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Title: FP1039/GSK3052230 with chemotherapy in patients with fibroblast growth factor (FGF) pathway deregulated squamous NSCLC or MPM

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Background: GSK3052230/FP1039 is a soluble fusion protein with the ECD of FGFR1c linked to the hinge and Fc regions of human IgG1 and acts as a ligand trap by sequestering FGFs involved in tumor growth and angiogenesis. In contrast to small molecule FGFR kinase inhibitors, GSK3052230 spares the hormonal FGF ligands, namely FGF19, 21 and 23. GSK3052230 combined with chemotherapy was efficacious in xenograft models of *FGFR1*-amplified NSCLC and malignant pleural mesothelioma (MPM) with FGF2 mRNA overexpression. A phase I monotherapy study determined 20mg/kg weekly as the maximum feasible dose (MFD) achieving the desired blood concentration, with no maximum tolerated dose (MTD) reached.

Methods: This study (NCT01868022 funded by GSK) will evaluate the safety and efficacy of GSK3052230 weekly infusion in combination with paclitaxel + carboplatin in previously untreated *FGFR1* amplified metastatic sqNSCLC (Arm A), in combination with docetaxel in *FGFR1* amplified metastatic sqNSCLC that has progressed after at least 1 line of chemotherapy (Arm B), or in combination with pemetrexed + cisplatin in patients with untreated and unresectable MPM (Arm C). Each arm involves a dose escalation phase utilizing the 3+3 design, followed by an expansion phase up to 30 patients (pts). Key endpoints include the MTD/MFD of GSK3052230 with chemotherapy, safety, response rates and duration.

Results: Thirty-four pts have been dosed with GSK3052230 at dose levels ranging from 5mg/kg to 20mg/kg in combination with chemotherapy across three Arms, n=15 (A), n=6 (B) and n=13 (C). Baseline characteristics: males/females 29/5; mean age 68.5 years; ECOG PS 0 (n=20), 1 (n=13), 2 (n=1). Most common AEs were: Arm A: asthenia, neutropenia; Arm B: neutropenia, diarrhea, rash; Arm C: decreased appetite, nausea, infusion reaction. Infusion reactions were seen in 8/34 (24%) pts (n=3 Grade (Gr)1, n=3 Gr2, n=2 Gr3). Serious AEs included: Arm A- neutropenia (n=4), fatigue (n=1), asthenia (n=1), fever (n=1), respiratory infection (n=1); Arm B- neutropenia (n=1), abdominal pain (n=1); Arm C-bowel perforation/ischemia (n=1), infusion reaction (n=1), elevated creatinine (n=1). No DLTs have been observed in sqNSCLC pts (Arms A and B). Three DLTs were reported in mesothelioma pts (Arm C 20mg/kg): Gr5 bowel perforation/ischemia, Gr4 elevated creatinine levels and Gr3 infusion reaction. MFD for Arm A is determined at 20mg/kg. Dose escalation is ongoing for Arms B and C. Preliminary PK results revealed no drug-drug interactions. At time of data-cutoff, 10 PR were observed among 23 patients evaluable for efficacy (ORR = 43%) and a clinical benefit rate of 78% with two ongoing subjects on study >300 days. Preliminary efficacy is as follows: Arm A (6 PR, 2 SD, 1 PD, 6= not-yet-evaluable (NE)), Arm B (4 SD, 1 PD, 1 NE), and Arm C (3 PR, 3 SD, 3 PD, 4 NE).

Conclusions: GSK3052230 is in general well tolerated in combination with chemotherapy. The MFD for GSK3052230 is 20mg/kg in combination with paclitaxel + carboplatin in first line sqNSCLC patients. Toxicities typically associated with small-molecule FGFR inhibitors, namely hyperphosphatemia and retinal, nail, and skin changes, were not observed. The initial activity and safety profile of GSK3052230warrant further study.