jassem, J.; Milanowski, J.; Popat, S.; Sanchez-Torres, J.M.; Novello, S.; et al. Randomized, phase III trial of figitumumab in combination with erlotinib versus erlotinib alone in patients with nonadenocarcinoma nonsmall-cell lung cancer. *Ann. Oncol.* **2015**, *26*, 497–504. [CrossRef]

127. Lacy, M.Q.; Alsina, M.; Fonseca, R.; Paccagnella, M.L.; Melvin, C.L.; Yin, D.; Sharma, A.; Enriquez Sarano, M.; Pollak, M.; Jagannath, S.; et al. Phase I, pharmacokinetic and pharmacodynamic study of the anti-insulinlike growth factor type 1 Receptor monoclonal antibody CP-751,871 in patients with multiple myeloma. *J. Clin. Oncol.* **2008**, *26*, 3196–3203. [CrossRef]

128. Murakami, H.; Doi, T.; Yamamoto, N.; Watanabe, J.; Boku, N.; Fuse, N.; Yoshino, T.; Ohtsu, A.; Otani, S.; Shibayama, K.; et al. Phase 1 study of ganitumab (AMG 479), a fully human monoclonal antibody against the insulin-like growth factor receptor type I (IGF1R), in Japanese patients with advanced solid tumors. *Cancer Chemother. Pharmacol.* **2012**, *70*, 407–414. [CrossRef]

129. Rosen, L.S.; Puzanov, I.; Friberg, G.; Chan, E.; Hwang, Y.C.; Deng, H.; Gilbert, J.; Mahalingam, D.; McCaffery, I.; Michael, S.A.; et al. Safety and pharmacokinetics of ganitumab (AMG 479) combined with sorafenib, panitumumab, erlotinib, or gemcitabine in patients with advanced solid tumors. *Clin. Cancer Res.* **2012**, *18*, 3414–3427. [CrossRef]

130. Fuchs, C.S.; Azevedo, S.; Okusaka, T.; Van Laethem, J.L.; Lipton, L.R.; Riess, H.; Szczylik, C.; Moore, M.J.; Peeters, M.; Bodoky, G.; et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: The GAMMA trial. *Ann. Oncol.* **2015**, *26*, 921–927. [CrossRef]

131. Strosberg, J.R.; Chan, J.A.; Ryan, D.P.; Meyerhardt, J.A.; Fuchs, C.S.; Abrams, T.; Regan, E.; Brady, R.; Weber, J.; Campos, T.; et al. A multi-institutional, phase II open-label study of ganitumab (AMG 479) in advanced carcinoid and pancreatic neuroendocrine tumors. *Endocr. Relat. Cancer* **2013**, *20*, 383–390. [CrossRef] [PubMed]

132. Okusaka, T.; Ikeda, M.; Fukutomi, A.; Kobayashi, Y.; Shibayama, K.; Takubo, T.; Gansert, J. Safety, tolerability, pharmacokinetics and antitumor activity of ganitumab, an investigational fully human monoclonal antibody to insulin-like growth factor type 1 receptor, combined with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer: A phase 1b study. *Jpn. J. Clin. Oncol.* **2014**, *44*, 442–447. [CrossRef] [PubMed]

133. Tap, W.D.; Demetri, G.; Barnette, P.; Desai, J.; Kavan, P.; Tozer, R.; Benedetto, P.W.; Friberg, G.; Deng, H.; McCaffery, I.; et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. *J. Clin. Oncol.* **2012**, *30*, 1849–1856. [CrossRef] [PubMed]

134. Robertson, J.F.; Ferrero, J.M.; Bourgeois, H.; Kennecke, H.; de Boer, R.H.; Jacot, W.; McGreivy, J.; Suzuki, S.; Zhu, M.; McCaffery, I.; et al. Ganitumab with either exemestane or fulvestrant for postmenopausal women with advanced, hormone-receptor-positive breast cancer: A randomised, controlled, double-blind, phase 2 trial. *Lancet Oncol.* **2013**, *14*, 228–235. [CrossRef]

135. Cohn, A.L.; Tabernero, J.; Maurel, J.; Nowara, E.; Sastre, J.; Chuah, B.Y.; Kopp, M.V.; Sakaeva, D.D.; Mitchell, E.P.; Dubey, S.; et al. A randomized, placebo-controlled phase 2 study of ganitumab or conatumumab in combination with FOLFIRI for second-line treatment of mutant KRAS metastatic colorectal cancer. *Ann. Oncol.* **2013**, *24*, 1777–1785. [CrossRef]

136. Abou-Alfa, G.K.; Capanu, M.; O'Reilly, E.M.; Ma, J.; Chou, J.F.; Gansukh, B.; Shia, J.; Kalin, M.; Katz, S.; Abad, L.; et al. A phase II study of cixutumumab (IMC-A12, NSC742460) in advanced hepatocellular carcinoma. *J. Hepatol.* **2014**, *60*, 319–324. [CrossRef]

137. Philip, P.A.; Goldman, B.; Ramanathan, R.K.; Lenz, H.J.; Lowy, A.M.; Whitehead, R.P.; Wakatsuki, T.; Iqbal, S.; Gaur, R.; Benedetti, J.K.; et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: Phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). *Cancer* **2014**, *120*, 2980–2985. [CrossRef]

138. Rajan, A.; Carter, C.A.; Berman, A.; Cao, L.; Kelly, R.J.; Thomas, A.; Khozin, S.; Chavez, A.L.; Bergagnini, I.; Scepura, B.; et al. Cixutumumab for patients with recurrent or refractory advanced thymic epithelial tumours: A multicentre, open-label, phase 2 trial. *Lancet Oncol.* **2014**, *15*, 191–200. [CrossRef]

139. Anderson, P.M.; Bielack, S.S.; Gorlick, R.G.; Skubitz, K.; Daw, N.C.; Herzog, C.E.; Monge, O.R.; Lassaletta, A.; Boldrini, E.; Papai, Z.; et al. A phase II study of clinical activity of SCH 717454 (robatumumab) in patients with relapsed osteosarcoma and Ewing sarcoma. *Pediatr. Blood Cancer* **2016**, *63*, 1761–1770. [CrossRef]

140. Lin, E.H.; Lenz, H.J.; Saleh, M.N.; Mackenzie, M.J.; Knost, J.A.; Pathiraja, K.; Langdon, R.B.; Yao, S.L.; Lu, B.D. A randomized, phase II study of the anti-insulin-like growth factor receptor type 1 (IGF-1R) monoclonal antibody robatumumab (SCH 717454) in patients with advanced colorectal cancer. *Cancer Med.* **2014**, *3*, 988–997. [CrossRef]

141. Ko, A.H.; Murray, J.; Horgan, K.E.; Dauer, J.; Curley, M.; Baum, J.; Louis, C.U.; Lugovskoy, A. A multicenter phase II study of istiratumab (MM-141) plus nab-paclitaxel (A) and gemcitabine (G) in metastatic pancreatic cancer (MPC). *J. Clin. Oncol.* **2016**, *34*, TPS481. [CrossRef]

142. Ko, A.H.; Cubillo, A.; Kundranda, M.; Zafar, S.F.; Meiri, E.; Bendell, J.; Alguel, H.; Rivera Herrero, F.; Ahn, E.; Watkins, D.; et al. CARRIE: A Randomized, Double-blind, Placebo-controlled Phase 2 Study of Istiratumab (MM-141) plus Nab-Paclitaxel and Gemcitabine versus Nab-Paclitaxel. In Proceedings of the 2018 EMSO Congress, Munich, Germany, 19–23 October 2018.

143. Mahadevan, D.; Sutton, G.R.; Arteta-Bulos, R.; Bowden, C.J.; Miller, P.J.; Swart, R.E.; Walker, M.S.; Haluska, P.; Munster, P.N.; Marshall, J.; et al. Phase 1b study of safety, tolerability and efficacy of R1507, a monoclonal antibody to IGF-1R in combination with multiple standard oncology regimens in patients with advanced solid malignancies. *Cancer Chemother. Pharmacol.* **2014**, *73*, 467–473. [CrossRef]

144. Maiso, P.; Ocio, E.M.; Garayoa, M.; Montero, J.C.; Hofmann, F.; Garcia-Echeverria, C.; Zimmermann, J.; Pandiella, A.; San Miguel, J.F. The insulin-like growth factor-I receptor inhibitor NVP-AEW541 provokes cell cycle arrest and apoptosis in multiple myeloma cells. *Br. J. Haematol.* **2008**, *141*, 470–482. [CrossRef]

145. Scotlandi, K.; Manara, M.C.; Nicoletti, G.; Lollini, P.L.; Lukas, S.; Benini, S.; Croci, S.; Perdichizzi, S.; Zambelli, D.; Serra, M.; et al. Antitumor activity of the insulin-like growth factor-I receptor kinase inhibitor NVP-AEW541 in musculoskeletal tumors. *Cancer Res.* **2005**, *65*, 3868–3876. [CrossRef] [PubMed]

