Selumetinib in paediatric patients with *BRAF*-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial

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Summary

Background Paediatric low-grade glioma is the most common CNS tumour of childhood. Although overall survival is good, disease often recurs. No single universally accepted treatment exists for these patients; however, standard cytotoxic chemotherapies are generally used. We aimed to assess the activity of selumetinib, a MEK1/2 inhibitor, in these patients.

Methods The Pediatric Brain Tumor Consortium performed a multicentre, phase 2 study in patients with paediatric low-grade glioma in 11 hospitals in the USA. Patients aged 3–21 years with a Lansky or Karnofsky performance score greater than 60 and the presence of recurrent, refractory, or progressive paediatric low-grade glioma after at least one standard therapy were eligible for inclusion. Patients were assigned to six unique strata according to histology, tumour location, NF1 status, and *BRAF* aberration status; herein, we report the results of strata 1 and 3. Stratum 1 comprised patients with WHO grade I pilocytic astrocytoma harbouring either one of the two most common *BRAF* aberrations (*KIAA1549–BRAF* fusion or the $BRAF^{V600E}$ [Val600Glu] mutation). Stratum 3 comprised patients with any neurofibromatosis type 1 (NF1)-associated paediatric low-grade glioma (WHO grades I and II). Selumetinib was provided as capsules given orally at the recommended phase 2 dose of 25 mg/m^2 twice daily in 28-day courses for up to 26 courses. The primary endpoint was the proportion of patients with a stratum-specific objective response (partial response or complete response), as assessed by the local site and sustained for at least 8 weeks. All responses were reviewed centrally. All eligible patients who initiated treatment were evaluable for the activity and toxicity analyses. Although the trial is ongoing in other strata, enrolment and planned follow-up is complete for strata 1 and 3. This trial is registered with ClinicalTrials.gov, number NCT01089101.

Findings Between July 25, 2013, and June 12, 2015, 25 eligible and evaluable patients were accrued to stratum 1, and between Aug 28, 2013, and June 25, 2015, 25 eligible and evaluable patients were accrued to stratum 3. In stratum 1, nine (36% [95% CI 18–57]) of 25 patients achieved a sustained partial response. The median follow-up for the 11 patients who had not had a progression event by Aug 9, 2018, was 36·40 months (IQR 21·72–45·59). In stratum 3, ten (40% [21–61]) of 25 patients achieved a sustained partial response; median follow-up was 48·60 months (IQR 39·14–51·31) for the 17 patients without a progression event by Aug 9, 2018. The most frequent grade 3 or worse adverse events were elevated creatine phosphokinase (five [10%]) and maculopapular rash (five [10%]). No treatment-realted deaths were reported.

Interpretation Selumetinib is active in recurrent, refractory, or progressive pilocytic astrocytoma harbouring common *BRAF* aberrations and NF1-associated paediatric low-grade glioma. These results show that selumetinib could be an alternative to standard chemotherapy for these subgroups of patients, and have directly led to the development of two Children's Oncology Group phase 3 studies comparing standard chemotherapy to selumetinib in patients with newly diagnosed paediatric low-grade glioma both with and without NF1.

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Introduction

Paediatric low-grade glioma is the most common CNS tumour in children.[1] The mainstay of therapy is complete surgical resection because this can be curative; however, children for whom a gross total resection is not achievable often require additional therapy.[1,2] Several first-line chemotherapy regimens exist, including combinations of carboplatin and vincristine; combinations of thioguanine, procarbazine, lomustine, and vincristine; and vinblastine monotherapy.[3,4] 5-year overall survival with chemotherapy

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Research in context

Evidence before this study

Before initiation of this phase 2 clinical trial, all relevant preclinical and early-phase clinical trial research in both adults and children evaluating glioma biology and MAPK pathway inhibition was considered. Between roughly April 2, 2013, and July 5, 2013, we searched PubMed for paediatric low-grade glioma, selumetinib, MAPK pathway, *BRAF*^{V600E} (Val600Glu) mutation, and *KIAA1549–BRAF* fusion using the serach terms "pediatric low-grade glioma", "MAPK pathway", "selumetinib", "MEK inhibition", "BRAFV600E mutation", "BRAFKIAA1549 fusion", and "AZD6244" (selumetinib, original name). No date restrictions were set and we only searched for papers in English. The data quality was robust and consistent, verifying that abnormal Ras-MAP kinase signalling is the most common genetic aberration in paediatric low-grade glioma and that targeting of this pathway in cell lines and animal models led to tumour regression. Phase 1 clinical trials in both children and adults suggested the safety and preliminary activity of selumetinib, a non-ATP-competitive small molecule inhibitor of MEK1/2. These data led to the development of this phase 2 trial of selumetinib in patients with recurrent, refractory, or progressive paediatric low-grade glioma.

Added value of this study

To our knowledge, selumetinib is one of the first prospectively studied and active molecularly targeted agents in paediatric low-grade glioma, providing a new alternative treatment for patients with neurofibromatosis-type-1-associated paediatric low-grade glioma and those with paediatric low-grade glioma harboring the most common *BRAF* aberrations. These phase 2 data verified the findings reported in the phase 1 study and better delineated the specific subpopulations of patients with paediatric low-grade glioma who are most sensistive to selumetinib, and also further defined duration of response, visual outcomes, and toxicity.

Implications of all the available evidence

These data have led directly to two large randomised phase 3 Children's Oncology Group studies in newly diagnosed neurofibromatosis-associated and sporadic paediatric low-grade glioma, testing activity, visual outcomes, quality of life, and patient-reported outcomes of selumetinib compared with standard chemotherapy. Taken together, these data could shape the future treatment framework for patients with paediatric low-grade glioma.

in the most recent Children's Oncology Group (COG) paediatric low-grade glioma study,[3] CCG A9952, for children without neurofibromatosis type 1 (NF1), was excellent (86% [SE 2·2]), but the same study showed 5-year progression-free survival of only 45% (SE 3·2), emphasising the need for alternative therapies. A separate evaluation of those children with NF1 in the CCG A9952 study who were non-randomly assigned to carboplatin and vincristine revealed a 5-year overall survival of 98% (SE 1) and progression-free survival of 69% (SE 4).[5] In addition to shorter progression-free survival outcomes, many children with low-grade glioma have functional morbidities such as visual disturbances, motor disabilities, poor quality of life (QOL), and neuropsychological deficits.[6–9]

Classic chemotherapy exposes children to toxic effects such as myelosuppression, allergic reactions, peripheral neuropathy, constipation, secondary malignancies, and infertility.[3] Although effective, radiotherapy increases the risk of secondary malignancy, ototoxicity, endocrinopathies, and neurocognitive decline.[10,11] Radiotherapy is often avoided in young children, especially those with NF1, for whom there is even greater risk of secondary malignancy and moyamoya disease.[2,12] NF1 is a genetic disorder caused by loss-of-function alterations in *NF1*, a negative regulator of the MAPK pathway. Approximately 15–20% of patients with NF1 will develop paediatric low-grade glioma, most commonly within the optic pathway and brainstem.[13]

