PBI-05204, an inhibitor of Akt, FGF-2, NF-κb and p70S6K

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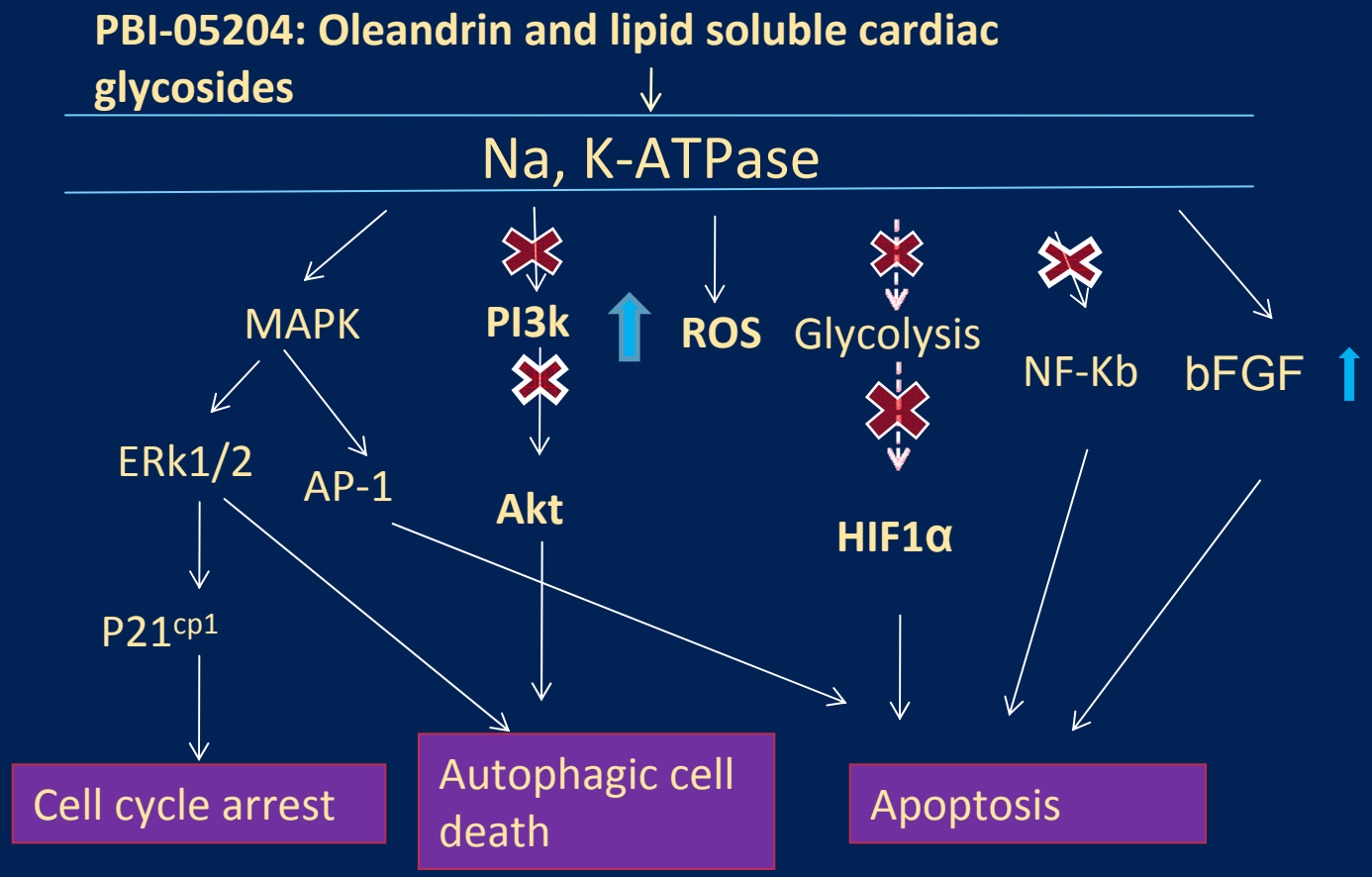
Introduction

- PBI-05204, a concentrated extract of Nerium Oleander containing oleandrin, a cardiac glycoside, which inhibits Na-K ATPase pump activity through the α-3 subunit.

- Over-expression of the α-3 subunit in malignant cells strongly correlates with tumor proliferation.

