BTK Inhibitors in Follicular NHL

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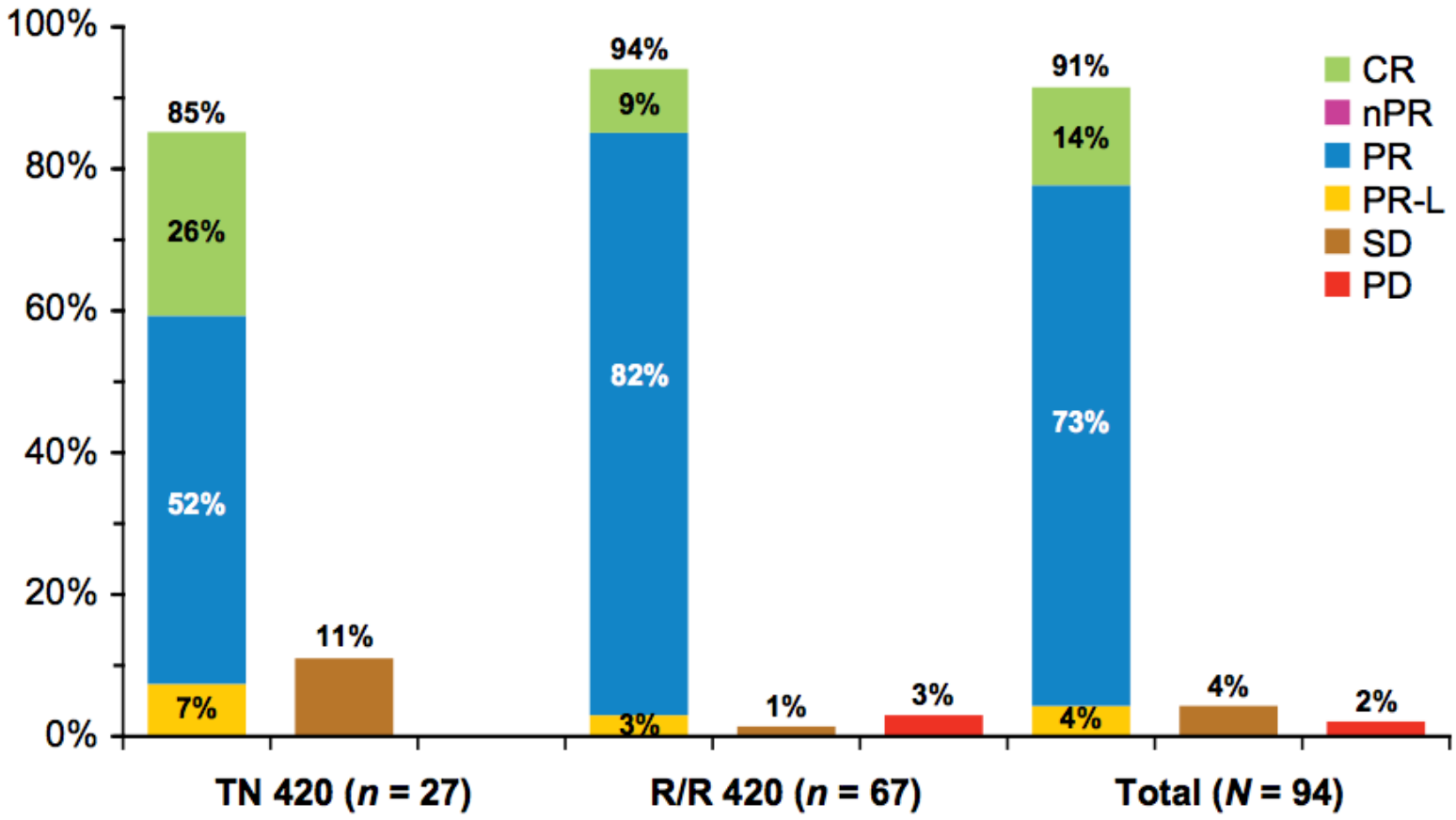
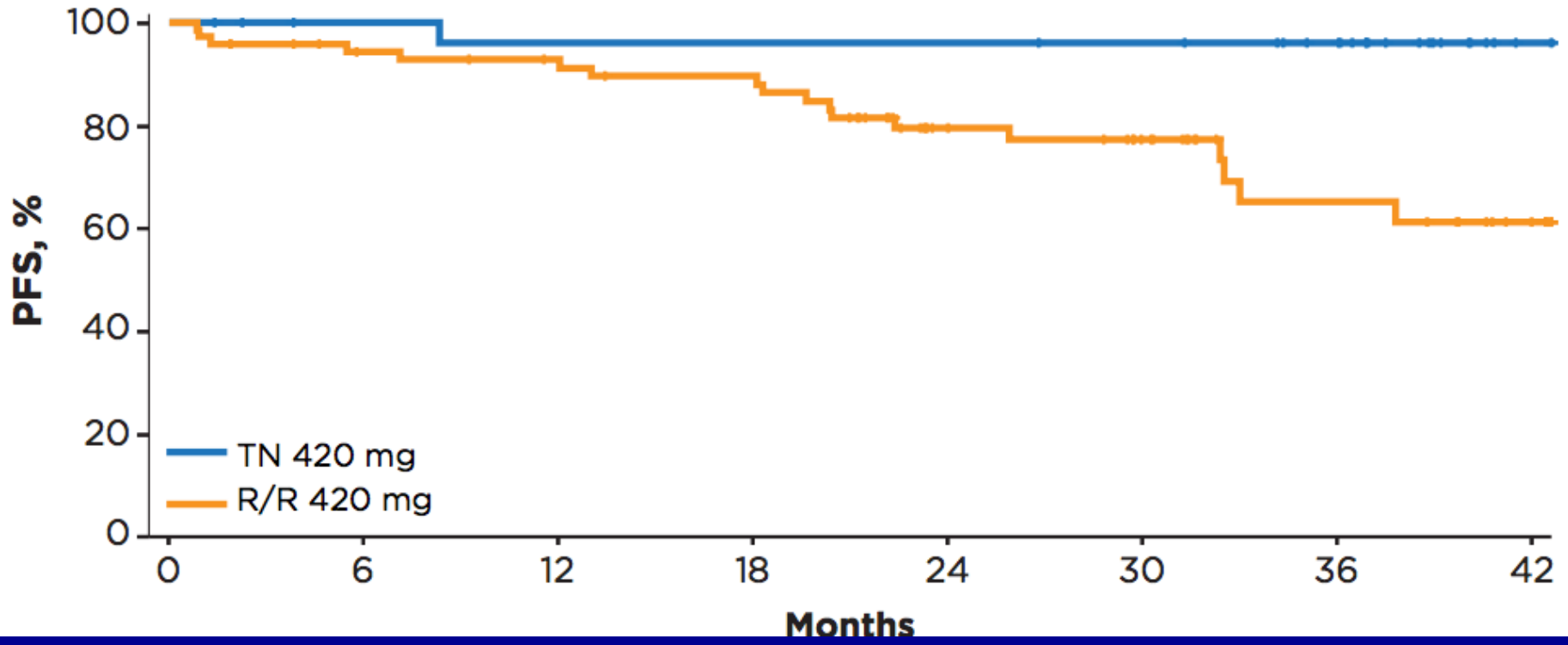
Ibrutinib in CLL



