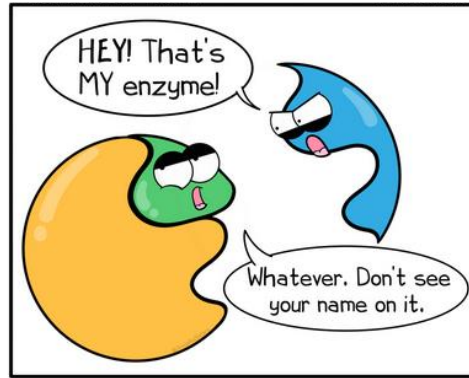


Pathways Inhibitors for CLL Therapy



Competitive Inhibitors: If it fits, it sits.



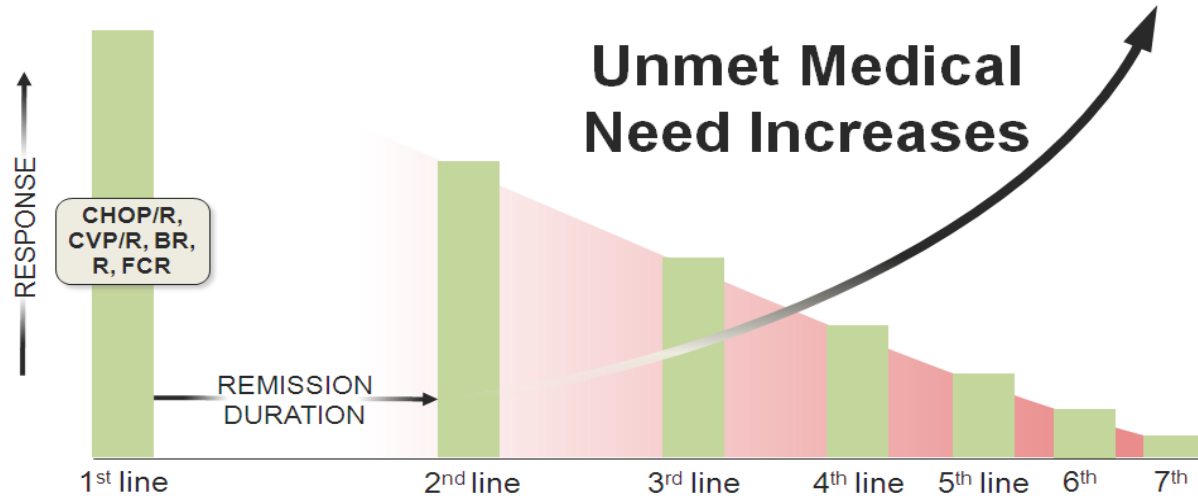
DONALD AND BARBARA
ZUCKER SCHOOL *of* MEDICINE
AT HOFSTRA/NORTHWELL

Jacqueline C. Barrientos, MD, MS
Feinstein Institute for Medical Research
Zucker School of Medicine at Hofstra/Northwell

Disclosures

- Research & Support/P.I.: Pharmacyclics/Abbvie, Oncternal
- Scientific Advisory Board: Pharmacyclics/AbbVie, Acerta, Genentech, Bayer, Gilead
- Honoraria: Janssen
- I will be discussing off-label use of drugs

