# Supplementary materials

## Methods

### Inclusion criteria

In addition to those listed in the main manuscript, inclusion criteria for Part 1 and 2 were:

* Age ≥18 years
* Adequate organ function including renal function (based on blood creatinine and urine protein/creatinine ratio); and normal left-ventricular ejection fraction
* Histologically- or cytologically-confirmed diagnosis of one of the following solid tumor malignancies that was not responsive to standard therapy, or for which there was no approved or curative therapy, or for subjects that refused standard therapy:
* Endometrioid cancer
* Prostate cancer
* Ovarian cancer
* Non-small cell lung cancer
* Glioblastoma
* Breast cancer (triple negative: estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2-negative)
* Gastric adenocarcinoma
* Colorectal cancer
* Head/neck squamous cell carcinoma
* Melanoma
* Presence of a tumor with a documented phosphatase and tensin homolog (PTEN) deficiency using an analytically-validated immunohistochemistry assay or other correlative assay (eg, fluorescent in situ hybridization). Determination of PTEN deficiency using archival tumor was acceptable. Where archival tissue was not available or did not confirm PTEN deficiency, a fresh tumor sample was acceptable for screening, and those with PTEN deficiency were eligible.
* Progression on standard therapy
* Eastern Cooperative Oncology Group performance status: 0 or 1

### Exclusion criteria

* Patient has undergone chemotherapy, radiotherapy, immunotherapy, or other anti-cancer therapy including investigational drug(s) within 14 days prior to the first dose of GSK2636771
* History of congenital platelet function defect (eg, Bernard–Soulier syndrome, Chediak–Higashi syndrome, Glanzmann thrombasthenia, storage pool defect)
* Patients with brain metastases of non-central nervous system (CNS) primary tumors are excluded if their brain metastases are:
  + Symptomatic
  + Treated (surgery, radiation therapy) but not clinically and radiographically stable 1 month after local therapy (as assessed by contrast enhanced magnetic resonance imaging or computed tomography)
  + Asymptomatic and untreated but >1 cm in the longest dimension.
* Cardiovascular risk:
  + QT interval corrected by Fridericia’s formula ≥470 msec
  + Other clinically significant electrocardiogram, abnormalities including second degree (Type II) or third degree atrioventricular block
  + History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, or stenting or bypass grafting within the past 6 months
  + Class III or IV heart failure as defined by the New York Heart Association functional classification system
  + Baseline cardiac troponin I >10% coefficient of variation (CV).
* Pregnant or lactating female
* Any malignancy related to human immunodeficiency virus (HIV) or solid organ transplant; history of known HIV, history of known Hepatitis B virus (HBV) positive surface antigen (patients with documented laboratory evidence of HBV clearance may be enrolled) or positive Hepatitis C virus antibody confirmed by recombinant immunoblot assay
* Any serious or unstable pre-existing medical, psychiatric, or other condition (including laboratory abnormalities) that could have interfered with patient’s safety or providing informed consent
* Presence of any clinically significant gastrointestinal (GI) abnormalities or other condition that may alter absorption such as malabsorption syndrome or major resection of the stomach or bowels
* Known active infection requiring parenteral or oral anti-infective treatment
* Evidence of severe or uncontrolled systemic diseases (eg, unstable or uncompensated respiratory, hepatic, renal or cardiac disease)
* Active peptic ulcer disease or history of abdominal fistula, GI perforation, or intra- abdominal abscess within 28 days prior to first dose of study treatment

### Supplementary Figure 1: Study design

### Supplementary Figure 2: LNCAP and DU-145 prostate cancer cells were treated with 1 or 10 μM GSK2636771 for up to 48 hours and probed with the indicated antibodies

### Supplementary Figure 3: Glucose and insulin levels after treatment with GSK2636771 in fasted mice.

Mice (n=3/group) were dosed orally for 3 days with vehicle, GSK2636771, or GSK2126458 (a pan PI3K/mTOR inhibitor) then starved for 20 hours before receiving a final dose of compound. Blood was collected at 0, 0.5, 1, 2, and 4 hours after the last dose. Mean values are presented; errors bars represent standard deviations.

mTOR, mammalian target of rapamycin

**Supplementary Figure 4: Investigation of the p.L1049R mutation identified in a patient with castration-resistant prostate cancer**.

