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Phase I, Pharmacokinetics (PK), Pharmacodynamic (PD) Study of Lapatinib (L) in Combination With Sorafenib (S) in Patients With Advanced Refractory Solid Tumours

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Background: A large body of experimental evidence supports the relevance of ERBB-dependent and VEGF-dependent pathways in cancer pathogenesis and progression, their functional links and implications in acquired resistance to targeted therapies. Combined targeting of ERBB receptors and VEGF-dependent signaling pathways has proven to be a successful strategy in preclinical studies. L is a dual HER2/EGFR tyrosine kinase inhibitor, S is an oral multikinase inhibitor (VEGFR-2,3, PDGFR-b, Flt-3, Raf-1 and c-KIT). We conducted a phase I dose-escalation study to assess the maximum tolerated dose (MTD), safety/tolerability, PK, PD and preliminary antitumour activity of the combination of these two agents (NCT00984425).
Methods: Patients (pts) with advanced malignancies refractory to standard therapy were eligible. A traditional 3+3 dose escalation schema was employed. Dose levels (DL) were 1) L 750 mg + S 200 mg BID; 2) L 1000 mg + S 200 mg BID; 3) L 1000 mg + S 400 mg BID; 4) L 1250 mg+ S 400 mg BID. L and S were given together on a continuous schedule with a 28-day cycle. Once the MTD has been determined, additional 9 patients were enrolled in the PK part of the study and received L alone during a "running-in" period for two weeks before starting with the combined schedule.
Results: 30 pretreated pts (median 3 previous lines, range 1−6) were enrolled, M/F: 19/11, median age: 65 yrs (25−76), PS: 0/1 = 15/15. DLTs were observed in 2 pts, one at DL 2 [grade (G) 3 fatigue] and one at DL 3 (G3 rash). The MTD was reached at DL4. The most common toxicities were fatigue (64%), diarrhea (61%), anemia (61%), rash (43%), and hand-foot syndrome (29%). G3 treatment-related AEs were reported in 9 pts (32%) (anemia, fatigue, diarrhea, hyponatremia, hypokalemia, rash, LDH and phosphatase alkaline increase) and G4 AST/ALT increase in one pt. Pts received a median of 2 cycles (1−14). Among 28 evaluable pts (3 ongoing), 1 had CR (thymic cancer), 4 PR (prostate, colorectal, breast, and thymic cancers) and 12 SD (4 colorectal, 3 gastric, 2 pancreatic, 1 prostate, 1 breast, 1 bladder cancers), with a DCR of 61%. Median clinical benefit duration was 8 wks (2−43). Preliminary PK data suggest that S may alter L concentrations.
Conclusions: The combination of L + S is safe and well tolerated. L 1250 mg + S 400 mg BID is the recommended dose for phase II trials. Preliminary evidence of anticancer activity has been observed. Updated clinical and biological data will be presented at the meeting.

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A Phase I Study Evaluating GDC-0941, a Pan-phosphoinositide-3 Kinase (PI3K) Inhibitor, in Patients (pts) With Advanced Solid Tumours, Multiple Myeloma, and PIK3Ca Mutant (mt) Tumours

