

Pierre Fabre Response to Clarification Requests – Outstanding Answers 13/09/10

Section B: Clarification on cost-effectiveness data

Question B4 Page 76; table B31). The mean values and standard errors for OS and PFS hazard ratios presented in this table do not match those in table B32 (p78). Please explain the reason for this discrepancy

Response:

The hazard ratios used for VFL+BSC are reported in table B32: Estimates of OS for patients receiving vinflunine+BSC were calculated using the multivariate hazard ratio for vinflunine+BSC; an assumption of proportional hazards between events was maintained beyond trial duration (Figure B10b). Health outcomes for patients receiving VFL+BSC were calculated using multivariate hazard ratios for vinflunine (OS and PFS) from Study L007 IN 302 P1/Bellmunt (study 302). The hazard of experiencing an event (either disease progression or death) for patients receiving VFL+BSC was assumed to be proportional to the event hazard rates in the BSC group, based on findings from multivariate Cox regression analysis which adjusted for significant prognostic factors at randomization or baseline including: (1) visceral involvement; (2) pelvic irradiation (3) ECOG performance status; (4) alkaline phosphatase; and (5) haemoglobin. The effect of VFL+BSC on OS and PFS, respectively, was significant after adjusting for the five prognostic factors. A Weibull survival model was used to extrapolate PFS and OS for patients receiving BSC beyond the duration of follow-up in study 302 (i.e. 2.4 years). All analyses conducted using data from Study 302 were undertaken for the eligible patient population.

Question B5 Page 78; Table B32. Please provide the source of the estimates (mean and SE) used for the risk of adverse events with vinflunine plus BSC. Please explain the differences between these values and those presented in Table B34 (page 86).

Response:

- Severe adverse events (grades 3 and 4) in study 302 which could have an impact on HRQL were presented in Table 34.
- In the model (Table 32) or the economic evaluation (question 6.4.22), were identified medical-resource use for the management of constipation (grades 3 and 4) (20.2% [vinflunine+BSC], 0.9% [BSC]), febrile neutropenia (grades 3 and 4) resulting in hospitalization (5.2% [vinflunine+BSC], 0% [BSC]), and abdominal pain (grades 3 and 4) resulting in hospitalisation (1.2% [vinflunine+BSC], 0.7% [BSC]). Fatigue and injection-site reactions, while frequent in Study 302, were deemed not to involve additional utilisation of medical-care services and were not included.