**A**, The *PIK3CB* L1049R mutation is homologous to H1047R in *PI3KCA*, as reported in a patient with glioblastoma (www.cbioportal.org); **B,** Confirmation of the presence of the *PIK3CB* p.L1049R mutation was achieved using Sanger sequencing; **C,** PC3 cells were transduced with pHTBBV1.1 (using baculovirus gene transfer into mammalian cells) expressing wt *PIK3CB* or the p.L1049R mutant at a range of multiplicity of infections, and analyzed using Western blot.

AKT, protein kinase B; APC, Adenomatous polyposis coli; AR, androgen receptor; ATM, ataxia telangiectasia mutated; BRAF, v-raf murine sarcoma viral oncogene homolog B; CHD1, chromodomain helicase DNA binding protein 1; CNS, central nervous system; CNV, copy number variation; CRPC, castration-resistant prostate cancer; DNA, deoxyribonucleic acid; GE, gastrointestinal; GMB, glioblastoma; H&N, head and neck; KRAS, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NE/Non, not evaluable; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide-3-kinase; qPCR, quantitative polymerase chain reaction; PD, progressive disease; *PI3K*, phosphoinositide-3-kinase; PR, partial response; PSA, prostate-specific antigen; PTEN, phosphatase and tensin homolog; SD, stable disease; wt, wild type

### Supplementary Table 1: 3 + 3 dose escalation guidelines

|  |  |
| --- | --- |
| **Number of subjects with DLT** | **Action** |
| 0 out of 3 subjects | Escalate to next dose level |
| 1 out of 3 subjects | Accrue 3 additional evaluable subjects at current dose level for a total of 6 evaluable subjects |
| 1 out of 6 subjects | Escalate to next dose level |
| 2 or more subjects in a dosing cohort  (up to 6 subjects) | MTD was exceeded; de-escalate to a lower dose, or expand previous cohort to 6 evaluable subjects |

DLT, dose-limiting toxicity; MTD, maximum tolerated dose.

### Supplementary Table 2: Customized sequencing panel

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ABL1 | BUB1B | DAXX | FBXO11 | HRAS | MAP2K2 | NOTCH1 | PTCH1 | TNFAIP3 |
| AKT1 | CARD11 | DDB2 | FBXW7 | HSPH1 | MAP2K4 | NOTCH2 | PTEN | TNFRSF14 |
| AKT2 | CBL | DDR2 | FGFR2 | IDH1 | MAP3K1 | NPM1 | PTPN11 | TP53 |
| ALK | CBLB | DICER1 | FGFR3 | IDH2 | MAP4K3 | NR3C1 | RAC1 | TSC1 |
| AMER1 | CD79A | DNMT3A | FH | IKZF1 | MDM2 | NRAS | RB1 | TSC2 |
| APC | CD79B | ECT2L | FLCN | IL6ST | MED12 | PALB2 | RET | TSHR |
| AR | CDC73 | EGFR | FLT3 | IL7R | MEN1 | PAX5 | ROS1 | U2AF1 |
| ARID1A | CDH1 | EP300 | FOXA1 | INPP4B | MET | PBRM1 | SDHB | VHL |
| ARID2 | CDK12 | EPCAM | FUBP1 | INPP5D | MLH1 | PDGFRA | SETD2 | WT1 |
| ASXL1 | CDK4 | ERBB2 | GATA1 | JAK1 | MSH2 | PHF6 | SF3B1 | XPC |
| ATM | CDKN1B | ERBB3 | GATA2 | JAK2 | MSH6 | PHLPP1 | SLC7A8 | ZNF2 |
| ATRX | CDKN2A | ERBB4 | GATA3 | JAK3 | MTOR | PIK3CA | SMAD4 | ZRSR2 |
| BAP1 | CHD1 | ERCC5 | GNA11 | KDM6A | MUTYH | PIK3CB | SMARCA4 |  |
| BCL6 | CHEK2 | ESR1 | GNAQ | KDR | MYC | PIK3CD | SMARCB1 |  |
| BCOR | CIC | EZH2 | GNAS | KIT | MYD88 | PIK3R1 | SMO |  |
| BRAF | CREBBP | FAM46C | GPC3 | KLF6 | NF1 | PIK3R2 | SPOP |  |
| BRCA1 | CRLF2 | FANCA | GRIN2A | KMT2D | NF2 | PMS2 | SRC |  |
| BRCA2 | CSF1R | FANCD2 | H3F3A | KRAS | NFE2L2 | PPP2R1A | STK11 |  |
| BRIP1 | CTNNB1 | FANCE | HIST1H3B | KTM2C (MLL3) | NFKBIA | PRDM1 | SUFU |  |
| BTK | CYLD | FAS | HNF1A | MAP2K1 | NKX3-1 | PRKAR1A | TERT |  |