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Background: The PI3K-PTEN-AKT signaling pathway is deregulated in a wide variety of cancers. GDC-0941 is a potent and selective inhibitor of class I PI3K under evaluation in this phase I study of pts with refractory cancer.
Material and Methods: A 2-stage phase I study (GDC4254g) of single-agent GDC-0941 was initiated in pts with refractory cancer and ECOG performance status of 0−1. Stage 1 utilized a 3+3 escalation design to evaluate the maximum tolerated dose (MTD) in pts with advanced solid tumours. Stage 2 is an expansion phase including pts with multiple myeloma, PIK3CA mt tumours, and tumours evaluable by magnetic resonance imaging (MRI) methods. Single-dose and steady state pharmacokinetics (PK) and pharmacodynamics (PD) of oral GDC-0941 were evaluated. GDC-0941 is administered QD on a 21/28- or 28/28-day schedule. Objectives include: evaluating pS6 in paired tumour biopsies and pAKT in platelet rich plasma (PRP), evaluating the use of imaging modalities (FDG-PET and functional MRI studies), and correlating clinical activity with PIK3CA mt status and PTEN expression in tumour tissue.
Results: Forty-three pts have been enrolled in 12 cohorts (15–450 mg QD). Drug-related adverse events (AEs) reported in ⩾10% of pts were nausea, fatigue, diarrhea, vomiting, rash, dysgeusia, and decreased appetite. The MTD was exceeded at 450 mg QD on a 21/28-day dose schedule with dose-limiting toxicities of grade (g) 3 maculopapular rash in 2 pts. Other drug-related AEs ⩾g3 have been g3 fatigue, g3 neutropenia, and g4 hyperglycemia. GDC-0941 displays dose-proportional PK. Decreased levels of pAKT in PRP correlated with GDC-0941 plasma concentrations. Signs of clinical activity include a partial response (49% decrease in target lesions) by RECIST in a pt with melanoma (V600E RAF mt) treated at 330 mg for 9.5 months (mo); a small bowel GIST (cKIT exon 9 mt) pt treated at 450 mg for 7.2 mo with 49% decrease by FDG-PET and 75% decrease in pS6 IHC staining in paired tumour biopsies; and an ovarian cancer (PTEN negative) pt treated at 100 mg on study for ~5 mo with 30% decrease by FDG-PET, 56% decrease in pS6 staining in paired biopsies, and 80% decrease in CA-125.
Conclusions: GDC-0941 is generally well tolerated below 450 mg QD with signs of clinical activity. Decreases in pAKT levels in PRP and in pS6 staining in paired tumour biopsies are consistent with downstream modulation of the PI3K pathway. Final determination of the recommended phase II dose and schedule is ongoing.

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Cutaneous Manifestations of Selumetinib, a New MEK Inhibitor

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Background: Selumetinib is a potent oral MEK1/2 inhibitor tested in patients with melanomas, pancreatic and non-small cell lung cancers.
Methods: A retrospective study of the skin manifestations of all patients treated with selumetinib in France in a phase II study evaluating selumetinib versus temozolomide (N = 19).
Results: All patients except for one (18/19; 95%) presented with at least one cutaneous side effect. The spectrum of skin manifestations is close to that observed with EGFR inhibitors: follicular papulopustular rash, xerosis, hair and nail changes. Two additional symptoms, edema and erysipelatoid reactions, were observed that could be imputable to selumetinib.
Conclusion: Skin manifestations induced by selumetinib are extremely frequent with a partial overlap with those observed with anti-EGFR agents.

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Phase I Study of Pazopanib(P) Monotherapy and Conbined With Lapatinib(L) in Japanese Patients(pts) With Solid Tumours (VEG109693)

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Background: Pazopanib (Votrient®) is an oral angiogenesis inhibitor targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-kit. Lapatinib (Tykerb®/Tyverb®) is a potent inhibitor of ErbB1 and ErbB2. Several lines of evidence support the use of combined inhibition of VEGFR and ErbB in the treatment of certain malignancies. The present study was initiated to confirm recommended dose of P monotherapy and combination with L and to determine pharmacokinetics (PK) in Japanese pts.
Methods: Pts with solid tumours were enrolled. In part A (P dose escalation), dose levels were 1) 400 mg/day on day1 followed by 800 mg/day (400 → 800), 2) 800 → 800 and 3) 1000 → 1000. In part B (P+L), dose levels were 1) 400/1000 mg/day (P/L), 2) 400/1500, 3) 800/1000 and 4. 600/1250. At Part B level 4, pts received P600 or L1250 alone from day 1 to 15. From day 16, P600 in combination with L1250 was administered. DLTs and safety were evaluated in each part. PK data were obtained on days 1 and 22 of part A and days 15 and 37 of part B level 4. (NCT00516672; Trial Sponsor: GSK; Status: Concluded)
Results: No DLT was observed in part A and B. In part A, hypertension, diarrhea, rash, AST, lipase elevation and neutropenia were most frequent AEs, the majority of which were of grade 1/2. In part B, hypertension, rash, nausea, dysgeusia, anorexia, fatigue and TSH elevation were commonly observed, diarrhea was reported in all pts, the majority of which were of grade 1/2. AUC_{0-24} (μg·hr/mL) after single dose of P on day1 is shown in the table. The relation between dose and AUC was not linear and there is no difference between P800 and P1000. AUC_{0-24} on day 22 of P shown