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Clinical Trial

Zotiraciclib (TG02) for newly diagnosed glioblastoma in the elderly or for recurrent glioblastoma: The EORTC 1608 STEAM trial



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ABSTRACT

Background: Zotiraciclib (TG02) is an oral multi-cyclin dependent kinase (CDK) inhibitor thought to inhibit tumor growth via CDK-9-dependent depletion of survival proteins such as c-MYC and MCL-1 which are frequently overexpressed in glioblastoma.

Methods: EORTC 1608 (NCT03224104) (STEAM) had a three parallel group (A,B,C) phase Ib, open-label, non-randomized, multicenter design in IDH wild-type newly diagnosed glioblastoma or anaplastic astrocytoma. Groups A and B explored the maximum tolerated dose (MTD) of TG02 in elderly patients, in combination with hypofractionated radiotherapy alone (group A) or temozolomide alone (group B), according to O⁶-methylguanine DNA methyltransferase promoter methylation status determined centrally. Group C explored single agent activity of TG02 at first relapse after temozolomide chemoradiotherapy with a primary endpoint of progression-free survival at 6 months (PFS-6). Tumor expression of CDK-9, c-MYC and MCL-1 was determined by immunohistochemistry.

Results: The MTD was 150 mg twice weekly in combination with radiotherapy alone (group A) or temozolomide alone (group B). Two dose-limiting toxicities were observed at 150 mg: one in group A (grade 3 seizure), one in group B (multiple grade 1 events). Main toxicities included neutropenia, gastrointestinal disorders and hepatotoxicity. PFS-6 in group C was 6.7%. CDK-9, c-MYC and MCL-1 were confirmed to be expressed and their expression was moderately cross-correlated. High protein levels of MCL-1 were associated with inferior survival.

Conclusions: TG02 exhibits overlapping toxicity with alkylating agents and low single agent clinical activity in recurrent glioblastoma. The role of CDK-9 and its down-stream effectors as prognostic factors and therapeutic targets in glioblastoma warrants further study.

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1. Introduction

The current standard of care for patients with newly diagnosed glioblastoma, isocitrate dehydrogenase (IDH) wildtype, is surgery as safely feasible followed by radiotherapy with concomitant temozolomide and six cycles of maintenance temozolomide chemotherapy [1,2]. No pharmacological agent has been shown to improve survival when combined with temozolomide in that setting [1,3]. The poor activity of temozolomide in patients with tumors without methylation of the promoter region of the O⁶-methylguanine DNA methyltransferase (*MGMT*) gene has triggered a series of experimental clinical trials where temozolomide was omitted in this large subgroup of patients, mostly with the goal to prevent additive toxicity [4]. Recurrence of glioblastoma is inevitable, and standards of care for recurrent glioblastoma are poorly defined. A minority of patients in the range of 20% may be candidates for second surgery or re-irradiation, but neither of these interventions has been shown to prolong survival in a randomized clinical trial [1].

Zotiraciclib (TG02) is a brain-penetrant oral multi-kinase inhibitor that inhibits cyclin-dependent kinases (CDK)– 1, – 2, – 5, – 7 and – 9 and various other tyrosine kinases at nanomolar concentrations. Inhibition of CDK-9, the main target of TG02, prevents phosphorylation of RNA polymerase II [5]. CDK-9 inhibition depletes short-lived survival proteins such as c-MYC or MCL-1, a member of the BCL-2 family, and induces apoptosis in myeloma and glioblastoma cells [6,7]. c-MYC has been confirmed as a therapeutic target in a genetic glioma model with conditional c-MYC inhibition [8]. Increased MCL-1 protein levels have been linked to inferior outcome in glioblastoma [9], and MCL-1 levels may be increased at recurrence [10]. Genetic or pharmacological suppression of MCL-1 sensitizes glioblastoma cells to tumor necrosis factor-related apoptosis-inducing ligand [11]. These data warranted the clinical evaluation of TG02 in glioblastoma.

2. Patients and methods

2.1. Study design

EORTC 1608 (NCT03224104) (STEAM) was a phase Ib trial with a three-parallel group (A, B, C) open-label, non-randomized, multicenter design. Groups A and B determined the maximum tolerated dose (MTD) and the recommended phase II dose of TG02 in elderly patients with IDH-wildtype newly diagnosed glioblastoma or anaplastic astrocytoma in a classical 3 + 3 dose escalation and safety study in combination with hypofractionated radiotherapy alone (40 Gy in 15 fractions) (group A) or temozolomide alone (200 mg/m², days 1–5 of 28-day cycles) (group B) (Note A.1). Patient allocation to groups A versus B was guided by *MGMT* promoter methylation status determined centrally by methylation-specific PCR at HistoGeneX (Antwerp, Belgium). Group C

explored single agent TG02 activity in IDH-wildtype anaplastic astrocytoma or glioblastoma at first relapse after initial treatment with temozolomide chemoradiotherapy with a primary endpoint of progression-free survival at 6 months (PFS-6). Secondary objectives included efficacy, quality of life, and safety. Specific inclusion criteria are summarized in Note A.1. The trial was conducted at 9 sites in 4 countries (Note A.2) and enrolment lasted from June 2018 to July 2021.

2.2. Treatment

Details on the clinical trial history and the major amendment 3 are provided in Note A.3, Fig. 1 and Fig. A.1. After major amendment 3, group A patients received TG02 at an initial dose (dose level 1) of 100 mg orally twice weekly on days 1, 4, 8, 11, 15 and 18 in combination with hypofractionated radiotherapy (40 Gy in 15 fractions of 2.66 Gy) for 3 weeks (days 1–21). Seven days after completing combination therapy, patients started maintenance cycles of single agent TG02 until progression, unacceptable toxicity or for up to 12 months. TG02 was administered on days 1, 4, 8, 11, 15, 18, 22 and 25 of each 28-day maintenance cycle.

Group B patients received TG02 at an initial dose (dose level 1) of 100 mg orally twice weekly with temozolomide. TG02 was taken on days – 7, – 4, 1, 4, 22 and 25 of a first 28-day cycle. As of cycle 2, TG02 was given on days 1, 4, 22 and 25 of 28-day cycles. Temozolomide was given in the standard 28-day cycle regimen (200 mg/m²) for 5 out of 28 days starting at day 1. Therapy continued until disease progression, unacceptable toxicity or for up to 12 cycles.

Group C patients received single agent TG02 at 150 mg orally twice weekly. TG02 was administered on days 1, 4, 8, 11, 15, 18, 22 and 25. Dose reduction to 100 mg twice weekly was permitted. Therapy continued until disease progression, unacceptable toxicity or up to 12 cycles, or longer if felt to be in the best interest of the patient.

2.3. Outcome measures

Primary endpoint in groups A and B were the MTD and the recommended phase II dose. Primary endpoint in group C was PFS-6 defined by RANO criteria based on local assessment [12]. Secondary endpoints and definitions of outcome measures are provided in Note A.1.

2.4. Biomarker assessment

Expression of the candidate TG02 targets was assessed by immunohistochemistry (Note A.4).

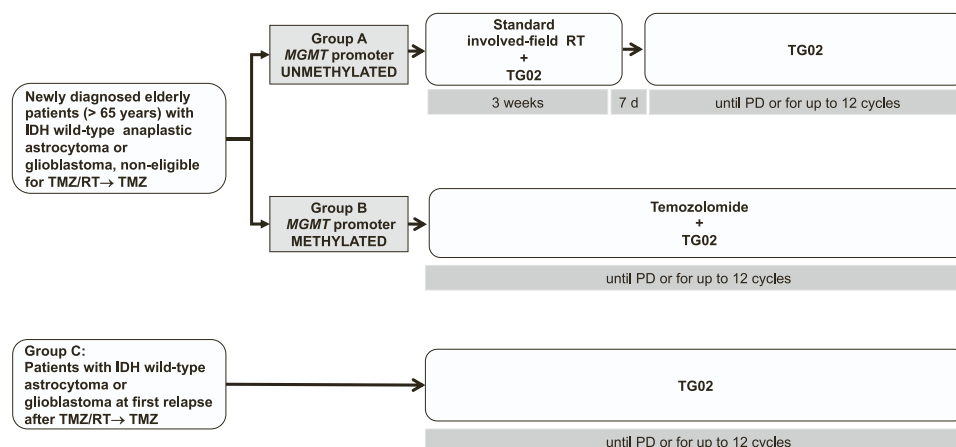


Fig. 1. Study design of EORTC 1608.

2.5. Statistical design

In groups A and B, a classical 3 + 3 multi-center dose-finding phase I design was chosen. In group C, a single arm phase II design was applied. Study decision rule was based on an A'Hern one-stage design with P0, the largest PFS rate at 6 months which, if true, implied that the therapeutic activity of TG02 was too low taken as 20%, and P1, the lowest PFS rate at 6 months which, if true, implied that the therapeutic activity of TG02 was adequate was taken as 40%. Detailed information on statistical design and analysis is provided in [Note A.5](#). Arms A and B were prematurely closed upon decision of the company. Arm C was fully enrolled.

2.6. Ethics statement

All patients gave written informed consent, and the study was approved by the local ethical committees and competent authorities.

