

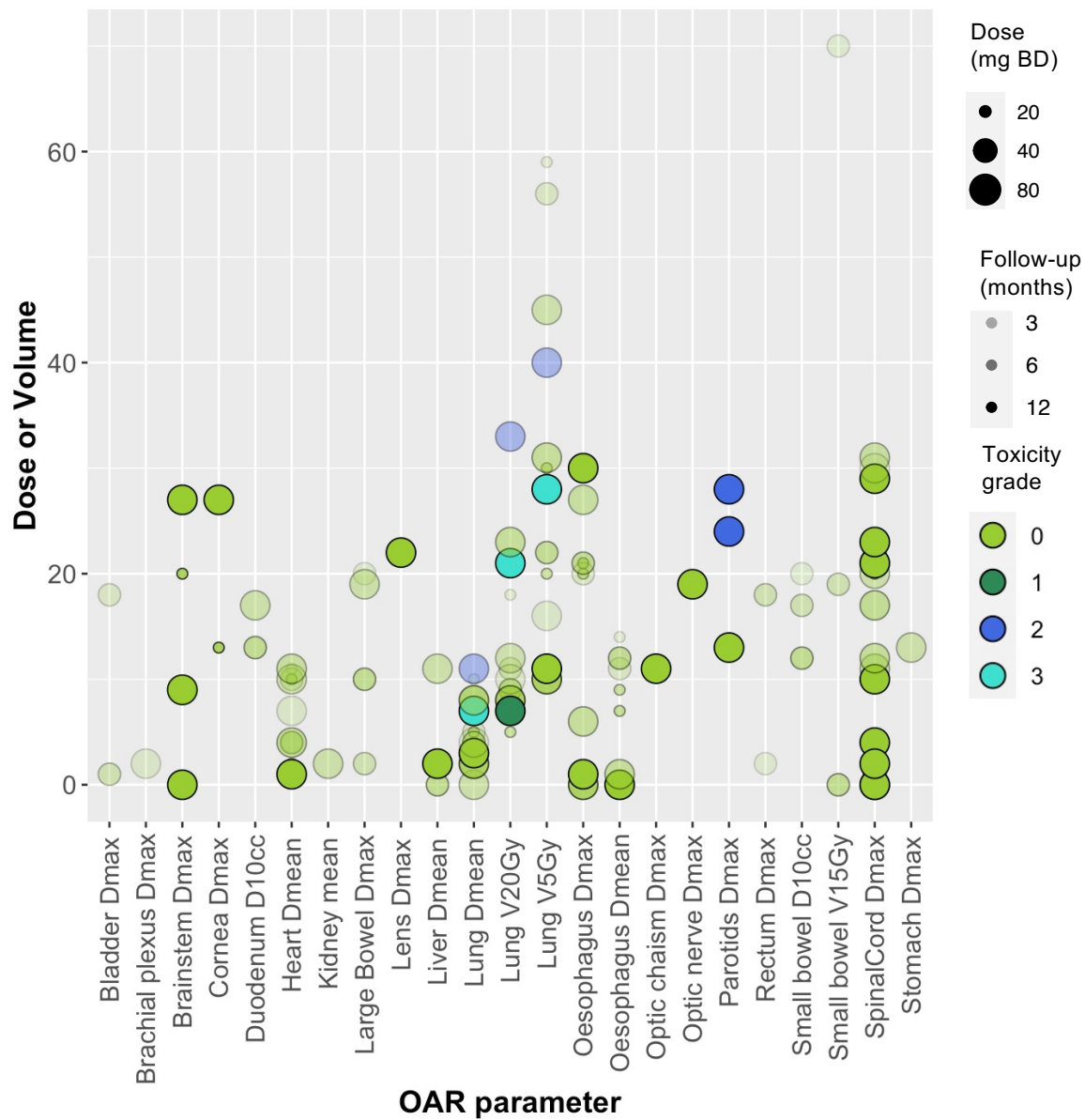
# **Supplementary information file of Tumor control and immune activation through palliative irradiation and ATR inhibition, PATRIOT Part C: a phase Ib trial**

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Affiliations:

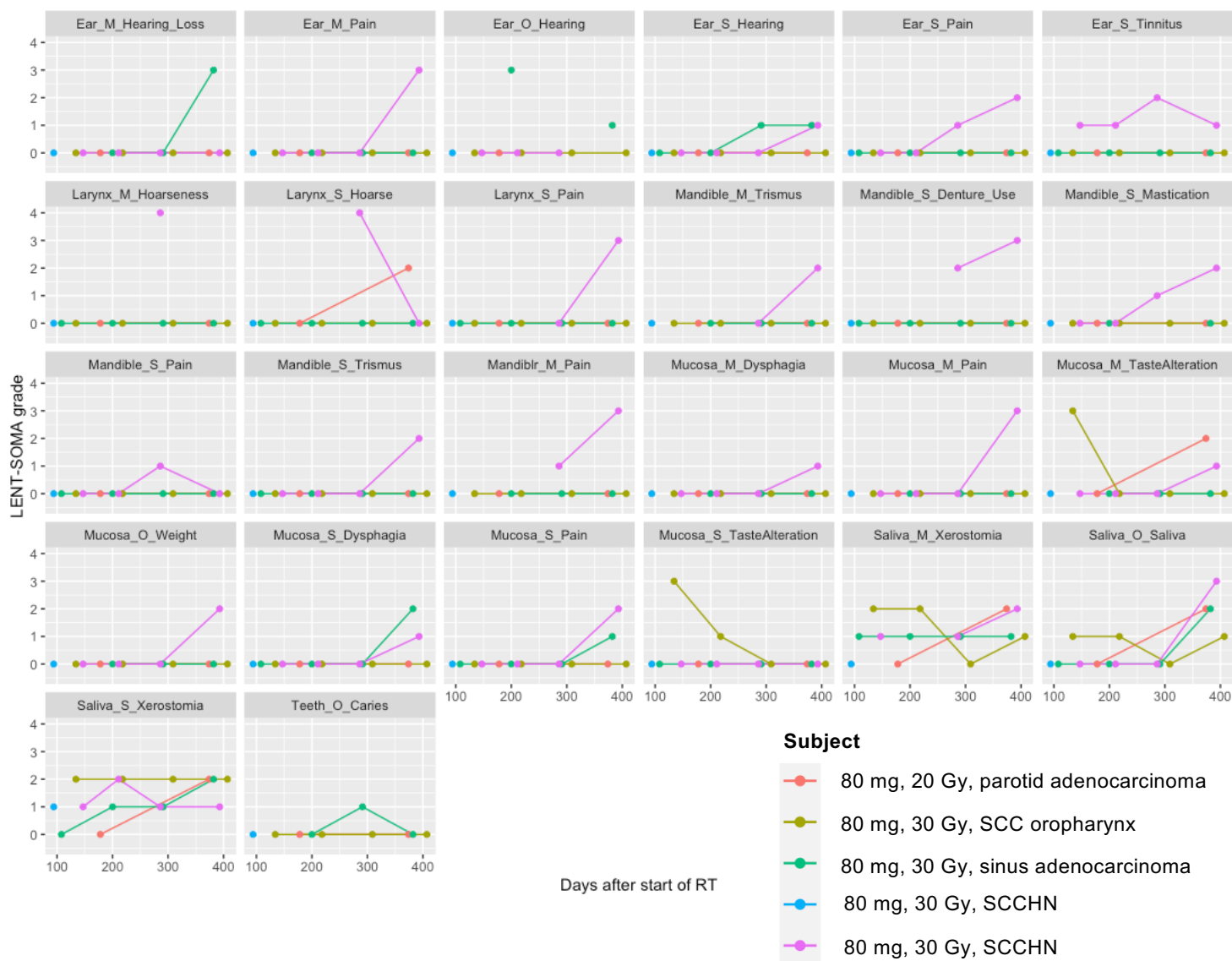
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## **Supplementary note 1: supplementary figures and tables**



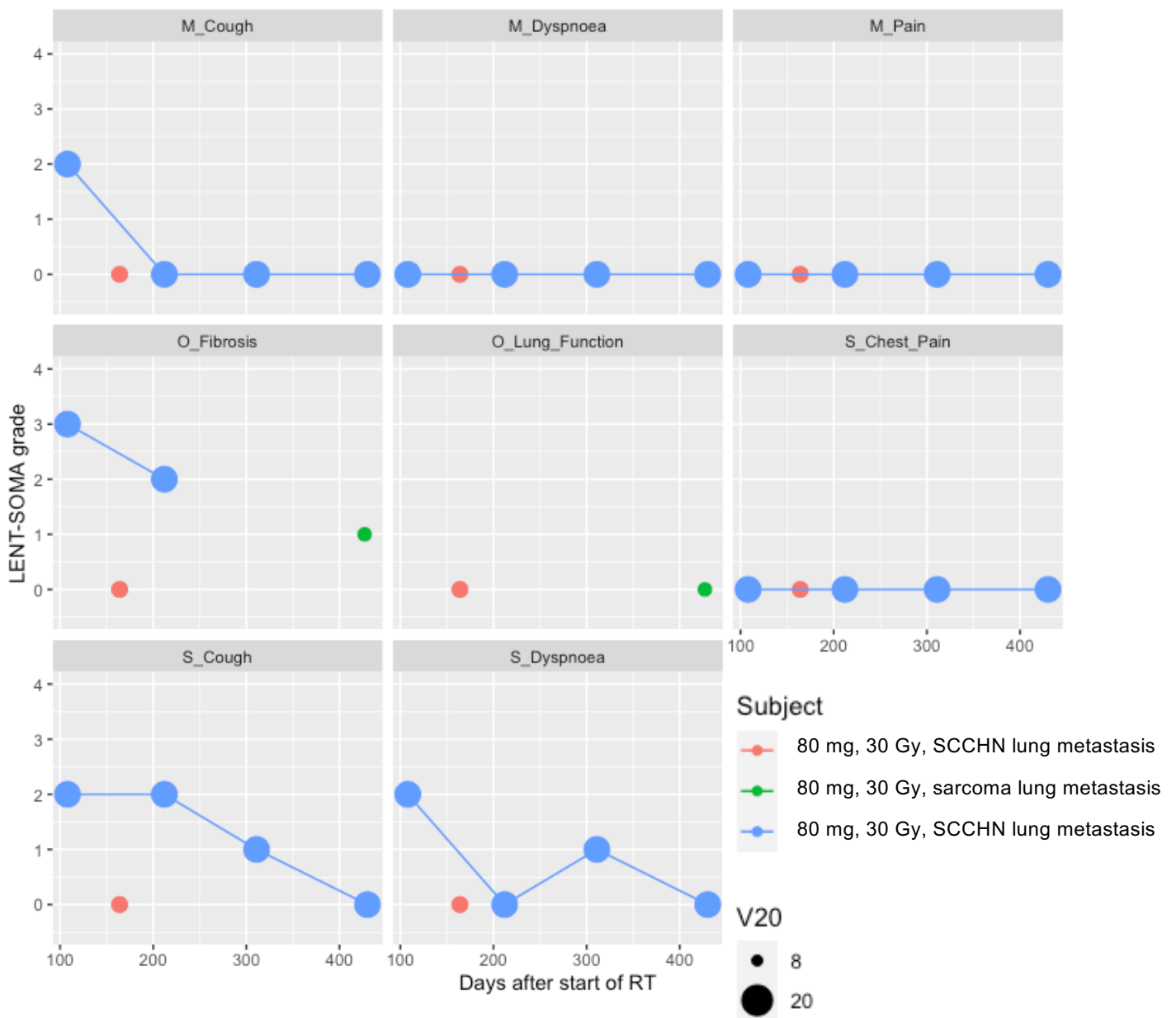
### Supp. Fig. 1: dose-volume parameters and late toxicity grading

Full dose-volume parameters for all patients with late toxicity recording (extended from Fig. 1E). Color indicates grade of toxicity, size indicates ceralasertib dose and density indicates length of available follow-up.



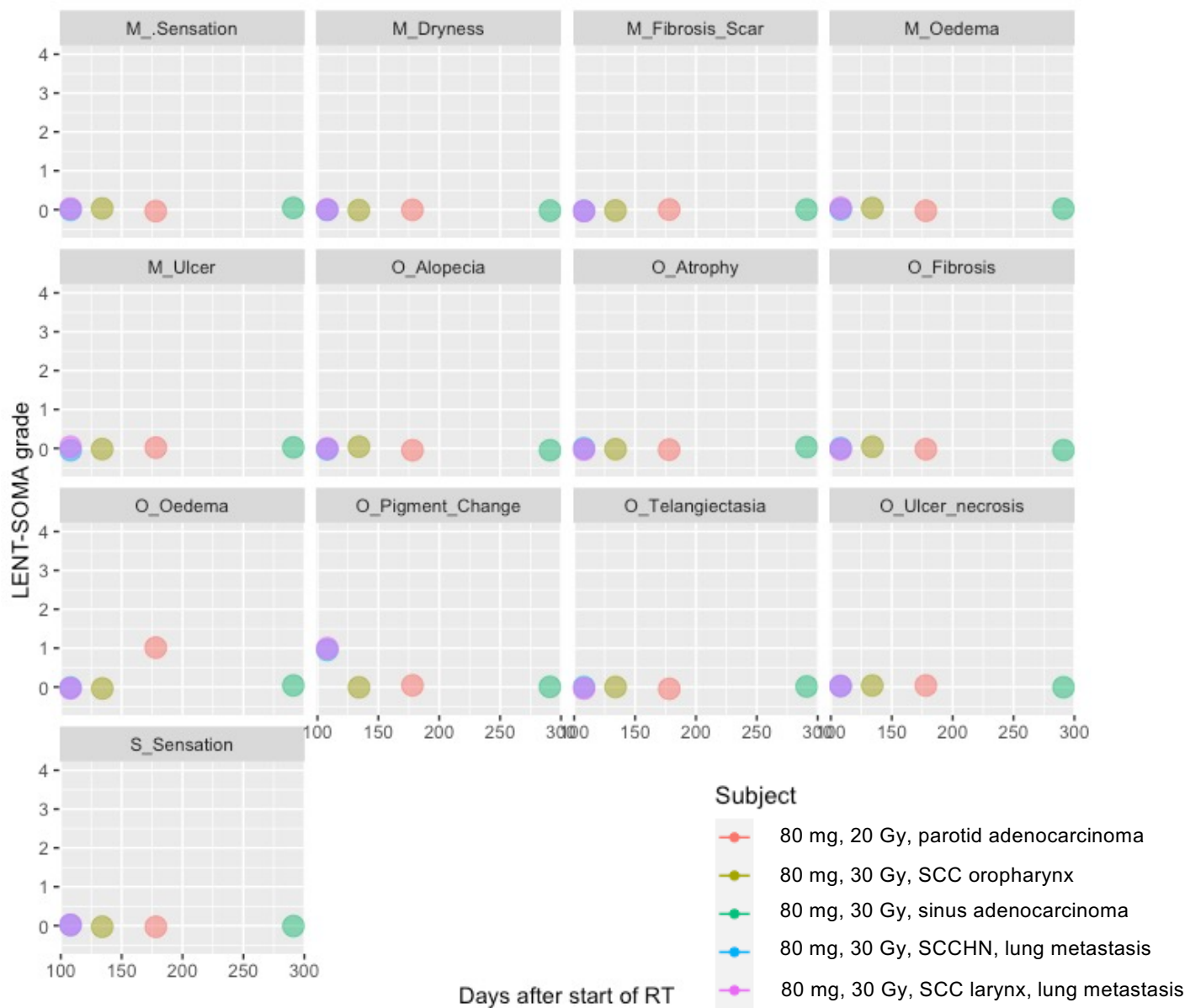
## Supp. Fig. 2: late toxicity scoring, head and neck

LENT-SOMA scores for the head and neck-related scales, for those patients receiving radiotherapy to the head and neck region. Domains not graphed scored 0 for all participants. S: subjective, O: objective; M: management; A: Analytic. Scales from Int. J. Radiation Oncology Biol. Phys. 31(5):1049-1091, 1995

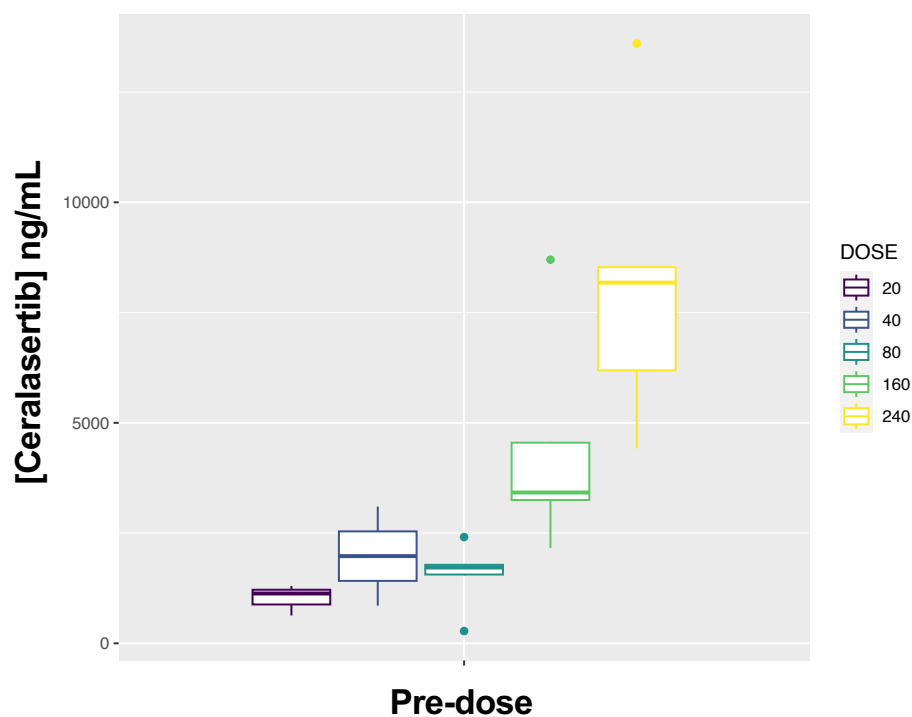


### Supp. Fig. 3: late toxicity scoring, lung

LENT-SOMA scores for the lung scale, for those patients receiving radiotherapy to the lung. Size of point represents the V20Gy (percent of total lung volume receiving at least 20 Gy). S: subjective, O: objective; M: management; A: Analytic. Scales from Int. J. Radiation Oncology Biol. Phys. 31(5):1049-1091, 1995

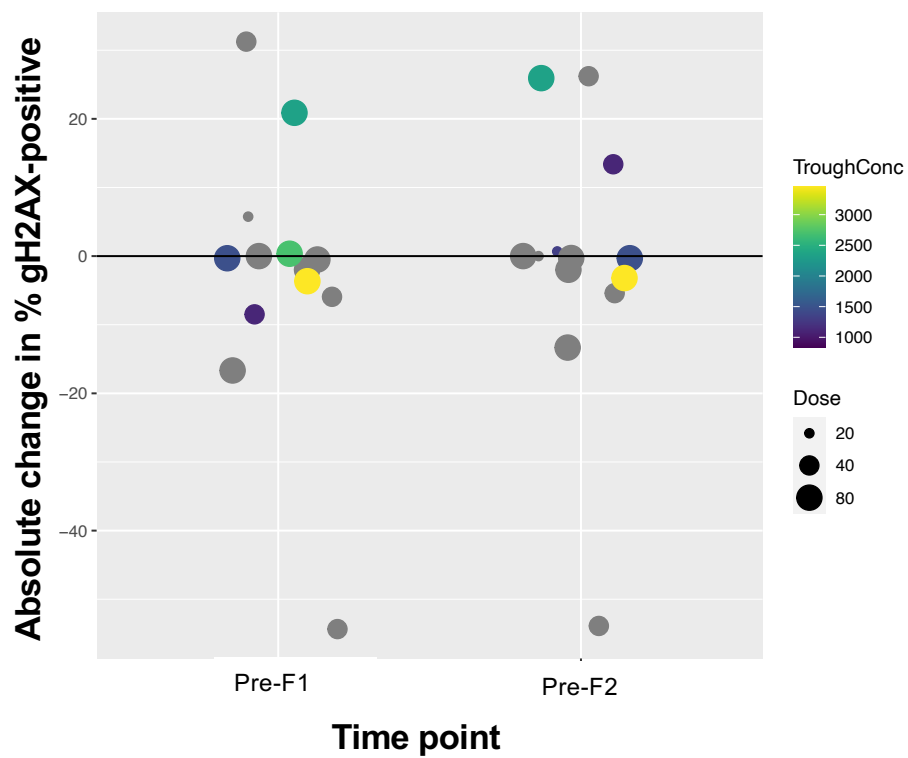


**Supp. Fig. 4: late toxicity scoring, skin**  
 LENT-SOMA scores for the skin-related scales  
 S: subjective, O: objective; M: management;  
 A: Analytic. Scales from Int. J. Radiation  
 Oncology Biol. Phys. 31(5):1049-1091, 1995



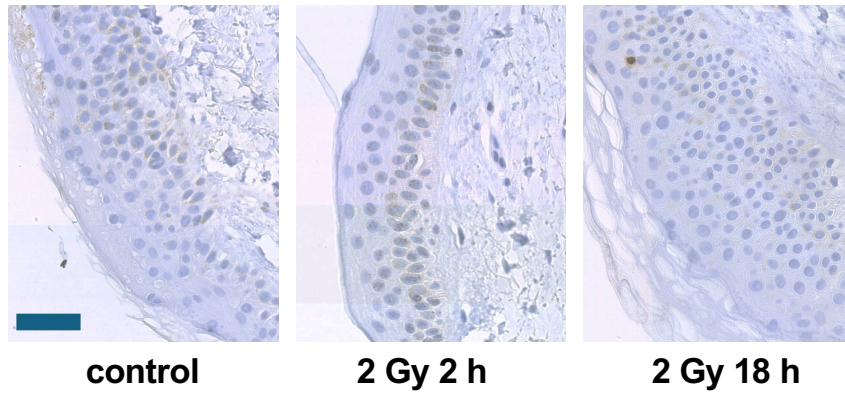
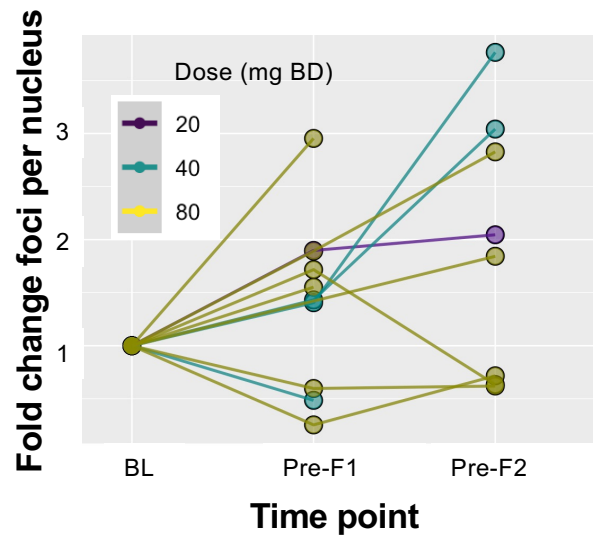
### Supp. Fig. 5 : monotherapy pharmacokinetics

Summary of plasma ceralasertib levels from the dose escalation monotherapy part of the study (Dillon et al. ref. 10). Box: 25-75 percentile; line: median; whisker: 1.5 x IQR; points: outside 1.5 x IQR N = 3 (20 mg); 3 (40 mg); 6 (80 mg); 6 (160 mg); 6 (240 mg) individual participants per group.

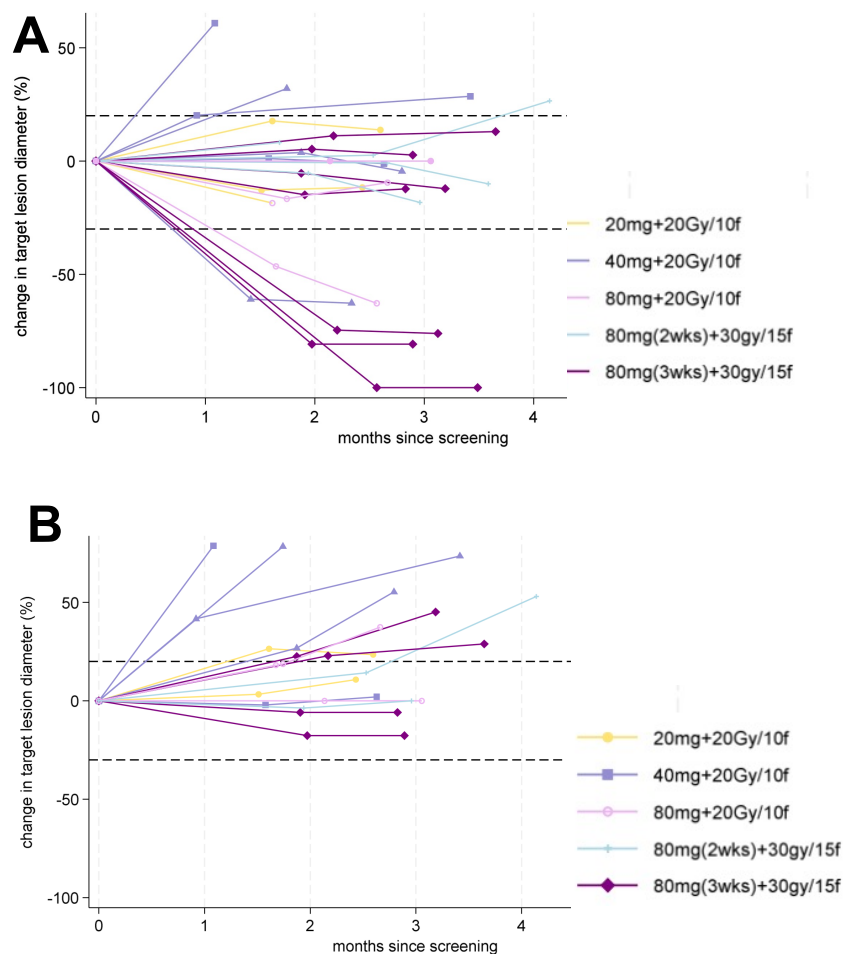


**Supp. Fig. 6: PBMC DNA damage**

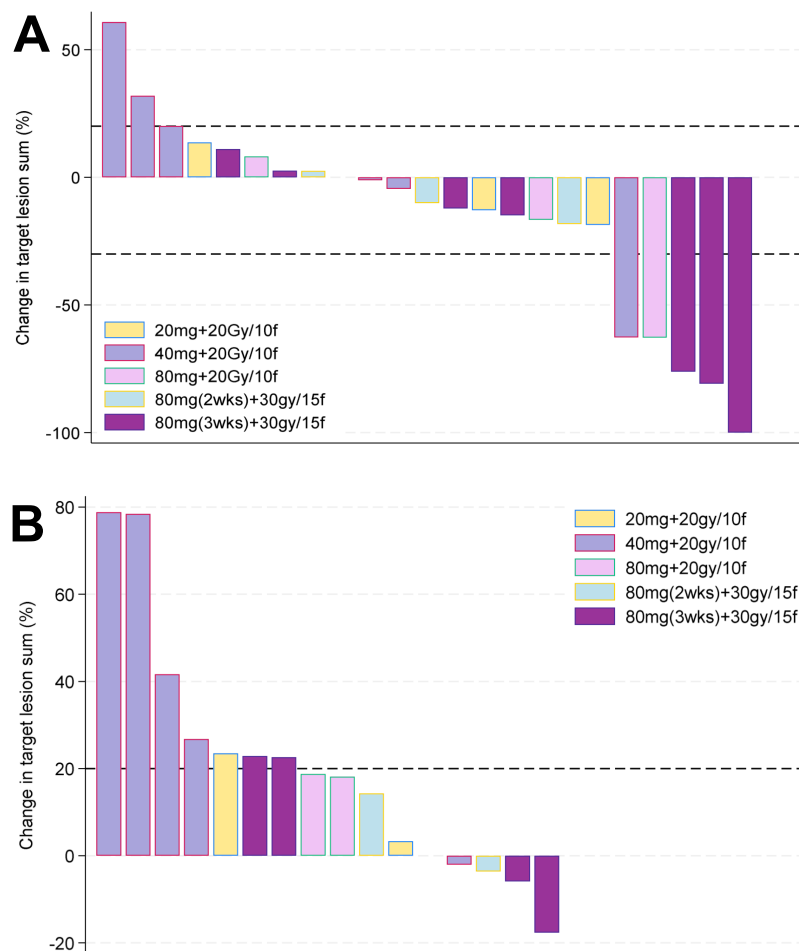
PBMC gH2AX levels, measured by immunofluorescence. Absolute change in percentage of cells with more than 5 foci, compared with baseline sample for the same participant.

**A****B****Supp. Fig. 7: DNA damage in skin biopsies**

**A:** Ex vivo skin biopsies, irradiated and fixed at the indicated time points before staining for  $\gamma$ H2AX by IHC. Scale bar = 50  $\mu$ m. **B:** Fold-change in number of  $\gamma$ H2AX foci in skin punch biopsies, at baseline, before fraction 1 (after 3-7 days' cerlasertib) and before fraction 2 (after 1 fraction of 2 Gy). Normalised data from Fig. 2D.