- Oleandrin **inhibits**-

1. **FGF-2 export** through membrane interaction with the Na-K ATPase pump.
2. **Activation of NF-κb** and causes cell death by inducing Fas expression in tumor cells and forming autophagosomes.
3. **Phosphorylation of Akt**, causing increased MAPK expression; both indicating impending cell injury and death.
4. **mTOR effector protein phosphorylation, p70S6K and S6.**



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

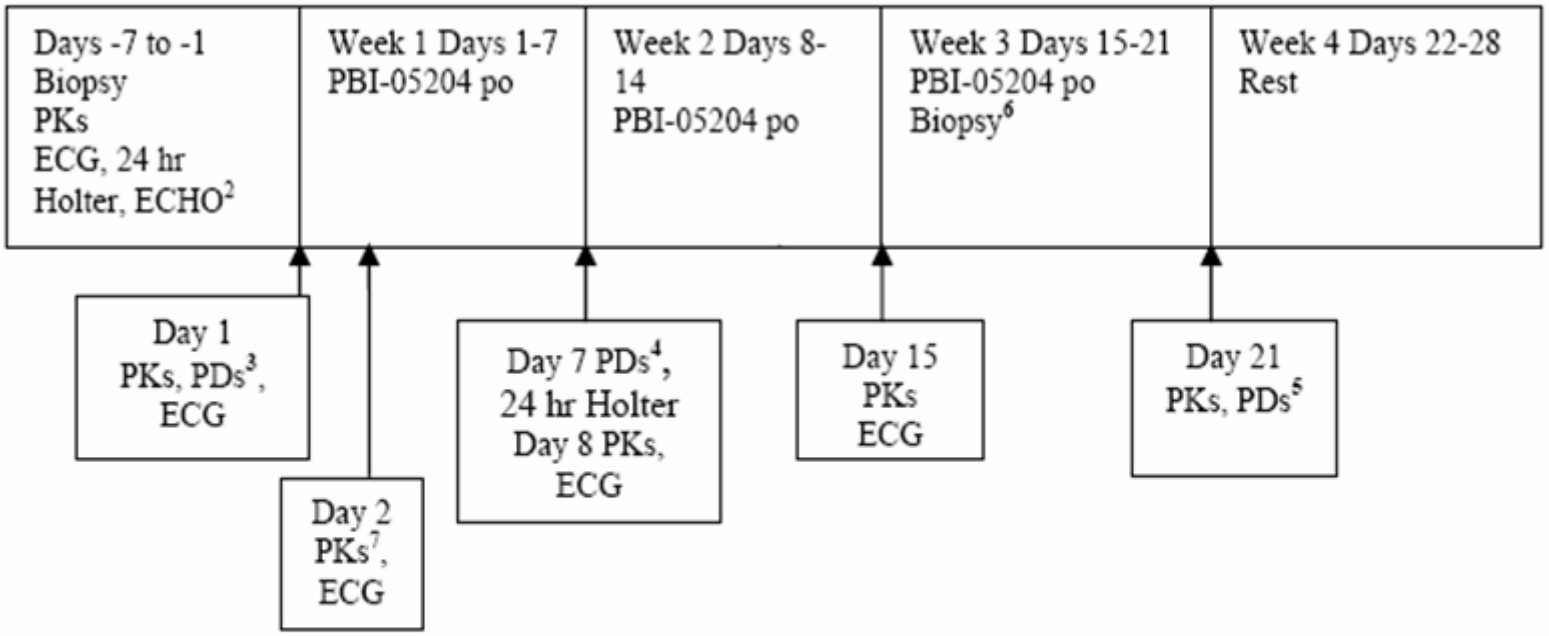
Objectives

- To determine the maximum tolerated dose (MTD) or biologically effective dose (BED).
- To characterize where possible the Pharmacodynamic (PD) and Pharmacokinetic (PK) parameters.
- To determine initial tumor activity.

Study Design

- Conventional 3+3 Phase I dose escalation design.
- PBI-05204 was given orally for 21 days of 28 days.
- Correlative studies including PKs, optional biopsies and PBMCs were obtained.
- EKG's, 24-hour Holter monitor and Echo performed.
- 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%.
- Patients remained on study until tumor progression or unacceptable toxicities occurred.

