Final Results of a First-in-Human Phase I Trial of PBI-05204, an Inhibitor of Akt, FGF-2, NF-Kb and p70S6K in Advanced Cancer Patients

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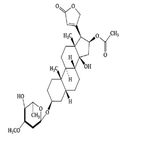
Introduction

PBI-05204, derived from *Nerium oleander* contains Oleandrin, a cardiac glycoside, which inhibits α-3 subunit of the Na-K ATPase pump. The Na-K ATPase pump is composed of α and β subunits. Over-expression of the α-3 subunit in malignant cells strongly correlates with the tumor proliferation. Oleandrin inhibits FGF-2 export through membrane interaction with the Na-K ATPase pump. In addition, it also inhibits activation of NF-Kb and causes cell death by inducing Fas expression in tumor cells and forming autophagosomes. PBI and Oleandrin inhibit phosphorylation of Akt, causing increased MAPK expression; both indicating impending cell injury and death. PBI-05204 also inhibits p70S6K, decreasing mTOR activity



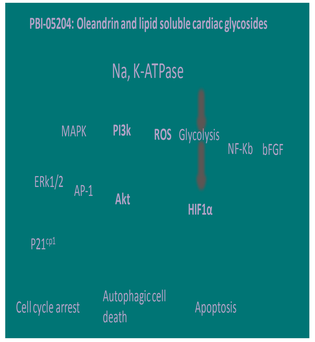
Structure of Oleandrin

(2R,3S,4S)-4-(Acetyloxy)-3-[(2,6-dideoxy-3-O-methyl-α-L-arabino-hexopyranosyl)oxy]-14-hydroxycard-20(22)-enolide]

MW 576.73

Nerium oleander

Mechanism of action



Red cross – Down-regulation; Blue arrow – Up-regulation; Dash arrow – hypothesized down regulation

Objectives

1. To determine the maximum tolerated dose (MTD) or biologically effective dose (BED)
2. To 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. PBI-05240 was given orally for 21 days of 28 days.
3. Correlative studies including PKs, optional biopsies and PBMCs were obtained on days -7 to -1, days 1, 2, 8, 15 and 21.
4. EKG's, 24-hour Holter monitoring and Echo were also obtained.
5. Toxicity adaptive dosing Dose was increased by 100% if no 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 then subsequent dose escalation was resumed at 100%.
6. Patients remained on study until tumor progression or unacceptable toxicities occurred.

Key Eligibility Criteria

1. ≥18 yrs old with evidence of metastatic or locally advanced primary solid malignancies who are not candidates for standard therapy.
2. Measurable disease, as defined by RECIST
3. ECOG performance status ≤ 1
4. Adequate hematologic, renal, and hepatic function
5. Patients with symptoms of brain metastasis are not eligible unless brain metastasis are ruled out by CT or MRI and/or fully treated surgically or with WBRT.

Dose levels

Dose level \	1	2	3	4	5	6	7	8	Total
Oleandrin dose (mg/kg)	0.0083	0.0167	0.0334	0.0668	0.1002	0.1503	0.2255	0.3383	
	(n=3)	(n=3)	(n=17)	(n=4)	(n=3)	(n=3)	(n=7)	(n=6)	(N =46)

- MTD is DL7 (0.02255) mg/kg
- DL3 initially showed the most down regulation of pAkt and mTOR effectors, p70S6K and pS6, DL3 was expanded to enroll 14 more patients and determined to be the BED (biologically effective dose)

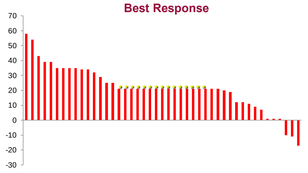
Demographics and Patient Characteristics

