40TH ANNUAL MEETING ON

WOMEN'S CANCER™

February 5-8, 2009

Henry B. Gonzalez Convention Center

San Antonio, Texas

Hedgehog pathway inhibitor cyclopamine suppresses Gli1 expression and inhibits serous ovarian cancer xenograft growth

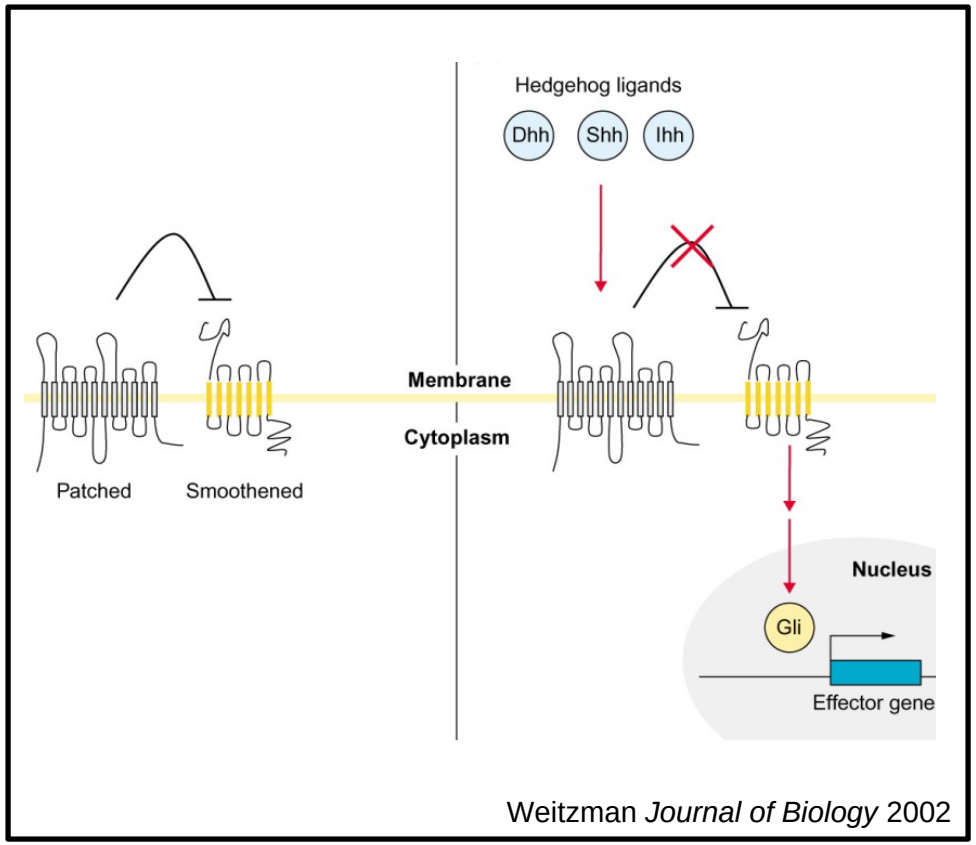
Growdon WB, McCann CR, Curley M, Friel AM, Mandley E, Ferguson J, Foster R, MacDougal J, Rueda BR

SGO
Society of Gynecologic Oncologists

Outline

- **Hedgehog pathway and cancer**
- **Hypothesis**
- **Methods**
- **Results**
- **Conclusions**

Heightened activation of the Hedgehog (Hh) pathway implicated in numerous solid tumor malignancies



Weitzman *Journal of Biology* 2002

Hypothesis

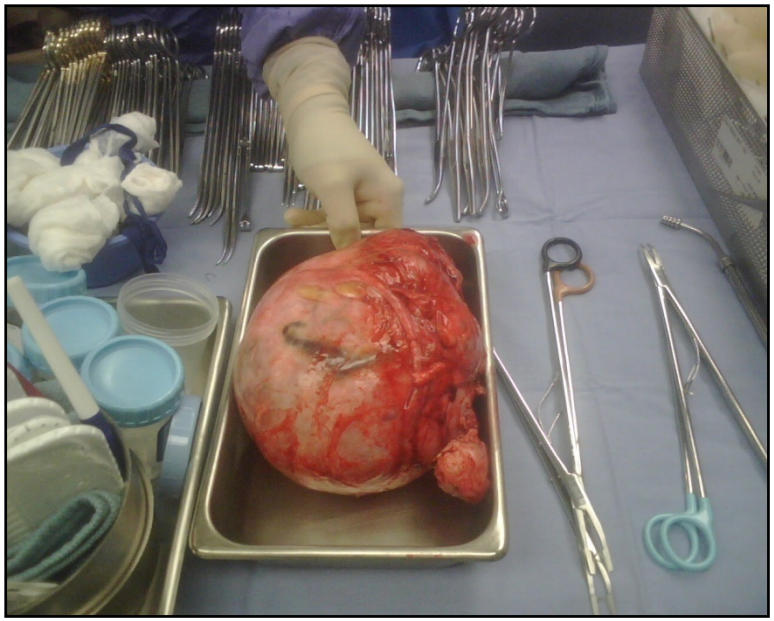
Hh pathway inhibition potentiates conventional cytotoxic chemotherapy for ovarian cancer

