Official Title: A Phase 1b/2a Basket Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Combination Therapy With the Anti-CD19 Monoclonal Antibody Tafasitamab and the PI3K Inhibitor Parsaclisib in Adult Participants With Relapsed/Refractory Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia (topMIND)

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Clinical Study Protocol

INCMOR 0208-101

A Phase 1b/2a Basket Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Combination Therapy With the Anti-CD19 Monoclonal Antibody Tafasitamab and the PI3Kδ Inhibitor Parsaclisib in Adult Participants With Relapsed/Refractory Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia (topMIND)

Product:	**INCMOR0208 (tafasitamab)** **INCB050465 (parsaclisib)**
IND Number:	**121,474**
EudraCT Number:	**2020-005591-35**
Phase of Study:	**1b/2a**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE, USA 19803**
Original Protocol:	**14 DEC 2020**
Amendment 1:	**08 OCT 2021**
Amendment 2:	**13 SEP 2022**

INVESTIGATOR'S AGREEMENT

I have read the INCMOR 0208-101 Protocol Amendment 2 (dated 13 SEP 2022) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

(Printed Name of Investigator)

(Signature of Investigator) (Date)

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LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
ADA	antidrug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
ASCT	autologous stem cell transplantation
AST	aspartate transaminase
AUC_t	area under curve
BTK	Bruton tyrosine kinase
CFR	Code of Federal Regulations
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration
CMR	complete metabolic response
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CR	complete response
CRR	complete response rate
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography
CTC	common toxicity criteria
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CxDx	Cycle x Day x
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board

Abbreviations and Special Terms	Definition
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed, paraffin-embedded
FL	follicular lymphoma
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iDSMB	internal Data Safety Monitoring Board
IEC	independent ethics committee
IRB	institutional review board
IRC	independent review committee
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous

Abbreviations and Special Terms	Definition
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MALT	mucosa-associated lymphoid tissue
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	Non-Hodgkin lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PHL	Potential Hy's Law
PI3K	phosphoinositide 3-kinase
PJP	*Pneumocystis jirovecii* pneumonia
PK	pharmacokinetic
PMR	partial metabolic response
PR	partial response
QD	once daily
QW	once weekly
R/R	relapsed or refractory
R-CHOP	rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease

Abbreviations and Special Terms	Definition
SLL	small lymphocytic lymphoma
SoA	schedule of activities
SOP	standard operating procedure
t(11;14)	translocation t(11;14)(q13;q32)
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. PROTOCOL SUMMARY

Protocol Title:

A Phase 1b/2a Basket Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Combination Therapy With the Anti-CD19 Monoclonal Antibody Tafasitamab and the PI3Kδ Inhibitor Parsaclisib in Adult Participants With Relapsed/Refractory Non-Hodgkin Lymphoma or Chronic Lymphocytic Leukemia (topMIND)

Protocol Number: INCMOR 0208-101

Objectives and Endpoints:

Table 1 presents the primary objectives and endpoints.

Table 1: Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
Dose confirmation period (Phase 1b): To determine the safety, tolerability, and DLTs of combination therapy with tafasitamab + parsaclisib in participants with R/R NHL or CLL who have been previously treated with at least 2 prior lines of systemic antilymphoma therapy.	Incidence and severity of TEAEs and incidence of DLTs.
Dose expansion period (Phase 2a): To assess the preliminary efficacy of combination therapy with tafasitamab + parsaclisib in participants with R/R NHL or CLL who have been previously treated with at least 2 prior lines of systemic antilymphoma therapy.	ORR, defined as the percentage of participants having best response of CR/CMR or PR/PMR per investigator assessment.

Overall Design:

Table 2 presents the key study design elements.

Table 2: Key Study Design Elements

Study Phase	Phase 1b/2a
Clinical Indication	Treatment of patients with R/R B-cell malignancies who have been previously treated with at least 2 prior lines of systemic antilymphoma/antileukemia therapy.
Population	Male and female participants at least 18 years of age who have R/R B-cell malignancies including R/R DLBCL, R/R MCL, R/R FL, R/R MZL, or R/R CLL/SLL. Participants must have been adequately pretreated and have failed to respond to at least 2 prior lines of systemic antilymphoma/antileukemia therapy.
Number of Participants	A total of approximately 100 participants will be enrolled into the 5 different disease-specific cohorts (up to 20 evaluable participants per cohort). • The dose confirmation period will include up to 50 evaluable participants in 5 cohorts (10 evaluable participants per cohort). • The dose expansion period will include up to 50 additional participants in 5 cohorts (10 evaluable participants per cohort).
Study Design	This is a single-arm, open-label, Phase 1b/2a, multicenter basket study that includes 5 disease-specific cohorts to which participants will be assigned based on the histology of their underlying disease.
Estimated Duration of Study Participation	The estimated study duration for a study participant includes the following: • Up to 28 days for screening • Continuous treatment in consecutive 28-day cycles until treatment discontinuation criteria are met (disease progression, withdrawal by physician/participant decision, unacceptable toxicity) • Safety follow-up, 90 days after discontinuing study treatment • Survival follow-up until study completion criteria are met It is estimated that an individual will participate for approximately 24 months. Participants who are receiving long-term benefit may be transferred to a company-sponsored rollover study after completion of this study.
DSMB	Yes (internal)
Coordinating Principal Investigator	TBD

Treatment Groups and Duration:

The safety, tolerability, PK, and preliminary efficacy of combination therapy with tafasitamab and parsaclisib will be assessed in a dose confirmation period followed by a dose expansion period. Participants will be assigned to 1 of 5 disease-specific cohorts based on the histology of their underlying disease:

- Cohort 1: R/R DLBCL
- Cohort 2: R/R MCL
- Cohort 3: R/R FL
- Cohort 4: R/R MZL
- Cohort 5: R/R CLL/SLL

During the dose confirmation period, participants will be enrolled in 1 of the 5 cohorts in a parallel fashion. Each cohort will enroll 10 evaluable participants, and each participant will be observed for a DLT evaluation period of 1 cycle (28 days). Participants must have received at least 3 of 4 doses of tafasitamab and 21 days of treatment with parsaclisib 20 mg QD during the first cycle (28 days) or have experienced a DLT to be considered evaluable for the dose confirmation period. Participants who are considered not evaluable will be replaced.

An iDSMB will review data once the 10th DLT-evaluable participant from any cohort completes the DLT evaluation period (C1D28 or experiences a DLT). Reviews will be repeated every 4 months thereafter. The occurrence of 2 DLTs within the first 10 DLT-evaluable participants will also trigger iDSMB review of overall safety data and specifics from the case.

The decision to continue enrollment into each of the malignancy subtype cohorts will be based on the frequency of DLTs observed in the first 10 evaluable participants and review of ongoing safety data. After the safety review is completed and the dose confirmation decision is made, the dose expansion period for that cohort will begin, and up to 10 additional participants will be enrolled (up to a total of 20 evaluable participants in each cohort across both study periods; see Figure 1).

Tafasitamab will be administered at 12 mg/kg IV on Days 1, 8, 15, and 22 of Cycles 1 through 3 and then Days 1 and 15 of each 28-day cycle from Cycle 4 onward. Parsaclisib will be self-administered at a dose of 20 mg QD for 8 weeks, followed by a dose of 2.5 mg QD thereafter.

No dose escalation will be performed in this study.

Study treatment will be administered until progression of disease, withdrawal of consent, or unacceptable toxicity (see Section 7.1). Data on OS will be collected until study completion criteria are met (see Section 8.8.3).

Study assessments are provided in Table 3. Appendix H provides guidance on performing assessments during the current COVID-19 global pandemic.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Figure 1: Study Design Schema

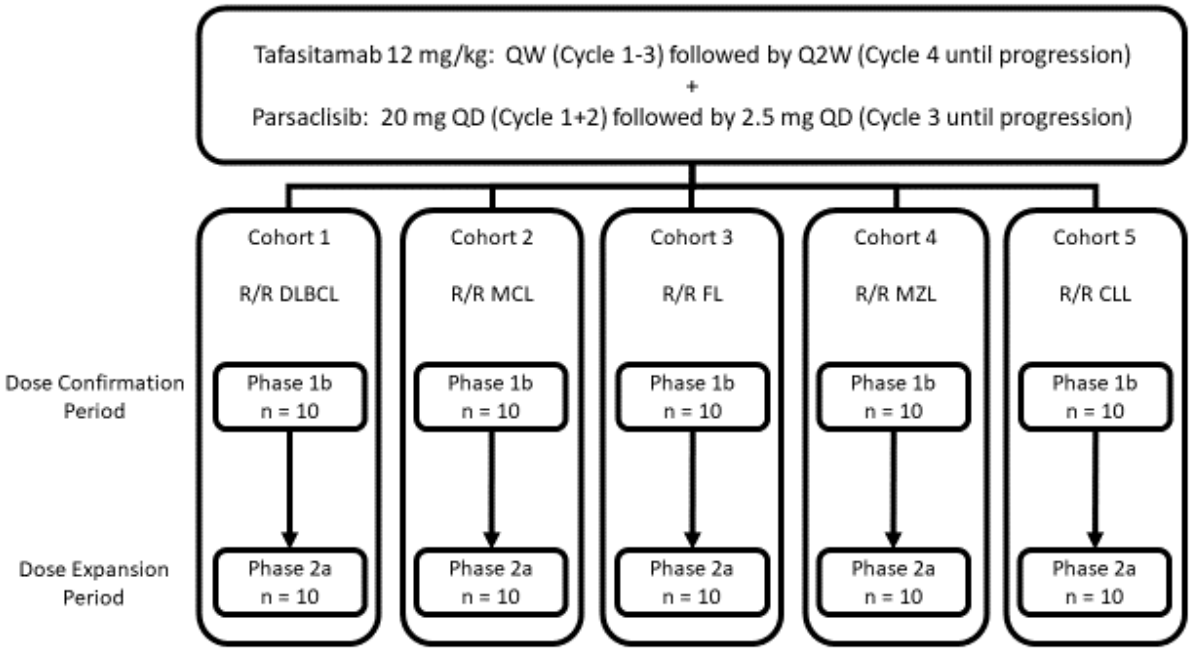


Table 3: Schedule of Activities

Visit Day (Range)	Screening	Treatment						EOT	Follow-up			Notes
		Cycles 1-3				Cycle 4 Onward			Safety	Disease	Survival	
	Days −28 to −1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 22 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)		EOT + 90 d	Post-Treatment	Last Visit + 12 Wk (± 7 d)	
Administrative procedures												
Informed consent	X											
Contact IRT	X	X				X		X	X			
Inclusion/exclusion criteria	X	X										Verify eligibility on C1D1.
General/disease medical history	X											
Prior/concomitant medications	X	X						X	X			
PJP prophylaxis		X										Required while receiving study treatment and for 2-6 months after the last dose of study treatment.
Dispense parsaclisib		X				X						
Administer parsaclisib		X	X	X	X	X	X					20 mg QD: Cycle 1, 2: Days 1-28. 2.5 mg QD: C3D1 onward Given on-site on PK assessment days.
IRR prophylaxis		X*	X*	X*	X	X	X					*Mandatory for first 3 doses.
Administer tafasitamab		X	X	X	X	X	X					12 mg/kg IV Cycles 1-3: Days 1, 8, 15, and 22 Cycle 4 onward: Days 1 and 15 only
Distribute reminder cards		X	X	X	X	X	X					
Assess treatment compliance			X	X	X	X	X	X				

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment						EOT	Follow-up			Notes
		Cycles 1-3				Cycle 4 Onward			Safety	Disease	Survival	
	Days −28 to −1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 22 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)		EOT + 90 d	Post-Treatment	Last Visit + 12 Wk (± 7 d)	
Safety assessments												
AE assessments	X	X	X	X	X	X	X	X	X			
Physical examination	X							X	X	X		Height at screening only.
Vital signs/weight	X	X	X	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X	X	X	X		
B symptoms/ constitutional symptoms	X	X	X	X	X	X	X	X	X	X		
12-lead ECG	X	X*						X				*Repeat only if indicated.
LVEF assessment	X											
OS											X	Repeat every 12 weeks (± 7 d).
Efficacy assessments												
Bone marrow core biopsy and bone marrow aspirate	X							X*				*If positive at screening and within 28 days of achieving a radiologic CR.
PET of the neck, chest, abdomen, and pelvis	X							X*				*Only if FDG-avid disease at baseline: if a radiologic CR is achieved based on CT or MRI earlier than EOT, confirmatory PET must be performed within 28 days (± 14 days). Combined PET/CT and PET/MRI may be used if the CT or MRI is performed with contrast.

Table 3: Schedule of Activities (Continued)

Visit Day (Range)	Screening	Treatment						EOT	Follow-up			Notes
		Cycles 1-3				Cycle 4 Onward			Safety	Disease	Survival	
	Days −28 to −1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 22 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)		EOT + 90 d	Post-Treatment	Last Visit + 12 Wk (± 7 d)	
Contrast-enhanced CT or MRI of the neck, chest, abdomen, and pelvis	X*	Every 8 weeks (± 1 week) for Year 1 Every 12 weeks (± 2 weeks) for Year 2-3 Every 24 weeks (± 2 weeks) for Year 4 onward						X		X**		*Participants with suspected CNS involvement or those with a known history of CNS lymphoma must undergo CT/MRI of the head at screening to exclude active CNS disease. **Participants discontinuing study treatment prior to disease progression must be followed with CT/MRI per the same schedule.
Local laboratory assessments												
Hematology	X	X	X	X	X	X	X	X	X	X		
Serum chemistry	X	X	X	X	X	X	X	X	X			
HBV/HCV	X											
HIV	X*											*Required outside of the United States only.
CMV	X	X				X*		X				*Day 1 of Cycles 4-12 and then every 12 weeks (± 1 week) thereafter (C15D1, C18D1, etc).
Pregnancy testing (serum)	X							X				WOCBP only; repeat after screening if urine pregnancy test is positive.
Pregnancy testing (urine)		X				X			X			WOCBP only

Table 3: Schedule of Activities (Continued)

	Screening	Treatment						EOT	Follow-up			Notes
		Cycles 1-3				Cycle 4 Onward			Safety	Disease	Survival	
Visit Day (Range)	Days −28 to −1	Day 1	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 22 (± 1 d)	Day 1 (± 1 d)	Day 15 (± 1 d)		EOT + 90 d	Post-Treatment	Last Visit + 12 Wk (± 7 d)	
Urinalysis	X							X				
Coagulation	X							X				
Lipid panel	X							X				
Endocrine function	X							X				
[redacted]												

EDTA = ethylenediaminetetraacetic acid.

2. INTRODUCTION

2.1. Background

2.1.1. B-Cell Malignancies

Non-Hodgkin lymphoma is the most common hematologic malignancy in adults. The majority of NHLs are of B-cell origin, with multiple different histological subtypes that confer different clinical outcomes (Habermann et al 2006, Shingleton et al 2020, Swerdlow et al 2016). Apart from the histopathologic classification of NHLs, they are also commonly categorized as indolent or aggressive lymphomas based on their clinical characteristics.

- Indolent lymphomas are slowly progressing and responsive to therapy; however, they are generally considered incurable; indolent lymphomas include FL, MZL, CLL/SLL, and others (Sehn 2016).
- Aggressive lymphomas are rapidly progressing but usually responsive to therapy and often curable; aggressive lymphomas include DLBCL, MCL, and others (Swerdlow et al 2016).

2.1.1.1. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma is the most common NHL, representing approximately 40% of all NHLs. Its rate of incidence continues to increase, with a median age at diagnosis of 64 years. Diffuse large B-cell lymphoma is an aggressive B-cell NHL, and the majority of patients present with advanced disease. Diffuse large B-cell lymphoma is increasingly recognized as a heterogeneous disorder with distinct cell of origin subtypes, each arising from different stages of normal B-cell development. Several studies have shown that the distinct cell of origin subtypes, germinal center B-cell type and activated B-cell type, have unique mutational profiles and different prognostic outcomes (Flowers et al 2010, Lenz et al 2008, Schmitz et al 2018, Vaidya and Witzig 2014).

2.1.1.1.1. First-Line Therapy

The immunochemotherapy regimen consisting of the anti-CD20 mAb rituximab plus CHOP chemotherapy is the current standard of care for the treatment of newly diagnosed DLBCL (Sehn et al 2018). Although the addition of rituximab to CHOP dramatically improves outcomes compared with CHOP alone, 30% to 40% of cases of DLBCL are still primarily refractory or relapse (Coiffier et al 2010, Habermann et al 2006).

2.1.1.1.2. Treatment for Relapsed/Refractory Disease

Patients with disease that progresses or relapses after first-line treatment are evaluated for their eligibility for intensified salvage treatment strategies that can lead to long-term remissions. Examples of such salvage chemotherapy include DHAP (cisplatin, cytarabine, dexamethasone), VIM (etoposide, ifosfamide, methotrexate or mitoxantrone), ICE (ifosfamide, carboplatin, etoposide), and ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin). For patients with chemotherapy-sensitive disease, ASCT as consolidation therapy significantly improves the

outcome of second-line therapy. Approximately 10% to 50% of patients treated with an intensified regimen as second-line therapy achieve long-term remission and cure (Philip et al 1995).

Unfortunately, only approximately 50% of patients with R/R DLBCL are eligible for an intensified treatment strategy, mainly due to cardiac comorbidities, decreased hematopoietic reserve, reduced hepatic function, or advanced age, restricting the benefit of this aggressive approach to a relatively small subset of patients (Morrison et al 2015). Similarly, only younger and fit patients can be evaluated for allogeneic stem cell transplantation (Truelove et al 2015).

Several treatment regimens have been described for patients who have a relapse after intensified second-line treatment or who are not eligible for an intensified second-line regimen. None of these regimens, however, have a confirmed potential for long-term remission or cure. The median survival for patients who have had a relapse after second-line therapy is < 1 year, and median survival for those not responding to second-line therapy is < 6 months (Colosia et al 2014). For elderly patients in particular, participation in a clinical study is recommended in this situation (Pfreundschuh 2010).

In summary, although some patients with R/R DLBCL can achieve remission with second-line chemotherapy followed by consolidation with high-dose chemotherapy and ASCT, the majority will die of the disease. Thus, the development of a more effective initial therapy is essential to improve long-term outcomes.

2.1.1.2. Mantle Cell Lymphoma

Mantle cell lymphoma accounts for approximately 3% to 6% of all NHL cases (Cheah et al 2016) in Western countries. Approximately 3 out of 4 patients with MCL are male, and the disease occurs approximately twice as frequently in white patients as compared with black patients. The median age at diagnosis is 68 years (Schulz et al 2007). The most common form of MCL, referred to as classic MCL, is genetically characterized by the reciprocal t(11;14) that leads to the overexpression of CCND1, which drives tumor growth and division (Campo and Rule 2015).

The median OS for treated patients with MCL is approximately 8 to 10 years. Currently available treatments are not considered curative (Schulz et al 2007); therefore, an unmet medical need exists for patients with MCL.

2.1.1.2.1. First-Line Therapy

Most patients with MCL (70%) have advanced-stage disease at diagnosis (Argatoff et al 1997). There is currently no method to guide treatment, but the Mantle Cell Lymphoma International Prognostic Index has been developed to facilitate risk-adapted treatment (Hoster et al 2008). This index is based on 4 factors: age, performance status, lactate dehydrogenase level, and leukocyte count. Additional prognostic factors evaluated include Ki-67, gene expression profiling, MRD, MCL cell type, peripheral blood absolute monocyte count at diagnosis, and beta$_2$-microglobulin level (Leukemia & Lymphoma Society 2014).

Multiple approaches are used in the first-line treatment of MCL, but treatment typically consists of chemotherapy plus an immunotherapy (ie, chemoimmunotherapy). Treatment options include conventional chemoimmunotherapy alone or followed by maintenance rituximab, conventional

chemoimmunotherapy followed by high-dose chemotherapy and ASCT, intensive chemoimmunotherapy, and conventional chemoimmunotherapy plus involved-field radiation therapy. Unfortunately, none of these modalities are curative (Cheah et al 2016).

2.1.1.2.2. Treatment for Relapsed/Refractory Disease

Most patients will experience serial relapse and can use any number of approved therapies or unapproved therapies in clinical studies. The best order of treatment for these therapies is not known, and choice of therapy will depend on a number of factors, including prior treatment, patient comorbidities and performance status, and expected toxicities. In the United States, approved therapies for MCL include ibrutinib, lenalidomide, and bortezomib. Ibrutinib (Wang et al 2013), lenalidomide (Goy et al 2013), and bortezomib (Fisher et al 2006) received accelerated approval based on the ORR observed in single-arm, Phase 2 studies; bortezomib (in combination with chemotherapy) was also approved in a randomized Phase 3 study of previously untreated participants with MCL (Robak et al 2015). In the European Union, ibrutinib, lenalidomide, and temsirolimus (Hess et al 2009) are approved for the treatment of adult patients with R/R MCL; bortezomib (in combination with chemotherapy) is approved for the treatment of adult patients with previously untreated MCL who are unsuitable for hematopoietic stem cell transplantation.

2.1.1.3. Follicular Lymphoma

Follicular lymphoma is defined as a lymphoma of germinal center B cells, including centrocytes and centroblasts, that has at least a partially follicular pattern. These bone marrow–derived cells undergo somatic hypermutation and class switching of the B-cell receptors, which leads to immunoglobulin diversity and selects B cells that produce high-affinity antibodies (Kahl and Yang 2016). Central to the early transformation and pathophysiology of FL is the t(14;18)(q32;18) translocation found in approximately 90% of cases of FL and that leads to overexpression of BCL2 (Pastore et al 2015). Follicular lymphoma is also positive for the B-cell markers CD10, CD19, CD22, and usually CD20 but is always negative for CD5 (Barekman et al 2001).

