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Table of Contents

1 Overview of MEDI-573 7

1.1 Regulatory History 7

1.1.1 United States 7

1.1.2 Europe 7

1.1.3 Japan 7

2 Disease Background 8

2.1 Insulin-like Growth Factor 8

2.2 Sarcoma 10

2.3 Compounds Targeting the IGF Axis 13

2.4 Treatment Options for Sarcoma 17

3 Nonclinical Data Supporting Clinical Studies 21

4 Clinical Experience in Adults 22

4.1 Overview of Clinical Studies 22

4.1.1 Advanced Solid Tumors (Study MI-CP184 and Study D-5621C00006). 22

4.1.2 Metastatic Breast Cancer (Study MEDI-573-1030) 23

4.1.3 Advanced Hepatocellular Carcinoma (Study MEDI-573-1028) 23

4.2 Clinical Data Summary 23

4.2.1 Advanced Solid Tumors (Study MI-CP184) 24

5 Development Plan in Patients With Sarcoma 25

6 Summary and Considerations for MEDI-573 Pediatric Development in Sarcoma 25

7 References 27

List of In-text Tables

Table 2.3-1 Activity of IGF-targeting Monoclonal Antibodies Administered as Monotherapy to Patients with Various Sarcomas 15

Table 2.4-1 Activity of Current Treatments for Soft Tissue and Bone Sarcomas.. 19

List of In-text Figures

Figure 2.1-1 IGF Signaling 8

Figure 2.2-1 Incidence Rates of Sarcoma Subtypes..... 11

Figure 2.2-2 Metastatic vs. Non-Metastatic Distribution of Incident Ewing's Sarcoma Cases (Age 0-21 and 21+) 12

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AI	aromatase inhibitor
Akt	protein kinase B
ALT	alanine aminotransferase
AMG 479	ganitumab
AST	aspartate aminotransferase
C32	clone 32 cell line (which ectopically overexpresses human insulin-like growth factor-II and human insulin-like growth factor 1 receptor in a NIH3T3 cell line)
CP-751,871	figitumumab
CR	complete response
EFS	event-free survival
ESFT	Ewing's sarcoma family of tumors
EU	European Union
FTIH	first-time-in-human
HCC	hepatocellular carcinoma
HER2−	human epidermal growth factor receptor 2 negative
hIGF-I, -II	human insulin-like growth factor -I, -II
hIGF-1R	human insulin-like growth factor 1 receptor
IGF	insulin-like growth factor
IGFBP	IGF binding protein
IGF-1R	insulin-like growth factor 1 receptor
IgG2λ	immunoglobulin G lambda
IM	immunogenicity
IND	Investigational New Drug
IR	insulin receptor
IR-A	insulin receptor A isoform
IR-B	insulin receptor B isoform
IRS-1	insulin receptor substrate 1
IV	intravenous
MAb	monoclonal antibody
MAPK	mitogen-activated protein kinase

Abbreviation	Definition
MBC	metastatic breast cancer
mRNA	messenger ribonucleic acid
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PD	progressive disease
PNET	primitive neuroectodermal tumor
PR	partial response
Q3Wk	once every 3 weeks
QWk	once every week
SAE	serious adverse event
SD	stable disease
STS	soft tissue sarcoma
TKI	tyrosine kinase inhibitor
TTP	time to progression

1 Overview of MEDI-573

MedImmune is pursuing the development of MEDI-573 as a potential anticancer therapy for patients with solid tumors. MEDI-573, a human immunoglobulin G2 lambda (IgG2λ) monoclonal antibody (MAb), is a dual-targeting human antibody that neutralizes the insulin-like growth factor (IGF)-I and IGF-II ligands, thus inhibiting insulin-like growth factor receptor (IGF-1R) as well as insulin receptor A isoform (IR-A) signaling pathways in a number of cancer cell lines overexpressing these receptors. MEDI-573 is the only MAb currently in clinical development that targets the IGF ligand instead of the IGF receptor.

Nonclinical studies in human cancer models suggest that MEDI-573 has the potential to achieve broad antitumor activity owing to its ability to inhibit both IGF-1R and IR-A pathways. Furthermore, MEDI-573 has the potential to achieve this without perturbing glucose homeostasis, which has been an adverse effect commonly observed with investigational agents that target IGF-1R (Atzori et al, 2009; Gualberto and Pollak, 2009; Weroha and Haluska, 2008).

1.1 Regulatory History

1.1.1 United States

An Investigational New Drug Application (IND) that was submitted to the Food and Drug Administration became active on 11 December 2008. There are 3 clinical studies ongoing under this IND.

1.1.2 Europe

MedImmune has not submitted a Pediatric Investigational Plan for MEDI-573.

1.1.3 Japan

A clinical trial is also currently ongoing in Japan under a Clinical Trial Notification that was submitted to the Pharmaceuticals and Medical Devices Agency and became active on 30 April 2011.

2 Disease Background

2.1 Insulin-like Growth Factor

Insulin-like growth factor I and IGF-II are growth factors involved in regulating cell proliferation, survival, differentiation, and transformation. Both growth factors are expressed ubiquitously and act as endocrine, paracrine, and autocrine growth factors (DeMeyts, 2004; Pollak, 2008; Tao et al, 2007; Ryan and Goss, 2008). The IGFs and insulin exhibit strong sequence similarities. The primary IGF receptor, IGF-1R, shares almost 60% homology with the insulin receptor (IR). Both IGF-1R and IR belong to the family of receptor tyrosine kinases. The IGF axis consists of ligands IGF-I and IGF-II, receptors IGF-1R and IGF-2R, and six high-affinity IGF-binding proteins (IGFBP) 1 to 6 (Figure 2.1-1). The bioavailability of IGFs is closely regulated by IGFBPs, which also act as carrier proteins and block receptor binding.

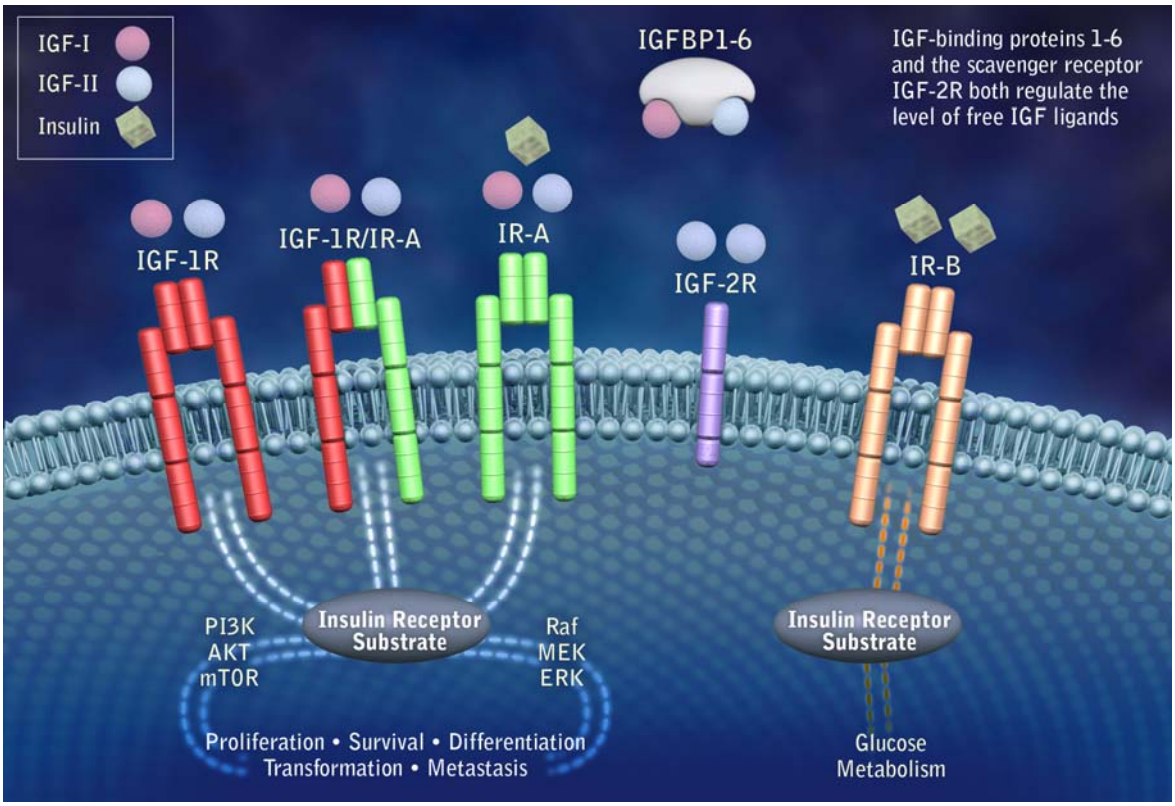

Figure 2.1-1 IGF Signaling

Two isoforms of IR, IR-A and IR-B, result from post-transcriptional alternative splicing. IR-A is a truncated version of the IR that lacks exon 11 (36 base pairs that encode 12 amino acids towards the C-terminus of the alpha subunit). IGF-II has been shown to bind IR-A with greater affinity than IGF-I. IGF-II and insulin both stimulate IR-A, which when activated by IGF-II results in mitogenic effects and increased survival, motility, and invasiveness of cancer cells (Gao et al, 2011). In contrast, IR-B is activated by insulin and is mainly responsible for maintaining glucose homeostasis.

Insulin-like growth factor-I and IGF-II exert their various actions through binding to the IGF-1R and IR-A homo- and heterodimers, activating multiple intracellular signaling cascades including the insulin receptor substrate (IRS) proteins, protein kinase B (Akt), and mitogen-activated protein kinase (MAPK) pathways (Sciacca et al, 1999; Chitnis et al, 2008; Baserga, 2009; Belfiore et al, 2009). Both IGF-1R and IR-A are involved in IGF signaling and play important roles in cancer development and progression (Frasca et al, 2008) and have been shown to protect cells from stress signals induced by cytotoxic agents, hypoxia, DNA damage, and oxidative stress (reviewed in Kurmasheva and Houghton, 2006).

The IGF pathway is commonly dysregulated in human cancers through increased expression of IGF-1R via a number of genetic alterations that lead to increased activity of transcription factors, upregulation of IGF-II due to loss of imprinting, or modified expression of the IGFBPs. High levels of circulating IGF-I are associated with an increased risk for development of several types of cancers (Renehan et al, 2004). Thus far, MedImmune's clinical program has focused on 3 solid tumors (breast, liver, and bladder cancers) in which IGF-1R, IGF-I, and/or IGF-II are upregulated.

Genetic alterations in the IGF pathway are prevalent in various types of sarcoma and the Pediatric Preclinical Testing Program Affymax database indicates high expression of IGF1R, IGF-I, or IGF-II in most Ewing's sarcoma family of tumors (ESFT), osteosarcomas, and rhabdomyosarcomas (Nationwide Children's Hospital, 2011). The ESFT secretes more IGF-I whereas rhabdomyosarcomas secrete more IGF-II (Minnitti et al, 1994; Scotlandi, 1996). IGF-1R and IGF-I are potent mediators of autocrine growth in ESFT (Scotlandi, 1996). In human osteogenic sarcoma cell lines IGF-I is highly expressed and has been shown to stimulate osteosarcoma cell growth (Kappel et al, 1994). Loss of imprinting at the IGF-II locus is detected in embryonal rhabdomyosarcoma (Zhan et al, 1994) and a genetic alteration that leads to chimeric transcription factors (PAX3-FKHR or PAX7-FKHR) leads to increased expression of IGF-1R in alveolar types of rhabdomyosarcoma (Gidding et al, 2000;

Thimmaiah et al, 2003). High levels of IGF-II messenger ribonucleic acid (mRNA) expression have been demonstrated in tumoral tissue obtained from patients with various rhabdomyosarcoma subtypes (Minniti et al, 1994) where IGF-II may play a role in the unregulated growth of these tumors. Rhabdomyosarcoma cell lines secrete IGF-II, which binds to IGF-1R, resulting in autocrine growth proliferation and increased cell motility (El-Badry et al, 1990). Conversely, ESFT patients that carry the EWS-FLI1 genetic alteration that upregulates a repressor of IGF-I signaling, IGFBP3, have an improved prognosis (de Alava et al, 2000; Prieur et al, 2004).

Given the strong disease linkage to the IGF signaling pathway, targeted therapeutic approaches that inhibit the IGF-1R receptor using MAbs have been explored in several types of sarcoma. Several MAbs have been evaluated in a panel of cell lines and demonstrated in vitro and in vivo antitumor activities in ESFT, osteosarcoma, and rhabdomyosarcoma (Kurmasheva et al, 2009; Houghton et al, 2010; Kolb et al, 2008; Kolb et al, 2010).

2.2 Sarcoma

Sarcomas are a heterogeneous group of rare tumors that arise from extraskeletal and skeletal connective tissue. Approximately 75% of sarcomas originate in soft tissue and account for an estimated 1% of all cancers diagnosed annually in the United States (US) (SEER, 2011). The rest originate in bone. The absolute number of sarcoma subtypes is debated and by some estimates may be as high as 100 (Brennan et al, 2008). This reflects the extreme heterogeneity of a group of diseases that encompasses a broad range of tumoral histologies with distinct genetic mutations, clinical features, natural histories, prognoses, and responses to applied interventions. Certain subsets of sarcoma, particularly ESFT, rhabdomyosarcoma, and osteosarcoma, occur more frequently in children, whereas other subsets, such as Kaposi's sarcoma, fibrohistiocytic tumors, and leiomyosarcoma predominantly occur in adults (SEER, 2011). Although heritable predisposition (eg, Li-Fraumeni syndrome and familial adenomatous polyposis), acquired genetic mutations (eg, p53), radiation exposure, chemotherapy, certain viruses (eg, HIV, human herpesvirus 8), and other insults have been implicated in the pathogenesis of this disease, in most cases the etiology is unclear (Brennan et al, 2008).

The ESFT consists of highly aggressive tumors of neuroectodermal origin that primarily affect children and young adults up to 40 years of age, with most tumors occurring in the second decade of life (Figure 2.2-1). After osteosarcoma, the ESFT is the second most

common bone tumor of childhood and adolescence (SEER, 2011). Although they can arise in bone or soft tissue, most ESFTs affect long, flat bones. Fewer than 500 new cases are reported annually in the US, where an estimated 30% of patients present with metastatic disease (Figure 2.2-2). Metastatic disease at the time of diagnosis is a key adverse prognostic factor and in one study, 5-year relapse free survival was shown to be 22% in patients with metastases at diagnosis vs 55% in those without ($p < 0.0001$) (Cotterill et al, 2000). As discussed in Section 2.1, IGF-1R and IGF-I are both upregulated in patients with ESFT and data from both nonclinical and clinical studies suggest that IGF-1R-targeting agents may elicit a clinically meaningful response in this sarcoma subset (Zha et al, 2009; Zha and Lackner, 2010; Gualberto and Pollak, 2009; Carden et al, 2009).

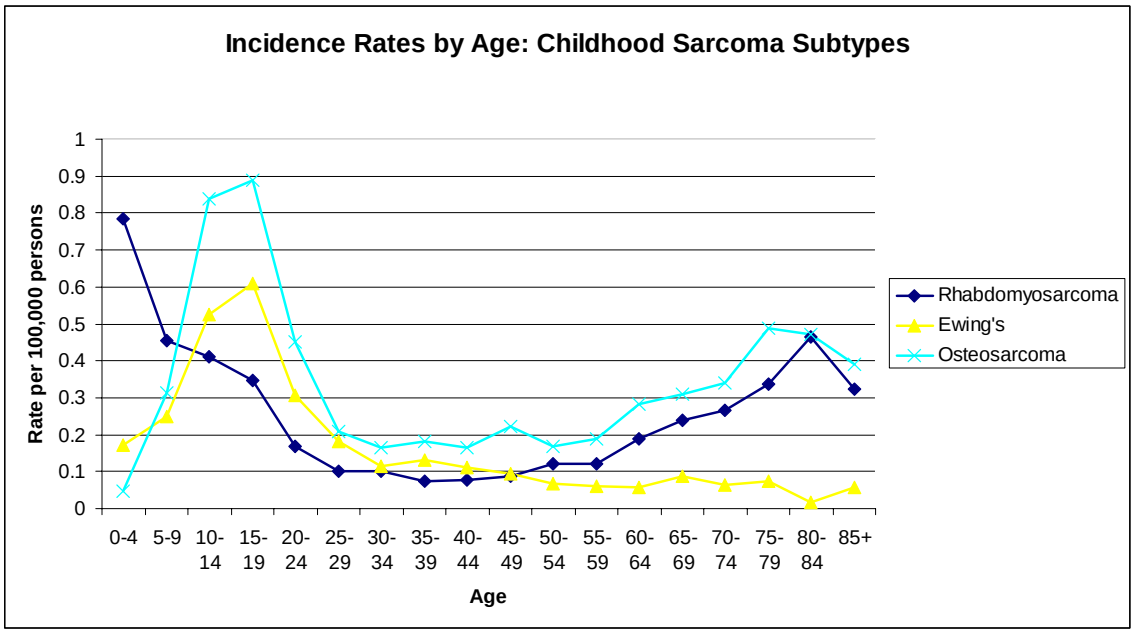

Figure 2.2-1 Incidence Rates of Sarcoma Subtypes

Source: Surveillance Research Program, 2011; SEER, 2011

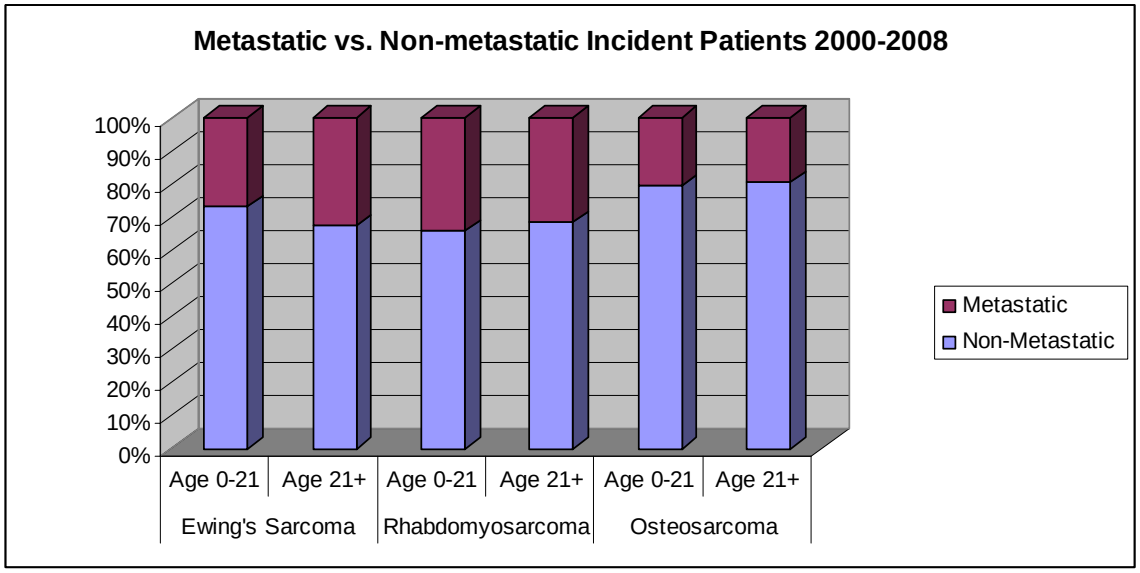

Figure 2.2-2 Metastatic vs. Non-Metastatic Distribution of Incident Ewing's Sarcoma Cases (Age 0-21 and 21+)

Source: Surveillance Research Program, 2011; SEER, 2011

Osteosarcoma, the most common primary bone tumor in children and adolescents, accounts for approximately 4% of pediatric cancers and typically occurs in long bones of the extremities proximal to the metaphyseal growth plates (Russell et al, 2008). An estimated 2 to 3 new cases occur per million annually in the US (SEER, 2011). While most osteosarcomas occur in adolescence (Figure 2.2-1), a period that coincides with the pubertal growth spurt as well as high concentrations of growth hormone and IGF-I (Arndt and Crist, 1999), approximately one third of osteosarcomas occur in patients over 40 years of age (Rikhof et al, 2009). An estimated 20% of these patients present with metastases at the time of diagnosis (Figure 2.2-2). The location and number of metastases, together with the completeness of surgical resection, have a major impact on 5-year event-free survival (Ferrari et al, 2003). Over the last 3 decades, outcomes have improved in large measure due to aggressive treatment with multi-agent chemotherapy and surgical resection (Longhi et al, 2006). Nevertheless, 5-year survival rates remain approximately 30% for patients with recurrent unresectable or metastatic disease (Bielack et al, 2009).

Rhabdomyosarcoma, the most common soft tissue sarcoma in children, arises from malignant mesenchymal tissue and has 2 major histologic subtypes, an embryonal form that generally affects children under 10 years of age, and an alveolar form that typically affects adolescents and young adults (Russell et al, 2008). Approximately 350 new cases are diagnosed annually in the US, where they account for an estimated 3-4% of childhood cancers

(Russell et al, 2008). Approximately 16% of patients present with metastatic disease by surgicopathologic staging, with 5-year survival rates ranging from 20 to 30% (Russell et al, 2008).

While diagnostic and therapeutic advances have improved outcomes for patients with sarcoma, the clinical needs of patients with recurrent/refractory or metastatic disease remain largely unmet. Moreover, the short- and long-term toxicities of existing treatments potentially limit therapeutic options beyond first-line therapy. Preliminary efficacy signals from studies testing IGF-1R-targeting MAbs in patients with various advanced sarcomas coupled with the general toxicity profile of this class of agents suggest that further testing in this disease setting is warranted.

2.3 Compounds Targeting the IGF Axis

Three major classes of therapeutic compounds that target the IGF axis are currently under development: (1) small molecule tyrosine kinase inhibitors (TKIs) that inhibit kinase activities of IGF-1R and IR, (2) antibodies that target IGF-1R, and (3) antibodies that target IGF ligands.

Tyrosine kinase inhibitors are small molecule compounds that bind to and inhibit the kinase activity of receptor tyrosine kinases. Due to the high degree of homology among the kinase domains, the majority of IGF-1R-targeting TKIs inhibit not only IGF-1R but also IR-A and IR-B (Weroha and Haluska, 2008). As a result, such TKIs can impair glucose homeostasis, as demonstrated by transient hyperglycemia documented in clinical trials (Weroha and Haluska, 2008).

Antibodies that target IGF-1R inhibit the binding of IGF to IGF-1R and are furthest along in clinical development. Many of these MAbs induce IGF-1R internalization and degradation upon binding to the receptor. Although they do not bind to IR, many of these MAbs partially modulate its activity, including that of IR-B, by binding to IGF-1R/IR-A or IGF-1R/IR-B hybrid receptors, which may contribute to transient, treatment-related hyperglycemia observed in as many as 10-20% of subjects administered various investigational agents that target the IGF pathway (Atzori et al, 2009). Although typically mild in nature, hyperglycemia has occasionally been dose limiting or has resulted in Grade 3-4 adverse events in various studies (Atzori et al, 2009; Gualberto and Pollak, 2009, Weroha and Haluska, 2008). IGF-1R-targeting MAbs have achieved complete and partial responses as monotherapy in patients with various sarcomas, including ESFT (Table 2.3-1). Despite preliminary evidence

of clinical activity, the therapeutic value of this novel approach remains incompletely tested given that the development of certain promising agents (eg, figitumumab, R1507) has been discontinued in some indications (Pappo et al, 2011; Jassem et al, 2010). Efficacy signals generated by these and other agents warrant further exploration of the potential therapeutic value of targeting the IGF pathway in patients with certain sarcomas.

Table 2.3-1 Activity of IGF-targeting Monoclonal Antibodies Administered as Monotherapy to Patients with Various Sarcomas

Agent	Study Phase/Cohorts	Dose (IV) & Schedule	Clinical Activity	Reference
Figitumumab (CP-751,871)	Phase 1 Sarcoma (n = 15); ESFT (n = 14)	20 mg/kg Q3Wk or Q4Wk	1 **CR** (ESFT) 1 **PR** (ESFT) 8 **SD** >4 months	Olmos et al, 2010
Ganitumab (AMG 479)	Phase 1 Advanced solid tumors (n = 53)	1 to 20 mg/kg Q2Wk	1**CR** (ESFT/PNET, response > 30 mo) 1**PR** (ESFT/PNET)	Tolcher et al, 2009
Ganitumab (AMG 479)	Phase 2 Relapsed/refractory ESFT (n = 19); DSRCT (n = 16)	12 mg/kg Q2Wk	2 **PR** (1 ESFT, 1 DSRCT) 5 **SD** >24 wk	Tap et al, 2010
RG1507	Phase 1 Pediatric subjects (3 to 17 y) with relapsed or refractory solid tumors (n = 31: 6 ES, 5 RS, 3 OST)	3 -9 mg/kg QWk or 16 mg/kg Q3Wk	No ORs 7 **SD** > 12 wk 2 ES **PD** at 18 wk 2 OST **SD** > 52 and > 78 wk	Bagatell et al, 2011
RG1507	Phase 2 Subjects (8 to 78 y) with Relapsed/refractory ESFT (n = 115)	9 mg/kg QWk (n=109) or 27 mg/kg Q3Wk (n=6)	**CR/PR** rate 10% **OS** 7.6 mo	Pappo et al, 2011
MEDI-573	Phase 1 (ongoing) Advanced solid tumors (n = 37)	0.5, 1.5, 5, 10, 15 mg/kg QWk 30 mg/kg q3Wk	No ORs 11 **SD** $\geq$ 3 mo (inc. 4 sarcomas, 1 liposarcoma > 87 wk)	Haluska et al, 2011

CR = complete response; DSRCT = desmoplastic small round cell tumors; ESFT = Ewing's sarcoma family of tumors; PR = partial response; OR =objective response; QWk = once weekly; Q3Wk = every 3 weeks; OST = osteosarcoma; ES = Ewing's sarcoma; PNET = primitive neuroectodermal tumor; RS = rhabdomyosarcoma; SD = stable disease; PD = progressive disease; OS = overall survival.

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MEDI-573 is the only MAb currently in clinical development that targets the IGF ligand instead of IGF-1R. MEDI-573 inhibits IGF-stimulated phosphorylation of both IGF-1R and IR-A, and the downstream signaling proteins IRS-1, Akt, and MAPK. It does not affect insulin-stimulated phosphorylation of IRs and their downstream signaling. MEDI-573 has been shown to inhibit IGF-II–induced proliferation of cells that express only IR-A with the same potency as cells that express only IGF-1R, in addition to the proliferation of heterogeneous cell populations that express both receptors. An IGF-1R–specific antibody tested in the same studies did not inhibit IGF-II activity mediated by IR-A, including in MDA-MB-231 breast cancer cell lines, which express high levels of IR-A along with moderate levels of IGF-1R that can hybridize with IR-A receptors. In in vivo studies, MEDI-573 demonstrated close to 90% tumor growth inhibition in mouse 3T3 tumors dependent on autocrine IGF signaling by ectopically overexpressing human IGF and IGF-1R. In these IGF-1R–dependent mouse models, the activity of MEDI-573 was shown to be comparable to that of IGF-1R–specific antibodies (Gao et al, 2011).

In general, agents that target the IGF axis exhibit acceptable safety profiles. The most characteristic treatment-related toxicity reported across IGF-1R–targeting MAbs and most TKIs remains transient Grade 1-2 hyperglycemia. Although serious glycemic complications rarely occur, this incompletely understood endocrine effect has been reported in up to 20% of subjects across studies of various IGF-targeting agents (Atzori et al, 2009; Gualberto and Pollak, 2009, Weroha and Haluska, 2008). The impact of hyperglycemia and associated increases in insulin levels has been postulated to mitigate or potentially override the antitumoral effects of drugs that target IGF-1R. One mechanism for resistance to IGF-1R–targeting therapies may relate to the unopposed effects of compensatory increases in insulin levels and associated increases in IGF-I and glucose levels. In addition, these MAbs do not inhibit the activation of IR-A homodimers by IGF-II, which may constitute a compensatory pathway by which tumors circumvent MAbs that target the IGF-1R.

Agent-specific differences in toxicity patterns emerging from clinical studies include hematologic (anemia, thrombocytopenia, lymphopenia), cardiovascular (deep venous thrombosis, cerebrovascular accident) and hepatic (transaminitis) events. Thus far, the most serious events have been documented with figitumumab. These events ultimately led to the discontinuation of 2 pivotal trials in non-small cell lung cancer (ADVancing IGF-1R in Oncology [ADVIGO]) in 2010 after data showed an imbalance of serious adverse events, including mortality, in the arm testing figitumumab and a low likelihood of meeting the primary endpoint of improved overall survival (OS) (Jassem et al, 2010).

2.4 Treatment Options for Sarcoma

Despite the development of improved treatments for various sarcomas over recent decades, patients with relapsed/refractory or metastatic disease have poor long-term outcomes (Cotterill et al, 2000). Cytotoxic chemotherapy is commonly used as part of multimodal therapy, though few agents have received regulatory approval for the treatment of sarcoma. In certain instances, the product label (ie, docetaxel) describes clinical responses that have been observed in the treatment of pediatric sarcoma. Regimens recommended by US and European Union (EU) clinical guidelines for metastatic soft tissue and bone sarcoma (NCCN [bone cancer], 2011; NCCN [soft tissue sarcoma], 2011; Hogendoorn et al, 2010; Casali et al, 2010) are primarily based on objective response rates (ORR) in Phase 1 and 2 and retrospective studies. Despite efforts to optimize the doses and schedules of different agent combinations, response rates in these patients remain low (Table 2.4-1).

The first-line treatment of patients with metastatic soft tissue sarcoma consists of an anthracycline-based regimen (typically doxorubicin) administered in combination with ifosfamide. Objective response rates reported for patients treated with chemotherapy regimens that include doxorubicin and ifosfamide range from 28-45% (Schutte et al, 1990; Steward et al, 1993; Santoro et al, 1995). The predominant regimen used in patients with recurrent/refractory disease is gemcitabine alone or in combination with docetaxel. In studies including pediatric patients, ORRs for the combination of gemcitabine and docetaxel have ranged from 29 to 50% (Mora et al, 2009; Navid et al, 2008). As described in Table 2.4-1, other chemotherapy combinations shown to be active in pediatric and adult patients with relapsed/recurrent disease include irinotecan plus temozolomide (Casey et al, 2009; Wagner et al, 2004; Wagner et al, 2007) and cyclophosphamide plus topotecan (Saylors et al, 2001; Hunold et al, 2006). High-dose ifosfamide is also recommended based on activity in the setting of relapsed/recurrent disease (Patel et al, 1997). Trabectedin is approved in Europe but not in the US for use in patients with advanced or metastatic soft-tissue sarcomas who have failed or are not suitable for first-line therapy with anthracyclines (doxorubicin or epirubicin) and ifosfamide, sequentially or in combination. This approval was based on an uncontrolled trial testing active agent administered IV using either a once-every-3-week (Q3Wk) or once-per-week (QWk) dose and schedule in 270 adults with advanced liposarcoma or leiomyosarcoma, all of whom had progressed on standard chemotherapy. This study demonstrated an improvement in the primary endpoint of time to progression (3.7 vs 2.3 months, favoring the Q3Wk over QWk infusion dose and schedule) (Demetri, 2009).

According to US clinical guidelines, standard chemotherapy for the first-line treatment of patients with metastatic Ewing's sarcoma includes vincristine, doxorubicin, and cyclophosphamide, with or without ifosfamide and etoposide (NCCN [bone cancer], 2011). This regimen has demonstrated 5-year event-free survival (EFS) of 22% in patients with metastatic bone sarcoma (Grier et al, 2003). Although the treatment of patients with relapsed/refractory Ewing's sarcoma is not standardized, US and EU clinical guidelines (NCCN [bone cancer], 2011; Hogendoorn et al, 2010) recommend the use of alkylating agents (cyclophosphamide and ifosfamide) in combination with topoisomerase inhibitors (etoposide or topotecan) or the combination of irinotecan and temozolomide (NCCN [bone cancer], 2011; Hogendoorn et al, 2010). Objective response rates for these combinations of agents are similar in patients with recurrent/refractory Ewing's sarcoma, ranging from 30 to 33% for cyclophosphamide plus topotecan (Saylors et al, 2001; Hunold et al, 2006); 27-63% for irinotecan plus temozolomide (Casey et al, 2009; Wagner et al, 2004; Wagner et al, 2007); and 35-51% for ifosfamide plus etoposide-containing regimens (Marina et al, 1993; Van Winkle et al, 2005). As described in Table 2.4-1, other chemotherapy combinations shown to be active in patients with relapsed/recurrent disease include high-dose ifosfamide (Patel et al, 1997; Ferrari et al, 2009) and gemcitabine in combination with docetaxel (Mora et al, 2009; Navid et al, 2008).

Clinical guidelines (NCCN [bone cancer], 2011) for the first-line treatment of patients with metastatic osteosarcoma recommend doxorubicin in combination with cisplatin, high-dose methotrexate, and/or ifosfamide which has shown 5-year EFS of 23-29% (Chou et al, 2009). Although there is no accepted standard for the treatment of patients with relapsed/refractory osteosarcoma, chemotherapy regimens typically include gemcitabine in combination with docetaxel, which has demonstrated ORRs of 29-50% in studies including pediatric patients with recurrent/refractory sarcoma (Mora et al, 2009; Navid et al, 2008). As summarized in Table 2.4-1, other active regimens include alkylating agents (cyclophosphamide or ifosfamide) with or without etoposide and/or carboplatin (Marina et al, 1993; Van Winkle et al, 2005).

Table 2.4-1 Activity of Current Treatments for Soft Tissue and Bone Sarcomas

Therapy	Patient Population	Median Age (y)	ORR (%)	Median DOR (mo)	Median PFS/ TTP (mo)	Median OS (mo)	Reference
First-Line							
Doxorubicin + ifosfamide	Unresectable or metastatic STS	49-50	28 -45	11	7.3	13.8 - 15	Santoro et al, 1995 Steward et al, 1993 Schutte et al, 1990
Vincristine + cyclophosphamide + doxorubicin and/or dactinomycin ± ifosfamide + etoposide	Metastatic bone sarcoma (Ewing's sarcoma and neuroectodermal tumor of bone)	10 - 17[a]	---	---	5-yr EFS: 22% 8-yr EFS: 20%	5-yr OS: 34-35% 8-yr OS: 29 - 32%	Grier et al, 2003 Miser et al, 2004
Cisplatin + doxorubicin + high-dose methotrexate ± ifosfamide	Metastatic osteosarcoma	0 - 30[a]	---	---	5-yr EFS: 23 - 29%	5-yr OS: 30 - 53%	Chou et al, 2009
Second-line and later lines							
Ifosfamide (high-dose)	Relapsed/refractory bone and STS	31 - 38	29- 57	---	---	---	Patel et al, 1997
Ifosfamide (high-dose)	Advanced/recurrent Ewing's sarcoma	17	34	---	---	12.3	Ferrari et al, 2009
Gemcitabine + docetaxel	Relapsed/refractory sarcoma (including Ewing's sarcoma and osteosarcoma)	13 - 17	29 - 50	3.8-10.5	2.3 - 5	---	Mora et al, 2009 Navid et al, 2008
Gemcitabine + docetaxel	Unresectable or metastatic STS	52-55	17 - 18.4	---	6.2	12.1 -17.9	Bay et al, 2006 Maki et al, 2007
Irinotecan + temozolomide	Recurrent/advanced solid tumors (including Ewing's sarcoma)	13-20	27 - 63	6 – 7.5	5 - 8.3	---	Casey et al, 2009 Wagner et al, 2007 Wagner et al, 2004

Table 2.4-1 Activity of Current Treatments for Soft Tissue and Bone Sarcomas

Therapy	Patient Population	Median Age (y)	ORR (%)	Median DOR (mo)	Median PFS/ TTP (mo)	Median OS (mo)	Reference
Cyclophosphamide + topotecan	Recurrent/refractory solid tumors (including rhabdomyosarcoma, osteosarcoma, and Ewing's sarcoma)	14-17	30 - 33	---	---	---	Saylors et al, 2001 Hunold et al, 2006
Ifosfamide + carboplatin + etoposide	Relapsed/recurrent solid tumors (including Ewing's sarcoma, osteosarcoma, and rhabdomyosarcoma)	12 - 14	35 - 51	---	---	11.8	Marina et al, 1993 Van Winkle et al, 2005
Trabectedin	Advanced/metastatic STS (liposarcoma and leiomyosarcoma)	53	1.6 - 5.6	---	2.3 - 3.7	11.8 - 13.9	Demetri, 2009

ORR= objective response rate; DOR = duration of response; PFS = progression-free survival; TTP = time to progression; OS = overall survival; EFS = event-free survival; STS = soft tissue sarcoma

[a] median age was not calculated; age range is presented

3 Nonclinical Data Supporting Clinical Studies

The results of in vitro pharmacology studies have shown that MEDI-573 inhibits both IGF-I- and IGF-II-stimulated phosphorylation of IGF-1R and that of downstream signaling proteins, including Akt and MAPK, in a number of engineered NIH-3T3 cell lines transfected to express human IGF-1R and either human IGF-I or -II. Furthermore, MEDI-573 inhibited autocrine phosphorylation of these signaling molecules. MEDI-573 was highly effective in inhibiting the phosphorylation of IR-A and insulin receptor substrate 1 (IRS-1) in cell lines that overexpressed IR-A, and inhibited IGF-II stimulated cell proliferation in both the IGF-1R and IR-A signaling pathways (Gao et al, 2011). Additionally, treatment of a rhabdomyosarcoma cell line (Rh0) with MEDI-573 in vitro inhibited IGF-I- and IGF-II-induced phosphorylation of IGF-1R and downstream signaling protein Akt. In vivo, treatment of tumor-bearing mice with MEDI-573 significantly inhibited the growth of implanted clone 32 (C32) and clone P12 (P12) tumors, which are mouse fibroblasts that overexpress human IGF-II and human IGF-1R, and human IGF-I and human IGF-1R, respectively. MEDI-573 has an approximate 7-fold reduced affinity for murine IGF-I, and adult mice do not produce IGF-II, thus limiting the assessment of in vivo antitumor activity in mouse tumor models.

