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INNOVATIVE KEYS TO HEALTH AND WELLBEING

Use of the anti-EGFR humanized monoclonal antibody nimotuzumab on the treatment of newly diagnosed children with DIPG or in recurrent or refractory children with high grade glioma: 10 years of experience

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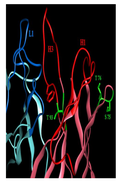
ABSTRACT

Background: Children glioma is a life-threatening condition with a survival rate of less than 1 year. Nimotuzumab, a unique and-EGFR humanized monoclonal antibody affinity differentiated during past 10 years had been used in combination with radiotherapy or radiochemotherapy on the treatment of newly diagnosed children with DIPG or as monotherapy in children with recurrent or refractory high grade glioma.
Objective: The aim of studies was to evaluate nimotuzumab in combination with radiotherapy or radiochemotherapy in newly diagnosed children with DIPG or as monotherapy in recurrent or refractory children with high grade glioma, as assessed by overall survival.
Methods: Patients with newly diagnosed DIPG or recurrent high grade glioma, KPS ≥ 50%, 3-18 years old, measurable disease, and with adequate renal and liver function were included in 4 clinical trials and 3 physician lead trials. Patients received i.v infusions of 150 mg/m^2 of nimotuzumab in combination with 54 Gy radiotherapy or radiochemotherapy for DIPG patients or 150 mg/m^2 of nimotuzumab as monotherapy on high grade glioma, weekly, for 6-8 weeks, and then every 2-3 weeks until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS) and secondary endpoints progression-free survival (PFS), overall response rate (ORR), clinical benefit rate (CBR), safety and quality of life.
Results: 112 newly diagnosed children with DIPG (50 male/62 female), median age 7.6 yrs old were recruited in 2 clinical studies and 1 physician lead study in Brazil, Cuba, Germany, Italy and Russia and 128 recurrent or refractory children with high grade glioma (66 male/62 female), median age 9.9 yrs old were recruited in 2 clinical studies and 2 physician lead studies in Canada, Cuba, Germany and United States. For newly diagnosed children with DIPG median OS ranged from 9.4 to 15.0 months and median PFS from 5.8 to 8.5 months and for recurrent or refractory children with high grade glioma median OS ranged from 5.5 to 9.2 months and median PFS from 1.7 to 2.1 months. For newly diagnosed children with DIPG, ORR was 23.4 % and CBR was 80.2 % and for recurrent or refractory children with high grade glioma ORR was 15.6 % and the CBR was 38.3 %. There were not Grade III/IV nimotuzumab related hematological and non-hematological toxicities and all patients improved the quality of life.
Conclusions: Use of nimotuzumab had been efficacious in newly diagnosis children with DIPG and in recurrent or refractory children with high grade glioma

INTRODUCTION

- Glioma is a rare but devastating cancer. Although temozolomide is currently the first-line standard of care for the treatment of glioma, temozolomide has shown minimal activity in high-grade glioma of childhood with no convincing evidence on its activity in diffuse intrinsic pontine glioma (DIPG). To date, there is no standard therapy to treat newly diagnosed DIPG or recurrent or relapse high grade glioma in children and adolescents.
- Nimotuzumab, formerly called h-R3, is a genetically engineered humanized mAb that recognizes an epitope located in the extracellular domain of human EGFR. It is an IgG$_1$ isotype that was obtained by transplanting the complementary determining regions (CDR) of the murine anti-EGFR mAb ior egf/r3 (IgG$_{2a}$) to a human framework assisted by computer modelling.
- Nimotuzumab blocks EGF and TGFα binding to the EGFR receptor and inhibits its intrinsic tyrosine kinase activity. In preclinical studies, nimotuzumab showed antiproliferative, proapoptotic, and antiangiogenic effects in tumors that overexpress EGFR, and enhanced radiosensitivity with reduction of tumor blood vessels and proliferation in the human GBM cell line U87MG.

