A phase 1a / 1b first-in-human, open-label, dose-escalation, safety, pharmacokinetic, and pharmacodynamic study of oral TP-0903, a potent inhibitor of AXL kinase administered daily for 21 days

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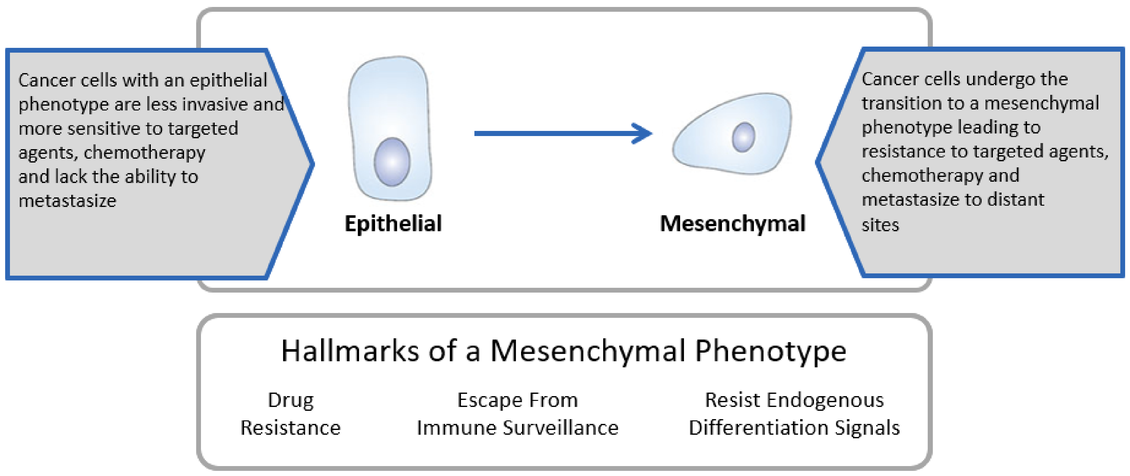
Background

Axl Promotes the Mesenchymal Phenotype in Cancer Cells[1]



TP-0903 is a potent inhibitor of Axl kinase which may

- reduce cancer cell metastasis
- target cancer cells that exhibit resistance to chemotherapeutics
- activate the anti-cancer immune response

Key Inclusion Criteria

- ≥18 years of age
- ECOG ≤1
- Patients enrolled in the Phase 1a study must:
  - Have a histologically confirmed diagnosis of advanced metastatic or progressive solid tumor
  - Be refractory to, or intolerant of, established therapy known to provide clinical benefit for their condition
- Patients enrolled in the Phase 1b study must meet criteria for one of the following tumor types:
  - Have tumors that have progressed despite immunotherapy and are felt to be appropriate for this type of treatment
  - EGFR+ NSCLC and progressed on ≤2 lines of oral TKIs and are felt to be appropriate for this type of treatment
  - BRAF, KRAS, or NRAS mutated CRC for whom there is no standard therapy remaining
  - Platinum refractory/ resistant ovarian cancer having any number of lines of prior therapy
  - BRAF-mutated melanoma that has not responded to immunotherapy or a combination BRAF/MEK inhibitor
- Adequate organ function
- ≥1 measurable/evaluable lesion

Key Exclusion Criteria

- Corrected QT interval (QTcF) of >450 msec in men and >470 msec in women
- Seizure disorder requiring anticonvulsant therapy
- Presence of symptomatic central nervous system metastatic disease or disease that requires local therapy such as radiotherapy, surgery, or increasing dose of steroids within the prior 2 weeks
- Severe chronic obstructive pulmonary disease with hypoxemia
- Major surgery, other than diagnostic surgery, within 2 weeks prior to Day 1
- Received treatment with radiation therapy, surgery, chemotherapy, or investigational therapy within 28 days or 5 half lives, whichever occurs first, prior to study entry (6 weeks for nitrosoureas or Mitomycin C)
- Significant surgery to the gastrointestinal tract that could impair absorption or that could result in short bowel syndrome with diarrhea due to malabsorption
- History of severe adverse reaction (e.g., hypersensitivity reaction, anaphylaxis) to sulfonamides

