Duvelisib
NDA 211155

Oncologic Drugs Advisory Committee Meeting

September 23, 2022

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Duvelisib in Patients with Relapsed or Refractory CLL or SLL

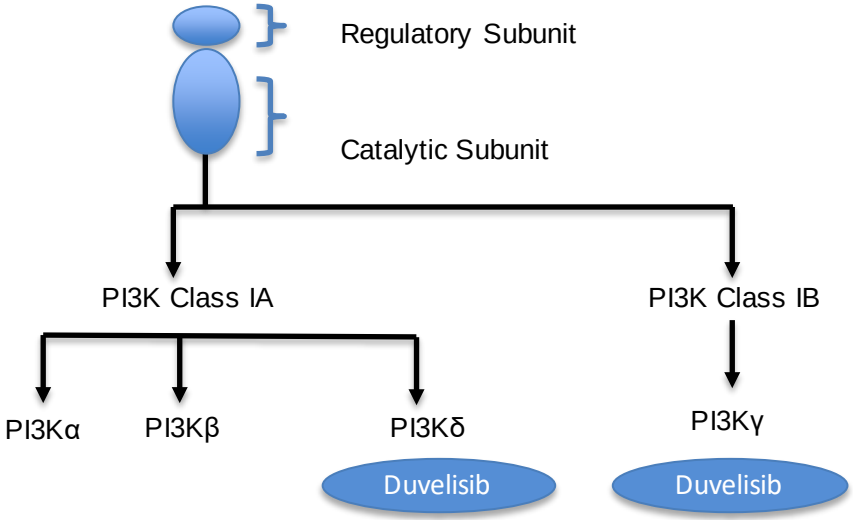
Issues

- DUO trial 5-year OS analysis and potential OS detriment
- Substantial toxicity and tolerability concerns
- Concerns regarding the selected dose
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

Abbreviations: CLL, chronic lymphocytic leukemia; OS, overall survival; PI3K, phosphatidylinositol-3 kinase; SLL, small lymphocytic lymphoma

Mechanism of Action and Toxicity

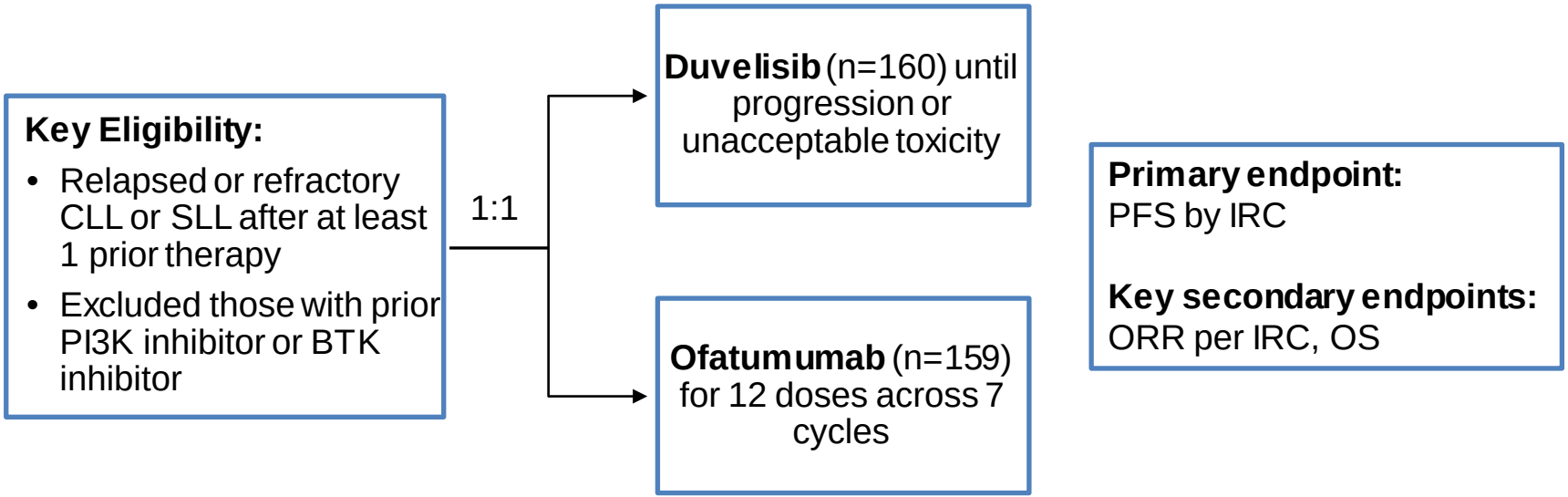
Duvelisib - PI3Kδ and PI3Kγ inhibitor



- PI3K delta (δ) and gamma (γ) isoforms preferentially expressed on immune-cells
- Delta (δ) and gamma (γ) isoforms are important for innate and adaptive immune cell function, including regulatory T cells
- Toxicities
  - Infections
    - Pneumonia, opportunistic infections, CMV reactivation
  - Cytopenias
  - Immune-mediated toxicities
    - Hepatitis, colitis, pneumonitis, rash

Abbreviations: CMV, cytomegalovirus; PI3K, phosphatidylinositol-3 kinase

DUO Trial (IPI-145-07) Schema



Approved Indication: Relapsed or refractory CLL or SLL after at least two prior therapies

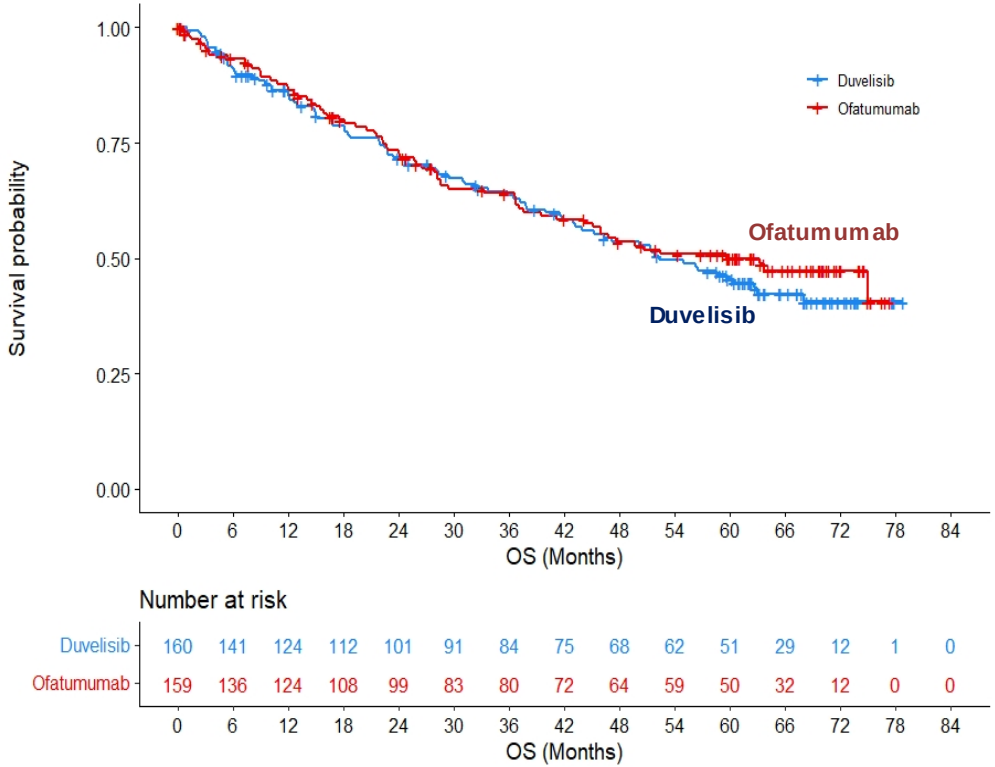
Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; PFS, progression-free survival; IRC, independent review committee; ORR, overall response rate; OS, overall survival

Initial Approval – Risk Mitigation and PMRs

- **Boxed Warning**
  - Infection
  - Diarrhea or Colitis
  - Rash
  - Pneumonitis
- **Warnings & Precautions**
  - Hepatotoxicity
  - Neutropenia
- **Communication REMS**
- **Postmarketing Requirements**
  - **Long-term Safety**
    - Assess the serious and fatal risks by characterizing long-term safety outcomes
  - **Overall Survival**
    - Assess a signal of fatal adverse reactions
    - 5-years of OS follow-up

Abbreviations: OS, overall survival; PMR, postmarketing requirement; REMS, risk evaluation and mitigation strategy

