

Appendix 3: Primary Study Results Before and After Amendment V

Amendment V changed the assigned dose of study drug from 0.50 mL/cm³ of tumor volume to 0.25 mL/cm³. In the same amendment, investigators were instructed to recalculate dose at each study visit, rather than calculating a fixed dose at Visit 1 and using the same amount throughout the study. Eligibility criteria were modified by Amendment V to exclude patients with tumors that involved or were in close proximity to the carotid arteries. A total of 178 patients were enrolled in Strata 1 and 2 of studies 414 and 514; 72 patients were enrolled before Amendment V and 106 patients after the amendment.

Demographics and baseline MTT volume were examined to determine what effects, if any, Amendment V had on the study samples. In most of these analyses, studies 414 and 514 were combined, as were strata 1 and 2.

1. 1 Demographics and MTT Volume

Table A3-1 shows patient age and gender before and after Amendment V.

Table A3-1: Patient Demographics, strata 1-2, combined studies

Characteristic	Before Amendment V n= 72	After Amendment V n= 106	All Patients n= 178
Age (years)			
Mean (sd)	63 (11.3)	60 (11.4)	61 (11.5)
Median	64	60	61
Range	40-87	33-84	33-87
Gender			
Male	64 (89%)	78 (74%)	142 (80%)
Female	8 (11%)	28 (26%)	36 (20%)

Mean and median age decreased slightly after Amendment V. In the post-amendment period the proportion of females enrolled increased, from 11% of patients to 26%.

Table A3-2 shows the MTT volume pre- and post-amendment. Mean and median tumor volumes for patients in strata 1- and 2 decreased slightly in the post-amendment period.

Table A3-2: Volume (cm³) of MTT at Treatment Visit 1 (Baseline), strata 1 & 2, combined studies

	Before Amendment V n= 72	After Amendment V n= 106	All Patients n= 178
Mean (sd)	7.2 (5.7)	6.9 (6.1)	7.0 (5.9)
Median	6.0	4.6	5.0
Range	0.13-20	0.49-20	0.13-20

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2 Response to Therapy

Key outcome variables were examined pre- and post-amendment, including MTT response and Patient Benefit rates. Table A3-3 shows MTT response rates before and after the amendment.

Table A3-3: MTT Response Before and After Protocol Amendment V, By Study, in Patients Randomized to CDDP/epi Gel

Study	Before Amendment V		After Amendment V		p-value ^a
	n	CR +PR response rate	n	CR +PR response rate	
414 (Stratum 1 & 2)	24	7 (29%)	38	14 (37%)	0.59
514 (Stratum 1 & 2)	21	6 (29%)	36	8 (22%)	0.53

^a Exact Cochran-Mantel-Haenszel test

The data in Table A3-3 are presented by study because the trends in the two studies were in opposite directions: in study 414, the pre-amendment response rate of 29% increased to 37% post-amendment. In study 514 the opposite effect was seen, with a decrease in response rate from 29% to 22%. These changes were consistent with chance variation, as shown by the p-values comparing the pre- and post-amendment rates in each study.

3 Response to Therapy, Combined Analysis by Stratum

Table A3-4: Summary of MTT Response Before and After Protocol Amendment V, Studies Combined, in Patients Randomized to CDDP/epi Gel

Stratum	Before Amendment V				After Amendment V			
	n	CR	PR	CR + PR	n	CR	PR	CR + PR
Stratum 1	22	5 (23%)	3 (14%)	8 (36%)	40	11 (28%)	4 (10%)	15 (38%) ^a
Stratum 2	23	3 (13%)	2 (9%)	5 (22%)	34	4 (12%)	3 (9%)	7 (21%) ^a
Strata 1 & 2	45	8 (18%)	5 (11%)	13 (29%)	74	15 (20%)	7 (9%)	22 (30%) ^a

^a p-value = 1 (Exact Cochran-Mantel-Haenszel test)

Table A3-4 shows the amendment's effects on response for the combined studies by MTT stratum. When the data are examined in this way, there is no substantive difference in rates of CR, PR or overall response (CR + PR) in either stratum.

2. 4 Patient Benefit

Differences in patient benefit rates observed before and after Amendment V were also evaluated. Benefit rates in each study pre- and post-amendment are shown in Table A3-5.