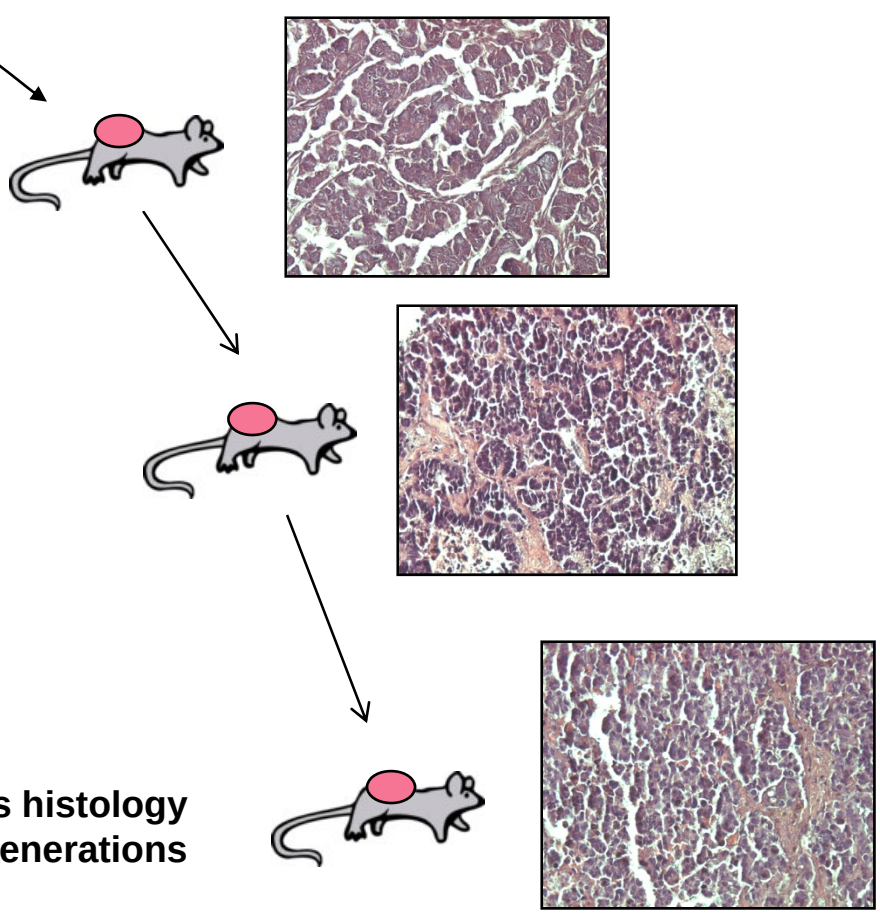
Goal

Characterize single agent and adjuvant activity of cyclopamine against a novel *in vivo* ovarian cancer model

Methods

Primary Xenograft Model





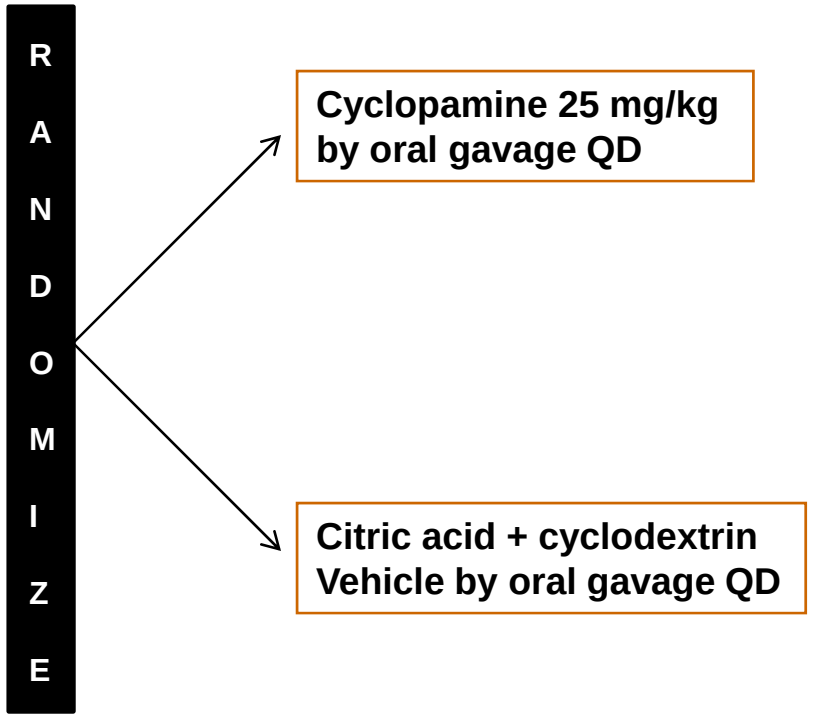
Preserved serous histology throughout transplant generations

Methods

Multiphase phase experimental design utilizing xenograft platform

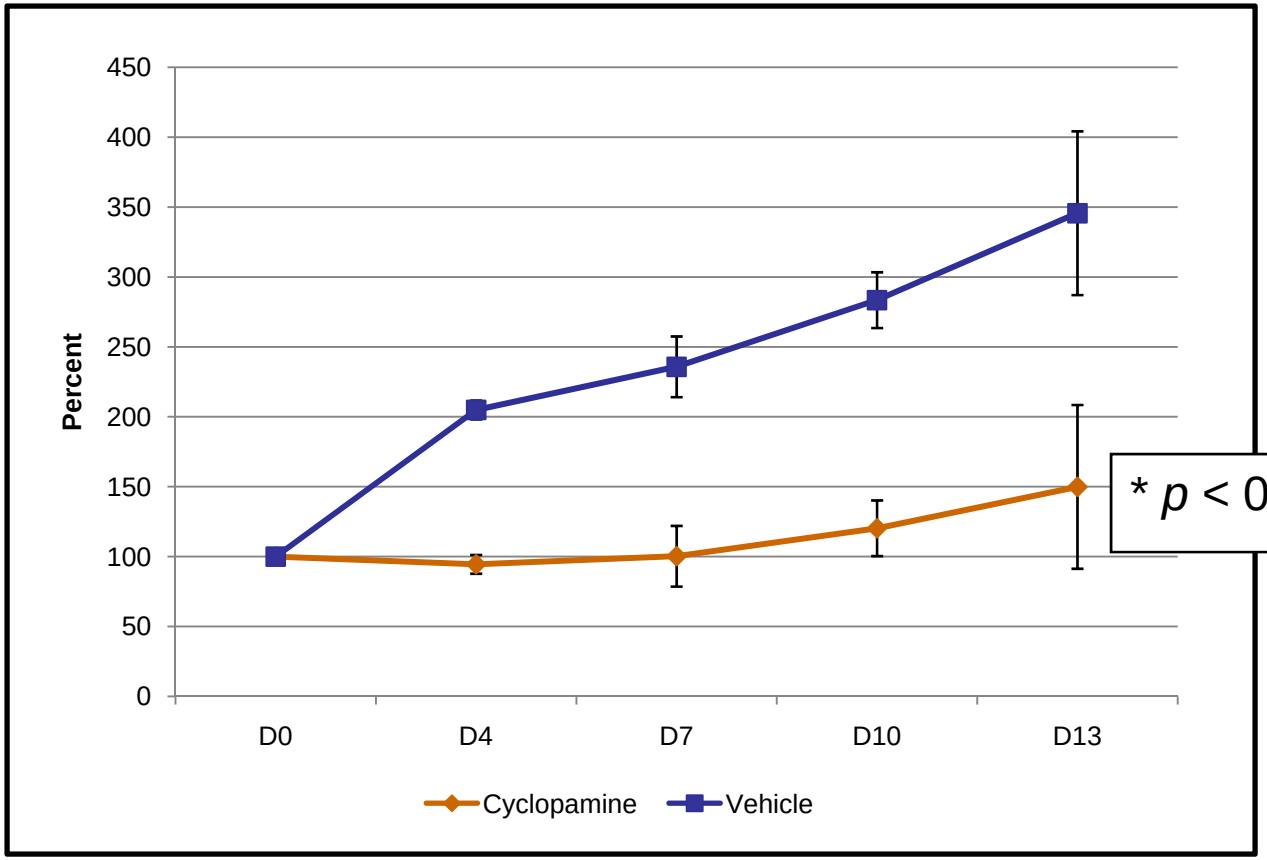
I. Cyclopamine single agent efficacy

12 NOD/SCID mice
All 6 weeks old
Matched xenograft tumors 300 – 600 mm^3



Results