	Total (N=46)
Sex	46
Men	20 (43.5 %)
Women	26 (56.5%)
Race	46
White	39 (84.8%)
Black/African American	6 (13.0%)
Asian	1 (2.2%)
Histology	46
Adenocarcinoma	40 (87.0%)
Squamous carcinoma	5 (10.9%)
Other	1 (2.2%)
ECOG Score at Baseline	46
0	15 (32.6%)
1	31 (67.4%)
Primary Tumor	46
Colorectal	14 (30.4 %)
Other *	11 (24.1 %)
Pancreatic	6 (13.0 %)
Breast	5 (10.9 %)
Melanoma	4 (8.7 %)
Renal	2 (4.3 %)
Bladder	2 (4.3 %)
Head and Neck	2 (4.3 %)

* urethral carcinoma, GIST, Sarcoma, esophageal cancer, ovarian cancer, Mucinous Adenocarcinoma of appendix, unclassified malignant epithelioid tumor, Fallopian tube, Gastro esophageal carcinoma, esophageal cancer, prostate cancer

Results

Best Response



- 45 out of 46 patients evaluable for response assessment, 1/46 withdraw consent after one week
- 1/45 patient - no measurable disease .
- Stable disease (SD) seen in 12/45 patients (27%) with various tumor types
- 7 had SD for ≥ 4 months, with bladder, colorectal, fallopian tube, breast, appendiceal and pancreatic carcinoma (2 pts)
- minor response in 3 patients-one each with colorectal (17% decrease), bladder (11% decrease) and fallopian tube cancer (10% decrease)
- longest duration of stable disease was 7 months in a patient with appendiceal carcinoma
- 15 patients had clinical disease progression before having re-staging scans

Related adverse events

System Organ Class / Preferred Term	Statistic	Dose Level (mg/kg) 0.0083 (N=3)	0.0167 (N=3)	0.0334 (N=17)	0.0668 (N=4)	Dose Level (mg/kg) 0.1002 (N=3)	0.15 (N=3)	0.2255 (N=7)	0.3383 (N=6)	Total (N=46)
Gastrointestinal disorders										
Abdominal pain										
Grade 1	n (%)	0	0	0	1 (25.0)	0	2 (66.7)	1 (14.3)	2 (33.3)	6 (13.0)
Constipation										
Grade 1	n (%)	1 (33.3)	0	1 (5.9)	1 (25.0)	1 (33.3)	0	0	1 (16.7)	5 (10.9)
Grade 2	n (%)	0	0	1 (5.9)	0	0	1 (33.3)	0	1 (16.7)	3 (6.5)
Diarrhea										
Grade 1	n (%)	0	0	2 (11.8)	0	1 (33.3)	2 (66.7)	3 (42.9)	4 (66.7)	12 (26.1)
Grade 2	n (%)	0	0	0	0	0	0	2 (28.6)	1 (16.7)	3 (6.5)
Nausea										
Grade 1	n (%)	0	1 (33.3)	2 (11.8)	1 (25.0)	0	0	3 (42.9)	4 (66.7)	11 (23.9)
Grade 2	n (%)	0	0	4 (23.5)	0	0	1 (33.3)	0	2 (33.3)	7 (15.2)
Grade 3	n (%)	0	0	1 (5.9)	0	0	0	0	0	1 (2.2)
Vomiting										
Grade 1	n (%)	0	0	2 (11.8)	0	0	0	1 (14.3)	4 (66.7)	7 (15.2)
Grade 2	n (%)	0	0	0	0	0	1 (33.3)	0	0	1 (2.2)
Grade 3	n (%)	0	0	1 (5.9)	0	0	0	0	0	1 (2.2)
Fatigue										
Grade 1	n (%)	0	0	2 (11.8)	0	0	0	1 (14.3)	2 (33.3)	5 (10.9)
Grade 2	n (%)	1 (33.3)	0	7 (41.2)	1 (25.0)	1 (33.3)	1 (33.3)	4 (57.1)	3 (50.0)	18 (39.1)
Grade 3	n (%)	0	0	2 (11.8)	0	0	0	0	1 (16.7)	3 (6.5)
Proteinuria										
Grade 1	n (%)	0	0	1 (5.9)	0	0	0	1 (14.3)	2 (33.3)	4 (8.7)
Grade 2	n (%)	0	0	0	0	0	0	0	0	0
Grade 3	n (%)	0	0	0	0	0	0	0	1 (16.7)	1 (2.2)

