An Update On The Clinical Activity Of Resimmune, a Targeted Therapy Directed To CD3 Receptor, In Patients With Cutaneous T Cell Lymphomas—CTCL

Arthur E. Frankel, MD[1], Jung H Woo, PhD[2*], Jeremy P Mauldin, PhD[2*], Francine M. Foss, MD[3], Madeleine Duvic, MD[4] and David M Neville Jr., MD[5*]

[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]Scott & White Healthcare, Temple, TX; [3]Yale University Cancer Center, New Haven, CT; [4]M.D. Anderson Cancer Center, Houston, TX; [5]Angimmune LLC, Rockville, MD

Poster session presented at: American Society of Hematology (ASH)

55th ASH Annual Meeting and Exposition. 2013 December 7-10; New Orleans, LA.
Program: Oral and Poster Abstracts
Session: 624. Lymphoma: Therapy with Biologic Agents, excluding Pre-Clinical Models: Poster III

Revised 03/14/2014 With Additional Data & Typographic Corrections

ABSTRACT

Cutaneous T cell lymphoma—CTCL is a malignancy of skin-tropic T cells. CTCL cells have ubiquitous overexpression of CD3. Although uncommon, CTCL has been estimated to affect 1,500 patients per year in the United States. There are multiple approved systemic therapies for CTCL, but responses are brief lasting months. Allogeneic stem cell transplantation may provide long-term remissions, but is suitable for only rare CTCL patients. Overall, CTCL has a long clinical course with relentless progression over months to years with estimated median survival of 3-5 years for stage IB-IIB patients.

The CD3 targeted agent, Resimmune, was synthesized and prepared for clinical use. It consists of the catalytic and translocation domains of diphtheria toxin fused to two anti-human CD3 Fv fragments. DNA encoding Resimmune protein was integrated into the *Pichia pastoris* genome, and recombinant protein was produced in *Pichia pastoris* via the secretory route (Woo, Protein Expr Purif 25, 270, 2002). Protein was purified by anion exchange and size exclusion chromatography. The CD3+ Jurkat cell line incubated with Resimmune yielded an IC_{50} for protein synthesis inhibition of 0.017pM. The CD3- Vero cell line incubated with Resimmune showed an IC_{50} >10pM. Mice, rats, and monkeys given total doses of >200µg/kg over four days showed only transient transaminasemia without histopathologic tissue injury or clinical signs or symptoms (Woo, Cancer Immunol Immunother 57, 1225, 2008). In a mouse model with human CD3e transfected lymphocytes, four logs of antigen positive cells were reproducibly depleted from nodes and spleen with 100µg/kg total dose of Resimmune (Thompson, Protein Eng 14, 1035, 2001).

Based on these findings, a Phase I study was initiated and this report serves to update the results of a single cycle of Resimmune given at 2.5-11.25 µg/kg 15 min IV infusion twice daily for 8 doses to 23 patients with CD3 positive malignancy, 19 CTCL patients, 3 PTCL patients and 1 patient with LGL leukemia. Of these patients 20 completed all eight doses of the study drug. There were 14 females and 9 males with ages 20-81 years. Two patients were naïve to systemic therapies, and all others had failed 1-4 prior treatments including interferon, bexarotene, gemcitabine,

