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First-in-human Study of CD19/BCMA Dual-targeting FastCAR-T GC012F (AZD0120) for Patients with Refractory Systemic Lupus Erythematosus

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Jingjing Feng[1] Jia Liu[2] Heng Cao[1] Mingming Zhang[1] Gui Li[2] Shan Fu[1] Guoqing Wei[1] Lihong Weng[2] Ruimin Hong[1] Lianjun Shen[2] Dawei Cui[1] Zhihong Liu[3] Jin Lin[1] Yongxian Hu[1] Wei Cao[2] He Huang[1]

[1] The First Affiliated Hospital, Zhejiang University School of Medicine, Bone Marrow Transplantation Center, Hangzhou, China, [2] Gracell Biotechnologies Ltd, Shanghai, China, [3] Liangzhu Laboratory, Hangzhou, China

Background

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibodies produced by pathogenic plasma cells, long-lived plasma cells, and memory B cells. Current treatments, including immunosuppressants, are not curative, leaving patients with limited therapeutic options. Studies have shown that CD19 CAR-T cell therapy can induce remission in refractory SLE (rSLE). Long-lived plasma cells contribute to persistent autoantibody production, particularly in late-stage disease. Targeting both B and plasma cells may help reset the autoreactome, eliminating pathogenic autoantibodies and improving clinical outcomes. We are investigating GC012F, a novel CD19/BCMA dual-targeting CAR-T, for treating rSLE.

Aims

This trial evaluates the safety and preliminary efficacy of GC012F in rSLE.

Methods

This single-arm, open-label, single-site Phase 1 trial (NCT05846347) included SLE patients with SLEDAI-2K scores ≥ 8, who failed at least two immunosuppressants and one biologic. Lymphodepletion was achieved using fludarabine (30 mg/m^2/day on days -5 to -3) and cyclophosphamide (1000 mg/m^2/day on day -3), followed by GC012F infusion on day 0 in three escalating dose groups (1, 2, and 3 ×10^5 CAR+ T cells/kg). Immunosuppressants were discontinued one week before leukapheresis, with bridging therapy allowed. CRS and ICANS were graded per ASTCT 2019 criteria, and adverse events were evaluated using CTCAE 5.0. Efficacy was assessed by LLDAS and DORIS, anti-nuclear antibodies, and discontinuation of SLE-specific therapies.

Results

As of Nov 12, 2024, 15 rSLE patients were enrolled. All received a single GC012F infusion in escalating dose groups (DL1: n=3; DL2: n=3; DL3: n=9). Median follow-up was 384 days (range: 172–526). Median age was 28 (range: 22–55), with 14 (93%) female, and median disease duration was 7.3 years (range: 1.3–23.7). Eleven patients had lupus nephritis, graded based on historical kidney biopsies. Baseline median SLEDAI score was 12 (range: 6–26).

No DLT was observed. Fourteen patients experienced CRS, with median onset at 5.5 days (range: 3–10) and median duration of 4.5 days (range: 2–16). Twelve patients had Grade 1 CRS. Two patients in the 3 ×10^5 CAR+ T cells/kg group had Grade 3 CRS, resolved with methylprednisolone. One patient had Grade 2 ICANS at Day 7, resolved with dexamethasone and levetiracetam. Infections occurred in 7 patients, all Grade 1 or 2. GC012F showed robust expansion, with a median peak CAR copy number of 40,270 copies/μg DNA (range: 14,009–104,642) and Tmax at 10 days (range: 7–11). B cell depletion occurred post-

infusion, with reconstitution by Day 56 (range: 56–168), showing >95% naïve B cells.

Glucocorticoids, immunosuppressants, and biologics were stopped before infusion. Improvement trends were noted in anti-nuclear antibodies (including anti-dsDNA) and complement levels. SLEDAI-2K scores showed sustained declines. At 6 months, 33% (5/15) of evaluable patients achieved DORIS remission, rising to 45% (5/11) at 9 months and 56% (5/9) at 12 months. DORIS remission was not achieved in some cases due to residual proteinuria or a flare in one non-renal patient at 6 months.

Summary/Conclusion

Preliminary results suggest that GC012F, a CD19/BCMA dual-targeting CAR-T therapy, has a favorable early safety profile and promising efficacy in rSLE patients. A Phase 1/2 study (NCT06530849) is ongoing to further evaluate its safety and efficacy.

Keyowrds: Autoimmune disease, CAR-T, Systemic lupus erythematosus, Immunotherapy