1Visual outcomes following everolimus targeted therapy for neurofibromatosis type 1-associated

2optic pathway gliomas in children

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Abbreviations	
VA	Visual acuity
NF1	Neurofibromatosis type 1
OPG	Optic pathway glioma
LGG	Low grade glioma
REiNS	Response evaluation in neurofibromatosis and schwannomatosis
MRI	Magnetic resonance imaging
VF	Visual field

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44**Abstract**

45Data for visual acuity (VA) after treatment of neurofibromatosis type 1-associated optic pathway

46gliomas (NF1-OPGs) is limited. We retrospectively collected VA, converted to logMAR, before

47and after targeted therapy with everolimus for NF1-OPG, and compared to radiologic outcomes

48(14/18 with NF1-OPG, 25 eyes [3 without quantifiable vision]). Upon completion of treatment,

49VA was stable in 19 eyes, improved in 4 eyes, and worse in 2 eyes; visual and radiologic

50outcome were discordant. In summary, the majority of children with NF1-OPG exhibited

51stabilization of their VA after everolimus treatment. A larger, prospective study will help

52delineate visual outcomes after targeted therapy.

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58 Introduction

59 Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by loss of 60 function alterations in the gene that encodes *neurofibromin*, a negative regulator of the 61 RAS/MAPK pathway. Nearly one-fifth of children with NF1 will develop a low grade glioma 62 (LGG) involving the optic pathway (NF1-OPG), [1] which has the potential to cause significant 63 visual dysfunction. While the impact of NF1-OPGs on VA in children has been examined, [2,3] 64 studies specifically evaluating visual outcomes after treatment have been limited, and include 65 heterogeneous patient populations with sporadic or NF1-OPGs undergoing various treatments.

66   To date, the impact of targeted therapy on visual outcome in NF1-OPGs is uncertain; it is 67 not clear if visual and radiologic outcomes are concordant. The purpose of this study was to 68 retrospectively evaluated the impact of oral everolimus treatment on visual acuity outcomes 69 leveraging a multicenter study of children with recurrent, radiographically progressive LGG. In 70 addition, we investigated the relationship between visual and radiologic outcomes.

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72 Subjects and Methods

73   This was an exploratory, retrospective analysis of vision outcome in a multicenter, open-74 label, phase II study of daily oral everolimus for recurrent radiographically-progressive NF1-75 LGGs, conducted by the NF Clinical Trials Consortium (NCT01158651). [4] The total cohort 76 included 23 participants from 10 sites, between 1 and 21 years of age, with recurrent LGG after 77 treatment with a carboplatin-containing regimen.

78   Visual acuity (VA) data pre-treatment and following completion of therapy with 79 everolimus were collected for participants with NF1-OPGs. VA was converted to logMAR. 80 Analyses were calculated on a per-subject and per-eye basis when appropriate. The Response

81Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria were utilized to assess

82VA outcomes.[5] VA improvement was defined as ≥0.2 logMAR improvement, whereas a

83worsening VA was defined as ≥0.2 logMAR decrease. A change of < 0.2 logMAR in either

84direction denoted stable vision. For per-subject analysis, response definitions were in

85accordance with previous studies on NF1-OPG VA outcomes.[2] If one eye showed VA

86progression, the event was coded as "VA worsening" for the subject, even if VA testing in the

87other eye was unchanged or improved. Similarly, if VA improved in one eye while the other was

88stable, this was coded as "VA improvement" for the subject. A comparison of VA outcomes with

89radiological outcomes was performed using descriptive statistics.

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91**Results**

92*Demographics*

93　　　A total of 23 children with NF1-LGGs were treated with everolimus. The clinical details

94and radiologic response of the entire cohort have been reported previously.[4] Eighteen of the 23

95study participants were treated for an OPG. Participating sites provided available VA data prior

96to and at the end of treatment with everolimus. Of these, 4/18 children did not have quantitative

97VA at the start of protocol therapy, and 3 children each had one eye without quantifiable VA.

98Visual outcomes were therefore available for 14 children and 25 total eyes.

99　　　Clinical characteristics of children with NF1-OPGs compared to non-OPG LGGs are

100shown in Table 1. As a group, children with OPG were younger at treatment start. Disease

101stability and/or tumor shrinkage, using 3-dimensional analysis by central review, was seen in

10211/18 children with OPG and 4/5 with a non-OPG LGG.