Cyclopamine precludes serous xenograft growth compared to vehicle

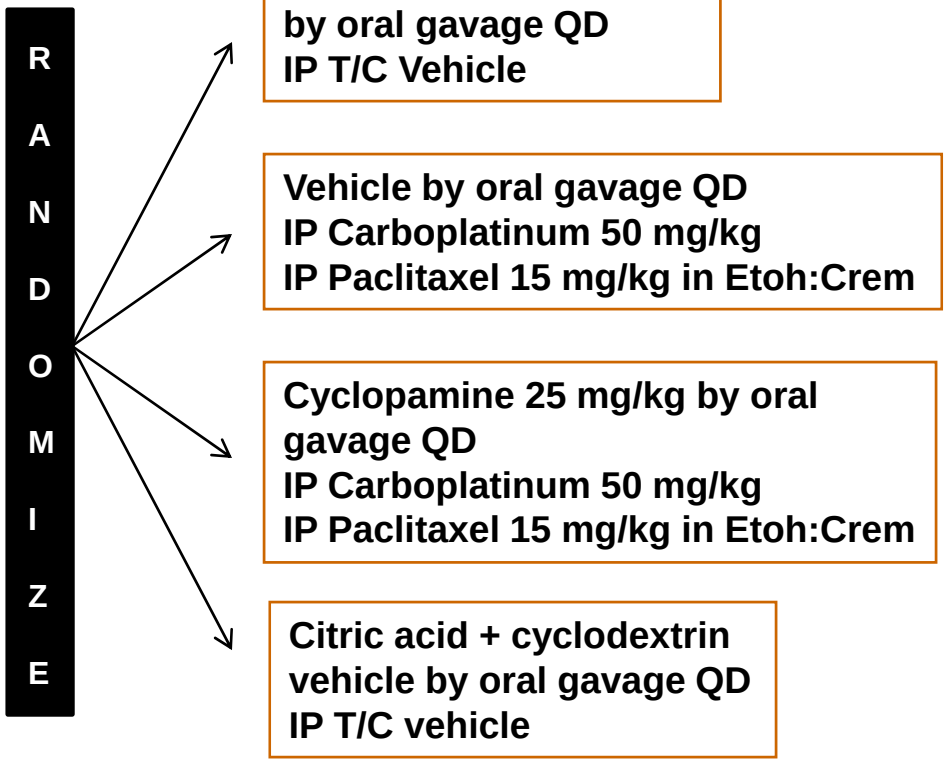


Methods

Multiphase phase experimental design utilizing xenograft platform

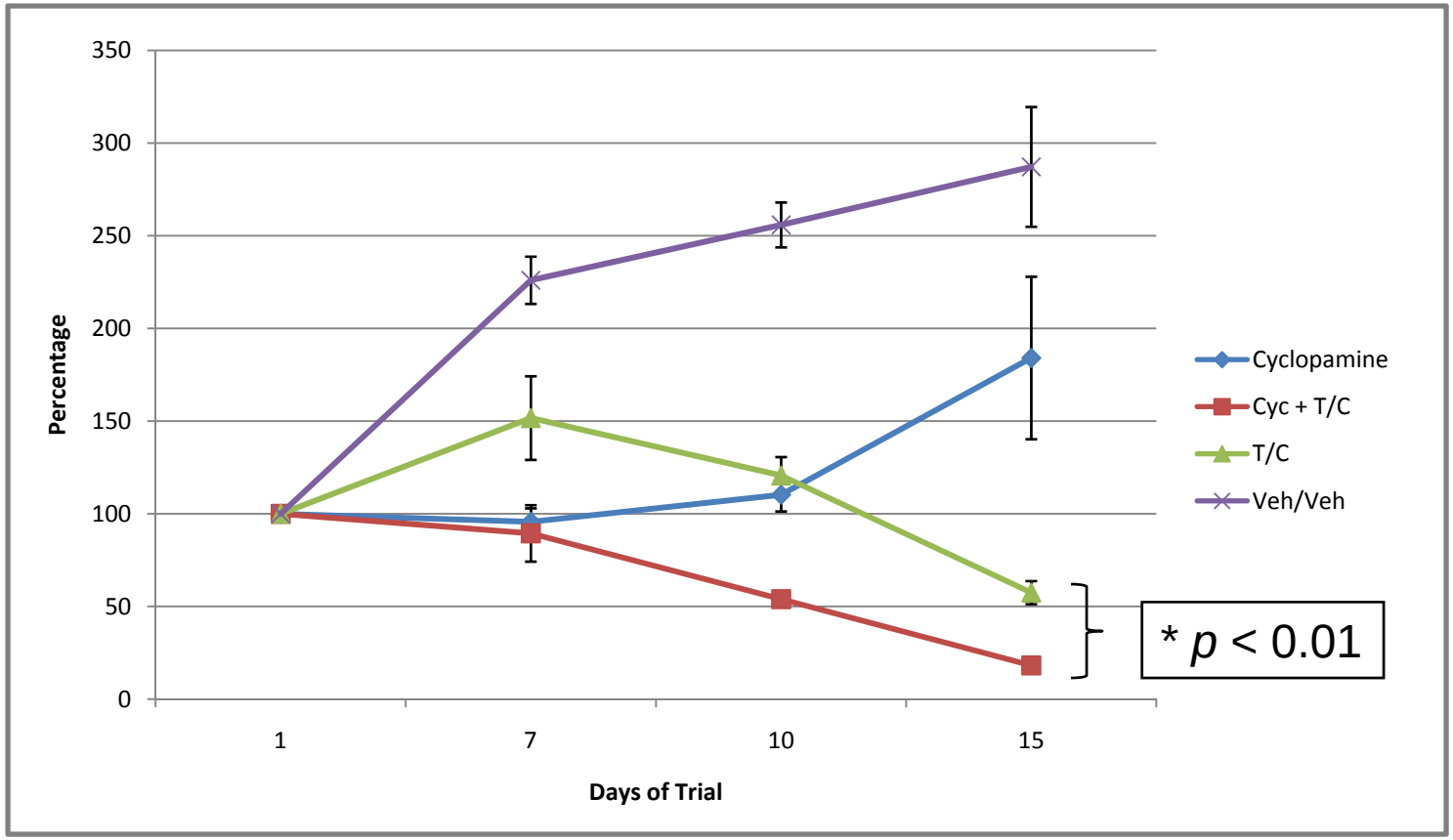
I. Cyclopamine adjuvant agent efficacy