3. Results

3.1. Group A – Elderly, MGMT promoter unmethylated

Twelve patients were enrolled, 3 patients at the 100 mg dose and 9 patients at the 150 mg dose ([Table A.1](#)). No DLT was observed at the 100 mg dose. One DLT (grade 3 seizure) was observed at 150 mg for the second patient. Four additional patients were treated at 150 mg for the DLT phase, and 3 further patients during the extension phase. No further DLT was observed in these 7 patients treated at 150 mg. The MTD was therefore determined as 150 mg ([Table 1](#), [Note A.6](#), [Table A.2](#)).

3.2. Group B – Elderly, MGMT promoter methylated

Nine patients were enrolled, 3 patients at 100 mg and 6 patients at 150 mg ([Table A.1](#)). No DLT was observed at 100 mg. One DLT (temozolomide dose reduction for grade 1 hyperthermia) was documented at 150 mg for the first enrolled patient. Five additional patients were treated at 150 mg during the DLT phase. No further DLT was observed in these 5 patients treated at 150 mg. No patients were enrolled in an extension phase. The MTD was thus determined as 150 mg ([Table 1](#), [Note A.6](#), [Table A.2](#)).

3.3. Group C – recurrent glioblastoma

3.3.1. Patients and treatment

Patient characteristics are summarized in [Table 2](#). After amendment 3, 50 patients were recruited in group C (phase II) at a TG02 starting dose of 150 mg. The median age was 57 years, 48 patients had glioblastoma, 2 patients had anaplastic astrocytoma, and 17 tumors (39%) had MGMT promoter methylation. Thirteen patients (26%) had the TG02 dose increased to 200 mg at cycle 2. The median number of TG02 cycles administered was 2 (range 1–26). Nineteen patients (38%) received 1 cycle, 25 patients (50%) had 2 cycles and 6 patients (12%) had 3 cycles or more. The median TG02 relative dose intensity was 76.7% (range 33.3–101.8%). Thirty-six patients (72%) had at least one cycle with schedule modification (delay) or dose not given or reduced.

Table 1

Dose limiting toxicity analysis.

	Dose level	DLT	DLT rate (%)	Description
Arm A	150 mg	1/6	16.7	66.7% TG02 relative dose intensity and 50% of the dose of radiotherapy for SAE seizure
Arm B	150 mg	1/6	16.7	Temozolomide < 75% due to multiple grade 1 adverse events

Table 2

Patient characteristics in group C, prior (250 and 200 mg) and after (150 mg) amendment 3.

	150 mg n= 50	200 mg n= 18	250 mg n= 6
Age at registration median and range	57 (19-75)	60 (21-71)	62.5 (50-71)
Sex			
Male, n (%)	40 (80.0)	12 (66.7)	5 (83.3)
Female, n (%)	10 (20.0)	6 (33.3)	1 (16.7)
KPS			
70-80, n (%)	19 (38)	5 (27.8)	1 (16.7)
90-100, n (%)	31 (62)	13 (72.2)	5 (83.3)
Tumor type			
glioblastoma	48 (96.0)	17 (94.4)	6 (100.0)
anaplastic astrocytoma	2 (4.0)	1 (5.6)	0 (0.0)
MGMT promoter status			
Methylated, n (%)	17 (34.0)	5 (27.8)	1 (16.7)
Unmethylated, n (%)	27 (54.0)	7 (38.9)	4 (66.7)
Unknown (%)	6 (12)	6 (33.3)	1 (16.7)
Surgery for recurrence			
Yes, n (%)	14 (28.0)	5 (27.8)	2 (33.3)
No, n (%)	36 (72.0)	13 (72.2)	4 (66.7)
Steroids at baseline			
Yes, n (%)	18 (36.0)	6 (33.3)	2 (33.3)
No, n (%)	32 (64.0)	12 (66.7)	4 (66.7)
Best response			
Partial response	1 (2.0)	0 (0.0)	0 (0.0)
Stable disease	4 (8.0)	4 (22.2)	2 (33.3)
Progressive disease	43 (86.0)	10 (55.6)	3 (50.0)
Not evaluable ⁽¹⁾	2 (4.0)	4 (22.2)	1 (16.7)
Progression-free survival at 6 months (PFS-6)	6.7% (2.9-12.5%) ⁽²⁾	14.8% (2.4-37.5%) ⁽²⁾	0.0% (NE-NE) ⁽²⁾
Progression-free survival number of events	44 ⁽²⁾	13 ⁽²⁾	5 ⁽²⁾
median PFS	1.9 (1.6-1.9) ⁽²⁾	2.1 (1.9-3.1) ⁽³⁾	1.7 (0.6-NE) ⁽³⁾
Overall survival number of events	38 ⁽²⁾	10 ⁽²⁾	3 *
median survival	7.1 months (4.90, 9.4)*	13.1 months (7.6-NE) ⁽³⁾	3. Months (1.7-NE) ⁽³⁾

Note: (1) In group C 150 mg, 2 patients had measurable disease at baseline, but no data on the follow-up scan was provided at the time of the analysis. In group C 200 mg, 2 patients had measurable disease at baseline, but no data on the follow-up scan was provided at the time of the analysis and 2 patients had no measurable disease at baseline. In group C 250 mg, one patient had measurable disease at baseline, but no data on the follow-up scan was provided at the time of the analysis. (2) In group C in the efficacy population (n = 46), PFS-6 80% CI of PFS (primary endpoint), 95% CI for median PFS and OS (secondary endpoint).