Abnormal MAPK pathway activation is the most common genetic aberration in paediatric low-grade glioma.[14–17] This is most often the result of activation of the *BRAF* oncogene, either through a tandem duplication resulting in a *KIAA1549–BRAF* fusion or through an activating point mutation, *BRAF*^{V600E} (Val600Glu).[18] Approximately 80–90% of pilocytic astrocytomas—the most common paediatric low-grade glioma—harbour the *KIAA1549–BRAF* fusion, whereas *BRAF*^{V600E} mutations are identified in approximately 10–20% of all paediatric low-grade gliomas.[19]

Several drugs that target the MAPK pathway have been developed. Selumetinib is a selective and potent orally available non-ATP-competitive small molecule inhibitor of MEK1/2. The Pediatric Preclinical Testing Program showed that selumetinib induced complete regression in a *BRAF*^{V600E} xenograft glioma model.[20] In 2017, the Pediatric Brain Tumor Consortium (PBTC) completed a phase 1 trial[21] of selumetinib in 38 children with recurrent, refractory, or progressive paediatric low-grade glioma, establishing the recommended phase 2 dose as 25 mg/m² twice daily. Five of 25 patients treated at the recommended phase 2 dose achieved a partial response.[21] Simultaneously, in a phase 1 trial,[22] 17 (71%) of 24 patients with NF1-associated plexiform neurofibromas had a partial response after selumetinib treatment. Both trials showed tolerable toxicities and the same recommended phase 2 dose.

These promising findings led to the development of this PBTC prospective phase 2 trial evaluating the activity of selumetinib at the recommended phase 2 dose in patients with recurrent, refractory, or progressive paediatric low-grade glioma (WHO grade I and II).

Herein, we report the results of strata 1 and 3. Strata 2, 4, 5, and 6 are ongoing.

Methods

Study design and participants

This multicentre, phase 2 trial was developed and performed by PBTC investigators in collaboration with the National Cancer Institute Cancer Therapy Evaluation Program (CTEP) in 11 hospitals in the USA (appendix p 7). Patients aged 3–21 years with recurrent, refractory, or progressive paediatric low-grade glioma were enrolled to six unique strata according to histology, tumour location, NF1 status, and *BRAF* aberration status. Herein, we report findings from strata 1 and 3, which represent patients with some of the most common types of recurrent paediatric low-grade glioma. Stratum 1 comprised patients with WHO grade I pilocytic astrocytoma harbouring either one of the two most common *BRAF* aberrations (*KIAA1549–BRAF* fusion or the $BRAF^{V600E}$ mutation). Stratum 3 comprised patients with imaging characteristics suggestive of a paediatric low-grade glioma or a biopsy-proven paediatric low-grade glioma (WHO grade I and II) and a clinical or genetic diagnosis of NF1. Data collection for the remaining strata is ongoing and will be reported separately. Stratum 2 comprises WHO grade I pilocytic astrocytoma not harbouring either one of the two most common aberrations; stratum 4 comprises optic pathway paediatric low-grade glioma not associated with NF1; stratum 5 comprises WHO grade I and II non-pilocytic astrocytoma harbouring either one of the two most common *BRAF* aberrations; and stratum 6 comprises paediatric low-grade glioma not associated with NF1 with tissue available for *BRAF* analyses that could not be classified into stratum 1, 2, or 5 owing to inadequate tissue quality or assay failure.

Patients with recurrent, progressive, or refractory disease after at least one standard therapy, including chemotherapy or radiotherapy, were eligible for inclusion. The last dose of known myelosuppressive chemotherapy must have been given at least 3 weeks before study registration and at least 6 weeks before if a nitrosourea. The last dose of any biological agent must have been given at least 7 days before study registration. For biological agents with a long half-life (>2 days) and for all monoclonal antibodies, at least three half-lives must have elapsed before registration. Patients must have had their last fraction of local irradiation to the target tumour at least 12 months before registration. Recurrent and progressive disease was defined as either a 25% increase in bi-dimensional tumour size or development of new lesions, or both. Patients with optic pathway tumours who had vision deterioration deemed secondary to the tumour without imaging progression were also eligible. A Lansky or Karnofsky performance score greater than 60 was required, and patients with any clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic, or other organ dysfunction) likely to interfere with the study procedures or results were excluded. Any neurological deficits were required to be stable for at least 1 week before registration. Patients with uncontrolled seizures were excluded. Few data are available on the pharmacokinetics of selumetinib in children younger than 3 years and the study required that a patient swallow capsules whole. For these reasons, patients younger than 3 years were excluded. Patients were required to have adequate complete blood counts, liver and renal function, left ventricular ejection fraction of at least 55%, and QTc interval less than 450 ms. Bi-dimensional measurable disease was required.

Data were analysed by the PBTC Operations Biostatistical Data Management Core. The protocol was approved by each site's local institutional review board. All patients or legal guardians provided written, informed consent and assent as required by the local institutional review board.

Procedures

Selumetinib was administered as capsules given orally at 25 mg/m² twice daily. Dosing adherence was monitored through patient diaries and pill counts. Each treatment course was 28 days, and patients could receive up to 26 courses in the absence of unacceptable toxicity or tumour progression. Patients were taken off treatment if they met criteria for progressive disease, as described below, or had unacceptable toxicity. Up to two dose reductions were allowed; however, re-escalation was not permitted. Dose-modifying toxicities included any selumetinib-related adverse event that resulted in a delay of treatment of longer than 7 days, any grade 3 or 4 non-haematological toxicity, and any grade 2 non-haematological toxicity that persisted for more than 7 days and was deemed medically significant or intolerable by patients to warrant treatment interruption, dose reduction, or both. Exceptions to non-haematological grade 3 dose-modifying toxicities comprised grade 3 nausea and vomiting for fewer than 5 days, grade 3 elevated alanine aminotransferase and aspartate aminotransferase that returned to eligibility criteria levels within 7 days of selumetinib cessation, grade 3 fever or infection for fewer than 5 days, grade 3 electrolyte abnormalities (hypophosphataemia, hypokalaemia, hypocalcaemia, or hypomagnesaemia) that were responsive to oral supplementation, and grade 3 asymptomatic creatine phosphokinase (CPK) elevation. Haematological dose-modifying toxicity comprised any grade 4 haematological toxicity (with the exception of lymphopenia) and grade 3 thrombocytopenia with associated bleeding. Full toxicity assessments were completed every 4 weeks and before each subsequent cycle and were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Required follow-up assessments comprised clinical examination, laboratory evaluations, ophthalmological

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See **Online** for appendix

examination, and MRI. MRI was done every 2 months during the first year and every 3 months thereafter. Patients whose tumour achieved a radiographc response (complete or partial response) as assessed locally underwent central radiographic review at the PBTC neuroimaging centre. Responses were based on two-dimensional MRI evaluation. A complete response was defined as complete tumour disappearance on T2-fluid attenuation inversion recovery (FLAIR) images, no new lesions, and disappearance of all enhancement on T1 post-contrast imaging. A partial response was defined as at least 50% tumour reduction (in two-dimensional area calculated as a product of two perpendicular linear measurements) on T2-FLAIR. Stable disease was defined as neither a sufficient increase nor a reduction to qualify as partial response or progressive disease. Progressive disease was a greater than 25% increase or development of new lesions. These response criteria were used both for local site and central imaging response assessments. As described in the phase 1 selumetinib trial,[21] initial imaging response definitions were based more heavily upon enhancement on imaging seen after administration of gadolinium than on T2 and FLAIR sequences. Since these definitions are not compatible with historical and current definitions, a protocol amendment using the above response criteria was approved (protocol version 17.1) on Aug 24, 2015.

