NU Study Number: NU 18H02
Other Study Number: IISR-2017-101972

A phase 1 study of R-CHOP plus SYK inhibitor TAK-659 for the front-line treatment of high-risk diffuse large B cell lymphoma (DLBCL)

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Study Intervention(s): TAK-659, R-CHOP

IND Number: 140223

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Funding Source: Takeda/Millennium Pharmaceuticals, Inc.

Version Date: **4.3.2020** (Amendment 4)

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LIST OF ABBREVIATIONS

ABC	Activated B Cell
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AML	Acute Myeloid Leukemia
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate Aminotransferase
BCR	B-cell Receptor
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DDI	Drug-Drug Interaction
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
$EC_{\#}$	Effective Concentration
ECOG	Eastern Cooperative Oncology Group
EPOCH-R	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, Rituximab
FISH	Fluorescent In Situ Hybridization
FOCBP	Female of Childbearing Potential
GCB	Germinal Center B-cell
G-CSF	Granulocyte Colony Stimulating Factor
H&PE	History & Physical Exam
IHC	Immunohistochemistry
IPI	International Prognostic Index
ITAM	Immunoreceptor Tyrosine Activation Motifs
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCCN-IPI	National Comprehensive Cancer Network - International Prognostic Index
NCI	National Cancer Institute
NOS	Not Otherwise Specified
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease

PET	Positron Emission Tomography
PFS	Progression Free Survival
PI3K	Phosphoinositide 3-kinase
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
R-CHOP	Rituximab; Cyclophosphamide; Doxorubicin; Vincristine; Prednisone
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
TEAE	Treatment-emergent Adverse Event
TNBC	Triple Negative Breast Cancer
WBC	White Blood Cells

STUDY SCHEMA

High-risk diffuse large B-cell lymphoma (DLBCL)
by one of the following:

- ABC/non-GCB subtype
- High-intermediate or high-risk group by NCCN-IPI (score ≥4)
- MYC gene rearrangement by FISH
- MYC overexpression by IHC (≥40%) and BCL2 overexpression by IHC (≥ 50%)
- Treatment naïve transformed low-grade lymphoma OR previously treated transformed low-grade lymphoma with prior treatment not including an anthracycline

↓

Cycle 1* (1 cycle = 21 days):
R-CHOP

Cycles 2-6:
R-CHOP + oral TAK-659 once daily starting at 60 mg**

***The first cycle of R-CHOP may take place on- or off-study. Those patients receiving R-CHOP prior to study registration must begin TAK-659 treatment within 21 days. Combination treatment will begin "Cycle 2" in both cases
****A 3+3 dose escalation method will be utilized to find the MTD. Dose levels are 60 mg, 80 mg, and 100 mg. All patients will have PK's drawn during Cycle 2 (Day 1, 2, 15, and 16) as outlined in section 5.0.

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Response Assessments
PET/CT after completion of Cycle 3 + PET/CT after Cycle 6

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Follow up visits at least every 6 months for up to 3 years from discontinuation of treatment

STUDY SUMMARY

Title	A phase 1 study of R-CHOP plus SYK inhibitor TAK-659 for the front-line treatment of high-risk diffuse large B cell lymphoma (DLBCL)
Version	4.3.2020(Amendment 4)
Study Design	Phase 1, open-label study
Study Center(s)	Northwestern University
Objectives	**Primary Objective** To determine the safety, tolerability, and maximum tolerated dose of TAK-659 when combined with R-CHOP in the front-line treatment of high-risk DLBCL **Secondary Objective** To assess preliminary efficacy of TAK-659 combined with R-CHOP in the front-line treatment of high-risk DLBCL **Exploratory Objective** To assess the pharmacokinetics of TAK-659 in combination with R-CHOP.
Sample Size	12-18 evaluable patients
Diagnosis & Key Eligibility Criteria	The study population will be patients with high-risk DLBCL by one of the following: ABC/non-GCB subtype, high-intermediate or high-risk group by NCCN-IPI (score ≥4), MYC gene rearrangement by FISH, MYC overexpression by IHC (≥40% and BCL2 overexpression by ICH ≥50%), or previously treated transformed low-grade lymphoma to large B cell lymphoma with prior treatment not including an anthracycline.
Treatment Plan	This is a single-arm, dose escalation phase I study. All patients will be treated with R-CHOP (without the addition of TAK-659) for cycle 1 and treatment for cycles 2-6 will include R-CHOP plus TAK-659. TAK-659 will be given orally continuously (days 1-21), once daily during these 21 day cycles (cycles 2-6) and be discontinued at the completion of cycle 6. Dosing of TAK-659 will be via a standard 3+3 dose escalation scheme, starting at 60 mg and increase to 80 mg followed by 100 mg, the target MTD. R-CHOP will be administered as per clinical standard, with rituximab, cyclophosphamide, doxorubicin, and vincristine given intravenously on day 1 and prednisone given orally on days 1-5 (or Day 2-6). PK blood samples will be obtained during the first cycle of combination therapy (Cycle 2) as outlined in section 5.0.
Statistical Methodology	A total of 12-18 evaluable patients will be enrolled and complete the study according to the 3 + 3 dose escalation scheme. Preliminary efficacy will be assessed by calculating the objective response rate (ORR) with 95% confidence interval at 3 months, and by estimating progression-free survival and overall survival at 12 and 18 months using Kaplan-Meier curves.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Diffuse large B cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, representing about 30% of all NHL. It is estimated that approximately 20,000 new cases of DLBCL are diagnosed annually in the US.[1] DLBCL is a form of aggressive B cell non-Hodgkin lymphoma and is invariably fatal without treatment. The standard treatment for patients with newly diagnosed DLBCL is R-CHOP (rituximab + cyclophosphamide + doxorubicin [hydroxydaunomycin] + vincristine [Oncovin®] + prednisone). Treatment with R-CHOP results in a 2-year progression-free survival (PFS) of approximately 75%, 5-year PFS of approximately 65%, 2-year overall survival (OS) of approximately 80%, and 5-year OS of approximately 75%.[2] DLBCL is highly heterogeneous in histology, clinical behavior, and underlying biology, and therefore exhibits significant variation with regards to outcome after therapy. There are several high-risk disease markers and poor prognostic factors that are associated with a high likelihood to be refractory to or relapse after treatment with R-CHOP, illustrating a need for improved therapies.

Cell of origin subtypes of DLBCL can be defined by gene expression profiling and correlated with immunohistochemistry via the Hans Algorithm into activated B cell (ABC)/non-germinal center B cell (non-GCB) subtype and germinal center B cell (GCB) subtype. ABC/non-GCB subtype DLBCL has an inferior outcome when treated with R-CHOP compared to the GCB subtype.[3-5] Efficacy outcomes (response rates and survival measures) associated with ABC/non-GCB DLBCL patients treated with R-CHOP vary depending on the study. In general, the 2-year progression free survival (PFS) of ABC/non-GCB DBLCL and GCB DLBCL are ~60% and ~80%, respectively.[3,6] The 5-year overall survival of ABC/non-GCB DBLCL has been reported at 56%.[3]

The human MYC oncogene is responsible for malignant transformation of several types of lymphoma, and is a sine qua non mutation associated with Burkitt lymphoma[7,8]. MYC has been found to be rearranged in up to 10% of cases of DLBCL.[9] MYC rearrangement and over expression are independent poor prognostic factors.[9,10] Other recurrent genetic translocations found in lymphoma, including BCL-2 and BCL-6, can co-occur with MYC rearrangement, which is referred to as “double-hit lymphoma”, and subsequently confers a particularly poor prognosis with a 3-year overall survival of 49%.[11-13]

Indolent/low-grade lymphomas transform to a more aggressive large B cell lymphoma at a frequency of approximately 2-3% per year over the first 5 years.[14] Transformed low-grade lymphoma to large B cell lymphoma in patients who received no prior treatment of their low-grade lymphoma (treatment-naïve transformed low-grade lymphoma) have outcomes similar to that of de novo DLBCL.[15,16] However, cases of previously treated transformed low-grade lymphoma have worse prognosis when compared to treatment-naïve transformed low-grade lymphoma.[15,16] Consolidative stem cell transplantation is considered in cases of previously treated transformed low-grade lymphoma because of this inferior prognosis.[16]

In addition to these disease-specific factors contributing to a worse prognosis, prognostic models that also account for patient-specific factors, such as the IPI and NCCN-IPI, are able to separate the higher risk groups from the lower risk groups. Using the NCCN-IPI, patients treated in the rituximab era with a high-intermediate risk score of 4-5 and a high-risk score of ≥6 had a 5-year overall survival of 64% and 33%, respectively.[17]

Relapsed/refractory DLBCL is associated with a poor prognosis with treatment options including salvage chemotherapy regimens and autologous stem cell transplant. Salvage regimens followed by stem cell transplant can result in a remission in approximately 40% of cases, but these remissions tend to be less durable.[18] Given the poor prognosis in the

relapsed/refractory setting, it would be ideal to have more high-risk patients achieve favorable outcomes using front-line therapy. R-CHOP has been compared to the more aggressive regimen dose-adjusted EPOCH-R in a randomized clinical trial of front-line therapy in patients with DLBCL. The results were presented at the American Society of Hematology annual meeting in December 2016, which demonstrated no difference in overall survival or event-free survival.[19] Therefore, the lymphoma community is continuing to investigate regimens that improve upon R-CHOP in the front-line treatment of DLBCL, especially in the high-risk setting.

1.2 R-CHOP Background & Overview

Combination chemotherapy with cyclophosphamide + doxorubicin [hydroxydaunomycin] + vincristine [Oncovin®] + prednisone (CHOP) was established as a standard treatment of DLBCL decades ago[20]. Rituximab, an anti-CD20 monoclonal antibody, was later combined with CHOP (R-CHOP) and improved clinical outcomes compared with CHOP alone, thus becoming the standard treatment of DLBCL.[21,22] R-CHOP has been compared to the more aggressive regimen dose-adjusted EPOCH-R in the front-line treatment of DLBCL, which demonstrated no difference in overall survival or event-free survival.[19] Therefore, R-CHOP has remained the standard of care for the front-line treatment of DLBCL. R-CHOP in the front-line treatment of DLBCL results in a 2-year PFS of approximately 75%, 5-year PFS of approximately 65%, 2-year OS of approximately 80%, and 5-year OS of approximately 75%.[2] Prognosis is significantly worse for certain subsets of DLBCL, as described above (section 1.1).

The individual drugs of R-CHOP are FDA approved for the treatment of non-Hodgkin lymphoma, which includes DLBCL. R-CHOP is typically given on 21-day cycles for a total of 6 cycles.[2,22] Intravenous rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), doxorubicin (50 mg/m²), and vincristine (1.4 mg/m² with maximum dose 2 mg) are all given on day 1. Prednisone (100 mg) is given orally on days 1-5. The adverse events of R-CHOP are well known given the number of years it has been used in clinical practice. Possible grade 3-4 adverse events include neutropenia, infection, febrile neutropenia, neurological toxicity, thrombocytopenia, nausea/vomiting, mucositis, and cardiac toxicity.[2]

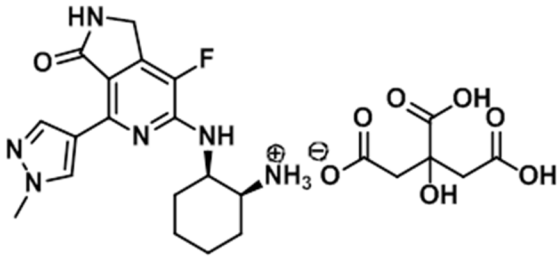
1.3 TAK-659 Background & Overview

TAK-659 is an orally (PO) bioavailable, potent and reversible inhibitor of SYK and FLT3 currently under development for the treatment of patients with advanced malignancies.

SYK is a nonreceptor protein tyrosine kinase with SH2-binding domains that bind to phosphorylated immunoreceptor tyrosine activation motifs (ITAMs) located in B and T cells and certain natural killer (NK) cells. SYK becomes activated upon ITAM binding and subsequently controls the activity of downstream signaling pathways ,eg, phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and nuclear factor kappa-B (NF-kB) that mediate diverse cellular responses, including proliferation, differentiation, and survival. The SYK pathway is implicated in hematological tumors as well as select solid tumors development (eg, Epstein-Barr virus [EBV]-mediated naso-pharyngeal tumors).

FLT3 is a receptor tyrosine kinase that plays a role in hematopoiesis. Activating mutations in tyrosine kinase genes, including FLT3, are found in approximately 30% of patients with de novo acute myelogenous leukemia (AML). Mutations in the FLT3 gene most often involve internal tandem duplication of the juxtamembrane domain coding region or point mutations of the tyrosine kinase domain, resulting in ligand-independent proliferation due to constitutive activation of the FLT3 receptor conferring poor prognosis for patients.[23,24]

Figure 1.a Chemical Structure of TAK-659



TAK-659 drug substance is a white to off-white crystalline powder. The pKa values were determined to be 0.95 (acidic) and 9.5 (basic).

1.3.1 Non-clinical Experience

1.3.1.1 Pharmacology

Nonclinical enzymatic and cell-based studies demonstrated that TAK-659 is a potent, reversible SYK and FLT3 inhibitor. TAK-659 inhibited SYK and FLT3 purified enzymes with a concentration producing 50% inhibition (IC_{50}) of 3.2 and 4.6 nM, respectively. Among a panel of kinases also inhibited by TAK-659, the IC_{50} ranged from 1.4- to 115-fold higher than those for SYK. In addition, in a study of the cellular kinase selectivity of TAK-659, the IC_{50} for TAK-659 in a cell line expressing SYK was 116 nM, which was lower than the IC_{50} for any other kinase tested in this model (about 2-fold lower than the next lowest IC_{50} for ROS).

TAK-659 inhibited the B-cell receptor (BCR) signaling pathway, as indicated by inhibition of the autophosphorylation of SYK, as well as inhibition of the phosphorylation of several downstream targets. TAK-659 potently inhibited SYK and FLT3 activities in hematopoietic malignancy-derived, cultured human cell lines, including T-cell lymphoblastoma, megakaryoblastoma, and AML, with a concentration producing half-maximal response (EC_{50}) ranging from 11 to 775 nM in sensitive cell systems. In an additional study in cultured human tumor cells treated with TAK-659, the EC_{50} ranged from 134 to >25,000 nM, with the greatest inhibitory effects observed in 2 diffuse large B-cell lymphoma (DLBCL) cell lines (OCI-Ly10 and HBL-1).

TAK-659 demonstrated significant antitumor activity after oral (PO) administration in HBL-1 (DLBCL cell line model; 120 mg/kg; $p<0.005$), PHTX-95L (primary DLBCL tumor; 30, 60, and 120 mg/kg; $p<0.001$), OCI-Ly10 (activated B-cell–like DLBCL [ABC-DLBCL] cell line model; 30, 60, and 90 mg/kg; $p<0.001$), TMD8 (DLBCL cell line model; 60 and 90 mg/kg; $p<0.001$ and 0.01, respectively), MV-4-11 (AML cell line model; 30 and 60 mg/kg; $p<0.001$), KG-1 (AML cell line model; 60 mg/kg; $p<0.001$), and PHTXM-32Ga (gastric cancer model; 60 mg/kg; $p<0.001$) mouse xenograft models. Tumor growth inhibition (TGI) correlated with markers of SYK pathway modulation in the models where it was analyzed (eg, HBL-1, PHTX-95L, and OCI-Ly10) and showed antitumor activity after TAK-659 treatment. Additionally, pharmacodynamic analysis of MV-4-11 tumors from mice treated with TAK-659 demonstrated an apparent reduction of SYK phosphorylation at tyrosine residues Y525/526 (phosphorylated SYK [pSYK] Y525/526), as well as an increase in terminal biomarker cleaved caspase-3, CC3, a critical marker of apoptosis.

In combination antitumor activity studies, treatment with TAK-659+idelalisib, TAK-659+azacytadine and TAK-659+MLN1117 was

additive and treatment with TAK-659+ibrutinib, TAK-659+bendamustine, TAK-659-venetoclax, TAK-659 + daunorubicin, and TAK-659+gemcitabine was synergistic. In a combination study of TAK-659+WX-mPD-1 (anti-programmed cell death protein 1 [PD-1]) (TAK-659 QD and WX-mPD-1 twice weekly [BIW] dosed for 3 weeks), durable TGI was observed until the last reported timepoint at Day 94. TAK-659+WX-mPD-1 demonstrated significant benefit ($p<0.001$) over TAK-659 and WX-mPD-1 single agent treatment in maintaining tumor regression. Preclinical studies show that SYK inhibition results in loss of myeloid-derived suppressor cells (MDSCs) and activation of T-cell response both in vitro and in vivo. TAK-659 in combination with anti-PD-1 therapy has shown regulation of B cells, NK cells, and macrophages in syngeneic preclinical mouse models. The combination effects in immune cells are model and context dependent, and combination activity would be greatest in tumors where SYK-mediated MDSC or B-cell immunosuppression is active. The preclinical combination treatment of TAK-659 and anti-PD-1 therapy provides therapeutic advantage over single agent treatment with durable tumor growth inhibition, maintained complete responses, and a vaccinal memory effect. This effect could be indirectly attributed to the decrease in CD11b+ MDSC or B220+ B cells in the tumor-inflitrating lymphocytes of TAK-659-treated tumors. Therefore, the addition of TAK-659 to an anti-PD-1 agent could improve tumor regression via modulation of the tumor-infiltrating immune cells and other immune cells in the tumor microenvironment[25].

1.3.1.2 Pharmacokinetics

In nonclinical species, TAK-659 has good oral bioavailability, low plasma protein binding, moderate to large volumes of distribution, and moderate to high plasma clearance. TAK-659 was relatively stable with low extent of metabolism in human liver microsomes, S9, and hepatocytes; therefore, the metabolism is expected to be low in humans. TAK-659 is a major substrate of CYP3A4/5 and P-gp; thus, there is potential for an interaction between the corresponding inhibitor and inducer drugs. TAK-659 is not anticipated to perpetrate CYP- or P-gp/BCRP-mediated interactions in the clinic.

1.3.1.3 Toxicology

The nonclinical toxicology assessment of TAK-659 supports clinical trials in patients with advanced malignancies. GLP-compliant studies were conducted in accordance with ICH S9 guidance. In summary, the TAK-659 nonclinical toxicology profile supports its use in patients with advanced malignancies on the basis of the following:

- Target organ toxicities were similar between rats and dogs, were generally monitorable and reversible, and included hematopoietic and lymphoid systems, GI mucosa, bone physis, and testicular and ovarian gametes.
- Target organs specific to the rat included reversible and monitorable effects on the lens of the eye and urothelium of bladder and kidney.
- Dose-limiting toxicity in dogs was pharmacologically mediated hematopoietic and lymphoid depletion/atrophy in dogs, and these same effects were prominent in rats; however, urolithiasis was dose limiting in a single rat.
- Based on results from in vitro Ames assays and in vitro and in vivo micronucleus evaluations, TAK-659 is considered genotoxic (mutagenic and aneugenic) with a benefit:risk ratio that is acceptable in patients with advanced cancers.

