SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Temodal. This scientific discussion has been updated until 1st September 2005. For information on changes after this date please refer to module 8B.

1. Introduction

Temodal, with the active ingredient temozolomide (INN), is an alkylating agent intended for the treatment of paediatric and adult patients with malignant glioma, such as GBM or AA, showing recurrence or progression after standard therapy. In patients 3 years or older, previously untreated with chemotherapy, Temodal is administered at a dose of 200 mg/m² once daily for 5 days per 28-day cycle. In patients previously treated with chemotherapy, the initial dose is 150 mg/m^2 once daily, to be increased in the second cycle to 200 mg/m^2 daily, providing the absolute neutrophil count (ANC) is ?1.5 x 10^9/l and the thrombocyte count is ?100 x 10^9 /l on Day 1 of the next cycle.

Temozolomide is a prodrug and converts spontaneously to MTIC which is also the known active metabolite of dacarbazine. The main advantage of temozolomide over dacarbazine lies in its circumvention of hepatic metabolism.

The incidence of brain tumours ranges from 1-10 cases/100,000 of which primary malignant gliomas comprise over 60%. The age-specific incidence of malignant glioma increases from 5/100,000 for those aged under 30, to a peak of 20 cases/100,000 at the age of 75.

Using standard multimodality treatment, malignant or high-grade gliomas have a median survival approximately in the range 1 – 2 years from initial diagnosis.

The primary therapy of GBM includes surgery, radiotherapy and chemotherapy. Complete surgical excision of GBM is usually not feasible due to infiltrative tumour growth. Postoperative irradiation has been demonstrated to significantly prolong survival and is a part of the current standard therapy of GBM. Adjuvant chemotherapy with nitrosourea-based chemotherapy has led to a further modest increase in progression-free and overall survival, but is still controversial due to the fact that disadvantages such as adverse effects and hospitalisation may not outweigh the usually small survival benefit.

After primary therapy practically all patients will present with recurrent disease. In this situation no standard therapeutic approach can be defined and the prognosis is poor. Chemotherapy is often administered to patients with good performance status, either in addition to local measures or in patients who are not amenable to local therapies. Different agents have been tested as mono- or combination therapy in phase II trials revealing sometimes a relatively high fraction of responses (defined as complete response [CR], partial response [PR] or stable disease [SD]) which are, however, in general of short duration. No chemotherapeutic regimen can be considered as efficacious in terms of a proven survival benefit or proven palliative benefit compared to best supportive care or another chemotherapeutic option.

In progressive/recurrent GBM, the evaluation of efficacy of chemotherapy is difficult. Changes in the size and shape of enhancing lesions in MRI scans are difficult to measure, in particular in the presence of post-surgical changes. Therefore, PFS based only or mainly on MRI data need to be augmented by data demonstrating clinical benefit.

2. Part II: Chemical, pharmaceutical and biological aspects

The pharmaceutical and chemical documentation and the expert report were comprehensive and well presented. Part II of the dossier reflected a good quality of Temodal capsules.

Composition and product development

Temodal is presented as a conventional formulation in (hard) gelatine capsules, for oral use. The four strengths 5 mg, 20 mg, 100 mg and 250 mg contain the same excipients but in different proportions.

All clinical trial formulations were identical to those proposed for marketing. Temodal is presented in Type I amber glass bottles with child-resistant polypropylene caps.

Active substance

The synthesis of temozolomide is a three-stage process, using 4-amino-5-imidazole carboxamide hydrochloride as a basis. The synthesis involves unusual risks, since an intermediate compound is explosive and a reagent is extremely toxic by inhalation. Because of these risks temozolomide is manufactured by a contract manufacturer specialising in the manufacture of hazardous drug substances. There are ten potential synthesis impurities

Temozolomide is slightly soluble in water and acidic aqueous solutions (3.1 mg/ml). It has no protic functional group and log K_D is approximately 1.3. The identification is a combination of HPLC and IR; the latter test also ensures the correct polymorphic form. Related substances are determined by HPLC. Some limits in the drug substance specification are slightly above what has actually been found. However, even though the doses used in the preclinical safety studies have not exceeded the doses to be given in therapy, it is the opinion of the CPMP that these minor differences in the impurity profile of a substance that is rather toxic in itself, will not represent a safety concern.

The proposed specifications are supported by the batch analysis results (n = 22).

pH, moisture and temperature affect the stability of temozolomide. The retest period for the active substance is 24 months stored at 2°C to 8 °C, or 12 months if stored at 20 °C to 25 °C. A visual test will be done on each batch prior to its use, as colour is a sensitive indicator of moisture mediated degradation.

Excipients

Stearic acid is manufactured by a process that excludes the possibility of transmission of BSE. Lactose and gelatine (present in the capsule shells) are manufactured from raw material solely originating from the USA. The risk for BSE transmission of these materials can thus be judged to be negligible.

The excipients are either tested according to Ph.Eur./B.P. where relevant or to a harmonised NF/Ph.Eur. monograph or according to USP/NF.

Finished product

Temodal is presented as conventional capsules containing a non-granulated powder mixture. The critical process parameters were found to be active substance blending times, lubricant blending times, number of lactose dilutions (5-mg strength only) and capsule filler speed.

The product is being manufactured in a facility that holds the necessary Manufacturing Authorisation (see Annex II of the Opinion).

Identification of temozolomide is performed by two chromatographic procedures (reversed phase HPLC and straight phase TLC) which give a greater assurance of the correct identity.

Total degradation products are limited to 1.0% at release. Dissolution testing utilises the USP acceptance plan (Q=80% in 30 minutes) for stages 1 and 2. Stage 3 has been abandoned.

Microbial quality will be tested annually.

The batch analysis results (n=24) confirm satisfactory compliance with specifications and uniformity of the product at release.

The accepted shelf-life is 24 months when stored below 30 °C, as defined in the SPC.

In summary, the documentation of substances, materials, methods of production as well as the quality controls is sufficient to ensure a product of appropriate and consistent quality.

3.   Part III: Toxico-pharmacological aspects

The summary of preclinical documentation that was submitted provides a good overview of the design, performance and results of all studies.

Pharmacodynamics

Temozolomide acts as an alkylating agent and this mechanism of action mainly entails a cytotoxic effect on rapidly proliferating cells. In the different species employed for pharmaco-toxicological tests this effect is consistent with that observed in humans.

In vitro studies

Temozolomide was compared with other alkylating agents in its mechanism of cytotoxicity in connection with the role of guanine O^6 alkylation. The conclusion of the study was that temozolomide is a cytotoxic agent the activity of which is correlated with the level of DNA repair protein O^6-methylguanin-DNA-methyl-transferase (AGAT) in the tumour cell-line.

The toxicity of temozolomide on a range of human and murine tumour cell-lines shows a wide variation. Cell-lines with low AGAT levels such as GM892 are sensitive while cell-lines with high AGAT levels such as Raji, JAR, MAC 16 and A549 are resistant to temozolomide.

In vivo studies

The antitumour activity was tested in several studies in mice. In the first study it was tested in comparison to DTIC (dacarbazine). It was shown that a very similar antitumour activity-profile exists in these two alkylating substances.

In addition, temozolomide showed its antitumour activity in 5 murine solid tumour models. Temozolomide, like DTIC, demonstrates a good antitumour activity, both given intraperitoneally (i.p.) and orally.

General pharmacodynamics

No specific studies in animal models or alternatively in isolated organs were performed in the field of safety pharmacology (peripheral and central nervous system), despite the fact that temozolomide passes the brain and that there are signs of an impaired central nervous system. However, data on cardiovascular, renal and CNS effects may be evaluated from the toxicology studies.

In addition cytotoxic effects on bone marrow progenitor cells *in vitro* were assessed in human primary bone marrow granulocyte/macrophage precursor cells. The results indicate that temozolomide has some effects on human bone marrow progenitor cells *in vitro* at clinically achievable concentrations, but may be less myelotoxic than BCNU at equimolar concentrations.

A separate study was performed to evaluate the effect of temozolomide on gastrointestinal function in rats. There was no ulcerogenicity and no effects on intestinal motility.

Pharmacokinetics

Studies have been performed in rat, dog and in humans.

Oral bioavailability of the drug was complete in rats and dogs of both genders. Whole body autoradiography data in male rats showed a rapid and extensive distribution of ^{14}C-temozolomide to all tissues. Metabolic studies were performed in mouse, rat, dog and human. The metabolism is comparable in all species. The excretion of ^{14}C-temozolomide was determined in mouse, rat, dog and human. The main pathway for excretion was via the kidneys, only small amounts of radioactivity were excreted via faeces or as CO_2. In humans and animals there is a good oral bioavailability and there is neither significant metabolism nor accumulation.

Toxicology

Single dose toxicity

Single dose toxicity studies were performed in mice, rats, and Beagle dogs. The maximum non-lethal dose was 500 mg/m² (oral, i.p.) in mice, 750 (oral) and 1000 mg/m² (i.p.) in rats and 200 (males) – 1500 mg/m² (females) in dogs.

Repeated dose studies

Repeated dose toxicity studies in rats and dogs of up to 6-months duration were conducted using dosing regimens consisting of a 5-day treatment period followed by a 23-day period without treatment, referred to as a cycle. In rats, doses of 50 mg/m²/day were generally well tolerated up to 3 cycles and in dogs up to 6 cycles. Target organs at higher doses were the haematopoietic and lymphoreticular systems, gastrointestinal tract and testes. Except for effects on testes, there was a tendency to recovery during the no-treatment periods. In addition, in rats, toxicity to the mammary gland, the thyroid gland and the ocular system was evident. Retinal degeneration appears only at very high toxic and fatal doses. Neoplastic changes were noted at 125 mg/m²/day in a 6-cycle study and in

female rats, tumours were evident at all doses, starting from a cumulative dose of 750 mg/m². In a 3-cycle study, masses were palpable already on day 62 at a dose of 200 mg/m²/day.