Coutre et l, Clijn Cancer Res 25:1149, 2017

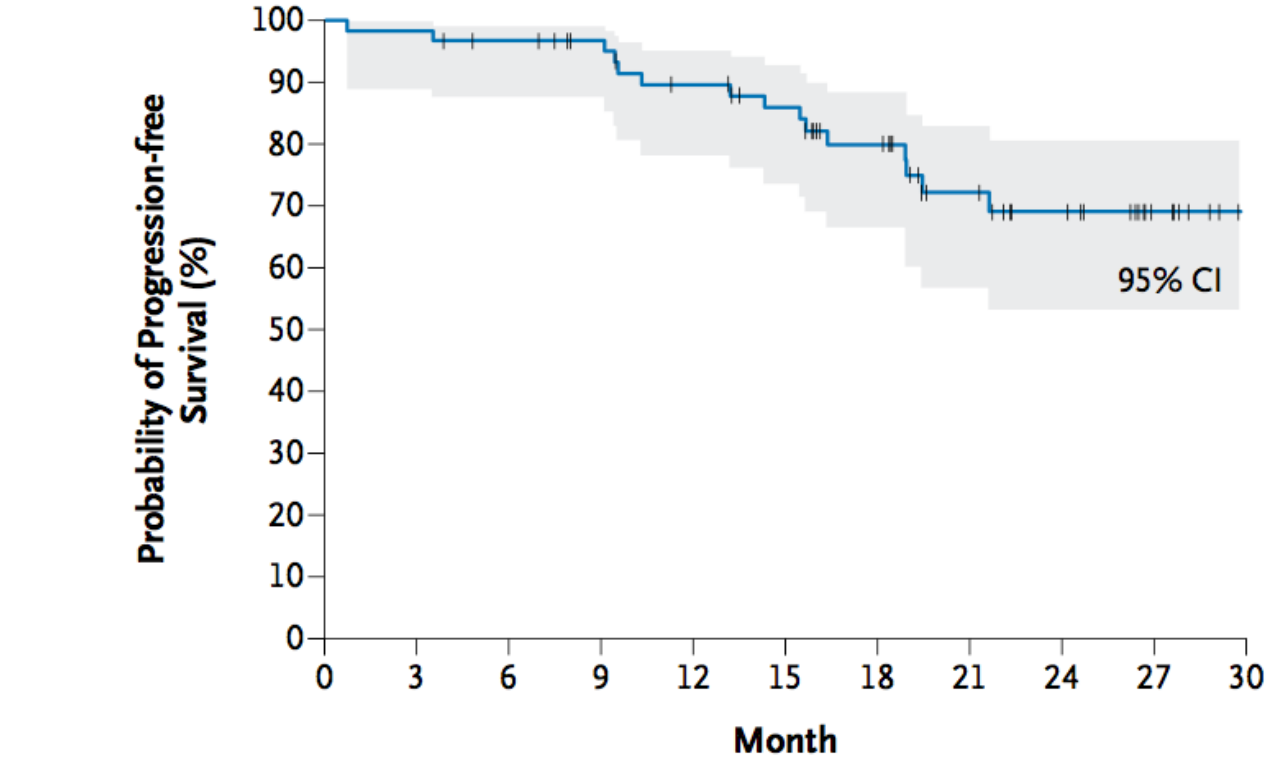
PFS With Ibrutinib in CLL



Coutre et l, Clijn Cancer Res 25:1149, 2017

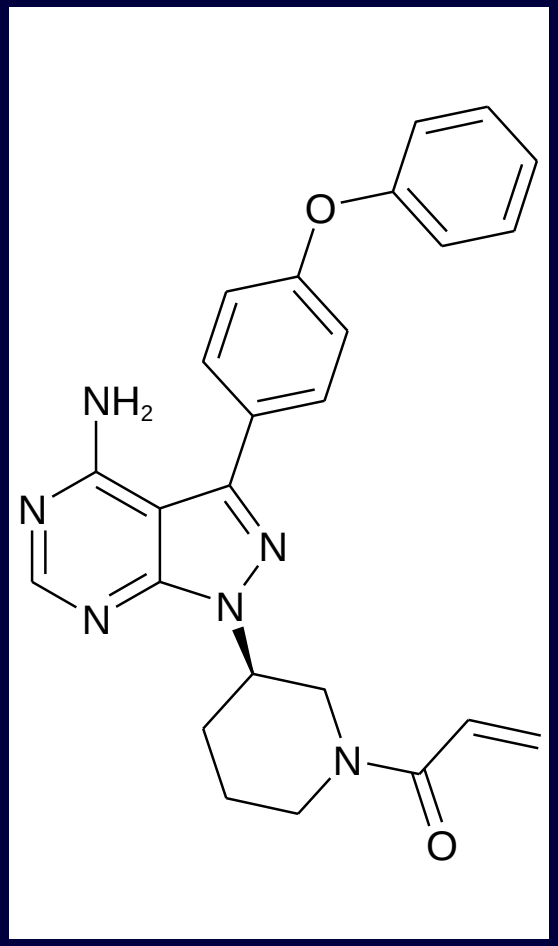
Ibrutinib in WM

ORR – 90.5%
Major – 70%



Treon et al, NEJM 372: 1430, 2015

Ibrutinib (PCI-32765), a selective inhibitor of BTK



- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T-cells or NK-cells
- In CLL cells promotes apoptosis and inhibits CLL cell migration and adhesion
- Phase I/II data of single agent ibrutinib in relapsed/refractory CLL patients demonstrated a high frequency of durable response (O'Brien ASH 2011)

Phase II Consortium: Ibrutinib Monotherapy in Relapsed/Refractory FL

- Single-agent ibrutinib associated with antitumor responses in relapsed/refractory FL
  - ORR: 28%
  - ORR in rituximab-sensitive disease: 42%
  - ORR in rituximab-insensitive disease: 6%
  - 1-yr PFS: 50%

Bartlett NL, et al. ASH 2014. Abstract 800.

DAWN Study: Patient Characteristics at Baseline

	All Treated Patients (N = 110)
Median age (range), years	61.5 (28-87)
Male, n (%)	67 (60.9)
ECOG performance status, n (%)	
0	55 (50.0)
1	55 (50.0)
FLIPI score, n (%)[a]	
0-1	21 (19.1)
2	25 (22.7)
3-5	64 (58.2)

[a]Derived at baseline.

ECOG, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index.

Patient Characteristics at Baseline

	All Treated Patients (N = 110)
Refractory disease, n (%)[a,b]	45 (40.9)
Bulky disease (> 6 cm), n (%)	21 (19.1)
Prior lines of therapy, n (%)	
Median (range)	3 (2-13)
2	49 (44.5)
3-6	53 (48.2)
> 6	8 (7.3)
Median time (range) from initial diagnosis, months	52.16 (6.9-312.6)
Median time (range) from end of last therapy to first dose, months	4.24 (0.5-32.4)

[a]Refractory disease was defined as failure to achieve at least partial response to the last regimen prior to study entry.
[b]94/110 (85%) patients had progressed within 6 months on last prior line of therapy.

Disposition and Exposure

	All Treated Patients (N = 110)
Median treatment duration (range), months	**7.0 (1-37+)**
Median duration of follow-up (range), months	27.7 (1.1-37.1)
Study treatment phase disposition, n (%)	
Discontinued study treatment	110 (100)
Primary reason for discontinuation	
Progressive disease or relapse	72 (65.5)
Rolled into long-term extension study (NCT01804686)	13 (11.8)
Physician decision	10 (9.1)
Adverse event	7 (6.4)
Death	4 (3.6)
Withdrawal of consent	3 (2.7)
Lost to follow-up	1 (0.9)

DAWN Trial:Primary End Point: IRC-Assessed Clinical Response With Single-Agent Ibrutinib

	All Treated Patients (N = 110)	
Clinical response, n (%)		95% CI
Overall response rate (ORR)	**23 (20.9)**	13.7-29.7
Complete response (CR)	12 (10.9)	5.8-18.3
Partial response (PR)	11 (10.0)	5.1-17.2
Stable disease (SD)	34 (30.9)	22.5-40.4
Progressive disease (PD)	47 (42.7)	33.3-52.5
Not evaluable/unknown	6 (5.5)	2.0-11.5

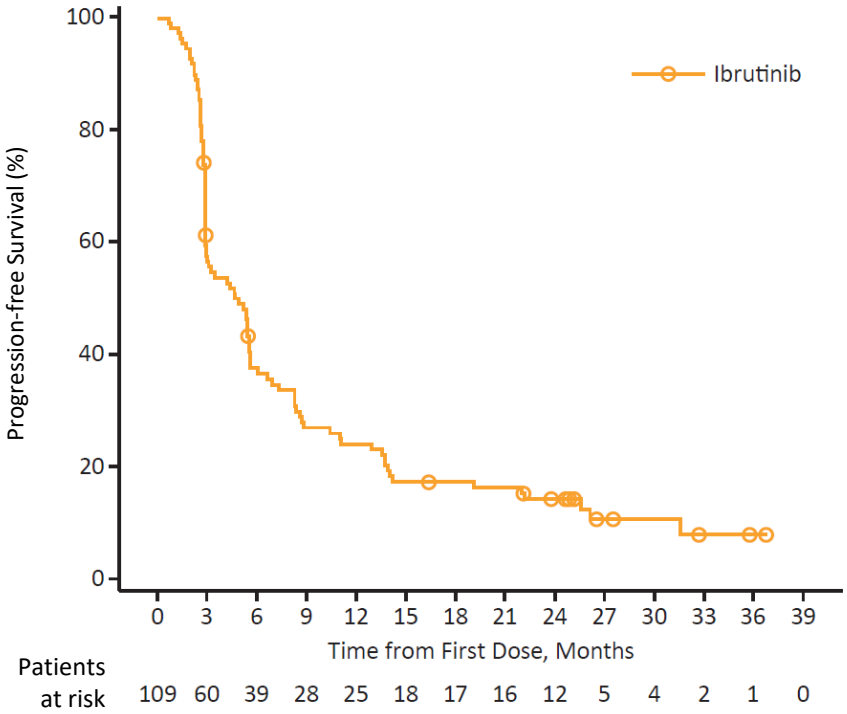
- Disease control rate (ORR + SD for ≥ 6 months) was 33.6% (37/110)

CI, confidence interval.

58th ASH Annual Meeting 2016, DAWN Study, Gopal A, et al.

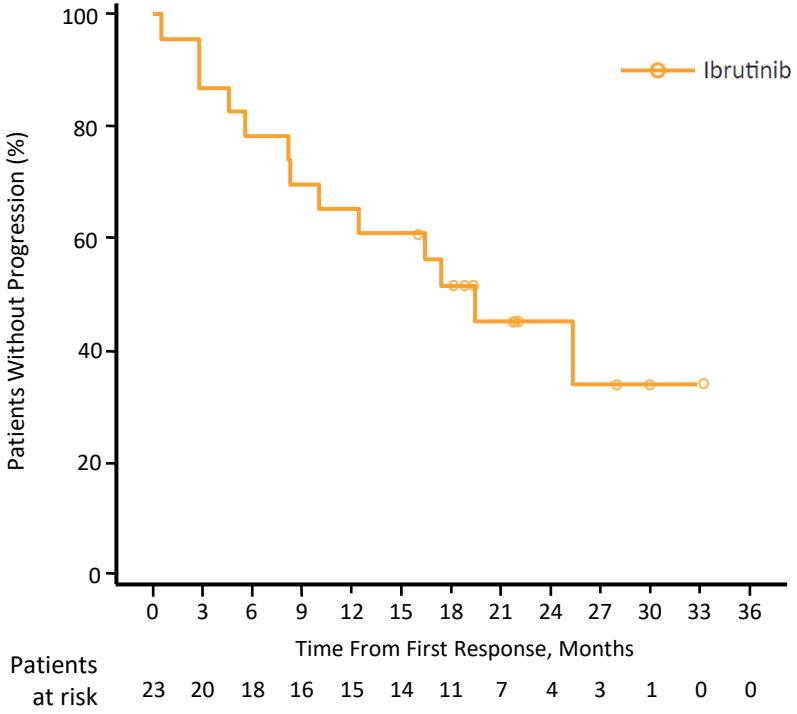
Progression-Free Survival and Duration of Response

