NHS England

Evidence review: Temozolomide as adjuvant treatment for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy

NHS England

Evidence review: Temozolomide as adjuvant treatment for people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy

First published: Month Year

Updated: Not applicable

Prepared by: The NICE Medicines and Technologies Programme on behalf of NHS England Specialised Commissioning

The content of this evidence review was up-to-date in December 2018. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Key points

Regulatory status:

Temozolomide is licensed for:

- adults with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy.
- adults, young people and children (aged 3 years and over) with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Temozolomide is not licensed for the treatment of people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using temozolomide is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Overview

This review considers adjuvant temozolomide (following surgery and radiotherapy) in people with newly-diagnosed grade III anaplastic astrocytoma without evidence of 1p/19q codeletion.

Anaplastic astrocytomas are high-grade brain tumours that develop from astrocytes, which are star-shaped cells that surround and protect nerve cells in the central nervous system. 1p/19q codeletion refers to deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q). In general, people without 1p/19q codeletion do not respond well to chemotherapy and have a worse prognosis.

Temozolomide is a type of chemotherapy. It is an alkylating agent derived from dacarbazine. Temozolomide has high bioavailability and crosses the blood‑brain barrier where it is spontaneously hydrolysed to its active form. It is toxic to cancer cells due to inhibition of tumour cell DNA replication. Temozolomide is taken orally.

This evidence review includes the pre-planned interim analysis of an ongoing open-label, phase III, multi-centre, randomised controlled trial (RCT). The study includes 745 adults with newly-diagnosed anaplastic glioma without 1p/19q codeletion (anaplastic astrocytoma).

The study included 4 treatment groups:

1. Radiotherapy with adjuvant temozolomide (n=185)
2. Radiotherapy plus concurrent temozolomide with adjuvant temozolomide (n=188)
3. Radiotherapy plus concurrent temozolomide (n=185)
4. Radiotherapy alone (n=187)

Concurrent therapy is treatment given at the same time as other therapies. Concurrent temozolomide was given at the same time as radiotherapy. Concurrent temozolomide was given daily, for a maximum of 7 weeks.

Adjuvant therapy is additional cancer treatment given after the primary treatment to lower the risk of the cancer coming back. Adjuvant temozolomide was started 4 weeks after radiotherapy was completed. Adjuvant temozolomide was given for a maximum of 12 four-week cycles.

This study found that people treated with adjuvant temozolomide had better overall survival and progression-free survival compared with people not treated with adjuvant temozolomide. Grade 3 and 4 toxicities (severe, life-threatening or disabling adverse events) were common, occurring in around 1 in 10 people treated with temozolomide.

The interim results found the hazard ratio (HR) for overall survival for adjuvant temozolomide was 0.65 (99.145% confidence interval [CI] 0.45 to 0.93, p=0.0014). Overall survival at 5 years was 55.9% for people treated with adjuvant temozolomide, compared with 44.1% for people not treated with adjuvant temozolomide.

Median progression-free survival was 42.8 months for people treated with adjuvant temozolomide, compared with 19.0 months for people not treated with adjuvant temozolomide. Progression-free survival at 5 years was 43.1% in people treated with adjuvant temozolomide, compared with 24.3% in people not treated with adjuvant temozolomide.

The impact of adjuvant temozolomide treatment on health-related quality of life and cognition are not reported in the interim analysis.

Over a median 27 month follow-up, 8–12% of people treated with temozolomide (n=549; including people treated with concurrent temozolomide) had grade 3 (severe) or grade 4 (life-threatening or disabling) toxicity. The most common toxicities were haematological, including thrombocytopenia, neutropenia and leukopenia. Non-haematological toxicities included infections, constitutional symptoms and gastrointestinal events. Increases in aminotransferase concentration, an indicator of possible liver damage, occurred in 5 participants (1%) receiving temozolomide. In total, 30 people (8%) discontinued treatment with adjuvant temozolomide because of toxicity, although further details of these discontinuations are not reported in the interim analysis.

These are interim results of an ongoing clinical trial, and as such follow-up is immature and the study underpowered. Adverse event reporting is incomplete; details on mild to moderate adverse events and reasons for treatment discontinuation are not provided.

Contents

1. Introduction

Background and current guidance

Gliomas are brain tumours that develop from glial cells, the cells that surround and protect nerve cells (neurones) in the central nervous system (CNS). There are 3 main types of glioma: astrocytoma, oligodendroglioma and ependymoma (Cancer Research UK: Glioma in adults).

Astrocytomas are the most common type of glioma. Astrocytomas develop from cells called astrocytes, which are star-shaped glial cells. Astrocytomas are classified by the World Health Organisation (WHO) grading system based on how fast the cells grow and the likelihood of them spreading to nearby tissue.

- Grade I and II astrocytomas are 'low-grade' tumours, meaning they are slow growing and unlikely to spread to other parts of the brain.
- Grade III and IV astrocytomas are 'high-grade' tumours, meaning they are fast growing and more likely to spread to other parts of the brain. They are also referred to as 'malignant' or 'cancerous' tumours.

The most common type of astrocytoma are grade IV astrocytomas, which are called glioblastoma. Grade III astrocytomas are called anaplastic astrocytomas and are less common.

Deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), referred to as 1p/19q codeletion. Codeletion of 1p/19q is associated with improved sensitivity to chemotherapy treatment and a better prognosis for patients. People without 1p/19q codeletion do not respond as well to chemotherapy and have a worse prognosis (van den Bent et al. 2006). The 2016 WHO classification of tumours of the central nervous system (CNS) classifies tumours based on their genetic and histological characteristics. Tumours with a mutation in the gene encoding isocitrate dehydrogenase (IDH) and a 1p/19q codeletion are classed as oligodendroglioma; tumours without 1p/19q codeletion are astrocytomas.

