Study P3K112826

Phosphoinositide 3-kinase inhibitor GSK2126458: Clinical Activity in Select Patient Populations Defined by Predictive Markers

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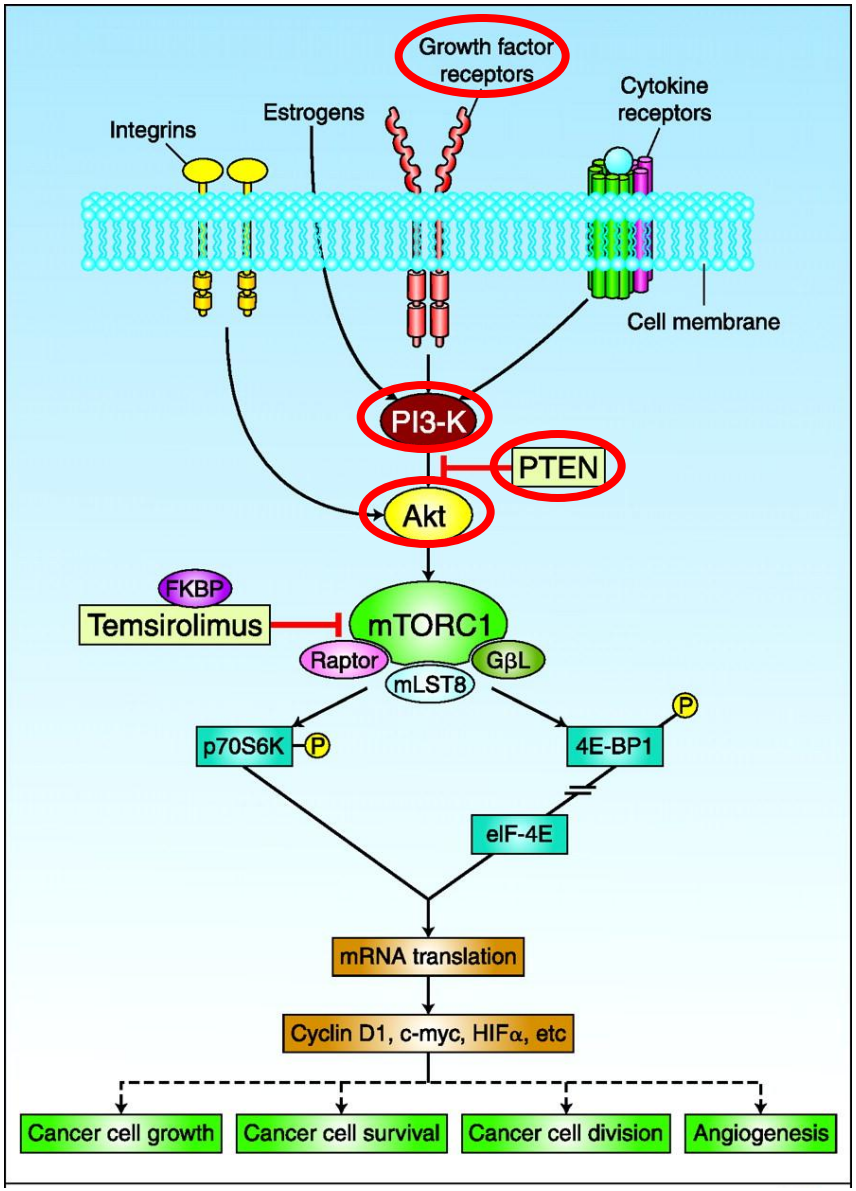
Disclosures

- **Stock Ownership:**
  - Shannon R. Morris, Deborah A. Smith, Joseph F. Kleha, Michael Durante, Laurel Adams, Joel Greshock
- **Membership on an advisory board or board of directors:**
  - Adil Daud
- **Corporate-sponsored research:**
  - Pamela Munster, Jennifer Specht, E. Claire Dees, Antoinette R. Tan, Adil Daud, Gerald S Falchook, Razelle Kurzrock
- **Other Substantive Relationships:**
  - Shannon R. Morris (GSK), Deborah A. Smith (GSK), Joseph F. Kleha (GSK), Michael Durante (GSK), Laurel Adams (GSK), Joel Greshock (GSK).

PI3K is an Important Cancer Target

The phosphoinositide 3-kinase (PI3K) pathway:

- central regulator of cell growth, proliferation and survival
- is among the most commonly activated pathways in human cancer.
- is frequently mutated in human cancers
- Mutations provide an opportunity for prospective patient selection to streamline clinical development



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GSK2126458 Background

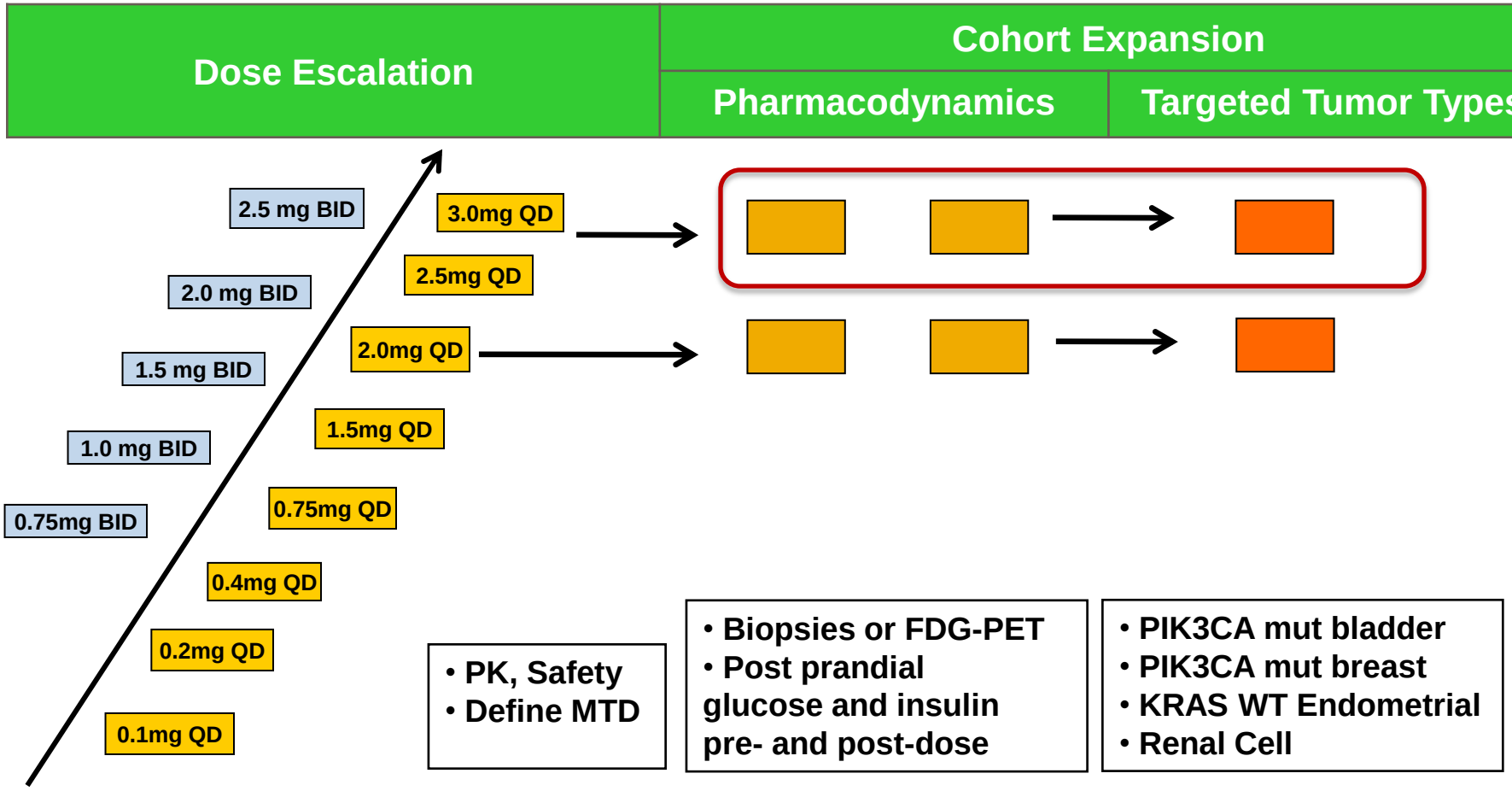
- **GSK2126458** a potent, orally bioavailable inhibitor of phosphoinositide 3-kinase. This is a novel molecularly targeted cancer therapeutic agent and is intended to be used as either monotherapy or in combination with other cancer therapies for the treatment of patients with tumors driven by activated PI3K pathway.
- **GSK2126458** inhibits all four isoforms of PI3K as well as mTORC1 and mTORC2, and is particularly potent against common mutations of PI3K.

Human Enzyme	Apparent K_i (nM)
p110α/p85α	0.019 ± 0.01
p110β/p85α	0.13 ± 0.03
p110δ/p85α	0.024 ± 0.01
p100γ	0.060 ± 0.008
E542K	0.0078 ± 0.03
E545K	0.0078 ± 0.03
H1047R	0.0094 ± 0.03

Most common mutations of p110α

mTOR Complexes	Apparent K_i (nM)
mTORC1	0.18 ± 0.01
mTORC2	0.3 ± 0.1

P3K112826 Study Design

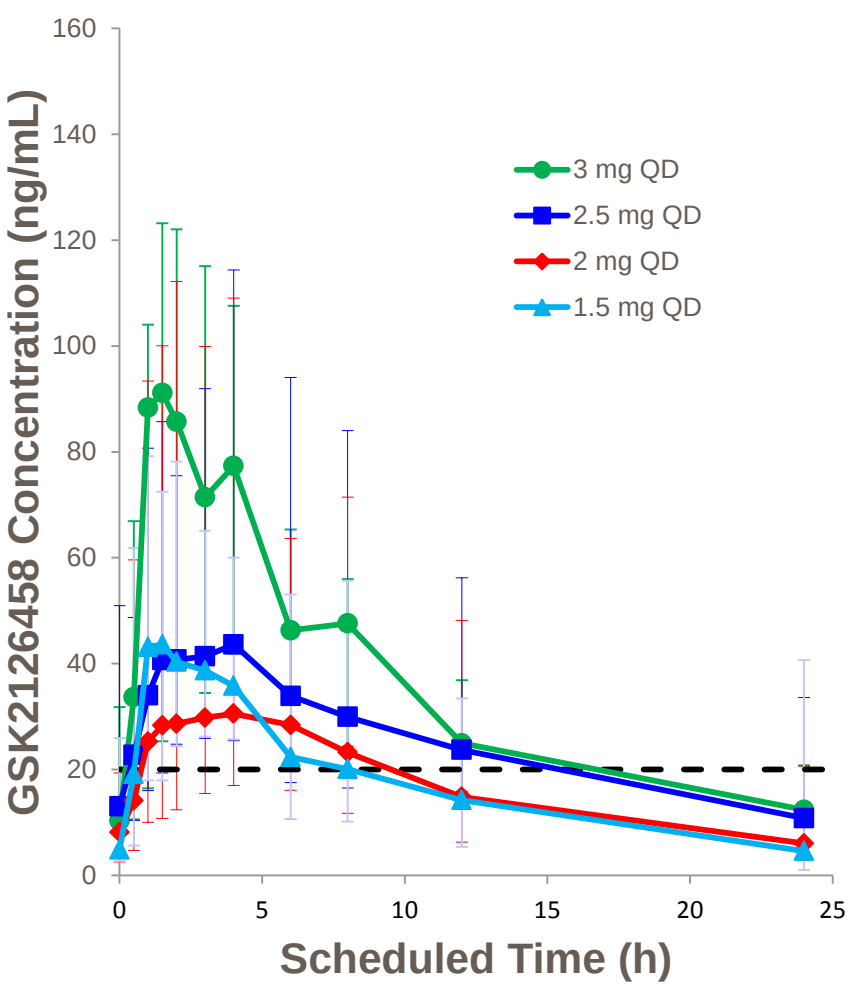


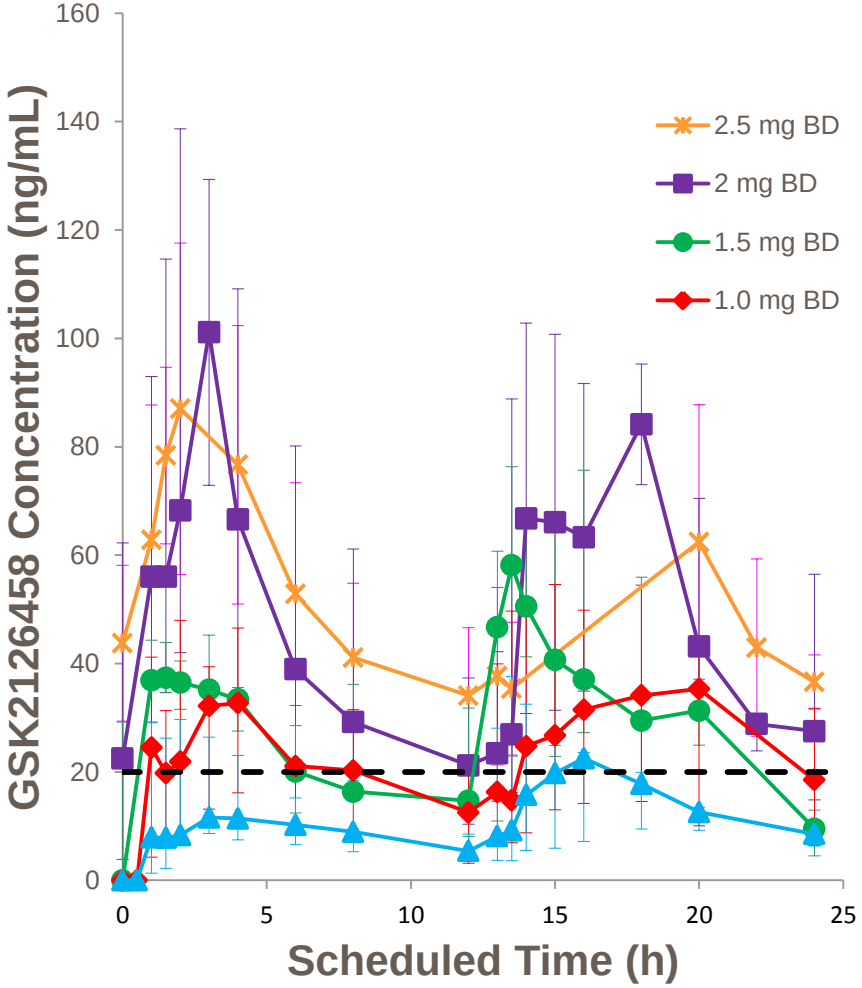
Patient Characteristics

Characteristic	Total (N=170)
Mean age, years (range)	57 (22-85)
Male, n (%)	86 (51)
Race; n (%) Not Hispanic/Latino Hispanic/Latino	 166 (98%) 4 (2%)
Tumor Type, n (%)	
Colon/Rectum	31 (18)
Renal Cell	24 (14)
Breast	22 (13)
Bladder	17 (10)
Endometrial	15 (9)
Other	61 (36)

Genetic Testing	Total (N=170)
PIK3CA Mutation Status	
Positive	18 (11)
Wildtype	50 (29)
Unknown	102 (60)
KRAS Mutation Status	
Positive	10 (6)
Wildtype	49 (29)
Unknown	111(65)

Median (range) GSK2126458 Concentration vs Time:
Day 15 Once (left panel) and Twice (right panel) Daily





Black line represents projected concentration (20 ng/mL) from nonclinical PK/PD study needed to inhibit pAKT ~60%

Comparison of Preliminary Exposures for Total Daily Dose (Twice Daily vs Daily): on Day 15

Dose (mg)	n	Cmax[a] (ng/mL)	Tmax[b] (h)	AUC24 (ng*h/mL)	C24 (ng/mL)	Time above 20 ng/mL[c] (h)
1.0 mg BD	5	62.8 (43) (30.9-104)	4.0 (1.5-15.0)	871 (37) (360-1194)	24.1 (56) (7.3-36.9)	19.1 (2.4-24)
2.0 mg QD	18	44.7 (64) (6.2-112)	3.0 (1.0-12.0)	507 (55) (222-1194)	8.6 (66) (2.9-20.6)	9.6 (0.0-23.9)
1.5 mg BD	4	65.6 (23) (49.3-84.5)	14.5 (13.0-16.0)	808 (26) (594-1083)	17.6 (22) (12.5-21.0)	19.3 (13.3–23.9)
3.0 mg QD	5	82.8 (41) (41.9–123)	3.0 (1.5-4.0)	813 (34) (428-1196)	12.5[d] (65) (4.4-20.8)	13.9 (3.9-24.0)
2.0 mg BD	3	104 (39) (59.1-139)	2.0 (1.5-2.0)	1287 (38) (746-1677)	39.6 (39) (26.3-56.5)	21.2 (14.8-24.0)
2.5 mg QD (MTD)	18	54.3 (43) (25.9-114)	3.0 (1.0-6.0)	653 (43) (363-1502)	12.6 (3.9-33.6)	12.4 (0.0-24.0)
2.5 mg BD	2	62.1, 118	1.5, 2.0	787, 1662	31.6, 41.6	24.0, 24.0

a. N ≤ 2, displays are individual values, otherwise, values represent mean (%CV) and range;
b.Tmax reported as median and range
c. >20 ng/mL projected therapeutic range
d. n =4

- Similar exposure levels for total daily dose.
- BID dosing = Higher average trough levels and time above nonclinical target concentrations.

Most Common AE's Regardless of Relationship to Study Drug
Across All Doses: QD vs BID (N=170)

Adverse Event *Dose limiting toxicities	QD Dosing n (%) (n=142)	QD Dosing G ≥ 3, n (%)	BID Dosing n (%) (n=28)	BID Dosing G ≥ 3, n (%)
Any Event	**142 (100)**	**64 (45)**	**28 (100)**	**18 (64)**
Fatigue	64 (45)	8 (6)	12 (43)	3 (11)
*Diarrhea	60 (42)	12 (8)	16 (57)	0 (0)
Nausea	59 (55)	2 (1)	12 (43)	1 (4)
Vomiting	40 (28)	1 (<1)	2 (7)	1 (4)
Decreased Appetite	36 (25)	1 (<1)	13 (46)	3 (11)
Dyspnea	26 (18)	6 (4)	1 (4)	1 (4)
Pyrexia	21 (15)	0 (0)	1 (4)	1 (4)
*Hyperglycemia	19 (13)	6 (4)	5 (18)	2 (7)
Abdominal Pain	17 (12)	4 (3)	5 (18)	1 (4)
Back Pain	17 (12)	0 (0)	5 (18)	0 (0)
Constipation	17 (12)	0 (0)	6 (21)	0 (0)
Cough	17 (12)	0 (0)	4 (14)	1 (4)
UTI	17 (12)	4 (3)	4 (14)	0 (0)
Peripheral Edema	16 (11)	0 (0)	3(11)	1 (4)
Anemia	15 (11)	7 (5)	2 (7)	1 (4)
*Rash	15 (11)	1 (<1)	5 (18)	2 (7)
Headache	14 (10)	2 (1)	5 (18)	1 (4)

Most Common AEs Related to Study Drug

Across All Doses: QD vs BID;(N=170)

Adverse Event *Dose limiting toxicities	QD Dosing n (%), (N=142)	QD Dosing G ≥ 3, n (%)	BID Dosing n (%) (n=28)	BID Dosing G ≥ 3, n (%)
Any Event	102 (72)	30 (21)	25 (89)	9 (32)
*Diarrhea	42 (30)	12 (8)	15 (54)	0 (0)
Fatigue	38 (27)	3(2)	6 (21)	1 (4)
Nausea	34 (24)	1 (<1)	6 (21)	0 (0)
Decreased Appetite	22 (15)	1 (<1)	5 (18)	0 (0)
*Hyperglycemia	16 (11)	1 (<1)	5 (18)	2 (7)
Vomiting	11 (8)	0 (0)	1 (4)	0 (0)
Blood Glucose Increased	10 (7)	3 (2)	1 (4)	0 (0)
Dry Skin	8(6)	1 (<1)	1 (4)	0 (0)
*Rash	8 (6)	1 (<1)	4 (14)	0 (0)
Mucosal Inflammation	7 (5)	1 (<1)	5 (18)	0 (0)

PD Markers: Methods and Results

- Methods
  - Immunohistochemistry platform used to assess proteomic changes in subset of patients
  - Pre-treatment biopsies compared to post-treatment (14-28 days after first dose)
    - Key phosphorylated proteins of PI3K/AKT signaling assessed (e.g. pAKT/AKT)
    - Cell Cycle markers also analyzed (e.g. Ki-67)
    - Biopsies: 13 pairs collected from 9 different tumor types
      - 2 Breast / 2 Colorectal / 2 Endometrial / 2 Pancreatic / 1 Renal Cell / 1 Gastric / 1 Thymus / 1 Oropharyngeal / 1 Urethral
- Results
  - IHC analysis of pre and post dose biopsies as well as FDG-PET analysis of pre and post dose scans show variable/inconsistent results which make it difficult to show a dose/response relationship

Tumor Genetics Summary

- **Breast (N=22)**
  - 14 at doses ≥ 1.5mg QD; 2 at doses ≥ 1.5mg BID
  - 8 subjects with PIK3CA mutation
  - 1 subject with wild type PIK3CA but HER2 positive
  - 1 Partial Response seen in 8 subjects with PIK3CA mutant breast cancer

- **Endometrial (N=15)**
  - 10 enrolled at doses ≥ 2mg QD; 4 enrolled at doses ≥ 1.0mg BID
  - 7 with KRAS WT disease
  - 1 Partial Response

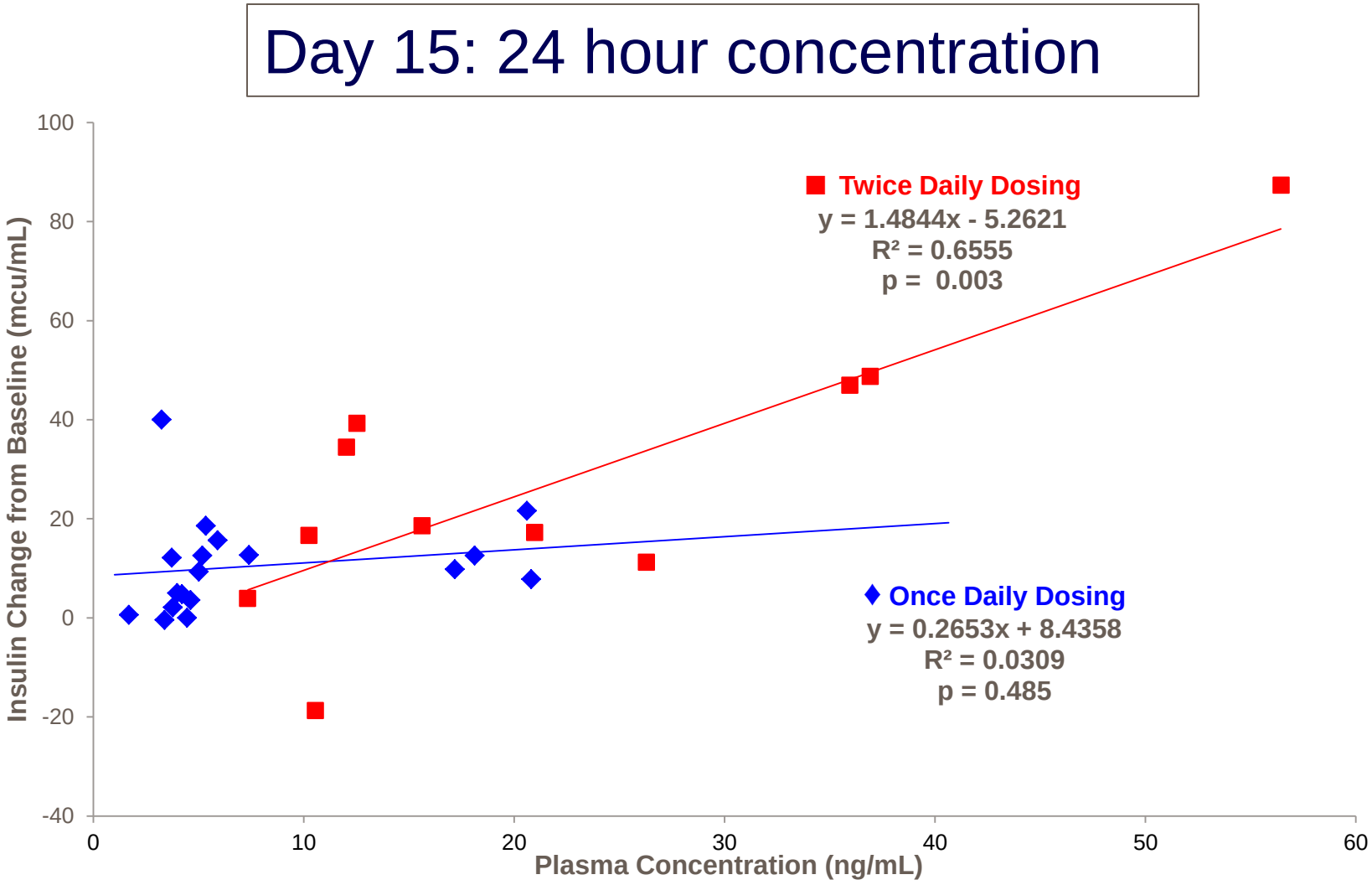
Tumor Genetics Summary

- **Bladder (N=17)**
  - All enrolled at doses ≥ 1.5mg QD; none at BID
  - 10 Tumors tested for PTEN protein levels scored by Immunohistochemistry.
  - All 10 tumors stained positive for the PTEN protein
  - 2 unconfirmed Partial responses were seen

Number of subjects (n=17)	PIK3CA Status	PR
17		2/17 (11%)
9	WT	0
8	unknown	2/8 (25%)

- **Renal Cell (N=24)**
  - Enrolled at QD doses of 0.4 mg to 3.0mg (12 subjects at 2 mg QD)
  - 23 tumors were WT for the common activating mutation to KRAS and PIK3CA by circulating DNA.
  - 2 confirmed responses were WT as assessed in circulating DNA.
  - 1 non-responder had PIK3CA mutation by circulating DNA

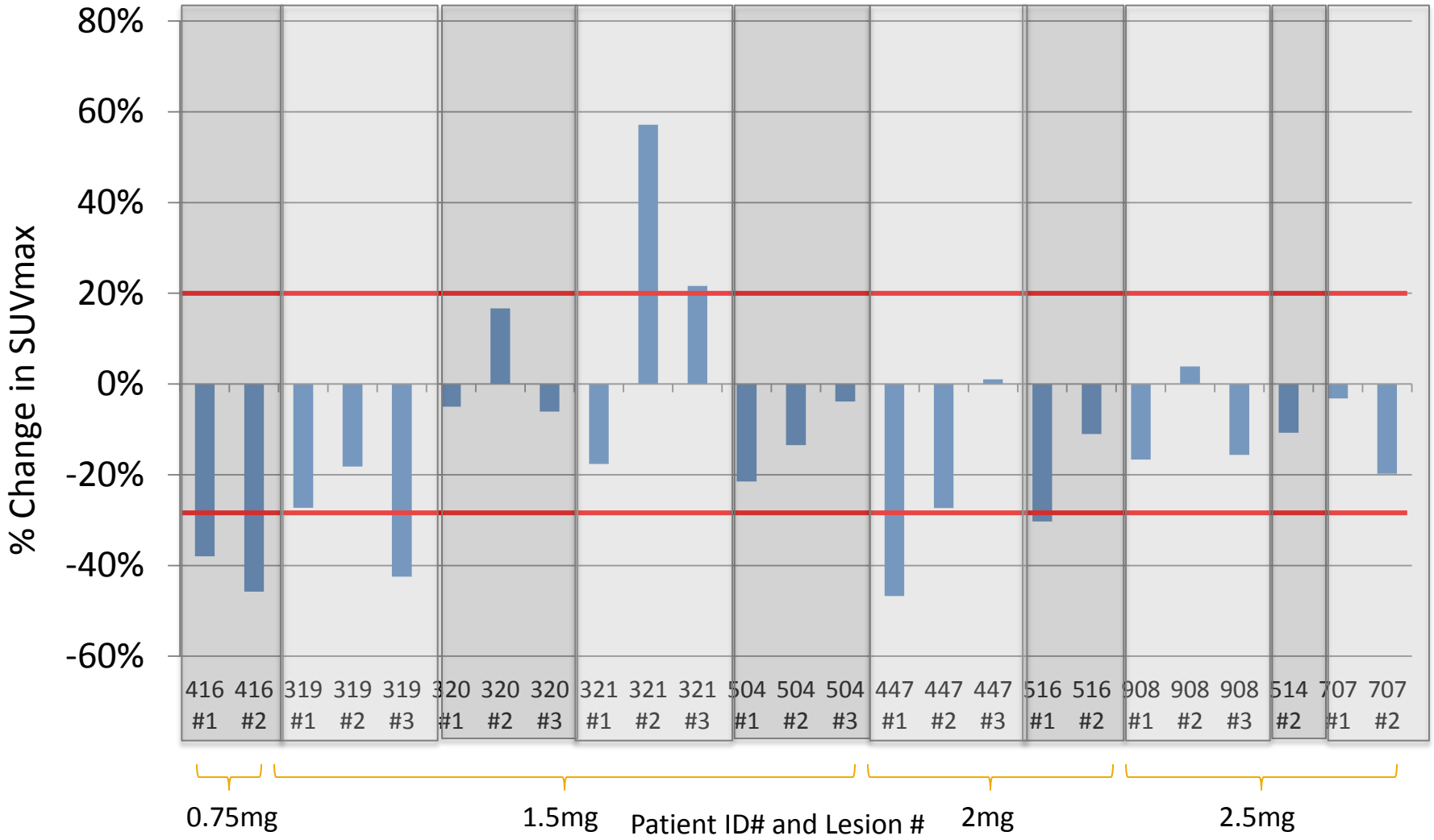
Preliminary Data: Insulin Change from Baseline versus GSK2126458 Blood Concentration



FDG-PET: % Change in SUV_{max} by Tumor Lesions

Intra-patient tumor variability was high.

Few tumors met the -30% PERCIST cut-off.



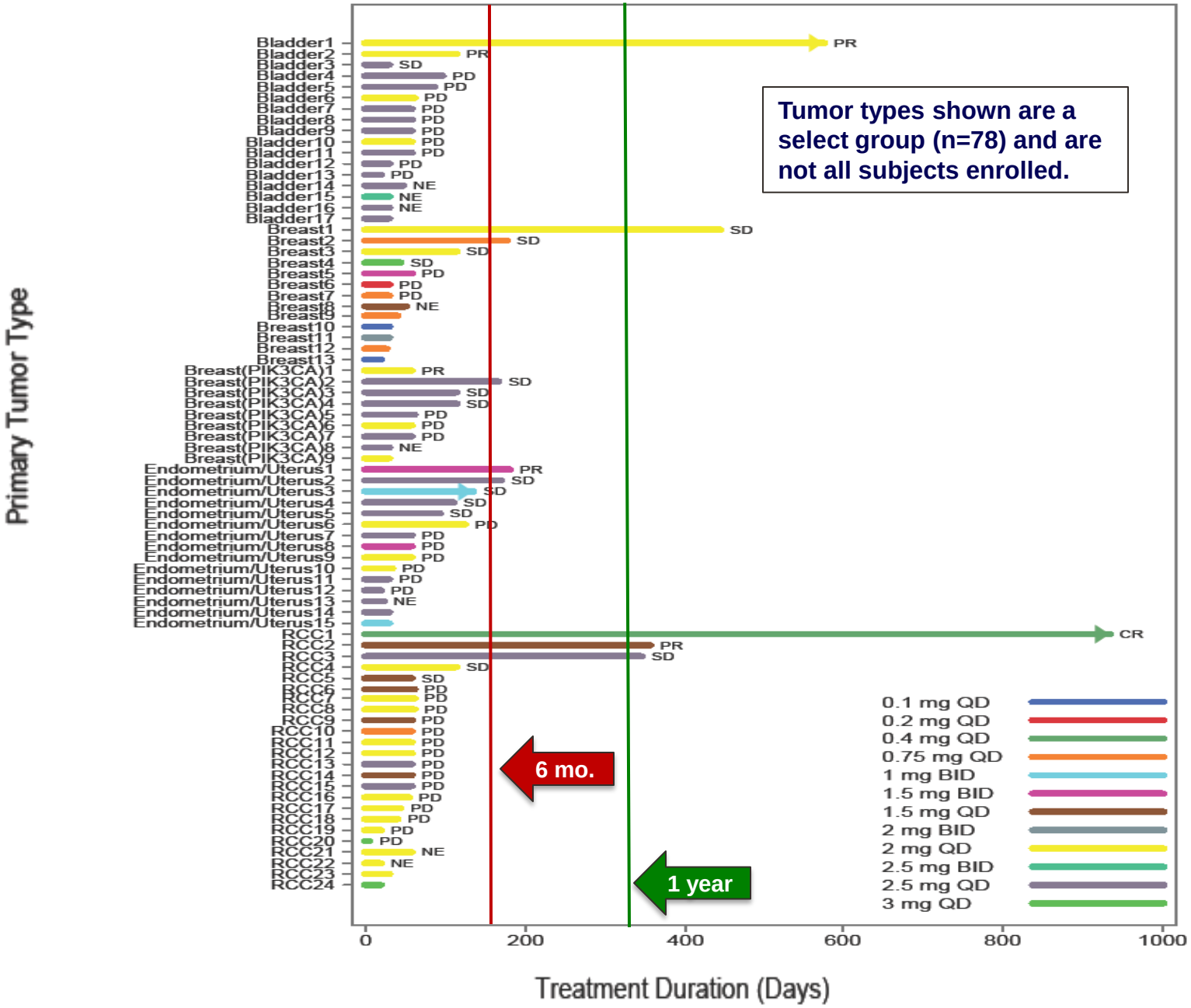
Clinical Benefit in Targeted Patient Populations

Investigator-Assessed Best Unconfirmed Response Rate

Tumor Type	CR	PR	SD	CR+PR+SD/N (%)*
Bladder cancer (regardless of mutational status) (N=17)	0	2	1	3/17 (18%)
PIK3CA mutant Bladder cancer (N=0)	0	0	0	0 (0%)
Breast cancer (regardless of mutational status) (N=22)	0	1	7	8/22 (36%)
PIK3CA mutant Breast cancer (N=8)	0	1	2	3/8 (38%)
Endometrial cancer (regardless of mutational status) (N=15)	0	1	4	4/15 (27%)
KRAS wild type endometrial cancer(N=7)	0	1	3	4/7 (57%)
Renal cell cancer (regardless of mutational status) (N=24)	1	1	3	5/24 (21%)
All Patients	**1**	**8**	**37**	**46/170 (27%)**

*Frequencies displayed are only relative to subject counts in the rows in which they appear.

Duration of Treatment: Best Unconfirmed Response



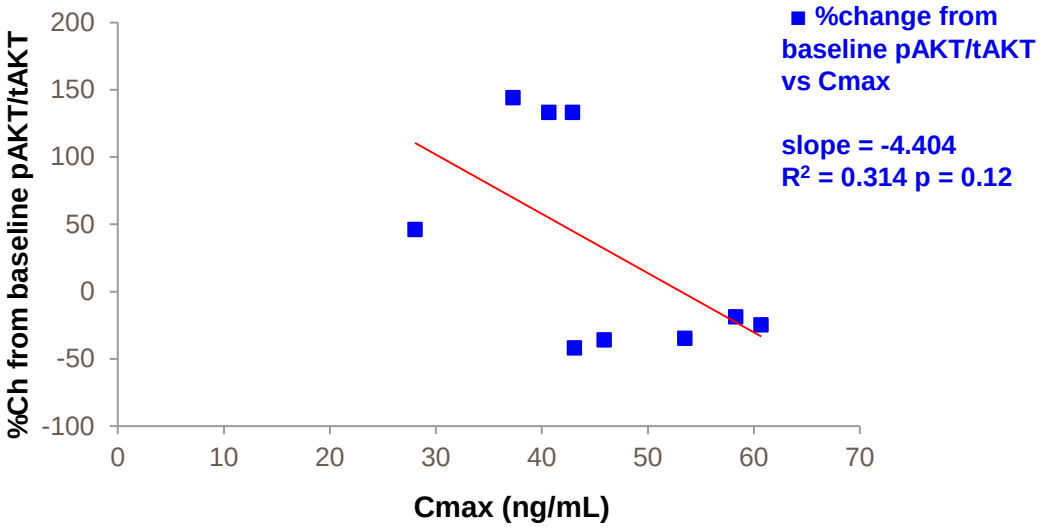
CONCLUSIONS

- BID is Recommended over QD dosing
  - Improved PK profile manifested as higher trough concentrations and time above target concentrations.
  - Improved PK profile does not occur at the expense of tolerability, i.e. adverse event profile similar between the two schedules with the caveat that the N was small for BID dosing and no formal statistical comparison was made.
- GSK2126458 is well tolerated with toxicities comparable to other agents in its class.
- IHC analysis of pre and post dose biopsies as well as FDG-PET analysis of pre and post dose scans show variable/inconsistent results which make it difficult to show a dose/response relationship
- MTD was found to be 2.5mg BID
- DLT: diarrhea, fatigue, and rash (all G3).
- Concentration response relationship between GSK2126458 blood concentrations and increases in serum insulin change from baseline values which suggest insulin is a surrogate marker for target modulation.
- GSK2126458 showed limited activity in KRAS WT endometrial cancer and PIK3CA mutant breast cancer and promising activity in bladder cancer and RCC (activity in a particular tumor/mutation combinations was seen in a small numbers of patients)
- Response Rate (N=170): 1 subject with a CR (> 32mo +), 8 subjects with PR (5%), 37 subjects with Stable disease (22%), 80 subjects with PD (47%), 46 subjects Not evaluated or unknown (26%).

BACK UP

PD Markers: PI3K Signaling

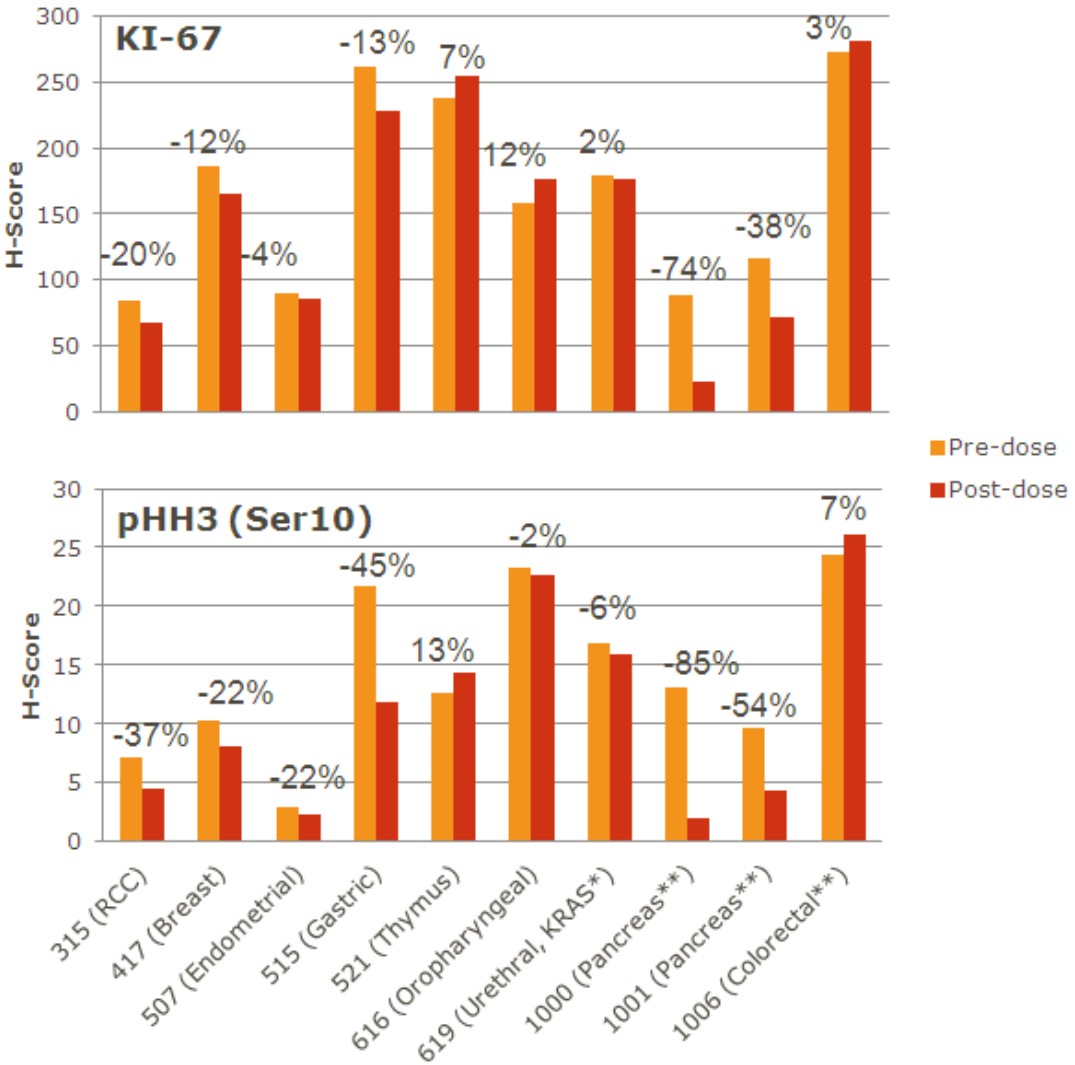
- Variable changes to pAKT/AKT ratio after dosing
  - 8/13 had some decrease in pAKT
  - 1/13 (7%) with decrease in pAKT/AKT ratio
- Inconsistent changes seen in other proteins measured- including pPRAS40/PRAS40 & pp70S6K/p70S6K
- Changes in pAKT shows inverse trend with Cmax in these patients



PD Markers: Cell Cycle Markers

- The **Ki-67** protein, a cellular marker for proliferation, showed inconsistent changes.
  - 8/13 (62%) had some decrease in Ki-67
  - 1/13 (7%) had decrease > 40%

Example:



- Phospho Histone H3 is a core histone protein forming a major constituent of chromatin: *Only phosphorylated during mitosis.*
  - Low staining in most patients
  - 10/13 (77%) pts had decreases in pHH3 in tumors after dosing
  - 3/13 with decrease showed > 40% reduction

Ongoing Subjects

Subject	Age	Sex	Cancer Type	First Dose	Exposure	Status	Response Assessment *19July2012*
309	48	M	Renal Cell PIK3CA WT	29Dec2009	29Dec09 to 04Oct10 @ **0.4mgQD** ---------- 08Sep10 to present @ **1.5mg QD**	Cycle 32	Complete Response
432	75	M	Bladder PIK3CA WT	05 Oct 2010	05Oct10 to 01June11 @ 2mg QD ---------- 15Jun11 present @ **1mg BID**	Cycle 23	Partial Response
619	52	F	Urethral Adenocarcinoma KRAS Positive PIK3CA WT	03 March 2011	03 Mar 11 to present @ **2.5mg QD**	Cycle 17	Partial Response
987	52	F	Soft tissue Sarcoma Spindle Cell KRAS WT PIK3CA WT	07 Sep 2011	07Sep11 to present @ **2.0mg BID**	Cycle 11	Partial Response