

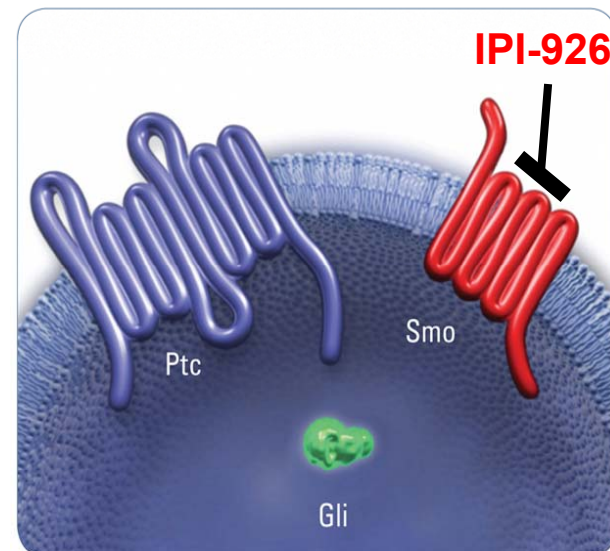
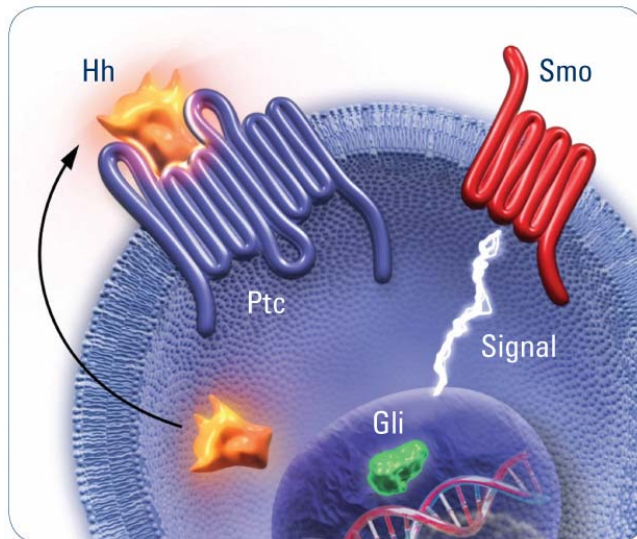
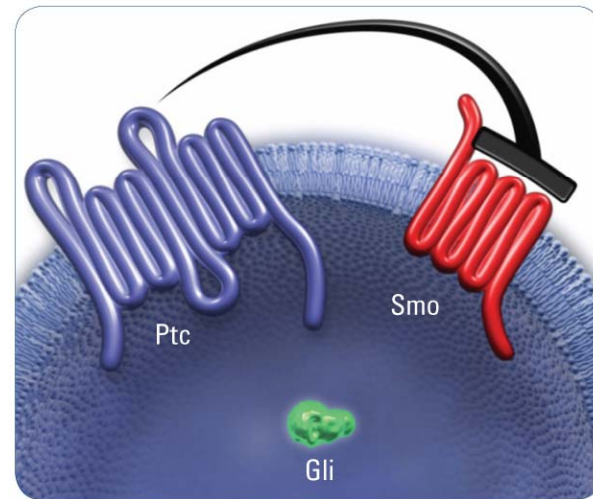
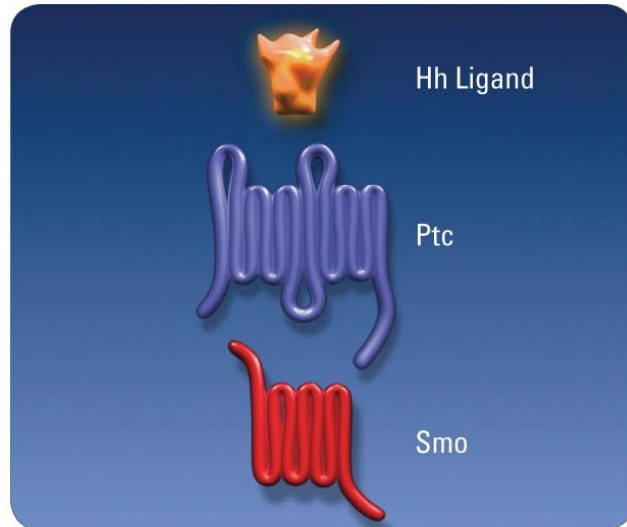
Hedgehog Signaling in Castration Resistant Prostate Cancer

