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BRIEF REPORT

Feasibility and antitumour activity of the FGFR inhibitor erdafitnib in three paediatric CNS tumour patients

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Abstract

Alterations of the fibroblast growth factor (FGF) signalling pathway are increasingly recognized as frequent oncogenic drivers of paediatric brain tumours. We report on three patients treated with the selective FGFR1–4 inhibitor erdafitinib. Two patients were diagnosed with a posterior fossa ependymoma group A (PFA EPN) and one with a low-grade glioma (LGG), harbouring FGFR3/FGFR1 overexpression and an *FGFR1* internal tandem duplication (ITD), respectively. While both EPN patients did not respond to erdafitinib treatment, the *FGFR1*-ITD-harbouring tumour showed a significant decrease in tumour volume and contrast enhancement throughout treatment. The tumour remained stable 6 months after treatment discontinuation.

KEYWORDS
CNS tumours, ependymoma, erdafitinib, fibroblast growth factor receptor, internal tandem duplication (ITD), low-grade glioma, paediatrics

Abbreviations: CNS, central nervous system; EPN, ependymoma; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; ITD, internal tandem duplication; pLGG, paediatric low-grade glioma.

1 | INTRODUCTION

Activation of fibroblast growth factor (FGF) signalling is present in 4% of paediatric central nervous system (CNS) malignancies[1] and in up to 11% in the subgroup of paediatric low-grade glioma (pLGG) patients. Of all fibroblast growth factor receptor (*FGFR*)-altered pLGGs, 42% harbour *FGFR1*-ITDs (internal tandem duplications).[2] These epidemiological data support the idea that alterations in *FGFR* are relatively frequent in paediatric CNS tumours, which presents an opportunity to pharmacologically target FGFR. First promising results on treatment with FGFR inhibition in young glioma patients have been published within the RAGNAR study[3] and on Debio1347.[4] Moreover, activation of FGFR signalling has been demonstrated in other high-risk paediatric brain tumour entities, such as ependymoma (EPN).[5,6]

Erdafitinib (Balversa; erdafitinib [JNJ-42756493] was discovered in collaboration with Astex Pharmaceuticals) is a selective FGFR1–4 tyrosine kinase inhibitor that has been approved by the United States Food and Drug Administration (FDA) for the treatment of urothelial cancer harbouring *FGFR2* or *FGFR3* alterations.[7] Here, we report on our clinical experience with erdafitinib treatment in three paediatric patients diagnosed with recurrent or progressive CNS tumours.

2 | MATERIALS AND METHODS

Patients were treated at the General Hospital/Medical University of Vienna. Erdafitinib was indicated as targeted therapy within the multidisciplinary paediatric CNS precision tumourboard. Erdafitinib therapy was based on a compassionate use programme after written informed consent was obtained from the patients and/or their parents who agreed to the recording of their clinical, radiological and molecular data. The study was approved by the Ethics Committee of the Medical University of Vienna (EK 1244/2016). Tumour material was evaluated according to standard operating procedures and availability of material, resulting in an in-depth molecular analysis within INFORM[8,9] of the tumour tissue of Patient 3. Tumour tissue from Patients 1 and 2 showed high immunohistochemical (IHC) expression levels of FGFR3 and 1, respectively, and FGFR inhibitor therapy was initiated based on preclinical evidence in EPN.[5] Radiological images were reviewed by a senior paediatric neuro-radiologist.

As no paediatric-specific phase 1 study has been completed so far, initial erdafitinib dose was chosen based on guidance provided by the pharmaceutical company (Janssen Pharmaceuticals), with a starting dose of oral 3-mg tablets, once daily for children less than 12 years old and oral 5-mg tablets, once daily for adolescents 12 to less than 15 years old.

Patient characteristics are summarized in Table 1.