- TAK-659 was not phototoxic in hairless mice.
- TAK-659 was locally tolerated after oral gavage administration.
- On the basis of in vitro and in vivo safety pharmacology studies, TAK-659 has low potential for cardiovascular (CV), respiratory, or central nervous system (CNS) effects in patients.

Detailed information regarding the nonclinical pharmacology and toxicology of TAK-659 can be found in the Investigator's Brochure (IB).

1.3.2 Clinical Experience

TAK-659 is being evaluated in a number of indications including NHL, AML, and advanced solid tumors (including triple-negative breast cancer [TNBC], non-small cell lung cancer [NSCLC], and head and neck squamous cell carcinoma [HNSCC]). Currently there are 4 ongoing studies (C34001, C34002, C34003 and C34005). A summary of the studies is given in the table below.

Table 1. Overview of TAK-659 Clinical Studies

Protocol No.; Status	Study Objective(s)	Study Design and Population	Dose, Regimen, Route, Duration
C34001; ongoing	Primary: safety, tolerability, MTD/RP2D. Secondary: PK, pharmacodynamics, preliminary efficacy.	Open-label, multicenter, phase 1, dose escalation study of TAK-659 in adult patients with advanced solid tumors and lymphoma malignancies.	Increasing oral doses of 60 mg, 80 mg, 100 mg, and 120 mg QD were assessed during dose escalation; a RP2D of 100 mg QD is being further explored in patients with lymphoma during dose expansion.
C34002; ongoing	Primary: safety, tolerability, and MTD/RP2D in the phase 1b dose-finding portion and preliminary efficacy in the phase 2 dose expansion portion. Secondary: PK, pharmacodynamic, and differential efficacy depending on FLT3 mutation.	Open-label, multicenter, phase 1b/2, dose escalation study of TAK-659 in adult patients with relapsed or refractory AML.	Starting dose of 60 mg QD; dose has been escalated to 100 mg, 120 mg, 140 mg, and 160 mg QD and will be evaluated at 80 mg BID. Dose escalation is ongoing until MTD or RP2D is reached.
C34003; ongoing	Primary: determine MTD/RP2D of TAK-659 in combination with nivolumab and efficacy of the combination. Secondary: safety, tolerability, and efficacy of the combination; PK of TAK-659.	Open-label, multicenter, phase 1b, dose escalation and dose expansion study of TAK-659 in combination with nivolumab in adult patients with advanced solid tumors.	Starting dose of 60 mg QD; dose has been escalated to 100 mg QD. Once determined, RP2D will be used in expansion cohorts.
C34004, ongoing	Primary: efficacy. Secondary: progression-free survival and efficacy.	Open-label, single-arm, multicenter, phase 2 study of TAK-659 in adult patients with relapsed or refractory DLBCL.	100 mg QD in 28-day treatment cycles.

Protocol No.; Status	Study Objective(s)	Study Design and Population	Dose, Regimen, Route, Duration
C34005; on-going	Primary: to determine MTD/RP2D when administered with each of the combination partners. Secondary: PK of TAK-659 and preliminary efficacy with each of the combination partners.	Open-label, multicenter, phase 1b, dose escalation study of TAK-659 in combination with 1 of 5 combination partners (bendamustine, bendamustine+rituximab, gemcitabine, lenalidomide, and ibrutinib) in adult patients with NHL after at least 1 prior line of therapy.	Starting dose of 60 mg QD; dose will be escalated to 100 mg QD until MTD is reached.
C34007; ongoing	Primary: to determine safety, tolerability, and MTD/RP2D and to characterize plasma and urine PK. Secondary: to evaluate preliminary efficacy.	Open-label, multicenter, 2-part, phase 1 study in East Asian adult patients, including a dose escalation in patients with NHL and an expansion in patients with DLBCL	Starting dose of 60 mg QD; dose will be escalated to 100 mg QD and will then follow 20 mg increments until MTD and/or RP2D is reached. Expansion phase will use RP2D.
C34008 Ongoing	Primary: determine the MTD and/or RP2D of TAK-659 and venetoclax, and to evaluate safety and tolerability Secondary: PK and preliminary efficacy of TAK-659 and venetoclax	*Dose Escalation Phase:* adult patients with advanced NHL of any histology, refractory or relapsed after at least 1 prior line of therapy with no effective standard therapy available. *Safety Dose Expansion Phase:* MTD/RP2D in 2 safety expansion cohorts, advanced DLBCL and FL.	*TAK-659:* dose escalation from 60 mg in 20 mg increments and/or decrements in continuous dosing and intermittent dosing regimens. *Venetoclax:* initially with a ramp-up to a target dose of 400 mg with escalation to 800 mg or 1200 mg and/or de-escalation to a 200 mg target. Expansion phase will use MTD/RP2D of the combination
MLN1117-1003; completed	Primary safety: to determine DLT MTD/RP2D for MLN1117 when administered with each of the combination partners. Primary efficacy: to evaluate the ORR as the primary efficacy measure of MLN1117 in combination with each of the combination partners in patients with gastric or gastroesophageal adenocarcinoma	An umbrella study to evaluate MLN1117 in combination with taxanes (docetaxel or paclitaxel) and other investigational anticancer agents (including TAK-659) for the treatment of patients with previously treated advanced and metastatic gastric and gastroesophageal adenocarcinoma	Details are included in the MLN1117 Investigator's Brochure.

AML=acute myeloid leukemia, BID=twice daily, DLBCL=diffuse large B-cell lymphoma, DLT=dose limiting toxicity, MTD=maximum tolerated dose, NHL=non-Hodgkin lymphoma,

ORR=overall response rate, PK=pharmacokinetics, QD=once daily dosing, RP2D=recommended phase 2 dose.

1.3.2.1 Pharmacokinetics

Preliminary plasma PK results were available from lymphoma, solid tumor, and AML patients enrolled in the dose escalation phases of Studies C34001 and C34002. In addition, preliminary urine PK results were available from lymphoma and solid tumor patients enrolled in the dose escalation cohorts of Study C34001. TAK-659 was characterized by fast absorption (overall median T_{max} of 2 hours) in patients with hematologic and non-hematologic malignancies. Moderate variability was observed among dose-normalized steady-state AUC_{τ} values in lymphoma, solid tumor, and AML patients (coefficient of variation of 49.6%, 40.6%, and 38.8%, respectively). An approximately dose-proportional increase in steady state AUC_{τ} was observed over the 60 to 160 mg range in patients with AML. Mean accumulation ratios ranging from 1.9-fold to 2.6-fold and mean peak-to-trough ratios ranging from 3.2 to 5.7 were observed across the study populations after repeated QD dosing for 15 days. On the basis of data in lymphoma and solid tumor patients, renal clearance accounted for 30-34% of TAK-659 apparent clearance, and therefore at least 30-34% of TAK-659 systemic clearance. Active tubular secretion appeared to be the predominant component of renal clearance, based on comparison of unbound renal clearance to glomerular filtration rate. Terminal disposition half-life will be determined in a single dose PK run-in phase of the indolent NHL expansion cohort of C34001.

Additional details on TAK-659 PK are provided in the TAK-659 IB.

1.3.2.2 Drug-Drug Interactions

To date, no drug-drug interaction (DDI) studies have been conducted in humans. Because the metabolic and disposition pathways of TAK-659 remain to be fully characterized in humans in vivo, the risk of PK DDIs between TAK-659 and concomitantly administered drugs has been informed by data obtained from human in vitro systems.

In vitro studies indicate that TAK-659 is a substrate of P-gp and is metabolized by CYP3A4/5, CYP2D6, and CYP1A2, with relative contributions of 69.1% to 73.0%, 16.6% to 30.9%, and 0% to 8.40% for these respective CYPs. There is a potential risk for TAK-659 PK to be altered by drugs that are strong CYP3A inhibitors or inducers, or P-gp inhibitors or inducers. Consequently, until such potential interactions can be assessed in vivo, concomitant treatment with CYP3A strong inhibitors or inducers or with P-gp inhibitors or inducers should be avoided in clinical studies of TAK-659. Treatment with CYP3A strong inhibitors or inducers or P-gp inhibitors or inducers must be discontinued within a designated timeframe before the first dose of TAK-659 as specified in the individual study protocols.

In cell-based assays, TAK-659 was not a substrate of the efflux transporter BCRP or the uptake transporters OAT1, OAT3, OCT2, OATP1B1, or OATP1B3. Therefore, there is low predicted risk for inhibitors or inducers of these transporters to affect TAK-659 exposure.

TAK-659 was not a potent reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 in human liver microsomes at concentrations

up to 100 μM (IC_{50} values >100 μM), nor a time-dependent inhibitor of these same CYPs at concentrations up to 50 μM. In addition, TAK-659 was not an inducer of CYP1A2, 2B6, or 3A activity or mRNA expression levels in human hepatocytes at concentrations up to 50 μM. Furthermore, TAK-659 was not an inhibitor of the efflux transporters P-gp or BCRP in Caco-2 cells at concentrations up to 100 μM. When these in vitro findings are viewed in context of the C_{max} observed at doses up to 120 mg QD in patients with lymphoma or solid tumors or at doses up to 160 mg QD in patients with AML, there is low predicted risk for TAK-659 to cause DDIs via induction or inhibition of CYP enzymes, P-gp, or BCRP.

1.3.2.3 Drug-Food Interactions

To date, the effect of food on the PK of TAK-659 has not been characterized in humans. Accordingly, TAK-659 should be administered on an empty stomach, at least 1 hour before and no sooner than 2 hours after food and beverages except water.

Because grapefruit juice is considered a strong CYP3A inhibitor, there is a potential risk for TAK-659 PK to be altered by grapefruit-containing food and beverages. Accordingly, consumption of grapefruit-containing food and beverages is prohibited during clinical studies of TAK-659.

1.3.2.4 Clinical Pharmacodynamics

Plasma inhibitory activity assays have been performed on plasma samples from a number of patients in the Study C34002 to examine TAK-659 activity on FLT3 signaling pathways levels. Up to 70% inhibition of FLT-3 phosphorylation was observed in samples from patients in the 60 and 100 mg cohorts and ≥90% inhibition in patients in the 120 mg cohort as of the date of data cutoff.

1.3.2.5 Clinical Efficacy

As of the 22 October 2016 datacut, there were 58 response-evaluable patients in Study C34001. Response data were available for 57 patients at the time of the data cut.

Among response-evaluable patients with DLBCL with available data, best responses of CR and PR were reported for 8 patients and 4 patients, respectively. Of the 12 patients with DLBCL who responded, 2 had transitioned to stem cell transplant prior to the data cutoff and 6 were still receiving study drug as of the data cutoff; 1 patient has been on study for 19 cycles and another patient for 29 cycles. Seven patients had a best response of stable disease (SD), and 22 patients experienced progressive disease (PD). No response-evaluable patients with solid tumors had a best response of CR or partial response (PR). One patient had a best response of SD, and the remaining 9 patients experienced PD. Among the 2 response-evaluable patients with CLL, 1 had PR and was on study in Cycle 4 as of the data cutoff and 1 had SD. Four patients with indolent lymphomas responded to treatment with TAK-659. One patient with mucosa-associated lymphoid tissue lymphoma achieved a CR and is still on study in Cycle 10 as of the data cutoff, 3 patients with FL achieved PR, and 1 patient had SD. One of the FL responders remains on study in Cycle 22 as of data cutoff.

1.3.3 Summary of Safety

As of 22 October 2018, 338 patients have been dosed with TAK-659, including 143 patients in the Study C34001, 43 patients in Study C34002, 41 patients in Study C34003, 49 patients in Study C34004, 41 patients in C34005, 10 patients in Study C34007, and 11 patients in C34008. TEAEs, from the 22 October 2018 analysis of TAK-659 single agent studies (C34001, C34002, C34004, and C34007) and TAK-659 combination studies (C34003, C34005, and C34008), were generally as expected on the basis of nonclinical toxicology findings of TAK-659 and the patient population being studied. Overall, 244 (99.6%) of 245 patients in the TAK-659 single agent studies and all 93 patients in the TAK-659 combination studies experienced ≥1 TEAE. The most common TEAEs reported (□30% of patients) in these single agent studies and combination studies (N=93) have been AST increased (49% and 40%), pyrexia (46% and 49%), amylase increased (36% and 28%), fatigue (34% and 39%), anemia (34% each), diarrhea (33% and 34%), blood creatine phosphokinase increased (26% and 33%), lipase increased (30% and 26%), and hypophosphatemia (30% and 32%).

Overall, Grade ≥3 TEAEs occurred in 91% (222 of 245) of patients in the single agent studies and 84% (78 of 93) of patients in the combination studies. The most common Grade 3 or greater TEAEs (≥10% of patients) in the single agent studies and the combination studies have been amylase increased (20% and 10%), anemia (20% and 25%), hypophosphatemia (18% and 26%), lipase increased (16% and 11%), neutropenia (16% and 23%), febrile neutropenia (15% and 6%), blood creatine phosphokinase increased (11% and 15%), thrombocytopenia (11% and 13%), fatigue (5% and 11%), AST increased (10% and 8%), and pneumonia (10% and 4%). Overall, SAEs occurred in 76% (186 of 245) patients in the single agent studies and 50% (60 of 93) patients in the combination agent studies. The most treatment common treatment-emergent SAEs in the single agent and combination studies were pyrexia (14% each), febrile neutropenia (12% and 8%), pneumonia (11% and 4%), and febrile neutropenia (12% and 8%). As of 22 October 2018, there have been 85 deaths: 45 patients in Study C34001, 25 patients in Study C34002, 7 patients in Study C34003, 4 patients in C34004, and 8 patients in Study C34005. No deaths have been reported in Studies C34007 and C34008. Most causes of death were considered related to the disease under study or complications thereof and were not considered related to study treatment.

1.3.3.1 Potential Risks Based on TAK-659 Clinical Studies

Identified Risks
Infection
Infections, including pneumonia, *P jirovecii* pneumonia, CMV, and sepsis are an important identified risk for subjects receiving TAK-659 treatment. In single agent TAK-659 studies (C34001, C34002, C34004, and C34007), most patients (63%) experienced at least 1 TEAE of any grade classified under the infections and infestations SOC as defined by the MedDRA. Pneumonia was the most frequently reported TEAE (16%), followed by CMV infection (11%). Pneumonia (10%), and sepsis (6%) were the most frequently reported Grade ≥3 TEAEs. In TAK-659 combination studies (C34003, C34005, and C34008), 54% (50 of 93 patients) experienced at least 1 TEAE of any grade classified under the infections and infestations SOC as defined by the MedDRA. Pneumonia

and oral candidiasis were the most frequently reported TEAEs (9% each), followed by urinary tract infection (8%). Pneumonia (4%)was the only reported Grade ≥3 TEAE. The majority of the CMV infections were reactivations.
Investigators are advised to closely monitor patients for infections throughout TAK-659 treatment. Patients should be advised to report fever and should be assessed for further management as per standard medical practice. Recommendations regarding monitoring and use of anti-infective prophylaxis are included in each study-specific protocol.

Pneumonitis
Pneumonitis has been added as a potential risk of TAK-659. There were 3 SAEs of pneumonitis, all reported in Study C34001 and considered by the investigator to be related to study treatment. The first patient developed pneumonitis 46 days after starting treatment with TAK-659 at 80 mg QD. The event of pneumonitis was considered related to TAK-659 treatment. It was determined to be an unanticipated problem and was reported to health authorities. Pneumonitis was added as a potential risk of TAK-659, safety letters were sent to the study sites, and the drug safety information in ICFs was updated. The event was the first SAE of pneumonitis in the TAK-659 program. Subsequently, 2 new SAE cases of pneumonitis have been reported during the current reporting period; 1 patient with DLBCL who experienced pneumonitis 34 days after starting and 10 days after discontinuation of treatment with TAK-659 at a dose of 100 mg QD and another patient with CLL who experienced pneumonitis 3 months after starting TAK-659 at a dose of 100 mg QD. Pneumonitis has been reported in clinical experiences of other BCR pathway kinase inhibitors. No other safety signals or changes to the known benefit-risk profile of TAK-659 in relation to the additional cases of pneumonitis were identified from review of these SAEs. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies

Lipase Elevations
Asymptomatic elevation in lipase is an important potential risk of TAK-659. In nonclinical studies, lipase was sporadically elevated at high doses of TAK-659 in both rats and dogs; however, there was no evidence of microscopic organ damage. A TEAE of lipase increased was reported in 16% (any Grade) and 14% (Grade ≥3) of subjects treated with TAK-659. Theselipase elevations were generally asymptomatic. There was 1 SAE of pancreatitis reported in the safety database in subjects treated with TAK-659. Monitoring of serum lipase should be performed according to the study protocol.

Lymphoid and Hematopoietic Effects
Lymphoid and hematopoietic effects are an important potential risk for subjects receiving TAK-659 treatment. Neutropenia (any Grade) was reported in 20% of subjects treated with TAK-659 as a single agent and in combination; Grade ≥3 neutropenia in 18%, and febrile neutropenia (any Grade) in 13% of subjects treated. Neutropenia is commonly observed in hematologic malignancies and this may provide alternative

causality. Neutropenia management guidelines are provided in study protocols. Granulocyte colony stimulating factors can be used for supportive measures; guidance for their use is per routine local oncology practice, as well as protocol-specific.

1.3.3.2 Potential Risks and Benefits based on non-clinical studies

Potential risks identified from nonclinical studies in dogs and rats include:

- Lymphoid and hematopoietic effects that include lymphoid depletion and myelosuppression that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased susceptibility to infection, bleeding, and/or anemia.
- Epithelial effects on the intestinal tract, urinary tract, and lens.
- Intestinal effects included minimal-to-slight mucosal hemorrhaging.
- Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis that led to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.
- Reproductive system effects, including decreased spermatozoa and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries.
- Possible mutation of the deoxyribonucleic acid (DNA).
- ≥1.07-μM TAK-659 can inhibit ADP- and collagen-mediated human platelet aggregation in the context of this in vitro study.
- Growth plate thickening and disorganization (not relevant to adults).
- Risks listed above are based on toxicology findings in the nonclinical studies with TAK-659; they may or may not present with similar severity in humans. All of the identified nonclinical target organ toxicities were generally reversible and are anticipated to be manageable with clinical monitoring and intervention. Clinical study protocols for TAK-659 will include regular monitoring for the potential AEs specified for this compound using routine laboratory evaluations, urinalysis, physical examinations, disease assessment, and eye exams. The timing of these tests and evaluations will be detailed in the protocol Schedules of Events. Additional tests and evaluations will be symptom- and finding-guided based on the standard of care. It is possible that administration of TAK-659 will result in toxicities that were not observed or predicted from the studies completed in rats and dogs.