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Abstract #3857

Role of Smoothened (Smo) in malignant activation of the Hedgehog (Hh) pathway



M. Tremblay et al. J.Med. Chem. 2009

Opportunities for Hh pathway inhibition

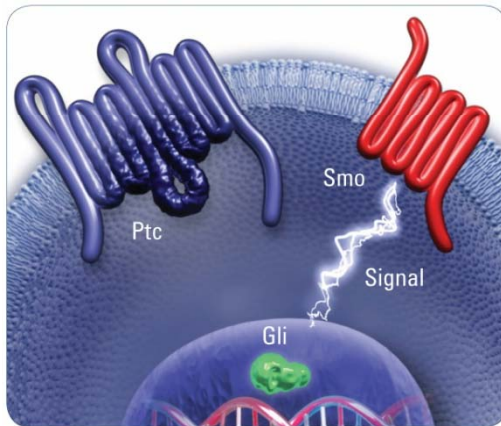
Ligand Independent

Ligand Dependent

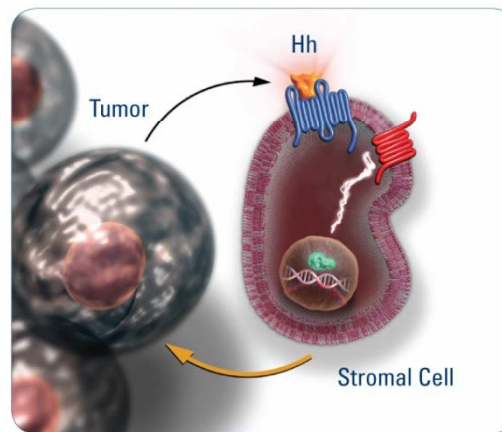


Genetic Mutations

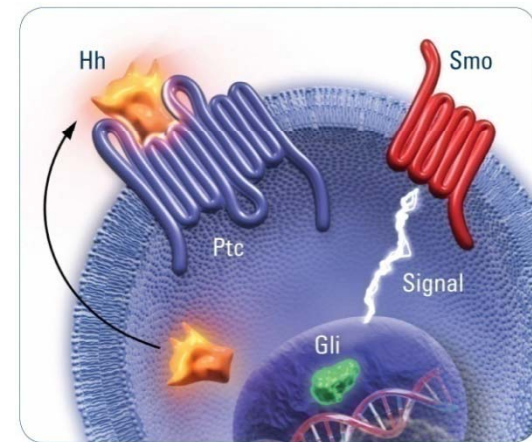
Paracrine Signaling ↔ **Signaling to tumor cell**



