

ODAC Pediatric Subcommittee
November 1, 2011

**Development of Votrient™
(Pazopanib) in Pediatric Oncology**

Preview

- **Ultimate goal of pazopanib development in pediatrics is to increase cure rate**
- **Efficacy and safety experience in adults**
- **Preclinical studies to support pediatric development**
- **Current pediatric development plans**
- **Results of pediatric Phase I study**
- **Approach to overcoming challenges to pazopanib development in pediatrics**

Pazopanib

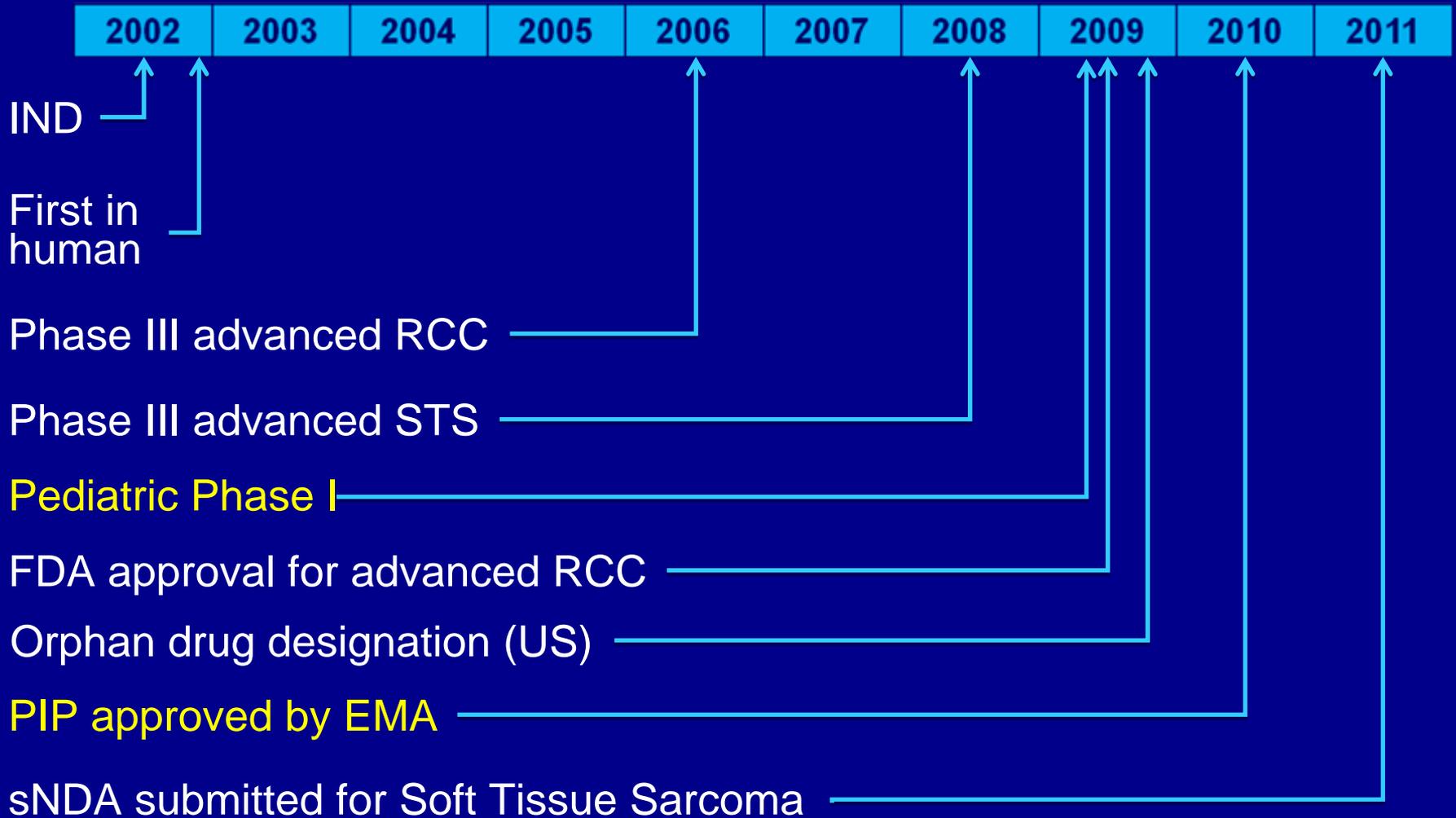


Kinase Affinity Profile

	K_i^{app} (nM)
VEGFR-1	15
VEGFR-2	8
VEGFR-3	10
PDGFR- α	30
PDGFR- β	14
c-Kit	2.4

- Selectively inhibits VEGF-mediated endothelial cell proliferation
- Inhibits angiogenesis in *in vivo* assays
- Arrests growth of human tumor xenografts in mice

