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Clinical Trial

First-in-human phase I study of the bromodomain and extraterminal motif inhibitor BAY 1238097: emerging pharmacokinetic/pharmacodynamic relationship and early termination due to unexpected toxicity

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Abstract ***Background:*** Bromodomain and extraterminal motif (BET) protein inhibition is a promising cancer treatment strategy, notably for targeting *MYC*- or BRD4-driven diseases. A first-in-human study investigated the safety, pharmacokinetics, maximum tolerated dose and recommended phase II dose of the BET inhibitor BAY 1238097 in patients with advanced malignancies.

Material and methods: In this phase I, open-label, non-randomised, multicentre study, patients with cytologically or histologically confirmed advanced refractory malignancies received oral BAY 1238097 twice weekly in 21-day cycles using an adaptive dose-escalation design at a starting dose of 10 mg/week. Model-based dose–response analysis was performed to guide dose escalation. Safety, pharmacokinetics, pharmacodynamics and tumour response were evaluated.

Results: Eight patients were enrolled at three dose levels (10 mg/week, n = 3; 40 mg/week, n = 3; 80 mg/week, n = 2). Both patients receiving 80 mg/week had dose-limiting toxicities (DLTs) (grade 3 vomiting, grade 3 headache and grade 2/3 back pain). The most common

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adverse events were nausea, vomiting, headache, back pain and fatigue. Pharmacokinetic analysis indicated a linear dose response with increasing dose. Two patients displayed prolonged stable disease; no responses were observed. Biomarker evaluation of *MYC* and *HEXIM1* expression demonstrated an emerging pharmacokinetic/pharmacodynamic relationship, with a trend towards decreased *MYC* and increased *HEXIM1* expression in response to treatment.

Conclusion: The study was prematurely terminated because of the occurrence of DLTs at a dose below targeted drug exposure. Pharmacokinetic modelling indicated that an alternate dosing schedule whereby DLTs could be avoided while reaching efficacious exposure was not feasible. Registration number: NCT02369029.

1. Introduction

Bromodomain and extraterminal motif (BET) family members are epigenetic readers that bind acetylated proteins, facilitating the localisation of transcription factors and other coactivators to upregulate transcription [1–3]. In cancer, the epigenome is often dysregulated, leading to downregulation of tumour suppressor genes and upregulation of oncogenes and transcriptional activators, such as c-Myc [4]. Although direct targeting of c-Myc is challenging because of the lack of a clear ligand-binding domain [5–7], studies have reported specific transcriptional downregulation of *MYC* and its downstream targets in response to BET inhibition, leading to antiproliferative effects in preclinical models of multiple myeloma [5] and lymphoma [8], as well as antitumour activity in models of acute myeloid leukaemia [9] and a range of solid cancers [7,10–13]. BET inhibition, therefore, appears to be a promising therapeutic strategy, especially in the context of *MYC*-driven tumours.

BAY 1238097 (Bayer AG, Berlin, Germany) (Fig. 1) is a potent (submicromolar) and highly selective BET inhibitor demonstrated to suppress *MYC* gene expression and inhibit tumour growth in xenograft mouse models of lymphoma [1]. Treatment with BAY 1238097 has also exhibited antitumour efficacy in a preclinical melanoma xenograft model [14].

Here, we describe the first-in-human phase I study designed to investigate the safety, pharmacokinetics, maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of BAY 1238097 in patients with advanced malignancies.

2. Materials and methods

This study was approved by relevant independent ethics committees and institutional review boards and was compliant with the Declaration of Helsinki and Good Clinical Practice. All patients provided written, informed consent.

2.1. Study design

This was a phase I, open-label, non-randomised, multicentre, dose-escalation study. The primary objectives were to determine the safety, pharmacokinetics, MTD and RP2D of BAY 1238097 in patients with advanced malignancies. The secondary objective was to evaluate tumour response. Additional objectives included pharmacodynamic biomarker evaluation of *MYC* and *HEXIM1* mRNA expression.

