

A Phase 1 Study of IPI-926, an Inhibitor of the Hedgehog Pathway, in Patients with Advanced or Metastatic Solid Tumors

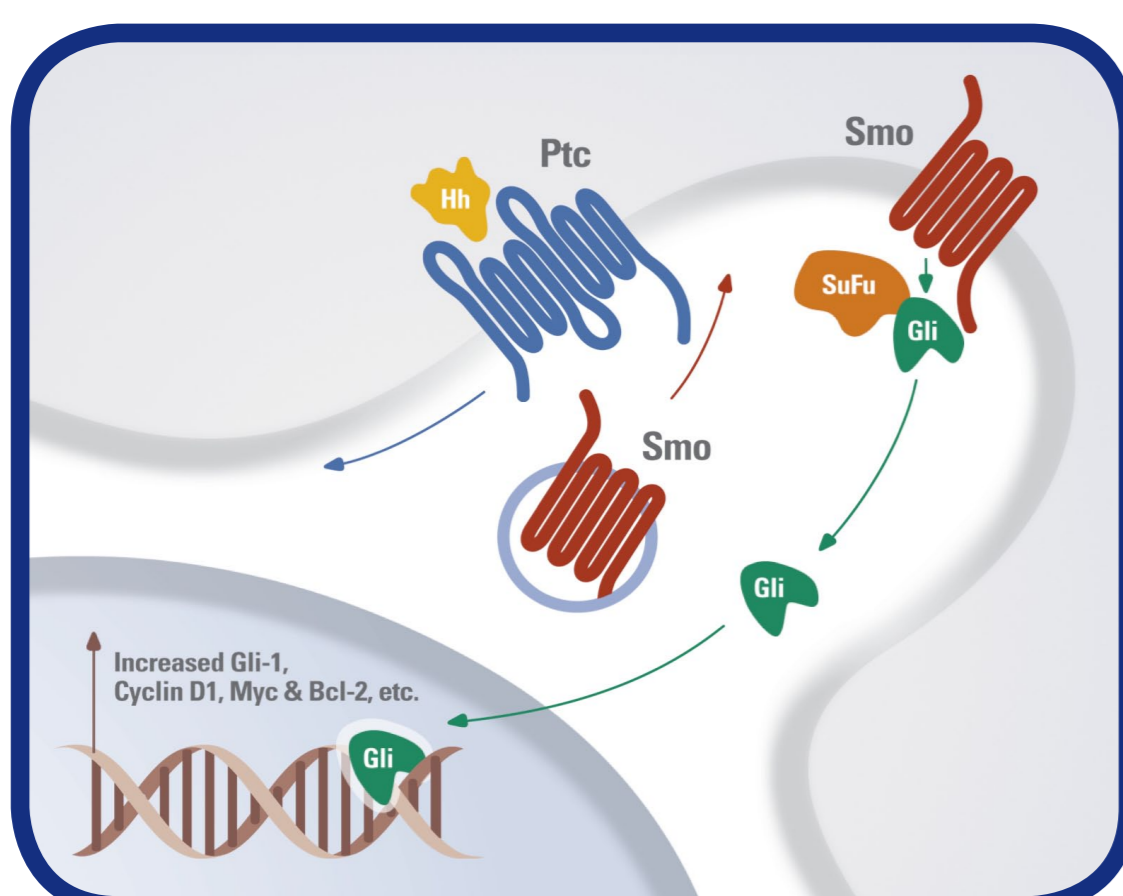
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Background

- The Hedgehog (Hh) signal transduction pathway plays a critical role in cell differentiation and patterning during development, but is inactive in most adult cells.
- In certain cancers, malignant activation of the pathway is ligand-dependent. In the presence of Hh ligand, inhibition of the G-protein coupled receptor-like Smoothened (Smo) by the twelve transmembrane receptor Patched (Ptc) is relieved, enabling activation of Gli transcription factors, which activate expression of genes that promote tumor growth and survival.
- In basal cell carcinomas (BCC) and some medulloblastomas, malignant activation of the Hh pathway is ligand-independent and due to a genetic mutation.
- Inhibition of Smo disrupts malignant activation of the Hh pathway by ensuring that Gli transcription factors are held in an inactive form.
- IPI-926 is a potent, orally delivered small molecule that is currently being investigated as an inhibitor of Smo.



