# original article

# Temozolomide plus pegylated interferon alfa-2b as first-line treatment for stage IV melanoma: a multicenter phase II trial of the Dermatologic Cooperative Oncology Group (DeCOG)

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**Background:** Combination of temozolomide (TMZ) with nonpegylated interferon alfa is associated with increased efficacy in terms of response rates compared with monotherapy. A multicenter phase II study was carried out to assess the activity and toxicity of TMZ plus pegylated interferon alfa-2b (peg-IFNα-2b), hypothesizing improved efficacy due to modified pharmacokinetic properties of the novel interferon (IFN) formulation.

**Patients and methods:** In all, 124 patients with stage IV melanoma without prior chemotherapy and no cerebral metastases were treated with 100 µg peg-IFNα-2b s.c. per week and oral TMZ 200 mg/m$^2$ (days 1–5, every 28 days). Primary study end point was objective response, and secondary end points were overall and progression-free survival (PFS) and safety.

**Results:** In all, 116 patients were assessable for response: 2 (1.7%) had a complete response and 19 (16.4%) a partial response (overall response rate 18.1%). Of total, 25.0% achieved disease stabilization and 56.9% progressed. Overall survival was 9.4 months; PFS was 2.8 months. Grade 3/4 thrombocytopenia occurred in 20.7% and grade 3/4 leukopenia in 23.3%.

**Conclusions:** The efficacy of TMZ plus peg-IFNα-2b in this large phase II study is moderate and comparable to published results of the combination of TMZ with non-peg-IFN. Likewise, the safety profile of peg-IFNα-2b seems to be similar to non-peg-IFN when combined with TMZ.

**Key words:** metastatic melanoma, pegylated interferon alfa-2b, temozolomide

## introduction

Metastatic melanoma patients have a dismal prognosis mostly due to the unsatisfactory efficacy of chemotherapy. With response rates ranging from 6% to 15% and a median progression-free survival (PFS) of 2–3 months in large randomized trials, there clearly is a need to improve systemic therapy [1]. Regarding responsiveness to treatment, advanced melanoma is comparable to metastatic renal cell carcinoma (RCC), which is one of the most uniformly resistant solid tumors in oncology. But in contrast to RCC, in which tyrosine kinase inhibitors sunitinib and sorafenib have

recently revealed convincing therapeutic activity [2], no significant progress has been made as to advanced melanoma therapy by now. One of the most promising agents regarding approval appears to be the alkylating agent temozolomide (TMZ). A large randomized trial by Middleton et al. [3] had shown an activity of TMZ at least equal to that of dacarbazine (DTIC) with a small but statistically nonsignificant impact on survival and quality of life (QoL). Its advantage over DTIC is the oral availability and its ability to cross the blood–brain barrier. Further data are expected to clarify its role in delaying the occurrence of cerebral metastases. Currently, TMZ is being tested in comparison to DTIC in metastatic melanoma by the European Organization for Research and Treatment of Cancer (EORTC) (EORTC 18032) aiming for registration of a dose-intensified schedule of TMZ.

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Interferon alfa (IFNα) has been proven to have antitumoral activity in a variety of neoplastic diseases including stage IV melanoma. Pegylated interferon alfa-2b (peg-IFNα-2b) is a covalent conjugate of recombinant IFNα-2b with a 12 000 Da polyethylene glycol moiety. Pegylation of IFNα-2b results in a product whose clearance is lower than that of non-peg-IFNα-2b. At effective therapeutic doses, peg-IFNα-2b has an ~10-fold greater $C_{max}$ and a 50-fold greater area under the curve than IFNα-2b. The longer mean half-life permits a reduced dosing frequency [4]. Modifying the pharmacokinetic profile of IFNα-2b by pegylation may improve its activity and tolerability. Peg-IFN has been previously demonstrated to increase efficacy in hepatitis C compared with non-peg-IFN [5]. Likewise, its activity has been indicated in metastatic solid tumors including melanoma. In a phase I/II study, 35 patients with a variety of advanced solid tumors received different doses of peg-IFNα-2b. While the overall rate of complete responses (CRs) was 11.4% (4 out of 35), within the group of melanoma patients, 2 out of 6 (33%) achieved a CR [6].

