Istiratumab exhibits antiproliferative activity in Ewing sarcoma and rhabdomyosarcoma

Abstract 7052

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Abstract:

Istiratumab (prior MM-141) is a fully human tetravalent bi-specific antibody that binds and co-inhibits IGF-1R and ErbB3 (HER3). Istiratumab inhibits ligand binding to abrogate PI3K/AKT signaling resulting in antiproliferative activity in various cancers alone and in combination with mTOR inhibitor everolimus or chemotherapy, including in a human Ewing sarcoma model. Following Phase I and Phase II trials in advanced solid and pancreatic cancers, the molecule was abandoned by Merrimack Pharmaceuticals and was subsequently acquired by Pegascy.

To consolidate our decision to proceed with a pediatric study, we explored our MAPPYACTS sequencing data on recurrent or refractory pediatric cancers for alterations in both pathways. Mutations in IGF-1R and HER3 occur rarely in pediatric cancers, some tumors exhibit IGF-1R amplification. Most tumors expressed moderate levels of IGF-1R with high expression in neuroblastoma samples and amplified osteosarcoma; IGF-2R is expressed in most cancers. IGF1 was lowly expressed in neuroblastoma and sarcoma but highly in choroid plexus carcinoma whereas IGF2 was highly expressed in most tumor types, particularly rhabdomyosarcoma, hepatoblastoma and ependymoma that are known to exhibit LOH. HER3 was found expressed in RMS, hepatoblastoma, a proportion of high grade glioma and carcinomas, its ligand NRG1 was found high only in single samples of sarcoma subtypes. Moreover, we observed IRS2 and IRS1 overexpression in about 80% of Ewing sarcoma samples. Overall, the activity of these pathways encouraged us to explore further the antitumor activity of istiratumab in pediatric cancers.

We evaluated antiproliferative activity in Ewing sarcoma (TC-71, TC-106, CHLA-99, TC-205), alveolar (Rh41, Rh30) and embryonal (RD) rhabdomyosarcoma of istiratumab alone and in combination with the IRS1/2 inhibitor NT219 or HDAC inhibitor panobinostat. Istiratumab exhibited antiproliferative activity at 0.1 and 1 µM against most cell lines as determined by WST-1 assay. Strong growth inhibition (60-70%) was noted in TC-71 and TC-106, moderate inhibition (26%) in CHLA-99, whereas TC-205 was not sensitive. 35-45% growth inhibition was achieved in rhabdomyosarcoma RD, Rh30 and Rh41, similar to EBV-positive nasopharynx carcinoma C666. Antiproliferative effects of istiratumab were enhanced by addition of NT219 at 0.1 µM or panobinostat in the 3 Ewing sarcoma cell lines tested. Similarly, the addition of IGF1 but not NRG1 in low serum growing conditions reinforced the observed activity of istiratumab in Ewing sarcoma cell lines. Evaluations to determine biomarkers for sensitivity are ongoing.

Conclusion: Istiratumab has antiproliferative activity in sarcomas and will be evaluated in molecularly selected pediatric malignancies and Ewing sarcoma within the AcSé-ESMART trial.

Background / Rationale:

After promising results in the 2010s with treatments targeting IGF-1R, particularly in Ewing sarcoma, we now have the opportunity to reassess this therapeutic pathway with a new bispecific antibody, Istiratumab, which targets both IGF-1R and ERBB3. Our objective is to better understand the role of IGF-1R signaling in the carcinogenesis of this disease and to identify the patients most likely to respond to this targeted treatment.

As part of the European AcSé-ESMART proof-of-concept trial (NCT02813135), we will open a new treatment arm with Istiratumab for patients with relapsed or refractory Ewing sarcoma or other pediatric tumors harboring alterations in the IGF-1R and/or the ERBB3 pathways. To better characterize the mechanisms of response and resistance to this treatment, we will use novel technologies, including in addition to DNA and RNA sequencing, proteomics and metabolomics, as well as the development of patient derived avatars.

These in-depth analyses will help optimize patient selection in future clinical trials with IGF-1R +/- ERBB3-targeted therapies. We are confident that this translational research will provide a significant step forward in the development of Istiratumab for the treatment of pediatric cancers.