Although FL is a biologically heterogeneous disease with widely varying outcomes, the prognosis for individual patients can be made based on clinical and laboratory findings. The most widely used risk model for FL is the Follicular Lymphoma International Prognostic Index, which includes 5 adverse prognostic factors: age older than 60 years, Ann Arbor Stage III to IV, hemoglobin level < 120 g/L, 4 or more involved nodal areas, and elevated serum lactate dehydrogenase level (Solal-Céligny et al 2004). Following treatment, patients can be assessed for MRD, which refers to the small number or cancer cells that may remain after treatment and may lead to relapse.

2.1.1.3.1. First-Line Therapy

Some patients with early-stage FL (Ann Arbor Stage I or II) who develop symptoms may be treated with radiation therapy alone. Advanced-stage (Ann Arbor Stage III-IV), Grade 1 to 3a FL is often treated according to the degree of tumor burden (low vs high) and the presence or absence of FL symptoms (eg, fever, night sweats, unexplained weight loss, etc). Asymptomatic patients with a low tumor burden may be candidates for watchful waiting, whereas those with a high tumor burden may receive R-CHOP. Symptomatic patients with a low tumor burden may

receive either single-agent rituximab or R-CHOP, whereas patients with a high tumor burden may receive R-CHOP or CHOP.

Based on an analysis of 588 patients receiving R-CHOP as initial FL therapy, approximately 20% of patients experienced early PD, defined as PD within 2 years of diagnosis. The 5-year OS was 50% in the early PD group compared with 90% in patients without early PD (Casulo et al 2015).

2.1.1.3.2. Treatment for Relapsed/Refractory Disease

There are several options for patients with FL who experience relapse after initial treatment (Kahl and Yang 2016). The use of single-agent bendamustine was approved by the FDA in 2008 for use in patients with indolent B-cell NHL that progressed within 6 months of treatment with rituximab (Treanda® 2013). In 2016, the FDA and the European Commission approved the use of obinutuzumab in combination with bendamustine followed by maintenance therapy with obinutuzumab in patients with FL whose disease progressed within 6 months of prior rituximab-based therapy (Gazyva® 2016, Sehn 2016). Autologous stem cell transplantation is another option available to some patients after relapse.

The first-in-class PI3Kδ inhibitor idelalisib (Zydelig® 2016) was granted accelerated approval in 2014 by the FDA based on a single-arm study enrolling participants with FL (N = 72) with disease that was refractory to at least 2 prior therapies (Gopal et al 2014). The approved indication was for the treatment of patients with relapsed follicular B-cell NHL who had received at least 2 prior systemic therapies. Idelalisib was also approved in Europe, based on the same study, for the treatment of adult patients with FL that is refractory to 2 prior lines of treatment. In September 2017, a pan PI3K inhibitor, copanlisib (Aliqopa® 2017), was also granted accelerated approval by the FDA based on a single-arm study enrolling participants with FL (N = 104) who had received at least 2 prior systemic therapies. The ORR for idelalisib in a double-refractory FL population was 54% (Zydelig® 2016); the ORR for copanlisib in participants with R/R FL who had received at least 2 prior therapies was 59% (Aliqopa® 2017). Other agents (eg, lenalidomide, venetoclax, ibrutinib) are being evaluated in clinical studies.

Although the majority of patients will respond to these first-line therapies, the natural history of FL is characterized by continuous relapse. Thus, despite significant progress in the management of patients with FL, an unmet need still exists.

2.1.1.4. Marginal Zone Lymphoma

Marginal zone lymphomas, a group of indolent (slow-growing) NHL B-cell lymphomas, account for approximately 10% of all histologically diagnosed NHL cases in Western countries (Cuneo and Castoldi 2006). The average age at diagnosis is 60 years, and it is slightly more common in women than in men (Lymphoma Research Foundation 2017).

Marginal zone lymphomas originate from memory B lymphocytes normally present in a distinct microanatomic compartment called the "marginal zone" of the secondary lymphoid follicles (Zinzani 2012). The subtypes of MZL share a similar immunophenotype that is positive for the B-cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and usually CD23 (Swerdlow et al 2016).

The latest lymphoma classification identifies 3 subtypes of MZL according to the involved site and characteristic molecular findings (Swerdlow et al 2016):

- Extranodal MZL (MALT)
- Nodal MZL
- Splenic MZL

2.1.1.4.1. First-Line Therapy

Treatment selection for patients with MZL depends on disease characteristics, including type, stage, and location, as well as other patient characteristics, such as age and overall health. Because MZL is most often a slow-growing disease, a watch-and-wait approach is appropriate until symptoms appear.

Helicobacter pylori–positive gastric extranodal MZL/MALT lymphoma is initially treated with antibiotics in combination with proton pump inhibitors. In patients with symptomatic nongastric MALT lymphoma, treatment may include surgery for certain sites (lung, breast) or radiation therapy. Initial treatment for advanced disease usually includes immunotherapy and chemotherapy, including bendamustine plus rituximab and R-CHOP.

When treatment is necessary in patients with symptomatic nodal MZL, options include radiation therapy, chemotherapy and/or immunotherapy, and other treatments commonly used in other types of slow-growing lymphomas, such as FL.

Some patients with splenic MZL may undergo a splenectomy. Patients ineligible for surgery may receive low-dose radiation of the spleen or rituximab with or without chemotherapy. In some cases, because of the association of this type of lymphoma with HCV, interferon with or without antiviral therapy may be given to patients who show evidence of HCV infection.

2.1.1.4.2. Treatment for Relapsed/Refractory Disease

Asymptomatic patients may be observed (watch-and-wait), and radiotherapy may be considered for patients with MZL who have localized relapses. If systemic treatment is required, chemoimmunotherapy can be repeated after long initial remissions (≥ 24 months). Autologous stem cell transplantation may be considered in fit patients with clinically aggressive relapse. In other cases, an alternate chemoimmunotherapy regimen can be used (Zucca et al 2020).

In a Phase 2 trial, single-agent therapy with ibrutinib showed antilymphoma activity in MZL, including nodal MZL. In January 2017, ibrutinib was granted accelerated approval from the FDA for the treatment of patients with MZL who require systemic therapy and have received at least 1 prior anti-CD20–based therapy. The PI3K inhibitor copanlisib has also demonstrated significant efficacy and a manageable safety profile in heavily pretreated patients with R/R MZL (Zucca et al 2020).

Several other drugs and drug combinations are being studied in clinical trials of MZL and include chemotherapy agents (bendamustine), mAbs (blinatumomab, obinutuzumab, pembrolizumab, and ibritumomab), antibody drug conjugate (brentuximab), small molecules (idelalisib, copanlisib, duvelisib, TGR-1202, and venetoclax), proteasome inhibitors (bortezomib), immunomodulators (lenalidomide and ublituximab), and radioimmunotherapy strategies (^{90}Y-ibritumomab tiuxetan).

2.1.1.5. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia is the most common leukemia in the Western world, and the median age at diagnosis is 72 years. The overall incidence is 4.2 cases per 100,000 people/year; however, it increases to > 30 cases per 100,000 people/year for people older than 80 years. In the WHO classification, SLL and CLL are considered to be a single entity. The diagnosis of CLL is established by the following criteria (Hallek et al 2018):

- Presence of ≥ 5000 monoclonal B lymphocytes/µL in the peripheral blood (clonality of these B lymphocytes needs to be confirmed by flow cytometry).
- Blood smear showing leukemic cells as small, mature-appearing lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernible nucleoli and having partially aggregated chromatin. Larger, atypical lymphocytes or prolymphocytes must not exceed 55%.

Chronic lymphocytic leukemia cells express CD5, CD19, CD20, and CD23. Surface immunoglobulin, CD20, and CD79b usually have lower expression compared to normal B cells.

The diagnosis of SLL requires the presence of lymphadenopathy and/or splenomegaly with a peripheral B-lymphocyte count of $< 5 \times 10^9$/L and should be confirmed by histopathologic evaluation of a lymph node biopsy. Small lymphocytic lymphoma cells show the same immunophenotype as CLL.

2.1.1.5.1. First-Line Therapy

Studies have shown that early treatment with chemotherapeutic agents does not improve OS in patients with low- and intermediate-risk CLL (Rai 0, I-II), so treatment should only be initiated in patients with symptomatic, active disease as defined by significant disease-related symptoms (B symptoms), threatened end-organ function, steroid-refractory autoimmune cytopenias, and/or progressive bulky disease, anemia, or thrombocytopenia (NCCN 2021). In high-risk CLL (Rai III-IV), progressive cytopenia constitutes treatment indication.

First-line treatment is usually stratified by patient-specific and disease-related factors (NCCN 2021), particularly by the presence or absence of the del(17p)/TP53 mutation, which is associated with a more aggressive disease course and refractoriness to many conventional therapies.

- For patients with CLL/SLL without the del(17p)/TP53 mutation, treatment with ibrutinib, acalabrutinib and/or obinutuzumab, or venetoclax + obinutuzumab is recommended. Other treatment options include immunochemotherapy with bendamustine, chlorambucil, or other regimens plus anti-CD20 mAbs such as rituximab and obinutuzumab. For patients younger than 65 years who have no significant comorbidities, chemotherapy regimens including fludarabine in combination with anti-CD20 mAbs are recommended.
- For patients with CLL/SLL with the del(17p)/TP53 mutation, treatment with ibrutinib, acalabrutinib and/or obinutuzumab, venetoclax + obinutuzumab, alemtuzumab and/or rituximab, high-dose methylprednisolone + rituximab, or obinutuzumab monotherapy is recommended.

2.1.1.5.2. Treatment for Relapsed/Refractory Disease

Similar to first-line therapy, treatment at relapse should only be initiated when patients are symptomatic.

First-line treatment may be repeated if the relapse or progression occurs at least 24 to 36 months after therapy and if the TP53 mutation was excluded. In patients with disease that is refractory to first-line therapy or if relapse occurs within 2 to 3 years after therapy, the therapeutic regimen should be changed. In addition to the treatment regimens recommended for first-line therapy, PI3K inhibitors such as duvelisib or idelalisib in combination with rituximab can be used (NCCN 2021). Other recommended regimens include alemtuzumab and/or rituximab, high-dose methylprednisolone + rituximab, lenalidomide and/or rituximab, or monotherapy with idelalisib or obinutuzumab.

2.1.2. Tafasitamab

Tafasitamab, also known as INCMOR00208, MOR00208, and XmAb®5574, is an Fc-engineered mAb that binds to the human B-cell surface antigen CD19 and is produced by recombinant DNA technology in Chinese hamster ovary cells. Tafasitamab is being developed for use in patients with CD19+ B-cell malignancies, including R/R ALL, R/R NHL such as DLBCL, R/R indolent NHL such as FL and MZL, treatment-naive DLBCL, treatment-naive CLL/SLL/PLL, R/R CLL/SLL/PLL, and RT. Tafasitamab in combination with lenalidomide, is approved for the treatment of adult patients with R/R DLBCL not otherwise specified, including DLBCL arising from low-grade lymphoma, who are not eligible for ASCT, in the US, Canada, the European Union, and other countries. For an overview of clinical studies of tafasitamab, please refer to the tafasitamab IB.

CD19 is expressed on a variety of B-cell lymphomas and normal B cells and has been shown to be expressed also in cases where rituximab is ineffective due to CD20 downregulation or other factors (Davis et al 1999, Gerber et al 2009). Due to its lineage-specific expression pattern, targeting CD19 has clinical utility as a therapeutic approach to NHL (Hammer 2012). The increased binding of tafasitamab to FcγR, due to its Fc region, significantly enhances in vitro antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and its direct cytotoxic effects (apoptosis) on the tumor cells compared with the nonengineered parental murine antibody. Tafasitamab has not been shown to mediate complement-dependent cytotoxicity (tafasitamab IB).

In a Phase 1 study of 27 participants with relapsed/refractory CLL who received 1 prior line of therapy (XmAb5574-01), tafasitamab monotherapy at doses ranging from 0.3 mg/kg (n = 1) to 12 mg/kg (n = 16) was generally well tolerated, with Grade 1/2 infusion reactions reported as the most common AEs. Grade 3 and 4 toxicities occurred in 5 participants and included neutropenia, thrombocytopenia, increased aspartate aminotransferase, febrile neutropenia, and tumor lysis syndrome. Preliminary efficacy was also observed: on the basis of physical examination and laboratory studies, 18 participants (66.7%) achieved PR and the remaining 9 participants (33.3%) achieved SD. Using CT criteria as well as examination and laboratory data, 8 participants (29.6%) achieved a PR, with an additional 16 participants (59.3%) achieving SD by physical examination criteria and laboratory studies (Woyach et al 2014).

MOR208C201 is a Phase 2a, open-label, multicenter study of single-agent tafasitamab in participants with R/R NHL. As of the data cutoff date of 28 SEP 2018, responses as assessed by

the investigator were seen in 3 of the 4 studied subgroups: 25.7% of participants with DLBCL, 29.4% with FL, and 27.3% with other indolent NHLs. In a sensitivity analysis excluding participants without a postbaseline response assessment, the ORR was 36.0% in the DLBCL, 32.3% in the FL, and 30.0% in the other indolent NHL subgroups. The safety profile of tafasitamab was favorable, with only 4 of 92 participants (4%) experiencing a serious adverse reaction, no treatment-related deaths, and no evidence for significant late toxicities.

2.1.2.1. Tafasitamab Pharmacokinetics

2.1.2.2. Tafasitamab Immunogenicity

No treatment-emergent or treatment-boosted ADAs were detected for tafasitamab, and the pre-existing antibodies did not affect the PK, safety, or efficacy of tafasitamab. The ADA results are summarized in the tafasitamab IB.

2.1.3. Parsaclisib

Parsaclisib (INCB050465) is a potent, selective inhibitor of PI3Kδ (50% inhibitory concentration = 1.1 ± 0.5 nM), with approximately 20,000-fold selectivity for the other PI3K family members. Parsaclisib does not significantly inhibit (< 30% inhibition) a broad panel of kinases when tested at a concentration of 100 nM (refer to the parsaclisib IB). Parsaclisib is potent (50% inhibitory concentration of ≤ 10 nM) in cell-based assays relevant to the pathogenesis of B-cell malignancies, such as PI3Kδ-mediated signaling and growth of human B-cell lines.

As of the data cutoff date of 30 MAR 2021, parsaclisib is being evaluated in 10 ongoing clinical studies, and is also available in a Phase 2, open-label, multicenter rollover study. Parsaclisib was evaluated in 1035 unique participants as monotherapy and/or in combination therapy in participants with advanced malignancies, B-cell malignancies, advanced solid tumors, and pSS in 7 completed studies, and in healthy participants in 2 completed studies.

Additional trial design and safety information from these trials can be found in the parsaclisib IB.

2.1.3.1. Parsaclisib Pharmacokinetics

Based on an ex vivo whole blood assay, parsaclisib 20 mg QD provided exposure ranging from approximately 2-fold above the IC_{90} at trough to 19-fold above the IC_{90} at peak.

Study INCB 50465-101 was a Phase 1/2 study that examined parsaclisib monotherapy dose escalation (5-45 mg QD) and dose expansion (20 mg and 30 mg QD). In this study, the vast majority (93%) of responses occurred by the first assessment (~ 9 weeks) in participants with R/R DLBCL (n = 23), FL (n = 14), MZL (n = 9), or MCL (n = 9; data cutoff date of 18 AUG 2017). For the participants with NHL who received parsaclisib monotherapy, an objective response was achieved by 7 of 23 participants (30%) with DLBCL, 10 of 14 participants (71%) with FL, 7 of 9 participants (78%) with MZL, and 6 of 9 participants (67%) with MCL. Among the 72 participants treated with parsaclisib monotherapy, the most common (≥ 30%) nonhematologic TEAEs of any grade were diarrhea/colitis (36%), nausea (36%), fatigue (31%), and rash (31%). New or worsened Grade 3/4 neutropenia occurred in 19% of participants based on laboratory data. The t_{max} of parsaclisib was 0.5 to 1 hour, the terminal half-life was approximately 8.6 to 11.5 hours, and the exposure appeared to be dose-proportional between 5 mg and 45 mg QD at steady state. The PK analyses demonstrated robust and sustained pathway inhibition at all dose levels tested (Forero-Torres et al 2019, parsaclisib IB).

The continuation of parsaclisib at a daily but lower dose (2.5 mg) is expected to provide sufficient exposure (estimated to be approximately 1 × IC_{90} at peak) to maintain PI3K pathway inhibition while minimizing the frequency of late-onset AEs that may lead to study treatment withdrawal. Evaluation of this dosing regimen is ongoing in 3 Phase 2 studies in participants with FL (INCB 50465-203), MZL (INCB 50465-204), and MCL (INCB 50465-205). Preliminary data from participants receiving this regimen suggest that continuous QD dosing has demonstrated benefit in both aggressive and indolent NHL, and the emerging safety profile is consistent with that known for parsaclisib.

2.1.3.2. Parsaclisib Phase 2 Studies

In Study INCB 50465-203 (FL) and Study INCB 50465-204 (MZL), participants were randomized to receive 20 mg QD for 8 weeks followed by either 20 mg QD (Treatment A) or 2.5 mg QD (Treatment B). The primary efficacy endpoint is ORR, as determined by an IRC assessment of response according to CT-based response criteria for lymphomas.

In Study INCB 50465-203, eligible participants had histologically confirmed Grade 1, 2, or 3a FL previously treated with at least 2 prior systemic therapies with documented progression or documented failure to achieve a response after the most recent systemic treatment regimen.

A per-protocol interim futility analysis was conducted when the first 50 participants (Treatment A and Treatment B combined) were treated and had at least 9 weeks of follow-up. The cutoff date for this interim analysis was 20 MAY 2019. Among the 50 participants, the ORR as determined by the IRC was 62.0% (95% CI: 47.2%, 75.3%), with 25 of 50 participants achieving a PR and 6 achieving a CR.

An ad hoc analysis was subsequently performed (data cutoff date of 17 JAN 2020). Among 96 participants evaluable for efficacy (Treatment A, n = 22; Treatment B, n = 74), the IRC-assessed ORR was 69.8% (95% CI: 59.6, 78.7) and the CRR was 13.5%. The median time to response for participants achieving a PR or CR was 8 weeks, with 74.6% of the responses

occurring at the first disease assessment (Week 8). The median DOR was not reached (95% CI: 9.2 months, not estimable) among responders overall, and the median PFS was 15.8 (95% CI: 11.3, 15.8) months overall. Enrollment was ongoing at the time of data cutoff.

In Study INCB 50465-204, eligible participants had pathologically confirmed nodal, extranodal, or splenic MZL previously treated with at least 1 prior systemic treatment regimen, including at least 1 anti-CD20 mAb, with documented progression or documented failure to achieve a response after the most recent systemic treatment regimen. A per-protocol interim futility analysis was conducted on Cohort 2 (BTK inhibitor–naive) after the first 30 participants were treated (Treatment A and Treatment B combined) and had at least 9 weeks of follow-up. The cutoff date for this interim analysis was 08 JAN 2019. Among the 30 participants, the ORR as determined by the IRC was 46.7% (95% CI: 28.3%, 65.7%), with 14 of 30 participants achieving a PR. An ad hoc analysis was subsequently performed (data cutoff date of 17 JAN 2020). Among 94 participants evaluable for efficacy (Treatment A, n = 28; Treatment B, n = 66), the IRC-assessed ORR was 54.3% (95% CI: 43.7, 64.6) and the CRR was 6.4%. The median time to response for participants achieving a PR or CR was 8 weeks, with 72.5% of the responses occurring at the first disease assessment (Week 8). The median DOR was 9.3 (95% CI: 6.2, not estimable) months among responders overall, and the median PFS was 13.8 (95% CI: 8.8, not estimable) months overall. Enrollment was ongoing at the time of data cutoff.

The open-label, multicenter, Phase 2 study INCB 50465-205 is evaluating parsaclisib in participants with R/R MCL. Eligible participants had pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14); at least 1 but no more than 3 prior systemic treatment regimens; and documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen. The primary efficacy endpoint is ORR, as determined by a blinded IRC assessment of response according to CT-based response criteria for lymphomas. The study was divided into 2 cohorts: ibrutinib-experienced (Cohort 1) and BTK inhibitor–naive (Cohort 2). Participants were assigned to receive 20 mg QD for 8 weeks followed by either 20 mg QD (Treatment A) or 2.5 mg QD (Treatment B). In a per-protocol interim futility analysis for Cohort 2 (BTK inhibitor–naive, n = 30 participants, data cutoff date of 08 JAN 2019), an IRC-assessed ORR of 66.7% (95% CI: 47.2%, 82.7%) and a CRR of 16.7% was observed. The futility boundary was not crossed, and the study continued. In an additional ad hoc analysis for Cohort 2 (n = 92 participants, data cutoff date of 17 JAN 2020), the IRC-assessed ORR was 66.3% (95% CI: 55.7, 75.8) and the CRR was 15.2%. The median time to response for participants achieving a PR or CR was 7.9 weeks, with 88.5% of the responses occurring at the first disease assessment (Week 8). The median DOR was 11.0 (95% CI: 6.6, 14.7) months among responders overall, and the median PFS was 11.1 (95% CI: 5.8, 16.6) months overall. Enrollment was ongoing at the time of data cutoff (17 JAN 2020).

In summary, parsaclisib has demonstrated a compelling ORR in these ongoing Phase 2 studies with an acceptable safety profile.

2.1.4. PI3Kδ and CD19/CD20 Combinations

2.1.5. Preclinical

In vitro experiments on CLL cell line MEC-1 or primary CLL cells showed synergistic potential of tafasitamab in combination with idelalisib, a PI3Kδ inhibitor (tafasitamab IB).

