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Golidocitinib as salvage therapy before allogeneic hematopoietic stem cell transplantation in refractory Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis

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Running head: JAK1 Inhibition for Refractory EBV-HLH

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outcome interpretation. ZW and JW gave suggestions for polish and revise. ZW and JW oversaw the study's clinical management and assumed overall responsibility for research integrity. All authors read and approved the final manuscript.

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Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by uncontrolled lymphocyte/macrophage activation and pathological overproduction of proinflammatory cytokines, resulting in life-threatening multi-organ dysfunction [1]. Traditionally, HLH is classified as primary and secondary. Epstein-Barr virus-associated HLH (EBV-HLH) is considered a major subtype of secondary HLH (sHLH) [2]. Despite standard etoposide-based therapy, a substantial proportion of patients with EBV-HLH fail to respond or develop relapsed/refractory disease, highlighting the need for effective salvage strategies [3]. Emerging cytokine-targeted strategies have shown potential in managing refractory HLH [4]. We describe the first documented case of refractory EBV-HLH successfully treated with the selective JAK1 inhibitor golidocitinib, demonstrating rapid clinical improvement without adjunctive therapies.

A 57-year-old female presented with persistent fever (39°C), pancytopenia (WBC 1.5×10^9/L, platelets 68×10^9/L), hyperferritinemia and markedly elevated transaminases. Positron emission tomography/computed tomography (PET/CT) demonstrated splenomegaly and multi-regional hypermetabolic lymphadenopathy. Diagnostic evaluation for HLH revealed elevated soluble CD25 (11,507 pg/mL), fulfilling HLH-2004 criteria. Histopathological evaluation of the abdominal lymph nodes revealed architectural effacement by an infiltrate of medium-sized atypical cells, predominantly EBER-positive T cells, consistent with a diagnosis of EBV-positive lymphoproliferative disease (EBV-LPD, grade 2–3). Quantitative PCR assays demonstrated significantly elevated EBV-DNA loads in both plasma (3.34×10^5

copies/mL) and peripheral blood mononuclear cells (PBMCs) (2.6×10^6 copies/mL), indicating active viral replication. Subset analysis of peripheral blood lymphocytes demonstrated multilineage EBV involvement, with EBV-DNA detectable in $CD19^+$ B cells, $CD56^+$ NK cells, $CD8^+$ T cells, and $CD4^+$ T cells. Rheumatologic diseases, malignancies, and known genetic HLH defects were excluded, suggesting that EBV infection was the likely trigger of HLH in this patient. The patient was started on induction therapy with the standard HLH-94 protocol. During this treatment course, a single dose of tislelizumab was additionally administered. However, tislelizumab was immediately discontinued due to the development of a suspected drug-related fever. The patient subsequently continued and completed a 4-week course of the HLH-94 regimen. This treatment approach resulted in significant symptomatic relief and a reduction in hepatic inflammation.

Three weeks after completion of the initial HLH-94 treatment, the patient experienced disease relapse, characterized by recurrent high fever (39°C) and persistently high EBV viral loads, with plasma levels of 2.7×10^4 copies/mL and PBMCs reaching 6.9×10^6 copies/mL. The patient developed progressive pancytopenia (granulocytes 1.22×10^9/L, hemoglobin 73 g/L, platelets 90×10^9/L), accompanied by hyperferritinemia and hepatosplenomegaly. The presence of hemophagocytosis in the bone marrow, in conjunction with the aforementioned clinical and laboratory features, confirmed the diagnosis of refractory HLH. Given the patient's refractory hyperinflammation, golidocitinib was administered as an off-label therapy. Written informed consent for this off-label treatment was obtained from the patient's family

