Published in final edited form as:

Br J Haematol. 2015 November ; 171(4): 463–470. doi:10.1111/bjh.13603.

Phase II study of an AKT inhibitor MK2206 in patients with relapsed or refractory lymphoma

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Summary

We conducted a phase II study of the AKT inhibitor, MK2206 in patients with relapsed or refractory lymphoma of any histology excluding Burkitt lymphoma or lymphoblastic lymphoma. MK-2206 was administered orally at 200 mg once weekly in 28-d cycles up to 12 cycles in the absence of progression or significant toxicity. The dose was adjusted based on tolerance. A total of 59 patients were enrolled. The final doses patients received were 300 mg ($n = 33$), 250 mg ($n = 2$), 200 mg ($n = 16$) and 135 mg ($n = 8$). Based on intent-to-treat analysis, objective response was observed in 8 (14%) patients (2 complete response and 6 partial response), with median response duration of 5.8 months. The overall response rate was 20% in 25 patients with classical Hodgkin lymphoma. Rash was the most common toxicity (any grade 53%, Grade 3 in 15%) and was observed in a dose-dependent manner. The correlative cytokine analysis showed paradoxical increase in several cytokines, which may be explained by negative feedback mechanism induced by the on-target effect of AKT inhibitor. Our data demonstrate that MK2206 has a favourable safety profile with a modest activity in patients with relapsed Hodgkin lymphoma. The future studies should explore mechanism-based combinations (clinicaltrials.gov NCT01258998).

Keywords

lymphoma; clinical trials; target therapy; AKT

The phosphoinositide 3-kinase (PI3K)/AKT/mechanistic mammalian target of rapamycin (mTOR) signalling pathway plays a central role in regulating cell survival and proliferation

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Authorship contributions

Y.O. collected data, analysed data, provided patient care and wrote the paper. M.F., J.R., L.F., N.F., F.S., L.W.K., S.N., and M.W. provided patient care and edited the paper. A.C. provided patient care and collected data. L.F. designed study and analysed data. A.Y. designed and supervised the clinical trial, provided patient care, analysed data and wrote the paper.

Conflict of interest statements

Authors disclosed no conflict of interest.

(Georgakis & Younes, 2006; Jia *et al*, 2008). Constitutive activation of this pathway has been observed in a variety of cancers, including classical Hodgkin lymphoma (cHL) and non-Hodgkin lymphoma, and is implicated in promoting cancer cell growth and survival (Vivanco & Sawyers, 2002; Osaki *et al*, 2004; Hay, 2005; Jia *et al*, 2008; Yuan & Cantley, 2008; Engelman, 2009).

Inhibition of PI3K, AKT or mTOR kinases have been shown to confer anti-proliferative effect and apoptosis in a variety of lymphoma types *in vitro* (Vivanco & Sawyers, 2002; Osaki *et al*, 2004; Hay, 2005; Georgakis & Younes, 2006; Jia *et al*, 2008; Yuan & Cantley, 2008; Engelman, 2009). Based on these studies, novel agents that target this pathway have been tested in clinical trials for relapsed or refractory lymphomas. The first agents tested in clinical trials were the mTOR inhibitors, everolimus and temsirolimus. Although mTOR inhibitors demonstrated clinical activity with response rates up to 35%, treatment was associated with Grade 3/4 thrombocytopenia (>30%). (Yee *et al*, 2006; Witzig *et al*, 2011; Johnston *et al*, 2012a; Renner *et al*, 2012) There are multiple potential reasons for mTOR inhibitors to have limited clinical activity. First, mTOR only weakly induces apoptosis but predominantly induces cell cycle arrest and autophagy. Second, mTOR inhibitors frequently activate phosphorylated AKT by a feedback loop, presumably by TOR complex 2, which in turn attenuates the antitumour effect. Therefore, targeting upstream molecules, such as AKT or PI3K may be more advantageous. In fact, PI3K and AKT inhibitors are more potent apoptosis-inducers than mTOR inhibitors *in vitro*.