The NICE guideline on brain tumours (primary) and brain metastases in adults recommends adjuvant temozolomide (up to 12 cycles) after surgery and radiotherapy for people who have newly-diagnosed IDH-wildtype or mutated grade III glioma without 1p/19q codeletion (anaplastic astrocytoma) and a Karnofsky performance status of 70 or more.

Product overview

Mode of action

Temozolomide is an alkylating agent derived from dacarbazine. It has high bioavailability and crosses the blood‑brain barrier where it is spontaneously hydrolysed to its active form. It is toxic to cancer cells due to inhibition of tumour cell DNA replication (NICE technology appraisal: temozolomide for the treatment of recurrent malignant glioma).

The summary of product characteristics (SPC) for temozolomide states that temozolomide is a triazene, which undergoes rapid chemical conversion at physiologic pH to the active

monomethyl triazenoimidazole carboxamide (MTIC). The cytotoxicity of MTIC is thought to be due primarily to alkylation at the O6 position of guanine with additional alkylation also occurring at the N7 position. Cytotoxic lesions that develop subsequently are thought to involve aberrant repair of the methyl adduct.

Regulatory status

Temozolomide is licensed for:

- adults with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment.
- adults, young people and children (aged 3 years and over) with malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy.

Temozolomide is not licensed for the of treatment people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using temozolomide is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

Dosing information varies for the licensed indications of temozolomide and can be found in the SPC for temozolomide.

Dosing information for temozolomide as adjuvant treatment for people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy (an off-label indication) is discussed in the summary of included studies section of this evidence summary.

2. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the search terms section for more information). The research questions for this evidence review are:

1. In patients with newly-diagnosed grade III anaplastic astrocytoma without evidence of 1p/19q codeletion what is the clinical effectiveness of 12 months of adjuvant temozolomide following surgery and radiotherapy compared to surgery and radiotherapy alone?
2. In patients with newly-diagnosed grade III anaplastic astrocytoma without evidence of 1p/19q codeletion what is the safety of 12 months of adjuvant temozolomide following surgery and radiotherapy compared to surgery and radiotherapy alone?
3. In patients with newly-diagnosed grade III anaplastic astrocytoma without evidence of 1p/19q codeletion what is the cost-effectiveness of using 12 months adjuvant temozolomide following surgery and radiotherapy compared to surgery and radiotherapy alone?

The searches for evidence to support the use of temozolomide as adjuvant treatment for people with newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

3. Summary of included study

This evidence review includes 1 phase III, randomised, open-label study with a 2 x 2 factorial design (van den Bent et al. 2017 [interim results from the CATNON trial]).

A summary of the included studies is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
van den Bent et al. 2017 Interim results from the CATNON trial[1] Phase 3, randomised, open-label study with a 2 x 2 factorial design. Conducted across 137 centres in Europe, North America and Australia.	745 adults (median age 42.2 years [range 18.3 to 82.3], 57% male) with newly-diagnosed anaplastic glioma[2] without 1p/19q codeletion. Participants were required to have WHO performance status scores of 0–2, adequate haematological, renal and liver function, and be taking stable or decreasing doses of corticosteroids. Across the whole study population, 29% were taking corticosteroids at study entry and 12% had previous surgery for a low-grade tumours. Regarding surgery type before radiotherapy, 20% of participants had a biopsy, 47% partial tumour removal and 31% total tumour removal.	**Intervention** Radiotherapy with adjuvant temozolomide (n=185) Radiotherapy plus concurrent temozolomide with adjuvant temozolomide (n=188) **Comparison** Radiotherapy alone (n=187) Radiotherapy plus concurrent temozolomide (n=185) The radiotherapy dose was 59.4 Gy, given in 33 fractions of 1.8 Gy. Adjuvant temozolomide was started 4 weeks after completion of radiotherapy, for a maximum of 12 treatment cycles. A treatment cycle consists of 28 days: 5 treatment days followed by a 23 day treatment interruption. For the first cycle, participants received temozolomide 150 mg/m^2. If no or minor toxicity was seen the dose was increased to 200 mg/m^2 for the subsequent cycles.	Overall survival

Abbreviations: Gy, gray

[1] This is a pre-planned interim analysis. Interim analysis for efficacy was planned when 219 deaths had occurred. At the time of the interim analysis, 99.6% of the required participants (745/748) had been recruited.

[2] Anaplastic glioma includes anaplastic astrocytoma, anaplastic oligodendroglioma and anaplastic oligoastrocytoma.

Since this trial was designed, the WHO classification of tumours of the CNS has been updated. In the new 2016 classification, all gliomas with 1p/19q codeletion are classified as oligodendroglioma and all without 1p/19q codeletion as astrocytoma.

The diagnosis of oligoastrocytoma is strongly discouraged in the 2016 WHO classification, since nearly all tumours with histological features suggesting both an astrocytic and an oligodendroglial component can be classified as either astrocytoma or oligodendroglioma using genetic testing.

Details of the excluded studies are listed in the section on evidence selection.

4. Results

An overview of the results for clinical effectiveness, safety and tolerability can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

Clinical effectiveness

This sections considers the following research question: In people with newly diagnosed grade 3 anaplastic astrocytoma without evidence of 1p/19q codeletion, what is the clinical effectiveness of 12 months of adjuvant temozolomide (following surgery and radiotherapy) compared to surgery and radiotherapy alone?

