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Review

# Ewing sarcoma: The clinical relevance of the insulin-like growth factor 1 and the poly-ADP-ribose-polymerase pathway



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## KEYWORDS

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**Abstract Background:** In the last three decades the outcome for patients with localised Ewing sarcoma (ES) has improved significantly since the introduction of multimodality primary treatment. However, for patients with (extra-) pulmonary metastatic and/or non-resectable relapsed disease the outcome remains poor and new treatment options are urgently needed. Currently the insulin-like growth factor 1 receptor (IGF-1R) pathway and the poly-ADP(adenosinediphosphate)-ribose-polymerase (PARP) pathway are being investigated for potential targeted therapies.

**IGF-1R:** The IGF-1R pathway is known to be deregulated by the *EWSRI-FLII* translocation which makes it a potential target for therapy. Clinical trials have been reported in which only ES patients were treated with an IGF-1R inhibitor, either as single agent or in combination. In total 291 ES patients were included in these trials, in which two (0.7%) complete responses, 32 (11%) partial responses of which some durable, and 61 (21%) stable diseases were observed.

**PARP:** In the presence of a PARP inhibitor DNA strand breaks cannot be efficiently repaired, leading to cell death. The first phase II trial with ES patients was recently published and showed no clinical responses, which may have been due to the drug being non-effective as a single agent.

**Discussion:** The IGF-1R pathway is an interesting target for ES and should be explored further, as biomarkers to select patients that might benefit from treatment are lacking. PARP

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inhibitors as single agent have so far failed to show improvement in outcome. Future directions include dual insulin receptor/IGF-1R blockade with linsitinib as well as chemotherapy –PARP combinations. Both therapeutic strategies are currently being explored.

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## 1. Background

Ewing sarcoma (ES) is the third most common primary bone sarcoma after osteosarcoma and chondrosarcoma. However it is still rare with an overall incidence of 2.9 new cases/1,000,000 every year in the United States [1]. In children and adolescents ES is mainly localised in bone, with a peak incidence at 15 years of age [2]. In adults, ES localises more frequently primarily in soft tissue or organs. The tumour is diagnostically defined by a reciprocal translocation, causing a fusion of the *EWSRI*-gene on chromosome 22 with a member of the ETS (E26 transformation-specific) family of transcription factors [3]. The most common translocation (85%) is the t(11;22)(q24;q12), fusing *EWSRI* to *FLII*. Other rare ETS and non-ETS fusion partners have been described, and so far it is unclear whether the latter should be considered a separate entity [3]. The *EWSRI*-ETS translocation type does not influence the outcome or reaction on chemotherapy [4,5]. Proven genetic prognostic factors are TP53 mutations [6], *CDKN2A* deletions [7], 1q gain [8] and *Stag2* mutations [9–12].

With current multimodal treatment options, including surgery, conventional chemotherapy and radiotherapy, the 5-year survival for localised disease is 60%. However, for patients that present with metastatic disease other than lung involvement only, the 5-year survival is below 20%. The outcome for patients with relapsed or refractory ES is even worse with a 5-year survival as low as 10% [13]. Therefore, new treatment strategies are urgently needed. Currently the insulin-like growth factor 1 receptor (IGF-1R) pathway and the poly-ADP-ribose-polymerase (PARP) pathway are being investigated for potential targeted therapies. In our opinion these two pathways represent the main area of early clinical studies in ES in the recent years deserving an in-depth review. Therefore, here we summarise current knowledge in an attempt to stimulate further treatment development for ES.

## 2. Insulin-like growth factor 1 receptor pathway in Ewing sarcoma

### 2.1. Insulin-like growth factor 1 receptor pathway

IGF-1R is a tyrosine kinase receptor which is 84% homologous to the insulin receptor (IR) and is widely expressed in human tissues [14]. Binding of the ligands