Laboratory assessments, including complete blood count, full chemistry panel, liver function tests, and CPK, were done every 4 weeks and before each subsequent cycle. Echocradiograms were done every 3 months. Patients with an optic pathway tumour enrolled to stratum 3 had ophthalmological examinations for visual acuity every 3 months. All *BRAF* testing was done centrally at the Brigham and Women's Hospital, Harvard Medical School (Boston, MA, USA). Formalin-fixed paraffin-embedded unstained slides were analysed for *3′BRAF* duplication, which leads to *KIAA1549–BRAF* fusion, by fluorescence in-situ hybridisation.[21] Samples were deemed positive or present for *3′BRAF* duplication if more than 15% of nuclei showed an extra copy of *3′BRAF* signal. Although this test is not a direct assessment of *KIAA1549–BRAF* fusion, it captures the *3′BRAF* tandem duplication event leading to *KIAA1549–BRAF* fusion. PCR amplification and dye termination sequencing of exon 15 of the *BRAF* gene with specific primers was used for $BRAF^{V600E}$ mutation testing.[21]

Pharmacokinetic studies evaluated the disposition of selumetinib and its active metabolite N-desmethyl-selumetinib on day 1, course 1 in consenting patients. Blood samples were collected before a dose and 1, 3, and 8 h (give or take 1 h) after selumetinib administration. A non-compartmental approach was used to establish the maximum concentration (C_{max}), time to maximum concentration (t_{max}), area under the plasma concentration–time curve from 0 to t_{last} (AUC_{0-8}), and the apparent oral clearance.

Pre-trial fresh frozen tumour material and paired blood samples were collected from consenting patients for whole exome and RNA sequencing analyses and done at the German Cancer Research Center (Heidelberg, Germany) to identify genomic alterations in the MAPK pathway or recurrent genomic alterations in other pathways. When only formalin-fixed paraffin-embedded tumour was available, DNA methylation array analysis for tumour subgrouping and generation of copy number plots as well as gene panel sequencing using a targeted neuro-oncology-specific gene set were done.[23,24] Putative alternative events (eg, novel *BRAF* fusions) were detected based on a combination of gene panel data and copy number information. Alternative *BRAF* fusion genes were detected by integrating RNA sequence data and copy number data inferred from exome sequencing or DNA methylation array results (Illumina Infinium MethylationEPIC Bead Chip Array, Illumina, San Diego, CA, USA). Suspected fusions were verified by PCR and Sanger Sequencing testing.

Outcomes

The primary endpoint was the proportion of patients who achieved a stratum-specific objective response (partial response or complete response) as assessed by the local site and sustained for at least 8 weeks.

Secondary endpoints comprised progression-free survival (defined as the time from treatment initiation until disease progression or death from any cause or time to last follow-up for patients without these events) in each of the six separate strata; associations between *BRAF* aberrations and treatment response and progression-free survival in patients for whom relevant biological data were available; MAPK aberrations by a combination of whole-exome and RNA sequencing; and characterisation of the inter-patient and intra-patient variability in the pharmacokinetics of selumetinib administered at the recommended phase 2 dose. All secondary endpoints that relate to strata 1 and 3 are presented here. Similar information for strata 2, 4, 5, and 6 will be reported elsewhere as the data become available.

Statistical analysis

Identical Simon's Minimax designs were used to determine the sample size for each stratum; an unacceptable response proportion was 10% and a desirable response proportion was 30%, leading to a sample size of 25 patients per stratum with 10% type 1 error and 90% power. An interim analysis was planned after 16 patients, and at least two responses were required to expand accrual to 25. The final success threshold was at least five responses in 25 patients. Interim analyses were done on Oct 28, 2014, based on 16 patients for stratum 1, and on Feb 24, 2018, based on 13 patients for stratum 3.

All eligible patients who initiated treatment were evaluable for the activity and toxicity analyses. Eligible

patients with available assessments or samples were also evaluable for the secondary analyses.

The Kaplan-Meier estimator was used for progression-fre survival calculations, and, if necessary, the log-rank test or Cox proportional hazards model was used for comparisons. Log-log transformation was applied to survival function to obtain confidence intervals. Log-rank tests and Cox proportional hazards models were used to explore associations between progression-free survival and various covariates to identify predictive biomarkers of response. Fisher's exact test and logistic regression were used to explore associations between response and various covariates. Analyses of the association of age at treatment and tumour size with response and progression-free survival, and association of MRI response and visual acuity were done post hoc. All statistical analyses were done in SAS (version 9.4).

This study is registered with ClinicalTrials.gov, number NCT01089101.

Role of the funding source

The American Lebanese Syrian Associated Charities provided funding and infrastructure support for the Operations Biostatistical Data Management Core personnel, but had no involvement in study design, patient recruitment, data collection, data analysis, data interpretation, or writing of the report. CTEP provided input on study design, approved the trial and its amendments, served as the investigational new drug sponsor, and reviewed the manuscript before submission. CTEP was not directly involved in patient enrolment, data collection, data analysis, or data interpretation. AstraZeneca reviewed the manuscript; however, they did not have a direct role in study design, patient recruitment, data collection, data analysis, data interpretation, or writing of the report. JF, AO-T, and SW had full access to all of the data in the study, and JF had final responsibility for the decision to submit for publication.

Results

38 patients were screened for possible enrolment in stratum 1, 26 (68%) of whom screened positive for either the *KIAA1549–BRAF* fusion or the *BRAF*^{V600E} mutation and were enrolled between July 25, 2013, and June 12, 2015 (figure 1). One (4%) of 26 was subsequently found to be ineligible because they had received radiotherapy within 12 months of registration, leaving 25 eligible and evaluable patients for analyses in stratum 1. An interim analyses of the first 16 eligible and evaluable patients was done on Oct 28, 2014. The interim threshold of two or more objective responses was attained, and thus accrual was expanded to the planned sample size of 25 patients. 18 (72%) of 25 eligible and evaluable patients had tumours that harboured a *KIAA1549–BRAF* fusion and seven (28%) a *BRAF*^{V600E} mutation. Demographic data and baseline characteristics are shown in table 1. 24 (96%) of 25 patients in stratum 1 received previous chemotherapy (median of three different chemotherapy regimens, range 1–6). 24 (96%) patients had previous surgery and five (20%) had previously received radiotherapy.