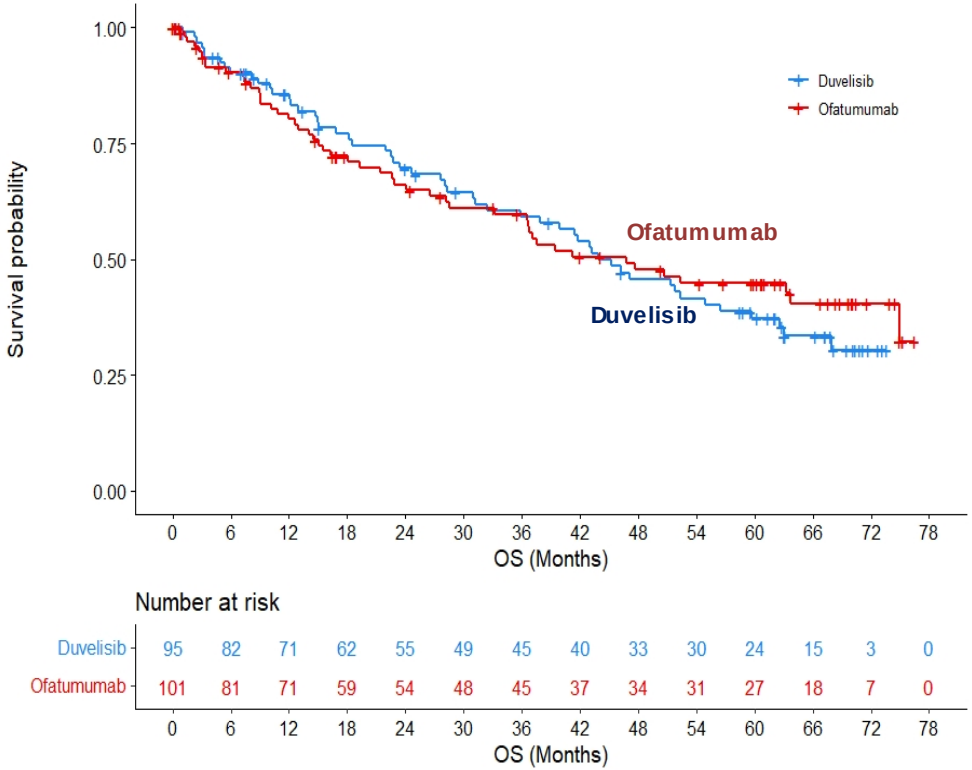
DUO Trial 5-Year OS Update Demonstrates a Potential OS Detriment (ITT Population)



ITT Population	Duvelisib N = 160	Ofatumumab N = 159
OS events, n (%)	80 (50.0)	70 (44.0)
Median OS (months) (95% CI)	52.3 (41.8, 68.0)	63.3 (41.2, NE)
Hazard Ratio (95% CI)	1.09 (0.79, 1.51)	

Abbreviations: CI, confidence interval; ITT, intent to treat; OS, overall survival

DUO Trial: Potential OS Detriment, Patients with ≥2 Prior Therapies



	Duvelisib N = 95	Ofatumumab N = 101
OS events, n (%)	53 (55.8)	49 (48.5)
Median OS (months) (95% CI)	43.9 (32.4, 56.5)	46.8 (28.6, 74.9)
Hazard Ratio (95% CI)	1.06 (0.71, 1.58)	

Abbreviations: CI, confidence interval; OS, overall survival

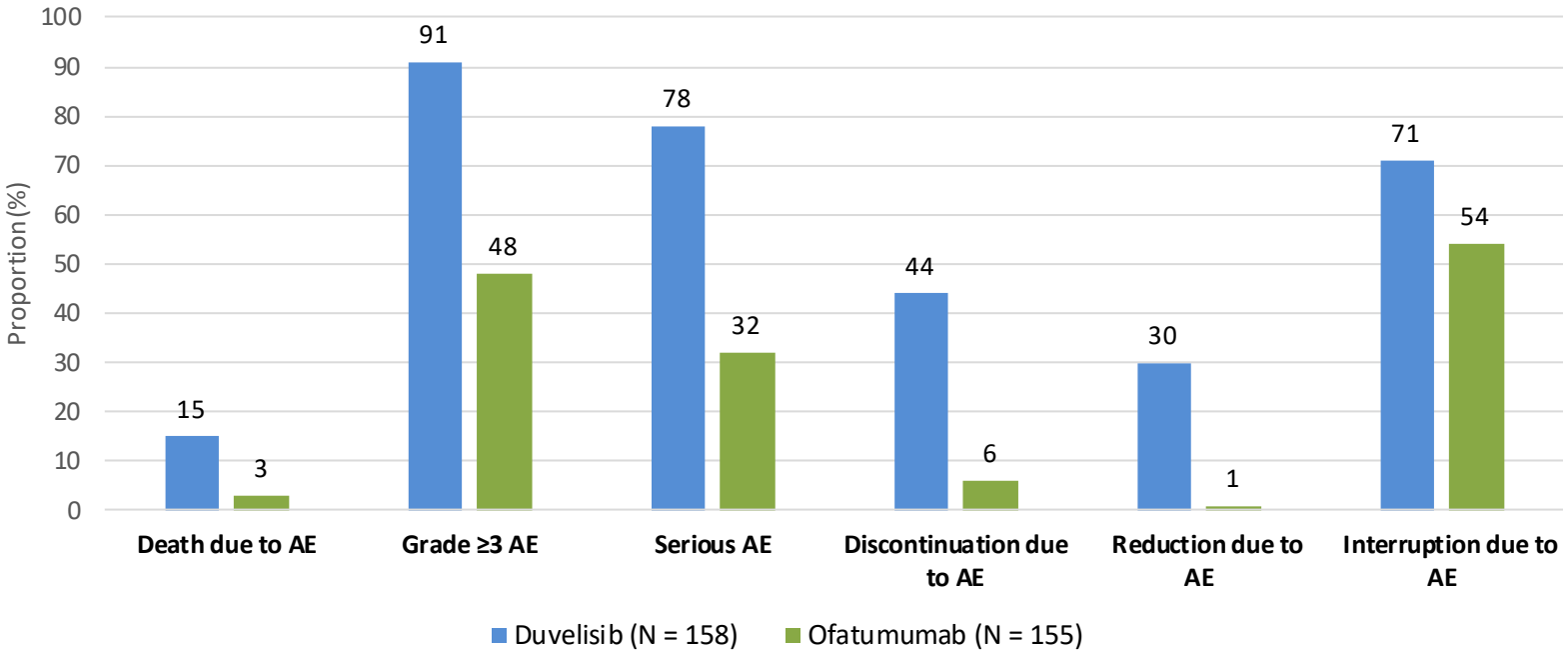
Overall Survival Data Indicates a Safety Concern

- **Higher number of deaths with duvelisib**
  - Duvelisib: **50%** (80/160) vs. Ofatumumab: 44% (70/159)
- **Higher rate of death due to adverse events with duvelisib in safety population**
  - Duvelisib: **15%** (23/158) vs. Ofatumumab: 3% (5/155)
- **Fatal adverse events with duvelisib were primarily due to infection**
  - Fatal infections: Duvelisib: **9%** (14/158) vs. Ofatumumab: <1% (1/155)

Overall Survival Data Indicates a Safety Concern

- **Higher number of deaths with duvelisib**
  - Duvelisib: **50%** (80/160) vs. Ofatumumab: 44% (70/159)
- **Higher rate of death due to adverse events with duvelisib in safety population**
  - Duvelisib: **15%** (23/158) vs. Ofatumumab: 3% (5/155)
- **Fatal adverse events with duvelisib were primarily due to infection**
  - Fatal infections: Duvelisib: **9%** (14/158) vs. Ofatumumab: <1% (1/155)
- **Crossover**
  - Deaths following crossover
    - Duvelisib: **10%** (9/90) vs. Ofatumumab: 0 (0/9)
  - Crossover may have caused harm to the control group

Higher Rates of Toxicities with Duvelisib



Abbreviations: AE, adverse event

Differences in Toxicity Driven by Infection and Immune-Mediated Toxicities

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	109 (69)	**53 (33)**	67 (43)	17 (11)
Neutropenia*	104 (66)	**76 (48)**	79 (51)	55 (35)
Diarrhea-Colitis[1]	90 (57)	**40 (25)**	21 (13)	3 (2)
AST/ALT Increase*	66 (42)	**11 (7)**	21 (13)	2 (1)
Rash[1]	42 (27)	**19 (12)**	23 (15)	1 (<1)
Pneumonitis[1]	14 (9)	**6 (4)**	1 (<1)	0

* Based on laboratory data
[1] Grouped term

Abbreviations: AST, aspartate aminotransferase; ALT alanine aminotransferase

Tolerability and Dosing Concerns

- Dose: 25 mg BID

- High rates of treatment modifications due to toxicity
- Exposure-response relationships for safety
- Lack of an exposure-response for efficacy

- Limited dose exploration
- Identifying an optimal dose remains uncertain

Abbreviations: BID, twice daily

PI3K Inhibitor ODAC – April 2022 Meeting

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
DUO	• Previously treated CLL/SLL • **Duvelisib** vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
312-0123	• Untreated CLL • Bendamustine and rituximab ± **idelalisib**	8% (12/157)	3% (4/154)	3.34 (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± **idelalisib**	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± **idelalisib**	8% (27/320)	6% (9/155)	1.51 (0.71, 3.23)
CHRONOS-3	• Previously treated indolent NHL • Rituximab ± **copanlisib**[#]	18% (56/307)	21% (32/151)	0.87[#] (0.57, 1.35)
UNITY-CLL	•Untreated and previously treated CLL •**Umbralisib** + ublituximab vs GC	*	*	1.23 (*)

[#]Concern for early mortality in copanlisib arm; *Data not available publicly
Abbreviations: NHL, non-Hodgkin lymphoma; GC, obinutuzumab and chlorambucil

PI3K Inhibitor Withdrawals

Labeled Indications Withdrawn

PI3K Inhibitor	Withdrawn Indication	Date
Duvelisib	Follicular lymphoma	December 17, 2021
Idelalisib	Follicular lymphoma Small lymphocytic lymphoma	February 18, 2022
Umbralisib	Follicular lymphoma Marginal zone lymphoma	May 31, 2022

NDA Applications Withdrawn

PI3K Inhibitor	Withdrawn Indication	Date
Copanlisib	Follicular lymphoma Marginal zone lymphoma	December 17, 2021
Umbralisib	Chronic lymphocytic leukemia	April 15, 2022

PI3K Inhibitor ODAC Considerations

- The data with the PI3K inhibitors is problematic and concerning
  - Inadequate dose-finding
  - Class-effect toxicity profile and chronic administration
  - Use of PFS endpoint in the setting of substantial toxicity
  - Concerning pattern of PFS benefit followed by OS detriment
- "If we are not improving length of life, but exposing patients to toxicity and decreasing quality of life, are we truly helping our patients?"
- "Benefit-risk remains critical, especially in setting of a disease with a prolonged natural history or in the context of later line therapy when a patients life expectancy is most limited by their disease"
- "First, do no harm; products should be safe and effective"

Duvelisib FDA Safety Alert
June 2022

FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib)

Consider risks and benefits of continued use versus other treatments

FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib) | FDA

Considerations for a Current Assessment of Benefit-Risk

- Overall survival is an objective measure of clinical benefit
  - OS is an efficacy and a safety endpoint
  - FDA issued a postmarketing requirement for 5-year OS data
- The 5-year OS data from the DUO trial demonstrate a potential OS detriment
  - The OS detriment is a safety concern and suggest potential harm
- Substantial toxicity and poor tolerability
- Dosing concerns and limited dose exploration
- Data from the PI3K inhibitor class is relevant

Treatment Options for CLL and Indolent NHL

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

Drug/Combination	Indication
Ibrutinib (2013)	CLL/SLL; WM; MZL after 1 prior CD20-based therapy*
Idelalisib (2014)	Relapsed CLL
Venetoclax (2016)	CLL/SLL
Acalabrutinib (2017)	CLL/SLL
Copanlisib (2017)	Relapsed FL after 2 prior therapies*
Duvelisib (2018)	R/R CLL/SLL after at least 2 prior therapies
Zanubrutinib (2019)	WM; R/R MZL after 1 prior CD20-based regimen*
Tazemetostat (2020)	R/R FL positive for EZH2 mutation after 2 prior therapies*; R/R FL with no alternative options*
Axicabtagene ciloleucel (2021)	R/R FL after at least two prior lines*
Tisagenlecleucel (2022)	R/R FL after at least two prior lines*

* Indicates accelerated approval

Abbreviations: CLL, Chronic lymphocytic leukemia; NHL, non-Hodgkin lymphomas, R/R: relapsed, refractory, Flu/cy: Fludarabine, cyclophosphamide, FL, follicular lymphoma, MZL, Marginal zone lymphoma, WM, Waldenström's macroglobulinemia

Discussion and Vote

- **Discussion:** Discuss the benefit-risk profile of duvelisib for the currently indicated population considering the updated results of the DUO trial.

- **Vote:** Given the potential detriment in overall survival, duvelisib-associated toxicity, concerns with the selected dose, and the safety issues with the PI3K inhibitor class, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after at least two prior therapies?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Duvelisib
NDA 211155

Oncologic Drugs Advisory Committee Meeting
September 23, 2022

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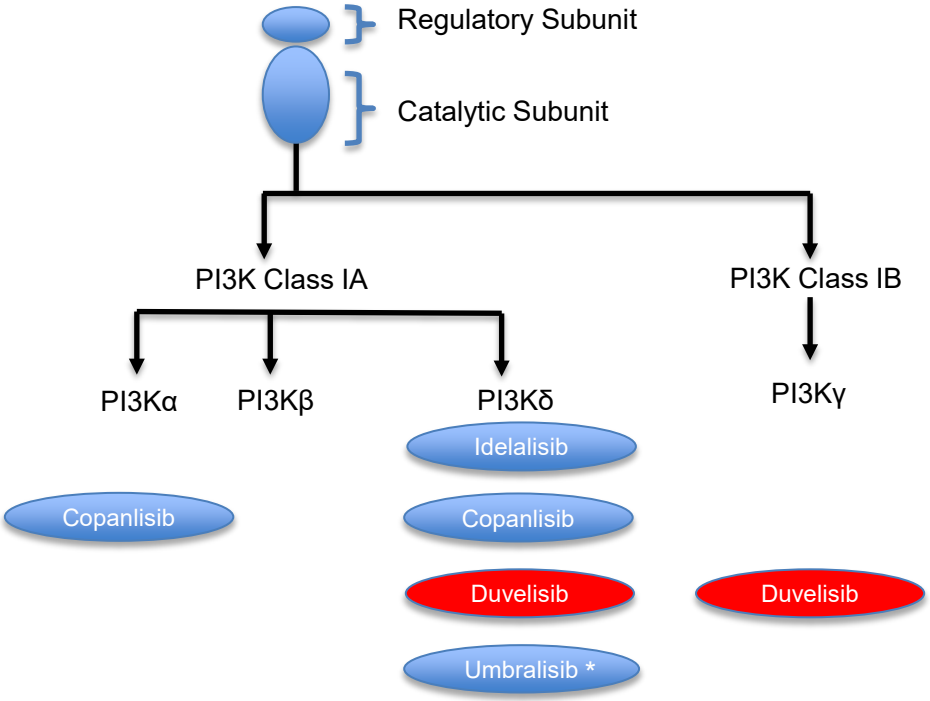
PI3K Inhibitor Drug Class



PI3K Toxicity

- Infection
- Cytopenias
- Immune-mediated toxicity
  - Diarrhea or colitis
  - Hepatotoxicity
  - Pneumonitis
  - Rash

* Withdrawn from the U.S. market in May 2022; PI3K, phosphatidylinositol 3-kinase

Major Issues

Issues

- DUO trial 5-year OS analysis and potential OS detriment
- Toxicity and tolerability concerns
- Concerns regarding the selected dose
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