(IGF-1 and IGF-2) to the IGF-1R or the IR induces receptor dimerization, resulting in trans-autophosphorylation of the receptors (Fig. 1). This receptor phosphorylation recruits the downstream signalling proteins IR substrate (IRS) 1, 2 and 4 and the Src homology 2 domain containing transforming proteins to the cell membrane [14]. The subsequent phosphorylation of these proteins induces the activation of the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinases (MAPK) pathways resulting in stimulation of cellular proliferation, cell motility and inhibition of apoptosis [14]. IGF-1 and IGF-2 are mainly produced by the liver in response to the presence of growth hormone and are found in the circulation bound to the IGF binding proteins (IGFBP1-6), which regulate their bioavailability in peripheral tissues. The bioavailability of IGF-2 is also regulated by the IGF-2R, which does not confer intracellular signalling [15]. IGFBP3 is the most abundant IGF binding protein, which forms a ternary complex with insulin-like growth factor acid-labile subunit and accounts for 80% of all IGF binding. In addition to its role in normal cellular development (foetal growth and linear growth of the skeleton and other organs), the IGF signalling pathway has been implicated in malignant transformation and disease progression [16–18]. Interestingly, patients with congenital deficiency of IGF-1 seem protected from the development of malignancies [19] and cells with a dominant negative mutation in IGF-1R fail to undergo malignant transformation and *in vivo* tumourigenesis [20]. Furthermore, many tumours and cell lines have increased expression of IGF-1 or IGF-1R [21]. In addition, numerous studies have shown that higher plasma concentrations of IGF-1 are associated with increased cancer risk, in particular for breast, prostate and colon cancer [22–31].

### 2.2. Insulin-like growth factor 1 receptor pathway activity and its inhibition in Ewing sarcoma: preclinical data

Interestingly, the peak incidence of primary bone ES correlates with the increased levels of the IGF ligands in puberty. In 1990 it was already shown that IGF1 is expressed in ES carrying a t(11;22) translocation and that blocking the IGF-1 loop inhibits cell growth [32]. Subsequent studies using ES cell lines confirmed these findings [33]. In 1997 a study using fibroblast cell lines from an IGF-1R knock-out mouse and a wild type

