A Phase 2, Single-arm, Open-label Study of Olverembatinib, CD3/CD19 Bispecific T-cell Engager, and Chidamide in Patients With Newly Diagnosed Philadelphia Chromosome-positive Acute Lymphoblastic Leukemia

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1.Background introduction

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) accounts for approximately 25% of cases in younger patients and over 40% in older patients diagnosed with ALL[1, 2]. TThe presence of the Ph rearrangement gives rise to the BCR-ABL1 fusion gene, which has been associated with poorer outcomes. A significant feature of Ph+ ALL is the deletion of the IKZF1 gene (IKZF1del), observed in more than 70% of Ph+ ALL patients[3, 4]. Ph+ ALL patients with IKZF1del exhibit poor molecular responses, resistance to therapy, and higher rates of relapse[5–7]. Before the advent of tyrosine kinase inhibitors (TKIs), the complete response (CR) rate and prognosis of Ph+ ALL were extremely poor. The combination of chemotherapy with TKIs has improved the CR rate to 90%, providing more patients with the opportunity to undergo allogeneic hematopoietic stem cell transplantation (allo-HSCT)[8–11].

While chemotherapy plus TKIs has improved the complete response (CR) rate in Ph+ ALL, it has also led to an increase in non-relapse mortality (NRM). The NRM during induction therapy ranges from 1-3% for children, 10-20% for younger adults, and over 20% for older patients[12]. TThe unsatisfactory NRM is attributed to the bone marrow toxicity of multi-drug chemotherapy. Therefore, there is a need for a low-toxic or even chemo-free regimen. The GIMEMA group has been a leader in exploring chemo-free treatments for Ph+ ALL since the era of first-generation (1G) TKIs. The LAL 0201 study reported a 100% CR rate with a chemo-free regimen in 30 patients older than 60 years. These patients were treated with a TKI, prednisone, and central nervous system prophylaxis[13]. The LAL 1205 trial included 55 adult patients with Ph+ ALL, where the induction therapy comprised the second-generation (2G) TKI dasatinib and prednisone, with subsequent consolidation therapy decided by investigators. A 100% CR rate was achieved after induction therapy, and NRM was 0. However, most patients had a positive minimal residual disease (MRD), and long-term survival was poor. These trials demonstrated that the CR rate and safety were favorable, and the chemo-free regimen was feasible, but addressing the issues of poor MRD response and long-term survival is crucial..

The poor long-term survival of Ph+ ALL is often attributed to drug-resistant mutations, including the T315I mutation, which can be detected in over 75% of relapsed/refractory Ph+ ALL patients[14–16]. The emergence of more efficient third-generation (3G) TKIs offers potential solutions to overcome resistance and improve the complete molecular response (CMR) rate. Phase 2 trials involving 3G TKIs as monotherapy have shown promising results, with a CMR rate of 38% and a 1-year overall survival (OS) of 40%[17]. Combining 3G TKIs with chemotherapy, such as in the PACE trial, demonstrated a 100% complete response rate and a 5-year OS of 73% in Ph+ ALL patients[18]. Meta-analyses comparing 3G TKIs with 1/2G TKIs revealed higher CMR and 3-year OS rates with the use of 3G TKIs.

While the combination of 3G TKIs and chemotherapy may improve long-term survival, the high non-relapse mortality (NRM) associated with chemotherapy remains a challenge, especially in

older patients. Substituting chemotherapy with immunotherapy, such as blinatumomab, a CD3/CD19 bispecific T-cell engager (BiTE), has shown promise. Blinatumomab, approved by the FDA for relapsed/refractory ALL, has demonstrated a 36% complete response rate, an 88% CMR rate in responders, and a median OS of 9 months as monotherapy[19, 20]. In relapse/refractory Ph+ ALL, combining blinatumomab with TKIs has shown efficacy, with a CMR rate and 1-year OS of 75% and 73%, respectively[21]. Inspired by these findings, chemo-free regimens (BiTE+TKI) are being explored for newly diagnosed Ph+ ALL. The D-ALBA study reported on blinatumomab plus dasatinib as a chemo-free regimen for newly diagnosed Ph+ ALL[22]. This study included 63 patients, and after dasatinib induction, 29% achieved CMR. Subsequent blinatumomab consolidation therapy improved CMR to 60%, with a median OS and disease-free survival (DFS) of 95% and 88%, respectively.

