Immunological and clinical activity of a galectin-3 inhibitor (GR-MD-02) plus anti-PD-1 in a first-in-human phase I clinical trial

William L. Redmond[1], Yoshinobu Koguchi[1], Christopher Fountain[1], Rachel Sautter[1], Peter G. Traber[2], and Brendan D. Curti[1]

[1]Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Portland, OR 97213; [2]Galectin Therapeutics, 4960 Peachtree Industrial Blvd, Norcross, GA 30071

Background

- Galectin-3 (Gal3), a lectin family member, is expressed by numerous cancers and immune cell subsets and is associated with reduced survival in patients with metastatic melanoma.
- Extracellular (secreted) Gal3 induces immune suppression via inhibiting TIL function, promoting M2 macrophage polarization, and mobilizing myeloid cells from the bone marrow to promote a metastatic niche within the tumor.
- Preclinical data revealed Gal3 blockade (GR-MD-02) and agonist aOX40 or checkpoint blockade (aCTLA-4; aPD-1) immunotherapy enhanced tumor-specific immunity and improved survival.
- Hypothesis: Gal3 inhibition plus checkpoint blockade will improve TIL function while inhibiting tumor growth and metastasis.
- We initiated a first-in-human phase 1 clinical trial of GR-MD-02 and anti-PD-1 in patients with metastatic melanoma, non-small cell lung cancer (NSCLC) or head and neck squamous cell carcinoma (HNSCC) (NCT02575404).

Clinical Trial Design

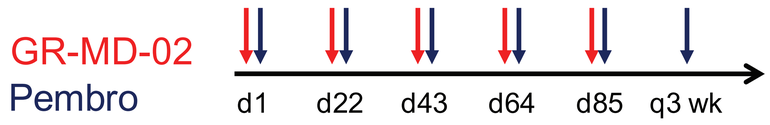
Primary objective

Determine a safe dose of GR-MD-02 used in combination with a flat dose (200 mg) of pembrolizumab (pembro).

Secondary objectives

1) Measure the response rate (RR) to GR-MD-02/pembro in patients with metastatic melanoma who have had melanoma progression after ipilimumab and/or BRAF targeted therapy.
2) Measure the RR to GR-MD-02/pembro in patients with recurrent or metastatic HNSCC with disease progression during or after platinum-containing chemotherapy.
3) Measure the RR to GR-MD-02/pembro in patients with metastatic melanoma, NSCLC or HNSCC with tumor progression after pembrolizumab monotherapy.
4) Assess the biological activity of GR-MD-02/pembro via immunological monitoring.

Cohort	GR-MD-02 dose (mg/kg)
1	2
2	4
3	8



Patient Summary

Subject	Diagnosis	Gender	Age	Sites of Disease	Prior Treatments	Response	Cohort
1	Melanoma	Male	76	SQ, lung	Surgery, IL-2, RT, oncolytic virus, ipi	PR	1
2	Melanoma	Female	63	SQ, muscle, LN	Interferon, ipi	SD, then PD	1
3	Melanoma	Female	82	SQ, bone, LN	Surgery, RT	PD	1
4	Melanoma	Male	62	Brain, bone, lung, SQ, LN, liver	IL-2, ipi, nivo	SD, then PD	1
5	Oral head and neck SCC	Male	55	LN	Surgery	SD on imaging, clinical PD	1
6	Melanoma	Male	55	SQ, LN, lung	Interferon, ipi	Did not receive study agents	N/A
7	Melanoma	Male	65	SQ, LN, lung	Vemurafenib, Dabrafenib + Trametinib	CR	1
8	Melanoma	Female	70	LN, lung	Surgery, IL-2, RT	PR	2
9	Melanoma	Male	83	Lung, pleura	Surgery	CR	2
10	Melanoma	Male	37	LN	Surgery	PR	2

Results

Figure 1. Clinical response to GR-MD-02/pembro immunotherapy.