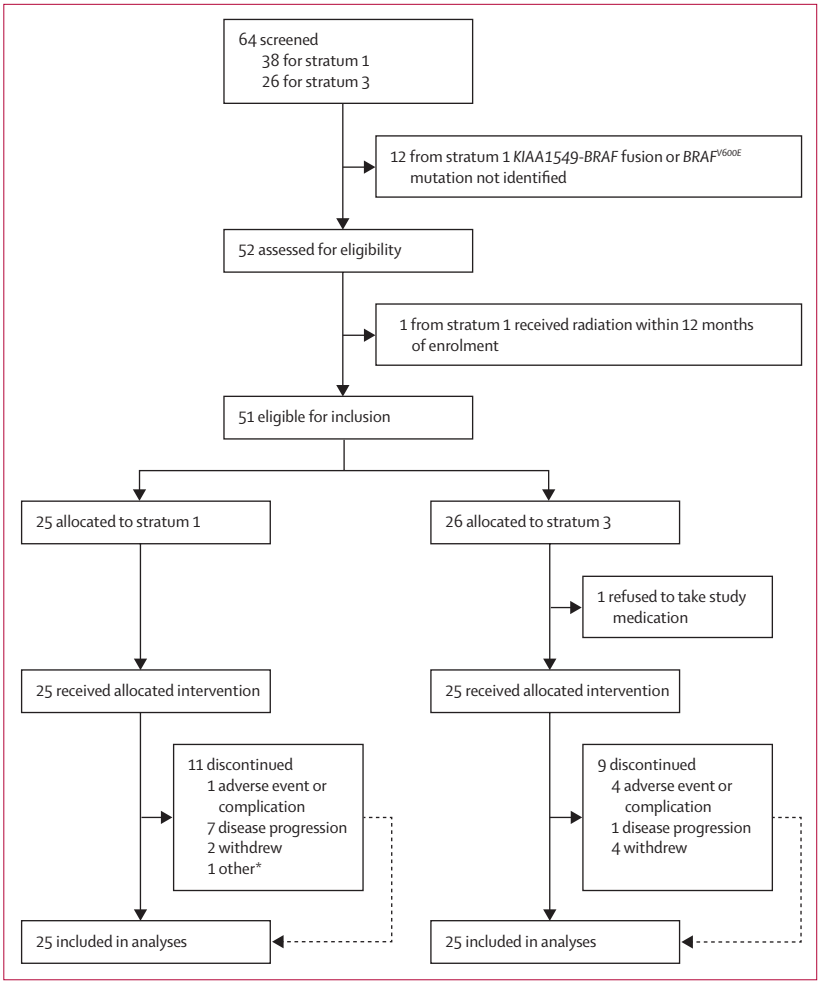

Figure 1: **Trial profile**

*Patient met progressive disease criteria per initial disease assessment definitions (revised in protocol version 17.1).

Nine of 25 patients (36% [95% CI 18–57]) achieved a sustained response (complete or partial response) for the purposes of the primary objective. Eight (89%) of nine partial responses were confirmed centrally; the ninth had a 43% tumour reduction on central review. The median time to a partial response was 7·54 months (IQR 7·31–12·40). The best response while on treatment by local assessment was partial response in nine patients (36% [18–57]), stable disease in nine patients (36% [18–57]), and progressive disease in seven patients (28% [12–49]).

2-year progression-free survival in stratum 1 was 70% (95% CI 47–85; figure 2A). Among the 18 patients with tumours with a *KIAA1549–BRAF* fusion, seven (39% [17–64]) had a partial response, compared with two (29% [4–71]) of seven patients with tumours with *BRAF*^{V600E}. There was no association between mutation

	Stratum 1 (n=25)	Stratum 3 (n=25)
Age at diagnosis, years	4·4 (0·3–19·1)	3·1 (0·6–12·2)
Age at study entry, years	9·2 (3·9–20·8)	10·2 (3·5–16·6)
Sex		
Male	12 (48%)	15 (60%)
Female	13 (52%)	10 (40%)
Ethnic origin		
Hispanic or Latino	3 (12%)	0
Non-Hispanic	22 (88%)	24 (96%)
Unknown	0	1 (4%)
Number of previous therapies*, median (IQR)	4 (3–5)	3 (2–4)
Race		
Asian	1 (4%)	0
Black	1 (4%)	0
White, non-Hispanic	23 (92%)	22 (88%)
Unknown	0	3 (12%)
Diagnosis		
Astrocytoma, NOS	0	2 (8%)
Glioma, NOS	0	19 (76%)
Pilocytic astrocytoma	25 (100%)	4 (16%)
Tumour location		
Brain stem	6 (24%)	5 (20%)
Brain, NOS	0	1 (4%)
Cerebellum, NOS	2 (8%)	0
Cisterna interpeduncularis	1 (4%)	0
Corpus callosum, NOS	0	2 (8%)
Cerebral hemisphere	2 (8%)	2 (8%)
Hypothalamus, NOS	9 (36%)	2 (8%)
Lateral ventricle, NOS	1 (4%)	0
Optic tract	1 (4%)	13 (52%)
Supratentorial brain, NOS	1 (4%)	0
Thalamus, NOS	2 (8%)	0

Data are median (range) or n (%), unless otherwise specified. *Including chemotherapy, radiotherapy, and surgery. NOS=not otherwise specified.

Table 1: **Demographics and baseline characteristics**

type and response rate (Fisher exact p=1). 14 (56%) of 25 patients completed all 26 courses of therapy with stable or responsive disease (sustained partial response). Figure 3A shows the greatest percentage change in locally assessed bi-dimensional measurements.

Age at treatment and tumour size were not associated with response or progression-free survival in post-hoc analyses (appendix pp 8–10). The specific *BRAF* aberration was not associated with response (appendix p 8), but was associated with progression-free survival: patients whose tumours harboured a $BRAF^{V600E}$ mutation had a shorter progression-free survival than did those whose tumours harboured the *KIAA1549–BRAF* fusion (*BRAF* fusion: eight events; $BRAF^{V600E}$: six events; p=0·046; figure 2C). 14 (56%) of 25 patients' disease had progressed by Aug 9, 2018: nine (64%) while on therapy and five (36%) while off treatment. The median time to progression was 22·93 months (IQR 7·24–27·34). Median follow-up for all eligible and evaluable patients (n=25) from treatment initiation to these analyses was 26·94 months (IQR 9·22–36·40). 11 (44%) of 25 patients had not progressed as of Aug 9, 2018, with a median follow-up since treatment initiation of 36·40 months (IQR 21·72–45·59). In patients who had not progressed, median follow-up since stopping selumetinib was 12·50 months (IQR 6·64–21·38) as of Aug 9, 2018.

Between Aug 28, 2013, and June 25, 2015, 26 eligible patients were enrolled in stratum 3 (figure 1). One (4%) patient refused to take any study drug, leaving 25 eligible and evaluable patients. 13 (52%) of the 25 patients had an optic pathway glioma. Three (12%) patients provided tumour samples and all three were negative for *BRAF* aberrations. Demographic data and baseline characteristics are shown in table 1. All 25 patients in stratum 3 received previous chemotherapy (median of three different chemotherapy regimens, range 1–6). Nine (36%) patients had previous surgery and one (4%) had received radiotherapy previously.

Ten of 25 patients (40% [95% CI 21–61]) achieved a sustained response (complete or partial response) for the purposes of the primary objective. Nine (90%) of ten partial responses were confirmed centrally, and the tenth had a 49% tumour reduction on central review. The median time to partial response was 3·57 months (IQR 1·76–5·36). One of the ten patients who achieved a partial response at course 4, which was sustained until course 10, subsequently developed progressive disease while on therapy at course 13. Therefore, for the purposes of defining best response, there were nine partial responses (36% [18–57]), stable disease in 15 (60% [39–79]), and progressive disease in one (44% [1–20]).

2-year progression-free survival in stratum 3 was 96% (95% CI 74–99; figure 2C; one event during treatment) and eight events by Aug 9, 2018). 16 (64%) of 25 patients completed all 26 courses of therapy with either stable or responsive disease (sustained partial response). Figure 3B shows the greatest percentage change in locally assessed bi-dimensional measurements. Age at treatment and tumour size were not associated with response or progression-free survival according to post-hoc analyses (appendix pp 11–13). Insufficient data on *BRAF* aberration status were available to assess this as a predictive marker. Eight (32%) of 25 patients had progressed by Aug 9, 2018: one (13%) while on therapy and seven (88%) while off treatment. The median time to progression was 27·95 months (IQR 25·74–37·84). Median follow-up for all eligible and evaluable patients (n=25) from treatment initiation to these analyses was 42·12 months (IQR 27·93–49·52). 17 (68%) of 25 patients had not progressed as of Aug 9, 2018, with a median follow-up since treatment initiation of 48·60 months (IQR 39·14–51·31). In patients who had not progressed, median follow-up since stopping selumetinib was 25·49 months (IQR 14·38–28·83) as of Aug 9, 2018.

Figure 4 shows dosing, duration of response, and duration of follow-up for all patients enrolled in both strata. The median time off therapy for all eligible and evaluable patients in both strata who had not progressed (n=28) was 20·28 months (IQR 10·33–26·68).

In stratum 3, ten (77%) of 13 patients with an optic pathway glioma had Snellen visual acuity comparisons in at least one eye at baseline and 1 year on therapy. Among the 18 evaluable eyes (in ten patients), there was improvement in visual acuity (≥0·2 logMAR improvement) in two eyes (11%) and stability (neither ≥0·2 logMAR improvement, nor worsening) in 16 (89%) eyes. No patient had worsening (≥0·2 logMAR worsening). Therefore, two (20%) patients had improved visual acuity and eight (80%) had stable visual acuity. Based upon Goldmann perimetry testing comparisons at baseline and 1 year, nine (90%) patients had stable visual fields and one (10%) had improvement. There was no obvious relationship between imaging response and vision as the two patients with visual improvement both had stable imaging.

23 (46%) of 50 patients participated in the optional pharmacokinetic studies. Median C_{max} was 1719 nM (IQR 917–6201), t_{max} was 1·40 h (1·20–2·30), and AUC_{0-8} was 3959 nM×h (3464–4951). Median apparent oral clearance was 10·9 L/h (9·0–16·0). Median AUC_{0-8} for the N-desmethyl-selumetinib was 327 nM×h (266–446). A linear association was noted between age and apparent oral selumetinib clearance (Spearman correlation coefficient; r=0·50; p=0·01). The association between selumetinib exposure and toxicity could not be investigated because only one patient had a grade 4 adverse event.

Complete DNA methylation profiles were generated for five patients from stratum 1 and one from stratum 3. These data were used to investigate DNA methylation-based tumour subgrouping (appendix p 14). Three (60%) of five cases in stratum 1 displayed the typical *KIAA1549–BRAF* fusion and one (20%) harbored a $BRAF^{V600E}$ mutation. In the fifth stratum 1 case, no *BRAF* aberration was identified. This patient's tumour screened positive for the *KIAA1549–BRAF* fusion; however, the *KIAA1549–BRAF* fusion was not detected based on DNA panel sequencing or copy number analyses, possibly owing to the low tumour purity (high normal tissue content) in this sample. Despite the absence of confirmation, this patient had a partial response on imaging. No obvious additional pathogenic mutations beyond *NF1* were identified in stratum 3 tumours. The small number of samples precluded any formal assessment of association with responses.

The most common drug-related toxic effects in both strata are shown in table 2. The most frequent grade 3 or worse adverse events were elevated CPK (five [10%]) and maculopapular rash (five [10%]; table 2). All drug-related toxic effects and all grade 3 and 4 adverse events in both strata are reported in the appendix (pp 1–5).

In stratum 1, ten (40%) of 25 patients required a dose reduction owing to toxic effects and one (4%) required two dose reductions (figure 4; appendix p 6). In stratum 3, eight (32%) of 25 patients required a dose reduction owing to toxic effects. No deaths were reported in the study. In stratum 1, one patient discontinued study drug owing to toxic effects: a grade 3 rash. In stratum 3, four patients discontinued study drug owing to toxic effects: grade 2 intolerable paronychia (n=1), grade 3 gastric haemorrhage (n=1), grade 2 intolerable fatigue (n=1), and grade 2 intolerable dyspnoea (n=1).

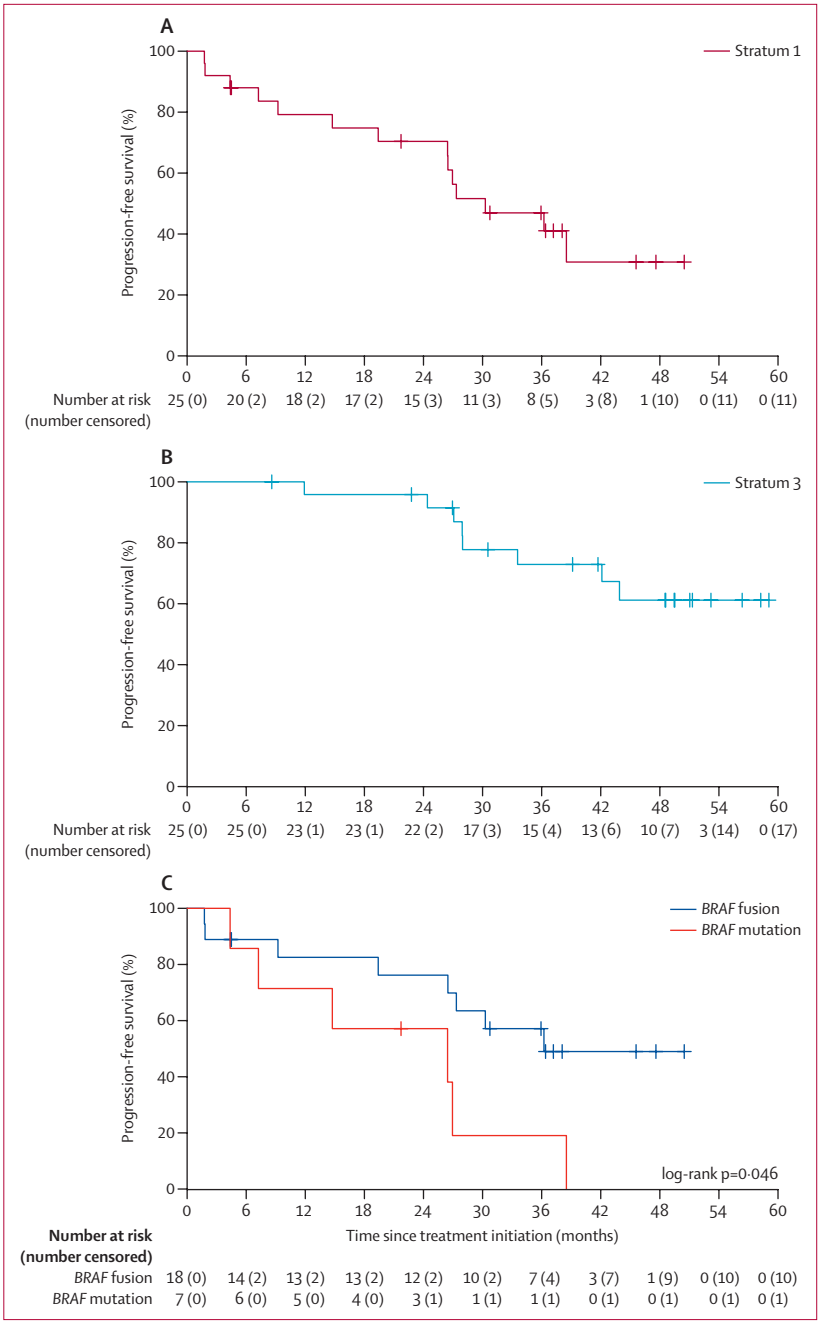

Figure 2: **Progression-free survival**
Stratum 1 (A), stratum 3 (B), and stratum 1 (C) according to specific *BRAF* aberration.

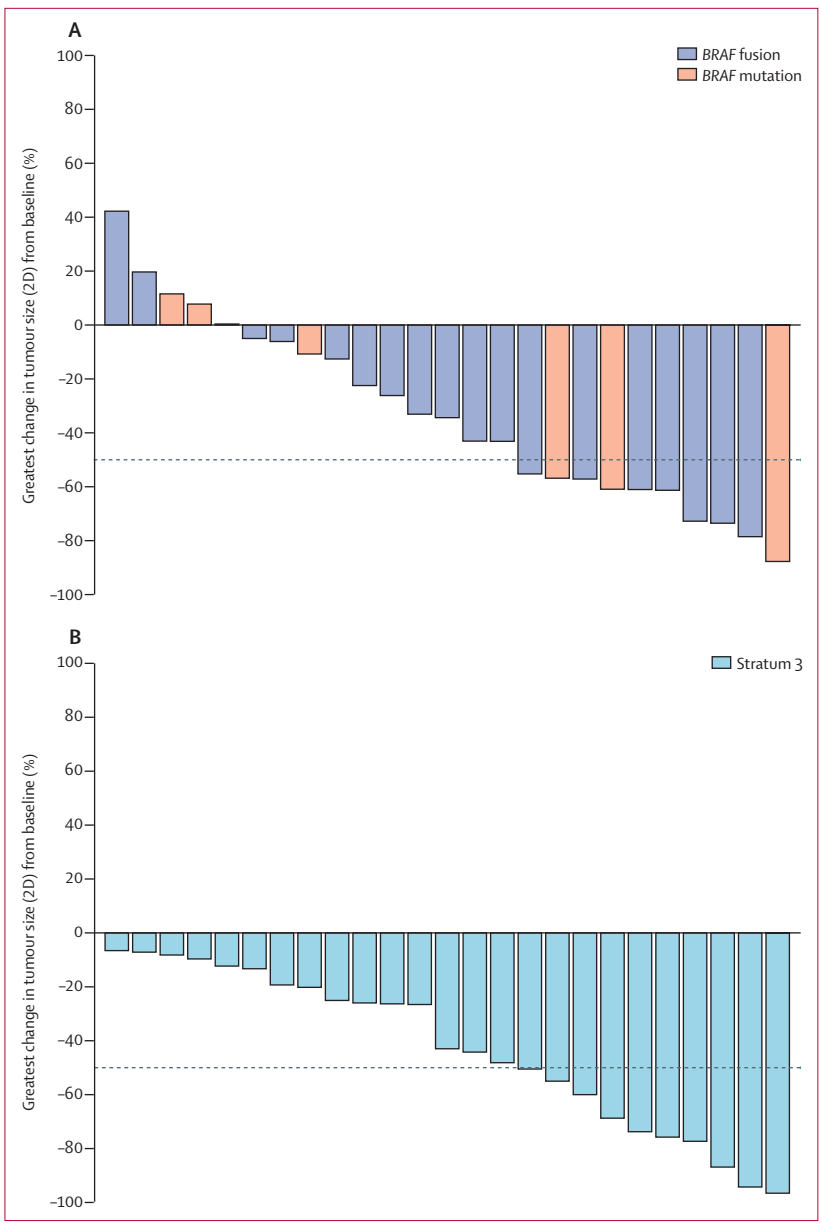

Figure 3: **Waterfall plots of the maximum percentage change in 2D tumour size**
Maximum percentage change from baseline in 2D tumour sizes during treatment in stratum 1 by *KIAA1549–BRAF* fusion and *BRAF*^{V600E} mutation (A) and in stratum 3 (B) . The grey dashed lines show 50% tumour reduction from baseline, which signifies a partial response. 2D=two-dimensional.

Discussion

In this multicentre, phase 2 study, selumetinib was active in recurrent, refractory, or progressive pilocytic astrocytoma with common *BRAF* aberrations and NF1-associated paediatric low-grade glioma. Both treatment strata assessed surpassed their statistical predetermined success thresholds based on response proportion.

In stratum 1, the proportion of partial responses in patients with tumours harbouring *KIAA1549–BRAF* fusions was higher than that for patients with tumours with *BRAF*^{V600E} mutations, but the specific *BRAF* aberration was not statistically predictive of response. It was, however, predictive of progression-free survival: patients with paediatric low-grade glioma who harboured a *BRAF*^{V600E} mutation had shorter progression-free survival than those with *KIAA1549–BRAF* fusions. This finding is similar to those from a report[25] in which progression-free survival was shorter in patients with paediatric low-grade glioma with *BRAF*^{V600E} mutations than in those with paediatric low-grade glioma with wild-type *BRAF* and *KIAA1549–BRAF* fusion when treated with chemotherapy and radiotherapy. Our data are, to our knowledge, the first to show the same negative prognostic value of a *BRAF*^{V600E} mutation in a homogenous group of paediatric low-grade glioma tumours treated prospectively with a MEK inhibitor. In patients with NF1-associated paediatric low-grade glioma, ten (40% [95% CI 21–61]) of 25 had a partial response, and only one patient progressed while on therapy. Several patients in both strata achieved between 1% and 49% tumour shrinkage and these observed stable disease outcomes are clinically beneficial. Since most patients will not die from their disease, current opinions are that progression-free survival and functional outcomes are as important as radiographic response.[15,19]

Progression-free survival and response data in this study compare favourably to those from previous trials in patients with recurrent paediatric low-grade glioma. In a phase 2 study of weekly vinblastine monotherapy in 50 evaluable patients with recurrent and refractory paediatric low-grade glioma,[26] 36% of patients achieved a response; however, the designation of minor response was included as a response for patients with 25–50% reduction in two-dimensional tumour measurements, which would have been categorised as stable disease in our study. If this designation were included in the current study, the proportion of patients achieving an overall response would increase. 5-year overall survival with vinblastine was 93·2% (SE 3·8) and event-free survival was 42·3% (7·2).[26] A PBTC phase 2 study[27] of bevacizumab and irinotecan in 35 evaluable patients with recurrent paediatric low-grade glioma showed 2-year progression-free survival of 47·8% (SE 9·3). Two (6%) of 35 patients had a documented response and patients received a median of 12 courses of therapy.

