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Phase I trial of the MEK inhibitor selumetinib in combination with thoracic radiotherapy in non-small cell lung cancer

K. Haslett [a], P. Koh [b,c], A. Hudson [a], W.D. Ryder [b], S. Falk [a], D. Mullan [a], B. Taylor [a], R. Califano [a,b], F. Blackhall [a,b,1], C. Faivre-Finn [a,b,*,1]

[a] The Christie NHS Foundation Trust, United Kingdom
[b] University of Manchester, United Kingdom
[c] New Cross Hospital, United Kingdom

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ABSTRACT

Background: The RAS/RAF/MEK/ERK signalling pathway has a pivotal role in cancer proliferation and modulating treatment response. Selumetinib inhibits MEK and enhances effects of radiotherapy in pre-clinical studies.

Patients and methods: Single-arm, single-centre, open-label phase I trial. Patients with stage III NSCLC unsuitable for concurrent chemo-radiotherapy, or stage IV with dominant thoracic symptoms, were recruited to a dose-finding stage (Fibonacci 3 + 3 design; maximum number = 18) then an expanded cohort (n = 15). Oral selumetinib was administered twice daily (starting dose 50 mg) commencing 7 days prior to thoracic radiotherapy, then with radiotherapy (6–6.5 weeks; 60–66 Gy/30–33 fractions). The primary objective was to determine the recommended phase II dose (RP2D) of selumetinib in combination with thoracic radiotherapy.

Results: 21 patients were enrolled (06/2010–02/2015). Median age: 62y (range 50–73). M:F ratio 12 (57%):9(43%). ECOG PS 0:1, 7(33%):14(67%). Stage III 16(76%); IV 5(24%). Median GTV 64 cm^3 (range 1–224 cm^3). 15 patients comprised the expanded cohort at starting dose. All 21 patients completed thoracic radiotherapy as planned and received induction chemotherapy. 13 (62%) patients received the full dose of selumetinib.

In the starting cohort no enhanced radiotherapy-related toxicity was seen. Two patients had dose-limiting toxicity (1x grade 3 diarrhoea/fatigue and 1x pulmonary embolism). Commonest grade 3–4 adverse events: lymphopaenia (19/21 patients) and hypertension (7/21 patients). One patient developed grade 3 oesophagitis. No patients developed grade ≥3 radiation pneumonitis. Two patients were alive at the time of analysis (24 and 26 months follow-up, respectively). Main cause of first disease progression: distant metastases ± locoregional progression (12/21 [57.1%] patients). Six patients had confirmed/suspected pneumocystis jiroveci pneumonia.

Conclusion: We report poor outcome and severe lymphopenia in most patients treated with thoracic radiotherapy and selumetinib at RP2D in combination, contributing to confirmed/clinically suspected pneumocystis jiroveci pneumonia. These results suggest that this combination should not be pursued in a phase II trial.

ClinicalTrials.gov reference: NCT01146756.

1. Introduction

Lung cancer is the most common cancer globally. The majority of patients are not suitable for surgery for medical or technical reasons and radiotherapy (RT) is often the only curative treatment technically possible. Unfortunately, in these circumstances, the prognosis is often very poor, partly due to the radioresistance of NSCLC. Relapse within the RT field is common and generally these patients cannot be cured. Recent technological advances have permitted higher RT doses to be delivered to tumours. However, as observed in the RTOG 0617 study, higher RT doses (beyond the standard of care of 60 Gy) are associated with worse outcomes in locally advanced NSCLC, likely due to poorer survival from excess cardiac toxicity [1]. It is therefore postulated that selective biolog-

* Corresponding author at: The Christie NHS Foundation Trust, United Kingdom.
E-mail address: Corinne.Finn@nhs.net (C. Faivre-Finn).
[1] Joint last authors.

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ical manipulation of the tumour to make it more radiosensitive may be the best approach to improve outcomes for locally-advanced NSCLC.