These encouraging data along with the results of a previous randomized trial of the Dermatologic Cooperative Oncology Group (DeCOG), in which TMZ plus non-peg-IFNα-2b induced significantly higher response rates than TMZ alone [7], lead to the design of the current DeCOG phase II study with identical inclusion and exclusion criteria as applied in the previous study. The doses and schedules used in this trial are on the basis of former studies of TMZ in combination with IFNα-2b [8, 9], as well as on a phase I dose escalation study of peg-IFNα-2b [10]. We here report on the treatment of 124 advanced melanoma patients with this novel combination.

# patients and methods

### study design and patients

This study was designed as an open-labeled prospective multicenter phase II trial to investigate objective response (primary objective) and the overall survival (OS) and PFS as well as the safety profile (secondary objectives).

The protocol was approved by the Ethics Committee of the J.W. Goethe-University, Frankfurt am Main (Germany) and by the local committees of all participating centers. The trial was carried out in accordance with an assurance filed with and approved by the Department of Health and Human Services.

Eligibility criteria were identical with the previous clinical phase III study comparing TMZ and TMZ plus non-peg-IFNα-2b [7] and included written informed consent; histologically confirmed melanoma stage IV American Joint Committee on Cancer (AJCC) with no prior systemic therapy in stage IV and measurable disease; a Karnofsky performance status of ≥60%; age between 18 and 75 years; adequate bone marrow function (white blood cell > 3.0/nl, platelets > 100/nl), adequate renal function (serum creatinine clearance more than two times the upper limit of normal) and hepatic function (bilirubin level < 1.5 mg/dl). Prior treatment (adjuvant, stage II/III) had to have been completed at least 4 weeks before first drug exposure. Patients were not eligible if they had evidence of central nervous system metastases or severe cardiac, pulmonary, metabolic, psychiatric or other serious comorbidities or if they were pregnant or nursing patients. Individuals with unknown primary melanoma could also participate, while patients with primary ocular or mucosal melanoma were excluded.

The combination treatment was carried out on an outpatient basis with a minimum of two cycles planned up to progression. TMZ (200 mg/m$^2$; Temodar®), provided by Schering-Plough Inc., Kenilworth, NJ, was taken orally as capsules (5, 20, 100 and 250 mg) in doses according to body surface per meter square on days 1–5 every 28 days. Peg-IFNα-2b (PegIntron® by Schering-Plough) was administered s.c. by the patient once weekly after adequate instruction at a flat dose of 100 μg. If no toxic effects of more than grade I National Cancer Institute—Common Toxicity Criteria (NCI–CTC) occurred after the first cycle, the peg-IFNα-2b dosage could be increased to 150 μg/week. In case of hematologic toxic effects, more than grade II dose reductions for TMZ and peg-IFNα-2b were mandatory. TMZ was reduced to 150 or 100 mg/m$^2$ TMZ after grade III or grade IV toxicity, the dosage for peg-IFNα-2b was reduced in two steps to 80 and 50 μg/week after first or second occurrence of grade III toxicity.

### safety assessments and evaluation of response

Laboratory tests (hematology, chemistry and urine analysis) were carried out before treatment and on days 14, 22 and 27. Side-effects were classified according to the NCI–CTC.

Metastatic disease was assessed before treatment and after every second cycle in 8-week intervals by computed tomography (CT) of chest and abdomen and magnetic resonance imaging or CT of the brain. Response criteria according to the World Health Organization Handbook for reporting results of cancer treatment were applied. CR was defined by disappearance of all measurable metastatic lesions. Partial response (PR) was defined as >50% decrease in disease bulk; stable disease was described as <25% decrease or increase in disease bulk. Disease progression was defined as either the appearance of new lesions or an increase in disease >25%. There was no centralized review of the radiology files provided.

### statistical analysis

The sample size was planned according to the number of patients in one arm of the former randomized phase III study comparing TMZ and TMZ plus non-peg-IFNα-2b carried out by the same study group [7], hypothesizing a response rate of the current combination at least as good as the previously applied combination of TMZ and non-peg-IFN which achieved an overall response of 24.1%. Certainly, only a descriptive comparison with this group of patients could be carried out. The patients' characteristics, response rates and toxic effects were compared using chi-square test, Kruskal–Wallis test or Wilcoxon test. OS was evaluated by descriptive analysis using Kaplan–Meier estimates of the survival curves and the log-rank test for comparisons of the OS time and time to progressive disease. Statistical analyses were carried out with the statistical software SPSS 13.0 (SPSS Inc., Chicago, IL).

