

patients with newly-diagnosed glioblastoma multiforme demonstrated a statistically significant improvement in overall survival (OS) compared with RT alone (Figure 1).

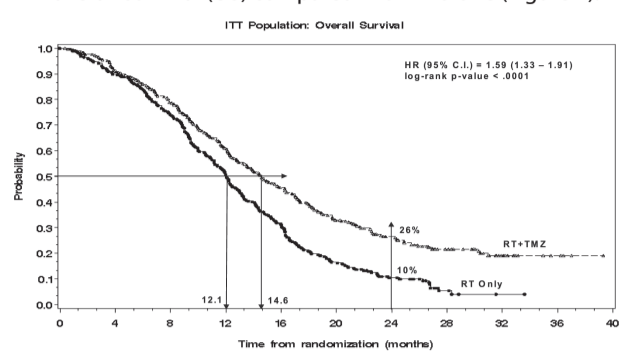


Figure 1 Kaplan-Meier curves for overall survival (intent-to-treat population)

The results from the trial were not consistent in the subgroup of patients with a poor performance status (WHO PS=2, n=70), where overall survival and time to progression were similar in both arms. However, no unacceptable risks appear to be present in this patient group.

Recurrent or progressive malignant glioma

Data on clinical efficacy in patients with glioblastoma multiforme (Karnofsky performance status [KPS] \geq 70), progressive or recurrent after surgery and RT, were based on two clinical trials with oral TMZ. One was a non-comparative trial in 138 patients (29 % received prior chemotherapy), and the other was a randomised active-controlled trial of TMZ vs procarbazine in a total of 225 patients (67 % received prior treatment with nitrosourea based chemotherapy). In both trials, the primary endpoint was progression-free survival (PFS) defined by MRI scans or neurological worsening. In the non-comparative trial, the PFS at 6 months was 19 %, the median progression-free survival was 2.1 months, and the median overall survival 5.4 months. The objective response rate (ORR) based on MRI scans was 8 %.

In the randomised active-controlled trial, the PFS at 6 months was significantly greater for TMZ than for procarbazine (21 % vs 8 %, respectively – chi-square $p = 0.008$) with median PFS of 2.89 and 1.88 months respectively (log rank $p = 0.0063$). The median survival was 7.34 and 5.66 months for TMZ and procarbazine, respectively (log rank $p = 0.33$). At 6 months, the fraction of surviving patients was significantly higher in the TMZ arm (60 %) compared with the procarbazine arm (44 %) (chi-square $p = 0.019$). In patients with prior chemotherapy a benefit was indicated in those with a KPS \geq 80.

Data on time to worsening of neurological status favoured TMZ over procarbazine as did data on time to worsening of performance status (decrease to a KPS of < 70 or a decrease by at least 30 points). The median times to progression in these endpoints ranged from 0.7 to 2.1 months longer for TMZ than for procarbazine (log rank $p < 0.01$ to 0.03).

Recurrent anaplastic astrocytoma

In a multicentre, prospective phase II trial evaluating the safety and efficacy of oral TMZ in the treatment of patients with anaplastic astrocytoma at first relapse, the 6 month PFS was 46 %. The median PFS was 5.4 months. Median overall survival was 14.6 months. Response rate, based on the central reviewer assessment, was 35 % (13 CR and 43 PR) for the intent-to-treat population (ITT) n=162. In

43 patients stable disease was reported. The 6-month event-free survival for the ITT population was 44 % with a median event-free survival of 4.6 months, which was similar to the results for the progression-free survival. For the eligible histology population, the efficacy results were similar. Achieving a radiological objective response or maintaining progression-free status was strongly associated with maintained or improved quality of life.

Paediatric population

Oral TMZ has been studied in paediatric patients (age 3-18 years) with recurrent brainstem glioma or recurrent high grade astrocytoma, in a regimen administered daily for 5 days every 28 days. Tolerance to TMZ is similar to adults.

5.2 Pharmacokinetic properties

TMZ is spontaneously hydrolyzed at physiologic pH primarily to the active species, 3-methyl-(1H-imidazo[4,5-b]pyridin-2-yl)imidazole-4-carboxamide (MTIC). MTIC is spontaneously hydrolyzed to 5-aminoimidazole-4-carboxamide (AIC), a known intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA mainly at the O⁶ and N⁷ positions of guanine. Relative to the AUC of TMZ, the exposure to MTIC and AIC is ~ 2.4 % and 23 %, respectively. *In vivo*, the $t_{1/2}$ of MTIC was similar to that of TMZ, 1.8 hr.

Absorption

After oral administration to adult patients, TMZ is absorbed rapidly, with peak concentrations reached as early as 20 minutes post-administration (mean time between 0.5 and 1.5 hours). After oral administration of ¹⁴C-labelled TMZ, mean faecal excretion of ¹⁴C over 7 days post-dose was 0.8 % indicating complete absorption.

Distribution

TMZ demonstrates low protein binding (10 % to 20 %), and thus it is not expected to interact with highly protein-bound substances.

PET studies in humans and preclinical data suggest that TMZ crosses the blood- brain barrier rapidly and is present in the CSF. CSF penetration was confirmed in one patient; CSF exposure based on AUC of TMZ was approximately 30 % of that in plasma, which is consistent with animal data.

Elimination

The half-life ($t_{1/2}$) in plasma is approximately 1.8 hours. The major route of ¹⁴C elimination is renal. 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.

Plasma concentrations increase in a dose-related manner. Plasma clearance, volume of distribution and half-life are independent of dose.

Special populations

Analysis of population-based pharmacokinetics of TMZ revealed that plasma TMZ clearance was independent of age, renal function or tobacco use. In a separate pharmacokinetic study, plasma pharmacokinetic profiles in patients with mild to moderate hepatic impairment were similar to those observed in patients with normal hepatic function.

Paediatric patients had a higher AUC than adult patients; however, the maximum tolerated dose (MTD) was 1,000 mg/m² per cycle both in children and in adults.

5.3 Preclinical safety data

Single-cycle (5-day dosing, 23 days non-treatment), 3- and 6-cycle toxicity studies were conducted in rats and dogs. The primary targets of toxicity included the bone marrow, lymphoreticular system, testes, the gastrointestinal tract and, at higher doses, which were lethal to 60 % to 100 % of rats and dogs tested, degeneration of the retina occurred. Most of the toxicity showed evidence of reversibility, except for adverse events on the male reproductive system and retinal degeneration. However, because the doses implicated in retinal degeneration were in the lethal dose range, and no comparable effect has been observed in clinical studies, this finding was not considered to have clinical relevance.

TMZ is an embryotoxic, teratogenic and genotoxic alkylating agent. TMZ is more toxic to the rat and dog than to humans, and the clinical dose approximates the minimum lethal dose in rats and dogs. Dose-related reductions in leukocytes and platelets appear to be sensitive indicators of toxicity. A variety of neoplasms, including mammary carcinomas, keratocanthoma of the skin and basal cell adenoma were observed in the 6-cycle rat study while no tumours or pre-neoplastic changes were evident in dog studies. Rats appear to be particularly sensitive to oncogenic effects of TMZ, with the occurrence of first tumours within 3 months of initiating dosing. This latency period is very short even for an alkylating agent.

Results of the Ames/salmonella and Human Peripheral Blood Lymphocyte (HPBL) chromosome aberration tests showed a positive mutagenicity response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: anhydrous lactose, colloidal anhydrous silica, sodium starch glycolate type A, tartaric acid, stearic acid.

Capsule shell:

5 mg: gelatin, titanium dioxide (E 171), sodium laurilsulfate, yellow iron oxide (E 172), indigo carmine (E 132).

20 mg:

gelatin, titanium dioxide (E 171), sodium lauril sulfate, yellow iron oxide (E 172)

100 mg:

gelatin, titanium dioxide (E 171), sodium lauril sulfate, red iron oxide (E172).

140 mg:

gelatin, titanium dioxide (E 171), sodium lauril sulfate, indigo carmine (E 132).

180 mg:

gelatin, titanium dioxide (E 171), sodium lauril sulfate, yellow iron oxide (E 172), red iron oxide (E 172)

250 mg:

gelatin, titanium dioxide (E 171), sodium lauril sulfate

Printing ink:

shellac, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, black iron oxide (E 172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Do not use after the expiry date shown on the packing.

6.4 Special precautions for storage

Bottle presentation

Do not store above 30 °C. Store in the original bottle in order to protect from moisture. Keep the bottle tightly closed.

Sachet presentation

Do not store above 30 °C.

6.5 Nature and contents of container

Bottle presentation

Type I amber glass bottles with polypropylene child-resistant closures containing 5 or 20 hard capsules. The carton contains one bottle.

Sachet presentation

Sachets are composed of linear low density polyethylene (innermost layer), aluminium and polyethylene terephthalate.

Each sachet contains 1 hard capsule and is dispensed in a cardboard carton. The carton contains 5 or 20 hard capsules, individually sealed in sachets.

Not all pack sizes or presentations may be marketed.

6.6 Special precautions for disposal and other handling

Capsules should not be opened. If a capsule becomes damaged, contact of the powder contents with skin or mucous membrane must be avoided. If Temodal comes into contact with skin or mucosa, it should be washed immediately and thoroughly with soap and water.

Patients should be advised to keep capsules out of the sight and reach of children, preferably in a locked cupboard. Accidental ingestion can be lethal for children.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom

8. MANUFACTURED BY

Orion Corporation Tengstrominkatu 8 Finland-20360 Turku

9. PACKAGED AND RELEASED BY

Schering-Plough Labo N.V., Industriepark 30, B-2220 Heist-op-den-berg, Belgium

10. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 January 1999 Date of latest renewal: 26 January 2009

11. DATE OF REVISION OF THE TEXT

May 2018 Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

(THIS IS A MEDICAMENT)

Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you. Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Keep medicament out of reach of children

Council of Arab Health Ministers Union of Arab Pharmacists

