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

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

**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* | | | | |
| 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.
*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* | 13 (100·0) | 4 (100·0) | 14 (87·5) | 31 (93·9) |
| 95% CI for response rates† | 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.
*Patients classified as non-responders are patients without post-baseline progression and a response assessment within 8 weeks before treatment.
†95% CIs for response rates were constructed using the Blyth-Still-Cassella method.

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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## 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.

## 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.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the 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.

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# Primary cutaneous acral CD8$^+$ T-cell lymphomas relapse more frequently in younger patients

Primary cutaneous acral CD8$^+$ T-cell lymphoma (PCA-CD8$^+$ TCL), originally named indolent primary cutaneous CD8$^+$ T-cell lymphoproliferation, is a rare entity that was classified as "provisional" in the recently revised World Health Organization (WHO) classification of haematopoietic and lymphoid tissue tumours (Swerdlow *et al*, 2016). PCA-CD8$^+$ TCL usually has a favourable prognosis.

Except for one reported case with extracutaneous involvement (Alberti-Violetti *et al*, 2017), only cutaneous relapses have been described. However, these relapses have not yet been clinically characterized.

Herein, we update a case of PCA-CD8$^+$ TCL, with a very late relapse, that had originally been reported by Petrella *et al* (2007). We analysed the literature and compared clinical characteristics of patients with relapsing and non-relapsing disease.

In July 2006, a 29-year-old woman with no remarkable medical history was referred for a painless nodule on the left ear helix of 4 months duration (Fig 1A). Histological examination of the surgically excised lesion found a dense and diffuse proliferation of monomorphous, medium-sized T cells throughout the dermis and subcutis. The tumour-cell immunophenotype was CD3$^+$CD8$^+$CD4$^-$TIA1$^+$granzyme B$^-$CD2$^+$CD5$^+$CD7$^-$CD30$^-$CD56$^-$CD99$^+$ and Ki67 < 10%. T-cell receptor gene analysis showed monoclonal rearrangement. Staging, including computed-tomography (CT) scan, bone marrow biopsy and complete blood count, was normal. No circulating T-cell clone was found. *Borrelia burgdorferi* serology was negative. Radiotherapy was delivered, obtaining a complete response.

Seven years later she was referred again for 2 slowly enlarging, poorly defined papules on the right ear helix (Fig 1B). No enlarged lymph nodes were found during physical examination. Positron-emission tomography–CT scan and peripheral blood tests, including complete blood count and T-cell clonality, were normal or negative. Papule histological features were very similar to those of the initial lesion, except for the deeper location of the cellular proliferation, resulting in a thicker Grenz zone. Radiotherapy was again delivered, followed several weeks later by complete remission. After three more years of follow-up, no recurrence has occurred.

Since the initial description of this entity by Petrella *et al* (2007), 54 PCA-CD8$^+$ TCL cases have been published, predominantly involving the ear ($n$ = 31). Recurrences/progression occurred in 11 (20%) of these cases, including our patient and 5 others involving the ear. Characteristics at initial diagnosis and relapse/progression of these 8 men and 3 women, median age 47 (range: 29–69) years at diagnosis, are detailed in Table I.

Initially, all relapsing patients' lesions were papules or nodules, except one with multiple lesions who also had plaques. At onset, three of the 11 patients had at least 2