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POSTER ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

Seven-Day Vein-to-Vein Point-of-Care Manufactured CD19 CAR T Cells (GLPG5201) in Relapsed/Refractory CLL/SLL Including Richter's Transformation: Results from the Phase 1 Euplagia-1 Trial

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Background
Despite treatment advances, chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) remain incurable. Patients (pts) with concurrent Richter's transformation (RT) have poor prognoses with limited treatment options. Chimeric antigen receptor (CAR) T-cell products targeting CD19 have shown activity in pts with CLL/SLL or RT, yet data are limited and no therapies are approved. Due to limited treatment options and short survival of pts with RT, rapid treatment delivery is essential. A novel decentralized and automated point-of-care (PoC) manufacturing model was developed to administer fresh, autologous CAR-T treatments within 7 days of apheresis. An update on the Phase (Ph) 1 Euplagia-1 trial of PoC manufactured GLPG5201 is presented.
Methods
Euplagia-1 (CTIS: 2022-501686-47-00) is a Ph1/2 study of PoC-manufactured GLPG5201 in pts with R/R CLL or SLL, including pts with RT. Pts with CD19+ R/R CLL/SLL with ≥2 prior therapy lines are eligible. Pts with RT are eligible regardless of prior therapy. GLPG5201, an anti-CD19/41BB CAR-T therapy, is administered as a fresh product following fludarabine/cyclophosphamide lymphodepleting chemotherapy. Upon screening, pts receive daily ibrutinib until leukapheresis. The primary objectives are safety and determining a recommended Ph2 dose (Ph1), and objective response rate (ORR; Ph2). Secondary objectives include additional efficacy measures, pharmacokinetics and feasibility of PoC manufacturing.
Results
As of April 26, 2023, 12 pts were enrolled in Ph1 at dose level (DL) 1 (35×10^6 CAR+ T cells, n=6) or DL2 (100×10^6 CAR+ T cells, n=6) at a single institution. All pts were diagnosed with R/R CLL, 7/12 with concurrent RT. Median age was 66 years (range 58-71); 8/12 pts were male. Median prior lines of therapy were 4 (range 2-10); 10/12 pts received a BTK inhibitor, 9/12 pts venetoclax, and 1 pt an allogeneic stem-cell transplant. Five of 7 pts with RT relapsed after, or were refractory to, R-CHOP. Six of 12 pts had a TP53 mutation, 1 pt had a 17p deletion; 11 pts had an unmutated IGHV status and 2 had a complex karyotype reported.
GLPG5201 was manufactured for all pts and administered as a fresh infusion. Median vein-to-vein time was 7 days (range 7-14). Due to lower manufactured CAR+ T cell yield, 3 pts received DL1 instead of the intended DL2. A preserved early memory phenotype for CD4+ and CD8+ CAR T cells was observed in the final product, compared with apheresis starting material (**Figure**).
Most treatment emergent adverse events (TEAEs) were Grade 1-2; most Grade ≥3 events were hematological (**Table**). Six (50%) pts had Grade 1-2 cytokine release syndrome (CRS), with no CRS Grade ≥3. No neurotoxicity was reported. A dose limiting toxicity occurred in 1 pt (Grade 4 neutropenia, DL2), which was manageable and within expectations in this pt population. No unexpected GLPG5201-related toxicities were observed; no deaths occurred while pts were on study.
Eleven pts responded to treatment (best ORR 92%). Complete response (CR) was observed for 9 pts (CR rate [CRR] 75%). ORR and CRR were 83% and 67% at DL1, and 100% and 83% at DL2, respectively. All but 1 pt with RT responded (ORR 86%); CR was achieved by 5/7 pts with RT (CRR 71%). One pt with RT was refractory with CD19-negative disease. At the time of analysis, 9/11 (82%) pts had ongoing responses; duration was up to 9 months post-infusion (median follow-up 3.2 months; range 1-9). Two pts progressed after an initial response, 1 pt with CD19-negative disease.

Robust CAR T-cell expansion was observed in all pts by qPCR, with a median maximum expansion of 4.4×10^5 copies/μg DNA (C_{max}). Median T_{max} was 14 days (range 9-20 days). Median $AUC_{0\text{-}28d}$ was 5.3×10^6 copies/μg DNA × days. GLPG5201 could be detected in peripheral blood up to 9 months post-infusion.

Conclusion

Data from 12 pts enrolled in the Ph1 Euplagia-1 study demonstrate that PoC CAR-T manufacturing with a short vein-to-vein time is feasible. GLPG5201 is administered as a fresh product; median vein-to-vein time is 7 days. There are no unexpected safety findings, and no CRS Grade ≥3 or any ICANS are reported. Efficacy data are encouraging, with a 92% best ORR and 75% CRR; 6/7 pts with RT responded. With this novel PoC manufacturing model, an early phenotype of less differentiated CAR T cells is preserved in the final product. GLPG5201 demonstrates rapid *in vivo* expansion and durable persistence post-infusion . Euplagia-1 is ongoing, and updated data will be presented.

