SARAH CANNON
Research Institute

DUVELISIB IN PATIENTS WITH REFRACTORY INDOLENT NON-HODGKIN LYMPHOMA AND CLL

Ian W. Flinn, M.D., Ph.D.
Director, Lymphoma Program
Sarah Cannon Research Institute
Nashville, Tennessee

Disclosures

- Verastem
- Infinity
- TG
- Gilead
- Kite
- Unum
- Genentech
- Roche
- Celgene
- Arqule
- Beigene
- Trillium
- Seatle Genetics
- Janssen
- Pharmacyclics
- Abvie
- Forty Seven

On Targets Effects of Inhibition of PI3K

δ

On target effects of PI3K-δ inhibition

- Potent reduction of proliferation of malignant B cells (e.g. CLL)
  - Peluso (2014) Blood 124:328; Balakrishnan (2015) Leukemia 29:1811
- Inhibition of CLL cell egress from circulation into spleen
  - Chen (2015) ASH presentation

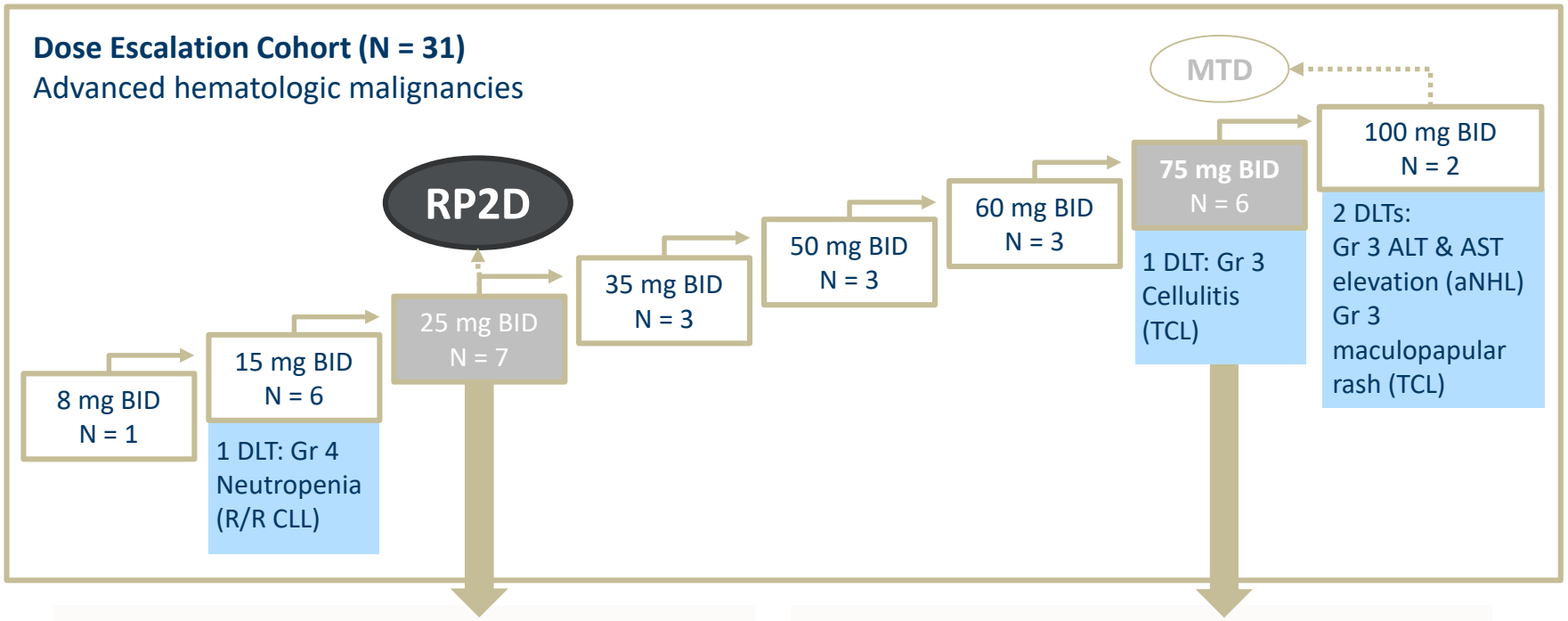
γ

On target effects of PI3K-γ inhibition

- Inhibition of CD4+ T cells that enable CLL cell survival
  - Chen (2015) ASH presentation
- Inhibition of M2 macrophages that support CLL/FL cell survival
  - Kaneda (2016) Nature 539:437; De Henau (2016) Nature 539:443

DUVELISIB HEMATOLOGICAL MALIGNANCIES

PHASE 1 STUDY (IPI-145-02)



Expansion Cohorts: 25 mg BID (N = 59)

- CLL, iNHL, mantle cell lymphoma
- Treatment-naïve CLL

Expansion Cohorts: 75 mg BID (N = 118)

- CLL, iNHL, mantle cell lymphoma
- T-cell lymphomas

<u>Exploratory cohorts</u>

- Aggressive B-cell lymphomas
- Myeloid neoplasms
- T- or B-cell leukemia/lymphoma

NCT01476657

Study IPI-145-02 (Phase 1): EFFICACY

overall response rate in R/R & TN CLL

	n [a]	CR n (%)	PR n (%)	SD [b] n (%)	PD n (%)	ORR n (%)
R/R, All doses	52	1 (2)	29 (56)	21 (40)	1 (2)	**30 (58)**
R/R, up to 25 mg BID	30	1 (3)	16 (53)	12 (40)	1 (3)	**17 (57)**
Unmutated IGHV	20	1 (5)	11 (55)	8 (40)	0	**12 (60)**
TP53 mt / del(17p)	15	1 (7)	6 (40)	7 (48)	1 (7)	**7 (48)**
Treatment-Naïve, 25 mg BID	17 [c]	0	15 (88)	2 (12)	0	**15 (88)**
TP53 mt /del(17p)	9	0	8 (89)	1 (11)	0	**8 (89)**

a: Includes efficacy evaluable patients only = at least one response assessment or PD without a response assessment
b: Stable disease includes patients with PR + lymphocytosis
c: 1 patient withdrew consent prior to the first efficacy assessment at Cycle 3 Day 1, and was not in the efficacy evaluable population