Study Objectives

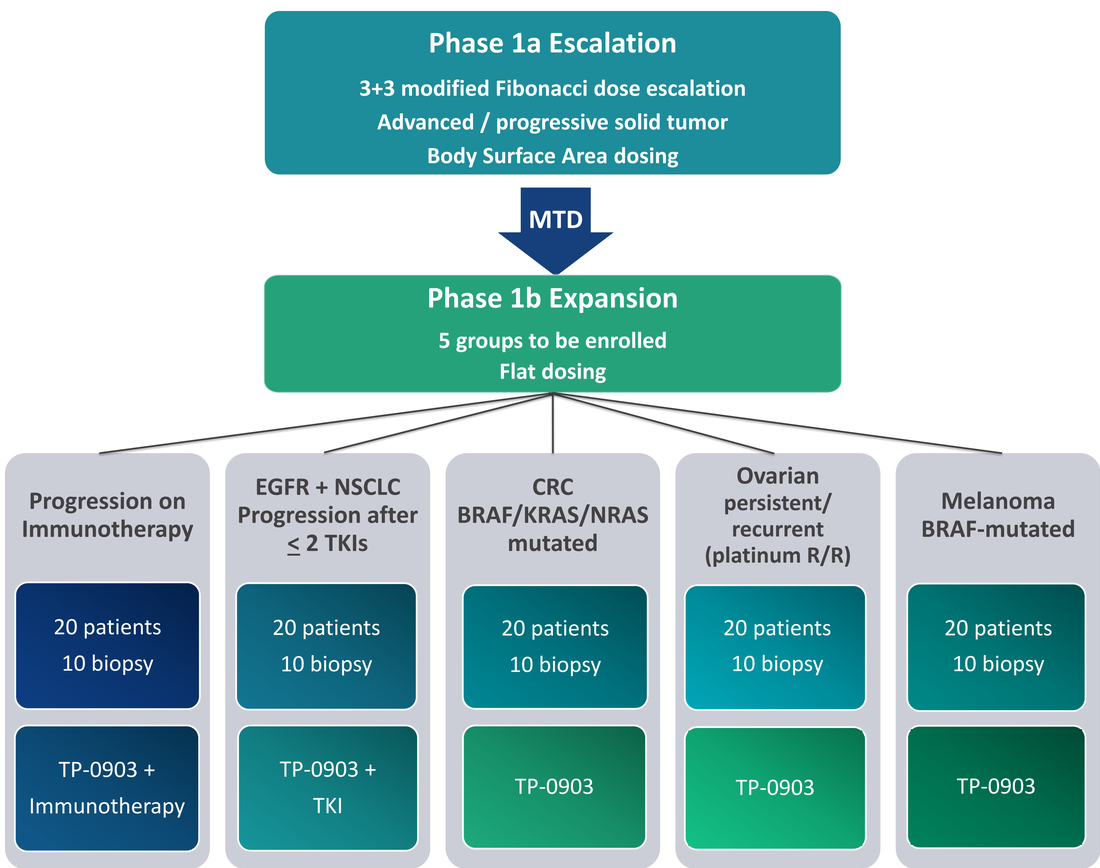
Primary Objectives

- To determine the maximum tolerated dose (MTD), dose-limiting toxicities (DLTs) and treatment emergent adverse events of oral TP-0903 administered daily for the first 21 days every 4 weeks, over a range of doses in patients with advanced solid tumors.

Secondary Objectives

- To establish the pharmacokinetics of orally administered TP-0903
- To observe patients for any evidence of antitumor activity of TP-0903 by objective radiographic assessment
- To study the pharmacodynamics of TP-0903 administration:
  - assess biomarkers in tumor tissue
  - assess biomarkers in peripheral blood mononuclear cells (PBMCs), plasma, and serum
  - determine *in vivo* markers of AXL deregulation (in patients treated at the MTD) by:
    - evaluating tumor biopsies in patients with easily accessible, low-risk tumors (as defined by local interventional radiology)
    - assessing immune function and/or response using immunohistochemistry (IHC), flow cytometry, or other molecular methodologies
- To establish the Recommended Phase 2 Dose (RP2D) for future studies with TP-0903

Study Design



Study Enrollment

Phase 1a Escalation:

Enrollment opened	December 2016
Current Enrollment	20 patients
	Cohort 7 (21mg/m^2)

Phase 1b Expansion

Anticipated Start	September 2018
Planned Enrollment	100 patients
	(20 patients per group)

References

[1]Jane Antony and Ruby Yun-Ju Huang. "AXL-Driven EMT State as a Targetable Conduit in Cancer" Cancer Res. 2017 Jul 15;77(14):3725-3732

Contacts

Clinicaltrials.gov Identifier: NCT02729298
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