BCC
Medulloblastoma

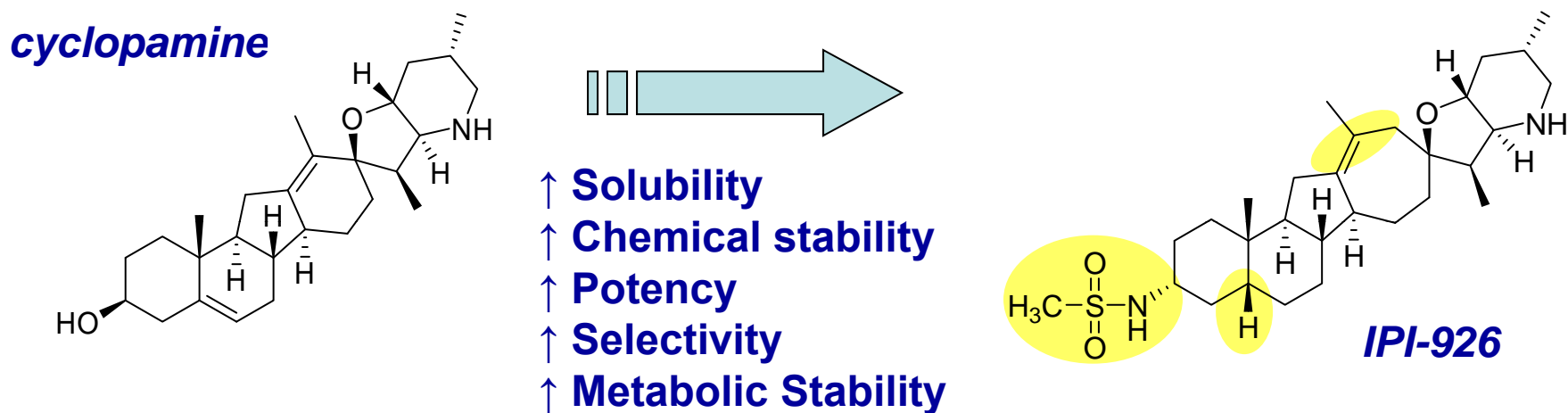


Pancreatic, SCLC,
Ovarian, Prostate



CML ,CLL, MM,
SCLC

IPI-926: A potent and orally active Smo inhibitor derived from the natural product cyclopamine

