The Van Cutsem et al. (82) study contains an exemplary presentation that shows Kaplan-Meier curves for the entire study population, along with Kaplan-Meier curves for a subgroup within this population. This type of presentation is a frequent theme in reporting clinical trials in oncology, as well as for immune disorders, infections, metabolic diseases, and other disorders.

8. Anti-sense drug for melanoma and subgroup analysis – the Bedikian study

In the study of melanoma of Bedikian et al. (83) the study drug was oblimersen, a drug that is an anti-sense RNA. This drug is an 18-base phosphorothioate anti-sense oligonucleotide that binds to the first six codons of the bcl-2 mRNA open-reading frame and mediates RNA cleavage by RNase H. The goal of this drug is to prevent expression of the bcl-2 gene. Dacarbazine, as single-agent therapy, is the standard of care for melanoma (84). The Bedikian study took the form of an "add-on" design, because the control group had dacarbazine only, while the study drug group received oblimersen plus dacarbazine. Dacarbazine alone was the active control. The two study arms were as follows:

- Arm A. Dacarbazine plus oblimersen
- Arm B. Dacarbazine alone.

The study design is further distinguished in that, shortly after enrollment, subjects were tested for serum lactate dehydrogenase (LDH), and stratified into subgroups, according to high LDH versus normal LDH. Elevated LDH was defined as a baseline serum level at least 1.1 times the upper limit of normal. Tumors were evaluated at 6-week intervals. After completing chemotherapy, tumors were evaluated every 2 months for at least 2 years. Visual inspection of the Kaplan-Meier plots (not reproduced here) showed that arm A showed better results than arm B, where a separation between the two curves was first discernible at 2 months (plots of PFS), and at about 8 months (plots of overall survival). Data on PFS were also more dramatic in terms of hazard ratios, as indicated in Table 12.4.

The study drug improved the endpoints of PFS and overall survival for the entire study population as well as for the subgroup with normal serum LDH (Table 12.4). Subgroup analysis revealed that this improvement resulted from the contribution of a subgroup of a normal LDH subject. But with the subgroup of high LDH subjects, oblimersen does not have a significant influence on efficacy.

[82] Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *New Engl J Med*. 2009;360:1408–1417.

[83] Bedikian AY, Millward M, Pehamberger H, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol*. 2006;24:4738–4745.

[84] Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. *J Clin Oncol*. 2007;25:5426–5434.