However, long-term survival outcomes with BiTE plus TKI in Ph+ ALL patients were unsatisfactory, particularly in the IKZF1del subgroup[23]. In the GIMEMA D-ALBA study, patients with IKZF1del had the worst prognosis. As IKZF1del is a frequent concomitant mutation in Ph+ ALL, targeting this mutation may further improve outcomes with a chemo-free regimen. Histone deacetylase (HDAC) inhibitors, such as chidamide, have shown promise in tumor treatment. Preclinical studies demonstrated that chidamide can activate transcription of the IKZF1 gene, induce the expression of ikaros, and inhibit the proliferation of IKZF1del ALL cells. A single-arm trial evaluating chidamide in Ph-like ALL suggested that chidamide can improve the poor outcomes of IKZF1del ALL by increasing the expression of ikaros. A post-hoc analysis in the IKZF1del subgroup demonstrated a 3-year event-free survival (EFS) of 64.8% with chidamide compared to 28.9% with chemotherapy alone. Multivariate analysis indicated that chidamide can eliminate the poor outcomes associated with IKZF1del mutation.

These results underscore the potential of TKI combined with BiTE in improving clinical outcomes in newly diagnosed Ph+ ALL. However, the efficacy of 1/2G TKIs may be insufficient, and the efficacy of BiTE is inadequate in the IKZF1del subgroup, leading to unsatisfactory long-term survival. Therefore, the suggestion is that combining 3G TKIs and chidamide with BiTE may achieve better CMR and long-term survival in Ph+ ALL.

2.Objectives of the trial

2.1 Primary objective

We aim to explore the efficacy and safety of ABC regimen. The primary endpoint is the complete molecular remission （CMR） at 3 months in adult Ph+ ALL.

2.2 Secondary objectives

To explore

- The 5-year overall survival
- The 5-year event-free survival
- Number of grade >3 adverse events
- IKZF1del subgroup analysis
- $IKZF1^{plus/CD20}$ subgroup analysis

3.Inclusion and exclusion criteria

3.1Inclusion criteria

- Signed written informed consent.
- Newly diagnosed adult B-precursor Ph+ ALL patients.
- Age greater or equal to18 years.
- ECOG Performance Status 0 or 1.
- Ineligible for allo-HSCT.
- Renal and hepatic function as defined below:
  - AST (GOT), ALT (GPT), and AP <2 x upper limit of normal (ULN).
  - Creatinine clearance equal or greater than 50 mL/min.
- Pancreatic function as defined below:
  - Serum amylase less or equal to 1.5 x ULN
  - Serum lipase less or equal to1.5 x ULN.
- Normal cardiac function.
- Negative HIV test, negative HBV DNA and HCV RNA.
- Negative pregnancy test in women of childbearing potential.

3.2Exclusion criteria

- History of receiving systemic chemotherapy or CAR-T therapy for ALL.
- Impaired cardiac function, including any one of the following:
  - LVEF <45% as determined by MUGA scan or echocardiogram.
  - Complete left bundle branch block.
  - Use of a cardiac pacemaker.
  - ST depression of >1mm in 2 or more leads and/or T wave inversions in 2 or more contiguous leads.
  - Congenital long QT syndrome.
  - History of or presence of significant ventricular or atrial arrhythmia.
  - Clinically significant resting bradycardia (<50 beats per minute).
  - QTc >450 msec on screening ECG (using the QTcF formula).
  - Right bundle branch block plus left anterior hemiblock, bifascicular block.
  - Myocardial infarction within 3 months prior to starting olverembatinib.
  - Angina pectoris.
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of olverembatinib or chidamide (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).
- History of or current autoimmune disease.
- History of or current relevant CNS pathology.
- Presence of CNS leukemia.
- History of or current autoimmune disease.
- History of other malignancies.
- Presence active infection.
- Nursing women or women of childbearing potential not willing to use an effective form of contraception during participation in the study and at least 3 months thereafter or male patients not willing to ensure effective contraception during participation in the study and at least three months thereafter.

4.Study design

4.1General design

Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) is now a relatively favorable-risk leukemia with the development of potent BCR::ABL1 tyrosine kinase inhibitors (TKIs). Achievement of an early and deep complete molecular remission (CMR) is an important

end point in Ph+ ALL and identifies patients who may not need allogeneic hematopoietic stem cell transplantation (allo-HSCT). The chemotherapy-free D-ALBA trial of dasatinib and blinatumomab was safe and effective in patients with newly diagnosed Ph-positive ALL and resulted in an estimated 3-year OS rate of 80% (NEJM 2020, 2022). To further improve the outcomes, the potent third-generation TKIs, ponatinib and olverembatinib (ASH 2023, abs 1504), were added to chemotherapy or immunotherapy, resulted in an overall CMR rate of 84%-90%, a 5-year survival rate of 73%, most patients did not undergo allo-HSCT.

Of note, IKZF1plus subgroup still stands for high-risk for Ph+ALL and exhibit poor outcome even in TKI plus blinatumomab, which indicate IKZF1del confers resistance to immunotherapy. our previous study found that HDACi tucidinostat/chidamide could restore the expression and functionality of IKZF1 in IKZF1del samples, including increased expression of CD19 and reduced focal adhesion (Blood (2021) 138 (Supplement 1): 514.).

