# ARST08P1: A Pilot Study to Evaluate Novel Agents (Temozolomide and Cixutumumab [IMC-A12, Anti-IGF-IR Monoclonal Antibody, IND #100947, NSC #742460]) in Combination With Intensive Multi-Agent Interval Compressed Therapy for Patients With High-Risk Rhabdomyosarcoma

| Type | Status | Age Range (yrs.) | Sponsor |
|---|---|---|---|
| Interventional | Open Label | up to 49 years | CCHMC |

## Rationale

Drugs used in chemotherapy, such as temozolomide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Monoclonal antibodies, such as cixutumumab, can block tumor growth in different ways. Some block the ability of tumor cells to grow and spread. Others find tumor cells and help kill them or carry tumor-killing substances to them. Giving temozolomide and cixutumumab together with combination chemotherapy may kill more tumor cells.

## Purpose

This clinical trial is studying the side effects and how well giving temozolomide and cixutumumab together with combination chemotherapy works in treating patients with metastatic rhabdomyosarcoma.

## Objectives

### Primary

- To determine the feasibility of administering cixutumumab in combination with an intensive multi-agent interval compressed chemotherapy regimen for the treatment of high-risk metastatic rhabdomyosarcoma (RMS).
- To determine the feasibility of adding temozolomide to vincristine and irinotecan in these patients.
- To assess immediate and short-term side effects of concurrent temozolomide, vincristine, and irinotecan with radiotherapy in these patients.
- To determine the feasibility of administering cixutumumab in combination with an intensive multi-agent interval compressed chemotherapy regimen comprising temozolomide, vincristine, and irinotecan in these patients.

### Secondary

- To gain a preliminary estimate of the response rate to cixutumumab and/or temozolomide, vincristine, and irinotecan in these patients.
- To obtain preliminary efficacy data for cixutumumab and/or temozolomide in combination with an intensive multi-agent interval compressed chemotherapy regimen in these patients.
- To determine the effectiveness of detecting metastatic disease with fludeoxyglucose F 18 positron emission tomography (FDG PET) and to compare assessment of response using standard imaging techniques with response assessed by FDG PET.
- To assess changes in serum levels of IGF-I, IGF-II, IGF-BP3 as biomarkers of IGF-IR inhibition.

## Eligibility

Ages Eligible for Study: up to 49 Years

## Outline

This is a multicenter, dose-escalation study of cixutumumab. Patients are assigned to 1 of 3 treatment groups according to the timing of their enrollment onto the study.

- Group 1: Patients receive vincristine sulfate IV on day 1 of weeks 1-5, 7, 8, 11, 12, 15, 16, 20-24, 28, 29, 32, 33, 35, 38, 41-44, 47, 48, 50, and 51; irinotecan hydrochloride IV over 90 minutes on days 1-5 of weeks 1, 4, 20, 23, 47, and 50; ifosfamide IV over 1 hour and etoposide IV over 1-2 hours on days 1-5 of weeks 9, 13, 17, 26, and 30; doxorubicin hydrochloride IV on days 1 and 2 of weeks 7, 11, 15, 28, and 32; cyclophosphamide IV over 30-60 minutes on day 1 of weeks 7, 11, 15, 28, 32, 35, 38, 41, and 44; dactinomycin IV on day 1 of weeks 35, 38, 41, and 44; and cixutumumab IV over 1 hour on day 1 of weeks 1-51. Patients also undergo radiotherapy* on days 1-5 of weeks 20-24.
- Group 2: Patients receive vincristine sulfate, irinotecan hydrochloride, ifosfamide, etoposide, doxorubicin hydrochloride, cyclophosphamide, and dactinomycin and undergo radiotherapy* as in group 1. Patients also receive oral temozolomide on days 1-5 of weeks 1, 4, 20, 23, 47, and 50.
- Group 3: Patients receive vincristine sulfate, irinotecan hydrochloride, ifosfamide, etoposide, doxorubicin hydrochloride, cyclophosphamide, dactinomycin, and cixutumumab and undergo radiotherapy* as in group 1. Patients also receive temozolomide as in group 2.
- NOTE: *Patients with parameningeal tumors and evidence of intracranial extension or those requiring emergency radiotherapy may receive radiotherapy starting in week 1; cixutumumab should be withheld during radiotherapy..

Patients in groups 1 and 3 may undergo blood sample collection at baseline and after completion of week 6 for IGF-I, IGF-II, and IGF-BP3 biomarker analysis.

After completion of study therapy, patients are followed up periodically for up to 10 years.

## Disease Characteristics

- Newly diagnosed, biopsy-confirmed metastatic rhabdomyosarcoma (RMS) or ectomesenchymoma, including the following:Embryonal RMS (for patients 10 to 49 years of age)
  - Alveolar RMS or ectomesenchymoma (for patients under 50 years of age)
- RMS with parameningeal and paraspinal primary tumors, including those with intracranial extension by contrast MRI showing that the primary tumor touches, displaces, invades, distorts, or otherwise causes signal abnormality of the dura in brain or spinal cord in contiguity to the primary site, are allowed
- Has undergone initial surgery (including biopsy) that provided the definitive diagnosis within the past 42 days
- Enrollment on COG-D9902 required

## Patient Characteristics

- ECOG performance status (PS) 0-2
- ANC ≥ 750/µL*
- Platelet count ≥ 75,000/µL*

- Creatine clearance or radioisotope GFR ≥ 70 mL/min/1.73m2 OR maximum serum creatinine based on age/gender as follows:
  - 0.4 mg/dL (for patients 1 to 5 months of age)
  - 0.5 mg/dL (for patients 6 to 11 months of age)
  - 0.6 mg/dL (for patients 1 year of age)
  - 0.8 mg/dL (for patients 2 to 5 years of age)
  - 1.0 mg/dL (for patients 6 to 9 years of age)
  - 1.2 mg/dL (for patients 10 to 12 years of age)
  - 1.5 mg/dL (males) or 1.4 mg/dL (females) (for patients 13 to 15 years of age)
  - 1.7 mg/dL (males) or 1.4 mg/dL (females) (for patients ≥ 16 years of age)
- Urinary tract obstruction by tumor allowed provided the above renal function criteria are met AND there is unimpeded urinary flow established via decompression of the obstructed portion of the urinary tract
- Total bilirubin ≤ 1.5 times upper limit of normal (ULN) for age (unless there is evidence of biliary obstruction by the tumor)
- Shortening fraction ≥ 27% by ECHO OR ejection fraction ≥ 50% by radionuclide angiogram
- Not pregnant or nursing
- Negative pregnancy test
- Fertile patients must use effective contraception during and for ≥ 3 months after the last dose of cixutumumab
- No uncontrolled infection
- No known type I or type II diabetes mellitus (for patients enrolled in groups 1 or 3) NOTE: *Abnormal blood counts allowed provided bone marrow biopsy or aspirate confirm bone marrow involvement by RMS

## Prior Concurrent Therapy

- No prior chemotherapy or radiotherapy except corticosteroids or emergent radiotherapy
- No concurrent growth hormone therapy
- No concurrent sargramostim

## Who should I contact for more information?

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