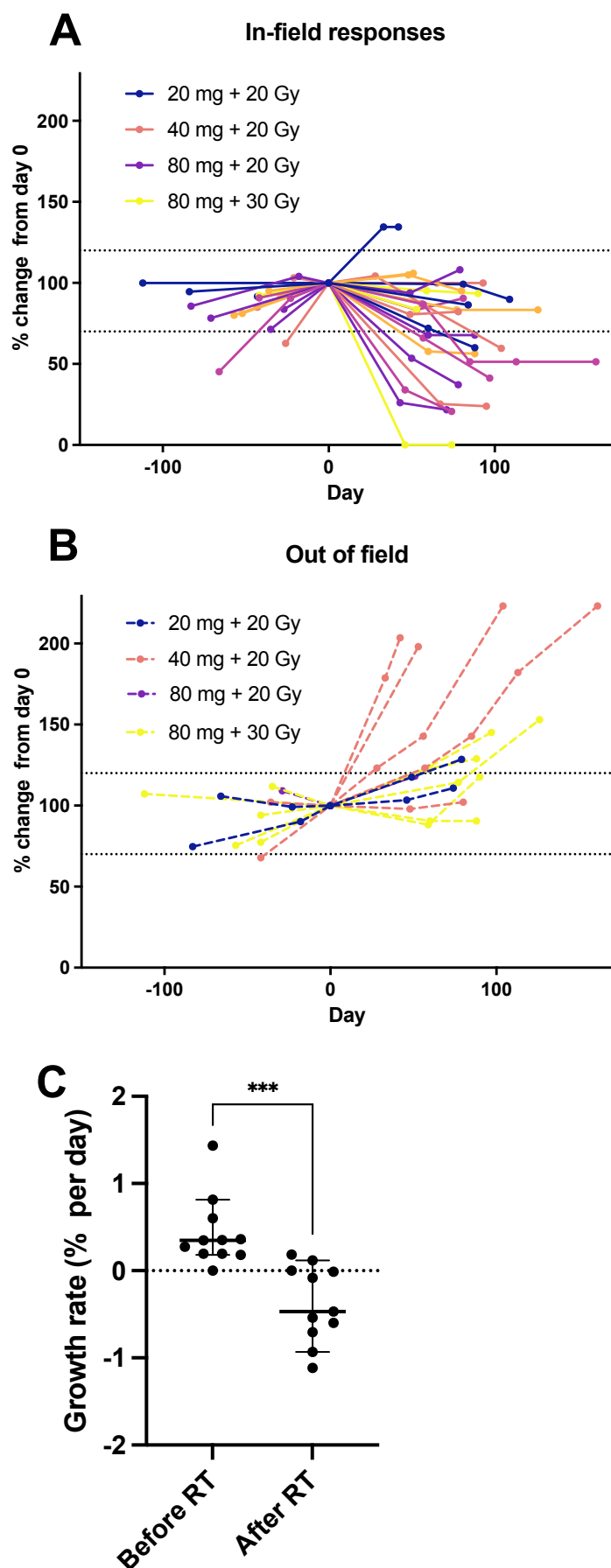


**Supp. Fig. 8: change in lesion size for overall target lesions and unirradiated lesions**  
 Spider diagram for overall sum of longest diameters of (A) overall target lesions (irradiated and unirradiated) and (B) unirradiated lesions only.



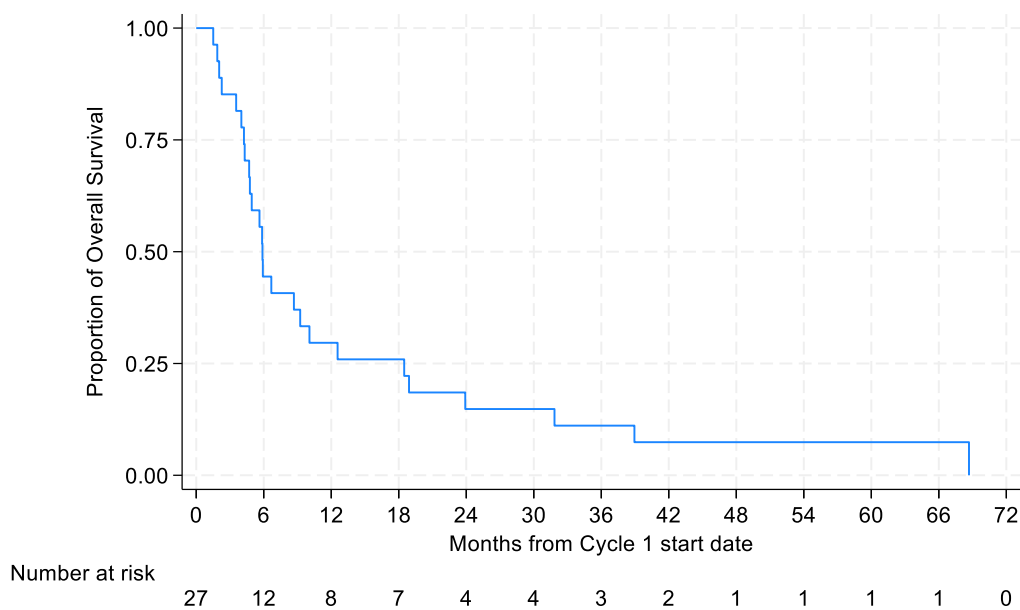
**Supp. Fig. 9: overall target lesion and unirradiated target lesion best change in diameter.**

Waterfall plot for overall sum of longest diameters of (A) overall target lesions (irradiated and unirradiated) and (B) unirradiated lesions only.



### Supp. Fig. 10: tumour growth kinetics

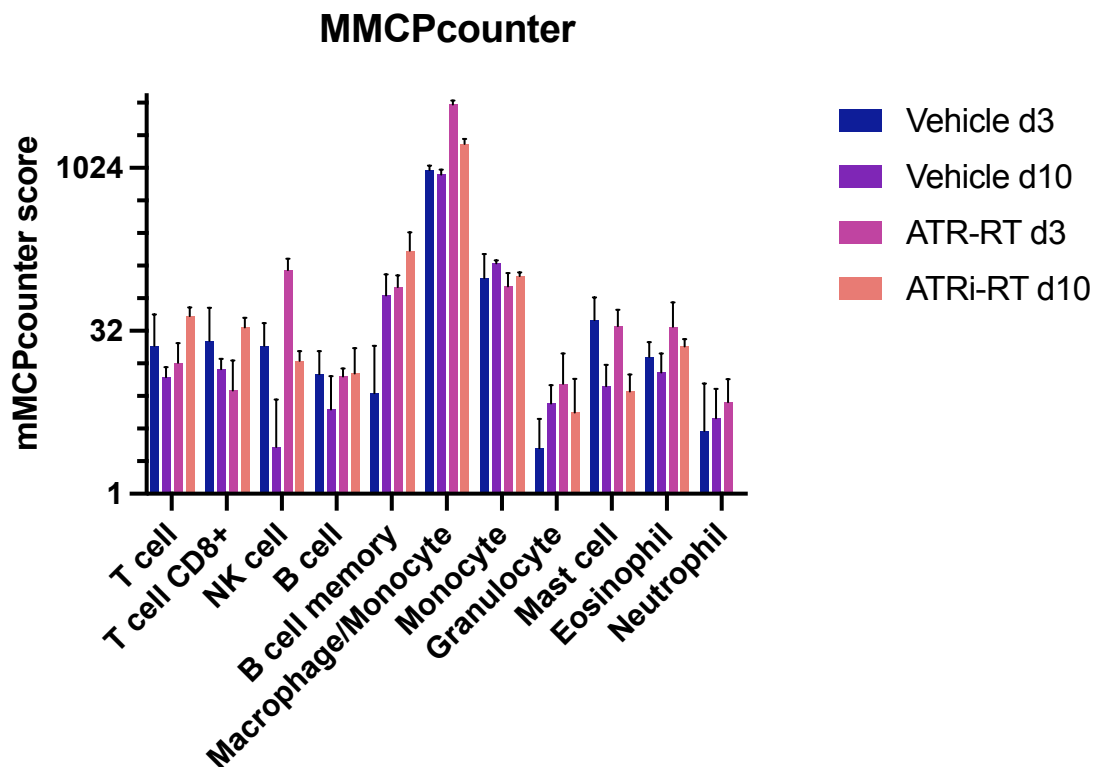
Available prior measurements were taken from target lesions, with the baseline screening scan designated day 0. Irradiated and, where available, lesions outside the radiation field are shown in panel A and B, respectively. Normalised to day 0 measurement. C: tumour growth rates from irradiated target lesions were calculated (in percent change per day compared to screening lesion measurement) for the tumours shown in (A). N = 11 participants per group. Median and 95% CI displayed. \*\*\* two-tailed  $p = 0.001$  by Wilcoxon test.



| Median OS (95% CI)  |                   |
|---------------------|-------------------|
|                     | (months)          |
| Overall Patients    | 5.9 (4.3 – 10.1)  |
| 20mg+20gy/10f       | 4.8 (3.6 – NR)    |
| 40mg+20gy/10f       | 4.0 (1.5 – NR)    |
| 80mg+20gy/10f       | 4.3 (1.9 – NR)    |
| 80mg(2wks)+30gy/15f | 8.7 (4.7 – NR)    |
| 80mg(3wks)+30gy/15f | 18.5 (2.3 – 38.9) |

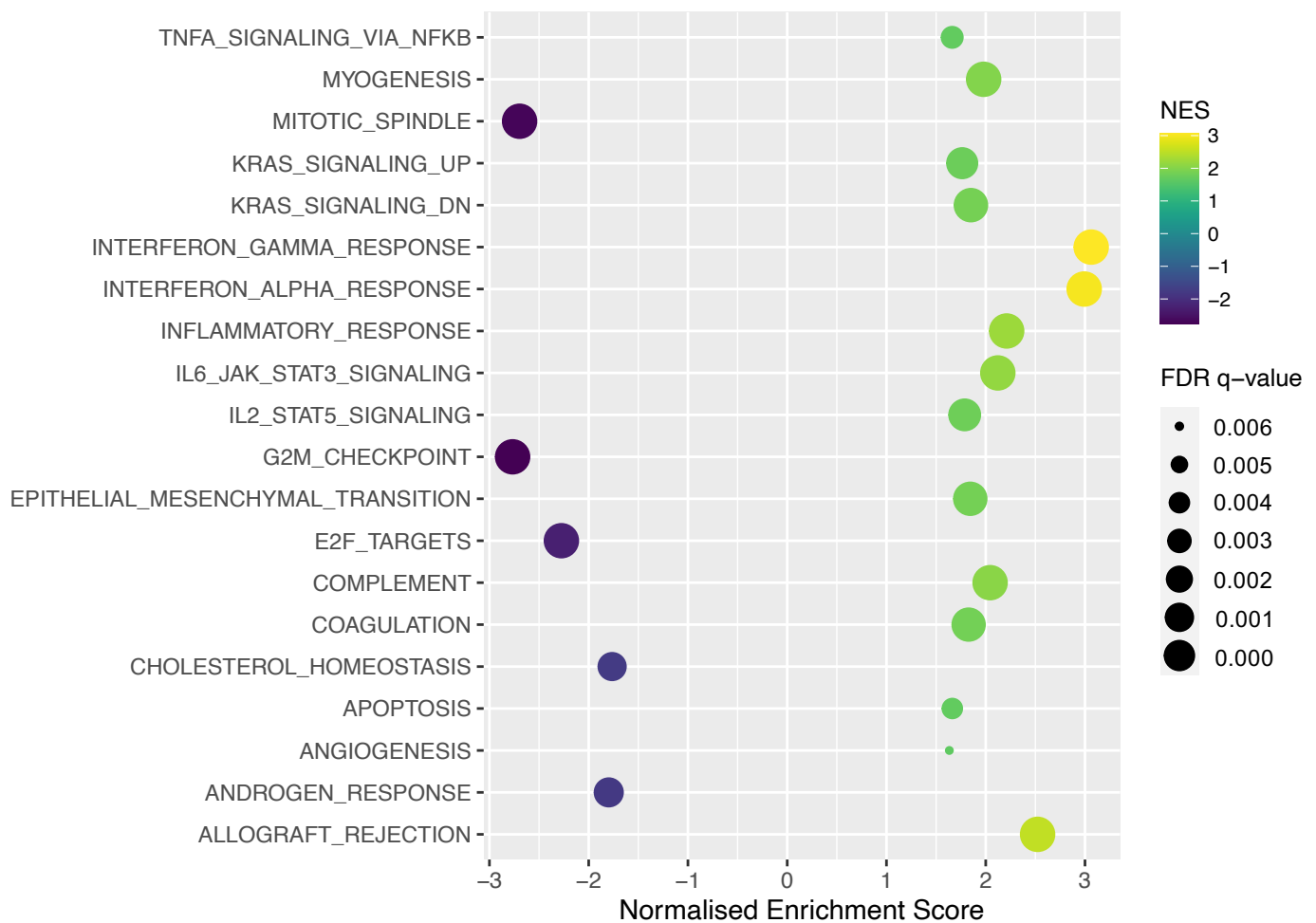
### Supp. Fig. 11: Overall Survival

Kaplan Meier plot of overall survival from treatment start (cycle 1 day 1) – overall patients. \* NR = Not reached the upper 95% confidence limit. Table indicates the overall survival in months and 95% confidence interval by treatment cohort.

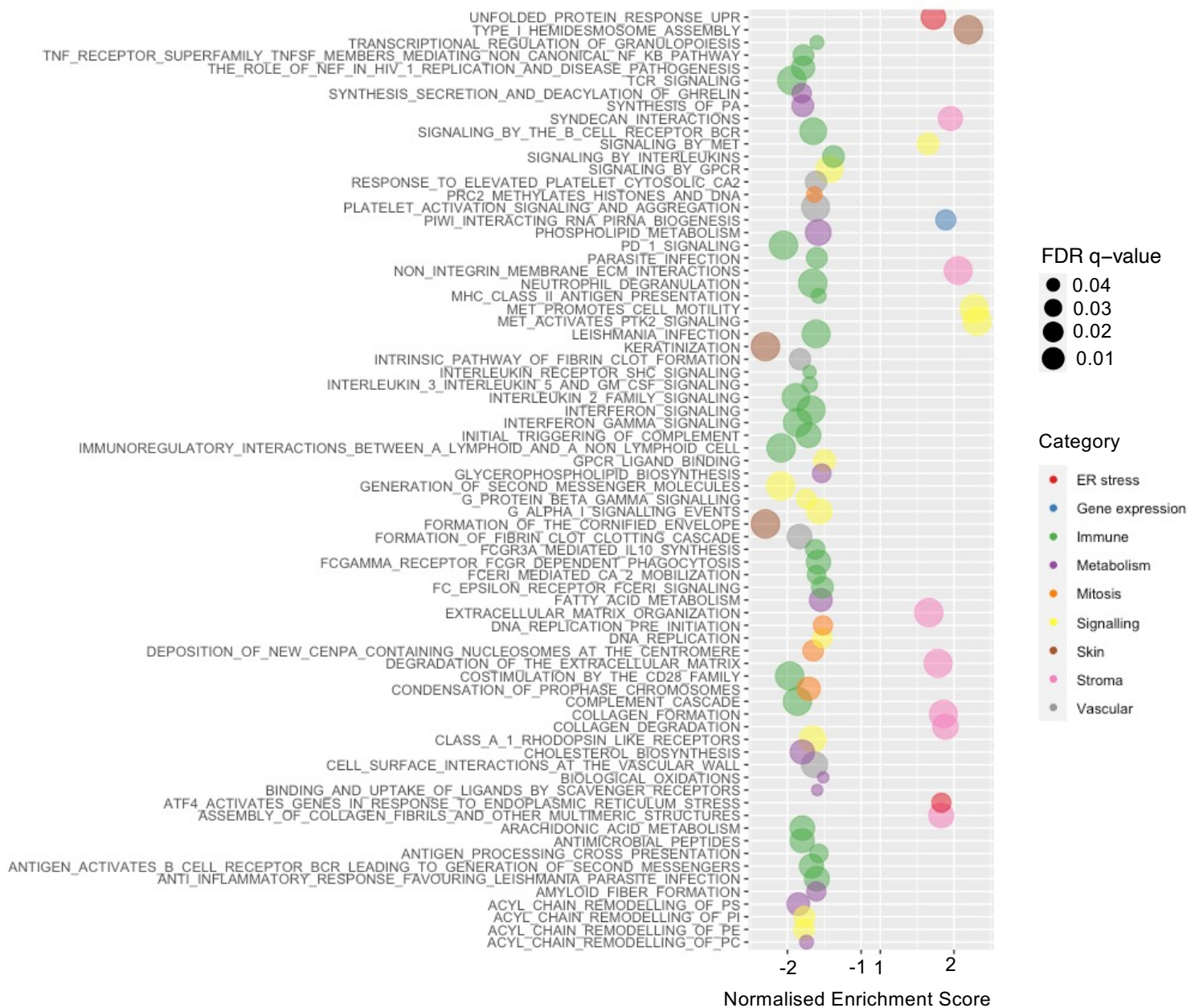


**Supp. Fig. 12: MOC2 mouse SCCHN model cell type deconvolution**  
 C57Bl/6 mice bearing MOC2 tumours were treated with ceralasertib 75 mg/kg and 8 Gy in 4 daily fractions. RNA was extracted from tumours at day 3 or day 10 after completion of treatment and RNAseq performed. RNAseq counts were analysed using mMCPcounter. Mean scores presented for each cell type. Normalised data are shown in fig. 4F. N = 3 animals per group. Error bars: SD.

Petitprez, F., Levy, S., Sun, CM. et al. The murine Microenvironment Cell Population counter method to estimate abundance of tissue-infiltrating immune and stromal cell populations in murine samples using gene expression. *Genome Med* 12, 86 (2020).  
<https://doi.org/10.1186/s13073-020-00783-w>



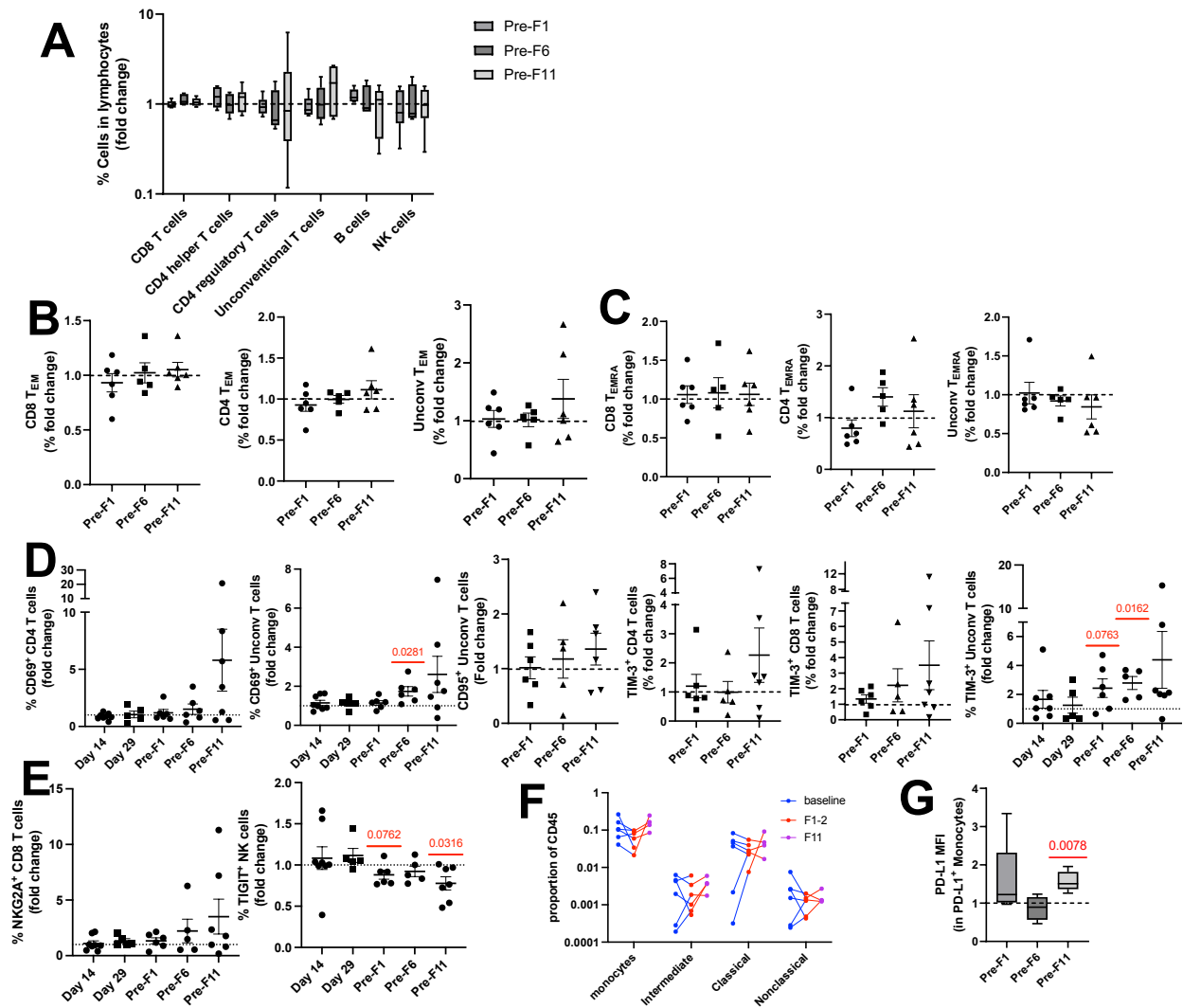
**Supp. Fig. 13: Gene set enrichment analysis for MOC2 murine SCCHN model**  
Day 3 ATRi+RT (n=3 tumours) vs day 3 vehicle-only (n=3 tumours) differential gene expression data was analysed using GSEA, with the 'Hallmarks' dataset. Normalised enrichment score and false discovery rate (FDR) Q-values are shown for each of the hallmarks. Analogous to the human data presented in fig. 4D



### Supp. Fig. 14: Human tumour GSEA (Reactome gene set)

RNASeq data from tumour biopsies (baseline and pre-fraction 2), shown in fig 4C were analysed using GSEA, with the 'reactome' gene set. Genes with FDR-Q < 0.05 were categorized into broad functional categories (colour codes).





### Supp. Fig. 16: additional flow cytometry data

A – fold change in percentage of cells in lymphocyte compartment, compared with baseline. Pre-F1, -F6, -F11 = samples taken prior to first fraction of radiotherapy (after 3-7 days of ceralasertib 80 mg BD), prior to 6<sup>th</sup> and prior to 11<sup>th</sup> fraction, respectively

B – fold change in proportions of effector memory (CCR7-CD45RA<sup>-</sup>)T cells compared with baseline

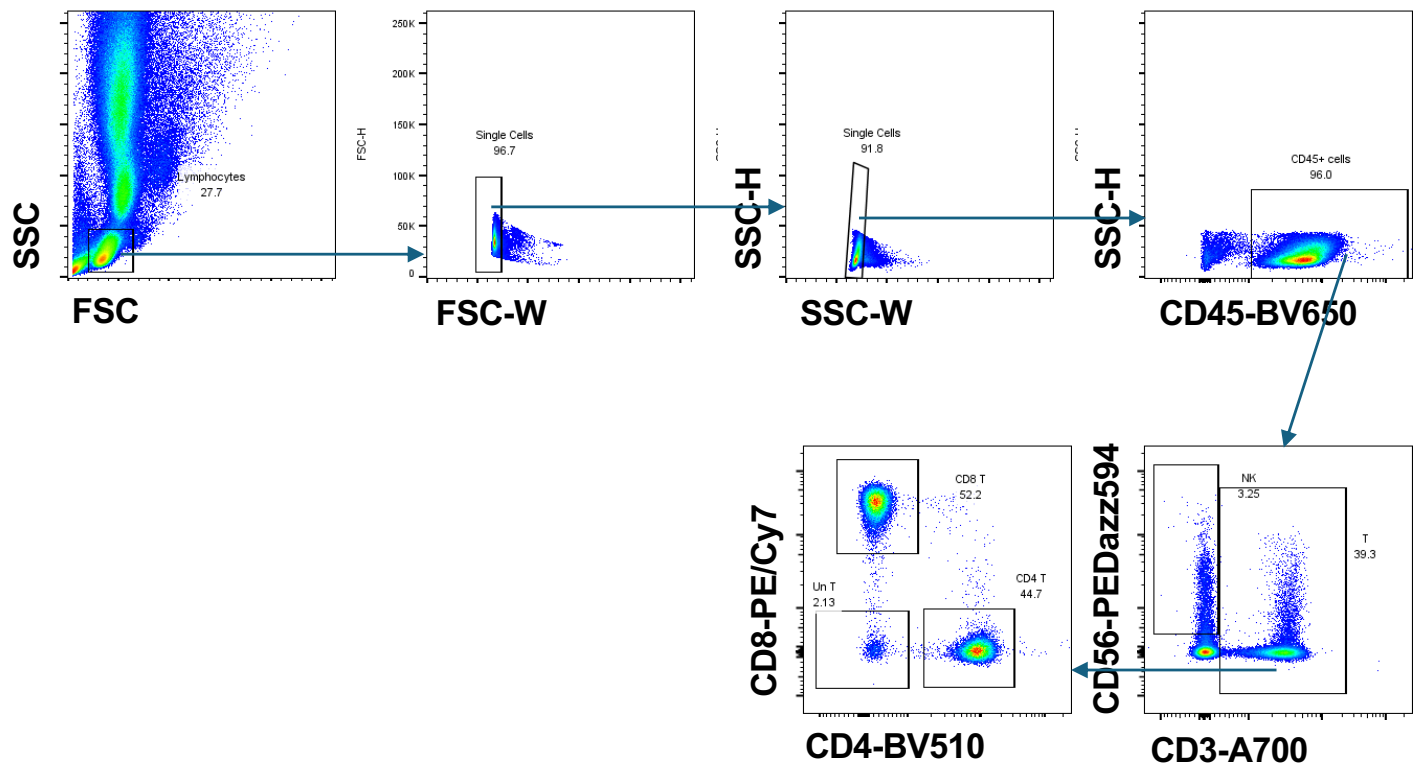
C – fold change proportions of effector memory-RA (CCR7-CD45RA<sup>+</sup>)T cells compared with baseline

D – fold change in percentage of CD45<sup>+</sup> cells of the indicated populations. Significance = p-value by one sample t-test compared with theoretical mean of 1. 'Day 14' and 'Day 29' = fold change compared with baseline for patients treated with drug alone to day 14, then 2 weeks' break to day 29 (no radiotherapy) in part B of PATRIOT.

E – fold change in percentage of indicated populations, compared with baseline sample. Significance = p-value by one sample t-test compared with theoretical mean of 1.