Single- and multiple-dose toxicity studies have been conducted using cynomolgus monkeys. MEDI-573 was given as a 30-minute IV infusion administration of up to 60 mg/kg/week for 13 weeks in cynomolgus monkeys. The no observable adverse effect level was 60 mg/kg/week. Although no adverse effects were observed, a dose-dependent decrease in serum IGF-I and IGF-II levels (pharmacodynamic marker) was observed. MEDI-573 was fully pharmacologically active with plasma concentrations at or above the concentration needed for full suppression of serum IGF-I and IGF-II. The following non-adverse changes were present in animals given MEDI-573: (a) treatment-related, dose-dependent effects on hematology parameters (decreased red blood cell count, hematocrit, and hemoglobin, and increased reticulocyte count) at all doses; (b) decreased serum alkaline phosphatase in the 10 and 60 mg/kg/dose groups; (c) increased incidence of minimal thymic atrophy; and (d) increased incidence of minimal liver vacuolization. The effects on hematology parameters and the decreased serum alkaline phosphatase were not considered adverse due to the small magnitude of change. The liver vacuolization and thymic atrophy were not considered adverse because these changes were minimal in severity, did not show a clear dose response with regard to incidence or severity, and likely represent normal physiologic processes in the

liver and thymus (eg, glycogen in the cytoplasm of hepatocytes and early stage of normal thymic involution, respectively) (MedImmune unpublished data).

MEDI-573 targets the IGF-I and IGF-II ligands and thereby inhibits IGF-mediated signal transduction. Nonclinical studies in cancer models suggest that MEDI-573 has the potential to achieve broad antitumor activity owing to its ability to inhibit both IGF-1R and IR-A pathways. Furthermore, MEDI-573 has potential to achieve this without perturbing glucose homeostasis (Gao et al, 2011), an adverse effect observed with investigational agents that target IGF-1R (Atzori et al, 2009).

4 Clinical Experience in Adults

4.1 Overview of Clinical Studies

Four clinical studies with MEDI-573 are underway: a first-time-in-human study (MI-CP184) in patients with advanced solid tumors, a Phase 1 study (D-5621C00006) in adult Japanese subjects, a Phase 1b/2 study (MEDI-573-1030) in patients with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2−) metastatic breast cancer (MBC), and a Phase 1b/2 study (MEDI-573-1028) in patients with advanced hepatocellular carcinoma (HCC). The Phase 1 Japanese study and the Phase 1b/2 study in MBC were initiated in the second quarter of 2011; the Phase 1b/2 study in HCC is poised for initiation in the third quarter of 2011. Data are not yet available from these studies.

4.1.1 Advanced Solid Tumors (Study MI-CP184 and Study D-5621C00006)

A Phase 1 multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity (IM), pharmacodynamics, and antitumor activity of MEDI-573 administered intravenously QWk or once every 3 weeks (Q3Wk) in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists was initiated in 2009. In the dose-escalation phase, subjects received MEDI-573 administered QWk at doses of 0.5, 1.5, 5, 10, or 15 mg/kg as a 60-minute infusion or Q3Wk at doses of 30 mg/kg administered as a 90-minute IV infusion. The 5 and 15 mg/kg QWk doses were selected for further evaluation in the dose-expansion phase in which safety, PK, pharmacodynamics, and efficacy will be examined in subjects with advanced bladder cancer. The expansion in bladder cancer subjects is currently ongoing.

A Phase 1 multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of MEDI-573 administered IV QWk or Q3Wk in adult Japanese subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists was initiated in the second quarter of 2011.

4.1.2 Metastatic Breast Cancer (Study MEDI-573-1030)

A Phase 1b/2, multicenter, open-label study to evaluate the safety, tolerability, antitumor activity, and pharmacology of MEDI-573 in combination with an aromatase inhibitor (AI) in adult subjects with HR+, HER2-negative MBC not deemed amenable to curative surgery or curative radiation therapy is ongoing. In the Phase 1b portion of the study, 2 cohorts are being examined in which subjects receive a lower dose and higher dose of MEDI-573 with an AI. In the Phase 2 portion of the study, approximately 255 subjects with HR+, HER2-negative MBC will be randomly assigned in a 1:1:1 ratio to receive a lower dose of MEDI-573 and an AI (Arm 1), a higher dose of MEDI-573 and an AI (Arm 2), or an AI alone (Arm 3). In both phases of the study, MEDI-573 will be administered via IV infusion and an AI will be given orally once daily.

4.1.3 Advanced Hepatocellular Carcinoma (Study MEDI-573-1028)

A Phase 1b/2, multicenter, open-label study to evaluate the safety, tolerability, antitumor activity, and pharmacology of MEDI-573 in combination with sorafenib in adult subjects with unresectable or metastatic HCC has recently been initiated. In the Phase 1b portion of the study, 2 cohorts are being examined in which subjects receive a lower dose or higher dose of MEDI-573 with sorafenib. In the Phase 2 portion of the study, approximately 204 subjects with unresectable or metastatic HCC will be randomly assigned in a 1:1:1 ratio to receive either a lower dose of MEDI-573 in combination with sorafenib (Arm 1), a higher dose of MEDI-573 in combination with sorafenib (Arm 2), or single-agent sorafenib (Arm 3). In both phases of the study, MEDI-573 will be administered via IV infusion and sorafenib will be given orally twice daily.

4.2 Clinical Data Summary

As of the date of this briefing document, clinical data are available for one study in advanced solid tumors.

4.2.1 Advanced Solid Tumors (Study MI-CP184)

As of a data cutoff date of 18 August 2011, 37 subjects have received MEDI-573 in Study MI-CP184. The number of treatment cycles administered among all subjects ranged from 1 to 29 with a median of 2 cycles. Serum exposure of MEDI-573 increased in a dose-dependent manner across all dose levels evaluated. Both IGF-I and IGF-II concentrations were shown to decrease following administration of 0.5, 1.5, 5, 10, 15 mg/kg QWk or 30 mg/kg Q3Wk doses of MEDI-573. At doses above 5 mg/kg, MEDI-573 produced sustained suppression of both IGF-I and IGF-II throughout the study. Tumor response data are available for 27 of the 37 subjects treated (tumor response assessments had not been performed for 10 subjects as of the data cutoff date), of whom 11 (40.7%) had a best response of stable disease (including one patient with liposarcoma lasting 87+ weeks) and 16 (59.3%) developed progressive disease.

