DR. DALE BIXBY (Orcid ID : 0000-0001-6885-8239)

DR. JORGE E. CORTES (Orcid ID : 0000-0002-8636-1071)

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Safety and efficacy of vismodegib in relapsed/refractory acute myeloid leukaemia: results of a phase Ib trial

Dale Bixby[1], Richard Noppeney[2], Tara L. Lin[3], Jorge Cortes[4], Jürgen Krauter[5], Karen Yee[6], Bruno C. Medeiros[7], Alwin Krämer[8], Sarit Assouline[9], Walter Fiedler[10], Natalie Dimier[11], Brian P. Simmons[12], Todd Riehl[12], Dawn Colburn[12]

[1]Bone Marrow Transplant and Acute Leukemia Department, University of Michigan, Ann Arbor, MI, [2]Klinik für Hämatologie, Universitätsklinikum Essen, Essen, Germany, [3]Department of Medical Oncology, University of Kansas Cancer Center, Kansas City, KS, [4]Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, [5]Department of Haematology and Oncology, Klinikum Braunschweig, Braunschweig, Germany, [6]Department of Haematology and Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [7]Department of Hematology, Stanford University, Stanford, CA, [8]Clinical Cooperation Unit Molecular Haematology/Oncology, German Cancer Research Centre (DKFZ) and Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany, [9]Department of Oncology, Jewish General Hospital, Montreal, QC, Canada, [10]Department of Haematology,

University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [11]Biostatistics, Roche Products Ltd, Welwyn Garden City, UK, [12]Product Development Oncology, Genentech Inc., South San Francisco, CA

Corresponding author:

Dale Bixby
Bone Marrow Transplant and Acute Leukemia Department
University of Michigan
F4811A UH South
1500 E Medical Center Drive
Ann Arbor
MI 48109 USA

Tel: +1 734-936-9814
E-mail: dbixby@umich.edu

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Acute myeloid leukaemia (AML) is the most common acute leukaemia affecting adults (Visser *et al*, 2012). Leukaemia stem cells (LSCs) have been shown to perpetuate AML (Bonnet & Dick, 1997), and Hedgehog signalling is involved in the maintenance of LSCs (Fukushima *et al*, 2016). Increased expression of the Hedgehog signalling target transcription factors *GLI1* and *GLI2* is associated with poor survival rate in AML and is correlated with the *FLT3* mutation (Wellbrock *et al*, 2015). Results of a preclinical study showed that an inhibitor of the receptor Smoothened (SMO) could attenuate the leukaemia-initiating potential of AML cells and sensitise them to cytotoxic chemotherapy with cytarabine (Fukushima *et al*, 2016). In a phase I dose-finding study of glasdegib (PF-04449913) in patients with myeloid malignancies, one of 28 patients with AML experienced

complete remission with incomplete blood count recovery, and four experienced partial remission with incomplete blood count recovery (Martinelli *et al*, 2015).

Vismodegib is a Hedgehog pathway inhibitor (HPI) that binds to and inhibits SMO (Sekulic *et al*, 2012) and is currently approved for treatment of adults with metastatic or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy. We report here the results of a completed single-arm, open-label phase Ib study conducted to evaluate the safety and efficacy of vismodegib in adult patients with relapsed/refractory AML without prior HPI treatment.

All patients recruited had relapsed/refractory AML; patients with acute promyelocytic leukaemia (M3 subtype) were excluded. Patients were stratified by poor-risk cytogenetics (per National Comprehensive Cancer Network guidelines [NCCN Guidelines®] for AML; O'Donnell *et al*, 2017), *FLT3* mutations with intermediate-risk cytogenetics, or neither. Patients received vismodegib 150 mg orally, once daily until disease progression, intolerable toxicity or withdrawal of consent. Treatment interruption up to 14 days (before Week 8) or up to 4 weeks (after Week 8) was permitted to manage adverse events (AEs).

A total of 47 patients were screened for enrolment from 12 study sites in Germany, Canada and the United States, and 38 received at least one dose of vismodegib between September 2013 and September 2014, when the study was terminated by the sponsor because of lack of efficacy. Table I shows the baseline characteristics of the overall patient population by prognostic factor subgroup. All enrolled patients had received prior cancer therapy; most had received more than one therapy, including hypomethylating agents, immunomodulators and targeted signalling pathway inhibitors. At the end of the study (data cut-off 3 November 2014), all 38 patients had discontinued treatment with vismodegib, 19 patients (50.0%) because of progressive disease (Supplementary Fig 1). The median follow-up was 113·9 days (range 6–337 days).