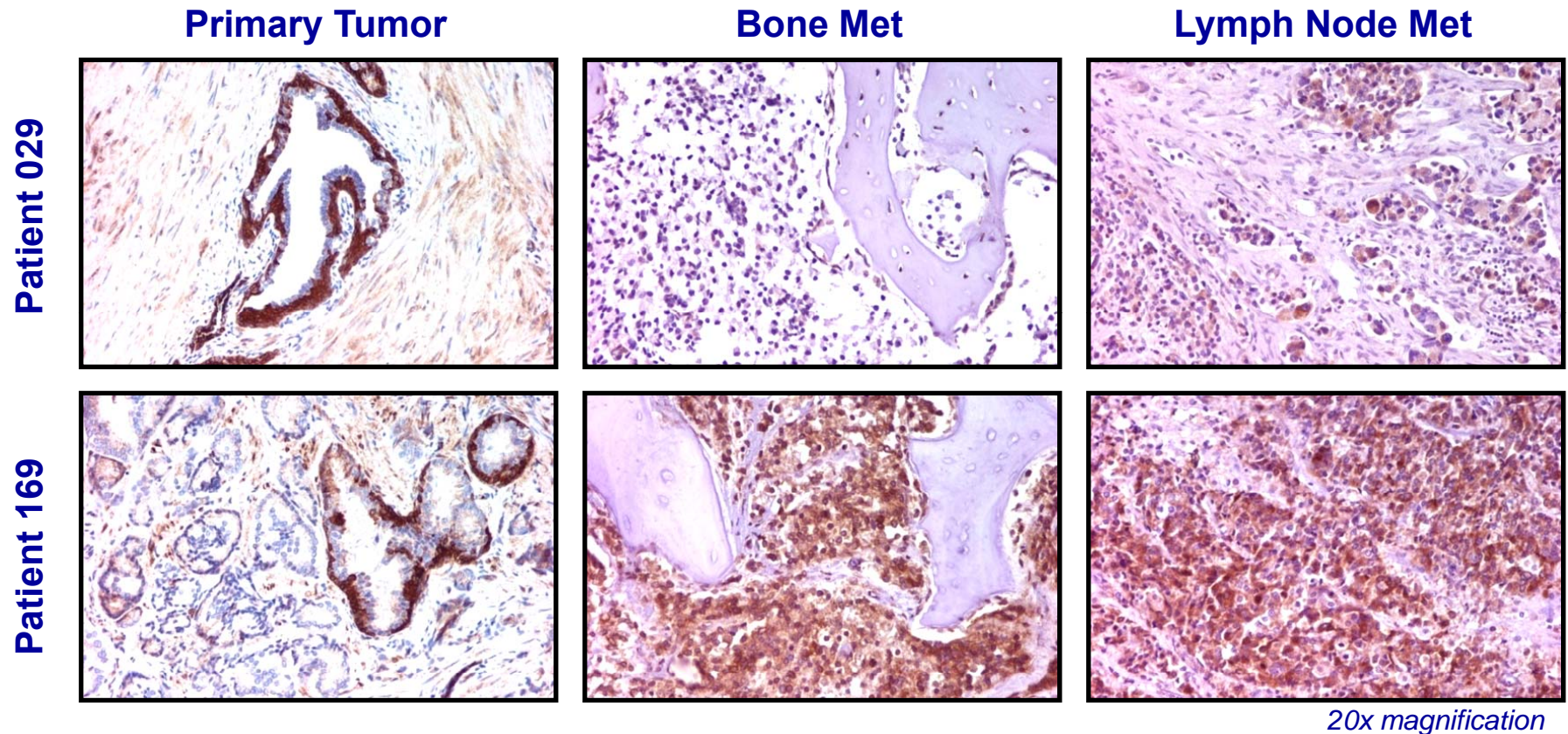


	C3H10 Diff. IC50 (nM)	Smo binding (nM)
cyclopamine	260	114
IPI-926	7	2

Castration resistant prostate cancer (CRPC) – a potential role for Hh inhibition to improve outcomes

- **Prostate cancer (PrCa)**
 - *most common non-skin malignancy*
 - *second most common cause of cancer death for men in the US*
- **For men with symptomatic CRPC, docetaxel chemotherapy is the standard of care, but outcomes are mediocre**
 - *2.4 mo. improvement in survival (16.5 to 18.9 mo.), with poor radiographic response rates (12%) (Tannock et al.)*
- **Several lines of evidence point to a pathogenic role for the Hh pathway in translational CRPC with bone metastases**
 - *Androgen deprivation up-regulates ligand expression in vitro (Chen et al)*
 - *Hh ligand specifically promotes bone metastasis (Zunich et al)*
 - *Hh ligand expression higher in metastases than 1^o tumor (Karhadkar et al)*
 - *PrCa xenograft growth inhibition with various Smo inhibitors (Yang et al)*

SHh ligand is highly expressed in human prostate tumors and metastases



Prostate Tissue	Total of # Samples	SHh Positive	SHh Negative	Percent Positive
Primary Tumor	5	5	0	100%
Metastases	10	8	2	80%

LuCaP 23.1 and LuCaP 35v are primary xenograft models of prostate cancer

LuCaP 23.1 and 35v xenografts were derived from lymph node metastases from patients with PrCa.

LuCaP 23.1 Castration Sensitive

- *Passaged in **intact** ♂ mice*
- *Expresses wild type AR*
- *Secretes high levels of PSA*

