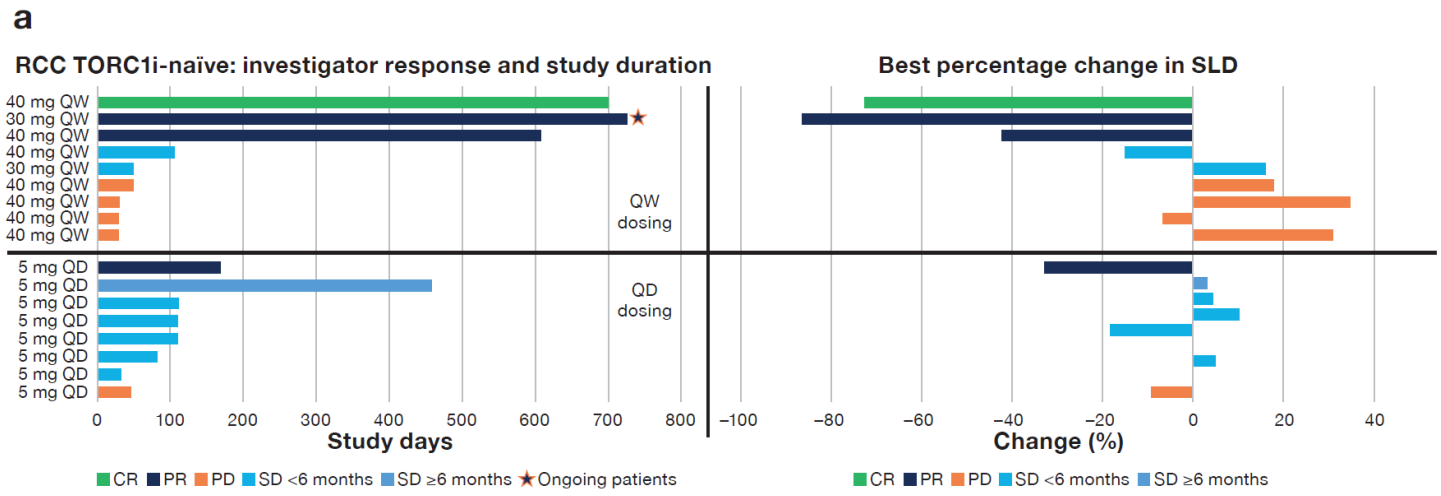
## SUPPLEMENTARY MATERIALS

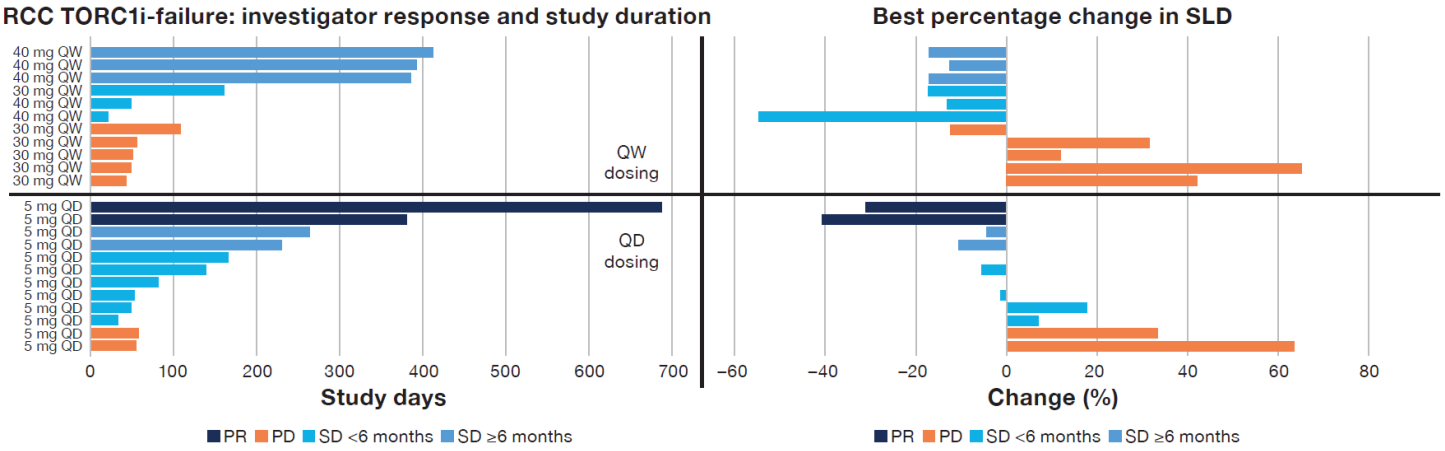
### Results

### Figures

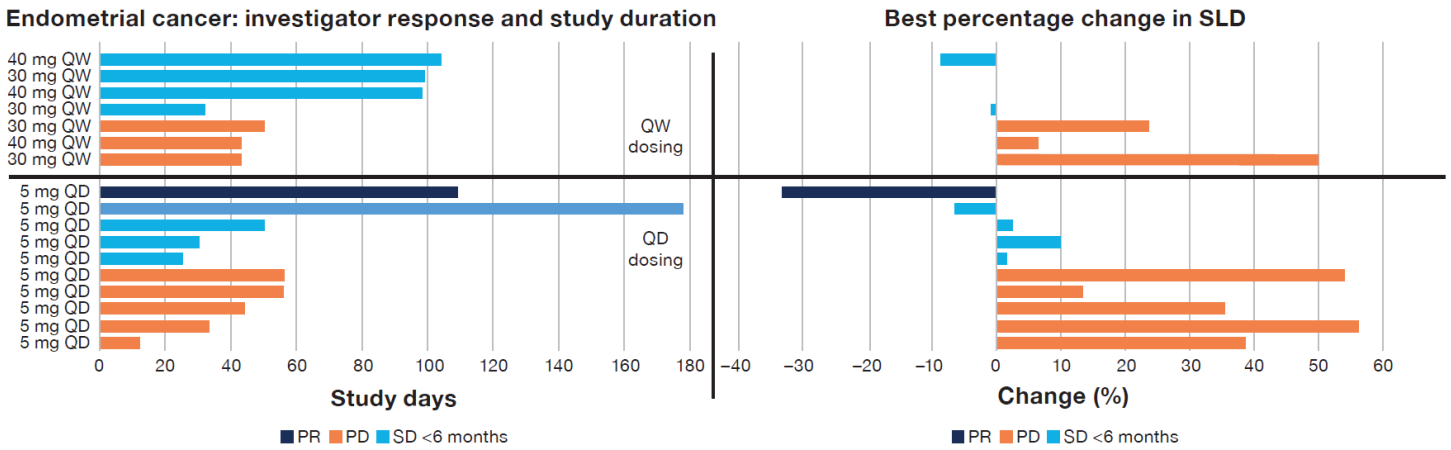
**Supplementary Fig. 1** Study duration and best percentage change of tumour size by dosing schedule in patients with (**a**) TORC1 inhibitor (TORC1i)−naïve RCC, (**b**) RCC with TORC1i-failure, (**c**) endometrial cancer, or (**d**) bladder cancer. *CR* complete response, *PD* progressive disease, *PR* partial response, *QD* once daily, *QW* once weekly, *RCC* renal cell