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Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032)

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ABSTRACT

Purpose: To compare the efficacy of an extended schedule escalated dose of temozolomide versus standard dose dacarbazine in a large population of patients with stage IV melanoma.

Patients and methods: A total of 859 patients were randomised to receive oral temozolomide at 150 mg/m^2/day for seven consecutive days every 2 weeks or dacarbazine, administered as an intravenous infusion at 1000 mg/m^2/day on day 1 every 3 weeks. The primary endpoint was overall survival (OS), using an intent-to-treat principle. EudraCT number 2004-000654-23 NCI registration number NCT00005052.

Results: Median OS was 9.1 months in the temozolomide arm and 9.4 months in the dacarbazine arm, with a hazard ratio (HR) of 1.00 (95%confidence interval [CI]: 0.86, 1.17; P = 0.99).

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Median progression-free survival (PFS) was 2.3 months in the temozolomide arm and 2.2 months in the dacarbazine arm, with a HR of 0.92 (95%CI: 0.80, 1.06; P = 0.27). In patients with measurable disease, overall response rate was higher in the temozolomide arm than in the dacarbazine arm (14.5% versus 9.8%, respectively), but the median duration of response was longer for dacarbazine. The extended schedule, escalated dose temozolomide arm showed more toxicity than the standard dose, single agent dacarbazine arm. The most common non-haematological treatment emergent adverse events reported in both treatment arms were nausea, fatigue and vomiting and constipation.

Conclusion: Extended schedule escalated dose Temozolomide (7 days on 7 days off) is feasible and has an acceptable safety profile, but does not improve OS and PFS in metastatic melanoma when compared to standard dose dacarbazine.

1. Introduction

The worldwide incidence of melanoma is increasing rapidly and has almost doubled in the last 10 years.[1,2] The disease stage of melanoma at diagnosis is the major determinant of prognosis and survival, and though early stage disease is often cured by surgical excision of the primary tumour melanoma with distant spread is often fatal.[3,4] Patients with stage IV metastatic melanoma have a poor prognosis, with a median overall survival (OS) of 8 months and a 2-year survival rate of 11%.[5,6] Surgery and radiotherapy have a limited role in the treatment of metastatic stage IV melanoma, and chemotherapy remains the mainstay of treatment, although other approaches, such as biotherapy with cytokines, have been attempted with some, albeit limited success.[7,8] The alkylating agent dacarbazine is approved for metastatic melanoma, and it is often used as a single agent, following the results of several studies that demonstrated that combination therapies failed to improve median OS over dacarbazine alone.[7,8] Dacarbazine is generally well tolerated but response rates from randomised trials are low,[7,9,10] and a survival benefit over observation has never been demonstrated. A number of agents and combination therapy regimens have been compared with dacarbazine in randomised trials, but none have demonstrated a significant benefit in OS.[7,8] Therefore, there is an urgent need to develop therapies for the treatment of metastatic melanoma that improve survival.

Temozolomide is an imidazotetrazine-based DNA alkylating agent that hydrolyses to the same active alkylating moiety, methyl-triazenyl imidazole carboxamide (MTIC) as dacarbazine, but has a different route of activation; dacarbazine requires hepatic cytochrome p450 for activation, whereas temozolomide is activated at normal physiologic pH.[11] The potential advantages of temozolomide over dacarbazine are its oral route of administration, with near 100% bioavailability and extensive tissue distribution.[12–14] Early phase I and II studies demonstrated that temozolomide has anti-melanoma activity in patients with metastatic disease, and suggested that temozolomide would have comparable efficacy to that of dacarbazine in this setting.[12,15–17] In a large, randomised phase III trial, the 'classical regimen' of temozolomide (200 mg/m^2/day on days 1–5, repeated every 28 days) demonstrated equivalent efficacy with dacarbazine (250 mg/m^2/day for 5 days, repeated every 3 weeks) in terms of response rate (13.5% versus 12.1% for dacarbazine) and median OS (7.7% versus 6.4% for dacarbazine) in patients with metastatic melanoma.[18] Although there was a trend for improved survival with temozolomide, the OS advantage was not statistically significant.

