PDGFRα Antibody
Olaratumab, LY3012207, IMC-3G3

Drug Discovery Platform: Cancer Angiogenesis and Tumor Microenvironment
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

### Key Inclusion Criteria
- No more than two prior lines of systemic therapies (neoadjuvant and adjuvant therapies will not be considered as a prior line of therapy) for advanced or metastatic disease and should be suitable to receive gemcitabine and docetaxel therapy. All previous therapies must have been completed ≥4 weeks (28 days) prior to enrollment (phase 1b) or randomization (phase 2).
- Availability of tumor tissue or willing to undergo a pretreatment biopsy of primary or metastatic tumor for future central pathology review and translational research (if archived tissue is unavailable).
- Adequate hematologic, organ, and coagulation function within 2 weeks (14 days) prior to enrollment or randomization.

### Key Exclusion Criteria
- Gastrointestinal stromal tumor or Kaposi sarcoma.
- Active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of enrollment or randomization. Participants with a history of a CNS metastasis previously treated with curative intent (eg, stereotactic radiation or surgery) who have not progressed on follow-up imaging, have been asymptomatic for at least 60 days, and are not receiving systemic corticosteroids and/or anticonvulsants, are eligible. Participants with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before enrollment or randomization to rule out brain metastasis.
- Prior treatment with gemcitabine, docetaxel, and/or olaratumab. Participants previously enrolled in I5B-MC-JGDJ (NCT02451943) or any other blinded study with olaratumab are not eligible to participate in this trial.
- Electively planned or will require major surgery during the course of the study.
- Pregnant or breast-feeding.
- Active symptomatic fungal, bacterial, or viral infection, including HIV or hepatitis A, B, or C.

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02659020].

* This clinical trial is being conducted globally.

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### Phase 1b
- **Primary endpoint:** Recommended phase 2 dose of olaratumab in combination with gemcitabine and docetaxel.

### Phase 2
- **Primary endpoint:** Overall survival.

Participants may continue on study drug until disease progression, unacceptable toxicity, or other withdrawal criteria is met.

† Olaratumab or placebo equivalent is administered intravenously (IV) on days 1 and 8 of a 21-day cycle.

‡ Docetaxel is administered IV on day 8 of a 21-day cycle.

§ Gemcitabine is administered IV on days 1 and 8 of a 21-day cycle.

|| Olaratumab† + docetaxel‡ + gemcitabine§

Placebo‡ + docetaxel‡ + gemcitabine§

**PDGFRα Antibody Olaratumab, LY3012207, IMC-3G3**
Key Inclusion Criteria

- Solid tumor, excluding lymphomas and melanoma, but including central nervous system (CNS) tumors, that is relapsed or refractory and not amenable to curative treatment
- Measurable and/or nonmeasurable but evaluable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Response Assessment in Neuro-Oncology (RANO) Criteria or MacDonald Criteria should be used for CNS tumors
- Lansky (<16 years of age) or Karnofsky (≥16 years of age) performance score of ≤50
- Adequate hematologic, organ, and coagulation function 2 weeks (14 days) prior to first dose of study drug, including:
  - Absolute neutrophil count ≥750 mm³, platelets ≥75,000/mm³, hemoglobin ≥8 g/dL
  - Total bilirubin ≤1.5x upper limit of normal (ULN) for age, alanine aminotransferase and aspartate aminotransferase ≤3.0x ULN
  - Creatinine within the normal limits based on age/gender
  - Adequate coagulation function as defined by international normalized ratio ≤1.5 or prothrombin time ≤1.5x ULN, and partial thromboplastin time ≤1.5x ULN
- Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug

Key Exclusion Criteria

- Prior treatment within 21 days of the initial dose of study drug with an investigational product or nonapproved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
- Prior bone marrow or solid organ transplant
- Active fungal, bacterial, and/or known severe viral infection, including HIV or hepatitis A, B, or C
- Pregnant or breast-feeding
- For doxorubicin combination arm:
  - Left ventricular dysfunction (left ventricular ejection fraction of <50%)
  - Prior anthracycline therapy

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02677116].

* This clinical trial is being conducted in the United States.
The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

Key Inclusion Criteria
- Soft tissue sarcoma for which olaratumab and doxorubicin would be appropriate therapy
- Participants with a diagnosis of grade 1 liposarcoma are eligible if there is histological or radiographic evidence of evolution to more aggressive disease. Participants with Kaposi’s sarcoma and gastrointestinal stromal tumors will be excluded
- Must have potentially resectable disease (as assessed by the study investigator) and have a primary tumor lesion deemed amenable to serial biopsy
- Consent to undergo mandatory serial peripheral whole blood and tumor tissue sampling

Key Exclusion Criteria
- Active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of enrollment
- Participants with a history of a CNS metastasis previously treated with curative intent (e.g., stereotactic radiation or surgery) and have not progressed on follow-up imaging, have been asymptomatic for at least 60 days, and are not receiving systemic corticosteroids and/or anticonvulsants are eligible. Participants with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before enrollment to rule out brain metastasis
- Prior treatment with doxorubicin, epirubicin, idarubicin, and/or other anthracyclines or anthracenediones
- Prior treatment with olaratumab
- PDGFRα Antibody
  - Olaratumab, LY3012207, IMC-3G3
  - Olaratumab is administered intravenously (IV) on days 1 and 8 of a 21-day cycle.
  - Starting with cycle 2, doxorubicin is administered IV on day 1 of a 21-day cycle for up to seven cycles.

Primary endpoint: Change in circulating tumor cells and expression of PDGFRα, PDGFRβ, and associated ligands

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT02783599].

* This clinical trial is being conducted globally.
Target
Platelet-derived growth factor receptor α (PDGFRα) is expressed in multiple tumor types, and its aberrant activation has been implicated in cancer. Coexpression of PDGFRα and PDGFs, consistent with autocrine-mediated growth, has been reported in sarcomas and glioblastomas. Gene amplification and activating mutations of PDGFRα have been found in subsets of glioblastomas, non-small cell lung cancers, and gastrointestinal stromal tumors. PDGFRα expression has been associated with increased metastatic potential in preclinical models. Paracrine stimulation of PDGFRα-positive stromal cells has been shown in preclinical studies to enhance tumor growth by providing factors for angiogenesis and extracellular matrix remodeling.

Molecule
Olaratumab (LY3012207, IMC-3G3) is a human IgG1 monoclonal antibody designed to bind to human PDGFRα with high affinity and block PDGF-AA, PDGF-BB, and PDGF-CC ligands from binding to the receptor.

Clinical Development
Olaratumab is being investigated in a phase I pediatric clinical trial and in clinical trials in patients with sarcoma.

References: