UMBRALISIB…
&
THE SAGA OF THE PI3K INHIBITORS

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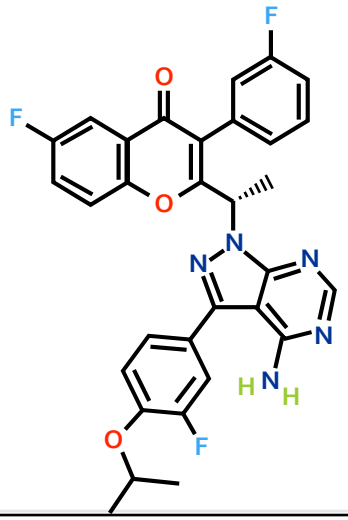
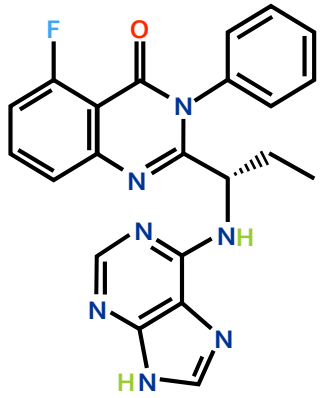
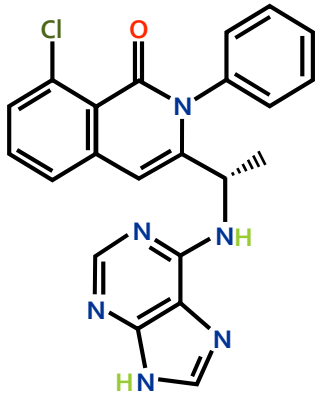
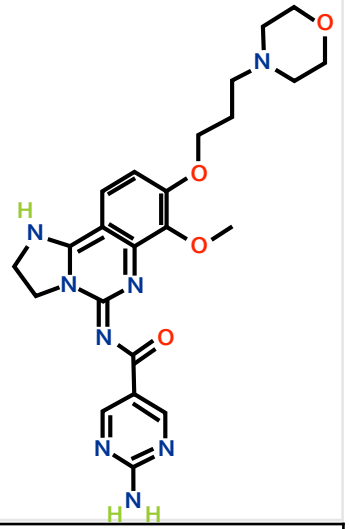
New Drugs in Hematology
Bologna, Royal Hotel Carlton
May 18-19-20, 2022

DISCLOSURE

- Research Funding: Merck, Celgene/BMS, Astex Pharmaceutical, NomoCan Pharmaceutical
- Scientific Advisory Board/ Consulting : Myeloid Therapeutics, Daiichi Sankyo, Kyowa Kirin, Kymera Therapeutics, SecuraBio

PI3K INHIBITORS OVERVIEW
Umbralisib is a Dual Inhibitor of PI3Kδ and CK1ε

Umbralisib[1]	Idelalisib[1]	Duvelisib[1]	Copanlisib[2]
			

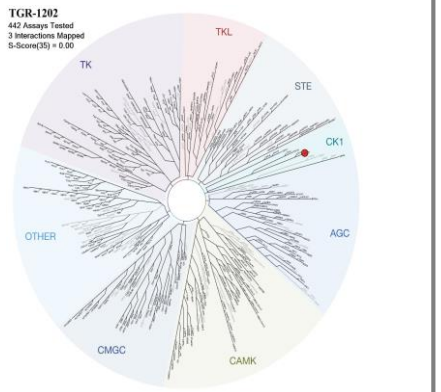
Isoform	K_d (nM)			
PI3kα	>10000	600	40	0.04
PI3Kβ	>10000	19	0.89	1.5
PI3Kγ	1400	9.1	0.21	0.31
PI3Kδ	6.2	1.2	0.047	0.068
CK1ε	180	>30,000	>30,000	>6,000

- Umbralisib is an oral, once daily, dual inhibitor of PI3Kδ and CK1ε
- Umbralisib has >1000-fold greater selectivity for PI3Kδ compared to α and β isoforms[3]
- Umbralisib also has **>200-fold** greater selectivity for PI3Kδ relative to **PI3Kγ**

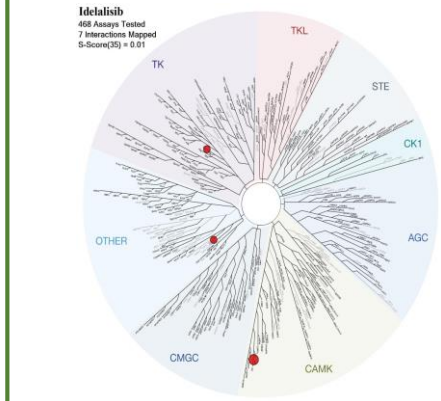
UMBRALISIB IS THE MOST SELECTIVE PI3KI AVAILABLE:

Kinome Scans Reveal Substantial Differences in PI3K Isoform Selectivity

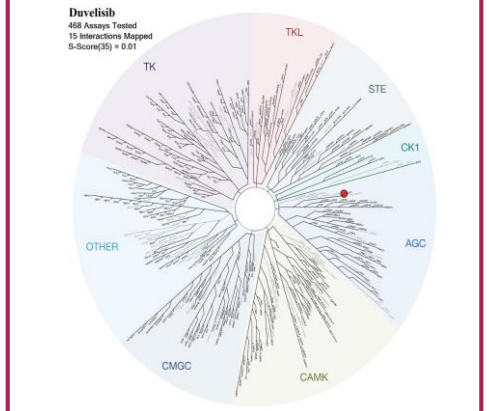
Umbralisib



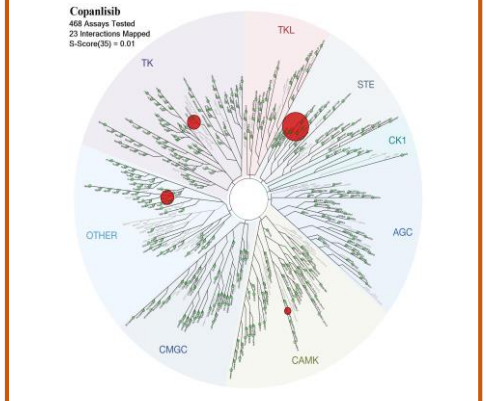
Idelalisib



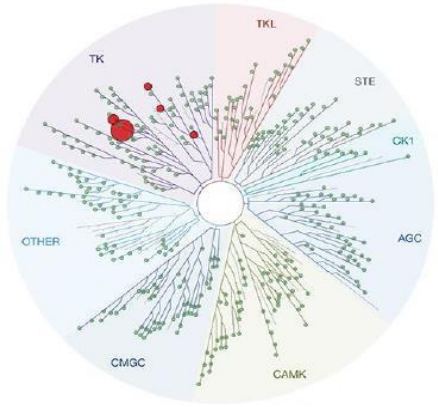
Duvelisib



Copanlisib

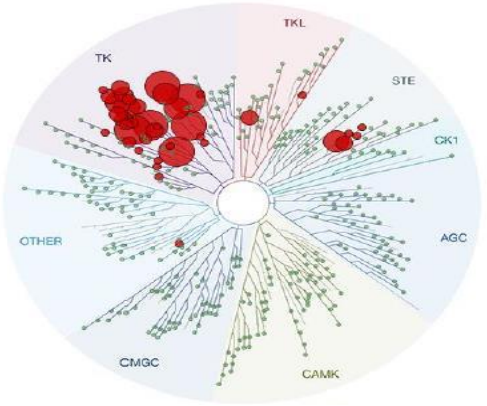


008-001-068 (Acalabrutinib) @ 1000nM



Does Anyone Doubt the More Selective Features of Acalabrutinib Don't Account for the Clinical Differences Between These Drugs?

Ibrutinib @ 1000nM



PI3K INHIBITORS: SELECTIVITY RELATES TO TOXICITY

The PI3K -δ -ɣ isoforms → express on leukocytes
Infection: pneumonia,
opportunistic infection
CMV reactivation
Immune-mediated Toxicities: important for T-lymphocytes regulatory function →hepatitis, pneumonitis, colitis, rash

→ *Younger patients & less heavily pre-treated patients higher risk!*

The PI3K-α isoform is ubiquitously expressed and essential to cellular growth and metabolism, glucose homeostasis → Hypertension & hyperglycemia