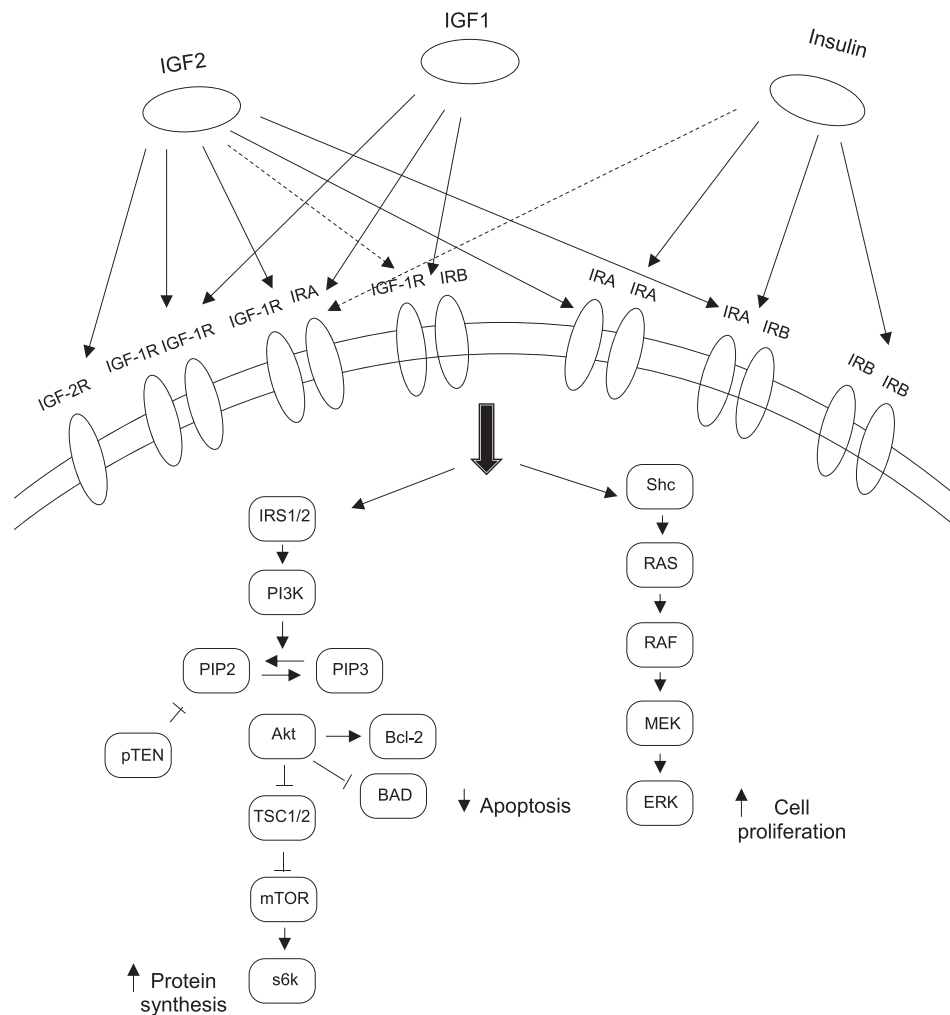


Fig. 1. The IGF pathway showing the stream molecules as well as the parallel activation route of the insulin pathway. Activation of the IGF or IR receptor by IGF-1, IGF-2 or insulin activates the PI3K-Akt pathway which can upregulate *Bcl2* and downregulate *BAD* resulting in apoptosis and it can downregulate the mTOR pathway resulting in increased protein synthesis. It can also activate the *RAS/RAF/MEK/ERK* pathway resulting in increased cell proliferation. IGF: insulin-like growth; IR: insulin receptor; *BAD*: Bcl-2 associated death promotor; *Bcl-2*: B-cell lymphoma 2; mTOR: mammalian target of rapamycin.

mouse was described in which the altered expression of IGF-1R was studied in the presence of the *EWSR1-FLII* fusion [34]. It was shown that the wild type cells that contained the fusion protein had a greater degree of ligand-stimulated IRS-1 phosphorylation, thus giving evidence that altered IGF-1R signalling by expression of the *EWSR1-FLII* fusion protein is required to transform fibroblasts. IGF-1R expression is often positive in ES cell lines and in patient tumour tissue [33]. Higher expression levels of IGF-1R, IR and IGF-1 mRNAs were significantly correlated with better clinical outcome in ES, in which high levels of circulating IGF-1 were associated with lower risk of disease progression and death [35]. Interestingly, it has been described that the *EWSR1-FLII* fusion protein can directly bind the IGF1R promoter, thereby repressing its activity [36] (Fig. 2).

Other fusions in addition to *EWSR1-FLII* have been described in ES including *EWSR1-ERG* and *FUS-ERG*.

When the three different fusions were introduced into mouse progenitor cells the expression profiles differed, but all three fusions were able to activate the IGF-1 promoter and induced IGF-1 expression, while *FLII* or *ERG* alone was not able to do this [37]. In ES mouse xenografts, a selective IGF-1R kinase inhibitor (NVP-AEW541) decreased migration, metastases, vasculogenesis and angiogenesis [38]. Side effects included significant weight loss at the start of the treatment and high blood glucose levels.

### 2.3. Combined inhibition of insulin-like growth factor 1 receptor and other pathways

IGF-1R inhibitors have been combined with other anti-tumour drugs in ES. For example, an inhibitor of endocytosis was studied in combination with an IGF-1R tyrosine kinase inhibitor. It was shown that blockade of receptor internalisation inhibited the phosphorylation of