At lethal doses in the toxicity studies there were signs of potential CNS effects, such as tremors and prostration (in mice), hypoactivity, hunched posture and partial closure of the eyes (mice and rats) and elevated body temperature (dogs). Clinically only nausea and vomiting have been observed as potential CNS effects.

No cardiovascular effects have been seen. There were no renal changes attributed to treatment with temozolomide.

It could have been expected that the toxicological profile observed in the pharmaco-toxicological trials would be very similar to or the same as in humans. However, the results show that the rats and dogs used in the studies have to be considered more sensitive to toxic effects. The therapeutic dose of 200 mg/m² used and tolerated in humans is already within the lethal range for animals. Therefore, patients should be carefully monitored.

In general, the pattern of toxicity seen with temozolomide, targeted at organs with relatively rapidly proliferating cells, is consistent with its mechanism of action and other alkylating agents are known for similar toxicity.

Genotoxicity

Two studies were conducted. A mammalian microsome, reverse mutation assay was conducted. Doses up to 2500 μg/plate were tested. Temozolomide caused an increase in the frequency of mutations in all strains tested, with or without metabolic activation.

In the human peripheral blood lymphocyte assay temozolomide was tested with two different donors at doses up to 1000 μg/ml dissolved in deionised water. In one of the tests positive results were seen at all treatment conditions.

Temozolomide was considered positive for inducing chromosome aberrations in cultured human lymphocytes with or without metabolic activation.

Carcinogenicity

No specific studies have been undertaken and are not required. Repeat dose toxicity studies show that temozolomide has a carcinogenic potential, which could be expected of this kind of compound. Rats appear to be particularly sensitive to oncogenic effects of temozolomide, with the occurrence of the first tumours within three months of initiating dosing. This latency period is very short even for an alkylating agent and is comparable to DTIC.

Reproductive and development toxicity studies

Two studies have been conducted, one dose range-finding developmental study in rats and one in rabbits. In the rat study doses up to 150 mg/m² were not maternally toxic, but resulted in in-utero deaths of foetuses and growth retardation.

In the rabbit study a total of 41% of the foetuses had malformations in the dose group of 150 mg/m². The no effect level was considered to be 25-50 mg/m².

Local tolerance

An irritation study was conducted prior to the main sensitisation study. Temozolomide was administered to 20 albino guinea pigs. A slight dermal reaction was observed in 3 animals. Temozolomide was not considered to be a dermal sensitiser.

Ecotoxicity/Environmental risk assessment

An estimate of the maximum environmental concentration resulting from the use of the product was developed based on projections of sales and flows to sewer systems. The environmental impact is not expected to be significant.

4.   Part IV: Clinical aspects

In general the Temodal dossier was of high quality. The pharmacodynamic and pharmacokinetic properties of temozolomide in adults and in children 3 years of age or older have been characterised adequately in phase I trials, involving a total of 113 patients.

Three phase II trials for the approved indication have been conducted involving a total of 525 patients (ITT Population), of which 412 received temozolomide.

The clinical trials were performed according to GCP standards and agreed ethical principles.

a)   Clinical pharmacology

(1)   Pharmacodynamics

At physiological pH temozolomide undergoes non-enzymatic hydrolysis to MTIC which is considered as an active metabolite. MTIC spontaneously degrades to the reactive methyl-diazonium ion and AIC. The antineoplastic activity of MTIC is thought to be primarily due to alkylation of DNA at the O^6 and N^7 position of guanine.

(i)   Dose finding studies

DLT and MTD for temozolomide were investigated in 4 phase I trials, which included in total 92 patients. The studies followed the conventional phase I design and used the 5 day schedule and a total dose range of 500 – 1250 mg/m², except for one trial in which this dose range was administered as a single dose. Three trials were conducted in adults and one in paediatric patients.

DLT consisting of grade 4 neutropenia and grade 4 thrombocytopenia occurred at 1000 mg in two of the trials in adults. Thus, 750 mg/m²/cycle was determined as the MTD. In the third trial grade 4 thrombocytopenia occurred as the DLT at the 1250 mg/m²/cycle, with the MTD being 1000 mg/m²/cycle. 40% of the patients in the dose escalation phase of this trial had received prior chemotherapy compared to 82% and 96% in the two other trials. This might explain the different MDT's and for the phase II trials a starting dose of 750 mg/m²/cycle and 1000 mg/m²/cycle for patients with and without prior chemotherapy respectively were selected.

For paediatric patients grade 4 thrombocytopenia and grade 4 neutropenia were defined as DLT for good-risk (no history of prior treatment with nitrosureas and/or craniospinal irradiation) patients at 1200 mg/m²/cycle. The MTD was 1000 mg/m²/cycle. In the poor-risk patients the MTD could not be determined due to slow and limited patient accrual.

Other adverse events seen in adults were nausea and vomiting, fatigue, headache, pain, constipation, fever and anorexia. No treatment-related deaths were reported.

Non-haematological treatment-related adverse events occurring in at least two children were vomiting, nausea, heamatoma, headache, somnolence, fatigue and pain in good-risk patients and vomiting, nausea and pain in poor-risk patients. Non-haematological treatment-related grade 3 or 4 adverse events were vomiting, pain, hyperesthesia, hepatic failure, respiratory insufficiency and renal failure, each occurring in 1 patient except for pain which was reported in 2 patients. One treatment related death has been reported in a paediatric poor-risk patient, misstratified to the good-risk arm.

(2)   Pharmacokinetics

Pharmacokinetic data analysis was made using model-independent methods. A population pharmacokinetic analysis included plasma samples from 359 patients in three phase I and three phase II studies. In the phase I studies patients with advanced cancer without bone marrow involvement were enrolled. In the phase II studies patients with GBM or AA were enrolled. In most studies both male and female patients were included.

After oral administration to adult patients, temozolomide is absorbed rapidly with t_{max} between 0.5 and about 1.5 hours. After absorption, temozolomide was rapidly converted to the active substance, MTIC, and subsequently to AIC. Mean t_{max} values for MTIC were 1.5 to 2.0 hr after a single dose, and mean t_{max} of AIC was 2.5 hr. C_{max} values for MTIC and AIC were 2.5 – 4.7% and 13% of those for temozolomide, respectively. The data indicate complete oral bioavailability of the drug. Mean AUC values ranged from 14.3-15.5 µg.hr/ml for a dose of 100 mg/m² to 176 µg.hr/ml for a dose of 1,000 mg/m².

The mean apparent volume of distribution ranged from 0.35 l/kg to 0,63 l/kg on day 1 of cycle 1 and was independent of the dose. Temozolomide demonstrates low protein binding (10% to 20%), and thus it is not expected to interact with highly protein bound agents.

In plasma, temozolomide undergoes non-enzymatic hydrolysis to MTIC, which further degrades to AIC and the reactive diazonium ion. AIC is an intermediate of the biosynthesis of purines and expected to be non-toxic.

After oral administration of ^{14}C -labelled temozolomide, mean faecal excretion of ^{14}C over 7 days post-dose was 0.8%. The total recovery of ^{14}C is low, probably because of the incorporation of AIC into the tissue purine pool. Following oral administration, approximately 5% to 10% of the dose is recovered unchanged in the urine over 24 hours, and the remainder excreted as temozolomide acid, 5-aminoimidazole-4-carboxamide (AIC) or unidentified polar metabolites.

(3)   Special populations

Nineteen paediatric patients (age range 3 to 17 years) were evaluable for PK. Temozolomide was absorbed rapidly with a mean t_{max} in the range of 1.27 to 1.87 h in the different dose groups. The C_{max} (1.36 to 1.75 h) and AUC (24.0-48.7 µg.h/ml) were higher than in adults. This did not result in a higher myelotoxicity presumably due to a higher bone marrow reserve in children. Dose-related increases in C_{max} and AUC were observed. The mean terminal phase half-life, mean body clearance and mean volume of distribution were independent of the dose and comparable to the values in adults. Mean urinary recovery of unchanged temozolomide and mean renal clearance were also consistent with results in adults. Following multiple dosing no accumulation of temozolomide in plasma was observed.

No pharmacokinetic trials in patients with renal dysfunction have been performed. In the population pharmacokinetic analysis (with patients having an estimated creatinine clearance above 20 ml/min/m²) renal function had no effect on the clearance of temozolomide.

The plasma pharmacokinetic profile of temozolomide in patients with mild to moderate hepatic dysfunction was similar to that observed in patients with normal hepatic function. Based on the pharmacokinetic properties of temozolomide and the limited clinical data available hepatic or renal dysfunction is not expected to significantly reduce temozolomide clearance.

In the population pharmacokinetic analysis age had no effect on the clearance of temozolomide. Elderly patients had the lowest median nadir neutrophil and platelet count and a higher incidence (not statistically significant in this small number of patients) of neutropenia and thrombocytopenia (see section 4.4 of the SPC).

(i)   Interaction studies

Administration of Temodal with ranitidine did not result in alterations in the extent of absorption of temozolomide.

Administration of Temodal with food resulted in a 33% decrease in C_{max} and a 9% decrease in AUC. Although the clinical significance of these changes is unclear, Temodal should be administered in the fasting state.

Based on an analysis of population pharmacokinetics observed in Phase II trials, co-administration of dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2 receptor antagonists, or phenobarbital did not alter the clearance of temozolomide. Co-administration with valproic acid was associated with a small but statistically significant decrease in clearance of temozolomide.

