10.2 Protocol Violations and Exemptions

Subject eligibility based on inclusion and exclusion criteria is shown in Listing 16.2.1.1. “Exemptions” were cases in which a subject was approved to enter the study, or to remain in the study, despite a protocol violation. All exemptions granted prior to study enrollment were documented on a protocol exemption request form, and a 3-digit exemption code was provided to the site for entry in the IVRS randomization system. Subjects granted such an exemption were considered to have not violated the protocol.

In certain instances, protocol violations were reported to the medical monitor using a protocol exemption form in order to seek approval for a subject to remain in the study. The medical monitor reviewed the case and, if appropriate, granted permission for the subject to stay in the study. Such post-hoc exemptions did not exempt the violation. CRO maintained a list of post-enrollment exemptions submitted, approved, and denied.

10.2.1 Protocol Violations Leading to Exclusion from Efficacy Analyses

Table 1 provides a summary of protocol violations that led to exclusion from efficacy analyses by treatment group. This information is provided by subject in Listing 16.2.1.3.

Table 1: Number (%) of subjects with protocol violations leading to exclusion from efficacy analyses by treatment group: Intent-to-Treat Population

Category	ANTICANCER plus DTIC (N = 357) n (%)[a]	DTIC (N = 353) n (%)[a]
Subjects excluded from efficacy analysis because of protocol violations	29 (7.5)	32 (8.3)
Did not receive at least 1 cycle of protocol therapy	21 (5.4)	25 (6.5)
Did not meet all eligibility criteria or received an exemption	9 (2.3)	5 (1.3)
Received other anti-melanoma medication during the treatment phase	0 (0.0)	1 (0.3)
Did not have confirmed normal brain scan result at baseline	3 (0.8)	5 (1.3)

Cross-reference: Table 14.1.6; Listings 16.2.1.3 [SJD: Other anti-melanoma medication in Listing 16.2.4.18]

[a] Percentages were calculated using N, the total number of subjects in the group, as the denominator.

In subjects in both treatment groups, the most frequent protocol violations leading to subject exclusion from the efficacy analysis were: not receiving at least 1 cycle of protocol therapy (ANTICANCER plus DTIC, 21 [5.4%] subjects; DTIC, 25 [6.5%] subjects).

The second most frequent protocol violation was: neither meeting all eligibility criteria or receiving an exemption (ANTICANCER plus DTIC, 9 [2.3%] subjects; DTIC, 5 [1.3%] subjects]. Of the 9 subjects in the ANTICANCER plus DTIC group, 1 subject completed 8 cycles of study therapy and was excluded for drug administration noncompliance (12401); 3 subjects completed 2 cycles and discontinued from the study because of disease progression (10801, 12801, 90138); 2 subjects completed 1 cycle and were discontinued because of subject ineligibility because mucosal melanoma (50010), and urticaria (30309); and 2 subjects were excluded from starting study therapy because of prior cyclophosphamide therapy (96202), and abnormal liver function (92801). [No information about the 9th subject, 82604, not in Listing 16.2.1.2.] Of the 5 subjects in the DTIC group, 1 completed 8 cycles of study therapy, had stable disease or responded to therapy (15201), 1 subjects completed 4 cycles of therapy and discontinued from the study because of disease progression (94202), 1 subject completed 2 cycles of therapy and discontinued from the study because of disease

progression, 1 subject completed 1 cycle of therapy and discontinued from the study because baseline lesions were immeasurable (93802), and 1 subject was not treated because he was found to have brain metastases (10906).

One subject (12301) was excluded from the efficacy analysis because he had received an additional anti-melanoma medication, tamoxifen, for one month, during which time he completed 1 cycle of study therapy.

The fourth reason for excluding subjects from efficacy analysis was when they lacked a confirmed normal brain scan at baseline. In the ANTICANCER plus DTIC group, 3 subjects were so excluded: 2 subjects were not given study therapy (91701, 92001) and 1 subject died after completing 1 cycles of study therapy (11001). In the DTIC group, 5 subjects were excluded because of lack of baseline brain scans; 1 subject completed 8 cycles of study therapy, and was responding or had stable disease (60107), 1 subject completed 2 cycles and discontinued the study because of disease progression (13601) and 3 subjects were not given study therapy because of brain metastases (10906), disease progression (13601) and death (90701).

10.2.2 Post-Enrollment Exemptions

A listing of those subjects who received a post-enrollment exemption, including the nature of the exemption(s), is included in Section 16.5.1.

10.3 Subjects Included in Efficacy, Pharmacokinetic/Pharmacodynamic, and Safety Analyses

Data from the Intent-to-Treat Population and the Per-Protocol Population were analyzed for efficacy. The Intent-to-Treat Population included 386 subjects in the ANTICANCER plus DTIC group and 385 subjects in the DTIC group. The Per-Protocol Population comprised all randomized subjects who completed 1 cycle of protocol therapy and were not excluded from analysis because of protocol violations or exemptions or receiving treatment for melanoma other than protocol therapy. These totaled 357 (92.5%) subjects in the ANTICANCER plus DTIC group and 353 (91.7%) subjects in the DTIC group, Table 14.1.1.

The Safety Population comprised all randomized subjects who received any protocol therapy (ANTICANCER plus DTIC, 371 [96.1%] subjects; DTIC, 360 [93.5%] subjects). Data from untreated subjects (for adverse events only) and data from the Safety Population were analyzed for safety.