FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

September 23, 2022

NDA 211155

Duvelisib (COPIKTRA)

Sponsor: Secura Bio, Inc.

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 Duvelisib New Drug Application (NDA) 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.

Table of Contents

Table of Tables

Table of Figures

Glossary

AA	Accelerated approval
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
CR	Complete response
CRi	Complete response with incomplete marrow recovery
DOR	Duration of response
E-R	Exposure-response
FDA	Food and Drug Administration
FL	Follicular lymphoma
HR	Hazard ratio
IA	Interim analysis
IRC	Independent Review Committee
ITT	Intent-to-treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MZL	Marginal zone lymphoma
NDA	New Drug Application
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival
PI3K	Phosphatidylinositol 3-kinase
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response

SAE	Serious adverse event
SAP	Statistical analysis plan
SEER	Surveillance, epidemiology, and end results
SLL	Small lymphocytic lymphoma
TEAE	Treatment-emergent adverse event
USPI	U.S. Prescribing Information

Introduction

Purpose of the Advisory Committee (AC) Meeting

The FDA is convening this Oncologic Drugs Advisory Committee (ODAC) meeting to discuss updated overall survival data with duvelisib from the DUO trial, safety and tolerability concerns with duvelisib and the PI3K inhibitor class, and concerns with the selected dose of duvelisib, which will inform a current evaluation of the benefit-risk of duvelisib.

The topics for discussion include:

- Discuss whether the current data demonstrate that duvelisib is safe in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
- Discuss how the available data impacts a current assessment of benefit-risk for duvelisib in the indicated population, patients with relapsed or refractory CLL or SLL who have received at least two prior therapies.

Context for Issues to Be Discussed at the AC

Duvelisib is a phosphatidylinositol 3-kinase (PI3K) inhibitor indicated for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

Study IPI-145-07 (DUO trial) was a randomized (1:1), open label, actively-controlled trial evaluating duvelisib versus ofatumumab in 319 adults with CLL or SLL after at least 1 prior therapy. The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC). Key secondary endpoints were overall response rate and overall survival.

In September 2018, based on the results of the DUO trial, duvelisib was granted regular approval for adult patients with CLL or SLL after at least 2 prior therapies. At that time, the analysis of PFS in the intent-to-treat (ITT) population, those with at least 1 prior therapy, demonstrated a PFS advantage in the duvelisib arm with a median PFS of 13.1 months (95% confidence interval [CI]: 12.1, 16.8) compared to 9.9 months (95% CI: 9.2, 11.3) in the ofatumumab arm with a hazard ratio (HR) of 0.52 (95% CI: 0.39, 0.69, p-value <0.0001). An advantage in overall response rate (ORR) was also seen on the duvelisib arm, with IRC-assessed ORR of 73.8% (95% CI: 66.9, 80.6) compared to 45.3% (95% CI: 37.5, 53.0) in the ofatumumab arm.

However, substantial toxicity was also observed, including fatal events. The primary safety issues identified with duvelisib included serious or fatal infections, diarrhea or colitis, rash, pneumonitis, hepatotoxicity, and neutropenia. Because of the toxicity concerns, the efficacy of duvelisib in patients with CLL or SLL with 2 or more prior therapies was evaluated. Of the 196 patients with 2 or more prior therapies, treatment with duvelisib demonstrated an improvement in PFS with a median PFS of 16.4 months (95% CI: 12.0, 20.5) in the duvelisib arm compared to 9.1 months (95% CI: 7.9, 10.7) in the ofatumumab arm with a HR of 0.40 (95% CI: 0.27, 0.59), demonstrating consistency with the efficacy results in the ITT population. Therefore, taking the safety concerns into consideration, the benefit-risk evaluation in those patients with 2 or more prior therapies was determined to be favorable and the indication granted was in patients with CLL or SLL who have received at least 2 prior therapies.

At the time of the initial approval, the median overall survival (OS) in the ITT population for both duvelisib and ofatumumab were not reached, with a median follow-up of 24 months for both treatment arms. There were 46 deaths (29%) in the duvelisib arm and 45 deaths (28%) in the ofatumumab arm, with an estimated HR of 0.99 (95% CI: 0.65, 1.50). In the indicated population, those with 2 or more prior therapies, median OS was not reached with 28 deaths (29%) in the duvelisib arm and 34 deaths (34%) in the ofatumumab arm, with an estimated HR of 0.82 (95% CI: 0.49, 1.37).

Due to the toxicity concerns with duvelisib and immature OS data, FDA issued a postmarketing requirement (PMR) under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act to assess a signal of fatal adverse reactions. Therefore, FDA required submission of overall survival data from the DUO trial with 5 years of follow-up.

The 5-year OS analysis from the DUO trial was submitted in June 2021 and FDA conducted an efficacy and safety evaluation based on a data cutoff of January 22, 2021. Analysis of efficacy is based on the ITT population of 319 patients and in the indicated population of 196 patients who received at least 2 or more prior therapies. Safety is based on all patients who received at least one dose of study treatment.

Efficacy:

OS:

ITT Population

- With a median of 63-months of follow-up, the median OS in the ITT population was 52.3 months (95% CI: 41.8, 68.0) in the duvelisib arm and 63.3 months (95% CI: 41.2, NE) in the ofatumumab arm with an estimated HR of 1.09 (95% CI: 0.79, 1.51). There were 80 deaths (50%) in the duvelisib arm and 70 deaths (44%) in the ofatumumab arm.

Patients with ≥2 prior therapies:

- With a median of 63-months of follow-up, the median OS in patients with 2 or more prior therapies was 43.9 months (95% CI: 32.4, 56.5) in the duvelisib arm and 46.8 months (95% CI: 28.6, 74.9) in the ofatumumab arm with an estimated HR of 1.06 (95% CI 0.71, 1.58). There were 53 deaths (56%) in the duvelisib arm and 49 deaths (49%) in the ofatumumab arm.

PFS per Investigator:

ITT Population

- With a median of 52-months of follow-up, the median PFS in the ITT population was 17.8 months (95% CI: 15.1, 22.0) in the duvelisib arm and 9.6 months (95% CI: 9.3, 11.4) in the ofatumumab arm with an estimated HR of 0.37 (95% CI: 0.28, 0.49). There were 114 PFS events (71%) in the duvelisib arm and 134 PFS events (84%) in the ofatumumab arm.

Patients with ≥2 prior therapies:

- With a median of 52-months of follow-up, the median PFS in patients with 2 or more prior therapies was 17.8 months (95% CI: 12.7, 22.8) in the duvelisib arm and 9.3 months (95% CI: 7.6, 9.5) in the ofatumumab arm with an estimated HR of 0.35 (95% CI: 0.25, 0.50). There were 73 PFS events (77%) in the duvelisib arm and 84 PFS events (83%) in the ofatumumab arm.

Safety:

- Fatal adverse events (AEs) occurred in 23 patients (15%) in the duvelisib arm and 5 patients (3%) in the ofatumumab arm.
- Grade 3 or greater adverse events occurred in 144 patients (91%) in the duvelisib arm and 75 patients (48%) in the ofatumumab arm.
- Serious adverse events occurred in 124 patients (78%) in the duvelisib arm and 50 patients (32%) in the ofatumumab arm.
- Adverse events leading to treatment discontinuation occurred in 70 patients (44%) versus 9 patients (6%), dose reduction in 48 patients (30%) versus 2 patients (1%), and dose interruption in 112 patients (71%) versus 83 patients (54%) in the duvelisib arm compared to the ofatumumab arm, respectively

Brief Description of Issues for Discussion at the AC

Potential Detriment in Overall Survival

With a median overall survival follow-up of 63 months, there is a higher rate of death in the duvelisib arm compared to the ofatumumab arm in both, the ITT population (50% vs. 44%) and the indicated population (patients with ≥2 prior therapies, 56% vs. 49%). In the ITT population, median OS favors the ofatumumab arm with a median of 63.3 months (95% CI: 41.2, NE) compared to 52.3 months (95% CI: 41.8, 68.0) in the duvelisib arm, with a HR of 1.09 (95% CI: 0.79, 1.51). In the indicated population, the median OS is 46.8 months (95% CI: 28.6, 74.9) in the ofatumumab arm compared to 43.9 months (95% CI: 32.4, 56.5) in the duvelisib arm with a HR of 1.06 (95% CI: 0.71, 1.58).

While overall survival was a descriptive secondary endpoint in the DUO trial, the 5-year OS results in the setting of a benefit in PFS and ORR indicate that the potential detriment in OS is a primary safety concern.

The FDA would like to highlight the following regarding the 5-year OS results:

- The 5-year overall survival analysis was issued as a postmarketing requirement per Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act based on concerns of fatal and serious toxicity with duvelisib and immature OS data at the time of approval.

- Death due to an adverse event occurred in 23 patients (15%) treated with duvelisib and 5 patients (3%) treated with ofatumumab. The primary difference in fatal adverse events was infection, with 14 patients (9%) experiencing a fatal infection with duvelisib compared to 1 patient (<1%) with ofatumumab.

- In the evaluation of PFS, in the duvelisib arm, there were 31 patients (19.4%) that experienced death prior to progression versus 12 patients (7.6%) in the ofatumumab arm. In patients with CLL or SLL, progression isn't necessarily an indication for treatment.

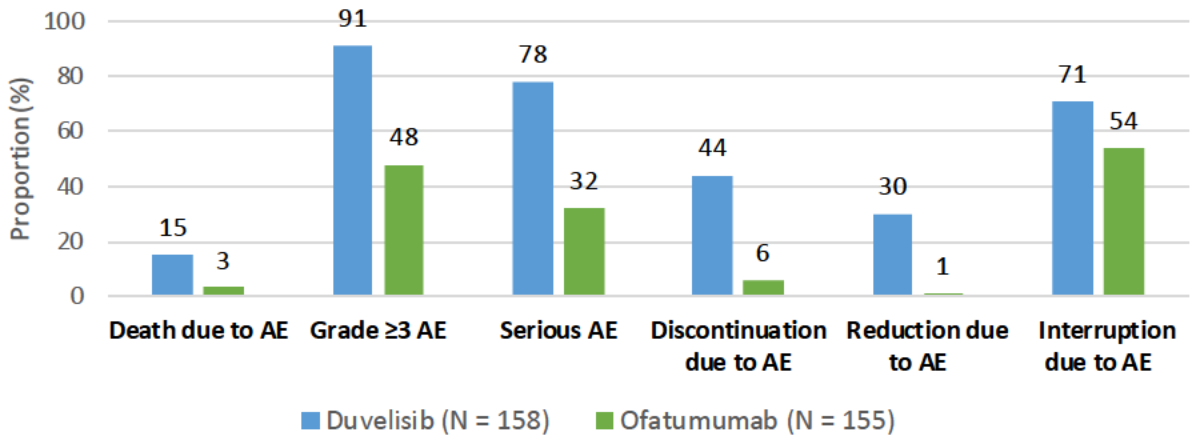
- A substantial number of patients crossed over from ofatumumab to receive duvelisib upon progressive disease (57%). Of those patients, 10% experienced a fatal adverse event.

In general, overall survival is considered the most reliable cancer endpoint as it is an objective measure of clinical benefit. For randomized controlled trials (RCT) in diseases such as CLL with prolonged survival and the potential for multiple therapeutic interventions, PFS is often used as the primary endpoint. Regardless, for RCTs with a PFS endpoint, FDA requires submission of OS data as it is considered both an efficacy and a safety endpoint. The updated OS data from the DUO trial, which is an important determinant of overall benefit-risk, suggests the potential for harm to patients treated with duvelisib. Therefore, a re-evaluation of the overall benefit-risk of duvelisib in patients with relapsed or refractory CLL or SLL, based on new information about a potential OS detriment in the context of an improvement in PFS and ORR but substantial toxicity, is warranted.

Substantial Toxicity and Poor Tolerability

Duvelisib is associated with substantial toxicity that includes fatal or serious infection, diarrhea or colitis, rash, pneumonitis, hepatotoxicity, and neutropenia. Within the DUO trial, patients treated with duvelisib experienced higher rates of Grade ≥3 adverse events, serious adverse events (SAE), and dose modifications due to AEs. A summary of the differences in safety between the arms in the DUO trial is shown in Figure 1 below.

Figure 1: DUO Trial Summary of Safety



Dose reductions were not permitted for ofatumumab.
Abbreviations: AE, adverse event
Source: FDA analysis, data cutoff 1/22/2021

The difference in toxicity between arms is primarily driven by infections, predominantly pneumonia, and immune-mediated toxicities of diarrhea or colitis, rash, and pneumonitis, as shown in Table 1 below. Notably, the rates of Grade ≥3 infection and immune-mediated toxicities are 2 to 3 times, or more, higher in the duvelisib arm compared to the ofatumumab arm. These toxicities are expected with duvelisib, given the mechanism of action, in which duvelisib affects immune modulation and T regulatory cell function, and are consistent with the toxicities seen across the class of PI3K inhibitors.

Table 1: DUO Trial Adverse Events of Special Interest

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	114 (72)	56 (35)	67 (43)	17 (11)
Neutropenia*	105 (66)	76 (48)	80 (52)	55 (35)
Diarrhea-Colitis[1]	94 (59)	43 (27)	21 (14)	3 (2)
AST/ALT Increase*	69 (44)	12 (8)	22 (14)	2 (1)
Rash[1]	46 (29)	21 (13)	23 (15)	1 (<1)
Pneumonitis[1]	14 (9)	6 (4)	1 (<1)	0

[1]Grouped term, see Appendix 3
*Based on laboratory data
Data cutoff 1/22/2021
Source: FDA analysis

Dosing Concerns

The dose of duvelisib was selected based on the traditional dose selection design to determine the maximum tolerated dose (MTD). The dose of 75 mg twice daily (BID) was identified as the MTD. Dose expansion at the 25 and 75 mg BID doses generated activity and toxicity data that, in conjunction with nonclinical data and analysis of

pharmacokinetic (PK) and pharmacodynamic (PD) data, lead to the selection of the 25 mg BID dose for further testing. However taken together with the new information suggesting a potential detriment in OS, the high levels of toxicity and the high rates of treatment discontinuation, dose reductions, and dose interruptions seen in the DUO trial (Figure 1), the 25 mg BID dose of duvelisib appears to be too high. In the dose selection trial, data from lower doses of duvelisib were not sufficiently explored. Activity was observed at doses as low as 8 mg BID and higher rates of grade 3-4 treatment emergent AEs and dose modifications due to AEs were seen with higher levels of exposure. These findings suggest that a lower dose of duvelisib may be efficacious and more tolerable and further dose exploration to optimize the dose is warranted.

PI3K Inhibitor Class Concerns

On April 21, 2022, the Oncologic Drugs Advisory Committee convened to discuss the PI3K inhibitor drug class and the data requirements for future approvals of PI3K inhibitors in patients with hematologic malignancies.

Six randomized trials of PI3K inhibitors in hematologic malignancies have demonstrated detriments in overall survival. This observation of OS detriments in the setting of an advantage or potential advantage in PFS across multiple randomized trials within the same drug class is unprecedented in oncology. The overall survival information in these trials was early and represented a low number of events, yet the same pattern was 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 that the potential detriment in overall survival was due to toxicity.

The committee members voted in favor of using randomized data to support future approvals of PI3K inhibitors, given the observed toxicities with the class of drugs and the detriments in OS seen across multiple randomized trials. The discussion held at the ODAC included topics such as the lack of adequate dose-finding, the toxicity profile of the class, concerning trends in OS, including in the DUO trial, the safety concerns with chronic administration, and bias when using PFS as the primary efficacy metric. The committee members highlighted the importance of OS in informing the benefit-risk evaluation in the setting of substantial toxicity and the need for adequate data to ensure that a drug is safe and effective, and to rule out the potential for harm.

The discussion that occurred related to the importance of OS as the paramount endpoint to evaluate the benefit-risk of a drug for patients with cancer, further supporting the need to re-evaluate the benefit-risk of duvelisib with the updated OS information, which suggests a possible detriment in overall survival.

Current Benefit-Risk

Based on the issues outlined above and discussed in detail in the remainder of the briefing document, there are significant concerns with the benefit-risk profile of duvelisib in patients with CLL or SLL. The concerns include a potential detriment in overall survival, substantial toxicity, tolerability concerns, and dosing concerns. These findings, in the setting of a PFS and ORR benefit, suggest a primary safety concern with a toxicity profile that is consistent with that seen across the class of PI3K inhibitors. In light of the updated survival information with duvelisib, coupled with the recent information on the class of PI3K inhibitors in hematologic malignancies, the benefit-risk assessment of duvelisib in patients with CLL or SLL warrants re-evaluation.

Background

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia 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.[1] 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.[1] 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.[2] Chromosomal abnormalities of 17p deletion or 11q deletion, unmutated immunoglobulin heavy chain 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.[3,4] Treatment can range from observation to immunochemotherapy to targeted therapies; however, progressive disease alone is not necessarily an indication to treat.

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

Table 2 below lists the FDA-approved treatment regimens for patients with CLL or SLL, which include chemotherapy, immunotherapy, BTK inhibitors, PI3K inhibitors, and a BCL2 inhibitor. Prior to the introduction of targeted therapies, the standard treatment for CLL or SLL was chemotherapy alone. With improvement in outcomes seen with addition of anti-CD20 antibodies to chemotherapy, the standard of care became chemoimmunotherapy, most commonly FCR (fludarabine, cyclophosphamide, rituximab), and BR (bendamustine, rituximab).[2]

Since the approval of targeted agents for patients with CLL or SLL, the first of which was ibrutinib, the first-in-class BTK inhibitor, in 2014, followed by the approval of next-generation BTK inhibitors and the BCL2 inhibitor, venetoclax, the treatment paradigm has evolved further. Targeted therapies have replaced chemoimmunotherapy as front-line treatment in the majority of patients, including in those with high-risk genomics, such as del(17p) or TP53 mutation, due to high response rates and demonstrated survival advantages compared to chemoimmunotherapy or immunotherapy alone.[5] Certain targeted therapies have also demonstrated a superior toxicity profile compared to chemoimmunotherapy and may allow patients to avoid toxicities commonly associated with more toxic chemoimmunotherapy regimens.[5] The approval of agents with superior safety and efficacy profiles and the availability of multiple effective targeted therapies and chemoimmunotherapy regimens in the front-line and beyond represent significant advancements in the treatment landscape of CLL and SLL in recent years.

Table 2: FDA Approved Treatments for CLL and Indolent NHL

Drug/Combination	Indication
Chlorambucil (1957)	CLL and lymphomas
Cyclophosphamide (1959)	Malignant lymphomas
Vincristine (1963)	NHL
Doxorubicin (1974)	NHL
Fludarabine (1991)	R/R CLL
Rituximab (1997) and Rituximab Hycela (2017)	R/R FL; Untreated FL in combination and as maintenance; CLL with flu/cy
Zevalin (2002)	R/R FL
Bendamustine (2008)	CLL
Ofatumumab (2009)	Untreated CLL with chlorambucil; With flu/cy for relapsed CLL; Extended treatment after 2 lines; Refractory CLL
Obinutuzumab (2013)	With chlorambucil for untreated CLL; With bendamustine for R/R FL; With chemo for untreated FL
Lenalidomide (2013)	In combination with rituximab for relapsed FL or relapsed MZL

Drug/Combination	Indication
Ibrutinib (2013)	CLL/SLL; CLL/SLL with 17p del; WM; MZL after 1 prior CD20-based therapy
Idelalisib (2014)	Relapsed CLL
Venetoclax (2016)	CLL/SLL
Acalabrutinib (2017)	CLL/SLL
Copanlisib (2017)	Relapsed FL after 2 prior therapies *
Duvelisib (2018)	R/R CLL/SLL after at least 2 prior therapies
Zanubrutinib (2019)	WM; R/R MZL after 1 prior CD20-based regimen*
Tazemetostat (2020)	R/R FL positive for EZH2 mutation after 2 prior therapies*; R/R FL with no alternative options*
Axicabtagene ciloleucel (2021)	R/R FL after two or more lines of therapy*
Tisagenlecleucel (2022)	R/R FL after two or more lines of therapy*
Abbreviations: CLL, chronic lymphocytic leukemia, FL, follicular lymphoma, Flu/cy, fludarabine and cyclophosphamide, MZL, marginal zone lymphoma, NHL, non-Hodgkin lymphoma, R/R, relapsed or refractory, SLL, small lymphocytic lymphoma, WM, Waldenström's macroglobulinemia *Indicates accelerated approval Source: FDA analysis	

Drug Description

The phosphatidylinositol 3-kinase family is a family of enzymes in the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling axis, which is involved in cell surface receptor signaling and tissue-dependent cellular functions. This pathway has been found to be constitutively activated in multiple B-cell malignancies, including in CLL and SLL. There are four tissue-specific isoforms of PI3K (α, β, δ, and γ), which demonstrate differential distribution across tissues and signaling receptors.

Duvelisib is a kinase inhibitor that inhibits both PI3Kδ and PI3Kγ. PI3Kδ is expressed in normal and malignant B cells; inhibition of PI3Kδ reduces the proliferation of hematologic tumor cells, while allowing for survival of normal immune cells.[6] PI3Kγ plays a role in recruitment and differentiation of cells that support B-cell growth, such as CD4+ T cells and M2 tumor-associated macrophages; inhibition of PI3Kγ reduces the differentiation and migration of these support cells.[6]

The toxicity profile of PI3K inhibitors consists primarily of infections, including opportunistic infections, and immune-mediated toxicities and is related to the effects of PI3K inhibition of lymphocyte subsets, including T-regulatory lymphocytes. Infections may occur in part because of treatment-related cytopenias, but also because of modulation of the immune system via PI3K inhibition. For immune-mediated toxicities, it is postulated that decreased regulatory T cell activity and increased CD8 cytotoxicity damages normal tissue, leading to the immune-mediated toxicities associated with PI3K inhibition. The key immune-mediated toxicities associated with the overall PI3K inhibitor drug class include diarrhea or colitis, autoimmune hepatotoxicity, pneumonitis, and rash. The effects of PI3K inhibition on blood pressure homeostasis and glucose homeostasis are limited to inhibition of the PI3Kα isoform; resultant toxicities from alpha inhibition include hypertension and hyperglycemia. A diagram of the PI3K inhibitors that have received FDA approval and the isoforms that they inhibit is shown in Appendix 1.

Regulatory History

Duvelisib was granted regular approval in 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.

In September 2018, duvelisib also was granted accelerated approval (AA) for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies. The primary data to support the FL indication were from a global Phase 2 study IPI-145-06, a single-arm trial in which 83 patients with FL who were refractory to both rituximab and either chemotherapy or radioimmunotherapy were treated with duvelisib 25 mg BID until disease progression or unacceptable toxicity. The primary endpoint was ORR by IRC, according to modified IWG criteria. In the FL cohort, ORR by IRC was 42% (95% CI: 31, 54). As the accelerated approval was based on results of a single-arm trial, a postmarketing requirement was issued to conduct a randomized trial with duvelisib in patients with relapsed or refractory (R/R) FL to confirm clinical benefit. The FL indication was voluntarily withdrawn on December 17, 2021, due to the company's inability to conduct a clinical trial to verify clinical benefit of duvelisib in patients with FL.

Table 3, shown below, provides an overview of the relevant regulatory interactions.

Table 3: Communications and Meetings

Date	Event	Topic and Comments

9/24/2018	Initial Approvals
	
	Postmarketing Requirements Issued
		• **Regular Approval:** Treatment of adult patients with relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma after at least two prior therapies
		  ◦ PMR 3494-2: Characterize the safety of long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg twice daily. Include evaluation, supplemented by narratives, of deaths in the absence of treated progressive disease, serious adverse reactions, and adverse reactions of special interest.
		  ◦ PMR 3494-3: Submit reports and datasets for overall survival 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.
		• **Accelerated Approval:** Treatment of adult patient with relapsed or refractory follicular lymphoma after at least two prior systemic therapies
		  ◦ PMR 3494-1: Conduct a randomized phase 3 clinical trial in patients with relapsed or refractory follicular lymphoma that verifies and isolates the clinical benefit of duvelisib. The primary endpoint would be progression-free survival as determined by an independent review committee.

Date	Event	Topic and Comments
11/1/2018	Teleconference – FL Indication	• Discussed the design and feasibility of Study IPI-145-327 to confirm clinical benefit of duvelisib in patients with R/R FL.
6/28/2019	Submission of OS data with 3 Years of Follow Up from DUO trial	• Consistent with OS results from initial NDA submission • In the ITT population, median OS was 49.3 months on the duvelisib arm and 47.6 months on the ofatumumab arm (HR 0.99; CI 0.70, 1.40). • In patients with 2 or more prior therapies, median OS was 46.3 months on the duvelisib arm and 41.2 months on the ofatumumab arm (HR 0.89, 95% CI: 0.58, 1.38).
10/15/2020	Transfer of Ownership	• Verastem Inc. to Secura Bio.
1/22/2021	OS Data Cutoff– DUO trial	• Data cutoff for 5-year OS data for DUO trial
2/9/2021	Sponsor Communication – FL Indication	• Agency notified of closure of Study IPI-145-327 due to enrollment feasibility
6/30/2021	Submission of OS data with 5 Years of Follow Up from DUO trial	• Suggested possible OS detriment in OS in the duvelisib arm in the ITT population and in patients with 2 or more prior therapies
9/22/2021	Label Update – CYP3A4 Inducers	• Based on Study VS-0145-131, drug interaction study in healthy subjects • Label updated with dosing recommendation for coadministration with moderate CYP3A inducers
10/21/2021	Teleconference – FL Indication	• Sponsor stated that alternative trial designs were discussed internally but each had feasibility and enrollment challenges. • Due to inability to conduct a confirmatory with due diligence, Sponsor indicated intent to voluntarily withdrawal FL indication
11/22/2021	Teleconference – FL Indication	• Sponsor confirmed inability to meet regulatory requirements for AA to confirm clinical benefit of duvelisib in FL population due to a changing clinical landscape and noted plans for withdrawal of the FL indication. Discussed regulatory steps for voluntary withdrawal.
12/17/2021	Voluntary Withdrawal of Follicular Lymphoma Indication	• FL indication withdrawn due to lack of confirmation of clinical benefit.
3/11/2022	Teleconference – DUO trial & CLL Indication	• Agency noted that high-level efficacy and safety data with duvelisib would be discussed at the upcoming PI3K inhibitor ODAC to be held April 21,2022. • Agency noted significant concerns with 5-year OS analysis of the DUO trial, inquired about communication to the public and healthcare providers, and indicated that a duvelisib-specific ODAC would be pursued if the Sponsor planned to continue marketing of duvelisib. • Sponsor agreed to issue a Dear Healthcare Provider (DHCP) letter.

Date	Event	Topic and Comments
4/28/2022	Teleconference – DUO trial & CLL Indication	• Agency requested update on Sponsor's plans for continued marketing of duvelisib. • Sponsor proposed to revise the U.S. Prescribing Information (USPI) with the updated OS analysis and indicated that their position is that duvelisib continues to have a positive benefit-risk in patients with R/R CLL and SLL. • Discussed DHCP letter and plan for dissemination.
6/14/2022	Teleconference – September ODAC	• Notified Sponsor of plans to hold a duvelisib-specific ODAC in September 2022.
6/30/2022	FDA Drug Safety Communication	• Agency issued a drug safety communication concerning the possible increased risk of death and serious side effects with duvelisib. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-possible-increased-risk-death-and-serious-side-effects-cancer-drug-copiktra

Trial IPI-145-07 (DUO Trial)

Trial Design

IPI-145-07 (DUO) is a randomized (1:1), actively-controlled, Phase 3 trial evaluating duvelisib compared to ofatumumab in patients with CLL or SLL after at least 1 prior line of therapy. The primary endpoint was progression-free survival per an independent review committee and key secondary endpoints were ORR and OS. Randomization was stratified according to 17p deletion status (presence vs. absence), refractory disease or early relapse to purine analog-based therapy (yes vs. no), and grade 4 neutropenia or thrombocytopenia at baseline (yes vs. no).

Key Eligibility Criteria

Eligible patients met the following criteria:

- ≥18 years of age with active CLL or SLL
- Meeting at least one of the IWCLL 2008/IWG criteria for requiring treatment
- Had progression or relapse after at least 1 previous CLL or SLL therapy and were not appropriate for treatment with a purine analog based-regimen
- Measurable disease with a lymph node or tumor mass >1.5cm in at least 1 dimension by CT
- ECOG performance status 0-2.

Patients were excluded if they met any of the following criteria:

- Richter's transformation or prolymphocytic leukemia
- Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura
- Refractory to ofatumumab
- Had prior allogeneic transplant
- Had previously received a PI3K inhibitor or Bruton's tyrosine kinase (BTK) inhibitor.

The following baseline laboratory results were required at the time of screening:

- Platelet count 10,000 cells/mm3
- Hemoglobin > 8.0 g/dL
- Serum creatinine ≤2 x upper limit of normal (ULN)
- Total bilirubin ≤1.5 x ULN
- Serum AST or ALT ≤3 x ULN

Full protocol eligibility criteria are included in Appendix 2: DUO Trial Eligibility Criteria.

Treatment

Treatments were administered as follows:

- Duvelisib: Administered orally (as capsules) twice daily in 28-day cycles, with the exception of Cycle 1, which was 21 days. The starting dose was 25 mg BID, with dose modifications permitted based on the occurrence of toxicities and at the discretion of the Investigator.

  Duvelisib treatment was administered continuously for up to 18 cycles until disease progression or unacceptable toxicity, whichever occurred first. Additionally, criteria for discontinuing treatment prior to 18 cycles in those with demonstrated CR/CRi (CLL) or CR (SLL) and for continuing treatment for up to 39 total cycles in those with documented evidence of response and disease requiring continued

treatment according to IWCLL/IWG criteria following 18 cycles were also provided. See Appendix 3 for the full guidelines for duvelisib treatment duration as outlined in the protocol.

- Ofatumumab: Administered as 12 doses over 7 cycles with a starting dose of 300 mg IV on Day 1, followed by 7 weekly doses of 2000 mg IV, followed by 2000 mg IV monthly for 4 months.

Crossover to the alternative treatment arm upon IRC-confirmed disease progression was permitted.

Efficacy Evaluation

Primary and Secondary Endpoints

The primary endpoint was PFS, defined as the time from randomization to the first documentation of progressive disease, as determined by independent review, or death due to any cause.

The key secondary endpoints were:

- Overall response rate, with overall response (based on independent review) defined as best response of complete response (CR), complete response with incomplete marrow recovery (CRi), partial response (PR), or partial response with lymphocytosis (PRwL) according to IWCLL or revised IWG Response criteria.
- Overall survival, defined as time from randomization to death.

Efficacy Analyses

The sample size determination was based on the primary endpoint of PFS only. Therefore, the sample size calculation did not take into account the endpoint of OS, despite being included as a key secondary endpoint.

A total of 185 PFS events were determined to provide approximately 93% power to detect a hazard ratio of 0.6 using a one-sided log-rank test at a 2.5% overall significance level, with one interim analysis planned at 50% information time for both efficacy and futility. If the study was not stopped at the interim analysis, the final analysis would be performed when approximately 185 PFS events had occurred. The study design employed the Lan-DeMets spending function for O'Brien-Fleming boundary as the alpha spending function and the Hwang-Shih-DeCani gamma (-4) spending function as the beta spending function. The futility boundary of this study was non-binding.

Two interim analyses and one final analysis were planned for OS without prespecification of available OS information. The first OS interim analysis was to be performed at the time of the planned PFS interim analysis after 93 PFS events had occurred. The second interim analysis of OS was to be performed at the planned PFS final analysis after 185 PFS events had occurred. The final analysis of OS was to take place after the completion of follow-up for all patients, which was defined as up to 6 years after randomization or until death.

Overall response rate was included as key secondary efficacy endpoint and tested at an overall one-sided alpha level of 0.025 based on gatekeeping approach. Overall response rate would be tested only if PFS was declared statistically significant.

Safety Evaluation

The safety evaluation included an assessment of the safety profile in the 158 patients treated with duvelisib and 155 patients treated with ofatumumab on the DUO trial. The percentage of patients with serious adverse events, treatment-emergent adverse events (TEAE) leading to discontinuation, dose reduction and dose interruption, adverse events of special interest (AESI) were summarized. As laboratory-based adverse events are usually under-reported in the adverse event dataset compared to the lab dataset, the FDA's rates of laboratory abnormalities

were based on the lab dataset with the exception of the rates for SAEs. All SAE rates were based on the AE dataset. Adverse events of special interest included infection, diarrhea or colitis, neutropenia, rash, transaminase elevation, and pneumonitis. Infection AESIs were assessed based on the infections system organ class. Events recorded as medical history or adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1.

Results – DUO Trial

The data cutoff for analysis of the DUO trial was May 19, 2017, for the primary efficacy analysis. The data cutoff for the updated OS analysis and safety analysis was January 22, 2021.

Patient Population

Demographics and Baseline Characteristics

The ITT population included all patients who were randomized, with treatment group designated according to randomization. In the 319 patients in the ITT population, the median age was 69 years (range 39 to 90), 60% were male, 92% were White, <1% were Black, and 5% not reported, and the majority of patients were enrolled in Europe (74%). Demographic characteristics, shown in Table 4 below, were balanced between treatment arms. However, in general, there was an underrepresentation of racial and ethnic minorities and patients enrolled in the U.S.

Table 4: DUO Trial Demographics (ITT Population)

	Duvelisib N = 160	Ofatumumab N = 159	Total N = 319
Age, years			
Median (Min, Max)	69 (39, 90)	69 (39, 89)	69 (39, 90)
≥65 years, n (%)	112 (70)	105 (66)	217 (68)
Sex, n (%)			
Male	96 (60)	95 (60)	191 (60)
Female	64 (40)	64 (40)	128 (40)
Race, n (%)			
White	150 (94)	142 (89)	292 (92)
Black	1 (<1)	1 (<1)	2 (<1)
Not Reported	6 (4)	9 (6)	15 (5)
Other or Unknown	3 (2)	7 (4)	10 (3)
Ethnicity, n (%)			
Not Hispanic or Latino	130 (81)	133 (84)	263 (82)
Hispanic or Latino	8 (5)	7 (4)	15 (5)
Not Reported or Unknown	22 (14)	19 (12)	41 (13)
Region, n (%)			
Europe	115 (72)	120 (75)	235 (74)
United States	30 (19)	21 (13)	51 (16)
Other	15 (9)	18 (11)	33 (10)
ECOG, n (%)			
0-1	149 (93)	142 (89)	291 (91)
2	11 (7)	17 (11)	28 (9)
Source: FDA analysis			

Table 5 summarizes the disease characteristics and prior therapies in the ITT population. The majority of patients had CLL (98%), 24% had 17p deletion, 19% had TP53 mutation, 17% had IgHV mutation, and 46% had bulky disease. The median number of prior therapies was 2 (range 1 to 10), with 61% of patients having 2 or more prior therapies. Nineteen percent of patients were refractory or had early relapse, defined as progression <12 months after fludarabine or pentostatin.

Table 5: DUO Trial Disease Characteristics (ITT Population)

Characteristic	Duvelisib N = 160 n (%)	Ofatumumab N = 159 n (%)	Total N = 319 n (%)
Diagnosis			
CLL	155 (98)	157 (99)	312 (98)
SLL	5 (3)	2 (1)	7 (2)
Cytogenetics			
17p deletion	33 (21)	44 (28)	77 (24)
TP53 mutation	31 (19)	29 (18)	60 (19)
IgHV mutation	29 (18)	25 (16)	54 (17)
Tumor Burden			
ALC ≥25 x 10^9/L	91 (57)	84 (53)	175 (55)
Bulky disease	74 (46)	72 (45)	146 (46)
Number of Prior Therapies			
Median (Min, Max)	2 (1, 10)	2 (1, 8)	2 (1, 10)
1	64 (40)	58 (36)	122 (38)
2	45 (28)	46 (29)	91 (28)
≥3	50 (31)	55 (35)	105 (33)
Refractory/Early Relapse			
Yes	25 (16)	36 (23)	61 (19)
Prior Treatment			
Purine-based	96 (60)	113 (71)	209 (65)
Alkylator	148 (92)	151 (95)	299 (94)
Chlorambucil	62 (39)	51 (32)	113 (35)
Bendamustine	59 (37)	61 (38)	120 (38)
Cyclophosphamide	95 (59)	111 (70)	206 (65)
Anti-CD20	125 (78)	132 (83)	257 (81)
Rituximab	123 (74)	131 (83)	254 (80)
Ofatumumab	3 (2)	4 (2)	7 (2)
Obinutuzumab	1 (<1)	3 (2)	4 (1)
Source: FDA analysis			

Exposure by treatment arm is summarized in Table 6 below. The median exposure duration for patients on the duvelisib arm was 12 months compared to 5 months on the ofatumumab arm.

Duvelisib was administered continuously until disease progression or unacceptable toxicity. Ofatumumab was given and completed by 6 months per the U.S. prescribing information[7].

Table 6: DUO Trial Exposure (ITT Population)

Parameter		Duvelisib N = 160	Ofatumumab N = 159
Exposure duration, months	Median	12	5
	Range	0.2, 72	0, 6
	Q1, Q3	5, 22	3, 5
Cycles initiated	Median	12	7
	Range	1, 41	1, 7
	Q1, Q3	6, 21	5, 7

[a] Cycle length is 28 days
Data cutoff 1/22/2021
Source: FDA analysis

Efficacy Results

Primary Endpoint - PFS

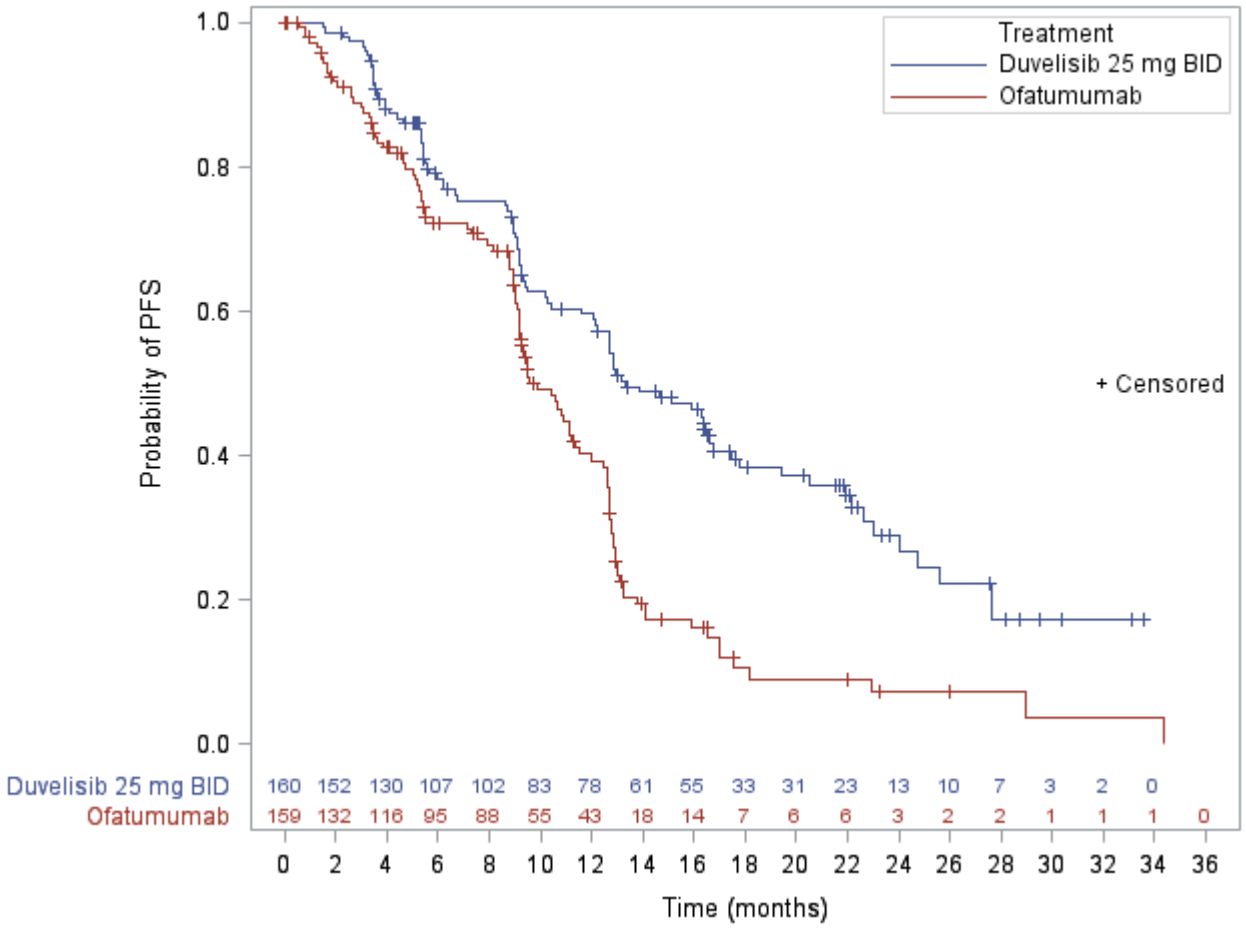
In the initial evaluation, the DUO trial demonstrated that treatment with duvelisib was associated with a statistically significant improvement in PFS per IRC compared to ofatumumab, with a HR of 0.52 (95% CI: 0.39, 0.69) and one-sided p-value <0.0001 per stratified log-rank test. The median PFS was 13.3 months for duvelisib and 9.9 months for ofatumumab. Despite the statistically significant PFS in favor of duvelisib, the benefit of 3 months in median PFS was modest for patients with CLL/SLL after one prior therapy. In the PFS per IRC analysis, a higher proportion of patients on the duvelisib arm died before progression (12%) compared to the ofatumumab arm (6%), raising a concern for increased death due to toxicity with duvelisib. Table 7 provides a summary of PFS per IRC for the ITT population and Figure 2 shows the Kaplan-Meier (KM) curves for PFS per IRC in the ITT population.

Table 7: DUO Trial PFS per IRC (ITT Population)

	Duvelisib N = 160	Ofatumumab N = 159
Number of Patients with PFS Events, n (%)	93 (58.0)	110 (69.2)
Progression	74 (46.3)	101 (63.5)
Death	19 (11.9)	9 (5.7)
Number of Patients Censored, n (%)	67 (41.9)	49 (30.8)
KM Estimate, month		
Median PFS (95% CI)	13.3 (12.1, 16.8)	9.9 (9.2, 11.3)
Median follow-up (95% CI)	21.6 (16.6, 22.1)	16.5 (14.0, 23.2)
Hazard Ratio[1] (95% CI)	0.52 (0.39, 0.69)	
p-value[2]	<0.0001	

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; PFS, progression-free survival
[1] Stratified Cox proportional hazards model.
[2] One-sided stratified log-rank test.
Data cutoff 5/19/2017
Source: FDA analysis

Figure 2: Kaplan-Meier Curves for PFS per IRC (ITT Population)



Data cutoff 5/19/2017
Source: FDA analysis

Since the primary efficacy analysis of PFS per IRC assessment (data cutoff 5/19/2017) demonstrated a statistically significant PFS advantage, all subsequent PFS analyses were considered exploratory. As shown in Table 8, with a median follow-up of 52 months, PFS per investigator demonstrated similar findings to the initial evaluation. As noted with the initial PFS evaluation, a higher proportion of patients on the duvelisib arm (19%) died before progression compared to the ofatumumab arm (8%). This reiterates the continued concern for an increased risk of death due to toxicity with duvelisib.

Table 8: DUO Trial Updated PFS per Investigator (ITT Population)

	Duvelisib N = 160	Ofatumumab N = 159
PFS Events, n (%)	114 (71.3)	134 (84.3)
Progression	83 (51.9)	122 (76.7)
Death before progression	31 (19.4)	12 (7.5)
Censored, n (%)	46 (28.8)	25 (15.7)
Median PFS (months) (95% CI)	17.8 (15.1, 22.0)	9.6 (9.3, 11.4)
Hazard Ratio (95% CI) [a]	0.37 (0.28, 0.49)	

Abbreviations: CI, confidence interval; PFS, progression-free survival
[a] Stratified Cox proportional hazards model.
Data cutoff 1/22/2021
Source: FDA analysis

For PFS results in the indicated population, those who have received at least 2 prior therapies, refer to Appendix 4.

Secondary Endpoints

Overall Response Rate

Following the initial evaluation of PFS, overall response rate per IRC was analyzed as a key secondary endpoint and included patients that achieved a complete response or partial response. ORR was tested at an overall one-sided alpha level of 0.025. Overall response rate was higher for duvelisib (73%; 95% CI: 66, 80) compared to ofatumumab (45%; 95% CI: 38, 53) and statistically significant with an odds ratio of 3.4 (95% CI: 2.09, 5.43) and one-sided p-value <0.0001 (stratified Cochran-Mantel-Haenszel test). Based on IRC, the estimated median duration of response (DOR) was 11.1 months with duvelisib and 9.3 months with ofatumumab. Table 9 below provides a summary of ORR per IRC.

Table 9: DUO Trial Overall Response Rate per IRC (ITT Population)

Response, n (%)	Duvelisib N = 160	Ofatumumab N = 159
CR	1 (0.6)	1 (0.6)
CRi	0 (0.0)	0 (0.0)
PR	116 (72.5)	71 (44.7)
SD	34 (21.3)	63 (39.6)
PD	2 (1.3)	10 (6.3)
Other[1]	6 (3.8)	14 (8.8)
ORR (CR, CRi, or PR)		
n (%)	117 (73.1%)	72 (45.3%)
p-value[2]	<0.0001	
Odds ratio (95% CI)	3.4 (2.1, 5.4)	
Median DOR, months (95% CI)	11.1 (9.2, 18.3)	9.3 (7.7, 11.0)

Abbreviations: CR, complete response; CRi, CR with incomplete marrow recovery; DOR, duration of response; PR, partial response, SD, stable disease, PD, progressive disease
[1]Other includes Unknown and No Evidence of Disease.
[2]Cochran-Mantel-Haenszel test controlling for pooled randomization strata.

Data cutoff 5/19/2017
Source: FDA Analysis

For ORR results in the indicated population, those who have received at least 2 prior therapies, refer to Appendix 4.

Overall Survival

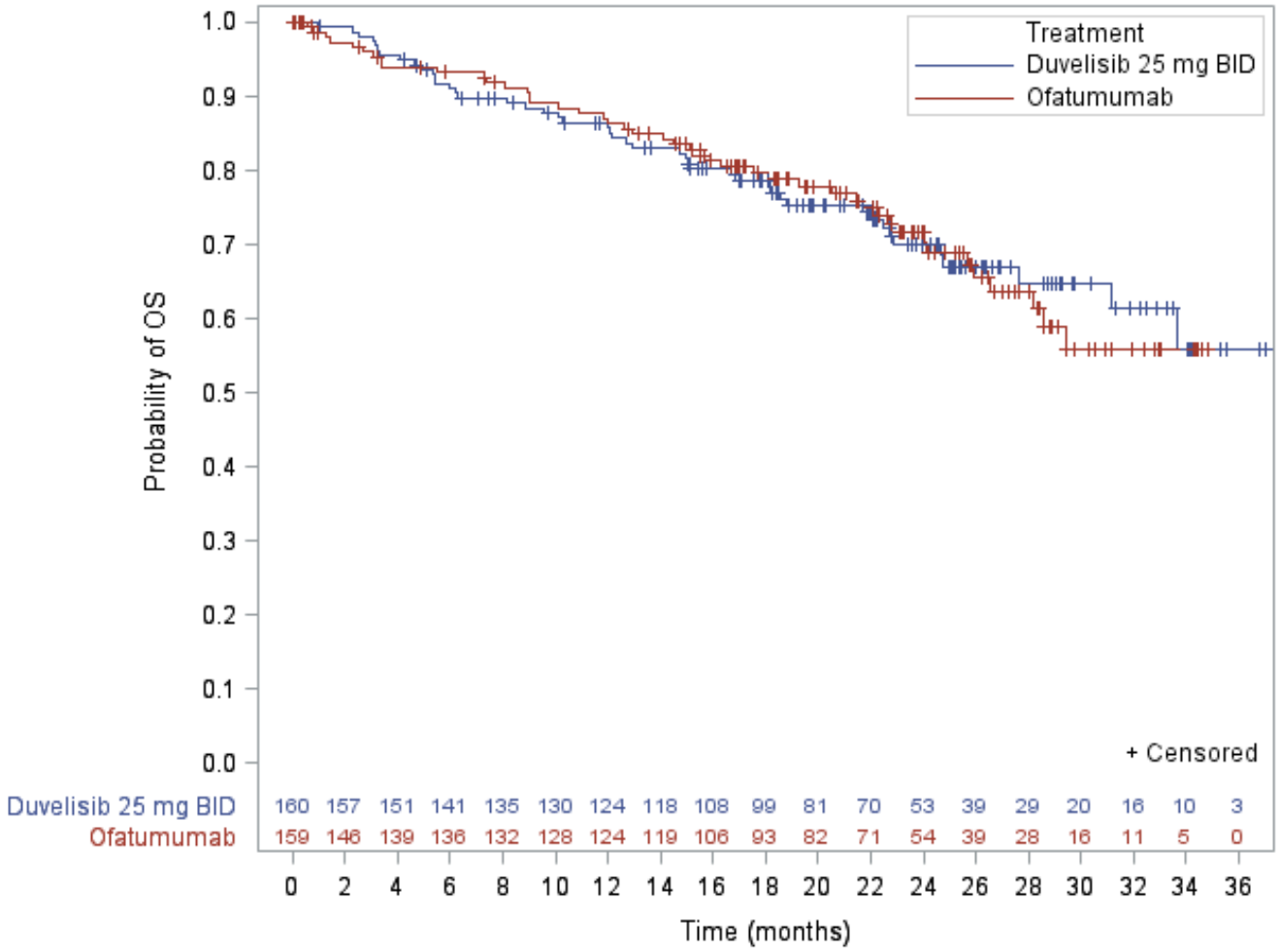
The analysis of overall survival at the time of the initial PFS analysis was immature with a hazard ratio of 0.99 (95% CI: 0.65, 1.50). Table 10 below provides a summary of the initial OS results in the ITT population and the indicated population. The Kaplan-Meier curves for OS per IRC in the ITT population and the indicated population are shown in Figures 3 and 4, respectively. Of the 319 patients in the ITT population, 46 patients (29%) died in the duvelisib arm and 45 patients (28%) died in the ofatumumab arm. The median OS for both duvelisib and ofatumumab were not estimable, with a median follow-up of 24 months for both treatment arms. Of the 196 patients in the indicated population, there were 28 deaths (29%) in the duvelisib arm and 34 deaths (34%) in the ofatumumab arm, with an estimated hazard ratio of 0.82 (95% CI: 0.49, 1.37). The median OS for both duvelisib and ofatumumab were not estimable, with a median follow-up of 24 months.

Table 10: DUO Trial Overall Survival Interim Analysis

	ITT Population (≥1 prior therapy)		Indicated Population (≥2 prior therapies)	
	Duvelisib N = 160	Ofatumumab N = 159	Duvelisib N = 95	Ofatumumab N = 101
Deaths, n (%)	46 (28.8)	45 (28.3)	28 (29.5)	34 (33.7)
Patients censored, n (%)	114 (71.3)	114 (71.7)	67 (70.5)	67 (66.3)
KM estimate, month				
Median OS (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (27.6, NE)	NE (24.1, NE)
Median follow-up (95% CI)	23.8 (22.0, 25.2)	23.7 (22.0, 25.4)	23.9 (21.7, 25.4)	23.7 (21.5, 26.2)
Hazard ratio[1] (95% CI)	0.99 (0.65, 1.50)		0.82 (0.49, 1.37)	

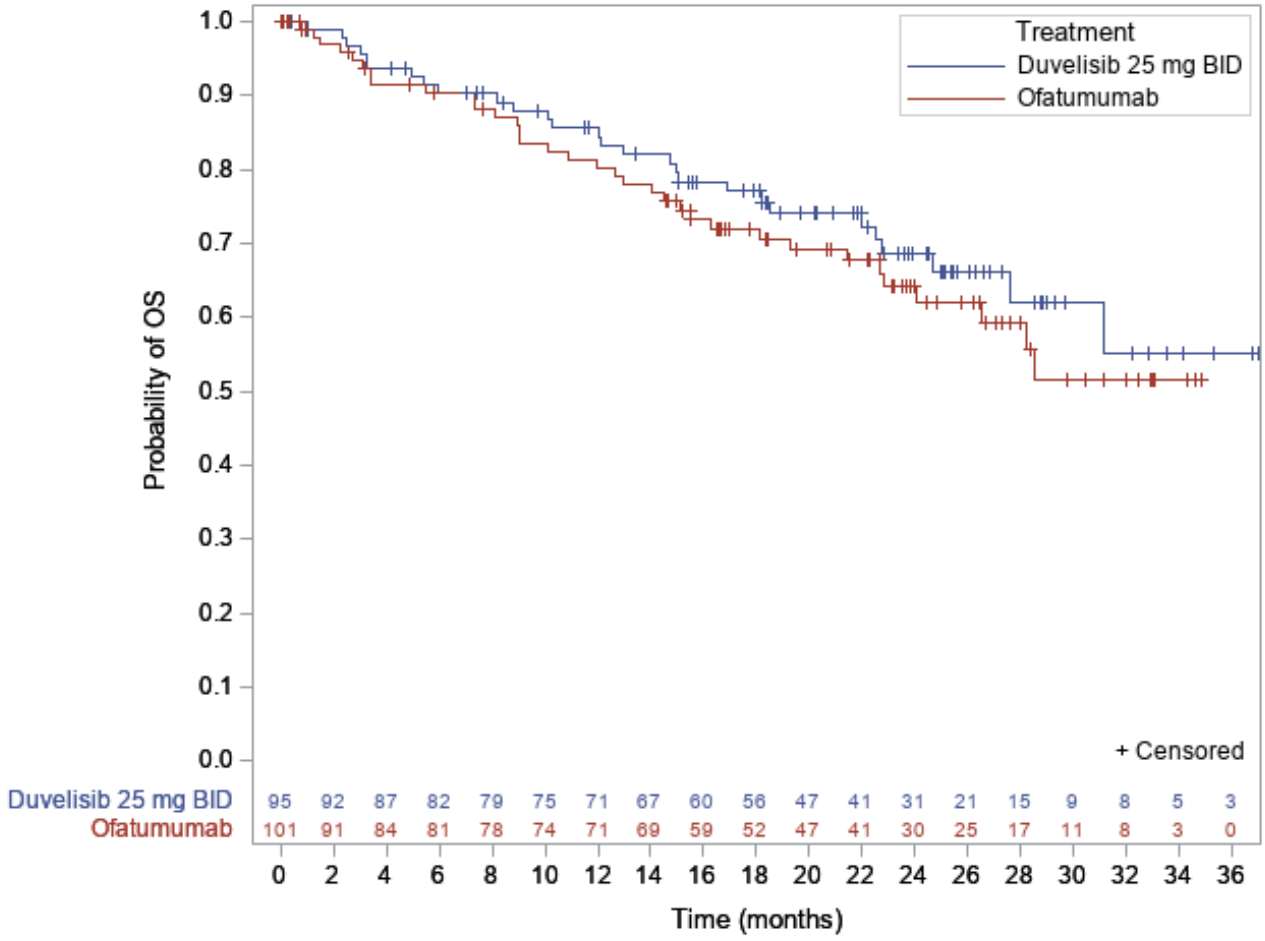
Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; OS, overall survival
[1] Stratified Cox proportional hazards model.
Data cutoff 5/19/2017
Source: FDA analysis

Figure 3: Kaplan-Meier Curves for Overall Survival (ITT Population)



Data cutoff 5/19/2017
Source: FDA analysis

Figure 4: Kaplan-Meier Curves for Overall Survival (Patients With ≥2 Prior Therapies)



Data cutoff 5/19/2017
Source: FDA analysis

The data for the 5-year analysis of overall survival was submitted in June 2021. The 5-year OS results, with an estimated median follow-up time of 63 months in both arms, in both the ITT population and the indicated population are summarized in Table 11. The OS hazard ratio was 1.09 (95% CI: 0.79, 1.51) in the ITT population and 1.06 (95% CI: 0.71, 1.58) in the indicated population. Kaplan-Meier curves of OS for the ITT population and the indicated population are shown in Figures 5 and 6, respectively.

Table 11: DUO Trial 5-Year OS Analysis

	ITT Population (≥1 prior therapy)		Indicated Population (≥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 (95% CI) [a]	1.09 (0.79, 1.51)		1.06 (0.71, 1.58)	
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)

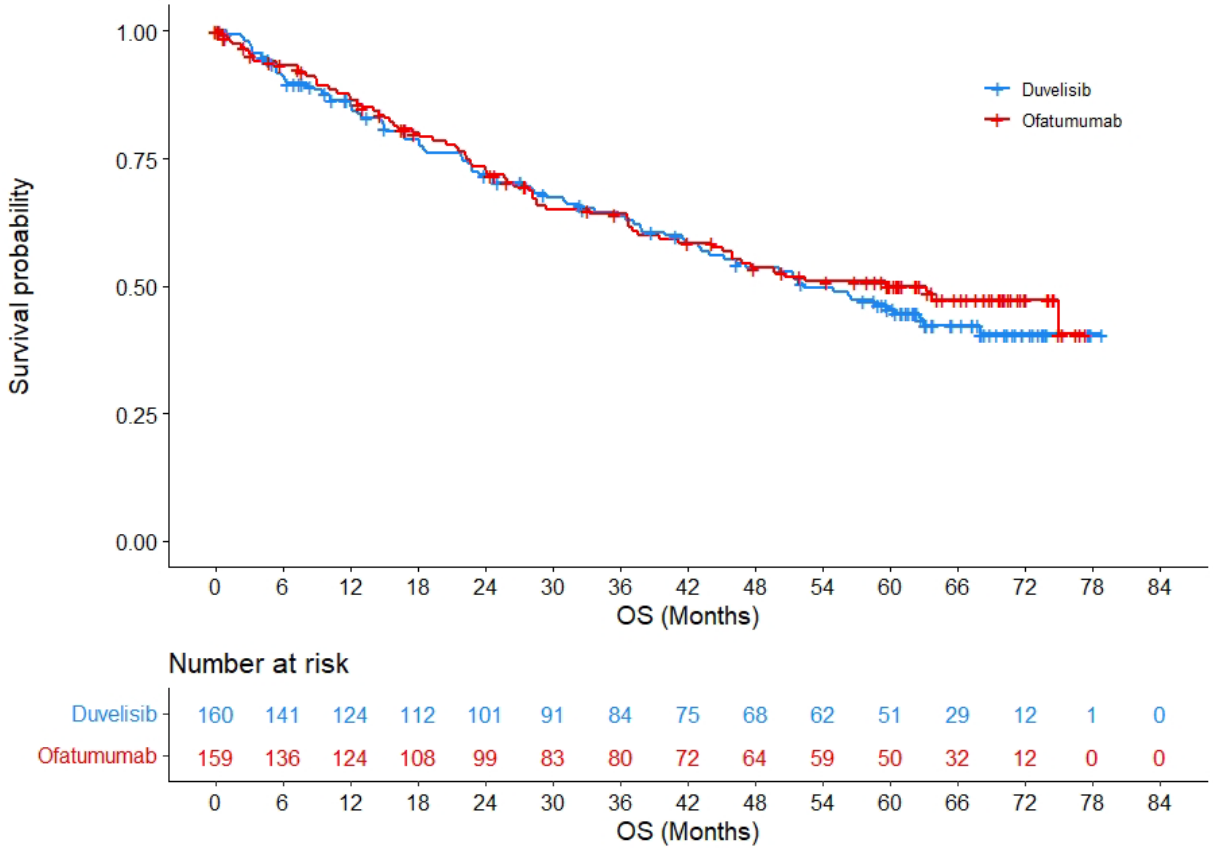
Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival

[a] Stratified Cox proportional hazards model.

Data cutoff: 1/22/2021

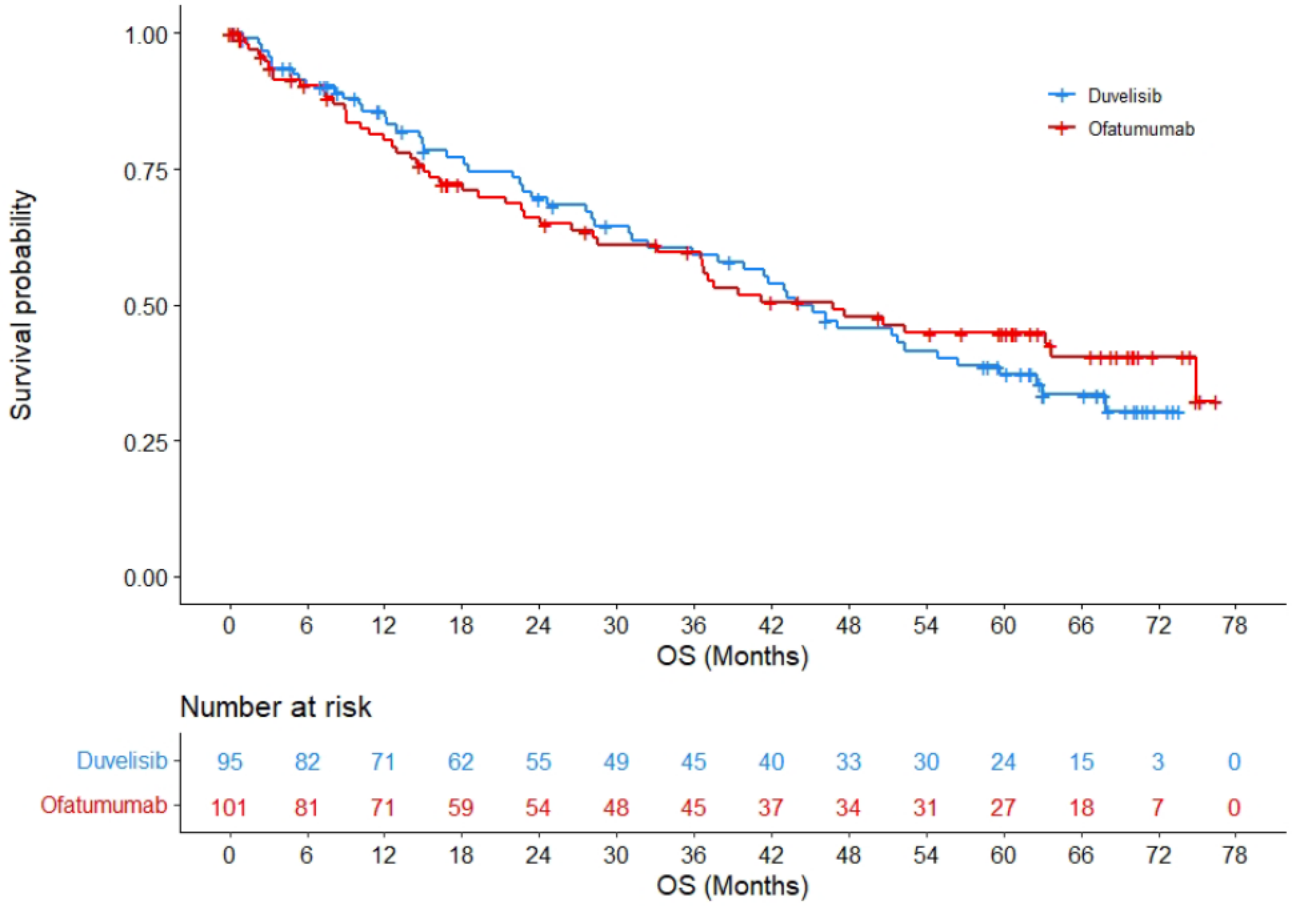
Source: FDA analysis

Figure 5: 5-Year OS Analysis Kaplan-Meier Curves for OS (ITT Population)



Data cutoff 1/22/2021
Source: FDA analysis

Figure 6: 5-Year OS Analysis Kaplan-Meier Curves for OS (Patients With ≥2 Prior Therapies)



Data cutoff: 1/22/2021
Source: FDA analysis

Safety Results

The safety population in the DUO trial included 158 patients who received duvelisib and 155 patients who received ofatumumab. Table 12 below provides an overview of safety in the DUO trial.

Table 12: DUO Trial Summary of Safety

Outcome	Duvelisib N = 158	Ofatumumab N = 155
Median exposure, months (range)	11.6 (0.2, 72)	5.3 (0, 6)
Toxicity, n (%)		
Death due to AE	23 (15)	5 (3)
Grade ≥3 AE	144 (91)	75 (48)
SAE	124 (78)	50 (32)
Actions due to AE, n (%)		
Discontinuation	70 (44)	9 (6)
Dose reduction	48 (30)	2 (1)
Dose interruption	112 (71)	83 (54)
Abbreviations: AE, adverse event; SAE, serious adverse event		

Outcome	Duvelisib N = 158	Ofatumumab N = 155
Data cutoff 1/22/2021 Source: FDA analysis		

In patients treated with duvelisib, the most common (≥20%) adverse events were diarrhea or colitis, neutropenia, pyrexia, fatigue, pneumonia, rash, upper respiratory infection, anemia, cough, and nausea.

Deaths

Shown in Table 13 is a summary of the causes of death in the ITT population. Notably, there is a higher rate of death due to adverse events in the duvelisib arm (14%) compared to the ofatumumab arm (3%).

Table 13: DUO Trial Summary of Deaths (ITT Population)

	Duvelisib N = 160 n (%)	Ofatumumab N = 159 n (%)
Total Deaths	80 (50)	70 (44)
Adverse events	23 (14)	5 (3)
Progressive Disease	21 (13)	26 (16)
Other	23 (14)	28 (18)
Unknown	13 (8)	11 (7)
Data cutoff 1/22/2021 Source: FDA analysis		

Shown in Table 14 is a summary of the causes of death in patients with two or more prior therapies. In this population, there were 13 deaths (14%) due to adverse events in the duvelisib arm and 4 deaths (4%) due to adverse events in the ofatumumab arm.

Table 14: DUO Trial Summary of Deaths (Patients With ≥2 Prior Therapies)

	Duvelisib N = 95 n (%)	Ofatumumab N = 101 n (%)
Total Deaths	52 (55)	49 (49)
Adverse events	13 (14)	4 (4)
Progressive Disease	14 (15)	19 (19)
Other	16 (17)	18 (18)
Unknown	9 (9)	8 (8)
Data cutoff 1/22/2021 Source: FDA analysis		

In the safety population, the primary cause of death due to an adverse event with duvelisib was infection (9%) as shown in Table 15 below.

Table 15: DUO Trial Deaths Due to Adverse Events Based on FDA Adjudication in the Safety Population

	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Total Deaths	79 (50)	70 (45)

	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Adverse events	23 (15)	5 (3)
Infection	14 (9)	1 (<1)
Respiratory	4 (3)	0
Cardiac	1 (<1)	0
Neurologic	1 (<1)	0
SPM	0	1 (<1)
General*	1 (<1)	1 (<1)
Hepatic	0	1 (<1)
Renal	0	1 (<1)
Unknown	2 (1)	0

Abbreviation: SPM, second primary malignancy
*General health deterioration
Data cutoff 1/22/2021
Source: FDA analysis

Serious Adverse Events and Grade ≥3 Adverse Events

Serious adverse events occurred in 78% (124/158) in the duvelisib arm versus 32% (50/155) in the ofatumumab arm. The most common SAEs in the duvelisib arm were infection (40%) and diarrhea or colitis (25%). The most common SAEs and Grade 3 or greater adverse events were similar.

Table 16 below displays the Grade 3 or greater adverse events in ≥5% of patients in the DUO trial.

Table 16: DUO Trial Grade ≥3 Adverse Events in ≥5%

System Organ Class Preferred Term	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Grade ≥3 adverse event	144 (91)	75 (48)
Blood and lymphatic system		
Neutropenia*	76 (48)	55 (35)
Anemia*	35 (22)	10 (6)
Thrombocytopenia*	25 (16)	13 (8)
Gastrointestinal		
Diarrhea-Colitis[1]	43 (27)	3 (2)
AST increased*	5 (3)	2 (1)
ALT increased*	12 (8)	1 (<1)
Infections and infestations		
Pneumonia[1]	36 (23)	5 (3)
Skin and subcutaneous disorders		
Rash	21 (13)	1 (<1)

*Based on laboratory data
[1]Grouped term, see Appendix 3
Data cutoff 1/22/2021
Source: FDA analysis

Treatment Modification due to Adverse Events

Treatment modifications due to adverse events are summarized in Table 17 below. Compared to ofatumumab, there were more treatment discontinuations (44% vs 6%) and dose interruptions (71% vs 54%) in the duvelisib arm. There was a high rate of dose reductions (30%) in the duvelisib arm; dose reductions were prohibited for ofatumumab. In the duvelisib arm, diarrhea-colitis and rash were the most common reasons for discontinuation or reduction. Pneumonia was also a common cause of discontinuation and interruption for duvelisib.

Table 17: DUO Trial Treatment Modifications Due to Adverse Events

	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Discontinuation due to AE	70 (44)	9(6)
Diarrhea-colitis[1]	19 (12)	0 0
Rash	9 (6)	0 0
Pneumonia	6 (4)	0 0
Pneumonitis	5 (3)	0 0
Dose reduction due to AE	48 (30)	2(1)
Diarrhea-colitis[1]	13 (8)	0 0
Rash	7 (4)	0 0
Neutropenia	6 (4)	0 0
AST/ALT increased	6 (4)	0 0
Dose interruption due to AE	112 (71)	83 (54)
Diarrhea-colitis[1]	41 (26)	0
Pneumonia	24 (15)	6 (4)
Neutropenia	20 (13)	11 (7)
Rash	18 (11)	13 (8)
Infusion-related reaction	0	27 (17)

[1]Grouped term, see Appendix 3
Data cutoff 1/22/2021
Source: FDA analysis

The high rate of treatment modifications with duvelisib indicate poor tolerability and uncertainty whether the selected dose of 25 mg BID is appropriate. See Appendix 5 for additional information on the dosing considerations for duvelisib.

Adverse Events of Special Interest

Adverse events of special interest are presented in Table 18 below. The rate of any grade and Grade 3 or greater adverse events for each adverse event of special interest were notably higher in the duvelisib arm compared to the ofatumumab arm.

Table 18: DUO Trial Adverse Events of Special Interest

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	114 (72)	56 (35)	67 (43)	17 (11)
Neutropenia*	105 (66)	76 (48)	80 (52)	55 (35)
Diarrhea-Colitis[1]	94 (59)	43 (27)	21 (14)	3 (2)
AST/ALT Increase*	69 (44)	12 (8)	22 (14)	2 (1)

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Rash[1]	46 (29)	21 (13)	23 (15)	1 (<1)
Pneumonitis[1]	14 (9)	6 (4)	1 (<1)	0

[1]Grouped term, see Appendix 3
*Based on laboratory data
Data cutoff 1/22/2021
Source: FDA analysis

Issues

Potential Overall Survival Detriment with Duvelisib

The 5-year OS results from the DUO trial demonstrate a potential detriment in overall survival in patients treated with duvelisib compared to those treated with ofatumumab, with a HR of 1.09 (95% CI: 0.79, 1.51) in the ITT population. There were more deaths in the duvelisib arm (n=80, 50%) compared to the ofatumumab arm (n=70, 44%). Median OS favors ofatumumab with a median of 63.3 months (95% CI: 41.2, NE) compared to 52.3 months (95% CI: 41.8, 68.0) in the duvelisib arm in the ITT population. The potential overall survival detriment with duvelisib, in the setting of an observed PFS and ORR benefit, suggests that the potential detriment arises from safety issues.

More deaths due to AEs occurred on the duvelisib arm (n=23; 15%) compared to the ofatumumab arm (n=5; 3%) in the safety population. Infection was the greatest driver of deaths due to adverse events on the duvelisib arm. In the duvelisib arm, 9% (n=14/158) of patients experienced a fatal infection versus <1% (n=1/155) of patients on the ofatumumab arm. Notably, the DUO trial was designed to evaluate a continuously administered regimen, duvelisib, compared to a fixed duration regimen with ofatumumab at 7 cycles. Nevertheless, the FDA considers the OS results of the DUO trial indicative of the risk imparted by the treatment as it is intended to be administered. The higher rate of deaths due to adverse events with duvelisib, along with the OS findings, raises concern for potential harm and lack of clinical benefit.

Impact of Crossover on Overall Survival

There was a substantial amount of crossover in the DUO trial, with 90 patients (57%) who crossed over from ofatumumab to receive duvelisib and 9 patients (6%) who crossed over from duvelisib to receive ofatumumab.

The presence of substantial crossover can impact the assessment of time-to-event endpoints such as overall survival. In the case of a drug that beneficially affects an intermediate endpoint such as PFS but has significant toxicity concerns, there is the possibility that substantial crossover may mask a difference between treatment groups that would have favored the control arm by causing harm to the control group. While the interpretation of overall survival is more challenging in the context of crossover, the outcomes of patients following crossover can be examined and additional statistical analyses can be performed to further characterize its impact.

The rates of fatal AEs following crossover were explored, given the toxicity concerns with duvelisib, and statistical analyses were conducted to assess the impact of crossover on the OS results. The results of these analyses are presented below, and support the finding of potential harm with duvelisib.

In those who crossed over from duvelisib to ofatumumab (n=9), there were no deaths due to AEs, while in those who crossed over from ofatumumab to duvelisib (n=90), there were 9 deaths due to AEs (10%), predominantly due to infection. This reiterates the risk of fatal infection with duvelisib and the potential harm to patients.

Table 19: DUO Trial Deaths Due to Adverse Events Following Subsequent Crossover Treatment with Duvelisib or Ofatumumab

	Duvelisib to Ofatumumab N = 9 n (%)	Ofatumumab to Duvelisib N = 90 n (%)
Adverse events	0	9 (10)
Infection	0	5 (6)
Cardiac	0	2 (2)
Respiratory	0	1 (1)
General	0	1 (1)
Data cutoff 1/22/2021 Source: FDA analysis		

To assess the impact of crossover on OS between the two treatment arms, two model-based survival analyses were conducted. The first analysis employed a marginal structural model (MSM) with inverse probability treatment weights (IPTW). The second analysis was based on a rank preserving failure time model (RPFTM).

The results from the two model-based analyses, shown in Table 20 below, take into account the effect of crossover and are consistent with the OS results from the primary analysis, supporting the potential for harm and a potential detriment in OS. Refer to Appendix 7 for additional details related to the methods used for these two analyses.

Table 20: DUO Trial - Impact of Crossover Effect using Different Statistical Models

Method	OS HR (95% CI)
Primary Analysis	
5-Year OS - ITT	1.09 (0.79, 1.51)
Model Based Causal Inference	
MSM-IPTW	1.06 (0.72, 1.59)
Rank Preserving Failure Time Model (RPFTM)	1.22 (0.88, 1.67)
Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; MSM-IPTW, marginal structural model with inverse probability treatment weights; OS, overall survival Data cutoff: 1/22/2021 Source: FDA's analysis	

OS Sensitivity Analyses

Additional post-hoc analyses were conducted to assess the consistency of the OS effect, including 1) OS analysis at different time points, 2) Unstratified Cox model for treatment effects on OS, 3) Cox model adjusting for region (US

vs. Non-US), 4) Cox model using multivariable Cox regression, and 5) Subgroup analysis for OS by baseline characteristics.

Table 21 and Figure 7 below provide the FDA's additional OS analysis results. The post-hoc and subgroup analyses demonstrate a similar trend as that from the primary OS analysis in the ITT population (HR 1.09, 95% CI: 0.79, 1.51), supporting the concern for potential harm and lack of clinical benefit regarding OS. Of note, all post-hoc analyses are considered hypothesis-generating and exploratory.

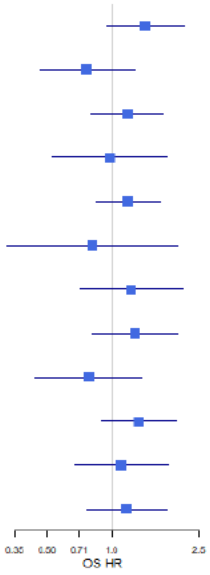
Table 21: Summary of FDA OS Sensitivity Analyses

Analysis	HR (95% CI)
ITT OS analysis (data cut-off: 05/19/2017)	0.99 (0.65, 1.50)
ITT OS analysis* (data cut-off: 01/22/2021)	1.09 (0.79, 1.51)
ITT unstratified Cox Model*	1.11 (0.80, 1.53)
ITT analysis adjusting for region (US vs non-US)	1.13 (0.82, 1.55)
ITT analysis using multivariable Cox regression [a]	1.15 (0.83, 1.58)

* The analysis was based on FDA's adjudicated cause of death
[a] Cox model adjusting treatment, age, >2= prior therapies (Yes vs. No), deletion of 17p or tP53 mutation (Yes vs. No)
Data cutoff 1/22/2021
Source: FDA analysis

Figure 7: Forest Plot of Hazard Ratio of Overall Survival in Major Subgroups

Group		Deaths DUV	Deaths OFA	OS Hazard Ratio (95% CI)
Gender	Male (n=191)	52	40	1.42 (0.94, 2.14)
	Female (n=128)	28	30	0.76 (0.46, 1.28)
Age	>=65 (n=217)	60	48	1.17 (0.80, 1.72)
	<65 (n=102)	20	22	0.98 (0.53, 1.79)
Region	non-US (n=268)	70	61	1.18 (0.84, 1.67)
	US (n=51)	10	9	0.81 (0.33, 2.00)
del17p or TP53 mutation	Yes (n=100)	28	25	1.23 (0.72, 2.12)
	No (n=167)	43	33	1.28 (0.81, 2.02)
Refractory/Early Relapse to Purine Trt	Yes (n=98)	24	24	0.78 (0.44, 1.37)
	No (n=221)	56	46	1.33 (0.90, 1.97)
Prior anti-cancer therapy <12 month	Yes (n=115)	32	31	1.10 (0.67, 1.80)
	No (n=203)	48	39	1.16 (0.76, 1.78)



Data cutoff: 1/22/2021
Source: FDA's analysis

Statistical Considerations in OS Analysis

The FDA would like to highlight the following additional considerations related to the statistical methods used to evaluate survival in a randomized clinical trial.

- The OS hazard ratio is the conventional approach to capturing the survival profile in a randomized trial and was the pre-specified method for analysis of overall survival in the DUO trial. Analysis results from other approaches, such as the restricted mean survival time (RMST) approach, are heavily dependent on the time interval used for calculation and a small time interval shift could cause changes in the results that might alter the conclusion. In the DUO trial, RMST analysis is a post-hoc analysis without alpha adjustment and one should be cautious in the interpretation of analysis results from RMST analysis. These evaluations of overall survival via RMST are considered hypothesis-generating, rather than inferential. See Appendix 6 for OS by RMST.

- Subgroup analyses, which are not pre-specified at the initiation of the study and are not supported by an adequate sample size, should not be considered as evidence to support a treatment effect. The subgroup analysis in a population of refractory patients that was conducted by the Sponsor is a post-hoc, exploratory, hypothesis-generating analysis subject to "random high" bias and the probability of Type I error is increased when multiple analyses are conducted. The analysis of overall survival in this limited population does not provide evidence supporting a conclusion for a treatment effect. Refer to Appendix 8 for additional considerations related to subgroup analyses.

In general, overall survival is considered the paramount endpoint in randomized trials in patients with cancer, given that the evaluation of overall survival informs efficacy, as well as safety. Due to the toxicity concerns identified and the immaturity of OS data at the time of the primary analysis of the DUO trial, the importance of an evaluation of overall survival with adequate follow up is further highlighted. We consider the 5-year overall survival data from the DUO trial in the ITT population and indicated population as evidence that there is a potential for harm to patients with duvelisib.

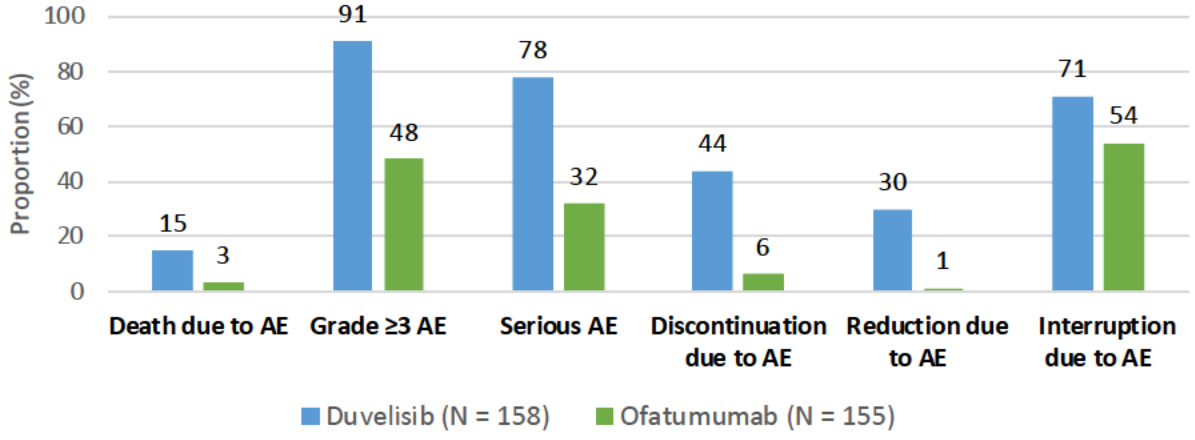
Other Regulatory Agencies

Of note, the regulatory actions of other agencies, such as the European Medicines Agency, are not relevant to the discussion at the ODAC and FDA regulatory decisions. The FDA must make regulatory decisions that are consistent with the U.S. legal and regulatory framework. That framework requires us to consider whether the updated survival and safety information from the DUO trial and the PI3K inhibitor class provides evidence of clinical benefit with duvelisib in accordance with its U.S.-approved indication. The information discussed at the ODAC should be viewed independently to inform decisions regarding benefits and risks of duvelisib for the indicated U.S. patient population.

Substantial Toxicity and Poor Tolerability

Treatment with duvelisib demonstrated substantial toxicity. The duvelisib arm had higher rates of grade 3 or greater adverse events, serious adverse events, and treatment modifications due to adverse events, as shown in Figure 8 below.

Figure 8: DUO Trial Summary of Safety



Dose reductions were not permitted for obinutuzumab.
Abbreviations: AE, adverse event
Source: FDA analysis, Data cutoff 1/22/2021

The difference in toxicity between arms is primarily driven by infection and immune-mediated toxicities associated with the PI3K inhibitor class of diarrhea or colitis, hepatotoxicity, rash, and pneumonitis. Notably, the rate of grade 3 or greater infection is higher in the duvelisib arm (35%) compared to the ofatumumab arm (11%) and the incidence of grade 3 or greater PI3K inhibitor-associated toxicities, other than neutropenia, are 2 to 3 times or more higher in the duvelisib arm compared to the ofatumumab arm. These findings are consistent with the mechanism of action of duvelisib, with its impact on regulatory T-cell function and immune modulation, and with the toxicity profile seen across the PI3K inhibitor class.

Table 22: DUO Trial Adverse Events of Special Interest

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	114 (72)	56 (35)	67 (43)	17 (11)
Neutropenia*	105 (66)	76 (48)	80 (52)	55 (35)
Diarrhea-Colitis[1]	94 (59)	43 (27)	21 (14)	3 (2)
AST/ALT Increase*	69 (44)	12 (8)	22 (14)	2 (1)
Rash[1]	46 (29)	21 (13)	23 (15)	1 (<1)
Pneumonitis[1]	14 (9)	6 (4)	1 (<1)	0

[1]Grouped term, see Appendix 3
*Based on laboratory data
Data cutoff 1/22/2021
Source: FDA analysis

Patient-Reported Outcomes (PRO)

The FDA disagrees with the Sponsor's statement that duvelisib had a positive impact on quality of life compared to ofatumumab. First, this claim is primarily based on the results from the EuroQol-5 Dimension (EQ-5D), which is a

generic preference based instrument, and does not adequately capture important and relevant symptoms and function in the trial population.

The results from the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) showed no improvement with duvelisib treatment compared to ofatumumab. Regardless, no meaningful interpretation can be made from the PRO results from FACIT and EQ-5D as the PRO endpoints and methods were insufficient to assess tolerability or to detect meaningful differences between arms in the DUO trial. Given the substantial toxicity and tolerability issues discussed, a more comprehensive approach to patient-reported symptoms and function should have been undertaken in the DUO trial.

The significant toxicity profile of duvelisib was evident at the time of initial approval. While the overall benefit-risk assessment in patients who had received 2 or more prior lines of therapy was favorable at the time, the presence of these significant toxicity findings was a key consideration in the decision to issue a postmarketing requirement to characterize long-term safety and submit OS results with 5 years of follow-up. Based on the results of the 5-year OS analysis, which indicate a potential detriment in overall survival and potential harm to patients on the duvelisib arm, a reassessment of the toxicity data and the overall benefit-risk profile of duvelisib is warranted. In the context of the 5-year OS results, the high rates of Grade ≥3 AEs, SAEs, and treatment modifications seen with continuous treatment with duvelisib suggest an unfavorable toxicity and tolerability profile and should be considered in a current overall benefit-risk assessment.

Dosing Concerns

The approved 25 mg BID oral dosage of duvelisib, administered until disease progression or unacceptable toxicity, was based on a dose-escalation/dose-selection trial of duvelisib monotherapy for patients with advanced hematologic malignancies (Study IPI-145-02) designed to establish the maximum tolerated dose (MTD).

During the dose escalation phase of Study IPI-145-02, 33 patients received duvelisib at doses ranging from 8 mg BID to 100 mg BID. In this phase, the MTD was determined to be 75 mg BID. Dose expansion further evaluated two doses [25 mg BID (n=59) and 75 mg BID (n=118)] in 177 patients with a variety of malignancies. The overall response rate in the dose escalation and dose expansion phase is shown in Table 23.

Table 23: Summary of Best Overall Response by Dose for All Patients in Study IPI-145-02

	Duvelisib Dose Administered (BID)							
	8 mg N = 1	15 mg N = 6	25 mg N = 66	35 mg N = 3	50 mg N = 3	60 mg N = 4	75 mg N = 124	100 mg N = 3
ORR, n (%)	1 (100)	2 (33)	43 (65)	3 (0)	2 (67)	2 (50)	42 (34)	0 (0)
Source: IPI-145-02 CSR								

In a subset of those patients, the evaluation of best overall response in patients with indolent NHL, R/R CLL, and treatment-naïve CLL is shown in Table 24 below with activity observed at doses as low as 8 mg BID.

Table 24: Summary of Best Overall Response by Dose for Patients with Indolent NHL, R/R CLL, and Treatment-Naïve CLL in Study IPI-145-02

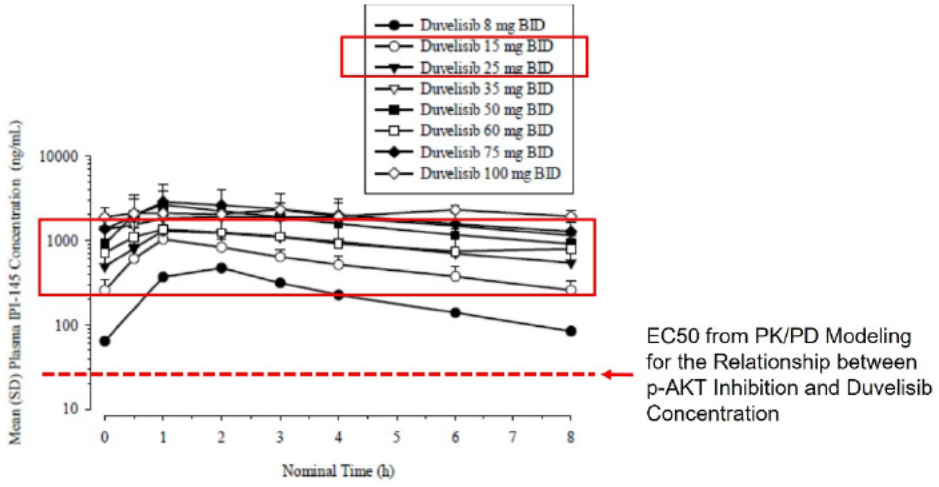
	Dose (administered BID)									
	8 mg		15 mg		25 mg		50 mg		75 mg	
	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)	N	ORR (95% CI)
Indolent NHL			1	100%	14	64.3%	1	100%	15	46.7%

	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)
				(2.5, 100)		(35.1, 87.2)		(2.5, 100)		(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)				
Abbreviation: TN, treatment naive Source: IPI-145-02 CSR										

Data from the expansion cohorts indicate that ORR was comparable between the 25 mg and 75 mg BID doses, although activity was seen at 15 mg BID, albeit in a very limited number of patients. Grade ≥3 treatment-emergent adverse events were seen in 80% and 87% of patients at the 25 mg and 75 mg BID doses, respectively. These data support the selection of the 25 mg dose over the 75 mg dose, but the suitability of the 15 mg dose remained unexplored.

In ex vivo studies to assess effectiveness of duvelisib, the effect of duvelisib on the second messenger system p-AKT was assessed. The PD data, shown in Figure 9 below, suggested that maximal p-AKT suppression was observed at plasma concentrations that would be achieved at the 25 mg BID dose, and higher duvelisib concentrations did not provide additional suppression of p-AKT levels. Although this supported the selection of the 25 mg dose, lower doses were not tested and the concentrations necessary for p-AKT suppression will also be achieved at doses as low as 15 mg BID.

Figure 9: Mean Duvelisib Plasma Concentrations following Multiple Dose Oral Administration of Duvelisib – Cycle 2, Day 1 with reference p-AKT inhibition EC50

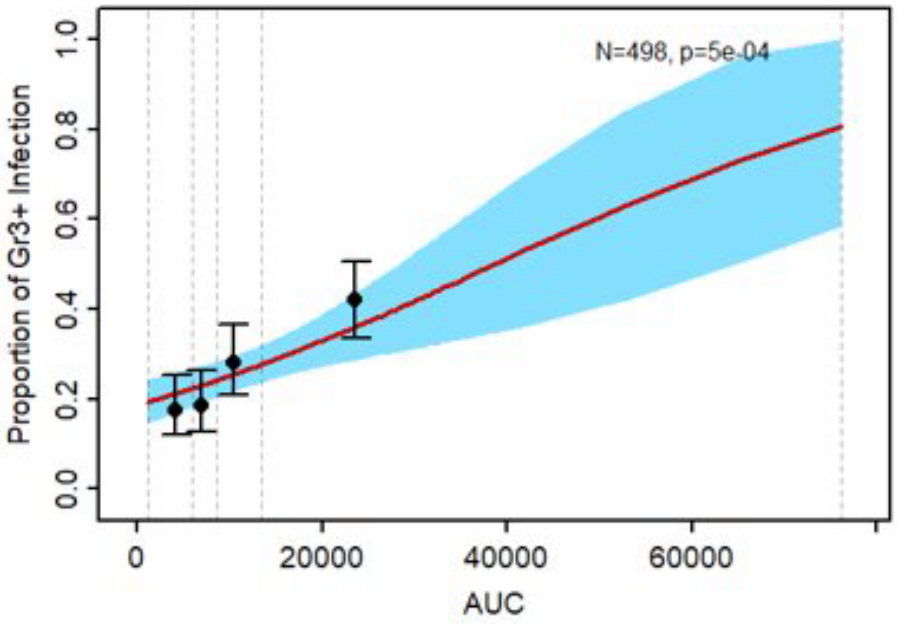


Source: Based on data from IPI-145-02 CSR

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 exposure-response (E-R) relationships were observed between duvelisib exposure and efficacy endpoints in the two studies (i.e., IPI-145-06 and IPI-145-07) due to limitations with the narrow dose/exposure range. The limited dose exploration in the dose finding studies in a small number of patients also precluded 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 infection in the dose range of 8 mg to 75 mg as shown in Figure 10

below. The E - R analyses for safety also showed significant positive relationships between the probability of Grade 3 or higher pneumonia and transaminase increase, as shown in Figure 15 in Appendix 5.

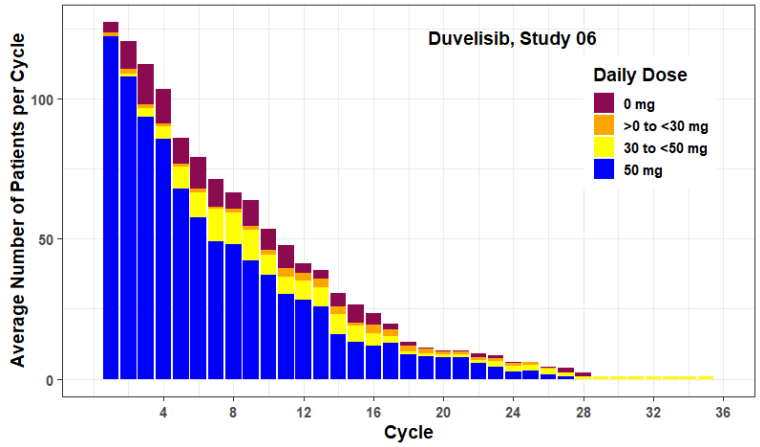
Figure 10: Exposure-Response Relationships for Grade 3 or Higher Infection



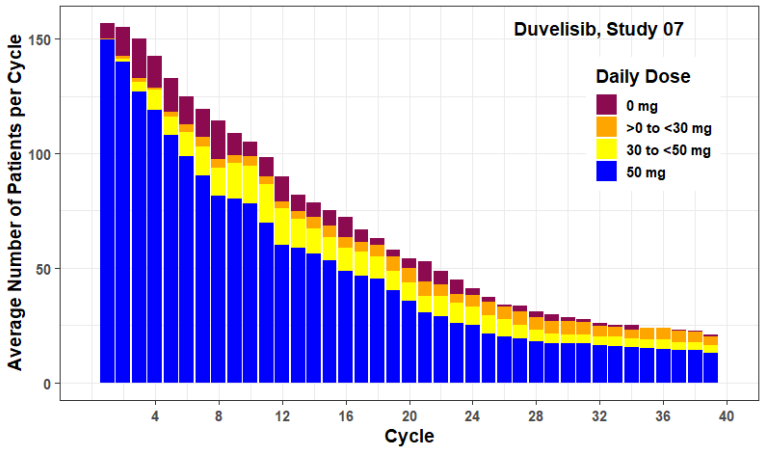
Source: NDA 211155 Multidisciplinary Review at Drugs@FDA

In Studies IPI-145-06 and IPI-145-07, at the 25 mg BID dose, 84% of patients experienced Grade 3-4 TEAEs. The most common TEAEs were 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 Figure 11 below.

Figure 11: 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



Source: Based on NDA 211155, Submission 0265

As shown in Figure 8 and Table 17, approximately 30% of patients experienced a dose reduction due to AE in study IPI-145-07 and approximately 71% of patients had to interrupt their dosing dose to AEs**.** The most common TEAEs leading to dose reduction of duvelisib in DUO Trial were diarrhea or colitis (8%), transaminase elevation, neutropenia, and rash (4% each).

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.

PI3K Inhibitor Class Concerns

On April 21, 2022, the Oncologic Drugs Advisory Committee convened to discuss the PI3K inhibitor drug class and the data requirements for future approvals of PI3K inhibitors in patients with hematologic malignancies. The issues discussed included concerning trends in overall survival in multiple randomized trials, toxicity of the PI3K inhibitor class, inadequate dose optimization, and trial design considerations regarding the limitations of single-arm trials.

The PI3K inhibitors discussed and the trials supporting the initial approvals of PI3K inhibitors in hematologic malignancies and the post-approval developments are summarized in the table below.

Table 25: 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)		
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) [6] 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	5-year 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)		

Initial Approval Information [a]	Post-Approval Trials	Outcome
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) [7] • Interim OS, HR 1.23 [8 c, e]	Voluntary withdrawal of BLA/NDA based on UNITY-CLL (4/2022) Voluntary withdrawal of FL/MZL indications (4/2022)

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

Six randomized trials of PI3K inhibitors in hematologic malignancies have demonstrated detriments in overall survival in the setting of an advantage or potential advantage in PFS, which is unprecedented in oncology. The overall survival information in these trials were early and represented a low number of events, yet the same pattern was 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 that the potential detriment in overall survival was due to toxicity.

The PI3K inhibitors have substantial toxicities that can be fatal or serious. The toxicities observed are driven by PI3K-associated toxicities of infection and immune-mediated toxicities related to the mechanism of action of these agents. In the randomized trials evaluating PI3K inhibitors, each trial has shown higher rates of Grade 3 or greater toxicity, serious adverse events, and treatment modifications; with the differences in safety driven by the PI3K-associated toxicities.

Given the toxicity concerns with the PI3K inhibitor class, adequate dose exploration and optimization is warranted. The PI3K inhibitors exhibit a narrow range between an effective and toxic dose. Across the class, there has been limited dose exploration. For each approved PI3K inhibitor, there were exposure response relationships for safety, primarily for PI3K-associated toxicities, however, exposure response relationships for efficacy were generally not observed. In general, there has been insufficient dose exploration as monotherapy and in combination for these agents.

The initial evaluation of benefit-risk for PI3K inhibitors in patients with indolent non-Hodgkin lymphoma (NHL) were based on single-arm trials. 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.

The ODAC voting question was:

- Given the observed toxicities with the PI3K inhibitor class, previous randomized trials with a potential detriment in OS, and a narrow range between effective and toxic doses, should future approvals of PI3K inhibitors be supported by randomized data?

The ODAC voted in favor (16 – yes, 0 – no, 1 – abstain) of requiring randomized data to support future approvals of PI3K inhibitors in patients with hematologic malignancies.

The committee members all agreed that the information presented, including the OS data across multiple randomized controlled trials and the toxicity profile seen across the drug class, was concerning. The discussion regarding endpoints and trial design for PI3K inhibitors included consensus that the use of PFS as the primary efficacy metric should be evaluated in the context of OS and that OS is the paramount endpoint in informing benefit-risk for a drug class with substantial toxicities. The committee members reiterated how crucial the benefit-risk assessment is and discussed the necessity of adequate data to ensure the safety and efficacy of a drug and to rule out potential for harm.

The discussion held at the class-wide PI3K inhibitor ODAC highlighted the importance of the OS endpoint and raised the need for inclusion of OS data with adequate follow up in the overall benefit-risk assessment of this class of drugs. In line with the discussions from the class-wide ODAC, we consider the new information available from the 5-year OS analysis of the DUO trial to be important data that must be incorporated into the benefit-risk assessment of duvelisib.

Current Benefit-Risk

The FDA considers the results of the 5-year OS analysis to significantly impact the assessment of the benefit-risk profile of duvelisib in patients with CLL or SLL. The initial approval of duvelisib was based on a PFS advantage demonstrated in the duvelisib arm in both the ITT population and the indicated population, those who had received at least 2 prior lines of therapy. At the time of initial approval, overall survival data were immature with a hazard ratio of 0.99 (95% CI: 0.65, 1.50) and in light of the significant toxicities seen on the duvelisib arm, a postmarketing requirement was issued to submit OS results with 5 years of follow up. The 5-year OS results, with a hazard ratio of 1.09 in the ITT population and 1.06 in the indicated population, in the setting of a primary PFS and ORR advantage, indicate a primary safety concern with treatment with duvelisib.

While a comprehensive benefit-risk assessment is performed during the initial review of a drug, the FDA considers new information that becomes available in the post-marketing setting to be important in guiding the continuous reassessment of benefit-risk. In the case of duvelisib in patients with R/R CLL or SLL, the initial approval was based on a PFS endpoint and we consider that with the availability of new information on OS, an endpoint that is a direct measure of clinical benefit, reassessment of the benefit-risk of duvelisib for this indication is warranted.

The 5-year OS data, taken together with the toxicity profile, which is consistent with the toxicity profile seen across the PI3K inhibitor drug class, tolerability concerns, and uncertainty regarding the selected dose of duvelisib, suggest that the current-benefit risk profile of duvelisib is unfavorable and indicate the potential for harm to patients.

Additional Issues

Some additional issues raised during the FDA review of the DUO trial and 5-year OS data include the following:

- Population: The DUO trial excluded patients who had previously received a PI3K inhibitor or a BTK inhibitor and did not include any patients who received the Bcl-2 inhibitor, venetoclax. At the time that the study

was designed and initiated, the rationale for excluding patients who had received a BTK inhibitor was based on common mechanisms of the agents, with both BTK inhibitors and PI3K inhibitors targeting the B-cell receptor signaling pathway.

We note that since initiation of the DUO trial, the field of CLL/SLL treatment has evolved significantly, with the approval of multiple BTK inhibitors and venetoclax, in the front-line setting and beyond.[2] Given that current patients with relapsed or refractory CLL or SLL are likely to have been exposed to one or more BTK inhibitors and to venetoclax, there is uncertainty about the applicability of efficacy results from the DUO trial to the current U.S. patient population.

- Treatment: Fixed vs. Continuous Therapy: We note that the DUO trial was designed to evaluate a fixed duration treatment (ofatumumab) compared to continuous therapy (duvelisib). While a continuous regimen may result in cumulative toxicity compared to a fixed-dose regimen, we consider this evaluation in the context of a randomized trial to allow a comparative assessment of efficacy and safety of the treatments as they are intended to be administered and adequately qualifies the risk with the respective treatments. Further, duvelisib is associated with late-onset infections and immune-mediated toxicities, reinforcing the risk of continuous administration and the need to assess safety throughout treatment.

- Death before progression: At the time of the primary analysis, 21 patients (13.1%) on the duvelisib arm died before progression, compared to 12 patients (7.5%) on the ofatumumab arm. At the time of the 5-year OS analysis, the difference between arms became more pronounced, with 31 patients (19.4%) on the duvelisib arm who died before progression and 12 patients (7.5%) on the ofatumumab arm who died before progression. The higher rates of death before progression on the duvelisib arm and the increase in deaths before progression on the duvelisib arm relative to the ofatumumab arm with additional follow up support the OS and toxicity/tolerability data suggesting a primary safety concern with duvelisib. Notably, in patients with CLL and SLL, progression isn't necessarily an indication for treatment, which is an important consideration given the rate of death prior to progression with duvelisib.

- Control Arm: The selected control arm of ofatumumab may not be generalizable or applicable to a U.S. patient population given the current treatment landscape, in which targeted therapies with demonstrated survival advantages, have replaced the use of chemoimmunotherapy or immunotherapy alone. Even at the time of trial conduct, only 16% of patients were enrolled in the U.S.

Conclusions

The results from the DUO trial demonstrate a potential detriment in overall survival and potential harm to patients treated with duvelisib. Due to the toxicity concerns with duvelisib at the time of initial approval, FDA issued a postmarketing requirement per Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act to submit OS results with 5 years of follow up from the DUO trial based on concerns of fatal and serious toxicity with duvelisib.

With a median OS follow up of 63 months in both arms at the time of the 5-year OS analysis, in the ITT population, there were 80 deaths (50%) in the duvelisib arm and 70 deaths (44%) in the ofatumumab arm with an estimated HR of 1.09 (95% CI 0.79, 1.51). At the time of the 5-year OS analysis, in the indicated population, those who had received ≥2 prior lines of therapy, there were 53 deaths (55.8%) in the duvelisib arm and 49 deaths (48.5%) in the ofatumumab arm with an estimated HR of 1.06 (95% CI 0.71, 1.58). In the setting of a benefit in PFS and ORR, the potential detriment in OS indicates a safety concern. There is a higher rate of death due to adverse events in the

duvelisib arm (15%) compared with the ofatumumab arm (3%). The major difference in deaths due to adverse events is fatal infections, 9% in the duvelisib arm and <1% in the ofatumumab arm.

The DUO trial allowed crossover upon confirmed disease progression, which can impact the assessment of overall survival. Nevertheless, of the 90 patients that crossed over from ofatumumab to receive subsequent duvelisib, 10% of patients experienced fatal adverse events, primarily due to infection. Because of the risk of fatal toxicity with duvelisib, the allowance of crossover may mask a difference between the treatment arms which may have favored the control arm. Therefore, it is noteworthy that despite the allowance of crossover, a signal for potential harm to patients treated with duvelisib is observed and reinforced by the safety findings.

Safety analysis of the DUO trial showed high rates of toxicity and treatment modifications on the duvelisib arm. Treatment with duvelisib was associated with higher rates of grade 3 or greater toxicity, serious adverse events, and treatment modifications due to adverse events. The difference in toxicity between the arms was primarily driven by infection and immune-mediated toxicities of diarrhea-colitis, hepatotoxicity, rash, and pneumonitis. There were higher rates of treatment discontinuation and dose interruptions due to AEs on the duvelisib arm compared to the ofatumumab arm.

There is uncertainty regarding the appropriateness of the 25mg BID dose of duvelisib. The high rates of treatment modification suggest tolerability concerns. There was limited dose finding with a limited number of patients in the dose escalation study, which limits the ability to explore exposure-response relationships for efficacy. Exposure-response analysis for safety suggests a higher rate of certain Grade ≥3 PI3K-associated toxicities over a range of doses evaluated. Ultimately, further dose exploration may be needed to identify a duvelisib dose that is efficacious and has a more tolerable safety profile.

Overall survival is considered an important metric of both safety and efficacy and thus, serves as an objective measure of clinical benefit. Taken together, the data from the 5-year OS analysis from the DUO trial, along with the toxicity, tolerability, and dosing concerns outlined above suggest that the current benefit-risk of duvelisib in patients with relapsed or refractory CLL or SLL is not favorable.

Topics for Discussion

Discuss whether the available data

- Demonstrates that duvelisib is safe in patients with relapsed or refractory CLL/SLL
- Impacts the current assessment of benefit-risk in the remaining duvelisib indication for patients with relapsed or refractory CLL/SLL.

References

1. Noone AM, H.N., Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds), SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, poster to SEER web site, April 2018.
2. Burger, J.A., Treatment of Chronic Lymphocytic Leukemia, NEJM 2020, Jul 30; 383 (5): 460-473
3. Francis, S., M. Karanth, G. Pratt, J. Starczynski, L. Hooper, C. Fegan, C. Pepper, D. Valcarcel, D. W. Milligan and J. Delgado (2006). The effect of immunoglobulin VH gene mutation status and other prognostic factors on the incidence of major infections in patients with chronic lymphocytic leukemia. Cancer 107(5): 1023-1033.
4. Stilgenbauer, S. (2015). Prognostic markers and standard management of chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program 2015: 368-377.

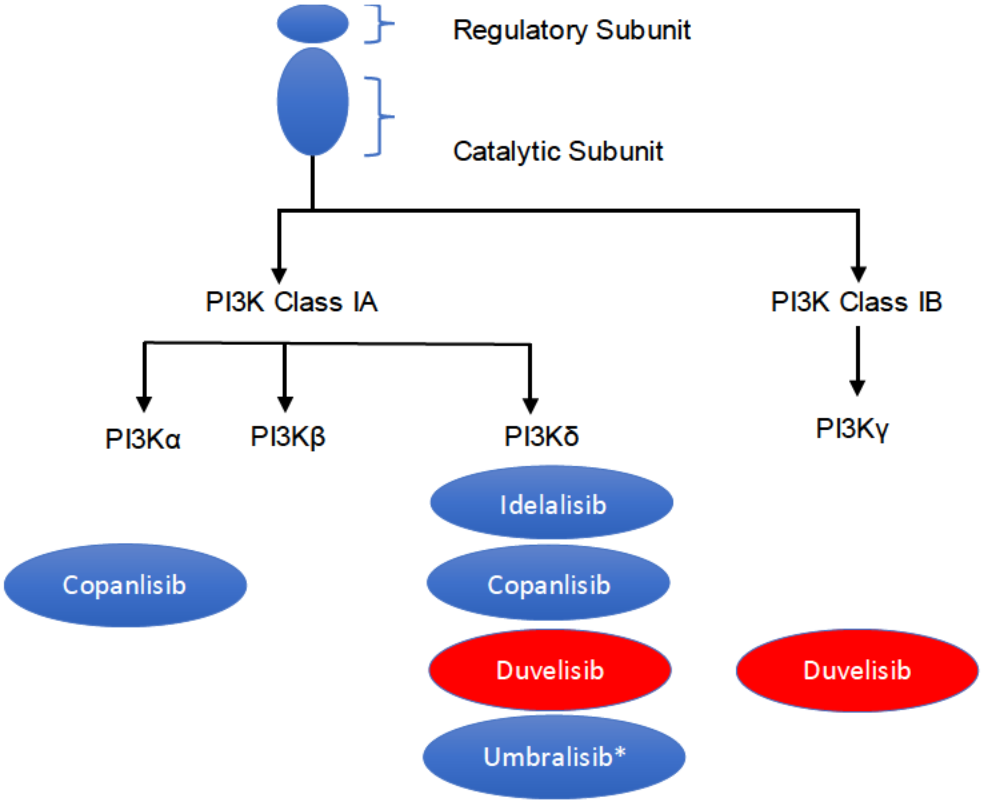
5. Bohn, JP. Agony of choice—selecting chronic lymphocytic leukemia treatment in 2022. memo 15, 121–124 (2022). https://doi.org/10.1007/s12254-022-00804-x
6. Balakrishnan K, Peluso M, Fu M, Rosin NY, Burger JA, Wierda WG, Keating MJ, Faia K, O'Brien S, Kutok JL, Gandhi V. The phosphoinositide-3-kinase (PI3K)-delta and gamma inhibitor, IPI-145 (Duvelisib), overcomes signals from the PI3K/AKT/S6 pathway and promotes apoptosis in CLL. Leukemia. 2015 Sep;29(9):1811-22.
7. Novartis Pharmaceuticals Corporation ARZERRA (Ofatumumab), injection, for intravenous use. Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125326s062lbl.pdf. Accessed August 29, 2022.
8. Xu, Q. and D. Przepiorka (2021). Using marginal structural models to analyze the impact of subsequent therapy on the treatment effect in survival data: Simulations and clinical trial examples. Pharmaceutical Statistics 20(6): 1088-1101.

Appendices

Appendix 1: PI3K Inhibitor Overview

Activating mutations of PI3K are common in hematologic malignancies and affect multiple cellular functions including proliferation, motility, and metabolism. Multiple isoform-specific PI3K inhibitors have received FDA approval for hematologic malignancies; the drugs and the isoforms that they inhibit are shown in Figure 12 below. Duvelisib is a dual delta and gamma PI3K inhibitor.

Figure 12: Overview of the PI3K Inhibitor Drug Class



*Withdrawn from the U.S. market in May 2022

Appendix 2: DUO Trial Eligibility Criteria

Inclusion Criteria: Subjects were required to meet all of the following criteria:

1. ≥ 18 years of age
2. Diagnosis of active CLL or SLL that meets at least one of the IWCLL 2008 criteria for requiring treatment (Binet Stage ≥ B and/or Rai Stage ≥ I)
3. Disease that has progressed during or relapsed after at least one previous CLL/SLL therapy
4. Not appropriate for treatment with a purine-based analogue regimen (per NCCN or European Society for Medical Oncology [ESMO] guidelines), including relapse ≤ 36 months from a purine-based chemoimmunotherapy regimen or relapse ≤ 24 months from a purine-based monotherapy regimen
5. A cytogenetics or FISH analysis of the leukemic cells within 24 months of randomization is required to document the presence or absence of del(17p). Note: if a sample from within 24 months is not available, it should be evaluated as part of the screening laboratory evaluation to inform stratification
6. Measurable disease with a lymph node or tumor mass > 1.5 cm in at least one dimension as assessed by computed tomography (CT)
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (corresponds to Karnofsky Performance Status [KPS] ≥ 60%)
8. Willingness by subject to be randomized to receive either ofatumumab or duvelisib at the dose and schedule defined in the protocol
9. Must meet the following laboratory parameters:
   - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≤ 3 x upper limit of normal (ULN)
   - Total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 2.0 x ULN
   - Hemoglobin ≥ 8.0 g/dL with or without transfusion support
   - Platelet count ≥ 10,000 µL with or without transfusion support
10. For women of childbearing potential (WCBP)**:** negative serum β-human chorionic gonadotropin (βhCG) pregnancy test within 1 week before randomization (WCBP defined as a sexually mature woman who has not undergone surgical sterilization or who has not been naturally post-menopausal for at least 24 consecutive months [women ≤ 55 years] or 12 consecutive months [women > 55 years])
11. Willingness of male and female subjects who are not surgically sterile or postmenopausal to use medically acceptable methods of birth control from the first dose of study drug to 30 days after the last dose of duvelisib and for 12 months after last dose of ofatumumab. Sexually active men, and women using oral contraceptive pills, should also use barrier contraception
12. Ability to voluntarily sign consent for and adhere to the entire study visit schedule and all protocol requirements

13. Signed and dated institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF) before any study specific screening procedures are performed

Exclusion Criteria: Subjects were excluded from the study if they met any of the following criteria:

1. History of Richter's transformation or prolymphocytic leukemia
2. Autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP) that is uncontrolled or requiring > 20 mg once daily (QD) of prednisone (or equivalent) to maintain hemoglobin > 8.0 g/dL or platelets > 10,000 µL without transfusion support
3. Refractory to ofatumumab (defined as progression or relapse < 12 months of receiving ofatumumab monotherapy or < 24 months of receiving an ofatumumab-containing regimen)
4. Prior allogeneic transplant (prior autologous stem cell transplant > 6 months prior to study entry is permitted)
5. Known central nervous system (CNS) lymphoma or leukemia; subjects with symptoms of CNS disease must have a negative CT scan or negative diagnostic lumbar puncture prior to randomization
6. Prior exposure to a PI3K inhibitor (e.g., GS-1101, duvelisib) or a Bruton's tyrosine kinase (BTK) inhibitor
7. Use of any of the following medications or procedures within the specified timeframe:
   - Use of live or live attenuated vaccines within 30 days prior to randomization
   - Chemotherapy, radiation therapy, or ablative therapy within 3 weeks of randomization
   - Tyrosine kinase inhibitor within 7 days of randomization
   - Other investigational therapy (not included above) within 3 weeks of randomization
8. Ongoing treatment with chronic immunosuppressants (e.g., cyclosporine) or systemic steroids > 20 mg prednisone (or equivalent) QD.
9. History of tuberculosis treatment within the preceding two years
10. Ongoing systemic bacterial, fungal, or viral infections at the time of initiation of study treatment (defined as requiring intravenous [IV] antimicrobial, antifungal or antiviral agents)
    a. Subjects on antimicrobial, antifungal or antiviral prophylaxis are not specifically excluded if all other inclusion/exclusion criteria are met and there is no evidence of active infection at randomization
11. Human immunodeficiency virus (HIV) infection
12. Prior, current or chronic hepatitis B or hepatitis C infection
13. History of alcohol abuse or chronic liver disease (other than metastatic disease to the liver)
14. Unable to receive prophylactic treatment for pneumocystis or herpes simplex virus (HSV)
15. Baseline QTcF > 480 ms (average of triplicate readings) Note: This criterion does not apply to subjects with a right or left bundle branch block (BBB)

16. Unstable or severe uncontrolled medical condition (e.g., unstable cardiac function, unstable pulmonary condition), or any important medical illness or abnormal laboratory finding that would, in the investigator's judgment, increase the subject's risk while participating in this study
17. Concurrent active malignancy other than nonmelanoma skin cancer or carcinoma in situ of the cervix, bladder, or prostate not requiring treatment. Subjects with previous malignancies are eligible provided that they have been disease free for ≥ 2 years
18. History of stroke, unstable angina, myocardial infarction, or ventricular arrhythmia requiring medication or mechanical control within the last 6 months
19. Administration of medications or foods that are strong inhibitors or inducers of CYP3A within 2 weeks of randomization
20. Prior surgery or gastrointestinal dysfunction that may affect drug absorption (e.g., gastric bypass surgery, gastrectomy)
21. Major surgery or invasive intervention within 4 weeks prior to randomization
22. Pregnant or breastfeeding women
23. Hypersensitivity to ofatumumab or its excipients

Appendix 3: Duvelisib Treatment Duration Guidelines per Protocol

Treatment discontinuation due to benefit after < 18 complete cycles of duvelisib therapy:

Prior to completion of 18 cycles of duvelisib therapy, discontinuation of duvelisib may be considered, after discussion with the medical monitor, should a CLL subject demonstrate a CR/CRi per IWCLL 2008 criteria or an SLL subject demonstrate a CR per IWG 2007 criteria. The timing of duvelisib treatment discontinuation relative to the duration of a CR should be considered as follows:

- < 12 months of duvelisib therapy: duration of CR/CRi > 6 months before discontinuation
- ≥ 12 months of duvelisib therapy: duration of CR/CRi > 3 months before discontinuation

Disease response assessments by CT scan will continue every 6 cycles until disease progression.

Treatment discontinuation after 18 or more complete cycles of duvelisib therapy:

After completion of 18 cycles (beginning on Day 1 Cycle 19) of duvelisib therapy, discontinuation of duvelisib may be considered if a subject demonstrates the following responses (per modified IWCLL criteria/IWG criteria or as otherwise indicated of > 3 months duration:

- CR or CRi
- Partial response (that includes all target lesions ≤ 1.5 cm in diameter) but with a peripheral blood absolute lymphocyte count (ALC) ≥ 4,000/µL (Rai Stage 0)
- Persistent lymphadenopathy > 50% of baseline (with at least 1 target lesion ≥ 1.5 cm in diameter) and persistent lymphocytosis ≥ 4,000/µL (and > 50% of baseline)

Disease response assessments by CT scan will continue every 6 cycles until disease progression.

Treatment continuation after 18 or more complete cycles of duvelisib therapy:

Duvelisib therapy may continue if there is potential benefit to the subject based on the following disease response assessments (per IWCLL criteria /IWG criteria or as otherwise indicated at the end of 18 cycles (Day 1 Cycle 19) of duvelisib therapy:

- CR or CRi < 3 months duration
- PR with or without lymphocytosis
- SD

Disease response assessments by CT scan will continue every 6 cycles while the subject remains on duvelisib treatment.

Appendix 4: Efficacy Results in the Approved Indication (≥2 Prior Lines of Therapy)

The DUO trial required at least one prior therapy in patients with relapsed or refractory CLL or SLL. In the trial population, the median number of prior therapies was 2 (range 1, 10), with 60% of patients having 2 or more prior therapies. Because of the severity of the safety profile with duvelisib along with safety concerns with a same-in-class agent, idelalisib, the efficacy of duvelisib in patients with CLL or SLL with 2 or more prior therapies was evaluated.

Demographics and Baseline Characteristics

In the subset population of patients with two or more prior therapies (N = 196), the median age was 69 years, 59% were male, and 88% had an ECOG performance status of 0 to 1. The demographic characteristics were relatively balanced between treatment arms and are shown in Table 26 below.

Table 26: DUO Trial Demographics (Patients With ≥2 Prior Therapies)

	Duvelisib N = 95	Ofatumumab N = 101
Age, years		
Median (Min, Max)	70 (40, 90)	68 (44, 89)
≥65 years, n (%)	68 (72)	69 (68)
Sex, n (%)		
Male	59 (62)	56 (55)
Female	36 (38)	45 (45)
Race, n (%)		
White	90 (95)	93 (92)
Black	0	1 (1)
Not Reported	3 (3)	3 (3)
Other or Unknown	2 (2)	4 (4)
Region, n (%)		
Europe	71 (75)	82 (81)
United States	18 (19)	9 (9)
Other	6 (6)	10 (10)
ECOG, n (%)		
0-1	87 (92)	90 (89)
2	8 (8)	11 (11)
Source: FDA analysis		

Table 27 below summarizes the disease characteristics and prior therapies in the subset population of patients with two or more therapies. There were 29% to 36% of patients who were refractory or had early relapse, defined as progression <12 months after fludarabine or pentostatin.

Table 27: DUO Trial Disease Characteristics (Patients With ≥2 Prior Therapies)

	Duvelisib N = 95 n (%)	Ofatumumab N = 101 n (%)
Diagnosis		
CLL	92 (97)	99 (98)
SLL	3 (3)	2 (2)
Cytogenetics		
17p deletion	18 (19)	25 (25)
TP53 mutation	17 (18)	16 (16)
IGHV mutation	17 (18)	15 (15)
Tumor Burden		
Bulky disease	49 (52)	53 (45)
Number of Prior Therapies		
Median (Min, Max)	3 (2, 10)	3 (2, 8)
2	45 (47)	46 (46)
3	28 (29)	28 (28)
≥4	22 (23)	27 (27)
Refractory/Early Relapse		
Yes	28 (29)	36 (36)
Source: FDA analysis		

The median exposure duration for patients on the duvelisib arm was 13 months compared to 5 months on the ofatumumab arm as shown in Table 28 below.

Table 28: DUO Trial Exposure (Patients With ≥2 Prior Therapies)

Parameter		Duvelisib N = 95	Ofatumumab N = 101
Exposure duration, months	Median	13	5
	Range	0.2, 37	0, 6
	Q1, Q3	7, 20	3, 5
Cycles initiated	Median	14	7
	Range	1, 41	1, 7
	Q1, Q3	8, 22	4, 7
[a] Cycle length is 28 days Data cutoff 1/22/2021 Source: FDA analysis			

Efficacy Results – Primary Endpoint

Progression Free Survival

In patients with two or more therapies, treatment with duvelisib was associated an improvement in PFS per IRC compared to ofatumumab with a HR of 0.40 (95% CI: 0.27, 0.59). In this subgroup, 55 patients (58%) in the duvelisib arm and 70 patients (69%) in the ofatumumab arm experienced PFS events. The

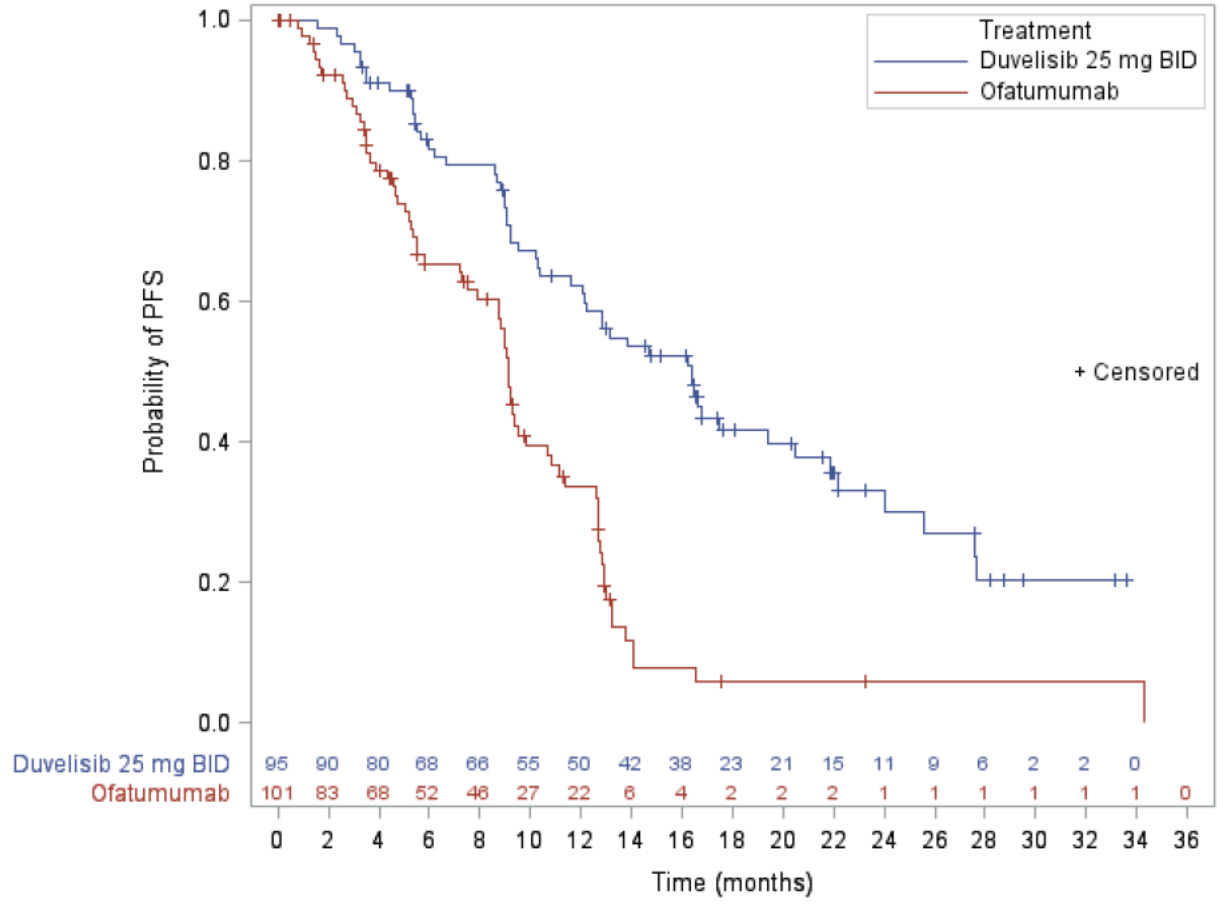
median PFS was 16.4 months for duvelisib and 9.1 months for ofatumumab. The PFS results in patients who have received 2 or more therapies are shown in Table 29 below and Kaplan-Meier curves for PFS in Figure 13 below.

Table 29: Subgroup Analysis of PFS per IRC in Patients With ≥2 Prior Therapies

	Duvelisib N = 95	Ofatumumab N = 101
Number of patients with PFS events, n (%)	55 (57.9)	70 (69.3)
Progression	44 (46.3)	62 (61.4)
Death	11 (11.6)	8 (7.9)
Number of patients censored, n (%)	40 (42.1)	31 (30.7)
KM estimate, month		
Median PFS (95% CI)	16.4 (12.0, 20.5)	9.1 (7.9, 10.7)
Hazard ratio[1] (95% CI)	0.40 (0.27, 0.59)	

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; PFS, progression-free survival
[1] Unstratified Cox proportional hazards model
Data cutoff: 5/19/2017
Source: FDA analysis

Figure 13: Kaplan-Meier Curves for PFS per IRC in Patients With ≥2 Prior Therapies



Data cutoff: 5/19/2017

Source: FDA analysis

Shown in Table 30 below are the PFS per investigator results with a median follow-up of 52 months in patients who have received 2 or more therapies. As noted with the initial PFS evaluation, a higher proportion of patients on the duvelisib arm (22%) died before progression compared to the ofatumumab arm (11%).

Table 30: DUO Trial PFS per Investigator in Patients With ≥2 Prior Therapies

	Duvelisib N = 95	Ofatumumab N = 101
PFS Events, n (%)	73 (76.8)	84 (83.2)
Progression	52 (54.7)	73 (72.3)
Death before progression	21 (22.1)	11 (10.9)
Censored, n (%)	22 (23.2)	17 (16.8)
Median PFS (months) (95% CI)	17.8 (12.7, 22.8)	9.3 (7.6, 9.5)
Hazard Ratio (95% CI) [a]	0.35 (0.25, 0.50)	

Abbreviations: CI, confidence interval; PFS, progression-free survival
[a] Stratified Cox proportional hazards model.
Data cutoff 1/22/2021
Source: FDA analysis

Efficacy Results – Secondary Endpoints

Overall Response Rate

Overall response rate per IRC in patients with two or more therapies was higher for duvelisib (78%) compared to ofatumumab (39%). The median DOR in the responders was 11.3 months for duvelisib and 8.0 months for ofatumumab. Table 31 below provides a summary of ORR per IRC in patients with two or more prior therapies.

Table 31: Subgroup Analysis of ORR per IRC in Patients With ≥2 Prior Therapies

Response, n (%)	Duvelisib N = 95	Ofatumumab N = 101
PR	74 (77.9)	39 (38.6)
SD	15 (15.8)	46 (45.5)
PD	1 (1.1)	5 (5.0)
Other	5 (5.3)	11 (10.9)
ORR (CR or PR)		
n (%)	74 (77.9)	39 (38.6)
Odds ratio (95% CI)	5.60 (2.99, 10.50)	
Median DOR, month (95% CI)	11.3 (7.4, 18.8)	8.0 (7.4, 10.9)

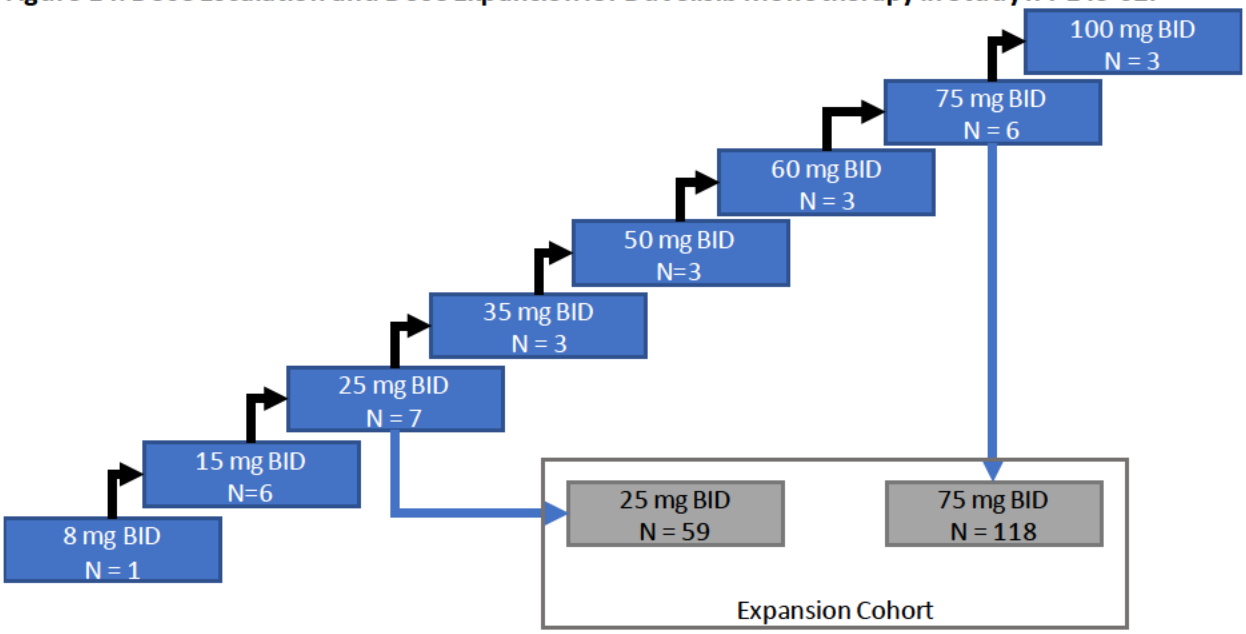
Abbreviations: DOR, duration of response; PR, partial response; SD, stable disease; PD, progressive disease
[1]Other includes Unknown and No Evidence of Disease
Data cutoff: 5/19/2017
Source: FDA analysis

Overall Survival

For the overall survival results in patients with two or more prior therapies, refer to the Overall Survival results section.

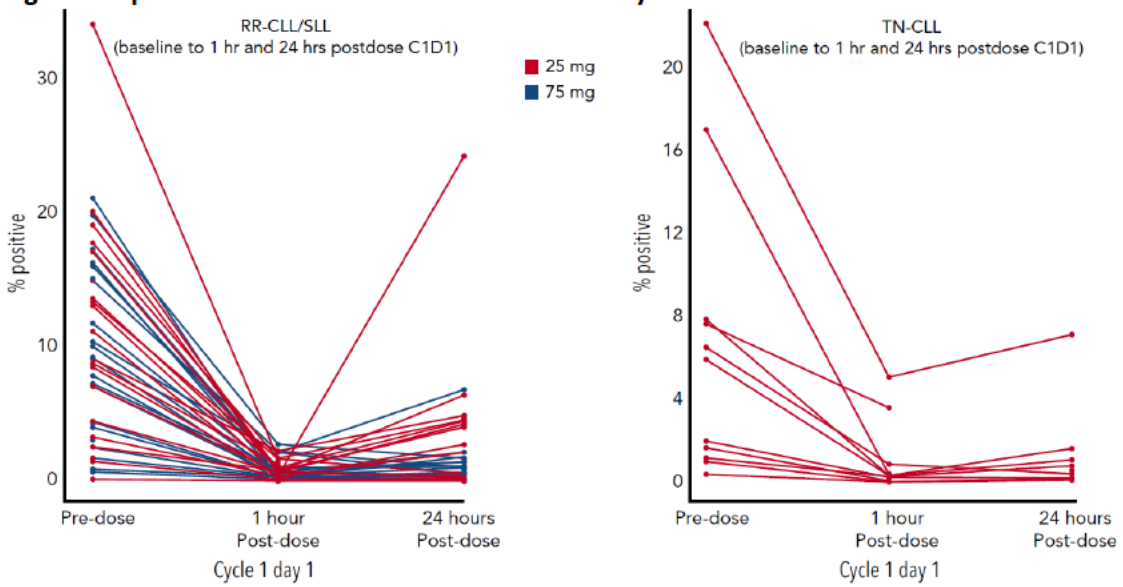
Appendix 5: Clinical Pharmacology Supplemental Data

Figure 14: Dose Escalation and Dose Expansion for Duvelisib Monotherapy in Study IPI-145-02.



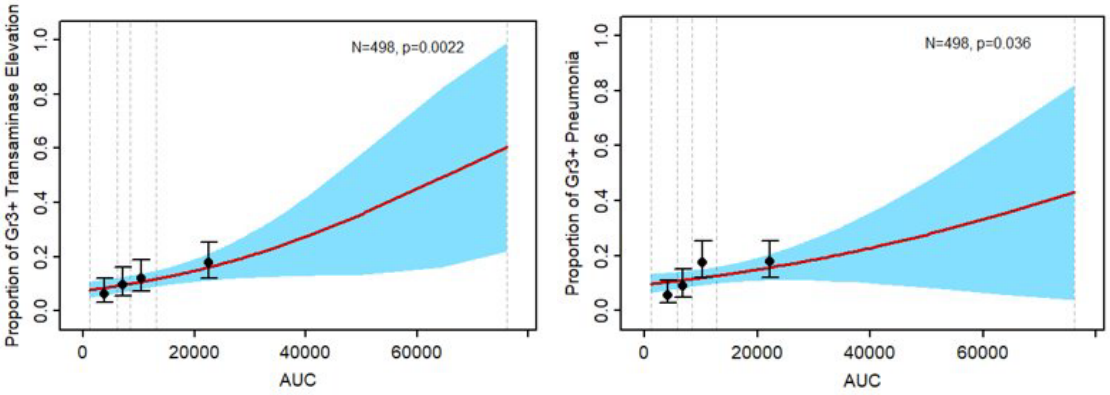
Source: Based on IPI-145-02 CSR

Figure 15: pAKT Percent Positive in CLL Cells in Study IPI-145-02



Source: Blood. 2018 Feb 22; 131(8): 877–887.

Figure 16: Exposure-Response Relationships for Grade ≥3 Transaminase Increase and Pneumonia



Source: NDA 211155 Multidisciplinary Review at Drugs@FDA

Appendix 6: RMST (Restricted Mean Survival Time) Analysis

Table 32 below shows the OS results based on the restricted mean survival time (RMST), summarizing the comparisons between the two treatment arms. Different truncated time points were used in the analysis.

Table 32 Analysis of RMST for OS (ITT population)

	75 months	60 months	48 months	36 months
Duvelisib Month (95% CI)	47.9 (43.5 to 52.3)	41.6 (38.2, 45.0)	35.6 (33.0, 38.2)	28.6 (26.8, 30.4)
Ofatumumab Month (95% CI)	49.2 (44.6 to 53.8)	42.0 (38.5, 45.5)	35.8 (33.2, 38.5)	28.8 (27.0, 30.6)
Difference Month (95% CI)	-1.3 (-7.7, 5.1)	-0.4 (-5.3, 4.5)	-0.2 (-3.9, 3.5)	-0.2 (-2.8, 2.4)

Data cutoff: 1/22/2021
Source: FDA analysis

In the ITT population, the differences between the two treatment arms were similar across different time points. Importantly, the RMST approach is heavily dependent on the time interval used for the calculation. For instance, a small time interval shift could cause changes in the results that might alter the interpretation. Additionally, the evaluation of OS using RMST was a post-hoc analysis without alpha adjustment. Therefore, the OS analysis results from an RMST analysis should be interpreted with caution and are considered hypothesis-generating.

Appendix 7: DUO Trial Crossover Analysis – Impact on Overall Survival

A substantial amount of crossover occurred in the DUO trial with 90 patients (57%) crossing over from ofatumumab to duvelisib and 9 patients (6%) crossing over from duvelisib to ofatumumab upon disease progression. To assess the impact of crossover on OS between the two arms, casual inference model-based approaches were conducted. The model based approaches included a marginal structural model (MSM) with inverse probability treatment weights (IPTW) and rank preserving failure time model (RPFTM).

Model Based Causal Inference Approach

1. **Marginal structural model (MSM) with inverse probability treatment weights (IPTW)[8]**

   The marginal structural model with inverse probability treatment weights was used to account for the effects due to the intercurrent event. The key step in the MSM-IPTW analysis was calculation of the weight for each patient. For patient *i*, the stabilized weight based on the inverse probability at a particular time point t_{ij} can be estimated as

$$sw_{ij}(t_{ij}) = \prod_{k=0}^{k=j} \frac{P(A_{ik} = a_{ik} | \bar{A}_{ik-1} = \bar{a}_{ik-1}, \bar{V}_i = \bar{v}_i)}{P(A_{ik} = a_{ik} | \bar{A}_{ik-1} = \bar{a}_{ik-1}, \bar{B}_{ik} = \bar{b}_{ik}, \bar{V}_i = \bar{v}_i)},$$

   where *A* is the treatment for patient *i* at time t_{ij} (time points ranging from *k* = 0 to *k* = *j*). The numerator is the probability of the observed treatment at each time point conditioned on the observed treatment history of the previous time points and *V* denotes other fixed covariates. The denominator is the probability of the observed treatment at each time point conditioned on the observed treatment history of the previous time point, the observed time-varying covariate history at the current time point (B_{ik}), and the fixed covariate V_i. This method will only provide unbiased estimates if the created pseudo-population has the same prognosis as the original population, and this is an untestable assumption (no unmeasured confounders assumption), since it requires the set of factors determining crossover to be known and measured at appropriate time points in the trial.

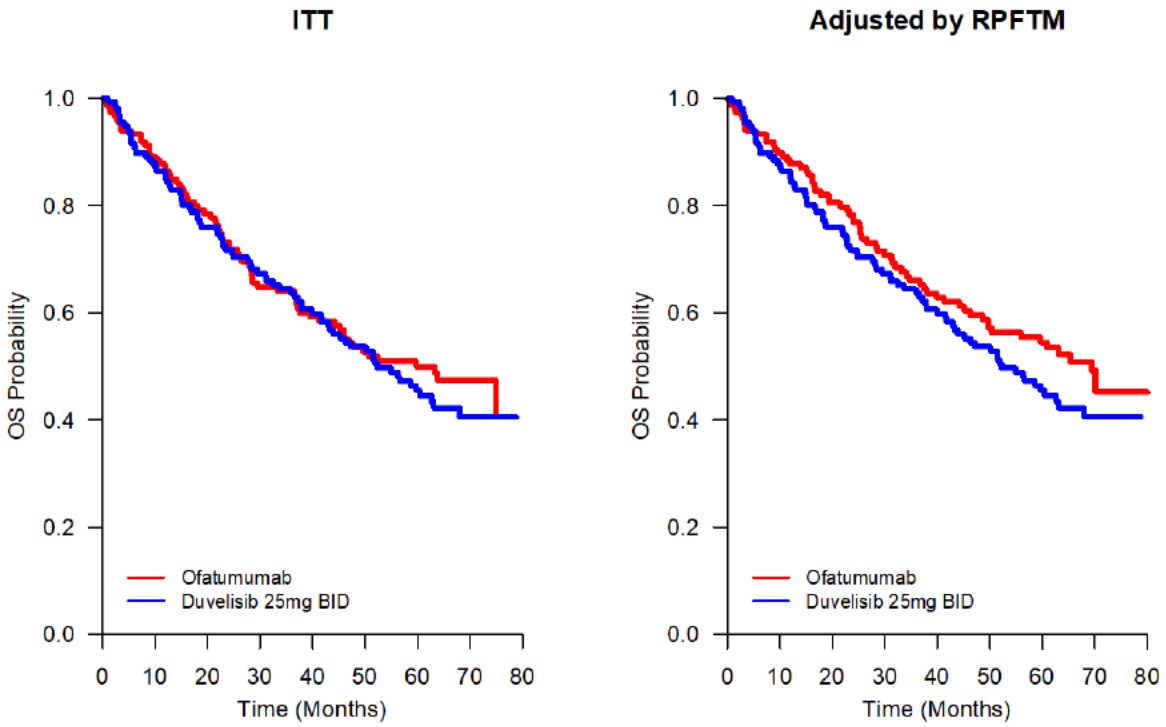
   The analysis result using MSM-IPTW method demonstrated that the adjusted HR was 1.064 (95% CI: 0.716, 1.591).

2. **Rank Preserving Failure Time Model (RPFTM)**

   In general, a RPFTM analysis serves as a sensitivity analysis to assess the impact of such imbalanced crossover patterns on OS between the two arms. The RPFTM model implies that the order of treatments does not impact treatment effect known as "common treatment effect" assumption. In the Sponsor's analysis, it was assumed that duvelisib acts by multiplying survival time by a given factor once a patient starts treatment. Importantly, this is not a testable assumption and, in this case, the application of RPFTM may need further theoretical justification. In addition, the assumption of a common treatment effect for the RPFTM model is challenging to justify.

   The figure below shows the Kaplan-Meier curves for overall survival based on the ITT analysis (left) and adjusted by RPFTM (right). In the ITT analysis, the HR was 1.09 (95% CI: 0.79, 1.51), while the adjusted HR via RPFTM was 1.22 (95% CI: 0.88, 1.67).

Figure 17: DUO Trial OS KM Curves – ITT population and adjusted by RPFTM



Source: Sponsor's Analysis

The OS analyses by the two model-based approaches are consistent with the OS results in the ITT population. The potential for harm with duvelisib cannot be ruled out by the results observed in these sensitivity analyses. Given that the underlying assumptions of the adjustment methods for crossover described above can in principle not be proven to be true, estimates derived from these causal models should be interpreted with caution.

Table 33: DUO Trial - Impact of Crossover on OS by Different Assessment Methods

Method	OS HR (95% CI)	Nominal P-value
Primary Analysis		
5-Year OS - ITT	1.09 (0.79, 1.51)	0.592
Model Based Causal Inference		
MSM-IPTW	1.06 (0.72, 1.59)	0.759
Rank Preserving Failure Time Model (RPFTM)	1.22 (0.88, 1.67)	0.169
Abbreviations: CI, confidence interval, HR, hazard ratio, ITT, intent-to-treat, MSM-IPTW, marginal structural model with inverse probability treatment weights, OS, overall survival,		

Appendix 8: Statistical Issues with Exploratory Analyses, Subgroup Analyses and Multiplicity

The Sponsor's Position

The Sponsor analyzed the subgroup of refractory patients in the DUO trial (N = 98). Refractory patients were defined in the protocol as progressing <12 months after purine analog-based therapy and was included as a stratification factor. At the final OS analysis in the refractory subgroup, the HR was 0.77 (95% CI: 0.43, 1.38) in favor of duvelisib. The Sponsor indicated that there was a benefit in OS in heavily pre-treated or refractory patients treated with duvelisib compared with ofatumumab.

The FDA's Position

The refractory subgroup was not prospectively included in the statistical analysis plan with control for type I error rate. The estimate of the treatment difference in OS for the refractory subgroup (HR=0.77, 95% CI=0.43, 1.38) has lower precision (wide confidence interval) because of a smaller sample size. The OS results for the refractory subgroup is considered as exploratory, unless the precision of the subgroup estimate has been considered properly in planning the sample size or the variability of the treatment effect is sufficiently small in the subgroup. While subgroup analyses have an important role in clinical trials, a substantial risk for biased conclusions may be produced by conducting exploratory analyses with an intention to establish a population with a favorable treatment effect and benefit-risk profile.

In exploratory analyses, particularly when conducting in search of favorable evidence, the effect sizes of outcomes with favorable estimates are likely overestimated because of random high bias that can later experience "regression to the mean" (Fleming 2010). An "exploratory" subgroup analysis might be used to assess internal consistency of study results, such as investigating whether the results in the ITT population are applicable to all patients. The evaluation of subgroup analysis is considered as hypothesis generating, rather than inferential. Therefore, the subgroup analysis of the refractory population in the DUO trial needs to be interpreted with caution.

Finally, FDA guidance and ICH E9 published in 1998 includes the following statements on exploratory subgroup analyses and pre-specifying analyses:

- Any conclusion of treatment efficacy (or lack thereof) or safety based solely on exploratory subgroup analyses is unlikely to be accepted.
- Only results from analyses envisaged in the protocol (including amendments) can be regarded as confirmatory.

Appendix 9: FDA Grouped Preferred Terms

The following grouped preferred terms were used in the review of safety for duvelisib.

FDA Grouped PT	Included	Excluded
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain, Abdominal discomfort, Epigastric discomfort	Abdominal distension, Abdominal rigidity
Abscess	Abscess, specific types of abscess (e.g., limb/tooth/subcutaneous/Staphylococcal/perirectal/joint)	
Anemia	Anemia, Anemia macrocytic, Hemorrhagic anemia, Hemoglobin decreased, Hematocrit decreased, RBC count decreased	Pancytopenia
Arrhythmia	Arrhythmia, Arrhythmia supraventricular, Atrial fibrillation, Atrial flutter, Bradyarrhythmia, Bradycardia, Sinus bradycardia, Atrial tachycardia, Paroxysmal arrhythmia, Sinus arrhythmia, Sinus tachycardia, Supraventricular extrasystoles, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular extrasystoles, Ventricular fibrillation, Ventricular tachycardia, Cardiac flutter, Extrasystoles, Heart rate irregular	Palpitations
Bronchospasm	Bronchospasm, Wheezing, Asthma	
Cardiac failure	Cardiac failure, Congestive cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiac failure congestive, Cardiac failure chronic	[Cardiac arrest, Cardiac hypertrophy, Ejection fraction decreased, Left ventricular dysfunction, Diastolic dysfunction, Ventricular dysfunction, Ventricular hypokinesia]
Candidiasis	Candidiasis, Candida infection, Oropharyngeal candidiasis, Oral candidiasis, Intertrigo candida, Genital candidiasis, Vulvovaginal candidiasis	Candiduria, Vulvovaginal mycotic infection
Chest pain	Chest discomfort, Chest pain, Noncardiac chest pain, Angina pectoris	Musculoskeletal chest pain
Colitis	Colitis, colitis erosive, enterocolitis, enterocolitis hemorrhagic, colitis microscopic, colitis ulcerative	Colitis ischemic, enterocolitis infectious, CMV colitis, pseudomembranous colitis

FDA Grouped PT	Included	Excluded
Conjunctivitis	Conjunctivitis, Conjunctivitis allergic/bacterial/infective/viral	
Cough	Cough, Productive cough, Upper airway cough syndrome	
Depression	Depression, Depressed mood, Depressive symptom, major depression	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Colitis, Ileitis, Clostridium difficile colitis, gastroenteritis
Dizziness	Dizziness, Dizziness exertional, Dizziness postural, Vertigo, Vertigo positional	
Dyspnea	Dyspnea, Dyspnea exertional, Dyspnea paroxysmal nocturnal	[Acute respiratory failure, Respiratory failure, Tachypnea, Respiratory rate increased, Wheezing, Bronchospasm]
Edema	Generalized edema, Face edema, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema	Localized edema, Joint swelling, Eyelid edema, Lip edema, Periorbital edema, Mouth edema, Edema genital, Lymphedema, Lymphatic edema, Catheter site edema, Scrotal edema
Fatigue	Asthenia, Fatigue, Lethargy, ECOG performance status worsened	Malaise
Gastroenteritis	Gastroenteritis, Gastroenteritis viral, Campylobacter gastroenteritis	
Gastrointestinal hemorrhage	Gastric hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Upper gastrointestinal hemorrhage, Gastrointestinal hemorrhage, Intestinal hemorrhage, Melena, Rectal hemorrhage, Small intestinal hemorrhage	Hemorrhoidal hemorrhage
Headache	Headache, tension headache, sinus headache	
Hemorrhage intracranial	Hemorrhage intracranial, subdural hematoma, subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatocellular injury, Hepatotoxicity	Hepatic failure, Hepatic encephalopathy

FDA Grouped PT	Included	Excluded
Herpes virus infection	Herpes simplex, Herpes simplex pneumonia, Herpes virus infection, Herpes zoster, Herpes dermatitis, Herpes ophthalmic, Oral herpes, [Genital herpes], Herpes zoster ophthalmic, Varicella, Varicella zoster virus infection	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hyperglycemia	Hyperglycemia, Blood glucose increased	
Hypersensitivity	Drug hypersensitivity, Hypersensitivity, Urticaria, Angioedema, Anaphylactic reaction, Anaphylactic shock	Infusion related reaction, Skin reaction, Swollen tongue, Erythema multiforme
Hypertension	Hypertension, Essential Hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypokalemia [a]	Hypokalemia, blood potassium decreased	
Hypoesthesia	Hypoesthesia, Hypoesthesia oral	
Hypotension	hypotension, Diastolic hypotension, Orthostatic hypotension	
Influenza	Influenza, H1N1 influenza	
Injection site reaction	Injection site erythema, Injection site extravasation, injection site reaction	
Leukopenia	Leukopenia, White blood cell count decrease	
Lower respiratory tract infection	Bronchitis, specific types of bronchitis (Bronchitis bacterial/viral), Bronchiolitis, Lower respiratory tract infection viral, Lung infection	
Lymphopenia	Lymphopenia, lymphocyte count decreased	
Mucositis	Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Tongue ulceration, Oral pain, Oral discomfort, Oral mucosal blistering, Oral mucosal erythema, Oropharyngeal pain or discomfort	Proctalgia, Proctitis, Radiation mucositis, Vaginal inflammation, Gingival pain, Gingival swelling, Gingivitis, Gingival erythema, Glossitis, Mucosal hemorrhage, Esophagitis, Erosive esophagitis, Gastrointestinal tract irritation

FDA Grouped PT	Included	Excluded
Muscle spasms	Muscle spasms, Muscle contracture, Muscle contractions involuntary, Muscle spasticity	
Musculoskeletal pain	Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain	Arthralgia, Flank pain, Noncardiac chest pain
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Cardiac arrest
Nausea	Nausea, Retching	
Neuropathy peripheral	Neuropathy peripheral, Peripheral sensory neuropathy, Peripheral sensorimotor / motor neuropathy, Neuralgia	Hypoesthesia, Paresthesia, Sensory loss, Peripheral nerve palsy, [Polyneuropathy]
Neutropenia	Neutropenia, Neutrophil count decreased	Pancytopenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma	Squamous cell carcinoma
Otitis	Otitis media, otitis media acute, otitis externa	
Paresthesia	Paresthesia, Paresthesia oral	
Pneumonia	Pneumonia, specific types of pneumonia (e.g. pneumonia bacterial/herpes simplex/influenza/ legionella/pneumococcal/mycoplasma/pneumocystis jirovecii/atypical/pseudomonas/staphylococcal/ streptococcal/Bordetella/CMV/klebsiella/RSV/viral) Bronchopneumonia, Bronchopulmonary aspergillosis, Lung infection	Pneumonia aspiration
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, lung infiltration	
Pruritus	Excoriation, Pruritus, Pruritus generalized, Pruritus allergic, Prurigo	Eye pruritus
Pulmonary edema	Pulmonary edema, Pulmonary congestion	
Pulmonary hemorrhage	Pulmonary hemorrhage, Pulmonary alveolar hemorrhage	
Rash	Dermatitis, Dermatitis allergic/atopic/bullous/exfoliative/psoriasiform, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Exfoliative rash, Rash, Rash generalized, Rash erythematous/macular/ maculopapular/papular/pruritic/pustular, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome,	Dermatitis acneiform, Dermatitis contact, Dermatitis infected Herpes dermatitis, Skin exfoliation, Eczema, Rosacea, Seborrheic Dermatitis,

FDA Grouped PT	Included	Excluded
	Perivascular dermatitis, Skin reaction, skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis	Seborrheic keratosis, Actinic keratosis, Acrodermatitis, Acne, Rosacea, Pityriasis rosea, Poikiloderma, Chronic actinic dermatitis, Macule, Psoriasis
Renal insufficiency	Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal failure, Renal failure acute/chronic, Renal impairment, Nephropathy, Nephropathy toxic, Hypercreatinemia	Renal disorder
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection)	Upper / lower respiratory tract infection
Sepsis	Bacteremia, Sepsis, Septic shock, Sepsis syndrome, specific types of sepsis or bacteremia (e.g. Staphylococcal), Septic embolus, Neutropenic sepsis, Urosepsis	Candida sepsis, Device related infection
Skin infection	Skin infection, Skin bacterial infection, Staphylococcal skin infection, Erysipelas, Impetigo, specific types of impetigo (e.g. Staphylococcal impetigo), Periorbital cellulitis, Cellulitis, Dermatitis infected, Infected skin ulcer	Intertrigo candida, Skin candida, other references to candida infection
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Pancytopenia
Thrombosis or thromboembolism	Deep vein thrombosis, Embolism, Peripheral embolism, Pulmonary embolism, Thrombosis, Thrombosis in device, specific sites of thrombosis (e.g., jugular vein, aortic, intracranial venous sinus thrombosis)	Air embolism, Embolism, Septic embolism, Thrombophlebitis superficial
Transaminase elevation	Alanine aminotransferase increased, aspartate aminotransferase increased, transaminase increased, hepatitis acute, hepatitis, hypertransaminasemia, hepatic enzyme increased, acute hepatic failure, drug-induced liver injury, hepatic failure, hepatocellular injury, hepatotoxicity	Hepatic encephalopathy
Upper respiratory tract infection	Acute sinusitis, Chronic sinusitis, Laryngitis, Laryngitis viral, Nasopharyngitis, Pharyngitis, specific types of pharyngitis (e.g. Viral pharyngitis, Pharyngitis streptococcal), Rhinitis, Viral rhinitis, Sinusitis, Tonsillitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral upper respiratory tract infection, Rhinovirus infection, Tracheitis, Bacterial tracheitis, Tracheobronchitis	Respiratory tract infection, Rhinitis allergic, Rhinorrhea, Sinus congestion

FDA Grouped PT	Included	Excluded
Urinary tract infection	Cystitis, Urinary tract infection + specific types (e.g. Escherichia UTI), Pyelonephritis, Kidney infection	Bacteriuria, Candiduria, Dysuria, Urine leukocyte esterase positive
Visual impairment	Altered visual depth perception, Vision blurred, Visual acuity reduced, Visual impairment, Vision decreased, Visual field defect, Blindness, Diplopia	
Wound infection	Wound infection, specific types of wound infection (e.g. Wound infection staphylococcal)	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

[a] Grouping for other lab-related AEs was similar.