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THE ROLE OF PI3K INHIBITORS IN NON-HODGKIN'S LYMPHOMA

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PI3K PATHWAY IN B-CELL MALIGNANCIES

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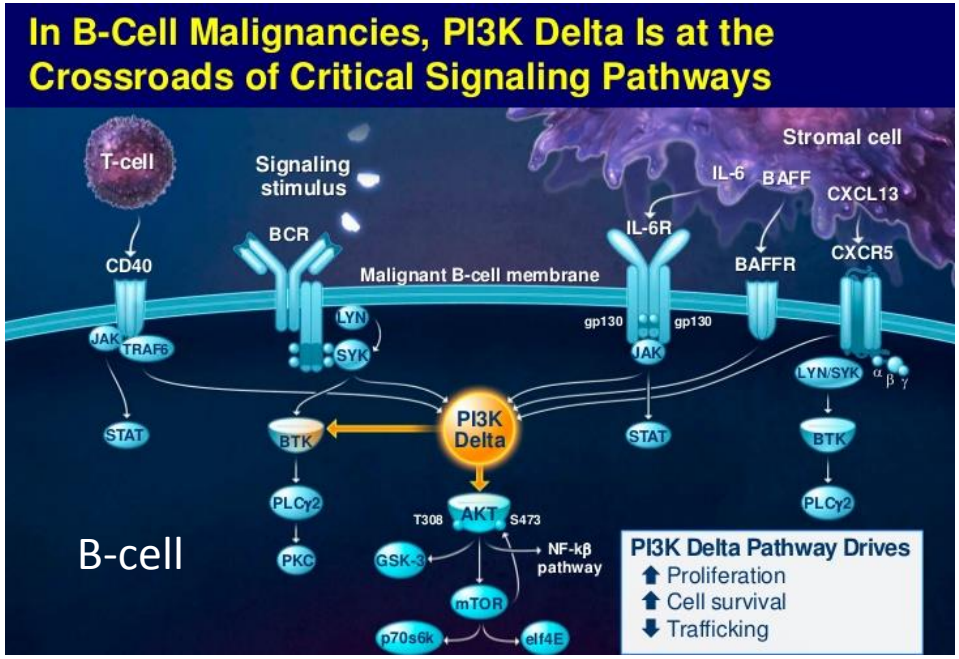
- Phosphoinositide 3-kinase (PI3K) is a lipid kinase whose catalytic subunit has four isoforms: α, β, γ, and δ. The α- and β-isoforms are widely expressed in many tissues[1]
- In B-lymphocytes, the δ-isoform (PI3Kδ) plays a central role in normal B-cell development and function. This pathway is frequently hyperactive in B-cell cancers, making PI3Kδ a promising target for the therapy of indolent non-Hodgkin's lymphoma[1]
- Targeted inhibition of the PI3K pathway has emerged as a therapeutic strategy for B-cell malignancies with three FDA-approved agents and several others being explored
  - While the δ-isoform has remained the main target for most molecules in this class of drug, evaluation of other isoforms have increased due to concern about resistance to treatment being mediated by alternative isoforms[2]



FDA, Food and Drug Administration; PI3K, phosphoinositide 3-kinase

1. Gopal AK, et al. N Engl J Med 2014;370:1008-1018; 2. Wang X, et al. Acta Pharmacol Sin 2015;36(10):1170-1176

IDELALISIB

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- The first approved agent for this class was the PI3Kδ-isoform specific inhibitor, idelalisib
- Approved in 2014 for 3rd-line treatment of patients with relapsed FL or relapsed SLL based on the results of the phase 2 "DELTA" study[1,2]
- This study enrolled 125 patients with indolent lymphoma, with FL and SLL compromising the majority of the patients[1]

FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase; SLL, small lymphocytic lymphoma

1. Gopal AK, et al. N Engl J Med 2014;370:1008-1018; 2. idelalisib prescribing information 2018

IDELALISIB RESPONSE DATA

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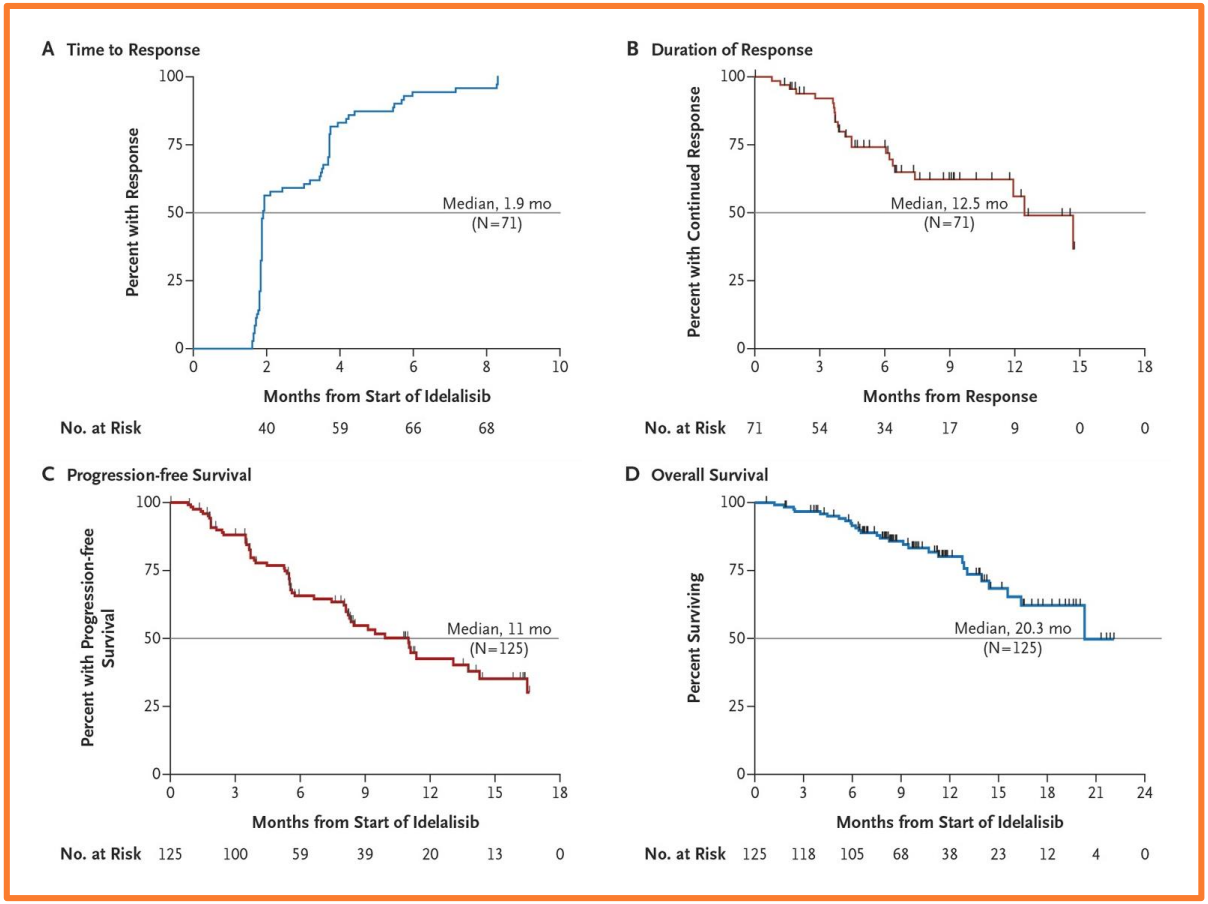
Kaplan–Meier Curves for Secondary End Points[1]

- Responses were noted across all subtypes, with a **median DOR** of 12.5 months and a **median PFS** of 11.0 months[1]
- The **median OS** was 20.3 months[1]



DOR, duration of response; Mo, months; OS, overall survival; PFS, progression-free survival

1. Gopal AK, et al. N Engl J Med 2014;370:1008-1018

IDELALISIB RESPONSE DATA

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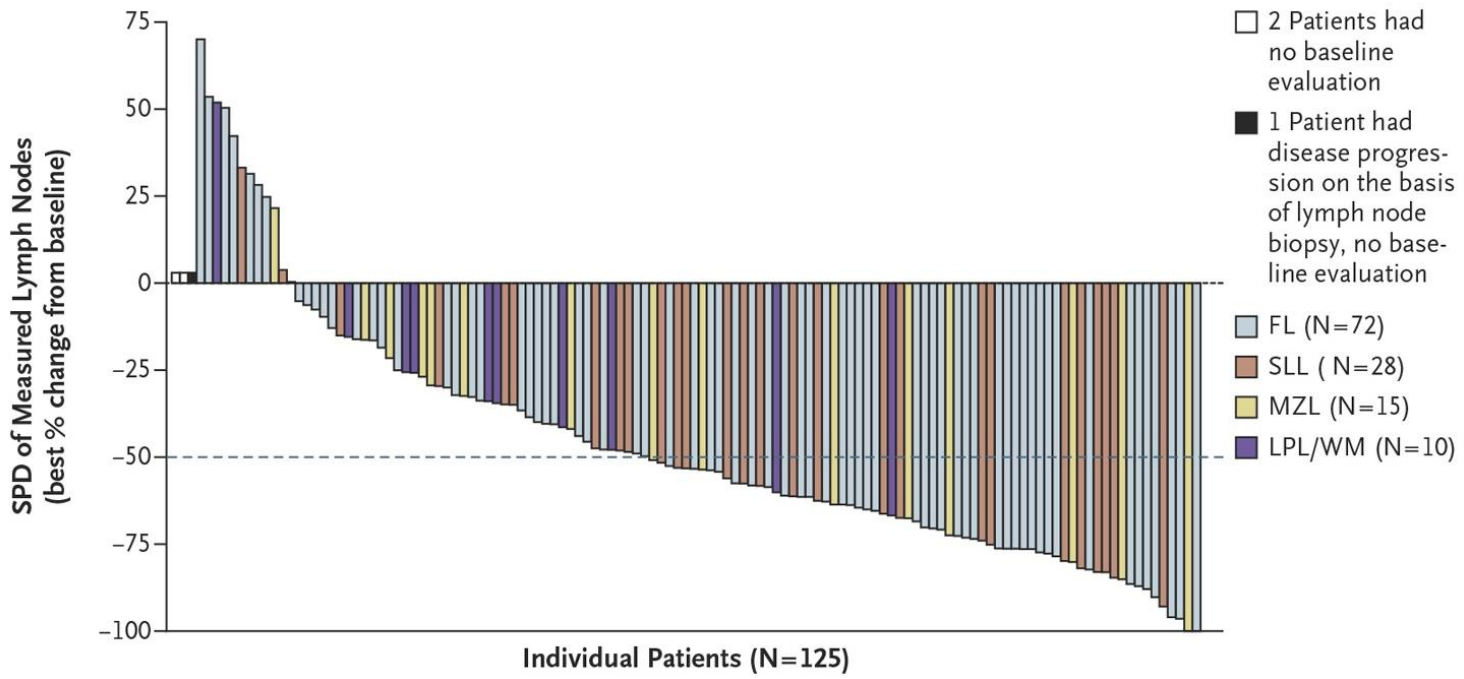
Best Overall Response[1]



- The **ORR** was 57% (CR: 6%; PR: 50%)[1]

CR, complete response; FL, follicular lymphoma; LPL/WM, lymphoplasmacytic lymphoma with or without Waldenström's macro-globulinemia; MZL, marginal-zone lymphoma; ORR, overall response rate; PR, partial response; SLL, small lymphocytic lymphoma; SPD, sums of the products of the perpendicular dimensions

1. Gopal AK, et al. N Engl J Med 2014;370:1008-1018

IDELALISIB AE PROFILE[1]

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- The **most common AEs** during the trial were diarrhea, fatigue, nausea, cough, fever, transaminitis and neutropenia
  - The most common grade ⩾3 AEs were diarrhea (colitis), pneumonia, and dyspnea
- **Onset of AE** was notable for grade ⩾3 transaminitis (median 6.3 weeks from treatment start) and grade ⩾3 diarrhea (median 6 months)
- The **clinical experience** with respect to the AE profile has mirrored the data reported in the trial, with the exception of a higher incidence of additional autoimmune manifestations (pneumonitis, rash, etc.) and infection in the "real world" experience. This has limited the utilization of idelalisib in spite of the efficacy of the agent

Adverse Events during Treatment*

Event or Abnormality	Grade	
	Any no. (%)	⩾3 no. (%)
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

*Included are adverse events and selected laboratory abnormalities that occurred during treatment in 10% or more of the 125 patients in the study, regardless of whether the event was related to the study drug. AE, adverse event; ALT, alanine aminotransferase; AST aspartate aminotransferase

1. Gopal AK, et al. N Engl J Med 2014;370:1008-1018

COPANLISIB

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- Copanlisib was approved in 2017 for patients with relapsed FL who have received at least two prior lines of therapy
- This was based on data from the "CHRONOS-1" trial[1]. It was recently granted breakthrough designation for relapsed MZL based on data from this trial. Unlike others in the class, copanlisib is a pan-PI3K inhibitor with greatest specificity for the α-, and δ-subtypes (Table)
- In addition to having a unique specificity, copanlisib differs from other targeted agents in the same class with regard to IV versus oral administration and intermittent (3w on; 1w off) versus daily dosing

Comparative Potency and Isoform Selectivity*

	Parsaclisib[2]	Copanlisib[3]	Idelalisib[4]	Umbralisib[5]
PI3Kδ IC_{50}, nM	1	0.7	2.5	22
Fold selectivity				
PI3Kα	~20,000	0.5	820	>10,000
PI3Kβ	~20,000	3.7	565	>50
PI3Kγ	~20,000	6.4	89	>48

*Biochemical assay.

