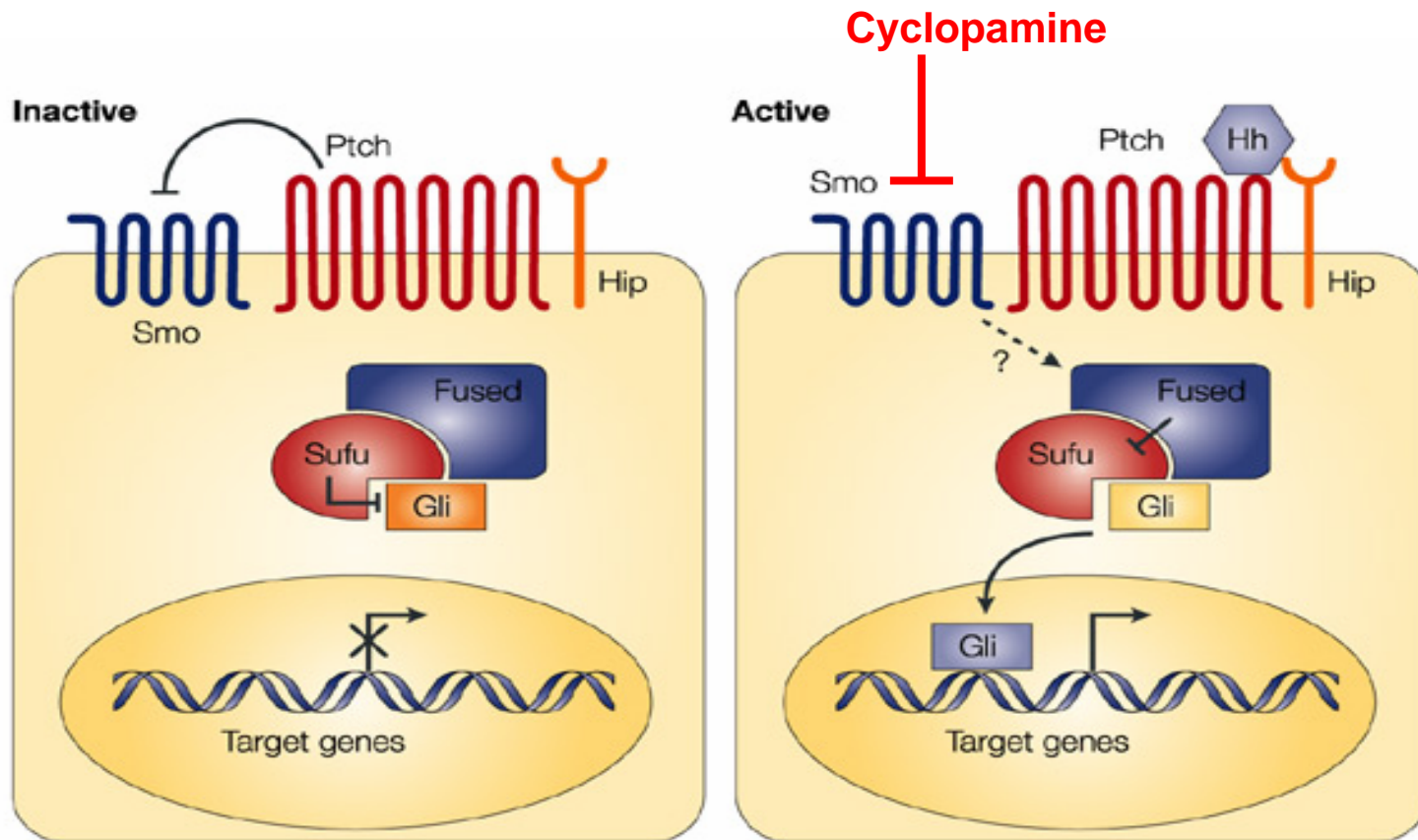


Activity of IPI-926, a potent HH pathway inhibitor, in a novel model of medulloblastoma derived from Ptch/HIC +/- mice

