National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

ERC1671 for treating progressed or recurrent progressed or recurrent grade IV glioma (glioblastoma or gliosarcoma)

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	No comments were received on the appropriateness of the remit		
Wording	The Brain Tumour Charity	No alternative wording suggested	None
	The Association of British Neurologists	Yes	None
	ERC Belgium	Please replace the word "vaccine" by "immunotherapy"	Comment is not relevant to the remit. Actioned in Technology section
Timing Issues	The Brain Tumour Charity	Glioblastoma is the most common type of high grade primary brain tumour in adults. The prognoses for individuals diagnosed with glioblastoma is dismal, with 40% of adults with brain cancer surviving only for a year or more.	None

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		Additionally, progressions-free survival post recurrence/progression is just 10 weeks (1). The poor prognosis is attributed to a distinct lack of treatment options for glioblastoma patients. Therefore, this appraisal will be crucial in building the evidence base for the clinical efficacy and cost effectiveness of this treatment. If ERC1671 is demonstrated to be clinically efficacious and cost effective for treatment of recurrent or progressed glioblastoma, it has the potential of becoming a crucially needed new treatment option. This would have serious implications on the current NICE guidelines to treat progressed or recurrent glioblastoma and has the potential to result in the development of new guidance. (1) Gallego O, Nonsurgical treatment of recurrent glioblastoma. Curr Oncol. 2015 Aug ; 22(4): e273–e281	
	The Association of British Neurologists	There is an urgency given the need to improve outcomes for GBM	None
Additional comments on the draft remit	The Brain Tumour Charity	None	None

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	The Brain Tumour Charity	Overall, the background information provides a comprehensive overview of the current standard of treatment for patients with recurrent or progressed glioblastoma in the NHS. However, it is also worth noting that the drug 5-ALA (5-Amino-Levulinic Acid) also known as the “pink drink” has shown promise in improving tumour resection and progression free survival for both newly diagnosed and recurrent/progressed high grade tumours (2,3,4). 5-ALA is taken orally by patients with high grade tumours, including glioblastoma, several hours before surgery. During surgery, the surgical team use blue light to identify cancerous cells which glow pink as a result of 5-ALA conversion to protoporphyrinogen IX in the tumour cells. This allows the identification of malignant cells at the tumour margin, resulting in the resection of more cancerous tissue. 5-ALA is part of NICE guidance on managing primary brain tumours and brain metastases in adults. This surgical aid has been rolled out across England and Wales, and is already available in Scotland and Northern Ireland. Therefore, we recommend the inclusion of this surgical aid within the draft scope. Furthermore, the categorisation and description of glioblastoma should be reviewed by NICE following an update by the World Health Organisation (WHO) on the classification of Tumour of the Central Nervous System (5). The updated WHO classifications expand upon the genetic subtypes of glioblastoma and their accompanying genetic profile, especially the TERT promoter mutations. These updates reflect an improved knowledge of the	We have decided not to incorporate the suggested details about the use of 5-Amino-levulinic acid because this is not essential information for describing the current pathway of care and because it is one of several recommendations on techniques for resection for glioma in the NICE guideline, so it would not be appropriate to prioritise this advice over the other guidance. The background section has been edited to clarify that gliomas are categorised according to the World Health Organisation criteria 2016

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		biological characteristics of the tumour type and how they influence an individual's response to treatment. (2) Pichlmeier U, Bink A, Schackert G, Stummer W. Resection and survival in glioblastoma multiforme: An RTOG recursive partitioning analysis of ALA study patients. Neuro-Oncol. 2008 Dec;10(6):1025–34. (3) Stummer W, Tonn J-C, Mehdorn HM, Nestler U, Franz K, Goetz C, et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article. J Neurosurg. 2011 Mar; 114(3):613–23. (4) Hadjipanayis CG, Widhalm G, and Stummer W, What is the Surgical Benefit of Utilizing 5-ALA for Fluorescence-Guided Surgery of Malignant Gliomas? Neurosurgery. 2015 Nov; 77(5): 663–673. (5) Louis D.N, Perry A, Reifenberger G, von Deimling, A, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Feb; 131(6):803-820.	
	The Association of British Neurologists	**"Grade 1 or 2 tumours are considered 'low-grade' and usually classed as benign or non-cancerous, although they may transform into malignant tumours.** We would recommend changing this statement as grade II tumours are no longer considered "benign" as they will ultimately transform into higher grade malignant tumours.	The background text had been edited in line with the comment and to clarify that gliomas are categorised according to the World Health Organisation criteria 2016

