Study No: MEK112110

Title : An Open-Label, Dose-Escalation, Phase IB/ II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the MEK Inhibitor GSK1120212 in Combination with Oral Everolimus in Subjects with Solid Tumors

Rationale: Research using cell lines as well as cancer subjects demonstrates an interaction between the MAPK and PI3K signalling pathways. As GSK1120212 inhibits the MAPK pathway and everolimus inhibits the PI3K pathway, combining these 2 therapeutic agents could simultaneously block both pathways and thereby achieve a greater anti-tumor effect.

Phase: IB/II

Study Period: 17 Aug 2009 to 08 Nov 2011

Study Design: This was a Phase IB/II, open-label, dose-escalation, multi-center, non-randomized study. Following determination of the recommended Phase II regimen (RP2R) in the GSK1120212 and everolimus combination, a Phase IB expansion cohort in 20 subjects with pancreatic cancer was planned. However, after enrolment of 9 subjects to the pancreatic cohort, it became apparent that the dose and regimen were not optimal and dose escalation cohorts were re-opened. The study was not able to satisfactorily identify a RP2R. Therefore, Phase II of the study, which was to assess clinical activity in subjects with KRAS-mutant NSCLC at the RP2R, was not conducted

Centres: Dr Jeffrey R Infante, Sarah Cannon Research Institute, Nashville TN, and Dr Anthony Tolcher, South Texas Accelerated Research Therapeutics, San Antonio TX

Indication: Solid tumors

Treatment: GSK1120212 (0.25mg, batch numbers 081157753, 091228159, 081169933; 1mg, batch number 081169934) and everolimus (2.5mg, Lot 091235580; 5mg, Lot 091235581) were administered orally, after at least 1 hour of fasting. Fasting continued for 2 hours after dosing. Ten dose cohorts were investigated.

Daily Dosing Cohorts: Six dose escalation cohorts were explored, with both GSK1120212 and everolimus administered orally once daily

GSK1120212 Once Daily	Everolimus Once Daily	Number of Subjects
0.5mg	5mg	6
1mg	5mg	6
1mg	7.5mg	4
1.5mg	5mg	4
1.5mg	7.5mg	4
2mg	5mg	6

Pancreatic Expansion Cohort: The GSK1120212 2mg/Everolimus 5mg regimen was recommended to be used in pancreatic expansion cohort. To further reduce the incidence and severity of mucosal inflammation/stomatitis, everolimus dosing was modified to 5 days on/2 days off.

GSK1120212 Once Daily	Everolimus Once Daily for 5 Days Followed by 2 Days Off	Number of Subjects
2mg	5mg	9

Intermittent Everolimus Cohorts: Due to high occurrence of mucosal inflammation/stomatitis in the pancreatic cohort, dose escalation cohorts were re-opened.

GSK1120212 Once Daily	Intermittent Everolimus	Number of Subjects
2mg	5mg once daily for 7 days, followed by 7 days off drug	12
2mg	5mg Day 1, 3, 5 every week	12
2mg	7.5mg Day 1, 3, 5 every week	4

Objectives: The primary objective of the Phase IB part of the study was to determine the safety, tolerability and recommended Phase II dose and regimen of GSK1120212 and everolimus dosed orally in combination.

Statistical Methods: No formal statistical hypotheses were tested. Analysis was focused on comparison between dose cohorts and was descriptive and exploratory. All safety data were listed and summarized according to the GSK IDSL standards. PK analyses of plasma GSK1120212 and whole blood everolimus concentration-time data were conducted using non compartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2 (Pharsight Corporation, Sunnyvale, CA).

