We conclude that combining drugs with relatively low single-agent activity, leads to improved results in these patients. This effect has also been shown when oxaliplatin and irinotecan were combined in fluorouracil-resistant colorectal carcinoma, as compared to their single-agent activity (Scheithauer *et al*, 1999). Our results are certainly comparable with those of Nomoto *et al*, who also used irinotecan in combination with cisplatin in relapsed disease; however, details regarding platinum sensitivity of their patients were not given (Nomoto *et al*, 2002). These *in vitro* and *in vivo* observations lead us to question whether single-agent phase II studies, conducted in a highly refractory patient population may best be able to identify potentially useful cytotoxics, and certainly a negative result must be accepted with some degree of caution.

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Reply: Irinotecan in patients with relapsed or cisplatin-refractory germ cell cancer: a phase II study of the German Testicular Cancer Study Group

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Sir,

In their letter, Powles *et al* disagree with our conclusions drawn from the results of a phase II study on single-agent irinotecan in patients with refractory germ cell cancer (Kollmannsberger *et al*, 2002b). At the same time, they question whether single-agent phase II studies may be the best way to identify new potentially active drugs in these patients. This statement is based on preclinical as well as on preliminary clinical data, which must, however, be thoroughly discussed.

Preclinical studies demonstrating an increased level of expression of topoisomerase I in germ cell cancer specimens or an impressive activity of SN 38, the active metabolite of irinotecan, in cisplatin-resistant germ cell cancer cell lines, form a strong rationale for the evaluation of irinotecan in refractory germ cell cancer patients. However, since we know from many other agents that an *in vitro* activity may not always translate into clinical activity, these preclinical findings do not allow to draw the conclusion that irinotecan is active in refractory germ cell cancer patients. Evidence for clinical activity of new agents can only be provided by prospective clinical trials. Single-agent studies are typically employed to obtain hints of the potential activity of a new agent and to form a rationale for potential combinations. Of course, single-agent studies cannot detect a synergism with other drugs. Combination regimens in patients with refractory germ cell cancer may lead to improved results, but these combinations should include active drugs. Our study investigating irinotecan in

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refractory patients included 15 patients and none of them responded. Thus, the probability for a false rejection of an active drug was less than 5% (study design according to Gehan, 1961), which makes a clinical activity with >20% response rate of irinotecan unlikely. We agree with Powles *et al* that the negative results of a single phase II study should still be considered carefully. However, our study investigating irinotecan single-agent therapy in patients with refractory germ cell cancer was the second study that tested a topoisomerase I inhibitor in these patients. Topotecan, the second clinically available topoisomerase I inhibitor, has also been ineffective in relapsed or refractory germ cell cancer patients (Puc *et al*, 1995).

Based on the proven, but moderate activity of single-agents such as paclitaxel, oral etoposide, oxaliplatin or gemcitabine with response rates of 15–20% and median overall survival periods of 3–6 months in patients with refractory disease, the investigation of combinations of active drugs is appropriate. Hinton *et al* (2001) were the first who combined two drugs and demonstrated the feasibility and efficacy of combination chemotherapy even in heavily pretreated germ cell cancer patients. The rationale for the combination of paclitaxel and gemcitabine, however, was based on the activity of both drugs when given as single-agent therapy (Motzer *et al*, 1994; Bokemeyer *et al*, 1996, 1999; Einhorn *et al*, 1999). In their letter, Powles *et al* report a very high response rate of 67% and a median survival of 11+ months for the combination of oxaliplatin, paclitaxel and irinotecan. These favourable results, although still do not prove the activity of irinotecan in these patients since the two other drugs, oxaliplatin and paclitaxel, have been shown to be active in refractory germ cell cancer (Bokemeyer *et al*, 1996; Kollmannsberger *et al*, 2002a). A high activity of oxaliplatin/paclitaxel has already been demonstrated in cisplatin-resistant patients with metastatic ovarian cancer indicating that this combination may act synergistically and can overcome cisplatin resistance (Faivre *et al*, 1999). Thus, although not yet proven in a formal study, the combination of the two agents is very likely to be also active in refractory patients. Thus, the results reported by Powles may have been achieved solely with oxaliplatin/paclitaxel and the potential additional benefit of irinotecan cannot be derived from that study. In addition, patient selection plays an important role. In the study by Miki *et al* investigating the combination of irinotecan and cisplatin in relapsed germ cell cancer patients, only four of 18 patients had previously received high-dose chemotherapy plus blood stem cell support and in three patients, cisplatin/irinotecan was used as second-line therapy indicating that this may have been a rather favourable patient group. Moreover, no details were given about the cisplatin sensitivity of these patients (Miki *et al*, 2002). Similarly in the ongoing study by Powles using a combination of oxaliplatin, paclitaxel and irinotecan, only 22% of patients were cisplatin-refractory and 22% had previously received high-dose chemotherapy, which demonstrates still a more favourable risk profile of these patients in contrast to our study. In all our previous studies on refractory patients, the majority of these patients had been pretreated with high-dose chemotherapy or were truly cisplatin-refractory.

Thus, despite a strong rationale from *in vitro* results that had led us to investigate the use of irinotecan in relapsed or cisplatin-refractory germ cell cancer, no evidence for a clinically meaningful activity of irinotecan has thus far been provided. We clearly agree that patients with refractory germ cell cancer need to be treated within prospective clinical trails in order to learn more about possible therapeutic strategies.

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