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Table A3-5: Patient Benefit Rate Before and After Protocol Amendment V, By Study, in Patients Randomized to CDDP/epi Gel

Study	Before Amendment V			After Amendment V			p-value ^a
	n	No. with Benefit	Benefit Rate	n	No. with Benefit	Benefit Rate	
414 (Stratum 1 & 2)	24	10	(42%)	38	11	(29%)	0.41
514 (Stratum 1 & 2)	21	5	(24%)	36	6	(17%)	0.50

^a Exact Cochran-Mantel-Haenszel test

In both studies, Patient Benefit decreased following the amendment, from 42% to 29% in Study 414 and from 24% to 17% in Study 514. As with MTT response, these changes are well within the limits of expected sampling variability, the fact that the direction of change is the same in both studies raises the question of whether this is a true effect. As for MTT response, the effect of the amendment on benefit was examined by stratum in the combined studies; results are shown in Table A3-6.

Table A3-6: Benefit Rate Before and After Amendment V, by Stratum

Stratum	Before Amendment V			After Amendment V			p-value ^a
	n	Benefiters	Benefit rate	n	Benefiters	Benefit rate	
Stratum 1	22	8	36%	40	12	30%	0.78
Stratum 2	23	7	30%	34	5	15%	0.19
Strata 1&2	45	15	33%	74	17	23%	0.28

^a Exact Cochran-Mantel-Haensel test

Rates of Patient Benefit decrease in both strata, with the larger decrease seen in Stratum 2. The decrease in benefit in both studies and in both strata was investigated to evaluate whether factors other than the amendment may have influenced the results observed pre-and post-amendment.

As discussed in Section 6.4.2, Patient Benefit is influenced by two treatment goals: the patient's primary treatment goal and the investigator's primary treatment goal. Because it is more difficult to detect the attainment of a palliative goal than a preventive goal, a change in the distribution of palliative vs. preventive goals after Amendment V (specifically, an increased tendency by investigators to select palliative goals over preventive goals) would be expected to decrease the apparent benefit attainment rate. Therefore, we examined the percentage of palliative and preventive primary goals selected by investigators pre- and post-amendment. The distribution of palliative and preventive primary goals is shown in Table A3-7.

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Table A3-7: Investigator's Choice of Primary Goal

Treatment	Before Amendment V n=72		After Amendment V n=106	
	Palliative Goal Selected	Preventive Goal Selected	Palliative Goal Selected	Preventive Goal Selected
CDDP/epi gel	24 (53%)	21 (47%)	53 (72%)	21 (28%)
Placebo	15 (56%)	12 (44%)	21 (66%)	11 (34%)
Total	39	33	74	32

Before Amendment V, investigators selected preventive primary goals for nearly half their patients; in addition, the proportion of patients for whom a primary preventive goal was selected was nearly equal in the blinded treatment groups. After the amendment, in contrast, preventive goals were selected by investigators in only 28% of CDDP/epi gel patients and 34% of placebo patients. However, the change in goal selection supports the hypothesis that the observed decrease in benefit rate in both studies, may be due to the less frequent selection of primary preventive goals after the amendment.

Rates of attainment of investigator-selected palliative and preventive primary goals were then examined separately pre- and post-amendment. If the attainment rates of preventive and palliative goals, examined separately, were the same before and after Amendment V then we would be justified in concluding that the overall decrease in benefit rate was due to the change in distribution of goal selection. For completeness, rates of attainment of patient-selected goals were also examined. Table A3-8 shows the attainment rates of palliative and preventive goals selected before and after Amendment V.