Inhibition of PI3Kδ does not significantly affect the effector mechanisms induced by anti-CD20 mAbs such as rituximab or obinutuzumab and provides an effective in vivo therapeutic combination (Palazzo et al 2018). Combination treatment of idelalisib and anti-CD20 mAb have shown clinical benefit compared to anti-CD20 mAb alone for patients with relapsed CLL in Phase 3 studies (Jones et al 2017, Sharman et al 2019). The combination treatments of idelalisib plus rituximab and duvelisib monotherapy are approved for patients with relapsed CLL in the United States and European Union.

2.1.5.1. Tafasitamab + Idelalisib in Relapsed/Refractory Chronic Lymphocytic Leukemia (COSMOS Study)

An open-label, multicenter, Phase 2 study (COSMOS Study, NCT02639910) was performed to evaluate the safety and preliminary clinical activity of tafasitamab combined with idelalisib or venetoclax in 2 independent cohorts of study participants with R/R CLL who were pretreated with a BTK inhibitor. Tafasitamab 12 mg/kg was administered as an IV infusion weekly for Cycles 1 to 3 (with an additional loading dose on Day 4 in Cycle 1), every other week for Cycles 4 to 6, and monthly from Cycle 7 onward (with each cycle lasting 28 days).

As of the data cutoff date of 08 OCT 2019, all 11 participants treated with tafasitamab and idelalisib were included in the safety analysis set and experienced TEAEs (244 events). Most TEAEs reported were Grade 1 or 2 severity (181/244 events). The most common TEAEs were anemia (63.6%), dyspnea (54.5%), and cough (54.5%). The most common ≥ Grade 3 TEAEs were hematologic and included neutropenia (45.5%), anemia (27.3%), and thrombocytopenia (27.3%). Eight participants (72.7%) had 19 treatment-emergent SAEs. Hematologic SAEs included anemia (1 patient, Grade 3), thrombocytopenia (1 patient, Grade 3), and pancytopenia (1 patient, Grade 2). The most common nonhematologic SAE was pneumonia (2 patients, ≥ Grade 3). Four participants (36.4%) had SAEs suspected to be related to tafasitamab (cardiac failure, acute pancreatitis, pneumonia, arthralgia), and 7 participants (63.6%) had SAEs suspected to be related to idelalisib (cardiac failure, pneumonia, bronchitis, septic shock, upper respiratory tract infection, acute pancreatitis, increased C-reactive protein level, pancytopenia). Tafasitamab treatment was interrupted due to TEAEs in 10 participants (90.9%), mainly due to IRRs (in 5/11 participants, 45.5%). The IRRs were Grade 2 in 4 of 5 participants and Grade 3 in 1 participant. No participants discontinued tafasitamab permanently due to IRRs. Idelalisib treatment was interrupted due to TEAEs in 9 participants (81.8%), and 5 participants (45.5%) permanently discontinued idelalisib due to TEAEs.

A best response of CR or PR was achieved in 10 of 11 participants (90.9%; CR: n = 1, PR: n = 9).

2.1.5.2. Parsaclisib + Rituximab in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (Study CITADEL-112)

Study INCB 50465-112 (CITADEL-112; NCT03424122) is an ongoing Phase 1, open-label, dose-finding study to evaluate the safety and tolerability of parsaclisib combined with rituximab and other therapies in participants with previously treated B-cell lymphoma. As of the data cutoff date (30 MAR 2020), 13 participants in this study received the combination of parsaclisib 20 mg QD for 8 weeks followed by 20 mg QW plus rituximab, and 7 participants remained ongoing with treatment. Treatment-emergent AEs were reported in all 13 participants; the most frequently occurring TEAEs were neutropenia (7 participants, 53.8%) and anemia, back pain, increased blood creatinine level, diarrhea, hypomagnesemia, and IRR (3 participants each, 23.1%). There were no reported fatal TEAEs. Serious TEAEs occurred in 3 participants (23.1%) and included abdominal sepsis, diarrhea, pneumonia, pneumonitis, and streptococcal pneumonia in 1 participant (7.7%) each. A TEAE of diarrhea in 1 participant (7.7%) led to parsaclisib discontinuation (parsaclisib IB).

2.2. Study Rationale

These preliminary data from combinations of tafasitamab with a PI3Kδ inhibitor and parsaclisib with an anti-CD20 mAb have demonstrated encouraging efficacy signals with a manageable safety profile in patients with B-cell malignancies. Further examination of the safety, tolerability, PK, and efficacy of the combination of tafasitamab and parsaclisib for R/R NHL and R/R CLL is required and provides the scientific and clinical rationale for this study.

This basket study is designed to evaluate the combination treatment of tafasitamab and parsaclisib in participants with R/R NHL or CLL. Both study drugs will be tested at their established doses and dosing regimens in 5 different disease cohorts (see Table 4):

Table 4: Disease Cohorts in Basket Study INCMOR 0208-101

Cohort 1	R/R DLBCL
Cohort 2	R/R MCL
Cohort 3	R/R FL
Cohort 4	R/R MZL
Cohort 5	R/R CLL or SLL

After confirmation of the safety and tolerability of combination therapy in the dose confirmation period of the study (up to n = 10 evaluable participants in each cohort), each cohort will be opened separately for inclusion of additional participants in the dose expansion period of the study (up to a total of n = 20 evaluable participants in each cohort for both study periods).

2.2.1. Justification for Dose

The RP2D have been identified for each individual drug that will be combined in this study.

- Tafasitamab will be administered at 12 mg/kg IV on Days 1, 8, 15, and 22 for Cycles 1 to 3; starting with Cycle 4 and continuing through subsequent cycles, tafasitamab will be administered at the same 12 mg/kg IV dose only on Days 1 and 15.

- Parsaclisib will be self-administered at a dose of 20 mg QD for 8 weeks, followed by a dose of 2.5 mg QD.

Based on the mechanisms of action of both drugs and previously described results from the COSMOS study, the combination of tafasitamab and parsaclisib is not expected to result in drug-drug interactions or exacerbate the known safety profile of either individual drug. Therefore, full doses of both agents when given as monotherapy will be studied in combination in the current study.

2.3. Benefit/Risk Assessment

Based on the available data from nonclinical and clinical studies of tafasitamab and parsaclisib, the potential benefit of combination therapy with both compounds outweighs potential risks. Tafasitamab administered at 12 mg/kg with initial weekly administrations as monotherapy or in various combination therapies was generally well-tolerated and showed a manageable safety profile in the clinical development program of this drug. Parsaclisib has demonstrated a well-tolerated and manageable safety profile in both aggressive and indolent NHL.

Safety data from clinical trials with tafasitamab monotherapy and combination therapy showed that the most frequent AE is IRR, which occurred with tafasitamab in combination with idelalisib or venetoclax. Most of the IRRs were nonserious AEs of Grade 1 or 2, and participants were able to complete their dose after intermittent pausing of the infusion and symptomatic treatment.

Further frequent effects observed during tafasitamab treatment, regardless of causality and severity, included hematologic events of neutropenia, thrombocytopenia, anemia, leukopenia, and febrile neutropenia and nonhematologic events of diarrhea, nausea, rash, asthenia, peripheral edema, headache, upper and lower respiratory tract infection, urinary tract infection, cough, dyspnea, pyrexia, fatigue, hypokalemia, and tumor lysis syndrome.

Adverse events were observed in participants administered parsaclisib monotherapy in inflammatory and autoimmune indications (N = 35), with the most common (in ≥ 10% of participants) being diarrhea and pyrexia (22.9% each); headache and rash (14.3% each); and autoimmune hemolytic anemia, nausea, and peripheral edema (11.4% each). Parsaclisib has effects on the immune system and serious infection events have occurred in patients treated with parsaclisib, including PJP, CMV, and COVID-19. Due to the severity, these events may impact the benefit-risk balance of parsaclisib if not managed appropriately. Furthermore, a pharmacological effect of concurrent corticosteroid use or recent rituximab therapy can contribute to further immunosuppression, and such effects pose an additional risk of infection. In an effort to manage this risk, guidelines for managing serious infections have been implemented in this study and include careful monitoring and supportive care measures. If supportive care interventions are unsuccessful and causes other than parsaclisib-related infections have been ruled out, then either parsaclisib dose modification or permanent discontinuation is recommended. Participants are required to receive a standard PJP prophylaxis regimen while receiving parsaclisib as described in Section 6.7.1.2. Information regarding the additional risks of diarrhea or colitis, neutropenia, and severe cutaneous reactions is outlined in the Warnings and Precautions section of the parsaclisib IB. Dose modification guidance and supportive care guidelines for these AEs have been implemented in this study, and participants will be closely monitored for evidence of toxicities, including long-term toxicities.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of parsaclisib may be found in the parsaclisib IB.

Based on current experience with each compound in combination therapies similar to those in this study (tafasitamab + idelalisib in R/R CLL; parsaclisib + rituximab in R/R B-NHL), the observed safety profiles of tafasitamab and parsaclisib were consistent with their known safety profiles, and no synergistic toxicity is expected in this clinical basket study.

Considering the hypothesized activity of combination therapy with tafasitamab and parsaclisib in each of the diseases to be evaluated in this clinical basket study, and the expected safety profiles of tafasitamab and parsaclisib to be consistent with the described safety profiles for each drug, the benefit/risk evaluation of this combination is considered favorable and allows the evaluation of clinical safety and efficacy in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tafasitamab and parsaclisib may be found in the tafasitamab IB and parsaclisib IB, respectively.

3. OBJECTIVES AND ENDPOINTS

Table 5 presents the objectives and endpoints. All efficacy endpoints will be evaluated according to investigator assessment using the Lugano criteria (Cheson et al 2014; see Appendix C) for NHL and the iwCLL criteria (Hallek et al 2018; see Appendix D) for CLL.

A post hoc independent review of radiologic scans and supporting data may be conducted for independent efficacy analyses, if appropriate.

Table 5: Objectives and Endpoints

Objectives	Endpoints
Primary	
Dose confirmation period (Phase 1b): To determine the safety, tolerability, and DLTs of combination therapy with tafasitamab + parsaclisib in participants with R/R NHL or CLL who have been previously treated with at least 2 prior lines of systemic antilymphoma therapy.	Incidence and severity of TEAEs and incidence of DLTs.
Dose expansion period (Phase 2a): To assess the preliminary efficacy of combination therapy with tafasitamab + parsaclisib in participants with R/R NHL or CLL who have been previously treated with at least 2 prior lines of systemic antilymphoma therapy.	ORR, defined as the percentage of participants having best response of CR/CMR or PR/PMR per investigator assessment.
Secondary	
To estimate the PK of tafasitamab when given as combination therapy with parsaclisib.	PK parameters of tafasitamab when given in combination with parsaclisib. C_{trough} (ie, predose), C_{max}, t_{max}, C_{min}, and AUC_t will be summarized by descriptive statistics.
Exploratory	
[redacted]	

Table 5: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

4. STUDY DESIGN

4.1. Overall Design

Key elements of the study design are described in Table 2.

The overall objective of this single-arm, open-label, Phase 1b/2a, multicenter basket study is to evaluate whether the anti-CD19 mAb tafasitamab and the PI3Kδ inhibitor parsaclisib can be safely combined at the RP2D and dosing regimen that was established for each of the 2 compounds as a treatment option for adult participants with R/R B-cell malignancies.

The safety, tolerability, PK, and preliminary efficacy of combination therapy with tafasitamab and parsaclisib will be assessed in a dose confirmation period followed by a dose expansion period. Participants will be assigned to 1 of 5 disease-specific cohorts based on the histology of their underlying disease:

- Cohort 1: R/R DLBCL
- Cohort 2: R/R MCL
- Cohort 3: R/R FL
- Cohort 4: R/R MZL
- Cohort 5: R/R CLL/SLL

During the dose confirmation period, participants will be enrolled in 1 of the 5 cohorts in a parallel fashion. Each cohort will enroll 10 evaluable participants, and each participant will be observed for a DLT evaluation period of 1 cycle (28 days). Participants must have received at least 3 of 4 doses of tafasitamab and 21 days of treatment with parsaclisib 20 mg QD during the first cycle (28 days) or have experienced a DLT to be considered evaluable for the dose confirmation period. Participants who are considered not evaluable will be replaced.

An iDSMB will review data once the 10th DLT-evaluable participant from any cohort completes the DLT evaluation period (C1D28 or experiences a DLT). Reviews will be repeated every 4 months thereafter. The occurrence of DLTs in 2 or more of the first 10 DLT-evaluable participants will also trigger iDSMB review of overall safety data and specifics from the case.

The decision to continue enrollment into each of the malignancy subtype cohorts will be based on the frequency of DLTs observed in the first 10 evaluable participants and review of ongoing safety data. After the safety review is completed and the dose confirmation decision is made, the dose expansion period for that cohort will begin, and up to 10 additional participants will be enrolled (up to a total of 20 evaluable participants in each cohort across both study periods; see Figure 1).

Tafasitamab will be administered at 12 mg/kg IV on Days 1, 8, 15, and 22 of Cycles 1 through 3 and then Days 1 and 15 of each 28-day cycle from Cycle 4 onward. Parsaclisib will be self-administered at a dose of 20 mg QD for 8 weeks, followed by a dose of 2.5 mg QD thereafter.

No dose escalation will be performed in this study.

Study treatment will be administered until progression of disease, withdrawal of consent, or unacceptable toxicity (see Section 7.1). Data on OS will be collected until study completion criteria are met (see Section 8.8.3).

Study assessments are provided in Table 3.

4.2. Overall Study Duration

The study begins when the first participant signs the study ICF. The end of the study is defined as the date of receipt of the last data point from the last participant that is required for OS analysis.

Up to 28 days are permitted for screening. Treatment will be administered in consecutive 28-day cycles as long as participants are receiving benefit and have not met any criteria for treatment discontinuation, and a safety follow-up visit will occur 90 days after the last dose of study drug. It is estimated that an individual will participate for approximately 24 months.

4.3. Study Termination

The investigator retains the right to terminate study participation at any time, according to the terms specified in the study contract. The investigator is to notify the IRB/IEC of the study's completion or early termination in writing, send a copy of the notification to the sponsor or sponsor's designee, and retain 1 copy for the site study regulatory file.

The sponsor may terminate the study electively if, for example, required by regulatory decision or upon advice of the iDSMB (see Section 5.6). If the study is terminated prematurely, the sponsor will notify the investigators, the IRBs and IECs, and the regulatory bodies of the decision and reason for termination of the study.

5. STUDY POPULATION

Deviations from eligibility criteria are not permitted because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Men and women aged ≥ 18 years at the time of consent.
2. Ability to comprehend and willingness to sign a written ICF and comply with all study visits and procedures.
3. Histologically confirmed R/R B-cell malignancy of the following types:
    a. Cohort 1: DLBCL not otherwise specified, T-cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus–positive DLBCL of the elderly, Grade 3b FL, high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma), histological transformation from an earlier diagnosis of low-grade lymphoma (such as FL, MZL, CLL) into DLBCL
    b. Cohort 2: MCL with documentation of either overexpression of cyclin D1 or t(11;14)
    c. Cohort 3: FL Grade 1, 2, and 3a
    d. Cohort 4: MZL, including extranodal, nodal, and splenic subtypes
    e. Cohort 5: CLL or SLL
4. Willingness to undergo biopsy requirements for the study, including an incisional, excisional, or core needle lymph node or tissue biopsy (or have archival lymph node or tissue from the most recent biopsy) and undergo bone marrow biopsy/aspirate collections as appropriate.
5. Received at least 2 prior systemic treatment regimens as follows:
    a. Cohorts 1 and 2 (DLBCL, MCL): Must have been previously treated with at least 1 prior chemoimmunotherapy regimen that included an anti-CD20 antibody. This includes treatments such as chemotherapy plus rituximab or obinutuzumab, with or without rituximab or obinutuzumab maintenance. *Note*: At least 6 doses of anti-CD20 chemoimmunotherapy must have been given in prior therapy.
    b. Cohorts 3 and 4 (FL, MZL): Must have been previously treated with at least 1 prior chemoimmunotherapy or immunotherapy regimen that included an anti-CD20 antibody. This includes treatments such as rituximab or obinutuzumab monotherapy or chemotherapy plus rituximab or obinutuzumab, with or without rituximab or obinutuzumab maintenance. *Note*: At least 6 doses of anti-CD20 immunotherapy must have been given in prior therapy.
    c. Cohort 5 (CLL/SLL): Must have been previously treated with at least 1 prior systemic therapy including a BTK inhibitor regimen or chemoimmunotherapy regimen that included an anti-CD20 antibody.

6. Relapsed, progressive, or refractory NHL or CLL:
    a. Relapsed: PD after response of CR to prior therapy.
    b. Progressive: PD after response of PR or stable disease to prior therapy.
    c. Refractory: achieved less than PR to the last prior therapy, or achieved a CR or PR that lasted < 6 months before PD.
7. For Cohorts 1 to 4 and Cohort 5/SLL: radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures > 1.5 cm in the longest transverse diameter and ≥ 1.0 cm in the longest perpendicular diameter as assessed by CT or MRI.
8. ECOG performance status of 0 to 2.
9. Life expectancy > 3 months.
10. LVEF ≥ 50%.
11. Laboratory results at screening as follows:
    a. Hemoglobin level ≥ 8 g/dL (unless secondary to bone marrow involvement by NHL/CLL, as demonstrated by recent bone marrow aspiration and bone marrow biopsy).
    b. ANC ≥ 1.5×10^9/L (unless secondary to bone marrow involvement by NHL/CLL, as demonstrated by recent bone marrow aspiration and bone marrow biopsy).
    c. Platelet count ≥ 75×10^9/L (unless secondary to bone marrow involvement by NHL/CLL, as demonstrated by recent bone marrow aspiration and bone marrow biopsy).
    d. Total serum bilirubin level ≤ 1.5 × ULN, or ≤ 5 × ULN in cases of Gilbert syndrome or documented liver involvement by lymphoma.
    e. ALT, AST, and alkaline phosphatase level ≤ 3 × ULN, or ≤ 5 × ULN in cases of documented liver involvement.
    f. Serum creatinine clearance ≥ 50 mL/min either measured or calculated using a standard Cockcroft and Gault formula (Cockcroft and Gault 1976).
12. Willingness to avoid pregnancy or fathering children based on the following criteria.
    a. Male participants with childbearing potential must agree to take appropriate precautions to avoid fathering children (with at least 99% certainty) from screening through 6 months after the last dose of study treatment and must refrain from donating sperm during this period. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.
    b. Female participants with childbearing potential must have a negative serum pregnancy test at screening and must agree to take appropriate precautions to avoid pregnancy (with at least 99% certainty) from screening through 90 days (or 180 days if required by local regulations) after the last dose of study treatment. They must also agree to regular urine pregnancy testing through the study treatment period. They must also refrain from breastfeeding and donating oocytes during the course of the study and for 3 months after the last dose of study treatment. Permitted methods that are at least 99% effective in preventing pregnancy (see Appendix A) should be communicated to the participants and their understanding confirmed.

c. Female participants without childbearing potential (ie, surgically sterile with a hysterectomy and/or bilateral oophorectomy OR ≥ 12 months of amenorrhea and at least 50 years of age) are eligible.
d. *Note:* Female participants who have been amenorrheic for at least 12 months resulting from chemo/radiotherapy are considered of childbearing potential and should agree to use adequate contraceptive measures (see Appendix A).

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Any other histological type of lymphoma according to the WHO 2016 classification of lymphoid neoplasms, for example, primary mediastinal B-cell lymphoma, Burkitt lymphoma, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (gray zone lymphoma); primary effusion lymphoma; primary cutaneous DLBCL, leg type; intravascular B cell lymphoma.
2. History of or evidence of CNS lymphoma (primary and secondary).
3. Any anticancer and/or investigational therapy (eg, chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, hormonal therapy, or tumor embolization) within 30 days or 5 half-lives (whichever is greater) prior to the first dose of study treatment (C1D1).
4. Inadequate recovery (> Grade 1) from toxicity and/or complications from a major surgery before C1D1.
5. Use or expected use during the study of any prohibited medications, including potent CYP3A4 inhibitors or inducers, within 14 days or 5 half-lives (whichever is longer) before C1D1.
6. Allogeneic stem cell transplantation within the past 6 months, or ASCT within 3 months before C1D1.
7. Previous treatment with CD19-targeted therapy (eg, CD19-CAR-T therapies, other CD19 mAbs, including bispecific and antibody-drug conjugates) or PI3K inhibitors.
8. Treatment with corticosteroids at doses greater than physiologic doses (prednisone equivalent dose > 10 mg/day) within 7 days of starting study treatment.
9. Clinically significant cardiac disease, including unstable angina, acute myocardial infarction, New York Heart Association Class II to IV congestive heart failure, uncontrolled arrhythmia, and/or cardiac conduction issues, within 6 months of C1D1.
10. Clinically significant concurrent, uncontrolled medical condition, including, but not limited to, renal, hepatic, hematologic, GI, endocrine, pulmonary, neurological, cerebral, or psychiatric disease.
11. Current or previous other malignancy within 3 years of study entry, except cured basal or squamous cell skin cancer, superficial bladder cancer, prostate intraepithelial neoplasm, or carcinoma in situ of the cervix.
12. Active graft-versus-host disease.

13. History of stroke or intracranial hemorrhage within 6 months before C1D1.
14. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment within 30 days of C1D1.
15. Any of the following:
    a. Known positive test result for hepatitis C (HCV antibody serology testing) and a positive test result for HCV RNA. Participants with positive serology must have been tested locally for HCV RNA and are eligible in case of negative HCV RNA test results.
    b. Known positive test results for chronic HBV infection (defined by HBsAg positivity). Participants with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA was undetectable (local test result), provided that they are willing to undergo ongoing DNA testing. Antiviral prophylaxis may be administered as per institutional guidelines. Participants who have protective titers of HBsAb after vaccination or prior but cured hepatitis B are eligible.
    c. Known seropositive for or history of active viral infection with HIV.
16. Inability to swallow and retain oral medication, malabsorption syndrome, disease significantly affecting GI function, total resection of the stomach or small bowel, ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
17. History of hypersensitivity to compounds of similar biological or chemical composition to tafasitamab, parsaclisib, and/or the excipients contained in the study treatment formulations (refer to the tafasitamab IB and the parsaclisib IB for more details).
18. History of serious allergic reactions, including anaphylaxis and toxic epidermal necrolysis.
19. History or evidence of interstitial lung disease.
20. Exposure to vaccination with live vaccine within 30 days prior to C1D1, or anticipated need for such vaccination during treatment.
21. Currently pregnant or breastfeeding.
22. Any condition that would, in the investigator's judgment, interfere with full participation in the study, including administration of study treatment and attending required study visits; pose a significant risk to the participant; or interfere with interpretation of study data.