Challenges in the Treatment of CLL

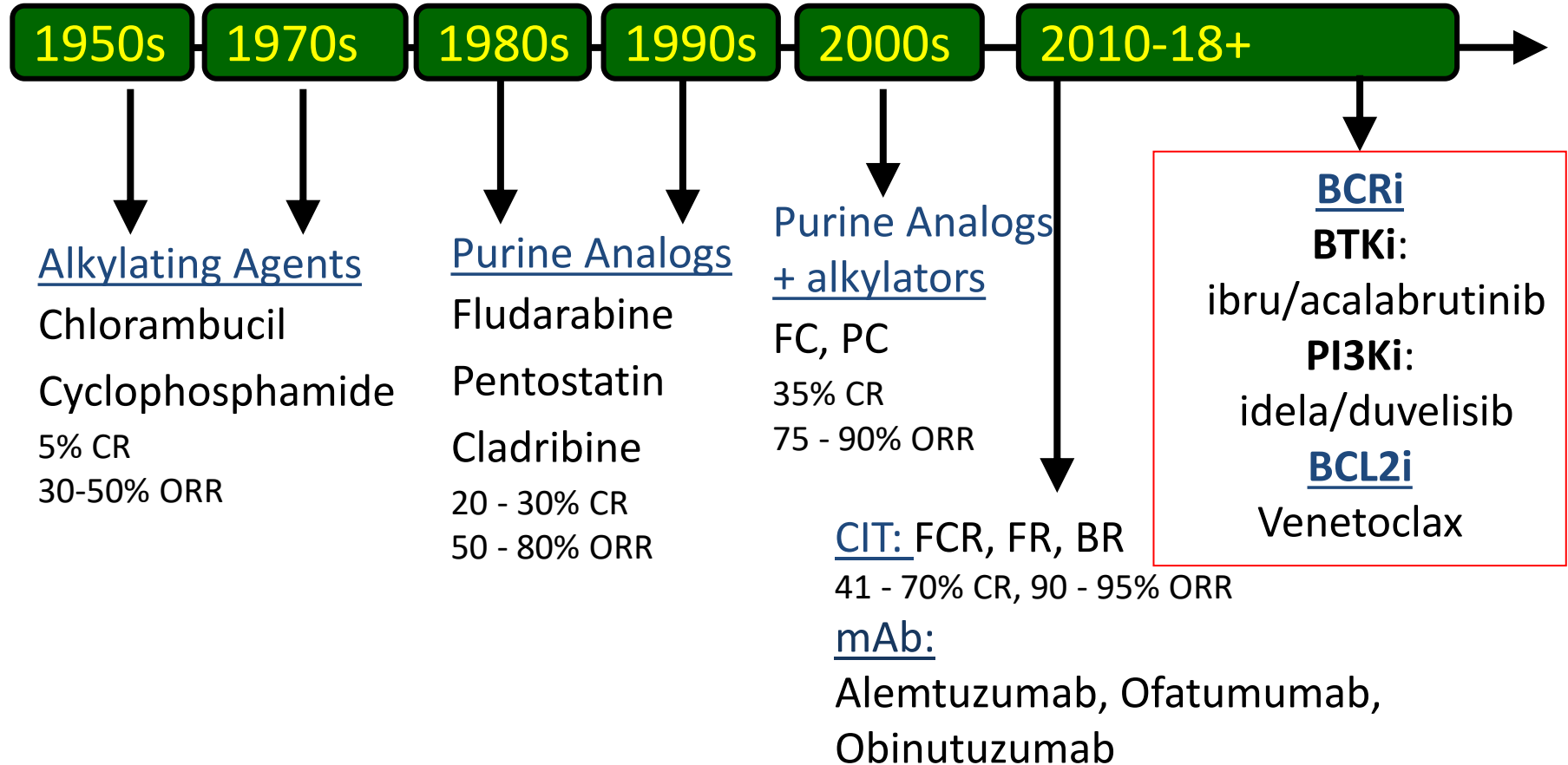


Drugs with new mechanisms of action are needed that have substantial single-agent activity and can be combined with current and emerging treatment options

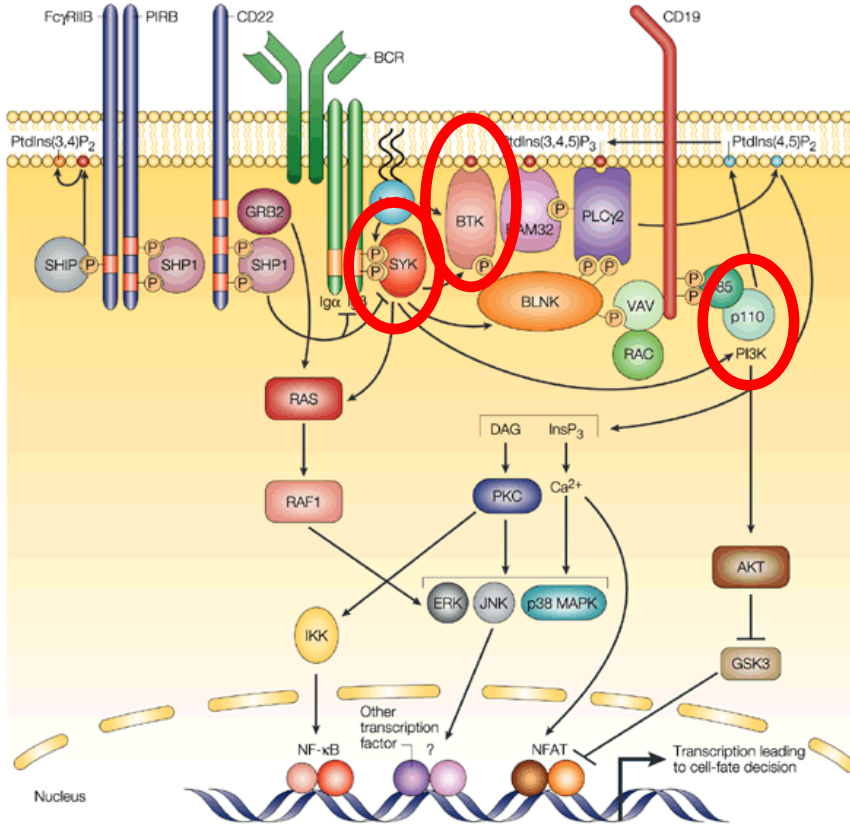


"I think you'll be interested in the next patient. He's ninety two years old and accompanied by his parents."