There is a preclinical rationale supporting the enhancement of the efficacy of RT by targeted drug through five exploitable radiobiological mechanisms [2–5]. However previous early-phase RT combination studies with targeted agents in lung cancer have demonstrated variable outcomes. Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors, as the most frequently used targeted agents in NSCLC, have the most clinical trial and real-world experience in combination with RT [6,7]. Generally, they are well tolerated when given concurrently with thoracic RT. One study in poor prognosis patients with locally advanced NSCLC demonstrated additional toxicity with erlotinib and radical dose RT but this was not reported in other studies [8]. Unfortunately, survival figures in phase II studies have been disappointing, most likely due to the small proportion of patients with EGFR mutations in trials of predominantly non-Asian patients, with no selection for specific driver mutations. Studies in populations enriched for EGFR mutation suggest some benefit for combination of EGFR inhibition and RT [9].

Overall these data are suggestive that if known actionable mutations can be targeted then there may be survival benefit from combining targeted agents with RT. The limiting factor is that approximately half of NSCLC cases have no known actionable mutations. MEK inhibition is an attractive target for combination studies as it lies downstream of a number of frequently identified oncogenic mutations in NSCLC including KRAS, EGFR, BRAF, and MEK1 itself. Whilst there are many MEK inhibitors at different stages of development, selumetinib has been the most investigated in NSCLC, although there is conflicting data regarding its benefit in addition to chemotherapy. Preclinical studies suggest a radiosensitising effect from MEK inhibition [10,11].

Our study is the first to our knowledge to evaluate the safety of combining MEK inhibition using selumetinib with radical dose thoracic RT for NSCLC.

2. Materials and methods

2.1. Study overview

This study was a prospective, single-arm, single-centre, open-label phase I trial of concurrent selumetinib with thoracic RT. Recruitment to a dose-finding stage using a Fibonacci 3 + 3 design (maximum number = 18) to evaluate safety and tolerability of selumetinib was followed by recruitment of an expanded cohort (n = 15). Oral selumetinib was administered as a single agent twice daily commencing 7 days prior to RT, then in combination with thoracic RT for 6–6.5 weeks (60–66 Gy in 30–33 fractions). Selumetinib was then stopped on the final day of RT.

Participants gave written informed consent and the study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines. The trial was a granted ethics committee approval on 31/12/2009. Patients gave consent for surplus tumour tissue taken at diagnosis to be analysed in the study.

2.2. Patients

Patients were eligible if they were ≥18 years of age, with histological or cytological confirmation of NSCLC, either inoperable stage III or stage IV (TNM classification, 7th edition) with dominant chest symptoms, and previously untreated by RT or investigational agents. Prior chemotherapy was permitted provided the interval of day 8 of the last cycle of chemotherapy and day 1 of selumetinib dosing was ≥2 weeks. Thoracic disease needed to be encompassable within a radical RT treatment volume. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, Medical Research Council (MRC) dyspnoea score ≤2 and a life expectancy of >3 months. Additional inclusion criteria were: forced expiratory volume in one second (FEV1) and gas transfer factor for carbon monoxide (DLCO) both >40% of predicted, left ventricular ejection fraction (LVEF) >50% on baseline echocardiogram, glomerular filtration rate (GFR) >50 ml/min, white cell count >3 × 10^9/l, neutrophil count 1.5 × 10^9/l, haemoglobin 10.0 g/dl and platelet count >100 × 10^9/l, aspartate aminotransferase (AST) / alanine aminotransferase (ALT) < 2.5 × upper limit of normal (ULN) and bilirubin < 1.5 × ULN. Exclusion criteria included: mixed non-small cell and small cell tumours, presence of clinically significant fluid accumulations in the third spaces which could not be adequately drained prior to study inclusion, history of interstitial pneumonitis, uncontrolled diabetes, hypertension defined as a systolic blood pressure ≥160 or diastolic blood pressure ≥100 (antihypertensive medication was permitted to achieve the parameters), myocardial infarction, or unstable or uncontrolled angina, congestive heart failure within 1 year of enrolment, major surgery within 4 weeks, and known brain metastases (brain imaging was not mandatory if asymptomatic).

2.3. Study design

Screening and baseline assessments were included in the pre-treatment evaluation on all patients within 21 days prior to trial entry (e.g. history, examination, electrocardiogram (ECG), echocardiogram, ophthalmic evaluation), computed tomography (CT) scan and pulmonary function tests within 28 days and baseline bloods within 24 h of starting selumetinib.