ABSTRACT

vorinostat, chlorambucil, etoposide, pralatrexate, doxil, romidepsin, methotrexate, CHOP, and brentuximab vedotin. None of the Resimmune treated patients who were free of pre-existing cardiac disease had dose-limiting toxicities. In this group side effects were mild-moderate and transient with fevers, chills, nausea, transaminasemia, hypoalbuminemia, lymphopenia, reactivation of EBV and CMV, and hypophosphatemia. Toxicities responded to antipyretics, anti-emetics, albumin infusions, rituximab treatment and valgancyclovir. One patient with compensated congestive heart failure experienced Gr 4 vascular leak syndrome and died from congestive heart failure. One patient with severe pulmonoary hypertension died from vascular leak syndrome. A prior history of cardiac disease is now an absolute exclusion from the study with the exception of well controlled essential hypertension. Among measured patients, there was a 3 log decline in normal, circulating T cells by day 5 that recovered by day 14. Because of the potential risk of vascular leak syndrome toxicities at higher doses, the MTD was defined as 7.5 µg/kg x 8 doses as a trade off between efficacy and toxicity in the high-response patient subgroup. Cmax ranged from 1.9-40.7ng/mL and half-life from 5-66min. Pretreatment anti-DT titers were 0.9-251µg/mL and day 30 post-therapy increased to 5-4059 µg/mL. Twenty patients were evaluable for response. There were 7 responses, all in CTCL, for a response rate of 35%. There were four CRs (20% CR rate). Two CRs are over 5-years duration, one over 4-years and one over 2-years Patients with IB or IIB disease and mSWAT <50 comprise a high-response patient subgroup with an overall response rate of 87.5% and CR rate of 50%. The long time required to convert from a PR to a CR in the absence of any additional therapy beyond the four treatment days suggest an additional anti-tumor mechanism beyond immunotoxin-induced killing such as immunomodulation. Accrual of patients with mSWAT scores of 50 or less is ongoing.

THE DISEASE

Cutaneous T cell lymphoma—CTCL is a malignancy of skin-tropic T cells. CTCL cells have ubiquitous overexpression of CD3. Although uncommon, CTCL has been estimated to affect 1,500 patients per year in the United States. There are multiple approved systemic therapies for CTCL, but responses are brief lasting months. Allogeneic stem cell transplantation may provide long-term remissions, but is suitable for only rare CTCL patients. Overall, CTCL has a long clinical course with relentless progression over months to years with estimated median survival of 3-5 years for stage IB-IIB patients. New therapies are needed.

NEW DRUG

A New Drug, Resimmune, targets T cells via CD3 and a toxic fusion protein.

It consists of the catalytic and translocation domains of diphtheria toxin fused to two anti-human CD3 Fv fragments. DNA encoding Resimmune protein was integrated into the *Pichia pastoris* genome, and recombinant protein was produced in *Pichia pastoris* via the secretory route (Woo, Protein Expr Purif 25, 270, 2002).

In a mouse model with human CD3e transfected lymphocytes, four logs of antigen positive cells were reproducibly depleted from nodes and spleen with 100µg/kg total dose of Resimmune (Thompson, Protein Eng 14, 1035, 2001).

Based on these findings, a phase 1 study was initiated and this report serves to update the results of a single cycle of Resimmune given at 2.5-11.25µg/kg 15 min IV infusion twice daily for 8 doses to 23 CTCL patients.