Study Population	Total (n=67)
Number of subjects completed as planned, n (%):	67 (100)
Reasons for subject withdrawal, n (%)	
Lack of efficacy	49 (73)
Adverse events	6 (9)
Withdrew consent	5 (7)
Investigator discretion	4 (6)
Study closed [1]	3 (4)

1. Subjects were eligible to enter the rollover study MEK114375.

Demography	Total (n=67)
Age in Years,	
Mean (SD)	57.1 (13.46)
Median (range)	61.0 (18-81)
Sex, n (%)	
Female:	36 (54)
Male:	31 (46)
Weight (kg), Mean (SD)	75.84 (14.672)
Race, n (%)	
African American/African Heritage	4 (6)
Asian – Japanese Heritage	1 (1)
White/Caucasian/European Heritage	60 (90)
White – Mixed Race	1 (1)
Mixed Race	1 (1)

Pharmacokinetics Endpoints

Summary Statistics of GSK1120212 Derived Plasma Pharmacokinetic Parameters

Treatment	N	AUC(0-t) [1] (ng*hr/mL) Geometric mean (CVb%)[2] (range)	Cmax (ng/mL) Geometric mean (CVb%)[2] (range)	tmax (hr) Median (range)
GSK 0.5 mg + EVE 5 mg	6	21.1 (33.0) (14.7 - 36.5)	4.34 (34.2) (2.6 - 6.9)	1.00 (1.0 – 4.1)
GSK 1 mg + EVE 5 mg	6	60.6 (27.4) (39.5 - 76.7)[3]	11.6 (32.2) (7.0 - 14.5)[3]	1.07 (1.0 – 6.0)[3]
GSK 1 mg + EVE 7.5 mg	4	59.6 (24.1) (47.8 - 76.6)[4]	12.3 (29.0) (10.2 - 17.1)[4]	2.03 (1.0 – 4.0)[4]
GSK 1.5 mg + EVE 5 mg	4	73.3 (49.2) (39.2 - 119)	15.2 (51.4) (8.0 - 25.4)	2.00 (1.0 – 5.3)
GSK 1.5 mg + EVE 7.5 mg	2	101 (NA) (85.9 - 119)	19.2 (NA) (15.8 - 23.4)	4.00 (4.0 – 4.0)
GSK 2 mg + EVE 5 mg	5	126 (15.4) (98.1 - 146)	26.4 (21.6) (19.4 - 32.9)	2.00 (1.0 – 4.0)
GSK 2 mg + EVE 5 mg [5D/7D] (Pancreatic)	9	89.4 (39.6) (46.9 - 164)[5]	17.2 (37.5) (8.8 - 28.2)[5]	2.02 (2.0 – 6.0) [5]
GSK 2 mg + EVE 5 mg [7D/14D]	12	99.0 (50.0) (52.1 - 223)[6]	19.2 (51.7) (9.8 - 40.5)[6]	2.07 (1.0 – 6.0)[6]
GSK 2 mg + EVE 5 mg [3xWK]	12	128 (40.3) (48.8 - 212)	26.0 (45.4) (8.5 - 41.1)	2.00 (1.0 – 4.1)
GSK 2 mg + EVE 7.5 mg [3xWK]	3	171 (16.2) (150 - 205)	32.6 (16.2) (27.6 - 38.1)	2.00 (2.0 – 4.0)

1. AUC(0-t)=AUC(0-6)
2. CVb% not provided if n=2
3. n = 5
4. n = 3
5. n = 7
6. n = 10

Summary Statistics of Everolimus Whole Blood Pharmacokinetic Parameters

Treatment	N	AUC(0-t) [1] (ng*hr/mL)	Cmax (ng/mL)	tmax (hr)