Progression-Free Survival



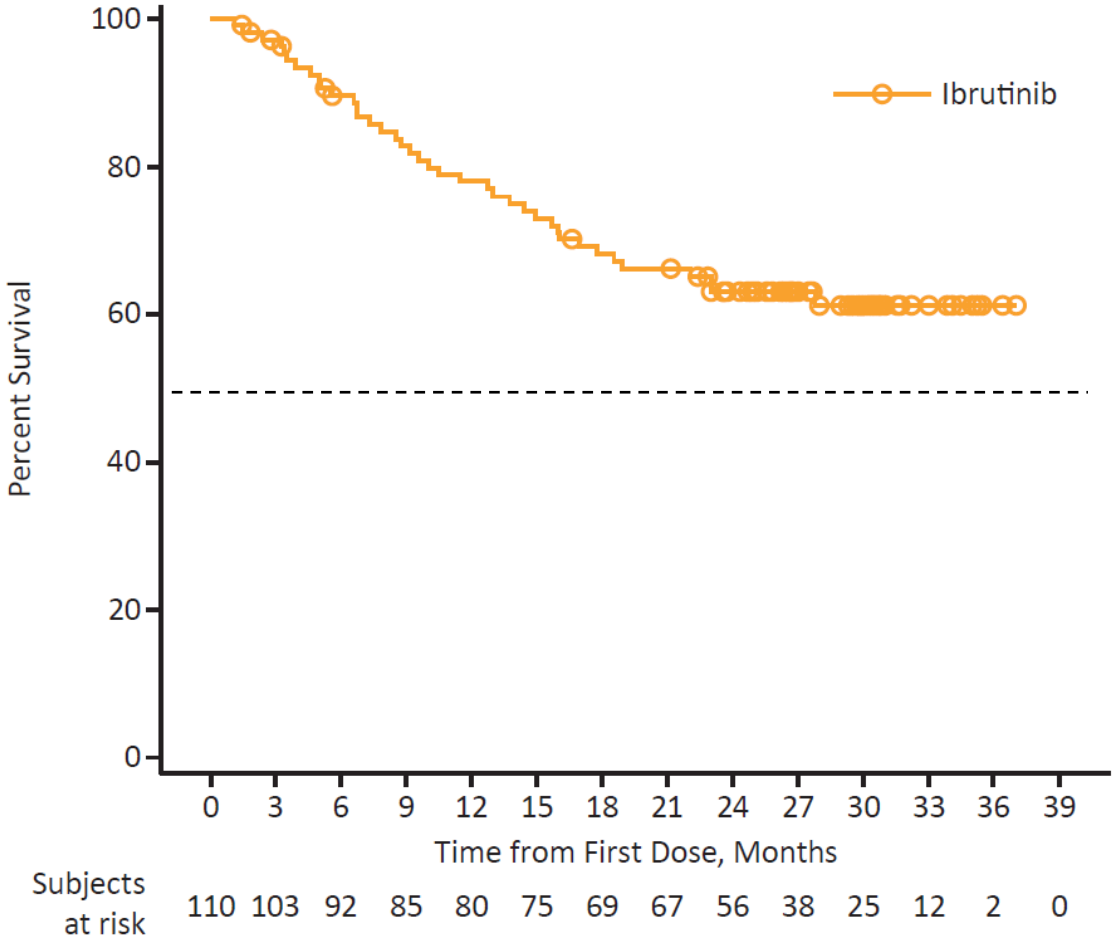
Median PFS 4.6 months

Duration of Response



Median DOR 19.4 months

Overall Survival

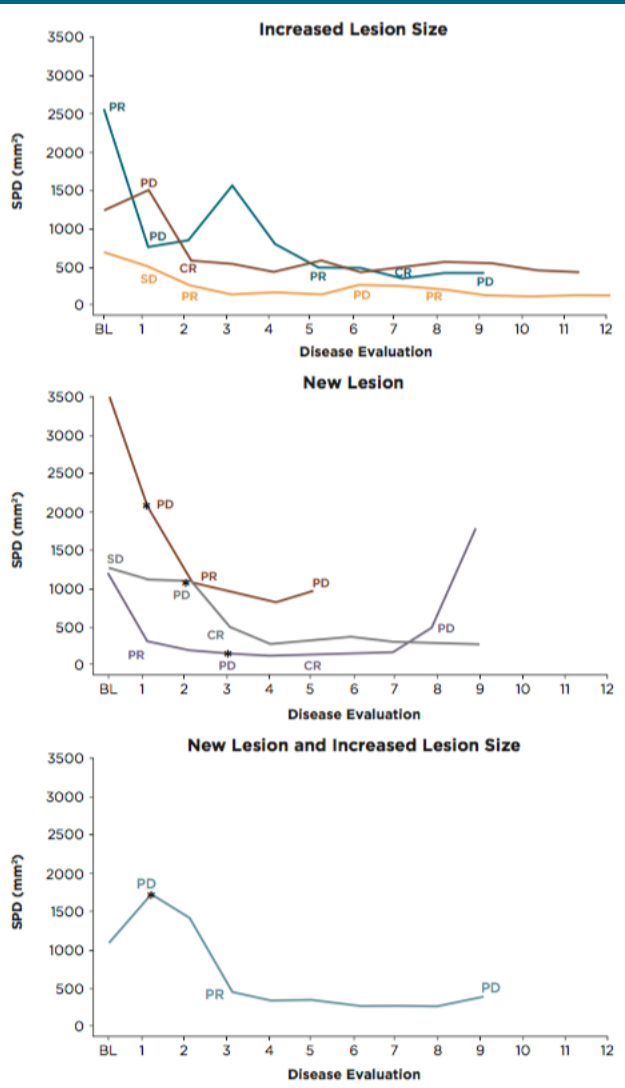


58th ASH Annual Meeting 2016, DAWN Study, Gopal A, et al.

Pseudoprogression in FL with Ibrutinib: the Phase II DAWN Study

- ≥ 2 prior txs; PD < 12 mos
- 37 pts identified with pseudoprogression
  - Median 22 (11.6-59.6) wks
  - 2CR, 1 PR maintained response for > 8 mo – 1PD
  - 1CR, 1 PR – response > 8 mo before PD
  - 1PR responded > 1 yr, D/C adverse event
- Downregulation of T-regs (also in other responders, not non-responders)

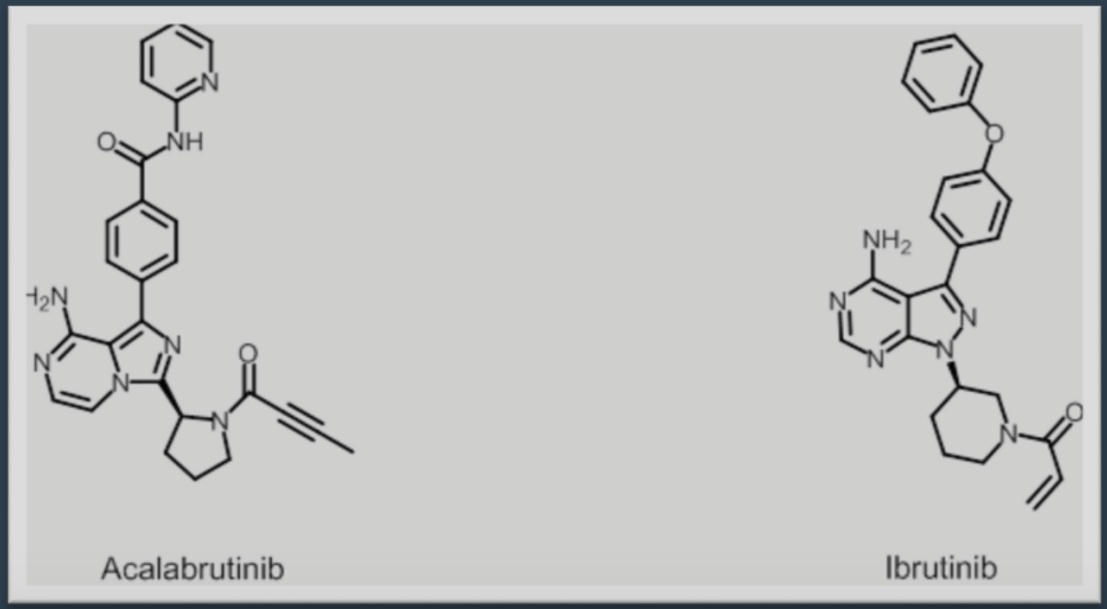
Pseudoprogression in FL On Ibrutinib



58th ASH Annual Meeting 2016, DAWN Study, Gopal A, et al.

Acalabrutinib: A potent and selective 2nd generation Bruton Tyrosine Kinase (Btk) inhibitor

- **Acalabrutinib was developed to increase the degree of Btk inhibition**
  - Has less avid binding to Btk than first generation Btk inhibitors
  - Very low binding to interleukin-2 inducible T-cell kinase (ITK), TEC protein tyrosine kinase (TEC), and epidermal growth factor receptor (EGFR)
- **Acalabrutinib selectively binds with a short half-life allowing twice-daily dosing and near total Btk inhibition**
  - Potentially reducing drug resistance
- **Acalabrutinib, a second generation Btk inhibitor, appears to improve substantially on the specificity of first generation Btk inhibitors**



Byrd, J,et al. *N Engl J Med* 2016; 374:323-332.
Wilson, WH. N Engl J Med 2016; 374:386-388.