carcinoma, *SD* stable disease, *SLD* sum of longest diameters, *TORC1* target of rapamycin complex 1



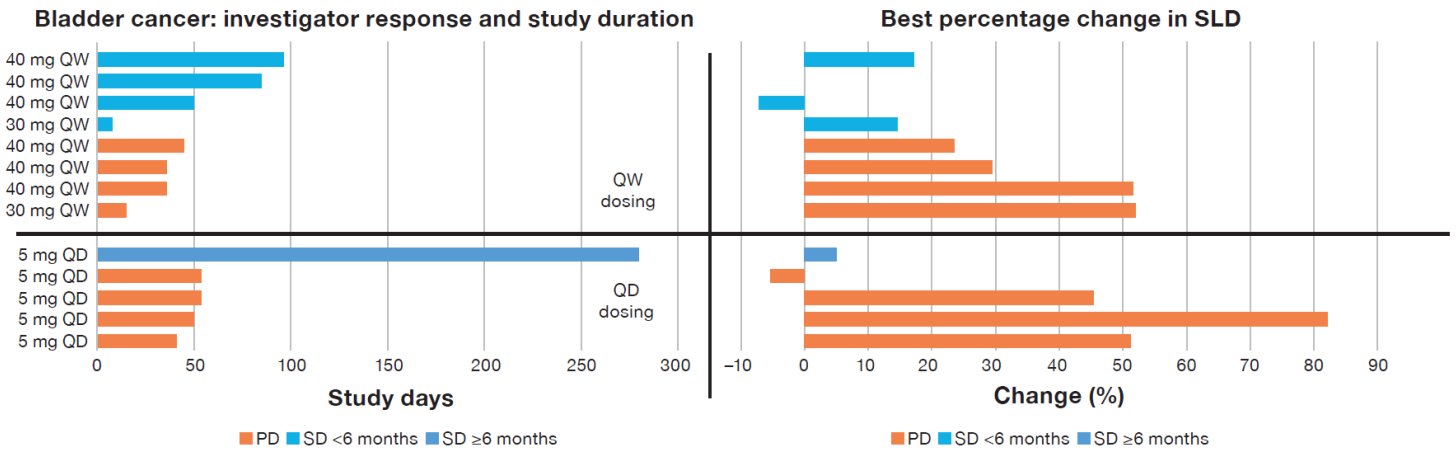
**b**


RCC TORC1i-failure: investigator response and study duration
Best percentage change in SLD
40 mg QW
40 mg QW
40 mg QW
30 mg QW
40 mg QW
40 mg QW
30 mg QW
30 mg QW
30 mg QW
30 mg QW
30 mg QW
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
QW dosing
QD dosing
0
100
200
300
400
500
600
700
Study days
−60
−40
−20
0
20
40
60
80
Change (%)
PR
PD
SD <6 months
SD ≥6 months
PR
PD
SD <6 months
SD ≥6 months