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		"Gliomas are graded according to their likely growth rate, from grade 1 (slowest growing) to grade 4 (fastest growing). The types of glioma are further identified by the cells they develop from (astrocytoma, ependymoma and oligodendroglioma) and increasingly, by molecular genetics such as isocitrate dehydrogenase (IDH) mutation status and 1p/19q codeletions.". Since the publication of the WHO classification of brain tumours 2016, the grouping of grade I-II and III-IV is becoming more outdated and the importance of molecular genetics has been recognised. The name of tumours can change depending on the molecular genetics and therefore the name of the tumour is no longer purely dependent dependant on the name of the cell from which they are derived. The molecular genetics of the tumours now strongly impacts the type of glioma diagnosed.	
The technology/ intervention	The Brain Tumour Charity	Yes, the description of the technology is accurate.	None
	The Association of British Neurologists	**"It has been studied in a clinical trial in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), cyclophosphamide and bevacizumab in adults with recurrent glioblastoma who have not previously received treatment with bevacizumab.** This is not factually correct. It is being studied. The results are not known and this scoping exercise is too early. It would be better conducted after this study has been published though the evidence is still likely to be insufficient due to the comparator used in this trial.	The text has been edited to say 'It is being studied…'
	ERC Belgium	- The EU (EMA approuved) name is SITOIGANAP - Replace the word "Vaccine" by "immunotherapy"	The text has been edited in line with the comments

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Population	The Brain Tumour Charity	Research into the molecular subtypes and genes which play a role in glioblastoma development is starting to provide some information about who may respond better to certain treatments. Many studies have been done to identify biomarkers that can be used to predict survival outcomes. For example, mutations to the IDH-1 and TERT gene are often linked with longer-term overall survival rates in patients with high grade glioma. (6) MGMT methylation tests can be useful in glioblastoma for predicting how effective temozolomide based treatment is likely to be; however, MGMT status is currently not taken into account when deciding treatment regimens, in part due to a lack of treatment options. Further understanding of molecular markers such as these will benefit drug target identification and treatment for glioblastoma patients. (6) The Brain Tumour Charity. Biomarkers (Information Factsheet) [Internet]. Available from: https://wwww.thebraintumourcharity.org/media/filer_public/a1/1c/a11cfb68-e57c-42ab-baf8-c09be974466c/biomarkers_v_20a.pdf	Discussion at the scoping workshop confirmed that tests for biomarkers and MGMT methylation tests do not, in isolation, inform treatment decisions in the population of interest for this appraisal in current NHS practice. For this reason it does not seem necessary to edit the text of the population section to reflect any details about these tests.
	The Association of British Neurologists	Population should be grouped accordingly to molecular markers, e.g. IDH status, MGMT status	Discussion at the scoping workshop confirmed that tests for biomarkers and MGMT methylation tests do not, in isolation, inform treatment decisions in

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			the population of interest for this appraisal in current NHS practice. For this reason it does not seem necessary to edit the text of the population section to reflect any details about these tests.
	ERC Belgium	Please modify the section population by: “Adults with progressive or recurrent grade IV glioma (glioblastoma and gliosarcoma), who failed radiation and temozolomide”.	The text has been edited to say ‘grade IV glioma (glioblastoma and gliosarcoma)’ in line with the comment. The suggested wording ‘who have failed treatment’ has not been incorporated because it does not align with the NICE style guide, (however, the meaning is considered to be captured by the current text which states that the population of interest has disease that has ‘progressed or recurred following treatment’)

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Comparators	The Brain Tumour Charity	The comparators listed within the draft scope are currently used in the NHS.	None
Outcomes	The Brain Tumour Charity	We believe that the outcomes listed by NICE for this Health Technology Appraisal are appropriate, as they correlate with the endpoints sought in current ERC1671 trials, namely progression-free survival. Note that in the comparator arm in the ongoing phase II clinical trial 'ERC1671/GM-CSF/Cyclophosphamide for the Treatment of Glioblastoma Multiforme' patients are treated with ERC1671 in combination with GM-CSF and cyclophosphamide plus bevacizumab. The drug bevacizumab is not licensed in the UK for the treatment of brain tumours.	None
	The Association of British Neurologists	Yes	None
Economic analysis	The Brain Tumour Charity	The economic analysis provided within draft scope does not reference the impact of a GBM on carers. Thus, it is vital that this impact is taken into consideration when estimating the clinical and cost effectiveness this particular technology.	The following text has been added to the economic analysis section of the scope 'The reference case stipulates that all direct health effects, whether for patients or, when relevant, carers should be considered'.
Equality and Diversity	The Brain Tumour Charity	Recruitment for clinical trials for ERC1671 has been restricted to adults with a Karnofsky performance status of ≥ 70 (at assessment) which is defined as "cares for self; unable to carry on normal activity or to do active work".	The scope population is not limited by Karnofsky status, so this is not