CLL Drug Development Timeline



Targeting of BCR signaling in CLL



BCR-associated kinases are targets of new drugs in preclinical and clinical development:

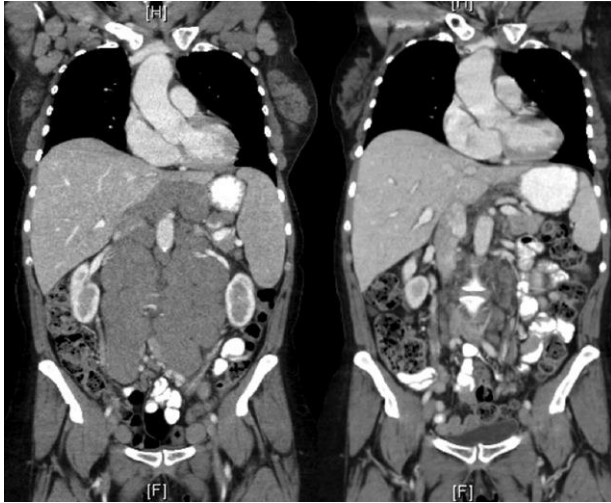
- **SYK** (Spleen tyrosine kinase) inhibitors: fostamatinib, entospletinib
- **BTK** (Bruton's tyrosine kinase) inhibitors: Ibrutinib, acalabrutinib, zanubrutinib, tirabrutinib
- **PI3K** (Phosphatidylinositol 3-kinase) inhibitors: Idelalisib, duvelisib, copanlisib, umbralisib

Effect of BCR inhibitors

Rapid reduction in:

- Lymph node volume
- Disease related symptoms

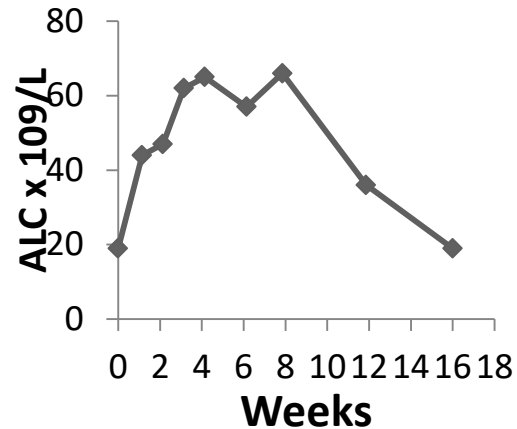
**“redistribution
lymphocytosis”**



Pre

2 months

Absolute Lymphocyte Count



Novel Targeted Agents and the Need to Refine Clinical End Points in Chronic Lymphocytic Leukemia

Bruce D. Cheson, *Lombardi Comprehensive Cancer Center, Georgetown University Hospital, Washington, DC*

John C. Byrd, *The Ohio State University, Columbus, OH*

Kanti R. Rai, *Long Island Jewish Medical Center, New Hyde Park, NY*

Neil E. Kay, *Mayo Clinic, Rochester, MN*

Susan M. O'Brien, *The University of Texas MD Anderson Cancer Center, Houston, TX*

Ian W. Flinn, *Sarah Cannon Research Institute, Nashville, TN*

Adrian Wiestner, *National Institutes of Health, Bethesda, MD*

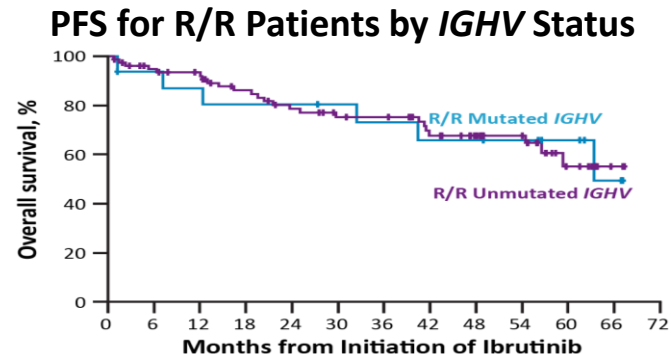
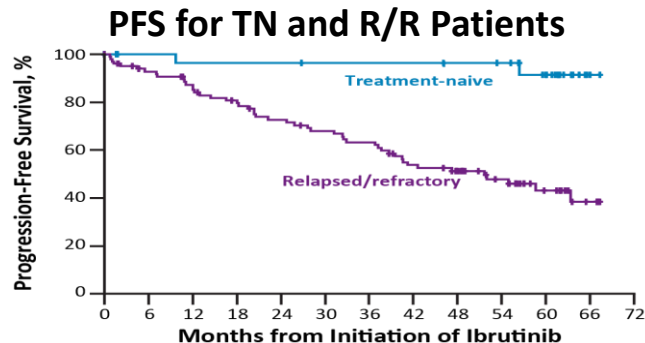
Thomas J. Kipps, *Moore's Cancer Center, University of California San Diego, San Diego, CA*

have served as useful surrogate markers for assessing the clinical benefit of therapy, thereby accelerating the pace of approval of novel agents for use in the treatment of patients.

Whereas the defined criteria of CR, PR, SD, and PD have helped to stratify patients into subgroups that correlate with PFS in many studies involving the use of traditional chemotherapy, it has recently become evident that these definitions may not faithfully predict outcome with newer agents under clinical investigation. In particular, the current definition of PD may not adequately serve as a surrogate marker for poor outcome, particularly for therapeutics that activate CLL B cells for subsequent immunologic destruction or generate an altered trafficking of B cells from different compartments to the blood.

BTK inhibitors

5-Year Experience Ibrutinib in Patients With TN and R/R CLL/SLL



PFS Summary		TN (n=31)	R/R (n=101)
Median, months (95% CI)		Not reached	52
60-month, %		92	43
Median by cytogenetics, months	<i>IGHV</i> unmutated		43
	<i>IGHV</i> mutated		63
	Del(11q)		55
	Del(17p)		26
	No del(11q), del(17p), trisomy 12 or del(13q)		Not reached
Median by prior therapies, months (95% CI)	1-2		63
	3		59
	≥4		39

BTK Inhibitors in CLL

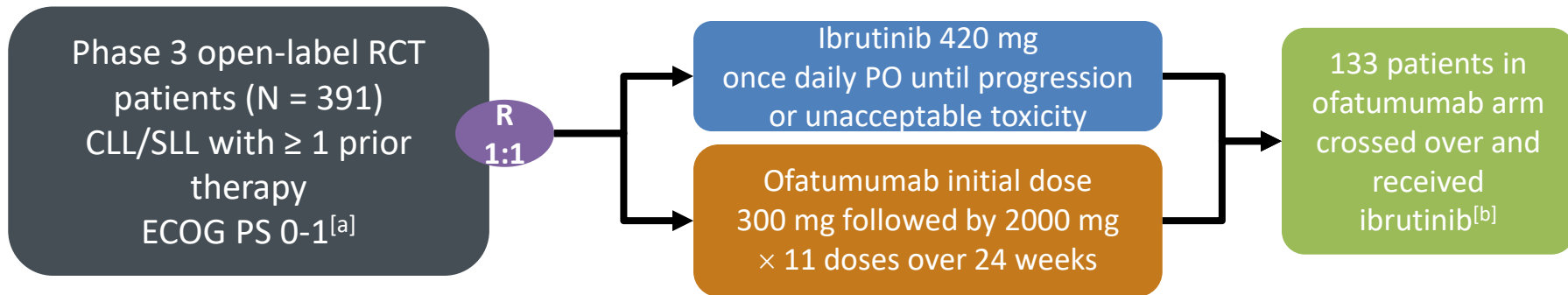
On-Label and Off-Label Uses

- Ibrutinib
 - FDA-approved in R/R CLL (2014) and front-line CLL (2016)^[a]
- Acalabrutinib
 - FDA-approved in R/R MCL^[b]
 - NCCN-recommended for use in R/R CLL based on available evidence^[c]

BTK inhibition has changed the therapeutic landscape for CLL

RESONATE

Ibrutinib in Previously Treated CLL



Parameter	Ibrutinib	Ofatumumab	HR (P Value)
Median PFS, mo ^[b]	NR	8.1	0.133 (<.0001)
3-y PFS, % ^[b]	59	3	NR