PI3K inhibitors, such as idelalisib, duvelisib, buparlisib and BAY80-6946, have shown clinical activity in lymphoma (Rodon *et al*, 2013). There has however been no clinical data with AKT inhibitors in lymphoma. MK-2206 is the first allosteric inhibitor of AKT to enter clinical development, with a nanomolar inhibitory potency against AKT1 and AKT2. MK-2206 demonstrated AKT inhibition and antiproliferative activity as single agent and in combination with other agents in multiple human cancer cell lines. MK-2206 synergized antitumour effects of chemotherapeutic agents *in vivo* and *in vitro* (Hirai *et al*, 2010; Li *et al*, 2012) and may overcome mTOR inhibitor resistance in B-cell lymphoma (Petrich *et al*, 2012). Based on such clinical data, MK-2206 has been tested clinically as a single agent in advanced solid tumours (Yap *et al*, 2011) or acute myeloid leukaemia (Konopleva *et al*, 2014) and in combination with chemotherapy (Molife *et al*, 2014). MK-2206 was well tolerated, with evidence of AKT signalling blockade in these studies. We conducted a phase II study of MK2206 in patients with relapsed or refractory lymphoma, to assess the activity and safety of this agent. In this study, weekly dosing of MK-2206 was explored based on the result of phase I study showing sustained AKT blockade and a pharmacokinetic profile of weekly dose of MK2206 (Biondo *et al*, 2011).

Materials and methods

This was an open-label, single arm phase II study of MK-2206 in patients with lymphoma. This study was approved by the institutional review board, and was registered at clinicaltrials.gov (identifier NCT01258998). All patients enrolled in this study gave written informed consent. The primary objective of the study was to determine the overall response rate [complete response (CR) plus partial response (PR)]. The secondary objectives included

evaluation of the safety profile of MK-2206 and determination of the event-free survival (EFS) of MK-2206.

Eligibility

Eligible patients were required to have lymphoma of any histology, excluding Burkitt lymphoma or lymphoblastic lymphoma, that had relapsed or been refractory after at least one treatment regimen and have no curative option available. Other inclusion criteria included: 18 years of age; measurable disease ≥ 2 cm; Eastern Cooperative Oncology Group Performance Status 0–1; absolute neutrophil count $\geq 1.5 \times 10^9/\text{l}$; platelet count $\geq 75 \times 10^9/\text{l}$; serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN); total bilirubin $\leq 1.5 \times$ ULN ($\leq 3.0 \times$ ULN if lymphomatous involvement in the liver); transaminase levels $\leq 2.5 \times$ ULN ($\leq 5.0 \times$ ULN if lymphomatous involvement in the liver); and glycated haemoglobin (HbA1c) $\leq 8\%$. Patients were ineligible if they were pregnant, had received chemotherapy or radiotherapy within the 3 previous weeks, had human immunodeficiency virus infection, active viral hepatitis, impaired cardiac function (QTc > 450 ms, heart rate < 50 bpm) or were on medications that are known strong inhibitors of CYP450A4.

Treatment and toxicity assessment

Based on preclinical and clinical experience, weekly oral dosing was considered adequate in achieving peak target inhibition and also better tolerated than more frequent dosing, such as daily or every other day dosing (Biondo *et al*, 2011). In this study, MK-2206 was administered orally once weekly in 28-d cycles up to 12 cycles in the absence of progression or significant toxicity. The initial dose in this study was 200 mg, to be administered at least 2 h before or after a meal. Toxicity was graded based on Common Terminology Criteria for Adverse Events Version 4 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). If a patient experienced toxicity of Grade 3 or greater, the dose was interrupted until the toxicity decreased to Grade 1 or better, or to baseline, and the patient resumed treatment at a lower level, according to Table I. If a patient experienced Grade 2 toxicity that was considered unacceptable by the patient or the treating physician, the dose could be reduced in a similar fashion. The dose interruption was allowed for up to 3 weeks. Patients were withdrawn from the study if the toxicity did not recover to Grade 2 or better (or within 1 grade of starting values for pre-existing laboratory abnormalities) from a treatment-related toxicity. Once a dose was decreased, it could not be increased at a later time. On the other hand, if, after 2 weeks of treatment, a patient did not experience any treatment-related toxicities $\geq$ Grade 2, the dose could be escalated to the next dose level, according to Table I. If after another 2 weeks of therapy no Grade 2 or higher related toxicities were experienced, the dose level could be increased again to the next higher dose level.