No studies have been conducted to determine the effect of temozolomide on the metabolism or elimination of other drugs. However, since temozolomide does not require hepatic metabolism and exhibits low protein binding, it is unlikely that it would affect the pharmacokinetics of other medicinal products.

b)   Clinical experience

(1)   Efficacy

(a)   Glioblastoma multiforme

The following studies in GBM have been carried out:

(2)   Table 1

Study number	(3) Design	ITT population (Eligible histology population)	Primary end-point
C94-091	Open, multicenter, randomised, phase II, temozolomide vs. procarbazine in adult patients with GBM at first relapse	225 (210)	PFS at 6 months
194-122	Open, multicenter, non-comparative, phase II, in adult patients with GBM at first relapse	138 (128)	PFS at 6 months

Efficacy data for paediatric patients derive from the I93-125 trial.

(i)   Trial description

(ii)   C94-091

Patients with histologically proven supratentorial GBM with tumour progression or recurrence (first relapse) after standard therapy were eligible for the trial. An independent central histology review was conducted.

Temozolomide patients received a 5-day per cycle treatment with a starting dose of 200 mg/m²/day (no prior chemotherapy) or 150 mg/m²/day (prior chemotherapy) orally. Procarbazine patients received a 28-day per cycle treatment regimen with a starting dose of 150 mg/m²/day (no prior chemotherapy) or 125 mg/m²/day (chemotherapy). Repeat cycles could be administered every 28 days (temozolomide) and 56 days (procarbazine) following the first dose of each cycle until unacceptable toxicity or disease progression. Procarbazine was selected as a comparator based on limited data indicating that modest response rates were shown in three non-comparative trials. Furthermore, in the adjuvant setting procarbazine was better than methylprednisolone and comparable to BCNU with respect to overall survival. Considering that no chemotherapeutic agent of proven efficacy in recurrent GBM is available, the choice of procarbazine was appropriate.

The primary endpoint was PFS at 6 months. Progression was defined as progression on MRI scans and/or neurological deterioration. MRI scans were also evaluated by a central review committee blinded for treatment assignment. Secondary end-points were overall survival, objective response rate and health-related quality of life (HQL). This trial was not planned to show superiority over procarbazine. The protocol did not define criteria for judgement of superiority or equivalence in relation to the comparator. Instead progression free survival at 6 months for temozolomide was supposed to be 20% and with 100 patients in this arm, the 95% CI for this effect would be 12-28%. Thus, under these assumptions, the lower limit boundary for this effect would be above the 10%, which was considered by the investigators to be the limit for non-effectiveness.

(iii)   I94-122

GBM patients at first relapse who had failed conventional therapies at initial diagnosis were recruited.

Patients received a 5-day per cycle treatment with a starting dose of 200 mg/m²/day (no prior chemotherapy) or 150 mg/m²/day (prior chemotherapy) orally. Repeat cycles could be administered every 28 days following the first dose of each cycle until unacceptable toxicity or disease progression.

Also in this study, the primary endpoint was progression-free survival at 6 months, defined as in trial C94-091. Secondary objectives were the evaluation of health-related quality of life, safety and population pharmacokinetics.

In both studies treatment with study drug was to continue until death, disease progression, unacceptable toxicity, and request for withdrawal or until a maximum of 1 or 2 years of treatment. For all trials Kaplan-Meyer survival curves have been submitted.

(iv)   Results

(v)   C94-091

All patients enrolled had failed previous radiotherapy, and the majority (67%) of patients also had failed nitrosourea-based chemotherapy at initial diagnosis: 65% in the temozolomide arm and 68% in the procarbazine arm. Twenty percent of patients had surgery at relapse. The median time to relapse from initial diagnosis was 7.0 months for the temozolomide group and 8.4 months for the procarbazine group.

(4)   Table 2

		Temozolomide	Procarbazine	p-value
PFS[a]	6 months rate (95% CI)	21% (13-29%)	8% (3-14%)	0.008[b]
	median	2.9 months	1.9 months	0.006[c]
PFS based on central reviewer's MRI assessment	6 months rate (95% CI)	21% (12-30%)	8% (2-13%)	
	median	3.5 months	2.0 months	0.041[c]
Overall survival	6 months rate (95% CI)	60 (51-70%)	44 (35-53%)	0.019[b]
	median	7.3 months	5.7 months	0.33[c]
Complete response[d]		0%	0%	
Partial response[d]		5%	5%	
Stable disease[d]		40%	27%	

[a] defined as MRI progression and/or neurological worsening, [b] chi square test, [c] log rank test, [d] based on central reviewer's MRI assessment

Results calculated from the time of start of treatment.

Progression was due to clinical and/or neurological deterioration in 18 and 17 patients with temozolomide and procarbazine, respectively, to MRI progression in 47 and 44 patients with temozolomide and procarbazine, respectively and to both neurological/clinical deterioration and MRI progression in 32 and 29 patients with temozolomide and procarbazine, respectively.

For those patients who remained progression free at 6 months, quality of life scores in 7 domains (Table 3), post hoc considered to be those most relevant for patients with brain tumours, were improved over baseline in 5 domains for temozolomide and were lower than baseline in all 7 domains for procarbazine patients. However, it should be observed that methodological difficulties prohibit firm conclusions.

(5)   Table 3

Mean (SD) HQL Score Change from Baseline in Progression Free Survivors at 6 Months (Study No. C94-091)							
Group	Functioning Scale [a]			Symptom Scale [b]			
	Role	Social	Global QOL	Visual disorder	Motor dysfunction	Communication deficit	Drowsiness
TMZ (n=20)	6.1 (21.7)	8.8 (27.4)	-3.4 (30.9)	8.0 (29.0)	-2.3 (28.3)	-4.1 (22.6)	-15.8 (25.7)
PCB (n=8)	-16.7 (33.3)	-25.0 (40.8)	-2.1 (28.1)	6.3 (8.7)	11.1 (17.8)	16.7 (20.6)	8.3 (29.5)
a: Functioning scale score ranges from 0 to 100 with a high score representing a high functioning; a positive change score means improvement in functioning.							
b: Symptom scale score ranges from 0 to 100 with a high score representing a worse symptom; a negative change score means improvement in symptom.							

Despite the acknowledged need for focus on clinical benefit in patients with recurrent malignant glioma, the protocol rather focused on MRI findings which is not an established surrogate endpoint. This is considered to be a substantial shortcoming. In order to define the clinical benefit of temozolomide more directly, further analyses of time to neurological and clinical worsening have been conducted on prospectively collected data. These data are more heavily censored than the predefined

analyses as no regular neurological follow-up examinations had been planned for patients classified as having progressive disease based on MRI scans.

The following results are available:

(6)   Table 4

	Median (months)		logrank p-value		Event rate (6-months %) (censored)		χ^2 p-value
	TMZ (n=112)	P (n=113)			TMZ (n=112)	P (n=113)	
Time to neurological failure	4.2	3.5	0.035		62 (41)	74 (53)	0.013 NA
Time to KPS ≤60	5.6	3.5	0.007		56 (51)	78 (55)	0.002 NA
Time to decrease of KPS by at least 30 points	6.7	5.1	0.003		46 (69)	69 (66)	0.006 NA
Worst clinical case	3.8	2.3	0.01		65 (38)	81 (47)	0.005 NA

Abbreviations: Event rate (6-months %): percentage of patients who have experienced the event at 6 months; TMZ, Temozolomide; P, Procarbazine; NA, not applicable; Worst clinical case, time to the first of any of the clinical events (neurological failure or KPS ≤60 or decrease of KPS by at least 30 points).

Thus, data on neurological and clinical progression available for approximately half of the patients in both groups in the comparative study largely support the MRI-based PFS findings. It seems unreasonable to believe that there would be an inverse relationship between MRI PFS and clinical progression for the half of patients censored for these analyses, which would be needed if there was truly no difference between the treatment groups in clinical progression. Therefore, it seems reasonable to conclude that a benefit in MRI progression correlates to clinical benefit. However, from a principle point of view, it would have been preferable in these studies to evaluate all patients until clinical worsening (symptom relief) by evaluators separated from the study and blinded for treatment allocation.

The benefit of temozolomide was shown in patients without prior nitrosourea-based chemotherapy while in previously treated patients it appears to be limited to those with good (i.e., ≥ 80) Karnofsky Performance Status (KPS), (Table 5).

(7)   Table 5

	Prior chemotherapy				No prior chemotherapy			
	Median (months)		Event-free at 6-months (%)		Median (months)		Event-free at 6-months (%)	
	TMZ	P	TMZ	P	TMZ	P	TMZ	P
PFS eligible histology population	1.97	1.88	18	9	3.91	1.91	22	7
PFS excluding patients with baseline KPS=70	2.76	1.88	27	12	4.11	2.14	21	6

Abbreviations: see Table 4; TMZ, Temozolomide; P, Procarbazine.

(8)   I94-122

All patients enrolled had failed previous radiotherapy, and 29% also had failed nitrosourea-based therapy at initial diagnosis. Thirteen percent of patients had surgery at relapse. The median time to relapse from initial diagnosis was 8.1 months.

The 6-month PFS was 19% (95% CI: 12%-26%). The median PFS was 2.1 months. The analysis of event-free survival was similar. Median overall survival was 5.4 months. Forty-six percent of patients were alive beyond 6 months. Response rate based on the central reviewer assessment was 8% (2 CR and 9 PR) for the ITT population. Including 60 patients with SD as response, the response rate was 51%.

(a)   Anaplastic Astrocytoma

After the granting of the Marketing Authorisation the Marketing Authorisation Holder applied for an extension of the indication with AA. The results of one clinical trail were submitted.