Study Design

- Study Design**
- Phase 1 dose-escalation in patients with advanced / metastatic solid tumors
- Study Objectives**
- Determine safety, PK (plasma), PD (skin biopsy), anti-tumor activity
- Key Eligibility Criteria**
- Adults with pathologically confirmed diagnosis of locally advanced / metastatic solid tumors with no available standard therapy
 - ECOG performance status 0-2; life expectancy > 3 months
 - Adequate hepatic and renal function
- Dosing Schedule**
- Once daily on 28-day cycles
 - 1-6 patients per cohort for dose escalation to maximum tolerated dose (MTD)
 - Doses evaluated to date: 20 mg (1 patient), 30 mg (1 patient), 40 mg (1 patient), 60 mg (1 patient), 90 mg (1 patient), 130 mg (46 patients – trial expansion at this dose, including BCC), 160 mg (6 patients), 200 mg (3 patients)

Baseline Demographics

Baseline Demographic	BCC (N=24)	Non BCC (N=36)
Age (years)		
Median	60	60
Range	50 - 87	42 - 74
Sex, n (%)		
Male	20 (83.3)	18 (50.0)
Female	4 (16.7)	18 (50.0)
Diagnosis, n (%)		
Basal Cell Carcinoma	24 (100)	0
Pancreatic Cancer	0	6 (16.7)
Ovarian Cancer	0	4 (11.1)
Chondrosarcoma	0	3 (8.3)
Colorectal Cancer	0	3 (8.3)
Adenocystic Carcinoma	0	2 (5.6)
Lung Cancer, Non-Small Cell	0	2 (5.6)
Lung Cancer, Small Cell	0	2 (5.6)
Neuroendocrine Carcinoma	0	2 (5.6)
Oropharyngeal Cancer	0	2 (5.6)
Squamous Cell Carcinoma of the Skin	0	2 (5.6)
Other*	0	8 (22.2)
Years from Diagnosis to First Dose		
Median	9	3.1
Range	0.3 - 61	1 - 14
Stage at Screening (BCC only), n (%)		
Locally Advanced	10 (41.7)	--
Metastatic	14 (58.3)	--
History of Gorlin Syndrome (BCC only), n (%)	3 (12.5)	--
Previous Therapies, n (%)		
Surgery	21 (87.5)	33 (91.7)
Systemic therapy	12 (50.0)	32 (88.9)
Radiotherapy	10 (41.7)	17 (47.2)

*Other diagnoses in 1 patient each: Cervical, Eccrine Carcinoma, Gastric, Prostate, Rectal, Salivary Gland, Small Cell - Unknown Primary, Uterine Carcinosarcoma

Safety Results

Adverse Events (AEs) by MedDRA Preferred Term	< 130 mg (N=5)	130 mg (N=46)	160 mg (N=6)	200 mg (N=3)	Total (N=60)
Any Related AE*, n (%)	1 (20.0)	24 (52.2)	3 (50.0)	2 (66.7)	30 (50.0)
Fatigue, n (%)					
Grade 1	1 (20.0)	6 (13.0)	0	0	7 (11.7)
Grade 2	0	6 (13.0)	1 (16.7)	0	7 (11.7)
Grade 3	0	1 (2.2)	0	0	1 (1.7)
Nausea, n (%)					
Grade 1	1 (20.0)	9 (19.6)	1 (16.7)	0	11 (18.3)
ALT increased, n (%)					
Grade 1	0	1 (2.2)	0	0	1 (1.7)
Grade 2	0	1 (2.2)	1 (16.7)	1 (33.3)	3 (5.0)
Grade 3	0	2 (4.3)	1 (16.7)	1 (33.3)	4 (6.7)
AST increased, n (%)					
Grade 1	0	2 (4.3)	0	1 (33.3)	3 (5.0)
Grade 2	0	2 (4.3)	1 (16.7)	0	3 (5.0)
Grade 3	0	0	1 (16.7)	1 (33.3)	2 (3.3)
Diarrhoea, n (%)					
Grade 1	0	6 (13.0)	0	0	6 (10.0)
Dysgeusia, n (%)					
Grade 1	1 (20.0)	4 (8.7)	0	0	5 (8.3)
Alopecia, n (%)					
Grade 1	0	3 (6.5)	0	1 (33.3)	4 (6.7)
Dyspepsia, n (%)					
Grade 1	0	1 (2.2)	0	0	1 (1.7)
Grade 2	1 (20.0)	1 (2.2)	0	0	2 (3.3)
Vomiting, n (%)					
Grade 1	0	3 (6.5)	0	0	3 (5.0)
Abdominal pain, n (%)					
Grade 1	1 (20.0)	0	0	0	1 (1.7)
Grade 2	0	1 (2.2)	0	0	1 (1.7)
Constipation, n (%)					
Grade 1	0	2 (4.3)	0	0	2 (3.3)
GGT increased, n (%)					
Grade 2	0	2 (4.3)	0	0	2 (3.3)
Hyperbilirubinaemia, n (%)					
Grade 1	0	0	1 (16.7)	1 (33.3)	2 (3.3)
Insomnia, n (%)					
Grade 1	0	2 (4.3)	0	0	2 (3.3)
Muscle spasms, n (%)					
Grade 1	0	1 (2.2)	0	1 (33.3)	2 (3.3)
Oedema peripheral, n (%)					
Grade 1	0	2 (4.3)	0	0	2 (3.3)
Paraesthesia, n (%)					
Grade 1	0	2 (4.3)	0	0	2 (3.3)