- 2 dose-limiting toxicities occurred at DL 8 (grade 3 proteinuria and fatigue thus the MTD was DL7 (0.2255 mg/kg), no other grade ≥ 3 adverse events observed

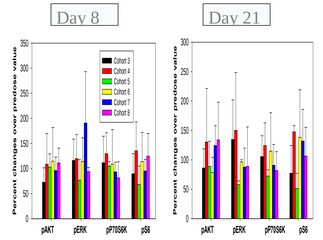
Most common drug related adverse events include –
- Fatigue (56.1%)
- Nausea (41.5 %)
- Constipation (41.5 %)
- Abdominal pain/discomfort (41.5 %)
- Diarrhea (39.0 %)

Cardiac Adverse events

- Cardiac Disorders were reported in 10 pts (24.4%), all grade 1, except for 1 pt with grade 2 SVT
- EKG and 24-hour Holter monitor changes observed were minor, inconsistent and not clinically significant
- Observed drug related adverse events
  - First degree Atrioventricular block, in 2/46 (4.3%)
  - Second degree Atrioventricular block, in 1/46 (2.2%)
  - Palpitation in 2/46 (4.3%)
  - Supraventricular tachycardia in 1/46 (2.2%)

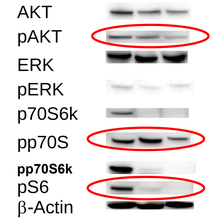
Pharmacodynamics data

Expression of phospho- Akt pERK, pP70S6K and pS6 in PMBC's



Data are presented as Mean SD p= 0.127

A.



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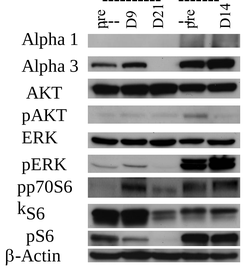


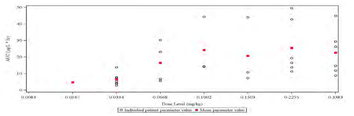
Western blot analysis of PBMC or biopsy material in one patient of cohort 5 (A) and one patient in cohort 3 (B). Down regulation of pAkt and mTOR effector, p70S6K and pS6 was observed.

Summary of Pharmacodynamic analysis

- Overall expression of pAkt and mTOR effector in PBMCs on day 8 and 21 was not statistically significant over pre dose values (p= 0.127)
- Western blot analysis of PBMC or biopsy in some patients showed down regulation of pAkt and mTOR effector, p70S6K and pS6
- The effect of PBI on other oncogenic pathway associated proteins in PBMC is currently being examined by reverse phase proteomic array method

Pharmacokinetics data

Oleandrin dose vs. AUC



- Dose dependent increases in mean oleandrin C_{max} observed (0.4 to 2 ng/ml (Cohort 2-5 QD dosing). C_{max} was reduced as expected in cohorts 6-8 as a function of divided daily dosing
- Oleandrin plasma concentrations as high as 5 ng/ml were observed in Cohort 5. No severe cardiac-related toxicity observed at any dose level. A trend was observed for a dose-dependent increase in Mean AUC
- Compared to other cardiac glycosides, mean oleandrin $t_{1/2b}$ was short (8.9 hrs vs. 36-48 hrs), with volume and clearance comparable

Conclusions

- PBI-05204 is well tolerated up to 10.2 mg/kg dose. oral dose daily for 21 days (28 d cycle), MTD is DL7 0.2255 mg/kg
- No significant cardiac toxicities have been observed
- A dose-dependent increase observed in mean plasma oleandrin concentration at 2 hrs post dose
- Down regulation of pAkt and mTOR effectors, p70S6K and pS6 was observed in some patients
- 7 had SD for ≥ 4 months, with , breast, appendiceal and pancreatic carcinoma (2 pts) bladder, colorectal, fallopian tube