2.3.1. Selumetinib

The recommended phase II dose of selumetinib as a monotherapy is 75 mg twice daily. The aim of the study was to determine the recommended phase II dose of selumetinib in combination with standard dose thoracic RT. Using the modified Fibonacci scheme each cohort contained 3 to 6 patients. The initial dose of selumetinib was 50 mg twice daily (starting cohort), with the intention to escalate to a maximum dose of 75 mg twice daily or de-escalate to a dose of 75 mg once daily (Table 1). Oral selumetinib was administered as a single agent twice daily commencing 7 days prior to RT, then in combination with thoracic RT for 6 – 6.5 weeks (60–66 Gy in 30–33 fractions); the drug was then stopped on the final day of RT.

2.3.2. Thoracic RT

The first fraction of RT was delivered 7 days after the first dose of selumetinib. The minimum interval between the last chemotherapy administered and the first day of RT was 14 days. A total RT dose of 60–66 Gy was delivered in 30–33 fractions, 2 Gy per fraction, over 40–45 days. The gross tumour volume (GTV) was defined as residual tumour (minimum of 2 cm in the expanded cohort) and involved lymph nodes (nodal involvement on CT defined as pre-chemotherapy nodes >1 cm in short axis). The clinical target volume (CTV) was defined as the GTV plus a 0.5 cm margin in all directions. The CTV to planning target volume (PTV) expansion followed standard departmental protocols accounting for the use of 3D or 4DCT (e.g. 3D-CT 1.3 cm margin superiorly and inferiorly, and 1.0 cm margin laterally, at the 95% isodose, for 4D-CT 0.9 cm margin superiorly and inferiorly, and 0.7 cm margin laterally). Prophylactic nodal irradiation was not permitted. Patients could be treated with either 3D conformal RT or intensity modulated radiotherapy. The dose was specified at the international commission on radiation units (ICRU) reference point and fully corrected for heterogeneity. The dose distribution

Table 1
Dose Levels of selumetinib with thoracic RT.

Cohort	Dose level	RT Dose (Gy)	Selumetinib dose and schedule	Minimum number of evaluable patients
De-escalation cohort	0	60–66	75 mg OD	3
Starting cohort	1	60–66	50 mg BD	3
Escalation cohort	2	60–66	75 mg BD	3
Expanded Cohort	X	60–66	RP2D	15

within the PTV should ideally be within ±5% of the prescribed dose, and no more than ±7% of the prescribed dose.

The normal tissue constraints (for a standard dose of 2 Gy per fraction): maximum dose to spinal cord ≤48 Gy, the percentage of lung minus PTV receiving more than 20 Gy would not exceed 35% (V20 = 35%, based on dose-volume histograms), the mean lung dose was also recorded (mean dose to lung minus GTV) and the heart could receive the total dose to <30% of its volume. For >50% of cardiac volume, dose <50% of the total dose was recommended. Cone beam or orthogonal images were obtained on days 1 to 3 (or 2 to 4) and weekly thereafter. Additional cone beam imaging was at the discretion of the Principal Investigator, if during treatment any discrepancies were noted on the RT planning CT scan.

2.3.3. Outcomes and objective measures

The primary objective was to determine the recommended phase II dose (RP2D) of selumetinib in combination with thoracic RT. The secondary objectives included safety, dose delivery for selumetinib and RT, overall response rate (ORR) by response evaluation criteria in solid tumours (RECIST) [12] and local control by Green criteria [13], Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method.

Dose-limiting toxicity (DLT) was assessed during treatment and until 12 weeks after completion of thoracic RT and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0). The following toxicities which may be considered to be related to the combination of selumetinib and RT were defined as DLTs: grade ≥3 dyspnoea, oesophagitis or pneumonitis that persisted for >7 days and any of the following toxicity: neutropenia with fever grade ≥3, thrombocytopaenia with bleeding grade ≥3, toxicity resulting in administration of ≤80% of the planned course of selumetinib and toxicity leading to interruption of RT for >7 days. All adverse events were reviewed by an investigator and by the safety review committee to assess if they were attributable to selumetinib in combination with RT. Dose levels of selumetinib with thoracic RT are shown in Table 1. Final dose escalation/de-escalation decisions were made at the discretion of the safety review committee. The protocol stated the RP2D of selumetinib will be the dose level at which < 2/6 patients experience DLT. The protocol outlined specific guidelines for dose modifications and interruptions; a summary is outlined in Table 2. For any grade ≤3 toxicity, treatment with RT could continue at the discretion of the Principal Investigator (PI). Selumetinib was discontinued if the dose interruption was ≥2 weeks.