FDA, Food and Drug Administration; FL, follicular lymphoma; IC, inhibitory concentration; IV, intravenous; PI3K, phosphatidylinositol 3-kinase; MZL, marginal zone B-cell lymphoma; W, week

1. Dreyling M, et al. J Clin Oncol 2017;35:3898-3905; 2. Shin N, et al. AACR 106th Annual Meeting. April 18–22, 2015; Philadelphia, PA, USA. Abstract 2671; 3. Liu N, et al. Mol Cancer Ther 2013;12:2319-2330; 4. Lannutti BJ, et al. Blood 2011;117:591-594; 5. Burris HA, et al. Lancet Oncol 2018;19:486-496

COPANLISIB RESPONSE DATA

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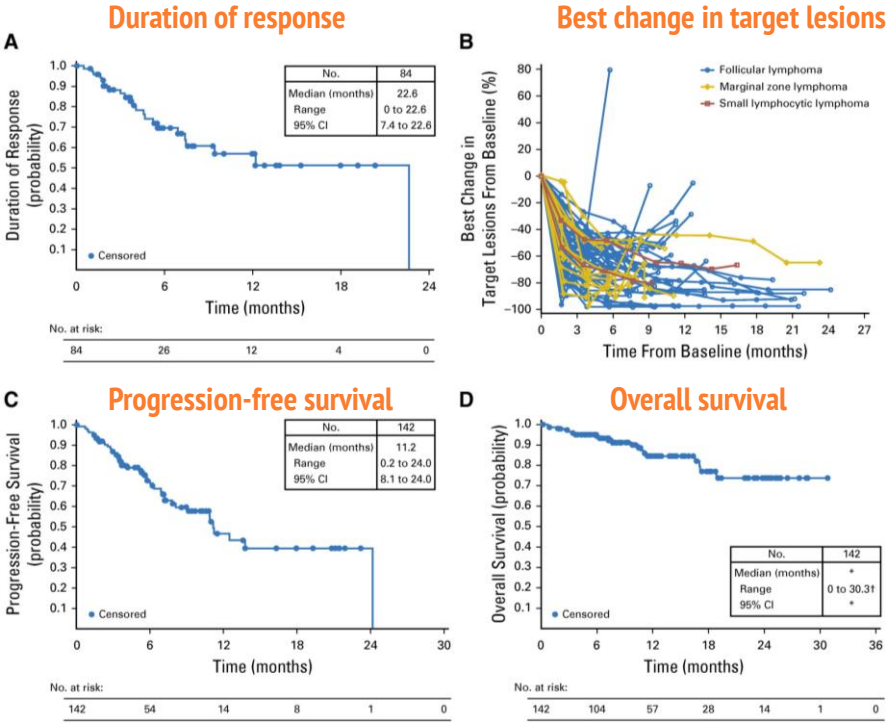
- The **CHRONOS-1** trial enrolled a total of 142 patients with R/R indolent lymphoma[1,2]
- The study demonstrated impressive efficacy (**ORR:** 61%), specifically in patients with FL (ORR: 59%; CR: 20%; PR: 39%)[1]
- The **overall median DOR** was 14.1 months, with patients with FL achieving a median DOR of 12.2 months[1]
- The **median PFS** was 12.5 months for all patients[1]



Secondary efficacy end points (June 2016 data cutoff)[2]. A. duration of response; **B.** change in the sum of longest diameter of target lesions over time for patients with at least PR as the best response; **C.** progression-free survival; **D.** overall survival as assessed by independent review for the full analysis set. (*) Not evaluable. (†) Censored observation.

CI, confidence interval; CR, complete response; DOR, duration of response; FL, follicular lymphoma; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory

1. Dreyling M, et al. Blood 2018;132: Abstract 1595; 2. Dreyling M, et al. J Clin Oncol 2017;35:3898-3905

COPANLISIB RESPONSE DATA

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RESPONSE (FULL ANALYSIS SET; JUNE 2016 DATA CUTOFF)[1]

Best response	Tumor, No. (%)				
	FL (n=104)	MZL (n=23)	SLL (n=8)	LPL/WM (n=6)	Total (N=142)*
Complete response	15 (14)	2 (9)	0	0	17 (12)
Partial response	46 (44)	14 (61)	6 (75)	1 (17)	67 (47)
Stable disease	35 (34)†	4 (17)	1 (13)	3 (50)	43 (30)†
Progressive disease	2 (2)	0	1 (13)	0	3 (2)
Not evaluable	0	1 (4)	0	0	1 (< 1)
Not available‡	6 (6)	2 (9)	0	2 (33)	11 (8)
Objective response rate 95% CI§	61 (59) 49 to 68	16 (70) 47 to 87	6 (75) 35 to 97	1 (17) 0.4 to 64	84 (59) 51 to 67
Disease control rate¶ 95% CI§	91 (88) 80 to 93	20 (87) 66 to 97	7 (88) 47 to 100	4 (67) 22 to 96	122 (86)¶ 79 to 91

*One patient with diffuse large B-cell lymphoma was included because the initial investigator assessment was indolent non-Hodgkin lymphoma, which was later confirmed by the investigator and central pathology review to be diffuse large B-cell lymphoma.
†Includes one patient with unconfirmed early stable disease (stable disease was assessed <7 weeks after start of treatment).
‡Of the full analysis set of 142 patients, data for 11 (8%) were not available for the analysis of the primary efficacy variable (objective response rate).
§95% CIs by exact binomial calculation.
¶One patient with unconfirmed stable disease and four with stable disease or partial response recorded >35 days form the last treatment were excluded from the calculation.

