CPAG Summary Report for Clinical Panel – Temozolomide as adjuvant treatment for people with newly diagnosed anaplastic astrocytoma without 1p/19q codeletion following surgery and radiotherapy [URN: 1691]

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	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 92/373 people (25%) treated with adjuvant temozolomide died, and 129/372 people (35%) 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.
2.	Progression free survival	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 (n=373) 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 (n=372). 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.
3.	Mobility	Not measured
4.	Self-care	Not measured
5.	Usual activities	Not measured
6.	Pain	Not measured
7.	Anxiety / Depression	Not measured
8.	Replacement of more toxic treatment	Not measured
9.	Dependency on care giver / supporting independence	Not measured
10.	Safety	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.
11.	Delivery of intervention	Not measured

Other health outcome measures determined by the evidence review		
No	Outcome measure	Summary from evidence review
1.	Overall survival for adjuvant temozolomide, adjusted by age (>50 years vs. ≤50 years)	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 less, HR 4.04 (99.145% CI 2.78 to 5.87, p<0.001). These results suggest that people aged less than 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.
2.	Overall survival for adjuvant temozolomide, adjusted by WHO performance status (>0 vs. 0)	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.
3.	Overall survival for adjuvant temozolomide, adjusted by 1p loss of heterozygosity (yes vs. no)	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.
4.	Overall survival for adjuvant temozolomide, adjusted for presence of oligodendroglial elements (yes vs. no)	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.
5.	Overall survival for adjuvant temozolomide, adjusted by MGMT-promotor methylation status before randomisation (methylated vs. unmethylated)	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.