Overall survival

The interim results from an ongoing open-label RCT reported by van den Bent et al. (2017) involving 745 adults with anaplastic glioma without 1p/19q codeletion, found that people treated with up to 12 cycles of adjuvant temozolomide (following surgery and radiotherapy; treatment cycle consists of 5 treatment days followed by a 23 day treatment interruption) had significantly better overall survival compared with people not treated with adjuvant temozolomide (primary efficacy outcome).

The hazard ratio (HR) for overall survival for adjuvant temozolomide was 0.65 (99.145% confidence interval [CI] 0.45 to 0.93, p=0.0014).

Overall survival at 5 years was 55.9% (95% CI 47.2 to 63.8) for people treated with adjuvant temozolomide, compared with 44.1% (95% CI 36.3 to 51.6) for people not treated with adjuvant temozolomide.

Median overall survival could not be calculated because the minimum number of deaths had not occurred in the adjuvant temozolomide groups at the time of the interim analysis.

Sub-group analysis of overall survival:

The investigators assessed overall survival in people treated with 12 cycles of adjuvant temozolomide, adjusted for the following baseline characteristics: age, WHO performance status, 1p loss of heterozygosity, presence of oligodendroglial elements and MGMT [O6-methylguanine-DNA methyltransferase] promotor methylation before randomisation.

The investigators found that people aged over 50 years had significantly worse overall survival compared with people aged 50 years and under (HR 4.04, 99.145% CI 2.78 to 5.87, p<0.0001). People found to have MGMT-promotor methylation before randomisation had significantly better overall survival compared with people without MGMT-promotor methylation (HR 0.49, 99.145% CI 0.26 to 0.93, p=0.0031).

WHO performance score, 1p loss of heterozygosity and presence of oligodendroglial elements did not significantly affect overall survival in people treated with adjuvant temozolomide (all p>0.01).

It should be noted that such sub-group analyses of interim trial results are likely to be underpowered and should be interpreted with caution. The final results of the study are needed to determine which subgroups of people may benefit most from treatment with adjuvant temozolomide.

Progression-free survival

The RCT by van den Bent et al. (2017) found that people treated with adjuvant temozolomide had significantly better progression-free survival compared with people not treated with adjuvant temozolomide (secondary efficacy outcome).

Median progression-free survival was 42.8 months (95% CI 28.6 to 60.6) for people treated with adjuvant temozolomide, compared with 19.0 months (95% CI 14.4 to 24.6) for people not treated with adjuvant temozolomide.

Progression-free survival at 5 years was 43.1% (95% CI 35.0 to 50.9) in people treated with adjuvant temozolomide, compared with 24.3% (95% CI 17.7 to 31.6) in people not treated with adjuvant temozolomide.

Health-related quality of life

In the CATNON study, health-related quality of life was assessed using the EORTC QLQ-C30 and QLQ-BN20 questionnaires, however these results are not reported in the interim analysis by van den Bent et al. (2017).

Cognitive effects

In the CATNON study, cognition was assessed using the Mini-Mental State Examination questionnaire however these results are not reported in the interim analysis by van den Bent et al. (2017).

Safety and tolerability

This sections considers the following research question: In people with newly diagnosed grade 3 anaplastic astrocytoma without evidence of 1p/19q codeletion, what is the safety of

12 months of adjuvant temozolomide (following surgery and radiotherapy) compared to surgery and radiotherapy alone?

The interim results from an ongoing open-label RCT (van den Bent et al. 2017) reported that over a median 27 month follow-up, 8–12% of people treated with temozolomide (n=549; including people on concurrent therapy) had grade 3–4 toxicity. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Grade 3 toxicity refers to severe adverse events and grade 4 refers to life-threatening or disabling adverse events.

The majority of grade 3–4 toxicities were haematological in nature, with the most frequent events in the adjuvant temozolomide group (n=182) being thrombocytopenia (9.3%), neutropenia (4.4%), leukopenia (2.2%) and anaemia (1.1%). The most frequently reported non-haematological grade 3–4 toxicities in people treated with adjuvant temozolomide were infections (7.9%), constitutional symptoms (which were not defined in the paper, but normally include fever, weight-loss and fatigue; 6.8%) and gastrointestinal events (5.6%).

Grade 3–4 increases in aminotransferase concentration, an indicator of possible liver damage, occurred in 5 participants (1%) receiving temozolomide. In 2013, the MHRA issued a safety warning on the risk of hepatic injury, including fatal hepatic failure, with temozolomide.

In total, 30 people (8%) discontinued treatment with adjuvant temozolomide because of toxicity, although further details are not reported.

Across the 2 adjuvant temozolomide groups, 262 participants completed or stopped taking temozolomide before the interim analysis. Of these, 167 participants (64%) had at least 1 cycle of temozolomide delayed. The reasons for a delay were haematological adverse events (28%), non-haematological adverse events (6%), both haematological and non-haematological adverse events (3%) and reasons not related to treatment (47%).

The SPC for temozolomide reports the frequency of adverse events from clinical trials involving people with newly-diagnosed glioblastoma and recurrent or progressive malignant glioma. Very common (reported by 1 in 10 people or more) adverse events include:

- anorexia
- headache
- constipation, nausea and vomiting
- rash
- alopecia
- fatigue
- neutropenia, lymphopenia or thrombocytopenia.

Cost-effectiveness

This sections considers the following research question: In people with newly diagnosed grade 3 anaplastic astrocytoma without evidence of 1p/19q codeletion, what is the cost effectiveness of 12 months of adjuvant temozolomide (following surgery and radiotherapy) compared to surgery and radiotherapy alone?

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of adjuvant temozolomide in people with newly-diagnosed grade III anaplastic astrocytoma without evidence of 1p/19q codeletion. The study included in this evidence review did not include an outcome investigating cost-effectiveness.

