1. SYNOPSIS

Name of Sponsor/Company	**Name of Finished Product**	**Name of Active Ingredient**
Kite Pharma, Inc.	Axicabtagene ciloleucel	Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-ζ chimeric antigen receptor

Protocol Number:

KTE-C19-101 (ZUMA-1)

Title of Study:

A Phase 1/2 Multicenter Study Evaluating the Safety and Efficacy of KTE-C19 in Subjects with Refractory Aggressive Non-Hodgkin Lymphoma (ZUMA-1)

Investigators and Study Centers:

The study was conducted at 24 centers (23 in the US and 1 center in Israel). A full list of investigators and study centers if provided in the clinical study report appendix.

Publications:

See Appendix 16.1.11

Study Period:	**Phase of Development:**
First subject enrolled in Phase 1: 21 Apr 2015 Data cut-off for primary analysis: 27 Jan 2017	1/2

Objectives:

Primary Objectives:

The primary objective of Phase 1 was to evaluate the safety of axicabtagene ciloleucel regimens.

The primary objective of Phase 2 was to evaluate the efficacy of axicabtagene ciloleucel as measured by objective response rate (ORR) in subjects with refractory aggressive non-Hodgkin lymphoma (NHL); namely, diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (TFL).

Secondary Objectives:

The secondary objectives of Phase 2 included assessing the safety and tolerability of axicabtagene ciloleucel and additional efficacy endpoints.

Methodology:

ZUMA-1 is an ongoing Phase 1/2 multicenter, open-label study that is evaluating the safety and efficacy of axicabtagene ciloleucel in subjects with refractory aggressive NHL. Phase 1 has been completed. Phase 2 is

ongoing: enrollment and treatment have been completed for Cohorts 1 and 2, and follow-up is continuing for survival status. A third cohort is ongoing and will be reported separately.

Axicabtagene ciloleucel is a novel, autologous chimeric antigen receptor (CAR) T-cell based immunotherapy that targets CD19-expressing tumors, such as NHL. The anti-CD19 CAR T-cell product is produced by engineering a subject's own T cells, obtained through leukapheresis, to express the anti-CD19 CAR.

Following screening and enrollment in both Phase 1 and Phase 2, leukapheresis was performed at the clinical trial sites. Activated T cells from the leukapheresis product were transduced with a retroviral vector containing the anti-CD19 CAR transgene. The transduced T cells were then further expanded for several days in the presence of recombinant IL-2, then washed and cryopreserved to generate the final product.

In Phase 1 (Cohort A1), subjects received a conditioning chemotherapy regimen followed by axicabtagene ciloleucel. Doses are described under "Test Product, Dose, and Mode of Administration." DLTs in Phase 1 were defined as any of the following occurring within the 30 days after axicabtagene ciloleucel infusion:

- Grade 4 neutropenia lasting longer than 21 days from the day of cell transfer.
- Grade 4 thrombocytopenia lasting longer than 35 days from the day of cell transfer.
- Any axicabtagene ciloleucel-related AE requiring intubation, including Grade 4 confusion requiring intubation for airway protection.
- All other Grade 3 toxicities lasting more than 3 days and all Grade 4 toxicities, with the exception of the following, which are not considered DLTs:
    - Aphasia/dysphasia or confusion/cognitive disturbance which resolved to Grade 1 or less within 2 weeks and to baseline within 4 weeks.
    - Grade 3 fever.
    - Myelosuppression (includes bleeding in the setting of platelet count less than 50 $x10^9$/L and documented bacterial infections in the setting of neutropenia), defined as lymphopenia, decreased hemoglobin, neutropenia and thrombocytopenia unless neutropenia and thrombocytopenia met the DLT definition described above.
    - Immediate hypersensitivity reactions occurring within 2 hours of cell infusion (related to cell infusion) that are reversible to a Grade 2 or less within 24 hours of cell administration with standard therapy.
    - Grade 3 or 4 hypogammaglobulinemia.

No additional cohorts were enrolled because the axicabtagene ciloleucel dosing regimen explored in Cohort A1 was deemed by the safety review team to be safe and appropriate for initiating Phase 2 (see Safety Results). Thus, hereafter, Phase 1 Cohort A1 will be referred to as Phase 1.

