FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting
April 21, 2022

Phosphatidylinositol 3-Kinase (PI3K) Inhibitors in Hematologic Malignancies

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the phosphatidylinositol 3-kinase (PI3K) inhibitor drug class to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Abbreviations

AE	adverse event
AUC	area under the curve
B	bendamustine
BID	twice daily
BR	bendamustine + rituximab
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete remission, complete response
CSR	clinical study report
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
ER	exposure-response
FL	follicular lymphoma
GC	obinutuzumab plus chlorambucil
HR	hazard ratio
IA	interim analysis
IgHV	immunoglobulin heavy chain
iNHL	indolent non-Hodgkin lymphoma
IRC	independent review committee
ITT	intent-to-treat
LOU	limitations of use
LPL	lymphoplasmacytic lymphoma
MCL	mantle cell lymphoma
MM	multiple myeloma
MRD	minimal residual disease
MTD	maximal tolerated dose
MZL	marginal zone lymphoma
NE	not evaluable, not estimable
NHL	non-Hodgkin lymphoma
NR	not reported, not reached
ORR	objective response rate, overall response rate
OS	overall survival
PD	progressive disease, pharmacodynamic
PFS	progression-free survival
PI	prescribing information
PI3K	phosphatidylinositol-3 kinase
PI3Ki	phosphatidylinositol-3 kinase inhibitor
PFS	progression-free survival

PK	pharmacokinetic
PMC	post-marketing commitment
PMR	post-marketing requirement
PR	partial remission, partial response
PRO	patient reported outcome
R	rituximab
RCT	randomized controlled trial
REMS	risk evaluation and mitigation strategy
R/R	relapsed or refractory
RDI	relative dose intensity
SAE	serious adverse event
SAP	statistical analysis plan
SAT	single-arm trial
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the products of longest perpendicular diameters
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TTP	time to progression
USPI	U.S. prescribing information
U2	ublituximab in combination with umbralisib
WM	Waldenström's macroglobulinemia

1 Executive Summary

Phosphatidylinositol 3-kinase (PI3K) inhibitors have been approved in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and marginal zone lymphoma (MZL) and are being developed in patients with B-cell and T-cell non-Hodgkin lymphoma (NHL).

There are several central issues relating to the development of PI3K inhibitors in hematologic malignancies: concerning trends in overall survival (OS) in multiple randomized controlled trials (RCTs), toxicities of the PI3K inhibitor class, inadequate dose optimization, and trial design considerations regarding the limitations of single-arm trials. Alpelisib, a PI3K alpha-specific inhibitor approved in breast cancer and PIK3CA-related overgrowth spectrum, is not included in this discussion.

This document discusses the class of PI3K inhibitors as a whole, their unique toxicities, and considerations regarding the best drug development approach for future PI3K inhibitors for patients with hematologic malignancies. The experience with this class provides a framework to re-examine PI3K inhibitor development for hematologic malignancies, with the overarching question of whether single-arm trials of PI3K inhibitors should be avoided as a regulatory strategy in favor of randomized controlled trials. To support a class discussion of the appropriate development approach, relevant data for each of the approved PI3K inhibitors in hematologic malignancies are highlighted. For each drug, the Appendix provides a detailed summary of the regulatory history, clinical development, and the design and results of the clinical trials.

2 Background

2.1 Regulatory History and Development Paradigm for Approved PI3K Inhibitors in Hematologic Malignancies

Rationale for PI3K inhibitor development in hematologic malignancies

PI3Ks regulate multiple cellular processes including cell growth, proliferation, differentiation, survival, migration, and metabolism.[1,2] Constitutive activation of the PI3K signaling pathway is common in hematologic malignancies. Dysregulated PI3K signaling promotes the survival and proliferation of malignant lymphocytes and is the rationale for therapeutic targeting of PI3K isoforms in hematologic malignancies. Activation of PI3K signaling can occur through several mechanisms, including mutations of downstream effector proteins, upstream kinase activating mutations, epigenetic or genetic silencing of negative regulators of PI3K, and rarely in hematologic malignancies, *PIK3CA* mutations.[3]

Overview of PI3K inhibitor approvals in hematologic malignancies

Four PI3K inhibitors, each inhibiting the PI3K delta isoform and some also inhibiting other isoforms, have received FDA approval for indications involving relapsed or refractory (R/R)

indolent NHL or CLL: idelalisib, copanlisib, duvelisib, and umbralisib. Trials supporting the initial FDA approvals of PI3K inhibitors in hematologic malignancies and the post-approval developments are summarized in Table 1.

Regular approval in CLL was based on improvements in progression-free survival (PFS) observed in RCTs and was granted to idelalisib and duvelisib. In contrast, the initial approvals for indolent NHLs, including FL and MZL, were accelerated approvals based on durable overall response rates (ORRs) observed in single-arm trials, with requirements that postmarketing RCTs confirm clinical benefit by demonstrating improvement in PFS. Accelerated approval requires substantial evidence of efficacy and safety, and is based on an intermediate endpoint that is reasonably likely to predict clinical benefit such as durable ORR. Continued marketing was contingent upon verification of clinical benefit in a clinical trial(s). Although an improvement in OS was not required for continued marketing of these agents, FDA requires submission of survival data for drugs approved using PFS endpoints, as OS is both an efficacy and safety endpoint.

Table 1: Status of FDA-Approved PI3K Inhibitors for Hematologic Malignancies

Initial Approval Information [a]	Post-Approval Trials	Outcome
Idelalisib (PI3Kδ inhibitor)		
2014: Regular approval: Relapsed CLL in combination with rituximab [b] • RCT of idelalisib + rituximab vs. Pbo + rituximab in relapsed CLL – PFS, HR 0.18 (95% CI: 0.10, 0.31) – OS immature	2016: 3 RCTs halted in CLL or iNHL for increased deaths and serious toxicities • Idelalisib + BR vs. Pbo + BR in untreated CLL • Idelalisib + rituximab vs. Pbo + rituximab in R/R iNHL • Idelalisib + BR vs. Pbo + BR in R/R iNHL Pooled analysis, idelalisib arms vs. control • Deaths, 7.4% vs.3.5% • OS, HR 2.29 (95% CI: 1.26, 4.18)	Warning and limitations of use added to prescribing information
2014: Accelerated approval: Relapsed FL and SLL after ≥2 systemic therapies based on SAT • FL: ORR, 54% (95% CI: 42, 66); DOR, median not reached • SLL: ORR, 58% (95% CI: 37, 77); DOR, median 11.9 months	Required postmarketing trial: Slow accrual to trial evaluating idelalisib dosage in R/R FL	Voluntary withdrawal of FL and SLL indications (2/2022)
Copanlisib (PI3Kα and PI3Kδ inhibitor)		

Initial Approval Information [a]	Post-Approval Trials	Outcome
2017: Accelerated approval: Relapsed FL after ≥2 systemic therapies based on SAT • ORR, 59% (95% CI: 49, 68); DOR, median 12.2 months	CHRONOS-3: RCT of copanlisib + rituximab vs. Pbo + rituximab in relapsed iNHL • PFS, HR 0.52 (95% CI: 0.39, 0.69) [4] • Interim OS, HR 0.87 (0.57, 1.35) [c]	Voluntary withdrawal of NDA based on CHRONOS-3 (12/2021)
Duvelisib (PI3Kδ and PI3Kγ inhibitor)		
2018: Regular approval: R/R CLL or SLL after ≥2 therapies • DUO: RCT of duvelisib vs. ofatumumab in R/R CLL after ≥1 therapy – PFS, HR 0.52 (95% CI: 0.39, 0.69) – OS immature	Final analysis, duvelisib vs. ofatumumab: • OS, HR 1.09 (95% CI: 0.79, 1.51) [d]	Under FDA review
2018: Accelerated approval: R/R FL after ≥2 systemic therapies based on SAT • ORR, 42% (95% CI: 31, 54); 43% of responses were ongoing at ≥6 months and 17% at ≥12 months	Required postmarketing trial: RCT never initiated for commercial reasons	Voluntary withdrawal of FL indication (12/2021)
Umbralisib (PI3Kδ and CK1ε inhibitor)		
2021: Accelerated approval: R/R FL after ≥3 systemic therapies and R/R MZL after ≥1 anti-CD20 based regimen based on SAT • FL: ORR, 43% (95% CI: 34, 52); DOR, median 11.1 months • MZL: ORR, 49% (95% CI: 37, 62); DOR, median not reached	UNITY-CLL: RCT of umbralisib + ublituximab vs. obinutuzumab + chlorambucil in untreated and R/R CLL • PFS, HR 0.55 (95% CI: 0.41, 0.72) [5] • Interim OS, HR 1.23 [6 c, e]	Scheduled for ODAC, April 22, 2022

Abbreviations: BR, bendamustine + rituximab; CI, confidence interval; CK, casein kinase; CLL, chronic lymphocytic leukemia; DOR, duration of response; FL, follicular lymphoma; HR, hazard ratio; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; NDA, new drug application; ORR, overall response rate; OS, overall survival; Pbo, placebo; PFS, progression-free survival; RCT, randomized controlled trial; R/R, relapsed or refractory; SAT, single-arm trial; SLL, small lymphocytic lymphoma

[a] Indications are excerpted. Approval endpoints are from the U.S. Prescribing Information on initial approval date.

[b] In patients in whom rituximab alone would be considered appropriate therapy due to comorbidities.

[c] OS data reflect later data cutoff.

[d] In total study population of patients with ≥1 prior therapy.

[e] 95% CI not available publicly.

Source: FDA analysis unless otherwise noted

Safety and overall survival

Although PI3K inhibitors have demonstrated durable ORRs and/or improvements in PFS, they have also demonstrated substantial toxicity, impacting the overall benefit-risk. Notable toxicities of these agents include fatal or serious infections, neutropenia, immune-mediated toxicities including diarrhea, colitis, hepatotoxicity, pneumonitis, and dermatologic toxicity, and with

copanlisib, hyperglycemia and hypertension. Serious adverse reactions have been observed in as many as 65% of patients in some trials and severe (Grade ≥3) adverse reactions in as many as 85%. These and additional toxicities reduce tolerability and frequently lead to dose interruptions, reductions, or permanent discontinuations, which in registrational trials have been as high as 64%, 29%, and 35%, respectively. As later discussed, inadequate dose optimization with focus on maximal or near-maximal tolerated doses has been a general issue across PI3K inhibitor development and likely compounds the tolerability issues.

The distinct mechanisms of action of PI3K inhibitors result in a differentiated safety profile, depending on the isoform targeted.[7] The delta and gamma isoforms are preferentially expressed on leukocytes, and targeting of these isoforms results in infections, neutropenia, and immune-mediated toxicities: hepatitis, colitis, pneumonitis, and rash. Infection may occur because of treatment-related cytopenias including neutropenia and because of immune system modulation by PI3K inhibition. With regards to the immune-mediated toxicities, the delta isoform is important for T regulatory cell survival and function. It is thought that the decreased T regulatory cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with these products. The alpha isoform is ubiquitously expressed and is essential to cellular growth and metabolism and glucose homeostasis. Toxicities from alpha inhibition include hyperglycemia and hypertension.

Six randomized controlled trials of PI3K inhibitors in indolent NHL or CLL have raised concerns for potential detriments in OS for the PI3K inhibitor arm due to increased toxicity.[4,5,8-11] PFS was the primary efficacy endpoint and in those trials where enrollment and analysis was completed, improved efficacy based on PFS was demonstrated for the PI3K inhibitor arm. The positive impact on efficacy in the setting of concerning OS findings suggests that the OS findings are driven by toxicity. The safety findings in these and other PI3K inhibitor trials will be described in detail. Because OS can only be meaningfully evaluated in randomized trials, these worrisome findings challenge the paradigm of basing accelerated approvals of PI3K inhibitors on single-arm trials.

2.2 Disease Context

2.2.1 Chronic Lymphocytic Leukemia

CLL is the most common type of leukemia in Western countries, with an incidence in the United States of 4.9 cases per 100,000 per year. The disease has a male predominance and median age at diagnosis of 70 years, with >65% of patients being diagnosed at age 65 or later.[12] CLL is characterized by the clonal proliferation and accumulation of malignant B lymphocytes in the peripheral blood, bone marrow, and secondary lymphoid organs. The presentation and clinical course of CLL is, however, highly variable. Patients with CLL can have asymptomatic, indolent disease with some never requiring therapy, while others have active disease with progressive lymphocytosis, cytopenias, lymphadenopathy, hepatosplenomegaly, B symptoms (i.e., fevers,

night sweats, weight loss), recurrent infections, and autoimmune complications.[13] Chromosomal abnormalities of 17p deletion or 11q deletion, unmutated immunoglobulin heavy chain (IGHV) status, β2-microglobulin >3.5 mg/L, lymphocyte doubling time <12 months, and age >60 years are poor prognostic markers and factor into treatment decisions, along with clinical stage and symptomatology. Treatment can range from observation to immunochemotherapy to targeted therapies; however, progressive disease alone is not necessarily an indication to treat.

Despite high response rates to initial treatment, relapse is common and relapsed or refractory disease is often characterized by resistance to chemotherapy. The generally indolent nature of CLL allows patients to receive intermittent treatment with periods of remission or stable disease, but successive treatments tend to yield diminished response rates and shorter durations of response.[14] Treatments for patients with CLL have advanced, yet the disease remains largely incurable and new drugs and approaches are needed. Appendix Section 7.9 provides a list of FDA-approved treatments for patients with CLL.

Small lymphocytic lymphoma (SLL), an indolent form of NHL, is the same biological entity as CLL except with disease primarily in the lymph nodes, compared to the bone marrow and blood in CLL. SLL and CLL have similar treatment paradigms and expected clinical outcomes.

2.2.2 Indolent Non-Hodgkin Lymphoma – FL and MZL

Follicular lymphoma (FL) is the most common (70%) indolent NHL, with an estimated 15,000 new cases in the U.S. annually.[15] The median age at diagnosis is 65 years. Marginal zone lymphoma is the second most common form (5% to 15%) of indolent NHL, with an estimated 7,500 new cases in the U.S. annually.[16] Three subtypes of MZL, namely splenic, nodal, and mucosal-associated lymphoid tissue (MALT) lymphomas, compromise 20%, 10%, and 70% of MZL cases, respectively.[17]

FL and MZL are indolent diseases and the underlying biology of FL and MZL contributes to the variation in presentation, varied prognosis, risk of relapse, and progressive risk of transformation to high-grade lymphoma. Patients initially may be asymptomatic, however, the majority of patients with FL have advanced stage disease at diagnosis and for MZL, the clinical disease characteristics vary depending on the subtype.[15,18] The FL International Prognostic Index (FLIPI) risk-stratifies newly diagnosed patients according to baseline characteristics, although the strongest determinant of survival is progression of disease within 2 years following diagnosis or initiation of first-line treatment.[15,19] For MZL, long-term outcome also appears less favorable in patients with progression of disease within 2 years of initiating therapy.[20]

Treatment for patients with FL or MZL ranges from observation to targeted therapy to chemotherapy or chemoimmunotherapy, and occasionally to more aggressive approaches such as hematopoietic stem cell transplantation. Asymptomatic patients are typically managed with observation until they manifest symptoms that warrant treatment.

First-line systemic therapy generally consists of anti-CD20-based therapy either as monotherapy or in combination with chemotherapy. In the relapsed or refractory setting, there are a number of treatment options and treatment decisions take into consideration comorbidities, symptomatic disease, as well as prior therapy.[21] However, despite these advances in treatment and available treatment options, FL and MZL remain largely incurable diseases, with patients experiencing multiple relapses until ultimately succumbing to the disease or to complications of its treatment. New treatments and approaches are needed for patients with indolent NHL. See Appendix 7.9 for a list of FDA-approved treatments for patients with indolent NHL.

3 Issues

3.1 Overall Survival

Six randomized trials evaluating a PI3K inhibitor have demonstrated a higher rate of death or concerning OS results suggesting potential harm to patients (Table 1).[4,5] The randomized trials demonstrated or suggested a favorable effect on PFS and other efficacy parameters such as ORR. Therefore, the adverse effect on OS is likely driven by PI3K inhibitor toxicity.

The observation of a potential detriment in OS across this many randomized trials is unprecedented in oncology. For each trial, there is a low number of observed OS events (as low as 3% to 20% of the planned sample size without a pre-specified plan for evaluating OS), leading to uncertainty of the specific OS estimate. However, based on the confidence intervals for the HRs, potential harm to patients cannot be ruled out. Taken together, these are not isolated observations, but rather repeated observations across multiple trials of different PI3K inhibitors in patients with indolent lymphoid malignancies. Herein, we highlight the relevant randomized trials exhibiting concerning OS results with PI3K inhibitors.

3.1.1 PI3K Inhibitor Randomized Trials

3.1.1.1 Idelalisib

A double-blind, placebo-controlled RCT, comparing idelalisib + rituximab to placebo + rituximab supported the 2014 regular approval of idelalisib in relapsed CLL based on a primary PFS endpoint (Study GS-US-312-0116; Appendix 7.5.1.1). Subsequently, three double-blind, placebo-controlled RCTs evaluating idelalisib combination regimens were terminated early because of increased deaths and increased serious toxicity in the idelalisib arms. These trials evaluated idelalisib in combination with rituximab or bendamustine plus rituximab in patients with CLL or indolent NHL (Table 2). The higher death rates were driven by fatal infections, including sepsis, pneumonia, and opportunistic infections. These findings resulted in safety alerts,[22] additional warnings in prescribing information, and limitations of use in the indication statement.

Table 2 summarizes deaths in the terminated idelalisib trials. Kaplan-Meier curves of OS are shown in Figure 1. There is high variability in the HR estimates, but based on the upper bounds of the confidence intervals, the risk of death in the idelalisib arms can be multiple times higher than in the control arm.

Refer to Appendix 7.5.2 for details of trial designs and efficacy results.

Table 2: Deaths in Terminated Idelalisib Randomized Trials

Trial	Population	Randomization & Treatment [b]	Deaths, Idelalisib arm	Deaths, Control arm	OS HR (95% CI) [c]
GS-US-312-0123	Untreated CLL	1:1 Idelalisib + BR Placebo + BR	8% (12/157)	3% (4/154)	3.34 (1.08, 10.39)
GS-US-313-0124	Previously treated indolent NHL [a]	2:1 Idelalisib + rituximab Placebo + rituximab	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
GS-US-313-0125	Previously treated indolent NHL [a]	2:1 Idelalisib + BR Placebo + BR	8% (27/320)	6% (9/155)	1.51 (0.71, 3.23)

Abbreviations: BR, bendamustine + rituximab; LPL, lymphoplasmacytic lymphoma; WM, Waldenström's macroglobulinemia

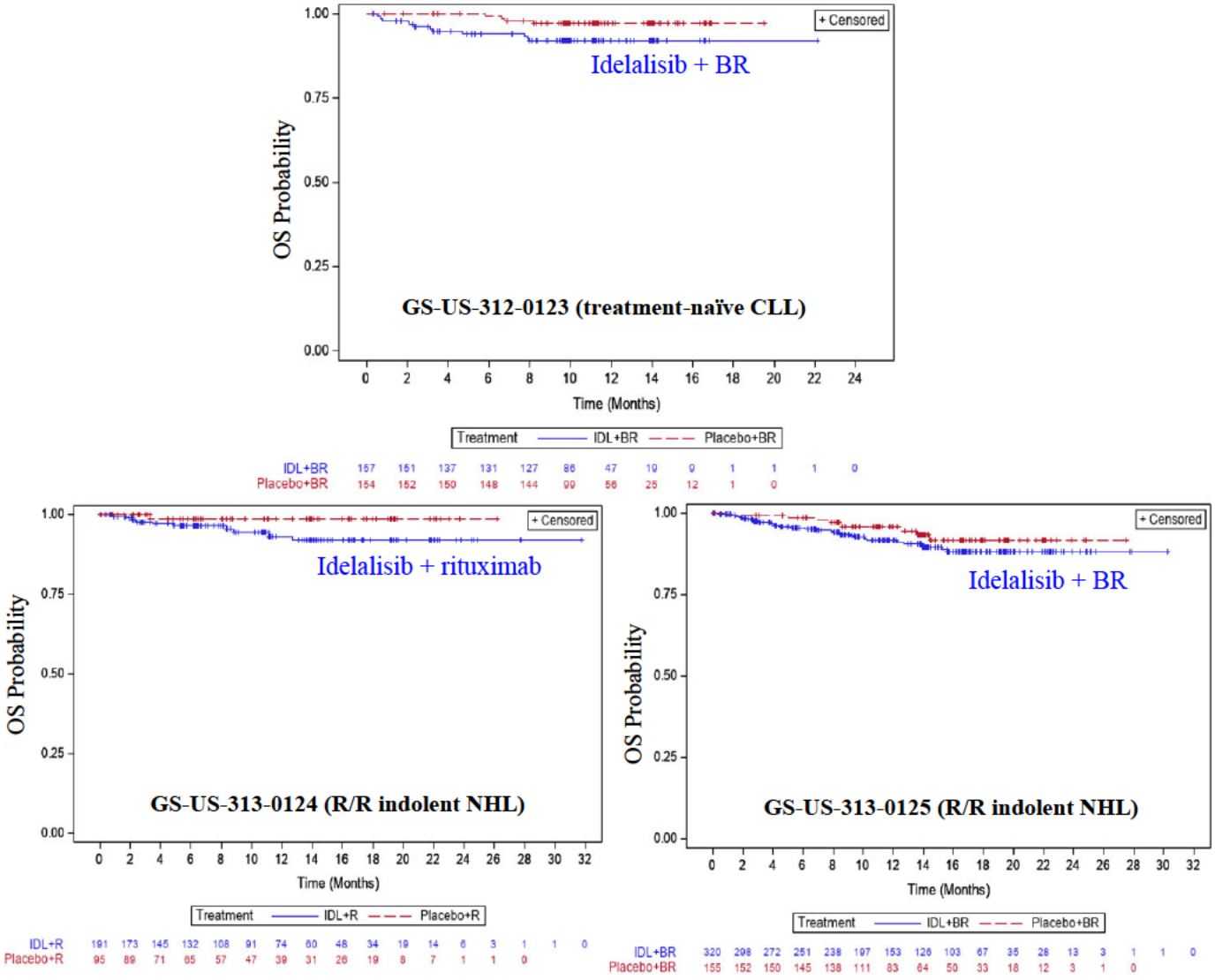
[a] FL, MZL, SLL, LPL/WM

[b] Idelalisib dose: 150 mg BID

[c] Control arm is the reference group.

Source: Individual clinical study reports (CSRs)

Figure 1: Kaplan-Meier Curves of OS in Terminated Idelalisib Trials



Source: FDA analysis

3.1.1.2 Copanlisib

The accelerated approval of copanlisib in R/R FL after ≥ 2 systemic therapies was based on a single-arm trial (Appendix 7.6.1). CHRONOS-3 is a randomized, double blind, placebo-controlled trial of copanlisib + rituximab vs. placebo + rituximab in patients with relapsed indolent NHL after CD20-directed therapy (Table 3).[4] Although there was a statistically significant PFS improvement in the copanlisib + rituximab arm (see Appendix 0), the trial

exhibited concerning trends in mortality and the potential for harm during approximately the first 2 years for those randomized to copanlisib + rituximab.