		Geometric mean (CVb%)[2] (range)	Geometric mean (CVb%)[2] (range)	Median (range)
GSK 0.5 mg + EVE 5 mg	6	154 (32.0) (101 - 209)[3]	48.1 (17.4) (39.8 - 59.1)[3]	1.00 (1.0 – 1.0)[3]
GSK 1 mg + EVE 5 mg	6	86.2 (30.3) (65.0 - 124)[3]	25.6 (43.7) (17.3 - 41.4)[3]	1.05 (1.0 – 2.0)[3]
GSK 1 mg + EVE 7.5 mg	4	182 (37.1) (138 - 309)	61.4 (54.9) (35.6 - 121)	1.50 (1.0 – 2.0)
GSK 1.5 mg + EVE 5 mg	4	144 (39.4) (98.5 - 211)[4]	47.1 (56.8) (31.8 - 85.9)[4]	1.13 (1.0 – 2.0)[4]
GSK 1.5 mg + EVE 7.5 mg	2	453 (NA) (288 - 714)	126 (NA) (93.7 - 169)	1.00 (1.0 – 1.0)
GSK 2 mg + EVE 5 mg	5	113 (26.0) (75.9 - 148)	38.5 (31.0) (27.9 - 57.3)	1.00 (1.0 – 4.0)
GSK 2 mg + EVE 5 mg [5D/7D] (Pancreatic)	9	110 (57.5) (38.9 - 161)[5]	33.3 (66.6) (10.1 - 48.4)	1.54 (1.0 – 4.0)[5]
GSK 2 mg + EVE 5 mg [7D/14D]	12	85.9 (49.7) (36.6 - 150)[6]	25.8 (70.3) (8.2 - 52.7)[6]	1.00 (1.0 – 4.0)[6]
GSK 2 mg + EVE 5 mg [3xWK]	12	82.0 (96.4) (9.8 - 233)	25.2 (132.4) (1.8 - 90.9)	1.04 (1.0 – 4.1)
GSK 2 mg + EVE 7.5 mg [3xWK]	3	181 (26.0) (137 - 227)	50.0 (41.0) (35.3 - 76.6)	1.98 (1.0 – 2.0)

