

Supplementary Figure Legends:

Supplemental Figure S1. Pharmacokinetic day profiles of different LY3023414 doses.

LY3023414 concentration versus time for LY3023414 doses of 20-325mg on (a) arithmetic scale (b) logarithmic scale. (c) LY3023414 concentration versus time for 450mg LY3023414. Abbreviations: DBS = Dried Blood Spot

Supplemental Figure S2. (a) Mean percent change from baseline in p4EBP1 concentration versus nominal time by LY3023414 dose levels for cycle 1 day 1. (b) Mean blood glucose percent change from baseline versus nominal time by LY3023414 dose levels for cycle 1 day 1. After the 4-hour time point patients were allowed to eat, and thus increase in the curves past 4-hours reflect the impact of the meal rather than effect of LY3023414 on glucose levels. (c) Mean C-peptide percent change from baseline versus nominal time by LY3023414 dose levels for Cycle 1, Day 1. Abbreviations: Adj = adjusted

Supplemental Figure S3. (a) Simulation of LY3023414 concentration versus time relative to EC50 inhibition of mTOR as measured by decrease in phosphorylation of 4EBP1. (b) PK/Pharmacodynamic relationship of target engagement vs LY3023414 concentration. Abbreviations: Cav = Mean blood concentration, PBMC= peripheral blood mononuclear cells, MEFL= Mean Equivalent Fluorochrome

Supplemental Figure S4. (A) Duration of LY3023414 Treatment. Each bar represents an individual patient. (B) Tumor types in patients with percent change in tumor size administered with different doses of LY3023414.

Supplemental Table T1: Ratio of Midazolam Pharmacokinetic parameters following administration midazolam alone and in combination with LY3023414

| | Midazolam | | Hydroxy-midazolam | |
|---------|--|-------------------------------------|--|-------------------------------------|
| | Ratio of AUC _∞ +LY:alone | Ratio C _{max} +LY:alone | Ratio of AUC _∞ +LY:alone | Ratio C _{max} +LY:alone |
| N | 9 | 9 | 9 | 9 |
| GeoMean | 1.46 | 0.94 | 1.31 | 0.70 |
| CV% | 30.5 | 29.6 | 55.6 | 57.2 |
| 90% CI | (1.21 – 1.76) | (0.78 – 1.12) | (0.95 – 1.81) | (0.50 – 0.97) |

Abbreviations: AUC_∞ = area under the concentration time curve from time zero to infinity post-dose; CI = confidence interval; CV% = coefficient of variation; GeoMean = geometric mean; N = sample size.

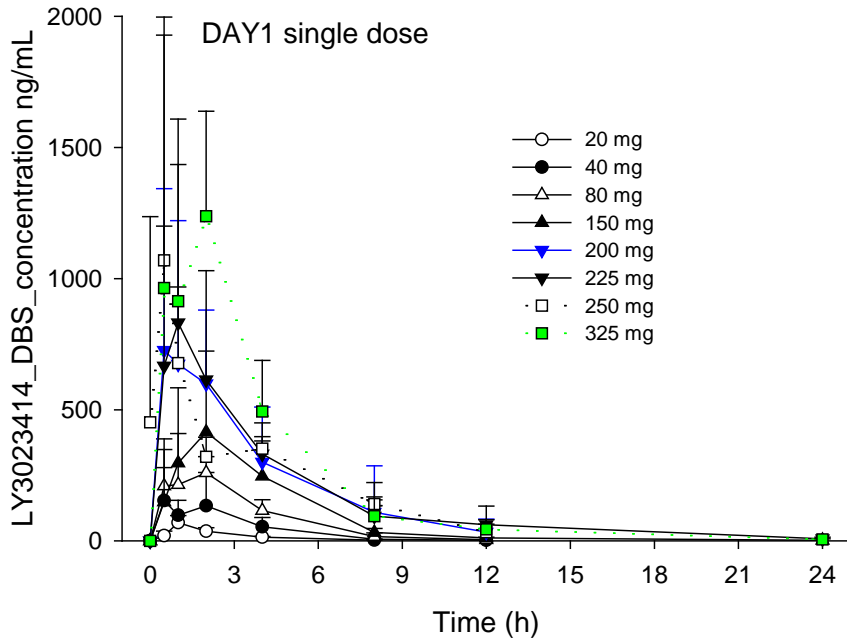
Supplemental Table T2: TEAEs occurring in $\geq 10\%$ patients regardless of causality (N=47)

