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Supplementary information

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Defactinib with avutometinib in patients with solid tumors: the phase 1 FRAME trial

In the format provided by the authors and unedited

Cohort	Complete response n (%)	Partial response n (%)	Stable disease n (%)	Progressive disease n (%)	Number of responders	Response rate (95% CI)
Dose Escalation	0 (0%)	5 (41.7%)	6 (50%)	1 (8.3%)	5/12	41.7% (15.2% - 72.3%)
***KRAS*^{M} NSCLC**	0 (0%)	2 (10.5%)	9 (47.4%)	8 (42.1%)	2/19	10.5% (1.3% - 33.1%)
LGSOC	0 (0%)	8 (44.4%)	10 (55.6%)	0 (0%)	8/18	44.4% (21.5% - 69.2%)
CRC	0 (0%)	0 (0%)	3 (30%)	7 (70%)	0/10	0% (0% - 30.8%)
PC	0 (0%)	0 (0%)	4 (50%)	4 (50%)	0/8	0% (0% - 36.9%)
EOC	0 (0%)	0 (0%)	1 (50%)	1 (50%)	0/2	0% (0% - 84.2%)
***KRAS*^{G12V} NSCLC**	0 (0%)	0 (0%)	6 (85.7%)	1 (14.3%)	0/7	0% (0% – 41%)
ST-Biopsy	0 (0%)	0 (0%)	5 (83.3%)	1 (16.7%)	0/6	0% (0% - 45.9%)
Overall (combining escalation and expansion cohorts)	0 (0%)	15 (18.3%)	44 (53.7%)	23 (28%)	15/82	18.3% (10.6% - 28.4%)

Supplementary Data Table 1

Antitumour activity

Summary of RECIST v1.1 objective response rate by cohort, based on confirmed responses only, in the REP population. A response (complete response or partial response) was considered confirmed if two consecutive observations were not less than four weeks apart. Responses not meeting these criteria were considered unconfirmed according to RECIST v1. CI: confidence interval; NSCLC: non-small cell lung cancer; LGSOC: low-grade serous ovarian cancer; CRC: RAS mutant colorectal cancer; PC: pancreatic cancer; EOC: RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); *KRAS*^{G12V}-NSCLC: G12V specific KRAS mutant non-small cell lung cancer; ST: solid tumours (enriched for those with RAS mutations biopsy cohort).

Cohort	Median PFS (months)	95% confidence interval	Median TTP (months)	95% confidence interval
Dose Escalation	4.8	3.7 - NA	4.8	3.7 - NA
***KRAS*^{M} NSCLC**	3.3	2.1 - 9.6	3.3	2.1 - 9.6
LGSOC	20.5	12.0 - NA	20.5	12.0 - NA
CRC	1.7	1.6 - NA	1.7	1.6 - NA
PC	2.6	1.6 - NA	2.6	1.6 - NA
EOC	4.3	1.4 - NA	4.3	1.4 - NA
***KRAS*^{G12V} NSCLC**	5.3	2.8 - NA	5.3	2.8 - NA
STC	4.7	3.6 - NA	4.7	3.6 - NA

Supplementary Data Table 2

Median progression free survival (PFS) and time to progression (TTP)

From the first combination dose in the REP population, with 95% confidence intervals, by cohort. Sensitivity analysis for PFS and TTP from trial entry yielded similar results (data not shown). PFS: progression free survival; TTP: time to progression; NSCLC: non-small cell lung cancer (*KRAS* mutated) ; LGSOC: low-grade serous ovarian cancer; CRC: RAS mutant colorectal cancer; PC: pancreatic cancer; EOC: *RAS/RAF* mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related*); KRAS*^{G12V}-NSCLC: G12V specific *KRAS* mutant non-small cell lung cancer; STC: solid tumours (enriched for those with RAS mutations).

Cohort	Complete response n (%)	Partial response n (%)	Stable disease n (%)	Progressive disease n (%)	Number of responders	Response rate (95% CI)
LGSOC	0 (0%)	8 (44.4%)	10 (55.6%)	0 (0%)	8/18	44.4% (21.5% - 69.2%)
Overall (expansion cohorts)	0 (0%)	10 (18.5%)	26 (48.1%)	18 (33.3%)	10/54	18.5% (9.3% - 31.4%)

Supplementary Data Table 3

Antitumour activity in patients in the expansion cohorts treated at R2PD.

Summary of RECIST v1.1 objective response rate for patients on RP2D (Dose: 3.2mg + 200mg) in expansion cohort (LGSOC vs overall), based on confirmed responses only, in the REP population. Overall includes LGSOC patients. LGSOC: low-grade serous ovarian cancer. A response (complete response or partial response) was considered confirmed if two consecutive observations were not less than four weeks apart. Responses not meeting these criteria were considered unconfirmed according to RECIST v1. CI: confidence interval.

Web appendix 2: CONSORT-DEFINE downloadable checklist

Recommended checklist items to consider in an early phase dose-finding clinical trial report from CONSORT 2010 and CONSORT-DEFINE checklists[^]

Please cite as: Yap C, Solovyeva O, de Bono J, et al. Enhancing reporting quality and impact of early phase dose-finding clinical trials: CONSORT Dose-finding Extension (CONSORT-DEFINE) guidance. *BMJ* 2023;383:e076387. doi:10.1136/bmj-2023-076387

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No[¤]
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Title and abstract					
	1a	Identification as a randomised trial in the title	1a[†]	Identification as an early phase dose-finding (eg, first-in-human, dose escalation or de-escalation, phase 1, phase 1/2, expansion, dose titration) and, if applicable, randomised trial in the title or abstract	Manuscript: Title and abstract shortened as per journal specification
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts)	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT-DEFINE for abstracts)	Manuscript: Abstract covers important aspects but is limited by word limit
Introduction					
Background and objectives	2a	Scientific background and explanation of rationale	2a.1[†]	Description of research question(s) and justification for undertaking the trial, including summary of relevant clinical studies (published and unpublished) examining benefits and harms for each intervention	Manuscript: covered under introduction
			2a.2*	Summary of key findings from relevant non-clinical or preclinical research	Manuscript: Covered in introduction
			2a.3*	Summary of findings from previously generated preclinical and translational studies to support any planned biomarker substudies (where applicable)	Manuscript: Covered in introduction

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No[¤]
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
	2b	Specific objectives or hypotheses	2b†	Specific objectives (eg, relating to safety, activity, pharmacokinetics, pharmacodynamics, recommended dose(s))	Manuscript: Introduction and methods sections
Methods					
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	3a.1†	Description of trial design elements, such as dose escalation or de-escalation strategy, number of treatment groups, allocation ratio if relevant, and details of any prespecified trial adaptations	Manuscript: Methods section
			3a.2*	Trial design schema to show the flow of major transition points (eg, dose escalation to dose expansion, phase 1 to phase 2, single ascending dose to multiple ascending dose)	Manuscript: Figure 1
			3a.3*	Statistical methods or rationale underpinning the trial design	Manuscript Methods section
			3a.4*	Starting dose(s) with rationale	Manuscript: Methods section, determination of starting dose
			3a.5*	Range of planned dose levels with rationale	Manuscript: Figure 1 Protocol: Page 34
			3a.6*	Presentation of planned dose levels (eg, as a diagram, table, or infographic), where applicable	Manuscript: Figure 1
			3a.7*	Skipping of dose level(s), if applicable	N/A
			3a.8*	Planned cohort size(s) (eg, fixed, flexible, adaptive)	Manuscript Methods section

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No[¤]
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
			3a.9*	Dose allocation method within a dose level (including sequence and interval between dosing of participants, eg, sentinel or staggered dosing)	Protocol page 35
			3a.10*	Dose expansion cohort(s), if applicable, with rationale	Manuscript: Page 3 and Figure 1
			3a.11*	Criteria for progression to the next part of the trial (eg, phase 1 to phase 2, single ascending dose to multiple ascending dose), where applicable	Protocol: Page 24
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	3b†	Important changes to the design or methods after trial commencement (eg, insertion of unplanned additional doses) outside the scope of the prespecified adaptive design features, with reasons	Protocol amendments listed on page 5 of protocol
Participants	4a	Eligibility criteria for participants	4a		Manuscripts Methods section and protocol page 29-30
	4b	Settings and locations where the data were collected	4b		Manuscript Methods section
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5a†	Interventions for each dose level (within each group) with sufficient details to allow replication, including administration route and schedule showing how and when they were actually administered	Manuscript: Results section: Dose escalation

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No¤
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
			5b*	Criteria for dose discontinuation, dose modifications, and dosing delays of allocated interventions for a given trial participant (eg, dose change in response to harms, participant request, or improving or worsening disease)	Protocol: Page 37
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6a†	Primary and secondary outcomes, including the specific measurement variable, analysis metric, method of aggregation, and time point for each outcome. Explanation of the clinical relevance of chosen outcomes is strongly recommended. Any other outcomes used to inform prespecified adaptations should be described with the rationale	Manuscript methods and Reporting summary
	6b	Any changes to trial outcomes after the trial commenced, with reasons	6b†	Any unplanned changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	7a†	Estimated number of participants (minimum, maximum, or expected range) needed to address trial objectives and how it was determined, including clinical and statistical assumptions supporting any sample size and operating characteristics	Manuscript methods section

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No[¤]
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	7b†	Prespecified interim decision making criteria or rules that guided the trial adaptation process (eg, dosing decision to (de-)escalate); prespecified and actual timing and frequency of interim data reviews and the information to inform trial adaptations	Manuscript: Results section: Dose escalation Protocol: Page 24-25
Randomization (if applicable)					
Sequence generation	8a	Method used to generate the random allocation sequence	8a		N/A
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8b†	Type of randomisation; details of any restrictions (such as blocking and block size); any prespecified adaptive assignment rules or algorithm leading to adjustments in the allocation ratio, including timing and frequency of updates; any changes to the allocation rule following trial adaptation decisions	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9		N/A
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10		N/A

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No¤
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Blinding	11a	If done, who was blinded after assignment to interventions (eg, participants, care providers, and how	11a		N/A
	11b	If relevant, description of the similarity of interventions	11b		N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12a.1†	Statistical methods for primary and secondary outcomes and any other outcomes used to make prespecified adaptations	Manuscript: methods section
			12a.2*	For the implemented adaptive design features, statistical methods used for estimation (eg, safety, dose(s), treatment effects) and to make inferences	N/A
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12b†	Statistical methods for additional analyses (eg, subgroup and adjusted analyses, pharmacokinetics or pharmacodynamics, biomarker correlative analyses)	N/A
			12c*	Analysis population(s) (eg, evaluable population for dose-finding, safety population)	Supplementary data: Supplementary Figure 1
			12d*	Strategies for handling intercurrent events occurring after treatment initiation (eg, how dosing adjustments were handled) that can affect either the interpretation or the existence of the measurements associated with the clinical question of interest, and any methods to handle missing data	Supplementary data: Statistical analysis plan page

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No¤
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Results					
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	13a†	For each group, the number of participants who were assigned to each dose level at each interim analysis (eg, for dosing decisions), received intended treatment, and were analysed for the primary outcome and, if applicable, any other outcomes used to inform prespecified adaptations	Supplementary data Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	13b†	For each group, losses and exclusions after allocation to each dose level, together with reasons	Supplementary data Figure 1
Recruitment	14a§	Dates defining the periods of recruitment and follow-up	14a§		Manuscript methods page
	14b§	Why the trial ended or was stopped	14b§		N/A
			14c*	Trial adaptation decisions made (including on what basis they were made, and when) in light of the prespecified decision making criteria and observed accrued data	Manuscript: Results: dose escalation. Figure 1
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	15†	Baseline demographic and clinical characteristics across each dose level within each group, where appropriate	Manuscript: Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	16†	For each group, the number of participants (denominator) included in each analysis across each dose level, and whether the analysis was by original assigned interventions	Manuscript: Figure 1 Supplementary data Figure 1

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No¤
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	17a†	For each primary and secondary outcome, results for each dose level within each group, and the estimated effect size and its precision, if applicable	Manuscript: Results Figure Table 2,3 Extended data Figure 1-6
	17b§	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	17b§		N/A
			17c*	Report interim results used to inform interim decision making such as dose escalation, de-escalation, or staying at the same dose	Manuscript: Page4-5 and Figure 1
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	18		Supplementary data: Supplementary figure 1-5 and supplementary table 1-3
Harms	19	All important harms or unintended effects in each group	19†	All important harms (eg, adverse events or effects, toxicities) reported by dose level in each group (for specific guidance, see CONSORT for harms (2))	Manuscript Table 1
Discussion					
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	20		Manuscript discussion section
Generalizability	21	Generalisability (external validity, applicability) of the trial findings	21		Manuscript discussion section

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No¤
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	22		Manuscript discussion section
Other information					
Registration	23	Registration number and name of trial registry	23		Manuscript: Abstract
Protocol	24	Where the full trial protocol can be accessed, if available	24		Protocol uploaded
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	25		Manuscript: Acknowledgement section.
Data monitoring			26a*	Composition of any decision making or safety review committee or group; summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details can be found (such as in a charter or protocol)	Protocol: Page 25
			26b*	Description of who had access to interim results and made the interim and final decision to terminate the trial (or part(s) of the trial, eg, end of dose escalation), and measures to safeguard the confidentiality of interim information	Protocol: Page 25

Category and section	Standard CONSORT 2010 checklist item		CONSORT-DEFINE checklist item for EPDF Trials		Addressed on Page No[¤]
	Item No	CONSORT 2010	Item No	CONSORT-DEFINE	
Dissemination			27*	Specify, if applicable, whether and when results (such as safety and/or activity) were reported externally (eg, through scientific presentations, journal publication, or the trial website) while the trial (or part(s) of the trial) was still ongoing	AACR Annual Meeting 2020 CT143 - Phase I study of the combination of a RAF-MEK inhibitor CH5126766 and FAK inhibitor defactinib in an intermittent dosing schedule with expansions in *KRAS* mutant cancers AACR Annual meeting 2021 CT019 - A phase I trial of the combination of the dual RAF-MEK inhibitor VS-6766 and the FAK inhibitor defactinib: Evaluation of efficacy in KRAS mutated NSCLC.

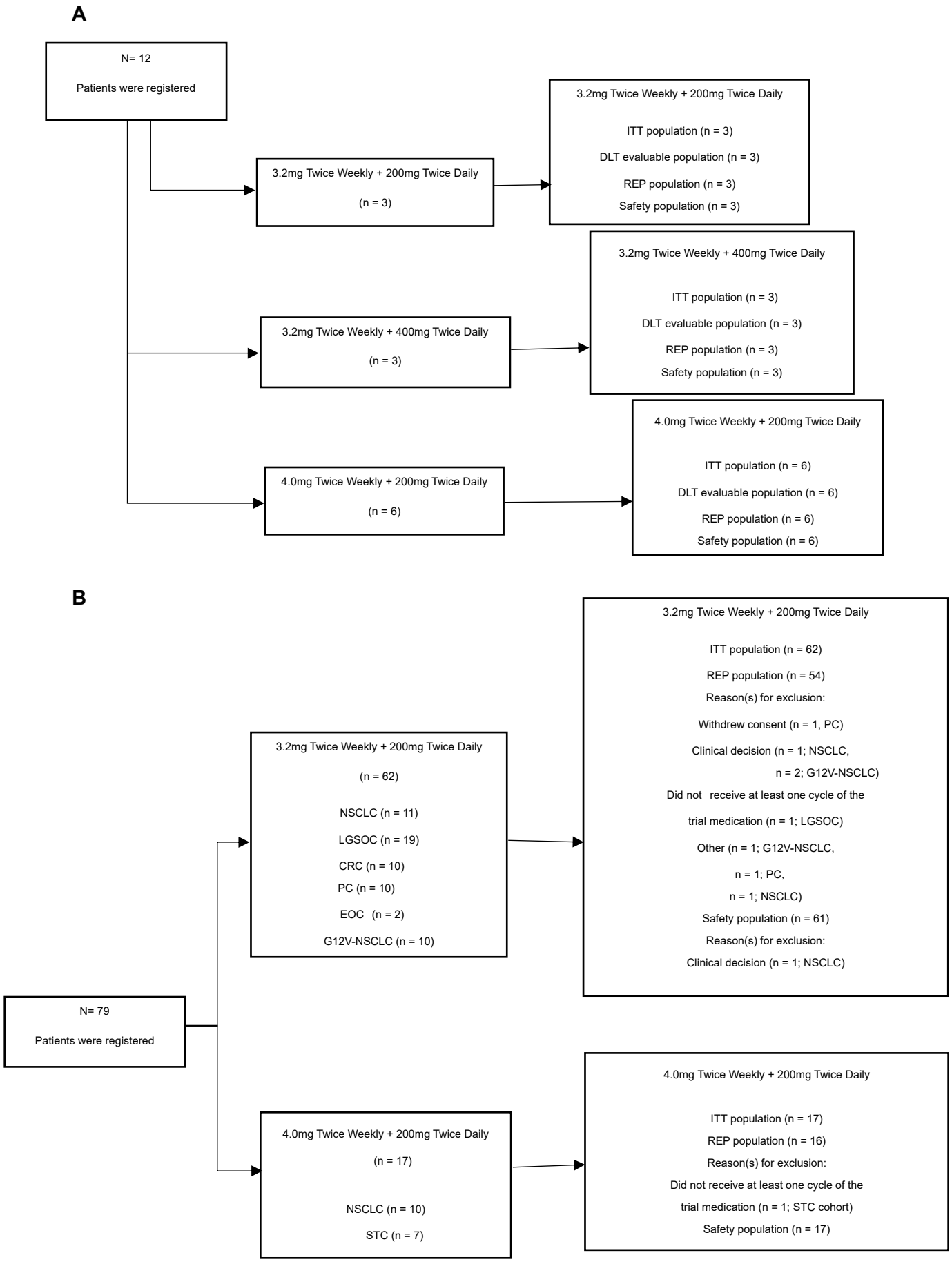
CONSORT=CONonsolidated Standards Of Reporting Trials; DEFINE=Dose-finding Extension; EPDF=early phase dose-finding.

^ This checklist should be used in conjunction with the CONSORT explanation and elaboration document (3) for important clarifications on the checklist items. Empty items in the CONSORT-DEFINE column indicate no modification from the standard CONSORT item. CONSORT extensions for non-pharmacological treatments and outcomes might also be relevant (4). Note that the term “dose” in the checklist can be considered synonymous and used interchangeably with dosage, or dosing regimen (dose or schedule), or a unit dose.

¤ If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).
* New items that should only be applied in reference to CONSORT-DEFINE.
† Modified items that require reference to both CONSORT and CONSORT-DEFINE.
§ Item wording remains unchanged in reference to CONSORT, but additional CONSORT-DEFINE explanatory text has been provided to clarify additional considerations for early phase dose-finding trials (web appendix 3).

Supplementary Data Table 4

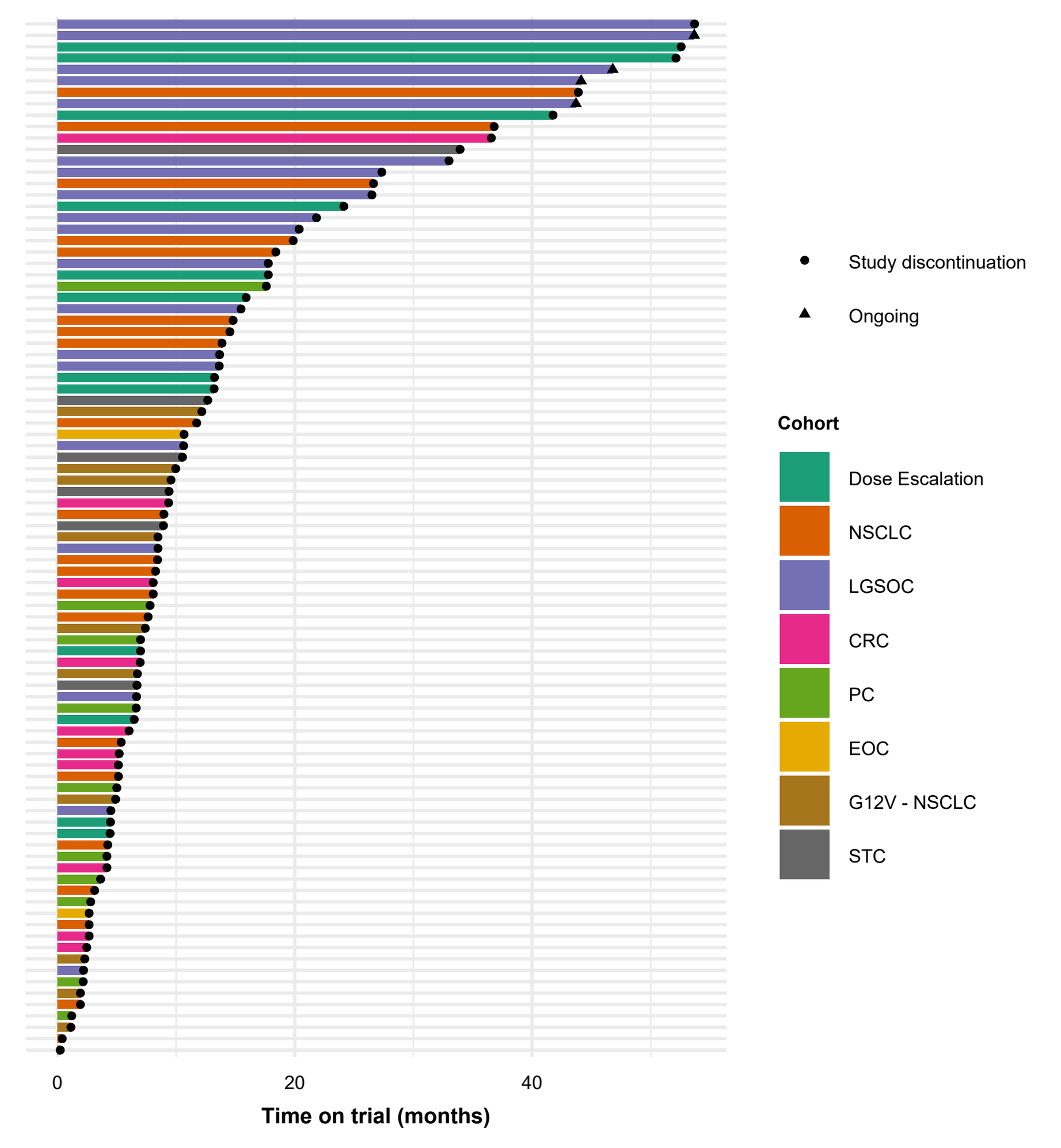
CONSORT-DEFINE checklist for early phase clinical trial publications


A
N= 12
Patients were registered
3.2mg Twice Weekly + 200mg Twice Daily
(n = 3)
3.2mg Twice Weekly + 200mg Twice Daily
ITT population (n = 3)
DLT evaluable population (n = 3)
REP population (n = 3)
Safety population (n = 3)
3.2mg Twice Weekly + 400mg Twice Daily
(n = 3)
3.2mg Twice Weekly + 400mg Twice Daily
ITT population (n = 3)
DLT evaluable population (n = 3)
REP population (n = 3)
Safety population (n = 3)
4.0mg Twice Weekly + 200mg Twice Daily
(n = 6)
4.0mg Twice Weekly + 200mg Twice Daily
ITT population (n = 6)
DLT evaluable population (n = 6)
REP population (n = 6)
Safety population (n = 6)
B
N= 79
Patients were registered
3.2mg Twice Weekly + 200mg Twice Daily
(n = 62)
NSCLC (n = 11)
LGSOC (n = 19)
CRC (n = 10)
PC (n = 10)
EOC (n = 2)
G12V-NSCLC (n = 10)
3.2mg Twice Weekly + 200mg Twice Daily
ITT population (n = 62)
REP population (n = 54)
Reason(s) for exclusion:
Withdrew consent (n = 1, PC)
Clinical decision (n = 1; NSCLC,
n = 2; G12V-NSCLC)
Did not receive at least one cycle of the
trial medication (n = 1; LGSOC)
Other (n = 1; G12V-NSCLC,
n = 1; PC,
n = 1; NSCLC)
Safety population (n = 61)
Reason(s) for exclusion:
Clinical decision (n = 1; NSCLC)
4.0mg Twice Weekly + 200mg Twice Daily
(n = 17)
NSCLC (n = 10)
STC (n = 7)
4.0mg Twice Weekly + 200mg Twice Daily
ITT population (n = 17)
REP population (n = 16)
Reason(s) for exclusion:
Did not receive at least one cycle of the
trial medication (n = 1; STC cohort)
Safety population (n = 17)

Supplementary Data Figure 1

Patient flow diagrams

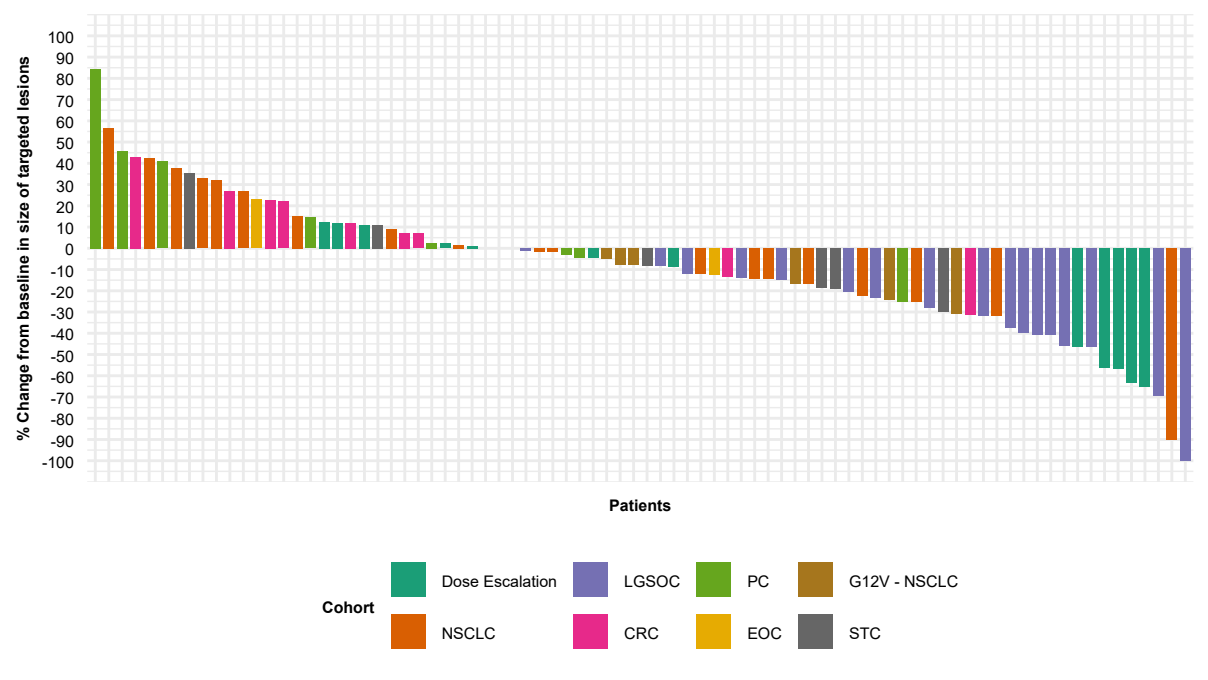
Flow diagram of patients in (A) the dose escalation cohort and (B) the dose expansion cohorts, with analysis populations. DLT: dose-limiting toxicity; IIT: intention to treat; REP: response evaluable patient; NSCLC: non-small cell lung cancer; LGSOC: low-grade serous ovarian cancer; CRC: *RAS* mutant colorectal cancer; PC: pancreatic cancer; EOC: RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); G12V-NSCLC: G12V specific KRAS mutant non-small cell lung cancer; STC: solid tumours (enriched for those with RAS mutations).


