Phase I Dose Escalation Study of Taselisib (GDC-0032), an Oral PI3K Inhibitor, in Patients with Advanced Solid Tumors

Dejan Juric,[1] Ian Krop,[2] Ramesh K. Ramanathan,[3] Timothy R. Wilson,[4] Joseph A. Ware,[4] Sandra M. Sanabria Bohorquez,[4] Heidi M. Savage,[4] Deepak Sampath,[4] Laurent Salphati,[4] Ray S. Lin,[4] Huan Jin,[4] Hema Parmar,[4] Jerry Y. Hsu,[4] Daniel D. Von Hoff,[5] Jose Baselga[6]

[1]Massachusetts General Hospital Cancer Center, Boston, MA;
[2]Dana-Farber Cancer Institute, Boston, MA;
[3]Mayo Clinic, Scottsdale, AZ;
[4]Genentech, Inc., South San Francisco, CA, USA;
[5]Virginia G. Piper Cancer Center Honor Health, Scottsdale, AZ;
[6]Memorial Sloan Kettering Cancer Center, New York, NY.

SUPPLEMENTARY DATA

Supplementary Table S1. Patient Demographics and Disease Characteristics

	All patients (%)
Age	
Mean	57.7
Median	55.5
Min-Max	34-82
Sex, n (%)	
Male	11 (32.4)
Female	23 (67.6)
ECOG Status, n (%)	
0	20 (58.8)
1	14 (41.2)
Time from primary diagnosis (months)	
Mean	61.1
Median	37.6
Min-Max	2.1-363.0
Prior systemic therapies	
Mean	4.9
Median	4.0
Min-Max	2.0-13.0

Supplementary Table S2. Treatment-Related Adverse Events of Grade 3 or Higher Observed in either Cycle 1 or Cycle ≥2

	3 mg (n=6)	5 mg (n=3)	8 mg (n=4)	12 mg (n=10)	16 mg (n=11)	All (N=34)
Adverse events of ≥ grade 3 in cycle 1						
Total no. patients with ≥1 AE	0	0	0	2 (20.0%)	4 (36.4%)	6 (17.6%)
Total no. AE	0	0	0	4	8	12
Hyperglycemia	0	0	0	2 (20.0%)	3 (27.3%)	5 (14.7%)
Renal Failure Acute	0	0	0	1 (10.0%)	0	1 (2.9%)
Diarrhea	0	0	0	0	1 (9.1%)	1 (2.9%)
Fatigue	0	0	0	0	1 (9.1%)	1 (2.9%)
Adverse events of ≥ grade 3 in cycle ≥ 2						
Total no. patients with ≥1 AE	0	0	0	4 (40.0%)	5 (45.5%)	9 (26.5%)
Total no. AE	0	0	0	9	8	7
Rash[a]	0	0	0	3 (30.0%)	2 (18.2%)	4 (11.8%)
Diarrhea	0	0	0	0	2 (18.2%)	2 (5.9%)
Pruritus	0	0	0	2 (20.0%)	0	2 (5.9%)
Colitis	0	0	0	1 (10.0%)	0	1 (2.9%)
Fatigue	0	0	0	0	1 (9.1%)	1 (2.9%)
Lung infection	0	0	0	0	1 (9.1%)	1 (2.9%)
Pneumonitis	0	0	0	0	1 (9.1%)	1 (2.9%)
Skin exfoliation	0	0	0	0	1 (9.1%)	1 (2.9%)
Stomatitis	0	0	0	1 (10.0%)	0	1 (2.9%)

[a]Rash includes the following terms: rash, rash erythematous, rash maculopapular, exfoliative rash.

For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Cycle 1 is defined as AE Start Day ≤ Study Day 35. Cycle ≥2 is defined as AE Start Day > Study Day 35.

Supplementary Table S3. Adverse Events in ≥ 10% of Patients Regardless of Attribution

	3 mg (n=6)	5 mg (n=3)	8 mg (n=4)	12 mg (n=10)	16 mg (n=11)	All (N=34)
Total no. patients with ≥1 AE	6 (100%)	3 (100%)	4 (100%)	10 (100%)	11 (100%)	34 (100%)
Total no. AEs	54	30	37	191	184	496
Nausea	3 (50.0%)	2 (66.7%)	1 (25.0%)	8 (80.0%)	7 (63.6%)	21 (61.8%)
Diarrhea	1 (16.7%)	2 (66.7%)	1 (25.0%)	7 (70.0%)	9 (81.8%)	20 (58.8%)
Fatigue	2 (33.3%)	1 (33.3%)	2 (50.0%)	6 (60.0%)	8 (72.7%)	19 (55.9%)
Decreased appetite	1 (16.7%)	2 (66.7%)	2 (50.0%)	6 (60.0%)	7 (63.6%)	18 (52.9%)
Vomiting	1 (16.7%)	2 (66.7%)	0	4 (40.0%)	7 (63.6%)	14 (41.2%)
Hyperglycemia	0	0	2 (50.0%)	3 (30.0%)	8 (72.7%)	13 (38.2%)
Pyrexia	1 (16.7%)	1 (33.3%)	1 (25.0%)	5 (50.0%)	3 (27.3%)	11 (32.4%)
Rash[a]	0	1 (33.3%)	1 (25.0%)	4 (40.0%)	4 (36.4%)	10 (29.4%)
Stomatitis[b]	0	0	0	6 (60.0%)	4 (36.4%)	10 (29.4%)
Dizziness	0	2 (66.7%)	1 (25.0%)	2 (20.0%)	3 (27.3%)	8 (23.5%)
Dehydration	0	0	1 (25.0%)	2 (20.0%)	4 (36.4%)	7 (20.6%)
Hypokalemia	1 (16.7%)	1 (33.3%)	0	2 (20.0%)	3 (27.3%)	7 (20.6%)
Cough	2 (33.3%)	0	1 (25.0%)	3 (30.0%)	0	6 (17.6%)
Dyspnea	1 (16.7%)	0	1 (25.0%)	3 (30.0%)	1 (9.1%)	6 (17.6%)
Headache	1 (16.7%)	0	0	3 (30.0%)	2 (18.2%)	6 (17.6%)
Anemia	1 (16.7%)	0	0	3 (30.0%)	1 (9.1%)	5 (14.7%)
Pruritus	0	0	1 (25.0%)	4 (40.0%)	0	5 (14.7%)
ALT increased[c]	0	1 (33.3%)	0	1 (10.0%)	2 (18.2%)	4 (11.8%)
Chills	0	2 (66.7%)	1 (25.0%)	1 (10.0%)	0	4 (11.8%)
Hyponatremia	0	0	0	1 (10.0%)	3 (27.3%)	4 (11.8%)

[a]Rash includes the following terms: rash, rash erythematous, rash maculopapular

[b]Stomatitis includes the following terms: stomatitis, mucosal inflammation, lip ulceration

[c]ALT: alanine aminotransferase

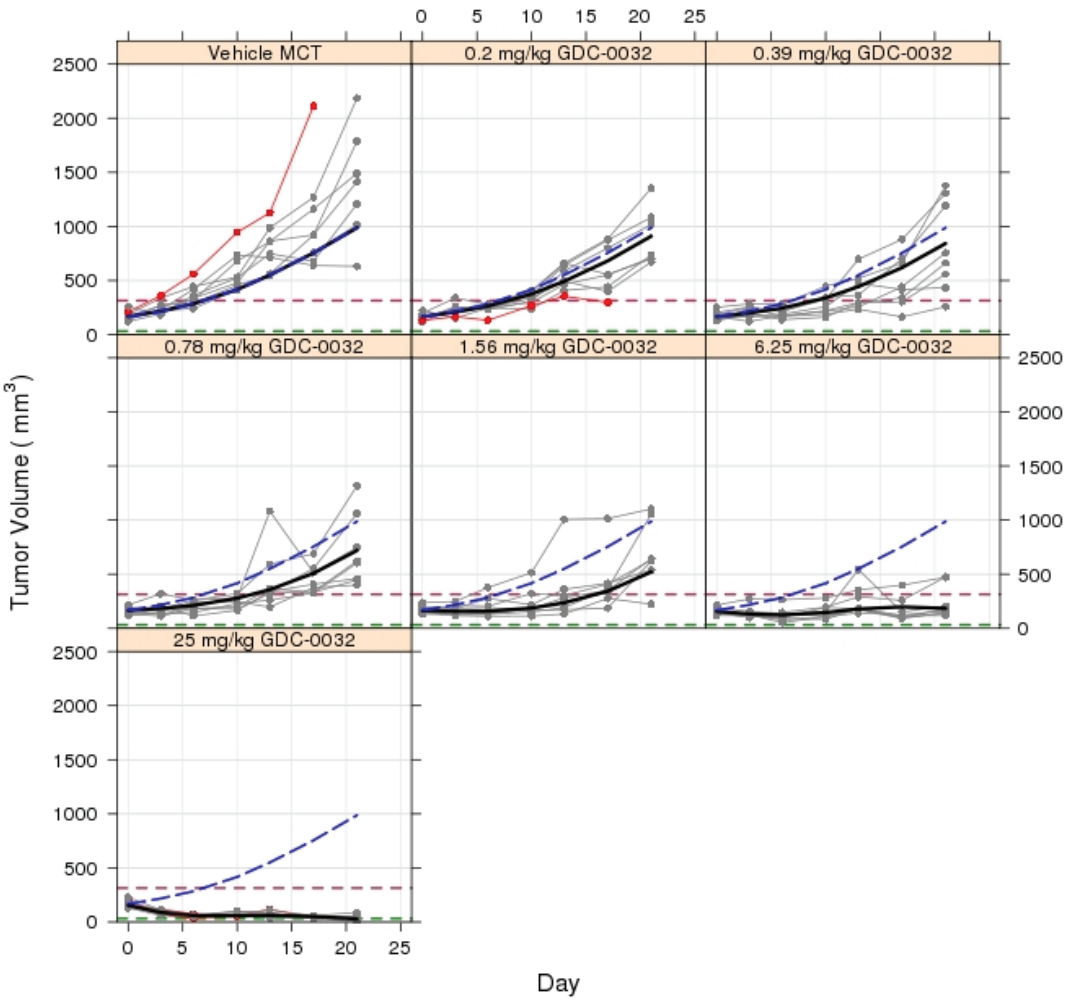
Supplementary Table S4. Adverse Events of Grade 3 or Higher Regardless of Attribution

	3 mg (n=6)	5 mg (n=3)	8 mg (n=4)	12 mg (n=10)	16 mg (n=11)	All (N=34)
Total no. patients with ≥1 AE	1 (16.7%)	0	2 (50%)	9 (90.0%)	10 (90.9%)	22 (64.7%)
Total no. AE	1	0	2	26	20	49
Hyperglycemia	0	0	0	2 (20.0%)	3 (27.3%)	5 (14.7%)
Rash[a]	0	0	0	3 (30.0%)	1 (9.1%)	4 (11.8%)
Hypokalemia	0	0	0	2 (20.0%)	1 (9.1%)	3 (8.8%)
Diarrhea	0	0	0	0	2 (18.2%)	2 (5.9%)
Fatigue	0	0	0	0	2 (18.2%)	2 (5.9%)
Pneumonitis	0	0	0	1 (10.0%)	1 (9.1%)	2 (5.9%)
Pruritus	0	0	0	2 (20.0%)	0	2 (5.9%)
ALT increased[b]	0	0	0	0	1 (9.1%)	1 (2.9%)
Anemia	0	0	0	1 (10.0%)	0	1 (2.9%)
Ascites	0	0	0	1 (10.0%)	0	1 (2.9%)
Ataxia	0	0	0	1 (10.0%)	0	1 (2.9%)
Cardiac failure congestive	0	0	0	1 (10.0%)	0	1 (2.9%)
Colitis	0	0	0	1 (10.0%)	0	1 (2.9%)
Dyspnea	0	0	0	1 (10.0%)	0	1 (2.9%)
Exfoliative rash	0	0	0	0	1 (9.1%)	1 (2.9%)
Facial nerve disorder	0	0	0	0	1 (9.1%)	1 (2.9%)
Flank pain	1 (16.7%)	0	0	0	0	1 (2.9%)
Headache	0	0	0	1 (10.0%)	0	1 (2.9%)
Hepatic failure	0	0	0	1 (10.0%)	0	1 (2.9%)
Hyponatremia	0	0	0	1 (10.0%)	0	1 (2.9%)
Jaundice cholestatic	0	0	1 (25.0%)	0	0	1 (2.9%)
Lung infection	0	0	0	0	1 (9.1%0	1 (2.9%)
Pneumonia	0	0	1 (25.0%)	0	0	1 (2.9%)
Renal failure acute	0	0	0	1 (10.0%)	0	1 (2.9%)
Respiratory syncytial virus infection	0	0	0	0	1 (9.1%)	1 (2.9%)
Skin exfoliation	0	0	0	0	1 (9.1%)	1 (2.9%)
Stomatitis	0	0	0	1 (10.0%)	0	1 (2.9%)
Urinary tract infection	0	0	0	1 (10.0%)	0	1 (2.9%)

[a]Rash includes the following terms: rash, rash erythematous, rash maculopapular

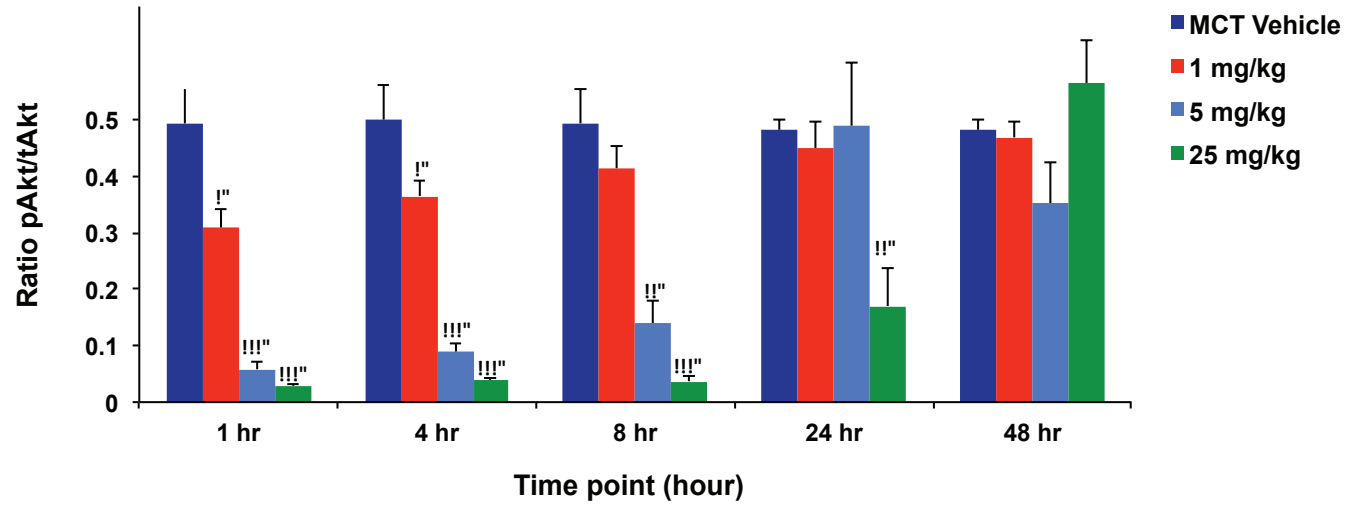
[b]ALT: alanine aminotransferas

Supplementary Figure S1. Trellis plot of individual and fitted tumor volumes to day 21 following treatment with taselisib (GDC-0032). Bold, solid black lines indicate the fitted tumor volume for each treatment group. Grey lines indicate individual animals present in the study until the last day of data collection (day 21). Red lines indicate individual animals for which there were no data at the last day of data collection due to tumor volumes reaching endpoint or not completing the course of treatment. Bold dotted blue lines indicate the fitted tumor volume for the vehicle control group to order to compare anti-tumor responses in the treated group.



Supplementary Figure S2. PI3K pathway suppression was evaluated in KPL-4 tumor xenografts following a single oral dose of 1, 5 and 25 mg/kg taselisib or MCT (0.5% methylcellulose/0.2% Tween-80) vehicle at the time points indicated. Levels of (A) phosphorylated Akt (pAkt) to total Akt (tAkt), (B) phosphorylated PRAS40 (pPRAS40) to total PRAS40 (tPRAS40), or (C) phosphorylated S6 ribosomal protein (pS6RP) to total S6RP (tS6RP) in tumor xenografts was measured by electrochemiluminescence using a Mesoscale Discovery or Luminex based assay as described in Methods. Statistical significance in PI3K pathway markers reduction was determined by Student's t -test comparing taselisib treated animals to vehicle control treated mice. *$p < 0.05$; **$p < .001$; ***$p < 0.0001$.

A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0.2
0.3
0.4
0.5
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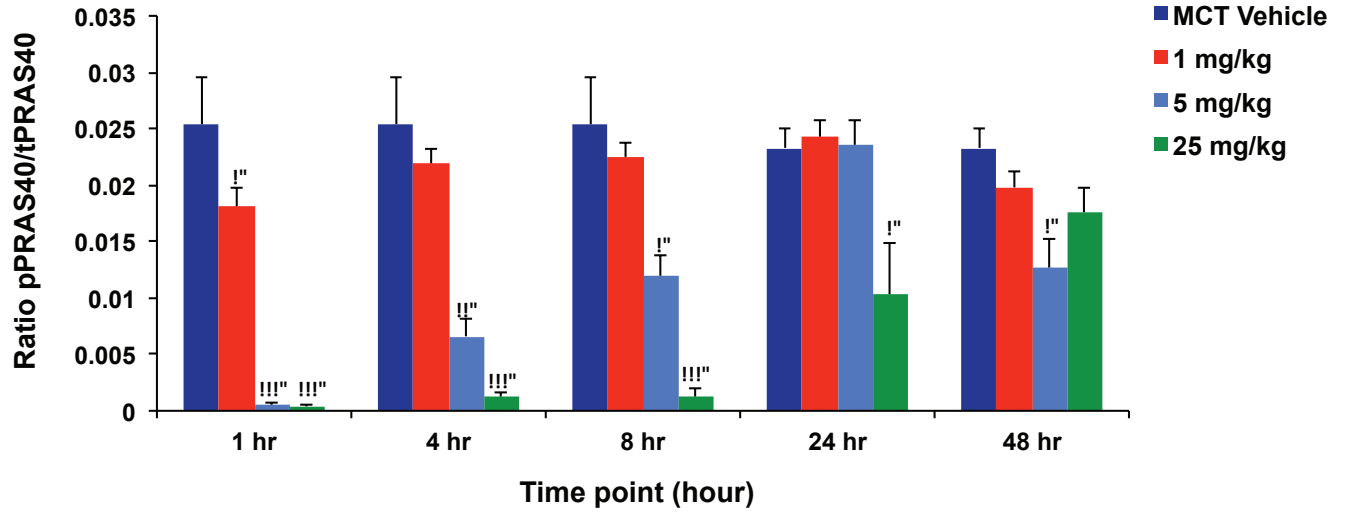
4 hr
8 hr
24 hr
48 hr
Time point (hour)
MCT Vehicle
1 mg/kg
5 mg/kg
25 mg/kg

B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0.025
0.03
0.035
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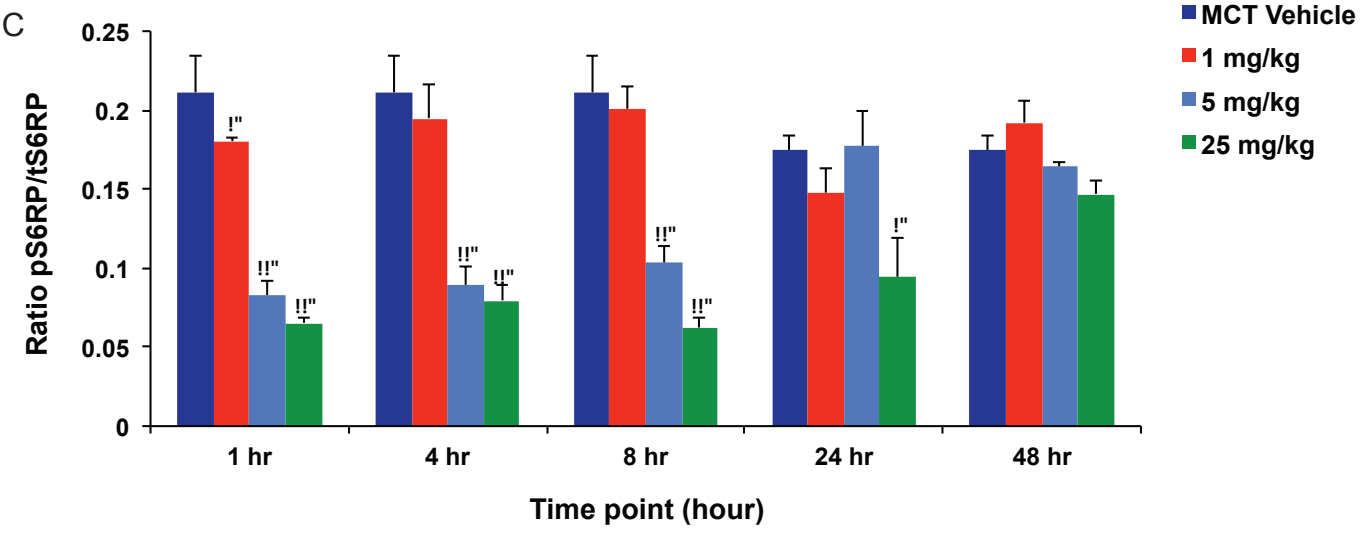
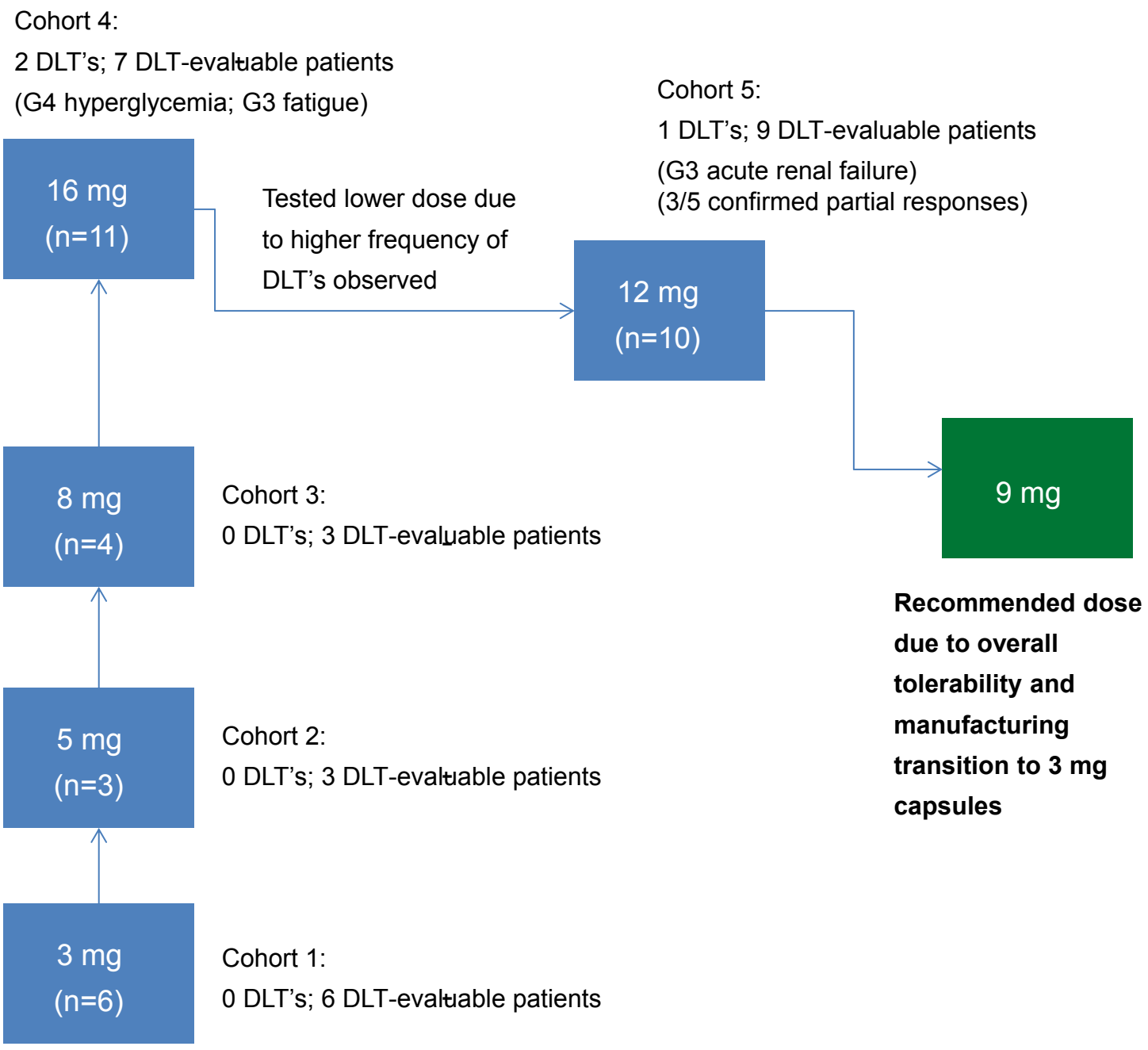
48 hr
Time point (hour)
MCT Vehicle
1 mg/kg
5 mg/kg
25 mg/kg

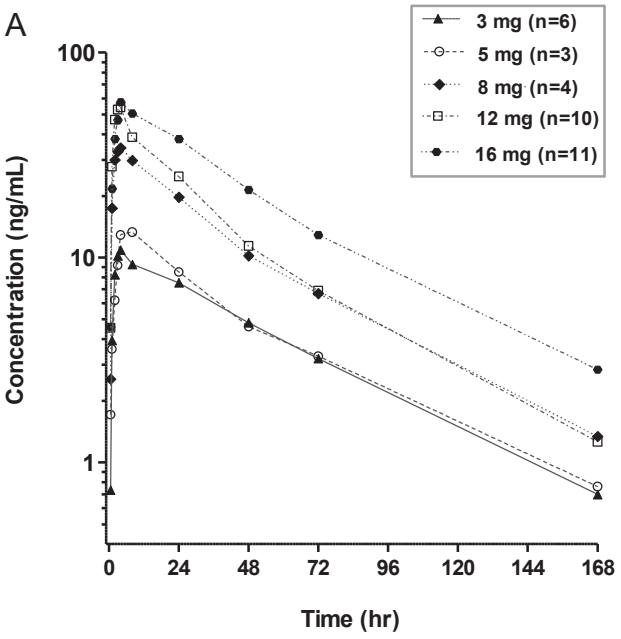
C

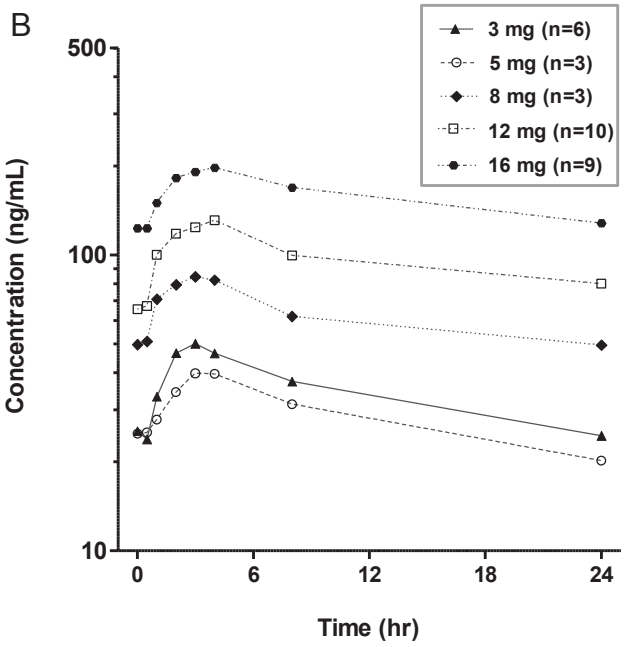

Ratio pS6RP/tS6RP
0
0.05
0.1
0.15
0.2
0.25
1 hr
4 hr
8 hr
24 hr
48 hr
Time point (hour)
MCT Vehicle
1 mg/kg
5 mg/kg
25 mg/kg

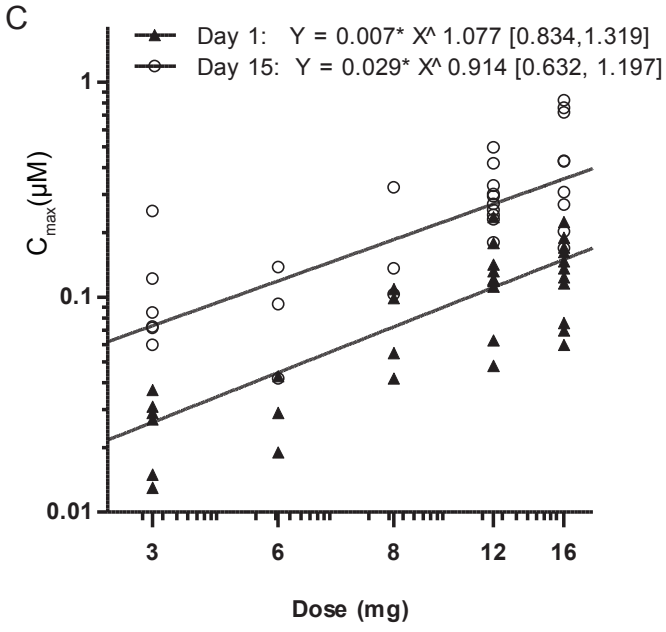
Supplementary Figure S3. Schematic showing the decision-making related to selection of recommended dose for future studies.

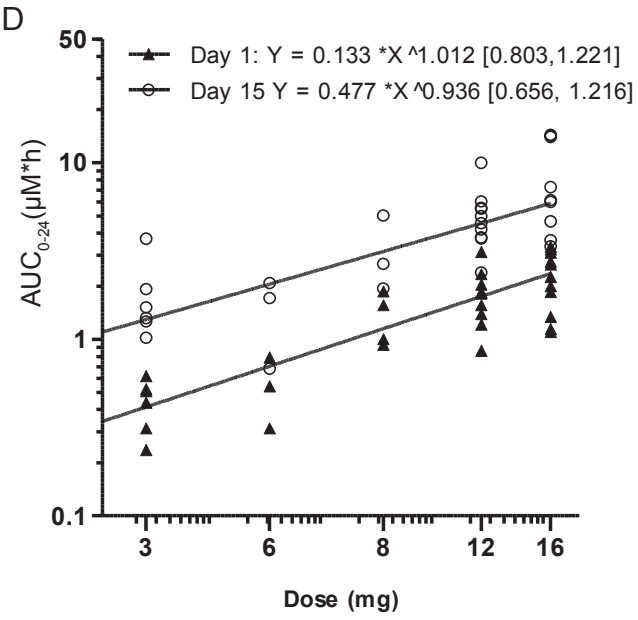


Supplementary Figure S4. Mean plasma concentration vs. time following single dose on day 1 (A) and multiple dose on day 15 (B). Taselisib displayed linear pharmacokinetics.
(C) Cmax vs. dose following single dose (day 1) and multiple dose (day 15).
(D) AUC0-24 vs. dose following single dose (day 1) and multiple dose (day 15).

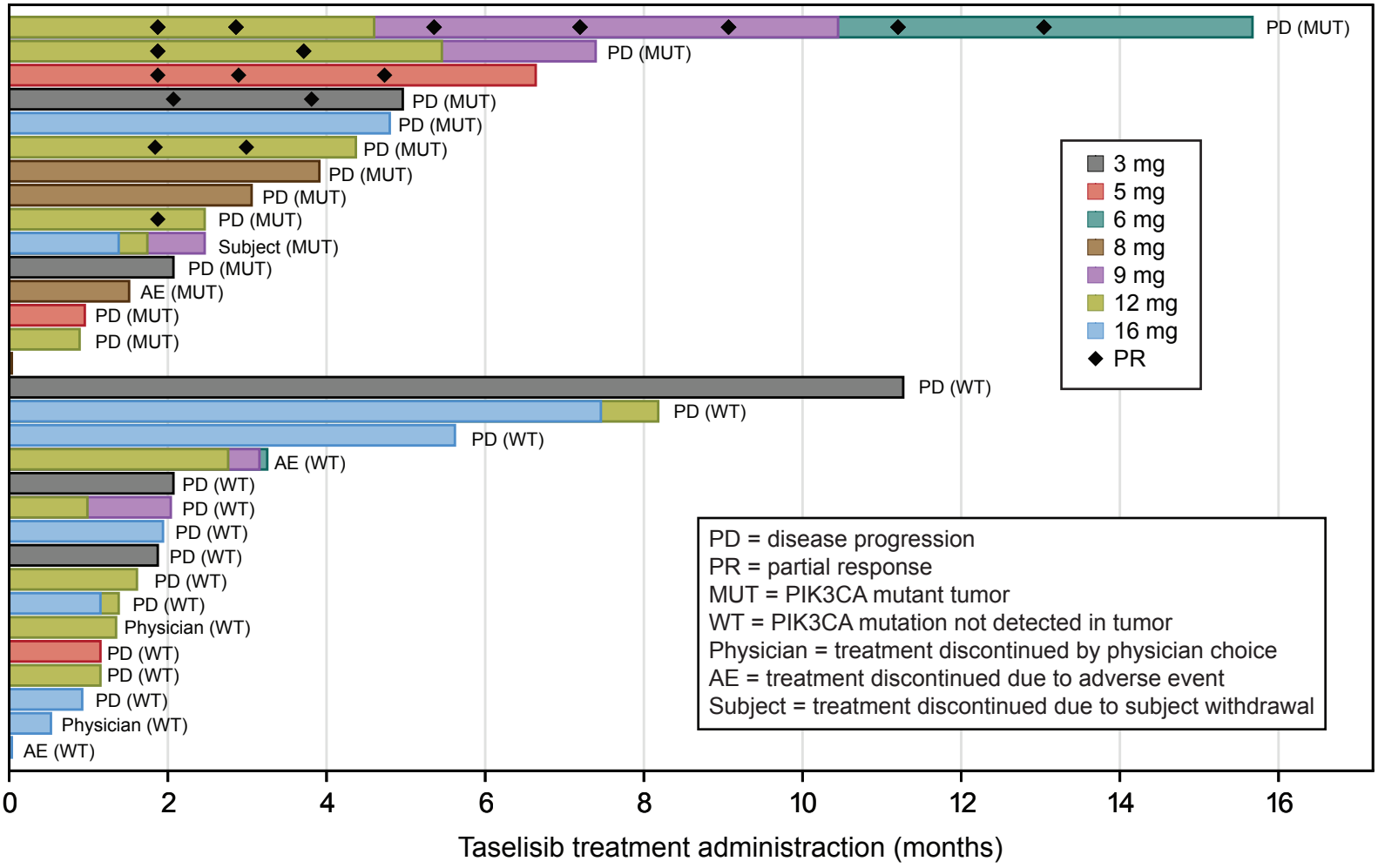




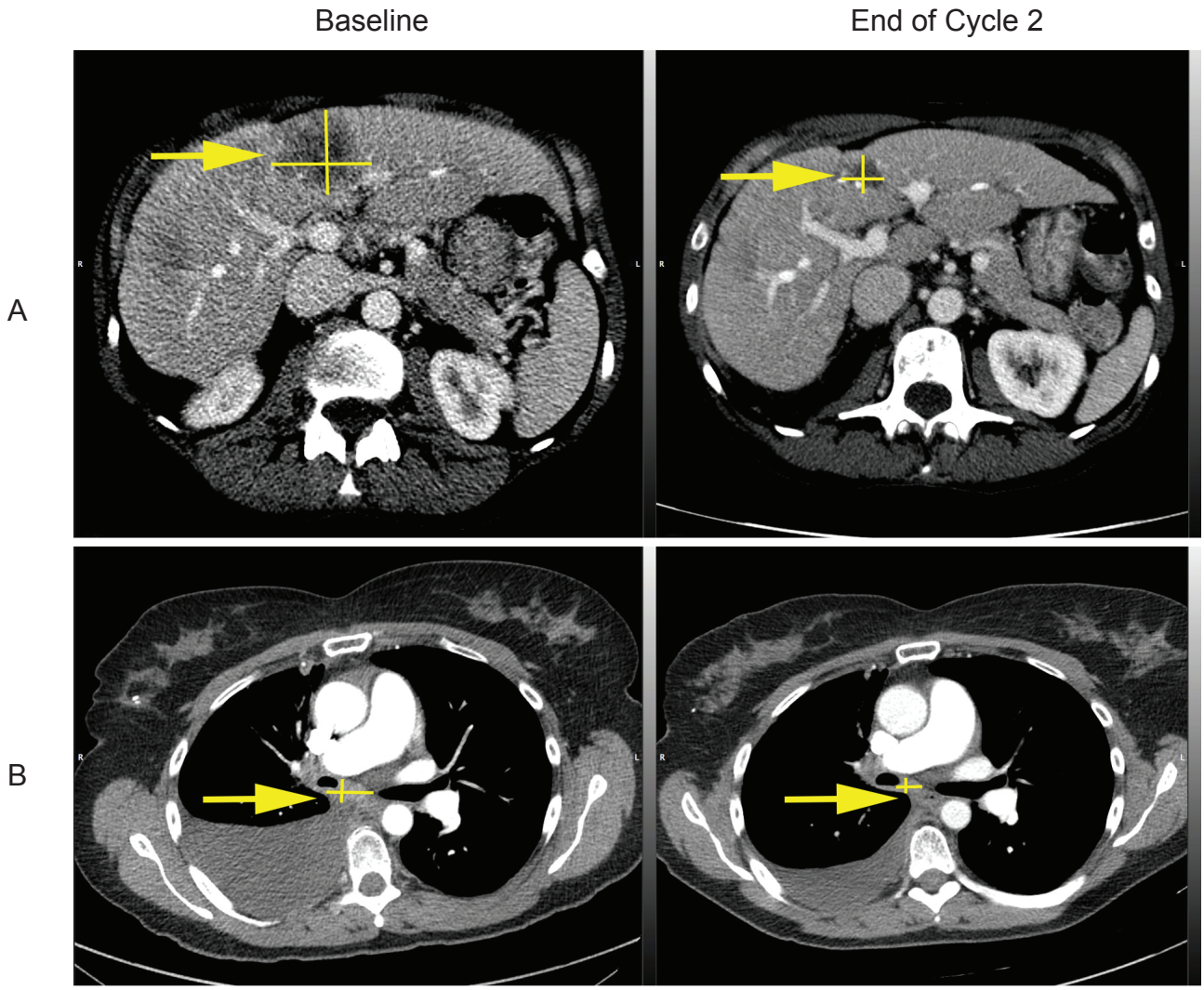




Supplementary Figure S5. Duration of treatment of patients treated via *PIK3CA* mutation status and dose level.



Supplementary Figure S6. Antitumor activity observed with taselisib treatment. (A) Confirmed partial response in patient treated at 12 mg QD. Patient with ER+/ HER2- metastatic breast cancer with PIK3CA mutant tumor (H1047R). Prior therapies of tamoxifen, capecitabine, and anastrozole. cPR (RECIST -32%) after two cycles of treatment with decrease in tumor markers (CA15.3 (434 90), CEA (61 10) and improvement of hypercalcemia. Patient on treatment until disease progression at 5 months. (B) Confirmed partial response in patient at 5 mg QD. Patient with ER+/HER2+ metastatic breast cancer with PIK3CA mutant tumor (H1047R). Prior therapies of paclitaxel/trastuzumab, letrozole/trastuzumab, exemestane/trastuzumab. cPR (RECIST -32%) after two cycles of treatment with decrease in multiple lymph nodes and R pleural effusion. Patient on treatment until disease progression at 7 months.



Supplementary Figure S7. Example of patient with partial response upon taselisib treatment and changes in circulating tumor DNA (ctDNA).