β-Alethine, An Immunostimulatory Drug That Synergizes With Anti-PD1 Therapy

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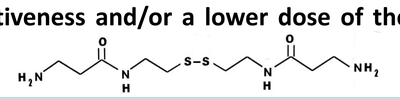
ABSTRACT

In humans, β-alethine has previously been found to be non-toxic, with no drug related adverse reactions reported in Phase I/II, modulate the immune system and reduce even large lymphoma masses (up to 75% decrease in volume) in patients who have been heavily pretreated so long as they are not anergic. As a single agent, it was shown to reduce the growth of slow-growing myeloma and melanoma in mouse tumor models. For more aggressive or faster growing murine tumors, including breast cancer and B16 melanoma, combination therapy of β-alethine with chemotherapeutics was more effective than the chemotherapeutic alone, resulting in reduction of both primary tumor and in the development of metastases. Of note, β-alethine did not increase toxicity due to the chemotherapy, in fact, it appeared to decrease toxicity.

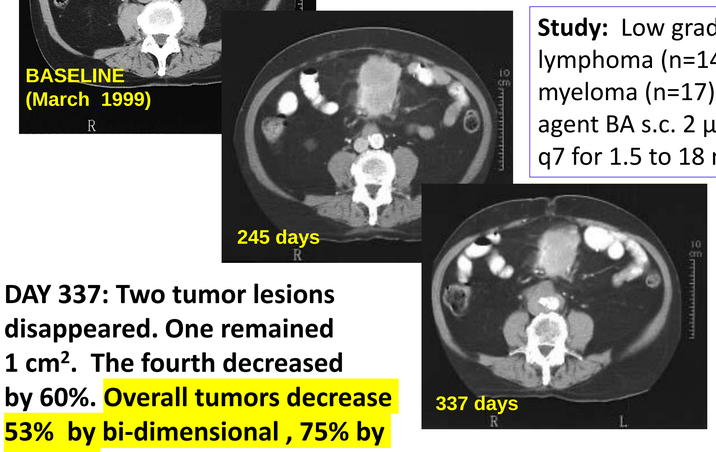
Recently we have found that application of β-alethine to mouse cells in vitro or injection into intact mice modulates the number of cells expressing checkpoint inhibitors and the level of checkpoint inhibitors on their surface. In order to evaluate anti-cancer activity, DBA mice were given the syngeneic Cloudman melanoma. Tumors were allowed to grow for 15 days. Mice were treated either vehicle, β-alethine (s.c.) and/or anti-PD1 (50 ug/mouse, i.p.). Anti-PD1 and β-alethine, as single agent therapies, appeared to potentially slow the growth of the melanoma, but this effect was not statistically significant for individual groups. However, the combination of anti-PD1 and β-alethine completely stopped melanoma growth and this effect was highly statistically significant (p < .0001). Thus, therapeutic application of β-alethine in combination with checkpoint therapies may enhance the checkpoint therapies, potentially allowing for greater effectiveness and/or a lower dose of these therapeutic antibodies.



Introduction: HUMAN PHASE I/II

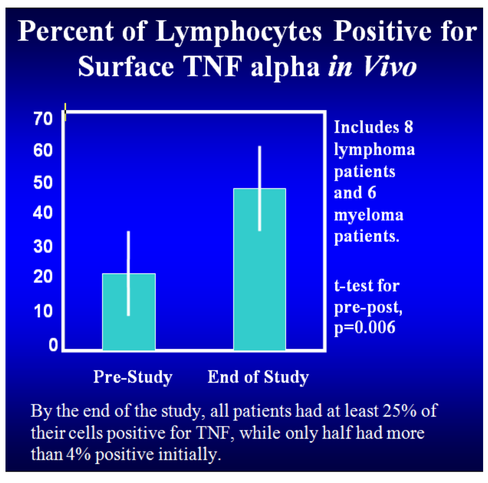
Pt HC #202 Lymphoma

Pt. history
1983: Small bowel obstruction due to low-grade B-cell lymphoma.
1983-1989: Low dose chlorambucil (CB).
1989: A second small bowel obstruction.
1994: 8 x 5 cm mass. Rx: High-dose CB followed by low dose CB. 1995: Decreased from 8 x 5 cm to 5 x 3 cm (62.5%)
1999: 10 x 9 cm at trial pre-study screening.