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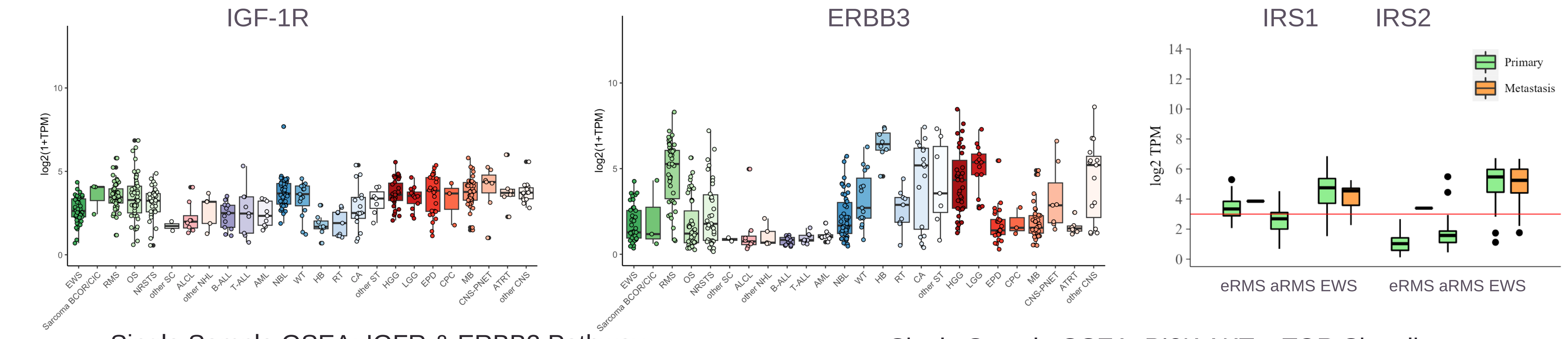
Results: Bioinformatic Analysis - Tumors from Patients