5. Discussion

Evidence strengths and limitations

The CATNON study, interim results of which are reported by van den Bent et al. (2017), is the first RCT to assess temozolomide for the treatment of grade III anaplastic glioma without codeletion of 1p/19q.

The most important limitation of the evidence is that it is based on the interim results of an ongoing clinical trial. At the time of the interim analysis 30% of participants had died, and 46% had disease progression, meaning follow-up was still immature (median follow-up 27 months). Because of this, median overall survival could not be calculated, and the study was underpowered for all outcomes. The trial entry on clinicaltrials.gov states that the final data collection date for the primary outcome measure in the CATNON study is expected in January 2022 (NCT00626990).

The interim analysis only reports survival outcomes and adverse events. The CATNON study also investigated the impact of treatment on health-related quality of life and cognition, although these results are not reported in the interim analysis by van den Bent et al.

Adverse event reporting is incomplete, with only grade 3 (severe) and grade 4 (life-threatening or disabling) toxicities reported in the interim analysis. Details on grade 1 and 2 toxicities (mild and moderate) are not reported. The authors report that 30 people (8%) receiving adjuvant temozolomide discontinued treatment because of toxicity, but no further details are provided.

The study used an open-label design, meaning participants and investigators knew which treatments were being given; this may have introduced bias. However, it should be noted that the interim analysis only reports on survival and toxicity outcomes, and patient-reported outcomes (for example, quality of life) are not included. As stated in the Cochrane Handbook, a lack of blinding may not impact on objective, non-patient-reported outcomes, such as mortality.

The CANTON study employed a 2 x 2 factorial design, with 4 treatment groups-

- Two groups received adjuvant temozolomide:
    1. Radiotherapy with adjuvant temozolomide (n=185)
    2. Radiotherapy plus concurrent temozolomide with adjuvant temozolomide (n=188)
- Two groups did not receive adjuvant temozolomide:
    3. Radiotherapy alone (n=187)
    4. Radiotherapy and concurrent temozolomide (n=185)

Results are reported for people treated with adjuvant temozolomide compared with people not treated with adjuvant temozolomide. This combining of different trial arms means that any treatment effect of concurrent temozolomide cannot be assessed.

The study did not compare temozolomide to other adjuvant chemotherapy regimens.

The study included people with anaplastic glioma without 1p/19q codeletion. The CATNON study protocol states that this includes people with anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic astrocytoma. However, based on the 2016 WHO classification of tumours of the central nervous system (CNS), all tumours with 1p/19q codeletion are now classified as anaplastic astrocytomas, so the population described in this study is relevant to the review questions for this evidence review.

Other treatments

No other adjuvant treatments are generally considered at the same stage in the management pathway for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy.

6. Conclusion

Anaplastic astrocytomas without 1p/19q codeletion are high-grade brain tumours that generally do not respond well to chemotherapy treatment.

The interim results from an ongoing open-label RCT (the CATNON trial) suggest that people treated with adjuvant temozolomide have better overall survival and progression-free survival, compared with people not treated with adjuvant temozolomide. Sub-group analyses suggest that temozolomide may be more effective in people aged 50 years or under and in people with MGMT-promoter methylation. However, the final results of the study are needed to determine which subgroups of people may benefit most from treatment with adjuvant temozolomide.

The impact of adjuvant temozolomide treatment on health-related quality of life and cognition are not reported in the interim analysis of the CATNON trial.

Grade 3 and 4 adverse events (severe, life-threatening or disabling) were reported by in around 1 in 10 people treated with adjuvant temozolomide, the most common being haematological adverse events. In total, 8% of people treated with adjuvant temozolomide discontinued treatment because of toxicity, and some people in the study had to delay a cycle of temozolomide treatment because of adverse events. Hepatic injury, including fatal hepatic failure, is a safety concern with temozolomide, and 1% of people in the study had grade 3–4 increases in aminotransferase concentration. Details of grade 1 and 2 (mild and moderate) adverse events are not reported in the interim analysis.

7. Evidence summary table

Use of radiotherapy with adjuvant temozolomide vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: van den Bent et al. 2017 (interim results from the CATNON trial)							
P1- Phase 3, randomised, open-label study with a 2 × 2 factorial design This is a pre-planned interim analysis of an ongoing study. Interim analysis for efficacy was planned when 219 deaths had occurred. At the time of the interim analysis, 99.6% of the required participants (745/748) had been recruited.	137 centres in Europe, North America and Australia. 745 adults aged 18 years and over (median age 42.2 years [range 18.3 to 82.3], 56% male) with newly-diagnosed anaplastic glioma without 1p/19q codeletion. Participants were required to have WHO performance status scores of 0–2, have adequate haematological, renal, and liver function, and be taking stable or decreasing doses of corticosteroids. Across the whole study population, 29% were taking corticosteroids at study entry and 12% had previous surgery for a low-grade tumours.	**Intervention** Radiotherapy with adjuvant temozolomide (n=185) Radiotherapy and concurrent temozolomide plus adjuvant temozolomide (n=188) **Comparison** Radiotherapy alone (n=187) Radiotherapy plus concurrent temozolomide (n=185). The radiotherapy dose was 59.4 Gy, given in 33 fractions of 1.8 Gy. Adjuvant temozolomide was started 4 weeks after completion of radiotherapy, for a maximum of 12 treatment cycles. A treatment cycle consists of 28 days: 5 treatment days followed by a 23 day treatment interruption. For	Primary Clinical effectiveness	Overall survival[1] Adjusted for performance status score, age, 1p loss of heterozygosity, presence of oligodendroglial elements, and MGMT-promoter methylation status.	At the time of the interim analysis, 92 people (25%) treated with adjuvant temozolomide and 129 people (35%) not treated with adjuvant temozolomide had died. The hazard ratio [HR] for overall survival for adjuvant temozolomide was 0.65 (99.145% CI 0.45 to 0.93, p=0.0014).[1] Overall survival at 5 years was 55.9% (95% CI 47.2 to 63.8) in people treated with adjuvant temozolomide, compared with 44.1% (95% CI 36.3 to 51.6) in people not treated with adjuvant temozolomide.	P1 Primary research using quantitative approaches 7/10 The research questions and design are clearly stated. The design is appropriate for the study type, but is limited by an open-label design, which may have introduced bias. The methods are clearly described.	Direct study focusing on people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	Progression-free survival Defined as the time from randomisation to the date of first disease progression (radiological or neurological/clinical) or death.	At the time of the interim analysis, disease progression had occurred in 144 people (39%) treated with adjuvant temozolomide, compared with 200 people (54%) not treated with adjuvant temozolomide. Median progression-free survival was 42.8 months (95% 28.6 to 60.6) for people treated with adjuvant temozolomide, compared with 19.0 months (95% CI 14.4 to 24.6) for people not treated with adjuvant temozolomide.		