### Supplementary Table 3: Summary of AEs occurring in >20% of all patients, treatment-related AEs and SAEs

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Preferred term, n (%)** | **Dose-selection cohort** | **Dose-escalation cohort** | | | **PD cohort** | **Expansion cohort** | **Total** |
|  | **25 mg**  **n=3** | **25–350 mg**  **n=23** | **400 mg**  **n=6** | **500 mg**  **n=4** | **50–350 mg**  **n=17** | **400 mg**  **n=12** | **(N=65)** |
| **Any AE (any grade)** | 3 (100) | 23 (100) | 6 (100) | 4 (100) | 17 (100) | 12 (100) | 65 (100) |
| Diarrhea | 1 (33) | 11 (48) | 1 (17) | 1 (25) | 9 (53) | 8 (67) | 31 (48) |
| Nausea | 2 (67) | 9 (39) | 2 (33) | 2 (50) | 7 (41) | 5 (42) | 27 (41) |
| Vomiting | 1 (33) | 9 (39) | 1 (17) | 1 (25) | 6 (35) | 2 (17) | 20 (31) |
| Fatigue | 1 (33) | 8 (35) | 1 (17) | 3 (75) | 2 (12) | 2 (17) | 17 (26) |
| Anemia | 0 | 7 (30) | 0 | 0 | 5 (29) | 3 (25) | 15 (23) |
| Abdominal pain | 2 (67) | 7 (30) | 1 (17) | 1 (25) | 3 (18) | 1 (8) | 15 (23) |
| Decreased appetite | 0 | 4 (17) | 1 (17) | 1 (25) | 6 (35) | 3 (25) | 15 (23) |
| Headache | 1 (33) | 6 (26) | 0 | 0 | 2 (12) | 4 (33) | 13 (20) |
| **Treatment-related AEs** | 3 (100) | 22 (96) | 5 (83) | 4 (100) | 15 (88) | 11 (92) | 60 (92) |
| **Any SAE** | 1 (33) | 7 (30) | 0 | 1 (25) | 9 (53) | 6 (50) | 24 (37) |
| **Fatal SAEs** | 0 | 0 | 0 | 0 | 0 | 1 (8) | 1 (2) |

AE, adverse event; PD, pharmacodynamics; SAE, serious AE.

### Supplementary Table 4: PK parameters following single dose oral dosing of GSK2636771 (PK population)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameter term, n (%)** | **Dose-selection cohort** | **Dose-escalation cohort** | | | | | | |
|  | **25 mg**  **n=3** | **25 mg**  **n=6** | **50 mg**  **n=4** | **100 mg**  **n=3** | **200 mg**  **n=3** | **350 mg**  **n=7** | **400 mg**  **n=6** | **500 mg**  **n=4** |
| **Cmax, ng/mL\*** | n=3  1105 (50) | n=6  844 (24) | n=4  1594 (28) | n=3  2368 (41) | n=3  6312 (15) | n=7  8060 (33) | n=6  5493 (57) | n=4  7221 (35) |
| **Tmax, h, median (range)** | n=3  4.00  (3.00, 6.00) | n=6  4.04  (1.03, 6.00) | n=4  4.00  (2.08, 6.17) | n=3  4.00  (3.00, 8.00) | n=3  3.97  (3.02, 6.00) | n=7  4.20  (4.00, 7.97) | n=6  3.03  (2.00, 6.10) | n=4  5.08  (3.00, 10.1) |
| **AUC(0–24), h·ng/mL\***  **AUC(0–∞), h·ng/mL**  **t½, h\*** | n=3  15729 (68)  n=3  25327 (79)  n=3  17.7 (16) | n=6  11430 (38)  n=6  19726 (51)  n=6  19.0 (20) | n=4  22019 (23)  n=4  38792 (21)  n=4  19.8 (11) | n=3  22763 (49)  n=3  31833 (69)  n=3  15.0 (63) | n=3  84137 (26)  n=2  128472 (6)  n=2  18.0 (8) | n=7  116138 (37)  n=6  236041 (48)  n=6  21.1 (15) | n=6  67051 (38)  n=2  161874 (15)  n=2  23.2 (27) | n=4  108483 (44)  n=3  190798 (62)  n=3  23.0 (8) |