ABC study is a phase 2, single-arm, open-label study of Olverembatinib, CD3/CD19 Bispecific T-cell Engager, and Chidamide in patients with newly diagnosed Philadelphia Chromosome-positive acute lymphoblastic leukemia (Ph+ALL). This study combined third generation TKI (Olverembatinib), histone deacetylase inhibitors (Chidamide) and CD3/CD19 bispecific T-cell engager (Blinatumomab) as first line regimen (ABC regimen) for Ph+ ALL. We aim to explore the efficacy and safety of ABC regimen. The primary endpoint is the complete molecular remission （CMR） at 3 months, secondary endpoints are overall survival (OS), event-free survival (EFS), adverse event (AE), IKZF1del, IKZF1plus, IKZF1lpus/CD20 subgroup EFS/OS.

The ABC regimen include pre-phase, induction, consolidation and maintenance treatment.
Phase One. Induction Consolidation, for 1 year.
1.1 Pretreatment ×1 cycle. Prednisone，1mg/kg/d, from day 1 to 14;
1.2 Induction Therapy × 1 cycle. A: OlverembAtinib (at a dose of 40 mg Qod), from day 8 to 42. B: Blinatumomab (at a dose of 28 μg per day), from day 15 to 28. C: Chidamide (at a dose of 10 mg Qod), from day 9 to 41.
1.3 Consolidation Block × 5 cycles. A: Olverembatinib (at a dose of 40 mg Qod) was administered from day 1 to 42. B: Blinatumomab (at a dose of 28 μg perday) was administered from day 1 to 14. C: Chidamide (at a dose of 10 mg Qod) was administered from day 14 to 41.
Phase Two. Maintenance Therapy, for 3 years.
2.1 A: Olverembatinib (at a dose of 40 mg Qod) was administered from day 1 to 42.
C: Chidamide (at a dose of 10 mg Qod) was administered from day 14 to 41.
Phase Three. Follow-up, for 5 years.

CNS prophylaxis will be carried out with medicated lumbar punctures (MTX 15 mg, Methylprednisolone 20 mg): the first CNS prophylaxis will be administered during the prephase. The 2-6 times prophylaxis will be administered during induction therapy, subsequently, CNS prophylaxis will be administered at the end of each cycle of consolidation treatment.

4.2Primary endpoint

Complete molecular response (CMR) at 3 months.

4.3Secondary endpoint

- 5-year overall survival rate
- 5-year event-free survival rate
- Number of grade >3 adverse events
- IKZF1del subgroup analysis
- $IKZF1^{plus/CD20}$ subgroup analysis

5.Toxicity management

5.1 Toxicity of BiTE

While BiTE has demonstrated improved clinical outcomes, its associated toxicity should not be underestimated. Currently, the toxicity reactions of BiTE in treating hematologic malignancies can be categorized as follows:

5.1.1Cytokine Release Syndrome (CRS)

CRS is a common occurrence in cell therapy. In early BiTE phase II trials, two patients with a high tumor burden developed grade 4 CRS. Subsequently, dexamethasone and cyclophosphamide were employed for pre-treatment in patients with a high tumor burden, resulting in no further occurrences of $\geqslant$ grade 3 CRS[19]. In subsequent Phase II and III trials, dexamethasone pre-treatment was applied to patients with blast cells exceeding 50% in the bone marrow and 15,000/μL in peripheral blood or elevated lactate dehydrogenase (LDH) levels[24]. Life-threatening CRS has been reported in patients undergoing BiTE therapy, typically manifesting within 2 days of infusion initiation. The median time for CRS regression is 5 days (in cases of regression). CRS symptoms include fever, headache, nausea, fatigue, hypotension, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), elevated total bilirubin, and disseminated intravascular coagulation (DIC).

CRS involves a systemic inflammatory response mediated by elevated levels of cytokines and inflammatory factors such as IL-2, IL-6, IL-8, IL-10, TNF-α, and INF-γ. Clinical studies have observed increased IL-10, IL-6, and IFN-γ levels during the first cycle of BiTE therapy[25].

Elevated IL-6 and IL-10 levels may be associated with the occurrence of CRS after BiTE therapy, potentially linked to hemophagocytic syndrome (HPS) or macrophage activation syndrome (MAS)[26].

Early identification of CRS is crucial. During the induction treatment phase with Blinatumomab, a low dose of 9μg/day for the first 7 days and pre-treatment with dexamethasone are recommended as prophylaxis for CRS. All patients receive dexamethasone prophylaxis when initiating BiTE infusion, increasing the dose, or interrupting for more than 4 hours. Tocilizumab, an IL-6 receptor antagonist, has revolutionized CRS treatment since its successful use by Maude SL et al. Tocilizumab effectively alleviates CRS symptoms without interfering with the proliferation and survival of CAR-T cells in vivo. Currently, Tocilizumab is the first-line treatment for severe CRS, with a recommended FDA-approved dosage of 8mg/kg administered intravenously over one hour. If the initial administration does not improve CRS symptoms, it can be repeated within the next 24-72 hours[27-29].

（1）Cytokine Release Syndrome，CRS：

Table 1. CRS Grading System：

Grade 1	Symptoms are not life threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)
Grade 2	Symptoms require and respond to moderate intervention: ● Oxygen requirement <40% FiO_2; ● Hypotension responsive to IV fluids **or** low dose of one vasopressor; ● Grade 2 organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention: ● Oxygen requirement ≥40% FiO_2; ● Hypotension requiring high dose or multiple vasopressors; ● Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms: ● Requirement for ventilator support; ● Grade 4 organ toxicity (excluding transaminitis);
Grade 5	Death.

Based on the NCI Common Terminology Criteria for Adverse Events (CTCAE) version;

Patients suspected of severe CRS (grade 3-4) should be closely monitored, and transferred to the intensive care unit if necessary. Immunosuppressants should be given for treatment, and the preferred choice is the IL-6 receptor blocker, Tocilizumab. Mild CRS can be treated with glucocorticoids.

5.1.2Neurotoxicity

In clinical trials involving ALL patients treated with BiTE, approximately 65% experienced central nervous system (CNS) toxicity, with CNS adverse events of grade 3 or higher accounting for 7-14%. Neurological events, such as headache and tremor, were the most common, occurring within the first two weeks of BiTE therapy. Specifically, around 13% of patients encountered severe CNS toxicity (grade 3 or higher), including encephalopathy, tics, speech disorders, consciousness disorders, confusion, disorientation, coordination disorders, and balance issues[30, 31]. The grading principles refer to the appendix.

The precise mechanism of neurotoxicity induced by BiTE remains unclear. Retrospective studies suggest associations between neurotoxicity and a history of more than two previous salvage treatments or neurological diseases. However, baseline IL-6 levels or tumor burden do not seem linked to the severity of neurotoxicity[32]. Potential mechanisms may involve the disruption of the blood-brain barrier due to treatment or disease, along with the release of cytokines after binding to CD19-positive cells in the CNS.

For CNS events of grade 3 or lower, most studies recommend suspending Blinatumomab treatment and waiting for recovery. In cases of neurotoxic events of grade 4 or higher, BiTE therapy is discontinued. When facing grade 3 toxicity, it is advisable to discontinue BiTE until achieving grade 1 for three consecutive days. After this recovery period, Blinatumomab treatment at 9 μg/day can be reinstated. If CNS toxicity escalates during this phase, permanent discontinuation of Blinatumomab is recommended. In the absence of CNS adverse reactions, the dose can be restored to 28 μg/day after seven days. If grade 3 CNS toxicity persists for over one week or if there is more than one seizure episode, discontinuation of medication is also recommended.

Steroids remain pivotal in the treatment of neurotoxicity and can be used for severe symptoms such as encephalopathy or aphasia. Supportive treatment, including antiepileptic drugs for seizures, should be considered as needed. One study demonstrated the concurrent administration of levetiracetam (500mg, bid) during Blinatumomab administration to prevent neurotoxicity[22].

（2）Neurotoxicity：

Table2 Immune effector Cell-Associated Neurotoxicity Syndrome（ICANS）grading system.

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE Score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level	Awakens	Awakens	Awakens only	Patient is

of consciousness**	spontaneously	to voice	to tactile stimulus	unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly; or Non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between.
Motor findings***	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP / Cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor finds, raised ICP/cerebral edema) not attributable to any other cause.

*A patient with an ICE score of 0 may be classified as having Grade 3 ICANS if the patient is awake with global aphasia. But a patient with an ICE score of 0 may be classified as having Grade 4 ICANS if the patient is unarousable.

**Depressed level of consciousness should be attributable to no other cause (e.g. no sedating medication)

***Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0 but they do not influence ICANS grading.

Table3 ICE Grading System

ICE Grading System

● **Orientation:** Orientation to year, month, city, hospital**:** 4 points
● **Naming:** Name 3 objects (e.g., point to clock, pen, button)**:** 3 points
● **Following commands:** (e.g., Show me 2 fingers or Close your eyes and stick out your tongue)**:** 1 point
● **Writing:** Ability to write a standard sentence (e.g., The national flag of China is a five-star red flag)**:** 1 point
● **Attention:** Count backwards from 100 by ten**:** 1 point

Score 10: No impairment

Score 7-9: Grade 1 ICANS

Score 3-6: Grade 2 ICANS

Score 0-2: Grade 3 ICANS

5.1.2.1 Management recommendations for status epilepticus

Non Convulsive Status Epilepticus, NCSE

• Assess airway, respiration, and circulation, and check blood sugar.

• Control epilepsy with lorazepam 0.5mg IV, and if necessary, increase by 0.5mg every 5 minutes until a total of 2mg is used.

• Levetiracetam 500mg IV to maintain dose.

• If the epilepsy persists, transfer to ICU for monitoring, with phenobarbital 60mg IV.

• After remission of NCSE, maintain the following dosage: lorazepam 0.5mg q8h IV; Levetiracetam 1000 mg q12h IV; Phenobarbital 30mg q12h IV.

Non Convulsive Status Epilepticus, NCSE

• Evaluate airway, respiration and circulation and check blood glucose.

• Transfer to ICU care.

• Lorazepam 2mg IV, if uncontrolled, additional 2mg IV for seizure control, total dosage 4mg.

• Levetiracetam 500mg IV push to maintain dose.

• If persistent seizures cannot be controlled, add phenobarbital 15 mg/kg.

• Maintain the following doses after remission of convulsive status epilepticus maintenance status: lorazepam 0.5 mg q8h IV 3 times daily; levetiracetam 1000 mg q12h IV; phenobarbital 30 mg q12h IV.

• If seizures are difficult to control, continuous EEG monitoring should be performed.

All drug doses are for adults.

5.1.2.2 Recommendations for the management of increased intracranial pressure

Optic papilla edema* grade 1 or 2 accompanied by cerebrospinal fluid pressure (CSF) <20 mmHg without hydrocephalus

• Acetazolamide 1000 mg IV followed by 250-1000 mg IV q12h (adjust drug dosage based on renal function and acid-base balance, monitor 1-2 times daily)

Optic papilla edema* grade 3,4 or 5 accompanied by any imaging evidence of cerebral edema, or cerebrospinal fluid pressure (CSF) ≥ 20 mmHg

• CRES grade 4 recommends the use of high-dose glucocorticoids such as : methylprednisolone 1g / day.
• Raise the head of the bed by 30 degrees.
• Arterial carbon dioxide (PaCO2) is brought to 28-30 mmHg by hyperventilation, and this state is maintained for no more than 24h.
• Hypertonic therapy: use of mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as indicated below)
- Mannitol: initial dose 0.5-1g/kg; maintenance dose 0.25-1g/kg q6h while monitoring metabolism and serum osmolality every 6h, if serum osmolality ≥320 mOsm/kg or osmotic pressure difference ≥40, discontinue mannitol.
- Hypertonic saline: the initial dose of 3 % hypertonic saline 250ml; the rate is maintained at 50-75 ml/h while electrolytes are monitored every 4 h. The infusion is discontinued if the serum sodium level is ≥155 mEq/l.
- For impending brain herniation: give 30 ml of 23.4% hypertonic saline initially; repeat after 15 minutes if needed.
• If the patient has ommaya reservoir, the cerebrospinal fluid drainage pressure is less than 20 mmHg.
• Neurology and anesthesiology consultations are invited in case of EEG bursts of inhibitory electrical activity.
• Metabolic analysis is performed every 6h and head CT scans are performed daily, while the doses of the above drugs are adjusted to prevent recurrent cerebral edema, renal failure, electrolyte abnormalities, hypovolemia and hypotension.
All drug doses are for adult subjects;

5.1.3 Hypoglobulinemia

In a Phase II study, immunoglobulin levels were monitored for a long period in 6 MRD+ ALL patients. The levels of immunoglobulin G (IgG) in all responders decreased to the lowest point of baseline by 29%, and no IgG decrease was observed in one unresponsive patient[33]. The TOWER study reported that 6% of patients receiving Blinatumomab treatment developed hypoglobulinemia, while among patients receiving chemotherapy, this proportion was 1%[24]. BiTE activated T cells not only attack tumor cells, but also normal tissues expressing the same antigen, causing damage to normal tissues, which is known as the "on-target/off-tumor" toxic reaction. B cell deficiency is a typical on-target/off-tumor toxicity response in BiTE treatment of B cell malignancies, which can be effectively treated through immunoglobulin replacement therapy.
In addition, many studies have reported neutropenia, although its rate are lower than those in the chemotherapy group. The incidence of various infections, including bloodstream infections, catheter-related infections, fungal infections, and bacterial sepsis, is as high as 25%. Therefore, the need for immunoglobulin replacement therapy and antibiotics prophylaxis can be considered.

6.Evaluation

6.1 Efficacy evaluation

The primary endpoint of this study is the complete molecular remission rate (CMR) at 3 months of treatment. The secondary endpoints are 5-year overall survival (OS) and event-free survival (EFS).

6.2 Safety evaluation

All patients who have received at least one drug treatment in this study will be included in the safety analysis. All data will be analyzed based on the actual treatment received, and variables for safety analysis include AEs, clinical laboratory tests, examination results, and physical examination results.

