Response

We thank Drs Bregni and Pedrazzoli, who are both members of the European Blood and Marrow Transplantation group, to give us another chance to emphasize that high-dose chemotherapy is clearly toxic and not superior to standard chemotherapy for the treatment of small-cell lung cancer (SCLC) and that the medical community should put its energy and money in new treatment approaches. Drs Bregni and Pedrazzoli suggest that some limitations of the study, eg, low patient number, high toxic death rate, low compliance in the high-dose arm, and weak subgroup analyses, might have contributed to the null findings. Indeed, the points they have raised in no way affect any part of the study or of the conclusions that we hereby confirm and stand by.

The design modification was made primarily because of slow accrual and without any prior knowledge of the accumulating evidence. The sequential design that was eventually adopted controlled the probability of an erroneous conclusion of the same magnitude as the original fixed sample design. The sample size to be reached if the trial had not stopped at any of the three interim analyses would have been larger than initially planned: This was the price to pay to allow for a sequential design. Thus, the change in design and a legitimate interim analysis cannot be considered as possible causes for missing a potentially real effect. Virtually no clinical trial is designed to test the interaction between treatment and prognostic factors, and ours was no exception. We may have provided stronger evidence, but definitely no reliable answer, to the question of benefit to subgroups, because our study would not have had the statistical power for that purpose, even if it had reached the full sample size.

When we presented data on relative dose intensity of the high-dose arm, we did so considering the actual drug dose and schedule that was received by each patient in relation to the intended protocol dose of the standard dose arm for that patient. We therefore can indeed claim an average threefold increase in dose, despite the fact that some patients did not receive complete treatment. Moreover, the compliance to the standard dose was also far from being complete.

Concerning the evidence supporting intensification in SCLC, the picture is not nearly as optimistic as Drs Bregni and Pedrazzoli suggest. Their conclusion in a recent publication (1) is that there is no evidence to support the use of high-dose chemotherapy in solid tumors, except, maybe, for breast cancer. Should there be a promising and less toxic chemotherapy, we would agree with Drs Bregni and Pedrazzoli that it would deserve attention, but this option is not on the horizon for SCLC thus far and even if it was, it would have to withstand competition from other, at least as interesting, novel therapeutic alternatives,

as suggested by Dr Bunn in his very supportive editorial (2) discussing our paper.

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References

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Notes

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