F – monocyte subsets as a proportion of CD45 (Classical CD14<sup>+</sup>CD16<sup>-</sup>, intermediate CD14<sup>+</sup>CD16<sup>+</sup>, nonclassical CD14<sup>dim</sup>CD16<sup>+</sup>)

G – fold change in monocyte PD-L1 mean fluorescence intensity with treatment, significance = Wilcoxon test vs. hypothetical median of 1



### Supp Fig 17: flow cytometry gating strategy

Lymphocyte gating strategy shown for data in Fig. 5C–G and Supp. Fig. 16. FSC: forward scatter, SSC: side scatter: W: width, H: height. Example given for gating CD4 and CD8 T-cells.

| Treatment                         | Below diaphragm  | Above diaphragm  |
|-----------------------------------|------------------|------------------|
|                                   | n                | n                |
| Actual RT dose:                   |                  |                  |
| 20                                | 6                | 10               |
| 30                                | 0                | 11               |
| RT fractions:                     |                  |                  |
| 10                                | 6                | 10               |
| 15                                | 0                | 11               |
| Field size 1 (cm <sup>2</sup> ):  |                  |                  |
| Median (IQR)                      | 13.2 (12.1–14.4) | 11.5 (9.8–15.0)  |
| (Range)                           | (10.3–18.5)      | (7.5–20.5)       |
| Field size 2 (cm <sup>2</sup> ):  |                  |                  |
| Median (IQR)                      | 11.1 (9.7–15.3)  | 11.5 (8.8–15.6)  |
| (Range)                           | (9.6–16.1)       | (7.2–20.5)       |
| Equivalent Square:                |                  |                  |
| Median (IQR)                      | 12.5 (10.8–14.6) | 11.3 (10.1–15.2) |
| (Range)                           | (9.9–17.2)       | (7.5–84.0)       |
| Actual RT technique:              |                  |                  |
| Direct field                      | 1                | 0                |
| IMRT/VMAT/3DCRT (n=1)             | 0                | 7                |
| Parallel pair/ virtual simulation | 5                | 13               |
| Unavailable                       | 0                | 1                |
| Energy:                           |                  |                  |
| 10 MV                             | 1                | 1                |
| 6 MV                              | 4                | 20               |
| Not recorded                      | 1                | 0                |

**Supp Table 1: Radiotherapy treatment details**

| ATM-G1       | ATR    | CIN    | DSB      | EXCISION | FANC             | HR       | MMR     |           |  |  |
|--------------|--------|--------|----------|----------|------------------|----------|---------|-----------|--|--|
| ATM*         | ATR    | AURKA  | CDK12    | LIG1     | C17orf70 / FANCA | BABAM1   | MLH1    |           |  |  |
| CDKN1A (p21) | ATRIP  | POLD1* | H2AFX    | LIG4     | DNA2             | BARD1    | MLH3    |           |  |  |
| CDKN2A (p16) | ATRAX  | POLD2  | RNF168   | RECOVERY | FANCA            | BRCA1    | MSH2    |           |  |  |
| CDKN2B       | CDC25A | POLD3  | SLX4*    |          | FANCB            | BRCA2    | MSH3    |           |  |  |
| CHEK2        | CDC25C | POLD4  |          |          | BLM              | FANCC    | BRIP1   | MSH6      |  |  |
| KAT5         | CHEK1  | POLE   |          |          | EME1             | FANCD2   | DCLRE1C | PMS2      |  |  |
| MDC1         | CLSPN  | PTEN   |          |          | MUS81            | FANCE    | EXO1    | RECQL     |  |  |
| MDM2         | HUS1   | NER    |          |          | WRN              | FANCF    | GEN1    | ONCOGENES |  |  |
| MDM4         | RAD1   |        | NHEJ     | SWI/SNF  | FANCG            | PALB2*   |         |           |  |  |
| MRE11A       | RAD17  | ERCC1* | SETMAR   | ARID1A*  | FANCI            | PARP1*   | BRAF    |           |  |  |
| NBN          | RAD9A  | ERCC4* | TP53BP1* | ARID1B   | FANCL            | PARP2    | CCND1   |           |  |  |
| PRKDC        | RBBP8  | XRCC1* | XRCC5    | ARID2    | FANCM            | Rad51    | CCNE1*  |           |  |  |
| RAD50        | RPA1   |        | XRCC6    | SMARCA4  | XRCC2            | RAD51AP1 | HRAS    |           |  |  |
| TP53         | TOPBP1 |        | SMARCB1  | TLS      |                  | RAD51B   | KRAS    |           |  |  |
|              |        |        |          |          |                  | RAD51C   | MYC*    |           |  |  |
|              |        |        |          |          |                  | RAD51D   | MYCL*   |           |  |  |
|              |        |        |          |          |                  | MAD2L2   | MYCN*   |           |  |  |
|              |        |        |          |          |                  | REV3L*   | NRAS    |           |  |  |
|              |        |        |          |          |                  | XRCC3    |         |           |  |  |
|              |        |        |          |          |                  | XRCC4    |         |           |  |  |

**Supp Table 2:** genes of interest in sequencing panel, used for selection. \* Signifies those with published data to support ATRi sensitization

|         |         |          |
|---------|---------|----------|
| ABCB1   | HLA-A   | RAD51D   |
| ADPRHL2 | HLA-B   | RB1      |
| ARID1A  | HLA-C   | RIF1     |
| ATM     | HLTF    | SHLD1    |
| ATR     | HUWE1   | SHLD2    |
| BRCA1   | KMT2B   | SHLD3    |
| BRCA2   | KMT2C   | SHPRH    |
| CCNB1   | KRAS    | SLC2A1   |
| CDC25A  | LRRC8A  | SLC25A40 |
| CDC25B  | LRRC8D  | SLC31A1  |
| CDC7    | MAD2L2  | SMARCAL1 |
| CDK2    | MRE11   | SMG7     |
| CDK12   | PALB2   | SMG8     |
| CHD4    | PARG    | SMG9     |
| CHEK1   | PARP1   | SRY      |
| CST     | PAXIP1  | STN1     |
| DBF4    | PIK3CA  | TEN1     |
| ERBB2   | PPP2R1A | TP53     |
| EZH2    | PPP2R2A | TP53BP1  |
| FBXW7   | RAD51B  | ZRANB3   |
| FOXM1   | RAD51C  |          |

**Supp Table 3:** panel of genes used in plasma DNA sequencing

| Histology                        | Ceralasertib (mg BD) | RT | BOR | Gene             | Variant                          | TP53 | ATM % | Ki67 % | CCNE1 % | ARID1A H | type   |
|----------------------------------|----------------------|----|-----|------------------|----------------------------------|------|-------|--------|---------|----------|--------|
| Digital papillary adenocarcinoma | 40                   | 20 | SD  | ARID1A AKT1      | P1115R E17K                      | wt   | 99    |        | 21      | 260      | tumour |
| SCCHN                            | 40                   | 20 | SD  | HRAS PI3KCA      | G12S Q546K                       | mut  | 100   |        | 76      | 110      | tumour |
| SCCHN                            | 40                   | 20 | PR* | Nil              | N/A                              | wt   |       |        | 57      | 280      | tumour |
| Ductal adenocarcinoma parotid    | 80                   | 20 | PR  | WEE1             | R581*                            | mut  |       | 45     |         | 280      | tumour |
| SCC maxillary antrum             | 80                   | 20 | SD  | CDKN2 A/B        | Deletion                         | mut  |       | 51     | 25      |          | tumour |
| SCCHN                            | 80                   | 30 | PR  | BRCA1            | E730fs                           | wt   |       |        |         |          | tumour |
| Adenocarcinoma maxillary antrum  | 80                   | 30 | SD  | ARID1B           | V1074fs                          | wt   |       | 4      |         |          | tumour |
| SCCHN                            | 80                   | 30 | CR  | Nil              | N/A                              | mut  |       |        |         |          | tumour |
| Clear cell tumour maxilla        | 20                   | 20 | SD  | Nil              | N/A                              | wt   |       |        |         | 130      | plasma |
| SCCHN                            | 80                   | 30 | PR  | ATM RAD51B KMT2B | Deletion<br>Deletion<br>Deletion | wt   |       | 44     |         |          | plasma |
| SCCHN                            | 80                   | 30 | SD  | BRCA1 FBXW7      | H1195N M522I                     | mut  |       | 78.5   |         |          | plasma |

#### Supp Table 4: Tumor profiling.

DNA sequencing (either tumour or plasma); tumour immunohistochemical analysis for ATM (% nuclear positive), Ki67 (% nuclear positive), Cyclin E1 (% nuclear positive) and ARID1A (H-score out of 300). Deletion of one or 2 alleles cannot be determined on plasma sequencing.

\*This patient had a PR on imaging at 8 weeks, followed by a durable clinical CR.

| Mix 1  |               |             |             |
|--------|---------------|-------------|-------------|
| Target | Fluorophore   | Supplier    | Dilution    |
| NKG2D  | BV421         | Biolegend   | 5 uL/sample |
| CD4    | BV510         | Biolegend   | 1:200       |
| CD45   | BV650         | Biolegend   | 1:300       |
| TCRγδ  | FITC          | Biolegend   | 1:50        |
| CD25   | PE            | Biolegend   | 5 uL/sample |
| CD56   | PE-Dazzle 594 | Biolegend   | 1:100       |
| CD73   | APC           | Biolegend   | 5 uL/sample |
| CD62L  | PerCp Cy5.5   | Biolegend   | 1:100       |
| CD3    | AF700         | Biolegend   | 1:100       |
| CD8    | Pe-Cy7        | Biolegend   | 1:300       |
| CD127  | APC-Cy7       | Biolegend   | 5 uL/sample |
| Mix 2: |               |             |             |
| NKp46  | BV421         | Biolegend   | 5uL/sample  |
| CD4    | BV510         | Biolegend   | 1:200       |
| CD45   | BV650         | Biolegend   | 1:300       |
| TCRγδ  | FITC          | Biolegend   | 1:50        |
| OX-40  | PE            | Biolegend   | 5uL/sample  |
| CD56   | PE-Dazzle 594 | Biolegend   | 1:100       |
| 4-1BB  | APC           | Biolegend   | 5uL/sample  |
| NKp30  | PerCp Cy5.5   | Biolegend   | 5uL/sample  |
| CD3    | AF700         | Biolegend   | 1:100       |
| CD8    | Pe-Cy7        | Biolegend   | 1:300       |
| CD69   | APC-Cy7       | Biolegend   | 5uL/sample  |
| Mix 3: |               |             |             |
| NKG2A  | BV421         | BD          | 5uL/sample  |
| CD4    | BV510         | Biolegend   | 1:200       |
| CD45   | BV650         | Biolegend   | 1:300       |
| TCRγδ  | FITC          | Biolegend   | 1:50        |
| PD-1   | PE            | Biolegend   | 5uL/sample  |
| CD56   | PE-Dazzle 594 | Biolegend   | 1:100       |
| LAG-3  | APC           | R&D Systems | 10uL/sample |
| TIGIT  | PerCp Cy5.5   | eBioscience | 5uL/sample  |
| CD3    | AF700         | Biolegend   | 1:100       |
| CD8    | Pe-Cy7        | Biolegend   | 1:300       |
| TIM-3  | APC-Cy7       | Biolegend   | 5uL/sample  |

| Mix 4: |               |             |            |
|--------|---------------|-------------|------------|
| CD45RO | Pacific Blue  | Biolegend   | 5uL/sample |
| CD4    | BV510         | Biolegend   | 1:200      |
| CD45   | BV650         | Biolegend   | 1:300      |
| CD45RA | FITC          | Biolegend   | 1:100      |
| CCR7   | PE            | Biolegend   | 1:100      |
| CD56   | PE-Dazzle 594 | Biolegend   | 1:100      |
| CD27   | APC           | Biolegend   | 1:100      |
| CD62L  | PerCp Cy5.5   | Biolegend   | 1:100      |
| CD3    | AF700         | Biolegend   | 1:100      |
| CD8    | Pe-Cy7        | Biolegend   | 1:300      |
| CD16   | APC-Cy7       | Biolegend   | 1:100      |
| Mix 5: |               |             |            |
| CD56   | BV421         | Biolegend   | 5uL/sample |
| CD4    | BV510         | Biolegend   | 1:200      |
| CD45   | BV650         | Biolegend   | 1:300      |
| TCRγδ  | FITC          | Biolegend   | 1:50       |
| LAP    | PE            | Biolegend   | 5uL/sample |
| CTLA-4 | PE-Dazzle 594 | Biolegend   | 5uL/sample |
| ICOS   | APC           | Biolegend   | 5uL/sample |
| CD57   | PerCp Cy5.5   | Biolegend   | 5uL/sample |
| CD3    | AF700         | Biolegend   | 1:100      |
| CD8    | Pe-Cy7        | Biolegend   | 1:300      |
| CD95   | APC-Cy7       | Biolegend   | 5uL/sample |
| Mix 6: |               |             |            |
| PVR    | BV421         | Biolegend   | 5uL/sample |
| CD19   | BV510         | Biolegend   | 1:100      |
| CD45   | BV650         | Biolegend   | 1:300      |
| CD3    | FITC          | Biolegend   | 1:100      |
| PD-L1  | PE            | Biolegend   | 5uL/sample |
| CD38   | PE-Dazzle 594 | Biolegend   | 1:100      |
| CD27   | APC           | Biolegend   | 1:100      |
| CD62L  | PerCp Cy5.5   | Biolegend   | 1:100      |
| CD14   | AF700         | Biolegend   | 1:100      |
| HLA-E  | Pe-Cy7        | Biolegend   | 1:100      |
| CD56   | APC-Cy7       | Biolegend   | 5uL/sample |
| Mix 7: |               |             |            |
| NKG2A  | BV421         | BD          | 5uL/sample |
| CD8    | BV510         | Biolegend   | 1:100      |
| CD45   | BV650         | Biolegend   | 1:300      |
| CD69   | FITC          | Biolegend   | 1:100      |
| PD-1   | PE            | Biolegend   | 5uL/sample |
| CD38   | PE-Dazzle 594 | Biolegend   | 1:100      |
| CD56   | APC           | Biolegend   | 1:100      |
| TIGIT  | PerCp Cy5.5   | eBioscience | 5uL/sample |
| CD3    | AF700         | Biolegend   | 1:100      |
| CD57   | Pe-Cy7        | Biolegend   | 1:100      |
| CD16   | APC-Cy7       | Biolegend   | 1:100      |

**Supp Table 5: Flow cytometry antibodies**  
Antibodies used for staining of PMBCs

## **Supplementary note 2: main study protocol**



*The* ROYAL MARSDEN  
NHS Foundation Trust

A Phase I Study to assess the Tolerability, Safety and  
Biological Effects of a Specific Ataxia Telangiectasia and  
Rad3-Related (ATR) Inhibitor (AZD6738) as a Single  
Agent and in Combination with Palliative Radiation  
Therapy in Patients with Solid Tumours

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## PROTOCOL AMENDMENT LOG

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| <p>Substantial Amendment 1 – 25 September 2014</p>        | <ul style="list-style-type: none"> <li>• To conduct pharmacodynamic studies on tumour and normal tissue has become an exploratory objective rather than a secondary objective as the assays to determine this require development</li> <li>• Clarification on description of grade 3 haematological toxicity</li> <li>• TSC safety evaluation timeframe definition refined</li> <li>• Timings for blood samples now allow a greater timeframe for assessment of samples</li> <li>• Addition of a new route of administration for the drug to allow it to be dispersed in water if patients have difficulty swallowing</li> <li>• Further information on the disposal of the pharmacokinetic samples sent to an external laboratory</li> <li>• Sections on analysis and sample preparation have been removed as these are covered in a separate laboratory manual</li> <li>• For tumour marker assays the analysis definition and target compounds have been made broad rather than mentioning specific tumour markers</li> <li>• Treatment schedule and the text explaining the treatment in more detail has been changed accordingly for consistency and both have been updated to allow a time window of <math>\pm 2</math> days for each visit study visits.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p>Substantial Amendment 2 – 8<sup>th</sup> June 2015</p> | <ul style="list-style-type: none"> <li>• Changes to the primary objective of the trial to include the combination of the IMP with radiotherapy.</li> <li>• Change in trial design to allow the radiotherapy combination part of the study (PART C) to run in parallel with the dose escalation phase of the study (Part A), using a dose for part C which has already been shown to be safe and tolerable during part A.</li> <li>• Flexibility in the protocol to allow for changes in dosing schedule based on emerging pharmacokinetic data.</li> <li>• Rationale for patient selection in Part B has been clarified to include details of biopsies required to screen for biomarkers to determine sensitivity to the study drug. Participants will not have a delay in treatment whilst waiting for the biopsy results. The results will be used for data analysis purposes to evaluate response to the study drug and to define further patient sub groups who may benefit from the drug.</li> <li>• Clarification on the design for Part C of the trial including details on the radiotherapy cohorts, patient selection, dosing and duration of treatment.</li> <li>• Addition of wording for administering the study drug via feeding tubes.</li> <li>• Further details on the biomarker analysis for tumour biopsy samples. The wording has been changed to be flexible in the analyses that will be performed on these samples.</li> <li>• Addition of a paragraph to include details on genetic analysis that will be performed on blood and biopsy samples during Part B only. Permission is also being sought to use samples collected during Part A for genetic analysis. Consent hasn't been sought to use the samples in this way (the consent form only states for future research) and as some patients who have given research blood samples will have passed away therefore we will be unable to re-consent.</li> </ul> |

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|                                             | <ul style="list-style-type: none"> <li>• Addition of an intense pharmacokinetic schedule in Part A of the study to gather more data as information so far has not been adequate to determine the half-life of the study drug. It is envisaged that more extensive sampling after a single dose and after 2 weeks of continuous dosing, will clarify this. It is estimated that 6 patients will be required to have intense PK sampling before reverting back to the standard PK sampling.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Substantial Amendment 3 – 07 June 2016      | <ul style="list-style-type: none"> <li>• The addition of a new clinical trial site, Oxford NHS Foundation trust, that will participate in Part C (AZD6738 + radiotherapy) alone.</li> <li>• Modification of part B schema to allow inclusion of up to 14 additional patients i.e. increase in sample size from n=36 up to n= a maximum of 50 patients, dependent on the number of patients that are positive for certain biomarkers, allowing us to enrichment for patient populations that may gain clinical benefit with this treatment.</li> <li>• Clarification of the dose limiting toxicity window (DLT), and treatment timings (AZD 6738 and radiotherapy) for part C.</li> <li>• Clarify that arms count as H&amp;N/thorax and legs as abdo/pelvis for part C cohorts.</li> <li>• Require that reticulocyte counts be collected routinely.</li> <li>• Amend entry criteria to allow inclusion of long-term hormonal anti-cancer therapy in part C and remove requirement for measurable disease progression before entry into part C.</li> <li>• Update radiation delivery to require DVH (dose-volume histogram) to be submitted for each part C patient, but removal of requirement for prospective submission of organ radiation doses.</li> <li>• Clarification to allow patients to restart AZD6738 after long break if patient is gaining clinical benefit.</li> <li>• Correction of other errors and omissions and some wording added for clarification</li> </ul> |
| Substantial Amendment 4 – 16 December 2016  | <ul style="list-style-type: none"> <li>• Addition of 3 sites for PART C only</li> <li>• Changes to the Reference Safety Information in updated IB version 5.0 dated 10<sup>th</sup> October 2016</li> <li>• Changes to the Protocol to include the possibility of assessing multiple dose schedules simultaneously in PART B</li> <li>• Changes to the Protocol to include to PART C follow-up the possibility to make contact with the referring team or GP in order to obtain a minimum set of follow-up information should patients not attend follow-up visits for the 12 month duration.</li> <li>• Changes to Protocol, PIS and GP to reflect the changes in Reference Safety Information</li> <li>• Changes to Protocol, PIS and GP for clarification and consistency.</li> <li>• 2 additional versions of the diary card created for additional drug schedules (3 weeks on, 1 week off and 5 days on, 2 days off)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Substantial Amendment 5 – 04 September 2017 | <ul style="list-style-type: none"> <li>• Change to Guys and St. Thomas' NHS Foundation Trust Principal Investigator</li> <li>• Changes to the protocol include 20 Gy cohort in Part C the safety review committee may decide the recommended dose to proceed is lower than the MTD with radiation, or the recommended phase 2 monotherapy dose, based on emerging toxicity and efficacy data.. In this case, a decision may be made to escalate the radiation dose and/or initiate expansion cohorts at a lower dose level than the MTD, and the MTD would not have to be determined.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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|                           | <ul style="list-style-type: none"> <li>• Changes to the protocol include 30 Gy cohort in Part C the 30 Gy will be administered with recommended dose to proceed from the 20 Gy cohorts</li> <li>• Changes to the protocol include the drugs prolonging the Q-T Interval. Caution should be applied when co-administering drugs which can cause prolongation of the QT interval. These drugs should be avoided where possible and closer monitoring of the patient and the QTc should be undertaken if they are co-administered. A list of drugs prolonging QTc is given in appendix 6.</li> </ul> <p>Changes to the protocol include appendix 6: drugs prolonging the Q-T interval, the following drugs should be used in caution: Antimicrobials: erythromycin, clarithromycin, moxifloxacin, fluconazole, ketoconazole<br/> Antiarrhythmics: dronedarone, sotalol, quinidine, amiodarone, flecainide<br/> Antipsychotics: risperidone, fluphenazine, haloperidol, pimozide, chlorpromazine, quetiapine, clozapine<br/> Antidepressants: citalopram, escitalopram, amitriptyline, clomipramine, dosulepin, imipramine, lofepramine<br/> Antiemetics: domperidone, droperidol, ondansetron, granisetron</p>                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Substantial amendment 6.0 | <ul style="list-style-type: none"> <li>• Temporary recruitment hold to allow implementation of corrective and preventative actions (see below)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Substantial amendment 7.0 | <ul style="list-style-type: none"> <li>• Modification to part B screening process: future subjects entering part B will be screened for deficiency in DNA damage response using archival tissue, eligible patients will then proceed to full trial screening</li> <li>• Restart recruitment after corrective and preventative actions: <ul style="list-style-type: none"> <li>○ Clarification of data required for dose escalation decisions in SRC charter</li> <li>○ Reference in protocol to SRC charter document</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Substantial amendment 8.0 | <ul style="list-style-type: none"> <li>• Changes to the Reference Safety Information in updated IB version 7.0 dated 16<sup>th</sup> November 2018, Table 42 in section 5.6.</li> <li>• Changes to Protocol, PIS to reflect the changes in Reference Safety Information</li> <li>• Changes to Protocol, PIS for clarification and consistency.</li> <li>• Changes to the protocol to include part B patients may be selected based on molecular and/or immunohistochemical testing of tumour tissue.</li> <li>• Changes to the protocol to include the part B dose escalation phase will be reviewed of part B safety data, a different (higher or lower) dose level may also be evaluated, provided the total dose per 28 day cycle does not exceed the MTD established in part A.</li> <li>• Changes to the protocol in the inclusion criteria to include: able to swallow, absorb and retain oral medication/gastrostomy/nasogastric tube.</li> <li>• Updated text to the protocol in the exclusion criteria to include: 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 highly effective forms of contraception (oral, injected or implanted hormonal contraception and condom, have an intra-uterine device and condom, diaphragm with spermicidal gel and condom) for four weeks before starting treatment, during the trial and for six months afterwards are considered eligible.</li> <li>• Changes to the protocol in the exclusion criteria to separate the questions:</li> </ul> |

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|                           | <ul style="list-style-type: none"> <li>○ Uncontrolled hypertension requiring clinical intervention.</li> <li>○ Hypertension requiring 2 or more antihypertensive agent.</li> <li>• Changes to the protocol to include the following in section 10.4.3, 10.4.4 &amp; 10.4.5: administration dose and schedule of AZD 6738 is determined by the SRC letter.</li> <li>• Changes to the protocol to include the following in section 10.4.4 &amp; 10.4.5: Radiation Therapy administration - 20 Gy in 10 fractions to 30 Gy in 15 fractions and the duration of drug exposure (10 versus 15 fractions sensitised with AZD6738)</li> <li>• Changes to the protocol to section 10.4.4 &amp; 10.4.5 for clarification and consistency to reflect section 10.2. Evaluation during Treatment.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Substantial amendment 9.0 | <ul style="list-style-type: none"> <li>• Changes to the Reference Safety Information in updated IB version 8.0 dated 12th November 2019, section 6.2.6 Reproductive Precautions and to reflect the text in the PIS for Part B &amp; C.</li> <li>• Changes to the protocol 3.4.4 Duration of treatment expansion short – the radiotherapy dosing schedule should be continued for 2 days after the completion of radiation. After this, the dose and schedule will be changed to the recommended monotherapy dose and schedule. This option can be confirmed or modified by the Safety Review Committee based on emerging data. A dose break may be introduced between completion of radiotherapy and commencement of maintenance dosing; this may be recommended by the Safety Review Committee.</li> <li>• Changes to the protocol in section 3.12. Safety Review Committee (SRC) – Removal of the CR-UK's medical advisor or delegate from the committee agreed by CR-UK the SRC is driven by the sponsor and not mandatory for the medical advisor or delegate to attend</li> <li>• Changes to the protocol in section 4. Patient Selection criteria for parts A and B: <ul style="list-style-type: none"> <li>○ <b>Additional Text:</b> 1. Diagnosis of histologically or cytologically documented solid tumour refractory to conventional treatment, or for which no conventional therapy exists (<b>other than palliative radiotherapy for part C</b>) or is declined by the patient. (For part C, long-standing (greater than 3 months) hormonal anti-cancer therapy is permitted. <b>For part B and C, long-standing (greater than 3 months) LHRH (luteinising hormone-releasing hormone) analogue therapy is permitted to continue for patients with prostate carcinoma</b>)</li> <li>○ <b>Additional Text:</b> ≥ 30 Albumin</li> <li>○ <b>Additional Text:</b> 3.Presence of putative markers of sensitivity to AZD6738 defined on analysis of tumour material, <b>plasma DNA or germline mutational analysis</b> (for part B only).</li> <li>○ <b>Removed Text:</b> 14.Haematuria: +++ on microscopy or dipstick</li> </ul> </li> </ul> |

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|                             | <ul style="list-style-type: none"> <li>• Changes to the protocol in section 7.2. Radiation Delivery to include, in the expansion cohort will continue to take maintenance AZD6738 until <b>disease</b> progression or unacceptably toxicity.</li> <li>• Changes to the protocol in section 7.6.3.1 Anticoagulant Therapy: Subcutaneous heparin/low molecular-weight heparin is permitted. Please contact the study sponsor regarding other anticoagulant therapy.</li> <li>• Changes to the protocol in section 10.1.2 Part B pre-screening in clarity of the text: Where participants have had tumour material analysed previously, in a laboratory accredited for clinical samples, this result may be used instead of further screening of archival material. Patients known to have germline DNA damage response mutations may be accepted for pre-screening after discussion with sponsor.</li> <li>• Changes to throughout the protocol reference to remove: Functional MRI (section: 10.1.4, 10.2.2, 10.4.3, 12.2) This is no longer applicable.</li> <li>• Changes to contraception throughout the protocol to reference CTFG guidelines (section 4.2, 10.4.3, 10.4.4, 10.4.5, 10.4.6, 13.9)</li> </ul> |
| Substantial Amendment 10.0  | <ul style="list-style-type: none"> <li>• Addition of section to reduce intensity of study-related assessments after December 2023 for those participants remaining on AZD6738: section 10.2.2, section 16.7. This is to reduce the study burden on participants ongoing after publication.</li> <li>• Addition of 80 mg tablet, to reflect anticipated changes in IMP tablet availability</li> <li>• Clarification that AZD6738 is an inducer of CYP1A2</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Substantial Amendment 11/12 | <ul style="list-style-type: none"> <li>• Addition of section to reduce intensity of study-related assessments after December 2023 for those participants remaining on AZD6738: section 10.2.2, section 16.7. This is to reduce the study burden on participants post publication.</li> <li>• Addition of 80 mg tablet, to reflect anticipated changes in IMP tablet availability.</li> <li>• Clarification that AZD6738 is an inducer of CYP1A2, CYP3A4 and CYP2B6</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Substantial amendment 13    | <ul style="list-style-type: none"> <li>• Updated toxicity management guidelines in case of prolonged cytopenia of Grade 3 or higher that lasts for <math>\geq 2</math> weeks and does not resolve with study treatment interruption. These include referral to hematologist, weekly blood counts and/or bone marrow aspirate/biopsy evaluation, as needed</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation     | Definition                                                   |
|------------------|--------------------------------------------------------------|
| ABPI             | Association of the British Pharmaceutical Industry           |
| ADC              | apparent diffusion coefficient                               |
| AE               | adverse event                                                |
| alk phos/ALP     | alkaline phosphatase                                         |
| ALT              | alanine aminotransferase                                     |
| AML              | acute myeloid leukaemia                                      |
| ANC              | absolute neutrophil count                                    |
| APTT             | Activated partial thromboplastin time                        |
| AST              | aspartate aminotransferase                                   |
| ATM              | Ataxia telangiectasia mutated                                |
| ATR              | Ataxia telangiectasia and Rad3-related                       |
| AUC              | area under the curve                                         |
| BP               | blood pressure                                               |
| BCRP             | Breast cancer resistance protein                             |
| BD               | Twice daily (bis in die)                                     |
| BSA              | Body surface area                                            |
| °C               | degrees Celsius                                              |
| Chk1             | Checkpoint kinase 1                                          |
| Chk2             | Checkpoint kinase 2                                          |
| CI               | Chief Investigator                                           |
| C <sub>max</sub> | maximum observed plasma concentration                        |
| CPT              | Cell Preparation Tube                                        |
| CR               | complete response                                            |
| CRF              | case report form                                             |
| CR-UK            | Cancer Research UK                                           |
| CT               | computed tomography                                          |
| CTA              | clinical trial authorisation                                 |
| CTCAE            | Common Terminology Criteria for Adverse Events               |
| CYP              | Cytochrome P450                                              |
| Day              | calendar day                                                 |
| DDR              | DNA damage response                                          |
| DLT              | dose limiting toxicity                                       |
| DMR              | Dose modification ratio                                      |
| DNA-PK           | DNA-dependent protein kinase                                 |
| DSB              | Double strand break                                          |
| DW-MRI           | Diffusion-weighted MRI                                       |
| DYRK3            | Dual specificity tyrosine-phosphorylation-regulated kinase 3 |
| ECG              | Electrocardiogram                                            |
| ECMC             | Experimental cancer medicines centre network                 |
| ECOG             | Eastern Cooperative Oncology Group                           |
| EDTA             | Ethylenediaminetetra-acetic acid                             |
| ELISA            | Enzyme-linked immunosorbent assay                            |
| EORTC            | European Organisation for Research and Treatment of Cancer   |
| GGT              | Gamma-glutamyl transpeptidase                                |
| GCLP             | Good Clinical Laboratory Practice                            |
| GCP              | Good Clinical Practice                                       |
| G-CSF            | Granulocyte Colony Stimulating Factor                        |
| g/dL             | gram(s) per decilitre                                        |
| GFR              | Glomerular Filtration Rate                                   |
| GI <sub>50</sub> | Concentration for half-maximal growth inhibition             |
| GMP              | Good Manufacturing Practice                                  |
| GSK3b            | Glycogen synthase kinase 3 beta                              |
| Gy               | Gray                                                         |
| Hb               | Haemoglobin                                                  |