R/R CLL: 57% ORR by iwCLL, including 1 CR

- Median time to iwCLL response = 1.9 months

TN CLL: 88% ORR by iwCLL

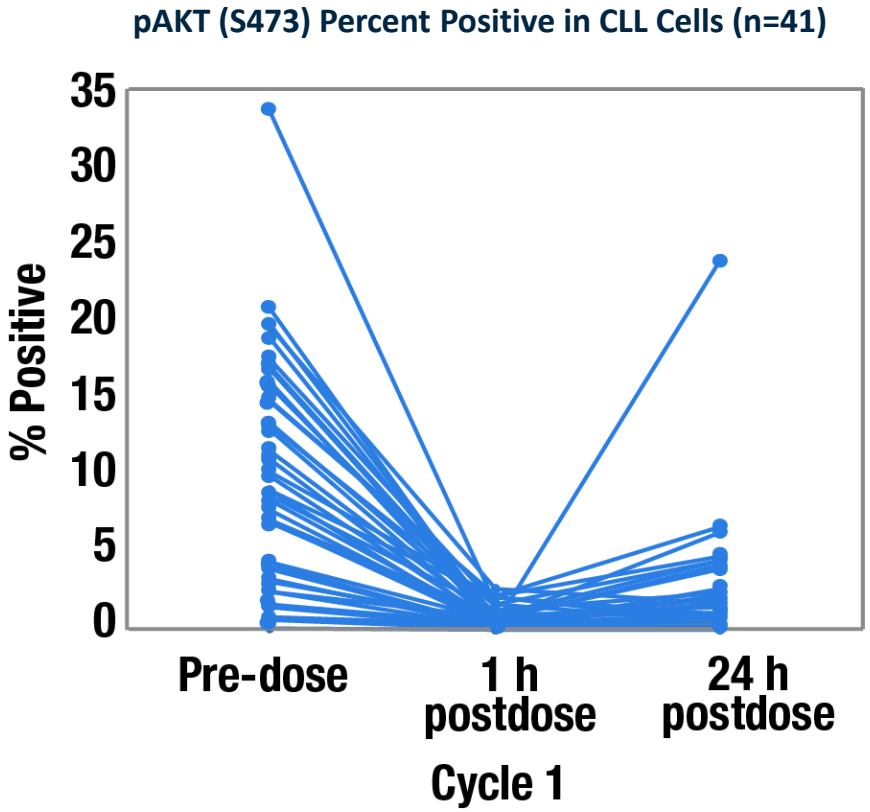
- Median time to iwCLL response = 3.7 months
- 7 of 15 (47%) responses occurred by the first assessment (Cycle 3 Day 1)

Source: O'Brien et al., ASH 2014 – R/R CLL; Patel et al., ASCO 2015 – TN CLL
R/R – Relapsed/Refractory; TN – Treatment naïve

Study IPI-145-02 (Phase 1): PD

Duvelisib pharmacodynamics in CLL in R/R CLL

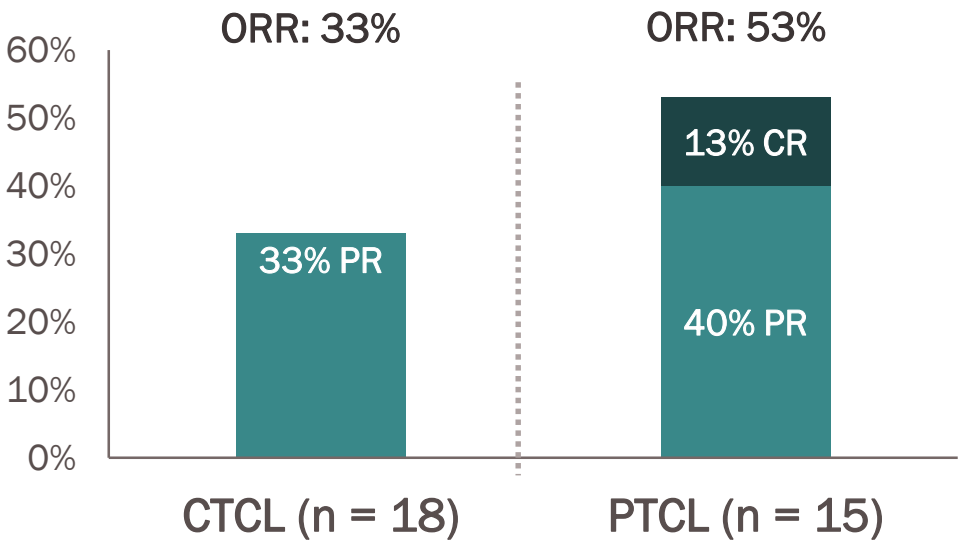
Single dose induces rapid inhibition of PI3K signaling, with no dose-dependent differences observed



Source: Flinn et al., Blood 2018
R/R – Relapsed/Refractory

EARLY SIGNALS OF ACTIVITY IN T CELL LYMPHOMA SUPPORTIVE OF FURTHER CLINICAL INVESTIGATION

T CELL LYMPHOMA COHORT IN COMPLETED PHASE 1



- Early evidence of activity in Cutaneous T-cell Lymphoma (CTCL) and Peripheral T-cell lymphoma (PTCL) with monotherapy duvelisib up to 75 mg BID
- Adverse events were generally Grade 1-2, reversible, and clinically manageable

CR: Complete Response; PR: Partial Response
ORR: Overall Response Rate, CR + PR
Progressive disease (PD): CTCL 6 of 18 patients, PTCL 6 of 15 patients

Source: Horwitz et al., ASH 2014 Phase 1 data

Phase 2 trial to confirm activity of duvelisib monotherapy in relapsed/refractory PTCL

Actively enrolling

Patient population

- Includes all common PTCL sub-types
- No limit of prior therapies
- No transformation to aggressive lymphoma
- ECOG Performance Status ≤2

Duvelisib 25mg BID[1]
N=10

Duvelisib 75mg BID
N=10

[1]Cohort 1: At Cycle 1, if CR/PR: maintain dose; If SD and tolerable: increase dose; if PD: discontinue if intolerable

Duvelisib Optimal Dose
N=100

Study end points

Primary (Expansion phase):
- ORR on optimal dose

Secondary:
- Safety, DoR, DCR, PFS, OS
- % able to reach optimal dose
- Safety

Exploratory:
- PK/PD markers

ClinicalTrials.gov Identifier: NCT03372057

Goal: Establish optimal dose and confirm monotherapy activity

Trial design details:

- At least one prior therapy for PTCL; for CD30+ ALCL, patients must have failed or are ineligible or intolerant to brentuximab vedotin
- Intra-patient dose escalation in Cohort 1 is allowed

DYNAMO™

A phase 2 study of duvelisib monotherapy in double refractory iNHL populations

Double refractory* iNHL patients
N=129

Duvelisib
25 mg BID

PHASE 2 STUDY, FINAL ANALYSIS COMPLETED

Study Points

Primary: Overall response rate (ORR) by Independent Review Committee (IRC)

Key secondary:
- Safety
- Duration of response (DOR)
- Progression-free survival (PFS)
- Overall survival (OS)

* Heavily pretreated patient population:
- Median number of prior treatments = 3
- Inclusion criteria: Refractory to both rituximab (R) and a chemotherapy regimen or radioimmunotherapy (RIT)

- ✓ Accrual complete November 2015
- ✓ Final analysis (April 2016) presented at ASH 2016
- ✓ Mature follow up (March 2017) presented at ICML 2017

DYNAMO™

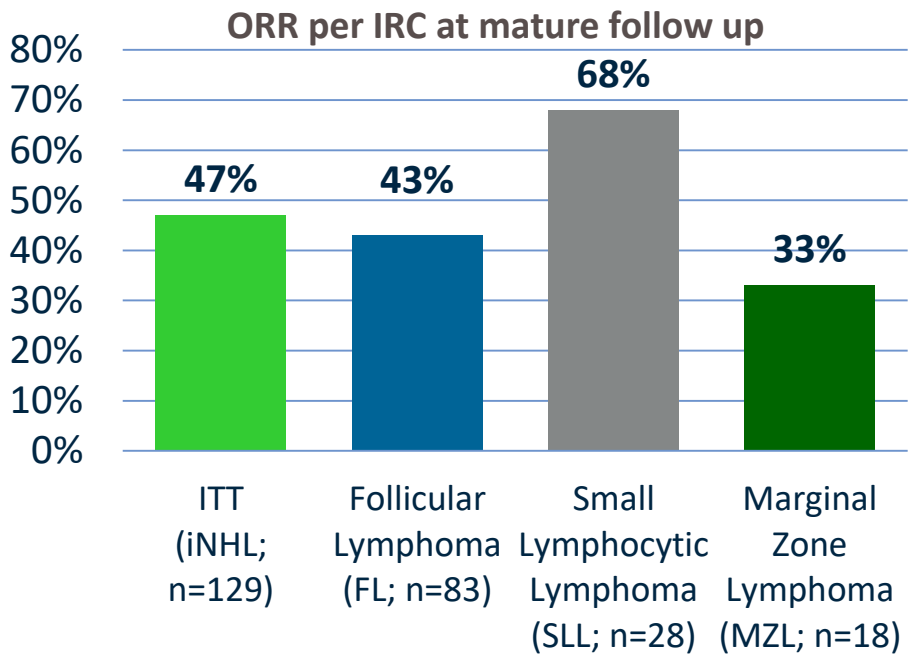
Met primary endpoint of ORR by IRC in double refractory iNHL patients at final analysis

Primary endpoint:

- ORR by IRC at per-protocol final analysis: (p=0.0001)

Secondary endpoints:

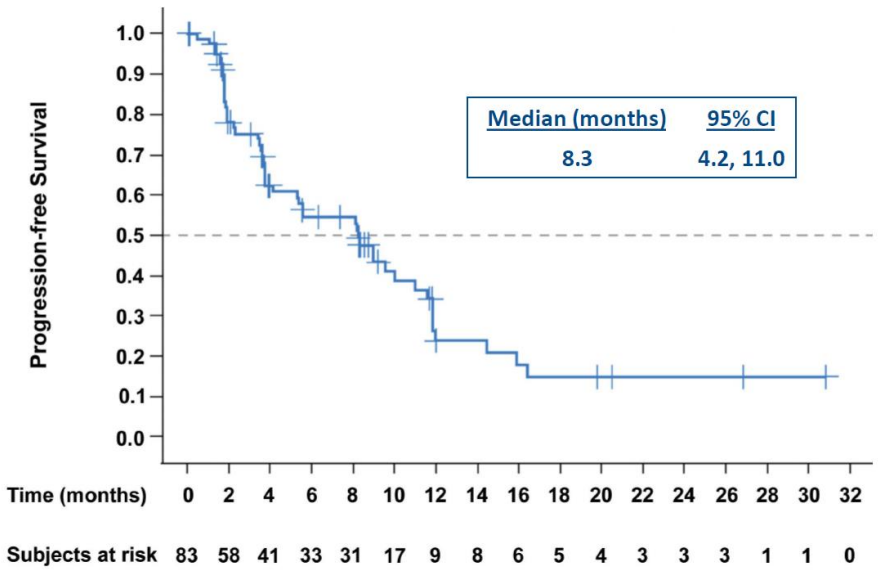
- Median PFS on duvelisib: 9.0 months
- Median DOR: 10 months



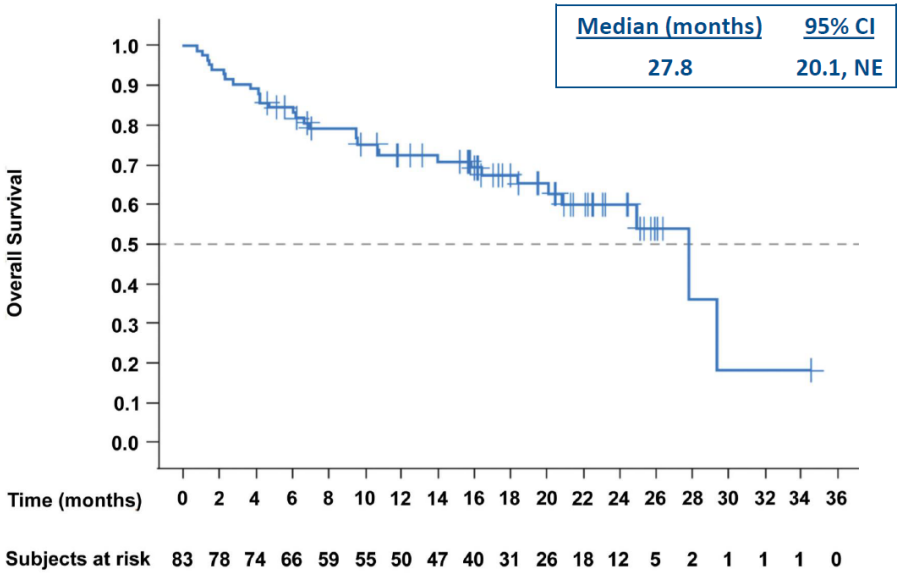
Source: Zinzani et al., ICML 2017

DYNAMO
Progression-Free Survival and Overall Survival per IRC

PFS per IRC



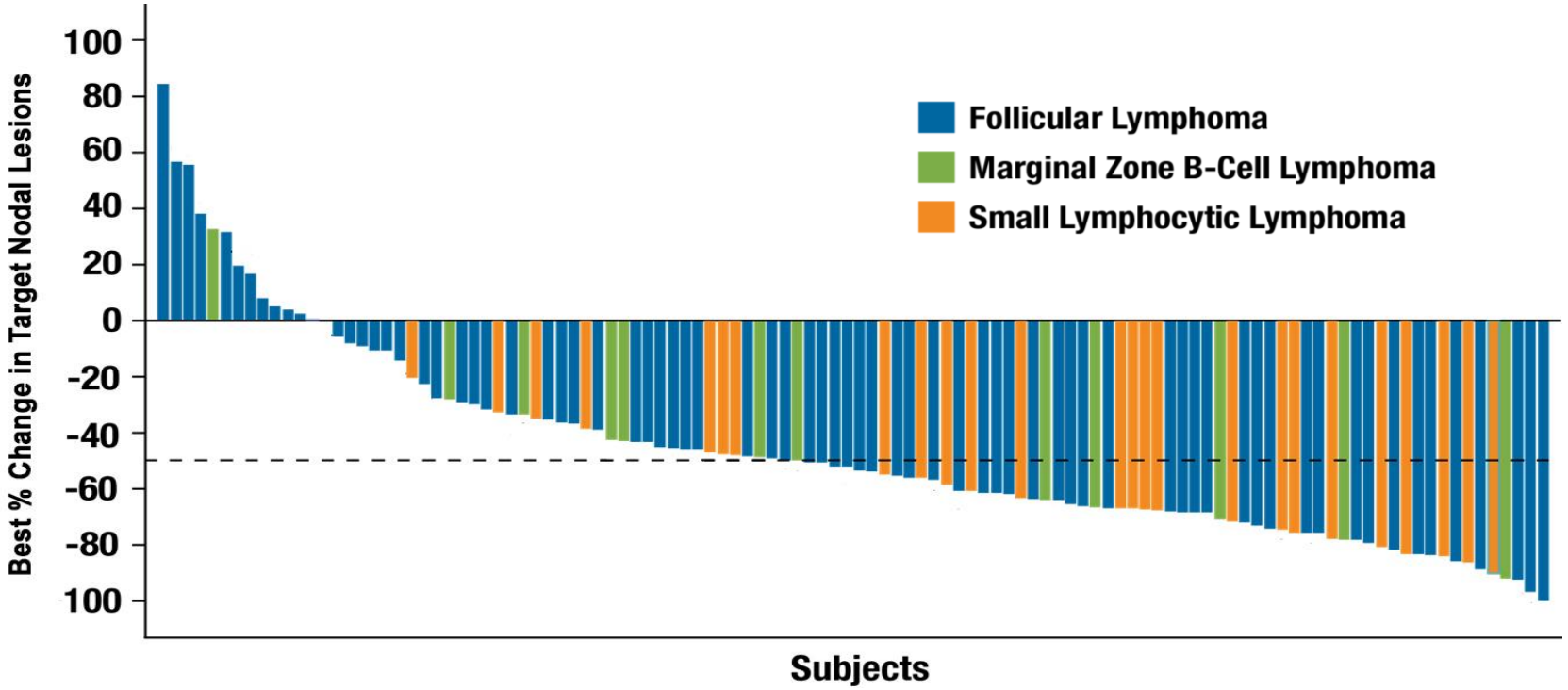
Overall Survival



Source: Zinzani et al., ICML 2017

DYNAMO™

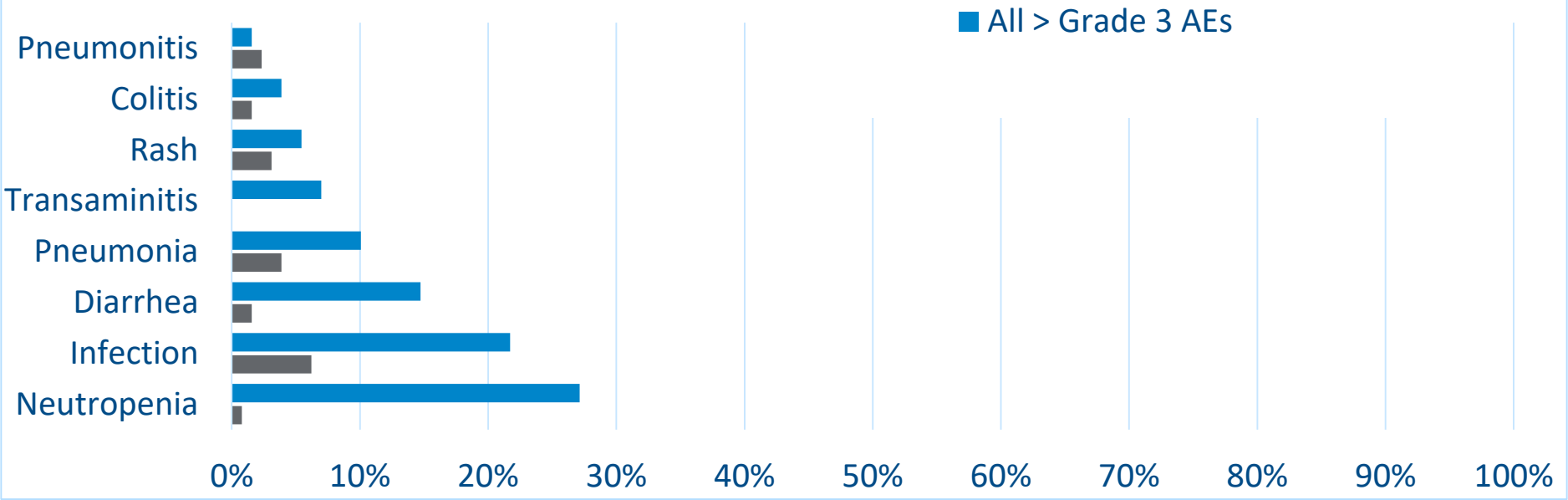
88% of patients in the DYNAMO™ study had reduction in target lymph nodes by IRC