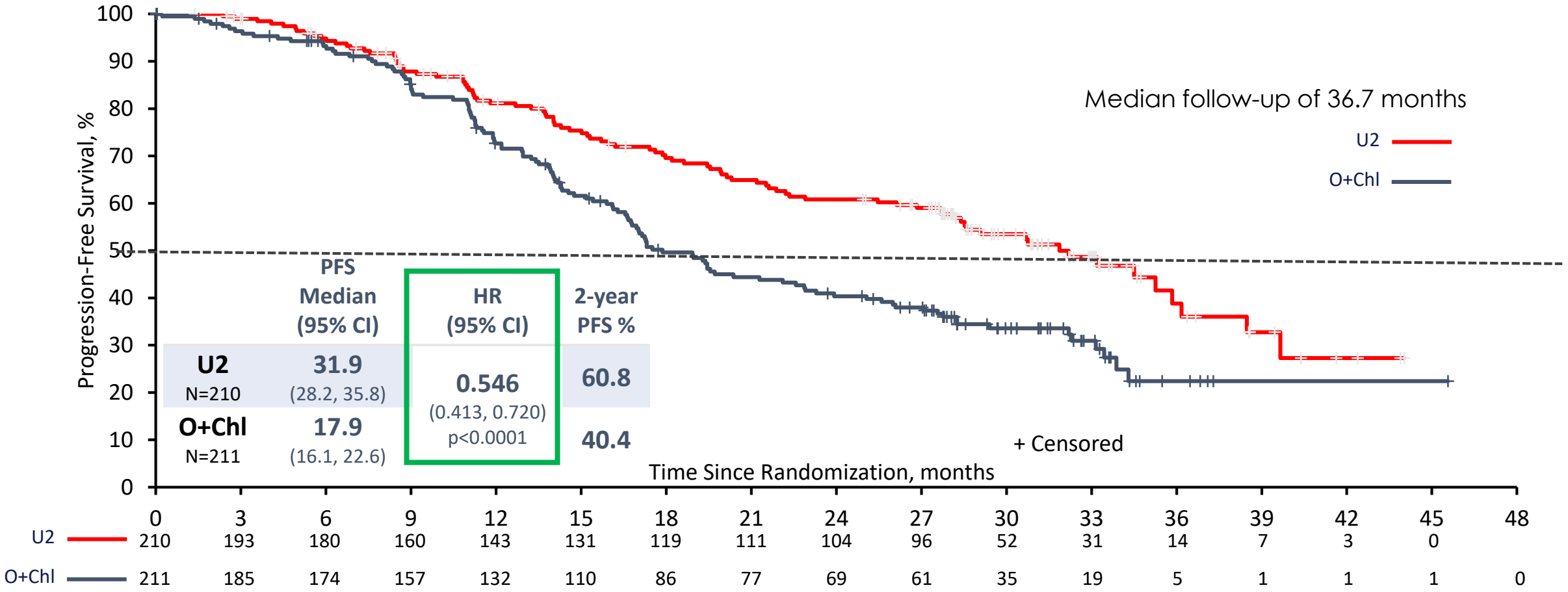
	Idelalisib (n=146)	Copanlisib (n=244)	Duvelisib (n=442)	Umbralisib (n=371)
Grade ≥ 3 AE	71%	85%	84%	51%
SAEs	50%	51%	65%	26%
Discontinuation due to AE	23%	24%	65%	26%
Dose Reduction due to AE	41%	24%	23%	10%

Grade ≥ 3	Idelalisib (n=146)	Copanlisib (n=244)	Duvelisib (n=442)	Umbralisib (n=371)
Infection	23%	23%	27%	20%
Neutropenia	28%	29%	43%	17%
Diarrhea/Colitis	14%	5%	23%	7%
AST/ALT Increase	18%	2%	8%	7%
Rash	4%	2%	9%	3%
Pneumonitis	5%	7%	7%	1%
Hyperglycemia	-	34%	-	-
Hypertension	-	29%	-	-