0
20
40
Time on trial (months)
Study discontinuation
Ongoing
Cohort
Dose Escalation
NSCLC
LGSOC
CRC
PC
EOC
G12V - NSCLC
STC

Supplementary Data Figure 2

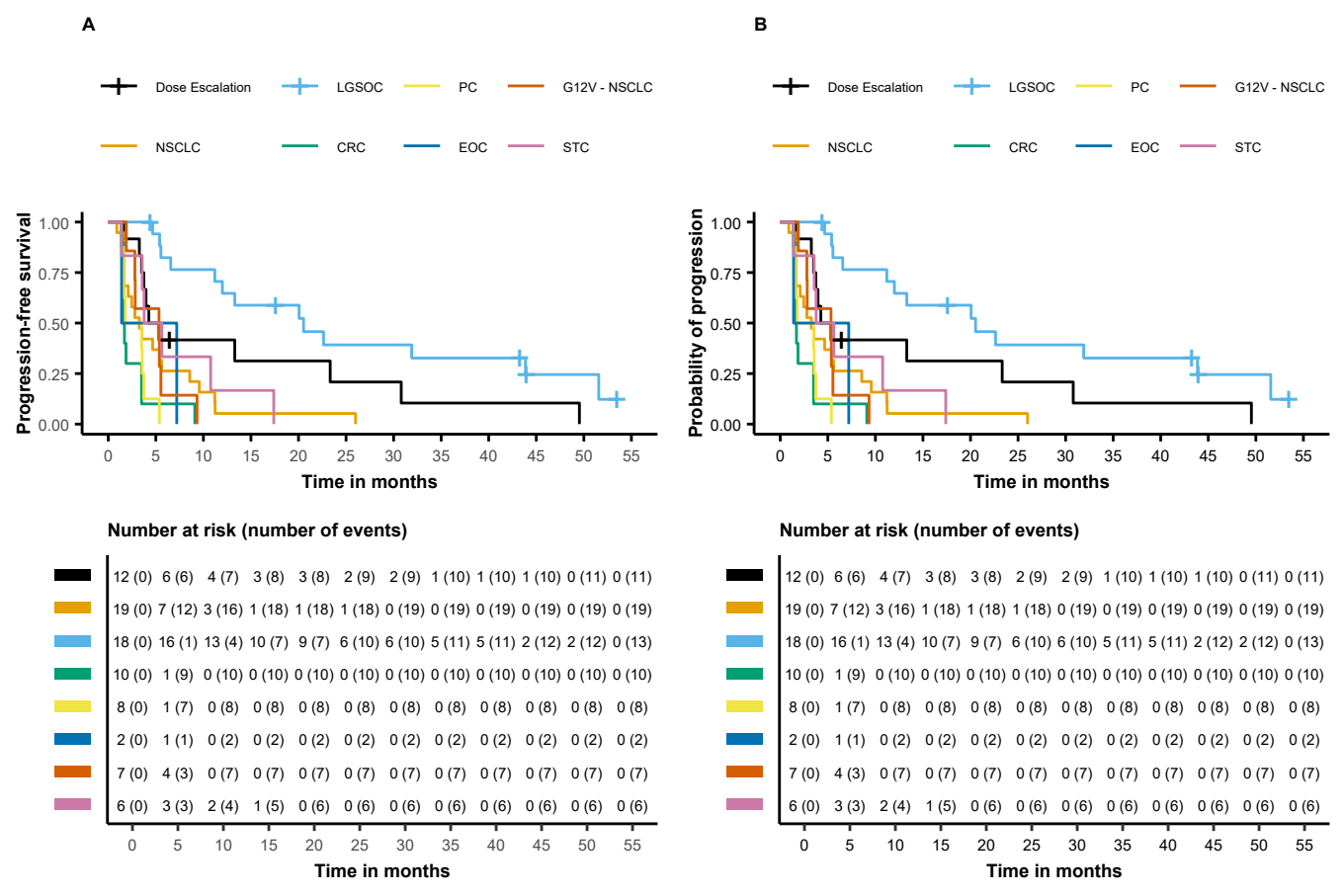
Follow up

Swimmer plot of time on trial by patient in the ITT population. NSCLC: non-small cell lung cancer; LGSOC: low-grade serous ovarian cancer; CRC: *RA*S mutant colorectal cancer; PC: pancreatic cancer; EOC: *RAS/RAF* mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); G12V-NSCLC: G12V specific KRAS mutant non-small cell lung cancer; ST-Biopsy chorts: solid tumours enriched for those with *RAS* mutations biopsy cohort.


% Change from baseline in size of targeted lesions
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Patients
Cohort
Dose Escalation
LGSOC
PC
G12V - NSCLC
NSCLC
CRC
EOC
STC

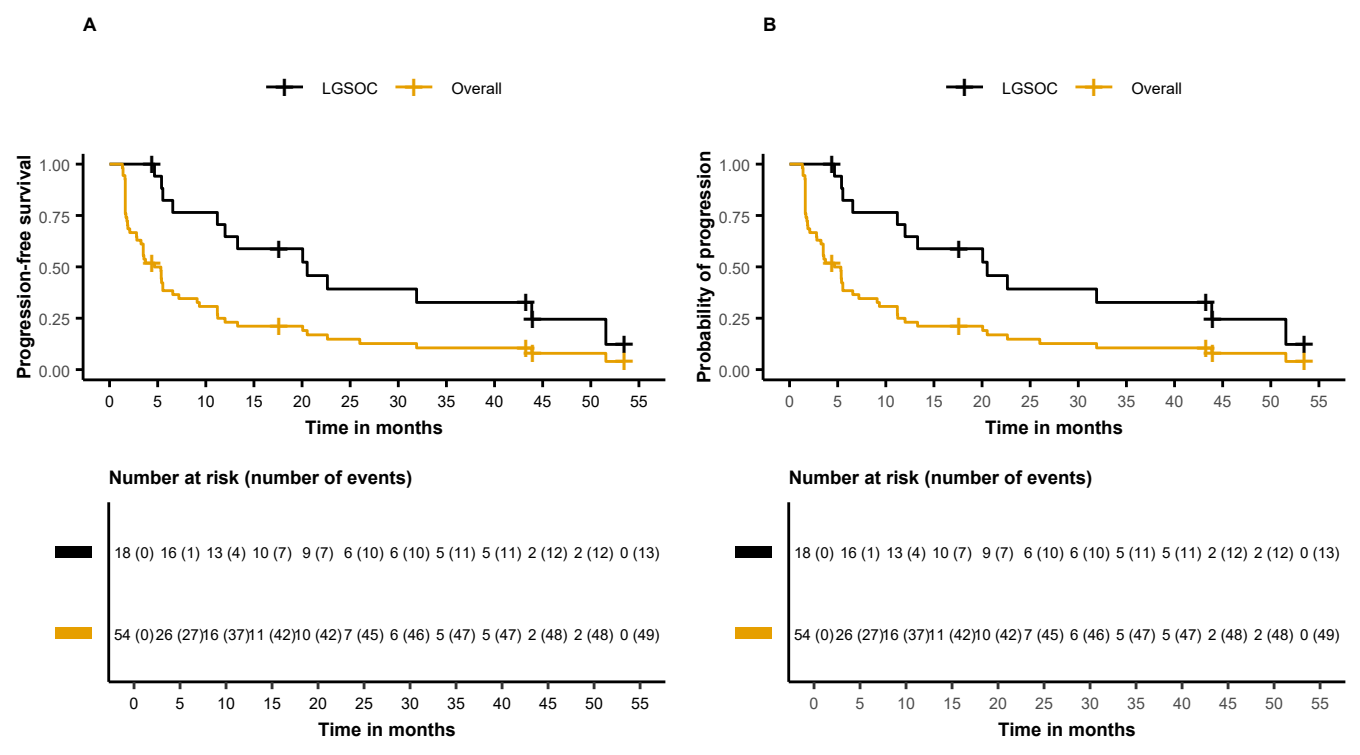
Supplementary Data Figure 3

Waterfall plot of change in size of targeted tumour lesions compared to baseline in the REP population, by cohort. NSCLC: non-small cell lung cancer; LGSOC: low-grade serous ovarian cancer; CRC: RAS mutant colorectal cancer; PC: pancreatic cancer; EOC: RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); G12V-NSCLC: G12V specific *KRAS* mutant non-small cell lung cancer; ST: solid tumours (enriched for those with RAS mutations-biopsy cohort).


A
Dose Escalation
LGSOC
PC
G12V - NSCLC
NSCLC
CRC
EOC
STC
Progression-free survival
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
Number at risk (number of events)
12 (0) 6 (6) 4 (7) 3 (8) 3 (8) 2 (9) 2 (9) 1 (10) 1 (10) 1 (10) 0 (11) 0 (11)
19 (0) 7 (12) 3 (16) 1 (18) 1 (18) 1 (18) 0 (19) 0 (19) 0 (19) 0 (19) 0 (19) 0 (19)
18 (0) 16 (1) 13 (4) 10 (7) 9 (7) 6 (10) 6 (10) 5 (11) 5 (11) 2 (12) 2 (12) 0 (13)
10 (0) 1 (9) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10)
8 (0) 1 (7) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8)
2 (0) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2)
7 (0) 4 (3) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7)
6 (0) 3 (3) 2 (4) 1 (5) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6)
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
B
Dose Escalation
LGSOC
PC
G12V - NSCLC
NSCLC
CRC
EOC
STC
Probability of progression
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
Number at risk (number of events)
12 (0) 6 (6) 4 (7) 3 (8) 3 (8) 2 (9) 2 (9) 1 (10) 1 (10) 1 (10) 0 (11) 0 (11)
19 (0) 7 (12) 3 (16) 1 (18) 1 (18) 1 (18) 0 (19) 0 (19) 0 (19) 0 (19) 0 (19) 0 (19)
18 (0) 16 (1) 13 (4) 10 (7) 9 (7) 6 (10) 6 (10) 5 (11) 5 (11) 2 (12) 2 (12) 0 (13)
10 (0) 1 (9) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10) 0 (10)
8 (0) 1 (7) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8) 0 (8)
2 (0) 1 (1) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2) 0 (2)
7 (0) 4 (3) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7) 0 (7)
6 (0) 3 (3) 2 (4) 1 (5) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6) 0 (6)
0 5 10 15 20 25 30 35 40 45 50 55
Time in months

Supplementary Data figure 4

Kaplan-Meier curves of (A) progression free survival (PFS) and (B) time to progression (TTP) from the first combination dose in the REP population. Sensitivity analysis for PFS and TTP from trial entry yielded similar results (data not shown). NSCLC: non-small cell lung cancer; LGSOC: low-grade serous ovarian cancer; CRC: RAS mutant colorectal cancer; PC: pancreatic cancer; EOC: *RAS/RAF* mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); *KRAS*^{G12V}-NSCLC: G12V specific KRAS mutant non-small cell lung cancer; ST-biopsy: solid tumours (enriched for those with *RAS/RAF* mutations).


A
LGSOC
Overall
Progression-free survival
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
Number at risk (number of events)
18 (0) 16 (1) 13 (4) 10 (7) 9 (7) 6 (10) 6 (10) 5 (11) 5 (11) 2 (12) 2 (12) 0 (13)
54 (0) 26 (27) 16 (37) 11 (42) 10 (42) 7 (45) 6 (46) 5 (47) 5 (47) 2 (48) 2 (48) 0 (49)
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
B
LGSOC
Overall
Probability of progression
1.00
0.75
0.50
0.25
0.00
0 5 10 15 20 25 30 35 40 45 50 55
Time in months
Number at risk (number of events)
18 (0) 16 (1) 13 (4) 10 (7) 9 (7) 6 (10) 6 (10) 5 (11) 5 (11) 2 (12) 2 (12) 0 (13)
54 (0) 26 (27) 16 (37) 11 (42) 10 (42) 7 (45) 6 (46) 5 (47) 5 (47) 2 (48) 2 (48) 0 (49)
0 5 10 15 20 25 30 35 40 45 50 55
Time in months

Supplementary Data Figure 5

Kaplan-Meier curves of patients showing progression free survival and time to progression in patients who received RP2D in the expansion cohorts

(A) progression free survival (PFS) and (B) time to progression (TTP) from the first combination dose for patients on RP2D (Dose: 3.2mg + 200mg) in expansion cohort (LGSOC vs overall) in the REP population. Sensitivity analysis for PFS and TTP from trial entry yielded similar results (data not shown). Overall includes LGSOC patients. LGSOC: low-grade serous ovarian cancer.

FRAME: A Phase I trial of the combination of Defactinib (VS-6063) (FAK inhibitor) and VS-6766 (RO5126766) (a dual RAF/MEK inhibitor) in patients with advanced solid tumours.

Statistical Analysis Plan

clinical data – efficacy/safety analyses

Version 1.0

04/08/2022

This statistical analysis plan is based on protocol version 5.1 [21/04/2021]

IRAS number: 225064

Sponsor reference number: CCR4642

EUDRACT number: 2017-001035-39

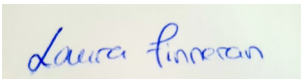
All approved versions of the SAP will be stored in the Statistical Section of the Trial Master File.

This statistical analysis plan is a framework to guide statistical analysis and may be supplemented by additional and exploratory analyses. Trial statisticians reserve the right to amend analysis methods as appropriate after discussion with the ICR-CTSU Scientific Lead.

For the final version to be used for the principal analysis of the primary endpoint only:

This statistical analysis plan has been approved by the following personnel:

Trial Statistician: Laura Finneran

Signed:  **Date: _04/08/2022__**

ICR-CTSU Scientific Lead: Prof Christina Yap

Signed:  **Date: 04/08/2022**

Chief Investigator: Prof Udai Banerji

Signed:  **Date: 08/08/2022**

Document history

Version	Date	Author	Changes made* (*including justifications and timing of SAP revisions in relation to trial milestones)

Contents

1 Introduction

This analysis plan details the principal statistical analyses of safety and preliminary efficacy data for publication of the FRAME trial. Pharmacokinetic and pharmacodynamics data analyses are not covered by this document. The SAP will be used to guide statistical analysis and to minimise bias due to data-driven choices of analysis. Once approved the SAP will be stored in the Trial Master File and can be viewed on request. Any deviations from the analysis plan will be documented in the Statistical Analysis Report.

2 Trial Design and Methods

2.1 Trial design

This is a multi-centre, investigator-initiated, dose escalation, Phase I trial of the combination of the FAK inhibitor, Defactinib, and the dual RAF/MEK inhibitor, VS-6766 in patients with advanced solid tumours.

There are two parts to this study, the dose escalation phase and the dose expansion phase. In the dose escalation phase, cohorts of 3 to 6 patients will be enrolled to determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D). This will be followed by a dose expansion phase to further characterise the safety and tolerability and to assess the pharmacodynamic activity of the combination.

Up to 24 patients with solid tumours will be treated in the dose escalation phase of this study. Once the MTD has been determined a further 86 patients will be enrolled to the dose expansion phase to further characterise the safety and tolerability and to assess the pharmacodynamic activity of the combination. There will be 7 cohorts in the dose expansion phase: 20 patients with KRAS mutant non-small-cell lung cancer (NSCLC); 20 patients with low grade serous ovarian cancer (LGSOC); 10 patients with RAS mutant colorectal cancer (CRC); 10 patients with pancreatic cancer; 10 patients with RAS/RAF mutant endometroid ovarian cancer; 10 patients with G12V specific KRAS mutant NSCLC and 6 patients with solid tumours (enriched for those with RAS mutations) that have consented and are willing to undergo biopsies at three time points throughout the study.

2.2 Trial objectives

2.2.1 Primary objectives

- To propose a recommended dose for Phase II evaluation by establishing the maximum tolerated dose of the combination of VS-6766 and Defactinib.
- To assess the safety and toxicity profile of the combination of VS-6766 and Defactinib.

2.2.2 Secondary objectives

- To characterise the pharmacokinetic profile of VS-6766 in combination with Defactinib– *Not covered by this SAP*

2.2.3 Tertiary objectives

- To document any possible anti-tumour activity in patients.
- To study the pharmacodynamic profile of VS-6766 alone and in combination with Defactinib in pre-treatment and post-treatment biopsies and PBMC's - *Not covered by this SAP*
- To assess putative predictive biomarkers of response and resistance to the combination of VS-6766 and Defactinib.

2.3 Randomisation/recruitment procedures

Patients will be enrolled following completion of an eligibility checklist. No randomisation will take place. Please see section 2.6 for full inclusion/exclusion criteria.

2.4 Endpoints

2.4.1 Primary

- Determination of a dose at which no more than one patient out of up to six patients at the same dose level experience a highly probable or probable drug-related dose limiting toxicity.
- Determination of causality of each adverse event to VS-6766 and Defactinib and grading severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

2.4.2 Secondary

- Determination of the PK parameters (C_{max}, terminal half-life and area under curve) of VS-6766 and Defactinib when dosed together – *Not covered by this SAP*

2.4.3 Tertiary

- Determination of disease response by RECIST criteria version 1.1 and collection of data related to progression free survival.
- Quantification of biomarkers such as p-MEK, p-ERK and p-FAK, E-cadherin and vimentin and enumeration of T cell populations which express CD8, CD4 and CD25 – *Not covered by this SAP*
- Correlation of antitumour activity of the combination of VS-6766 and Defactinib with the detection of putative predictive biomarkers of response and resistance in archival tumours and plasma DNA.

2.5 Sample size and power

A traditional 3+3 design is used for the dose escalation part of this study. The final sample size will be determined by the number of dose levels which need to be explored in order to determine the RP2D.

In order to further characterise the tolerability, safety, PK and efficacy of the combination of VS-6766 and Defactinib in NSCLC, LGSOC, colorectal cancer, pancreatic cancer, endometroid ovarian cancer and G12V KRAS NSCLC. 20 NSCLC patients, 20 LGSOC patients, 10 colorectal cancer patients, 10 pancreatic patients, 10 endometroid ovarian cancer patients 10 G12V KRAS NSCLC patients will be treated in the dose expansion phase at the dose level selected in the dose

escalation phase. If the true response rate is 20%, the probability of seeing 0 responses is <0.1% and the probability of seeing 2 or more responses is 99.9%. The 80% confidence interval if the response rate is 10% is (6.4%, 16.0%), the 80% confidence interval if the response rate is 20% is (14.3%, 26.4%) and the 80% confidence interval if the response rate is 30% is (23.7%, 37.5%).

An additional 6 patients with advanced solid tumours will also be recruited to characterise the pharmacodynamics of the combination.

2.6 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 2.6.1 and 2.6.2).

2.6.1 Inclusion criteria:

1. **Dose escalation:**
   Histologically or cytologically proven solid tumours, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient enriching for patients with RAS mutant solid tumours.

   Dose expansion:
   Histologically or cytologically proven advanced non-small-cell lung cancer (NSCLC) with a documented KRAS mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(20 patients)**.
   OR
   Histologically or cytologically proven advanced low grade serous ovarian cancer (LGSOC), refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(20 patients)**.
   OR
   Histologically or cytologically proven advanced colorectal cancer (CRC) with a documented RAS mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients)**.
   OR
   Histologically or cytologically proven advanced pancreatic cancer or metastatic pancreatic cancer, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Endometroid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related) with a documented RAS or RAF mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Histologically or cytologically proven advanced non-small-cell lung cancer (NSCLC) with a documented KRAS G12V specific mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Histologically or cytologically proven RAS mutant solid tumours, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient. Patient must have biopsiable disease, be willing and has consented to undergo biopsies at three time-points **(6 patients)**.

2. Predicted life expectancy of at least 12 weeks

3. World Health Organisation (WHO) performance status of 0 or 1

4. Haematological and biochemical indices within the ranges shown below. These measurements must be performed within two weeks (Day -14 to Day 1) before the patient goes on the trial.

Laboratory Test	**Value required**
Haemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Serum bilirubin	≤ 1.5 x upper limit of normal (ULN)
Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)	≤ 2.5 x (ULN) unless raised due to tumour in which case up to 5 x ULN is permissible
Either: Calculated creatinine clearance Or: Serum creatinine	 ≥ 50 mL/min (uncorrected value) ≤ 1.5 x ULN

5. Men and women aged 18 years or over.

6. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.

7. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

8. **Dose escalation**
Measurable disease according to RECIST 1.1 or evaluable disease. All radiology studies must be performed within 28 days prior to registration.

Dose expansion
Measurable disease according to RECIST 1.1, all radiology studies must be performed within 28 days prior to registration.

9. Corrected QT interval (QTc) < 470 ms (as calculated by the Fridericia correction formula, averaged over 3 ECGs).

10. Agrees to the use of archival paraffin embedded tissue and has archival tumour tissue available.

2.6.2 Exclusion criteria:

1. Radiotherapy (except for palliative reasons), endocrine therapy, biological therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C) before treatment.

2. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1 toxicities, which in the opinion of the Investigator and the DDU should not exclude the patient.

3. Known untreated or active central nervous system (CNS) metastases (progressing or requiring corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
    - Evaluable or measurable disease outside the CNS is present.

- Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the baseline disease assessment for at least 28 days.

4. Ability to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to use two medically approved forms of contraception (oral, injected or implanted hormonal contraception and condom, have an intra-uterine device and condom, diaphragm with spermicidal gel and condom) from time of consent, during the trial and for six months afterwards are considered eligible.

5. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using one form of medically approved contraception [condom plus spermicide] during the trial and for six months afterwards). Men with pregnant or lactating partners should be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

6. Major surgery within 4 weeks prior to entry to the study (excluding placement of vascular access), or minor surgery within 2 weeks of entry into the study and from which the patient has not yet recovered.

7. Treatment with warfarin. Patients on warfarin for DVT/PE can be converted to LMWH.

8. Known history of Gilbert's Syndrome.

9. Acute or chronic pancreatitis.

10. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.

11. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

12. Patients with the inability to swallow oral medications or impaired gastrointestinal absorption due to gastrectomy or active inflammatory bowel disease.

13. Concurrent ocular disorders:

    a) Patients with history of glaucoma, history of retinal vein occlusion (RVO), predisposing factors for RVO, including uncontrolled hypertension, uncontrolled diabetes
    b) Patient with history of retinal pathology or evidence of visible retinal pathology that is considered a risk factor for RVO, intraocular pressure > 21 mm Hg as measured by tonometry, or other significant ocular pathology, such as anatomical abnormalities that increase the risk for RVO.
    c) Patients with a history of corneal erosion (instability of corneal epithelium), corneal degeneration, active or recurrent keratitis, and other forms of serious ocular surface inflammatory conditions

14. Concurrent congestive heart failure, prior history of class III/ IV cardiac disease (New York Heart Association [NYHA]), myocardial infarction within the last 6

months, unstable arrhythmias, unstable angina or severe obstructive pulmonary disease.

15. Patients exposed to strong CYP3A4 and strong CYP2C9 inhibitors within 7 days prior to the first dose.

    N.B. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information.

16. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I study of VS-6766 in combination with Defactinib. Participation in an observational trial would be acceptable.

17. Symptoms of COVID-19 and/or documented current COVID-19 infection (the patient can be reassessed for eligibility following a full recovery and negative COVID-19 test)

18. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

3 Safety review committee and interim analyses

As this is a phase I trial, there are stopping rules for toxicity during this study:

Regular weekly to 2-weekly safety reviews will be conducted between the Principal Investigator or delegate(s) from each investigational site and DDU Clinical Trials Manager or delegate.

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability of VS-6766 in combination with Defactinib.

The decision may be to:

1. Proceed with dose escalation
2. Expand the cohort to a maximum of 6 evaluable patients
3. De-escalate the dose
4. Define the MTD (where 6 evaluable patients are assessed)
5. Stop the study

Formal review will occur once there are at least 3 evaluable patients at a dose level. Decisions will be based on all relevant data available from all dose levels evaluated in the ongoing study and will include: available safety information, DLTs, CTCAE Grade ≥ 2 toxicity data and available PK and PD data from evaluable patients. Any dose interruptions and reductions will be taken into account.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients. Patients must NOT be dosed at a higher dose level until after the SRC have agreed this and such communication has been received.

Once the MTD is reached, this combination will be further evaluated in the dose expansion phase. During dose expansion, SRC meetings will be held as required for safety review. Additional SRC meetings will be organised in the event of any safety concerns.

The SRC will consist of:

- Chief Investigator or delegate (which can be the Principal Investigator)
- Principal Investigator or delegate from each investigational site
- DDU Pharmacovigilance Officer or delegate
- DDU Clinical Trials Manager or delegate
- Senior ECMC clinician (who is not CI)

Further internal or external experts may be consulted.

No other interim analyses are planned.

4 Data completeness/consistency

It is expected that the majority of missing data will be missing at random and therefore it is not expected that imputation methods will be used for individual patients or variables.

5 Patient disposition and follow-up

5.1 Patient flow through trial/recruitment

Patient flow through the trial will be described including the number of patients entered into and evaluable in each cohort and the number of patients who discontinued along with the reasons for discontinuation. This will be presented in a tabular format.

5.2 Treatment compliance

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

In the dose escalation cohorts, listings will be provided for each dose with a line per-patient, per-cycle indicating doses received and any changes from originally prescribed dose/schedule.

For each expansion cohort, data will be summarised by cycle indicating the number of patients at each cycle with changes to the originally prescribed dose.

Reasons for treatment discontinuations will be tabulated for each of the cohorts.

6 Analysis populations

Analysis populations are defined as follows:

- **Safety Population:** This population includes any patient who at least one administration of the IMPs, VS-6766 and/or Defactinib
- **Intention to treat (ITT):** This population contains all patients enrolled into the study (regardless of whether they were later found to be ineligible, a protocol violator, given the wrong treatment/dose allocation, never treated etc.).
- **Response Evaluable patient population (REP):** Patients must receive at least one cycle of the trial medication, have baseline RECIST assessment and have had at least one post baseline RECIST assessment to be evaluable for response. Patients who progress prior to the first scheduled post baseline RECIST assessment would still be evaluable for response.
- **DLT evaluable population:** All eligible escalation patients that have received the combination of VS-6766 and Defactinib and either:

1. have completed minimum safety evaluation requirements and have received at least 5 out of 6 doses of VS-6766 (or 5 out of 7 doses in patients requiring the run-in dose) and 32 out of 42 doses of Defactinib during the first cycle at a specified new dose level;

OR

2. have experienced a DLT during the first cycle at a specified new dose level

7 Timing of analyses

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive 1 cycle of treatment and have completed their 'off-study' visit (i.e. 28 days after the last dose of VS-6766 and/or Defactinib).

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

8 Analysis methods

8.1 Baseline characteristics

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.
Data will be presented separately for each of the following cohorts:

- Dose escalation cohort
- KRAS mutant non-small-cell lung cancer (NSCLC) cohort
- Low grade serous ovarian cancer (LGSOC) cohort
- RAS mutant colorectal cancer (CRC) cohort
- Pancreatic cancer cohort
- RAS/RAF mutant endometroid ovarian cancer cohort
- G12V specific KRAS mutant NSCLC cohort
- Solid tumours (enriched for those with RAS mutations) cohort

8.2 Analysis of primary endpoint

The safety population will be used to assess safety and tolerability. Adverse events will be tabulated separately for each dose level/schedule by body system, severity grade and relatedness to trial treatment. Laboratory variables will be classified using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and those matching the definition for adverse events will be tabulated for each dose level/schedule by severity grade. Safety data will be presented in the 7 cohorts outlined above and for the escalation cohorts will be tabulated by dose level.For MTD determination, the DLT evaluable patient population will be used. MTD is determined as the highest dose at which no more than one patient out of up to six patients at the same dose level experience a highly probable or probable drug-related dose limiting toxicity.

8.3 Analysis of secondary endpoint(s)

Secondary endpoints relate to pharmacokinetic data and are not covered by this analysis plan.

8.4 Analysis of tertiary endpoint(s)

The response evaluable population will be used for analysis of tertiary endpoints.

For patients in the expansion phase, objective responses (complete response & partial responses) and the best tumour response including stable disease achieved by each patient while on trial will be presented in the data listings by cohort. Response rates will be reported with 95% confidence intervals overall and by cohort.

Progression free survival (PFS) will be calculated twice using 2 different calculations;

1- from trial entry until the time of documented disease progression or death (whichever occurs first) – (method as per the protocol)
2- from first combination dose until the time of documented disease progression or death (whichever occurs first) – (preferred method for reporting)

Patients who are alive and event free or lost to follow up at the time of analysis will be censored at the time the patient was last known to be alive and progression free. A Kaplan Meier graph and median PFS will be presented overall and by cohort.

Response rates and PFS will also be reported for low grade ovarian patients based on RAS mutation status, and in NSCLC patients based on G12V status.

Time to progression will be calculated twice using 2 different calculations and will be presented in the data listings by cohort;

1- from trial entry until date of confirmed progressive disease – (method as per the protocol)
2- from first combination dose until date of confirmed progressive disease – (preferred method for reporting)

8.5 Exploratory analyses

Any other analyses not documented in the SAP will be considered exploratory and hypothesis generating.

8.6 Subgroup analyses

Analyses of response rate by subgroups are exploratory in nature and will include, but are not limited to: RAS mutation status (low grade ovarian patients), G12V status (NSCLC patients).

9 Statistical software and analysis program locations

Analysis will be conducted using Stata version 16 or R version 4.2.0 (or subsequent versions for either software). Toxicities will be grouped by body system according to the latest version of MedDRA available (i.e. MedDRA level 1 – system organ class).

All programs will be stored in the analyses folder for FRAME on the ICR-CTSU server. Only the FRAME trial statistician(s), ICR-CTSU IT staff, Director and Deputy Directors of ICR-CTSU will be able to see the analysis folder. Programmes will be stored under the type of analysis e.g. Study report. All official analysis reports that are to be circulated externally of ICR-CTSU will be password protected. Hard copies of reports will be stored securely in the statistical section of the FRAME trial master file held in a locked fire proof cupboard with restricted access.

FRAME: A Phase I trial of the combination of Defactinib (VS-6063) (FAK inhibitor) and VS-6766 (RO5126766) (a dual RAF/MEK inhibitor) in patients with advanced solid tumours.

Sponsor protocol number: CCR4642

EudraCT number: 2017-001035-39

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VERSION HISTORY:

Version No.	Date of issue	Reason for update
1.0	07-Sep-17	Initial version submitted for Regulatory and Ethics approval
2.6	04-Ap-19	Addition of two dose expansion cohorts: 20 patients with low grade serous ovarian cancer, 10 patients with RAS mutant colorectal cancer. Increase to overall recruitment number.
3.0	27-Sep-19	Addition of PI. Removal of C3D15 and C4D15 visits.
4.0	30-Jun-20	Addition of three dose expansion cohorts: 10 patients with pancreatic cancer, 10 patients with RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related) and 10 patients with G12V specific KRAS mutant NSCLC. Increase to overall recruitment number. Inclusion of COVID-19 guidelines. Increase of Defactinib storage temperature to 15-30°C.
5.1	21-Apr-21	Change of RO5126766 name to VS-6766. Change of VS-6063 name to Defactinib. Change of supply arrangements for VS-6766 (RO5126766). Schedule change allowed where more appropriate then dose reduction. Stipulation that initial dose of VS-6766 (RO5126766) should be taken in hospital for both run-in (if applicable) and C1D1. COVID-19 vaccination guidance. Addition of optional standalone end of study biopsy at progression. New versions of the IB for VS-6766(RO5126766) and Defactinib (VS-6063)
6.0	23-Jan-23	Updated definition of progression free survival. Removal of mydriasis from eye test. Longer drug interruptions permitted for SAEs and AEs that are not drug related. Confirmation that patients should receive their C2D1 dose in clinic, as with their first run-in dose and C1D1 dose. Confirmation that from C3D1 onwards, patients can have assessments performed 24 hours before they dose on Day 1 of a cycle. Correction of inconsistencies regarding quantities of blood samples taken for PD analysis in section 8.
7.0	29-Oct-24	Corrected typographical error in Figure 3: Drug schema (Defactinib 200mg to 400mg for cohorts 2b and 3) in line with Table 1: Dose escalation for VS-6766 or Defactinib.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABPI	Association of the British Pharmaceutical Industry
AE	adverse event
alk phos	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BAD	biologically active dose
BP	blood pressure
BSA	body surface area
^{0}C	degrees Celsius
CDM	Clinical Data Manager
CI	Chief Investigator
CIRB	Central Institutional Review Board
CLT	total body clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CRA	Clinical Research Associate
CRF	case report form
CR-UK	Cancer Research UK
CSM	Clinical Study Manager
CT	computerised tomography
CTA	clinical trial authorisation
CTCAE	Common Terminology Criteria for Adverse Events
Day	calendar day
DCF	data clarification form
DDU	Drug Development Unit
DLT	dose limiting toxicity
ECG	electrocardiogram
EDTA	ethylene diamine tetra-acetic acid
EORTC	European Organisation for Research and Treatment of Cancer
EPD	early progressive disease
FAK	Focal adhesion kinase
FDG	fluorodeoxyglucose
FU	Formulation Unit
GCP	Good Clinical Practice
g/dL	gram(s) per decilitre
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
Hb	haemoglobin
HR	Hazard Ratio
HCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
ICH GCP	International Conference on Harmonisation of Good Clinical Practice
IHC	Immunohistochemistry
IMP	investigational medicinal product
ITF	Investigator Trial File
LVEF	left ventricular ejection fraction

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
MAD	maximum administered dose
mg/m^2	milligram per square metre
MHRA	Medicines and Healthcare products Regulations Agency
MRI	magnetic resonance imaging
MRT	mean residence time
MTD	maximum tolerated dose
NCI	National Cancer Institute
PBMC	Peripheral blood mononuclear cells
PD	progressive disease
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic
PR	partial response
PRP	Platelet-rich plasma
QC	quality control
QP	Qualified Person
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RPM	revolutions per minute
SAE	serious adverse event
SD	stable disease
SGDCF	site generated data clarification form
SDV	source data verification
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse (drug) reaction
$T_{1/2}$	terminal elimination half-life
T_{max}	time to reach C_{max}
ULN	upper limit of normal
USM	urgent safety measure
V_{SS}	steady state volume of distribution
WFI	Water for Injection
WBC	white blood cell
WHO	World Health Organisation

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as an Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki (Appendix 2), the applicable regulations of the relevant NHS Trusts and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

INVESTIGATOR'S NAME: _____

SIGNATURE: _____

DATE: _____

1 The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.

2 ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

1 PROTOCOL SUMMARY

1.1 Full title

FRAME: A Phase I trial of the combination of Defactinib (VS-6063) (FAK inhibitor) and VS-6766 (RO5126776) (a dual RAF/MEK inhibitor) in patients with advanced solid tumours.

1.1.1 Short title

Phase I trial of Defactinib and VS-6766.

1.2 Clinical trial primary objective

The primary objective is to propose a recommended dose for Phase II evaluation by establishing the maximum tolerated dose of the combination of VS-6766 and Defactinib and to assess the safety and toxicity profile of the combination of VS-6766 and Defactinib. Full details of secondary and tertiary objectives can be found in Section 3.1.

1.3 Design

This is a multi-centre, investigator-initiated, dose escalation, Phase I trial of the combination of the FAK inhibitor, Defactinib, and the dual RAF/MEK inhibitor, RO5126766 in patients with advanced solid tumours. VS-6766 is the same compound as RO5126766 and CH5126766.

There are two parts to this study, the dose escalation phase and the dose expansion phase. In the dose escalation phase, cohorts of 3 to 6 patients will be enrolled to determine the maximum tolerated dose (MTD) and recommended Phase II dose (RP2D). This will be followed by a dose expansion phase to further characterise the safety and tolerability and to assess the pharmacodynamic activity of the combination.

1.4 Administration schedule

VS-6766 will be administered orally twice a week on Monday/Thursday or Tuesday/Friday at least one hour prior or two hours after a meal. The starting dose of VS-6766 will be 3.2mg once a day, twice a week and can be escalated to a maximum of 4mg once a day, twice a week.

Defactinib will be administered orally twice a day immediately after a meal. The starting dose of Defactinib will be 200mg twice daily and can be escalated to a maximum of 400mg twice daily.

A cycle length is 4 weeks (28 days). Combination dosing (VS-6766 and Defactinib) will commence on Cycle 1 Day 1 for 3 weeks followed by one week without either drug in week 4 (i.e. 3 weeks on, 1 week off). For patients consenting to optional biopsies, a run-in dose of VS-6766 will be administered on a single day anywhere between Days -7 to Day -3 in order to facilitate pharmacodynamic (PD) biomarker analysis. Therefore, for patients undergoing biopsies the first cycle will be 5 weeks long and subsequent cycles will consist of 4 weeks.

If this schedule is not tolerated, alternative schedules may be explored following discussion by the Safety Review Committee.

1.5 Treatment group

Up to 24 patients with solid tumours will be treated in the dose escalation phase of this study. Once the MTD has been determined a further 86 patients will be enrolled to the dose expansion phase to further characterise the safety and tolerability and to assess the pharmacodynamic activity of the combination. There will be 7 cohorts in the dose expansion phase: 20 patients with KRAS mutant non-small-cell lung cancer (NSCLC); 20 patients with low grade serous ovarian cancer (LGSOC); 10 patients with RAS mutant colorectal cancer (CRC); 10 patients with pancreatic cancer; 10 patients with RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related); 10 patients with G12V specific KRAS mutant NSCLC and 6 patients with solid tumours (enriched for those with RAS mutations) that have consented and are willing to undergo biopsies at three time points throughout the study (as defined in section 8.2.1).

1.6 Trial timelines and accrual rate

It is expected that the trial recruitment duration will be 72 months with an expected accrual rate of approximately 1-2 patients per month across 2 centres in the dose escalation and approximately 2-3 patients per month across 3 centres in the dose expansion. A total of up to 80 patients will be entered into this trial, depending on how many patients are required to determine the MTD and RP2D during the dose escalation.

2 INTRODUCTION

2.1 Background

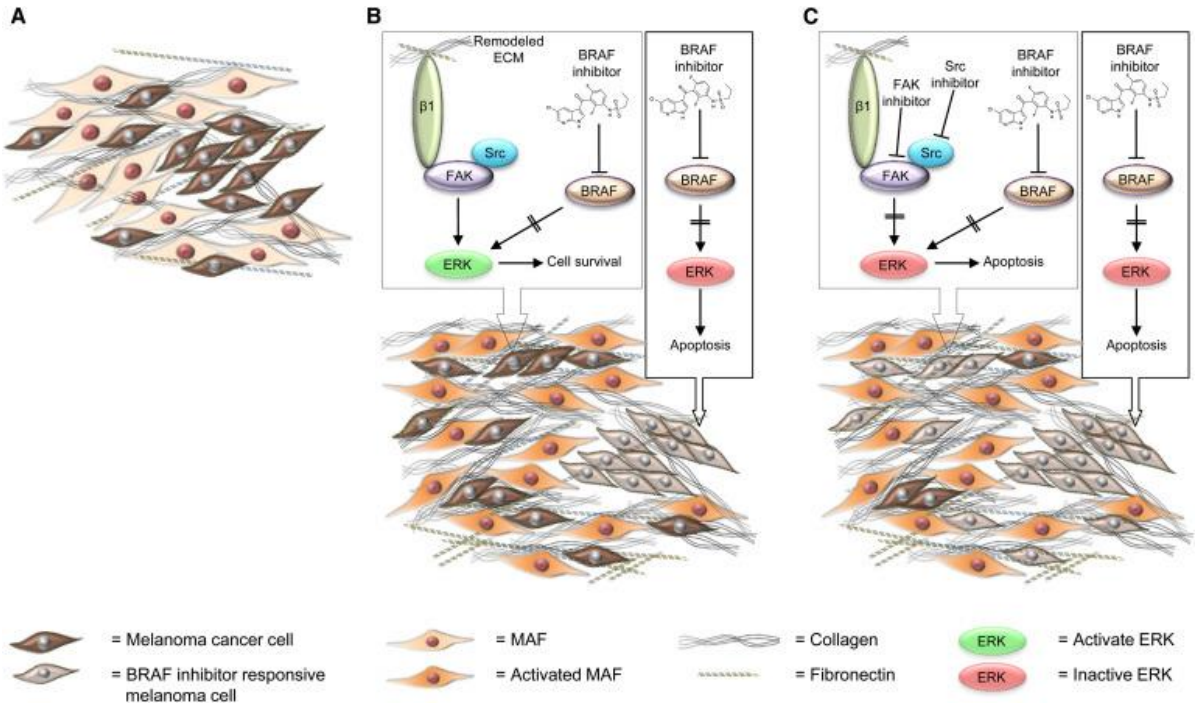
2.1.1 Background on MEK and FAK inhibitors

The RAS-RAF-MEK pathway has been targeted in anticancer drug development over the last two decades with differing degrees of success. Targeting EGFR, the epidermal growth factor receptor upstream on the pathway, was one of the first successes in colorectal and non-small-cell lung cancers and improved survival in molecularly selected patients [1, 2, 3]. BRAF inhibitors have recently enjoyed success in the treatment of melanoma with Vemurafinib extending survival in patients with BRAF mutant melanoma. However, treatment is not curative and responses are finite [4, 5]. The mechanisms of resistance vary but include: gatekeeper mutations developing secondary mutations in the kinase domain, as with EGFR inhibitors, and activation or secondary mutations in other pathways such as with BRAF inhibitors [5, 6, 7, 8, 9]. RAS mutations have been well documented in various cancers and remain a very attractive target, but attempts to develop drugs that inhibit its kinase activity have failed [5, 6, 7, 8, 9]. Other attempts to inhibit farnesylation have also met with limited results and have not been clinically successful [10, 11]. There remains an unmet need to treat RAS driven cancers with a molecularly targeted agent. The tumours driven by RAS encompass common tumours including pancreatic, colorectal, lung and ovarian cancers [5, 6, 7, 8, 9].

The two main downstream targets of RAS are RAF and MEK. While BRAF inhibitors are successful in BRAF mutant cancers, they are not effective in BRAF wild type cancers and are even thought to accelerate RAS driven tumours and have caused squamous cells carcinomas in normal skin [4, 12]. While drugs such as sorafenib were developed as CRAF inhibitors, it is widely accepted that their activity is due to VEGF inhibition. Biologically, MEK inhibitors have the advantage that they are downstream of multiple kinases that drive cancer such as RAS and RAF and will be less susceptible to resistance due to the development of secondary mutations upstream. However, critically, it only inhibits one pathway distally and cancer cells could activate multiple other parallel signal transduction pathways [13, 14]. It is thus widely believed that with a few exceptions, MEK inhibitors will be used in combination with other targeted agents [15].

FAK is a cytosolic protein kinase which has multiple effects on a cancer cell and its environment. It is associated with drug resistance as it can be activated in cancer cells when it is exposed to other signal tyrosine kinase inhibitors. FAK can also be activated by cellular stress and receptor tyrosine kinase inhibitors and signal through critical nodes in signal transduction pathway such as MEK [16]. It has been shown that targeting FAK kinase activity has the potential to modulate intra-tumoral Treg levels establishing an immunosuppressive tumour microenvironment. These findings suggest that FAK may have a significant impact on tumour stroma, restoring anti-tumour immunity [17]. In addition, it was recently shown that BRAF inhibition activates the stroma cells (melanoma activated fibroblasts MAFs) leading to FAK-dependent melanoma survival signalling and that extracellular matrix-derived signals can support residual disease as shown in Figure 1. BRAF and FAK inhibition showed synergy in preclinical models and it has been hypothesized that FAK targeting may attenuate divergent signalling from cell adhesion receptors and RTKs to cell survival and that may provide some benefit over simply targeting ERK signalling [18].

Figure 1



2.2 Investigational medicinal product

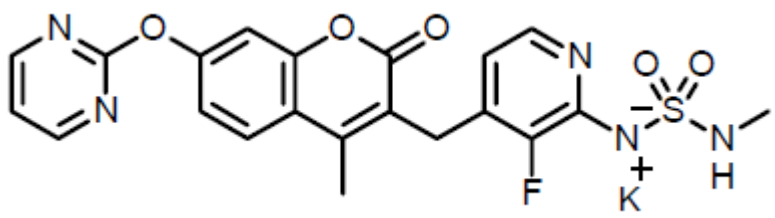
2.2.1 VS-6766 (RO5126766)

2.2.1.1 Overview of VS-6766

VS-6766, previously known as RO5126766 and CH5126766, is a dual RAF/MEK inhibitor which inhibits BRAF, CRAF and MEK. It has undergone a phase I trial and expectedly, the dose limiting toxicities have been chronic skin toxicity and acute eye toxicity [19]. The drug has shown proof of mechanism inhibition of downstream biomarkers such as p-ERK in normal tissue and in tumour.

2.2.1.2 Structure of VS-6766

The chemical structure of VS-6766 is as follows:



2.2.1.3 Mechanism of action of VS-6766

VS-6766 is a highly selective, dual RAF and MEK inhibitor. VS-6766 inhibited RAF family enzymes and MEK1 with a 50% inhibitory concentration (IC_{50}) of 0.056 µM (RAF-1), 0.019 µM (BRAF), 0.0082 µM (BRAF V600E), and 0.16 µM (MEK1). VS-6766 does not inhibit other serine/threonine and tyrosine kinases in enzyme assays against 32 kinases (The Institute of Cancer Research) and in the ATP competitive binding assay against 253 kinases (Ambit Biosciences). VS-6766 is the first example of a tandem MAPK signalling pathway inhibitor and provides a new strategy for cancer therapy.

2.2.1.4 Non-clinical anti-tumour activity

In in vitro cell-based assays, VS-6766 inhibited the phosphorylation of both MEK1/2 and ERK1/2, the direct substrates of RAF and MEK1/2, respectively, in a dose-dependent manner. The effects of VS-6766 on cell growth from the blocking of the RAF/MEK kinase were evaluated in various cancer cell lines, with wild-type and mutated KRAS and BRAF. A broad spectrum of anti-proliferation activity was observed; in particular in melanoma, non-small cell lung cancer (NSCLC), pancreatic cancer and colorectal cancer cells. For additional information, please refer to the Investigator's Brochure.

In vivo anti-tumour activities of VS-6766 were evaluated in xenograft models. VS-6766 demonstrated a potent and wide spectrum of anti-tumour activities in diverse human tumour xenograft models, including NSCLC, pancreatic, colorectal, melanoma, acute myelocytic leukaemia (AML), and hepatocellular carcinoma. Preferential efficacy was observed both in B-raf and Ras mutated tumours. Especially, K-ras and B-raf mutated tumours exhibited better responsiveness to VS-6766 with complete tumour regressions observed.

