1. To determine the maximum tolerated dose (MTD) or biologically effective dose (BED)
2. Characterize where the Pharmacodynamic and Pharmacokinetic parameters
3. To determine initial tumor activity

Study Design

1. Conventional 3+3 phase I dose escalation design.
2. PB-05204 was given weekly for 21 days of 28 days.
3. Cumulative studies including PKA, optional biomarkers and PBMCs were obtained on day 0, day 14 and 21.
4. ERK, 24-hour HALT monitoring and Echo were also obtained.
5. Toxicity adaptive dosing: Dose was increased if 100% or related grade 2 adverse event (AE) was observed and increased by 50% if a grade 2 AE occurred. If no other grade 2 AE were observed dose was increased by 30%.
6. Patients remained on study until tumor progression or unacceptable toxicities occurred.

Mechanism of action

- PBI and Oleandrin in malignant cells strongly correlates with the activation of NF-Kb and causes cell death by export through membrane interaction with the Na-K ATPase pump.
- In addition, it also inhibits activation of NF-κB and causes cell death by export through membrane interaction with the Na-K ATPase pump.
- Reduced cytotoxic effect of pAkt and mTOR effectors, p70S6K and pS6 was observed in some patients.
- Decreased biologically effective dose (BED) was observed over predose value.

Results

**3 dose-limiting toxicities occurred at DL 5 (grade 3 proteinuria and fatigue thus the MTD was DL 5 (0.2255 mg/kg), no other grade 3 adverse events observed**

Most common drug related adverse events include –

- Fatigue (33.3%)
- Neutropenia (14.3%)
- Constipation (11.6%)
- Abdominal pain (14.3%)
- Diarrhea (25.0%)

**Cardiac Adverse events**

- Cardiac Disorders were reported in 10 pts (24.4%), all grade 1, except for 1 pt with grade 2 AEl.
- AEG and 24-hour Holter monitoring changes observed were minor, inconsistent and not clinically significant.
- Oleandrin plasma concentrations as high as 5 ng/ml were observed in Cohort 5. No severe cardiac effect was observed in patients.
- First degree Atrioventricular block, in 2/46 (4.3%)
- Second degree Anteriorventricular block, in 1/46 (2.2%)

**Pharmacokinetic data**

- Orebéric was reduced as expected in cohort 6-4 as a function of divided daily dosing.
- Overall, no significant cardiac toxicities have been observed.
- Orebéric plasma concentrations as high as 5 ng/ml were observed in Cohort 5. No severe cardiac effect was observed in patients.
- First degree Atrioventricular block, in 2/46 (4.3%)
- Second degree Anteriorventricular block, in 1/46 (2.2%)
- Oleandrin, an inhibitor of Akt, FGF-2, NF-Kb and p70S6K in advanced Cancer Patients.

**Conclusions**

- Overall 3 dose-limiting toxicities occurred at DL 5 (grade 3 proteinuria and fatigue thus the MTD was DL 5 (0.2255 mg/kg), no other grade 3 adverse events observed.
- Western-blot analysis of PBMC or biopsy in some patients showed down regulation of pAkt and mTOR effectors, p70S6K and p53.
- The effect of PBI on other oncogenic pathway associated proteins in PBMC is currently being examined by reverse phase proteomic array method.

**Pharmacokinetic analysis**

- Overall expression of pAkt and mTOR effector in PBMCs on day 8 and 21 was not statistically significant over pre dose values (p<0.05).
- Western-blot analysis of PBMC or biopsy in some patients showed down regulation of pAkt and mTOR effectors, p70S6K and p53.
- Diarrhea (33.3%)
- Neutropenia (14.3%)
- Constipation (11.6%)
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- Diarrhea (25.0%)

**Pharmacodynamics data**

- Overall expression of pAkt and mTOR effector in PBMCs on day 8 and 21 was not statistically significant over pre dose values (p<0.05)
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