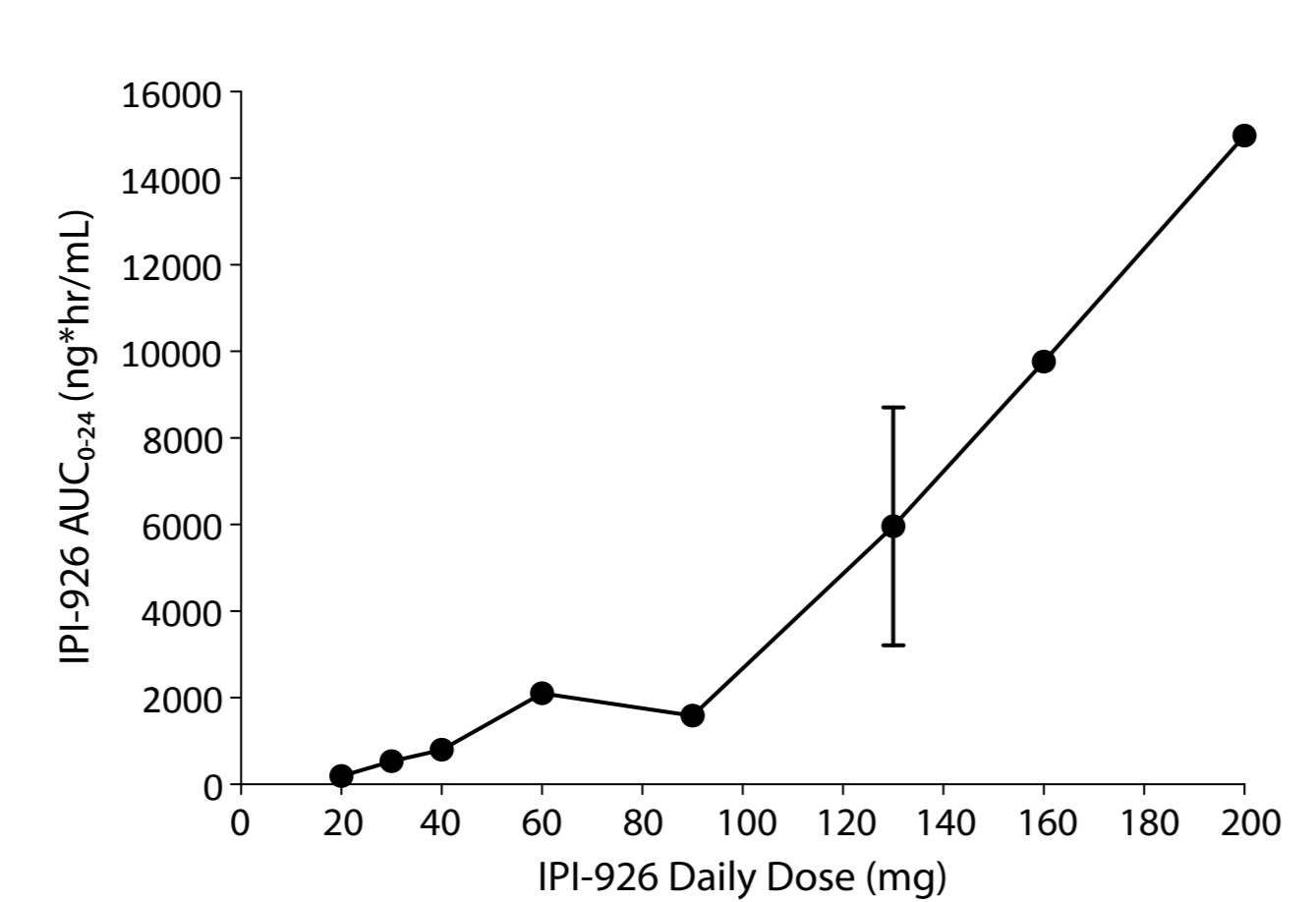
* Related, treatment-emergent AEs in ≥ 2 patients, worst Grade on study.