Both dacarbazine and temozolomide methylate the O^6-guanine of DNA, generating cytotoxic adducts that result in the initiation of cellular repair mechanisms or apoptosis. These adducts can be repaired by O^6-methylguanine-DNA methyltransferase (MGMT), and upregulation of this DNA repair enzyme is associated with tumour resistance to temozolomide.[19] Sequential dosing of temozolomide can deplete MGMT, potentially overcoming MGMT-mediated resistance and increasing the efficacy and perhaps the toxicity of temozolomide.[16] A number of extended temozolomide dosing schedules are currently being evaluated.[20] A phase I dose escalation study investigated two alternative temozolomide dosing regimens, a once-daily dosing regimen for 21 days every 4 weeks and once daily for 7 days repeated every 2 weeks; both regimens demonstrated significant reductions in MGMT levels in peripheral blood lymphocytes.[21] Furthermore, both regimens indicated that it was possible to administer a 2.1-fold greater exposure to temozolomide per 28-day period in comparison with the classical regimen of 200 mg/m^2/day for 5 days every 28 days.

Based on these findings we conducted a large, randomised, open-label, phase III study of extended schedule and escalated dose of temozolomide versus standard dose dacarbazine in patients with metastatic melanoma to determine if the extended schedule of temozolomide is a more effective treatment than standard single-agent dacarbazine.

2. Patients and methods

2.1. Patients

Eligibility requirements for the study included: histologically confirmed, surgically incurable or unresectable, AJCC stage IV melanoma, age $\geqslant$18 years, evaluable disease, (PET-only evaluable disease was not allowed), adequate performance status (World Health Organization [WHO] or Eastern Cooperative Oncology Group [ECOG] status 0 or 1), and adequate haematological (absolute neutrophil count [ANC] $>1.5\times10^9$/L, platelet count $>100\times10^9$/L, and a haemoglobin >10 g/dL

[>6.2 mmol/L]), renal (serum creatinine $\leqslant 1.5 \times$ upper limit of normal [ULN]) and hepatic (total bilirubin $\leqslant 1.5 \times$ ULN, lactate dehydrogenase [LDH] $\leqslant 2 \times$ ULN, and alanine aminotransferase [ALT] or aspartate aminotransferase [AST] $\leqslant 2.5 \times$ ULN and $\leqslant 5 \times$ ULN in case of liver metastasis) function. Previous chemotherapy and cytokine therapy for stage IV disease were not allowed. However, previous adjuvant cytokine or vaccine therapy for resected stage I–III disease, palliative surgery for distant metastases disease, previous vaccine therapy (other than cytokine) for stage IV disease, and prior cytokine or chemotherapy for local–regional disease by isolated limb perfusion therapy were allowed. Patients must have recovered from any effects of major surgery or previous adjuvant treatment and all patients must have discontinued prior allowable therapy for at least 4 weeks prior to randomisation. Patients with cutaneous and mucosal melanoma were allowed. Patients who were pregnant or nursing, who had previous cancer within 5 years of randomisation, had concurrent malignancies at other sites with the exception of surgically cured carcinoma *in situ* of the cervix and basal or squamous cell carcinoma of the skin, with ocular melanoma, with evidence of brain metastases, or those with any clinically uncontrolled infectious disease were excluded from the study. Written informed consent was obtained from all patients, prior to performing any study-related procedures.

2.2. Treatment

Patients were randomised 1:1 to receive either temozolomide or dacarbazine. Temozolomide was administered orally once a day at a dose of 150 mg/m^2/day for seven consecutive days every 2 weeks. Dacarbazine was administered as an intravenous infusion at 1000 mg/m^2/day on day 1 every 3 weeks. Temozolomide treatment cycles were defined as a 6-week period and dacarbazine treatment cycles were defined as a 3-week period, which were repeated until disease progression, unacceptable toxicity, patient refusal (not related to toxicity) or decision by the treating physician. Dose reductions for haematological and non-haematological toxicities were based on the National Cancer Institute Common Toxicity Criteria (NCI-CTC) and were permanent for both treatments.[22] Other chemotherapeutic agents, immunological, biological or radiation therapy and other investigational drugs were prohibited during the study.