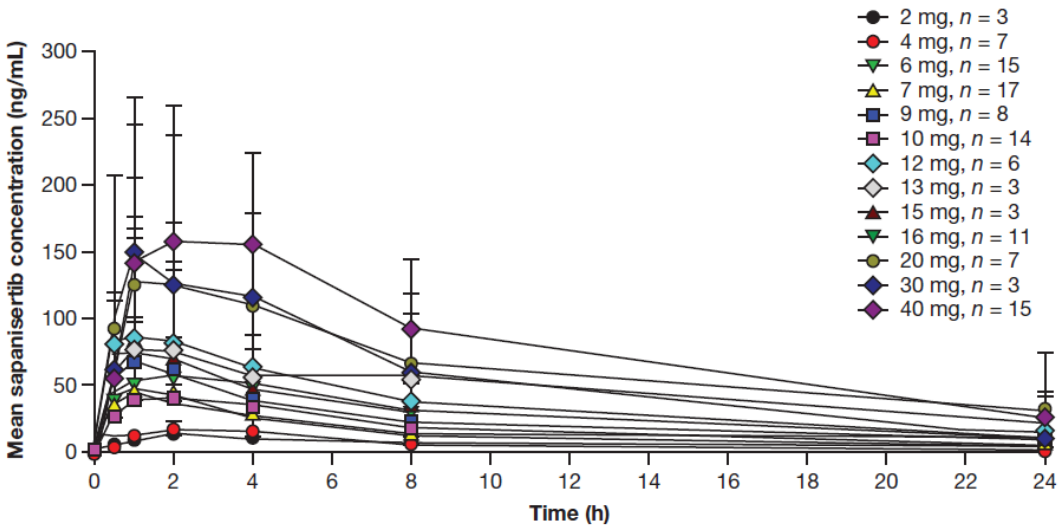
**C**


Endometrial cancer: investigator response and study duration
Best percentage change in SLD
40 mg QW
30 mg QW
40 mg QW
30 mg QW
30 mg QW
40 mg QW
30 mg QW
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
QW dosing
QD dosing
0 20 40 60 80 100 120 140 160 180
Study days
−40 −30 −20 −10 0 10 20 30 40 50 60
Change (%)
PR PD SD <6 months
PR PD SD <6 months