The adaptive study design contained three parts: (1) dose escalation in patients with solid tumours to determine the MTD_{solid}; (2) expansion at the MTD_{solid} dose level; and (3) dose escalation in patients with haematologic malignancies and expansion at the identified $MTD_{haematologic}$ dose (supplementary Fig. S1). Part 3

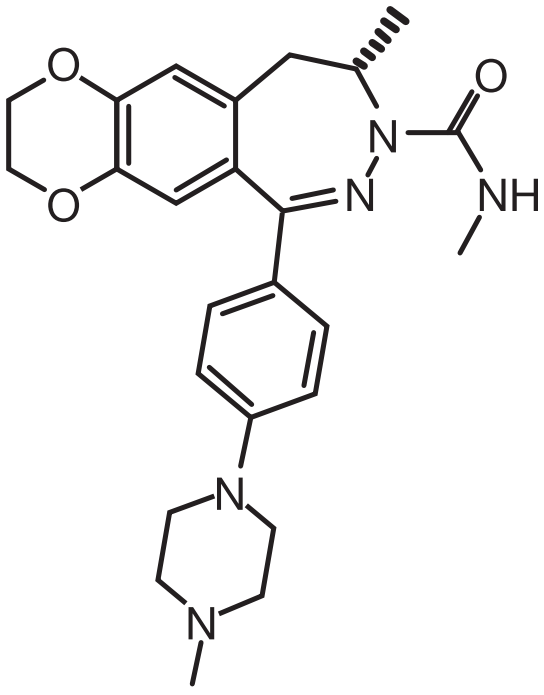

Fig. 1. Chemical structure of BAY 1238097.

was to start in parallel with part 1 once pharmacodynamic engagement was observed, defined as ≥50% inhibition of *MYC* and/or ≥2-fold induction of *HEXIM1* mRNA levels in patients with solid tumours.

Patients received oral BAY 1238097 twice weekly in a 21-day cycle at a starting dose of 10 mg weekly, with dosing planned on days 1, 4, 8, 11, 15 and 18 of each cycle. The ready-to-use undiluted solution was administered orally on an empty stomach at 2 mg/ml via disposable dosing pipette. The patient was requested to drink a glass of water immediately after administration. Treatment was taken on an outpatient basis, except on prespecified days for visits to the hospital for study-related procedures. A model-based dose–response analysis of dose-limiting toxicity (DLT) rates was performed after each dose level. The dose predicted to yield 20% DLT rates was reported as a best candidate for the next dose cohort. Dosing was planned to increase in successive cohorts as follows: 40 mg, 80 mg, 160 mg, 320 mg, 480 mg and 640 mg per week, with escalation to the next cohort if no DLTs were reported. Treatment was continued until tumour progression, unacceptable toxicity or withdrawal from the study. Additional details regarding study design and DLTs are provided in the supplementary file.

2.2. Patients

Eligibility criteria included patients aged ≥18 years with advanced histologically or cytologically confirmed malignancies refractory to standard treatment or for whom standard therapy was not feasible or refused by the patient. Eligible malignancies included advanced solid tumours or lymphomas for part 1 (dose escalation), with the addition of malignant melanomas for part 2 (expansion phase). Haematologic malignancies including acute myeloid leukaemia, acute lymphocytic leukaemia, chronic lymphocytic leukaemia and multiple myeloma were eligible for study part 3 (escalation and expansion). Further details on patient criteria are included in the supplementary file.

2.3. Assessments

Safety was assessed at screening, continuously during treatment and up to 30 days after discontinuation and included physical examination, laboratory tests, 12-lead electrocardiogram, left ventricular ejection fraction evaluation and adverse event (AE) assessment. AEs were assessed using the Medical Dictionary for Regulatory Activities, version 18.1, and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Details on plasma sample collection for pharmacokinetic analysis and peripheral blood collection for pharmacodynamic biomarker investigations of *MYC* and *HEXIM1* mRNA are provided in the supplementary file.

Tumour response in parts 1 and 2 was assessed by computed tomography at the baseline, followed by every two cycles, unless disease progression was observed, as per the Response Evaluation Criteria in Solid Tumors, version 1.1.

2.4. Statistical analysis

The incidence of patients with DLTs during cycle 1 was modelled as a function of BAY 1238097 dose using Bayesian logistic regression to guide dose selection. Results are descriptive in nature, with no planned confirmatory analysis. Additional details are provided in the supplementary file.