2.2.1.5 Animal pharmacology

In a 4-week repeated-dose toxicity study of VS-6766 in rats, skin lesion and tissue mineralization effects on the epithelium and findings in the gastrointestinal tract, the lymphohaematopoietic system, the bone, and the liver were observed. Two male rats died during the dosing or withdrawal period. The cause of death was attributed to haemorrhage in the stomach due to vascular rupture related to vessel mineralization.

From the results of safety pharmacology studies, no critical effects on the central nervous, the respiratory, and the cardiovascular systems were observed in rats or monkeys, and an in vitro study revealed that the effect on hERG currents was not concerning. There was no genotoxicity in any of the in vitro and in vivo tests.

VS-6766 markedly suppressed the activation of the MAPK pathway in peripheral blood mononuclear cells (PBMC) as evidenced by the significant inhibition of the PMA-induced phosphorylation of both MEK and ERK. Clear correlation of pharmacokinetics (PK) and pharmacodynamics (PD) was observed.

VS-6766 is mainly metabolized by CYP3A4. Excretion of VS-6766 and its metabolites into urine and faeces was almost completed within 48 h post-dose, suggesting both renal and biliary elimination. In rat urine, mainly the demethylated derivative and three unknown metabolites were observed; the parent compound was only a minor component.

VS-6766 showed low potential for drug-drug interactions mediated by CYP inhibition at pharmacologically relevant concentrations. Exposure of VS-6766 may be affected by CYP3A4 inhibitors or inducers.

2.2.1.6 Toxicology

Observed adverse effects following repeated administration were reversible, and they were considered to pose a reasonable safety risk/benefit profile for human subjects receiving a repeated oral administration in a well-controlled clinical setting. Based on the non-clinical safety data available, no major concerns were identified and data supported the Phase I clinical study to investigate the pharmacokinetics, pharmacodynamics, safety, and tolerability of VS-6766 in consenting cancer patients.

2.2.1.7 Clinical experience

The First in Human (FIH) Phase I trial was conducted in the Drug Development Unit (DDU) at The Royal Marsden Hospital. Expectedly, the dose limiting toxicities were chronic skin toxicity and acute eye toxicity [19]. Fifty-two patients received RO5126766 at doses of 0.1–2.7 mg (QD), 2.7–4.0 mg (4-days-on, 3-days-off schedule (4/3)) or 2.7–5.0 mg (7-days-on, 7-days-off schedule (7/7)). The most common DLTs were elevated creatine phosphokinase (CPK) n=3 and blurred vision, n=3. MTDs for each of the dosing schedules were 2.25 mg (QD), 4.0 mg (4/3) and 2.7 mg (7/7). The most frequent adverse events (AEs) were rash-related (94.2%) and gastrointestinal disorders, predominantly diarrhoea and stomatitis (79%). C_{max} was reached 1–2 hours after dosing, with a mean terminal half-life of ~60 hours. Target inhibition was demonstrated in both normal skin and tumour tissue. Tumour shrinkage was observed in 42.2% of patients evaluable for response, including three partial responses (two confirmed and one unconfirmed). Efficacy findings were also supported by fluorodeoxyglucose positron emission tomography (FDG-PET) imaging data, which showed a reduction of FDG uptake in 71% of patients between baseline and Day 15.

VS-6766 PK parameters were linear and time-independent with a substantially longer half-life than has been reported for other specific MEK inhibitors [12, 20, 21]. Plasma concentrations and exposure increased dose-proportionally and all doses of VS-6766 achieved plasma concentrations known to be effective in preclinical models [22]. VS-6766 had a favourable PK/PD profile and encouraging preliminary anti-tumour activity in this population of heavily pre-treated patients, achieving tumour shrinkage in >40% of patients across all dose levels. Based on observed DLTs, MTDs, safety, PK/PD assessments, efficacy and the long-term expected tolerability a dose regimen of 2.7 mg (4/3) was proposed for further investigation in Phase II trials (RP2D).

The FIH Phase I trial explored high dose intensity schedules which were limited by a $t_{1/2}$ of 60 hrs and a challenging toxicity profile. A subsequent, ongoing, investigator-initiated Phase I trial has explored intermittent dosing schedules and aims to determine if a lower dose intensity can still achieve significant target modulation and be clinically effective and tolerable. On evaluating two different schedules, the study showed that VS-6766 was more tolerable when administered at an intermittent twice weekly dosing schedule. The MTD/RP2D was determined to be 4 mg twice weekly. The drug has shown proof of mechanism inhibition of downstream biomarkers such as p-ERK in normal tissue and tumour. Encouraging clinical activity has been observed in *RAS*- and *RAF*-mutated malignancies at the RP2D even in a population pre-treated with other MEK inhibitors, particularly in KRAS mutant lung cancer.

2.2.1.8 Pharmacokinetics

The Phase I study demonstrated that, after oral administration of a single dose of VS-6766, plasma concentrations increased rapidly with C_{max} reached 1–2 hours after dosing with a mean

terminal half-life of approximately 60 hours. Apparent systemic clearance was 6 mL/min. Plasma exposure of VS-6766 increased approximately dose-proportionally. Steady state was reached by Day 15 and drug accumulations of between 2- and 7-fold were observed. PK parameters were consistent with that predicted by pre-clinical models [22].

2.2.1.9 Pharmacodynamics

As the RAS/RAF/MEK (MAPK/ERK) pathway is at the centre of muscle signalling networks a direct role of MEK inhibition in CPK elevation cannot be excluded [23, 24]. High exposure at steady state was significantly associated with an increased blood CPK. Of note, no keratoacanthoma or SCC were reported in this study of VS-6766 compared with the high incidence seen with the RAF inhibitors GSK2118436 and PLX4032, which has been linked to activation of ERK signalling in normal tissue without RAF mutations [25]. Furthermore, 65% (26/40) of normal skin biopsies analysed in this study showed a significant (i.e. >20%) reduction in pERK.

Target inhibition, studied by quantifying pERK in PBMCs, was concentration-dependent and consistent with that seen with other MEK inhibitors [20, 21, 26]. A reduction in pERK between baseline and Day 15 was seen in approximately half the tumours and a third of the skin biopsies. Increases in Ki67 in some skin samples may be related to skin toxicity. This was accompanied by a reduction in tumour cell proliferation and an increase in apoptosis, each seen in half the post-treatment tumour biopsies analysed. There was no clear relationship between dose and any of the biomarkers analysed. The small number of biopsy pairs available limited any conclusions that could be drawn.

2.2.1.10 Efficacy

Tumour shrinkage was seen in approximately 40% of patients, including two confirmed and one unconfirmed PR. One patient in each of the three dosing schedules achieved PR. Efficacy findings were supported by FDG-PET imaging data with 71% of patients experiencing a reduction of FDG uptake after 15 days of treatment.

VS-6766 appeared to be particularly active against melanoma, similar to other MEK and RAF inhibitors [12, 21]. RAF inhibitors such as dabrafenib and vemurafenib have demonstrated high response rates and improvement in PFS in patients with melanoma expressing the BRAF (V600) mutation [27, 28, 29], but are ineffective in tumours with wild-type BRAF. In the phase I study, VS-6766 achieved two PRs (confirmed and unconfirmed) in patients with BRAF (V600E)-mutant melanomas and one confirmed PR in a BRAF-wild-type melanoma tumour (although this tumour did contain an NRAS mutation). This novel activity, compared with specific RAF inhibitors, in a patient wild-type for BRAF may reflect the dual RAF/MEK inhibitory properties of VS-6766.

For additional information concerning VS-6766, refer to the Investigator Brochure.

2.2.2 Defactinib (VS-6063)

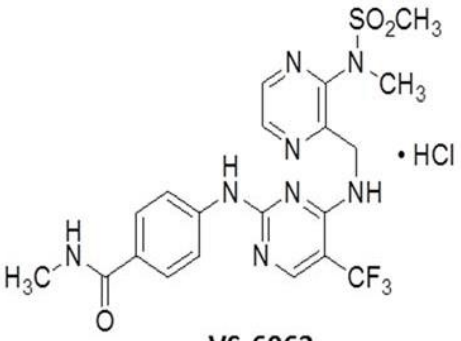
2.2.2.1 Overview of Defactinib

Defactanib was previously known as VS-6063. Defactinib is a small molecule, orally available potent adenosine-5'-triphosphate (ATP)-competitive, reversible inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2).

2.2.2.2 Structure of Defactinib

The active ingredient used for the current Defactinib clinical supplies is the hydrochloride salt.

The Chemical Structure of Defactinib is as follows:

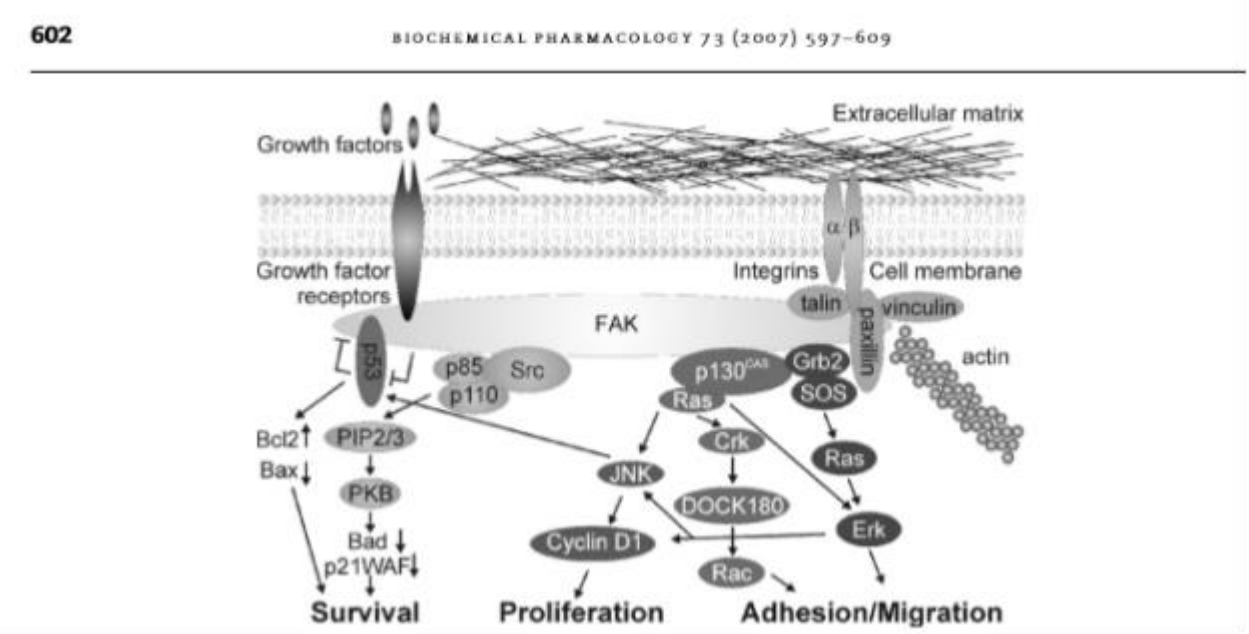


VS-6063

2.2.2.3 Mechanism of action of Defactinib

FAK and Pyk2 are members of the same family of non-receptor protein tyrosine kinases sharing significant sequence homology and are implicated as important integrating molecules in signal transduction cascades (Figure 2). High expression of the protein tyrosine kinase FAK has been frequently demonstrated to be associated with invasive and metastatic malignancies, implicating FAK in malignant progression of multiple epithelial tumours [30]. The role of Pyk2 in tumorigenesis is not as well established. However, recently Pyk2 upregulation was identified as a critical mechanism of feedback following inhibition of FAK function in endothelial cells implicating the dual inhibition of both FAK and Pyk2 as a potential strategy for targeting tumour angiogenesis [31]. A comprehensive evaluation of selectivity against a large panel of other kinases in enzyme assays demonstrated that Defactinib was highly selective for FAK and Pyk2 kinases strongly suggesting that its predominant pharmacologic activity is mediated by inhibition of FAK and Pyk2 kinases.

Figure 2



Defactinib has demonstrated antitumor efficacy in multiple human tumour xenograft models in mice including glioma, ovarian, colon, and pancreatic carcinoma models. In these studies, oral administration of Defactinib resulted in significant growth inhibition of established tumours at well tolerated dose levels.

To date, 6 clinical studies of single-agent treatment with Defactinib have been initiated in subjects with non-hematologic malignancies. The first-in-human (FIH) study (conducted by Pfizer), Study B0761001, was a safety, pharmacokinetics (PK) and pharmacodynamic study of single and multiple-doses of Defactinib administered orally at increasing dose levels (12.5 mg to 750 mg) administered twice daily under fasted conditions in subjects with advanced non hematologic malignancies. This study established the Defactinib dose of 400 mg twice daily to move forward in Phase II clinical studies.

2.2.2.4 Toxicology

A detailed review of nonclinical toxicology, PK and pharmacodynamic findings for Defactinib are provided in the Investigator's Brochure. Based on the nonclinical studies conducted with Defactinib, the liver and gall bladder, GI tract, hematopoietic system, testes/epididymis, and cardiovascular system have been identified as potential targets. With the exception of hepatobiliary and testicular toxicities, the toxicities observed in the nonclinical studies for each of the 2 compounds may reasonably be expected to reverse following drug discontinuation. Appropriate monitoring in humans includes serial liver function testing, routine blood biochemical and haematological parameters, urinalyses, vital signs, and electrocardiograms (ECGs).

2.2.2.5 Non-clinical anti-tumour activity

Oral administration of Defactinib demonstrated antitumor efficacy in multiple human tumour xenograft models in mice including glioma, ovarian, colon, pancreatic, breast and mesothelioma models.

For additional information concerning Defactinib, refer to the Investigator Brochure.

2.2.2.6 Clinical experience

The clinical data in subjects with KRAS mutant non-small cell lung cancer (Study Defactinib-201) has recently been published. Fifty-three patients with KRAS mutant NSCLC were enrolled across 9 US sites as of the data cut-off date (13-Mar-2015) [32]. Forty-seven patients were enrolled to one of the four molecularly defined cohorts. The median age was 62 years (range 33-80); 48% were female. The median number of prior lines of therapy was 3 (range 1-8). Fifteen (28%) patients met the 12 week PFS endpoint, with one patient achieving a PR. Median PFS was 46 days (range 12-205 days). Eight patients remained on study as of the data cut-off date. Clinical efficacy did not correlate with secondary mutation status across this KRAS mutant population. Adverse events considered at least possibly related to Defactinib were experienced by thirty-five patients (76%). The majority of these were grade 1 or 2. Eleven patients (24%) experienced at least possibly related grade 3-5 events, including 2 grade 5 respiratory failure events. Underlying disease was a confounding factor in many patients. The most commonly reported treatment emergent adverse events of any grade were fatigue (24%) and increased bilirubin (24%).

Defactinib has been evaluated in ten clinical studies to date: five clinical studies of single-agent treatment with Defactinib in subjects with non-hematologic malignancies, two combination studies with Defactinib in subjects with non-hematologic malignancies and three clinical studies in healthy volunteers.

To date, a total of 391 patients have received VS 6063. Forty-one of these patients received Defactinib in healthy volunteer studies (Defactinib-103, Defactinib-105, Defactinib-106), and the remaining 350 patients received Defactinib for advanced cancer. These include 177 patients who have received Defactinib in an open-label study (studies B0761001, Defactinib-101, Defactinib-102, Defactinib-104, Defactinib-201, and Defactinib-203) and 173 patients who received Defactinib in one randomized blinded placebo-controlled phase 2 study (study Defactinib-202). Of these 350 patients with cancer, 307 received Defactinib as monotherapy and 43 received Defactinib in combination, 22 in combination with paclitaxel and 21 in combination with the Verastem investigational agent VS-5584. In addition, 171 patients received placebo in a Defactinib clinical study (Study Defactinib-202).

Clinical studies conducted to date indicate that Defactinib has a safety (AE and laboratory) profile that is clinically manageable at the doses administered. Based on the review of the cumulative data the potential risks identified in association with Defactinib justify the continued investigation of Defactinib in subjects with advanced cancer.

For further information on clinical studies with VS6063 please refer to the Investigator Brochure.

2.3 Rationale for the proposed trial and dosing regimen

There is evidence that focal adhesion kinase (FAK) activation can drive the emergence of resistance after inhibition of the RAS-RAF-MEK pathway. In this trial we propose the combination of VS-6766 (RO5126766) a dual RAF/MEK inhibitor with an intermittent schedule, which has shown promising activity in *KRAS* mutant tumours with the FAK inhibitor Defactinib (VS-6063).

From previous phase I and II trials Defactinib is safe and tolerable with activity against *KRAS* mutant tumours. The combination of FAK and RAS-RAF-MEK inhibition may show additive activity and provide the proof of concept for FAK driven emergence of resistance following inhibition of the RAS-RAF-MEK pathway. Rationale for this study is based upon clinical data on each individual agent; there is no pre-clinical data available for the combination of VS-6766 with Defactinib.

The dosing regimen for Defactinib is 400 mg twice daily administered continuously for 21 days followed by 7 days break, in 28 day cycles. This regimen is based on the findings of the Phase I FIH study and supporting nonclinical data. In the FIH study, subjects received doses of 12.5 to 750 mg twice daily for 21 days. Exposure did not increase significantly above 425 mg twice daily; therefore, the maximum tolerated dose (MTD) was not established and the observed half-life was 9 hours supporting the twice daily dosing schedule. The Phase I trial for VS-6766 evaluated 3 schedules and determined the RP2D as 4mg 2 days per week (Mondays and Thursdays) with high efficacy and lower toxicity compared to more dose intense schedules. We believe that the intermittent dosing of the VS-6766 together with the Defactinib will prove to be a safe and tolerable combination. We aim to reach the RP2D for both VS-6766 and Defactinib in combination.

3 TRIAL DESIGN

3.1 Clinical trial objectives and endpoints

3.1.1 Primary objectives and endpoints

Primary objectives	Endpoints
To propose a recommended dose for Phase II evaluation by establishing the maximum tolerated dose of the combination of VS-6766 and Defactinib.	Determination of a dose at which no more than one patient out of up to six patients at the same dose level experience a highly probable or probable drug-related dose limiting toxicity, as defined in Section 3.1.3 of the protocol.
To assess the safety and toxicity profile of the combination of VS-6766 and Defactinib.	Determination of causality of each adverse event to VS-6766 and Defactinib and grading severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

3.1.2 Secondary objectives and endpoints

Secondary objectives	Endpoints
To characterise the pharmacokinetic profile of VS-6766 in combination with Defactinib.	Determination of the PK parameters (C_{max}, terminal half-life and area under curve) of VS-6766 and Defactinib when dosed together.

3.1.3 Exploratory objectives and endpoints

Tertiary objectives	Endpoints
To document any possible anti-tumour activity in patients.	Determination of disease response by RECIST criteria version 1.1 and collection of data related to progression free survival.
To study the pharmacodynamic profile of VS-6766 alone and in combination with Defactinib in pre-treatment and post-treatment biopsies and PBMC's.	Quantification of biomarkers such as p-MEK, p-ERK and p-FAK, E-cadherin and vimentin and enumeration of T cell populations which express CD8, CD4 and CD25.
To assess putative predictive biomarkers of response and resistance to the combination of VS-6766 and Defactinib.	Correlation of antitumour activity of the combination of VS-6766 and Defactinib with the detection of putative predictive biomarkers of response and resistance in archival tumours and plasma DNA.

3.2 Definition of dose limiting toxicity

The dose limiting toxicity (DLT) and maximum tolerated dose (MTD) are defined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

A DLT is defined as a highly probable or probable **drug (VS-6766 and/or Defactinib)-related** toxicity which meets at least one of the following criteria and occurs during Cycle 1:

- Grade 4 neutropenia or Grade 4 thrombocytopenia *see note;
- Grade ≥3 thrombocytopenia associated with clinically significant bleeding;

- febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (absolute neutrophil count [ANC] <1.0 x 10^9/L and fever ≥38.5°C);
- infection (documented clinically or microbiologically) with Grade 3 or 4 neutropenia (ANC <1.0 x 10^9/L);
- Grade ≥3 total bilirubin with associated Grade 3 or 4 aspartate transaminase (AST) and alanine transaminase (ALT)
- Grade 3 or 4 toxicity to organs other than the bone marrow. This includes Grade 3 and 4 biochemical AEs as DLTs.
- EXCLUDING:
  - Grade 3 nausea in patients who have not received optimal treatment with anti-emetics;
  - Grade 3 or 4 vomiting in patients who have not received optimal treatment with anti-emetics;
  - Grade 3 or 4 diarrhoea in patients who have not received optimal treatment with anti-diarrhoeals;
  - Grade 3 AST or ALT (unless increased by 2 or more grades from baseline);
  - Grade 3 bilirubin;
  - Grade 3 CPK elevation.
- Grade 3 skin toxicity occurring after dose reduction or if cessation of dosing and adequate supportive care measures for up to 2 weeks the toxicity does not improve to Grade ≤ 2;
- Grade 3 ophthalmological toxicity;
- Inability to receive at least 5 doses of VS-6766 and at least 32 doses of Defactinib out of the total number of doses given in Cycle 1;
- Delay of starting Cycle 2 dosing by >2 weeks due to treatment-related toxicities which have not resolved to baseline or ≤ Grade 1.
- Any other toxicity which the investigator deems to be dose-limiting.
- Death.

A DLT excludes:

- Alopecia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance.

*** Note: In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia, a full blood count must be performed at least on Day 5 after the onset of the event to determine if a DLT has occurred. Continue to monitor the patient closely until resolution to Grade 3 or less.**

If a patient has had a dose increase (from an initial dose level to a higher dose level), and then experiences one of the AEs listed above as DLTs, this patient should not be considered in the assessment of the higher dose level.

Should any change be made to the grade or causality of an AE during the trial that may alter its DLT status, the Drug Development Unit (DDU) must be informed immediately as this may affect dose escalation decisions.

All significant toxicities recorded throughout the study will be considered in the determination of the Phase II dose.

3.3 Definition of maximum tolerated dose

If 2 out of up to 6 patients at the same dose level experience a DLT as defined above, the MTD will be determined to be the dose level below that at which the DLT occurred. If cohort 1 is not tolerated, the study will stop and no further patients will be treated. If cohort 1 is tolerated recruitment to cohorts 2a and 2b will start simultaneously. If both these cohorts are tolerated, dose level 3 will be explored. If only cohort 2a is tolerated and not cohort 2b or vice versa, cohort 3 will

not be explored and either cohort 2a or 2b (whichever is tolerated) will be considered as the maximally tolerated dose. In the event that both cohort 2a and 2b are tolerated and cohort 3 is not tolerated, toxicity, PK and PD will be used to choose between the two cohorts, while recommending a Phase II dose. A minimum of 6 patients will need to be treated in a cohort to confirm a maximally tolerated dose. Decisions on dose escalation and determining the recommended Phase II dose will be made following review of all the relevant toxicity data by the Safety Review Committee.

3.4 Safety Review Committee (SRC)

As this is a phase I trial, there are stopping rules for toxicity during this study:

Regular weekly to 2-weekly safety reviews will be conducted between the Principal Investigator or delegate(s) from each investigational site and DDU Clinical Trials Manager or delegate.

After each dose level during the dose escalation phase of the study, a SRC will evaluate the safety and tolerability of VS-6766 in combination with Defactinib.

The decision may be to:

1. Proceed with dose escalation
2. Expand the cohort to a maximum of 6 evaluable patients
3. De-escalate the dose
4. Define the MTD (where 6 evaluable patients are assessed)
5. Stop the study

Formal review will occur once there are at least 3 evaluable patients (as defined in section 3.3) at a dose level. Decisions will be based on all relevant data available from all dose levels evaluated in the ongoing study and will include: available safety information, DLTs, CTCAE Grade ≥ 2 toxicity data and available PK and PD data from evaluable patients. Any dose interruptions and reductions will be taken into account.

The decisions and decision-making of the SRC on the next dose level will be documented and provided to the investigators prior to dosing any new patients. Patients must NOT be dosed at a higher dose level until after the SRC have agreed this and such communication has been received.

Once the MTD is reached, this combination will be further evaluated in the dose expansion phase. During dose expansion, SRC meetings will be held as required for safety review. Additional SRC meetings will be organised in the event of any safety concerns.

The SRC will consist of:

- Chief Investigator or delegate (which can be the Principal Investigator)
- Principal Investigator or delegate from each investigational site
- DDU Pharmacovigilance Officer or delegate
- DDU Clinical Trials Manager or delegate
- Senior ECMC clinician (who is not CI)

Further internal or external experts may be consulted by the SRC as necessary.