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104 *Visual Outcomes*

105   The majority of children were assessed using Snellen visual acuity. There was an

106 improvement in VA (≥ 0.2 logMAR improvement) in 4/25 eyes (16%), stability (neither ≥ 0.2

107 logMAR improvement nor worsening) in 19/25 eyes (76%), and VA worsening (≥ 0.2 logMAR

108 worsening) in 2 eyes (8%). On a per subject analysis of VA outcome, 12/14 had stable or

109 improved vision after treatment, and 2/14 had worsening of vision. For the children with

110 quantifiable VA, there was no correlation between MRI responses and VA on a per-eye or per-

111 subject analysis (Table 2).

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113 **Discussion**

114   NF1-OPGs are rarely life-threatening; however, they are often associated with significant

115 impact on vision. Although the goal of treatment is visual preservation/improvement, previous

116 clinical trials have mostly focused on MRI outcomes, rather than visual outcomes. Towards this

117 goal, REiNS criteria were established to standardize visual assessments for NF1-OPG.

118 Everolimus has activity as a single agent for radiographically progressive NF1-LGG following

119 standard upfront treatment with a carboplatin-containing therapy.[4] In an exploratory analysis, we

120 assessed visual outcome data on a subset of participants with NF1-OPGs.

121   While age-appropriate VA normative data are available and the methods of VA

122 assessment have good test-retest reliability,[5] formal evaluations in children with NF1 may be

123 confounded by the presence of learning difficulties or attention deficit disorder.[5] VA

124 assessments, both by per-eye and by per-subject evaluation, were largely stable and/or improved

125 in our study.

126   To date, this is the largest study to examine the impact of targeted therapy on visual

127outcomes in NF1-OPGs. A multicenter study of children with previously untreated NF1-OPG

128retrospectively evaluated visual outcomes after traditional chemotherapy.[2] Improvement in VA

129was noted in 32% of patients, while 40% had stable VA and 28% had worsening VA.

130Selumetinib, a MAP/ERK Kinase I/II inhibitor demonstrated activity in patients with recurrent,

131refractory or progressive LGG, including a stratum of children with NF1 associated LGG.[6] VA

132outcome was available for 10/13 patients with NF1-OPG, among which there was improvement

133in VA in 2/18 eyes and stability in 16/18 eyes. No patient experienced worsening acuity.

134Interestingly, an improvement or worsening of visual outcome in our cohort did not always

135correlate with radiologic outcome. Similar to our results, in both of the aforementioned studies,

136there was no correlation between radiographic response and VA. Although our cohort was too

137small to draw a definitive conclusion, this observation underscores the need to specifically assess

138for VA loss in children with OPGs, rather than use MRI as the sole outcome.

139   There were several limitations of this study. The visual outcome data were not collected

140prospectively. In addition, these data reflect multiple methods of VA testing, thereby limiting

141our ability to establish a singular method for analyzing visual outcome. We did not collect

142outcome of visual fields (VF) or other visual function assessments, such as optical coherence

143tomography. Although formal VF testing may not be achievable for very young children, the

144age at which children can start to be tested is clinically relevant in the context of symptomatic

145NF1-OPGs.

146   Identification of effective, well-tolerated therapies for NF1-associated OPG is of

147paramount importance. Despite the retrospective nature of the analysis, these findings highlight

148the need to incorporate visual function, with both VA and VF, as functional clinical outcomes at

149presentation, after treatment, and throughout the clinical course of OPG management. A recent

150international consensus panel recommended that future studies of pediatric LGG should include

151functional outcomes, including visual function[7] and specific functional outcomes for children

152with NF1 have also been recommended.[5] The current Children's Oncology Group study

153(NCT03871257) compares standard chemotherapy to selumetinib and includes VA outcomes as

154a co-primary endpoint coupled with other functional outcomes and quality of life measure as

155important secondary objectives.

156   Taken together, we retrospectively analyzed visual outcome data from a large,

157multicenter study of everolimus for NF-OPGs to evaluate the impact of targeted therapy on

158visual function. Future prospective studies will be necessary to evaluate the impact of OPGs on

159VA and VF as independent functional outcome metrics for treatment efficacy in clinical trials.

167**Conflict of Interest**

168MWK served on a Novartis Scientific Advisory Board unrelated to everolimus

169BRK is on a medical advisory panel for SpringWorks Therapeutics

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