Trial description

C/194-123 is a non-comparative multicentre study of temozolomide in patients with AA at first relapse. 162 patients were enrolled. All patients had been treated with radiotherapy at initial diagnosis, 60% had also received a nitrosourea-containing chemotherapy. Temozolomide was administered orally at a starting dose of 200 mg/m² and 150 mg/m² in patients without and with prior chemotherapy, respectively, once a day for 5 days, repeated every 28 days.

Results

PFS at 6 months was 46% (95% CI 39% - 54%), median PFS was 5.4 months. Event-free survival at 6 months was 44% (95% CI 36% - 51%). Median overall survival was 14.6 months. Thirteen complete and 43 partial responses determined by central MRI review were reported, for an objective response rate of 35%. Forty-three patients had stable disease. HQL responses were frequent in patients with objective CR or PR or stable disease. The safety profile of temozolomide in AA patients was similar as in the GBM studies.

Concerning the 13 CR reported in this trial, an independent MRI evaluation confirmed 5 CRs. The remaining 8 patients were classified as PR or stable disease of a clinically meaningful duration. The outcome of malignant glioma patients with CR, PR or stable disease following first-line chemotherapy does not seem to differ. However, the outcome is worse in patients with progressive disease. Therefore the rate of CR, PR or prolonged disease stabilisation might be of higher clinical relevance than the CR rate alone. In summary, a pronounced cytostatic effect was acknowledged in these 13 patients.

As C/194-123 is the only clinical trial in AA, it is of particular importance that the response rate is not biased by ineligible and presumably more chemosensitive histologies such as oligodendroglioma. Forty-four of 162 enrolled patients had a non-eligible histology according to the central pathology: 19 patients were diagnosed as GBM, 6 patients as anaplastic oligodendroglioma, 6 patients as oligodendroglioma, 13 patients as other low-grade histologies. For 7 patients, histology was not available. It is acknowledged that in a subgroup analysis, median PFS and median overall survival were similar in the eligible histology population and the ITT population. Response rates of patients with eligible reveal essentially the same results as in the ITT population.

Reference was made to a historical control group of patients with relapsed AA treated with single agent or combination chemotherapy (UCSF database). Six-months event-free survival rates were slightly higher with temozolomide. However, 95% CI were largely overlapping. Thus, the antineoplastic activity of temozolomide seemed to be at least similar to other agents used in this setting, but not outstanding.

AA and GBM originate from the same cell type. Patients with AA and GBM have often been enrolled in the same clinical trials, without stratification, although histology is a prognostic factor for survival. In general, cytostatic agents active in GBM are also active in AA. In the adjuvant setting, the benefit of chemotherapy is more pronounced in AA than in GBM. Although data are sparse, recurrent AA is also believed to be more chemosensitive than recurrent GBM. This is supported by the results of the temozolomide trials, with an overall response rate of 35% in recurrent AA (C/194-123) and 5% and 8% in GBM (trial C94-091 and 194-122, respectively).

No randomised clinical trial of temozolomide vs. another therapeutic option in patients with recurrent AA was submitted. However, a small palliative benefit of temozolomide has been demonstrated in a randomised trial in recurrent GBM. If there were arguments supporting extrapolation of the observed beneficial effect in recurrent GBM to AA, the new indication recurrent AA would seem acceptable with the limited non-comparative data available.

In addition the MAH has provided the CR/PR/SD rate and Kaplan-Meier curves for PFS and OS in the eligible histology population of the AA study, revealing essentially the same results as in the ITT population.

(b)   Clinical studies in specific populations

Study I93-125, a phase I study enrolled paediatric patients (<18 years, mean 9 years) with advanced cancers, no bone marrow involvement, and WHO performance status of 0,1 or 2. Patients were stratified by presence or absence of prior nitrosourea therapy and craniospinal irradiation. In this study, 15 of 28 patients enrolled had relapsed primary CNS tumours, either high-grade astrocytomas or brain stem gliomas. Preliminary efficacy in paediatric patients with malignant glioma was seen, including 2 PR and 1 SD in 10 brain stem glioma. Two out of 5 patients with high-grade astrocytoma had responses of CR and PR, respectively. An additional patient had stable disease at 4 months.

(9)   Safety

(10)   Patient exposure

The overall patient exposure/safety data for temozolomide were obtained from a safety database comprising information from 1030 patients in 21 studies.

The safety database also includes trials for other indications, which have not been authorised.

(11)   Adverse events, including serious adverse events

The proportion of patients that died within 30 days of the last study treatment administration was 5 and 14% for studies 194-123 (AA) and 194-122 (GBM), respectively. These fatal events were mostly judged unrelated to temozolomide administration. Two deaths, related to intratumoural haemorrhage and cerebral ischemia, were judged possibly related to study medication. In the pooled safety population of 1030 patients, 35 and 13% of the patients had grade 3 and grade 4 adverse events, respectively (NCI-CTC). The majority of these events were judged disease related. The safety profile of temozolomide in AA patients was similar as in the GBM studies.

In clinical trials, the most frequently occurring treatment-related undesirable effects were gastrointestinal disturbances, specifically nausea (43%) and vomiting (36%). These effects were usually grade 1 or 2 (1 - 5 episodes of vomiting in 24 hours) and were either self-limiting or readily controlled with standard anti-emetic therapy. The incidence of severe nausea and vomiting was 4%. Severe myelosuppression, predominantly thrombocytopenia, was dose-limiting, and occurred in 8% of all patients. Severe anaemia was reported in 3% of patients and severe neutropenia in 4% of patients. Myelosuppression was predictable (usually within the first few cycles, with the nadir between Day 21 and 28), and recovery was rapid, usually within 1-2 weeks. No evidence of cumulative myelosuppression was observed.

Other adverse events reported frequently include fatigue (22%), constipation (17%), and headache (14%). Anorexia (11%), diarrhoea (8%), rash, fever, and somnolence (6% each) were also reported. Less common (2% to 5%) and in descending order of frequency were asthenia; pain, including abdominal pain; dizziness; weight loss; dyspnoea; dyspepsia; alopecia; rigors; pruritus; malaise; taste perversion and paresthesia.

2. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Pre-clinical pharmacology and toxicology

With regard to the pharmacodynamics the mechanism of action is reasonably well established. Metabolic studies were performed in mouse, rat, dog and human. The metabolism is comparable in all species. Overall the toxicology program revealed that the primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract. This information has been included in the SPC.

Efficacy

GBM

At present, in patients with GBM at progression/first relapse after standard treatment no well-established therapy is available. In this situation, procarbazine was accepted as a comparator. A small palliative benefit of temozolomide on PFS which significantly differs from that of procarbazine was shown in a clinical trial. The benefit of temozolomide in patients previously treated with nitrosourea based chemotherapy appears to be limited to those with KPS of 80 or better.

AA

No randomised trial in recurrent AA has been submitted. Based on the non-comparative data alone, the therapeutic indication of anaplastic AA would not meet the requirements of the *CPMP Note for Guidance on the Evaluation of Anticancer Medicinal Products in Man*.

However, a palliative benefit of temozolomide has been shown in recurrent GBM. In view of the antineoplastic activity in recurrent AA demonstrated in a non-comparative trial, the similarities of AA and GBM and the higher chemoresponsiveness of AA, it seems reasonable to conclude that the palliative effects of temozolomide in recurrent GBM can be extrapolated to AA. In addition the Marketing Authorisation Holder agreed to undertake a comparative Phase III study in first line treatment of Anaplastic Astrocytoma with concomitant radiation. The study will enrol approximately 400 patients over 40 months with 36 months of follow-up. The comparative arm will include BCNU (with concomitant radiation) and the primary endpoint will be survival. Thus, inclusion of recurrent AA in the therapeutic indication is recommended.

Children

Although the experience in paediatric patients is limited, paediatric patients are not excluded from treatment with temozolomide as there is no evidence that the tumour biology differs in children 3 years of age and older and adults, and therapy of high grade gliomas is similar in paediatric and adult patients. Furthermore, tolerance to Temodal seems to be as good as in adult patients.

Safety

The safety profile is favourable, with low and manageable toxicity. Myelosuppression is the DLT and nausea and vomiting are the most frequent non-haematological adverse events. The safety profile is in accordance with that expected from pre-clinical studies.

Benefit/risk assessment

The CPMP acknowledged that a small palliative benefit in patients with GBM at first relapse or progression after surgery and radiotherapy with or without adjuvant chemotherapy has been demonstrated in one open study in which procarbazine acted as a comparator. Further data from randomised clinical trials would have been desirable. However, there is currently no other well-established treatment option for these patients with a short life expectancy. Furthermore, temozolomide has low and manageable toxicity and is administered orally without requiring hospitalisation.

In view of the antineoplastic activity in recurrent AA demonstrated in a non-comparative trial, the similarities of AA and GBM and the higher chemoresponsiveness of AA, it seems reasonable to conclude that the palliative effects of temozolomide in recurrent GBM can be extrapolated to AA.

Based on the available data on quality, safety and efficacy, the CPMP considered by consensus the benefit/risk profile of Temodal in the treatment of malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy to be favourable.

6. Update of Clinical Safety post-authorisation

- The following undesirable effects were included in the SPC in April 2002: pancytopenia, leukopenia, anaemia, allergic reactions (including anaphylaxis urticaria, angioedema, exanthema, erythroderma,) and erythema multiforme. The Package Leaflet was revised accordingly.