3. Results

3.1. Patient characteristics

Eleven patients were enrolled into the dose-escalation phase, and eight received at least one treatment dose of BAY 1238097; three patients each received 10 or 40 mg/week, and two patients received 80 mg/week. Overall, five treated patients were female and the median age was 65.5 years (range: 44–76) (supplementary Table S1). All eight patients had advanced solid tumours (stage IV) and had previously received systemic chemotherapy.

3.2. Dose escalation and safety

The three patients each receiving 10 or 40 mg/week completed at least one cycle of treatment without DLTs. Both patients in the 80 mg/week cohort experienced confirmed DLTs and did not complete one cycle of treatment: one patient (proximal colon cancer) experienced grade 3 vomiting, grade 3 headache and grade 3 back pain and a second patient (distal colon cancer) experienced grade 3 vomiting, grade 3 headache and grade 2 back pain, with no evidence of intracranial hypertension, all scoring as DLTs. Further details of DLTs and management are provided in the supplementary file. Owing to the occurrence of these confirmed DLTs at a dose level below the minimal targeted pharmacokinetic exposure, further enrolment in the study was halted. The study was discontinued when the last patient reached disease progression.

All eight patients experienced at least one treatment-emergent AE (TEAE), most commonly nausea, vomiting and headache in five patients each and back pain and fatigue in four patients each. The majority of TEAEs (78.3%) were of grade 1 or 2. Seventeen grade 3 TEAEs occurred in six patients: headache (three patients); vomiting, hypertension and back pain (two patients each) and events of anaemia, oesophageal haemorrhage, upper respiratory tract infection, thoracic vertebral fracture, ischaemic stroke, dyspnoea, hypertension, increased troponin and hyponatraemia (one patient

each). One grade 4 event occurred (tracheal obstruction in a patient at the 40 mg/week dose). No grade 5 events were reported within 30 days of study drug administration. One death caused by bilateral ischaemic stroke was reported 55 days after treatment discontinuation for troponin elevation and was deemed not to be drug related.

Six patients experienced at least one treatment-emergent serious AE (SAE). Vomiting was the only SAE reported in more than one patient. All six patients had treatment-emergent SAEs of grade 3, with one patient reporting a treatment-emergent SAE of grade 4.

Three patients experienced TEAEs that led to permanent study drug discontinuation: grade 3 ischaemic stroke (one patient; 40 mg/week), not drug related, grade 3 vomiting (two patients; 80 mg/week) and grade 3 headache (one patient; 80 mg/week), both considered drug related.

Six patients experienced drug-related TEAEs (two per dose level), most frequently nausea, headache, back pain and vomiting (Table 1). The majority of drug-related TEAEs were of grade 1 or 2 (83.8%). Six patients experienced grade 3 events: grade 3 headache in three patients, grade 3 vomiting in two patients and grade 3 back pain in one patient. No grade 4 drug-related events occurred.

3.3. Pharmacokinetic analysis and modelling

Plasma pharmacokinetic parameters were evaluated in all eight patients treated in the dose-escalation phase. BAY 1238097 demonstrated apparent dose linearity in the area under the curve (AUC) from 0 to 72 h after drug administration and maximum observed plasma concentration (C_{max}) (Fig. 2). BAY 1238097 geometric mean pharmacokinetic parameters are provided in supplementary Table S2.

Predictions were based on preclinical xenograft data (MOLP-B16, with $AUC_{(0-24)}$ of 1.3 mg h/L) [personal communication] translated to clinical exposures and schedule using pharmacokinetic/pharmacodynamic modelling [15] and resulted in a predicted efficacious BAY 1238097 dose in humans of 500 mg/week on a twice-weekly dosing schedule (250 mg/dose event). To achieve the predicted efficacious exposure via an alternate schedule while minimising C_{max}, and therefore limiting toxicity, it was estimated that dosing would need to reach at least 20 mg thrice daily (420 mg/week) [personal communication]. However, the severity and onset of observed AEs coincided with BAY 1238097 C_{max}, limiting the maximum dose per dose event to 20 mg/day (40 mg/week) (Fig. 3).

3.4. Efficacy

No response was observed among the eight patients treated with BAY 1238097; two patients achieved stable disease for six treatment cycles, despite disease progression under prior therapy, and two patients experienced progressive disease at first evaluation. The remaining patients were not evaluable, or data were not available.

