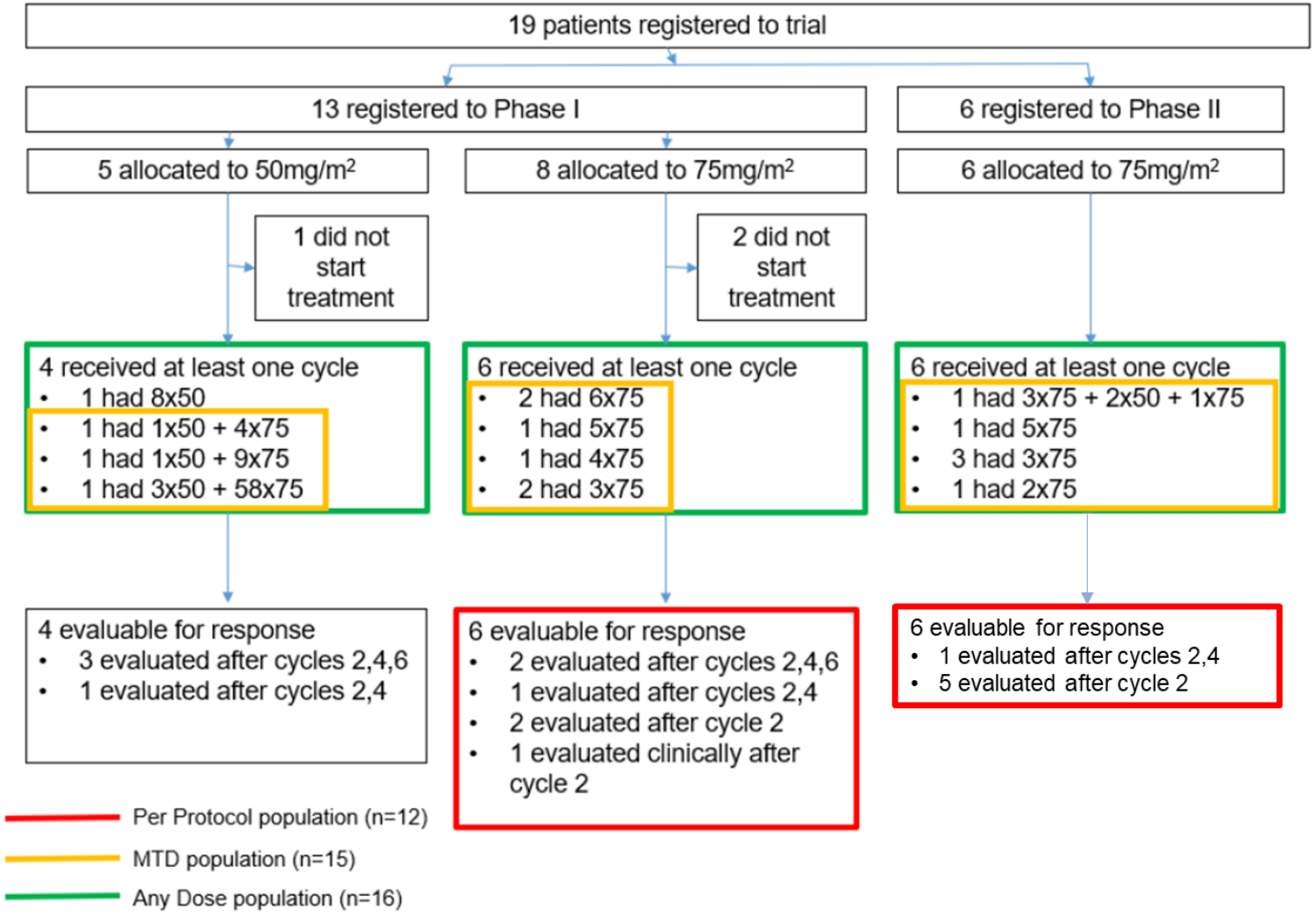
1. Participant Flow



2. Baseline Characteristics

Table 1: Baseline Characteristics

Characteristic		Dose Allocation 50 mg b.d.	75 mg b.d.	Overall
N		4	12	16
Age (years)				
	Mean	50.3	44.0	45.6
	Sd	9.9	6.8	7.9
	Median	48.7	43.2	44.4
	Range	39.9, 63.7	33.7, 56.4	33.7, 63.7
Sex (N (%))				
	Male	4 (100)	11 (91.7)	15 (93.8)
	Female	0	1 (8.3)	1 (6.3)
Ethnicity (N (%))				
	Caucasian	3 (75)	9 (75)	12 (75)
	Black - African	1 (25)	2 (16.7)	3 (18.8)
	Mixed	0	1 (8.3)	1 (6.3)
Height (cm)				
	Mean	172.8	173.2	173.1
	Sd	11.6	10.1	10.1
	Median	168.0	176.5	173.0
	Range	165.0, 190.0	154.0, 184.0	154.0, 190.0
Weight (Kg)				
	Mean	87.3	77.7	80.1
	Sd	24.6	15.7	17.9
	Median	76.8	73.9	74.9
	Range	71.5, 124.0	55.7, 100.4	55.7, 124.0
Photographic Assessment Lesion Grade (N (%))				
	More Than 0 Less Or Equal To 10 Lesions	1 (25)	2 (16.7)	3 (18.8)
	More Than 10 Less Or Equal To 50 Lesions	2 (50)	7 (58.3)	9 (56.3)
	More Than 50 Lesions	1 (25)	2 (16.7)	3 (18.8)
	Missing Data	0	1 (8.3)	1 (6.3)
WHO Performance Status (N (%))				
	0	3 (75)	10 (83.3)	13 (81.2)
	1	1 (25)	1 (8.3)	2 (12.5)
	2	0	1 (8.3)	1 (6.3)

3. Outcome Measures

3.1 Primary Outcome