The inhibition of glucose transport into the cell by AKT/mTOR inhibitors may render insulin ineffective. According to the protocol, Grade 3 hyperglycaemic events (>13.875 mmol/l) should lead to consultation with an endocrinologist. If glucose levels did not return to Grade 1 or lower within 1 week of appropriate therapy, patients should have a dose modification. The goal of therapy was to keep fasting glucose <8.325 mmol/l, random blood glucose levels <10 mmol/l, and HbA1c $< 8\%$. Glucose monitoring was performed weekly,

during the first cycle of therapy, and on day 1 of subsequent cycles, prior to drug administration.

Response assessment

Response assessment was performed every 2 cycles of therapy using the Cheson *et al* (2007) criteria, and the response was coded as CR, PR, stable disease or progressive disease. In patients who had bone marrow involvement at the time of enrolment, bone marrow evaluation was repeated when radiographically in CR. After discontinuation of therapy, patients were followed every 3 months for the first 2 years, then every 6 months thereafter, or until progression.

Statistical consideration

Patients were enrolled separately for the following five histology cohorts: (i) relapsed or refractory cHL, (ii) indolent lymphoma, (iii) diffuse large B cell lymphoma (DLBCL), (iv) mantle cell lymphoma (MCL) and (v) peripheral T-cell lymphoma (PTCL). The primary endpoint was the objective response rate (ORR) at 4 months. The target response rate for each histology cohort was 30%, 50%, 40%, 30% and 30%, respectively. A response rate lower than 10%, 30%, 20%, 10% and 10%, respectively, was considered a failure. A Simon's MiniMax two-stage design was used for each cohort with $\alpha = 0.1$ and $\beta = 0.1$. In the first stage, 2/16, 8/28, 4/19, 2/16 and 2/16 responses were required to continue each cohort to the second stage, respectively. Total responses of 5/25, 16/39, 11/36, 5/25 and 5/25 respectively in each cohort were considered sufficiently active to warrant further study.

Response duration was calculated from the first day of documented response to the day of disease progression. EFS was calculated from the day of study enrolment to the day of documented disease progression, change in treatment to a different regimen or death from any cause. For response duration and EFS, patients who proceeded to stem cell transplant after this treatment was censored at the time of such decision.

Correlative cytokine analysis

Serum cytokines levels are measured in consenting patients on days 1, 8 and 22 of the first cycle. Twenty-nine cytokines were analysed including VEGF, EGF, Eotaxin, G-CSF, GM-CSF, IFN- α 2, IFN- γ , IL1 α , IL1 β , IL1Ra, IL2, IL3, IL4, IL5, IL6, IL7, IL8, IL10, IL12 (p40), IL12 (p70), IL13, IL15, IL17, IP10, MCP1, MIP1 α , MIP1 β , TNF α , and TNF β . Serum cytokines and chemokine were measured using the Human Cytokine/Chemokine Magnetic Beads Panel kits (Cat. No. HCYTMAG-60K-PX29; Millipore, Billerica, MA, USA) on Luminex-100 ELISA System (Luminex Corporation, Austin, TX, USA). This was an exploratory analysis and the results are shown descriptively. Significance of the changes in the cytokine levels from baseline was analysed by Wilcoxon signed rank test. *P* values < 0.05 were considered statistically significant.

Results

Patient characteristics

Between January 2011 and November 2012, 59 patients were enrolled. Cohort 1 (cHL) enrolled 25 patients as planned. Other cohorts, however, were closed early due to lack of response. Table II lists the baseline characteristics of these patients. Overall, this was a heavily treated population with median number of prior treatment regimen of 4 (range 1–10); 24 (48%) had undergone stem cell transplantation.