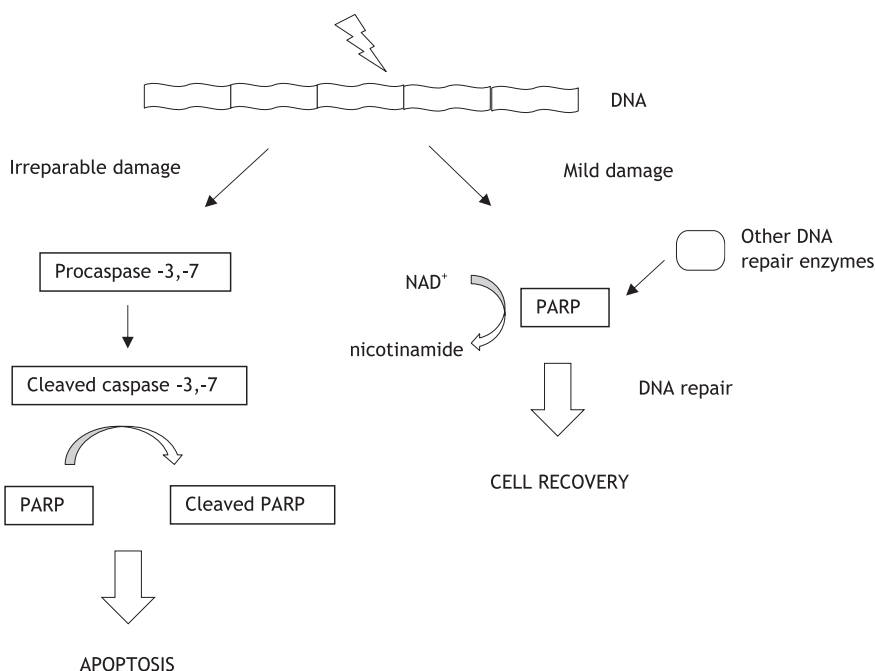


Fig. 2. The PARP pathway showing activation of the apoptosis route. By mild DNA damage PARP is activated and with the aid of other DNA repair enzymes  $NAD^+$  is transformed in nicotinamide and the cell recovers. If there is irreparable DNA damage, the procaspase-3 and -7 are cleaved which subsequently cleaves PARP, resulting in apoptosis. PARP: poly-ADP-ribose-polymerase;  $NAD^+$ : nicotinamide adenine dinucleotide.

Akt and MAPK, reduced proliferation rate and increased apoptosis. Strikingly, this effect was greatly enhanced by combining the endocytosis inhibitor with a tyrosine kinase inhibitor, thereby identifying a new therapeutic approach for IGF-1R dependent neoplasms [39].

Very recently, promising results were achieved *in vitro* and *in vivo* by combining IGF-1R inhibition with the DNA minor groove binding agent trabectedin [40]. Trabectedin was shown to increase IGF-1R expression by improving the binding of *ESWRI-FLII* to the IGF-1R promoter. Inhibition of IGF-1R, either by the specific AVE1642 human antibody or by the dual IGF-1R/IR inhibitor OSI-906 (linsitinib) greatly potentiated the efficacy of trabectedin in ES cell lines as well as in ES xenografts providing rationale for the combination treatment.

The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase which is critical in many cellular processes such as cell proliferation and survival [41]. Aberrant mTOR signalling is known to conduct tumour cell survival and is therefore an interesting target for therapy [42–44]. Because mTOR plays an important role in the PI3K/Akt pathway downstream of the IGF-1R receptor, inducing cell proliferation by phosphorylation of the s6k protein, [45], inhibition of mTOR could be a promising therapeutic option in tumours with upregulated IGF-1R signalling [46]. However, tumour cells *in vitro* and *in vivo* treated with mTOR inhibitor as a monotherapy can develop

resistance, probably due to the activation of a feedback loop after blocking of the mTOR pathway, resulting in upregulated Akt phosphorylation via an IGF-1R dependent mechanism [47–49]. This provides rationale for the combination of an mTOR inhibitor with an IGF-1R inhibitor to overcome resistance to either treatment as a monotherapy. Another reason for the combination treatment is that using immunohistochemistry and immunofluorescence it was found that approximately 25% of ES harbour a *PTEN* deficiency which leads to enhanced AKT activation with decreased apoptosis and increased growth, rendering cells less sensitive to IGF-1R inhibition [50]. The combination of an IGF-1R and an mTOR inhibitor may give a therapeutic benefit. *In vivo* xenograft models it has been shown that the combination gives an enhanced anti-tumour activity compared to monotherapy [51,52].

Another important player in activation of the PI3K/Akt/mTOR pathway is *ErbB3*, a tyrosine kinase receptor [53] and combined IGF-1R and *ErbB3* inhibition may result in complete blockage of the IGF pathway thereby inducing apoptosis. Recently, MM-141, an IGF-1R and *ErbB3* bispecific antibody was developed and the first preclinical results were published [54]. *ErbB3* activation was proven to be an escape mechanism for different solid tumour cells, including ES cells, treated with IGF-1R inhibitors. MM-141 has demonstrated to decrease the levels of IGF-1R and *ErbB3* *in vivo*, thereby providing a strong clinical rationale for

further development of IGF-1R and *ErbB3* antibodies. Currently, a phase I study is enrolling patients with solid tumours who are being treated with MM-141 as a monotherapy and a phase II study is recruiting patients with metastatic pancreatic cancer who are being treated with MM-141 combined with paclitaxel and gemcitabine (NCT01733004 and NCT02399137).

#### 2.4. Clinical trials with insulin-like growth factor 1 receptor inhibition in Ewing sarcoma

Recently a phase II trial was published treating patient with recurrent or refractory bone or soft tissue sarcomas with the IGF-1R monoclonal antibody (MoAb) R1507 [55]. This study concluded that the IGF-1R antibody R1507 has a favourable toxicity profile but limited activity in bone and soft tissue sarcomas. A subgroup of the enrolled patients did have a durable response and further studies are needed.

Several clinical trials have been conducted to evaluate the efficacy of IGF-1R inhibition specific in ES patients (Table 1). In six trials different IGF-1R antibodies were tested as a monotherapy, including two trials with figitumumab<sup>®</sup> [56,57], two trials with cixutumumab<sup>®</sup> [58,59], one trial with R1507 [60] and one with ganitumumab<sup>®</sup> [61]. A total of 311 patients were included in these trials with two (0.6%) complete responses (CRs), 31 (9.9%) partial responses (PRs) and 66 (21%) patients with stable disease (SD). Some of these responses were durable up to more than 2 years. These results and the results from other studies show that these antibodies are well tolerated and require almost no dose reductions, with the exception of ganitumumab<sup>®</sup> in which all patients had an adverse event reported and 45% of the patients required a dose reduction.

Sarcoma patients were treated with cixutumumab<sup>®</sup>, an IGF-1R MoAb, combined with the mTOR inhibitor temsirolimus<sup>®</sup> [62]. The study was divided into two cohorts. The first cohort received cixutumumab<sup>®</sup> 6 mg/kg

weekly intravenously and temsirolimus<sup>®</sup> 25 mg intravenously weekly. In the second cohort patients received cixutumumab<sup>®</sup> 6 mg/kg intravenously weekly and temsirolimus<sup>®</sup> 37.5 mg intravenously weekly. All 17 ES patients were enrolled in the first cohort. In total, seven ES patients (35%) had an objective response, being five minor responses and two CR. In one of these patients the response lasted more than 27 months although the patient had previously developed resistance to another IGF-1R inhibitor. The treatment was well tolerated and most common adverse events were thrombocytopenia, mucositis, hypercholesterolaemia, hypertriglyceridaemia and hyperglycaemia. Three patients required dose reductions but they were re-escalated without recurrence of toxicity.

### 3. Poly-ADP-ribose-polymerase pathway in Ewing sarcoma

#### 3.1. Poly-ADP-ribose-polymerase pathway

PARPs are a family of proteins which are activated upon DNA damage [63]. They detect single strand breaks and recruit the enzymatic DNA repair machinery. Mostly PARP-1, and to a lesser extent PARP-2, are responsible for this mechanism [64]. If PARP is inactivated by caspase cleavage, cells are more prone to go into apoptosis upon DNA damage. PARP inhibitors seem a promising therapeutic approach for tumours harbouring a germline *BRCA1/2* mutation, including ovarian and breast cancer [65,66].

#### 3.2. Poly-ADP-ribose-polymerase inhibition in Ewing sarcoma

The sensitivity of ES cells to PARP inhibitors was discovered when several hundred cancer cell lines were screened for drug-sensitivity [67]. Moreover, *EWSRI-FLII* positive ES cell lines and xenografts were shown to

Table 1

Trials conducted with an IGF-1R inhibitor enrolling exclusively ES patients showing the name of the author, the phase of the study, the drug tested, the dosage of the tested drugs, number of patients included, the response rate and the biomarkers tested.

Author	Phase	Drug	Dose	Nb of ES pts	Response for ES pts	Biomarkers tested
Juergens [56]	II	Figitumumab <sup>®</sup>	30 mg/kg/4 week	107	15 PR, 25 SD	Free IGF-I levels, total IGF-I level
Olmos [57]	Expansion cohort	Figitumumab <sup>®</sup>	20 mg/kg/4 week	16	1 CR, 1 PR, 6 SD	None
Malempati [58]	II	Cixutumumab <sup>®</sup>	6 mg/kg/week and 9 mg/kg/week	36	3 PR, 5 SD	IGF-I level, IGF-II level, IGF-IR level
Schöffski [59]	II	Cixutumumab <sup>®</sup>	10 mg/kg/2 week	18	1 PR, 5 SD	None
Pappo [60]	II	R1507	9 mg/kg/w	109	1 CR, 10 PR, 18 SD	Total IGF-I level
Tap [61]	II	R1507	27 mg/kg/3 week	6		
Naing [62]	II	Ganitumumab <sup>®</sup>	12 mg/kg/3 week	19	1 PR, 7 SD	IGF-I level
	II	Cixutumumab <sup>®</sup> and Temsirolimus <sup>®</sup>	6 mg/kg/week and 25 mg/kg/week	17	2 CR, 5 MR	None