\*Data presented as geometric mean (CVb%).

AUC(0–24), area under the concentration-time curve from time 0 to 24 hours; AUC(0–∞), area under the concentration-time curve from time 0 to infinity; Cmax, maximum observed plasma concentration; CVb, coefficient of biological variation; PK, pharmacokinetic; Tmax, time to reach Cmax; t½, terminal half-life.

### Supplementary Table 5: PK parameters following single daily oral dosing of GSK2636771 (PK population)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter, n (%)** | **PD cohort** | | | | |
|  | **50 mg**  **n=2** | **100 mg**  **n=4** | **200 mg**  **n=5** | **350 mg**  **n=6** |
| **Cmax, ng/mL\*** | n=2  1320 (36) | n=4  3038 (28) | n=5  4007 (61) | n=6  7126 (42) |
| **Tmax, h, median (range)** | n=2  2.88  (2.00, 3.75) | n=4  4.04  (2.00, 10.1) | n=5  7.85  (3.17, 9.75) | n=6  4.01  (2.92, 8.00) |
| **AUC(0–24), h·ng/mL\***  **AUC(0–∞), h·ng/mL**  **t½, h\*** | n=2  18489 (21)  n=1  29391  n=1  13.1 | n=4  38966 (30)  n=4  67492 (22)  n=4  19.8 (42) | n=5  53783 (62)  n=3  126278 (58)  n=3  18.3 (11) | n=6  103812 (44)  n=5  178453 (67)  n=5  18.7 (36) |

\*Data presented as geometric mean (CVb%).

AUC(0–24), area under the concentration-time curve from time 0 to 24 hours; AUC(0–∞), area under the concentration-time curve from time 0 to infinity; Cmax, maximum observed plasma concentration; CVb, coefficient of biological variation; PD, pharmacodynamic; PK, pharmacokinetic; Tmax, time to reach Cmax;; t½, terminal half-life.

### Supplementary Table 6: PK parameters following multiple dose oral dosing of GSK2636771 (PK population)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Preferred term, n (%)** | **Dose-escalation cohort** | | | | **Expansion cohort** |
|  | **50 mg**  **n=2** | **100 mg**  **n=4** | **200 mg**  **n=5** | **350 mg**  **n=6** | **400 mg**  **n=4** |
| **Cmax, ng/mL\*** | n=2  2855 (42) | n=1  5223 | n=3  9865 (14) | n=4  15753 (12) | n=4  14075 (27) |
| **Tmax, h, median (range)** | n=2  3.06  (2.03, 4.08) | n=1  8.00  (8.00, 8.00) | n=3  4.20  (4.00, 6.17) | n=4  6.02  (4.00, 9.83) | n=4  8.15  (6.08, 9.92) |
| **AUC(0–τ), h·ng/mL\*** | n=1  27050 | n=1  82572 | n=3  123035 (31) | n=3  185811 (13) | n=2  290100 (12) |

\*Data presented as geometric mean (CVb%).

AUC(0–τ), area under the concentration-time curve over the dosing interval; Cmax, maximum observed plasma concentration; CVb, coefficient of biological variation; PK, pharmacokinetic; Tmax, time to reach Cmax.

**Supplementary Table 7: Next-generation sequencing of tumor biopsy samples (see separate Excel file)**

**Supplementary Table 8: Copy number variations for patients with tumor biopsy samples available (see separate Excel file)**

**Supplementary Table 9: Summary of copy number variations as assessed by polymerase chain reaction (see separate Excel file)**