3.5. Biomarker evaluation

Evaluation of plasma mRNA expression levels of *MYC* and *HEXIM1* showed evidence of an emerging direct-effect type pharmacokinetic/pharmacodynamic relationship (Fig. 4; supplementary Fig. S2). Overall, *MYC* plasma mRNA levels tended to decrease in response to

Table 1
Summary of drug-related TEAEs.

n (%)	BAY 1238097 dose							
	10 mg/week (n = 3)		40 mg/week (n = 3)		80 mg/week (n = 2)		Total (N = 8)	
Any drug-related TEAE[a]	2 (66.7)		2 (66.7)		2 (100)		6 (75.0)	
Serious	0		0		2 (100)		2 (25.0)	
Resulting in dose modification	0		0		1 (50.0)		1 (12.5)	
Leading to discontinuation	0		0		2 (100)		2 (25.0)	
Drug-related TEAEs in ≥2 patients overall[b]	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3
Headache	1 (33.3)	0	2 (66.7)	1 (33.3)	2 (100)	2 (100)	5 (62.5)	3 (37.5)
Nausea	1 (33.3)	0	2 (66.7)	0	2 (100)	0	5 (62.5)	0
Back pain	0	0	1 (33.3)	0	2 (100)	1 (50.0)	3 (37.5)	1 (12.5)
Vomiting	0	0	1 (33.3)	0	2 (100)	2 (100)	3 (37.5)	2 (25.0)
Diarrhoea	1 (33.3)	0	0	0	1 (50.0)	0	2 (25.0)	0
Decreased appetite	1 (33.3)	0	0	0	1 (50.0)	0	2 (25.0)	0
Limb discomfort	0	0	2 (66.7)	0	0	0	2 (25.0)	0
Myalgia	0	0	2 (66.7)	0	0	0	2 (25.0)	0

TEAE, treatment-emergent adverse event.
[a] Includes adverse events that started or worsened after the first day of study drug administration up to 30 days after the end of treatment with study drug.
[b] Medical Dictionary for Regulatory Activities, version 18.1, preferred terms.

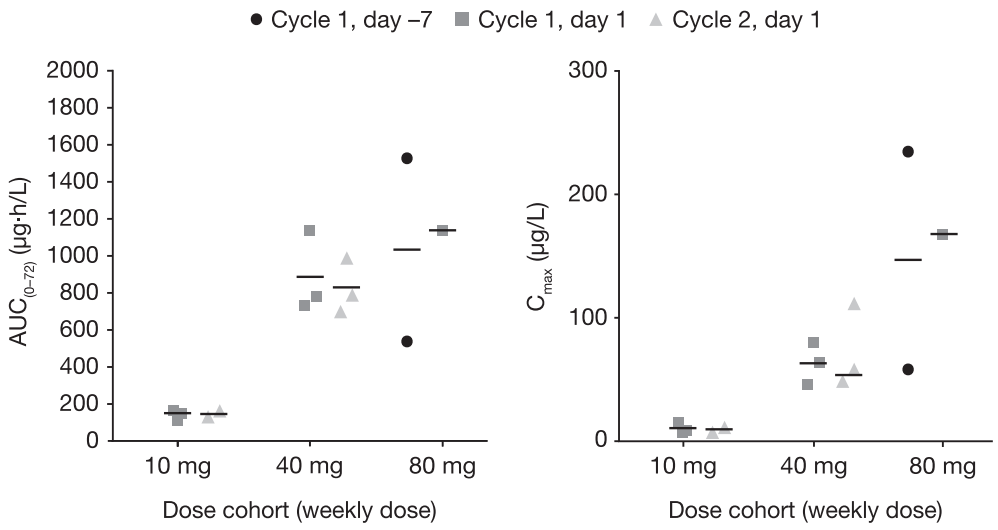

Fig. 2. Clinical pharmacokinetic parameters of BAY 1238097. $AUC_{(0-72)}$ (left) and C_{max} values (right) are indicated for plasma samples from each of the patients at each of the three BAY 1238097 dose levels on cycle 1, day −7; cycle 1, day 1 and cycle 2, day 1. $AUC_{(0-72)}$, area under the curve from 0 to 72 h; C_{max}, maximum observed plasma concentration.

