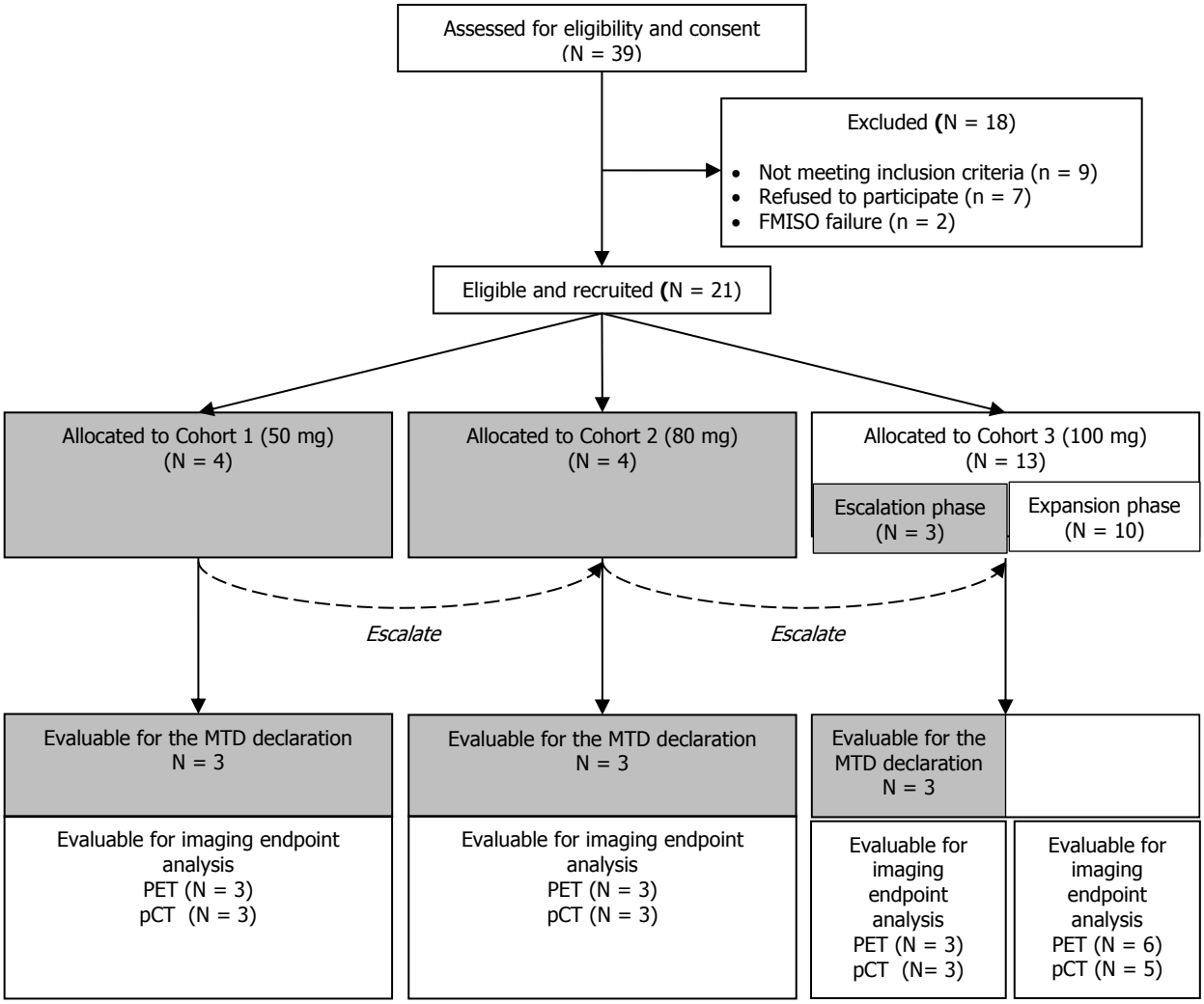
A CR-UK phase I study of BKM120 in patients with non-small cell lung cancer (NSCLC) receiving thoracic radiotherapy
ISRCTN04813360

1. PARTICIPANT FLOW

Figure 1: CONSORT Flow Diagram



2. BASELINE CHARACTERISTICS

Table 1: Baseline Characteristics

Characteristics	Dose escalation phase			Expansion Cohort (n=10)	Total (n = 21)
	Cohort 1 (n = 4)	Cohort 2 (n = 4)	Cohort 3 (n = 3)		
	% (n)[1] or median (min-max)[1]				
Age [years]	64 (58 – 77)	72 (63 – 75)	68 (68 – 72)	68 (52- 78)	69 (52 – 78)
Sex					
Male	50% (2)	50% (2)	33% (1)	20% (2)	33% (7)
Female	50% (2)	50% (2)	67% (2)	80% (8)	67% (14)
TNM stage					
IV	100 (4)	100 (4)	100 (3)	100 (10)	100 (21)
Gross tumour volume*	111 (13 – 510)	135 (29 – 204)	54 (40 – 219)	99 (8 – 250)	101 (8 – 510)
Histology					
Adenocarcinoma	75 (3)	25 (1)	33 (1)	60 (6)	52 (11)