FIGURE 1. Nimotuzumab, an anti-EGFR humanized mAb



- Is an anti-EGFR humanized monoclonal antibody as 5 mg/mL in 10 mL vials
- IgG$_1$ isotype
- Has an affinity constant of 4.5 x 10^{-9} M.

In vitro:
(i) inhibits tumor cell proliferation,
(ii) induces cell cycle arrest,
(iii) inhibits angiogenesis,
(iv) induces apoptosis on different human tumor cell lines, and
(v) Induces immunogenic cell death by activation of proteins: calreticulin, ERp67, HSP60, HSP70, HSP90 and upregulation of HLA Class 1 MHC proteins
(vi) Induces Natural Killer (NK) mediated Dendritic Cells (DC) priming leading to a generation of an anti-EGFR specific T-cells

In vivo:
(i) induces complete regression of well-established human cancer xenograft in nude mice as monotherapy or in combination with radiotherapy or chemotherapy,
(ii) inhibits tumor cell proliferation and angiogenesis and increases the number of apoptotic tumor cells alone or in combination with radiotherapy.
(iii) reduces the number of small microsatellite tumors administered alone or in combination with radiation therapy on U87 glioma tumors
(iv) its chronic use has shown to be effective in reducing the number of CD133+ radioresistant cancer stem cells on U87 glioma tumors

TABLE 1. Differences of anti-EGFR monoclonal antibodies

Antibody	cetuximab	nimotuzumab	panitumumab
Host cells	SP20 cells	NSO cells	CHO
Type of molecule	Chimeric	Humanized	Fully human
Ig Subclass	IgG$_1$	IgG$_1$	IgG$_2$
Dissociation constant, K$_D$(M)	5.1 x 10^{-10}	4.5 x 10^{-9}	5.0 x 10^{-11}
Binding properties to the EGFR	Monovalent binding	Bivalent binding	Monovalent binding
Incidence of all grade rash and skin reaction adverse events (%)	88[a]	2.1[b]	89[c]

[a]cetuximab product insert, [b]nimotuzumab product insert, [c]panitumumab product insert

METHODS

STUDY OBJECTIVES:

- **Study OSAG 101-BSC-05**: Multicentre phase III trial to explore the feasibility and efficacy of the h-R3 monoclonal antibody (nimotuzumab) simultaneously to conventionally fractionated local radiotherapy in the treatment of children and adolescents with newly diagnosed DIPG
- **Study IIC RD EC-097/EF-090**: To evaluate the efficacy of nimotuzumab in children and adolescents with newly diagnosed brain stem gliomas
- **Study BN-001 PED-04**: To evaluate effectiveness of a humanized EGFR antibody on the treatment of pediatric and adolescents with chemotherapy-resistant high-grade glioma.
- **Study YMB-1000-013**: to determine the efficacy of the use of the EGF-R antibody nimotuzumab monotherapy in the treatment of recurrent or refractory brain stem glioma
- **Expanded Access Program**: to evaluate the effectiveness of the monotherapy treatment of the anti-EGFR monoclonal antibody nimotuzumab in children and adolescents with high-grade glioma

INCLUSION / EXCLUSION CRITERIA:

FIRST LINE TREATMENT ON NEWLY DIAGNOSED DIPG PATIENTS:

Inclusion criteria: pediatric patients with newly diagnosed DIPG which have been documented by conventional imagery methods (MRI, CAT), Age ≥3 years old ≤ 18 years old, life expectancy ≥ 12 weeks, laboratory parameters for hematological, liver and renal functions must be within the normal defined limits, and both parents or legal guardian(s) must express in writing the will to allow the patient to participate in the study by signing the informed consent within others.

