Dual-targeting of IGF-1R and ErbB3 Pathways in Ewing's Sarcoma Cellular Models with Istiratumab (MM-141), a Bispecific, Tetravalent Monoclonal Antibody

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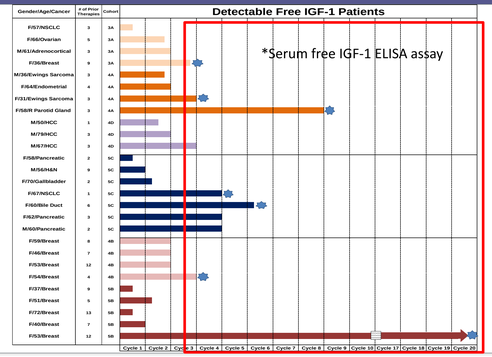
Abstract #5838

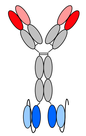
Background

Ewing's sarcoma family tumors (ES) are aggressive tumors that often present as metastatic in bone and soft tissue and predominantly affect adolescents and younger adults. Current treatment for ES includes surgical resection followed by loco-regional radiotherapy and chemotherapy. Survival rates for patients with metastatic disease continue to offer a particularly difficult clinical challenge, with a five-year survival rate of 20-30% for these patients. ES is primarily a genetic disease caused by fusion between the 5' segment of the Ewing sarcoma breakpoint region 1 gene (EWSR1) on chromosome 22 and the 3' portion of Friend leukemia virus integration site 1 (FLI1) on chromosome 11. Fusions of EWSR1 and other ETS transcription factors result in dis-regulated transcription factors which promote malignant progression of ES tumors. Recent studies have shown that most ES cell lines and clinical samples express IGF-1R. Importantly, an activated IGF-1R pathway appears to be a prerequisite for malignant transformation by the EWS-FLI1 translocation, presumably via activation of the PI3K-AKT and MAPK pathways. These findings have led to the preclinical and clinical evaluation of multiple IGF-1R-targeted therapeutics with varying results. Clinical experience with anti-IGF1R targeting therapies has demonstrated striking anticancer activity in minor subsets of patients with ES. Importantly, the paucity of a clinically useful biomarker to select patients continues to hinder IGF-1R drug development in ES. Istiratumab is an investigational, bi-specific, monoclonal antibody that acts as a tetravalent inhibitor of PI3K/AKT/mTOR, a major pro-survival pathway tumor cells use as a resistance mechanism to anticancer therapies. Istiratumab is designed to interfere with this pathway by blocking ligand-induced signaling through the IGF-1R and ErbB3 receptors, based on findings that ErbB3 activation mediates resistance to the IGF-1R blockade.

Istiratumab Phase 1 results: Free IGF-1 Associated with Longer Durations



MM-141 Overview and IGF-1 In Ewing's Sarcoma



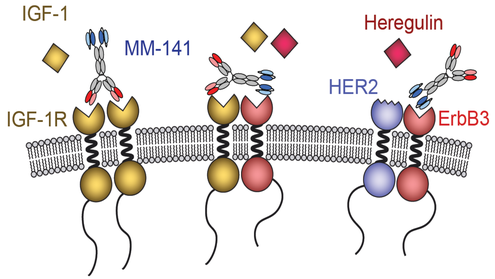
Anti-IGF-1R IgG1 antibody (K_D=0.3nM)

genetically fused with

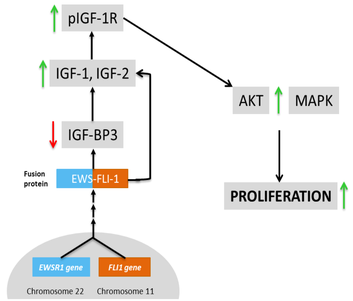
anti-ErbB3 antibody fragment (K_D=0.9nM)

MM-141 inhibits PI3K/AKT/mTOR by:

- blocking growth factor induced signaling via IGF-1R and ErbB3
- degrading receptor complexes of IGF-1R and ErbB3 including their heterodimers with ErbB2 and IR



EWS1:FLI-1 Fusion Protein Directly Upregulates IGF-1R Signaling in Ewing's Sarcoma

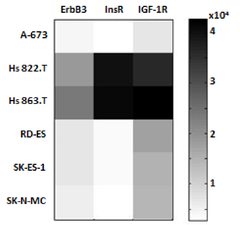


- Fusion protein represses miRNAs that negatively regulate IGF pathway, leading to upregulation (McKinsey *et al*, 2011)
- Fusion protein represses IGFBP-3, leading to increased free IGF-1 (Prieur *et al*, 2004)
- Targeting patients with Higher Levels of IGF-1R may offer clinical benefit
- Retrospective analyses of figitumumab revealed a strong association between pretreatment serum IGF-1 and on-treatment survival benefit