3. Results

Between June 2010 and February 2015, 21 patients were enrolled (6 to the dose finding stage and 15 to the expanded cohort). Baseline characteristics for both the dose finding cohort and expanded cohort are presented in Table 3. The majority of patients had stage III disease (76%) and were ECOG performance status 1 (67%) at trial entry. A total of 21 patients with inoperable stage III (n = 16) or stage IV (n = 5) NSCLC were given selumetinib 50 mg twice daily (dose level 1 and expanded cohort) with concomitant thoracic RT.

3.1. Treatment summary

In the starting cohort, there were interruptions to the delivery of selumetinib in 4 patients due to: hypotension (1 day), acneiform rash (3 days), social reasons (1 day) and a serious adverse event described when the patient was admitted with diarrhoea and fatigue (2 days). In the expanded cohort there were interruptions to the delivery of selumetinib in 4 patients due to: patient forgetting to take the medication (1 day), hypertension (9 days), unknown reason (in 2 patients – 2 days and 5 days). Out of 21 patients, 13 (62%) received the full dose of selumetinib and 8 (38%) received 80–100% of the prescribed dose.

All 21 patients received induction standard of care chemotherapy; 18 (86%) received 4 cycles, and 2 (9%) 3 cycles and 1 (5%) 5 cycles. The most commonly used regime was carboplatin and gemcitabine (n = 12, 57%) followed by cisplatin and pemetrexed (n = 4, 19%), cisplatin and gemcitabine (n = 3, 14%) and carboplatin and pemetrexed (n = 2, 10%). All 21 patients completed thoracic RT as planned, 12 (57%) received 66 Gy in 33 fractions, 1 received (5%) 64 Gy in 32 fractions and 8 (38%) received 60 Gy in 30 fractions, over a mean duration of 44 days (40–48). Doses of radiation received by the thoracic organs at risk are summarised in Table 4. The median V20 was 32.2% (17.6–35%) and median MLD was 17.8 Gy (10.5–24.1)

Due to the heterogeneity seen in stage III and IV NSCLC there was a wide range of GTV and PTV volumes (Table 3). No RT treatments were concluded early thus all patients received the initial planned dose.

3.2. Toxicity

In the starting cohort no enhanced RT-related toxicity was seen but two patients were considered to have DLTs. One patient was admitted to hospital with grade 3 diarrhoea and prolongation of hospitalisation by grade 3 fatigue and grade 2 radiation oesophagitis. Diarrhoea is an expected toxicity with selumetinib but due to the duration of this serious adverse event was classified as a DLT. The second patient developed a pulmonary embolism during week 3 of RT. Pulmonary embolisms are commonly diagnosed in cancer patients, often on routine interval CT scans. As selumetinib could not be ruled out as a contributing factor and it was decided by the safety review committee that this should be counted as a DLT but not attributable to the combination of RT and selumetinib. Given the 2 DLTs dose escalation was not considered. The safety review committee judged that due to the small number of very heterogeneous patients in the starting cohort and no observed enhancement of expected RT-induced toxicity (skin, oesophagitis, pneumonitis) the 50 mg twice daily dose warranted further evaluation in an expanded cohort. The dose finding part of the trial was closed and recruitment to the expanded cohort of 15 patients at the dose of 50 mg twice daily was opened. Therefore we present the most common adverse events of both cohorts together (Table 5).

The commonest grade 3–4 adverse event was lymphopenia (grade 3 in 17/21 patients and grade 4 in 2/21 patients) and hypertension (7/21 patients). Out of the 21 patients, 3 patients had confirmed pneumocystis jiroveci pneumonia (PJP)) and an additional 3

Table 2
Summary of guidelines for dose modifications and interruptions.

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-haematological			Continue same dose	Continue same dose (except if elevated AST/ALT selumetinib withheld)
Omit until grade ≤1, or returned to baseline. Resume same/reduced dose at discretion of PI	Omit until grade ≤1, or returned to baseline. Reduce dose/	discontinue at discretion of PI		
Haematological	Continue same dose	Continue same dose (except if neutropenia/thrombocytopaenia selumetinib withheld)	Omit until grade ≤2, or returned to baseline. Resume same/reduced dose at discretion of PI	Omit until toxicity grade ≤1, or returned to baseline. Reduce dose/discontinue at discretion of PI

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3
Patient characteristics.