In Phase 2, subjects with refractory DLBCL were enrolled into Cohort 1 and subjects with refractory PMBCL or refractory TFL were enrolled into Cohort 2. Subjects received the same conditioning chemotherapy regimen and the same axicabtagene ciloleucel doses specified for Phase 1.

In both phases, hydration and mesna were used prophylactically during the conditioning chemotherapy and Tylenol 650 mg PO and Benadryl 12.5 mg IV were used prophylactically prior to the axicabtagene ciloleucel infusion. The initiation of axicabtagene ciloleucel infusion was to occur within 30 minutes of thawing the cryopreserved product. The time for infusion of the entire bag was not to exceed 30 minutes. To ensure subject

safety, all subjects were hospitalized during and for a minimum of 7 days following the infusion. Subsequently, subjects returned to the clinic at the completion of Week 2 (± 2 days), Week 4 (± 3 days), Month 2 (± 1 week), and Month 3 (± 1 week) for efficacy and safety assessments. After Month 3, disease assessments occurred every 3 months until Month 18, every 6 months from Year 2 to Year 5, and then annually thereafter or until disease progression. Follow up for survival occurred until death or full consent withdrawal.

The following assessments/procedures/data collection were conducted: informed consent (baseline visit only); general medical history including previous treatments for NHL (baseline visit only); physical examination, including vital signs and performance status; neurological assessments; blood draws for complete blood count (CBC) and lymphocyte subsets, chemistry panels; antibodies to FMC63 (the parental murine antibody used for development of the anti-CD19 variable regions of the CAR construct); antibodies to bovine serum albumin; and the presence of replication competent retrovirus (RCR). Anti-CD19 CAR T cell levels in blood were determined over time. Pharmacodynamic effects were assessed using 13 analytes encompassing a panel of homeostatic, inflammatory, and immune modulating cytokines, chemokines, and immune effector–related markers in serum.

Adverse events (AEs) were collected from the start of leukapheresis until 90 days after the axicabtagene ciloleucel infusion; SAEs were collected from screening. After Month 3 and until 24 months, or disease progression, whichever occurred first, only the following targeted AEs and SAEs were to be collected: neurologic events, hematologic events, infections, autoimmune disorders, and secondary malignancies.

Subjects who achieved a partial response (PR) or complete response (CR) had an option to receive a second course of conditioning chemotherapy and axicabtagene ciloleucel if their disease subsequently progressed > 3 months following the axicabtagene ciloleucel infusion, CCI [redacted]

Number of Subjects:

Phase 1

Planned enrollment: 6 to 24 subjects.

Enrolled: 8 subjects

Phase 2

Planned enrollment: Sufficient subjects to obtain CCI [redacted] who had had the opportunity to undergo the 6-month disease assessment.

Enrolled: 111 subjects

Diagnosis and Main Criteria for Inclusion:

Key elements of the inclusion criteria are listed below.

1. Histologically confirmed DLBCL, PMBCL, or TFL
2. Chemotherapy-refractory disease, defined as one or more of the following:
    a. No response to first-line therapy (primary refractory disease); subjects who are intolerant to first-line therapy chemotherapy were excluded.
    b. No response to second or greater lines of therapy
3. Refractory after ASCT, defined as occurrence of disease progression or relapse ≤ 12 months after ASCT (must have biopsy proven recurrence in relapsed subjects) or, if salvage therapy was given after ASCT, the subject must have had no response to or relapsed after the last line of therapy

4. Prior therapy including anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen
5. Measurable disease according to the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (hereafter referred to as IWG 2007 criteria) (Cheson et al, 2007).
6. No evidence of CNS lymphoma
7. Age 18 or older
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Adequate hematologic, renal, hepatic, pulmonary and cardiac function

Key elements of the exclusion criteria are listed below.