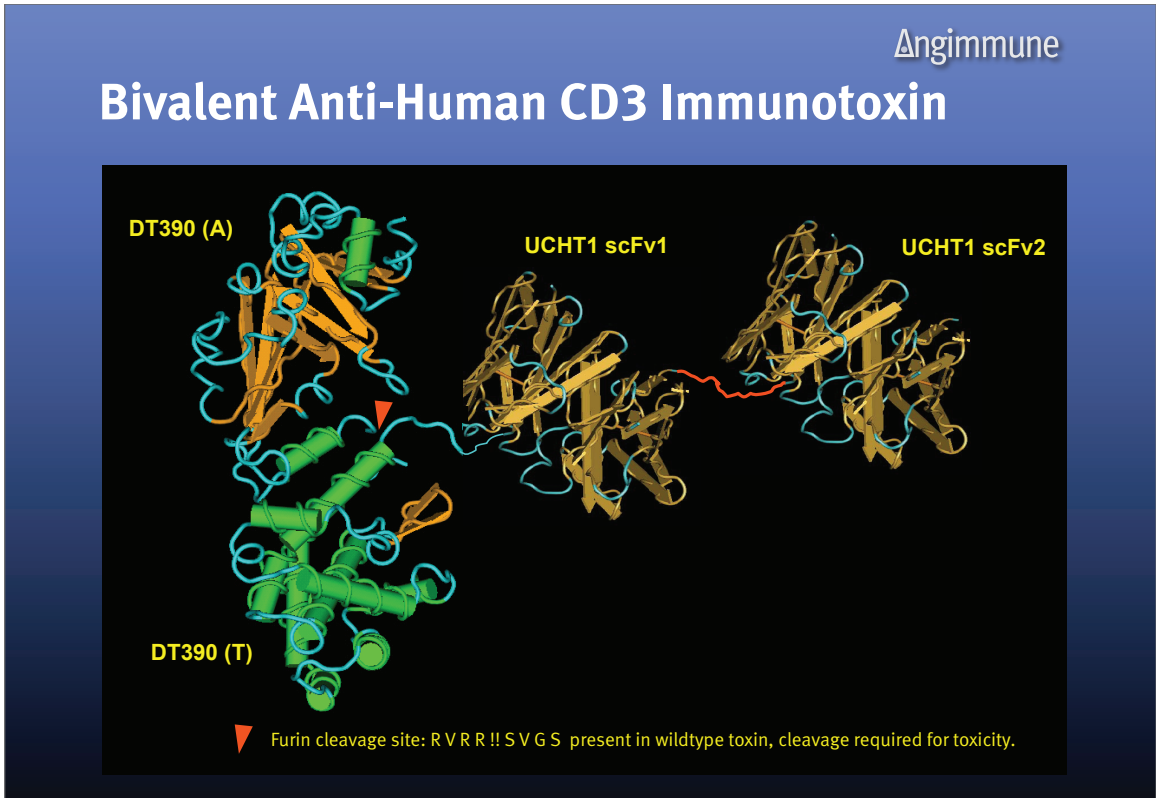


Table of CTCL/PTCL Patient characteristics*

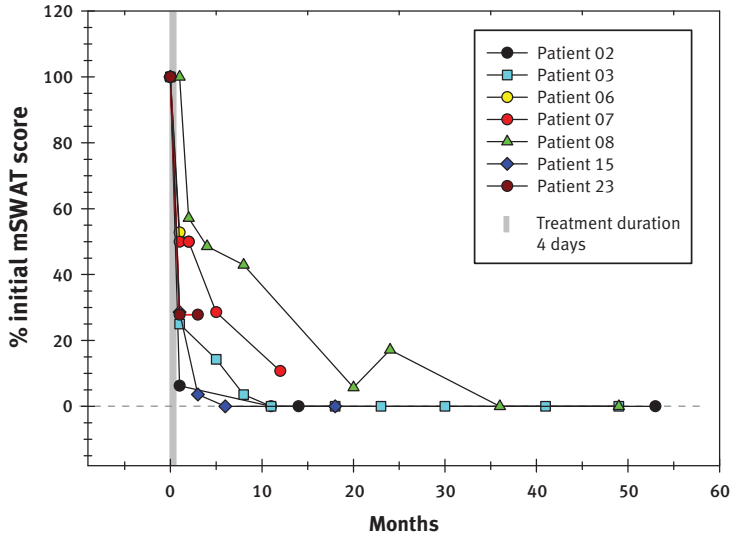
Pt. no.	Age (yr)/Gender	Stage	Prior Therapies
1	47/F	IIB	Nitrogen mustard, Interferon, Bexarotene
2	78/M	IB	CHOP
3	58/F	IB	Psoralen+UVA, Fludarabine, Nitrogen mustard, Bexarotene, Dexamethasone, Gemcitabine, Vorinostat
4	48/M	IIB	Triamcinolone, Bexarotene, Nitrogen mustard, UVB, Gemcitabine
5	64/F	IB	Accutane, Bexarotene, UVB
6	73/F	IB	Nitrogen mustard, Bexarotene
7	39/M	IIB	Narrow band UVB, Clobetasol
8	50/F	IV	Narrow band UVB
9	84/F	IV	UVB, Interferon, Chlorambucil, Etoposide, Targretin
10	69/M	PTCL IV	CHOP, Prednisone
11	76/M	III	Pralatrexate, UVB, corticosteroid cream
12	49/F	PTCL	Local x-ray, Targretin, Doxil, Istodax
13	81/F	IV4A	Gemzar, Doxil, Vorinostat, Targretin
14	49/F	IV4A	Topical nitrogen mustard, oral Targretin, photophoresis
15	61/M	IB	Nitrogen mustard, Interferon, Bexarotene, Vorinostat
16	51/F	IIB	Nitrogen mustard, Interferon, Bexarotene, gemcitabine, radiation
17	71/M	III	Pralatrexate, Bexarotene, romidepsin
19	20/F	IIB	Romidepsin, pralatrexate, gemcitabine
20	52/M	PTCL	RT, Doxil, gemcitabine, navelbine, oxaliplatin
21	56/F	III	Romidepsin, gemcitabine, vedotin, brentuximab
22	60/M	IIB	CHOP, SGN-35, Targretin, methotrexate
23	41/F	IIB	Targretin, methotrexate, Nitrogen mustard, Interferon, Local x-ray, PUVA, Soriatane

* CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone. # Patients #9 and #10 were excluded in this trial because they developed their underlying diseases.

CLINICAL RESPONSES

Among 20 evaluable patients, we observed seven responses for a response rate of 35%. There were four CRs (20% CR rate). Three of the CRs are over 4-years duration and may represent cures. The long time required to convert from a PR to a CR in the absence of any additional therapy beyond the four treatment days suggests an additional anti-tumor mechanism beyond immunotoxin induced killing of tumor cells. A likely possibility is immunomodulation mediated by the transient depletion of normal T cells.

Clinical Response Over Time for Responding Patients as Judged by mSWAT Scores



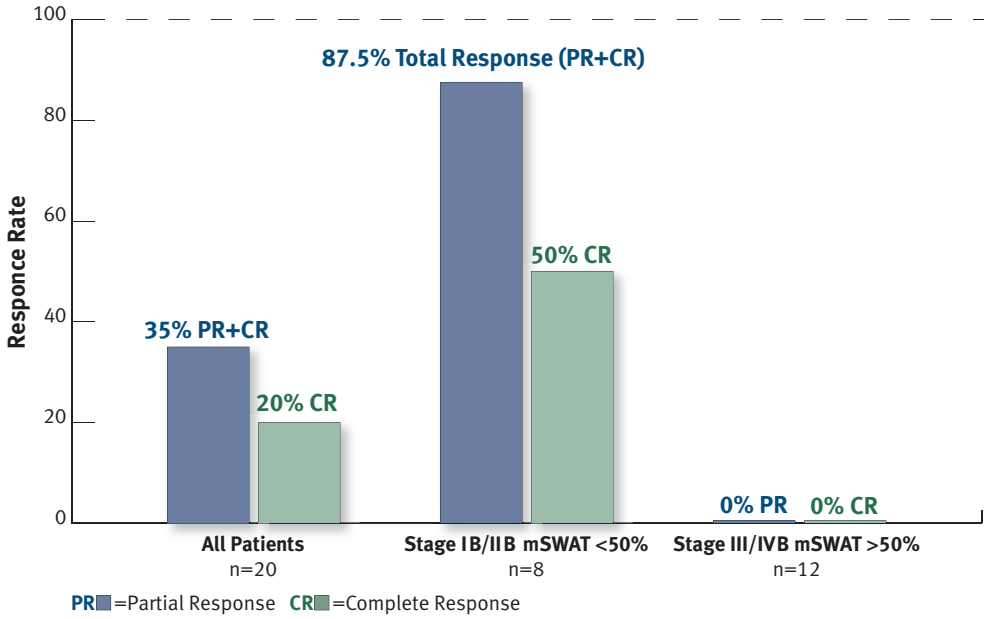
Changes of % initial mSWAT score for patients #2, 3, 6, 7, 8, 15 and 23. Recurrence of skin tumors occurred in patients #2 at 18 months, #6 at 3 months and #7 at 14 months post treatment. At 53 months patient #2 was in CR.

