Phase 1 trial of ralimetinib (LY2228820) with radiotherapy plus concomitant temozolomide in the treatment of newly diagnosed glioblastoma

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Abstract (250 words):

Background and purpose: This phase 1 trial aimed to determine the maximum tolerated dose (MTD; primary objective) of a p38-MAPK inhibitor, ralimetinib, with radiotherapy (RT) and chemotherapy (TMZ), in the treatment of newly diagnosed glioblastoma (GBM) patients.

Materials and methods: The study was designed as an open-label dose-escalation study driven by a Tite-CRM design and followed by an expansion cohort. Ralimetinib was administered orally every 12 hours, 7 days a week, for 2 cycles of 2 weeks at a dose of 100, 200 or 300 mg/12h. Patients received ralimetinib added to standard concurrent RT (60 Gy in 30 fractions) with TMZ (75 mg/m²/day) and 6 cycles of adjuvant TMZ (150 to 200 mg/m² on days 1 to 5 every 28 days).

Results: The MTD of ralimetinib was 100 mg/12h with chemoradiotherapy. The three patients treated at 200 mg/12h presented a dose-limiting toxicity: one patient had a grade 3 face edema, and two patients had a grade 3 rash and grade 3 hepatic cytolysis (66%). Of the 18 enrolled patients, 15 received the MTD of ralimetinib. At the MTD, the grade ≥ 3 adverse events during concomitant chemoradiotherapy were hepatic cytolysis (2/15 patients), dermatitis/rash (1/15), lymphopenia (1/15) and nausea/vomiting (1/15). No interaction of TMZ and ralimetinib when administrated concomitantly has been observed. Inhibition of pMAPKAP-K2 (-54%) was observed in peripheral blood mononuclear cells.

Conclusion: This phase 1 trial is the first trial to study the combination of a p38-MAPK inhibitor, ralimetinib, with radiotherapy (RT) and chemotherapy (TMZ), in the treatment of newly diagnosed glioblastoma (GBM) patients. The MTD of ralimetinib was 100 mg/12h. The most frequent dose-limiting toxicities were hepatic cytolysis and rash.

Keywords: ralimetinib, radiotherapy, temozolomide, glioblastoma, phase I clinical trial

Introduction

Glioblastoma (GBM) is the most common and aggressive adult primary brain tumor [1, 2]. Although radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ) has increased patient survival, long-term prognosis remains poor, with a median survival of 15 months [3, 4]. Tumor progression most often occurs inside the irradiated tumor volume [5], showing the high radioresistance of these tumors. Mitogen-activated protein kinase (MAPK) cascades are key signaling pathways involved in the regulation of cell proliferation, survival and differentiation. Activation of p38-MAPK has been associated with a poor prognosis in GBM [6]. P38-MAPK activation represents a compensatory response by tumor cells to environmental stressors such as RT and chemotherapy [7, 8]. Therefore, combining the current treatment of GBM with p38-MAPK inhibition represents a promising opportunity.

Ralimetinib (LY2228820), a selective inhibitor of α- and β-isoforms of p38-MAPK, reduces phosphorylation of its cellular direct target, MAPK-activated protein kinase 2 (MAPKAP-K2). Preclinical studies demonstrated that ralimetinib had antitumor activity [9] and enhanced sensitivity to TMZ in GBM xenograft models [10]. Ralimetinib has also been tested in different phase 1 or 2 clinical trials alone or combined with hormono/chemotherapy [11–13]. However, before this study, no clinical trials had tested ralimetinib in combination with RT ± chemotherapy.

Here, we report the results of the first phase 1 trial to evaluate the combination of ralimetinib (a p38-MAPK inhibitor) with RT and chemotherapy (TMZ) in the treatment of newly diagnosed GBM. The primary objective was to determine the recommended dose of ralimetinib in combination with TMZ and RT. The secondary objectives were to characterize the pharmacokinetics drug-drug interaction and impact of ralimetinib on MAPKAP-K2 activation in peripheral blood mononuclear cells (PBMC).