CI, confidence interval; FL, follicular lymphoma; LPL/WM, lymphoplasmacytoid lymphoma/Waldenstrom macroglobulinemia; MZL, marginal zone lymphoma; SLL, small lymphocytic lymphoma

1. Dreyling M, et al. J Clin Oncol 2017;35:3898-3905

COPANLISIB AE PROFILE[1]

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- The **most common treatment-related AEs** noted during the clinical trial were transient hyperglycemia and transient hypertension (both are drug-specific AEs related to copanlisib's PI3kα inhibition)
  - Additional AEs included diarrhea, fatigue, neutropenia and fever
- The highest incidence of grade 3/4 events (other than hyperglycemia or hypertension) were neutropenia and lung infections
- SAEs included lung infection (13%), hyperglycemia (5%), neutropenia (4%), fever (3%) and diarrhea (2%)
- Non-infectious pneumonitis was reported in 11 patients and colitis in 1 patient

Summary of Common Treatment-Emergent Adverse Events (June 2016 data cutoff)

	Grade, No. (%)			
Adverse event	**All**	**3**	**4**	**5**
Any treatment-emergent adverse event	140 (99)	75 (53)	38 (27)	6 (4)
Nonhematologic toxicities				
Hyperglycemia	71 (50)	48 (34)	10 (7)	0
Diarrhea	48 (34)	7 (5)	0	0
Fatigue	43 (30)	3 (2)	0	0
Hypertension	43 (30)	34 (24)	0	0
Fever	36 (25)	6 (4)	0	0
Nausea	33 (23)	1 (1)	0	0
Lung infection	30 (21)	18 (13)	3 (2)	2 (1)
Oral mucositis	28 (20)	4 (3)	0	0
Upper respiratory infection	26 (18)	4 (3)	0	0
Cough	23 (16)	0	0	0
Maculopapular rash	18 (13)	1 (1)	0	0
Constipation	17 (12)	0	0	0
Bronchial infection	16 (11)	2 (1)	0	0
Flu-like symptoms	16 (11)	1 (1)	0	0
Anorexia	15 (11)	0	0	0
Skin infection	15 (11)	1 (1)	0	0
Hematologic toxicities				
Decreased neutrophil count	42 (30)	11 (8)	23 (16)	0
Decreased platelet count	29 (20)	9 (6)	1 (1)	0
Anemia	22 (15)	6 (4)	0	0
Adverse events of special interest				
Pneumonitis (noninfectious)	11 (8)	2 (1)	0	0
Colitis	1 (1)	0	1 (1)	0
Laboratory toxicities				
Elevated AST*	39 (28)	1 (1)	1 (1)	0
Elevated ALT*	32 (23)	1 (1)	1 (1)	0

NOTE: Includes adverse events in ≥10% of the 142 patients who received treatment.
*One patient missing.

AE, adverse event; ALT, alanine aminotransferase; AST aspartate aminotransferase; SAE, serious AE

1. Dreyling M, et al. J Clin Oncol 2017;35:3898-3905

DUVELISIB

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- Duvelisib was approved in 2018 for treatment of patients with R/R CLL or SLL after at least two prior therapies
- Duvelisib is a dual inhibitor of the PI3Kδ and γ-isoforms, with an IC_{50} of 2.5 and 27 nM respectively[1]
- The **"DYNAMO" trial** led to the approval for R/R FL after at least two prior therapies
  - 129 patients with R/R indolent lymphoma[2]
  - This study demonstrated safety and efficacy data on par with idelalisb, with an **ORR** of 47.3% and subset-specific responses of 42.2% in FL and 67.9% in SLL[2]
  - AEs of special interest were: diarrhea (48.8%), colitis (7.8%), transaminitis (10.1%), pneumonitis (7.8%), and infection (2.3%)[2]
  - For the entire study cohort the **median DOR** was 10 months and the **median PFS** was 9.5 months[2]
  - These results are illustrated on the following slides

AE, adverse event; CLL, chronic lymphocytic leukemia; DOR, duration of response; FL, follicular lymphoma; IC, inhibitory concentration; PI3K, phosphoinositide 3-kinase; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma

1. Winkler DG, et al. Chem Biol 2013;20:1364-1374; 2. Flinn IW, et al. J Clin Oncol 2019;37:912-922

DUVELISIB RESPONSE DATA (FULL ANALYSIS SET)[1]