FDA ODAC Meeting April 2022

UNITY-CLL MET THE PRIMARY ENDPOINT OF PFS

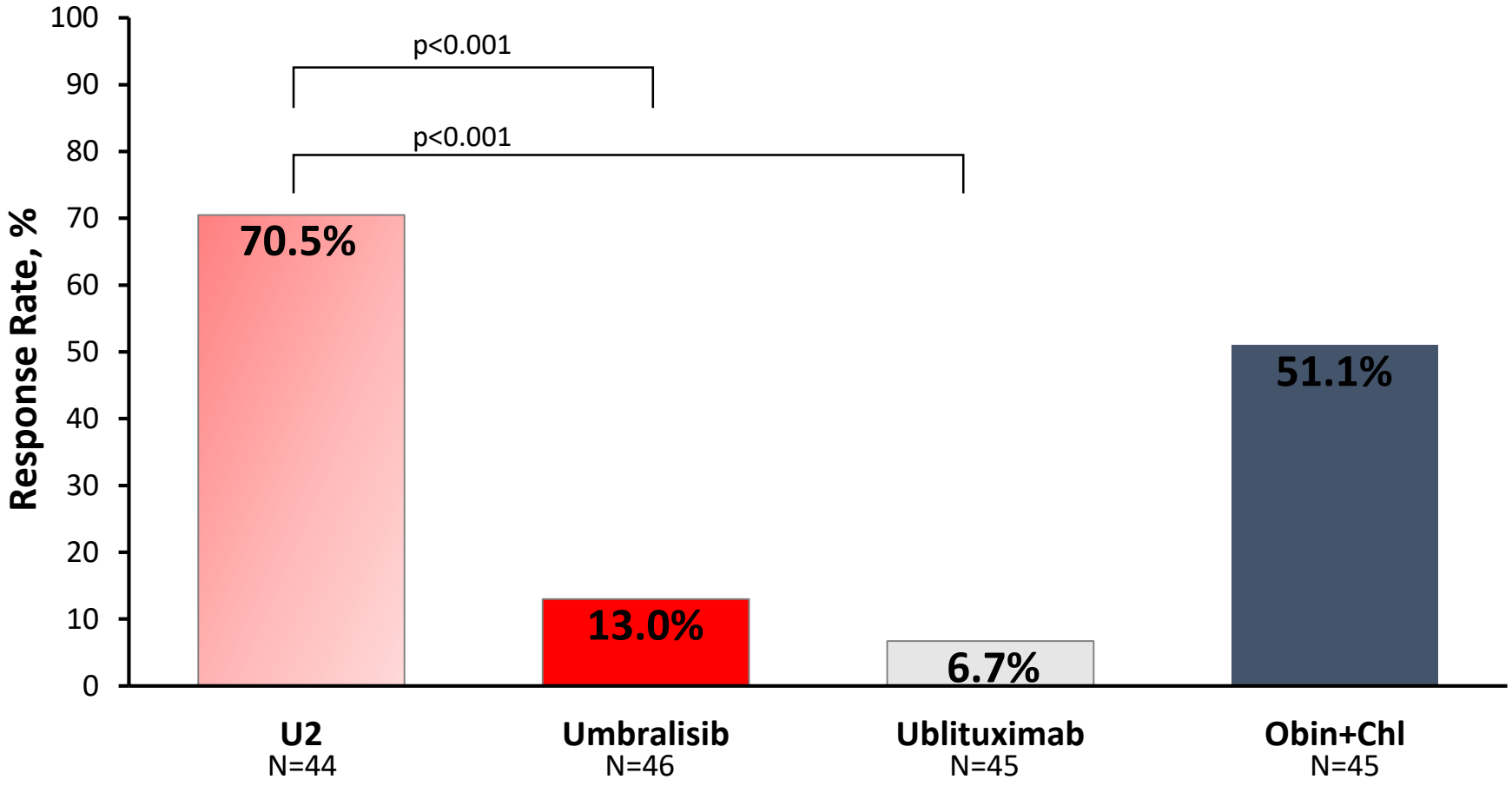
UTX-TGR-304, ITT population



Gribben et al; Blood 2020
Jacobs et al; ASH 2021
Pinilla-Ibarz et al; ASH 2021

KEY SECONDARY ENDPOINT MET WITH CLINICALLY MEANINGFUL IMPROVEMENT IN ORR

UTX-TGR-304

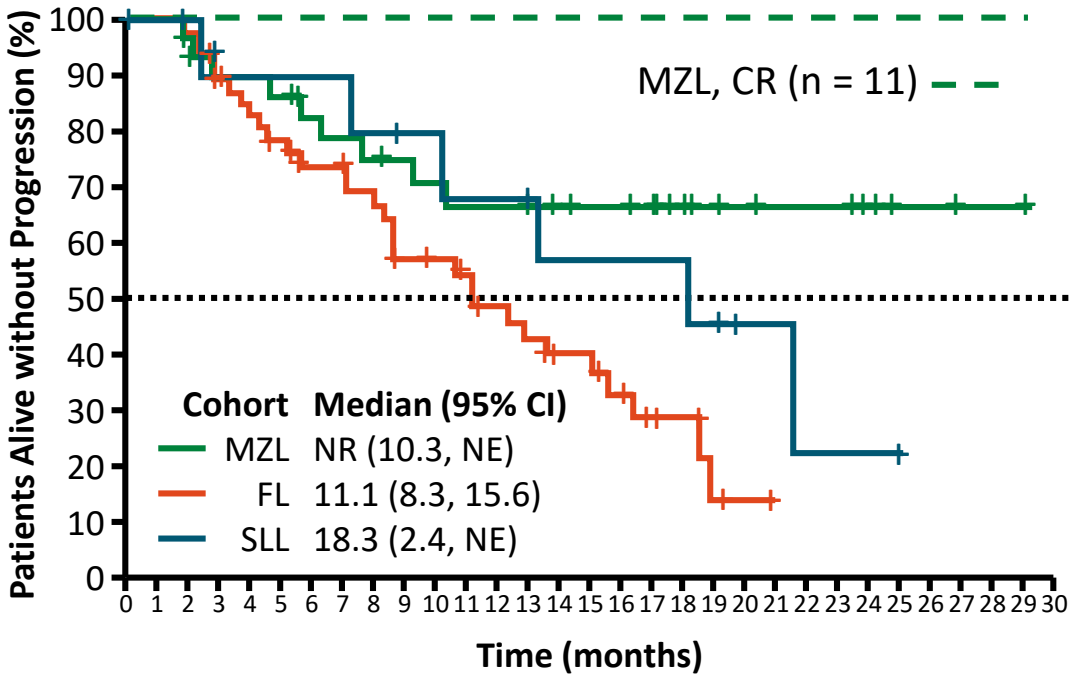


Gribben et al; Blood 2020

UNITY-NHL (iNHL Cohort):