Patient characteristics	n = 21
Sex	
Female	9 (43%)
Male	12 (57%)
Age	
Median (years)	62
Range (years)	50–73
ECOG PS	
0	7 (33%)
1	14 (67%)
Stage	
IIIa	5 (24%)
IIIb	11 (52%)
IV	5 (24%)
Histology	
Adenocarcinoma	9 (43%)
Squamous cell carcinoma	9 (43%)
Other	3 (14%)
Lung function	median (range)
FEV1 (litres)	2.3 (0.9–5)
DLCO (% predicted)	65 (33–99)
GTV	
Median (cm^3)	31
Range (cm^3)	1–224
PTV	
Median (cm^3)	360
Range (cm^3)	241–785

Abbreviations: Eastern Cooperative Oncology Group; PS, performance status; FEV1, forced expiratory volume in 1 s, DLCO, diffusing capacity of the lung for carbon monoxide; GTV, gross tumour volume; PTV, planning target volume.

Table 4
Normal tissue dosimetry.

Organ at risk	Dose characteristic: median (range)
Lung	
V5 Gy (Lung – PTV)	65.7% (36.9–81.3)
V20 Gy (Lung – PTV)	32.2% (17.6–35)
MLD (Lung – GTV)	17.8 Gy (10.5–24.1)
Oesophagus	
V35 Gy	41.9% (16.1–73.5)
Maximum dose	66.2 Gy (60.2–68.5)
Length oesophagus >40 Gy	10.8 cm (0.6–18.0)
Heart	
V30 Gy	27.9% (1.3–45.5)
V40 Gy	18.8% (0.6–24.1)
Spinal cord	
Maximum dose	44.2 Gy (35.6–47.6)

Abbreviations: V5, volume receiving ≥5 Gy, V20, volume receiving ≥20 Gy; MLD, Mean Lung Dose; V35, volume receiving ≥35 Gy, V30, volume receiving ≥30 Gy, V40, volume receiving ≥40 Gy.

patients were treated empirically for PJP. One patient died within 25 days of completing treatment (selumetinib and RT) from PJP following a myocardial infarction. Only one patient developed grade 3 oesophagitis and no patient developed grade ≥ 3 radiation pneumonitis. Three patients out of 21 (14%) developed a pulmonary embolism.

3.3. Overall response and survival

Response assessment by RECIST three months following completion of treatment showed 1 patient had a complete response, 3 patients had a partial response, 7 patients had stable disease, 8 patients had progressive disease and 2 patients were deceased. Applying the Green criteria (residual radiographic abnormality assessed by chest CT at 3 and 6 months after completion of thoracic RT, which then remains stable for an additional 6 months or more) (17), 3 out of 8 alive patients had controlled disease at 1 year. Out of the 19 deaths, 18 were reported as lung cancer deaths and 1 cardiovascular death. The main cause of first relapse was disease progression from distant metastases (9/21, 43%), then locoregional progression (4/21, 19%) and both distant metastases and locoregional progression (3/21, 14%).

Two patients were still alive at the time of analysis with 24 and 26 months follow-up, both of whom were alive with disease. The 1-year survival was 44% for stage III disease and 20% for stage IV, 2-year survival was 31% for stage III and 0% for stage IV (Fig. 1). The 1-year PFS was 23.8% and 2 year PFS was 9.5%. The median OS was 9.7 months (95% confidence interval (C.I) 5.9–17.6.) and median PFS was 6.9 months (95% CI 3.0–10.6).

4. Discussion

This is the first phase I trial assessing selumetinib in combination with thoracic RT in patients with lung cancer. The combination of thoracic RT and selumetinib was feasible at the starting dose of 50 mg twice daily, with all patients completing radical RT and >80% receiving the full prescribed dose of selumetinib. In the starting cohort expected RT-related toxicity was not enhanced by the addition of selumetinib. Since two patients were considered to have DLTs, with one DLT not attributable to the combination of RT and selumetinib, dose escalation was not considered and patients in the expanded cohort were treated at the starting dose of 50 mg twice daily.