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation      | Definition                                                                    |
|-------------------|-------------------------------------------------------------------------------|
| HNSTD             | Highest non-severely toxic dose                                               |
| IC <sub>50</sub>  | Half maximal inhibitory concentration                                         |
| ICMJE             | International Committee of Medical Journal Editors                            |
| IHC               | immunohistochemistry                                                          |
| IMP               | investigational medicinal product                                             |
| INR               | International normalised ratio                                                |
| IR                | Ionising radiation                                                            |
| ITF               | Investigator Trial File                                                       |
| L/h               | litres per hour                                                               |
| LDH               | Lactate Dehydrogenase                                                         |
| LENT-SOMA         | Late Effects of Normal Tissue - Subjective, Objective, Management, Analytical |
| LVEF              | left ventricular ejection fraction                                            |
| MAD               | Maximum administered dose                                                     |
| MDS               | myelodysplastic syndrome                                                      |
| mg                | Milligram                                                                     |
| mg/m <sup>2</sup> | milligram per square metre                                                    |
| MHRA              | Medicines and Healthcare products Regulations Agency                          |
| mmHg              | Millimetres of mercury                                                        |
| MRI               | magnetic resonance imaging                                                    |
| MTD               | maximum tolerated dose                                                        |
| mTOR              | Mammalian target of rapamycin                                                 |
| MTS               | Tetrazolium dye assay                                                         |
| NCI               | National Cancer Institute                                                     |
| OATP1B1           | Organic anion-transporting polypeptide 1B1                                    |
| PARP              | Poly (ADP-ribose) polymerase                                                  |
| PBMC              | Peripheral blood mononuclear cells                                            |
| PD <sub>c</sub>   | pharmacodynamics                                                              |
| PD                | progressive disease                                                           |
| P-gp              | P-glycoprotein                                                                |
| PET               | positron emission tomography                                                  |
| PFS               | Progression free survival                                                     |
| PI                | Principal Investigator                                                        |
| PI3K              | Phosphoinositide 3-kinase                                                     |
| PI4KCA            | Phosphatidylinositol 4-kinase alpha                                           |
| PI4KB             | Phosphatidylinositol 4-kinase, catalytic, beta                                |
| PIP5K2A           | Phosphatidylinositol-5-phosphate 4-kinase, type II, alpha                     |
| PIKK              | Phosphoinositide 3-kinase related kinase                                      |
| PK                | Pharmacokinetic                                                               |
| PR                | partial response                                                              |
| PT                | Prothrombin time                                                              |
| QC                | quality control                                                               |
| QP                | Qualified Person                                                              |
| QT <sub>c</sub>   | Corrected Q-T interval                                                        |
| REC               | Research Ethics Committee                                                     |
| RECIST            | Response Evaluation Criteria in Solid Tumours                                 |
| RPA               | Replication protein A                                                         |
| SAE               | serious adverse event                                                         |
| SD                | stable disease                                                                |
| SDV               | source data verification                                                      |
| SOP               | standard operating procedure                                                  |
| SPC               | Summary of Product Characteristics                                            |
| SRC               | safety review committee                                                       |

## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

| Abbreviation      | Definition                                           |
|-------------------|------------------------------------------------------|
| STD <sub>10</sub> | Severely toxic dose for 10% of animals               |
| SUSAR             | suspected unexpected serious adverse (drug) reaction |
| T <sub>1/2</sub>  | terminal elimination half-life                       |
| TSC               | Trial Steering Committee                             |
| T <sub>max</sub>  | time to reach C <sub>max</sub>                       |
| TGI               | Tumour growth inhibition                             |
| ULN               | upper limit of normal                                |
| USM               | urgent safety measure                                |
| 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<sup>1</sup>, the guidelines of Good Clinical Practice (GCP) 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: \_\_\_\_\_

**Sponsor Signature:**

On behalf of Sponsor

NAME: \_\_\_\_\_

SIGNATURE: \_\_\_\_\_

DATE: \_\_\_\_\_

---

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

# 1. Introduction

## 1.1. Background disease

Patients with advanced cancers often have limited therapeutic options; there is a need for new systemic treatments which offer the possibility of tumour control without the toxicity associated with traditional cytotoxic chemotherapy. Recent reports on the activity of poly (ADP-ribose) polymerase (PARP) inhibitors as targeted therapies for certain cancers with specific defects in DNA damage response pathways have promoted the concept of “synthetic lethality”[1]. This term describes a phenomenon in which a cancer-specific deficiency in one signalling pathway renders tumour cells selectively sensitive to targeted therapy. An alternative strategy to PARP inhibition involves drugs that inhibit ataxia telangiectasia and Rad3-related (ATR) pathway signalling. Such agents have the potential to exploit the fact that cancer cells with a defective ATM-Chk2-p53 pathway are over-reliant on a functional G2/M cell cycle checkpoint in order to repair DNA damage[2]. As such, it is reasonable to expect that ATR inhibitors may have single-agent activity in some cancers. Importantly, ATR inhibitors are also likely to enhance responses to other established DNA damage-inducing therapies, such as radiation.

Radiotherapy plays an essential role in cancer treatment – it has been estimated that more than 40% of patients should receive radiation at some point in their treatment[3]. Many patients will receive radical radiation or chemoradiation for localised disease – however, despite recent advances in radiation techniques and the use of concomitant chemoradiotherapy, patients with solid tumours such as head and neck, thoracic, gastrointestinal and genitourinary cancers have suboptimal cure rates. These primary tumour sites account for a huge cancer burden in the UK: 5,400 (head and neck), 40,000 (lung), 7,900 (oesophagus), 7,700 (pancreas), 38,600 (colorectum), and 2,800 (cervix)[4]. Consequently, any strategy to increase the efficacy of radiotherapy by sensitising tumours to radiation without increasing normal tissue toxicity would have a significant overall impact for a diverse range of patients.

## 1.2. Background therapeutic information

### 1.2.1 ATR and ATR inhibition

Ataxia Telangiectasia and Rad3-Related (ATR) is a serine/threonine protein kinase and member of the phosphoinositide 3-kinase related kinase (PIKK) family. It is a key serine/threonine protein kinase involved in regulating DNA damage response (DDR) signalling caused by DNA replication-associated stress[5]. During normal DNA replication, ATR is recruited at stalled replication forks which can progress to DNA double strand breaks (DSBs) if left unrepaired. ATR is also recruited to single strand DNA coated with replication protein A (RPA) following single strand DNA damage or the resection of DNA double strand breaks. Recruitment and activation of ATR leads to cell cycle arrest in the S phase while the DNA is repaired and the stalled replication fork is resolved, or nuclear fragmentation and entry into programmed cell death (apoptosis). Loss of ATR function leads to the inability to resolve stalled replication forks, the accumulation of DNA damage and rapid cell death exemplified by nuclear fragmentation. ATR deletion is embryonic lethal in mice, however severe ATR hypomorphism is tolerated in humans leading to Seckel Syndrome. Normal cells from patients with Seckel Syndrome have reduced ATR function[6] and show extensive DNA breaks when subjected to replication stress[7].

Ataxia Telangiectasia Mutated (ATM) is a related kinase that is recruited to DNA double strand breaks and, like ATR, has both checkpoint signalling and repair functions. In normal cells, there is a significant interplay between ATR and ATM as stalled replication forks can be converted into double strand breaks through further DNA damage and the resection of double strand breaks generates single stranded DNA. ATM works in conjunction with ATR to efficiently resolve replication-associated DNA damage creating a co-dependency with loss of one leading to a greater reliance on the other to maintain genomic stability. Failure to resolve this damage leads to genomic instability and, if sufficiently high and persistent, cell death. ATM is thought to be a tumour suppressor and during tumourigenesis ATM can be inactivated or lost providing a selection advantage for the tumour cell. ATM is reported to be inactivated in subsets of B-cell malignancies[8, 9], head and neck[10], breast[11] and lung[12] cancers through chromosomal deletion (11q23), promoter hypermethylation, loss-of-function mutations or through microRNA-mediated mechanisms[13]. As well as the ATM protein itself, loss-of-activity of the ATM signalling pathway may also be caused by defects in downstream ATM substrate proteins such as MRE11A, CHK2 or p53. In addition to a defective ATM-pathway, oncogene activation such as through c-Myc overexpression or in hypoxic tumour microenvironments leads to increased DNA replication stress, with an accumulation of stalled replication forks which forces a dependence on ATR function for their resolution[5, 14]. These tumours may be dependent on the remaining DDR pathways which can then be selectively targeted by inhibitors of ATR. This concept of exploitation of dependencies between pathways for anti-cancer therapy has been termed Synthetic Lethality or Synthetic Sickness. This has recently been exemplified by the promising clinical activity of PARP inhibitors against BRCA-deficient cancers<sup>9[15, 16]</sup>

Increasing the exogenous replication stress with approaches that generate DNA strand breaks in the tumour cell, for example through radiation or chemotherapy, should also lead to increased sensitivity to ATR inhibition. Thus radiation, cisplatin and hydroxyurea are more efficacious in tumour cells where kinase-dead ATR has been expressed[17, 18], and overexpression of a mutated form of ATR observed in Seckel cells increases their sensitivity to cross-linking platinum and alkylating agents[19, 20].

ATR inhibitors have potential for killing cancer cells in a number of different clinical settings:

- Monotherapy: in tumour cells in which ATM function is lost or in tumours with high levels of baseline replication stress
- Combination: in combination with DNA damaging chemotherapy or radiotherapy which increase the threshold level of replication stress or induce DNA strand breaks

## **2. Trial objectives**

### **2.1. Primary objectives**

1. To determine the feasibility and safety of administration of single-agent AZD6738 in patients with solid tumours;
2. To determine the feasibility and safety of administration of AZD6738 in combination with radiotherapy in patients with solid tumours in the (i) head and neck or thorax, or (ii) abdomino-pelvic regions during different schedules of fractionated palliative radiotherapy.

### **2.2. Secondary objectives**

1. To guide dose and schedule selection for subsequent studies of AZD6738 as a single-agent or with palliative or radical radiotherapy;
2. To assess preliminary anti-tumour activity (by RECIST response) of AZD6738 as a single-agent and in combination with palliative radiotherapy;

### **2.3. Exploratory objectives**

1. To conduct pharmacodynamic studies on tumour and normal tissue.
2. To conduct exploratory functional imaging studies using multi-parametric MRI as a surrogate measure of anti-tumour efficacy;
3. To assess the value of putative predictive biomarkers for response to AZD6738.

### 3. Trial Design

This is an open-label, multi-centre, dose-escalating, phase I study of a novel DNA repair inhibitor (AZD6738) in patients with advanced solid cancer.

#### 3.1. Overview

In this study, we propose to evaluate AZD6738, initially as a single agent and then in combination with palliative radiotherapy in order to assess the safety and tolerability of the compound in these two settings.

In the first part (part A) of the study, patients will be recruited to a dose-escalation protocol of AZD6738 in a 3+3 design. Initial dose cohorts will be single patient cohorts with 100% dose escalation, until any grade 2 toxicity is seen (maximum of 3 single patient cohorts), after which the design will switch to 3+3. During this dose-escalation phase, patients will not be selected based on ATM pathway status, although there will be a retrospective analysis of ATM pathway function using archival tumour samples. The dose-escalation part of the study will include pharmacokinetic analysis. In addition, tumour and normal tissue (hair follicle, peripheral blood mononuclear cells (PBMC)) samples will be collected for pharmacodynamic analysis to confirm drug-on-target effects. Subsequently, an additional group of patients will be recruited into expansion cohorts (part B, with varying drug dosing schedules). The number of cohorts will depend on the need to adjust the dosing schedule during dose-escalation in Part A.

In Part C of the study, two groups of patients (those with head and neck/thoracic malignancies or abdomino-pelvic disease) with a standard indication for palliative radiation will be enrolled in parallel tracks in a 3+3 design with the aim of making definitive statements about tolerability and/or dose-limiting toxicity of AZD6738 in combination with radiation. If possible, patients with cutaneous/subcutaneous disease will be recruited to each cohort in order to maximise opportunities for obtaining tumour and normal tissue samples for pharmacodynamic analyses. Two expansion cohorts will be treated with maintenance AZD6738 after radiotherapy completion.

For part C, the studies in patients with head and neck cancer or thoracic malignancies (part C1: disease between the skull base and the diaphragm) and abdomino-pelvic malignancies (part C2: disease between the diaphragm and pelvic floor) will run in parallel enabling recruitment of homogeneous patient populations that will allow sound conclusions to be drawn about the toxicities of the treatment combination across a broad range of normal tissues. The inclusion of limited numbers of patients with cutaneous/subcutaneous disease should not adversely affect conclusions about treatment tolerability. For details on the study drug, the radiation dose (20 Gy in 10 fractions to 30 Gy in 15 fractions) and the duration of drug exposure (10 versus 15 fractions sensitised with AZD6738), see Figure 2 and schedule of events in section 10.4.

Expansion cohorts will be recruited at the recommended dose to proceed in part C, consisting of a total of 12 additional patients (6 in C1 and 6 in C2), expanding each cohort at the recommended dose to proceed to 12 patients.

In these expansion cohorts, patients will continue to take AZD6738 as maintenance therapy after the completion of radiotherapy. The MTD may be different in parts C1

and C2. Thus, if there are no DLTs, 24 patients with head and neck/thoracic and 24 patients with abdomino-pelvic malignancies will be recruited. In the unlikely event that a DLT occurs at every dose level, a maximum of 36 patients will be recruited to each parallel arm of the study. All patients within the trial will commence radiotherapy on a Monday to standardise the dose of radiosensitiser received.

Part B will open after dose escalation has been completed in part A; part C may open in parallel with part A, at a dose level 2 levels below the currently tolerated part A dose or at another dose level as per Safety Review Committee decision, where there is predicted biological activity based on clinical, PK or PD data. The decision to open in parallel will be based on review of emerging toxicity data from Part A and will be discussed with the Trial Management Group and permission sought from the Ethics committee. If a patient is eligible for both parts B and C, or A and C then they should enter part C if there is a definite indication for radiotherapy.

## **3.2. Part A (Figure 1)**

Initial dose escalation of single-agent AZD6738, with safety and toxicity endpoints, single and multiple dose pharmacokinetics.

### **3.2.1 Dose selection**

A starting dose of 20 mg BD will be used based on animal toxicity studies.

ICH S9 recommends that a starting clinical dose for a first-in-human study should be 1/10 the severely toxic dose in 10% of the animals in rodent, or if non-rodents are the more appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD). For AZD6738, rats are considered the appropriate species to use. An  $STD_{10}$  was not reached, but 35 mg/kg/day has been used in the allometric calculations as the highest dose tested.

The human equivalent dose (HED), derived from the rat data at 35 mg/kg/day, is 35.7 mg for a 60 kg patient, using allometric scaling:

Rat  $STD_{10}$  = 35 mg/kg (210 mg/m<sup>2</sup>)

1/10 of  $STD_{10}$  = 21 mg/m<sup>2</sup>

1/10 of  $STD_{10}$  was tolerated in dogs (21 mg/m<sup>2</sup> in dogs = 1.05 mg/kg)

21 mg/m<sup>2</sup> is starting dose

21 x 1.7 (to convert to human) = 35.7 mg/day

Because 35 mg/kg/day in male rats is less than the  $STD_{10}$ , and considering the practicality of dosing BD, the start dose in humans has been increased slightly to 40 mg per day, given as 20 mg BD.

The preclinical toxicology data supports continuous dosing in humans. However preclinical modelling data predicts efficacy with a better therapeutic index (with respect to bone marrow suppression) from intermittent dosing. Continuous dosing will be explored in part A of the study and, depending upon the outcome of part A, intermittent dosing schedules will be examined subsequently.

### **3.2.2 Single dose administration**

A single dose will be administered followed by pharmacokinetic studies for 24 hours, or 7 days in the case of intense PK sampling cohorts (see sections 10.2.1 and 10.4.1). After this, continuous dosing will proceed with further pharmacokinetic and toxicity assessments.

### 3.2.3 Continuous dosing and dose escalation

Investigation schedule for continuous dosing is shown in sections 10.2.1 and 10.4.1. Recruitment will be to single patient cohorts initially (maximum of 3 dose levels), followed by a 3+3 design. A proposed dose escalation is outlined in Table 1. Dose escalation will only occur when the previous cohort has completed one full cycle of treatment. Decisions to escalate to the next level, or, when appropriate, to an intermediate level or onto a modified dosing schedule, will be made by the Safety Review Committee (see section 3.12) based on review of required data. Actual dose levels and increments may be adjusted depending upon the point at which toxicity is observed.

Rules for AZD6738 dose escalation are as follows.

- *If 0/3 patients exhibit dose limiting toxicity at this dose level:* Dose escalation to the next dose level may begin in a new cohort of patients
- *If 1/3 patients exhibit dose limiting toxicity at this dose level:* Expand dose level to a total of 6 patients. If no further DLT events seen, dose escalation to the next dose level may begin in a new cohort of patients. If 1 or more further DLT events are seen (i.e. 2 or more of 6 patients), this dose level will be considered the maximum administered dose (MAD).
- *If 2/3 patients exhibit dose limiting toxicity* this dose level will be considered the maximum administered dose (MAD).

If 2 subjects in a cohort experience DLTs, recruitment to the cohort should be stopped, the MAD defined, and a lower dose level should be explored to define MTD. Patients in the cohort who are tolerating treatment well may continue at the current dose level, if agreed by the investigator and sponsor, otherwise they should be de-escalated.

Dose escalation will only occur when the previous cohort has completed 1 full cycle of treatment. Initial cohorts will consist of 1 patient; at the development of the first CTCAE 4.03 grade 2 toxicity, 2 further patients will be recruited at this dose level. Initial dose escalation will be in steps of 100%, with smaller dose escalations subsequently. Decisions to escalate to the next level, or, when appropriate, to an intermediate level or onto an altered dose schedule (including changing the number of doses per day or the number of days of dosing per cycle), will be made by the Safety Review Committee (see section 3.12) based on review of all the required data. Actual dose levels and increments may be adjusted depending upon the point at which toxicity is observed.

**Table 1: proposed dose escalation schema for part A**

\*these cohorts are recommended intermediate dose-levels for de-escalation

| Cohort | Dose of AZD6738 |
|--------|-----------------|
| 1      | 20mg BD         |
| 2      | 40mg BD         |
| 2a*    | 60mg BD         |
| 3      | 80mg BD         |
| 3a*    | 120mg BD        |
| 4      | 160mg BD        |
| 4a*    | 200mg BD        |
| 5      | 240mg BD        |

### 3.2.4 Dose de-escalation

If a DLT is observed in 2 or more of up to 6 treated subjects in dose level 1 then Part A will be closed to accrual and treatment of all subjects stopped.

### 3.2.5 Duration of treatment

Treatment cycles will be repeated until:

- Progressive disease (by RECIST1.1, see appendix 3, section **Error! Reference source not found.** and **Error! Reference source not found.**)
- Unacceptable toxicity is encountered.
- Withdrawal of consent
- If the patient becomes pregnant
- Any event which in the judgment of the investigator would affect patient safety, the ability to deliver treatment or the primary study endpoints

### 3.2.6 Inpatient dose escalation

Inpatient dose escalation is permitted on this study. If a patient has disease stabilisation or response on treatment (after at least 2 cycles of treatment), and the cohort taking the next dose level above have completed the DLT window and tolerated treatment well, then dose escalation to the currently tolerated dose level on the study will be permitted at the discretion of the investigator, following approval by the sponsor.

## 3.3. Part B (Figure 1)

Part B will allow enrichment of patient groups for putative markers of sensitivity to AZD6738. Patients may be selected based on molecular and/or immunohistochemical testing of tumour tissue. Part B will allow assessment of one or more dose schedules. A dose schedule refers to the timing of continuous dosing and breaks without drug dosing (for example: three weeks on, one week off; one week on, one week off and so on).

### 3.3.1 Dose selection

The dose chosen for part B will be the MTD established in part A. Dose-schedules chosen for part B will be determined after a review of safety and PK data from part A of the study by the safety review committee. Multiple dose schedules may be assessed simultaneously, these will be adapted based on emerging data and may include, but are not limited to, continuous dosing, 21 days on followed by 7 days off, 14 days on followed by 14 days off, 5 days on followed by 2 days off. After review of part B safety data by the safety review committee, a different (higher or lower) dose level may also be evaluated, provided the total dose per 28-day cycle does not exceed the MTD established in part A.

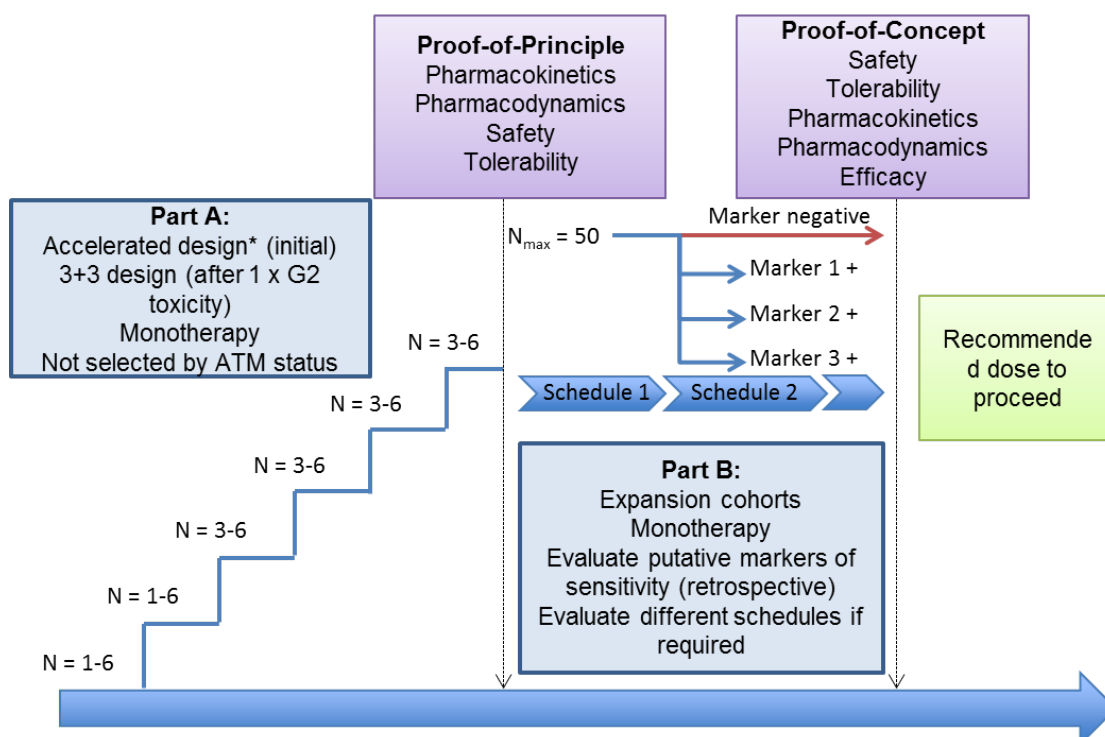


**Figure 1: Trial design (parts A and B)**

### 3.3.2 Patient selection

Patients entering part B will be asked to consent for a fresh biopsy, this will be mandatory for entry into part B. For the early part of this phase of the study, participants will not wait for the results of the biopsy analysis before dosing begins. Participants in the later parts will require analysis of archival tumour material and fresh blood sample for analysis of germline DNA prior to entering the study and, if accepted to proceed, will require a fresh biopsy prior to commencing study drug. Tumour material will be analysed for putative markers of sensitivity to AZD6738, which include immunohistochemical analysis of protein expression levels, and sequencing of tumour genetic material. Patients will be accepted into the study if their tumours have abnormalities in the DNA damage response, high levels of replication or replication stress; other groups or markers may be included depending upon emerging data. The total number of patients in part B will not exceed 50 patients. Response rates will be compared between groups and selection strategies may be updated as more information becomes available. Participants may be found to be ineligible for this part of the study entry based on their biopsy analysis. Full details of analyses required will be in the laboratory manual. Repeat biopsy on treatment and at progression is desirable, but not mandatory.

### 3.3.3 Duration of treatment

As per part A (section 3.2.5)

## 3.4. Part C (Figure 2)

This part of the study comprises combination of AZD6738 and palliative radiotherapy. Patients will be treated in a 3+3 design, in parallel cohorts depending on the site of irradiation – head and neck/thorax and abdomen/pelvis. This design aims to divide patients into homogeneous groups in order to provide more meaningful data on site-

specific toxicities. Additionally, part C will assess the effect of drug dose escalation, radiation dose escalation and number of sensitized radiation fractions.

At the start of each new dose level, one patient will be treated and be followed for a minimum of 2 weeks post-treatment. This is the anticipated time window in which the radiation reaction will reach its peak following palliative radiotherapy. Thereafter, the other two patients in the dose level can be recruited simultaneously (starting radiotherapy a minimum of 2 weeks after the first patient completed radiotherapy). New cohorts will only be opened after a 3-week period of observation following completion of radiotherapy treatment.

Minimum cohort size will be three participants, who will be individually assessed for safety and DLT. The DLT window in part C will end 2 weeks after the completion of radiotherapy. If one out of three subjects in a dose group experiences a DLT during the treatment, three more subjects will be added to that dose group. The head and neck/thorax and abdomino-pelvic groups will be assessed independently for toxicity. In the event that a generic toxicity (e.g. exacerbation of skin toxicity) is seen that is relevant to both parallel tracks, these data will be made available to all investigators and the Safety Review Committee for their consideration. If there are <2 DLT and once all subjects treated in dose level 1 have undergone safety evaluation for a minimum of 2 weeks after the end of radiotherapy, the first patient in dose level 2 may be recruited.

There may be an expansion cohort (n=6 for part C1, n=6 for part C2) at the recommended phase II schedule in part C, the dose to use during the expansion phase will be agreed by the Safety Review Committee based on toxicities seen during earlier cohorts of part C. These patients will continue maintenance AZD6738 after the completion of radiotherapy using the recommended dose schedule based on data collected in part A. They will continue until disease progression or unacceptable toxicity as for part B (see section 3.2.5). They will undergo the same investigation and monitoring schedule as part B after the completion of radiotherapy (see section 10.4.3).

### **3.4.1 Patient selection**

Patients will be stratified according to site of irradiation: between skull base and diaphragm (including upper limbs) will be head and neck/thorax arm C1; between diaphragm and pelvic floor, and including lower limbs, will be abdomino-pelvic arm C2. There will be no selection based on molecular/genetic status in this part of the study. If possible, patients with cutaneous or subcutaneous tumours requiring radiotherapy will be included, in order to facilitate biopsy of these areas.

### **3.4.2 Dose selection and escalation**

Table 1 is a guide for dose escalation, however, decisions to escalate to the next level, or, when appropriate, to an intermediate level or onto an altered dose schedule, will be made by the Safety Review Committee (see section 3.1.2) based on review of all the required data as per the SRC charter. If the MTD in part A is level 1 or 2, the starting dose in combination with radiation will be decided by the Safety Review Committee.

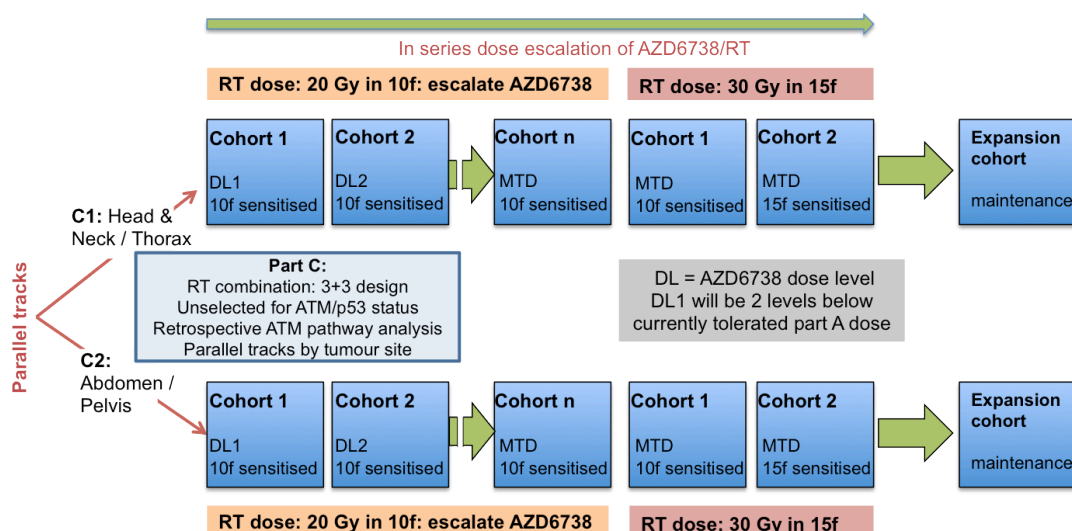


**Figure 2: trial design (part C)**

### 3.4.2.1 20 Gy Cohorts

This group will be treated with 20Gy in 10 fractions, with AZD6738 for 3 to 7 days prior to radiation, during radiation and for 2 days after. The dose of AZD6738 will be escalated by cohort but the duration of AZD6738 treatment will remain the same. Dose will be escalated until the MTD with radiation is reached, or until the recommended phase 2 monotherapy dose established in part A is reached. Alternatively, the safety review committee may decide that the recommended dose to proceed is lower than the MTD with radiation, or the recommended phase 2 monotherapy dose, based on emerging toxicity and efficacy data. In this case, a decision may be made to escalate the radiation dose and/or initiate expansion cohorts at a lower dose level than the MTD, and the MTD would not have to be determined. Initially 3 patients in C1 and 3 patients in C2 will be recruited. C1 and C2 will be treated independently.