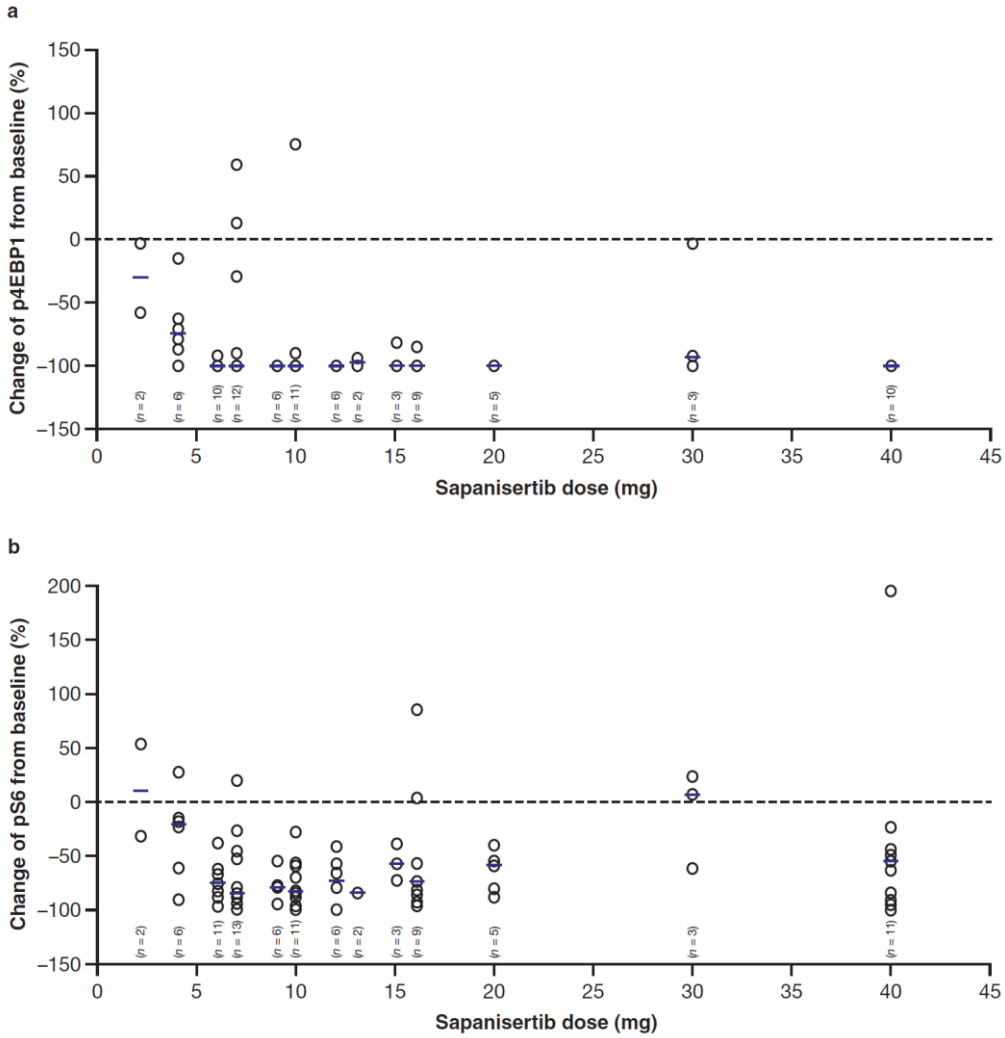
**d**

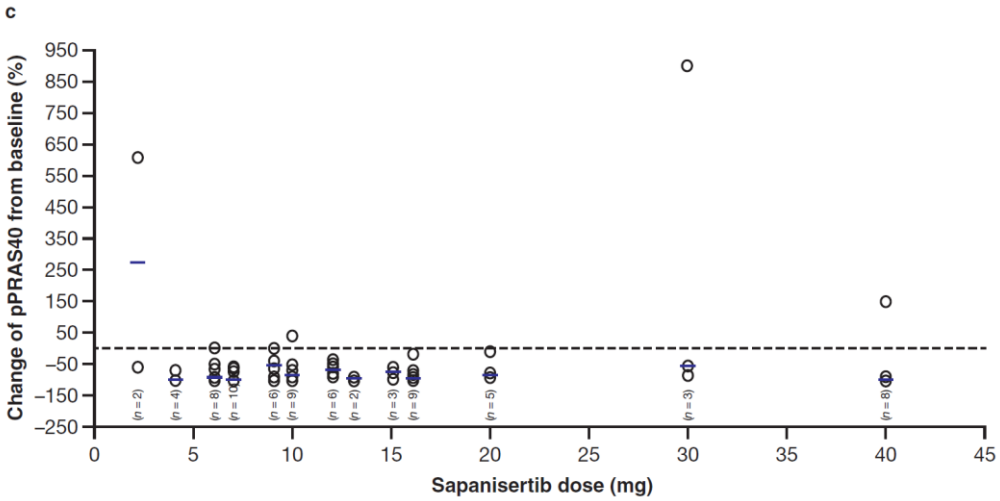

Bladder cancer: investigator response and study duration
Best percentage change in SLD
40 mg QW
40 mg QW
40 mg QW
30 mg QW
40 mg QW
40 mg QW
40 mg QW
30 mg QW
5 mg QD
5 mg QD
5 mg QD
5 mg QD
5 mg QD
QW dosing
QD dosing
0
50
100
150
200
250
300
Study days
−10
0
10
20
30
40
50
60
70
80
90
Change (%)
PD
SD <6 months
SD ≥6 months
PD
SD <6 months
SD ≥6 months

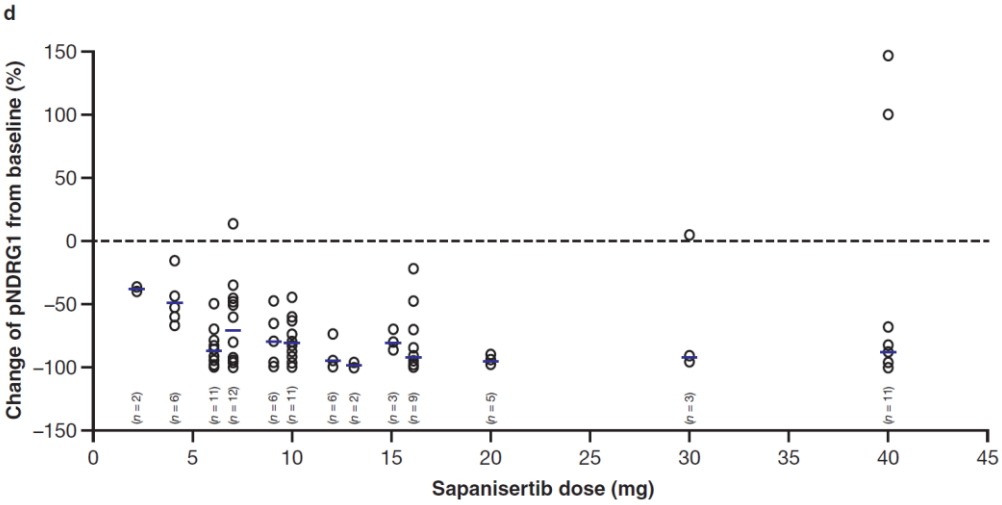
**Supplementary Fig. 2** Mean (SD) plasma concentration–time profiles of single-dose sapanisertib on cycle 1, day 1. Error bars indicate SD. *SD* standard deviation



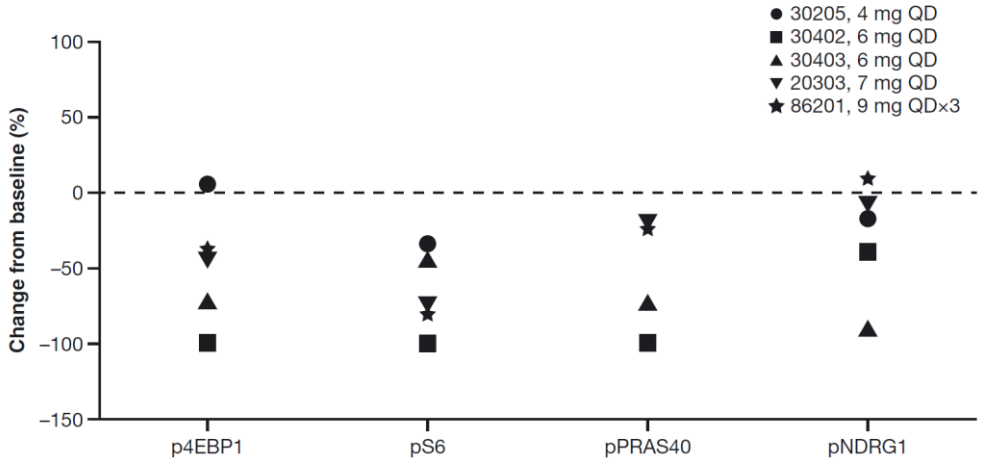
**Supplementary Fig. 3** Pharmacodynamic analysis shows treatment-related inhibition of mammalian target of rapamycin complex 1 (mTORC1/2) biomarkers (**a**) p4EBP1, (**b**) pS6, (**c**) pPRAS40, and (**d**) pNDRG1 in skin 2–4 h post-dose on any dosing day between days 8–15