1. AUC(0-t)=AUC(0-6).
2. CVb% not provided if n=2.
3. n = 4
4. n = 3
5. n = 6
6. n = 9

Safety results: AE and SAE data were collected from the start of the investigational product, and continued until the Final Study Visit.											
	GSK 0.5mg EVE 5mg (n=6)	GSK 1mg EVE 5mg (n=6)	GSK 1mg EVE 7.5mg (n=4)	GSK 1.5mg EVE 5mg (n=4)	GSK 1.5mg EVE 7.5mg (n=4)	GSK 2mg EVE 5mg (n=6)	GSK 2mg EVE 5mg 5D/7D Pancreatic (n=9)	GSK 2mg EVE 5mg 7D/14D (n=12)	GSK 2mg EVE 5mg 3xWK (n=12)	GSK 2mg EVE 7.5mg 3xWK (n=4)	Total (n=67)
Any AE	6 (100)	6 (100)	4 (100)	4 (100)	4 (100)	6 (100)	9 (100)	12 (100)	12 (100)	4 (100)	67 (100)
Most Frequent AEs (reported by at least 2 subjects in any group):											
Fatigue	4 (67)	4 (67)	2 (50)	2 (50)	3 (75)	5 (83)	4 (44)	9 (75)	5 (42)	3 ((75)	41 (61)
Diarrhea	2 (33)	3 (50)	1 (25)	1 (25)	4 (100)	2 (33)	7 (78)	3 (25)	6 (50)	1 (25)	30 (45)
Mucosal inflammation	2 (33)	2 (33)	1 (25)	2 (50)	2 (50)	2 (33)	3 (33)	7 (58)	5 (42)	2 (50)	28 (42)
Nausea	3 (50)	2 (33)	0	1 (25)	4 (100)	3 (50)	5 (56)	4 (33)	4 (33)	1 (25)	27 (40)
Vomiting	3 (50)	0	1 (25)	0	3 (75)	3 (50)	6 (67)	5 (42)	2 (17)	2 (50)	25 (37)
Pyrexia	1 (17)	3 (50)	0	1 (25)	2 (50)	2 (33)	2 (22)	6 (50)	2 (17)	1 (25)	20 (30)
Decreased appetite	2 (33)	2 (33)	1 (25)	0	3 (75)	1 (17)	3 (33)	4 (33)	3 (25)	0	19 (28)
Dermatitis acneiform	0	3 (50)	3 (75)	2 (50)	1 (25)	2 (33)	2 (22)	1 (8)	3 (25)	1 (25)	18 (27)
Constipation	2 (33)	2 (33)	0	1 (25)	2 (50)	2 (33)	2 (22)	4 (33)	1 (8)	1 (25)	17 (25)
Stomatitis	1 (17)	2 (33)	1 (25)	0	1 (25)	2 (33)	4 (44)	3 (25)	3 (25)	0	17 (25)
Dry skin	2 (33)	2 (33)	0	1 (25)	0	1 (17)	0	4 (33)	5 (42)	0	15 (22)
Edema peripheral	0	3 (50)	1 (25)	1 (25)	0	1 (17)	4 (44)	3 (25)	2 (17)	0	15 (22)
Pruritis	0	2 (33)	1 (25)	2 (50)	0	0	0	3 (25)	6 (50)	1 (25)	15 (22)
Rash	2 (33)	0	0	0	0	0	5 (56)	3 (25)	3 (25)	2 (50)	15 (22)
Exfoliative rash	0	2 (33)	0	0	1 (25)	2 (33)	0	3 (25)	5 (42)	0	13 (19)
Cough	2 (33)	3 (50)	0	0	2 (50)	0	0	2 (17)	3 (25)	0	12 (18)
Anemia	0	3 (50)	0	1 (25)	1 (25)	1 (17)	2 (22)	3 (25)	0	0	11 (16)
Dizziness	1 (17)	0	1 (25)	0	1 (25)	0	3 (33)	0	3 (25)	0-	9 (13)
Epistaxis	0	1 (17)	0	1 (25)	1 (25)	0	3 (33)	1 (8)	1 (8)	1 (25)	9 (13)
Abdominal pain	0	0	1 (25)	0	1 (25)	3 (50)	0	2 (17)	0	1 (25)	8 (12)
Asthenia	1 (17)	1 (17)	0	0	1 (25)	0	2 (22)	2 (17)	1 (8)	0	8 (12)
Chills	0	0	0	0	2 (50)	1 (17)	2 (22)	2 (17)	1 (8)	0	8 (12)
Dehydration	0	1 (17)	0	1 (25)	2 (50)	1 (17)	1 (11)	2 (17)	0	0	8 (12)
Dry mouth	0	0	1 (25)	1 (25)	1 (25)	0	2 (22)	2 (17)	1 (8)	0	8 (12)
Dyspnea	2 (33)	1 (17)	0	0	0	0	3 (33)	1 (8)	1 (8)	0	8 (12)
Acne	3 (50)	0	0	1 (25)	1 (25)	1 (17)	0	1 (8)	0	0	7 (10)

Aspartate aminotransferase increased	1 (17)	0	0	0	0	0	1 (11)	1 (8)	3 (25)	1 (25)	7 (10)
Hypokalemia	1 (17)	0	1 (25)	0	1 (25)	0	2 (22)	1 (8)	0	1 (25)	7 (10)
Oral pain	0	3 (50)	0	0	0	1 (17)	0	1 (8)	1 (8)	0	6 (9)
Pneumonia	0	2 (33)	0	0	1 (25)	0	2 (22)	0	0	0	5 (7)
Skin fissures	0	0	1 (25)	0	0	0	1 (11)	1 (8)	2 (17)	0	5 (7)
Urinary tract infection	0	0	1 (25)	0	0	0	1 (11)	1 (8)	2 (17)	0	5 (7)
Alanine aminotransferase increased		0	0	0	0	0	0	1 (8)	2 (17)	0	4 (6)
Alopecia	0	0	0	0	0	0	1 (11)	0	3 (25)	0	4 (6)
Blood bilirubin increased	0	0	0	0	0	0	1 (11)	0	3 (25)	0	4 (6)
Muscular weakness	0	0	0	0	0	0	2 (22)	2 (17)	0	0	4 (6)
Pain		0	0	0	0	0	0	1 (8)	0	2 (50)	4 (6)
Anxiety	0	0	0	0	0	0	0	1 (8)	0	2 (50)	3 (4)
Dysphagia	0	0	0	0	0	0	0	1 (8)	2 (17)	0	3 (4)
Face edema	0	1 (17)	0	0	0	0	2 (22)	0	0	0	3 (4)
Hyperhidrosis	0	0	0	1 (25)	0	0	0	2 (17)	0	0	3 (4)
Neuropathy peripheral	0	1 (17)	0	0	0	2 (33)	0	0	0	0	3 (4)
Sinus congestion	0	0	0	0	0	0	1 (25)	0	2 (17)	0	3 (4)
Syncope	0	0	0	1 (8)	0	2 (33)	0	0	0	0	3 (4)
Abdominal distension	0	0	0	2 (17)	0	0	0	0	0	0	2 (3)
Malaise	0	0	2 (22)	0	0	0	0	0	0	0	2 (3)
Pulmonary embolism	0	0	0	0	0	0	0	0	2 (17)	0	2 (3)