5.3. Lifestyle Considerations

No restrictions to diet or lifestyle are required.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not subsequently receive study treatment.

Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the result to be in error. Additionally, a participant who fails screening may repeat the screening process 1 time if the investigator believes there has been a change in eligibility status. Participants who rescreen must reconsent and be assigned a new participant number.

5.5. Replacement of Participants

Participants who do not experience a DLT and do not receive at least 3 doses of tafasitamab and 21 days of treatment with parsaclisib 20 mg QD will be replaced to ensure that there are 10 evaluable participants within each disease-specific cohort.

5.6. Data Safety Monitoring Board

An iDSMB will review data once the 10th DLT-evaluable participant from any cohort completes the DLT evaluation period (C1D28 or experiences a DLT). Reviews will be repeated every 4 months thereafter. The occurrence of DLTs in 2 or more of the first 10 DLT-evaluable participants will also trigger an iDSMB review. Details regarding the composition and responsibilities of the iDSMB are provided in the charter.

6. STUDY TREATMENT

6.1. Study Treatments Administered

Table 6 presents the study treatment information.

Table 6: Study Treatment Information

	Study Drug 1	Study Drug 2
Study drug:	Tafasitamab	Parsaclisib
Mechanism of action:	[redacted]	
Dosage formulation:		
Unit dose strength(s)/ dosage level(s):		
Administration instructions:		
Packaging and labeling:		
Storage:		
Status of treatment in participating countries:		

6.2. Preparation, Handling, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received and any discrepancies are reported and resolved before use.

Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure,

environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator or authorized site staff.

The investigator (or designee) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities. The investigator or designee must maintain records that document the following:

- Delivery of study drugs to the study site.
- Inventory of study drugs at the site.
- Participant use of the study drugs, including pill and vial counts from each supply dispensed.
- Lot numbers and/or vial numbers of study drug.
- Return of study drug to the investigator or designee by participants

The investigational product must be used only in accordance with the Protocol. The investigator will also maintain records adequately documenting that the participants were provided the specified study drug. These records should include dates, quantities, and any available batch or serial numbers or unique code numbers assigned to the investigational product and study participants.

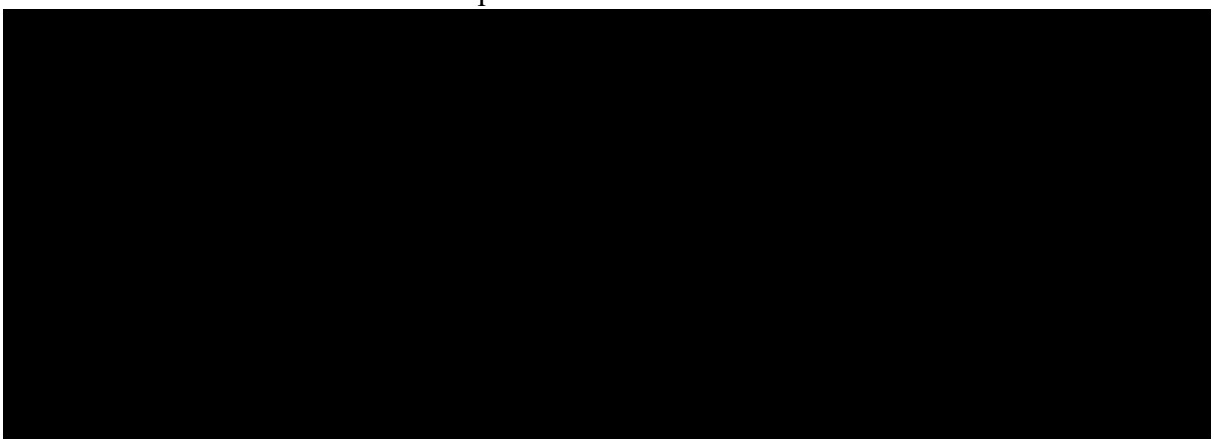
Completed accountability records will be archived by the site. The investigator or designee will be expected to collect and retain all used, unused, and partially used containers of study drug until verified by the study monitor (unless otherwise agreed to by the sponsor). At the conclusion of the study, the investigator or designee will oversee shipment of any remaining study drug back to the sponsor or its designee for destruction according to institutional SOPs. If local procedures mandate on-site destruction of the investigational supply, the site should (where local procedures allow) maintain the investigational supply until the study monitor inspects the accountability records in order to evaluate compliance and accuracy of accountability by the investigative site. At sites where the study drug is destroyed before monitor inspection, the monitors rely on documentation of destruction per the site SOP.

6.2.1. Tafasitamab

Tafasitamab will be dosed at 12 mg/kg based on actual body weight via IV infusion. Tafasitamab will be administered on Days 1, 8, 15, and 22 of Cycles 1 through 3 and then Days 1 and 15 of each 28-day cycle from Cycle 4 onward. Lyophilized powder must be reconstituted and diluted prior to infusion.

6.2.1.1. Reconstitution

Reconstitution of tafasitamab should be performed as follows:



6.2.1.2. Dilution

Dilution of tafasitamab should be performed as follows:

6.2.1.3. Administration

6.2.2. Parsaclisib

Participants will self-administer parsaclisib as an oral treatment. Parsaclisib will be administered as 20 mg QD for 8 weeks followed by 2.5 mg QD.

Parsaclisib should be taken at approximately the same time each day.

Administration of parsaclisib will be calendar-based. Delays or interruptions in study treatment will not affect the dosing schedule of parsaclisib; 20 mg QD will be administered only during the first 8 weeks (Days 1-56); all participants will switch to 2.5 mg QD on Day 57.

Treatment with parsaclisib will continue until a criterion is met for treatment discontinuation.

Parsaclisib will be administered in the study clinic on days when blood samples are collected for PK as indicated in Table 3 and Section 8.4.

See Appendix F for instructions to participants for handling parsaclisib.

6.3. Measures to Minimize Bias: Randomization and Blinding

All participants will be centrally assigned to study treatment using an IRT system. Instructions for the IRT system will be provided to each site prior to study initiation. Full details will be provided in the IRT Manual.

Study treatment will be dispensed and administered at the study visits in accordance with the SoA in Table 3. Returned study treatment should not be redispensed.

This is an open-label study; there is no randomization, and no comparisons will be made between participants or against historical controls. Measurements of safety and efficacy are objective measurements, and only comparisons to pretreatment conditions will be made.

6.4. Study Treatment Compliance

Compliance with all study-related treatments should be emphasized to the participant by site personnel, and appropriate steps should be taken to optimize compliance during the study. Compliance with parsaclisib will be calculated by the sponsor based on the drug accountability (eg, tablet counts) documented by the site staff and monitored by the sponsor/designee. Participants will be instructed to bring all unused study drugs with them to the study visits in order for site personnel to conduct tablet counts to assess study drug accountability.

Compliance with tafasitamab administration will be calculated by the sponsor based on study drug accountability and infusion records documented by the site staff and monitored by the sponsor/designee.

6.5. Dose-Limiting Toxicity and Determination of the Recommended Phase 2 Dose

6.5.1. Definition of a Dose-Limiting Toxicity

Dose-limiting toxicity will be defined as the occurrence of any of the toxicities in Table 7 up to and including Day 28 (Cycle 1/Day 28), except those with a clear alternative explanation. All DLTs will be assessed for severity by the investigator using CTCAE v5.0 criteria.

During the DLT evaluation period, participants who receive at least 3 of 4 doses of tafasitamab and 21 days of parsaclisib 20 mg QD or have a DLT will be considered evaluable for the dose confirmation period.

Dose reductions for individual participants may be made based on events observed at any time during the treatment period; however, for the purposes of opening each expansion cohort, decisions will be made based on events that are observed from the first day of study treatment administration through and including the final day of Cycle 1 (Cycle 1/Day 28).

An event clearly associated with the underlying disease, disease progression, a concomitant medication, or comorbidity will not be considered a DLT.

Table 7: Definition of Dose-Limiting Toxicity

Toxicity	Definition
Nonhematologic	• Any liver function abnormalities that meet the definition of Hy's law[a]. • ≥ Grade 4 tumor lysis syndrome or Grade 3 tumor lysis syndrome requiring dialysis. • ≥ Grade 4 fatigue lasting for ≥ 7 days. • ≥ Grade 4 IRR. • ≥ Grade 3 CRS. • Any other ≥ Grade 3 nonhematologic toxicity except nausea, vomiting, electrolyte abnormality, or liver function abnormality
Hematologic	• ≥ Grade 3 hematologic toxicities lasting for > 3 days excluding neutropenia and lymphocytopenia (also excluding thrombocytopenia in Groups 3 and 5). • Grade 4 neutropenia (ANC < 0.5×10^9/L) lasting for ≥ 7 days in participants with pretreatment ANC > 1×10^9/L under appropriate use of G-CSF (if G-CSF is required to manage neutropenia, the neutropenia is considered a DLT in Cohorts 1 and 2). • Grade ≥ 4 thrombocytopenia in Cohorts 3 and 5. • Febrile neutropenia.
General	• Any death not clearly due to the underlying disease or extraneous causes. • Any toxicity other than described above that (in the opinion of the investigator) is potentially life-threatening and cannot be controlled with standard measures. • Any other toxicity that a primary investigator and the sponsor agree on being reported as a DLT.

[a] Hy's law is defined as 1) ALT or AST elevation > 3 × ULN, 2) total bilirubin > 2 × ULN without initial findings of cholestasis (elevated serum alkaline phosphatase), and 3) no other apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including but not limited to viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.5.2. Procedures for Cohort Review

Telephone conferences will be scheduled by the sponsor with study investigators to review cohort-specific data and overall safety data, to adjudicate individual high-grade AEs as potentially dose-limiting, and guide other major study decisions.

The decision to continue enrollment into each of the malignancy subtype cohorts will be based on the frequency of DLTs in the first 10 DLT-evaluable participants and review of ongoing

safety data. After the safety review is completed and the dose confirmation decision is made, the dose expansion period for that cohort will begin, and up to 10 additional participants will be enrolled (up to a total of 20 evaluable participants in each cohort across both study periods).

6.5.3. Dose-Limiting Toxicity Stopping Rules

Participants in each of the disease-specific cohorts will be assessed for safety and tolerability using a continuous monitoring approach.

During the dose confirmation period, the occurrence of a DLT in ≥ 2 participants in a disease-specific cohort will trigger an iDSMB review. Enrollment will be halted in only that specific cohort until the iDSMB review is complete and the determination to continue enrollment (with or without protocol modifications) is made. The iDSMB review will result in nonbinding recommendations on further study conduct, that is, continue without modifications, continue with modifications, or terminate enrollment in the cohort. Please refer to the iDSMB charter for additional details.

Any DLT should be monitored until it resolves to baseline or appears to have stabilized for a minimum of 7 days. Participants should be seen as often as medically indicated to ensure appropriate management of the event.

6.6. Dose Modifications

Treatment interruptions and modifications may occur for individual study participants.

6.6.1. Management of Dose-Limiting Toxicities or Other Urgent Situations

Investigators may employ any measures or concomitant medications necessary to manage a DLT or other urgent situation after discussion with the sponsor (whenever possible).

6.6.2. Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug

Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness of an event that may affect whether or not a participant should continue on study treatment.

Adverse events that have a clear alternative explanation or transient (≤ 72 hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose reduction rules.

Because participants may enter the study with extensive pretreatment and/or severe bone marrow infiltration by the primary disease, dose modifications listed in Table 8 are provided as general guidance. Individual decisions regarding dose reduction should be made using clinical judgment and in consultation with the sponsor's medical monitor, taking into account relatedness of the AE to the study drug(s) and the participant's underlying condition.

Table 8: Guidelines for Interruption and Restarting of Study Treatment

Adverse Event	Value or Grade	Recommendation
Grade 3/4 neutropenia judged to be related to study drugs	ANC decreases to < 1.0×10^9/L for at least 7 days **OR** ANC decreases to < 1.0×10^9/L with an associated body temperature ≥ 38.5°C (101.3°F) **OR** ANC decreases to < 0.5×10^9/L	Interrupt tafasitamab and parsaclisib dosing. Follow CBC every 7 days. Growth factors (eg, G-CSF) and antimicrobial prophylaxis are to be used, as per local guidelines.
	ANC returns to ≥ 1.0×10^9/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or parsaclisib at the same dose. Monitor as clinically indicated.
Grade 2-4 thrombocytopenia judged to be related to study drugs	Platelet count decreases to < 75×10^9/L	Interrupt tafasitamab and parsaclisib dosing. Follow CBC every 7 days.
	Platelet count decreases to ≥ 75×10^9/L	Provided all other criteria are fulfilled, resume dosing of tafasitamab and/or parsaclisib at the same dose. Monitor as clinically indicated.
Other clinically significant toxicities judged to be related to study drugs	Grade 3	Interrupt the administration of the study drug(s) to which the toxicity is judged to be related to up to 28 days until the toxicity has resolved to ≤ Grade 1.
	Toxicities resolve to ≤ Grade 1	Restart tafasitamab and parsaclisib at the same doses. If assessed as related to parsaclisib, restart at the next lower dose of parsaclisib (see Table 11). Monitor as clinically indicated.
	Recurrent Grade 3 after 2 dose reductions of parsaclisib	Discontinue tafasitamab and parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.
	Grade 4	Discontinue tafasitamab and parsaclisib administration and follow-up per Protocol. Exceptions require approval of sponsor.

CBC = complete blood count.

Note: If, based on medical judgment, the treating physician considers a laboratory parameter change or AE not to be a study drug– related toxicity, but to represent a natural fluctuation in or progression of the underlying disease, then it is at the physician's discretion and assessment of the individual risk/benefit ratio to determine whether the participant should be dosed. The decision and rationale behind the decision should be documented in the source data.

6.6.2.1. Tafasitamab Dose Modifications for Cytokine Release Syndrome and Infusion-Related Reactions

Dose reductions of tafasitamab are not permitted. Drug interruptions or discontinuation may occur in the case of severe IRRs, allergic reactions, infections, febrile neutropenia, or severe hematologic toxicity. Delaying the tafasitamab dose is permitted for no more than 2 days (eg, if dosing was planned on Day 8, delaying that dose is allowed up to Day 10). Alternatively, an infusion of tafasitamab may be skipped completely, and the next scheduled dose will be administered (eg, if an infusion is skipped on Day 8, the next dose will be administered on Day 15). In the event tafasitamab administration is interrupted due to toxicity, other regularly scheduled assessments should still be performed.

Some mAb treatments in NHL have been associated with Grade 3 IRRs during the first infusion in participants. These IRRs have been ameliorated or eliminated by fractionating the dose into 2 infusions separated by at least 24 hours. If the full dose of tafasitamab cannot be administered in 1 day, the dose may be split into a second administration that must be given on the subsequent day. After the occurrence of a first-dose Grade 3 IRR, the next 3 infusions for this participant will be split: one-third of the dose administered on the original schedule followed by the remaining two-thirds on the next day, with each infusion administered over 2 hours. If there are no IRRs with the 3 consecutive split infusions, then the investigator can consider reverting to a single 2-hour infusion for the subsequent infusions.

Infusion-related reactions have commonly been reported for participants with CLL or NHL treated with tafasitamab. Infusion-related reaction will be defined according to the NCI CTCAE v5.0 definition of IRR and CRS. Table 9 provides guidance for the management of IRRs by grade.

Table 9: Management of Infusion-Related Reactions/Cytokine Release Syndrome

IRR Grade	CRS Grade	Interventions
2	1	The infusion should be stopped immediately. The participant should receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) as clinically indicated. Once the symptoms have been resolved or reduced to Grade 1 (IRR only) according to investigator assessment, the infusion can be continued at an infusion rate of 50% of the speed so far. If, after 1 hour, the participant's symptoms do not return and vital signs are stable, the infusion rate may be increased every 30 minutes, as tolerated, to the baseline rate. If a participant who developed a Grade 2 IRR or Grade 1 CRS receives further infusions of tafasitamab, then premedication should be given before all subsequent infusions of tafasitamab throughout the study.

Table 9: Management of Infusion-Related Reactions/Cytokine Release Syndrome (Continued)

IRR Grade	CRS Grade	Interventions
3	2	The infusion should be stopped immediately. The participant must receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator). After the complete resolution of all symptoms, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25% of the speed so far. If, after 1 hour, the participant's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50% of the baseline speed. If, after the resumption of the infusion, symptoms return (irrespective of grade), the infusion must be stopped immediately and the infusion tubing should be disconnected from the participant. Based on the investigator's decision, the participant may receive further tafasitamab provided clinically appropriate precautions were undertaken. If a participant who developed a Grade 3 IRR or Grade 2 CRS receives further infusions, then premedication should be given before all subsequent infusions of tafasitamab throughout the study. If precluded from further tafasitamab administrations, the participant may continue treatment with parsaclisib.
4	3 or 4	The infusion should be stopped immediately and the infusion tubing should be disconnected from the participant. The participant must receive appropriate treatment with an antihistamine and/or acetaminophen or methylprednisolone (or equivalent) and, if necessary, further medications (ie, epinephrine, bronchodilator). The participant must not receive any further tafasitamab infusions but may continue treatment with parsaclisib as per protocol.

6.6.2.2. Dose Modifications for Parsaclisib

Dose modification guidance for AEs that have been previously observed in participants receiving parsaclisib or are potential class-effect AEs are provided in Table 10.

The starting dose and dose reduction levels of parsaclisib are provided in Table 11 and Table 12.

Table 10: Toxicity Management Guidelines for Parsaclisib

Adverse Event	Recommendation
Chemistry	
AST and/or ALT is Grade 3 (> 5.0 × ULN). *Note:* In participants with liver metastasis–related elevations at baseline, contact sponsor to discuss clinical management.	**Step 1:** Interrupt both tafasitamab and parsaclisib. Monitor weekly until the toxicity has resolved to ≤ Grade 1 (< 3.0 × ULN). **Step 2:** Restart tafasitamab at the same dose and parsaclisib at next lower dose with medical monitor approval. Monitor as clinically indicated.
Other toxicities	
Diarrhea (Grade 1)	**Step 1:** Treat with antimotility agents (eg, 2 mg loperamide followed by 2 mg every 4 hours or after every unformed stool) and initiate supportive care. Monitor approximately every 48 hours until resolved. If not improved after 48 hours, treat per guidance for Grade 2.
Diarrhea (Grade 2)	**Step 1:** Interrupt tafasitamab and parsaclisib. Perform workup for infection (including CMV, *Clostridium difficile*, etc) immediately. Initiate or continue supportive care. Monitor approximately every 48 hours until resolution. **Step 2:** If improved within 48 hours and/or infection* is confirmed, restart tafasitamab and parsaclisib at the same schedule and dose after resolved to ≤ Grade 1 and continue to monitor. *For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** If not improved within 48 hours and infection is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids, switch to IV steroids. **Step 4:** When diarrhea resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standards of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisolone or equivalent) and diarrhea is ≤ Grade 1, restart parsaclisib at the next lower dose with approval of the medical monitor. **Step 5:** If Grade 2 diarrhea reoccurs, treat per guidance for diarrhea (≥ Grade 3)/noninfectious colitis. **Step 6:** If ≥ Grade 2 diarrhea reoccurs a third time, permanently discontinue parsaclisib.

Table 10: Toxicity Management Guidelines for Parsaclisib (Continued)

Adverse Event	Recommendation
Diarrhea (≥ Grade 3) Noninfectious colitis (any grade; confirmed or suspected)	**Step 1:** Interrupt tafasitamab and parsaclisib. Perform workup for infection (including CMV, *C difficile*, etc) immediately. Initiate or continue supportive care. Consider colonoscopy with biopsy for diarrhea ≥ Grade 3 and/or if symptoms[a] are suggestive of colitis. Monitor every 48 hours until resolution. **Step 2:** If infection* is ruled out, start oral steroids, or consider IV steroids if participant is being given IV fluids. If no improvement with oral steroids within 48 hours, switch to IV steroids. *For infectious diarrhea/colitis, follow institutional standard of care guidelines and restart parsaclisib according to clinical judgment after resolved to ≤ Grade 1. Consult with medical monitor if needed. **Step 3:** When diarrhea/colitis resolves to ≤ Grade 1, continue supportive care and taper steroids according to institutional standards of care. When taper is complete (eg, no steroid or ≤ 10 mg/day prednisolone or equivalent) and diarrhea/colitis is ≤ Grade 1, restart tafasitamab and parsaclisib as described herein and with approval of the medical monitor. Continue to monitor. **Step 4:** If ≥ Grade 3 diarrhea/colitis (any grade) reoccurs, permanently discontinue parsaclisib.
Pneumonitis (Grade 1)	**Step 1:** Interrupt tafasitamab and parsaclisib until the toxicity has resolved. **Step 2:** Restart tafasitamab at the same dose and parsaclisib at next lower dose. Monitor as clinically indicated.
Pneumonitis (≥ Grade 2)	Permanently discontinue tafasitamab and parsaclisib.
Skin toxicity (eg, rash, pruritus, etc, unless otherwise specified) (Grade 2-3)	**Step 1:** Interrupt tafasitamab and parsaclisib until the toxicity has resolved to ≤ Grade 1. **Step 2:** Restart tafasitamab and parsaclisib at the same dose. If assessed as related to parsaclisib, restart at the next lower dose.
Exfoliative dermatitis (Grade 1)	**Step 1:** Interrupt tafasitamab and parsaclisib until the toxicity has resolved. **Step 2:** Restart tafasitamab at the same dose and parsaclisib at the next lower dose. Monitor as clinically indicated.
Exfoliative dermatitis (≥ Grade 2)	Permanently discontinue tafasitamab and parsaclisib.
Intestinal perforation (any grade)	Permanently discontinue tafasitamab and parsaclisib.
PJP infection	Interrupt tafasitamab and parsaclisib. Permanently discontinue tafasitamab and parsaclisib if PJP infection is confirmed.

Table 10: Toxicity Management Guidelines for Parsaclisib (Continued)

Adverse Event	Recommendation
CMV infection	Participants with CMV viremia without associated clinical signs of CMV infection should be carefully monitored. Consider interrupting tafasitamab and parsaclisib for participants with CMV viremia and clinical signs of infection until the infection has resolved. Restart tafasitamab at the same dose and parsaclisib reduced by 1 dose level if approved by the medical monitor.
Varicella zoster infection	Interrupt tafasitamab and parsaclisib. Restart tafasitamab and/or parsaclisib only by approval of the medical monitor.
Any Grade 1 or Grade 2 toxicity unless otherwise specified	Continue tafasitamab and parsaclisib. Treat the toxicity; monitor as clinically indicated.

[a] Diarrhea accompanied by abdominal pain and/or mucus or blood in stool.

Table 11: Dose Levels for Parsaclisib

	Dose, C1D1 to C2D28 (Day 1 to Day 56)	Dose, C3D1 to EOT (Day 57 to EOT)
Starting dose	20 mg QD	2.5 mg QD
First dose reduction	10 mg QD	1 mg QD
Second dose reduction	5 mg QD	Not applicable

6.6.2.3. Supportive Care Guidelines for Diarrhea/Colitis

Participants should be instructed to immediately report any event of diarrhea, irrespective of grade. Treatment with parsaclisib may be modified according to the guidelines in Table 12 to allow for resolution of diarrhea/colitis.

Participants should receive appropriate supportive care measures as deemed necessary by the investigator. For any ≥ Grade 1 diarrhea, participants should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. Participants should try to eat 5 to 6 small meals per day; low-fat, high-protein foods; and cooked instead of raw vegetables. Participants may supplement their diet with bananas, rice, applesauce, and toast to reduce the number of bowel movements and may also try crackers, gelatin, noodles, or oatmeal. Participants should avoid fried, fatty, greasy, or spicy foods; milk, milk products, and acidic drinks; high-fiber foods and foods that cause gas; and alcohol, caffeine, and herbal supplements.

For each occurrence, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infections (including CMV), which might require additional supportive care.

It may be necessary to perform additional procedures, such as colonoscopy with biopsy, as part of evaluation of the event. Note that several courses of steroid tapering may be necessary because symptoms may worsen when the steroid dose is decreased. Any procedure performed must be captured in the appropriate eCRF.

Participants should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain or cramping, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

Table 12: Dose Modifications for Parsaclisib for Diarrhea/Colitis

Parsaclisib Current Dose	Dose Modification
≥ 2.5 mg QD	20 mg QW
1 mg QD	20 mg QW or 10 mg QW
20 or 10 mg QW	Restart next lower dose 10 mg QW or 5 mg QW
5 mg QW	Permanently discontinue

6.6.2.4. Supportive Care Guidelines for Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia are known adverse reactions for tafasitamab and also appear to be PI3Kδ class-effect toxicities. Investigators should ensure that participants understand the need to seek medical care when they have conditions that could become life-threatening in the presence of cytopenias (eg, neutropenic fever or bleeding with low platelet count). Participants should be instructed to report immediately any signs of infection, unexpected bleeding, or sudden, extremely painful headaches.

6.6.2.5. Management of Hypogammaglobulinemia

Hypogammaglobulinemia induced by depletion of normal B-cells is a potential on-target toxicity of the anti-CD19 mAb tafasitamab. In the clinical development program for tafasitamab, cases of hypogammaglobulinemia have been observed as follows:

- In 3 studies with tafasitamab monotherapy (XmAb5574-01 [NCT01161511] in R/R CLL, MOR208C201 [NCT01685008] in R/R NHL, and MOR208C202 [NCT01685021] in R/R B-cell acute lymphoblastic leukemia), 2 of 141 total participants (1.4%) experienced Grade 2 hypogammaglobulinemia.
- In Study L-MIND (MOR208C203 [NCT02399085] in R/R DLBCL), 5 of 81 participants (6.2%) experienced hypogammaglobulinemia (Grade 1: n = 3, Grades 2 and 3: n = 1 each), with 2 of these cases (2.5%; Grade 1: n = 1, Grade 3: n = 1) occurring during the combination treatment phase with tafasitamab + lenalidomide.

In this study, immunoglobulin levels (IgG, IgA, IgM) will be measured at the timepoints listed in Table 3. Study participants experiencing hypogammaglobulinemia should be managed in accordance with local guidelines.

6.6.3. Criteria for Permanent Discontinuation of Study Drug

The occurrence of unacceptable toxicity will require that the study drug be permanently discontinued. Unacceptable toxicity is defined as follows:

- The occurrence of an AE related to the study drug that, in the judgment of the investigator or the sponsor's medical monitor, compromises the participant's ability to continue study-specific procedures or is considered not to be in the participant's best interest.
- A persistent AE requiring a delay of study treatment for more than 14 days unless a greater delay has been approved by the sponsor.

6.7. Concomitant Medications and Procedures

All concomitant medications and treatments (including over-the-counter or prescription medicines, vitamins, vaccines, and/or herbal supplements) must be recorded in the eCRF. Any prior medication received up to 28 days before the first dose of study treatment and 90days after the last dose of study treatment, or until the participant begins a new anticancer therapy, whichever occurs first, will be recorded in the eCRF. Any change in the dose of these medications will also be recorded. Concomitant medications administered for treatment of SAEs should be recorded even if the SAE is reported beyond 90 days after the last dose of study treatment. Concomitant treatments/procedures that are required to manage a participant's medical condition during the study will also be recorded in the eCRF. The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.7.1. Permitted Medications and Procedures

6.7.1.1. Premedication for Tafasitamab Infusions/Infusion-Related Reaction Prophylaxis

Tafasitamab infusions should be administered to participants after premedication with oral acetaminophen (eg, 650-1000 mg), an antihistamine such as diphenhydramine hydrochloride (eg, 50-100 mg), and glucocorticosteroids (eg, 100 mg IV prednisone or prednisolone or equivalent) 30 to 60 minutes prior to starting each infusion.

Premedication is mandatory for the first 3 doses. For participants who do not experience ≥ Grade 2 IRRs or ≥ Grade 1 CRS to tafasitamab during the first cycle, premedication will be optional for subsequent antibody infusions at the discretion of the investigator. Otherwise, premedication should be continued for subsequent administrations.

6.7.1.2. *Pneumocystis jirovecii* Pneumonia Prophylaxis

All participants are required to receive a standard PJP prophylaxis regimen which is determined by the investigator. Examples of standard PJP prophylaxis therapies for this population include trimethoprim-sulfamethoxazole, atovaquone, dapsone (diaminodiphenyl sulfone) with or without pyrimethamine, and pentamidine (NCCN 2021). Because of reports of cross-sensitivity between sulfonamides and dapsone, all participants who have a known or suspected allergy to sulfonamides must receive either inhaled pentamidine or atovaquone for PJP prophylaxis. Prophylaxis should be given while participants are receiving study treatment and should continue for at least 2 to 6 months after the last dose of study treatment.

Pneumocystis jirovecii pneumonia prophylaxis will be locally sourced and reimbursed by the sponsor. The contents of the label will be in accordance with all applicable regulatory requirements. Further details are available in the Pharmacy Manual.

6.7.1.3. Supportive Care Measures

Supportive care should be administered to participants as per the institutional policy at the site for the standard therapy that the participant will receive. Additional information may be available in the appropriate package inserts. This includes the use of prophylactic growth factors, which should be based on the American Society of Clinical Oncology guidelines for the use of prophylactic growth factors (Smith et al 2015) and the investigator's clinical judgment.

6.7.2. Prohibited Medications and Procedures

6.7.2.1. Anticancer Therapy

No radiotherapy (including limited-field radiotherapy) is permitted after the screening PET/CT scan for initial disease assessment has been performed.

The use of concurrent antineoplastic therapies, including but not limited to chemotherapies, hormonal therapy, immunotherapy, biological response modifiers, mAbs with or without conjugation, radioisotope therapies, stem cell transplant, and targeted small molecules, is not permitted during the treatment period of this study.

After disease progression has been reported, additional antineoplastic therapies are permitted at the discretion of the investigator and in accordance with the local treatment guidelines. New antineoplastic therapy should be recorded in the eCRF as appropriate.

6.7.2.2. Live Vaccines

Because of the immunosuppressive effects of study treatment, administration of any live vaccine is not recommended during the treatment period and at least 6 months after EOT. Thereafter, the decision to administer live vaccines is at the investigator's discretion.

6.7.2.3. Potent CYP3A4 Inhibitors and Inducers

Use of potent inhibitors and inducers of CYP3A4 is prohibited (see Appendix E). Based on the low overall bioavailability of topical ketoconazole, there are no restrictions on topical ketoconazole.

6.7.3. Restricted Medications and Procedures

Restricted medications and procedures include the following:

- Outside of tafasitamab infusion prophylaxis, the use of systemic corticosteroid doses ≤ 10 mg/day prednisone (or equivalent) is permitted but discouraged from the screening visit through EOT.
- Outside of tafasitamab infusion prophylaxis, short courses of systemic corticosteroid doses > 10 mg/day prednisone or equivalent are permitted only in the case of severe or life-threatening complications that cannot be controlled with other drugs but are otherwise discouraged from the screening visit through EOT.

- The use of moderate inhibitors and inducers of CYP3A4 (see Appendix E) is permitted with caution.
- Localized radiotherapy will be permitted if administered as treatment for pain or impending compression fractures and with prior approval of the medical monitor.

6.8. Treatment After the End of the Study

Participants who are receiving continued benefit at the end of the study may be transferred to a company-sponsored rollover study after completion of this study.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT WITHDRAWAL

7.1. Discontinuation of Study Treatment

The decision to discontinue study treatment will not constitute study completion. If study treatment is discontinued, the treatment period will be considered complete, and the follow-up period will begin.

7.1.1. Reasons for Discontinuation

Participants **must** be discontinued from study treatment for the following reasons:

- The participant becomes pregnant.
- Progression of disease per Lugano criteria (Cheson et al 2014) for NHL or the iwCLL criteria (Hallek et al 2018) for CLL.
- Initiation of new anticancer therapy.
- Consent is withdrawn.
  Note: Consent withdrawn means that the participant has explicitly indicated that he/she does not want to be followed any longer; in this case, no further data, except data in the public domain, may be solicited from or collected on the participant. Participants may choose to discontinue study treatment and remain in the study to be followed for progression and survival; however, this must be appropriately documented in both source documentation and the eCRF.
- Further participation would be injurious to the participant's health or well-being, in the investigator's medical judgment.
- Unacceptable toxicity.
- The study is terminated by the sponsor.
- The study is terminated by the local health authority, IRB, or IEC.

A participant **may** be discontinued from study treatment as follows:

- If, during the course of the study, a participant is found not to have met eligibility criteria, the medical monitor, in collaboration with the investigator, will determine whether the participant should be withdrawn from study treatment.
- If a participant is noncompliant with study procedures or study treatment administration in the investigator's opinion, the sponsor should be consulted for instruction on handling the participant.

7.1.2. Discontinuation Procedures

In the event that the decision is made to permanently discontinue study treatment, the EOT visit should be conducted. Reasonable efforts should be made to have the participant return for a follow-up visit. The last date of the last dose of study treatment and the reason for study treatment discontinuation will be recorded in the eCRF.

If a participant is discontinued from study treatment:

- The study monitor or sponsor must be notified.
- The reason(s) for discontinuation must be documented in the participant's medical record and the primary reason for discontinuation must be included in the eCRF.
- The EOT visit should be performed.
- The status of the participant should be updated to EOT in the IRT system.
- Participants must be followed for safety until the time of the follow-up visit or until study treatment–related toxicities resolve, return to baseline, or are deemed irreversible, whichever is longest.

7.2. Participant Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

See Table 3 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative and General Procedures

8.1.1. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
  - Informed consent must be obtained before any study-related procedures are conducted, unless otherwise specified by the Protocol.
  - Informed consent must be obtained using the IRB/IEC-approved version in a language that is native and understandable to the participant. A template will be provided by the sponsor or its designee. The sponsor or its designee must review and acknowledge the site-specific changes to the ICF template. The ICF must include a statement that the sponsor or its designee and regulatory authorities have direct access to participant records.
  - The ICF must contain all required elements and describe the nature, scope, and possible consequences of the study in a form understandable to the study participant.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the applicable requirements and regulations for the countries in which the study is being conducted as well as the IRB/IEC or study center.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection laws. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must provide consent to the most current version of the ICF during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

8.1.2. Screening Procedures

Screening is the interval between signing the ICF and enrollment into the study. Screening may not exceed 28 days. Assessments that are required to demonstrate eligibility may be performed over the course of 1 or more days during the screening process.

Procedures conducted as part of the participant's routine clinical management (eg, blood count, imaging study) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedure meets the Protocol-defined criteria and has been performed in the screening timeframe (ie, after providing consent and within 28 days of C1D1). Assessments may occur outside the 28-day window for those that are suitable for enrollment but may not be feasible to repeat. For participants who are enrolled in the study, information associated with eligibility requirements must be entered into the appropriate eCRF pages.

Results from the screening visit evaluations will be reviewed to confirm eligibility before enrollment or the administration of study treatment. Tests with results that fail eligibility requirements may be repeated once during screening if the investigator believes the results to be in error. For screening assessments that are repeated, the most recent available result before treatment assignment will be used to determine eligibility. Treatment should start as soon as possible but within 3 days after the date of enrollment.

See Sections 5.4 and 5.5 for information regarding screen failures and replacement of participants, respectively.

8.1.2.1. Tumor or Lymph Node Sample

Participant eligibility will be based on the site's local assessment of the pathologic diagnosis. Of important note, excisional/incisional or core needle biopsy are acceptable methods of assessment; however, a pathologic diagnosis based on fine-needle aspiration is not acceptable for eligibility. All participants must have an archival tumor or lymph node tissue specimen available for submission to central pathology; if an archival specimen is not available for submission, then a repeat biopsy is required before enrollment.

All tumor specimens must be reviewed locally and then sent to central pathology, preferably during the screening period and no later than 8 weeks after enrollment.

8.1.2.2. Bone Marrow Biopsy and Examination

For all participants, a bone marrow core biopsy and aspirate must be obtained as indicated in the SoA (see Table 3) and should be evaluated locally except in the following circumstances:

- Baseline PET scan showed that the participant has FDG-avid disease in the bone marrow (PET-avid bone marrow; see Section 8.2.2), or
- Participant had a bone marrow examination performed as per standard of care within approximately 60 days of enrollment, or
- Participant had a bone marrow examination performed after the last treatment for FL or MZL, and the results showed lymphoma involvement of the bone marrow.

All bone marrow examinations should include a unilateral biopsy and an aspiration. If no such recent bone marrow samples are available, then repeat biopsy will be required. All bone marrow aspirate samples must be submitted to central pathology, preferably during the screening period but no later than 8 weeks after enrollment.

The pathology report result from the site's local bone marrow examination will be captured in the eCRF.

8.1.3. Interactive Response Technology System

Each participant will be identified in the study by a participant ID number, which is a combination of the site ID and participant number. Site staff should contact the IRT to obtain the participant ID number during screening. Upon determining that the participant is eligible for study entry, the IRT will be contacted to obtain the treatment assignment. Additionally, the IRT will be contacted at each regular study visit to update the study drug supply. Additional details are provided in the IRT Manual.

8.1.4. Distribution of Reminder Cards

Participants will be provided with a reminder card at each visit. The reminder card will indicate the date/time of the next visit and will also remind the participant that they should not take their morning dose of parsaclisib at home on days when PK samples will be drawn, because they will take it in the clinic after samples have been collected. The reminder cards for visits when PK samples are drawn will have an area on which the date and time of the last dose taken (from the previous day) and the time and contents of their last meal before the visit should be recorded.

8.1.5. Demography and Medical History

8.1.5.1. Demographics and General Medical History

Demographic data and general medical history will be collected at screening by the investigator or qualified designee and will include year of birth/age, race, ethnicity, medical and surgical history, and current illnesses. Medical history will include relevant medical or surgical treatment within the last 10 years that are considered to be clinically significant by the investigator.

8.1.5.2. Disease Characteristics and Treatment History

A disease-targeted medical and treatment history will be collected at screening. Details regarding the participant's malignancy under study, including date of diagnosis, initial and current cancer stage, tumor histology, relevant disease characteristics, and prior treatments, including systemic treatments, radiation, and surgical procedures, will be collected in the eCRF.

8.1.5.3. Prior and Concomitant Medications and Procedures

Data regarding prior and concomitant medications and procedures as described in Section 6.7 will be collected in the eCRF.

8.2. Efficacy Assessments

8.2.1. Computed Tomography Scan or Magnetic Resonance Imaging

Objective assessment of tumor status is required using appropriate disease-specific techniques in order to determine responses, which will be logged into the eCRF. The criteria of Cheson et al (2014) or Hallek et al (2018) will be used, and the recommended method for measuring and following tumor burden will be CT scan to include the neck, chest, abdomen, and pelvis. For radiologic assessment, a CT scan with contrast (if contrast is possible) will be performed. Contrast-enhanced MRI will be performed if CT scan with contrast is medically contraindicated as assessed by the investigator or if the frequency of CT scan defined in the SoA is not accepted by local IRBs/IECs. Of important note, participants with suspicion of CNS involvement or those with a known history of CNS lymphoma must undergo CT/MRI of the head at screening to exclude active CNS disease.

If CT (or MRI) scan was performed as standard of care before signing the ICF but within 28 days of enrollment, then the results from that assessment may be recorded in the eCRF in lieu of a study-specific assessment. All CT (or MRI) scan assessments will be scheduled from the date of enrollment and will be calendar-based. Delays or interruptions in study treatment administration will not affect the SoA. The same imaging modality (CT or MRI) and technique (eg, the use of contrast, slice thickness for scans) that was used at screening should be used throughout the study for each participant.

The schedule for CT/MRI assessments is shown in Table 3. This schedule also applies to participants who discontinue study treatment for reasons other than disease progression until disease progression, withdrawal of consent, end of the study, or death, whichever occurs first.

8.2.2. Fluorodeoxyglucose–Positron Emission Tomography

Positron emission tomography of the neck, chest, abdomen, and pelvis using [18F]-FDG is required in all participants to evaluate disease burden, including disease involvement in the bone marrow, at screening and at subsequent postbaseline timepoints (see Table 3). Fluorodeoxyglucose-PET assessments performed as standard of care before signing the ICF but within 28 days of enrollment may be used in lieu of a study-specific assessment. Combined PET/CT or combined PET/MRI may be used for radiologic assessment provided that the CT or MRI is performed with contrast (see Section 8.2.1).

If a participant with FDG-avid disease in the bone marrow (PET-avid bone marrow) at baseline achieves a radiologic CR based on CT or MRI earlier than EOT, a PET scan must be performed to confirm the assessment of CR within 28 days (± 14 days) of the participant fulfilling the criteria for radiologic CR. If a PET scan is performed to confirm a CR prior to Week 24, then no additional PET scans are required.

For CT scans or MRI indicating PD before the EOT visit, PET/CT or PET/MRI assessment must also be performed within 4 weeks (± 2 weeks) for confirmation.

Response assessment will be performed each time a radiologic assessment (CT scan/MRI or PET/CT or PET/MRI) is performed using the appropriate criteria for the participant's disease.

8.2.3. Confirmatory Bone Marrow Biopsy and Examination

In participants who achieve a radiologic CR, a confirmatory bone marrow biopsy will be collected for local pathology assessment, except in the following circumstances:

- Participant has no lymphoma involvement in the bone marrow based on either bone marrow examination or PET at baseline, or
- Participant has lymphoma involvement in the bone marrow based on PET at baseline (in which case, confirmatory PET will be performed [see Section 8.2.2]).

The confirmatory bone marrow biopsy should be performed within 28 days of the participant fulfilling the criteria for radiologic CR.

All bone marrow examinations should include a unilateral biopsy and, if clinically feasible, an aspiration.

The pathology report result from the site's local bone marrow examination will be captured in the eCRF.

Sample collection requirements and processing instructions will be provided in the Central Laboratory Manual.

8.2.4. Independent Review Committee

All radiologic imaging (CT or MRI and PET) will be submitted to a central radiology vendor for review. An exploratory analysis of imaging data and applicable clinical data may be performed using the Lugano criteria (Cheson et al 2014) for NHL and the iwCLL criteria (Hallek et al 2018) for CLL. Scans should be submitted within 4 weeks of completion.

8.2.5. Medical Resource Utilization and Health Economics

Not applicable.

8.3. Safety Assessments

See Section 6.6 for dose modification guidelines for relevant laboratory or other safety assessment abnormalities.

8.3.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until at least 90 days after the last dose of study treatment or until the start of new anticancer therapy. Adverse events for enrolled participants that begin or worsen after informed consent should be recorded on the Adverse Events Form in the eCRF regardless of the assumption of a causal relationship with the study treatment. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative). The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, are considered related to the study treatment/procedures, or caused the participant to discontinue study treatment. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, such as "How are you feeling?", is the preferred method to inquire about AE occurrences. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits or through physical examinations, laboratory tests, or other assessments. The definition, reporting, and recording requirements for AEs are described in Section 9.

All SAEs will be reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.3.2. Physical Examinations

Physical examinations must be performed by a medically qualified individual, such as a licensed physician, physician assistant, or an advanced registered nurse practitioner, as local law permits. Abnormalities identified after the first dose of study treatment constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Investigators should pay special attention to clinical signs related to previous serious illnesses.

At the screening visit, a comprehensive physical examination should be conducted. The comprehensive physical examination will include height (screening only) and body weight and assessment(s) of the following organ or body systems: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver, spleen); extremities; and lymph nodes; as well as a brief neurological examination. Additional physical examinations will be performed at the timepoints indicated in Table 3.

During the study, participants will be assessed by the investigator or medically qualified designee per institutional standard of care. These assessments should be an evaluation as indicated by participant symptoms, AEs, or other findings and documented on the AE eCRF.

8.3.3. Vital Signs

Vital sign measurements (to be taken before blood collection for laboratory tests) include blood pressure, pulse, respiratory rate, weight, and body temperature. If vital signs cannot be taken before blood collection for laboratory tests, there must be a minimum of 30 minutes from the completion of the blood collection procedures to the beginning of the vital signs collection. Blood pressure and pulse will be taken with the participant in the recumbent, semirecumbent, or sitting position after 5 minutes of rest.

Abnormal vital sign results identified after the first dose of study treatment may constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment.

8.3.4. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group performance status (Oken et al 1982; see Appendix B) will be assessed at the timepoints listed in Table 3. Performance status must be assessed by a medically qualified individual and recorded in the eCRF.

8.3.5. B Symptoms/Constitutional Symptoms

B symptoms will be assessed at screening and throughout the conduct of the study (see Table 3). B symptoms include fever > 38°C (100.4°F), night sweats, and weight loss > 10% within the prior 6 months. For participants with CLL or SLL, assessment of constitutional symptoms will also include assessment of fatigue (Hallek et al 2018).

8.3.6. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in Table 3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All 12-lead ECGs will be performed with the participant in a recumbent or semirecumbent position after 5 minutes of rest.

8.3.7. Left Ventricular Ejection Fraction Assessments

A 2-dimensional echocardiogram or cardiac multigated acquisition scan will be obtained during the screening period to evaluate cardiac function and assess LVEF.

8.3.8. Laboratory Assessments

See Table 13 for the list of clinical laboratory tests to be performed and Table 3 for the timing and frequency. A certified laboratory local to the investigative site will perform all clinical laboratory assessments for safety (eg, blood chemistries, hematology assessments, coagulation tests, endocrine function, and urinalysis). The investigative site will enter the laboratory results and laboratory normal ranges into the eCRF. Additional testing may be required by the sponsor based on emerging safety data. Additional tests may also be performed if clinically indicated.

Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 90 days after the last dose of study treatment

should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

Screening laboratory assessments must be performed within 28 days before C1D1. If performed more than 28 days before C1D1, then the tests must be repeated and eligibility confirmed before study treatment administration on C1D1.

Laboratory sample collection on C1D1 must be performed prior to administration of study treatment. After Cycle 1, predose laboratory procedures can be conducted before study treatment administration (within the allotted visit window), and results should be reviewed by the investigator or qualified designee and found to be acceptable before a new cycle of treatment is initiated.

See Section 9.1 for information regarding laboratory abnormalities that should be recorded as AEs in the eCRF. Additionally, if laboratory values from laboratory assessments performed at the institution's local laboratory require a change in participant management (eg, require treatment) or are considered clinically significant by the investigator (eg, SAE, AE, dose modification), then the result(s) of the specific laboratory assessment(s) must be recorded in the eCRF.

Table 13: Required Laboratory Analytes

Chemistry	Hematology	Urinalysis With Microscopic Examination (only if blood in urine is suspected)	Virus Serology	Coagulation
Sodium Potassium Calcium Chloride Phosphate Creatinine Blood urea nitrogen Uric acid ALT AST Total bilirubin Direct bilirubin (if total bilirubin > ULN) Amylase Lipase C-reactive protein Total protein Albumin Alkaline phosphatase Lactate dehydrogenase Glucose	Complete blood count: • Hemoglobin • Hematocrit • Platelet count • Red blood cell count • White blood cell count Differential count: • Neutrophils (ANC must be provided) • Basophils • Eosinophils • Lymphocytes • Monocytes	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein	HBsAg Anti-HBs Anti-HBc HBV-DNA Anti-HCV HCV-RNA HIV CMV	PT aPTT INR
		Lipid Panel	**Endocrine Function**	**Pregnancy Testing**
		Total cholesterol Triglycerides LDL HDL	TSH T_4 T_3/FT_3	Female participants of childbearing potential only.
		Immunoglobulins		
		Serum IgG Serum IgA Serum IgM		

anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; anti-HCV = antibody to hepatitis C virus; aPTT = activated partial thromboplastin time; HDL = high-density lipoprotein; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; LDL = low-density lipoprotein; PT = prothrombin time; T_3/FT_3 = triiodothyronine/free triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone.

Note: Laboratory studies will be performed locally. Additional tests may be required, as agreed by the investigator and sponsor, based on emerging safety data or to rule out a diagnosis.

8.3.8.1. Pregnancy Testing

A serum pregnancy test will be required for all WOCBP during screening and at the EOT visit.

Urine pregnancy tests will be performed locally as outlined in Table 3, as medically indicated (eg, in case of loss of menstrual cycle, when pregnancy is suspected), or per country-specific requirement (note that country-required urine pregnancy testing will be outlined and communicated to investigational sites under separate cover). If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test.

If the serum pregnancy test is negative after a urine test was positive, the investigator will assess the potential benefit/risk to the participant and determine whether it is in the participant's best interest to resume study treatment and continue participation in the study.

If a pregnancy is confirmed by a serum pregnancy test, see Section 9.7 for reporting requirements.

8.3.8.2. Viral Serology Testing

8.3.8.2.1. Hepatitis

Hepatitis screening assessments will be performed at the screening visit to rule out hepatitis infection; required analytes are shown in Table 13. Hepatitis tests should be performed early in the screening process due to the length of time needed to obtain the results.

8.3.8.2.2. Human Immunodeficiency Virus

Participants enrolled outside of the United States must have an HIV immunoassay test at screening to ensure negative HIV status. Human immunodeficiency virus testing is optional for participants enrolled in the United States.

8.3.8.2.3. Cytomegalovirus

Samples for CMV DNA will be collected at screening and at the timepoints listed in Table 3. Participants with CMV viremia without associated clinical signs of CMV infection should be carefully monitored during the conduct of the study.

8.4. Pharmacokinetic Assessments

Whole blood samples will be collected from all enrolled participants for the measurement of serum concentrations of tafasitamab and plasma concentrations of parsaclisib as specified in Table 14. The exact date and time of each sample will be recorded in the eCRF, along with the date and time of the last dose of study drug preceding the blood draw and the time of the most recent meal. Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual.

After the predose PK sample is drawn, participants will begin study treatment.

Table 14: Pharmacokinetic Blood Sample Timing

Drug	Study Visit	Timing of Sample
Tafasitamab	[redacted]	
Parsaclisib		

8.4.1. Urine Sample Collection

Urine samples will be collected at the timepoints listed in Table 3 for the analytes listed in Table 13.

[redacted]

[redacted]

8.6. Unscheduled Visits

Unscheduled visits may occur as clinically indicated and can also be used for visits that occur outside of visit windows; these visits should be noted in the eCRF as an unscheduled visit.

8.7. End of Treatment and/or Early Termination

When the participant permanently discontinues study treatment (ie, tafasitamab and parsaclisib), the EOT visit should be conducted. If the EOT visit coincides with a regular study visit, the EOT evaluations will supersede those of that scheduled visit, and the data should be entered in the EOT visit in the eCRF. The participant should be encouraged to return for the follow-up visit.

8.8. Follow-Up

8.8.1. Safety Follow-Up

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 90 days after the EOT visit (or after the last dose of study treatment if the EOT visit was not performed). Adverse events and SAEs must be reported up until 1) at least 90 days after EOT/last dose of study treatment or the start of a new anticancer therapy or 2) until toxicities resolve, return to baseline, or are deemed irreversible, whichever is longer. Reasonable efforts should be made to have the participant return for the follow-up visit and report any AEs that may occur during this period.

If a participant is scheduled to begin a new anticancer therapy before the end of the safety follow-up period, the safety follow-up visit should be performed before a new anticancer therapy is started. Once a new anticancer therapy has been initiated, the participant will move into the survival follow-up period.

8.8.2. Post-Treatment Disease Follow-Up

Participants who discontinue study treatment for reasons other than disease progression will move into the disease status follow-up period and should be assessed by radiologic imaging as specified in Table 3 to monitor disease status. Every effort should be made to collect imaging information regarding disease status until the start of new anticancer therapy or disease progression.

Sites are still required to submit imaging tumor assessments for independent review.

8.8.3. Survival Follow-Up

Once a participant has received the last dose of study treatment and has confirmed disease progression or starts a new anticancer therapy, the participant will move into the survival follow-up period and should be contacted by telephone, email, or visit at least every 12 weeks (+ 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

For participants who entered the survival follow-up period of the study, the site will use continuing participant records to supply data on subsequent treatment regimens, tumor assessments (if discontinued treatment for a reason other than progression), and OS in the eCRF. For participants who do not intend to return to the study investigator for their ongoing care, follow-up should be maintained by phone contact, patient records, and public records/databases as specified in Table 3.

8.8.4. Participant Completion of Study

Participants will be considered as having completed the study if the participant:

- withdraws consent from further survival follow-up, or
- is lost to follow-up, or
- death occurs.

All participants will be considered as having completed the study should the sponsor decide to terminate the study.

9. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

9.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. • An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) are to be reported as an AE. • Abnormal laboratory test results are to be reported as an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study treatment. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition/disease, including either an increase in the frequency and/or intensity of the condition, is to be reported as an AE. • New conditions detected or diagnosed after the start of study treatment administration are to be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction are to be reported as an AE. • Signs and/or symptoms from dosing errors of a study treatment (eg, overdose) or a concomitant medication are to be reported as an AE. • "Lack of efficacy," "disease progression," or "failure of expected pharmacological action" will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) will be reported as an AE if it occurs after obtaining informed consent. If the condition is present before entering the study, then it should be captured as medical history. • Pre-existing diseases or conditions with expected fluctuations in signs or symptoms should be reported as an AE only if the investigator judges the fluctuation to have worsened more than expected during study participation.

9.2. Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurs. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment or planned surgery (eg, stent replacement, hip surgery) is not considered an SAE.

Hospitalization for a medical intervention in which no unfavorable medical occurrence occurred (ie, elective procedure or routine medical visit) is not considered an SAE.

d. Results in persistent or significant disability/incapacity

- The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is an important medical event

An important medical event is an event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, secondary malignancies, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency or drug abuse, or suspected transmission of an infectious agent via a medicinal product. Secondary malignancies should always be considered SAEs.

9.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed should be recorded on the Adverse Event Form in the eCRF. AEs/SAEs should be reported for enrolled participants, but only SAEs need to be reported for screen failure participants. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF. For detailed information, refer to the eCRF guidelines.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the Adverse Event Form in the eCRF.
- There may be rare instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted by the site staff on the copies of the medical records before submission. These records can be submitted to Incyte Pharmacovigilance by email/fax per the contact information listed in the Study Reference Manual.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine the following:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment: suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at the final safety follow-up visit.
- The action taken with regard to study treatment as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 9.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on the Adverse Event Form and the treatment should be specified on the appropriate eCRF.

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age-appropriate activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The relationship to each study drug must be assessed. The relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are medical facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the possibility of a relationship.
- The investigator will also consult the RSI in the parsaclisib IB and the tafasitamab IB in making his/her assessment.
- Alternative causes, such as underlying or concurrent disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality based on the available information for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and submit the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- Once an AE is detected, it should be followed in the AE eCRFs until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE.

- Updated SAE information will be recorded in the originally completed eCRF and reported to Incyte Pharmacovigilance (in the SAE eCRF) until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Any updated SAE data (including SAEs being downgraded to nonserious) will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.

See Appendix G for the management of potential Hy's Law cases.

9.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study treatment or study procedures), all SAEs occurring after the participant has signed the ICF through the last safety visit or at least 90 days after the last dose of study treatment ***or*** until the participant starts a new anticancer therapy must be reported to the sponsor (or designee) immediately, without undue delay but not later than within **24 hours** of obtaining knowledge of its occurrence unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) immediately, without undue delay but not later than within 24 hours of it being available.

Investigators are not obligated to actively seek SAE information after the safety follow-up visit or 90 days after the last dose of study treatment. If the investigator learns of any SAE, including death, at any time during this period and he/she considers the event to be reasonably related to study treatment or study participation, then the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Prompt notification by the investigator to the sponsor regarding an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the RSI of the parsaclisib IB or the tafasitamab IB and is thought to be related to the study treatment, the sponsor or its designee may urgently require further information from the investigator for expedited reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of the study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAE via the EDC system (primary method) or by completing the Serious Adverse Event Report Form in English (only if the EDC system is not available). The contact information for Incyte Pharmacovigilance by email/fax is listed in the Study Reference Manual. • In circumstances where the EDC system is not accessible for reporting SAE information (initial and/or follow-up SAE information) to the sponsor within 24 hours, refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form. Once the EDC system is functional, the SAE report should be retrospectively added to the EDC system and follow-up should be completed through the EDC. The original copy of the Serious Adverse Event Report Form and the email or facsimile confirmation sheet must be kept at the study site (refer to the Incyte Reference Guide for Completing the Serious Adverse Report Form). • Follow-up information is also recorded in the eCRF and transmitted to Incyte Pharmacovigilance via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event, treatment provided, action taken with study drug(s) because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs.

9.5. Events of Clinical Interest

An ECI is an AE (serious or nonserious) that Incyte wishes to document in an organized manner for monitoring or understanding. An ECI does not require rapid communication by an investigator to Incyte unless it meets criteria for rapid communication as an SAE (see Section 9.2).

The following laboratory abnormalities and/or clinical AEs are considered ECIs:

- Tafasitamab:
  - Tumor lysis syndrome
  - IRRs
  - Allergic reactions to study drug ≥ Grade 3
  - CRS
  - Secondary primary malignancy
  - Hepatitis B reactivation
  - Progressive multifocal leukoencephalopathy.

- Parsaclisib:
  - ALT ≥ 5 × ULN
  - AST ≥ 5 × ULN
  - Colitis
  - Diarrhea ≥ Grade 3
  - Intestinal perforation
  - Rash ≥ Grade 3
  - Exfoliative dermatitis
  - Pneumonitis
  - PJP infection
  - CMV infection
  - Herpes simplex virus infection
  - Varicella zoster virus infection

9.5.1. Adverse Events of Special Interest

Not applicable.

9.6. Emergency Unblinding of Treatment Assignment

Not applicable.

9.7. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study treatment, the following procedures should be followed in order to ensure safety:

- The study treatment must be discontinued immediately (female participants only).
- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or its designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 9.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

9.8. Warnings and Precautions

Special warnings or precautions for the study drugs, derived from safety information collected by the sponsor or its designee, are presented in the parsaclisib IB and the tafasitamab IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study as necessary. If new significant risks are identified, they will be added to the ICF.

Infection with SARS-CoV-2, the coronavirus that causes COVID-19, is more frequent and severe in patients with hematologic dysfunction (Jee et al 2022). The presence of hematologic malignancy, baseline neutropenia and lymphopenia, B-cell depletion, and other factors have been identified as risk factors for loss of humoral immunity to COVID-19, poor vaccine response, viral persistence, and severe disease (Lee et al 2022, Lyudovyk et al 2022, Shree et al 2022). Targeting B-cell function, proliferation, and survival with various therapies are current strategies for improving the outcome of several hematologic malignancies. PI3Kδ inhibition with parsaclisib alone or in combination with other therapies, which may also suppress humoral immunity, has the potential to negatively impact SARS-CoV-2 infection risk, vaccine effectiveness, recovery from COVID-19, and disease severity (Cheson 2022). Investigators and participants participating in trials of parsaclisib, alone or in combination, need to be aware of these potential risks and consider the local standards of care and available therapies for disease prevention, vaccination, and infection management of COVID-19.

9.9. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 9.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

9.10. Treatment of Overdose

Overdose is not an SAE unless it meets the criteria of an SAE (see Section 9.3).

Overdose of parsaclisib is defined as any daily dose > 20 mg within the first 8 weeks of the study and > 2.5 mg for the rest of the study within a 24-hour time period (± 4 hours).

Overdose of tafasitamab is defined as any dose > 120% of the protocol-specified dose per single infusion.

Overdose with concomitant medication will not be recorded in the eCRF unless it resulted in an AE.

In the event of an overdose, the investigator should do the following:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Obtain a plasma sample for PK analysis if requested by the medical monitor.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant. Incyte does not recommend specific treatment for an overdose; treatment of overdose for either study drug should consist of general supportive measures.

10. STATISTICS

10.1. Sample Size Determination

Up to 10 evaluable participants will be treated in each of the 5 disease-specific cohorts during the dose confirmation period. Enrollment into a cohort will be halted if the dose is not considered tolerable or once 10 evaluable participants have been treated for 28 days.

If the dose confirmation period for a disease-specific cohort confirms the dose is tolerable, that particular cohort will be opened for enrollment into the dose expansion period. Up to 10 additional participants will be enrolled up to a total of 20 evaluable participants in each of the 5 disease-specific cohorts (up to 100 evaluable participants in the whole study).

With 10 participants in each disease-specific cohort during the dose confirmation period, there is approximately 89.3% probability of observing at least 1 DLT if the underlying DLT rate is 20% and 97.2% probability of observing at least 1 DLT if the underlying DLT rate is 30%. If ≤ 1 of 10 participants in each disease-specific cohort during the dose confirmation period experience a DLT, the upper limit of the 95% 1-sided CI for the underlying DLT rate will not be > 39.5%. If none of 10 participants experience a DLT in each disease-specific cohort during the dose confirmation period, the upper limit of the 95% 1-sided CI for the underlying DLT rate will not be > 25.9%.

With 10 participants in each disease-specific cohort, there is approximately 97.2% probability of observing at least 1 objective response during the dose confirmation period if the underlying

response rate is 30%. For a reference of the precision of the ORR estimate with 10 or 20 participants in each disease-specific cohort, the 2-sided 95% CIs for different observed ORRs ranging from 10% to 100% are provided in Table 15.

Table 15: Two-Sided 95% Confidence Interval for Different ORR Estimates

Sample Size	Observed ORR	95% CI
n = 10	10%	(0.3%, 44.5%)
	20%	(2.5%, 55.6%)
	30%	(6.7%, 65.3%)
	40%	(12.2%, 73.8%)
	50%	(18.7%, 81.3%)
	60%	(26.2%, 87.8%)
	70%	(34.8%, 93.3%)
	80%	(44.4%, 97.5%)
	90%	(55.5%, 99.8%)
	100%	(69.2%, 100.0%)
n = 20	10%	(1.2%, 31.7%)
	20%	(5.7%, 43.7%)
	30%	(11.9%, 54.3%)
	40%	(19.1%, 63.9%)
	50%	(27.2%, 72.8%)
	60%	(36.1%, 80.9%)
	70%	(45.7%, 88.1%)
	80%	(56.3%, 94.3%)
	90%	(68.3%, 98.8%)
	100%	(83.2%, 100.0%)

10.2. Populations for Analysis

The populations for analysis are provided in Table 16.

Table 16: Populations for Analysis

Population	Description
All-screened set	All participants who signed the ICF.
FAS	The FAS includes all participants who received at least 1 dose of study drug. The FAS will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all safety and efficacy data.
DLT evaluable set	The DLT evaluable set will include all participants who received at least 3 of 4 doses of tafasitamab and 21 days of treatment with parsaclisib 20 mg QD during the first cycle (28 days) or have experienced a DLT. Participants who are considered not evaluable will be replaced.
Efficacy evaluable set	The efficacy evaluable population includes all participants enrolled in the study who have received at least 1 dose of study drug and completed a baseline scan and meet at least one of the following criteria: • ≥ 1 post baseline scan • The participant has participated in the study for a minimum of 42 days • The participant has discontinued from treatment or died prior to the first scheduled postbaseline scan
PK evaluable set	The PK evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 postdose PK plasma sample.
Immunogenicity analysis set	All participants who received at least 1 dose of study treatment and have at least 1 evaluable anti-tafasitamab antibody (ADA) assessment.

10.3. Level of Significance

This is an exploratory study, and no formal statistical tests will be performed. Unless otherwise specified, all CIs will be 95%.

10.4. Statistical Analyses

All statistical analyses are exploratory in nature. Continuous variables will be summarized using means, medians, standard deviations, minimums, and maximums. Categorical variables will be summarized using frequency counts and percentages.

10.4.1. Safety Analyses

Safety analyses will be conducted for the FAS.

Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study treatment until 90 days after the last dose of study treatment) will be tabulated by preferred term and system organ class for all events, treatment-related events, events of Grade 3 or higher, serious events, fatal events, and events leading to treatment discontinuation or modification. Dose-limiting toxicities will be listed for participants during the dose confirmation period of the study.

Quantitative safety variables and their changes from baseline (laboratory, vital signs, ECG, etc) will be summarized with descriptive statistics. Abnormal values will be flagged and tabulated based on predefined criteria.

The clinical laboratory data will be analyzed using summary statistics. Descriptive statistics of the value and change from baseline at each assessment time will be provided. For laboratory parameters that have CTC grading, shift tables will be provided showing change in CTC grade from baseline to the worst postbaseline grade. In addition, distributions of key laboratory parameters may be plotted over time; these values will also be classified into NCI CTCAE toxicity grades and tabulated.

Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time. Vital sign results will be reviewed for clinically notable abnormalities.

Descriptive statistics and mean change from baseline will be determined for each ECG parameter at each assessment time. Electrocardiogram results will be reviewed for clinically notable abnormalities. Participants exhibiting clinically notable ECG abnormalities will be listed.

Measures of exposure (eg, days of exposure, dose intensity, etc) of tafasitamab and parsaclisib will be summarized using summary statistics.

10.4.2. Efficacy Analyses

All efficacy endpoints will be analyzed using the FAS.

10.4.2.1. Overall Response Rate

Overall response rate is defined as the percentage of participants experiencing a best overall response of CR/CMR or PR/PMR according to the Lugano criteria (Cheson et al 2014) for NHL and the iwCLL criteria (Hallek et al 2018) for CLL based on investigator assessment at any time during the study before disease progression and start of a new antilymphoma treatment.

The ORR and its 95% exact binomial CIs will be summarized. Participants whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These participants will be included in the denominators in the calculations of ORR.

10.4.2.2. Complete Response Rate

Complete response rate is defined as the percentage of participants experiencing a best overall response of CR/CMR according to the Lugano criteria (Cheson et al 2014) for NHL and the iwCLL criteria (Hallek et al 2018) for CLL based on investigator assessment at any time during the study before disease progression and start of a new antilymphoma treatment. The CRR and its 95% exact binomial CIs will be summarized. Participants whose baseline disease assessment or on-study response assessments cannot be adequately assessed for response will be considered as nonresponders. These participants will be included in the denominators in the calculations of CRR.

10.4.2.3. Progression-Free Survival

Progression-free survival is defined as the time from the date of first dose of study treatment until the first documented disease progression according to the Lugano criteria (Cheson

et al 2014) for NHL and the iwCLL criteria (Hallek et al 2018) for CLL per investigator assessment or death due to any cause, whichever occurs first. Censoring of PFS will follow FDA guidance (FDA 2015, FDA 2018). Details will be provided in the SAP. The total number of participants whose disease progressed or who died and the number of participants censored will be summarized. Kaplan-Meier estimation of median PFS and its 95% CIs will be summarized.

10.4.2.4. Duration of Response

Duration of response is defined as the time from first documented CR/CMR or PR/PMR until the date of first documented disease progression or death due to any cause, whichever occurs first, among participants who achieve a CR/CMR or PR/PMR according to the Lugano criteria (Cheson et al 2014) for NHL and the iwCLL criteria (Hallek et al 2018) for CLL per investigator assessment. Censoring of DOR will follow the same algorithm as the censoring of PFS noted above. Total number of objective responders, number of participants whose disease progressed or who died, and number of participants censored will be summarized. Kaplan-Meier estimation of median DOR and its 95% CIs will be summarized.

10.4.2.5. Overall Survival

Overall survival is defined as the time from the date of first dose of study treatment until death due to any cause. Details will be provided in the SAP. Total number of participants who died and number of participants censored will be summarized. Kaplan-Meier estimation of median OS and its 95% CIs will be summarized.

10.4.3. Exploratory Analyses

10.5. Interim Analysis

Not applicable.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Investigator Responsibilities

- The Protocol, Protocol Amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC and health authorities before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB/IEC, and institutional requirements.
- Any amendments to the Protocol will require approval from both health authorities and the IRB/IEC before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB/IEC requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB/IEC. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.
  - The investigator must not destroy any records during the retention period associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.

– All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

11.1.1. Identification of the Coordinating Principal Investigator

A coordinating principal investigator will be appointed by the sponsor before the end of the study. As part of their responsibilities, the coordinating principal investigator will review the final CSR. Agreement with the final CSR will be documented by the dated signature of the coordinating principal investigator.

11.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol, such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for the following:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Managing and reconciling the data generated and/or collected, including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for the following:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically and/or centrally (eg, laboratory data, imaging data, biomarker data, photographs, diary data) or as otherwise specified in the Protocol.

- Maintaining adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial participants. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source data are, in general, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed and available at the investigator's site. Examples of source documents are original documents, data, and records (eg, hospital records; electronic hospital records; clinical and office charts; laboratory notes; memoranda; participants' diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; participants' files; and e-records/records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- Sending participants' data, either as unique samples, copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
  - As required by privacy and data protection regulations and Incyte's privacy policies, if any photographs of participants are to be taken, the photographs must be limited to the area of the face or the body that is strictly necessary and the photographs should be masked (ie, identifying features such as eyes, mouth, scars, tattoos, or unique markings or features should be either obscured with a black bar or digitally pixelated so as to not permit the reidentification of the participants and preserve their confidentiality) by a specially designated photography vendor prior to sending the photographs to Incyte or any other third-party vendors for analysis or further processing.

  - In accordance with French regulations, sites in France must perform the masking before the photographs are transferred, including to any specially designated photography vendor, Incyte, or any other third party vendors for analysis or further processing. In addition, the participant's specific consent for photographs shall be collected.

- Permitting study-related monitoring, sponsor audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

11.3. Data Quality Assurance

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations). The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Further, monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues, Protocol deviations, and monitoring techniques (eg, central, remote, or on-site monitoring) are provided in the monitoring plan.

Quality tolerance limits will be predefined in the operational manual to identify systematic issues that can impact participants' safety, efficacy results and analysis, and/or reliability of study results. These predefined parameters will be monitored during the study and can be adjusted during the study upon data review. Important deviations from the quality tolerance limits and remedial actions taken, including reporting to IRBs/IECs and health authorities if applicable, will be summarized in the CSR.

11.4. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that personal information is handled in accordance with local data protection laws (including but not limited to HIPAA and GDPR) as applicable, and the sponsor operates comprehensive data privacy and data security programs that are applicable to this study. Appropriate notice, or notice and consent (as may be required by each applicable jurisdiction), for collection, use, disclosure and/or transfer (if applicable) of personal information must be obtained in accordance with local data protection laws. Appropriate data protection terms that comply with applicable laws will be included in relevant study agreements.

To ensure confidentiality of records and protect personal data, participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

In the event of a data breach involving participant data, the sponsor or its designee will follow the sponsor's incident response procedures. The precise definition of a data breach varies in accordance with applicable law but may generally be understood as a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data. In accordance with its incident response procedures, the sponsor will assess the breach to consider its notification and remediation obligations under applicable law.

11.5. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure Form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Clinical Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

11.6. Publication Policy

By signing the study Protocol, the investigator and their institution agree that the results of the study may be used by the sponsor, Incyte Corporation, for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

11.7. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

12. REFERENCES

Aliqopa [prescribing information]. New York, NY: Bristol Myers Squibb; 2017.

Argatoff LH, Connors JM, Klasa RJ, Horsman DE, Gascoyne RD. Mantle cell lymphoma: a clinicopathologic study of 80 cases. Blood 1997;89:2067-2078.

Barekman CL, Aguilera NS, Abbondanzo SL. Low-grade B-cell lymphoma with coexpression of both CD5 and CD10. A report of 3 cases. Arch Pathol Lab Med 2001;125:951-953.

Campo E, Rule S. Mantle cell lymphoma: evolving management strategies. Blood 2015;125:48-55.

Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study [published correction appears in J Clin Oncol 2016;34:1430]. J Clin Oncol 2015;33:2516-2522.

Cheah CY, Seymour JF, Wang ML. Mantle cell lymphoma. J Clin Oncol 2016;34:1256-1269.

Cheson BD. Death and clinical trials in the plague years. Accessed July 21, 2022. https://ascopost.com/issues/july-10-2022/death-and-clinical-trials-in-the-plague-years

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-3068.

Clinical Trials Facilitation and Coordination Group. Recommendations related to contraception and pregnancy testing in clinical trials. 2020.

Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 2010;116:2040-2045.

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

Colosia A, Njue A, Trask PC, et al. Clinical efficacy and safety in relapsed/refractory diffuse large B-cell lymphoma: a systematic literature review. Clin Lymphoma Myeloma Leuk 2014;14:343-355.e6.

Cuneo A, Castoldi G. Marginal zone B-cell lymphoma. Atlas Genet Cytogenet Oncol Haematol 2006;10:180-183.

Davis TA, Czerwinski DK, Levy R. Therapy of B-cell lymphoma with anti-CD20 antibodies can result in the loss of CD20 antigen expression. Clin Cancer Res 1999;5:611-615.

European Medicines Agency. Guidance of the management of clinical trials during the COVID-19 (coronavirus) pandemic. 2020.

Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma. J Clin Oncol 2006;24:4867-4874.

Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin 2010;60:393-408.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2018.

Food and Drug Administration. Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. 2015.

Forero-Torres A, Ramchandren R, Yacoub A, et al. Parsaclisib, a potent and highly selective PI3Kδ inhibitor, in patients with relapsed or refractory B-cell malignancies. Blood 2019;133:1742-1752.

Gazyva [prescribing information]. South San Francisco, CA: Genentech, Inc; 2016.

Gerber HP, Kung-Sutherland M, Stone I, et al. Potent antitumor activity of the anti-CD19 auristatin antibody drug conjugate hBU12-vcMMAE against rituximab-sensitive and -resistant lymphomas. Blood 2009;113:4352-4361.

Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 2014;370:1008-1018.

Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. J Clin Oncol 2013;31:3688-3695.

Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121-3127.

Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018;131:2745-2760.

Hammer O. CD19 as an attractive target for antibody-based therapy. MAbs 2012;4:571-577.

Hess G, Herbrecht R, Romaguera J, et al. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the treatment of relapsed or refractory mantle cell lymphoma. J Clin Oncol 2009;27:3822-3829.

Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood 2008;111:558-565.

Jee J, Foote MB, Lumish M, et al. Chemotherapy and COVID-19 outcomes in patients with cancer. J Clin Oncol 2022;38:3538-3546.

Jones JA, Robak T, Brown JR, et al. Efficacy and safety of idelalisib in combination with ofatumumab for previously treated chronic lymphocytic leukaemia: an open-label, randomised phase 3 trial. Lancet Haematol 2017;4:e114-e126.

Kahl BS, Yang DT. Follicular lymphoma: evolving therapeutic strategies. Blood 2016;127:2055-2063.

Lee CY, Shah MK, Hoyos D, et al. Prolonged SARS-CoV-2 infection in patients with lymphoid malignancies. Cancer Discov 2022;12:62-73.

Lenz G, Wright G, Dave SS, et al; Lymphoma/Leukemia Molecular Profiling Project. Stromal gene signatures in large-B-cell lymphomas. N Engl J Med 2008;359:2313-2323.

Leukemia & Lymphoma Society. Mantle cell lymphoma facts. 2014.

Lymphoma Research Foundation. Getting the Facts. Marginal zone lymphoma. 2017.

Lyudovyk O, Kim JY, Qualls D, et al. Impaired humoral immunity is associated with prolonged COVID-19 despite robust CD8 T cell responses. Cancer Cell 2022;40:738-753.

Morrison VA, Hamlin P, Soubeyran P, et al. Diffuse large B-cell lymphoma in the elderly: impact of prognosis, comorbidities, geriatric assessment, and supportive care on clinical practice. An International Society of Geriatric Oncology (SIOG) expert position paper. J Geriatr Oncol 2015;6:141-152.

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma Version 1.2021. 2021.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

Palazzo A, Herter S, Grosmaire L, et al. The PI3Kδ-selective inhibitor idelalisib minimally interferes with immune effector function mediated by rituximab or obinutuzumab and significantly augments B cell depletion in vivo. J Immunol 2018;200:2304-2312.

Parsaclisib Investigator's Brochure. Wilmington, DE: Incyte Corporation.

Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. Lancet Oncol 2015;16:1111-1122.

Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. Blood 2010;116:5103-5110.

Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med 1995;333:1540-1545.

Robak T, Huang H, Jin J, et al. Bortezomib-based therapy for newly diagnosed mantle-cell lymphoma. N Engl J Med 2015;372:944-953.

Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med 2018;378:1396-1407.

Schulz H, Bohlius JF, Trelle S, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007;99:706-714.

Sehn LH. Introduction to a review series: the paradox of indolent B-cell lymphoma. Blood 2016;127:2045-2046.

Sehn LH, Congiu AG, Culligan DJ, et al. No added benefit of eight versus six cycles of CHOP when combined with rituximab in previously untreated diffuse large B-cell lymphoma patients: results from the international Phase III GOYA study. Blood 2018;132(suppl 1):783 [abstr].

Sharman JP, Coutre SE, Furman RR, et al. Final results of a randomized, phase III study of rituximab with or without idelalisib followed by open-label idelalisib in patients with relapsed chronic lymphocytic leukemia. J Clin Oncol 2019;37:1391-1402.

Shingleton J, Wang J, Baloh C, et al. Non-Hodgkin lymphomas: malignancies arising from mature B cells. Cold Spring Harb Perspect Med 2020:a034843.

Shree T, Shankar V, Lohmeyer JJK, et al. CD20-targeted therapy ablates de novo antibody response to vaccination but spares preestablished immunity. Blood Cancer Discov 2022;3:95- 102.

Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3199-3212.

Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index Blood 2004;104:1258-1265.

Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood 2016;127:2375-2390.

Tafasitamab Investigator's Brochure. Planegg, Germany: MorphoSys AG.

Treanda [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2013.

Truelove E, Fox C, Robinson S, et al. Carmustine, etoposide, cytarabine, and melphalan (BEAM)-Campath allogeneic stem cell transplantation for aggressive non-Hodgkin lymphoma: an analysis of outcomes from the British Society of Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2015;21:483-488.

Vaidya R, Witzig TE. Prognostic factors for diffuse large B-cell lymphoma in the R(X)CHOP era. Ann Oncol 2014;25:2124-2133.

Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-516.

Woyach JA, Awan F, Flinn IW, et al. A phase 1 trial of the Fc-engineered CD19 antibody XmAb5574 (MOR00208) demonstrates safety and preliminary efficacy in relapsed CLL. Blood 2014;124:3553-3560.

Zinzani P. The many faces of marginal zone lymphoma. Hematology Am Soc Hematol Educ Program 2012;2012:426-432.

Zucca E, Arcaini L, Buske C, et al; ESMO Guidelines Committee. Marginal zone lymphomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31:17-29.

Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2016.

APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS AND DEFINITIONS

Definitions

WOCBP: A woman who is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal with 1 of the following:[a]
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Women on HRT and whose menopausal status is in doubt will be required to use 1 of the nonhormonal, highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

For male participants of reproductive potential[b]

The following methods during the Protocol-defined timeframe in Section 5.1 are highly effective:

- Use of a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
- Vasectomy with medical assessment of the surgical success (verified by site personnel's review of the participant's medical records)
- Sexual abstinence[c]
  - Abstinence from penile-vaginal intercourse

The following are **not** acceptable methods of contraception:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method.
- Male condom with cap, diaphragm, or sponge with spermicide.
- Male and female condom used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

For female participants who are WOCBP

The following methods during the Protocol-defined timeframe in Section 5.1 that can achieve a failure rate of < 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation.[d]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[d]
  - oral
  - injectable
  - implantable[e]
- Intrauterine device[e]
- Intrauterine hormone-releasing system[e]
- Bilateral tubal occlusion[e]
- Vasectomized partner[e,f]
- Sexual abstinence[c]

[a] Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
[b] If the male participant has a partner with childbearing potential, the partner should also use contraceptives.
[c] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
[d] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
[e] Contraception methods that in the context of this guidance are considered to have low user dependency.
[f] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success.
Source: Clinical Trials Facilitation and Coordination Group 2020.

APPENDIX B. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE SCORES

Grade	Performance Status
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken et al 1982.

APPENDIX C. LUGANO CLASSIFICATION FOR RESPONSE ASSESSMENT

Site	PET-Based Response	CT-Based Response
	CMR	**Complete Radiologic Response (All of the Following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3 with or without a residual mass on a 5-point scale[a]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, immunohistochemistry negative
	PMR	**PR (All of the Following)**
Lymph nodes and extralymphatic sites	• Score 4 or 5a with reduced uptake compared with baseline and residual mass(es) of any size • At interim, these findings suggest responding disease • At EOT, these findings suggest 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 × 5 mm as the default • When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm but smaller than normal, use actual measurement
Nonmeasured lesions	Not applicable	Absent/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 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, consider further evaluation with MRI or biopsy.	Not applicable
	No Metabolic Response	**Stable Disease**
Target nodes/nodal masses, extranodal lesions	Score of 4 or 5a with no significant change in FDG uptake from baseline at interim or EOT	< 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 Metabolic Disease	**PD (Requires at Least 1 of the Following)**
Individual target nodes/nodal lesions	Individual target nodes/nodal lesions: • Score 4 or 5a with an increase in intensity of uptake from baseline and/or • New FDG-avid foci consistent with lymphoma at interim or EOT assessment Extranodal lesions: • New FDG-avid foci consistent with lymphoma at interim or EOT assessment New lesions: • New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. Bone marrow: • New or recurrent FDG-avid foci	PPD progression: • An individual node/lesion must be abnormal with all of the following: – LDi > 1.5 cm – Increase by ≥ 50% from PPD nadir – Increase in LDi or SDi from nadir: o 0.5 cm for lesions ≤ 2 cm o 1 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 • New or clear progression of pre-existing nonmeasured lesions • Regrowth of any previously resolved lesions • 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 • New or recurrent involvement of the bone marrow

LDi = longest transverse diameter of lesion; PPD = cross-product of the longest transverse diameter and perpendicular diameter; SDi = shortest axis perpendicular to the longest transverse diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

APPENDIX D. iwCLL RESPONSE DEFINITIONS

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥ 1.5 cm	Decrease ≥ 50% (from baseline)[a]	Increase ≥ 50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size[b]	Spleen size <13 cm; liver size normal	Decrease ≥ 50% (from baseline)	Increase ≥ 50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline	Change of −49% to +49%
B	Platelet count	≥ 100×10^9/L	≥ 100×10^9/L or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL	Change of −49% to +49%
	Hemoglobin	≥ 11 g/dL (untransfused and without erythropoietin)	≥ 11 g/dL or increase ≥ 50% over baselines	Decrease of ≥ 2 g/dL from baseline secondary to CLL	Increase < 11.0 g/dL or <50% over baseline, or decrease < 2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥ 50% on successive biopsies	No change in marrow infiltrate

CR = complete remission (all of the criteria have to be met); PD = progressive disease (at least 1 of the criteria of Group A or Group B has to be met); PR = partial remission (at least 2 of the parameters of Group A and 1 parameter of Group B need to improve if previously abnormal; if only 1 parameter of both Groups A and B is abnormal before therapy, only 1 needs to improve); SD = stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

[a] Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

[b] Spleen size is considered normal if 13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.

APPENDIX E. CYP3A4 INHIBITORS AND INDUCERS

CYP3A4 inhibitors or inducers may alter parsaclisib concentration. These include, but are not limited, to the drugs listed below.