Materials and Methods

Patients

Eligible patients were 18 to 75 years of age with newly diagnosed and histologically confirmed GBM, with a recursive partitioning analysis (RPA) of class III or IV [14], and adequate hematologic and hepatic function. Patients receiving corticosteroids were eligible if they received a stable or decreasing dose for at least 14 days before enrollment.

Patients with a history of other malignancy within 5 years prior to enrollment, diagnosis of inflammatory bowel disease, diarrhea of any cause ≥ CTCAE grade 2, a major bowel resection that would alter oral drug absorption, and/or concurrent administration of immunosuppressive therapy were excluded. All patients provided written informed consent prior to enrollment.

Study design and treatment plan

The study was approved by the ethics committee and the national regulator and registered with www.clinicaltrials.gov (NCT02364206).

This phase I study was an open-label, multicenter dose-escalation study with an expansion cohort. The dose escalation was driven by a Tite-CRM (Time to event Continual Reassessment Method) [15] method with 3 ralimetinib dose levels. Cohorts of 3 to 6 patients were treated, with a minimum of 6 patients at the recommended dose.

Ralimetinib. Ralimetinib was given orally every 12 hours, 7 days a week, for 2 cycles of 2 weeks [11] (Figure 1), at 100 (dose 1), 200 (dose 2) or 300 mg/12h (dose3). The first cycle started one week before the beginning of RT and the second during the 4^{th} and 5^{th} weeks of RT.

Radiotherapy. For irradiation, all patients were immobilized with custom thermoplastic masks. Target volume and organs at risk delineation was done by a dedicated CT-scan in the treatment position matched and fused with contrast-enhanced T1-weighted and Flair MRI sequences. The gross tumor volume (GTV) was defined as the contrast enhancement area in the T1-weighted MRI sequence, including the tumor bed for patients with partial or complete resection. The clinical target volume (CTV) was defined as the addition of a geometric tridimensional 1-cm margin around the GTV that was

corrected to the anatomical borders. The CTV also included hyperintensity in the Flair MRI sequence. The planning target volume (PTV) was defined as the addition of a geometric tridimensional 4-mm margin around the CTV. RT consisting of fractionated focal irradiation at a dose of 2 Gy per fraction was given once daily five days per week over a period of 6 weeks, for a total dose of 60 Gy. Three-dimensional conformal RT and Intensity-Modulated RT (IMRT) were allowed.

Temozolomide: Concomitant TMZ at a dose of 75 mg/m^2 per day was given 7 days per week from the first day of RT until the end of RT. Four weeks after RT, patients received a maximum of 6 cycles of adjuvant TMZ according to the standard 5-day schedule every 28 days (at a dose of 150 mg/m²/day for the first cycle and then at 200 mg/m²/day in the absence of toxicity).

Patient evaluation

Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria version 4.03 (NCI-CTCAE v4.03). The neurologic status of patients was evaluated by clinical assessment and Mini-Mental State Examination (MMSE) and evaluation of corticoid dosage.

Disease evaluations were based on RANO criteria (Response Assessment in Neuro-Oncology) [16]. Magnetic Resonance Imaging (MRI) was performed within 28 days before the initiation of the study treatment, 4 weeks after the end of RT, every 8 weeks during the adjuvant period, and subsequently every 3 months during the first 2 years.

Biomarkers assessment

A central pathology review and biomarker assessment has been implemented on FFPE blocks used for diagnosis. ATRX, PTEN protein scoring, CD34, IDH1 R132H mutation, and pMAPKAPK-2 were detected by immunohistochemistry. MGMT promoter methylation was performed by a pyrosequencing methylation assay [17, 18].

Pharmacokinetic assay

Ralimetinib and TMZ concentrations were determined by a multiparameter method using a liquid chromatography/tandem mass spectrometry assay. Whole blood samples were collected on days

(D) 7 (ralimetinib), 28 (TMZ) and 35 (ralimetinib and TMZ) with a 10-point kinetic analysis at 10h (Figure 1). Pharmacokinetic analyses included the area under the plasma concentration/time curve to the last sampling time point (AUC), peak observed concentration (Cmax), and time to Cmax (Tmax).