LuCaP 35v Castration Resistant

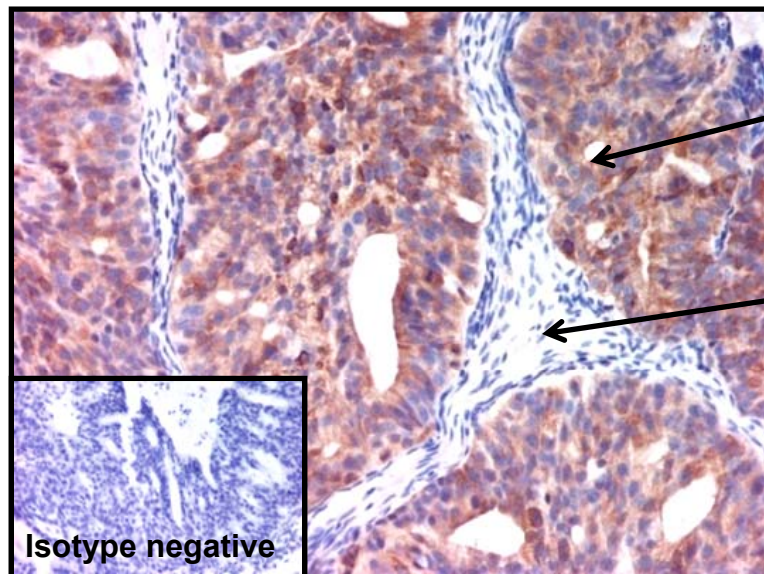
- *Derived from patient following hormonal ablation treatment*
- *Passaged in **castrated** ♂ mice*
- *Expresses wild type AR*
- *Secretes high levels of PSA*



LuCaP 23.1 and LuCaP 35v are primary xenograft models of prostate cancer

Human SHh Ligand Staining

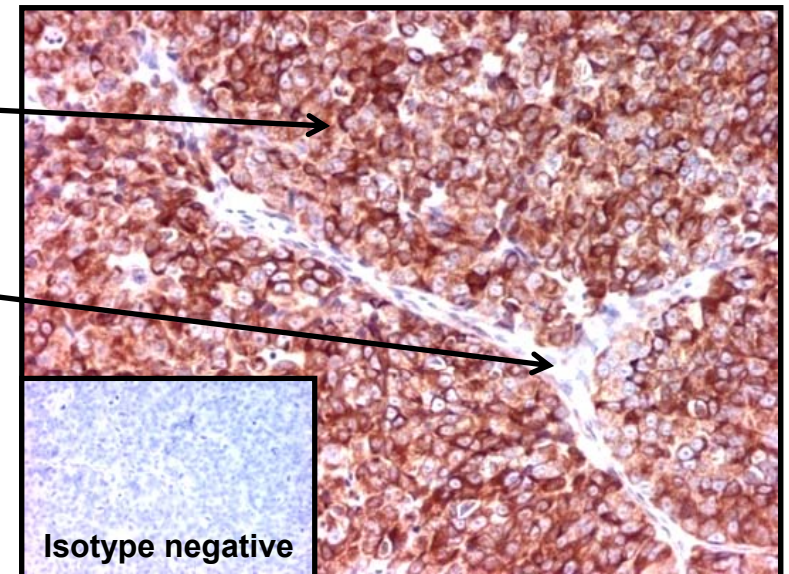
LuCaP 23.1
Castration Sensitive



Tumor cells
(human)