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		However, due to the location of the tumour, individuals with a glioblastoma may rapidly deteriorate below a performance status of 70, thereby excluding them participating in the trial. As mentioned in the scope document, treatment decisions take into account Karnofsky performance status; therefore, it is important that any assessment of clinical and cost effectiveness consider the impact on all patients.	considered to be an equalities issue at this point. The generalisability of the trial population to the scope population will be considered by the appraisal committee. The committee will be aware of the need to ensure equality of access for treatments for people with disabilities
Other considerations	The Brain Tumour Charity	None	None
Innovation	The Brain Tumour Charity	Given the dismal survival rates for this tumour type, there is an urgent need to develop effective novel therapies. Therapies are increasingly limited with regards to recurrent and progressed glioblastoma. ERC1671 addresses this unmet need by employing new and innovative practise to provide treatment to a population where there are currently limited therapeutic choices. The first use of ERC1671 showed it to be safe, potentially effective and generally well tolerated (7). The most recent published update from the on-going Phase II clinical trial using ERC1671 in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) (Leukine® or sargramostim), reported median overall survival (OS) of patients treated with	The committee will consider the innovative nature of ERC1671 throughout the course of the appraisal

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		ERC1671 plus bevacizumab as 12 months. In the placebo plus bevacizumab group, median OS was reported to be 7.5 months (8). (7) Schijns V.E.J.C, et al, First clinical results of a personalized immunotherapeutic vaccine against recurrent, incompletely resected, treatment-resistant glioblastoma multiforme (GBM) tumors, based on combined allo- and auto-immune tumor reactivity. Vaccine. 2015 May: 33(23): 2690-2696 (8) Bota DA, et al, Phase II study of ERC1671 plus bevacizumab versus bevacizumab plus placebo in recurrent glioblastoma: interim results and correlations with CD4+ T-lymphocyte counts. CNS Oncol. 2018 Jul; 7(3): CNS22.	
	The Association of British Neurologists	It is not possible to say this as yet there is no evidence that this is an effective/step-change treatment. This scoping exercise should be delayed.	The timing of the scoping exercise has been aligned to information provided by the company about the anticipated regulatory timeline. For this reason, it would not be appropriate to delay the scope at present. If the regulatory timelines change due to the timelines for evidence generation (or any other reason) then the

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			scoping timelines will be adjusted accordingly
Questions for consultation	The Brain Tumour Charity	Given the patient population designated for the treatment, the most appropriate place for ERC1671 within the existing NICE pathway would be in the "recurrent Grade IV glioma" section, which currently outlines the standard of care for recurrent glioblastoma patients (9). If proven to improve overall survival in clinical trials, ERC1671 could rapidly become the standard of care for glioblastoma patients, which would have implications for existing NICE guidance on Temozolomide, procarbazine, lomustine and vincristine (PCV), and new guidance being developed on the pathway for Primary Brain Tumours and Cerebral Metastases. (9) National Institute for Health and Care Excellence. Brain Cancers - an integrated view of everything NICE has said [Internet]. Available from: https://pathways.nice.org.uk/pathways/brain-cancers#content=view-node%3Anodes-newly-diagnosed-high-grade-glioma	None
	NCRI-ACP-RCP-RCR	Our experts believe that it would have to be delivered as per the trial; however cyclophosphamide and bevacizumab are not currently used for recurrent GBM treatment. **Have all relevant comparators for ERC1671 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for glioblastoma in patients with disease that has progressed or recurred following treatment with radiotherapy and temozolomide? Should further radiotherapy or surgery be considered relevant comparators for ERC1671?**	The company confirmed at the scoping workshop that they are still intending to pursue a monotherapy licence for ERC1671 so no changes have been made to the intervention section of the scope. Carmustine implants [gliadel wafers] and

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		There is no agreed standard treatment for recurrent GBM. Surgery, radiotherapy, gliadel wafers and second line chemotherapy (CCNU) are all used in in various combinations depending on time to recurrence, patient performance status, 'resectability' of recurrent tumour. **How should best supportive care be defined?** **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom ERC1671 is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Not defined in trial **Where do you consider ERC1671 will fit into the existing NICE pathway, Brain cancer: glioma?** This is a phase 2 randomised trials. Results need confirming in a larger trial of effectiveness and in comparison to UK standard of care for recurrent GBM (which currently does not include bevacizumab or cyclophosphamide).	radiotherapy have been added to the list of comparators No changes have been made to the outcomes in the scope in line with discussions at the scoping workshop No subgroups have been added to the scope in line with discussions at the scoping workshop
	ERC Belgium	**Would ERC1671 be delivered alone or in combination with GM-CSF, cyclophosphamide and bevacizumab as in the clinical trial?** ERC Belgium will request an authorization for ERC1671 only. Cyclophosphamide and bevacizumab are available on the market. GM-CSF improves ERC1671 efficiency but is not mandatory.	The company confirmed at the scoping workshop that they are still intending to pursue a monotherapy licence for ERC1671 so no changes have been