2.3. Clinical evaluation

A pre-study evaluation was completed for all patients within 2 weeks prior to randomisation. Patients continued to have regular scheduled evaluations during each treatment cycle, which included physical exam, ECOG performance status (PS), monitoring of adverse events, serious adverse events (SAEs) and laboratory tests. Radiological evaluation of disease was performed every 9 weeks in both treatment arms. Responses were assessed using WHO response criteria.[23] Objective tumour response was measured according to the Response Evaluation Criteria in Solid Tumours (RECIST) criteria.[24] Toxicities and the severity of adverse events (AEs) were graded according to the NCI-CTC.[25] After the treatment ended, irrespective of the reason, all patients were followed for survival every 9 weeks. All antitumour and salvage therapies were recorded. Patients who discontinued due to toxicity were followed up for disease progression every 9 weeks using radiological assessments.

2.4. Statistical methods

The duration of survival was calculated from the date of randomisation until death, irrespective of the cause. The progression free survival was calculated from the date of randomisation until first progression or death, whichever occurred first. For patients who achieved a complete (CR) or partial remission (PR), the duration of response was calculated from the date of first CR or PR until the date of first relapse or progression.

The primary endpoint of this study was OS from randomisation. In this population the expected median OS is approximately 6–9 months and the 2 year survival rate is approximately 10%. The aim of the study was to detect a hazard ratio of 0.77 which, under exponential distribution assumption, corresponds to an increase of median OS from 7.2 months to 9.4 and an increase in the 2-year survival from 10% to 17%. In order to detect such a difference (logrank 2-sided test, alpha = 0.05 and beta = 0.10) between the two treatment arms a total of 616 patients had to be followed up until death (whatever the cause). These calculations were made in East-3 (EAST-3. Cytel Software Corporation. Cambridge, MA, USA), and took into consideration that one interim analysis is done after 340 events. The planned interim analysis of this study was cancelled because enrolment was completed before 340 deaths were reached.

Randomisation, performed centrally at the EORTC Headquarters, was stratified by performance status (0 versus 1) and institution, using a minimisation technique[26]:

For the duration of survival and PFS, an Intention to treat (ITT) analysis was performed with all patients included in the analysis according to the treatment group assigned by randomisation independent of the patient's eligibility and the treatment actually received.

For the toxicity analyses (based on CTCAE grading), all patients who started the treatment allocated by randomisation, and who have properly been documented were included. For the response rate analysis (based on RECIST criteria), all patients with measurable lesions were to be included. The Fisher exact test was used to compare the response rate between the two treatment arms.

Kaplan–Meier technique was used to estimate survival-type distributions and the standard errors (SE) of the estimates were obtained via the Greenwood formula.[27] The logrank 2-sided test and the Cox proportional hazards model stratified for the initial performance status provided at randomisation were used for the treatment comparison of the survival-type distributions and to estimate the HR corresponding to treatment and its 95% confidence interval.[26] For confirmatory purposes, additional multivariate analyses were performed using the Cox Proportional Hazards model in order to determine prognostic importance of baseline factors and to adjust the treatment comparison for such factors. Exploratory subgroup analyses were performed; for these, the 99% CI of treatment HR were computed.

3. Results

3.1. Patients

Between October 2004 and May 2007, 859 patients were enrolled in 92 sites in 20 countries, including the European Union, Switzerland, the United States of America, South Africa and Latin America. 429 patients were randomised to receive temozolomide and 430 to receive dacarbazine. Patient demographics were comparable between the two treatment arms regarding age, sex, performance status and LDH at baseline. At randomisation, 596 patients were indicated as having a PS = 0 (294 patients in the dacarbazine arm versus 302 patients in the temozolomide arm) and 262 patients a PS = 1 (136 dacarbazine and 127 temozolomide) (Fig. 1) (Table 1).

Of all randomised patients, 14 patients in each arm (3.3%) were subsequently considered to be ineligible. Nine patients (2.1%) in each arm received no treatment. The Consort flow diagram is shown (Fig. 2).

