FDA Introductory Comments

Oncologic Drugs Advisory Committee Meeting
April 21, 2022

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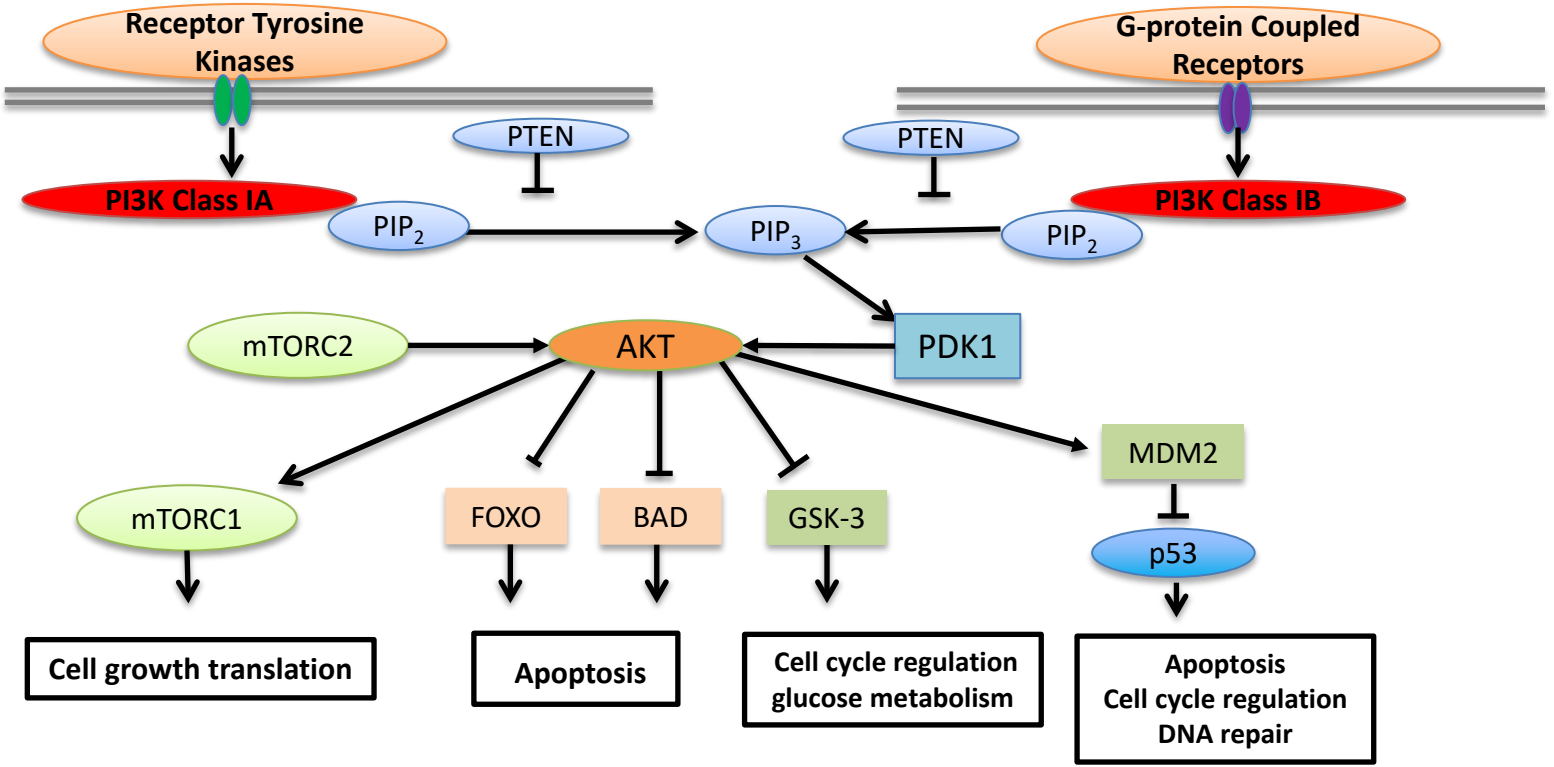
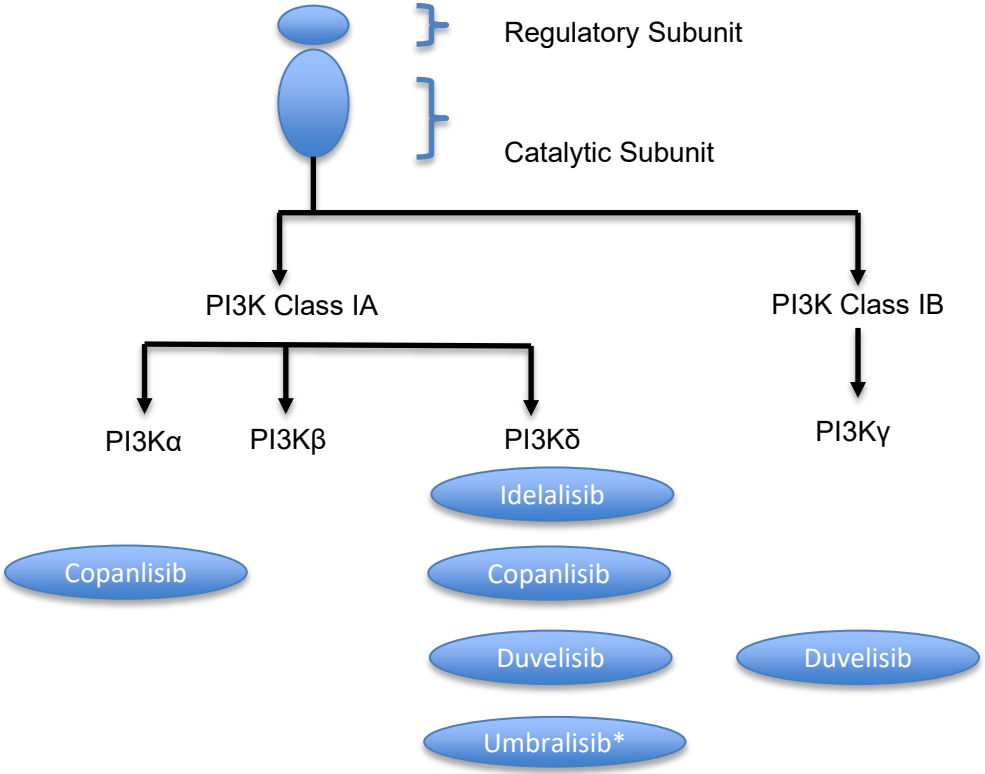
PI3K Inhibitor Overview



Abbreviations: PI3K: Phosphatidylinositol 3-kinase

PI3K Inhibitor Overview



Isoform IC50 (nM)

	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
Idelalisib	820	565	89	**2.5**
Copanlisib	**0.5**	**3.7**	**6.4**	**0.7**
Duvelisib	1602	85	27	**2.5**
Umbralisib	> 10000	1116	1065	**22**

* Also inhibits casein kinase CK1ε

PI3K Inhibitor Toxicities

- PI3K
  - Delta (δ) and Gamma (γ) isoforms are preferentially expressed on leukocytes
    - Infections
      - Pneumonia, opportunistic infections, CMV reactivation
    - Immune-mediated toxicities
      - δ isoform is important for $T_{regulatory}$ lymphocyte function
      - Hepatitis, pneumonitis, colitis, and rash
        - » Younger patients or those less heavily pretreated may be at greater risk
  - Alpha (α) isoform is ubiquitously expressed and essential to cellular growth and metabolism, glucose homeostasis
    - Results in hyperglycemia and hypertension

Abbreviations: CMV-Cytomegalovirus

PI3K Inhibitor Toxicities

	Idelalisib N= 146	Copanlisib N= 244	Duvelisib N= 442	Umbralisib N= 371
Grade ≥ 3 AE	71%	85%	84%	51%
SAEs	50%	51%	65%	26%
Discontinuations due to AE	23%	24%	35%	15%
Dose Reduction due to AE	41%	24%	23%	10%
Grade ≥ 3 Infection	23%	23%	27%	20%
Grade ≥ 3 Neutropenia	28%	29%	43%	17%
Grade ≥ 3 Diarrhea/Colitis	14%	5%	23%	7%
Grade ≥ 3 AST/ALT increase	18%	2%	8%	7%
Grade ≥ 3 Rash	4%	2%	9%	3%
Grade ≥ 3 Pneumonitis	5%	7%	7%	1%
Grade ≥ 3 Hyperglycemia	-	34%	-	-
Grade ≥ 3 Hypertension	-	29%	-	-

Abbreviations: AE- Adverse Event; SAE- Serious Adverse Event

PI3K Inhibitor Toxicities

Boxed Warning

Idelalisib
- Hepatotoxicity
- Diarrhea/colitis
- Pneumonitis
- Infections
- Intestinal perforation

Duvelisib
- Infections
- Diarrhea/colitis
- Cutaneous reactions
- Pneumonitis

Warnings and Precautions

Hepatotoxicity
- I, D, U

Diarrhea/colitis
- I, D, U

Pneumonitis
- I, C, D

Infections
- I, C, D, U

Cutaneous reactions
- I, C, D, U

Neutropenia
- I, C, D, U

Hyperglycemia
- C

Hypertension
- C

Intestinal perforation
- I

Communication REMS

Idelalisib

Duvelisib

Abbreviations: I- Idelalisib; D- Duvelisib; U- Umbralisib; C- Copanlisib

PI3K Inhibitor Regulatory History

2014

Idelalisib

- Relapsed follicular lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL) in patients who have received two prior systemic therapies (AA)
- Relapsed chronic lymphocytic leukemia (CLL) in combination with rituximab in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

2017

Copanlisib

- Relapsed FL who have received at least two prior systemic therapies (AA)

2018

Duvelisib

- Relapsed or refractory FL after at least two prior systemic therapies (AA)
- Relapsed or refractory CLL or SLL after at least two prior therapies

2021

Umbralisib

- Patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20 based regimen (AA)
- Patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy (AA)

Duvelisib relapsed FL indication voluntarily withdrawn (12/2021)

2022

Idelalisib relapsed FL and SLL indications voluntarily withdrawn (2/2022)

Umbralisib FL and MZL indications voluntarily withdrawn (4/2022)

Abbreviations: AA- Accelerated Approval, FL- Follicular lymphoma, CLL- Chronic lymphocytic leukemia, SLL- Small lymphocytic lymphoma, MZL- Marginal zone lymphoma

Regulatory Approval Pathways

- Regular Approval

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Provides a meaningful benefit over available therapy
  - Approval is based on an endpoint reasonably likely to predict clinical benefit or an intermediate endpoint
  - Post-approval trials to verify anticipated clinical benefit

21 CFR 314.510

Evidentiary Criteria for Approval

- Drugs granted accelerated approval or regular approval must meet the same statutory standards for safety and effectiveness
- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling
- Effectiveness
  - Substantial evidence of effectiveness
    - Based on adequate and well-controlled investigations
    - The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics.
FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Treatment Options for CLL and iNHL

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

Drug/Combination	Indication
Ibrutinib (2013)	CLL/SLL; CLL/SLL with 17p del; WM; MZL after 1 prior CD20-based therapy*
Idelalisib (2014)	Relapsed CLL
Venetoclax (2016)	CLL/SLL
Acalabrutinib (2017)	CLL/SLL
Copanlisib (2017)	Relapsed FL after 2 prior therapies *
Duvelisib (2018)	R/R CLL/SLL after at least 2 prior therapies
Zanubrutinib (2019)	WM; R/R MZL after 1 prior CD20-based regimen*
Tazemetostat (2020)	R/R FL positive for EZH2 mutation after 2 prior therapies*; R/R FL with no alternative options*
Umbralisib (2021)	R/R MZL after 1 prior CD20 based regimen*; R/R FL after 3 prior therapies*
Axicabtagene ciloleucel (2021)	R/R FL after two lines*

* Indicates accelerated approval

Abbreviations: CLL: Chronic lymphocytic leukemia; iNHL: Indolent non-Hodgkin lymphomas; R/R: relapsed, refractory; MCL: Mantle cell lymphoma; Flu/cy: Fludarabine, cyclophosphamide; FL: follicular lymphoma; MZL: Marginal zone lymphoma; NHL- Non-Hodgkin lymphoma; WM: Waldenstrom's macroglobulinemia

Issues for Discussion

- Potential Detriment in Overall Survival
- Toxicity and Tolerability
- Dosing
- Limitations of Single-arm Trials

Multiple Randomized Trials with Concerning Overall Survival

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
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)
DUO	• Previously treated CLL • Duvelisib vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
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

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, GC, Obinutuzumab + Chlorambucil, NHL, non-Hodgkin lymphoma, PI3Ki, phosphatidylinositol 3-kinase inhibitor

PI3K Inhibitor Dosing Concerns

- Limited dose exploration
- Exposure-response relationships for safety
- Lack of an exposure-response relationship for efficacy
- High rates of discontinuation, interruption and modification