Use of radiotherapy with adjuvant temozolomide vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	Surgery before radiotherapy: 20% of participants had a biopsy, 47% partial tumour removal and 31% total tumour removal.	the first cycle, participants received temozolomide 150 mg/m^2. If no or minor toxicity was seen the dose was increased to 200 mg/m^2 for the subsequent cycles.			Progression-free survival at 5 years was 43.1% (95% CI 35.0 to 50.9) in people treated with adjuvant temozolomide, compared with 24.3% (95% CI 17.7 to 31.6) in people not treated with adjuvant temozolomide.	Results generally support the author's conclusions, although limited as this is an interim analysis of an ongoing study, and follow-up is immature. Results are not reported separately for each treatment arm and the study may have included people with tumours other than anaplastic astrocytoma.	
			Secondary Clinical effectiveness	Overall survival for adjuvant temozolomide, adjusted by age (>50 years vs. ≤50 years) [1]	Across the 2 adjuvant temozolomide treatment arms, 115 people (31%) were aged over 50 years and 258 people (69%) were aged 50 years or under. People aged over 50 years treated with adjuvant temozolomide had significantly worse overall survival compared with people aged 50 years or less, HR 4.04 (99.145% CI 2.78 to 5.87, p<0.001).		
			Secondary Clinical effectiveness	Overall survival for adjuvant temozolomide, adjusted by WHO performance status (>0 vs. 0) [1]	In total, 220 people (59%) treated with adjuvant temozolomide had a WHO performance score of 0 (meaning they are able to carry out all normal activity without restriction) and 153 people (41%) had a score more than 0 (meaning they had a range of restrictions, from being restricted in strenuous activity [score of 1] to being ambulatory and capable of all self-care but unable to carry out any work activities [score of 2]). There was no statistically significant difference in overall survival for people with a WHO performance score of >0 compared with people with a score of 0,		

Use of radiotherapy with adjuvant temozolomide vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					HR 1.36 (99.145% CI 0.94 to 1.96, p=0.0273).		
			Secondary Clinical effectiveness	Overall survival for adjuvant temozolomide, adjusted by 1p loss of heterozygosity (yes vs. no) [1]	Across the adjuvant temozolomide groups, 27 people (7%) had loss of heterozygosity for chromosome 1p and 346 people (93%) did not. Loss of heterozygosity for chromosome 1p can include deletion of chromosome 1p. In van den Bent et al. (2017), there was no statistically significant difference in overall survival for people with 1p loss of heterozygosity compared with people without loss of heterozygosity, HR 1.56 (99.145% 0.84 to 2.88, p=0.0572).		
			Secondary Clinical effectiveness	Overall survival for adjuvant temozolomide, adjusted for presence of oligodendroglial elements (yes vs. no) [1]	Oligodendroglial elements were present in 86 people (23%) treated with adjuvant temozolomide and not present in 287 people (77%). The presence of oligodendroglial elements did not have a statistically significant effect on overall survival, HR 1.20 (99.145% CI 0.81 to 1.76, p=0.2230).		
			Secondary Clinical effectiveness	Overall survival for adjuvant temozolomide, adjusted by MGMT-promotor methylation status before randomisation	In the adjuvant temozolomide groups, MGMT-promoter methylation status results were available before randomisation for 139 people (37%). People with MGMT-promotor methylation had significantly better overall survival		

Use of radiotherapy with adjuvant temozolomide vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
				(methylated vs. unmethylated) [1]	compared with people not methylated (HR 0.49, 99.145% CI 0.26 to 0.93, p=0.0031).		
			Secondary Safety	Grade 3 (severe) and grade 4 (life-threatening or disabling) adverse events[2]	8–12% of participants treated with temozolomide (n=549, including people treated with adjuvant and concomitant temozolomide, and both) had a grade 3–4 toxicity. The most frequently reported haematological grade 3–4 toxicities in the adjuvant temozolomide group (n=182) were: thrombocytopenia (9.3%), neutropenia (4.4%), leukopenia (2.2%) and anaemia (1.1%). The most frequency reported non-haematological grade 3–4 toxicities in the adjuvant temozolomide group were infections (7.9%), constitutional symptoms (6.8%) and gastrointestinal events (5.6%). The authors state that apart from constitutional and gastrointestinal events, most non-haemotological events were considered to be unrelated to temozolomide treatment. 5 participants (1%) receiving temozolomide had grade 3–4 increases in aminotransferase concentrations.		

