

## Appendix 4: Treatment Outcomes: Stratum 3

The protocols for each phase III, placebo controlled randomized study (414-94-2 and 514-94-2) stated that Stratum 3 patients (those with MTT volume  $>20 \text{ cm}^3$ ) would not be analyzed for efficacy, but would be included in all other analyses. The Analysis Plan stated that Stratum 3 patients would be analyzed descriptively. This appendix separately summarizes the disease characteristics, MTT response rates, and Patient Benefit rates in Stratum 3, including inferential comparison of MTT response rates in the CDDP/epi gel and placebo groups. Stratum 3 (MTT  $>20 \text{ cm}^3$ ) was closed after the enrollment of 46 patients. Response rate and benefit rates were lower in Stratum 3 than in Stratum 1 or 2.

**Table A4-1:** Patients enrolled in Stratum 3

Study	CDDP/epi Gel	Placebo Gel	TOTAL
414	14	9	23
514	17	6	23
TOTAL	31	15	46

**Table A4-2:** Treatment Termination Status – Stratum 3, Blinded Phase

	CDDP/Epi Gel (%)	Placebo Gel (%)
	n = 31	n = 15
Completed six treatments	7 (23%)	0 (0%)
Early response with less than six treatments	2 (6%)	0 (0%)
Disease progression, local	3 (10%)	7 (47%)
Disease progression, systemic	8 (26%)	4 (27%)
Adverse event	4 (13%)	1 (7%)
Other <sup>a</sup>	7 (2%)	3 (20%)
TOTAL	31	15

<sup>a</sup> Delay in scheduled dosing for  $>2$  weeks; need for confounding therapy; patient decision; other.

Nine patients (29%) completed all six treatments or stopped early because of a response to CDDP/epi gel. Placebo-treated patients developed local progression more frequently. CDDP/epi gel patients more frequently stopped because of an adverse event.

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**Table A4-3:** Patient Demographics

	CDDP/epi Gel	Placebo Gel	Combined
Characteristic	n=31	n= 15	n= 46
Age (years), n	31	15	46
Mean (SD)	62 (11)	63 (16)	62 (13)
Median	61	63	61
Range	42-88	38-91	38-91
Gender, n	31	15	46
Male	22 (71%)	12 (80%)	34 (74%)
Female	9 (29%)	3 (20%)	12 (26%)
Ethnicity, n	31	15	46
White	25 (81%)	13 (87%)	38 (83%)
Black	3 (10%)	0	3 (7%)
Hispanic	2 (6%)	1 (7%)	3 (7%)
American Indian	0	0	0
Asian	1 (3%)	1 (7%)	2 (4%)
Weight (kg), n	31	15	46
Mean (SD)	62 (13)	59 (13)	61 (13)
Median	60	56	60
Range	40-83	41-84	40-84
Karnofsky Performance Status, n	31	15	46
100-90	8	1	9
80-70	19	11	30
60-50	4	3	7
40	0	0	0

**Table A4-4:** Location of MTT and of All Tumors Treated in Treatment Phase

Location	CDDP/epi Gel n=31		Placebo Gel n=15		Total n=46	
	MTT	ALL	MTT	ALL	MTT	ALL
Tumor(s) Treated						
Total n (tumors)	31	38	15	17	46	55
Cervical	14	20	7	7	21	27
Oral cavity	7	7	3	3	10	10
Facial	6	7	2	4	8	11
Laryngopharyngeal	3	3	2	2	5	5
Nasopharyngeal	0	0	0	0	0	0
Cranial	0	0	1	1	1	1
Chest wall	1	1	0	0	1	1

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**Table A4-5:** Cancer Treatment History

	CDDP/epi Gel n (%)	Placebo Gel n (%)	Total n (%)
Total n	31	15	46
Surgery	0 (0%)	1 (7%)	1 (2%)
Surgery and radiation	14 (45%)	4 (27%)	18 (39%)
Surgery, radiation, and systemic chemotherapy	12 (39%)	9 (60%)	21 (46%)
Radiation and systemic chemotherapy	3 (10%)	1 (7%)	4 (9%)
Surgery and systemic chemotherapy	2 (6%)	(0 (0%))	2 (4%)

Patients in Stratum 3 had somewhat lower Karnofsky Performance Status than Stratum 1 and 2 (KPS 90-100: 20% vs. 37%). The MTT was most frequently cervical, oral cavity, and facial as in Stratum 1 and 2. Previous treatment history is similar.

**Table A4-6:** Extent of Exposure to Treatment with CDDP/epi gel or Placebo — Stratum 3

	Blinded Period		Open-Label Period	
	CDDP/epi Gel n=31	Placebo Gel n=15	CDDP/epi Gel <sup>a</sup> n=6	Placebo Gel <sup>a</sup> n=16
<b>No. of Rxs</b>				
1	3 (10%)	1 (7%)	0 (0%)	3 (30%)
2	9 (29%)	8 (53%)	0 (0%)	1(10%)
3	5 (16%)	5 (33%)	0 (0%)	3(30%)
4	3 (10%)	1 (7%)	3 (50%)	1(10%)
5	4 (13%)	0 (0%)	3 (50%)	1(10%)
6	7 (23%)	0 (0%)	0 (0%)	1(10%)
7 or more	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<b>Cumulative Dose (mL)</b>				
mean	25	17	33	23
median	20	14	35	19
SD	16.6	8.5	15.4	20.9
range	3.8 - 60	4 - 30	14 - 50	2 - 60

<sup>a</sup>Original randomization group

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**Table A4-7:** Overall Response Rate of MTT – Blinded Phase

Stratum	CDDP/epi Gel			Placebo Gel			Exact p <sup>b</sup>
	n	Response Rate (%)	95% CI <sup>a</sup>	n	Response Rate (%)	95% CI <sup>a</sup>	
Stratum 3	31	13% <sup>c</sup>	(3.6-30)	15	0% <sup>c,d</sup>	(0-22%)	0.15
Stratum 1	62	37%	(25-50%)	29	3%	(0.87-18%)	<0.001
Stratum 2	57	21%	(11-34%)	30	0%	(0-12%)	0.015
Strata 1 & 2	119	29%	(21-38%)	59	2%	(0.04-12%)	<0.001

<sup>a</sup> Clopper-Pearson exact 95% confidence interval

<sup>b</sup> For stratified comparisons, p-values are Cochran-Mantel-Haenszel test p-values, as calculated by SAS procedure MULTTEST. For unstratified active vs. placebo comparisons, p-values are Fisher's exact test p-values, as calculated by SAS procedure FREQ.

<sup>c</sup> In Stratum 3, 14% of CDDP/epi gel treated patients achieved benefit, but no placebo patients did.

<sup>d</sup> 10 placebo patients crossed over to receive open label CDDP/epi gel.

**Table A4-8:** Patient Benefit Rates – Blinded Phase

Stratum	CDDP/epi Gel		Placebo Gel	
	n	Benefit Rate (%)	n	Benefit Rate (%)
Stratum 3	31	16%	15	0%
Stratum 1	62	32%	29	17%
Stratum 2	57	21%	30	7%
Strata 1 & 2	119	27%	59	12%

It is likely that the lower response and benefit rate in stratum 3 maybe due to the larger tumor size and the shorter time patients remained in therapy because of progressive distant or local cancers.