3.1.1 Phase I Determination of the Maximum Tolerated Dose (MTD)

Table 2: Dose decision information for each patient recruited to phase I of SCART

Cohort	Dose Allocated	Date Registered	Included	DLT
1	50mg b.d.	21-Aug-2012	No	N/A
		17-Sep-2012	Yes	No
		19-Sep-2012	Yes	No
		25-Sep-2012	Yes	No
		31-Oct-2012	Yes	No
2	75mg b.d.	02-Nov-2012	No	N/A
		21-Dec-2012	Yes	No
		19-Mar-2013	Yes	No
		30-Apr-2013	No	N/A
		21-Jun-2013	Yes	Yes
2 Expansion	75mg b.d.	29-Aug-2013	Yes	No
		29-Aug-2013	Yes	No
		04-Dec-2013	Yes	No

Each row of the table represents an individual patient.

3.1.2 Phase I Highly Active Anti-Retroviral Therapy (HAART) Drug Levels

Table 3: Percentage changes in patients antiviral concentrations measured from Cycle 1 Day 1 to Cycle 1 Day 15 and Cycle 5 Day 1

Drug	Time Point	Concentration (ng/ml)	% Change
Efavirenz	Cycle 1 Day 1	4545	
	Cycle 1 Day 15	4180	-8.0
	Cycle 5 Day 1	6257	37.7
Emtricitabine	Cycle 1 Day 1	331	
	Cycle 1 Day 15	335	1.2
	Cycle 5 Day 1	375	13.3
Tenofovir	Cycle 1 Day 1	90	
	Cycle 1 Day 15	51	-43.3
	Cycle 5 Day 1	55	-38.9
Darunavir	Cycle 1 Day 1	1674	
	Cycle 1 Day 15	7690	359.4
Emtricitabine	Cycle 1 Day 1	55	
	Cycle 1 Day 15	203	269.1
Ritonavir	Cycle 1 Day 1	94	