Twelve patients (24%) had at least one cycle with schedule modification, 30 patients (60%) had at least one cycle with dose not given. Twelve patients (24%) had at least one cycle with dose reduction, including 7 patients (14%) for adverse events: fatigue grade 3–4 (n = 2); neutropenia grade 3 (n = 3); pneumonia grade 3 (n = 1), anorexia grade 3 (n = 1). Another three patients (6%) were coded as for patient decision, one as “for administrative reasons” and one “unknown”. Some patients had multiple events (schedule modification, dose not given and dose reduction). One patient was still on treatment at the time of the analysis whereas 49 patients had discontinued TG02. The reasons for TG02 discontinuation were progressive disease in 43 patients (86%), toxicity in 3 patients (6%), and withdrawal by patient/investigator in 3 patients (6%). The toxicity profile of TG02 at the three different starting doses is summarized in [Table A.3](#). The most relevant toxicities were hematological and gastrointestinal.

3.3.2. Outcome

The number of patients free of progression at 6 months per local assessment was 3 among the 50 patients enrolled (6.7%, 80% CI 2.5–14.3%). All three had MGMT promoter-methylated tumors. Median PFS was 1.9 months (95% CI 1.6–1.9 months). It was 1.9 months (95% CI 1.2–2.1 months) in patients with MGMT promoter-methylated tumors and 1.8 months (95% CI 1.1–2.0 months) in patients with MGMT

promoter-unmethylated tumors.

Median PFS was similar, 1.8, 2.1 and 1.7 months in patients treated at 150 mg (n = 50), 200 mg (n = 1) or 250 mg (n = 6) (Table 2). Median neurological PFS was 2.3 months (95% CI 1.9–4.7 months). Neurological PFS at 6 months was 29.8% (95% CI 16.7–44.1%). Median clinical deterioration-free survival was 1.9 months (95% CI 1.6–1.9). Clinical deterioration-free survival at 6 months was 17.3% (95% CI 7.9–29.8%).

Forty-six patients in the efficacy population, i.e. all patients who were eligible and received at least one dose of TG02, were assessed for

response. Per local assessment, one partial response among 39 patients with target disease at baseline was observed with a duration of 12 months that was ongoing at database lock. No complete response was noted. Stable disease was noted in 4 patients (8%) at 150 mg, 4 patients (22%) at 200 mg and 2 patients (33%) at 250 mg.

3.3.3. Post-progression course and survival

Twenty-five patients (50%) received further anti-cancer treatment, in all cases, further anti-cancer treatment was started after progression; 21 patients were not further treated. Three patients were lost to follow-

