region, affecting not only stage-specific survival comparisons between populations, but also between different types of hospital. Similarly, clinicians in specialist oncological institutions are more likely to carry out more exhaustive and 'aggressive' staging to establish appropriate therapy, and enrol their patients in clinical trials.

Knowledge, not only of disease stage at diagnosis but also the staging procedures used to define that stage is, therefore, vital for interpreting survival differences. Unfortunately, information on the diagnostic procedures used for defining disease stage is rarely available to population-based cancer registries. The EUROCARE Working Group is seeking to obtain information on disease stage, staging procedures and treatments for a representative sample of incident cases in European populations for colorectal, breast, testis, stomach and prostate cancers (data not shown). A major EUROCARE priority is to carry out stage-specific survival comparisons, based on the staging procedures actually used. Controlling for these variables will enable us to assess the extent to which survival differences depend on different treatments or differences in treatment effectiveness in relation to early versus late diagnosis.

1. Berrino F, Gatta G, Chessa E, Valente F, Capocaccia R. and the EUROCARE Working Group. Introduction: the EUROCARE II study. *Eur J Cancer* 1998, **34**, 2139–2153.
2. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med* 1985, **312**, 1604–1608.

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Comments on: *Treatment of Metastatic Malignant Melanoma with Dacarbazine Plus Fotemustine*, Seeber, *et al.*, *Eur J Cancer* 1998, 34, 2129–2131

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We read with interest the paper of Seeber and colleagues [1] that reported on the clinical activity of a regimen including dacarbazine (DTIC) 200 mg/m^2 on day 1 and fotemustine (FM) 100 mg/m^2 on day 2, recycled every 4 weeks in 63 patients (14 of whom were previously treated with chemotherapy) with advanced melanoma. These authors observed 3 complete and 4 partial responses, for an overall response rate of 11% (95% confidence interval (CI) 5–22%). Although no overall survival of the whole series was reported, it can be argued from their Figure 1, showing survival curves according to response to treatment that the median duration of survival of this population should have been approximately 6–7 months, corresponding to the median survival time of the patients (52%) showing stable disease with this regimen. We also have utilised a combination of DTIC + FM, with the addition of r-interferon α between courses, for the treatment of patients with advanced melanoma [2]. However, we have administered FM 100 mg/m^2 on day 1, followed by DTIC 250 mg/m^2 on days 2–5, every 3 weeks, obtaining 4 complete and 13 partial responses among 43 chemonaïve (but 22 had previously received adjuvant interferon α) patients with advanced melanoma, for an overall response rate of 40% (95% CI 25–56%). The median survival time of our series was 40 weeks and the 2 year probability of survival was 13%. We have subsequently conducted a further trial testing the addition of cisplatin (CDDP), 25 mg/m^2 on days 3 and 4 to a regimen including FM 100 mg/m^2 on day 1 and DTIC 300 mg/m^2 on days 2–4, recycling every 3–4 weeks, with granulocyte macrophage-colony stimulating factor (GM-CSF) support when needed. Among 60 chemonaïve patients, 11 complete and 12 partial responses were registered, for an overall activity rate of 38% (95% CI 26–62%). The median survival time resulted of 39 weeks and the 2 year projected survival was 32% [3]. Therefore, based on our whole experience of more than 100 treated patients, we are confident that at least 30% of patients treated with a regimen including FM + DTIC ± CDDP could reach a major response and that some of them may also enjoy prolonged survival. Although the comparison of results obtained in different series of patients is always difficult to interpret and therefore should be considered with caution, we wonder why Seeber and colleagues reported such dismal activity with their regimen. A possible explanation might be the dosages and schedule they adopted, with an unusual low dose of DTIC given every 4 weeks, that translated into a poorly intensive treatment. Their aim was to avoid the life-threatening pulmonary toxicity from DTIC + FM combination. However, this kind of unpredictable toxicity has been reported only when both drugs were administered together on the same day [4–6]. On the contrary, when DTIC was given at increasing doses (400, 500, 800 mg/m^2) 4 h before FM (100 mg/m^2) every 4 weeks, the resulting response rate was linearly related to DTIC dosage, being 24, 30 and 40%, respectively [6], confirming the clinical relevance of an adequate treatment. In our experience with the FM + DTIC sequential treatment, no patient suffered from pulmonary side-effects and no difference in activity according to main metastatic site was observed in either series. Therefore, when the drugs are given 24 h apart, a peculiar cytotoxicity on lung tissues could be ruled out. Since we share the hope of Seeber and coworkers that an objective remission may be associated with longer survival, we also believe that, in the palliative treatment of the advanced disease, every effort should be made to deliver active combination chemotherapy at the maximum recommended dose to increase the likelihood of achieving a rapid tumour shrinkage without excessive toxicity.

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1. Seeber A, Binder M, Steiner A, Wolff K, Pehamberger H. Treatment of metastatic malignant melanoma with dacarbazine plus fotemustine. *Eur J Cancer* 1998, **34**, 2129–2131.
2. Comella P, Daponte A, Casaretti R, *et al.* Fotemustine and decarbazine plus recombinant interferon alpha2a in the treatment of advanced melanoma. *Eur J Cancer* 1997, **33**, 1326–1329.
3. Daponte A, Comella P, Cellerino R, *et al.* Combined immunochemotherapy with cisplatin, dacarbazine, fotemustine, and interferon α2b in advanced melanoma. A phase II study of the Italian Melanoma Study Group (IMSG). Proceedings of the Ninth International Congress on Anti-Cancer Treatment, Paris, 2–5 February 1999.
4. Aamdal S, Gerard B, Bohman T, D'Incalci M. Sequential administration of dacarbazine and fotemustine in patients with disseminated malignant melanoma—an effective combination with unexpected toxicity. *Eur J Cancer* 1992, **28A**, 447–450.
5. Gerard B, Aamdal S, Lee S-M, *et al.* Activity and unexpected lung toxicity of the sequential administration of two alkylating agents—dacarbazine and fotemustine—in patients with melanoma. *Eur J Cancer* 1993, **29A**, 711–719.
6. Lee SM, Margison GP, Woodcock AA, Thacker N. Sequential administration of varying doses of dacarbazine and fotemustine in advanced malignant melanoma. *Br J Cancer* 1993, **67**, 1356–1360.