CYP3A4 Inhibitors

Inhibitor	Therapeutic Class
Potent Inhibitors	
VIEKIRA PAK	Antivirals
indinavir/ritonavir	Protease inhibitors
tipranavir/ritonavir	Protease inhibitors
ritonavir	Protease inhibitors
cobicistat (GS-9350)	None
ketoconazole	Antifungals
indinavir	Protease inhibitors
troleandomycin	Antibiotics
telaprevir	Antivirals
danoprevir/ritonavir	Antivirals
elvitegravir/ritonavir	Treatments of AIDS
saquinavir/ritonavir	Protease inhibitors
lopinavir/ritonavir	Protease inhibitors
itraconazole	Antifungals
voriconazole	Antifungals
mibefradil	Calcium channel blockers
LCL161	Cancer treatments
clarithromycin	Antibiotics
posaconazole	Antifungals
telithromycin	Antibiotics
grapefruit juice DS	Food products
conivaptan	Diuretics
nefazodone	Antidepressants
nelfinavir	Protease inhibitors
saquinavir	Protease inhibitors
ribociclib	Kinase inhibitors
idelalisib	Kinase inhibitors
boceprevir	Antivirals
Moderate Inhibitors	
erythromycin	Antibiotics
fluconazole	Antifungals
atazanavir/ritonavir	Protease inhibitors

Inhibitor	Therapeutic Class
darunavir	Protease inhibitors
diltiazem	Calcium channel blockers
darunavir/ritonavir	Protease inhibitors
dronedarone	Antiarrhythmics
crizotinib	Kinase inhibitors
atazanavir	Protease inhibitors
letermovir	Antivirals
GSK2647544	Alzheimer disease & dementia treatments
aprepitant	Antiemetics
casopitant	Antiemetics
amprenavir	Protease inhibitors
faldaprevir	Antivirals
imatinib	Antineoplastic agents
verapamil	Calcium channel blockers
netupitant	Antiemetics
nilotinib	Kinase inhibitors
grapefruit juice	Food products
tofisopam	Benzodiazepines
cyclosporine	Immunosuppressants
ACT-178882	Renin inhibitors
ciprofloxacin	Antibiotics
Magnolia vine (*Schisandra sphenanthera*)	Herbal medications
isavuconazole	Antifungals
cimetidine	H_2-receptor antagonists
FK1706	Central nervous system agents
Weak Inhibitors	
tabimorelin	Hormone replacements
amlodipine	Calcium channel blockers
ranolazine	Cardiovascular drugs
breviscapine	Herbal medications
lomitapide	Other antilipemics
fosaprepitant (IV)	Antiemetics
Seville orange (*Citrus aurantium*) juice	Food products
amiodarone	Antiarrhythmics
diosmin	Herbal medications
chlorzoxazone	Muscle relaxants
M100240	Antihypertensive agents
fluvoxamine	Antidepressants

Inhibitor	Therapeutic Class
ranitidine	H_2-receptor antagonists
goldenseal	Herbal medications
clotrimazole	Antifungals
tacrolimus	Immunosuppressants
palbociclib	Kinase inhibitors
cilostazol	Antiplatelets
ticagrelor	Antiplatelets
peppermint oil	Food products
ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase inhibitors
Guan Mai Ning	Herbal medications
osilodrostat	Adrenal steroidogenesis inhibitors
AZD2327	Depression treatments
piperine	Food products
resveratrol	Food products
roxithromycin	Antibiotics
suvorexant	Hypnotics - sedatives
propiverine	Anticholinergics
isoniazid	Antibiotics
berberine	Herbal medications
oral contraceptives	Oral contraceptives
delavirdine	NNRTIs
daclatasvir	Antivirals
simeprevir	Protease inhibitors
atorvastatin	HMG CoA reductase inhibitors (Statins)
tolvaptan	Vasopressin antagonists
almorexant	Hypnotics - sedatives
GSK1292263	Other antilipemics
evacetrapib	CETP inhibitors
linagliptin	Dipeptidyl peptidase 4 inhibitors
grazoprevir *(ingredient of Zepatier)*	Antivirals
lacidipine	Calcium channel blockers
cranberry juice	Food products
pazopanib	Kinase inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food products
flibanserin	Central nervous system agents

Inhibitor	Therapeutic Class
lapatinib	Kinase inhibitors
brodalumab	Immunomodulator biologics
goldenseal	Herbal medications
clotrimazole	Antifungals
tacrolimus	Immunosuppressants
palbociclib	Kinase inhibitors
cilostazol	Antiplatelets
ticagrelor	Antiplatelets
peppermint oil	Food products
ivacaftor	Cystic fibrosis treatments
GSK2248761	Transcriptase inhibitors
Guan Mai Ning	Herbal medications
osilodrostat	Adrenal steroidogenesis inhibitors
AZD2327	Depression treatments
piperine	Food products
resveratrol	Food products
roxithromycin	Antibiotics
suvorexant	Hypnotics - sedatives
propiverine	Anticholinergics
isoniazid	Antibiotics
berberine	Herbal medications
oral contraceptives	Oral contraceptives
delavirdine	NNRTIs
daclatasvir	Antivirals
simeprevir	Protease inhibitors
atorvastatin	HMG CoA reductase inhibitors (Statins)
tolvaptan	Vasopressin antagonists
almorexant	Hypnotics - sedatives
GSK1292263	Other antilipemics
evacetrapib	CETP inhibitors
linagliptin	Dipeptidyl peptidase 4 inhibitors
grazoprevir (ingredient of Zepatier®)	Antivirals
lacidipine	Calcium channel blockers
cranberry juice	Food products
pazopanib	Kinase inhibitors
fostamatinib	Other
everolimus	Immunosuppressants
blueberry juice	Food products

Inhibitor	Therapeutic Class
flibanserin	Central nervous system agents
lapatinib	Kinase inhibitors
brodalumab	Immunomodulator biologics
AMD070	Fusion inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin receptor antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous agents
ginkgo	Herbal medications
teriflunomide	Other immunomodulators
AMD070	Fusion inhibitors
alprazolam	Benzodiazepines
Tong Xin Luo	Herbal medications
glecaprevir and pibrentasvir	Antivirals
bicalutamide	Antiandrogens
sitaxentan	Endothelin receptor antagonists
azithromycin	Antibiotics
obeticholic acid	Miscellaneous agents
ginkgo	Herbal medications
teriflunomide	Other immunomodulators

CYP3A4 Inducers

Inducers	Therapeutic Class
Potent Inducers	
rifampin	Antibiotics
mitotane	Other antineoplastics
avasimibe	Other antilipemics
rifapentine	Antibiotics
apalutamide	Antiandrogens
phenytoin	Anticonvulsants
carbamazepine	Anticonvulsants
enzalutamide	Antiandrogens
St John's Wort extract	Herbal medications
lumacaftor	Cystic fibrosis treatments
rifabutin	Antibiotics
phenobarbital	Anticonvulsants

Inducers	Therapeutic Class
Moderate Inducers	
ritonavir and St. John's wort	None
semagacestat	Alzheimer disease treatments
efavirenz	NNRTIs
tipranavir and ritonavir	Protease inhibitors
dabrafenib	Kinase inhibitors
lesinurad	Antigout and uricosuric agents
bosentan	Endothelin receptor antagonists
genistein	Food products
thioridazine	Antipsychotics
nafcillin	Antibiotics
talviraline	NNRTIs
lopinavir	Protease Inhibitors
modafinil	Psychostimulants
PF-06282999	Myeloperoxidase inactivators
etravirine	NNRTIs
lersivirine	NNRTIs
telotristat ethyl	Antidiarrheals
Weak Inducers	
eslicarbazepine	Anticonvulsants
telaprevir	Antivirals
daclatasvir and asunaprevir and beclabuvir	Antivirals
amenamevir	Antivirals
garlic	Food products
bexarotene	Other antineoplastics
sarilumab	Immunomodulator biologics
artesunate and mefloquine	Antimalarials
amprenavir (fosamprenavir)	Protease inhibitors
raltegravir	HIV-integrase strand transfer inhibitors
vemurafenib	Kinase inhibitors
troglitazone	Thiazolidinediones
dicloxacillin	Antibiotics
sorafenib	Kinase inhibitors
rufinamide	Anticonvulsants
sirukumab	Immunomodulator biologics
pleconaril	Antivirals
ginseng	Herbal medications
boceprevir	Antivirals
sulfinpyrazone	Antigout and uricosuric agents

Inducers	Therapeutic Class
ginkgo	Herbal medications
vinblastine	Vinca alkaloids
nevirapine	NNRTIs
armodafinil (R-modafinil)	Psychostimulants
ticagrelor	Anticoagulants and antiplatelets
LCL161	Cancer treatments
vicriviroc and ritonavir	Treatments of AIDS
ritonavir	Protease inhibitors
prednisone	Corticosteroids
oxcarbazepine	Anticonvulsants
danshen	Herbal medications
clobazam	Benzodiazepines
echinacea	Herbal medications
ticlopidine	Anticoagulants and antiplatelets
isavuconazole	Antifungals
brivaracetam	Anticonvulsants
Stribild®	Treatments of AIDS
pioglitazone	Thiazolidinediones
VIEKIRA PAK	Antivirals
dexamethasone	Corticosteroids
terbinafine	Antifungals
quercetin	Food products
glycyrrhizin	Herbal medications
aprepitant	Neurokinin-1 receptor antagonists
pretomanid (PA-824)	Antibiotics
safinamide	Monoamine oxidase B inhibitors
oritavancin	Antibiotics
AZD 7325	Anxiolytics
methylprednisolone	Corticosteroids
topiramate	Anticonvulsants

AIDS = acquired immunodeficiency syndrome; NNRTI = non-nucleoside reverse transcriptase inhibitor.

APPENDIX F. INSTRUCTION TO PARTICIPANTS FOR HANDLING PARSACLISIB

The participant must be instructed in the handling of parsaclisib as follows:

To store study drug at room temperature.

- To remove only the number of tablets needed from the study drug bottle at the time of administration.
- Not to remove doses in advance of the next scheduled administration.
- To make every effort to take doses on schedule.
- If a dose is missed by more than 12 hours during the once-daily administration, then that dose should be skipped, and the next scheduled dose should be taken at the usual time.
- To report any missed doses.
- To keep study drug in a safe place and out of reach of children.
- To bring all used and unused study drug bottles to the site at each visit.

APPENDIX G. MANAGEMENT OF POTENTIAL HY'S LAW CASES

INTRODUCTION

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets PHL criteria at any point during the study.

The investigator participates, in conjunction with Incyte clinical project and pharmacovigilance representatives, in the review and assessment of cases fulfilling PHL criteria to ascertain whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug.

The investigator fulfills requirements for the recording of data pertaining to PHL or Hy's law cases and AE/SAE reporting according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

For the purpose of this process, definitions are as follows:

Potential Hy's Law

An increase in AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at any point during the study. The elevations do not have to be at the same time or within a specified timeframe.

Hy's Law

An increase in AST or ALT ≥ 3 × ULN and total bilirubin > 2 × ULN, where no other reason can be found to explain the combination of increases (eg, elevated serum ALP indicating cholestasis, viral hepatitis, another drug).

ACTIONS REQUIRED IN CASES OF AST OR ALT > 3 × ULN OR TOTAL BILIRUBIN ≥ 2 × ULN

Identification and Determination of Potential Hy's Law

To identify cases of AST or ALT > 3 × ULN or total bilirubin > 2 × ULN and consequently determine whether the participant meets PHL criteria, please follow the instructions below:

- Review the laboratory report and if a participant has AST or ALT > 3 × ULN OR total bilirubin > 2 × ULN at any visit:
  - Determine without delay whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits.
  - Enter the laboratory data into the laboratory eCRF as soon as possible.

Potential Hy's Law Criteria Not Met

If the participant has NOT had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Perform follow-up on subsequent laboratory results according to Table 3.

Potential Hy's Law Criteria Met

If the participant has had AST or ALT ≥ 3 × ULN AND total bilirubin > 2 × ULN at any point in the study (the elevations do not have to be at the same time or within a specified timeframe), irrespective of ALP, please follow the instruction below:

- Have participant interrupt study drug.
- Notify Incyte study team without delay.
  - The investigator, or designee, should contact the medical monitor to discuss and agree upon an approach for the study participant's follow-up and the continuous review of data.
- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as medically indicated.
- Investigate the etiology of the event and perform any relevant diagnostic investigations as discussed with the medical monitor.
- Enter the laboratory data into the laboratory CRF as soon as possible.
- If at any time (in consultation with the medical monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

REVIEW AND ASSESSMENT

No later than 3 weeks after the biochemistry abnormality is initially detected and the criteria for PHL is met, the medical monitor, Incyte pharmacovigilance physician, and investigator will discuss and review available data and agree on whether there is an alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the study drug. Participant matter experts will be included in the review as appropriate.

Evaluation of Alternative Causes

In order to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, the following alternative etiologies should be considered, including but not limited to:

- Active viral hepatitis
- Alcoholic and autoimmune hepatitis

- Hepatobiliary disorders
  - Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gallbladder and ductal imaging studies, especially if alkaline phosphatase is increased. Malignant interruption of the biliary tract also should be considered.
- Concomitant treatment
- Other causes such as systemic infections (eg, bacterial, fungal, viral), nonalcoholic steatohepatitis, and cardiovascular diseases

Actions After Review and Assessment

According to outcome of the review and assessment, please follow the instructions below:

If there **is** an agreed alternative explanation for the AST or ALT **and** total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE.

- If the alternative explanation is not an AE, record the alternative explanation on the appropriate CRF if possible.
- If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the standard study processes.
- Have participant resume study drug as per Protocol guidelines.

If it is agreed that there is no explanation that would explain the AST or ALT and total bilirubin elevations:

- Have participant permanently discontinue study drug and perform end-of-treatment procedures.
- Report an SAE (report term "Hy's Law").
  - The 'medically important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's law case, a causality assessment of related should be assigned.
- If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's law case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made. Report an SAE (report term "Potential Hy's Law") applying serious criteria and causality assessment as per above.

ACTIONS REQUIRED FOR REPEAT EPISODES OF AST OR ALT > 3 × ULN AND/OR TOTAL BILIRUBIN > 2 × ULN

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

If the alternative cause for the previous occurrence of PHL was not chronic or progressing malignant disease, please follow the process for PHL review and assessment as described in this appendix.

If the alternative cause for the previous occurrence of PHL was chronic or progressing malignant disease, please follow the instructions below:

- Determine whether there has been a significant change* in the participant's condition.
  - If there is no significant change, no action is required.
  - If there is a significant change, follow the process described for PHL review and assessment as described in this appendix.

* A 'significant' change in the participant's condition refers to a clinically relevant change in ALT, AST, or total bilirubin, or associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

APPENDIX H. PANDEMIC MITIGATION STRATEGIES AND INSTRUCTIONS

The current COVID-19 global pandemic presents numerous challenges to the ongoing conduct of clinical trials. In line with the European Medicines Agency's Guidance on the Management of Clinical Trials During the COVID-19 (Coronavirus) Pandemic (2020), the sponsor has issued the following Protocol considerations to ensure participant safety is maintained and appropriate benefit/risk analyses are taken into consideration with respect to the completion of study procedures and maintaining the investigational product supply chain.

Recognizing the flexibility required to manage the impact of the pandemic on this clinical trial, additional details will be added to respective study manuals and project plan documents and communicated to the investigative sites as needed.

Eligibility

Although SARS-CoV-2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A participant should be excluded if he/she has a positive test result for SARS-CoV-2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV-2. Participants with active infections are excluded from study participation as per the exclusion criteria (see Section 5.2). When the infection resolves, the participant may be considered for rescreening.

Study Site Visits

If local travel restrictions, quarantine requirements, or the investigator's risk/benefit assessment preclude a participant's ability to attend study visits on-site, site staff may elect to perform the following:

- In order to minimize participant risk, study visits may be conducted via telemedicine modalities (phone or video). At a minimum, a review of AEs, concomitant medications, and study drug compliance must be completed. Periodic on-site visits should resume once possible.
- In order to support investigator oversight of safety and disease management, the participant may be asked to perform some laboratory tests or study procedures (eg, ECG) at a local (proximate) hospital laboratory or facility closer to the participant's residence rather than at the investigational site. In this case, the investigator will provide the participant with the list of parameters to be checked. These tests should be performed in certified laboratories.

Investigational Medicinal Product Dispensation and Distribution

In order to ensure the continuity in clinical supplies within the constraints imparted by the pandemic, the site staff may supply study drug as follows:

- Investigators may dispense an additional supply of parsaclisib tablets to compensate for an interval between on-site visits that may be longer than required by the SoA (see Table 3).

- Alternatively, if the participant cannot attend a visit at the study site, an adequate supply of parsaclisib may be shipped to the participant by the investigator or appropriately delegated staff (eg, the study pharmacy staff) using a third-party service if duly authorized by the participant. The study site may use their own preferred courier, provided the courier adheres to certain standards (eg, use of personal protection equipment, maintenance of temperature-controlled transit environment), or one centrally contracted by the sponsor.

Clinical Trial Monitoring

Study monitoring visits may be postponed; however, the study monitor will continue to employ off-site monitoring practices such as routine communication methods (eg, phone calls, emails, video visits) to review information on trial progress, participant status, and information on issue resolution. The study monitor will remotely review data entered into the EDC for accuracy and completeness, and remote source data verification may be implemented with agreement of the principal investigator and institution, as applicable.

If the study monitor cannot be on-site to perform the final drug accountability for reconciliation purposes, and the operation cannot be postponed, it may be performed by a pharmacist from the hospital pharmacy or by the study coordinator/data manager with suitable training. The study drug can be returned to the sponsor by the hospital pharmacy directly or destroyed in accordance with local practices, if applicable, and with sponsor approval.

Direct Contracts With Third Parties/Specialized Service Companies

If necessary, direct contracts can be established with third-party local physicians to conduct activities related to the clinical management of participants for whom the investigator is responsible and maintains oversight. In such situations, the investigator is required to provide the local physician with a delegation letter listing all delegated activities. The sponsor, through the study investigator or institution, will reimburse the local physician for the test/procedures conducted outside of the standard of care.

APPENDIX I. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1	08 OCT 2021
Amendment 2	13 SEP 2022

Amendment 2 (13 SEP 2022)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to include sponsor recommendations regarding COVID-19 monitoring and management, to update data privacy requirements in accordance with the EU Clinical Trials Regulation directive, and to include revisions made in Administrative Changes 2, 3, and 4.

1. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Updated the "Survival" column heading to "Last Visit + 12 Wk (± 7 d)," added a note to the "Tafasitamab ADA (preinfusion)" row to include collection of on-treatment samples every 4 cycles from Cycle 4 (C4D1, C8D1, etc), and updated the "MRD and DNA mutational analysis (blood EDTA)" row to include collection of on-treatment samples at Cycle 4 Day 1 and Cycle 13 Day 1 only.

   Rationale for change: To align with the survival follow-up frequency stated in Section 8.8.3, to align with new information regarding collection of PK and ADA samples at the same timepoints, and to reduce sample collection requirements.

2. **Section 2.3, Benefit/Risk Assessment; Section 9.8, Warnings and Precautions**

   Description of change: Added text related to recommendations for COVID-19 monitoring and management in patients with hematologic malignancies.

   Rationale for change: Recommendations arising out of ongoing safety surveillance.

3. **Section 6.6.2, Criteria and Procedures for Dose Interruptions and Adjustments of Study Drug**

   Description of change: Deleted repeated paragraph.

   Rationale for change: Editorial correction.

4. **Section 8.1.2, Screening Procedures**

   Description of change: Added text to allow assessments to occur outside the 28-day window for those that are suitable for enrollment but may not be feasible to repeat.

   Rationale for change: Clarification.

5. **Section 8.1.2.1, Tumor or Lymph Node Sample; Section 8.1.2.2, Bone Marrow Biopsy and Examination; Section 8.2.1, Computed Tomography Scan or Magnetic Resonance Imaging; Section 8.2.2, Fluorodeoxyglucose–Positron Emission Tomography**

   Description of change: Changed "randomization" to "enrollment" because there is no randomization in this study.

   Rationale for change: Clarification.

6. **Section 10.2, Populations for Analysis (Table 16: Populations for Analysis)**

   Description of change: Add a row defining the DLT evaluable set.

   Rationale for change: This population set will be defined for analyzing DLT results from the dose confirmation part of the study. This population will be more conservative for the calculation of DLT percentage.

7. **Section 11.3, Data Privacy and Confidentiality of Study Records**

   Description of change: Updated text to align with EU Clinical Trials Regulation directive.

   Rationale for change: Updated information.

8. **Incorporation of administrative changes.** Other regulatory guidance and administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Amendment 1 (08 OCT 2021)

Overall Rationale for the Amendment:

The primary purpose of the amendment is to modify the operating characteristics of the iDSMB, update the time interval that must elapse before performing the safety follow-up visit, and update the biomarker sample collection schedule. Additional changes are summarized below.

1. **Section 1, Protocol Summary; Section 4.1, Overall Design; Section 5.6, Data Safety Monitoring Board; Section 6.5.2, Procedures for Cohort Review**

   Description of change: Revised operating characteristics to enable iDSMB reviews to occur after the 10th DLT-evaluable participant, irrespective of cohort, completes the DLT evaluation period. Revised criteria for cohort review to clarify that aggregated safety data will be used to facilitate opening of dose expansion cohorts.

   Rationale for change: DSMB feedback after initial kickoff meeting.

2. **Section 1, Protocol Summary (Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 4.2, Overall Study Duration; Section 6.7, Concomitant Medications and Procedures; Section 8.3.1, Adverse Events; Section 8.3.8, Laboratory Assessments; Section 8.8.1, Safety Follow-Up; Section 9.4, Reporting of Serious Adverse Events; Section 10.4.1, Safety Analyses**

   Description of change: Updated the EOT safety follow-up to 90 days after last dose of study treatment.

   Rationale for change: Standardization across the tafasitamab program for safety follow-up requirements to perform visit after 5 half-lives since last dose.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Changed preinfusion medication to IRR prophylaxis regimen.

   Rationale for change: General clarification.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 8.3.3, Vital Signs**

   Description of change: Included measurement of weight to the vital signs assessments.

   Rationale for change: General clarification to ensure regular monitoring of weight with vital sign assessments.

5. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Added a column under follow-up period to align with post-treatment disease follow-up assessments; added physical examination, vital signs/weight, ECOG performance status, B symptoms/constitutional symptoms, contrast-enhanced CT or MRI, and hematologic parameters where appropriate as part of post-treatment disease follow-up.

   Rationale for change: To clarify the required assessments for post-treatment disease follow-up.

6. **Section 1, Protocol Summary (Table 3: Schedule of Activities)**

   Description of change: Revised biomarker sampling schedule, added plasma proteomics sample collection at C4D1, and decreased the number of on-treatment MRD/DNA mutational and FACS samples to be collected.

   Rationale for change: To align with the translational research plan after initial protocol.

7. **Section 2.1.2, Tafasitamab**

   Description of change: Updated tafasitamab background.

   Rationale for change: To align with the most current IB and approval status.

8. **Section 2.1.3, Parsaclisib**

   Description of change: Updated parsaclisib background.

   Rationale for change: To align with the most current IB.

9. **Section 6.1, Study Treatments Administered (Table 6: Study Treatment Information)**

   Description of change: Updated parsaclisib dosage formulation, and updated approval status information due to recent approvals in European Union and Canada.

   Rationale for change: Editorial clarifications.

10. **Section 6.6.2.1, Tafasitamab Dose Modifications for Cytokine Release Syndrome and Infusion-Related Reactions**

    Description of change: Included provisions to split the dose of tafasitamab if the full dose cannot be administered in 1 day.

    Rationale for change: Standardization across the tafasitamab program to manage IRRs and CRS.

11. **Section 6.6.2.5, Management of Hypogammaglobulinemia**

    Description of change: Added a new section to provide investigators with guidance on appropriate management of hypogammaglobulinemia.

    Rationale for change: Standardization across the tafasitamab program.

12. **Section 6.6.3, Criteria for Permanent Discontinuation of Study Drug**

    Description of change: Added a new section with permanent study drug discontinuation criteria.

    Rationale for change: To provide guidance to investigators on the definitions of unacceptable toxicity.

13. **Section 8.3.5, B Symptoms/Constitutional Symptoms**

    Description of change: Updated to include that assessment of constitutional symptoms for participants with CLL or SLL will include assessment of fatigue.

    Rationale for change: Clarification.

14. **Section 8.8.4, Participant Completion of Study**

    Description of change: Added a new section to clarify participant completion of study definitions.

    Rationale for change: Investigator feedback on initial version.

15. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

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Approval Task	PPD PPD Immuno-Oncology De 13-Sep-2022 15:43:25 GMT+0000
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