Vismodegib treatment produced minimal clinical efficacy in patients with relapsed or refractory AML (Table II). Overall response rate comprised complete response (CR), CR with incomplete blood count recovery (CRi) or partial response (PR), and was 6.1% in the efficacy population. One patient experienced CRi at Day 57 (duration of response, 13 weeks) and one patient experienced PR at Day 26 (duration of response, 6 weeks); neither had poor-risk cytogenetics or *FLT3*-positive disease. The median duration of overall survival in all treated patients was 3·4 months (95% confidence interval [CI] 2·3–3·9); 33 patients died during the study, mainly because of disease progression (27 deaths). No deaths were considered related to vismodegib.

In general, treatment with vismodegib was well-tolerated and most patients achieved a high cumulative dose intensity (median 99·6%; Table SI). Overall, 97·4% of patients experienced at least one AE on study (Table S2). The most common AEs were pyrexia, nausea, dysgeusia and epistaxis (Table S3). Alopecia, frequently associated with HPIs, occurred in 7·9% (three of 38) of patients overall. Grade ≥3 AEs were reported in 84·2% of patients overall. The most common of these were febrile neutropenia (21·1%), anaemia (15·8%), thrombocytopenia (15·8%), hyponatraemia (10·5%), hypoxia (10·5%), lung infection (10·5%) and pyrexia (10·5%). Serious AEs (SAEs) were reported in 26 (68·4%) patients (Table S4). Five patients (13·2%) experienced a total of six SAEs that were considered related to vismodegib: grade 3 pyrexia (two cases), grade 2 oesophageal pain and grade 4 mucosal inflammation (both in one patient), ongoing grade 1 abdominal pain and grade 3 nausea (one case each).

The AE profile was probably driven by patients' underlying disease. The most common AEs are typical of patients with AML or are consistent with those seen in studies of vismodegib in patients with advanced basal cell carcinoma (BCC) (Lacouture *et al*, 2016). The most common SAEs and grade ≥3 AEs were infection and blood disorders, both of which are common in patients with relapsed or refractory AML, as is pyrexia. No new vismodegib safety signals were identified in this study.

In summary, vismodegib as a single agent produced minimal clinical efficacy in patients with relapsed/refractory AML, similar to other preliminary studies of HPI treatment in patients with myeloid malignancies with abnormal Hedgehog pathway signalling (Martinelli *et al*, 2015; Tibes *et al*, 2015). Single-drug treatment is unlikely to produce significant durable responses in the absence of chemotherapy to clear the bulk leukaemia cell population (Pollyea *et al*, 2014). In the current study, detection of biomarkers of LSC response (e.g., changes in expression of Hedgehog ligands or target genes, such as *GLI1* [Martinelli *et al*, 2015], was not possible; therefore, an effect of vismodegib on LSCs cannot be ruled out.

The two patients who responded were not *FLT3* mutation positive. *FLT3* mutation is associated with increased *GLI1* and *GLI2* expression and poor survival outcomes (Wellbrock *et al*, 2015). If the constitutive receptor tyrosine kinase activity of mutant *FLT3* induces GLI transcription factor expression through cross-talk between signalling pathways, inhibiting Hedgehog signalling through SMO is unlikely to have an effect. Further investigation of combined targeted therapies may be warranted.

For future studies, combination treatments that target the bulk leukaemia population and LSC-targeted therapy, such as HPIs, are more likely to show clinical benefit than LSC-targeted agents alone. Given the role of Hedgehog signalling in maintaining LSCs, HPIs may be suited to maintenance therapy after induction of a response by chemotherapy.

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Conflict of interest statement

