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Titolo Tesi:

Children with Neurofibromatosis type 1 and Optic Pathway Glioma: A collaborative research to design innovative clinical trials based on functional outcomes

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Premessa alla tesi

Questo progetto di tesi vuole riassumere il lavoro svolto nel corso di questi anni in qualità di dottorando di ricerca, con indirizzo in Oncoematologia, Immunologia e Genetica.

L'argomento scelto è stato quello dei bambini affetti da glioma delle vie ottiche associati a NF1 e del loro outcome dopo il trattamento chemioterapico.

In particolare, la tesi è suddivisa in tre parti secondo un ordine cronologico.

Il progetto di dottorato è stato un percorso di ricerca collaborativa in cui sono stati discussi e presentati a livello internazionale dati preliminari di studi clinici multicentrici, in collaborazione con gruppo di lavoro multidisciplinare di esperti.

Durante questo percorso, il dottorando ha partecipato inoltre ai maggiori appuntamenti scientifici sull'argomento, con l'obiettivo finale di disegnare ed elaborare un nuovo studio clinico basato su un disegno innovativo e su *outcome* funzionali.

Le diverse parti della tesi, oltre che essere una serie di passaggi fondamentali verso l'obiettivo, rappresentano quindi la prima tappa di un progetto collaborativo a medio termine di cui il dottorando si sta facendo carico.

Il progetto è stato redatto in inglese alla luce della composizione del gruppo collaborativo al quale l'autore ha partecipato durante l'intero corso del dottorato, mantenendo un profilo internazionale di partecipante attivo e propositivo e nel quale gruppo l'autore ha guadagnato un ruolo di crescente importanza e progressiva autorevolezza.

Riassunto

I gliomi delle vie ottiche (OPG) associati a neurofibromatosi di tipo 1 (NF1) rappresentano il 10-15% dei gliomi a basso grado (LGG), che sono i tumori del sistema nervosa centrale più frequenti in età pediatrica. La strategia terapeutica attuale che prevede l'utilizzo di chemioterapia ha dimostrato dai dati dello studio europeo SIOP-LGG2004 NF1+ una sopravvivenza libera da malattia pari a circa 74.5% a cinque anni. Dai dati preliminari analizzati, tuttavia, gli esiti funzionali in termini di deficit visivo sono ancora poco studiati. I dati preliminari di funzionalità visiva, mostrano che l'acuità visiva migliora in 23% dei pazienti e fino a metà (46%) dei bambini trattati con chemioterapia presentano una visione compromessa alla fine del follow-up. Tali dati dimostrano che nonostante una buona sopravvivenza libera da malattia l'*outcome* visivo sia insoddisfacente e sottolineano l'importanza di documentare ed analizzare la funzionalità visiva quale *end point* primario. Non è chiaro quali possano essere i fattori che influenzano il rischio di perdita del visus e quali pazienti possano beneficiare dal trattamento chemioterapico attuale.

Uno studio retrospettivo mono istituzionale, condotto durante la permanenza presso il centro di oncologia *Institut Gustave Roussy* (Francia), ha cercato di identificare la presenza di fattori radiologici distinti e associati a una diversa risposta alla chemioterapia nei bambini affetti da OPG e NF1. I dati dello studio dimostrano che la presenza di un glioma esteso alle regioni esterne alle vie ottiche (multicentrico) sia associato a una risposta meno favorevole alla chemioterapia. Un coinvolgimento delle regioni delle radiazioni ottiche (PLAN 4) sembra inoltre in parte responsabile di una prognosi peggiore. È possibile utilizzare i criteri radiologici identificati per confermare i dati dello studio pilota su casistiche più ampie.

Un workshop multidisciplinare, condotto a livello europeo ha permesso di analizzare i dati clinici e radiologici di una popolazione selezionata di bambini con NF1 e OPG, rivedendo a priori e posteriori i fattori che possano influenzare le indicazioni alla chemioterapia o all'osservazione, con l'obiettivo di individuare possibili fattori di rischio per un deficit visivo da un lato e, dall'altro, i fattori associati a un possibile beneficio del trattamento chemioterapico. La funzione visiva iniziale, l'estensione del tumore, l'evoluzione clinica e radiologica sono i criteri sui quali è basata la selezione dei pazienti in diversi gruppi di rischio. Su questi criteri è stata elaborata una strategia terapeutica innovativa, che comprende un braccio osservazionale per i pazienti definiti a basso rischio (gruppo A) mentre una randomizzazione tra osservazione e trattamento è prevista per i pazienti del gruppo di rischio intermedio (gruppo B). Per i pazienti del gruppo B, randomizzati a ricevere il trattamento e per quelli ad alto rischio (gruppo C) candidati invece direttamente a ricevere il trattamento, una successiva randomizzazione a tre diversi bracci di chemioterapia comprendenti un braccio con una terapia biologica è stata elaborata grazie all'utilizzo di una metodologia statistica innovativa (MAMS). Tale metodologia statistica dovrebbe permettere di valutare in contemporanea più di due bracci di trattamento randomizzati e di scartare il peggiore (o selezionare il migliore), riducendo la numerosità necessaria per le risposte ai quesiti dello studio. Uno studio prospettico condotto dai colleghi nordamericani su bambini con NF1 e nuova diagnosi di OPG dovrebbe permettere di validare i fattori prognostici noti e/o individuare ulteriori possibili fattori che influenzano le indicazioni al trattamento e l'*outcome* visivo. Il gruppo europeo

sta valutando la partecipazione a tale studio che arruolerà i pazienti nei prossimi 2-3 anni, con l'obiettivo di implementare i criteri di rischio proposti nello studio europeo futuro.
Infine è stato presentato il lavoro collaborativo di stesura delle linee guida proposte, in corso di approvazione dal gruppo europeo, per la valutazione standardizzata della funzionalità visiva e l'interpretazione clinica e statistica dell'*outcome* visivo, principale *end-point* funzionale proposto nel prossimo studio in bambini affetti da NF1 e OPG.

Abstract

Neurofibromatosis type 1 associated optic pathway gliomas (OPG) are relatively frequent (10-15%) among childhood low-grade glioma (LGG), the most common pediatric brain tumor neoplasm.
Overall therapeutic strategy includes the use of first line chemotherapy for progressive tumor and has shown to be well tolerated and effective to control tumor growth, considering a 5 yrs-PFS of 74.5%, in the prospective SIOP-LGG NF1+ 2004 study data. However, preliminary data regarding visual outcome reveal how, despite good tumor control rate, the functional outcome of many children with NF1 OPG is still unsatisfactory. In fact from the SIOP prospective series, about 45% of children treated with chemotherapy had a bilaterally compromised visual acuity at last follow-up, with some degree of visual improvement in a minority of children. These data pinpoint the importance of considering vision rather than radiology as a primary outcome measure in these patients. Prognostic factors analysis showed that surgery is a risk factor for worse PFS. These data failed to demonstrate significant differences by age, gender, tumor site, indication to treatment.
A retrospective study was undertaken during the French period at the *Institut Gustave Roussy* to identify possible radiology factors that may predict response to chemotherapy. Results have shown that OPG involving the optic radiation (PLAN 4) and multi-site tumors have a worse response to chemotherapy. The prognostic impact of these factors needs to be confirmed in a larger and prospective population.
A multidisciplinary workshop was held in Europe, with the aim to analyse case by case, clinical presentation and radiological tumor aspects. From this clinical ground we tried to analyse factors influencing the risk of progression and the possible benefit of chemotherapy. We discussed and proposed factors determining treatment indication according to a risk-based strategy. This strategy includes an observation arm for children at low risk, a randomization between observation and treatment in children at uncertain or intermediate risk and a further, multiple treatments randomized arm for children at high risk. This innovative multi-arms multi-stage (MAMS) study design will speed up the results of randomised trials by “picking the winner” between multiple arms by interim analysis and will reduce number of patient required to answer scientific questions for such rare diseases. A US-lead NF1 OPG natural history study with the aim to develop evidence based criteria for treatment indication, to which European Centres will collaborate, will prospectively generate additional information that could implement and modify this risk based proposed strategy within the next years.
The collaborative guideline for visual assessment and visual outcome interpretation in OPG clinical trials is presented. Visual outcome, based on a standardized visual assessment, will be the primary outcome of new trials evaluating treatment efficacy, in children with NF1 OPG. These aspects are of paramount relevance for a successful interpretation and comparison of data from the upcoming international studies.

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1. Introduction

1.1. Optic pathway glioma in children

The most common solid tumours in children are primary brain tumours, contributing more than 20% of all childhood neoplasms and representing the leading cause of cancer-related death in children. Of the primary brain tumours, gliomas represent the most frequent pathologic type. [1,2,3]

In children, the most common glioma is the WHO grade I pilocytic astrocytoma (PA). These tumours typically arise during the first two decades of life, without a clear sex predilection.

PAs can occur sporadically or in the context of the neurofibromatosis type 1 (NF1)-inherited cancer syndrome. In either case, PAs usually affect midline structures, including the cerebellum, optic pathway and brain stem. [1,2,4]

Optic pathway gliomas (OPG) arise in 15%–20% of children with neurofibromatosis type 1 (NF1), occur preferentially in young children and cause vision loss in as many as half of those affected. NF1-associated OPGs usually present at a younger age than sporadic OPGs [1,2,5,6]. NF1-associated gliomas are typically detected by 4–5 years of age and rarely grow after age 10 years, whereas some cases are diagnosed in the second decade of life. In children with NF1, PAs may form anywhere, between the optic nerve and the optic radiations, although the anterior optic pathway (optic nerves and chiasm) is most frequently involved. Infiltration of the post-chiasmal optic radiations is found about 10 to 20% of individuals with NF1-associated OPG, and is usually associated with more aggressive clinical behaviour [3]. Whereas sporadic OPG usually affects only one optic nerve, it is common to encounter bilateral optic nerve in NF1 associated OPG. (Figure n. 1).

Pathogenesis of OPG involves both fusion of the KIAA1549 and BRAF genes, which predominate in sporadic pilocytic astrocytoma and loss of neurofibromin, in NF1 associated tumors. BRAF tandem duplication as a result of the gene fusion, results in increased BRAF kinase function. Deregulated BRAF kinase activity leads to increased mitogen-activated protein kinase (MAPK) pathway signalling, leading to higher levels of cell proliferation [5]. Somatic BRAF tandem duplication and gene fusion and rearrangement are specific to sporadic OPG and mutually exclusive with NF1 mutations. In NF1 mouse models complete loss of neurofibromin (Nf1-/-) as a result of somatic mutation in pre-neoplastic cells, only in a permissive microenvironment, where haplo-insufficient neurofibromin activity (Nf1+/-) is present in every other cell, makes tumor cells growing [6,7,8,9].

In the NF1 context, the increased mTOR pathway signalling and reduced cAMP level seems to be the two most relevant driving pathways for OPG proliferation and survival in children with NF1[9,10]. (Figure n. 2 and n. 3). These causing genetic mutation occur in specific susceptible pre-neoplastic cells (glial or stem cells) within particular brain regions. As example, murine NF1 OPG most likely arise from neuroglia progenitors residing within the third ventricular zone. [2].

Figure n.1: Tumor site distribution between sporadic and NF1 associated low grade glioma [1,2,3]

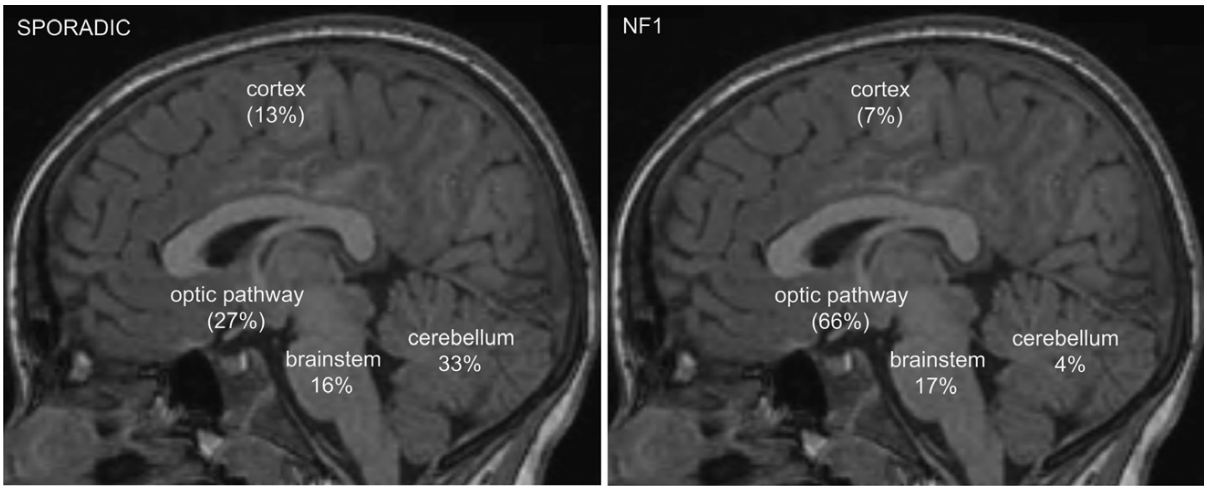


Figure n.2: Possible molecular pathways involved in NF1 OPG [2]

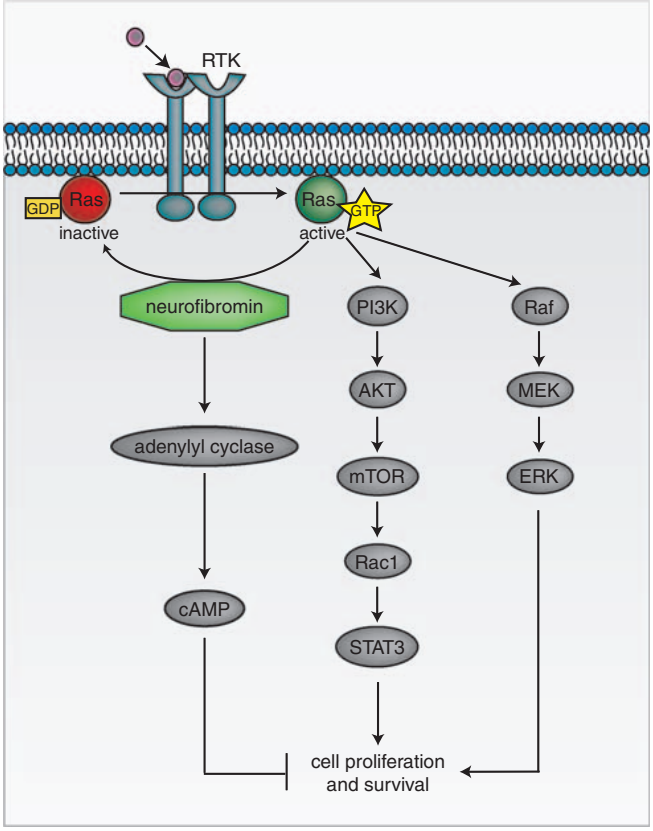
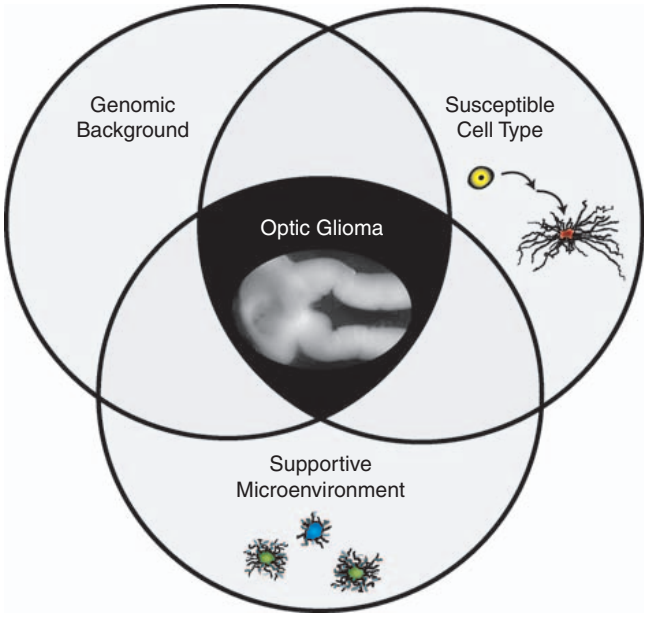


Figure n.3: Tumor micro-environment and the OPG development [2]



When an NF1-associated OPG is discovered, tumor can be large and exhibit various degree of contrast enhancement on magnetic resonance imaging. However, neither the size nor degree of contrast enhancement correlates with the clinical behaviour of the tumour. In this regard, the clinical course of NF1-associated OPGs tends to be more indolent compared to their sporadic counterparts.

Children with NF1 may be asymptomatic and OPG may be detected only by screening MRI. A minority of cases, however, present with various symptoms, including visual loss and other neurological or endocrine signs. [10 -13].

The natural history of children with NF1 and OPG is heterogeneous, ranging from progressive disease to spontaneous tumor regression [13-18]. Also visual prognosis is rather unpredictable, with both patients whose vision is normal and children who suffer severe visual impairment including blindness. In fact, while 15% of patients with NF1 develop OPGs, only one-third of children require treatment for clinical (visual loss) and/or radiological progression. First-line treatment in the majority of cases is carboplatin/vincristine chemotherapy. Response rates range from 30% to 50%, and as many as 70% of children exhibit no further tumour growth while on treatment. [14-23].

1.1 The SIOP-LGG studies

The International Society of Pediatric Oncology (SIOP) is the first example of how international collaboration makes feasible to run large randomized clinical trials even in rare diseases.

A first collaborative LGG group was established under the collaboration of neuro-oncologists from Italy, UK and Germany, leading to the first prospective trial with a common strategy for children with LGG, namely the SIOP-LGG1 study. Results of the SIOP-LGG 1 study are now published in peer review journals. [25].

After the SIOP-LGG1 a second generation of studies, the SIOP-LGG 2004 was designed, including a randomized study comparing standard chemotherapy (2 drugs) and intensified induction chemotherapy (3 drugs) and prolonging treatment from 12 to 18 months. The study opened in 2003-2004, in more than 15 participating European countries and is nowadays one of the largest prospective trial in children with brain tumour. Preliminary results of this second generation trial in children with LGG have been recently presented at major neuro-oncology congresses and will be soon published.

Ten years later, the SIOP-LGG 201x is under construction and dedicated SIOP-LGG working subgroups focused on different aspects of childhood LGG. A randomized prospective study for children with LGG without NF1, namely *LoGGic* Europe Trial, is now going to open within the next two years all over Europe comparing the standard of care with a different chemotherapy regimen with a possibly less neurotoxic regimen. A second randomization question will then compare different treatment durations (18 Vs. 12 months). Since 2011 a separate NF1 LGG multidisciplinary sub-group is working on a separate protocol for children with NF1 associated OPG and most of this thesis refers to the collaborative research done or under development in this international working sub-group.

1.2 Classic and Functional outcomes

The classic end points in childhood brain tumor advanced clinical trials included overall (OS) as primary and progression-free-survival (PFS) as secondary outcome respectively. Especially for childhood LGG, where OS is almost universally very favourable (around 85-90%), the PFS has become a relevant outcome to understand the chronic natural history of this chronic disease.

Progression-free survival (PFS) in neuro-oncology is usually defined as the time from study enrolment until a patient has any of the following events: tumor progression, defined by imaging; neurological worsening due to tumor; sustained increase in steroid dose necessary to keep symptoms controlled; or death. However a drawback of PFS is that it depends on assessment by imaging which is not necessarily a reliable and an objective means by which to define progression [16]. In addition, it is feared that, in some instances, improved tumor control may be obtained at the cost of increased long-term toxicity resulting, in some cases, in unsatisfactory health-related quality of life. These aspects are particularly worrisome in childhood LGG, a disease that is more like a chronic disease than a life-threatening malignant cancer. In fact the risk long-term tumor and treatment related side effects must be carefully taken into account in the clinical management.

To date, also OPG clinical trials in children have focused on imaging outcomes, with tumor response and/or progression-free survival used as measures of treatment success. However, increasing evidence from case reports, case series, and larger studies indicates that imaging outcomes do not correlate with visual outcomes following treatment. In fact, in a large multi-institutional retrospective review, only one-third of subjects had concordant visual and imaging outcomes. Since the primary goal of treatment is preservation of visual function, therapeutic success should be based on visual rather than imaging endpoints. [16, 17,18].

Collaborative groups in US and Europe have been more recently working together with the objective to identify robust endpoints that can be incorporated into future clinical trials and used to most effectively define and compare treatment efficacy. The *Response assessment Evaluation in children with Neurofibromatosis and Swannomatosis* (REiNS) Visual Outcomes Committee headed by M.J Fisher, from the Children's Hospital of Philadelphia (CHOP) and Rob Avery (Children's National Medical Centre, Washington DC) is a good example of collaboration between US group and European experts where a discussion of unsolved and critical aspects regarding visual outcome in NF1 associated OPG lead to find a common language and the publication of shared guidelines for next generation clinical trials. [18]

1.3 The need for Innovative Trial Designs

Different cytotoxic chemotherapy drugs or regimen have been historically used to treat children with LGG and OPG, showing that it is possible to avoid or defer radiotherapy in a relevant percentage of children. [19].

This approach has been considered particularly interesting and useful for children with NF1 associated tumors, as these children at particularly high risk of post radiation vascular complications (moya moya) and/or second tumors. [22, 23].

The only two randomised trials in childhood LGG, one in US, comparing vincristine-carboplatin to a multidrug regimen (TPCV) [24] and the other in Europe (SIOP-LGG2004) comparing vincristine-carboplatin induction phase to an intensified regimen containing etoposide for the first 10 weeks failed to demonstrate significant differences between arms. Moreover, despite in the SIOP-LGG2004 treatment (vincristine-carboplatin) was prolonged from 12 to 18 months to improve outcome compared to the previous study, no randomized trial ever compared different treatment durations. [25]

Two randomised questions will be launched in the next SIOP-LGG 2015 study called LoGGic Europe with two different treatment arms (vincristine-carbo Vs. vinblastine-carbo) and two different treatment durations (12 Vs. 18 months). A graphical representation of the overall LGG strategies and the non NF1 SIOP-LGG (LoGGic) trial flow diagrams are presented in figure n.4 and 5.

Figure n.4: Overall flowchart of next trials in children with LGG

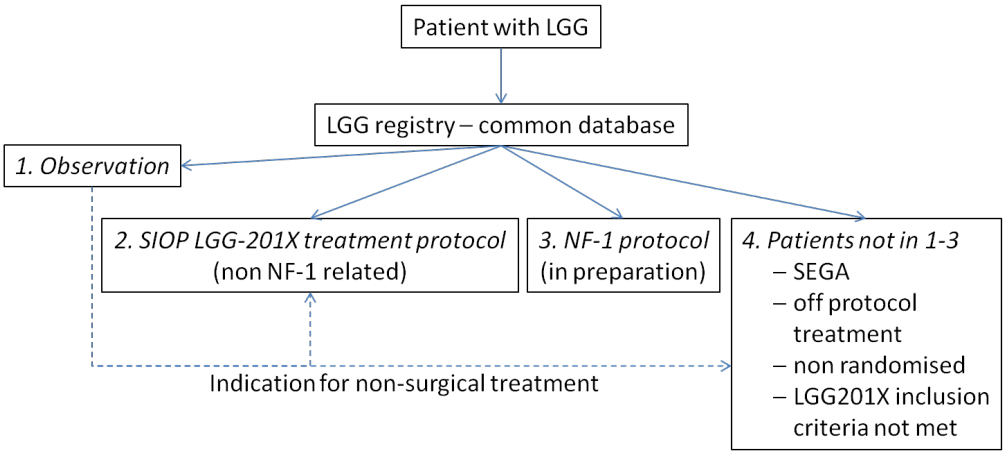
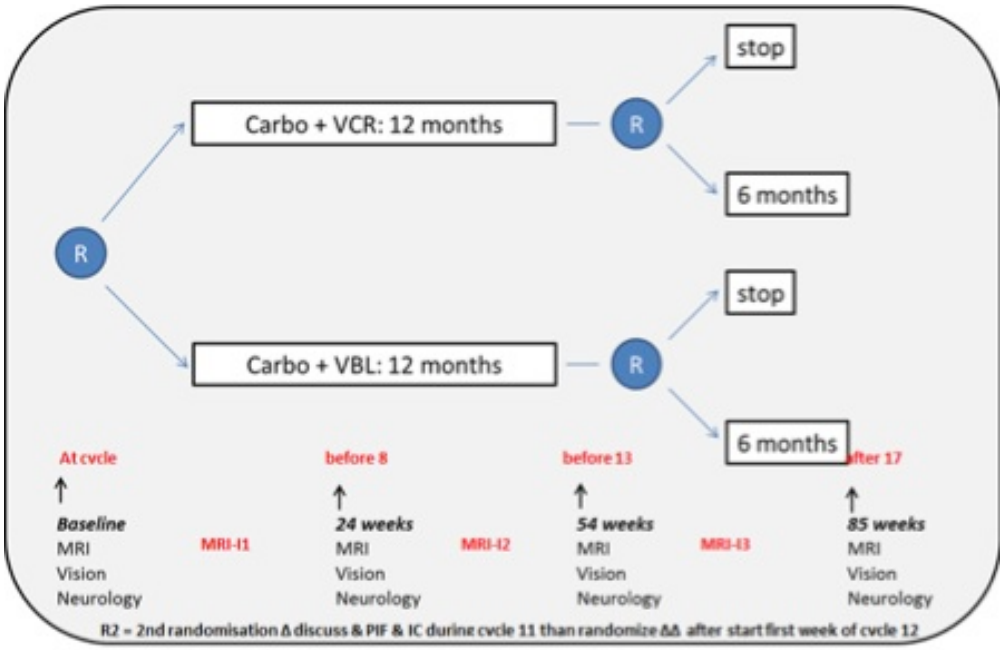


Figure n.5: Overall double-randomized treatment strategy in children without NF1 and LGG



Given the rare incidence of OPG, particularly in the NF1 study group, collaborative efforts must met with innovative design criteria to reduce as lower as possible the number of patients to detect any difference when comparing two or more treatments.