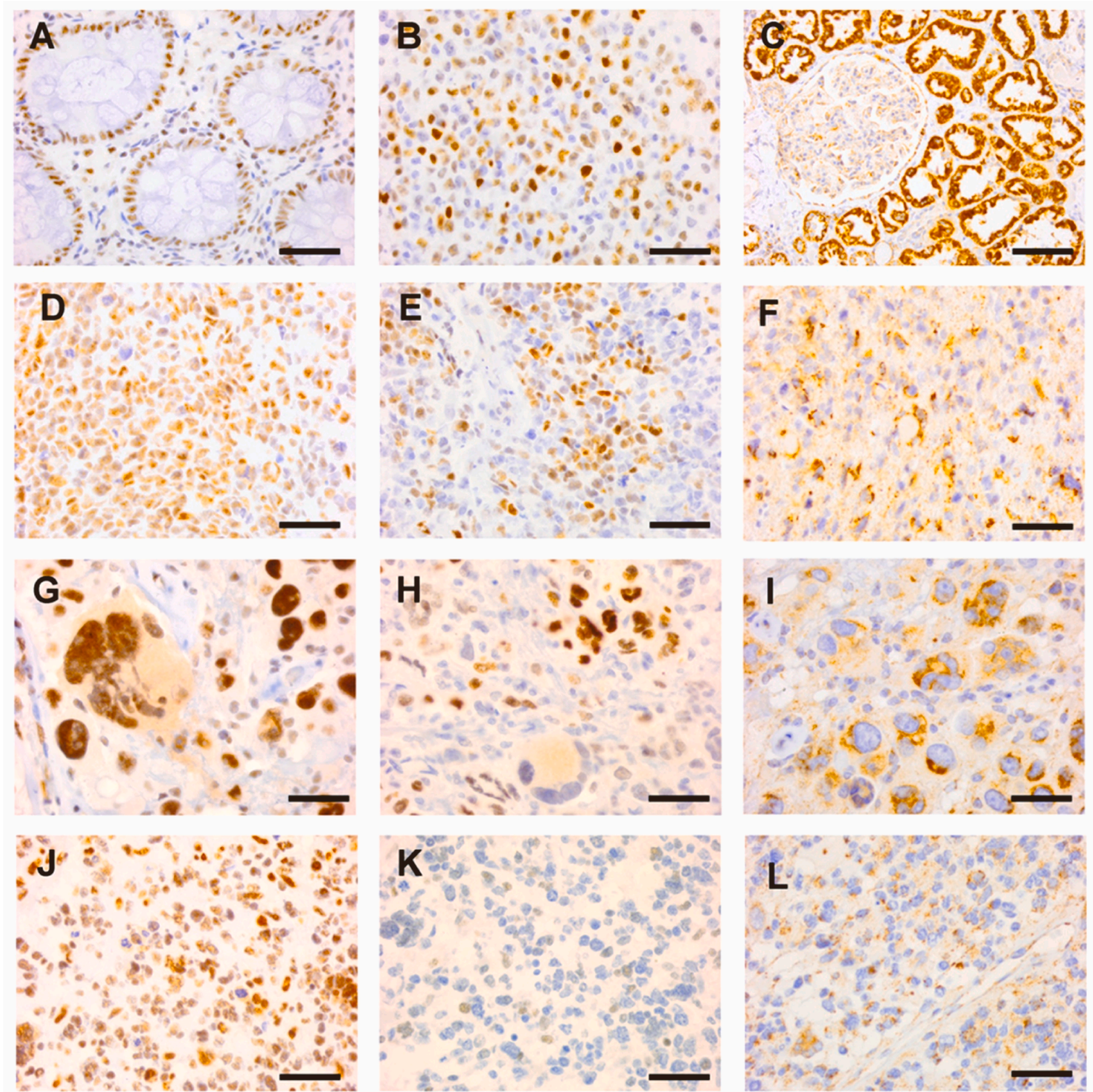


Fig. 2. TG02 target expression in newly diagnosed glioblastoma. Exemplary immunohistochemical stainings for CDK-9 (A,D,G,J), c-MYC (B, E, H, K) and MCL-1 (C, F, I, L) in control tissue samples (A, colon tissue; B, aggressive B cell lymphoma; C, kidney tissue), as well as 3 selected gliomas from the study (D-F, G-I, J-L). Note that CDK-9 is expressed in the vast majority of glioma cell nuclei (D, G, J). In contrast, nuclear expression of c-MYC (E, H, K) and cytoplasmic expression of MCL-1 (F, I, L) are more heterogeneous across the depicted cases. Original microscopic magnification: 400x, size bar 50 μ

up. A next further systemic therapy was given in all 25 patients who received further tumor-specific treatment.

Thirty-eight patients died. Median OS was 7.1 months (95% CI 4.9–9.4 months). It was 11.3 months (95% CI 4.4–14.9 months) in patients with *MGMT* promoter-methylated tumors and 6.2 months (95% CI 3.1–8.3 months) in patients with *MGMT* promoter-unmethylated tumors. OS at 1 year was 21.8% (95% CI 10.8–35.2%). It was 42.9% (95% CI 17.7–66.0%) in patients with *MGMT* promoter-methylated tumors. No patient with a *MGMT* promoter-unmethylated tumor was alive at 1 year. Median OS was similar, 7.1, 13.1 and 9.3 months in patients treated at 150 mg (n = 50), 200 mg (n = 1) and 250 mg (n = 6) (Table 2).

3.4. Biomarker studies

Exemplary results of immunohistochemical stainings for CDK-9, c-MYC and MCL-1 are shown in Fig. 2. Tumor cells with nuclear CDK-9 expression were detected in 102 of 105 tumors with the majority of tumors (90 of 105 tumors, 86%) showing immunoreactivity in more than 50% of the tumor cells (Fig. 2D,G,J). Nuclear expression of c-MYC was also detected in most tumors (81 of 102 tumors, 79%), albeit the fractions of positive tumor cells were lower and there was more pronounced inter- and intratumoral heterogeneity when compared to CDK-9 (Fig. 2E,H,K). Cytoplasmic MCL-1 expression was detected in 100 of 101 tumors (99%) and was often widespread within the tumor tissue, although staining intensity and fraction of positive cells varied (Fig. 2F,I,L) (Fig. A.2, Note A.7). Evaluable tissue samples from pairs of pre-treatment primary glioblastoma and recurrent glioblastoma resected after TG02 treatment were only available from two patients (Fig. A.3, Note A.8).