Treatment dose and duration

The protocol allowed a dose adjustment based on tolerance and toxicity. The final dose that patients received were 300 mg ($n = 33$), 250 mg ($n = 2$), 200 mg ($n = 16$) and 135 mg ($n = 8$). The median treatment duration was 2.3 months (range 0.5–13.5). The reasons for discontinuation of therapy were progression of lymphoma ($n = 47$), completion of 12 cycles ($n = 3$), prolonged rash despite dose interruption ($n = 3$), transplant ($n = 2$), patients' choice other than toxicity or disease progression ($n = 3$) and non-compliance ($n = 1$).

Response

Of all 59 patients treated in this study, 8 patients experienced objective response (two CR and six PR, overall response rate 14%). The median duration of response in responders was 5.8 months (range, 1.8–11.6 months). The changes in the sum of the product of diameters of target lesions are shown as a waterfall chart in Fig 1. This waterfall chart excludes five patients who did not have radiographic response evaluations due to clinical disease progression ($n = 4$) or poor compliance to the protocol schedules ($n = 1$).

Of 25 patients with cHL, five patients experienced PR (ORR 20%). Responses were observed regardless of the number of regimens or prior autologous stem cell transplantation; median numbers of prior treatment regimens were 6 (range 4–7) and 4.5 (range 2–8) in 5 responders and 18 non-responders, respectively. Response rate in indolent lymphoma ($n = 9$) was 22% [one CR in small lymphocytic lymphoma (SLL), lasting for 3.5 months, and one PR in follicular lymphoma (FL), lasting for 5.8 months]. One patient with MCL achieved PR (response rate 9%). There was no clinical response observed in T-cell lymphoma (total $n = 3$) and DLBCL (total $n = 11$).

The median EFS duration in all patients was 2.8 months. The median EFS durations in those with cHL, DLBCL and MCL were 3.6, 1.8 and 1.9 months, respectively (Fig 2).

Toxicity

All 59 patients who received at least one dose of treatment were assessed for toxicity. All haematological toxicity, Grade 3/4 toxicities at least possibly related to the study drug, in addition to Grade 1/2 toxicity at least possibly related to the study drug, seen in 5%, are shown in Table III. Rash was the most common toxicity observed in this study (any Grade 53%, Grade 3 in 15%). Rash was observed in a dose-dependent manner, and the dose interruption and reduction made the continuation of the drug possible, except for three patients who had prolonged rash, leading to treatment termination. Elevations of blood

glucose levels were also commonly observed, with any grade in 57% and Grade 3/4 in 5%. The Grade 4 hyperglycaemia was observed in the context of rapid disease progression and this patient did not resume treatment. All cytopenias are reported in Table III. It should be noted that this is a previously heavily treated population. The treatment was otherwise generally well tolerated.

Correlative cytokine analysis during therapy

Serum cytokines levels were measured in 36 consenting patients on days 1, 8 and 22 of the first cycle. Several of cytokine levels increased after the treatment with MK2206. The cytokine levels on both days 8 and 22 were significantly higher compared to the baseline for IL10, IL8, IP10, MCP1 and TNF α , though the clinical significance of these changes may be small (Fig 3). In contrast, none of the cytokines showed significant decrease in their levels when analyses were performed in all patients or when analysed according to histology (11 cHL, 6 DLBCL, 8 MCL, 4 FL, 3 MZL, 1 SLL, and 3 PTCL). In this population of 36 patients analysed for cytokine changes, only 2 experienced clinical responses (one cHL, one FL). The changes of cytokine levels during treatment were not significantly associated with the response (comparison between patients achieving PR versus others). It should be noted, however, that this exploratory analysis is based on a very limited number of patients.

Discussion

PI3K/AKT/mTOR pathway has been considered an attractive target of therapy in lymphoma (Table IV). The first target extensively evaluated in clinical trials was mTOR, which can be inhibited by everolimus or temsirolimus. Everolimus has shown promising activity in refractory or recurrent cHL, with an overall response rate of 42% (Johnston *et al*, 2012b). Everolimus has also been tested in other subtypes of lymphoma, showing moderate activity. Temsirolimus may have a better clinical activity in MCL (Witzig *et al*, 2005). More recently, a PI3K inhibitor has been tested in clinical trials and has shown clinical activities. The first in the class drug, idelalisib, inhibits PI3K delta (PIK3CD) and has shown clinical activities in indolent lymphoma (Gopal *et al*, 2014) and MCL (Kahl *et al*, 2014). The drug was generally well tolerated, and was not associated with significant cytopenia. This drug however, seems to have limited activity in DLBCL (Flinn *et al*, 2013a) or Hodgkin lymphoma (Younes *et al*, 2013) as a single agent (Younes *et al*, 2013). A pan-PI3K inhibitor, IPI145, has also been tested in a relatively large phase I study, showing clinical activity in indolent lymphomas (Flinn *et al*, 2013b).

The AKT inhibitor MK2206 has been investigated in the treatment of solid tumours and leukaemia. The first-in-man trial of MK2206 determined that the maximum tolerated dose was 60 mg orally on alternate days, and showed that two patients with pancreatic neuroendocrine tumours had minor response (Yap *et al*, 2011). In a study of MK2206 for acute myeloid leukaemia, the schedule was 200 mg weekly and there was one response out of 19 patients treated (Konopleva *et al*, 2014). In that study, it was concluded that this inhibitor had insufficient clinical antileukaemic activity when given alone at tolerated doses, and alternative approaches were to be explored.

The correlative cytokine analysis was performed in a limited number of patients in the present study. The levels of several cytokines (IL10, IL8, IP10, MCP1 and TNF α) increased after treatment with MK2206. Some of these changes may potentially be the consequence of accelerate tumour growth, but some may be due to a negative feedback loop mechanism that may be an on-target effect. A recent preclinical study has demonstrated that targeting AKT with its allosteric inhibitor AKTi1/2 resulted in paradoxical AKT phosphorylation and activation of downstream signalling in leukaemia samples (Bertacchini *et al*, 2014). Our result needs to be interpreted with caution given the limited number of samples analysed and relatively high family-wise error rate associated with the analyses of 29 cytokines.

The current study is the first to evaluate an agent that targets AKT in lymphoma. It should be noted that the study allowed flexible dose modification, and the toxicity, particularly rash, seems to be dose-dependent. On the other hand, there were no apparent associations observed between the final doses given and the responses. The study showed that the AKT inhibitor MK2206 can induce responses in cHL and indolent lymphoma, and thus warrants further investigation of the drug in these diseases. The single agent activity, however, seems to be low against DLBCL, T-cell lymphoma or MCL. This lack of response may be related to the increase in some cytokine levels after therapy with MK2206, as discussed above. Other possible mechanisms of resistance to the treatment with AKT inhibitors may include suboptimal inhibition of AKT phosphorylation at low concentrations or development of alternative survival pathway (Konopleva *et al*, 2014).

In summary, the activity of MK2206 as a single agent is, at best, modest in lymphoma. Future studies should aim at optimizing the dose and schedule of AKT inhibitors, and explore mechanism-based combination strategies with chemotherapy or other molecular target therapies.

Acknowledgments

The study was conducted with the support of Cancer Therapy Evaluation Program of National Cancer Institute, USA.

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Fig 1.

The waterfall chart showing the changes of tumour size. The figure shows 54 patients. Five patients that did not undergo formal tumour measurement after treatment. *Indicates complete metabolic response defined by fluorodeoxyglucose-positron emission tomography scan. HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma.

Fig 2. Progression free survival. The curves are for classical Hodgkin lymphoma (cHL, $n = 25$), diffuse large B-cell lymphoma (DLBCL, $n = 11$) and mantle cell lymphoma (MCL, $n = 7$). Other subtypes had <5 patients in each cohort and thus, the curves were not generated for them.