7.Safety monitoring, reporting and medical treatment

7.1 Definition of Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE may therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or noninvestigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

7.2 Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (see Annex IV, ICH-E2A Guideline). Note: The sponsor collects AEs starting with the signing of the ICF (refer to Section Adverse Events, for time of last AE recording).

7.3 Serious adverse event (SAE)

A SAE based on ICH and EU guidelines on pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is medically important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

These should usually be considered serious

7.4 Special reporting situations

Safety events of interest on a sponsor study drug that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of a sponsor study drug
- Inadvertent or accidental exposure to a sponsor study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study drug, eg, name confusion)

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE form.

7.5 Reporting procedures

7.5.1 All adverse events

All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure (which may include contact for follow-up of safety). Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported. All events that meet the definition of a SAE will also be reported as SAE, regardless of whether they are protocol-specific assessments. All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AEs to study therapy. All measures required for AE management must be recorded in the source document. The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities.

7.5.2 Serious adverse events

All SAEs occurring during the study must be reported to PI within 24 hours of their knowledge of the event. All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

Suspected transmission of an infectious agent by a medicinal product will be reported as a SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- Disease progression should not be recorded as an AE or SAE; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition.
- A standard procedure for protocol therapy administration will not be reported as a SAE.
- Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a SAE.
- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an AE.
- A procedure planned before entry into the study (must be documented in the CRF). Prolonged hospitalization for a complication considered to be at least possibly related to the study drug remains a reportable SAE.

7.5.3 Pregnancy

All initial reports of pregnancy must be reported to PI within 24 hours of their knowledge of the event. Abnormal pregnancy outcomes (eg, spontaneous abortion, stillbirth and congenital anomaly) are considered serious adverse events and must be reported as a SAE. Any subject who becomes pregnant during the study must discontinue further study treatment. Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported by the study-site personnel within 24 hours of their knowledge of the event. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.Trial termination / suspension criteria

8.1 Suspension criteria:

- Serious safety issues arise in the test;
- The research unit requests a suspension;
- There are major errors in the trial protocol during the trial that made it difficult to evaluate the safety and efficacy of the treatment;
- The administrative department requests the suspension

8.2 Termination criteria:

All subjects can withdraw from the study at any stage of the trial, regardless of whether a reason is provided. Subjects who withdraw from the study will not be discriminated against or retaliated against for doing so, and their medical entitlements will not be affected. If the researcher accidentally enroll the subjects who do not meet the inclusion criteria, the subjects should immediately withdraw from the study after discovery, and inform the research unit or its representative in time, and re-enroll the subjects as a substitute. In the absence of exceptional circumstances, according to the judgment of the researcher, if the subject continues to participate in the study, there will be a safety hazard that seriously threatens life and the subject should be notified in time to withdraw from the study. In addition, subjects may withdraw from discontinuation of treatment or from this study under the following conditions:

- During the course of the trial, if a subject develops an intolerable AE or a clinically significant laboratory outlier, at the discretion of the investigator, the subject may choose to withdraw from the study and appropriate measures shall be taken with respect to him/her. At this time the investigator should report to the research unit or its designee;
- Subjects are reluctant to continue to participate in this study;
- Subjects with poor compliance should withdraw from the study when they have a serious impact on the safety and efficacy data analysis of the experiment;
- Subjects should be withdrawn from this study when the investigator or research unit discontinues this study for any reason;

If the subjects withdraw from the study after receiving BiTE treatment, they need to complete the inspection items required to withdraw from the visit in the visit flow chart.

9.Data management

9.1 Data management

- Researchers must ensure that the data is true, complete and accurate;
- Any corrections to the test record should be made only by underlining, marginal notation of the changed data, justification, signature and date by the investigator, and not by erasing or overwriting the original record;
- Laboratory examination items are complete.

9.2 Data recording

The data about the subjects on the case report form should be recorded by means of a subject code, and the subjects should be identified only by the subject code or their initials.

9.3 Completion and transfer of case reports

The case report form is completed by the investigator and must be completed for each enrolled case. The completed case report form is reviewed by the Clinical Research Associate and the first copy is transferred to the data manager for data entry and management.

9.4 Data Entry and Modification

Professional data management unit is responsible for data entry and management. The data management software was implemented to compile the data entry program for data entry and management. In order to ensure the accuracy of the data, double entry and proofreading should be carried out by two data administrators independently.

For the questions in the case report form, the data managers will have the Data Rating Questionnaire(DRQ) and send questions to the researchers through the clinical monitors. The researchers should answer and return as soon as possible. The data managers will modify, confirm and input the data according to the researchers' answers, and can send DRQ again if necessary.

9.5 Data Audit and locking

The main researchers, data administrators and statistical analysts confirm the statistical analysis population, lock the database after solving all data questions, and sign the audit report at the same time.