Responses to ibrutinib were also observed in patients with del(17p) CLL

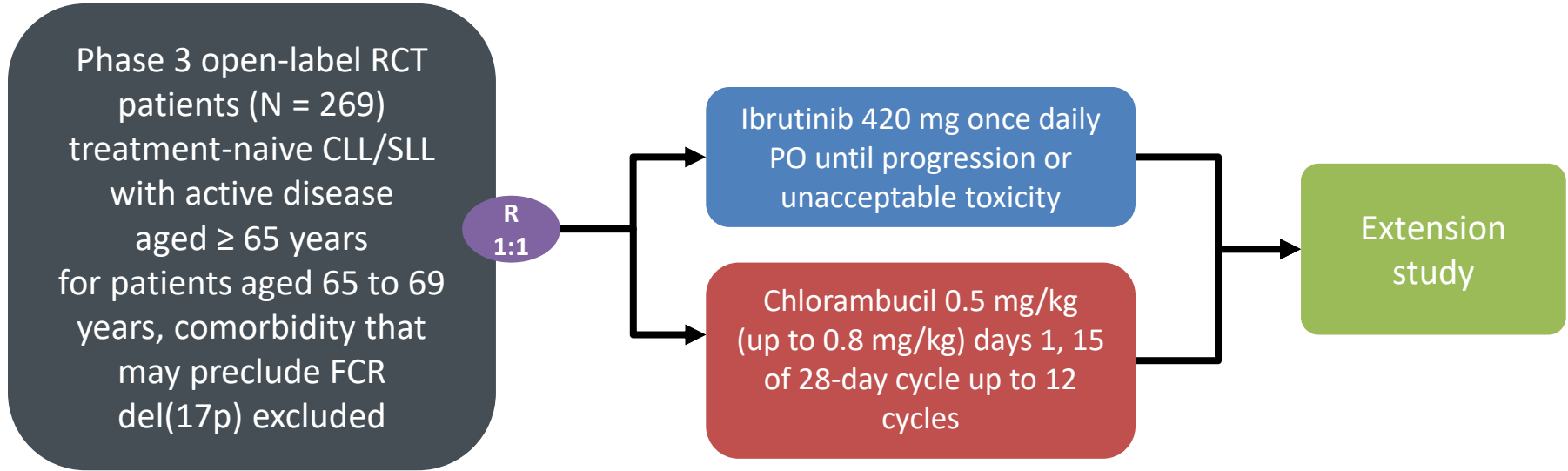
RESONATE

Safety Profile of Ibrutinib in Previously Treated CLL

- Key AEs: diarrhea (48%), fatigue (28%), nausea (26%), pyrexia (24%), anemia (23%)^[a]
- Key grade ≥ 3 AEs: neutropenia (16%), pneumonia (7%); 10 patients developed AF^[a]
- Some toxicities occur in first 3 to 4 months and resolve^[b]
- Some toxicities *may* relate to off-target effects of ibrutinib

RESONATE-2

Ibrutinib in Previously Untreated CLL



– Ibrutinib vs chlorambucil

- ORR \rightarrow 86% vs 35% ($P < .001$)^[a]
- Median PFS \rightarrow NR vs 18.9 mo (HR 0.16; $P < .001$)^[a]
- 24-mo OS \rightarrow 95% vs 84% (HR 0.16; $P = .001$)^[b]

Toxicities With Ibrutinib in RESONATE-2

Selected AE	Primary Analysis % ^[a]	Follow-Up % ^[b]
Diarrhea	42	45
HTN	4	20
Arthralgia	16	20
AF	6	10
Major hemorrhage	4	7

- Common grade ≥ 3 AEs: neutropenia, infection^[a]
- Toxicities range from mild nuisances to serious events

Ibrutinib Has Many Off-Target Effects

Kinase	IC ₅₀ , nM	BTK Selectivity, Fold
BTK	0.5	--
BLK*	0.5	1
BMX*	0.8	1.6
CSK	2.3	4.6
FGR	2.3	4.6
BRK	3.3	6.6
HCK	3.7	7.4
EGFR*	5.6	11.2
YES	6.5	13
ErbB2*	9.4	18.8
ITK*	10.7	21.4
JAK3*	16.1	32.2
FRK	29.2	58.4
LCK	33.2	66.4
RET	36.5	73
FLT3	73	146
TEC*	78	156

Off-target effects could potentially lead to toxicities

*Kinases that contain a cysteine residue aligning with Cys-481 in BTK.
Honigberg LA, et al. *Proc Natl Acad Sci U S A*. 2010;107:13075-13080.



Atrial Fibrillation and Ventricular Arrhythmias

- Analysis in 582 patients treated at OSU^[a]
 - Estimated cumulative incidence of **AF** by time on tx:
 - 6 mo: 5.9%
 - 12 mo: 7.5%
 - 24 mo: 10.3%
 - Median time to onset of AF: 7.6 mo
 - Rate of AF increased ~4-fold with ibrutinib vs non-ibrutinib therapy (3.3 vs 0.84/100 PY)
- **Ventricular arrhythmias**^[b]
 - Very uncommon, but frequency increased vs general population (788 vs 200 to 400/100,000 PY)

Ibrutinib-Associated Bleeding

Expert Observations and Suggestions

- Most often grade 1, self-limited ecchymosis, epistaxis, hematuria
- In case of life-threatening emergency, transfuse platelets
- Have patient stop ibrutinib for 3 to 7 days before a planned surgical procedure
 - 7 days for major surgery or if CNS involved
 - Recheck after procedure to determine when safe to restart

Ibrutinib-Associated Hypertension

Expert Observations and Suggestions

- Incidence increases as patients stay on treatment longer
- Best agent to control HTN unknown
- Most patients require multiple agents
- Involve cardiology to ensure optimal management

Development of Ibrutinib Resistance

- Most commonly due to acquired mutations in *BTK* or *PLCG2*
 - Detected in 85% of patients with relapse
- Most frequent BTK mutation: C481S
- Mutations are detectable a median of 9.3 months before clinical relapse
- Testing for mutations may allow for closer monitoring, possibly earlier intervention