20 NOD/SCID mice
All 6 weeks old
Matched xenograft tumors 300 – 600 mm^3



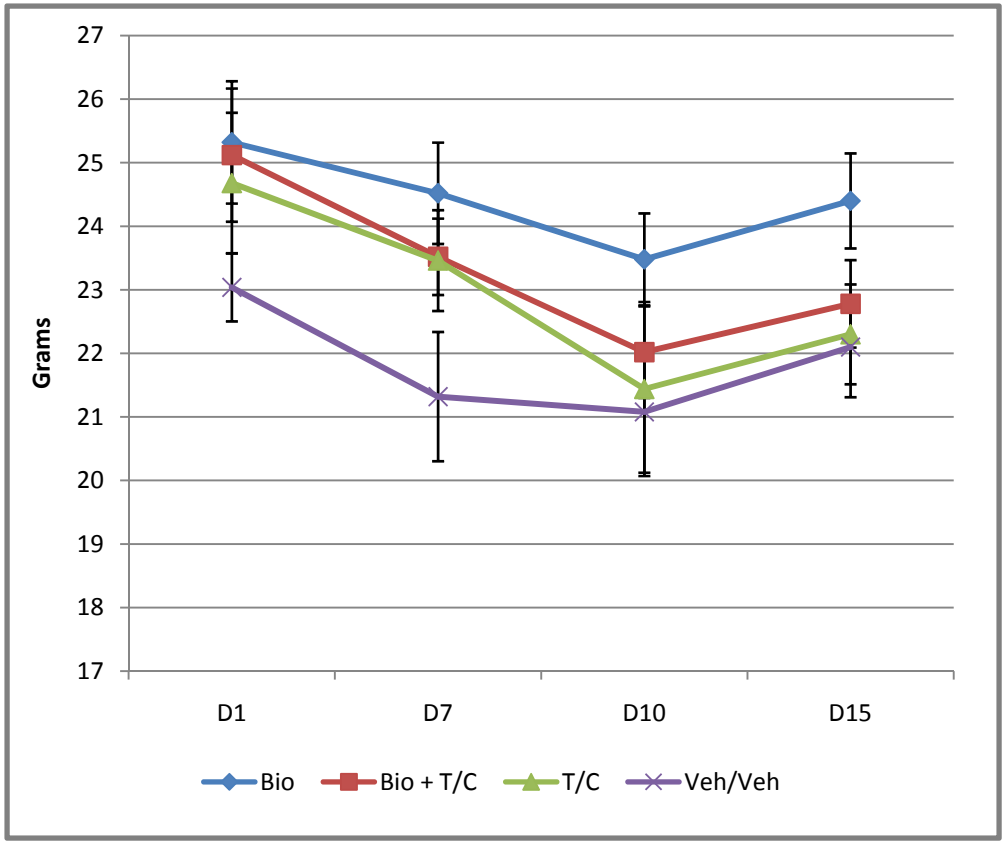
Results

Cyclopamine exhibits both single agent and synergistic efficacy to preclude serous ovarian tumor xenograft growth

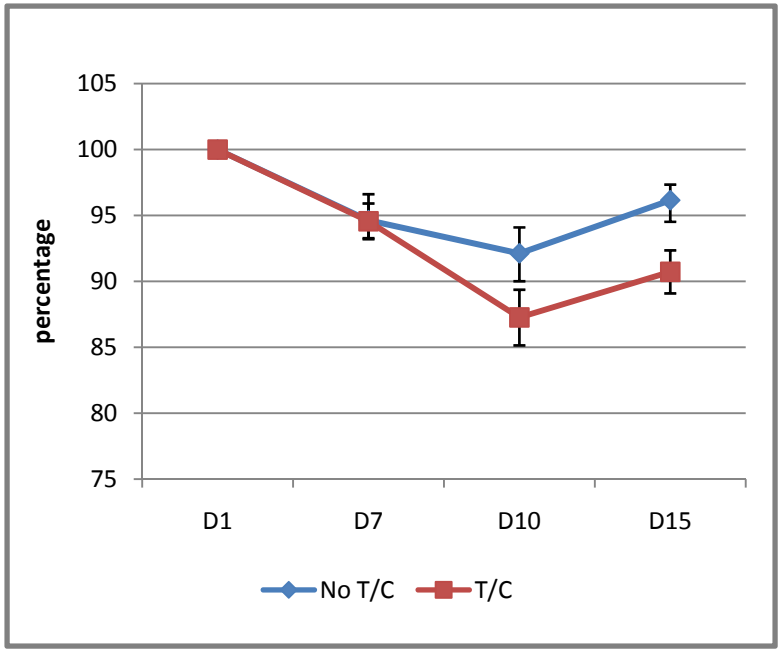


Results

All treated animals exhibited a similar pattern of weight loss

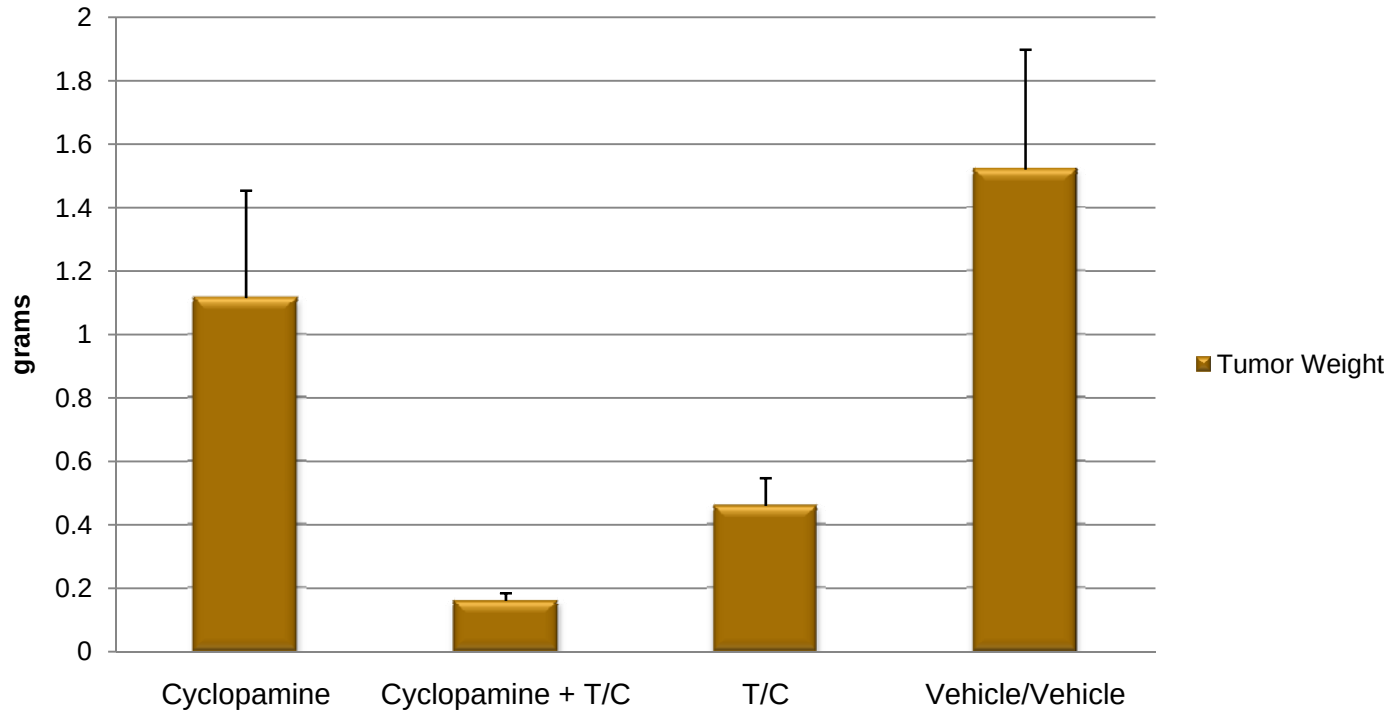


T/C therapy was associated with a greater weight loss



Results

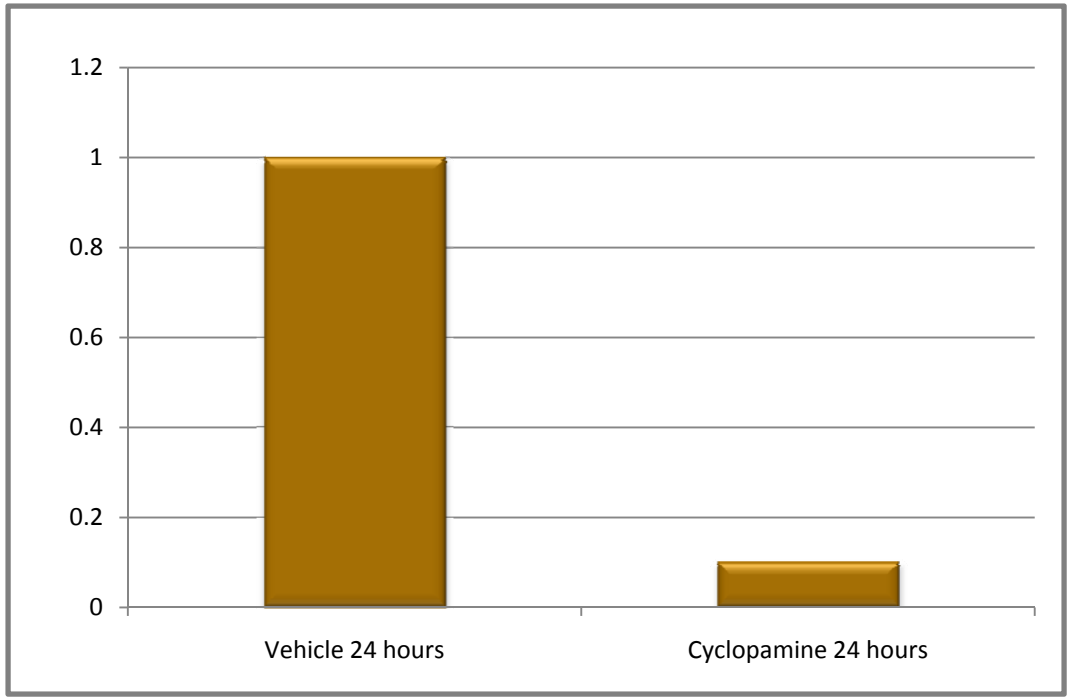
Cyclopamine in concert with T/C manifested the lowest tumor mass after 14 days compared to all other therapies



Pooled tumor weights after treatment with the four different regimens

Results

Quantitative RT-PCR revealed that after 24 hours, Gli1 mRNA levels in the human compartment were reduced 10x following administration of cyclopamine



No differences in PTCH, SMO, SHH, DHH, IHH mRNA levels were observed between vehicle and cyclopamine treated human tumor cells

Conclusions

- **Inhibition of the Hh pathway precluded proliferation of serous ovarian cancer xenografts**
- **Cyclopamine demonstrated efficacy as a single agent and adjuvant therapy**
- **Treatment was associated with decreased levels of Gli1**
- **Human therapies for ovarian cancer directed against the Hh cascade merit exploration in clinical trials.**