Cycles are 4 weeks each[1]



[1] PBI-05204 given daily (through cohort 5) or twice daily as a divided dose (cohort 6+)
[2] for patients with cardiomyopathy who have not had an echocardiogram three months prior
[3] Taken pre-dose
[4] Scheduled for Day 7 ± 2 days
[5] Scheduled for Day 21 ± 2 days
[6] Scheduled for any time during Days 15-21
[7] Only for subjects on QD dosing

Key Eligibility Criteria

- ≥18 yrs old with evidence of metastatic or locally advanced primary solid malignancies who are not candidates for standard therapy.
- Measurable disease, as defined by RECIST.
- ECOG performance status ≤ 1.
- Adequate hematologic, renal, and hepatic function.
- 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.

Overview

- Patient disposition
- Patient characteristics
- Adverse events
- Summary of adverse events
- Median change in 12-Lead EKG parameters
- 24-Hour Holter monitor data
- Summary of Cardiac adverse events
- Best response
- Pharmacokinetics data
- Pharmacodynamics data
- Conclusion

Patient Disposition

PBI Dose level	Number of patients	DLT's*
(mg/kg)	(n)	(n)
1 (0.0083)	3	0
2 (0.0167)	3	0
3 (0.0334)	3	0
4 (0.0668)	4	0
5 (0.1002)	3	0
6 (0.1500)	3	0
7 (0.2255)	3	0

*DLT –dose limiting toxicity; no DLTs yet observed

Table 1. Patients' baseline characteristics (n=22)

Characteristics		
Gender, *n* (%)		
Male	12	(55)
Female	10	(45)
Race, *n* (%)		
Caucasian	20	(91)
Others	2	(9)
Median Age, (y)	55	
Age Range	35 – 75	
ECOG, *n* (%)		
0	12	(55)
1	10	(45)
Diagnosis, *n* (%)		
Colorectal	10	(45)
Gastro-esophageal	2	(10)
Pancreatic	2	(10)
Ovarian	1	(5)
Breast	1	(5)
Head & Neck	1	(5)
Bladder	1	(5)
Prostate	1	(5)
Other	3	(14)
Number of prior chemotherapy regimens, *n* (%)		
1	1	(5)
2	5	(23)
3	4	(18)
≥4	12	(56)

Related Adverse Events**

Category	Grade	Dose level 1	Dose level 2	Dose level 3	Dose level 4	Dose level 5	Dose level 6	Dose level 7	Total
	mg/kg	0.0083	0.0167	0.0334	0.0668	0.1002	0.15	0.2255	
		(n=3)	(n=3)	(n=3)	(n=4)	(n=3)	(n=3)	(n=3)	(N =22)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiac									
Atrioventricular block (first degree)	1or 2	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	2 (9)
Palpitations	1or 2	0 (0)	1 (33)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	2 (9)
Supraventricular tachycardia	1or 2	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (5)
Ventricular extrasystoles	1or 2	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (5)
Hypertension	1or 2	0 (0)	1 (33)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9)
EKG									
QT prolongation		0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Metabolic/Laboratory									
AST	1 or 2	1 (33)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9)
Creatinine	1 or 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Brain natriuretic peptide	1 or 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	1 (5)
Troponin I	1 or 2	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9)
Thyroid function test abnormal	1 or 2	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)	0 (0)	1 (5)
Constitutional Symptoms									
Fatigue	1 or 2	1 (33)	0 (0)	1 (33)	1 (25)	0 (0)	0 (0)	1 (33)	4 (18)
Edema	1 or 2	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Myalgia/muscle cramps	1 or 2	1 (33)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	2 (67)	4 (18)
Anorexia	1 or 2	0 (0)	2 (67)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (9)
Hot flashes	1 or 2	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Gastrointestinal									
Dry Mouth	1 or 2	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Nausea	1 or 2	0 (0)	1 (33)	1 (33)	1 (25)	0 (0)	0 (0)	0 (0)	3 (14)
Vomiting	1 or 2	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Diarrhea	1 or 2	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	1 (33)	2 (67)	4 (18)
Constipation	1 or 2	1 (33)	0 (0)	1 (33)	1 (25)	0 (0)	0 (0)	0 (0)	3 (14)
Abdominal pain/discomfort	1 or 2	1 (33)	1 (33)	0 (0)	1 (33)	0 (0)	2 (67)	1 (33)	6 (27)
Abdominal distension	1 or 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Flatulence	1 or 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (5)
Blood/Bone Marrow									
Anemia	1 or 2	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	1 (33)	2 (9)
Respiratory									
Dyspnea	1 or 2	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)

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*No Grade 3 or higher Adverse Event observed

**Adverse events are Possibly/Probably/Definitely related.

Summary of Adverse Events

- No grade 3 or higher adverse event noted.