Acalabrutinib

A More Selective BTK Inhibitor

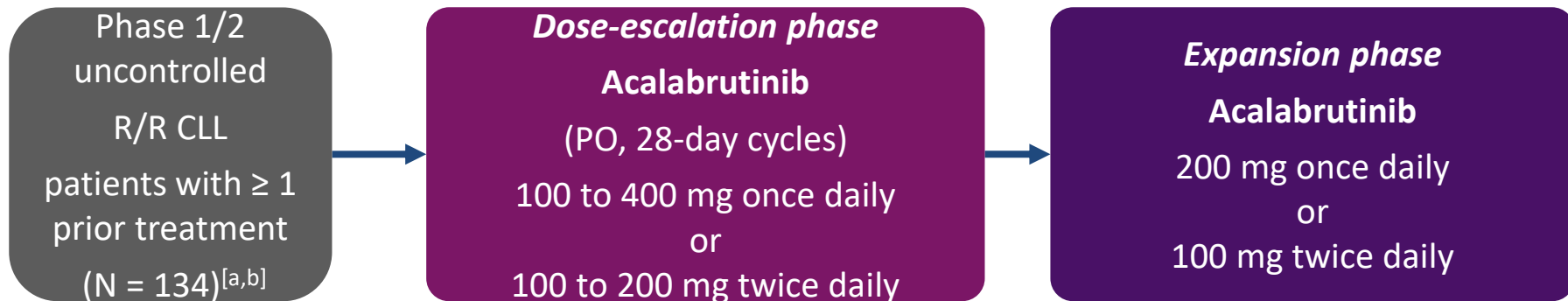
Less off-target
kinase inhibition
compared with
ibrutinib in vitro

Kinase Inhibition Average IC₅₀ (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10
ITK	>1000	4.9
BMX	46	0.8
TXK	368	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

ACE-CL-001

Acalabrutinib in R/R CLL



- Updated analysis at ASH 2017:^[b]
 - ORR 85% (93% including PRL); CR 2%
 - Median DOR NR; 18-mo DOR 85%
 - Median PFS NR; 18-mo PFS 88%

Toxicities Associated With Acalabrutinib

– Key AEs:

- Headache (46%), diarrhea (43%), URTI (28%), fatigue (27%), nausea (27%)

– Key grade ≥ 3 AEs:

- Neutropenia (11%), pneumonia (10%); HTN (3%), AF (2%)

– *Acalabrutinib-associated headache:*

- Occurs ~90 min after administration and resolves
- May occur more frequently in morning

Acalabrutinib in Ibrutinib-Intolerant Patients

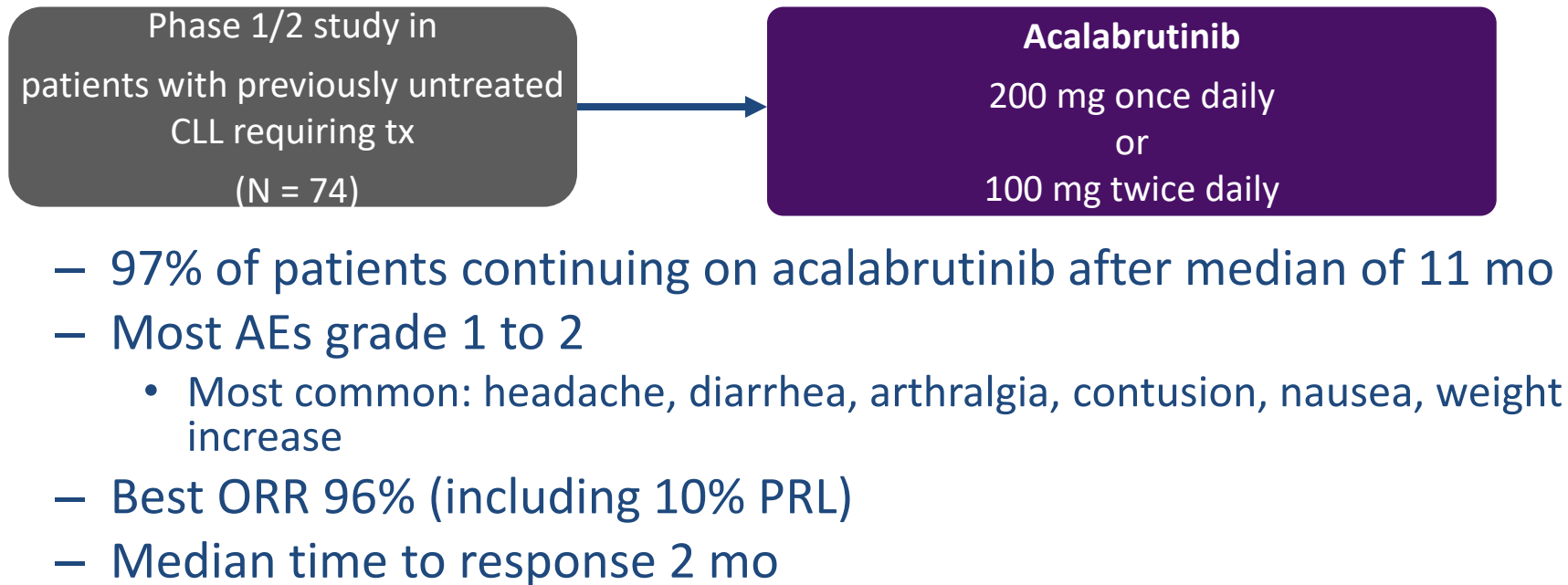
Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)