Adverse Events (Median 14.3 Months of Follow-up)

Reported in ≥5% patients

Adverse Events (Treatment-Related), n (%)	Grade 1-2	Grade 3	N=61
Headache	12 (20)	–	12 (20)
Increased tendency to bruise	7 (12)	–	7 (12)
Petechiae	7 (12)	–	7 (12)
Diarrhea	6 (10)	–	6 (10)
Ecchymosis	5 (8)	–	5 (8)

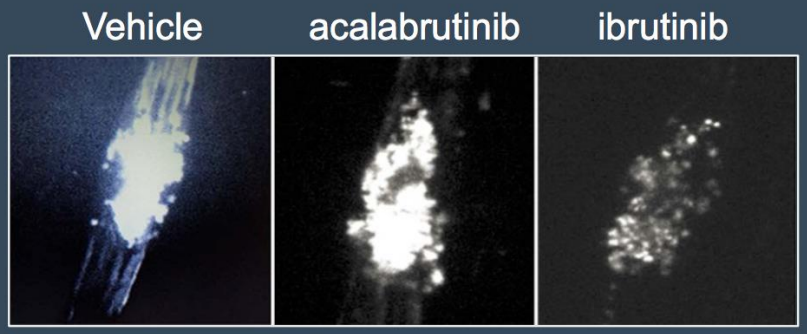
Reported in ≥20% patients

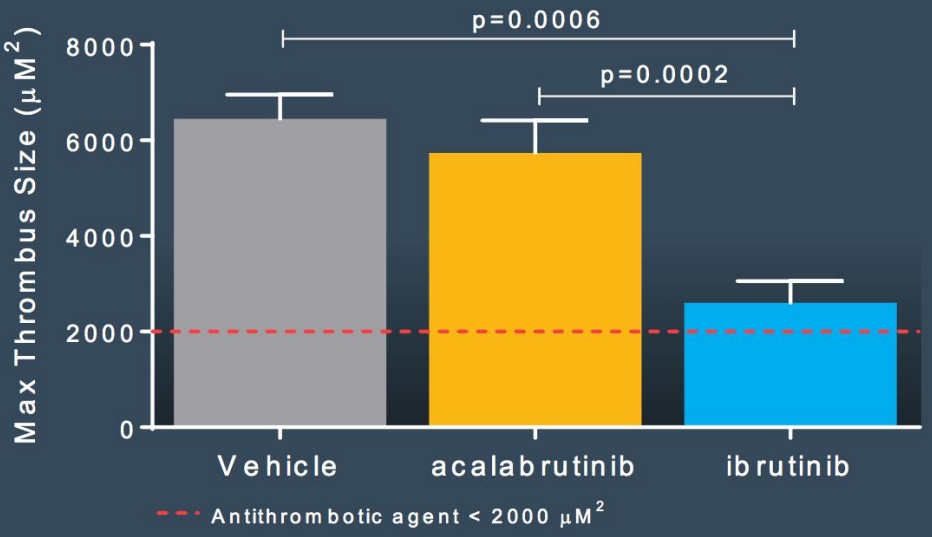
Adverse Events (Treatment-Emergent), n (%)	Grade 1-2	Grade 3	N=61
Headache	26 (43)	–	26 (43)
Diarrhea	23 (38)	1 (2)	24 (39)
Increased weight	15 (25)	1 (2)	16 (26)
Pyrexia	12 (20)	2 (3)	14 (23)
Upper respiratory tract infection	14 (23)	–	14 (23)
Fatigue	11 (18)	2 (3)	13 (21)
Peripheral edema	13 (21)	–	13 (21)

01Oct2015; R/R CLL patients.

Acalabrutinib Does Not Impair Thrombus Formation *In Vivo*

- A side effect of Tec kinase inhibition is bleeding due to impaired platelet aggregation
- Acalabrutinib does not inhibit Tec which results in no impairment of thrombus formation
- METHODS:
  - Fluorescently labelled human platelets were pre-incubated with vehicle, acalabrutinib or ibrutinib.
  - The platelets were then administered to mice.
  - A laser was used to induce vascular injury





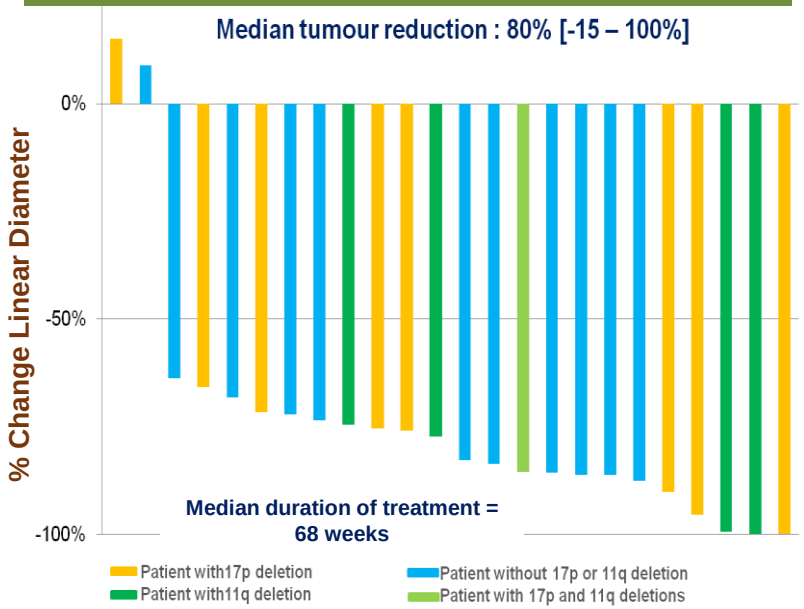
Covey, et al. *Cancer Res.* 2015;2596.

Study ONO-4059POE001 (Phase 1b)

ONO/GS-4059 has completed a single agent Phase 1 dose escalation study in CLL and NHL

Data is investigator reported and has not been audited or corroborated by Gilead

CLL Response[1]



NHL Response[2,3]

Disease	Best ORR % (n)
Mantle cell	60% (10)
Non-GCB DLBCL	47% (15)
Waldenstrom's	33% (3)
GCB-DLBCL	0% (2)
Follicular	0% (5)
Marginal zone	0% (1)

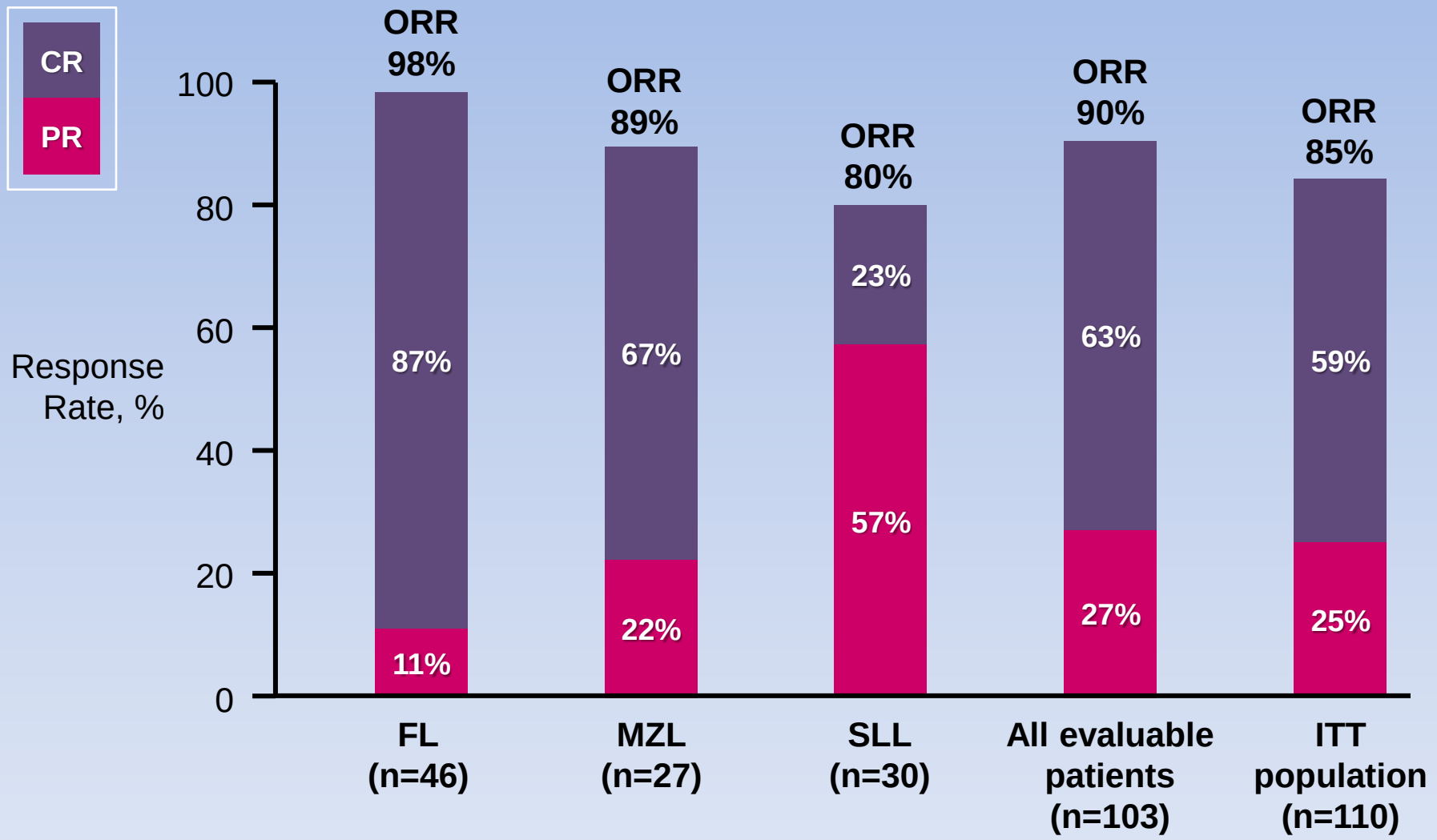
- Best Overall Response (BOR):
  - All patients: 21/25 (89%)
  - 17p deletion: 8/9 (89%)
  - Refractory disease: 13/15 (87%)

- Responses in non-GCB DLBCL, MCL, and WM

1. Fegan C, et al. Abstract #3328. ASH, 2014
2. Rule S, et al. Abstract #P461. EHA, 2014
3. Data on File

Lenalidomide + Rituximab (R2) in Untreated Indolent Lymphoma

Response Rates



Fowler NH, et al. *Lancet Oncol.* 2014,15:1311-1318.

Phase 2 Study of Ibrutinib Plus Rituximab in Treatment-Naïve FL: Efficacy

Efficacy Outcomes*		Arm 1: Ibrutinib-R (N=60)
ORR, %		82%
CR		30%
PR		52%
SD		18%
Median time to best response, months (range)		2.7 (1.1-13.6)
PFS	Median, months (range)	NR (0.92-16.6)
	12-month rate (95% CI)	86% (72.8, 93.1)
OS	Median, months (range)	NR (5.8-19.3)
	12-month rate (95% CI)	98% (88.6, 99.8)
Median DOR, months (range)		NR (0.03-11.9)
Median duration of ibrutinib treatment, months (range)		12.55 (0.8-19.6)

Fowler et al. ASH 2015. Abstract 470.