To explore the passage of ralimetinib across the blood-brain barrier, an optional substudy was proposed with a ralimetinib dosage in cerebrospinal fluid 7 days after administration.

Pharmacodynamic assay

The pharmacodynamic of ralimetinib was explored through the assessment of pMAPKAP-K2 on anisomycin-stimulated PBMC by flow cytometry. Pharmacodynamic analyses were conducted on plasma samples collected at the predose on D1, and after treatment administration on D7 (ralimetinib), D28 (TMZ), D35 (ralimetinib and TMZ) (Figure 1).

Statistical considerations

The recommended dose was the maximum tolerated dose (MTD) of ralimetinib. The MTD was defined as the highest dose tested in which a dose-limiting toxicity (DLT) was experienced by no more than 33% of patients. DLT was defined as any grade 3–4 toxicity except alopecia, nausea, and vomiting which can be rapidly controlled with appropriate measures. Only toxicities occurring between the first day of ralimetinib until 2 weeks after the end of RT were considered for DLT assessment.

Due to the exploratory nature of the current study and the relatively low number of patients, mainly descriptive statistics were used. The safety population consisted of all patients who received any dose of ralimetinib.

Progression-free survival (PFS) and overall survival (OS) were measured from study enrollment. PFS and OS curves and estimates were constructed using the Kaplan–Meier method. Predictive factors of PFS were investigated using univariate Cox regressions and a multivariate model including parameters with $p < .25$ in the univariate analysis.

Comparisons of pharmacokinetic and pharmacodynamic parameters at different times and doses were assessed by paired t-test, Welch's t-test or Wilcoxon's rank test (depending on the distribution of

data and without multiple-comparisons correction due to the exploratory nature of the analysis and very small sample size).

The statistical significance threshold was set at 5%. Statistical analyses were performed using R software.

Results

Between June 2015 and December 2016, 9 patients were enrolled in the phase 1 study (cohort 1 at dose 1: n=6; cohort 2 at dose 2: n=3); and 9 patients in the expansion cohort dose 1). Patient characteristics at baseline are presented in Table 1. All enrolled patients received at least one dose of ralimetinib: 15 received ralimetinib at 100 mg/12h and 3 at 200 mg/12h. 15 completed the 2 cycles of ralimetinib through radiochemotherapy and 15 completed the 6 cycles of adjuvant TMZ. A dose reduction of ralimetinib (between cycles) was implemented for 2 patients (treated at 200 mg) due to toxicity. In addition, six patients interrupted ralimetinib treatment due to toxicity (n=4: 2 for each dose), the patient's decision (n=1) and non-respect of the treatment schedule (n=1). This last patient was withdrawn from the study for non-compliance with the administration schedule (without concomitant administration of ralimetinib with chemoradiotherapy due to RT offset for technical reasons) but was evaluated for safety. One patient treated at 200 mg/12h permanently discontinued ralimetinib treatment for toxicity.

In the Phase 1 part, none of the first 3 patients treated at dose 1 had a DLT, allowing for dose 2 assessment. The three patients treated at 200 mg/12h presented a DLT: one patient had a grade 3 face edema, and two patients had a grade 3 rash and grade 3 hepatic cytolysis (Table 2). According to study design, 3 more patients were treated at dose 1. Of these three patients, only one patient presented a DLT consisting of grade 3 lymphopenia. None of the DLT was related with RT. All these DLT were reversible with appropriate measures. The MTD of ralimetinib was then considered to be 100 mg/12h (dose 1) and was used in the expansion cohort. Three of the 9 patients of the expansion cohort presented a DLT: 2 had hepatic cytolysis (1 of grade 3, another of grade 4 with cholestasis, and 1 with a rash (grade 3). Among the 15 patients (6 in phase 1 and 9 in the expansion cohort) treated at 100 mg/12h, DLT occurred in a total of 4 patients (27%) which confirmed the recommended dose of 100 mg/12h.