| CTCAE Term, n (%) | Any Grade | Grade ≥ 3 or higher |
|----------------------------------|------------------|--|
| Patients with any adverse event | 46 (97.9) | 22 (46.8) |
| Vomiting | 25 (53.2) | 1 (2.1) |
| Nausea | 24 (51.1) | 1 (2.1) |
| Fatigue | 20 (42.6) | 2 (4.3) |
| Decreased Appetite | 16 (34.0) | 0 (0) |
| Abdominal Pain | 14 (29.8) | 2 (4.3) |
| Diarrhea | 14 (29.8) | 0 (0) |
| Anemia | 13 (27.7) | 2 (4.3) |
| Constipation | 9 (19.1) | 0 (0) |
| Hypokalaemia | 8 (17.0) | 1 (2.1) |
| Cough | 8 (17.0) | 0 (0) |
| Asthenia | 7 (14.9) | 2 (4.3) |
| Urinary Tract Infection | 7 (14.9) | 1 (2.1) |
| Headache | 7 (14.9) | 0 (0) |
| Stomatitis | 6 (12.8) | 0 (0) |
| Pyrexia | 6 (12.8) | 0 (0) |
| Blood Creatinine Increased | 6 (12.8) | 0 (0) |
| Dizziness | 6 (12.8) | 0 (0) |
| Pruritus | 6 (12.8) | 0 (0) |
| Weight Decreased | 5 (10.6) | 1 (2.1) |
| Abdominal Distension | 5 (10.6) | 0 (0) |
| Paraesthesia Oral | 5 (10.6) | 0 (0) |
| Back Pain | 5 (10.6) | 0 (0) |
| Dyspnoea | 5 (10.6) | 0 (0) |
| Gastrooesophageal Reflux Disease | 5 (10.6) | 0 (0) |
| Oedema Peripheral | 5 (10.6) | 0 (0) |

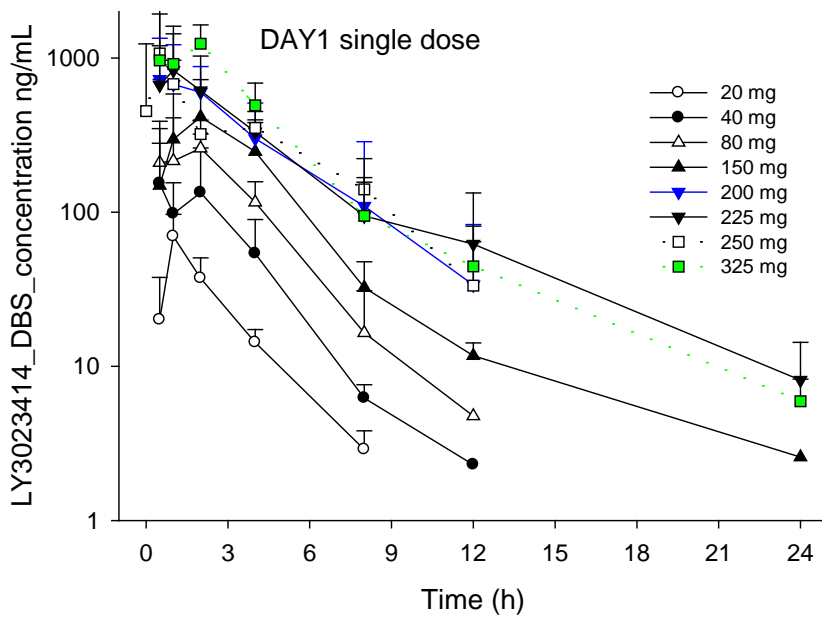
Abbreviations: N = total number of population within each CTCAE grade category; n = number of patients in specified category; TEAE = treatment-emergent adverse events. TEAEs reported by preferred pooled terms. Data reported includes cohorts A, A2 and B1 only.