Our results for patients with NF1-associated paediatric low-grade glioma align with results published for patients with NF1 with plexiform neurofibromas. In the phase 1 plexiform neurofibroma trial,[22,28] MRI volumetric imaging was used to evaluate response. Approximately 70% of patients were classed as partial responders, defined as at least 20% tumour volume reduction, and most patients showed some degree of tumour shrinkage. These volumetric response definitions differ from the classic bi-dimensional 50% shrinkage classically used to define a partial response in paediatric low-grade glioma and used in the current study, perhaps explaining the

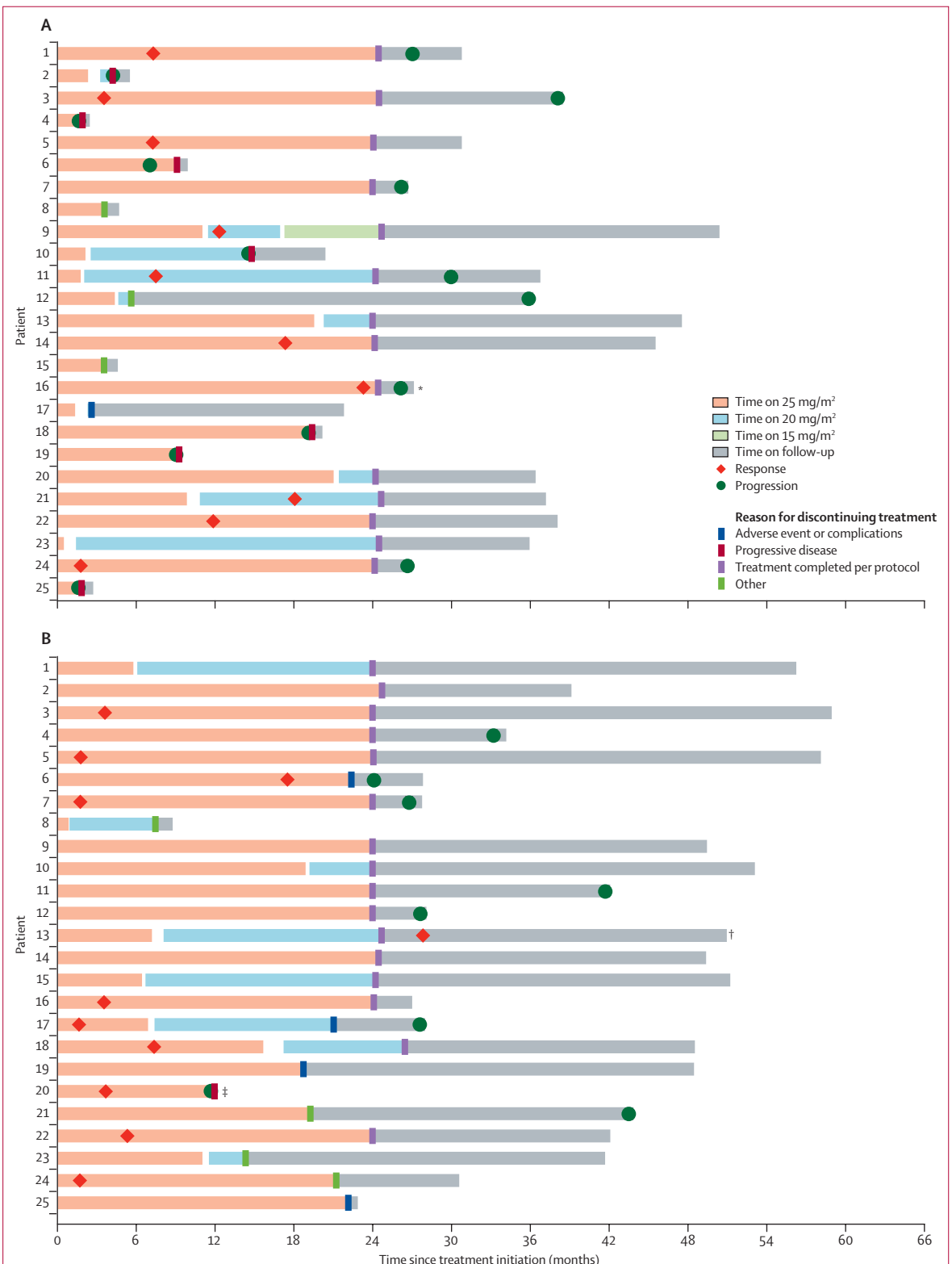

Figure 4: **Dosing, duration of treatment, reason for discontinuing treatment, and follow-up in stratum 1 (A) and stratum 3 (B)**
*Patient had a partial response at course 25, but it was not sustained and was not counted towards the primary success criteria. †Patient had a response, but because it was during off treatment, it was not counted towards the primary success criteria. ‡Patient had partial response from course 4 to course 10 and then had disease progression at course 13.

	Grade 1–2	Grade 3	Grade 4
Abdominal pain	12 (24%)	0	0
Alanine aminotransferase increased	20 (40%)	1 (2%)	0
Alkaline phosphatase increased	11 (22%)	0	0
Alopecia	7 (14%)	0	0
Anaemia	28 (56%)	0	0
Anorexia	6 (12%)	0	0
Aspartate aminotransferase increased	25 (50%)	0	0
Creatine phosphokinase increased	34 (68%)	5 (10%)	0
Constipation	11 (22%)	0	0
Cough	7 (14%)	0	0
Creatinine increased	7 (14%)	0	0
Diarrhoea	27 (54%)	2 (4%)	0
Dizziness	5 (10%)	0	0
Dry skin	28 (56%)	0	0
Duodenal ulcer	29 (58%)	0	0
Dyspnoea	30 (60%)	0	0
Oedema limbs	13 (26%)	0	0
Ejection fraction decreased	19 (38%)	1 (2%)	0
Erythema multiforme	5 (10%)	0	0
Fatigue	28 (56%)	0	0
Gastric haemorrhage	0	1 (2%)	0
Headache	14 (28%)	1 (2%)	0
Hyperglycaemia	10 (20%)	0	0
Hypertension	11 (22%)	0	0
Hypoalbuminaemia	31 (62%)	0	0
Hypocalcaemia	9 (18%)	0	0
Hypokalaemia	12 (24%)	0	0
Hypomagnesaemia	18 (36%)	0	0
Hyponatraemia	5 (10%)	0	0
Hypophosphataemia	7 (14%)	0	0
Lymphocyte count decreased	19 (38%)	0	1 (2%)
Lymphocyte count increased	21 (42%)	0	0
Metabolism and nutrition disorders–other	5 (10%)	0	0
Mucositis oral	7 (14%)	0	0
Nausea	21 (42%)	0	0
Neutrophil count decreased	14 (28%)	3 (6%)	0
Paronychia	19 (38%)	3 (6%)	0
Pericardial effusion	20 (40%)	0	0
Platelet count decreased	8 (16%)	0	0
Pruritus	10 (20%)	0	0
Rash acneiform	29 (58%)	2 (4%)	0
Rash maculopapular	26 (52%)	5 (10%)	0
Skin and subcutaneous tissue disorders–other	25 (50%)	0	0
Skin infection	7 (14%)	1 (2%)	0
Tooth infection	0	1 (2%)	0
Vomiting	22 (44%)	0	0
Weight gain	5 (10%)	1 (2%)	0
White blood cell decreased	19 (38%)	0	0

Data are number of patients (%). All grade 1 and 2 attributable toxic effects reported in ≥10% of patients combining both strata 1 and 3 are listed. Grade 1 and 2 non-attributable toxic effects were not reported per protocol. All grade 3 and 4 toxic effects combining both strata are also included. The highest grade observed within a patient for each toxicity is reported. No deaths were reported.