Overall, the most common adverse events (AE) (all grades and for the entire study period) were asthenia (78%), nausea/vomiting (72%), dermatitis/rash (61%), headache (61%), constipation (44%), hepatic cytolysis (44%), and alopecia (39%) (Table 3). Twelve patients experienced one or more severe

(grade ≥ 3) AE (67%). The most frequently severe AE for the entire study period were dermatitis/rash in 22% (4/18), hepatic cytolysis in 22% (4/18), and lymphopenia in 11% (2/18) of patients. Considering only patients treated at the recommended dose of 100 mg, severe AE were observed in 5 patients during the concomitant period (33%): hepatic cytolysis in 13% (2/15), cholestasis in 7% (1/15), dermatitis/rash in 7% (1/15), lymphopenia in 7% (1/15), and nausea/vomiting in 7% of patients (1/15). No death related to treatment was reported. No patient presented a grade ≥ 3 radio-induced toxicity.

Concerning pharmacokinetic, mean Cmax after ralimetinib alone at 100 mg/12h was 300 ± 64 ng/mL vs 827 ± 144 ng/mL at 200 mg/12h (p=0.048) (Figure 2). Mean $AUC_{0\text{-}10}$ after ralimetinib alone at 100 mg/12h was 1725 ± 292 ng.h/mL vs 3598 ± 673 ng.h/mL at 200mg/12h (p=0.09). Tmax was not significantly different between both doses. No interaction of TMZ and ralimetinib when administrated concomitantly has been noted, just as no significant differences have been observed in Cmax, Tmax and AUC for both drugs when administrated concomitantly than when administrated alone (ralimetinib: D7 vs D35; TMZ: D28 vs D35), but the study is under-powered for this type of analysis (supplementary data). Patient No. 8 presented an accumulation of 2 molecules ralimetinib and TMZ at D35. One patient treated at 100 mg/12h had cerebral fluid detection of ralimetinib. Ralimetinib dosage was 29 ng/mL in cerebral fluid *vs* 125 ng/ml in plasma at the same time (180 min post administration). Concerning pharmacodynamic, as shown in Figure 3, ralimetinib induced a strong inhibition of pMAPKAP-K2 (54%) in PBMC as early as 1 hour after the first oral intake. A similar effect was observed on D7 (52%) and D35 (56%) with TMZ. The results obtained for one patient at 200 mg were very close to those observed at 100 mg and were therefore pooled to present the data (on average 62%).

We reported the efficacy outcomes of the 15 patients treated at the recommended dose (100 mg/12h). At the last follow-up (median of 41.4 months), 10/15 patients had a progression and 9/15 were dead. The 6-month, 1-year, and 2-year PFS rates were, respectively, 92.9% (95% CI [80-100]), 50% (95% CI [29-85]), and 35.7% (5% CI [17-73]). The median PFS was 12.8 months IC95 (7.9 lower boundary of 95% CI), whereas the median overall survival was 24.5 months (16.5 lower boundary of 95% CI). In multivariate analysis, we found a link between the IDH1 mutation and a better prognosis

(HR of 0.116; 95% CI, 0.014-0.995 for PFS), as widely described, in addition to an association between PTEN expression in the tumour and a poorer prognosis (HR of 10.5; 95%CI, 1.12-10.5 for PFS).

Discussion

Our trial was the first to evaluate the combination of ralimetinib, a p38-MAPK inhibitor, with RT and TMZ in the treatment of newly diagnosed GBM. We met our primary objective with a recommended dose (RD) of ralimetinib at 100 mg/12h.

This dose was lower than the RD of ralimetinib determined in previous phase I trials. In the first phase I study in advanced cancer, the RD was 300 mg/12h [11] as monotherapy or with tamoxifen. In a randomized phase Ib/II test on the combination of gemcitabine and carboplatine +/- ralimetinib for women with ovarian cancer, the RD was 200 mg/12h (D1-10 q21d) [12]. Another phase I study assessing the combination of ralimetinib with prexasertib (checkpoint kinase 1 inhibitor) in patients with advanced or metastatic cancer [13] did not succeed in establishing a RD of ralimetinib. With a model-based 3+3 dose escalation, no DLT was observed in the cohort of 3 patients treated at 100 mg/12h, though 3/6 patients experienced DLT at a dose of 200 mg/12h (D1 to 14).