10. History of allogeneic SCT
11. Prior CD19 targeted therapy with the exception of subjects who received axicabtagene ciloleucel in this study and are eligible for retreatment
12. Prior CAR therapy or other genetically modified T-cell therapy
13. Presence of fungal, bacterial, viral, or other infection that was uncontrolled or requiring IV antimicrobials for management
14. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement

Test Product, Dose, and Mode of Administration:

Investigational Product:

Axicabtagene ciloleucel is an autologous product and the intended subject was identified by a unique subject ID number, subject initials and date of birth. Axicabtagene ciloleucel is supplied as a cryopreserved product. Axicabtagene ciloleucel is administered after a conditioning chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, both administered daily for 3 days.

Phase 1 and 2

Subjects received a single infusion of axicabtagene ciloleucel at a target dose of 2 x 10^6 anti CD19 CAR T cells/kg (± 20%). The minimum dose to be administered was 1 x 10^6 anti-CD19 CAR T cells/kg. For subjects weighing greater than 100 kg, a maximum flat dose of 2 x 10^8 anti CD19 CAR T cells was to be administered. The entire bag of axicabtagene ciloleucel was to be infused.

Duration of Treatment:

Following leukapheresis, subjects received a 3-day-cycle of conditioning chemotherapy followed by a single infusion of axicabtagene ciloleucel approximately 3 days later; subjects were followed for at least 30 days for safety observations.

Reference Therapy, Dose, and Mode of Administration:

Not applicable. However, the ORR was compared with that of prespecified control rate (see Statistical Methods).

Endpoints for Evaluation:

Primary Endpoint

- Phase 1: Incidence of adverse events defined as dose-limiting toxicities (DLT).
- Phase 2: Objective response rate (ORR), defined as a CR or PR per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (Cheson 2007) as determined by study investigators. All subjects who did not meet the criteria for an objective response by the analysis cut-off date were considered non-responders.

Key Secondary Endpoint(s) for Phase 2:

- ORR according to the central review, based on the IWG 2007 criteria (Cheson et al, 2007).
- Duration of Response (DOR) according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007).
- Progression Free Survival (PFS) according to the investigator's assessment, and by central review, both based on IWG 2007 criteria (Cheson et al, 2007).
- Overall Survival (OS).
- Safety: Incidence of AEs, significant laboratory abnormalities, and presence of RCR or antibodies to FMC63 or bovine serum albumin in subjects' blood.

Pharmacokinetic and Pharmacodynamic Endpoints

Levels and persistence of anti-CD19 CAR T cells and cytokines in serum samples.

Product Characteristics

Weight-adjusted axicabtagene ciloleucel dose, transduction rate, total CAR T cells, total T cells, CD4/CD8 ratio, and T-cell memory phenotypes.

Statistical Methods:

Analysis Populations for Primary and Secondary Endpoints in the Primary Analysis

a) Full analysis set – all enrolled subjects

b) Modified intent-to-treat (mITT) (defined for Phase 2 only) set – all subjects treated with at least 1.0 x 10^6 anti-CD19 CAR T cells/kg. The mITT analysis set was used for efficacy analyses in Phase 2.
CCI [redacted]

c) Safety analysis set – all subjects treated with any dose of axicabtagene ciloleucel.

d) DLT-evaluable set (Phase 1 only) – subjects treated in Phase 1 who either (1) received the target number of cells (2.0 x 10^6 anti-CD19 CAR T cells/kg [± 20%]) and were followed for at least 30 days after

axicabtagene ciloleucel infusion; or (2) received a cell dose lower than the target but experienced a DLT during the 30 days post infusion.

Statistical Hypothesis

Cohort 1 and Cohort 2 in Phase 2 were designed to differentiate between a treatment that has a true response rate of 20% or less and a treatment with a true response rate of 40% or more. The hypothesis is that the ORR for subjects treated with axicabtagene ciloleucel in Cohorts 1 and 2 is significantly greater than 20%. The prespecified 20% control response rate was based on a review of published outcome data for patients with refractory DLBCL, defined as those who either never responded (ie, progressive disease [PD] or stable disease [SD] as best response to the last line of therapy) or relapsed within 12 months after ASCT.

For Phase 2, CCI 1 primary analysis were planned. CCI

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DOR, PFS, and OS were analyzed using the Kaplan-Meier method.