0 Time is first day of Resimmune treatment, which ends on day 4. There is no further treatment.

The long time required to convert from a PR to a CR in the absence of any additional therapy beyond the four treatment days suggest an additional anti-tumor mechanism beyond immunotoxin-induced killing such as immunomodulation.

Resimmune can induce long-term remissions in cutaneous T cell lymphoma.

Response versus Patient Subgroup Based on Disease Stage and Skin Coverage[1]



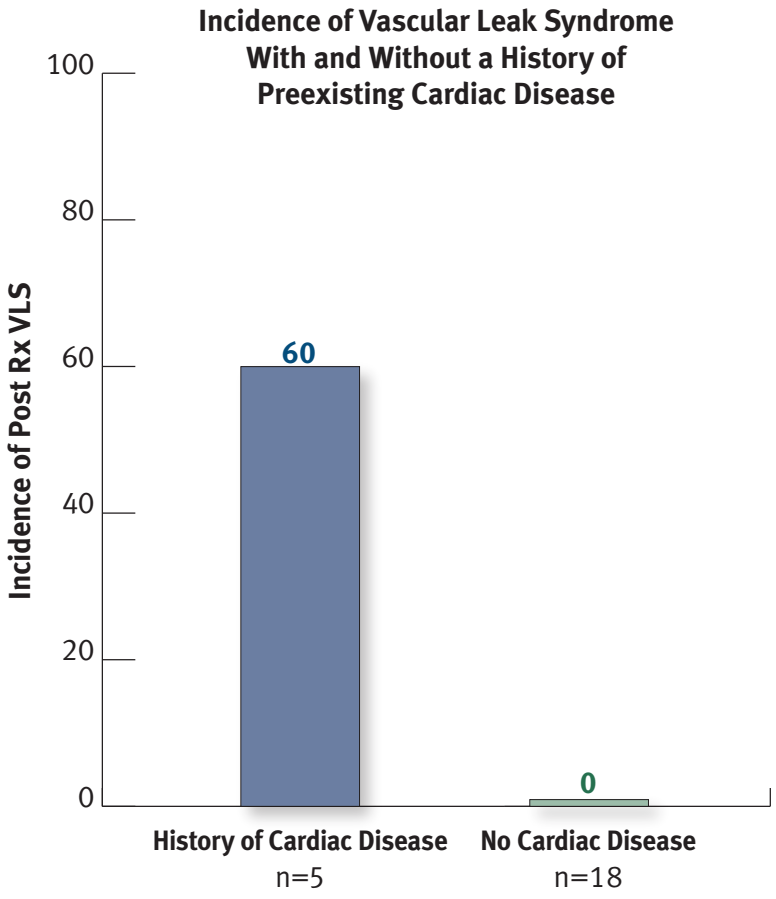
A typical responding patient to one treatment course. This patient was a CR at 6 months.

Patient RS-15, Before, left, and 38 days after immunotoxin treatment, right. mSWAT 26 › 8. CR at day 180 that continues to present (2 years).

Once previous cardiac disease was listed as an exclusion, side effects were mild-moderate and transient with fevers, chills, nausea, transaminasemia, hypoalbuminemia, lymphopenia, reactivation of EBV and CMV, and hypophosphatemia. Toxicities responded to antipyretics, anti-emetics, albumin infusions, rituximab treatment and valgancyclovir.

Toxicities Associated With Resimmune Treatment

Vascular leak syndrome (VLS) is the major toxic manifestation of Resimmune and other immunotoxin fusion proteins and can lead to death. Our data shows that VLS is more pronounced in patient populations who have preexisting heart disease, probably due to the rise in angiopoetin-2 levels in heart disease that destabilize the vascular endothelium (Wang, X et al., 2012. Biomarkers 17, 745-749). We had 5 patients with a history of preexisting cardiac disease including arrhythmias and the incidence of VLS was 60% in this group. In contrast we had 18 patients without a history of heart disease and the incidence of VLS was 0 in this group.