10.Statistical considerations

10.1 Sample size

This study is designed to evaluate the activity of Olverembatinib, Chidamide plus Blinatumomab in adult Ph+ ALL, in terms of percentage of patients who achieve a CMR at 3 months. The estimated ORR rate of ABC regimen in the treatment of Ph+ALL is about 95%. ; this percentage was estimated on the basis of a pilot study. The number of patients required to demonstrate this hypothesis with a power of 90% and a Type I error probability of 5%, and considering a 10% drop-out, is 67

10.2 Analysis

Response achievement will be evaluated in terms of percentage of successful responses over all

eligible and evaluable patients enrolled in the study (following an Intention-To-Treat principle). All AEs will be tabulated. All reported toxicities will be correlated with clinical outcome. Patients' characteristics will be summarized by means of cross-tabulations for categorical variables or by means of quantiles for continuous variables. In univariate analysis non-parametric tests will be performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables or response rate, Mann-Whitney and Kruskal-Wallis test in case of continuous variables) and logistic regression will be performed in multivariate analysis to assess the effect of clinical and biologic factors on CMR rate. OS will be defined as the time from treatment start to death from any cause. DFS will be defined as the time from the achievement of CHR to relapse, death, or date of last follow-up for patients alive in first CHR. CMR duration will be defined as the time form the achievement of CMR to molecular relapse, death or date of last follow-up for patients alive in first CMR. The OS, DFS and duration of CMR probabilities will be estimated using the Kaplan-Meier method. CIR will be calculated from the achievement of CHR to relapse or date of last follow-up for patients alive in first CHR, using the cumulative incidence method and considering death in CHR as competing risk. Subgroups comparisons will be performed for descriptive purposes. Differences in terms of OS, DFS duration of CMR will be evaluated by means of Log-Rank test in univariate analysis and by means of the Cox regression model in multivariate analysis, after assessment of proportionality of hazards. CIR will be estimated by cumulative incidence curves using the proper non-parametric method. The Gray test will be applied for significance tests on cumulative incidence curves. Median follow-up time will be estimated by reversing the codes for the censoring indicator in a Kaplan-Meier analysis. Confidence intervals will be calculated at 95% level and forest plots wil be used to summarize differences among subgroups. All analysis will be performed using the SPSS software.

10.3 Safety analyses

Analysis of safety data will be conducted on the safety population, which includes all subjects who receive at least 1 dose of study medication. This population will be used for all safety analyses and all analyses of treatment compliance and exposure. All data will be analyzed according to the treatment subjects actually received. The safety variables to be analyzed include AEs, clinical laboratory tests (hematology and chemistry), physical examination results, ECGs, and deaths. Safety variables will be tabulated by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum; or n and percent). No formal statistical testing is planned.

11.Study management

11.1 GCP

Regulatory organization and implementation of GCP:

1)Both drug registration applicants and researchers should adopt standard operating procedures to implement the quality control and quality assurance system of clinical trials.

2)The original data must meet the GCP requirements of our country.

3)The laboratory test results must be accurate and reliable.

4)The observations and findings used was verified to ensure the reliability of the data.

5)Established a complete study organization and clarified the responsibilities of personnel at all levels.
6)The main researchers were responsible for total quality control and carried out the duties of personnel at all levels.
7)The main researchers were responsible for designing the study scheme, informed consent form, and implemented it with the consent of the drug registration applicant. After the end of the study, the main researchers wrote the summary report of the study.
8)The designated researcher was responsible for formulating the test implementation rules and SOP used in the trial.
9)All participants was organized by the trial team before the study, and all the participants must be trained by GCP.
10)Doctors and nurses participating in the trial should strictly abide by the provisions of the scheme, proceed in accordance with the procedures, and were not allowed to change them at will.
11) The designated statistician was responsible for the overall statistical processing of the data.

11.2 Privacy protection

All the data of the participants during the study were entered into the computer for confidential storage and analysis, and if necessary, the relevant institutions may audit the records to confirm the authenticity, accuracy and completeness of the data, and the data obtained from the study may also be published in academic journals, but the names of the participants will not be published and the privacy of the participants will be kept confidential.
We took additional precautions to ensure the confidentiality of documents and prevented the identification of participants from genetic data. However, under special circumstances, some people may see a participant 's genetic data and personal identification number. For example, in the case of medical first aid, the sponsor, his doctor or researcher, may know the participant identification number and has access to the participant 's genetic data. In addition, relevant regulators require access to relevant documents.