IRC-Assessed DoR and PFS

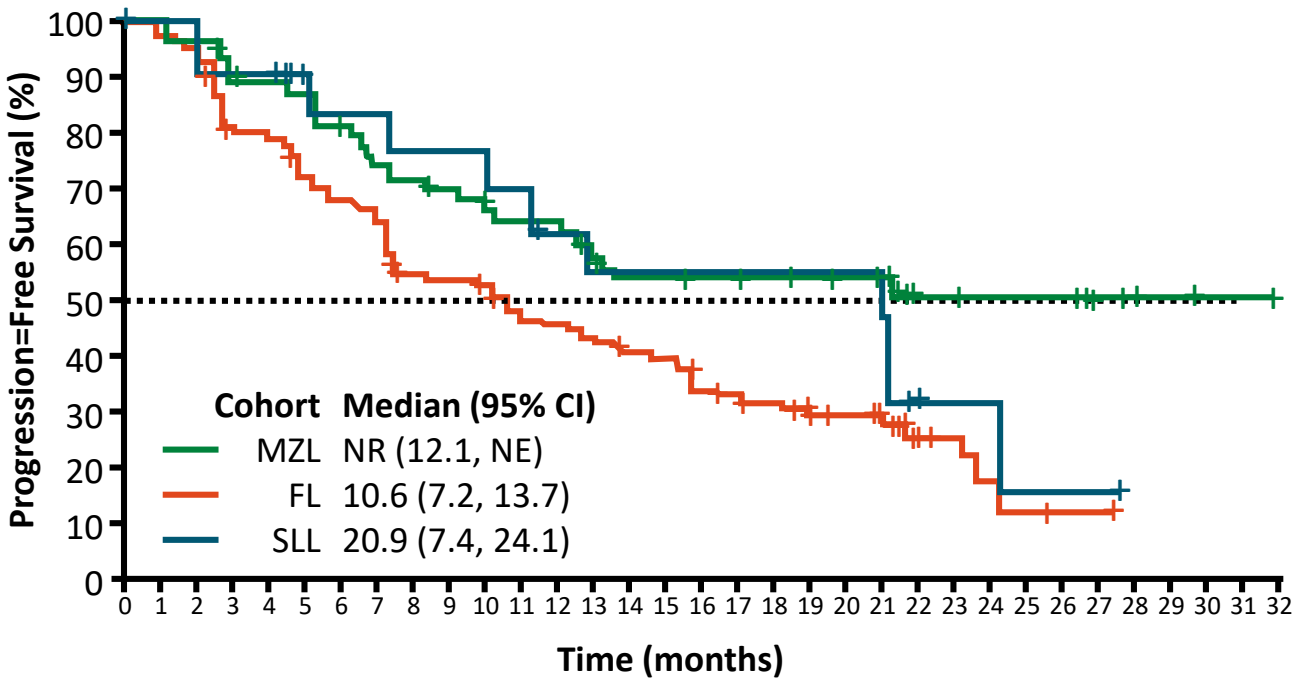
DoR



No. at risk

MZL	34	31	29	26	26	25	22	21	20	19	18	17	17	17	15	14	14	13	10	8	7	6	6	5	4	2	2	1	1	1	0
FL	53	50	49	43	39	36	32	32	28	24	23	20	17	15	12	11	9	9	5	2	1	0									
SLL	11	11	10	9	9	9	9	9	8	7	7	6	6	6	5	5	5	5	5	4	2	2	1	1	1	1	0				

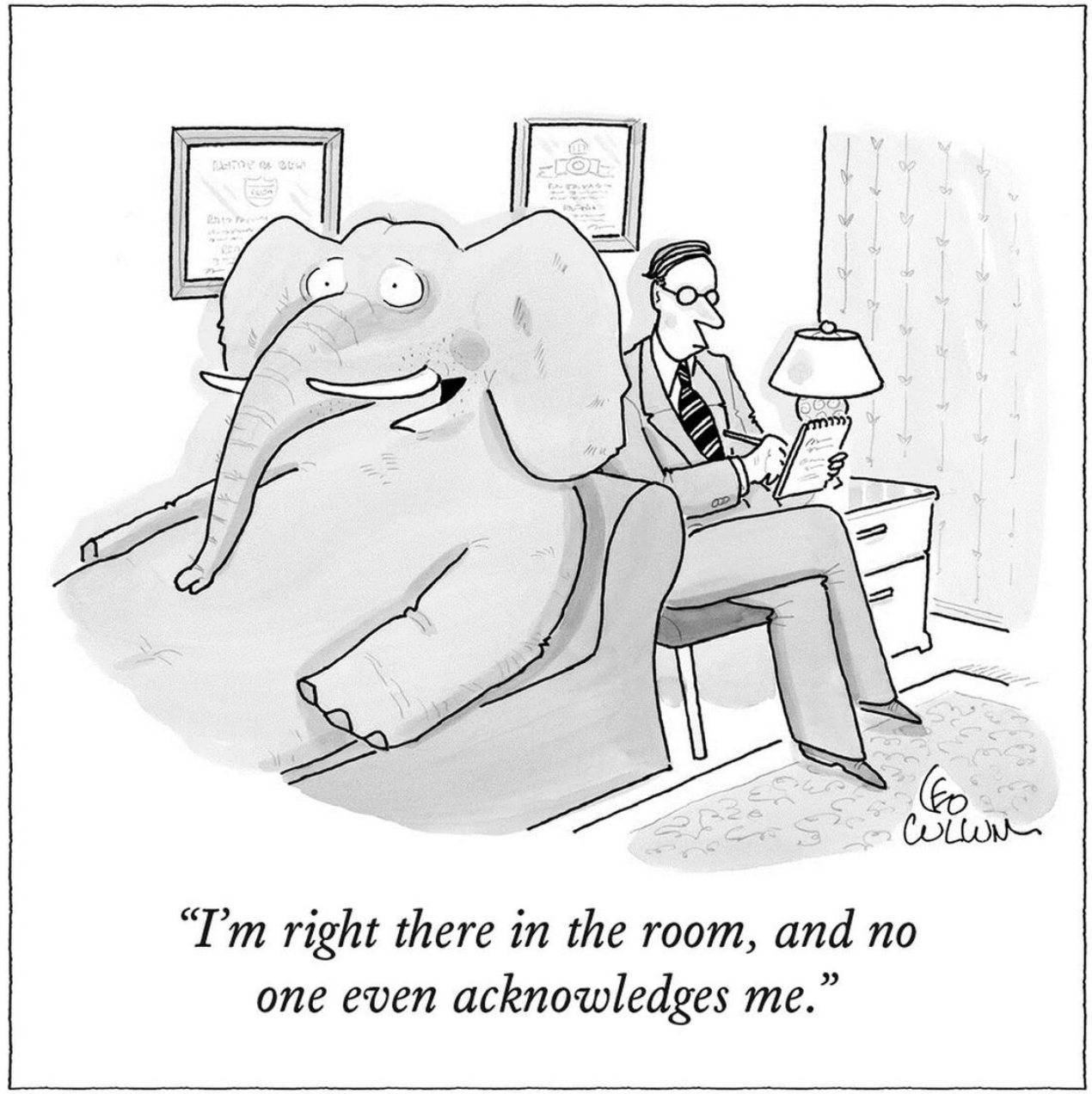
PFS



No. at risk

MZL	69	64	62	51	50	48	43	39	38	36	34	32	32	28	25	25	24	24	24	23	22	21	18	10	10	9	9	4	2	2	1	1	0
FL	117	115	111	92	90	79	73	68	56	55	53	46	44	41	37	37	28	31	28	27	22	21	17	8	7	2	1	1	0				
SLL	22	21	21	18	18	13	12	12	11	11	10	10	8	7	7	7	7	7	7	7	7	5	2	2	1	1	1	0					

Fowler NH et al; J Clin Oncol 2021



"I'm right there in the room, and no one even acknowledges me."

PI3K INHIBITORS ARE MAKING THE NEWS

January 18, 2022 | 1 min read SAVE

Gilead withdraws Zydelig indication for lymphoma, leukemia subtypes

ADD TOPIC TO EMAIL ALERTS

Gilead Sciences has decided to voluntarily withdraw its accelerated approval of idelalisib for two blood cancer indications.

The FDA in 2014 granted accelerated approval to idelalisib (Zydelig, Gilead Sciences) for treatment of relapsed follicular B-cell non-Hodgkin lymphoma and relapsed small lymphocytic leukemia.

Bayer Pulls Aliqopa Combo Filings In EU, US & Other Markets – But May Resubmit

25 Jan 2022 | NEWS

by Neena Brizmohun

@ScripRegNeena | neena.brizmohun@informa.com

Parsaclisib New Drug Application Withdrawn for Relapsed/Refractory MCL, MZL, and Follicular Lymphoma

February 1, 2022

Hayley Virgil

Secura Bio Withdraws Duvelisib Relapsed/Refractory Follicular Lymphoma Indication in the United States

December 6, 2021

Kristi Rosa

Secura Bio, Inc. has decided to voluntarily withdraw the indication of duvelisib for use in patients with relapsed or refractory follicular lymphoma following at least 2 previous systemic therapies.