Table 3: CHRONOS-3 Study Design

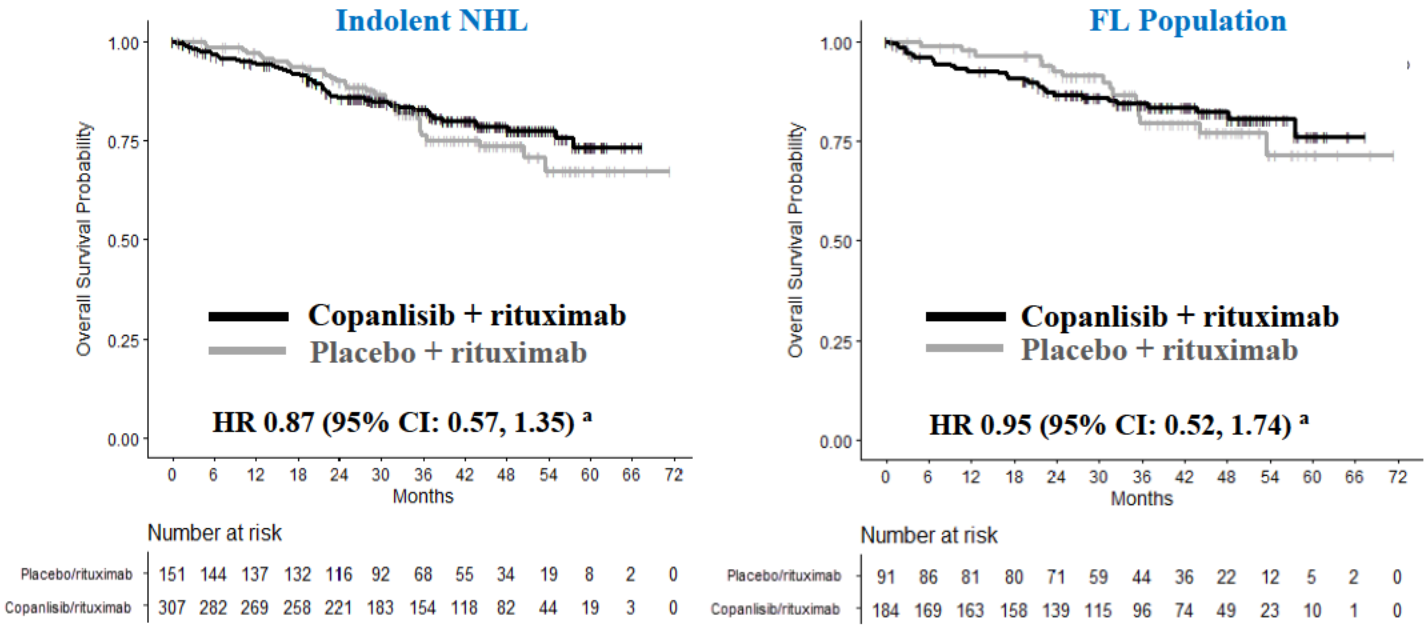
Trial	Population	Randomization & Treatment Arms	Endpoints
17067 (CHRONOS-3)	Relapsed indolent NHL [a] Progression-free or treatment-free ≥12 mo after last anti-CD20 therapy, or Unwilling or unfit to receive chemotherapy, and progression-free or treatment-free ≥6 mo after last anti-CD20 therapy	2:1 Copanlisib + rituximab [b] Placebo + rituximab	Primary: PFS Secondary: include efficacy in FL and MZL combined, PROs, OS

Abbreviations: PROs, patient-reported outcomes
[a] FL, MZL, SLL, LPL/WM
[b] Copanlisib dose: 60 mg IV on Days 1, 8, and 15 of a 28-day cycle
Source: Matasar MJ et al 2021[4]

Figure 2 shows interim OS Kaplan-Meier curves for the total study population and the FL subpopulation. No OS hypothesis testing, including power calculations or anticipated information fraction, was prespecified in the statistical analysis plan. Because the proportional hazards assumption may not hold, interpreting the HR for OS may be challenging. In the overall study population, the estimated 2-year OS was 86% (95% CI: 81, 89) in the copanlisib + rituximab arm and 90% (95% CI: 84, 96) with placebo + rituximab. In patients with FL (the largest subpopulation), the estimated 2-year OS was 87% (95% CI: 81, 91) and 93% (95% CI: 84, 97), respectively (Appendix 0, Table 27).

There is high uncertainty in the estimates due to limited OS data at the time of analysis; however, potential harm to patients in the copanlisib + rituximab arm cannot be ruled out. Importantly, the CHRONOS-3 trial enrolled patients suitable for rituximab monotherapy, which should be considered when assessing the OS results because these patients had indolent disease that did not require intensive treatment.

Figure 2: Kaplan-Meier Curves of OS in CHRONOS-3



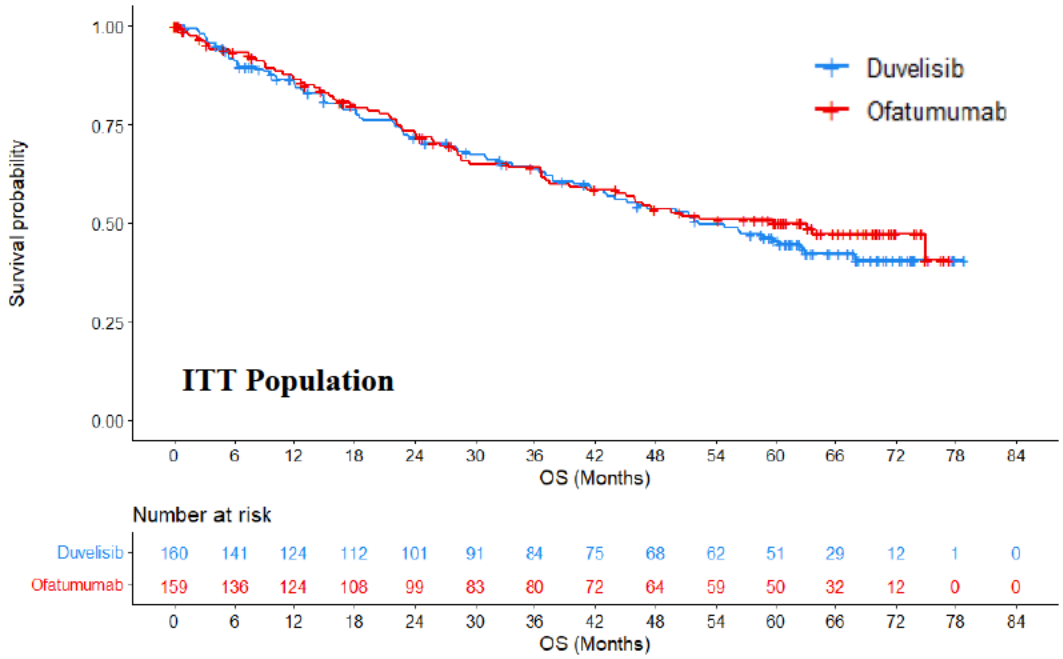
[a] Control arm is the reference group
Source: FDA analysis. Data cutoff: August 2021

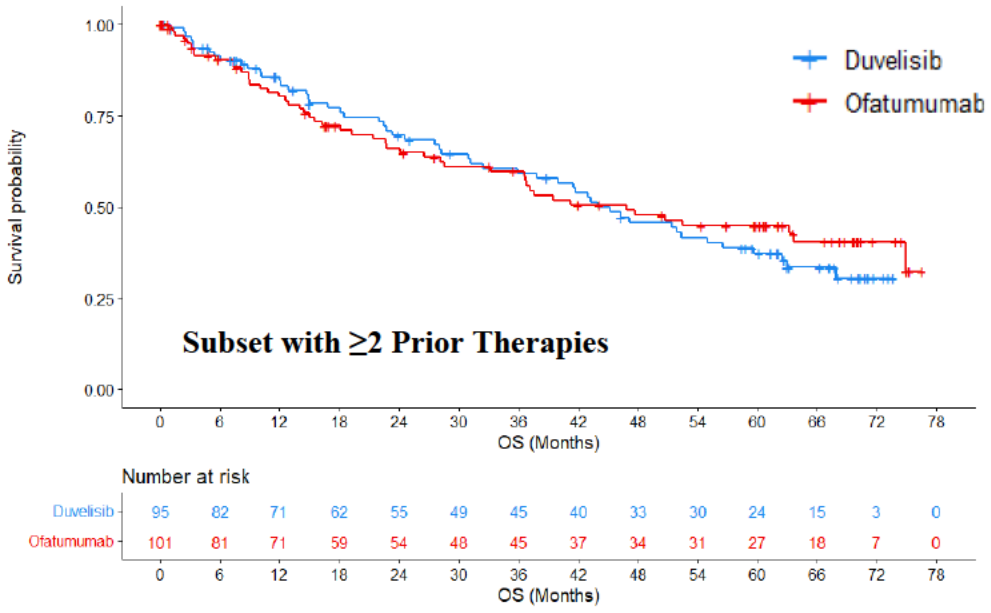
3.1.1.3 Duvelisib

Duvelisib received regular approval for patients with R/R CLL/SLL after ≥2 prior therapies based on Study IPI-145-07 (DUO),[23] a randomized open-label trial that demonstrated a statistically significant improvement in PFS with duvelisib compared to ofatumumab in patients with previously treated CLL/SLL (HR 0.52; 95% CI: 0.39, 0.69). Details are provided in Appendix 7.7.1. Although the trial enrolled patients with 1 prior line of therapy, FDA restricted the indication to a more heavily pretreated population, where the benefit-risk appeared more favorable.

OS, a key secondary endpoint, was immature at the time of the primary PFS analysis. Final 5-year OS data, submitted as a post-marketing requirement, revealed concerning trends in the OS curves, favoring the control arm. The figures and table below show the final OS results for the total study population and the subpopulation with ≥2 prior therapies (approved indication).

Figure 3: Kaplan-Meier Curves of Final OS Analysis in DUO Study





Source: FDA analysis. Data cutoff: 6/22/2020

Table 4: Summary of Final OS Data in DUO Study

	Total Study Population (≥1 prior therapy)		Approved Indication (≥2 prior therapies)	
	Duvelisib (N=160)	Ofatumumab (N=159)	Duvelisib (N=95)	Ofatumumab (N=101)
Deaths, n (%)	80 (50.0)	70 (44.0)	53 (55.8)	49 (48.5)
Median OS, months (95% CI)	52.3 (41.8, 68.0)	63.3 (41.2, NE)	43.9 (32.4, 56.5)	46.8 (28.6, 74.9)
HR for OS (95% CI) [a]	1.09 (0.79, 1.51)		1.06 (0.71, 1.58)	

[a] Stratified Cox proportional hazards model.
Source: FDA analysis. Data cutoff: 6/22/2020

3.1.1.4 Umbralisib

On February 3, 2022, FDA issued a drug safety alert about a possible increased risk of death in recipients of umbralisib.[11] The safety alert was based on data from UNITY-CLL, a RCT of U2 (umbralisib plus ublituximab, an investigational CD20-directed antibody) vs. chlorambucil plus obinutuzumab in patients with previously untreated or treated CLL.[5] Whereas PFS was significantly improved in the U2 arm (HR 0.55; 95% CI: 0.41, 0.72), interim OS outcomes tended to favor the control arm (HR 1.10; 95% CI: 0.75, 1.59).[5] These issues are slated for discussion at the April 22, 2022, ODAC meeting. Umbralisib has not been examined in RCTs as a single agent.

Accordingly, FDA has placed multiple clinical trials involving ublituximab and umbralisib on clinical hold pending evaluation of increased ublituximab and umbralisib-associated deaths.

3.1.2 Overall Survival as a Safety Endpoint

OS is considered an objective measure of clinical benefit and is the ultimate endpoint in oncology trials. Survival is considered the most reliable cancer endpoint, and when studies can be conducted to adequately assess survival, it is usually the preferred endpoint.

However, in diseases with prolonged survival of many years and the potential for multiple therapeutic interventions, the practical evaluation of OS has limitations and has resulted in accepting other, earlier endpoints, such as durable ORR and PFS. Unlike evaluating OS as an efficacy endpoint with a well-defined statistical plan to ensure control of findings due to chance, the OS analysis for safety in PI3K inhibitor trials has been largely descriptive; only one of the six PI3K inhibitor trials with concerning OS findings included formal hypothesis testing of this endpoint (the duvelisib DUO trial). Regardless, for RCTs with a PFS endpoint, FDA requires submission of OS data as it is considered both an efficacy and a safety endpoint.

There is uncertainty in the OS estimates in these trials, with wide confidence intervals for the HR and relatively large upper bounds. Although not formally powered for statistical testing and having a limited number of events in some instances, a worrisome trend in OS, particularly in the context of drugs with favorable effects on anti-tumor efficacy but substantial toxicity, is an important determinant of overall benefit-risk. Potential harm cannot be ruled out, whether from toxicities that occur due to PI3K inhibitor treatment or potentially from higher complication rates during subsequent anti-cancer therapy which can be challenging to identify. As such, OS is an important metric of safety as well as efficacy.

3.2 Toxicity

Within multiple randomized trials evaluating a PI3K inhibitor as a single-agent or in combination with a CD20 antibody or chemoimmunotherapy, the assessment of safety has demonstrated substantial toxicity in the PI3K inhibitor cohort. In nearly all of the RCTs, patients randomized to the PI3K inhibitor arm experienced increased rates of fatal adverse events (AEs), serious adverse events (SAEs), Grade 3 or greater AEs, and treatment modifications or discontinuation due to AEs. Risk mitigation strategies to communicate the risks associated with these products have included Warnings and Precautions in labeling; limitations of use (LOU) (idelalisib); and, for idelalisib and duvelisib, boxed warnings and a communications risk evaluation and mitigation strategy (REMS). These risk mitigation strategies are employed to highlight the serious risks and to ensure the drug is safe and effective for its intended use.

In the development programs for the PI3K inhibitors, patient-reported outcomes were either not collected or focused on sparse disease-related symptom assessment. In both single-arm trials and randomized trials, it is feasible to conduct rigorous collection of patient-reported treatment-related symptoms, overall side effect bother, and physical functioning to inform tolerability of the selected doses. However, across PI3K inhibitor class development, early and comprehensive measurement of patient-reported symptoms was not performed.

The following sections summarize selected safety and tolerability data with the approved PI3K inhibitors.

3.2.1 Randomized Trials

3.2.1.1 Idelalisib

The regulatory history of idelalisib is summarized in Appendix 7.1 and the design and efficacy results of registrational trials are summarized in Appendix 7.5.1. As mentioned, idelalisib was granted regular approval in July 2014 for patients with relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate. The approval

was based on the 312-0116 study, a randomized, placebo-controlled trial that demonstrated a statistically significant benefit in PFS in the idelalisib plus rituximab arm vs. placebo plus rituximab with an estimated HR of 0.15 (95% CI, 0.09 to 0.25).

At the same time, idelalisib as monotherapy was granted accelerated approval for patients with relapsed FL or SLL after at least 2 prior systemic therapies, based on an ORR of 54% and 58%, respectively, with associated durability from a single-arm trial.

As noted, following the initial approval of idelalisib, three double-blind, placebo-controlled RCTs evaluating idelalisib combination regimens were terminated early because of increased deaths and increased serious toxicity in the idelalisib arms. These trials evaluated idelalisib in combination with rituximab or bendamustine plus rituximab in patients with CLL or indolent NHL.

The table below provides a summary of safety and select toxicities from the three RCTs that were terminated early.

Table 5: Summary of Safety and Select Toxicities in Idelalisib Randomized Trials Terminated Early in CLL and Indolent NHL

Study	312-0123 Untreated CLL		313-0124 R/R indolent NHL		313-0125 R/R indolent NHL	
Treatment Arm	**I + BR N = 156**	**Pbo + BR N = 154**	**I + R N = 198**	**Pbo + R N = 95**	**I + BR N = 317**	**Pbo + BR N = 155**
Median exposure, months (Range)	12.1 (0.2, 22.1)	14.5 (0.3, 21.8)	6.0 (0.1, 26.6)	9.6 (0.1, 26.3)	6.5 (0.1, 34.2)	13.8 (0.2, 31.3)
Toxicity, n (%)						
Death due to AE	12 (8)	3 (2)	8 (4)	0	20 (6)	5 (3)
Grade ≥3 AE	150 (96)	124 (80)	170 (86)	24 (25)	293 (92)	96 (62)
SAE	113 (72)	68 (44)	103 (52)	11 (12)	229 (72)	58 (37)
Actions due to AEs, n (%)						
Discontinuation	60 (38)	12 (8)	88 (44)	7 (7)	145 (46)	22 (14)
Dose Reduction	16 (10)	14 (9)	77 (39)	3 (3)	104 (33)	15 (10)
Dose Interruption	115 (74)	68 (44)	127 (64)	19 (20)	205 (65)	45 (29)
AEs of Special Interest, n (%)						
Grade ≥3 Infection	71 (45)	31 (20)	43 (22)	4 (4)	127 (40)	30 (19)
Grade ≥3 Neutropenia*	102 (65)	99 (64)	23 (12)	10 (10)	130 (41)	57 (37)
Grade ≥3 Diarrhea or Colitis	14 (9)	5 (3)	38 (19)	2 (2)	40 (13)	0
Grade ≥3 ALT/AST Increase*	41 (26)	2 (1)	96 (48)	0	86 (27)	1 (<1)
Grade ≥3 Rash	26 (17)	16 (10)	16 (8)	1 (1)	59 (19)	2 (1)
Any Grade Pneumonitis	10 (6)	4 (3)	12 (6)	1 (1)	25 (8)	2 (1)

* Based on laboratory data.
Abbreviations: BR, bendamustine + rituximab; I, idelalisib; Pbo, placebo; R, rituximab
Source: Individual study CSRs

Table 6 provides a summary of safety and select toxicities from three additional randomized trials evaluating idelalisib in patients with relapsed or refractory CLL, including the 312-0116 trial that supported the idelalisib approval in relapsed CLL.

Table 6: Summary of Safety and Selected Toxicities in Idelalisib Randomized Trials in Relapsed or Refractory CLL

Study	312-0116 Relapsed CLL		312-0119 R/R CLL		312-0115 R/R CLL	
Treatment Arm	**I + R N = 110**	**Pbo + R N = 108**	**I + O N = 173**	**O N = 86**	**I + BR N = 207**	**BR N = 209**
Median exposure, months (range)	8.1 (0.3, 19.5)	4.6 (0.1, 14.6)	13.9 (0.2, 36.5)	4.2 (0.3, 6.7)	18.2 (0, 43.4)	11.1 (0.5, 28.5)
Toxicity, n (%)						
Death due to AE	4 (4)	11 (10)	26 (15)	6 (7)	25 (12)	19 (9)
Grade ≥3 AE	81 (74)	58 (54)	160 (92)	48 (56)	196 (95)	163 (78)
SAE	65 (59)	43 (40)	133 (77)	36 (42)	147 (71)	94 (45)
Actions due to AEs, n (%)						
Discontinuation	19 (17)	13 (12)	71 (41)	20 (23)	68 (33)	31 (15)
Dose reduction	16 (14)	0	42 (24)	NA	34 (16)	13 (6)
Dose interruption	42 (38)	19 (18)	110 (64)	42 (49)	122 (59)	49 (23)
AEs of Special Interest, n (%)						
Grade ≥3 infection	36 (33)	25 (23)	77 (44)	26 (30)	108 (52)	60 (28)
Grade ≥3 neutropenia*	46 (42)	33 (31)	85 (49)	28 (33)	151 (73)	132 (63)
Grade ≥3 diarrhea or colitis	13 (12)	0	48 (28)	1 (1)	28 (13)	4 (2)
Grade ≥3 ALT/AST increase*	10 (9)	1 (<1)	20 (12)	1 (1)	47 (23)	8 (4)
Grade ≥3 rash	4 (4)	1 (<1)	10 (6)	2 (2)	13 (6)	0
Any grade pneumonitis	6 (5)	1 (<1)	11 (6)	0	7 (3)	2 (1)

* Based on laboratory data
Abbreviations: NA, not applicable; O, ofatumumab; Pbo, placebo; R, rituximab
Source: Individual study CSRs, Zydelig USPI, and NDA 206545 reviews at Drugs@FDA

3.2.1.2 Copanlisib

The regulatory history of copanlisib is summarized in Appendix 7.2 and the design and efficacy results of copanlisib trials are summarized in Appendix 7.6. As mentioned, copanlisib was granted accelerated approval in R/R FL after ≥2 systemic therapies based on a single-arm trial. With the initial approval of copanlisib, infection, hyperglycemia, hypertension, pneumonitis, neutropenia, and rash were included as Warnings and Precautions in the label.

The subsequent CHRONOS-3 trial, a randomized, double blind, placebo-controlled trial of copanlisib + rituximab vs. placebo + rituximab in patients with relapsed indolent NHL after CD20-directed therapy (Table 3) was submitted to FDA in May 2021.[4] The table below provides a summary of safety and select toxicities from CHRONOS-3 trial.

Table 7: Summary of Safety and Selected Toxicities in the Copanlisib CHRONOS-3 Trial

Outcome	Copanlisib + Rituximab N = 307	Placebo + Rituximab N = 146
Median exposure, months (range)	8.3 (0.2, 54.0)	10.8 (0.2, 46.6)
Toxicity, n (%)		
Death due to AE	6 (2)	1 (<1)
Grade ≥3 AE	280 (91)	83 (57)
SAE	145 (47)	27 (18)
Actions due to AE, n (%)		
Discontinuation	96 (31)	12 (8)
Dose reduction 45 mg 30 mg	 83 (27) 28 (9)	 10 (7) 0
Dose Interruption	207 (67)	52 (36)
AEs of Special Interest, n (%)		
Grade ≥3 hyperglycemia*	207 (67)	17 (12)
Grade ≥3 hypertension	127 (41)	15 (10)
Grade ≥3 infection	67 (22)	12 (8)
Grade ≥3 neutropenia*	122 (40)	35 (24)
Grade ≥3 diarrhea or colitis	18 (6)	0
Grade ≥3 AST/AST increase*	10 (3)	4 (3)
Grade ≥3 rash	8 (3)	1 (<1)
Any grade pneumonitis	25 (8)	2 (1)
* Based on laboratory data Source: CHRONOS-3 CSR and FDA analysis		

3.2.1.3 Duvelisib

The regulatory history of duvelisib is summarized in Appendix 7.3 and the design and efficacy results of duvelisib trials are summarized in Appendix 7.7. As mentioned, duvelisib was granted regular approval in September 2018 for patients with relapsed or refractory CLL or SLL after at least two prior therapies. The approval was based on the DUO study, a randomized, actively-controlled trial that demonstrated a statistically significant benefit in PFS in the duvelisib arm vs. ofatumumab with an estimated HR of 0.52 (95% CI: 0.39, 0.70). At the same time, duvelisib was granted accelerated approval for patients with relapsed or refractory FL after at least 2 prior systemic therapies, based on an ORR of 42% with associated durability from a single-arm trial.

The table below provides a summary of safety and select toxicities from the DUO trial.

Table 8: Summary of Safety and Selected Toxicities in the Duvelisib DUO Trial

Outcome	Duvelisib N = 158	Ofatumumab N = 155
Median exposure, months (range)	11.6 (0.2, 37.0)	5.3 (0, 6.0)
Toxicity, n (%)		
Death due to AE	19 (12)	7 (4)
Grade ≥3 AE	138 (87)	75 (48)
SAE	115 (73)	50 (32)
Actions due to AE, n (%)		
Discontinuation	57 (36)	9 (6)
Dose reduction	46 (29)	2 (1)
Dose interruption	123 (78)	15 (10)
AEs of Special Interest, n (%)		
Grade ≥3 infection	53 (33)	17 (11)
Grade ≥3 neutropenia*	76 (48)	55 (35)
Grade ≥3 diarrhea or colitis	41 (26)	3 (2)
Grade ≥3 AST/AST increase*	11 (7)	2 (1)
Grade ≥3 rash	18 (11)	1 (<1)
Any grade pneumonitis	13 (8)	1 (<1)

* Based on laboratory data
Source: NDA 211155 review at Drugs@FDA, Copiktra USPI, and DUO CSR

3.2.1.4 Umbralisib

The regulatory history of umbralisib is summarized in Appendix 7.4, and the design and efficacy results of umbralisib trials are summarized in Appendix 7.8. The data for umbralisib in combination with ublituximab in the UNITY-CLL trial will be discussed at the April 22, 2022, ODAC meeting.

3.2.2 Monotherapy Data

Table 9 summarizes safety and selected toxicities of interest of PI3K inhibitors when administered as monotherapy in patients with hematologic malignancies. Cross-trial comparisons of safety are not intended.

Table 9: Selected PI3K Inhibitor Toxicities When Administered as Monotherapy

	Idelalisib[1] N = 146	Copanlisib[2] N = 244	Duvelisib[3] N = 442	Umbralisib[4] N = 371
Median exposure, months (Range)	6.1 0.3, 26.4	4.3 0.2, 47.4	9.0 0.1, 53	5.9 0.1, 75.1
Toxicity				
Death due to AE	5%	4%	4%	1%
Grade ≥3 AE	71%	85%	84%	51%
SAE	50%	51%	65%	26%
AEs of Special Interest				
Grade ≥3 Infection	23%	23%	27%	20%
Grade ≥3 Neutropenia [a]	28%	29%	43%	17%
Grade ≥3 Diarrhea or Colitis	14%	5%	23%	7%
Grade ≥3 AST/ALT Increase [a]	18%	2%	8%	7%
Grade ≥3 Rash	4%	2%	9%	3%
Any Grade Pneumonitis	5%	7%	7%	1%
Grade ≥3 Hyperglycemia [a]	-	34%	-	-
Grade ≥3 Hypertension	-	29%	-	-
Actions due to AE				
Discontinuation	23%	24%	35%	15%
Dose Reduction	41%[b]	24%	23%	10%
Dose Interruption	41%[b]	64%	64%	45%

[a] Incidence based on laboratory data

[b] A dose reduction or interruption due to an adverse event occurred in 41% of patients

[1] Idelalisib, N = 146, includes 60% FL, 21% SLL, 11% MZL, 8% LPL; Idelalisib is administered at 150 mg orally twice daily in a 28-day treatment cycle.

[2] Copanlisib, N = 244, includes 52% FL, 11% MZL, 9% diffuse large B-cell lymphoma (DLBCL), 5% CLL, 4% mantle cell lymphoma (MCL), 4% SLL, 3% LPL/WM and 12% other hematologic malignancies; Copanlisib is administered at 60 mg iv on Days 1, 8, and 15 of a 28-day treatment cycle.

[3] Duvelisib, N = 442, include 64% CLL, 22% FL, 9% SLL, 4% MZL, 1% other hematologic malignancies; Duvelisib is administered at 25 mg orally twice daily in a 28-day treatment cycle.

[4] Umbralisib, N = 371, includes 40% FL, 22% MZL, 20% with DLBCL and mantle cell lymphoma, 12% with CLL or SLL, and 6% with other hematologic malignancies; Umbralisib is administered at 800 mg orally once daily in a 28-day treatment cycle

Source: Idelalisib – NDA 205858 clinical review at Drugs@FDA; Copanlisib – NDA 209936 multidisciplinary review at Drugs@FDA; Duvelisib – NDA 211155 multidisciplinary review at Drugs@FDA; Umbralisib – NDA 213176 multidisciplinary review at Drugs@FDA

Fatal AEs in these trials ranged from 1% to 5%, Grade ≥3 AEs from 51% to 85%, and SAEs from 26% to 65%. When administered as monotherapy, these PI3K inhibitors are associated with high rates of treatment modifications, with discontinuation in up to 35% of patients.

The pattern of AEs of special interest is consistent across trials and, as summarized in Section 2.1, includes infection, neutropenia, diarrhea or colitis, hepatotoxicity, rash, and pneumonitis. Copanlisib is also associated with hyperglycemia and hypertension since it inhibits the PI3K-

alpha isoform in addition to the delta isoform; in these trials (N=244), the incidence of Grade 3 and 4 hyperglycemia (blood glucose >250 mg/dL or >500 mg/dL and hospitalization indicated) was 34%, and the incidence of Grade 3 hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated) was 29%. The distinct mechanisms of action of the PI3K inhibitors result in the unique and differentiated safety profile.

3.2.3 Risk Mitigation

Because of the toxicity profile of PI3K inhibitors, there is a need to adequately mitigate risk to ensure the safe and effective use of the drug in the intended patient population. Several measures, including a boxed warning, warnings and precautions, a risk evaluation and mitigation strategy, and limitations of use were included with the approvals of the respective PI3K inhibitors.

1. Boxed Warning
   A boxed warning is used, in part, to highlight an adverse reaction so serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug; or serious adverse reactions that can be mitigated by appropriate use of the drug.

2. Warnings & Precautions
   Warnings and precautions are used to describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant and have implications for prescribing decisions or for patient management.

3. Risk Evaluation and Mitigation Strategy
   A REMS is a drug safety program required for certain drugs with serious safety concerns to help ensure the benefits of the drug outweigh its risks. A REMS is designed to reinforce medication use behaviors and actions that support the safe use of the drug.

4. Limitations of Use
   An LOU is included when there is reasonable concern or uncertainty about a drug's risk-benefit profile. An LOU is indicated when awareness of information is important for healthcare providers to ensure safe and effective use of the drug or to identify a patient population in which the drug should generally not be used.

The table below provides a summary of the risk mitigation used for the four approved PI3K inhibitors.

Table 10: FDA Risk Mitigation for Approved PI3K Inhibitors

Risk	Boxed Warning	Warning & Precaution	REMS
Infection	I, D	I, C, D, U	I, D
Diarrhea or Colitis	I, D	I, D, U	I, D
Cutaneous Reactions	D	I, C, D, U	D
Pneumonitis	I, D	I, C, D	I, D
Neutropenia	-	I, C, D, U	-
Hepatotoxicity	I	I, D, U	I
Intestinal Perforation	I	I	I
Hyperglycemia	-	C	-
Hypertension	-	C	-

Abbreviations: C, copanlisib; D, duvelisib; I, Idelalisib; U, umbralisib
Source: FDA review

Idelalisib has two limitations of use based on the data from randomized trials evaluating idelalisib in combination with rituximab or bendamustine and rituximab in patients with CLL or indolent NHL.

- Idelalisib is not indicated and is not recommended for first-line treatment of any patient, including patients with CLL, SLL, FL, and other indolent NHL.
- Idelalisib is not indicated and is not recommended in combination with bendamustine and rituximab, or in combination with rituximab for the treatment of patients with FL, SLL, and other indolent NHL.

3.3 Dosing

Determination of the dose for a patient population is an important process that should occur early in drug development. Ideally, sufficient information should be gathered to balance the maximum efficacy against the least amount of toxicity. This dose optimization is especially important for drugs like PI3K inhibitors, which have a narrow range between effective and toxic doses. Dose optimization necessitates that sufficient pharmacokinetic, pharmacodynamic, safety and activity data is collected across a sufficient range of doses in early studies. For the PI3K inhibitor class of drugs, dose optimization was generally not achieved, in part because the focus was on determining the maximum tolerated dose.

Use of a MTD approach

As with many drug development programs, the dose selection approach used for the PI3K inhibitors was based on the goal of determining the maximum tolerated dose (MTD) of the drug. This approach is based on the assumption that maximum efficacy will be achieved at the highest dose tolerable in the patient. The shortcoming of this approach is that lower doses, which may offer significant efficacy with reduced toxicity, are generally not explored extensively. With PI3K inhibitors, the MTD was not determined for all of these products. Nevertheless, lower efficacious doses with reduced toxicity were generally not adequately explored.

3.3.1 Monotherapy

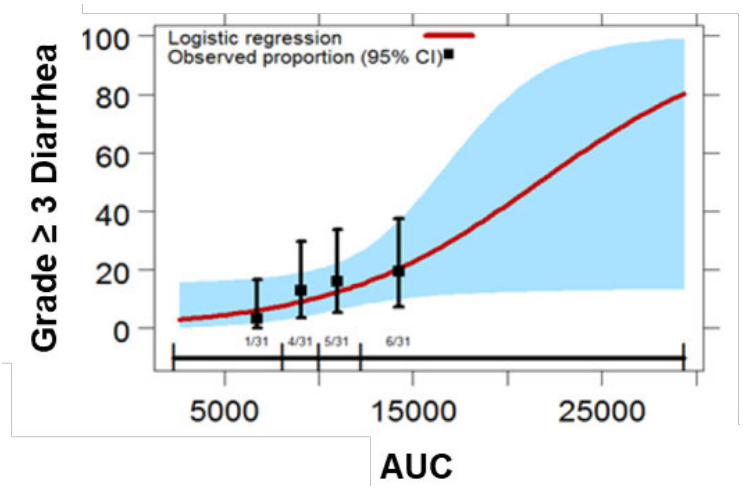
3.3.1.1 Idelalisib

The approved dosage of idelalisib is 150 mg orally BID, administered until disease progression or unacceptable toxicity. Dose selection for idelalisib, as monotherapy, was determined based on the results of study 101-02, in which idelalisib was administered to patients with hematologic malignancies. Briefly, 191 patients with mantle cell lymphoma (MCL), indolent NHL (iNHL), CLL, diffuse large B-cell lymphoma (DLBCL), acute myeloid leukemia (AML) and multiple myeloma (MM) were enrolled at doses of 50, 100, 200, and 350 mg BID. Given the observed toxicities identified at higher doses, including elevated ALT/AST, additional dose exploration was conducted with 150 and 300 mg daily (QD), 150 QD (21 days on, 7 days off), and in additional patients at 50 mg BID and 100 mg BID. Subsequently, the 150 mg BID dose level was expanded with more patients. The number of patients with MCL, iNHL, CLL, and DLBCL included in the study by dose and the best overall response, as reported by the sponsor, is shown in Appendix II, Table 33 with clinical activity seen at doses as low as 100 mg BID.

While the MTD was not reached, Grade ≥3 elevations in ALT/AST were observed at 150 mg BID and higher. Notably, absorption plateaued at this dose and less than dose proportional increases in exposures (i.e., Cmax and AUC) were observed. Furthermore, the change in lymph node area plateaued at the Q2 exposure quartile for Ctrough (see Appendix II, Figure 30), and approximately 90% of the patients had Ctrough concentrations at steady state that exceeded the in vitro IC 90 for PI3Kδ at the 100 mg BID and higher dose. For these reasons, the 150 mg BID was selected as the phase 2 dose for idelalisib. However, the 100 mg BID dose also demonstrated responses and comparable AEs.

Based on data from Studies 101-09 and 312-0116, no exposure response relationship for efficacy was identified, due to the limited data available from the one dose level (150 mg BID) available. However, a significant exposure-response (E-R) relationship for Grade ≥3 diarrhea was identified in patients with iNHL (Figure 4).

Figure 4: Exposure-Response for Idelalisib AUC and Grade ≥3 Diarrhea in Patients with Indolent NHL



Source: NDA 205858 Clinical Pharmacology Review at Drugs@FDA

Analysis of the dose modifications from study GS-US-1101-09 in patients with iNHL, who were administered idelalisib at 150 mg BID, indicated significant dose reductions, interruptions and delays as early as cycle 2 of treatment (Appendix II, Figure 31) indicating significant toxicity manifested early with treatment.

Although the 150 mg BID dose was selected and showed efficacy, there is considerable toxicity. As lower dose levels also demonstrated activity, it remains unclear if a lower dose of idelalisib (e.g., 100 mg BID) may be efficacious and more tolerable. As such, a PMR was issued requiring the conduct of a trial to establish a safe and effective dose for patients with R/R FL. The fulfillment of this PMR was delayed several times, and the PMR had not been completed when the indication was withdrawn due to difficulty enrolling patients.

3.3.1.2 Duvelisib

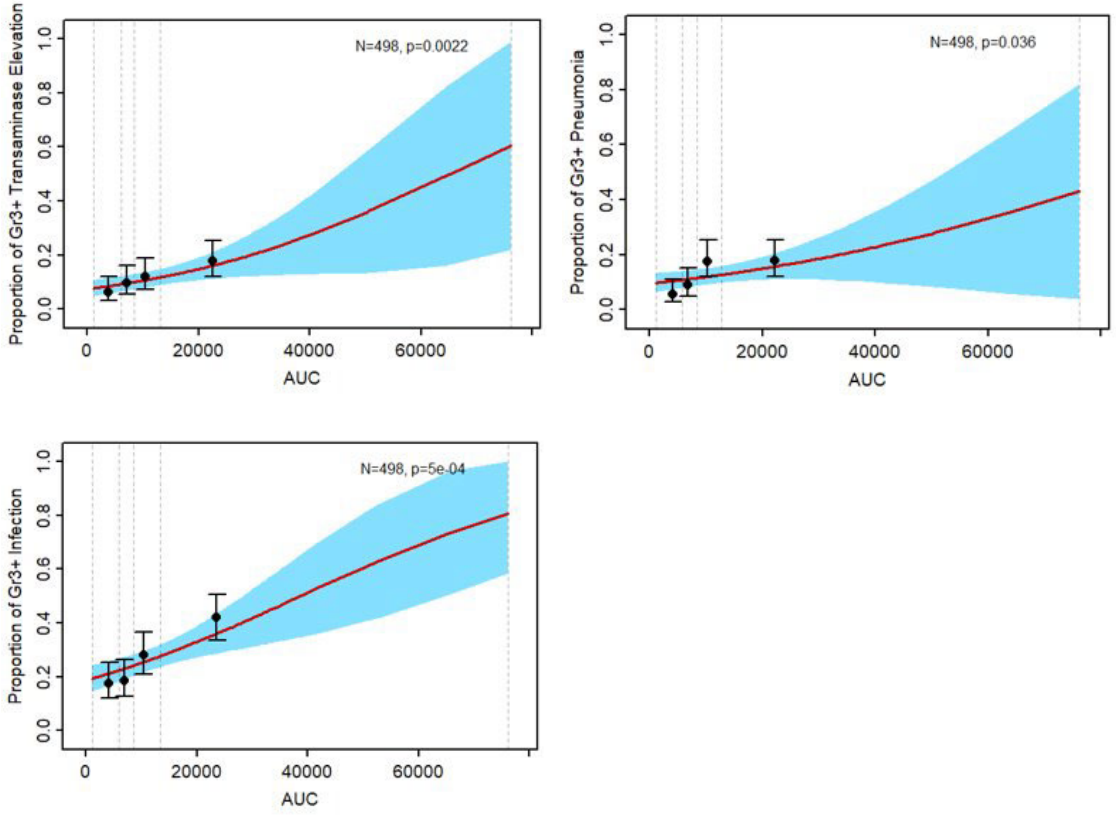
The approved dosage of duvelisib is 25 mg orally BID, administered until disease progression or unacceptable toxicity. Dose selection for duvelisib monotherapy was based on data from Study IPI-145-02 in subjects with advanced hematologic malignancies. During the dose escalation phase of Study IPI-145-02, 31 subjects received duvelisib at doses from 8 mg BID to 100 mg BID (8 mg: n=1; 15 mg: n=6; 25 mg: n=7; 35 mg: n=3; 50 mg: n=3; 60 mg: n=3; 75 mg: n=6; 100 mg: n=2). The MTD was determined to be 75 mg BID. The dose expansion phase of Study IPI-145-02 further evaluated two doses (25 mg BID and 75 mg BID) in 177 patients (25 mg: n=59; 75 mg: n=118). The number of patients with iNHL, R/R CLL, and treatment-naïve CLL included in the study by dose and the best overall response, as reported by the sponsor, is shown in Appendix II, Table 34 with activity observed at doses as low as 8 mg BID.

Data from the expansion cohorts indicate that ORR was comparable between the 25 mg and 75 mg BID doses, although some activity was seen at 15 mg BID. Grade ≥3 treatment-emergent adverse events (TEAEs) were 80% and 87% at the 25 mg and 75 mg BID doses, respectively.

While the available the PD data suggested that maximal p-AKT effects were observed at plasma concentrations that would be achieved at the 25 mg BID dose, higher duvelisib concentrations did not provide additional suppression of p-AKT levels. Notably, these concentrations will also be achieved at doses as low as 15 mg BID.

As the selected phase 2 dose, the 25 mg BID dose was further explored in the Study IPI-145-06 and IPI-145-07. No positive E-R relationships were observed between duvelisib exposure and efficacy endpoints in the two registration studies as it is limited by the narrow dose/exposure range in the two registration studies (i.e., IPI-145-06 and IPI-145-07). The limited dose exploration in the dose finding studies in a small number of patients also precludes the availability of robust data for such exploration. However, E-R analysis for safety suggested a positive relationship between duvelisib exposure and the probability of Grade ≥3 transaminase increase, infection, and pneumonia in the dose range of 8 mg to 75 mg (Figure 5).

Figure 5: Exposure-Response Relationships for Grade ≥3 Transaminase Increase, Pneumonia, and Infection



Source: NDA 211155 Multidisciplinary Review at Drugs@FDA

In Study IPI-145-06 and IPI-145-07, at the 25 mg BID dose, 84 % of patients experience Grade 3-4 TEAEs. The most common TEAEs are diarrhea or colitis (50%), neutropenia (34%), rash (31%), fatigue (28%), pyrexia (26%), cough (25%), nausea (23%), pneumonia (21%), upper respiratory infection (21%), and anemia (20%). Dose modifications (dose interruptions, reductions, and discontinuations due to AE) occurred early, and increased over time in the FL and CLL/SLL populations enrolled in Studies IPI-145-06 and IPI-145-07 and are shown in Appendix II, Figure 32.

As shown in Table 11, approximately 23% of patients experienced a dose reduction due to AE in studies IPI-145-06 and IPI-145-07 and approximately 60% of patients had to interrupt their dosing dose to AEs**.** Sixty-eight percent of patients achieved a relative dose intensity (RDI) ≥90% and 78% had a RDI ≥80%. The most common TEAEs leading to dose reduction of duvelisib in patients with hematologic malignancies were diarrhea or colitis (6%), transaminase

elevation (4%), neutropenia (3%), rash, and febrile neutropenia (2% each).

Table 11: Duvelisib Dose Discontinuations, Reductions, and Dose Interruptions Due to TEAEs in Studies IPI-145-06 and IPI-145-07

Type of dose modification	FL N= 96 n (%)	CLL/SLL N= 303 n (%)	All Heme N= 442 n (%)
Discontinuation Due to AE	28 (29)	115 (38)	156 (35)
Dose reduction due to AE	21 (22)	71 (23)	101 (23)
Dose interruption due to AE	56 (58)	195 (64)	282 (64)
Abbreviations: Heme, hematologic malignancies Source: NDA 211155 Multidisciplinary Review at Drugs@FDA			

Given the limited data at doses lower than 25 mg BID, the flat exposure-response for efficacy, the increased safety events with higher exposures, and the rates of dose modifications due to AEs, a lower dose of duvelisib may be efficacious and more tolerable.

3.3.1.3 Copanlisib

The approved dosage of copanlisib is 60 mg IV on Days 1, 8, and 15 of a 28-day cycle. For copanlisib monotherapy, dose selection was based on Study 12871 (NCT00962611), a phase I dose-escalation study conducted predominantly in patients with solid tumors. In this study, five doses (0.1 mg/kg to 1.2 mg/kg IV on Days 1, 8, and 21 every 28 days) were tested in 1 to 7 patients with solid tumors per dose level (Appendix II, Figure 33). The dose of 1.2 mg/kg was only administered to 2 subjects in Cycle 5 as 1 of the 3 subjects experienced DLTs after the first copanlisib dose, and 0.8 mg/kg was selected as the MTD and expanded.

For the MTD expansion cohorts at 0.8 mg/kg, 25 patients with solid tumors (16 breast cancer patients) and 9 patients with NHL were enrolled. Table 12 summarizes dose modifications for the patients with NHL.

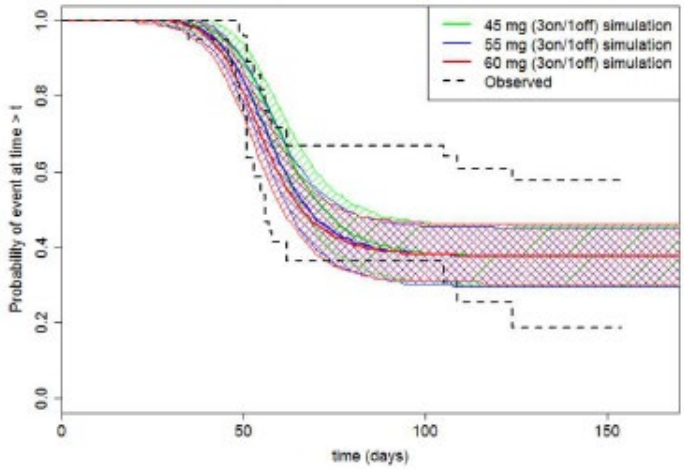
Table 12: Copanlisib Dose Modifications (Expansion Cohorts at 0.8 mg/kg)

Type of dose modification	Cohort 6 (0.8 mg/kg) NHL (n=9)
Total number (%) of subjects with modification	6 (66.7%)
Total number (%) of subjects with dose delay	5 (55.6%)
Total number (%) of subjects with dose interruption	5 (55.6%)
Total number (%) of subjects with dose reduction	2 (22.2%)
Source: Study 12871 CSR	

It is important to note that no additional dose exploration was conducted at lower doses;

however, an evaluation of the relation between copanlisib dose and safety as well as between dose and preliminary efficacy data are shown in Figure 6 and indicate that doses as high as 60 mg may not be necessary.

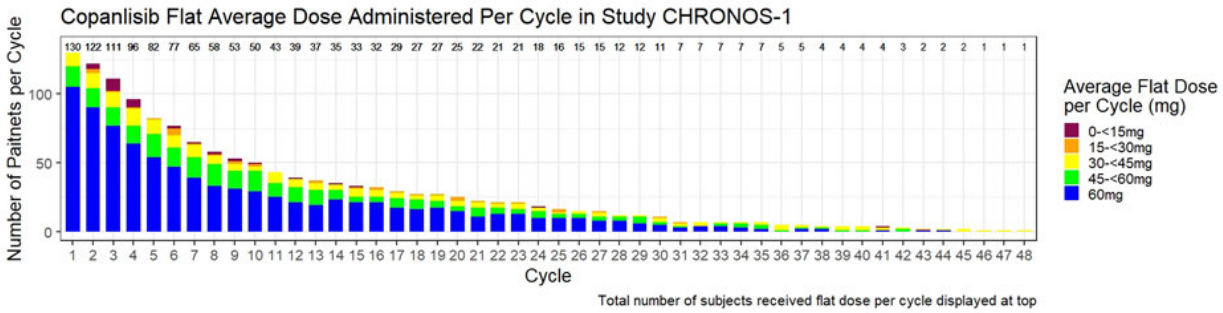
Figure 6: Exposure-Response Simulations of Copanlisib Doses to Achieve a Clinical Response



Source: Sponsor analysis based on PK/PD data from Studies 12871, 15205, and 16349.

In the CHRONOS–1 trial (Study 16348, part B), no significant exposure-response relationship was observed for efficacy, due to the limited doses and exposures evaluated in the clinical studies. For the safety analysis, Grade ≥3 AEs increased with AUC, but did not each statistical significance over the limited range of exposures available for the single dose evaluated. However, considerable dose modifications (i.e., dose interruptions, delays or reductions) were required in 120 patients (84.5%) in the pivotal study CHRONOS-1 (Figure 7).

Figure 7: Dose Interruptions, Modifications and Reductions for Copanlisib by Cycle



Source: NDA 209936 Multidisciplinary Review at Drugs@FDA

The toxicity of the pivotal trial and the limited phase 1 data indicate that a lower dose of copanlisib may be efficacious and more tolerable.

3.3.1.4 Umbralisib

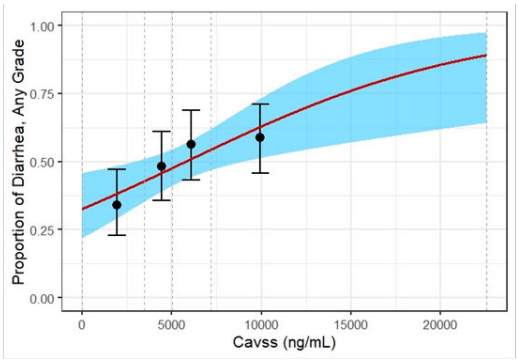
The approved dosage of umbralisib is 800 mg orally QD, continued until disease progression or unacceptable toxicity. For umbralisib monotherapy, two formulations were developed and tested in parallel in Study TGR-1202-101. The systemic exposures obtained with the micronized formulations were almost two-fold higher than the unmicronized version and ultimately the micronized formulation was selected for further development based on better pharmacological properties.[24,25] The dose used in the clinical trials was selected based on study TGR-1202-101 which was designed to determine the MTD. Dose escalation studies were conducted with both formulations.

For the micronized formulation, in the initial dose escalation stage, 200 mg QD (n=3), 400 mg QD (n=3), 800 mg QD (n=3), 1000 mg QD (n=7), 1200 mg QD (n=3) and 1800 mg QD (n=2) were tested. Two DLTs were observed at 1800 mg QD, and the 800 mg QD (n=3), 1000 mg QD (n=10) and 1200 mg QD (n=17) cohorts were subsequently expanded. The 1200 mg QD dose was deemed the MTD.[25]

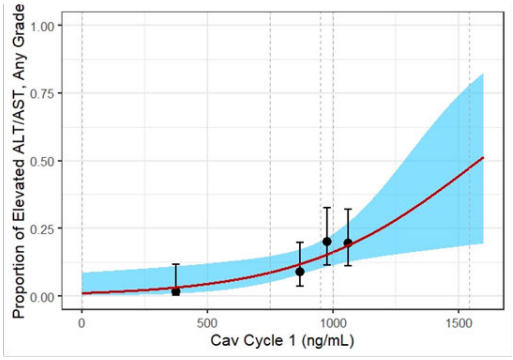
The response rates and the AEs observed per dose level were not clearly presented and were limited by the small number of patients evaluated at each dose for the micronized formulation. In some cases, the observations for the unmicronized and the micronized formulations were pooled, making the interpretation difficult, given the differences in exposure.[24,25] Based on these data, the 800 mg micronized formulation was selected for study of umbralisib. However, the lack of clarity regarding the phase 1 study outcomes, and pharmacodynamic data suggest that lower doses, including 600 mg which was untested, might have been suitable doses as well.

The sponsor submitted exposure-response analyses for efficacy for studies TGR-1202-101 and UTX-TGR-205 for MZL (n=37) and FL (n=79) populations in the original NDA. This relationship was flat across the doses tested in patients with MZL. Significant relationships were observed for C_{minss} and ORR, across the doses tested in patients with FL. Exposure-response analyses for safety based on studies TGR-1202-101 (n=83) and UTX-TGR-205 (N = 140) indicated statistically significant correlations between exposure and any grade diarrhea, any grade elevations of ALT/AST, and Grade ≥3 elevations of ALT/AST (Figure 8).

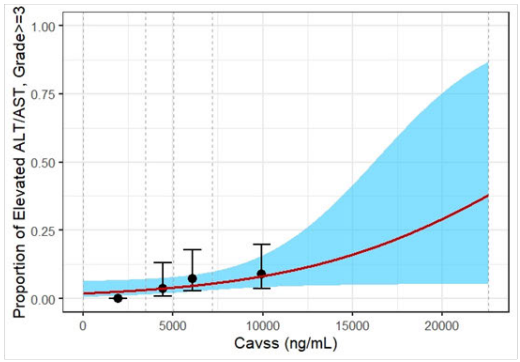
Figure 8: Exposure Response Relationships for Umbralisib for Diarrhea and AST and ALT Elevations for MZL and FL Populations in Studies TGR-1202-101 and UTX-TGR-205



Umbralisib (mono), Any grade Diarrhea



Umbralisib (mono), Any grade ALT/AST



Umbralisib (mono), ≥ grade 3 ALT/AST

Abbreviations: mono, monotherapy
Source: NDA 213176 Multidisciplinary Review at Drugs@FDA

It is important to note that the 800 mg QD dosage was associated with significant AEs, and the dose modification rate due to AE was 57.4%, which included 45.3% dose interruptions, 10.5% dose reductions and 15.4% dose discontinuations in all patients who received at least 1 dose of single-agent umbralisib.

Considering the exposure-response relationships for increased safety events with increased exposure, the increased dose modifications over time at the 800 mg dose, the lack of clinically significant association between increased exposure and an increased probability of response for MZL, and the need to balance efficacy and safety for patients with FL, a lower dose of umbralisib may be efficacious and more tolerable and should have been explored.

3.3.2 Combination Therapy

3.3.2.1 Idelalisib in Combination

For idelalisib in combination with either bendamustine (I+B) or rituximab (I+R), limited dose exploration was assessed in study 101-07 in patients with iNHL, MCL or CLL. Idelalisib doses of 100 mg BID and 150 mg BID were tested because they had shown clinical activity in Study 101-02. Patient were enrolled to receive Idelalisib 100 mg BID with rituximab (n=12) or bendamustine (n=12), or idelalisib 150 mg BID with rituximab (n=39) or bendamustine (n=39).

While initial safety results indicated that both doses could be given with rituximab or bendamustine, the 150 mg BID dose was selected to be explored in combination with BR. Safety and efficacy by dose level was not reported; safety and efficacy data were pooled across doses and the rationale for selecting the 150 mg BID in combination with rituximab and bendamustine was unclear. However, there were significant dose reductions at the 150 mg dose in combination with rituximab and bendamustine (Table 13).

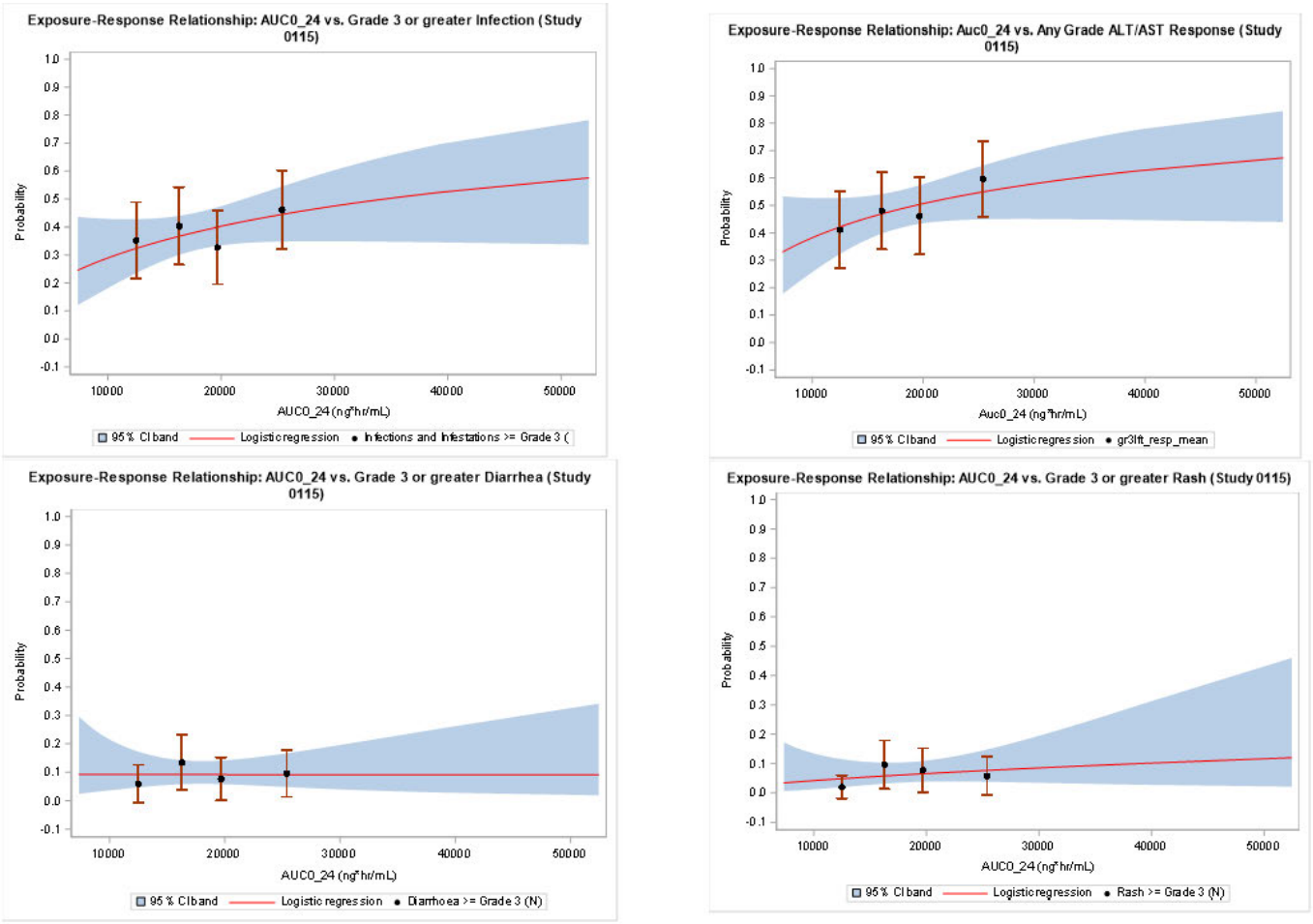
Table 13: Summary of Idelalisib Dose Reductions for Patients Receiving Idelalisib with Rituximab, Bendamustine, or Rituximab and Bendamustine in Study 101-07

Idelalisib dose reduction	Idelalisib +R (N = 51)		Idelalisib +B (N = 51)		Idelalisib +BR (N = 33)
	100 mg BID (n=12)	150 mg BID (n=39)	100 mg BID (n=12)	150 mg BID (n=39)	150 mg BID (n=33)
Reduced to 100 mg BID	N/A	10 (26%)	N/A	13 (33%)	10 (30%)
Reduced to 75 mg BID	4 (33%)	3 (8%)	3 (25%)	5 (13%)	1 (3%)
Reduced to 50 mg BID	1 (8%)	1 (3%)	0	1 (3%)	0

Abbreviations: R, rituximab; B, bendamustine
Source: Study 101-07 CSR.

In Study GS-US-312-0115, which evaluated idelalisib 150 mg BID in combination with BR, no exposure-response relationship was observed for efficacy because of the limited range of exposure available from only one dose level, which suggests that the dose achieved exposures above that associated with maximal efficacy, and lower doses may achieve such exposures as well. It is important to note that exposure-response relationships for safety did show a positive trend for Grade ≥3 infections and any grade ALT or AST elevation within the exposure range of the idelalisib concentrations observed with the evaluated dosing regimen (Figure 9) suggesting that lower doses may result in a lower incidence of the evaluated safety events.

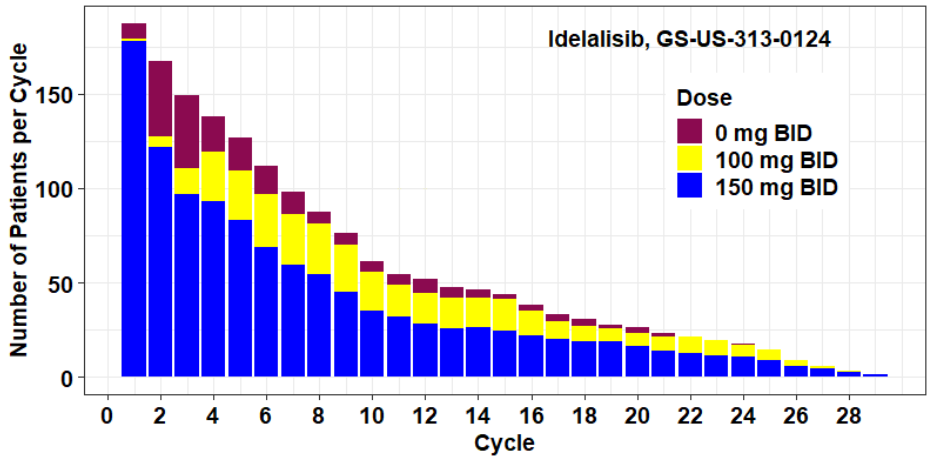
Figure 9: Exposure-Response Relationships for Infections, Diarrhea, ALT/AST Elevations, and Rash



Source: NDA 205858 S-6 Clinical Pharmacology Review and GS-US-312-0115 CSR

As shown below (Figure 10), the combination of idelalisib and rituximab resulted in a number of dose reductions and interruptions for idelalisib in patients with previously treated iNHL as early as Cycle 1 in study GS-US-313-0124.

Figure 10: Dose Interruptions, Reductions and Modifications for Idelalisib by Cycle

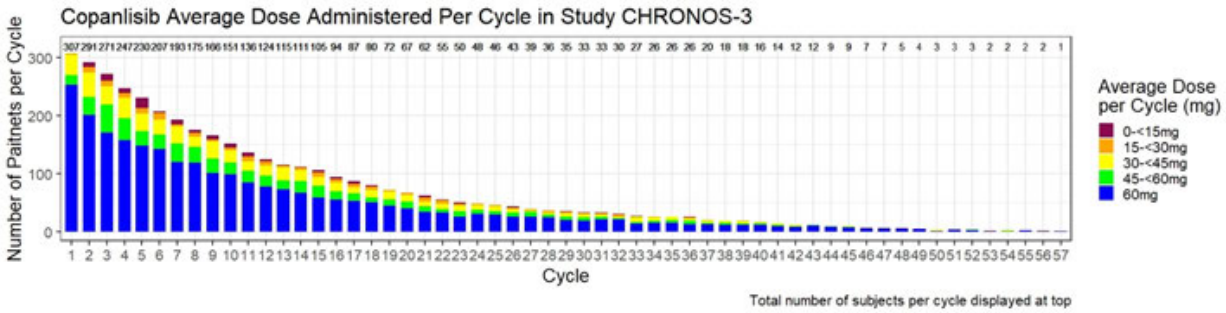


Source: NDA 205858 S-6 Clinical Pharmacology Review and GS-US-313-0124 CSR

3.3.2.2 Copanlisib + Rituximab

No dose finding study for copanlisib in combination with rituximab was conducted and the approved copanlisib monotherapy dose was applied in the combination treatment (copanlisib + rituximab) in CHRONOS-3. With this in mind, we note that in CHRONOS-3, the AEs in the copanlisib + rituximab arm were substantially greater than the rituximab alone arm. Furthermore, dose was reduced or discontinued in approximately 60% of the patients by Cycle 3 (see Figure 11).

Figure 11: Dose Interruptions, Modifications and Reductions for Copanlisib by Cycle



Source: FDA analysis of CHRONOS-3 data submitted to FDA

As seen with the previous drugs, for copanlisib in combination therapy, significant dose reductions and interruptions were observed, suggesting that the dose was too high.

3.3.2.3 Umbralisib + Ublituximab

The dosing considerations for umbralisib in combination with ublituximab will be discussed as part of the April 22, 2022 ODAC meeting.

3.3.3 Summary of Dosing Issues with PI3K Inhibitors

Overall, these examples demonstrate that the doses selected for further development of the PI3K inhibitors lead to considerable toxicity, as reflected by the exposure-response relationships for AEs for these drugs and the dose modifications that were necessitated in the patients. For duvelisib, copanlisib and umbralisib, as well as the combination therapies with idelalisib and with copanlisib, additional exploration of lower doses may yield efficacious doses with less toxicity.

3.4 Limitations of Single-Arm Trials

The initial evaluation of benefit-risk for PI3K inhibitors in patients with indolent NHL (primarily FL and MZL) were based on single-arm trials. FDA considers data from single-arm trials to support potential approval to facilitate access to effective treatments in patients with a serious and life-threatening disease and an unmet need. However, single-arm data has inherent limitations that include, but are not limited to:

- Assessment of safety is challenging
  - In the absence of a comparator arm, the observed side effects could be attributed to the drug or to the underlying disease.
  - Follow-up is often relatively short and the ability to characterize long-term safety is limited.
- Assessment of efficacy is challenging
  - The assessment of efficacy relies on a historical control or comparison across populations which is less robust and has known limitations.
  - Response rates may not predict clinical benefit.
  - Time-to-event endpoints such as PFS ad OS cannot be accurately interpreted in single-arm trials.
- Benefit-risk assessment
  - Difficult to balance the observed efficacy with toxicity to appreciate the true benefit-risk in the intended population.

Clinical data from single-arm trials limits the interpretation of efficacy and safety. Randomized trials are the most efficient way to control for confounding factors and therefore the best way to study risks as well as benefits. Randomized assignment to treatment and control would provide unbiased comparisons for both known and unknown factors.

4 Conclusions

The consistent findings of decrements in overall survival in six randomized trials, in the setting of an advantage or potential advantage in PFS, is unprecedented in oncology. The overall survival information is early and represents a low number of events, yet, we have the same pattern observed across multiple trials. Further, in each trial, there was a higher rate of death due to adverse events in the PI3K inhibitor arm, suggesting the potential detriment in overall survival may be due to toxicity.

The experience with the PI3K inhibitors in hematologic malignancies illustrates challenges with the current paradigm of using ORR in single-arm trials to support initial approval.

First, there was limited exploration of lower doses prior to choosing maximum or near maximum tolerated doses for subsequent registrational trials. Although an exposure-response relationship exists for AEs associated with the drugs in this class, an exposure-response relationship for efficacy has not necessarily been observed. More robust dose exploration trials to clarify the relationship between ORR and toxicities would have potentially avoided selecting an excessively toxic dose with its resultant concerning trends in OS. Current FDA advice, conducted under Project Optimus, emphasizes the need to characterize dose response and safety evaluations prior to embarking on registrational trials.[26]

Second, the consequences of not performing further dose exploration were complicated by selecting a single-arm study design for initial registration in some cases. The safety analysis of data from single-arm trials is confounded by the absence of a control, which can pose challenges in accurately attributing AEs to either drug or the underlying disease. Because sponsors may select a dose to achieve the highest ORR without carefully considering a benefit-risk analysis, toxicities are compounded and may contribute to the worrisome OS results seen repeatedly in multiple RCTs of these agents. Additionally, while single-arm trials allow for the evaluation of ORR, they cannot accurately assess PFS and OS. Randomized trials are the most effective method to control for confounding factors and allow for assessment of important measurements such as PFS, OS, and patient report outcomes.

Lastly, OS data should be fully collected and analyzed, as OS is an important metric in the benefit-risk determination, especially for products with significant toxicity. Randomized trials should be prospectively planned to allow for an adequate assessment of survival and other measurements of clinical benefit.

Future studies should be designed with additional opportunities to evaluate patient safety, and there should be a high likelihood that when a study is completed it can indicate an acceptable benefit-risk profile, which includes evaluation of the impact on survival as both a safety and efficacy metric.

5 Topics for Discussion

Please discuss the observed toxicity of the PI3K inhibitor class and whether randomized data are warranted to support the evaluation of benefit-risk in patients with hematologic malignancies.

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7 Appendix I: Regulatory History and Clinical Trial Results

The regulatory history of each PI3K inhibitor approved for hematologic malignancies is summarized. Indication statements, post-marketing requirements (PMRs), and post-marketing commitments (PMCs) may be paraphrased.

7.1 Idelalisib Regulatory History and Development

1. **Idelalisib indications**
   - Approved July 2014 for the treatment of:
     - Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities (regular approval)
     - Relapsed FL in patients who have received at least two prior systemic therapies (accelerated approval)*
     - Relapsed SLL in patients who have received at least two prior systemic therapies (accelerated approval)*

       **** FL and SLL indications subsequently withdrawn February 18, 2022***

2. **Risk mitigation**
   - Boxed Warning in initial labeling for fatal and serious toxicities including hepatoxicity, diarrhea and colitis, pneumonitis, and intestinal perforation. Additional Warnings and Precautions included severe cutaneous reactions, anaphylaxis, neutropenia, and embryo-fetal toxicity.
   - Communication REMS established under initial approval to address risks of hepatoxicity, colitis, intestinal perforation, and pneumonitis
   - 2016: Based on Sponsor's termination of 3 RCTs due to increased deaths in the idelalisib arms,
     - FDA healthcare alert issued March 2016.
     - LOU: idelalisib is not indicated and is not recommended for first-line treatment of any patient. New Warning and Precaution added for serious infections.
   - 2018 – Labeling revised to include information from terminated RCTs and update the LOU: idelalisib is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of FL. New PMR (below) issued to verify clinical benefit of idelalisib in FL.
   - February 2022: LOUs updated, coupled with voluntary withdrawal of FL and SLL indications:
     - Idelalisib is not indicated and is not recommended for first-line treatment of any patient, including patients with CLL, SLL, FL, and other indolent NHLs
     - Idelalisib is not indicated and not recommended in combination with

bendamustine and rituximab, or in combination with rituximab for the treatment of patients with FL, SLL, and other indolent NHLs

3. **PMRs/PMCs**
   - Three accelerated approval PMRs and 6 safety PMRs were originally issued:
     - Accelerated approval PMR (2180-1): Design and conduct a prospective trial and provide the full final report and datasets to evaluate dose reductions in patients who achieve a response or have stable disease in order to optimize the safety and efficacy of chronic administration of idelalisib in patients with FL or SLL. Final Report due 12/2019
     - Accelerated approval PMR (2180-2) Submit the complete final report and data showing clinical efficacy and safety from trial GS-US-313-0124, a Phase 3. double-blind, placebo-controlled trial of idelalisib in combination with rituximab in subjects with previously treated indolent NHLs. Final Report due 01/2018
     - Accelerated approval PMR (2180-3): Submit the complete final report and data showing clinical efficacy and safety from trial GS-US-313-0125, a Phase 3, double-blind, placebo controlled trial of idelalisib in combination with BR in subjects with previously treated indolent NHLs. Final Report due 8/2019.
     - PMR, pneumonitis (2180-4): Conduct a study to characterize the incidence, diagnosis, and effective treatment of idelalisib-related pneumonitis based on data and pooled analyses from randomized trials in indolent NHL and CLL. Final Report due 11/2020
     - PMR, long-term safety (2180-5): Conduct a trial to provide evidence sufficient to characterize the long-term safety of idelalisib. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial 101-99, phase 1/2 extension study of safety and durability of idelalisib in hematologic malignancies. Final Report due 12/2019
     - PMR, long-term safety (2180-6): Conduct a trial to provide evidence sufficient to characterize the long-term safety of idelalisib. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in patients with previously treated indolent NHLs. Final Report due 12/2019
     - PMR, long-term safety (2180-7): Conduct a trial to provide evidence sufficient to characterize the long-term safety of idelalisib when used in combination with other agents such as bendamustine and rituximab. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in patients with previously treated indolent NHLs. Final Report due

12/2019

- PMR, long-term safety (2180-8): Conduct a trial to provide evidence sufficient to characterize the long-term safety of idelalisib when used in combination with an anti-CD20 drug regimen. Submit the complete final report and data from trial GS-US-312-0119, a Phase 3, randomized study of idelalisib in combination with ofatumumab in patients with previously treated CLL. Final Report due 12/2019
- PMR, long-term safety (2180-9): Conduct a trial to provide evidence sufficient to characterize the long-term safety of idelalisib when used in a combination therapy regimen. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-312-0117, a Phase 3, 2-arm extension study of idelalisib in patients with previously treated CLL. Final Report due 12/2019

- Based on review of the terminated studies, FDA released 4 PMRs (2180-2, 2180-3, 2180-6, and 2180-7) due to prohibitive toxicity in the idelalisib arms, and issued a new PMR January 2018 to confirm clinical benefit in patients with FL.
  - Accelerated approval PMR (2180-10): Conduct a trial establishing a safe and effective dosing regimen of idelalisib in patients with relapsed or refractory FL who have no other therapeutic options and require treatment. Include a dosing regimen arm with a 21 day of a 28 day treatment cycle. Final Report due 12/2026

4. **Withdrawal of FL and SLL indications, February 2022**
   - Idelalisib FL and SLL indications were voluntarily withdrawn by Sponsor effective February 18, 2022, due to lack of confirmation of clinical benefit in patients with R/R FL or SLL. Sponsor cited challenges with recruitment to the above accelerated approval PMR study.

7.2 Copanlisib Regulatory History and Development

1. **Copanlisib indication**
   - Approved September 2017 for the treatment of adult patients with relapsed FL who have received at least two prior systemic therapies (accelerated approval)

2. **Risk mitigation**
   - Labeling includes Warnings and Precautions for infections, hyperglycemia, hypertension, non-infectious pneumonitis, neutropenia, severe cutaneous reactions, and embryo-fetal toxicity.

3. **PMRs/PMCs**
    - Accelerated approval PMR based on CHRONOS-4 (3273-1): In order to verify the clinical benefit of copanlisib, submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of copanlisib in combination with immunochemotherapy vs. immunochemotherapy alone in patients with relapsed FL, MZL, SLL, or LPL/WM. The primary endpoint is PFS. Enroll approximately 520 patients. Final Report due 09/2022
    - PMR, long-term safety (3273-2): Characterize the long-term safety of copanlisib as monotherapy and in combination with immunotherapy and immunochemotherapy, along with safety-related concomitant medication use, in patients with hematological malignancies. Submit annual interim and final reports and integrated analysis datasets, from a prospective cohort of at least 400 patients for at least 5 consecutive years. Final Report due 07/2023
    - PMR, QT study (3273-3): Complete and submit results of a study to determine the effect of copanlisib on QT/QTc interval in subjects with advanced solid tumors and NHL. Final Report due 06/2019
    - PMR, safety in CHRONOS-3 (3273-4): In order to characterize the safety of copanlisib from a randomized controlled trial, submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of copanlisib in combination with rituximab in patients with relapsed FL, MZL, SLL, and LPL /WM. Enroll at least 400 patients. Final Report due 06/2021
    - PMR, dosing in hepatic and renal impairment (3273-5): Amend and complete your ongoing clinical pharmacokinetic trial to determine an appropriate safe dose of copanlisib in subjects with moderate and severe hepatic impairment and in subjects with severe renal impairment. Final Report due 07/2021
    - PMR, drug-drug interactions (3273-6): Conduct a clinical pharmacokinetic (PK) trial to evaluate the effect of copanlisib on the pharmacokinetics of metformin. Final Report due 05/2020

4. **Supplemental NDA, submitted May 2021 based on CHRONOS-3, withdrawn December 2021**
    - sNDA based on CHRONOS-3, a RCT of rituximab + copanlisib vs. rituximab + placebo in relapsed indolent NHL. Indications proposed for:
        - Previously treated B-cell indolent NHL (including FL, MZL, SLL, and LPL/WM) in combination with rituximab
        - Relapsed MZL after ≥2 prior systemic therapies.
    - Designated confirmatory trial in FL, CHRONOS-4, ongoing (copanlisib +/- chemoimmunotherapy for R/R FL/MZL).

7.3 Duvelisib Regulatory History and Development

1. **Duvelisib indications**
    - Approved September 2018 for the treatment of adult patients with:
        - Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after at least two prior therapies (regular approval)
        - Relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies (accelerated approval)*

            **** FL indication subsequently withdrawn December 17, 2022***

2. **Risk mitigation**
    - Communication REMS issued with original approval.
    - Labeling includes Boxed Warnings for fatal and/or serious infections, diarrhea or colitis, cutaneous reactions, and pneumonitis; other Warnings and Precautions consist of hepatotoxicity, neutropenia, and embryo-fetal toxicity.
    - Sponsor posted Dear Healthcare Professional letter in March 2022 regarding updated OS data from the DUO (IPI-145-07) trial in CLL/SLL.

3. **PMRs/PMCs**
    - Accelerated approval PMR for FL indication (3494-1): Conduct a randomized phase 3 clinical trial in patients with relapsed or refractory FL that verifies and isolates the clinical benefit of duvelisib. The primary endpoint would be PFS as determined by an independent review committee (IRC). Final Report due 12/2024
        - Status: Not fulfilled. Trial not initiated.
    - PMR, longer-term safety (3494-2): Characterize the safety of long-term use of duvelisib monotherapy in patient with hematologic malignancies treated with a planned dose of 25 mg twice daily on Trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI 145-12 combined. Include evaluations, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, and adverse reactions of special interest. Final Report due 11/2020
    - PMR, OS in CLL trial (3494-3): Submit reports and datasets for OS from trial IPI-145-07 with 5 years of follow-up, with an interim report after 3 years of follow-up, measured from the last patient's randomization date. Include causes of death and narratives for death in the absence of treated disease progression. Final Report due 06/2021
    - PMC, drug-drug interactions (3494-4): Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of duvelisib. Final Report due 01/2020
    - PMC, lower dosage formulation (3494-5): To allow dose reduction of duvelisib in patients who do not tolerate 15 mg twice daily, develop and test the product characteristics of a lower strength (5 mg or 10 mg) duvelisib formulation. Final

Report due 12/2019

4. **Withdrawal of FL indication December 2021**
   - Duvelisib FL indication was voluntarily withdrawn effective December 17, 2021, due to lack of confirmation of clinical benefit. Required confirmatory trial never initiated by Sponsor for business reasons.