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Efficacy	Response by IRC, N. (%)	Response by investigator, No. (%)
All patients (N=129)		
ORR (CR + PR) 95% Exact binomial CI	61 (47.3) 38.4 to 56.3	77 (59.7) 50.7 to 68.2)
Best response		
CR	2 (1.6)	4 (3.1)
PR	59 (45.7)	73 (56.6)
SD	42 (32.6)	38 (29.5)
PD	18 (14.0)	8 (6.2)
Unknown	7 (5.4)	6 (4.7)
No evidence of disease*	1 (0.8)	0
Median DOR by IWG, months 95% CI	10.0 6.3 to 10.5	10.0 6.5 to 12.5
Median PFS, months 95% CI	9.5 8.1 to 11.8	10.0 8.3 to 11.7
Median OS, months 95% CI	28.9 21.4 to NE	– –
Median TTR, months Range	1.87 1.4-11.7	1.87 1.0-12.3
Follicular lymphoma (n=83)		
ORR (CR + PR) 95% Exact binomial CI	35 (42.2) 31.4 to 53.5	44 (53.0) 41.7 to 64.1
Best response		
CR	1 (1.2)	2 (2.4)
PR	34 (41.0)	42 (50.6)
SD	29 (34.9)	28 (33.7)
PD	14 (16.9)	7 (8.4)
Unknown	5 (6.0)	4 (4.8)

Efficacy	Response by IRC, N. (%)	Response by investigator, No. (%)
Small lymphocytic lymphoma (n=28)		
ORR (CR + PR) 95% Exact binomial CI	19 (67.9) 47.6 to 84.1	24 (85.7) 67.3 to 96.0
Best response		
CR	0	1 (3.6)
PR	19 (67.9)	23 (82.1)
SD	4 (14.3)	3 (10.7)
PD	3 (10.7)	0
Unknown	1 (3.6)	1 (3.6)
No evidence of disease*	1 (3.6)	0
Marginal zone B-cell lymphoma (n=18)		
ORR (CR + PR) 95% Exact binomial CI	7 (38.9) 17.3 to 64.3	9 (50.0) 26.0 to 74.0
Best response		
CR	1 (5.6)	1 (5.6)
PR	6 (33.3)	8 (44.4)
SD	9 (50.0)	7 (38.9)
PD	1 (5.6)	1 (5.6)
Unknown	1 (5.6)	1 (5.6)

*No evidence of disease at baseline and no postbaseline assessment of PD in one patient with a single extranodal target lesion (nasopharynx) evaluated as CR by the investigator.

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; IWG, International Working Group; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

1. Flinn IW, et al. J Clin Oncol 2019;37:912-922

DUVELISIB RESPONSE DATA[1]

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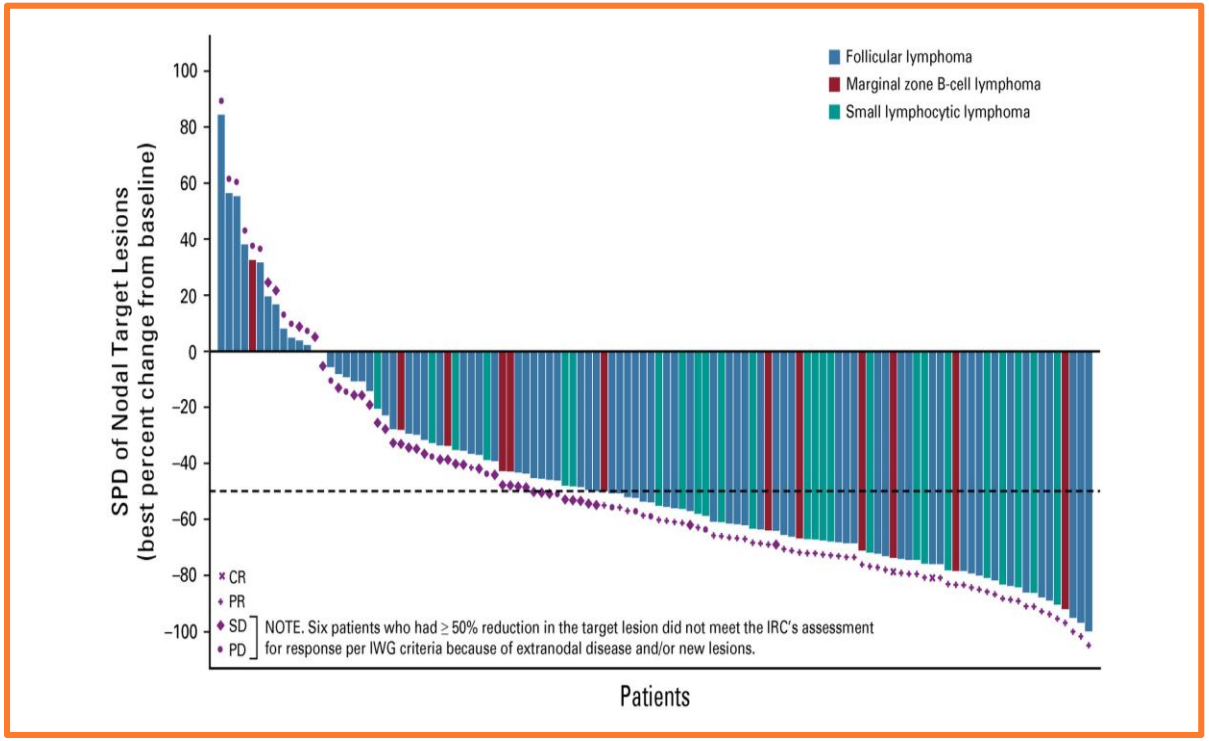
- Best percent change in the SPD of nodal target lesions per IRC (full analysis set)