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		Have all relevant comparators for ERC1671 been included in the scope? Which treatments are considered to be established clinical practice in the NHS for glioblastoma in patients with disease that has progressed or recurred following treatment with radiotherapy and temozolomide? Should further radiotherapy or surgery be considered relevant comparators for ERC1671? How should best supportive care be defined? Despite all advancements in glioblastoma (GBM) care, the vast majority of patients relapse. At the time of recurrence after the first-line standard of care including surgery, radio- and chemo-therapy, further treatment options are limited [1, 2]. Repeat surgery is often considered as supportive care, but tumor cells infiltrating the brain and spinal cord many times prevent a significant surgical resection. At the same time, invasive tumor cells appear to be more resistant to cytotoxic drug therapy and to have a higher proliferative potential. In general, the treatment of recurrent GBM by repeat surgery, re-irradiation, and further chemotherapy may increase the symptom-free interval and moderately extend overall survival, primarily in patients with good performance status [3, 4]. In the ESMO guideline, Stupp et al. specifies relapsing GBM best treatments are investigational clinical protocols [5]. The only FDA targeted treatment approved for recurrent GBM patients is the angiogenesis inhibitor bevacizumab, a humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF) [6]. When used alone or in combination with a cytotoxic agent, it improves imaging parameters for most patients, but duration of benefits is transient and short lived. In a phase II study, Taal et al. demonstrated comparable survival curves between BEV and Lomustine [7]. However, their impact on prolonging overall survival (OS) appears limited, especially when used outside the clinical trial settings [8-10]. ERC1671 is a cell-based immunotherapy aiming to induce a strong immune alloreaction in target patient. The phase II clinical study of ERC1671 compares the investigational treatment after debulking surgery to placebo in	made to the intervention section of the scope. No changes have been made to the outcomes in the scope in line with discussions at the scoping workshop No subgroups have been added to the scope in line with discussions at the scoping workshop It was clarified at the scoping workshop that the trial population only includes patients with a Karnofsy performance status of at least 70 and this is the population that are likely to receive ERC1671 in practice (as opposed to those with a Karnofsy performance status of at least 60 as indicated in this comment). It was also noted at the workshop that all the patients included in the clinical trial had CD4

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		patients receiving the best FDA standard of care, bevacizumab, comparable in term of efficiency to the NICE recommended chemotherapy lomustine, without impacting the immune system as observed with chemotherapeutic agents. **Are the outcomes listed appropriate?** Yes (OS, PFS, RR, AE, QoL) **Are there any subgroups of people in whom ERC1671 is expected to be more clinically effective and cost effective or other groups that should be examined separately?** In the clinical phase II trial, the immune system is evaluated. CD3+/CD4+ helper T lymphocytes count is monitored. The maximum count and the end of treatment count is highly correlated with overall survival in patients treated with ERC1671 but not in the placebo group. ERC1671 is partially manufactured from patients' tumor, implicating partial tumor surgery feasibility. **Where do you consider ERC1671 will fit into the existing NICE pathway, Brain cancer: glioma?** In the NICE "Brain cancer: glioma" flowchart, ERC1671 should be considered as a treatment option for recurrent grade III and IV glioma. The NICE elements to take in account fitting with ERC1671 treatment should be considered as following: • Karnofsky performance status: better response if >60 • Person preference	count > 450/mcL and that fitness for repeat (i.e. post progression/recurrence) surgery to collect tumour tissue would determine whether patients were able to receive ERC1671 in practice. However, it was not considered necessary to specify these characteristics in the definition of the scope population The committee will consider the innovative nature of ERC1671 throughout the course of the appraisal