Source: Zinzani et al., ICML 2017

DYNAMO™

Side effects associated with duvelisib are well characterized and manageable



- Few discontinuations due to severe AEs of interest
- Serious opportunistic infections < 4%: PCP (unconfirmed) (n=1); CMV (n=2); fungal pneumonia (n=2)
- Deaths attributed to treatment (n=6)*

*colitis (n=1); toxic epidermal necrolysis/sepsis syndrome (n=1); drug reaction/eosinophilia/systemic symptoms (n=1); pneumonitis/pneumonia (n=1); viral infection (n=1); septic shock (n=1)

Source: Zinzani et al., ICML 2017

DYNAMO™ Data supporting FL accelerated approval

Efficacy in Patients with Relapsed or Refractory FL

Overall Response Rate (ORR) assessed by IRC

Endpoint	FL N = 83
ORR, n (%) [a]	**35 (42%)**
95% CI	(31, 54)
CR, n (%)	1 (1%)
PR, n (%)	34 (41%)
Duration of response	
Range, months	0.0+ to 41.9+
Patients maintaining response at 6 months, n/N (%)	15/35 (43%)
Patients maintaining response at 12 months, n/N (%)	6/35 (17%)

Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; ORR = overall response rate; PR = partial response

[a] Per IRC according to Revised International Working Group criteria

+ Denotes censored observation

Source: Copiktra USPI, 2018

Duvelisib is approved for the treatment of adult patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies. Accelerated approval was granted in this indication based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

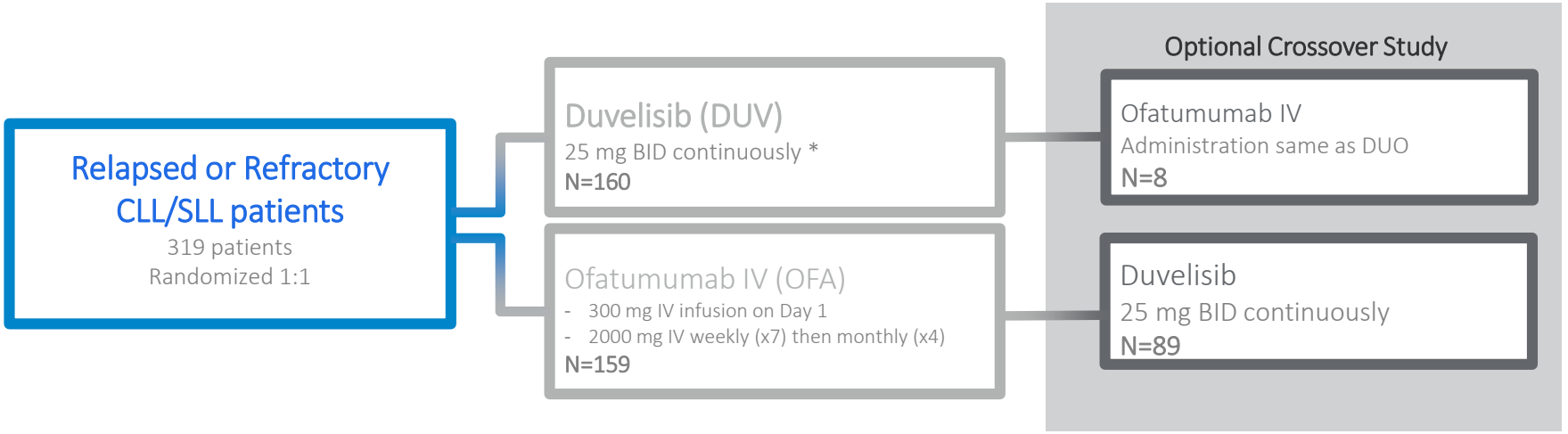
For full prescribing and safety information, please refer to the Package Insert and Important Safety Information available at www.COPIKTRA.com.

DYNAMO™
Study conclusions

- Duvelisib monotherapy is clinically active in double refractory iNHL
  - ORR of 47% per IRC (p=0.0001)
  - 88% of patients had tumor reduction
  - Responses were durable (median 10 months)
- Duvelisib has a well-characterized and manageable safety profile observed to date
- The DYNAMO study showed that duvelisib monotherapy has a favorable benefit-risk profile in refractory iNHL patients, and may represent an important treatment option in this population

Source: Zinzani et al., ICML 2017

DUO™
A phase 3 randomized study in relapsed/refractory CLL/SLL



Response per modified iwCLL/IWG Criteria **

- Assessed by independent review committee (IRC)
- Cycle 3 (C3), C5, C7, C11, C15, C19, every 6 months thereafter
- CT scan, CBC, disease related symptoms, BM biopsy ***
- Survival assessment every 6 months

Endpoints

- PFS (primary)
- ORR, DOR, OS (secondary)
- Safety (AEs and lab abnormalities)

Adapted from: Flinn et al., ASH 2017

DUO™

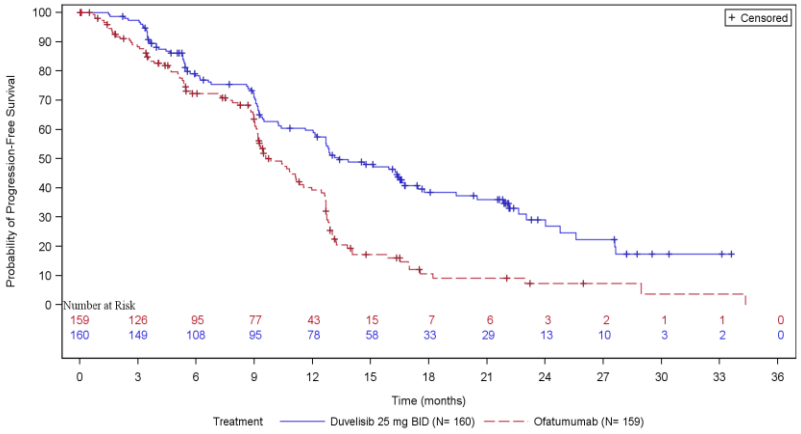
* Patients may have stopped treatment at C18 for CR/PR >3 months at discretion of Investigator

** Lymphocytosis not considered disease progression; PR = 2 Group A and 1 Group B Criteria

*** Required for confirmation of CR/CRi

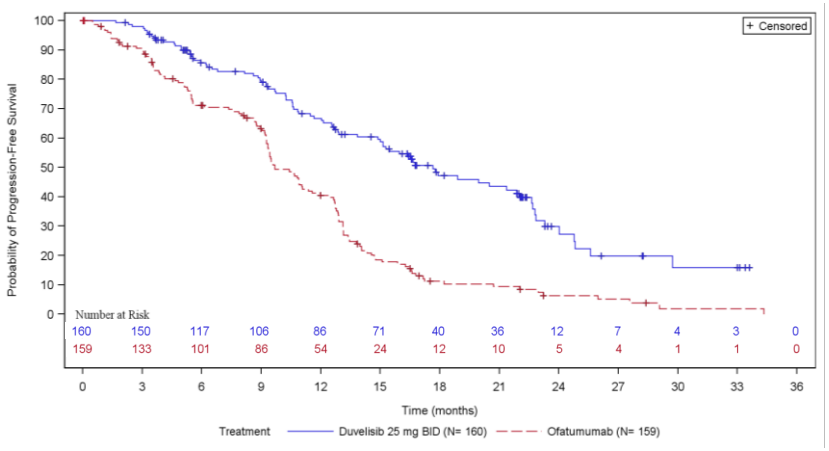
DUO
Met primary endpoint of PFS

IRC Assessment



	DUV	OFA
Median PFS (Months)	13.3	9.9
95% CI	12.1, 16.8	9.2, 11.3
Hazard ratio	0.52	
p-value	< 0.0001	

Investigator Assessment

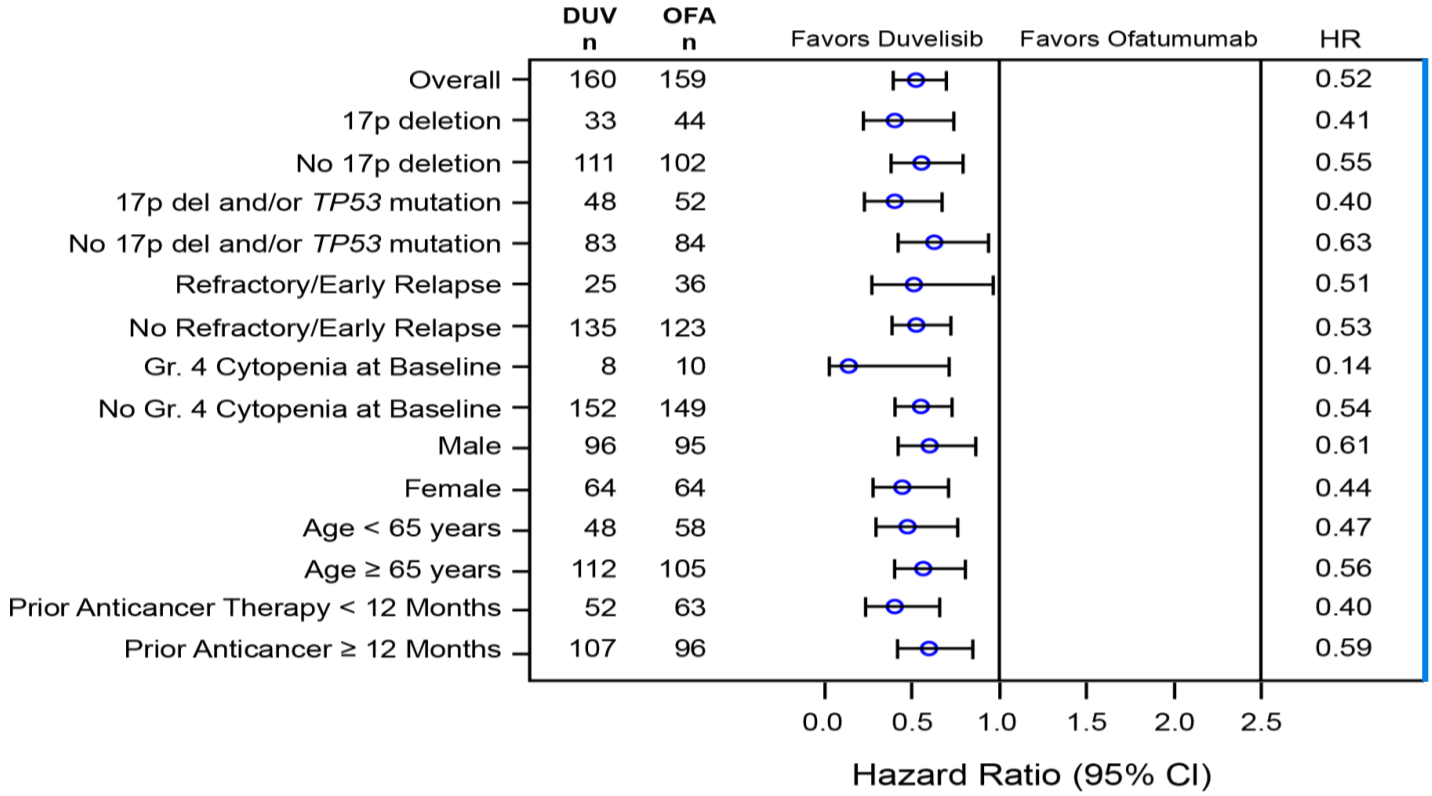


	DUV	OFA
Median PFS (Months)	17.6	9.7
95% CI	15, 22	9, 11
Hazard ratio	0.40	
p-value	< 0.0001	

- 89 patients on OFA arm received duvelisib in crossover study, achieving an ORR of 73% and a median PFS of 15 months per Investigator assessment