- The **ORR** was 47.3% (SLL: 67.9%; FL: 42.2%; MZL: 38.9%)

CR, complete response; FL, follicular lymphoma; IRC, independent review committee; IWG, International Working Group; MZL, marginal zone B-cell lymphoma; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the product of the longest perpendicular dimensions

1. Flinn IW, et al. J Clin Oncol 2019;37:912-922

DUVELISIB RESPONSE DATA (FULL ANALYSIS SET)[1]

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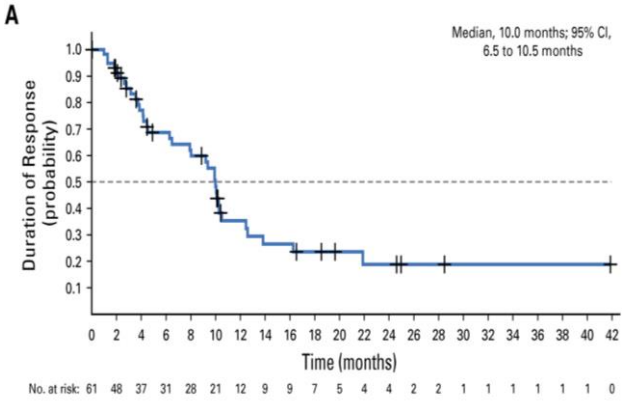
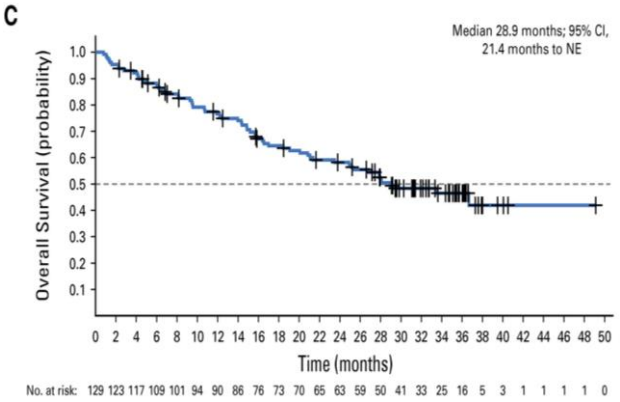
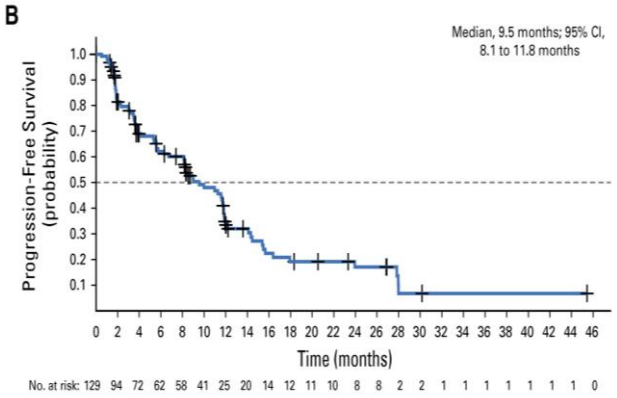
Duration of response per IRC assessment



Overall survival



Progression-free survival per IRC assessment



- Responses were durable, with a **median DOR** of 10 months[1]
- The **median PFS** was 9.5 months and **median OS** was 28.9 months[1]

CI, confidence interval; DOR, duration of response; IRC, independent review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival

1. Flinn IW, et al. J Clin Oncol 2019;37:912-922

DUVELISIB AE PROFILE[1]

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- All-Grade TEAEs (> 10%) or Grade ≥3 TEAEs (> 5%) (full analysis set)

