III. SCIENTIFIC DISCUSSION

3.1. Introduction

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.

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.

Clinical Efficacy

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	**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	**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

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.

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.

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.

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:

Protocol No. P00458

	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)

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.

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)	Treatment								Hazard Ratio (KM)[b]
	RT Only				RT+TMZ				
	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

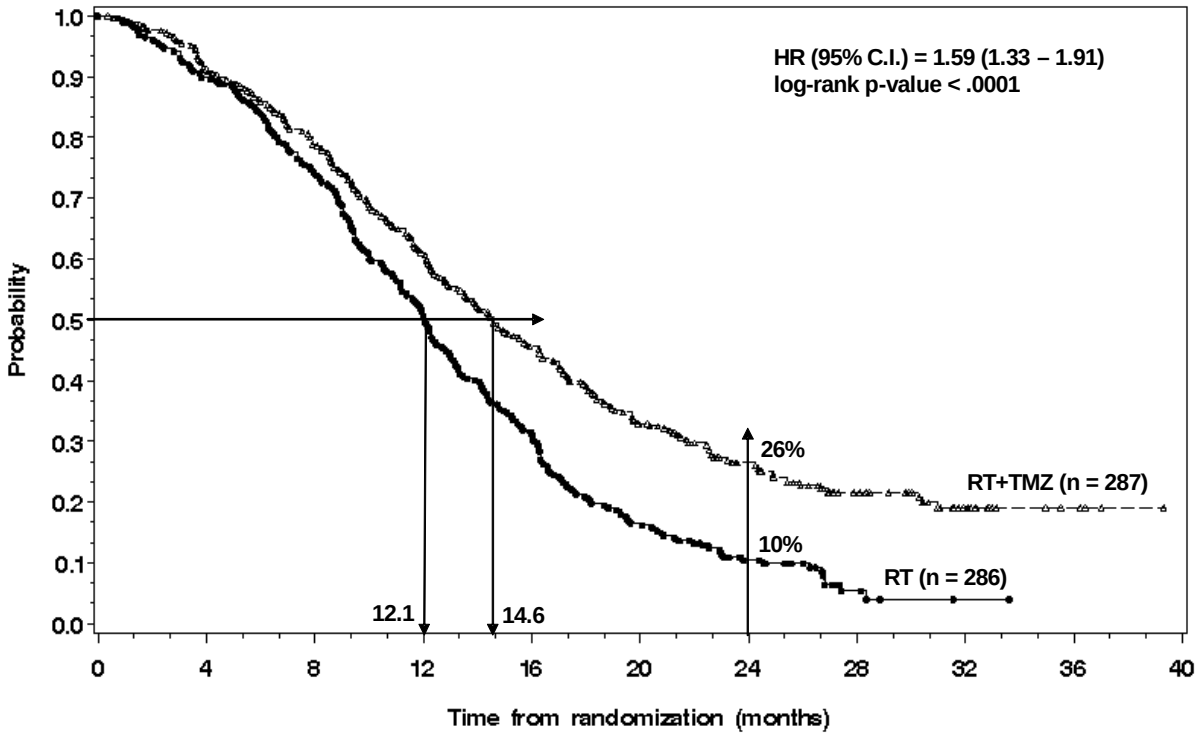
Study Number / Histology	Treatment (No. of Subjects)	Dosage	Progression-Free Survival Median (months)	Overall Survival		
				Median (months)	1-Year (%)	2-Year (%)
EORTC 26981/22981 GBM, newly diagnosed	RT+TMZ (287)	Radiotherapy 60 Gy[a] + TMZ 75 mg/m^2/day po daily x 42 days, then TMZ 150-200 mg/m^2/day 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.

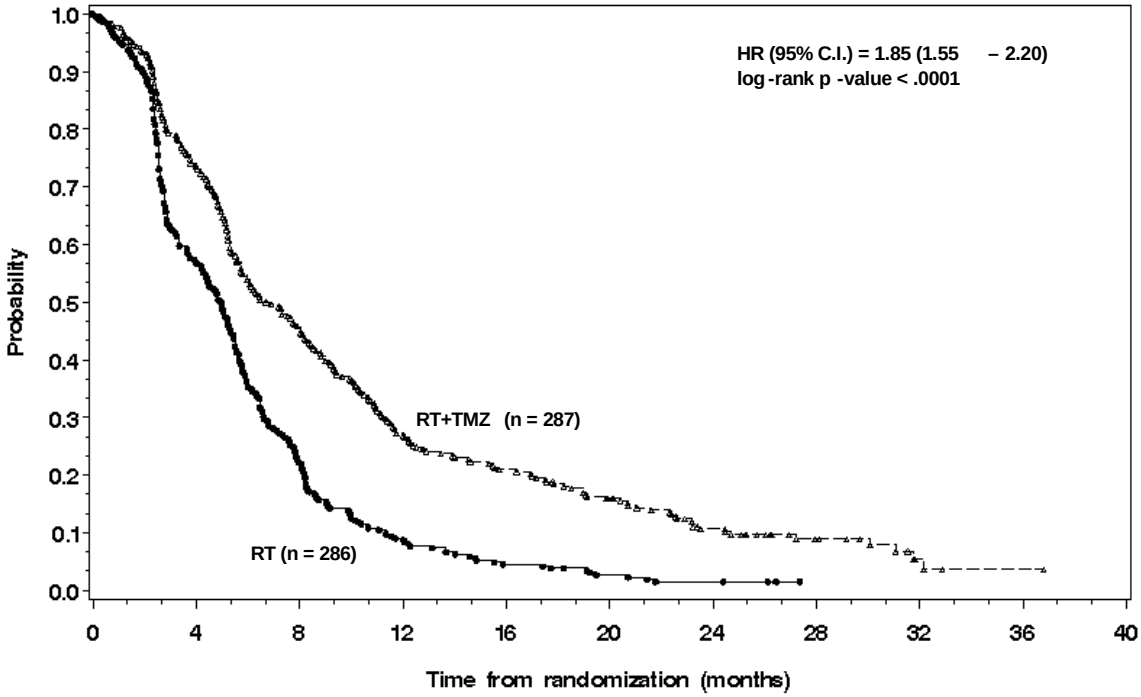
Kaplan-Meier Curves for Overall Survival

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).

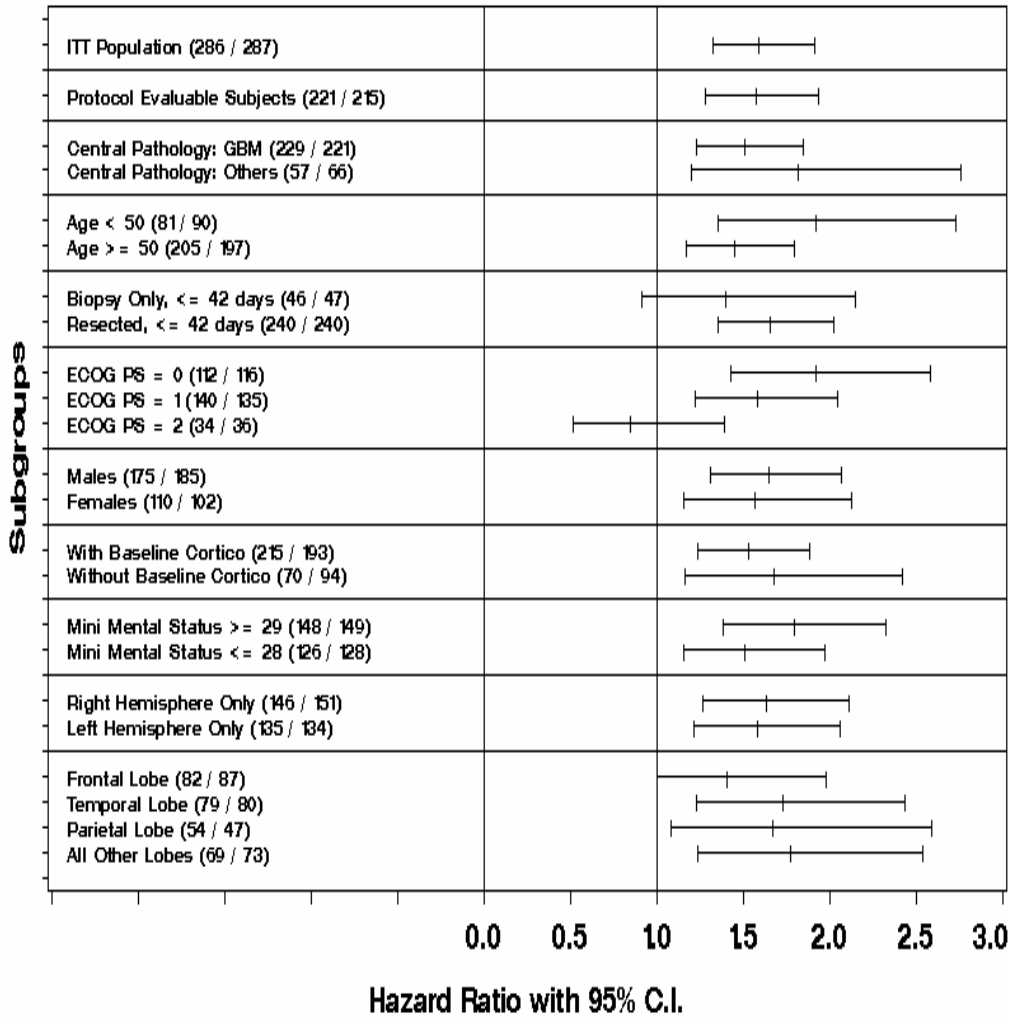
Figure 2. Kaplan-Meier Estimates for Progression-Free Survival (ITT Population)



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

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) .



Discussion of clinical efficacy

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

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.

Temozolomide Exposure, Concomitant phase

		RT+TMZ (N=288)
Number (%) of Subjects	Treated Not treated	282 (97.9) 6 (2.1)
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)
Days Dosed	Median Range	42.0 4.0-55.0

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

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).

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.

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.

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).

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.

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.