Abbreviations: OS, overall survival

Duvelisib Approval

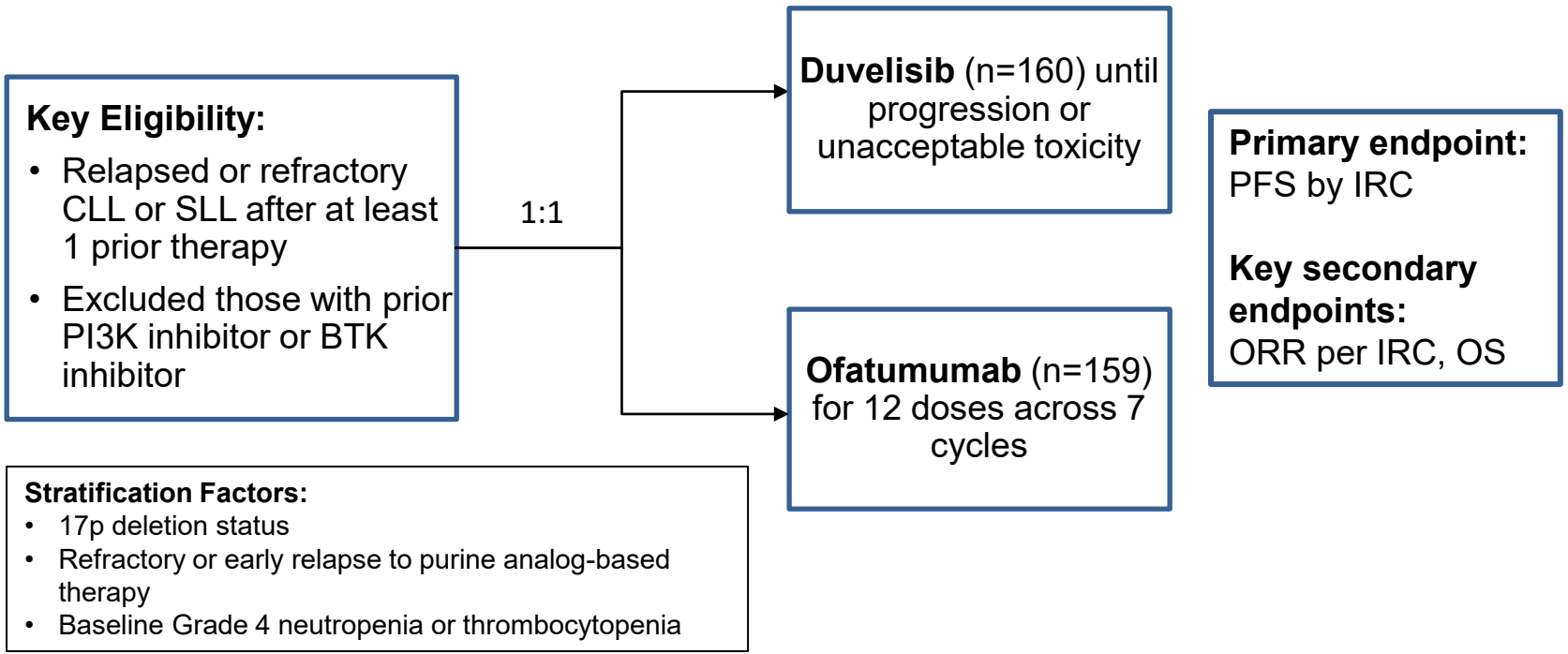
- Granted accelerated approval in patients with relapsed or refractory FL in September 2018
  - Due to inability to conduct a trial to verify benefit, FL indication was voluntarily withdrawn in December 2021

- Granted regular approval in patients with relapsed or refractory CLL or SLL after at least two prior therapies in September 2018

- Duvelisib Dose: 25 mg BID

Abbreviations: BID, two times a day; CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; SLL, small lymphocytic lymphoma

DUO Trial (IPI-145-07) Schema



Abbreviations: BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma

Efficacy Data Supporting Approval for CLL/SLL (Patients with ≥2 Prior Therapies)

	Duvelisib N = 95	Ofatumumab N = 101
Progression-Free Survival		
PFS Events, n (%)	55 (58)	70 (69)
Median PFS, months (95% CI)	16.4 (12.0, 20.5)	9.1 (7.9, 10.7)
Hazard Ratio (95% CI)	0.40 (0.27, 0.59)	
Overall Response Rate		
ORR Events, n (%)	74 (78)	39 (39)
Odds ratio (95% CI)	5.60 (2.99, 10.50)	
Overall Survival		
OS Events, n (%)	28 (29)	34 (34)
Hazard Ratio (95% CI)	0.82 (0.49, 1.37)	

Abbreviations: ORR, overall response rate; OS, overall survival; PFS, progression-free survival

Duvelisib in CLL/SLL: Mitigation Measures

- Communication Risk Evaluation and Mitigation Strategy (REMS) issued and boxed warning added to USPI to address risk of fatal and/or serious toxicities

- Postmarketing requirements:
  - PMR 3494-2: Characterize the safety of long-term use of duvelisib monotherapy in patients with hematologic malignancies treated with a planned dose of 25 mg BID in multiple studies, including trial IPI-145-07 (DUO trial)
  - PMR 3494-3: Submit reports and datasets for overall survival from trial IPI-145-07 with 5 years of follow-up

Abbreviations: BID, two times a day; CLL, chronic lymphocytic leukemia; PMR, post marketing requirement; SLL, small lymphocytic lymphoma; USPI, U.S. Prescribing Information

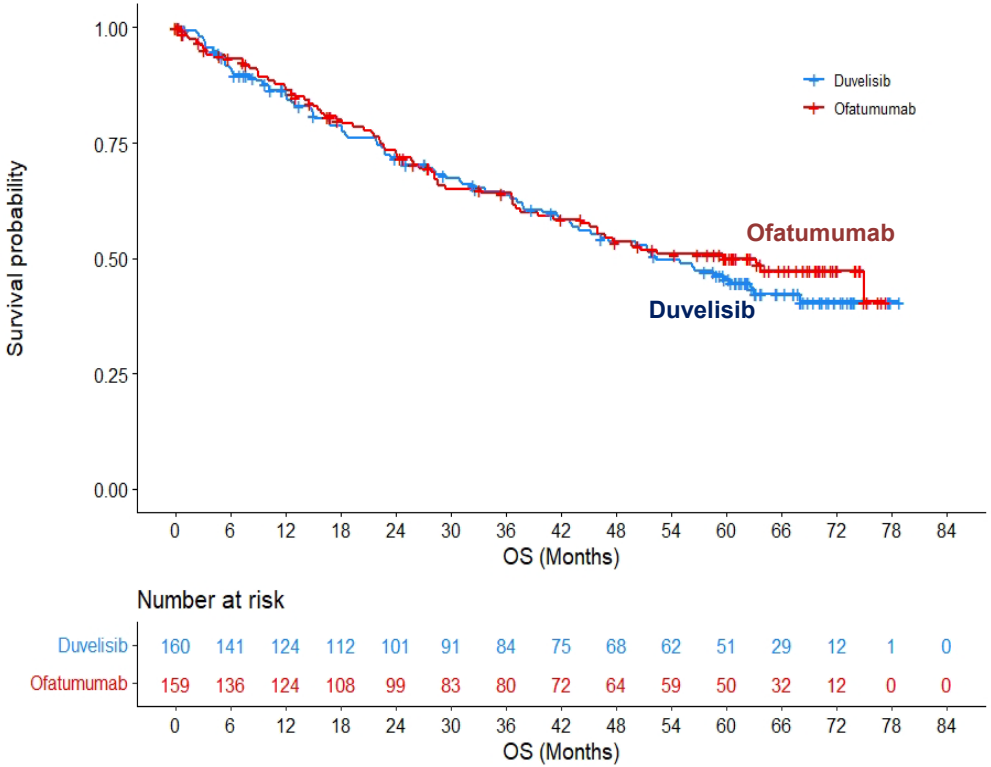
Major Issues

Issues

- DUO trial 5-year OS analysis and potential OS detriment
- Toxicity and tolerability concerns
- Concerns regarding the selected dose
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