Rules for AZD6738 dose escalation are as follows.

- *If 0/3 patients exhibit dose limiting toxicity at this dose level:* Dose escalation to the next dose level may begin in a new cohort of patients
- *If 1/3 patients exhibit dose limiting toxicity at this dose level:* Expand dose level to a total of 6 patients. If no further DLT events seen, dose escalation to the next dose level may begin in a new cohort of patients. If 1 or more further DLT events are seen (i.e. 2 or more of 6 patients), this dose level will be considered the maximum administered dose (MAD).
- *If 2/3 patients exhibit dose limiting toxicity* this dose level will be considered the maximum administered dose (MAD).

The head and neck/thorax and abdomino-pelvic groups will be assessed independently for toxicity. If 2 or more subjects in the 20 Gy cohorts experience a DLT during or after radiotherapy, the previous lower dose will be the recommended dose for study in the second stage of Part C (where the RT dose is escalated to 30 Gy in 15 fractions). Intra-subject dose escalations are not permitted.

### 3.4.2.2 30 Gy Cohorts

This group will also have a 3+3 design and will receive a radiation dose of 30Gy in 15 fractions. This will be given with the maximum tolerated dose of AZD6738 with

radiation established in the 20 Gy cohorts. In the event that a MTD with radiation is not defined in the 20 Gy cohorts, the 30 Gy cohorts will be administered with the recommended dose to proceed from the 20 Gy cohorts. 30 Gy cohort 1 will have 10 fractions of radiation with AZD6738 and 5 fractions without AZD6738. 30 Gy cohort 2 will have all 15 fractions of radiation with AZD6738. AZD6738 will continue for 2 days after fraction 10 or 15, respectively. 30 Gy cohort 2 will open if, after a 3-week period of observation after completion of radiotherapy, the combination of AZD6738 and radiation is tolerable in 30 Gy cohort 1.

If 1 patient in 30 Gy cohort 1 experiences a DLT, the cohort will be expanded from 3 to 6 patients. If 1 or fewer participants out of 6, experiences a DLT then 30 Gy cohort 2 can be opened. If 2 or more participants experience a DLT then 30 Gy-cohort 2 will not open. . Further dose escalation steps or conversion to intermittent schedules are permitted in the 30 Gy stage of part C.

#### **3.4.2.3 Expansion cohort**

An expansion cohort of 6 patients (in addition to the 3 already treated in the highest dose cohort) in each arm of part C (i.e. 6 patients in part C1: head and neck/thorax and 6 patients in part C2: abdomino-pelvic) may be treated at the recommended phase II dose in part C for both the head and neck/thorax and abdomino-pelvic arms (these doses may differ for part C1 and part C2). Participants may proceed onto single agent maintenance AZD6738 at the discretion of the investigator. These participants will continue the recommended phase II dose with radiation for 4 weeks after radiation completion and subsequently convert to the monotherapy recommended phase II dose and schedule.

#### **3.4.3 Dose de-escalation**

If a DLT in at least 2 of up to 6 treated subjects is observed at the initial dose level, then one dose level lower will be evaluated as shown in Table 1. If a DLT is again observed in 2 of up to 6 subjects the lower dose level, continued recruitment will be stopped and the Safety Review Committee will discuss what further dose evaluation is appropriate (including once daily or non-continuous dosing).

#### **3.4.4 Duration of treatment**

In part C, treatment with AZD6738 will start at a specified time before the start of radiotherapy. Durations of treatment for part C are specified in section 10.2.3. If these durations are not tolerated at the lowest evaluated dose, then the number of days dosing with AZD6738 may be reduced after discussion with the safety review committee.

The 2 expansion cohorts at the end of part C1 and C2 may be treated with maintenance AZD6738 after the completion of radiotherapy. The schedule will be determined based on the data collected in part A and B. In the event that the recommended dose or schedule of AZD6738 as monotherapy and during radiation are different, for patients proceeding onto maintenance AZD6738, the radiotherapy dosing schedule should be continued for 2 days after the completion of radiation. After this, the dose and schedule will be changed to the recommended monotherapy dose and schedule, this option can be confirmed or modified by the Safety Review Committee based on emerging data. A dosing break may be introduced between completion of radiotherapy and commencement of maintenance dosing; this may be recommended by the Safety Review Committee. From the completion of

radiotherapy, patients will have investigations and follow-up as for part B, with an additional CT scan at 4 weeks after completion of radiotherapy (see section 10.2.3). Therapy will continue until disease progression or unacceptable toxicity (as in section 3.2.5)

### **3.5. Withdrawal from study**

Subjects that are withdrawn from the study during the first seven days of AZD6738 treatment will be replaced unless they are withdrawn due to drug-related toxicity. Toxicity data from these patients will not be considered in decisions regarding dose escalation or de-escalation.

A subject may withdraw from the trial at any time at his/her request, or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible.

If the subject withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data.

### **3.6. End of study**

The end of study will be the last visit of the last patient in the study.

### **3.7. Follow-up**

In parts A and B, participants will be followed up weekly for the first 4 weeks, until resolution to baseline of all acute toxicities. Two-weekly follow-up will continue for those with ongoing toxicity after the first month. Monthly follow-up is required only for those AEs and SAEs considered drug-related (definite, probable or possible) that are present at time the patient stops the study drug. Monthly follow-up to continue until resolution to baseline, stabilisation or patient starts another anti-cancer treatment. Lab tests should be repeated until resolution or stabilisation of drug-related laboratory abnormalities

In part C, patients will be followed for acute toxicity as per parts A and B. They will be reviewed again at 3 monthly intervals for 1 year, to assess for long-term toxicity. This will be graded at each visit according to the relevant LENT-SOMA scale for the irradiated site (see appendix 4). Further investigations at these visits are only required if clinically appropriate, until resolution to baseline or stabilisation of any abnormalities. If clinical review is not possible, an attempt should be made, through contact with the referring team or general practitioner, to establish whether (a) the survival status of the subject, (b) whether there is any severe late toxicity from the drug-radiation combination and (c) whether there is local control of the tumour.

Patients, in Part B and C, who have confirmed disease progression and receiving compassionate care will move into the survival follow up phase where they will be followed up for safety monitoring every 12 weeks to determine their disease/survival status. This is done by reviewing the patient's medical notes and/or contacting the

patient or GP directly. Patients will remain on this follow up until death, withdrawal of consent, or the end of the study whichever occurs first.

### 3.8. Number of participants

The number of participants required depends upon the number of DLTs observed. It is estimated that the minimum number of patients will be 3 in part A, 12 in part B and 6 in part C. It is estimated that the maximum number of participants will be 26 in part A, 50 in part B and 72 in part C. Therefore the overall total number of participants will be 21-150.

### 3.9. Laboratory safety assessments

The following parameters will be evaluated at times indicated in the Schedule of Events (section 10.4):

**Table 2: Laboratory safety assessments**

| <b>Haematology:</b> | <b>Chemistry:</b> Serum/plasma | <b>Coagulation</b> | <b>Urinalysis</b> |
|---------------------|--------------------------------|--------------------|-------------------|
| blood               |                                |                    |                   |
| Haemoglobin         | Sodium                         | Prothrombin time   | Blood             |
| Reticulocytes       | Potassium                      | INR                | Protein           |
| MCV                 | Urea                           |                    | Glucose           |
| Leukocyte count     | Creatinine                     | Activated partial  |                   |
| Absolute            | Phosphate                      | thromboplastin     |                   |
| leukocyte           | Magnesium                      | time               |                   |
| differential count: | Glucose                        |                    |                   |
| Neutrophils         | Total and corrected            |                    |                   |
| Lymphocytes         | Calcium                        |                    |                   |
| Monocytes           | Total protein, Albumin         |                    |                   |
| Basophils           | Alkaline phosphatase           |                    |                   |
| Eosinophils         | Bilirubin                      |                    |                   |
|                     | ALT and AST                    |                    |                   |
|                     | Urate, LDH                     |                    |                   |
| Platelet count      | Amylase                        |                    |                   |
| Reticulocyte count  | Cardiac Enzymes                |                    |                   |
|                     | (Troponin and/or CPK)          |                    |                   |
|                     | GGT (gamma glutamyl            |                    |                   |
|                     | transaminase/transpeptidase)   |                    |                   |

Further tests may be added and timing of samples altered for subsequent groups of patients following the review of data from a group of patients.

### 3.10. Definition of dose-limiting toxicity

AEs will be graded according to the NCI CTCAE v4.0.3. This can be accessed at <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>. All AEs should be considered to be related to the study drug unless this relationship can be definitively excluded (for example, a pre-existing toxicity or condition). The first treatment cycle will be used to assess for DLT.

#### 3.10.1 Part A and B

1. Haematological toxicity
  - a. Grade 3 thrombocytopenia with bleeding
  - b. Grade 4 thrombocytopenia
  - c. Grade 4 neutropenia lasting >7 days in the absence of growth factor support
  - d. Grade 4 neutropenia of any duration accompanied by fever  $\geq 38.5^{\circ}\text{C}$  and/or systemic infection
  - e. Any other grade  $\geq 4$  haematological toxicity
2. Cardiovascular toxicity
  - a. Clinically significant hypotension defined as an asymptomatic fall in systolic blood pressure more than 20mmHg to below 70mmHg persisting for at least 10 minutes
  - b. Symptomatic orthostatic fall in systolic blood pressure of more than 20mmHg compared to resting supine blood pressure
  - c. Prolongation of QTc >0.5 seconds (using an appropriate correction QTcB (Bazett) or QTcF (Fridericia))
3. Gastrointestinal/hepatic toxicity
  - a. ALT or AST >5 times ULN; ALP >5 times ULN with elevated gamma-GT
  - b. ALT or AST >3 times ULN (or ALP >3 times ULN with elevated gamma-GT) with the appearance of symptoms associated with a clinical diagnosis of hepatitis including right upper quadrant pain or tenderness, fever, rash or eosinophilia (>5%)
  - c. [ALT or AST >3 times ULN] and [total bilirubin >2 times ULN] or INR >1.5x ULN (unless patient receiving warfarin) (or other evidence of impaired liver synthetic function)
4. Any other grade 3-4 non-haematological toxicity occurring during the time period from the first dose to the end of the first cycle
  - a. Excluding grade 3 diarrhoea which resolves to grade 1 within 24 hours of medical management
  - b. Excluding grade 3 nausea or vomiting if ameliorated by medical management
  - c. Excluding grade 3 fatigue unless there is an increase by 2 grades from baseline
5. Any dose in cycle 1, or the start of cycle 2, delayed by more than 7 days due to toxicity or patient unable to complete cycle 1 at the planned dose due to toxicity (parts A and B only)
6. Any other toxicity that is greater than baseline, is clinically significant and/or unacceptable, does not respond to supportive care, results in a disruption of dosing schedule of more than 14 days or is considered to be dose-limiting by the investigators.

In order to define DLT, subjects should not be prophylactically prescribed anti-diarrhoeal agents or growth factor support.

### **3.10.2 Part C**

- As for parts A and B (section 3.10.1)
- Grade 3/4 radiation-induced skin or mucosal toxicity\*.
- Inability to tolerate one week of combination therapy due to toxicity.

\*With regard to cutaneous and mucosal toxicity, reactions that are judged by the investigators to be significantly in excess of an expected radiation reaction will be considered to be due to the combination of AZD6738 and radiation i.e. grade 3/4 skin or mucosal reaction with 20 Gy in 10F or 30 Gy in 15F. DLT window for part C is from the first dose of AZD6738 until 2 weeks after the completion of radiotherapy.

### **3.10.3 Notification of DLT**

The CI must be notified of a DLT within 24 hours of an investigator learning of the event. All participating sites will immediately be notified of the DLT. Participating investigators will review drug-related toxicities before escalating or de-escalating to a different dose level (see Safety Review Committee, section 3.12)

## **3.11. Definition of maximum tolerated dose**

The MTD for AZD6738 (as a single-agent or with radiation therapy) will be defined as the dose below that at which more than 1 out of 6 subjects experience a DLT. Patients that do not complete treatment either because of rapid disease progression or through choice will not be considered as a DLT unless they have developed an adverse event (as defined in section 3.10). They will need to be replaced if less than 80% of planned treatment was completed. The recommended phase II dose for further evaluation of AZD6738 either as a single-agent or in combination with radiotherapy will be the dose level at or below MTD. In the event that dose-limiting toxicity does not occur, an MTD will not be defined. In that case, the dose recommended for future study will be the maximum dose.

Six patients with sufficient exposure for the patient to be evaluated for safety are required to determine the MTD.

## **3.12. Safety Review Committee (SRC)**

After each dose level during the dose escalation phases of the study, an SRC will take place to evaluate the safety and tolerability of AZD6738 or of the combination of AZD6738 and radiotherapy to decide the next dose.

The SRC will consist of:

- Principal Investigator or delegate from each investigational site
- RM CTU Operations Manager or delegate
- Observer from AstraZeneca
- Senior ECMC clinician (who is not CI)
- Chairperson (must be independent of the investigators)

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

The SRC will review and assess data once each cohort has completed a cycle of treatment, or more often if necessary (for example when there are 3 evaluable patients in a cohort or 2 dose-limiting toxicities in a cohort). The SRC will review and assess all available safety data from the cohort, together with available pharmacokinetic and pharmacodynamic data to make a decision on the dose for the next cohort of patients. Any dose interruptions and reductions will be taken into account. Specific detail regarding the data which will be considered by the SRC is given in the SRC Charter document.

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

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.

## 4. Patient Selection criteria for parts A and B

### 4.1. Inclusion criteria

1. Diagnosis of histologically or cytologically documented solid tumour refractory to conventional treatment, or for which no conventional therapy exists (other than palliative radiotherapy for part C) or is declined by the patient. (For part C, long-standing (greater than 3 months) hormonal anti-cancer therapy is permitted. For part B and C, long-standing (greater than 3 months) LHRH (luteinising hormone-releasing hormone) analogue therapy is permitted to continue for patients with prostate carcinoma)
2. Part B only: documented disease progression prior to study entry and measurable disease by RECIST 1.1 within 4 weeks of study entry
3. Presence of putative markers of sensitivity to AZD6738 defined on analysis of tumour material, plasma DNA or germline mutational analysis (for part B only).
4. Evidence of measurable or evaluable disease by RECIST 1.1
5. All acute toxic effects of any prior chemotherapy or surgical procedures must have resolved to Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03) Grade  $\leq 1$ . Surgery must have occurred at least 14 days prior to study enrolment.
6. Age must be 18 years or over.
7. ECOG performance status 0-1 (part A); 0-2 (parts B and C)
8. Life expectancy of at least 3 months.
9. Patients must have normal organ and bone marrow function measured within 7 days prior to administration of study treatment as defined below:
  - Haemoglobin  $\geq 9.0$  g/dL
  - Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$
  - White blood cells (WBC)  $> 3 \times 10^9/L$
  - Platelet count  $\geq 100 \times 10^9/L$
  - Albumin  $\geq 30$ g/L
  - AST and ALT  $< 3$  times ULN
  - Total bilirubin  $< 1.5$  times ULN
  - PT/APTT ( $< 1.5$  x upper limit of normal)
  - INR  $< 1.5$  and no other evidence of impaired hepatic synthetic function
  - Glomerular filtration rate (GFR)  $> 50$  mL/min, as assessed using the standard methodology at the investigating centre (i.e. Cockcroft-Gault, MDRD or CKD-EPI formulae, EDTA clearance or 24 hour urine collection)
  - Serum creatinine  $< 1.5$  times ULN
  - Negative serum pregnancy test for females of childbearing potential
10. Signed informed consent indicating that the subject is aware of the neoplastic nature of their disease and have been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.
11. Willing and able to comply with scheduled visits, tissue sampling, treatment plan, and laboratory tests.
12. Able to swallow, absorb and retain oral medication/gastrostomy/nasogastric tube.
13. Part B only: tumour site amenable to fresh biopsy (clinical or radiologically-guided)

## 4.2. Exclusion criteria

1. Therapy with any other investigational medical product (IMP) concurrently or within 28 days prior to signing of consent.
2. Investigational medicinal products, endocrine therapy, immunotherapy or chemotherapy during the previous four weeks (six weeks for nitrosoureas, mitomycin-C) before treatment.
3. Receiving, or having received, concomitant medications, herbal supplements and/or foods that significantly modulate CYP3A4 or P-gp activity (wash out periods of two weeks, but three weeks for St. John's Wort). Note these include common azole antifungals, macrolide antibiotics and other medications listed in 7.6.1 and 7.6.2 **Error! Reference source not found..**
4. Pregnant or breast-feeding women.
5. 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 highly effective forms of contraception (section 13.9) Non-child-bearing potential is confirmed by fulfilling one of the following criteria at screening:
  - a. Post-menopausal (defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments)
  - b. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
  - c. Amenorrhoeic for 12 months and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and plasma oestradiol levels in the postmenopausal range for the institution
6. Male patients with partners of child-bearing potential (unless they agree to take measures not to father children will be required to use highly effective methods of contraception as detailed for female participants (section 13.9). Male patients must agree to abstain from sperm donation during exposure to AZD6738 and 6 months after.
7. Clinically significant cardiac disease including:
  - a. pre-existing arrhythmia,
    - i. Mean resting QTc >470 msec obtained from 3 electrocardiograms (ECGs) in 24 hours
    - ii. Clinically important abnormalities in rhythm, conduction or morphology of resting ECG (including complete left bundle-branch block, third degree heart block)
  - b. Any factor increasing the risk of QTc prolongation or arrhythmia
    - i. Hypokalaemia
    - ii. Congenital long QT syndrome
    - iii. Immediate family history of long QT syndrome or unexplained sudden death below the age of 40 years
  - c. uncontrolled angina pectoris
  - d. myocardial infarction 1 year prior to study entry
  - e. unstable cardiac arrhythmias
  - f. Cardiac failure
    - i. reduced LVEF <50%
    - ii. New York Heart Association (NYHA) grade 2-4 cardiac failure
8. Known HIV positive or active hepatitis B or C infection
9. Uncontrolled active infection

10. Symptomatic and progressive or steroid-requiring brain metastases or leptomeningeal disease involvement.
11. Uncontrolled hypertension requiring clinical intervention.
12. Hypertension requiring 2 or more antihypertensive agents
13. Relative hypotension (<100/60mmHg) or clinically relevant orthostatic hypotension, including a fall in blood pressure of >20mmHg
14. Hepatic or renal function that, in the opinion of the investigator, is unstable or worsening
15. Dementia or altered mental status that would prohibit informed consent.
16. A known hypersensitivity to AZD6738 or any excipient of the product.
17. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Principal Investigator, would make the subject inappropriate for this study.

## **5. Patient Selection criteria for Part C**

### **5.1. Inclusion criteria**

1. As for Section 4.1.
2. Symptomatic disease or disease that (in the judgment of the clinician) is likely to cause symptoms within a short period of time such that palliative radiotherapy is indicated or justified.
3. Disease suitable for localised short-course palliative radiotherapy.

### **5.2. Exclusion criteria**

1. As for section 4.2.
2. Prior radiotherapy to the treatment site.

## **6. Patient enrolment**

All patients who provide informed consent including any screen failures must be entered onto the patient enrolment log provided by RM CTU to each 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 eligibility and enrolment checklist should be completed prior to enrolment. To enrol a patient, contact RM-CTU (see below). The person enrolling the patient will be asked to provide a copy of the completed eligibility and enrolment checklist to the RM-CTU. A trial number and dose level allocation will be allocated to that patient and confirmed by email to the site.

## **7. Therapeutic regimens, expected toxicity, dose modifications**

### **7.1. Drug administration**

AZD6738 will be administered as monotherapy in parts A and B. Patients will receive twice daily oral dosing and a variety of schedules will be investigated. In the absence of unacceptable toxicity or disease progression, subjects may receive AZD6738 for an indefinite period at the discretion of the investigator. During part C, patients will be given a short course of AZD6738 (most likely 16-23 days depending on part A pharmacokinetic data) before, during and after a 2- or 3-week course of palliative radiotherapy. In the expansion phase of Part C, patients will receive maintenance therapy with AZD6738. No premedication is required for any cohort of the schedule.

### **7.2. Radiation delivery**

Patients with solid tumours located within the head and neck, thoracic, abdominal or pelvic regions (regardless of the primary tumour site or histology) that require palliative radiotherapy will be considered for entry into this trial.

For all patients the minimum radiotherapy field size will be 7.5 x 7.5 cm (or equivalent square for irregularly-shaped fields) with a maximum equivalent square field size for irradiated tissue of 15 x 15 cm in the head and neck/thorax/abdomen and 20 x 20 cm in the pelvis.

For all patients, radiotherapy will be planned based on a CT scan obtained in the treatment position (either virtually simulated or CT-simulated). The dose will be prescribed to Dmax (which may be specified at the depth of the tumour) using a directly applied treatment field for superficial tumours or to the mid-plane for deep-seated tumours using a parallel-opposed field arrangement or the 100% isodose if dosimetric information is available.

The following normal tissue structures will be contoured in all patients at the time of radiotherapy planning when they are within the irradiated volume: heart, lung, brainstem, spinal cord, kidneys, liver, small and large intestine, bladder. This will allow collection of data on radiation dose delivered to critical normal structures, which can subsequently be correlated with toxicity outcomes. Dose-volume histograms should be submitted to the PATRIOT trial manager in hard copy or by email for each patient in part C detailing the absolute dose received by the relevant organs at risk.

Treatment verification with on-board imaging will be carried out as per departmental protocol.

All patients within the trial will commence radiotherapy on a Monday to standardise the schedule of delivery of study drug and radiation. Expansion cohorts will continue to take maintenance AZD6738 until disease progression or unacceptable toxicity.

### **7.3. Criteria for ongoing treatment**

A new cycle of treatment may begin if (on a sample taken a maximum of 96h before the start of the new cycle):

- Absolute neutrophil count greater than or equal to  $1.5 \times 10^9/L$
- Platelet count greater than or equal to  $75 \times 10^9/L$
- Non-haematological toxicities have returned to baseline, or grade 1 or less (at the discretion of the investigator, grade 2 or less if this does not pose a safety risk to the patient)

A treatment delay or interruption of more than 14 days due to lack of recovery from hematologic toxicity must be discussed with the CI. If toxicity is acceptable, and the patient is gaining clinical benefit, it may be possible to continue the study drug at a reduced dose.

## 7.4. Management of toxicity

In part A, no dose reduction is permitted in cycle 1, unless restarting following a DLT, after agreement from TSC. After cycle 1, dose reductions are permitted as outlined below. If DLT occurs, as defined in Section 3.9, treatment with AZD6738 will be discontinued until toxicity improves to NCI-CTCAE v 4.0.3 grade 1 or less. If the dose interruption is for less than 14 days, AZD6738 can then be restarted at the next lower dose level, or discontinued, as the investigator sees fit.

Any other toxicity observed during the course of the study could be managed by interruption of the dose if deemed appropriate by the Investigator. Dosing may be resumed at either the same dose level or the next lower dose level evaluated, at the investigators discretion. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion (in parts A and B – and during maintenance treatment in the expansion phase of part C). A single interruption of 3 days is allowed during radiotherapy in part C. If the interruption is any longer than this the CI must be informed. Re-starting AZD6738 after longer interruptions may be possible if the participant is gaining clinical benefit, this will be decided after discussion with the CI.

AZD6738 must be interrupted until the patient recovers completely or the toxicity reverts to NCI-CTCAE v 4.03 grade 1 or less.

Where toxicity reoccurs following re-challenge with AZD6738 and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue treatment with AZD6738.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be related to administration of AZD6738.

In case of prolonged cytopenia of Grade 3 or higher that lasts for  $\geq 2$  weeks and does not resolve with study treatment interruption. These include referral to haematologist, weekly blood counts and/or bone marrow aspirate/biopsy evaluation, as needed.

## 7.5. Dose modifications in part C

In addition to the guidelines in section 7.4, for patients in part C, dose reductions will primarily involve the dose of AZD6738 and not the dose of radiotherapy, since the latter represents the recommended standard treatment. The radiotherapy dosing schedule will only be amended if deemed to be in the clinical interest of the patient by

the investigators. Cutaneous and mucosal toxicity and other radiotherapy-related reactions will be recorded according to CTCAE v.4.03, however, only adverse events that are judged by the investigators to be significantly in excess of an expected radiation reaction (i.e. grade 3 or greater) will be considered to be due to the combination of AZD6738 and radiation.

If DLT occurs, treatment with AZD6738 will be discontinued until toxicity resolves and then the patient can be treated at the next lower dose level of AZD6738. Radiotherapy can be continued if this is deemed safe and clinically indicated.

## 7.6. Concomitant therapy

### 7.6.1 AZD6738 and CYP3A4

**See appendix 5 for an abbreviated list (amended for those available in the UK only) of medications to be used with caution with AZD6738.**

The use of any natural/herbal products or other “folk remedies” should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the eCRF.

AZD6738 is an investigational drug for which no data on in vivo interactions are currently available. In vitro data have shown that the principal enzyme responsible for elimination of AZD6738 is CYP3A4 (responsible for approximately 90%) and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving AZD6738, until 28 days after the last dose of AZD6738.

Potent inhibitors of CYP3A4 are not permitted during the study. Moderate and weak inducers or inhibitors are permitted during the study but caution should be exercised and participants should be monitored closely for possible drug interactions:

**Potent inhibitors of CYP3A4:** may increase exposure to AZD6738 more than 5-fold

|                   |                |                |
|-------------------|----------------|----------------|
| boceprevir        | itraconazole   | ritonavir      |
| clarithromycin    | ketoconazole   | saquinavir     |
| conivaptan        | lopinavir/ RIT | telaprevir     |
| elvitegravir/ RIT | mibefradil     | telithromycin  |
| fluconazole       | nefazodone     | tipranavir/RIT |
| grapefruit juice* | nelfinavir     | troleandomycin |
| indinavir         | posaconazole   | voriconazole   |

**Moderate Inhibitors of CYP3A4:** may increase exposure to AZD6738 by 2- to 5-fold

|               |              |                   |
|---------------|--------------|-------------------|
| amprenavir    | crizotinib   | grapefruit juice* |
| aprepitant    | cyclosporine | imatinib          |
| atazanavir    | darunavir    | schisandra        |
| casopitant    | diltiazem    | sphenanthera      |
| cimetidine    | dronedarone  | tofisopam         |
| ciprofloxacin | erythromycin | verapamil         |

**Weak Inhibitors of CYP3A4:** may increase exposure to AZD6738 by 1.25– to 2-fold

|              |                    |                 |
|--------------|--------------------|-----------------|
| alprazolam   | berberine (herbal) | clotrimazole    |
| amlodipine   | bicalutamide       | cranberry juice |
| atorvastatin | chlorzoxazone      | delavirdine     |
| azithromycin | cilostazol         | fluvoxamine     |

|                     |                     |                       |
|---------------------|---------------------|-----------------------|
| fosaprepitant (IV)  | oral contraceptives | Seville orange juice* |
| ginkgo (herbal)     | pazopanib           | sitaxentan            |
| goldenseal (herbal) | peppermint oil      | tabimorelin           |
| isoniazid           | propiverine         | tacrolimus            |
| ivacaftor           | ranitidine          | ticagrelor            |
| lacidipine          | ranolazine          | tolvaptan             |
| linagliptin         | resveratrol         |                       |
| nilotinib           | roxithromycin       |                       |

For patients taking any of the above, the required wash-out period prior to starting AZD6738 is 5 half-lives.

\*Grapefruit: Patients should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits e.g., grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1-2 teaspoons (15 g) of Seville orange marmalade daily.

**Potent Inducers of CYP3A4:** AZD6738 AUC may decrease by  $\geq 80\%$  or clearance increase by more than 5 fold (400%)

|               |               |                |
|---------------|---------------|----------------|
| avasimibe     | nevirapine    | rifampin       |
| carbamazepine | phenobarbital | St John's Wort |
| enzalutamide  | phenytoin     |                |
| mitotane      | rifabutin     |                |

**Moderate Inducers of CYP3A4:** AZD6738 AUC may decrease by 50-80% or clearance increase by 2-5 fold (100-400%)

|              |             |              |
|--------------|-------------|--------------|
| semagacestat | genistein   | thioridazine |
| talviraline  | lersivirine | tipranavir   |
| bosentan     | lopinavir   | ritonavir    |
| efavirenz    | modafinil   |              |
| etravirine   | nafcillin   |              |

**Weak Inducers of CYP3A4:** AZD6738 AUC may decrease by 20-50% or clearance increase by less than 2 fold (100%)

|                           |                    |                |
|---------------------------|--------------------|----------------|
| pleconaril                | garlic             | rufinamide     |
| troglitazone              | gingko             | sorafenib      |
| amprenavir                | ginseng            | sulfinpyrazone |
| aprepitant                | glycyrrhizin       | telaprevir     |
| armodafinil (R-modafinil) | methylprednisolone | terbinafine    |
| bexarotene                | nevirapine         | topiramate     |
| boceprevir                | oxcarbazepine      | vemurafenib    |
| clobazam                  | pioglitazone       | vicriviroc     |
| danshen                   | prednisone         | ritonavir      |
| dexamethasone             | quercetin          | vinblastine    |
| echinacea                 | raltegravir        |                |
|                           | ritonavir          |                |

For patients taking any of the above potent and moderate inducers of CYP3A4, the required wash-out periods prior to starting AZD6738 is 5 half-lives

AZD6738 is an inducer of CYP3A4, CYP1A2 and CYP2B6. Caution should be applied with co-administration of drugs that are either completely metabolised by CYP3A4,

CYP1A2 and/or CYP2B6 or that are CYP3A4 and/or CYP2B6 substrates and also have a narrow therapeutic index. These include:

**Drugs known to be metabolised by CYP3A4 and have a narrow therapeutic index**

- Alfentanil, Cyclosporine, Dihydroergotamine, Ergotamine, Fentanyl, Pimozide, Quinidine, Sirolimus, Tacrolimus, Astemizole, Cisapride, Terfenadine

**Drugs known to be metabolised by CYP2B6 and have a narrow therapeutic index**

- Cyclophosphamide, Ifosfamide, Efavirenz, Bupropion, Propofol, Thiopental, Sorafenib, alfentanil, ketamine, methadone, methoxetamine, nevirapine, selegiline, sertraline, tamoxifen, valproic acid

After registration if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the CI. A decision to allow the patient to continue in the study will be made on a case-by-case basis in consultation with the CI and Safety Review Committee.