The type and pattern of AEs observed to date have generally been consistent with the underlying neoplastic conditions of subjects enrolled on the study. Approximately one-third of the 37 subjects treated to date experienced serious adverse events (SAEs), with weight decrease and hypoglycemia (both occurring in the same subject) considered to be treatment-related. Seven subjects discontinued treatment due to adverse events. The most common AEs have been those pertaining to general disorders, metabolism and nutrition disorders, laboratory investigations, and gastrointestinal disorders, and include decreased appetite, fatigue, nausea, diarrhea, vomiting, abdominal pain, anemia, urinary tract infection, peripheral edema, increased blood alkaline phosphatase, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), increased creatinine, and rash. The Grade 3/4 adverse events experienced by more than 1 subject were increased ALT (3 subjects, 8.1%), fatigue, increased AST, and increased blood alkaline phosphatase (2 subjects each, 5.4%). Only 1 Grade 3/4 event (hypoglycemia in the 15-mg/kg dose cohort) was considered to be treatment-related.

Metabolic AEs involving perturbed glucose homeostasis, among the most common toxicities documented for IGF-1R-targeting MAbs (eg, figitumumab, cixitumumab, ganitumab, dalotuzomab) and small molecules were observed at relatively low frequencies. Two out of 37 subjects (5.4%) reported hyperglycemia (1 Grade 1 episode and 1 Grade 3 episode) and, as discussed above, 1 subject experienced Grade 4 treatment-related hypoglycemia. No dose-limiting toxicities have been observed.

5 Development Plan in Patients With Sarcoma

MedImmune is considering an open-label Phase 2 study of MEDI-573 in adult and pediatric patients with sarcoma (ie, ESFT, rhabdomyosarcoma, and osteosarcoma) who have received 1 prior line of chemotherapy. The study will consist of an adult arm in which subjects will receive MEDI-573 administered IV and a pediatric dose-evaluation arm in which 3 to 6 subjects (≥ 2 and ≤ 18 years of age) in each of 2 dose cohorts will receive MEDI-573 given IV. Additional pediatric subjects could be enrolled in the study if no untoward safety signals are observed in the pediatric dose-evaluation cohorts. The primary objectives of the study will be to evaluate the ORR in the adult arm, and the safety and PK of MEDI-573 in the pediatric arm. Secondary objectives will include safety, PK, IM, and antitumor activity as measured by progression-free survival (PFS), OS, and clinical benefit rate.

6 Summary and Considerations for MEDI-573 Pediatric Development in Sarcoma

The paucity of active agents for the treatment of soft tissue and bone sarcomas underscores the high unmet need of pediatric and adult patients with this exceedingly rare group of diseases. However, there are several challenges unique to the treatment of sarcoma and to the design of sarcoma trials that must be addressed in order to hasten the development of effective agents in this setting.

As summarized in Table 2.4-1, several chemotherapy regimens have shown activity, but no single regimen has demonstrated superiority over other regimens. The lack of a clearly superior comparator complicates the design of sarcoma trials. Moreover, while agents that target the IGF axis are generally expected to achieve their optimal potential when coadministered in combination with other therapeutics, data from multiple trials suggest that clinical benefit (including durable objective responses) may be achieved even when these agents are administered as monotherapy in various sarcomas (Table 2.3-1).

The low incidence of metastatic soft tissue and bone sarcoma also makes it challenging to accrue patients to a randomized trial. There is also the question of the appropriate mix of adult and pediatric patients to be enrolled in a Phase 2 sarcoma trial. As described in Table 2.4-1, there is precedence for conducting clinical trials with mixed populations of adult and pediatric patients with both soft tissue and bone sarcomas; such trials offer the possibility for more expeditious development of a promising new agent in pediatric populations.

Another key question involves the choice of the appropriate primary endpoint for randomized Phase 2 and Phase 3 trials in sarcoma. Phase 2 trials in sarcoma have traditionally used an endpoint of ORR. Sarcoma lends itself to the use of ORR as a measure of clinical benefit because spontaneous remissions rarely occur and there is a general consensus that ORR is a prerequisite for clinical benefit in adult and/or pediatric sarcoma (George, 2007). Although ORR is not a validated surrogate for clinical benefit in this trial setting, it still allows for an earlier assessment of potential efficacy compared to either PFS or OS. Subsequent later-phase studies would be powered to show clinical benefit in terms of improved PFS, OS, or possibly, clinical benefit rate in order to determine whether a promising signal in RR ultimately translates into long-term benefit.

Several recently initiated Phase 3 trials in patients with metastatic bone and/or soft tissue sarcoma are utilizing PFS as a primary endpoint**.** The combination of palifosfamide and doxorubicin is being studied in a first-line setting in patients with metastatic soft tissue sarcoma to determine if this combination improves PFS over doxorubicin alone (Clinicaltrials.gov identifier: NCT01168791). Similarly, trabectedin is being compared to doxorubicin in patients with previously untreated advanced or metastatic soft tissue sarcoma (Clinicaltrials.gov identifier: NCT01189253) to determine if trabectedin shows an improvement in PFS. In the relapsed/refractory setting, pazopanib is being tested against placebo in patients with metastatic soft tissue sarcoma (second and later lines) to determine if it improves PFS (Van Der Graaf et al, 2011). Similarly, a recently completed Phase 3 trial in metastatic soft tissue and bone sarcoma in the maintenance setting demonstrated that ridaforolimus improved PFS as compared to placebo (Chawla et al, 2011). Although these trials support the use of PFS as a primary endpoint, the recognized benefit of disease stabilization in the setting of sarcoma makes endpoints such as 6-month PFS and clinical benefit rate (CR + PR + SD) worthy of consideration as well.

MedImmune looks forward to receiving guidance from the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee on ways to develop MEDI-573 in pediatric patients with sarcoma (ie, ESFT, osteosarcoma, and rhabdomyosarcoma). Specifically, MedImmune wishes to discuss the following:

- Does the Committee think that MEDI-573 is at the appropriate stage of development to begin testing in pediatric patients with sarcoma in order to collect PK and safety data?

- Provided that no untoward safety signals are observed in the pediatric dose-evaluation cohorts of the proposed Phase 2 trial, could additional pediatric patients be enrolled along with adult subjects?
- Is the proposed age group of 2 to 18 years acceptable for pediatric subjects that would be enrolled in the proposed Phase 2 sarcoma study?

- Can the Committee provide feedback on what they would like to see in terms of additional clinical trials to support the further development of MEDI-573 in pediatric patients with sarcoma?
  - Could a Phase 2 trial include a mixed population of both adult and pediatric patients?
  - Is a randomized trial required?
  - What endpoint would be considered to be an appropriate measure of clinical benefit (eg, PFS, OS, clinical benefit rate)?
  - What comparator would be appropriate?

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