- Most common drug related adverse events include –

1. Abdominal pain/discomfort in 6/22 patients (27%)
2. Diarrhea, myalgias, fatigue in 4/22 patients(18% each)
3. Nausea, constipation in 3/22 patients (14% each)

Change in Median 12-Lead EKG Parameters- Baseline to Cycle 1 Day 15 (C1D15)

Dose Level	Heart Rate (beats/min)	RR (sec)	PR (msec)	QRS (msec)	QTc (msec)	Axis (degree)
1 (0.0083 mg/kg)						
Baseline	62	0.97	193	107	418	50
Change from baseline to C1 D15	10	-0.14	-23	-4	-13	-5
2 (0.0167 mg/kg)						
Baseline	82	0.74	146	85	417	-5
Change from baseline to C1 D15	-11	0.11	8	16	-22	-5
3 (0.0334 mg/kg)						
Baseline	86	0.7	144	83	399	30
Change from baseline to C1 D15	-4	0.02	6	4	-2	-5
4 (0.0668 mg/kg)						
Baseline	81	0.74	154	83	389	10
Change from baseline to C1 D15	3	-0.02	9	-3	-3	-5
5 (0.1002 mg/kg)						
Baseline	60	1	176	92	424	20
Change from baseline to C1 D15	-12	0.14	6	-3	-30	-5
6 (0.1500 mg/kg)						
Baseline	71	0.85	182	87	416	35
Change from baseline to C1 D15	12	-0.13	3	6	6	5
7 (0.2255 mg/kg)						
Baseline	68	0.89	157	96	422	35
Change from baseline to C1 D15	25	-0.24	7	-8	9	0
Total						
Baseline	78	0.77	157	87	417	30
Change from baseline to C1 D15	3	-0.02	7	-3	-13	-5

24-Hour Holter Monitor Data

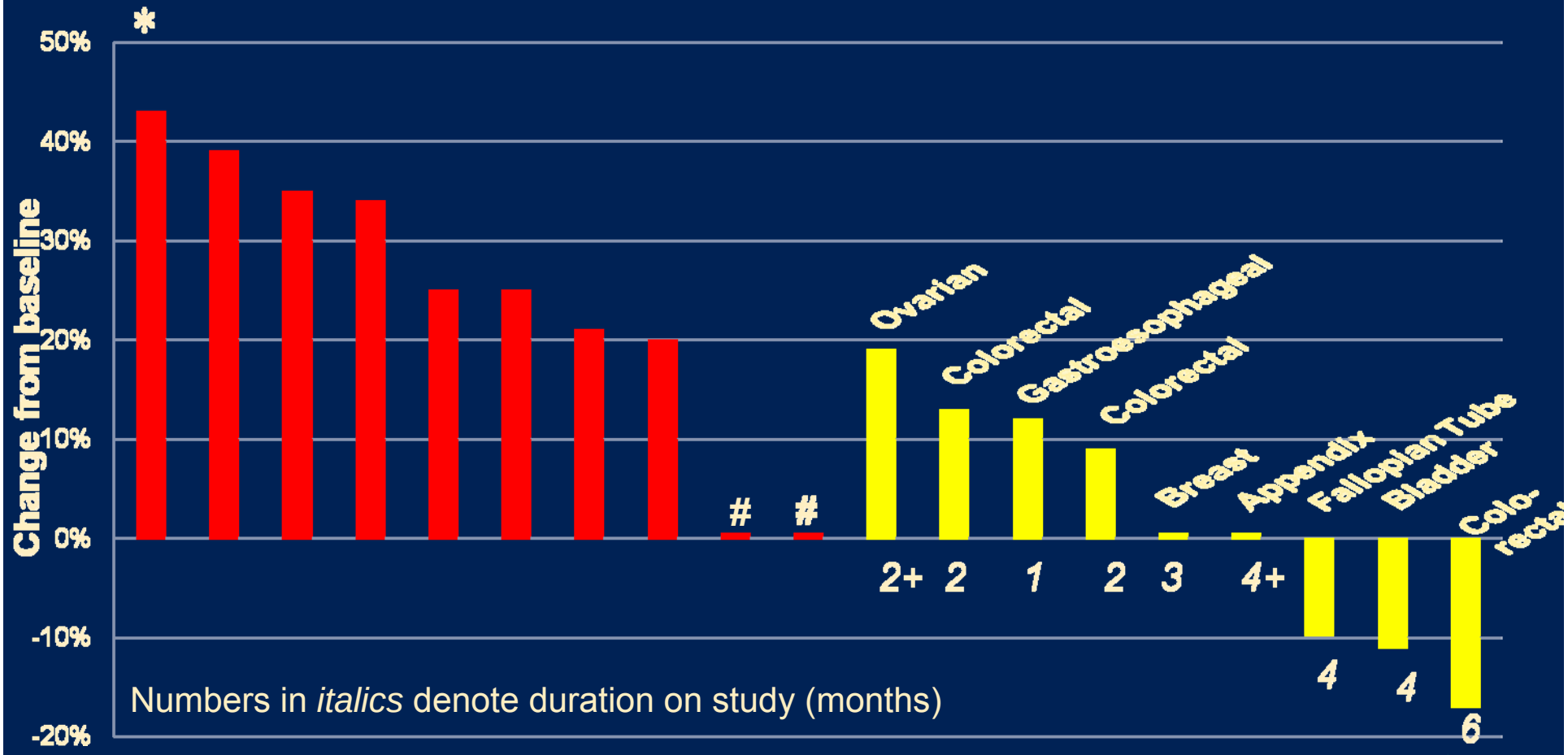
Dose level	Change from Baseline (Cycle 1 Day 7)	
1 (0.0083 mg/kg)	Mean Heart Rate (beats/min)	Ventricular Ectopy Beats
Patient 1	6	-1
Patient 2	4	6
Patient 3	0	293
2 (0.0167 mg/kg)		
Patient 1	16	-2
Patient 2	-4	-144
Patient 3	-4	-4
3 (0.0334 mg/kg)		
Patient 1	12	-5
Patient 2	-10	-2
Patient 3	-13	-11
4 (0.0668 mg/kg)		
Patient 1	-3	511
Patient 2	1	-1
Patient 3	-3	67
Patient 4	3	796
5 (0.1002 mg/kg)		
Patient 1	27	-44
Patient 2	8	513
Patient 3	-7	6
6 (0.1500 mg/kg)		
Patient 1	0	2
Patient 2	4	7
Patient 3	-12	-25
7 (0.2255 mg/kg)		
Patient 1	0	-102
Patient 2	12	-4
Patient 3	1	-1

Summary of Cardiac Adverse Events

- No cardiac adverse event ≥ grade 2 observed.
- Only grade 1 adverse event seen in 5/22 patients (23%).
- EKG and 24-hour Holter monitor changes observed were minor, inconsistent and not clinically significant.
- Observed drug related adverse events -

1. First degree Atrioventricular block, palpitations, hypertension in 2/22 patients (9% each)
2. Supraventricular tachycardia, ventricular extrasystole in 1/22 patients (5% each)
3. EKG abnormality- QTc prolongation in 1/22 patients (5%).

Best Response By RECIST



Progressive disease
Stable disease

20/22 patients evaluable by RECIST
* - 233% increase
# 2/22 - progression with new metastases
1/22 - clinical progression
1/22 - non-measurable disease

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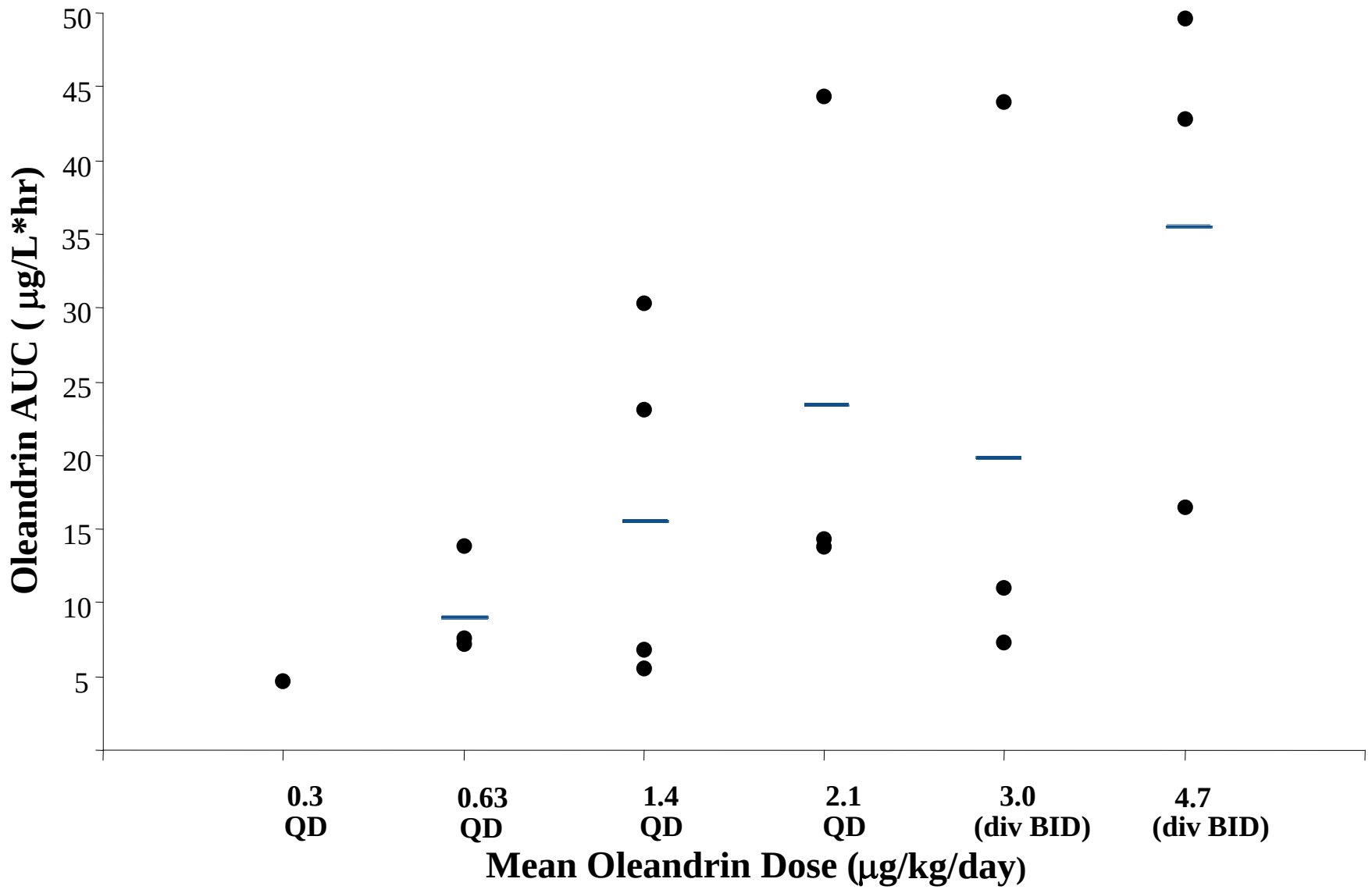
Summary of Best Response

- Stable disease was seen in 9/20 patients (45%) with various tumor types after first restaging (2 months).
- Out of these, minor response was seen in 3 patients-one each with colorectal (17% decrease), bladder (11% decrease) and fallopian tube cancer (10% decrease).
- The longest duration of stable disease was 6 months in a colorectal cancer patient.