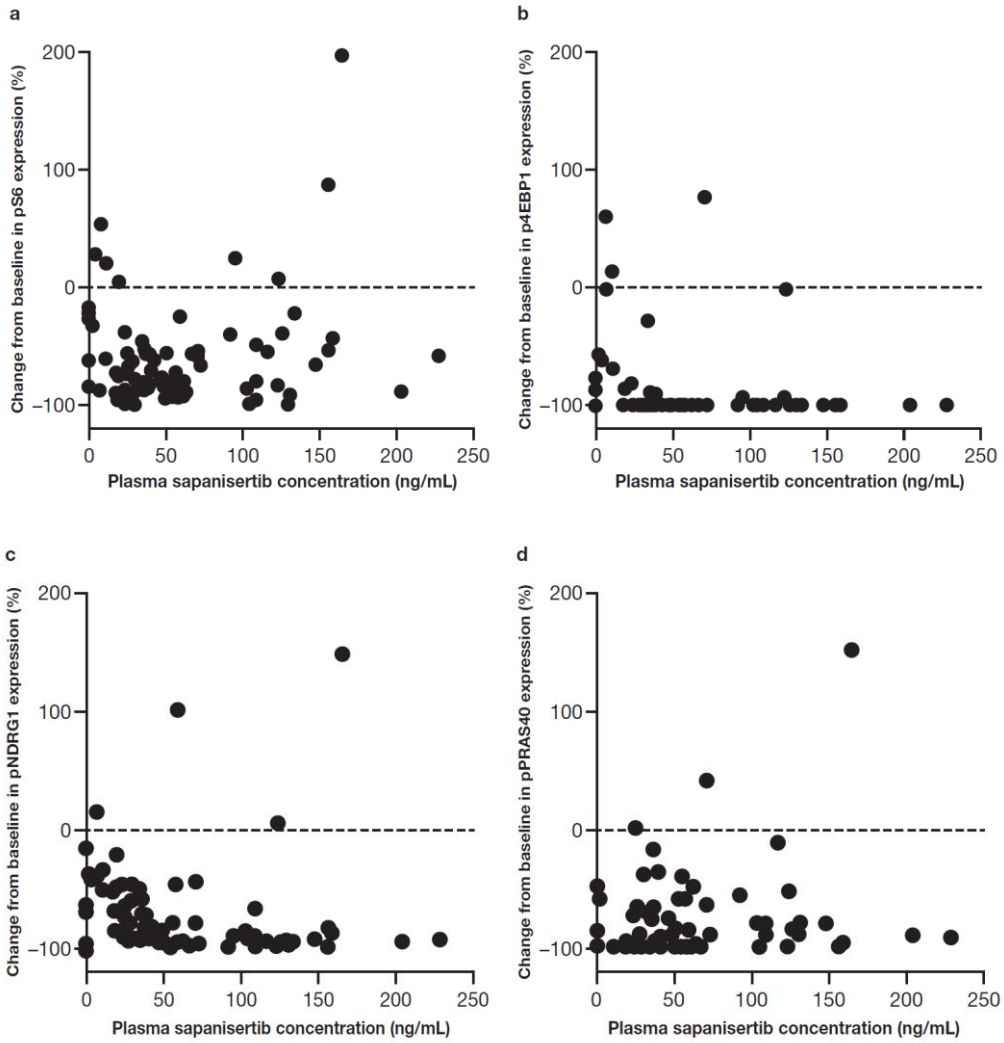

c
Change of pPRAS40 from baseline (%)
950
850
750
650
550
450
350
250
150
50
−50
−150
−250
(n = 2)
(n = 4)
(n = 8)
(n = 10)
(n = 6)
(n = 9)
(n = 6)
(n = 2)
(n = 3)
(n = 9)
(n = 5)
(n = 3)
(n = 8)
0
5
10
15
20
25
30
35
40
45
Sapanisertib dose (mg)


d
Change of pNDRG1 from baseline (%)
150
100
50
0
−50
−100
−150
(n = 2)
(n = 6)
(n = 11)
(n = 12)
(n = 6)
(n = 11)
(n = 6)
(n = 2)
(n = 3)
(n = 9)
(n = 5)
(n = 3)
(n = 11)
0
5
10
15
20
25
30
35
40
45
Sapanisertib dose (mg)

**Supplementary Fig. 4** Percentage change from baseline of pharmacodynamic markers p4EBP1, pS6, pPRAS40, and pNDRG1 in tumour biopsies. *QD* once daily, *QD×3d* QD for 3 days on/4 days off



**Supplementary Fig. 5** Sapanisertib concentration versus target of rapamycin complex 1 (TORC1) biomarkers ([**a**] pS6 and [**b**] p4EBP1) and TORC2 biomarkers ([**c**] pNRDG1 and [**d**] pPRAS40)



**Supplementary Table 1.** Summary of safety profiles of sapanisertib by dosing schedule

| | Sapanisertib dosing schedule | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose-escalation phase | | | | | Expansion phase | | | |
| AE, *n* (%) | QD 2–7 mg (*n* = 31) | QD×3dQW 6–20 mg (*n* = 33) | QD×5dQW 7–13 mg (*n* = 22) | QW 7–40 mg (*n* = 30) | Total (*n* = 116) | QD 5 mg (*n* = 39) | QW 30 mg (*n* = 17) | QW 40 mg (*n* = 26) | Total (*n* = 82) |
| Any AE | 31 (100) | 33 (100) | 22 (100) | 30 (100) | 116 (100) | 39 (100) | 17 (100) | 26 (100) | 82 (100) |
| Any treatment-related AE | 31 (100) | 32 (97) | 21 (95) | 28 (93) | 112 (97) | 39 (100) | 17 (100) | 26 (100) | 82 (100) |
| Any grade ≥3 AE | 19 (61) | 25 (76) | 14 (64) | 18 (60) | 76 (66) | 30 (77) | 9 (53) | 19 (73) | 58 (71) |
| Any treatment-related grade ≥3 AE | 14 (45) | 19 (58) | 8 (36) | 8 (27) | 49 (42) | 18 (46) | 6 (35) | 14 (54) | 38 (46) |
| Any AE resulting in treatment discontinuation | 11 (35) | 7 (21) | 6 (27) | 4 (13) | 28 (24) | 7 (18) | 3 (18) | 2 (8) | 12 (15) |
| Any AE resulting in dose modification/interruption | 22 (71) | 21 (64) | 12 (55) | 13 (43) | 68 (59) | 27 (69) | 8 (47) | 20 (77) | 55 (67) |
| Any SAE | 13 (42) | 17 (52) | 10 (45) | 10 (33) | 50 (43) | 19 (49) | 6 (35) | 9 (35) | 34 (41) |
| Any treatment-related SAE | 4 (13) | 9 (27) | 4 (18) | 0 | 17 (15) | 5 (13) | 3 (18) | 4 (15) | 12 (15) |
| On-study deaths | 1 (3) | 2 (6) | 0 | 1 (3) | 4 (3) | 0 | 2 (12) | 1 (4) | 3 (4) |
| Median number of cycles, median (range) | 2 (1–13) | 2 (1–33) | 2 (1–40) | 2 (1–58) | 2 (1–58) | 2 (1–25) | 2 (1–26) | 2 (1–25) | 2 (1–26) |