Alliance 051103: Phase I Study of Rituximab, Lenalidomide, and Ibrutinib in Previously Untreated Follicular Lymphoma

CS Ujjani[1], SH Jung[2], B Pitcher[2], P Martin[3], SI Park[4], KA Blum[5], SM Smith[6], MS Czuczman[7], MS Davids[8], JP Leonard[3], BD Cheson[1]

[1]Georgetown University, [2]Alliance Statistics and Data Center, Duke University, [3]Weill Cornell Medical College, [4]University of North Carolina, [5]Ohio State University, [6]University of Chicago, [7]Celgene Corporation, [8]Dana-Farber Cancer Institute

Ujjani et al Blood 128:2510, 2016

Response

	Overall (n = 22)	DL 0 (n = 3)	DL 1 (n = 3)	DL 2 (n = 16)
ORR	**95%**	100%	100%	94%
CR*	63%	67%	33%	69%
PR	32%	33%	67%	25%
SD	5%	0	0	6%

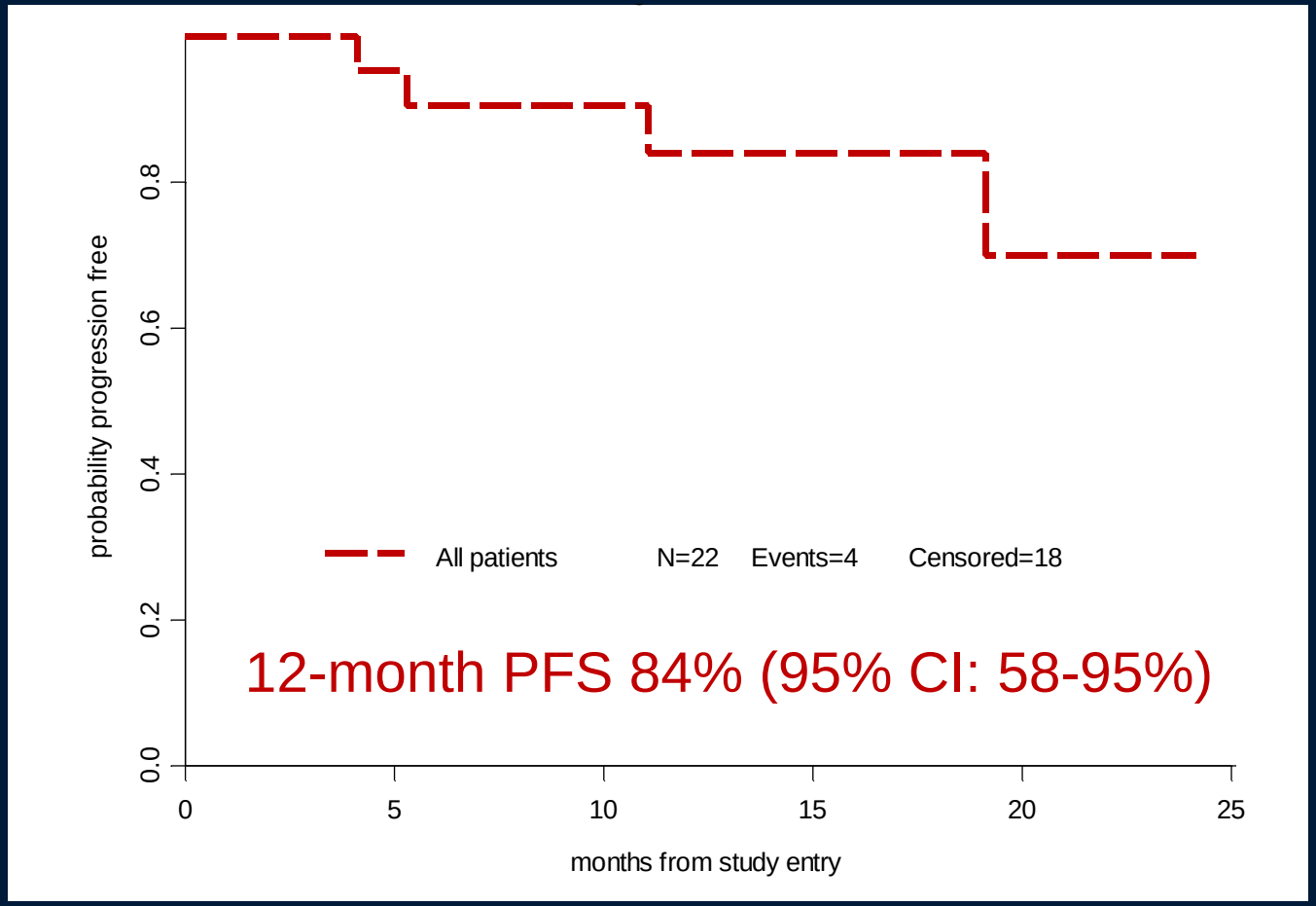
- Median time to first response: 2.3 months (1.9-11.1)
- Median time to best response: 5.5 months (1.9-20.2)

* 8 patients who achieved a negative PET/CT did not undergo confirmatory bone marrow biopsy

Ujjani et al Blood 128:2510, 2016

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Progression-Free Survival

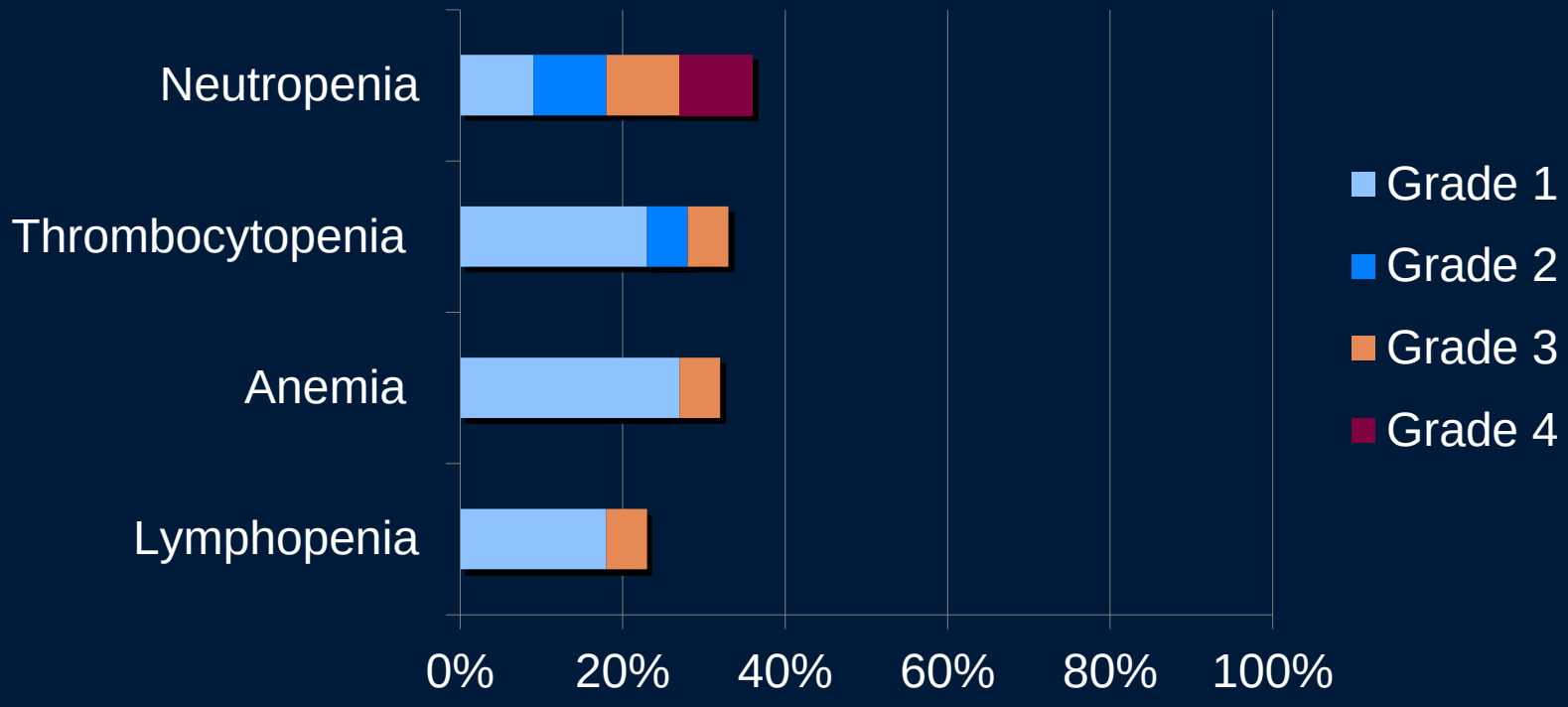


- Median follow-up of 12.3 months (2.3-24.1)
- All patients still alive

Ujjani et al Blood 128:2510, 2016

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

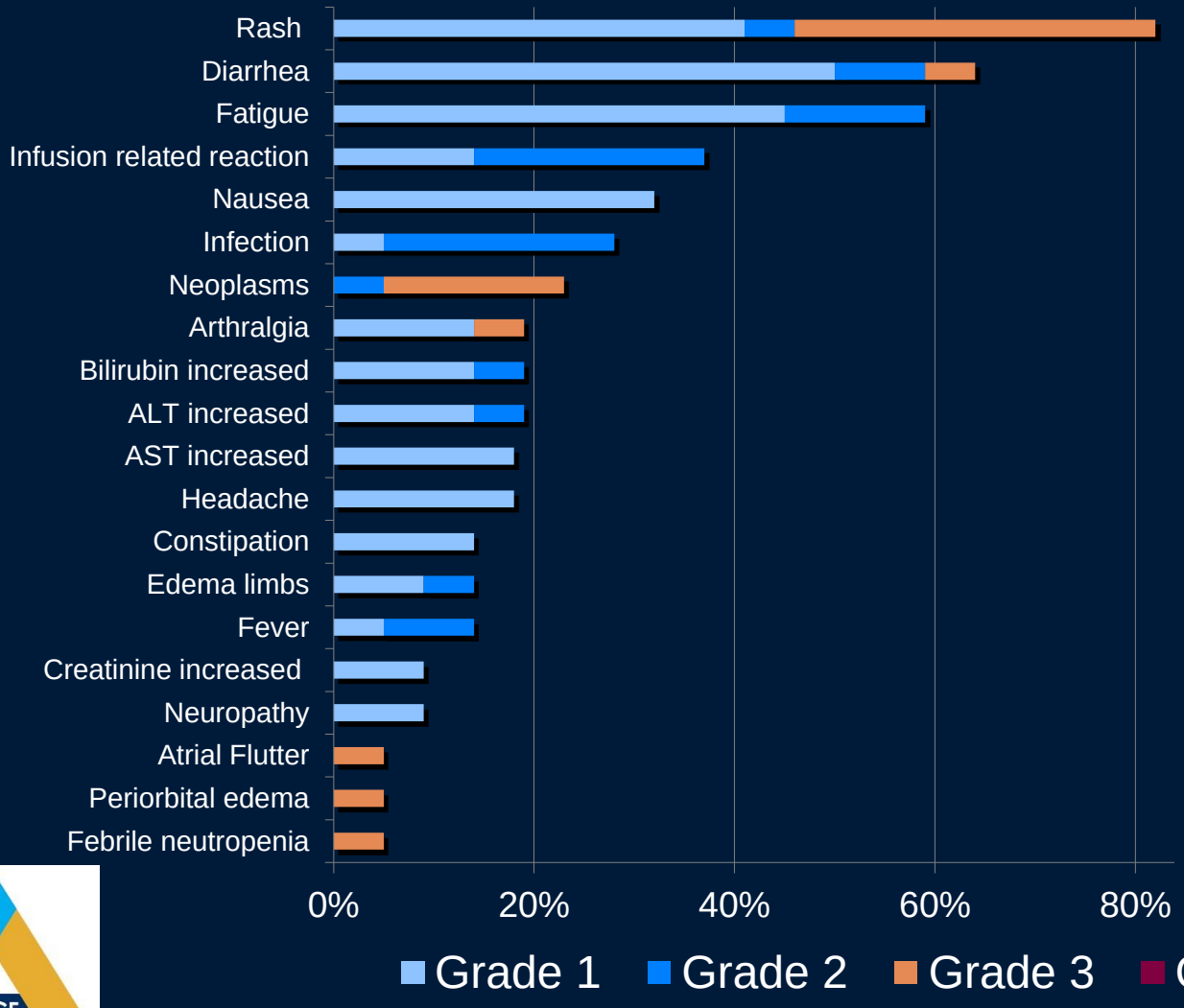
Adverse Events: Hematologic



Hematologic toxicity profile was similar to R-Len in front-line setting

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Adverse Events: Non-Hematologic



Compared to R-Len in front-line, there was increased:

- Rash
- Diarrhea
- Arthralgia
- Neoplasm
  - Cutaneous (2)
  - Carcinomas (3)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Rash

	Overall (n = 22)	DL 0 (n = 3)	DL 1 (n = 3)	DL 2 (n = 16)
All Grades	**82%**	100%	67%	81%
Grade 1/2	46%	67%	33%	44%
Grade 3	36%	33%	33%	38%

- Definitions based on NCI CTCAE criteria, version 4.03
  - Grade 1: < 10% body surface area (BSA) involved
  - Grade 2: 10-30% BSA involved, limiting instrumental activities of daily living (ADLs)
  - Grade 3: > 30% BSA involved, limiting self care ADLs

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Follow up

- 11 of 22 patients required dose reduction due to toxicity (7 due to rash)
- 12 patients have discontinued therapy due to:
  - Progression (n=2)
  - Adverse events (n=6)
    - Grade 3 rash (2), Grade 3 atrial flutter (1), Grade 3 diarrhea (1), hypertension (1), depression (1)
  - Patient decision (n=2)
  - Carcinoma requiring systemic therapy (n=2)

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Ujjani et al Blood 128:2510, 2016

Safety and Activity of the Chemotherapy-free Triplet of Ublituximab, TGR-1202, and Ibrutinib in Relapsed B-cell Malignancies

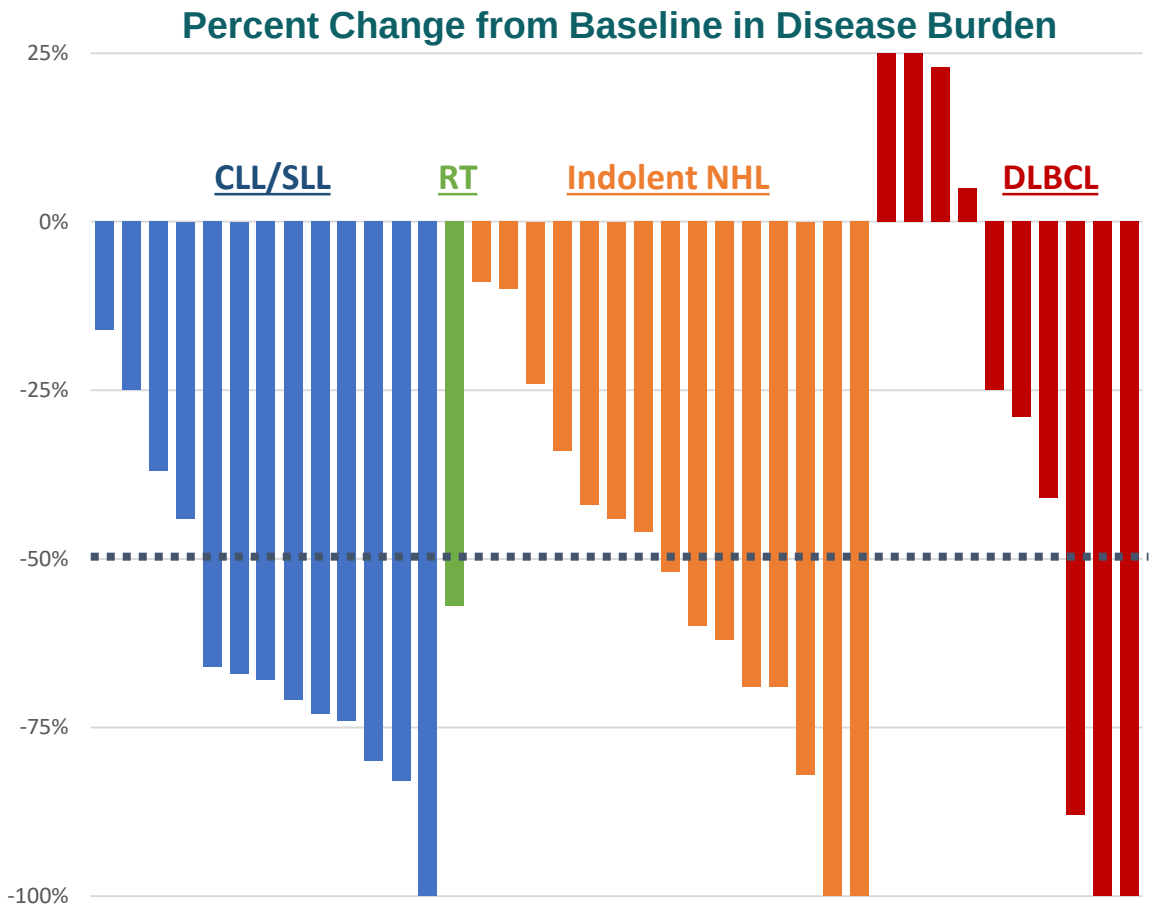
Nathan Fowler, MD[1], Loretta Nastoupil, MD[1], Matthew Lunning, DO[2], Julie Vose, MD[2], Tanya Siddiqi, MD[3], Christopher Flowers, MD[4], Jonathon Cohen, MD[4], Jan Burger, MD, PhD[1], Marshall T. Schreeder, MD[5],
Myra Miguel, RN[1], Susan Blumel, RN, BSN[2], Brianna Phye, BS[3], Emily K. Pauli, PharmD[5], Kathy Cutter, RN[5], Peter Sportelli[6], Hari P. Miskin, MS[6], Michael S. Weiss[6], Swaroop Vakkalanka, PhD[7], Srikant Viswanadha, PhD[8] and Susan O'Brien, MD[9]

[1]MD Anderson Cancer Center, Houston, TX; [2]University of Nebraska Medical Center, Omaha, NE; [3]City of Hope National Medical Center, Duarte, CA; [4]Emory University/Winship Cancer Institute, Atlanta, GA; [5]Clearview Cancer Institute, Huntsville, AL; [6]TG Therapeutics, Inc., New York, NY; [7]Rhizen Pharmaceuticals S.A, La Chaux-de-Fonds, Switzerland; [8]Incozen Therapeutics, Hyderabad, India; [9]University of California Irvine Cancer Center, Orange, CA.

