GLIMMER-01: Phase 1/2 Trial of a First-in-class Bi-sialidase (E-602) in Combination with Cemiplimab in Patients with PD-(L)1-resistant Solid Tumors

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Introduction

Sialoglycans, glycans that terminate with a sialic acid, have emerged as a critical glyco-immune checkpoint that impairs antitumor response by inhibiting innate and adaptive immunity[1]. E-602 is a first-in-class fusion protein consisting of an engineered human sialidase (Neu2) fused to the IgG1 Fc region. It functions by cleaving sialic acids from sialoglycans present on immune and tumor cells, enhancing the function of NK cells, macrophages, and T cells by reducing the engagement of inhibitory Siglecs on immune cells. In Phase 1, E-602 monotherapy was tolerable at doses up to 30 mg/kg and achieved dose-dependent pharmacodynamic (PD) effects, including circulating immune cell desialylation, increased peripheral cytokine secretion, and enhanced peripheral T cell activation[2]. Here we present the safety, efficacy and tumor PD effects of E-602 combination with Cemiplimab (anti-PD-1) in PD-(L)1-resistance cancer patients.

Desialylation of Tumors to Relieve Sialoglycan-Mediated Suppression and Reinvigorate the Anti-Cancer Immune Response

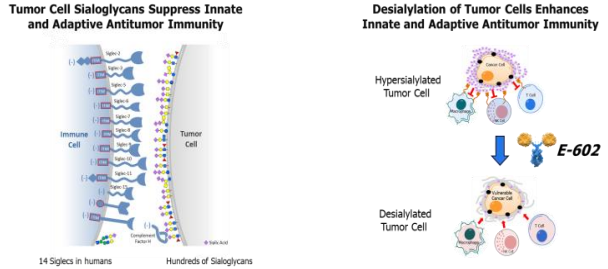


Figure 1. Schematic representation of the sialoglycan-Siglec immune checkpoint axis (left) and E-602's mechanism of action (MoA) in desialylating tumor cells to enhance antitumor immune responses (right). On the left, sialoglycans bind to inhibitory Siglecs on various immune cell types, suppressing immune responses at immune synapses. On the right, cleaving sialic acids from tumor cells at immune synapses removes sialic acid-mediated immune suppression (E-602's MoA of desialylation of immune cells is not shown in the figure).

Overview of GLIMMER-01

GLIMMER-01 (**Gl**ycan Mediated **Imm**un**e R**egulation) is a Phase 1/2, first-in-human, open label, dose escalation and expansion study of E-602 administered as monotherapy (part 1) and in combination with anti-PD-1 Cemiplimab (part 2) to evaluate the safety, pharmacokinetics, pharmacodynamics and antitumor activity in participants with advanced cancers (NCT05259696).

E-602 Monotherapy Dose Escalation (Part 1)[2]*

- Dose escalation: 1, 3, 10, 20, 30 mg/kg
- Demonstrated safety (well tolerated, no MTD)
- PK half-life: 18-26 hours
- Established proof-of-mechanism
  - Desialylation increased T cell activation in blood
  - Desialylation led to a dose-dependent increase in peripheral cytokines IP-10, TNF-α, and MIP-1β
- Determined RP2D 20mg/kg
  - Based on PD of T cell activation

* Luke, *et al*, AACR 2023 annual meeting, abstract #9654

E-602 + Cemiplimab Combination (Part 2)

- Primary endpoints
  - Safety and tolerability of the combination
  - Objective response rate
- Dose and schedule
  - E-602: 20mg/kg, Q1W
  - Cemiplimab: 350 mg, Q3W
- PD-(L)1 resistant cancer patients (n=21)
  - NSCLC (n=12); melanoma (n=8); EGJ (n=1)
  - Median Age: 66 years (Range 42 - 82);
  - Female: 11 / 21 (52%)
  - ECOG PS of 1 at screening: 14/21 (67%)
  - Tumor biopsies before and during treatment
  - Frequency of Baseline Tumor Hypersialylation: 15/20 (75%)

Results

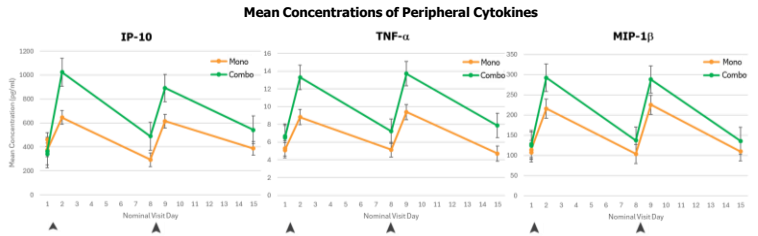
Safety: E-602 in Combination with Cemiplimab

- No DLTs at 20 mg/kg E-602 in combination with cemiplimab
- One Treatment Related SAE of Grade 3 infusion related reaction

Frequency of Treatment-Related AEs Occurring in > 1 Patient (**Table 1**)

Adverse Event N=21 participants	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Infusion related reaction		8 (38%)	1 (5%)	
Fatigue	1 (5%)	2 (10%)		
Chills	2 (10%)			
Nausea	2 (10%)			

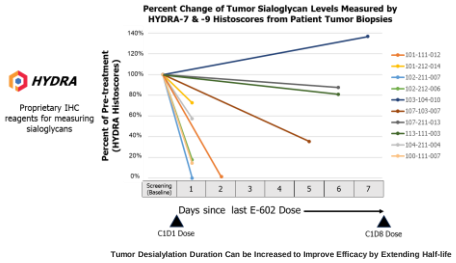
E-602 + Cemiplimab Resulted in a Greater Increase of Peripheral Cytokines than E-602 Monotherapy



▲ E-602 Administration; Mono: E-602 (20mg/kg); Combo: E-602 (20mg/kg) + Cemiplimab

Figure 2. Comparison of changes in peripheral cytokines, including IP-10, TNF-α, and MIP-1β (key biomarkers frequently elevated by checkpoint inhibitors) between E-602 monotherapy (20 mg/kg, Q1W) and E-602 (20 mg/kg, Q1W) combination with Cemiplimab (350 mg, Q3W). In the dose escalation of E-602 as a monotherapy (Part I of the GLIMMER-01 trial), E-602 demonstrated a dose-dependent increase in circulating levels of IP-10, TNF-α, and MIP-1β[2]. The cytokine modulation profile at the same E-602 dose level (20 mg/kg) was selected for comparison with the E-602 monotherapy and E-602 combination with Cemiplimab.

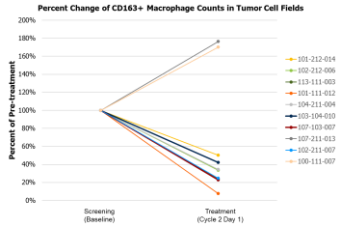
E-602 + Cemiplimab Led to Tumor Desialylation Lasting 2-5 Days, Despite E-602 Rapid Clearance With a Half-life of ~1 Day



9/10 patients showed tumor desialylation
(Excluding patients with baseline HYDRA histoscore ≤ 20)

Figure 3. Comparison of tumor sialoglycan levels measured with Palleon's proprietary IHC reagents, *HYDRA*-7 and -9, in tumor biopsies from patients pre- and post-E-602 treatment. Post-treatment *HYDRA* histoscores were normalized to baseline (pre-treatment) scores.

E-602 + Cemiplimab Decreased CD163+ Tumor-Associated Macrophages Within Tumors



8/10 patients showed a decrease in tumor-associated macrophages in tumors
(Excluding patients with baseline HYDRA histoscore ≤ 20)

Figure 4. Comparison of tumor-associated macrophage (CD163+ M2 macrophage) counts in tumor biopsies from patients pre- and post- E-602 treatment. Post-treatment macrophage counts were normalized to baseline (pre-treatment) levels.

Patients With Hypersialylation at Baseline Trended toward Better Clinical Outcomes than Patients Lacking Hypersialylation

These Data Support Desialylation of Tumor Cells with Hypersialylation as a Promising Therapeutic Strategy

Best Overall Response by Hypersialylation Status in PD-(L)1 Resistant Patients (**Table 2**)

Patients (PD-(L)1 resistant melanoma and NSCLC)		PR	SD	PD
Patients with **Hypersialylation** (*HYDRA* ≥20)	n=15	1* (7%)	6** (40%)	8 (53%)
Patients **Lacking Hypersialylation** (*HYDRA* <20)	n=5	0 (0%)	0 (0%)	5 (100%)

* Remains on therapy > **12 months** with complete resolution of liver mets, 80% reduction of other mets
** Duration of SD 3-6 months

Confirmed Partial Response in Anti-PD-1 Resistant Melanoma Patient

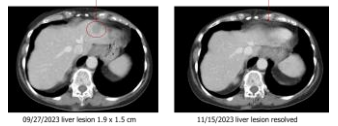


Figure 5. Computed tomography scans of an anti-PD-(L)1 resistant melanoma patient showed a confirmed partial response. The patient previously received adjuvant Ipilimumab and Nivolumab, and metastatic treatments with Nivolumab, Ipilimumab, Talimogene laherparepvec, and Binimetinib; all were discontinued due to complications or PD. Disease sites included the chest wall, liver, and left thigh, with non-target lesions in the ileum and breast. The last ICI treatment was given in November 2019, 3.9 years before starting E-602.

Conclusions

- Glycan editing (desialylation) of cell surface glycans offers a potential novel therapeutic approach to treat cancer.
- E-602, a first-in-class engineered human sialidase Fc fusion, has demonstrated safety, proof-of-mechanism, and early antitumor activity in combination with Cemiplimab for patients with PD-(L)1-resistant solid tumors.
- Future goal: Increase tumor desialylation duration to improve antitumor activity
  - Increase drug exposure by optimizing the human sialidase for extended half-life
  - Enhance tumor targeting by incorporating a tumor targeting arm (TAA-targeted sialidase)

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References

1. Crocker P.R., Varki A. Siglecs, sialic acids and innate immunity. Trends Immunol. 2001 Jun; 22(6):337-42.2
2. Luke, et al, AACR 2023 annual meeting, abstract #9654.