April 13, 2008

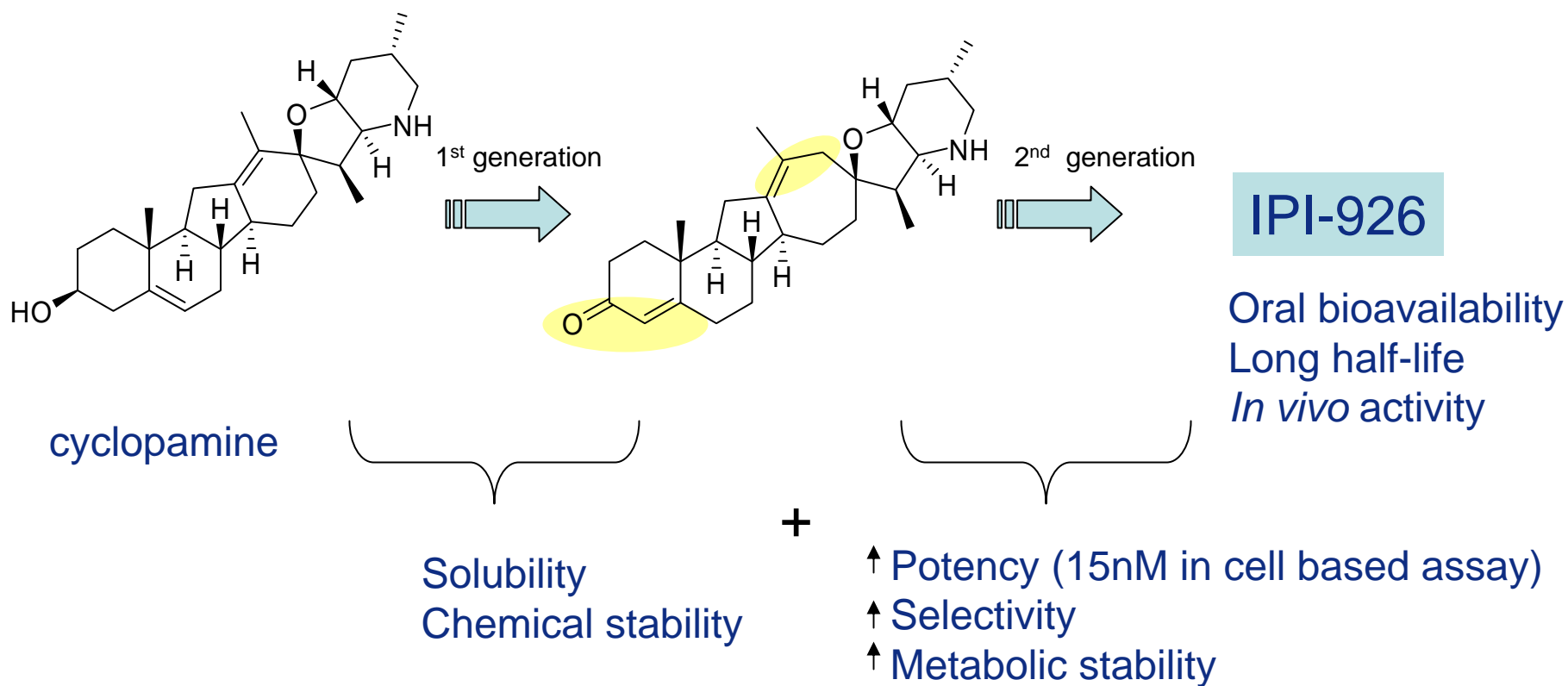
M. Pink, J. Proctor, K. Briggs, J. MacDougall, N. Whitebread, M. R. Tremblay, M. Grogan, V. Palombella, A. Castro, J. Adams, M. Read, I. M. Corcoran-Schwartz, T. Harcke, C. G. Eberhart, D. N. Watkins, J. Sydor **Abstract #1588**

The Hedgehog signaling pathway

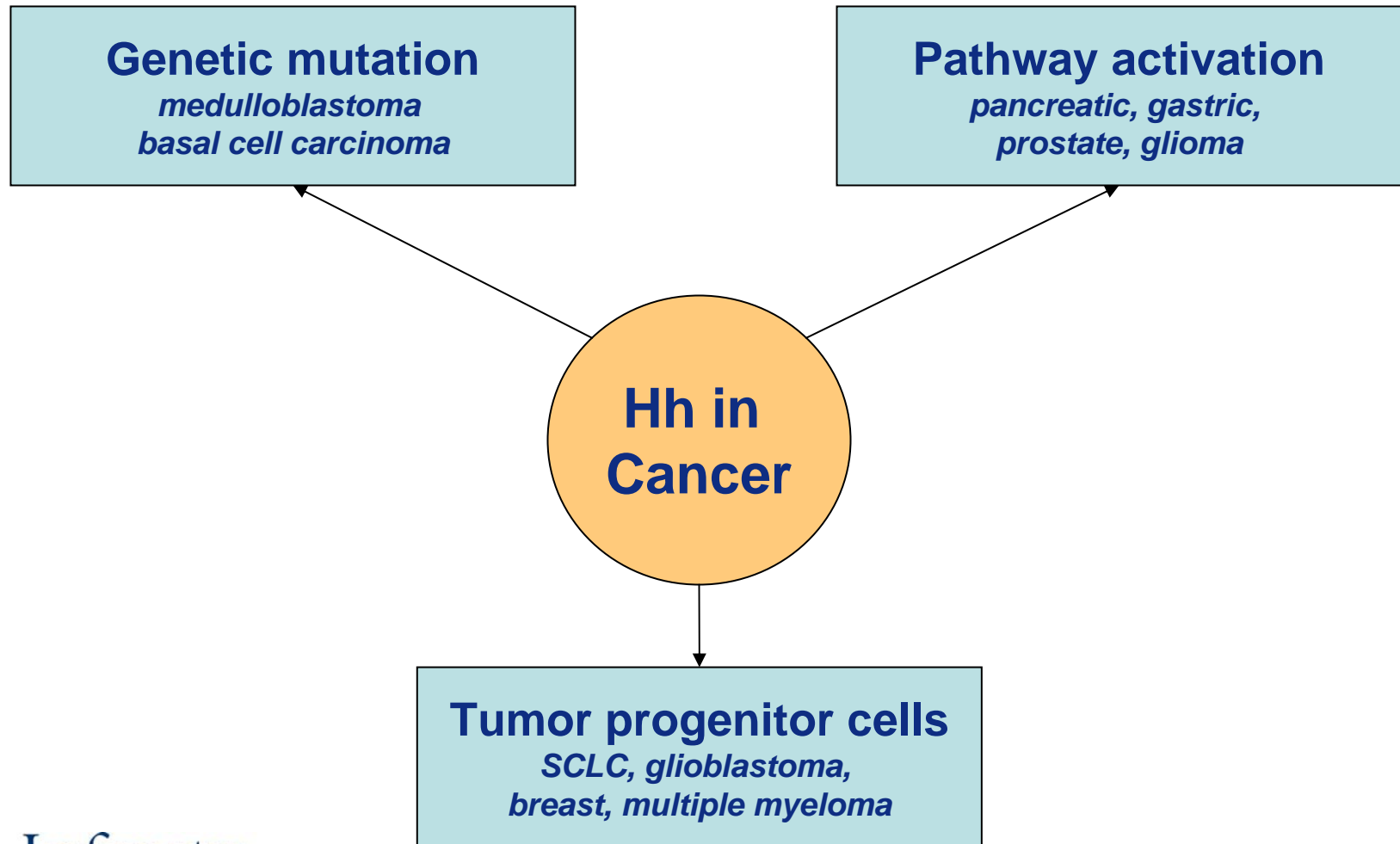


*Chen et al., 2002 **G&D** 16:2743

Discovery of IPI-926



Role of the Hedgehog pathway in cancer



Medulloblastoma

- **Clear rationale for evaluation of hedgehog inhibition**
- **Most common malignant brain tumor of pediatric cancer patients**
 - *20% with mutation in PTCH gene*
- **Multi-modality treatment includes surgery, radiation, and chemotherapy**
 - *Often curable (60% 5-year survival), but profound long-term consequences from treatment*

Murine model of medulloblastoma: Ptch/HIC-1 +/-

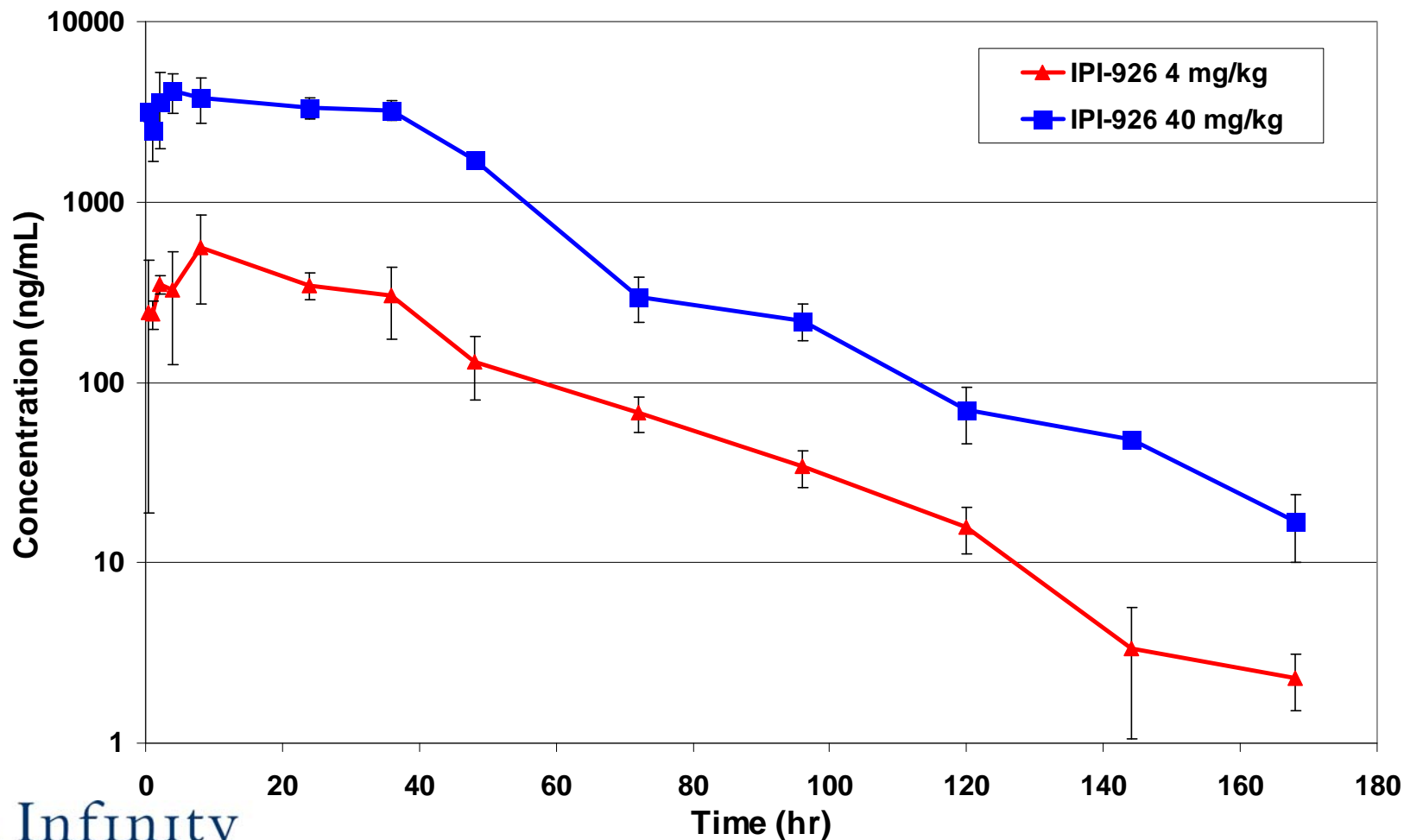
- **Derived from mice that are heterozygous for loss of function mutations in Ptch1 and Hypermethylated in Cancer 1 (HIC 1)**
 - *Develop spontaneous medulloblastoma in 40% of mice**
 - *HIC 1 mutation is important in tumor incidence on the Ptch +/- background**
 - *Most frequent genetic defect in sporadic human medulloblastoma**
- **B837Tx was developed from a murine genetic medulloblastoma tumor**
 - *Passaged as a subcutaneous allograft*
 - *Aggressive growth rate*
 - *Hh pathway dependent*

PK/PD relationship of IPI-926 in B837Tx Tumor model

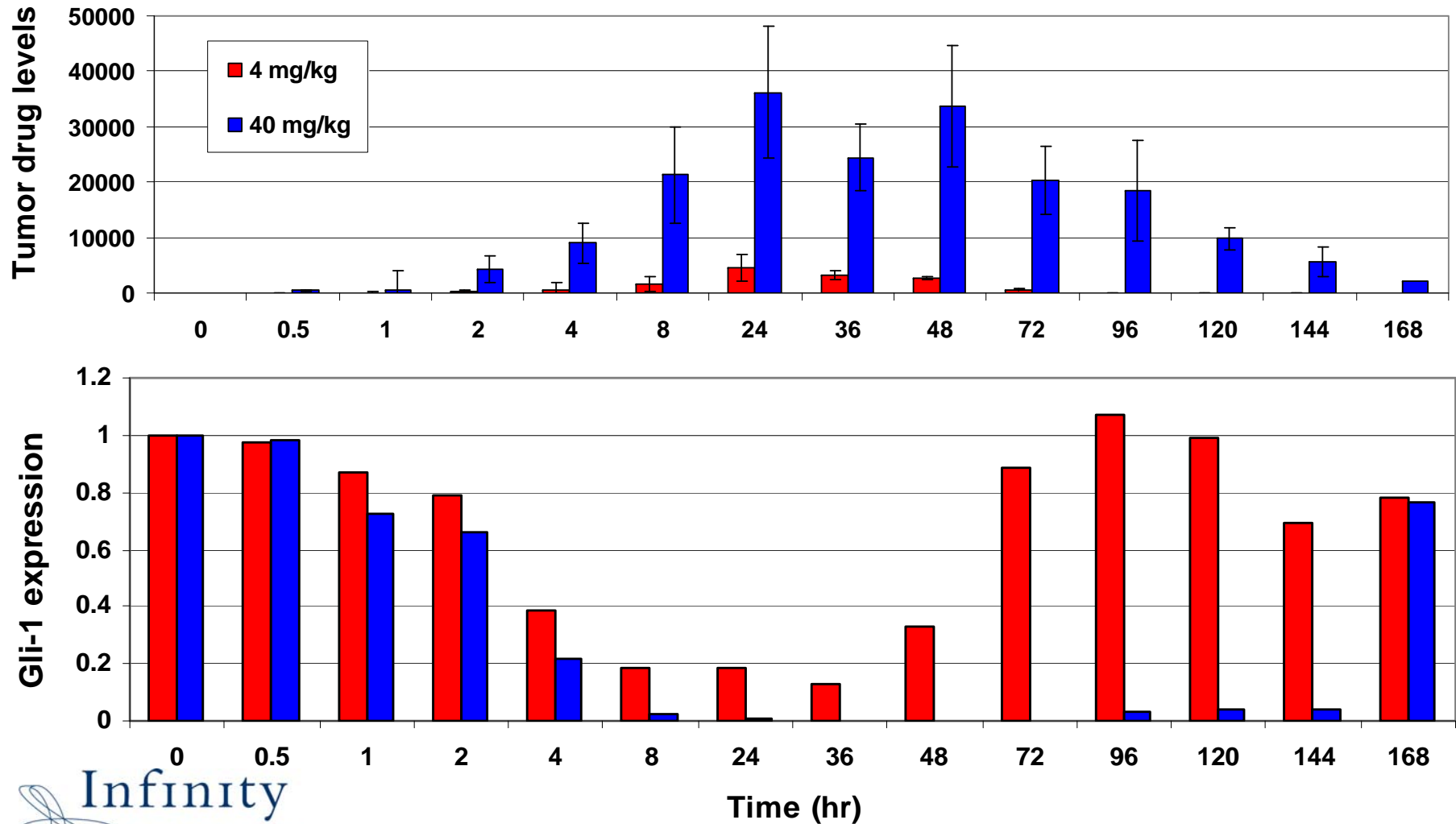
Study Outline

- Single oral administration of 4 or 40mg/kg**
- Plasma and tumor collected out to 168 hours post dose**
- Evaluated plasma levels, tumor drug concentration and Gli 1 inhibition**

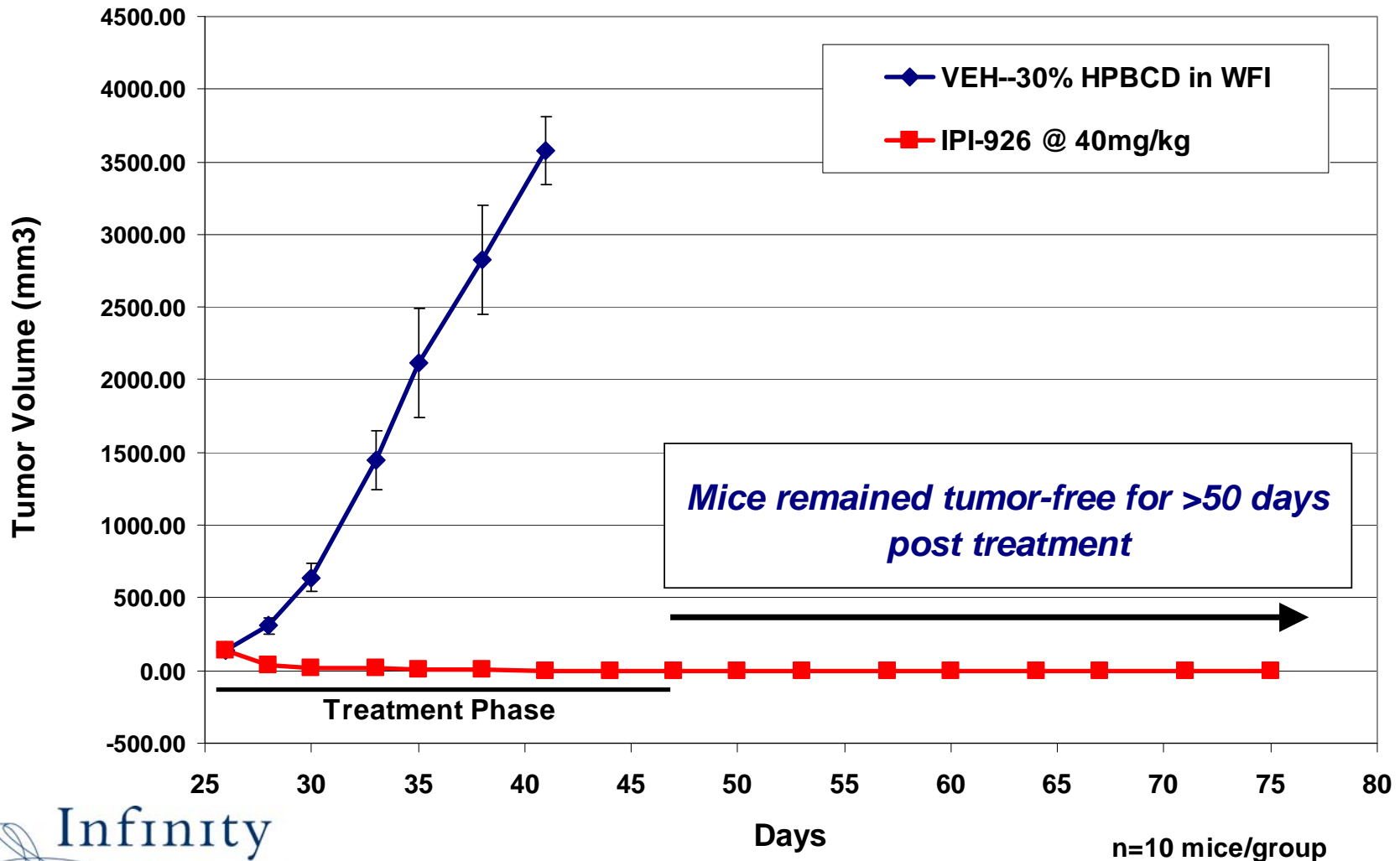
Plasma levels of IPI-926 following a single dose of 4 and 40mg/kg in B837Tx tumor-bearing mice



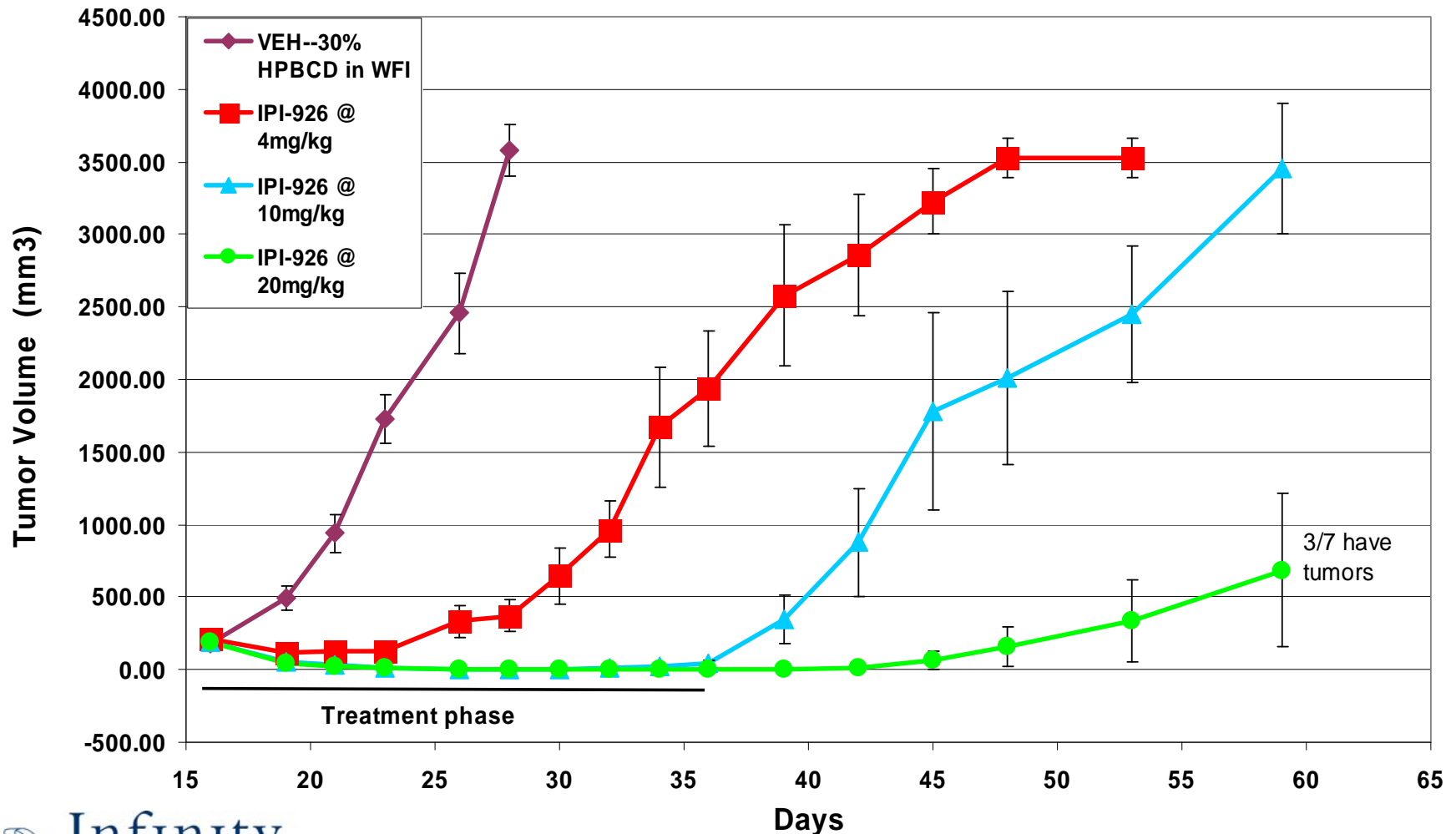
Duration and degree of Gli-1 inhibition correlates with tumor drug concentration



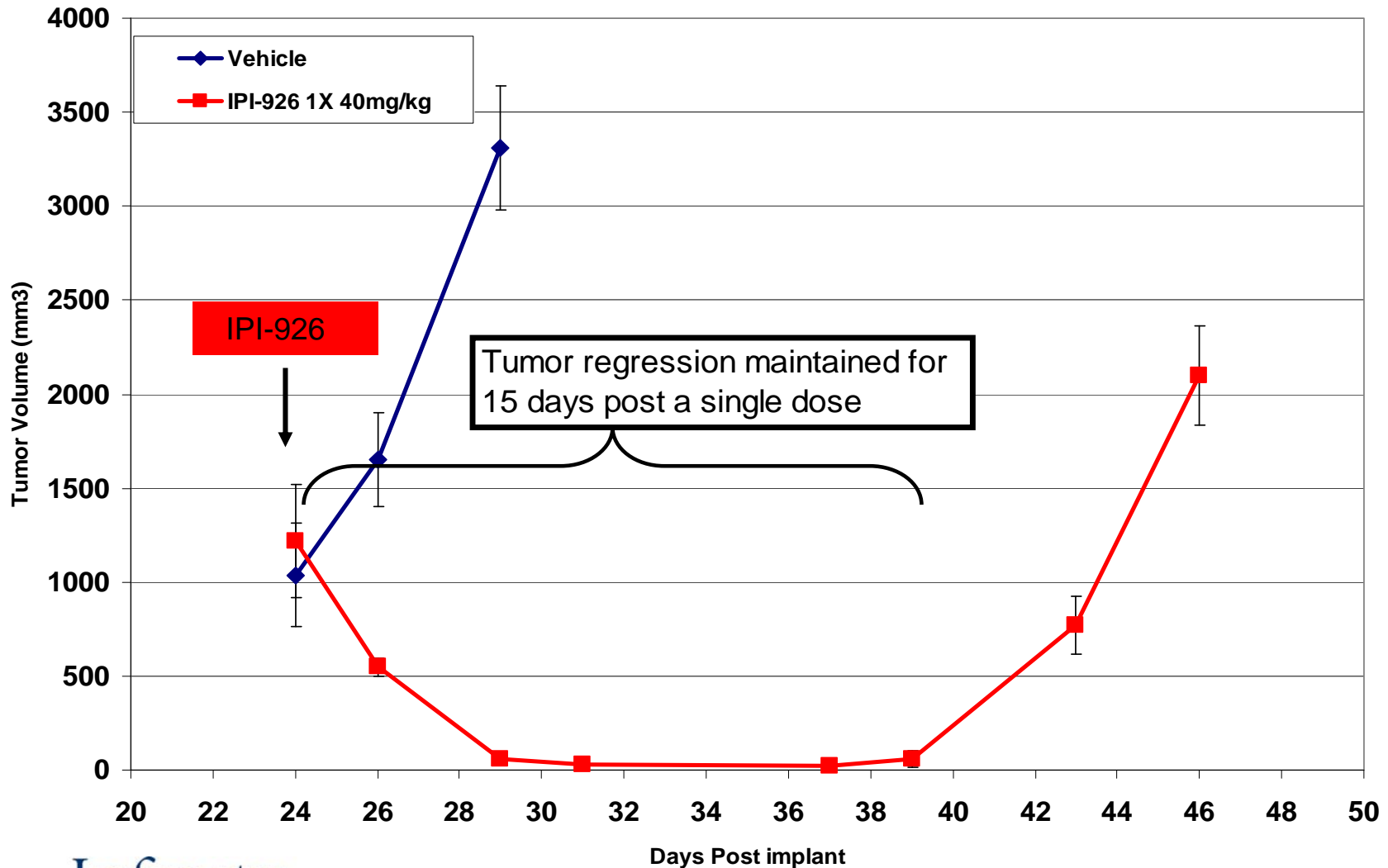
Daily oral administration of IPI-926 @ 40mg/kg resulted in complete tumor regression



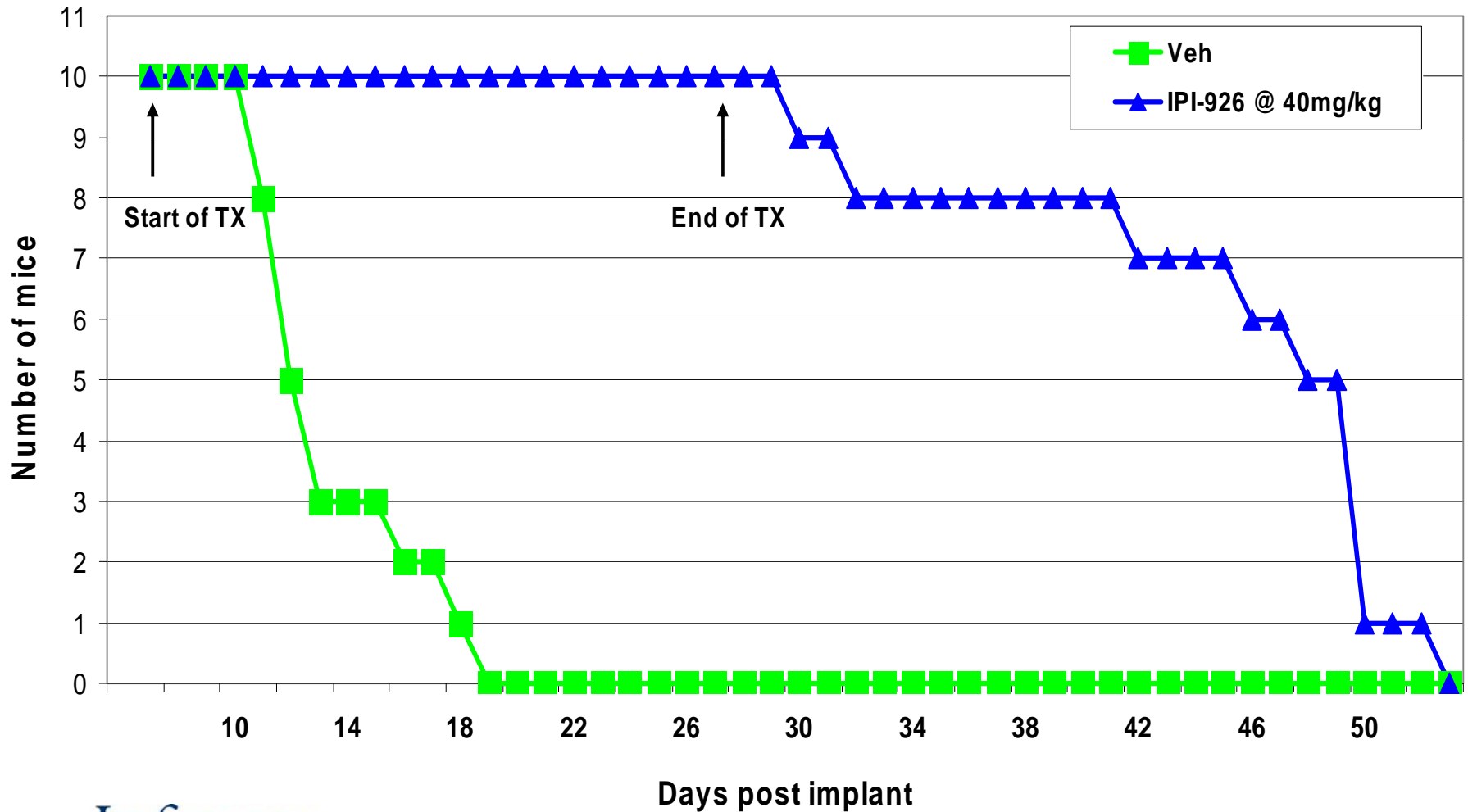
Dose dependent inhibition of B837Tx tumor growth with daily oral administration of IPI-926



Single administration of IPI-926 @ 40mg/kg maintained tumor regression for 15 days



IPI-926 @ 40mg/kg/day promotes survival of mice bearing orthotopically implanted B837Tx tumor



Summary/Conclusions of IPI-926

- **Summary**

- *Potent hedgehog pathway inhibitor*
- *Plasma half-life of 10-24 hr in multiple species*
- *Established PK/PD relationship*
- *Pathway inhibition results in tumor regression and significant survival benefit*

- **Conclusions**

- *Oral administration of IPI-926 achieves therapeutic levels in plasma and tumors in preclinical studies*
- *Half-life and duration of action affords flexibility for frequency of dose administration*

Acknowledgements

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D Neil Watkins