PRESENTED AT: ASCO Annual '15 Meeting

TGR-1202 + Ublituximab Doublet

- 55 patients treated to date
  - 60% ≥3 prior therapies
  - 51% refractory to prior therapy
- Combination well tolerated
  - Minimal Gr. 3/4 AE's
- Clinical activity demonstrated in CLL, indolent NHL, and aggressive NHL

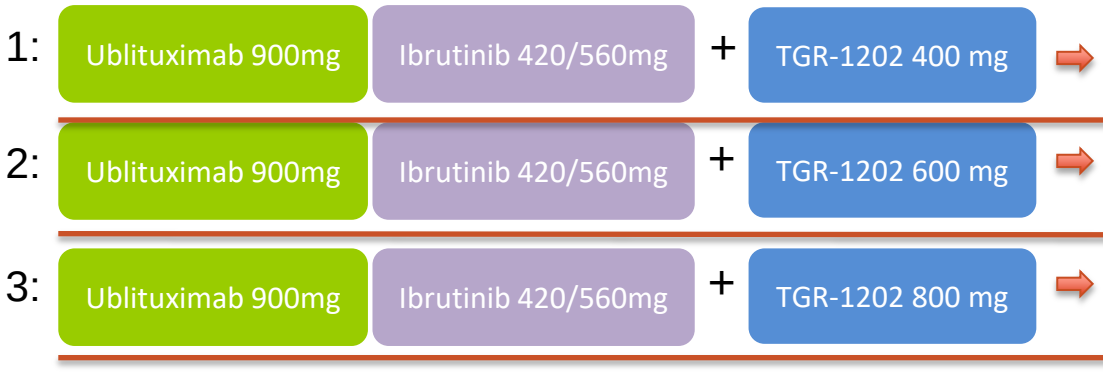


Lunning et al, ASCO 2015

Safety: TGR-1202 + Ublituximab + Ibrutinib

Cohort Summary

- CLL and NHL cohorts evaluated separately



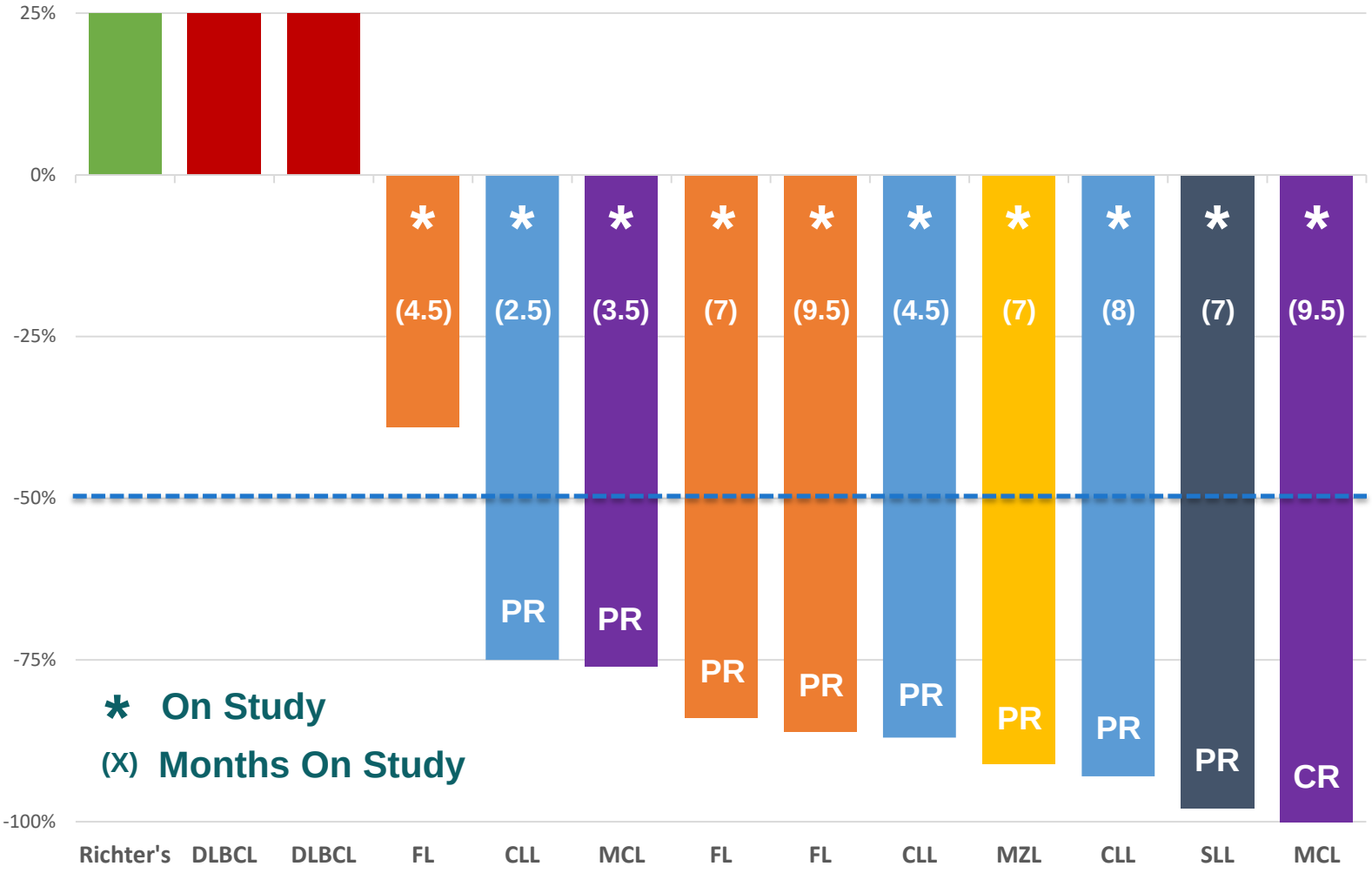
	NHL Pts	# DLT	CLL Pts	# DLT
1:	3	0	5	1*
2:	4	0	0	0
3:	4	0	0	0

**DLT of reactivated varicella zoster – no additional DLT's to date in CLL cohort*

- Median time on study = 4 mos (range 1 – 9 mos)
- DLT in CLL 400 mg cohort
- 800 mg TGR-1202 cohort cleared in NHL

Activity in NHL: TGR-1202 + Ublituximab + Ibrutinib

Best Percent Change from Baseline in Disease Burden



Ongoing Trials With Btk Inhibitors in FL

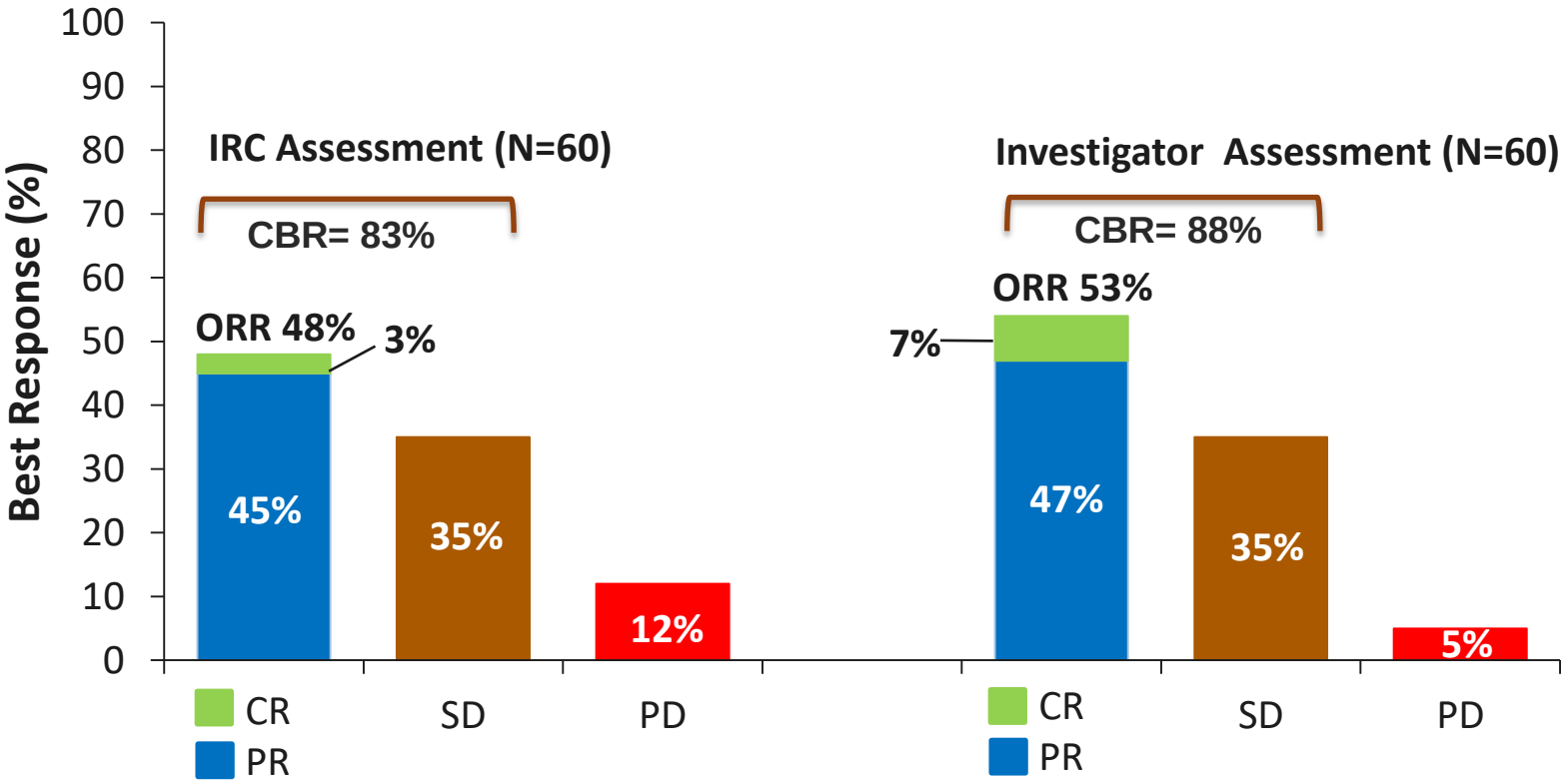
Drugs	Disease Status	Sponsor
Acalabrutinib (ACP-196)+pembrolizumab	R/R	Acerta
Acalabrutinib+ACP-319	R/R	Acerta
Acalabrutinib+rituximab	R/R	Acerta
Ono/GS-4059+idelalisib/entospletinib+obinutuzumab	R/R	Gilead
Ibrutinib+Venetoclax	R/R	Georgetown
Ublituximab+ibrutinib	R/R	TG Therapeutics
Ublituxumab+TGR-1202+ibrutinib	Front-line	TG Therapeutics

Single-Agent Ibrutinib Demonstrates Efficacy and Safety in Patients with Relapsed/Refractory Marginal Zone Lymphoma: A Multicenter, Open-Label, Phase 2 Study

Ariela Noy, MD[1], Sven de Vos, MD, PhD[2], Catherine Thieblemont, MD, PhD[3], Peter Martin, MD[4] , Christopher Flowers, MD[5], Franck Morschhauser MD, PhD[6], Graham P. Collins, MD, PhD[7], Shuo Ma, MD, PhD[8], Morton Coleman, MD[9], Shachar Peles, MD[10], Stephen Smith, MD[11,12], Jacqueline Barrientos, MD[13], Alina Smith[14], Brian Munneke, PhD[14], Isaiah Dimery, MD[14], Darrin Beaupre, MD, PhD[14], Robert Chen, MD, PhD[15]

[1]Department of Medicine, Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]APHP, Hopital Saint-Louis, Hemato-oncology Department – Paris Diderot University, Sorbonne Paris-Cité, Paris, France; [4]Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY; [5]Winship Cancer Institute of Emory University, Atlanta, GA; [6]Hematologie, Centre Hospitalier Universitaire, Université de Lille, EA GRIIOT, Lille, France; [7]Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [8]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL; [9]Center for Lymphoma and Myeloma, New York-Presbyterian Hospital and Weill Medical College, New York, NY; [10]Florida Cancer Specialists, Atlantis, FL; [11]Department of Medicine, Division of Medical Oncology, University of Washington, Seattle, WA; [12]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [13]CLL Research Treatment Program, Hofstra Northwell School of Medicine, Long Island NY;[14]Pharmacyclics, LLC, an AbbVie Company, Sunnyvale, CA; [15]City of Hope National Medical Center, Duarte, CA

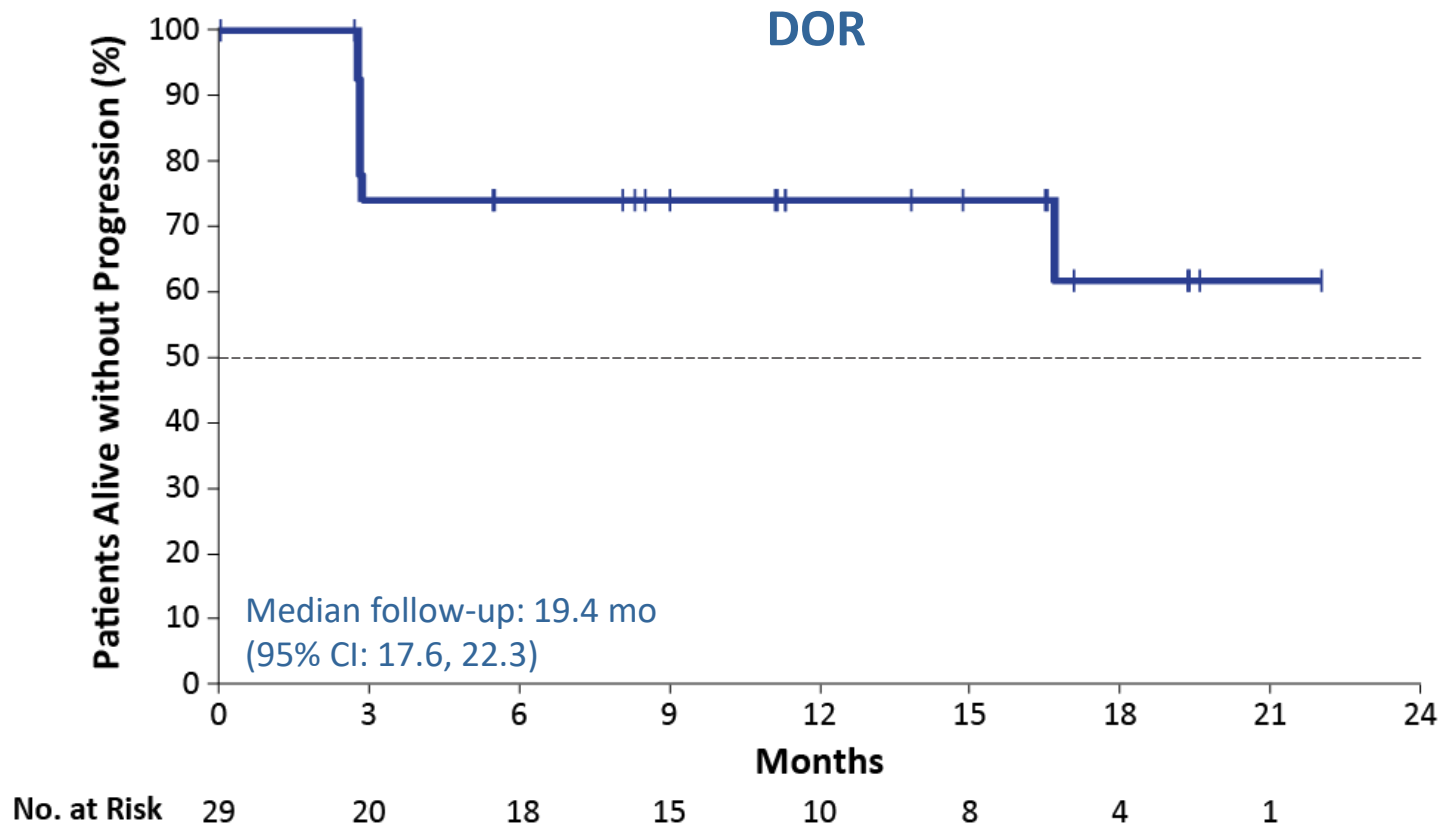
Ibrutinib Results in Clinical Benefit in the Majority of Patients With R/R MZL



- Clinical efficacy (IRC assessment) as judged by ORR was 48%, and clinical benefit rate (CBR = PR+CR+SD) was 83%.
- Concordance rate for ORR between IRC and investigator assessment was 85%.
- Median time to initial response: 4.5 months and to best response: 5.2 months.

ASH 2016, PCYC-1121, Noy et al.

Ibrutinib Demonstrated Durable Responses

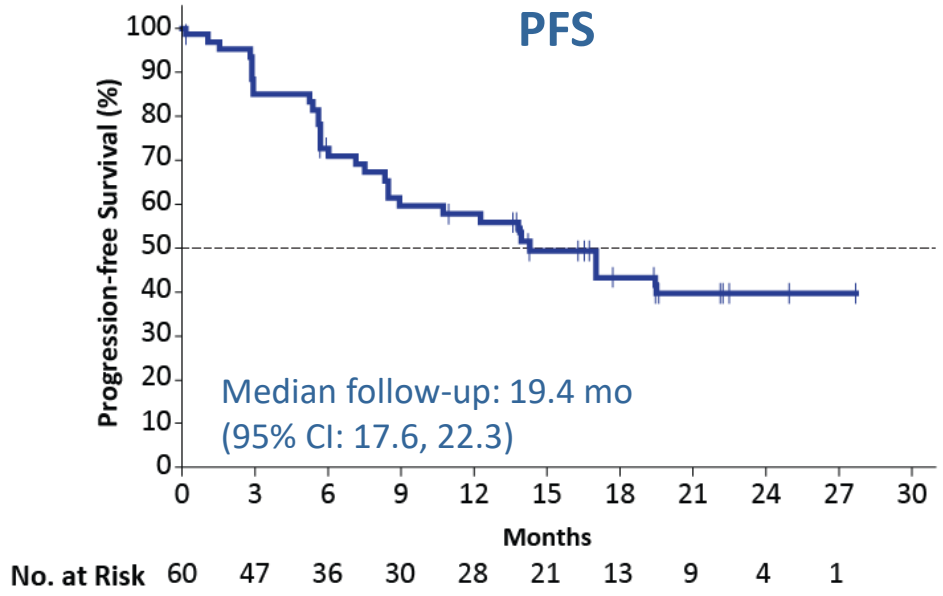


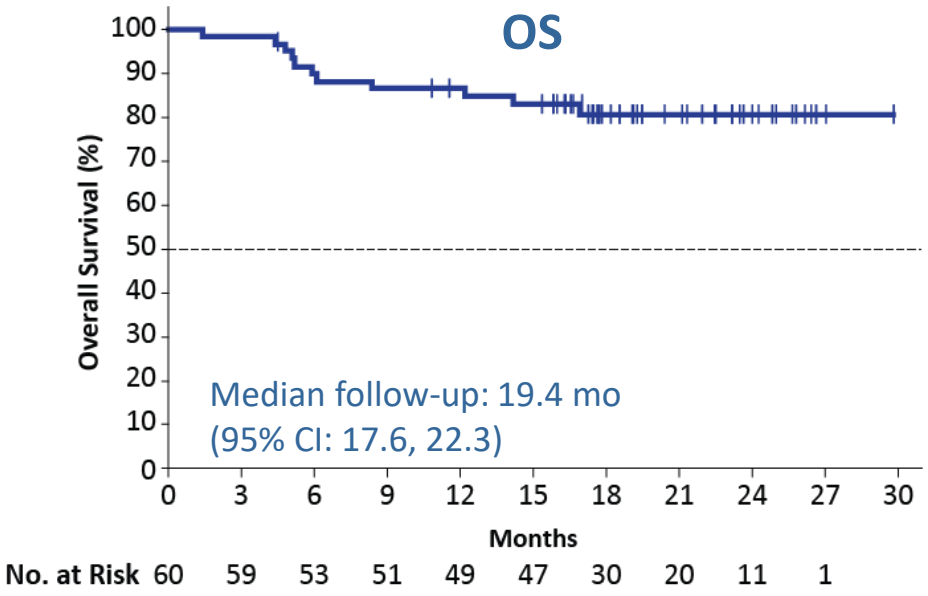
	IRC	Investigator
Median DOR (95% CI)	NR (16.7, NR)	19.4 mo (7.3, NR)
18-mo DOR rate	62%	54%

NR, not reached

ASH 2016, PCYC-1121, Noy et al.

Progression-Free Survival and Overall Survival





	IRC	Investigator
Median PFS (95% CI)	14.2 (8.3, NR)	15.7 (12.0, NR)
18-mo PFS rate	45%	49%

	Investigator
Median OS (95% CI)	NR (NR, NR)
18-mo OS rate	81%

- Median PFS by MZL subtype was 19.4 months (95% CI, 8.2-NR) for splenic, 13.8 months (95% CI, 8.3-NR) for extranodal, and 8.3 months (95% CI, 2.8-NR) for nodal MZL.

NR, not reached

ASH 2016, PCYC-1121, Noy et al.

Conclusions

- Btk inhibitors have modest single agent activity in follicular NHL
- Greater activity in CLL, WM, MZL
- Thus far, combinations have not been paradigm changing
- Further research would be facilitated by availability of new biomarkers
- Potential to improve patient outcome?