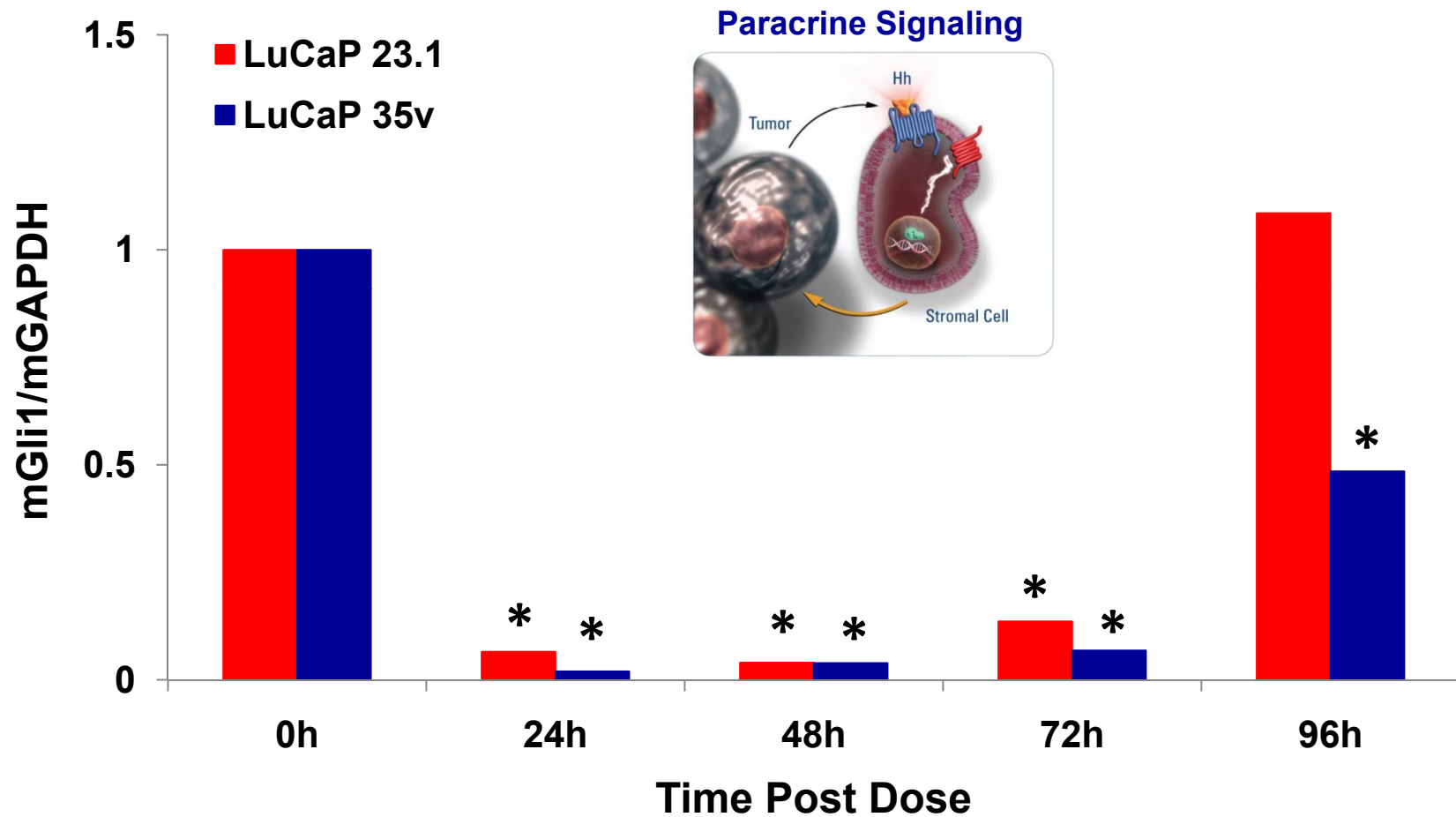
Tumor
stroma
(mouse)

LuCaP 35v
Castration Resistant



20x magnification

Stromal Gli1 inhibition following single oral dose of 40mg/kg IPI-926 in primary xenograft models of PrCa