In the entire cohort, the expression levels of CDK-9 and its indirect targets, c-MYC (r = 0.29, p = 0.007) and MCL-1 (r = 0.38, p = 0.0004) were correlated, supporting a regulatory role for CDK-9. In addition, c-MYC and MCL-1 expression levels were also correlated (r = 0.23, p = 0.036). In univariate analyses, none of the 3 markers showed significant PFS and OS correlations in pooled groups A+B and group C. No multivariate analyses were performed. The MCL-1 split by the median (<8 / >8) showed a difference in OS from surgery in the entire cohort (A/B+C, p = 0.06). Median OS from surgery was 27.4 months if MCL1 was less or equal to 8 but only 15.2 months for MCL-1 values larger than 8. In both stepwise and LASSO selection analysis, MCL1 was the only factor to be selected among sex, extent of resection and *MGMT* promoter methylation (Note A.5, Fig. 3).

4. Discussion

This is the first and definitive report of EORTC-1608 (STEAM), a three-group parallel study exploring a potential role for the multi-kinase inhibitor, TG02, in patients with glioblastoma. The rationale for exploring this agent in glioblastoma was its profound activity in cell culture models including glioma stem cell models, broad coverage of potentially relevant targets and encouraging blood brain barrier penetration [7,13]. Furthermore, expression of the indirect targets of TG02, c-MYC and MCL-1, had been documented [8–10], and strong expression of its direct target, CDK-9, was confirmed here (Fig. 2).

Groups A and B aimed at developing TG02 as an add-on to treatment of glioblastoma in the elderly stratified by *MGMT* promoter methylation status, based on the strong predictive role of *MGMT* promoter methylation status for benefit from radiotherapy alone versus temozolomide treatment [14,15]. The rationale of these arms was to explore TG02 in a setting where no excessive toxicity from a triple combination with radiotherapy and temozolomide was to be expected. A TG02 dose of 150 mg administered in a continuous twice weekly schedule with radiotherapy and in a twice weekly schedule in alternating weeks with temozolomide was identified as the MTD and recommended phase II