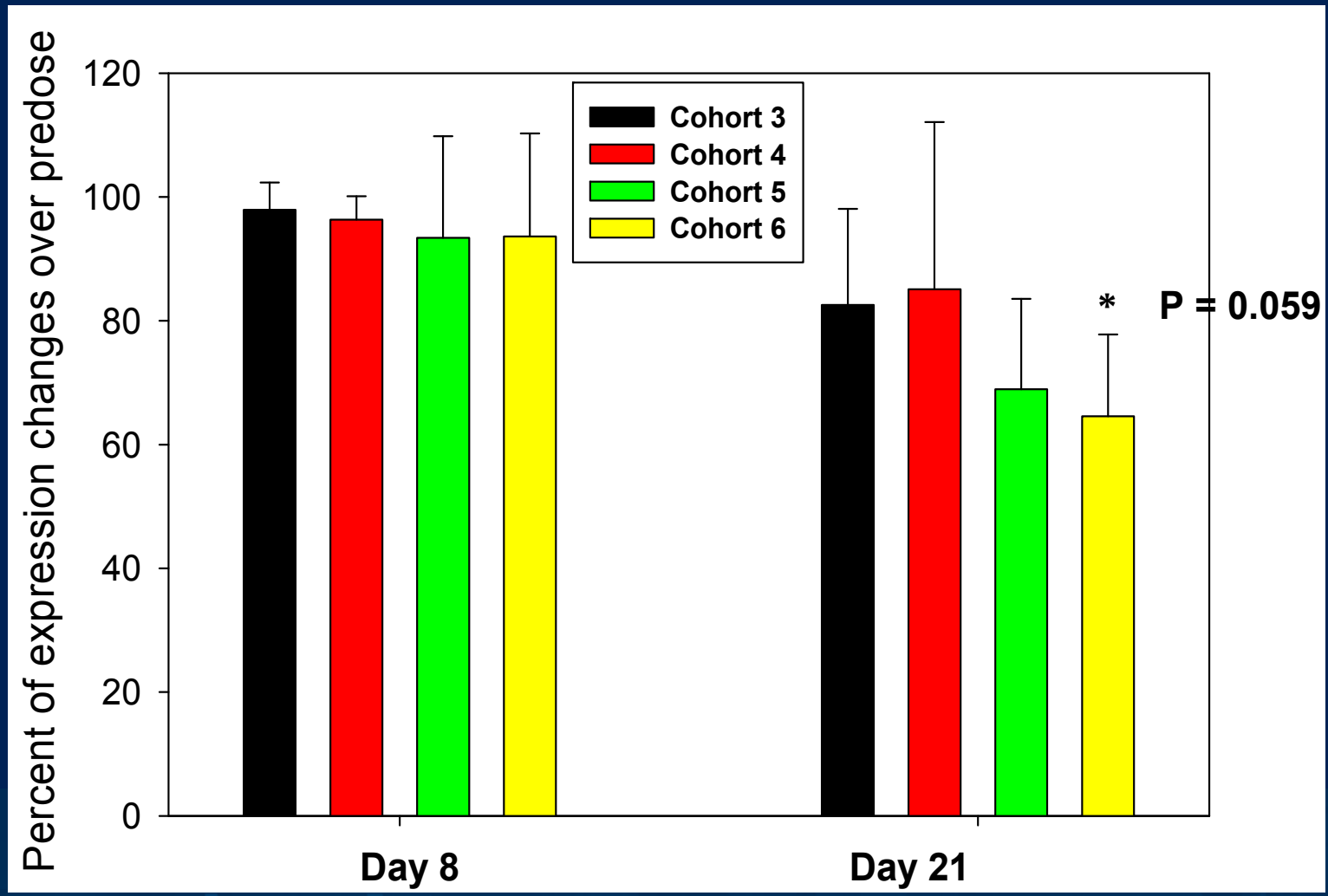
Oleandrin Dose vs. AUC



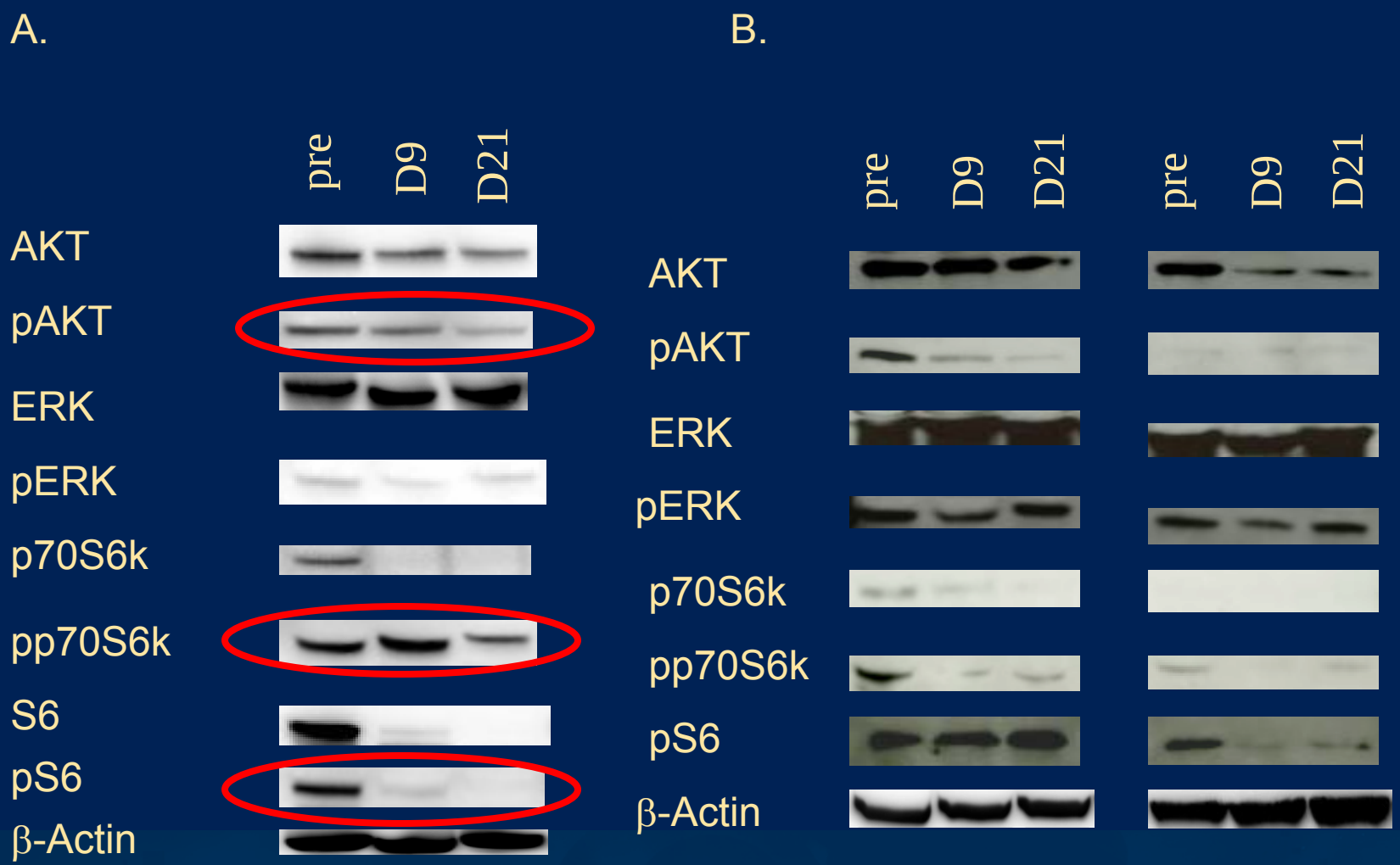
Pharmacokinetic Summary

- A dose-dependent increase observed in mean plasma oleandrin concentration at 2 hrs post dose. Day 8, mean plasma oleandrin concentration measured at 2 hr (0.93 ng/ml (Cohort 3) to 2.41 ng/ml (Cohort 7)).
- No severe cardiac-related toxicity has been observed to date within this plasma concentration range.
- A trend was observed for a dose-dependent increase in Mean AUC.
- Compared to digoxin PKs ($t_{1/2\gamma}$ = 36hrs, Cl = 0.16 L/hr/kg), Vss = 6.7 L/kg), mean oleandrin $t_{1/2\beta}$ was relatively short, with volume and clearance comparable.

Expression of phospho-Akt in PMBC's



Data are presented as Mean ± SD, * p = 0.059



Western blot analysis of PBMC in one patient of cohort 5 (A) and 2 patients in cohort 6 (B). Down regulation of pAkt and mTOR effector, pp70S6K and pS6 were observed in all of these three patients

Summary of Pharmacodynamic analysis

- Western blot analysis in PBMCs showed a trend toward reduction of phosphorylation of Akt, p70S6K, and S6 in a time and dose dependent manner suggesting PBI-05204 is capable of inhibiting oncogenic cell signaling PI3kinase/mTOR pathways.

- Continuing assessment of NA, K-ATPase, α-3 subunit expression with respect to reduction of PI3 kinase/mTOR protein expression is ongoing.

Conclusion

- PBI-05204 is well tolerated up to 0.2255 mg/kg dose, dose escalation is ongoing.
- No grade 3 or higher adverse events noted.
- No significant cardiac adverse events have been observed.
- Activity has been shown in diverse tumor types.
- PD analysis has shown a trend toward reduction of phosphorylation of Akt, p70S6K, and S6.
- PK analysis has shown a dose dependent increase in mean plasma oleandrin concentration.

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