after a thorough discussion of the potential risks and benefits. The subsequent prospective clinical study evaluating golidocitinib in HLH has been reviewed and approved by the Institutional Review Ethics Committee of Beijing Friendship Hospital, Capital Medical University (approval No. 2025-P2-218-02). According to the criteria proposed by Marsh et al.[5], the patient was considered to have refractory HLH. Salvage therapy with JAK1 inhibitor golidocitinib (150 mg, once daily) was initiated, based on the dosing regimen evaluated in the phase I clinical study by Song et al. [6]. No concomitant antiviral therapy, glucocorticoids, cytotoxic agents, including etoposide, or intravenous immunoglobulin were used. The patient did not require transfusion of red blood cells, platelets, plasma, or other blood products during this period. During episodes of neutropenia, granulocyte colony-stimulating factor was administered intermittently by subcutaneous injection at 5 μg/kg to promote leukocyte recovery. Given the neutropenic status, ceftizoxime and voriconazole were administered prophylactically during hospitalization. Fever resolved within 48 hours, and platelets normalized (174×10^9/L), marrow hemophagocytosis cleared, accompanied by rapid declines in ferritin (13,137.6→3,664.3 μg/L) and transaminases (ALT 89 U/L→normal, AST 266.5 U/L→normal) by day 7. Anemia improved and splenomegaly regressed within 5 weeks. Four clinical indicators improved after initiation of golidocitinib monotherapy (Figure 1). Furthermore, several cytokines, including ST2, IL-1RA, and IL-18, maintained significantly elevated levels through day 3 of treatment. Subsequent measurements on day 11 revealed marked reductions in these specific biomarkers. However, the EBV-DNA loads did not change

significantly in plasma or PBMCs. No golidocitinib-related adverse events were observed. On day 45 after initiation of golidocitinib, the patient underwent allo-HSCT in a state of partial response. The transplant was performed using a haploidentical related donor, with a conditioning regimen comprising teniposide, busulfan, cyclophosphamide, and anti-T-lymphocyte globulin (ATLG). Post-transplant hematopoietic engraftment was successfully achieved, with neutrophil and platelet recovery on days 14 and 13, respectively. Serial monitoring showed persistently undetectable peripheral blood EBV-DNA levels, and no clinical or laboratory signs of HLH relapse were observed. At the last follow-up, 12 months after allo-HSCT, the patient was alive and remained in continuous complete remission. The clinical course and treatment timeline are summarized in Figure 2.

To elucidate the cytokine-modulating effects observed during golidocitinib therapy, we conducted parallel in vitro analyses using a mixed lymphocyte reaction (MLR) model. Co-culture of mature dendritic cells (DCs) with allogeneic T cells triggered robust secretion of canonical HLH-driving cytokines, specifically IFN-γ, IL-6, and TNF-α. They are the fundamental mediators of T-cell and macrophage hyperactivation, accurately mirroring the core hyperinflammatory milieu in HLH patients. Golidocitinib pretreatment dose-dependently suppressed the production of these key cytokines (Figure 3).

Although ruxolitinib and other JAK inhibitors have shown therapeutic potential in HLH [7], their hematologic toxicity and infection risks remain concerning [8], primarily because non-selective JAK1/2 inhibition interferes with JAK2-dependent

hematopoiesis, often exacerbating cytopenias. Notably, selective JAK1 inhibitors may offer improved safety profiles, as evidenced by murine HLH models showing therapeutic efficacy without significant toxicity through JAK1-specific blockade [9]. Mechanistically, preclinical studies reveal that JAK1 inhibition suppresses inflammatory cascades via modulation of $CD8^+$ T-cell metabolic pathways and cytokine gene expression [10]. In this case, golidocitinib—a new-generation oral JAK1 inhibitor with 200–400-fold selectivity over other JAK isoforms [6]—achieved rapid inflammatory control in our refractory EBV-HLH case, manifested by normalized body temperature, >90% ferritin reduction, and sequential declines in ST2, IL-1RA, and IL-18 levels. However, we must emphasize that extrapolating the favorable safety and tolerability observed in this single case requires caution; these findings must be validated in larger cohorts.

Prior research has also revealed its substantial antitumor effects in relapsed or refractory peripheral T-cell lymphoma (PTCL) [6]. EBV infection can not only trigger HLH but also contribute to the development of EBV-LPD. A previous study demonstrated constitutive STAT3 activation in EBV-positive T- or NK-cell lines [11], which may drive the abnormal proliferation of lymphocytes. Since JAK1 typically phosphorylates and activates STAT proteins [12], it is speculated that JAK1 inhibitors might thwart the development of lymphoproliferative lesions by inhibiting STAT3 phosphorylation in these EBV-positive cell lines. Collectively, this case suggests that golidocitinib's precision targeting of JAK1 positions it as a promising bridging strategy for refractory EBV-HLH, primarily by enabling the rapid control of

hyperinflammation. While its direct antiviral or antitumor effects remain unproven based on current data, further prospective studies and our ongoing clinical trial will systematically evaluate its long-term efficacy, investigate its full therapeutic potential, and optimize dosing protocols.