11.3 Situations during study

1)Protocol amending: if the protocol is to be revised after it has been approved by the Ethics Committee, a "statement of revision of the protocol" shall be drawn up and signed by the PI. The protocol can be amended by approving of the PI and the drug registration applicant;
2)the amended protocol must be submitted to the ethics committee before being executed;
3)No one participating in the trial shall violate the protocol. In the event of a violation of the protocol, it is necessary to write a description and notify the drug registration applicant, who has the right to decide whether the trial will continue or not;
4)If the participant violates the protocol slightly, the researcher should promptly notify the applicant for drug registration, discuss together, and deal with the violation and shedding of the participant; a slight deviation that does not affect the safety of the participant or the integrity of the trial scheme is called a mild violation.
5)Any adverse events (adverse event, AE) or serious adverse events (severe adverse event,SAE) that occur during the trial will be reported and dealt with in accordance with the requirements of

the program and SOP.

11.4 Quality control and assurance

11.4.1 Quality assurance

The sponsor or the cooperative unit entrusted by the sponsor to be responsible for all or part of the responsibilities and tasks related to this study(including CRO, SMO, statistical units, clinical centers, etc.) should establish their own quality assurance systems, perform their respective duties, strictly follow the clinical trial plan, and adopt corresponding standard operating procedures to ensure the implementation of clinical trial quality control and quality assurance system.

11.4.2 Quality assurance of clinical trial process

Before the start of the clinical trial, the researchers should receive the training of the trial scheme, so that the researchers can have a well-grounded understanding of the clinical trial scheme and the specific connotation of each indicator. Quality control personnel should check the basic conditions of clinical trials to ensure that the conditions of clinical trials can meet the requirements of the program. In the course of the trial, the researchers should conscientiously carry out the clinical operation according to the requirements of the institutional SOP and the trial plan, and record it in a true, timely, complete and standardized manner. The quality control personnel check the quality of the test process and the corresponding original records. After the experiment, the research unit collates the corresponding project documents, which are checked and archived by the quality control personnel. The quality assurance department of the clinical research unit conducts an enforceable inspection of the trial. When non-conformities are found, promptly notify the researcher and the person in charge of the unit to make corrections, and follow up the corrections.

11.4.3 Responsibilities of sponsor

The sponsor is responsible for initiating, applying for, organizing and providing funds for this clinical trial. The sponsor submitted the application for clinical trial to the China Food and Drug Administration in accordance with the provisions of China's GCP, The measure of Drug Registration and other legal documents, and may also entrust contract research organizations (CRO) to carry out some work and tasks in clinical trials.

The sponsor selected the institutions and researchers of the clinical trial and recognizes their qualifications and conditions to ensure the completion of the trial.

When the sponsor provided experimental drugs to researchers, the management system and recording system of experimental drugs were established.

11.4.4 Responsibilities of the researchers

The clinical study is conducted in accordance with the moral, ethical and scientific principles as well as program design and regulation set out in the Helsinki Declaration and China's GCP.

The researchers are responsible for making medical decisions related to clinical trials to ensure

that participant s are treated in time when they develop AE during the trial. Researchers are aware of the procedures and requirements for reporting SAE, and record and report these events as required.
Researchers should put the data into eCRF accurately, completely, timely and legally, and accept the supervision or inspection of sponsors, inspectors, inspectors dispatched by CRO, or drug supervision and administration departments to ensure the quality of clinical trials.

11.4.5 Publication of research data

The sponsor has exclusive right to the data of this study. Except with the written consent of the sponsor. With regard to manuscripts and publication, the sponsor has the final say.

12.Ethics

12.1 Ethics committee

Prior to the start of the trial, researchers are required to submit the researcher's manual, trial scheme, informed consent, CRF and experimental drug test report (based on submission), as well as any other information given to the participant s, to the ethics committee for approval. Any changes to the study scheme must be approved by the Ethics Committee.

12.2 Informed consent

Qualified researchers must explain to each participant the nature, purpose, procedures, expected time, potential risks and benefits, and any discomfort that may arise in the informed consent in detail. Each participant must know that participation in the trial is voluntary and that he / she can withdraw from the trial and his / her informed consent at any time without affecting his / her subsequent treatment or relationship with the therapist.
The informed consent form should be given in a standard format and in non-professional language as far as possible. Each informed consent must include all of the above and a voluntary declaration. The informed consent form should be submitted to the Ethics Committee for approval.
After explaining the basic contents of the trial, and the researchers have been convinced that each participant who participates in the trial knows about the purpose of the trial, each participant will be asked to sign his name and date on the informed consent form. Participants should read and consider their statements before signing and dating, and an informed consent form should be obtained and kept after signing. The participants were not allowed to enter the test if the informed consent form was not signed without informed consent.

12.3 Other

When the participants are unable to participate in informed consent independently, there must be a reliable fair witness or legal representative present in the whole process of informed consent. The choice of fair witness or legal representative shall not infringe upon the participant 's right to confidentiality. After the participant 's oral consent, the fair witness or legal representative should sign and date the informed consent form to prove that the information is

accurate.

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