Fig 3.
Changes in cytokine levels during therapy.

Table I

MK2206 dosing in lymphoma patients.

Dose level	MK-2206 dose
-2	90 mg weekly
-1	135 mg weekly
0	200 mg weekly
1	250 mg weekly
2	300 mg weekly

Table II

Patient characteristics.

Characteristics		N (total 59)
Age (years)	Median (range)	57 (20–81)
Sex	Male/female	39/20
Histology	Classical Hodgkin lymphoma	25
	Diffuse large B-cell lymphoma	11
	Mantle cell lymphoma	11
	Follicular lymphoma	4
	Marginal zone B-cell lymphoma	3
	Small lymphocytic lymphoma	2
	Angioimmunoblastic T-cell lymphoma	2
	Peripheral T-cell lymphoma, not otherwise specified	1
	Median number of prior regimens (range)	4 (1–10)
Prior autologous stem cell transplant		24 (48%)

Table III

Toxicity.

Toxicity	Grade	1		2		3		4		Any	
		N	%	N	%	N	%	N	%	N	%
General	Fatigue	12	20	0	0	0	0	0	0	12	20
	Anorexia	2	3	2	3	0	0	0	0	4	7
Gastrointestinal	AST elevation	4	7	0	0	0	0	0	0	4	7
	Constipation	3	5	0	0	0	0	0	0	3	5
	Diarrhoea	4	7	0	0	0	0	0	0	4	7
	Nausea	8	14	1	2	0	0	0	0	9	15
Endocrine	Hyperglycaemia	25	42	6	10	2	3	1	2	34	58
Renal	Elevated creatinine	3	5	1	2	0	0	0	0	4	7
Ophthalmology	Conjunctivitis	2	3	2	3	0	0	0	0	4	7
Dermatology	Rash	18	31	4	7	9	15	0	0	31	52
	Dry skin	4	7	0	0	0	0	0	0	4	7
	Pruritus	3	5	2	3	1	2	0	0	6	10
	Anaemia	5	8	0	0	0	0	0	0	5	8
Haematological	Thrombocytopenia	11	19	4	7	0	0	0	0	15	25
	Neutropenia	4	7	3	5	2	3	1	2	10	17
	Lymphopenia	2	3	6	10	3	5	2	3	13	22

Table IV
Response rates from selected clinical trials of agents targeting PI3K/AKT/mTOR pathway for lymphoma.

	mTOR inhibitor		PI3K inhibitor		AKT inhibitor	
	Everolimus (Zent et al, 2010; Witzig et al, 2011; Johnston et al, 2012b)	Temsirolimus (Witzig et al, 2005; Smith et al, 2010)	Idelalisib (Flinn et al, 2013a; Younes et al, 2013; Gopal et al, 2014; Kahl et al, 2014)	Duvelisib (Flinn et al, 2013b; Horwitz et al, 2014)	BAY80-6946 (Dreyling et al, 2013)	Buparlisib (Younes et al, 2014) MK2206 (present study)
cHL	24/57 (42%)		3/20 (15%)	33% (n = 3)		20% (n = 25)
DLBCL/transformed FL	14/47 (30%)	9/32 (28%)		0/10 (0%)	2/17 (11%)	0% (n = 9)
MCL	6/19 (32%)	13/34 (38%)	16/40 (40%)	4/6 (67%)	5/6 (83%)	9% (n = 11)
Follicular	3/8 (38%)	21/39 (54%)	39/72 (54%)	13/19 (68%) in all indolent lymphoma	4/10 (40%)	25% (n = 4)
SLL/CLL	4/22 (18%)	2/18 (11%)	SLL 17/28 (61%) CLL 30/54 (56%)	16/31 (52%)	6/9 (67%)	50% (n = 2)
T-cell lymphoma				13/31 (42%)	2/4 (50%)	0% (n = 3)

cHL, classical Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; SLL/CLL, small lymphocytic leukaemia/chronic lymphocytic leukaemia.