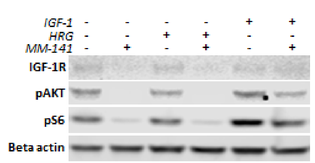
Huang *et al* (2011) *PLoS One*, **6** (10): e26060
Subbiah *et al* (2009) *Curr Treat Opt Oncol*, **10**, No. 1-2: 126-140

Results

HER3, InsR & IGF1R are differentially expressed in EWS cell lines

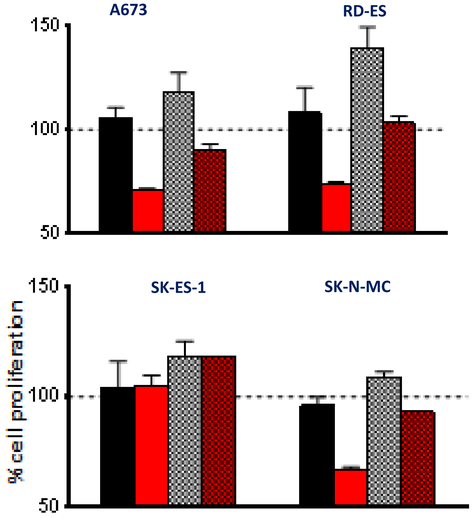


Istiratumab inhibits expression of basal and ligand-activated signaling proteins in RD-ES cells



Assay Conditions: Protein lysates generated from RD-ES cells treated with IGF-1 (50nM), HRG (5nM) +/- MM-141 (250nM) for 4 hours were immunoblotted, and expression of IGF-1R, pAKT and pS6 tested.

Istiratumab inhibits HRG & IGF1 induced proliferation in EWS cell lines

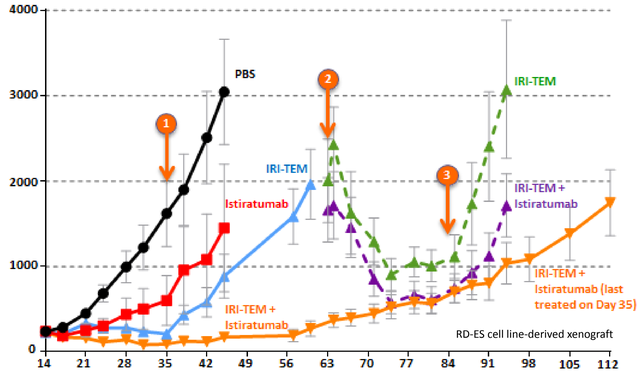


Assay Conditions: EWS cells (5000/well) were treated with HRG (■; 5nM), HRG + MM-141 (■; 250nM), IGF-1 (■; 50nM), or IGF-1 + MM-141 (■). Cell proliferation was measured after 5 days using CellTiter-Glo®. Percent cell proliferation is plotted relative to untreated (----) cells.

1 Day 35: Tumor growth rate analysis indicated that co-treatment of IRI-TEM + Istiratumab (-▼-) significantly inhibited tumor growth compared to all other treatment groups, including IRI-TEM (-▲-). **At this point (day 35), all drug treatment of mice was stopped** to evaluate the impact of a "drug holiday" on tumor re-growth

2 Day 63: Tumors in mice previously treated with IRI-TEM (-▲-) quickly re-grew following treatment suspension. To test whether these tumors were still sensitive to treatment, mice in this group were re- randomized to receive IRI-TEM (-▲-) or IRI-TEM + istiratumab (-▲-) to test tumor sensitivity to re-treatment

3 Day 84: Following 3 weeks of retreatment, tumor growth had stabilized in both treatment groups. At this point, drug treatment was again stopped to evaluate the effect of a second "drug holiday" on tumor growth



Drug Dosing Conditions
Irinotecan: 0.2 mg/kg, QDx5, intraperitoneal (IP); TMZ: 5 mg/kg, QDx5, oral gavage; Istiratumab: 30mg/kg, Q2W, IP

CONCLUSIONS

Istiratumab was designed to inhibit pro-survival signaling by co-blocking IGF-1R and ErbB3 signaling

- Ewing sarcoma (EWS) tumors are dependent on IGF-1 signaling pathway
- EWS-FLI-1 fusion protein induces IGF-1

ErbB3 is upregulated in EWS, rhabdomyosarcoma (RMS), osteosarcoma (OS) and clear cell sarcoma in soft tissue (CCSST)

Co-treatment of istiratumab and irinotecan/temodar significantly inhibited tumor growth (p<0.005) compared to either -tem or istiratumab treatment alone

Istiratumab is being developed in patients with high free-IGF-1 levels:

- Phase 1 data showed patients with high free IGF-1 levels stayed on treatment longer
- Double-blind, randomized, placebo-controlled Phase 2 trial of istiratumab in combination with gemcitabine and nab-paclitaxel in free IGF-1+ Frontline Metastatic Pancreatic Cancer is ongoing
- Further investigation as a potential therapy for EWS patients is warranted