Exclusion criteria: patients with low grade brain stem glioma (i.e. focal, cerebromedullar, tectal brain stem gliomas), patients previously treated with a monoclonal antibody, patients who previously received some type of cancer treatment including chemotherapy, immunotherapy or radiation therapy, concurrent cancer treatment which is not part of the study protocol, pregnant or nursing patients, patients with a chronic disease (i.e. cardiopathy, diabetes, high blood pressure) at the time of inclusion, patients with hypersensitivity to the drug or to a similar drug, febrile condition, severe septic condition and/or serious or acute allergic condition, patients participating in another clinical study with the intent to treat their tumor at the time of inclusion and presence of a second tumor.

RECURRENT OR RELAPSING HIGH GRADE GLIOMA:

Inclusion criteria: histologically verified diagnosis of a high-grade glioma (WHO III and IV) (not applicable or necessary for intrinsic pontine glioma), age ≥ 3 years to ≤ 20 years, adequate hematological, renal, and hepatic function (CTC grade ≤ 2), condition is measurable by X-ray in at least one dimension, life expectancy ≥ 4 weeks and written consent from parents/legal guardian, and, if possible, children, after being informed.

Exclusion criteria: a history of prior use of EGFR-targeting agents (monoclonal antibodies, tyrosine kinase inhibitors), recent introduction of an "alternative" curative treatment method after progressive diagnosis, and during this study, more than one line of treatment (i.e. more than one progression after initial therapy) for the disease, had radiation therapy completed within 12 weeks of enrollment, previous chemotherapy completed ≤ 2 weeks prior to enrollment , and pregnancy in females of childbearing age

STATISTICAL ANALYSIS:

- Analyses of demography, baseline characteristics, safety and efficacy was performed on the data set of all treated patients
- **Demographics and baseline characteristics**: were summarized using descriptive statistics
- **Primary efficacy analysis**: The primary estimate of median overall survival (OS), progression-free-survival (PFS), overall response rate (ORR) and disease control rate (DCR) was estimated on the basis of Intent-To-Treat population
- Primary analysis of survival was conducted by means of a log-rank test using Kaplan-Meier curves. Median OS, PFS and their 95% confidence interval (CI) were calculated by each tumor localization using a Cox regression model

RESULTS

TABLE 2. PATIENTS DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Study Number	Number of patients	Sex		Median age (yr)	KPS or Lansky index, N (%)			Tumor localization
		Male	Female		< 70	70-80	90-100	
First line treatment								
OSAG 101-BSC-05	42	16	26	7.6	10 (23.8)	23 (54.8)	9 (21.4)	DIPG
IIC RD EC-097/EF-090	45	19	26	7.9	6 (13.3)	17 (37.8)	22 (48.9)	DIPG
MILANO-IST	25	15	10	6.1				DIPG
Recurrent or refractory								
BN-001 PED-04	22	17	5	8.9	8 (36.4)	11 (50)	3 (13.6)	DIPG
	13	7	6	12.2	7 (53.8)	5 (38.5)	1 (7.7)	GBM
	12	5	7	10.3	5 (41.7)	4 (33.3)	3 (25)	AA
YMB-1000-013	46	21	25	6.0	14 (30.4)	17 (37)	15 (32.6)	DIPG
Expanded access program in Cuba 1	3	0	3	10.8	2 (66.7)	1 (33.3)	0	AA
Expanded access program in Cuba 2	9	5	4	10	4 (44.4)	1 (11.1)	4 (44.4)	DIPG
	5	3	2	10.2	3 (60)	1 (20)	1 (20)	GBM
	3	2	1	8.3	1 (33.3)	2 (66.7)	0	AA

DIPG, diffuse intrinsic pontine glioma, GBM, glioblastoma, AA, anaplastic astrocytomas, N, number of patients