Use of radiotherapy with adjuvant temozolomide vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
			Secondary Safety	Treatment discontinuation because of toxicity	In total 30 people (8%) discontinued treatment with adjuvant temozolomide because of toxicity. No further details are reported in the interim analysis.		
Critical appraisal summary: These are interim results of an ongoing clinical trial, and as such follow-up is immature and the study underpowered. The study was open-label, meaning participants and investigators knew which treatment was being given. Results for both arms of the trial given adjuvant temozolomide are reported together; it is not clear whether concurrent temozolomide treatment affected results. Adverse event reporting is incomplete; details on mild to moderate adverse events and reasons for treatment discontinuation are not provided.							
Footnotes [1] For the outcomes looking at overall survival, the nominal significance level for the rejecting the null hypothesis (no efficacy) was 0.0084. For these outcomes the confidence intervals were 99.145% [2] Scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0. In which grade 3 refers to severe adverse events and grade 4 refers to life-threatening or disabling events.							

8. Grade of evidence table

Use of radiotherapy with adjuvant temozolomide Vs. no adjuvant temozolomide to treat newly-diagnosed anaplastic glioma without 1p/19q codeletion					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**

Overall survival	van den Bent et al. 2017	7/10	Direct study	B	This outcome looks at how long participants survived for, calculated from the date of randomisation to the date of death from any cause. The median follow-up was 27 months, during which time 92 people treated with adjuvant temozolomide died, and 129 people not treated with adjuvant temozolomide died. Median overall survival could not be calculated for participants treated with adjuvant temozolomide. The hazard ratio (HR) for overall survival was 0.65 (99.145% confidence interval [CI] 0.45 to 0.93, p=0.0014). Overall survival at 5 years was 55.9% (95% CI 47.2 to 63.8) for people treated with adjuvant temozolomide, compared with 44.1% (95% CI 36.3 to 51.6) in people not treated with adjuvant temozolomide. These results suggest that adjuvant temozolomide improves overall survival in people with newly-diagnosed anaplastic glioma without 1p/19q codeletion compared with no adjuvant temozolomide. These are interim results from an ongoing clinical trial, as such follow-up is immature and the study is underpowered for all outcomes. Median overall survival could not be calculated at the time of the interim analysis. The final results of the study are needed before final conclusions on the impact of adjuvant temozolomide on overall survival can be made.
Progression-free survival	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at how long a person lives with their disease without it getting worse. The outcome measured the time from randomisation to the date of first disease progression (radiological or neurological/clinical) or death. The median progression-free survival for people treated with adjuvant temozolomide was 42.8 months (95% 28.6 to 60.6), compared with 19.0 months (14.4 to 24.6) for people not treated with adjuvant temozolomide. Progression-free survival at 5 years was 43.1% (95% CI 35.0 to 50.9) in people treated with adjuvant temozolomide, compared with 24.3% (95% CI 17.7 to 31.6) in people not treated with adjuvant temozolomide. These results suggest that adjuvant temozolomide increases the time a person can live with anaplastic glioma without 1p/19q codeletion without it getting worse. On average people treated with adjuvant temozolomide lived with their disease without it getting for around 2 years more than people not taking adjuvant temozolomide. These are interim results from an ongoing clinical trial, as such follow-up is immature and the study is underpowered for all outcomes. The final results of the study are needed before final conclusions on the impact of adjuvant temozolomide on progression-free survival can be made.
Overall survival for adjuvant temozolomide, adjusted by age (>50 years vs. ≤50 years)	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at whether age affected overall survival in people treated with adjuvant temozolomide. The study found that people aged over 50 years treated with adjuvant temozolomide had significantly worse overall survival compared with people aged 50 years or under, HR 4.04 (99.145% CI 2.78 to 5.87, p<0.001).

					These results suggest that people aged under 50 years treated with adjuvant temozolomide may live longer compared with people aged over 50 years. As discussed above, there are interim results from an ongoing study, and outcomes, particularly sub-group analyses, are underpowered. The final results of the CATNON study are needed before subgroups are patients who may respond better to treatment with adjuvant temozolomide can be identified.
Overall survival for adjuvant temozolomide, adjusted by WHO performance status (>0 vs. 0)	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at whether WHO performance status (a measure of general wellbeing) affected overall survival in people treated with adjuvant temozolomide. The study found no statistically significant difference in overall survival for people with a WHO performance score of >0 compared with people with a score of 0, HR 1.36 (99.145% CI 0.94 to 1.96, p=0.0273). These results suggest that WHO performance status before starting treatment does not affect overall survival in people treated with adjuvant temozolomide. As discussed above, there are interim results from an ongoing study, and outcomes, particularly sub-group analyses, are underpowered. The final results of the CATNON study are needed before subgroups are patients who may respond better to treatment with adjuvant temozolomide can be identified.
Overall survival for adjuvant temozolomide, adjusted by 1p loss of heterozygosity (yes vs. no)	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at whether 1p loss of heterozygosity (deletion of the 1p chromosome) affected overall survival in people treated with adjuvant temozolomide. In other studies, deletion of chromosome 1p has been associated with better patient outcomes (Zhao et al. 2014). The study found no statistically significant difference in overall survival for people with 1p loss of heterozygosity compared with people without loss of heterozygosity, HR 1.56 (99.145% 0.84 to 2.88, p=0.0572). These results suggest that 1p loss of heterozygosity does not affect overall survival in people treated with adjuvant temozolomide. As discussed above, there are interim results from an ongoing study, and outcomes, particularly sub-group analyses, are underpowered. The final results of the CATNON study are needed before subgroups are patients who may respond better to treatment with adjuvant temozolomide can be identified.
Overall survival for adjuvant temozolomide, adjusted for presence of oligodendroglial elements (yes vs. no)	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at whether presence of oligodendroglial elements affected overall survival in people treated with adjuvant temozolomide. The study found the presence of oligodendroglial elements did not have a statistically significant impact on overall survival, HR 1.20 (99.145% CI 0.81 to 1.76, p=0.2230).