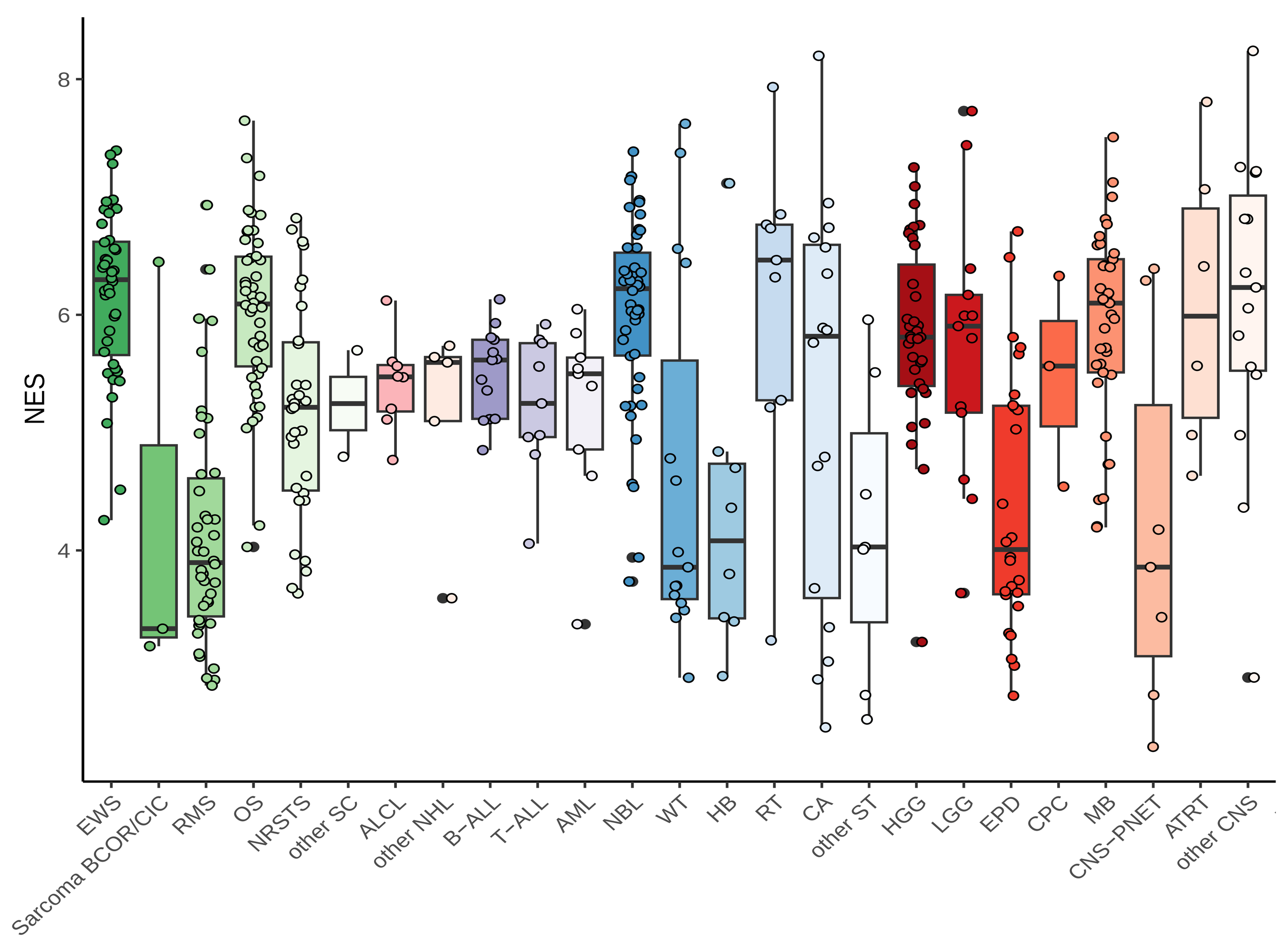
Genomics

Mutations in IGF-1R and HER3 occur rarely in pediatric cancers, some tumors exhibit IGF-1R amplification.

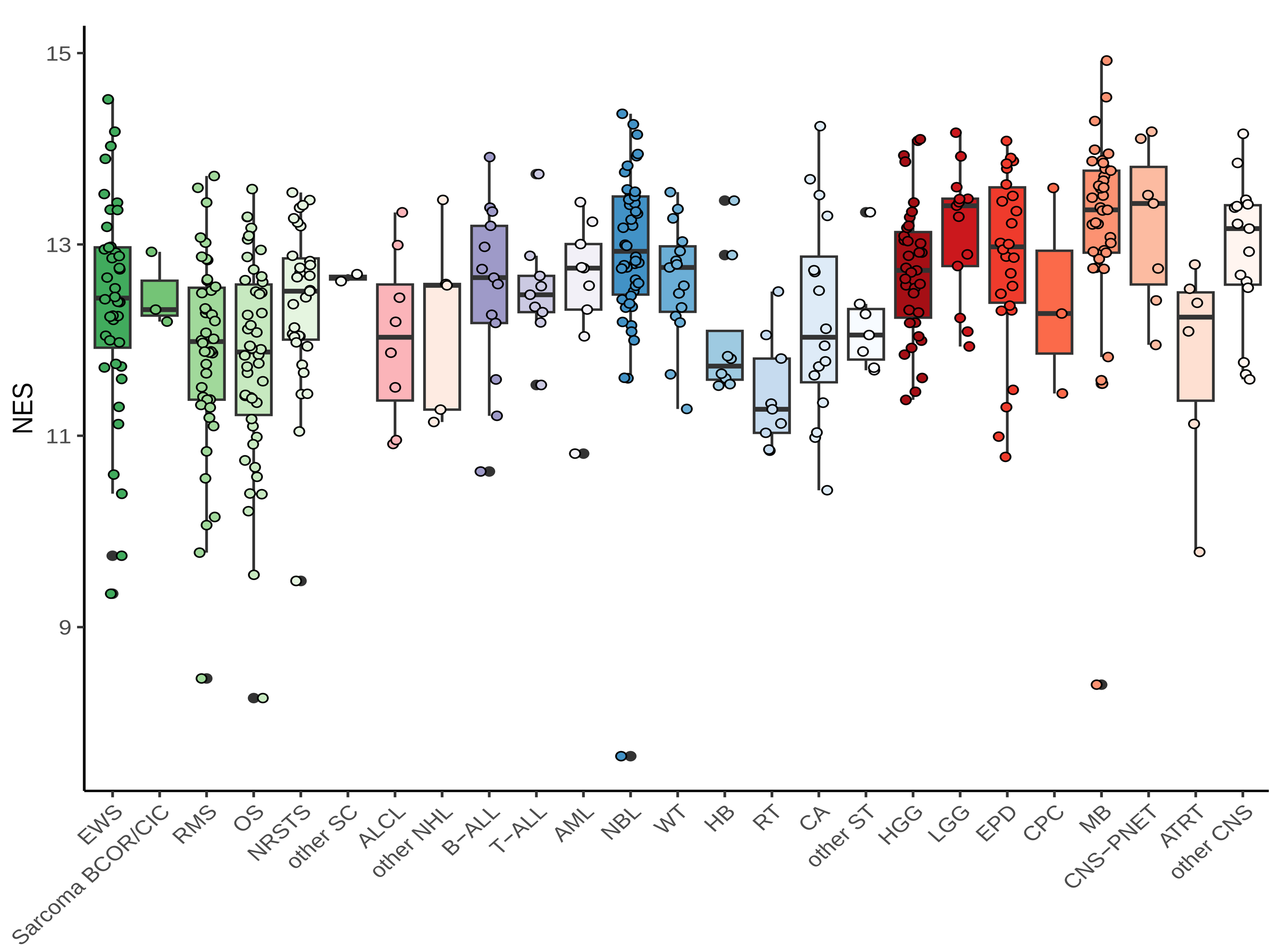
Transcriptomics



Single Sample GSEA: IGFR & ERBB3 Pathway



Single Sample GSEA: PI3K AKT mTOR Signaling



We observed IRS2 and IRS1 overexpression in about 80% of Ewing sarcoma samples. The overall activity of IGFR & ERBB3 pathway and downstream PI3K AKT mTOR signaling were higher in Ewing sarcoma. This encouraged us to explore further the antitumor activity of istiratumab in pediatric cancers