In the current trial, DLTs were consistent with the known toxicities of ralimetinib (asthenia, nausea, rash, constipation, vomiting, pruritus and hepatic cytolysis) and well-established side effects of RT and TMZ. All patients treated at 200 mg/12h experienced a grade 3 rash (/edema) and only one (7%) at 100 mg/12h with a 9% grade ≥ 3 rash, as described in the first ralimetinib phase 1 trial [11]. One patient (treated at 100 mg/12h) had grade 3 lymphopenia. Even if this toxicity is well established with TMZ [3, 4], it has also been described with ramelitinib [11]. Four patients (22%) experienced grade ≥ 3 hepatic cytolysis during concomitant period (all resolved after stopping ralimetinib and TMZ, allowing restarting of TMZ and TMZ maintenance). Hepatic cytolysis has been recently observed in conjunction with ralimetinib use and was also a potential side effect of TMZ, with up to 26% grade 3 enzyme elevations associated with TMZ in GBM patients [19–24]. Other series have reported fewer rates of liver enzyme elevation [19–23]. Also, several cases of severe cholestatic hepatitis have been reported [25–28] with the onset of injury within 1 to 7 months of starting TMZ. In the randomized double-blind placebo-controlled phase Ib/II study of gemcitabine and carboplatin +/- ralimetinib in recurrent ovarian cancer, grade 3-4 elevated alanine aminotransferase was more frequent in the ralimetinib arm (19.7%

vs 3.8%) [12]. In our study, the occurrence of grade 3 hepatic cytolysis on 2 patients (66%) treated at 200 mg/12h, with one at D14 (7 days after TMZ start) raises the question of a potential increased liver toxicity with ralimetinib and TMZ. However, among the 15 patients treated at 100 mg/12h, only 13% experienced severe hepatic cytolysis, both rapidly reversible with appropriate measures. Nevertheless, appropriate liver monitoring seems essential in future trials, especially as TMZ might also induce sever hepatotoxicity. No severe toxicity related to RT was reported, demonstrating that ralimetinib was well tolerated in combination with RT.

Despite the small number of patients, the PK parameters were in accordance with previous PK analysis of ralimetinib monotherapy [11]. No evidence of significant drug-drug interaction between ralimetinib and TMZ has been highlighted. One patient presented an accumulation of ralimetinib and TMZ at D35, attesting to an idiosyncratic metabolic problem. While UGT enzymes were involved in the metabolic clearance of ralimetinib, the genotype of UGT1A1*1/*1 and UGT1A4*1a/*1b of this patient, with a usual glucoroconjugation capacity, does not explain the observed accumulation.

In our study, ralimetinib administrated at 100 mg/12h demonstrated a pharmacodynamic response with a significant inhibition of pMAPKAP-K2 in PBMC of around 50-60% as observed with a 300 mg/12h dose [11]. A critical issue in brain tumor therapy is whether the drug penetrates the blood-brain barrier to reach the target. Dosage of ralimetinib in the cerebral fluid was possible for only one patient, but it showed that ralimetinib could go across the BBB with a favorable ratio of approximately 24% (vs blood). Further studies would be needed to determine the pharmacodynamic response of ralimetinib within the tumor and tumor microenvironment; however, technical issues in obtaining GBM biopsies create limitations.

The small sample size of the expansion cohort with a total of 15 patients treated at the RD of ralimetinib represents an important limitation of these data. The planned phase II trial (n=40) was discontinued due to an industry decision to stop providing ralimetinib before the end of recruitment. However, the first results of the efficacy of the association of a p38-MAPK inhibitor alongside RT and TMZ for the treatment of GBM were encouraging, with a PFS rate at 6 months of 93%, a PFS of 12.6

months and a OS of 24.5 months compared with historical data of the standard of care [3, 4]. These results should be interpreted with caution, taking into account the high percent of IDH-1 mutant GBM (27%) and of MGMT methylated patients (31% of known methylation status). Future randomized trials are needed to evaluate the efficacy of ralimetinib in combination with chemoradiotherapy in GBM.