Safety Analysis

All safety analyses were conducted using the safety analysis set. The demographic and baseline disease characteristics, axicabtagene ciloleucel product characteristics, axicabtagene ciloleucel pharmacokinetics, and levels of serum cytokines were analyzed. AEs events of interest included identified risks (cytokine release syndrome [CRS]; neurologic AEs; cytopenias, including febrile neutropenia; and infection) and potential risks (autoimmune disorders, secondary malignancies, tumor lysis syndrome, and immunogenicity [development of antibodies to axicabtagene ciloleucel]).

Laboratory results collected at baseline and through the axicabtagene ciloleucel treatment period were graded according to NCI Common Toxicity Criteria (CTCAE version 4.03). The subject incidence of concomitant medication usage was summarized by the following selected medication categories: steroids, tocilizumab, vasopressors, and immunoglobins. The subject incidence of positive blood tests for RCR and antibodies to FMC63 or bovine serum albumin were tabulated.

Summary of Results:

Disposition

In Phase 1, eight subjects were enrolled. All 8 of the enrolled subjects underwent leukapheresis and 7 subjects (88%) received both conditioning chemotherapy and axicabtagene ciloleucel. One subject discontinued prior to conditioning chemotherapy due to the need for immediate therapy for disease progression. Of the 7 subjects treated with axicabtagene ciloleucel, 6 subjects received the target cell infusion and 1 subject received an axicabtagene ciloleucel dose less than the target dose. Therefore, 6 subjects were evaluable for DLTs per protocol and 7 subjects were evaluable for safety.

In Phase 2, at the time 92 subjects in Cohorts 1 and 2 had been followed for 6 months, a total of 111 subjects had undergone leukapheresis. Thus, the full analysis set comprises 111 subjects. Of these, 103 subjects (93%) were treated with conditioning chemotherapy with 101 subjects treated with axicabtagene ciloleucel. Of the 8 subjects who did not receive axicabtagene ciloleucel, 2 subjects died due to disease progression prior to treatment, 4 subjects experienced AEs that precluded treatment, and 2 subjects had non-measurable disease prior to treatment.

Demographics and Baseline Characteristics

In Phase 1, all 7 treated subjects had DLBCL. In Phase 2, 76% of the 101 subjects had DLBCL, 8% had PMBCL and 16% had TFL.

Across both phases, all subjects were refractory to standard of care therapy or had relapsed within 12 months after undergoing autologous stem cell transplant (ASCT). Most of the patients had stage III/IV disease, were refractory to second or greater line therapy, and nearly half had high-intermediate/high risk IPI scores at study entry.

Axicabtagene ciloleucel was successfully delivered to the site for all 8 of the subjects (100%) who underwent leukapheresis in Phase 1. In Phase 2, the cell product was delivered to the site for 110 of the 111 subjects in the full analysis set. The median (range) time from leukapheresis to delivery of the product to the study site in Phase 1 was 16 days (14 to 23 days) and was 17 days (14 to 51 days) in Phase 2.

Efficacy –Phase 2

Primary Endpoint

At IA2, Cohort 1 met the primary endpoint and hence was not tested at the primary analysis. Therefore, all data described in this synopsis are based on results for Cohorts 1 and 2 combined. Results for individual cohorts were consistent and are presented in Module 5, ZUMA-1 Clinical Study Report.

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Secondary Endpoints

The median time to response (CR or PR) was 1.0 month (range: 0.8 to 6.0 months), and the median time to CR was 1.0 month (range: 0.8 to 7.0 months). The median DOR was 8.1 months, with a median (95% CI) follow-up time of 5.1 months (4.9, 5.7 months).

PFS estimates at 6 months, 9 months, and 12 months were 49.0%, 43.3%, and 34.7%, respectively. The median duration of PFS was 5.9 months. PFS estimates among subjects with a best overall response of CR at 6 months, 9 months, and 12 months were 77.4%, 71.6%, and 57.5%, respectively. PFS estimates among subjects with a best overall response of PR at 3 months and 6 months were 41.6% and 18.2%, respectively.