Methods:

Bioinformatic Analysis

A comprehensive analysis of IGF-1R and HER3/ERBB3 pathway alterations across the entire MAPPYACTS cohort of recurrent and refractory pediatric malignancies. This retrospective study will leverage whole-exome and RNA sequencing data to characterize the types, frequencies, and tumor distributions of these alterations. We utilized the MAPPYACTS dataset, which consisted of 632 samples from 624 pediatric patients with successful WES and RNA tumor sequencing results at treatment failure (Berlanga et al., 2022).

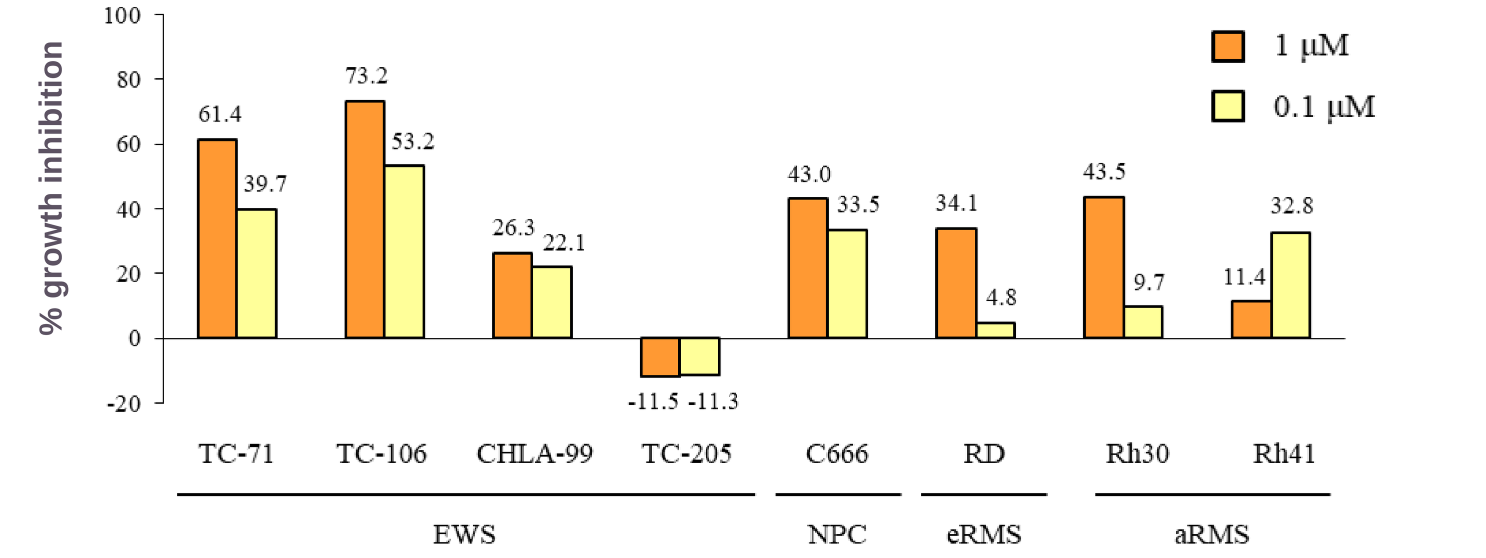
In vitro proliferation assay

Kinetics of in vitro cell growth of Rh41, Rh30 (alveolar) and RD (embryonal) RMS, TC-71, TC-106, CHLA-99 and TC-205 Ewing sarcoma cell lines (kindly provided by the Children's Oncology Group Cell Culture/Xenograft Repository) was evaluated in the presence of istiratumab (0.1 and 1 mM), and combination with NT219 (IRS1/2 inhibitor) or panobinostat (HDAC inhibitor) and analysed by WST-1 assay.

