



Fondation du Centre
Pluridisciplinaire d'Oncologie

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CHUV BH 06 - Rue du Bugnon 46 - 1011 Lausanne

ZOOM VEG109603 - Pazopanib

Indication	Tumeur solide , localement avancée ou métastatique
Title	An Open-Label, Safety, Pharmacokinetic and Pharmacodynamic Dose escalation Phase Ib Study of Pazopanib in combination with Epirubicin or Doxorubicin in Subjects with Advanced Solid Tumors
Protocol ID	VEG109603-Pazopanib
Phase	Ib
Sponsor	GlaxoSmithKline
Local Principal Investigator	Dr J. Bauer
Primary Objective	To determine the OTR (optimum tolerated regimen) of the combination of oral once daily pazopanib administered in Arms A-C: <ul style="list-style-type: none"> • Arm A: days 1 to 21 inclusive, and epirubicin (day 3 of each 21-day cycle). • Arm B: days 1 to 8 inclusive, and epirubicin (day 3) • Arm C: days 13 to 20 inclusive, and epirubicin (day 3) • For Arm D: To determine the OTR of the combination of pazopanib and doxorubicin, according to a schedule selected from A, B and C
Trial design	This open-label, two-part, Phase I, dose escalation study is designed to determine the OTR (optimum tolerated regimen) of pazopanib in combination with epirubicin (part 1: Arms A-C) or doxorubicin (part 2: Arm D) in the treatment of advanced solid tumors using the standard cohort-of-3 design. For each of the parallel study arms there will be a dose escalation phase to determine the OTR and a cohort expansion phase where up to 12 subjects will be accrued to evaluate the safety of the OTR regimen. While there will be limited sampling for drug concentrations during the escalation phase, there will be minor changes in dosing days during cohort expansion to allow for full pharmacokinetic analysis.
Inclusion/exclusion criteria	Inclusion Criteria include the following : <ul style="list-style-type: none"> ○ Subjects must provide written informed consent prior to performance of study specific procedures or assessments, and must be willing to comply with treatment and follow up. ○ Histologically or cytologically confirmed diagnosis of advanced solid tumor that has failed standard therapy or for which there is no standard therapy and is indicated for treatment with anthracyclines. ○ Age ≥ 18 years

- Eastern Cooperative Oncology Group (ECOG) Performance status 0-1.
- Less than or equal to two prior lines of chemotherapy for advanced disease.
- Patients with metastatic disease to the brain should have definitive therapy for their brain metastases, should be asymptomatic. (Patients with previously treated brain metastases who are asymptomatic, off steroids and anti-seizure medications for greater than 3 months are eligible for study).
- Adequate organ system function.
- There must be measurable disease or evaluable disease on CT scan for subjects to be included in the cohort expansion phase. Measurable disease is not a criterion for subjects enrolling in the dose escalation phase.
- A female subject is eligible to enter and participate in the study if she is:
 - Of non-childbearing potential.
 - Childbearing potential, including any female who has had a negative serum pregnancy test at screening and within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception.
 - A male with a female partner of childbearing potential is eligible to enter and participate in the study if he uses a barrier method of contraception or abstinence during the study.
- Has a left ventricular ejection fraction (LVEF) \geq 50% of ULN based on MUGA/ECHO.
- Able to swallow and retain oral medication.
- Has a life expectancy of at least 12 weeks.

Exclusion Criteria include the following:

- Prior use of pazopanib or prior treatment with epirubicin > 450 mg/m² or doxorubicin > 240 mg/m² cumulative dose. Prior therapy with other angiogenesis inhibitors is permitted.
- Clinically significant gastrointestinal abnormalities which might interfere with oral dosing.
- Any unstable or serious concurrent condition (e.g., active infection requiring systemic therapy).
- Poorly controlled hypertension (systolic blood pressure [SBP] of \geq 140 mmHg, or diastolic blood pressure [DBP] of \geq 90 mmHg).
- Prolongation of corrected QT interval (QTc) > 480 msec.
- History of one or more cardiovascular conditions within the past 6 months.
- History of cerebrovascular accident (CVA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound,

	<p>fracture, or ulcer.</p> <ul style="list-style-type: none">○ Has had any chemotherapy, radiotherapy, investigational agent, biological therapy or hormonal therapy within the last 14 days and/or not recovered from a prior therapy.○ Has psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.○ Is pregnant or lactating.
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