## **7.6.2 AZD6738 and OATP1B1 and BCRP**

AZD6738 is an inhibitor of human OATP1B1 and BCRP and may increase exposure to concomitantly administered OATP1B1 substrates, through reduced extraction from the portal vein [22, 23]. Caution should be applied with co-administration of substrates of OATP1B1 and/or BCRP as AZD6738 may increase their exposure. Co-administration of substrates of OATP1B1 and/or BCRP should be suitably documented in the patient's medical records.

These include:

These lists are not intended to be exhaustive and appropriate medical judgment is required. Please contact AstraZeneca with any queries you have on this issue. Please refer to full prescribing information for all drugs prior to co-administration with AZD6738.

**Drugs known to be substrates of OATP1B1**

|                                 |                                                                                                                                                                  |
|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anti-cancer:</b>             | irinotecan, methotrexate, paclitaxel, docetaxel                                                                                                                  |
| <b>Cardiovascular:</b>          | atorvastatin, bosentan, enalapril, ezetimibe, fluvastatin, lovastatin, olmesartan, rosuvastatin, pitavastatin, pravastatin, simvastatin, valsartan, telmisartan, |
| <b>Anti-infective:</b>          | caspofungin, benzylpenicillin, cefazolin, cefalexin, rifampicin                                                                                                  |
| <b>HIV protease inhibitors:</b> | saquinavir, lopinavir, darunavir                                                                                                                                 |
| <b>Others:</b>                  | fexofenadine, glibenclamide, repaglinide                                                                                                                         |

Caution should be applied when using these drugs during the study: the effect and/or levels of these drugs should be monitored, particularly if they have a narrow therapeutic index.

**Drugs known to be substrates of BCRP:**

Anthracyclines, Daunorubicin, Doxorubicin, Topotecan, Irinotecan, Methotrexate, Imatinib, Mitoxantrone, nucleoside analogues, prazosin, pantoprazole, rosuvastatin and other statins, teriflunomide, chlorothiazide

### **7.6.3 Other Concomitant Medications**

Patients are allowed to receive supportive care therapies (excluding cytokine growth factors) concomitantly during the trial. No growth factor support, blood products or prophylactic antibiotics are permitted during the DLT assessment period in part A of the study. Following this, other medications will be permitted at the Investigator's discretion. No other chemotherapy, immunotherapy, hormonal cancer therapy (with the exception of bisphosphonates for bone disease and corticosteroids provided the dose is stable before and during the trial), or experimental medications are permitted during the trial and, if possible, for up to four weeks after the last dose of AZD6738. Any disease progression that requires other specific anti-tumour therapy will be cause for discontinuation from the trial.

The following concomitant therapies warrant special attention:

#### **7.6.3.1 Anticoagulant Therapy**

Patients who are taking warfarin may participate in this trial; however, it is recommended that the INR be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Subcutaneous heparin/low molecular-weight heparin is permitted. Please contact the study sponsor regarding other anticoagulant therapy.

#### **7.6.3.2 Anti-emetics**

Patients will not initially be routinely pre-treated with an anti-emetic regimen before therapy unless the radiation field involves the stomach, liver, duodenum or small intestine. If, after starting treatment, the patient develops nausea and vomiting that is considered related to the trial drug, radiation, or the combination of radiation and trial drug, then anti-emetic medication will be prescribed and prophylactic antiemetic therapy should then be considered for subsequent treatment days.

#### **7.6.3.3 Colony Stimulating Factors**

The routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during part A. The use of G-CSF after part A is at the discretion of the principal investigators. Patients who are on recombinant human erythropoietin prior to trial entry may continue on this therapy. The use of recombinant erythropoietin for patients not currently receiving erythropoietin and who have symptomatic anaemia during treatment may be considered upon discussion with the principal investigators.

#### **7.6.3.4 Live Vaccines**

Live virus and bacterial vaccines should not be administered, e.g. yellow fever, measles, rubella, mumps, typhoid, mycobacterium tuberculosis (BCG), Yersinia pestis (EV). An increased risk of infection by the administration of these vaccines has been observed with conventional chemotherapy and the effects with AZD6738 are unknown.

The following vaccines are examples of killed vaccines – influenza, cholera, bubonic plague, polio vaccine, hepatitis A and rabies, the administration of which are allowed.

#### **7.6.3.5 Drugs prolonging the Q-T Interval**

Caution should be applied when co-administering drugs which can cause prolongation of the QT interval. These drugs should be avoided where possible and closer monitoring of the patient and the QTc should be undertaken if they are co-administered. A list of drugs prolonging QTc is given in appendix 6.

**All medications (prescriptions or over-the-counter medications) continued at the start of the trial or started during the trial or until 4 weeks from the end of the last protocol treatment and different from the trial medication must be documented in the eCRF.**

## **8. Other precautions**

### **8.1. Antidote and overdose**

There is no known antidote to AZD6738. Any patient who receives a higher dose than stated in the protocol should be monitored, and if symptomatic, treated with appropriate supportive care until recovery. Overdose must be reported as an AE (see section 13.1.2)

### **8.2. Sun protection**

AZD6738 has been associated with photosensitivity reactions. For this reason, it is recommended that study participants take measures to avoid sun exposure and use appropriate sun protection or high SPF sunscreen while they are taking AZD6738.

## **9. Pharmaceutical Information**

### **9.1. Supply of AZD6738**

All study drug supplied by AstraZeneca 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. The drug will be labelled, QP released and distributed by Fisher Clinical services.

Patients will be supplied with sufficient medication for each visit. There will be sufficient tablets in the bottle to cover the visit window.

Please refer to the pharmacy manual for further information.

### **9.2. Pharmaceutical data**

#### **9.2.1 Formulation of AZD6738**

The drug product is presented as direct compression tablets containing 20, 80 or 100 mg of AZD6738 drug substance.

AZD6738 coated tablets contain a blend of AZD6738, mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate and silicon dioxide. The coating is Opadry®-II white.

#### **9.2.2 Storage conditions and stability**

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

AZD6738 tablets should be stored below 30°C in induction sealed HDPE bottles until use.

Please refer to the Investigator Brochure for detailed information on storage conditions and stability.

#### **9.2.3 AZD6738 administration**

AZD6738 administration will start on day 1 of each cycle.

AZD6738 may be administered as whole tablets by mouth, dispersed in water by mouth, or dispersed in water and administered by nasogastric or gastrostomy tube.

Patients must fast (water to drink only) from at least 2 hours prior to taking a dose to at least 1 hour post-dose for all doses.

Patients should swallow the medication whole with a glass of water (in the morning and the evening at the same time every day). This is to ensure a dose interval of approximately 12 hours. If participants are unable to swallow the tablets whole, then it is acceptable to disperse tablets in a glass of water. This should be documented on the eCRF and the method of administration (whole tablets or dispersed) should remain constant through the study where possible.

##### **9.2.3.1 Instructions for dispersal**

The tablets should not be crushed. Tablets will break up into a fine dispersion within 10 to 15 minutes when they are dropped whole into drinking water (or water for injection or purified water) at room temperature. The dispersion is chemically stable providing this process occurs immediately prior to administration to or by the patient. The following procedure is recommended for administering dispersed whole tablets to patients who are unable to swallow:

Drop the required number of AZD6738 tablets required for a single dose into an appropriate container (ideally glass to help confirm removal of all the dispersed material) containing approximately 100 mL of drinking water at room temperature. Stir the liquid occasionally to ensure complete break-up of the tablets. When the tablets have broken up into a fine dispersion (approximately 10 to 15 minutes) it can be administered to or by the patient.

To ensure delivery of the whole dose, rinse the container with approximately 50 mL amount of drinking water to ensure removal of any material adhering to the walls of the container and administer the additional water to the patient. Administration to the patient should occur immediately after dispersion is complete.

#### **9.2.3.2 Instructions for nasogastric/gastrostomy administration**

1. Dispense required number of tablets in a 100 mL glass beaker.
2. Add 50mL of water for injection and swirl gently until tablets are disintegrated to give dispersion.
3. Flush the feeding tube with 20 mL of water.
4. Draw entire quantity of AZD6738 tablet dispersion into a 50 mL syringe.
5. Connect the syringe to the feeding tube and administer the entire quantity.
6. Rinse the beaker with 25 mL of water and draw the entire rinsate into the same 50mL syringe used in step 4/5 and administer the entire quantity.
7. Rinse the beaker with further 25 mL of water and draw the entire rinsate into the same 50mL syringe used in step 4/5/6 and administer the entire quantity.

Tablet dispersion should be administered within 2 hours of preparing the dispersion.

#### **9.2.3.3 Missed doses and vomiting**

If vomiting occurs shortly after the AZD6738 tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of two hours after that scheduled dose time. If greater than two hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

### **9.3. AZD6738 accountability**

Accurate records of all AZD6738 shipments, tablets dispensed, and all IMP destroyed must be maintained. This inventory record must be available for inspection at any time by members of the sponsoring trial team. IMP supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

Participants will be asked to return any unused drug and empty packaging. The Investigator undertakes not to destroy any unused IMP without the approval of the

sponsor. Once approval is in place, any unused IMP may be destroyed according to local hospital procedures and properly accounted for using the IMP Destruction Form and also on the IMP Accountability Record or returned to the manufacturer at the end of the trial. During the course of the trial the RM CTU / designee will check the numbers of tablets of AZD6738 shipped to the centre, the number used and the number destroyed. The pharmacy will give an account of any discrepancy.

## **10. Investigations Schedule**

### **10.1. Baseline assessments**

#### **10.1.1 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 (AZD6738). Patients will be given sufficient time to consider their options and discuss with their medical team as required by GCP guidelines.

Only the Principal Investigator (PI) and those Sub-Investigator(s) delegated responsibility by the PI, having signed the Study Team Responsibilities Signature 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. 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 and AZD6738 and must also ensure that the patient is aware of the following points.

- The known toxicity of the IMP and the possibility of experiencing side-effects.
- That IMP is 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) provided with information about appropriate medically approved contraception (refer to Section 4.2).
- 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 site file. A copy of the signed consent form must also be filed in the patient's medical records.

#### **10.1.2 Part B pre-screening**

Some patients entering part B will have analysis of archival tumour material for deficiencies in the DNA damage response systems, the population in part B will be enriched for these. This part of the study (part B pre-screening) is covered by a separate consent form. Patients will consent to having their archival material analysed and provide a blood sample for buffy coats. Patients with tumour or circulating tumour DNA mutations or other factors thought to confer a deficient DNA damage response (criteria will be agreed by the trial management group) will be accepted for proceeding to full study screening within 6 weeks of tissue receipt. See laboratory manual for further details. Where participants have had tumour material analysed previously, in a laboratory accredited for clinical samples, this result may be used instead of further screening of archival material. Patients known to have germline DNA damage response mutations may be accepted for pre-screening after discussion with the sponsor. A fresh biopsy will still be required before starting AZD6738.

Pre-screening investigations:

- Send archival material
- Blood sample for buffy coat

### **10.1.3 Evaluations within 4 weeks (28 days) of starting AZD6738**

The baseline studies will be common to all patients with respect to safety assessments. Evaluation of tumour parameters will depend upon the tumour type and site, and will encompass sufficient clinical, radiological and chemical studies for the evaluation of stage, dissemination, tumour load and tumour-induced symptoms and organ dysfunction. Primary tumour blocks / frozen specimens or fine needle biopsy of metastatic sites may be requested to allow analysis of the surrogates of ATR-Chk1 and ATM-Chk2-p53 pathway function. Analysis may include, but not limited to, assessment of proliferation index and ATM by immunohistochemistry; assessment of genetic deficiencies in replication stress response and DNA breakage repair. Fresh tumour biopsy will be mandatory in part B. Fresh tumour biopsy is optional for parts A and C.

Baseline examinations should be performed prior to and as close to the trial start as possible and the interval should not exceed seven days except for radiological studies (not including multi-parametric MRI for pharmacodynamic assessment), where a period of up to four weeks prior can be permissible. The treatment and assessment schedules are summarised in section 10.4.

Evaluations within 4 weeks (28 days) of starting AZD6738:

- Radiological disease assessment (staging CT/MRI)
- Baseline echocardiogram or MUGA
- Part B: Fresh tumour biopsy to be taken within 4 weeks of starting AZD6738 in patients accepted for the study.

### **10.1.4 Evaluations within 1 week (seven days) of starting AZD6738:**

- Review of inclusion/exclusion criteria.
- Full medical history and demographics
- Physical examination, including visible or palpable tumour, both irradiated and unirradiated (clinical disease assessment to be within 7 days and as close as possible to starting AZD6738)
- Measurements of height, weight and body surface area
- Evaluation of performance status (ECOG)
- vital signs:
  - heart rate;
  - Blood Pressure: lying (after lying for at least 5 minutes) and standing (after standing for 3 minutes)
  - respiratory rate
  - temperature)
- ECG
- Serum pregnancy test where relevant
- Laboratory tests (blood/urine samples) to confirm eligibility:
  - Haematology and coagulation – haemoglobin (Hb), white blood cells (WBC) with differential count (neutrophils, lymphocytes, monocytes,

basophils, eosinophils), platelets, mean cell volume (MCV), PT (with INR calculation) and APTT, Reticulocytes

- Biochemistry– sodium, potassium, calcium, phosphate, magnesium, urea, creatinine, total protein, albumin, ALT, AST, ALP, GGT, LDH, bilirubin, urate, glucose, amylase, cardiac enzymes (Troponin I and/or CPK).
- Urinalysis – Dipstick for protein, glucose and blood (microscopy if more than one positive test).
- Tumour markers – if appropriate (if there is a recognised tumour marker for this tumour type). To be repeated at the start of each treatment cycle.
- PDc sample collection (Blood for PBMC, hair follicle collection) (mandatory in Part B and optional in part C)
- Blood and plasma for immune profiling and storage, (for future analysis such as DNA sequencing) (optional in part C)
- Tumour biopsy if patient consents and if this is deemed safely accessible for PDc analysis. (within 1 week of starting AZD6738 for Part C only)
- Normal skin punch biopsy – preferably within irradiated volume (for part C only and is optional)

## 10.2. Evaluations during treatment

### 10.2.1 Part A: dose escalation

PK sampling for part A will depend upon whether the study is currently using intense PK sampling or standard sampling. Intense sampling will be used until the investigators have decided there is sufficient PK information to change to the standard sampling schedule. This will be decided at a safety review committee meeting.

#### 10.2.1.1 Intense PK sampling cohorts

Treatment cycles will be 4 weeks long; dosing will be continuous twice daily dosing. A single dose will be administered in each cohort at the start of the trial one week prior to continuous dosing (i.e. day -7) for single-dose pharmacokinetic analysis. The first cycle (day 1) will commence 7 days after the single dose has been administered. With the exception of days -7 to 2, these assessments may take place up to 2 days before or after the day specified. For days -7 to 2, blood tests, clinical examination, weight, performance status and vital signs can be assessed up to 2 days prior to dosing.

##### *Day -7 (single dose administration)*

- Physical examination, clinical disease assessment
- Measurement of weight
- Evaluation of performance status (ECOG)
- Concomitant medication annotation
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4
- Administration of AZD6738 single dose (fasting 1h before and 2h after for PK days)
- Pharmacokinetics pre-dose and at 15 and 30 minutes, 1, 2, 4, 8, 10-12 hours after AZD6738 administration. (Timings should be as close as possible to these timings, however the exact time of sampling should be written on the pharmacokinetic sample to allow accurate calculation)

*Day -6*

- Pharmacokinetics at 24 hours after AZD6738 administration

*Day -5*

- Pharmacokinetics at 48 hours after AZD6738 administration

*Day -4*

- Pharmacokinetics at 72 hours after AZD6738 administration (this sample is recommended, but not mandatory)

*Day 1 (start of cycle 1, start of continuous dosing)*

- Physical examination
- Toxicity assessment
- Measurement of weight
- Concomitant medication annotation
- Vital signs as detailed in section 10.1.4
- ECG
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Pharmacokinetics pre-dose. Commencement of AZD6738 continuous dosing (fasting 1h before and 2h after for PK days)

*Day 8 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

*Day 15 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Pharmacokinetics at pre-dose, 15 and 30 minutes, 1, 2, 4, 8 and 10-12 hours post-dose
- Blood for PDc analyses, hair follicle sampling, optional tumour biopsy to be repeated on day 15 or 22 (preferably day 15)

*Day 22 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

*Day 29 (cycle 2, day 1)*

- Physical examination and clinical disease assessment

- Toxicity assessment
- Weight
- Evaluation of performance status (ECOG)
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis / Tumour markers as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Pharmacokinetics at 4 weeks (pre-dose only, cycle 2 only)
- ECG
- Repeat echocardiogram / MUGA at 4 weeks (+/- 1 week)
- AZD6738 continuous dosing

*Cycle 2 onwards: review at 2 weekly intervals with:*

- Physical examination, clinical disease assessment
- Toxicity assessment
- Evaluation of performance status (ECOG) Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Imaging for tumour response at 8 weekly intervals (+/- 1 week)
- Repeat echocardiogram / MUGA at 8 weekly intervals (+/- 1 week)
- If applicable, serum tumour markers at each cycle
- ECG at the start of each cycle (maximum 96h before)

### **10.2.1.2 Standard PK sampling**

Treatment cycles will be 4 weeks long, dosing will be continuous twice daily dosing. A single dose will be administered in each cohort at the start of the trial one day prior to continuous dosing (i.e. day 0) for single-dose pharmacokinetic analysis. The first cycle (day 1) will commence 24 hours after the single dose has been administered. With the exception of days 0, 1 and 15, these assessments may take place up to 2 days before or after the day specified. For days 0 and 1, blood tests, clinical examination, weight, performance status and vital signs can be assessed up to 2 days prior to dosing.

*Day 0 (single dose administration)*

- Physical examination, clinical disease assessment
- Measurement of weight
- Evaluation of performance status (ECOG)
- Concomitant medication annotation
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4
- Pharmacokinetics at 30 minutes pre-dose
- Administration of AZD6738 single dose (fasting 1h before and 2h after for PK days)
- Pharmacokinetics pre-dose and at 15 and 30 minutes, 1, 2, 4, 8, 24 hours after AZD6738 administration. (Timings should be as close as possible to these timings, however the exact time of sampling should be written on the pharmacokinetic sample to allow accurate calculation)

*Day 1 (start of cycle 1)*

- Physical examination
- Toxicity assessment

- Concomitant medication annotation
- Vital signs as detailed in section 10.1.4
- ECG
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Pharmacokinetics at pre-dose (same sample as 24 hours post-dose day 0)
- Commencement of AZD6738 continuous dosing

#### *Day 8 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

#### *Day 15 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Pharmacokinetics pre-dose and 15, 30 minutes, 1, 2, 4, 8, 10-12 hours post-dose
- Blood for PDc analyses, hair follicle sampling, optional tumour biopsy to be repeated on day 15 or 22 (preferably day 15)
- 

#### *Day 22 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

#### *Day 29 (cycle 2, day 1)*

- Physical examination and clinical disease assessment
- Toxicity assessment
- Weight
- Evaluation of performance status (ECOG)
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis / Tumour markers as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Pharmacokinetics at 4 weeks (pre-dose only, cycle 2 only)
- Repeat echocardiogram / MUGA at 4 weeks (+/- 1 week)
- Commencement of AZD6738 continuous dosing (twice daily)

#### *Cycle 2 onwards: review at 2 weekly intervals with:*

- Physical examination, clinical disease assessment
- Toxicity assessment
- Evaluation of performance status (ECOG)
- Vital signs as detailed in section 10.1.4

- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Imaging for tumour response at 8 weekly intervals (+/- 1 week)
- Repeat echocardiogram / MUGA at 8 weekly intervals (+/- 1 week)
- If applicable, serum tumour markers at each cycle
- ECG at the start of each cycle (maximum 96h before)

### 10.2.2 Part B: dose expansion

N.b. Pharmacokinetic sampling in part B should be done on the day on PDc analysis, pre-dose and 4-8 hours post dose: to coincide with timing of PDc analysis (not required unless PDc samples taken).

The following assessments may take place up to 2 days before or after the day specified.

#### *Day 1 (start of cycle 1)*

- Physical examination, clinical disease assessment
- Measurement of weight
- Evaluation of performance status (ECOG)
- Concomitant medication annotation
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry/ Tumour markers as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Commencement of AZD6738 continuous dosing (twice daily)

#### *Day 8 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

#### *Day 15 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Blood for PDc analyses, hair follicle sampling, optional tumour biopsy to be repeated on day 15 or 22 (\*note: if patients are on 2 weeks on, 2 weeks off schedule then these samples should be taken at day 15)
- Blood for immune profiling (selected patients only)
- Pharmacokinetics to be done on day of repeat PDc analysis: pre-dose and 4-8 hours post dose: to coincide with PDc analysis (not required unless PDc samples taken).

#### *Day 22 (cycle 1)*

- Physical examination
- Toxicity assessment
- Vital signs as detailed in section 10.1.4

- Haematology / Biochemistry as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Tumour Biopsy (optional) – if not taken on day 15

*Day 29 (cycle 2, day 1)*

- Physical examination, clinical disease assessment
- Toxicity assessment
- Evaluation of performance status (ECOG)
- Weight
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis / Tumour markers as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- Blood for immune profiling (selected patients only)
- ECG
- Repeat echocardiogram / MUGA at 4 weeks (+/- 1 week)

*Cycle 2 onwards: review at 2 weekly intervals with:*

- Physical examination
- Toxicity assessment
- Evaluation of performance status (ECOG)
- Weight
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- ECG at the start of each cycle (maximum 96h before)
- Imaging for tumour response at 8 weekly intervals (+/- 1 week)
- Repeat echocardiogram / MUGA at 8 weekly intervals (+/- 1 week). If applicable, serum tumour markers at each cycle
- Blood for PDc analyses and hair follicle sampling on cycle 2 day 15 only.

*Patients continuing on AZD6738 after December 2023.*

Patients will be reviewed at intervals consistent with standard-of-care and routine investigations prior to each cycle satisfying the criteria in section 7.3.

As a minimum SAEs as per section 13.1.2 will be reported.

### **10.2.3 Part C: combination with radiotherapy**

Assessments may take place up to 2 days before or after the day specified, Day -8 to -4 assessments can take place up to 3 days before starting AZD6738. PDc sampling is not mandatory in Part C.

*Day -8 to -4: Review prior to Day 1 AZD6738*

- Physical examination
- Clinical disease assessment
- Measurement of weight
- Evaluation of performance status (ECOG)
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4

- Blood for immune profiling (selected patients only)
- If patient consents PDc sample collection (Blood for PBMC, hair follicle collection and skin punch biopsy)
- Instructions on commencement of AZD6738, continuous dosing to start on day -7 to -3 (longer period is desirable however exact timing of start of AZD6738 in relation to radiotherapy is flexible to allow for variation in radiotherapy planning and urgency of treatment).

*Day 1: start of radiotherapy, and days 2-5 if clinically indicated*

- Physical examination
- Toxicity assessment
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Commencement of radiotherapy (Monday to Friday only)
- PDc sample collection: before first radiation fraction (if patient consents: skin punch biopsy from within irradiated area, hair follicle collection, irradiated tumour biopsy if easily accessible). Where possible samples will be taken before the first fraction of radiotherapy and again 16-24 hours after the first fraction (before the second fraction of radiotherapy), from the irradiated area. PBMC blood samples, if patient consents, to be taken before the first fraction and again 16-24 hours after the first fraction (before the second fraction of radiation).
- Bloods for PK analysis to be done on day of PDc samples, pre-dose and 4-8h post-dose to coincide with PDc sample (post-dose not required if PDc sample not taken).
- Blood for immune profiling to be taken before first fraction of radiotherapy (selected patients only)
- Continuation of AZD6738

*Day 2:*

- Repeat skin punch, tumour sampling PBMC blood test and hair follicle sampling prior to second radiation fraction
- Bloods for PK analysis to be done on day of PDc samples, pre-dose and 4-8h post-dose to coincide with PDc sample (post-dose not required if PDc sample not taken).

*Day 8: Start of week 2 radiation (and days 9-12 if clinically indicated)*

- Physical examination
- Measurement of weight
- Toxicity assessment
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Blood for immune profiling to be taken before first fraction of radiotherapy (selected patients only)
- Continuation of AZD6738 for 2 days after radiotherapy has finished (20 Gy cohort; 30 Gy cohort 1 to finish AZD6738 dosing the day before fraction 11 of radiotherapy)

- Continuation of radiotherapy

*Day 15 (and days 16-19 if clinically appropriate): After end of radiation for 20 Gy cohorts, beginning of third week for 30 Gy cohorts*

- Physical examination
- Measurement of weight
- Evaluation of performance status (ECOG)
- Toxicity assessment
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)
- Blood for immune profiling (selected patients only)
- Continue radiotherapy (30 Gy cohorts only)
- Continuation of AZD6738 (30 Gy cohort 2 only: AZD6738 dosing to finish 2 days after the completion of radiotherapy)

*Day 22 (30 Gy cohort 2 only)*

- Physical examination
- Measurement of weight
- Evaluation of performance status (ECOG)
- Toxicity assessment
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (tests for monitoring only – results are not required to allow ongoing dosing)

Expansion cohorts

*Day 29 (cycle 2, day 1)*

- Physical examination
- Clinical disease assessment
- Toxicity assessment
- Evaluation of performance status
- Weight
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis / Tumour markers as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- ECG
- Repeat echocardiogram / MUGA at 4 weeks (+/- 1 week)

*4 weeks (+/- 1 week) after RT completion*

- Repeat tumour response imaging
- Clinical disease assessment

*8 weeks (+/- 1 week) after RT completion*

- Repeat tumour response imaging (minimum of 28 days from previous imaging)

*Otherwise: continue as for part B: cycle 2 onwards: review at 2 weekly intervals with:*

- Physical examination
- Toxicity assessment

- Evaluation of performance status
- Weight
- Vital signs as detailed in section 10.1.4
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (permissible to use values from maximum 96h before)
- ECG
- Imaging for tumour response at 8 weekly intervals (+/- 1 week)
- Repeat echocardiogram / MUGA at 8 weekly intervals (+/- 1 week)
- If applicable, serum tumour markers at the start of each cycle
- Clinical disease assessment at the start of each cycle

### **10.3. Evaluations during follow-up**

#### **10.3.1 Parts A and B**

Patients should be followed up until resolution of treatment related toxicities: weekly for four weeks and then 2-4 weekly for maximum three months, with the following:

- Physical examination, including visible or palpable tumour
- Measurement of weight
- Evaluation of performance status (ECOG)
- Toxicity assessment
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis as detailed in section 10.1.4 (if required, until resolution or stabilisation of abnormalities)
- Plasma storage at progression (for patients who have had stabilisation or response to therapy)
- Biopsy at progression (optional, see below)

Further disease imaging or monitoring is not required after stopping study medication. Participants who have no toxicity or laboratory abnormality do not require further follow-up (parts A and B).

For those participants who have, after a response or stabilisation of disease, terminated the study due to disease progression and have had a biopsy at baseline, a repeat biopsy should be taken in consenting patients for whom the procedure is deemed safe, this will be used to investigate potential mechanisms of resistance to AZD6738.

Once a patient has confirmed disease progression and is receiving compassionate care, the patient will move into the survival follow up phase and will be followed up for safety monitoring every 12 weeks to determine their disease/survival status. This is done by reviewing their medical notes and / or contacting the patient or GP directly. Patients will remain on this follow - up until death, withdrawal of consent, or the end of the study, whichever occurs first. Due to reported cases of MDS/AML associated with ceralasertib use, survival follow-up should include whether the participant has developed these.

#### **10.3.2 Part C**

Patients will be followed up weekly until resolution of acute toxicity related to AZD6738 and radiation. Patients will have irradiated tumour site imaged (CT or MRI) at week 4

and at week 8 after the completion of radiotherapy. Patients will have a repeat echocardiogram / MUGA at 4 weeks. After this, patients will be followed up routinely by their referring oncology team. Surviving patients will be reviewed monthly up to 3 months after completion of radiotherapy, and then at 6, 9 and 12 months for assessment of late toxicity. At each follow-up, patients will have the following:

- Physical examination, including visible or palpable tumour, both irradiated and unirradiated
- Adverse Events annotation
- Measurement of weight
- Evaluation of performance status (ECOG)
- Toxicity assessment (CTCAE v4.03 up to 3 months, LENT-SOMA 3 months and after, see appendix 4)
- Concomitant medication annotation
- Vital signs
- Haematology / Biochemistry / Urinalysis, if clinically appropriate, as detailed in section 10.1.4

Once a patient has confirmed disease progression and is receiving compassionate care, the patient will move into the survival follow up phase and will be followed up for safety monitoring every 12 weeks to determine their disease/survival status. This is done by reviewing their medical notes and / or contacting the patient or GP directly. Patients will remain on this follow - up until death, withdrawal of consent, or the end of the study, whichever occurs first.

## 10.4. Schedule of events

### 10.4.1 Part A: Dose escalation: Intense PK sampling cohorts

| Observation/Investigation                          | Baseline/Pre-study   |               |                           |                 | Standard Evaluation for Treatment                     |                |                          |                | Off treatment and Follow-up      |                                                          | Refer to  |
|----------------------------------------------------|----------------------|---------------|---------------------------|-----------------|-------------------------------------------------------|----------------|--------------------------|----------------|----------------------------------|----------------------------------------------------------|-----------|
|                                                    | Within 4 weeks       | Within 7 days | Day -7                    | Days -6, -5, -4 | Day 1 Cycle 1 day 1                                   | Days 8, 15, 22 | Day 29 Cycle 2 day 1 (g) | Cycle 2 Day 15 | Follow-up Weekly (first 4 weeks) | Follow-up: two-weekly (until resolution of toxicity) (c) |           |
| Written informed consent                           | X                    |               |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Demographics                                       |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Medical history                                    |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Toxicity and adverse event evaluation              | From date of consent |               | review at each attendance |                 |                                                       |                |                          |                | X (c)                            | Until resolution (d)                                     | 7.4       |
| Concomitant treatments                             |                      | X             | review at each attendance |                 |                                                       |                |                          |                | X                                | X                                                        | 7.6, 18.5 |
| Radiological (CT, MRI, X-ray) disease assessment   | X                    |               |                           |                 | 8 weekly after commencement of continuous AZD6738 (f) |                |                          |                |                                  |                                                          | 18.3      |
| Tumour serum markers                               |                      | X             |                           |                 |                                                       |                | X (g)                    |                |                                  |                                                          |           |
| Pregnancy test (serum)(a)                          |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Clinical disease assessment                        |                      |               | X                         |                 |                                                       |                | X                        |                | X                                | X                                                        |           |
| Physical examination                               |                      | X             | X                         |                 | X                                                     |                | X                        | X              | X                                | X                                                        |           |
| Height                                             |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Weight                                             |                      | X             | X                         |                 | X                                                     |                | X                        |                | X                                | X                                                        |           |
| Body surface area (BSA)                            |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          |           |
| Vital Signs                                        |                      | X             | X                         |                 | X                                                     | X              | X                        | X              | X                                | X                                                        |           |
| ECOG performance status                            |                      | X             | X                         |                 |                                                       | X              | X                        | X              | X                                | X                                                        |           |
| Laboratory tests: haematology and biochemistry (b) |                      | X             | X                         |                 | X                                                     | X              | X                        | X              | X                                | (j)                                                      | 3.9       |
| Urinalysis                                         |                      | X             |                           |                 | X                                                     |                | X                        | X              | X                                | (j)                                                      | 3.9       |
| Electrocardiogram (ECG)                            |                      | X             |                           |                 | X                                                     |                | X(g)                     |                | (j)                              |                                                          |           |
| Echocardiogram / MUGA                              | X                    |               |                           |                 | To be repeated at 4 weeks, then every 8 weeks         |                |                          |                |                                  |                                                          |           |
| AZD6738 administration                             |                      |               | X                         |                 | X                                                     |                | X                        |                |                                  |                                                          | 7.1       |
| Plasma for AZD6738 pharmacokinetics (i)            |                      |               | X (i)                     | X (i)           | X (i)                                                 | X (i)          | X (i)                    |                |                                  |                                                          | 11        |
| Blood for pharmacodynamic assays                   |                      | X             |                           |                 |                                                       | X (h)          |                          |                |                                  |                                                          | 12        |
| Buffy coat storage                                 |                      | X             |                           |                 |                                                       |                |                          |                |                                  |                                                          | 12        |
| Plasma isolation and storage (k)                   |                      | X             |                           |                 |                                                       | X              |                          |                | X                                |                                                          | 12        |
| Hair follicle sampling                             |                      | X             |                           |                 |                                                       | X (h)          |                          |                |                                  |                                                          | 12        |
| Tumour biopsy (e)                                  |                      | X             |                           |                 |                                                       | X (h)          |                          |                |                                  |                                                          | 12        |

(a) If the patient is a woman of child bearing potential.

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(c) Two-weekly follow-up for first 4 weeks, followed by 4 weekly follow-up, until resolution of all acute toxicity

(d) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) that are present at time the patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.

(e) Tumour biopsy to be performed in those patients that consent at baseline

(f) Repeat radiological disease assessments every 8 weeks while on study

(g) Investigations to be repeated at start of each cycle (i.e. day 1)

(h) to be done once between day 15 or 22 (preferably day 15).

(i) Pharmacokinetics: after the first dose (day -7), samples will be taken pre-dose and at 15 and 30 minutes, 1, 2, 4, 8, 10-12, 24, 48 and 72 hours (72h sample recommended, not mandatory). A pre-dose sample will be taken at day 7. After 2 weeks of continuous dosing (day 15), samples will be taken pre-dose and at 15 and 30 minutes, 1, 2, 4, 8, 10-12 hours. A pre-dose sample will be taken on day 29. See section 10.2.1.1

(j) Repeat if clinically indicated, to resolution or stabilisation of abnormalities

(k) plasma to be stored at baseline, day 15 and at progression, in responding participants

## 10.4.2 Part A: Dose escalation: Standard PK sampling cohorts

| Observation/Investigation                          | Baseline/Pre-study            |               | Standard Evaluation for Treatment                     |                           |                   |                                |                   | Off treatment and Follow-up             |                                                                    | Refer to  |
|----------------------------------------------------|-------------------------------|---------------|-------------------------------------------------------|---------------------------|-------------------|--------------------------------|-------------------|-----------------------------------------|--------------------------------------------------------------------|-----------|
|                                                    | Within 4 weeks                | Within 7 days | Day 0                                                 | Day 1<br>Cycle 1<br>day 1 | Days 8,<br>15, 22 | Day 29<br>Cycle 2<br>day 1 (g) | Cycle 2<br>Day 15 | Follow- up<br>Weekly (first 4<br>weeks) | Follow-up: two-<br>weekly (until<br>resolution of<br>toxicity) (c) |           |
| Written informed consent                           | X                             |               |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Demographics                                       |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Medical history                                    |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Toxicity and adverse event evaluation              | From date of informed consent |               | review at each attendance                             |                           |                   |                                |                   | X (c)                                   | Until resolution (d)                                               | 7.4       |
| Concomitant treatments                             |                               | X             | review at each attendance                             |                           |                   |                                |                   | X                                       | X                                                                  | 7.6, 18.5 |
| Radiological (CT, MRI, X-ray) disease assessment   | X                             |               | 8 weekly after commencement of continuous AZD6738 (f) |                           |                   |                                |                   |                                         |                                                                    | 18.3      |
| Tumour serum markers                               |                               | X             |                                                       |                           |                   | X (g)                          |                   |                                         |                                                                    |           |
| Pregnancy test (serum)(a)                          |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Clinical disease assessment                        |                               |               | X                                                     |                           |                   | X                              |                   | X                                       | X                                                                  |           |
| Physical examination                               |                               | X             | X                                                     | X                         |                   | X                              | X                 | X                                       | X                                                                  |           |
| Height                                             |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Weight                                             |                               | X             | X                                                     |                           |                   | X                              |                   | X                                       | X                                                                  |           |
| Body surface area (BSA)                            |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    |           |
| Vital Signs                                        |                               | X             | X                                                     | X                         | X                 | X                              | X                 | X                                       | X                                                                  |           |
| ECOG performance status                            |                               | X             | X                                                     |                           | X                 | X                              | X                 | X                                       | X                                                                  |           |
| Laboratory tests: haematology and biochemistry (b) |                               | X             | X                                                     | X                         | X                 | X                              | X                 | X                                       | (j)                                                                | 3.9       |
| Urinalysis                                         |                               | X             |                                                       | X                         |                   | X                              | X                 | X                                       | (j)                                                                | 3.9       |
| Electrocardiogram (ECG)                            |                               | X             |                                                       | X                         |                   | X (g)                          |                   | (j)                                     |                                                                    |           |
| Echocardiogram / MUGA                              | X                             |               | To be repeated at 4 weeks, then every 8 weeks         |                           |                   |                                |                   |                                         |                                                                    |           |
| AZD6738 administration                             |                               |               | X                                                     | X                         |                   | X                              |                   |                                         |                                                                    |           |
| Plasma for AZD6738 pharmacokinetics (i)            |                               |               | X (i)                                                 | X (i)                     | X (i)             | X (i)                          |                   |                                         |                                                                    | 7.1       |
| Buffy coat storage                                 |                               | X             |                                                       |                           |                   |                                |                   |                                         |                                                                    | 12        |
| Plasma isolation and storage (k)                   |                               | X             |                                                       |                           | X                 |                                |                   | X                                       |                                                                    | 12        |
| Tumour biopsy (e)                                  |                               | X             |                                                       |                           | X (h)             |                                |                   |                                         |                                                                    | 12        |

(a) If the patient is a woman of child bearing potential.

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(c) Two-weekly follow-up for first 4 weeks, followed by 4 weekly follow-up, until resolution of all acute toxicity

(d) Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) that are present at time the patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.

(e) Tumour biopsy to be performed in those patients that consent at baseline

(f) Repeat radiological disease assessments every 8 weeks while on study

(g) Investigations to be repeated at start of each cycle (i.e. day 1)

(h) to be done once on day 15 or 22 (preferably day 15)

(i) Pharmacokinetics: after the first dose (day 0), samples will be taken pre-dose and at 15 and 30 minutes, 1, 2, 4, 8 and 24 hours. On day 15, samples will be taken pre-dose and at 15 and 30 minutes, 1, 2, 4, 8 and 10-12 hours. Subsequently pre-dose samples will be taken on day 29. See section 10.2.1.2

(j) Repeat if clinically indicated, to resolution or stabilisation of abnormalities

(k) plasma to be stored at baseline, day 15 and at progression, in responding participants

### 10.4.3 Part B: Dose expansion

| Observation/Investigation                          | Baseline/Pre-study                          |                            | Standard Evaluation for Treatment                     |                  |                   |                | Off treatment and Follow-up       |                                                          |                    | Refer to         |
|----------------------------------------------------|---------------------------------------------|----------------------------|-------------------------------------------------------|------------------|-------------------|----------------|-----------------------------------|----------------------------------------------------------|--------------------|------------------|
|                                                    | Within 4 weeks of IMP start                 | Within 7 days of IMP start | Day 1                                                 | Day 8, 15, 22    | Cycle 2 day 1 (g) | Cycle 2 Day 15 | Follow- up Weekly (first 4 weeks) | Follow-up: two-weekly (until resolution of toxicity) (c) | Survival Follow Up | Protocol section |
| Written informed consent                           | X                                           |                            |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Request archival tissue                            | X                                           |                            |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Demographics                                       |                                             | X                          |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Medical history                                    |                                             | X                          |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Adverse event evaluation                           | From date of pre-screening informed consent |                            | review at each attendance                             |                  |                   |                | X (c)                             | Until resolution (d)                                     |                    | 7.4              |
| Concomitant treatments                             |                                             | X                          | review at each attendance                             |                  |                   |                | X                                 | X                                                        |                    | 7.6, 18.5        |
| Radiological (CT, MRI, X-ray) disease assessment   | X                                           |                            | 8 weekly after commencement of continuous AZD6738 (f) |                  |                   |                |                                   |                                                          |                    | 18.3             |
| Tumour serum markers                               |                                             | X                          | X                                                     |                  | X (g)             |                |                                   |                                                          |                    |                  |
| Pregnancy test (serum) (a)                         |                                             | X                          |                                                       |                  | X (a)             |                | X(a)                              |                                                          |                    | 13.9             |
| Clinical disease assessment                        |                                             |                            | X                                                     |                  | X                 |                | X                                 | X                                                        |                    |                  |
| Physical examination                               |                                             | X                          | X                                                     | X                | X                 | X              | X                                 | X                                                        |                    |                  |
| Height                                             |                                             | X                          |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Weight                                             |                                             | X                          | X                                                     |                  | X                 |                | X                                 | X                                                        |                    |                  |
| Body surface area (BSA)                            |                                             | X                          |                                                       |                  |                   |                |                                   |                                                          |                    |                  |
| Vital Signs                                        |                                             | X                          | X                                                     | X                | X                 | X              | X                                 | X                                                        |                    |                  |
| ECOG performance status                            |                                             | X                          | X                                                     |                  | X                 | X              | X                                 | X                                                        |                    |                  |
| Laboratory tests: haematology and biochemistry (b) |                                             | X                          | X                                                     | X                | X                 | X              | X                                 | (j)                                                      |                    | 3.9              |
| Urinalysis                                         |                                             | X                          |                                                       |                  | X                 | X              | (j)                               | (j)                                                      |                    | 3.9              |
| Electrocardiogram (ECG)                            |                                             | X                          |                                                       |                  | X (g)             |                | (j)                               |                                                          |                    |                  |
| Echocardiogram / MUGA                              | X                                           |                            | repeated at 4 weeks, then every 8 weeks               |                  |                   |                |                                   |                                                          |                    |                  |
| AZD6738 administration (m)                         |                                             |                            | X                                                     | X                | X                 | X              |                                   |                                                          |                    | 7.1              |
| Plasma for AZD6738 pharmacokinetics (h,i)          |                                             | X                          |                                                       | X                |                   | X              |                                   |                                                          |                    | 11               |
| Buffy coat storage                                 |                                             | X                          |                                                       |                  |                   |                |                                   |                                                          |                    | 12               |
| Plasma isolation and storage (l)                   |                                             | X                          |                                                       | X                |                   |                | X                                 |                                                          |                    | 12               |
| Tumour biopsy (e)                                  | X                                           |                            |                                                       | X (h) (optional) |                   |                |                                   |                                                          |                    | 12               |
| PBMC and hair follicle                             |                                             | X                          |                                                       | X (h)            |                   | X              |                                   |                                                          |                    | 12               |
| Mortality                                          |                                             |                            |                                                       |                  |                   |                |                                   |                                                          | X                  |                  |

(a) If the patient is a woman of child bearing potential Monthly pregnancy test must be conducted (for female of childbearing potential) during treatment period (if the participant treatment schedule is longer than 1 cycle). A final pregnancy test must be conducted in all female participants of childbearing potential at the end of the relevant systemic exposure (5 half-lives after the last administration of AZD6738)

(c) Two-weekly follow-up for first 4 weeks, followed by 4 weekly follow-up, until resolution of all acute toxicity

(e) Fresh tumour biopsy will be mandatory in part B and repeat optional biopsy on treatment and at progression is desirable

(g) Investigations to be repeated at start of each cycle (i.e. day 1)

(i) pharmacokinetic samples in part B to be timed with PDc sampling as per section

(k) plasma to be stored at baseline, day 15 and at progression, in responding participants

(m) Administration dose and schedule of AZD6738 is determined by the SRC

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(d) Monthly follow-up required ONLY for those Aes and SAEs considered drug-related (highly probable, probable or possible) that are present at time the patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.

(f) repeat radiological disease assessments every 8 weeks while on study

(h) to be done once on day 15 or 22 (preferably day 15)

(j) Repeat if clinically indicated, to resolution or stabilisation of abnormalities.

## 10.4.4 Part C: Radiotherapy combination: 20 Gy cohorts

| Observation/Investigation                                 | Baseline/Pre-study            |                              | Standard Evaluation for Treatment                                                                       |                 |         |       |        | Off treatment and Follow-up       |                           |                               |                    | Refer to         |
|-----------------------------------------------------------|-------------------------------|------------------------------|---------------------------------------------------------------------------------------------------------|-----------------|---------|-------|--------|-----------------------------------|---------------------------|-------------------------------|--------------------|------------------|
|                                                           | Within 4 weeks(of IMP Start)  | Within 7 days (of IMP start) | Day -8 to -4                                                                                            | Day 1(RT start) | Day 1-5 | Day 8 | Day 15 | Follow- up Weekly (first 4 weeks) | Follow-up: two weekly (c) | Follow-up: 3, 6, 9, 12 months | Survival Follow up | Protocol section |
| Written informed consent                                  | X                             |                              |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Demographics                                              |                               | X                            |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Medical history                                           |                               | X                            |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Adverse event evaluation                                  | From date of informed consent |                              | review at each attendance                                                                               |                 |         |       |        | X                                 | X                         | X                             |                    | 7.4              |
| Concomitant treatments                                    |                               | X                            | review at each attendance                                                                               |                 |         |       |        | X                                 | X                         | X                             |                    | 7.6, 18.5        |
| Radiological (CT, MRI, X-ray) disease assessment          | X                             |                              | At the end of Week 4 after the end of radiotherapy. At the end of week 8 after the end of radiotherapy. |                 |         |       |        |                                   |                           |                               |                    | 18.3             |
| Tumour serum markers                                      |                               | X                            |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Pregnancy test (serum)(a)                                 |                               | X                            |                                                                                                         |                 |         |       |        | X (a)                             |                           |                               |                    | 13.9             |
| Clinical disease assessment                               |                               |                              | X                                                                                                       |                 |         |       |        | X (at 4 weeks)                    | X                         | X                             |                    |                  |
| Physical examination                                      |                               | X                            | X                                                                                                       | X               |         | X     | X      | X                                 | X                         | X                             |                    |                  |
| Height                                                    |                               | X                            |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Weight                                                    |                               | X                            | X                                                                                                       |                 |         | X     | X      | X                                 | X                         |                               |                    |                  |
| Body surface area (BSA)                                   |                               | X                            |                                                                                                         |                 |         |       |        |                                   |                           |                               |                    |                  |
| Vital Signs                                               |                               | X                            | X                                                                                                       | X               |         | X     | X      | X                                 | X                         | X                             |                    |                  |
| ECOG performance status                                   |                               | X                            | X                                                                                                       |                 |         |       | X      | X                                 | X                         | X                             |                    |                  |
| Laboratory tests: haematology and biochemistry (b)        |                               | X                            | X                                                                                                       | X               |         | X     | X      | X                                 | (h)                       | (h)                           |                    | 3.9              |
| Urinalysis                                                |                               | X                            |                                                                                                         | X               |         | X     | X      | X                                 | (h)                       | (h)                           |                    | 3.9              |
| Electrocardiogram (ECG)                                   |                               | X                            |                                                                                                         |                 |         |       |        |                                   | (h)                       |                               |                    |                  |
| Echocardiogram / MUGA                                     | X                             |                              |                                                                                                         |                 |         |       |        | at 4 weeks only                   |                           |                               |                    |                  |
| AZD6738 administration (j)                                |                               |                              | X                                                                                                       | X               | X       | X     | X      |                                   |                           |                               |                    | 7.1              |
| Radiotherapy (Monday-Friday only) (k)                     |                               |                              |                                                                                                         | X               | X       | X     |        |                                   |                           |                               |                    | 7.2              |
| Plasma for AZD 6738 pharmacokinetics (optional) (f)       |                               |                              |                                                                                                         |                 | X       |       |        |                                   |                           |                               |                    | 11               |
| Plasma isolation and storage (i)                          |                               | X                            |                                                                                                         |                 | X       |       |        |                                   |                           | X                             |                    | 12               |
| PBMC, hair follicles and skin punch biopsy (optional) (g) |                               | X                            |                                                                                                         | X               | X       |       |        |                                   |                           |                               |                    | 12               |
| Tumour biopsy (optional) (e)                              |                               | X                            |                                                                                                         |                 | X       |       |        |                                   |                           |                               |                    | 12               |
| Mortality                                                 |                               |                              |                                                                                                         |                 |         |       |        |                                   |                           |                               | X                  |                  |

(a) If the patient is a woman of child bearing potential. Monthly pregnancy test must be conducted (for female of childbearing potential) during treatment period (if the participant treatment schedule is longer than 1 cycle). A final pregnancy test must be conducted in all female participants of childbearing potential at the end of the relevant systemic exposure (5 half-lives after the last administration of AZD6738)

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(c) Monthly follow-up required ONLY for those Aes and SAEs considered drug-related (highly probable, probable or possible) that are present at time the patient comes off the trial. Monthly follow-up to continue until resolution, to baseline, stabilisation or patient starts another anti-cancer treatment.

(e) Tumour biopsy to be performed in those patients that consent at baseline and 1-2 hours post radiation on any of Days 1 to 5.

(f) Pharmacokinetic samples in part C to be timed with PDc sampling (pre-dose and post-dose to coincide with PDc sampling; not required if PDc samples not taken) as per section 10.2.3

(g) In consenting patients, hair follicle and skin punch biopsy and PBMC will be taken before fraction 1 and again before fraction 2 of radiotherapy (see section 12.1.3 for details).

(h) Repeat if clinically indicated, to resolution or stabilisation of abnormalities

(j) administration dose and schedule of AZD 6738 is determined by the SRC letter

(i) plasma to be stored at baseline, and at progression, in responding participants

(k) Radiation Therapy administration – 20 Gy in 10 fractions and sensitised with AZD6738

## 10.4.5 Part C: Radiotherapy combination: 30 Gy cohorts

| Observation/Investigation                             | Baseline/Pre-study          |                            | Standard Evaluation for Treatment                                                             |                   |         |       |          |            |           | Off treatment and Follow-up      |                           |                               |                    | Refer to         |
|-------------------------------------------------------|-----------------------------|----------------------------|-----------------------------------------------------------------------------------------------|-------------------|---------|-------|----------|------------|-----------|----------------------------------|---------------------------|-------------------------------|--------------------|------------------|
|                                                       | Within 4 weeks of IMP start | Within 7 days of IMP start | Day -8 to -4                                                                                  | Day 1 of RT start | Day 1-5 | Day 8 | Day 8-15 | Day 15, 22 | Day 15-19 | Follow-up Weekly (first 4 weeks) | Follow-up: two weekly (c) | Follow-up: 3, 6, 9, 12 months | Survival Follow up | Protocol section |
| Written informed consent                              | X                           |                            |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Demographics                                          |                             | X                          |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Medical history                                       |                             | X                          |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Adverse event evaluation                              | From date of consent        |                            | review at each attendance                                                                     |                   |         |       |          |            |           | X                                | Until resolution (c)      | X                             | X                  | 7.4              |
| Concomitant treatments                                |                             | X                          | review at each attendance                                                                     |                   |         |       |          |            |           | X                                | X                         | X                             |                    | 7.6, 18.5        |
| Radiological (CT, MRI, X-ray) disease assessment      | X                           |                            | At the end of Week 4 after the end of radiotherapy. At 8 weeks after the end of radiotherapy. |                   |         |       |          |            |           |                                  |                           |                               |                    | 18.3             |
| Tumour serum markers                                  |                             | X                          |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Pregnancy test (serum )(a)                            |                             | X                          |                                                                                               |                   |         |       |          |            |           | X (a)                            |                           |                               |                    | 13.9             |
| Clinical disease assessment                           |                             |                            | X                                                                                             |                   |         |       |          |            |           | X (at 4 weeks)                   | X                         | X                             |                    |                  |
| Physical examination                                  |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                                | X                         | X                             |                    |                  |
| Height                                                |                             | X                          |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Weight                                                |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                                | X                         |                               |                    |                  |
| Body surface area (BSA)                               |                             | X                          |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               |                    |                  |
| Vital Signs                                           |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                                | X                         | X                             |                    |                  |
| ECOG performance status                               |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                                | X                         | X                             |                    |                  |
| Laboratory tests: haematology and biochemistry (b)    |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                                | (h)                       | (h)                           |                    | 3.9              |
| Urinalysis                                            |                             | X                          |                                                                                               |                   |         | X     |          | X          |           | X                                | (h)                       | (h)                           |                    | 3.9              |
| Electrocardiogram (ECG)                               |                             | X                          |                                                                                               |                   |         |       |          |            |           | (h)                              |                           |                               |                    |                  |
| Echocardiogram / MUGA                                 | X                           |                            |                                                                                               |                   |         |       |          |            |           | X (at 4 weeks only)              |                           |                               |                    |                  |
| AZD6738 administration (j)                            |                             |                            | X                                                                                             | X                 | X       | X     | X        |            |           |                                  |                           |                               |                    | 7.1              |
| Radiotherapy (Monday-Friday only)                     |                             |                            |                                                                                               | X                 | X       | X     | X        |            | X         |                                  |                           |                               |                    | 7.2              |
| Plasma for AZD6738 pharmacokinetics (optional) (f)    |                             |                            |                                                                                               |                   | X       |       |          |            |           |                                  |                           |                               |                    | 11               |
| Plasma isolation and storage (i)                      |                             | X                          |                                                                                               |                   | X       |       |          |            |           |                                  | X                         | X                             |                    | 12               |
| PBMC, hair follicles and skin punch biopsy (optional) |                             | X                          |                                                                                               | X                 | X (g)   |       |          |            |           |                                  |                           |                               |                    | 12               |
| Tumour biopsy (e) (optional)                          |                             | X                          |                                                                                               |                   | X       |       |          |            |           |                                  |                           |                               |                    | 12               |
| Mortality                                             |                             |                            |                                                                                               |                   |         |       |          |            |           |                                  |                           |                               | X                  |                  |

(a) If the patient is a woman of child bearing potential. Monthly pregnancy test must be conducted (for female of childbearing potential) during treatment period (if the participant treatment schedule is longer than 1 cycle). A final pregnancy test must be conducted in all female participants of childbearing potential at the end of the relevant systemic exposure (5 half-lives after the last administration of AZD6738)

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(c) Two-weekly follow-up until resolution of acute toxicity. Monthly follow-up required ONLY for those AEs and SAEs considered drug-related (highly probable, probable or possible) that are present at the time that the patient comes off study. Monthly follow-up should continue until resolution to baseline, stabilisation or the patient starts another anti-cancer treatment. After this, patients will be assessed at 3, 6, 9 and 12 months for late toxicity

(e) Tumour biopsy to be performed in those patients that consent at baseline and 1-2 hours post radiation on any of Days 1 to 5.

(f) Pharmacokinetic samples to be timed with PDc sampling as per section 10.2.3

(g) In consenting patients, hair follicle and skin punch biopsy and PBMC will be taken before fraction 1 and again before fraction 2 of radiotherapy (see section 12.1.3 for details).