					These results suggest that the presence of oligodendroglial elements does not affect overall survival in people treated with adjuvant temozolomide. As discussed above, there are interim results from an ongoing study, and outcomes, particularly sub-group analyses, are underpowered. The final results of the CATNON study are needed before subgroups are patients who may respond better to treatment with adjuvant temozolomide can be identified.
Overall survival for adjuvant temozolomide, adjusted by MGMT-promotor methylation status before randomisation (methylated vs. unmethylated)	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at whether MGMT-promoter methylation status affected overall survival in people treated with adjuvant temozolomide. The study found people with MGMT-promotor methylation had significantly better overall survival compared with people without MGMT-promotor methylation (HR 0.49, 99.145 CI 0.26 to 0.93, p=0.0031). These results suggest that people with MGMT-promoter methylation treated with adjuvant temozolomide may live longer compared with people without MGMT-promoter methylation. As discussed above, there are interim results from an ongoing study, and outcomes, particularly sub-group analyses, are underpowered. The final results of the CATNON study are needed before subgroups are patients who may respond better to treatment with adjuvant temozolomide can be identified.
Adverse events	van den Bent et al. 2017	7/10	Direct study	B	This outcome looked at the number of people treated with temozolomide who had a grade 3–4 toxicity (severe, life-threatening or disabling adverse events). Details on grade 1–2 toxicities (mild and moderate adverse events) are not reported. Toxicities may or may not have been caused by the study treatment. Over the median 27 month follow-up, 8–12% of people treated with temozolomide (n=549; including people on concurrent therapy) had grade 3–4 toxicity. Many of the adverse events were haematological, including thrombocytopenia, neutropenia and leukopenia. Non-haematological events included infections, constitutional symptoms (for example fever, weight-loss and fatigue) and gastrointestinal events. Increases in aminotransferase concentration, an indicator of possible liver damage, occurred in 5 participants (1%) receiving temozolomide. In total 30 people (8%) discontinued treatment with adjuvant temozolomide because of toxicity. These results suggest that around 1 in 10 people treated with temozolomide will have severe, life-threatening or disabling adverse events. These events include haematological adverse events and raised liver aminotransferases. The median follow-up was 27 months; the final results of the CATNON study are needed before the longer-term safety profile of temozolomide in this population is known.

9. Literature search terms

Search strategy	

P – Patients / Population
 	
Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?
	• Newly-diagnosed patients with grade III anaplastic astrocytoma (primary brain tumour) without evidence of 1p/19q codeletion:
	• Data to be presented separately as permits for:
	  ○ All ages
	  ○ Adults
	  ○ Children

I – Intervention Which intervention, treatment or approach should be used?	• Surgery (including biopsy only), radiotherapy and adjuvant temozolomide for up to 12 cycles
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	• Surgery (including biopsy only) and radiotherapy
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	*Critical to decision-making:* • 5 year survival • Median survival • Progression-free survival • Overall survival • Measures of unplanned health care for example emergency admissions *Important to decision-making:* • Quality of life • Safety measures for example adverse events, abnormal laboratory indices • Need for second or third line treatment • Measures of cost-effectiveness for example incremental cost-effectiveness ratio (ICER)

Assumptions / limits applied to search
Inclusion criteria • Articles published in English in peer reviewed journals in the last 10 years that include patients with grade III anaplastic astrocytoma (primary brain tumour) without evidence of 1p/19q codeletion • Study type: Randomised controlled trial **Exclusion criteria** • Those grade III anaplastic astrocytoma (primary brain tumour) WITH evidence of 1p/19q codeletion that is anaplastic oligodendroglioma or glioblastoma • Studies not published in English • Abstracts • Letters • Commentaries • Conference papers • Studies without comparators (including before and after studies) • Papers published greater than 10 years ago

10. Search strategy

Database search strategies

Database: Medline

Platform: Ovid

Version: 1946 to October 10 2018

Search date: 11/10/2018

Number of results retrieved: 187

Search strategy:

Database: Ovid MEDLINE(R) <1946 to October 10, 2018>
Search Strategy:
---
1 (temozolomide or temodal or temomedac or temcad or temodar).tw. (4905)
2 Astrocytoma/ (14141)
3 (anaplastic adj3 astrocytoma*).tw. (2651)
4 or/2-3 (15295)
5 1 and 4 (318)
6 animals/ not humans/ (4470149)
7 5 not 6 (316)
8 limit 7 to english language (293)
9 (2008* or 2009* or 201*).ed. (8534214)
10 8 and 9 (187)

Additional search for anaplastic glioma (see below) 15/10/2018 38 refs

Database: Medline in-process

Platform: Ovid

Version: October 10 2018

Search date: 11/10/2018

Number of results retrieved: 21

Search strategy:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 10, 2018>

Search Strategy:
---
1 (temozolomide or temodal or temomedac or temcad or temodar).tw. (862)
2 Astrocytoma/ (0)
3 (anaplastic adj3 astrocytoma*).tw. (167)
4 or/2-3 (167)

5 1 and 4 (25)
6 animals/ not humans/ (0)
7 5 not 6 (25)
8 limit 7 to english language (24)
9 (2008* or 2009* or 201*).dt. (2657971)
10 8 and 9 (21)

15/10/2018 additional search 10 refs

Database: Medline epubs ahead of print

Platform: Ovid

Version: October 10 2018

Search date: 11/10/2018

Number of results retrieved: 3

Search strategy:

Database: Ovid MEDLINE(R) Epub Ahead of Print <October 10, 2018>

Search Strategy:
---
1 (temozolomide or temodal or temomedac or temcad or temodar).tw. (184)
2 Astrocytoma/ (0)
3 (anaplastic adj3 astrocytoma*).tw. (32)
4 or/2-3 (32)
5 1 and 4 (3)
6 animals/ not humans/ (0)
7 5 not 6 (3)
8 limit 7 to english language (3)

Additional search 15/10/2018 2 refs

Database: Medline daily update

Platform: Ovid

Version: October 10 2018

Search date: 11/10/2018

Number of results retrieved: 0

Search strategy

As above

0 results from 15/10/2018 search

Database: Embase

Platform: Ovid

Version: 1974 to 2018 October 10

Search date: 11/10/2018

Number of results retrieved: 138

Search strategy:

Database: Embase <1974 to 2018 October 10>
Search Strategy:
---
1 *temozolomide/ (5166)
2 (temozolomide or temodal or temomedac or temcad or temodar).tw. (11998)
3 or/1-2 (12311)
4 (anaplastic adj3 astrocytoma*).tw. (4026)
5 3 and 4 (485)
6 nonhuman/ not human/ (4219093)
7 5 not 6 (482)
8 limit 7 to (books or chapter or conference abstract or conference paper or "conference review" or editorial or letter or note) (240)
9 7 not 8 (242)
10 (2008* or 2009* or 201*).dc. (14333730)
11 9 and 10 (148)
12 limit 11 to english language (138)

15/10/2018 additional search 56 references

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL;

Platform: Wiley

Version:

CDSR –Issue 10 of 12, October 2018

CENTRAL – Issue 9 of 12, September 2018

Search date 11/10/2018

Number of results retrieved: CDSR 2 ; CENTRAL 221 ;.

Additional search 15/10/2018 1 CDSR ref 19 central

Search Name:

Date Run: 11/10/2018 13:24:24

Comment:

ID	Search	Hits
#1	(temozolomide or temodal or temomedac or temcad or temodar):ti,ab,kw	934
#2	MeSH descriptor: [Astrocytoma] explode all trees	593
#3	(anaplastic near/3 astrocytoma*):ti,ab,kw	121
#4	#2 or #3	660
#5	#1 and #4	223

Platform: CRD

(temozolomide OR temodal OR temomedac OR temcad OR temodar) AND (anaplastic astrocytoma*)
WHERE LPD FROM 01/10/2008 TO 11/10/2018

DARE – 2 of 4, April 2015 (legacy database) 1 (repeat of CDSR record)

HTA – 4 of 4, October 2016 (legacy database) 0

NHS EED – 2 of 4, April 2015 (legacy database) 0

0 refs from additional search 15/10/2018

Trials registry search strategies

clinicaltrials.gov

Search date: 10/10/2018

Number of results retrieved: 14

Search strategy:

: anaplastic astrocytoma | Temozolomide | Phase 3, 4

Also searched for Temodar and Temodal

Clinicaltrialsregister.eu

Search date: 10/10/2018

Number of results retrieved: 5

Search strategy: temozolomide AND anaplastic astrocytoma phase 3 and 4

11. Evidence selection

A literature search was conducted which identified 509 unique references (see search strategy for full details). These references were screened using their titles and abstracts, and 1 reference was obtained, assessed for relevance and included in the evidence summary.

No other published randomised or non-randomised studies were included based on title and abstract. Most references were excluded on title and abstract because of:

- Population (study did not include people with grade III anaplastic astrocytoma).
- Intervention (study did not investigate adjuvant temozolomide).
- Evidence (commentaries / review articles not included).

12. Related NICE guidance and NHS England clinical policies

Brain tumours (primary) and brain metastases in adults (2018) NICE guideline NG99

Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (2007) NICE technology appraisal TA121

Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (2001, last updated 2016) NICE technology appraisal TA23

NHS England has not issued any policies on managing newly-diagnosed anaplastic astrocytoma without 1p/19q codeletion with temozolomide.

13. Terms used in this evidence summary

Abbreviations

Term	Definition
Gy	Grey
IDH	Isocitrate dehydrogenase
MGMT	O6-methylguanine-DNA methyltransferase
RCT	Randomised controlled trial

Medical definitions

Term	Definition
1p/19q codeletion	Deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q).
Adjuvant	Additional cancer treatment given after the primary treatment to lower the risk of the cancer coming back.
Anaplastic astrocytoma	A type of brain tumour. Develops from astrocytes.
Anaplastic oligoastrocytoma	A type of brain tumour. Develops from astrocytes and oligodendrocytes.
Anaplastic oligodendroglioma	A type of brain tumour. Develops from oligodendrocytes.
Astrocyte	Star-shaped cells that surround and protect nerve cells in the central nervous system.
Concurrent	Treatment given at the same time as other therapies.
Factorial design	A study that investigates the effects of more than one independent variable on a given outcome. For example, a 2x2 factorial design can test the effects of 4 separate interventions.
Glioblastoma	A type of brain tumour.
Glioma	Brain tumours that develop from glial cells.
Glial cells	Cells that surround and protect nerve cells in the central nervous system.
Karnofsky performance status	A measure of functional impairment. 80-100: Able to carry on normal activity and to work; no special care needed. 70-50: Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. 0-50: Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.
Malignant	A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Malignant cells can also spread to other parts of the body through the blood and lymph systems.
WHO performance status	A measure of functional impairment. 0: able to carry out all normal activity without restriction 1: restricted in strenuous activity but ambulatory and able to carry out light work 2: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours 3: symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden 4: completely disabled; cannot carry out any self-care; totally confined to bed or chair.

14. References

van den Bent MJ, Baumert B, Erridge B et al. (2017) Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for

1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet 390:1645–53