To test multiple experimental treatments against a control treatment in the same trial provides several advantages over doing so in separate trials. The main advantage is a reduced sample size due to a shared control group being used instead of a separate control group for each treatment. Other advantages include that direct comparisons can be made between experimental treatments and that it is administratively easier to apply for and run one multi-arm clinical trial compared to several traditional trials. Multi-arm multi-stage (MAMS) clinical trials include interim analyses so that experimental treatments can be dropped if they are ineffective; also, if desired, the trial can be designed so that it allows early stopping for efficacy if an effective experimental treatment is found [26]. The MAMS design and concepts have been first presented by Keith Weathley a bio-statistician from the Birmingham clinical trial unit, involved in the NF1-OPG group.

With a relatively reduced number of patients enrolled for each arm, the MAMS design would "pick the winner" among multiple arms where a difference is first detected. Some experimental arms are indeed dropped off by interim analysis for a "lack of benefit".

This innovative design then combines an accelerated development of significant results, by increasing participation rate and patients accrual, minimizing costs by comparing several different possible treatments to standard of care in the same trial.

More interestingly, such a flexible design would allow bring in new drugs/arms during the course of the trial as soon as data from phase I-II will become available and of some interest. This latter aspect is of particular relevance in the context of a disease like LGG, where biologic studies and whole genomic sequencing are rapidly revealing the undiscovered molecular basis of LGG and identifying multiple targets for new molecules and drugs that are already in early clinical trials.

2. Outline of the thesis

Part 1 focuses on preliminary results of the previous SIOP-LGG 2004 NF1 prospective trial, focusing on the OPG NF1 sub-group treated with chemotherapy. Patient characteristics, overall strategy, indications to treatment, administration and toxicity of chemotherapy, PFS and possible prognostic factors are presented. The Author, orally at the SIOP 2012 congress, has presented these results. This part focuses also on the preliminary visual outcome analysis in children with NF1 associated OPG treated with CT, presented orally by the Author, at the International Society of Pediatric Neuro-Oncology congress (ISPNO) in 2012.

Part 2 focuses on the international experience at the French *Institute Gustave Roussy* (IGR). During this 10 months period a retrospective analysis was performed in collaboration local oncologists and radiologists, with the aim to identify possible clinical-radiological related aspects in children with NF1 OPG and treated with chemotherapy. The Author at recent international working group meetings presented this study and a manuscript has been now submitted for publication.

The part n.3 focuses on the contribution of the Author to the development and design the next prospective randomized trials for children with NF1 and OPG. It includes reports and original data from the 1st multidisciplinary workshop (radiology and ophthalmology) as well as the treatment indication criteria SIOP-E proposal including a randomised strategy between observation and treatment and notes of the recent investigator meeting on a natural history prospective US study, in children with newly diagnosed NF1 OPG. Finally the proposed strategy for the SIOP E-NF1 OPG study treatment arm, based on a multi-arms multi stage (MAMS) design is presented together with the proposed SIOP-E guidelines for visual assessment and visual outcome for clinical trials in children with OPG.

3. Part 1: The prospective SIOP-LGG2004 NF1 chemotherapy study

3.1 Preliminary analysis of children with NF1 and LGG treated with chemotherapy [27]

Enrico Opocher, Angela De Paoli, Gianluca De Salvo on behalf of the SIOP-LGG NF1 subgroup

The SIOP-LGG 2004 NF1 study includes a non-randomized chemotherapy strategy based on the combination vincristine-carboplatin for treatment duration of 18 months in children with NF1 and progressive LGG. This study population represents the largest cohort of prospectively collected data on childhood NF1 associated LGG and chemotherapy treatment, until now, with more than 250 patients with NF1 and LGG (OPG n= 224, other sites n = 44) enrolled until 31st of December 2011. The clinical and demographic characteristics of the study population are presented in table n. 1 separated by OPG and other sites (non OPG) tumors. Data from children with NF1 associated extra-OPG tumors (Other sites) were not reported here.

The OPG sub-group analysis

Two hundred and twenty four children (n =224) with NF1 and OPG were treated with CT. Median age was 3.6 and 5.1 years at OPG diagnosis and at start of CT respectively. About 10% of patients were younger than 2 years at the start of CT, while 46.9% were > 5 years of age at enrolment. There was a slightly female vs. male preponderance among children with OPG treated with CT (58 Vs. 42%). Tumor site distribution was defined according to the classic Dodge staging. Thirty-four (15.2%) children had a tumor confined to one/both optic nerve/s (Dodge I); while 52 (32%) patients had an OPG with involvement of optic nerve and/or chiasm (Dodge II) and the other 137 children (61%) had a post chiasmatic diffusion of OPG (Dodge III). In 18% of children it was reported a multiple site tumor involvement along with the primary OPG. As NF1 is a well known multiple cancer predisposition syndrome these multiple tumors were not classified as metastatic.

Table n.1: Characteristics of the study population (NF1 LGG treated with CT)

NF1 patients treated with CT	OPG (n = 224)	Other sites (n = 44)	Overall (n = 268)
Gender			
Male	94 (42%)	23 (52.3%)	
Female	130 (58%)	21 (47.7%)	
Median Age Years (range)			
At diagnosis	3.6 (0.1-16)	6.8 (1.8-16.7)	4.1 yrs.
At enrolment	5.1 (0.4-17)	8.1 (1.8-17.2)	5.1 yrs.
NF1 type			
Sporadic	89 (39.7%)	17 (38.6%)	106 (39.6%)
Familial	99 (44.2%)	22 (50%)	121 (45.1%)
Not known	36 (16.1%)	5 (11.4%)	41 (15.3%)
Site of tumor			
OPG	224 (100%)	-	83.6%
Supratentorial midline	-	21 (47.7%)	
(others)	-	8 (18.2%)	
Brainstem	-	7 (15.9%)	
Cerebral hemisphere	-	8 (18.2%)	
Dodge stage			
I (optic nerve only)	34 (15.2%)	-	
II (nerve + chiasm)	52 (23.2%)	-	
III (post chiasmatic)	137 (61.2%)	-	
Multiple site	42 (18.8%)	12 (27.3%)	54 (20.1%)

As shown in table n.2, in more than half of the patients (54.5%) treatment indication was visual decline without radiological tumor changes. Primary tumor radiological change was instead the primary indication to start CT in 13.8 % without and in 9.8% with accompanied visual deterioration respectively. A small number of patients were treated because of other reasons (19.6%) or severe symptoms including threat to vision (2.2%).

Table n.2: Indications to treatment

Indication to treat	OPG	Other sites	Overall
Tumor growth only	31 (13.8%)	12 (27.3%)	43 (16.0%)
Visual deterioration only	122 (54.5%)	4 (9.1%)	126 (47.0%)
Tumor growth and visual deterioration	22 (9.8%)	1 (2.3%)	23 (8.6%)
Severe symptoms	5 (2.2%)	10 (22.7%)	15 (5.6%)
Others	44 (19.6%)	17 (38.6%)	61 (22.8%)

Treatment was relatively well tolerated (Table n.3). Hematological and neurological were the two most frequent toxicities with 90% of patients with hematological and 21% neurological grade 3 or 4 toxicity. At least one hospitalization was necessary in 122 children during chemotherapy (46.6%). Allergy to Carboplatin was frequent (n = 161) occurring at median time from diagnosis of 8.5 months (range 5.5 -11.8 months) and requiring change to alternative arm in 103 and chemo interruption in 18 children (12%) patients. Alternative regimens included cisplatin and cyclophosphamide and vincristine or vinblastine single agent weekly, upon to the physician decision.

Table n. 3: Overall CT related toxicities

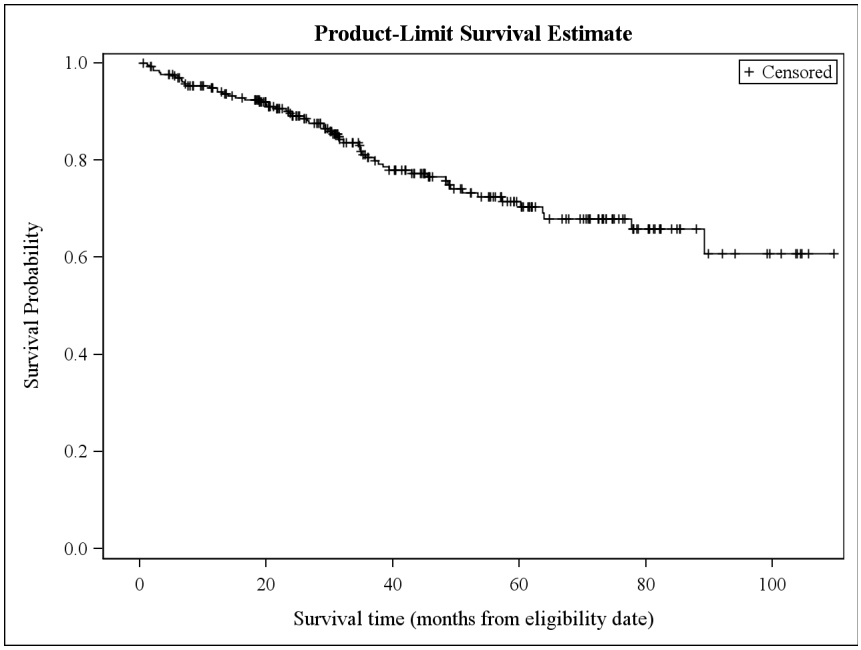
	Optic Pathway **Glioma** **N=219**
Haematologic Grade	
0/nm	15 (6.8)
1-2	6 (2.7)
3-4	198 (90.4)
Neurologic Grade	
0/nm	80 (36.5)
1-2	91 (41.6)
3-4	48 (21.9)
Others Grade	
0/nm	13 (5.9)
1-2	96 (43.8)
3-4	110 (50.2)
Toxic death	1 (0.5)

Data regarding progression free survival are available for 263 out of the 268 treated children. It is worth to remember that the definition of PFS included death (for all reasons), progression of a residual tumor, relapse following complete remission or appearance of new or progression of existing metastases. The PFS was essentially a radiology based outcome measure, not taking systematically into account the visual outcome possibly unrelated to radiological tumor changes.

After a median follow-up was 41.4 months (0.5 – 109.7) the 5yrs-PFS in the overall group of NF1 associated LGG group was 71.4% (95%CI 63.9 -77%) see figure n.5. There were 58 events (progressions). Analysis by tumor location showed that PFS in the OPG subgroup was slightly better (5yrs-PFS = 74.5%) compared to other sites (68.3%).

Results of the study population were presented as oral abstract at the SIOP 2012 congress [27]

Figure n.5: The overall 5yrs-PFS 71.4% (95%CI 63.9 -77%) of the 263 children with NF1 LGG



Prognostic factors analysed were age, tumor site, gender, indications to treatment, any surgery performed are summarized in table n.4

Table n. 4: Univariate analysis of prognostic factors for PFS

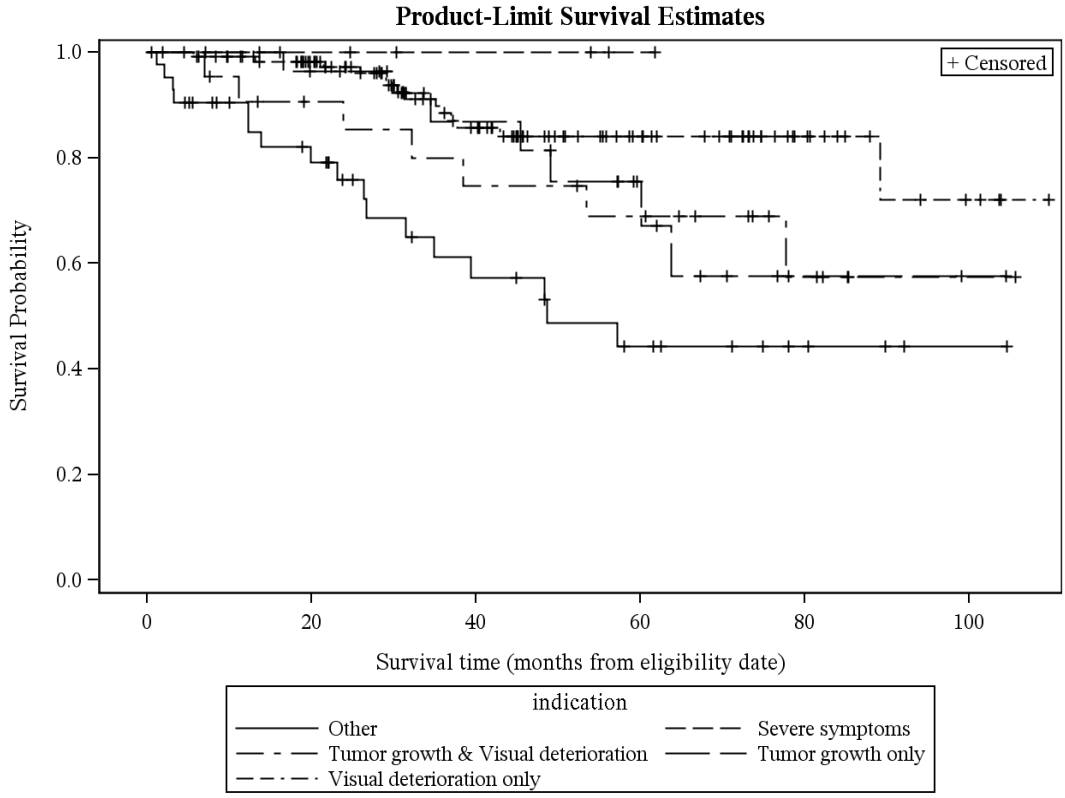
Characteristic	N	N. failed	5-yrs PFS (95%CI)	*P*-value
Gender				
Male	97	13	76.1 (61.6-85.8)	0.5975
Female	125	20	75.2 (59.3-85.5)	
Age, years				
≤5	106	17	69.8 (52.8-81.7)	0.5772
>5	116	16	81.9 (69.5-89.6)	
Age, years				
≤2	21	5	40.4 (7.2-73.2)	0.3100
2-5	85	12	77.9 (61.9-87.8)	
>5	116	16	81.9 (69.5-89.6)	
Age, years				
≤2	21	5	40.4 (7.2-73.2)	0.1263
>2	201	28	80.5 (71.4-87.0)	
Any surgery				
Yes	33	11	52.8 (28.2-72.5)	<0.0001
No	189	22	79.8 (68.7-87.4)	
Dodge classification*				
Stage 1: optic nerve only	31	2	94.4 (66.6-99.2)	0.2851
Stage 2: chiasma +/- optic nerve	43	6	82.9 (65.3-92.1)	
Stage 3: chiasma + diencephalic extension	126	22	67.3 (51.6-78.9)	
Dodge classification*				
Stage 2: chiasma +/- optic nerve				0.4202
Stage 3: chiasma + diencephalic extension				

Overall the only variable associated with significantly better PFS seemed to be radiological vs. surgical OPG diagnosis (p <0.0001). It seems also that young children tended to have a worse PFS, but different cut off used for analysis (<2, 2-5 or > 5, 8 years) were not significant.

A trend towards a better PFS (p = 0.28) is described in children with less extensive OPG (Dodge stage I means optic nerve/s only) having a slightly better PFS compared to Dodge II-III OPG. Gender seems not to be associated with different outcome.

Analysis of PFS by different treatment indications (in figure n.6) reveals that patients with visual deterioration as the sole indication to treatment (without radiologic progression) had a better outcome (5yrs-PFS = 84.1%) compared to radiological progression (5yrs-PFS = 75.6%) or a combination of clinical and radiological progression (5yrs-PFS = 68.9%) or other reasons (5yrs-PFS = 44%).

Figure n.6. PFS by treatment indications in OPG subgroup only



3.2 Visual outcome in children with NF1 OPG after chemotherapy [28]

When the SIOP-LGG2004 study was designed the primary outcome was the PFS according to a standardized overall strategy. Visual information was not mandatory for patient enrolment. As a result of this visual assessment was either not done or not standardized in as many as 60% of children with OPG and NF1 and treated with CT and data regarding visual outcome, when first analysed, were significantly incomplete.

Despite significant efforts to retrieve and analyse visual function data this lack of complete information limited and hamper any relevant and accurate conclusion on this functional critical aspect. This is particularly worrisome, as we have previously shown that about 50% of children have received chemotherapy because of visual loss as the main indication to treatment.

According to a definition of change of 0.2 log MAR or more as a visual change (improvement/decline) a preliminary analysis of visual outcome *per patients* in the NF1 LGG group showed that visual improvement, at least in term of VA, occurred in 23% of enrolled children. VA remained stable in 32% and worsened in 35% of children, despite chemotherapy. More than half of the children with NF1 and OPG who underwent chemotherapy for progressive disease had a positive response to chemotherapy (considering stable and improved visual acuity cumulative rate).

We used WHO based definition of different threshold for visual acuity preservation, stating the vision was preserved (not impaired) if visual acuity (VA) was > 3/10 in both eyes, partially preserved if VA was > 3/10 in the best eye or compromised if VA was < 3/10 in both eyes.

Among the 50 evaluable patients, at start of treatment vision was preserved in 22% (n =11), while it was partially preserved in 34% (n =17) and compromised in 42% (n= 21) of children. In one patient VA was missing at diagnosis.

At the last follow-up vision was preserved in 28% (n = 14), partially preserved in 26% (n = 13) and compromised in 46% (n = 23)(see figure n.7) [28]

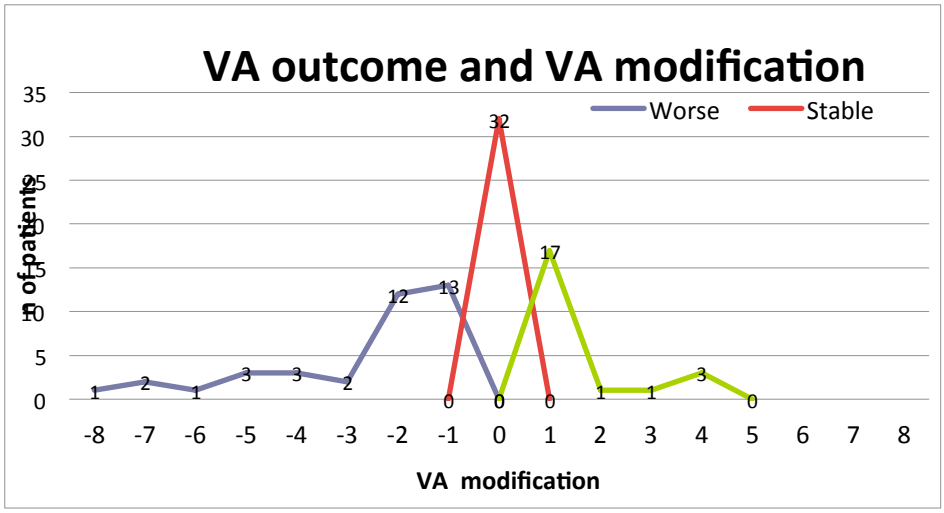
According the previously defined categories of visual impairment, 11% of patients improved from a lower to a better vision category, while 70% remained in the same category and 18% deteriorated to a worse category after chemotherapy.

Figure n.7: visual preservation at diagnosis/enrolment (row) and at the last follow-up (column)

	FOLLOW-UP FORM				
Frequency Percent Row Pct Col Pct	Compromised	Partial	Preserved	Not done	Total
ENROLMENT/DIAGNOSIS FORM					
Compromised	18 36.00 85.71 78.26	1 2.00 4.76 7.69	2 4.00 9.52 14.29	0 0.00 0.00 .	21 42.00
Partial	4 8.00 23.53 17.39	9 18.00 52.94 69.23	4 8.00 23.53 28.57	0 0.00 0.00 .	17 34.00
Preserved	1 2.00 9.09 4.35	2 4.00 18.18 15.38	8 16.00 72.73 57.14	0 0.00 0.00 .	11 22.00
Not done	0 0.00 0.00 0.00	1 2.00 100.00 7.69	0 0.00 0.00 0.00	0 0.00 0.00 .	1 2.00
Total	23 46.00	13 26.00	14 28.00	0 0.00	50 100.00

The magnitude of visual changes in patients with visual acuity decline (defined as change in acuity scoring system) was higher than the one of those of patients with visual improvement, in the OPG NF1 sub-group, as shown in figure n.8. This underlines that a qualitative changes in in terms of visual acuity should be encountered coupled with a quantitative evaluation of the magnitude of such visual changes and, perhaps, the absolute value of visual acuity at the end of treatment.

Figure n.8 Magnitude of visual acuity changes according to type of change



4. Part 2: The retrospective study at IGR

During the PhD time frame a 10 months period was conducted in France, working as senior clinical resident at one of the leading centre for pediatric solid tumors, the Institut Gustave Roussy (IGR), in Villejuif. A side from clinical duties and on calls activities the student also worked on a project in collaboration with local pediatric oncologists and local radiologists to better understand if there is a possible clinical-radiological correlation in children with NF1 and OPG. The following retrospective analysis is now a final draft to be submitted to a peer-review journal for publication and is here presented as relevant part of the PhD thesis.

4.1 Radiological features and response to chemotherapy in a retrospective cohort of children with NF-1 and progressive optic pathway glioma: A pilot study

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The goal of our study was to describe radiological (magnetic resonance imaging) features of OPG in children with NF1 at the time of diagnosis and to determine any potential radiologic predictive factor of response to chemotherapy.

Methods

We collected the files of all pediatric patients who underwent chemotherapy for progressive OPG in the context of NF1 between Jan 1999 and 2011 at IGR institution (45 patients files initially retained). We retrospectively screened radiological tumors presentation at the time of diagnostic and faced those imaging criteria to radiologic and clinical response to chemotherapy. A retrospective, observational design was used, conducted by 4 physicians: 2 neuro-radiologists and 2 pediatric oncologists. The Ethics Committee of the hospital approved the study.

Eligibility Criteria

The NF1 status was defined according to the consensus criteria published in 1988. Patients who had undergone first line chemotherapy for their progressive, symptomatic, or threatening OPG were selected. Progression could be defined either radiological (significant enlargement of the

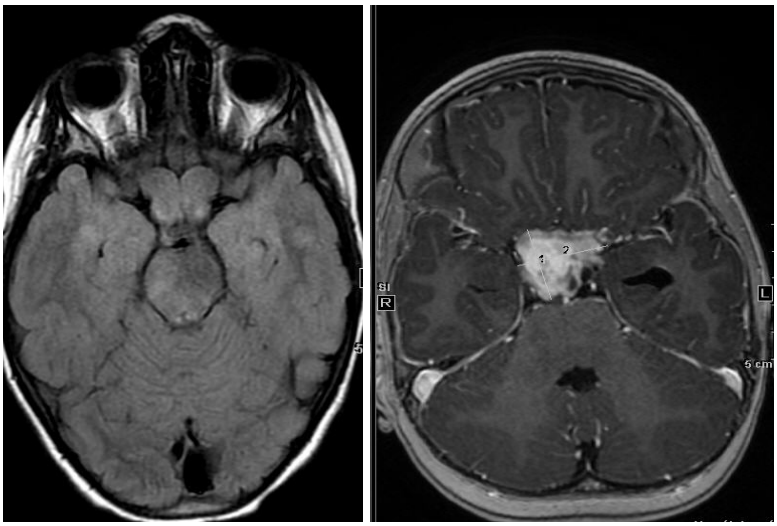
tumor, newly contrast uptake, progression of residual tumor after surgical debulking) and/or clinically (significant deterioration of vision or new neurologic signs). Histologic confirmation of the diagnosis was not mandatory for the study; indeed biopsy or debulking of those kinds of tumors is rarely performed. Chemotherapy regimen used drugs recommended by the International Society of Paediatric Oncology (SIOP), according to Baby Brain (BBSFOP) or SIOP-LGG protocols. Only children for whom at least two magnetic resonance imaging examinations were available were retained for analysis: one performed before any kind of treatment, and one performed at the end of chemotherapy. The baseline magnetic resonance imaging (MRI) must have been performed in the month prior the first day of treatment. The acquisition protocols were not identical for each patient because of the retrospective nature of the study, however, all examinations should include at least a T2-weighted (FLAIR or not) axial plane, a T2 weighted additional plane (coronal or sagittal), and a T1 weighted injected plane. Among 45 files initially selected only 23 were eligible for analysis, responding to all the previously listed criteria.

Radiological analysis and evaluation

For each patient, we first reviewed the magnetic resonance imaging scan made at presentation, and then the scan made at the end of chemotherapy. We performed this analysis blind to clinical data. The radiological analysis consisted of two different stages. First we determined different groups of tumors, based on their imaging characteristics, second we measured radiological response to chemotherapy. The final analysis confronted radiological and clinical response to chemotherapy with radiological defined tumors groups. Radiological variables taken into account to identify tumors groups were: the tumoral extend along optics pathway based on Dodge modified classification, the presence or not of a tumoral enhancement (focal or diffuse), the global tumoral presentation (purely infiltrative form or exophytic and mixed form), and the presence of a concomitant extra-optic pathway tumor (see figure n.1).

Figure n.1: examples of Infiltrant (a) Vs. shaped (b) morphology aspects

a b



Tumor involvement of the optic nerves, chiasm, and proximal optic tracts was defined according to the presence of thickening on T1 or T2-weighted images. Enhancement after a gadolinium injection was also considered indicative of involvement. The distal optic tracts were considered involved if they appeared hyper intense on T2-weighted images, or enhanced after gadolinium injection. Because of the well-known irregular form of these tumors, we choose to evaluate tumoral volume by measuring the product of the three largest diameters of the solid part of the tumor (2 perpendicular diameters in a plane and a third diameter in a perpendicular plane). When tumor involved only optic nerve the evaluation of thickening was qualitative, because normal dimensions of the optic nerve on magnetic resonance have not been defined quantitatively. All measures were manually made in a uniform manner. The same measures planes were used each time for the same patient. Response criteria were based on percentage of tumor volume reduction and significant decrease of enhancements. Each patient was classified in Complete Response (CR), partial Response (PR), Minor response (MR), stable disease (SD) or progressive disease (PD). We then classified these 4 kinds of response into two main groups: Success (CR, PR, MR) or Failure (SD, PD).