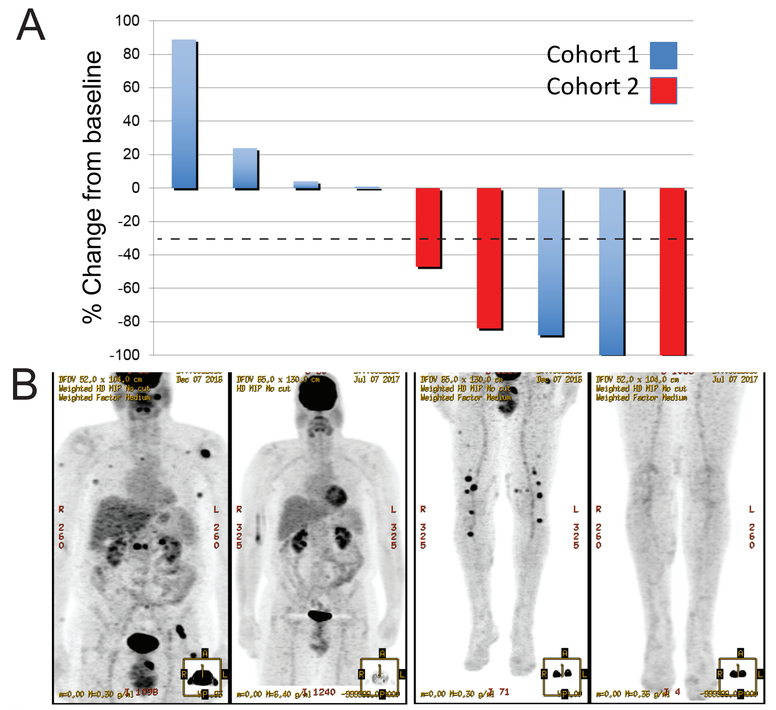


Figure 1. A) Waterfall plot of best clinical response (RECIST 1.1) post-treatment. B) PET scan comparing baseline to day 169. There are multiple FDG-avid melanoma deposits in subcutaneous, soft tissue and osseous sites that resolved. C) CT scan comparing baseline to day 85 showing resolution of a large intramuscular melanoma deposit.

Figure 2. Increased granzyme B+ CD8 T cells at baseline correlates with clinical response to GR-MD-02/pembro.

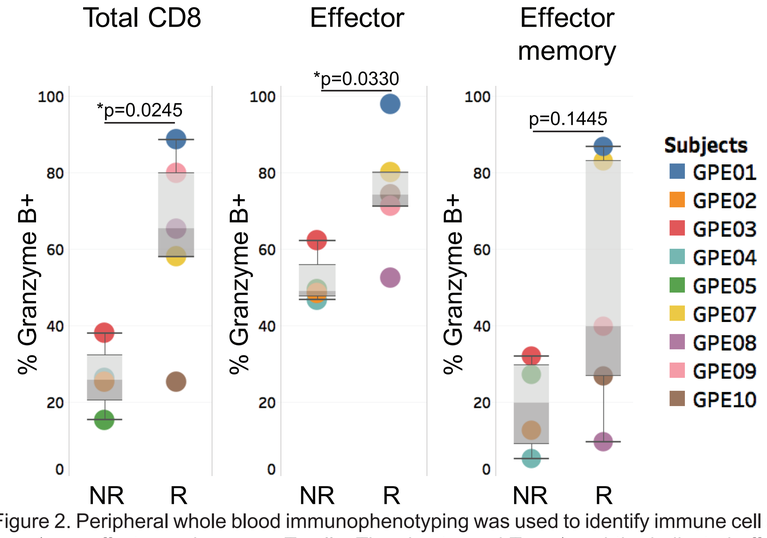


Figure 2. Peripheral whole blood immunophenotyping was used to identify immune cell subsets (e.g., effector and memory T cells, Th subsets, and Tregs) and the indicated effector molecules. GzmB expression in total, effector (CCR7-CD45RA+), and effector memory (CCR7-CD45RA-) CD8 T cells was determined. NR=non-responders; R=responders

Results

Figure 3. Increased perforin+ CD8 T cells at baseline correlates with clinical response to GR-MD-02/pembro.