Lymphoid and Hematopoietic Effects

Lymphoid and hematopoietic effects were observed in animals. Lymphoid and hematopoietic depletion consisted of depletion of bone marrow hematopoietic precursors and decreased lymphocytes in lymphoid tissues. There were correlative decreases in circulating lymphocytes, eosinophils, neutrophils, and reticulocytes, along with decreases in thymic and splenic weights. These effects were dose dependent, pharmacologically mediated, and generally reversible.

Intestinal, Renal, and Lens Epithelial Effects and Related Epithelial Effects

In rats, the primary epithelial effects were lens epithelium disorganization/hyperplasia and renal and urinary bladder transitional epithelium hyperplasia. Other effects on epithelial tissues included

stomach glandular mucosa hemorrhage, cecum crypt necrosis, lacrimal gland atrophy/necrosis, and mammary gland and skin hair bulb single-cell atrophy/necrosis. Increases in serum amylase, lipase, magnesium, urea, and creatinine, along with sporadic hematuria and proteinuria, were considered a result of the renal lesions and, to a lesser extent, reflective of subclinical dehydration. The lens hyperplasia had some single-cell necrosis and correlated with slight axial subcapsular anterior cortical lens opacity. All the epithelial effects in rats were reversed by the end of the 28-day recovery period, with the possible exception of lens opacity (which, mechanistically, is expected to be reversible).

In dogs, the primary epithelial effect was on the intestine and included minimal to slight hemorrhage of the intestinal mucosa (ileum, cecum, and/or colon). There were also coccidia (parasite) in the ileum and/or cecum, and their presence was considered secondary to the observed intestinal lymphoid depletion and associated decreased immunity. Increased incidence of liquid/soft feces was observed and was consistent with intestinal changes. All intestinal effects were reversed by the end of the 28-day recovery period.

During the clinical studies, patients will receive eye exams to monitor for any changes to the eye lens; effects on other epithelial tissues will be monitored via routine laboratory tests, urinalysis, physical examinations, and adverse event (AE) monitoring as detailed in the protocol.

Reproductive Effects
Effects on the reproductive systems included testicular seminiferous epithelium degeneration and decreased spermatozoa in the epididymides with correlative decreased mean testicular weights in male rats and dogs and minimally increased corpora luteal necrosis in female rats. The reproductive effects are expected to be reversible.

Skeletal Effects
Effects on the growth plate and related structures were observed in animals. The effects were dose dependent, pharmacologically mediated, and reversible and included thickening/disorganization of the physis (femur and sternum) and articular-epiphyseal junction, and retention/disorganization of the primary spongiosa. Additionally, the effects on the growth plate would not be relevant to adult patients whose bone growth plate is closed.

Genotoxicity
TAK-659 was mutagenic in an Ames assay (*S typhimurium* TA1537) after metabolic activation with rat liver enzymes and was aneugenic in micronucleus evaluations. Increased micronucleus formation in human peripheral blood lymphocytes was primarily associated with positive kinetochore staining and, thus, was positive for aneugenic genotoxicity. Spleen tyrosine kinase has been implicated in mitotic spindle function (20); therefore, the aneugenic effect of TAK-659 was consistent with its pharmacologic mechanism of action. Based on the genotoxic nature of TAK-659, its toxicity profile would be acceptable for patients with advanced malignancies.

1.4 Rationale for the Current Study

The prognosis and outcomes of high-risk subsets of DLBCL treated with standard R-CHOP are not acceptable and require significant improvement with novel therapies (see section 1.1). There is increased expression of B cell receptor (BCR) signaling components among the molecularly characterized BCR/proliferation subtype of DLBCL, including but not limited to spleen tyrosine kinase (SYK), a non-receptor cytoplasmic tyrosine kinase.[28] SYK plays a critical role in BCR signaling-driven tumorigenesis. TAK-659 (Takeda Pharmaceutical Company Limited) is a selective, reversible, and potent inhibitor of SYK. With the hypothesis that TAK-659 may generate pronounced antitumor effects in lymphomas including DLBCL, it is being clinically investigated in early phase clinical trials. Updated results of a phase 1, dose-escalation with expansion cohorts study of single agent TAK-659 in mostly relapsed/refractory lymphoma patients was recently presented at the International Conference on Malignant Lymphoma in Lugano, Switzerland in June 2017.[10] The maximum tolerated dose (MTD) has been determined to be 100 mg by mouth once daily. 65 patients with relapsed/refractory DLBCL have been treated on study with single agent TAK-659. Encouraging clinical responses have been seen in these heavily pretreated DLBCL patients with 12 of 45 (27%) achieving an objective response. 8 of 45 patients (18%) have obtained a complete response, and most of these have been durable at time of last follow-up. These responses have been seen in both the ABC/non-GCB and GCB DLBCL subtypes. Of the drug-related serious adverse events seen with TAK-659, there does not appear to be a significant overlapping toxicity profile with that of standard chemotherapy regimens such as R-CHOP.

Pre-clinical mouse models have demonstrated an anti-tumor vaccinal memory effect in mice previously treated with TAK-659 with concurrent anti-PD-1 therapy.[29] When these mice with syngeneic tumors are treated with TAK-659 with or without concurrent anti-PD-1 therapy, some mice achieve objective responses including complete responses. The mice that remain alive in complete remission after 90 days in the combination group are re-inoculated with the same tumor cells. The majority of these mice maintained an inhibitory tumor growth response with no tumor formation, suggesting an anti-tumor vaccinal memory effect of TAK-659 with concurrent anti-PD-1 therapy.

Based on these results, including TAK-659 in front-line therapy may potentially lead to higher response rates and more durable remissions. Therefore, it is worthwhile investigating TAK-659 in combination with R-CHOP in this area of need in the front-line treatment of high-risk DLBCL. We hypothesize that the administration of TAK-659 in combination with R-CHOP to patients with high-risk DLBCL in the front-line setting will have an acceptable toxicity profile and lead to improved durable responses and outcomes. TAK-659's MTD as a single agent has been determined to be 100 mg daily, however, the MTD may be different when combined concurrently with R-CHOP. Therefore, a dose escalation of TAK-659 is necessary in combining with the standard dosing of R-CHOP.

1.5 Exploratory Studies

Pharmacokinetics of the novel combination of TAK-659 and R-CHOP will be explored.

2.0 OBJECTIVES

2.1 Primary Objective & Endpoint

To determine the safety, tolerability, and maximum tolerated dose of TAK-659 when combined with R-CHOP in the front-line treatment of high-risk DLBCL

Toxicity and tolerability will be assessed by history and physical, including vital signs and ECOG performance status, and laboratory values to determine incidence and grade of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities, as defined by the NCI CTCAE v5.0. Maximum tolerated dose will be evaluated using a 3+3 dose escalation method. Patients will be evaluated for dose-limiting toxicities (DLT's) during the second cycle (21 days) of combination treatment. Dose escalations will be followed as described in section 4.3.

2.2 Secondary Objectives & Endpoints

To assess preliminary efficacy of TAK-659 combined with R-CHOP in the front-line treatment of high-risk DLBCL

:

2.2.1 Overall response rate (ORR), using Lugano criteria (2014), will be defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) as assessed by the investigators.This will be assessed at 3 months.

2.2.2 Progression free survival (PFS) will defined as the time from study enrollment until progression/recurrence of lymphoma or death from any cause. This will be assessed at 12 and 18 months.

2.2.3 Overall survival (OS) will be defined as the time from study enrollment until death from any cause. This will be assessed at 12 and 18 months.

2.3 Exploratory Objectives

To characterize the PK of TAK-659 in combination with R-CHOP.

Endpoint: Summary statistics of maximum (peak) plasma concentration (C_{max}), first time to reach maximum (peak) plasma concentration (T_{max}), area under the plasma concentration versus time curve (AUC), and terminal disposition half-life ($t_{1/2}$) by cohort and day.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with previously untreated high-risk diffuse large B-cell lymphoma (DLBCL). This trial will be conducted at Northwestern University.

A total of 12-18 evaluable subjects will be needed for this trial. Approximately 3 potentially eligible patients are seen per month, and it is anticipated that at least 1 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Reem Karmali, at (312) 695-0990.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a pathologically confirmed diagnosis of DLBCL (including DLBCL NOS, DLBCL GCB type, DLBCL ABC/non-GCB type, T-cell/histiocyte-rich large B cell lymphoma, high-grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, and high-grade B cell lymphoma NOS).
NOTE: DLBCL transformed from low-grade lymphoma among treatment-naïve patients or patients previously treated with a non-anthracycline containing regimen are permitted.

3.1.2 Patients may have completed the first cycle of R-CHOP (off study not combined with TAK-659) ≤ 30 days prior to the first dose of TAK-659 or plan to receive the first cycle of R-CHOP after registration.

3.1.3 Patients must have at least one high-risk feature, including:

- ABC/non-GCB subtype determined by gene expression profiling or Hans algorithm by immunohistochemistry per treating institution standards,
- high-intermediate or high-risk group by NCCN-IPI with score ≥4, at time of diagnosis,
- MYC gene rearrangement (by FISH),
- MYC overexpression by IHC (≥40%) and BLC2 overexpression by IHC (≥50%),
- DLBCL transformed from low-grade lymphoma among treatment-naïve patients or previously treated transformed low-grade lymphoma with prior treatment not including an anthracycline.

NOTE: BCL2 and/or BCL6 aberrancy are not required for enrollment, but assessment for rearrangement by FISH and overexpression by IHC are required if there is presence of MYC rearranged by FISH.

3.1.4 Patients must have measurable disease (defined as ≥1.5 cm in diameter) with correlated FDG-avidity on PET scan

3.1.5 Patients must have recovered (i.e., ≤ Grade 1 toxicity) from the reversible effects of prior anticancer therapy, if applicable.

3.1.6 Patients must be age ≥ 18 years with a life expectancy of greater than 3 months.

3.1.7 Patients must exhibit an ECOG performance status of 0-2.

3.1.8 Patients must have adequate organ and bone marrow function within 14 days prior to registration, as defined below:

Bone Marrow Reserve**:	
absolute neutrophil count	≥ 1,000/mcL
platelets	≥ 75,000/mcl (NOTE: Patients with bone marrow involvement may be eligible with platelets ≥50,000)
hemoglobin	≥ 8 g/dL
NOTE: RBC and platelet transfusion allowed ≥14 days prior to registration. *Note: Cytopenias felt to be disease related will not be excluded from the trial.*	
Hepatic	
total bilirubin	≤ 1.5x institutional upper limit of normal (ULN)
AST(SGOT)/ALT (SGPT)	≤ 2.5 X institutional ULN
Renal	
Creatinine clearance	≥ 60 mL/min either as estimated by the Cockcroft-Gault equation (See Appendix B)
Lipase ≤1.5 x ULN and amylase ≤1.5xULN with no clinical symptoms suggestive of pancreatitis or cholecystitis	

3.1.9 Patients must have blood pressure ≤Grade 1.
NOTE: Hypertensive patients are permitted if their blood pressure is controlled to ≤Grade 1 by hypertensive medications. The actual blood pressure value ONLY will be assessed/graded using the CTCAE v5 hypertension criteria.

3.1.10 Patients must meet criteria for appropriate contraception, listed as follows.
Female patients must meet at least one of the following criteria:

- Are postmenopausal with last menstrual period at least 1 year before registration OR
- Are surgically sterile, OR
- If they are of childbearing potential,
  - Agree to practice 1 highly effective method of contraception and one additional effective (barrier) method at the same time, from the time of signing the informed consent through 180 *days* after the last dose of study drug, or
  - Agree to practice true abstinence, when is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.
  - Agree not to donate eggs (ova) during the course of this study or 180 days after receiving their last dose of study drug.

Male patients, even if surgically sterilized (i.e., status post-vasectomy), must:

- Agree to practice effective barrier contraception during the entire study treatment period and through *180 days* after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] and withdrawal

are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Agree not to donate sperm during the course of this study or within 180 days after receiving their last dose of study drug.

3.1.10 FOCBP must have a negative pregnancy test ≤7 days prior to registration on study.

3.1.11 Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3.1.12 Patients must have the ability to swallow oral medication.

3.1.13 Patients must be willing and able to complete study-required procedures.

3.2 Exclusion Criteria

3.2.1 Patients with exposure to chemotherapy or immunotherapy ≤ 30 days prior to starting study treatment are not eligible.
NOTE EXCEPTION: Patients may receive a bridge of rituximab or steroids prior to C1 of R-CHOP. Additionally, patients can receive their first cycle of R-CHOP prior to enrolment on trial (off study).

NOTE: If patient is registered prior to completion of washout, start date of treatment will need to be confirmed prior to registration. Please see assigned QAM with questions.

3.2.2 Patients with prior exposure to a SYK inhibitor are not eligible.
NOTE: Examples of SYK inhibitors include fostamatinib (R788), entospletinib (GS-9973), cerdulatinib (PRT062070), and TAK-659[30].

3.2.3 Patients with untreated brain metastases or leptomeningeal metastases are not eligible.

3.2.4 Patients with known hypersensitivity (e.g. anaphylactic and anaphylactoid reactions) to TAK-659 or components of R-CHOP are not eligible.

3.2.5 Patients with history of drug-induced pneumonitis requiring treatment with steroids; history of idiopathic pulmonary fibrosis, organizing pneumonia, or evidence of active pneumonitis on screening imaging are not eligible

NOTE: A history of radiation pneumonitis in the radiation field (fibrosis) is permitted

3.2.6 Patients with known hepatitis B surface antigen positive, or known or suspected active hepatitis C infection are not eligible.

3.2.7 Patients who are known to be human immunodeficiency virus (HIV) positive are not eligible.

3.2.8 Patients must not have had autologous stem cell transplant within 6 months prior to registration.

3.2.9 Patients must have not had allogeneic stem cell transplant at any time.

3.2.10 Patients who have received systemic anticancer treatment (including investigational agents) or radiotherapy less than 3 weeks before the first dose of study treatment (≤ 5 times half-life for large molecule agents or ≤4 weeks with evidence of disease progression if 5 times half-life is > 4 weeks) are not eligible.

NOTE EXCEPTION: This does not apply to C1 dosing of R-CHOP: it is expected that all patients will receive R-CHOP for C1 either on or off study. Patients will also be allowed to receive rituximab and/or steroids as a bridge prior to C1 of R-CHOP as an exception as outlined in Section 3.2.1.

NOTE: If patient is registered prior to completion of washout, start date of treatment will need to be confirmed prior to registration. Please see assigned QAM with questions.

3.2.11 Use or consumption of the following substances is not permitted:

- Medications or supplements that are known to be inhibitors of P-gp and/or strong reversible inhibitors of CYP3A within 5 times the inhibitor half-life (if a reasonable half-life estimate is known), or within 7 days (if a reasonable half-life estimate is unknown), before the first dose of study drug. The use of these agents is not permitted during the study.
- Medications or supplements that are known to be strong CYP3A mechanism-based inhibitors or strong CYP3A inducers and/or P-gp inducers within 7 days, or within 5 times the inhibitor or inducer half-life (whichever is longer), before the first dose of study drug. The use of these agents is not permitted during the study.
- Grapefruit-containing food or beverages within 5 days before the first dose of study drug. Note that grapefruit-containing food and beverages are prohibited during the study.

3.2.12 Patients who have major surgery, per PI discretion, ≤ 14 days before the first dose of study drug and those who have not recovered fully from any complications from surgery are not eligible.

3.2.13 Patients who have systemic infection requiring parenteral antibiotic therapy or other serious infection (bacterial, fungal or viral) ≤ 21 days before the first dose of study drug are not eligible.
NOTE: Patients who are at substantial risk of developing an infection may receive prophylaxis at the start of study treatment per investigator's discretion.

3.2.14 Patients with an active secondary malignancy that requires treatment are not eligible.
NOTE EXCEPTION: Patients with low grade active malignancies such as prostate cancer, non-melanoma skin cancer or carcinoma in situ of any type, which do not need treatment, are not excluded, Similarly, patients with a history of inactive breast cancer on hormone therapy are not excluded.

3.2.15 Patients with known GI disease or GI procedure that could interfere with the oral absorption or tolerance of TAK-659 [per PI discretion] are not eligible (this may include difficulty swallowing tablets or diarrhea >Grade 1 despite supportive therapy).

3.2.15 Patients who have known CNS lymphomatous involvement are not eligible.

3.2.16 Patients who have an uncontrolled intercurrent illness, in the opinion of the investigator, including, but not limited to any of the following, are not eligible:

- Uncontrolled pulmonary disease
- Active CNS disease that would interfere with study participation
- Active infection requiring parenteral systemic treatment
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.17 Patients with any of the following cardiovascular conditions are excluded:

- Acute myocardial infarction within 6 months before starting study drug.
- Current or history of New York Heart Association Class III or IV heart failure (see Appendix C).
- Evidence of current, uncontrolled cardiovascular conditions including cardiac arrhythmias, hypertension, angina, pulmonary hypertension, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Friderichia corrected QT interval (QTcF) >450 milliseconds (msec) (men) or >475 msec (women) on a 12-lead ECG during the Screening period.
- Abnormalities on 12-lead ECG including, but not limited to, changes in rhythm and intervals that, in the opinion of the investigator, are considered to be clinically significant.
- Abnormal left ventricular function (EF < 50%, as indicated by baseline ECHO).

3.2.18 Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of TAK-659.

4.0 TREATMENT PLAN

4.1 Overview

Patients will receive the R-CHOP regimen for a total of six 21-day cycles. Starting with Cycle 2, patients will initiate combination treatment with oral TAK-659 once daily for a total of five 21-day cycles. All patients will receive one cycle of R-CHOP before initiating TAK-659. The first R-CHOP cycle may be received on-study (after completing screening procedures and registering to the study), OR prior to study registration. If a patient has already completed one cycle of R-CHOP, they must register and begin treatment with TAK-659 within 30 days after initiating the R-CHOP regimen. The off-study R-CHOP regimen will be referred to as “Cycle 1”, and study treatment will then begin on “Cycle 2 Day 1” with TAK-659 given in combination with R-CHOP.

Table 4.1: Treatment Administration Summary

Agent	Dose	Route	Schedule		Cycle Length
TAK-659	60 mg - 100 mg[1]	PO	once daily continuously for 5 cycles (Cycle 2-6)		3 weeks (21 days)
R-CHOP[2]					
Rituximab[3]	375 mg/m^2	IV	Day 1	For 6 cycles (Cycle 1-6; C1 may take place before[4] or after registration)	3 weeks (21 days)
Cyclophosphamide	750 mg/m^2	IV	Day 1		
Doxorubicin	50 mg/m^2	IV	Day 1		
Vincristine	1.4 mg/m^2 (Maximum dose:2 mg) in NS 50 mL administered IV over 10 mins	IV	Day 1		
Prednisone[5]	100 mg [Two 50mg tablets once daily]	PO	Days 1-5 (or Days 2-6)		

[1] Patients will undergo a 3+3 dose escalation of TAK-659 as detailed in section 4.3. The starting dose will be 60 mg with subsequent dose levels at 80 mg and 100 mg. In the event that the starting dose is determined to be too toxic, a dose level -1 has been included at 40 mg. On days with combination treatment, TAK-659 should be given before starting R-CHOP administration with consideration for pre-medications and TAK-659 PK’s.