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		• Time from last treatment: Immunosuppressive drugs decrease ERC1671 efficacy and should be not used during ERC1671 treatment. Immune cells count should be monitored prior starting treatment. • Tumor molecular markers: NA • Last treatment received: Surgery is included in the ERC1671 process (collection of tumor tissue). **NICE equality commitment.** No concern - ERC is compliant **Do you consider ERC1671 to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** There is a significant unmet clinical need for the therapy of malignant glioma, where patients are faced with dismal prognosis. Concurrent temozolomide with radiotherapy followed by adjuvant systemic temozolomide has produced a median survival of about 15 months, and this regimen is now the standard of care for GBM [5, 11, 12]. Despite these intense therapeutic efforts, the tumor returns in the vast majority of patients. When relapsing, according the size of the tumor, KPS, tumor localization, statistics suggest an imminent death. Based on the above, it is clear that regardless of current treatment regimens, glioma patients continue to have dismal prognosis and novel treatments are urgently needed. ERC1671 is an innovative advance medicinal product (ATMP – Ref EMA: EMA/CAT/324279/2012) using patient immune system to destroy residual glioma cells.	

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		Clinical experience with ERC1671 is based on compassionate program and phase II clinical trial: There are a total of 10 patients with a KPS above 60 that were treated with ERC1671 in a terminal stages compassionate program. No significant side effects potentially attributable to the therapy were witnessed. The expected OS for those GBM patients is 5-8 months, and their 6-month progression-free survival (PFS) is around 30% [13]. In comparison, patients treated with ERC1671 shows the following: 6-month OS is 100%, 12-month OS is 40%, and median OS is 46 weeks (10.5 months). Historic controls (data from [14] have 6-month OS of 33% and median OS of 23 weeks (5.3 months). Thus, this dataset reveals a striking improvement of OS over current clinical practice (log rank test, p<0.0001), with minimal toxicity. In the placebo-controlled phase II trial NCT01903330, current interim data of ERC1671 treated group shows a median OS of 328 days, with one patient surviving >2 years, vs placebo median OS of 197 days. Placebo patients crossing to the treatment have a median OS of 391 days. Toxicity analysis showed an equal distribution of adverse events (AE) between the vaccine and placebo groups, with no grade 4 or 5 toxicities 5. **Do you consider that the use of ERC1671 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits**. No	

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		To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No Ref : 1. Gallego, O., Nonsurgical treatment of recurrent glioblastoma. Curr Oncol, 2015. 22(4): p. e273-81. 2. Weller, M., et al., Standards of care for treatment of recurrent glioblastoma--are we there yet? Neuro Oncol, 2013. 15(1): p. 4-27. 3. Montemurro, N., et al., Second surgery for recurrent glioblastoma: A concise overview of the current literature. Clin Neurol Neurosurg, 2016. 142: p. 60-64. 4. Greco, W.R., G. Bravo, and J.C. Parsons, The search for synergy: a critical review from a response surface perspective. Pharmacol Rev, 1995. 47(2): p. 331-85. 5. Stupp, R., et al., High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol, 2014. 21 Suppl 5: p. v190-3. 6. Diaz, R.J., et al., The role of bevacizumab in the treatment of glioblastoma. J Neurooncol, 2017. 133(3): p. 455-467. 7. Taal, W., et al., Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol, 2014. 15(9): p. 943-53.	

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		8. Abrams, D.A., et al., Timing of surgery and bevacizumab therapy in neurosurgical patients with recurrent high grade glioma. J Clin Neurosci, 2015. 22(1): p. 35-9. 9. de Lemos, M.L., et al., Clinical effectiveness of bevacizumab in patients with recurrent brain tumours: A population-based evaluation. J Oncol Pharm Pract, 2018. 24(1): p. 33-36. 10. Wang, Y., et al., The Role of a Single Angiogenesis Inhibitor in the Treatment of Recurrent Glioblastoma Multiforme: A Meta-Analysis and Systematic Review. PLoS One, 2016. 11(3): p. e0152170. 11. Stupp, R., et al., Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol, 2009. 10(5): p. 459-66. 12. Stupp, R., et al., Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med, 2005. 352(10): p. 987-96. 13. Santoni, M., et al., Protracted low doses of temozolomide for the treatment of patients with recurrent glioblastoma: A phase II study. Oncol Lett, 2012. 4(4): p. 799-801. 14. Barker, F.G., 2nd, et al., Survival and functional status after resection of recurrent glioblastoma multiforme. Neurosurgery, 1998. 42(4): p. 709-20; discussion 720-3.	
Additional comments on the draft scope	The Brain Tumour Charity	None	None
	The Association of British Neurologists	It is too early to consider this drug for the treatment of glioma – there is insufficient scientific data for its use in this population	The timing of the scoping exercise has been aligned to

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			information provided by the company about the anticipated regulatory timeline. For this reason, it would not be appropriate to delay the scope at present. If the regulatory timelines change due to the timelines for evidence generation (or any other reason) then the scoping timelines will be adjusted accordingly

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None