CR = complete response ES = Ewing sarcoma; MR = minor response; Nb = number; PR = partial response; pts = patients; SD = stable disease; IGF: insulin-like growth.

be highly sensitive to the PARP-1 inhibitor olaparib, especially in comparison to osteosarcoma and rhabdomyosarcoma cell lines without the ETS rearrangement [68]. More specifically, the *EWSR1-FLI1* and the *EWSR1-ERG* fusion genes were shown to interact with PARP-1. Strikingly, even cell lines from heavily pre-treated and relapsed patients were extremely sensitive to olaparib. Although treatment with olaparib accentuated DNA damage, this did not have an effect on short-term cell viability. In 2012, an additional mode of action of PARP inhibitors has been found, in which trapped PARP-DNA complexes are highly toxic to cells because of DNA replication blockade [69]. It is shown that the trapped PARP-DNA complexes are even more toxic to cells than the accumulating DNA damage in the presence of PARP inhibitors. The combination of PARP inhibitors and cytotoxic drugs was tested in *in vitro* and *in vivo* assays [70]. Interestingly, synergy was most notable in medulloblastoma and ES cell lines. In ES xenograft models the maximum tolerated dose of olaparib, cyclophosphamide and topotecan was determined and used in a combination treatment schedule [70]. With the single treatment of olaparib 88% of PARP-1 inhibition was detected, which increased to 100% when combined with cyclophosphamide and topotecan. A synergistic effect was found between olaparib and irinotecan with two to three times more growth inhibition than that with single treatment. Talazoparib, another PARP inhibitor, showed a synergistic effect *in vitro* when combined with temozolomide in ES cell lines [71]. The PARP inhibitor olaparib was combined with trabectedin and showed a synergistic effect in several ES cell lines and an increase in apoptotic rate [72]. When the combination was tested in a xenograft model a reduction in tumour growth was seen. The combination of PARP-1 inhibition with radiotherapy was also investigated [73]. It was found that after low levels of radiation, PARP-1 activation was significantly increased in ES cell lines and only mild in non-ES cells. The combination treatment of olaparib and radiotherapy in ES cells leads to a synergistic decrease in proliferation and colony formation. Moreover, in xenograft models the combination treatment stopped tumour growth, emphasising the potential as a new therapeutic approach for ES [73].

### 3.3. Clinical trials with poly-ADP-ribose-polymerase inhibitors in Ewing sarcoma

Since the discovery of PARP inhibitors as a therapeutic option for ES patients in 2012, only one clinical trial including ES patients has been published [74].

This phase II trial included ES patients with recurrent/metastatic disease who were not responding to previous therapy. A total of 12 patients were treated with olaparib 400 mg twice a day, administered orally. All patients were evaluated for response, and no CR or

PR was seen. However, in four patients SD was achieved ranging from 10.9 to 18.4 weeks. The median progression free survival was only 5.7 weeks. The drug was well tolerated with two grade 3 toxicities (anaemia and thrombocytopenia).

## 4. Discussion

Preclinical studies have revealed the IGF-1R and PARP pathway as promising new targets for ES and these observations have led to several clinical studies.

Regarding the IGF-1R pathway five pharmaceutical companies went in parallel to the niche indication ES for rapid approval in an orphan disease. Despite some durable responses the overall results of these studies were disappointing and as a result all companies stopped further development of IGF-1R pathway inhibitors for ES [75]. We think that this decision was made too fast and that IGF-1R antibodies can work in ES, but they should be tested in the right patient population. To find the right patient population it is very important to understand the biological rationale behind this treatment so that specific patients' schedules and doses can be selected to reach positive results for the individual patients. Good non-heterogeneous biomarkers are needed to stratify patients to assess the right treatment schedule and to determine response during treatment [76,77]. In preclinical studies the resistance mechanism for ES to IGF-1R has been studied. Resistant cells switch from IGF-1/IGF-1R signalling to IGF-2/IR-A signalling [39,78,79]. Therefore, one could postulate that ES patients should be treated with a dual IGF-1R and IR-A inhibitor, such as linsitinib (OSI-906). The EuroSarc consortium ([www.eurosarc.eu](http://www.eurosarc.eu)) initiated the LINES (eurosarc trial of LINSitinib in advanced Ewing Sarcoma) study (ISRCTN 94236001), which is currently the only remaining open study for ES patients with a drug targeting the IGF-1R receptor. This is a phase II study in which refractory and/or relapsed ES patients are being treated with the dual IGF-1R and IR inhibitor linsitinib in a single arm Bayesian design. Patients will undergo mandatory tumour biopsies during the treatment for translational research and this will be compared to pre-treatment material to monitor response at the molecular level and to look for possible biomarkers. Pharmacokinetic assays will be conducted testing for IGF-1, IGF-2, IGF1BP3 and insulin levels on blood samples. The tumour core biopsies will be used to test for phosphoproteome/kinase assays of pre-treatment kinome IGF-1R pathway activation. Quantitative immunoassays for IGF-1R, IRS1, pS6, *FOXO* and *EGFR1* will be performed using multi-spectral confocal image segmentation and random forest analysis (LINES protocol Annex 1). This study will hopefully answer the question why inhibition of the IGF pathway may work in some patients and not in others.