Dose Limiting Toxicities (DLTs) with Resulting Cohort Expansion and Trial Modification

- AEs of transaminitis observed (3 were DLTs)
 - Asymptomatic, reversible Grade 3 (DLTs): 2 pts at 200 mg, 1 pt at 160 mg
 - Grade 2 transaminitis with Grade 1 total bilirubin (non-DLT): 1 patient at 160 mg
- Review of all related AEs indicated that all events of transaminitis were asymptomatic and reversible; no ALT and AST elevation ≥ 10 x ULN was observed
- Therefore, the 130 mg cohort was expanded to evaluate both safety and activity
- Trial was then modified to allow asymptomatic Grade 3 transaminitis (< 10 x ULN) and dose escalation was recommenced
- Patients are currently being enrolled into the 160 mg cohort

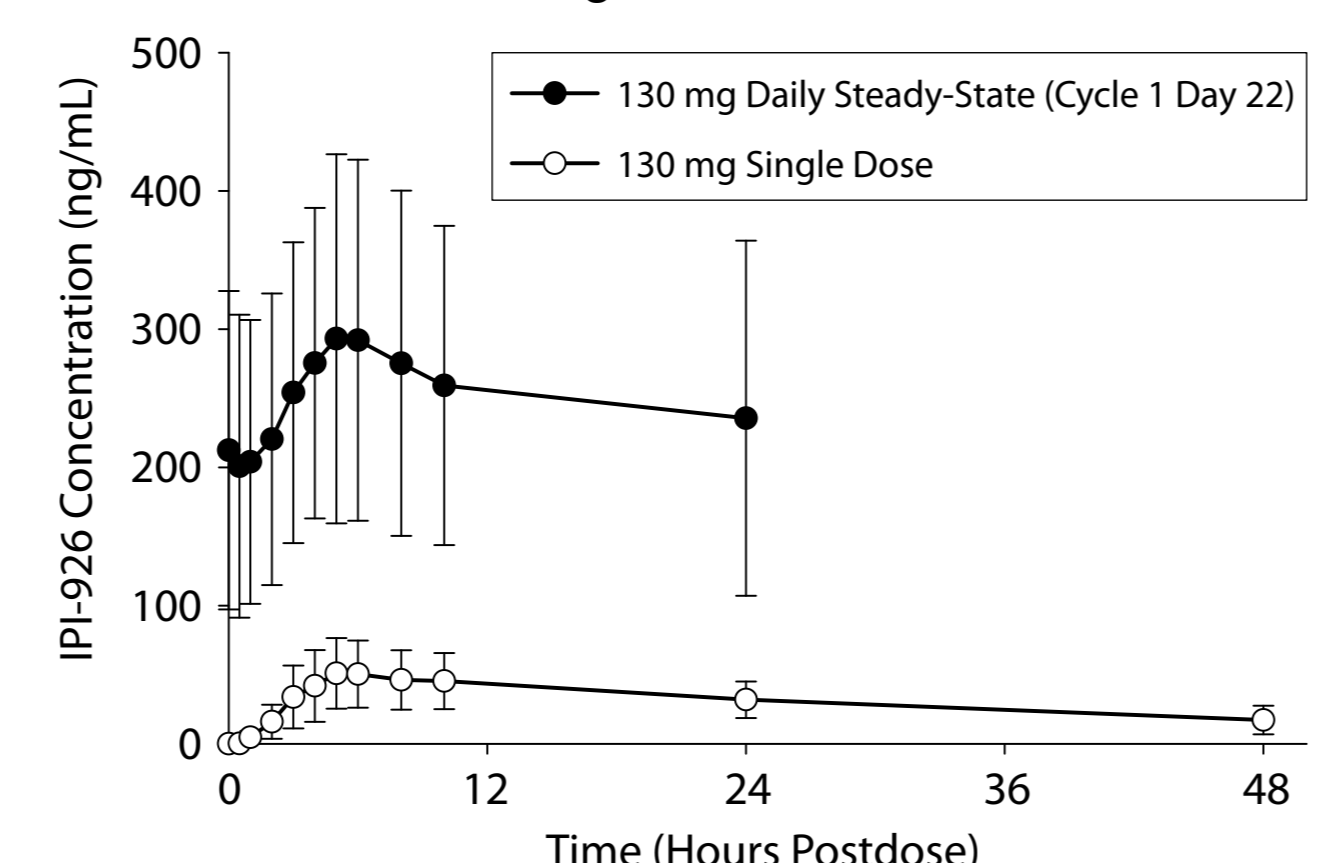
Pharmacokinetics and Pharmacodynamics

Mean (±SD) Plasma IPI-926 AUC Values on Cycle 1 Day 22 Following Repeated Once-Daily Administration of IPI-926