3.5 Patient evaluability

All patients receiving at least one administration of the IMPs, VS-6766 and/or Defactinib, will be evaluable for safety.

Escalation

For decisions on dose escalation an evaluable patient is defined as an eligible patient that has received the combination of VS-6766and Defactinib and either:

- has completed minimum safety evaluation requirements and has received at least 5 out of 6 doses of VS-6766 (or 5 out of 7 doses in patients requiring the run-in dose) and 32 out of 42 doses of Defactinib during the first cycle at a specified new dose level;

OR

- has experienced a DLT during the first cycle at a specified new dose level (as per section 3.1.3).

Evaluability & Response

Patients must receive at least one cycle of the trial medication, have baseline RECIST assessment and have had at least one post baseline RECIST assessment to be evaluable for response. Patients who progress prior to the first scheduled post baseline RECIST assessment would still be evaluable for response. To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal product's (IMP) VS-6766 and Defactinib are given.

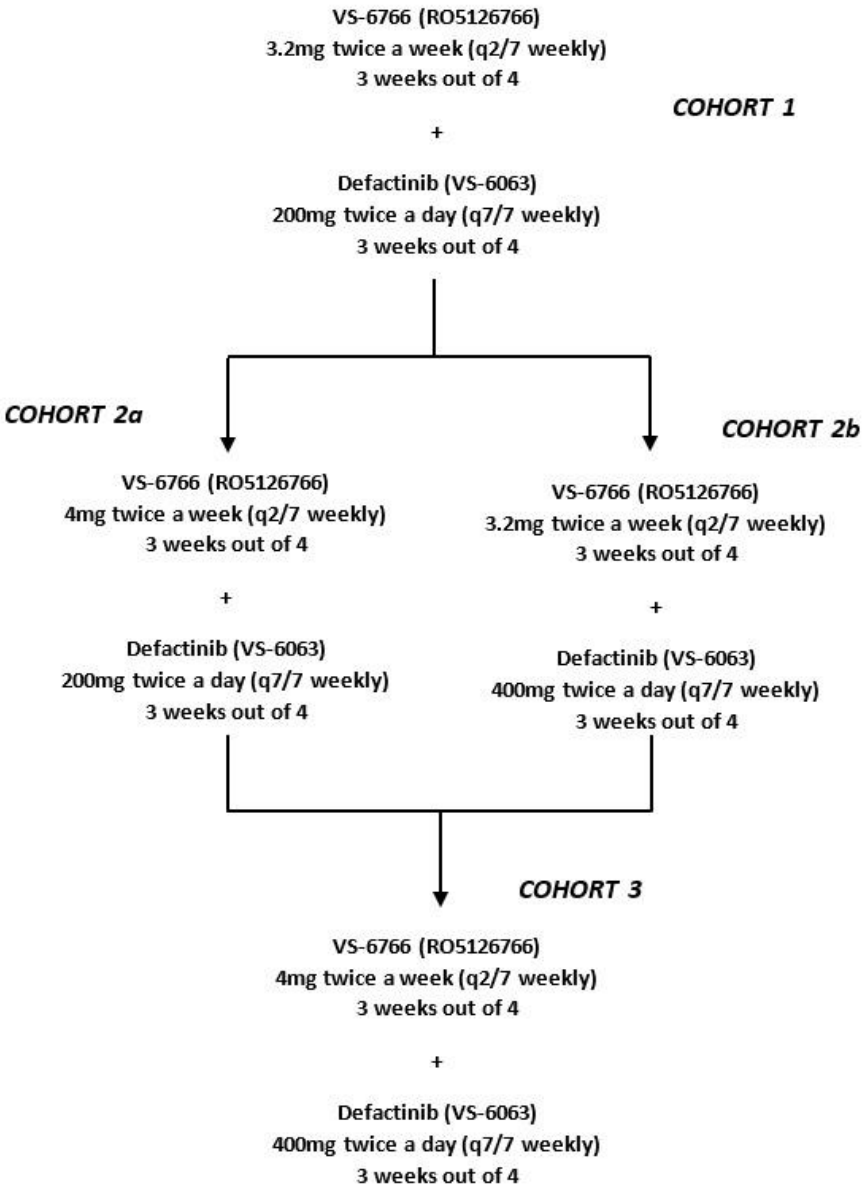
3.6 Design of the clinical trial

This is a multi-centre, Phase I, dose escalation trial evaluating the combination of a FAK inhibitor (Defactinib) with a RAF/MEK inhibitor (VS-6766) for the treatment of solid tumours.

There are two parts to this study: Dose Escalation and Dose Expansion.

Dose Escalation: escalating doses of VS-6766 and Defactinib will be evaluated in patients with advanced solid tumours. Dose escalation will follow a 3+3 design with a maximum of four patient cohorts. Each cohort will initially treat three patients, with a one week interval between the first and the second patient in each cohort. In the event of a dose limiting toxicity, the cohort will be expanded to six patients. A cohort will not be considered tolerable if two or more patients incur dose limiting toxicities. The dose escalation scheme is detailed below.

Figure 3. Schema of dose escalation



If cohort 1 is not tolerated, the study will stop and no further patients will be treated. If cohort 1 is tolerated recruitment to cohorts 2a and 2b will start simultaneously. If both these cohorts are tolerated, dose level 3 will be explored. If only cohort 2a is tolerated and not cohort 2b or vice versa, cohort 3 will not be explored and either cohort 2a or 2b (whichever is tolerated) will be considered as the maximally tolerated dose. In the event that both cohort 2a and 2b are tolerated and cohort 3 is not tolerated, available toxicity, PK and PD data will be used to choose between the 2 cohorts, while recommending a Phase II Dose. A minimum of 6 patients will need to be treated in a cohort to confirm a maximally tolerated dose.

Thus the maximal number of patients who can potentially be treated in the dose escalation cohort will be 6 x 4 cohorts = 24.

Decisions on dose escalation and determining the recommended Phase II dose will be made by the Safety Review Committee. Once the MTD has been determined an expansion cohort of 86 patients will be enrolled to further characterize the safety and tolerability and to assess the pharmacodynamic activity of the combination.

Dose Expansion: a total of 86 patients will be enrolled into the dose expansion phase to further characterise the safety and tolerability of the combination.

There will be 7 cohorts:

1) advanced NSCLC with documented KRAS mutation **(20 patients)**;

2) LGSOC **(20 patients)**;

3) CRC with documented RAS mutation **(10 patients)**;

4) Pancreatic cancer **(10 patients)**

5) RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related) **(10 patients)**

6) G12V specific KRAS mutant NSCLC **(10 patients)**

7) Advanced solid tumours (enriched for those with RAS mutations) with tumours accessible to biopsy **(6 patients)**.

It is expected that the trial recruitment duration will be 72 months with an expected accrual rate of approximately 1-2 patients per month across 2 centres in the dose escalation and approximately 2-3 patients per month across 3 centres in the dose expansion.

Pharmacokinetic and pharmacodynamic studies:

Blood samples for PK analysis will be taken for all patients in the dose escalation. Samples for pharmacokinetic studies will be collected for 48hrs after combination dosing (on a day where Defactinib and VS-6766 is taken) during Cycle 1 Week 2 or 3 (Cycle 1 Day 8-21).

Biopsies for PD analysis will be collected from patients enrolled to the solid tumour biopsy cohort in the dose expansion and are optional for all other patients in either part of the study. Biopsies will be collected at baseline (within 28 days before starting treatment), then 1-24 hours after the single VS-6766 dose during the Day -7 to Day-3 dosing run-in and then 1-24 hours post-RO5126766-dose on a day of combination (VS-6766 and Defactinib) dosing during Cycle 1 or Cycle 2.

4 PATIENT SELECTION

4.1 Eligibility criteria

The patient must fulfil the eligibility criteria (listed in Sections 4.1.1 and 4.1.2).

4.1.1 Inclusion criteria:

1. **Dose escalation:**
   Histologically or cytologically proven solid tumours, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient enriching for patients with RAS mutant solid tumours.

   Dose expansion:
   Histologically or cytologically proven advanced non-small-cell lung cancer (NSCLC) with a documented KRAS mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(20 patients)**.
   OR
   Histologically or cytologically proven advanced low grade serous ovarian cancer (LGSOC), refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(20 patients)**.
   OR
   Histologically or cytologically proven advanced colorectal cancer (CRC) with a documented RAS mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients)**.
   OR
   Histologically or cytologically proven advanced pancreatic cancer or metastatic pancreatic cancer, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Endometroid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related) with a documented RAS or RAF mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Histologically or cytologically proven advanced non-small-cell lung cancer (NSCLC) with a documented KRAS G12V specific mutation, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient **(10 patients).**
   OR
   Histologically or cytologically proven RAS mutant solid tumours, refractory to conventional treatment, or for which no conventional therapy exists or is declined by the patient. Patient must have biopsiable disease, be willing and has consented to undergo biopsies at three time-points **(6 patients)**.

2. Predicted life expectancy of at least 12 weeks

3. World Health Organisation (WHO) performance status of 0 or 1 (Appendix 1)

4. Haematological and biochemical indices within the ranges shown below. These measurements must be performed within two weeks (Day -14 to Day 1) before the patient goes on the trial.

Laboratory Test	**Value required**
Haemoglobin (Hb)	≥ 9.0 g/dL
Absolute neutrophil count (ANC)	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Serum bilirubin	≤ 1.5 x upper limit of normal (ULN)
Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)	≤ 2.5 x (ULN) unless raised due to tumour in which case up to 5 x ULN is permissible
Either: Calculated creatinine clearance Or: Serum creatinine	 ≥ 50 mL/min (uncorrected value) ≤ 1.5 x ULN

5. Men and women aged 18 years or over.

6. Written (signed and dated) informed consent and be capable of co-operating with treatment and follow-up.

7. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

8. **Dose escalation**
Measurable disease according to RECIST 1.1 or evaluable disease. All radiology studies must be performed within 28 days prior to registration.

Dose expansion
Measurable disease according to RECIST 1.1, all radiology studies must be performed within 28 days prior to registration.

9. Corrected QT interval (QTc) < 470 ms (as calculated by the Fridericia correction formula, averaged over 3 ECGs).

10. Agrees to the use of archival paraffin embedded tissue and has archival tumour tissue available.

4.1.2 Exclusion criteria:

1. Radiotherapy (except for palliative reasons), endocrine therapy, biological therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, Mitomycin-C) before treatment.

2. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1 toxicities, which in the opinion of the Investigator and the DDU should not exclude the patient.

3. Known untreated or active central nervous system (CNS) metastases (progressing or requiring corticosteroids for symptomatic control). Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:
    - Evaluable or measurable disease outside the CNS is present.
    - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the baseline disease assessment for at least 28 days.

4. Ability to become pregnant (or already pregnant or lactating). However, those female patients who have a negative serum or urine pregnancy test before enrolment and agree to use two medically approved forms of contraception (oral, injected or implanted hormonal contraception and condom, have an intra-uterine device and condom, diaphragm with spermicidal gel and condom) from time of consent, during the trial and for six months afterwards are considered eligible.

5. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children by using one form of medically approved contraception [condom plus spermicide] during the trial and for six months afterwards). Men with pregnant or lactating partners should be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

6. Major surgery within 4 weeks prior to entry to the study (excluding placement of vascular access), or minor surgery within 2 weeks of entry into the study and from which the patient has not yet recovered.

7. Treatment with warfarin. Patients on warfarin for DVT/PE can be converted to LMWH.

8. Known history of Gilbert's Syndrome.

9. Acute or chronic pancreatitis.

10. At high medical risk because of non-malignant systemic disease including active uncontrolled infection.

11. Known to be serologically positive for hepatitis B, hepatitis C or human immunodeficiency virus (HIV).

12. Patients with the inability to swallow oral medications or impaired gastrointestinal absorption due to gastrectomy or active inflammatory bowel disease.

13. Concurrent ocular disorders:

    a) Patients with history of glaucoma, history of retinal vein occlusion (RVO), predisposing factors for RVO, including uncontrolled hypertension, uncontrolled diabetes
    b) Patient with history of retinal pathology or evidence of visible retinal pathology that is considered a risk factor for RVO, intraocular pressure > 21 mm Hg as measured by tonometry, or other significant ocular pathology, such as anatomical abnormalities that increase the risk for RVO.
    c) Patients with a history of corneal erosion (instability of corneal epithelium), corneal degeneration, active or recurrent keratitis, and other forms of serious ocular surface inflammatory conditions.

14. Concurrent congestive heart failure, prior history of class III/ IV cardiac disease (New York Heart Association [NYHA] - refer to Appendix 4), myocardial infarction within the last 6 months, unstable arrhythmias, unstable angina or severe obstructive pulmonary disease.

15. Patients exposed to strong CYP3A4 and strong CYP2C9 inhibitors within 7 days prior to the first dose.

    N.B. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/table.aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information.

16. Is a participant or plans to participate in another interventional clinical trial, whilst taking part in this Phase I study of VS-6766 in combination with Defactinib. Participation in an observational trial would be acceptable.

17. Symptoms of COVID-19 and/or documented current COVID-19 infection (the patient can be reassessed for eligibility following a full recovery and negative COVID-19 test)

18. Any other condition which in the Investigator's opinion would not make the patient a good candidate for the clinical trial.

4.2 Patient enrolment

All patients who provide informed consent including any screen failures must be entered onto the patient enrolment log provided by the DDU to the investigational site.

Before enrolling the patient in the trial, the Investigator or designated representative should confirm the patient is eligible to enter the trial. An enrolment form should be completed prior to enrolment. To enrol a patient, email the completed enrolment form (see below). A trial number and dose level allocation will be allocated. The original enrolment form should be filed within the Investigator Trial File.

To enrol a patient please email the completed eligibility and enrolment form to:

FRAME@icr.ac.uk (Monday – Friday 09:00-17:00)

5 TREATMENT

5.1 Selection of the Phase I starting dose and schedule

Rationale for the dosing regimen:

Phase I trials for VS-6766 have determined the RP2D as 4mg administered 2 days per week (Mondays and Thursdays) with high efficacy and lower toxicity compared to more dose intense schedules. We believe that the intermittent dosing of the VS-6766 together with the Defactinib will prove to be a safe and tolerable combination. We aim to reach the RP2D for both IMPs in combination.

The dosing regimen for Defactinib is 400 mg twice daily administered in continuous 21 day cycles. This regimen is based on the findings of the Phase I FIH study and supporting nonclinical data. In the FIH study, subjects received doses of 12.5 to 750 mg twice daily for 21 days. Exposure did not increase significantly above 425 mg twice daily; therefore, the maximum tolerated dose (MTD) was not established and the observed half-life was 9 hours supporting the twice daily dosing schedule.

VS-6766 will be administered twice a week on either Monday and Thursday or Tuesday and Friday. A cycle of treatment will comprise 28 days however VS-6766 will only be administered for 3 out of every 4 weeks. The starting dose will be 3.2mg once a day given orally.

Defactinib will be administered every day for 3 out of every 4 weeks, i.e. 21-days-on, 7-days-off. The starting dose will be 200mg twice a day given orally.

Taken into account that this is a novel combination, lower starting doses have been selected, with planned escalations to reach 4mg VS-6766 and 400mg Defactinib if toxicities permit.

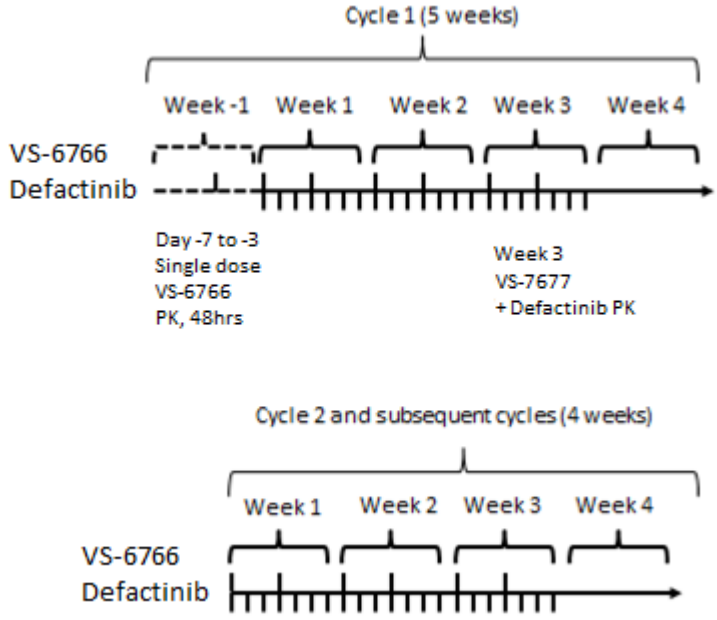
5.2 Dosing schedule/treatment schedule

VS-6766 will be administered orally once a day on 2 days per week (Mondays and Thursdays or Tuesdays and Fridays) for 3 out of 4 weeks. VS-6766 should be taken 1 hour before or 2 hours after a meal. Defactinib will be administered orally twice a day for 3 out of 4 weeks. Defactinib should be taken immediately after a meal. One cycle consists of 28 days and neither drug should be taken in the last week of any cycle.

For patients undergoing biopsies in either part of the study, there will be a ‘run in’ dose of VS-6766 on a single day anywhere between Day -7 to Day -3 in order to facilitate PD analysis. Combination dosing (VS-6766 and Defactinib) will then commence on Cycle 1 Day 1 for 3 weeks followed by one week without either drug in week 4. Thus the first cycle will be 5 weeks and the subsequent cycles will consist of 4 weeks.

On PK days in the dose escalation, patients should have a meal and then immediately take their morning dose of Defactinib. Patients should then fast for 2 hours before taking their dose of VS-6766. Timing of PK samples should be calculated from the time of Defactinib dosing.

Figure 4. Schema of drug administration for Cycles 1 and 2



Each cohort will initially treat 3 patients, with a 7 day interval between the first and the second patient in each cohort. In the event of a dose limiting toxicity, the cohort will be expanded to 6 patients.

During the dose expansion phase VS-6766 and Defactinib will be given at the dose and schedule determined during the dose escalation phase in repeating 28-day cycles.

5.3 Dose escalation scheme

Dose escalation will follow a standard 3+3 dose escalation scheme exploring a maximum of 4 patient cohorts as shown in the table below.

Table 1: Dose escalation for VS-6766 or Defactinib

Dose Level	VS-6766	Defactinib	Estimated number of patients
1	3.2mg twice a week (q2/7 weekly) 3 weeks out of 4	200mg twice a day (q7/7) 3 weeks out of 4	3+3
2a*	4mg twice a week (q2/7 weekly) 3 weeks out of 4	200mg twice a day (q7/7) 3 weeks out of 4	3+3
2b*	3.2mg twice a week (q2/7 weekly) 3 weeks out of 4	400mg twice a day (q7/7) 3 weeks out of 4	3+3
3	4mg twice a week (q2/7 weekly) 3 weeks out of 4	400mg twice a day (q7/7) 3 weeks out of 4	3+3

**Cohort 2a and 2b will be run in parallel*

Each cohort will initially treat 3 evaluable patients, with a one week interval between the first and the second patient in each cohort. In the event of a dose limiting toxicity, the cohort will be expanded to 6 evaluable patients. A cohort will not be considered tolerable if 2 or more patients incur dose limiting toxicities.

If the dose regimen in cohort 1 is not tolerated, the study will stop and no further patients will be treated. If the dose regimen in cohort 1 is tolerated recruitment to cohorts 2a and 2b will start simultaneously. If both these cohorts are tolerated, dose level 3 will be explored. If only cohort 2a is tolerated and not cohort 2b or vice versa, cohort 3 will not be required and either cohort 2a or 2b (whichever is tolerated) will be considered as the maximum tolerated dose. In the event that the dose in both cohort 2a and 2b are tolerated and in cohort 3 is not tolerated, toxicity, PK and PD data will be used to choose between the 2 cohorts, while recommending a Phase II dose. A minimum of 6 patients will need to be treated in a cohort to confirm a maximum tolerated dose.

Decisions on dose escalation will be made by the Safety Review Committee (see Section 3.4). Dose escalation will continue until MTD(s) are reached. Once the MTD has been determined an expansion cohort of 56 patients will be enrolled to further characterize the safety and tolerability and to assess the pharmacodynamic activity of the combination.

Whilst cohorts 2a and 2b are both open to recruitment, patients will be allocated alternately between the 2 cohorts starting with cohort 2a. If, however, the next cohort to be allocated is temporarily closed to recruitment (for example awaiting a safety decision), recruitment will continue to the other cohort alone until both cohorts are open.

Patients will be dosed on a flat scale and not by body weight or body surface area.

5.3.1 Intra-patient dose escalations

If the dose of VS-6766 or Defactinib has been reduced due to a DLT, it will not be increased again in the same patient.

Intra-patient dose escalation can be considered for patients treated in the dose escalation phase of the study after 2 cycles of treatment, providing the patient is not experiencing unacceptable toxicity and provided that at least 3 patients at the higher dose level cohort have all reached the end of the DLT period without experiencing a dose-limiting toxicity.

Patients that have undergone a dose reduction to a lower dose level due to toxicity may NOT re-escalate.

In the expansion phase of the study, dose escalations will not be permitted.

5.3.2 Expansion of dose level(s)

If 1 instance of DLT (as defined in Section 3.1.3) is observed in 3 patients, up to 6 patients will be treated at that dose. If 1 out of 6 patients experience a DLT, dose escalation will continue. If 2 out of up to 6 (i.e. between 2 and 6) patients experience a DLT dose escalation will stop and this dose will be defined as the maximum administered dose (MAD). At least 3 more patients will be treated at a dose below the MAD to define the MTD.

The MAD could also equal the MTD in the event that dose escalation is stopped before two DLTs are observed at a given dose level, due to the expectation that higher dose levels would be too toxic to administer to patients.

5.4 Dose modifications

If a patient experiences a clinically significant and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered as required. One or both IMP's may be reduced, depending on the causality of the toxicity.

If the drug-related toxicity resolves or reverts to Grade ≤ 1 within 14 days of onset treatment with the combination of VS-6766 or Defactinib may be restarted at the same dose. This is with the exception of elevated CK or rash, these toxicities should resolve or revert to Grade ≤ 2 within 14 days of onset, to restart treatment with the combination of VS-6766 or Defactinib at the same dose. If it is necessary to interrupt the dose again the patient should be treated at a reduced dose level. Patients can have more than one dose reduction (see Table 2 below). In the event a toxicity cannot be clearly associated with one study drug, both drugs will be dose reduced.

Table 2: Dose reductions

	VS-6766	**Defactinib**
1st Dose Reduction	3.2mg once daily MT/TF for 3 out of 4 weeks	200mg twice daily continuous dosing for 3 out of 4 weeks
2nd Dose Reduction	2.4mg once daily MT/TF for 3 out of 4 weeks	200mg once daily continuous dosing for 3 out of 4 weeks
3rd Dose Reduction	2.4mg once daily MT/TF for 2 out of 4 weeks	200mg once daily continuous dosing for 2 out of 4 weeks

An alternative to dose reductions is reducing the length of treatment per cycle. This could include a two and half weeks on-one and a half week off or two weeks on and two weeks off schedule. This can be used (but is not limited to) when patients have been on treatment for over four months of treatment and have chronic toxicities. Dose reduction should be explored prior to exploring a schedule switch. This is on the discretion of the investigator following discussion with the study team where thought to be a more appropriate alternative to dose reductions.

If despite appropriate dose reductions and/or delays, the patient experiences unacceptable toxicities specifically attributed to either VS-6766 or Defactinib then consideration will be given to the patient continuing on single agent treatment with the approval of the Chief Investigator.

In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Once the dose has been reduced it may not be re-escalated.

If a dose interruption is required within a cycle, the clock doesn't stop and cycles and visit dates continue until the end of the cycle. If a dose is delayed between cycles, the patient will have unscheduled visits until treatment is restarted at the next cycle. Patients may have their cycle delayed by up to two weeks.

Adverse events assessed by the Investigator as exclusively related to underlying disease, medical condition or concomitant treatment will not be taken into consideration for treatment interruption

and dose reduction. If treatment must be delayed for reasons other than toxicity, contact the Chief Investigator to discuss the reasons for delay and plans for resuming study therapy. A dose interruption lasting longer than 28 days is permitted for reasons other than toxicity.

In cases involving drug related toxicity, IMP may be interrupted for a maximum of 28 days including the scheduled week off. In exceptional cases where the patient maintains a minimum of partial response whilst interrupted or delayed they may be given permission to continue on study by the Chief Investigator when the 28 days has been exceeded.

5.5 Dose interruptions due to COVID-19

If a patient tests positive for COVID-19 during the study, treatment will be interrupted until the patient becomes asymptomatic, has tested negative for the virus and it is deemed safe for them to continue on study. During treatment interruption the patient will be followed up regularly by phone.