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

PI3K Inhibitor Withdrawals

- Idelalisib
  - Initial accelerated approval for R/R FL or SLL after 2 prior therapies in 2014
    - 3 Subpart H PMRs were issued:
      - PMR 1: Dose optimization in R/R FL and SLL among responders
      - PMR 2: Safety and efficacy from GS-US-313-0124, a phase 3 trial of idelalisib + rituximab in previously treated iNHL
      - PMR 3: Safety and efficacy from GS-US-313-0125, a phase 3 trial of idelalisib + bendamustine+ rituximab in previously treated iNHL
  - March 2016, 3 trials terminated for increased deaths, including -0124 and 0125 confirmatory trials

Abbreviations: FL- follicular lymphoma; SLL- Small lymphocytic lymphoma; iNHL- Indolent Non-Hodgkin Lymphoma; R/R- relapsed refractory; PMR- postmarketing requirement

PI3K Inhibitor Withdrawals

- Idelalisib (cont.)
  - FDA regulatory actions based on increased deaths
    - Limitation of use added to the label that idelalisib is not indicated for first-line treatment, is not indicated in combination with bendamustine and rituximab in FL, and updates to the boxed warning and warnings and precautions
    - New PMR issued 2180-10 to conduct a trial to establish the safe and effective dose of idelalisib in patients with R/R FL who have no other therapeutic options
      - Study GS-US-313-1580
  - February 2022
    - Citing challenges in enrollment to the confirmatory trial, the sponsor decided to voluntarily withdraw the indication from the U.S. market

Abbreviations: FL- follicular lymphoma; R/R- relapsed refractory; PMR- postmarketing requirement

PI3K Inhibitor Withdrawals

- Duvelisib
  - Initial accelerated approval for R/R FL after 2 prior therapies in 2018
    - 1 Subpart H PMR was issued
      - PMR 3494-1: Conduct a randomized phase 3 trial in patients with R/R FL that verifies the clinical benefit.
  - December 2021
    - Citing changes in the treatment landscape, the sponsor decided to voluntarily withdraw the indication from the U.S. market

Abbreviations: FL- follicular lymphoma; R/R- relapsed refractory

PI3K Inhibitor Withdrawals

- Umbralisib Update- April 15, 2022
  - Voluntary withdrawal of umbralisib and ublituximab applications for the U2 regimen based on the UNITY-CLL trial
    - Overall survival concerns
  - Voluntary withdrawal of the FL and MZL indications for umbralisib under accelerated approval

Abbreviations: FL- follicular lymphoma; MZL- Marginal zone lymphoma

Single Arm Trial Limitations

- Safety findings are challenging to interpret
  - E.g., attribution to the drug or underlying disease
- Efficacy findings are challenging to interpret
  - Response rates may not predict clinical benefit
  - Reliance on cross-trial comparisons to determine if the product provides a benefit over available therapy is difficult
- Time-to-event endpoints (e.g., PFS and OS) are not interpretable

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

Overall Survival Endpoint

- Safety and an efficacy endpoint
  - E.g., attribution to the drug or underlying disease
- Incorporates the effect of toxicity

Discussion Topic

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

Voting Question

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


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Phosphatidylinositol 3-kinase (PI3K) Inhibitors in Hematologic Malignancies

Oncologic Drugs Advisory Committee Meeting
April 21, 2022

Nicholas Richardson, DO, MPH
Division of Hematologic Malignancies II
Office of Oncologic Diseases

Outline

Purpose

- Approach for future PI3K inhibitors developed for patients with hematologic malignancies

Approved PI3K inhibitors

- Idelalisib
- Copanlisib
- Duvelisib
- Umbralisib

Issues

- Potential detriment in overall survival
- Toxicity and tolerability
- Dosing
- Limitations of single-arm trials

Abbreviation: PI3K, phosphatidylinositol 3-kinase

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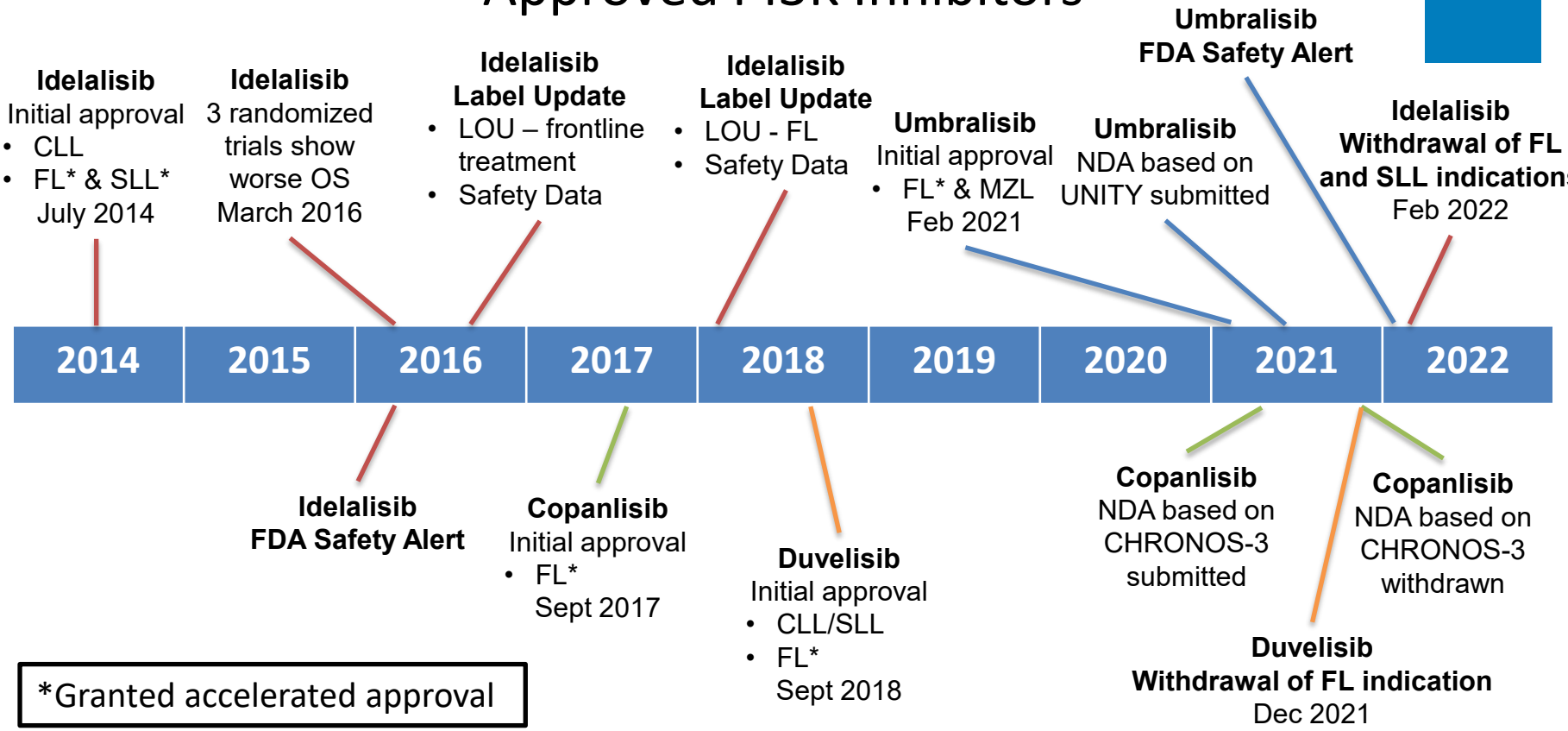
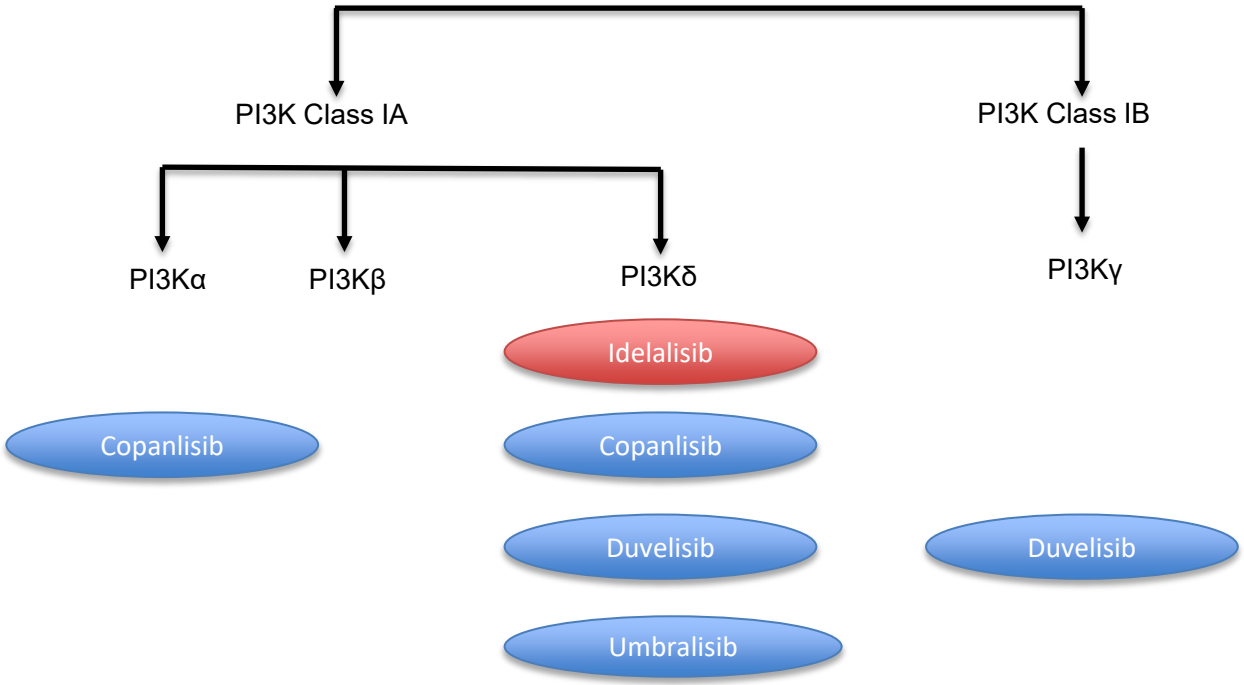
Approved PI3K Inhibitors



*Granted accelerated approval

Abbreviations: CLL, chronic lymphocytic leukemia, FL, follicular lymphoma, LOU, limitation of use, MZL, marginal zone lymphoma, NDA, new drug application, OS, overall survival, SLL, small lymphocytic lymphoma

Idelalisib (Zydelig)



Abbreviation: PI3K, phosphatidylinositol 3-kinase

Idelalisib Approvals

- Granted regular approval in relapsed CLL in July 2014
  - Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities

Study 312-0116			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (1:1) Placebo-controlled	Relapsed CLL	Idelalisib + Rituximab (I + R) Placebo + Rituximab (Pbo + R)	Primary: Progression-free survival (PFS)

	I + R N = 110	**Pbo + R N = 110**
PFS Events, n (%)	25 (23)	70 (64)
Median PFS, months (95% CI)	19.4 (12.3, NR)	6.5 (4.0, 7.3)
Adjusted HR (95% CI)	0.15 (0.09, 0.24)	

 Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, HR, hazard ratio, NR, not reached

Idelalisib Approvals

- Granted accelerated approval in relapsed FL and SLL in July 2014
  - Relapsed FL and SLL in patients who have received at least two prior systemic therapies

Study 101-09				
Design	**Population**	**Treatment**	**Endpoint**	**ORR (95% CI)**
Single-arm trial	Relapsed FL (N = 72) Relapsed SLL (N = 26)	Idelalisib 150 mg orally twice daily	Primary: Overall response rate (ORR)	FL = 54% (42, 66) SLL = 58% (37, 77)

Abbreviations: FL, follicular lymphoma, SLL, small lymphocytic lymphoma

Idelalisib Approval Components

Boxed Warning

- Hepatotoxicity
- Diarrhea or Colitis
- Pneumonitis
- Intestinal Perforation

Communication REMS

- Inform providers of serious risks

Accelerated Approval Postmarketing Requirements

- Dose optimization
- Two randomized trials in indolent NHL
  - Idelalisib ± Rituximab
  - Idelalisib ± BR

Warnings & Precautions

- Rash
- Neutropenia
- Anaphylaxis

Safety Postmarketing Requirements

- Pneumonitis
- Long-term safety

Abbreviations: BR, bendamustine and rituximab, NHL, non-Hodgkin lymphoma, REMS, risk evaluation and mitigation strategy

March 2016
Three Randomized Trials Terminated Due to Increased Deaths

Study	Population	Treatment Arms
312-0123	Untreated CLL	• Idelalisib + BR • Placebo + BR
313-0124	Previously treated indolent NHL (excluded rituximab refractory)	• Idelalisib + rituximab • Placebo + rituximab
313-0125	Previously treated indolent NHL (excluded bendamustine refractory)	• Idelalisib + BR • Placebo + BR

Idelalisib Dose: 150 mg twice daily (BID) for all studies
Bendamustine Dose: 90 mg/m^2, up to 6 cycles
Rituximab dose: 375 mg/m^2, dose schedule varied across studies

Abbreviations: BR, bendamustine and rituximab, CLL, chronic lymphocytic leukemia, NHL, non-Hodgkin lymphoma