Supplemental Figure S1: Pharmacokinetic day profiles of different LY3023414

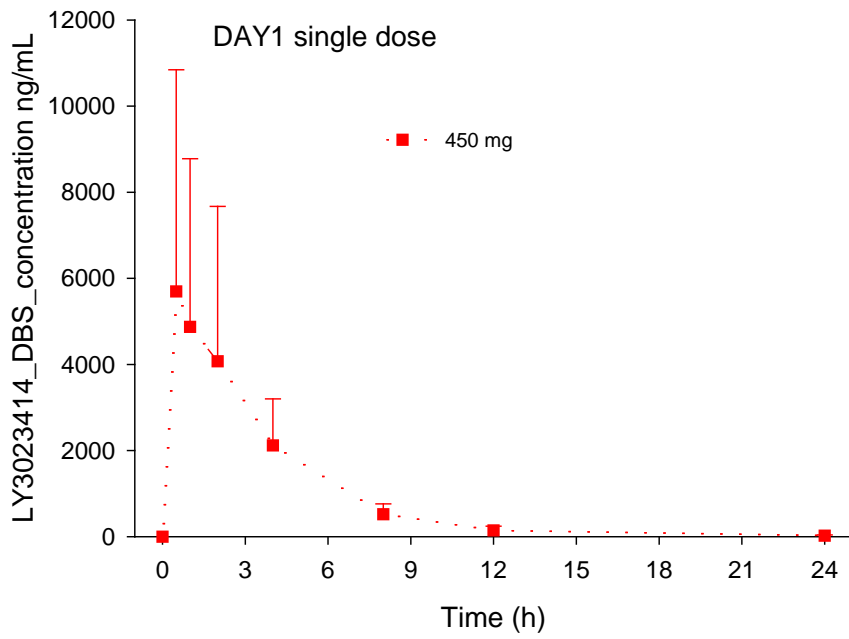
Panel A



Panel B

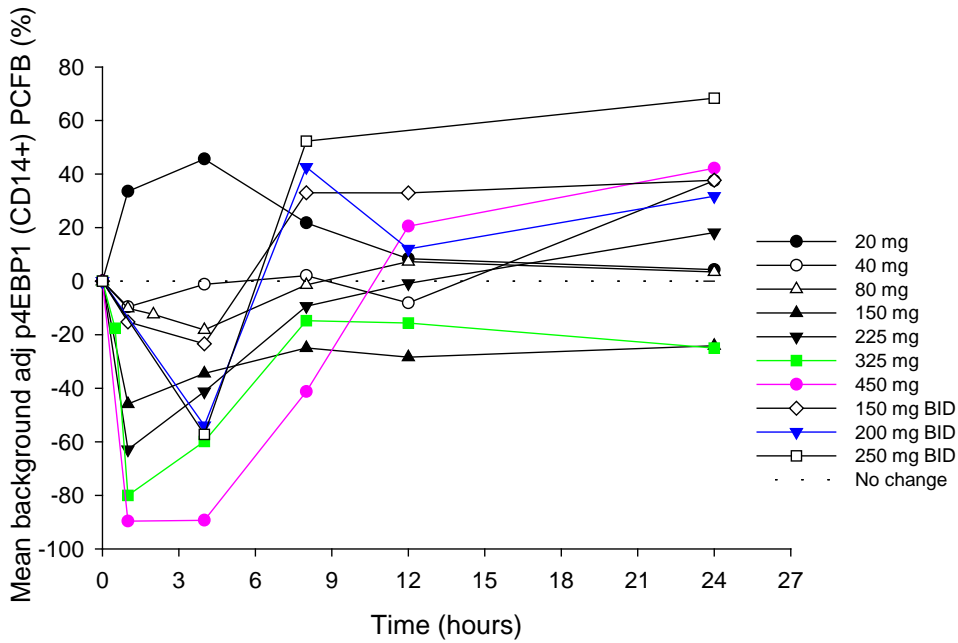


Panel C



Excludes one patient who had a dosing error (received 225 mg BID on Cycle 1, Day 1 rather than 250 mg BID).