5.6 Toxicity management guidelines

5.6.1 Hyperbilirubinemia

Raised bilirubin has been observed with Defactinib. These increases are generally transient and not associated with increases in AST or ALT. Increased bilirubin often resolves spontaneously even with continued drug treatment. The following dose modifications for Defactinib are suggested in the event of increased bilirubin.

• If the Grade 3 or 4 raised bilirubin is not associated with an increase in AST or ALT, the bilirubin value must return to ≤ Grade 2 before resuming Defactinib at the current dose level.

• If on retreatment bilirubin returns to ≥Grade 3, withhold treatment with Defactinib until toxicity is ≤ Grade 2 or bilirubin returns to baseline levels then decrease the Defactinib dose by one dose level (see Section 5.4).

• If on retreatment bilirubin increases to ≥Grade 2 and is associated with a ≥Grade 2 increase in AST and/or ALT, permanently discontinue Defactinib.

5.6.2 Rash

Treatment-related rash is commonly manifested as maculo-papular or acneiform rash, with or without pruritus**. Prophylactic steroid creams should be given to prevent the occurrence of serious rash.** Guidelines for treating rash are found in the following table:

Table 3: Guidelines for the treatment of rash

Grade of rash	Recommended action
Grade 1	•Continue with IMP's and consider prophylactic steroid cream
Grade 2	•Consider giving Doxycycline 100mg OD for 14 days • Increase steroid cream frequency or strength as clinically appropriate
Grade 3	• Hold dosing of both IMPs

	• Treat rash with topical corticosteroids and/or systemic corticosteroids (oral or IV). Hold study treatment as long as systemic corticosteroids are being given. • Consider dermatological consultation • If rash improves to Grade ≤ 2 and upon completion of any systemic corticosteroids, resume RO5126766 at one dose level lower and Defactinib at the same dose or one dose level lower (as per Section 5.4).
Grade 4	• Permanently discontinue IMPs • Treat with topical corticosteroids and/or systemic corticosteroids. • Consider dermatological consultation

5.7 Duration of treatment

Treatment should continue unless (a) the patient asks to be withdrawn, (b) there is evidence of disease progression or (c) the patient is experiencing unacceptable toxicity or for any of the reasons listed in Section 11.

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.7.1 Replacement of patients

Patients who do not complete one cycle of dosing with VS-6766 and Defactinib for reasons other than toxicity will be replaced.

5.8 Concomitant medication and treatment

Concomitant medication may be given as medically indicated. Details (including doses, frequency, route and start and stop dates) of the concomitant medication given must be recorded in the patient's medical records and the case report form (CRF). The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

The patient must not receive other anti-cancer therapy or investigational drugs while on the trial.

Radiotherapy may be given concomitantly for the control of bone pain however the irradiated lesions will not be evaluable for response, unless they are clearly progressing at the time of initiating systemic therapy.

In *in vitro* studies, Defactinib has been shown to be metabolised by CYP2C9 and CYP3A4. *In vitro* studies have shown that Defactinib inhibits CYP2C9 and CYP3A4 in human liver microsomes. Extrapolation to expected human exposure indicates the potential for inhibition or induction of CYP enzymes is low. VS-6766 is metabolised mainly by CYP3A4.

Therefore, it is recommended that:

- Concomitant use of strong inhibitors of CYP3A4 or CYP2C9 are prohibited. Concomitant use of moderate or weak inhibitors of CYP3A4 or CYP2C9 should be avoided if possible or used with caution.

- Concomitant use of strong inducers of CYP3A4 or CYP2C9 should be avoided if possible or used with caution. Concomitant use of moderate or weak inducers of CYP3A4 or CYP2C9 should be used with caution.

- Compounds that are substrates for CYP3A4 or CYP2C9 should be used with caution.

Concomitant medications that are strong CYP3A4 inducers and CYP2D9 substrates should be avoided by patients. Please refer to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for an exhaustive list of medications to be avoided.

If subjects require anticoagulation an alternative to warfarin should be used. Patients who require anticoagulation but cannot discontinue warfarin are excluded from this study. For subjects requiring the start of anti-coagulation therapy during the course of any Defactinib trial, alternatives to warfarin should be used.

Routine use of colony stimulating factors (CSFs) is not permitted during this study; furthermore, patients should not receive prophylactic growth factors.

Use of erythropoietin is allowed.

Use of stimulators of thrombopoiesis is not allowed.

Supportive or other palliative measures are permitted, with any exceptions as noted.

5.8.1 COVID-19 Vaccine Guidance

If possible patients should not receive the vaccine during the first cycle of treatment as it may be difficult to differentiate between AE's related to IMP and the vaccine. If the patient has a date for a vaccination and has not commenced dosing with either IMP it is recommended that their first dose is postponed at least 1 week following vaccination.

If the patient is already on study, both drugs should be withheld for 3 days if possible prior to and after vaccination, which should be scheduled during the week off treatment at the end of a cycle to minimise dosing interruptions. Alternatively, multiple doses of treatment from the 2nd cycle onwards may be missed for this reason.

Patients must have been made aware there is no data about the safety of trial medication during COVID-19 vaccination or any effects of the trial medication on the efficacy of the vaccine. This must be clearly documented in the patients' medical notes.

This guidance applies for all licensed COVID-19 vaccines and to each dose of vaccine individually.

5.8.2 Advice for patients

It is not known whether the preclinical changes seen in the male animal reproductive organs, after treatment with Defactinib, will be fully reversible or will permanently affect the ability to produce healthy sperm following treatment. Therefore, if male patients wish to father children they should be advised to arrange for sperm cryopreservation prior to the start of study treatment.

Patients should be advised to avoid sun exposure, use sunscreen (sun protection factor [SPF] 50 or higher) containing zinc or titanium oxide rather than synthetic sunblocks, protective clothing and lip balm with sunscreen. Patients should use soap-free face cleansers (such as no-rinse cleansing gel twice a day). It is recommended to use an antimicrobial soap for armpits and genitals and mild soap for showering. Patients should use an alcohol-free, oil-free moisturizing cream twice daily. Gloves should be worn to protect the patients' hands when household cleaning is performed.

6 PHARMACEUTICAL INFORMATION

6.1 Supply of IMP

A complete certificate of analysis and a Qualified Person (QP) certification must be provided with each batch of IMP and be retained in the Investigator Trial File (ITF)/Pharmacy File.

All study drug will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice, stating that the drug is for clinical trial use only and should be kept out of the reach and sight of children. When VS-6766 was known as RO5126766, it was supplied by Chugai. VS-6766 will be packaged, QP released and labelled by PCI Pharma Services under contract to Verastem, once all the RO5126766 stock supplied by Chugai has been used. Defactinib (VS-6063) will be supplied by Verastem and will also be QP released and labelled by PCI Pharma Services. Formulation, storage and administration data for VS-6766 (RO5126766) remain the same for both Chugai and Verastem produced IMP. Further information on both drugs is provided in the Pharmacy Manual.

VS-6766 (RO5126766) and Defactinib will only be dispatched to sites after receipt of confirmation that the regulatory checklist is complete.

For information on all IMP and re-ordering of supplies, contact the DDU Clinical Trials Manager responsible for the trial who will arrange further supplies.

6.2 Pharmaceutical data: VS-6766

6.2.1 Formulation of VS-6766

VS-6766 will be supplied as hypromellose (HPMC) capsules for oral administration at a dosage strength of 0.8 mg. The capsule fill consists of VS-6766 and the inactive ingredients mannitol and magnesium stearate.

6.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area. VS-6766 must be stored at 2-8 C protected from light.

6.2.3 VS-6766 administration

VS-6766 will be administered on a twice weekly (Monday and Thursday) schedule under fasting conditions (approximately 1 hour **prior** or 2 hours after a meal). Treatment will be for three weeks followed by a week off in every 28 day cycle. The starting dose, based on the previous Phase I trial will be 3.2 mg given orally as a single daily dose.

Run-in doses should be supervised in clinic with VS-6766 dispensed to the patient immediately prior to dosing and then returned to pharmacy following the supervised dose. C1D1 dosing should be performed in clinic before the patient then leaves with their supply.

A sufficient supply of study drug will be dispensed to the subject by the Investigator or trained designee for the subject to take on an outpatient basis between visits.

6.3 Pharmaceutical data: Defactinib

6.3.1 Formulation of Defactinib

Defactinib is formulated as a white to off-white oval tablet for oral administration and supplied in single unit dose strength of 200 mg. In addition to Defactinib, formulation components include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, and magnesium stearate. Packaging and labelling will be prepared to meet all regulatory requirements.

6.3.2 Storage conditions

All supplies must be stored in a secure, limited access storage area.

The labelled storage condition for the drug product is “Store between 15 and 30°C (59 and 86°F).” Bottles are labelled with pill strength and other information as per local regulatory requirements.

6.3.3 Defactinib administration

Patients will receive Defactinib orally immediately after a meal twice daily (approximately every 12 hours). The starting dose will be 200mg. Treatment will be continuous for three weeks followed by a week off in every 28 day cycle.

A sufficient supply of study drug will be dispensed to the subject by the Investigator or trained designee for the subject to take on an outpatient basis between visits.

6.4 Study drug accountability

Accurate records of all IMP shipments, tablets/capsules dispensed, and all tablets/capsules returned must be maintained. This inventory record must be available for inspection at any time by members of the Drug Development Unit (DDU). IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator delegates responsibility for IMP management to the Pharmacist. The Pharmacist undertakes not to destroy any unused IMP unless directed to by the DDU. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record. During the course of the trial the Clinical Research Associate will check the numbers of capsules of VS-6766/tablets of Defactinib shipped to the centre, the number used and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

7 INVESTIGATIONS SCHEDULE

In cases where a patient has investigations at a different hospital, for example weekly blood samples, then it is the Investigator's responsibility to ensure he/she receives and reviews the results. The results must be recorded on the eCRF and the reports from the other hospitals must be available for source data verification. Laboratory reference ranges, including effective dates, and evidence of laboratory accreditation must be obtained from all laboratories used.

7.1 Pre-treatment evaluations

Details of all evaluations/investigations for enrolled patients, including relevant dates, required by the protocol must be recorded in the medical records so that the eCRF can be checked against the source data.

Please also refer to the tabulated Schedule of Assessments in Section 7.5.

7.1.1 Obtaining written informed consent

Written informed consent must be obtained from the patient before any protocol-specific procedures are carried out and within four weeks before the patient's first dose of the IMP (VS-6766 and Defactinib). Initial discussion and signing of the informed consent must not occur on the same day, as the patient must be given time to think about their commitment to the trial.

Patients with non-small-cell lung cancer who are being considered for the NSCLC cohort in the dose expansion without prior documentation of a G12V KRAS mutation will be asked to give their written consent to pre-screening KRAS G12V mutation analysis. Patients with endometrioid cancer who are being considered for the endometrioid cohort in the dose expansion without prior documentation of a RAS and/or RAF mutation will be asked to give their written consent to pre-screening RAS and/or RAF mutation analysis. This should be carried out in the same was at the main consent process but may be performed up to 24 weeks prior to enrolment into the study. Only once the presence of these mutations is confirmed may the patient give their consent to participate in the main study. Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, and have signed the Study Site Delegation Log, are permitted to gain informed consent from patients and sign the consent form. All signatures must be obtained before the occurrence of any medical intervention required by the protocol (ICH GCP 4.8.8 and 8.3.1.2). The date of the signatures of both the patient and the PI/Sub-Investigator should be the same.

The PI or the Sub-Investigator must inform the patient about the background to, and present knowledge of the normal management of their disease. The PI or the Sub-Investigator must also inform the patient about the IMPs (VS-6766 and Defactinib). The patient should also be made aware of the following points:

- The known toxicity of the IMPs and the possibility of experiencing side-effects.
- That the IMPs are new and that the exact degree of activity is at present unknown, but that treating him/her will contribute to further knowledge.
- The potential dangers of becoming pregnant (or the patient's partner becoming pregnant) and he/she has been given information about appropriate medically approved contraception. (refer to Section 9.6).

- That he/she may refuse treatment either before or at any time during the trial and that refusal to participate will involve no penalty or loss of benefits to which they are otherwise entitled.

- Whom to contact for answers to pertinent questions about the research and their rights, and also who to contact in the event of a research-related injury.

A copy of the consent form and patient information sheet must be given to the patient to keep and the original consent form and patient information sheet, must be filed in the Investigator Trial File (ITF).

COVID-19 guidelines: If a patient tests positive for COVID-19 during the screening period, they will not be deemed eligible to proceed with the study at that time. Once they have recovered, tested negative for COVID-19 and are asymptomatic, screening can proceed and the patients' eligibility will be ascertained again at that point.

7.1.2 Evaluations within twenty-four weeks

- Written informed consent for RAS G12V mutation pre-screening (patients without a documented KRAS G12V mutation who are being considered for the NSCLC cohort in the dose expansion).

- Written informed consent for RAS and/or RAF mutation pre-screening (patients without a documented RAS and/or RAF mutation who are being considered for the endometrioid cohort in the dose expansion).

- Collection of blood sample for RAS and/or RAF mutation status (if applicable). A single blood sample will be collected up to 24 weeks prior to C1D1 and prior to the patient's informed consent to the main study.

- Collection of archival tissue for KRAS mutation status if applicable.

  NB: Patients being considered for the NSCLC cohort in the dose expansion with a documented RAS G12V mutation, or those being considered for the endometrioid cohort in the dose expansion with a documented RAS and/or RAF mutation will not require pre-screening.

7.1.3 Evaluations within four weeks (28 days)

The following must be performed/obtained **within the four weeks before** the patient receives the first dose.

- Written informed consent (as detailed in Section 7.1.1);

- Demographic details;

- Medical history including prior diagnosis, prior treatment, concomitant diseases and concomitant treatment;

- Acquisition of archival tissue (as detailed in Section 8.3.1);

- Tumour biopsy: biopsies will be collected from patients enrolled in the solid tumour biopsy expansion cohort **(mandatory)**. Biopsies are optional for dose escalation and all other dose expansion cohorts. The first biopsy should be taken at baseline within 28 days prior to first dose (see Section 8.2.1).

- Collection of blood sample for PD analysis (biopsy patients only): to be collected on the same day as the biopsy within 28 days before first dose (see Section 8.2.2).

- Coagulation (if applicable): PT, aPTT and INR should be tested prior to each biopsy as per institutional standard practice (at minimum within 7 days prior to biopsy);
- Tumour serum markers (if applicable);
- Radiological disease assessments: Computerised Tomography (CT) scan of the chest, abdomen and pelvis; or Magnetic Resonance Imaging (MRI) scan of the abdomen and pelvis, with CT scan of the chest. Radiological measurements must be performed **within four weeks before** the patient receives the first dose. If a standard of care scan is available within this time frame then this may be used as baseline but should be clearly documented as standard of care.
- Ophthalmological examination including history, slit-lamp examination in full, including retro illumination technique, corneal examination to detect signs of mineralization, fundoscopic examination (photo documentation if possible), visual acuity and intra-ocular pressure measurement.
- Blood sample and buccal swab for circulating free DNA analysis (as detailed in Section 8.3.2).

Note that all adverse events (AEs) must be monitored and recorded in the eCRF from the time the patient consents to any protocol-specific procedure (see Section 9 for further details).

7.1.4 Evaluations within two weeks (14 days)

The following must be performed **within the two weeks before** the patient receives the first dose:

- **Clinical disease measurements**: If applicable (i.e. patients with clinically assessable disease);
- **Complete physical examination**: Cardiovascular, respiratory, abdominal, central and peripheral nervous system, dermatological and any other system which might be relevant to the patient's medical history;
- **Vital signs**: Height, weight, WHO performance status, temperature, supine blood pressure (BP) and pulse rate;
- **Electrocardiogram (ECG)**: Resting 12-lead ECG, conducted in triplicate taken up to 5 minutes apart, with manual calculation of QT interval (QTc**F**);
- **Laboratory tests (blood/urine samples) to confirm eligibility**:
    - Haematology – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils and lymphocytes) and platelets;
    - Biochemistry – sodium, potassium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (alk phos), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), gamma-glutamyltranspeptide (GGT) and creatine phoshokinase (CPK);
    - Urinalysis – pH, specific gravity, glucose, protein and blood.
- **Serum or urine human chorionic gonadotropin (HCG) test** to rule out pregnancy at trial entry; results must be obtained and reviewed before the first dose of the IMP is administered, if applicable (i.e. women of child bearing potential).

7.1.5 Evaluations during VS-6766-run-in (Day-7 to Day-3) (biopsy patients only)

Run-in doses should be supervised in clinic with VS-6766 dispensed to the patient immediately prior to dosing and then returned to pharmacy following the supervised dose.

The following must be performed **within 24 hours** prior to the run in dose:

- **Physical examination**: Cardiovascular, respiratory, abdominal, central and peripheral nervous system, dermatological and any other system which might be relevant to the patient's medical history;
- **Vital signs**: WHO performance status, temperature, supine BP and pulse rate;
- **Laboratory tests**:

  Haematology and biochemistry: detailed in Section 7.1.4. Haematology and biochemistry should be within 24 hours before VS-6766 administration and results should be available prior to dosing.

  Coagulation (if applicable): PT, aPTT and INR should be tested prior to each biopsy as per institutional standard practice (at minimum within 7 days prior to biopsy).

- **Tumour biopsy:** Biopsies will be collected from patients enrolled in the solid tumour biopsy expansion cohort **(mandatory)**. Biopsies are optional for dose escalation and all other dose expansion cohorts. The second biopsy should be taken during the run-in period, any day between Day-7 and Day-3 following a single administration of VS-6766, 1 and 24 hours post-VS-6766-dose (see Section 8.2.1).
- **Collection of blood sample for PD analysis (biopsy patients only)**: to be collected on the same day as the biopsy, Day-7 to Day-3 (see Section 8.2.2).

7.2 Evaluations during the trial

Patients will be followed up weekly during Cycles 1 and 2, then seen on Day 1 of each cycle thereafter. C1D1 and C2D1 dosing should be performed in clinic before the patient then leaves with their supply. From C3D1 onwards, assessments on Day 1 of a cycle can be performed up to 24 hours before dosing for that cycle commences.

NB: There will be no visit windows in Cycle 1, or on Day 1 of Cycle 2.. For interim safety visits (Cycle 2 onwards, Day 8, 15 or 22) a window of +/- 4 days is acceptable. The cycle length must always remain 28 days.

- **Physical examination**: When clinically indicated, a symptom-directed physical examination will be performed on the first day of each cycle before VS-6766 and Defactinib administration.
- **Vitals**: WHO performance status, temperature, pulse rate and supine BP must be repeated at each visit, before the administration of VS-6766 and Defactinib. Bodyweight should be taken on Day 1 of every cycle.
- **Adverse events and concomitant treatments**: At each visit, before VS-6766 and Defactinib administration, an assessment of any AE experienced since the previous visit must be made by the Investigator or Research Nurse and the start and stop dates of the AE together with the relationship of the event to treatment with VS-6766 and Defactinib must be recorded in the medical records. All AEs must be graded according to NCI CTCAE Version 4.0. Any concomitant treatment must also be recorded in the medical records and in the eCRF. (See Section 9 for further details regarding AE reporting requirements.)
- **Laboratory tests**:

Haematology and biochemistry: must be repeated weekly during cycles 1 and 2and every 4 weeks (i.e. prior to dosing on Day 1 of each cycle) thereafter. Haematology and Biochemistry may be performed the day prior to dosing. If on a day of dosing, haematology, biochemistry and urinalysis should be before VS-6766 and Defactinib administration.

- Haematology: detailed in Section 7.1.4.
- Biochemistry: detailed in Section 7.1.4.
- Urinalysis: repeated pre-dose on Day 1 of each cycle, as detailed in Section 7.1.4.

Coagulation (if applicable): PT, aPTT and INR should be tested prior to each biopsy as per institutional standard practice (at minimum within 7 days prior to biopsy).

- **Tumour serum markers (if applicable)**: must be performed at baseline and repeated every 2 cycle(s)/8 weeks.
- **Electrocardiogram (ECG)**: resting 12-lead ECG, conducted in triplicate taken up to 5 minutes apart, with manual calculation of QT interval (QTc**F**); to be performed on Cycle 2 Day 1 and thereafter as clinically indicated.
- **Ophthalmological examination**: This will be repeated at the end of Cycle 1 (between Cycle 1 Day 22 and pre-dose Cycle 2 Day 1) and at the end of Cycle 2 (between Cycle 2 Day 22 and pre-dose Cycle 3 Day 1). The result must be available prior to dosing. Further ophthalmological examinations may be performed in addition to these if clinically indicated. Detailed in Section 7.1.3.
- **Assessment of disease**: This must be repeated every 2 cycle(s)/8 weeks of continuous treatment, i.e. between C2D22-C3D1, C4D22-C5D1, C6D22-C7D1 etc. (Refer to Section 10). For patients who continue on treatment after six cycles the frequency may be reduced.
- **Tumour biopsy:** Biopsies will be collected from patients enrolled in the solid tumour biopsy expansion cohort **(mandatory)**. Biopsies are optional for dose escalation and all other dose expansion cohorts. The third biopsy should be taken on any day of VS-6766 and Defactinib combination dosing during the first two cycles, between 1 and 24 hours post- VS-6766-dose (see Section 8.2.1).

  Collection of blood sample for PD analysis (biopsy patients only): to be collected on the same day as the biopsy, on any day of VS-6766 and Defactinib combination dosing during the first two cycles (see Section 8.2.2).
- **Collection of blood sample for PK analysis (dose escalation phase only):** Samples for pharmacokinetic analysis will be taken on a day of VS-6766 administration during the second or third week of combination dosing during Cycle 1 (Cycle 1 Day 8-21). Blood for PK analysis will be collected from all patients in the dose escalation phase at the following time points: pre-dose then post-dose at 30 mins, 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, 24 hrs and 48 hrs. Please refer to section 8.1.
- **Blood sample for circulating free DNA analysis**: will be taken at the end of every 2 cycles for up to 6 cycles as per Section 8.3.2, i.e. C3D1 & C5D1.
- COVID-19 guidelines: Any deviations from the protocol in scheduled samples due to COVID-19 infection (confirmed by testing) will be discussed and agreed with the Chief Investigator and will be carefully documented for each patient.

7.3 Evaluations at 'off-study' visit

Evaluations at the 'off-study' visit must be performed within 28 days after the last dose of VS-6766 and Defactinib. The following investigations must be done:

- a symptom-directed physical examination including WHO performance status, temperature, pulse rate, supine BP and bodyweight;
- haematology tests: detailed in Section 7.1.4;
- biochemistry tests: detailed in Section 7.1.4;
- urinalysis: detailed in Section 7.1.4;
- Serum or urine human chorionic gonadotropin (HCG) test if applicable (i.e. women of child bearing potential).
- ECG: detailed in Section 7.1.4;
- Ophthalmological examination: detailed in Section 7.1.3;
- Blood sample for circulating free DNA analysis;
- assessment of tumour disease, unless assessment has been performed within the previous four weeks (28 days);
- assessment of AEs (also see Section 7.4); and
- assessment of concomitant treatments.
- Optional standalone biopsy at progression

7.4 Follow-up

Patients will be followed up for 28 days after the last administration of VS-6766 and/or Defactinib. If any AEs and SAEs are considered to have a highly probable, probable or possible causal relationship to VS-6766 and/or Defactinib, and are still present 28 days after the last administration of VS-6766 and/or Defactinib, or occur in the 28 days post VS-6766 and/or Defactinib administration; then the patient will be followed up monthly afterwards until resolution, to baseline or stabilisation of these events, unless the patient starts another anti-tumour treatment.

7.5 Schedule of events

1 cycle = 28 days****

Observation/Investigation	Baseline/Pre-study			Run-in**	Cycles 1 & 2				Cycles 3 & 4*****	Cycle 5 onwards	Off study and Follow-up	
	Within 24 weeks prior to first dose	Within 4 weeks prior to first dose	Within 2 weeks prior to first dose	Day -7 to Day -3	Day 1	Day 8	Day 15	Day 22	Day 1	Day 1	Off study: within 28 days after last dose of IMP	Follow-up: monthly(c)
Pre-screening informed consent*	X											
Blood sample for RAS and/or RAF mutation testing*	X											
Written informed consent		X										
Demographics & medical history		X										
Adverse event evaluation		X		Continually review							X	Until resolution (a)
Concomitant treatments		X		Continually review							X	
Historical tumour sample	X											
Radiological (CT, MRI) disease assessment (b)		X							X C3D1	X (b)	X	
Clinical disease assessment (if applicable) (b)			X						X C3D1	X (b)	X	
Tumour serum markers (if applicable) (b)		X							X C3D1	X (b)	X	
Ophthalmological examination (c)		X			X C2D1				X C3D1		X	
Triplicate electrocardiogram (ECG)			X		X C2D1						X	
Pregnancy test (serum or urine HCG) (d)			X								X	
Physical examination			X	X	X				X	X	X	
WHO performance status & Vital signs			X	X	X	X	X	X	X	X	X	
Urinalysis			X		X				X	X	X	
Laboratory tests: haematology and biochemistry (e)			X	X	X	X	X	X	X	X	X	To resolution of drug-related lab AEs

Coagulation**		X		X	X					x	
Tumour biopsy**		X		X	X					x	
Blood for pharmacodynamic (PD) analysis**		X		X	X					x	
Blood for pharmacokinetic (PK) assays***						X C1					
Blood for ctDNA analysis		X						X C3D1	X C5D1	X	
Buccal swab		X									
VS-6766 administration				X	X	X	X	X	X		
Defactinib administration					X	X	X	X	X		

* Pre-screening informed consent followed by a blood sample (and archival tissue if applicable) for RAS and/or RAF mutational analysis will be taken from patients being considered for the **dose expansion NSCLC and endometrioid cohorts**, unless RAS and/or RAF mutation status is already known. This can be evaluated up to 24 weeks before first dose.