These results represent the first proof-of-concept study to report the outcomes of a p38-MAPK inhibitor with RT and chemotherapy in newly diagnosed GBM. Another p38-inhibitor compound, LY3007113, has been tested in advanced cancer patients. Further development is not planned because its toxicity, which produced symptoms such as tremors and rashes, precluded achieving a biologically effective dose [43]. Grade $\geq$ 3 treatment-related adverse events included upper gastrointestinal hemorrhage and increased hepatic enzyme. SCIO-469 (Talmapimod), BIRB-796 (Doramapimod) and Losmapimod have shown interesting anti-tumoral activity in preclinical models of multiple myeloma [29–31] [32], epidermoid carcinoma [33] and cervical cancer [34] or NSCLC (PDX mouse model) [35]. So far, however, its administration in men has only been tested in the field of anti-inflammatory research [36] or in patients with myelodysplastic syndrome [37], post-myocardial infarction [38], or facioscapulohumeral muscular dystrophy (recent orphan drug status of losmapimod by FDA).

This phase I trial showed that combining ralimetinib with standard chemoradiation for newly diagnosed GBM was feasible. The most frequent and critical dose-limiting toxicity was hepatic cytolysis. The MTD of ralimetinib was determined at 100 mg/12h. These results represent the first proof-of-concept of an association of a p38-MAPK inhibitor with RT and chemotherapy justifying further randomized trials.

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Figure captions

Figure 1: Treatment scheme during the concurrent phase.

Radiotherapy (RT), Temozolomide (TMZ), pharmacokinetic (PK).

Figure 2: Pharmacokinetic profiles at 100 and 200 mg/12h on Day 7 of cycle 1

Figure 3: pMAPK-K2 percent inhibition from baseline in PBMCs

Flow cytometry activation of anisomycin-stimulated PBMCs. Paired T-test, * $p<0.001$

Tables :

Table 1: Patient characteristics

Characteristic	Phase 1 (n=9)	Phase 1 + Expansion (n=18)
Median age (range), years	59 (27-66)	58 (27-68)
Sex, n (%)		
Male	2 (22)	9 (50)
Female	7 (78)	9 (50)
RPA class, n (%)		
III	1 (11)	3 (17)
IV	8 (89)	15 (83)
Karnofsky performance status, n (%)		
100	3 (33)	6 (33)
90	2 (22)	6 (33)
80	4 (45)	5 (28)
70	0 (0)	1 (6)
Extent of primary resection		
Gross total resection	4 (44)	6 (33)
Subtotal resection	5 (56)	12 (67)
Immunohistochemistry		
IDH1 mutated	3 (33%)	4 (22%)
ATRX mutation	3 (33%)	4 (22%)
p53 (high)	4 (44%)	6 (33%)
PTEN expression		
Tumor	1 (11%)	5 (28%)
Endothelial cells	6 (67%)	11 (61%)
CD34	1 (11%)	4 (22%)
pMAPKAP-K2	85 (10-170)	80 (10-170)
MGMT methylation		
Unmethylated	2 (22%)	7 (39%)
Methylated	7 (78%)	12 (67%)

Table 2. Overview of dose-limiting toxicities

Patient N°	Center N°	Dose level Ralimetinib	Toxicity ≥ 3	Timing	Treatment related
4 (phase 1)	1	200 mg/12h	Gr 3 face edema	Day 13	Ralimetinib
5 (phase 1)	3	200 mg/12h	Gr 3 rash Gr 3 hepatic cytolysis	Day 11 Day 30	Ralimetinib TMZ and/or ralimetinib
6 (phase 1)	3	200 mg/12h	Gr 3 rash Gr 3 hepatic cytolysis	Day 16 Day 14	Ralimetinib Ralimetinib
8 (phase 1)	1	100 mg/12h	Gr 3 lymphopenia	Day 54	TMZ
10 (expansion)	3	100 mg/12h	Gr 4 hepatic cytolysis Gr 4 cholestasis	Day 40 Day 61	TMZ and/or ralimetinib TMZ
11 (expansion)	3	100 mg/12h	Gr 3 hepatic cytolysis	Day 47	TMZ
16 (expansion)	3	100 mg/12h	Gr 3 rash	Day 12	Ralimetinib