Supplemental Figure S2 (a): Time course of mean 4EBP1 phosphorylation following LY3023414 administration



Supplemental Figure S2: (b) Time course of mean blood glucose levels following LY3023414 administration

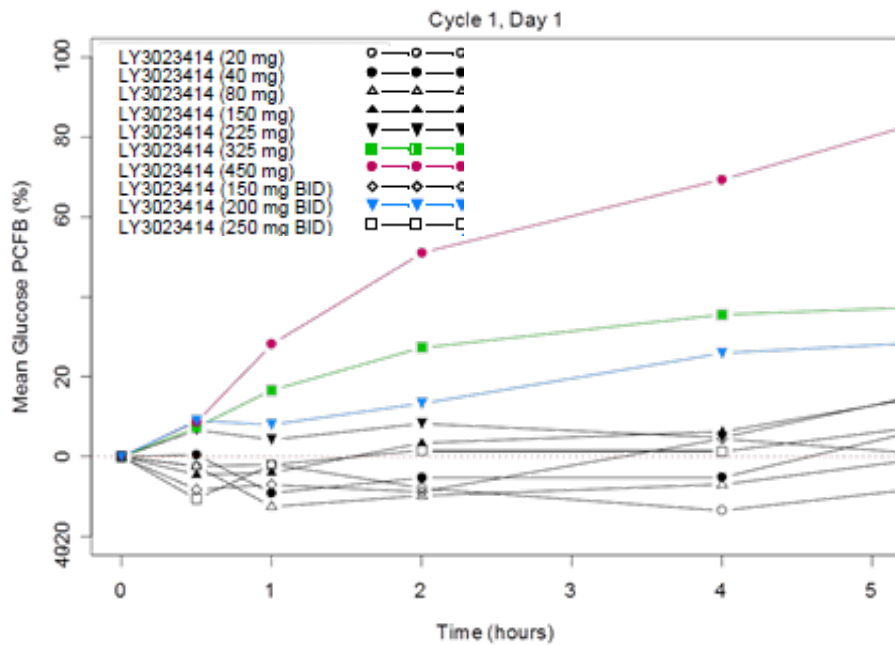
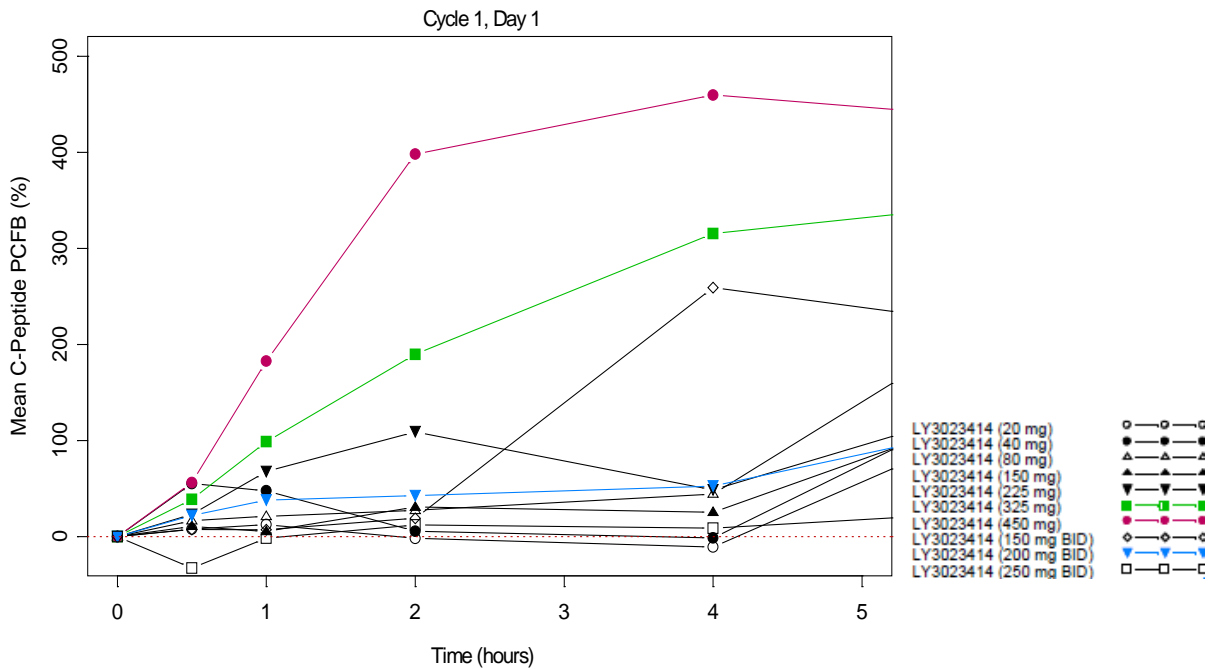


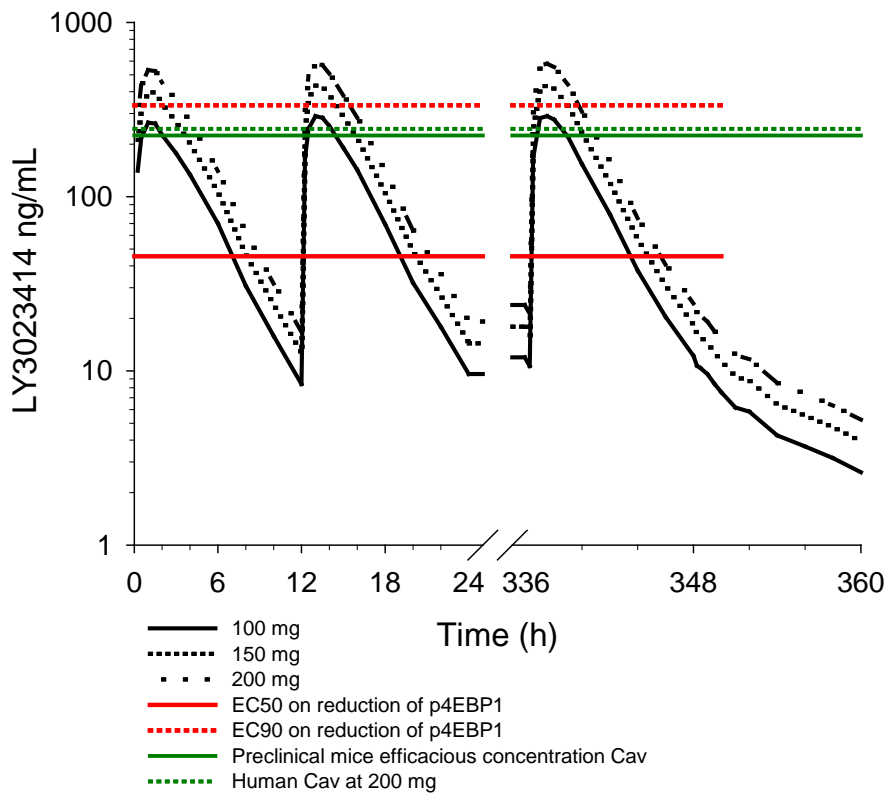
Figure S2: (c) Time course of mean C-peptide levels following LY3023414 administration.



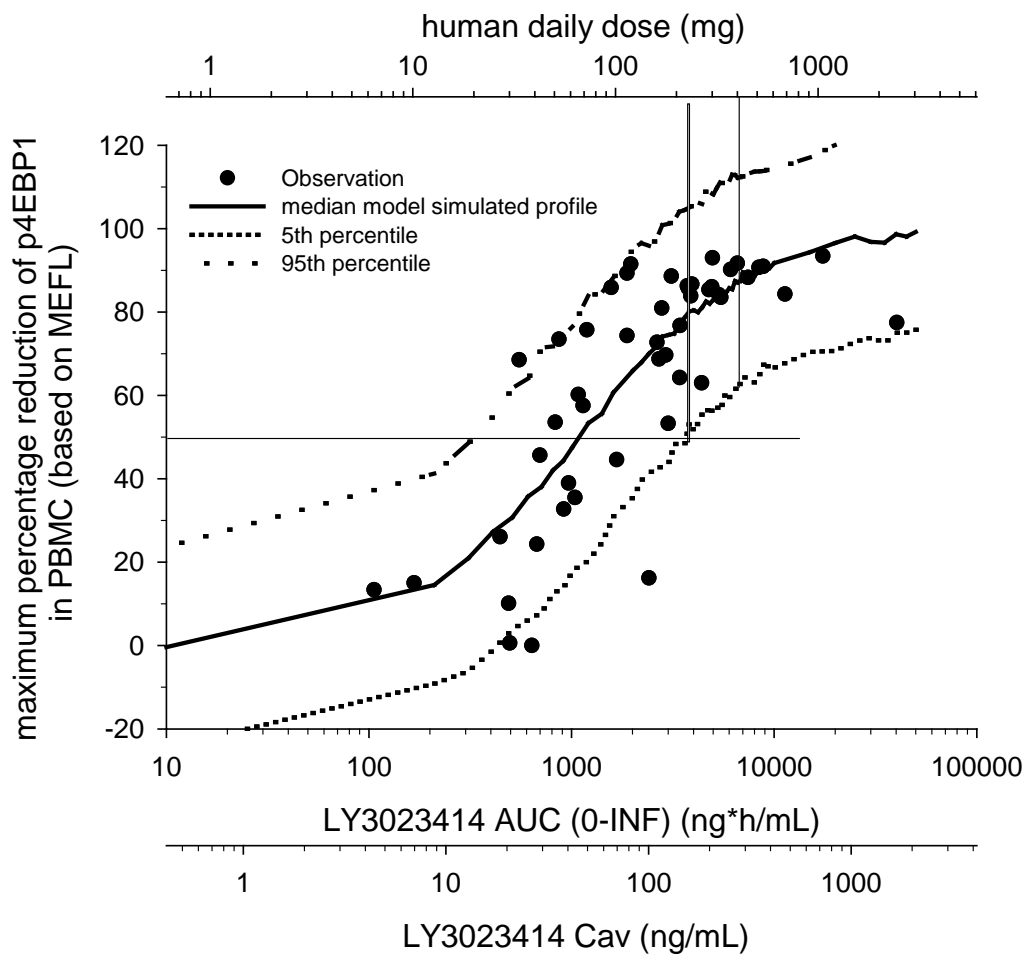
Abbreviations: BID = twice daily; PCFB = percent change from baseline.

Excludes one patient who had a dosing error (received 225 mg BID on Cycle 1, Day 1 rather than 250 mg BID).

Supplemental Figure S3 (a): Simulation of LY3023414 concentration versus time relative to EC50 inhibition of mTOR (as measured by p4EBP1).



Supplemental Figure S3 (b): PK/Pharmacodynamic relationship of target engagement versus LY3023414 concentration



Supplemental Figure S4B: Tumor types in patients with percent change in tumor size administered with different doses of LY3023414