[2] Investigator may choose to administer G-CSF (filgrastim/tbo-filgrastim or pegfilgrastim) with Cycle 1 per standard ASCO guidelines. It is also highly recommended for Cycle 2-6 (combination therapy).

[3] Acetaminophen 650 mg PO and diphenhydramine 50-100 mg IV or PO 30-60 minutes prior to rituximab. Permitted to give corticosteroids prior to rituximab (up to 10 mg prednisone equivalent), in addition to the scheduled prednisone as part of R-CHOP, as per the discretion of the investigator.

[4] If R-CHOP is administered off-study prior to registration, TAK-659 treatment must begin ≤30 days after initiating R-CHOP.

[5] On any clinic day (for study treatment), patients should NOT take prednisone before coming to clinic, but should hold and bring the prednisone tablets to clinic.

4.2 Treatment Administration

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's lymphoma.

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

4.2.1 TAK-659

TAK-659 should be taken on an empty stomach at least 1 hour before and no sooner than 2 hours after ingestion of food and/or beverages other than water. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed doses of TAK-659. Patients must swallow the tablets whole; the tablets must not be chewed, crushed, or manipulated in any way before swallowing.

Patients should be instructed to take their study medication at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient fails to take TAK-659 one day, or if a patient does not take TAK-659 at their scheduled dosing time (± 6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments to account for the missed dose on subsequent days, for example, by taking a double dose of study drug(s) on the following day. Patients should record any skipped doses in their dosing diary (and resume dosing at the next scheduled time with the prescribed dosage).

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after TAK-659 ingestion, patients should not re-dose following emesis and should record the time of the emesis in their dosing diary. Patients should resume dosing at the next scheduled time with the prescribed dosage.

Unless otherwise specified, on clinic visit days, patients should be instructed to hold their dose until pre-dose assessments are performed in the clinic. PK blood samples will also be obtained during Cycle 2 as specified in section 5.0. Every effort will be made to obtain PK sampling as outlined. However, if samples cannot be obtained due to patient factors such as poor venous access, deferring PK sampling would be acceptable. On days with combination treatment, TAK-659 will be given before starting R-CHOP administration.

4.2.2 R-CHOP

R-CHOP will be administered per standard of care guidelines over 21-day cycles as detailed below. If the first cycle of R-CHOP is given off-study, dosing details may vary from those detailed below per institutional practice. Starting with Cycle 2, ANC must be ≥ 1,000 cells/mm^3 to begin the cycle. Delay cycle up to 2 weeks if these values are not met on Day 1 of the cycle. Contact the Principal Investigator and QAM if delay is greater than 2 weeks. Other dosing modifications and delays may be necessary according to section 4.4.2.

- Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone are all commercially available, FDA approved medications and will be given as standard of care.
- Rituximab 375 mg/m^2 IV infusion on Day 1 prior to CHOP chemotherapy. Dose rate titration per standard of care, defer to investigator.
- Cyclophosphamide 750 mg/m^2 IV Day 1
- Doxorubicin 50 mg/m^2 IV Day 1

- Vincristine 1.4 mg/m^2 (Maximum dose: 2 mg) in NS 50 mL administered IV over 10 mins on Day 1
- Prednisone 100 mg PO daily on Days 1-5 (or Days 2-6)
  - Patients will record oral prednisone dosing in their dosing diary to monitor compliance
  - On any clinic day (for study treatment), patients should NOT take prednisone before coming to clinic, but should hold and bring the prednisone tablets to clinic.

- G-CSF (filgrastim, tbo-filgrastim or pegfilgrastim) may also be administered prophylactically starting with Cycle 1 of R-CHOP at the investigator's discretion per standard ASCO guidelines. **It is also highly recommended for Cycle 2-6 (combination therapy).**

4.2.2.1 Pre-medications

- Oral pre-medication 650 mg of acetaminophen and 50-100 mg diphenhydramine hydrochloride IV or PO will be administered 30 to 60 minutes prior to starting each infusion of rituximab.
- All patients should receive hydration with 1 liter normal saline at 300-500 cc/hr with half administered before and half administered after cyclophosphamide.
- Patients who experience infusion reactions to rituximab should receive pre-medications per institutional guidelines

4.2.2.2 Rituximab

Rituximab will be administered intravenously at 375 mg/m^2 on day 1 of each cycle of R-CHOP, immediately prior to the start of chemotherapy (NOTE: Patients may receive subcutaneous rituximab as clinically indicated per institutional guidelines). The first rituximab infusion will be given with cycle 1 of R-CHOP without TAK-659 and should be infused a rates per standard of care, as per investigator discretion. For example, the first rituximab infusion could be started at 50 mg/hr, and increased in 50-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If this rate of escalation is well tolerated the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

4.2.2.3 Cyclophosphamide

Cyclophosphamide will be administered intravenously at 750 mg/m^2 on Day 1 of R-CHOP, per standard of care. The total dose of cyclophosphamide will be administered by IV. All patients should receive hydration with 1 liter normal saline at 300-500 cc/hr with half administered before and half administered after cyclophosphamide.

4.2.2.4 Doxorubicin HCl

Doxorubicin will be administered intravenously at 50 mg/m^2 on Day 1 of R-CHOP, per standard of care. Doxorubicin is administered intravenously over 3-5 minutes. Avoid extravasation, as severe local tissue necrosis may result. If patient has been treated with prior doxorubicin, manage risk for cardiomyopathy per standard practice.

4.2.2.5 Vincristine Sulfate

Vincristine will be administered intravenously at 1.4 mg/m^2 (Maximum dose: 2 mg) in NS 50 mL administered IV over 10 mins on Day 1 of R-

CHOP, per standard of care. Administer without further dilution by slow IV push. Precaution: Maximum single dose is 2 mg.

4.2.2.6 Prednisone

100 mg PO daily [2 tablets once daily] on Days 1-5. Prednisone may also be given from days 2-6 instead of Days 1-5. Patients will take oral prednisone as indicated by standard of care guidance. They will maintain a drug diary (along with oral TAK-659 doses) to monitor compliance of prednisone dosing.
Please note: On any clinic day (for study treatment), patients should NOT take prednisone before coming to clinic, but should hold and bring the prednisone tablets to clinic.

4.2.3 CNS Prophylaxis and Treatment

CNS prophylaxis with intrathecal methotrexate, intrathecal steroids and/or intrathecal cytarabine is permitted, timing and dosing at the discretion of the investigator. CNS prophylaxis with high-dose intravenous methotrexate and/or intravenous cytarabine is not permitted during the six cycles of treatment. CNS prophylaxis with high-dose intravenous methotrexate is permitted, however, if given after the completion of cycle 6. Specifically, IV HD-MTX for up to 6 doses is allowable 3 weeks after the completion of 6 cycles of TAK-659-R-CHOP. Dosing and schedule of HD-MTX is up to the discretion of the treating physician and should be carried out per institutional guidelines.

If during the trial, the CSF becomes cytologically positive indicative of CNS lymphomatous involvement, he or she must be removed from study treatment.

4.3 Phase I Dose Escalation Scheme

Patients will be enrolled to dose level 1 initially (TAK-659 60 mg). Dose escalation will proceed up to 80mg for dose level 2, and 100 mg for level 3. The table below summarizes the dose levels. A dose level -1 is included in the event that level 1 is determined to be too toxic.

Table 4.2: Dose Escalation Scheme

Dose Level	TAK-659	# of Patients^
Level -1	40 mg	3-6
Level 1*	60 mg	3-6
Level 2	80 mg	3-6
Level 3	100 mg	3-6

*Starting dose level
^A minimum of 3 patients will be treated per cohort; a total of 6 patients should be treated at whichever dose level is determined to be the MTD.

A standard “3+3” dose escalation design will be utilized. Initially, 3 patients will be enrolled at the starting dose (level 1), after which enrollment will be temporarily suspended until all 3 patients complete the DLT evaluation period (defined as cycle 2 of the study [the first 21-day cycle of TAK-659]).). Once all 3 patients complete the DLT period and toxicity data has been submitted, the Data and Safety Monitoring Committee (DSMC) will review the data and confirm the presence or absence of any DLTs (defined below). The following rules will be used at each dose level to determine whether or not to proceed to the next dose level:

- If 0 of 3 patients at a given dose level experience a DLT (defined below), then escalation will proceed to the next dose level.

- If 2 or 3 of 3 patients at a given dose level experience a DLT, then one of the following must occur:
  - If this happens at level 1, de-escalation to level -1 will occur.
  - If this happens at level 2 or beyond, the previous level will be declared the maximum tolerated dose (MTD).
  - If this happens at level -1, the study will be closed to further accrual and the regimen of TAK-659 + R-CHOP will be considered too toxic at any dose.
- If 1 of 3 patients at a given dose level experiences a DLT, then an additional 3 slots will be added (for a total of 6 patients at that level):
  - If 1 of 6 total experiences a DLT, then escalation will proceed to the next level.
  - If ≥ 2 of 6 total experience a DLT, the previous level will be declared the MTD.

NOTE: Whichever dose level is declared the MTD must have 6 total patients treated at that level. For example, if 3 patients are treated at level 2 and 0 patients experience DLT, escalation would then proceed to level 3. However, if ≥ 2 patients at level 3 experience DLT, enrollment to level 2 would need to be re-opened to enroll an additional 3 patients at that level (with 0 or 1 DLT observed in 6 total patients) in order to declare level 2 the MTD.

4.3.1 Definitions of Dose Limiting Toxicity

Although DLT-like events may occur at any point during treatment, only DLTs defined during Cycle 1 of TAK-659 (Cycle 2 of the study) will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels for purposes of MTD determination. Patients will be monitored through all cycles of therapy for treatment-related toxicities. Any DLT-like events occurring during Cycle 1 of R-CHOP treatment will have to be managed to resolution before starting Cycle 2 with TAK-659.

Toxicity will be evaluated according to the NCI CTCAE version 5.0. DLT is defined as any of the events listed below. All adverse events meeting this criteria will be considered DLT's unless the event is clearly unrelated to study therapy.

- Grade 4 neutropenia (ANC <500 cells/mm^3) unresolved to ≤Grade 1 (ANC >1500 cells/mm^3) or baseline for more than 7 consecutive days.
- ≥Grade 3 neutropenia (ANC <1000 cells/mm^3) with fever and/or infection, where fever is defined as an oral temperature ≥38.3°C.
- Grade 4 thrombocytopenia (<25,000/mm^3) unresolved to ≤Grade 1 (>75,000/mm^3) or baseline for more than 7 consecutive days or a platelet count <10,000/mm^3 at any time.
- ≥Grade 3 thrombocytopenia (<50,000/mm^3) with clinically significant bleeding.
- Grade 4 anemia.
- Any Grade 3 or greater non-hematologic toxicity with the following exceptions:
  - Grade 3 arthralgia/myalgia.
  - Grade 3 rash lasting ≤7 days with optimal treatment that includes topical steroid treatment, PO antihistamines, and pulse PO steroids, if necessary.
  - ≥Grade 3 nausea and/or vomiting and ≥ Grade 3 diarrhea that has resolved to < Grade 3 within 72 hours of optimal antiemetic and/ or antidiarrheal treatment. (All patients should receive optimal antiemetic and/ or antidiarrheal treatment according to standard of care. An optimal antiemetic regimen is defined as one that employs a 5-hydroxytyptamine 3 serotonin receptor [5-HT3] antagonist and a corticosteroid given in standard doses and according to standard schedules).
  - Transient Grade 3 fatigue (≤ 72 hours)
  - Asymptomatic lipase elevation (< Grade 4) in the absence of significant

amylase elevation (< Grade 3) considered not dose limiting by the treating physician.
    - Asymptomatic amylase elevation (< Grade 4) in the absence of significant lipase elevation (< Grade 3) considered not dose limiting by the treating physician.
    - Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (< Grade 3) considered not dose limiting by the treating physician.
- Inability to administer at least 75% of planned doses of study drug within Cycle 1 of TAK-659 (Cycle 2 of the study) due to treatment-related toxicity.
- Other TAK-659-related non-hematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require discontinuation of therapy with TAK-659.

4.4 Toxicity Management & Dose Delays/Modifications

4.4.1 Recommended TAK-659 Dose Modifications

TAK-659 is administered in continuous cycles; therefore, study drug should be administered continuously unless AEs occur that meet the dose modification criteria as outlined below.

Per the dose modification guidelines, patients who have the study drug held because of treatment-related or possibly related AEs may resume study drug treatment after resolution of the AE, but may either maintain the same dose level or have doses of study drug reduced (dose reduction) by at least 1 dose level. Dose reduction levels for TAK-659 are presented in the table below. When a dose reduction of TAK-659 occurs, the TAK-659 dose will be reduced to the next lower dose that has been established as a safe dose. The dose reduction of TAK-659 will, in general, follow a decrement of 20 mg. If initial dose adjustment does not provide sufficient relief, the dose of TAK-659 may be further reduced if the treating physician considers that the patient is benefiting from study treatment and may benefit at a further reduced dose of TAK-659. Up to 2 dose-level reductions of TAK-659 due to AEs are generally recommended. If more than 2 dose-level reductions of TAK-659 are needed to manage TAK-659-related AEs, discontinuation of treatment should be considered unless the treating physician feels the patient may benefit from continued study treatment after resolution of AEs to <Grade 1 or baseline, or a level (must be ≤Grade 2) that is determined to be acceptable by the investigator(s) based on benefit-risk assessment. Dose adjustments for R-CHOP are allowed based on standard of care guidelines as listed in Table 4.4 and Table 4.6.

Table 4.3: Dose Reduction Schedule for TAK-659

Dose Reduction Levels	**Dose (Unit)****
Planned Dose	
(-) 1 dose level	Planned dose minus 20 mg
(-) 2 dose level	Planned dose minus 40 mg

Please refer to Table 4.4 and 4.5 for management of hematologic and non-hematologic toxicities.

4.4.2 Recommended Dose Delays/Modifications for R-CHOP and TAK-659

Dose delays and modifications for the R-CHOP regimen will follow standard of care guidelines as listed in Table 4.4 and Table 4.6 below.

Table 4.4: Dose Adjustments for Hematologic Toxicities
The following criteria only apply to Day 1 of each cycle, prior to dosing, to allow for sufficient recovery of

cytopenias from the previous cycle of R-CHOP. If dosing is held for toxicity, patients should be reevaluated within 7 days to assess recovery for resuming treatment		
Criteria	**TAK-659 adjustments**	**R-CHOP adjustments**
Neutropenia		
Grade 1 (ANC < LLN - 1500 cells/mm^3)	Maintain dose level	Maintain all agents at dose level.
Grade 2 (ANC 1000-1,499 cells/mm^3)	Maintain dose level	Maintain all agents at dose level. Investigator may consider pegfilgrastim for all subsequent cycles.
Grade 3 (ANC 500-999 cells/mm^3)	Withhold dose until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3) or baseline. Maintain dose level if patient did not yet receive G-CSF when event occurred; If occurred after G-CSF, reduce TAK-659 one dose level (see Table 4.3)	Withhold all doses until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3). Filgrastim/tbo-filgrastim or pegfilgrastim should be administered for all subsequent cycles. Administration of colony stimulating factors at time of neutropenia is at the discretion of the investigator.
Grade 4 (ANC < 500 cells/mm^3)	Withhold dose until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3) or baseline. Maintain dose level if patient did not yet receive G-CSF when event occurred; If occurred after G-CSF, reduce TAK-659 one dose level (see Table 4.3)	Withhold all doses until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3). Filgrastim/tbo-filgrastim or pegfilgrastim should be administered for all subsequent cycles. Administration of colony stimulating factors at time of neutropenia is at the discretion of the investigator.
Febrile neutropenia (ANC < 500 cells/mm^3, fever ≥ 38.3°C)	Dose withheld until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3) or baseline and fever/infection recovered. Maintain dose level if patient did not yet receive G-CSF when event occurred; If occurred after G-CSF, reduce TAK-659 one dose level (see Table 4.3)	Withhold all doses until resolved to ≤ Grade 2 (ANC ≥ 1,000 cells/mm^3). Filgrastim/tbo-filgrastim or pegfilgrastim should be administered for all subsequent cycles. Administration of colony stimulating factors at time of neutropenia is at the discretion of the investigator. If febrile neutropenia occurs despite filgrastim/tbo-filgrastim or pegfilgrastim support, reduce doses of **cyclophosphamide** and **doxorubicin** by 25% for subsequent cycles. If toxicity recurs, **cyclophosphamide** and **doxorubicin** doses should be reduced by an additional 25% for subsequent cycles. If grade 4 neutropenia or febrile neutropenia persists/recurs despite two dose reductions, remove patient from protocol therapy.
Thrombocytopenia (PLT)		
Grade 1 (PLT LLN-75,000 cells/mm^3)	Maintain dose level	Maintain all agents at dose levels
Grade 2 (PLT 50,000-74,999 cells/mm^3)	Withhold all doses until resolved to ≤ Grade 1 (PLT ≥ 75,000 cells/mm^3) or baseline, then: If resolved in ≤ 7 days,	Withhold all doses until resolved to ≤ Grade 1 (PLT ≥ 75,000 cells/mm^3) or baseline. Maintain all agents at dose levels.

	then maintain dose level If resolved in > 7 days, then dose reduce by 1 dose level	
Grade 3 (PLT 25,000-49,999 cells/mm^3)	Withhold dose until resolved to ≤ Grade 1 (PLT ≥ 75,000 cells/mm^3) or baseline, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then dose reduce by 1 dose level	Withhold all doses until resolved to ≤ Grade 1 (PLT ≥ 75,000 cells/mm^3) or baseline. Maintain all agents at dose levels with next treatment. .
Grade 4 (PLT < 25,000 cells/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce by 1 dose level.	Withhold all doses until resolved to ≤ Grade 1 (PLT ≥ 75,000 cells/mm^3) or baseline. Maintain all agents at dose levels with next treatment.
Anemia		
Grade 3 anemia (Hgb <8.0 g/dL or transfusion indicated)	Withhold dose until resolved to ≤ Grade 1 (Hgb ≥ 10.0 g/dL) or baseline, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then dose reduce by 1 dose level.	Maintain all agents at dose levels. RBC transfusions at the discretion of the investigator.
Grade 4 anemia (life-threatening consequences or urgent intervention indicated related to anemia)	Withhold dose until resolved to ≤ Grade 1 (Hgb ≥ stati g/dL) or baseline, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then dose reduce by 1 dose level.	Maintain all agents at dose levels. RBC transfusions at the discretion of the investigator.