*AE* adverse event, *QD* once daily, *QD×3dQW* once daily for 3 days on and 4 days off each week, *QD×5dQW* once daily for 5 days on and 2 days off each week, *QW* once weekly, *SAE* serious AE

**Supplementary Table 2.** Treatment-related grade ≥3 adverse events (AEs) reported in ≥2 patients

| | Sapanisertib regimen | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose-escalation phase | | | | | Expansion phase | | | |
| AE, *n* (%) | QD 2–7 mg (*n* = 31) | QD×5dQW 7–13 mg (*n* = 22) | QD×3dQW 6–20 mg (*n* = 33) | QW 7–40 mg (*n* = 30) | Total (*n* = 116) | QD 5 mg (*n* = 39) | QW 30 mg (*n* = 17) | QW 40 mg (*n* = 26) | Total (*n* = 82) |
| Hyperglycaemia | 6 (19) | 1 (5) | 7 (21) | 2 (7) | 16 (14) | 5 (13) | 2 (12) | 6 (23) | 13 (16) |
| Asthenia | 1 (3) | 3 (14) | 4 (12) | 1 (3) | 9 (8) | 1 (3) | 0 (0) | 1 (4) | 2 (2) |
| Stomatitis | 0 (0) | 3 (14) | 5 (15) | 0 (0) | 8 (7) | 3 (8) | 0 (0) | 1 (4) | 4 (5) |
| Lymphopenia | 2 (6) | 0 (0) | 2 (6) | 1 (3) | 5 (4) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Fatigue | 0 (0) | 2 (9) | 0 (0) | 2 (7) | 4 (3) | 4 (10) | 2 (12) | 4 (15) | 10 (12) |
| Hypophosphatemia | 0 (0) | 0 (0) | 3 (9) | 0 (0) | 3 (3) | 3 (8) | 1 (6) | 2 (8) | 6 (7) |
| Nausea | 0 (0) | 1 (5) | 2 (6) | 0 (0) | 3 (3) | 1 (3) | 1 (6) | 2 (8) | 4 (5) |
| Pruritus generalised | 2 (6) | 0 (0) | 1 (3) | 0 (0) | 3 (3) | 1 (3) | 0 (0) | 0 (0) | 1 (1) |
| Rash maculo-papular | 2 (6) | 1 (5) | 0 (0) | 0 (0) | 3 (3) | 3 (8) | 0 (0) | 0 (0) | 3 (4) |
| Rash | 2 (6) | 0 (0) | 0 (0) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Thrombocytopenia | 2 (6) | 0 (0) | 0 (0) | 0 (0) | 2 (2) | 2 (5) | 1 (6) | 1 (4) | 4 (5) |
| Diarrhoea | 1 (3) | 0 (0) | 0 (0) | 1 (3) | 2 (2) | 2 (5) | 0 (0) | 1 (4) | 3 (4) |
| Dehydration | 0 (0) | 0 (0) | 1 (3) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 2 (8) | 2 (2) |

QD once daily, QW once weekly, QD×3dQW once daily for 3 days on and 4 days off each week, QD×5dQW once daily for 5 days on and 2 days off each week.

**Supplementary Table 3.** All-grade adverse events (AEs) of any cause by preferred term reported in ≥20% of patients by dosing schedule in the expansion phase

| | Sapanisertib regimen | | | |
|---|---|---|---|---|
| | Expansion phase | | | |
| AE, *n* (%) | QD 5 mg (*n* = 39) | QW 30 mg (*n* = 17) | QW 40 mg (*n* = 26) | Total (*n* = 82) |
| Fatigue | 25 (64) | 11 (65) | 24 (92) | 60 (73) |
| Nausea | 21 (54) | 13 (76) | 20 (77) | 54 (66) |
| Hyperglycaemia | 18 (46) | 12 (71) | 20 (77) | 50 (61) |
| Vomiting | 13 (33) | 10 (59) | 20 (77) | 43 (52) |
| Decreased appetite | 20 (51) | 7 (41) | 14 (54) | 41 (50) |
| Diarrhoea | 20 (51) | 8 (47) | 13 (50) | 41 (50) |
| Stomatitis | 19 (49) | 9 (53) | 12 (46) | 40 (49) |
| Constipation | 10 (26) | 8 (47) | 10 (38) | 28 (34) |
| Rash maculo-papular | 17 (44) | 3 (18) | 4 (15) | 24 (29) |
| Cough | 9 (23) | 5 (29) | 8 (31) | 22 (27) |
| Anaemia | 6 (15) | 2 (12) | 11 (42) | 19 (23) |
| Pruritus generalised | 12 (31) | 4 (24) | 3 (12) | 19 (23) |
| Abdominal pain | 7 (18) | 6 (35) | 4 (15) | 17 (21) |
| Dehydration | 6 (15) | 4 (24) | 7 (27) | 17 (21) |
| Dysgeusia | 10 (26) | 4 (24) | 3 (12) | 17 (21) |
| Dry mouth | 5 (13) | 3 (18) | 7 (27) | 15 (18) |
| Oedema peripheral | 9 (23) | 1 (6) | 5 (19) | 15 (18) |
| Pruritus | 10 (26) | 1 (6) | 4 (15) | 15 (18) |
| Urinary tract infection | 6 (15) | 1 (6) | 8 (31) | 15 (18) |
| Weight decreased | 6 (15) | 2 (12) | 7 (27) | 15 (18) |
| Blood creatinine increased | 5 (13) | 4 (24) | 5 (19) | 14 (17) |
| Pyrexia | 8 (21) | 1 (6) | 5 (19) | 14 (17) |
| Oropharyngeal pain | 3 (8) | 1 (6) | 9 (35) | 13 (16) |
| Dizziness | 9 (23) | 0 (0) | 3 (12) | 12 (15) |
| Headache | 4 (10) | 2 (12) | 6 (23) | 12 (15) |
| Arthralgia | 2 (5) | 2 (12) | 7 (27) | 11 (13) |
| Depression | 1 (3) | 4 (24) | 3 (12) | 8 (10) |