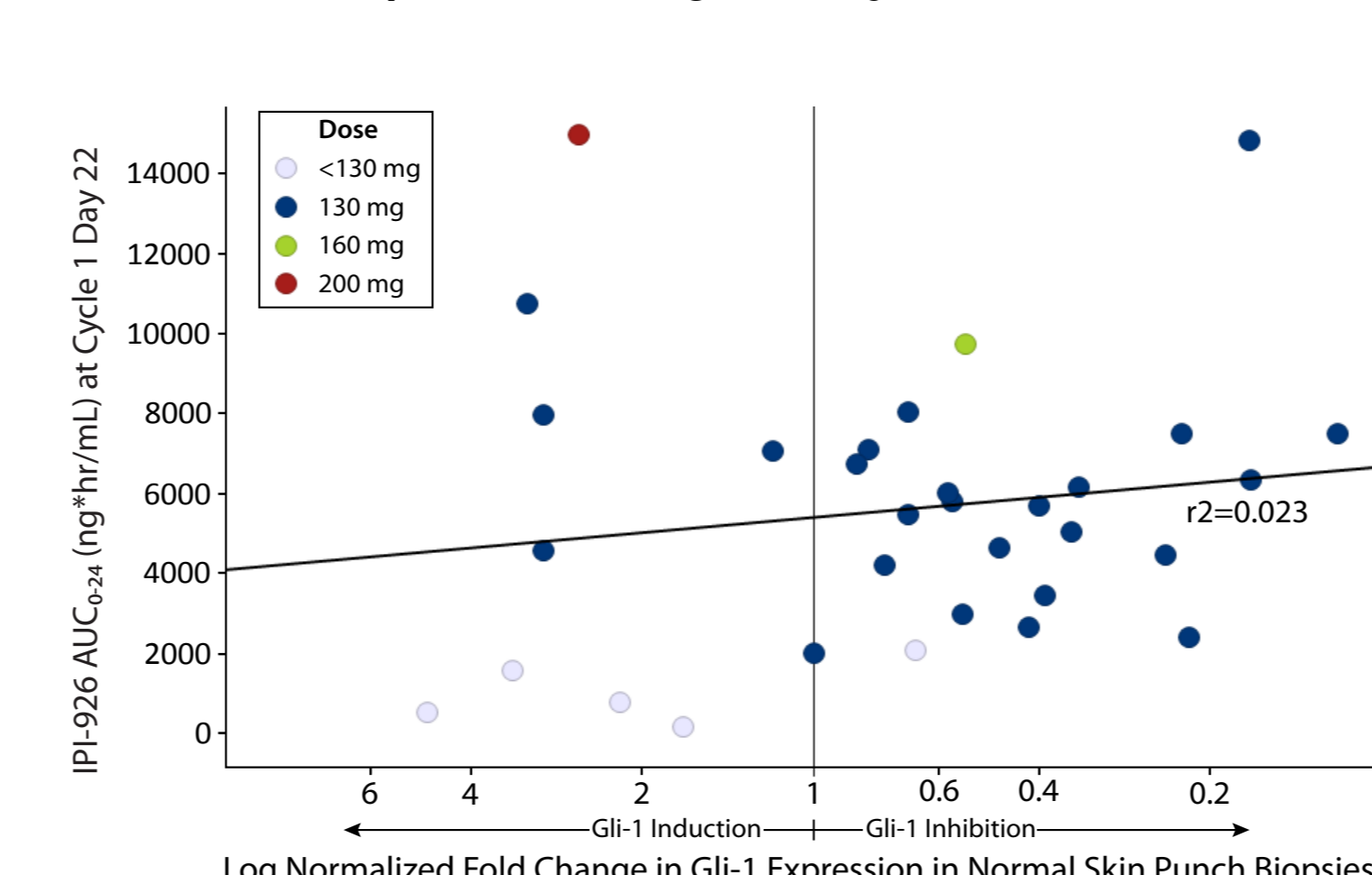
Steady-state plasma AUC increases slightly more than dose-proportionally.

Mean (±SD) Plasma IPI-926 Concentrations Following a Single 130 mg Dose and Following Repeated Once-Daily Administration of 130 mg IPI-926



At 130 mg dose level, repeat dose accumulation is observed, reflecting single dose elimination half-life values that typically ranged from 20-40 hours.