- The 5th PSUR of Temodal covering the period of 26 January 2001 to 25 January 2002 indicated an increased risk of bleeding disorders and infections assumed to temozolomide-induced thrombocytopenia and leukocytopenia. The MAH has updated section 4.8 of the SPC by describing these findings. Furthermore, the MAH has presented the undesirable effects in organ classes and has sorted them by observed frequency. The Package Leaflet was updated accordingly.

- Following the assessment of Temodal 6th PSUR the MAH has added information in section 4.8 (undesirable effects) addressing the potential occurrence of secondary tumours, in particular MDS and leukaemia, following treatment with temozolomide.
  In addition the MAH has added "opportunistic infections…" and "lymphopenia" under SPC 4.8, and instructions in the case of an overdose under 4.9 were strengthened. The Labeling and PL have been revised accordingly.
  In order to avoid the occurrence of "medication errors", dosing instructions had been clarified in the Package Leaflet.

7. Additional indication: Newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment

Glioblastoma multiforme (GBM) is the most common and most aggressive of the primary brain tumors in adults. It represents 15% to 20 % of all brain tumors and about 50 % of all gliomas. It is

highly malignant, infiltrates the brain extensively, and at times may become enormous before turning symptomatic.

The current World Health Organization (WHO) classification of primary brain tumors lists GBM as a Grade IV astrocytoma. GBM is slightly more common in men than in women; the male-to-female ratio is 3:2. While GBM occurs in all age groups, its incidence is increasing in elderly patients. A true increase in incidence of primary brain tumors exists, which cannot be explained by the aging population, better imaging techniques, or earlier detection at surgery.

GBM is an anaplastic, highly cellular tumor with poorly differentiated, round, or pleomorphic cells, occasional multinucleated cells, nuclear atypia, and anaplasia. Under the modified WHO classification, GBM differs from anaplastic astrocytomas (AA) by the presence of necrosis under the microscope.

The incidence of GBM is fairly constant worldwide. Among primary brain tumors, malignant astrocytomas are the most common in all age groups (however, brain metastases are more common). GBMs are the most common primary brain tumors in adults, accounting for 12-15% of intracranial tumors and 50-60% of primary brain tumors. GBM may develop de novo (primary GBM) or through secondary progression from a previously diagnosed low-grade or anaplastic glioma; most patients have primary GBM.

Morbidity is depending on the tumor location, progression, and pressure effects. The overall prognosis for GBM has changed little in the past 2 decades, despite major improvements in neuroimaging, neurosurgery, radiation treatment techniques, supportive care and new chemotherapy agents and regimens. Prognosis for GBM remains poor, the median survival is 9 to 12 months, the 2-year survival rates are between 8% and 12%.

The standard treatment of malignant gliomas includes maximum surgical resection, when feasible, followed by partial brain radiotherapy. Radiotherapy can be combined or followed by chemotherapy. Although clinical benefit of chemotherapy is only small, chemotherapy agents are used for the treament of GBM: Cytotoxic agents most commonly applied for chemotherapy are nitrosourea-based regimens such as BCNU (carmustine) and procarbazine, furthermore, vinca alkaloids, platinum compounds, cyclophosphamide, methotrexate are used.

3.2. Toxico-pharmacological

In vitro studies that explored the effect of temozolomide combined with X-irradiation on cell killing have shown the interaction was at least additive in 3 of 4 human tumor cell lines tested, with a strong potentiation seen in the D384 glioma line. Temozolomide also was shown to inhibit irradiation-induced glioma cell invasion in vitro.

3.3. Clinical aspects

Several clinical trials have already been performed to analyse the efficacy and safety of the treatment of patients with newly diagnosed GBM using radiotherapy and temozolomide as concomitant and subsequent monotherapy therapy. A summary is presented in table 1.

Table 1. Summary of Published Studies of Radiotherapy and Concomitant and subsequent monotherapy Temozolomide for the Treatment of Glioblastoma Multiforme

Reference (study design)	Histology / demographics	No. of Patients	Treatment	Median Survival (months)	1-Year Survival	2-Year Survival
Stupp (Phase 2, open-label)	new GBM / 39 M; 25 F median age=52 yr (range 24-70 yr)	64	RT+TMZ[a]	16 (11-21 95% CI)	58%	31% (36% 18 mon)
Lanzetta (Phase 2, open-label)	new GBM / 13 M; 8 F median age=44 yr (range 25-75 yr)	21	RT+TMZ[a]	15.7 (10.25-30.5 range)	58%	- (36% 18 mon)
Corsa (retrospective chart review)	GBM=93; AA=34; AO=3 / 74 M; 56 F mean age=57 yr (range 26-78 yr)	130	RT+TMZ[a] (n=65) 34=C+A 31=A only	16	-	-
			RT alone (n=65)	14	-	-
Athanassiou (Phase 3, randomized, open-label)	new GBM / na	110	RT+TMZ[b] (n=57)	-	55%	15%
			RT alone (n=53)	-	16%	0

a: Daily administration of TMZ (75 mg/m^2/day for 6 weeks) during radiotherapy, followed by monotherapy treatment with TMZ (150-200 mg/m^2/day x 5 days every 28 days for 6 cycles).

b: Daily administration of TMZ (75 mg/m^2/day for 6 weeks) during radiotherapy, followed by monotherapy treatment with TMZ (150 mg/m^2 days 1-5 and days 15-19 every 28 days for 6 cycles).

AA = anaplastic astrocytoma; AO = anaplastic oligodendroglioma; GBM = glioblastoma multiforme; RT = radiotherapy; TMZ = temozolomide; C+A = concomitant and monotherapy therapy; A only = monotherapy only.

Clinical Pharmacology

Temodal is an oral cytotoxic alkylating agent, a prodrug which undergoes nonenzymatic hydrolysis at physiological pH to its active metabolite 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC), as same as dacarbazine (DTIC). The cytotoxicity of temozolomide is thought to be due primarily to alkylation of DNA.

Temozolomide can cross the blood brain barrier with a concentration in the cerebral spinal fluid of approximately 20% to 40% of that found in plasma.

II

III   Dosage

In Phase 1 studies, the maximum tolerated dose (MTD) of temozolomide administered for days 1-5 of a 28-day cycle was 200 mg/m^2, with myelosuppression being the dose-limiting toxicity; for patients with extensive prior chemotherapy, the MTD was 150mg/m^2 daily for days 1-5 of a 28-day cycle. The MTD for the extended-dose schedule was found to be 85 mg/m^2/day over 42 days, with a recommended starting dose for newly diagnosed patients receiving concomitant RT of 75 mg/m^2/day for further investigation of temozolomide for the treatment of malignant gliomas.

The dosage recommended for relapsed glioma (one of the licensed indications) is 150 mg/m^2 for the initial cycle, 200 mg/m^2 for the second and subsequent cycles for pretreated patients. Chemotherapy-naive patients can begin with the higher dosage (200 mg/m^2) from the first cycle. Duration of 1 cycle is 28 days and temozolomide is given orally the first 5 days, then after 23 days a new cycle is to begin if no haematological occurs.

IV Clinical Efficacy

V

VI Main study

One clinical trial, (EORTC 26981/22981) was performed to prove the efficacy and safety for the broadened indication for temozolomide, in the treatment of patients with newly diagnosed GBM, as concomitant therapy to radiotherapy followed by monotherapy in comparison to radiotherapy alone.

This was a controlled, open-label, randomised multicenter phase 3 trial which included 573 patients (ITT population), 287 in the experimental arm (Radiotherapy + temozolomide: RT+TMZ) and 286 patients in the control arm (radiotherapy alone: RT). 85 study centers throughout Europe, Canada and Australia were involved. The studied period was from 17th August 2000 to 14th April 2004. The applicant declares that the trial was conducted in accordance with principles of Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice and local laws and regulations.

Objectives and endpoints

The primary objective was to determine the efficacy of temozolomide administration as a concomitant treatment to radiotherapy followed by monotherapy treatment for up to 6 cycles with respect to overall survival in subjects with newly diagnosed glioblastoma multiforme compared to radiotherapy alone.

Secondary objectives were to compare the two treatment arms with respect to toxicity profile, progression free survival and quality of life.

Overall survival was the primary efficacy endpoint.

Duration of survival was defined as time interval between the date of randomisation and the date of death. Subjects who were still alive when last traced were censored at the date of last follow up.

Progression free survival was the secondary endpoint. Progression free survival was defined as radiological, neurological or clinical progression, whatever occurs first, and as the time interval between the date of randomisation and the date of disease progression or death, whichever comes first. If neither event has been observed then the patient is censored at the date of the last follow-up examination.

The treatment schedule for both arms is summarized in the table 2 below.

Table 2. Treatment schedule / Dose regimens in trial EORTC 26981/22981:

	Experimental Arm: RT+TMZ	**Control Arm: RT Only**
0. Radiotherapy	**Focal Radiotherapy** 6 weeks, 60 Gy in 30 day´s fractions of 2 Gy/Day, 5 days a week	**Focal Radiotherapy** 6 weeks, 60 Gy in 30 day´s fractions of 2 Gy/Day, 5 days a week
1. Concomitant therapy	Concomitant with Radiotherapy: **Temozolomide:** 75 mg/m^2 orally daily for 6 weeks (42 days) and PCP prophylaxis	**VII No concomitant therapy**
2. Monotherapy	4 weeks after last Radiotherapy **Temozolomide:** 6 Cycles *Cycle 1:* 150mg/m^2 daily for 5 days every 28 days *Cycles 2 through 6:* 200mg/m2 daily for 5 days every 28 days	**VIII No monotherapy**
3. Follow up: Salvage therapy after disease progression	- Chemotherapy: Temozolomide or CCNU or Procarbazine or Vincristine or BCNU - Surgery	- Chemotherapy: Temozolomide or CCNU or Procarbazine or Vincristine or BCNU - Surgery

IX

Randomisation

Randomisation was based on the local pathology review. A central pathology review was performed either jointly by the three EU neuropathologists or by the one Canadian neuropathologist.