	Cycle 1 Day 15	246	161.7
Tenofovir	Cycle 1 Day 1	15	
	Cycle 1 Day 15	43	186.7
Darunavir	Cycle 1 Day 1	7284	
	Cycle 1 Day 15	4208	-42.2
	Cycle 5 Day 1	7628	4.7
Emtricitabine	Cycle 1 Day 1	1586	
	Cycle 1 Day 15	1935	22.0
	Cycle 5 Day 1	2281	43.8
Ritonavir	Cycle 1 Day 1	516	
	Cycle 1 Day 15	462	-10.5
	Cycle 5 Day 1	328	-36.4
Tenofovir	Cycle 1 Day 1	133	
	Cycle 1 Day 15	234	75.9
	Cycle 5 Day 15	230	72.9
Lopinavir	Cycle 1 Day 1	8366	
	Cycle 1 Day 15	8715	4.2
	Cycle 5 Day 1	11555	38.1
Ritonavir	Cycle 1 Day 1	Not provided	
	Cycle 1 Day 15	575	
	Cycle 5 Day 1	566	
Atazanavir	Cycle 1 Day 1	758	
	Cycle 1 Day 15	5797	664.8
Emtricitabine	Cycle 1 Day 1	437	
	Cycle 1 Day 15	837	91.5
Ritonavir	Cycle 1 Day 1	364	
	Cycle 1 Day 15	1585	335.4
Tenofovir	Cycle 1 Day 1	130	
	Cycle 1 Day 15	239	125.4
Darunavir	Cycle 1 Day 1	3487	
	Cycle 1 Day 15	9048	159.5
	Cycle 5 Day 1	6164	76.8
Emtricitabine	Cycle 1 Day 1	492	
	Cycle 1 Day 15	489	-0.6
	Cycle 5 Day 1	453	-7.9
Ritonavir	Cycle 1 Day 1	342	
	Cycle1 Day 15	564	64.9
	Cycle 5 Day 1	431	26.0
Tenofovir	Cycle 1 Day 1	90	
	Cycle 1 Day 15	40	-55.6
	Cycle 5 Day 15	143	58.9
Emtricitabine	Cycle 1 Day 1	577	
	Cycle 1 Day 15	755	30.8
	Cycle 5 Day 1	646	12.0
Lopinavir	Cycle 1 Day 1	9586	
	Cycle 1 Day 15	8050	-16.0
	Cycle 5 Day 1	9296	-3.0
Tenofovir	Cycle 1 Day 1	84	

	Cycle 1 Day 15	123	46.4
	Cycle 5 Day 1	135	60.7
Abacavir	Cycle 1 Day 1	1060	
	Cycle 1 Day 15	246	-76.8
Efavirenz	Cycle 1 Day 1	3378	
	Cycle 1 Day 15	3139	-7.1
Lamivudine	Cycle 1 Day 1	817	
	Cycle 1 Day 15	512	-37.3
Emtricitabine	Cycle 1 Day 1	16	
	Cycle 5 Day 1	960	5900
Maraviroc	Cycle 1 Day 1	46	
	Cycle 1 Day 15	183	297.8
	Cycle 5 Day 1	157	241.3
Tenofovir	Cycle 1 Day 1	60	
	Cycle 5 Day 1	104	73.3
Emtricitabine	Cycle 1 Day 1	272	
	Cycle 1 Day 15	214	-21.3
Raltegravir	Cycle 1 Day 1	65	
	Cycle 1 Day 15	1413	2073.8
Tenofovir	Cycle 1 Day 1	30	
	Cycle 1 Day 15	46	53.3

Each row of the table separated by a line represents an individual patient.