March 2016
Three Randomized Trials Terminated Due to Increased Deaths

Study	Population & Treatment	Deaths Idelalisib	Deaths Control	Hazard Ratio (95% CI)
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)

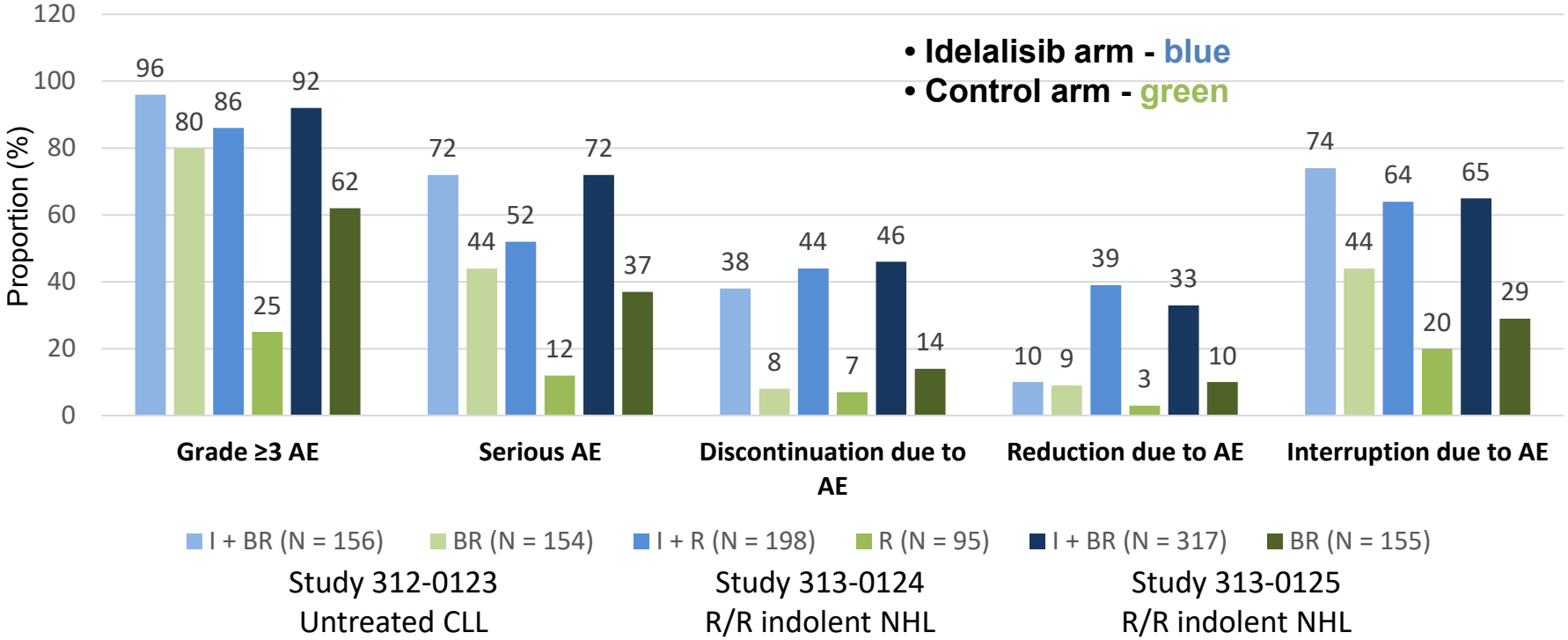
Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, NHL, non-Hodgkin lymphoma

Increased Deaths Due to Toxicity

	Study 312-0123 Untreated CLL		Study 313-0124 R/R indolent NHL		Study 313-125 R/R indolent NHL	
	I + BR N = 157	Pbo + BR N = 154	I + R N = 191	Pbo + R N = 95	I + BR N = 320	Pbo + BR N = 155
Total Deaths	12 (8%)	4 (3%)	10 (5%)	1 (1%)	27 (8%)	9 (6%)
Death due to AE	**12 (8%)**	3 (2%)	**8 (4%)**	0	**20 (6%)**	5 (3%)
Infection	8 (5%)	1 (<1%)	2 (1%)	0	8 (2%)	2 (1%)
Respiratory	0	0	2 (1%)	0	6 (2%)	0
Cardiac	2 (1%)	0	1 (<1%)	0	2 (<1%)	1 (<1%)

Abbreviations: AE, adverse event, BR, bendamustine and rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, Pbo, placebo, R, rituximab, R/R, relapsed or refractory

March 2016
Three Randomized Trials Demonstrated Increased Toxicity



Abbreviations: AE, adverse event, BR, bendamustine + rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, R, rituximab, R/R, relapsed or refractory

Difference in Toxicity Driven by PI3K-Associated Toxicities

	Study 312-0123 Untreated CLL		Study 313-0124 R/R indolent NHL		Study 313-125 R/R indolent NHL	
	I + BR N = 157	Pbo + BR N = 154	I + R N = 191	Pbo + R N = 95	I + BR N = 320	Pbo + BR N = 155
Grade ≥3 Infection	**45%**	20%	**22%**	4%	**40%**	19%
Grade ≥3 Neutropenia*	65%	64%	12%	10%	41%	37%
Grade ≥3 Diarrhea-Colitis	**9%**	3%	**19%**	2%	**13%**	0
Grade ≥3 ALT/AST increase*	**26%**	1%	**48%**	0	**27%**	<1%
Grade ≥3 Rash	**17%**	10%	**8%**	1%	**19%**	1%
Any Grade Pneumonitis	**6%**	3%	**6%**	1%	**8%**	1%

*Based on laboratory data

Abbreviations: BR, bendamustine and rituximab, CLL, chronic lymphocytic leukemia, I, idelalisib, NHL, non-Hodgkin lymphoma, Pbo, placebo, R, rituximab, R/R, relapsed or refractory

Randomized Data Led to Additional Safety Mitigation

- FDA Safety Alert
- Dear Healthcare Provider Letter
- Updated Boxed Warning and REMS
- Updated Safety Information in Label
- Limitations of Use
  - Idelalisib is not indicated and is not recommended for first-line treatment of any patient
  - Idelalisib is not indicated and is not recommended in combination with bendamustine and/or rituximab for the treatment of follicular lymphoma

Abbreviations: REMS, risk evaluation and mitigation strategy

Idelalisib Accelerated Approval Postmarketing Requirement (PMR) Updated

- The terminated -0124 and -0125 trials in indolent NHL were the confirmatory trials for the FL and SLL indications

- New PMR issued
  - Conduct a trial establishing a safe and effective dosing regimen of idelalisib in patients with relapsed or refractory FL who have no other therapeutic options and require treatment.
  - Ongoing Study 313-1580: *Dose Optimization Study of Zydelig in Follicular Lymphoma*

Abbreviations: FL, follicular lymphoma, NHL, non-Hodgkin lymphoma, SLL, small lymphocytic lymphoma

Withdrawal of Idelalisib FL and SLL Indications

- Study 313-1580: *Dose Optimization Study of Zydelig in Follicular Lymphoma*
  - Enrollment Challenges

- Inability to conduct a clinical trial to verify benefit
  - February 2022 – FL and SLL indications voluntarily withdrawn from U.S. market

Abbreviations: FL, follicular lymphoma, SLL, small lymphocytic lymphoma

Idelalisib Dosing Considerations

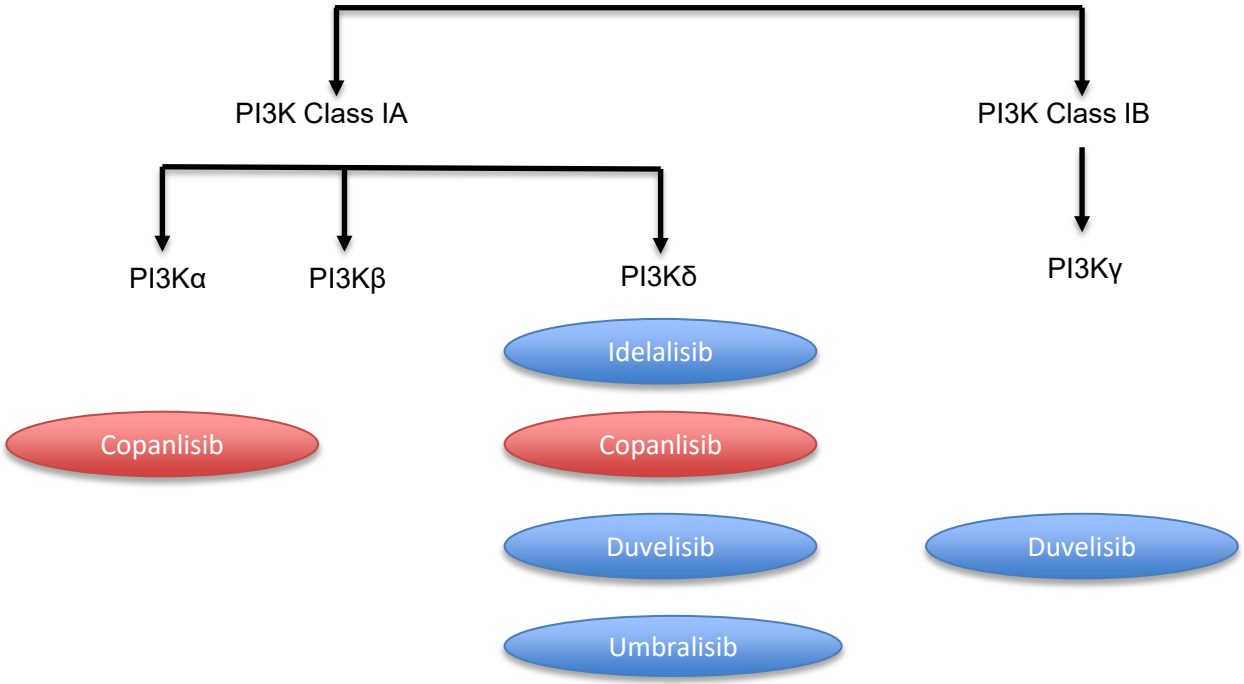
Idelalisib – approved dose 150 mg BID

- Monotherapy
  - Maximum tolerated dose (MTD) not reached
  - Exposure-response for efficacy plateaued at 150 mg BID
  - Higher exposure associated with increased risk of toxicity
  - High rates of treatment modifications due to toxicity
  - Lower doses (e.g., 100 mg BID) may be efficacious and tolerable

- Idelalisib Combination – 150 mg BID selected
  - Limited dose exploration
  - No E-R for efficacy
  - E-R relationship for safety
  - High rates of treatment modifications due to toxicity
  - Lower doses (e.g., 100 mg BID) may be efficacious and tolerable in combination

Abbreviations: E-R, exposure-response, PK, pharmacokinetic

Copanlisib (Aliqopa)



Abbreviation: PI3K, phosphatidylinositol 3-kinase

Copanlisib Approval

- Granted accelerated approval in relapsed follicular lymphoma (FL) in September 2017
  - Relapsed FL who have received at least two prior systemic therapies

CHRONOS-1				
Design	**Population**	**Treatment**	**Endpoint**	**ORR (95% CI)**
Single-arm trial	Relapsed FL (N = 104)	Copanlisib 60 mg IV on Days 1, 8, 15 of a 28-day cycle (3 weeks on/1 week off)	Primary: ORR	FL = 59% (49, 68)

Abbreviations: ORR, overall response rate

Copanlisib Toxicity in NHL

	Copanlisib N = 244
Median Exposure, months (range)	4.3 (0.2, 47.4)
Death due to Adverse Event	4%
Grade ≥3 Adverse Event	85%
Serious Adverse Event	51%
Discontinuation due to Adverse Event	24%
Reduction due to Adverse Event	24%
Interruption due to Adverse Event	64%

	Copanlisib N = 244
Grade ≥3 Hyperglycemia*	34%
Grade ≥3 Hypertension	29%
Grade ≥3 Infection	23%
Grade ≥3 Neutropenia*	29%
Grade ≥3 Diarrhea-Colitis	5%
Grade ≥3 ALT/AST increase*	2%
Grade ≥3 Rash	2%
Any Grade Pneumonitis	7%

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase, NHL, non-Hodgkin lymphoma

Copanlisib Approval Components

Warnings & Precautions

- Infection
- Hyperglycemia
- Hypertension
- Pneumonitis
- Neutropenia
- Rash

Accelerated Approval Postmarketing Requirements

- Randomized trial in indolent NHL
  - Copanlisib ± immunochemotherapy

Safety Postmarketing Requirements

- Long-term safety
- Safety from randomized trial in indolent NHL
- QT study
- Hepatic and renal impairment
- Drug-drug interaction

Abbreviations: NHL, non-Hodgkin lymphoma

CHRONOS-3 Study in Indolent NHL

CHRONOS-3			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (2:1) Placebo-controlled	Relapsed indolent NHL* (FL, MZL, SLL, WM)	Copanlisib + Rituximab (N = 307) Placebo + Rituximab (N = 151)	Primary: PFS

***Eligibility**

- Progression-free or treatment-free ≥12 months after last CD20 therapy

or

- Considered unfit for chemotherapy and progression-free or treatment-free ≥6 months after last CD20 therapy

Abbreviations: FL, follicular lymphoma, MZL, NHL, non-Hodgkin lymphoma, PFS, progression-free survival, SLL, small lymphocytic lymphoma, WM, Waldenström's macroglobulinemia

CHRONOS-3 PFS Results in Indolent NHL

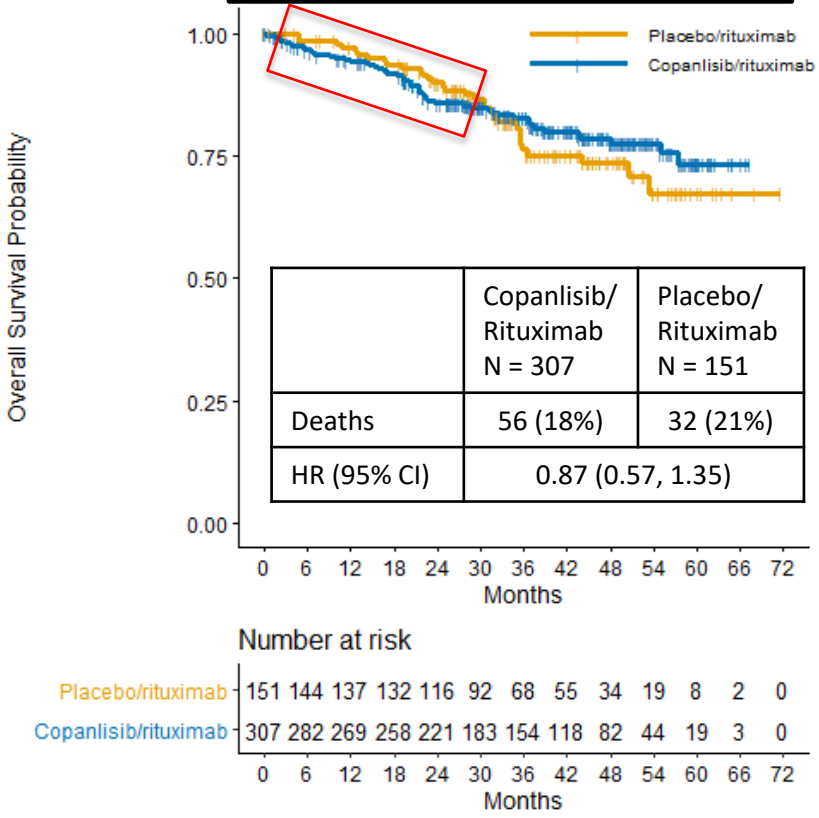
CHRONOS-3			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (2:1) Placebo-controlled	Relapsed indolent NHL (FL, MZL, SLL, WM)	Copanlisib + Rituximab (C + R) Placebo + Rituximab (Pbo + R)	Primary: PFS

	C + R N = 307	**Pbo + R N = 151**
PFS Events, n (%)	118 (38)	87 (58)
Median PFS, months (95% CI)	21.5 (17.8, 33.0)	13.8 (10.2, 17.5)
Adjusted HR (95% CI)	0.52 (0.39, 0.69)	

Abbreviations: CI, confidence interval, FL, follicular lymphoma, HR, hazard ratio, MZL, marginal zone lymphoma, NHL, non-Hodgkin lymphoma, PFS, progression-free survival, SLL, small lymphocytic lymphoma, WM, Waldenström's macroglobulinemia

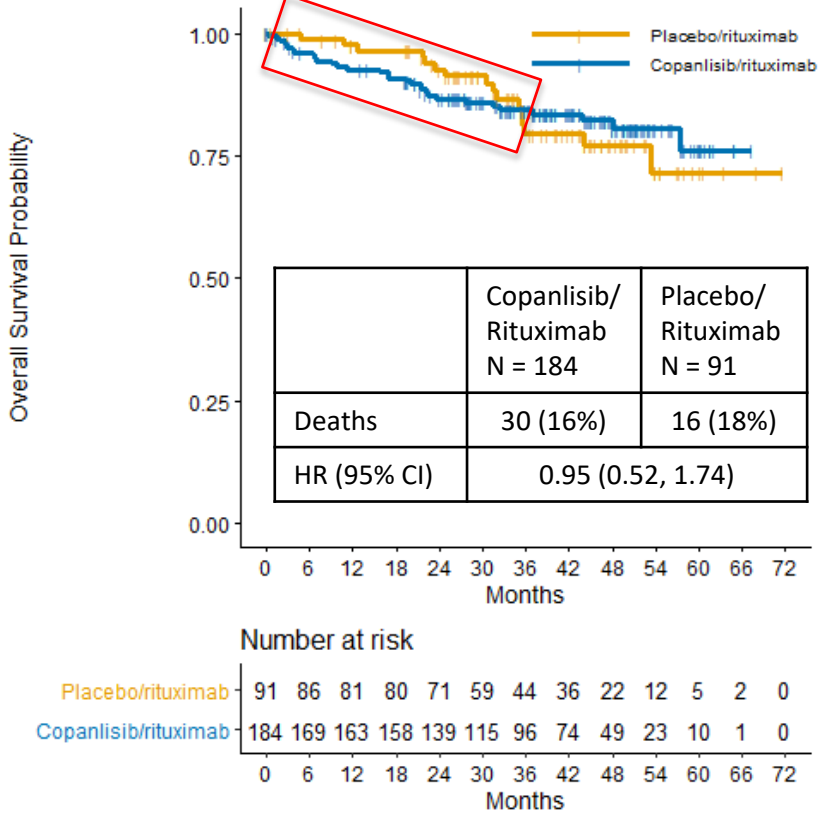
CHRONOS-3 Overall Survival Results

Indolent NHL – Intent-to-treat



	Copanlisib/ Rituximab N = 307	Placebo/ Rituximab N = 151
Deaths	56 (18%)	32 (21%)
HR (95% CI)	0.87 (0.57, 1.35)	

Follicular lymphoma



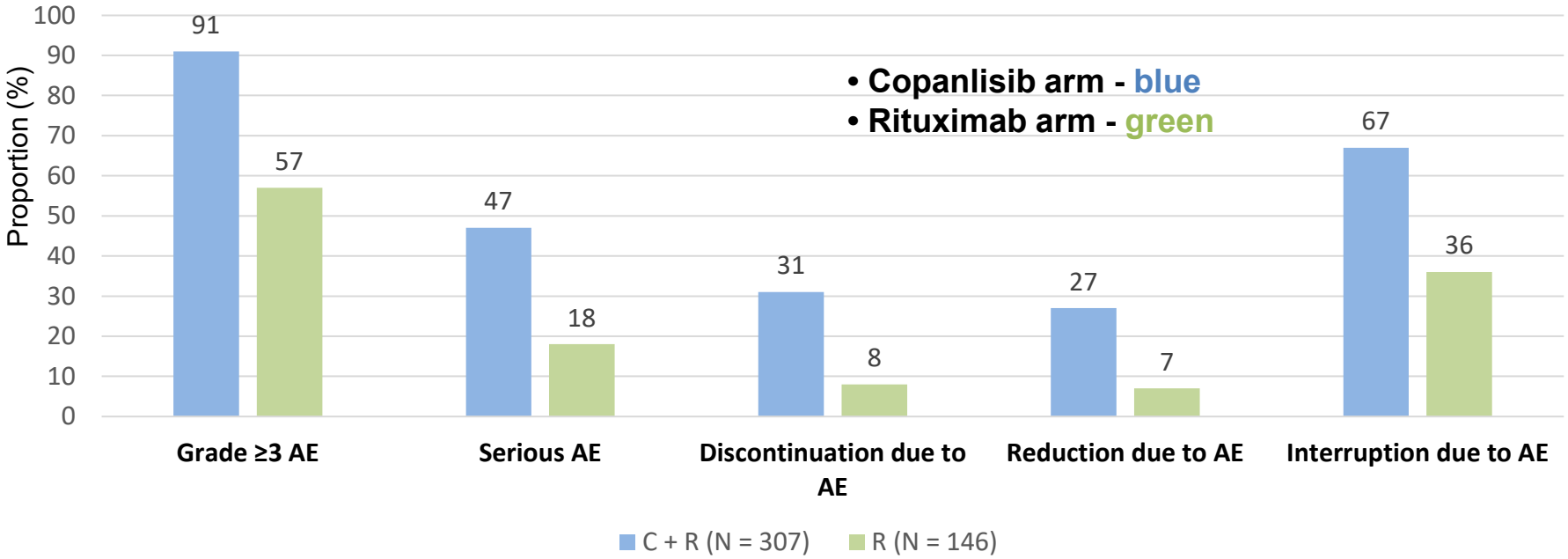
	Copanlisib/ Rituximab N = 184	Placebo/ Rituximab N = 91
Deaths	30 (16%)	16 (18%)
HR (95% CI)	0.95 (0.52, 1.74)	

CHRONOS-3 Deaths in Safety Population

	Copanlisib/Rituximab N = 307 n (%)	Placebo/Rituximab N = 146 n (%)
Total Deaths	56 (18%)	32 (22%)
Progressive disease	23 (7%)	8 (5%)
Adverse event	15 (5%)	1 (<1%)
Other	12 (4%)	15 (10%)
Unknown	6 (2%)	8 (5%)

Deaths due to adverse events were higher in the copanlisib arm

CHRONOS-3 Safety in Indolent NHL



Abbreviations: AE, adverse event, C, copanlisib, NHL, non-Hodgkin lymphoma, R, rituximab

Difference in Toxicity Driven by PI3K-Associated Toxicities

	CHRONOS-3 (Indolent NHL)	
	Copanlisib + Rituximab N = 307	**Placebo + Rituximab N = 146**
Grade ≥3 Hyperglycemia*	**67%**	12%
Grade ≥3 Hypertension	**41%**	10%
Grade ≥3 Infection	**22%**	8%
Grade ≥3 Neutropenia*	**40%**	24%
Grade ≥3 Diarrhea-Colitis	**6%**	0
Grade ≥3 ALT/AST increase*	3%	3%
Grade ≥3 Rash	**3%**	<1%
Any Grade Pneumonitis	**8%**	1%

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase, NHL, non-Hodgkin lymphoma, PI3K, phosphotidylinositol-3 kinase

CHRONOS-3 Application Withdrawal

- The supplemental new drug application based on CHRONOS-3 to support treatment of adult patients with indolent NHL was withdrawn from the FDA in December 2021

Abbreviations: NHL, non-Hodgkin lymphoma

Copanlisib Dosing Considerations

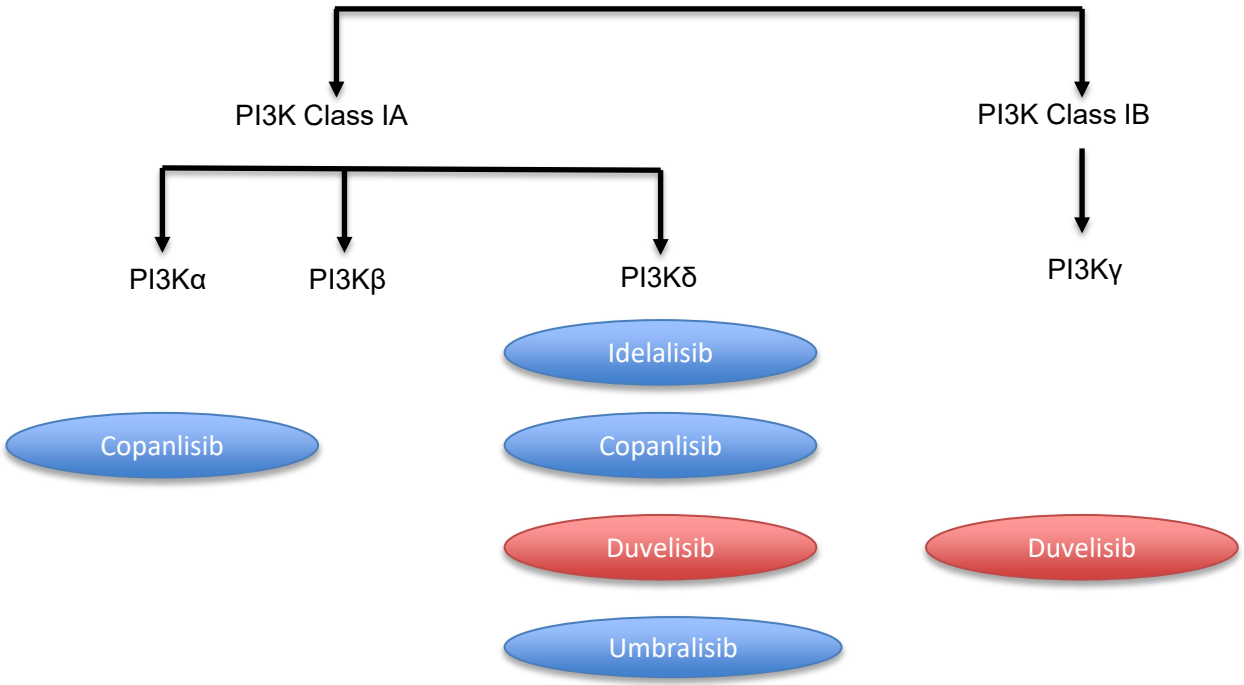
Copanlisib – approved dose 60 mg IV weekly (3 weeks on/1 week off)

- Monotherapy
  - Limited dose finding in hematologic malignancies
  - 0.8 mg/kg or 60 mg selected as maximum tolerated dose (MTD)
  - PK/PD data suggested comparable efficacy for 45 mg and 60 mg
  - No significant E-R relationships observed for efficacy or safety at 60 mg dose
  - High rates of treatment modifications due to toxicity at 60 mg

- Combination
  - No dose finding conducted for use in combination – 60 mg dose selected

Abbreviations: E-R, exposure-response, PD, pharmacodynamic, PK, pharmacokinetic

Duvelisib (Copiktra)



Abbreviation: PI3K, phosphatidylinositol 3-kinase

Duvelisib Approvals

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

Study IPI-145-07 (DUO)			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (1:1)	Relapsed or refractory CLL or SLL	Duvelisib (N = 160) Ofatumumab (N = 159)	Primary: Progression-free survival (PFS)

	Duvelisib N = 160	**Ofatumumab N = 159**
PFS Events, n (%)	93 (58)	110 (69)
Median PFS, months (95% CI)	13.3 (12.1, 16.8)	9.9 (9.2, 11.3)
Adjusted HR (95% CI)	0.52 (0.39, 0.69)	

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

Duvelisib Approvals

- Granted accelerated approval in relapsed or refractory FL in September 2018
  - Relapsed or refractory FL after at least two prior systemic therapies

Study IPI-145-06 (DYNAMO)				
Design	**Population**	**Treatment**	**Endpoint**	**ORR (95% CI)**
Single-arm trial	Relapsed or refractory FL (N = 83)	Duvelisib 25 mg orally twice daily	Primary: Overall response rate	FL = 42% (31, 54)

Abbreviations: FL, follicular lymphoma

Duvelisib Toxicity in NHL

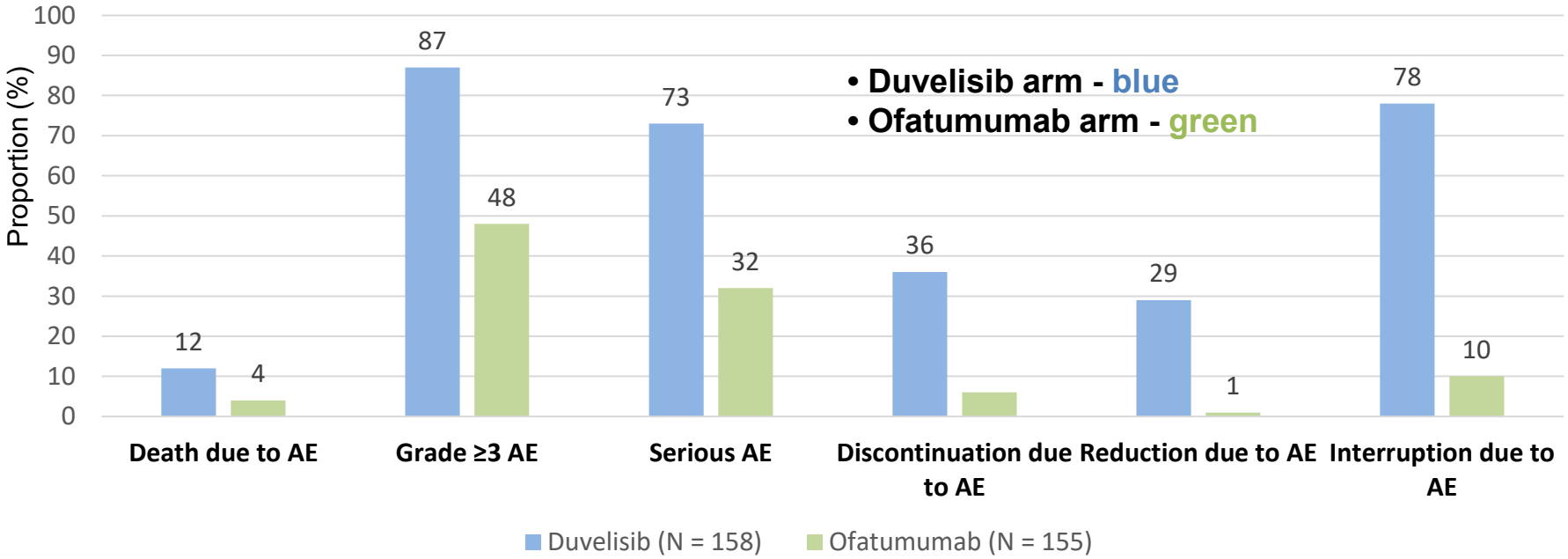
	Duvelisib N = 442
Median Exposure, months (range)	9.0 (0.1, 53.0)
Death due to Adverse Event	4%
Grade ≥3 Adverse Event	84%
Serious Adverse Event	65%
Discontinuation due to Adverse Event	35%
Reduction due to Adverse Event	23%
Interruption due to Adverse Event	64%

PI3K-Associated Toxicities	Duvelisib N = 442
Grade ≥3 Infection	27%
Grade ≥3 Neutropenia*	43%
Grade ≥3 Diarrhea-Colitis	23%
Grade ≥3 ALT/AST increase*	8%
Grade ≥3 Rash	9%
Any Grade Pneumonitis	7%

*Based on laboratory data

Abbreviations: AE, adverse event, ALT, alanine aminotransferase, AST, aspartate aminotransferase, NHL, non-Hodgkin lymphoma, PI3K, phosphatidylinositol 3-kinase

DUO Study Safety
Relapsed or Refractory CLL or SLL



Abbreviations: AE, adverse event, CLL, chronic lymphocytic leukemia, SLL, small lymphocytic lymphoma

Difference in Toxicity Driven by PI3K-Associated Toxicities

	DUO (CLL or SLL)	
	Duvelisib N = 158	**Ofatumumab N = 155**
Grade ≥3 Infection	**33%**	11%
Grade ≥3 Neutropenia*	48%	35%
Grade ≥3 Diarrhea-Colitis	**26%**	2%
Grade ≥3 ALT/AST increase*	**7%**	1%
Grade ≥3 Rash	**11%**	<1%
Any Grade Pneumonitis	**8%**	0

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase, CLL, chronic lymphocytic leukemia, PI3K, phosphatidylinositol 3-kinase, SLL, small lymphocytic lymphoma

Duvelisib Approval Components

Boxed Warning

- Infection
- Diarrhea or Colitis
- Rash
- Pneumonitis

Communication REMS

- Inform providers of serious risks

Accelerated Approval Postmarketing Requirements

- Randomized trial in relapsed or refractory FL that verifies the clinical benefit of duvelisib

Warnings & Precautions

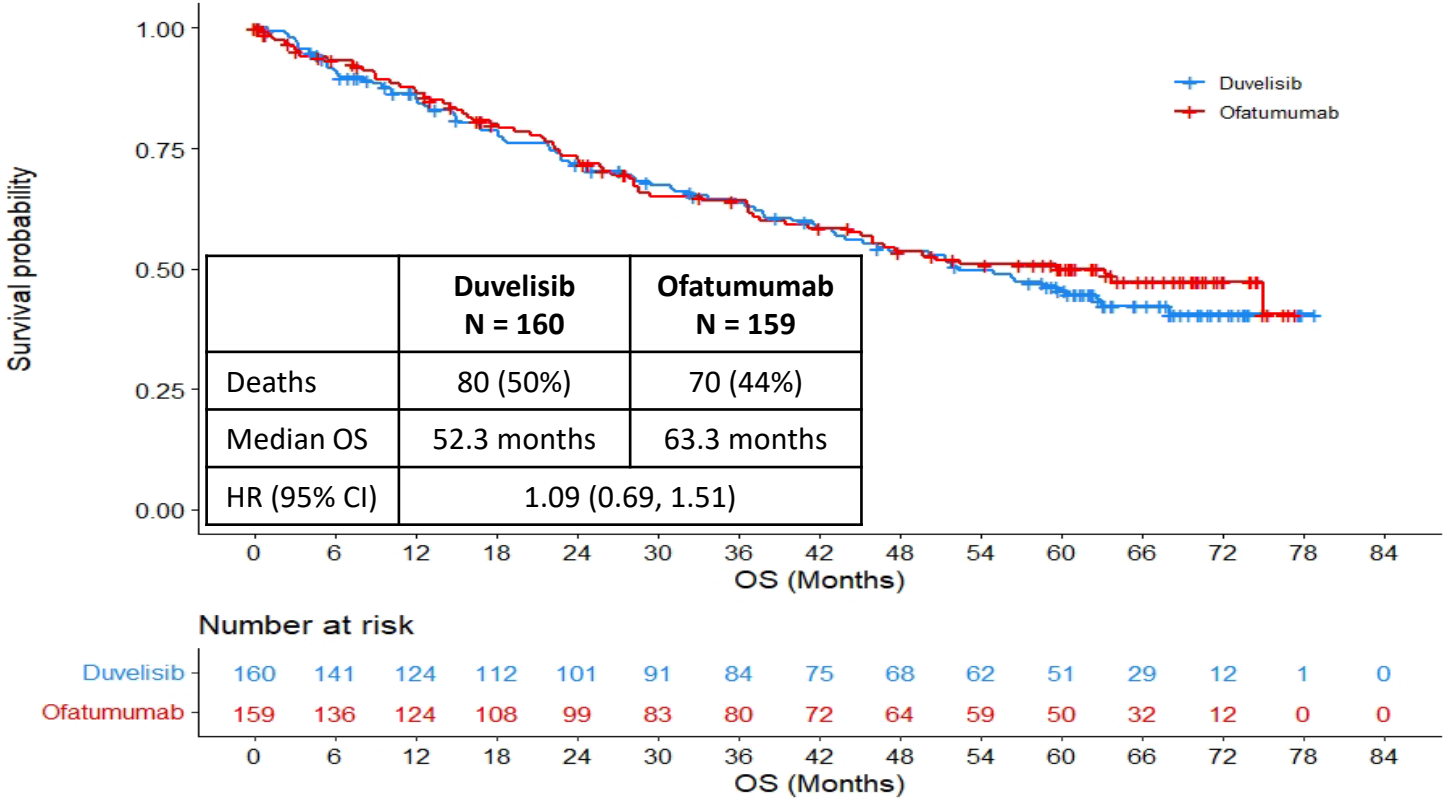
- Hepatotoxicity
- Neutropenia

Safety Postmarketing Requirements

- Long-term safety
- Final OS analysis of DUO trial

Abbreviations: FL, follicular lymphoma, OS, overall survival, REMS, risk evaluation and mitigation strategy

Final OS Analysis of DUO Trial



	Duvelisib N = 160	Ofatumumab N = 159
Deaths	80 (50%)	70 (44%)
Median OS	52.3 months	63.3 months
HR (95% CI)	1.09 (0.69, 1.51)	

Withdrawal of Duvelisib FL Indication

DUETTO			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (1:1)	Relapsed or refractory FL	Duvelisib + Rituximab Rituximab or R-CVP	Primary: Progression-free survival

- DUETTO: Never initiated

- Inability to conduct a clinical trial to verify benefit
  - December 2021 – FL indication voluntarily withdrawn from U.S. market

Abbreviations: FL, follicular lymphoma, R-CVP, rituximab, cyclophosphamide, vincristine, prednisone