# results

From October 2002 to July 2004, 124 patients with histologically confirmed metastatic melanoma were included in the study at 10 centers in Germany ($n = 9$) and Switzerland ($n = 1$). At the time of data analysis, 81.0% of patients had died from melanoma and median follow-up time was 9.4 months. All patients received oral TMZ on days 1–5 every 28 days plus s.c. peg-IFNα-2b once weekly ongoing. Four patients proved to be ineligible. In all, 120 patients were found to be eligible for treatment and made up the 'intent-to-treat' (ITT) population, thereof 116 patients were treated per protocol (Figure 1). Patient demographics showed a median age of 55.5 years and a performance status of 90% or more according to Karnofsky index in 88.3% of patients.

In accordance to the protocol, patients had not received prior systemic chemotherapy. In all, 31.6% of patients, however, had partial or complete surgical removal of local metastases, but exhibited measurable metastatic disease
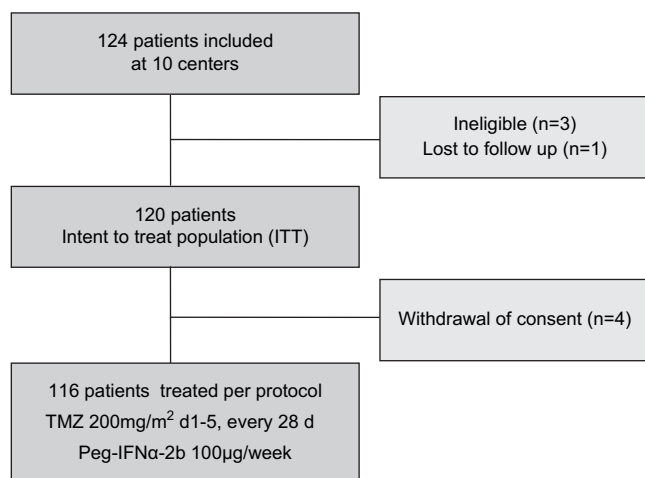


**Figure 1.** Study flow chart.

**Table 1.** Patient demographics and baseline disease characteristics (*n* = 120)

| | Number | % |
|---|---|---|
| Gender | | |
| Male | 80 | 66.7 |
| Female | 40 | 33.3 |
| Median age (range) | 55.5 (23–75) years | |
| Site of primary tumor | | |
| Head and neck | 14 | 11.6 |
| Trunk | 50 | 41.6 |
| Arms | 4 | 3.3 |
| Legs | 29 | 15.8 |
| Unknown primary site | 22 | 18.3 |
| Not reported | 1 | 0.8 |
| Median time from diagnosis to stage IV | 20.6 months | |
| Performance status (Karnofsky, %) | | |
| 100 | 69 | 57.5 |
| 90 | 37 | 30.8 |
| 80 | 7 | 5.8 |
| 70 | 4 | 3.3 |
| Not reported | 3 | 2.5 |
| Prior nonmedical therapy | | |
| Surgery | 38 | 31.6 |
| Radiotherapy | 7 | 5.8 |
| Stage (AJCC 2002) | | |
| M1a | 4 | 3.3 |
| M1b | 23 | 19.2 |
| M1c | 85 | 70.8 |
| Not evaluable due to missing LDH value | 8 | 6.7 |

M1a: distant skin, subcutaneous, or nodal metastases, normal LDH ; M1b: lung metastases, normal LDH; M1c: all other visceral metastases, normal LDH and any distant metastasis elevated LDH.
AJCC, American Joint Committee on Cancer; LDH, lactate dehydrogenase.

before chemotherapy, 5.8% received radiotherapy of nontarget lesion before study entry. More than two-thirds of the patients were grouped to AJCC stage M1c (Table 1).

## overall response, survival and PFS

In all, 21 of the 116 patients treated with TMZ plus peg-IFNα-2b responded to therapy (overall response rate 18.1%) and 25.0% achieved stable disease; the progression rate was 56.9% (Table 2). Specified by stage at the time of inclusion in the study, AJCC stage M1a patients achieved a remission in 75% (*n* = 3), decreasing to 21.7% (*n* = 5) in M1b and to 13.4% (*n* = 11) in M1c patients (*P* = 0.025). M1a: distant skin, subcutaneous, or nodal metastases, normal LDH (lactate dehydrogenase); M1b: lung metastases, normal LDH; M1c: all other visceral metastases, normal LDH and any distant metastasis elevated LDH.