Characteristics	Dose escalation phase			Expansion Cohort (n=10)	Total (n = 21)
	Cohort 1 (n = 4)	Cohort 2 (n = 4)	Cohort 3 (n = 3)		
Squamous cell	25 (1)	75 (3)	67 (2)	40 (4)	48 (10)
Prior chemotherapy treatment					
No	50 (2)	50 (2)	67 (2)	30 (3)	43 (9)
Prior surgical treatment					
No	100 (4)	100 (4)	100 (3)	40 (4)	71 (15)
Prior extra thoracic radiotherapy treatment					
No	100 (4)	75 (3)	100 (3)	70 (7)	81 (17)

[1] Percentage/median calculated over the total of patients per cohort
* Gross tumour volume data was only available for patients evaluable in the imaging analysis

3. OUTCOME MEASURES

Primary Analysis

Table 2: Summary result of the primary dose escalation analysis

No. of patients registered	Dose level (Cohort no.)	No. of patients treated with that dose level	No. of DLTs observed (evaluable patients with DLTs)	No. of patients without DLTs observed	
				No. of evaluable patients	No. of non-evaluable patients
11	50mg (C1)	4	0	3	1
	80mg (C2)	4	0	3	1
	100mg (C3)	3	0	3	0
Total		11	0	9	2

For further safety data, please refer to Section 4.

Secondary Analysis

Table 3: Responders by Cohort

Arm/Group Title	Dose Escalation Phase: Cohort 1	Dose Escalation Phase: Cohort 2	Dose Escalation Phase: Cohort 3 and Dose Expansion Phase
Overall Number of Participants Analysed	3	3	8
Responder	2 66.67%	0 0%	8 100%
Non-Responder	1 33.33%	3 100%	5

Table 4: 18-FMISO PET results

Arm/Group Title	Dose Escalation Phase: Cohort 1	Dose Escalation Phase: Cohort 2	Dose Escalation Phase: Cohort 3 and Dose Expansion Phase
Overall Number of Participants Analysed	3	3	9
Median (Inter-Quartile Range) Unit of Measure: TBRvolume			
First scan	44.4 (0.4 to 239)	51.3 (1.3 to 99.5)	33.1 (6.9 to 43.7)
Second scan	47.6 (0.4 to 233)	42.2 (1.1 to 75.6)	25.4 (4.9 to 42.0)
% change	7.1 (-2.5 to 14.3)	-17.6 (-24.1 to 16.7)	-19.9 (-41.9 to 14.6)

Table 5: pCT results

Arm/Group Title	Dose Escalation Phase: Cohort 1	Dose Escalation Phase: Cohort 2	Dose Escalation Phase: Cohort 3 and Dose Expansion Phase
Overall Number of Participants Analysed	3	3	8
Median (Inter-Quartile Range) Unit of Measure: mL/100g/min or mL/100g			
pCT blood flow 1st scan	64.2 (42 to 88.4)	102.2 (55.8 to 106.2)	63.9 (51.4 to 92.9)
pCT blood flow 2nd scan	60.2 (42.6 to 118.5)	-17.5 (-35.1 to 11.0)	-11.9 (-19.1 to 1.4)
pCT blood flow % change	1.4 (-6.2 to 34.0)	-17.5 (-35.1 to 11.0)	-15.0 (-33.7 to 16.7)
pCT blood volume 1st scan	4.0 (3.6 to 9.0)	6.5 (4.0 to 7.2)	5.8 (4.3 to 7.5)
pCT blood volume 2nd scan	3.8 (2.6 to 8.0)	4.7 (3.0 to 6.2)	5.6 (3.2 to 5.9)
pCT blood volume %	-11.1 (-27.8 to 5.0)	-25.0 (-34.7 to 4.6)	-21.2 (-46.3 to 6.2)

change			

Exploratory Analysis

Table 6: PRAS40 results

Arm/Group Title	Dose Escalation Phase: Cohort 1	Dose Escalation Phase: Cohort 2	Dose Escalation Phase: Cohort 3 and Dose Expansion Phase
Overall Number of Participants Analysed	3	3	9
Positive	2 66.67%	3 100%	4 44.44%
Negative	0 0%	0 0%	0 0%
Insufficient tissue	1 33.33%	0 0%	5

Table 7: Tumour PTEN level results

Arm/Group Title	Dose Escalation Phase: Cohort 1	Dose Escalation Phase: Cohort 2	Dose Escalation Phase: Cohort 3 and Dose Expansion Phase
Overall Number of Participants Analysed	2	3	4
Positive	1 50%	3 100%	3 75%
Negative	1 50%	0 0%	1 25%

pAKT data was not obtained due to the intra- and inter- patient variability seen on staining.