Table 2: **Adverse events**

response variation between the two trials. This common denominator of NF1 MAPK dysregulation seems to render these lesions more responsive to selumetinib therapy; however, the exact mechanisms of this increased susceptibility has yet to be elucidated.

Some patients did not respond and some progressed while on selumetinib. If additional molecular aberrations were found consistently among these less responsive tumours, combination therapies might be a potential strategy to overcome this resistance. A limitation of the current study was the scarcity of tissue available for more advanced molecular testing. Encouragingly, a substantial proportion of patients in both groups remained progression free at a median follow-up of 20·28 months since stopping selumetinib, showing that many paediatric low-grade gliomas can have prolonged stability even after cessation of therapy.

A large retrospective report of 4000 patients with paediatric low-grade glioma using Surveillance, Epidemiology and End Results data[29] revealed that 20-year overall survival was 87% (SE 0·8). The investigators concluded that future treatments should focus on disease control and minimisation of late effects. Also, a paediatric low-grade glioma international consensus panel[19] recommended that future studies should incorporate functional outcomes such as visual acuity, QOL, and motor function, since these morbidities are more common than mortality. Therefore, the activity of selumetinib is best evaluated in the context of toxicity, functional outcomes, and QOL.

As a MEK1/2 inhibitor, selumetinib has the benefit of avoiding the adverse event of paradoxical activation of the MAPK pathway that occurs when *BRAF–KIAA1549* aberrant paediatric low-grade glioma tumours are treated with direct *BRAF* inhibitors.[30] Overall, the toxicity profile of selumetinib was manageable, with few grade 3 and 4 toxic effects. This toxicity profile compares favourably to both upfront standard paediatric low-grade glioma chemotherapy and common chemotherapies used at the time of recurrence. In the CCG A9952 study,[3,5] 19% of patients developed grade 3–4 vincristine-associated peripheral neuropathy, and 26 (19%) of 137 in the carboplatin and vincristine group had grade 3–4 allergic reactions to carboplatin. In the CCG A9952 study,[3] depending upon the treatment group, 56–68% of patients developed grade 3–4 neutropenia, 15–35% had grade 3–4

thrombocytopenia, and 26–29% had grade 3–4 anaemia. In the phase 2 trial of weekly vinblastine,[26] the most common toxicities were haematological. 18 (36%) of 50 patients had grade 4 neutropenia requiring dose reduction and five patients required red blood cell transfusions. Five patients with NF1 also had grade 3 peripheral neuropathy. In the PBTC bevaicizumab and irinotecan trial,[27] the most common toxicities were grade 1 and 2 hypertension, fatigue, and epistaxis, and grades 1–4 proteinuria. These data contrast with the current study, in which only three (6%) of 50 patients had grade 3 neutropenia, one (2%) had grade 4 lymphopenia, and there were no grade 3 or 4 thrombocytopenia or anaemia events. There was no significant peripheral neuropathy or allergic reactions. As expected, grade 1 and 2 asymptomatic CPK elevation and grade 1 and 2 rashes were some of the most common attributable toxic effects reported with selumetinib. Rashes were often mitigated with topical supportive care. Some patients required selumetinib dose reductions; however, responses did not seem to be minimised in those patients requiring dose reductions, suggesting that the recommended phase 2 dose is not necessary for response. In the CCG A9952 study, patients with NF1 who were non-randomly assigned to carboplatin and vincristine had less toxic effects than patients without NF1 receiving carboplatin and vincristine.[3,5] Our data on selumetinib do not show this difference.

In a multi-institutional adult phase 2 study of selumetinib in patients with advanced biliary cancer, patients receiving selumetinib experienced an average of 5% non-fluid weight gain.[31] In the current study, five (10%) of 50 patients had grade 1 and 2 weight gain and one (2%) had a grade 3 weight gain. Although there is concern that this adverse event might be unrecognised and thus under-reported, future prospective studies are needed to evaluate this more completely in the paediatric population.

A limitation of the current trial is that QOL and patient-reported outcomes were not assessed; however, there are some notable differences in the administration of selumetinib and classic chemotherapy. Selumetinib requires monthly, shorter clinic visits and is taken orally with no requirement for central line placement, compared with weekly carboplatin and vincristine, bi-monthly bevacizumab and irinotecan, and weekly vinblastine visits, which often require a central line.

The visual function outcome data in patients with optic pathway glioma revealed stable or improved vision in all patients. Fisher and colleagues[32] reported on 115 previously untreated patients with NF1 with optic pathway glioma and retrospectively evaluated visual outcomes after chemotherapy. 32% of patients had visual acuity improvement, 40% had stable visual acuity, and 28% had worsening visual acuity. Similar to our data, there was no association between imaging and visual outcomes.[32] Although we included fewer patients, our data on selumetinib in patients with recurrent paediatric low-grade glioma compares favourably with Fisher and colleagues' data after classic chemotherapy in previously untreated patients.[32] A limitation of these data are the small patient numbers and the absence of more standard visual acuity assessments such a Teller acuity cards and HOTV testing.

To our knowledge, aside from the use of mTOR inhibitors in tuberous-sclerosis-associated subependymal giant cell astrocytoma,[33] which is rare in the paediatric population, selumetinib is one of the first prospectively tested and active molecularly targeted agents in paediatric low-grade glioma. These data provide a new alternative treatment for patients with multiply recurrent paediatric low-grade glioma. These data have also led directly to the development of two large multi-institutional, prospective, randomised, phase 3 COG trials in previously untreated patients comparing selumetinib with standard chemotherapy in both NF1-associated and sporadic paediatric low-grade glioma. In these forthcoming COG studies, functional outcomes including visual acuity, QOL, and neuropsychological and patient-reported outcomes are included as both primary and secondary objectives.

Contributors

JF acquired, analysed, and interpreted data; wrote the manuscript; approved the version to be published; and agreed to be accountable for all aspects of the study. AO-T, SW, CFS, DTWJ, SMP, and MJF conceived and designed the study, analysed and interpreted data, revised the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the study. TYP, AHL, NL, AB, RJP, SG, IFP, RIJ, LAD, and MS conceived and designed the study, revised the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the study. LBK, IQ, PGF, GD, PB, SGK, GV, JSS, AP, ZP, BT, JYJ, SSH, DSE, and SC revised the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the study. IJD and MF analysed and interpreted data, revised the manuscript, approved the version to be published, and agreed to be accountable for all aspects of the study.

Declaration of interests

RJP serves on a selumetinib plexiform neurofibroma advisory committee for AstraZeneca. RIJ participated in a paid selumetinib advisory board for AstraZeneca and was an employee of AstraZeneca from September 2014 to May 2017. MJF acted as an unpaid consultant for AstraZeneca and received travel reimbursement to participate in an advisory board meeting. All other authors declare no competing interests.

Data sharing

The PBTC makes de-identified research data, including patient-level information as well as a data dictionary, available to other investigators for use in research projects. Interested investigators may submit in writing a description of the research project, the specific data requested, and a list of investigators involved with the project and their affiliated research institutions. Once approved, the responsible investigator will be required to complete a Data Use Agreement as part of the conditions for data release. Requests for data will only be considered once the primary study analyses have been published.

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