Abbreviations: ANC = absolute neutrophil count; PLT = platelets.

Table 4.5: TAK-659 Dose Adjustments for Non-hematologic Toxicities

Criteria	TAK-659 adjustments
All Grade 3 Non-hematologic Toxicities If attribution to TAK-659 is felt to be possible, probable or definite: **with the exception of:** • nausea, vomiting and diarrhea • fatigue • Asymptomatic lipase elevation (< Grade 4) in the absence of significant amylase elevation (< Grade 3) considered not dose limiting • Asymptomatic amylase elevation (< Grade 4) in the absence of lipase elevation (< Grade 3) considered not dose limiting • Asymptomatic Grade 3 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin	Hold TAK-659 until resolution to Grade ≤ 1 or baseline. If resolved in ≤ 7 days, then maintain the dose level. If resolved in > 7 days, then dose reduce by 1 dose level. For the exceptions, maintain dose level. If there is question of relation to TAK-659, discuss with PI to determine appropriate course of action.

elevation (< Grade 3) considered not dose limiting • Grade 3 hypophosphatemia resolved to Grade ≤ 1 or baseline within 72 hours with phosphate repletion • Other asymptomatic Grade 3 laboratory abnormalities or clinical findings (including changes in blood pressure) that the investigator considers not clinically significant	
Grade 4 Non-hematologic Toxicities with the exception of: • Asymptomatic Grade 4 lipase elevation in the absence of significant amylase elevation (<Grade 3) • Asymptomatic Grade 4 amylase elevation in the absence of significant lipase elevation (<Grade 3) • Asymptomatic Grade 4 elevation of a single liver enzyme (AST or ALT) in the absence of significant bilirubin elevation (<Grade 3) • Grade 4 hypophosphatemia resolved to ≤Grade 1 or baseline within 72 hours with phosphate repletion • Other Grade 4 asymptomatic, enzyme elevations not considered clinically significant	Consider permanently discontinuing TAK-659, except in the case where the investigator determines the patient is obtaining a clinical benefit. Dose reduction of ≥1 dose level is required if study treatment resumes after resolution to ≤Grade 1 or baseline. For the exceptions, hold TAK-659 until resolution to Grade ≤ 1 or baseline. If resolved in ≤ 7 days, then maintain the dose level; If resolved in > 7 days, then dose reduce by 1 dose level;
Grade 2, 3, or 4 abnormalities in ejection fraction (EF)	Hold TAK-659 until cardiology assessment is completed to rule out other etiologies. If felt to be drug related, patient will discontinue study treatment.

Table 4.6: R-CHOP Dose Adjustments for Non-hematologic Toxicities

Criteria	R-CHOP adjustments
Ileus or constipation requiring hospitalization	The next dose of **vincristine** should be reduced by 25%. If symptoms do not recur at the reduced dose, then the **vincristine** dose may be re-escalated on subsequent cycles.
Sensory Neuropathy • Grade 2 sensory neuropathy	Can maintain or reduce **vincristine** by 25-50%, per investigator discretion.
• Grade 3 sensory neuropathy	Reduce **vincristine** by 25-50%, per investigator discretion. If symptoms improve, doses may be increased to previous levels.
• Grade 4 sensory neuropathy	Discontinue **vincristine**.
Motor Neuropathy • Grade 2 motor neuropathy	Reduce **vincristine** by 25%. If symptoms improve, doses may be increased to previous level.
• Grade 3 motor neuropathy	Reduce **vincristine** by 50%. If symptoms improve, doses may be increased to previous levels.
• Grade 4 motor neuropathy	Discontinue **vincristine**.
Hyperbilirubinemia • Bilirubin ≥ 3 mg/dL	Reduce **vincristine** by 50%. Dose can be re-escalated as hyperbilirubinemia improves.
• Bilirubin > 7 mg/dL	Hold **doxorubicin** until bilirubin returns to ≤ 7 mg/dL. No **doxorubicin** dose modifications will be made for increased bilirubin ≤ 7 mg/dL.

In general, the study drug(s) will resume only after the resolution of AEs to ≤Grade 1 or baseline or as specified in these dose modification guidelines. However, retreatment with study drug(s) could start when the AEs are resolved to a level deemed acceptable by the investigator.

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to CTCAE v5.0.

4.4.3 Criteria for Discontinuation of Study Drug(s)

TAK-659 dosing should be discontinued if patients experience a Grade 4 non-hematologic toxicity (except those listed in Table 4.5) and/or Grade 4 anemia. If TAK-659 dosing is delayed because of TAK-659 related toxicities for >21 consecutive days despite supportive care treatment for standard of care, stop TAK-659. Patients exceeding delays of >21 days for TAK-659 related toxicities may be considered on a case-by-case for continuing dosing with TAK-659. PI and DSMC approval should be obtained prior to continuing dosing with TAK-659

If a patient must discontinue study treatment with TAK-659, he or she will be removed from the study but may continue the R-CHOP regimen off-study.

4.4.4 Management of Clinical Events

Therapies that are required to manage AEs and control cancer symptoms are allowed based on standard clinical practice, unless specifically excluded. Supportive care agents, such as erythropoietin, G-CSF, blood products (RBC and platelet transfusions), and pain medications are permitted as needed per American Society of Hematology (ASH)/ASCO guidelines or local institutional practice. However, these agents should not be used in this study in a manner that would either help establish eligibility for the study or support escalation of study drug dose during dose escalation.

Prophylaxis Against Infection

Patients with advanced hematological malignancies may be at an increased risk of infection. Prophylactic use of antibiotic, antiviral, or antifungal medication can be considered as clinically indicated and as per local standard practice. In particular, lymphopenia can develop in association with either treatment or with the underlying disease (DLBCL).

Lymphopenia can be associated with reactivation of herpes zoster, CMV, herpes simplex and other viruses. Antiviral therapy such as acyclovir, gancyclovir, valacyclovir, or other antiviral agents may be initiated as clinically indicated although it is strongly recommended.
PJP prophylaxis should be initiated with C2 (first dose of combination treatment).

Given their degree of immunosuppression, patients with posttransplant lymphoproliferative disease are often at an increased risk of developing infections. Consideration should be given to antibiotic, antifungal, and antiviral prophylaxis during therapy, particularly if the patient is more prone to developing neutropenia.

Pneumonitis

Patients with serious lung events that do not respond to conventional antimicrobial therapy should be assessed for drug-induced pneumonitis after

ruling out infectious causes and alternative etiologies. If pneumonitis is suspected, TAK-659 treatment should be interrupted and the patient treated per standard of care. If pneumonitis is moderate/severe, discontinue TAK-659. Patients should be monitored for respiratory signs and symptoms throughout treatment and be advised to promptly report respiratory symptoms.

Edema (Including Periorbital)
Peripheral and periorbital edema have been observed in patients treated with TAK-659. Management of the event should follow the standard local practice and dose modification as required.

Rash With or Without Pruritus
Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone ≤ 10 mg per day or equivalent) is permitted.

Hypophosphatemia
Hypophosphatemia has been observed in patients treated with TAK-659. Consider prophylaxis; otherwise refer to dose modification guideline.

Enzyme Elevations (Transaminase, Amylase and Lipase, CPK and LDH Elevations)
Elevations of the enzymes above have been observed. Events are generally asymptomatic and reversible with dose interruption.

LDH elevations have been observed in the majority of patients exposed to TAK-659. These elevations have been asymptomatic and the clinical significance is unknown. No doses have been interrupted due to increased LDH; however, LDH elevations have been observed to be reversible in patients who had TAK-659 interrupted due to other reasons.

4.5 Concomitant Medications/Procedures

During the study, patients will be instructed not to take any additional medications (including over-the-counter products and supplements) without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is taking or has taken while on study. All concomitant medications (defined as any medication given during the study) and significant nondrug therapies, including physical therapy and blood transfusions, should be recorded from signing of the informed consent form (ICF) through 30 days after the last dose of study drug or the start of subsequent antineoplastic therapy, whichever occurs first.

4.5.1 Required/Permitted Concomitant Medications

Required ancillary medications administered during all cycles:
• Acetaminophen 650 mg PO and diphenhydramine 50-100 mg IV or PO 30-60 minutes prior to rituximab.
• PJP prophylaxis should be initiated with C2 (first cycle of combination therapy)
• Those patients who test positive for hepatitis B should be closely monitored for evidence of active HBV infection and hepatitis during and for several months after rituximab treatment, and should be managed at the discretion of the investigator, including possible antiviral medications.

- Steroids for anti-cancer treatment are permitted prior to cycle 1
- Topical, ocular, intra-articular, intranasal, and inhaled corticosteroids (with minimal systemic absorption) are permitted.

4.5.2 Prohibited Concomitant Medications

The following restrictions apply during the study:

- Any antineoplastic therapy other than TAK-659 and R-CHOP is prohibited during the study.
- Radiation therapy is prohibited during the study (note that, in general, the requirement for local radiation therapy indicates disease progression). Palliative radiotherapy for local pain/symptom control in a preexisting non-target lesion may be considered.
- Intravenous high-dose methotrexate and/or intravenous cytarabine is not permitted during study treatment.
- Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A are not permitted in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix A for a nonexhaustive list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA draft guidance for DDI studies.
  - Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole.
  - Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin.
  - Antimycobacterials: rifabutin, rifampin, rifapentine.
  - Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone.
  - Antidepressant: nefazodone.
  - Immunosuppressant: cyclosporine.
  - Calcium channel blockers: diltiazem, felodipine, mibefradil, verapamil.
  - Antiarrhythmics: amiodarone, dronedarone, quinidine.
  - Antiplatelet: ticagrelor.
  - Antilipid: avasimibe.
  - Other cardiovascular: captopril, carvedilol, ranolazine.
  - Vasopressin antagonist: conivaptan.
  - Food/herbals/supplements: grapefruit-containing food and beverages, St. John's wort, quercetin.

If a patient experiences an AE on study and TAK-659 dosing is temporarily interrupted because of that AE, the medications listed above and Appendix A may be used for AE management if there is no appropriate alternative treatment available per the investigator's judgment and the dosing is not concurrent with study drug. This situation should be evaluated by the principal investigator. Patients should be closely monitored for potential toxicities.

4.6 Precautions and Restrictions

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study.

Pregnancy

It is not known what effects TAK-659 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective methods of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing of the informed consent form through 180 days(or longer, as mandated by local labeling [eg, USPI, SmPC, etc;]) after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree to not donate eggs (ova) during the course of this study or 180 days after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:

- Agree to practice highly effective barrier contraception during the entire study treatment period and through 180 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the course of this study or 180 days after receiving their last dose of study drug.

4.7 Other Modalities or Procedures

4.7.1 ECG

All scheduled ECGs should be performed pre-dose, unless otherwise specified, and after the patient has rested quietly for at least 5 minutes in a supine position. When the timing of a PK or safety laboratory blood sample coincides with the timing of ECG measurements, the ECG will be completed before the collection of the blood sample. In some cases, it may be appropriate to repeat an abnormal ECG to rule out improper lead placement as contributing to the ECG abnormality.

4.7.2 Ophthalmic Exam

A slit lamp eye examination will be performed by an ophthalmologist at Screening; on Cycle 3 Day 1 (±2 weeks); and at EOT. On the basis of nonclinical toxicology findings with TAK-659 in rats, slit lamp examinations should focus on detecting any posttreatment changes in ocular lenses. Examination and photographing of the retina will be performed at Baseline but not during the study unless clinically indicated. Additional eye exams may also be performed as required. Additionally, patients will be carefully monitored for eye complaints at each visit and instructed to report visual symptoms as soon as they occur.

4.8 Duration of Therapy

Patients will continue treatment with TAK-659 and R-CHOP for up to 6 total cycles of 21 days (5 cycles of TAK-659 as combination therapy). The first cycle of R-CHOP may take place prior to study registration. Patients may discontinue before 6 cycles if any of the following occur:

- Disease progression

- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the as a whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.9 Duration of Follow Up

All patients will have an End of Treatment visit within 30 days after treatment discontinuation. In addition, patients will be followed for adverse events, including Serious Adverse Events, for 30 days after last dose of TAK-659. Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients will be followed for survival status every 6 months by routine clinic visit or phone call for up to 3 years from treatment discontinuation.

4.10 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression (clinical or radiological progression)
- Patient experiences unacceptable toxicity
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)
- The study is terminated
- Protocol violation

4.11 Patient Replacement

Patients who sign consent and/or receive R-CHOP but come off study before receiving TAK-659 may be replaced. Three patients within a dose level must be observed for one cycle (21 days) on TAK-659 before accrual to the next higher dose level may begin. If a patient is withdrawn from the study prior to completing 14 days of TAK-659 therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level. Patients missing 7 or more doses due to toxicity will not be replaced since these patients will be considered to have experienced a dose limiting toxicity.

5.0 STUDY PROCEDURES

Table 5.1: On-Study R-CHOP

	Screening	Study treatment period (1 cycle = 21 days, each visit ±3 days unless otherwise stated in footnotes)															Off treatment	
	Day -30 to Day 1	C1[1]		C2					C3		C4		C5		C6		EOT[15]	F/U[8]
		D1	D2-5	D1	D2	D8	D15	D16	D1	D15	D1	D15	D1	D15	D1	D15		
R-CHOP		X	X	X					X		X		X		X			
TAK-659 administration (21-day supply dispensed every cycle)				X					X		X		X		X			
Informed consent	X																	
Physical exam, Vital Signs[2], ECOG PS, AE assessment,	X	X		X		X	X		X	X	X	X	X	X	X	X	X	
12-lead ECG[3]	X			X			X		X		X		X		X		X	
ECHO[16]	X[16]										X[16]						X[16]	
Concomitant meds	X	X		X					X		X		X		X		X	
Patient diary review				X					X		X		X		X		X	
Viral hepatitis serologies (HBV and HCV)[4]	X																	
CBC with differential[11]	X	X		X		X	X		X	X	X	X	X	X	X	X	X	
Chemistry Panel[12]	X	X		X		X	X		X	X	X	X	X	X	X	X	X	
Mg, Phos, LDH, Amylase, Lipase	X	X		X		X	X		X	X	X	X	X	X	X	X	X	
T-cell panel[17]	X																X	
Study Labs[13]		X[13]		X[13]	X[13]		X[13]	X[13]			X[13]						X[13]	X[13]
Urinalysis	X						X		X		X		X		X		X	
Ophthalmic Exam[14]	X								X								X	
PET/CT	X[5]										X[6]						X[7]	
Pregnancy test (FOCBP)	X			X					X		X		X		X			
Survival/disease status assessment																		X[9]

[1] Patients will receive one cycle of R-CHOP monotherapy (Cycle 1) prior to starting combination therapy with TAK-659 (Cycles 2-6). Cycle 1 of R-CHOP can take place either prior to study registration ("off-study", ≤30 days prior to the first dose of TAK-659) or after study registration ("on-study"). Screening procedures must take place ≤30 days prior to "registration" unless otherwise specified.
[2] Vital signs include blood pressure
[3] Performed pre-dose and as instructed in section 4.7.1.

[4] Patients must have hepatitis serologies (HBV and HCV) ≤ 90 days prior to study registration.
[5] PET/CT should be obtained ≤ 60 days prior to first cycle of R-CHOP (on- or off-study as specified in footnote 1 and section 4.1) whenever possible with an optional diagnostic CT component. It is acceptable if a patient had a CT scan alone within the timeframe.
[6] PET/CT should be obtained day 15-21 of C3 or day 1 of C4
[7] PET/CT should be completed 4-6 weeks after Cycle 6 R-CHOP treatment
[8] Every 6 months (starting 6mo from C6) by routine clinic visit or phone call for up to 3 years, until recurrent lymphoma or death. Follow-up will include collection of survival data, progression/relapse and any new anti-cancer treatment.
[9] disease status assessment will simply include documenting whether patient is still in CR or with recurrent disease, as assessed by the investigator (and date of recurrence will be documented)
[10] A serum pregnancy test will be performed for women of childbearing potential at Screening.
[11] CBC will include hemoglobin, hematocrit, leukocytes (white blood cell [WBC] count), differential WBC count (lymphocytes [ALC], neutrophils [ANC]), and platelets.
[12] Chemistry panel (CMP) will include sodium, potassium, CO_2, chloride, BUN, creatinine, bilirubin, ALP, AST, ALT, GGT, total protein, albumin, glucose, urate, and calcium.
[13] Patients will have blood samples drawn for PK's and banking as outlined below. See separate lab manual for more details.

Correlative Blood Draws		
	Time Points**	**Sample Type**
C1D1	Pre-dose	Banking
C2D1	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose	PK and Banking* (*pre-dose only)
C2D2	Pre-dose	PK
C2D15	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose	PK
C2D16	Pre-dose	PK
C4D1	Pre-dose	Banking
EOT and time of relapse (if patient willing and feasible)	All patients will have an EOT sample drawn. If patient has not relapsed at EOT, an additional sample should be obtained at the time of confirmed progression, within 30 days if feasible.	Banking
**Timing of all samples (pre-dose and post-dose) is related to the time of TAK-659 dosing; The following windows are allowable for PK sample collection: Pre-dose (within 60 min before TAK-659 dose); 30 mins (±10 mins); 1 hour (±10 mins); 2 hours (±20 mins); 4 hours (±30mins); 8 hours (±30 mins), 24 hours (±60 mins).		

[14] Please see section 4.7.2 for further instructions on timing and conduct of ophthalmic exams.
[15] An End of Treatment (EOT) visit will take place within 30 days after completing last dose of study treatment OR before starting new anti-cancer therapy.

[16] For baseline ECHO, a window of 60 days prior to registration is acceptable.Grade 2, 3, or 4 toxicity of EF should require assessment by cardiology to rule out other etiologies. If felt to be drug related, patient should be discontinued from protocol treatment. For echocardiogram on C4D1, window for procedure can be -7 days and up to C4D1 but prior to dosing; timeline for EOT echo: within 30 days after completing

last dose of study treatment OR before starting new anti-cancer therapy.