Abbreviations: OS, overall survival

DUO Trial: Potential OS Detriment, ITT Population



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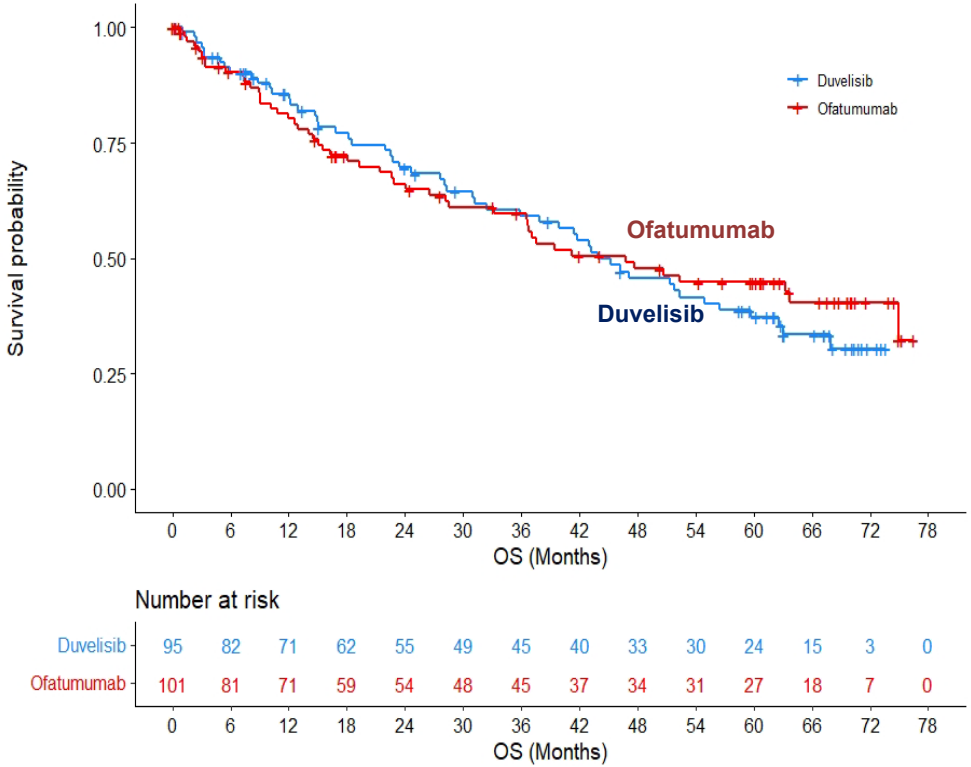
OS events, n (%)	80 (50.0)	70 (44.0)
Median OS (months) (95% CI)	52.3 (41.8, 68.0)	63.3 (41.2, NE)
Hazard Ratio (95% CI)	1.09 (0.79, 1.51)	

Abbreviations: CI, confidence interval; ITT, intent to treat; NE, non-estimable; OS, overall survival

DUO Trial: Potential OS Detriment, Patients with ≥2 Prior Therapies



	Duvelisib N = 95	Ofatumumab N = 101
OS events, n (%)	53 (55.8)	49 (48.5)
Median OS (months) (95% CI)	43.9 (32.4, 56.5)	46.8 (28.6, 74.9)
Hazard Ratio (95% CI)	1.06 (0.71, 1.58)	

Abbreviations: CI, confidence interval; OS, overall survival

DUO Trial: Higher Rates of Deaths Due to AEs with Duvelisib

	ITT Population		Patients with ≥2 Prior Therapies	
	Duvelisib N = 160 n (%)	Ofatumumab N = 159 n (%)	Duvelisib N = 95 n (%)	Ofatumumab N = 101 n (%)
Total Deaths	80 (50)	70 (44)	52 (55)	49 (49)
Adverse events	23 (14)	5 (3)	13 (14)	4 (4)
PD	21 (13)	26 (16)	14 (15)	19 (19)
Other	23 (14)	28 (18)	16 (17)	18 (18)
Unknown	13 (8)	11 (7)	9 (9)	8 (8)

Abbreviations: AE, adverse event; ITT, intention to treat; PD, progressive disease

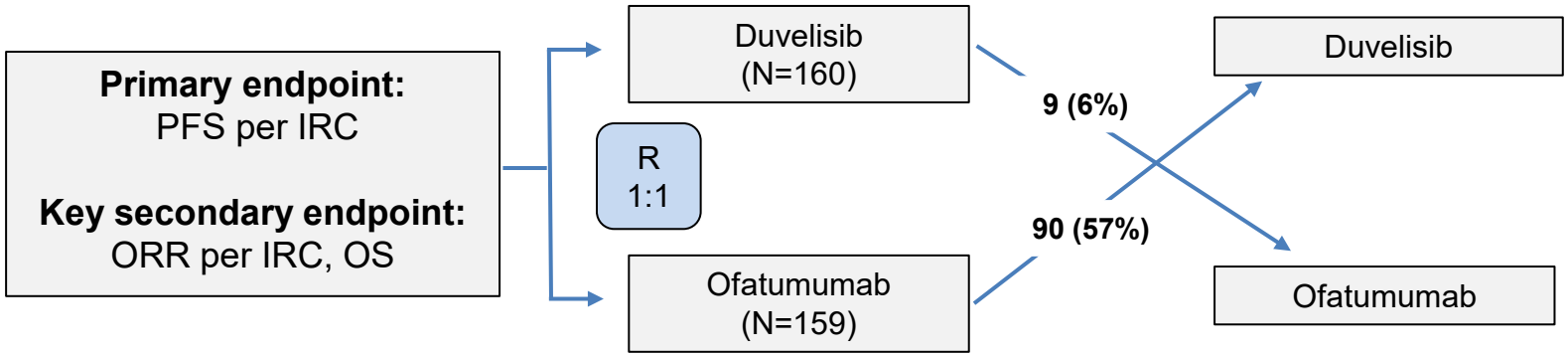
DUO Trial: FDA-Adjudicated Deaths Due to Adverse Events

	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Total Deaths	79 (50)	70 (45)
Adverse events	23 (15)	5 (3)
Infection	14 (9)	1 (<1)
Respiratory	4 (3)	0
Cardiac	1 (<1)	0
Neurologic	1 (<1)	0
SPM	0	1 (<1)
General*	1 (<1)	1 (<1)
Hepatic	0	1 (<1)
Renal	0	1 (<1)
Unknown	2 (1)	0

* General: duvelisib, general health deterioration; ofatumumab, fall down the stairs

Abbreviations: SPM, Second primary malignancy

DUO Trial: Crossover



Abbreviations: IRC, independent review committee; ORR, overall response rate; PFS, progression-free survival

Impact of Crossover

- Impact on OS
  - Crossover can impact the assessment of time-to-event endpoints
  - For a drug with a PFS benefit but substantial toxicity, crossover may cause harm to the control group and mask a difference that would have favored the control arm
- DUO trial
  - Potential detriment is seen despite substantial crossover
  - Based on additional analyses, concerns for the potential for harm with duvelisib remain

Abbreviations: OS, overall survival; PFS, progression-free survival

DUO Trial: High Rates of Death Due to AEs Following Crossover to Duvelisib

	Duvelisib to Ofatumumab N = 9 n (%)	Ofatumumab to Duvelisib N = 90 n (%)
Adverse events	0	9 (10)
Infection	0	5 (6)
Cardiac	0	2 (2)
Respiratory	0	1 (1)
General	0	1 (1)

Abbreviations: AE, adverse events

Crossover Sensitivity Analyses Demonstrate Consistent Potential OS Detriment

Method	Overall Survival HR (95% CI)
Primary Analysis	
5-year OS - ITT	1.09 (0.79, 1.51)
Model-Based Survival Analyses	
MSM-IPTW[1]	1.06 (0.72, 1.59)
RPFTM[2]	1.22 (0.88, 1.67)

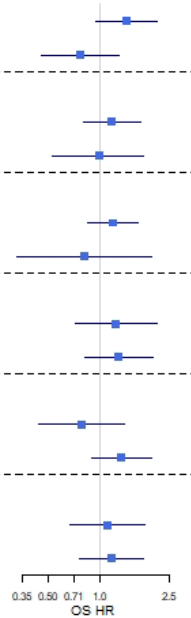
[1]MSM-IPTW: Marginal structural model with inverse probability treatment weights
[2]RPFTM:Rank preserving failure time

- Results are consistent with the primary OS analysis
- Analyses supportive of potential OS detriment

Abbreviations: OS, overall survival

Consistent Potential OS Detriment Across the Majority of Subgroups

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



Abbreviations: del17p, 17p deletion; DUV, duvelisib; OFA, ofatumumab; OS, overall survival

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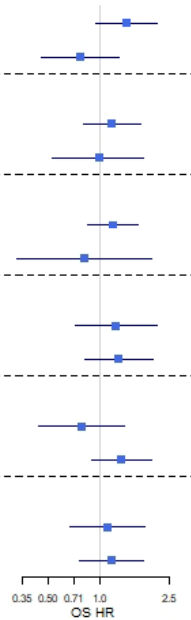

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Major Issues

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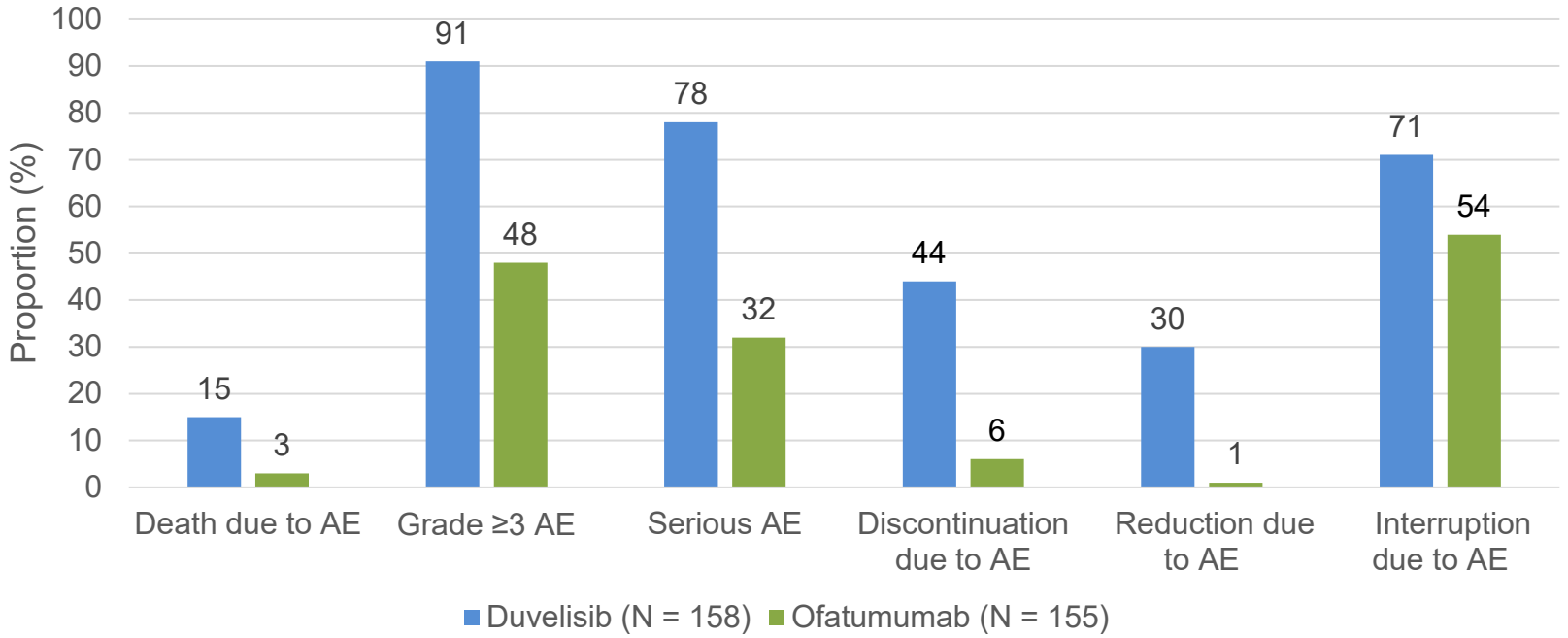
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

DUO Trial: Exposure Duration

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

* Cycle length 28 days

Higher Rates of Toxicities with Duvelisib



Abbreviations: AE, adverse event

Differences in Toxicity Driven by Infection and Immune-Mediated Toxicities

	Duvelisib N = 158 n (%)		Ofatumumab N = 155 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	109 (69)	**53 (33)**	67 (43)	17 (11)
Neutropenia*	104 (66)	**76 (48)**	79 (51)	55 (35)
Diarrhea-Colitis[1]	90 (57)	**40 (25)**	21 (13)	3 (2)
AST/ALT Increase*	66 (42)	**11 (7)**	21 (13)	2 (1)
Rash[1]	42 (27)	**19 (12)**	23 (15)	1 (<1)
Pneumonitis[1]	14 (9)	**6 (4)**	1 (<1)	0

* Based on laboratory data
[1] Grouped term

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Patient-Generated Data in the DUO Trial

- Patient-reported symptoms and function can inform safety and tolerability
- Two PRO instruments were used in the DUO trial:
  - EQ-5D
  - FACIT-F
- Limitations:
  - EQ-5D is a generic PRO instrument that does not include relevant treatment-related symptoms
  - No duvelisib benefit was observed from results from FACIT
- Overall, no meaningful conclusions can be made from the DUO trial PRO results due these limitations

Abbreviations: PRO, patient reported outcome

High Rates of Treatment Modifications Due to Adverse Events with Duvelisib

	Duvelisib N = 158 n (%)	Ofatumumab N = 155 n (%)
Discontinuation due to AE	70 (44)	9 (6)
Dose reduction due to AE	48 (30)	2 (1)
Dose interruption due to AE	112 (71)	83 (54)

Abbreviations: AE, adverse event

Duvelisib Dosing Concerns

Dose Finding

- The dose escalation study was designed to identify the maximum tolerated dose (MTD)
  - Doses from 8 to 100 mg BID were studied using a 3+3 design
  - 75 mg BID dose was the MTD

- Dose expansion was conducted at 25 and 75 mg BID dose levels
  - 25 mg BID was selected as the RP2D

Abbreviations: BID, two times per day; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Efficacy Demonstrated at Doses Lower than 25 mg

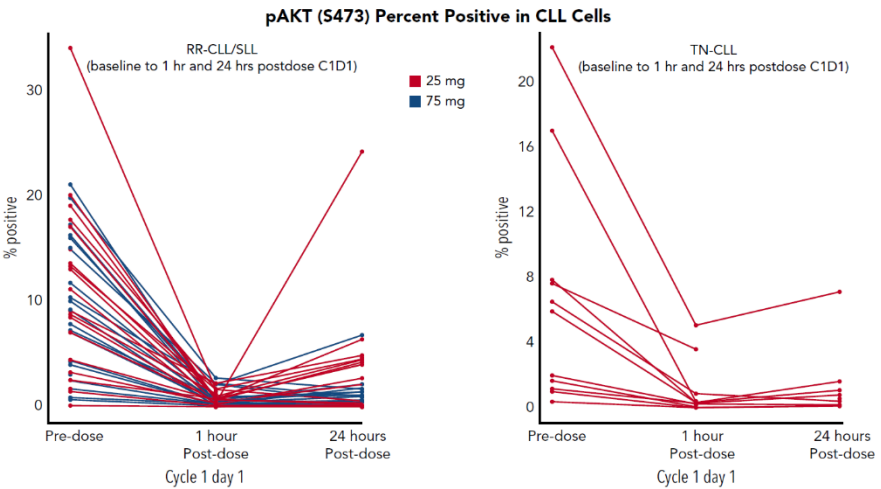
Study IPI-145-02: Best Overall Response by Dose

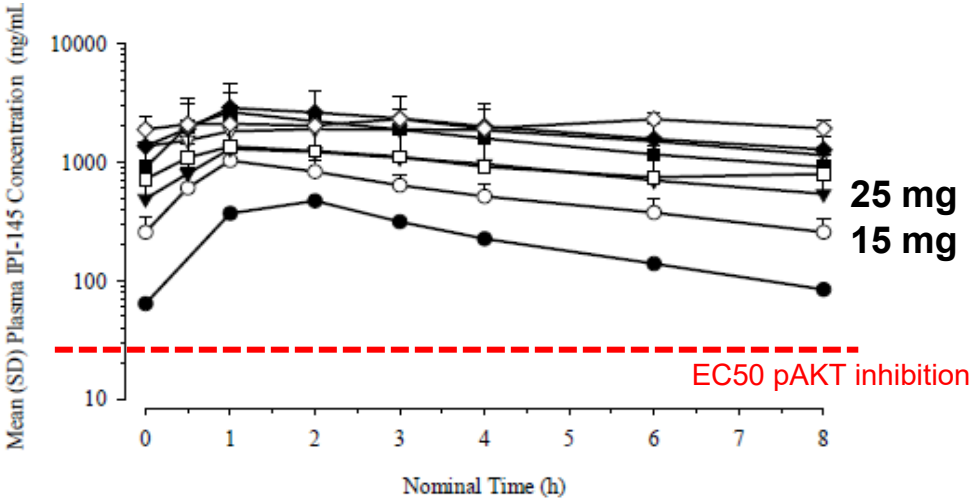
	Dose (mg)									
	8 mg		15 mg		25 mg		50 mg		75 mg	
	N	ORR*	N	ORR*	N	ORR*	N	ORR*	N	ORR*
iNHL			1	100 (2.5, 100)	14	64.3 (35.1, 87.2)	1	100 (2.5, 100)	15	46.7 (21.3, 73.4)
R/R CLL/SLL	1	100 (2.5, 100)	2	50 (1.3, 98.7)	28	57.1 (37.2, 75.5)			24	54.2 (32.8, 74.4)
TN CLL					18	83.3 (58.6, 96.4)				

* % (95% confidence interval)

Abbreviations: CLL, chronic lymphocytic leukemia; iNHL, indolent Non-Hodgkin's lymphoma; mg, milligrams; ORR, overall response rate; R/R, relapsed and refractory; SLL, small lymphocytic lymphoma TN, treatment naive

PK/PD Data Suggest that Lower Doses May Be Efficacious



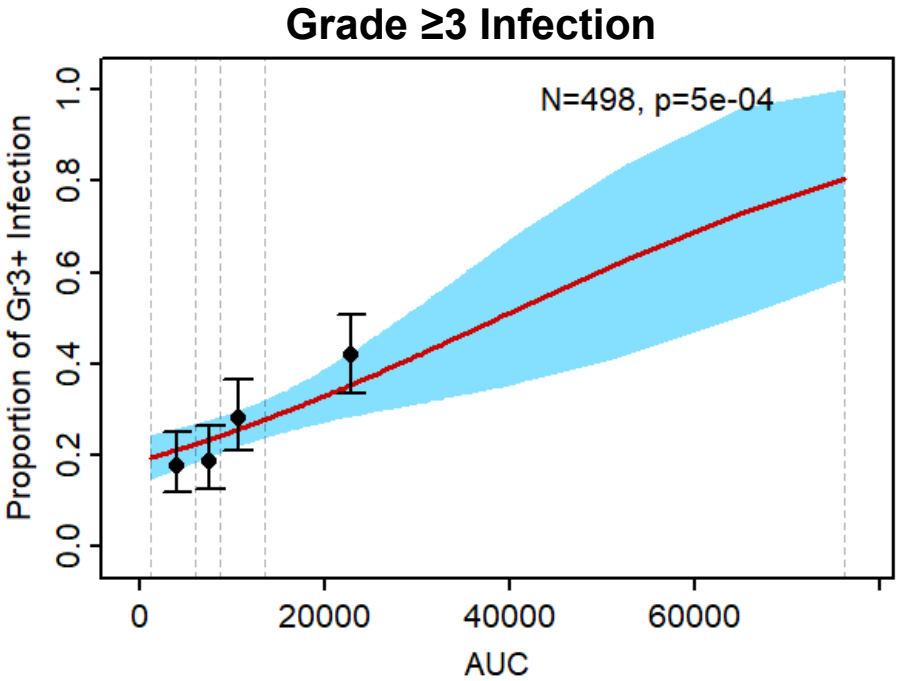


Pharmacodynamic marker p-AKT demonstrated near maximal suppression at 25 mg BID

Lower doses may also inhibit p-AKT substantially

Sources: Blood. 2018 Feb 22; 131(8): 877–887; IPI-145-02 CSR,
Abbreviations: BID, two times per day; EC50, half maximal effective concentration; p-AKT, Phosphorylated Akt; PD, pharmacodynamic; PK, pharmacokinetic

Duvelisib: Exposure-Response Relationship



- No positive E-R relationship for efficacy in DUO Trial
- E-R relationships for safety were observed between 8-75 mg BID for infections, pneumonia and transaminase elevation

Abbreviations: AUC, area under the curve; E-R, exposure-response

Concerns Regarding 25mg BID Dose

- Considerable dose modifications were observed with the 25 mg BID dose in DUO Trial

- Lower doses were not adequately studied but may be efficacious with better tolerability
  - Lack of E-R relationships for efficacy
  - Positive E-R relationships for safety at doses between 8-75 mg BID
  - Clinical activity at lower dose levels

Abbreviations: BID, two times per day; E-R, exposure-response

DUO Trial: Summary of Concerns

- **Overall Survival (5-Year Analysis)**
  - Higher rate of deaths in the duvelisib arm
  - Higher rate of fatal adverse events, primarily due to infection
  - Potential OS detriment with duvelisib in the setting of PFS and ORR advantage
- **Increased Toxicity**
  - Higher rates of Grade ≥3 AEs and SAEs
  - Higher rates of treatment modifications
  - Differences in toxicities driven by infection and immune-mediated toxicities
- **Dosing**
  - Exposure-response relationships for safety
  - Lack of clear exposure-response for efficacy
  - Limited dose exploration and optimization

Abbreviations: AE, adverse event; OS, overall survival; SAE, serious adverse event

Major Issues

Issues

- DUO trial 5-year OS analysis and potential OS detriment
- Toxicity and tolerability concerns
- Concerns regarding the selected dose
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

PI3K Inhibitor ODAC

- On April 21, 2022, an ODAC was convened to discuss key issues related to the PI3K inhibitor class:
  - Concerning trends in OS across multiple RCTs
  - Toxicities of the class
  - Inadequate dose optimization
  - Limitations of single-arm trials

Abbreviations: ODAC, Oncologic Drugs Advisory Committee; RCT, randomized controlled trial

Potential OS Detriments Demonstrated Across the PI3K Inhibitor Class

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
DUO	• Previously treated CLL/SLL • **Duvelisib** vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
312-0123	• Untreated CLL • Bendamustine and rituximab ± **idelalisib**	8% (12/157)	3% (4/154)	3.34 (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± **idelalisib**	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± **idelalisib**	8% (27/320)	6% (9/155)	1.51 (0.71, 3.23)
CHRONOS-3	• Previously treated indolent NHL • Rituximab ± **copanlisib**[#]	18% (56/307)	21% (32/151)	0.87[#] (0.57, 1.35)
UNITY-CLL	•Untreated and previously treated CLL •**Umbralisib** + ublituximab vs GC	*	*	1.23

[#]In the CHRONOS-3 trial, decreased overall survival was demonstrated in the first 2 years in the copanlisib arm, followed by a crossing of KM curves
*Not publicly available

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, obinutuzumab plus chlorambucil; NHL, non-Hodgkin lymphoma, OS, overall survival; SLL, small lymphocytic lymphoma

Recent PI3K Inhibitor Withdrawals

Withdrawal of Labeled Indications

PI3K Inhibitor	Withdrawn Indication	Date
Duvelisib	• Follicular lymphoma	December 17, 2021
Idelalisib	• Follicular lymphoma • Small lymphocytic lymphoma	February 18, 2022
Umbralisib	• Follicular lymphoma • Marginal zone lymphoma	May 31, 2022

Withdrawal of NDA Applications

PI3K Inhibitor	Withdrawn Indication	Date
Copanlisib	• Follicular lymphoma • Marginal zone lymphoma	December 17, 2021
Umbralisib	• Chronic lymphocytic leukemia	April 15, 2022

Abbreviations: NDA, new drug application

PI3K Inhibitors Impart Substantial Risk

Toxicities	Duvelisib N = 442	Idelalisib N = 146	Copanlisib N = 244	Umbralisib N = 371
Grade ≥3 Adverse Event	**84%**	71%	85%	51%
Serious Adverse Event	**65%**	50%	51%	26%
Grade ≥3 Infection	**27%**	23%	23%	20%
Grade ≥3 Neutropenia*	**43%**	28%	29%	17%
Grade ≥3 Diarrhea-Colitis	**23%**	14%	5%	7%
Grade ≥3 ALT/AST increase*	**8%**	18%	2%	7%
Grade ≥3 Rash	**9%**	4%	2%	3%
Any Grade Pneumonitis	**7%**	5%	7%	1%
*Based on laboratory data				

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

PI3K Inhibitors Have Substantial Tolerability Concerns

Treatment Modification	Duvelisib N = 442	Idelalisib N = 146	Copanlisib N = 244	Umbralisib N = 371
Discontinuation due to AE	**35%**	23%	24%	15%
Dose reduction due to AE	**23%**	41%	24%	10%
Dose interruption due to AE	**64%**	41%	64%	45%

Abbreviations: AE, adverse event

PI3K Inhibitor ODAC Remarks

- The data with the PI3K inhibitors is problematic and concerning
  - Inadequate dose-finding
  - Class-effect toxicity profile and chronic administration
  - Use of PFS endpoint in the setting of substantial toxicity
  - Concerning pattern of PFS benefit followed by OS detriment
- “If we are not improving length of life, but exposing patients to toxicity and decreasing quality of life, are we truly helping our patients?”
- “Benefit-risk remains critical, especially in setting of a disease with a prolonged natural history or in the context of later line therapy when a patients life expectancy is most limited by their disease”
- “First, do no harm; products should be safe and effective”