3.1.3 Phase I Pharmacokinetic data

Table 4: Selumetinib serum levels during Cycle 1

Dose	Day 1 Pre-Dose	2 Hours Post Dose	6 Hours Post Dose	Day 15 Pre-Dose
50 mg b.d	BLQ	201	26.5	36.7
50 mg b.d	BLQ	274	98.1	98.1
50 mg b.d	BLQ	304	48.5	124.0
50 mg b.d	BLQ	238	47.9	148.0
75 mg b.d	BLQ	247	452.0	302.0
75 mg b.d	BLQ	504	66.1	374.0
75 mg b.d	BLQ	1250	180.0	391.0
75 mg b.d	BLQ	1040	Not provided	113.0
75 mg b.d	BLQ	361	284.0	43.5
75 mg b.d	BLQ	1280	249.0	121.0

BLQ, below the level of quantification

Each row of the table represents an individual patient.

Table 5: N-Desmethyl serum levels during Cycle 1

Dose	Day 1 Pre-Dose	2 Hours Post Dose	6 Hours Post Dose	Day 15 Pre-Dose
50 mg b.d	BLQ	5.42	2.0	2.0
50 mg b.d	BLQ	15.8	10.0	6.5
50 mg b.d	BLQ	31.7	5.7	12.0
50 mg b.d	BLQ	34.8	6.2	17.2
75 mg b.d	BLQ	20.2	33.8	23.8
75 mg b.d	BLQ	40.8	5.0	17.2
75 mg b.d	BLQ	40.6	6.0	2.1
75 mg b.d	BLQ	26.7	Not provided	4.8
75 mg b.d	BLQ	10.5	9.3	2.0
75 mg b.d	BLQ	51.9	14.6	6.2

BLQ, below the level of quantification

Each row of the table represents an individual patient.

3.1.4 Phase II Objective Response

Table 6: Best responses recorded during the first 6 treatment cycles for each separately defined patient population for analyses.

Analysis Population (N (%))	Best Response			
	PR	SD	PD	Overall
Per Protocol	1 (9.09)	8 (72.73)	2 (18.18)	11 (100.0)
MTD	1 (7.14)	11 (78.57)	2 (14.29)	14 (100.0)
Any Dose	1 (6.67)	11 (73.33)	3 (20.0)	15 (100.0)

Per Protocol Population: - defined as the response evaluable Phase II patients (including those eligible from Phase I) that started selumetinib at the MTD and received at least one cycle.
MTD Population: - defined as patients from both Phase I and Phase II that have received Selumetinib at the MTD for at least one cycle.
Any Dose Population/Safety Population: - defined as the patients from both Phase I and II that received at least one dose of Selumetinib at any level.

3.2 Secondary Outcomes

3.2.1 Progression Free Survival Time (PFS)

Table 7: Progression free survival time (PFS) estimates with 90% confidence interval (CI) for the per protocol patient population.

PFS (months)	PFS Probability	PFS 90% CI
3	0.5714	(0.3051, 0.7618)
6	0.3810	(0.1553, 0.6065)

Table 8: Progression free survival time (PFS) estimates with 90% confidence interval (CI) for the MTD patient population.

PFS (months)	PFS Probability	PFS 90% CI
3	0.6600	(0.4170, 0.8209)
6	0.4400	(0.2227, 0.6384)

Table 9: Progression free survival time (PFS) estimates with 90% confidence interval (CI) for the any dose patient population.

PFS (months)	PFS Probability	PFS 90% CI
3	0.6185	(0.3876, 0.7843)
6	0.4123	(0.2080, 0.6069)

3.2.2 Tumour Size Response

Table 10: Any treatment dose patient population recorded tumour area size (mm^2) per visit.

Tumour Area Size (mm^2)	Visit Cycle 2	Cycle 4	Cycle 6
N	14	8	4
Mean	543.0	697.1	476.0
S.D.	483.5	527.5	438.7
Median	426.5	583.0	436.0
Range	21.0, 1725.0	77.0, 1660.0	78.0, 954.0

3.2.3 Nodularity Responses

Evaluation of nodularity (cutaneous lesions only):
1 = Greater than or equal to a 50% of raised lesions have become flat compared to baseline or best response.
2 = Greater than or equal to a 25% increase in the number of raised lesions compared to baseline or best response (minimum of 5 raised lesions).
3 = None of the above.