4. ADVERSE EVENTS

Table 8: Serious Adverse Events

	Dose Escalation Phase: Cohort 1		**Dose Escalation Phase: Cohort 2**		**Dose Escalation Phase: Cohort 3 and Dose Expansion Phase**	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	1/4 (25%)		2/4 (50%)		2/13 (15.38%)	
Metabolism and nutrition disorders						
Hypoalbuminaemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Respiratory, thoracic and mediastinal disorders						

Lower respiratory infection	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Lung infection	0/4 (0%)	0	1/4 (25%)	1	1/13 (7.69%)	1
Vascular disorders						
Peripheral Ischaemia	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0

Table 9: All Adverse Events

	Dose Escalation Phase: Cohort 1		Dose Escalation Phase: Cohort 2		Dose Escalation Phase: Cohort 3 and Dose Expansion Phase	
	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events	Affected / at Risk (%)	# Events
Total	4/4 (100%)		4/4 (100%)		12/13 (92.31%)	
Blood and lymphatic system disorders						
Anaemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Cardiac disorders						
Sinus Tachycardia	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Ear and labyrinth disorders						
Ear pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Eye disorders						
Diplopia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Heterophoria	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Gastrointestinal disorders						
Abdominal Pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Abdominal pain upper	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Constipation	2/4 (50%)	2	0/4 (0%)	0	4/13 (30.77%)	6
Diarrhoea	1/4 (25%)	2	0/4 (0%)	0	1/13 (7.69%)	1
Dyspepsia	0/4 (0%)	0	1/4 (25%)	1	1/13 (7.69%)	2

Dysphagia	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Nausea	2/4 (50%)	2	0/4 (0%)	0	3/13 (23.08%)	4
Stomatitis	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Vomiting	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
General disorders						
Chest Pain	3/4 (75%)	3	0/4 (0%)	0	1/13 (7.69%)	1
Fatigue	3/4 (75%)	3	3/4 (75%)	5	10/13 (76.92%)	13
Non-cardiac chest pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Peripheral swelling	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Pyrexia	0/4 (0%)	0	2/4 (50%)	2	0/13 (0%)	0
Infections and infestations						
Conjunctivitis	0/4 (0%)	0	0/4 (0%)	0	0/13 (0%)	0
Hyperhidrosis	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Lower Respiratory Tract Infection	1/4 (25%)	3	0/4 (0%)	0	1/13 (7.69%)	1
Lung Infection	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Nasopharyngitis	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Oral candidiasis	2/4 (50%)	2	0/4 (0%)	0	1/13 (7.69%)	1
Pneumonia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Injury, poisoning and procedural complications						
Radiation skin injury	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Radiotherapy Dermatitis	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Investigations						

Weight decreased	0/4 (0%)	0	1/4 (25%)	1	1/13 (7.69%)	1
Metabolism and nutrition disorders						
Decreased appetite	1/4 (25%)	1	2/4 (50%)	2	3/13 (23.08%)	4
Hypercalcaemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Hyperglycaemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Hypokalaemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Hyponatraemia	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Hypophosphataemia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Musculoskeletal and connective tissue disorders						
Arthralgia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Back pain	2/4 (50%)	2	0/4 (0%)	0	3/13 (23.08%)	3
Flank pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Musculoskeletal chest pain	0/4 (0%)	0	1/4 (25%)	1	1/13 (7.69%)	2
Musculoskeletal pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	2
Neck pain	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Pain in extremity	0/4 (0%)	0	2/4 (50%)	2	1/13 (7.69%)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Metastatic pain	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Nervous system disorders						
Dysgeusia	1/4 (25%)	1	0/4 (0%)	0	0/13 (0%)	0
Headache	0/4 (0%)	0	2/4 (50%)	2	2/13 (15.38%)	2
Lethargy	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1

Neuralgia	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Psychiatric disorders						
Depressed Mood	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Depression	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Insomnia	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Mood altered	0/4 (0%)	0	1/4 (25%)	1	1/13 (7.69%)	1
Nightmare	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Panic attack	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Personality Change	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Respiratory, thoracic and mediastinal disorders						
Bronchial Obstruction	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Cough	3/4 (75%)	3	4/4 (100%)	5	4/13 (30.77%)	4
Dyspnoea	3/4 (75%)	3	4/4 (100%)	4	2/13 (15.38%)	2
Dyspnoea exertional	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Haemoptysis	1/4 (25%)	1	2/4 (50%)	2	3/13 (23.08%)	3
Hiccups	1/4 (25%)	1	0/4 (0%)	0	2/13 (15.38%)	3
Peripheral ischaemia	0/4 (0%)	0	1/4 (25%)	1	0/13 (0%)	0
Skin and subcutaneous tissue disorders						
Dry skin †A	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Fungating wound	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Maculopapular rash	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Night sweats	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Rash	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1

Rash macular	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	2
Rash pruritic	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Skin Mass	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Skin Reaction	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1
Skin Reaction	0/4 (0%)	0	0/4 (0%)	0	1/13 (7.69%)	1