Clinical evaluation

Medical files were reviewed by one of the pediatric oncologist (EO) for data regarding: gender, age at treatment, symptoms at diagnosis, criteria indicating chemotherapy, chemotherapy regimen used. For visual assessment, they noted data from initial and post therapeutic ophthalmologic evaluation described in the files; at least a fundus examination and, when feasible according to the patient's age, measurement of visual acuity (VA) and visual field determination. From these data they determined both an objective visual response per eye and a visual overall response expected. They distinguished three kinds of objective visual response: "preserved" vision (AV> 3/10 for both eyes), "compromised" vision (AV< 3/10 for both eyes) or "partially preserved" vision (any other situation). The overall visual response expected for each patient was defined as "success" or "failure" of chemotherapy according to the presence or absence of an objective overall visual improvement at the end of treatment. Thus, treatment was considered successful not only when patients improved their visual acuity under treatment, but also if they maintained a unilateral preserved vision or improve a unilateral partially preserved vision (contralateral eye being compromised from diagnostic). Treatment was considered failed if patients had worsened their visual function or had not improved partially compromised vision at least for one eye *Statistical analysis.* The analysis of the relationship between radiological and clinical responses to chemotherapy and radiological defined tumors groups was done by Fischer test. P values <0.05 were considered significant. Statistical analysis was performed with XLSTAT ® software (XLSTAT ® Version 2012.5.01, Addinson)

Results

Between October 1999 and January 2012 45 children diagnosed with NF1-associated OPG were followed by one of the authors (JG) at the IGR. Twenty-two patients were excluded (reasons for exclusion were) and 23 were included as the study population. Patient characteristics are shown in table n.1. Among these 23 children 9 were males (39%) and 14 females (61%). Median age at the time of starting treatment was 45 months (range 6 months to 8 years) respectively, with 22% of children who were younger than 2 years of age, at the time of start of treatment. All of the 23 patients (100%) had at least one symptom at referral. In details 17 (74%) patients suffered some VA deficit in one or both eyes, while 10 had squint combined with some VA deficit, 2 children had nystagmus and 3 presented with proptosis. Three patients presented with symptoms related to intracranial hypertension. No included patients were asymptomatic at the start of treatment.

Table n. 1: Characteristic of the study population

Clinical characteristics at start of treatment	N of patients (n)	(%)
Sex		
F	14	61
M	9	39
Age at treatment		
> 2 years	18	78
≤ 2 years	5	22
Clinical presentation		
Amblyopic eye	17	74
Squint	10	43
Intracranial hypertension	3	13
Nystagmus	2	9
Exophthalmos	3	13
Surgical treatment		
None	18	78
Biopsy or Debulking	2	9
Ventricular-peritoneal derivation	3	13
Indication to treatment		
Clinical progression	5	22
Radiological progression	5	22
Clinical and radiological progression	4	17
Threat to vision	9	39
First line treatment		
BB SFOP	8	35
SIOP LGG1-2	12	52
Vinblastine	3	13

Considering VA as the main objective measure of visual function *per eye* and *per patients*, at referral (before starting treatment) 20 out of 23 patients (85%) had a severe VA deficit (Log Mar > 1.0) in one (11) or both eyes (9) with an overall median Log Mar VA of 0.7 (corresponding to 2/10 in decimals) for the 46 eyes included in the study. Only in 8 eyes and in 3 patients VA was considered normal or preserved (Log MAR < 0.2).

According to the PLAN (Dodge modified) classification [30] only 3 children had unilateral (n= 1) or bilateral (n= 2) optic nerve tumors (PLAN 1), while 3 other patients had a tumor involving the optic chiasm (PLAN 2) and 17 had a retro chiasmatic optic pathways diffusion (PLAN 3-4) (with or without hypothalamic involvement). Overall 15 patients (65%) had a bilateral tumor along the

optic pathways. Children with posterior involvement of the optic pathways (PLAN 4) tended to have more often a compromised vision (p=0,03) at start of treatment (see table n.2)

Table n.2: Visual presentation at OPG start of treatment and radiological features

	PLAN 1-2-3	PLAN 4	Enhancement	No enhancement	Infiltrative	Shaped/exophytic	OPG only	Extra OPG (multi-site)
Vision preserved (VA > 3/10 in both eyes)	2	1	1	2	3	0	2	1
Vision partially preserved (VA > 3/10 in the best eye)	6	5	9	2	8	3	7	4
Vision compromised (VA < 3/10 in both eyes)	1	8	8	1	5	4	4	5

Most of the patients (n=18) had OPG with homogeneous or heterogeneous contrast-enhancement (CE) most often in the chiasmatic part of the tumour. Presence of CE was unrelated to visual presentation at start of treatment (p = 0.10).

Eleven patients (48%) had an extra-optic pathway involvement with multiple site tumors located mainly in the mesencephalon region (n=9), thalamus, brain stem, or internal capsule in 6 patients each site respectively and basal ganglia in 2 cases. Indications to start chemotherapy were a visual deterioration or threat to vision without radiological progression in 14 children (60.8%) a radiological progression only in 5 children and a combined visual-radiological progression in the other 4 children. First-line chemotherapy consisted in the national protocol (Babe-SFOP) in 8 patients (35%) treated before 2003 and in the international SIOP-LGG 2004 study for the 12 children (52%) treated after 2004. In three children first line treatment was modified to weekly vinblastine because of early toxicity to vincristine-carboplatin. Radiological response to chemotherapy was the following: CR (1 patient), PR or MR (15 patients), patients), SD (5 patients). A reduction of CE and/or tumor volume (of more than 25%) was thus present in 70% of patient during or after CT. A progressive disease (PD) of OPG was documented in 2 patients with 4 others PD related to extra-optic pathways tumor progression with stable OPG.

Regarding visual outcome, analysed according to criteria recently described by *Fisher et Al* [16] we

could describe per subject VA improvement in 8 patients and in 12 eyes, a stable VA in 8 patients and in 20 eyes, while VA deterioration was documented in 6 patients and in 12 eyes. In one patient VA could not be precisely documented due to severely compromised vision before treatment (Log MAR > 1.3 bilaterally). Thirteen patients had a stable or improved VA combined with a preserved or partially preserved vision, at the end of treatment.

Concordance in response to CT (in terms of visual and radiological changes) was documented in 13 patients (56%). Among the 7 patients with VA improvement, a radiological response coincided in 5 patients and a SD in the other 2 patients. On the other side, among the 16 patients with some radiological response visual improvement was also present in 8 patients (50%).

Univariate analysis of radiological and visual response included the following radiological factors: tumor site/extension, presence of CE, tumor morphology, presence of extra OPG multiple site tumour as shown in table n.2.

Table n. 2: Radiological factors and outcome after chemotherapy

Dodge site **(PLAN classification)**	**Response radio** **Per cents (number)**	**Response visual**
1-2-3 (n =9)	89% (8)	78% (7)
4 (n = 14)	57% (8)	43% (6)
Chi-squared	p= 0.18	p= 0.19
Contrast enhancement		
Yes (n = 18)	83% (15)	50% (9)
No (n = 5)	20% (1)	80% (4)
Chi-squared	p= 0.02	p= 0.33
Tumor morphology		
Infiltrative (n = 16)	63% (10)	63% (10)
Shaped /exophitic (n = 7)	86% (6)	43% (3)
Chi-squared	p= 0.37	p= 0.65
Multi-site tumor (extra OPG)		
Yes (n= 10)	40% (4)	40% (4)
No (n = 13)	92% (12)	69% (9)
Chi-squared	p = 0.02	p= 0.22

According to the PLAN classification, it seems to exist a tendency towards a better radiological outcome among the 9 children with OPG without posterior involvement (optic radiation), indicated by radiological response in 8 out of 9 children with PLAN 1-3 and no response or PD in 6 out 14 children with more diffuse tumors (PLAN 4) (p = 0,18). A better visual outcome in children with less diffuse tumor along the optic pathways tended to confirm the prognostic impact of posterior OPG (p = 0,19).

Radiological outcome after CT was significantly worse for those children with multiple tumors (extra OPG) within the central nervous system (p = 0,02) and tumors without CE (p<0,05). Most often a reduction of CE preceded some degree of tumor size reduction. However these two radiological factors seem not to influence significantly the visual outcome (p = 0.33 and p = 0.4 respectively).

OPG was defined as infiltrative in 70% of children (n=16) while in 13% (n=3) it was more shaped/exophytic. In 4 (17%) children the aspect was "mixed" with both the components (infiltrative and exophytic). Morphological aspect of OPG (infiltrative Vs. shaped/exophytic) did not significantly predict radiological nor the visual response**,** with a noted tendency, to a better radiological response in the exophytic subtype (p = 0,37).

Discussion

We performed a pilot study to define OPG radiologic characteristics collecting a series of children with NF1 OPG with detailed radiological and clinical information, with the aim to correlate radiological factors and response to treatment, both in terms of radiological and visual outcome.

There are different radiological characteristics among children with NF1 OPG. These differences in radiological aspects of NF1 OPG can be reliably evaluated by experienced radiologists and may reveal possible differences in tumor behaviour.

There are few other studies trying to correlate vision and radiology in NF1 OPG. Chateil et Al, [29] collected from a retrospective series of 14 children with NF1 and OPG (10 only observed) showed that NF1 OPG in the chiasm are typically small and homogeneous, have no cystic component, and are variably enhanced by contrast media. In three of the present children with NF-1, a chiasmal lesion extended into the optic nerves, and in two others it extended into the posterior optic tract. These features suggest a tumoral process that infiltrates the entire optic tract.

In this study we have shown that patients with PLAN 4 OPG (involvement of optic radiations) had a particularly unfavourable response to chemotherapy. The PLAN (**P**adova, **L**eeds, **A**ugsburg, Nottingham) radiological classification of OPG that was first implemented in 2008 [30] might be more informative than the classic 1958 Dodge staging (I-II-III), offering a more detailed description of different parts of the optic pathways. The PLAN staging may then better correlate with visual presentation and outcome. We propose that PLAN classification may serve as the basis for future clinical trials in children with OPG focusing on visual outcome as the primary outcome.

Multi-site tumor involvement (including extra OPG tumors) has a particularly unfavourable prognosis. This situation should not be considered as metastatic tumor but rather a multi-site occurrence of tumor development due to NF1 tumor predisposition.

Limits of the study includes the small number of patients to perform statistical analyses and a recruitment bias where analysis is limited to patients who received treatment, that represent a selected and more aggressive disease. Within the overall NF1 OPG group, in fact, only a minority of patients present with progressive tumor and require treatment.

Another limitation is we found relatively low concordance between radiology and clinical outcome. This may reflect the absence of clinical-radiological correlation due to some hypotheses: a too late treatment (after irreversible nerve damage) or optic fibres degeneration unresponsive to classic cytotoxic treatment (as chemotherapy).

In conclusions this study underlines that OPG is a heterogeneous rather than a single radiological disease. Both clinical and radiological characteristics and behaviour are of complementary importance to better understand their natural history. This will require further close collaboration between oncologist and radiologist. We were able to demonstrate the feasibility of this pilot study and we initially defined radiologic criteria to analyse in larger multi-centric studies.

New radiological methods as diffusion tensor imaging (DTI) and fractional anisotropy measure may also be relevant and correlate with visual outcome (31). There will be soon a prospective collaborative study between US and Europe to evaluate these aspects in children with NF1 associated OPG.

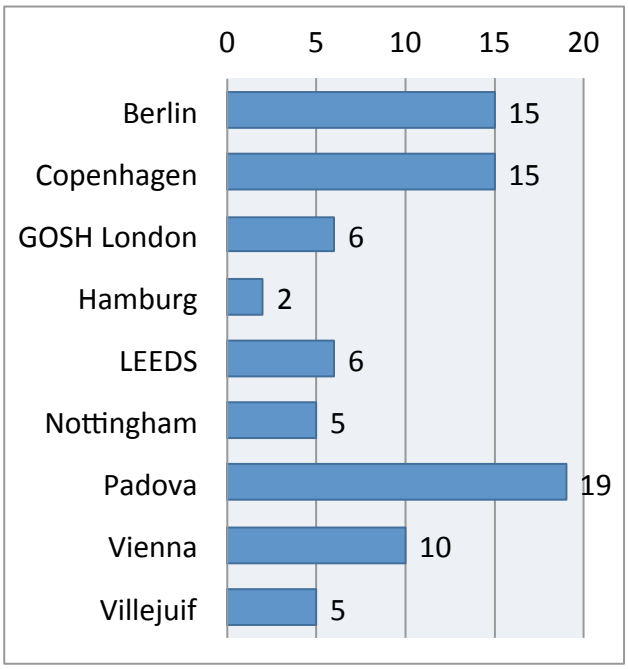
5. Part 3: The Development of the next SIOPE-NF1 OPG prospective trial

5.1 the Nottingham Workshop

In April 2014 a two days meeting was held in Nottingham with the intent to generate a multidisciplinary discussion on critical aspects of NF1 associated OPG, including radiological and visual aspects. Starting from a case by case discussion we analysed all cases of NF1 with OPG in a large database ad hoc, clinically and radiologically, one by one and classifying them (a priori & a posteriori) into the proposed categories of need to treatment. More than 25 experts, including oncologists, neurologists, ophthalmologists, neuroradiologists, and statisticians were involved in this process. The main goal of the workshop was to define more precisely treatment indication criteria, standardize the treatment questions for future cooperative studies and improve multidisciplinary care and treatment decision process allowing earlier referral of patients with NF1 OPG from other experts involved in the field of NF1 (NF-ologists).

Prior to the workshop, data of 105 children with OPG from 8 European centers were registered in the electronic database (figure n.). After exclusion of 8 patients (NF negative) and 14 patients (no MRI available at the time of analysis) data from 83 children have been analysed and represent the study population.

Figure n. 1: Number of registered patients from each Centre



The study population characteristics are described in table n. 2.

The male to female ratio was 1.2:1, and included 60 patients who were initially observed and 23 patients who underwent treatment (22 chemotherapy and 1 radiotherapy) as part of the initial strategy. Overall, between OPG diagnosis and last follow-up 38 patients were only observed, while 22 were treated after a certain observation phase and 23 were treated already at OPG diagnosis. Median age at diagnosis was 5.1 yrs (+/- 2.9 yrs), with significantly younger children among those who were treated (3.8 yrs) compared to those who were initially observed (5.5 yrs) (p= 0.016).

Table n.2: Study population and age at diagnosis according to different strategies

	n	Mean	±	SD	%
Gender					
Male	46				55%
Female	37				45%
Age of diagnosis (yr)	**83**	**5.1**	**±**	**2.9**	
Initial non-surgical management *(p=0.031)*					
Observation	60	5.5	±	3.1	
Chemotherapy	22	3.8	±	1.7	
Radiotherapy	1	8.6		.	
Overall treatment in 3 groups *(p=0.016)*					
Observation only	38	6.0	±	2.9	
Observation + Treatment	22	4.5	±	3.1	
Treatment only	23	4.0	±	1.9	
Interval between 1st and last scan (yr) *(p=0.16)*	**83**	**2.7**	**±**	**2.4**	
Observation only	38	2.8	±	1.8	
Observation + Treatment	22	3.3	±	3.8	
Treatment only	23	1.9	±	1.2	

Tumor site distribution of the study population, described in table n. 3, indicates that 35 children (42%) had a tumor confined to optic nerve/s, 16 had chiasmatic and 24 hypothalamic-chiasmatic involvement and 31 (37%) had tumor involvement of the post-chiasmatic tracts and radiations.

According to the different strategies (observation, treatment, observation + treatment) data show that tumor extending in the post-chiasmatic regions (PLAN 3-4) were more frequent (52% and 43% vs. 26%) in the observation + treatment and treatment only group respectively. Multiple site tumors also were more frequent in the treatment only group. These two radiological factors (PLAN 3-4 and multiple site OPG) may thus be associated with more severe disease course and need to treatment.

Table n.3: Tumor site PLAN classification and overall strategy

	Observation only (n=38)		Observation + Treatment (n=22)		Treatment only (n=23)	
	n	%	n	%	n	%
Dodge A Optic nerves	17	45%	10	48%	8	35%
Dodge B Chiasm	11	29%	2	10%	3	13%
Dodge C Optic tracts and radiations	10	26%	9	43%	12	52%
Hypothalamic involvement	9	24%	6	29%	9	39%
Multiple sites of OPG involvement	2	5%	2	10%	5	22%
Multiple sites of non OPG involvement	9	24%	2	10%	8	35%

5.1.1 The Radiology workshop report

T Jaspan, M Warmuth-Metz, P. Hernaiz-Driever, J Grill, A Sehested, S Avula, M Schmook, S Picton, M Lucchetta, T. Chambers & E. Opocher

Procedure: Prior to the meeting, Neuroradiologists from local participating centres evaluated the imaging of patients from their centre, using an agreed pro forma. The process began by the radiology group evaluating the MR imaging of two patients and modifying the classification system. This led to discussion of many key issues, described below. Afterwards one radiologist and one oncologist together, with group discussion to resolve uncertainties as they arose, assessed every centre's patients. Amendments/corrections were made to the responses from each centre and transcribed onto master forms and then submitted to Jo-Fen Liu for final analysis.

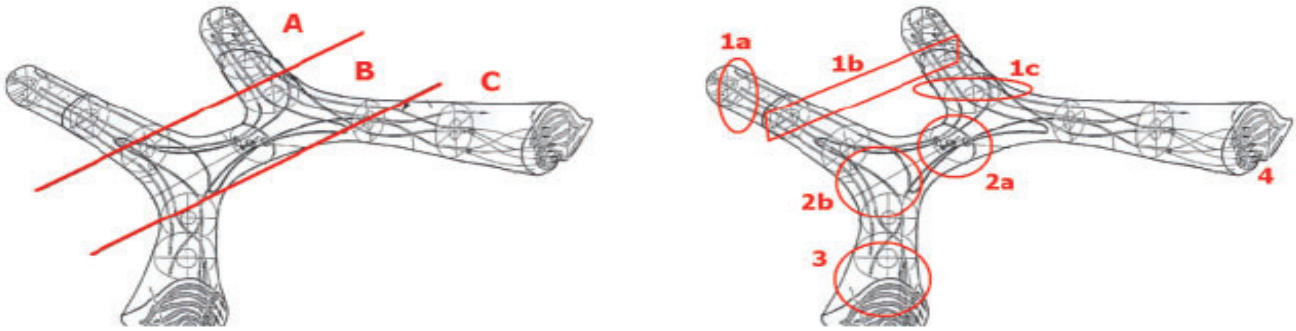
The following pairs were made for multidisciplinary *case by case* radiological discussion: *Copenhagen and Nottingham cases*: Tim Jaspan and Astrid Sehested, *Paris and Vienna cases*: Jacques Grill and Maria Schmook, *Berlin and Hamburg cases*: Pablo Hernaiz Driever and Monika Warmuth-Metz, *Leeds cases:* Sue Picton and Shivaram Avula, *GOSH and Padua cases*: Enrico Opocher, Marta Lucchetta and Monika Warmuth-Metz.

Some centres provided more than one response for the Dodge staging. This issue was discussed and it was agreed that the most posterior involvement present should be recorded.

The term Modified Dodge Classification (MDC) was used synonymously with the PLAN classification [30] (see Figure 1). For the MDC, all involved sites were recorded. Differences between the classification system described in the PLAN article and that used in the pro forma for the survey were noted. Some codes in the article were left out in the survey (highlighted in bold)

Fig 1. Dodge and Modified Dodge Classification (MDC) [30]

Original DC	MDC	Description	Subcategories	Description
A	1a	Single optic nerve	1a L/R	left/right
	1b	Bilateral optic nerve	1b L/R	left>right/right>left
	1c	Cisternal segment optic nerve	1c L/R/B	left/right/bilateral
			1cb L/R	left>right/right>left
B	2a	Central chiasmatic	2a	
	2b	Asymmetric chiasmatic	2b L/R	left>right/right>left
			2c L/R	left only/ right only
C	3	Optic tracts	3 L/R/B	
	3b	Asymmetric tracts	3b L/R	left>right/right>left
	4	Diffuse posterior tracts	4 L/R/B	left/right/bilateral
	4b	Asymmetric posterior tracts	4b L/R	left>right/right>left
	H+/−	Hypothalamic involvement		
	LM+/−	Leptomeningeal dissemintation		
	NF1+/−	Neurofibromatosis type 1		



Article	Survey
1a (1a L/R): ON	1a (1a L/R)
1b (1b L/R): Bilat ON)	1b
1c (1c L/R/B or 1cb L/R)	1c (1c L/R/B) junction nerve/ chiasm
2a: central chiasm	2a central chiasm
2b (L/R): Asymmetric chiasm	2b (L/R)
2c (L/R)	
3 (3 **L/R**/B): Optic tracts	3 optic tracts symmetric i.e. 3 b
3 b (3b L/R): Asymmetric tracts	3bR or 3bL

4: (4 **L/R**/B) Diffuse post. Tracts	4 diffuse posterior symmetric i.e. 4b
4b: (4bL/R) Asymmetric post. Tracts	4bL/R,
Hypothalamic involvement	Hypothalamic involvement
Leptomeningeal dissemination	Multi-site non-OPG tumour

The survey pro forma was not able to describe: 1b asymmetric involvement, involvement of only one side of the chiasm, optic tracts and posterior tracts involving only one side. This would be good to include in the study, and also to have a figure of the modified Dodge to aid classification.
In practice some of the extra codes were written in by hand in the forms, where necessary.
Involvement of 4, the posterior tracts, was defined as tumour commencing at the level of the geniculate ganglia and extending posteriorly in the region of the optic radiations.
Hypothalamic involvement: Definition of hypothalamic involvement based on anatomical localization proved difficult, with, many corrections being made. The anatomical definition of the hypothalamus was best assessed in the axial plane as the structure lying on either side of the anterior recess of the third ventricle, and on sagittal images as the region of the floor of the third ventricle between the chiasm and mammillary body on a midline image (Fig 2).
Patterns of disease seen included typical chiasmatic tumour without hypothalamic involvement (Fig 3) and tumour involving both the chiasm and hypothalamus (Fig 4). However, cases were identified that had Dodge A/MDC 1a or 1 b or 1c and hypothalamic tumour but with no chiasmatic tumour (Fig 5). It is not clear whether hypothalamic involvement is part of the OPG spectrum. Differentiation between a hypothalamic lesion encroaching upon the chiasm and a chiasmatic lesion involving the hypothalamus proved particularly difficult. The significance of hypothalamic tumour on vision was discussed, particularly in relation to involvement of the hypothalamus without major chiasmatic disease, or when the chiasm is only minimally involved. In addition the significance of radiological involvement of the hypothalamus on endocrine function was not known.

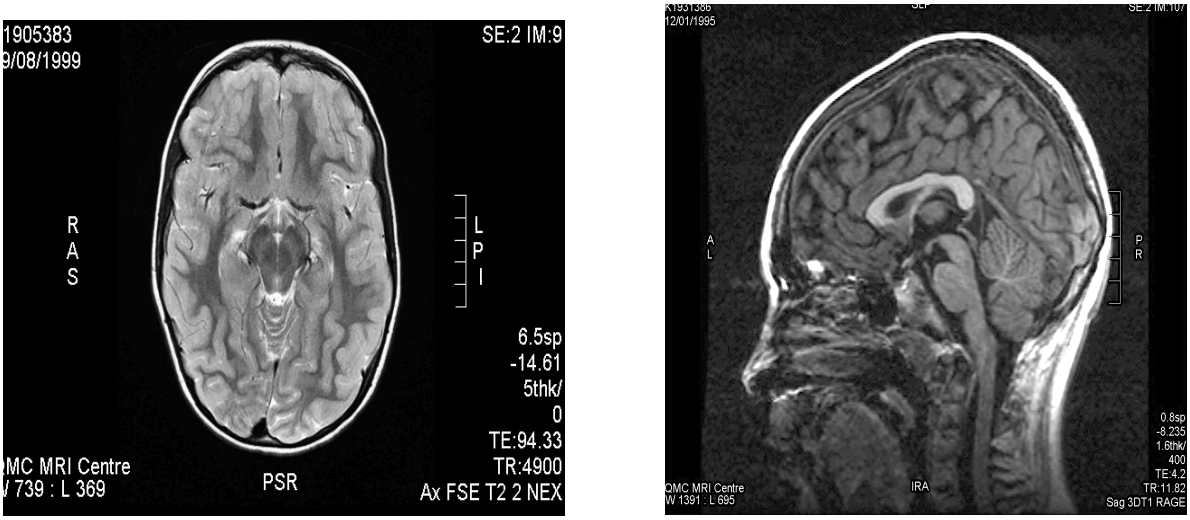


Figure 2. Normal hypothalamic anatomy. A - Axial T2. Short white arrow = mammillary body. Curved white arrow = hypothalamus. Black arrow = optic tract. White arrow = third ventricle. B. Sagittal T1.White arrow = optic chiasm. Short white arrow = mammillary body. Curved white arrow = hypothalamus.

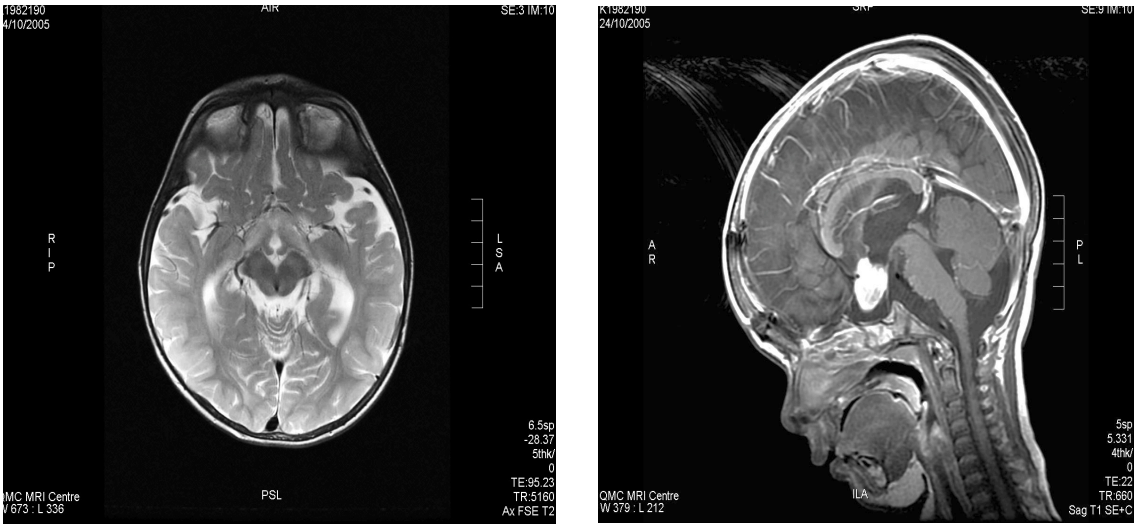


Fig 3. Chiasmatic and optic tract glioma with hypothalamic sparing. A. Axial T2 image showing chiasm and optic tract T2 hyperintense tumour and normal more hypointense hypothalamus. B. Sagittal T1 post Gadolinium image showing the enhancing chiasmatic tumour. Note that the region of the hypothalamus is spared.