Table 3: All adverse events and grade 3/4 AE

CTCAE Term	All patients (n=18)		All patients (n=18)		Concomitant period All patients		Concomitant period Ralimetinib (Dose level 1) (n=15)		Concomitant period Ralimetinib (Dose level 2) (n=3)		Adjuvant period All patients (n=17)		All patients (n=18) AE related to ralimetinib	
Grade	All grades		≥ Grade 3		≥ Grade 3 AE		≥ Grade 3 AE		≥ Grade 3 AE		≥ Grade 3 AE		All grades	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Asthenia	14	77.8%	1	5.6%							1	5.9%	1	5.6%
Nausea/vomiting	13	72.2%	1	5.6%	1	5.6%	1	6.7%					2	11,2%
Dermatitis/rash	11	61.1%	4	22.2%	4	22.2%	1	6.7%	3	100%			7	38.9%
Headache	11	61.1%	1	5.6%							1	5.9%		
Constipation	8	44.4%											1	5.6%
Hepatic cytolysis	8	44.4%	4	22.2%	4	22.2%	2	13.3%	2	66.7%			4	22.2%
Alopecia	7	38.9%												
Lymphopenia	5	27.8%	2	11.1%	1	5.6%	1	6.7%			1	5.9%		
Cholesterol increased	4	22.2%												
Conjunctivitis	4	22.2%											2	11.1%
Leukopenia	4	22.2%	1	5.6%							1	5.9%		
Pruritus	4	22.2%												
Pyrexia	4	22.2%											1	5.6%
Tremor	4	22.2%											2	11.1%
Abdominal pain	3	16.7%											1	5.6%
Anorexia	3	16.7%												
Arthralgia	3	16.7%												
Deterioration of higher functions	3	16.7%	1	5.6%							1	5.9%		
Hematocrit decreased	3	16.7%												
Edema	3	16.7%	1	5.6%	1	5.6%			1	33.3%			1	5.6%
Pain	3	16.7%	1	5.6%							1	5.9%		
Protein total decreased	3	16.7%												
Thrombocytopenia	3	16.7%												
Sensory disturbance	3	16.7%												
Anemia	2	11.1%												
Blood chloride increased	2	11.1%												
Blood glucose increased	2	11.1%												
Blood sodium decreased	2	11.1%												
Blood triglycerides increased	2	11.1%												
Blood urea increased	2	11.1%												
Eosinophil count increased	2	11.1%												
Epilepsy	2	11.1%	1	5.6%							1	5.9%		
Fungal infection	2	11.1%												
Hypercholesterolemia	2	11.1%												
Hypocalcemia	2	11.1%												
Monocyte count increased	2	11.1%												
Neutropenia	2	11.1%												
Neutrophil count increased	2	11.1%												
Stomatitis and ulceration	2	11.1%											2	11.1%
Motor dysfunction	2	11.1%												
White blood cell count	2	11.1%												
ALAT decreased	1	5.6%												
Allodynia	1	5.6%												
Aphasia	1	5.6%												
Balance disorder	1	5.6%												
Blood albumin decreased	1	5.6%												
Blood albumin increased	1	5.6%												
Blood calcium decreased	1	5.6%												
Blood glucose decreased	1	5.6%												
Blood magnesium increased	1	5.6%												
Blood potassium decreased	1	5.6%												
Blood sodium increased	1	5.6%												
Cholestasis	1	5.6%	1	5.6%	1	5.6%	1	6.7%					1	5.6%
Fall	1	5.6%												
Diarrhea	1	5.6%											1	5.6%
Dizziness	1	5.6%												
Epistaxis	1	5.6%												
GGT decreased	1	5.6%												
Haemorrhoids	1	5.6%												
Meaturia	1	5.6%												
Hot flush	1	5.6%											1	5.6%
Hypokalemia	1	5.6%												
Influenza-like illness	1	5.6%											1	5.6%
Irritability	1	5.6%												
Monocytopenia	1	5.6%												
Muscle spasms	1	5.6%												
Phlebitis	1	5.6%												
Phosphatase alcaline decreased	1	5.6%												
Blister	1	5.6%												
Renal failure	1	5.6%												
Tinnitus	1	5.6%												