Inhibition of human tumor-derived Gli1 was not observed

* p-value < 0.05 Student t-Test

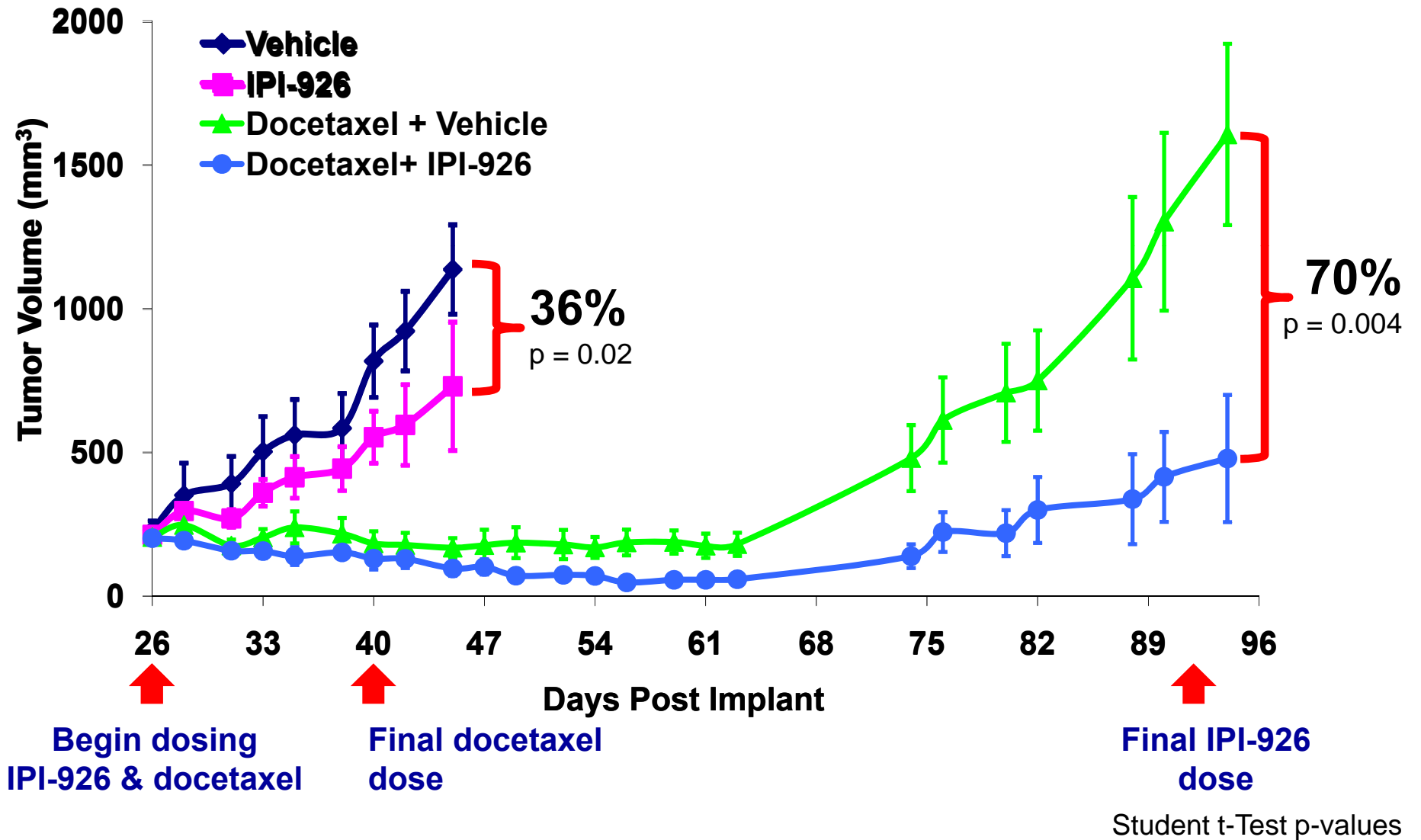
Evaluation of IPI-926 in LuCaP35v, a primary xenograft model of CRPC

- **Evaluation of anti-tumor activity of IPI-926 alone and in combination with docetaxel in CRPC primary xenograft model**

- **Study Outline**
 - *Single Agent:*
 - +/- 40 mg/kg IPI-926 QOD PO
 - *Combination:*
 - 20 mg/kg docetaxel Q14D IP +/- 40 mg/kg IPI-926 QOD PO



IPI-926 slows growth rate of LuCaP 35v, a primary model of CRPC, post-docetaxel treatment



Summary

- SHh ligand is highly expressed in clinical PrCa and primary xenograft samples
- Significant duration and degree of Gli1 inhibition in stroma observed with a single dose of IPI-926
- IPI-926 significantly improves the anti-tumor activity of docetaxel treatment in a patient-derived xenograft model of CRPC (LuCaP 35v)

Conclusion

- These pre-clinical results suggest an important role for the Hh pathway in the PrCa tumor-stroma microenvironment and provides rationale for evaluating IPI-926 in patients with CRPC.



The Infinity Team