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Figure legends

Figure 1. Dynamic changes in clinical indicators after initiation of golidocitinib monotherapy.

Serial changes in body temperature, hemoglobin, ferritin, and alanine aminotransferase levels are shown after the start of golidocitinib treatment. Day 0 indicates the initiation of golidocitinib monotherapy. Panels show changes in body temperature (A), hemoglobin (B), ferritin (C), and alanine aminotransferase (D). Ferritin was not available on day 21. ALT: alanine aminotransferase; Hb: hemoglobin.

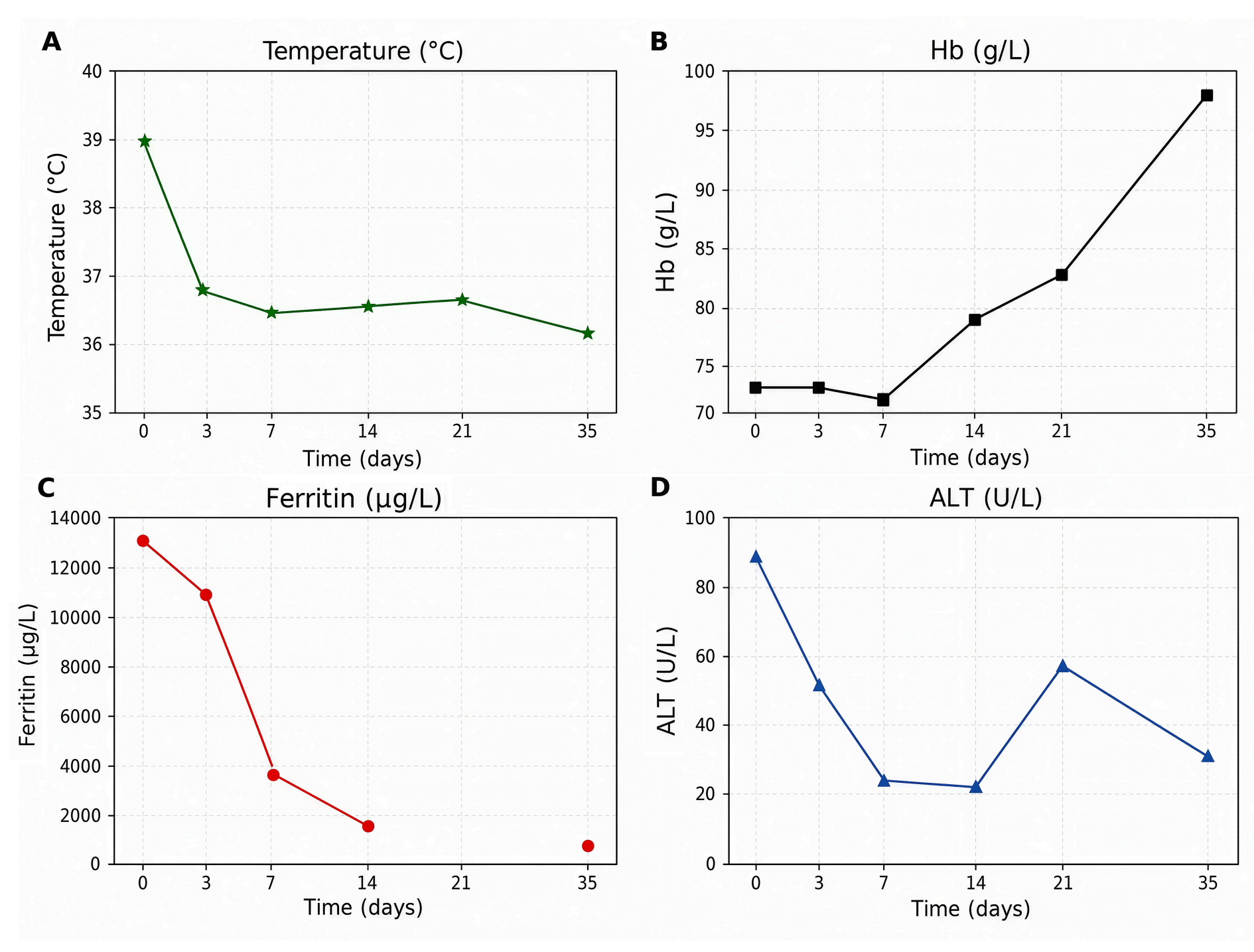
Figure 2. Clinical course and treatment timeline of the patient.