- Median duration of prior ibrutinib, 10.5 mo
- 73% of patients remained on treatment after a median of 9.5 mo
- 2 patients had discontinued acalabrutinib due to AEs

Caveats:

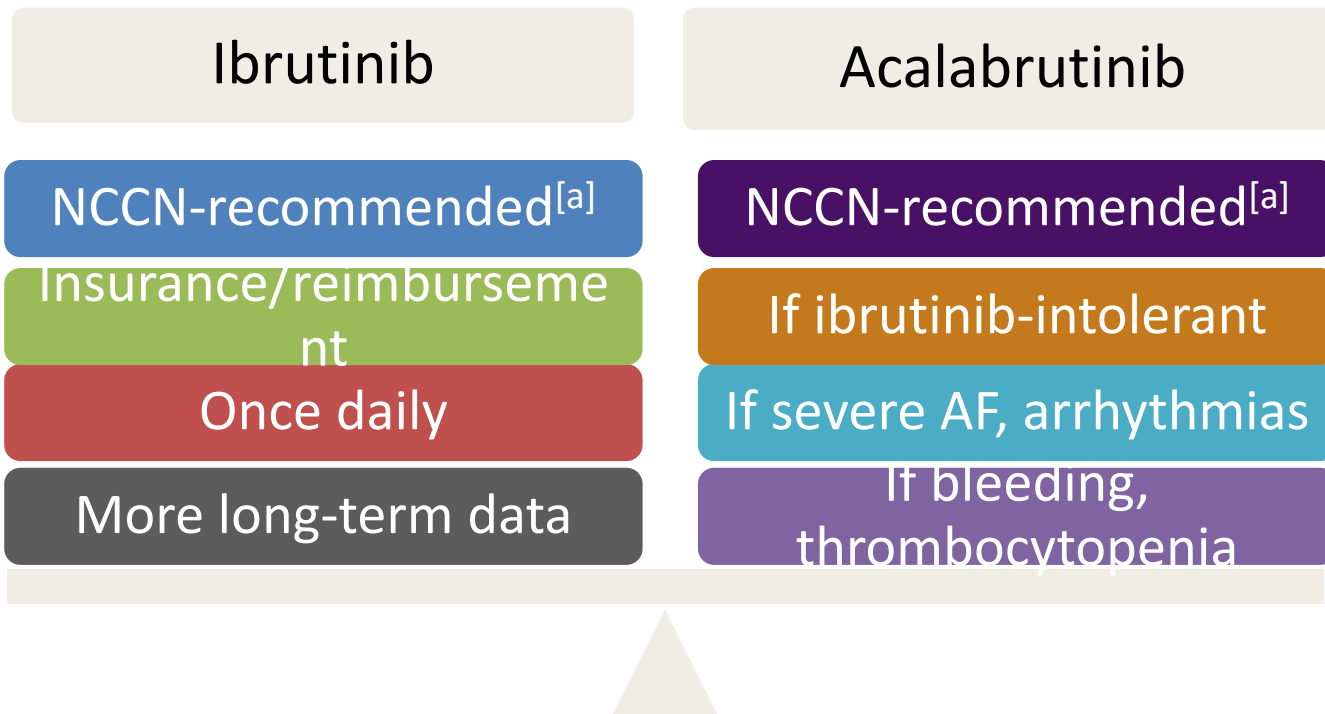
- Do not use acalabrutinib in ibrutinib-resistant patients; they share the same BTK binding site
- Acalabrutinib appears better tolerated, but some toxicities may take longer to emerge