As a large proportion of patients are deemed unsuitable for concurrent chemoRT, particularly in the UK, it is imperative that new effective treatments are investigated in combination with RT [14].

Table 5
Most common adverse events according to CTCAE v4.0.

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Early					
Radiation pneumonitis	15 (71%)	6 (29%)	0	0	0
Diarrhoea	13 (62%)	2 (10%)	1 (5%)	0	0
Constipation	8 (38%)	0	0	0	0
Dyspnoea	8 (38%)	10 (48%)	2 (10%)	0	0
Fatigue	8 (38%)	9 (43%)	2 (10%)	0	0
Rash acneiform	7 (33%)	9 (43%)	1 (5%)	0	0
Rash maculo-papular	4 (19%)	0	1 (5%)	0	0
Abnormal LFT's	3 (14%)	0	1 (5%)	0	0
Radiation oesophagitis	2 (10%)	15 (71%)	1 (5%)	0	0
Radiation dermatitis	7 (33%)	5 (24%)	1 (5%)	0	0
Lymphocyte count decreased	0	2 (10%)	17 (81%)	2 (10%)	0
Non-radiation pneumonitis	0	0	1 (5%)	0	0
Lung infection	0	5 (24%)	3 (14%)	0	1 (5%)
Hypertension	0	3 (14%)	7 (33%)	0	0
Thromboembolic event	N/A	N/A	3* (14%)	0	0
Late					
Radiation pneumonitis	3 (14%)	0	0	0	0
Lymphocyte count decreased	3	1	3 (14%)	0	0
Lung infection	0	2	1 (5%)	0	0
Dyspnoea	7	2	1 (5%)	0	0
Thromboembolic event	N/A	N/A	1 (5%)	0	0

*pulmonary embolism.
Abbreviations n/a, not applicable CTCAE v 4.0, Common Terminology Criteria for Adverse Events version 4.0 LFT, Liver Function Tests includes alanine aminotransferase increased/aspartate aminotransferase increased/GGT increased in one patient.

A promising strategy is to combine molecularly targeted drugs that act synergistically with RT with respect to tumour cell killing as an alternative to chemotherapy. If they do not result in excess normal tissue toxicity this could improve the therapeutic index of RT [15,16]. A key element to the success of such a strategy is to refine our understanding of the molecular mechanisms that mediate radioresistance to optimise the combination of molecularly targeted drugs and RT.

Bentzen et al described the radiobiological mechanisms that can be harnessed by adding a targeted drug to RT [2]. A number of different molecularly targeted agents have been studied in combination with RT in lung cancer patients. The data was summarised in a review by Koh et al [6] including EGFR inhibitors [17–20], proteasome inhibitors [21] and mTOR inhibitors [22,23]. Pneumonitis is a known side effect of some of the drugs investigated e.g. mTOR inhibitors even when the drugs are used alone [24] and thus pose a greater risk of toxicity when used in combination with RT. However, the combination of molecularly targeted drugs with radiation was usually tolerable but so far none have led to a change in clinical practice [1,7].

Both the UK National Cancer Research Institute Clinical and Translational RT Research Working Group (CTRad) and a joint AACR-ASTRO-FDA initiative highlighted the need to develop combinations of RT and molecularly targeted agents with clear roadmaps [16,25].

The MEK inhibitors are a family of targeted drugs which have been combined with chemotherapy and for the first time with thoracic RT in this study. There is a rationale for combining MEK inhibitors and RT. The mitogen activated protein kinase pathway comprising the RAS/RAF/MEK/ERK signalling cascade has a key role in the regulation of normal cell proliferation. Ionising radiation results in rapid activation of the RAS/RAF/MEK/ERK pathway in tumour cells [10]. In xenograft models, with or without the addition of radiation, selumetinib resulted in decreased phosphorylation of ERK, with more cells remaining in the G1 phase and fewer cells dividing [10]. Ionising radiation causes an increase in transforming growth factor alpha (TGF-a) a pro-survival growth factor, and it is thought that selumetinib may partly inhibit this process [11]. The mechanism of radiosensitisation by selumetinib is not fully understood but modification of hypoxia, inhibition of angiogenesis and interference with signal transduction pathways that increase tumour radioresponsiveness have been implicated [26]. Specifically, selumetinib may enhance radiosensitivity by antagonizing signal transduction elicited by the pro-survival and angiogenic factors TGF-a and VEGFa released following radiation. In addition, mutations to the oncogene KRAS, which can activate the RAS pathway, are found in 15–50% of NSCLC cases [27]. In KRAS mutant xenografts, selumetinib led to increased growth inhibition when used synergistically with cytotoxics (docetaxel, temozolamide) and targeted agents (gefitinib) compared to monotherapy [28,29].