** For those patients undergoing tumour biopsies a single run-in dose of VS-6766 is required between Day-7 and Day-3 prior to C1D1. Biopsies are mandatory in the **dose expansion biopsy cohort** and optional in the **dose escalation and dose expansion cohorts**. Three samples will be taken at the following time points: at baseline (within 4 weeks), following the run-in dose of VS-6766 between Day-7 and Day-3 (1-24 hours post- VS-6766-dose) and anytime during the first two cycles on day of combination dosing (1-24 hours post- VS-6766-dose). Each biopsy will be accompanied by a blood sample for PD analysis. Blood samples can be taken at any time on the day of biopsy. Coagulation should be tested prior to each biopsy as per institutional standard practice (at minimum within 7 days prior to procedure).
There is also the option for an optional standalone biopsy at progression.

*** Samples for PK analysis will be taken on a day of VS-6766 administration during the second or third week of combination dosing during Cycle 1 (Cycle 1 Day 8-21). Blood for PK analysis will be collected from all patients in the **dose escalation phase** at the following time points (timing of PK should be calculated from the time of Defactinib dosing): pre-dose then post-dose at 30 mins, 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, 24 hrs and 48 hrs. A window of +/- 15 mins is allowed on 30 mins, 1 hr, 2 hrs and 4 hrs post-dose samples. A window of +/- 1 hrs is allowed on 8 hrs, 12 hrs, 24 hrs and 48 hrs post-dose samples.

**** There will be no visit windows in Cycle 1, or on Day 1 of Cycle 2. For interim safety visits (Cycle 2 onwards, Day 8, 15 or 22) a window of +/- 4 days is acceptable. The cycle length must always remain 28 days.

***** Patients will be followed up weekly during Cycles 1 and 2, then seen on Day 1 of each cycle thereafter. These assessments can be performed within the 24 hours prior to dosing**.**

a) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) and present at time that patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.
b) Disease assessment must be performed at baseline and repeated every 2 cycle(s)/8 weeks of continuous treatment and at off study visit (unless assessment has been performed within the previous 4 weeks). For patients who continue on treatment after 6 cycles the frequency may be reduced. Clinical disease assessment and tumour markers should be assessed if applicable.

c) Ophthalmological examination: This must be performed at baseline (within 28 days prior to first dose), at the end of Cycle 1 (between Cycle 1 Day 22 and pre-dose Cycle 2 Day 1) and at the end of Cycle 2 (between Cycle 2 Day 22 and pre-dose Cycle 3 Day 1) and at the off study visit. The result must be available prior to dosing.

d) Pregnancy test only required if the patient is a woman of child bearing potential.

e) In the event of a Grade 4 neutropenia or Grade 4 thrombocytopenia a full blood count must be performed at least on Day 5 after the onset of the event to determine if a dose limiting toxicity has occurred. Continue close monitoring until resolution to Grade 3 or less.

8 PHARMACOKINETIC AND PHARMACODYNAMIC ASSESSMENTS

8.1 Pharmacokinetic Assays

Pharmacokinetic (PK) parameters will be measured in plasma according to agreed SOPs and validated methods. PK evaluation will be undertaken in each patient enrolled in the **dose escalation** phase of the study.

Samples for PK analysis will be taken on a day of VS-6766 administration during the second or third week of combination dosing during Cycle 1 (Cycle 1 Day 8-21).

Blood for PK analysis will be collected from patients at the following time points: pre-dose then post-dose 30 mins, 1 hr, 2 hrs, 4 hrs, 8 hrs, 12 hrs, 24 hrs and 48 hrs. A window of +/- 15 mins is allowed on 30 mins, 1 hr, 2 hrs and 4 hrs post-dose samples. A window of +/- 1 hrs is allowed on 8 hrs, 12 hrs, 24 hrs and 48 hrs post-dose samples.

As the fasting requirements of VS-6766 and Defactinib differ, the drugs cannot be taken at the same time. On PK days the morning dose of Defactinib should be taken first, immediately after a meal, followed by a two hour fast before taking the VS-6766. The timings of PK samples should be scheduled relative to the Defactinib dose.

The following parameters will be evaluated to obtain the dose-exposure relationship and the related AUC, terminal $t_{1/2,}$ C_{-max} of VS-6766 alone and in combination with Defactinib.

Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

8.2 Pharmacodynamic Assays

8.2.1 Tumour biopsies

The table on page 54 outlines the samples that are to be taken and the timepoints at which they should be taken.

Time Points	Pre-screening for mutation analysis*	Archival	Fresh biopsy to be formalin fixed and paraffin embedded**	Fresh biopsy to be snap frozen**	PD blood**	ctDNA	Buccal swab
Corresponding protocol section	**8.3.3**	**8.3.1**	**8.2.1**		**8.2.2**	**8.3.2**	
Pre-screening (within 24 weeks before first dose)	X	X					
Screening (within 28 days before first dose)			X		X	X	X
Day-7 to Day-3 (1-4 hours after the dose of V6766)			X				
Day-7 to Day-3 (on day of biopsy at any time)					X		
Post combination dosing during Cycle 1 or Cycle 2, on a day when both V6766 and Defactinib are given (biopsy: 1-4 hours after the dose of V6766) (PD blood: on day of biopsy at any time)			X		X		
C3D1						X	
C5D1						X	
Progression (if sample not taken in previous 4 weeks)**			X		X	X	

* Patients with NSCLC who are being considered for the NSCLC cohort in the dose expansion without prior documentation of a G12V KRAS mutation will be asked to give their written consent to pre - screening KRAS G12V mutation analysis. Patients with endometrioid cancer who are

being considered for the endometrioid cohort in the dose expansion without prior documentation of a RAS and/or RAF mutation will be asked to give their written consent to pre-screening RAS and/or RAF mutation analysis.

** Collection of tumour biopsies and corresponding PD blood samples are optional.

Patients whose tumours are easily and safely amenable to biopsy will be asked to consent for collection of three pre- and post-treatment tumour biopsies. These should be collected at the following time points:

- Baseline (within 28 days before first dose);
- Day-7 to Day-3 (1-24 hours after the dose of VS-6766);
- Post combination dosing during Cycle 1 or Cycle 2, on a day when both VS-6766 and Defactinib are given (1-24 hours after the dose of VS-6766).

As the fasting requirements of VS-6766 and Defactinib differ, the drugs cannot be taken at the same time. Therefore, the third biopsy following combination dosing should be scheduled from the time of VS-6766 dose.

Patients whose tumours are easily and safely amenable to biopsy will be asked to consent for collection of a standalone biopsy at progression. They do not need to have agreed to the set of optional biopsies while on study. This is a separate, standalone biopsy, stated separately at consent.

Collection of tumour biopsies is optional except for in the solid tumour cohort of the dose expansion where it is mandatory.

Samples of tumour will undergo analysis of candidate markers related to the drug's mechanism of action such as pERK, pMEK and pFAK. Tumour samples may also undergo staining for FOXP3, CCL5 and quantification of CD4+ and CD8+ T-cells. The specific type and number of biomarkers from the tumour samples will be decided during the course of the study and documented in the study records.

Core needle tumour biopsies will be taken according to local procedures and divided into 2 samples, one to be immediately snap frozen in liquid nitrogen or a dry ice bath for PD analysis and one to be formalin fixed and embedded in paraffin (FFPE) as per local procedures for PD biomarker analysis. Where there is limited tissue to biopsy, priority should be given to securing a FFPE sample over a snap frozen sample.

Tumour biopsies will be analysed at the laboratories of the Institute of Cancer Research or laboratories authorised by the Institute of Cancer Research. Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

8.2.2 Blood samples

PD blood samples (3 x 8ml) will be collected from those patients undergoing tumour biopsies on the same day as the biopsy (at any time during that day):

- Baseline (within 28 days before first dose);
- Day-7 to Day-3;
- Post combination dosing during Cycle 1 or Cycle 2, on a day when both VS-6766 and Defactinib are given.

PD blood samples will be analysed at the laboratories of the Institute of Cancer Research or laboratories authorised by the Institute of Cancer Research. Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

8.3 Predictive biomarkers assays

8.3.1 Collection of archival tumour specimens

Archival tumour material will be collected for **all patients** enrolled into the study. The tumour samples will preferably be in the form of a formalin fixed paraffin embedded block (tissue derived from the diagnostic tumour or a metastatic site). DNA extracted from archival tumour material will be analysed for genetic mutations that may impact on how patients respond to this treatment (for research purposes only). Analysis may be done retrospectively for patients.

Archival tumour biopsies will be analysed at the laboratories of the Institute of Cancer Research or laboratories authorised by the Institute of Cancer Research. Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

8.3.2 Analysis of circulating free DNA

Circulating free tumour DNA in plasma will be sequenced for genetic mutations according to agreed SOPs and validated methods.

2 x10 ml of plasma will be collected for **all patients** at baseline, at the end of every 2 cycles for up to 6 cycles and at progression. This is for the purpose of studying circulating free DNA and correlating it to response.

A germ line comparator in the form of a buccal swab sample will be collected at baseline only. This will be used to inform the genetic analysis of patient's tumour and not to study inheritable disease.

Samples will be analysed at the laboratories of Institute of Cancer Research or laboratories authorised by the Institute of Cancer Research. Please refer to the Study Laboratory Manual for handling, storage and shipment of samples.

8.3.3 Pre-screening collection of plasma sample for RAS and/or RAF mutation analysis of circulating free DNA

Patients with non-small-cell lung cancer who are being considered for the NSCLC cohort in the dose expansion, without prior documentation of a RAS G12V mutation, will be asked to give their written consent to pre-screening RAS G12V mutation analysis on ctDNA or on archival tissue if appropriate.

Endometrioid cancer patients who are being considered for the endometrioid cohort in the dose expansion, without prior documentation of a RAS and/or RAF mutation, will also be asked to give their written consent to pre-screening RAS and/or RAF mutation analysis on ctDNA or on archival tissue if appropriate.

2 x 10 mL blood for the preparation of circulating tumour DNA (ctDNA) will be taken in Streck tubes for analysis of RAS and/or mutations.

The blood sample should be taken up to 24 weeks before the patient receives their first dose.

NB. Confirmation of the presence of a RAS and/or RAF mutation must be received prior to the patients' consent to the main study and further eligibility screening.

9 ASSESSMENT OF SAFETY

9.1 Adverse event definitions

9.1.1 Adverse event

For eligible patients, serious adverse event (SAE) and adverse event (AE) collection and monitoring commences from the time the patient gives their written consent to participate in the trial and continues for 28 days after the last administration of VS-6766 and Defactinib.

Follow-up of AEs with a causality of possible, probable or highly probable will continue until the events resolve, stabilise or the patient starts another anti-cancer therapy.

An AE is any untoward, undesired or unplanned occurrence in a patient administered an IMP. An AE can be a sign, symptom, disease, and/or laboratory or physiological observation that may or may not be related to the IMP.

An abnormal laboratory parameter should be recorded as an AE if it is clinically significant or considered related to IMP.

An abnormal laboratory parameter is considered clinically significant if it meets the following criteria:

- is symptomatic;
- is treated with a con med;
- is treated with a medical procedure;
- requires an additional diagnostic test;
- results in a change in IMP dosing;
- results in the patient's withdrawal;
- meets the definition of DLT.

Abnormal lab parameters that are deemed not clinically significant and not related to IMP do not need to be recorded as AE's.

An AE includes but is not limited to those in the following list.

- A clinically significant worsening of a pre-existing condition. This includes conditions that may resolve completely and then become abnormal again.
- AEs occurring from an overdose of an IMP, whether accidental or intentional.

Other reportable events that must be treated as AEs are listed below.

- Pregnancy exposure to the IMP. Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of the last IMP administration, must be reported to the PV data manager in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Any AE associated with an overdose or incorrect administration of IMP. An overdose or incorrect administration of IMP is not an AE unless it results in untoward medical effects.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

9.1.2 Serious adverse events (SAEs)

An SAE is any AE, regardless of dose, causality or expectedness, that:

- results in death;
- is life-threatening;
- requires in-patient hospitalisation or prolongs existing in-patient hospitalisation (some hospitalisations are exempt from SAE reporting – see Section 9.2.1);
- results in persistent or significant incapacity or disability;
- is a congenital anomaly or birth defect;
- is any other medically important event.*

*A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent an SAE. It should be noted that medically important events may be identified before or at any point in the study.

SAEs should be reported by the investigator to the DDU immediately (i.e., no more than 24 hours after learning of the event) following the procedure described in section 9.2

9.1.3 Determining adverse event causality

The relationship of an AE to the IMP is determined as follows.

Highly probable • Starts within a time related to the IMP administration and • No obvious alternative medical explanation.
Probable • Starts within a time related to the IMP administration and • Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible • Starts within a time related to the IMP administration and • A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely • The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.
Not related • The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness, progressive malignancy etc) and must provide his/her opinion of the

causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

9.1.4 Expectedness

Assessment of expectedness to Defactinib will be made by the Chief Investigator (or delegate) against the current version of the Defactinib Investigator Brochure (IB Appendix E).

Assessment of expectedness to VS-6766 will be made by the Chief Investigator (or delegate) against the current version of the VS-6766 Investigator Brochure (IB Appendix 7).

9.1.5 Suspected, unexpected, serious, adverse reactions (SUSARs)

A SUSAR is a suspected, unexpected, serious adverse reaction. All AEs and SAEs will be assessed for seriousness, causality and expectedness. The DDU Pharmacovigilance (PV) Officer will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

9.2 Expedited reporting of serious adverse events to the Pharmacovigilance Officer, DDU

All SAEs, regardless of causality, must be reported to the DDU Pharmacovigilance (PV) Officer in an expedited manner.

SAEs should be documented on an SAE report form, using the completion guidelines provided.

The SAE report form should be <u>emailed</u> to the DDU Pharmacovigilance Officer within 24 hours of site staff becoming aware of the SAE.

Email address: <u>ddu-sae@icr.ac.uk</u>

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.0 must be used to grade each SAE, and the worst grade recorded. If new or amended information on a previously reported SAE becomes available, the Investigator should report this to the DDU data manager (PV) on a new SAE report form.

If the SAE has not been reported within the specified timeframes, a reason for lateness must be added when sending the SAE report form to the DDU.

Should the Investigator become aware of any drug-related SAEs after the patient goes ‘off study’, these must also be reported to the DDU Pharmacovigilance Officer within the specified timelines above.

9.2.1 Events exempt from being reported as SAEs

Events specified in this section do not require reporting as SAEs in this trial, unless hospitalisation is prolonged for any reason and then an SAE form must be completed. The events must still be recorded in the appropriate section of the case report form (CRF).

Screening period – SAEs occurring in the period prior to administration of VS-6766 and Defactinib from the time of informed consent to the day prior to cycle 1 day 1 of VS-6766and

Defactinib administration that are not related to the design or conduct of the trial are exempt from reporting.

Elective admissions – Elective admissions to hospital for procedures which were planned and documented in the medical records at the time of consent are not SAEs, and do not require SAE reporting. Hospitalisation for administration of the IMP according to the trial protocol is also exempt from being reported as an SAE, unless the hospitalisation is prolonged by any reason and then an SAE must be reported.

Death due to disease progression – cases of death due to disease progression do not require reporting unless considered related to IMPs.

9.3 Recording of adverse events and serious adverse events in eCRFs

All AEs, including SAEs, must be recorded in the eCRF for eligible patients. All concomitant medications, including herbal medications and supplements must be recorded. Any therapy used to treat the event must be recorded. The eCRF will be reconciled with the safety database during and at the end of the trial. Therefore, the sites should ensure the data entered on the SAE report form and the data entered into the eCRF are consistent. The Safety Review Committee and the Investigator(s) will regularly review the safety data from both the safety and the clinical database.

9.4 Follow-up of adverse events

Follow-up will continue until all the necessary safety data for the event has been gathered and until the drug-related AE or SAE has either resolved, returned to baseline or stabilised. The DDU data manager (PV) will make requests for further information to the trial site at regular intervals. Requested follow-up information should be reported to the DDU Pharmacovigilance Officer in a timely manner and as soon as possible after receipt of the follow-up request. For fatal or life-threatening cases, follow-up information should be reported as soon as possible.

9.5 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority.

The Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Chief Investigator or the DDU Clinical Trials Manager immediately either by:

- email: FRAME@icr.ac.uk; or
- telephone: 020 8722 4101

The notification must include:

- the date of the USM;

- who took the decision; and
- why action was taken.

The Sponsor will then notify the MHRA and the REC of USM initiation immediately (by phone) and within three days (in writing).

9.6 Pregnancy

The Investigator must make every effort to try and ensure that a clinical trial patient or a partner of a clinical trial patient does not become pregnant during the trial or for six months afterwards. This should be done as part of the consent process by explaining clearly to the patient the potential dangers of becoming pregnant and also providing each patient with information about appropriate medically approved contraception. Two forms of medically approved contraception should be used, such as:

- oral contraceptives and condom;
- intra-uterine device (IUD) and condom;
- diaphragms with spermicidal gel and condom.

Contraceptives should be used form the time the patient joins the trial, throughout the trial and for six months after completing the trial.

It should be explained to the patient that if his partner is pregnant or breast-feeding when he enters the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn baby or the baby being exposed to the VS-6766 and Defactinib.

However, if a patient or a partner of a patient does become pregnant, the reporting procedures below must be followed.

Any pregnancy occurring in a patient or a patient's partner during treatment with an IMP or occurring within six months of last IMP administration must be reported to the DDU Pharmacovigilance Officer within 24 hours of the site staff becoming aware of it using a Pregnancy Notification Form. It is the Investigator's responsibility to obtain consent for follow-up from the patient or patient's partner. The DDU Pharmacovigilance Officer will follow-up all pregnancies for the pregnancy outcome via the Investigator and document on the pregnancy form.

The Investigator must ensure that all patients are aware at the start of a clinical trial of the importance of reporting all pregnancies (in themselves and their partners) that occur whilst being treated with the IMP and occurring up to six months after the last IMP administration. The Investigator should offer counselling to the patient and/or the partner, and discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient and the baby should continue until the conclusion of the pregnancy, if the patient or patient's partner has consented to this.

10 ASSESSMENT OF EFFICACY

Disease must be measured according to the RECIST criteria (version1.1) given in Appendix 3.

10.1 Measurement of disease

Disease must be measured according to the RECIST criteria given in Appendix 3.

Previously irradiated lesions can be taken into account as measurable disease when they are clearly progressing at the time of initiating systemic therapy.

10.2 Timing and type of tumour assessments

A thorough clinical and radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the investigational medicinal product (IMP). The same methods that detect evaluable lesions at baseline must be used to follow these lesions throughout the trial. To ensure compatibility, the radiological assessments used to assess response must be performed using identical techniques. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumour effect of a treatment.

All radiological assessments must be performed within four weeks before starting treatment. The interval between the last anti-cancer therapy and these measurements must be at least four weeks (28 days). All clinical measurements to assess response must be done within **one** week before the patient starting treatment.

All complete (CR) and partial responses (PR) must be confirmed by two consecutive observations not less than four weeks apart.

Disease response in ovarian cancer patients may be determined by CA125 levels according to GCIG Criteria. CA125 levels will be measured and documented prior to initiation of study drug. Response and progression will be evaluated based on repeat tumour marker measurements performed every other cycle of therapy (approximately every eight weeks).

Copies of the scans must be available for external independent review if requested by the Drug Development Unit.

10.2.1 Baseline evaluations

These must include radiological measurements and as indicated chest, abdominal and pelvic computerised tomography (CT) scan, magnetic resonance imaging (MRI) and/or clinical measurements as appropriate. All areas of disease present must be documented (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded clearly on the scan reports. Any non-measurable lesions must be stated as being present. For clinical measurements, documentation by colour photography including a ruler to estimate the size of the lesion is strongly recommended, as this aids external independent review of responses. (See Section 1.2.1 of RECIST 1.1 criteria)

10.2.2 Evaluations during and at 'off-study'

Tumour assessments must be repeated every 2 cycle(s)/8 weeks if continuous treatment or more frequently, when clinically indicated. All lesions measured at baseline must be measured at every subsequent disease assessment, and recorded clearly on the scan reports. All non-measurable lesions noted at baseline must be noted on the scan report as present or absent.

All patients, who are removed from the trial for reasons other than progressive disease, must be re-evaluated at the time of treatment discontinuation, unless a tumour assessment was performed within the previous four weeks.

It is the responsibility of the Principal Investigator to ensure that the radiologists are aware of the requirement to follow-up and measure every target lesion mentioned at baseline and comment on the non-target lesions in accordance with RECIST 1.1 criteria.

10.3 Tumour response

All patients who meet the eligibility criteria, receive at least one cycle of trial medication and have a baseline assessment of disease and have at least one scheduled post baseline RECIST assessment will be evaluable for response by RECIST criteria (unless the patient progresses prior to this assessment). To be assigned a status of complete response (CR) or partial response (PR), changes in tumour measurements must be confirmed by repeat measurements performed no less than four weeks after the response criteria are met. To be assigned a status of stable disease (SD), follow-up measurements must have met the SD criteria at least once and at least six weeks after the initial dose of the investigational medicinal product (IMP) VS-6766 and Defactinib is given.

Tumour response should be classified as "not evaluable" (NE), only when it is not possible to classify it under another response category, for example, when baseline and/or follow-up assessment is not performed or not performed appropriately.

Expert reviewers appointed by DDU may undertake an independent review of all the Investigator's assessed objective responses (CR and PR). The expert reviewers will include at least one specialist who is not an Investigator in the trial. In case of disagreement between the Investigator's and the expert reviewers' assessment, discussion will take place between the two parties in order to reach a consensus. However, if it is not forthcoming, the assessment of the expert reviewers will be retained in the clinical study report. The eCRF will reflect the Investigator's opinion.

10.3.1 Recording of response in the eCRF

The applicable overall response category for each visit that includes disease assessment must be recorded in the eCRF, even though the criteria for determination of CR or PR by the protocol must be confirmed after two consecutive observations, no less than four weeks apart.

11 DISCONTINUATION OF TREATMENT/ WITHDRAWAL FROM TRIAL

The Investigator must make every reasonable effort to keep each patient on trial for the whole duration of the trial (i.e. until 28 days after last combination therapy administration). However, if the Investigator removes a patient from the trial or if the patient declines further participation, final 'off-study' assessments should be performed before any therapeutic intervention. All the results of the evaluations and observations, together with a description of the reasons for withdrawal from the trial, must be recorded in the medical records and in the eCRF.

Patients who are removed from the trial due to adverse events (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the eCRF and on the serious adverse event (SAE) report form where necessary.

The following are justifiable reasons for the Investigator to withdraw a patient from trial.

- Unacceptable toxicity
- AE/SAE
- Withdrawal of consent
- Serious violation of the trial protocol (including persistent patient attendance failure and persistent non-compliance)
- Sponsor's decision to terminate the trial
- Withdrawal by the Investigator for clinical reasons not related to the IMP
- Evidence of disease progression
- Symptomatic deterioration
- Pregnancy

Patients that are discontinued from the study are still evaluable as defined in section 5.5

12 DEFINING THE END OF TRIAL

The 'end of trial' is defined as the date when the last patient has completed the 'off-study' visit or the final follow-up visit (whichever is the latter).

It is the responsibility of the DDU to inform the Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) within 90 days of the 'end of the trial' that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the DDU, the DDU will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

The entire trial will be stopped when:

- The drug is considered too toxic to continue treatment before the required number of patients being recruited.
- The stated number of patients to be recruited is reached.
- The stated objectives of the trial are achieved.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the trial, DDU and the Investigators must ensure that adequate consideration is given to the protection of the patient's interest.