[17] T-Cell panel includes Total Tcell (CD3)(%); Total T cell(CD3)(/uL); Total Bcell (CD19)(%); Total B cell (CD19)(/uL); Total Natural Killer NK (CD16/CD56)(%); Total Natural Killer NK (CD16/CD56) (uL); Total Helper (CD3/CD4)(%); Total Helper (C3/C4) (/ul) ; Total Suppressor (CD3/CD8) ; Total Suppressor (CD3/CD8) (/uL); Helper/suppressor ratio

Table 5.2: Off-Study R-CHOP

	Cycle 1 R-CHOP (Off-study)	Screening	Study treatment period (1 cycle = 21 days, each visit ±3 days unless otherwise stated in footnotes)													Off treatment	
		Day -30 to Day 1	C2					C3		C4		C5		C6		EOT 15	F/U 8
			D1	D2	D8	D15	D16	D1	D15	D1	D15	D1	D15	D1	D15		
R-CHOP	X[1]		X					X		X		X		X			
TAK-659 administration (21-day supply dispensed every cycle)			X					X		X		X		X			
Informed consent		X															
Vital Signs[2], ECOG PS, AE assessment, Physical exam		X	X		X	X		X	X	X	X	X	X	X	X	X	
12-lead ECG[3]		X	X			X		X		X		X		X		X	
ECHO[16]		X								X[16]						X[16]	
Concomitant meds		X	X					X		X		X		X		X	
Patient diary review			X					X		X		X		X		X	
Viral hepatitis serologies (HBV and HCV)[4]		X															
CBC with differential[11]		X	X		X	X		X	X	X	X	X	X	X	X	X	
Chemistry Panel[12]		X	X		X	X		X	X	X	X	X	X	X	X	X	
Mg, Phos, LDH, Amylase, Lipase		X	X		X	X		X	X	X	X	X	X	X	X	X	
T-cell panel		X														X	
Study Labs[13]			X[13]	X[13]		X[13]	X[13]			X[13]						X[13]	X[13]
Urinalysis		X				X		X		X		X		X		X	
Ophthalmic Exam[14]		X						X								X	
PET/CT		X[5]								X[6]						X[7]	
Pregnancy test (FOCBP)		X	X					X		X		X		X			
Survival/disease status assessment																	X[9]

[1] Patients will receive one cycle of R-CHOP monotherapy (Cycle 1) prior to starting combination therapy with TAK-659 (Cycles 2-6). Cycle 1 of R-CHOP can take place either prior to study registration ("off-study", ≤30 days prior to the first dose of TAK-659) or after study registration ("on-study"). Screening procedures must take place ≤30 days prior to "registration" unless otherwise specified.
[2] Vital signs include blood pressure
[3] Performed pre-dose and as instructed in section 4.7.1.

[4] Patients must have hepatitis serologies (HBV and HCV) ≤ 90 days prior to study registration.
[5] PET/CT should be obtained ≤ 60 days prior to first cycle of R-CHOP (on- or off-study as specified in footnote 1 and section 4.1) whenever possible with an optional diagnostic CT component. It is acceptable if a patient had a CT scan alone within the timeframe.
[6] PET/CT should be obtained day 15-21 of C3 or day 1 of C4
[7] PET/CT should be completed 4-6 weeks after Cycle 6 R-CHOP treatment
[8] Every 6 months (starting 6mo from C6) by routine clinic visit or phone call for up to 3 years, until recurrent lymphoma or death. Follow-up will include collection of survival data, progression/relapse and any new anti-cancer treatment.
[9] disease status assessment will simply include documenting whether patient is still in CR or with recurrent disease, as assessed by the investigator (and date of recurrence will be documented)
[10] A serum pregnancy test will be performed for women of childbearing potential at Screening.
[11] CBC will include hemoglobin, hematocrit, leukocytes (white blood cell [WBC] count), differential WBC count (lymphocytes [ALC] and neutrophils [ANC]), and platelets.
[12] Chemistry panel (CMP) will include sodium, potassium, CO_2, chloride, BUN, creatinine, bilirubin, ALP, AST, ALT, GGT, total protein, albumin, glucose, urate, and calcium.
[13] Patients will have blood samples drawn for PK's and banking at the time points listed below. See separate lab manual for more details. *(Please note: If bio banking samples are not collected or patient refuses, it will not be a deviation).*

Correlative Blood Draws		
	Time Points**	**Sample Type**
C2D1	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose	PK and Banking* (*pre-dose only)
C2D2	Pre-dose	PK
C2D15	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose	PK
C2D16	Pre-dose	PK
C4D1	Pre-dose	Banking
EOT and time of relapse (if patient willing and feasible)	All patients will have an EOT sample drawn. If patient has not relapsed at EOT, an additional sample should be obtained at the time of confirmed progression, within 30 days if feasible.	Banking
** Timing of all samples (pre-dose and post-dose) is related to the time of TAK-659 dosing; The following windows are allowable for PK sample collection: Pre-dose (within 60 min before TAK-659 dose); 30 mins (±10 mins); 1 hour (±10 mins); 2 hours (±20 mins); 4 hours (±30mins); 8 hours (±30 mins), 24 hours (±60 mins).		

[14] Please see section 4.7.2 for further instructions on timing and conduct of ophthalmic exams.
[15] An End of Treatment (EOT) visit will take place within 30 days after completing last dose of study treatment OR before starting new anti-cancer therapy.
[16] For baseline ECHO, a window of 60 days prior to registration is acceptable.
Grade 2, 3, or 4 toxicity of ejection fraction (EF) requires assessment by cardiology to rule out other etiologies. If felt to be drug related, patient should be discontinued from protocol treatment. For echocardiogram on C4D1, window for procedure can be -7 days and up to C4D1 but prior to dosing; timeline for EOT echo: within 30 days after completing last dose of study treatment OR before starting new anti-cancer therapy.

[17] T-Cell panel includes Total Tcell (CD3)(%); Total T cell(CD3)(/uL); Total Bcell (CD19)(%); Total B cell (CD19)(/uL); Total Natural Killer NK (CD16/CD56)(%); Total Natural Killer NK (CD16/CD56) (uL); Total Helper (CD3/CD4)(%); Total Helper (C3/C4) (/ul) ; Total Suppressor (CD3/CD8) ; Total Suppressor (CD3/CD8) (/uL); Helper/suppressor ratio.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

6.1.1 Response will be evaluated, using the Lugano classification for assessment of Lymphoma.[31] See Appendix D for specific response assessment criteria.

6.1.2 Clinical evaluation and tumor assessments will be performed periodically, as shown in Table 6, based on evaluation of spleen and liver, physical examination for superficial disease and B symptoms, radiologic evaluation, and appropriate laboratory studies.

6.1.3 A lesion is categorized based on the location as either a nodal lesion or an extranodal lesion if it is located in organs other than lymph nodes or nodal mass, but including spleen and liver.

6.1.4 All tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

6.1.4.1 Measurable nodal and extranodal lesions:
A lesion will be called measurable if it can be measured accurately in 2 perpendicular dimensions and:

- For nodal lesion, if the long axis is >15 mm, regardless of the length of the short axis
- For extranodal lesion, if the long and short axes are ≥10 mm.

Patients should have at least one measurable nodal lesion greater than 20 mm in the long axis.
In cases where the patient has no measurable nodal lesions greater than 20 mm in the long axis at screening, then the patient must have at least one measurable extranodal lesion.

6.1.5 Classification of lymph nodes

6.1.5.1 Lymph nodes are classified according to their size and/or relationship to the disease:

- A lymph node meeting the measurability requirement, but with long axis > 15 mm (e.g. short axis cannot be measured accurately) will constitute a non-measurable nodal lesion.
- A lymph node not meeting the measurability criteria, but with a size of 11 mm to 15 mm in the long axis and >10 mm in the short axis will be checked for relationship to disease:
    - If it is thought to be disease related, it will constitute a non-measurable nodal lesion
    - If it is not thought to be disease related, it will constitute an abnormal lymph node, but not a lesion.

All other lymph nodes will be considered normal and will not constitute nodal lesions.

6.1.6 Criteria for normalization of lesions

6.1.6.1 The normalization of lesions is defined as follow:

- A measurable nodal lesion must become ≤ 15 mm in long axis to be considered normalized.
- A non-measurable nodal lesion must decrease to ≤10 mm in the short axis and be ≤ 15 mm in long axis to be considered normalized.
- An extranodal lesion must disappear completely (assigned a size of 0 mm x 0 mm) to be considered normalized.

6.2 Primary Endpoint

Endpoint: Toxicity and tolerability will be assessed by history and physical, including vital signs and ECOG performance status, and laboratory values to determine incidence and grade of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities, as defined in section 4.3.1 and by the NCI CTCAE v5.0. Patients will be evaluated for dose-limiting toxicities during the first cycle (21 days) of TAK-659 combined with R-CHOP (study Cycle 2) to determine the maximum tolerated dose.

6.2.1 Evaluable Patients

All patients who receive at least one dose of TAK-659 will be evaluable for general toxicity endpoints.

DLT-evaluable patients at each dose cohort will consist of patients who have met the minimal treatment and safety evaluation requirements of the study and/or who experience a DLT during Cycle 2. The minimum treatment and safety evaluation requirements are met, if, in Cycle 2, the patient has been treated with TAK-659 for ≥ 14 days (receiving at least 75% of planned doses of TAK-659 in Cycle 2) and observed for ≥ 21 days following the dose on Cycle 2, Day 1 (C2D1), and is considered to have sufficient safety data by both the investigators and Data Monitoring Committee (DMC) to conclude a DLT did not occur. Patients who do not meet these minimum requirements will be regarded as ineligible for inclusion as DLT-evaluable patients for the given dose cohort and may be replaced within the same cohort.

6.3 Secondary Endpoints

Endpoints:

6.3.1 Overall response rate (ORR), using Lugano criteria (2014), will be defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) as assessed by the investigators. Response will be assessed by PET/CT at screening, PET/CT after C3, and by PET/CT at the End of Treatment visit. All patients who receive at least one dose of TAK-659, have sites of measurable disease at baseline, and 1 post-baseline disease assessment are evaluable for this endpoint. This will be assessed at 3 months.

6.3.2 Progression free survival (PFS) will defined as the time from study enrollment until progression/recurrence of lymphoma or death from any cause. This will be assessed at 12 and 18 months.

6.3.3 Overall survival (OS) will be defined as the time from study enrollment until death from any cause. This will be assessed at 12 and 18 months.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high-risk monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.

- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is *life-threatening*.**
  The patient 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 *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- **Results in *persistent or significant disability or incapacity*.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF . Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study’s phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 5.0.
2) Grade the adverse event using the NCI CTCAE v 5.0.
3) Determine whether the adverse event is related to the protocol therapy.

Attribution categories are as follows:

- Definite: AE is clearly related to the study treatment.
- Probable: AE is likely related to the study treatment.
- Possible: AE may be related to the study treatment.
- Unlikely: AE not likely to be related to the study treatment.
- Unrelated: AE is clearly NOT related to the study treatment.

4) Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current protocol
- the drug package insert
- the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form, provided as a separate document, is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to Takeda

Adverse Events which are **serious** must be reported to Takeda Pharmacovigilance from the first dose of TAK-659 up to and including 30 days after administration of the last dose of TAK-659, or until the start of subsequent anticancer therapy, whichever occurs first. Any SAE that occurs at any time after completion of TAK-659 treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance. In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Reem Karmali also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's IEC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Takeda Pharmacovigilance:
Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event (using the NU CRO SAE Form and referencing the Takeda study number, IISR-2017-101972).

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Takeda Pharmacovigilance. The sponsor investigator must fax or email the SAE Form per the timelines above.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**

- **Intensity of the event(s):** Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Takeda Pharmacovigilance. In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1 202 315 3560
E-mail: takedaoncocases@cognizant.com

7.3.3.4.1 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:
Pregnancy Report Form (provided as a separate document)

8.0 DRUG INFORMATION

8.1 TAK-659

8.1.1 Other names

N/A

8.1.2 Classification - type of agent

SYK Inhibitor

8.1.3 Mode of action

TAK-659 inhibits SYK purified enzyme with a concentration producing 50% inhibition (IC50) of 2.0 and 3.2 nM.

8.1.4 Storage and stability

TAK-659 tablets should be stored in the original dispensing bottles at 1°C to 25°C (33.8°F-77°F) with excursions permitted to 30°C (86°F) as long as they do not exceed 7 days. All temperature excursions of the tablets must be reported back to the manufacturer for assessment and determination for continued use. The TAK-659 tablets must be used before the retest date indicated on the label and/or accompanying documentation. Throughout the duration of the clinical trial, the stability of the drug product will be monitored. TAK-659 tablets should remain in the original bottle provided to the investigational TAK-659 site and patients. Drug supply must be kept in an appropriate, limited access, secure place until it is dispensed to the enrolled patients.

Since TAK-659 is an investigational agent, it should be handled with due care. In the case of broken tablets, raising dust should be avoided during the clean-up operation. Damaged tablets may be harmful by inhalation, ingestion, or skin and/or eye contact. In the case of contact of damaged tablets with the eyes or skin, there should be immediate and thorough flushing and washing for at least 15 minutes with water (and soap for skin). Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of TAK-659, including that TAK-659 is to be taken as intact tablets.

A study drug accountability log must be completed for all study drug dispensed and administered to study patients.

8.1.5 Protocol dose specifics

The MTD for TAK-659 will be determined using a 3+3 dose escalation method. The starting dose will be 60 mg with possible escalation to 80 mg and 100 mg. Patients may be de-escalated to 40 mg if DLT’s are met at dose level 1.

8.1.6 Preparation

TAK-659 is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling TAK-659.

8.1.7 Route of administration for this study

Oral

8.1.8 Incompatibilities

The following restrictions apply during the study:

- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression). Palliative radiotherapy for local pain/symptom control in a preexisting nontarget lesion may be considered.

- Concurrent systemic administration of TAK-659 with inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A should be avoided in this study. In vitro studies indicate that TAK-659 is a substrate for P-gp and that, among CYP isozymes, TAK-659 is preferentially metabolized by CYP3A4/5. Refer to the list below and Appendix A for a nonexhaustive list of medications, supplements, and food products that are inhibitors or inducers of P-gp or strong inhibitors or inducers of CYP3A based on the US FDA draft guidance for DDI studies.
  - Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole.
  - Antibiotics: azithromycin, clarithromycin, erythromycin, telithromycin.
  - Antimycobacterials: rifabutin, rifampin, rifapentine.
  - Antiepileptics: carbamazepine, phenobarbital, phenytoin, primidone.
  - Antidepressant: nefazodone.
  - Immunosuppressant: cyclosporine.
  - Calcium channel blockers: diltiazem, felodipine, mibefradil, verapamil.
  - Antiarrhythmics: amiodarone, dronedarone, quinidine.
  - Antiplatelet: ticagrelor.
  - Antilipid: avasimibe.
  - Other cardiovascular: captopril, carvedilol, ranolazine.
  - Vasopressin antagonist: conivaptan.
  - Food/herbals/supplements: grapefruit-containing food and beverages, St. John's wort, quercetin.

8.1.9 Availability & Supply

TAK-659 will be supplied by Takeda.

TAK-659 20 mg, 60 mg, 100 mg, and additional dose strength tablets will be packaged into round, white, high-density polyethylene (HDPE) bottles with induction seal, desiccant pack, and polypropylene child resistant caps. Each bottle containing 30 tablets of TAK-659 will be labeled with either a single-panel or multilanguage label containing pertinent study information, country-specific requirements, and a caution statement.

8.1.10 Side effects

Potential risks from nonclinical studies in dogs and rats include:

- Lymphoid/hematopoietic effects that include lymphoid depletion and myelosuppression that are associated with thrombocytopenia, neutropenia, and reticulocytopenia. These findings may be associated with increased susceptibility to infection, bleeding, and/or anemia.
- Epithelial effects on the intestinal tract, urinary tract, and lens. Intestinal effects included minimal-to-slight mucosal hemorrhaging. Urinary and renal tract effects included hyperplasia of transitional epithelium in the kidney and bladder, dilatation and hemorrhage in the renal pelvis leading to hematuria and proteinuria, and urolithiasis with possible ureter obstruction. Lens effects included epithelium hyperplasia leading to anterior axial opacity.
- Reproductive system effects, including decreased spermatozoa and seminiferous tubule degeneration in the testis and corpora luteal necrosis in the ovaries. Possible mutation of DNA. Growth plate thickening and disorganization (not relevant to adults).
- Lymphoid and hematopoietic effects and reproductive system effects are considered important potential risks.

- Potential risks based on clinical observations:
- On the basis of data from Study C34001, asymptomatic elevation in lipase was added as an important potential risk of TAK-659. In nonclinical studies, asymptomatic lipase was sporadically elevated at high doses of TAK-659; however, there was no evidence of microscopic organ damage. In clinical studies to date, lipase elevations are reported commonly (≥ 10%). Patients in the current study will have frequent monitoring of amylase as outlined in the
- Cases of pneumonitis have been reported in clinical studies with BCR pathway kinase inhibitors including TAK-659, and pneumonitis is considered an important potential risk of TAK-659. Pneumonitis and other pulmonary toxicities are being closely monitored in TAK-659 clinical studies.

The benefits of TAK-659 have not been established; however, early signs of clinical antitumor activity were seen.
Further details regarding the risks and benefits associated with TAK-659 may be found in the current version of the TAK-659 IB.

8.1.11 Nursing implications

TAK-659 should be taken on an empty stomach at least 1 hour before and no sooner than 2 hours after ingestion of food and/or beverages other than water. Each tablet should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the prescribed doses of TAK-659. Patients must swallow the tablets whole; the tablets must not be chewed, crushed, or manipulated in any way before swallowing.

Patients should be instructed to take their study medication at approximately the same time each day and to not take more than the prescribed dose at any time. If a patient fails to take TAK-659 one day, or if a patient does not take TAK-659 at their scheduled dosing time (± 6 hours of the scheduled dosing time), that dose should be skipped, and the patient must not make dose adjustments to account for the missed dose on subsequent days, for example, by taking a double dose of study drug(s) on the following day. Patients should record any skipped doses in their dosing diary (and resume dosing at the next scheduled time with the prescribed dosage).

If severe emesis prevents the patient from taking a TAK-659 dose, that dose will be skipped. If emesis occurs after TAK-659 ingestion, patients should not re-dose following emesis and should record the time of the emesis in their dosing diary. Patients should resume dosing at the next scheduled time with the prescribed dosage.

8.1.12 Return and Retention of Study Drug

Patients will return unused tablets to the clinic. The clinical study team will be responsible for keeping accurate records of the clinical supplies received from Takeda, the amount dispensed to and returned not used by the subjects and the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

8.2 Rituximab

Please refer to the FDA-approved package insert for rituximab for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.2.1 Other names
Rituxan, IDEC-C2B8, chimeric anti-CD20 monoclonal antibody 8.7.2
Classification – type of agent Antibody.

8.2.2 Classification - type of agent
Chimeric murine-derived monoclonal antibody

8.2.3 Mode of action
Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions in vitro, and depletes B cells in vivo. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B cell lysis in vitro. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.2.4 Storage and stability
Intact vials should be stored under refrigeration. Dilute solutions for infusion (1-4 mg/mL) are stable for 24 hours under refrigeration, and for an additional 24 hours at room temperature.