Although >300 patients have been treated with selumetinib single agent on clinical trials worldwide with an acceptable toxicity profile, safety data is needed in combination with thoracic RT.

In this study we did not observe enhancement of expected RT induced toxicity such as radiation oesophagitis or pneumonitis. It should be pointed out that the quality control of grade 1–2 adverse events is not as robust as that of grade 3–4 adverse events as it is well known that doctors tend to underreport treatment-related toxicity compared to patients [30]. However since the primary endpoint of this study is based primarily on severe toxicity (grade 3 or more), such limitation is therefore acceptable. We report a high incidence of severe lymphopenia with 17 patients developing grade 3 (81%) and 2 patients grade 4 (9.5%). In comparison, in RTOG 0617 lower rates of severe lymphopenia were reported in the standard RT arms of 60 Gy in 30 fractions (13% grade 3 and 8% grade 4) (1). The severe lymphopenia seen in the majority of patients in our study has not been reported in other clinical trials investigating selumetinib; suggesting that the combination with thoracic RT in the sequential setting increases the risk of severe lymphopenia, with at least an additive effect.

We previously demonstrated that thoracic vertebrae V20, mean lung dose, and mean heart dose are associated with a higher risk of lymphopenia [31]. In addition, lymphopenia has been associated in another study with larger gross tumor volumes and lung V5 [32]. These findings are pertinent in the era of adjuvant immunotherapy in stage 3 NSCLC, since patients with lymphopenia at baseline or persistent lymphopenia during immunotherapy have a shorter