Secura Bio, Inc. has decided to voluntarily withdraw the indication of duvelisib

FDA Discourages Pursuit of Marketing Authorization for Zandelisib in MZL, Follicular Lymphoma

March 25, 2022

Kristi Rosa

The FDA has discouraged the pursuit of a marketing authorization of the PI3K inhibitor zandelisib in patients with follicular lymphoma or marginal zone lymphoma, citing the need for randomized trial data.

TG Therapeutics Announces Voluntary Withdrawal of the BLA/sNDA for U2 to Treat Patients with CLL and SLL

Apr 15, 2022

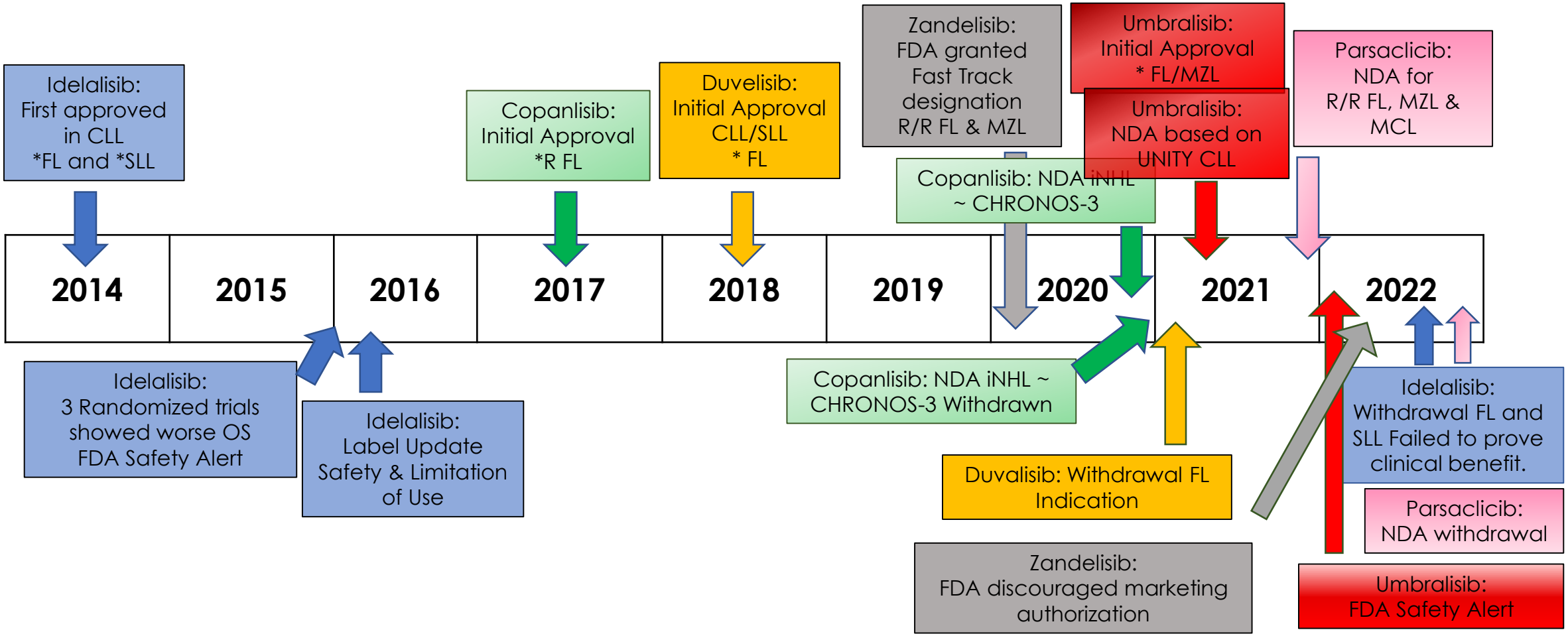
Company voluntarily withdraws UKONIQ® from sale for approved indications of relapsed/refractory MZL and FL

Company to host conference call, Monday, April 18, 2022 at 8:30 AM ET

PDF Version

THE SAGA OF PI3K INHIBITORS

FDA-Regulatory History



*FDA Granted Accelerated Approval

ACCELERATED APPROVAL PARADIGM:

APPROVAL of PI3K INHIBITORS WAS SUPPORTED BY SINGLE-ARM STUDIES

DRUGS GRANTED ACCELERATED APPROVAL in the US:

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

→ **REQUIREMENT FOR CONFIRMATORY TRIALS**

e.g. Withdrawal for idelalisib and duvelisib for inability to complete the confirmatory study

