To determine the safety and tolerability of ENMD-2076 monotherapy in treatment naïve/ lightly pre-treated metastaticSTS.

**Objectives**

**Primary Objective:**
- To determine the activity of ENMD-2076 as defined by the Clinical Benefit Rate (CBR) - CR + PR > SD > 6 months

**Secondary Objectives:**
- To determine the safety and tolerability of ENMD-2076
- Survival analysis in terms of Progression-Free Survival (PFS) and Overall Survival (OS)
- To determine overall response rate (ORR, RECIST 1.1) and duration of response (DOR)
- To perform correlative studies that may define patients with superior/inferior PFS

**Methods**

Single arm, open labeled phase II study of ENMD-2076 administered at 275 mg daily on a 28-day cycles

**Inclusion Criteria:**
- **ECOG 0 or 1**
- **Histological diagnosis of STS with exception of GIST**

**Exclusion Criteria:**
- Measurable disease within 4 weeks of study entry
- No more than 1 line of treatment in advanced/metastatic setting
- Adequate cardiac function with MUGA scan with EF > institutional lower limit of normal within 4 weeks of study entry
- Consent to access archival material for correlative studies or for fresh biopsy if no archival tissue available
- Known CNS metastases
- Uncontrolled hypertension, active angina pectoris, stroke or myocardial infarction within last 6 months requiring therapeutic anticoagulation
- Prior history of DVT or pulmonary embolism

**Patient Characteristics (n=23)**

<table>
<thead>
<tr>
<th>Medium Age (Range)</th>
<th>Gender Female/Male</th>
<th>ECOG PS*</th>
<th>0:1</th>
<th>12:11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology:</td>
<td></td>
<td>ASPS</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lipomysarcoma</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td># Prior Regimens:</td>
<td></td>
<td>1:0</td>
<td>7:16</td>
<td>1:0</td>
</tr>
</tbody>
</table>

**Adverse Events**

- **AE Terminology**
  - % Any grade (n)
  - % Grade >3 (n)
  - Hypertension (70/16) (56/13)
  - Fatigue (65/15) (4/1)
  - Albumin decreased (65/15) (0)
  - Diarrhea (41/11) (17/4)
  - Pyrexia (41/11) (0)
  - ALT increased (41/11) (35/8)
  - Dyspepsia (41/11) (0)
  - Weight decreased (43/10) (4/1)
  - AST increased (35/8) (8/2)
  - Reversible posterior leukocerebral/leukoencephalopathy (4/1) (4/1)
  - Colitis (4/1) (4/1)
  - Neutrophil count decreased (8/2) (4/1)

**Clinical Efficacy**

| Total number of evaluable pts | 12 |
| Best Response (n) | PR | 2 |
| SD | 11 |
| PD | 2 |
| Clinical Benefit Rate | PR + SD = 6 months | 11% |
| Median OS | Not reached |
| Median PFS | 2.7 mo (95% CI 1.7–4.3) |

**Conclusions**

- ENMD-2076 has shown clinical activity in pts with advanced STS, with clinical benefits and side effects profile typical of this class of agent.
- Drug toxicities were of low grade and tolerable.
- High grade toxicities included hypertension (56%), ALT increase (35%) and proteinuria (17%).
- All 4 patients who derived clinical benefit (2 PR and 2 SD > 6months) received ENMD-2076 in the first-line setting.
- Genetic variations in CCL4 and FLNB (FlaminB) are potentially associated with benefit from ENMD-2076 while gene variations in EGFR, and VEGFR1/3 polymorphism could be associated with lack of benefit. These findings warrant further investigation.

**References:**