7.4 Umbralisib Regulatory History and Development

1. **Umbralisib indications**
   - Approved February 2021 for the treatment of adult patients with:
     - Relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen (accelerated approval)
     - Relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy (accelerated approval)

2. **Risk mitigation**
   - Labeling includes Warnings and Precautions for infections, neutropenia, diarrhea or non-infectious colitis, hepatotoxicity, severe cutaneous reactions, allergic reactions due to inactive ingredient, and embryo-fetal toxicity.

3. **PMRs/PMCs**
   - Accelerated approval PMR (3999-1): Conduct a randomized, Phase 3 clinical trial that verifies and describes the clinical benefit of umbralisib in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma. Patients should be randomized to receive immunotherapy with or without umbralisib. The primary endpoint should be PFS, with secondary endpoints that include OS and ORR. Final Report due 06/2027
   - PMR, dosage in hepatic impairment (3999-2): Conduct a clinical pharmacokinetic study to determine a safe and appropriate dose of umbralisib in patients with moderate to severe hepatic impairment. Final Report due 09/2024
   - PMR, drug-drug interactions (3999-3): Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of a strong CYP3A and a moderate CYP2C9 inhibitor on the single dose pharmacokinetics of umbralisib to address the potential for excessive drug toxicity. Final Report due 06/2025
   - PMR, drug-drug interactions (3999-4): Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of a sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrate to address the potential for excessive drug toxicity. Final Report due 04/2025

- PMR, QT study (3999-5): Conduct a clinical study to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations. Final Report due 06/2027
- PMC, data in racial and ethnic minorities (3999-6): Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of umbralisib monotherapy and in combination with immunotherapy among U.S. racial and ethnic minority patients with FL or MZL. Final Report due 06/2028
- PMC, drug-drug interactions (3999-7): Conduct a clinical pharmacokinetic study with repeat doses of a strong CYP3A inducer on the single dose pharmacokinetics of umbralisib. Final Report due 06/2024

4. **Supplemental NDA in CLL submitted March 2021**
    - sNDA (under review) based on UNITY-CLL, an open-label RCT of umbralisib + ublituximab (U2) vs. obinutuzumab + chlorambucil in previously untreated and R/R CLL

7.5 Idelalisib Clinical Trials

7.5.1 Registrational Trials

7.5.1.1 CLL Study GS-US-312-0116

Study GS-US-312-0116, the registrational study for the idelalisib CLL indication granted regular approval, was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating idelalisib + rituximab vs. placebo + rituximab in previously treated CLL. The trial enrolled patients who required treatment and were deemed ineligible for standard chemoimmunotherapy due to comorbidities. Approval was based on the second interim analysis for efficacy (data cutoff, October 2013). The results herein are based on the final analysis (data cutoff, April 2014).

Subjects in the control arm with definitive disease progression could enroll in a separate, companion, double-blind extension study (GS-US-312-0117). In the extension study subjects took active blinded idelalisib therapy, with allocation based on the original primary study randomization.

Statistical Analysis Plan

Endpoints:
Primary: PFS by IRC
Key secondary: ORR, lymph node response, OS, CR

Randomization
1:1, stratified by:
- 17p deletion and/or TP53 mutation status
- Rai stage 0-II vs. III-IV
- IGHV mutation status
- Prior anti-CD20 antibody

Sample Size and Assumptions
- Planned: 200 subjects
- Analyzed: 220 (110 subjects each: idelalisib + R and placebo + R)
- PFS events required for primary analysis: 119
- Target HR = 0.57 (Median PFS improvement from 6 months to 10.5 months), with power of 0.85 and type-I error rate (2-sided) of 0.05

Sample size was based on PFS. There was no pre-planned hypothesis testing of OS with sufficient power.

Interim Analysis (IA)
Two formal IAs conducted:
- First IA, PFS analysis crossed significance boundary, stopping the blinded-phase of the study
- Second IA, PFS analysis crossed significance boundary (data cutoff October 2013)

Multiplicity
- Overall type I error controlled at a 2-sided significance level of 0.05
- If primary hypothesis was rejected, key secondary endpoints were sequentially tested.

Efficacy Results

Progression-Free Survival
PFS per IRC, by intent-to-treat (ITT) analysis, is shown in Table 14 and Figure 12. The study met its primary objective, demonstrating a statistically significant improvement in PFS in favor of idelalisib + rituximab.

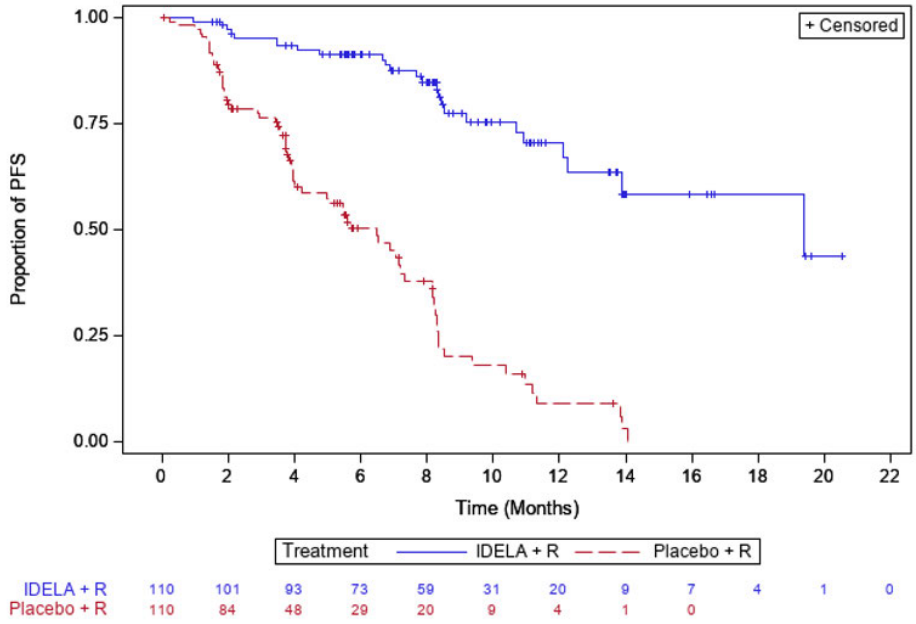
Table 14: Summary of PFS per IRC, Idelalisib Study GS-US-313-0116

	Idelalisib + Rituximab (N = 110)	**Placebo + Rituximab (N = 110)**
PFS Events, n (%)	25 (22.7)	70 (63.6)
Disease Progression	17 (15.5)	62 (56.4)
Death	8 (7.3)	8 (7.3)
Censored, n (%)	85 (77.3)	40 (36.4)
Median PFS (months) (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Adjusted HR (95% CI) [a]	0.15 (0.09, 0.25)	
P-value [b]	0.0001	

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors

[b] P-value was calculated using the stratified log-rank test.
Abbreviations: NR, not reached
Data cutoff 4/20/2014 (basis for final CSR). For subjects in the control arm who enrolled in the extension study, summary includes data up to the first dose of open-label idelalisib.
Source: FDA analysis.

Figure 12: Kaplan-Meier Curve of PFS by IRC, Idelalisib Study GS-US-313-0116



Data cutoff 4/20/2014
Source: FDA analysis

Overall Survival

OS data (ITT) are summarized in Table 15 and Figure 13. The OS results in this study indicated a potential survival benefit in the idelalisib + rituximab arm. However, this analysis is exploratory and descriptive only.

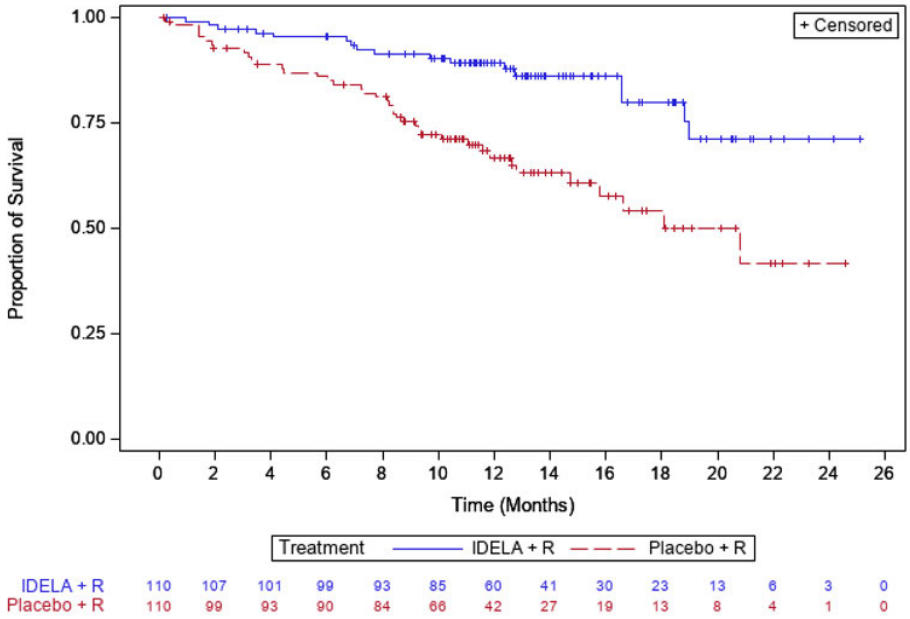
Table 15: Summary of OS, Idelalisib Study GS-US-313-0116

	Idelalisib + Rituximab (N = 110)	**Placebo + Rituximab (N = 110)**
Death, n (%)	17 (15.5)	40 (36.4)
Censored, n (%)	93 (84.5)	70 (63.6)
Median OS (months) (95% CI)	NR (NR, NR)	20.8 (14.8, NR)
Adjusted HR (95% CI) [a]	0.34 (0.19, 0.60)	
Nominal p-value [b]	0.0001	

[a] HR and 95% CIs were calculated using the Cox proportional hazards model, adjusted for randomization stratification factors
[b] P-value was calculated using the stratified log-rank test.
Analysis is based on data from Study GS-US-312-0116 and its extension study, GS-US-312-0117.

Data cutoff for Study GS-US-312-0116: 4/20/2014, data cutoff for Study GS-US-312-0117: 7/1/2014
Source: FDA analysis

Figure 13: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-313-0116



Data cutoff for Study GS-US-312-0116: 4/20/2014. Data cutoff for Study GS-US-312-0117: 7/1/2014
Source: FDA analysis

Safety Results
For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 6.

7.5.1.2 NHL Study 101-09

Study 101-09 (NCT01282424) was a phase 2, open-label, single-arm study of idelalisib monotherapy that supported the accelerated approvals in R/R FL and SLL. The trial enrolled 125 subjects, including 72 with FL and 26 with SLL who had ≥2 prior therapies and relapsed within 6 months after rituximab and an alkylating agent. The primary efficacy endpoint was ORR by IRC. In FL, the ORR was 54% (95% CI: 42, 66) with 8% CR and 46% PR (source: FDA analysis); the median duration of response (DOR) was not evaluable (range: 0+ to 14.8+ months). In SLL, the ORR was 58% (95% CI: 37, 77), all PRs, with an estimated median DOR of 11.9 months (range: 0+, 14.7+).

Safety Results
For a summary of safety with idelalisib monotherapy and selected toxicities, see Section 3.2.2.

7.5.2 Terminated RCTs of Idelalisib

Three RCTs involving idelalisib with rituximab or BR in were terminated in 2016 due to an increased risk of death and higher incidence of SAEs in the idelalisib arms. In each trial, the primary endpoint was PFS, with secondary endpoints that included ORR and OS. Analyses of OS are descriptive. Survival analyses are based on the intent-to-treat (ITT) population.

7.5.2.1 CLL Study GS-US-312-0123

Study GS-US-312-0123 (NCT01980888) was a Phase 3 placebo-controlled, blinded study evaluating idelalisib + BR vs. placebo + BR in previously untreated CLL. Crossover was not permitted. The study completed enrollment and was terminated early during the follow-up period.

PI3K inhibitor	Trial	Population	Randomization& Treatment	Enrolled	Endpoints
Idelalisib	GS-US-312-0123	Untreated CLL	1:1 Idelalisib + BR Placebo + BR	Total: 311 Idelalisib + BR: 157 Placebo + BR: 154	Primary: PFS

Statistical Analysis Plan

Endpoints:
Primary: PFS (planned per IRC; analyzed per investigator)
Key secondary: ORR, nodal response rate, CR rate, and OS

Randomization
1:1 to Group A (idelalisib + BR) or Group B (placebo + BR), stratified by:
- IgHV mutation status
- Rai stage 0-II vs. III-IV
- 17p deletion status

Sample Size
Planned: 280
Enrolled: 311
- Number of PFS events required for primary analysis: 121
- Target HR = 0.57 (median PFS improvement from 34 months to 60 months)
- Type-I error rate (2-sided): 0.05
- Power: 0.87

The sample size calculation was based on PFS only. There was no pre-planned OS sample size calculation based on appropriate hypothesis testing with sufficient power.

Efficacy Analyses

Due to the early termination of the study, efficacy data were not available for all subjects, and therefore the prespecified analyses were not conducted. The IRC evaluated suspected progressive disease that occurred before study termination. An analysis of investigator-assessed PFS and OS was conducted using the same data (data cut date 15 January 2016) that triggered the DMC's safety concern. The analysis with 23 events occurred approximately 20 months prior to the planned interim analysis (82 events). A study termination decision was made by the Sponsor in agreement with the DMC recommendations, based on risk of adding idelalisib to BR in the first-line setting overwhelming the potential benefit.

Efficacy Results

Progression-Free Survival

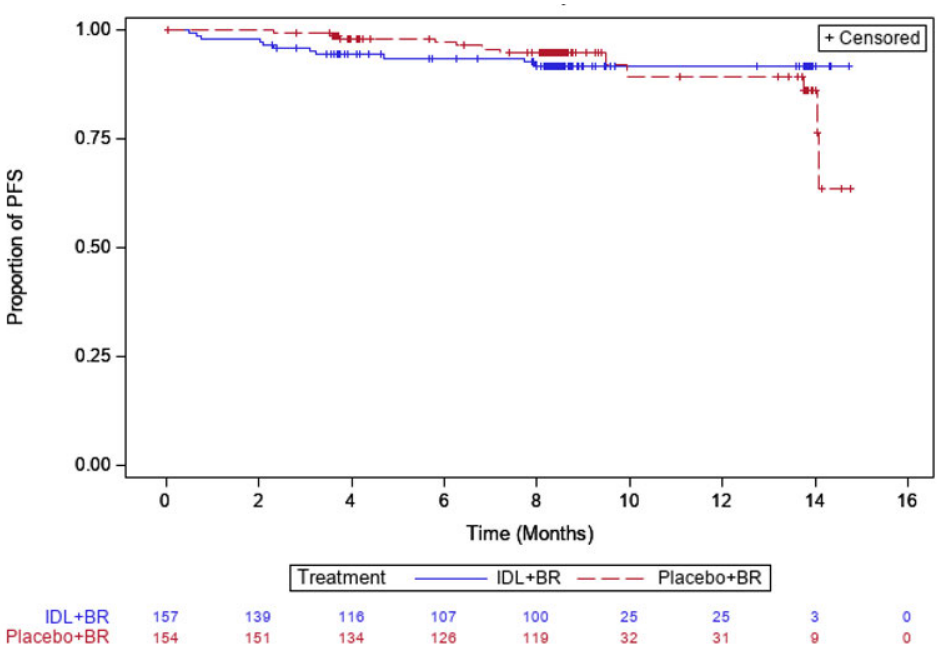
Investigator-assessed PFS is presented in Table 16 and Figure 14. Crossing Kaplan-Meier curves suggest that proportional hazard assumption is violated, and therefore interpretation of HR may be challenging.

Table 16: Summary of Investigator-Assessed PFS, Idelalisib Study GS-US-312-0123

	Idelalisib + BR (N = 157)	**Placebo + BR (N = 154)**
Events, n (%)	11 (7.0)	12 (7.8)
Disease Progression	0	10 (6.5)
Death	11 (7.0)	2 (1.3)
Censored, n (%)	146 (93.0)	142 (92.2)
Median PFS (months) (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI) [a]	1.10 (0.48, 2.52)	
Nominal p-value [b]	0.85	
PFS Rate at 24 weeks, % (95% CI)	93.5 (87.8, 96.5)	98.0 (93.8, 99.3)
PFS Rate at 48 weeks, % (95% CI)	91.7 (85.4, 95.3)	89.3 (77.3, 95.1)

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.
[b] Nominal p-value was calculated using the stratified log-rank test.
NR: not reached
Data cutoff 6/16/2016
Source: FDA analysis

Figure 14: Kaplan-Meier Curve of Investigator-Assessed PFS, Idelalisib Study GS-US-312-0123



Data cutoff 6/16/2016
Source: FDA analysis

Overall Survival

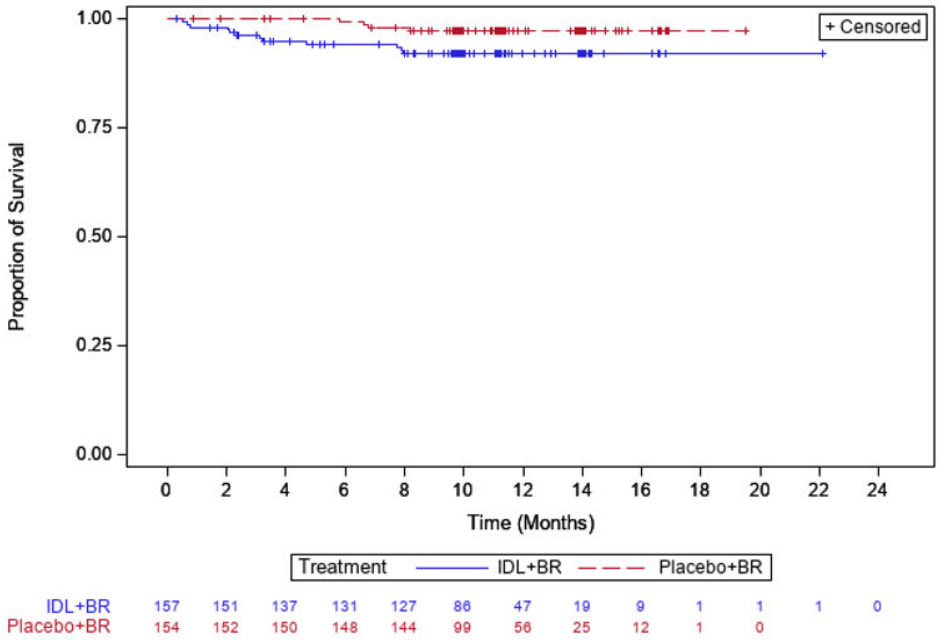
OS data are presented in Table 17 and Figure 15. The OS results are concerning because there is a potential increase in the risk of death in the idelalisib arm compared with the control arm. There is high variability in the HR estimates, but given the higher upper bound of the confidence intervals, the death hazard in the treatment can be multiple times higher than the control arm. No formal conclusions could be drawn based on the early interim analysis results.

Table 17: Summary of OS, Idelalisib Study GS-US-312-0123

	Idelalisib + BR (N = 157)	**Placebo + BR (N = 154)**
Deaths, n (%)	12 (7.6)	4 (2.6)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI) [a]	3.34 (1.08, 10.39)	
Nominal p-value [b]	0.055	
OS Rate at 6 months, % (95% CI)	94.1 (88.9, 96.9)	99.3 (95.3, 99.9)

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for stratification factors.
[b] Nominal p-value was calculated using the stratified log-rank test.
Data cutoff 6/16/2016
Source: FDA analysis

Figure 15: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-312-0123



Data cutoff 6/16/2016
Source: FDA analysis

Safety Results

For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 5.

7.5.2.2 NHL Study GS-US-313-0124

Study GS-US-313-0124 (NCT01732913) was a Phase 3, randomized, double-blind, placebo-controlled study in previously treated indolent NHL, comparing idelalisib + rituximab to placebo + rituximab. In the control arm, crossover was permitted upon centrally-confirmed disease progression. The trial was terminated early due to safety concerns.

PI3K inhibitor	Trial	Population	Randomization & Treatment	Enrolled	Endpoints
Idelalisib	GS-US-313-0124	R/R indolent NHL[a], excluding rituximab-refractory disease	2:1 Idelalisib + R Placebo + R	Total: 295 Idelalisib + R: 198 Placebo + R: 97	Primary: PFS
[a] FL, MZL, SLL, LPL/WM					

Statistical Analysis Plan

Endpoints:
Primary endpoint: PFS (planned per IRC; analyzed per investigator)
Key secondary: ORR, best % change in lymph node area, CR rate, and OS

Randomization
2:1, stratified by
- Tumor type: FL vs. other
- Tumor burden: high vs. low
- Time since completion of last systemic therapy: <18 months vs. longer

Sample Size
Planned: 375
Enrolled: 295 (198 in idelalisib + R group, 97 in placebo + R group)

- Number of PFS events required for primary analysis: 264
- Target HR = 0.67 (median PFS improvement from 12 months to 18 months)
- Type-I error rate (2-sided): 0.05
- Power: 0.85

The sample size calculation was based on PFS only. There was no pre-planned OS sample size calculation based on appropriate hypothesis testing with sufficient power.

Efficacy Analyses
Due to the early study termination, the prespecified efficacy analyses were not conducted. An analysis of investigator-assessed PFS and OS was conducted using the data that supported the DMC's safety analysis (data cutoff date 15 January 2016). This unplanned analysis (with 61 PFS events, i.e., definitive progression or death) occurred prior to the planned interim analysis (123 PFS events). The Sponsor concluded that the risk of adding idelalisib to rituximab in this population did not outweigh the potential benefit, and terminated the study in accordance with DMC recommendations.

Efficacy Results

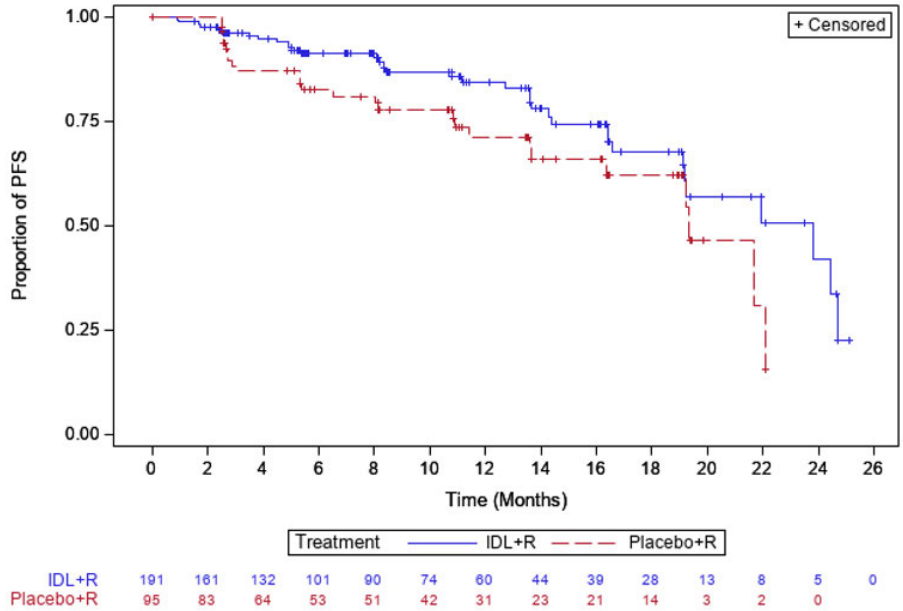
Progression-Free Survival
Investigator-assessed PFS is presented in Table 18 and Figure 16.

Table 18: Summary of Investigator-Assessed PFS, Idelalisib Study GS-US-313-0124

	Idelalisib + Rituximab (N = 191)	Placebo + Rituximab (N = 95)
Events, n (%)	35 (18.3)	26 (27.4)
Disease Progression	28 (14.7)	26 (27.4)
Death	7 (3.7)	0
Censored, n (%)	156 (81.7)	69 (72.6)
Median PFS (months) (95% CI)	23.8 (19.2, 24.7)	19.4 (16.4, 22.1)
Adjusted HR (95% CI) [a]	0.50 (0.29, 0.85)	
Nominal p-value [b]	0.034	
PFS Rate at 24 weeks, % (95% CI)	91.2 (85.2, 94.8)	82.6 (71.9, 89.6)
PFS Rate at 48 weeks, % (95% CI)	85.6 (77.8, 90.9)	73.6 (61.1, 82.7)

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.
[b] Nominal p-value was calculated using the stratified log-rank test.
Data cutoff 5/18/2016
Source: FDA analysis

Figure 16: Kaplan-Meier Curve of Investigator-Assessed PFS, Idelalisib Study GS-US-313-0124



Data cutoff 5/18/2016
Source: FDA analysis

Overall Survival

OS data are shown in Table 19 and Figure 17. The OS results are concerning because there is a potential increase in the risk of death in the idelalisib arm compared with the control arm. There is high variability in the HR estimates, but based on the higher upper bound of the confidence

intervals, the death hazard can be multiple times higher in the experimental arm. We cannot rule out potential harm based on these data. No formal conclusions could be drawn based on the early interim analysis results.

Table 19: Summary of OS, Idelalisib Study GS-US-313-0124

	Idelalisib + Rituximab (N = 191)	**Placebo + Rituximab (N = 95)**
Deaths, n (%)	10 (5.2)	1 (1.1)
Median OS (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI) [a]	4.74 (0.6, 37.12)	
Nominal p-value [b]	0.127	
OS Rate at 6 months, % (95% CI)	96.3 (92.1, 98.4)	98.6 (90.7, 99.8)

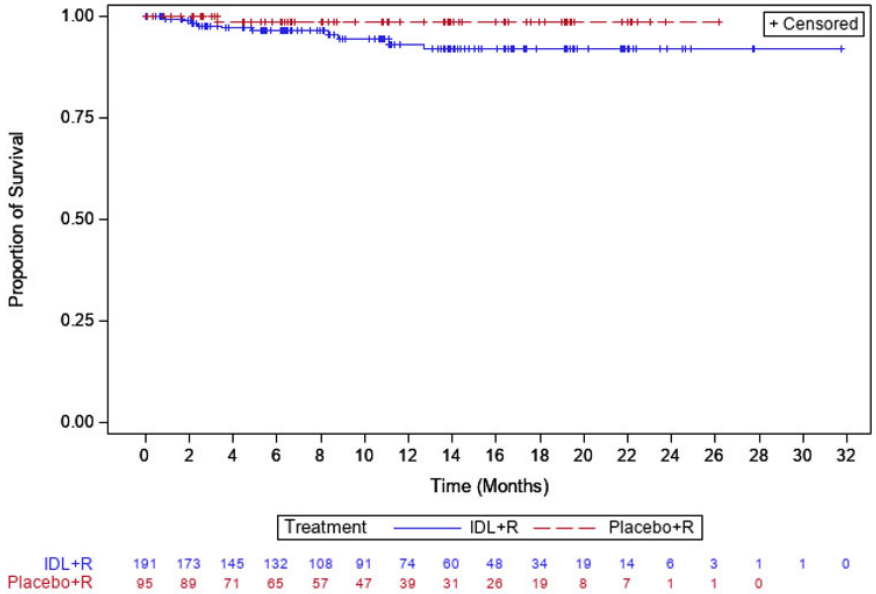
[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.

[b] Nominal p-value was calculated using the stratified log-rank test.

Data cutoff 5/18/2016

Source: FDA analysis

Figure 17: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-313-0124



Data cutoff 5/18/2016

Source: FDA analysis

Safety Results

For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 5.

7.5.2.3 NHL Study GS-US-313-0125

Study GS-US-313-0125 (NCT01732926) was a Phase 3, randomized, double-blind, placebo-controlled study in previously treated indolent NHL, evaluating idelalisib + BR vs. placebo + BR. The study completed enrollment and was terminated early during the follow-up period.

PI3K inhibitor	Trial	Population	Randomization & Treatment	Enrolled	Endpoints
Idelalisib	GS-US-313-0125	R/R indolent NHL [a] excluding bendamustine-refractory disease	2:1 Idelalisib + BR Placebo + BR	Total: 475 Idelalisib + BR: 320 Placebo + BR: 155	Primary: PFS
[a] FL, MZL, SLL, LPL/WM					

Statistical Analysis Plan

Endpoints:
Primary endpoint: PFS (planned per IRC; analyzed per investigator)
Key secondary: ORR, best % change in lymph node area, CR rate, and OS

Randomization
2:1, stratified by:
- Tumor type: FL vs. others
- Tumor burden: high vs. low
- Time since completion of last systemic therapy (<18 months vs. longer)

Sample Size
Planned: 450
Enrolled: 475
- Number of PFS events required for primary analysis: 267
- Target HR = 0.67 (median PFS improvement from 20 months to 30 months)
- Type-I error rate (2-sided): 0.05
- Power: 0.85

The sample size calculation was based on PFS only. There was no pre-planned OS sample size calculation based on appropriate hypothesis testing with sufficient power.

Efficacy Analyses
Due to early study termination, the prespecified efficacy analyses were not conducted. An analysis of investigator-assessed PFS and OS was conducted using the data that supported the DMC's safety analysis (data cutoff 15 January 2016). This unplanned analysis (with 100 PFS events) occurred approximately 4 months prior to the planned interim analysis (134 PFS events). The Sponsor concluded that the risk of adding idelalisib to BR did not justify the potential benefit, and terminated the study in accordance with the DMC recommendation.

Efficacy Results

Progression-Free Survival

The results of investigator-assessed PFS are presented in Table 20 and Figure 18.

Table 20: Summary of Investigator-Assessed PFS, Idelalisib Study GS-US-313-0125

	Idelalisib + BR (N = 320)	Placebo + BR (N = 155)
Events, n (%)	58 (18.1)	42 (27.1)
Disease Progression	37 (11.6)	38 (24.5)
Death	21 (6.6)	4 (2.6)
Censored, n (%)	262 (81.9)	113 (72.9)
Median PFS (months) (95% CI)	NR (25.5, NR)	NR (19.8, NR)
Adjusted HR (95% CI) [a]	0.74 (0.50, 1.10)	
Nominal p-value [b]	0.088	
PFS Rate at 24 weeks, % (95% CI)	92.7 (88.9, 95.2)	94.7 (89.6, 97.3)
PFS Rate at 48 weeks, % (95% CI)	83.2 (77.8, 87.3)	78.7 (70.5, 84.8)

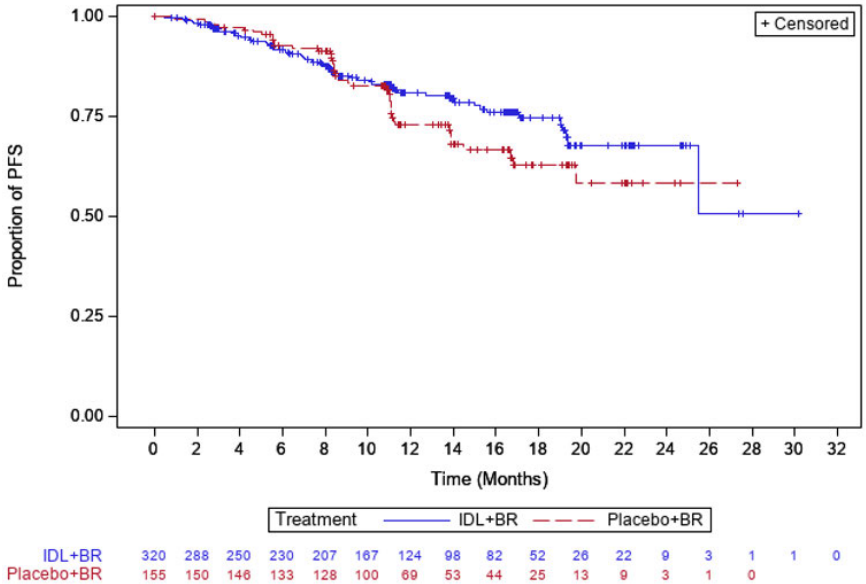
[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.

[b] Nominal p-value was calculated using the stratified log-rank test.

Data cutoff 5/17/2016

Source: FDA analysis

Figure 18: Kaplan-Meier Curve of Investigator-Assessed PFS, Idelalisib Study GS-US-313-0125



Data cutoff 5/17/2016

Source: FDA analysis

Overall Survival

OS data are shown in Table 21 and Figure 19. The OS results are concerning because there is a potential increase in the risk of death in the idelalisib arm. There is high variability in the HR estimates, but given the higher upper bound of the confidence intervals, the death hazard is higher in the experimental arm. We cannot rule out potential harm to patients based on OS data. No formal conclusions could be drawn based on the early interim analysis results.

Table 21: Summary of OS, Idelalisib Study GS-US-313-0125

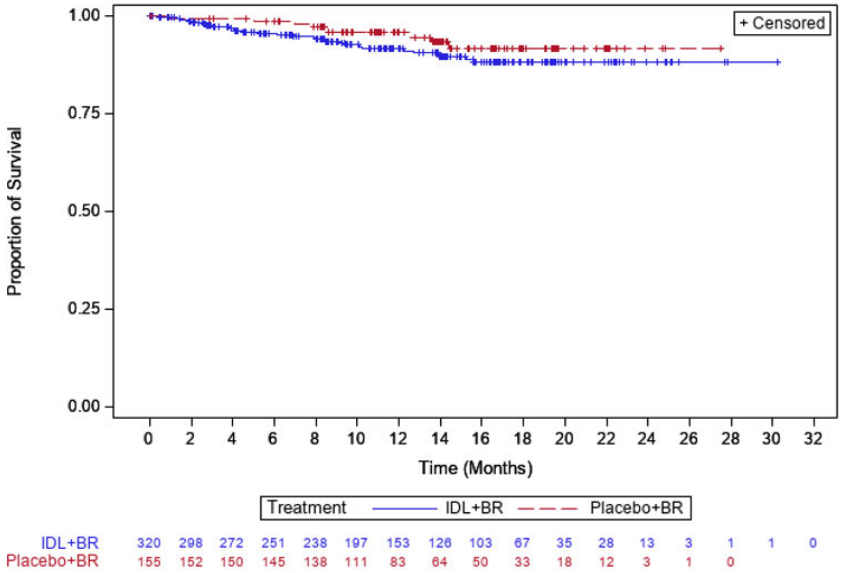
	Idelalisib + BR (N = 320)	**Placebo + BR (N = 155)**
Deaths, n (%)	27 (8.4)	9 (5.8)
Median OS (months) (95% CI)	NR (NR, NR)	NR (NR, NR)
Adjusted HR (95% CI) [a]	1.51 (0.71, 3.23)	
Nominal p-value [b]	0.287	
OS Rate at 3 months (95% CI)	97.7 (95.2, 98.9)	99.3 (95.5, 99.9)
OS Rate at 6 months (95% CI)	95.5 (92.4, 97.4)	98.7 (94.8, 99.7)

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for stratification factors.

[b] Nominal p-value was calculated using the stratified log-rank test.

Data cutoff 5/17/2016
Source: FDA analysis

Figure 19: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-313-0125



Data cutoff 5/17/2016
Source: FDA analysis

Safety Results

For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 5.

7.5.3 Other Trials Not Supporting Registration

7.5.3.1 CLL Study GS-US-312-0115

Study GS-US-312-0115 (NCT01569295) was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial in previously treated CLL, evaluating idelalisib + BR vs. placebo + PR, with a PFS primary endpoint. The trial was stopped at an interim efficacy analysis at 90% of total PFS events.

Statistical Analysis Plan

Endpoints:
Primary: PFS per IRC
Key secondary: ORR, lymph node response rate, OS, and CR rate

Randomization
1:1, stratified by:
- 17p deletion and/or TP53 mutation in CLL cells: either vs. neither (or indeterminate)
- IGHV mutation status: unmutated (or IGHV3-21) vs. mutated (or indeterminate)
- Disease status: refractory (progression < 6 months from completion of prior therapy) vs. relapsed

Sample Size
Planned: 390
Analyzed: 416 (207 in idelalisib + BR arm, 209 in placebo + BR arm)
- PFS events required for primary analysis: 260
- Difference to be detected: HR = 0.67 (Median PFS: 15 months in the placebo + BR group vs. 22.5 months in the idelalisib + BR group)
- Type-I error rate (2-sided): 0.05
- Power: 0.9

The ~135 deaths expected at the time of final analysis would provide >95% power to detect an HR of 0.45 for OS based on a log-rank test at a 2-sided alpha level of 0.032.

Interim Analysis
- First IA at 75% of PFS events (June 2015 data cutoff)
- Unplanned second IA (October 2015 data cutoff); study stopped early and treatment unblinded November 2015

Multiplicity
- Overall type I error at a 2-sided significance level of 0.05
- If primary hypothesis was rejected, key secondary endpoints were sequentially tested (2-sided significance level, 0.032)

Efficacy Results

Primary Endpoint: PFS

PFS per IRC (ITT analysis) is presented in Table 22 and Figure 20. The study met its primary objective.

Table 22: Summary of PFS per IRC, Idelalisib Study GS-US-313-0115

	Idelalisib + BR (N = 207)	**Placebo + BR (N = 209)**
Events, n (%)	84 (40.6)	149 (71.3)
Disease Progression	60 (29.0)	130 (62.2)
Death	24 (11.6)	19 (9.1)
Censored, n (%)	71 (40.8)	30 (34.5)
Median PFS (months) (95% CI)	20.8 (16.6, 26.4)	11.1 (8.9, 11.1)
Adjusted HR (95% CI) [a]	0.33 (0.26, 0.45)	
P-value [b]	0.0001	

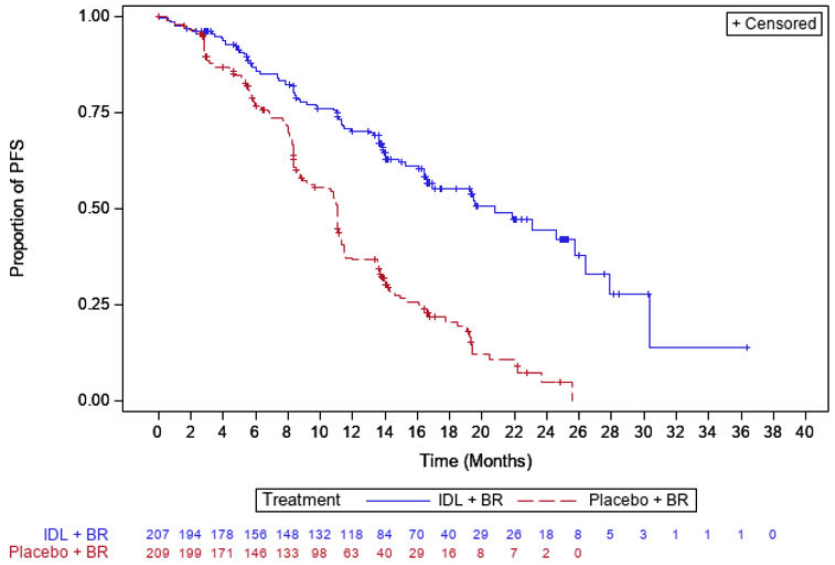
[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for stratification factors.

[b] P-value was calculated using the stratified log-rank test.

Data cutoff 10/7/2015

Source: FDA analysis

Figure 20: Kaplan-Meier Curve of PFS per IRC, Idelalisib Study GS-US-313-0115



Data cutoff 10/7/2015

Source: FDA analysis

Overall Survival

Approximately 135 total deaths were expected at the time of the final analysis. As of the data cutoff of October 7, 2015, 75% OS events had occurred with an adjusted HR = 0.62 (95% CI: 0.42, 0.92; nominal p-value from stratified log-rank test = 0.031). The prespecified p-value boundary was 0.032. However, according to the FDA statistical review conducted in November 2017, FDA cannot confirm that the OS results met the pre-specified criteria due to the following considerations:

1. The OS IA plan was not adequate due to lack of pre-specified numbers and timing of OS IAs. It was not clear why the analysis was performed on that date.
2. The results were very sensitive to the timing of follow-up. If more patients had relatively longer follow-up, the p-value would have been higher.

A follow-up analysis of OS was conducted when 91% of OS events had occurred (data cutoff May 2, 2016). These results are presented in Table 23 and Figure 21. Because this IA was not pre-specified, the OS results are considered exploratory and descriptive only. No formal conclusions could be drawn based on the OS results.

Table 23: Summary of OS, Idelalisib Study GS-US-313-0115

	Idelalisib + BR (N = 207)	**Placebo + BR (N = 209)**
Deaths, n (%)	53 (25.6)	70 (33.5)
Median OS (months) (95% CI)	NR (NR, NR)	40.6 (31.6, NR)
Adjusted HR (95% CI) [a]	0.67 (0.47, 0.96)	
Nominal p-value [b]	0.0364	

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors.

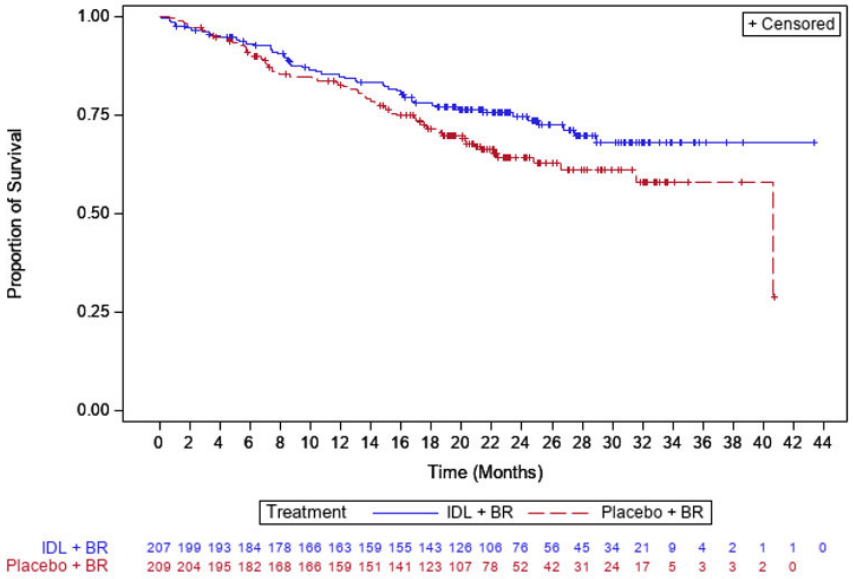
[b] P-value was calculated using the stratified log-rank test.

Abbreviations: NR, not reached

Data cutoff 5/2/2016

Source: FDA analysis

Figure 21: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-313-0115



Data cutoff 5/2/2016
Source: FDA analysis

Safety Results

For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 6.

7.5.3.2 CLL Study GS-US-312-0119

Study GS-US-312-0119 (NCT01659021) was a phase 3 randomized, open-label study evaluating idelalisib + ofatumumab vs. ofatumumab alone for previously treated CLL. The study demonstrated a statistically significant improvement in PFS with the addition of idelalisib.

Statistical Analysis Plan

Endpoints:
Primary: PFS per IRC
Key secondary: ORR, lymph node response rate, OS, PFS in 17p deletion and/or TP53 mutation subgroup, and CR rate

Randomization
2:1, stratified by:
- 17p deletion and/or TP53 mutation: either vs. neither (or indeterminate)
- IGHV mutation: unmutated (or IGHV3-21) vs. mutated (or indeterminate)
- Disease status: refractory to last prior therapy vs. relapsed

Sample Size
Planned: 255

Analyzed for efficacy: 261 (174 assigned to idelalisib + ofatumumab, 87 to ofatumumab alone)
- Number of PFS events required for primary analysis: 129
- Difference to be detected: HR = 0.57 (Median PFS: 8 months in control arm vs. 14 months in experimental arm)
- Type-I error rate (2-sided): 0.05
- Power: 0.85

Approximately 65 deaths were expected at the time of final analysis. This provided approximately 85% power to detect an OS HR of 0.45 (based on a log-rank test and 2-sided alpha level of 0.03).

Interim Analyses
- One IA was conducted at 75% of PFS events and the study continued until final analysis. The study met its primary objective at final analysis. The updated analysis was based on the data with 15.5 months of additional follow-up.

Multiplicity
- Overall type I error at a 2-sided significance level of 0.05
- If primary hypothesis was rejected, key secondary endpoints were sequentially tested at the 2-sided significance level of 0.03.

Efficacy Results

Progression-Free Survival

The study demonstrated a statistically significant improvement in PFS with idelalisib + ofatumumab vs. ofatumumab alone in patients with previously treated CLL. The final analysis of PFS by IRC (ITT) is presented in Table 24 and Figure 22. The adjusted HR was 0.24 (95% CI: 0.17, 0.35), confirming that the study met its primary objective.

Table 24: Summary of PFS by IRC, Idelalisib Study GS-US-313-0119

	Idelalisib + Ofatumumab (N = 174)	**Ofatumumab (N = 87)**
Events, n (%)	103 (59.2)	57 (65.5)
Disease Progression	76 (43.7)	51 (58.6)
Death	27 (15.5)	6 (6.9)
Censored, n (%)	71 (40.8)	30 (34.5)
Median PFS (months) (95% CI)	16.6 (13.6, 21.7)	8.0 (5.7, 8.2)
Adjusted HR (95% CI) [a]	0.24 (0.17, 0.35)	
P-value [b]	0.0001	

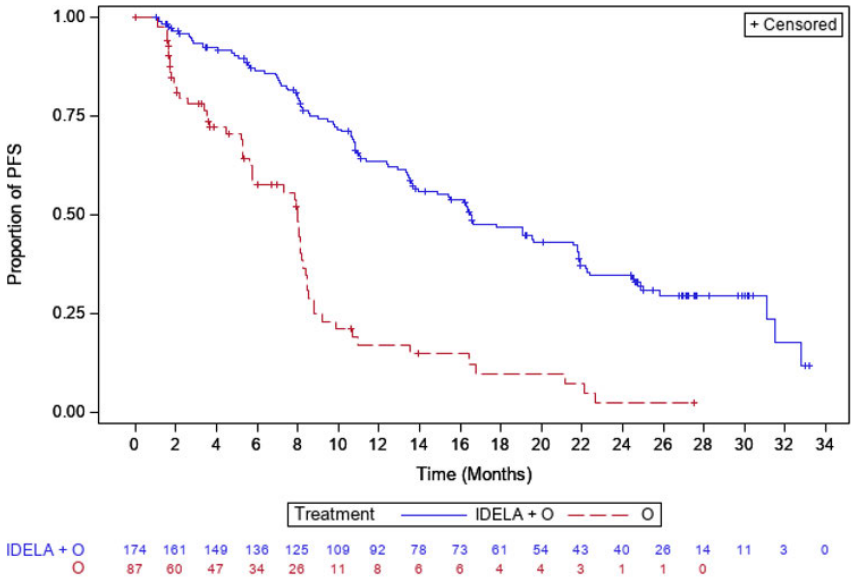
[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for stratification factors.

[b] P-value was calculated using the stratified log-rank test. The significance level was 0.018.

Data cutoff 5/2/2016

Source: FDA analysis

Figure 22: Kaplan-Meier Curve of PFS by IRC, Idelalisib Study GS-US-313-0119



Data cutoff 5/2/2016
Source: FDA analysis

Overall Survival

OS data are presented in Table 25 and Figure 23. The difference in OS between treatment arms was not statistically significant.

Table 25: Summary of OS, Idelalisib Study GS-US-313-0119

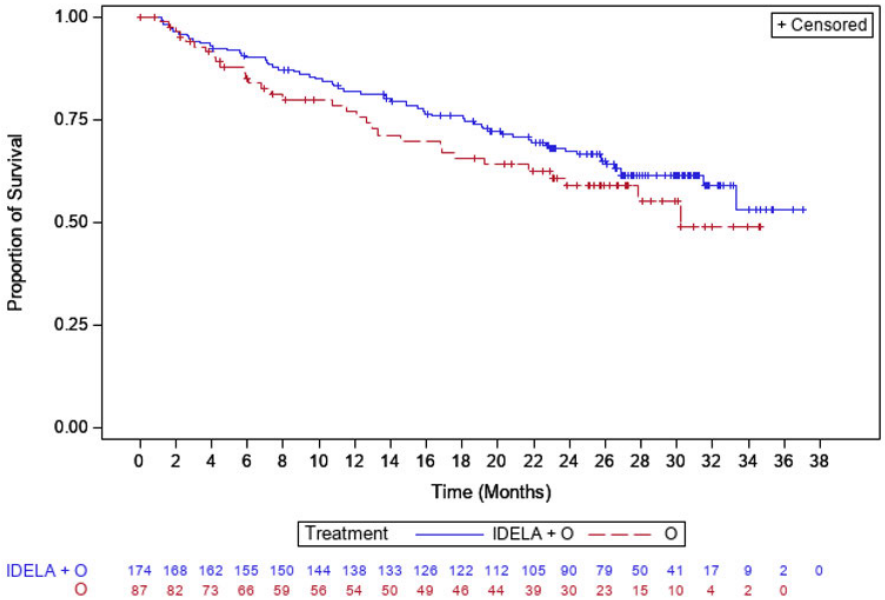
	Idelalisib + ofatumumab (N = 174)	**Ofatumumab (N = 87)**
Deaths, n (%)	63 (36.2)	32 (36.8)
Censored, n (%)	111 (63.8)	55 (63.2)
Median OS (months) (95% CI)	NR (31.5, NR)	30.2 (23.0, NR)
Adjusted HR (95% CI) [a]	0.74 (0.48, 1.14)	
Nominal p-value [b]	0.1995	

[a] HR and 95% CIs are calculated using the Cox proportional hazards model, adjusted for randomization stratification factors

[b] P-value was calculated using the stratified log-rank test.

Data cutoff 5/2/2016
Source: FDA analysis

Figure 23: Kaplan-Meier Curve of OS, Idelalisib Study GS-US-313-0119



Data cutoff 5/2/2016
Source: FDA analysis

Safety Results
For a summary of safety and selected toxicities, see Section 3.2.1.1, Table 6.

7.6 Copanlisib Clinical Trials

7.6.1 CHRONOS-1 – Follicular Lymphoma

CHRONOS-1 (NCT01660451) is a single-arm, multicenter, phase 2 clinical trial of copanlisib monotherapy that supported the accelerated approval in FL. The trial included 104 patients with relapsed FL after ≥2 therapies, including rituximab and an alkylating agent; 34% received 2 prior lines of therapy and 36% received 3 prior lines. Prior systemic therapies included chemoimmunotherapy (89%), chemotherapy alone (41%), and anti-CD20 therapy alone (37%). In FL, the IRC-assessed ORR was 59% (95% CI: 49, 68) with 44% PR and 14% CR. The estimated median DOR was 12.2 months (range, 0 to 22.6).

Safety Results
For a summary of safety and selected toxicities with copanlisib monotherapy, see Section 3.2.2.

7.6.2 CHRONOS-3 – Indolent NHL

CHRONOS-3 (NCT02367040) is a randomized, double-blind, placebo-controlled phase 3 trial comparing copanlisib + rituximab vs. placebo + rituximab in relapsed indolent NHL.[4] This trial is the basis for a supplemental NDA that was submitted in May 2021 and ultimately withdrawn in December 2021.

PI3Ki	Trial	Population	Randomization & Treatment	Enrolled	Endpoints
Copanlisib	CHRONOS-3	Relapsed iNHL[a] Progression-free or treatment-free ≥12 months after last CD20 therapy, or Unwilling or considered unfit to receive for chemo and progression-free or treatment-free ≥6 months after last CD20 therapy	2:1 [b] Copanlisib + R Placebo + R	Total: 458 Copanlisib + R: 307 Placebo + R: 151	Primary: PFS per IRC Key secondary: PFS in FL/MZL combined, ORR in FL/MZL, PROs
[a] FL, MZL, SLL, WM [b] Randomization stratified by: Histology (FL vs. other), progression-free or treatment-free for ≥12 months vs. unfit for chemotherapy, bulky disease, and prior PI3K inhibitor					

Efficacy Results

Progression-Free Survival

The study met its primary endpoint. PFS results are shown in Table 26 and Figure 24.

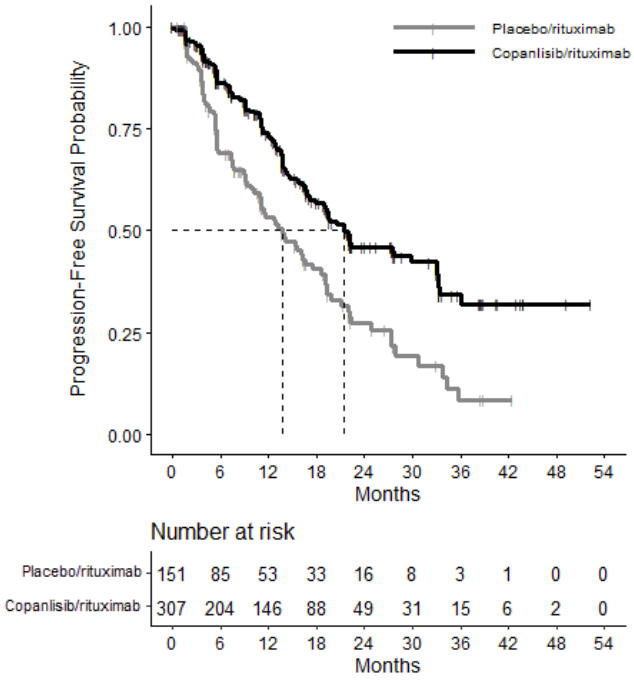
Table 26: PFS per IRC in CHRONOS-3 by Histology (Original Data)

	Indolent NHL (ITT)		FL		MZL	
	Copanlisib + rituximab N = 307	Placebo + rituximab N = 151	Copanlisib + rituximab N = 184	Placebo + rituximab N = 91	Copanlisib + rituximab N = 66	Placebo + rituximab N = 29
Events, n (%)	118 (38)	87 (58)	69 (38)	52 (57)	22 (33)	15 (52)
Progression	102 (33)	86 (57)	59 (32)	52 (57)	20 (30)	15 (52)
Death	16 (5)	1 (1)	10 (5)	0 (0)	2 (3)	0 (0)
Median PFS, months (95% CI)	21.5 (17.8, 33.0)	13.8 (10.2, 17.5)	22.2 (17.8, 33.1)	18.7 (10.2, 21.1)	22.1 (13.8, NE)	11.5 (5.6, 16.3)
HR (95% CI)	0.52 (0.39, 0.69)		0.58 (0.40, 0.83)		0.48 (0.25, 0.92)	

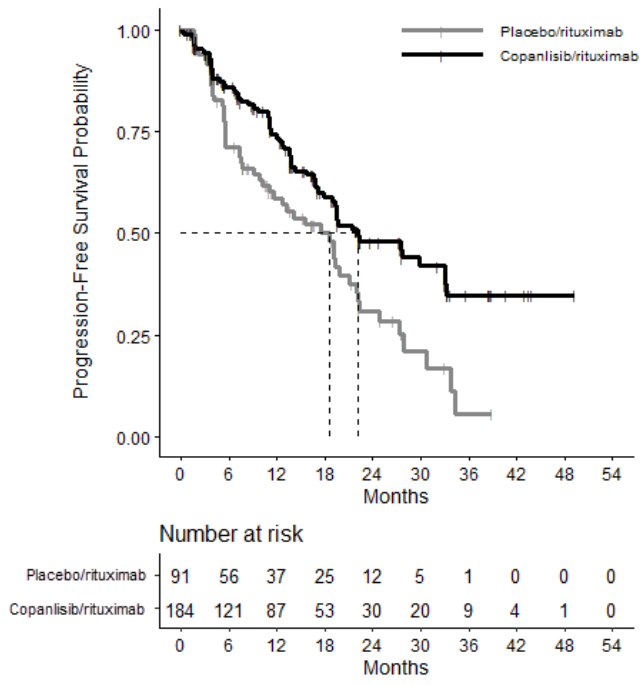
Abbreviations: NE, not estimable.
Data cutoff: August 2020.
Source: FDA analysis.

Figure 24: Kaplan-Meier Curves of PFS per IRC in CHRONOS-3

A) Indolent NHL (ITT)



B) FL subset



Data cutoff: August 2020
Source: FDA analysis

Overall Survival

An updated analysis of OS was performed and raised concern for a potentially higher risk of death in the copanlisib + rituximab arm (Table 27 and Figure 25).

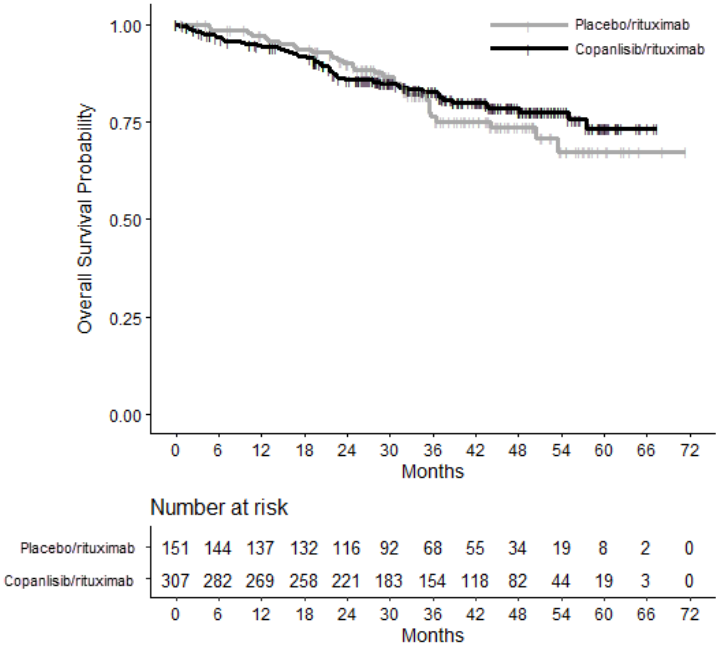
Table 27: OS in CHRONOS-3 by Histology (Updated Data)

	Indolent NHL (ITT)		FL		MZL	
	Copanlisib + rituximab N = 307	Placebo + rituximab N = 151	Copanlisib + rituximab N = 184	Placebo + rituximab N = 91	Copanlisib + rituximab N = 66	Placebo + rituximab N = 29
Deaths, n (%)	56 (18%)	32 (21%)	30 (16%)	16 (18%)	13 (20%)	5 (17%)
Median OS (95% CI)	NE	NE	NE	NE	NE	NE
HR (95% CI)	0.87 (0.57, 1.35)		0.95 (0.52, 1.74)		1.07 (0.38, 3.00)	
OS Rate at 1 y, % (95% CI)	94 (91, 96)	97 (93, 99)	93 (88, 96)	98 (91, 99)	97 (88, 99)	96 (76, 99)
Rate Difference at 1 y, % (95% CI)	-3 (-7, 2)		-5 (-11, 2)		0.5 (-9, 16)	
OS Rate at 2 y, % (95% CI)	86 (81, 89)	90 (84, 94)	87 (81, 91)	93 (84, 97)	86 (74, 93)	89 (69, 96)
Rate Difference at 2 y, % (95% CI)	-4 (-11, 3)		-6 (-14, 4)		-3 (-19, 19)	

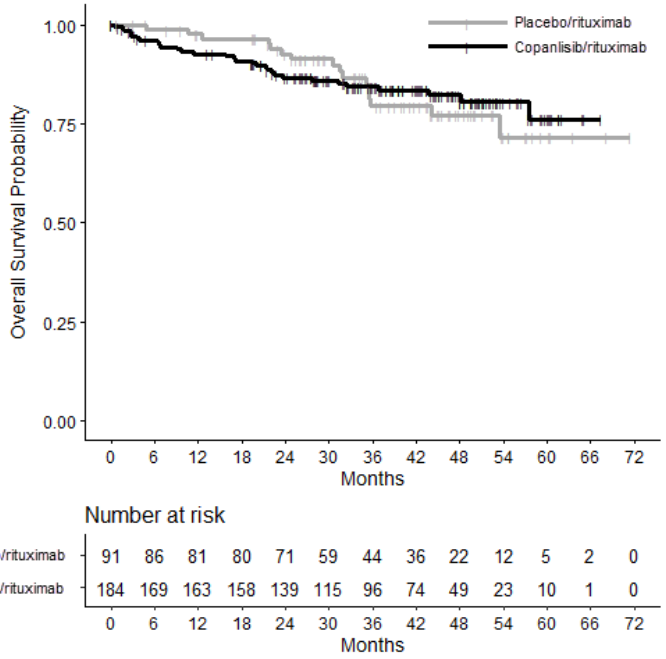
Abbreviations: NE, non-estimable
Data cutoff: August 2021
Source: FDA analysis, unstratified models

Figure 25: Kaplan-Meier Curves of OS in CHRONOS-3 (Updated Data)

A) Indolent NHL (ITT)



B) FL subset



Data cutoff: August 2021
Source: FDA analysis

OS was an exploratory endpoint in CHRONOS-3. No OS hypothesis testing, including power calculations or anticipated information fraction, was prespecified in the statistical analysis plan. HR values exceeding one indicate higher risk of death for the copanlisib/rituximab group.

The confidence intervals for the OS HR are wide due to the low number of observed deaths. Additionally, the upper bounds are above one, indicating potential for a higher risk of death for patients in the copanlisib + rituximab group.

The HR was estimated with the Cox proportional hazards model, which relies on a proportional hazards assumption. Crossing Kaplan-Meier curves and goodness-of-fit tests suggest that the proportional hazards assumption may not hold in the indolent NHL and FL populations. If the proportional hazards assumption does not hold, interpreting the HR may be challenging.

The median OS was non-estimable due to the low number of observed deaths. The percentage of patients surviving at the first and second year after randomization was estimated. Confidence intervals for the difference in % survival are wide due to the low number of observed deaths. A lower percentage of patients survived 2 years after randomization in the copanlisib + rituximab group compared to the placebo + rituximab group (Table 27).

While the wide confidence intervals of the OS HR and the survival percentage difference indicated estimate uncertainty, potential harm to patients in the copanlisib + rituximab arm cannot be ruled out.

Safety Results
For a summary of safety and selected toxicities, see Section 3.2.1.2, Table 7.

7.7 Duvelisib Clinical Trials

7.7.1 CLL Study IPI-145-07 (DUO)

The DUO trial (IPI-145-07, NCT02004522) is a phase 3 randomized, open-label trial that supported the regular approval of duvelisib in R/R CLL after ≥2 prior therapies. The trial evaluated duvelisib vs. ofatumumab in R/R CLL after ≥1 prior therapy, randomizing patients to received either duvelisib 25 mg orally BID until disease progression or unacceptable toxicity or ofatumumab for 7 cycles.

Statistical Analysis Plan

Endpoints:
Primary: PFS per IRC
Key secondary: ORR, OS

Randomization
1:1 to duvelisib or ofatumumab, stratified by:
- 17p deletion status
- Refractory disease or early relapse to purine analog-based therapy (yes/no)
- Grade 4 neutropenia or thrombocytopenia at baseline (yes/no)

Sample size
Planned: 300
Analyzed: 319

- Number of PFS events required for primary analysis: 185
- Target HR = 0.60 (median PFS improvement from 9 months to 15 months)
- Type-I error rate (1-sided): 0.025
- Power: 93%

Sample size was based on PFS only. There was no pre-planned OS sample size calculation based on appropriate hypothesis testing with sufficient power.

Efficacy Results

Progression-Free Survival
The primary PFS analysis (data cutoff, May 2017) is shown in Table 28 and Figure 26. The estimated PFS HR was 0.52 (95% CI: 0.39, 0.69) demonstrating a statistically significant improvement in PFS with duvelisib, translating into an estimated 3.4 month improvement in median PFS.

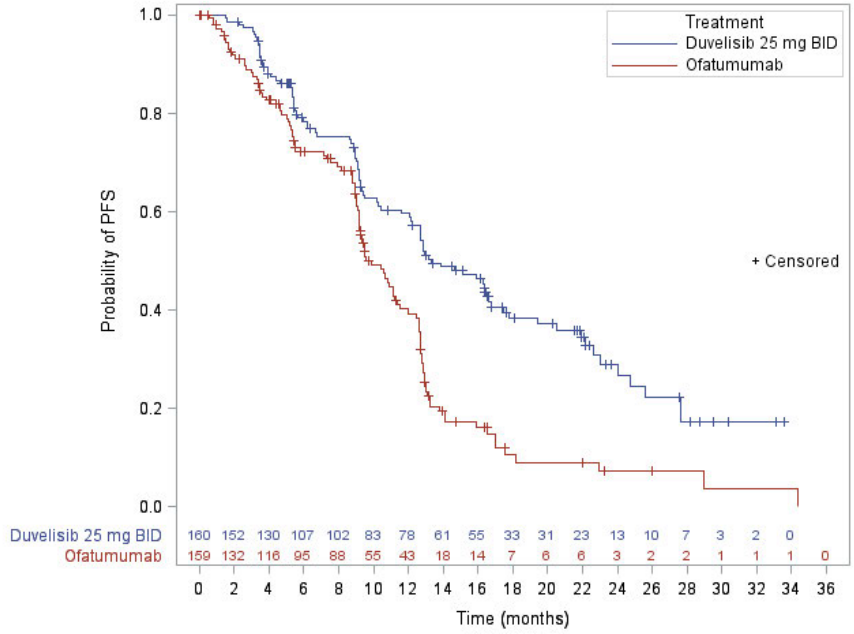
In patients with ≥2 prior lines (the approved indication), the PFS HR was 0.40 (standard error [SE], 0.2); the median PFS (SE) was 16.5 months (2.1) with duvelisib and 9.1 months (0.5) with ofatumumab (source: USPI).

Table 28: PFS per IRC (ITT Population), Duvelisib DUO Study – Primary Analysis

	Duvelisib (N = 160)	**Ofatumumab (N = 159)**
Events, n (%)	93 (58.0)	110 (69.2)
Progression	74 (46.3)	101 (63.5)
Death	19 (11.9)	9 (5.7)
Censored, n (%)	67 (41.9)	49 (30.8)
Median PFS (months) (95% CI)	13.3 (12.1, 16.8)	9.9 (9.2, 11.3)
HR (95% CI) [a]	0.52 (0.39, 0.69)	
p-value [b]	<0.0001	

[a] Stratified Cox proportional hazards model.
[b] One-sided stratified log-rank test.
Data cutoff 5/19/2017
Source: FDA analysis

Figure 26: Kaplan-Meier Curves of PFS per IRC (ITT Population), Duvelisib DUO Study – Primary Analysis



Data cutoff 5/19/2017
Source: NDA 211155 Multidisciplinary Review at Drugs@FDA

In the final analysis of DUO, PFS per IRC was not re-analyzed. A sensitivity analysis of PFS per investigator (Table 29) was consistent with the primary analysis.

Table 29: Summary of PFS per Investigator (ITT Population), Duvelisib DUO Study – Sensitivity Analysis

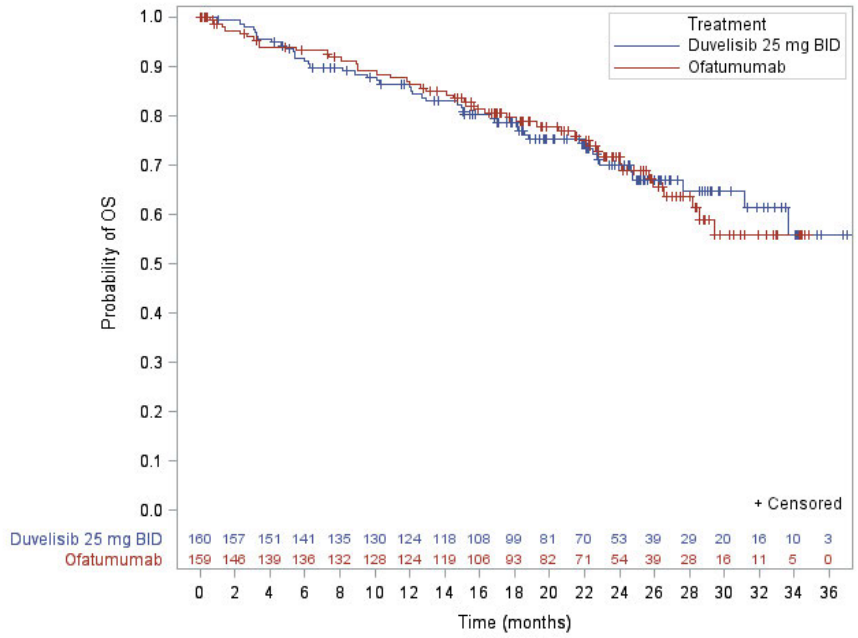
	Duvelisib (N = 160)	**Ofatumumab (N = 159)**
Events, n (%)	84 (52.5)	131 (82.4)
Progression	63 (39.4)	119 (74.8)
Death before progression	21 (13.1)	12 (7.6)
Censored, n (%)	76 (47.5)	28 (17.6)
Median PFS (months) (95% CI)	17.6 (15.0, 22.0)	9.7 (9.3, 11.4)
HR (95% CI) [a]	0.40 (0.30, 0.54)	
Nominal p-value [b]	<0.0001	

[a] Stratified Cox proportional hazards model.
[b] One-sided stratified log-rank test.
Data cutoff 6/22/2020
Source: FDA analysis

Key Secondary Endpoint – Overall Survival

In the ITT population, at the time of primary analysis, 90 patients (57%, 90/159) randomized to ofatumumab had crossed over to receive duvelisib and 8 patients (5%, 8/160) randomized to duvelisib had crossed over to received ofatumumab. An interim analysis of OS, conducted at the time of the primary PFS analysis (May 2017), was immature, and the median OS was not estimable in either arm (Figure 27). The OS HR was 0.99 (0.65, 1.50) with a nominal p-value of 0.48.

Figure 27: Kaplan-Meier Curves for OS (ITT Population), Duvelisib DUO Study – Primary Analysis



Data cutoff 5/19/2017
Source: NDA 211155 Multidisciplinary review at Drugs@FDA

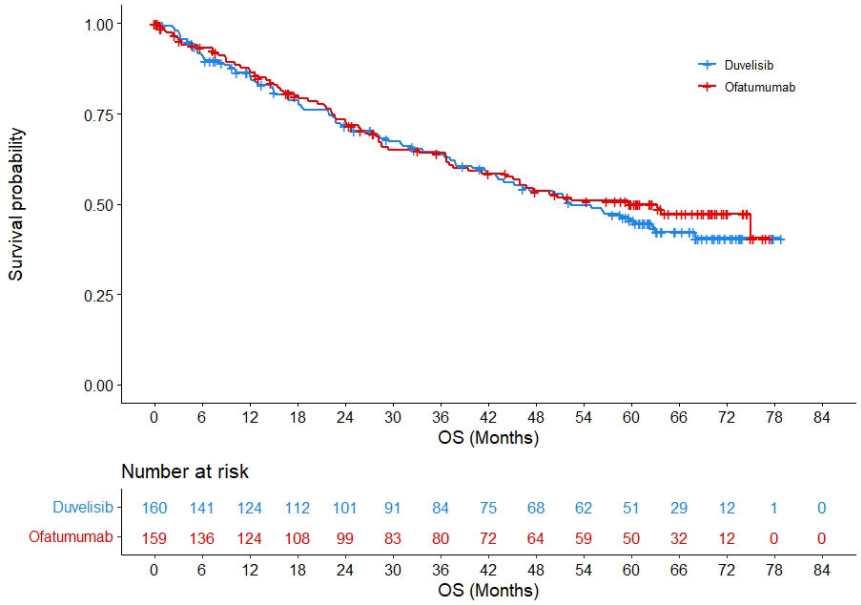
The final OS study results, with an estimated median follow-up time of 63 months in both arms, are summarized in Table 30. Kaplan-Meier curves of OS for the ITT population are shown in Figure 28; for Kaplan-Meier curves of OS for patients with ≥2 prior therapies, refer to Section 3.1.1.3, Figure 3. There is high variability in the HR estimates, but the upper bounds of the confidence intervals cannot rule out potential harm to patients in the duvelisib arm.

Table 30: Summary of OS, Duvelisib DUO Study – Updated Analyses

	ITT Population (≥1 prior therapy)		Approved Indication (≥2 prior therapies)	
	Duvelisib (N = 160)	Ofatumumab (N = 159)	Duvelisib (N = 95)	Ofatumumab (N = 101)
Deaths, n (%)	80 (50.0)	70 (44.0)	53 (55.8)	49 (48.5)
Median OS, months (95% CI)	52.3 (41.8, 68.0)	63.3 (41.2, NE)	43.9 (32.4, 56.5)	46.8 (28.6, 74.9)
HR for OS (95% CI) [a]	1.09 (0.79, 1.51)		1.06 (0.71, 1.58)	
Nominal p-value [b]	0.59		0.78	
OS rate (95% CI)				
1 year	0.86 (0.79, 0.90)	0.86 (0.80, 0.91)	0.86 (0.76, 0.91)	0.80 (0.70, 0.87)
2 years	0.72 (0.64, 0.78)	0.73 (0.65, 0.80)	0.70 (0.59, 0.78)	0.66 (0.55, 0.75)
3 years	0.64 (0.55, 0.71)	0.64 (0.55, 0.71)	0.59 (0.48, 0.69)	0.60 (0.49, 0.69)
4 years	0.54 (0.45, 0.61)	0.54 (0.46, 0.62)	0.46 (0.34, 0.56)	0.48 (0.36, 0.58)
5 years	0.46 (0.37, 0.54)	0.50 (0.41, 0.58)	0.37 (0.27, 0.48)	0.45 (0.34, 0.55)

[a] Stratified Cox proportional hazards model.
[b] Two-sided stratified log-rank test.
Source: FDA analysis. Data cutoff 6/22/2020

Figure 28 Kaplan-Meier Curves for OS (ITT Population), Duvelisib DUO Study – Updated Analysis



Data cutoff 6/22/2020
Source: FDA analysis.

Safety Results
For a summary of safety and selected toxicities, see Section 3.2.1.3, Table 8.