TABLE 3. CLINICAL RESPONSE TO THE TREATMENT

Study Number	Indication	Treatment	Response to the treatment					
			CR	PR	SD	PD	ORR (%)	DCR (%)
First line treatment								
OSAG 101-BSC-05	DIPG	RT + nimotuzumab	0	4	27	8	9.52	73.8
IIC RD EC-097/EF-090	DIPG	RT + nimotuzumab	0	20	14	11	44.4	75.6
MILANO-IST	DIPG	RT + vinorelbine + nimotuzumab	0	2	22	1	8.0	96.0
Recurrent or refractory								
BN-001 PED-04	DIPG	nimotuzumab	0	1	10	11	4.56	50.0
	GBM	nimotuzumab	0	0	3	10	0	23.1
	AA	nimotuzumab	0	1	2	8	8.33	25.0
	Total		**0**	**2**	**15**	**29**	**4.3**	**36.2**
YMB-1000-013	DIPG	nimotuzumab	0	2	7	17	4.4	19.6
Expanded access program in Cuba 1	AA	nimotuzumab	0	0	0	1	0	0
Expanded access program in Cuba 2	DIPG	nimotuzumab	2	1	2	4	33.3	55.6
	GBM	nimotuzumab	0	0	0	5	0	0
	AA	nimotuzumab	1	0	1	1	33.3	66.7
	Total		**3**	**1**	**3**	**10**	**23.5**	**41.2**

DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma; AA, anaplastic astrocytoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate

TABLE 4. Integrated summary of a systematic review

Indication	Treatment	Number of patients	Response to the treatment					
			CR	PR	SD	PD	ORR (%)	DCR (%)
First line treatment								
DIPG	RT + nimotuzumab	87	0	24	41	19	27.6	74.7
DIPG	RT + vinorelbine + nimotuzumab	25	0	2	22	1	8.0	96.0
Recurrent or refractory								
DIPG	nimotuzumab	77	2	4	19	32	7.79	32.5
GBM	nimotuzumab	18	0	0	3	15	0	16.7
AA	nimotuzumab	18	1	1	3	12	11.1	27.8
	Total	113	3	5	25	59	7.1	29.2

DIPG, diffuse intrinsic pontine glioma; GBM, glioblastoma; AA, anaplastic astrocytoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate

PROGRESSION FREE SURVIVAL AND OVERALL SURVIVAL

TABLE 5. PFS AND OS ON NEWLY DIAGNOSED CHILDREN AND ADOLESCENTS WITH DIPG

Parameter	OSAG 101 BSC-05	IIC RD EC-097 / EF-090	MILANO-IST
Treatment	RT + nimotuzumab	RT + nimotuzumab	RT + vinorelbine + nimotuzumab
Number of patients	42	45	25
PFS (months) [95 % CI]	5.60 [5.04 – 6.16]	8.23 [6.47 – 9.99]	8.50
1 yr PFS rate (%)	5.3	33.3	30.0
2 yr PFS rate (%)	NR	NR	12.0
OS (months) [95 % CI]	9.2 [7.55 – 10.85]	9.7 [7.99 – 11.41]	15
1 yr OS rate (%)	33.3	42.2	76.0
2 yr OS rate (%)	NR	NR	27.0

NR, no reported

TABLE 6. PFS AND OS ON RECURRENT OR REFRACTORY CHILDREN AND ADOLESCENTS WITH HIGH GRADE GLIOMAS

Parameter	BN-001 PED-04			YMB-1000-013	EXPANDED ACCESS PROGRAM IN CUBA 2
	DIPG	GBM	AA	DIPG	DIPG, GBM, AA
Treatment	nimotuzumab	nimotuzumab	nimotuzumab	nimotuzumab	nimotuzumab
Number of patients	22	13	12	46	17
PFS (months) [95 % CI]	1.53 [1.04–2.02]	1.67 [1.61-1.72]	1.67 [1.29-2.04]	1.8 [1.51-2.10]	NR
0.5 yr PFS rate (%)	18.2	0	16.7	4.8	NR
1 yr PFS rate (%)	4.5	0	0	0	NR
OS (months) [95 % CI]	4.67 [2.48-6.85]	3.47 [2.93-4.00]	6.33 [1.51-11.0]	3.1 [1.89-4.31]	9.17 [4.28-14.1]
1 yr OS rate (%)	9.1	0	25.0	7.6	35.3

NR, no reported

KAPLAN-MEIER CURVES

FIGURE 2. PFS and OS for newly diagnosed children and adolescents with DIPG tumors after treatment with radiotherapy and nimotuzumab.

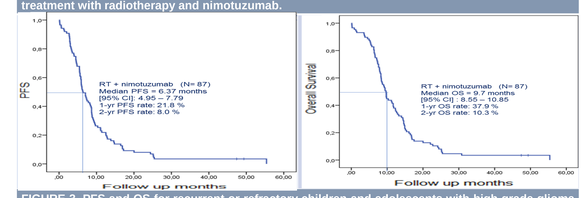
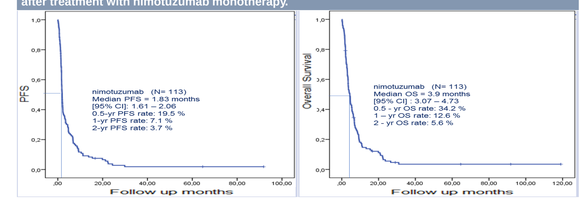


FIGURE 3. PFS and OS for recurrent or refractory children and adolescents with high grade glioma after treatment with nimotuzumab monotherapy.



SAFETY PROFILE

TABLE 7. Percentage of subjects with all grades related AEs occurring in more than 5.0% of newly diagnosed DIPG patients treated with radiotherapy and nimotuzumab

System Organ Class Preferred Term	Radiotherapy (54 Gy) + nimotuzumab (150 mg/m^2) (N=87)
	N[1](%)
Gastrointestinal disorders	
Constipation	5 (5.75%)
Vomiting	11 (12.64%)
Nervous system disorder	
Headache	7 (8.1%)
Skin and subcutaneous tissue disorders	
Alopecia	6 (6.90%)

[1]Reported number and percentages based on number of patients

TABLE 8. Percentage of subjects with all grades related AEs occurring in more than 5.0% of recurrent or refractory children and adolescents with high grade gliomas treated with nimotuzumab

System Organ Class Preferred Term	nimotuzumab (150 mg/m^2) (N=91)
	N[1](%)
Blood and lymphatic system disorders	
Leukopenia	6 (6.59%)
Gastrointestinal disorders	
Nausea	7 (7.69%)
Vomiting	5 (5.49%)
General disorders and administration site conditions	
Fatigue	5 (5.49%)
Skin and subcutaneous tissue disorders	
Erythema	5 (5.49%)

[1]Reported number and percentages based on number of patients

CONCLUSIONS

a) Treatment of radiotherapy in combination with the anti-EGFR monoclonal antibody nimotuzumab increased the progression free survival and overall survival on newly diagnosed children and adolescents with DIPG
b) Addition of nimotuzumab to radiotherapy increased 1-yr OS rate to 38 % and addition of nimotuzumab to radiotherapy and vinorelbine increased 1-yr OS rate to 76 % in newly diagnosed children and adolescents with DIPG
c) The use of nimotuzumab monotherapy in recurrent or refractory heavily pretreated children and adolescents with high grade glioma can achieve an overall response rate (ORR) of 7.1 %, and a disease control rate (DCR) of 29.2 %.
d) Nimotuzumab monotherapy in recurrent or refractory heavily pretreated children and adolescents with high grade glioma increases median PFS to 1.83 months, median OS to 3.90 months, 1-yr PFS rate to 7.1 % and 1-yr OS rate to 12.6 %.

ACKNOWLEDGEMENTS

- These studies were supported by Center of Molecular Immunology (Havana, Cuba), Eurofarma Laboratories (SP, Brazil), Fondazione IRCCS (Milan, Italy), Oncoscience AG (Hamburg, Germany) and YM BioSciences Inc (Toronto, Canada).
- Authors are thankful to all patients, children and adolescents and their families that were part of the studies and to all medical doctors that participated on these studies, without their participation it would have been impossible to conduct these studies.