The timeline summarizes the key clinical events and treatment course, including single-dose tislelizumab, 4 weeks of HLH-94 therapy, partial response, subsequent HLH relapse, golidocitinib monotherapy, allogeneic hematopoietic stem cell transplantation, and 12-month post-transplant follow-up. Allo-HSCT: allogeneic hematopoietic stem cell transplantation; HLH: hemophagocytic lymphohistiocytosis; PR: partial response.

Figure 3. Dose-response curves of golidocitinib inhibiting cytokine production in the human MLR.

Mixed lymphocyte reactions were cultured for three days in the presence of serially diluted golidocitinib solutions at concentrations of 0, 0.24, 2.44, 9.76, 39, 156, 625, 2500, and 10000 nM. Cytokine secretion in supernatants of cell cultures was subsequently measured using the MSD SECTOR® Imager. The experiment was repeated three independent times (n=3 replicates). For each run of experiment,

PBMCs from one donor were used to generate dendritic cells, while PBMCs from a separate donor were used for T cells. A total of 6 distinct donors were included in this study. All PBMC samples had cell viability > 90%. The IC_{50} values were calculated by fitting dose-response curves with a four-parameter logistic model in GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA). MLR: mixed lymphocyte reaction. MSD: meso scale discovery. PBMC: peripheral blood mononuclear cells.