Table 11: Any dose of treatment the patient population recorded nodularity occurrences by category per visit.

Nodularity Categories (N (%))	Visit Cycle 2	Cycle 4	Cycle 6
1	2 (12.5)	0 (0.0)	0 (0.0)
2	1 (6.3)	0 (0.0)	0 (0.0)
3	12 (75.0)	8 (80.0)	5 (83.3)
No data	1 (6.3)	2 (20.0)	1 (16.7)
Total	16 (100.0)	10 (100.0)	6 (100.0)

3.2.4 Oedema Responses

Evaluation of oedema (cutaneous lesions only):
1 = A resolution of all tumour-associated oedema.
2 = No significant increase in tumour-associated oedema compared to baseline or best response.
3 = Significant increase in tumour-associated oedema compared to baseline or best response.
4 = New tumour-associated oedema compared to baseline or best response.
5 = None of the above

Table 12: Any treatment dose patient population recorded oedema severity by category per visit.

Oedema Categories (N (%))	Visit Cycle 2	Cycle 4	Cycle 6
1	2 (12.5)	2 (20.0)	0 (0.0)
2	8 (50.0)	2 (20.0)	0 (0.0)
5	5 (31.3)	4 (40.0)	4 (66.7)
No data	1 (6.3)	2 (20.0)	2 (33.3)
Total	16 (100.0)	10 (100.0)	6 (100.0)

3.2.5 Pharmacodynamic Measures of Selumetinib in Combination with HAART

Assessed by (i) serum concentrations of angiogenesis markers including serum Ang-2, IL-6 and VEGF assessed by ELISA pre-study and on weeks 3, 6, 12 and 18 and (ii) biopsies taken at pre-study and at week 6 to assess pERK levels in tumour tissue and other downstream markers including c-myc, c-fos, changes in apoptosis markers such as Bad and Bcl-2, and adaptive changes in PI3K/Akt and other MAPK pathways such as JNK and p38.

Data not provided.

3.2.6 HIV-1 Viral Load

Table 13: Any dose population patient HIV-1 load (copies/ml) and corresponding percentage change from screening level (baseline), n (%).

Cycles Done	Screening HIV-1 Load, Change %	Pre-Treatment HIV-1 Load, % Change	Cycle1 Day22 HIV-1 Load, % Change	Cycle2 Day22 HIV-1 Load, % Change	Cycle4 Day22 HIV-1 Load, % Change	Cycle6 Day22 HIV-1 Load, % Change	Largest % Decrease	Largest % Increase
11	40	40;0	40;0	40;0	40;0	40;0	40;0	40;0
61	40			40;0	40;0	40;0	20;-50	270;575
5	40	40;0	40;0	40;0	40;0		40;0	40;0
8	40	40;0	75;87.5	40;0	40;0	40;0	40;0	75;87.5
6	40	40;0		40;0	40;0	40;0	40;0	40;0
6	40	40;0	40;0	40;0	40;0	40;0	40;0	40;0
4	40	40;0	40;0	40;0			40;0	40;0
3	40	40;0	40;0				40;0	40;0
2	108	62;-42.6	40;-62.9	59;-45.4			40;-62.9	108;0
3	40	40;0		40;0			40;0	40;0
3	40	40;0	40;0	40;0			40;0	40;0
5	40	40;0	40;0	40;0	40;0		40;0	40;0
2	40	40;0		40;0			40;0	40;0
6	40	40;0	40;0	80;100	40;0		40;0	80;100

N.B. The minimum and maximum levels recorded have been included for completeness, however, these readings were recorded in treatment continuation cycles outside of the six initial treatment cycles.

Each row of the table represents an individual patient.

3.2.7 CD4 Count Results

Table 14: Any dose patient population CD4 cell count (cells/mm3) and corresponding percentage change from screening level.

Cycles Done	Screening	Pre-Treatment	Cycle 3 Day 22	Cycle 6 Day 22	Largest % decrease	Largest % increase
11	215	190;-11.6	160;-25.6	183;-14.9	160;-25.6	215;0
61	260		353;35.8	395;51.9	167;-35.8	395;51.9
5	581	481;-17.2	911;56.8		481;-17.2	911;56.8
8	956	1108;15.9	1268;32.6	1151;20.4	956;0	1268;32.6
6	702	779;10.9	991;41.2	812;15.7	702;0	991;41.2
6	273	273;0	444;62.6	465;70.3	273;0	465;70.3
5	481	537;11.6	718;49.3		481;0	718;49.3
3	99	118;19.2			99;0	118;19.2
4	377	377;0	770;104.244		377;0	770;104.244
3	529	529;0			529;0	529;0
3	458	373;-18.5	391;-14.6		373;-18.5	458;0
5	558	558;0	757;35.7		558;0	757;35.7
2	371	371;0			371;0	371;0
6	834	1037;24.3	706;-15.3	1150;37.9	706;-15.3	1150;37.9

N.B. CD4 data for two patients were not obtained. The minimum and maximum levels recorded have been included for completeness.

Each row of the table represents an individual patient.

4. Adverse Events

Table 15: Adverse events by CTCAE v4.0 category and grade

	CTCAE Grade				
Adverse Event Category (N (%))	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Overall**
Blood and lymphatic system disorders	5 (1.6)	1 (1.8)	1 (10.0)	0 (0.0)	7 (1.9)
Cardiac disorders	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	9 (3.0)	3 (5.3)	0 (0.0)	0 (0.0)	12 (3.2)
Gastrointestinal disorders	47 (15.5)	13 (22.8)	0 (0.0)	0 (0.0)	60 (16.1)
General disorders and administration site conditions	33 (10.9)	5 (8.8)	1 (10.0)	0 (0.0)	39 (10.5)
Infections and infestations	3 (1.0)	6 (10.5)	1 (10.0)	0 (0.0)	10 (2.7)
Injury, poisoning and procedural complications	2 (0.7)	3 (5.3)	0 (0.0)	0 (0.0)	5 (1.3)
Investigations	133 (43.8)	7 (12.3)	4 (40.0)	0 (0.0)	144 (38.7)
Metabolism and nutrition disorders	13 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	13 (3.5)
Musculoskeletal and connective tissue disorders	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.1)
Nervous system disorders	7 (2.3)	0 (0.0)	0 (0.0)	1 (100.0)	8 (2.2)
Psychiatric disorders	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.8)
Renal and urinary disorders	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Respiratory, thoracic and mediastinal disorders	11 (3.6)	2 (3.5)	0 (0.0)	0 (0.0)	13 (3.5)
Skin and subcutaneous tissue disorders	29 (9.5)	17 (29.8)	3 (30.0)	0 (0.0)	49 (13.2)
Vascular disorders	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Total	**304 (100)**	**57 (100)**	**10 (100)**	**1 (100)**	**372 (100)**

Table 16: Serious Adverse Events category, outcome, and expectedness information by dose allocation

	Dose Allocation		
	50 mg b.d.	**75 mg b.d.**	**Overall**
Serious Adverse Event Category (N (%))			
Unrelated SAE	0	1	1
SAR	0	2	2
Total	**0**	**3**	**3**
Outcome (N (%))			
Resolved – no sequelae	0	2	2
Unresolved	0	1	1
Total	**0**	**3**	**3**
Expectedness (N (%))			
Yes	0	2	2
N/A	0	1	1
Total	**0**	**3**	**3**

SAE, serious adverse event; SAR, serious adverse reaction.