JK has received research funding from F. Hoffman-La Roche Ltd. TLL has received research funding from F. Hoffman-La Roche Ltd and Pfizer Inc. and honoraria from Jazz Pharmaceuticals. JC has received research funding from F. Hoffman-La Roche Ltd, Amphivena Therapeutics Inc., Astellas Pharma, Daiichi Sankyo, Janssen Pharmaceutica, Jazz Pharmaceuticals, Novartis and Pfizer Inc. and consultancy fees from Amphivena Therapeutics Inc., Astellas Pharma, Daiichi Sankyo, Janssen Pharmaceutica, Jazz Pharmaceuticals, Novartis and Pfizer Inc. KY has received research funding from Agensys, Inc., Astex Pharmaceuticals, GlaxoSmithKline, F. Hoffman-La Roche Ltd and Oncoethix SA, and has served on advisory boards for Celgene, Novartis, Pfizer Inc. and Tolero Pharmaceuticals, Inc. BCM has received research support and honoraria from F. Hoffman-La Roche Ltd. SA has served on advisory boards for Ariad Pharmaceuticals, Inc./Incyte Corporation, Bristol-Myers Squibb, Novartis and Pfizer Inc. and has received research funding from Novartis and F. Hoffman-La Roche Ltd. WF has received research funding from Amgen and Pfizer Inc.; royalties from Amgen; meeting and travel expenses from Amgen, Gilead Sciences, Jazz Pharmaceuticals and Teva Pharmaceutical Industries; and has served on advisory boards for Amgen, Ariad Pharmaceuticals, Inc./Incyte Corporation, Pfizer Inc. and Jazz Pharmaceuticals. BS, TR and DC are employees of Genentech Inc., and TR holds stock in F. Hoffmann-La Roche/Genentech, Inc. ND is an employee of Roche Products Ltd. DB, RN and AK have no conflicts of interest to disclose.

Author contributions

DC and BS participated in the study design. DB, RN, TLL, JC, JK, KY, BCM, AK, SA, WF, ND, BS, TR and DC participated in the collection, interpretation and analysis of data, and the development and review of the manuscript draft. All authors approved the final manuscript for submission.

Supporting Information

Additional supporting information can be found in the online version of this article.

Table SI. Study drug exposure in all treated patients.

Table S2. Summary of adverse events occurring in all treated patients.

Table S3. Adverse events of all grades occurring in ≥20% of all treated patients.

Table S4. Serious adverse events occurring in ≥2 of all treated patients.

Fig S1. Flow chart of patient disposition.

References

Bonnet, D. & Dick, J.E. (1997) Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nature Medicine,* **3,** 730–737.

Fukushima, N., Minami, Y., Kakiuchi, S., Kuwatsuka, Y., Hayakawa, F., Jamieson, C., Kiyoi, H. & Naoe, T. (2016) Small-molecule Hedgehog inhibitor attenuates the leukemia-initiation potential of acute myeloid leukemia cells. *Cancer Science,* **107,** 1422–1429.

Lacouture, M.E., Dreno, B., Ascierto, P.A., Dummer, R., Basset-Seguin, N., Fife, K., Ernst, S., Licitra, L., Neves, R.I., Peris, K., Puig, S., Sokolof, J., Sekulic, A., Hauschild, A. & Kunstfeld, R. (2016) Characterization and management of Hedgehog pathway inhibitor-related adverse events in patients with advanced basal cell carcinoma. *Oncologist,* **21,** 1218–1229.

Martinelli, G., Oehler, V.G., Papayannidis, C., Courtney, R., Shaik, M.N., Zhang, X., O'Connell, A., McLachlan, K.R., Zheng, X., Radich, J., Baccarani, M., Kantarjian, H.M., Levin, W.J., Cortes, J.E. & Jamieson, C. (2015) Treatment with PF-04449913, an oral smoothened antagonist, in patients with myeloid malignancies: a phase 1 safety and pharmacokinetics study. *Lancet Haematology,* **2,** e339–346.

O'Donnell, M.R., Tallman, M.S., Abboud, C.N., Altman, J.K., Appelbaum, F.R., Arber, D.A., Bhatt, V., Bixby, D., Blum, W., Coutre, S.E., De Lima, M., Fathi, A.T., Fiorella, M., Foran, J.M., Gore, S.D., Hall, A.C., Kropf, P., Lancet, J., Maness, L.J., Marcucci, G., Martin, M.G., Moore, J.O., Olin, R., Peker, D., Pollyea, D.A., Pratz, K., Ravandi, F., Shami, P.J., Stone, R.M., Strickland, S.A., Wang, E.S., Wieduwilt, M., Gregory, K. & Ogba, N. (2017) Acute Myeloid Leukemia, Version 3.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network,* **15,** 926–957.

Pollyea, D.A., Gutman, J.A., Gore, L., Smith, C.A. & Jordan, C.T. (2014) Targeting acute myeloid leukemia stem cells: a review and principles for the development of clinical trials. *Haematologica,* **99,** 1277–1284.