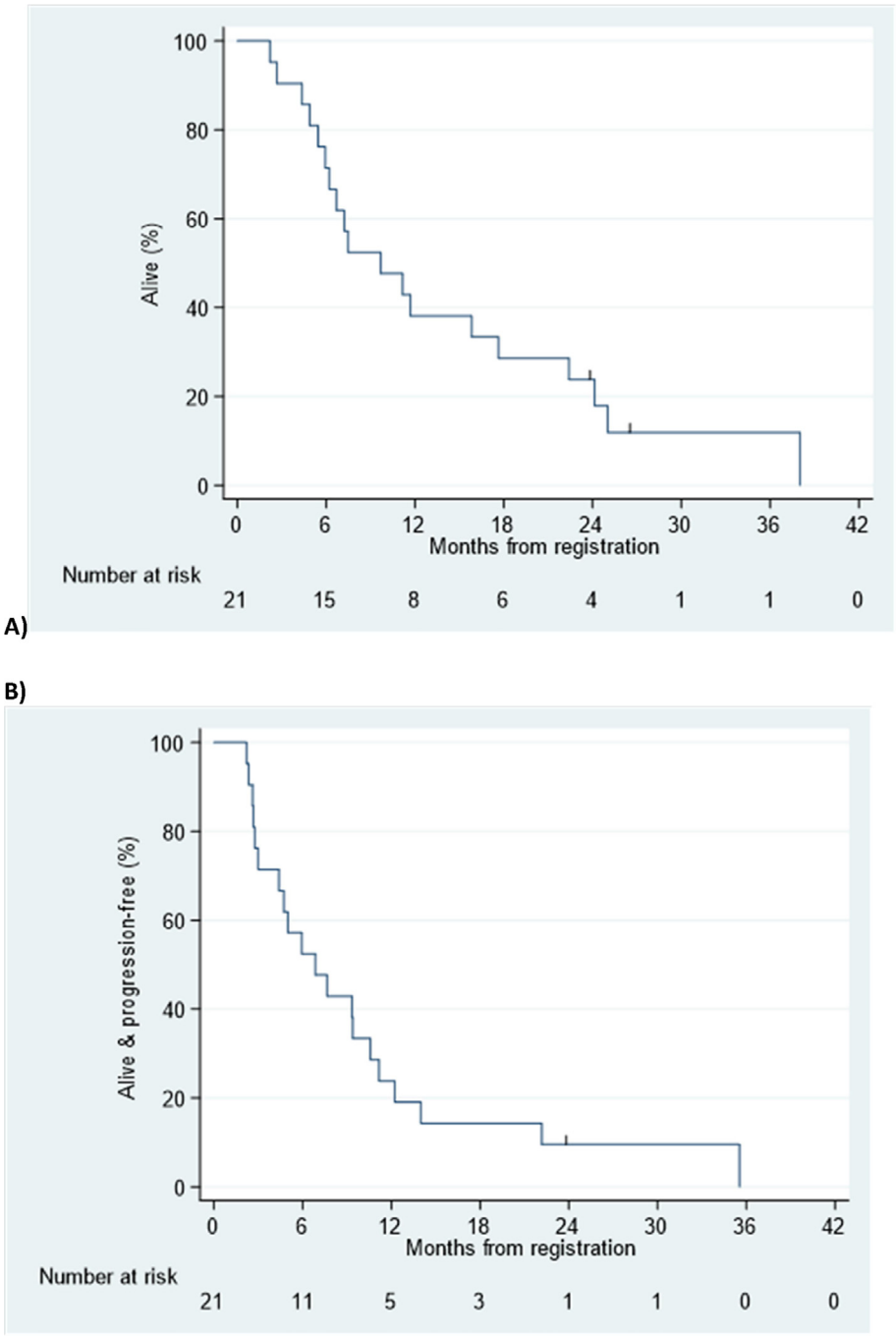

Fig. 1. A) Overall survival B) Progression-free survival.

time to disease progression [33]. It is therefore important to use radiotherapy techniques that can minimise the risk of lymphopenia in this setting [34].

It is likely that the severe lymphopenia has contributed to confirmed or clinically suspected cases of PJP in 6/21 patients in our study. In the non-HIV population, PJP is generally associated with significantly higher mortality rates (34–50%) compared to those with HIV (6–7%) (12–14). Given the intensive follow-up of patients on this phase I trial, patients were identified and treated quickly with antibiotics and there were no deaths directly as result of PJP infection. Severe lymphopenia in lung cancer patients treated with thoracic RT is known to be a poor prognostic factor for overall survival [31] and may in part explain the poor outcome reported in our study. Furthermore patient selection may have played a role as those included in our study had either locally advanced disease unsuitable for concurrent chemoRT or metastatic disease. However, outcome data of small single arm clinical trials should be interpreted with caution and results are mainly hypothesis generating.

The main limitation of this trial is the small number and the heterogeneity of the patient group in terms of stage and disease volume. In addition there was no stratification based on KRAS testing. Pre-clinical studies did suggest enhanced efficacy in NSCLC with activation of the RAS/RAF/MEK/ERK pathway due to the presence of KRAS mutation [28,29]. There was no archival tumour tissue suitable for KRAS testing in this study, mostly due to small

tumour biopsies being taken which undergo multiple testing at diagnosis leaving little tissue remaining. Ideally adequate tumour tissue should be obtained through repeat biopsies prior to enrolment in such studies but this step is logistically challenging and not always acceptable to patients. Furthermore less invasive circulating biomarkers that can be monitored longitudinally compared to tissue biopsies are required.

In the future there is a need to use more efficient design and recruit patients at multiple sites. Conventional early-phase clinical trials are typically designed to evaluate one RT-drug combination at a time. However, platform or umbrella trials provide an opportunity to study multiple targeted therapies in the same disease area in a more efficient and scientifically rich manner [16]. A multi-arm phase IB platform study to determine the recommended phase II doses and safety profiles of up to five DNA damage response inhibitors given in combination with fixed dose curative-intent RT in patients with stage IIB/III NSCLC was recently funded by Cancer Research UK [35]. This platform will allow the study of multiple drugs in combination with RT in an efficient and scientifically rich manner with a planned associated translational research programme.

In conclusion we report poor outcome and severe lymphopenia in most patients treated with the combination of thoracic radiotherapy and selumetinib, contributing to confirmed or clinically suspected cases of PJP. Taken together, these results, based on 21 patients, suggest that this combination should not be pursued in a subsequent phase II trial.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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