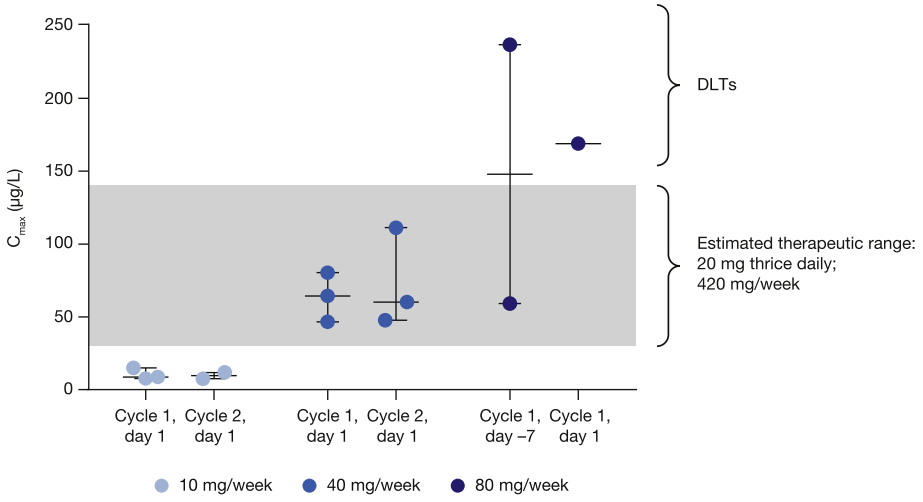

Fig. 3. Overlap of predicted potential efficacious range with dose-limiting toxicity exposure of BAY 1238097 at each of the three dose levels at the start of cycles 1 and 2. C_{max}, maximum observed plasma concentration; DLT, dose-limiting toxicity.

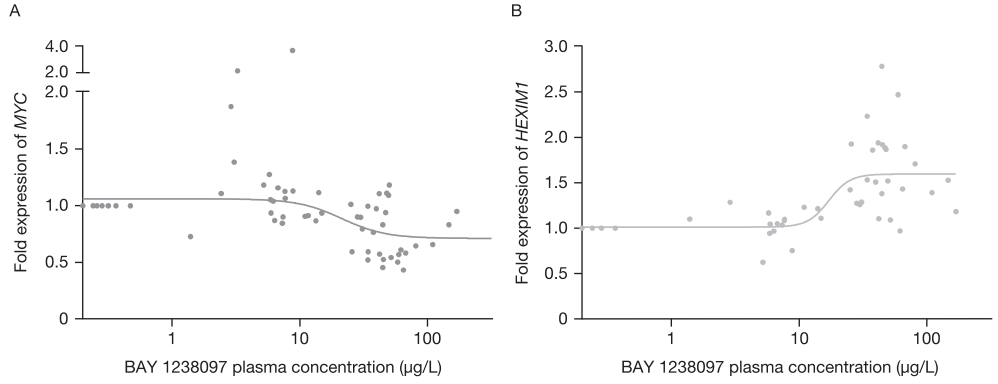

Fig. 4. Pharmacokinetic/pharmacodynamic relationship between fold expression of *MYC* (A) and *HEXIM1* (B) mRNA and plasma concentration of BAY 1238097.

BAY 1238097 compared with predose levels (Fig. 4A; supplementary Fig. S2A–B). *HEXIM1* plasma mRNA levels generally increased after BAY 1238097 dosing, with the greatest increase generally observed at the 40 mg/week dose level (Fig. 4B; supplementary Fig. S2C–D). This overall increase appeared to persist until 4 h after treatment. Owing to the exploratory experimental design and small sample size, valid statistical analysis was not considered feasible or relevant at the time of study termination.

4. Discussion

The aim of this first-in-human phase I study was to assess the safety and tolerability of the BET inhibitor BAY 1238097 in patients with advanced malignancies and to identify a MTD and RP2D. The study was prematurely discontinued because of unexpected severe toxicities in the initial dose-escalation phase at doses that were below the target dose exposure for efficacy.

Preclinical studies demonstrated promising efficacy of BAY 1238097 in inhibiting tumour growth in animal models of lymphoma, melanoma and lung cancer [1,16,17], and twice-weekly dosing was selected for clinical evaluation. This study used an adaptive dose-escalation design to determine the MTD, with reduced sample size to limit the number of patients treated with toxic doses. This approach, based in part on pharmacokinetics/pharmacodynamics data and on Bayesian models, is a viable alternative to the conventional 3 + 3 dose-escalation design, which has been shown to be suboptimal for some recent oncology drugs [18]. An adaptive study design better reflects real-world practice than a standard 3 + 3 design, as the flexibility after trial initiation allows for increased efficiency [19].