146. Garcia-Echeverria, C.; Pearson, M.A.; Marti, A.; Meyer, T.; Mestan, J.; Zimmermann, J.; Gao, J.; Brueggen, J.; Capraro, H.G.; Cozens, R.; et al. In vivo antitumor activity of NVP-AEW541-A novel, potent, and selective inhibitor of the IGF-IR kinase. *Cancer Cell* **2004**, *5*, 231–239. [CrossRef]

147. Wen, B.; Deutsch, E.; Marangoni, E.; Frascona, V.; Maggiorella, L.; Abdulkarim, B.; Chavaudra, N.; Bourhis, J. Tyrphostin AG 1024 modulates radiosensitivity in human breast cancer cells. *Br. J. Cancer* **2001**, *85*, 2017–2021. [CrossRef] [PubMed]

148. Luk, F.; Yu, Y.; Walsh, W.R.; Yang, J.L. IGF1R-targeted therapy and its enhancement of doxorubicin chemosensitivity in human osteosarcoma cell lines. *Cancer Invest.* **2011**, *29*, 521–532. [CrossRef]

149. Momose, I.; Kunimoto, S.; Osono, M.; Ikeda, D. Inhibitors of insulin-like growth factor-1 receptor tyrosine kinase are preferentially cytotoxic to nutrient-deprived pancreatic cancer cells. *Biochem. Biophys. Res. Commun.* **2009**, *380*, 171–176. [CrossRef]

150. Beauchamp, M.C.; Knafo, A.; Yasmeen, A.; Carboni, J.M.; Gottardis, M.M.; Pollak, M.N.; Gotlieb, W.H. BMS-536924 sensitizes human epithelial ovarian cancer cells to the PARP inhibitor, 3-aminobenzamide. *Gynecol. Oncol.* **2009**, *115*, 193–198. [CrossRef]

151. Vincent, E.E.; Elder, D.J.; Curwen, J.; Kilgour, E.; Hers, I.; Tavare, J.M. Targeting non-small cell lung cancer cells by dual inhibition of the insulin receptor and the insulin-like growth factor-1 receptor. *PLoS ONE* **2013**, *8*, e66963. [CrossRef]

152. Shaw, P.H.; Maughan, T.S.; Clarke, A.R. Dual inhibition of epidermal growth factor and insulin-like 1 growth factor receptors reduce intestinal adenoma burden in the Apc(min/+) mouse. *Br. J. Cancer* **2011**, *105*, 649–657. [CrossRef]

153. Lee, H.J.; Pham, P.C.; Hyun, S.Y.; Baek, B.; Kim, B.; Kim, Y.; Min, H.Y.; Lee, J.; Lee, H.Y. Development of a 4-aminopyrazolo[3,4-d]pyrimidine-based dual IGF1R/Src inhibitor as a novel anticancer agent with minimal toxicity. *Mol. Cancer* **2018**, *17*, 50. [CrossRef] [PubMed]

154. Feng, Y.; Zhao, Q.; Chen, W.; Wang, Y.; Crowder, K.; Dimitrov, D.S. A new bispecific antibody targeting non-overlapping epitopes on IGF2: Design, in vitro characterization and pharmacokinetics in macaques. *Exp. Mol. Pathol.* **2014**, *97*, 359–367. [CrossRef] [PubMed]

155. Zhao, Q.; Feng, Y.; Zhu, Z.; Dimitrov, D.S. Human monoclonal antibody fragments binding to insulin-like growth factors I and II with picomolar affinity. *Mol. Cancer Ther.* **2011**, *10*, 1677–1685. [CrossRef] [PubMed]

156. Zhao, Q.; Tran, H.; Dimitrov, D.S.; Cheung, N.K. A dual-specific anti-IGF-1/IGF-2 human monoclonal antibody alone and in combination with temsirolimus for therapy of neuroblastoma. *Int. J. Cancer* **2015**, *137*, 2243–2252. [CrossRef]

157. Lin, L.; Asthana, S.; Chan, E.; Bandyopadhyay, S.; Martins, M.M.; Olivas, V.; Yan, J.J.; Pham, L.; Wang, M.M.; Bollag, G.; et al. Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E748–E757. [CrossRef] [PubMed]

158. Gala, M.K.; Austin, T.; Ogino, S.; Chan, A.T. TFF2-CXCR4 Axis Is Associated with BRAF V600E Colon Cancer. *Cancer Prev. Res. (Phila)* **2015**, *8*, 614–619. [CrossRef]