Treatment allocation was done centrally directly on the EORTC Data Center Computer through the INTERNET network or by telephone to the EORTC Data Center.

Stratification

The protocol-specified prognostic factors for stratification at randomisation were: age (< 50 years vs ≥ 50 years), WHO-ECOG-performance status (0-1 vs.2) and extent of resection at surgery (biopsy only vs. complete/incomplete resection). Stratification by age was not conducted „due to an operational oversight". Stratification was also made by study center.

X   Interim analysis
An Independent Data Monitoring Committee (IDMC) was established to meet when the interim analyses or the final analysis had been performed by the statisticians to consider all aspects of the trial and, if necessary, to recommend changes in the conduct of the trial.
Two interim analyses were planned, at least only the first was performed in concordance with the study protocol after 236 patients were accrued and only 21 deaths had occurred. The independent committee decided to continue the trial without changes.

XI   Statistical evaluation
Kaplan-Meier estimates of the survival functions were obtained for the primary (OS) and secondary (PFS) endpoint. Differences between both treatment arms were compared using 2-sided log-rank test. The primary analysis was conducted on the intent-to-treat population (ITT). Subjects were analysed according to the treatment they were assigned to receive. In order to quantify the treatment effect, for each endpoint an unadjusted overall hazard ratio (HR) and its 95% 2-sided confidence interval (95% CI) were computed using the Cox proportional hazards regression model (Cox regression) with treatment arm as the sole explanatory variable. Furthermore, a protocol-available population was defined and the results were compared to those obtained from the ITT population.

Results

XII   Patient characteristics
Baseline demographic data:
103 female and 185 male patients were included in the trial arm (RT+TMZ) and 109 female and 175 male patients were included in the RT Only arm. Most patients were 50 years or older and had a performance status of 0 or 1. Median age of patients was 55 (range 18-70) and 56 (range 23-70) years in the trial and in the control arm. Baseline disease characteristics are resumed in table 3.

Concomitant medication
Pneumocystis carinii prophylaxis during the concomitant phase was mandatory in all patients receiving concomitant daily temozolomide regardless of lymphocyte count. If lymphopenia occurred, the PCP prophylaxis was continued until lymphopenia recovered to <= grade 1. Antiemetic therapy was used for patients receiving temozolomide. Corticosteroid usage was similar in both trial groups during the trial period. Antiepileptic agents like valproic acid were allowed to be used during the trial.

	RT Only n=285	RT+TMZ n=288
Histology, n (%)		
Central pathology review		
Eligible	228 (80)	222 (77)
GBM	200 (70)	188 (65)
GBM (giant cell)	2 (1)	4 (1)
GBM (with oligo comp)[a]	25 (9)	27 (9)
GBM (gliosarcoma)	1 (<1)	3 (1)
Ineligible	11 (4)	13 (5)
Astrocytoma	3 (1)	1 (<1)
Oligodendroglioma	5 (2)	3 (1)
Oligoastrocytoma Grade 3	1 (<1)	3 (1)
Other	2 (1)	6 (2)
No central pathology review/Undiagnosable	46 (16)	53 (18)
Type of Surgery, n (%)		
Brain biopsy only	46 (16)	47 (16)
Brain debulking (partial resection)	126 (44)	125 (43)
Brain debulking (total resection)	113 (40)	116 (40)
Weeks from Prior Procedure to Randomization		
Subjects with biopsy only, n (%)	46 (16)	47 (16)
Mean (wk)	3.9	3.6
Median (wk)	4.0	3.4
Range (wk)	1.9 - 6.0	1.1 - 5.9
Subjects with debulking, n (%)	239 (84)	241 (84)
Mean (wk)	4.0	4.3
Median (wk)	4.1	4.3
Range (wk)	0.0 - 6.1	1.0 - 6.0
WHO Performance Status, n (%)		
0	112 (39)	116 (40)
1	139 (49)	136 (47)
2	34 (12)	36 (13)

XIII Efficacy Results

The hazard ratio for overall survival was 1.59 (95% CI for HR=1.33-1.91). Kaplan Meier estimates of the survival distributions show an improvement achieved with RT + TMZ compared to RT alone. The median overall survival is 14.6 months for the trial arm and 12.1 months for the control arm. The one-year-survival was 61% for the RT + TMZ arm and 50% for the RT Only arm. The most significant results were obtained for the 2 year survival which was 26% for the RT + TMZ arm and 10 % for the RT Only arm.

Table 4.

Summary of Events, Censoring and Hazard-Ratios by Specified Time Intervals (ITT Population)

Time Interval (Months)	RT Only				RT+TMZ				Hazard Ratio (KM)[b]
	Censored	Dead	Cont.	Cum(%) Dead[a]	Censored	Dead	Cont.	Cum(%) Dead[a]	
>0–4	0	29	257	10	2	24	261	8	1.22
>4–8	1	45	211	26	0	36	225	21	1.27
>8–12	0	67	144	50	0	51	174	39	1.38
>12–16	1	55	88	69	3	44	127	55	1.48
>16–20	1	41	46	83	4	35	88	67	1.62
>20–24	7	16	23	90	15	16	57	74	1.70
>24–28	11	7	5	95	13	10	34	78	1.91
>28–32	3	1	1	96	16	3	15	81	1.94
>32	1	0	0	NI	15	0	0	NI	NI

a   Cumulative percent was calculated using the Kaplan-Meier method.

b: Kaplan-Meier (KM) estimates of hazard ratios at endpoints of intervals.

RT = radiotherapy, TMZ = temozolomide, Cont. = continued, Cum = cumulative, NI = not interpretable.

**Table 5. Summary of Efficacy Results for EORTC Trial 26981/22981**

Study Number / Histology	Treatment (No. of Subjects)	Dosage	Progression-Free Survival Median (months)	Overall Survival		
				Median (months)	1-Year (%)	2-Year (%)
EORTC 26981/22981 GBM, newly diagnosed	RT+TMZ (287)	Radiotherapy 60 Gy[a] + TMZ 75 mg/m^2/day po daily x 42 days, then TMZ 150-200 mg/m^2/day po 5 days/28 days for 6 cycles (4 weeks after RT)	6.90	14.59	61%	26%
	RT Only (286)	Radiotherapy 60 Gy[a]	4.98	12.09	50%	10%
			P <0.0001	P <0.0001		
		Hazard Ratio (95% CI)	1.85 (1.55-2.20)	1.59 (1.33-1.91)		

a: Radiotherapy was administered in 30 daily fractions of 2 Gy 5 times per week for 6 weeks.

EORTC = European Organisation for Research and Treatment of Cancer ; GBM = glioblastoma multiforme; po = *per os* (orally); RT = radiotherapy; TMZ = temozolomide.
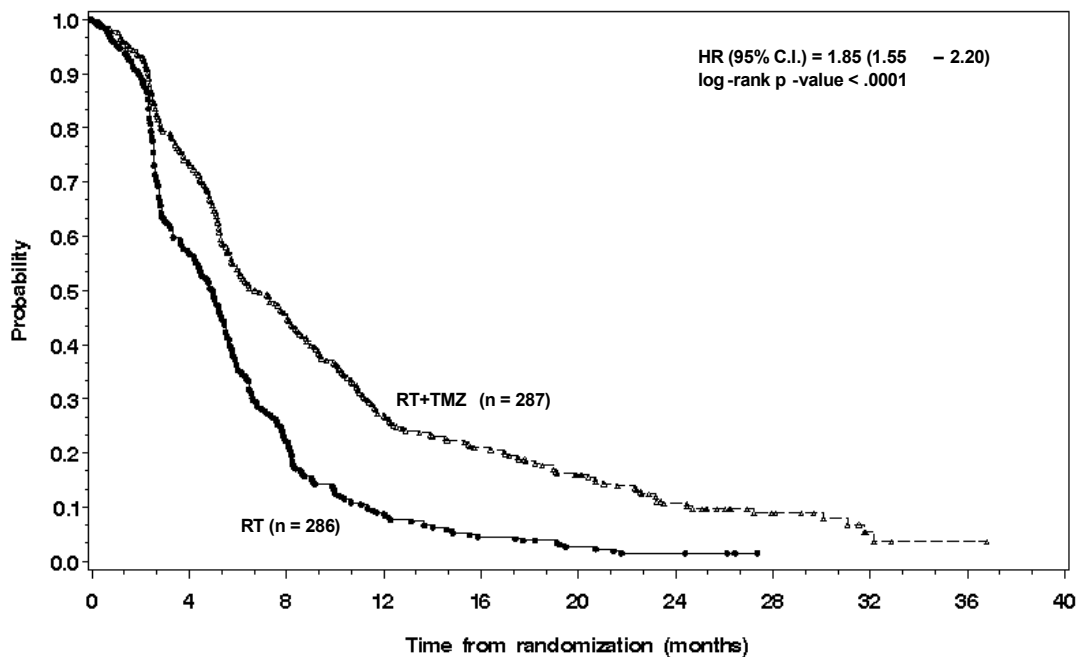
Kaplan-Meier Curves for Overall Survival