13 METHODOLOGY SUB-STUDY – PHASE I DESIGN

A methodology sub-study will be carried out within the FRAME trial; the aim of this Study Within a Trial (SWAT) is to investigate the relative performance of the 3+3 dose escalation design compared with a Bayesian approach for phase I trials.

The objective of this sub-study is to determine whether the same dose escalation/de-escalation decisions would be made had a Bayesian design been employed and to assess the relative efficiency of the designs.

This is an exploratory sub-study and results of this will not be used for clinical decision making. For the purposes of dose escalation decisions within FRAME only the 3+3 criteria as defined in section 5 will be used; results of the Bayesian CRM approach will not be made available to the SRC while the dose escalation phase is ongoing.

A separate analysis plan will be developed for this sub-study outlining the parameters required for the Bayesian design and analysis methods to be used.

14 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

In order to further characterise the tolerability, safety, PK and efficacy of the combination of VS-6766 and Defactinib in NSCLC, LGSOC, colorectal cancer, pancreatic cancer, endometroid ovarian cancer and G12V KRAS NSCLC. 20 NSCLC patients, 20 LGSOC patients, 10 colorectal cancer patients, 10 pancreatic patients, 10 RAS/RAF mutant endometrioid subtype of gynaecological cancers (ovarian, endometrial, endometriosis-related) patients; 10 G12V KRAS NSCLC patients will be treated in the dose expansion phase at the dose level selected in the dose escalation phase.

If the true response rate is 20%, the probability of seeing 0 responses is <0.1% and the probability of seeing 2 or more responses is 99.9%. The 80% confidence interval if the response rate is 10% is (6.4%, 16.0%), the 80% confidence interval if the response rate is 20% is (14.3%, 26.4%) and the 80% confidence interval if the response rate is 30% is (23.7%, 37.5%).

An additional 6 patients with advanced solid tumours will also be recruited to characterise the pharmacodynamics of the combination.

The final analysis will be conducted after one of the following conditions is met.

- The trial is terminated early (for example, due to toxicity).
- All patients have had the opportunity to receive 1 cycle of treatment and have completed their 'off-study' visit (i.e. 28 days after the last dose of VS-6766 and/or Defactinib).

Once one of the conditions is met, a data cut-off date will be established. All patient visits occurring on or before this date will be analysed and summarised in the final clinical study report. Any data collected after this date will be summarised in a supplemental report.

14.1 Presentation of data

Data will be presented in a descriptive fashion. Variables will be analysed to determine whether the criteria for the trial conduct are met. This will include a description of patients who did not meet all the eligibility criteria, an assessment of protocol violations, IMP accountability and other data that impact on the general conduct of the trial.

Baseline characteristics will be summarised for all enrolled patients. Patients who died or withdrew before treatment started or did not complete the required safety observations will be described and evaluated separately.

Treatment administration will be described for all cycles. Dose administration, dose modifications or delays and the duration of therapy will be described.

14.2 Safety

Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics. Laboratory variables will be described using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Adverse events (AEs) will be reported for each dose level and presented as tables of frequency of AEs by body system and by worse severity grade observed. Tables should indicate related and

unrelated events. Laboratory data will be presented by dose level at each observation time. Values outside normal limits will be identified and summarised by frequency distribution.

14.3 Pharmacokinetics

The plasma concentration/time data will be analysed using non-compartmental methods. The pharmacokinetic (PK) parameters to be determined for VS-6766 and Defactinib in combination include the maximum observed plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and the area under the plasma concentration time curve (AUC), and the terminal elimination half-life ($T_{1/2}$), mean residence time (MRT), total body clearance (CLT) and steady/state volume of distribution (V_{SS}).

14.4 Pharmacodynamics

The PD data will be presented by listings and summary statistics. The PK/PD data relationship will be explored.

14.5 Anti-tumour activity

Documenting anti-tumour activity is a tertiary objective of this trial. Patients must receive at least one cycle of the trial medication and have had at least one post baseline RECIST assessment (or have progressed prior to this assessment) to be evaluable for response. Objective responses (CR+PR), the best tumour response achieved by each patient while on trial and the time to progression will be presented in the data listings by cohort.

Response rates will be reported with 95% confidence intervals overall and by cohort.

Progression free survival (PFS) will be calculated from date of first dose (either combination or run-in dose) until the time of documented disease progression or death (whichever occurs first). Patients who are alive and event free or lost to follow up at the time of analysis will be censored at the time the patient was last known to be alive and progression free. A Kaplan Meier graph and median PFS will be presented overall and by cohort.

14.6 Methodology substudy

The following parameters and assumptions required for the running of the Bayesian design will be defined:

- The appropriate form of the dose-toxicity curve and a prior distribution for the parameters that determine this relationship

- Cohort size; whether a cohort of 3 will be used to match the 3+3 design or if posterior distributions will be updated more regularly e.g. after each patient, to determine the next dose

- Stopping rule; if the Bayesian method were to be employed would a fixed number of patients be used and the trial stopped once all patients allocated or a more formal stopping rule be employed

This sub-study will be subject to a separate statistical analysis plan (SAP) where the above considerations will be defined.

Analysis of the sub-study will be carried out at the earliest, after the first dose escalation decision has been made. Analysis of the sub-study will be largely descriptive in nature.

15 ADMINISTRATION

This trial is conducted under a clinical trial authorisation (CTA) and approval from the Medicines and Healthcare products Regulations Agency (MHRA) and the relevant Research Ethics Committee(s) will be obtained before the start of this trial. This trial is sponsored by The Institute of Cancer Research (ICR). Applicable regulatory requirements are described in this section.

15.1 Protocol deviations and amendments

Eligibility waivers are strictly prohibited. Protocol deviations will be recorded, will be considered at the time of study analysis and where appropriate, will be documented in the clinical study report.

Amendments to the protocol may only be made with the approval of the DDU, CI and statistician. Amendments will be subject to review by the sponsor. Ethics Committee favourable opinion (and MHRA approval if appropriate) will be obtained by the DDU on behalf of the CI before any substantial amendment can be implemented. Non-substantial amendments do not require REC / MHRA approval. Urgent safety measures may be implemented immediately where necessary but the sponsor should be informed immediately (see section 9.5).

15.2 Completion of the case report form (CRF)

Electronic CRFs (eCRFs) will be used to collect the data. The Investigator is responsible for ensuring the accuracy, completeness, clarity and timeliness of the data reported in the eCRFs.

Only the Investigator and those personnel who have signed the Study Team Responsibilities Signature Log/Delegation Log provided by the DDU and have been authorised by the Investigator should enter or change data in the eCRFs. All protocol required investigations must be reported in the eCRF. The Investigators must retain all source data (contained in original reports, traces and images from protocol investigations) for future reference.

Data will be entered into eCRFs from source documents by authorised site personnel.

Once data has been entered by the site personnel on the eCRF, the data will be reviewed and checked for error and inconsistencies by data management staff in the DDU.

Once the patient is ‘off study’ and the eCRF has been fully completed, the Investigator must provide a signature to authorise the complete subject casebook.

15.3 Trial performance and monitoring

15.3.1 Management of the study

The DDU Clinical Trials Manager will be responsible for the day to day coordination and management of the trial. The ICR Clinical Trials and Statistics Unit (ICR-CTSU) will act as custodian of the data on behalf of the sponsor. The DDU is responsible for all duties relating to pharmacovigilance in accordance with section 9.

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centre. The DDU must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the DDU Clinical Research Associate (CRA) is responsible for monitoring data quality in accordance with DDU's standard operating procedures (SOPs). Before the trial start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification before each monitoring visit.

It is the responsibility of the CRA to:

- review trial records and compare them with source documents;
- check pharmacodynamic samples and storage;
- discuss the conduct of the trial and the emerging problems with the Investigator;
- check that the drug storage, dispensing and retrieval are reliable and appropriate; and
- verify that the available facilities remain acceptable.

All unused drug supplied must be returned to the supplier, or if authorised by DDU properly destroyed at the Investigator site by an authorised person who will provide signed confirmation.

It is the responsibility of the DDU to inform the REC and MHRA within 90 days of the 'end of the trial' (i.e. last patient study visit) that the trial has closed.

15.3.2 Source document verification

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

All data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that both he/she and his/her study team records all relevant data in the medical records. The Investigator must allow the CTM direct access to relevant source documentation for verification of data entered into the eCRF, taking into account data protection regulations. Entries in the eCRF will be compared with patients' medical records and the verification will be documented on the source data verification (SDV) form and the monitoring report.

The patients' medical records, and other relevant data, may also be reviewed by appropriate qualified personnel independent from the DDU appointed to audit the trial, and by regulatory authorities. Details will remain confidential and patients' names will not be recorded outside the hospital.

15.4 Clinical study report

All clinical data will be presented at the end of the trial on final data listings. The CI, DDU and ICR-CTSU will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. A summary of the final clinical report will be provided by the DDU to the MHRA and to the Research Ethics Committee.

15.5 Record retention

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (such as those detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as scans,

trial related documents and copies of the eCRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation. Records must not be destroyed without prior written approval from the DDU.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

15.6 Ethical considerations

Before starting the trial, the protocol, patient information sheet and consent form must be approved by the ICR/RM joint Committee for Clinical Research and the appropriate Ethics Committee.

It is the Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor, Chief Investigator and Principal Investigators must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended).

15.7 Indemnity

The manufacturer of VS-6766 and Defactinib will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

15.8 Publication policy and press releases

The trial results will be submitted for publication in a relevant medical journal with authorship according to the criteria defined by the ICMJE (http://www.icmje.org). These state that: Authorship credit should be based 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Draft publications (manuscripts, abstracts, slides and posters) should be submitted to the DDU Clinical Trial Manager for circulation to the supplier and the ICR-CTSU to allow sufficient time for review prior to submission.

The DDU shall have for abstracts, slides and posters a twenty-one (21) day period and for manuscripts a thirty (30) day period to respond to the author with any revisions.

16 REFERENCES

Note for Guidance on Good Clinical Practice. ICH Topic E6. CSMP/ICH/135/95. EMEA, May 1996, updated September 1997 with post Step 4 errata included

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Communities L121/34-44*

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. **October 2005***. ENTR/F2/BL D(2003) CT 1 (Revision 2)*

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. **February 2006***. ENTR/CT 2 (Revision 1)*

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. **April 2006.** *ENTR/CT 3 (Revision 2)*

The **Medicines** for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 1031)

COMMISSION DIRECTIVE 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products. *Official Journal of the European Union L 91/13*

The Medicines for Human use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928).

1. Heinemann, V., S. Stintzing, T. Kirchner, S. Boeck and A. Jung (2009). "Clinical relevance of EGFR- and KRAS-status in colorectal cancer patients treated with monoclonal antibodies directed against the EGFR." Cancer Treat Rev 35(3): 262-271.

2. Fukuoka, M., Y. L. Wu, S. Thongprasert, P. Sunpaweravong, S. S. Leong, V. Sriuranpong, T. Y. Chao, K. Nakagawa, D. T. Chu, N. Saijo, E. L. Duffield, Y. Rukazenkov, G. Speake, H. Jiang, A. A. Armour, K. F. To, J. C. Yang and T. S. Mok (2011). "Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS)." J Clin Oncol 29(21): 2866-2874.

3. Hayes, G. M., L. Chinn, J. M. Cantor, B. Cairns, Z. Levashova, H. Tran, T. Velilla, D. Duey, J. Lippincott, J. Zachwieja, M. H. Ginsberg and H. v. d. H. E (2015). "Antitumor activity of an anti-CD98 antibody." Int J Cancer 137(3): 710-720.

4. Chapman, P. B., A. Hauschild, C. Robert, J. B. Haanen, P. Ascierto, J. Larkin, R. Dummer, C. Garbe, A. Testori, M. Maio, D. Hogg, P. Lorigan, C. Lebbe, T. Jouary, D. Schadendorf, A. Ribas, S. J. O'Day, J. A. Sosman, J. M. Kirkwood, A. M. Eggermont, B. Dreno, K. Nolop, J. Li, B. Nelson,

J. Hou, R. J. Lee, K. T. Flaherty, G. A. McArthur and B.-S. Group (2011). "Improved survival with vemurafenib in melanoma with BRAF V600E mutation." N Engl J Med 364(26): 2507-2516.

5. Fedorenko, I. V., K. H. Paraiso and K. S. Smalley (2011). "Acquired and intrinsic BRAF inhibitor resistance in BRAF V600E mutant melanoma." Biochem Pharmacol 82(3): 201-209.

6. Bos, J. L. (1989). "ras oncogenes in human cancer: a review." Cancer Res 49(17): 4682-4689.

7. Lopez-Chavez, A., C. A. Carter and G. Giaccone (2009). "The role of KRAS mutations in resistance to EGFR inhibition in the treatment of cancer." Curr Opin Investig Drugs 10(12): 1305-1314.

8. Nazarian, R. M., V. G. Prieto, D. E. Elder and L. M. Duncan (2010). "Melanoma biomarker expression in melanocytic tumor progression: a tissue microarray study." J Cutan Pathol 37 Suppl 1: 41-47.

9. Pallis, A., E. Briasoulis, H. Linardou, C. Papadimitriou, D. Bafaloukos, P. Kosmidis and S. Murray (2011). "Mechanisms of resistance to epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced non-small-cell lung cancer: clinical and molecular considerations." Curr Med Chem 18(11): 1613-1628.

10. Appels, N. M., J. H. Beijnen and J. H. Schellens (2005). "Development of farnesyl transferase inhibitors: a review." Oncologist 10(8): 565-578.

11. Sousa, S. F., P. A. Fernandes and M. J. Ramos (2008). "Farnesyltransferase inhibitors: a detailed chemical view on an elusive biological problem." Curr Med Chem 15(15): 1478-1492.

12. Flaherty, K. T., I. Puzanov, K. B. Kim, A. Ribas, G. A. McArthur, J. A. Sosman, P. J. O'Dwyer, R. J. Lee, J. F. Grippo, K. Nolop and P. B. Chapman (2010). "Inhibition of mutated, activated BRAF in metastatic melanoma." N Engl J Med 363(9): 809-819.

13. Fremin, C. and S. Meloche (2010). "From basic research to clinical development of MEK1/2 inhibitors for cancer therapy." J Hematol Oncol 3: 8.

14. Little, A. S., K. Balmanno, M. J. Sale, S. Newman, J. R. Dry, M. Hampson, P. A. Edwards, P. D. Smith and S. J. Cook (2011). "Amplification of the driving oncogene, KRAS or BRAF, underpins acquired resistance to MEK1/2 inhibitors in colorectal cancer cells." Sci Signal 4(166): ra17.

15. Dhillon, S. (2016). "Dabrafenib plus Trametinib: a Review in Advanced Melanoma with a BRAF (V600) Mutation." Target Oncol 11(3): 417-428.

16. SULZMAIER, F. J., JEAN, C. & SCHLAEPFER, D. D. 2014. FAK in cancer: mechanistic findings and clinical applications. Nat Rev Cancer, 14, 598-610.

17. Serrels, A., T. Lund, B. Serrels, A. Byron, R. C. McPherson, A. von Kriegsheim, L. Gomez-Cuadrado, M. Canel, M. Muir, J. E. Ring, E. Maniati, A. H. Sims, J. A. Pachter, V. G. Brunton, N. Gilbert, S. M. Anderton, R. J. Nibbs and M. C. Frame (2015). "Nuclear FAK controls chemokine transcription, Tregs, and evasion of anti-tumor immunity." Cell 163(1): 160-173.

18. Hirata, E., M. R. Girotti, A. Viros, S. Hooper, B. Spencer-Dene, M. Matsuda, J. Larkin, R. Marais and E. Sahai (2015). "Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin beta1/FAK signaling." Cancer Cell 27(4): 574-588.

19. Martinez-Garcia, M., U. Banerji, J. Albanell, R. Bahleda, S. Dolly, F. Kraeber-Bodere, F. Rojo, E. Routier, E. Guarin, Z. X. Xu, R. Rueger, J. J. Tessier, E. Shochat, S. Blotner, V. M. Naegelen and J. C. Soria (2012). "First-in-human, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of RO5126766, a first-in-class dual MEK/RAF inhibitor in patients with solid tumors." Clin Cancer Res 18(17): 4806-4819.

20. Banerji, U., et al., The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. Clin Cancer Res, 2010. 16(5): p. 1613-23.

21. LoRusso, P. M., S. S. Krishnamurthi, J. J. Rinehart, L. M. Nabell, L. Malburg, P. B. Chapman, S. E. DePrimo, S. Bentivegna, K. D. Wilner, W. Tan and A. D. Ricart (2010). "Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers." Clin Cancer Res 16(6): 1924-1937.

22. Ishii, N., N. Harada, and E.W. Joseph, A novel allosteric MEK inhibitor, CH5126766 (RO512766) suppresses RAF-mediated feedback induction of MEK phosphorylation. Nature Chemical Biology, 2011: p. (submitted).

23. Lawlor, M. A., X. Feng, D. R. Everding, K. Sieger, C. E. Stewart and P. Rotwein (2000). "Dual control of muscle cell survival by distinct growth factor-regulated signaling pathways." Mol Cell Biol 20(9): 3256-3265.

24. Garcia, R., J. Grindlay, O. Rath, F. Fee and W. Kolch (2009). "Regulation of human myoblast differentiation by PEBP4." EMBO Rep 10(3): 278-284.

25. Cichowski, K. and P. A. Janne (2010). "Drug discovery: inhibitors that activate." Nature 464(7287): 358-359.

26. O'Neil, B.H., et al., Phase II study of the mitogen-activated protein kinase 1/2 inhibitor selumetinib in patients with advanced hepatocellular carcinoma. J Clin Oncol, 2011. 29(17): p. 2350-6.

27. McArthur, G. A., P. B. Chapman, C. Robert, J. Larkin, J. B. Haanen, R. Dummer, A. Ribas, D. Hogg, O. Hamid, P. A. Ascierto, C. Garbe, A. Testori, M. Maio, P. Lorigan, C. Lebbe, T. Jouary, D. Schadendorf, S. J. O'Day, J. M. Kirkwood, A. M. Eggermont, B. Dreno, J. A. Sosman, K. T. Flaherty, M. Yin, I. Caro, S. Cheng, K. Trunzer and A. Hauschild (2014). "Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study." Lancet Oncol 15(3): 323-332.

28. Planchard, D., B. Besse, H. J. Groen, P. J. Souquet, E. Quoix, C. S. Baik, F. Barlesi, T. M. Kim, J. Mazieres, S. Novello, J. R. Rigas, A. Upalawanna, A. M. D'Amelio, Jr., P. Zhang, B. Mookerjee and B. E. Johnson (2016). "Dabrafenib plus trametinib in patients with previously treated BRAF-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial." Lancet Oncol.

29. Planchard, D., T. M. Kim, J. Mazieres, E. Quoix, G. Riely, F. Barlesi, P. J. Souquet, E. F. Smit, H. J. Groen, R. J. Kelly, B. C. Cho, M. A. Socinski, L. Pandite, C. Nase, B. Ma, A. D'Amelio, Jr., B. Mookerjee, C. M. Curtis, Jr. and B. E. Johnson (2016). "Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial." Lancet Oncol 17(5): 642-650.

30. Siesser, P. M. and S. K. Hanks (2006). "The signaling and biological implications of FAK overexpression in cancer." Clin Cancer Res 12(11 Pt 1): 3233-3237.

31. Weis, S. M., S. T. Lim, K. M. Lutu-Fuga, L. A. Barnes, X. L. Chen, J. R. Gothert, T. L. Shen, J. L. Guan, D. D. Schlaepfer and D. A. Cheresh (2008). "Compensatory role for Pyk2 during angiogenesis in adult mice lacking endothelial cell FAK." J Cell Biol 181(1): 43-50.

32. David E. Gerber, S. S. R., Daniel Morgensztern, Ronan Joseph Kelly, Timothy Francis Burns, Ariel Lopez-Chavez, David R. Spigel, Ahmad Mouhamad Wehbe, Rachel Sorensen, David T. Weaver, Joanna Horobin, Mitchell Keegan, Pier P. Scaglioni, D. Ross Camidge (2015). "A phase 2 study of defactinib (VS-6063), a cancer stem cell inhibitor that acts through inhibition of focal adhesion kinase (FAK), in patients with KRAS-mutant non-small cell lung cancer."

17 APPENDICES

17.1 APPENDIX 1: WHO PERFORMANCE SCALE

Activity Performance Description	Score
Fully active, able to carry out all normal activity without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work.	1
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	4

17.2 APPENDIX 2: DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

**Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964
amended by the 29th World Medical Assembly
Tokyo, Japan, October 1975,
and
the 35th World Medical Assembly,
Venice, Italy, October 1983
and
the 41st World Medical Assembly,
Hong-Kong, September 1989
and
the 48th General Assembly,
Somerset West, Republic of South Africa, October 1996**

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that, "A physician shall act only in patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognised between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I - BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II - <u>MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE</u>
(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III - <u>NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS</u>
(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

17.3 APPENDIX 3: MEASUREMENT OF DISEASE

Response Evaluation Criteria In Solid Tumours: Revised RECIST Guideline (version 1.1)

[Eisenhauer, 2009]

Baseline documentation of target and non-target lesions

- All baseline lesion assessments must be performed within 28 days of randomizations.
- Lymph nodes that have a short axis of <10mm are considered non-pathological and should not be recorded or followed.
- Pathological lymph nodes with <15mm and but 10mm short axis are considered non measurable.
- Pathological lymph nodes with 15mm short axis are considered measurable and can be selected as target lesions, however lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, and recorded and measured at baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Note: Cystic lesions thought to represent cystic metastases should not be selected as target lesions when other suitable target lesions are available.

Note: Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- All other lesions (or sites of disease) should be identified as non-target and should also be recorded at baseline. Non-target lesions will be group by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Efficacy assessment

Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [Eisenhauer, 2009].

See the Schedule of Events Table (Section 7.5) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post baseline assessments, a window of 14 days is permitted to allow for flexible scheduling.

- The following are required at baseline: CT for Chest/Abdomen/Pelvis or MRI for Abdomen/Pelvis and clinical disease assessment for palpable lesions. At each post baseline assessment, evaluations of the sites of disease identified by these scans are required except for brain scan and bone scans. Brain and Bone scans should be performed as clinically indicated.

Confirmation of CR and PR are required per protocol. Confirmation assessments must be performed no less than 4 weeks after the criteria for response have initially been met and may be performed at the next protocol scheduled assessment. If a confirmation assessment is performed prior to the next protocol schedule assessment, the next protocol scheduled evaluation is still required (*e.g.*

evaluations must occur at each protocol scheduled time point regardless of unscheduled assessments).

For subjects not known to have CNS disease at baseline brain scans should only be performed as clinically indicated (e.g. symptoms suggestive of CNS progression). For subjects with known CNS disease, a baseline brain scan is required and subsequent scans should be performed as clinically indicated.

Assessment guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion.
- All measurements should be taken and recorded in millimeters (mm), using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, confirmation by CT or MRI is required.
- Fluorodeoxyglucose (FDG)-PET is generally not suitable for ongoing assessments of disease. However FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scans correlates with the new site of disease present on CT/MRI or when a baseline FDG-PET was previously negative for the site of the new lesion. FDG-PET may also be used in lieu of a standard bone scan providing coverage
- allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the CRF.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler/callipers to measure the size of the lesion, is required. [Eisenhauer, 2009].

CT and MRI: <u>Contrast enhanced CT with 5mm contiguous slices is recommended.</u>
Minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimised for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible the same scanner should be used. [Eisenhauer, 2009].

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however chest CT is preferred over chest X-ray [Eisenhauer, 2009].

Brain Scan: Baseline brain scans are required, then contrast enhanced MRI is preferable to contrast enhanced CT.

Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion: A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

10 mm with MRI or CT when the scan slice thickness is no greater than 5mm. If the slice thickness is greater than 5mm, the minimum size of a measurable lesion must be at least double the slice thickness (*e.g*., if the slice thickness is 10 mm, a measurable lesion must be 20 mm).

10 mm calliper/ruler measurement by clinical exam or medical photography.

20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if 15mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion: All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions. Note: non-measurable only disease is not allowed per protocol.

Response Criteria

Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10mm in the short axis.

- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (*e.g*. percent change from baseline).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (*e.g*. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.

- Not Applicable (NA): No target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (*e.g*. sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10mm) they should still have a measurement reported in order not to overstate progression.

- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (*e.g* 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (*e.g*. <10 mm short axis).

- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥ 10 mm short axis.

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (*e.g*. non-target response does not have to be "Not Evaluable").

New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.
Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of overall response

Table 22 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 22 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

Note:

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 4 weeks.

If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria (recommended):

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

17.4 APPENDIX 4: NEW YORK HEART ASSOCIATION (NYHA) SCALE

Class I – patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain)

Class II – patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain)

Class III – patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain)

Class IV – patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.