3.2. Survival

At a median follow-up of 19 months, 645 patients died: 320 in the temozolomide arm versus 325 in the dacarbazine arm. There was no significant difference in the OS between the treatment arms (Fig. 3A). The median OS was 9.1 months for patients randomised in the temozolomide arm and 9.4 months for those in the dacarbazine arm. The one year survival rate was 34.4% (SE 2.4%) (temozolomide) versus 37.7% (SE 2.4%) (dacarbazine) and 2 year survival rate was 15.1% (SE 2.3%) (temozolomide) versus 13.4% (SE 2.2%) (dacarbazine). The HR stratified for the initial performance status was 1.00 (95% CI: 0.86, 1.17; $P = 0.99$).

PFS was similar between the two treatment arms (Fig. 3B). The median PFS was 2.3 months for the temozolomide arm and 2.2 months for the dacarbazine arm, with a HR stratified for the initial performance status of 0.92 (95% CI: 0.80, 1.06; $P = 0.27$).

3.3. Response to treatment

A total of 401 patients in the temozolomide arm and 388 patients in the dacarbazine arm had measurable disease and were evaluable for response. In the temozolomide and dacarbazine arms there were 8 (2%) and 4 (1%) CR, respectively, and 50 (12.5%) and 34 (8.8%) PR, respectively. The overall objective response rate for the temozolomide group was 14.5% (58/401 patients) compared with 9.8% (38/399 patients) for the dacarbazine group, with a difference of 4.7% (95% CI: 0.1, 8.9; $P = 0.05$) (Table 2). Median time from randomisation to response was similar ($P = 0.87$) in the two treatment arms: 2.3 months for the temozolomide group versus 2.2 months for the dacarbazine group. However, the duration of response was longer in patients treated with dacarbazine compared with patients treated with temozolomide: median was 11.2 months (95% CI, 6.2, 19.5 months) for dacarbazine group versus 4.6 months (95% CI 4.2, 6.3 months) for the temozolomide group (Fig. 3C).

3.4. Sub group and multivariate analyses of efficacy

As expected, patients with PS 0 at randomisation had a better median OS than those with PS 1 (10.1 months versus 7.1 months). There was no significant difference between the two treatment arms for each group: PS 0 (HR = 0.97, 99% CI 0.75, 1.24; $P = 0.72$) and PS1 (HR = 1.07, 99% CI 0.75, 1.52; $P = 0.62$). Similarly, patients with LDH ⩽ ULN at baseline had

Table 1 – Patient Demographics – all randomised patients.

	Temozolomide ($N = 429$) n, (%)	Dacarbazine ($N = 430$) n, (%)
Age, years		
<65	276 (64)	261 (61)
⩾65	153 (36)	169 (39)
Sex		
Male	250 (58)	253 (59)
Female	179 (42)	177 (41)
WHO ECOG performance status		
0	302 (70)	294 (68)
1	127 (30)	136 (32)
LDH		
⩽ULN	295 (69)	284 (66)
>ULN – ⩽2 × ULN	131 (31)	145 (34)
>2 × ULN	3 (<1)	1 (<1)
WBC (× 10^9/l)		
⩽10	357 (83)	359 (83)
⩾10	72 (17)	71 (17)

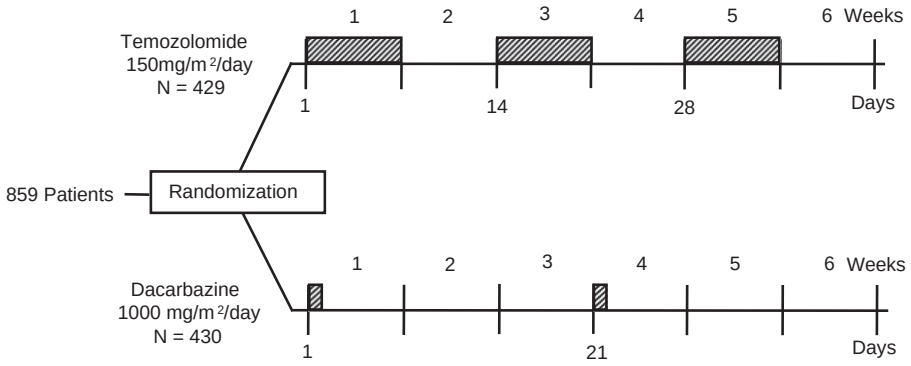

Fig. 1 – Treatment Regimen.