The median OS time in the ITT population was 9.4 months [95% confidence interval (CI) 7.96–11.01 months]. Specified by stage, the median OS was 27.6 months for stage M1a patients, 11.5 months for M1b and 8.7 months for M1c (Figure 2 a, b). Among the responding patients (complete and partial responders), median OS was 15.2 months, and in patients without remission OS was 8.6 months (*P* = 0.0089).

The PFS for all patients was 2.74 months (95% CI 1.59–3.83 months). Specified by stage, the median PFS was

**Table 2.** Response to treatment (*n* = 116)

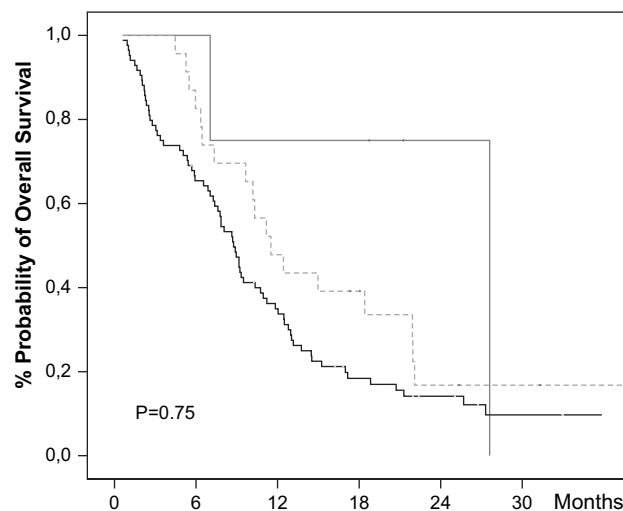| | Number | % |
|---|---|---|
| Complete response | 2 | 1.7 |
| Partial response | 19 | 16.4 |
| Overall response | 21 | 18.1 |
| Stable disease | 29 | 25.0 |
| Progressive disease | 66 | 56.9 |



**Figure 2.** Stage-specific median overall survival; M1a (bold line, blue), M1b (dotted line, red) and M1c (bold line, black). M1a: distant skin, subcutaneous, or nodal metastases, normal LDH (lactate dehydrogenase); M1b: lung metastases, normal LDH; M1c: all other visceral metastases, normal LDH and any distant metastasis elevated LDH.

17.0 months for M1a patients, 3.07 months for M1b and 2.7 months for M1c patients ($P = 0.296$, median test). Duration of response for patients with complete or partial remission showed a median of 11.7 months; 11 out of 21 (52.4%) patients with response survived longer than 12 months.

In all, 16 patients showed a PFS of 6 or more months. Concerning the total collective, 45 patients survived longer than 12 months (39.3%).

### safety

In total, 116 patients treated per protocol received an overall number of 490 cycles; a median of four cycles was administered to each patient (range 2–20 cycles). Hematologic side-effects were observed most frequently and were managed by dose modifications according to the protocol. In all, 50 patients received a modified scheme: reduced doses ($n = 33$), prolonged intervals ($n = 7$) or prolonged intervals and reduced doses ($n = 10$). Seven patients eventually discontinued treatment due to adverse events. Sixteen patients received the increased dose of 150 µg peg-IFNα-2b according to the protocol. Among all patients ($n = 116$), the incidence of hematologic toxicity in all NCI–CTC grades was 63.8% for leukopenia and 41.4% for thrombocytopenia. In all, 40.7% of patients suffered from mild anemia. Grade 3 and 4 toxic effects consisted primarily of leukopenia (23.3%) and thrombocytopenia (20.7%). The most common non-hematologic adverse events were nausea and vomiting (38%), constitutional symptoms as fever (22.4%) and elevation of liver enzymes (30.1%) (Table 3).

There was no statistical significant difference in the incidence of hematologic side-effects between patients treated with 100 and the small group who received 150 µg peg-IFNα-2b (leukopenia 65% versus 56.2%, $P = 0.9$; thrombocytopenia 44% versus 25%, $P = 0.44$).

One patient suffered from a nonlethal myocardial infarction during therapy, and in one patient a sarcoidosis was diagnosed shortly after the initiation of treatment. Another patient experienced acute renal failure with tubular necrosis possibly related to study medication, but recovered without sequelae. There were no treatment-related deaths.

