2 STUDY SYNOPSIS

Name of Company: Molecular Templates, Inc.	Individual Study Table	(For National Authority Use Only)
Name of Product: MT-3724	Referring to Module 5 of the Dossier	

Study Title

Pharmacokinetics, Pharmacodynamics, Safety and Tolerability of Multiple Dose Regimens of MT-3724 for the Treatment of Patients with Relapsed non-Hodgkin's B-Cell Lymphoma and B-Cell Chronic Lymphocytic Leukemia

Investigators/Sites

The study was conducted at 8 sites in 4 countries (5 sites in United States, 1 site in Canada, 1 site in Moldova and 1 site in Georgia). One principal investigator was present at each site. See Section 16.1.4 for additional details.

Publication (Reference)

None

Study Period

Part 1: 24 Feb 2015 to 29 Nov 2016, Part 2: 09 Oct 2017 to 11 Oct 2019

Phase of Development

Phase 1/2

Objectives

The primary objectives in Part 1 were to:

- Define the maximum tolerated dose (MTD) of a single cycle of MT-3724 given on Days 1, 3, 5, 8, 10 and 12 at which there are negligible side effects and/or at which maximum pharmacokinetic (PK)/pharmacodynamic (PD) parameter changes are observed.
- Determine PK and PD profiles of MT-3724 in escalating dose cohorts.

In Part 2 of the study, up to 40 additional subjects with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL) were treated with the adjusted MTD of MT-3724 (50 µg/kg/dose) in the MTD expansion cohort.

The primary objectives in Part 2 were to:

- Identify the frequency and nature of clinical and laboratory adverse events (AEs), both reported and observed, as a measure of safety and tolerability over repeated cycles of MT-3724 at the adjusted MTD (50 µg/kg/dose).
- Define PK and PD profiles of MT-3724 at the adjusted MTD (50 µg/kg/dose) in this subpopulation.

In the extension study, the primary objectives were to:

- Provide extended access to MT-3724 on a compassionate use basis
- Identify the frequency and nature of clinical and laboratory AEs over repeated cycles of MT-3724 beyond those administered in the Phase 1/1b study.

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The secondary objectives in Part 1 were to:

- Identify the frequency and nature of clinical and laboratory AEs, both reported and observed, as a measure of safety and tolerability over repeated cycles of MT-3724.
- Assess the PK and PD over repeated cycles of MT-3724 from Day 1 through Day 112.
- Assess the efficacy of MT-3724 in subjects with DLBCL.

Secondary objectives were not specified for Part 2 of the study.

Methodology

This was a multi-center, open-label, multiple-dose, dose-escalation study of MT-3724 conducted in 4 parts, where Parts 1 and 2 are completed and Part 3 is ongoing.

- Part 1–Evaluation of different doses of MT-3724 to determine the MTD in subjects with relapsed, refractory B-cell non-Hodgkin's Lymphoma (NHL) or chronic lymphocytic leukemia (CLL) who have previously responded to one or more approved anti-CD20 monoclonal antibody therapies.
- Part 2–Expansion of the MTD cohort to evaluate safety, tolerability, and potential efficacy in up to 40 additional subjects with DLBCL who were treated with MT-3724 at the MTD.
- Part 3–Addition of an expansion cohort at a dose of 50 µg/kg/dose in approximately 20 subjects with r/r DLBCL to collect addtional safety data for this dose identified in Part 1 and Part 2.
- Part 4–Phase 2 trial in approximately 90 subjects to assess the efficacy and safety in subjects with r/r DLBCL.

Part 1 and Part 2 were considered to be a Phase 1/1b design. This clinical study report (CSR) describes the findings of Part 1 and Part 2, with Part 3 still ongoing and Part 4 planned to start once Part 3 is completed. Results from Parts 3 and Parts 4 will be reported in a separate CSR.

In Part 1 (the core study), study drug was administered as an initial 12-day course followed by at least a 2-week observation period providing a study period of 28 days in total. The planned doses for Cohorts 1 through 7 were 5, 10, 20, 50, 100, 150, and 200 µg/kg/dose/day, respectively.

Subjects were eligible to receive up to 4 additional 6-dose cycles of MT-3724 provided that disease progression was not observed and based on the safety and tolerability of MT-3724 in that subject. In Part 1 of the study, Cycle 1 was 28 days and all additional cycles were 21 days. During the MTD expansion (Part 2), the cycle length for all cycles was 21 days. Each additional 6-dose cycle was to be separated by no less than a 9-day observation period, which provided a total cycle length of 21 days. After this observation period, the subject was able to progress to the next cycle.

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In Part 2 (the MTD expansion), subjects were to be treated at the MTD during each 21-day treatment cycle. Subjects were able to receive up to 5 total cycles in the absence of clear disease progression.

Number of Subjects (Planned and Enrolled)

A total of 27 subjects were enrolled and treated at 7 sites (1 site did not enroll any subjects). It was planned to enroll 20 to 40 subjects in Part 1, and to treat a maximum of 40 subjects in Part 2 of the study.

Diagnosis and Main Criteria for Inclusion

Adults 18 years or older, with life expectancy of more than 3 months. Histologically proven relapsed or refractory B-NHL incl. CLL (Part 1), or DLBCL only (Part 2); prior receipt of all approved treatments including at least one CD20 targeting agent (stem cell transplantation and chimeric antigen receptor T cells allowed); half-life based washout from prior CD20 monoclonal antibodies (Part 2 only)

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Study drug was provided in vials containing 2.0 ml MT-3724 (0.5 mg/ml). MT-3724 was diluted in 5% dextrose in water or normal saline for intravenous (IV) administration. Batch numbers can be found in Appendix 16.1.6.

The dose depended on the cohort in which the subject was enrolled. If subjects had been enrolled at a dose level higher than the dose determined to be the recommended Phase 2 dose (RP2D) at a later time, they could continue to be treated at the RP2D provided they had no dose limiting toxicities (DLTs) or evidence for disease progression.

Based on treatment emergent AEs leading to dose reduction that occurred at the originally determined MTD of 75 µg/dose/day in 2 overweight subjects, the RP2D was then adjusted down to 50 µg/kg/dose/day, and a dose cap of 6,000 µg/dose/day was instituted. Following treatment on Cycles 2 to 5, the subject continued to receive MT-3724 at the adjusted MTD (50 µg/kg/dose). No dose escalation was permitted above 50 µg/kg/dose. However, at the Investigator's discretion, the dose for any subject in the Part 2 expansion cohort could again be reduced by 25-33% for one or more doses in any cycle based upon a subject's response to 50 µg/kg/dose.

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

No comparator drug was used.

Duration of Treatment

Subjects received doses of MT-3724 on Days 1, 3, 5, 8, 10, and 12 for the infusion treatment windows. All doses were administered by IV infusion, and for Part 1, the infusion time was 2-4 hours, whereas for Part 2, the infusion time was 2 hours (± 15 minutes) with no relation to

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meals. The first 3 infusions of the first cycle were initiated early enough in the day to allow adequate time to complete the infusion and post-infusion observation and blood sample requirements.

For subjects in any dosing cohort who completed at least 4 of the 6 infusions in their first cycle and the missed infusions were not due to an MT-3724 related toxicity, then up to 4 additional cycles were to be administered on the same schedule (Days 1, 3, 5, 8, 10, and 12) and at the same dose, as long as that dose was not subsequently identified to be a toxic dose.

Assessments

Efficacy Assessments

There were no primary or secondary efficacy endpoints specified for Part 1 and Part 2 of this study. The exploratory efficacy endpoints were: Best overall response, objective responses rate, disease control rate, percentage change from baseline in tumor size, duration of response, duration of stable disease, progression-free survival, and overall survival.

Pharmacokinetic Assessments

PK serum samples were analyzed for concentrations of free MT-3724 and if indicated might have been analyzed for any other anti-CD20 biologic agent which the subject may had received prior to enrollment. The details of performed analyses and reported parameters are included in the Appendix 16.2.9.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Exploratory PD assessments included disease activity measures (clinical symptoms, disease response, and Eastern Cooperative Oncology Group [ECOG] performance score), flow cytometry (individual lymphocyte subset analyses will be presented graphically by dose and time based on 2 types of cell quantification; percent of baseline and absolute cell count, and immunogenicity (multiple anti-drug antibodies [ADA] serum sampling) over time. The details of performed analyses and reported parameters are included in the Appendix 16.2.9.

Safety

Safety was monitored throughout the study, and assessments included all AEs, DLTs, clinical laboratory parameters, vital signs, physical examination, concomitant medications, ECOG pathologic stage, electrocardiogram (ECG), and pregnancy.

Statistical Methods

Analysis Populations

The safety set included all subjects who received any amount of MT-3724. The PK Analysis Set consisted of all subjects from the safety set with sufficient serum concentration data to determine the primary PK parameters. The full analysis set consisted of all subjects from the safety set who had at least 1 tumor re-evaluation performed (scheduled or unscheduled).

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All safety and efficacy analyses were conducted in the following subsets in addition to the overall population: a) DLBCL versus 'mixed' or 'transformed' DLBCL histology (where data allowed), designated as NHL histological subtype. b) Subjects with negative versus positive serum rituximab level at screening in the overall population, designated as serum rituximab status at screening, and c) Subjects with negative versus positive serum rituximab level at screening in the DLBCL subsets.

Interim Analysis

No planned formal interim statistical analyses of the data.

Statistical Methods

Tabulations were produced for appropriate demographic, baseline, efficacy, and safety parameters. For categorical variables, summary tabulations of the number and percentage of subjects within each category (with a category for missing data) of the parameter were presented. For continuous variables, the number of subjects, mean, median, standard deviation (SD), minimum, and maximum values were presented. Time-to-event data were summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals (CIs), as well as the percentage of censored observations. This study was primarily descriptive in nature; therefore, there were no formal statistical hypothesis tests planned. Hypothesis testing was employed, if warranted.

Safety Analysis

Safety was evaluated from AEs, laboratory results, vital signs, ECG parameters and the changes from baseline in physical examination and medical history. No formal hypothesis-testing analysis of AE incidence rates were performed.

Results

Subject Disposition/Analysis Sets

A total of 27 subjects were enrolled in Parts 1 and 2 and treated. The majority of subjects (24 subjects [88.9%]) completed the core study. A total of 20 subjects (74.1%) participated in repeat cycles, and 3 subjects (11.1%) were treated for more than 5 cycles.

A total of 22 subjects (81.5%) discontinued early from the study; 14 subjects (51.9%) due to disease progression (28.6% of subjects in the 50 µg/kg dose group and 66.7% of subjects in the 75 µg/kg dose group), and 5 subjects (18.5%) due to AEs. One subject discontinued due to death, 1 subject due to a physician decision, and 1 subject due to a subject request.

The safety population set and PK population set consisted of 27 subjects (100.0%), and the full analysis set consisted of 23 subjects (85.2%).

Demographic And Other Baseline Characteristics

Demographic and baseline characteristics were generally well-matched between the cohorts, and no notable differences in age, sex, race, ethnicity, and medical/disease history were observed.

Efficacy Results

Subjects with serum rituximab-positive levels did not benefit from treatment with MT-3724. Of the 12 serum rituximab-negative subjects with DLBCL (including mixed follicular lymphoma [FL]/DLBCL), 5 subjects (41.7%) responded across the range of 5 to 50 µg/kg/dose. Two responses were complete, 3 were PRs including 1 subject with composite DLBCL post autologous stem cell transplantation (SCT) who had a complete metabolic response of a large mesenteric mass and proceeded to allogeneic SCT. One subject had SD with 49% tumor reduction; another 5 subjects had progressive disease. One additional subject in the FL group who had FL transformed from DLBCL post autologous SCT had SD with 47% tumor reduction.

The 2 subjects with complete remission (CR) discontinued (subject decision) due to reasons unrelated to safety events. Their duration of responses were 169 days and 90 days, respectively. The 3 subjects with partial remission (PR) discontinued after disease progression, and their duration of responses were 107, 120, and 75 days, respectively. Due to the limited treatment period following responses, no interpretation of the results could be made. Generally, the tumor burden in responders decreased with repeat treatment.

Overall, the observed best response rate of 41.7% in Part 1 and Part 2 in this often heavily pretreated population is encouraging and warrants further exploration in rituximab-negative subjects with r/r DLBCL.

Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, And Other Biomarkers

In Part 1 and Part 2, the PK, PD, and immunogenicity of MT-3724 was evaluated in subjects with relapsed or refractory NHL (DLBCL, FL and mixed histology) treated with MT-3724 by IV infusion at doses ranging from 5 to 100 µg/kg. MT-3724 was administered on Days 1, 3, 5, 8, 10, and 12 of each 21-day cycle, and for up to 5 cycles.

In conclusion, maximum observed serum concentration (C_{max}) and area under the curve (AUC) increased with increasing dose in an approximately dose-proportional manner from 5 to 100 µg/kg. Time to reach maximum plasma concentration (T_{max}) was generally observed at the first sampled time after the end of infusion. The half-life ($t_{½}$) ranged from 0.392 to 3.37 hours in individual subjects, with an average $t_{½}$ between 2 and 3 hours. Little to no accumulation was observed by the sixth MT-3724 dose on Cycle 1 Day 12. Due to high variability in the data, small sample size, and inconsistent sampling, PK-PD relationships were difficult to discern. In subjects with baseline $CD19^+$ cells of > 10 cells/µL and with at least 3 additional measurements of $CD19^+$ cells after baseline, the number of $CD19^+$ cells was decreased after one cycle of treatment and remained decreased through the end of study.

Immunogenicity was observed across all dose levels, from 5 to 100 µg/kg. Almost all ADA-positive results were associated with a neutralizing antibody (NAb)-positive result. At the Screening Visit, 5 of 27 subjects were ADA-positive with low ADA titers between 10 and 20. Immunogenicity at the Screening Visit was not associated with decreased plasma exposure to MT-3724 on Cycle 1 Day 1. By the end of study assessment, 15 of the 25 evaluable subjects

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were ADA-positive. ADA titers increased with the duration of treatment, and immunogenicity was associated with greatly decreased plasma exposure to MT-3724. Most subjects developed immunogenicity by Cycle 2, with some subjects developing immunogenicity with subsequent dosing. By Cycle 5 Day 1, 7 of the 8 evaluated subjects were ADA-positive. Safety events observed in the trial did not seem to correlate with presence of ADA/NAb. Tumor response was not observed to be confounded by presence of ADA and NAb. There were 2 subjects (Subject 1004 and Subject 13004) with decreasing tumor size while being NAb-positive, 1 of whom was a CR (Subject 13004). There was no definitive correlation between clinical outcome and immunogenicity since, of the 2 CR subjects, 1 subject (Subject 12003) was ADA-negative throughout the duration of treatment and the other subject (Subject 13004) was NAb-positive by the completion of Cycle 1.

Rituximab serum concentrations of at least 500 ng/mL on Cycle 1 Day 1 resulted in a response of progressive disease. All subjects who responded (CR, PR) had Rituximab serum concentrations less than 500 ng/mL, including the 2 CRs dosed at 50 µg/kg.

Safety

- All 27 subjects had at least 1 treatment-emergent adverse event (TEAE) and 26 subjects (96.3%) had at least 1 treatment-related TEAE. Twenty subjects (74.1%) had at least 1 TEAE with severity ≥ Grade 3, and 13 subjects (48.1%) had at least 1 treatment-related TEAE with severity ≥ Grade 3.
- There were no differences in incidences of the most common TEAEs between the cohorts. The most frequently reported TEAEs were oedema peripheral in 17 subjects (63.0%), diarrhoea, fatique, and myalgia in 11 subjects (40.7%) each, insomnia in 8 subjects (29.6%), and pyrexia, cough, and nausea in 7 subjects (25.9%) each.
- The most commonly reported Grade 3 or 4 treatment-related TEAEs included myalgia (3 subjects [11.1%]), pneumonia, decreased lymphocyte count, and arthralgia (2 subjects each [7.4%]). Also, Grade 3 or 4 neutropenia and decreased neutrophil count were reported for a total of 3 subjects (neutropenia 2 subjects [7.4%] and neutrophil count decrease 1 subject [3.7%]).
- The most frequent serious AEs were pneumonia in 4 subjects (14.8%), acute renal failure in 3 subjects (11.1%), and thrombocytopenia and hypercalcaemia in 2 subjects (7.4%) each. A total of 9 serious AEs in 6 subjects were classified as treatment-related. These included pneumonia (2 subjects), edema, edema peripheral, ileus, viral infection, hypertension, acute renal failure, and muscular weakness (1 subject each). Five of 6 subjects with treatment-related serious adverse events (SAEs) were receiving doses above the MTD of 50 µg/kg.
- Capillary leak syndrome was reported in 2 subjects and dose reductions were made. Both events resolved and the maximum severity was Grade 2.

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- One subject died during Cycle 2, 11 days after having received last dose of MT-3724 (Cycle 2, Dose 4). The cause of death was cardiac arrest that was considered unrelated to treatment and instead related to disease progression.

Conclusions

Part 1 and Part 2 of this study were first-in-human, multi-center, open-label, multiple dose, Phase 1/2, dose escalation studies of MT-3724 in subjects with relapsed or refractory B cell NHL who had previously responded to one or more approved anti-CD20 MAb therapies. The primary objectives were to define the MTD of MT-3724 with a tolerable AE profile and/or at which maximum PK/PD parameter changes are observed, and to determine PK and PD profiles of MT-3724.

In Part 1, the first 2 subjects treated at 100 µg/kg/dose had 1 DLT each (Grade 3 pneumonia and Grade 2 ileus). None of the other 19 subjects treated in Part 1 of the study at dose levels ≤ 75 µg/kg/dose had a DLT, including the 6 subjects treated at 75 µg/kg/dose. Therefore, 75 µg/kg/dose was initially declared to be the MTD for MT 3724 as monotherapy. Subsequently, 3 more subjects were enrolled and treated at 75 µg/kg/dose in Part 2 of the study, the expansion phase. Two of these 3 subjects had Grade 2 capillary leak syndrome (CLS) during Cycle 1 leading to dose delay and reduction. The CLS events occurred in obese subjects. Because these events led to dose reduction in both subjects, the DMC decided to adjust the MTD to 50 µg/kg/dose with a maximum dose capped at 6,000 µg/dose for MT-3724 when used as monotherapy.

CLS as the principal DLT in this study proved to be manageable: subjects tended to recover within a few weeks and continue treatment at a reduced dose of MT-3724 with no signs of recurrence, possibly also owing to the use of premediation before dosing, consisting of corticosteroids, antihistamines and non-steroidal anti-inflammatory drugs. When CLS occurred, using these drugs in addition to albumin or fluid replacement infusions, or diuretcis, as necessary based on specific symptoms e.g., edema, hypotension, proved successful in mitigating more severe or prolonged CLS episodes, and informed CLS management guidance in ongoing and future MT-3724 studies.

The C_{max} and AUC of MT-3724 increased in approximately dose-proportional manner from the lowest to the hightes dose, and half life was between 2 and 3 hours. The number of $CD19^+$ cells decreased after one cycle of treatment and remained depressed through the end of study. However, due to high variability in the data, small sample size, and inconsistent sampling, PK-PD relationships were difficult to discern.

Immunogenicity was observed across all dose levels, from 5 to 100 µg/kg. Almost all ADA-positive results were also associated with detection of NAbs. Safety events observed in the trial did not seem to correlate with presence of ADA/NAb. Importantly, tumor response did not appear tobe impacted by presence of ADAs or NAbs.

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In conclusion, MT-3724 demonstrated an encouraging safety and tolerability profile in 27 relapsed/refractory B-cell NHL or B-cell CLL subjects most of whom were elderly and had multiple prior biologic and chemotherapeutic treatments and multiple comorbidities at baseline.

Taking both safety and efficacy observations into consideration, monotherapy treatment with MT-3724 in subjects with r/r DLBCL and negative rituximab levels holds promise in this population where few other treatment options exist, especially once subjects are deemed ineligible for stem cell transplantation or chimeric antigen receptor T-cells, or relapse following these treatments. Also, combination with other agents that are effective in r/r DLBCL and have no significant overlapping toxicities should be considered.

Date of Report
22 January 2021