Key Milestones in Pazopanib Development



Pazopanib PK and PD in Adults

- Administered orally at a dose of 800 mg QD
- Mean half-life is approximately 31 hours
- Not extensively metabolized
 - Metabolism that does occur is primarily through CYP3A
- Correlation of higher trough plasma concentrations with lower plasma levels of sVEGR2 and higher BP

Biomarker Studies in Adults

- **Safety:**
 - UGT1A1 gene polymorphism (Gilbert's) associated with increased bilirubin
 - HFE gene mutations associated with increased ALT (preliminary finding)
- **Efficacy: No definitive predictive markers in aRCC**
 - IL-6: High plasma levels predictive, but patients with low levels also benefit
 - IL-8 and HIF1 gene polymorphisms: not known whether they are prognostic or predictive
- **Neither prognostic nor predictive markers have been identified in other tumor types including STS**

Pazopanib Safety in Adults

Warnings and precautions:

- Hepatic effects
- QT prolongation and torsades de pointes
- Hemorrhagic events
- Arterial thrombotic events
- Gastrointestinal perforation and fistula
- Hypertension
- Wound healing
- Hypothyroidism
- Proteinuria
- Pregnancy

Most common adverse reactions:

- Diarrhea
- Hypertension
- Hair color changes
- Nausea
- Anorexia
- Vomiting

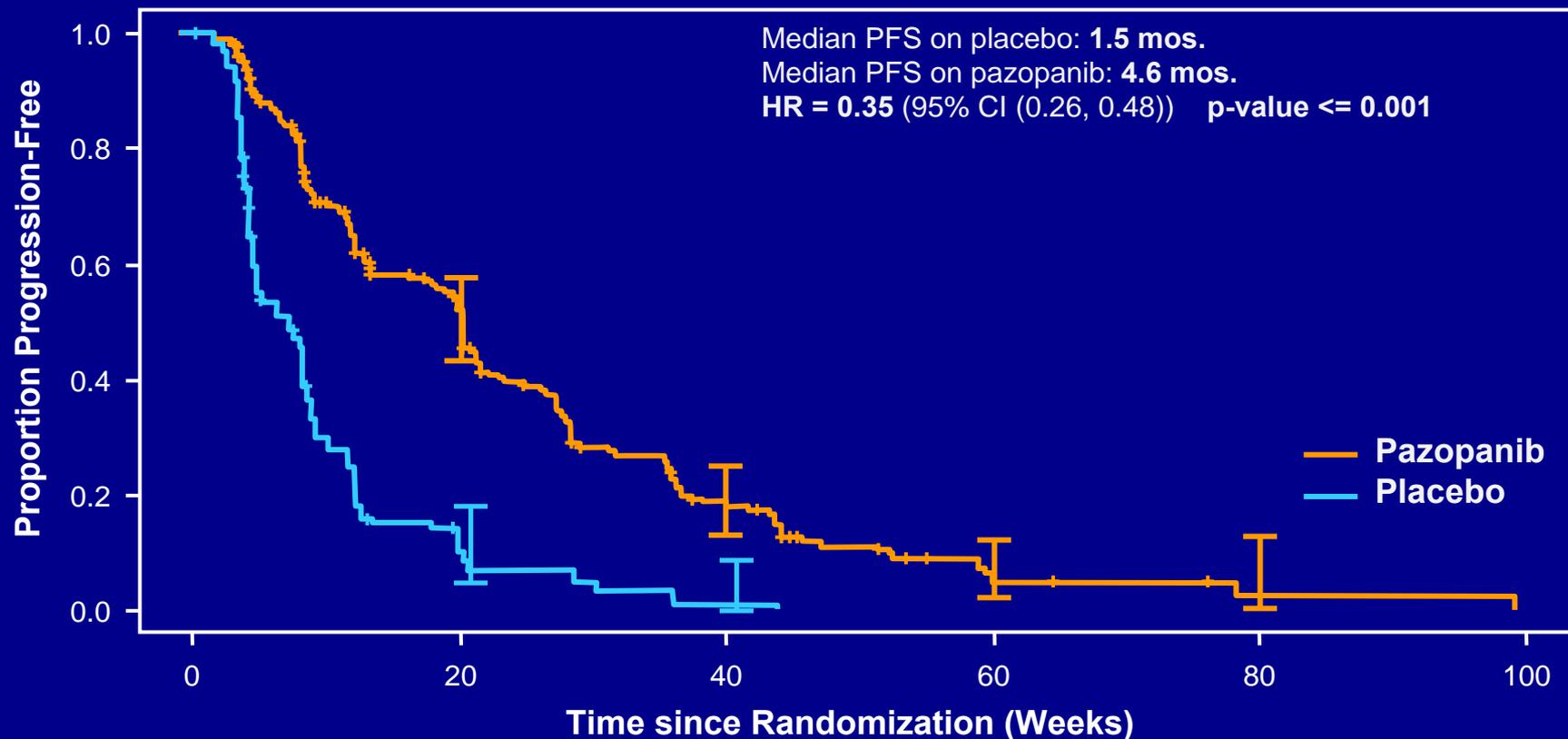
New safety data from the advanced STS trial:

- Myocardial dysfunction
- Venous thromboembolism
- Pneumothorax

Pazopanib Efficacy in Adults

- **Advanced renal cell carcinoma: randomized, double blind placebo controlled Phase III trial**
 - HR for PFS 0.46, 95% CI (0.34, 0.62), $p < 0.001$
 - Median PFS 9.2 mos. (pazopanib), 4.2 mos. (placebo)
 - HR for OS 0.91, NS
- **Relapsed/refractory soft tissue sarcoma: randomized, double blind placebo controlled Phase III trial**
 - HR for PFS 0.35, 95% CI (0.24,0.40), $p < 0.001$
 - Median PFS 4.6 mos. (pazopanib), 1.5 mos, (placebo)
 - HR for OS 0.82, NS (interim)

Relapsed/Refractory STS Primary Endpoint: PFS by Independent Review (ITT)



Subjects at Risk

Pazopanib	246	88	25	5	1
Placebo	123	8	1		

STS Study Histology

Included:

- Fibroblastic
- Fibrohistiocytic (pleomorphic undifferentiated sarcoma)
- **Leiomyosarcoma** (43%)
- Uncertain differentiation, including **synovial sarcoma** (10%)
- MPNST
- NOS
- Vascular STS
- Malignant glomus tumors
- Alveolar & pleomorphic rhabdomyosarcoma

Excluded:

- Adipocytic sarcoma
- GIST
- DFSP
- Mixed mesodermal uterine tumor
- Non alveolar & non pleomorphic rhabdomyosarcoma
- Osteosarcoma
- Ewing sarcoma/PNET
- Chondrosarcoma
- Mesothelioma
- Inflammatory myofibroblastic sarcoma

Additional Development in Adults

- **Phase III studies (on-going)**
 - Maintenance therapy in ovarian cancer
 - Adjuvant therapy in renal cell carcinoma
- **Phase III study (under consideration)**
 - First-line STS
- **Other tumor types investigated in adults include non-small cell lung cancer, breast cancer, cervical cancer, bladder cancer, thyroid cancer and glioblastoma**

Pediatric Development Plan

- **PIP**
 - Juvenile toxicity studies
 - Development of an age appropriate formulation
 - Phase I monotherapy study to assess safety and MTD
 - Phase II study in relapsed/refractory STS
 - Phase III study of pazopanib versus investigator choice in relapsed/refractory STS
- **Additional studies**
 - Phase I: cohort expansions for PK and PD
 - Phase II: additional strata
- **FDA/EMA class waiver for pediatric development in RCC**

Preclinical Studies to Support Pediatric Development

- **Juvenile Toxicology Studies**

- Effects on organ development in pre-weanling rats indicate pazopanib has the potential for similar effects on organ development in children less than 2 years of age
- Toxicity profile in rats 3 to 7 weeks of age similar to adult rats. Impairment of bone and tooth development anticipated in children

- **Preclinical Efficacy Studies**

- Xenograft studies (Pediatric Preclinical Testing Program) of pazopanib using RMS or Ewings sarcoma cell lines: small positive effect
- Other angiogenesis inhibitors active in preclinical pediatric sarcoma models

Phase I Study (ADV L0815) of Pazopanib in Children with Relapsed or Refractory Solid Tumors

- **Conducted by NCI-COG (PI is Dr. Julia Glade-Bender)**
- **Part 1 (Dose Escalation, Completed):**
 - Rolling 6 Phase I trial design
 - Starting dose ~60% of the approved adult dose
 - Administered once daily in 28 day cycles
 - Four planned dose levels: 275, 350, 450, 600 mg/m²
 - 27 subjects enrolled, 25 eligible, 23 evaluable
- **Part 2a (accrual complete): investigate PK of 50mg/mL powder for oral suspension**
- **Part 2b (accrual complete): investigate PD using DCE-MRI in subjects with recurrent/refractory STS**
- **53 patients total**

DLTs and MTD in Pediatric Phase I Study

Dose Level	Entered (N)	Evaluable (N)	DLT (N)	Type of DLT(N)
275 mg/m ²	7	6	1	Lipase (1)
350 mg/m ²	6	6	0	
MTD: 450 mg/m ²	7	6	1	One subject had both hypertension and proteinuria
600 mg/m ²	5	5	2	Hypertension (1) Amylase (1)

