EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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High-grade glioma expert meeting

List of questions

Questions to be sent in advance

- Please read carefully and answer the questions, give your comments on the topics.
- Please give your free suggestions to any issue you feel relevant to the meeting.
- Send your answers please before 15 November 2010 to Ralf.Herold@ema.europa.eu

Questions on topics of the high-grade glioma meeting

Area	Question	Answer
Characteristics of HGG in different populations	High-grade glioma (HGG) occur in all age ranges. At this time, for a broad discussion, HGG overall shall include glioblastoma [multiforme] (GBM, primary and secondary), anaplastic astrocytoma, anaplastic oligoastrocytoma and diffuse intrinsic pontine glioma (DIPG). At baseline and during treatment, there are a number of biological and / or clinical similarities as well as differences between adult GBM (taking into account primary, secondary and recently proposed molecular subtypes) and HGG in the paediatric population, and within the paediatric population are known.	
	– Overall, which biological, anatomical and / or clinical **subsets are most similar** in adult and paediatric populations with GBM / HGG? Please explain. – Which are the relevant biological and / or clinical **similarities** and **differences** at baseline (including molecular targets, pathways, tumour dependency)?	Most similar: Similarities at baseline: Differences at baseline:

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	– How do these similar and / or different factors impact the choice of diagnostic measures (including biopsies) and the choice of treatment options (including local and systemic treatments)? – For which if any outcomes are these important (e.g., overall survival, event-free survival, toxicity, sequelae)?	Impact of similarities and / or differences for choosing diagnostic and therapeutic options: Outcomes driven by baseline similarities and differences:
	– Which biological and / or clinical characteristics are not yet known to be associated with outcome but should be watched out for further developments? (E.g., immunological mechanisms, niche concepts, proteomics and epigenetics)	Developments to watch out for:
	– In which therapeutic setting is **temozolomide** (TMZ) regularly used in children with HGG? Where is TMZ usually **not** used?	TMZ is usually used in children with HGG: TMZ is usually **not** used in children HGG:
	Divergent outcome data seem to have been found in adults versus children with HGG; examples might be response to bevacizumab with and without irinotecan in recurrent disease, or to temozolomide. – What factors could explain the divergences in outcomes? – How do such factors impact paediatric study designs? – What is the experience with the progression-free survival rate at 6 months (PFS6) in the paediatric population? What is its meaning?	Factors potentially relevant to explain divergent outcome data: Consequences for paediatric study design: Experience with, and meaning of PFS6 in children with HGG:
Overall development approaches	Different principal **different scenarios** could be envisaged for clinical paediatric development of medicines for treating HGG in children. For example, there may be opportunities for **extrapolation** of efficacy shown in adult populations, based on non-controlled paediatric studies of pharmacokinetics, pharmacodynamics, safety, toxicity (any activity and survival would still be recorded). Extrapolation could also be discussed with respect to biological differences and similarities, and across all age subset (e.g., very young children).	

	On the other hand, paediatric studies powered to show efficacy would be needed if extrapolation is not possible, for example because of differences in biological characteristics at baseline or in pharmacodynamics, differences in lines of treatment or previous exposure, differences in clinical use such as combinations or sequence of treatment modalities between adult and paediatric populations. Such caveats are mentioned in the EMA Addendum on Paediatric Oncology.	
	– Are there further **scenarios** for clinical paediatric development of medicines for treating HGG in children? – Please **list the opportunities for extrapolating** efficacy to some or all subsets of the paediatric population? (e.g., across ages or across biological characteristics) – How, and from which subsets could efficacy be extrapolated to **very young children**? (i.e., birth to less than 3 to 5 years; e.g., from patients at recurrence?) – What are the non-clinical and / or clinical result data that indicate which of the different scenarios should be used as an appropriate paediatric development strategy?	Further scenarios: Opportunities for extrapolation: Extrapolation to very young children: Non-clinical / clinical data needed for decision-making on paediatric strategy:
Study design	Several questions pertain to clinical trials in paediatric populations.	
	– Can the following subsets be studied together (i.e., same study, same endpoints)? Please explain, if possible based on data. o All age subsets? o Grade III vs. grade IV? o Macroscopically resected vs. not? o DIPG and / or non-resectable diffuse HGG (e.g., diencephalic / thalamic)? – What are the consequences for the inclusion criteria and for the stratification criteria?	All age subsets? Grade III vs. grade IV? Macroscopically resected vs. not? DIPG and / or non-resectable diffuse HGG (e.g., diencephalic / thalamic)? Which subentities can be studied together in a one study? Factors to be used for stratification of treatment allocation (randomisation):