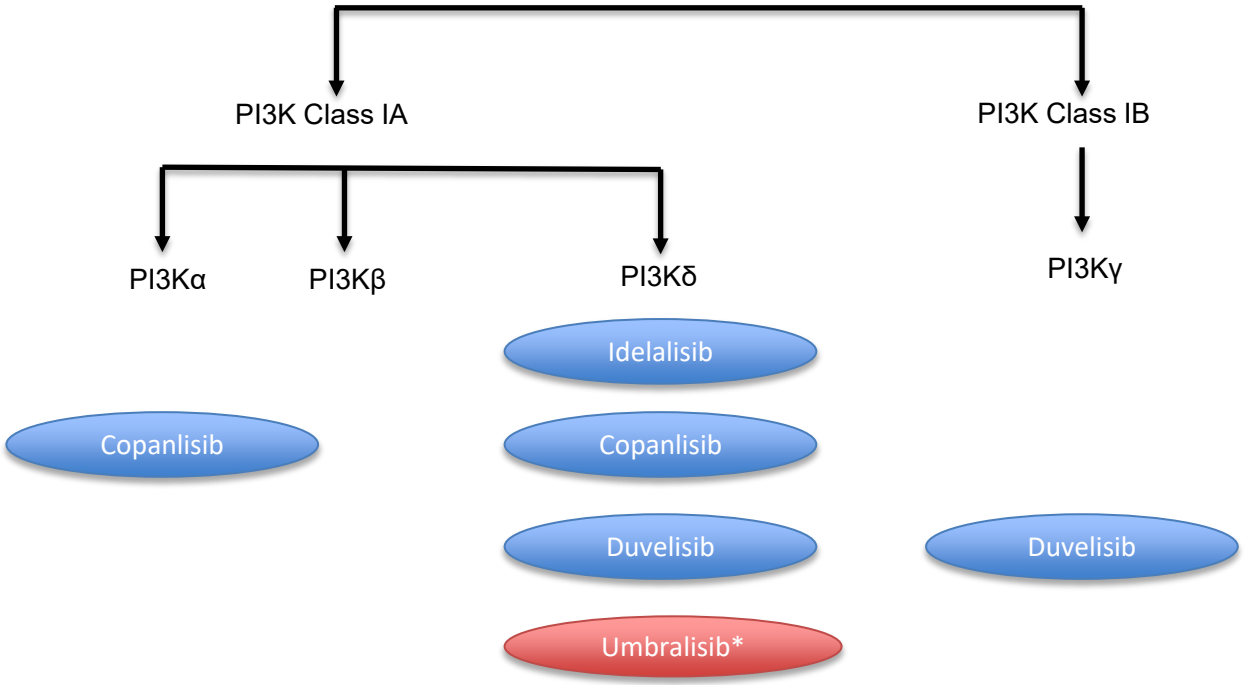
Duvelisib Dosing Considerations

Duvelisib – approved dose 25 mg BID

- Monotherapy
  - Limited dose finding
  - 75 mg BID identified as maximum tolerated dose (MTD)
  - No E-R relationship for efficacy observed at 25 mg BID
    - 25 mg BID and 75 mg BID had comparable efficacy; 15 mg BID also demonstrated activity
  - PD marker p-AKT showed near maximal suppression at 25 mg BID
  - E-R relationship for safety between 8 – 75 mg BID
  - High rates of treatment modifications due to toxicity at 25 mg BID

Abbreviations: E-R, exposure-response, PD, pharmacodynamic

Umbralisib (Ukoniq)



*Also inhibits C1kε
Abbreviations: PI3K, phosphatidylinositol 3-kinase

Umbralisib Approval

- Granted accelerated approval in relapsed or refractory FL and MZL in February 2021
  - Relapsed or refractory FL who have received at least three prior lines of systemic therapy
  - Relapsed or refractory MZL who have received at least one prior anti-CD20-based regimen

Study UTX-TGR-205				
Design	**Population**	**Treatment**	**Endpoint**	**ORR (95% CI)**
Single-arm trial	Relapsed or refractory FL (N = 117)	Umbralisib 800 mg orally daily	Primary: Overall response rate (ORR)	FL = 43% (34, 52)
	Relapsed or refractory MZL (N = 69)			MZL = 49% (37, 62)

Abbreviations: FL, follicular lymphoma, MZL, marginal zone lymphoma

Umbralisib FDA Safety Alert – UNITY-CLL Trial

UNITY-CLL			
Design	**Population**	**Treatment**	**Endpoint**
Randomized (1:1)	Untreated and previously treated CLL	Umbralisib + Ublituximab (U2) Obinutuzumab + Chlorambucil	Primary: Progression-free survival

- FDA issued a safety alert on February 3, 2022
  - Possible increased risk of death
    - Overall survival hazard ratio 1.23

Abbreviation: CLL, chronic lymphocytic leukemia

Umbralisib Withdrawal Update – April 15, 2022

- Voluntary withdrawal of umbralisib and ublituximab applications for the U2 regimen based on the UNITY-CLL trial
  - Overall survival concerns

- Voluntary withdrawal of the FL and MZL indications for umbralisib under accelerated approval

PI3K Inhibitor Class Issues

- Potential detriment in overall survival
- Toxicity and tolerability
- Dosing
- Limitations of single-arm trials

Multiple Randomized Trials with Concerning Overall Survival

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
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)
DUO	• Previously treated CLL/SLL • Duvelisib vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
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

Abbreviations: CI, confidence interval, CLL, chronic lymphocytic leukemia, GC, Obinutuzumab + Chlorambucil, NHL, non-Hodgkin lymphoma, PI3Ki, phosphatidylinositol 3-kinase inhibitor, SLL, small lymphocytic lymphoma

PI3K Inhibitors Impart Substantial Risk

	Idelalisib N = 146	Copanlisib N = 244	Duvelisib N = 442	Umbralisib N = 371
Grade ≥3 adverse event	71%	85%	84%	51%
Serious adverse event	50%	51%	65%	26%
Grade ≥3 Infection	23%	23%	27%	20%
Grade ≥3 Neutropenia*	28%	29%	43%	17%
Grade ≥3 Diarrhea-Colitis	14%	5%	23%	7%
Grade ≥3 ALT/AST increase	18%	2%	8%	7%
Grade ≥3 Rash	4%	2%	9%	3%
Any Grade Pneumonitis	5%	7%	7%	1%
Grade ≥3 Hyperglycemia*	-	34%	-	-
Grade ≥3 Hypertension	-	29%	-	-

*Based on laboratory data

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase, PI3K, phosphatidylinositol-3 kinase

In randomized trials, PI3K inhibitors have demonstrated

- Higher fatal adverse events
- Higher Grade ≥3 adverse events
- Higher serious adverse events
- Higher rates of treatment modifications due to adverse events

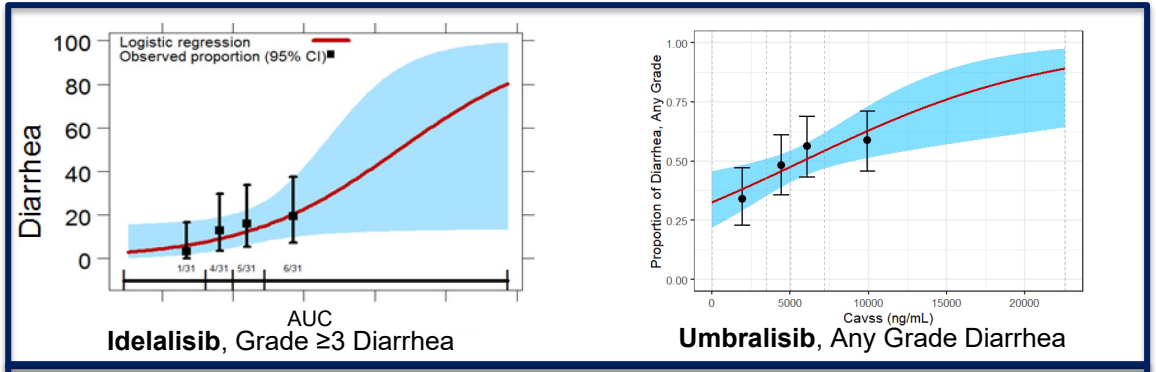
PI3K Inhibitor Dosing

- Limited dose exploration
- Exposure-response relationships for safety
- Lack of an exposure-response relationship for efficacy
- Identifying an optimal dose remains uncertain

Abbreviations: PI3K, Phosphatidylinositol-3 kinase

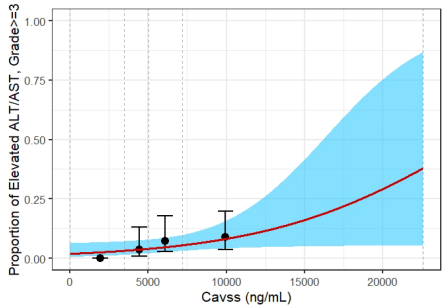
PI3K Inhibitors Have Exposure-Response for Safety

- PI3K Inhibitors have exposure-response relationships for safety
- PI3K inhibitors have not necessarily demonstrated exposure relationship for efficacy

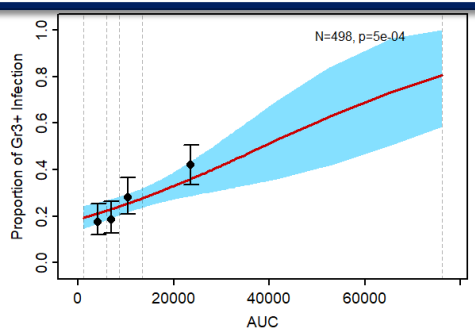


Idelalisib, Grade ≥3 Diarrhea

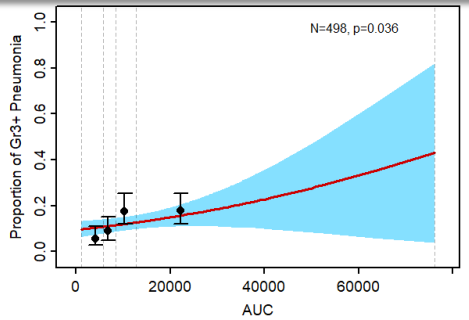
Umbralisib, Any Grade Diarrhea



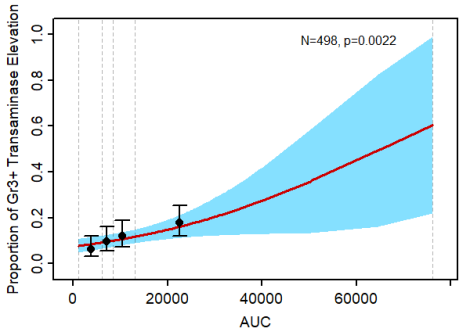
Umbralisib, Grade ≥3 ALT/AST



Duvelisib, Grade ≥3 Infection



Duvelisib, Grade ≥3 Pneumonia



Duvelisib, Grade ≥3 ALT/AST

PI3K Inhibitor Tolerability

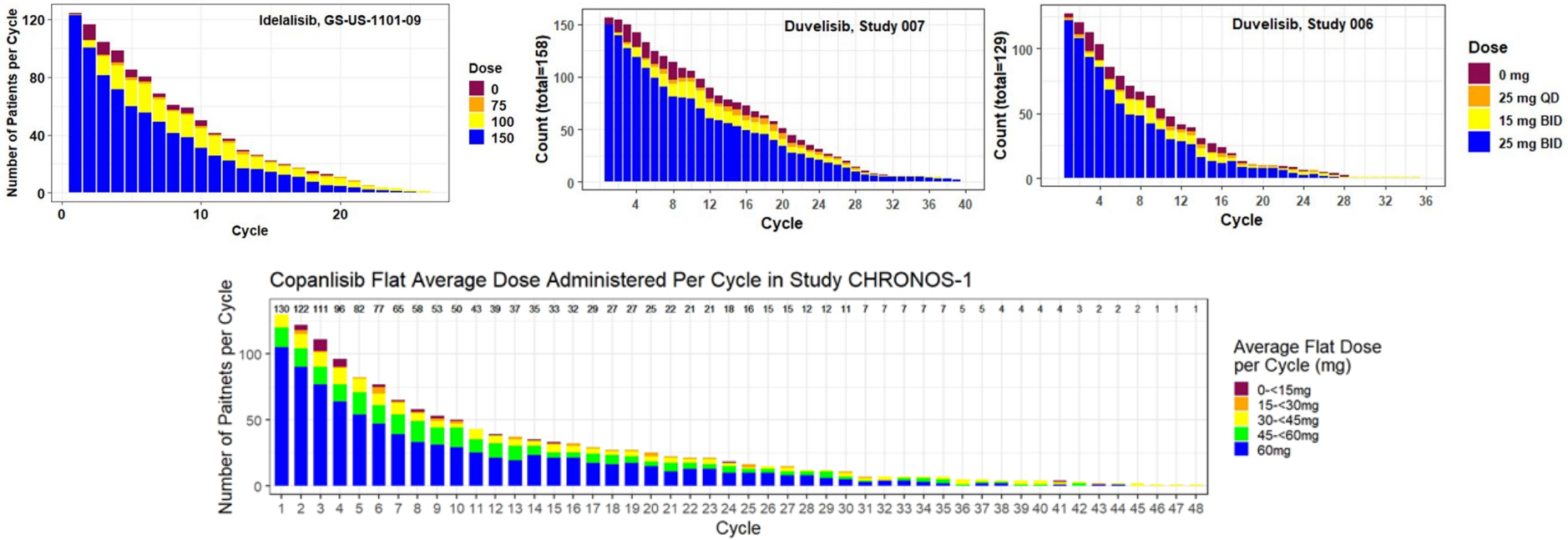
- PI3K inhibitor dosing impacts tolerability

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

Abbreviations: AE, adverse event, PI3K, phosphatidylinositol-3 kinase

PI3K Inhibitor Tolerability

- PI3K inhibitor doses may be poorly tolerated
- Patient-reported side effects in early phase trials can inform tolerability



Abbreviations: BID, twice daily, QD, once daily

Single-Arm Data to Support Approvals with PI3K Inhibitors

- Limitations of single-arm trials
  - Challenging to interpret safety and efficacy
  - Cross-trial comparisons
  - Response rate may not predict clinical benefit
  - Time-to-event endpoints are not interpretable

- Requirement for confirmatory trials
  - Indication withdrawals for idelalisib and duvelisib

Randomized Trials

- Preferred approach to demonstrating causal effects of a treatment
- Comparable groups with respect to known and unknown factors
  - Unbiased estimators of difference across randomized groups
- Reduces or balances selection bias
- Able to assess time-to-event endpoints

Overall Survival

- FDA requires overall survival information in any trial that uses PFS as a primary endpoint
- Overall survival is an objective measure of clinical benefit
- Overall survival is an efficacy and safety endpoint
  - Encompasses toxicity
  - Does not require same statistical considerations when used as a primary safety endpoint
- Overall survival can only be assessed in a randomized trial
- Supports benefit-risk determination

Evidentiary Criteria for Approval

- Safety
  - Sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.