Figure 1: (ITT Population: EORTC Trial 26981/22981)
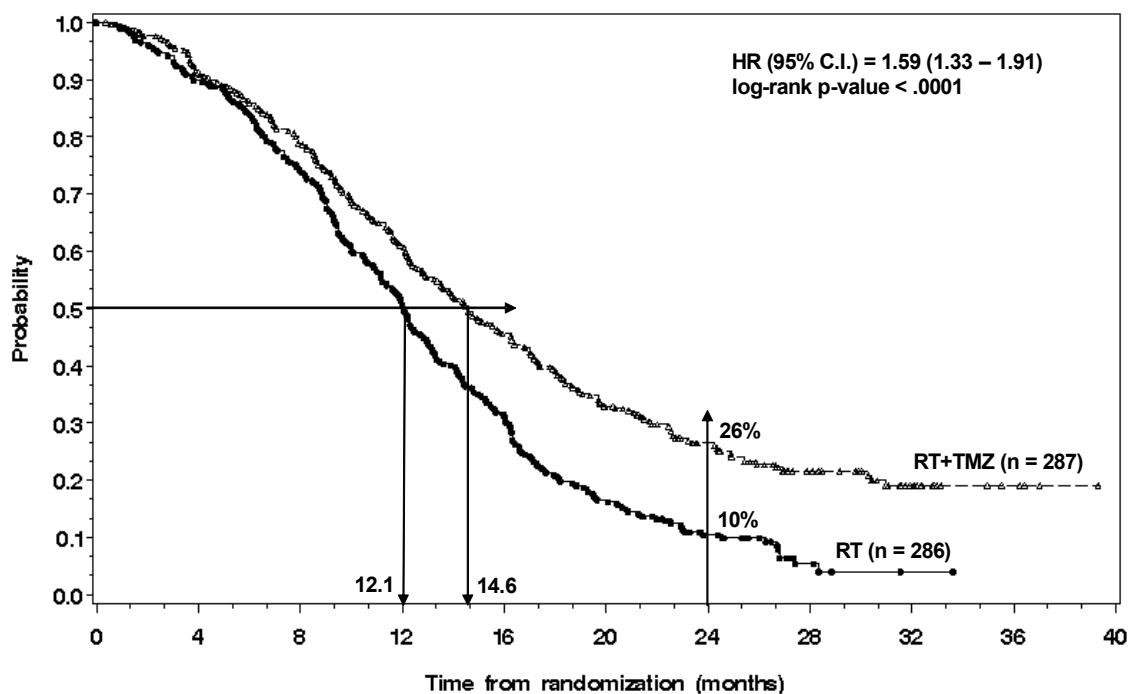
Median progression free survival was 6,9 months for patients of the trial arm and 4,98 months for patients of the control arm. The HR for progression-free survival was 1.85 (95% CI for HR = 1.55 to 2.20).

Figure 2. Kaplan-Meier Estimates for Progression-Free Survival (ITT Population)

The significant prolongation of progression-free survival on RT+TMZ compared to RT Only is depicted by the Kaplan-Meier curves (Figure 2). The benefit of RT+TMZ treatment over RT Only became apparent early (within 4 months) and was evident for more than 20 months.

Clinical studies in special populations / Examination of subgroups

20/25

The EORTC trial showed improvement for temozolomide in rather all subgroups. Those patients classified having ECOG performance status 2 showed less or no improvement. (see figure below) Overall Survival in Subgroups: Hazard Ratios with 95% Confidence Intervals (EORTC Trial 26981/22981). Numbers in parentheses indicate numbers of subjects (RT Only/RT+TMZ).

Numbers in parentheses indicate numbers of subjects (RT / RT+TMZ)
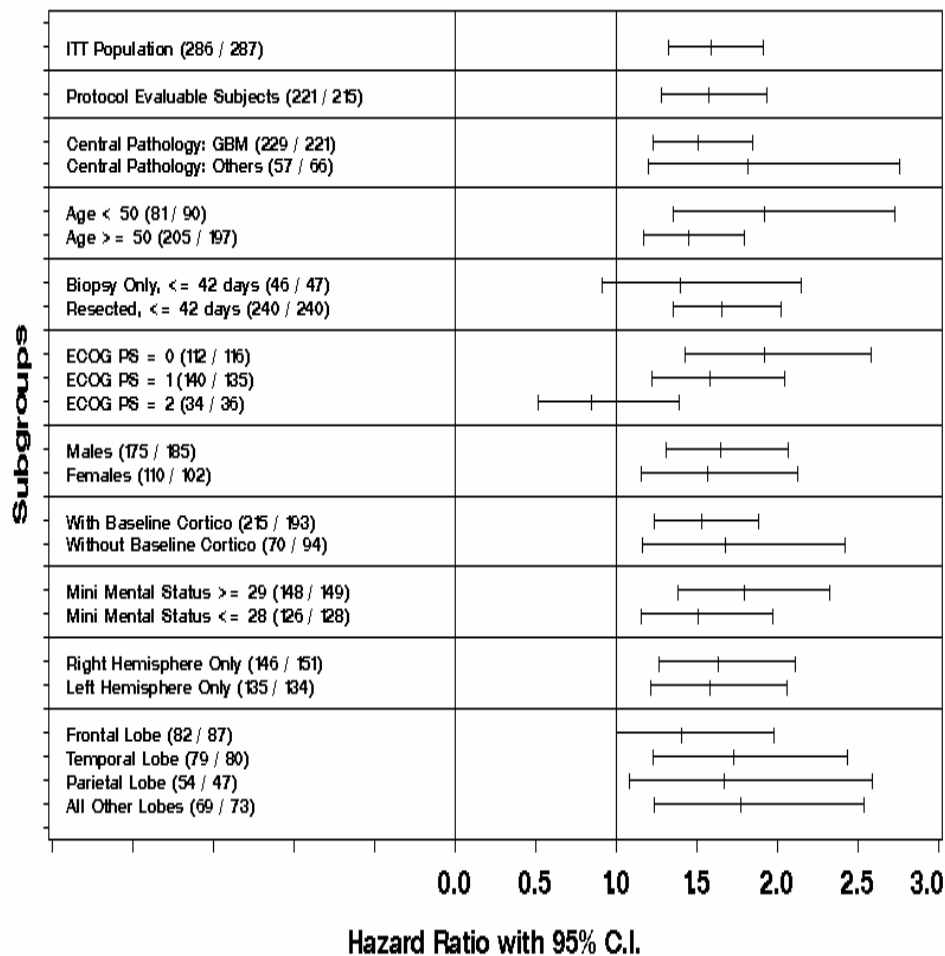
XIV Discussion of clinical pharmacology

The EORTC trial 26981/2298 is a well designed and adequately sized study. However, this study does not distinguish the relative contribution of drug administration during radiotherapy from the contribution of monotherapy, as the ideal design would have been a 4 arm trial (better still a 2x2 factorial). Nevertheless, the results show significant and consistent, thus convincing efficacy, supporting the beneficial effect of temozolomide administered concomitantly with radiotherapy followed by monotherapy in the treatment of patients with newly diagnosed GBM. Superior overall survival and progression-free survival compared with treatment with radiotherapy alone have been demonstrated. The median survival improvement from 12.09 to 14.59 months is less impressive, although highly significant, than the more than double (26 vs. 10%) survival at 2 years or more. According to the Kaplan-Meier plots the survival curves diverge during approximately 28 months.

Patients outcome was assessed for patients with brain biopsy only and with debulking therapy. Following a CHMP request the MAH provided additional data on the outcome of patients with debulking therapy with either partial resection or with complete resection demonstrating that treatment with temozolomide concomitant to radiotherapy (RT + TMZ) and subsequent monotherapy in newly diagnosed glioblastoma multiforme (GBM) subjects was superior to radiotherapy alone (RT Only) with respect to overall survival across all resected patients regardless of the extent of resection.

The overall survival results is consistent in all subgroups analysed with the exception of those with a poor performance status (ECOG PS=2). It raises some concern whether this subgroup should be

treated with temozolomide. However no unacceptable safety issues were identified in this group of patients.

Comparison of the two treatment arms with respect to quality of life was one of the secondary objectives of the study. However quality of life was not assessed by the MAH during the trialQuality of life data of temozolomide such as assessed in the EORTC Trial 26981/22981 should be provided and be in support of the reported improvement in progression-free and overall survival. A small negative impact of quality of life was seen in patients treated with combined radio- and chemotherapy. A positive influence on QOL could not be proven. However, a benefit in overall survival is important in the treatment of glioblastoma multiforme with a very limited prognosis. The final report will be provided by the applicant when it is accepted for publication

XV Clinical Safety

Patient exposure

More than 80% of patients received between >90 and 120 % of the planned dosage of temozolomide (% of 75mg/m^2/day for 42 days) during the concomitant phase.

Of the 237 patients who received > 90% of the intended dose intensity, 22 subjects had to interrupt due to toxicity or for reasons unrelated to study drug.

3.1   Temozolomide Exposure, Concomitant phase

		XVI RT+TMZ (N=288)
XVII Number (%) of Subjects	Treated Not treated	282 (97.9) 6 (2.1)
XVIII Relative Dose intensity (% of 75mg/m^2/day for 42 days) in (%)	≤70% >70-90% >90-110% >110-120% >120%	19 (6.6) 26 (9.0) 198 (68.8) 37 (12.8) 2 (0.7)
XIX Days Dosed	Median Range	42.0 4.0-55.0

RT+TMZ= radiotherapy plus temozolomide, N(%)= Number (percentage) of subjects

XX Extent of exposure to radiotherapy

Of the 285 subjects int the RT Only arm, 256 subjects (90%) received between >90% and 110% of the intended RT dose, 22 subjects (8%) received ≤ 90% of the intended dose and 7 (3%) subjects did not receive radiotherapy. Reasons for subjects receiving ≤ 90% was premature discontinuation due to worsening clinical status or radiological progression. Reasons for not receiving radiotherapy were subject´s refusal (N=5) and disease progression and other reason (N=1 each).

XXI Temozolomide Exposure, Monotherapy Phase

Generally more than 70% of subjects received temozolomide approximately every 28 days according to the protocol.

Across all 6 cycles, the monotherapy temozolomide dose was reduced for 4% to 9% of the subjects and dosing was delayed for 13% to 25% of the subjects. During cycles 1 and 2, the dose reductions and delays were primarily for nontreatment related reasons, such as physician subject, and/or institutional errors, administrative issues, subject's personal reasons and subject's health, During cycles 3-6, the percentage of subjects with dose reductions and delays were primarily due to hematological toxicity. While the percentage of dose delays due to hematological toxicity increased in

the later cycles, the protocol-specified dose could be delivered on schedule for the majority of subjects during the monotherapy phase.

Table 30 Temozolomide Dosing Status by Cycle During Adjuvant Phase

Protocol No. P00458

	Number (%) of Subjects					
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Received Adjuvant TMZ[a]	224	201	179	133	118	106
Adjuvant TMZ Reduced	8 (3.6%)	16 (8.0%)	16 (8.9%)	7 (5.3%)	5 (4.2%)	5 (4.7%)
Hematological toxicity	3 (1.3%)	6 (3.0%)	9 (5.0%)	4 (3.0%)	3 (2.5%)	4 (3.8%)
Non-hematological toxicity	0	1 (0.5%)	5 (2.8%)	1 (0.8%)	1 (0.8%)	0
Both hematological and non-hematological toxicity	0	0	1 (0.6%)	0	0	0
Nontreatment related	5 (2.2%)	9 (4.5%)	1 (0.6%)	2 (1.5%)	0	1 (0.9%)
Unknown	0	0	0	0	1 (0.8%)	0
Adjuvant TMZ Delayed	50 (22.3%)	26 (12.9%)	45 (25.1%)	24 (18.0%)	26 (22.0%)	19 (17.9%)
Hematological toxicity	8 (3.6%)	8 (4.0%)	27 (15.1%)	15 (11.3%)	13 (11.0%)	9 (8.5%)
Non-hematological toxicity	6 (2.7%)	3 (1.5%)	2 (1.1%)	0	0	1 (0.9%)
Both hematological and non-hematological toxicity	0	0	2 (1.1%)	0	0	1 (0.9%)
Nontreatment related	35 (15.6%)	13 (6.5%)	13 (7.3%)	8 (6.0%)	12 (10.2%)	8 (7.5%)
Unknown	1 (0.4%)	2 (1.0%)	1 (0.6%)	1 (0.8%)	1 (0.8%)	0

a: Two subjects received 7 cycles of adjuvant temozolomide.
TMZ = temozolomide.
Data Source: Section 14.3.5.3.1.

Data Source: Section 14.3.5.3.1.

Adverse events

Adverse events during the Concomitant Phase

Adverse events were reported in 91% and 92 % of the subjects in the RT Only and RT+TMZ arms, respectively. Severe/life threatening events were reported in 26% and 28% of the subjects in the RT Only and RT+TMZ arms, respectively.

The most frequently reported adverse events and their incidence in the RT Only and RT +TMZ arms respectively were: alopecia (63% vs. 69%), fatigue, (49% vs. 54 %), nausea (16% vs. 36%), vomiting (6% vs. 20 %), headache (17% vs. 19%), rash (15% vs. 19%), anorexia (9% vs. 19%) and constipation (6% vs. 18%).

Severe /life-threatening AEs were reported infrequently during the concomitant phase. The most common, with their incidence in the RT Only and RT+TMZ arms, respectively, were: fatigue (5% vs. 7%), convulsions (3% vs. 3%), thrombocytopenia (0 vs. 3%) and headache (4% vs. 2%).

Adverse events during the Monotherapy phase

Adverse events were reported in 92% of the patients during the monotherapy phase, with 37% reporting severe/life-threatening events, consistent with the safety profile seen in the concomitant phase.
Most adverse events were mild or moderate in severity (CTC grade 1 or 2). The most common AEs were: fatigue: (61%), alopecia (55%), nausea (49%), vomiting (29%), anorexia (27%) headache (23%), constipation (22%), rash (13%), convulsions (11%) and diarrhea (10%).

The most common severe/life-threatening AEs were: fatigue (9%), headache (4%), thrombocytopenia (4%), convulsions (3%), infection (3%), weakness (2%), confusion (2%), dysphasia (2%), hemiparesis (2%), neutropenia (2%), vomiting (2%) and deep venous thrombosis NOS (2%).

Adverse events with Temozolomide for the Concomitant and Monotherapy Phases Combined

Most subjects in the RT+TMZ arm reported AEs.
Considering the temozolomide concomitant and monotherapy treatment, for both treatment phases together, the most frequent treatment-related adverse events were alopecia (72%), fatigue (71%), nausea (57%), vomiting (37%), anorexia (32%), headache (30%), constipation (30%), rash (26%),

convulsions (13%), diarrhea (13%), stomatitis (13%), blurred vision (11%), and thrombocytopenia (10%).

Additionally, 49% of subject reported severe/life-threatening AEs. The most common of these AEs were fatigue (13%), convulsions (6%), headache (5%) and thrombocytopenia (5%).

Two confirmed cases of Pneumocystis carinii pneumonia (PCP) were noted, one in each treatment arm. Also two possible cases of PCP were noted, one in both arms.

Neutropenia Grad 3/4 based on AE and/or laboratory results occurred in 8% of the subjects in the RT+TMZ arm. Thrombocytopenia Grade 3/4 based on AE and/or laboratory results, occured in 14 %: No subjects in the RT Only arm reported neutropenia or thrombocytopenia Grade 3 or 4. Lymphocyte counts were not collected.

Serious adverse events and deaths

Of the 573 patients randomized to the pivotal trial, 480 subjects died at time of database lock; most of the subjects had died due to disease progression. In six subjects treated with temozolomide, death was attributed by the investigators to, or temporally associated with, serious adverse events (SAEs) considered at least possibly related to temozolomide, and occurred within 30 days of stopping therapy. These included pulmonary infection, respiratory insufficiency, aspiration pneumonitis and thrombocytopenia, pneumonia and coma, decreased consciousness and pneumonia. Thrombosis in the leg and a lung embolism were considered by SPRI to be possibly contributory in an additional patient's death.

Discontinuations due to hematological toxicity were observed in 0,4% (N=1) of RT Only treated patients and in 9% (N=26) of RT + TMZ treated patients (5,2% for hematological and 3,8% for non-hematological toxicity).

XXII Laboratory findings

Neutropenia and thrombocytopenia are the dose-limiting toxicities for temozolomide. When the laboratory results and reports for adverse events were combined, Grade 3 and Grade 4 neutrophil abnormalities, including neutropenic events were observed in 8% of patients and Grade 3 or grade 4 platelet abnormalities, including thrombocytopenic events were observed in 14% of patients treated with temozolomide during the trial.

Elevated SGPT level occurred with an incidence of 5% in the RT+TMZ arm across the concomitant and monotherapy phases; however, increases in liver transaminases were infrequent in the relapsed glioma studies included in the original marketing application. During the concomitant phase of the EORTC study, the incidence of elevated SGPT level was 4% in the RT+TMZ arm compared with 2% in the RT Only arm. Grade 3/4 "liver function abnormalities" in the RT+TMZ arm were more common during the concomitant phase (3%) than during the monotherapy phase (1%). In the RT Only arm, there was one subject with a Grade 3 "liver function abnormality" (elevated SGPT level). In addition to chemotherapy and radiotherapy, patients in the RT+TMZ arm were receiving multiple concomitant medications, including PCP prophylaxis during the concomitant phase and antiemetic therapy during the monotherapy phase. Some of these concomitant medications are also associated with abnormal liver function tests, therefore conclusions regarding the relationship of these laboratory abnormalities to temozolomide treatment are difficult.

XXIII Safety in special populations

No differences were observed concerning influence of age of patients on the safety of temozolomide. Among subjects receiving RT+TMZ, more female subjects than male subjects reported alopecia (78% vs 64%), nausea (50% vs 29%), anorexia (29 vs 14%), vomiting (25% vs 17%) and radiation injury (12% vs 4%).

Discussion of safety

The safety profile of temozolomide is well known from other clinical trials and from the clinical experience of treatment of patients with GBM showing recurrence or progression. The overall pattern of events during the monotherapy phase was consistent with the known safety profile of temozolomide.

The dose-limiting factor for temozolomide is hematological toxicity. No medical important new safety findings were made during the trial. The dosage used for the monotherapy treatment phase during the trial is consistent with the recommended dosage for the licensed indication, treatment of advanced GBM. It was to be expected that frequency of adverse events was higher in the RT+TMZ arm than in the RT Only arm. PCP prophylaxis was required during the concomitant phase and is recommended when temozolomide is administered with radiotherapy. This is already reflected in Section 4.4 of the SPC.

Benefit – risk assessment

The results of the EORTC trial have demonstrated a significant efficacy for temozolomide administrated as concomitant and subsequent monotherapy for the treatment of patients suffering from newly diagnosed GBM.

Concerning the investigated clinical endpoints of overall survival and progression free survival, clinical benefit was shown for the RT + TMZ arm in comparison to the RT Only arm: The 2-year survival for the trial arm was 26% in comparison to 10% for the control arm. Median progression free survival was improved in the trial arm: 6,9 months for patients with RT + TMZ treatment and 4,98 months for patients with RT Only therapy. For the indication of GBM with a poor prognosis, this is a small but relevant clinical benefit. Side effects and toxicity of treatment are well known and are acceptable.