(h) Repeat if clinically indicated, to resolution or stabilisation of abnormalities

(i) plasma to be stored at baseline, and at progression, in responding participants

(j) Administration dose of AZD 6738 is determined by each dose escalation SRC letter

(k) Radiation Therapy administration – 30 Gy in 10 fractions sensitised with AZD6738

10.4.6 Part C: Radiotherapy combination: Expansion cohorts

| Observation/Investigation                             | Baseline/Pre-study          |                            | Standard Evaluation for Treatment: radiotherapy phase                                         |                   |         |       |          |            |           | Maintenance phase             |                | Off treatment and Follow-up       |                           |                               |                    | Refer to |
|-------------------------------------------------------|-----------------------------|----------------------------|-----------------------------------------------------------------------------------------------|-------------------|---------|-------|----------|------------|-----------|-------------------------------|----------------|-----------------------------------|---------------------------|-------------------------------|--------------------|----------|
|                                                       | Within 4 weeks of IMP start | Within 7 days of IMP start | Day -8 to -4                                                                                  | Day 1 of RT start | Day 1-5 | Day 8 | Day 8-15 | Day 15, 22 | Day 15-19 | Cycle 2 Day 1 (g)             | Cycle 2 Day 15 | Follow- up Weekly (first 4 weeks) | Follow-up (c): two-weekly | Follow-up: 3, 6, 9, 12 months | Survival Follow up |          |
| Written informed consent                              | X                           |                            |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               |                    |          |
| Demographics                                          |                             | X                          |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               |                    |          |
| Medical history                                       |                             | X                          |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               |                    |          |
| Adverse event evaluation                              | From consent                |                            | Review at each attendance                                                                     |                   |         |       |          |            |           |                               |                | X                                 | To resolution (c)         | X                             |                    | 7.4      |
| Concomitant treatments                                |                             | X                          | Review at each attendance                                                                     |                   |         |       |          |            |           |                               |                | X                                 | X                         |                               |                    | 7.6      |
| Radiological (CT, MRI, X-ray) disease assessment      | X                           |                            | At the end of Week 4 after the end of radiotherapy. At 8 weeks after the end of radiotherapy. |                   |         |       |          |            |           | 8 weekly while on maintenance |                |                                   |                           |                               |                    | 18.3     |
| Tumour serum markers                                  |                             | X                          |                                                                                               |                   |         |       |          |            |           | X                             |                |                                   |                           |                               |                    |          |
| Pregnancy test (serum)(a)                             |                             | X                          |                                                                                               |                   |         |       |          |            |           |                               |                | X (a)                             |                           |                               |                    | 13.9     |
| Clinical disease assessment                           |                             |                            | X                                                                                             |                   |         |       |          |            |           | X                             |                | X (at 4 weeks)                    |                           | X                             |                    |          |
| Physical examination                                  |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                             | X              | X                                 | X                         | X                             |                    |          |
| Height                                                |                             | X                          |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               |                    |          |
| Weight                                                |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                             | X              | X                                 | X                         |                               |                    |          |
| Body surface area (BSA)                               |                             | X                          |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               |                    |          |
| Vital Signs                                           |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                             | X              | X                                 | X                         |                               |                    |          |
| ECOG performance status                               |                             | X                          | X                                                                                             | X                 |         | X     |          | X          |           | X                             | X              | X                                 | X                         | X                             |                    |          |
| Laboratory tests: haematology and biochemistry (b)    |                             | X                          |                                                                                               | X                 |         | X     |          | X          |           | X                             | X              | X                                 | (j)                       | (j)                           |                    | 3.9      |
| Urinalysis                                            |                             | X                          |                                                                                               |                   |         | X     |          | X          |           | X                             | X              | X                                 | (j)                       | (j)                           |                    | 3.9      |
| Electrocardiogram (ECG)                               |                             | X                          |                                                                                               | X                 | X       | X     |          | X          |           | X                             | X              | (j)                               |                           |                               |                    |          |
| Echocardiogram / MUGA                                 | X                           |                            |                                                                                               |                   |         |       |          |            |           | Every 8 weeks                 |                |                                   |                           |                               |                    |          |
| AZD6738 administration (f)                            |                             |                            | X                                                                                             |                   |         |       |          |            |           | X (f)                         |                |                                   |                           |                               |                    | 7.1      |
| Radiotherapy (Monday-Friday only)                     |                             |                            |                                                                                               | X                 | X       | X     | X        |            | X         |                               |                |                                   |                           |                               |                    | 7.2      |
| Plasma for AZD6738 pharmacokinetics (optional)(h)     |                             |                            |                                                                                               | X                 | X       |       |          |            |           |                               |                |                                   |                           |                               |                    | 11       |
| Plasma isolation and storage (i)                      |                             | X                          |                                                                                               |                   | X       |       |          |            |           |                               |                |                                   | X                         | X                             |                    | 12       |
| PBMC, hair follicles and skin punch biopsy (optional) |                             | X                          |                                                                                               | X                 | X (i)   |       |          |            |           |                               |                |                                   |                           |                               |                    | 12       |
| Tumour biopsy (e) (optional)                          |                             | X                          |                                                                                               |                   | X       |       |          |            |           |                               |                |                                   |                           |                               |                    | 12       |
| Mortality                                             |                             |                            |                                                                                               |                   |         |       |          |            |           |                               |                |                                   |                           |                               | X                  |          |

(a) If the patient is a woman of child bearing potential. Monthly pregnancy test must be conducted (for female of childbearing potential) during treatment period (if the participant treatment schedule is longer than 1 cycle). A final pregnancy test must be conducted in all female participants of childbearing potential at the end of the relevant systemic exposure (5 half-lives after the last administration of AZD6738)

(b) 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. Blood results are required for safety monitoring, the same-day results are not required to allow ongoing dosing. Blood results from up to 96 hours prior may be used to authorise a new cycle of treatment.

(c) Two-weekly follow-up until resolution of acute toxicity. Monthly follow-up required ONLY for those Aes and SAEs considered drug-related (highly probable, probable or possible) that are present at the time that the patient comes off study. Monthly follow-up should continue until resolution to baseline, stabilisation or the patient starts another anti-cancer treatment. After this, patients will be assessed at 3, 6, 9 and 12 months for late toxicity

(e) Tumour biopsy to be performed in those patients that consent at baseline and 1-2 hours post radiation on any of Days 1 to 5.

(f) AZD6738 to be taken before, during, and after radiotherapy, cycle 1. AZD6738 ends day 21. And the Maintenance AZD6738 starts from day 22 (cycle 2, day 1) by the recommended dose schedule based on data collected in part A. The same investigation and monitoring schedule as part B after the completion of radiotherapy

(g) Investigations to be carried out at the start of each cycle

(h) Pharmacokinetic samples to be timed with PDc sampling as per section 10.2.3

(i) In consenting patients, hair follicle and skin punch biopsy and PBMC will be taken before fraction 1 and again before fraction 2 of radiotherapy (optional) (see section 12.1.3 for details).

(j) plasma to be stored at baseline, and at progression, in responding participants

(j) Radiation Therapy administration – 30 Gy in 15 fractions sensitised with AZD6738

## 11. Pharmacokinetic assessments

### 11.1. Sample Collection

Samples are collected at the time intervals presented in the protocol. Whole blood will be collected in 2 mL Vacutainer tubes containing K<sub>2</sub>EDTA as anti-coagulant for the analysis of AZD6738 and AZ13368982.

Following collection, gently invert the samples 8-10 times and immediately place on ice.

### 11.2. Sample Processing

Samples must be centrifuged within 30 minutes of blood collection. For full details, consult the laboratory manual.

#### 11.2.1 Labels

Pre-printed labels with a unique Custom ID will be used on all sample and aliquot tubes.

Information on PK labels:

Study, Subject ID, Custom ID, Period, Visit, Time Nominal, Analyte and Biological Matrix.

Example of a PK blood sample label:

D5330C00001

123567-1                      Prd:1

Subject                      001

Day 1                      Predose

Visit: 2

AZD6738 Plasma 1



1 2 3 4 5 6 7 8 9

### 11.3. Shipment Instructions

Ship the aliquots frozen on dry ice. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours.

Samples should be placed in a courier box with a paper copy of the Sample Inventory. Samples should be boxed up with each subject's samples in profile order and listed in the same order on the Sample Inventory for ease of checking at the bioanalytical laboratory.

Once the courier has collected the samples, the sample receiver at the bioanalytical laboratory should be notified via email of the courier name, airway bill number, expected delivery date/time and shipment contact. An electronic sample inventory (Excel format, Request file) should also be attached to this email. The CbioA Program Manager should be copied on this correspondence.

Samples will be analysed by Covance Bioanalytical Services. The contact details and addresses for sample shipment will be provided in Laboratory sample handling guide.

#### **11.4. Sample disposal**

Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR. Anonymised samples will be retained for no more than 5 years after the CSR is finalised.

Incurring sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

## **12. Pharmacodynamic and Genetic Assessments**

### **12.1. Sample collection for pharmacodynamic biomarkers:**

Serial hair follicles and blood samples for preparation of peripheral blood mononuclear cells (PBMC) (as surrogate tissues for drug effect) will be obtained from consenting patients. If possible, paired tumour biopsies will be obtained before and during drug treatment. Samples will be taken, stored and subsequently processed and analysed according to standard operating procedures written by The Institute of Cancer Research. ICR GCLP laboratories will use validated assays in the ICR GCLP laboratories to measure drug-on-target effect (inhibition of Chk1 phosphorylation) and  $\gamma$ H2AX and Rad51foci (by confocal microscopy using digital imageQuant and ELISA) in tumour and normal tissue (skin/mucosa, hair follicles, PBMC), before treatment, after drug treatment and after drug plus radiation treatment. These studies will provide proof-of-mechanism data for the ability of the drug to modulate the target (inhibition of Chk1 phosphorylation) and, in the case of drug plus radiation combinations, proof-of-concept data for the approach of using ATR inhibition to maintain radiation-induced DNA double-strand breaks ( $\gamma$ H2AX assays).

Associations between pharmacodynamic data and drug/radiation dose and the number of sensitised fractions will be explored during the dose escalation and expansion phases of the study. Similarly, associations between pharmacodynamic and functional imaging data (see below) will be explored.

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

#### **12.1.1 Peripheral blood sampling (PBMC)**

10 mL of blood will be collected into CPT tubes for PDc analysis at the following time points:

Parts A and B

Baseline (once eligibility has been confirmed)

Once on day 15 – 22 (cycle 1) and once on day 15 (cycle 2)

Part C (optional)

Baseline (once eligibility has been confirmed)

After starting AZD6738, prior to first radiation fraction

Prior to second radiation fraction (16-24 hours after first fraction)

The approximate volume of blood drawn for PDc analysis will be 20 mL in parts A and B and 30 mL in part C.

Samples must be centrifuged within 30 min of sample collection. See laboratory manual for further information about sample handling.

### **12.1.2 Hair follicle collection**

Hair follicle samples will be collected at the following time points:

Parts A and B

Baseline (once eligibility has been confirmed)

Once on day 15 – 22 (cycle 1) and once on day 15 (cycle 2)

Part C (optional)

Baseline (once eligibility has been confirmed)

After starting AZD6738, prior to first radiation fraction

Prior to second radiation fraction (16-24 hours after first fraction)

At each time point the investigator or designee will pluck a minimum of eight hairs (eyebrow or head) with tweezers. Each hair should be checked by eye to ensure that a follicle bulb is present. The hairs will be placed bulb first into 10% formal saline for 30 minutes and then stored in 4% saline at 4 degrees until shipment. See the laboratory manual for full details.

### **12.1.3 Skin punch biopsies**

Optional skin punch biopsies will be taken at the following time points in Part C only:

Baseline (once eligibility has been confirmed)

After starting AZD6738, prior to first radiation fraction

Prior to second radiation fraction (16-24 hours after first fraction)

All skin biopsies will be taken from the irradiated volume where possible. If not possible, the baseline biopsy can be taken from skin over the forearm or back of the hand. The biopsies prior to first and second fractions of radiotherapy should both be from the irradiated volume.

The area to be biopsied will be cleaned and a local anaesthetic (lignocaine) applied. A Steifel biopsy punch (1-2 mm) should be used for taking the biopsies.

The punch biopsies will be processed as described in the laboratory manual.

### **12.1.4 Tumour biopsies**

Patients whose tumours are easily and safely amenable to biopsy will be asked to consent to a tumour biopsy prior to therapy (baseline) and a second biopsy during drug treatment (on day 15 or 22, parts A and B) or prior to the second fraction of radiotherapy (part C). Patients on Part B will also be asked to consent to a further biopsy at progression.

The baseline biopsy is mandatory in Part B and optional during treatment and at progression. All biopsies are optional in Parts A and C.

Tumour biopsies will be immediately snap frozen in liquid nitrogen then stored frozen at -80 °C until shipment.

## **12.2. Genetic assessments**

During part B, tumour tissue may be analysed for mutation in DNA damage response genes prior to study entry. This analysis may also be performed retrospectively during other parts of the study, to clarify markers of sensitivity to AZD6738, once participants have been taking study medication. Additionally, plasma and normal tissue (buffy coats from blood) will be stored for all patients entering the study, which may be used for DNA sequencing or other purposes. Normal tissue may be used for germline DNA sequencing to identify tumour-specific mutations, which may be linked to tumour response. Germline studies may identify mutations that are potentially significant to participants or their families. These will be disclosed to participants if they are of clinical significance for the participant or their family, unless participants specify on the informed consent form that they do not wish to be informed. In the event that a potentially significant germline mutation is found, the participant will be referred to the local clinical genetics unit, who will oversee the validation of results and subsequent management.

## **13. ASSESSMENT OF SAFETY**

### **13.1. Adverse event definitions**

#### **13.1.1 Adverse event**

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

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.
- Aes occurring from lack of efficacy of an IMP, for example, if the Investigator suspects that a drug batch is not efficacious or if the Investigator suspects that the IMP has contributed to disease progression.

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 RM-CTU in the same timelines as an SAE. These should be reported even if the patient is withdrawn from the trial.
- Overdose or inadvertent or accidental exposure to an IMP with or without an AE.
- Any AE that could be related to the protocol procedures, and which could modify the conduct of the trial.

#### **13.1.2 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 13.5.1);
- 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 one of the outcomes listed above.

For screening failures, serious adverse events (SAEs) will be reported to the RM-CTU from the date of consent until the date the patient is confirmed as ineligible. For eligible patients, 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 up

to 3 months after the last administration of AZD6738. 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. The reporting of SAE is not required for participants in the pre-screening part of the study, who have not yet signed the main consent form.

## 13.2. Determining adverse event causality

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

### Definite

- 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 definite.

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.

## 13.3. Expectedness

Assessment of expectedness for AZD6738 will be made against the Reference Safety Information in the latest version of the Investigator Brochure, Table 22 in section 5.6. This section lists the adverse reactions regarded as expected for safety reporting purposes (Reference Safety information).

. If updated versions of the investigator brochure are released during the course of the trial they will be assessed for any changes to this reference Safety Information, and assessment of expectedness will be made against the updated version after approval by the MHRA.

### **13.4. 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 Investigator and study team will rapidly report all SUSARs to the RM-CTU within 24 hours of becoming aware of the event. The RM-CTU will ensure that the RM R&D department, the MHRA and main REC are notified within the timelines specified in legislation (SI 2004/1031 as amended).

### **13.5. Expedited reporting of serious adverse events**

All SAEs, regardless of causality, must be reported to RM-CTU within 24 hours of knowledge of the event. SAEs should be documented on an SAE report form, using the completion guidelines provided. This form should be sent to:

Each episode of an SAE must be recorded on a separate SAE report form. The NCI CTCAE Version 4.03 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 RM-CTU on a new SAE report form. If the SAE has not been reported within the specified timeframes, a reason for lateness must be included when sending the SAE report form. Should the Investigator become aware of any drug-related SAEs after the patient goes 'off study', these must also be reported within the specified timelines above.

#### **13.5.1 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).

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, or to facilitate study procedures such as pharmacokinetic sampling according to the trial protocol, is also exempt from being reported as an SAE.

### **13.6. 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.

### **13.7. 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. Requested follow-up information should be reported to the RM-CTU 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.

### **13.8. 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 Sponsor immediately

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 Main REC within three days of USM initiation. The sponsor will distribute the response and any subsequent amendments to the trial sites.

CI Contact Details:

### **13.9. Pregnancy**

The Investigator must make every effort to try and ensure that a clinical trial patient or their partner does not become pregnant during the trial or for six months afterwards. This should be done and documented 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. Patients should be aware that any method that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
- transdermal progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner

- sexual abstinence

Contraceptives should be used for four weeks before the start of treatment, throughout the trial and for six months after completing the trial.

It should be explained to male patients that if his partner is able to become pregnant, is pregnant or breast-feeding when he enters the trial, he should use barrier method contraception (condom plus spermicidal gel) to prevent exposure to AZD6738. Male subjects must abstain from sperm donation during exposure to AZD6738 and 6 months thereafter. Female partners of male participants will be required to use highly effective methods of contraception as detailed for female participants. 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 or within six months of last IMP administration must be reported to the sponsor 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 pregnancy outcome must be reported to RM-CTU, using a Pregnancy Outcome 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 within 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.

## **14. Assessment of anti-tumour activity**

RECIST 1.1 criteria will be used to assess patient response to treatment by determining objective response rates. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (complete response, partial response, stable disease or progression of disease) are presented in Appendix 3.

The methods of assessment of tumour burden used at baseline CT or MRI scans of the chest, abdomen and pelvis must be used at each subsequent follow-up assessment (see schedule of events, section 10.4 for information on scheduling).

## **15. Statistical considerations**

### **15.1. General considerations**

This is an open-label, dose-escalating, non-randomised, multi-centre phase I study of continuous twice-daily oral administration of AZD6738 as a single agent and in combination with 2 schedules of palliative radiotherapy. The study will proceed in 3 separate parts. In part A, dose escalation will proceed to establish MTD, pharmacokinetic data and relate this to pharmacodynamic data from tumour and normal tissues. In part B, a number of dose schedules will be tested and the patient population will be enriched for p53 pathway abnormality in tumour tissue. In part C, AZD6738 will be combined with 2 schedules of palliative radiotherapy, toxicity and pharmacodynamic data in irradiated and un-irradiated tumour and normal tissue will be examined. Parts A and B will continue until toxicity or disease progression; part C will be confined to dosing before, during and after the course of radiotherapy, with expansion cohorts at the recommended phase 2 dose continuing maintenance AZD6738 until disease progression or unacceptable toxicity.

### **15.2. Definition of study endpoints**

#### **15.2.1 Primary endpoints**

1. Identifying the maximum tolerated dose (MTD) of AZD6738 as a single-agent;
2. Identifying the maximum tolerated dose (MTD) of AZD6738 in combination with palliative radiation schedules. It is possible that different MTDs may be reached in the parallel head and neck/thoracic and abdomino-pelvic studies.

#### **15.2.2 Secondary endpoints**

1. Determining causality of each adverse event in relation to AZD6738 and grading severity according to CTCAE version 4.03;
2. Single and multiple dose pharmacokinetics: measurement of plasma levels of AZD6738 at pre-defined intervals in the dose-escalation part of the study in order to establish pharmacokinetic parameters;
3. Any response (stable disease, partial response or complete response) in any of the patients by physical, tumour marker and/or radiographic assessments of tumours as determined by RECIST 1.1.

#### **15.2.3 Exploratory endpoints**

1. Measurement of pharmacodynamic biomarkers (e.g. pChk1, gamma-H2AX and Rad51) before and during treatment including PBMC, surrogate tissues (e.g. hair follicle) and in selected populations fresh tumour and normal tissue biopsies (within the irradiated volume for radiation cohorts), explore association with biomarker data and treatment response by RECIST
2. Correlation of multi-parametric MRI data with tissue biomarkers, and volumetric tumour response;
3. Predictive biomarkers evaluated in archival tissue.

### 15.3. Sample size

The sample size for this phase 1 trial is not based on a formal sample size calculation, as no formal statistical hypothesis is being tested. The total number of patients has been based on the desire to obtain adequate tolerability, safety, pharmacokinetic and pharmacodynamic data while exposing as few patients as possible to the IMP and procedures. The total number of patients required will depend upon the toxicities encountered and the number of dose cohorts required.

In Part A: The minimum number of patients will be 3, if there are 2 DLTs at the starting dose of 20mg BD. The maximum number of patients is expected to be 42, if 1 DLT is experienced at each of 7 dose levels, with 6 patients treated per dose level.

In Part B: the total number of patients will vary depending upon the number of patients who are identified as marker positive or negative. Recruitment may continue until a maximum of 50 patients have been recruited, or the study is closed. Response rates and duration of response will be analysed for patients with absence or presence of emerging putative markers of sensitivity to ATR inhibition.

In Part C: The minimum number of patients will be 3 in the head and neck / thoracic and 3 in the abdomen / pelvis cohorts, if there are 2 DLTs at the starting dose. If there is 1 DLT at each of 5 dose levels, with 6 patients treated per dose level and an additional 6 patients in the expansion cohort, there will be a maximum of 36 patients in each arm or 72 in part C.

### 15.4. Statistical analysis

All quantitative data will be presented as number of observations, mean, standard deviation, minimum and maximum values. Qualitative data will be presented as number of observations and percentages. When appropriate, data will be presented together with 95% confidence intervals.

**Toxicity:** The number and percentage of patients experiencing DLT or non-DLT toxicity in each dose level will be tabulated and the number of cohorts recruited will be recorded. Acute and late toxicity data will be tabulated by grade. Number and proportion of toxicity grades 1-4 and grade 3-4 will be reported.

**PD:** Pharmacodynamic data will consist of identifying differences in Chk1 phosphorylation and Rad51 and gamma-H2AX focus level before and during therapy.

**PK:** Pharmacokinetic parameters will be derived from sample data including peak plasma concentration ( $C_{max}$ ), minimum plasma concentration ( $C_{min}$ ) time to reach  $C_{max}$  ( $T_{max}$ ), elimination half-life ( $T_{1/2}$ ), area under the curve (AUC). In addition, comparison between single dose and multi-dose PK parameters will be made for assessment of steady-state drug accumulation.

**Response evaluation:** The response evaluation as determined by RECIST criteria will be presented as proportions and will also be displayed against the change in tumour size by waterfall plot. Part A and B have response assessment every 8 weeks (2 cycles), the first response assessment is therefore at 8 weeks, and they continue after that at 8 weekly intervals unless there is clinical measurable progression or toxicity. For part C, CT scan at 8 weeks after the end of radiotherapy is used to confirm

the response. The association of pChk1 levels, Rad51 and gamma-H2AX focus level with treatment response by RECIST will be explored.

**MRI evaluation:** The change in Apparent Diffusion Coefficient (ADC), and the volume transfer constant ( $K_{trans}$ ) between the same region of interest on the baseline and on-treatment multi-parametric MRI will be presented in absolute and percentage terms. The association of functional imaging parameters with treatment response (by RECIST) and pharmacodynamic biomarkers will be explored.

**Part A:** The toxicity, PK and PD parameters, response and association of the MRI data with the tumour response will also be evaluated as stated above.

**Part B:** The toxicity, PK and PD parameters, response and association of the MRI data with the tumour response will also be evaluated as stated above for each dose schedule separately.

**Part C:** The toxicity, PK and PD parameters, response and association of the MRI data with the tumour response will also be evaluated as stated above for each arm separately for each dose level. In the 30 Gy cohorts, all the above parameters will be reported at different radiotherapy levels.

**Expansion cohorts:** The toxicity, PK and PD parameters, response and association of the MRI data with the tumour response will be combined with the data from the selected dose and evaluated as stated above for each arm separately.

#### **15.4.1 Timing of analyses**

Toxicity data will be reviewed by the Safety Review Committee (SRC) prior to any decision regarding dose escalation or opening of new dose cohorts. The data required by the SRC to enable it to make such decisions is detailed in the SRC Charter.

For parts A, B and C, the end of study is the completion of the treatment or after 6 cycles of treatment. For Part C, the data can be analysed after 3 months of completion of radiotherapy for acute toxicities and after 1 year of completion of radiotherapy for long term toxicities in all the surviving patients.

## **16. ADMINISTRATION**

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

### **16.1. Protocol deviations and amendments**

Amendments to the protocol may only be made with the approval of the sponsor, CI and statistician. A protocol amendment will be subject to review by the sponsor before obtaining relevant approvals. Ethics Committee favourable opinion (and MHRA approval if appropriate) will be obtained by the CI before the amendment can be distributed to sites and implemented.

### **16.2. Completion of the electronic case report form (eCRF)**

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 completed the Study Team Responsibilities Signature Log/Delegation Log as authorised by the PI, should enter or change data in the eCRFs. All protocol required investigations must be reported in the eCRF. The Investigators must retain all original reports, traces and images from these investigations for future reference. The data will be entered in a clinical trials database (Macro V4).

Authorised site personnel may enter study-specific data directly into eCRFs, this includes but is not limited to vital signs. The eCRF will be signed electronically by the Investigator or by an authorised staff member. Study specific information will be entered into an eCRF visit by visit. Data that are derived should be consistent with the source documents or the discrepancies should be explained. All eCRF data should be anonymous, *i.e.* identified by study patient number only.

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 at the CTU.

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

### **16.3. Trial performance and monitoring**

#### **16.3.1 Management of the study**

The RM-CTU will be responsible for the day-to-day coordination and management of the trial. This includes all duties relating to pharmacovigilance in accordance with section 13. The RM-CTU in collaboration with ICR-CTSU will act as custodian of the eCRF data on behalf of the sponsor.

Before the trial can be initiated, the prerequisites for conducting the trial must be clarified and the organisational preparations made with the trial centres. The sponsor

must be informed immediately of any change in the personnel involved in the conduct of the trial.

During the trial the RM-CTU is responsible for monitoring data quality in accordance with relevant 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 sponsor to:

- review trial records and compare them with source documents;
- check pharmacodynamic samples and storage;
- discuss the conduct of the trial and any 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 supplies must be returned to Fisher Clinical Services or destroyed at the Investigator site by an authorised person who will provide signed confirmation of destruction.

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

### **16.3.2 Source document verification**

Unless agreed in writing, all data collected in the eCRF must be verifiable by the source data. Therefore it is the Investigator's responsibility to ensure that all relevant data is clearly recorded in the medical records. The Investigator must allow the RM-CTU 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 trial source data using a risk-based approach and the verification will be documented in the monitoring report.

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

### **16.3.3 Clinical study report**

All clinical data will be presented at the end of the trial on final data listings. The CI, along with sponsor-appointed statistician will prepare a clinical study report based on the final data listings. The report will be submitted to the Investigator(s) and The Royal Marsden NHS Foundation Trust / Institute of Cancer Research (sponsor) for review. A summary of the final clinical report must be provided by the sponsor to the MHRA and to the Research Ethics Committee.

### **16.3.4 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 (as 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 sponsor.

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. Records must be retained for a minimum of 5 years after study conclusion.

#### **16.4. Ethical considerations**

Before starting the trial, the protocol, patient information sheet and consent form must be approved by the RM/ICR joint Committee for Clinical Research. Once approved, the study may then be submitted to the relevant regulatory authorities.

It is the Chief/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 Chief/Principal Investigator must ensure this is documented in the patient's medical notes and the patient is re-consented, where appropriate.

The Sponsor and Chief/Principal Investigator 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).

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## 18. Appendices

### 18.1. Appendix 1: Published pre-clinical data

**Table 3: Published data showing radiosensitisation of solid tumour cell lines by ATR inhibition *in vitro***

| Author       | ATR Inhibitor | Cell Line                                                                                                                                                                                                                      |
|--------------|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pires[24]    | VE-821        | Colorectal (RKO, HCT116, DLD1)<br>Osteosarcoma (U2OS)<br>Glioblastoma (MG-U87)<br>Breast (MDA-MB-231, MDA-MB-468)<br>Bladder (VmCub1)<br>Cervical (HeLa)<br>Melanoma (SKmel28, IGR39)<br>Renal (RCC4)<br>Head and neck (SQ20B) |
| Fokas[25]    | VE-822        | Pancreas (MiaPaCa-2, PSN-1, PancM)                                                                                                                                                                                             |
| Peasland[26] | NU6027        | Breast (MCF7)                                                                                                                                                                                                                  |
| Prevo[27]    | VE-821        | Pancreas (MiaPaCa-2, PSN-1, PancM)                                                                                                                                                                                             |

**Table 4: Published data showing radiosensitisation by ATR inhibition *in vivo***

| Author    | ATR Inhibitor | Cell Line                                                 |
|-----------|---------------|-----------------------------------------------------------|
| Fokas[25] | VE-822        | Pancreas (MiaPaCa-2, PSN-1);<br>subcutaneous in nude mice |

## **18.2. Appendix 2: Common Terminology Criteria for Adverse Events (CTCAE) Version 4**

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 4.03 for toxicity and Serious Adverse Event reporting.

A copy of the CTC Version 4.03 can be downloaded from the NCI home page <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>

All appropriate treatment areas should have access to a copy of the CTC Version 4.03. met.

### **18.3. Appendix 4: LENT-SOMA Scales for all Anatomical Sites**

This study will utilize the LENT SOMA radiation toxicity grading system (Int. J. Radiation Oncology Biol. Phys., Vol. 31, No. 5, 1049-1091, 1995).

All appropriate treatment areas should have access to a copy of the LENT SOMA scoring system.

## 18.4. Appendix 5: Abbreviated list of Medications not to be co-prescribed with AZD6738

Some may be cautions rather than prohibitions: see protocol for full details

|                   |                |
|-------------------|----------------|
| Alfentanil        | Itraconazole   |
| Aprepitant        | Ketoconazole   |
| Atorvastatin      | Lovastatin     |
| Azithromycin      | Modafinil      |
| Bosentan          | Ofloxacin      |
|                   | Olmesartan     |
|                   | Phenobarbital  |
| Carbamazepine     | Phenytoin      |
| Caspofungin       | Pimozide       |
| Cimetidine        | Posaconazole   |
| Ciprofloxacin     | Pravastatin    |
| Cisapride,        |                |
| Clarithromycin    | Quinidine      |
| Clotrimazole      | Ranolazine     |
| Cyclosporine      | Repaglinide    |
| Dexamethasone     | Rifabutin      |
| Dihydroergotamine | Rifampicin     |
| Diltiazem         | Rosuvastatin   |
| Dronedarone       | Simvastatin    |
| Enalapril         | Sirolimus,     |
| Ergotamine        | St John's Wort |
| Erythromycin      | Tacrolimus     |
| Fentanyl          | Telithromycin  |
| Fexofenadine      | Telmisartan    |
| Fluconazole       | Terfenadine    |
| Fluvastatin       | Ticagrelor     |
| Fluvoxamine       | Tolvaptan      |
| Ginkgo            | Valsartan      |
| Glibenclamide     | Verapamil      |
| Grapefruit juice  | Voriconazole   |

## 18.5. Appendix 6: Drugs prolonging the Q-T interval

These should be used with caution, see section 7.6.3.5. This list is not exhaustive.

**Antimicrobials:** erythromycin, clarithromycin, moxifloxacin, fluconazole, ketoconazole

**Antiarrhythmics:** dronedarone, sotalol, quinidine, amiodarone, flecainide

**Antipsychotics:** risperidone, fluphenazine, haloperidol, pimozide, chlorpromazine, quetiapine, clozapine

**Antidepressants:** citalopram, escitalopram, amitriptyline, clomipramine, dosulepin, imipramine, lofepramine

**Antiemetics:** domperidone, droperidol, ondansetron, granisetron