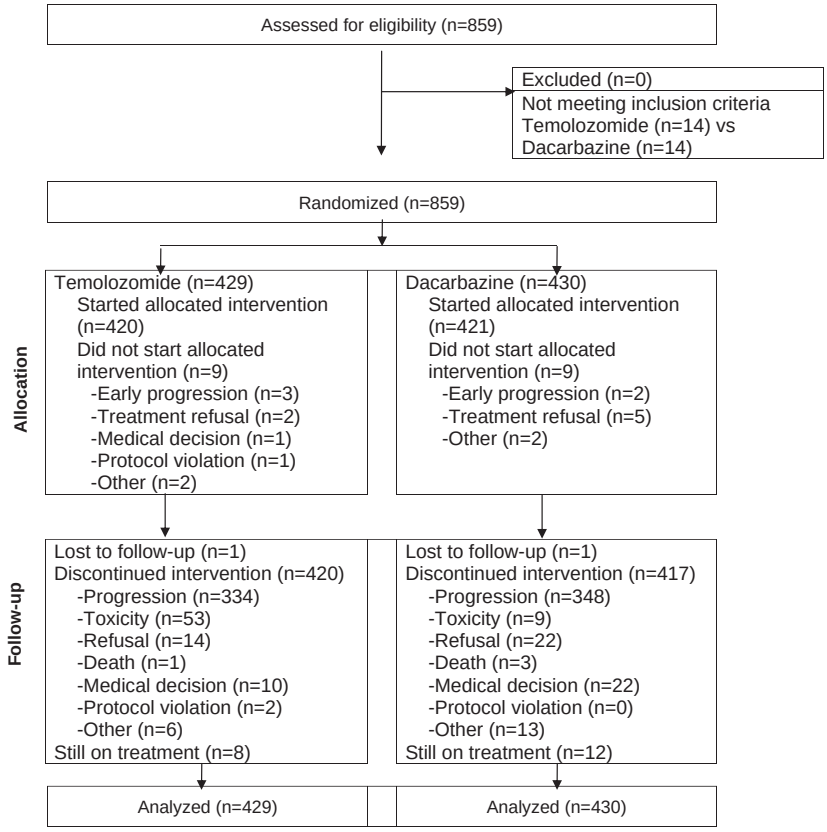

Fig. 2 – Consort flow diagram.

better median OS than with LDH > ULN (10.9 months versus 6.2 months). Again differences in outcome between the two treatment arms were consistently small in the two subgroups: LDH ⩽ ULN (HR = 1.04, 99% CI 0.80, 1.35; $P = 0.67$) and LDH > ULN (HR = 0.93, 99% CI 0.67, 1.29; $P = 0.55$).

In the entire patient population, multivariate analysis, using a Cox model, showed that initial LDH (>UNL versus ⩽ UNL: HR = 2.03, 95% CI 1.73, 2.40; $P < 0.0001$), WBC (⩾10 versus $< 10 \times 10^9$/l: HR = 1.48, 95% CI 1.21, 1.82; $p = 0.0001$) and PS (PS 1 versus PS 0: HR = 1.29, 95% CI 1.09, 1.53; $P = 0.003$) were the strongest independent prognostic factors, whereas sex (female versus male: HR = 0.88, 95% CI 0.75, 1.02; $P = 0.10$) and treatment (temozolomide versus dacarbazine: HR = 1.01, 95% CI 0.86, 1.18; $P = 0.91$) had no significant impact on OS.

No interaction between each of these three important prognostic factors and treatment difference has been

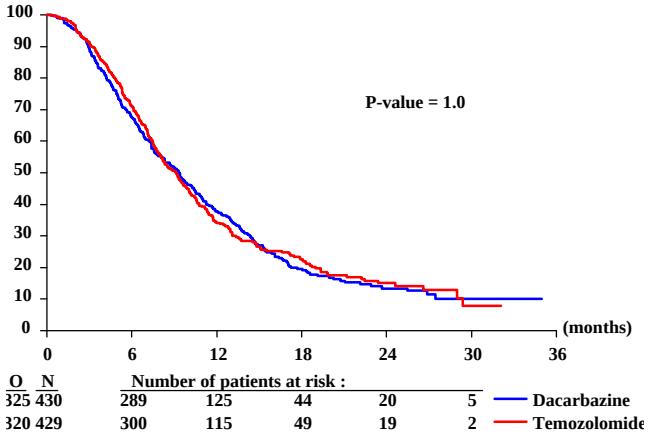

Fig. 3A – Overall survival by treatment group. O, observed number of deaths; N, number of patients; P-value given by the logrank test; Median estimate: 9.16 months (Temozolomide) vs 9.36 (Dacarbazine); Hazard ratio = 1.00, 95% confidence interval (0.86, 1.17).