→ FDA requires overall survival information in any trial that uses PFS as primary endpoint

OS is an objective measure of clinical benefit

OS is an efficacy and safety endpoint → encompasses toxicity and does not require statistical considerations when used

Food and Drug Administration

Federal agency

FDA ODAC MEETING (April 2022): MULTIPLE RANDOMIZED TRIALS WITH CONCERNING OS

STUDY	POPULATION & TREATMENT	Deaths PI3K Arm	Death Control Arm	Hazard Ratio
321-0123	• Untreated CLL • Bendamustine and Rituximab ± Idelalisib	8% (12/157)	3% (4/154)	3.34 (1.08 ,10.39)
313-0124	• Previously treated iNHL • Rituximab ± Idelalisib	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
313-0125	• Previously treated iNHL • 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% (70/149)	1.09 (0.79, 1.51)
CHRONOS-3	• Previously treated iNHL • Rituximab ± Copanlisib	18% (80/160)	21% (32/151)	0.87 (0.57, 1.35)
UNITY-CLL	• Untreated and previously treated CLL • Umbralisib + Ublituximab vs Obinotuzumab + Chlorambucil	-	-	1.23

FDA ODAC Meeting April 2022

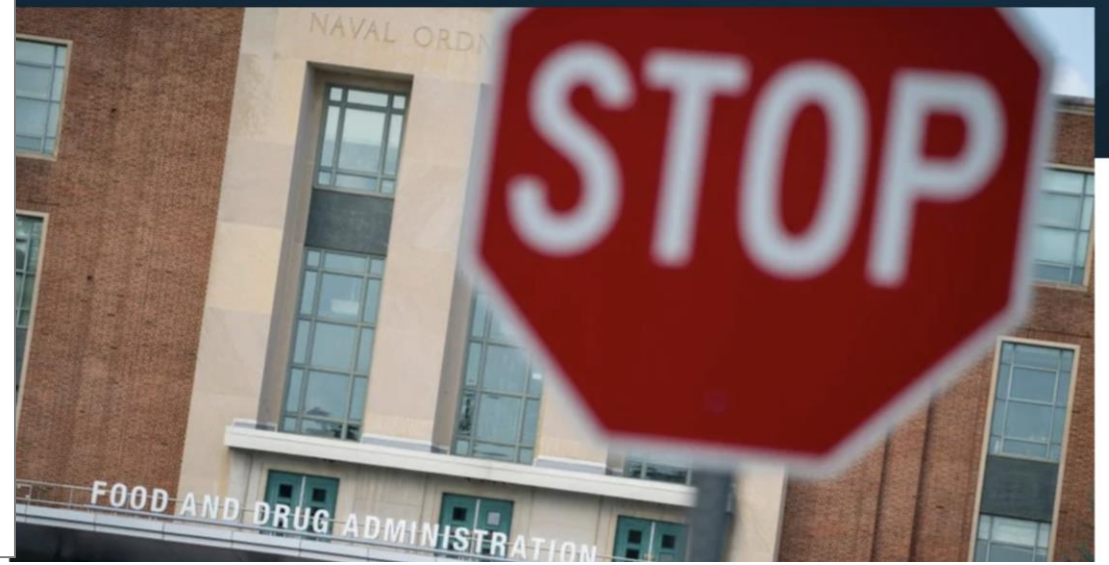
FDA MANDATES RANDOMIZED DATA TO SUPPORT APPROVAL OF PI3K INHIBITORS IN HEMATOLOGIC MALIGNANCIES

PHARMA

As safety signals mount, FDA aims to crack down on PI3K blood cancer nods

By **Angus Liu** · Apr 20, 2022 09:57am

U.S. FDA | PI3K | non-Hodgkin lymphoma | blood cancer



FDA's ODAC Casts Unanimous Vote for Randomized Data to Support PI3K Inhibitor Approvals in Hematologic Malignancies

April 22, 2022
Hayley Virgil

A unanimous vote cast by the FDA's Oncologic Drugs Advisory Panel highlighted a need for randomized clinical trial data to support FDA approvals of PI3K inhibitors for patients with hematologic malignancies.

WHERE DO WE GO FROM HERE?
Open Questions

- Should we require randomized trials in orphan blood cancers for registration?
- Is OS a good endpoint for these study?
- How do we leverage Covid impact in the future generation of trials?
- How are we going to advance the field in rare diseases?

"Sure, I fooled around with drugs when I was your age, but that was to protest the war."

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All Our PATIENTS and THEIR FAMILIES

Food and Drug Administration
Federal agency

FDA

MAYO CLINIC

Mount Sinai

Yale University

Veterans Health Administration

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

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AHN

THANK YOU!