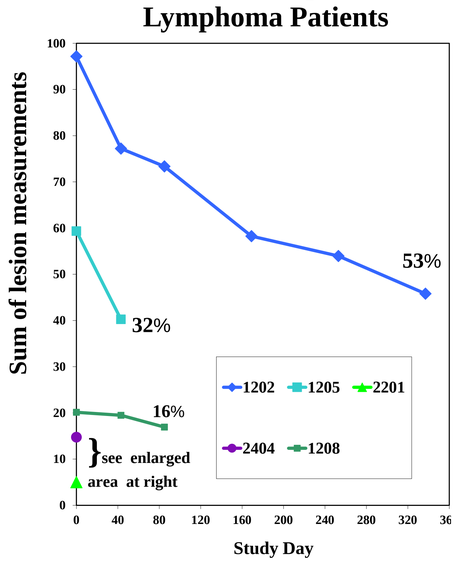


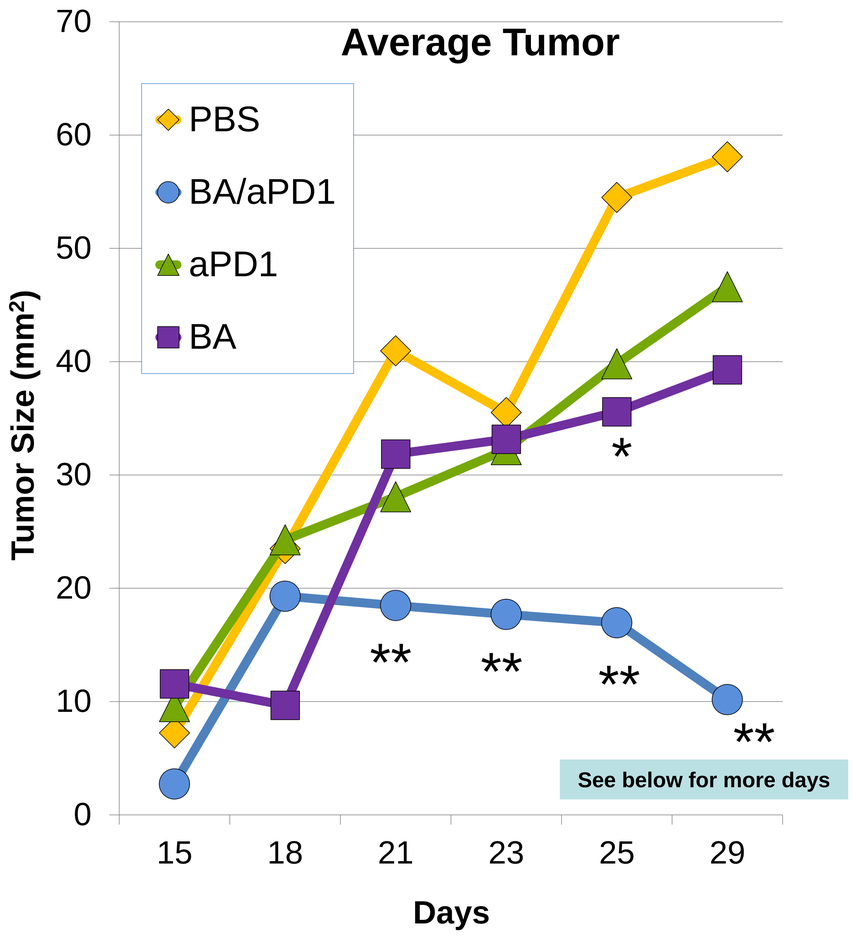
Study: Low grade B cell lymphoma (n=14); myeloma (n=17). Single agent BA s.c. 2 µg q14 or q7 for 1.5 to 18 months.

DAY 337: Two tumor lesions disappeared. One remained 1 cm². The fourth decreased by 60%. Overall tumors decrease 53% by bi-dimensional , 75% by volume.



References 1-4.

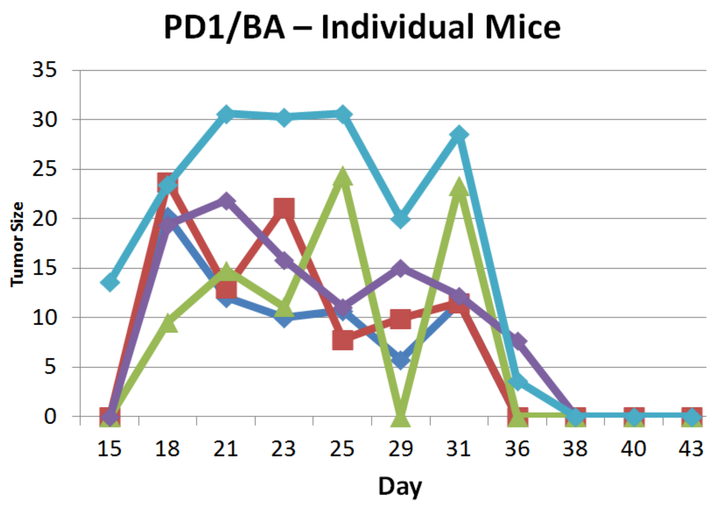




DBA mice were given the syngeneic Cloudman melanoma and treated with either vehicle, β-alethine (BA) weekly s.c, starting on day 15 and/or anti-PD1 i.p. on days 15, 18, and 21. BA alone was at 30 ng/kg or 30 mg/kg (not shown) and 30 mg/kg with anti-PD1; anti-PD1 was 50 µg/mouse. Anti-PD1 and β-alethine, as single agent therapies, appeared to potentially slow the growth of the melanoma, but the combination was highly synergistic.

From day 21 on, the combination differed significantly from PBS and from anti-PD1*. The combination differed from BA on day 23* and 29*. Additionally, PBS and BA differed on day 25*. Similar significant group differences continued beyond day 29 and in other dose groups. $p \leq .05$ (*), or $p < .005$ (**) (One-way ANOVAs)**

BA/aPD1: All animals went on to have complete responses. Chi-squared for complete remissions in all animals with anti-PD1 plus BA, vs. PBS $p < .0001$ (sample data below).

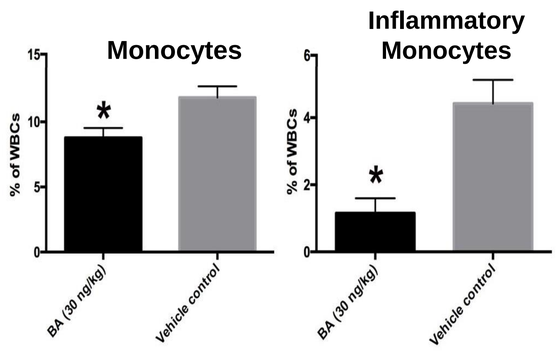


BA ONLY -- Biomarker Studies

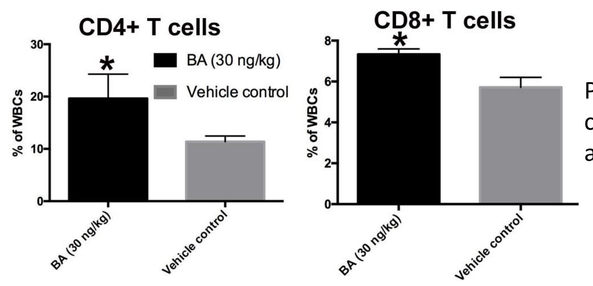
BA Only % Change in Exhausted T-Cells

	CD4 Cells	CD8 Cells
PD1	-48	- 81
Lag 3	-32	- 94
Tim 3	- 34	-95

Significant changes in ***checkpoint*** molecule expression in T cells 7 days after BA treatment in Cloudman tumor-bearing mice. All differences were at $p = 0.05$ or lower.



Percentages of circulating monocytes and inflammatory monocytes in Cloudman tumor bearing mice that were BA treated vs vehicle control treated, 7 days after receiving the first dose of BA.



Percentages of circulating CD4+ and CD8+ T-cells.

CONCLUSIONS

β-alethine (BA) a drug that is non-toxic, modulates the immune system and appears to have single agent anti-lymphoma effects in people, **is a pan checkpoint inhibitor,**

BA synergizes with anti-PD1, and

Complete response (CR) is the typical (90%) response to combination therapy.

FUTURE DIRECTIONS PARTNERSHIPS

Clinical sites and corporate partners are sought for the next stages. Preclinical collaborations are also solicited.
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