Abbreviations: ODAC, Oncologic Drugs Advisory Committee; OS, overall survival; PFS, progression-free survival

Major Issues

Issues

- DUO trial 5-year OS analysis and potential OS detriment
- Toxicity and tolerability concerns
- Concerns regarding the selected dose
- Safety concerns with the PI3K inhibitor drug class
- Current benefit-risk evaluation

Current Benefit-Risk Assessment and Overall Survival

- Benefit-risk is continuously assessed with availability of new information

Abbreviations: OS, overall survival; PFS, progression-free survival

Current Benefit-Risk Assessment and Overall Survival

- Benefit-risk is continuously assessed with availability of new information

- Overall survival is the most reliable cancer endpoint
  - Objective measure of clinical benefit
  - Both an efficacy and a safety endpoint
  - FDA requires OS information in any trial using PFS as a primary endpoint

Abbreviations: OS, overall survival; PFS, progression-free survival

Current Benefit-Risk Assessment and Overall Survival

- Benefit-risk is continuously assessed with availability of new information

- Overall survival is the most reliable cancer endpoint
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  - FDA requires OS information in any trial using PFS as a primary endpoint

- Postmarketing Requirement
  - 5-year OS analysis of DUO trial
  - Concerns with fatal and serious toxicity

Abbreviations: OS, overall survival; PFS, progression-free survival

Duvelisib FDA Safety Alert
June 2022

FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib)

Consider risks and benefits of continued use versus other treatments

FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib) | FDA

Duvelisib: Current Benefit-Risk Assessment

- Duvelisib in patients with relapsed or refractory CLL/SLL
  - Potential detriment in OS
  - Higher rate of death due to adverse events
  - High rates of toxicities and tolerability issues
  - Limited dose exploration and dose optimization
  - Consistent pattern of OS detriment seen across the PI3K inhibitor drug class

Abbreviations: CLL, chronic lymphocytic leukemia; OS, overall survival; SLL, small lymphocytic lymphoma

Current Benefit-Risk Assessment: Additional DUO Trial Considerations

- **Prior Treatments**
  - Patients with prior BTK inhibitor exposure excluded
  - No patients received a prior bcl-2 inhibitor

Abbreviations: BTK, Bruton's tyrosine kinase; bcl-2, B-cell lymphoma 2

Current Benefit-Risk Assessment: Additional DUO Trial Considerations

- **Prior Treatments**
  - Patients with prior BTK inhibitor exposure excluded
  - No patients received a prior bcl-2 inhibitor
- **Applicability to a U.S. Population**
  - Only 16% of patients enrolled in the U.S.
  - Over 90% of patients were White

Abbreviations: BTK, Bruton's tyrosine kinase; bcl-2, B-cell lymphoma 2

Current Benefit-Risk Assessment: Additional DUO Trial Considerations

- **Prior Treatments**
  - Patients with prior BTK inhibitor exposure excluded
  - No patients received a prior bcl-2 inhibitor
- **Applicability to a U.S. Population**
  - Only 16% of patients enrolled in the U.S.
  - Over 90% of patients were White
- **Control Arm**
  - Ofatumumab

Abbreviations: BTK, Bruton's tyrosine kinase; bcl-2, B-cell lymphoma 2

CLL/SLL Disease Context

- Criteria for treatment:
  - Active disease
  - Progression alone is not an indication for treatment
- In light of the OS findings, the meaningfulness of a modest PFS improvement is uncertain in patients with CLL or SLL

Abbreviations: CLL, chronic lymphocytic leukemia; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma

Treatment Options for CLL and Indolent NHL

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

Drug/Combination	Indication
Ibrutinib (2013)	CLL/SLL; WM; MZL after 1 prior CD20-based therapy*
Idelalisib (2014)	Relapsed CLL
Venetoclax (2016)	CLL/SLL
Acalabrutinib (2017)	CLL/SLL
Copanlisib (2017)	Relapsed FL after 2 prior therapies *
Duvelisib (2018)	R/R CLL/SLL after at least 2 prior therapies
Zanubrutinib (2019)	WM; R/R MZL after 1 prior CD20-based regimen*
Tazemetostat (2020)	R/R FL positive for EZH2 mutation after 2 prior therapies*; R/R FL with no alternative options*
Axicabtagene ciloleucel (2021)	R/R FL after at least two prior lines*
Tisagenlecleucel (2022)	R/R FL after at least two prior lines*

* Indicates accelerated approval

Abbreviations: CLL, Chronic lymphocytic leukemia; FL, Follicular lymphoma; Flu/cy, Fludarabine, cyclophosphamide; MZL, Marginal zone lymphoma; NHL, non-Hodgkin lymphomas, R/R: relapsed, refractory; WM, Waldenström's macroglobulinemia

Uncertain Benefit in the Indicated Population

- Current patients with R/R CLL or SLL with 2 prior therapies are likely to have been exposed to a BTK inhibitor and/or bcl-2 inhibitor
- Efficacy of duvelisib has not been evaluated in patients with prior BTK inhibitor or bcl-2 inhibitor

Abbreviations: ; bcl-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma

Conclusions

- Duvelisib in patients with relapsed or refractory CLL/SLL
  - Potential detriment in OS
  - High rates of toxicities and tolerability issues
  - Limited dose exploration and dose optimization
  - Consistent pattern of OS detriment seen across the PI3K inhibitor drug class

- New information of a potential OS detriment warrants reevaluation of overall benefit-risk of duvelisib in patients with R/R CLL/SLL

Abbreviations: CLL, chronic lymphocytic leukemia; OS, overall survival; SLL, small lymphocytic lymphoma

Discussion Topic

- Discuss the benefit-risk profile of duvelisib for the currently indicated population considering the updated results of the DUO trial.

Voting Question

- Given the potential detriment in overall survival, duvelisib-associated toxicity, concerns with the selected dose, and the safety issues with the PI3K inhibitor class, is the benefit-risk profile of duvelisib favorable in patients with relapsed or refractory CLL or SLL after at least two prior therapies?

Abbreviations: CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma


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Backup slides

Assessment of the Efficacy of Therapies Following Venetoclax Discontinuation in CLL Reveals BTK Inhibition as an Effective Strategy

Subsequent therapy	BTKi	BTKi	PI3Ki	CAR-T	Anti-CD20 absent
	Ibrutinib	Ibrutinib Acalabrutinib	Idelalisib		Rituximab Obinutuzumab
Agents	Acalabrutinib	Noncovalent BTKi BTKi exposed	Duvelisib	Anti-CD19	Ofatumumab
Pre-ven exposure	BTKi-naïve	33% BTKi intolerant 66% BTKi resistant	PI3Ki naïve BTKi exposed	BTKi exposed	
Patient number	44	30	17	18	19
Lines of therapy pre-ven, median (range)	2(0–8)	4 (1–11)	4 (1–6)	4 (1–10)	3 (1–9)
ORR	83.9%	53.4%	46.9%	66.6%	32%
CR	9.0%	10.0%	5.9%	33.3%	16%
PR	56.8%	26.7%	35.2%	33.3%	16%
PR-L	18.1%	16.7%	5.8%	0%	0%
SD	11.6%	23.3%	23.7%	5.7%	32%
PD	4.5%	23.3%	29.4%	27.7%	37%
Median PFS (months)	32	12	5	9	2
Median follow-up (months)	10.5	3.5	5.0	2.0	2.0
DC rate	38%	38%	78%	NA	72%
Reasons for DC (% discontinuations)					
CLL progression	21.4%	66.6%	58.3%	—	62%
Adverse event	14.3%	8.3%	25%	—	15.4%
Transformation	14.3%	—	16.7	—	7.6%
Planned cellular Tx	14.2%	—	—	—	—
Unrelated death	7.1%	8.3%	—	—	—
Sudden death on Tx	7.1%	16.6%	—	—	—
Patient preference	7.1%	—	—	—	—
Other	14.2%	—	—	—	15.3%

Abbreviations: abs, antibody; DC, discontinuation; Tx, therapy; Ven, venetoclax.

Mato, A., Roeker, L., Brander, D., Shadman, M, Schuster, S., Fox, C., Nabhan, C., Cheson, B., Eyre, T. et al. (2020). Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clinical Cancer Research*, *26*(14), 3589–3596. https://doi.org/10.1158/1078-0432.ccr-19-3815