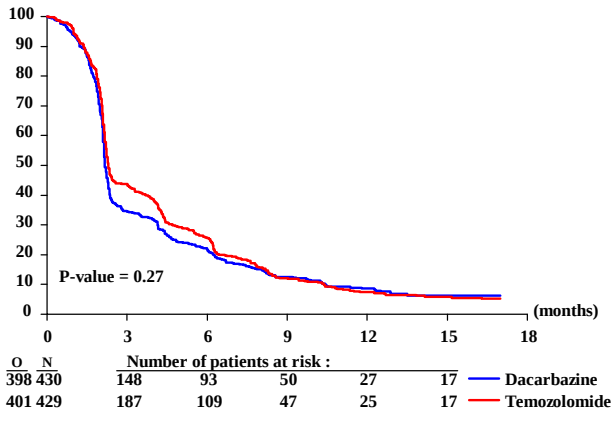

Fig. 3B – Progression-free survival. O, observed number of progressions or deaths; N, number of patients; P-value given by the logrank test; Median estimate: 2.30 months (Temozolomide) vs 2.17 months (Dacarbazine); Hazard ratio = 0.92, 95% confidence interval (0.80, 1.06).

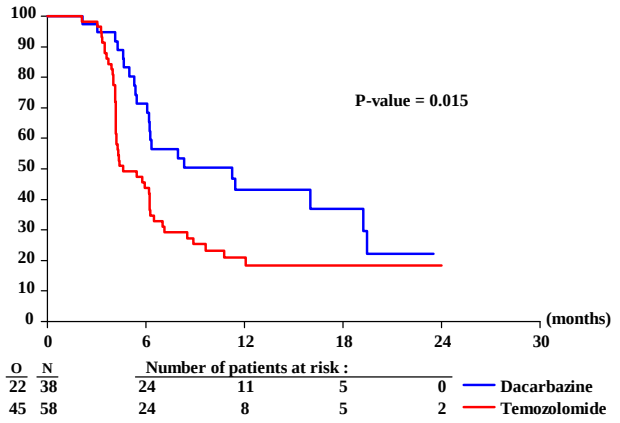

Fig. 3C – Duration of response. O, Observed number of relapses; N, number of patients; P-value given by the logrank test; Median estimate: 4.6 months (Temozolomide) vs 11.2 months (Dacarbazine); Hazard ratio = 1.87, 95% confidence interval (1.12, 3.12).

detected. For instance, in patients with LDH ⩽ ULN at baseline, who had a median OS of 10.9 months, the treatment difference was small (HR = 1.04, 99% CI 0.80, 1.35; *P*=0.67) as was in patients with LDH > ULN at baseline (median OS of 6.2 months): HR = 0.93, 99% CI 0.67, 1.29; *P*=0.55. Treatment results according to initial PS or WBC were similar as well (*data not shown*).

3.5. *Safety*

The percentage of patients reporting grade 3 and 4 adverse events (AEs) was 35% in the temozolomide arm and 29% in the dacarbazine arm. These differences are not unexpected given the dose intensification. The most frequently reported non-haematological AEs observed with temozolomide and dacarbazine were similar, and included nausea, fatigue, vomiting and constipation. There was a higher incidence of lab results of a grade 3 and 4 for lymphopenia (45 versus 8%) and thrombocytopenia (11 versus 6%) in patients treated with temozolomide compared with patients treated with dacarbazine (Table 3). However, the incidence of grade 3 and 4 neutropenia for all treated patients was higher in the dacarbazine arm than in the temozolomide arm (16% versus 10%, respectively).

There were 6 deaths as a result of AEs in the temozolomide arm and 7 in the dacarbazine arm. None of these deaths were attributed to the treatment.