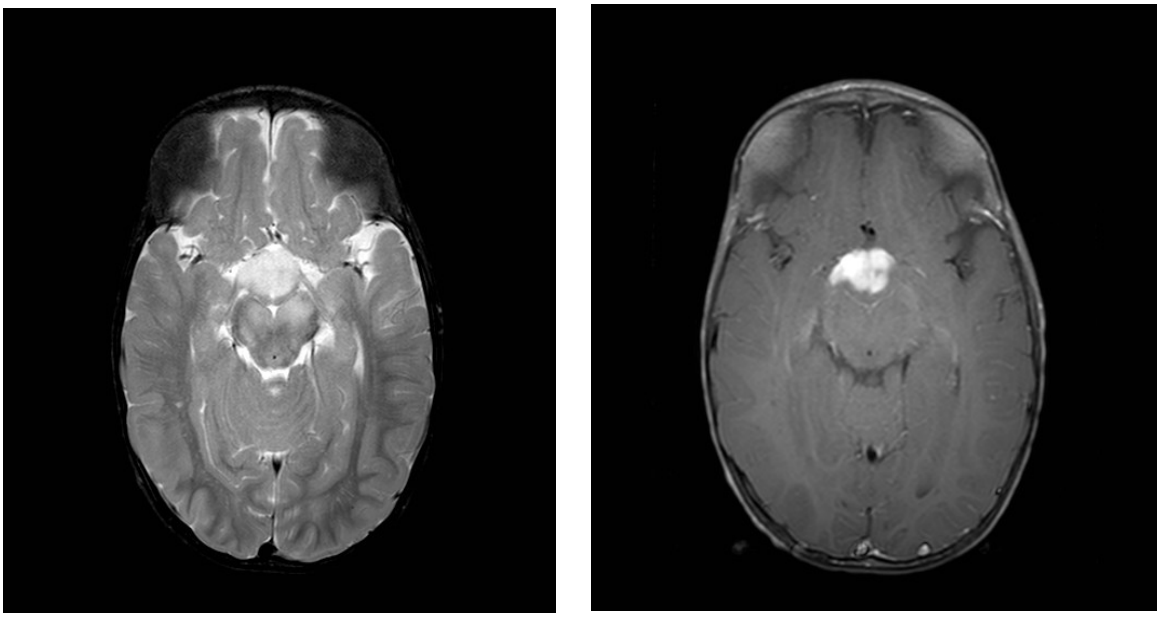


Fig 4. Chiasmatic, optic tract and hypothalamic involvement A. Axial T2 image showing hyperintense tumour involving the chiasm, right optic tract and hypothalamus B. Axial post gadolinium T1weighted image showing enhancement of all three components.

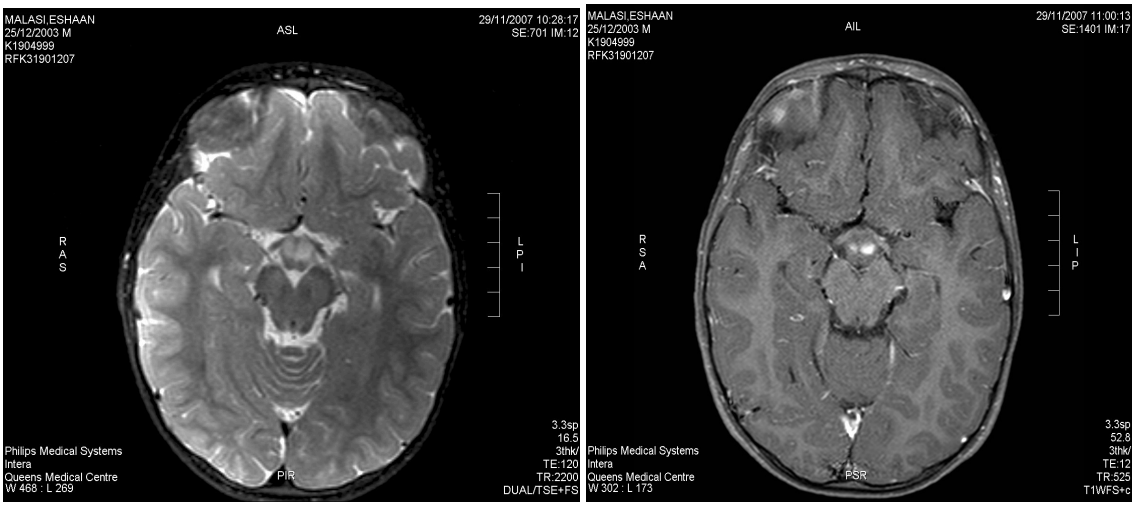


Fig 5. Hypothalamic involvement with chiasmatic sparing. A. Axial T2 showing normal tracts and chiasm and hyperintense hypothalamic tumour. B. Enhancement in the hypothalamic tumour.

OPG multi-site involvement was asked for in the survey. Following subsequent discussion, it was agreed that the most posterior involvement designated the Dodge status, as this defined the most significant impact on visual function. Using the MDC all involved sites were described. The issue of whether multiple foci of disease were part of the overall optic pathway tumour or represented separate tumours was discussed. It was agreed that the MDC enabled more accurate description of disease extent and involvement, providing better tumour localisation and as such was superior to the Dodge classification.

Non-OPG multi-site involvement

Imaging abnormality situated outside of the optic pathway could potentially represent glioma or FASI (Foci of Abnormality Signal Intensity). Common sites of abnormality were the temporal lobes, thalami, brainstem and cerebellar hemispheres (Fig 6,7). The septum pellucidum and corpus callosum were also noted to be involved in some cases. FASI was defined as an area of T2/FLAIR signal abnormality not associated with significant increased volume, mass effect or contrast enhancement. It was agreed that it could be very difficult to determine whether an area of abnormality represents a FASI or a glioma, particularly when present within the region of the optic pathway. Ultimately, this may only be resolved by serial scanning, although it was recognised that both FASI's and gliomas may spontaneously involute with time and maturity. It was agreed that further work was required to document the specific sites of involvement of non-OPG tumours and to differentiate between FASI's and tumours.

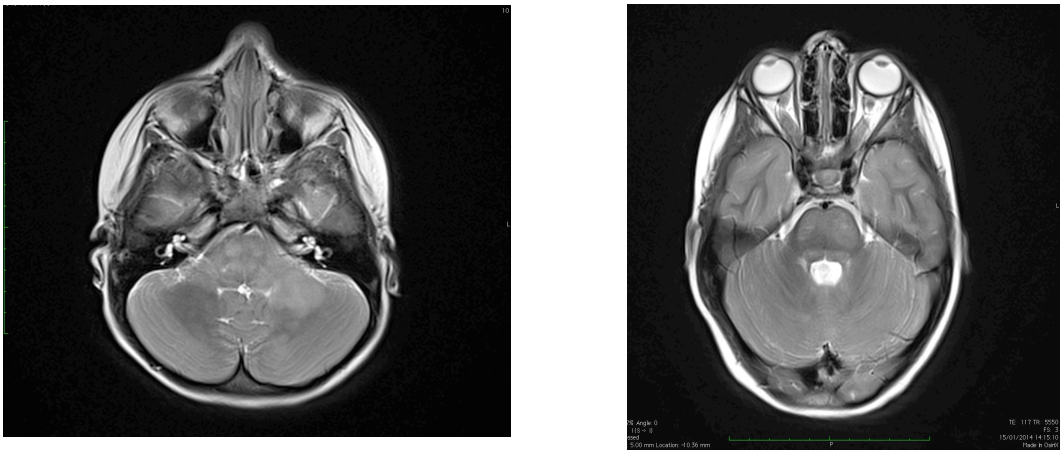


Fig 6. Brainstem lesions in two different patients. No enhancement associated with either lesion. A. Axial T2 image showing diffuse pontine T2 hyperintensity without significant expansion/mass effect. Possible FASI. B. Axial T2 image shows ill-defined T2 hyperintensity in the inferior pons and middle cerebellar peduncles (mcp) with mild expansion of the left mcp. Possible LGG.

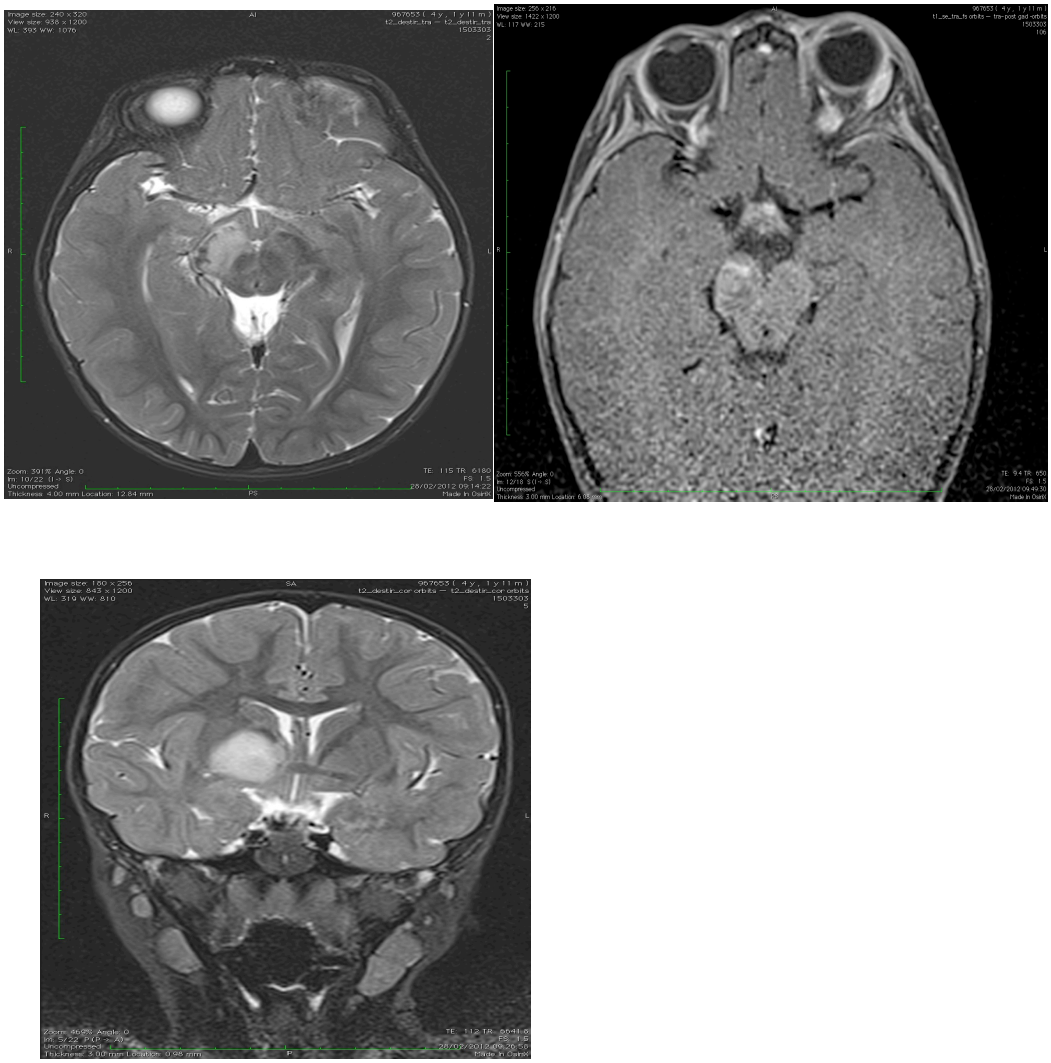


Fig 7. Axial T2, post Gd axial T1 and coronal T2 images in same patient. A) Non-expansive lesion in right cerebral peduncle. B) Mild enhancement seen on post Gd T1 images. Presumed LGG. C) Mildly expansive T2 lesion in right anterior basal ganglia– enhancement. Possible LGG.

5. ***Optic nerve involvement***. The diagnosis of optic nerve involvement was discussed as a group. Characteristics associated with optic nerve tumour include: enlargement of the nerve, tortuosity of the nerve, expansion of the optic nerve sheath and enhancement of the optic nerve.

Regarding enlargement of the optic nerve, the group agreed that there were no precise metrics for optic nerve size through all the paediatric ages. Tumour involvement of the nerve was determined by identifying one or more of the above criteria, enlargement of the optic nerve being a subjective judgement by the radiologist. The quality of images provided for this retrospective review was variable and not infrequently only non-dedicated orbital imaging was available for review. This further hampered accurate measurement of the optic nerves.

There was considerable discussion regarding the significance of the size of the optic nerve canal, and whether the relative constriction of a holo-nerve glioma by the optic canal could be a critical factor for visual field loss. Inherent difficulties measuring the optic nerve canal using MRI were discussed. The possibility of exacerbating damage to residual nerve function caused by neurovascular injury if the optic nerve canal is surgically opened was discussed but no consensus was reached.

6. ***Definition of progression or improvement in NF1-positive OPGs***.

Absolute measurements of NF1 related OPGs proved impossible in the majority of cases due to the heterogeneous and diffuse nature of the lesions, variable enhancement within a tumour between studies, the non-linear and spreading nature of these tumours and potential for some tumours to show regional areas of expansion and regression. It was agreed that volume calculations of these tumours was often non-meaningful. Response to the survey by the radiologists regarding tumour status was determined on the basis of a subjective overall evaluation, taking into consideration size, enhancement characteristics and regional involvement. The role of diffusion weighted imaging in the evaluation of tumour response to therapy was briefly discussed but was not addressed in depth. This would need to be the subject for a more detailed post hoc study. Volumetric evaluation using 3D volume acquisitions was also discussed. However experience in this area is as yet limited and has not been widely reported.

One area that was discussed subsequent to the meeting was the significance of new sites of involvement identified on follow-up scans and whether this could be reflected in a changing MDC classification. It was felt that this would be an unusual occurrence, and that response to therapy or tumour progression was in most cases not reflected by a change in the MDC status. Therefore, use of the MDC was not felt to be a reliable criterion for evaluating response to therapy in such cases.

7. ***Recommended imaging protocol***

The standard SIOP-E brain tumour imaging protocol was felt to be the basis for imaging of OPG, with mandatory two-plane T2/FLAIR images. Dedicated orbital imaging with post Gadolinium T1-weighted FS sequences provided more useful evaluation of enhancing intra orbital disease.

Proposed MRI protocol includes Axial T1, T2, coronal T2, FLAIR. DWI, Orbits coronal T1, STIR axial T2FS (3mm). Post Gad brain axial/sagittal T1, Orbits cor T1FS (3mm).

5.1.2 The Ophthalmologic workshop report

E Opocher, J. Fen-Liu, K Rothe-Nissen, C. Hammond, I. Simmons, A A. Azizi, D Hargrave & D.A. Walker on behalf of the workshop participants

The specific goal of the ophthalmology working section was to analyse visual data from the workshop database and, thereafter, discuss different aspects of visual function determining or possibly influencing initial strategy and final outcome of children with NF1 associated OPG.
Methods of the workshop were to set up a database from a large retrospective series of patient with NF1 and OPG, and to undergo a multidisciplinary case by case review of radiological aspects, visual presenting symptoms, treatment strategy, treatment received and final outcome in terms of visual and radiological response.

Before the workshop

In the 3 months prior to the workshop participating centres registered in an anonym zed database cases of children less than 18 years with NF1 and OPG (both observed and treated) with sufficiently detailed clinical and radiological information.
Visual database included VA and funduscopic examination at OPG diagnosis, at start/end of treatment (if treated), at the end of treatment (if treated) or after 18 months from diagnosis if only observed. VA data were registered or translated into a quantitative measure (log Mar) according to available conversion tables (Fig n. 1). Methods of VA measurements (Teller, LEA, HOTV, Snellen, etc.) or VA age adjustment were not specified.
Preliminarily to the workshop a statistician analysed visual data, according to different patients groups (observed, treated, initially observed and than treated) and possible correlations between visual and radiological data.

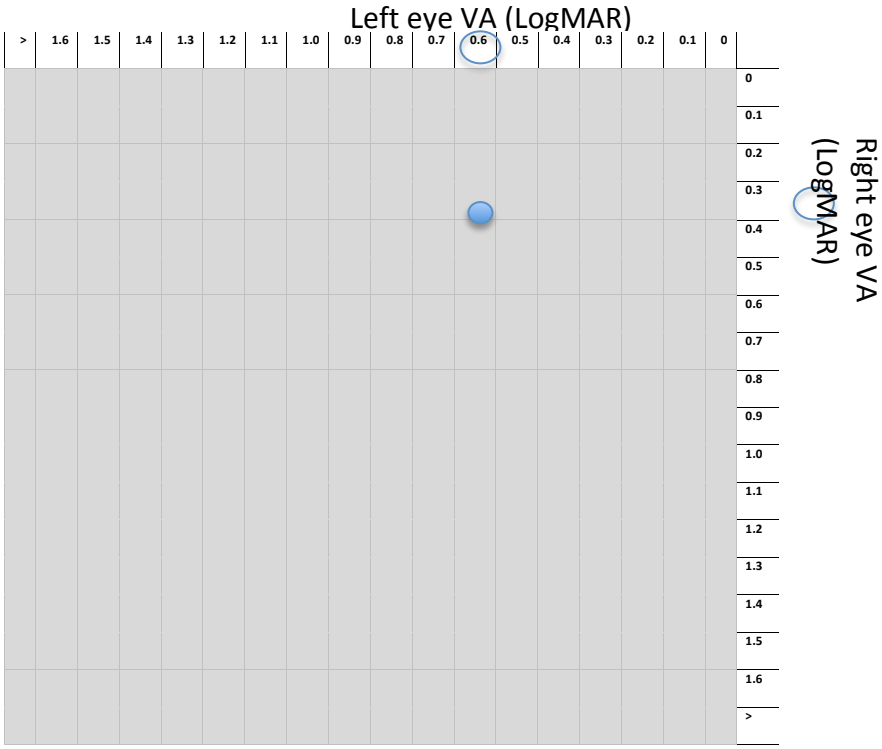
During the workshop

During the first part of the workshop preliminary data on patient characteristics, visual information, radiological information analysed were presented and discussed in a plenary session.
After this part, one group with different specialists representative presented on a round basis cases of children with NF1 associated OPG including age, presenting symptoms, initial visual assessment. VA was assessed monocular and quantitative data converted (if needed) from Snellen

to Log MAR units and represented, for both eyes of each patient, in a graph (see example Figure n.1)

Fig n.1: Conversion from Snellen equivalents and Log MAR and per patient VA assessment

	Lines on visual acuity chart	
logMAR	Feet	Meters
−0.1	20/16	6/5
0.0	20/20	6/6
0.1	20/25	6/7.5
0.2	20/32	6/10
0.3	20/40	6/12
0.4	20/50	6/15
0.5	20/63	6/20
0.6	20/80	6/24
0.7	20/100	6/30
0.8	20/125	6/38
0.9	20/160	6/48
1.0	20/200	6/60
1.1	20/250	6/75
1.2	20/320	6/96
1.3	20/400	6/120
1.4	20/500	6/150
1.5	20/640	6/192
1.6	20/800	6/240



Radiologic aspects (i.e. tumor site according to Dodge Modified Classification-MDC or PLAN) and overall strategies (observation Vs. treatment) were initially blinded to other participants. After this initial scenario, each participant commented the overall patient strategy. Indications to treatment initially proposed were discussed and defined in three categories as following: 1) no indication to treatment, 2) indication to treatment, 3) uncertainty between the two strategies.

Patient presentation continued with the full history, including overall strategy (observation Vs. treatment), visual outcome, response to treatment, other relevant information.

Results

Data from 83 children with NF1 and OPG from 8 participating centres were analysed for the ophthalmology report. Among these 83 children 28% had visual symptoms at OPG diagnosis, 10% of patients had proptosis, while 47% of children were diagnosed with OPG after screening MRI without any symptoms. Twenty-eight percent of children were treated already at OPG diagnosis while 72% of patients were initially observed. Of these patients 26% were treated after initial

observation. Overall 46% of patients were only observed until last follow-up, while 54% of patients were treated. Initial treatment strategy seems to vary according to presenting VA (Fig. n.2): patients with normal or near normal vision were most often observed without any initial intervention. The VA of patients who were treated at OPG diagnosis varied significantly with very heterogeneous values of VA, but with most of patients having a significant or severe VA deficit in both eyes.

Figure n.2 (a-b-c): Visual acuity at diagnosis according to different strategies

Fig. 2a: visual acuity in patients observed only

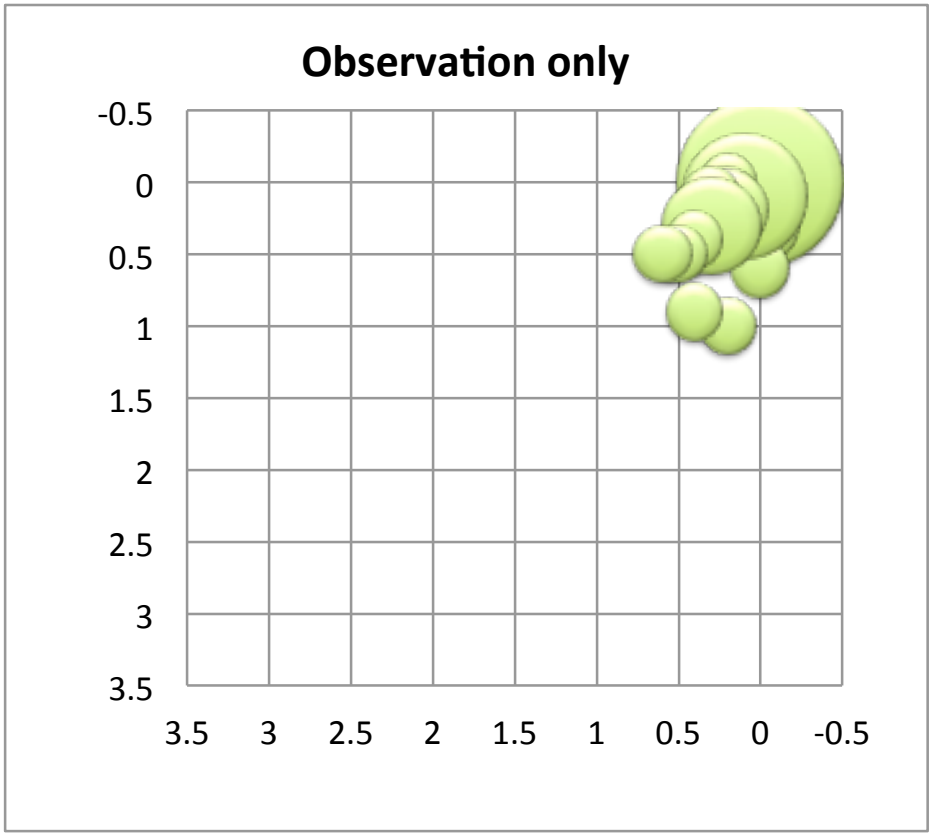


Figure 2b: logMAR visual acuity in patient treated after initial observation

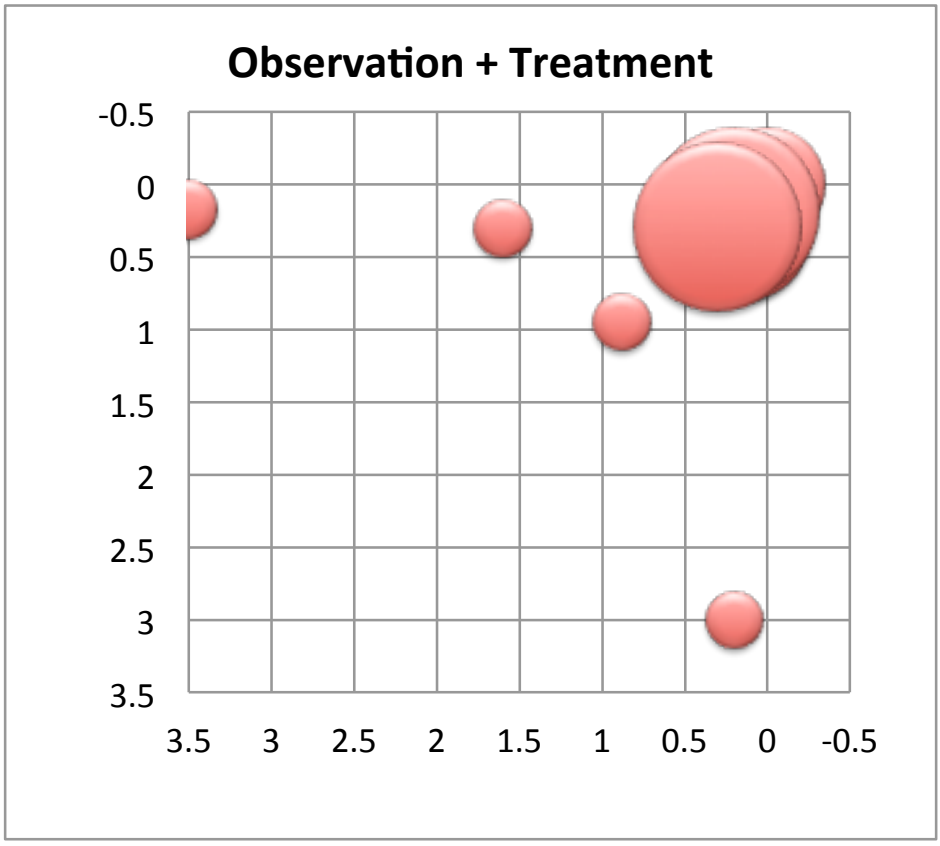
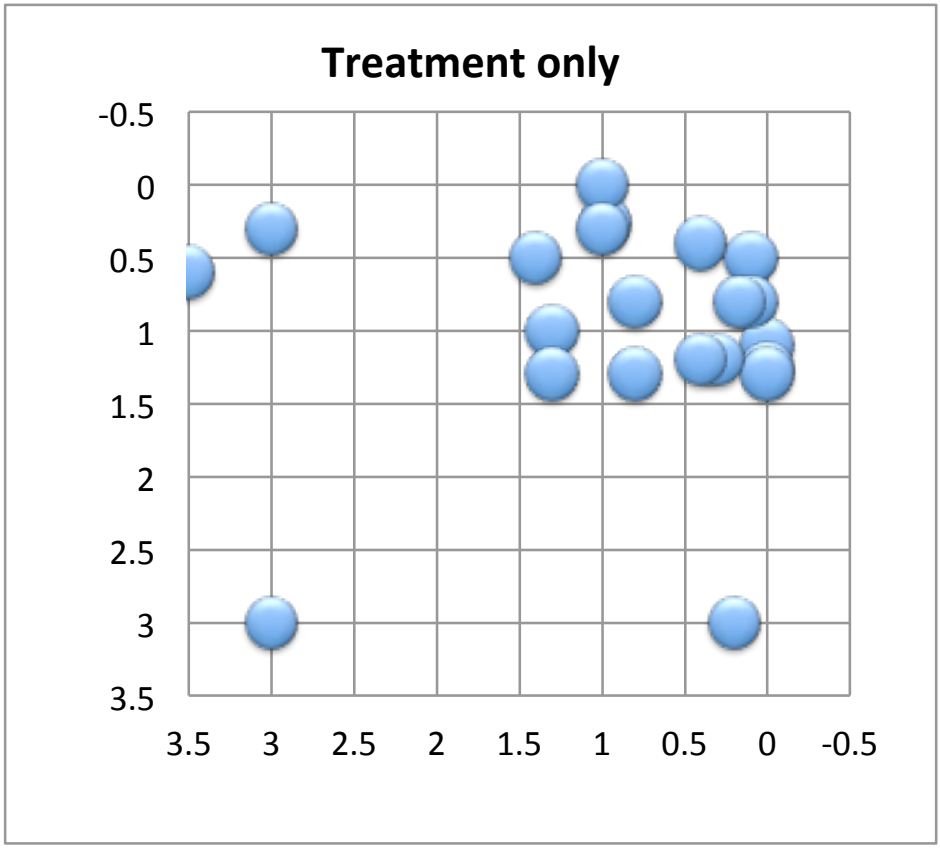


Fig. 2c: log MAR Visual acuity in patients treated only (without observation)



VA comparison in the two different groups (observed Vs. Treated) showed significant stable vision among patient observed and very heterogeneous changes among treated patients. (Figure n.3)
On the other side, for children presenting some degree of visual loss, visual outcome seemed highly variable and unpredictable. Overall, the number of patients who ended with a severe VA deficit (more than 1.0 Log MAR) increases over time, despite treatment strategies.

Figure N.3 (a-b): Comparison between initial and final visual acuity according to overall strategy

Fig. 3a (patient observed)

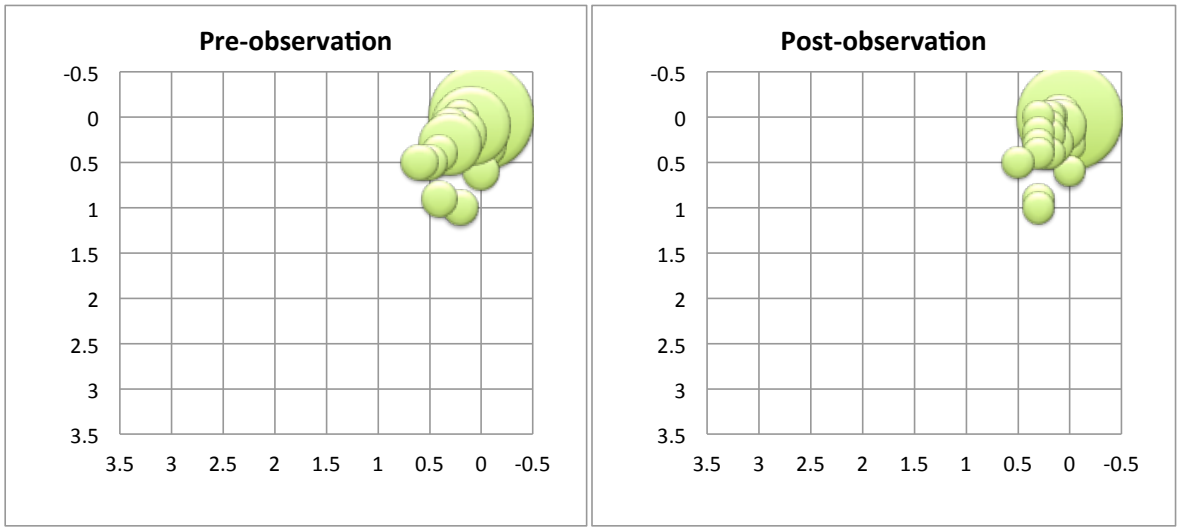
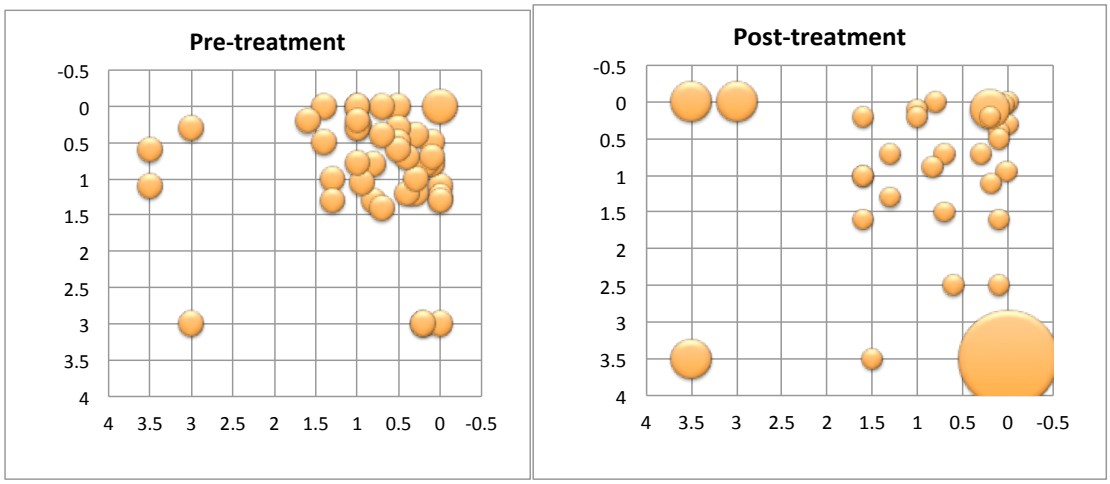


Fig. 3b (patients treated at diagnosis or after initial observation)



Visual acuity changes were analysed according to the 3 different groups and summarized in Table n.2 and n.3. Most of the children who were only observed until last follow-up had a stable vision compared to first assessment. After treatment visual improvement occurred in between 15-30%

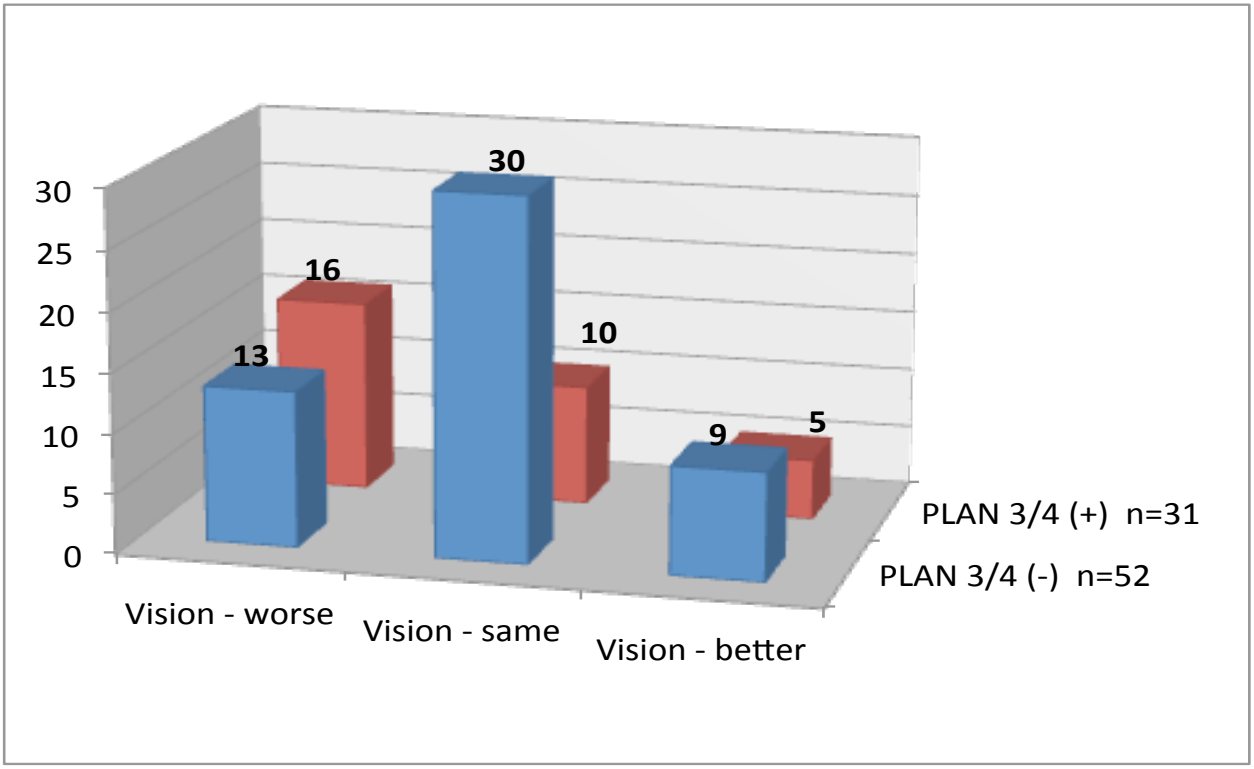
of children, depending on the initial strategy. Benefit from chemotherapy, in terms of visual improvement rate, seems not to differ significantly between immediate treatments vs. treatment after observation (17% Vs. 29%), as, perhaps, a result of a partial selection of patients with worse visual function already at the start of treatment in the former group.

Table n.4: Visual outcome according to the different strategies

Vision compared to 1st assessment	Observation only (n=38)		Observation + Treatment (n=22)		Treatment only (n=23)	
	n	%	n	%	n	%
The same	29	76%	6	29%	5	22%
Worse	5	13%	9	43%	15	65%
Better	4	11%	6	29%	4	17%

Children with post chiasmatic tumor involvement (PLAN 3-4) had more frequently visual deterioration (51 % Vs. 25%, p = 0.011), while, on the opposite side, those with tumor confined to optic nerve/s and/or chiasm (PLAN 1-2) tended more frequently (57% Vs. 29%) to have a stable VA during observation or treatment (Fig n.4).

Figure n. 4: VA changes according to tumor site (post-chiasmatic tumor involvement - PLAN 3-4)

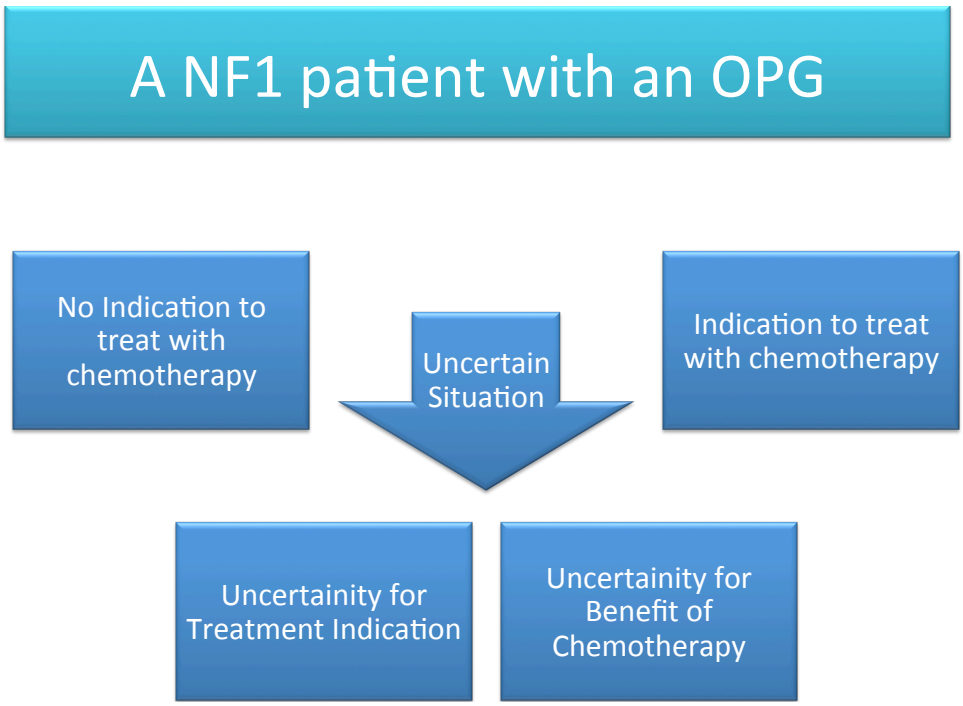


5.1.3 Indications to treatment and the risk based randomized strategy

E. Opocher, D.A. Walker, A. Sehested & J. Grill

A child with a newly diagnosed NF1 OPG may encounter four different clinical scenarios that pose different therapeutic dilemma, as shown in figure n.1. The clinical scenario can be summarised as: a) there is clearly no indication to treatment, b) there is clearly indication to treatment, c) there is uncertain need to treatment and d) there is an uncertain benefit from chemotherapy.

Figure n.1: Possible clinical scenarios in a NF1 patient with an OPG



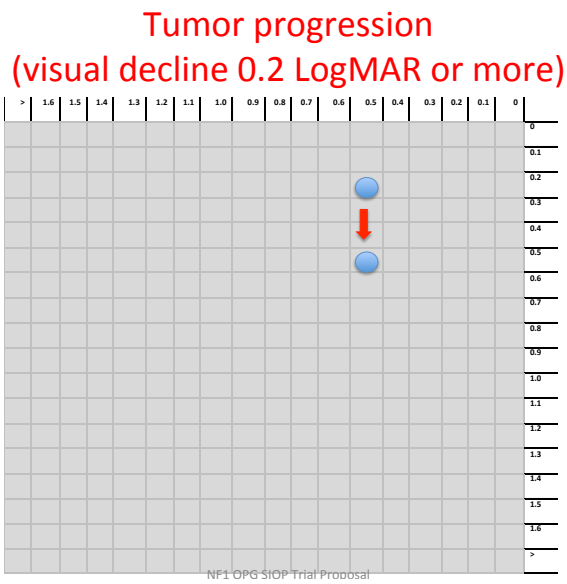
Prognostic factors will determine the risk of visual loss and influence indication (yes/no) and timing (early Vs. late) for treatment. On the other side, the possibility to know a priori which patient is most likely to respond to treatment determines the expected benefit of treatment and influence the type of treatment proposed (chemo Vs. others). A yes /unclear/no Indication to Treatment results from the combination of the risk of visual loss and the expected benefit of treatment proposed. Tumor, patient, and treatment related factors included visual decline, initial VA assessment, tumor site, gender, age, tumor progression and response to treatment. These factors were analysed as possible criteria influencing treatment indication, based on the available evidence and the additional information available during the workshop.

It is almost universally accepted from classic oncology trial that treatment should start in case of tumor progression. However, this might not be the case for children with NF1 and OPG. In fact, as the clinic-radiologic correlation is weak and/or still far from being determined, we have to consider radiologic and visual changes as complementary and separate outcomes. As many children with OPG may have visual loss without tumor progression, visual presentation including visual decline and threat to vision represent the two major criteria for treatment indication.

Visual decline

A reliable and consistent documentation of a visual decline of ≥ 0.2 Log MAR, in one or both eyes, is defined as visual progression (fig n. 2). To reduce the risk that a non accurate test, due to a poorly collaborative child, may determine a decision to start chemotherapy, it is necessary to retest any child whose acuity results are inconsistent with the overall clinical presentation and, in case of suspected visual decline, children should be re-tested (preferably by the same ophthalmologist and with good patient compliance and collaboration) within 2-3 weeks to confirm the visual changes. It is now agreed that unequivocal documented visual decline constitute the main indication to treatment in children with NF1 OPG, irrespectively from other factors.

Figure n 2: Graphical representation of VA loss definition



Threat to vision

When a patient with NF1 associated OPG undergoes a first ophthalmological assessment, at that time, exact degree of VA deficit may range from normal/near normal vision to severe hypo vision or blindness. Most children with NF1 with a newly diagnosed OPG will not present with any degree of visual loss and/or other vision-related signs/symptoms and may not need treatment for their OPG. Only a minority of patients (10-20%) will instead present with some degree of visual deficit.

In the previous SIOP-LGG 2003 study, a diagnosis of OPG was not a sufficient criterion to start treatment per se, in the absence of tumor progression and/or severe symptoms. Nevertheless, standardized definitions of what are severe "visual" symptoms and of what is "threat to vision" were not written or clear. As a consequence many children with a newly diagnosed OPG and presenting at diagnosis with a significantly compromised/low vision were not been treated until further tumor progression occurred. Consistent data from literature speculate that start of treatment, after a certain point of visual loss, might lead to a worse overall visual outcome due to irreversible neuronal damage of the optic pathways.

Thus, with the aim to prevent children with OPG from severe hypo vision/blindness, we defined low vision/threat to vision as a threshold of VA that might prompt treatment early at diagnosis of OPG.

Visual acuity data and respective risk zones for each eye should be then combined considering the risk of bilateral tumor involvement and consequent threat to bilateral vision. To take into account the overall threat to vision in case of unilateral Vs. bilateral disease and select patient for different strategies (observation Vs. treatment) we proposed to classify patients into 3 different risk groups (low-intermediate-high risk) according to various degree of visual impairment (WHO grade) and unilateral Vs. bilateral OPG by combination of VA data for each eye.

A VA of < 0.2 Log MAR was proposed as agreed value for definition of normal vision according to different WHO categories. Considering workshop data analysis and current experience from the St. Guy's London NF1 clinic (presented at the workshop by the ophthalmologist C. Hammond) patients with initial normal vision seem to have an overall excellent visual outcome. Based on this information, a low risk group shall be defined as those presenting with VA of < 0.2 log MAR in both eyes. A patient with VA of 0.2 – 0.5 log MAR in the worse eye might be considered at low risk as the best eye vision is still normal.

Children in this group (*group A*), with bilateral normal vision (< 0.2 log MAR) or mild unilateral visual impairment (< 0.5 log MAR in the worse eye) may be candidate to an initial observation strategy with regular ophthalmology and neuro-radiology follow-up. A change of strategy would be recommended in case of signs of tumor progression (clinical or radiological) or other influencing factors.

Patients with moderate visual impairment in one or both eyes may still have an unpredictable but still favourable long-term visual prognosis and may not need to receive any form of chemotherapy. However, waiting for further visual progression may lead to severe impairment, which might be prevented by the initiation of chemotherapy. Thus, an intermediate risk group shall be defined as one of the following: VA of 0.6 -0.9 in one eye (in case of unilateral OPG OR with < 0.2 in the other eye) or VA between 0.2 and 0.5 log MAR in both eyes, VA 0.6 -0.9 in the worse eye. Outcome in this group (group B) seems rather unpredictable and consequent strategy unclear, because of uncertain need to treatment. In addition, benefit of CT is unproven in case of a child with unilateral OPG presenting with a blind eye and normal VA in the other eye (i.e.: VA of > 1.3 in one eye and unilateral OPG OR VA < 0.2 in the other eye). In a randomized design we would consider randomize this group to receive treatment vs. observation. Other factors, as tumor site or radiological progression might also influence the decision to observe or treat a patient in this intermediate risk group.

Patients with a newly diagnosed unilateral OPG and severe (but still quantifiable) visual impairment in the affected eye (VA between 1.0 and 1.3 Log MAR) OR with a bilateral OPG and severe visual impairment in the worse eye, at first ophthalmologic examination constitute a high risk population in terms of threat to vision due to a borderline vision. A high-risk group (GROUP C) shall be defined then in case of: VA 1.0 -1.3 in the affected eye (unilateral OPG and/or VA < 0.2 in the other eye) or VA between 1.0 and 1.3 Log MAR in the worse eyes (bilateral OPG AND VA > 0.1 in the other eye). Because we still think it is of value to try to preserve minimal residual vision we proposed to candidate this group to start treatment without waiting for further visual loss. Children in this risk group should be treated at diagnosis, irrespectively from other factors and without further observation. A schematic representation of patient grouping is figured in table n.7.

An age adjusted VA of > 1.3 log MAR in one or both eyes is defined, according to the WHO and ICD-9, as profound visual impairment or blindness. From the available literature a child with a

blind eye has unrealistic chance to regain a functional vision. Furthermore, the REiNS group stated that below 1.3 log MAR of VA any change of VA is not well quantifiable or accurate.

Thus, patients with an OPG (i.e. isolated unilateral optic nerve glioma) and presenting and a blind eye/s (defined as VA of > 1.3 log MAR) in which other causes of blindness are excluded (intracranial hypertension) are not candidate as such to treatment, but is mandatory to exclude the presence of other visual and/or non visual criteria for starting treatment (i.e. low vision in the other eye, radiologic progression, progressive visual loss, etc.).

Table n. 3: Low vision ICD definitions and WHO scales of visual impairment

TABLE 3 – **RANGES of VISUAL ACUITY LOSS** in ICD-9, ICD-10 and in ICD-9-CM

Named Ranges of Vision Loss (ICO, 1978 and ICD-9-CM)		Numbered ranges (WHO, ICD-9)		Commonly used Definitions of "BLINDNESS" and LOW VISION				Visual Acuity			Linear scales	
								Decimal notation	U.S. notation	6 m notation	Letter count	Log MAR
(Near-)Normal Vision	Range of Normal Vision	(The ICD does not code normal conditions)						1.6	20/12	6/4	110	-0.2
								1.25	20/16	6/5	105	-0.1
								1.0	**20/20**	**6/6**	100	0
								0.8	20/25	6/7.5	95	0.1
	Mild Visual Impairment (near-normal vision)							0.63	20/32	6/10	90	0.2
								0.5	20/40	6/12	85	0.3
								0.4	20/50	6/15	80	0.4
								0.32	20/63	6/18	75	0.5
Low Vision	Moderate Visual Impairment	Low Vision - WHO	Group 1	Special Education Benefits – USA	"Legal Blindness" Benefits – USA	Low Vision – ICD-9, -10	Low Vision – ICD-9-CM	0.25	20/80	6/24	70	0.6
								0.2	20/100	6/30	65	0.7
								0.16	20/125	6/36	60	0.8
								0.125	20/160	6/48	55	0.9
	(20/200) Severe Visual Impairment		(6/60)		Blindness – ICD-6, -7, -8			**0.1**	**20/200**	**6/60**	**50**	**1.0**
			Group 2					0.08	20/250		45	1.1
								0.063	20/300		40	1.2
								0.05	20/400	3/60	35	1.3
	Profound Visual Impairment	Blindness - WHO	Group 3			Blindness – ICD-9, -10		0.04	20/500		30	1.4
								0.032	20/600	2/60	25	1.5
								0.025	20/800		20	1.6
								0.02	20/1000		15	1.7
(Near-) Blindness	Near-Blindness		Group 4				Blindness ICD-9-CM	less	less	1/60 or less	10	1.8
											5	1.9
	Blindness		Group 5					0.0	NLP	NLP	0	2.0

Table n.4: The proposed visual function zones definition

VA per eye (Log MAR)	Visual zones
VA < 0.2 Log MAR	**Green**
VA = 0.2 - 0.5 (mild visual impairment unilat/bilateral)	**Yellow (unilateral/bilateral)**
VA = 0.6 -0.9 (moderate visual impairment)	**Orange (unilateral/bilateral)**
VA =1.0 – 1.3 Log MAR (severe visual impairment)	**Red (unilateral/bilateral)**
VA > 1.3 Log MAR OR HM, LP, NLP *, Unquantifiable vision	**Unclassified**

*HM = Hand motion, LP = Light perception, NLP = No Light perception

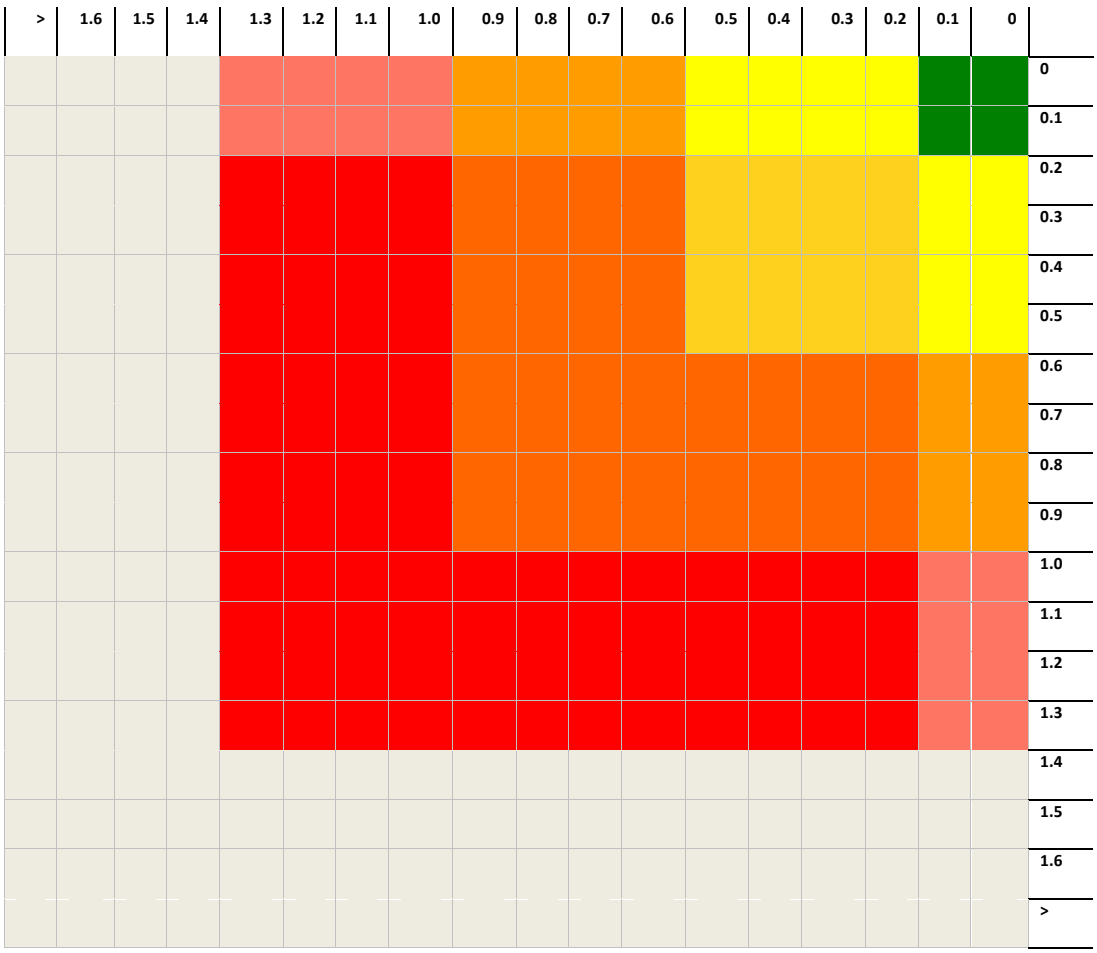


Table n 5: Patient grouping according to both eyes VA assessment (log MAR)

GROUPS	UNILATERAL OPG			BILATERAL OPG							
	Non affected Eye	Affected Eye		Better eye	Worse eye		Better eye	Worse eye		Better eye	Worse eye
A	< 0.2	< 0.2									
		0.2 – 0.5									
B		0.6 -0.9		0.2 -0.5	0.2 – 0.5		0.6 -0.9	0.6 -0.9			
					0.6 -0.9						
C		1.0 – 1.3			1.0 – 1.3			1.0- 1.3		1.0 – 1.3	1.0 -1.3
		> 1.3*			> 1.3			> 1.3			> 1.3

*group B (uncertain treatment) if one blind eye and normal contralateral unaffected eye (unilateral OPG)

Other possible influencing factors

Other factors may influence visual outcome in children with NF1 OPG and could therefore provide additional information regarding the need to treatment and the expected benefit of chemotherapy.

In particular post-chiasmatic tumor extension along the optic pathways was associated with a significantly higher probability of visual acuity loss (P = 0.048) in a retrospective study [32] Data from the current workshop analysis indicate similarly that children with post chiasmatic tumor involvement (PLAN 3-4) have a higher risk of visual loss. However it is still not clear if these patients will also benefit from chemotherapy. In fact, in the workshop analysis there was a significant number of children with post chiasmatic OPG having a normal (or near normal) vision without treatment. On the other side the number of patients who benefit from CT in terms of VA improvement (17 Vs. 16%), did not differ according to PLAN staging. Given this uncertain situation we could only recommend to closely observe children with post-chiasmatic OPG for signs of visual loss or threat to vision. Further information may be necessary and incoming prospective studies will soon allow confirm (or not) the prognostic role of tumor site and then, eventually, incorporate this factor in the treatment indication criteria, at least for the randomised trial (see table n.6).

Also the role of age is still unclear in children with NF1 OPG. In fact OPG rarely present in infancy (< 1 year), compared to the non NF1 OPG group, that is, at present knowledge the only evidence based criteria for worse prognosis. Different cut off of ages (< 2 yr., Vs. 2-5 yr., > 5 yr.) have been analysed in the NF1 group but results are somehow difficult to interpretate. There might be a trend over a worse prognosis in children younger than 2 years and in those older than 5 years of age. We concluded that a clear prognostic cut off for different age groups in NF1 OPG children cannot be defined and more information are needed to introduce age as a criteria for clear treatment indication. However very young children with NF1 and OPG should be carefully monitored as visual assessment might be challenging and the presence of other indication to treatment criteria should be taken into consideration.

TABLE n. 6: SUMMARY OF THE PROPOSED TREATMENT INDICATION CRITERIA

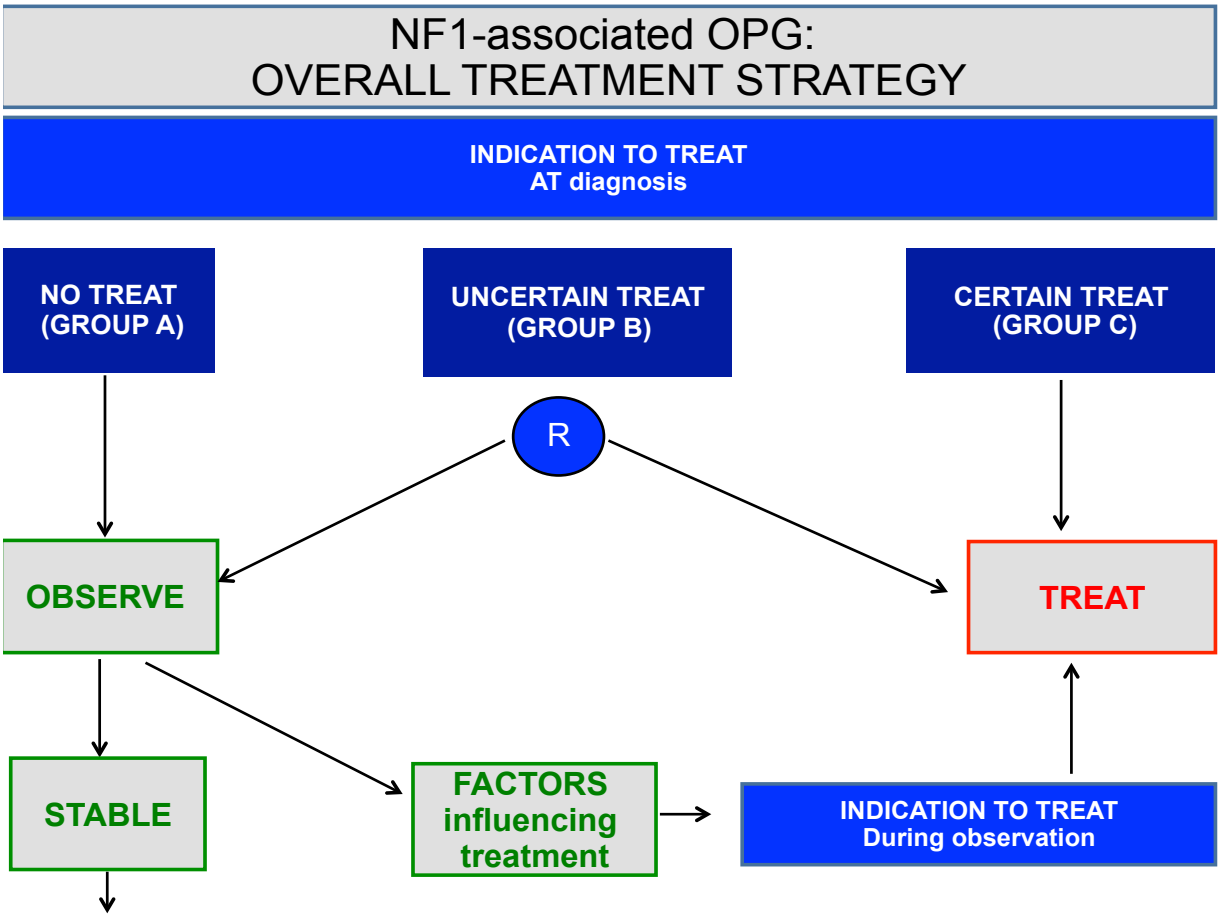
	No treatment	Uncertain treatment	Yes treatment
Vision related factors			
Initial VA assessment	Normal VA	Abnormal VA (non severe) Blindness unilateral (normal contralateral)	Threat to vision (severe) Blindness unilateral (abnormal contralateral)
VA changes over time	Stable VA	---	VA loss
Other visual signs of progression*	Absent	Present (at least one)	---
Radiology related factors			
Radiological progression	Stable	Progression (with normal VA)	Progression (with abnormal VA)
Post chiasmatic tumor involvement (PLAN 3-4)	No	Yes	---
Patient related factors			
Age	2- 5 years	< 2 years or > 5 years	---

***Including VF deterioration, Proptosis, Optic atrophy**

Patient selection for strategy

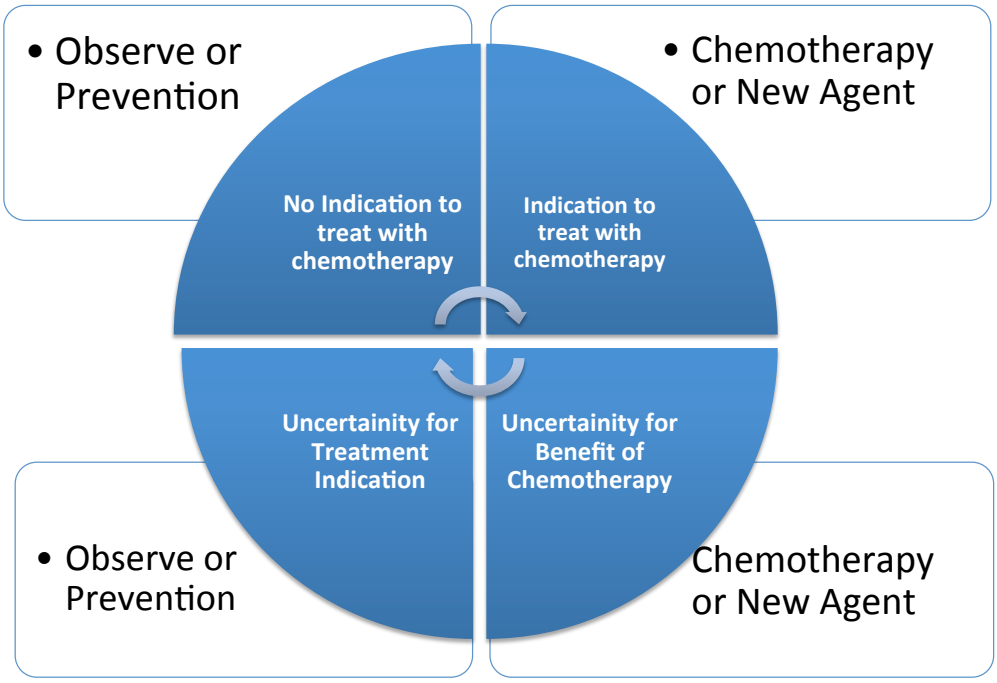
The selection of patients into different risk groups will lead to three different strategies. Children with newly diagnosed NF1 associated OPG who fall in the *group A* (low risk/no need to treatment) are candidate to observation, until follow-up or some influencing factor may become present. The group C is defined as high risk /certain need to treatment. Children falling at diagnosis or during observation into this group C will receive chemotherapy according to the treatment arm strategy (see further chapter on MAMS design). The group B represent a "grey zone" in between, defined as intermediate risk /uncertain need to treatment. Children in this group may therefore need or not chemotherapy, and any treatment could be or not be of benefit in this uncertain group. A randomized comparison between observation and treatment is likely to give us the higher change of answering the question of real need of treatment in such group of children with NF1 and OPG. With this in mind we propose to include such randomized design (comparing treatment Vs. observation) for group B patients.

Figure n.1: Overall risk based randomized strategy flow diagram



The risk based strategy aims to select patients with different risk and expected benefit from treatment. It includes observation, prevention, chemotherapy and new agents for some other patients. A diagram of the possible strategy for the specific clinical scenario is in figure n.1.

Figure n.2: Circle diagram of the four possible clinical scenarios and the proposed strategies



5.2 Developing evidence-based criteria for initiating treatment for NF1 OPG: The US registry

Update and summary of the Investigator Meeting held in Philadelphia (03/11/2014) on the collaboration proposal of the prospective study

E. Opocher & I. Simmons (European representative of the SIOP-LGG NF1 subgroup on behalf of the Study Chairs)

Principal Investigators / Study Chairs

Study Neuro-Oncologist: Michael J. Fisher, The Children's Hospital of Philadelphia Study Neuro-Ophthalmologist: Robert Avery, Children's National Medical Centre

Co-Investigators / Study Co-Chairs

Rosalie Ferner, Guy's and St. Thomas' Hospital David Gutmann, Washington University School of Medicine Robert Listernick, Lurie Children's Hospital of Chicago, Grant Liu, The Children's Hospital of Philadelphia

Study Hypothesis: Outcomes for tumors with involvement of the tracts/radiations will be worse than those without involvement

Primary Aims:

- To determine the prognostic factors for visual outcome for newly diagnosed OPGs

Secondary Aims:

- To determine the prognostic factors for radiographic progression for newly diagnosed OPGs.

For the subset of subjects undergoing treatment:

- To determine the prognostic factors for visual outcome (i.e. visual response to treatment)
- To determine the indications for treatment that are prognostic for visual and radiographic outcome
- To assess the correlation between visual and radiographic outcomes
- To evaluate the correlation between visual field and visual acuity outcomes o To understand the normal variability of visual acuity testing within and between subjects
- To determine the average duration of therapy needed to achieve a significant improvement in visual acuity (i.e., 0.2 log MAR improvement on two consecutive visits)
- To understand the prognostic predictive role of OCT in newly diagnosed children with NF1

and OPG (ancillary study n.1- Principal investigators R. Avery, Washington DC & G Liu, CHOP). OCT Methodology requirement: Table mounted (limited to Spectralis) 3.45 mm circle around the ONH, 10 x 10 mm volume of the macula OR HH_OCT (Bioptigen) 6 x 6 mm volume acquired of the ONH and macula.

- To understand the prognostic predictive role of Diffuse Tensor Imaging (DTI) MRI techniques (including Fractional Anisotropy FA) (Ancillary study n.2-principal investigator De Blank P.). Requirement 1.5 or 3 Tesla MRI performing DTI imaging

Impact of the Study

This information will provide hypothesis-generating data that may influence the future determination of the appropriate duration of therapy, as well as provide information helpful to determining whether a therapy should be continued or changed to another agent because of lack of visual response.

Publication policy

For each publication each site can have up to 2 authors
(presumably an ophthalmologist and a neuro-oncologist)
Each site can decide the 2 authors for each publication (we expect multiple publications)**.**
Study team member and additional member of the data analysis will also be Authors.
(We will acknowledge others involved and consider group authorship in case of author limit)

Data Use policy

All publications using study data must include a disclosure that "#subjects of this study were part of a larger natural history study of NF1 associated OPGs funded by CTF (Children's Tumor Foundation) and the Gilbert Family NF Institute".
If publishing on the prognostic factors for visual outcome (our primary outcome measure) using data included in this study, then consent from the study Publication Committee must be obtained first (We aimed to be generous/collaborative; All clinical trials publications will be approved).

Important notes from the Authors

Visual acuity should be tested in all children with Teller Acuity Cards (distance at 55 cm). There is some possibility to get funds from CTF to buy TAC in some participant centres.

Data could be asked and shared by participating authors for selected questions unrelated to the primary/secondary outcomes of the study. In Europe a collaborative prospective study for children with NF1 OPG will likely to be ready within the next 2-3 years. We may thus pilot our proposed strategy in the patients enrolled in the US study and get useful information for our risk-based strategy without excluding patients from one of the 2 studies.

5.3 The proposed SIOP-E Multi-arms multi stage (MAMS) strategy for children with NF1 associated OPG enrolled in the treatment arm

E. Opocher, D.A. Walker, D. Hargrave, K.Weathley, A. Sehested, & J.Grill

The proposed risk based strategy for children with NF1 associated OPG previously described includes a treatment arm for children in the *intermediate risk* group who are randomised to treatment (Vs observation) and for children into the *high risk* group and for which there is clear and immediate need to treatment. This latter group includes children with significant visual decline as well as those with threat to bilateral vision. We used the multi-arms multi-stage design to build up a multiple arm strategy with more than two treatment arms. We further reviewed available data on prospective phase II studies and/or case series to evaluate the best strategy to propose for this treatment arm, including necessarily the standard of care, but also, possibly, a new agent with sufficient data to be tested or compared in first line.

The classic chemotherapy strategy

Since 1996 and until today, in many countries the classic regimen combining vincristine and carboplatin, the Packer regimen, is considered the standard of care for children with NF1 associated OPG needing treatment. [33]

Other interesting regimens that have shown response in terms of PFS in relapsed LGG patients have been introduced by the Toronto group, with the use of vinblastine as weekly monotherapy, due to the very good toxicity profile and low cost of the drug. According to data on 9 patients with NF1 the PFS seems particularly favourable for this subgroup (NF1 LGG) (75 % +/- 15) compared to sporadic LGG (non NF1) and this regimen is now proposed in first line in some countries (as Canada).

The anti-angiogenetic strategy

Bevacizumab

Pilocytic astrocytoma tumor with limited growth potential but nonetheless highly vascularized. The idea of targeting neo-angiogenesis in a metronomic schedule to treat LGG first resulted in the use of vincristine and vinblastine, two agents with established anti-angiogenetic properties. More recently, the group from Washington DC [34] showed first that clinical and/or radiological

improvement was frequent with the use of the Bevacizumab, a highly selective anti-VEGFa monoclonal antibody already used for different tumor types when combined to another drug as Irinotecan. In particular, in terms of clinical benefit (albeit often temporary) results were somehow impressive and unexpected in children who received already multiple lines of treatments. However, the potential for long-term side effects of Bevacizumab, particularly in young children and in those with NF1, together with the costs of the drug limited the use and incorporation of such drug into first line academic trials upcoming without evidence from phase II randomised studies. We consider at the moment not feasible to propose a bevacizumab based randomized arm. A sponsored phase II study comparing Vinblastine Vs. Vinblastine and Bevacizumab at first line treatment is going to be launched soon by *Roche* in Canada Centres and first data will be available within the next 5-8 years.

The target therapy strategy

BRAF inhibitors

When first was discovered the role of BRAF alteration in children with LGG, there has been great enthusiasm on the possibility to target this pathway to treat LGG in children. As a direct consequence, Sorafenib (a multi-TKI and non selective BRAF inhibitor) gained major attraction due to the possibly to inhibit the BRAF pathway by an orally available drug. A phase II study has opened in US centres in 2010 [35] However, when first patients receiving sorafenib treatment experienced a significant tumor growth under treatment attributable to a paradoxical feedback loop the study prematurely closed and the drug is no more candidate for use in pediatric LGG.

mTOR inhibitors (Rapalogs)

Based on the rationale that NF1-associated brain tumors have an hyperactivation of the mammalian target of rapamycin pathway which may lead to tumor cell proliferation, several phase II studies have been launched in different US centres evaluating the orally available mTOR1 inhibitor, Everolimus (RAD0001). The first results from Boston Dana Farber's group (Kieran et Al) are now available and have been presented at recent ISPNO 2014 meeting [36]. These data show that 23 patients with a median age of 9 years (range, 3–17 years) were enrolled; all had received prior chemotherapy (average n. regimens = 2.7) including progression after a carboplatin-containing regimen. Median number of cycles of therapy was 10 (range, 1-12). Responses (by blinded central review) included 4 patients with PR (> 50% decrease) and 13 with stable disease. Six patients had progressive disease by one year. Overall therapy was well tolerated; two patients

discontinued therapy due to mouth sores (n = 1) and withdrawal of consent (n = 1). In conclusions, as stated by Authors, Everolimus was well tolerated in pediatric patients with progressive or recurrent LGGs and demonstrated activity in this multiply recurrent/progressive patient population. Incorporation of Everolimus into frontline LGG therapy is being proposed.

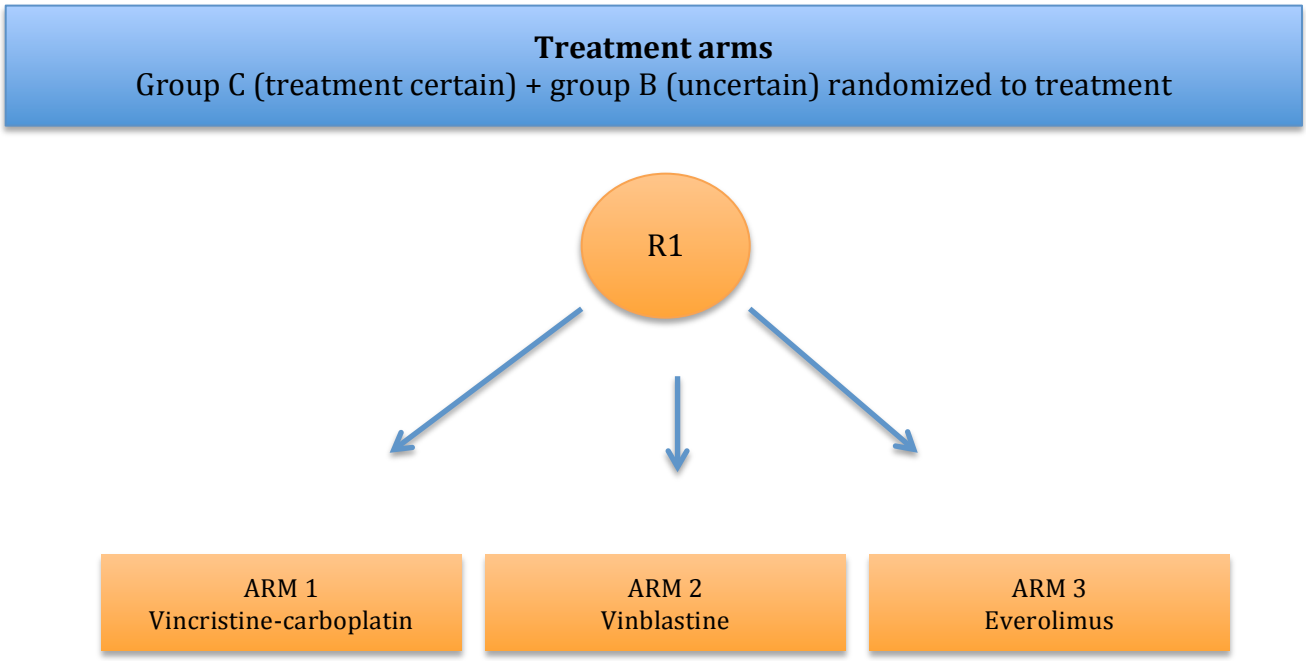
Nilotinib

A non sponsored academic SIOPE and ITCC phase I-II study is currently ongoing in France and other European countries evaluating the addition of a second generation multi-TKI (Nilotinib) to a more classic chemotherapy as vinblastine monotherapy for relapsed or refractory LGG including OPG with or without NF1 (VINILO trial). Patients in phase I receive the combination of drug at different dose regimen to identify the maximum tolerated dose (MTD), then, in the phase 2 of the trial, patients will be randomised to receive vinblastine with or without the addition of Nilotinib at the recommended phase 2 doses. Both radiological and clinical response will be evaluated. No results are available at the moment, with only few patients that have been registered until now, some of them with response in terms of tumor shrinking. Thus this combination may warrant further introduction in a MAMS design strategy, as soon as the results of the trial will be available.

The proposed treatment randomised strategy

Patients eligible to the MAMS randomised strategy for treatment arms included patients in previously defined Group C (high risk) and in Group B (uncertain group) but randomized to receive treatment arm (Vs. Observation arm). Patient enrolled in the treatment arm will be randomly assigned (1:1) to receive one of the 3 treatment arms for 18 months of treatment duration (or until progression).

Arm 1 (standard comparator arm)	Vincristine-carboplatin (as in the SIOP-LGG 2004 study)
Arm 2 (experimental)	Vinblastine 6 mg/m2/weekly single agent (as in Bouffet phase II study)
Arm 3 (experimental)	Everolimus 5 mg/m2/die orally for 18 months (as in Kieran phase II study)



Question of the first randomization (R1): *Is visual outcome of arm 2 or arm 3 compared to standard of care (arm 1 vincristine-carboplatin) non inferior but with reduced TOXICITY?*

A difference of 10 % in visual improvement rate was considered as meaningful of superiority in terms of efficacy. At the same time a 10% reduction of toxicity was considered as meaningful for defining a regimen as lower toxic (as summarized in the table below).

Table n.2: Possible results interpretations of the randomization R1

Outcome	Toxicity	New standard of care (SOC)
Exp better than standard (> 10%)	+ 10%	To be discussed
	=	VBL or everolimus
	- 10 %	VBL or everolimus
Exp non inferior to standard (+/- 10%)	+ 10%	VCR-CARBO
	=	To be discussed
	- 10%	VBL or everolimus
Exp inferior to standard (> 10%)	+ 10%	VCR-CARBO
	=	VCR-CARBO
	- 10%	To be discussed

Future study amendments

In a second phase of the MAMS strategy, in case of everolimus inferiority compared to the other two "classic" chemotherapy arms, we would propose to investigate if the addition of everolimus in combination to standard of care will improve visual outcome compared to the standard of care as results from the R1 phase.

Question of the second Randomization (R2): ***Does the addition of everolimus to the (new) standard of care improve visual outcome compared to the standard of care?***

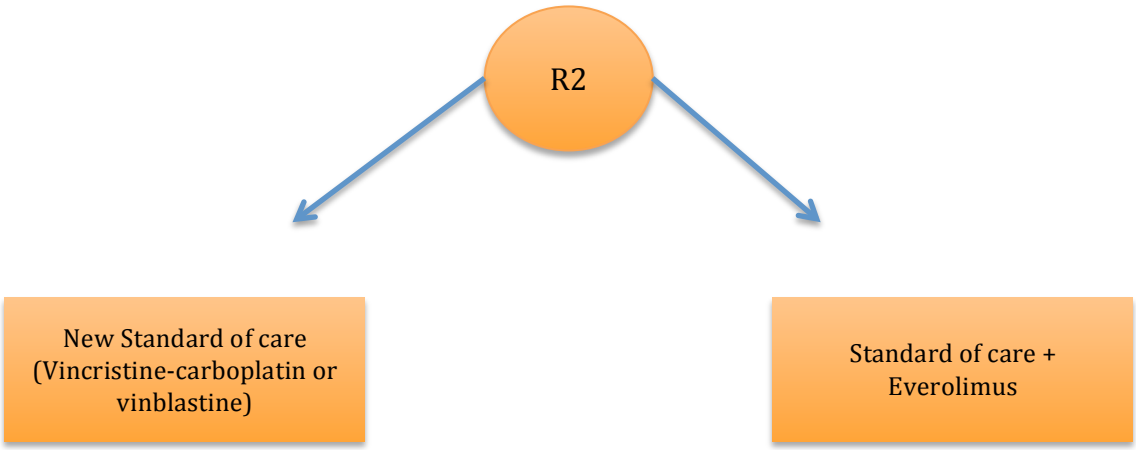
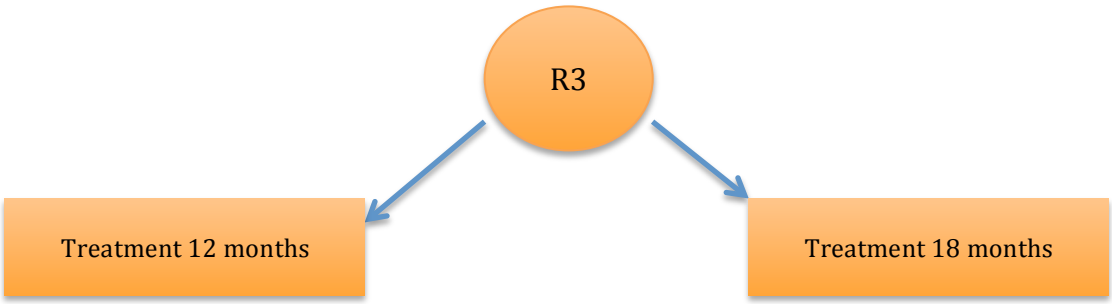


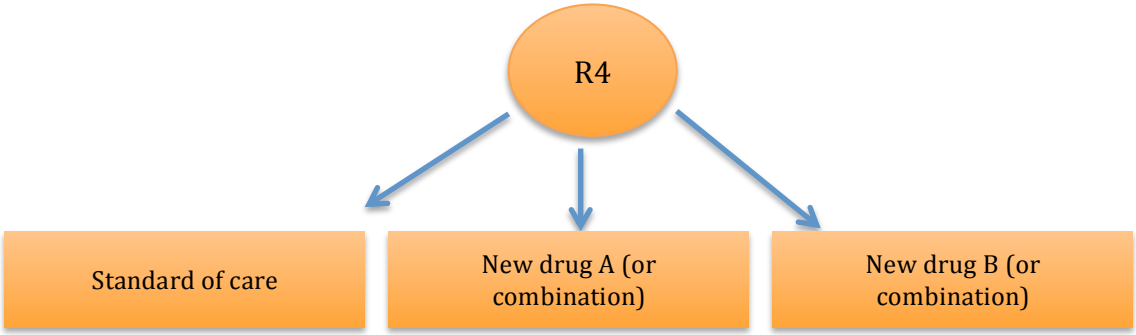
Table n.3: Possible results and interpretation of the randomization R2

Outcome	Toxicity	New regimen
Combination better (> 10%)	+ 10 %	To be discussed
	=	Add everolimus
	- 10 %	Add everolimus
Combination same (+/- 10%)	+ 10%	No everolimus
	=	No everolimus
	-	To be discussed
Combination worse (> 10%)	+	No everolimus
	=	No everolimus
	-	No everolimus

As soon as the interim analysis in the MAMS design will allow to drop off arms these arms will be excluded from the randomised strategy. If the study will be able to *pick the winner* among the different treatment arms a new randomization regarding duration of treatment will be introduced (12 Vs. 18 months).



Furthermore, as soon as current phase I-II studies will show valuable results and other drug will be available for comparison the new drugs/regimens will be incorporated in the overall randomisation of the treatment arm according to the MAMS design.



5.4 Visual assessment and outcome interpretation

Ophthalmological Guidelines for Clinical Trials in Children with OPG and NF1

Enrico Opocher, Ian Simmons, Kamilla Rothe-Nissen, Astrid Marie Sehested, Amedeo Azizi, Pablo Hernaiz-Driever, Renè Schmidt, on behalf of the E-SIOP-LGG brain tumor group and adapted from the REiNS group NF1 OPG functional outcome guidelines [37]

1. Visual Acuity as the best functional endpoint for clinical trials including children with OPG

Visual Acuity (VA) refers to the ability to resolve detail in foveal vision (or in the best available para-foveal area). The visual acuity value compares a subject's performance to the performance of a standard eye. If the subject needs letters that are twice as large or twice as close, visual acuity is said to be one half. If the letters need to be five times closer or larger, visual acuity is one fifth, etc. Despite VA describes only one aspect of visual performance for one retinal area, it reflects visual pathway integrity, making an effective screening tool for visual impairment and ideal candidate to objectively measure the visual impact of an OPG. Visual acuity measurement is essentially repeatable, under the same testing conditions and, most importantly, it is well understood by *non*-ophthalmologists. To date, VA is the only visual outcome measure that has been assessed to any major extent in OPG, as well as the only measure that has been shown to be sensitive to change with treatment, and is then considered universally the preferred modality to objectively measure the impact and burden of an OPG on the overall visual function.

Important note:

An expert ophthalmologist (and/or orthoptist if available) should test every infant or child (irrespectively of age) with a newly diagnosed OPG with the primary aim to quantify visual acuity (VA) in both eyes monocular.

2. How should VA be tested?

For the purpose of clinical trials, it is crucial that the selection of testing method is quantifiable so that the magnitude of change can be accurately measured over time.

There are multiple testing methods available to assess VA quantitatively. The choice of method depends on a various factors, including child's age, developmental/cognitive level, and ability to cooperate (see table n.1).

Table N. 1: Visual Acuity (VA) testing methodologies

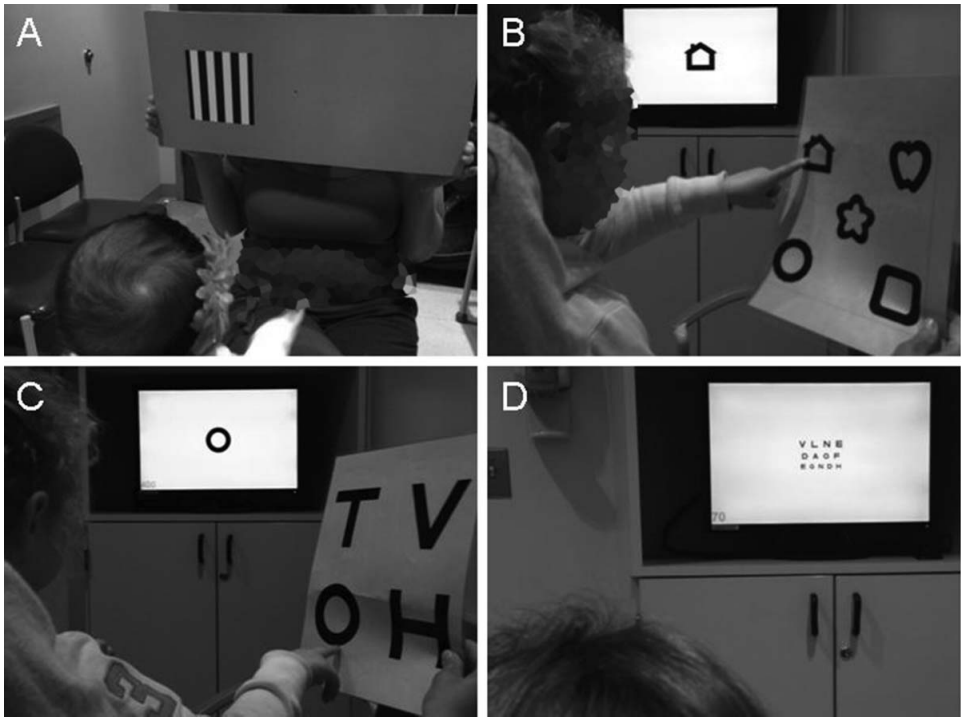
Age (years)	Test name	Test type VA	Normal VA	Reported VA	Limitations	Benefits
0.5 – 2	Teller Cards (TAC)	Preferential looking, Grating acuity	Age-based	Continuous variable	Labor intensive, Requires an experienced tester, Overestimates VA in those with poor vision	Validated measure used in clinical trials, valid across many ages,
3	LEA figures	Figure matching, recognition acuity	20/40	Not truly continue variable	Not standardized	Can be used in preliterate children
4	HOTV	Letter matching or identification, recognition acuity	20/30	Continuous variable	Can overestimate VA	Standardized computer-based testing is validated for use in clinical trials
5	Snellen	Letter identification, recognition acuity	20/25	Continuous variable	Requires full literacy, many not standardized	Standardized computer-based "ETDRS" testing is validated in clinical trial
≥6			20/20			

Quantitative testing methods (Teller acuity cards [TAC]) exist for children as young as 6 months of age and are reliable measures of VA. The TAC is a preferential looking test that relies on an infant's propensity to redirect his or her gaze toward a visually interesting stimulus (alternating high-contrast black and white lines). VA is quantified by knowing the distance to the stimulus and the width of the smallest lines the child is able to appreciate. In older children, testing methods measure the ability to recognize ("recognition acuity") a figure (e.g., Lea symbols) or letters (e.g., HOTV or Snellen). The complexity of the test increases with age, such that a higher level of cognition and cooperation is required to complete HOTV compared with Lea, and Snellen testing compared with HOTV. Although there is reasonable correlation of VA results between testing formats, transitioning between testing formats, as the child gets older may confound the interpretation of acuity changes over time. [38] Despite these limitations, there is no agreement in Europe on the use of a unique ophthalmologic testing method. Therefore we recommend that VA

should be measured using the most appropriate age-matched test. Children younger than 3 years need to be assessed by some form of preferential looking test (as TAC). In Children between 3 and 8 years this may be achieved using the HOTV matching letter test. Patients tested with different methods (TAC, HOTV, LEA, E-charts etc.…) will be eligible in the trial if the data provided can be quantified and translated into log MAR units.

Important note
Children's VA should be tested with the most appropriate age-matched test under best possible conditions (after lunch, etc.…) and with best correction (glass/contact lenses. In case of glass/lenses correction use this should be marked on the VA results for each eye respectively (right/left eye correction).

Figure 1: Different VA testing methodologies TAC (A), LEA (B), HOTV (C) and Snellen (D)



2.2 Which special considerations for infants with OPG?

Vision is a principal input for an infant's learning and development. Normal postnatal development of the eye and information processing in the brain depend on the quality of vision infants experience after birth. Every effort should be done to objectively evaluate and assess these children, which should be performed only by pediatric ophthalmologists with expertise in OPG and with the full range of instruments to best evaluate vision development and function for different age. When an infant undergoes ophthalmologic test with TAC the tester should attract the infant's attention so that the infant is looking straight ahead. Present each card for several short presentations rather than one long presentation. This helps prevent the infant from becoming bored. Depending on testing distance, VA values in Cy/degree, measured with TAC can be converted to Cy/cm using table n. 1 and then translated to log MAR.

Infants with OPG most often have huge hypothalamic/chiasmatic lesions, which may present with ventricular dilatation and various degrees of visual symptoms and signs, as nystagmus. These children have particularly challenging ophthalmologic assessment.

If an infant or child has horizontal nystagmus or convergent strabismus, it may be helpful to hold the TAC card vertically. This allows vertical eye and head position changes in response to the grating to be distinguished from the horizontal nystagmus or strabismus. However, since norms have not been established for this form of testing, acuity values obtained with this method should be interpreted with caution.

Most often infants and young children with nystagmus have a lower vision compared to those without nystagmus, in the same age group. Considering the difficulty to obtain reliable and quantitative VA data in this particular subgroup, the presence of nystagmus should be taken into account as an indirect sign of low vision, and might influence the overall indication to treatment even in the absence of clear signs of visual progression and/or low vision (see criteria below)

2.3 How to account for normal vision development in a young child with OPG?

It is important to consider that as normal VA improves with age in young children, an OPG occurring before 6 years of age may limit or reduce the potential to a normal visual development. Different age-based norms (e.g., 20/40 is normal at age 3 years, 20/20 is normal at age 6 years) are available from the literature depending on the testing methodology.

For very young children tested with TAC two sample age norm charts (one for binocular and one for monocular test results) are available in the TAC manual. The graph on the lower half of the sheet is used to plot the patient's acuities, to compare them to normal acuity for age, and to follow changes in acuity over time.

It's worth to emphasize that normal visual development is a range for age groups up to 6-7 years rather than a precise number and every translation from raw data to age-adjusted VA will be approximate calculation to be considered with caution for guiding clinical decision.

However, we feel it is important to consider both raw and age-adjusted VA in the visual assessment of a young child with OPG, as this information might influence clinical decision and outcome interpretation (i.e. a stable VA in a young child may be a sign of failure to develop normal vision and/or a sign of progression during observation or treatment).

A schematic summary of normal VA for specific age table is presented in table n.2

Table n 1.: Age adjusted VA (in feet and log MAR)

Age (yr.)	Normal VA (feet)	Normal VA (Log MAR)
0.5 – 2	Age-based curves	Age based curves
3	20/40	0.3
4	20/30	0.2
5	20/25	0.1
6 or older	20/20	0.0

Important note
Calculation of age-adjusted VA: Measured VA (log MAR)- Normal VA for age (based on table n 2 and/or appendix graph n 1-2): *i.e. a 4 years child with OPG and 0.7 log MAR VA in right eye corresponds to 0.7 log MAR (measured VA) – 0.2 (normal VA for age) = 0.5 log MAR*

2.4 Which special considerations for visual assessment of children with low vision?

Children with OPG may present at diagnosis with an already severely compromised visual function. For children with limited visual residual function, testing distance with the TAC should be

initially of 38 cm. If no response is obtained, the tester moves in to 19 cm. If no response is obtained at 19 cm, the tester can try the test at closer distance (9.5 cm).

In ideal conditions VA should be measured for both eyes monocular. However, in some circumstances (as some young children especially if blind or nearly blind) in one eye resist monocular vision testing on that eye. If monocular VA is not evaluable for both eyes, we suggest record quantitative data based on binocular vision specifying reasons for not achieving monocular vision testing in the e-CRF.

Important note
We recommend to refer as early as possible children with OPG and severe hypo vision (or blindness) to a specialized Centre with multidisciplinary rehabilitation competences

2.5 How should VA be reported?

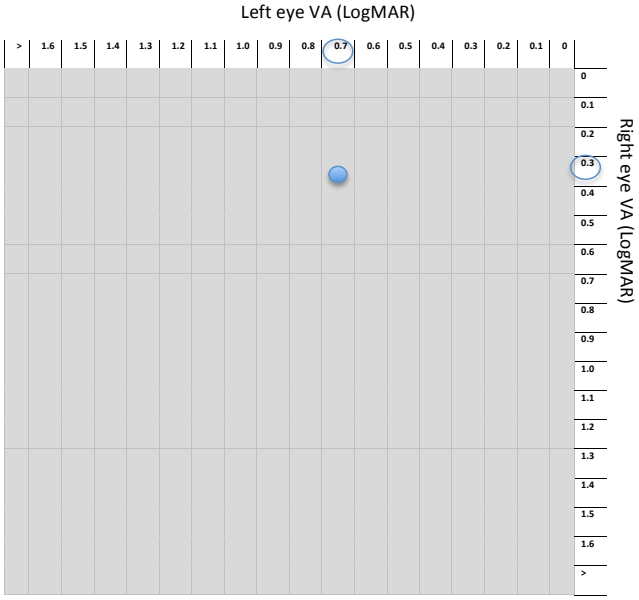
Clinically, VA is typically reported as a fraction (e.g., 20/20 in feet, 6/6 in meters), and change in acuity is usually described by the difference in the number of lines on the eye chart between testing sessions. In order to standardize the quantification of magnitude of change, we recommend that VA be reported using the logarithm of the minimum angle of resolution (log MAR). Intervals of change between lines on log MAR charts are therefore of equal magnitude. A conversion between Snellen equivalents and log MAR is summarized in table n. 2.

Important note
We recommend reporting and entering the raw VA data for each patient's visual assessment in the e-CRF. A central automatic calculator will generate a graphical report (see below) with the two eyes combined VA

Table n. 2: Conversion table between Snellen equivalents and log MAR

Visual Acuity	Lines on visual acuity chart		
log MAR	Feet	Meters	
- 0.1	20/16	6/5	
0.0	20/20	6/6	**10/10**
0.1	20/25	6/7.5	
0.2	20/32	6/10	**6/10**
0.3	20/40	6/12	**5/10**
0.4	20/50	6/15	
0.5	20/63	6/20	**3/10**
0.6	20/80	6/24	
0.7	20/100	6/30	**2/10**
0.8	20/125	6/38	
0.9	20/160	6/48	
1.0	20/200	6/60	**1/10**
1.1	20/250	6/75	
1.2	20/320	6/96	
1.3	20/400	6/120	**1/20**
1.4	20/500	6/150	
1.5	20/640	6/192	
1.6	20/800	6/240	**1/40**
> 1.6	**Hand motion (or light perception)**		
---	**No light perception**		

Fig.n.1 CRF-Bilateral VA graphical reporting system



2.6 What constitute visual progression or response ?

Visual acuity can vary by 0.1 log MAR if tested on two separate occasions even on the same day.
If there is a drop of VA equivalent to or greater than 0.2 log MAR on more than one occasion (at least 2 weeks apart), we should advise that children should have a full refraction and examination looking for anysometropia (difference in glasses prescription between the eyes) or strabismus. If either is identifies, a period of either occlusion or atropine penalization might be indicated to try to improve vision in the worse eye. If there is no anisometropia/squint, or the vision does not improve with treatment after 6 weeks, visual acuity decline should be considered.
If the results of a VA evaluation are in doubt because of poor effort or cooperation and/or in case of suspected visual decline it is mandatory to retest the child. Children should be re-tested in best possible patient compliance and collaboration conditions, within 1-2 weeks, to confirm the visual decline. If the results are still unreliable, then no data should be entered for that visit. If VA loss is confirmed, it is crucial to exclude refractive error, amblyopia, or other non-OPG-related causes.
We recommend defining a significant VA progression as a 0.2 or greater log MAR decline in VA in one or both eyes.

2.7 How often should VA be monitored while on treatment ?

At present, no evidence exists to recommend an ideal monitoring interval to determine visual progression or response in a clinical trial. Thus, we recommend monitoring visual function, in particular VA every 3 months while on treatment. Following completion of treatment, we recommend monitoring visual function at 3, 6, 12, 18, 24, 30, 36, 48, and 60 months.

2.8 What about other possible functional end points ?

Other possible visual parameters, as visual fields, colour vision, strabismus, nystagmus, optic disc swelling, optic disc pallor, proptosis, visual evoked potentials, will be considered relevant part of a comprehensive ophthalmologic examination in children with OPG, but will not be used as primary endpoints in this study.

Visual fields (VF)

Children with OPG in the previous SIOP-LGG trial were not uniformly assessed for VF. Furthermore data on VF were not standardized and rather incomplete and non consistent among different centres. We decided, according to the REiNS guidelines, that primary aim of visual assessment and primary outcome in children with OPG should be VA and VA changes. Nevertheless we consider VF testing a relevant aspect of the overall visual function assessment in children with OPG that may give, at least in some patients, complementary information to VA on the overall visual damage and function in children with OPG.

We proposed that visual assessment in children with OPG should include VF, at least as a secondary measure. We propose to use a standardized methodology for VF testing. The SVOP pediatric visual field analyser normally allows recording visual fields in 3 and 4 years old children and has been proposed by the core ophthalmologic group for clinical trial. If this is not available two eyes direct confrontation of VF shall be used as a simple test for collaborative children.

Visual evoked potentials (VEPs)

The role of VEPs in children with OPG is not fully understood and its use in clinical practice, particularly for a clinical trial, is not standardized nor recommended at present time. However we propose that some selected centres (which might be able to perform VEPs) collect prospectively VEP data in infants with OPG enrolled in this trial, where a quantitative and reliable measure of VA is particularly challenging.

Optical coherence tomography (OCT)

Measurement of retinal nerve fibre layer with the use of optical coherence tomography is rapidly becoming a highly attractive and objective measurement surrogate of visual function in children with OPG. However, despite promising data have been recently published on the diagnostic sensitivity of OCT, routine inclusion of OCT in clinical trials for OPG cannot be recommended at this time. Selected centres may perform OCT and collect prospectively data on OCT in children with newly diagnosed OPG and NF1, in order to get more information that will be required to determine whether abnormalities in Retinal Nerve Fibre Layer (RNFL) thickness may be predictive of future vision loss and whether changes in RNFL thickness over time correlate with changes in VA.

3. Visual response and visual outcome

3.1 Visual response as the primary outcome

Change in visual function is one of the primary endpoints of the LOGGIC trial, comparing in the randomized study two chemotherapy regimens VBL-carbo and VCR-Carbo and comparing different durations of CT (12 Vs. 18 months).

Change in VA as log MAR difference as a one-dimensional outcome measure will be calculated as the difference between VA at 12 months and VA at baseline (i.e. the start of treatment, if treated or at diagnosis in case of observation).

When reporting study results, we suggest reporting both per-subject and per-eye outcomes. The latter is standard in the ophthalmology literature and is important as vision may be affected in only one eye. However, in a subject with a unilateral optic nerve glioma, the unaffected eye should be excluded, as it will bias the results.

As suggested by the REiNS group it is critical to consider ceiling and floor effect for VA when establishing clinical trial enrolment criteria and analysing study data. For example, eyes with normal VA (20/20 5 0.0 log MAR or better) at baseline cannot improve and should be eliminated from a study targeting visual response. In contrast, blind eyes cannot worsen and should be excluded from studies of visual progression-free survival (PFS). Based on our definition of visual progression or response (0.2 log MAR or greater change), we recommend a ceiling of 0.2 log MAR below normal for age or 0.2 log MAR below a previous reliably documented VA. We set the floor at 1.36 log MAR (20/470), which is the VA equivalent of the lowest Teller acuity card from which a 0.2 log MAR decline can be measured with good reliability (using a standard testing distance of 55 cm). Based on these considerations, we recommend that one eye must be evaluable (0.2 log MAR below normal for age or below a previous reliably documented VA < 1.36 log MAR) in order to enrol in a therapeutic OPG trial. When analysing results, if the study endpoint is best visual response, then eyes with VA at the ceiling should be excluded. If the study endpoint is visual PFS, then eyes with VA at the floor should be excluded in the analysis.

Thus, three possible scenarios may be encountered during chemotherapy response assessment and visual outcome evaluation:

1. **VA worsens in at least one eye**

- This condition should be coded as a **progression event** and **this subject should be coded as a treatment failure and come off study** (*if visual loss and/or low vision were indications to treatment).*
- Non evaluable (roof/ceiling effect) eyes should be excluded from the visual outcome analysis

2. **VA improves in one eye and is stable (or improved) in the other eye**
    - This condition should be coded as a VA improvement and a positive response to chemotherapy
    - In case of bilateral VA improvement, one-dimensional calculation of overall patient VA improvement should encounter the VA changes in the *best-affected eye*, as this will have major impact on patient's overall vision.
    - Non evaluable (roof/ceiling effect) eyes should be excluded from the visual outcome analysis

3. **VA is stable in both eyes:**
    - This condition should be coded as a "partially" positive response to chemotherapy
    - Minor changes of VA (< 0.2 log MAR) in one or both eyes do not represent significant improvement/decline of VA in the main outcome analysis (comparing baseline-start of CT and 12 months)
    - However, long term minor VA trends will be unrevealed by analysing last examinations compared to the baseline
    - Non evaluable (roof/ceiling effect) eyes should be excluded from the visual outcome analysis

Important note
In case of inconsistent VA data or difficult interpretations of VA results (i.e. significant improvement in one eye but worsening in the other eye) single selected cases may be discussed with the central referral panel group to define the response/failure to treatment

Table n. 6: Visual change outcome clinical interpretation

VA changes Scenarios	Eye n.1	Eye n.2	Clinical Outcome Definition
1	↓	↓	**Progression**
1	↓	=	**Progression**
1	↓	↑	**Progression***
1	↓	Non evaluable	**Progression**
2	↑	↑	**Improvement**
2	=	↑	**Improvement**
2	Non evaluable	↑	**Improvement**
3	=	=	**Stable**
3	=	Non evaluable	**Stable**

Legend: ↓(VA loss), ↑(VA improvement), =(VA unchanged)

*Please consider with caution progression in these cases

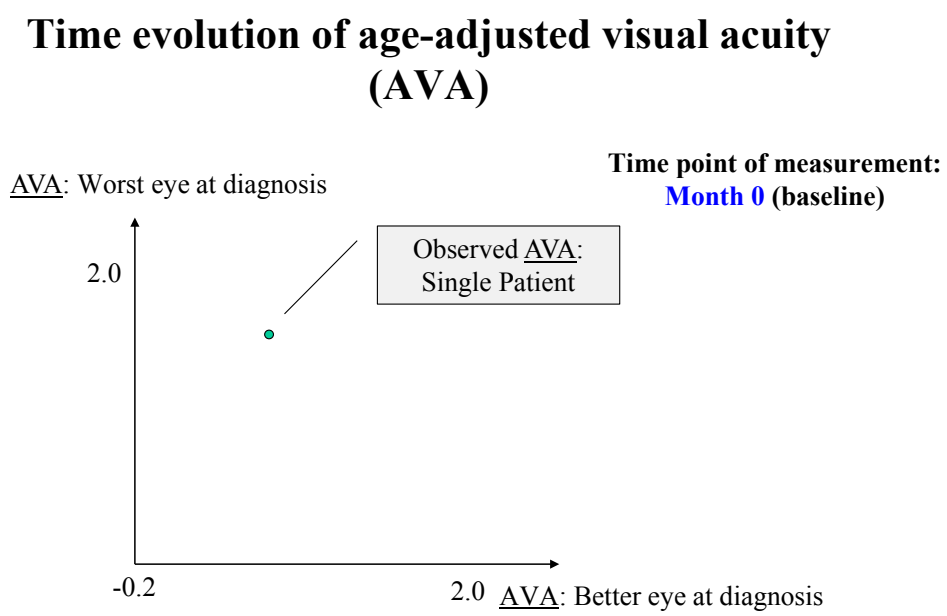
Statistical considerations & Proposal for the Primary Endpoint "Change in age-adjusted visual acuity"(ΔAVA)

Primary Endpoints of next SIOP-LGG and NF1 OPG trials are PFS defined as Progression free survival measured from time of randomization, PFS12 defined as Progression free survival measured from month 12 after time of randomization, change in visual acuity (ΔAVA), Change in neurological symptoms and EFS defined as event free survival measured from time of initial surgery.