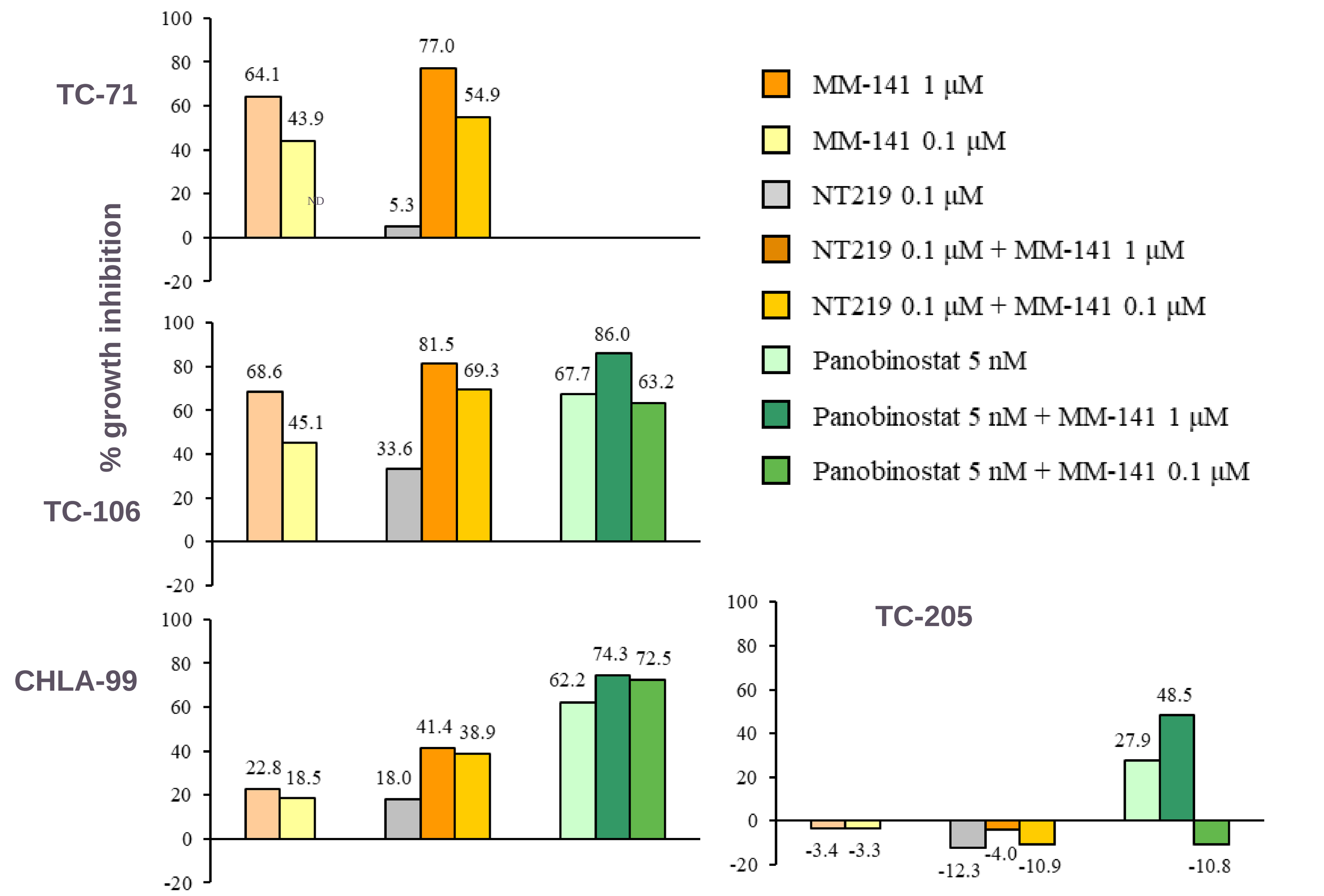
Results Drug Response:

Strong growth inhibition of istiratumab in Ewing sarcoma TC-71 and TC-106 and moderate in CHLA-99, lack of response in TC-205.

Moderate growth inhibition in RMS RD, Rh30 and Rh41.



The antiproliferative effects of istiratumab in Ewing sarcoma cells can be enhanced through combination with the IRS1/2 inhibitor NT219 or the pan HDACi panobinostat



Conclusion:

- IGF-1 pathway is widely expressed in pediatric cancers, whereas ERBB3 is expressed in rhabdomyosarcoma and hepatoblastoma; IRS1 and IRS2 overexpression if frequent in Ewing sarcoma
- Istiratumab has antiproliferative activity in sarcomas and can be enhanced by IRS or HDAC inhibitors
- A comprehensive pathway analysis in patients previously treated with IGF-1R antibodies is ongoing
- Istiratumab will be evaluated in molecularly selected pediatric malignancies and Ewing sarcoma within the AcSé-ESMART trial.