### discussion

TMZ, an imidazol derivative, is a second generation alkylating agent sharing its active metabolite with DTIC, which still

**Table 3.** Toxicity of treatment with TMZ and peg-IFNα-2b (in %, $n = 116$)

|  | Grade 0 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Leukopenia | 36.2 | 13.8 | 26.7 | 19.0 | 4.3 |
| Thrombocytopenia | 58.6 | 12.9 | 7.8 | 12.9 | 7.8 |
| Anemia | 59.3 | 28.8 | 9.3 | 2.5 | – |
| Nausea/emesis | 62.1 | 23.3 | 12.9 | 1.7 | – |
| Constitutional/fever | 77.6 | 14.7 | 6.9 | 0.9 | – |
| Liver enzyme elevation | 69.8 | 15.5 | 10.3 | 4.3 | – |

TMZ, temozolomide; peg-IFNα-2b, pegylated interferon alfa-2b.

remains the only 'standard' agent in metastatic melanoma [11]. TMZ has a remarkable penetration profile into all body tissues, including the brain and is absorbed rapidly and nearly completely after oral administration. After numerous trials of DTIC in combination with IFNα obtaining improved response rates without affecting survival, combining TMZ with cytokines or other agents such as thalidomide are being tested for obtaining an improvement of future melanoma therapy in stage IV disease. First results of three-phase II trials with TMZ and IFN combinations were presented in spring 2002, when the current study was planned [8, 9, 12]. As a novel IFN formulation was available, which showed superior results in infectious diseases such as hepatitis, the addition of peg-IFN to TMZ appeared to be promising and led to the design of the current study. By now, further regimens have been evaluated testing various combinations with TMZ: results of trials combining TMZ with interleukin-2, the Cox-2 inhibitor celecoxib or thalidomide have been published recently [13–15]. Likewise, the combination of peg-IFN with chemotherapy has been evaluated in different types of cancers as in glioblastoma or hepatocellular carcinoma [16, 17]. Furthermore, the efficacy of monotherapy with peg-IFNα-2a in metastatic melanoma has been shown lately in a dose-escalating study with 150 patients [18].

Our study is the first trial combining peg-IFN with standard dosed TMZ in metastatic melanoma, resulting in an overall response of 18.1%. PFS rate at 6 months was 13.8% for the total collective and 76.2% among the responding patients. In 2006, the results of a phase II trial with a low dose extended schedule of TMZ plus peg-IFNα-2b were published. Hwu et al. [19] administered TMZ daily (75 mg/m$^2$/day) for 6 weeks followed by a 2-week rest plus concomitant peg-IFNα-2b (0.5 µg/kg/week, s.c.) and reported a response rate of 31%. These response rates are comparable with those seen with TMZ plus non-peg-IFNα. Several studies with TMZ and non-peg-IFN obtained response rates between 12% and 35% [8–10, 12, 20] (Table 4). Danson et al. [8] conducted a randomized phase II trial comparing TMZ alone and combinations of TMZ with IFN or thalidomide. TMZ and IFN proved to be superior in terms of response rates to TMZ alone (PR 9% versus 15% and CR 0% versus 3%); the TMZ/thalidomide combination also exceeded TMZ monotherapy in clinical responses. The previous DeCOG trial [7] demonstrated an overall response of 24.1% for the TMZ and IFN combination. Patient's characteristics for the combination arm of the former DeCOG trial and the current study are similar; however, comparison of the results from the former and the current DeCOG trial did not reveal considerable differences and certainly no advantage for the peg-IFN as to the rates for partial remission (16.1% versus 16.4%), stable disease (17.5% versus 25%) and for progressive disease (57.7% versus 56.9%). Regarding CRs there was actually a clear discrepancy in favor of the nonpegylated formulation (8% versus 1.7%). The safety profile of both IFN preparations is regarded to be similar in general. Also in combination with TMZ, the applied doses of nonpegylated and peg-IFN display comparable toxic effects when compared with data from the literature (Table 4). The application of