Table 2 – Overall Response Rate – all measurable patients.

	Temozolomide (*N* = 401) *n*, (%)	Dacarbazine (*N* = 388) *n*, (%)
Complete response	8 (2.0)	4 (1.0)
Partial response	50 (12.5)	34 (8.8)
Stable response	94 (23.4)	89 (22.9)
Progressive disease	230 (57.4)	246 (63.4)
Not assessable	19 (4.7)	15 (3.9)

Table 3 – Toxicity (Grade 3–4), expressed as%.

	Temozolomide	Dacarbazine
Haematological toxicity	*N* = 417	*N* = 416
Leucopaenia	9	8
Neutropenia	10	16
Lymphopenia	45	9
Thrombocytopenia	11	6
Anaemia	3	2
Non-haematological toxicity	*N* = 420	*N* = 419
Fatigue	6	5
Vomiting	4	2
Nausea	3	3
Dyspnoea	2	2
Constipation	2	<1
Anorexia	2	<1
Other gastrointestinal	1	2
Dizziness	1	<1
Neurological (motor)	1	1
Cardiac	<1	1

Fifty-three patients (12%) in the temozolomide arm and 9 (2%) in the dacarbazine arm discontinued treatment due to toxicity, either due to the protocol-defined toxicity or toxicity based on investigators' judgment (Table 2).

4. Discussion

In our study in patients with metastatic melanoma, temozolomide at extended schedule and esclalated dose failed to improve median OS compared with dacarbazine. The patients in our study had comparable baseline characteristics between the treatment arms. Approximately 70% of the population had an ECOG performance status of 0 and 68% had a LDH level lower than the upper limit of normal. The study was adequately powered to detect improvement in median OS. The PFS for both dacarbazine and temozolomide was similar to that reported in other studies.[17,18] The response rates for both drugs were at the lower end of the range previously reported; with more than 90% of patients being evaluated. The complete and objective response rates were higher for the temozolomide arm; however, the median duration of response was longer in patients treated with dacarbazine. In a previous phase III study, comparing the standard temozolomide regimen with dacarbazine, the response rates are similar to those reported in our study, but the median duration of response was longer in the temozolomide group.[18] However in both studies the numbers of patients with responses are low and so the statistical power of these observations is weak.

This study confirms the previous observations that LDH, PS and also initial WBC have prognostic significance in metastatic melanoma but failed to show an interaction with the treatment arm[28,29] Both dacarbazine and temozolomide had acceptable safety profiles. Treatment-emergent adverse events, SAEs and grade 3 or greater toxicities were reported more frequently for dose-dense temozolomide than for single agent dacarbazine at standard dose. This increased frequency on the temozolomide treatment arm is not unexpected considering the dose-dense schedule. The safety profile of temozolomide was similar in nature to what is known about temozolomide and did not raise any new safety signals.

Decreased lymphocyte count was more frequent in the temozolomide arm, however, only one patient who was treated in the temozolomide arm was reported to have had an opportunistic infection.

Currently, the temozolomide regimen of 200 mg/m^2/day for 5 days every 28 days described by Middleton et al., is often used in patients with metastatic melanoma.[18] Although no improvement in efficacy was observed for temozolomide compared with dacarbazine treatment, our study demonstrates that use of the extended, escalated dosing regimen is also safe and feasible in patients with stage IV melanoma. Other alternative temozolomide regimens that suppress MGMT resistance are currently being investigated in patients with advanced cancer. Temozolomide is an oral agent and so has potential advantages over dacarbazine in terms of convenience. It is also known to cross the blood brain barrier which could potentially reduce incidence of brain metastases.[30] These factors along with its known pharmacokinetic and favourable safety profile make it an alternative agent with which to explore combinations with novel agents. In conclusion, extended schedule, escalated dose temozolomide (7 days on 7 days off) is feasible and has an acceptable safety profile, but does not improve the median OS and PFS in metastatic melanoma patients when compared to standard dose dacarbazine.

Conflict of interest statement

Consulted for/advised/and/or received honoraria from Shering Plough/Merck (P.P., D.S., D.R., J.B., A.E., H.K. and A.S.). W.J.-H. has research funded by Shering Plough.

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