SECURA BIO™

BRIEFING DOCUMENT
FOR THE SEPTEMBER 23, 2022,
US FDA ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

COPIKTRA (DUVELISIB)

NDA 211155

INDICATION: FOR THE TREATMENT OF ADULT PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA OR SMALL LYMPHOCYTIC LYMPHOMA AFTER AT LEAST TWO PRIOR THERAPIES

DATE FINALIZED: SEPTEMBER 01, 2022

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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LIST OF ABBREVIATIONS

Abbreviation or Special Term	Definition
AE	adverse event
AKT	protein kinase B
BAX	BCL-2-associated X protein
BCL-2	B-cell lymphoma-2
BCL-2i	B-cell lymphoma-2 inhibitor
BID	twice daily
BTK	Bruton's tyrosine kinase
BTKi	Bruton's tyrosine kinase inhibitor
CD20	cluster of differentiation 20
CI	confidence interval
CLL	chronic lymphocytic leukemia
CSR	clinical study report
CTCL	cutaneous T-cell lymphoma
DCO	data cutoff
del(17p)	chromosome 17p deletion
DHCP	Dear Health Care Professional
Diff	difference
DOR	duration of response
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimension
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	Food and Drug Administration
FL	follicular lymphoma
HR	hazard ratio
Ig	immunoglobulin
iNHL	indolent non-Hodgkin's lymphoma
IRC	independent review committee
ITT	intent to treat
IV	intravenous
KM	Kaplan-Meier
Lyn	Lck/yes-related novel protein tyrosine kinase
m	median

Abbreviation or Special Term	Definition
M2	alternatively activated (tumor-associated macrophage)
mAb	monoclonal antibody
MST	mean survival time
mTOR	mammalian target of rapamycin
N/A	not available
NF-κB	nuclear factor kappa B
NHL	non-Hodgkin's lymphoma
ODAC	Oncologic Drugs Advisory Committee
ORR	overall response rate
OS	overall survival
PD	progressive disease/disease progression
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PI3Ki	phosphatidylinositol 3-kinase inhibitors
PI3Kγ	phosphatidylinositol 3-kinase gamma
PI3Kδ	phosphatidylinositol 3-kinase delta
PLC	phospholipase C
PMC	post-marketing commitment
PMR	post-marketing requirement
PRO	patient-reported outcomes
PTCL	peripheral T-cell lymphoma
REMS	Risk Evaluation and Mitigation Strategies
R/R	relapsed or refractory
SEER	Surveillance, Epidemiology, and End Results
SLL	small lymphocytic lymphoma
SOC	System Organ Class
Syk	spleen tyrosine kinase
TCL	T-cell lymphoma
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLS	tumor lysis syndrome
TN	treatment naive
US	United States
USPI	United States Package Insert
VAS	visual analog scale

1.0 EXECUTIVE SUMMARY

Duvelisib (COPIKTRA®) received full approved from the United States Food and Drug Administration (US FDA) on September 24, 2018, for the treatment of adult patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have previously received ≥2 systemic therapies. Full approval was based on data from the randomized Phase 3 DUO trial (Study IPI-145-07), where duvelisib significantly prolonged progression-free survival (PFS) with higher response rates compared to ofatumumab. The safety profile of duvelisib is manageable and acceptable given the high unmet need of the indicated population.

Secura Bio, Inc. (the sponsor) acquired the rights to duvelisib in September 2020. Since the US approval of COPIKTRA in 2018, the sponsor and the predecessor New Drug Application (NDA) sponsor has met the 4 post-marketing requirements (PMRs): providing long-term safety data for duvelisib monotherapy at a dose of 25 mg twice daily (BID) (PMR 3494-2); providing an updated overall survival (OS) analysis at the conclusion of the DUO study for the purposes of a long-term safety evaluation (PMR 3494-3); conducting a clinical pharmacokinetic trial with repeat doses of a moderate cytochrome P450 3A4 (CYP3A4) inducer (PMC 3494-4); and implementing a robust communication Risk Evaluation and Mitigation Strategies (REMS) to support physicians in managing their patients on duvelisib.

This is unlike the context of an accelerated approval based on evidence of an effect on a surrogate endpoint in which FDA requires the post-approval submission of confirmatory evidence to verify and describe clinical benefit. Here, FDA required the post-market collection of OS data to further develop information about the safety of the drug.

FDA's benefit-risk assessment of duvelisib in 2018 led to full approval of the drug as a third-line or beyond therapy with a boxed warning included in the labeling that recognizes the potential for, among other things, fatal and/or serious toxicities (infections [31%], diarrhea or colitis [18%], cutaneous reactions [5%], pneumonitis [5%]) and cautions oncologists to monitor for symptoms and withhold treatment if a listed toxicity is suspected. At that time, FDA appropriately identified patients with R/R CLL/SLL who have received ≥2 prior systemic therapies as the population that could benefit from this treatment while balancing the risks. Those patients have limited therapeutic alternatives and a poor prognosis.

FDA has convened the Oncology Drug Advisory Committee (ODAC) to review the updated final OS data from the DUO trial submitted in response to PMR 3494-3. Based on the updated OS information, along with duvelisib safety data, the committee will discuss a current assessment of benefit-risk. A key question for the committee is whether the updated 5-year OS data from the DUO trial represents new evidence that would change the benefit-risk assessment of duvelisib in R/R CLL/SLL that was established in 2018.

The interpretation of 5-year OS data is confounded due to an extensive imbalance in crossover. Nonetheless, to the degree FDA considers such data as sufficiently interpretable, the final OS analysis from the DUO trial indicates no significant change or detriment to OS in patients treated with duvelisib, but rather confirms that the safety experience in the longer term is consistent with the original NDA data that led to approval, along with its approved labeling. As demonstrated below, the updated OS data under consideration by this ODAC are consistent with the safety

evidence provided in the NDA that supported full approval and do not alter the benefit-risk assessment of duvelisib in the Labeled Indication Population.

At the final OS analysis there were 3 more deaths on the duvelisib arm in the Labeled Indication Population. The difference in the mean survival time was consistent throughout the study and numerically higher in the duvelisib arm. The updated results do not constitute new evidence of clinical experience that indicate the drug is unsafe for use under the conditions of use in the Labeled Indication Population.

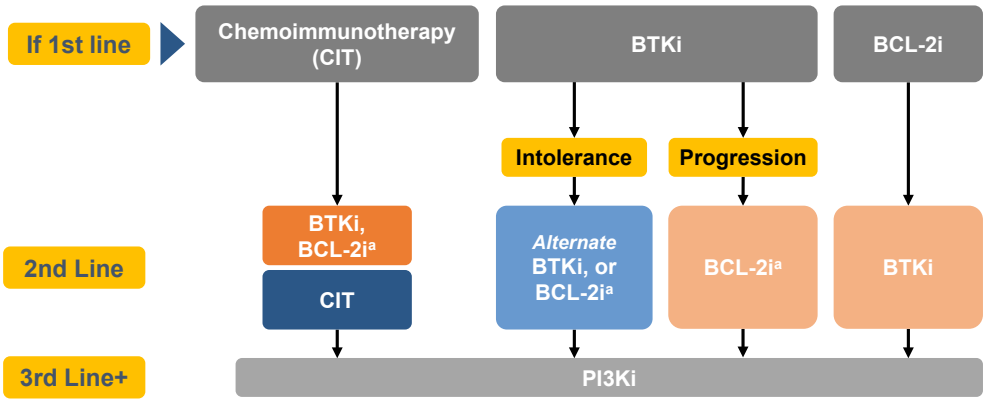
The totality of data continue to demonstrate a positive benefit-risk profile for duvelisib in the Labeled Indication Population of patients with R/R CLL who have previously received ≥2 prior therapies.[1]

1.1 Treatment Landscape and Unmet Need in the United States

Chronic lymphocytic leukemia is the most common adult leukemia in the US.[2, 3] Chronic lymphocytic leukemia and SLL are considered different presentations of the same disease, with the only difference being the lack of peripheral blood involvement in SLL.[4] In 2022, an estimated 20,160 people will be diagnosed with CLL in the US, and an estimated 4,410 people will die from the disease.[5] Agents targeting Bruton's tyrosine kinase (BTK) and B-cell lymphoma 2 (BCL2) are efficacious for many patients with R/R CLL, yet many patients will develop resistance and progressive disease (PD).[6] Despite these major advances in therapy, CLL remains an incurable, chronic disease, and most patients experience multiple relapses before ultimately succumbing to the disease or disease-related complications. Approximately 7,000 patients with CLL are expected to receive third-line or beyond therapy in 2022.[7]

The treatment paradigm for patients with CLL has been reasonably standardized across academic centers, although it is more varied in the community setting, where it is estimated that approximately 80% of CLL patients are treated.[8] In most academic centers, patients will be started on a BTK inhibitor (BTKi) or BCL-2 inhibitor (BCL-2i) plus an anti-cluster of differentiation 20 (CD20) monoclonal antibody (mAb). On treatment failure or occurrence of toxicity, patients will be given the alternate agent not chosen in the first line. On treatment failure or occurrence of toxicity in the second-line, phosphatidylinositol-3-kinase inhibitors (PI3Kis) are the only approved option for the third-line setting and beyond in the National Comprehensive Cancer Network (NCCN) guidelines[9] (**Figure A**).

Figure A: Therapy Considerations for Patients With R/R CLL



Abbreviations: BTKi = Bruton's tyrosine kinase inhibitor; BCL-2i = B-cell lymphoma 2 inhibitor; CIT = chemoimmunotherapy; CLL = chronic lymphocytic leukemia; PI3Ki = phosphatidylinositol-3-kinase inhibitor; R/R = relapsed or refractory; TLS = tumor lysis syndrome.
[a] BCL-2i usage generally limited to academic settings due to intensive TLS monitoring requirements.

Patients with R/R CLL represent an especially difficult population to treat, with higher rates of high-risk cytogenetics and resistance and more aggressive disease.[10] Most patients reaching third-line therapy will have already been treated with a BTKi or BCL-2i, most likely in combination with an anti-CD20 mAb. The most common reason for discontinuation of both BTKis and BCL-2i was toxicity (in 54% and 36% of patients, respectively).[11] The median OS in patients who progressed after 2 sequential lines of treatment with BTKi and BCL-2i therapy was 3.6 months (95% confidence interval [CI]: 2, 11 months).[12] Thus, the clinical challenge of double-refractory CLL disease (after treatment with BTKi and BCL-2i in the first- or second-line) is becoming more frequent and represents a population with dismal prognosis and high unmet need.

Furthermore, not all patients are optimal candidates for BTKis or BCL-2i because of comorbidities, contraindications, or intolerability.[11] There is an unmet need for agents with non-overlapping mechanisms of action and safety profiles, such as that provided by PI3Kis.

Duvelisib provides an effective and tolerable treatment option for difficult-to-treat patients with R/R CLL/SLL. In addition, duvelisib offers an all-oral monotherapy treatment regimen that provides added flexibility to patients in the third-line setting and beyond.

1.2 Overview of Duvelisib

Duvelisib is an oral, dual inhibitor of phosphatidylinositol-3-kinase delta (PI3Kδ) and phosphatidylinositol-3-kinase gamma (PI3Kγ). While PI3Kis have demonstrated efficacy in B-cell malignancies, the class is associated with the potential for severe immune-related adverse events (AEs). Targeting specific isoforms of PI3K has improved tolerability,[13] and physicians are experienced in administering duvelisib and managing class-related AEs. In addition, with the rise of immuno-oncologic agents, physicians have gained experience in managing immune-related AEs. Duvelisib is the only PI3Ki monotherapy with proven efficacy and no OS detriment in the third-line setting and beyond. Duvelisib does not require coadministration of an anti-CD20 mAb, which is important in the context of COVID-19 vaccination. Duvelisib provides a unique all-oral treatment option for the R/R CLL/SLL population, which has few remaining treatment options.

1.2.1 Clinical Development and Dose Rationale

As noted in FDA's Multi-Disciplinary Review of duvelisib dated February 5, 2018, adequate dose-ranging studies were conducted for duvelisib. The recommended dose of duvelisib for Phase 2 and Phase 3 studies in R/R CLL/SLL patients was determined based on a Phase 1, open-label, dose-escalation study in patients with advanced hematologic malignancy (Study IPI-145-02).[14] This study (n=210) tested duvelisib doses ranging from 8 mg to 100 mg twice daily (BID). The maximum tolerated dose was determined to be 75 mg BID, and 25 mg BID was selected for further evaluation in Phase 2 and 3 studies.

In Study IPI-145-02, clinically meaningful activity was observed in subjects with R/R CLL/SLL receiving 25 mg BID (n = 55): the overall response rate (ORR) was 57.1% (95% CI: 37.2, 75.5). With extended continuous dosing (median 24 weeks; maximum 167 weeks), the AE profile of duvelisib monotherapy was determined to be manageable. Based on Phase 1 response rates,

pharmacodynamics, and safety, duvelisib 25 mg BID was selected or further investigation in the Phase 3 DUO study in R/R CLL/SLL.[15]

1.2.2 Regulatory History of Duvelisib

- September 24, 2018: Duvelisib was approved for the treatment of R/R CLL/SLL after ≥2 prior therapies.
- September 30, 2020: Secura Bio acquires duvelisib from Verastem Oncology, Inc.
- November 13, 2020: Final report was submitted for long-term safety study of duvelisib (VS-0145-328).
- June 25, 2021: Updated OS from the DUO study was submitted in clinical study report (CSR) addendum (IPI-145-07 CSR Addendum 01).
- September 2021: FDA requested label modification to increase the recommended dose for patients on moderate CYP3A4 inducers.
- January 27, 2022: European Medicines Agency (EMA) review of the June 2021 data continued to support the positive benefit-risk profile of duvelisib.
- January-March 2022: FDA asked for additional statistical analysis for the April 21, 2022, ODAC discussing the PI3Ki class (sponsors were not invited).
- May 1, 2022: Sponsor submitted Dear Health Care Professional (DHCP) letter with updated OS data.
- May 6, 2022: After a thorough audit and review, FDA determined there are no changes to the REMS assessment plan described in the October 15, 2020, REMS Assessment Acknowledgment/REMS Assessment Plan Revision Letter.
- June 3, 2022: Prior approval supplement was submitted to update label with final OS data.
- June 15, 2022: FDA informed sponsor of plans to convene ODAC meeting.
- June 30, 2022: FDA publishes Drug Safety Communication and MedWatch alert regarding updated OS data.

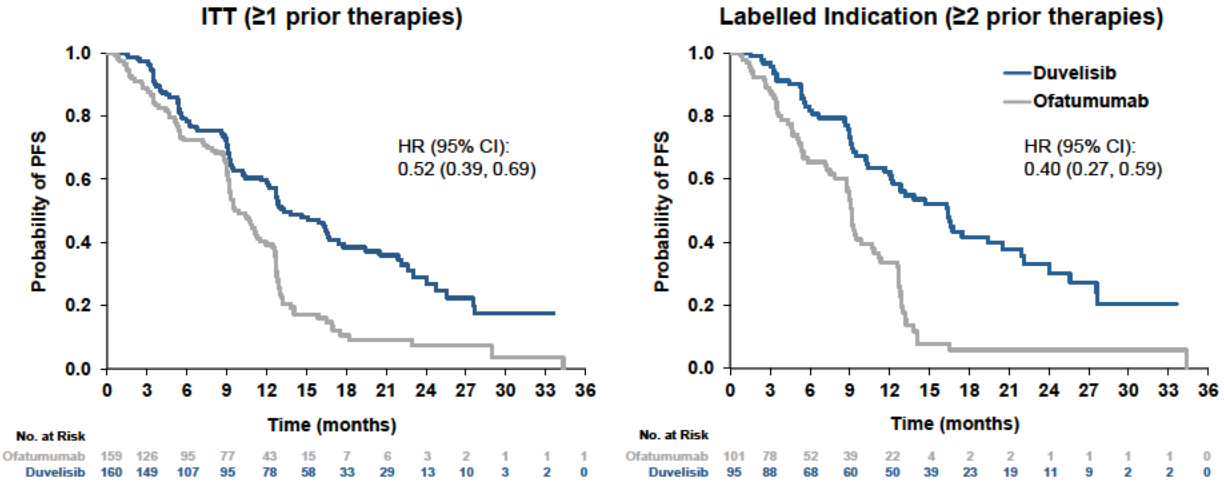
1.3 Basis of Regulatory Approval From DUO

Full approval of duvelisib in R/R CLL patients who previously received ≥2 prior therapies was based on the DUO trial (Study IPI-145-07), a global, Phase 3, randomized study of duvelisib versus ofatumumab monotherapy for patients with R/R CLL.[16] Patients enrolled in DUO who experienced confirmed PD were permitted to crossover to the opposite study treatment in the crossover extension study (Study IPI-145-12).

DUO met the primary endpoint of a statistically significant and clinically meaningful benefit in independent review committee (IRC)-assessed PFS in the duvelisib arm versus the ofatumumab arm in the Intent-to-Treat (ITT) Population based on International Workshop on Chronic Lymphocytic Leukemia criteria[4, 17] (**Figure B**). The median PFS in the ITT Population was 13.3 months for duvelisib and 9.9 months for the ofatumumab arm (hazard ratio [HR] 0.52; 95% CI: 0.39, 0.69; p<0.0001). Because of a more favorable benefit-risk ratio, FDA recommended approval for the subgroup of patients who had previously received ≥2 lines of therapy where the

PFS benefit was highly favorable (HR 0.40; 95% CI: 0.27, 0.59) and where the unmet need was the greatest.

Figure B: Duvelisib Monotherapy Significantly Improved PFS by Blinded IRC Compared With Ofatumumab



Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent to treat; PFS = progression-free survival.
Source: Left image adapted from *Blood*, 132(23), Flinn IW, et al, The Phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, 2446-2455, Copyright 2018, with permission from Elsevier[16]; Right image from FDA Multi-Disciplinary Review: Figure 4, Table 28 (ITT), Figure 10, Table 47 (Labeled). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

Since the original FDA approval in September 2018, the sponsor has diligently met PMRs for the Labeled Indication Population for long-term safety analysis and an updated OS analysis with at least 5 years of follow-up data.

1.4 Further Evaluation of Overall Survival in DUO

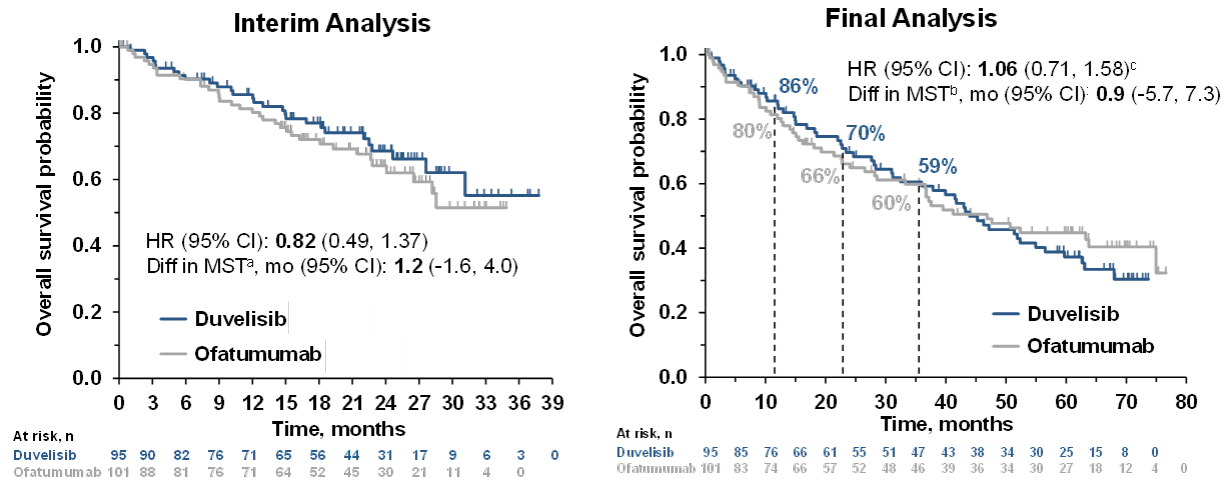
Because the OS data were immature at the time of full approval in 2018, FDA reviewers included a PMR in the approval requiring additional follow-up on long-term survival. The sponsor appreciates the value of OS data to inform prescribers, and the need for randomized data with an OS analysis to further inform a benefit-risk assessment, particularly in light of FDA's efforts to investigate potential survival detriments with the PI3Ki class of drugs.

As explained further in **Section 5.1**, the design of the crossover extension study (Study IPI-145-12) confounds the interpretation of the OS comparison between duvelisib and ofatumumab. While the DUO study initially began with approximately equal numbers of patients in each treatment arm (160 patients on duvelisib; 159 on ofatumumab), its extension study permitted patients to crossover to the opposite arm following PD. Overall, 90 of 101 patients who progressed in the ofatumumab arm crossed over to duvelisib, compared with 9 of 74 patients who progressed in the duvelisib arm crossing over to ofatumumab. The imbalance in treatment is further demonstrated by the fact that the actual maximum duration of treatment was 312 weeks (6 years) for duvelisib with a mean of 69 weeks (1.3 years), while the maximum duration of treatment with ofatumumab was only 26 weeks. Therefore, by the 3-year midpoint of the study, the vast majority of patients on the ofatumumab arm had received some exposure to duvelisib.

Due to the extensive and imbalanced crossover between the 2 arms, the final OS analysis is difficult to interpret. To the extent the study data are interpretable, the final OS analysis of DUO remains neutral and does not support a detriment to survival in patients randomized to duvelisib compared with those randomized to ofatumumab. Rather, it appears that OS is similar for the 2 treatment groups in both the ITT Population and the Labeled Indication Population.

As presented at the April 21 ODAC, **Figure C** shows that in the Labeled Indication Population, the OS rates favored the duvelisib arm at 1 and 2 years and were nearly identical at 3 years. It is not until late in the study, when very few patients remained on study medication, that the OS rates favored the ofatumumab arm. It should be noted that most patients originally randomized to ofatumumab had crossed over to duvelisib. These data suggest that late events occurring after patients discontinued study medication, rather than early deaths due to toxicity or infections, may explain the shift in the OS HR from the interim to the final analysis.

Figure C: Overall Survival at Interim and Final Analyses in Labeled Indication Population



Abbreviations: CI = confidence interval; Diff = difference; HR = hazard ratio; ITT = intent to treat; MST = mean survival time.
[a] Difference in MST (duvelisib-ofatumumab) with tau = 30 months.
[b] Difference in MST (duvelisib-ofatumumab) with tau = 60 months.
[c] Per FDA analysis.
Source: FDA April 21, 2022, ODAC BD Figure 28, Table 30.

Moreover, **Section 6.5** includes an analysis of causes of death on study. Briefly, at the final OS analysis there were 3 more deaths on the duvelisib arm in the Labeled Indication Population. Deaths before progression were higher in the patients originally randomized to duvelisib because of depletion of susceptible events in patients originally randomized to the ofatumumab arm. The difference in the mean survival time was consistent throughout the study and numerically higher in the duvelisib arm. A review of deaths due to AEs other than PD did not reveal a pattern suggestive of a drug relationship.

1.4.1 European Medicines Agency Review Conclusions

Section 6.2.2 describes the EMA review of the updated survival results from the DUO study. Briefly, the updated survival results were submitted by the sponsor to EMA in an application for

a Type II variation on August 27, 2021. The requested variation proposed amendments to the Summary of Product Characteristics to reflect the final OS results for both the ITT Population and the Labeled Indication Population. In privileged and confidential communications in the Type II Variation Assessment report dated January 27, 2022, EMA concluded that while the interpretation of the OS results was confounded by an imbalance in crossover, the benefit-risk balance of duvelisib remains positive.

1.5 Post-Marketing Safety

In accordance with FDA and international guidelines, the sponsor performs continuous and comprehensive review of worldwide sources of safety data for duvelisib from ongoing clinical trials and post-marketing experience. This continuous safety analysis and the review of any available efficacy data from ongoing trials of duvelisib and the Periodic Benefit Risk Evaluation Reports (PBRER) reports submitted to EMA have not identified any new safety signals and have continued to support the ongoing favorable benefit-risk profile of duvelisib.

1.6 Differentiation of Duvelisib in the PI3K Inhibitors Class

On April 21, 2022, FDA convened an ODAC meeting to discuss the PI3Ki class of drugs. FDA presented concerning trends in OS with PI3Kis.[18] However, comparisons across clinical trials of PI3Kis in various combinations with other chemotherapeutic agents, in varied study designs, and in different therapeutic contexts should be interpreted with caution. Findings from clinical studies with other marketed PI3Kis do not diminish the favorable benefit-risk profile of single-agent duvelisib for the treatment of R/R CLL/SLL.[19, 20]

As noted at the recent ODAC meeting on the topic of PI3Kis, combination regimens of PI3Kis with anti-CD20 mAbs may have increased toxicity and are problematic in the COVID-19 setting. In addition, most patients with R/R CLL have previously been treated with anti-CD20 mAbs. The only other marketed PI3Ki approved for R/R CLL, idelalisib, is approved in combination with anti-CD20 mAbs and may not be a suitable alternative for heavily pre-treated patients with R/R CLL. Duvelisib, as the only approved PI3Ki monotherapy, continues to meet an important unmet need for patients who are refractory or who cannot tolerate combination therapies.

1.7 Implications of New Information on Benefit-Risk Profile

In the primary analysis of the DUO trial, duvelisib demonstrated a statistically significant and clinically meaningful improvement in PFS in the duvelisib arm versus the ofatumumab arm in the overall ITT Population, and in the Labeled Indication Population with an HR of 0.40 (95% CI: 0.27, 0.59). This led to full approval of duvelisib in the Labeled Indication Population in 2018. In the final analysis of DUO with long-term follow-up, the PFS benefit (per investigator) remained clinically and statistically significant with no changes to the long-term safety profile. The final OS analysis from the DUO trial does not support the conclusion of a detriment in OS in patients treated with duvelisib and did not identify any new safety concerns. The updated OS data do not alter the benefit-risk assessment of duvelisib and do not constitute new evidence of clinical experience that indicate the drug is unsafe for use under the conditions of use in the Labeled Indication Population.

1.8 Unmet Need

Patients with R/R CLL represent an especially difficult-to-treat population with higher rates of high-risk cytogenetics and resistance and more aggressive disease who are more likely to require third- and fourth-line treatment options. Patients who are refractory to first- and second-line treatments with BTKis and BCL-2i have a particularly poor prognosis, with a median OS of 3.6 months.[12] For patients who have relapsed or are refractory to BTKis or BCL-2i, or who cannot tolerate combination regimens, there are no other targeted agents available outside of PI3Ki therapy.

Duvelisib is the only monotherapy PI3Ki regimen with proven efficacy in the third-line setting and beyond, with no detriment to OS. There remains an unmet need for agents with non-overlapping mechanisms of action and safety profiles, such as that provided by PI3Kis. Duvelisib provides a fully approved, effective, and tolerable treatment option for difficult-to-treat patients with R/R CLL/SLL. In addition, duvelisib offers an all-oral monotherapy treatment regimen that provides added flexibility for patients in the third-line setting and beyond.

2.0 DISEASE BACKGROUND AND UNMET NEED

2.1 Overview of Relapsed or Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the United States (US).[2, 3] In 2022, an estimated 20,160 people will be diagnosed with CLL in the US, and an estimated 4,410 people will die from the disease.[5] Chronic lymphocytic leukemia primarily occurs in the elderly and has a median age of onset of approximately 70 years of age. The incidence of CLL is higher among White patients than Black patients and is higher in males than females (ratio of 1.7:1). Chronic lymphocytic leukemia has a 5-year overall survival (OS) rate of 87.9% (based on Surveillance, Epidemiology, and End Results (SEER) Program data from 2011-2018). Due to the chronic nature of CLL, there are approximately 200,000 CLL patients in the US.[21]

Despite major advances in therapy, CLL remains an incurable, chronic disease, and most patients experience multiple relapses before ultimately succumbing to the disease or to disease-related complications. Approximately 7,000 patients with CLL are expected to receive third-line and beyond therapy in 2022.[7]

Chronic lymphocytic leukemia has a highly variable clinical course characterized by the progressive accumulation in blood, bone marrow, and lymphoid tissue of monoclonal B lymphocytes with a characteristic immunophenotype. Chronic lymphocytic leukemia and SLL are considered different presentations of the same disease, with the only difference being the lack of peripheral blood involvement in SLL.[4]

2.2 Characteristics of Patients With CLL

The median age at diagnosis for patients with CLL is 70 years, which presents unique challenges to disease management including the presence of many comorbidities, concomitant medications, and other geriatric complications such as cognitive impairment and frailty. The disease itself is heterogenous, with various cytogenetic features that can contribute to a poor prognosis, most notably chromosome 17p deletion (del[17p]) and *TP53* mutation.[22] In addition, the vast majority (>80%) of CLL patients are diagnosed and treated in the community setting, where the ability to use currently available or experimental therapies may be limited (e.g., monitoring of tumor lysis syndrome for BCL-2 inhibitor [BCL-2i]).[22]

Chronic lymphocytic leukemia is associated with disease-specific complications in the absence of therapy. This is demonstrated by the placebo arm of the Phase 3 CLL12 trial that randomized high-risk, treatment-naive patients with CLL to early intervention with ibrutinib or placebo.[23] Patients who received placebo had a 94.8% incidence of any-grade adverse event (AE), a 37.4% incidence of severe AEs, a 45.9% discontinuation rate, and a 3.2% incidence of fatal AEs. The frequency of any-grade diarrhea and infections in these patients was 18% and 71%, respectively, with grade ≥3 infections occurring in 14% of patients. These results highlight the complexity of managing CLL patients, especially in the refractory setting.

Despite a high incidence of comorbidities, the most common cause of death for CLL/SLL patients is disease progression and/or CLL-related complications, with infection being a common complication leading to death. In a prospective cohort study evaluating the natural history of CLL that enrolled 1143 patients between 2002 and 2014, 73% of deaths on study were attributed

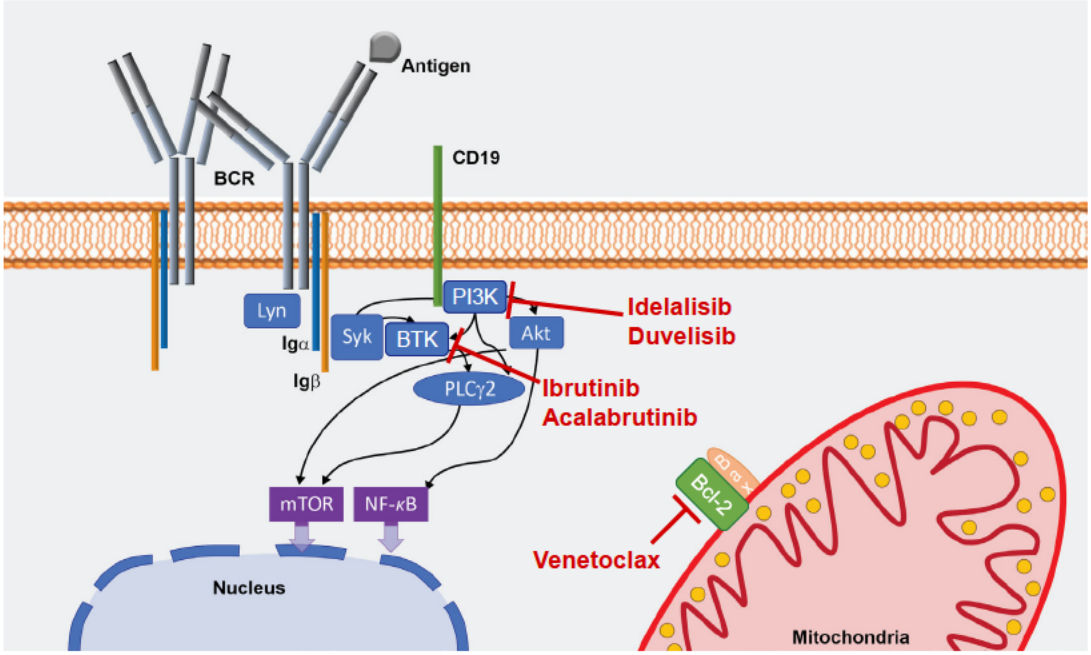
to CLL progression and complications.[24] Targeted therapies for CLL, all of which affect critical immune system functions, increase the risk for infection and require careful management. The longer patients are on treatment, the higher the risk of death due to infection.[25]

2.3 Biology of R/R CLL/SLL

In the past 2 decades, important progress has been made in the understanding of the biology of CLL and novel agents have been developed to target key components of the B-cell receptor pathway, namely Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3-kinase (PI3K) (**Figure 1**).[26] The BCL-2 inhibitor (venetoclax) is a drug that targets B-cell leukemia/lymphoma-2 (BCL-2), which has also shown to be effective in the treatment of CLL. These 3 classes of novel targeted drugs have been paradigm changing in the treatment of CLL.

Patients with R/R CLL represent an especially difficult population of patients to treat with higher rates of high-risk cytogenetics and resistance and more aggressive disease. Patients with del(17p) or *TP53* mutations have lower response rates to available therapy and are more likely to require second- or third-line treatment options.[10] In addition, although *TP53* mutations are relatively rare in newly diagnosed patients, the incidence sharply increases with disease progression, suggesting that *TP53* mutations may represent an evolutionary mechanism of resistance that is more prevalent in R/R CLL.[27]

Figure 1: Biology of CLL



Abbreviations: Akt = protein kinase B; Bax = BCL-2-associated X protein; BCL-2 = B-cell leukemia/lymphoma 2; BCR = B-cell receptor; BTK = Bruton's tyrosine kinase; CD = cluster of differentiation; CLL = chronic lymphocytic leukemia; Ig = immunoglobulin; Lyn = Lck/yes-related novel protein tyrosine kinase; mTOR = mammalian target of rapamycin; NF-κB = nuclear factor kappa B; PI3K = phosphatidylinositol-3-kinase; PLC = phospholipase C; SLL = small lymphocytic lymphoma; Syk = spleen tyrosine kinase.
Reprinted from Ferrer G, Emili Montserrat E. Critical molecular pathways in CLL therapy. *Mol Med*. 2018;24(1):9.[26] https://creativecommons.org/licenses/by/4.0/. Certain pathways and target agents have been removed.

2.3.1 Targeted Therapies Approved for CLL

There are only 3 categories of approved, targeted therapies for CLL.[26]

2.3.2 BTK Inhibitors

Ibrutinib and acalabrutinib are inhibitors of BTK. Ibrutinib is the most commonly used therapy across all lines of therapy for CLL.[2] Both ibrutinib and acalabrutinib are approved in combination with the anti-cluster of differentiation 20 (CD20) monoclonal antibody (mAb), obinutuzumab, for first-line treatment of CLL. Both therapies are also approved as monotherapies for R/R CLL. Bruton's tyrosine kinase inhibitors (BTKis) can cause diarrhea, arthralgia, and, most importantly, hemorrhage and cardiovascular complications (such as hypertension, atrial fibrillation, ventricular arrhythmias, and even sudden death [only with ibrutinib]), making them unsuitable for patients with select underlying conditions.[28, 29] Both ibrutinib and acalabrutinib have the same mechanism of action, and therefore share an overlapping pattern of toxicity and are sensitive to the same resistance mechanisms, which limits subsequent use of either agent following progression on the former.[30, 31]

2.3.3 BCL-2 Inhibitor

The only approved BCL-2i is venetoclax. For first-line treatment of CLL, BCL-2i is approved in combination with obinutuzumab. In R/R CLL, BCL-2i is approved in combination with rituximab or as a single-agent continuous therapy.[32] In the community setting, there are several logistical challenges to using BCL-2i, which requires frequent laboratory testing, monitoring of tumor lysis syndrome (which often requires point-of-service laboratory availability), and even hospitalization for safe administration. Given these challenges, many community centers have not yet adopted BCL-2i) as a mainstay of treatment.[8]

2.3.4 PI3Kis

Idelalisib and duvelisib are the 2 PI3K inhibitors (PI3Kis) currently approved for CLL. Idelalisib in combination with rituximab is approved for R/R CLL,[33] while duvelisib monotherapy is approved for patients with R/R CLL who have received ≥2 prior therapies.[1] These PI3Kis are the only approved options for third-line therapy if patients have already received prior BTKis or BCL-2i.[9]

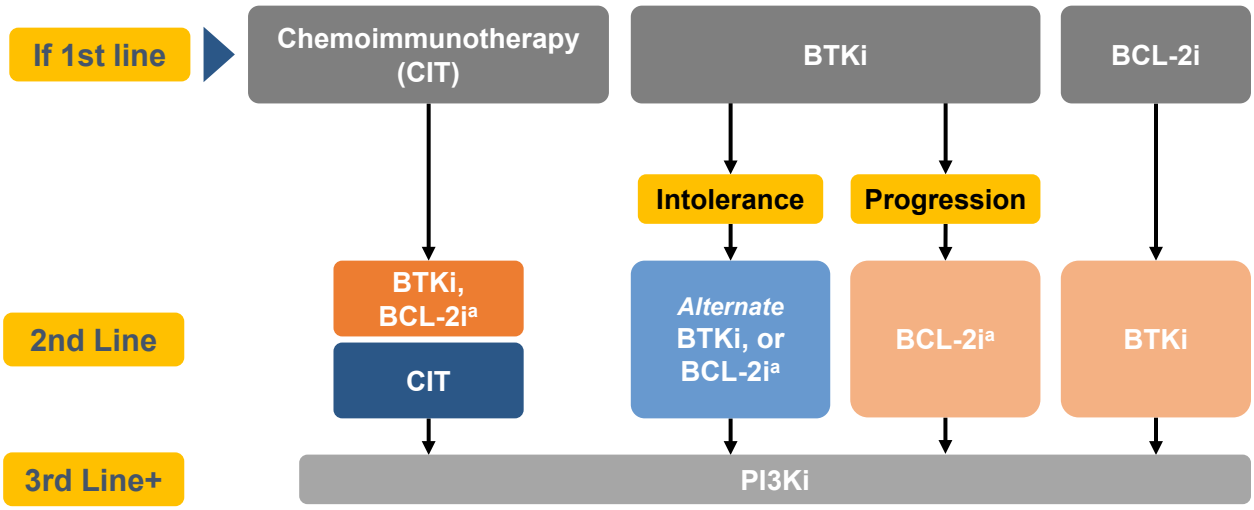
2.4 Current Treatment Considerations for R/R CLL/SLL

Given the long disease course, many patients experience multiple relapses before ultimately succumbing to the disease or disease-related complications. In a recent retrospective, observational study of 13,664 patients initially diagnosed with CLL, 2861 patients went on to receive first-line therapy within the 5-year study period (2014-2019). Of patients who received first-line therapy, 770 (29.6%) received a second-line therapy, and 199 (7%) received a third-line therapy.[34]

The treatment paradigm for patients with CLL has been reasonably standardized across academic centers, although it is more varied in the community setting, where it is estimated that approximately 80% of patients with CLL are treated.[8] In most academic centers, patients will be started on a BTKi or BCL-2i plus an anti-CD20 mAb. On treatment failure or the occurrence of toxicity, patients will be given the alternate agent not chosen in the first line. On treatment failure

or occurrence of toxicity in the second-line, PI3Kis are the only approved option for third-line therapy (**Figure 2**).

Figure 2: Therapy Considerations for Patients With R/R CLL

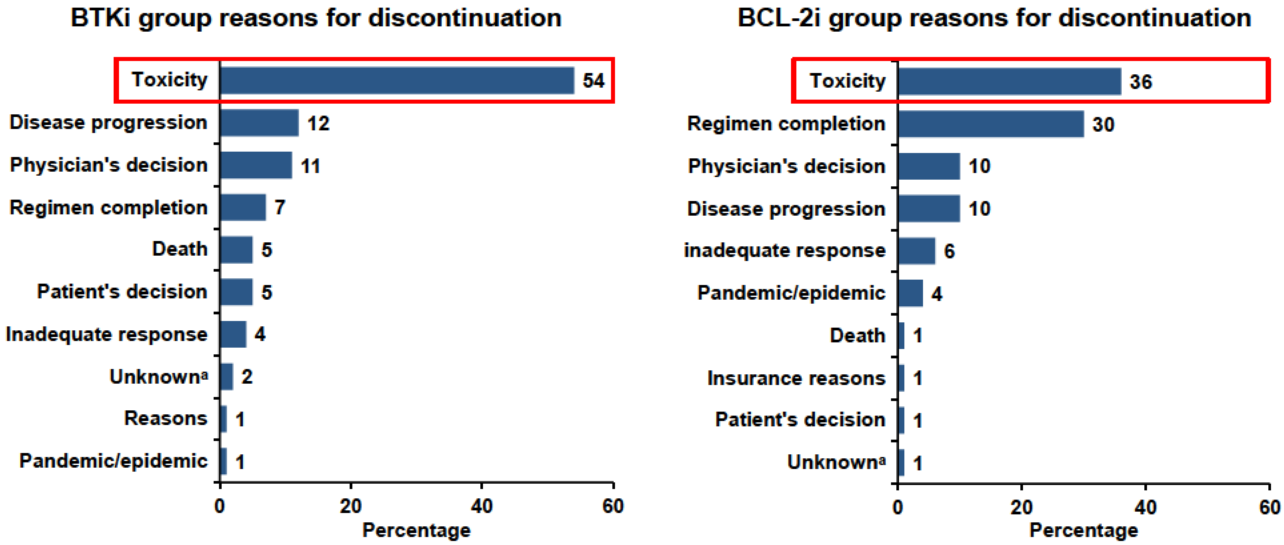


Abbreviations: BTKi = Bruton's tyrosine kinase inhibitor; BCL-2i = B-cell leukemia/lymphoma 2 inhibitor; CIT = chemoimmunotherapy; CLL = chronic lymphocytic leukemia; PI3Ki = phosphatidylinositol-3-kinase inhibitor; R/R = relapsed or refractory; TLS = tumor lysis syndrome.
[a] BCL-2i usage generally limited to academic settings due to intensive TLS monitoring requirements.

2.5 Limitations of Available Therapies

Most patients reaching third-line therapy will have already seen a BTKi or BCL-2i, most likely in combination with an anti-CD20 mAb. Most patients treated with a BTKi or BCL-2i in the first or second-line will eventually discontinue treatment and require next-line therapy. In a recent real-world study, high discontinuation rates were observed across all available therapies and lines of treatment; 73% of patients discontinued first-line treatment, 66% discontinued second-line treatment, and 59% discontinued third-line treatment within the 5-year observation period (2014-2019).[34] In a recent retrospective analysis of real-world data sources evaluating therapies in more than 1400 patients with CLL between 2016 and 2020, the most common reason for discontinuation of both BTKis and BCL-2i was toxicity (54% and 36%, respectively) (**Figure 3**).[11]

Figure 3: Reasons for Discontinuation of BTK and BCL-2 Inhibitors Based on Real-World Data



Abbreviations: BCL-2i = B-cell leukemia/lymphoma 2 inhibitor; BTKi = Bruton's tyrosine kinase inhibitor.
[a] Due to missing data.
Reprinted from *Blood*, 138(suppl 1), Smith TW, et al, Real-world evaluation of the treatment landscape for chronic lymphocytic leukemia [abstract], 1559, Copyright 2021, with permission from Elsevier.[11]

2.6 Unmet Need Met by Duvelisib

In the US, approximately 15,600 patients with CLL are expected to enter third-line therapy, with 7,000 patients expected to receive a third-line and fourth-line therapy in the same year in 2022.[7] Patients with R/R CLL represent an especially difficult population to treat, with higher rates of high-risk cytogenetics and resistance and more aggressive disease.[10] The median OS in patients who progressed after 2 sequential lines of treatment with BTKi and BCL-2i therapy was 3.6 months (95% confidence interval [CI]: 2, 11 months).[12] Furthermore, not all patients are optimal candidates for BTKis or BCL-2is in third-line due to comorbidities, contraindications, or intolerability.[2, 3] Real-world data indicates that patients who progressed after BTKi and BCL-2i, responded to PI3Ki therapy with an appreciable ORR.[35] Thus, the population of patients with double-refractory CLL disease (after treatment with BTKi and BCL-2i in the first- or second-line) is becoming more frequent and represents a population with high unmet need who may benefit from duvelisib.

For patients who have relapsed or are refractory to BTKis or BCL-2is, or who cannot tolerate combination regimens, there are no other targeted agents available outside of PI3Ki therapy. There remains an unmet need for agents with non-overlapping mechanisms of action and safety profiles, such as that provided by PI3Kis. Duvelisib provides a fully approved, effective, and tolerable treatment option for difficult-to-treat patients with R/R CLL/SLL. In addition, duvelisib offers an all-oral monotherapy treatment regimen that provides added flexibility for patients in the third-line setting and beyond.

3.0 OVERVIEW OF DUVELISIB

3.1 Duvelisib

Duvelisib is an oral, dual inhibitor of phosphatidylinositol-3-kinase delta (PI3Kδ) and phosphatidylinositol-3-kinase gamma (PI3Kγ). Inhibition of PI3Kδ blocks the survival and proliferation of malignant B cells,[36] whereas PI3Kγ inhibition disrupts the recruitment and differentiation of T cells and macrophages within the tumor microenvironment that support malignant B-cell maintenance.[37, 38] Duvelisib has demonstrated efficacy and safety and has been approved in several hematologic malignancies.

3.1.1 Approval in R/R CLL/SLL After ≥2 Prior Therapies

On September 24, 2018, duvelisib received full approval for the treatment of R/R CLL/SLL in patients who have received ≥2 prior systemic therapies. Full approval of duvelisib in CLL was based on the DUO trial (Study IPI-145-07; NCT02004522), a global, Phase 3, randomized study of duvelisib versus ofatumumab monotherapy for patients with R/R CLL.[16] The study met the primary endpoint of a statistically significant and clinically meaningful benefit in independent review committee (IRC)-assessed progression-free survival (PFS) compared with ofatumumab in the Intent-to-Treat (ITT) Population (patients who had received ≥1 prior therapy).

Because of a more favorable benefit-risk profile, the US Food and Drug Administration (FDA) recommended approval in R/R CLL/SLL patients who had received ≥2 prior therapies, for whom the unmet need is greatest. The Labeled Indication Population represented the majority of the patient population studied in DUO. Since the original FDA approval in September 2018, the sponsor has met all applicable post-marketing requirements (PMRs) and commitments (PMCs) for the labeled indication in accordance with milestone dates, including:

- **PMR 3494-2 (submitted November 13, 2020):** Safety of long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg twice daily (BID) in trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI-145-12 combined.
- **PMR 3494-3 (submitted June 25, 2021):** Submit reports for OS from trial IPI-145-07 with 5 years of follow-up, with an interim report after 3 years of follow-up, measured from the last patient's randomization date. Include causes of death and narratives for death in the absence of treated disease progression. Report was submitted, meeting the June 2021 deadline.
- **PMC 3494-4 (submitted October 31, 2019):** Conduct a clinical pharmacokinetic trial with repeat doses of a moderate CYP3A4 inducer on the single dose pharmacokinetics of duvelisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Final report with datasets was submitted, resulting in the FDA requirement to update the labeling to indicate that duvelisib dose should be increased from 25 mg BID to 40 mg BID when concomitant moderate CYP3A inducers are administered. Labeling update was approved on September 22, 2021.
- **Communication REMS (submitted October 15, 2020):** Implement an informational Risk Evaluation and Mitigation Strategies (REMS) to provide appropriate dosing and safety information to better support physicians in managing their patients on duvelisib. After a thorough audit and review, FDA determined there are no changes to the REMS assessment

plan described in the October 15, 2020, REMS Assessment Acknowledgment/REMS Assessment Plan Revision Letter (May 6, 2022).

3.2 Duvelisib Mechanism of Action (Dual PI3Kγ/δ Inhibitor)

PI3K is one of the most frequently aberrantly activated pathways in cancer, regulating a range of cellular activities, including metabolism, proliferation, and migration.[39] The Class 1 PI3K family includes 4 isoforms, referred to as PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ. The PI3Kδ isoform plays a key role in the differentiation and growth of B cells and has been established as an important therapeutic target for B-cell malignancies such as CLL. The PI3Kγ isoform is associated with the recruitment and differentiation of cells, such as $CD4^+$ T cells and alternatively activated (M2) tumor-associated macrophages, that support B-cell growth and survival.

While all approved PI3Kis are associated with on-target, class-associated side effects, pan-inhibition of all 4 PI3K isoforms, and dual inhibition of PI3Kα with PI3Kδ, has been associated with especially poor tolerability and immune-mediated toxicity.[13] Next-generation PI3Kis have improved isoform selectivity to retain clinical activity while reducing the frequency and intensity of class-associated toxicities.[38, 40]

3.3 Regulatory Background

In 2018, FDA granted full approved to duvelisib as third-line and beyond therapy for R/R CLL/SLL, based on the clinically meaningful and statistically significant PFS benefit demonstrated in the DUO trial, with a boxed warning in its labeling. The boxed warning included in the labeling recognizes the potential for, among other things, fatal and/or serious toxicities (infections [31%], diarrhea or colitis [18%], cutaneous reactions [5%], pneumonitis [5%]) and cautions oncologists to monitor for symptoms and withhold treatment if a listed toxicity is suspected (**Figure 4**).[1]

Figure 4: Boxed Warning for Duvelisib

WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS

See full prescribing information for complete boxed warning

- Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected. (5.1)
- Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA. (5.2)
- Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA. (5.3)
- Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA. (5.4)

Source: COPIKTRA USPI[1]

Given the high unmet medical need in this patient population, FDA considered the benefit-risk to be favorable in patients who had received ≥2 prior systemic therapies. As FDA has explained in draft guidance, this type of multifactorial "[b]enefit-risk assessment is . . . integrated into FDA's regulatory review of marketing applications for new drugs and biologics."[41] FDA describes its benefit-risk assessment as "a case-specific, multi-disciplinary assessment of science and medicine," which takes into account, among other things, "the therapeutic context in which the drug will be used," "the evidence submitted in the premarket application and/or generated in the postmarket setting," and "the uncertainties about the drug's benefit and risks."[41] By FDA's own account, "greater risk may be more acceptable if there are no available therapies."[41]

FDA has convened the Oncology Drug Advisory Committee (ODAC) to review the updated final OS data from the DUO trial submitted in response to PMR 3494-3. Based on the updated OS information, along with duvelisib safety data, the committee will discuss a current assessment of benefit-risk. A key question for the committee is whether the updated 5-year OS data from the DUO trial represents new evidence that would change the benefit-risk assessment of duvelisib in R/R CLL/SLL that was established in 2018.

Secura Bio recognizes that FDA's benefit-risk analysis continues throughout a drug's lifecycle. The updated OS data under consideration by this ODAC are consistent with the safety evidence provided in the New Drug Application (NDA) that supported full approval, and the benefit-risk profile of duvelisib in the labeled indication has not changed since 2018 when FDA approved duvelisib for the treatment of R/R CLL/SLL with a boxed warning and REMS to mitigate risks identified at the time. While Secura Bio understands FDA's concerns regarding the PI3Ki drug class, the updated results from DUO do not constitute new evidence of clinical experience that indicate the drug is unsafe for use under the conditions of use in the labeled indication on which the application was approved. The totality of data continue to demonstrate a positive benefit-risk profile for duvelisib in patients with R/R CLL.[1] Despite the risks, duvelisib continues to provide an important therapeutic option for patients with R/R CLL/SLL who have received ≥2 prior systemic therapies, a population with a high unmet medical need and a poor prognosis.

3.4 Regulatory History of Duvelisib in CLL/SLL

- September 24, 2018: Duvelisib was approved for the treatment of R/R CLL/SLL after ≥2 prior therapies.
- September 30, 2020: Secura Bio acquires duvelisib from Verastem Oncology, Inc.
- November 13, 2020: Final report was submitted for long-term safety study of duvelisib (VS-0145-328).
- June 25, 2021: Updated OS from the DUO study was submitted in clinical study report (CSR) addendum (IPI-145-07 CSR Addendum 01).
- September 2021: FDA requested label modification to increase the recommended dose for patients on moderate cytochrome P450 3A4 (CYP3A4) inducers.
- January 27, 2022: European Medicines Agency (EMA) review of the June 2021 data continued to support the positive benefit-risk profile of duvelisib.
- January-March 2022: FDA asked for additional statistical analysis for the April 21, 2022, ODAC discussing the PI3Ki class (sponsors were not invited).

- May 1, 2022: Sponsor submitted Dear Health Care Professional (DHCP) letter with updated OS data.
- May 6, 2022: After a thorough audit and review, FDA determined there are no changes to the REMS assessment plan described in the October 15, 2020, REMS Assessment Acknowledgment/REMS Assessment Plan Revision Letter.
- June 3, 2022: Prior approval supplement was submitted to update label with final OS data.
- June 15, 2022: FDA informed sponsor of plans to convene ODAC meeting.
- June 30, 2022: FDA publishes Drug Safety Communication and MedWatch alert regarding updated OS data.

3.5 Clinical Development Overview

Duvelisib's efficacy and safety has been demonstrated in a large and comprehensive clinical development program in multiple indications. This overview shows the completed or ongoing studies that were available at the time of duvelisib's approval (**Table 1**). Note that the long-term safety study of duvelisib monotherapy at a dose of 25 mg BID (Study VS-0145-328) formed the basis for the USPI safety data for duvelisib. One additional patient who crossed over from the ofatumumab arm to duvelisib in Study IPI-145-12 was included in the completed VS-0145-328 study, raising the total number of duvelisib-treated patients to 443.

Table 1: Overview of Completed Studies in Duvelisib Clinical Development Program

Study Number/ Status	Study Description	Indication(s)	Treatment Arms	Number of Patients	Ref(s)
Duvelisib Monotherapy					
IPI-145-02/ Completed	Phase 1, open-label, dose-escalation study in patients with advanced hematologic malignancy	R/R and TN CLL, relapsed iNHL, CTCL, PTCL other*	Duvelisib (8 mg – 100 mg BID)	158	Flinn 2018[14] Horwitz 2018 (TCL)[42] Flinn 2018 (iNHL)[43] O'Brien 2018 (CLL)[15]
DYNAMO (IPI-145-06)/ Completed	Phase 2, single-arm, open-label study	Refractory NHL, including FL, SLL, MZL	Duvelisib (25 mg BID)	129	Flinn 2019[44]
DUO (IPI-145-07)/ Completed	Phase 3, randomized, open-label, active-controlled study	R/R CLL/SLL	Duvelisib (25 mg BID) vs ofatumumab	319	Flinn 2018[16]
IPI-145-12/ Completed	Crossover extension study of IPI-145-07	R/R CLL/SLL	Duvelisib (25 mg BID) / ofatumumab crossover	98	Davids 2020[6]
VS-0145-328/ Completed	Long-term safety study of duvelisib in IPI-145-02, IPI-145-06, IPI-145-07, and IPI-145-12 combined	R/R CLL, R/R iNHL	Duvelisib (25 mg BID)	443	N/A

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; CTCL = cutaneous T-cell lymphoma; FL = follicular lymphoma; iNHL = indolent non-Hodgkin's lymphoma; MZL = marginal zone lymphoma; N/A = not available; NHL = non-Hodgkin's lymphoma; PTCL = peripheral T-cell lymphoma; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma; TCL = T-cell lymphoma; TN = treatment naive.

Source: FDA Multi-Disciplinary Review: Table 22.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

3.5.1 Dose Rationale

The recommended dose of duvelisib for Phase 2 and Phase 3 studies in R/R CLL/SLL patients was determined based on a Phase 1, open-label, dose-escalation study in patients with advanced hematologic malignancy (Study IPI-145-02; NCT01476657).[14] Study IPI-145-02 (n=210) tested duvelisib doses ranging from 8 mg to 100 mg BID. The maximum tolerated dose was determined to be 75 mg BID, and 25 mg BID was selected for further evaluation in Phase 2 and 3 studies.

In Study IPI-145-02 (n = 210) clinically meaningful activity was observed in patients with R/R CLL/SLL receiving 25 mg BID (n = 55): ORR was 57.1% (95% confidence interval [CI]: 37.2, 75.5). With extended continuous dosing (median 24 weeks; maximum 167 weeks), the AE profile of duvelisib monotherapy was considered manageable. Pharmacodynamic analyses performed in Study IPI-145-02 included changes in serine/threonine kinase AKT (protein kinase B), which is directly phosphorylated by PI3Ks. Results showed that duvelisib monotherapy led to a reduction in phosphorylated AKT, which was used as a pharmacodynamic marker for tumor cell PI3K inhibition in patients with CLL. In addition, the percentage of Ki67-positive CLL cells, an indicator of viable tumor cell proliferation, was significantly reduced following duvelisib administration. Based on Phase 1 efficacy, pharmacodynamics, and safety, duvelisib 25 mg BID was selected for further investigation in the Phase 3 DUO study in R/R CLL/SLL.[15]

In accordance with PMC 3494-4 a clinical pharmacokinetic trial was conducted with repeat doses of a moderate CYP3A4 inducer on the single-dose pharmacokinetics of duvelisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. The final report with datasets was submitted to FDA, resulting in the FDA requirement to update the labeling to indicate that duvelisib dose should be increased from 25 mg BID to 40 mg BID when concomitant moderate CYP3A inducers are administered. After extensive review of all safety information, FDA required the labeling to be updated, which was approved via prior approval supplement on September 22, 2021.

4.0 BASIS OF REGULATORY APPROVAL OF DUVELISIB FROM DUO

4.1 Study Design of DUO (Study IPI-145-07)

DUO is a completed, global, multicenter, randomized, open-label, Phase 3 study comparing duvelisib versus ofatumumab monotherapy for patients with R/R CLL.[16] In all, 319 patients with R/R CLL/SLL were randomized 1:1 to study treatment with duvelisib (n=160) or ofatumumab (n=159) at 62 clinical study sites in 11 countries. Patients were required to have active CLL or SLL requiring treatment, per the International Workshop on CLL[4] criteria or Revised International Working Group[45] criteria, that had progressed during or relapsed after ≥1 prior therapy. Patient stratification at randomization included the presence or absence of del(17p), grade 4 cytopenia, and refractoriness/early relapse to purine analog-based therapy (defined as progression <12 months after fludarabine/pentostatin).

Patients randomized to the duvelisib arm were treated with 25-mg capsules BID continuously in 28-day cycles except for the first cycle (21 days). Patients were allowed to take duvelisib until disease progression or unacceptable toxicity for up to 18 cycles. After 18 cycles, additional treatment with duvelisib was allowed based on the judgement of the investigator. Dosing for patients randomized to the ofatumumab arm was delivered via infusion based on the dose and schedule outlined in the approved product labeling for monotherapy in relapsed CLL at the time the study was initiated. Ofatumumab dosing could not exceed 12 doses (within 7 cycles).

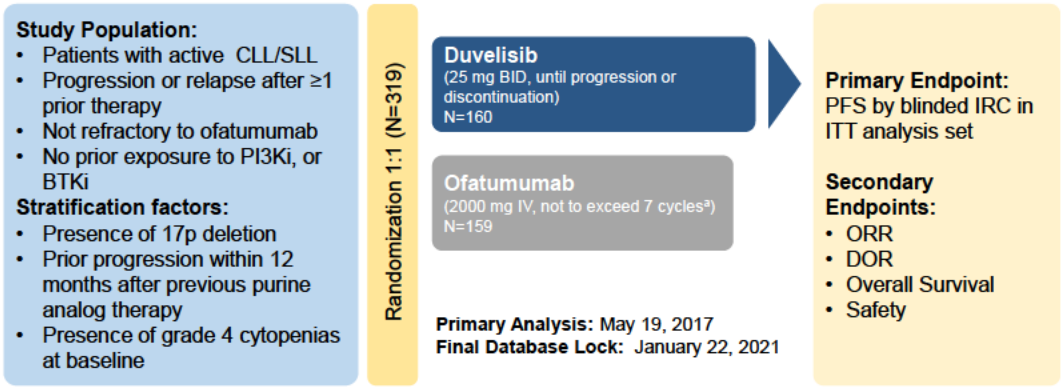
DUO was powered for PFS in the ITT Population, which is the traditional primary endpoint for full approval in CLL. The primary endpoint was PFS as determined by blinded IRC in the ITT analysis set per the International Workshop on CLL[4] criteria or Revised International Working Group criteria.[17] Secondary endpoints were ORR, OS, duration of response (DOR), and safety as shown in the schematic in **Figure 5**. Patient-reported outcomes were included as exploratory endpoints.

Patients with confirmed progression within 3 months of ending therapy were permitted to cross over to the opposite treatment arm in an optional crossover extension study (IPI-145-12). Indeed, almost all eligible patients (90/101) crossed over from ofatumumab treatment to the duvelisib arm.

The primary analysis of PFS was performed with a data cutoff date of May 19, 2017. The final analysis of OS took place at the end of follow-up of all subjects, per FDA PMR requirement. The date of the final database lock was January 22, 2021. Enrollment dates for DUO:

- First subject enrolled: January 21, 2014
- Last subject enrolled: December 9, 2015

Figure 5: DUO Trial: Study Design and Treatment

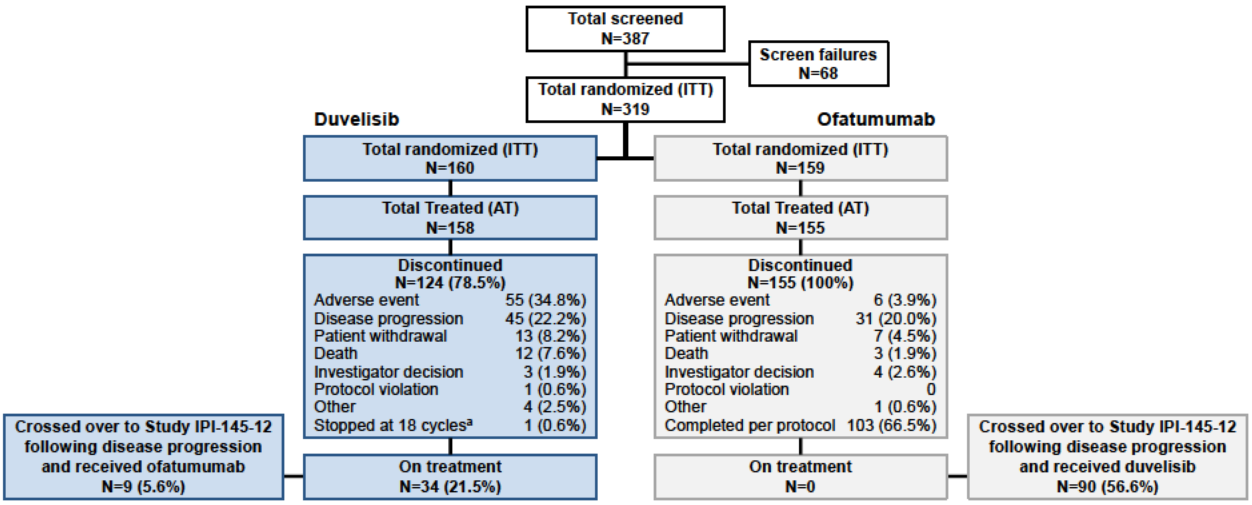


Abbreviations: BID = twice daily; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; DOR = duration of response; IRC = independent review committee; ITT = intent to treat; IV = intravenous; ORR = overall response rate; PFS = progression-free survival; PI3Ki = phosphatidylinositol-3-kinase inhibitor; SLL = small lymphocytic lymphoma.
[a] Treatment initiated with 8 weekly infusions, starting with an initial starting dose of 300 mg IV on Day 1 followed by 7 weekly doses of 2000 mg IV, followed by 2000 mg IV once per month for 4 months.
Source: CSR; FDA Multi-Disciplinary Review.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

4.2 Patient Disposition and Analysis Sets

Figure 6 shows the patient disposition for all patients screened in the study. Overall, 319 patients were randomized to treatment on study: 160 to duvelisib and 159 to ofatumumab. Of those randomized to duvelisib, 158 received study drug; of those randomized to ofatumumab, 155 received study drug.

Figure 6: Patient Disposition in DUO



[a] The protocol allowed for patients who had achieved a sustained (>3 months) response (complete or partial) at 18 months to discontinue treatment; patients may have received duvelisib >18 months at the discretion of the investigator.
Data cutoff: May 19, 2017.
Source: CSR Figure 1.

On the duvelisib arm, 124 (78.5%) subjects discontinued treatment, with the most common reasons for discontinuation being AEs (34.8%) and disease progression (PD) (22.2%). At the time of DCO, 34 (21.5%) of patients remained on duvelisib.

On the ofatumumab arm, 103 (66.5%) of subjects completed ofatumumab therapy per protocol and 31 (20.0%) discontinued due to PD prior to completing therapy.

The majority of patients who were eligible for crossover on the ofatumumab arm (90 out of 101 patients who progressed after receiving ofatumumab) crossed over to duvelisib in Study IPI-145-12, resulting in better responses in this group following crossover. In contrast, a small number of patients crossed over from the duvelisib arm to ofatumumab treatment (n=9). The imbalance in the number of patients crossing over to the alternate treatment arm is a confounding factor for time-to-event analyses, in particular for the OS analysis.

4.2.1 Baseline Demographic and Disease Characteristics

Because FDA approval was recommended for patients with R/R CLL/SLL with ≥2 prior therapies, the tables and figures that follow show the ITT Population (≥1 prior therapy) side by side with the Labeled Indication Population (≥2 prior therapies).

Baseline demographics and disease characteristics were generally well balanced between arms (**Table 2** and **Table 3**). The majority of patients from the ITT Population had received at least 2 prior therapies (the Labeled Indication Population), with >50% of this population receiving ≥3 prior therapies.

Table 2: Baseline Demographics for ITT Population and Labeled Indication Population

	ITT Population (≥1 prior therapy)		Labeled Indication Population (≥2 prior therapies)	
	Duvelisib (N=160)	Ofatumumab (N=159)	Duvelisib (N=95)	Ofatumumab (N=101)
Age, years				
Median (Min, Max)	69 (39, 90)	69 (39, 89)	70 (40, 90)	68 (44, 89)
≥65 years, n (%)	112 (70)	105 (66)	68 (72)	69 (68)
Sex, n (%)				
Male	96 (60)	95 (60)	59 (62)	56 (55)
Female	64 (40)	64 (40)	36 (38)	45 (45)
Race, n (%)				
White	150 (94)	142 (89)	90 (95)	93 (92)
Black	1 (<1)	1 (<1)	0	1 (1)
Not Reported	6 (4)	9 (6)	3 (3)	3 (3)
Other or Unknown	3 (2)	7 (4)	2 (2)	4 (4)
Region, n (%)				
Europe	115 (72)	120 (75)	71 (75)	82 (81)
United States	30 (19)	21 (13)	18 (19)	9 (9)
Other	15 (9)	18 (11)	6 (6)	10 (10)
ECOG PS, n (%)				

0-1	149 (93)	142 (89)	87 (92)	90 (89)
2	11 (7)	17 (11)	8 (8)	11 (11)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ITT = intent to treat; Max = maximum; Min = minimum; PS = performance status.
Source: FDA Multi-Disciplinary Review: Table 25 and Table 44.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

Table 3: Baseline Disease Characteristics for ITT Population and Labeled Indication Population

	ITT Population (≥1 prior therapy)		Labeled Indication Population (≥2 prior therapies)	
	Duvelisib (N=160)	Ofatumumab (N=159)	Duvelisib (N=95)	Ofatumumab (N=101)
Diagnosis				
CLL	155 (98)	157 (99)	92 (97)	99 (98)
SLL	5 (3)	2 (1)	3 (3)	2 (2)
Cytogenetics				
del(17p)	33 (21)	44 (28)	18 (19)	25 (25)
TP53 mutation	31 (19)	29 (18)	17 (18)	16 (16)
IGHV mutation	29 (18)	25 (16)	17 (18)	15 (15)
Tumor Burden				
ALC ≥25 x 10^9/L	91 (57)	84 (53)	-	-
Bulky disease	74 (46)	72 (45)	49 (52)	53 (45)
Number of Prior Therapies				
Median (Min, Max)	2 (1, 10)	2 (1, 8)	3 (2, 10)	3 (2, 8)
1	64 (40)	58 (36)	-	-
2	45 (28)	46 (29)	45 (47)	46 (46)
≥3	50 (31)	55 (35)	50 (53)	55 (54)
Refractory/Early Relapse				
Yes	25 (16)	36 (23)	28 (29)	36 (36)

Abbreviations: ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia; del(17p) = chromosome 17p deletion; *IGHV* = immunoglobulin heavy chain variable region gene; ITT = intent to treat; Max = maximum; Min = minimum; SLL = small lymphocytic lymphoma.
Source: FDA Multi-Disciplinary Review: Table 26 and Table 45.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

4.2.2 Prior Therapies

Patients in the DUO study were heavily pre-treated. The most common prior therapy in both arms was an alkylator agent (92% and 95% in the duvelisib and ofatumumab arms, respectively) (**Table 4**).

Table 4: Prior Therapies in DUO Study Populations at Baseline

	ITT Population (≥1 prior therapy)	
	Duvelisib (N=160)	**Ofatumumab (N=159)**
Prior Treatment, n (%)		
Purine-based	96 (60)	113 (71)
Alkylator	148 (92)	151 (95)
Chlorambucil	62 (39)	51 (32)
Bendamustine	59 (37)	61 (38)
Cyclophosphamide	95 (59)	111 (70)
Anti-CD20 mAb	125 (78)	132 (83)
Rituximab	123 (74)	131 (83)
Ofatumumab	3 (2)	4 (2)
Obinutuzumab	1 (<1)	3 (2)

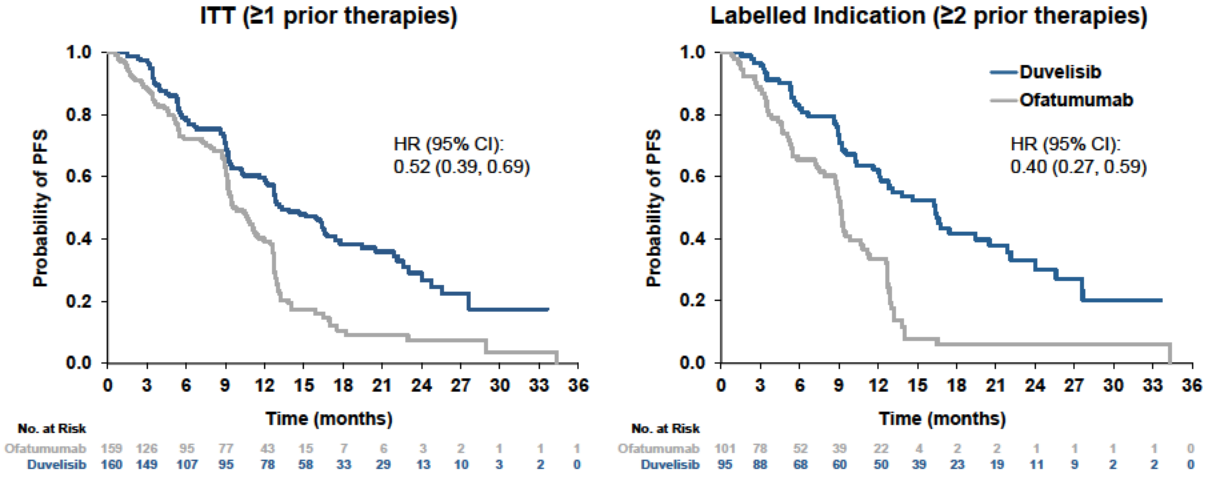
Abbreviations: CD20 = cluster of differentiation 20; ITT = intent to treat; mAb = monoclonal antibody.
Source: FDA Multi-Disciplinary Review: Table 26.
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

4.3 Summary of Efficacy in DUO

4.3.1 Progression-free Survival by Blinded IRC at Primary Analysis

DUO met the primary endpoint of a statistically significant and clinically meaningful benefit in IRC-assessed PFS in the duvelisib arm versus the ofatumumab arm in the ITT Population based on International Workshop on Chronic Lymphocytic Leukemia criteria.[4, 17] The median PFS (mPFS) in the ITT Population was 13.3 months for duvelisib and 9.9 months for the ofatumumab arm (hazard ratio [HR] 0.52; 95% CI: 0.39, 0.69; p<0.0001). The high-risk subgroup of patients who had previously received ≥2 lines of therapy (the Labeled Indication Population) was consistent with the ITT Population (HR 0.40; 95% CI: 0.27, 0.59) (**Figure 7**).

Figure 7: Duvelisib Monotherapy Significantly Improved PFS by Blinded IRC Compared With Ofatumumab

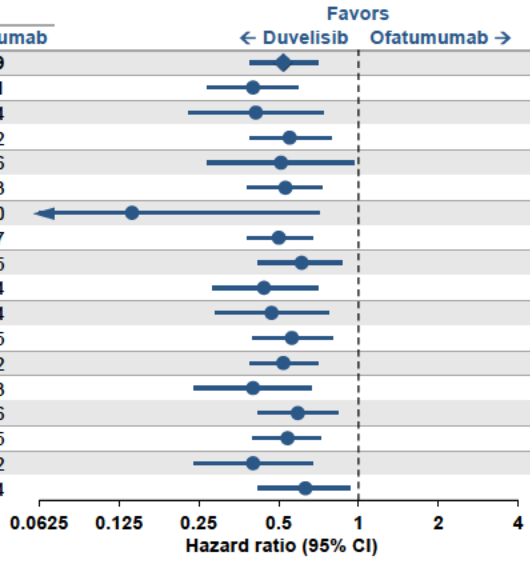


Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intent to treat; PFS = progression-free survival.
Source: Left image adapted from *Blood*, 132(23), Flinn IW, et al, The Phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, 2446-2455, Copyright 2018, with permission from Elsevier[16]; Right image from FDA Multi-Disciplinary Review: Figure 4, Table 28 (ITT), Figure 10, Table 47 (Labeled). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

Progression-free survival by blinded IRC was consistent across all prespecified subgroups, including patients with high-risk cytogenetics, del(17p) or *TP53* mutations, or <12 months from last dose of anticancer therapy (**Figure 8**).

Figure 8: Forest Plot of PFS by Blinded IRC Across Prespecified Subgroups

		Patients, n		HR (95% CI)
		Duvelisib	Ofatumumab	
ITT (≥1 prior therapy)		**160**	**159**	**0.52 (0.39, 0.70)**
≥2 prior therapies		**95**	**101**	**0.40 (0.27, 0.59)**
High-risk cytogenics	Yes	33	44	0.41 (0.23, 0.74)
	No	111	102	0.55 (0.39, 0.79)
Refractory/ Early relapse	Yes	25	36	0.51 (0.27, 0.96)
	No	135	123	0.53 (0.38, 0.73)
Cytopenia(s) at baseline	Grade 4	8	10	0.14 (0.03, 0.71)
Diagnosis	CLL	155	157	0.50 (0.38, 0.67)
Sex	Male	96	95	0.61 (0.42, 0.87)
	Female	64	64	0.44 (0.28, 0.70)
Age, yr	<65	48	54	0.47 (0.29, 0.77)
	≥65	112	105	0.56 (0.40, 0.80)
Race	White	150	142	0.52 (0.39, 0.70)
Prior anticancer therapy	<12 mo	52	63	0.40 (0.24, 0.66)
	≥12 mo	107	96	0.59 (0.42, 0.84)
Not previously treated with ofatumumab		157	155	0.54 (0.40, 0.72)
del(17p) or *TP53*	Yes	48	52	0.40 (0.24, 0.67)
	No	83	84	0.63 (0.42, 0.93)



Abbreviations: CI = confidence interval; CLL = chronic lymphocytic leukemia; HR = hazard ratio; IRC = independent review committee; ITT = intent to treat; PFS = progression-free survival; Refractory/Early relapse = refractory/early relapse to purine analog-based therapy; Prior anticancer therapy = most recent prior anticancer therapy from randomization.

Data cutoff: May 19, 2017
Source: CSR Figure 5
Adapted from *Blood*, 132(23), Flinn IW, et al, The Phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, 2446-2455, Copyright 2018, with permission from Elsevier.[16]

4.3.2 Secondary Endpoints

4.3.2.1 Overall Response Rate (ORR)

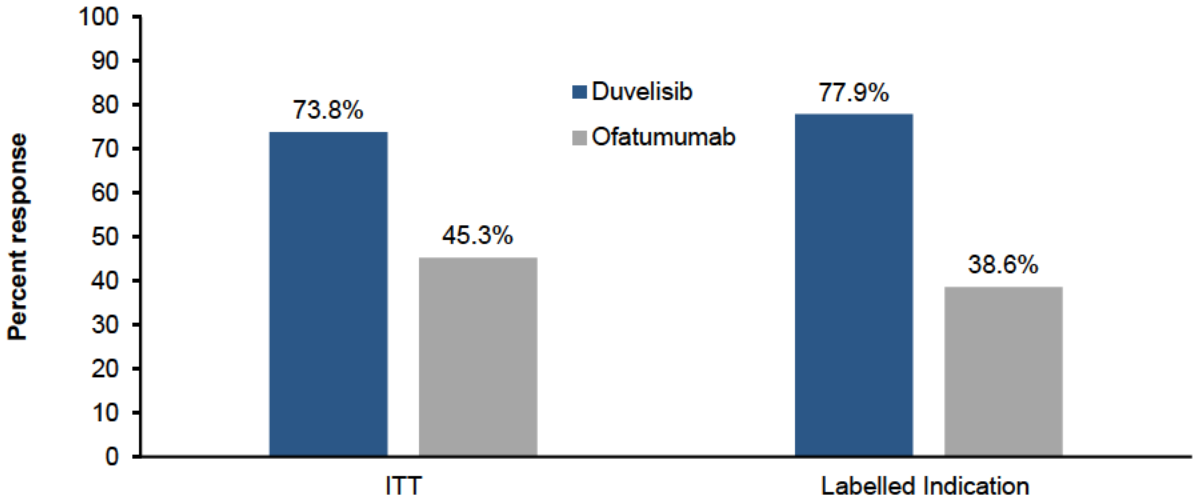
Patients on the duvelisib arm versus the ofatumumab arm experienced significantly higher ORR of 73.8% versus 45.3%, and 77.9% versus 38.6% in the ITT Population and the Labeled Indication Population, respectively (**Table 5** and **Figure 9**).

Table 5: Overall Response by Blinded IRC for ITT Population and Labeled Indication Population

	ITT Population (≥1 prior therapy)		Labeled Indication Population (≥2 prior therapies)	
	Duvelisib (N=160)	Ofatumumab (N=159)	Duvelisib (N=95)	Ofatumumab (N=101)
Response, n (%)				
CR	1 (0.6)	1 (0.6)	0	0
CRi	0	0	0	0
PR	116 (72.5)	71 (44.7)	74 (77.9)	39 (38.6)
PRwL	1 (0.6)	0	0	0
SD	34 (21.3)	63 (39.6)	15 (15.8)	46 (45.5)
PD	2 (1.3)	10 (6.3)	1 (1.1)	5 (5.0)
Other[a]	6 (3.8)	14 (8.8)	5 (5.3)	11 (10.9)
ORR (CR, CRi, PR, PRwL)				
n (%)	118 (73.8)	72 (45.3)	74 (77.9)	39 (38.6)
Odds Ratio (95% CI)	3.50 (2.16, 5.65)		5.60 (2.99, 10.50)	
Median DOR in responders, month (95% CI)	11.1 (9.2, 18.3)	9.3 (7.7, 11.0)	11.3 (7.4, 18.8)	8.0 (7.4, 10.9)

Abbreviations: CI = confidence interval; CR = complete response; CRi = complete response with incomplete marrow recovery; DOR = duration of response; IRC = independent review committee; ITT = intent to treat; ORR = overall response rate; PD = progressive disease; PR = partial response; PRwL = partial response with lymphocytosis; SD = stable disease.
[a] Other includes responses of Unknown due to missing, incomplete, or inadequate data; No Evidence of Disease, if radiological and clinical data indicate no disease involvement; and Not Evaluable if no target lesions were identified at baseline and the radiological and clinical data at post-baseline does not support the disease response of PD or Unknown.
Source: CSR Table 22 (ITT); FDA Multi-Disciplinary Review: Table 35, Table 46 (Labeled).
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

Figure 9: Duvelisib Monotherapy Significantly Improved Overall Response (CR, CRi, PR, PRwL) by Blinded IRC Compared With Ofatumumab



Abbreviations: CR = complete response; CRi = complete response with incomplete marrow recovery; IRC = independent review committee; ITT = intent to treat; PR = partial response; PRwL = partial response with lymphocytosis.
Source: CSR (ITT); FDA Multi-Disciplinary Review: Table 48 (Labeled)
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf
Adapted from *Blood*, 132(23), Flinn IW, et al, The Phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, 2446-2455, Copyright 2018, with permission from Elsevier.[16]

4.3.3 Overall Survival at Interim Analysis

At the time of the primary analysis, an interim analysis of OS was performed with a median follow-up of approximately 24 months in both arms. Overall survival was designed as an exploratory secondary endpoint of efficacy. This interim analysis showed no difference in OS between treatment groups in the ITT Population.

In the duvelisib arm, 46 (28.8%) patients died and 114 (71.3%) were censored for OS at the date of last contact; in the ofatumumab arm, 45 (28.3%) patients died and 114 (71.7%) were censored for OS at the date of last contact (ITT Population). The OS HR for duvelisib versus ofatumumab was 0.99 at this timepoint (95% CI: 0.65, 1.50). The OS HR in the Labeled Indication Population was 0.82 (95% CI: 0.49, 1.37) (**Table 6**).

At the time of the interim analysis of OS in the ITT Population, there was a -0.1-month difference in mean survival times (MST) within a 30-month time window favoring the ofatumumab arm (95% CI: -2.2, 1.9). In the Labeled Indication Population, the difference in MST favored the duvelisib arm by 1.2 months (95% CI: -1.6, 4.0).

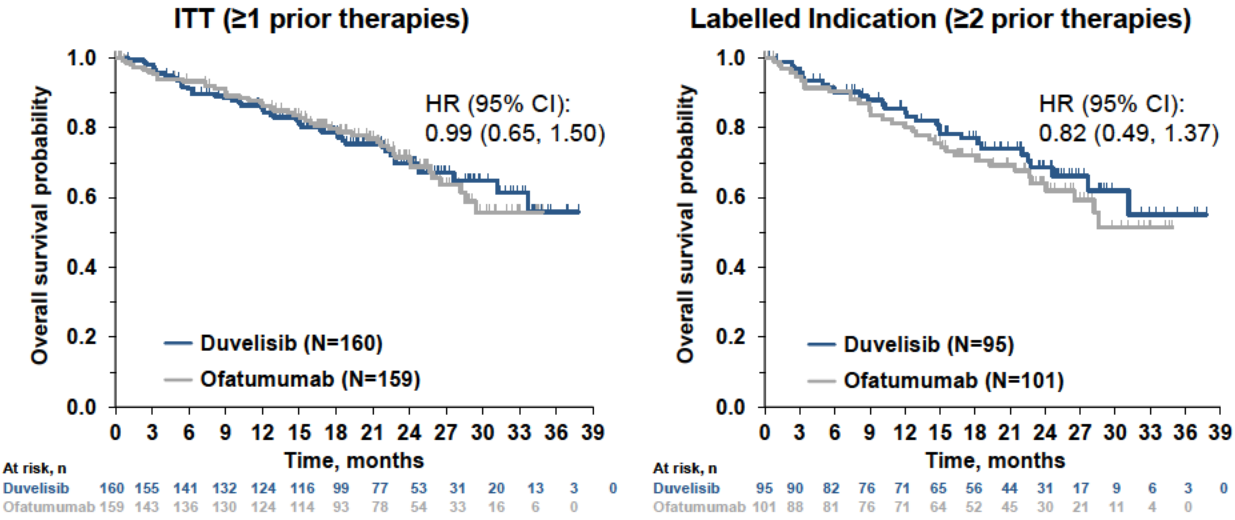
Figure 10 shows the OS Kaplan-Meier (KM) curves in the ITT Population and Labeled Indication at the interim analysis.

Table 6: Summary of Overall Survival in ITT Population and Labeled Indication Population at Interim Analysis

	ITT Population (≥1 prior therapy)		Labeled Indication 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)
Censored, n (%)	114 (71.3)	114 (71.7)	67 (70.5)	67 (66.3)
MST, months	24.4	24.6	24.1	22.9
Difference in MST (95% CI)[a]	-0.1 (-2.2, 1.9)		1.2 (-1.6, 4.0)	
HR (95% CI)[b]	0.99 (0.65, 1.50)		0.82 (0.49, 1.37)	

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; MST= mean survival time.
[a] Difference in MST (duvelisib-ofatumumab) with tau = 30 months.
[b] Stratified Cox proportional hazards model.
Data cutoff: May 19, 2017.
Source: FDA Multi-Disciplinary Review: Table 38, Table 49
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

Figure 10: Overall Survival at Interim Analysis in ITT Population and Labeled Indication Population



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat.
Data cutoff: May 19, 2017.
Source: CSR Figure 8 (ITT); Duvelisib OS Data Update_FINAL.pdf (Labeled); FDA Multi-Disciplinary Review: Table 49 (Labeled)
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211155Orig1Orig2s000MultidisciplineR.pdf.

4.3.4 Patient-Reported Outcomes

Patient-reported outcomes (PROs) were included as a protocol-specified exploratory objective to assess quality of life. The results indicate that duvelisib had a positive impact on quality of life

compared with ofatumumab treatment, with clinically meaningful improvements on the EuroQol-5 Dimension (EQ-5D) Index.

Patient-reported outcomes assessments were captured on Day 1 of Cycles 3, 5, 7, 11, 15, and 19 until PD, subject withdrawal, or initiation of additional anticancer therapy (also at end of treatment if >1 month from last administered questionnaire). For each scale, the patients' overall mean PRO score was determined that captures their overall experience through this period.

Table 7 shows the analysis of mean PRO scores over time. In the Labeled Indication Population, PRO scores favor the duvelisib arm across all scales. Nominally statistically significant differences were seen in 6 out of 10 scales. On the EQ-5D scale, patients treated with duvelisib showed a nominally statistically significant (p=0.0046) and clinically meaningful benefit compared with patients treated with ofatumumab (**Table 7**). A group difference of 0.06 on the EQ-5D Index meets the criteria for group minimal important difference based on literature values and is considered clinically meaningful.[46] In the ITT Population, differences in mean PRO scores were generally smaller in magnitude. In the Labeled Indication Population, the rates of worsening were nominally statistically significantly lower for patients on the duvelisib arm on the EQ-5D Index, EQ-5D visual analog scale, and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale (not shown).

Table 7: Analysis of Mean Patient-Reported Outcomes Scores Over Time

Scale	ITT Population (≥1 prior therapy) (duvelisib, N=156; ofatumumab, N=146)		Labeled Indication Population (≥2 prior therapies) (duvelisib, N=94; ofatumumab, N=97)	
	Difference in Means	Difference in Medians	Difference in Means	Difference in Medians
EQ-5D Index (UK)	-0.01	0.04	0	0.06
P value	p=0.0727		p=0.0046	
EQ-5D VAS	0.79	-0.03	4.3	3.9
P value	p=0.4328		p=0.0043	
Emotional Well-Being	0.63	1.08	0.8	1.4
P value	p=0.0203		p=0.1703	
Functional Well-Being	0.06	1.09	0.8	2.0
P value	p=0.9237		p=0.0917	
Physical Well-Being	0.28	0.51	0.9	1.4
P value	p=0.0751		p=0.0007	
Social and Family Well-Being	0.67	0.49	0.1	0.8
P value	p=0.0723		p=0.2665	
FACT-G Total	1.55	2.59	2.3	5.2
P value	p=0.0534		p=0.0109	
FACIT-Fatigue	0.52	-0.43	1.7	1.3
P value	p=0.2197		p=0.0657	

FACIT-F Trial Outcome Index	1.04	3.07	3.6	4.8
P value	p=0.2692		p=0.0123	
FACIT-F Total	2.1	2.87	4.1	6.1
P value	p=0.0486		p=0.0052	

Abbreviations: CI = confidence interval; EQ-5D = EuroQol-5 Dimension; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G = Functional Assessment of Cancer Therapy-General; HR = hazard ratio; ITT = intent to treat; VAS = visual analog scale.
Differences between treatment arms compared to reference values from literature.
P values calculated by Wilcoxon Rank-Sum Test.
Reprinted from Zinzani PL, et al. 2020 EHA. Abstract EP1737 [poster].[47]
Source: EHA Poster, Zinzani et al Table 1.

4.4 Updated Efficacy at Final Analysis of DUO

Updated efficacy results were provided to the agency on June 25, 2021, in the final analysis report for DUO. At the final analysis, the median PFS, ORR, and DOR by investigator assessment were consistent with the results at the time of the primary analysis. Overall survival results at the final analysis are presented in **Section 6.0**.

The mPFS at the final analysis was 17.85 months (95% CI: 15.16, 22.59) for duvelisib compared to 9.47 months (95% CI: 9.14, 11.14) for ofatumumab. The KM estimates of probability of PFS at 6 and 12 months were 86% and 66%, respectively, compared to 71% and 41%, respectively, for ofatumumab (not shown; IPI-145-07 CSR Addendum 01, June 25, 2021).

4.5 Labeled Safety Information

The US Prescribing Information (USPI) for duvelisib includes a warning for fatal and serious immune-mediated toxicities of infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.[1] The labeled safety information is based on a pooled safety set of N=442 patients with CLL/SLL or FL who received duvelisib 25 mg BID.

Serious, including fatal (18/442; 4%), infections occurred in 31% of patients receiving duvelisib 25 mg BID (N = 442). The most common serious infections were pneumonia, sepsis, and lower respiratory infections. The median time to onset of any-grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Prophylaxis for *Pneumocystis jirovecii* pneumonia and cytomegalovirus reactivation/infection (each of which occurred in 1% of patients treated with duvelisib 25 mg BID) is recommended, as well as dose interruption or reduction, or permanent treatment discontinuation.

Serious, including fatal (1/442; <1%) diarrhea or colitis occurred in 18% of patients receiving duvelisib 25 mg BID (N=442). The median time to onset of any-grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring within 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month).

Serious, including fatal (2/442; <1%), cutaneous reactions occurred in 5% of patients receiving duvelisib 25 mg BID (N = 442). Fatal cases included drug reaction with eosinophilia and systemic symptoms and toxic epidermal necrolysis. The median time to onset of any-grade cutaneous reaction was 3 months (range: 1 day to 29 months; 75th percentile: 6 months), with a median event duration of 1 month (range: 1 day to 37 months; 75th percentile: 2 months).

Serious, including fatal (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving duvelisib 25 mg BID (N = 442). The median time to onset of any-grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months.

4.6 Summary of Safety in DUO at Primary Analysis

4.6.1 Exposure and Safety Follow-up

When comparing the safety profile of duvelisib versus ofatumumab in the DUO trial, including the number of deaths in each arm, it is important to recognize that time on study drug was more than twice as long in the duvelisib arm. Duvelisib was administered continuously until disease progression or unacceptable toxicity, whereas ofatumumab was limited to 12 doses for a maximum of 7 cycles, per the approved product label.

In the primary analysis of safety, median exposure was 50.3 weeks in the duvelisib arm and 23.1 weeks in the ofatumumab arm.

Safety information in the DUO trial was collected continuously until 30 days after the last dose of study drug, after which patients were followed for clinical assessments only. Of note, disease-related AEs were not collected in the ofatumumab arm beyond a maximum of 26 weeks. This is relevant because patients with CLL are known to have a high background rate of AEs even in the absence of treatment. In the CLL12 trial of ibrutinib versus placebo in treatment-naive patients with CLL, a 43% incidence of severe AEs, a 14% incidence of grade ≥3 infections, and a 3.2% incidence of fatal AEs was observed in patients receiving placebo.[23]

Thus, safety data for both drug- and disease-related AEs for patients on the duvelisib arm were collected for nearly twice as long as the ofatumumab arm. To allow for a comparison during the time when safety data were being collected in both arms, safety data are presented for AEs with onset within the first 24 weeks after first study dose and for the overall study period. This 24-week period captures the vast majority of exposure to ofatumumab and allows for a more accurate comparison of the safety profile of the 2 drugs.

4.6.2 Treatment-Emergent Adverse Events

Table 8 provides the overall summary of safety. In the overall study period, the incidence of grade ≥3 AEs and severe treatment-emergent AEs (TEAEs) was higher for the duvelisib arm than for the ofatumumab arm. These data reflect the differences in safety data collection and exposure between the treatment arms. The incidence of TEAEs with onset within 24 weeks was higher for the duvelisib arm than for the ofatumumab arm; however, the incidence of AEs is more closely balanced during the time period with equal time on study drug and equal collection of AE data. As shown in **Table 9**, AEs in the system organ class (SOC) of gastrointestinal disorders and the SOC of infections and infestations were higher in the duvelisib arm than in the ofatumumab arm.

Table 8: Overall Summary of Treatment-Emergent Adverse Events (All-Treated Population)

	Overall Study Period		AE Onset Within 24 Weeks After First Dose	
Category	**Duvelisib (N=158)**	**Ofatumumab (N=155)**	**Duvelisib (N=158)**	**Ofatumumab (N=155)**
Any TEAE, n (%)	156 (98.7)	144 (92.9)	150 (94.9)	143 (92.3)
TEAE Grade ≥3, n (%)	138 (87.3)	75 (48.4)	103 (65.2)	73 (47.1)
Serious TEAE, n (%)	115 (72.8)	50 (32.3)	73 (46.2)	48 (31.0)
TEAE leading to discontinuation, n (%)	57 (36.1)	9 (5.8)	24 (15.2)	9 (5.8)
TEAE with outcome of death, n (%)	19 (12.0)	7 (4.5)	10 (6.3)	7 (4.5)
Duration of exposure, median weeks (Min, Max)	50.3 (0.9, 160.0)	23.1 (0.1, 26.1)	24.0 (1.7, 24.0)	24.0 (0.1, 24.0)

Abbreviations: AE = adverse event; Max = maximum; Min = minimum; TEAE = treatment-emergent adverse event.
Data cutoff: May 19, 2017.
Source: CSR Table 27 and Table 28.

Table 9: TEAEs by System Organ Class in Overall Study Period (All-Treated Population)

	Overall Study Period, n (%)	
System Organ Class	**Duvelisib (N=158)**	**Ofatumumab (N=155)**
Any TEAE	156 (98.7)	144 (92.9)
Blood and lymphatic system disorders	85 (53.8)	53 (34.2)
Gastrointestinal disorders	116 (73.4)	58 (37.4)
General disorders and administration site conditions	82 (51.9)	57 (36.8)
Infections and infestations	109 (69.0)	67 (43.2)
Injury, poisoning and procedural complications	28 (17.7)	42 (27.1)
Investigations	56 (35.4)	31 (20.0)
Metabolism and nutrition disorders	56 (35.4)	31 (20.0)
Nervous system disorders	45 (28.5)	41 (26.5)
Respiratory, thoracic and mediastinal disorders	68 (43.0)	46 (29.7)
Skin and subcutaneous tissue disorders	67 (42.4)	48 (31.0)
Vascular disorders	25 (15.8)	26 (16.8)

Abbreviation: TEAE = treatment-emergent adverse event.
Source: CSR Table 29.

The most common TEAEs of any grade and of grade ≥3 in the overall study period are shown in **Table 10**. The incidence of TEAEs associated with inhibition of PI3K (infections, diarrhea/colitis, pneumonitis, and rash) was higher in the duvelisib arm. The incidence of grade ≥3 PI3Ki-associated AEs in the duvelisib arm did not exceed 15% of patients during the overall study period. The TEAEs were generally manageable with early intervention, including steroids

in some cases as well as dose modifications as recommended by protocol; in most cases, the TEAEs did not lead to treatment discontinuation, and they were rarely fatal. This AE profile is consistent with the approved label. No new safety signals have been observed in either ongoing clinical trials or routine pharmacovigilance.

Table 10: Most Common (≥10% of Duvelisib-Treated Patients) TEAEs by PT of Any Grade or Grade ≥3 in Overall Study Period (All-Treated Population)

	Any Grade, n (%)		Grade ≥3, n (%)	
Preferred Term	**Duvelisib (N=158)**	**Ofatumumab (N=155)**	**Duvelisib (N=158)**	**Ofatumumab (N=155)**
Any AE	156 (98.7)	144 (93)	138 (87.3)	75 (48.4)
Hematologic AEs				
Neutropenia	52 (32.9)	32 (20.6)	48 (30.4)	27 (17.4)
Anemia	36 (22.8)	16 (10.3)	20 (12.7)	8 (5.2)
Thrombocytopenia	23 (14.6)	9 (5.8)	12 (7.6)	3 (1.9)
Nonhematologic AEs				
Diarrhea	80 (50.6)	19 (12.3)	23 (14.6)	2 (1.3)
Pyrexia	45 (28.5)	16 (10.3)	4 (2.5)	1 (0.6)
Nausea	37 (23.4)	17 (11.0)	0	0
Cough	33 (20.9)	22 (14.2)	2 (1.3)	0
Pneumonia	29 (18.4)	9 (5.8)	22 (13.9)	2 (1.3)
Constipation	26 (16.5)	13 (8.4)	1 (0.6)	0
Upper respiratory tract infection	25 (15.8)	12 (7.7)	0	0
Vomiting	23 (14.6)	10 (6.5)	0	0
Bronchitis	21 (13.3)	13 (8.4)	5 (3.2)	1 (0.6)
Colitis	21 (13.3)	2 (1.3)	19 (12.0)	1 (0.6)
Fatigue	20 (12.7)	19 (12.3)	2 (1.3)	2 (1.3)
Decreased appetite	20 (12.7)	5 (3.2)	0	1 (0.6)
Weight decreased	18 (11.4)	3 (1.9)	0	0
Asthenia	18 (11.4)	17 (11.0)	3 (1.9)	4 (2.6)
Dyspnea	16 (10.1)	9 (5.8)	4 (2.5)	0
Rash	16 (10.1)	18 (11.6)	3 (1.9)	1 (0.6)

Abbreviations: AE = adverse event; PT = preferred term; TEAE = treatment-emergent adverse event.
Adapted from *Blood*, 132(23), Flinn IW, et al, The Phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL, 2446-2455, Copyright 2018, with permission from Elsevier.[16]
Source: CSR Table 29 (Any grade); CSR Table 31, Table 14.3.1.4 (Grade ≥3).

Table 11 shows the incidence of TEAEs with onset within the first 24 weeks. The incidence of AEs is more closely balanced during the time period with equal time on study drug and equal collection of AE data. During the first 24 weeks, diarrhea was the most common AE in the duvelisib arm, and the incidence was higher in the duvelisib arm than in the ofatumumab arm.

Table 11: Most Common (≥10%) TEAEs by PT of Any Grade or Grade ≥3 Within 24 Weeks After First Dose (All-Treated Population)

	Any Grade, n (%)		Grade ≥3, n (%)	
Preferred Term	**Duvelisib (N=158)**	**Ofatumumab (N=155)**	**Duvelisib (N=158)**	**Ofatumumab (N=155)**
Any AE within 24 weeks after first dose	150 (94.9)	143 (92.3)	103 (65.2)	73 (47.1)
Diarrhea	48 (30.4)	19 (12.3)	7 (4.4)	2 (1.3)
Neutropenia	38 (24.1)	32 (20.6)	35 (22.2)	27 (17.4)
Pyrexia	31 (19.6)	16 (10.3)	3 (1.9)	1 (0.6)
Anemia	28 (17.7)	15 (9.7)	16 (10.1)	8 (5.2)
Nausea	27 (17.1)	17 (11.0)	0	0
Cough	21 (13.3)	22 (14.2)	2 (1.3)	0
Constipation	21 (13.3)	13 (8.4)	0	0
Upper respiratory tract infection	16 (10.1)	10 (6.5)	0	0
Thrombocytopenia	16 (10.1)	8 (5.2)	6 (3.8)	3 (1.9)
Rash	10 (6.3)	18 (11.6)	1 (0.6)	1 (0.6)
Infusion related reaction	0	30 (19.4)	0	6 (3.9)
Fatigue	14 (8.9)	19 (12.3)	0	2 (1.3)

Abbreviations: AE = adverse event; PT = preferred term; TEAE = treatment-emergent adverse event.
Source: CSR Table 14.3.1.24 (Any grade); CSR Table 14.3.1.25 (Grade ≥3).

4.6.3 TEAEs With Outcome of Death

Overall, fatal TEAEs were reported for a total of 26 patients (8.3%) while on treatment (defined as between first dose and 30 days after last dose) at the primary analysis data cutoff of May 19, 2017. There were 19 (12.0%) fatal TEAEs in the duvelisib arm and 7 (4.5%) in the ofatumumab arm at the time of the primary analysis (**Table 12**). Most fatal TEAEs were not considered related to treatment by the investigator.[16]

There were 4 fatal TEAEs in the duvelisib arm considered related to treatment: 2 caused by staphylococcal pneumonia probably related to treatment, and 1 each caused by general physical health deterioration and sepsis possibly related to treatment.

Table 12: TEAEs With an Outcome of Death (All-Treated Population)

	Patients, n (%)	
	Duvelisib (N=158)	**Ofatumumab (N=155)**
Patients with ≥1 TEAE resulting in death	**19 (12.0)**	**7 (4.5)**
Bronchopulmonary aspergillosis	2 (1.3)	0
Hemorrhagic stroke	2 (1.3)	0
Pneumonia staphylococcal	2 (1.3)	0
Bronchitis	1 (0.6)	0
Cardiac failure	1 (0.6)	0
Chronic obstructive pulmonary disease	1 (0.6)	0

Death	1 (0.6)	0
Enterococcal sepsis	1 (0.6)	0
Escherichia sepsis	1 (0.6)	0
General physical health deterioration	1 (0.6)	0
Mental impairment	1 (0.6)	0
Multi-organ failure	1 (0.6)	0
Pneumonia bacterial	1 (0.6)	0
Pneumonia *Pseudomonas aeruginosa*	1 (0.6)	0
Pseudomonal sepsis	1 (0.6)	0
Sepsis	1 (0.6)	0
Septic shock	1 (0.6)	0
Sudden death	1 (0.6)	0
Disease progression	0	2 (1.3)
Fall	0	1 (0.6)
Glioblastoma multiforme	0	1 (0.6)
Hepatic failure	0	1 (0.6)
Renal failure acute	0	1 (0.6)
Squamous cell carcinoma	0	1 (0.6)

Abbreviation: TEAE = treatment-emergent adverse event.
Source: CSR Table 36.

4.6.4 TEAEs Leading to Discontinuation

There were 57 patients out of 158 who discontinued duvelisib (36.1%) at the primary analysis data cutoff. Of the duvelisib-treated patients who discontinued treatment because of AEs, colitis and diarrhea were the only AEs occurring in ≥5% of patients (both 5%). Treatment discontinuations from the other immune-related toxicities of pneumonitis (2%) and elevated aspartate transaminase levels (1%) were infrequent.[16]

4.7 Summary of Duvelisib Safety at Final Analysis in DUO

At the time of the original CSR data cutoff of May 19, 2017, 34 patients were still receiving duvelisib. Updated safety information including these 34 patients was submitted to FDA in an addendum to the CSR dated June 25, 2021, when all patients had completed treatment (IPI-145-07 CSR Addendum 01, June 25, 2021). Because all ofatumumab patients had completed safety analyses before the primary data cutoff, there were no updates to safety information for ofatumumab patients at the final analysis.

Table 13 shows the overall summary of AEs at the final analysis of DUO compared with the primary analysis. Overall, there were no new significant safety findings reported at the final analysis. The incidence of TEAEs was generally consistent between the primary and final analyses.

Table 13: Overall Summary of AEs at Primary and Final Analysis

	Primary Analysis	Final Analysis
Category	**Duvelisib (N=158)**	**Duvelisib (N=158)**
Any TEAE, n (%)	156 (98.7)	158 (100.0)
TEAE grade ≥3, n (%)	138 (87.3)	144 (91.1)
Serious TEAE, n (%)	115 (72.8)	124 (78.5)
TEAE leading to discontinuation, n (%)	57 (36.1)	70 (44.3)
TEAE leading to dose hold, n (%)	123 (77.8)	112 (70.9)
TEAE leading to dose reduction, n (%)	46 (29.1)	48 (30.4)
TEAE with outcome of death, n (%)	19 (12.0)	24 (15.2)
Duration of Exposure, median weeks (Min, Max)	50.3 (0.9, 160.0)	47.3 (0.1, 311.6)

Abbreviations: AE = adverse event; Max = maximum; Min = minimum; TEAE = treatment-emergent adverse event.
Source: CSR Table 27, Table 28 (Primary analysis); CSR Addendum Table 8, Table 14.1.4 (Final analysis).

After a complete and exhaustive analysis of the DUO trial laboratory shift data in the final analysis versus the interim analysis, there are no clinically meaningful changes that would demonstrate any new safety signals that would cause potential harm; thus, there is no change in the benefit-risk ratio. All relevant hematology and chemistry laboratory data as per the original approval and final analysis are already contained within the product labeling.

4.8 Long-term Safety of Duvelisib Monotherapy in Combined Pool of Patients (Study VS-0145-328)

The approval of duvelisib in R/R CLL patients included a PMR to study long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg BID in trials IPI-145-02, IPI-145-06, IPI-145-07, and IPI-145-12 combined (PMR 3494-2). This PMR was fulfilled in a final report submitted to FDA on November 13, 2020. Overall, there were 443 patients with CLL/SLL or FL in the integrated safety analysis who received duvelisib at a dose of 25 mg BID (safety analysis set), with a median duration of exposure of 40 weeks in the All-Heme group (N=443).

The results with longer follow-up in Study VS-0145-328 were consistent with the results of DUO and formed the basis of the duvelisib USPI.

Table 14 shows the summary of deaths on study in patients treated with duvelisib monotherapy (25 mg BID). In the All-Heme group, 28 (6.3%) patients died as a result of an AE while on treatment. In the CLL/SLL subgroup, 26 (8.6%) patients died as a result of an AE while on treatment. In the survival follow-up, defined as >30 days after last dose, the most common cause of death was PD in all groups.

Table 14: Summary of Deaths in Study VS-0145-328

	Patients, n (%)		
	All Heme N=443	**CLL/SLL N=304**	**FL N=96**
On treatment, total	**47 (10.6)**	**36 (11.8)**	**10 (10.4)**
PD	16 (3.6)	7 (2.3)	8 (8.3)

Adverse event	28 (6.3)	26 (8.6)	2 (2.1)
Other	0	0	0
Unknown	3 (0.7)	3 (1.0)	0
Survival follow-up, total	**136 (30.7)**	**86 (28.3)**	**41 (42.7)**
Progressive disease	65 (14.7)	38 (12.5)	22 (22.9)
Adverse event	15 (3.4)	11 (3.6)	3 (3.1)
Not PD	3 (0.7)	0	2 (2.1)
Other	33 (7.4)	25 (8.2)	6 (6.3)
Unknown	20 (4.5)	12 (3.9)	8 (8.3)

Abbreviations: AE = adverse event; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = hematologic malignancies; PD = progressive disease; SLL = small lymphocytic lymphoma.
Note: Deaths on treatment are defined as deaths occurring between first dose and within 30 days after last dose. Deaths in follow-up are defined as deaths occurring >30 days after last dose. For subjects in Study IPI-145-02, the survival follow-up deaths are classified according to the electronic case report form question: "Was death due to disease progression?" As a result, all deaths from that study that were not due to PD are categorized as not PD. In Studies IPI-145-06, IPI-145-07, and IPI-145-12, the data were captured as PD, AE, other, and unknown.
Source: CSR Table 16.

Table 15 and **Table 16** show the rates of TEAEs resulting in death or treatment-emergent serious AEs. Note that the rates of TEAEs resulting in death, and serious AEs are higher in patients with R/R CLL than in patients with R/R FL, despite similar exposure times to duvelisib. This may reflect differences in the background rates of AEs associated with each disease. As described above, patients with CLL are known to have high rates of AEs even in the absence of treatment, including high rates of severe infections.[23]

Table 15: TEAEs Resulting in Death in >1 Patient Treated With Duvelisib 25 mg BID (Study VS-0145-328)

	Patients, n (%)		
	All Heme N=443	**CLL/SLL N=304**	**FL N=96**
Any TEAE resulting in death	**57 (12.9)**	**44 (14.5)**	**11 (11.5)**
Disease progression	14 (3.2)	6 (2.0)	7 (7.3)
General physical health deterioration	3 (0.7)	3 (1.0)	0
Death	2 (0.5)	2 (0.7)	0
Multi-organ failure	2 (0.5)	2 (0.7)	0
Pneumonia staphylococcal	2 (0.5)	2 (0.7)	0
Sepsis	2 (0.5)	2 (0.7)	0
Septic shock	2 (0.5)	2 (0.7)	0
Respiratory failure	2 (0.5)	2 (0.7)	0
Cardiac failure	2 (0.5)	2 (0.7)	0
Hemorrhagic stroke	2 (0.5)	2 (0.7)	0

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = hematologic malignancies; MedDRA = Medical Dictionary for Regulatory Activities; SLL = small lymphocytic lymphoma; TEAE = treatment-emergent adverse event.

Note: Adverse events are coded using MedDRA version 16.1. Patients are counted once within each system organ class and preferred term. Percentages are based on the number of patients in each analysis group for the Safety Analysis Set. Both system organ classes and preferred terms are sorted in decreasing frequency of the All-Heme 25 mg BID analysis group.
Source: CSR Table 17.

Table 16: Treatment-Emergent Serious Adverse Events by in >2% of Patients Treated With Duvelisib 25 mg BID (Study VS-0145-328)

	Patients, n (%)		
	All Heme N=443	**CLL/SLL N=304**	**FL N=96**
Any TESAE	**309 (69.8)**	**225 (74.0)**	**57 (59.4)**
Pneumonia	51 (11.5)	45 (14.8)	3 (3.1)
Diarrhea	47 (10.6)	34 (11.2)	9 (9.4)
Colitis	38 (8.6)	31 (10.2)	2 (2.1)
Febrile neutropenia	26 (5.9)	20 (6.6)	6 (6.3)
Pyrexia	16 (3.6)	12 (3.9)	4 (4.2)
Disease progression	14 (3.2)	6 (2.0)	7 (7.3)
Pneumonitis	14 (3.2)	8 (2.6)	4 (4.2)
Renal failure acute	13 (2.9)	9 (3.0)	4 (4.2)
Sepsis	10 (2.3)	8 (2.6)	2 (2.1)

Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; Heme = hematologic malignancies; MedDRA = Medical Dictionary for Regulatory Activities; SLL = small lymphocytic lymphoma; TESAE = treatment-emergent serious adverse event.
Note: Adverse events are coded using MedDRA version 16.1. Only TEAEs that were reported by ≥2% of patients in the All-Heme group are included in this table. Patients are counted once within each system organ class and preferred term. Percentages are based on the number of patients in each analysis group for the Safety Analysis Set. Both system organ classes and preferred terms are sorted in decreasing frequency of the All-Heme 25 mg BID analysis group.
Source: CSR Table 18.

5.0 PHASE 3 CROSSOVER EXTENSION STUDY (STUDY IPI-145-12)

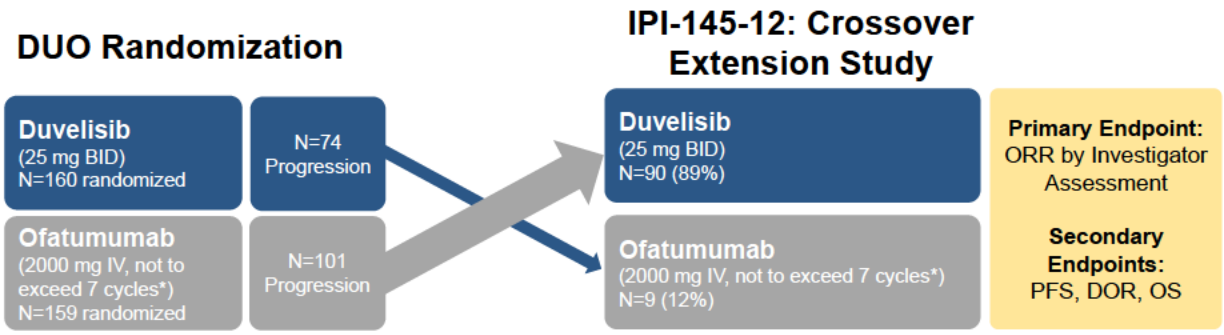
5.1 Study Design of Study IPI-145-12

The DUO crossover extension study (Study IPI-145-12; NCT02049515) is a completed, open-label, Phase 3 study that evaluated the efficacy and safety of duvelisib monotherapy in patients with R/R CLL/SLL who experienced PD while receiving ofatumumab in the DUO trial (**Figure 11**).

There were 101 patients originally randomized to the ofatumumab arm of DUO who experienced confirmed PD and 90 who crossed over to receive duvelisib in Study IPI-145-12. Patients who crossed over from ofatumumab to duvelisib had a median exposure to duvelisib of 43 weeks (range: 2-187 weeks), and 48% of patients received ≥12 cycles, with a median of 11 cycles (range: 1-48 cycles).

The primary endpoint was ORR as assessed by investigator assessment according to 2008 International Workshop on Chronic Lymphocytic Leukemia criteria with a modification for treatment-related lymphocytosis.[17] Secondary endpoints were PFS, DOR, and OS.

Figure 11: Study Design of Crossover Extension Study for DUO (Study IPI-145-12)



Abbreviations: BID = twice daily; DOR = duration of response; IV = intravenous; ORR = overall response rate; OS = overall survival; PFS = progression-free survival.

5.2 Efficacy in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)

5.2.1 Overall Response Rate by Investigator (Study IPI-145-12)

The investigator-assessed ORR in all patients treated with duvelisib after crossover was 77% (69/90). In patients who had del(17p) and/or *TP53* mutations at baseline, and in patients who had no prior response to ofatumumab, the response rates were 77% and 73% respectively (**Table 17**). Response rates were higher for patients after crossing over to duvelisib compared with a prior response rate of 45.3% for patients randomized to ofatumumab in the parent DUO trial.

Table 17: Overall Response Rate by Investigator Assessment in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)

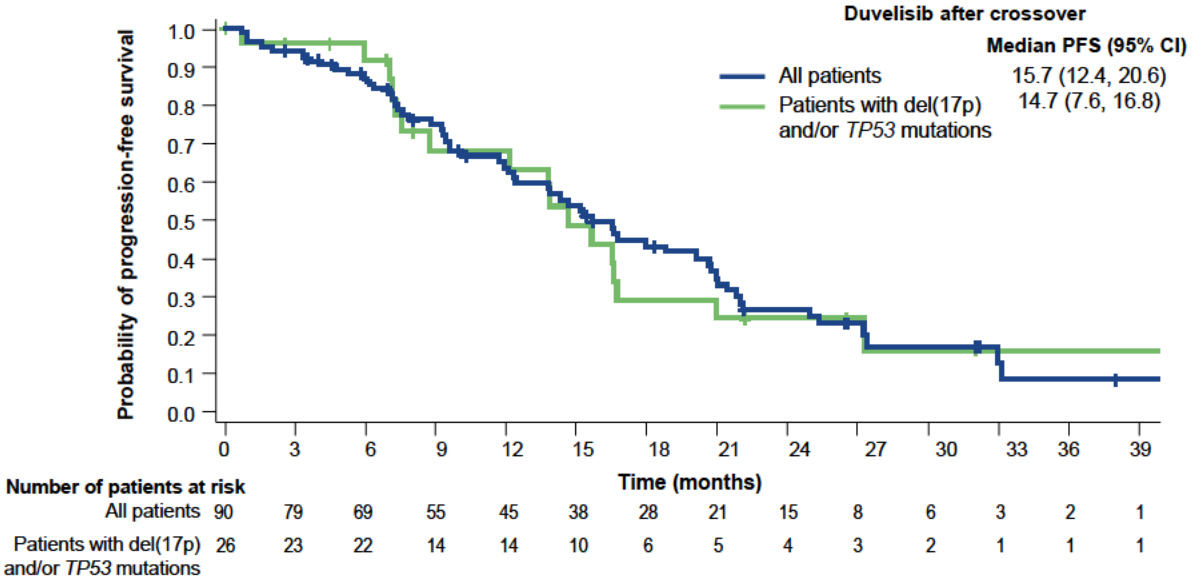
	Duvelisib After Crossover		
	All Patients N=90	**del(17p) and/or *TP53* Mutations N=26**	**No Prior Response to Ofatumumab N=64**
Overall response rate, n (%)	69 (77)	20 (77)	47 (73)
95% CI[a]	67.9, 85.4	60.7, 93.1	62.6, 84.3
Best overall response, n (%)			
CR	0	0	0
CRi[b]	4 (4)	3 (12)	1 (2)
PR	55 (61)	15 (58)	40 (63)
PRwL	10 (11)	2 (8)	6 (9)
SD	13 (14)	4 (15)	11 (17)
PD	1 (1)	0	1 (2)
Other[c]	7 (8)	2 (8)	5 (8)
Median DOR,[d] months (95% CI)	14.9 (9.0, 18.6)	11.3 (5.1, 21.2)	14.9 (7.3, 18.6)

Abbreviations: CI = confidence interval; CR = complete response; CRi = complete response with incomplete marrow recovery; del(17p) = chromosome 17p deletion; DOR = duration of response; PD = progressive disease; PR = partial response; PRwL = partial response with lymphocytosis; SD = stable disease.
[a] Binominal method; [b] Patients with CLL only; [c] Includes unknown responses due to missing, incomplete, or inadequate data; no evidence of disease if radiological and clinical data indicated no disease involvement; not evaluable if no target lesions were identified at baseline and the radiological and clinical data after baseline did not support the disease response of PD or unknown. [d] Patients with a response (all patients: n = 26 [before crossover], n = 69 [after crossover]; del[17p] and/or *TP53* mutations: n = 7 [before crossover], n = 20 [after crossover]).
Reprinted from *Clin Cancer Res*, Copyright 2020, 26(9), 2096-2103, Davids MS, et al, Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study, with permissions from AACR.[6]
Source: Davids et al, 2020, Table 2.

5.2.2 Progression-free Survival (Study IPI-145-12)

With a median follow-up of 13.5 months, mPFS was 15.7 months (95% CI: 12.4, 20.6) for the 90 patients who crossed over to duvelisib after confirmed PD on the ofatumumab arm. The mPFS was higher for ofatumumab patients after crossing over to duvelisib (15.7 months) compared with their prior response rates to ofatumumab in the DUO trial (9.4 months). In patients with del(17p) and/or *TP53* mutations at baseline, mPFS after crossing over to duvelisib was 14.7 months (95% CI: 7.6, 16.8) (**Figure 12**).

Figure 12: PFS in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)



Abbreviations: CI = confidence interval; del(17p) = chromosome 17p deletion; PFS = progression-free survival.
Reprinted from *Clin Cancer Res*, Copyright 2020, 26(9), 2096-2103, Davids MS, et al, Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study, with permissions from AACR.[6]
Source: Davids et al, 2020, Figure 2.

5.2.3 Overall Survival in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)

All patients in the parent DUO study were followed up for survival for 6 years from randomization. In patients who received duvelisib after crossover (n = 90), the median OS was 43 months and the estimated probability of survival was 91% at 6 months and 82% at 12 months.[6]

5.3 Safety in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)

The safety profile of duvelisib monotherapy after crossover from ofatumumab was manageable via dose interruption or reduction in this study and was similar to that observed in the DUO study. As typically observed with all CLL therapies, infections were relatively common with duvelisib, although the rate of febrile neutropenia was low at 3%. Neutropenia and diarrhea were the most common severe (grade ≥3) AEs reported at 23%, followed by colitis and pneumonia (11% each), similar to that observed for DUO (**Table 18** and **Figure 13**).

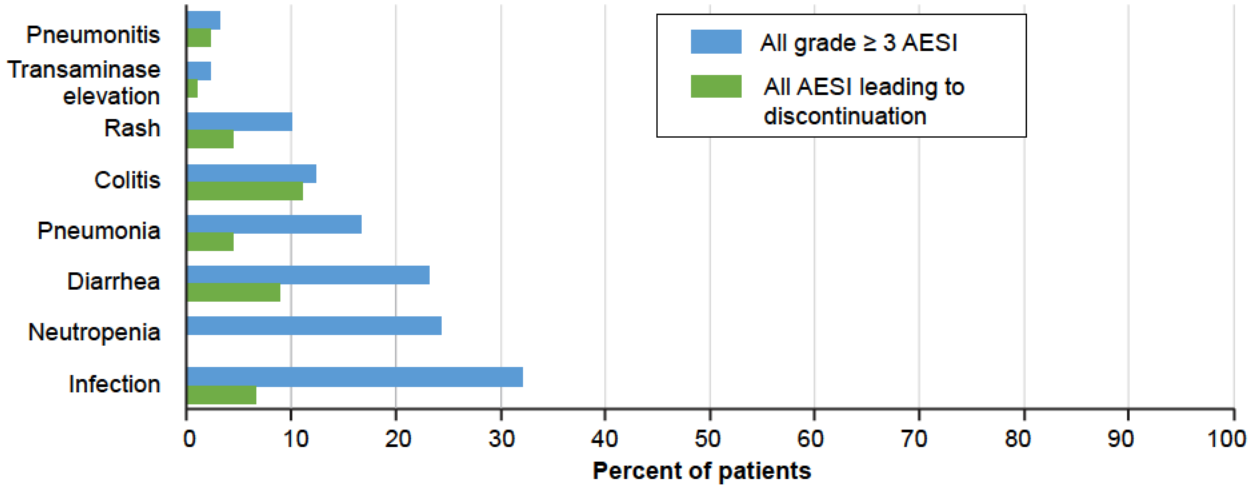
Table 18: TEAEs of Any Grade, and Grade ≥3 in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)

	Duvelisib After Crossover (n=90) n (%)	
	Any Grade	**Grade ≥3**
Any TEAE	90 (100)	80 (89)

Hematologic TEAEs in >5% of patients		
Neutropenia	23 (26)	21 (23)
Thrombocytopenia	9 (10)	5 (6)
Anemia	7 (8)	2 (2)
Nonhematologic TEAEs in >10% of patients		
Diarrhea	42 (47)	21 (23)
Pyrexia	22 (24)	4 (4)
Rash	21 (23)	4 (4)
Colitis	12 (13)	10 (11)
Pneumonia	12 (13)	10 (11)
Cough	12 (13)	0
Asthenia	11 (12)	0
Abdominal pain	10 (11)	1 (1)
Vomiting	10 (11)	0
Decreased appetite	9 (10)	0
Nausea	9 (10)	0

Abbreviation: TEAE = treatment-emergent adverse event.
Reprinted from *Clin Cancer Res*, Copyright 2020, 26(9), 2096-2103, Davids MS, et al, Efficacy and safety of duvelisib following disease progression on ofatumumab in patients with relapsed/refractory CLL or SLL in the DUO crossover extension study, with permissions from AACR.[6]
Source: Davids et al, 2020, Table 3

Figure 13: Rates of Grade ≥3 AESI and AESI Leading to Discontinuation in Patients Who Received Duvelisib After Crossover (Study IPI-145-12)



Abbreviation: AESI = adverse event of special interest.
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Source: Davids et al, 2020, Figure 3

6.0 FURTHER EVALUATION OF OVERALL SURVIVAL IN DUO

6.1 Methods of Updated OS Analysis

A prespecified, updated, final analysis of OS was performed at the completion of the DUO study for the both the ITT Population and the Labeled Indication Population, as well as the prespecified subgroup of patients refractory to purine analog therapy. The primary dataset of interest in which to evaluate updated OS is the population that corresponds with the FDA-approved labeled indication of patients with R/R CLL who have received ≥2 prior therapies.

To assess the group difference in OS the HR and MST were determined. The MST measures the area under the curve within a specific time window. Comparing the difference between 2 MSTs is statistically valid with no required model assumptions and is more stable as a summary of the survival curve than the HR.[48, 49]

From October through December 2020, prior to database lock on January 22, 2021, an investigation was performed in an effort to identify available information on patients' survival status. During this time, investigators were asked to provide details on patients' vital status. A detailed analysis of cause of deaths was conducted to search for any concerning patterns.

6.2 Impact of Crossover and Subsequent Therapy on Final OS Estimates

The DUO study included a crossover extension study (Study IPI-145-12); 90 of 101 patients (90%) originally randomized to the ofatumumab arm who experienced confirmed progression crossed over to receive duvelisib, and 9 of 74 patients (12%) originally randomized to the duvelisib arm who experienced confirmed progression crossed over to receive ofatumumab (**Figure 11**). Because crossover was optional, the relatively high number of patients who crossed over to duvelisib and the low number who crossed over to ofatumumab confounds the interpretation of the OS comparison between duvelisib and ofatumumab.

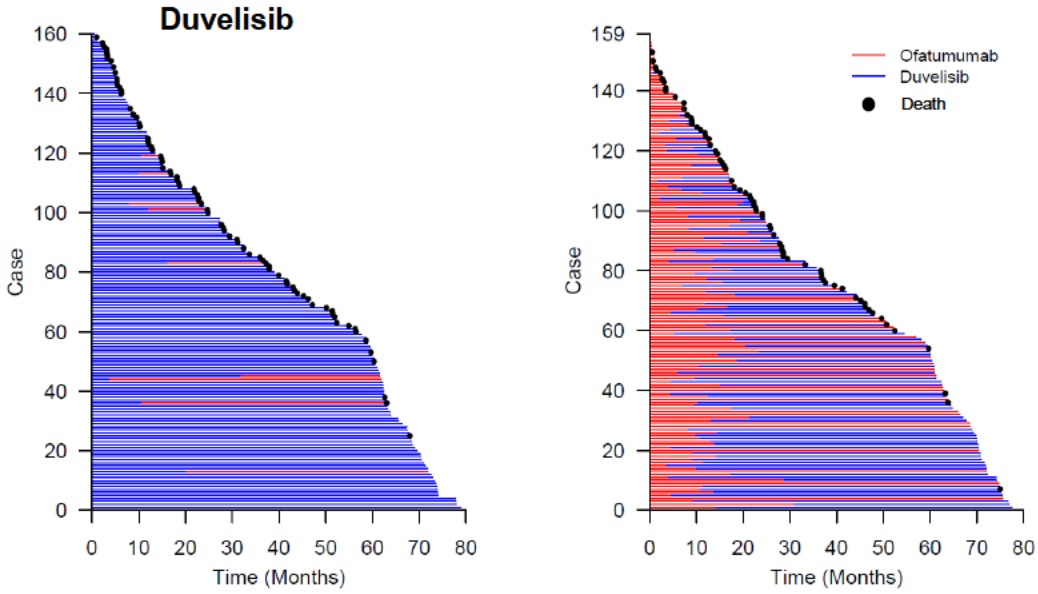
6.2.1 Analysis of Timing of Crossover

Figure 14 shows a swimmer plot of the OS times for all patients randomized to either the duvelisib or ofatumumab arm. The blue and red lines show the duration of follow-up for patients originally randomized to duvelisib or ofatumumab, respectively, until death or censoring. A change in color represents the time of crossover for that patient. Of 159 patients originally assigned to ofatumumab, 90 of the 101 patients with confirmed PD crossed over to duvelisib. In the 159-patient ofatumumab arm, the observed number of deaths was 70, and 89 patients were censored or lost-to-follow-up. The proportion of ofatumumab arm patients who crossed over to duvelisib among "deaths" was 58.6% (41/70), and that among "non-deaths" was 55.1% (49/89).

The imbalance in treatment is further demonstrated by the fact that the actual maximum duration of treatment was 312 weeks (6 years) for duvelisib with a mean of 69 weeks (1.3 years), while the maximum duration of treatment with ofatumumab was only 26 weeks. Therefore, by the 3-year midpoint of the study, the vast majority of patients on the ofatumumab arm had received some exposure to duvelisib. This means that as we near the 3-year midpoint of the curve, when we begin to see crossing of the KM curves (**Figure 15**), a majority of patients on the ofatumumab arm remaining on study would have had some exposure to duvelisib.

For these reasons, the final OS study was confounded due to the extensive imbalance in crossover between the 2 arms.

Figure 14: Swimmer Plot of Overall Survival and Time of Crossover on Study (ITT Population) (Study IPI-145-07)



Abbreviation: ITT = intent to treat.
Source: d02a-cross-ver-figure.pdf.

6.2.2 European Medicines Agency Review Conclusions

EMA reviewed the updated survival results from the DUO study, which were submitted by the sponsor to EMA in an application for a Type II variation on August 27, 2021. The requested variation proposed amendments to the Summary of Product Characteristics to reflect the final OS results for both the ITT Population and the Labeled Indication Population.

In privileged and confidential communications in the Type II Variation Assessment Report dated January 27, 2022, EMA noted that the interpretation of the OS results was difficult because of an imbalance in crossover and further therapies that were received after the study. For this reason, EMA considered it still possible that a lack of OS benefit could be associated with the important identified risks of serious AEs, including serious infections, which are under careful vigilance.

EMA also noted that the observation of a higher number of deaths before progression on the duvelisib arm compared to the ofatumumab arm could reasonably be attributed to the longer window of observation in the absence of PD in an elderly population with significant comorbidities. Ultimately, EMA concluded that the benefit-risk balance of duvelisib remains positive.

As a result of these conclusions, EMA updated the Summary of Product Characteristics to reflect the updated survival results from DUO in the Labeled Indication Population.

6.3 Updated OS Analysis in the ITT and Labeled Indication Populations

As addressed in **Section 6.2**, the updated OS data are heavily confounded due to extensive crossover between the 2 arms. However, the sponsor has undertaken an analysis subject to these significant caveats.

The results of the final OS analysis are summarized in **Table 19**. At a median follow-up of approximately 63 months, the HR for the ITT Population was 1.09 (95% CI: 0.79, 1.51), compared with an HR of 0.99 (95% CI: 0.65, 1.50) at the interim analysis. The OS HR in the Labeled Indication Population was 1.06 (95% CI: 0.71, 1.58) at the final analysis, compared with an HR of 0.82 (0.49, 1.37) at the interim analysis.

Note that the shift in HR from the interim to the final analysis likely reflects the instability of the HR estimate. In contrast, the 60-month MST difference was generally stable between the 2 data cutoff dates and may provide more interpretable and clinically meaningful information. The MST in the Labeled Indication Population was 39.5 months in the duvelisib arm and 38.6 months in the ofatumumab arm (**Table 19**), favoring the duvelisib arm by 0.9 months at the final analysis.

Due to the extensive and imbalanced crossover between the 2 arms, the final OS analysis is difficult to interpret. To the extent the study data are interpretable, the final OS analysis of DUO remains neutral and does not support a detriment to survival in patients randomized to duvelisib compared with those randomized to ofatumumab. Rather, it appears that OS is similar for the 2 treatment arms in both the ITT Population and the Labeled Indication Population.

Table 19: Summary of Overall Survival in ITT Population and Labeled Indication Population at Final Analysis

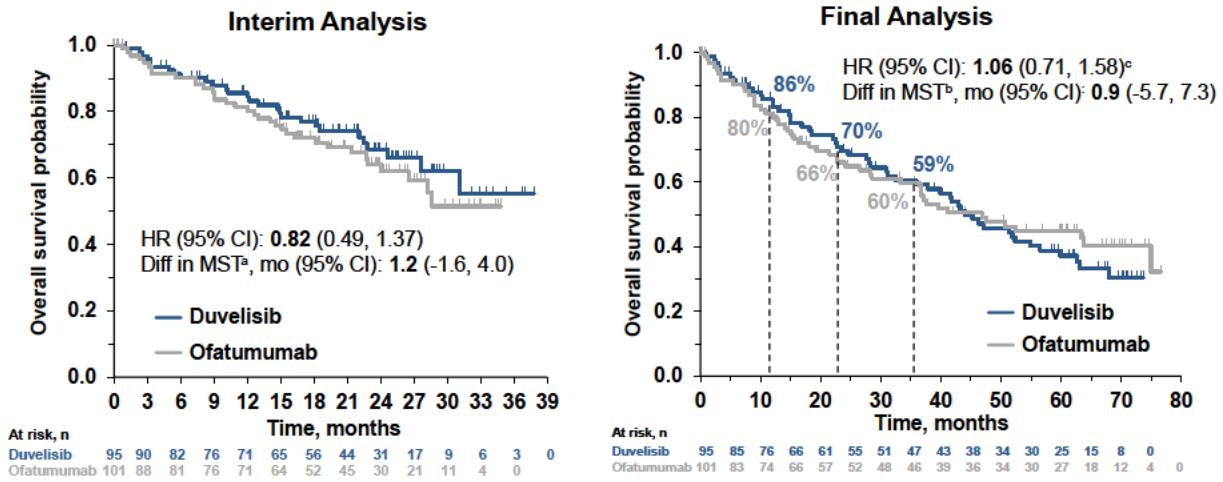
	ITT Population (≥1 prior therapy)		Labeled Indication Population (≥2 prior therapies)	
	Duvelisib (N=160)	Ofatumumab (N=159)	Duvelisib (N=95)	Ofatumumab (N=101)
Deaths, n (%)	80 (50.0)	70 (44.0)	53 (55.8)	49 (48.5)
MST, months	41.6	42.0	39.5	38.6
Difference in MST (95% CI) Nominal p value[a]	-0.4 (–5.3, 4.5)[b] p=0.87		0.9 (–5.7, 7.3)[c] p=0.80	
HR (95% CI)[d] Nominal p value[a]	1.09 (0.79, 1.51) p=0.59		1.06 (0.71, 1.58) p=0.78	
Overall survival 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)

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent to treat; MST= mean survival time.
[a] Two-sided stratified log-rank test.
[b] Difference in MST (duvelisib-ofatumumab) with tau = 30 months.
[c] Difference in MST (duvelisib-ofatumumab) with tau = 60 months.
[d] Stratified Cox proportional hazards model.
Data cutoff: June 22, 2020.
Source: FDA April 21, 2022, ODAC BD, Table 30 (ITT & Labeled); Duvelisib OS data update_FINAL, Table 2 (Labeled).

Figure 15 shows the KM curves for the Labeled Indication Population at the interim and final analyses. The OS rates favored the duvelisib arm at 1 and 2 years and were nearly identical at 3 years. It is not until late in the study, when very few patients remained on study medication, that

the OS rates favored the ofatumumab arm. It is also noteworthy that the curves cross at about 3 years, violating proportional hazards assumptions.

Figure 15: Overall Survival at Interim and Final Analyses in Labeled Indication Population



Abbreviations: CI = confidence interval; Diff = difference; HR = hazard ratio; ITT = intent to treat; MST = mean survival time.
[a] Difference in MST (duvelisib-ofatumumab) with tau = 30 months.
[b] Difference in MST (duvelisib-ofatumumab) with tau = 60 months.
[c] Per FDA Briefing Document from April 21, 2022, ODAC Meeting.
Source: FDA April 21, 2022, ODAC BD, Figure 28, Table 30.

The actual maximum duration of treatment with randomized study medication was 312 weeks (6 years) for duvelisib with a mean of 69 weeks (1.3 years); only 9 patients took medication for more than 2.5 years (IPI-145-07 CSR Addendum 01, June 25, 2021; Table 14.1.4). The maximum duration of treatment with ofatumumab was 26 weeks (0.5 year). Therefore, events in the second part of the KM curves may reflect post-randomization therapies and other factors that confound understanding of how the study medication influenced those late events.

These data suggest that late events after patients discontinued study medication, rather than early deaths due to toxicity or infections, may explain the shift in the OS HR from the interim to the final analysis.

These updated survival data were disseminated by the sponsor in a DHCP letter dated May 1, 2022.[50] The sponsor proposes updating the label to reflect the updated OS information, as described in the DHCP letter.

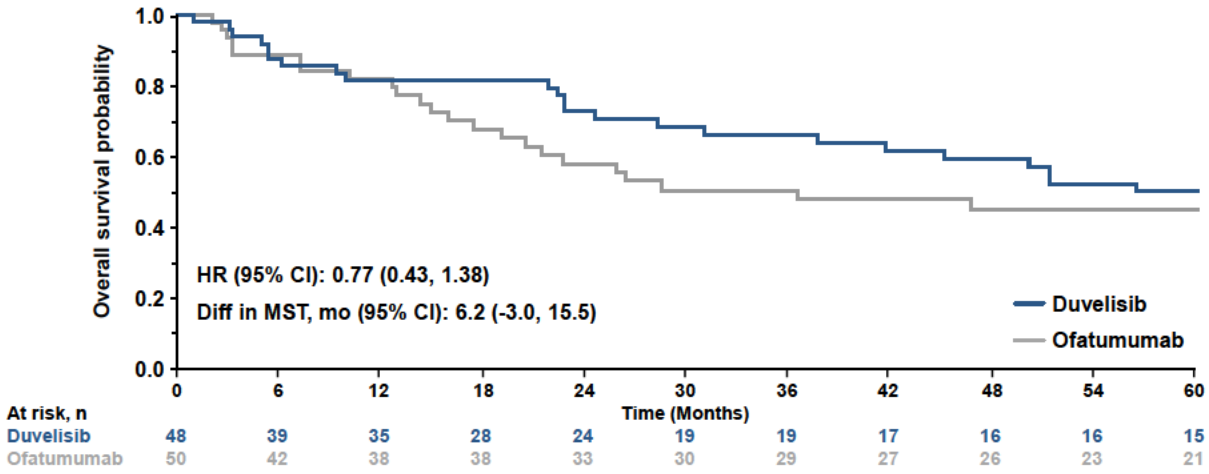
6.4 OS Analysis in Refractory Patient Subgroup

FDA presented a side-by-side analysis of the OS results for 6 randomized trials of PI3Kis in hematologic malignancies at the April 21 ODAC meeting. The greatest potential detriments in survival were noted for PI3Kis in combination with anti-CD20 mAbs, or in patients who were previously untreated. For example, an HR of 3.34 (95% CI: 1.08, 10.39) was found in the 312-0123 trial (NCT01980888) of bendamustine and rituximab plus idelalisib versus bendamustine

and rituximab without idelalisib in treatment-naive patients with CLL, while HRs were closer to or lower than 1 in previously treated patient populations. These data indicate a potentially greater benefit-risk ratio in patients who are heavily pre-treated or refractory.

As noted in **Section 6.2**, the final OS analysis of DUO was confounded due to the extensive imbalance in crossover between the 2 arms. Nevertheless, to explore the benefit-risk ratio in patients who are heavily pre-treated or refractory, we analyzed the prespecified subgroup of refractory patients in DUO. Refractory patients were defined in the protocol as progressing <12 months after purine analog-based therapy (fludarabine/pentostatin). The refractory population of DUO (n=110) is largely overlapping with the Labeled Indication Population (n=196), with 75 patients falling into both categories. At the final analysis in the refractory subgroup, the HR was 0.77 (95% CI: 0.43, 1.38) with a difference in MST of 6.2 months (95% CI: –3.0, 15.5) in favor of duvelisib (**Figure 16**). While this analysis is exploratory, these results are consistent with a trend towards a benefit in OS in heavily pre-treated or refractory patients treated with duvelisib compared with ofatumumab.

Figure 16: Overall Survival at Final Analysis (Prespecified Refractory Patient Subgroup[a])



Abbreviations: CI = confidence interval; HR = hazard ratio; MST = mean survival time.
[a] Refractory patients were defined in the DUO protocol as progressing <12 months after purine analog-based therapy (fludarabine/pentostatin).
Source: Sponsor Analysis

6.5 Cause of Deaths on Study

Analysis of the cause of deaths was undertaken for patients who were randomized and treated with at least one dose of study drug, which corresponds with the population examined for safety analyses (the All-Treated Population) (**Table 20**). Deaths due to PD, AEs other than PD, or unknown cause were evaluated based on the investigator's report. Note that AEs in this context refer to any death not attributed to PD based on the investigator's report, with no determination of relation to study drug treatment.

At the final OS analysis, in the overall population of patients that had received ≥1 prior therapy (ITT Population) there were 9 additional deaths on the duvelisib arm than on the ofatumumab arm. In the Labeled Indication Population of patients with ≥2 prior therapies, there were 3 more

deaths on the duvelisib arm at the time of the final OS analysis (**Table 20**). In the context of a benefit in PFS and ORR, this imbalance in deaths was investigated as a potential safety signal.

There was no one category of cause of death that drove the imbalance in the total number of overall deaths for each treatment. Overall, more patients on the ofatumumab arm died of PD than on the duvelisib arm in the overall ITT Population (16.8% vs. 13.9%, respectively) and in the Labeled Indication Population (19.4% vs. 15.1%, respectively).

In the Labeled Indication Population, there was a higher percentage of deaths due to AEs in the duvelisib versus ofatumumab arm, with deaths due to infection in 14.0% versus 9.2% of patients and deaths due to non-infection AEs occurring in 16.1% versus 8.2% of patients, respectively (**Table 20**). Since infections are one of the most common causes of death for patients with CLL, it is challenging to attribute causality for deaths due to infection to study drug.[24] A review of deaths due to AEs other than infection in the duvelisib arm did not reveal a pattern suggestive of a drug relationship. The AEs other than infection were a mix of conditions commonly seen in an elderly population including cardiovascular and pulmonary diseases as well as unrelated malignancies.

Due to the prolonged time of PFS, there were more deaths before PD on the duvelisib arm; these were generally offset by an increase in deaths due to PD on the ofatumumab arm.

There were more deaths due to unspecified AEs in the ofatumumab arm than the duvelisib arm. In the Labeled Indication Population, 5.1% of patients treated with ofatumumab had an AE of unspecified type compared to 0 in the duvelisib arm. This likely reflects the fact that patients in the ofatumumab arm went off study drug sooner and may have had less extensive follow-up with investigators afterwards.

Table 20: Summary of Cause of Deaths on Study at Final OS Analysis (All-Treated Population)

Category of deaths, n (%)	ITT Population (≥1 prior therapy)		Labeled Indication Population (≥2 prior therapies)	
	Duvelisib (N=158)	Ofatumumab (N=155)	Duvelisib (N=93)	Ofatumumab (N=98)
Total deaths on study	**79 (50.0)**	**70 (45.2)**	**52 (56.0)**	**49 (50.0)**
Progressive disease	22 (13.9)	26 (16.8)	14 (15.1)	19 (19.4)
Adverse event	43 (27.2)	33 (21.3)	28 (30.1)	22 (22.4)
Infection	20 (12.7)	15 (9.7)	13 (14.0)	9 (9.2)
COVID-19	1 (<1.0)	1 (<1.0)	1 (1.1)	1 (1.0)
AE other than infection[a]	23 (14.6)	12 (7.7)	15 (16.1)	8 (8.2)
AE unspecified	0	6 (3.9)	0	5 (5.1)
Unknown	14 (8.9)	11 (7.1)	10 (10.8)	8 (8.2)

Abbreviations: AE = adverse event; ITT = intent to treat; OS = overall survival.
[a] AEs other than infection included heart failure, cardiac arrest, respiratory failure, acute renal failure, hemorrhage, unrelated malignancy.

7.0 POST-MARKETING SAFETY

7.1 Risk Evaluation and Mitigation Strategies

As described in the USPI,[1] serious infections, serious diarrhea/colitis, severe cutaneous reactions, and pneumonitis are important identified risks for duvelisib.. At the time of full approval of duvelisib, FDA required a REMS to ensure the benefits outweighed the risks. The REMS included a Communication Plan and an assessment of that plan. Specifically, the REMS required "an evaluation of the providers' awareness and understanding of the risks of fatal and/or serious toxicities associated with duvelisib" including the 4 noted above. The sponsor has maintained compliance with the REMS and, in July 2021, completed a Knowledge, Attitude and Behavior Survey as required by FDA. The survey of 77 known prescribers and 78 potential subscribers showed an understanding of the key risks with duvelisib as summarized in the USPI Warnings.

7.2 Post-Marketing Surveillance

In accordance with FDA and international guidelines, the sponsor performs continuous and comprehensive review and investigation of the safety data for duvelisib from worldwide sources and provides quarterly and other periodic reports to document these activities.

Since approval there have been an estimated 489 patient-years of marketed use. Cumulative review of spontaneous reports and literature has not identified any new toxicity that has meaningfully changed the risk profile of duvelisib, and the safety profile of duvelisib remains consistent with the USPI. In the time period between approval in September 2018 and March 2022, a total of 50 fatal cases have been reported in patients who received duvelisib, 41 with limited information. The most common reported fatal events were death (n=33), PD (n=6), pneumonia (n=2), renal failure (n=2), and respiratory failure (n=2). In summary, no new safety data have emerged to support a conclusion that duvelisib is unsafe under the conditions of use described in the USPI. FDA's determination that the benefit-risk balance of duvelisib supports use in the approved indication of R/R CLL after ≥2 prior systemic therapies has not been undermined.

8.0 BENEFIT-RISK CONCLUSION

8.1 OS Results Across Multiple Randomized Trials of PI3Kis in CLL

When comparing OS analyses across multiple Phase 3 trials of PI3Kis in CLL, there is a trend towards more favorable results in more relapsed or refractory CLL settings, including for the monotherapy regimen used in the DUO trial of duvelisib.

Table 21 shows a listing of OS results across Phase 3 CLL trials. The first row demonstrates the concerns related to the use of PI3Kis in the treatment of patients with who are naive to treatment.

Within the DUO trial, a trend towards lower HRs and greater benefits in MST was observed on the duvelisib arm in patients with R/R CLL who have received a greater number of prior lines of therapy or who are refractory to prior lines of therapy (**Table 21**). These results support a continued favorable benefit-risk profile of duvelisib monotherapy for the Labeled Indication Population of patients with R/R CLL who have received ≥2 prior therapies.

Importantly, a recent pooled meta-analysis of all 5 randomized controlled studies of PI3Kis in CLL showed an overall OS HR of 0.71 (95% CI: 0.49, 1.01).[51]

Table 21: Listing of OS Results Across Randomized Trials of PI3Kis in CLL

Patient Population	Trial	Median Follow-up (Months)	Study Drug	Comparator	OS HR (95% CI)	Diff in MST (months)
TN CLL	312-0123	22.0[a]	Idelalisib + Bendamustine/ Rituximab	Placebo + Bendamustine/ Rituximab	3.34 (1.08, 10.39)	-
TN and R/R CLL	UNITY-CLL	36.7	Umbralisib + Ublituximab (U2)	Obinutuzumab + Chlorambucil	1.23[b]	-
R/R CLL. ≥1 prior therapy	DUO	63.0	Duvelisib	Ofatumumab	1.09 (0.79, 1.51)	-0.4
R/R CLL. ≥2 prior therapy (Labeled Indication Population)	DUO	63.0	Duvelisib	Ofatumumab	1.06 (0.71, 1.58)	0.9
Refractory[c] CLL	DUO	63.0	Duvelisib	Ofatumumab	0.78 (0.46, 1.34)	5.5
R/R CLL. Progression <24 months from last therapy[d]	313-0116[52]	Not disclosed	Idelalisib + Rituximab	Placebo + Rituximab	0.80 (0.5, 1.1)	-
R/R CLL, Progression <24 months from last therapy[e]	NCT01659021[53]	16.1	Idelalisib + Ofatumumab	Ofatumumab	0.74 (0.44, 1.25)	-

Abbreviations: CI = confidence interval; CLL = chronic lymphocytic leukemia; HR = hazard ratio; MST = mean survival time; OS = overall survival; R/R = relapsed or refractory; TN = treatment naive.
[a] Study was terminated at 22 months due to urgent safety concerns.

[b] Confidence intervals were not disclosed.
[c] Refractory patients were defined in the DUO protocol as progressing <12 months after purine analog-based therapy (fludarabine/pentostatin).
[d] Prior therapies with either a CD20 antibody-based regimen or at least 2 previous cytotoxic regimens were required. Patients had to be unable to receive cytotoxic therapies on the basis of cumulative illness rating scale scores greater than 6 points, decreased renal function, or cumulative marrow toxicity from prior therapy.
[e] Prior therapy with 2 or more cycles of a purine analog or bendamustine was required.

8.2 Implications of New Information on Benefit-Risk Profile of Duvelisib

In the primary analysis of the DUO trial, duvelisib demonstrated a statistically significant and clinically meaningful improvement in PFS in the duvelisib arm versus the ofatumumab arm in the overall ITT Population, and in the Labeled Indication Population with an HR of 0.40 (95% CI: 0.27, 0.59). This led to full approval of duvelisib in the Labeled Indication Population in 2018. In the final analysis of DUO with long-term follow-up, the PFS benefit (per investigator) remained clinically and statistically significant with no changes to the long-term safety profile.

The final OS analysis from the DUO trial relies on heavily confounded data. In its PMR for 5-year OS follow-up data from DUO, FDA acknowledged the limitations of the safety information to sufficiently address longer-term safety and so required the long-term extension for what it believed would be more sufficient information. Yet, the early and frequent crossover from ofatumumab to duvelisib upon progression (with few cross-overs from duvelisib to ofatumumab) substantially confounds the final OS results, as it mostly reflects the longer-term safety experience of duvelisib without a comparator. Nonetheless, to the degree FDA considers such data as sufficiently interpretable, the final OS analysis from the DUO trial indicates no significant change or detriment to OS in patients treated with duvelisib, but rather confirms that the safety experience longer term is consistent with the original NDA data that led to approval, along with its approved labeling.

In any event, the updated OS data do not support the conclusion of a detriment in OS in patients treated with duvelisib and do not identify any new safety concerns. The updated OS data do not alter the benefit-risk assessment of duvelisib and do not constitute new evidence of clinical experience that indicate the drug is unsafe for use under the conditions of use in the Labeled Indication Population.

Patients with R/R CLL represent an especially difficult-to-treat population with higher rates of high-risk cytogenetics and resistance and more aggressive disease who are more likely to require third-line treatment options and beyond. Patients who are refractory to first- and second-line treatments with BTKis and BCL-2i have a particularly poor prognosis, with a median OS of 3.6 months.[12] Given the continued high unmet medical need, the benefit-risk profile of duvelisib in this R/R population remains positive. Duvelisib is the only PI3Ki monotherapy with proven efficacy and no OS detriment in the third-line setting and beyond, and it provides a unique, all-oral treatment option for patients with R/R CLL/SLL, who have very few remaining treatment options.

8.3 Sponsor Recommendations

As proposed in the prior approval supplement submitted June 3, 2022, the sponsor has recommended updating the labeling to reflect the updated OS information in accordance with the disseminated DHCP letter dated May 1, 2022.

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