Toxicities in Pediatric Phase I Study

Key Toxicities	Maximum grade across all courses (total, 101 courses)				N=23
	G1	G2	G3	G4	
ALT	6		1		7 (30%)
Left ventricular systolic dysfunction	3	2			5 (22%)
Hypertension	2	9	2		13 (57%)
Proteinuria	9	1	1		11 (48%)
Hypothyroidism	2	3			5 (22%)
Prolonged QTc (N=9)					0 (0%)

- AE profile similar to that seen in adults
- Other Grade 3 AEs: lipase increased (1), amylase increased (1), phosphate decreased (1), myelodysplasia (1), hemoglobin decreased (1), leukocytes decreased (1), and neutrophils decreased (1)
- Grade 4 AEs: Neutrophils decreased (1)

PK and PD in Pediatric Phase I Study

- **PK:**
 - T_{1/2} approximately 24 hours
- **PD: Plasma biomarkers indicate target engagement**
 - Increase in plasma VEGF and PlGF levels
 - Decrease in sVEGR2 and endoglin levels

Clinical Activity in Pediatric Phase I Study

- Median number of cycles: 3 (Range 1-17)
 - 2 subjects remain on therapy
- 1 PR in subject with hepatoblastoma
- 4 SD for ≥ 6 months:
 - Alveolar soft part sarcoma
 - Osteosarcoma
 - Synovial sarcoma
 - Myxopapillary ependymoma

Approach to Later Phase Development of Pazopanib in Pediatrics

- **Initial focus on monotherapy in patients who have exhausted all accepted therapies**
 - Combination with chemotherapy in adults increases toxicity
 - Insufficient data to support front line use of monotherapy
- **Focus on sarcoma**
 - PFS improvement in STS in adults
- **Fulfill worldwide regulatory requirements for pediatric development**

Pediatric Phase II Study Concept

- **Single arm Simon 2-stage design to be conducted by NCI/COG with 7 potential strata:**
 - RMS (included in PIP)
 - Ewing family sarcoma (included in PIP)
 - Non-RMS STS (included in PIP)
 - Osteosarcoma
 - Evaluable neuroblastoma
 - Measurable neuroblastoma
 - Hepatoblastoma
- **RR in first stage for each stratum ($\geq 1/10$ subjects) will determine whether an additional 10 patients will be enrolled**
- **RR and PFS in second stage will determine characteristics of Phase III trial**

Approaches to Addressing Challenges in Pediatric Development

- **Long duration of trials due to limited number of subjects for clinical trials**
 - Working with cooperative groups essential
 - Consideration of study design including endpoints
- **Safety**
 - Exclude children younger than 2 because of role of the VEGF pathway in organ development
 - Monitor bone and tooth development
- **Continue efforts to develop oral suspension formulation with longer in-use shelf life (upon reconstitution)**
- **Combination therapy likely necessary to increase cure rate**
 - Build on results of monotherapy in pediatric Phase II study and Phase 1 studies of combination therapy in adults to explore combination therapy in pediatrics

Summary

- **Phase I pediatric study results defined MTD and showed an acceptable safety profile**
- **Plan to initiate single arm stratified Phase II study in 2012**
- **Further pediatric development will be guided by results of Phase II study**
- **Despite the challenges inherent in pediatric trials, and those specific to pazopanib, GSK is committed to the development of pazopanib in pediatric oncology**

Combination Therapy Experience in Adults

Combination Regimen	Maximum Tolerated Doses	Potential Limitations to Further Development
Pazopanib + Paclitaxel	Pazopanib 800 mg daily + Paclitaxel 80 mg/m ² on Days 1, 8 15 Q 28 days.	None
Pazopanib + Paclitaxel /Carboplatin	Pazopanib 200 mg QD + Paclitaxel 175 mg/m ² and Carboplatin AUC 5 Q 21 days.	24-38% dose reductions 77% dose interruptions Cumulative fatigue and cytopenias
Pazopanib + FOLFOX	Pazopanib 800 mg daily + full dose FOLFOX 6	70-93% dose interruptions 50-71% dose reductions Neutropenia
Pazopanib + CapeOX	Pazopanib 800 mg QD + Capecitabine 850 mg/m ² BID days 1-14 + Oxaliplatin 130 mg/m ² Q 21 days	43-71% interruptions 14-43% dose reductions Cumulative hand foot syndrome
Pazopanib + Lapatinib	Pazopanib 800 mg QD + Lapatinib 1500 mg QD Pazopanib 400 mg QD + Lapatinib 1000 mg QD	Diarrhea, LFT increase
Pazopanib + Premetrexed	Pazopanib 800 mg QD + Premetrexed 500 mg/m ² Q 21 days	33% dose reduction 47% interruptions >50% Grade 4 neutropenia