- Effectiveness
  - Substantial evidence of effectiveness
    - Based on adequate and well-controlled investigations
    - The drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling

Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics.
FD&C Act Section 505(d) (21 U.S.C. § 355(d))

Conclusions

- PI3K inhibitors demonstrate substantial toxicity
- Toxicity translated to potential detriment in overall survival
- Limited tolerability
- Insufficient dose exploration and optimization
- Single-arm trials in indolent NHL have limitations

- Sponsors are required to provide evidence that the drug is safe and effective

Discussion Topic

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

Voting Question

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

Backup Slides Shown

Patient-Generated Data in Oncology Drug Development

- "A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment" [1]
- FDA encourages sponsors to collect patient-reported symptoms, overall side effect bother, and physical/role functioning in oncology trials.[2]
- It is practical and feasible to collect patient-reported symptoms and function, including early phase trials, using existing methods/tools.
- PROs can inform dose selection, tolerability, and complement clinician-reported safety information.

[1]FOCR White Paper "Broadening the definition of tolerability in cancer clinical trials to better measure the patient experience" (2018)
[2]Draft Guidance "Core Patient-Reported Outcomes in Cancer Clinical Trials" (2021)

Overall Survival

- Overall survival (OS) is typically defined as the time from **randomization** to death from any cause
  - Randomization tends to balance all factors, known or unknown (e.g. survival interval initiation points)
- OS is a preferred **efficacy and a safety endpoint** in oncology clinical trials
  - An objective measure of clinical benefit
  - Incorporates impact of toxicity
- The non-parametric **log rank test** has typically been used as statistical test for significant differences in survival between treatments (when a hypothesis test is pre-specified)
- OS is typically summarized via **the hazard ratio (HR)** and comparisons of median survival time
  - According to convention, in oncology settings, HRs are calculated such that **values exceeding one indicate higher risk of death for the investigative treatment group**
  - **Confidence intervals** for the HR are evaluated in the absence of or in addition to a statistical test
  - Other descriptions, such as the probability of surviving to set timepoints can also be useful
  - A pre-specified ITT analysis is preferred; sensitivity analyses evaluate robustness of estimates
- **OS supports the overall benefit-risk determination for regulatory decisions**

Early OS Data

- Long natural history of certain diseases has motivated use of primary endpoints other than OS for efficacy claims
- Statistical analysis plans for trials using PFS or ORR as primary endpoints have not always included event-driven pre-specified OS analyses
  - HR interpretation may be challenging due to patients crossing-over treatments
  - Potential confounding due to subsequent therapies
  - Low ratio of events to sample size
  - OS usually considered exploratory in such settings
- **OS is a safety consideration, with particular class concerns:**
  - Pattern of observed OS HRs >1 (in more than one study)
  - Prior information on risk for products (AEs or risk of death - see label warnings)
  - The totality of evidence informs safety even in the absence of statistical testing
  - Observed OS results, prior information, and observed toxicity profiles should adequately rule out harm and help support a conclusion that the products are safe

Exploratory Analyses of OS for PI3K Class

- **Consider available survival information**
  - None of the studies for PI3K included prespecified number of OS events
  - Low number of observed events (as low as 3% of the planned sample size) leading to uncertainty in estimates
- **Estimated HR and confidence interval provide descriptive information**
  - Point estimates for HR >1 across multiple studies
  - Wide confidence intervals do not adequately rule out potential harm
- **Death rates by treatment arm provide important summaries**
  - Death rates were higher in investigative treatment arms

Summary of OS Evaluation

- The confidence intervals for the HR are wide, with large upper bounds. The large upper bounds indicate **death hazards may be up to multiple times that in the control arm**.

- There are **higher death rates in the investigative treatment groups** and OS HR estimates in several studies across the PI3K class

- While there are a low number of events and uncertainty in the estimates, when potentially harmful OS HRs are observed in multiple studies in the PI3K class, **a chance finding is questionable**.

Summary of OS for PI3K Inhibitors

- Sponsors have an obligation to demonstrate their products are safe and effective.

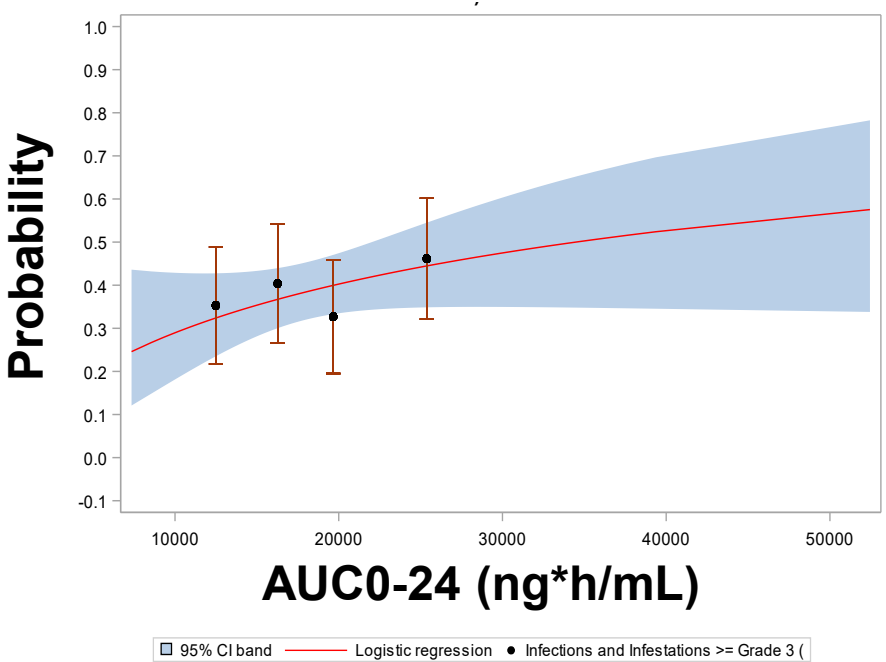
- The observed OS estimates, especially considering prior information, observed toxicity profiles, and questionable dose selection do not adequately rule out harm or support a conclusion that these products are safe.

Looking Forward
(Early OS in Randomized Studies)

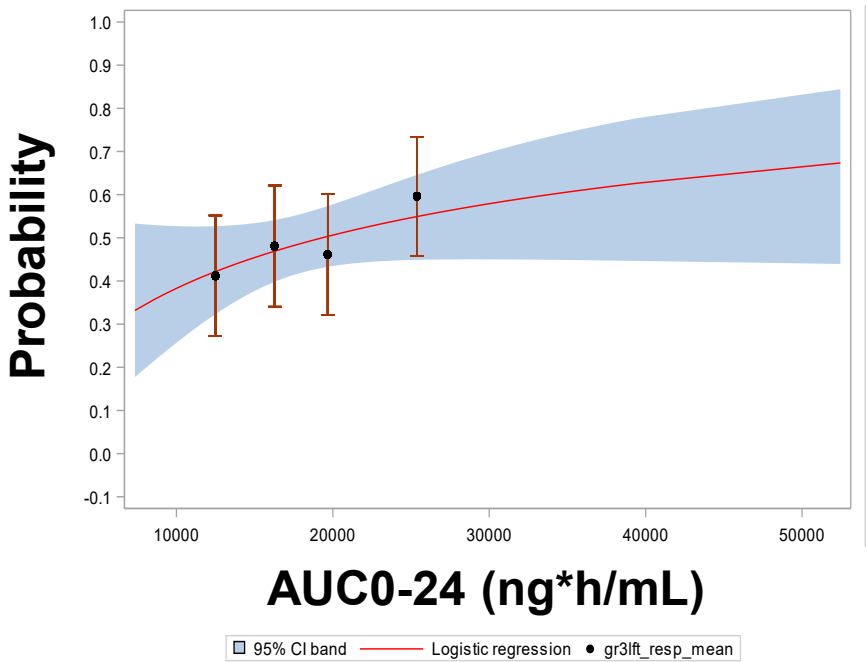
- While FDA has demonstrated its commitment to timely approval of safe and effective cancer treatments through use of earlier endpoints, survival is the paramount objective for interventions
  - **A plan for evaluating OS should be pre-specified** when designing studies even if not conducting hypothesis testing for efficacy
  - A pre-specified plan will be useful for a safety evaluation of OS, in which potential harm to patients may be adequately ruled out based on a pre-specified data cut
- **Sponsors have an obligation to demonstrate their products are safe and effective**
  - Approaches to early assessment and interpretation of OS may be useful, such as adapting trial monitoring approaches that may include:
    - Futility analyses
    - Bayesian prediction

Idelalisib Combination: E-R for Safety

Grade ≥ 3 Infection
(Study GS-US-312-0115)

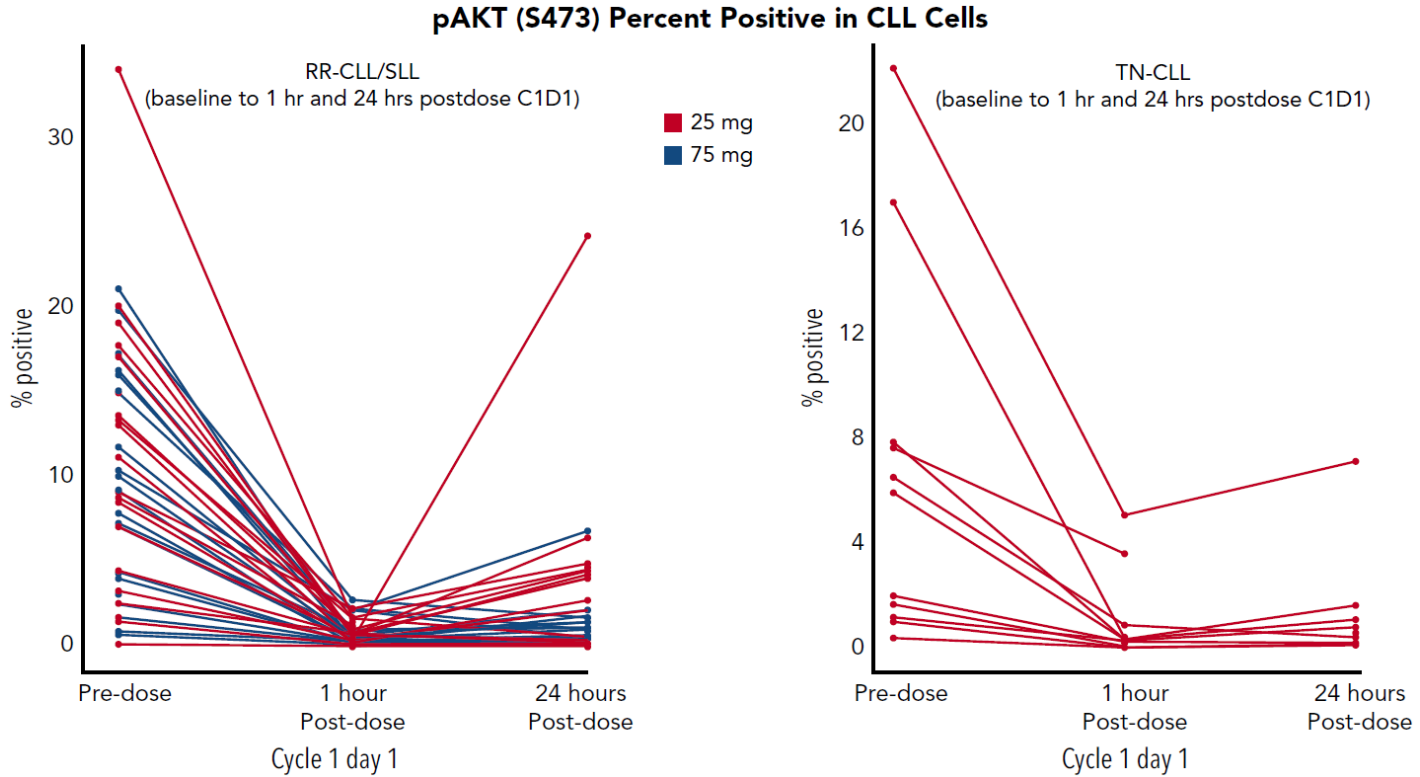


Any grade ALT/AST elevation
(Study GS-US-312-0115)