**Table 4.** TMZ and IFNα-2b in metastatic melanoma

| Author (reference) | $n$ | TMZ dose | IFNα-2b dose | OR | OS | PFS | Myelotoxicity (WHO grade III/IV) |
|---|---|---|---|---|---|---|---|
| Danson et al. [8] | 62 | 200 mg/m$^2$ (1) | 5 MU TIW | 18% | 7.7 months | ND | (A) Grade III/IV 21% (B) Grade III/IV 23% |
| Agarwala et al. [10] | 17 | 150 mg/m$^2$ (1) | 5–10 MU/m$^2$ TIW | 12% | 9 months | ND | (A) Grade III/IV 0% (B) Grade III/IV 12% |
| | 6 | 200 mg/m$^2$ (1) | 5 MU/m$^2$ TIW | 33% | | | (A) Grade III/IV 17% (B) Grade III/IV 33% |
| Richtig et al. [20] | 20 | 150 mg/m$^2$ (1) | 10 MU/m$^{2a}$ | 35% | 14.5 months | 124 days | (A) Grade III 6.4% |
| | 27 | 150 mg/m$^2$ (1) | 10 MU$^a$ | 22.2% | | | (B) Grade III 14.8% |
| Ridolfi et al. [12] | 40 | 200 mg/m$^2$ (1) | 5 MU TIW | 12.5% | 11.8 months | 2.6 months | (A) Grade III/IV 10% (B) Grade III/IV 25% |
| Kaufmann et al. [7] | 137 | 200 mg/m$^2$ | 5 MU/m$^2$ TIW | 24.1% | 9.7 | 3.3 months | (A) Grade III/IV 20.5% (B) Grade III/IV 22.7% |
| Garcia et al. [9] | 27 | 150 mg/m$^2$ (1) | 10 MU b.i.d | 18.5% | 9.5 | 1.87 months | (A) Grade III/IV 18.5% (B) Grade III/IV 7.4% |
| | | | Pegylated IFN | | | | |
| Hwu et al. [19] | 35 | 75 mg/m$^2$/day (2) | Peg-IFNα-2b 0.5 µg/kg/week | 31% | 12 | ND | (A) Grade III 40% |
| Own data | 124 | 200 mg/m$^2$ (1) | Peg-IFNα-2b 100 µg/week | 18.1% | 9.4 | 2.74 months | (A) Grade III/IV 23.3% (B) Grade III/IV 20.7% |
| | | (1) refers to days 1–5 every 28 days; (2) refers to 6 weeks on/2 weeks off | Nonpegylated IFN | | | | (A) refers to Leukopenia (B) refers to Thrombocytopenia |

$^a$Every other day.
TMZ, temozolomide; IFNα, interferon alfa; n, number of patients; OR, overall response; OS, overall survival; PFS, progression-free survival; WHO, World Health Organization; MIU, million IU; TIW, thrice weekly; ND, no data; BIW, twice weekly; Peg-IFNα-2b, pegylated interferon alfa-2b.

different dosing regimen for TMZ and IFN yet limits final conclusions. Up to now, there is one uniform treatment offered for all stage IV patients. Subgroups with differing prognosis within the stage IV population can be identified by stratifying patients. The sites of metastases and elevated serum levels of lactate dehydrogenase are useful to delineate the AJCC M categories into three groups: M1a, M1b and M1c, with 1-year survival rates ranging from 41% to 59% [21]. These subgroups also show a different outcome after chemotherapy. In our study collective, OS was varying between 27.6 months (M1a) and 8.7 months (M1c). Besides this, few data are available to predict a response to systemic therapy. Therefore, investigative efforts should be focused on identifying further predictive factors.

Whereas introduction of peg-IFNs has significantly improved the eradication rates in patients with chronic hepatitis C, potential therapeutic advantages of the peg-IFN formulation compared with non-peg-IFN are yet to be demonstrated in metastatic melanoma. It has been claimed that peg-IFN allows patients to achieve a higher exposure to IFNα than non-peg-IFNα without reaching dose-limiting toxicity and thereby enhancing activity. This effect possibly still is not achieved with the applied regimens so far. To our knowledge up to now, there is only one phase III trial comparing pegylated and non-peg-IFN in an oncologic indication. The study by Michallet et al. [22] published in 2004 could not demonstrate statistical noninferiority of peg-IFNα-2b in newly diagnosed chronic myelogenous leukemia. In terms of QoL and ease of administration peg-IFNs may display advantages over

conventional formulations, as the longer half-life allows for once weekly injections only. Addition of either nonpegylated or peg-IFN to TMZ chemotherapy, however, fails to significantly increase OS in advanced melanoma patients. Our results are thus in line with a recent Cochrane Database Systematic Review [23], indicating that using existing immunotherapeutics and chemotherapies no significant advantage has yet been achieved. As a consequence, combined chemoimmunotherapy protocols, including those containing new formulations such as peg-IFNs, should preferably be evaluated in clinical trials.

## conflict of interest statement

AH is a member of the speakers' bureau, consultant and investigator for Schering-Plough. DS had honoraria from Schering-Plough and is conducting research sponsored by Schering-Plough. All other authors: none declared.

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