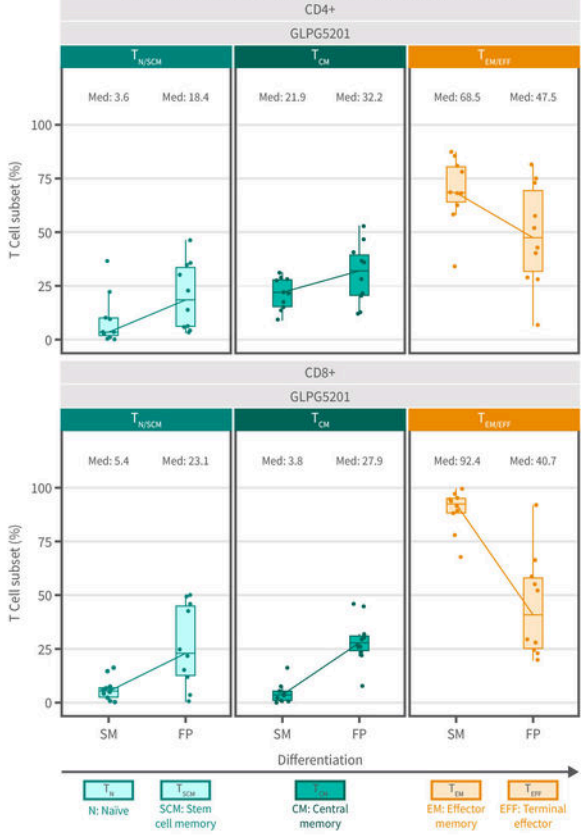
Disclosures Ortiz-Maldonado: *Kite:* Consultancy, Honoraria; *Celgene BMS:* Consultancy, Honoraria; *Miltenyi Biomedicine:* Consultancy; *Pfizer:* Consultancy; *Janssen:* Consultancy, Honoraria; *Novartis:* Consultancy. **Martinez-Cibrian:** *Kite:* Honoraria, Other: Travel support. **Verbruggen:** *Galapagos:* Current Employment, Current equity holder in publicly-traded company. **Spoon:** *Galapagos:* Current equity holder in publicly-traded company; *Cellpoint BV, a Galapagos company:* Current Employment, Current equity holder in publicly-traded company. **Liefaard:** *Cellpoint BV, a Galapagos company:* Current Employment. **Pont:** *Lyell Immunopharma:* Current equity holder in publicly-traded company; *Springworks Therapeutics:* Consultancy; *Cellpoint BV, a Galapagos company:* Current Employment, Current equity holder in publicly-traded company. **van Muyden:** *Cellpoint BV, a Galapagos company:* Current Employment, Current equity holder in publicly-traded company.

Table. TEAEs occurring in ≥2 patients (worst grade per patient).[a]

TEAE	Total (N=12) n (%)	Grade 1/2 n	Grade 3 n	Grade 4 n
Anemia	11 (91.7)	7	4	0
Neutropenia	9 (75.0)	0	1	8
Pyrexia	8 (66.7)	8	0	0
Thrombocytopenia	7 (58.3)	4	0	3
Cytokine release syndrome	6 (50.0)	6	0	0
Hypocalcemia	5 (41.7)	4	1	0
Hypoxia	3 (25.0)	3	0	0
Nausea	3 (25.0)	3	0	0
Upper respiratory tract infection	3 (25.0)	3	0	0
Arthralgia	2 (16.7)	2	0	0
Asthenia	2 (16.7)	2	0	0
Blood alkaline phosphatase increased	2 (16.7)	2	0	0
Blood bilirubin increased	2 (16.7)	1	1	0
Pleural effusion	2 (16.7)	2	0	0

Adverse events were coded using MedDRA version 25.0 preferred terms.
[a]Listed in order of decreasing incidence.
TEAE, treatment-emergent adverse event.

Figure. GLPG5201 preserves an early memory phenotype of CD4+ and CD8+ CAR T cells in the final product.



Exploratory flow cytometry analysis of T cell subsets in the apheresis starting material (SM) and final product (FP), showing box plots with first quartile (Q1), median (Q2) and third quartile (Q3), whiskers as well as all the individual datapoints. The whiskers extend from Q1 [Q3] to the smallest [largest] datapoint which is still within Q1 - 1.5 interquartile range (IQR) [Q3 + 1.5 IQR]. Data beyond the end of the whiskers are considered "outlying" points. GLPG5201 preserves naïve/stem cell memory T cells and central memory T cells in the FP compared to the SM. Phenotype percentages of CD4 or CD8 (gated on CAR+ T cells for FP) for paired patient samples (n=10): naïve/stem cell memory=CD45RO-CD197+, central memory=CD45RO+CD197+, effector memory/terminal effector=CD45RO-/+CD197-. Med: median.

Figure 1

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