The dose-escalation phase initially treated patients at BAY 1238097 10 mg/week. DLTs of grade 3 headache, vomiting and back pain were observed in both patients treated at the 80 mg/week dose level, leading to study termination. Pain symptoms such as headache, back pain and myalgia were very common and seen in most patients enrolled in this study from the first dose level onwards. BET proteins are ubiquitously expressed across a wide range of tissues including macrophages, T-cells, pancreatic-β cells and adipocytes [20]. On-target bystander toxicities of BET inhibitors (i.e. toxicities related to the inhibition of BET protein in non-tumour cells) often include bone marrow toxicities, most commonly thrombocytopaenia [21,22]. Thrombocytopaenia is, therefore, often considered to be a pharmacodynamic biomarker of BET inhibitor efficacy, suggesting that patients are exposed to an active dose of the drug. The non-haematologic nature of the toxicities observed with BAY 1238097, occurring as early as the first dose level, suggests the presence of off-target effects, even if BET inhibition cannot be definitively ruled out as a causative factor. These effects may be partly related to antagonism at adenosine transporters or reduced adenosine reuptake, as BAY 1238097 has demonstrated preclinical inhibition of the human adenosine transporter (IC_{50} 0.14 μM). Although the observed C_{max} in patients with severe headaches approached this degree of inhibition (data not shown), it remained insufficient to explain all of the observed AEs. Although distribution of BAY 1238097 into the central nervous system is not known, BAY 1238097 was shown to be a substrate for P-glycoprotein *in vitro* (efflux ratio of 6 in an L-MDR1 assay at similar concentrations to clinical unbound plasma concentrations [data not shown]). Therefore, BAY 1238097 had a low probability of crossing the blood–brain barrier, and it is unlikely that significant penetration into the central nervous system occurred. Overall, the precise mechanism underlying observed toxicities remains unclear, and sufficient drug exposure could not be achieved to reach active doses; therefore, no therapeutic window could be identified.

Pharmacokinetic assessments indicated dose linearity across the dose range tested. However, BAY 1238097 exposure was substantially below the predicted efficacious dose at study termination. Pharmacokinetic simulations of a feasible alternate schedule to minimise C_{max} while achieving the predicted efficacious exposure, including an estimate of population pharmacokinetic variability, indicated that a dose of 20 mg thrice daily (420 mg/week) may achieve efficacious exposure. However, a substantial proportion of patients at this dose and schedule were expected to have exposures in the range linked to the DLTs observed at 80 mg/week (40 mg/dose event) based on a putative toxicity threshold of 100 ng/mL for BAY 1238097 [personal communication]. The observed pharmacokinetic parameters and observed AEs in the eight patients who received treatment indicated that plasma levels of BAY 1238097 were substantially below the expected therapeutic threshold. It was, therefore, considered clinically unfeasible to reach an efficacious exposure range with an alternative dosing schedule while remaining below the concentrations observed to trigger DLTs in this study, leading to study termination.

Preclinical studies have suggested that *MYC* overexpression may represent a predictive biomarker for BET inhibitor efficacy [5,17]. Although the pharmacodynamic analysis of biomarkers was not completed in this study, there were overall trends towards modulation of two essential pharmacodynamic biomarkers of BET inhibition, that is, decreased *MYC* mRNA expression and increased *HEXIM1* expression after BAY 1238097 exposure. Taken together, these pharmacodynamic data suggest target engagement of BAY 1238097 *in vivo*. However, pharmacokinetic/pharmacodynamic modelling of *MYC* and *HEXIM1* at the administered doses demonstrated a low level of biomarker modulation

[personal communication]. These data should, therefore, be interpreted with caution, considering other factors may also influence *MYC* expression, including normal circadian oscillations [23].

Fifteen clinical trials of BET inhibitors are actively recruiting patients (www.cancer.gov/publications/dictionaries/cancer-drug; www.clinicaltrials.gov). Despite enthusiasm surrounding the antiproliferative effects of BET inhibitors, the BET family of proteins regulates a vast network of transcriptional pathways, raising concerns regarding the safety of systemic pan-BET inhibitors [20,24]. Further study into their biological properties and functions in a variety of cell types is necessary for successful development of these inhibitors. Moreover, selective inhibitors of individual BET family members might have improved efficacy and decreased toxicity compared with pan-BET inhibitors, as the patterns of activity are not identical among them [25].

5. Conclusion

In summary, the first-in-human phase I trial of BAY 1238097, a highly selective inhibitor of BET proteins, was prematurely terminated because of unexpected severe toxicities in the dose-escalation phase below the target exposure threshold; MTD and RP2D could not be identified. Pharmacokinetic and pharmacodynamic modelling indicated that no alternative dosing schedule corresponding to a tolerable therapeutic window could be designed.

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This study was supported by Bayer AG. The sponsor played a role in the design of the study, data interpretation, writing of the manuscript and the decision to submit for publication. Medical writing support for the manuscript was provided by Katie L. Beski, PhD, at Complete HealthVizion (Chicago, IL, USA), based on detailed discussion and feedback from all authors, and funded by the sponsor.

Conflict of interest statement

As part of the Drug Development Department (DITEP), S.P.-V. is a principal or subinvestigator of clinical trials for Aduro Biotech, Agios Pharmaceuticals, Amgen, Argenx Bvba, Arno Therapeutics, Astex Pharmaceuticals, AstraZeneca, Aveo, Bayer HealthCare AG, BBB Technologies BV, BeiGene, BioAlliance Pharma, BioNTech AG, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Ca, Celgene Corporation, Chugai Pharmaceutical Co., Clovis Oncology, Daiichi Sankyo, Debiopharm S.A., Eisai, Exelixis, Forma, GamaMabs, Genentech, Inc., Gilead Sciences, Inc, GlaxoSmithKline, Glenmark Pharmaceuticals, H3 Biomedicine, Inc., F. Hoffmann-La Roche AG, Incyte Corporation, Innate Pharma, IRIS Servier, Janssen, Kura Oncology, Kyowa Kirin Pharmaceutical Development, Lilly, Loxo Oncology, Lytix Biopharma AS, MedImmune, Menarini Ricerche, Merck Sharp & Dohme-Chibret, Merrimack Pharmaceuticals, Merus, Millennium Pharmaceuticals, Nanobiotix, Nektar Therapeutics, Novartis, Octimet Oncology NV, OncoEthix, OncoMed, Oncopeptides, Onyx Therapeutics, Orion Pharma, Oryzon Genomics, Pfizer, Pharma Mar, Pierre Fabre, Rigontec GmbH, Roche, Sanofi Aventis, Sierra Oncology, Taiho Pharma, Tesaro, Inc., Tioma Therapeutics, Inc., and Xencor; reports research grants from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, Merck, Novartis, Pfizer, Roche, and Sanofi; reports nonfinancial support (drug supplied) from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Johnson & Johnson, Lilly, MedImmune, Merck, NH TherAguix, Pfizer, and Roche; has received research funding from Boehringer Ingelheim, Merck KGaA, and Roche for research projects unrelated to this manuscript; has participated in advisory boards for Merck KGaA; and has benefitted from non-financial support (travel paid and congress registration) for attending symposia from AstraZeneca. C.M. reports conflicts of interest from Amgen, Astellas, AstraZeneca, Bayer, Celgene, Genentech, Ipsen, Janssen, Lilly, Novartis, Orion, Pfizer, Roche, and Sanofi. J.-C.S. is an employee of MedImmune since September 2017 and reports personal fees from AstraZeneca, Bayer, Sanofi, Servier, and Tarveda. N.B. is an employee of Certara UK Ltd. M.M. reports personal fees from Amgen, Array BioPharma, BioLineRx, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Immunocore, Merck, Novartis, Rigontec, and Roche; grants from AstraZeneca, GlaxoSmithKline, and Roche; study fees (institution only) from Array BioPharma, Bristol-Myers Squibb, Eisai, Immunocore, Merck, Millennium, Novartis, Pfizer, Regeneron, Replimune, Rigontec, TCBioPharm, and Vertex; other from Astellas (formerly OSI Pharmaceuticals); and nonfinancial support from Immunocore and Merck. A.O.W., F.E., M.O., and G.W. are employees of Bayer AG. K.H., V.W., and M.P. have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.12.020.

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