*QD* once daily, *QW* once weekly

**Supplementary Table 4.** Grade ≥3 adverse events (AEs) of any cause reported in ≥2 patients in the expansion phase

| | Sapanisertib regimen | | | |
|---|---|---|---|---|
| | Expansion phase | | | |
| Grade ≥3 AE, *n* (%) | QD 5 mg (*n* = 39) | QW 30 mg (*n* = 17) | QW 40 mg (*n* = 26) | Total (*n* = 82) |
| Hyperglycaemia | 5 (13) | 2 (12) | 6 (23) | 13 (16) |
| Fatigue | 5 (13) | 2 (12) | 4 (15) | 11 (13) |
| Hypophosphatemia | 4 (10) | 2 (12) | 2 (8) | 8 (10) |
| Anaemia | 1 (3) | 1 (6) | 3 (12) | 5 (6) |
| Nausea | 1 (3) | 2 (12) | 2 (8) | 5 (6) |
| Acute kidney injury | 2 (5) | 0 (0) | 2 (8) | 4 (5) |
| Rash maculo-papular | 3 (8) | 0 (0) | 1 (4) | 4 (5) |
| Stomatitis | 3 (8) | 0 (0) | 1 (4) | 4 (5) |
| Thrombocytopenia | 2 (5) | 1 (6) | 1 (4) | 4 (5) |
| Abdominal pain | 3 (8) | 0 (0) | 0 (0) | 3 (4) |
| Asthenia | 1 (3) | 0 (0) | 2 (8) | 3 (4) |
| Dehydration | 0 (0) | 0 (0) | 3 (12) | 3 (4) |
| Diarrhoea | 2 (5) | 0 (0) | 1 (4) | 3 (4) |
| Hyponatremia | 1 (3) | 1 (6) | 1 (4) | 3 (4) |
| Pain in extremity | 0 (0) | 2 (12) | 1 (4) | 3 (4) |
| Vomiting | 1 (3) | 1 (6) | 1 (4) | 3 (4) |
| Constipation | 0 (0) | 1 (6) | 1 (4) | 2 (2) |
| Dyspnoea | 2 (5) | 0 (0) | 0 (0) | 2 (2) |
| Haematuria | 2 (5) | 0 (0) | 0 (0) | 2 (2) |
| Hyperkalaemia | 2 (5) | 0 (0) | 0 (0) | 2 (2) |
| Hypertension | 1 (3) | 0 (0) | 1 (4) | 2 (2) |
| Hypokalaemia | 1 (3) | 1 (6) | 0 (0) | 2 (2) |
| Lymphopenia | 1 (3) | 0 (0) | 1 (4) | 2 (2) |
| Musculoskeletal chest pain | 1 (3) | 0 (0) | 1 (4) | 2 (2) |
| Pneumonia | 2 (5) | 0 (0) | 0 (0) | 2 (2) |
| Sepsis | 1 (3) | 1 (6) | 0 (0) | 2 (2) |
| Transitional cell carcinoma | 0 (0) | 1 (6) | 1 (4) | 2 (2) |

*QD* once daily, *QW* once weekly

**Supplementary Table 5.** Sapanisertib plasma pharmacokinetic parameters during (**a**) cycle 1, day 1 and (**b**) cycle 2, day 1

**a**

| Dose level | $T_{max}$ (h), median | $C_{max}$ (ng/mL) [%CV] | $AUC_{0–last}$ (ng*h/mL) [%CV] | $AUC_{0–24h}$ (ng*h/mL) [%CV] | $t_{½}$ (h) |
|---|---|---|---|---|---|
| 2 mg | 2.0 | 13.5 (16.7) | 65.4 (NA) | NA | NA |
| 4 mg | 2.0 | 19.1 (40.1) | 63.2 (32.5) | 178.4 (28.7) | 7.1 |
| 6 mg | 1.0 | 50.8 (45.5) | 124.3 (NA) | 354.3 (26.0) | 6.8 |
| 7 mg | 1.5 | 46.7 (62.1) | NA (NA) | 327.3 (33.0) | 6.9 |
| 9 mg | 1.1 | 75.9 (35.5) | 207.3 (NA) | 595.9 (25.8) | 7.5 |
| 10 mg | 2.8 | 48.4 (54.9) | 153.1 (NA) | 341.8 (60.1) | 6.4 |
| 12 mg | 2.0 | 99.5 (81.9) | NA | 730.2 (43.5) | 7.4 |
| 13 mg | 2.1 | 93.6 (63.0) | NA | 952.6 (59.6) | 8.7 |
| 15 mg | 2.0 | 56.7 (100.8) | NA | 517.8 (86.5) | 9.4 |
| 16 mg | 2.1 | 66.7 (68.5) | 124.9 (NA) | 688.7 (29.1) | 7.0 |
| 20 mg | 2.1 | 154.1 (45.0) | NA | 1262.8 (69.3) | 6.5 |
| 30 mg | 1.0 | 161.8 (45.8) | NA | 1076.8 (66.3) | 5.9 |
| 40 mg | 2.4 | 172.4 (48.6) | NA | 1639.5 (48.5) | 7.6 |

*%CV* percentage coefficient of variation, $AUC_{0–24h}$ area under the curve from time zero to 24 hours post-dose, $AUC_{0–last}$ area under the curve from time zero to time of last quantifiable concentration, *NA* not applicable, $t_{½}$ terminal disposition phase half-life, $T_{max}$ time of first occurrence of $C_{max}$

**b**

| Dose level | $T_{max}$ (h), median | $C_{max}$ (ng/mL) [%CV] | $AUC_{0–last}$ (ng*h/mL) [%CV] | $AUC_{0–24h}$ (ng*h/mL) [%CV] | $t_{½}$ (h) |
|---|---|---|---|---|---|
| QD Dosing Schedule | | | | | |
| 2 mg | 2.0 | 15.6 (101.2) | NA | 185.0 (63.5) | 8.1 (NA) |
| 4 mg | 3.8 | 20.3 (117.4) | 61.9 (NA) | 281.4 (49.8) | 10.3 (1.24) |
| 6 mg | 2.0 | 36.9 (48.5) | NA | 327.0 (22.6) | 7.3 (1.00) |
| 7 mg | 4.0 | 51.3 (91.9) | NA | 350.6 (52.0) | 5.63 (2.02) |
| QW Dosing Schedule | | | | | |
| 7 mg | 1 | 65.8 (NA) | NA | 350.8 (NA) | 5.6 (NA) |
| 10 mg | 2.9 | 36.2 (NA) | NA | NA | NA |
| 15 mg | 2.0 | 64.9 (30.1) | NA | 604.4 (33.6) | NA |
| 20 mg | 4.0 | NA | NA | NA | NA |
| 30 mg | 4.0 | 132.8 (48.4) | NA | 1120.9 (55.55) | 5.7 (NA) |
| 40 mg | 2.0 | 231.7 (40.7) | NA | 2222.1 (55.5) | 6.4 (1.86) |
| QDx3dQW Dosing Schedule | | | | | |
| 6 mg | 4.0 | 59.2 (20.7) | NA | 777.4 (NA) | 9.1 (NA) |
| 9 mg | 2.1 | 83.1 (34.4) | NA | 706.6 (33.1) | 6.9 (0.78) |
| 12 mg | 3.7 | 113.3 (22.0) | NA | 707.2 (NA) | 4.9 (NA) |
| 16 mg | 2.1 | 92.1 (75.4) | NA | 744.3 (56.3) | 6.6 (2.29) |
| 20 mg | 1.0 | NA | NA | NA | NA |
| QDx5dQW Dosing Schedule | | | | | |
| 7 mg | 1.5 | 49.7 (75.2) | NA | 362.5 (45.5) | 6.7 (0.49) |
| 10 mg | 2.0 | 57.0 (33.9) | NA | 366.4 (6.1) | 5.7 (1.30) |
| 13 mg | 2.0 | NA | NA | NA | NA |

*%CV* percentage coefficient of variation, $AUC_{0–24h}$ area under the curve from time zero to 24 hours post-dose, $AUC_{0–last}$ area under the curve from time zero to time of last quantifiable concentration, *NA* not applicable, $t_{½}$ terminal disposition phase half-life, $T_{max}$ time of first occurrence of $C_{max}$

## Supplementary Information: Ethics approval and consent to participate

### List of institutional review boards and independent ethics committees

- Alpha Independent Review Board, 1001 Avenida Pico, C-497, San Clemente, CA 93673, USA
- Cedars-Sinai Medical Center Institutional Review Board, Office of Research Compliance, 8383 Wilshire Blvd., Suite 742, Beverly Hills, CA 90211, USA
- Cleveland Clinic Institutional Review Board, 9500 Euclid Avenue, OS-1, Cleveland, OH 44195, USA
- Comite Etico de Investigacion Clinica, Hospital Clinico, Universtario de Valencia, Pabellion B, 1st Planta, Avenida Blasco Ibanez, 17, 46010 Valencia, Spain
- Comite Etico de Investigacion Clinica, Hospital de la Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain
- Henry Ford Health System, Research Administration, One Ford Place-2F, Detroit, MI USA 48202
- Indiana University Institutional Review Board, Office of Research Administration, 980 Indiana Avenue, Indianapolis, IN 46202, USA
- IntegReview Ethical Review Board, 3001 S. Lamar Blvd., Suite 210, Austin, TX 78704, USA
- Memorial Sloan Kettering Cancer Center Institutional Review Board B, 1275 York Avenue, New York, NY 10065, USA
- Office for Human Research Studies, 450 Brookline Avenue, OS229, Boston, MA 02215, USA
- Roswell Park Cancer Institutional Review Board, Elm & Carlton Streets, Buffalo, NY 14263, USA
- University of Miami Human Subjects Research Office, 1500 NW 12th Avenue, Suite I002, Miami, FL 33136, USA
- University of Michigan Medical School Institutional Review Board, 2800 Plymouth Road, Building 520, Room 3214, Ann Arbor, MI 48109-2800, USA
- Vanderbilt University Institutional Review Board, 1313 21st Avenue South, 504 Oxford House, Nashville, TN 37232-4315, USA

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