Table A3-8: Attainment Rates of Investigator Palliative and Preventive Goals and Patient Palliative Goals Before and After Amendment V

Goal type	Before Amendment V			After Amendment V		
	Selected	Attained	Attainment rate	Selected	Attained	Attainment rate
Investigator Palliative						
CDDP/epi Gel	24	4	17%	53	4	8%
Placebo	15	0	0%	21	1	5%
Investigator Preventive						
CDDP/epi Gel	21	13	62%	21	13	62%
Placebo	12	2	17%	11	4	36%
Patient Palliative						
CDDP/epi Gel	37	5	14%	64	6	9%
Placebo	21	1	5%	29	1	3%

Note: Fisher's Exact Test for comparison of attainment rates for placebo preventive goals, before vs. after amendment, $p=0.37$

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As can be seen in Table A3-8, the decrease in benefit rates cannot be completely explained on the basis of a shift in palliative or preventive goal selection: when palliative and preventive goals are examined separately, the attainment rate for palliative goals in patients treated with CDDP/epi gel decreased from 17% to 8% post-amendment, while the attainment rate for preventive goals did not change (62% in both periods). However, the concurrent increase in the placebo patients' attainment rate of preventive goals, from 17% to 36%, suggests that something in addition to treatment group could be influencing goal attainment. Attainment rates for primary patient palliative goals are also slightly lower after the amendment.

5 Safety, Combined Analysis

As shown in the table below, there was a pattern for most adverse events to have a lower incidence with lower dose of CDDP/epi gel. This may be due to a combination of the dose change and the effect of dose re-calculation for tumor volume at each treatment visit (as opposed to administration of a dose calculated using baseline tumor volume).

Table A3-10: Incidence of Adverse Events by Dose in blinded Treatment Phase

Adverse Event	CDDP/epi Gel (n = 150)		Placebo Gel (n = 75)	
	Before Amendment V (0.5 mL/cm ³)	After Amendment V (0.25 mL/cm ³)	Before Amendment V (0.5 mL/cm ³)	After Amendment V (0.25 mL/cm ³)
Body As A Whole				
Pain	50 (67%)	35 (47%)	20 (47%)	12 (38%)
Malignant neoplasm reactivated ^a	0 (0%)	7 (9%)	0 (0%)	1 (3%)
Infection	21 (28%)	5 (7%)	4 (9%)	4 (13%)
Fever	10 (13%)	5 (7%)	4 (9%)	1 (3%)
Headache	11 (15%)	6 (8%)	3 (7%)	2 (6%)
Swelling	10 (13%)	0 (0%)	2 (5%)	0 (0%)
Cardiovascular System				
Hemorrhage	13 (17%)	10 (13%)	5 (12%)	1 (3%)
Hypertension	11 (15%)	4 (5%)	4 (9%)	1 (3%)
Digestive System				
Vomiting	18 (24%)	9 (12%)	2 (5%)	0 (0%)
Nausea	16 (21%)	9 (12%)	3 (7%)	3 (9%)
Dysphagia	13 (17%)	7 (9%)	3 (7%)	4 (13%)
Constipation	14 (19%)	6 (8%)	2 (5%)	1 (3%)
Anorexia	12 (16%)	4 (5%)	1 (2%)	0 (0%)

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Table A3-10: Incidence of Adverse Events by Dose in blinded Treatment Phase

	CDDP/epi Gel (n = 150)		Placebo Gel (n = 75)	
Hemic and Lymphatic				
Anemia	13 (17%)	4 (5%)	3 (7%)	2 (6%)
Respi Continued				
Dyspnea	11 (15%)	6 (8%)	2 (6%)	5 (12%)
Nervous System				
Insomnia	6 (8%)	3 (4%)	4 (9%)	0 (0%)
Dizziness	9 (12%)	2 (3%)	5 (12%)	1 (3%)

^aCOSTART term for local or systemic disease progression when recorded as an adverse event

While the median number of blinded treatment visits was for both before and after the amendment, median total cumulative dose administered and median dose per visit were both reduced by 50% after Amendment V.

3. Conclusions

Data suggest that the changes to studies 414 and 514 due to Amendment V had little impact on the type of patients entering the study and on MTT response. However, an apparent decrease in the patient benefit rate subsequent to the amendment was noted, although the decrease was not statistically significant and therefore could be explained by sampling variability. The fact that the MTT response rate did not decrease after Amendment V makes the observed decrease in benefit rate particularly difficult to interpret. It can be partly explained by a lower percentage of patients with an investigator-selected preventive primary goal in the post-amendment period. Nevertheless, both before and after Amendment V, the Patient Benefit rate was higher in patients treated with CDDP/epi gel than in patients treated with placebo gel.