Source: Flinn et al., ASH 2017

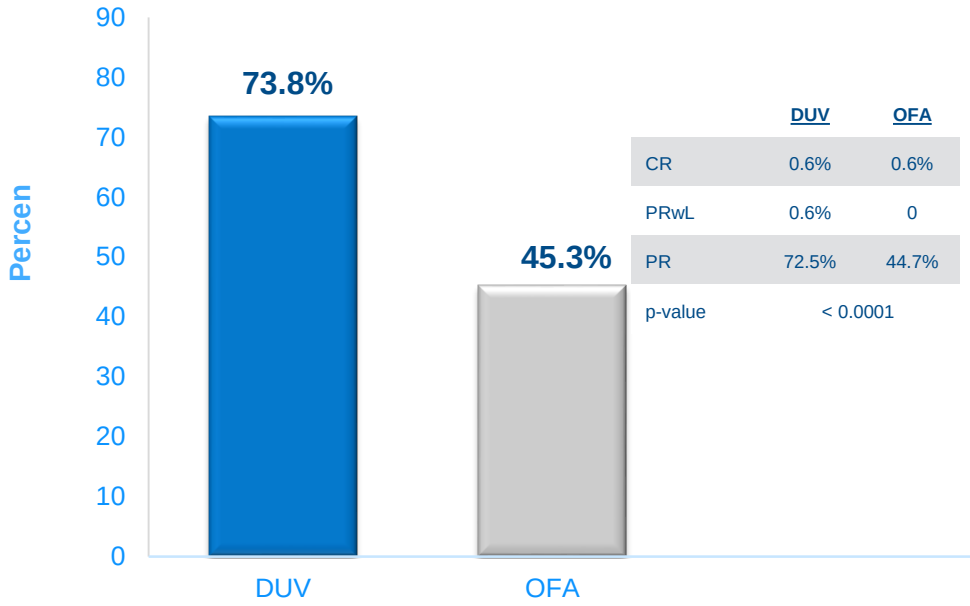
DUO™
Duvelisib maintained PFS advantage in all subgroups analyzed



Source: Flinn et al., ASH 2017

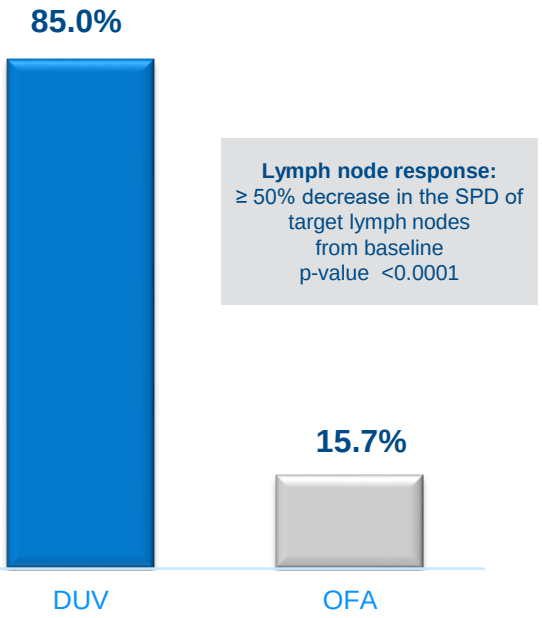
DUO™
Significantly higher ORR with duvelisib per IRC

Overall Response Rate



	DUV	OFA
CR	0.6%	0.6%
PRwL	0.6%	0
PR	72.5%	44.7%
p-value	< 0.0001	

Lymph Node Response Rate



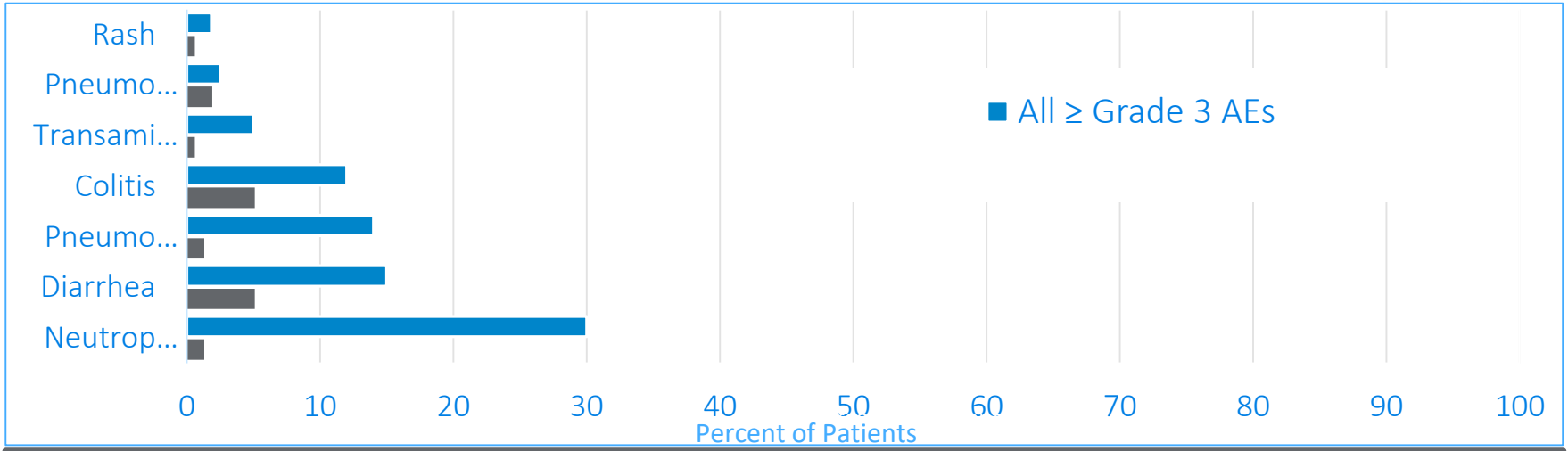
Lymph node response:
≥ 50% decrease in the SPD of target lymph nodes from baseline
p-value <0.0001

ORR in patients with 17p deletion: duvelisib 70% vs OFA 43% (p=0.0182)