		Factors to be used for stratified analyses (without allocation stratification):
	– Which if any factors might make PK / PD studies difficult in paediatric patients with CNS tumours? – How could the question be addressed, what is the impact and relevance of assessing CSF pharmacokinetics and / or pharmacodynamics?	PK / PD studies in children: CSF PK / PD studies in children:
	– Which **innovations** should be considered for conduction studies with children with HGG? E.g., innovative designs, innovative assessments	Innovations to be considered:
	Necessity of specific study designs: Control arms and choice of comparator, active or placebo, in paediatric HGG trials: There seem to be divergent views on the acceptability, limited experience, and very limited methodology-focused discussions.	
	– What is the medical practice for treatment of children with HGG when newly-diagnosed? (I.e., surgical strategies by location, radiation therapy options, concomitant and subsequent medicines) – What is the medical practice for treatment of children with HGG at progression / relapse?	Medical practice newly-diagnosed HGG in children: Medical practice relapsed / progressive HGG in children:
	– What are experiences and data in respect of controlled studies in HGG?	Experiences and methodological data on controlled designs and on choice of comparator:
	– Are there scientific reasons to exclude controlled studies in children with HGG, when newly-diagnosed and at relapse? If no, what would be actual scientific reasons for excluding this?	Scientific reasons for excluding controlled studies in a certain therapeutic setting:
Endpoints	**Endpoints for response** based on radiological criteria have recently published by the RANO group, as a refinement of the initial Macdonald criteria.	
	– What is the experience and the evidence in paediatric neuro-oncology for radiological response assessment? – What are differences in radiological response with respect to effects of	Data and / or publications addressing the question of the importance of evaluating radiological response in children with HGG:

	cytostatics or targeted agents in children with HGG? – What should be the details for radiological assessment, e.g., time points? – Are there any hindrances to implement blinded response assessment? – Is there a need or place for neuro-imaging methods beyond MRI, e.g. PET/SPECT in medicine development?	What is your experience using any radiological response criteria in children with HGG? Please expand: Differences between cytostatics and cytotoxics: Details for radiological assessments: Any hindrances to blinding the assessor? Need and / or usefulness of further neuro-imaging methods:
	– Is it reasonable to use the recently published RANO criteria for children? – If not, please explain why not? – If yes, which are the special considerations or caveats?	RANO criteria for children - yes or no: If no, why not? If yes, considerations or caveats?
	– How can the issues of pseudo-progression and pseudo-regression be accounted for in clinical trials in the paediatric population?	How to address?
	– What is the clinical value of radiological response and radiological PFS based on **conventional (Macdonald) criteria** for HGG response?	Value of conventional PFS?
	– How could any tumour rebound after cessation of a targeted therapy be studied?	How study rebound?
	– How should we take into account that targeted medicines may have a different pattern of recurrence i.e. within radiation area, marginal or remote metastatic relapses/ progressions?	How take account of different pattern of recurrence / progression? Clinical meaning of PFS different by medicine? Yes / no:

	– Has PFS a different clinical meaning for different types of medicines? In either case, please explain, referring to the applicable neuro-imaging method(s).	Please explain:
	– How can neuro-cognitive **functioning** and health-related **quality of life** be integrated as endpoints into paediatric studies?	How to integrate?
	For all oncology trials, including paediatric trials, overall survival data has to be collected, analysed and submitted. – Which further endpoints should be documented in paediatric HGG trials?	Further endpoints:
Priorities of medicines	Which characteristics (pharmacological, biological targets & clinical experience) would **prioritise** an anticancer medicine for study in children with HGG?	Desirable characteristics:
Timing of, and decision-making on initiating paediatric studies	There are uncertainties to which extent studies in adults can inform studies in children, and to which extent studies in HGG at relapse inform studies in newly-diagnosed patients (whether in children or adults). There seem to be situations where a medicine or a combination of medicines failed to show benefit in children with HGG at relapse, with the conclusion that this should now be studied in children newly-diagnosed with HGG. However the rationale for seeing these as different settings or not seems unclear.	
	– Can separate paediatric trials in newly diagnosed patients and in patients at relapse or progression be **started** at the same time, or do they have to follow a sequence? – Could a paediatric trial in relapsed patients **inform** the trial with newly diagnosed patients, or vice versa? – Which data support either approach? On which criteria should the initiation of paediatric studies relative to studies in adults be based? – What is the role of non-clinical efficacy and / or toxicity testing in this decision making?	Paediatric studies at the same time in patients with newly-diagnosed and relapsed HGG? Yes / no: Please explain the needed sequence: In which way would a trial in paediatric patients at relapse inform a trial in those with newly-diagnosed disease, if any: What data in adults is needed to start paediatric studies? What other data should be required to start paediatric studies?

		Role of non-clinical testing:
Existing data	There seem to be few large and / or developing databases documenting the course of children with HGG, aiming to comprehensively register such patients, e.g., in the health care setting of a given region or country. Such databases could serve several purposes, including designing studies and certain analyses.	
	– Which **historical data** are available (data quality, number of items and details and patients)?	Availability of data:
	– Are there plans to extend registries to cover the concerned paediatric population?	Plans:
	– In your view, how could such historic data be used for interpreting results?	Use of historic data: