**Background**

- ME-344 is a second-generation isoflavan-derived compound.
- ME-344 is derived from the demethylated metabolite of NV-128, the first-generation molecule in this class.
- ME-344 causes caspase-independent cell death in multiple human tumor cell lines including CD44+ glioblastoma overexpressing stem cells by interfering with mitochondrial energy generation.
- Treatment with ME-344 results in decreased mitochondrial ATP production and increased reactive oxygen species, with subsequent disruption of tumor cell mitochondrial integrity.
- Decreased ATP leads to formation of autophagic vacuoles via activation of AMP kinase and mTOR-1 and mTOR-2-dependent signaling pathways (see Figure 1).

**Methods**

- A 3+3 dose escalation design was utilized.
- 5 dose cohorts were planned: 1.25, 2.5, 5, 10, and 20 mg/kg.
- An intermediate 15 mg/kg dose level was explored.
- ME-344, formulated in 30% Captisol®, was administered IV over 30 minutes, weekly times 2.
- Tumor assessments were required at least every 12 weeks and scored according to RECIST v1.1.

**Results**

- Subject Disposition
  - Between May 17, 2012 and March 18, 2013, 30 subjects were enrolled.
  - The data cut-off is October 15, 2013.
- Adverse Events
  - **Subjects Enrolled (n = number of subjects experiencing an event)**
    - Small Cell Lung Cancer: 12 (n=8)
    - Non-Small Cell Lung Cancer: 10 (n=4)
    - Ovarian: 1 (n=3)
    - Breast: 1 (n=3)
    - Cervical Cancer of Unknown Primary: 1 (n=3)
    - Endometrial: 1 (n=3)
    - Pancreatic: 1 (n=3)
    - Colorectal: 1 (n=3)
    - Peritoneal NOS: 1 (n=3)
    - Sarcoma NOS: 1 (n=3)
    - Lung-Small Cell: 1 (n=3)
    - Melanoma: 1 (n=3)
    - Breast: 1 (n=3)
    - Endometrial: 1 (n=3)
    - Lung-Small Cell: 1 (n=3)
    - Pancreatic: 1 (n=3)
    - Peritoneal NOS: 1 (n=3)
    - Sarcoma NOS: 1 (n=3)
    - Lung-Small Cell: 1 (n=3)
    - Melanoma: 1 (n=3)
- Duration of ME-344 Infusion
  - ME-344 Maximum Tolerated Dose and the Recommended Phase 2 Dose
  - Pharmacokinetic Results
  - **Dose Limiting Toxocities**
  - **Pharmacokinetic Results**
  - **Treatment Emergent Adverse Events (TEAE) ≥ 10% and Clinically Significant Events (≥ number of subjects experiencing an event)**

**Conclusions**

- The ME-344 Maximum Tolerated Dose and the Recommended Phase 2 Dose was established at 10 mg/kg IV weekly.
- The primary DLT was peripheral neuropathy consistent with the proposed mechanism of action.
- At doses ≤10 mg/kg ME-344 was generally well tolerated for extended durations.
- Pharmacokinetics suggest a linear relationship between dose, Cmax and exposure increased with dose in a linear fashion.
- Further clinical development of ME-344 is warranted.