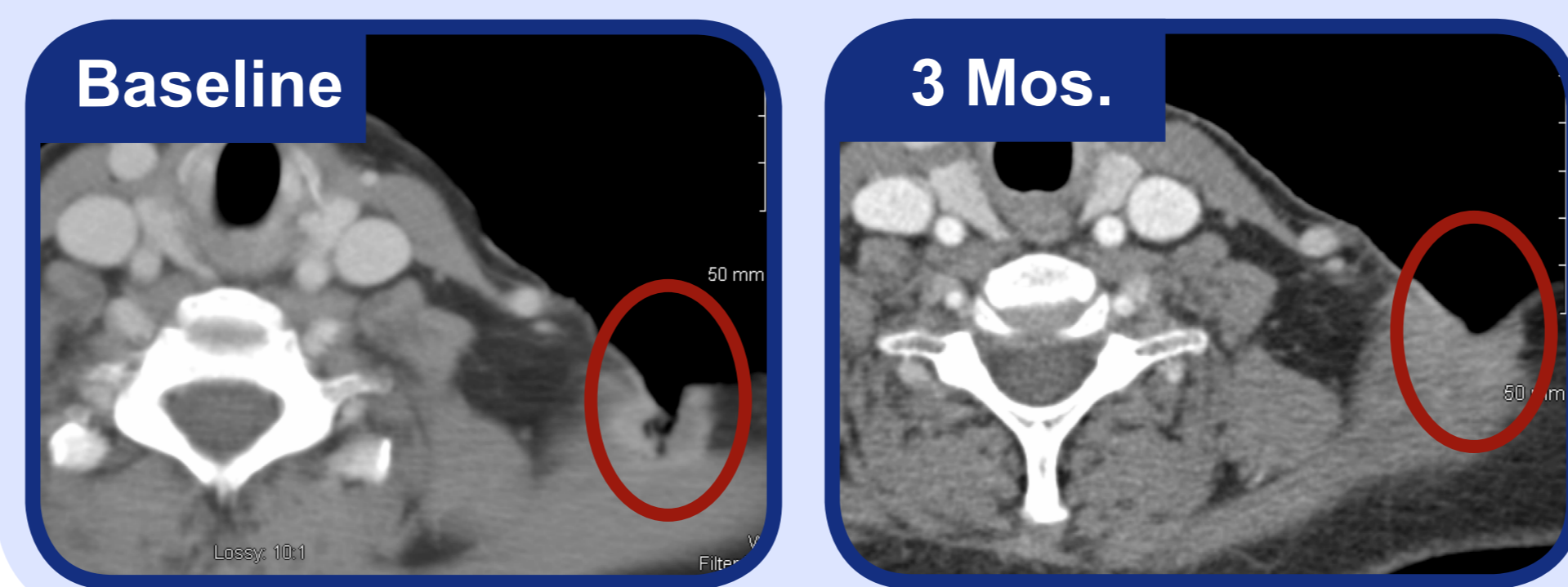
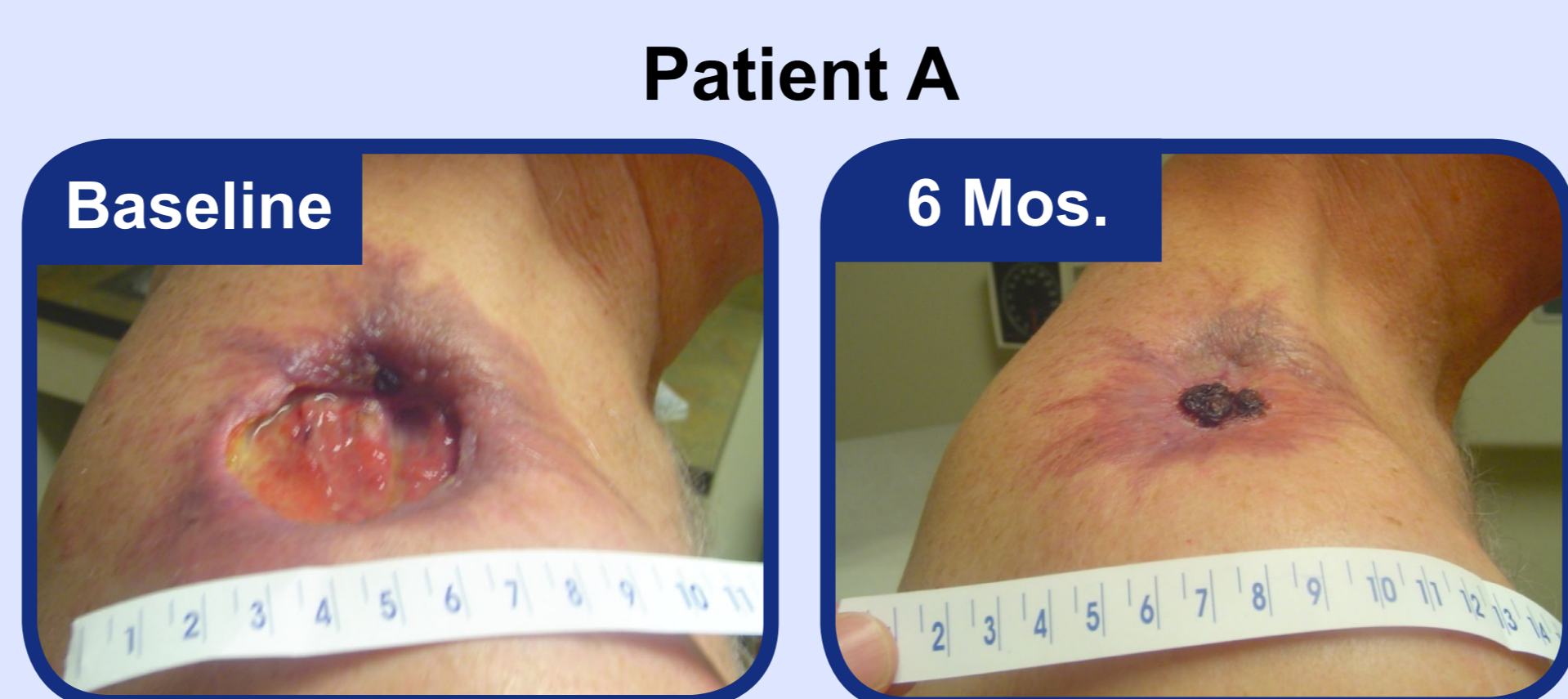
AUC vs. Gli-1 Expression Change on Day 22



Inhibition of Gli-1 expression in normal skin is seen in the majority of patients after 22 days of dosing (i.e., values < 1 in fold change in Gli-1 expression), although no relationship between plasma exposure and inhibition of Gli-1 expression is noted.

Examples of Clinical Activity of IPI-926 in 3 Different Patients with BCC

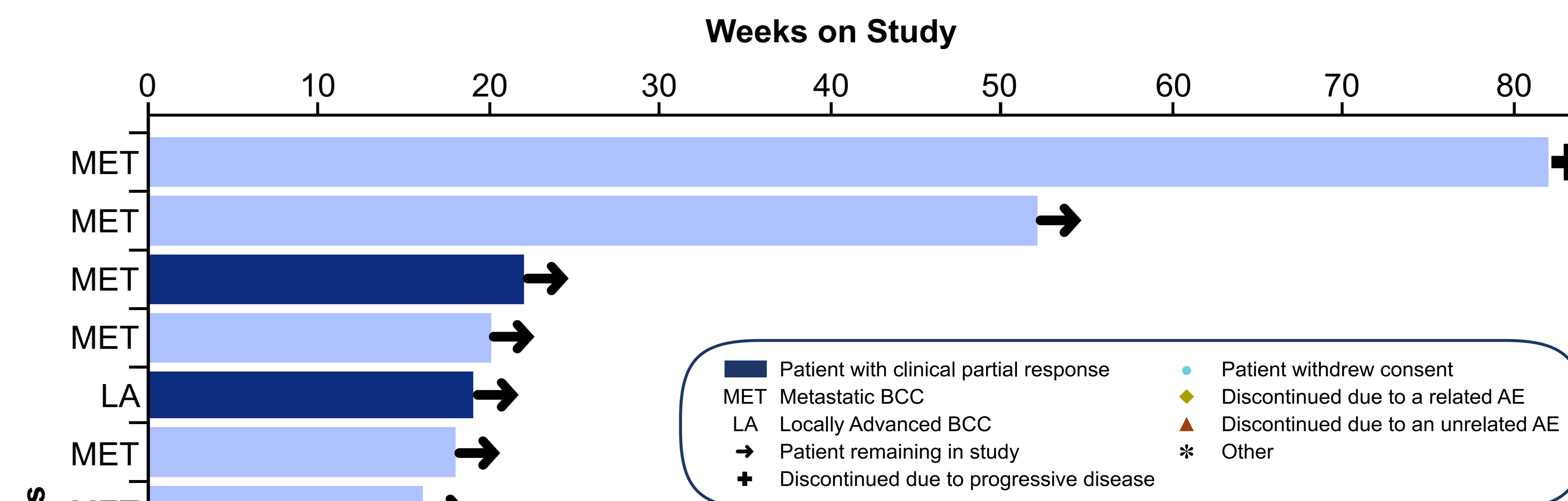
- All 3 patients were treated with 130 mg of IPI-926.
- Clinical partial responses take several months to manifest.



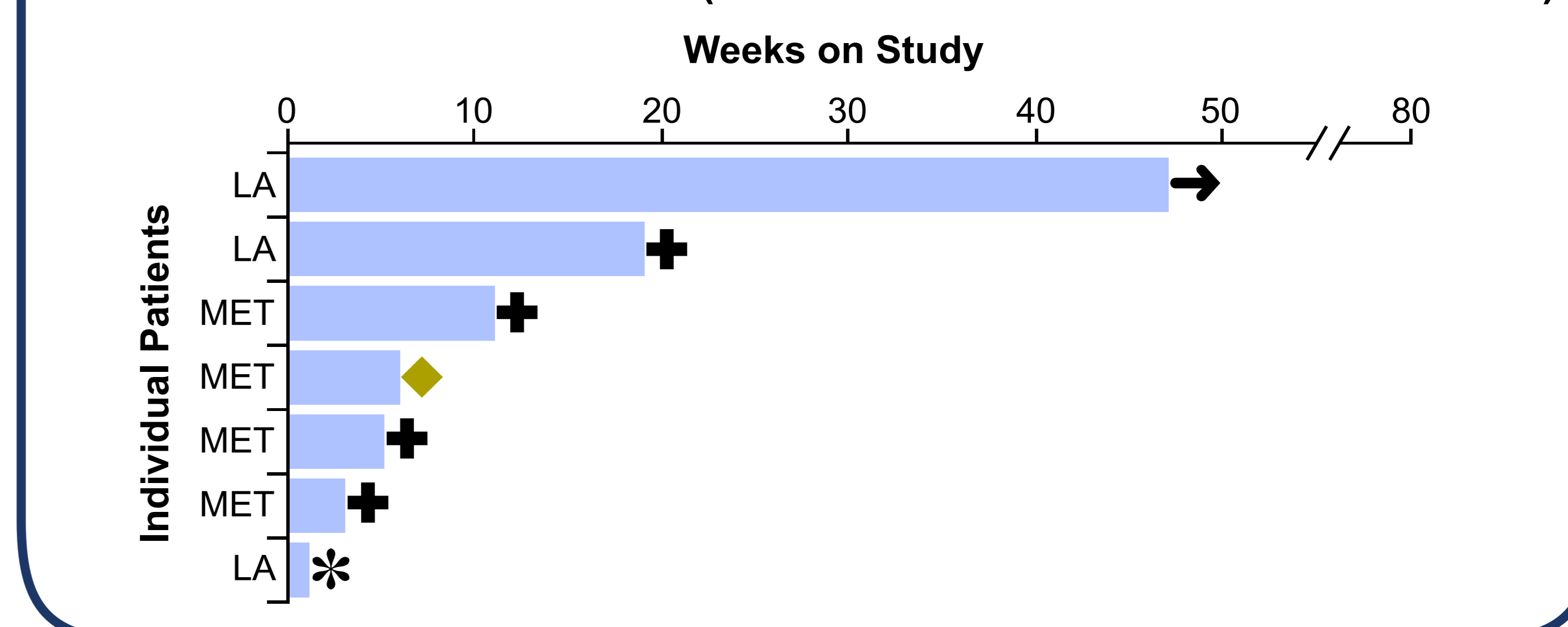
Evidence of Clinical Activity in Patients with BCC

- All partial responses noted to date have been in patients with BCC.
- 3 non-BCC patients to date have been on trial with stable disease for at least 6 months: adenocystic carcinoma of the nasopharynx (8 months and ongoing), neuroendocrine tumor (8 months), and chondrosarcoma (7 months and ongoing).

Clinical Outcomes to Date for Patients with BCC Who Have Not Had Prior Treatment with a Hh-Inhibitor



Clinical Outcomes to Date for Patients with BCC Who Have Had Prior Treatment with a Hh-Inhibitor (All Previous Treatment with GDC-0449)



Conclusions

- In this study, IPI-926 has been a well tolerated and clinically active inhibitor of the Hh pathway.
- Primary related AEs were Grade 1 and 2 fatigue and nausea. Asymptomatic, reversible transaminitis has also been observed.
 - Dose escalation to 160 mg and higher is ongoing under modified DLT criteria to allow asymptomatic Grade 3 transaminitis (< 10 x ULN).
 - The majority of related AEs were Grade 1 or 2. No Grade 4 or 5 related AEs have been observed.
- Clinical partial responses have been observed in patients with BCC.
 - To date, 4 clinical partial responses have been observed – several patients have not been treated long enough to assess clinical activity.
 - To date, only 1 BCC patient naïve to Hh-Inhibitor treatment has experienced disease progression.