OS rates at 6 months, 9 months, and 12 months were 79.8%, 68.4%, and 54.5%, respectively. The median follow-up time was 8.7 months among all subjects in the mITT set. OS rates among subjects with a best overall response of CR at 6, 9, and 12 months were 98.2%, 88.3%, and 64.5%, respectively. OS rates among subjects with a best overall response of PR at 6, 9, and 12 months were 64.3%, 52.6%, and 52.6%, respectively.

Efficacy – Phase 1

Results in Phase 1 were consistent with those in Phase 2, the ORR was 71% (5 responders among 7 subjects), with a CR rate of 57% (4 subjects) with a PR rate of 14% (1 subject). The Kaplan-Meier estimate of DOR was 60% after 3, 6, and 9 months of follow-up. Time to response was 1.0 month (range: 0.9 to 1.0 month). Three subjects have ongoing complete remission at 18+ months.

Pharmacokinetics

Anti-CD19 CAR T cells were measurable in peripheral blood within the first 14 days after the axicabtagene ciloleucel infusion in all evaluable subjects. The median peak level across all subjects was 41.9 cells/μL (range: 0.8 to 1513.7 cells/μL). Levels of anti-CD19 CAR T cells decreased toward background levels by 3 months of the cell infusion (range: 0 to 15.8 cells/μL), but were measurable at the last assessment in most evaluable (ie, responding) subjects. The median area under the plasma concentration vs time curve (AUC) from Day 0 to Day 28 ($AUC_{0\text{-}28}$) was 462.3 cells/μL·days. Subjects who responded to axicabtagene ciloleucel had higher peak levels and AUC at 1 month of anti-CD19 CAR T cells compared to nonresponders. Median peak levels of anti-CD19 CAR T cells in blood were significantly increased in subjects with Grade 3 or higher neurological events relative to levels in subjects with Grade 2 or lower neurological events.

Pharmacodynamics

Multiple cytokines in blood peaked within 14 days after axicabtagene ciloleucel infusion and declined towards baseline generally within 1 month. In particular, induction of IL-15, a homeostatic cytokine, was temporally associated with administration of the lymphodepleting conditioning chemotherapy regimen prior to infusion of axicabtagene ciloleucel. A greater than 2-fold induction of IL-15 at the peak was observed in 88 of 90 subjects (97.8%). Peak and/or cumulative levels through 1 month of the following biomarkers were correlated with both Grade 3 or higher CRS and Grade 3 or higher neurologic events: IL-6, IL-15, IL-2Rα, TNF-α, IFN-γ, IP-10, IL-10, VCAM-1, IL-1ra, IL-8, and granzyme B.

Safety – Phase 2

All safety data represent Cohorts 1 and 2 combined.

Exposure

The median total body surface area-adjusted dose of cyclophosphamide was 1500 mg/m^2 (min: 1329, max: 1500 mg/m^2). The median total body surface area-adjusted dose of fludarabine was 90 mg/m^2 (min: 81, max:

90 mg/m^2). A total of 100 subjects (99%) received ± 10% of the planned total dose of cyclophosphamide. A total of 101 subjects (100%) received ± 10% of the planned total dose of fludarabine.

The median weight-adjusted dose of axicabtagene ciloleucel was 2.00 x 10^6 CAR T cell/kg (min: 1.10 x 10^6, max: 2.20 x 10^6 CAR T cell/kg). The median total number of anti-CD19 CAR T cells in the axicabtagene ciloleucel infusion was 165.00 x 10^6 (min: 75.00 x 10^6, max: 200.00 x 10^6 CAR T cells). The median total number of T cells infused was 298.51 x 10^6 (min: 149.07 x 10^6, max: 760.46 x 10^6). A total of 100 subjects (99%) received ± 10% of the planned dose of 2.00 x 10^6 anti-CD19 CAR T cells/kg or 2.00 x 10^8 anti-CD19 CAR T cells for subjects weighing > 100 kg.

Product Characteristics

The median transduction rate was 52.6% (range: 21.6% to 85.1%). The median CD4/CD8 cell ratio was 0.9 (range: 0.03 to 5.81). The median ratio of (% T naïve + % T_{cm})/ (% T_{em}+ % T_{eff}) was 0.7 (range: 0.2 to 5.7). Median IFN-γ production in co-cultures of axicabtagene ciloleucel product and $CD19^+$ target cells was 5844.0 pg/mL (range: 381.0 to 17791.0 pg/mL).