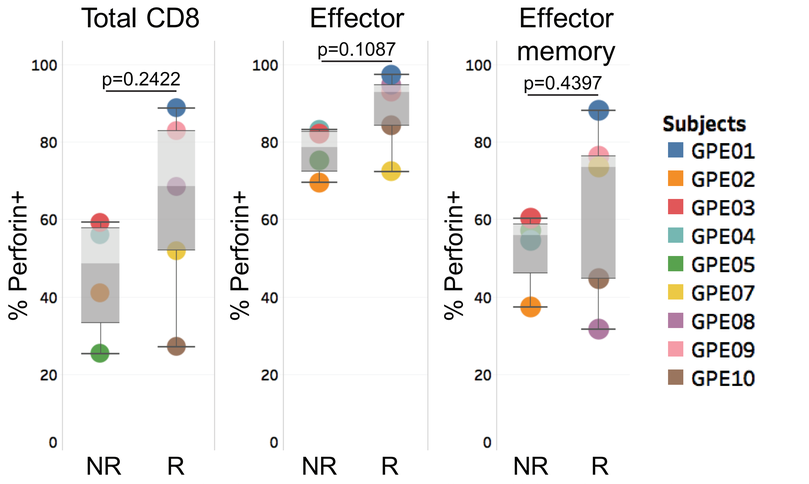


Figure 4. The extent of Prf expression in total, effector (CCR7-CD45RA+), and effector memory (CCR7-CD45RA-) CD8 T cells was determined by flow cytometry as in Fig. 3. NR=non-responders; R=responders

Figure 4. Differential regulation of Prf/GzmB in responders vs. non-responders following GR-MD-02/pembro immunotherapy.

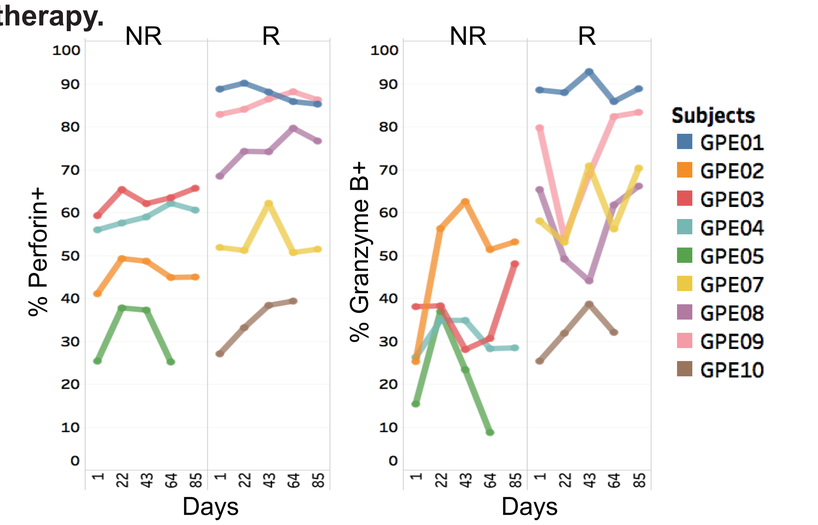


Figure 4. Peripheral whole blood immunophenotyping was conducted at the indicated time points. The extent of Prf and GzmB expression in total CD8 T cells was determined by flow cytometry. NR=non-responders; R=responders

Conclusions

-Gal3 inhibition with GR-MD-02 can be combined safely with aPD-1 checkpoint blockade in patients with metastatic disease.
-ORR 56% (2 CR + 3 PR; n=9); minimal AE's
-Increased level of Prf+ and GzmB+ CD8 T cells at baseline correlated with clinical response.
-Decreased frequency of MDSC in responders vs. non-responders at day 85 post-Tx (**see Poster #P492; Sturgill et al.**)
-Dose escalation of GR-MD-02 is ongoing and an expansion cohort in melanoma is planned. Additional exploratory data will be gathered on Prf+ and/or GzmB+ CD8 T cells and MDSC to assess if these are potential predictive biomarkers of response in the expansion cohort.

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