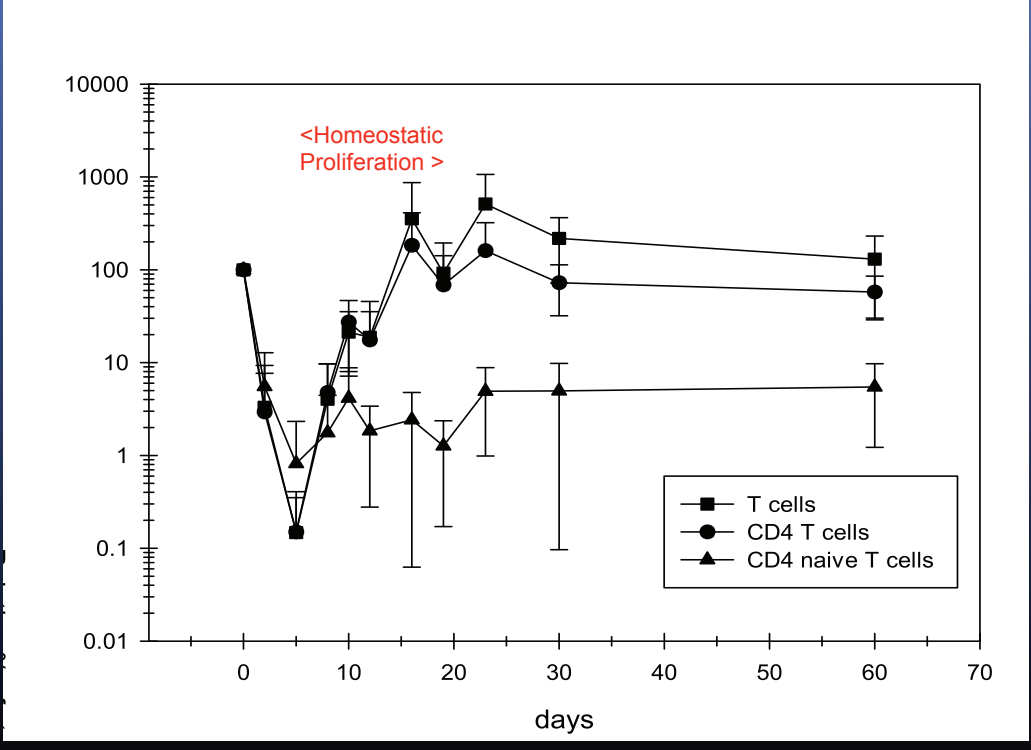


Possible Anti-tumor Mechanism Beyond Immunotoxin-induced Killing

Our 4-day treatment protocol produces patch and plaque regressions obvious at day 37. However, in spite of Resimmune's short serum half-life of 45 minutes, lesions including tumors continue to regress over the next 1-2 years in some cases as patients convert from partial responses to complete responses without additional treatment. We hypothesize that Resimmune activates the immune system to eliminate residual tumor not killed initially. The homeostatic proliferation of T cells following Blood T cell transient depletion may be responsible for the postulated immunomodulation that leads to conversion of PRs to CRs long after Resimmune has disappeared from the patient's circulation.

Angimmune

T cell subset repopulation following anti-CD3 immunotoxin in patients 1-5 in % of initial mean values.



CONCLUSION

Rethinking the time to initiate Resimmune treatment in CTCL Progression

There are many options available for treating stage IB/IIB disease that offer short-term responses but not long-term responses. Resimmune offers a 50% long-term complete response rate that extends out over 4-years in duration in many cases, providing pretreatment mSWATs are <50%. The safety record is good if preexisting cardiac disease is excluded. Early Resimmune treatment may be a cost-effective way of providing long-term patient benefits in this disfiguring and ultimately fatal disease.

Clinical Research Sponsored by:

Angimmune

www.angimmune.com

Poster session presented at: American Society of Hematology (ASH)

55th ASH Annual Meeting and Exposition. 2013 December 7-10; New Orleans, LA.
Program: Oral and Poster Abstracts
Session: 624. Lymphoma: Therapy with Biologic Agents, excluding Pre-Clinical Models: Poster III

Revised 03/14 /2014 With Additional Data & Typographic Corrections