TEAE	All Grades, No. (%)	Grade ≥3, No. (%)
No. of patients	**129**	**129**
Patients with at least one TEAE	128 (99.2)	114 (88.4)
Diarrhea	63 (48.8)	19 (14.7)
Nausea	38 (29.5)	2 (1.6)
Neutropenia	37 (28.7)	32 (24.8)
Fatigue	36 (27.9)	6 (4.7)
Cough	35 (27.1)	0
Anemia	34 (26.4)	19 (14.7)
Pyrexia	32 (24.8)	0
Rash	24 (18.6)	6 (4.7)
Thrombocytopenia	24 (18.6)	15 (11.6)
Vomiting	24 (18.6)	5 (3.9)
Decreased appetite	19 (14.7)	1 (0.8)
Headache	20 (15.5)	0

TEAE	All Grades, No. (%)	Grade ≥3, No. (%)
Edema peripheral	22 (17.1)	3 (2.3)
ALT increased	18 (14.0)	7 (5.4)
Back pain	17 (13.2)	1 (0.8)
Arthralgia	19 (14.7)	0
Abdominal pain	19 (14.7)	2 (1.6)
Hypokalemia	17 (13.2)	4 (3.1)
Constipation	15 (11.6)	0
Asthenia	15 (11.6)	3 (2.3)
AST increased	13 (10.1)	4 (3.1)
Night sweats	13 (10.1)	0
Febrile neutropenia	12 (9.3)	12 (9.3)
Lipase increased	12 (9.3)	9 (7.0)
Pneumonia	10 (7.8)	7 (5.4)
Colitis	10 (7.8)	7 (5.4)

AE, adverse event; ALT, alanine aminotransferase; AST aspartate aminotransferase; TEAE, treatment-emergent adverse event

1. Flinn IW, et al. J Clin Oncol 2019;37:912-922

PI3K INHIBITORS UNDER INVESTIGATION

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Umbralisib:

- A PI3Kδ inhibitor, structurally distinct from other PI3Kδ inhibitors. Umbralisib also uniquely inhibits casein kinase-1ε. Like most PI3Kδ inhibitors, umbralisib is dosed continuously with data thus far indicative of an improved safety profile compared to PI3Kδ inhibitors. It was recently granted breakthrough designation for MZL based on preliminary results from the UNITY-NHL trial[1]

Parsaclisib:

- Another 2nd-generation specific PI3Kδ inhibitor designed to have an improved safety profile. It demonstrated efficacy across several NHL subtypes in the initial phase 1/2 trial, yet AEs similar to idelalisib and duvelisib were noted. With most responses within 8 weeks of therapy and most of the AEs occurring after this time point, the treatment schedule (daily dosing for the first 9 weeks followed by weekly dosing thereafter) was adjusted to maximize response while minimizing toxicity.[2] The agent is being explored in several phase 2 trials[3]

MEI-401:

- A potent 2nd-generation selective PI3Kδ inhibitor with prolonged occupancy time on the PI3Kδ protein. Evaluated in patients with B-cell malignancies. At ASCO 2019, MEI-401 showed impressive responses as a single agent and in combination with rituximab among patients with FL. After initial dose escalation, patients were dosed at 60 mg daily. ORR with MEI-401 alone was 79% (CR: 26%) in FL patients (n=48). Although dosed continuously, an intermittent schedule is being explored during the trial to improve toxicity.[4] This is being further explored in a phase 2 trial[5]

AE, adverse event; CR, complete response; FL, follicular lymphoma; MZL marginal-zone lymphoma; NHL, Non-Hodgkin's Lymphoma; ORR, objective response rate; PI3K, phosphoinositide 3-kinase

1. Fowler NH, et al. J Clin Oncol 2019;37(suppl): Abstract 7506; 2. Forero-Torres A, et al. Blood 2019;133:1742-1752; 3. ClinicalTrials.gov - NCT03126019, NCT03235544, NCT03144674; 4. Zelentz AD, et al. J Clin Oncol 2019;37(suppl): Abstract 7512; 5. ClinicalTrials.gov - NCT03768505

CONCLUSIONS

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- PI3Kδ pathway is an **important survival pathway in B-cell lymphomas** and several agents have been developed to target this pathway to improve outcomes in this patient population
- Currently there are **three FDA-approved PI3K inhibitors** for patients with R/R FL, SLL, and CLL
- While efficacy results are promising, integration of this class of inhibitors into clinical practice has been hampered by infection and immune-related AEs. To overcome these limitations, newer agents have been developed which target different PI3K isoforms/or molecules (copanlisib, duvelisib, umbralisib)
- Additionally, alternative dosing schedules are being explored (copanlisib, parsaclisib, and MEI-401) in an attempt to improve efficacy, safety, duration of treatment and response
- The future of this class appears promising, but further study of the etiology and means to overcome the AEs will be required to fully exploit the full potential of PI3K inhibitors. Maturation of current preliminary data of newer agents will also help increase our understanding with regards to the optimal use of these agents

AE, adverse event; CLL, chronic lymphocytic leukemia; FDA, Food and Drug Administration; FL, follicular lymphoma; PI3K, phosphoinositide 3-kinase; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma

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