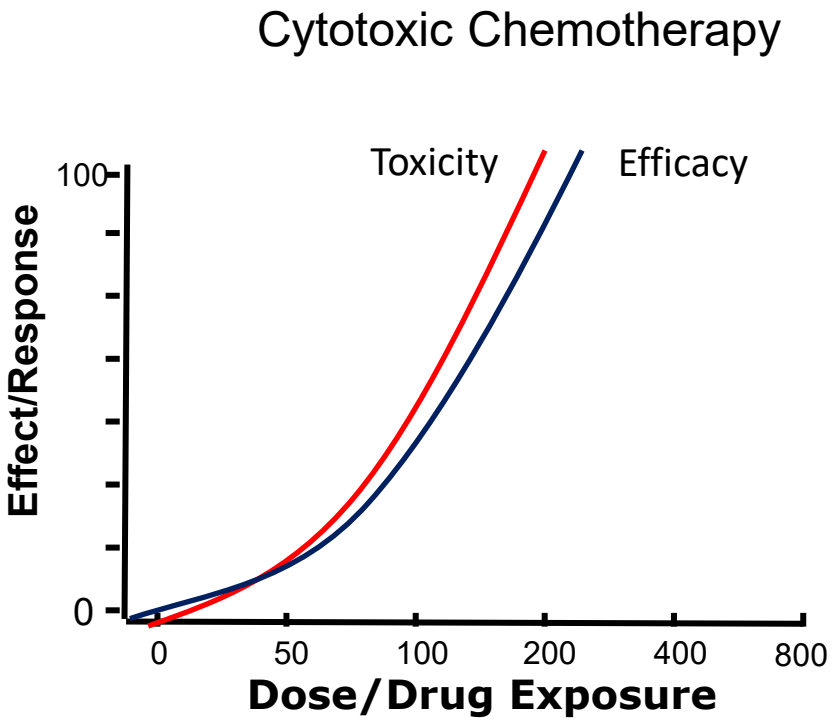
References: NDA 205858 S-6 Clinical Pharmacology Review

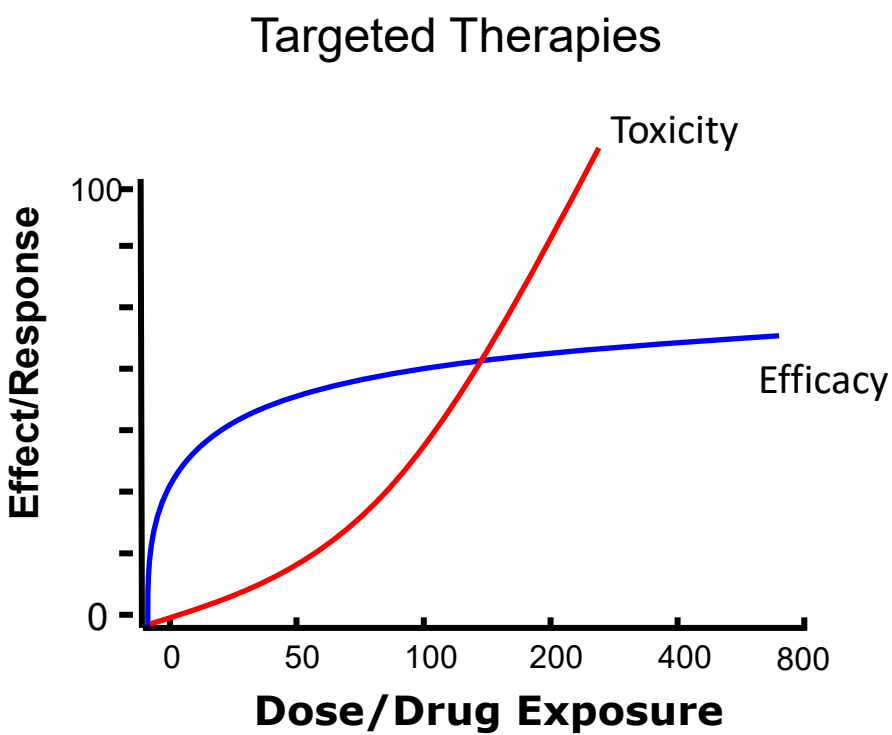
Duvelisib: PK/PD



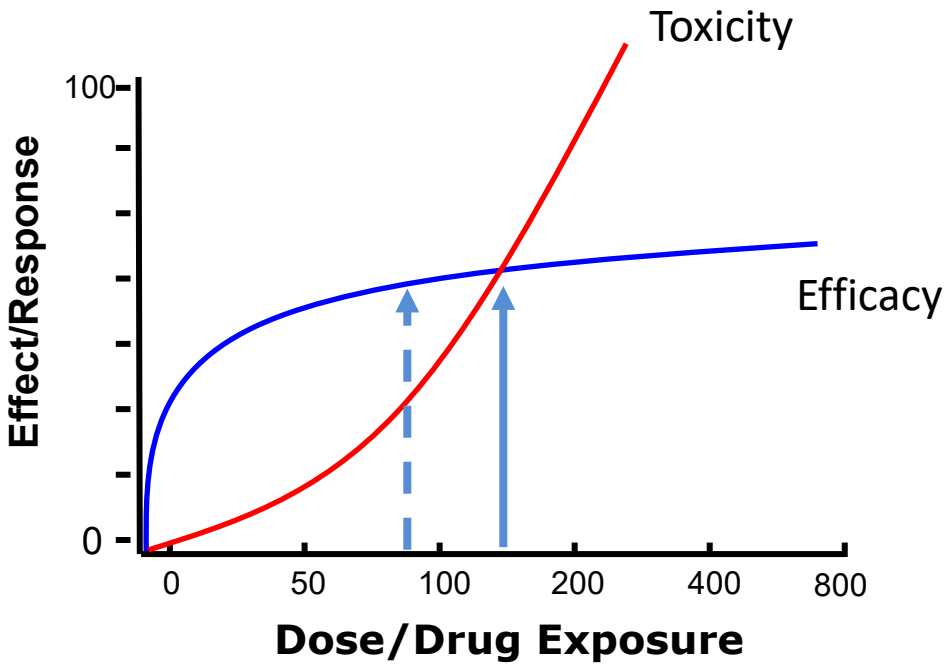
Blood. 2018 Feb 22; 131(8): 877–887.

Dose Selection for Oncology
Dose Optimization Rather Than MTD





What are the Dosing Implications for a Positive E-R for Safety, but Flat E-R Efficacy?



"More" is not always better

Efficacy may be on the plateau—increasing dose is unlikely to improve efficacy

E-R for **safety** indicates AEs are related to drug exposure

It may be possible to reduce dose without impacting efficacy while reducing AEs

Oncology Center of Excellence
Project Optimus

Mission: To ensure that doses of cancer drugs are optimized to maximize efficacy as well as safety and tolerability

Specific Goals

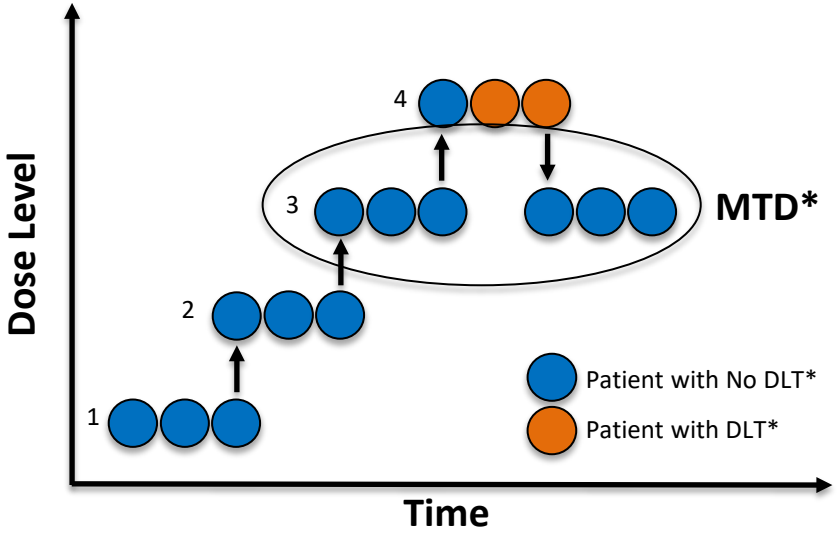
- Communicate expectations for dose-finding and dose optimization, through Guidance, workshops, other public meetings

- Provide opportunities for and encourage drug developers to meet with FDA Oncology Review Divisions early in their development programs, well before conducting trials intended for registration, to discuss dose-finding and dose optimization.

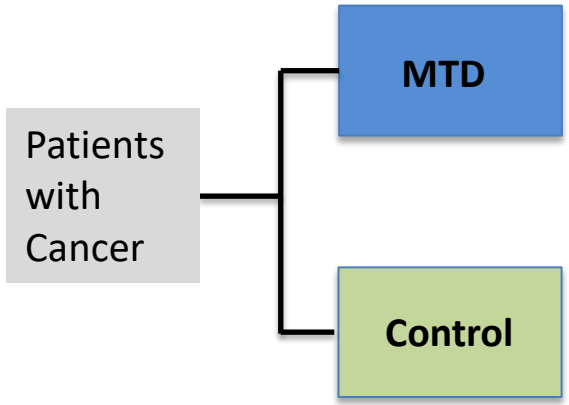
- Develop strategies for dose finding and dose optimization that leverages nonclinical and clinical data in dose selection, including randomized evaluations of a range of doses in trials. An emphasis of such strategies will be placed on performing these studies as early as possible in the development program and as efficiently as possible to bring promising new therapies to patients.

Traditional Dose Selection Strategy

Dose Escalation



Registration



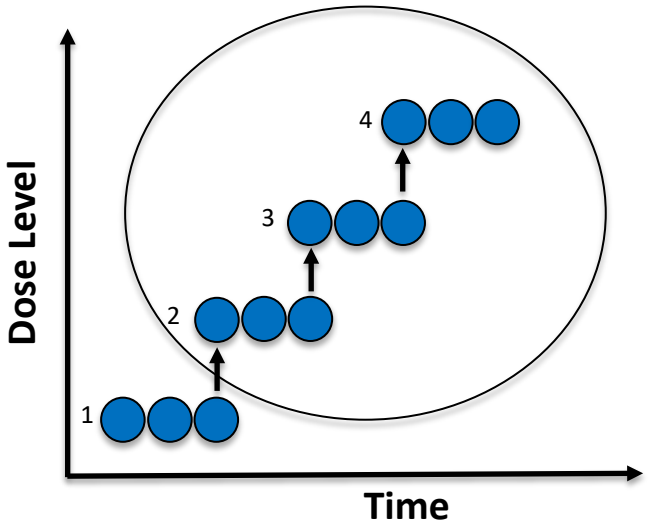
*DLT= Dose-limiting toxicity,
*MTD= Maximum tolerated dose

Hallmarks:

- Few patients at each dose
- Short observation period for DLTs
- Emphasis on DLTs, but not other safety

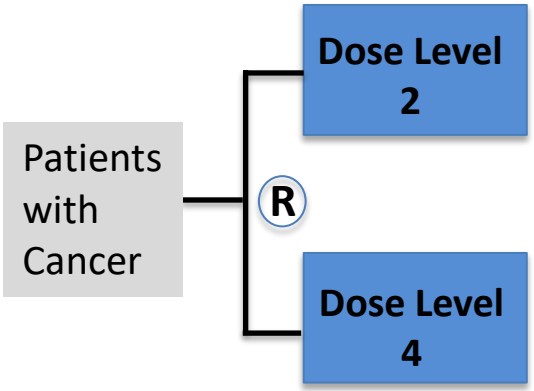
Updated: Optimized Dose Selection Strategy

Dose Escalation



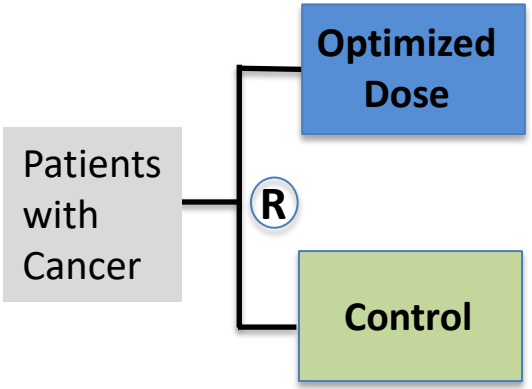
Select Dose Range

Dose Optimization



Randomized Evaluation of Several Dosages

Comparison to Standard-of-Care



Randomized Comparison to Standard-of-Care

Dose Optimization Strategies

- Give consideration to nonclinical data including in vitro/in vivo receptor occupancy/target engagement data
- Enroll sufficient patients to characterize the PK (e.g., linearity, absorption, elimination) of the drug after multiple doses
- Consider PK/PD relationships with biomarkers and study outcomes
- Utilize modeling and simulation to predict outcomes by dose level
- At the dose levels being considered, expansion of several dose cohorts may be necessary to assess activity and tolerability at other dose levels
- Randomized, parallel dose response trials may be an appropriate strategy to assess doses when feasible
- Multiple doses may be compared prior to or as a part of registration trial(s) by adding an additional dosage arm

Dose Optimization Strategies for Combinations

- Don’t simply use the approved monotherapy dose in the combination.
- Evaluate safety, efficacy, PK and E-R for efficacy/safety for each product alone first.
- For two new drugs, study multiple doses of both drugs, especially the more active drug/toxic drug
  - For add-on therapy, exploration of the approved drug may be warranted as well
- Utilize small dose escalation increments in the combination setting.
- Evaluate E-R for efficacy and safety for the combination regimen.
- Assess potential DDI which may increase systemic exposures higher than the monotherapy, especially at steady-state.