159. Parker, R.; Vella, L.J.; Xavier, D.; Amirkhani, A.; Parker, J.; Cebon, J.; Molloy, M.P. Phosphoproteomic Analysis of Cell-Based Resistance to BRAF Inhibitor Therapy in Melanoma. *Front. Oncol.* **2015**, *5*, 95. [CrossRef]

160. Ravi, R.; Noonan, K.A.; Pham, V.; Bedi, R.; Zhavoronkov, A.; Ozerov, I.V.; Makarev, E.; Artemov, V.A.; Wysocki, P.T.; Mehra, R.; et al. Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFbeta enhance the efficacy of cancer immunotherapy. *Nat. Commun.* **2018**, *9*, 741. [CrossRef]

161. Caporali, S.; Amaro, A.; Levati, L.; Alvino, E.; Lacal, P.M.; Mastroeni, S.; Ruffini, F.; Bonmassar, L.; Antonini Cappellini, G.C.; Felli, N.; et al. miR-126-3p down-regulation contributes to dabrafenib acquired resistance in melanoma by up-regulating ADAM9 and VEGF-A. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 272. [CrossRef]

162. Lee, S.C.; Min, H.Y.; Jung, H.J.; Park, K.H.; Hyun, S.Y.; Cho, J.; Woo, J.K.; Kwon, S.J.; Lee, H.J.; Johnson, F.M.; et al. Essential role of insulin-like growth factor 2 in resistance to histone deacetylase inhibitors. *Oncogene* **2016**, *35*, 5515–5526. [CrossRef] [PubMed]

163. Wang, Q.; Wu, X. Primary and acquired resistance to PD-1/PD-L1 blockade in cancer treatment. *Int. Immunopharmacol.* **2017**, *46*, 210–219. [CrossRef] [PubMed]

164. Li, H.; Li, C.W.; Li, X.; Ding, Q.; Guo, L.; Liu, S.; Liu, C.; Lai, C.C.; Hsu, J.M.; Dong, Q.; et al. MET Inhibitors Promote Liver Tumor Evasion of the Immune Response by Stabilizing PDL1. *Gastroenterology* **2019**, *156*, 1849–1861. [CrossRef] [PubMed]

165. Wilson, T.R.; Fridlyand, J.; Yan, Y.; Penuel, E.; Burton, L.; Chan, E.; Peng, J.; Lin, E.; Wang, Y.; Sosman, J.; et al. Widespread potential for growth-factor-driven resistance to anticancer kinase inhibitors. *Nature* **2012**, *487*, 505–509. [CrossRef]

166. Tominaga, K.; Shimamura, T.; Kimura, N.; Murayama, T.; Matsubara, D.; Kanauchi, H.; Niida, A.; Shimizu, S.; Nishioka, K.; Tsuji, E.I.; et al. Addiction to the IGF2-ID1-IGF2 circuit for maintenance of the breast cancer stem-like cells. *Oncogene* **2016**, *36*, 1276–1286. [CrossRef]

167. Zhao, X.; Liu, X.; Wang, G.; Wen, X.; Zhang, X.; Hoffman, A.R.; Li, W.; Hu, J.F.; Cui, J. Loss of insulin-like growth factor II imprinting is a hallmark associated with enhanced chemo/radiotherapy resistance in cancer stem cells. *Oncotarget* **2016**, *6*, 22191–22205. [CrossRef]

168. Xu, W.W.; Li, B.; Zhao, J.F.; Yang, J.G.; Li, J.Q.; Tsao, S.W.; He, Q.Y.; Cheung, A.L.M. IGF2 induces CD133 expression in esophageal cancer cells to promote cancer stemness. *Cancer Lett.* **2018**, *425*, 88–100. [CrossRef]

169. Benabou, E.; Salame, Z.; Wendum, D.; Lequoy, M.; Tahraoui, S.; Merabtene, F.; Chretien, Y.; Scatton, O.; Rosmorduc, O.; Fouassier, L.; et al. Insulin receptor isoform A favors tumor progression in human hepatocellular carcinoma by increasing stem/progenitor cell features. *Cancer Lett.* **2019**, *450*, 155–168. [CrossRef]

170. Kimura, G.; Kasuya, J.; Giannini, S.; Honda, Y.; Mohan, S.; Kawachi, M.; Akimoto, M.; Fujita-Yamaguchi, Y. Insulin-like growth factor (IGF) system components in human prostatic cancer cell-lines: LNCaP, DU145, and PC-3 cells. *Int. J. Urol.* **1996**, *3*, 39–46. [CrossRef]