Deaths

In Phase 2, a total of 30 of the 101 subjects treated with axicabtagene ciloleucel died. Two of the 30 deaths occurred within 30 days after the axicabtagene ciloleucel infusion. Twenty-five subjects died from disease progression. Two subjects died after receiving other cancer therapy. Three subjects (PPD , PPD , and PPD) died due to AEs. Two of the fatal AEs were related to axicabtagene ciloleucel: the first subject experienced Grade 5 hemophagocytic lymphohistiocytosis (also known as histiocytosis haematophagic) event on Day 40 in the setting of Grade 4 CRS; the second subject experienced Grade 5 anoxic brain injury on Day 34 following cardiac arrest in the context of CRS.

In Phase 1, four of the 7 subjects who received axicabtagene ciloleucel died. Three subjects died due to PD. One death occurred within 30 days of receiving axicabtagene ciloleucel; the death was caused by a fatal AE of intracranial hemorrhage on Day 16 that was considered related to conditioning chemotherapy and occurred in the only Phase 1 subject who experienced DLTs (Grade 4 encephalopathy and Grade 4 CRS). Following the occurrence of the DLT in Phase 1, the protocol was amended with respect to eligibility, study conduct, and toxicity management guidelines to ensure subject safety.

Adverse Events

In Phase 2, 95% of subjects had Grade 3 or higher AEs, 51% had SAEs, and 3 subjects (3%) had Grade 5 AEs. Two of the 3 Grade 5 AEs were related to axicabtagene ciloleucel (see Deaths). The most common Grade 3 or higher AEs included neutropenia (66%), anemia (43%), leukopenia (44%), febrile neutropenia (31%), thrombocytopenia (24%), and encephalopathy (21%).

Grade 3 or higher CRS occurred in 13% of subjects. All events had an onset within 2 weeks after the infusion of axicabtagene ciloleucel, and all resolved, with the exception of the 2 Grade 5 events, both of which followed ongoing CRS events that started within the first week after the cell infusion. Grade 3 or high neurologic events occurred in 28% of subjects. Two subjects had events with an onset more than 30 days after the cell infusion. All neurologic events resolved except one case of ongoing Grade 1 memory impairment. Rates of Grade 3 or higher CRS and neurologic events decreased over the course of the study: the incidence of Grade 3 or higher CRS decreased from 18% to 5%, and neurologic events decreased from 34% to 18% from IA2 compared with the 39 subjects enrolled after IA2.

Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 52%, 19%, and 3% of subjects, respectively; 6% of subjects each had a Grade 4 neutropenia or thrombocytopenia with a duration > 30 days. All prolonged Grade 4 cytopenias resolved. Grade 3 or higher infections occurred in 22% of subjects; in 12% of subjects these events had an onset > 30 days after the axicabtagene ciloleucel infusion. There were no autoimmune AEs, clinically significant cases of immunogenicity or axicabtagene ciloleucel-related TLS, and no subjects tested positive for presence of RCR.

The overall safety profile was similar for subjects with DLBCL, PMBCL, and TFL. Results in Phase 1 were consistent with those in Phase 2.

Conclusions:

The primary endpoint of ZUMA-1 was met: axicabtagene ciloleucel significantly improved ORR in subjects with refractory aggressive B-cell NHL compared with the pre-specified rate of 20%. Almost half of the subjects (44%) are still in response with a median 8.7 months follow-up. Median overall survival has not been reached. Consistent response rates were observed across subsets defined by disease stage, age, IPI scores, and refractory disease subset. The safety profile was manageable. CRS, neurologic events, and cytopenias were reversible and mostly occurred in the first month after cell infusion. The rates of severe adverse reactions decreased over the course of the trial and were managed with supportive care, tocilizumab, and corticosteroids. Axicabtagene ciloleucel may provide an important treatment option for patients with refractory aggressive NHL.

Date of the Report:

28 Jul 2017