Sekulic, A., Migden, M.R., Oro, A.E., Dirix, L., Lewis, K.D., Hainsworth, J.D., Solomon, J.A., Yoo, S., Arron, S.T., Friedlander, P.A., Marmur, E., Rudin, C.M., Chang, A.L., Low, J.A., Mackey, H.M., Yauch, R.L., Graham, R.A., Reddy, J.C. & Hauschild, A. (2012) Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *New England Journal of Medicine,* **366,** 2171–2179.

Tibes, R., Kosiorek, H.E., Dueck, A.C., Sproat, L., Palmer, J., Slack, J.L., Singh, D., Gebhart, E., Knight, E., Hashmi, S.K., Wilcox, R.A., Bogenberger, J.M., Mesa, R.A. & Al-Kali, A. (2015) Phase I/IB study of azacitidine and hedgehog pathway inhibition in myeloid malignancies. *Blood,* **126**, 1347

Visser, O., Trama, A., Maynadie, M., Stiller, C., Marcos-Gragera, R., De Angelis, R., Mallone, S., Tereanu, C., Allemani, C., Ricardi, U., Schouten, H.C. & Group, R.W. (2012) Incidence, survival and prevalence of myeloid malignancies in Europe. *European Journal of Cancer,* **48,** 3257–3266.

Wellbrock, J., Latuske, E., Kohler, J., Wagner, K., Stamm, H., Vettorazzi, E., Vohwinkel, G., Klokow, M., Uibeleisen, R., Ehm, P., Riecken, K., Loges, S., Thol, F., Schubert, C., Amling, M., Jucker, M., Bokemeyer, C., Heuser, M., Krauter, J. & Fiedler, W. (2015) Expression of Hedgehog pathway mediator GLI represents a negative prognostic marker in human acute myeloid leukemia and its inhibition exerts antileukemic effects. *Clinical Cancer Research,* **21,** 2388–2398.

Table I. Baseline characteristics and demographics.

Characteristic, *n* (%)	Poor-risk cytogenetics *n* = 15	*FLT3*-positive *n* = 4	Neither *n* = 19	All patients *N* = 38
Men	9 (60·0)	2 (50·0)	10 (52·6)	21 (55·3)
Women	6 (40·0)	2 (50·0)	9 (47·4)	17 (44·7)
Age, median (range), years	67·0 (23–84)	55·0 (48–60)	72·0 (23–79)	68·5 (23–84)
<60 years	4 (26·7)	3 (75·0)	4 (21·1)	11 (28·9)

≥60 years	11 (73·3)	1 (25·0)	15 (78·9)	27 (71·1)
Race				
Asian	1 (6·7)	0	1 (5·3)	2 (5·3)
Black/African American	1 (6·7)	0	1 (5·3)	2 (5·3)
White	13 (86·7)	4 (100·0)	17 (89·5)	34 (89·5)
Disease status at baseline[a]				
Primary refractory AML	9 (60·0)	1 (25·0)	5 (26·3)	15 (39·5)
Relapsed AML	6 (40·0)	3 (75·0)	14 (73·7)	23 (60·5)

AML, acute myeloid leukaemia.

[a]All enrolled patients had AML.

Table II. Best overall response rates (all treated patients).

Response, *n* (%)	Poor-risk cytogenetics *n* = 15	*FLT3*-positive *n* = 4	Neither *n* = 19	All patients *N* = 38
Responders	0	0	2 (12·5)	2 (6·1)
Non-responders[a]	13 (100·0)	4 (100·0)	14 (87·5)	31 (93·9)
95% CI for response rates[b]	0·0–22·5	0·0–52·7	2·3–35·4	1·1–19·2
CR [95% CI]	0 [0·0–22·5]	0 [0·0–52·7]	0 [0·0–19·8]	0 [0·0–9·2]
CRi [95% CI]	0 [0·0–22·5]	0 [0·0–52·7]	1 (6·3) [0·3–29·9]	1 (3·0) [0·2–15·6]
MLFS [95% CI]	0 [0·0–22·5]	0 [0·0–52·7]	0 [0·0–19·8]	0 [0·0–9·2]
PR [95% CI]	0[0·0–22·5]	0 [0·0–52·7]	1 (6·3) [0·3–29·9]	1 (3·0) [0·2–15·6]

CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; MLFS, morphological leukaemia-free state; NR, no response; PR, partial response.

[a]Patients classified as non-responders are patients without post-baseline progression and a response assessment within 8 weeks before treatment.

[b]95% CIs for response rates were constructed using the Blyth-Still-Cassella method.