3 | RESULTS

Patient 3 was diagnosed at the age of 5 years with a glioma, NOS grade II–III according to the World Health Organization (WHO) classification 2016, located in the mesencephalic region (Figure 1, Supplemental Figure S1A). First-line therapy included irradiation and temozolomide treatment according to the HERBY protocol.[10] Following initial tumour response (Supplemental Figure S1B), small new metastases were detected in the lateral ventricles at the end of therapy. An active surveillance strategy was chosen, showing a slow progression of the primary tumour over several years. Increasing circular contrast enhancement 7 years after diagnosis finally led to a re-biopsy in order to verify histology and investigate the molecular biology of the tumour. Histopathological diagnosis of the recurrence was a low-grade glioma, NOS. Molecular analysis revealed an ITD in *FGFR1*, and DNA methylation profiling scores were below the confidence level and showed different diagnoses depending on the classifier version used (Table S1), leading to the integrated diagnosis of a diffuse low-grade glioma, MAPK pathway-altered, according to the WHO classification 2021.[11] Based on tumour progression, metastases and the presence of *FGFR1*-ITD, treatment with erdafitinib was initiated. After 3 months of therapy with erdafitinib, a reduction in tumour volume and contrast enhancement were observed (Figure 1). Following treatment initiation, the patient experienced pain in the lower extremities, diarrhoea and dystrophic nail changes, resulting in a pause of treatment (Days 11–23), followed by a dose reduction from 5 to 4 mg/day, resulting in better clinical tolerability. During treatment, a significant growth hor-

TABLE 1 Patient characteristics and information on treatment.

	Patient 1	Patient 2	Patient 3
Sex	Female	Male	Male
Age at diagnosis in years	5	9	5
Diagnosis	Ependymoma	Ependymoma	pLGG, NEC
Alteration	FGFR3 overexpression	FGFR1 overexpression	*FGFR1*-ITD
Line of treatment	4th	6th	2nd
Age at start of erdafitinib in years	10	12	13
Erdafitinib dose at therapy initiation	0.2 mg/kg/day 3.1 mg/m^2	0.11 mg/kg/day 2.3 mg/m^2	0.07 mg/kg/day 2.7 mg/m^2
Duration of treatment	4 months	2 weeks	6.5 months

Abbreviations: FGFR, fibroblast growth factor receptor; ITD, internal tandem duplication; pLGG, NEC, paediatric low-grade glioma, not elsewhere classified.

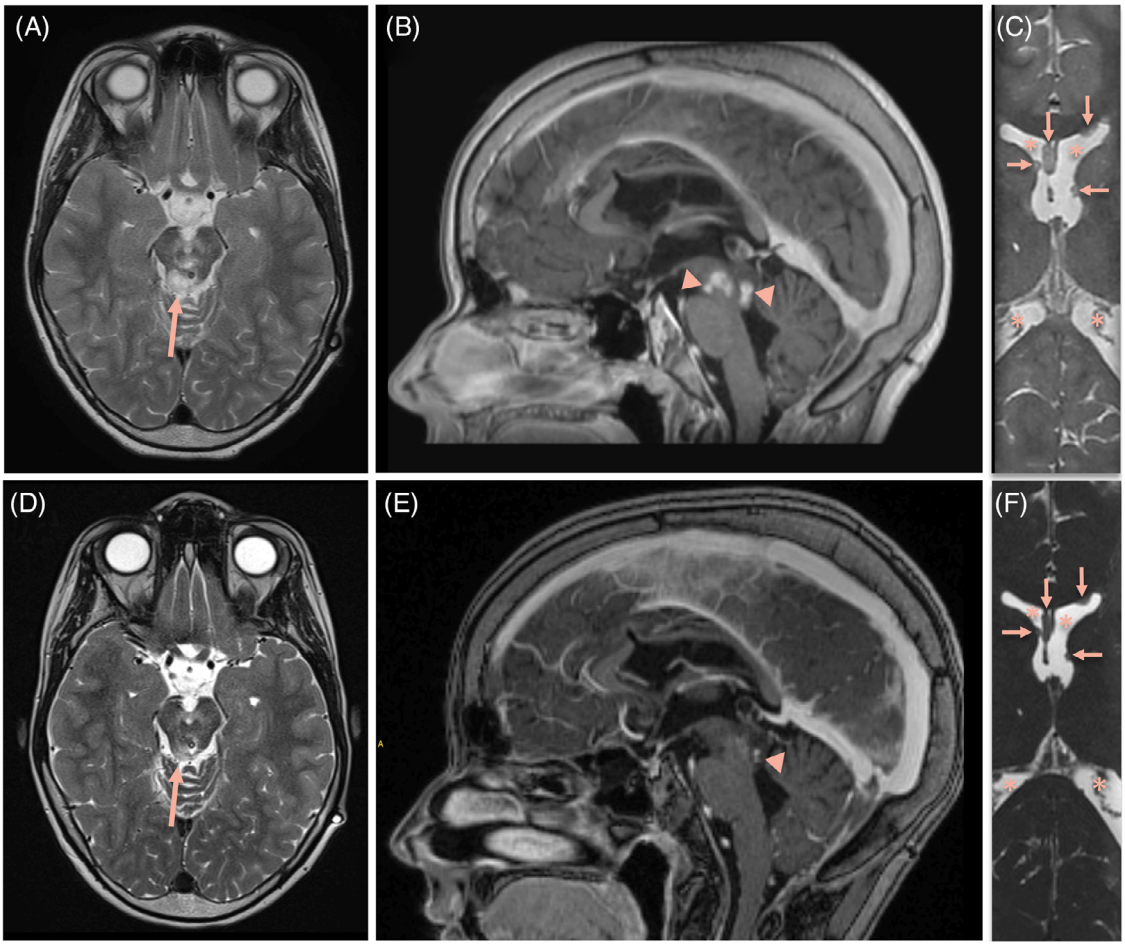

FIGURE 1 Magnetic resonance images of Patient 3 at initiation of erdafitinib treatment (upper row, A–C) and after 6 months of treatment (lower row, D–F). (A and D) Transversal T2-weighed images showing a hyperintense mesencephalic tumour (A) with a significant reduction in tumour volume after 6 months, as highlighted by the arrow (D). (B and E) Sagittal T1-weighed images showing multifocal contrast enhancement before treatment initiation (B, arrow heads), and significant reduction of contrast enhancement at the end of therapy (E, arrowhead). (C and F) Axial steady-state free precession (SSFP) images of the lateral ventricles (asterix) showing multiple small metastases (C, arrows) and minimal reduction in size at the end of treatment (F, arrows).

mone independent growth spurt was noted, which, in conjunction with massive dystrophic nail changes, led to cessation of treatment after 6.5 months. Prior to erdafitinib treatment, the patient had been started with growth hormone substitution. Hypogonadotropic hypogonadism was confirmed before and during treatment, still, the patient gained 9.8 cm of height during the 6 months of therapy. Stabilization of tumour size has been ongoing for 6 months after discontinuation of erdafitinib at the time of writing this report (Figure S2).

Patient 1 and Patient 2 were diagnosed with high-risk posterior fossa A (PFA) ependymoma indicated by presence of 1q gain[12,13] and did not respond to treatment with erdafitinib.[12] Both patients were heavily pre-treated, and erdafitinib was used as a fourth/sixth-line treatment for refractory tumours, respectively. In Patient 1, treatment was discontinued due to side effects (leg pain, dry skin, dysgeusia, brittle nails, diarrhoea, abdominal pain) and lack of response after 4 months. Notably, the patient had suffered from renal phosphate loss requiring oral substitution, which could be discontinued briefly after initiation of erdafitinib treatment. Patient 2 was started on erdafitinib at a late stage of the disease. Unfortunately, the clinical condition of the patient deteriorated, leading to cessation of treatment after only 2 weeks, excluding this patient from objective response evaluation. A computed tomography (CT) scan performed a few days later showed intra-tumoural bleeding, which was attributed to tumour progression and not to treatment with erdafitinib.

4 | DISCUSSION

Recent in-depth molecular analyses of large paediatric CNS tumour cohorts revealed that the prevalence of *FGFR*-ITDs in pLGG has been underestimated to date.[2] While mortality of these patients is low, a large proportion suffers from frequent recurrences and high disease morbidity.[14,15] Preliminary data on low-grade tumours with FGFR alterations suggest a more aggressive behaviour when compared to

low-grade tumours with KIAA1549:BRAF gene fusions,[16] highlighting the need for novel therapeutic approaches. Moreover, certain high-risk tumour types such as EPN have been shown to exhibit FGFR activation.[5,6] Erdafitinib is expected to have sufficient blood–brain barrier penetration.[17] Current literature reports on seven paediatric patients treated with FGFR inhibitors to date, five with Debio1347[4] and two with erdafitinib as part of the RAGNAR study.[3] These reports include four LGG and three HGG patients with *FGFR* fusions or mutations, showing promising results (six of seven partial response or stable disease), which is in-line with the response observed in our patient with the *FGFR1*-ITD in a low-grade glioma. Importantly, patients with *FGFR*-ITDs were not included in both previous reports.[3,4] However, evidence for *FGFR*-ITDs as important oncogenic drivers increases, and our data suggest erdafitinib as a potential targeted medication for this population. There are also preliminary data on the use of MEK inhibitors for *FGFR*-altered tumours[18] with the advantage of well-known side effects. However, due to the upstream localization of FGFR, activation of alternative pathways must be considered, and clinical efficacy remains to be elucidated.

The preclinical data, the positive IHC staining for FGFR in the two described EPN patients in combination with the lack of other therapeutic options led to the decision to use erdafitinib for treatment despite the yet undetermined significance of IHC as biomarker for FGFR activation. However, Patient 1 with FGFR3 overexpression did not show response to treatment with erdafitinib, and Patient 2 with FGFR1 overexpression was not evaluable due to rapid disease progression. The differences in response might be attributed to the limited significance of FGFR overexpression as a biomarker for response to FGFR inhibition[19] and/or to the aggressive and heavy pre-treatment these two EPN patients had received prior to erdafitinib, leading to the assumption that other molecular drivers may have been present at the time of therapy initiation. Therefore, further evaluation of predictive biomarkers is needed to identify patient subgroups who may benefit, while sparing side effects in patients who are not predicted to respond to monotherapy with FGFR inhibitors.

Our experience highlights the importance of meticulous monitoring of side effects when applying treatments approved for adults in the paediatric population. Most side effects experienced by our patients, such as diarrhoea, dystrophic nail changes/onycholysis, pain in the lower extremities, abdominal pain and dysgeusia, were in-line with previous reports in the adult population.[7] However, we did also observe a distinct growth spurt, a phenomenon that is probably limited to the paediatric population[20] and in-line with the use of FGFR inhibitors for treatment of children with achondroplasia in ongoing trials (NCT04265651). By clinical assessment, we did not attribute the observed tumour bleeding to treatment with erdafitinib but to massive tumour progression, intensive previous treatment and the terminal disease stage of the patient. However, side effects including tumour bleeding need to be closely monitored in the future, considering descriptions of tumour bleeds in patients treated with various kinase inhibitors.[21–23] Together with the observations on slipped capital femoral epiphyses occurring during treatment,[24] the importance of weighing the advantages and drawbacks of FGFR inhibitor treatment for pLGG is highlighted.

5 | CONCLUSION

In conclusion, treatment with erdafitinib may have potential for a selected cohort of paediatric CNS tumour patients. While the majority of side effects were in-line with observations in the adult population, the influence of FGFR inhibition on growth has to be further explored. Defining the exact molecular alterations that predict patient's response and specifying the optimal dose for paediatric patients are imperative to elucidate the further role of erdafitinib in treatment of paediatric CNS tumours.

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CONFLICT OF INTEREST STATEMENT

The authors have declared that no conflict of interest exists.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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