171. Sciacca, L.; Mineo, R.; Pandini, G.; Murabito, A.; Vigneri, R.; Belfiore, A. In IGF-I receptor-deficient leiomyosarcoma cells autocrine IGF-II induces cell invasion and protection from apoptosis via the insulin receptor isoform A. *Oncogene* **2002**, *21*, 8240–8250. [CrossRef]

172. Yang, L.; Li, J.; Ran, L.; Pan, F.; Zhao, X.; Ding, Z.; Chen, Y.; Peng, Q.; Liang, H. Phosphorylated insulin-like growth factor 1 receptor is implicated in resistance to the cytostatic effect of gefitinib in colorectal cancer cells. *J. Gastrointest. Surg.* **2011**, *15*, 942–957. [CrossRef] [PubMed]

173. Greenall, S.A.; Donoghue, J.; Johns, T.G.; Adams, T.E. Differential Sensitivity of Human Hepatocellular Carcinoma Xenografts to an IGF-II Neutralizing Antibody May Involve Activated STAT3. *Transl. Oncol.* **2018**, *11*, 971–978. [CrossRef] [PubMed]

174. Alley, E.W.; Lopez, J.; Santoro, A.; Morosky, A.; Saraf, S.; Piperdi, B.; van Brummelen, E. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): Preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol.* **2017**, *18*, 623–630. [CrossRef]

175. Guazzelli, A.; Bakker, E.; Krstic-Demonacos, M.; Lisanti, M.P.; Sotgia, F.; Mutti, L. Anti-CTLA-4 therapy for malignant mesothelioma. *Immunotherapy* **2017**, *9*, 273–280. [CrossRef] [PubMed]

176. Tazzari, M.; Brich, S.; Tuccitto, A.; Bozzi, F.; Beretta, V.; Spagnuolo, R.D.; Negri, T.; Stacchiotti, S.; Deraco, M.; Baratti, D.; et al. Complex Immune Contextures Characterise Malignant Peritoneal Mesothelioma: Loss of Adaptive Immunological Signature in the More Aggressive Histological Types. *J. Immunol. Res.* **2018**, *2018*, 5804230. [CrossRef]

177. Omuro, A.; Vlahovic, G.; Lim, M.; Sahebjam, S.; Baehring, J.; Cloughesy, T.; Voloschin, A.; Ramkissoon, S.H.; Ligon, K.L.; Latek, R.; et al. Nivolumab with or without ipilimumab in patients with recurrent glioblastoma: Results from exploratory phase I cohorts of CheckMate 143. *Neuro-Oncology* **2018**, *20*, 674–686. [CrossRef] [PubMed]

178. Majd, N.; de Groot, J. Challenges and strategies for successful clinical development of immune checkpoint inhibitors in glioblastoma. *Expert Opin. Pharmacother.* **2019**, *13*, 1609–1624. [CrossRef] [PubMed]

179. Royal, R.E.; Levy, C.; Turner, K.; Mathur, A.; Hughes, M.; Kammula, U.S.; Sherry, R.M.; Topalian, S.L.; Yang, J.C.; Lowy, I.; et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J. Immunother.* **2010**, *33*, 828–833. [CrossRef]

180. Aglietta, M.; Barone, C.; Sawyer, M.B.; Moore, M.J.; Miller, W.H., Jr.; Bagala, C.; Colombi, F.; Cagnazzo, C.; Gioeni, L.; Wang, E.; et al. A phase I dose escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. *Ann. Oncol.* **2014**, *25*, 1750–1755. [CrossRef]

181. Huang, F.; Chang, H.; Greer, A.; Hillerman, S.; Reeves, K.A.; Hurlburt, W.; Cogswell, J.; Patel, D.; Qi, Z.; Fairchild, C.; et al. IRS2 copy number gain, KRAS and BRAF mutation status as predictive biomarkers for response to the IGF-1R/IR inhibitor BMS-754807 in colorectal cancer cell lines. *Mol. Cancer Ther.* **2015**, *14*, 620–630. [CrossRef]

182. Jiang, X.; Zhou, J.; Giobbie-Hurder, A.; Wargo, J.; Hodi, F.S. The activation of MAPK in melanoma cells resistant to BRAF inhibition promotes PD-L1 expression that is reversible by MEK and PI3K inhibition. *Clin. Cancer Res.* **2013**, *19*, 598–609. [CrossRef] [PubMed]