A
Temperature (°C)
Temperature (°C)
40
39
38
37
36
35
0
3
7
14
21
35
Time (days)
B
Hb (g/L)
Hb (g/L)
100
95
90
85
80
75
70
0
3
7
14
21
35
Time (days)
C
Ferritin (µg/L)
Ferritin (µg/L)
14000
12000
10000
8000
6000
4000
2000
0
0
3
7
14
21
35
Time (days)
D
ALT (U/L)
ALT (U/L)
100
80
60
40
20
0
0
3
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14
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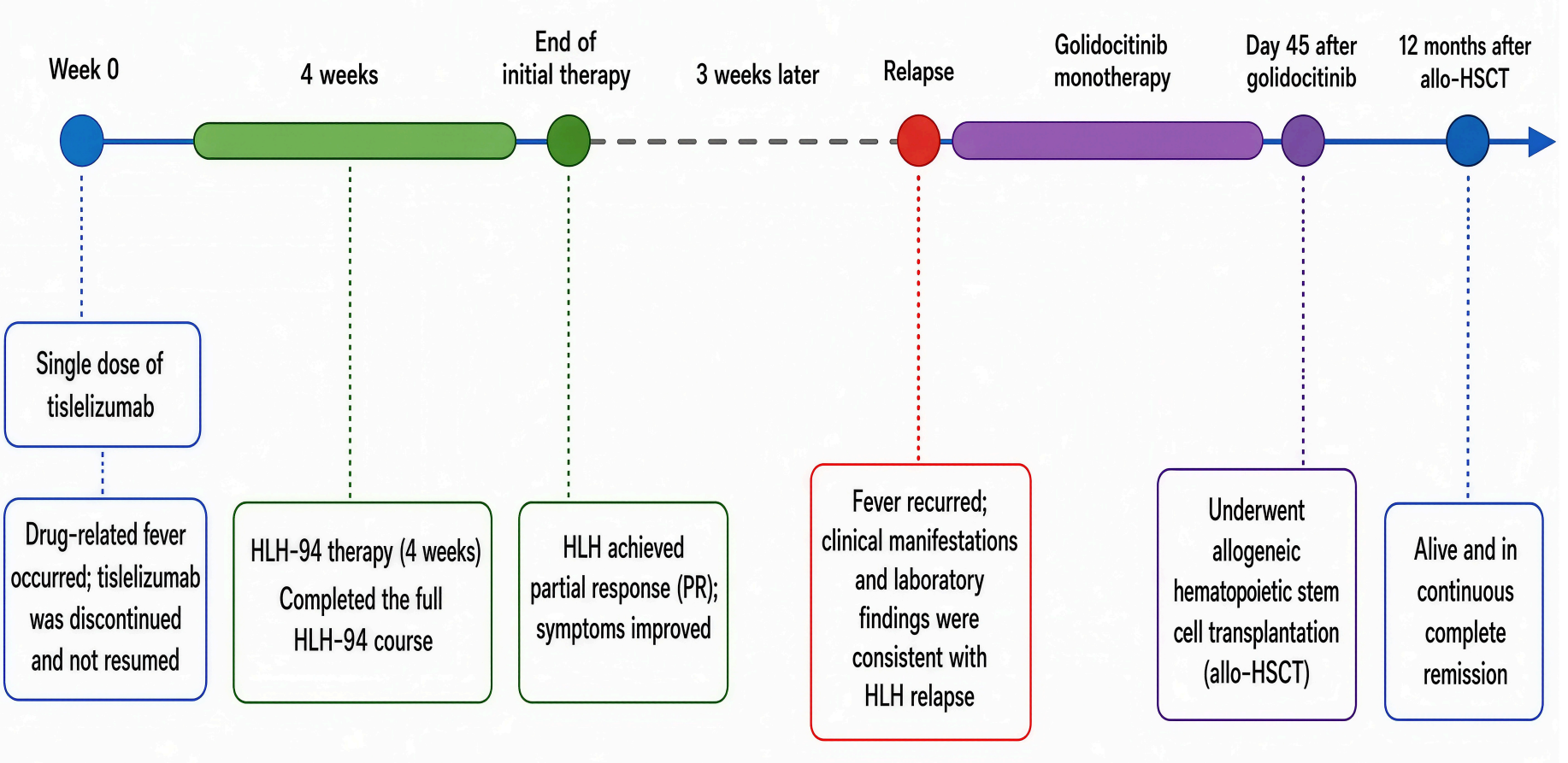
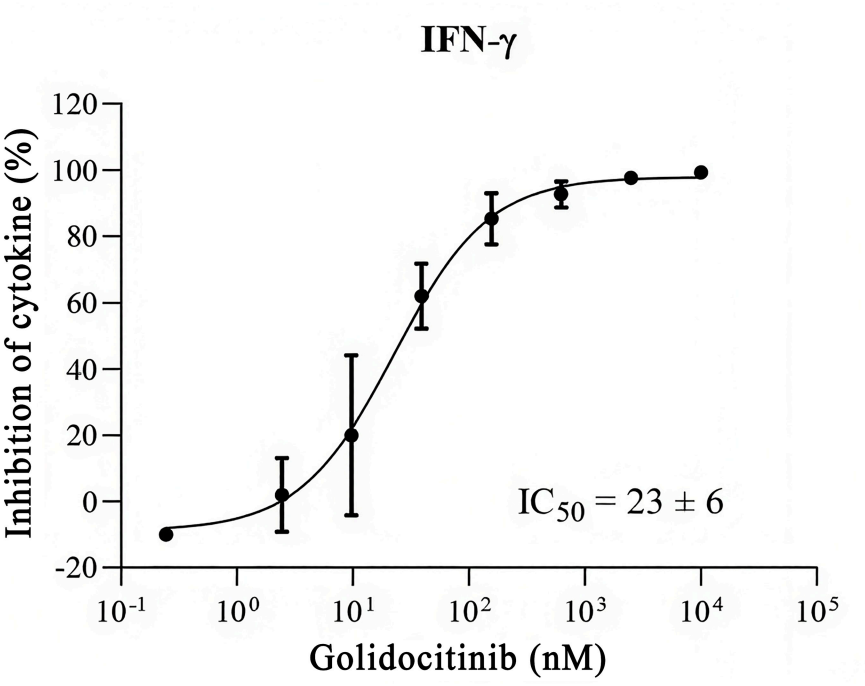
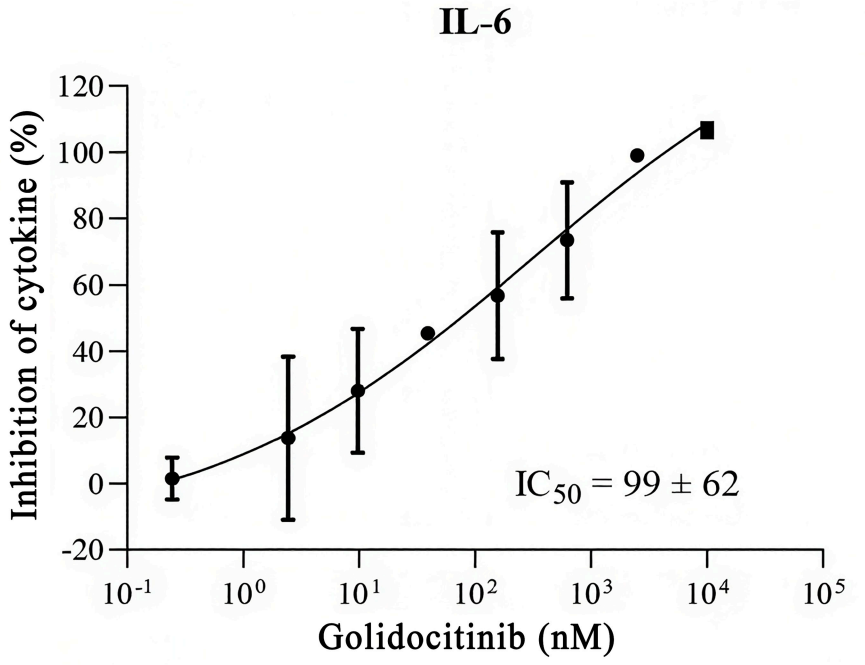
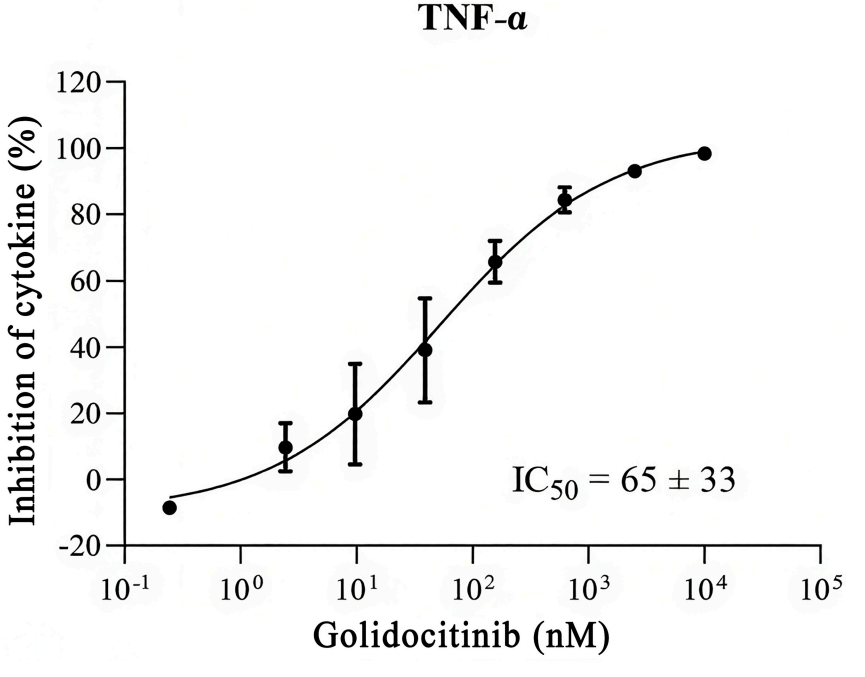
35
Time (days)


Week 0
4 weeks
End of initial therapy
3 weeks later
Relapse
Golidocitinib monotherapy
Day 45 after golidocitinib
12 months after allo-HSCT
Single dose of tislelizumab
Drug-related fever occurred; tislelizumab was discontinued and not resumed
HLH-94 therapy (4 weeks)
Completed the full HLH-94 course
HLH achieved partial response (PR); symptoms improved
Fever recurred; clinical manifestations and laboratory findings were consistent with HLH relapse
Underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT)
Alive and in continuous complete remission


IFN-γ
Inhibition of cytokine (%)
120
100
80
60
40
20
0
-20
IC50 = 23 ± 6
10-1
100
101
102
103
104
105
Golidocitinib (nM)


IL-6
Inhibition of cytokine (%)
120
100
80
60
40
20
0
-20
IC50 = 99 ± 62
10-1
100
101
102
103
104
105
Golidocitinib (nM)


TNF-α
Inhibition of cytokine (%)
120
100
80
60
40
20
0
-20
IC50 = 65 ± 33
10-1
100
101
102
103
104
105
Golidocitinib (nM)