

Information Request for BLA 125518:

1. Our review of durable responders per the EAC evaluation, we disagreed with three of the EAC assessments for DR:
 - a. 003023 (talimogene laherparepvec): Progressive Disease not a durable response for PR (L2 progressed by CT)
 - b. 053004 (GM-CSF): Progressive Disease not a durable response for PR (per EAC)
 - c. 066017 (talimogene laherparepvec): not evaluable, too many missed. We were not able to confirm a durable response. In addition BIMO identified study conduct issues with the site.

Therefore, the FDA-determined durable response rate was 15.6 % in the talimogene laherparepvec arm and 1.4 % in the GM-CSF arm. The unadjusted odds ratio of DRR was 12.8 with 95% confidence interval (CI): 3.1 to 53.7. Please acknowledge.

We are continuing to review some individual subjects – see Q #2:

Comparison of Response Assessment between EAC and investigator

	INV DR	INV NON DR	TOTAL
EAC DR - n (%)	44(30.8)	7(4.9)	51(35.7)
EAC –Non DR - n (%)	14(9.8)	78(54.5)	92(64.3)
Total - n (%)	58(40.6)	85(59.4)	143(100.0)

2. Please confirm that the above table is correct, and that the following subjects were the 14 subjects with DRs by the investigators and not by the EAC. If so, please provide the EAC-CRF documents and datasets for the following subjects on 005/05:
 - BVX00505-005003
 - BVX00505-010007
 - BVX00505-013004
 - BVX00505-020001
 - BVX00505-031002
 - BVX00505-035025
 - BVX00505-037008
 - BVX00505-045023
 - BVX00505-065003
 - BVX00505-065007
 - BVX00505-065012
 - BVX00505-067006
 - BVX00505-078008
 - BVX00505-107008

If possible, please provide these by Friday, March 13, 2015. The format used in the previous EAC-CRF documents was quite helpful in our review, so if possible, please use the same format. These subjects are durable responders per the local investigator and not the EAC by our review. If there are additional subjects who were durable responders per the local investigator and not the EAC, please provide that information as well.

If available please submit lesion datasets for all the subjects evaluated by the EAC.

3. With regards to prior therapy, please confirm the following (especially excisions) or provide your own revised table.

Table 1 Summary of Prior Therapies

CATEGORY Subcategory	GM-CSF (N = 141) n (%)	talimogene laherparepvec (N = 295) n (%)
PRIOR SURGERY	123 (87.2)	277 (93.9)
Excision *	108 (76)	240 (81)
Lymphadenectomy	65 (46.1)	165 (55.9)
Amputation	5 (3.5)	15 (5.1)
Lymphadenectomy	65 (46.1)	165 (55.9)
PRIOR NON SURGICAL THERAPY	88 (62.4)	203 (68.8)
Biologic therapy	45 (31.9)	99 (33.6)
interferon alfa-2b	35 (24.8)	72 (24.4)
interleukin-2	17 (12.1)	39 (13.2)
Chemotherapy	40 (28.4)	87 (29.5)
Investigational treatment	19 (13.5)	55 (18.6)
ipilimumab	3(2.1)	11 (3.7)
Limb perfusion	16 (11.3)	33 (11.2)
Radiation therapy	23 (16.3)	79 (26.8)

[Source: Reproduced from BLA submission] * Dataset PR

Please clarify the numbers of subjects who had recurrent disease at baseline by arm and the numbers of previously untreated patients who were enrolled. Please confirm that subjects with recurrent disease were restaged at screening.

We note that your analysis of response and survival suggested that efficacy was different in subjects who had a history of prior therapy:

Line of therapy (IVRS) ^b				
First line	0/65 (0.0)	33/138 (23.9)	NE	<0.0001
Second line or greater	3/76 (3.9)	15/157 (9.6)	2.57 (0.72, 9.16)	0.1908

Have you performed any analysis to suggest whether the type of prior therapy (Biological vs chemotherapy) made a difference?

4. With regards to size of baseline lesions in responders vs. non responders, please confirm the following or provide your own revised table.

Number and size of baseline lesions, DRs vs non-responders based on investigator assessments)

	Durable Responders	Nonresponders
N	51	368
Mean	8.03	9.55
Std Dev	6.25	8.51
Upper 95% Mean	9.8	10.42
Lower 95% Mean	6.3	8.67
75.0% quartile	12	13
50.0% median	6	7
25.0% quartile	3	4
Mean Baseline Size CM2	13.0	31.60
Median Baseline Size CM ²	4.5	11.15
Std Dev	40.2	128.8
Minimum Size	0.2	0.27
Maximum Size	280 (subject #-010004)	2297.21 (subject Pt # 203003)

Source: TR dataset