Acknowledgements

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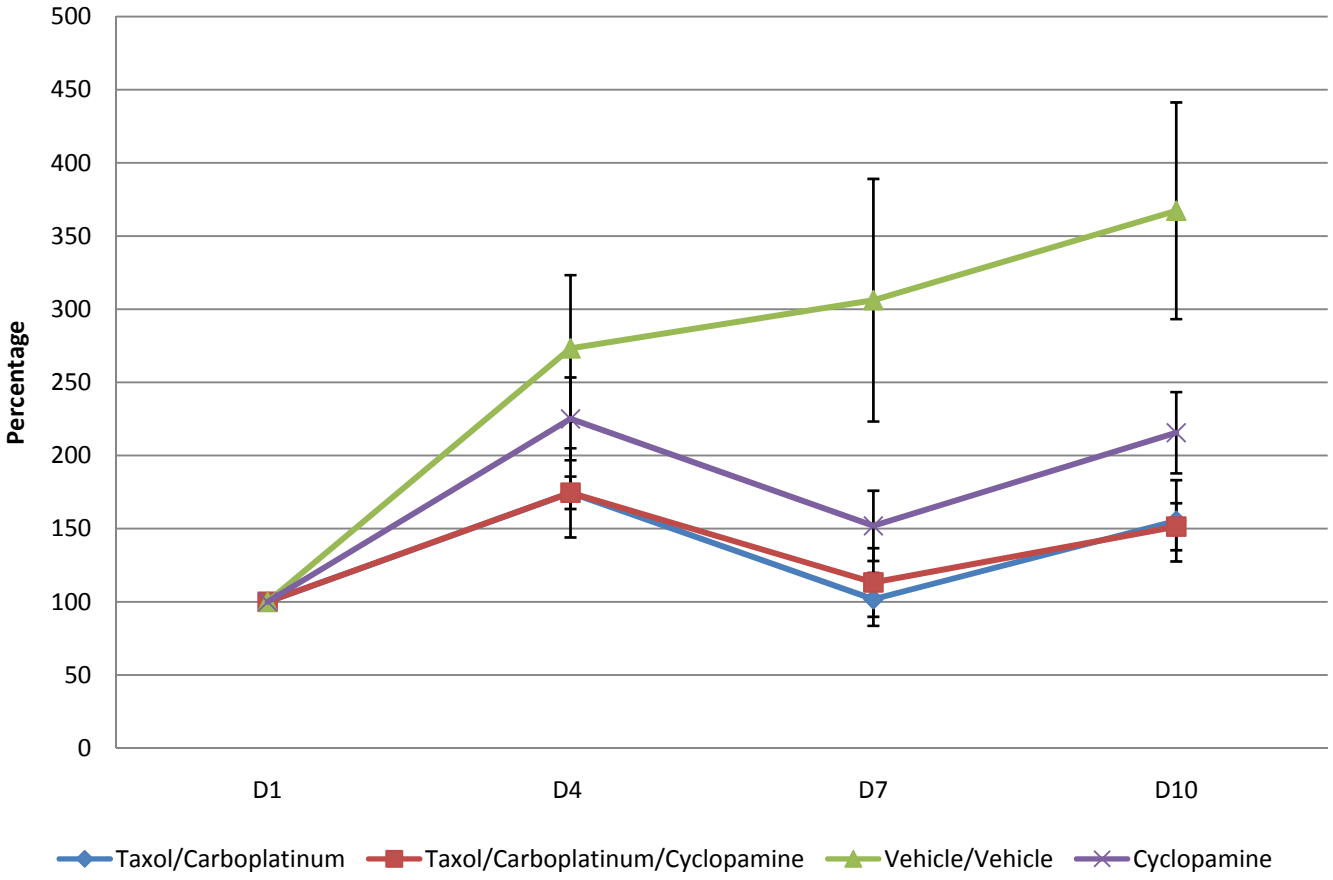
Second trial of cyclopamine as single agent and adjuvant treatment for platinum insensitive serous ovarian cancer in a xenograft tumors



Methods

Three phase experimental design utilizing xenograft platform

PHASE I

Treat mice with matched xenograft tumors with cyclopamine or vehicle by oral gavage and harvest after timed intervals to assess for pharmacokinetic effects on cellular targets

PHASE II

Treat two cohorts of mice with matched xenograft tumors with cyclopamine or vehicle by oral gavage and follow animal weight and tumor growth over the course of 21 days. Harvest tumors to assess for effects on cellular targets.

PHASE III

Treat four cohorts of mice with matched xenograft tumors with oral cyclopamine, intra-peritoneal (IP) Paclitaxel/Carboplatinum (T/C), cyclopamine + T/C or vehicle (oral and IP) and follow animal weight and tumor growth over the course of 21 days. Harvest tumors to assess for effects on cellular targets.