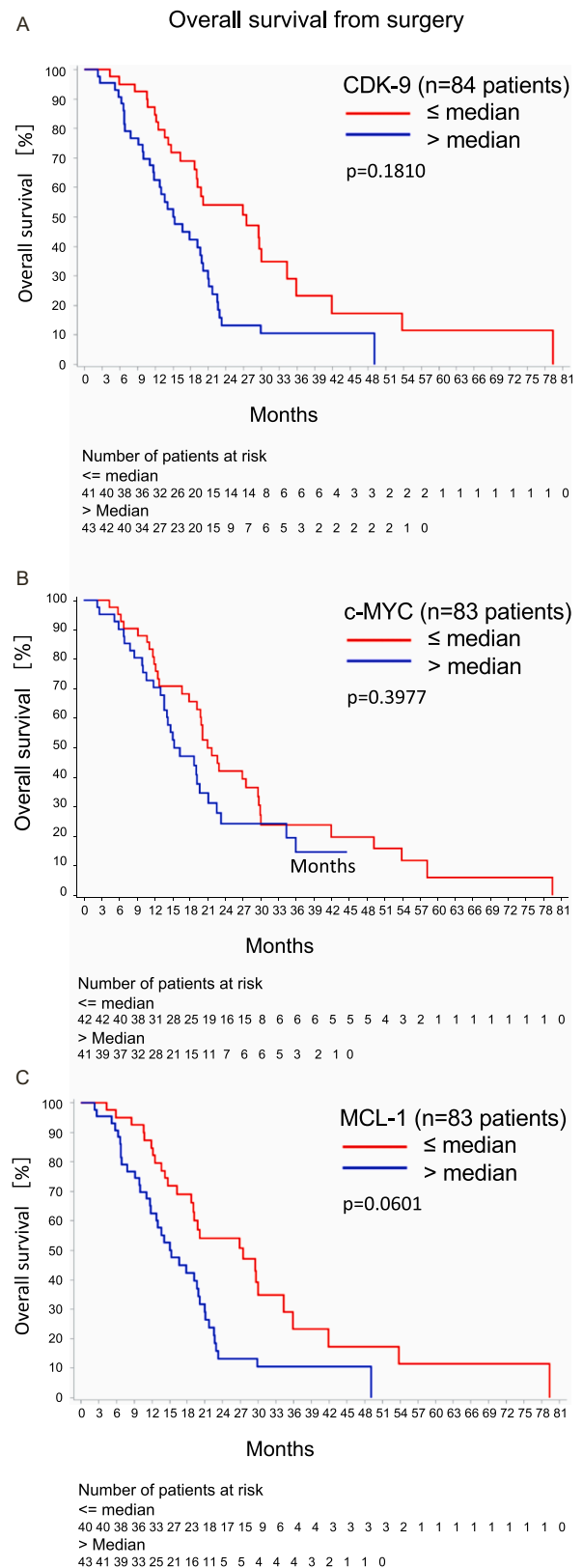


Fig. 3. Prognostic associations of semiquantitative immunohistochemical expression levels of CDK-9, c-MYC and MCL-1. Kaplan-Meier survival curves showing the association with overall survival stratified according to semiquantitative immunohistochemical scores split by the median calculated for (A) CDK-9 (n = 84 patients), (B) c-MYC (n = 83 patients) and (C) MCL-1 (n = 83 patients).

dose (Table 1). While sample sizes are small, PFS and OS did not suggest activity exceeding that expected for radiotherapy alone or temozolomide alone in this patient population [14,15].

Group C demonstrated that TG02 has insufficient single agent activity in recurrent glioblastoma at clinically tolerated doses. There was no apparent difference in outcome between patients treated with different doses of TG02. Another clinical trial assessed TG02 in combination with two different dosing schedules of temozolomide in recurrent glioblastoma [16]. The MTD in this setting was 250 mg given four times per 28 days, and the outcome results appeared to favor one week on one week off temozolomide over metronomic temozolomide. Due to the study design, no conclusion as to the efficacy of TG02 as an add-on to temozolomide could be derived. Together with the limited single agent activity shown in our study, the future of TG02 in the setting of recurrent glioblastoma remains doubtful, also because of the strongly overlapping toxicity profile with alkylating agents, with myelosuppression and hepatotoxicity as the leading toxicities. These would also render combinations with lomustine, the standard of care in recurrent disease, challenging.

In conclusion, there is probably no promising path forward for TG02 in the current treatment landscape of glioblastoma. Yet, the negative prognostic associations of high MCL-1 levels may warrant its further exploration as a therapeutic target in glioblastoma.

Author statement

Experimental design and its implementation: ELR, TG, MW. Acquisition, analysis, or interpretation of data: all authors. Statistical analysis: TG. Writing of the manuscript: all authors.

Availability of the full protocol

Upon reasonable request to EORTC.

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Declaration of Competing Interest

ELR has received a grant research from Bristol Meyer Squibb and honoraria for lectures or advisory board from Bayer, Janssen, Leo Pharma, Pierre Fabre, Servier and Seattle Genetics. JFu received honoraria for lectures and consultation from the following for-profit companies: Novartis, Seagen. FD received honoraria for advisory board and lectures from Novocure and Servier. PH has an advisory role at BMS, Glaxo Smith Kline, MSD, Novocure, is in the speakers bureau of Lilly, medac, Novocure, Seagen and has received travel grants from Lilly, medac, Novocure, Seagen. OLC received research support from Novocure and honoraria from BMS. MP has received research grants from Pfizer and Roche and honoraria for advisory boards from Bayer. PR has received honoraria for lectures or advisory board participation from Alexion, Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm,

Merck Sharp and Dohme, Midatech Pharma, Novocure, QED, and Roche and research support from Merck Sharp and Dohme and Novocure. MvdB received honoraria for advisory boards from Genenta, Boehringer, Astra Zeneca, Chimerix, Roche, Fore Biotherapeutics and Servier. MW has received research grants from Quercis and Versameb, and honoraria for lectures or advisory board participation or consulting from Bayer, Curevac, Medac, Merck (EMD), Novartis, Novocure, Orbus, Philogen, Roche and Sandoz. TG, JFe, JJ, CAM, DG, SC, MC and GR declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113475.

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Update

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Corrigendum



Corrigendum to “Zotiraciclib (TG02) for newly diagnosed glioblastoma in the elderly or for recurrent glioblastoma: The EORTC 1608 STEAM trial” [Eur J Cancer 198 (2024) 113475]

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The authors regret to advise of an error in Fig. 3A. By error, the survival curves shown were identical as in Fig. 3C. The corrected Fig. 3A is shown here:

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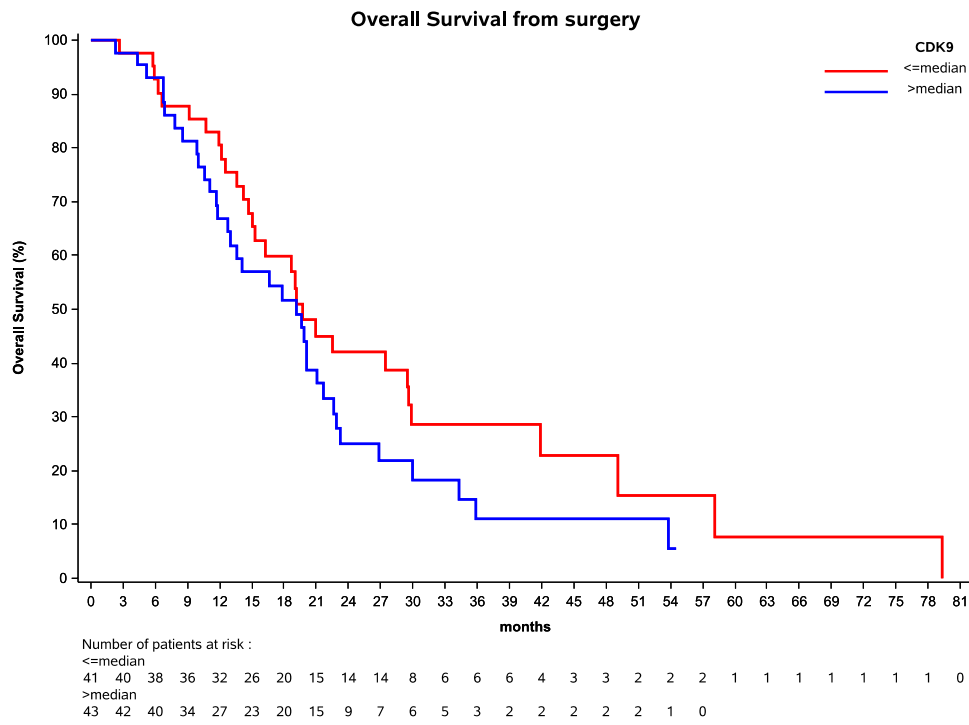
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<https://doi.org/10.1016/j.ejca.2024.114066>

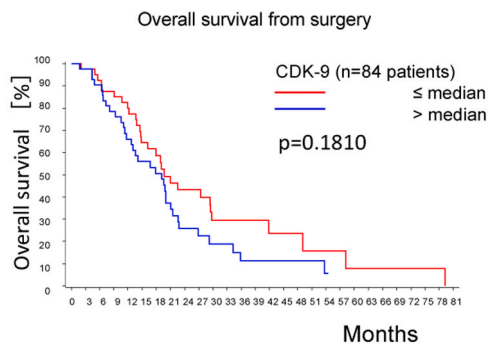
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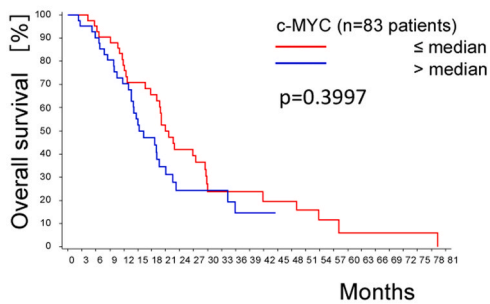


The authors would like to apologise for any inconvenience caused.
 Corrected Fig. 3 panel. Prognostic associations of semiquantitative

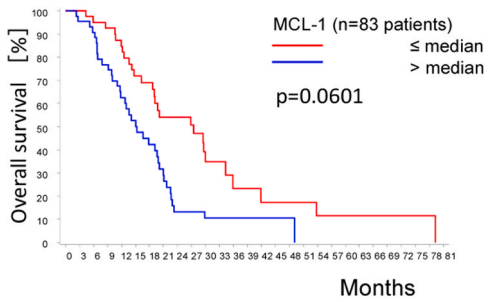
immunohistochemical expression levels of CDK-9, c-MYC and MCL-1.
 .



Number of patients at risk
 <= median
 41 40 38 36 32 26 20 15 14 14 8 6 6 6 4 3 3 2 2 2 1 1 1 1 1 1 0
 > Median
 43 42 40 34 27 23 20 15 9 7 6 5 3 2 2 2 2 2 1 0



Number of patients at risk
 <= median
 42 42 40 38 31 28 25 19 16 15 8 6 6 6 5 5 4 3 2 1 1 1 1 1 1 1 0
 > Median
 41 39 37 32 28 21 15 11 7 6 6 5 3 2 1 0



Number of patients at risk
 <= median
 40 40 38 36 33 27 23 18 17 15 9 6 4 4 3 3 3 2 1 1 1 1 1 1 1 1 0
 > Median
 43 41 39 33 25 21 16 11 5 4 4 4 3 2 1 1 0

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