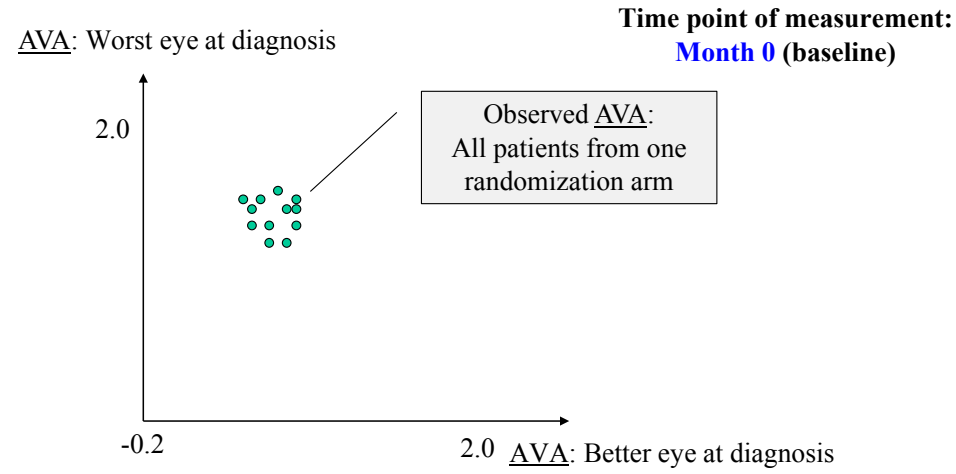
Regarding the main question "change in visual acuity" the trial aim to demonstrate possible superiority of one treatment regimen over another comparing VA measured by log MAR for each eye baseline and month 12. For each eye, the value of VA ranges from -0.2 (normal vision) to 2.0 (blindness), i.e. higher values are unfavourable. Time points of measurement are: before start of treatment (baseline) and at month 12, 18, 24, 30, and 60 after start of treatment. Measurement of VA applies to all patients of age ≥ 6 months at the date of randomization. For each eye, age-adjusted visual acuity (AVA) is defined as the difference of "visual acuity (VA)" and "age normal visual acuity". "Age normal visual acuity" is a correcting term taking the values 0.24, 0.16, 0.07, 0.01, or 0.00 for patients aged 30-35, 36-47, 48-59, 60-72, >72 months at the point of time of measurement of visual function, respectively. For each eye, change in age-adjusted visual acuity

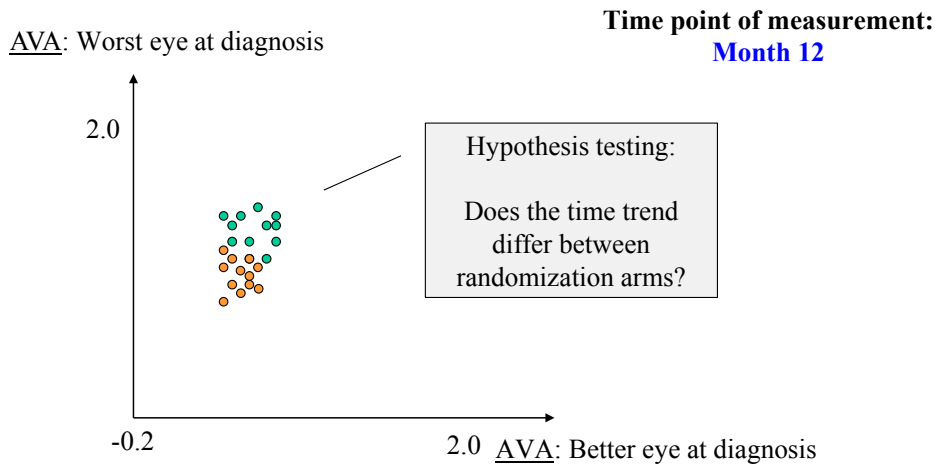
(ΔAVA) is defined as the difference in age-adjusted visual acuity (AVA) between the baseline measurement and the measurement at month 12. Let ΔW (resp. ΔB) denote the observed ΔAVA for the eye with the worse (resp. better) AVA at the baseline measurement. Therefore, ΔW and ΔB both take values in the interval (-2.2, 2.2) with smaller values being unfavourable and with higher values being favourable. Example: Consider a patient aged 34 months at baseline measurement with baseline VA of 0.3 and 0.6 log MAR for the left and right eye, respectively. Assume that his VA at month 12 is 0.1 and 0.3 log MAR for the left and right eye, respectively. So, the right eye is the worse eye at baseline measurement, and we obtain • ΔW=(0.6–0.24)–(0.3–0.16)=0.22and • ΔB=(0.3–0.24)–(0.1–0.16)=0.12

Null hypothesis H3: The change in visual acuity (ΔAVA) in patients treated with regimen A does not differ from ΔAVA in patients treated with regimen B. This analysis will be performed within the following population: All patients with:(i) age ≥ 6 months at the date of baseline measurement, (ii) an observed value for age-adjusted visual acuity (AVA) in the interval (0.2, 1.36) for both eyes at baseline measurement. The observed values from both eyes shall be taken into account in the analysis (i.e. 2-dimensional outcome instead of 1-dimensional). Then, null hypothesis H3 may be analysed by fitting a repeated measurements model. (see graphical illustration)



Time evolution of age-adjusted visual acuity (AVA)





3.2 Visual quality of life (QOL) as a secondary visual outcome measure

Patient-reported outcomes, specifically those assessing quality of life (QOL), have emerged as important measures for use in clinical treatment trials. VA loss has been reported to affect markedly an individual's employment and overall QOL. For example, moderate vision loss may have only a modest impact on QOL for a 3-year-old, whereas in an adolescent the same degree of vision loss may result in the inability to drive a motor vehicle, which might result in a more profound effect on QOL. To evaluate the direct impact of vision loss on particular QOL domains, vision-specific QOL instruments have been developed for adults and were found to correlate with the degree of visual impairment. Visual ability and QOL measures that assess the impact of vision

loss in children have been examined in a variety of pediatric eye diseases, with most designed to evaluate children between 8 and 18 years of age. The Children's Visual Function Questionnaire (CVFQ) is the only instrument designed to evaluate children 8 years of age and younger, the time during which most patients with OPG become symptomatic. The CVFQ could be considered as a secondary outcome measure in children 8 years of age and younger.

The CVFQ is a set of 2 instruments (one targeted to children under 3 years of age, one to children age 3 to 7 years) developed to measure the impact of visual impairment on the quality of life of young children and their families. Its intended use is primarily for research purposes and may include the assessment of efficacy of different therapeutic approaches for eye disorders in infancy and early childhood and of methods of early visual stimulation and rehabilitation.

Important note
The CVFQ is a public document available without charge to all researchers provided that they identify the measure as such in all publications. Users should also cite the following article: Felius J, Stager DR Sr, Berry PM, Fawcett SL, Stager DR Jr, Salomão SR, Berezovsky A, Birch EE. Development of an instrument to assess vision-related quality of life in young children. *American Journal of Ophthalmology,* 2004; **138**(3): 362-372 [39]

For children older than 8 years another specific WHO questionnaire called WHO/PBD Visual Functioning Questionnaire (20 item) is similarly available from the WHO website and referred as "CONSULTATION ON DEVELOPMENT OF STANDARDS FOR CHARACTERIZATION OF VISION LOSS AND VISUAL FUNCTIONING, Geneva, 4-5 September 2003" [40]

Important note
For the purpose of the study the CVFQ (<8 years) and the WHO/PBD (> 8 years old) questionnaires will be translated in different languages and piloted as secondary visual outcome measures at OPG diagnosis, at start of treatment and at the last follow-up

Discussion

Preliminary results from the prospective SIOP-LGG2004 NF1 study indicate that the outcome of children affected by OPG and NF1 and treated with chemotherapy is satisfactory, in terms of progression free survival (5 years-PFS = 74.5%). The lack of randomised trials comparing different regimen coupled with the few other prospective data available that separately analysed outcome in children with NF1 OPG should lead to consider vincristine-carboplatin for duration of 18 months as the standard of care for this group of patients. Bouffet et Al in a phase II study evaluated vinblastine alone as a possible alternative to the standard regimen, showing promising results in relapsed children with LGG. When the NF1 group of LGG (9 patients) is separately analysed a PFS of 75% (+/- 15%) with the use of vinblastine seems at least as effective as vincristine-carboplatin in this group of children [41]. Also given the excellent toxicity profile and the cheapness of vinblastine it should be considered as a valid strategy to be tested in first line alone or in combination with other new agents. However, it is worth to remember that the small number of NF1 patients in this study limits the external validity and a large randomised trial is required to confirm these promising data.

A recently published COG randomised trial compared a multi-drug alchilant based regimen TPCV to vincristine-carboplatin for 12 months in children with LGG, showing slightly better PFS for the former regimen [42]. No separate data for NF1 children were provided, thus no conclusions could be made from the available data, regarding use and effectiveness of TPCV in children with NF1 and OPG. However, at least in Europe, the potential risk of chemotherapy induced second tumor that have the drugs included in the TPCV, makes this regimen fairly unattractive for NF1 LGG group. The risk of second neoplasms with the use of DNA-damaging drugs, coupled with the Cisplatin induced ototoxicity in children with NF1 and OPG, potentially affected by other significant comorbidities (visual deficits) make the strategy used in Milan and published by Massimino et Al, (VP16 –Cisplatin), even at lower doses, nowadays, not preferable. [43]

Treatment duration (between 12 and 18 months) represent another unsolved question for chemotherapy in children with OPG and NF1. An historical comparison with the published HIT-LGG NF1 data by Hernaiz-Driever et Al [44] may indicate that a 5 yr-PFS of 73% after 12 months of chemotherapy seems at least not inferior to the 71.4 % from the SIOP-LGG2004 where treatment was prolonged to 18 months. However we should be cautious with such an historical comparison where different selection criteria and indications to treatment were used. We should indeed take into account the weakness of any historical comparison with no randomised direct comparison.

One major concern about the vincristine-carboplatin strategy emerged from the SIOP-LGG2004 NF1 study analysis was the unexpected high rate of carboplatin allergy (60%) occurring at a median time of 8.5 months and leading to change to alternative chemotherapy at a median time of 10.4 months from the start of treatment. With detailed guidelines for allergy management we believe the vincristine-carboplatin drop out rate could be significantly reduced and thus not jeopardize a randomised comparison between different regimens as proposed in the next trial design. However, with the potential availability of promising and low toxic alternative regimens it will become more difficult to re-expose a child to carboplatin when first allergic event will occur.

Another potential limit of the standard of care is that, despite vincristine-carboplatin is still considered a well-tolerated chemotherapy, there is a significant neurotoxicity of vincristine. Neurotoxicity was similar in NF1 and non-NF1. R. Jackaci et Al [45] first evaluated the combination of vinblastine and carboplatin, in view of the possibly reduced neurotoxicity of vinblastine compared to vincristine. Early data have shown that the combination is feasible, but for sure, more hematotoxic. For this reason, the NF1 working group finds this regimen as not appropriate.

However the question of reduced neurotoxicity by using vinblastine instead of vincristine with carboplatin is going to be answered in a randomised trial in children without NF1 and LGG in Europe.

The prospective SIOP-LGG2004 NF1 data failed to individuate significant independent prognostic factors for PFS, with only surgery as a risk factor for worse outcome. This data may be influenced by selection of worse patients who underwent surgery.

Different indications to treatment have different outcome and children whose primary indication is visual loss have excellent tumor control rate in terms of PFS. The lack of correlation between radiology and vision and of complete visual data hampers any further data interpretation.

Different studies analysed possible prognostic factors in children with NF1 and OPG. Age, tumor site, presenting symptoms, gender, and response to CT are among the most important prognostic factors from most of the available studies [46,47,48,50]. However, these studies also suffer methodological limitations including retrospective design, radiological PFS, incomplete visual outcome data, inconsistent visual testing methodologies, and non-separate analysis for NF1+ or OPG.

One of the studies focusing on visual outcome in children with NF1 OPG treated with chemotherapy have shown that post-chiasmatic tumor involvement and age (< 2 years or > 5 years) are the only prognostic factors for worse visual outcome [16]. However, the independent prognostic role of post chiasmatic (Dodge III or PLAN 3-4) tumor involvement is still unclear and

needs further evidence that might be provided by the incoming prospective US natural history study.

Since the primary goal of NF1 OPG treatment is preservation of visual function, we analysed visual outcome data available from the large study population of SIOP-LGG2004 NF1 trial. Despite more than 220 children with OPG and NF1 were registered in the SIOP database, visual outcome reliable and complete data were available only for 50 children (23%). From this cohort we could extrapolate that visual outcome is still unsatisfactory after chemotherapy, as only 23% documented some visual improvement. One of the few large studies focused on visual outcome after chemotherapy in children with NF1 OPG by Fisher et Al [16], have shown similarly that less than 1/3 of patients (32%) had a visual improvement. In the IGR retrospective study visual acuity (VA) improved in 36% of patients. A systematic review has also confirmed that the VA improvement rate is very limited (14%) after chemotherapy [49]

All these information collectively (table n .9) seem to indicate that although VA improvement is uncommon, it is still possible with chemotherapy in patients with a frequency between 23% and 36%.

Table n.9: VA changes after chemotherapy

VA changes after CT Per eye and (per patient)	Fisher MJ (Neuro-oncology 2012)	SIOP-LGG2004 NF1+	IGR series
N. Evaluable eyes	168	92	50
Improved VA	22% eyes (32% patients)	24% eyes (23% Patients)	26% eyes (36% patients)
Stable VA	57% eyes (40% patients)	34% eyes (32% patients)	48% eyes (36% patients)
Worse VA	21% eyes (28% patients)	40% eyes (35% patients)	26% eyes (28% patients)
Missing data	---	10%	---

The overall degree of visual preservation (defined as VA > 3/10) at the end of treatment should be also considered as a parameter of treatment success, with as many as 46% of children with OPG in the SIOP-LGG NF1 study who had a compromised vision at the last follow-up. Only 14 patients (28%) had a preserved vision (VA ≥ 3/10 in both eyes) and 13 patients (26%) had a partially preserved vision (VA ≥ 3/10 in at least one eye).

Few other studies consider visual preservation, as the IGR retrospective study and the prospective French study by Laithier et Al [50] and showing similar (39%) even more (60%) patients respectively, with a compromised vision after chemotherapy.

Table n.10: Visual preservation after treatment in children with NF1 OPG

NF1 OPG visual acuity preservation after CT	Laithier et Al (n = 46)	SIOP-LGG NF1 2004 (n = 50)	IGR series (n = 23)
Preserved (> 3/10 in both eyes)	18 (40%)	14 (28%)	3 (13%)
Partially preserved (> 3/10 in one eye)		13 (26%)	11 (48%)
Compromised (< 3/10 in both eyes)	28 (60 %)	23 (46%)	9 (39%)

Preliminary data on visual outcome in this NF1 OPG cohort, shows that ascertainment of visual performance was surprisingly poor. Available, albeit incomplete information shows that visual acuity was already compromised in almost half of children who underwent treatment, not changing significantly between before and after treatment.

Considering efficacy of chemotherapy to improve in terms of better visual preservation category, as a more clinically relevant measure, we have shown that visual preservation category remained unchanged in 2/3 of children but was infrequently associated with change to a better vision category (11%). This data adds useful information that should be also taken into account when a patients starts chemotherapy.

In order to better understand treatment outcomes for this tumor, future OPG clinical trials will need to mandate visual function assessment and consider visual acuity (change and preservation) as primary outcome measures.

Visual decline and threat to vision were the two only factors determining indications to treatment according to a risk based strategy. One of two factors may be sufficient to start chemotherapy.

If visual decline is the main criteria for starting treatment has been agreed with the US group, the absolute visual function at diagnosis is another relevant criteria.

Despite classifying VA into categories (e.g., good, fair, poor) is recognized problematic by other groups, as small non functional changes in VA can result in a change in VA category and categorization of visual acuity is artificial, a definition of normal vision, abnormal vision and threat

to vision represent an innovative and patient's based measure that the European group decided to implement by introducing into in the risk based strategy. We believe that initial and last-follow-up visual assessment should define this measurement as this information may provide more clinically relevant information than only changes in VA after treatment.

Based on the risk of visual loss resulting in patient selection within one of the three risk group (A-B-C) we elaborated three different strategies including an observation arm for group A, a treatment arm (group C) and a randomisation between observation and treatment for the group B (uncertain indication-intermediate risk).

How to group patients into different risk groups is a critical issue that needs to be evidence based and shared among different stakeholders that are involved in the care of children with NF1 and OPG. The European collaboration to the US natural history prospective study that aims to identify evidence based criteria for starting treatment will be therefore of paramount importance to contribute to confirm and harmonize prognostic criteria that have been now proposed in the European risk based strategy.

A randomised strategy comparing observation vs. chemotherapy has however some limitations including the feasibility from a parent's perspective to accept his child to be randomly assigned to observation vs. chemotherapy. The potential toxicity of chemotherapy however balances the unclear benefit of chemotherapy. Therefore we have to give a role to uncertainty by such strategy. We should therefore first convince ourselves as well as the parents that this randomised strategy will be the only correct way to answer this unsolved critical question.

The opportunity to have a multiple treatments arm including standard of care and low toxic regimen and a biological agent as everolimus and the MAMS design that should allow to pick the winner between the randomised arms seems very innovative and attractive. This also will likely represent a potential major step forward in the adaptive design of the next NF1 OPG treatment strategy, where study duration is expected to be 8-10 years.

Response to chemotherapy might be an additional factor predictive of visual prognosis that warrants some consideration in the overall discussion. In fact the the paper published by *Laithier et Al* [50] including 85 children with progressive OPG treated with BB-SFOP chemotherapy, has shown that visual outcome might be influenced by the quality of response to chemotherapy (P = 0.0304). Among the 36 children with a good response to chemotherapy, 18 (50%) had a visual acuity 3/10 in the best eye (i.e., preserved vision) at the last follow-up. Among the 49 children with a poor response or progression of the tumor during chemotherapy, only 14 (28%) had a visual

acuity 3/10 in the best eye. A positive response to chemotherapy can be then considered a predictive factor for a positive outcome. What might be feasible would be to design a response-based strategy and continue chemotherapy only in case of real benefit (response) and randomize patient to continue vs. stop treatment in case of stable disease. This will be an alternative strategy to distinguish between natural history of OPG and chemotherapy effect. This hypothesis, however, at the moment has not been considered for the next NF1 OPG study.

The thesis also provides the guidelines for a standardized visual assessment in children with NF1 and OPG enrolled in clinical trials, adapted from the published guidelines from the US-REiNS group. These guidelines state that visual assessment and outcome should base on visual acuity as the primary outcome measure. The proposed draft includes reccomendation to how to test children, how to report data, how to interpret outcome on a clinical or statistical basis.

Important note underline the most critical and important aspect of the various parts of the guidelines to make these guidelines as clear and easy as possible to have the best adherence and compliance from local study investigators, which ultimately fill in the CRF forms.

These ophthalmology guidelines are currently being discussed within a multidisciplinary working group including oncologists and ophthalmologist and a final version will be hopefully ready within the next few months. Still controversies exist regarding the use of raw Vs age adjusted VA data and the interpretation of visual outcome according to bilateral change in VA.

The final version of this draft will be the ophthalmology chapter of the upcoming NF1 OPG SIOP-study protocol.

A prospective evaluation of vision-related quality of life with the validated children visual function questionaire (CVFQ) is also included in these guidelines. There has been common agreement with the US group to use this questionaire in order to have relevant information on the quality of life of this group of children. This represent a second major step forward towards a functional based outcome measure.

Multidisciplinary team discussion table need to be constantly maintained to pursue ophthalmologic commitment and render specific ophthalmologic evaluation practical also for non-ophthalmologists that will have to take the final decision on treating or not a child with NF1 and OPG.

The future strategies for treating children with NF1 OPG

The MEK inhibitors

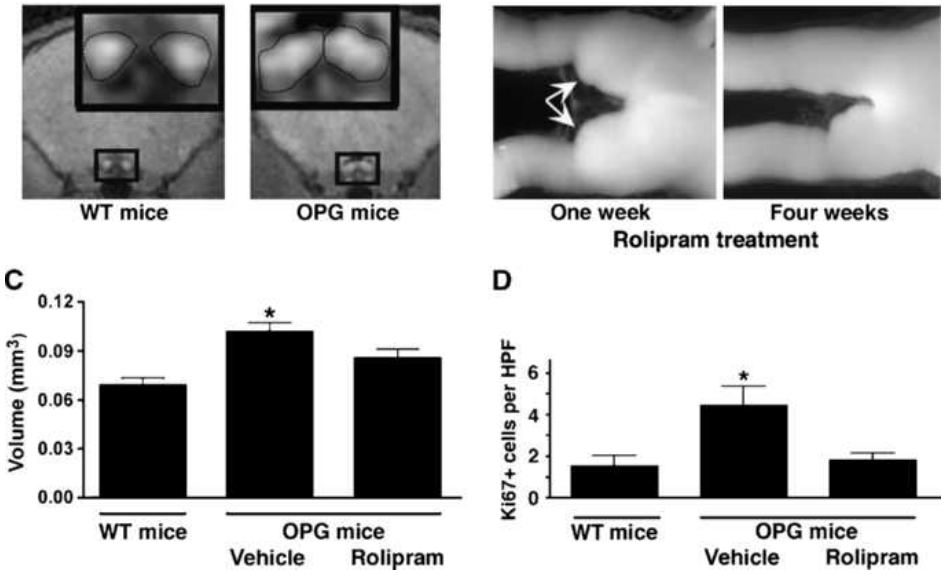
A phase I-II trial launched by Astra-Zeneca with the orally available drug Selumetinib, a selective MEK inhibitor is currently recruiting patients, in the US countries. Early phase I results have been transmitted confidentially to a SIOP Europe representative from the US group principal investigator, showing a very high response rate in children with both sporadic (non NF1) and NF1 associated OPG. This drug (or other MEK inhibitor now available) have shown very promising phase I-II data and the introduction of MEK inhibitors in clinical practice for children with OPG will be possible within the next 3-5 years. However, significant remarks and criticisms remain about sustainability of response and long-term side effects that should be carefully monitored, as they are at the present time largely unknown.

The neuroprotective strategy

The phosphodiesterase IV (PDE IV) inhibitors

Fascinating mouse models have first shown a role of decreased level of cyclic adenosine monophosphate (cAMP) in NF1 associated gliomagenesis [51, 52]. In fact, in addition to RAS regulation, neurofibromin positively controls intracellular cAMP levels. While neurofibromin loss in NF1-associated neuroglia cells leads to increased RAS and RAS pathway activation, reduced neurofibromin expression results in attenuated intracellular cAMP levels. Several researches have now shown from mouse model that neurons with reduced cAMP level are at highest risk of early neuronal damage. In the mouse model, drug capable to increase intracellular level of cAMP (phosphodiesterase IV inhibitors as Rolipram) have shown to reduce tumor proliferation (see figure below) and might be a very attractive approach for treating (or prevent) OPG in NF1 children. However there is not any open phase I study to test this hypothesis.

Figure: Tumor volume before and after PDE4i (Rolipram) treatment in mice with NF1 OPG [51]



The Nerve Growth Factor (NGF) eye drops

About 50 years after the discovery of the nerve growth factor (NGF) by Rita Levi Montalcini, an engineered NGF based eye drop has been recently developed with the goal to restore visual function in patients with neuronal damage including children with OPG. A pilot study [53] was performed by the team leaded by R. Riccardi, in Rome, showing objective visual evoked potentials (VEPs) and subjective visual fields improvement in most of the patients (adults or children) after one week of treatment with the NGF eye drops. Results of this study have been published recently and as stated by the study authors "conjunctival NGF may be a beneficial adjunct therapy for visual loss in patients with OPG, possibly exerting its effects on residual viable optic pathway". Thus the idea of an NGF eye drop local treatment in children with NF1 OPG represent one of the most appealing approach for visual saving strategies as will avoid systemic chemo-toxicity. However, the pilot study should be confirmed in a larger unselected population. Furthermore, the lack of a commercially available NGF eye drops formulation limits the implementation of such strategy at the moment.

In conclusions this thesis is comprehensive project in three chronologic parts, with the ultimate objective to develop and design of the SIOP-Europe future strategy for children with NF1 associated OPG.

We have first shown from the SIOP-LGG 2004 NF1 prospective study, the limits of a PFS outcome analysis and the challenge of correct visual data interpretation when data are collected in unstandardized manner. Visual outcome should be then considered separately from radiological outcome, and functional outcome is the primary outcome measure, based on a standardized visual assessment methodology. This approach only will make comparable results between different clinical trials around the world.

Considering the paucity of randomised trials in rare disease and the difficulty to launch a new clinical trial nowadays, it is critical to have a well designed trial to raises the right questions and have an answer in a reasonable time frame. The risk based strategy that takes into account both the risk of visual loss and the expected benefit of chemotherapy will most likely be the appropriate strategy to give us the unsolved issue of whether a patient really needs treatment and whether chemotherapy is likely to be the answer. The MAMS innovative design in the upcoming NF1 OPG study will likely to help to give an answer as quickly as possible.

Every new trial in children with NF1 OPG should evaluate the effectiveness of any intervention to preserve or improve visual function at the lowest possible cost and, at introduce as soon as possible biological target therapies or neuroprotective agents [54] that will more likely improve visual outcome when the risk of visual burden is significant and the expected benefit of classic chemotherapy is unclear.

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