8.2.5 Protocol dose specifics
Rituximab will be administered as an IV infusion at 375 mg/m2 on day 1 of each cycle of R-CHOP, as detailed in section 4.0. Oral premedication 650 mg of acetaminophen and 50-100 mg diphenhydramine hydrochloride IV or PO will be administered 30 to 60 minutes prior to starting each infusion of rituximab. The first rituximab infusion will be given with cycle 1 of R-CHOP without TAK-659 and should be infused a rates per standard of care, as per investigator discretion. For example, the first rituximab infusion could be started at 50 mg/hr, and increased in 50-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If this rate of escalation is well tolerated the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

8.2.6 Preparation
The desired dose of rituximab should be diluted in 0.9% NaCl or D5W to a final concentration of 1-4 mg/mL. The solution should be mixed by gently inverting the bag.

8.2.7 Route of administration for this study
IV

8.2.8 Incompatibilities
Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

8.2.9 Availability & Supply
Rituximab is commercially available in 10 mL and 50 mL single-use vials containing 100 mg or 500 mg rituximab solution, respectively, at a concentration of 10 mg/mL.

8.2.10 Side effects
The most severe serious adverse events associated with rituximab include severe infusion reactions, tumor lysis syndrome, and severe mucocutaneous

reactions. Severe infusion reactions consisting of hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock may be fatal. Most reported fatal reactions occurred within 24 hours of the first dose of rituximab.

Tumor lysis syndrome resulting in renal failure has been described, and occasional fatalities noted. Tumor lysis syndrome is more likely in patients with high numbers of circulating malignant cells (≥ 25,000/µL). Severe mucocutaneous reactions associated with rituximab include Stevens-Johnson syndrome and toxic epidermal necrolysis. The onset of these reactions has been from 1-3 weeks.

Less severe infusion reactions are common with rituximab. These include fever, chills, and dyspnea. The mechanism of rituximab infusion reactions is thought to be secondary to release of cytokines. If a reaction occurs, then the infusion should be stopped until the symptoms resolve, and then restarted at a 50% slower rate.

Recent reports describe hepatitis B reactivation with fulminant hepatitis, hepatic failure and death in some patients with hematologic malignancies treated with rituximab. The majority of these patients received rituximab in combination with chemotherapy. The median time to diagnosis of hepatitis was approximately 4 months after starting rituximab and approximately 1 month after the last dose. Exacerbation or reactivation of other viral infections has also been reported with rituximab. Recent reports describe JC virus reactivation leading to progressive multifocal leukoencephalopathy (PML) in patients who were receiving rituximab. Patients presenting with new neurologic findings (e.g., major changes in vision, unusual eye movements, loss of balance or coordination, confusion) should be evaluated for PML.

8.2.11 Nursing implications

Oral pre-medication 650 mg of acetaminophen and 50-100 mg diphenhydramine hydrochloride IV or PO will be administered 30 to 60 minutes prior to starting each infusion of rituximab. Rituximab will be administered as an intravenous infusion at 375 mg/m2 on day 1 of each cycle of R-CHOP, immediately prior to the start of chemotherapy. The first rituximab infusion will be given with cycle 1 of R-CHOP without TAK-659 and should be infused a rates per standard of care, as per investigator discretion. For example, the first rituximab infusion could be started at 50 mg/hr, and increased in 50-mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr. If this rate of escalation is well tolerated the second and subsequent infusions can begin at a rate of 100 mg/hr and increase in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

8.3 Cyclophosphamide

Please refer to the FDA-approved package insert for cyclophosphamide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.3.1 Other names

Cytoxan®; Neosar®, CTX, CPM

8.3.2 Classification - type of agent

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.3.3 Mode of action
Cyclophosphamide metabolites are thought to disrupt cell division primarily by crosslinking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.3.4 Storage and stability
Intact vials should be stored at room temperature. Reconstituted and diluted solutions are stable for 24 hours at room temperature and 6 days if refrigerated.

8.3.5 Protocol dose specifics
The total dose of cyclophosphamide will be administered by IV. All patients should receive hydration with normal saline at the following volumes (based on cyclophosphamide dose levels) and rates with half administered before and half administered after cyclophosphamide.

8.3.6 Preparation
Refer to Package Insert for preparation instructions

8.3.7 Route of administration for this study
IV

8.3.8 Incompatibilities
Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same isoenzyme. Inhibitors of 3A4 (e.g., itraconazole) could theoretically inhibit activation and inducers of 3A4 (e.g., phenytoin) could theoretically enhance activation of cyclophosphamide to active alkylating species. For the most part, such interactions have not yet been documented clinically.

8.3.9 Availability & Supply
Cyclophosphamide is commercially available, and will not be provided by the study.

8.3.10 Side effects
Myelosuppression, hemorrhagic cystitis (patients must be well-hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) usually at doses higher than those used in this study

8.3.11 Nursing implications
The total dose of cyclophosphamide will be administered by IV.
All patients should receive hydration with 1 liter normal saline at 300-500 cc/hr with half administered before and half administered after cyclophosphamide.

8.4 Doxorubicin HCl
Please refer to the FDA-approved package insert for doxorubicin for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.4.1 Other names
Adriamycin PFSTM, Adriamycin RFSTM, Rubex®, hydroxydaunorubicin, hydroxydaunomycin, ADR

8.4.2 Classification – type of agent
Anthracycline antibiotic.

8.4.3 Mode of action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II

8.4.4 Storage and stability

Intact vials of doxorubicin solution should be stored in the refrigerator. Intact vials of powder for reconstitution should be stored at room temperature. Reconstituted solutions are stable for 7 days at room temperature and 15 days under refrigeration when protected from light. Commercially available solutions labeled as such are intended to be multidose vials. Compatibility and stability studies were conducted by the Pharmaceutical Development Service [60], Pharmacy Department, NIH Clinical Center, simulating concentrations of each drug that would be applicable to this trial. Admixtures of vincristine, doxorubicin, and etoposide in 0.9% Sodium Chloride Injection, in polyolefin-lined IV bags were stable for up to 72 hours at room temperature, provided that the concentration of etoposide was < 250 mcg/ml.

8.4.5 Protocol dose specifics

Doxorubicin will be administered at a 50 mg/m2 on day 1 of each cycle.

8.4.6 Preparation

Refer to package insert for preparation instructions

8.4.7 Route of administration for this study

IV

8.4.8 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.4.9 Availability & Supply

Doxorubicin is commercially available

8.4.10 Side effects

Hematologic: Leukopenia (dose-limiting), thrombocytopenia, anemia. Nadir in 10-14 days with recovery usually in 21 days.
Dermatologic: alopecia (usually complete; reversible) radiation recall reactions; increased sensitivity to sunlight.
Gastrointestinal: nausea and vomiting (doxorubicin is generally considered moderately to highly emetogenic), anorexia, diarrhea, mucositis (stomatitis, esophagitis).
Cardiovascular: cardiomyopathy may occur and is related to total cumulative lifetime dose. The risk for cardiomyopathy increases with total doses > 450 mg/m2. ECG changes and less often, arrhythmias, are seen. Rarely, sudden death has occurred.
Other: Red discoloration of urine for 24-48 hours after drug administration. Doxorubicin is a vesicant and can cause tissue necrosis if extravasated, especially at the concentration usually employed for bolus injections (i.e., 2 mg/mL).

8.4.11 Nursing implications

Doxorubicin is administered intravenously over 3-5 minutes. Avoid extravasation, as severe local tissue necrosis may result.

8.5 Vincristine Sulfate

Please refer to the FDA-approved package insert for vincristine sulfate for product information, extensive preparation instructions, and a comprehensive list of adverse events.

8.5.1 Other names

VCR, Leurocristine sulfate, Oncovin®, Vincasar PFS, LCR

8.5.2 Classification - type of agent

Vinca alkaloid (tubulin inhibitor).

8.5.3 Mode of action

Vincristine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.5.4 Storage and stability

Unopened vials should be stored under refrigeration and protected from light. Commercially available solutions labeled as such are intended to be multidose vials.

8.5.5 Protocol dose specifics

Vincristine will be given at a dose 1.4 mg/m² (with maximum dose 2 mg) in NS 50 mL administered IV over 10 mins on day 1 of each cycle.
.

8.5.6 Preparation

Refer to package insert for preparation instructions

8.5.7 Route of administration for this study

IV

8.5.8 Incompatibilities

Furosemide; some in-line filters; polysiloxan containers used in portable delivery services.

8.5.9 Availability & Supply

Vincristine is commercially available in 1 mL, 2 mL, and 5 mL vials in a concentration of 1 mg/mL.

8.5.10 Side effects

The most common toxicity associated with vincristine is neurotoxicity. Peripheral manifestations of neurotoxicity include: numbness of extremities, paresthesias, loss of deep tendon reflexes, neuropathic pain and muscle weakness. GI manifestations of neurotoxicity include constipation, and adynamic ileus. Cranial nerve manifestations include: diplopia, hoarseness, tinnitus, jaw pain (the latter usually occurring with the first dose of vincristine). Orthostatic hypotension & SIADH may also be seen. Vincristine is a vesicant and may cause tissue necrosis upon extravasation. This is more likely with bolus injections as opposed to dilute infusions

8.5.11 Nursing implications

Vincristine should befurther diluted in 50 mL 0.9% sodium chloride to final concentration 0.0015 – 0.08 mg/ml and infused over 10 minutes
Precaution: Maximum single dose is 2 mg.

8.6 Prednisone

Please refer to the FDA-approved package insert for prednisone for product information and a comprehensive list of adverse events.

8.6.1 Other names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred

8.6.2 Classification – type of agent

Adrenal corticosteroid

8.6.3 Mode of action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.6.4 Storage and stability

Store tablets, solutions and syrup in tightly closed containers at room temperature.

8.6.5 Protocol dose specifics

100 mg PO daily [2 tablets once daily] on Days 1-5 (or Days 2-6).
Please note: On any clinic day (for study treatment), patients should NOT take prednisone before coming to clinic, but should hold and bring the prednisone tablets to clinic.

8.6.6 Preparation

Not applicable.

8.6.7 Route of administration for this study

Oral

8.6.8 Incompatibilities

None known.

8.6.9 Availability & Supply

Commercially available 50 mg tablets will be used

8.6.10 Side effects

Side effects likely to be encountered with intermittent high doses include: GI (dyspepsia, ulceration), insomnia, and hyperglycemia. Occasionally a “withdrawal syndrome” after short-term high doses, such as in this study, manifest muscle aches and pains. Immunosuppression with risk of infection is also seen.

9.0 CORRELATIVES/SPECIAL STUDIES

Patients will have blood samples collected for pharmacokinetic (PK) analysis and future unspecified research.

PK samples will be collected during Cycle 2, when TAK-659 and R-CHOP are first given in combination, at the time points listed below:

PK Sample Timing (in relation to TAK-659 dosing)**	
C2D1	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose
C2D2	Pre-dose

C2D15	Pre-dose, 0.5, 1, 2, 4, and 8 hours post-dose
C2D16	Pre-dose
**The following windows are allowable for PK sample collection: Pre-dose (within 60 min before TAK-659 dose); 30 mins (±10 mins); 1 hour (±10 mins); 2 hours (±20 mins); 4 hours (±30mins); 8 hours (±30 mins), 24 hours (±60 mins).	

The PK samples will be collected and stored at the Robert H Lurie Cancer Center of Northwestern University Pathology Core Facility (PCF) and shipped to Q2 solutions for analysis. Please refer to laboratory manual for contact information and details about collection, processing, storage and shipment of samples.

Blood samples for banking and future unspecified research will be collected at the time points listed below:

Samples for Banking	
C1D1	Pre-dose**
C2D1	Pre-dose**
C4D1	Pre-dose**
EOT & time of relapse (if patient willing and feasible)	All patients will have an EOT sample drawn. If patient has not relapsed at EOT, an additional sample should be obtained at the time of confirmed progression, within 30 days.
**All pre-dose samples should be collected within 60 minutes before 60 minutes within 60 minutes before R-CHOP with C1 or within 60 minutes prior to TAK-659 dose for C2D1 and C4D1	

(Please note: If bio banking samples are not collected or patient refuses, it will not be a deviation).
See separate lab manual for further details on collection and shipping.

9.1 Specimen Banking

Blood samples are mandatory (if patient willing) and will be collected for our Biobank at C1D1 (pre-dose), C2D1 (pre-dose), C4D1 (pre-dose), at completion of therapy and at relapse/progression. *(Please note: If bio banking samples are not collected or patient refuses, it will not be a deviation).*

Patient samples for banking will be collected for this study. They will be received by the Robert H Lurie Cancer Center of Northwestern University Pathology Core Facility (PCF) and will be sent to,be processed and stored at Dr. Gordon's laboratory. Specimens will be stored indefinitely or until they are used up, and such samples may be shared with researchers at other institutions. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Please refer to laboratory manual for contact information and details about collection, processing and storage of samples.

Dr. Reem Karmali will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Northwestern University. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Northwestern University for publication and any licensing agreement will be strictly adhered to.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a Phase I dose escalation study that will accrue between 12 and 18 patients.

10.2 Sample Size and Accrual

The design of the study is described in detail in Section 4.3. If there are insufficient patients evaluable for toxicity at the end of 18 patients, the protocol will be amended to add the required number of additional patients.

10.3 Data Analyses Plans

Sections 6.2 and 6.3 define evaluability for toxicity, DLT determination and response (ORR).

Using only patients evaluable for toxicity (Section 6.2.1), safety and tolerability of TAK-659 will be determined by summarizing all adverse events as to type, timing, frequency, severity and attribution.

Dose limiting toxicities are defined in Section 4.3.1. The determination of maximum tolerated dose is defined in Section 4.3. The MTD will be determined using only patients who are evaluable for DLT determination (Section 6.2.1).

Preliminary efficacy of TAK-659 will be assessed by calculating the ORR with 95% exact binomial confidence intervals, using all response-evaluable patients (Section 6.3) as the denominator. ORR is defined as the percentage of subjects with a confirmed complete response (CR) or partial response (PR) as assessed by the investigators. This will be assessed at 3 months

Using all patients at all doses, progression-free survival and overall survival at 12 and 18 months will be assessed using Kaplan-Meier curves.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the

implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

Amendments to the protocol will be initiated and maintained by the assigned Medical Writer. Requests for revisions may come from multiple sources, including but not limited to the Principal Investigator, study team, drug company, or FDA. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Novocure. Amendments will be distributed by the lead institution (Northwestern) to all participating sites upon approval by the Northwestern University IRB.
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11.3 Registration Procedures

For potential patients, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable), and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda Pharmacovigilance (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance

For PIPELINE Products:
Phone: 1-844-ONC-TKDA (1-844-662-8532)
Email: GlobalOncologyMedInfo@takeda.com
Fax: 1-800-881-6092, Hours Mon – Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.

11.5 Data Submission

Data collection for this study will be done through NOTIS. Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a patient is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Generally, all data for phase I patients, or any safety run-ins during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection of adverse events and baseline data from the time of registration to the date of screen failure.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to CTO website for additional information). The level of risk attributed to this study requires high risk monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level.. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change. Such modifications also need to be reported to the FDA, as applicable, within the appropriate timelines

11.6.2 Other Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the Institutional Review Board (IRB). Protocol deviations must be reported according to the policies and procedures of the IRB of record.

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants
- Has compromised the rights and welfare of the research subject
- Has damaged the scientific integrity of the data collected for the study
- Results from willful or knowing misconduct on the part of the investigator(s)
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies

All protocol deviations will be documented by the study team on a paper or electronic deviation tracking log (see NOTIS for copy of log) as they occur. The deviation tracking log must be made available upon request for review by the assigned QAM. The deviation tracking log must be reviewed, signed, and dated by the investigator prior to each monitoring visit, or otherwise in a timely manner, whichever occurs first. The PI signed and dated deviation tracking log will be uploaded to eCRFs prior to each scheduled monitoring visit or upon request.

Deviations will be reviewed per the DSMP.

11.8 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use

only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

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APPENDICES

Appendix A: Medications, Supplements, & Food Products to be avoided & to be Used Cautiously

Table 1: Medications, Supplements, and Food Products that are Strong CYP3A and/or P-gp Inhibitors or Inducers

Medication, Supplement, or Food Product (a, b)		Required Washout Period Before First Dose
Strong CYP3A Reversible Inhibitors and/or P-gp Inhibitors		
amiodarone	ketoconazole	5 times the inhibitor half-life (if a reasonable half-life estimate is known), or 7 days (if a reasonable half-life estimate is unknown)
azithromycin	itraconazole	
captopril	nefazodone	
carvedilol	posaconazole	
cyclosporine	quercetin	
diltiazem	quinidine	
dronedarone	ranolazine	
erythromycin	ticagrelor	
felodipine	verapamil	
	voriconazole	
Strong CYP3A Mechanism-based Inhibitors		
clarithromycin (c)		7 days, or 5 times the inhibitor half-life, whichever is longer
conivaptan (c)		
mibefradilc (c) (d)		
telithromycin		
grapefruit-containing foods and beverages		5 days
Strong CYP3A Inducers and/or P-gp Inducers		
avasimibe (e)	rifabutin	7 days, or 5 times the inducer half-life, whichever is longer
carbamazepine	rifapentine	
phenobarbital	rifampin	
phenytoin	St. John's wort	
primidone		

(a) Note that the list of strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers is not exhaustive and is based on the FDA Draft DDI Guidance (Sources: fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf and fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm). If a medication, supplement, or food/beverage is suspected or known to be a P-gp inhibitor or inducer and/or strong CYP3A inhibitor or inducer but is not on the list, then its use must be discussed on a case-by-case basis by the PI to assess the relative benefit and risk.
(b) Note that medications used to treat HIV or hepatitis C infection that are strong CYP3A inhibitors or inducers and/or P-gp inhibitors or inducers are not included in this list, as patients with known HIV infection or known or suspected active hepatitis C infection are excluded from study participation. The list also does not include oncology medications because they are prohibited during the study.
(c) Also inhibitor of P-gp.
(d) Withdrawn from the US market due to safety reasons.
(e) Not marketed in the US.

Appendix B: Cockcroft-Gault Equation

For male subjects:

Creatinine clearance =

$$\frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

OR

$$\frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

For female subjects:

Creatinine clearance =

$$\frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

OR

$$\frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine[µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Appendix C: New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

- Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[32]

NU Study Number: NU 18H02
Other Study Number: IISR-2017-101972

APPENDIX D – LUGANO 2014 RESPONSE CRITERIA

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	**Complete metabolic response**	**Complete radiologic response (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion		Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	Not applicable	None
Bone marrow	None No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	**Partial metabolic response**	**Partial remission (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but	Not applicable

	reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	
No response or stable disease	**No metabolic response**	**Stable disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	**Progressive metabolic disease**	**Progressive disease requires at least 1 of the following**
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than	Regrowth of previously resolved lesions

	another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	A new node _ 1.5 cm in any axis A new extranodal site _ 1.0 cm in any axis; if _ 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to Lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Amendment 1 (FDA Response) – August 6th, 2018			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Cover Page	Listed IND Number as "TBD"	Includes IND Number: 140223	Administrative; newly available information post-FDA submission
3.2.19 (Exclusion Criteria)	n/a	Adds abnormalities of left ventricular function as an exclusionary cardiovascular condition	FDA request; the current TAK-659 IB lists 2 cases of LV dysfunction when administered with other anticancer agents.
4.3.1 (Definitions of Dose Limiting Toxicity)	DLT definition includes AE's meeting the listed criteria that are considered at least possibly related to therapy with study drug.	Updates language to be more stringent; all AE's meeting the listed criteria will be considered DLT's unless the event is clearly unrelated to study therapy	FDA request; encourages more stringent monitoring of DLT's
4.4.2 (Recommended Dose Delays / Modifications for R-CHOP or TAK-659)	n/a	Adds stipulation for holding drug in the case of Grade 3 or 4 EF toxicity. Cardiology assessment should take place to determine etiology, and patient should be discontinued if related to study drug.	In response to FDA request to add cardiology monitoring for known cases of LV dysfunction.
5.0 (Study Procedures; Table 5.1 & 5.2)	n/a	Adds Echo at baseline, post-Cycle 3, and End of Treatment	FDA request to monitor left ventricular dysfunction; there have been 2 cases when TAK-659 was administered with other anticancer agents.
References	n/a	Moves "Reference" section to before the Appendices	Administrative change for consistency with internal protocols.
Amendment 1b (FDA Response Part 2) – August 8th, 2018			
Section(s) Affected	***Prior Version***	***Amendment 1b Changes***	***Rationale***
3.2.19 (Exclusion Criteria)	Defines LV function abnormality as EF < 45%	Changes definition to EF < 50%	FDA request
4.4.2 (Recommended Dose Delays / Modifications for R-CHOP or TAK-659; table 4.5); 5.0 (Study Procedures Table 5.1 & 5.2 #16)	TAK-659 was to be held for Grade 3 or 4 EF toxicity	TAK-659 will also be held for Grade 2 EF toxicity, pending evaluation by cardiology	FDA request; adds more stringent LV function monitoring in light of recent toxicities
Amendment 2 – January 2nd, 2019			
Section(s) Affected	***Prior Version***	***Amendment 1b Changes***	***Rationale***
Cover Page	Reference Northwestern University's Clinical Research Office	Updates to reference the Clinical Trials Office at Northwestern University	***Administrative update***

Section 1.3 Background information	Previous language	Updated with information based on latest Investigator's brochure received from Takeda/ Millennium Pharmaceuticals, Inc.	***Update made based on latest Tak-659 IB edition 6 dated 1.15.19***
Study summary Section 2.2 and 6.3 Secondary endpoints and objectives and Section 10 (statistics)	All objectives were stated together	Divided the objectives into subsections. Also specified that For ORR assessment will be done at 3 months and for PFS assessment will be done at 12 and 18 months. OS has also been added as a secondary objective and will be assessed at 12 and 18 months.	***For increased clarity and specificity. To be able to report results as early as possible.***
Section 3.1.8 Inclusion criteria	Creatinine clearance was stated to be calculated by C-G equation or based on urine collection (12 or 24 hours)	The 12-24 hour urine collection option has been removed	***Based on information received from Takeda***
Section 3.1.9 Inclusion criteria	Stated that, patients must have blood pressure ≤Grade 1. *NOTE: Hypertensive patients are permitted if their blood pressure is controlled to ≤Grade 1 by hypertensive medications*	Added language to the note stating" *The actual blood pressure value ONLY will be assessed/graded using the CTCAE v5 hypertension criteria".*	***For added clarity***
Section 3.2.19	List of cardiovascular conditions in the exclusion criteria	Added hypertension to the list	***For clarity and to be in alignment with inclusion criteria 3.1.9***
Section 4.1 (table) Treatment administration summary Footnote 2. and Section 4.2.2 (R-CHOP administration)	Stated that, investigator may choose to administer G-CSF (filgrastim/tbo-filgrastim or pegfilgrastim) with Cycle 1 per standard ASCO guidelines	Added language to state that it is highly recommended for Cycle 2-6 (combination therapy)	***For safety***
4.1 (Overview); 4.2.1 (TAK-659)	n/a	Adds that TAK-659 should be given before starting R-CHOP administrative, with	***For clarity.*** ***Was previously unclear which treatment should***

		consideration for pre-medications and TAK-659 PK's	***be given first***
Study summary; Table 4.1, footnote 5 Section 4.2.2 Section 4.2.2.2 Section 8.6.5 (Prednisone dose specifics)	Prednisone as part of R-CHOP regimen was stated to be taken from day1-5. No language regarding prednisone dosing on clinic visit days.	Added language to state that Prednisone can be taken on Days 2-6 instead of Days 1-5 as part of R-CHOP regimen. Also, clearly states that on any clinic day (for study treatment), patients should NOT take prednisone before coming to clinic, but should hold and bring the prednisone tablets to clinic	***For clarity and flexibility***
Section 4.10 Removal of subjects	One of the criteria stated that subject would be removed if patient demonstrates disease progression.	Added language to specify that progression can be clinical or radiological	***For clarity***
5.0 (Study Procedures, #11 – Table 5.1 & 5.2)	n/a	Breaks down differential WBC count by specifying that lymphocytes and neutrophils are required	***Clarification***
5.0 (Study Procedures, #13 – Table 5.1 & 5.2); 9.0 (Correlative / Special Studies)	Pre- and post-dose timing of correlative samples did not specify which drug they were in relation to	Clarifies that pre- and post-dose timing of samples should be in relation to TAK-659 dosing	***Clarification***
Section 5.1 and 5.2 Study procedure tables	T-cell panel was included in both tables but the specific parameters were not stated.	Introduced Footnote 17 in both tables to state the complete T-cell panel that is required to be done.	***To ensure consistency across all patients and study sites***
Table 5.2 (Off-Study R-CHOP, #1)	There was a discrepancy between the screening window in the table (-21 days) and footnote 1 (≤30 days)	Changes footnote 1 to say that screening procedures should take place ≤30 days prior to registration.	***Correction of discrepancy; patients who received off-study R-CHOP require a shorter screening window to keep treatment timing consistent***

Section 5.1, 5.2 Study procedure tables Footnote 13 and Section 9.0 (Correlatives)	Previous details did not clearly state what might count as a deviation regarding collection of bio banking samples.	Added language to state that Sample collection at EOT & time of relapse (if patient willing and feasible) *and* If bio banking samples are not collected or patient refuses, it will not be a deviation).	***For clarity and flexibility***
Section 5.1.and 5.2 study procedure tables	Footnote 8:Follow-up details Footnote15 End of Treatment visit will occur within 30 days after completing study treatment	Footnote 8: Added language to specify that follow-up will include collection of survival data, progression/relapse and any new anti-cancer treatment. Footnote 15 : Added language to state that EOT visit may occur either as stated before OR before starting new anti-cancer therapy.	***For clarity and completeness***
8.2.5 (Protocol Dose Specifics – Rituximab)	Rituximab was to be administered “immediately prior to the start of chemotherapy”	Rituximab should be administered “as detailed in section 4.0”	***Clarification; previous language was confusing since rituximab may be considered part of the chemotherapy regimen; details in 4.0 are sufficient and should be referenced to avoid confusion***

Section 4(table 4.1); Section 4.2.2; Section 8.5.5 and Section 8.5.11 Vincristine sulphate administration as part of R-CHOP	Language indicated that Vincristine would be administered as IV push throughout protocol except in Section 8.5.11 which indicated that it should be diluted in 25 or 50 mL 0.9% sodium chloride to final concentration 0.0015 – 0.08 mg/ml and infused over 10 minutes	Language modified to indicate that Vincristine will be given as IVPB. It now reads as " Vincristine will be given at a dose 1.4 mg/m² (with maximum dose 2 mg) in NS 50 mL administered IV over 10 mins on day 1 of each cycle."	***Correction of discrepancy and in order to align with institutional policy***
Section 8.6.5 and 8.6.9 and Section 4 (table 4.1) and 4.2.2.6	Prednisone tablets were stated in several different strengths and syrup was also included.	Updated language to clearly state that commercial supply of 50mg prednisone tablets will be prescribed as 2 tablets once daily PO to achieve a dose of 100mg daily.	***For clarity and convenience and to minimize deviations***
Section 9.0 Correlatives/Special studies	The PK sample analysis laboratory had not been specified. The banking samples were to be stored at NU PCF.	Inserted language to state that PK samples will be received by NU PCF and shipped to Q2 solutions for analysis. The banking samples will now be received by NUPCF and processed and stored at Dr.Gordon's laboratory.	***Logistical update***
Section 11.9 Publication policy	Previous template language	Updated with most current template language for publication policy	***Administrative update***

Amendment 3 dated 10.24.19			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Title page	Listed Craig Boddy as Sub-I Alfred Rademaker as Biostatistician	Removed Craig Boddy Removed Alfred Rademaker and added Denise Scholtens, PhD as Biostatistician	***Both have left Northwestern University*** ***Added new biostatistician who has taken over the study.***
Throughout	Study was stated to be single center	Term single center removed	***For flexibility, since affiliate sites may join us in the near future***
Section 3.1.3 Inclusion criteria and schema	Eligibility criteria included patients with several high risk features which included “previously treated transformed low-grade lymphoma to large B cell lymphoma with prior treatment not including an anthracycline.”	This criteria has been updated to” DLBCL transformed from low-grade lymphoma among treatment-naïve patients or previously treated transformed low-grade lymphoma with prior treatment not including an anthracycline. “	***To increase flexibility of eligibility criteria***
Section 3.1.4 Inclusion criteria	Patients with measurable disease on PET scan required a definite Deauville score for eligibility	Removed the requirement of a specific Deauville score	***To increase flexibility of eligibility criteria and to minimize protocol deviations***
Section 3.2.1 Exclusion criteria	Exclusion criteria stating prior treatment specifications	Added language to clarify that the note is an exception to the rule, which states that “Patients may receive at most 1 cycle of R-CHOP, rituximab, or systemic corticosteroids within this timeframe.”	***For increased clarity***

Section 3.2.10	Exclusion criteria for patients receiving prior systemic anticancer or radiotherapy. The accompanying note mentions prior R-CHOP cycle.	The accompanying note has been modified to state that patients may receive systemic steroids or rituximab in addition to R-CHOP and references to appropriate sections have been made.	***For clarity and to be in alignment with updates made to the rest of the protocol***
Section 3.2.14 Exclusion criteria	Exclusion criteria regarding secondary malignancies. The accompanying note stated that patients with certain cancers are not excluded if they have undergone complete resection and are considered disease free at the time of registration.	The accompanying note has been modified to state that "Patients with low grade active malignancies such as prostate cancer, non-melanoma skin cancer or carcinoma in situ of any type, which do not need treatment, are not excluded. Similarly, patients with a history of inactive breast cancer on hormone therapy are not excluded"	***To increase flexibility of eligibility criteria and to comply with DSMC recommendation***
Section 3.2.15	Exclusion criteria stated that patients with known GI disease or GI procedure that could interfere with absorption or tolerance of TAK-659 are not eligible.	Language added to clarify that this will be per PI discretion.	***In order to keep wriggle room to include patients that the PI may think are clinically appropriate to go on trial.***
Section 3.2.16	Exclusion criteria for steroids	This criteria has been removed since language regarding steroids has been updated in the protocol (as described above) [steroids for anti-cancer treatment are allowed prior to Cycle 1].	***For consistency***

Section 4.2.3 CNS prophylaxis and treatment	Previous language stating specific details regarding CNS prophylaxis and treatment. It included statement "CNS prophylaxis with intrathecal methotrexate, and/or intrathecal cytarabine is permitted, at the discretion of the investigator."	Statement updated to include intrathecal steroids and timing and dosing will be per Pi discretion. Also added language: Specifically, IV HD-MTX for up to 4 doses is allowable 3 weeks after the completion of 6 cycles of Nivo-R-CHOP. Dosing and schedule of HD-MTX is up to the discretion of the treating physician and should be carried out per institutional guidelines.	***For increased clarity***
Section 4.5.1 Required concomitant medications	. Language regarding required ancillary drugs	Modified the section heading to Required/Permitted medication. Added language regarding permitted steroids. Steroids for anti-cancer treatment are permitted prior to cycle 1 Moved topical steroid use language to permitted concomitant medication section from the prohibited section	***For clarity and consistency***
Section 4.5.2 Prohibited Concomitant Medications	Language included steroids	Removed language regarding steroids, since modified steroid related language has now been added to the permitted concomitant medications section(4.5.1)	***For clarity and consistency***
Section 5.1 and 5.2 Study procedure tables for patients with "On and off study R-CHOP schedules"	The Study treatment period at the top of the table was stated as "1 cycle=21 days, each visit +/-3 days ". Footnote 16 of both tables Had language regarding cardiologic assessment for	Added language clarifying that this statement is applicable " unless otherwise stated in footnotes"(specific instructions that may differ) Added language to state that the C4D1 echo can be done within a window of (-7days) but prior to dosing. Also,	***For increased clarity and flexibility***

	toxicity. Footnote 17 of both tables had language stating details regarding T-cell panel.	timeline for echo at EOT has been clearly stated. One of the components, Total B-cell (CD3)(/uL) has been corrected to Total T cell(CD3)(uL) Updated position of 'X' s in both tables for increased clarity	***Correction of error***
Section 8.1.8 Incompatibilities	Language regarding treatment with steroids and statement regarding anti-neoplastic therapy during study treatment.	Both statements removed.	***To align with the rest of the protocol and to remove redundant language***
Section 11.7 Adherence to protocol	Term Promptly reportable non-compliance used	Updated to RNI (Reportable New Information)	***To align with current IRB requirements***

Amendment 4 dated 4.3.2020			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Title page	List of Sub-Investigators at NU Listed Denise Scholtens, PhD as Biostatistician	Removed list of Sub-Investigators at NU Removed Denise Scholtens, PhD and added Masha Kocherginsky, PhD as biostatistician , along with her contact email address	***Administrative update [since it is not a mandatory requirement to list sub-investigators]*** ***Change in biostatistician assignment.***
Section 3.1.8 Inclusion criteria	Criterion listing the laboratory values to assess adequate organ and bone marrow function	A note added, stating: ‘‘Cytopenias felt to be disease related will not be excluded from the trial.”	***For flexibility and clarity***
Section 3.1.2 Inclusion criteria	Patients may have completed the first cycle of R-CHOP (off study not combined with TAK-659) ≤ 21 days prior to the first dose of TAK-659 or plan to receive the first cycle of R-CHOP after registration	The ≤ 21 days has been changed to ≤ 30 days	***Correction of discrepancy. To align with Section 5 footnote***
Throughout	Language stating that patients may have completed the first cycle of R-CHOP (off study not combined with TAK-659) ≤ 21 days prior to the first dose of TAK-659	The ≤ 21 days has been changed to ≤ 30 days	***For consistency***

Section 3.2.1 Exclusion criteria	Patients with exposure to chemotherapy or immunotherapy ≤ 30 days prior to starting study treatment are not eligible Note: Patients may receive at most 1 cycle of R-CHOP, rituximab, or systemic corticosteroids within this timeframe	Language in the note has been re-worded to state: "Patients may receive a bridge of rituximab or steroids prior to C1 of R-CHOP. Additionally, patients can receive their first cycle of R-CHOP prior to enrolment on trial (off study)."	***For increased clarity***
Section 3.2.10 Exclusion criteria	Patients who have received systemic anticancer treatment (including investigational agents) or radiotherapy less than 3 weeks before the first dose of study treatment (≤ 5 times half-life for large molecule agents or ≤4 weeks with evidence of disease progression if 5 times half-life is > 4 weeks) are not eligible. Note exception: Patients may receive R-CHOP Cycle 1 as outlined in section 4.1 or systemic corticosteroids or rituximab as specified in section 3.2.1	The language in the note has been reworded to state: "This does not apply to C1 dosing of R-CHOP: it is expected that all patients will receive R-CHOP for C1 either on or off study. Patients will also be allowed to receive rituximab and/or steroids as a bridge to C1 of R-CHOP as an exception as outlined in section 3.2.1"	***For increased clarity*** ***To align with section 3.2.1***
Table 4.5 TAK-659 Dose Adjustments for Non-hematologic Toxicities	Table for dose adjustments for non-hematologic toxicities. But attribution was not clearly stated Other asymptomatic Grade 3 laboratory abnormalities that the investigator considers not clinically significant	Added language to appropriate columns: "If attribution to TAK-659 is felt to be possible, probable or definite." "If there is question of relation to TAK-659, discuss with PI to determine appropriate course of action." Modified to add other clinical findings (including HTN) along with grade 3 laboratory abnormalities, which the investigator considers not clinically significant	***For increased clarity and flexibility***

Table 4.6 R-CHOP dose adjustments for non-hematologic toxicities	Previous directives for Sensory neuropathy: Grade 3 neuropathy : "Reduce vincristine by 25-50%, per investigator discretion. If symptoms improve, doses may be increased to previous levels" There was no Grade 2	Added grade 2 directives: "Grade 2 sensory neuropathy- Can maintain or reduce vincristine by 25-50%, per investigator discretion " Grade 3 directive remains the same	***For accuracy***
Section 4.4.3 Criteria for Discontinuation of Study Drug(s)	Previous instructions	Added language: Patients exceeding delays of >21 days for TAK-659 related toxicities may be considered on a case-by-case for continuing dosing with TAK-659. PI and DSMC approval should be obtained prior to continuing dosing with TAK-659	***For flexibility***
Section 4.4.4 Management of Clinical events Prophylaxis against infections	Previous language which included the statement that PJP prophylaxis should be considered at the start of study treatment	Reworded and modified some of the previous language for prophylaxis against infections. The PJP prophylaxis is now required to be as follows: "PJP prophylaxis should be initiated with C2 (first dose of combination treatment)."	***For accuracy and clarity***

Section 4.5.5 Required/permitted concomitant medications	Previous list	Added language "PJP prophylaxis should be initiated with C2 (first cycle of combination therapy)"	***To be consistent with Section 4.4.4***
Section 5.1 and Section 5.2 Study procedure tables	PET/CT should be obtained ≤ 30 days prior to first cycle of R-CHOP (on- or off-study) The baseline ECHO window as 30 days like other screening procedures	The window for PET/CT scan has been increased from $\leq$ 30 to $\leq$ 60 days. The window for baseline ECHO has been increased from 30 to 60 days. Footnote 16 now states: "For baseline ECHO, a window of 60 days prior to registration is acceptable."	***For increased flexibility and to avoid additional testing***
Section 5.2 Study procedures table [Off-study R-CHOP]	The Screening procedures window was ≤ 21 days	The screening procedures window has been increased to ≤ 30 days	***For consistency and convenience***

Section 11 Study management	Previous template language	Updated with most current version of NU protocol template language	***Administrative update***