MoAbs targeting the tumorigenic pathways, such as IGF-1R may theoretically have a dual working mechanism. On the one hand they block pathways having an anti-tumour working mechanism, and on the other hand they may also stimulate an immunological response inducing a reaction of the patients own immune system against the tumour cells [80]. Natural killer (NK) cells were found to play an important role in this antibody-dependent cell-mediated cytotoxicity (ADCC) [81]. NK cells can be activated by Fc-receptors (FcR) bound to the target cells by antibodies, thereby being able to lyse the target cells and shred cytokines to activate the adaptive immune system. Several studies show that patients have a different FcR genotype and those with a higher FcR affinity respond better to MoAbs. This finding can also be used as a biomarker and to select patients for the treatment with IGF-1R antibodies [82–86]. This dual working mechanism provides a theoretical advantage of antibody treatment compared to tyrosine kinase inhibitors which lack the ADCC anti-tumour mechanism.

Regarding the PARP inhibitors, they have been developed more recently and have been tested with various successes in other tumour types such as breast, lung, prostate, fallopian tube and pancreatic cancer, glioblastoma and haematologic malignancies. So far, only the results of one trial with ES patients were presented and results of monotherapy treatment in this study were unsatisfactory. Different theories about the lack of treatment effect with PARP monotherapy were suggested by the authors of this study, e.g. secondary epigenomic alterations that may render the PARP pathway insignificant [74]. However, the exact mechanism still has to be found. Preclinical models suggest that PARP inhibition may show better results in combination with chemotherapy or radiotherapy [70,73,87]. A phase I combination study of the PARP inhibitor olaparib with temozolomide in ES is open for recruitment (NCT01858168) and a phase I study combining olaparib with niraparib, another PARP inhibitor, and temozolomide, an alkylating agent, is also enrolling patients with incurable ES (NCT02044120). To evaluate a possible effect of PARP inhibition as monotherapy versus combined therapy, more clinical studies must be conducted. Measuring the PARP pathway down regulation by recording levels of the PARP pathway caspases before and after the drug exposure in tumour biopsies in different treatment conditions will help to find the optimal dosage and combination schedule.

Biomarkers need to be tested in preclinical and clinical studies to identify patient populations with a higher likelihood to respond to certain treatment schedules. Hereby more personalised medicine can be conducted with hopefully better outcome results. IGF-1 was found to be a negative prognostic marker in different types of carcinoma [88,89]. ES patients with elevated levels of free or total IGF-1 before the treatment had a better

overall survival [56]. Another protein which has been found to be overexpressed in various tumour types, like breast, head and neck, colon, pancreas and non-small cell lung cancer, can be used as a biomarker to predict response is *Rad51* [90–97]. *Rad51* functions as a DNA double strand break repair protein thereby inducing stabilisation of the genome. Overexpression of *Rad51* has been found to result in reduced proliferation and a more instable genome [98,99]. Preclinical testing has to be conducted to determine if these biomarkers are also usable in ES. Hopefully a lesson was learnt from the problems which rose with the development of IGF-1R antibodies in clinical trials, so far the development of PARP inhibitors seems to go more structured.

In conclusion, both pathways are interesting potential targets for ES as they either hypothetically interact with the *EWSRI-FLII* or *EWSRI-ERG* fusion product and/or show promising (pre)clinical data. Therapeutic strategies should therefore definitely be explored further, and we will need to better understand which patients are responding and as a result of which underlying molecular mechanism. Other ways forward may include dual blockade such as with linsitinib and conventional chemotherapy or radiotherapy combined with PARP inhibitors. Both strategies are currently being explored clinically.

#### Conflict of interest statement

None declared.

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