Source: Flinn et al., ASH 2017

DUO™

AEs of special interest infrequently led to duvelisib discontinuation

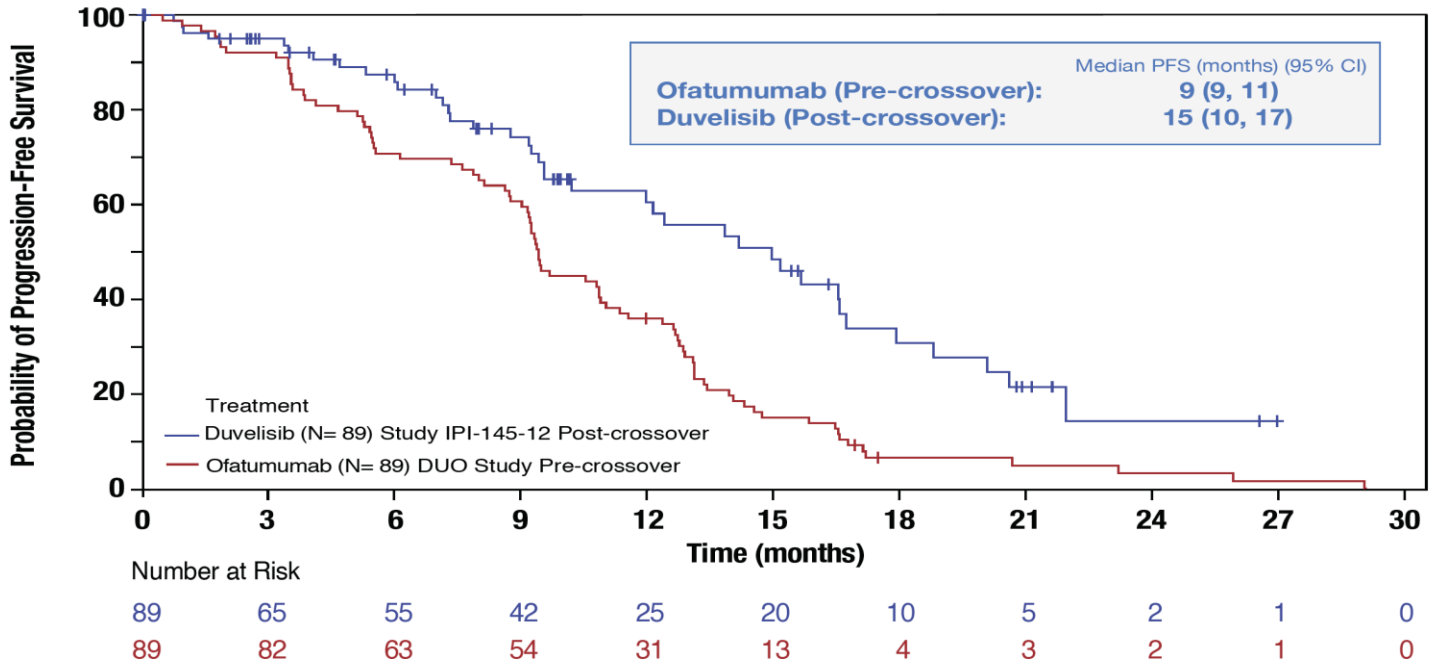


- Severe opportunistic infections (6%): bronchopulmonary aspergillosis (n=4), fungal infection (n=2), *Pneumocystis jiroveci* pneumonia (n=2)*, and cytomegalovirus colitis (n=1)
  - No severe Herpes zoster infections
- Treatment-related AEs leading to death (n=4): general health deterioration (n=1); pneumonia staphylococcal (n=2); sepsis (n=1)

*Neither patient on prophylaxis at the time of the event

Source: Flinn et al., ASH 2017

DUO Crossover Extension Study
Progression-Free Survival Per Investigator Assessment



Source: Kuss et al., ASCO 2018

Efficacy supporting full approval in CLL/SLL

Greater benefit/risk for patients receiving two or more prior therapies

Efficacy in CLL or SLL After at Least Two Prior Therapies

Outcome per IRC	Duvelisib N = 95	Ofatumumab N = 101
PFS		
Number of events, n (%)	55 (58%)	70 (69%)
Progressive disease	44	62
Death	11	8
Median PFS (SE), months [a]	16.4 (2.1)	9.1 (0.5)
Hazard Ratio (SE),[b] Duvelisib/ofatumumab	0.40 (0.2)	
Response rate		
ORR n (%) [c]	74 (78%)	39 (39%)
CR	0 (0%)	0 (0%)
PR	74 (78%)	39 (39%)
Difference in ORR, % (SE)	39% (6.4)	

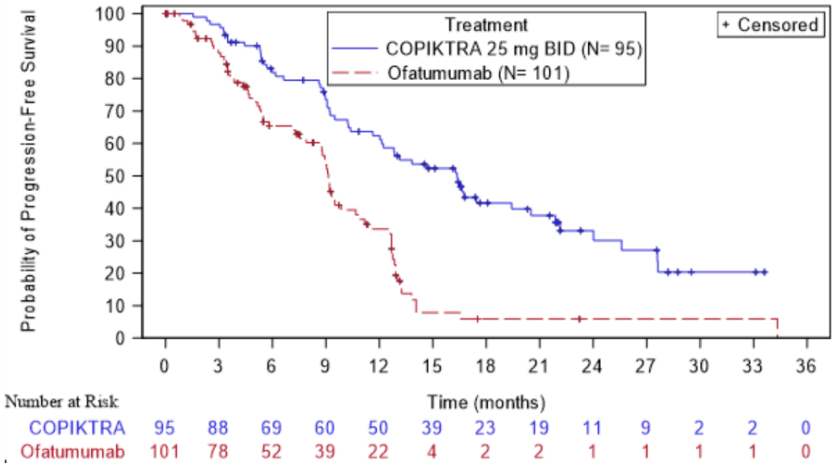
Abbreviations: CI = confidence interval; CR = complete response; IRC = Independent Review Committee; PFS = progression-free survival; PR = partial response; SE = standard error

[a] Kaplan-Meier estimate

[b] Standard Error of ln(hazard ratio) = 0.2

[c] IWCLL or revised IWG response criteria, with modification for treatment-related lymphocytosis

Kaplan-Meier Curve of PFS per IRC In Patients with at Least 2 Prior Therapies



Source: Copiktra USPI, 2018

Duvelisib is approved for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

For full prescribing and safety information, please refer to the Package Insert and Important Safety Information available at www.COPIKTRA.com.

Conclusions:

- Duvelisib monotherapy is clinically active in double refractory iNHL
  - ORR of 47% per IRC (p=0.0001)
  - 88% of patients had tumor reduction
  - Responses were durable (median 10 months)
- DUO met the primary endpoint for PFS: duvelisib monotherapy achieved significant improvement in PFS vs OFA
  - PFS per investigator response assessment significantly favored duvelisib vs OFA (17.6 m vs 9.7 m; $p < 0.0001$)
  - Similar benefit in CLL/SLL patients with 17p deletion
  - Duvelisib achieved significant improvement in ORR vs OFA (74% vs 45%; $p < 0.0001$) per iwCLL/IWG
  - Duvelisib significantly reduced lymph node burden > 50% in most patients vs OFA (85% vs 16%)
- Duvelisib has a well-characterized and manageable safety profile observed to date
- Duvelisib is an important new treatment option for patients with CLL/SLL and follicular Lymphoma with 2 prior therapies