Deaths: A total of 6 subjects died. None of the deaths were considered related to study drugs.											
	GSK 0.5mg EVE 5mg (n=6)	GSK 1mg EVE 5mg (n=6)	GSK 1mg EVE 7.5mg (n=4)	GSK 1.5mg EVE 5mg (n=4)	GSK 1.5mg EVE 7.5mg (n=4)	GSK 2mg EVE 5mg (n=6)	GSK 2mg EVE 5mg 5D/7D Pancreatic (n=9)	GSK 2mg EVE 5mg 7D/14D (n=12)	GSK 2mg EVE 5mg 3xWK (n=12)	GSK 2mg EVE 7.5mg 3xWK (n=4)	Total (n=67)
Primary cause of death											
Disease under study	0	0	0	0	0	0	0	1 (8)	3 (25)	0	4 (6)
Gastrointestinal hemorrhage	0	0	0	0	0	0	1 (11)	0	0	0	1 (1)
Pneumonia	0	0	0	0	0	0	1 (11)	0	0	0	1 (1)
Time from last dose											
≤28 days	0	0	0	0	0	0	2 (22)	1 (8)	2 (17)	0	5 (7)
>28 days	0	0	0	0	0	0	0	0	1 (9)	0	1 (1)
Serious Adverse Events: Serious adverse events reported by at least 2 subjects in the study are listed below. All 3 occurrences of mucosal inflammation were considered to be related to study drugs. Other SAEs considered related to study drugs were reported for 1 subject each, and were alanine aminotransferase increased, blood bilirubin increased, dehydration, diarrhea, hypokalemia, nausea, pancreatitis, pyrexia, thrombocytopenia, and vomiting.											
	GSK 0.5mg EVE 5mg (n=6)	GSK 1mg EVE 5mg (n=6)	GSK 1mg EVE 7.5mg (n=4)	GSK 1.5mg EVE 5mg (n=4)	GSK 1.5mg EVE 7.5mg (n=4)	GSK 2mg EVE 5mg (n=6)	GSK 2mg EVE 5mg 5D/7D Pancreatic (n=9)	GSK 2mg EVE 5mg 7D/14D (n=12)	GSK 2mg EVE 5mg 3xWK (n=12)	GSK 2mg EVE 7.5mg 3xWK (n=4)	Total (n=67)
Any SAE	0	4 (67)	1 (25)	1 (25)	3 (75)	2 (33)	4 (44)	3 (25)	4 (33)	0	22 (33)
Any SAE Reported by Two or More Subjects:											
Pneumonia	0	2 (33)	0	0	1 (25)	0	1 (11)	0	0	0	4 (6)
Mucosal inflammation	0	1 (17)	0	0	1 (25)	0	0	1 (8)	0	0	3 (4)
Gastrointestinal hemorrhage	0	0	0	0	0	1 (17)	1 (11)	0	0	0	2 (3)
Pyrexia	0	1 (17)	0	0	0	0	0	1 (8)	0	0	2 (3)
Vomiting	0	0	0	0	1 (25)	0	1 (11)	0	0	0	2 (3)