7.7.2 NHL Study IPI-145-06

Study IPI-145-06 (NCT01882803) is a single-arm, multicenter, open-label trial of duvelisib monotherapy, dosed at 25 mg BID, that supported the accelerated approval in FL. The study included 83 patients with FL refractory to rituximab and to either chemotherapy or radioimmunotherapy.

Efficacy was based on IRC-assessed ORR and DOR. Patients had a median of 3 prior lines of therapy (range: 1 to 10). ORR was 42% with 41% PR and 1% CR. Of patients achieving response (n=35), 43% maintained a response at 6 months and 17% maintained a response at 12 months. DOR ranged from 0+ to 41.9+ months (source: USPI).

Safety Results
For a summary of safety and selected toxicities of duvelisib monotherapy, see Section 3.2.2.

7.8 Umbralisib Clinical Trials

7.8.1 NHL Study UTX-TGR-205

Study UTX-TGR-205 (NCT02793583) is an open-label, multicenter, single-arm trial of umbralisib monotherapy (800 mg QD) that supported the accelerated approvals in R/R FL and MZL. The primary endpoint was ORR per IRC.

FL: The trial enrolled patients with R/R FL after ≥2 systemic therapies, including an anti-CD20 monoclonal antibody and alkylating agent. Of 117 patients with FL evaluated, the median number of prior lines of therapy was 3 (range: 1 to 10), with 36% of patients having refractory disease to last therapy. The ORR was 43% (95% CI: 34, 52) with 39% PR and 3% CR. The estimated median DOR was 11.1 months (95% CI: 8.3, 16.4), with range of 0+ to 20.9+ months.

MZL: The trial enrolled patients with R/R MZL after ≥1 systemic therapy, including an anti-CD20 monoclonal antibody. Of 69 patients with MZL evaluated (38 extranodal, 20 nodal, 11 splenic), the median number of prior lines of therapy was 2 (range: 1 to 6), with 26% of patients having refractory disease to last therapy. The ORR was 49% (95% CI: 37, 62) with 33% PR and 16% CR. The median DOR was not reached (95% CI: 9.3 months, NE); DOR ranged from 0+ to 21.8+ months.

Safety Results
For a summary of safety and selected toxicities with umbralisib monotherapy, see Section 3.2.2.

7.8.2 UNITY-CLL

The UNITY-CLL trial is the subject of the ODAC meeting on April 22, 2022.

Briefly, the UNITY-CLL trial (NCT02612311) is a randomized (1:1), multicenter, actively-controlled trial that evaluated ublituximab in combination with umbralisib (U2) compared to obinutuzumab plus chlorambucil (GC) in patients with treatment naïve and relapsed or refractory CLL.[5] The primary endpoint was PFS per IRC. Randomization was stratified according to 17p deletion and treatment status (treatment-naive vs. previously treated).

The UNITY-CLL trial included ublituximab and umbralisib monotherapy arms to support an evaluation of contribution of effect. Patients were initially randomized 1:1:1:1 to Arms A to D as listed below. Following the establishment of contribution of effect, subsequent patients were randomized 1:1 to U2 or GC.

Treatments were administered as follows:

- Ublituximab and Umbralisib (Arm A)
  - Ublituximab: Administered at 150 mg on Day 1, 750 mg on Day 2, and 900 mg on Day 8 and 15 in Cycle 1, 900 mg on Day 1 for Cycles 2 to 6, and 900 mg on Day 1 every 3 cycles beyond Cycle 6 until progressive disease or unacceptable toxicity.
  - Umbralisib: 800 mg orally once daily continuously until progressive disease or unacceptable toxicity.
- Obinutuzumab and Chlorambucil (Arm B)
  - Obinutuzumab: Administered at 100 mg on Day 1, 750 mg on Day 2, and 1,000 mg on Day 8 and 15 in Cycle 1, and 1,000 mg on Day 1 for Cycles 2 to 6.
  - Chlorambucil: 0.5 mg/kg on Day 1 and 15 of Cycles 1 to 6 and obinutuzumab 100 mg on Day 1, 750 mg on Day 2, and 1,000 mg on Day 8 and 15 in Cycle 1, and 1,000 mg on Day 1 for Cycles 2 to 6.
- Ublituximab (Arm C)
  - Administered at 150 mg on Day 1, 750 mg on Day 2, and 900 mg on Day 8 and 15 in Cycle 1, 900 mg on Day 1 for Cycles 2 to 6, and 900 mg on Day 1 every 3 cycles beyond Cycle 6 until progressive disease or unacceptable toxicity.
- Umbralisib (Arm D)
  - 800 mg orally once daily continuously until progressive disease or unacceptable toxicity.

Progression-free survival

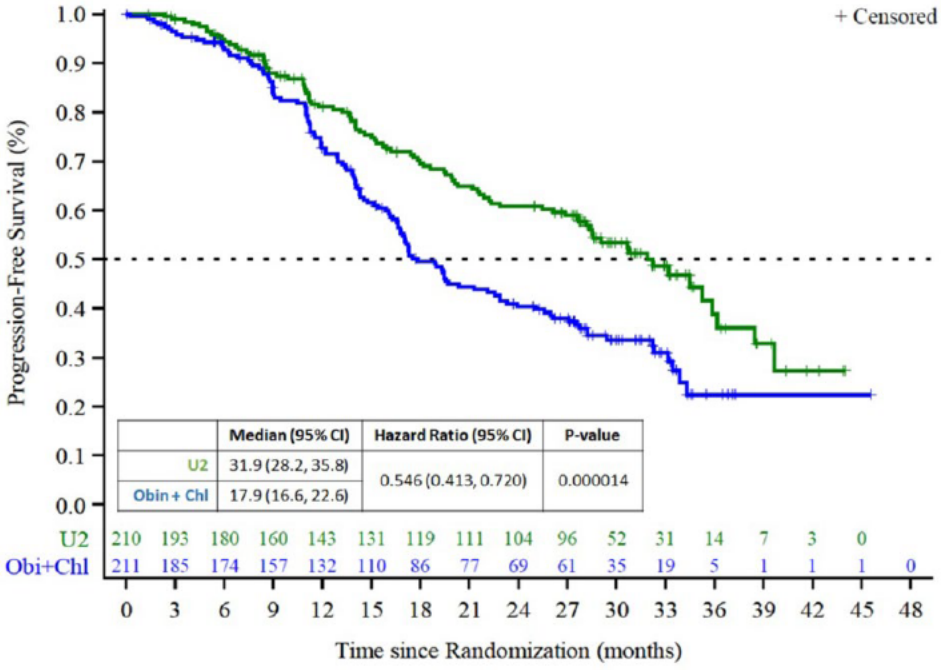
PFS by IRC is shown in Table 31 and Figure 29. The study met its primary objective, demonstrating a statistically significant improvement in PFS in favor of U2.

Table 31: Summary of PFS per IRC in UNITY-CLL (ITT Population)

	U2 N = 210	GC N = 211
Median PFS (95% CI), months	31.9 (28.2, 35.8)	17.9 (16.6, 22.6)
Hazard Ratio (95% CI)	0.546 (0.413, 0.720)	
p-value	<0.0001	

Abbreviations: GC, obinutuzumab and chlorambucil; U2, ublituximab and umbralisib
Source: Gribben JG et al. 2020[5]

Figure 29: Kaplan-Meier Curves for PFS per IRC in UNITY-CLL (ITT Population)



Abbreviations: Obin, obinutuzumab; Chl, chlorambucil
Source: Gribben JG et al. 2020[5]

Overall survival

The overall survival data with UNITY-CLL will be discussed at the ODAC meeting on April 22, 2022.

Safety Results

The safety data from UNITY-CLL will be discussed at the ODAC meeting on April 22, 2022.

7.9 FDA-Approved Treatment Options for Patients with Indolent NHL and CLL

Table 32: FDA-Approved Therapies for Indolent NHL and CLL

Drug/Combination	Initial Approval	Current Indication(s)
Chlorambucil	1957	Treatment of chronic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant FL, and Hodgkin's disease
Cyclophosphamide	1959	Treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma
Vincristine	1963	In combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas
Doxorubicin	1974	Treatment of Hodgkin lymphoma and NHL
Fludarabine	1991	Adult patients with B-cell CLL whose disease has not responded to or has progressed during or after treatment with at least one alkylating-agents containing regimen
Rituximab and **Rituximab Hycela**	1997 2017	Adult patients with NHL • Relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL as a single agent • Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy • Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy
		Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide
Ibritumomab tiuxetan	2002	Treatment of adult patients with relapsed or refractory, low-grade or follicular B-cell NHL
		Treatment of adult patients with previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy
Lenalidomide	2005 ¥	Treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib
		In combination with a rituximab product, is indicated for the treatment of adult patients with previously treated FL
		In combination with a rituximab product, is indicated for the treatment of adult patients with previously treated MZL

Drug/Combination	Initial Approval	Current Indication(s)
Bendamustine	2008	Treatment of CLL
		Treatment of indolent B-cell NHL that has progressed during or within six months of treatment with a rituximab-containing regimen.
Ofatumumab	2009	Treatment of CLL • In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate • In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL • For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL • For the treatment of patients with CLL refractory to fludarabine and alemtuzumab
Obinutuzumab	2013	In combination with chlorambucil, for the treatment of patients with previously untreated CLL
		In combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen
		In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, II or IV FL
Ibrutinib	2013	Treatment of patients with MCL who have received at least one prior therapy*
		Treatment of patients with CLL/SLL
		Treatment of patients with CLL/SLL with 17p deletion
		Treatment of patients with Waldenström's macroglobulinemia
		Treatment of patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy*
Idelalisib	2014	Treatment of patients with relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
		[*Withdrawn*: Relapsed FL in patients who have received at least two prior systemic therapies*]
		[*Withdrawn:* Relapsed SLL in patients who have received at least two prior systemic therapies*]
Venetoclax	2016	Treatment of adult patients with CLL or SLL
Acalabrutinib	2017	Treatment of adult patients with MCL who have received at least one prior therapy*
		Treatment of adult patients with CLL or SLL
Copanlisib	2017	Treatment of adult patients with relapsed FL who have received at least two prior systemic therapies*

Drug/Combination	Initial Approval	Current Indication(s)
Duvelisib	2018	Treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies
		[*Withdrawn:* Treatment of adult patients with relapsed or refractory FL after at least two prior systemic therapies*]
Zanubrutinib	2019	Treatment of adult patients with MCL who have received at least one prior therapy*
		Treatment of adult patients with Waldenström's macroglobulinemia
		Treatment of adult patients with relapsed or refractory MZL who have received at least one anti-CD20-based regimen*
Tazemetostat	2020	Treatment of adult patients with relapsed or refractory FL whose tumors are positive for EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies*
		Treatment of adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options*
Umbralisib	2021	Treatment of adult patients with relapsed or refractory MZL who have received at least one prior anti-CD20-based regimen*
		Treatment of adult patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy*
Axicabtagene ciloleucel	2017 €	Treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy*

* Indicates approval under accelerated approval
¥ Initial approval; first iNHL approval was in 2013
€ Initial approval; first iNHL approval was in 2021
£ Initial approval; first iNHL approval was in 2021

Source: FDA analysis. Approvals as of March 2022.

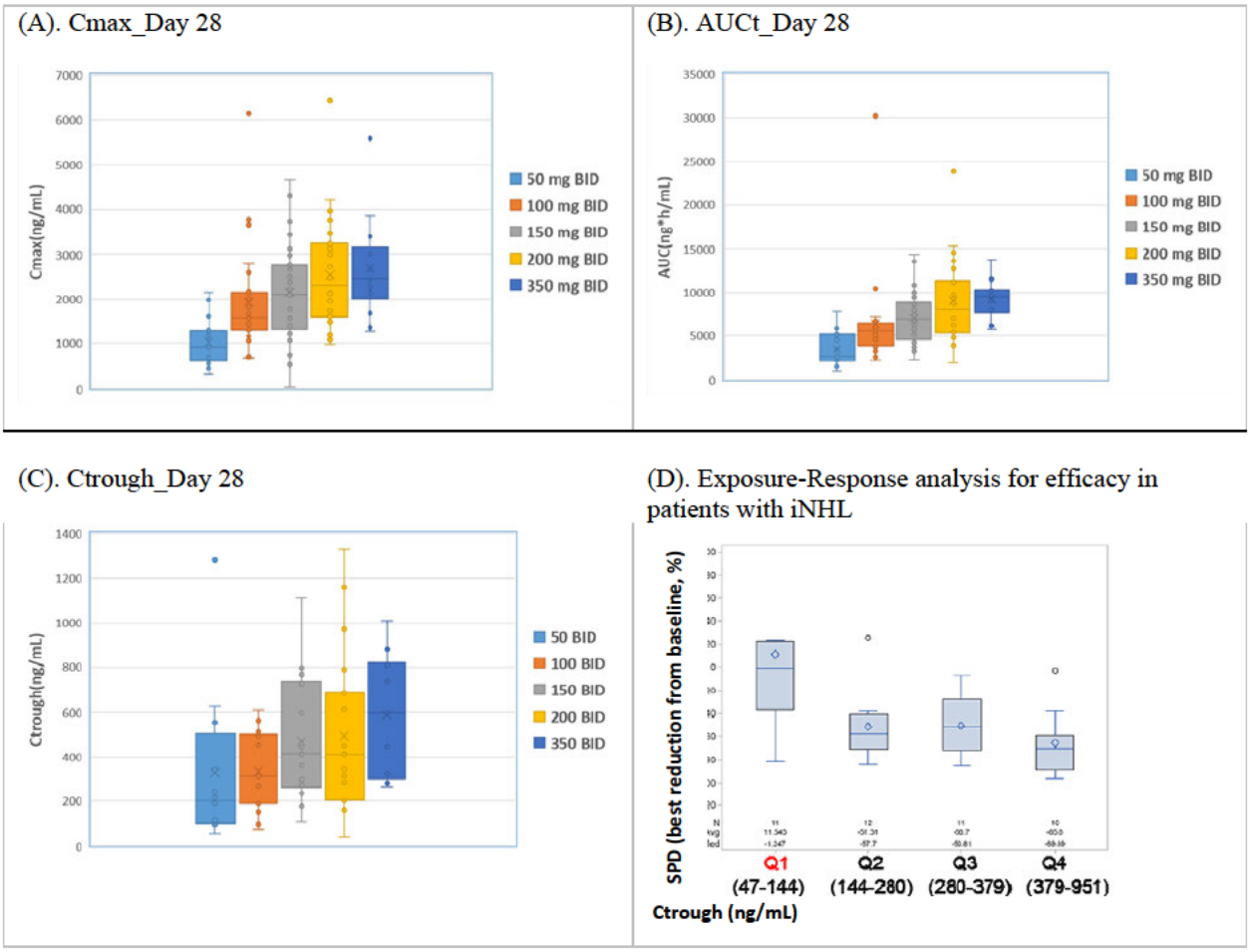
8 Appendix II: Clinical Pharmacology: Supplemental Data

8.1 Idelalisib

Table 33: Summary of Best Overall Response by Dose for Patients with MCL, iNHL, CLL, and DLBCL in Study 101-02 Given Idelalisib

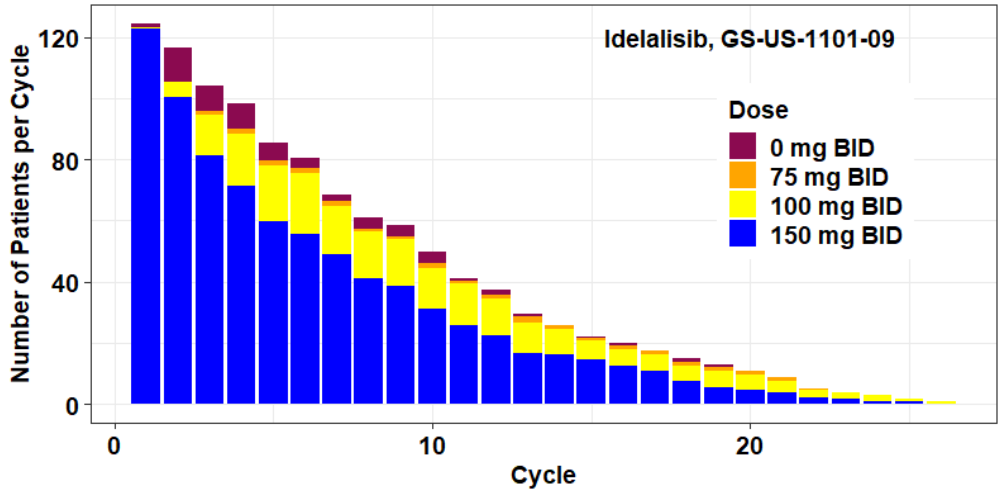
Dose Level	MCL (N = 40)		iNHL (N = 64)		CLL (N = 54)		DLBCL (N = 9)	
	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)
50 mg BID	5	20 (0.5, 71.6)	7	14.3 (0.4, 57.9)	5	40 (5.3, 85.3)	0	
150 mg QD	7	28.6 (3.7, 71)	9	33.3 (7.5- 70.1)	0		0	
100 mg BID	7	14.3 (0.4, 57.9)	7	85.7 42.1, 99.6	11	45.5 (16.7, 76.6)	0	
150 mg BID × 21 days	5	20 (0.5, 71.6)	12	25 (5.5, 57.2)	0		0	
300 mg QD	4	75 (19.4, 99.4)	5	60 (14.7, 94.7)	10	60 (26.2, 87.8)	0	
150 mg BID	6	50 (11.8, 88.2)	10	30 (6.7, 65.2)	11	45.5 (16.7, 76.6)	4	0 (0, 60.2)
200 mg BID	3	100 (29.2, 100)	10	60 (26.2, 87.8)	10	60 (26.2, 87.8)	3	33.3 (0.8, 90.6)
350 mg BID	3	66.7 (9.4, 99.2)	4	100 (39.8, 100)	7	71.4 (29, 96.3)	2	0 (0, 84.2)
Source: Study 101-02 CSR								

Figure 30: Relationship between Day 28 Plasma Exposures and Best On-Study Changes in Lymph Node Area in Evaluable Patients in Trial 101-02 Administered Idelalisib



Abbreviations: BID: Twice daily; SPD: sum of products of greatest perpendicular diameters of index lesions.
Source: Based on NDA 205858 Clinical Pharmacology Review at Drugs@FDA

Figure 31: Dose Interruptions, Reductions and Modifications for Idelalisib by Cycle



Source: Based on Study GS-US-1101-09 CSR and NDA 205858 Clinical Review at Drugs@FDA

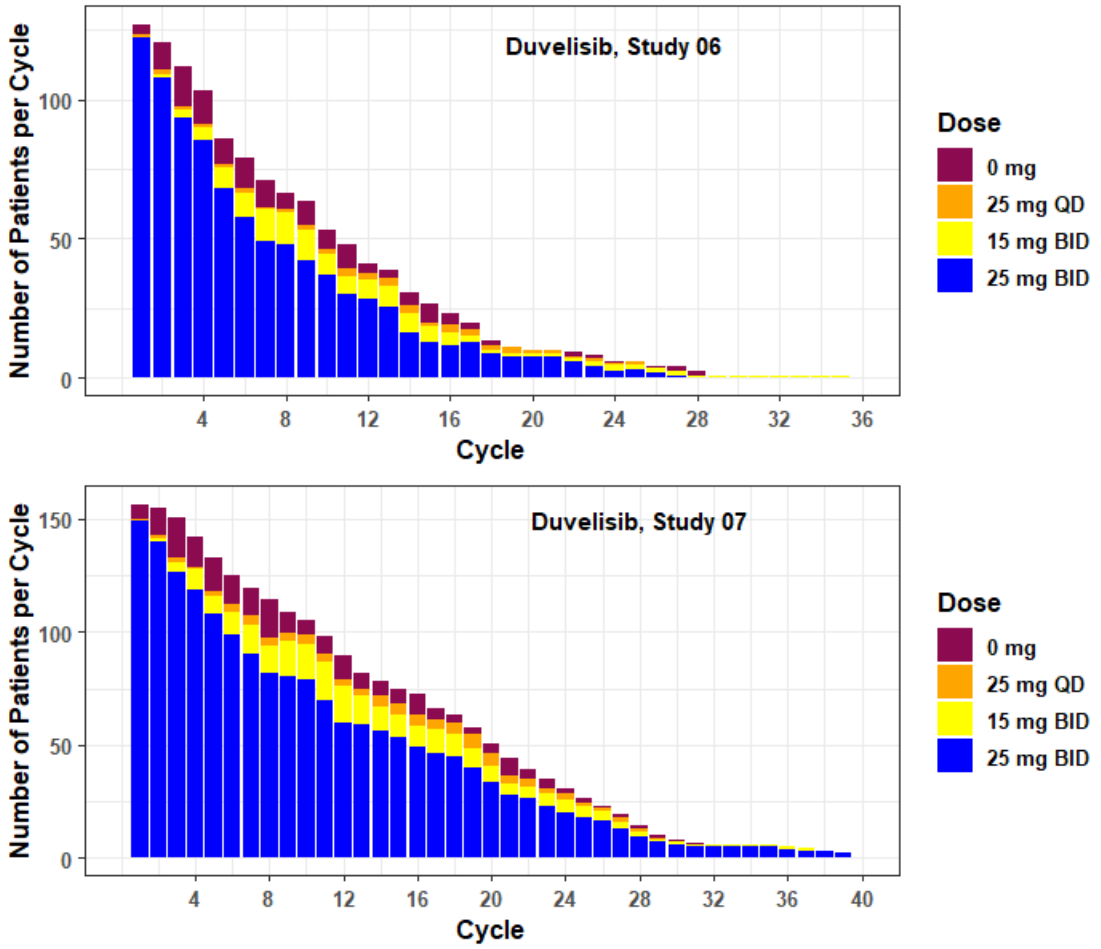
8.2 Duvelisib

Table 34: Summary of Best Overall Response by Dose for Patients with Indolent NHL, R/R CLL, and Treatment-Naïve CLL in Study IPI-145-02

	Dose (administered BID)									
	8 mg		**15 mg**		**25 mg**		**50 mg**		**75 mg**	
	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)
Indolent NHL			1	100 (2.5, 100)	14	64.3 (35.1, 87.2)	1	100 (2.5, 100)	15	46.7 (21.3, 73.4)
R/R CLL/SLL	1	100 (2.5, 100)	2	50 (1.3, 98.7)	28	57.1 (37.2, 75.5)			24	54.2 (32.8, 74.4)
TN CLL					18	83.3 (58.6, 96.4)				

Abbreviations: TN, treatment naive
Source: IPI-145-02 CSR

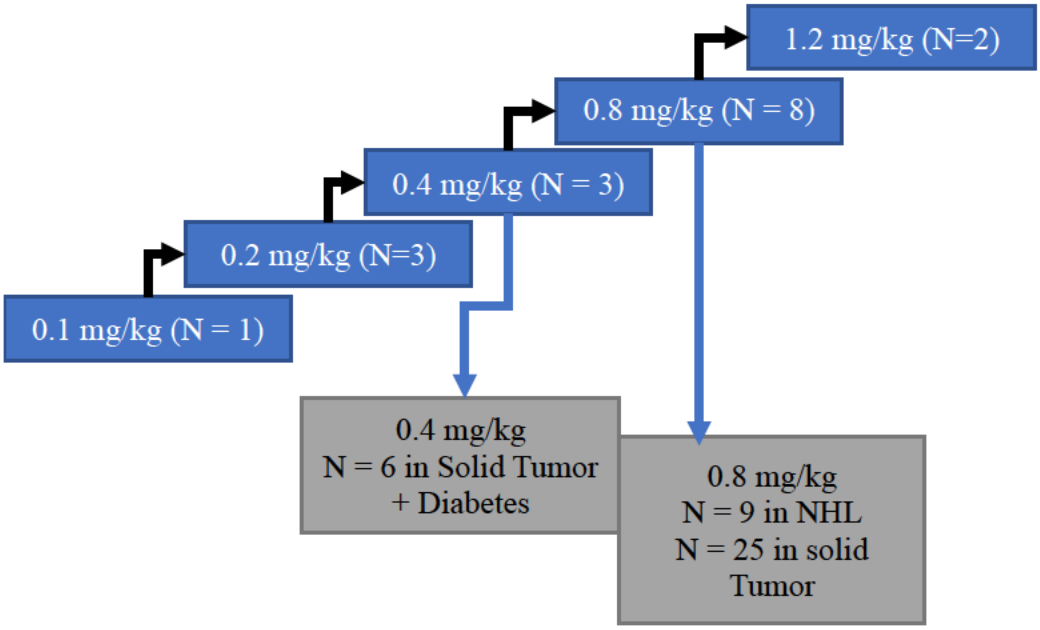
Figure 32: Dose Interruptions, Reductions and Modifications for Duvelisib by Cycle in Studies IPI-145-006 and IPI-145-007



Source: Reproduced from Duvelisib Multidisciplinary Review at Drugs@FDA

8.3 Copanlisib

Figure 33: Dose Escalation and Expansion Schema for Copanlisib in Study 12871



Source: Based on NDA 209936 Multidisciplinary Review at Drugs@FDA