Figure 1

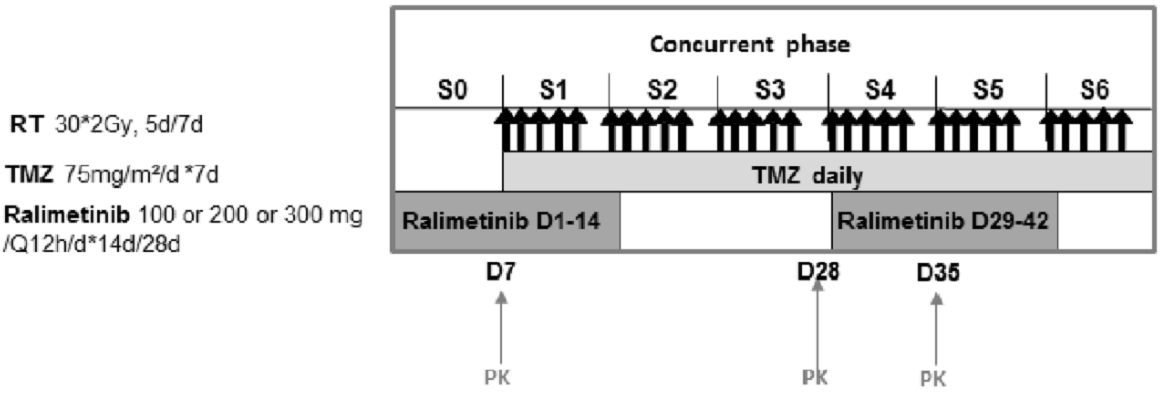


Figure 2

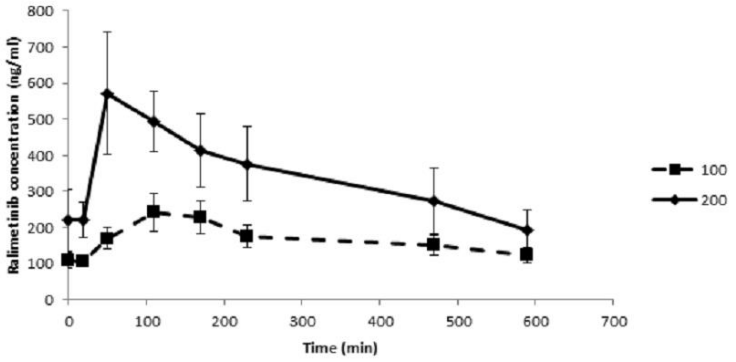
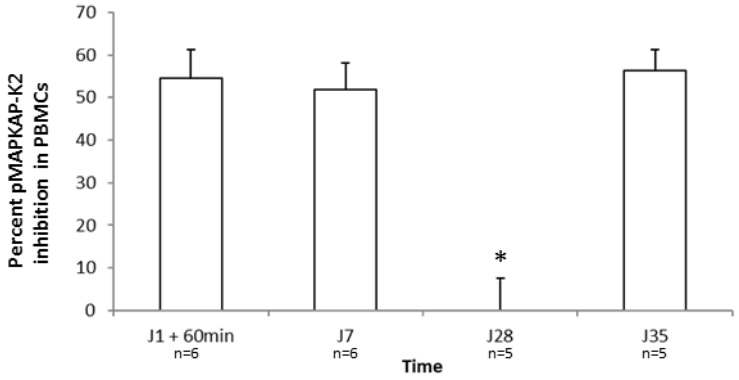

Ralimetinib concentration (ng/ml)
800
700
600
500
400
300
200
100
0
0
100
200
300
400
500
600
700
Time (min)
100
200

Figure 3


Percent pMAPKAP-K2 inhibition in PBMCs
70
60
50
40
30
20
10
0
*
J1 + 60min
n=6
J7
n=6
J28
n=5
J35
n=5
Time