Acalabrutinib in Front-Line CLL



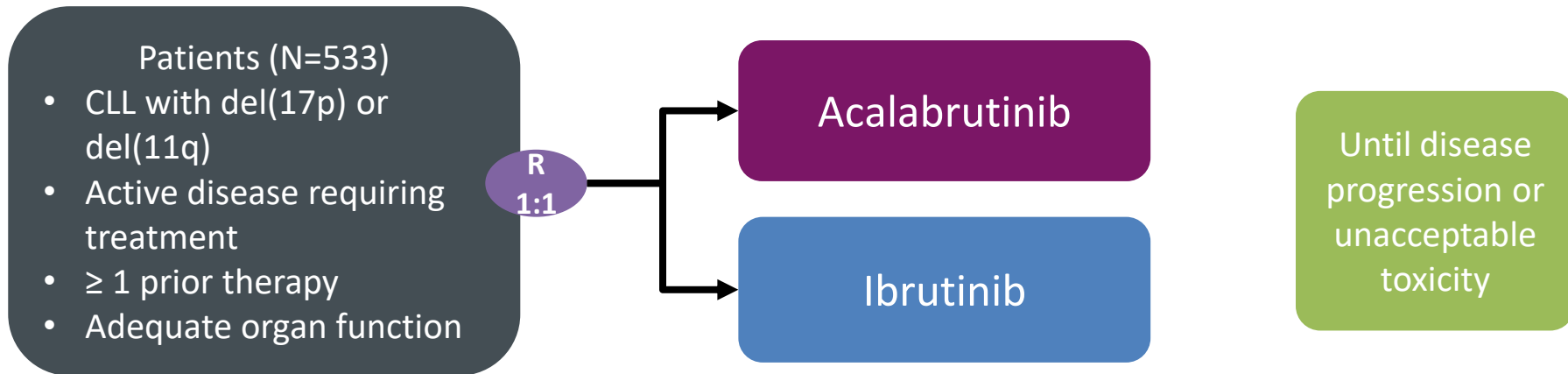
Choosing Between BTK Inhibitors

Guideline Recommendations and Expert Opinion



ELEVATE CLL R/R

Acalabrutinib vs Ibrutinib in Previously Treated High-Risk CLL



Primary outcome: PFS (noninferiority)

Secondary outcomes: grade ≥ 3 infections; Richter's transformation; AF; OS

Other Supportive Care Issues

Tumor flare

- During drug interruption: steroids, acetaminophen
- At relapse: continue ibrutinib at least until starting new therapy

Arthralgia/myalgia

- Acetaminophen, short course NSAIDs, steroids
- Often resolves

Neutropenia

- May require growth factor support
- Often occurs without infection and resolves

Opportunistic infections

- Prophylaxis for selected patients
- Watch for drug-drug interactions

Next-Generation BTK Inhibitors

Irreversible inhibitors

- GS-4059 (ONO-4059) (tirabrutinib)^[a]
- BGB311 (zanubrutinib)^[b]
 - Phase 3 underway^[c]

Reversible inhibitors

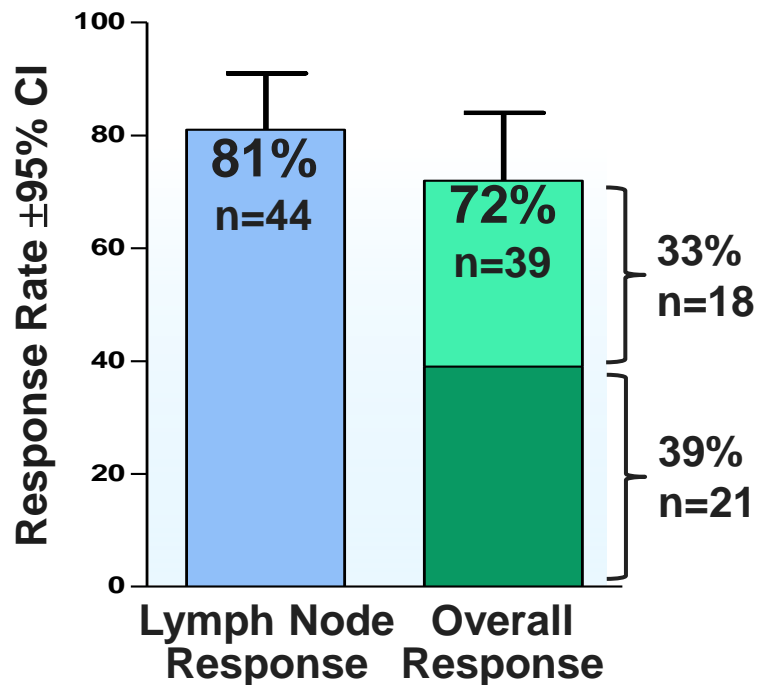
- GDC-0853^[d]
- SNS-062 (vecabrutinib)^[e]
- ARQ-531^[f]

- Early data indicate activity with novel irreversible BTK inhibitors; larger trials awaited
- Reversible inhibitors are earlier in development

a. Walter HS, et al. *Blood*. 2017;129:2808-2810; b. Tam CS, et al. *Blood*. 2016;128:642; c. ClinicalTrials.gov. NCT03336333; d. Crawford JJ, et al. *J Med Chem*. 2018;61:2227-2245; e. Neuman LL, et al. *Blood*. 2016;128:2032; f. Reiff SD, et al. *Blood*. 2016;128:3232.

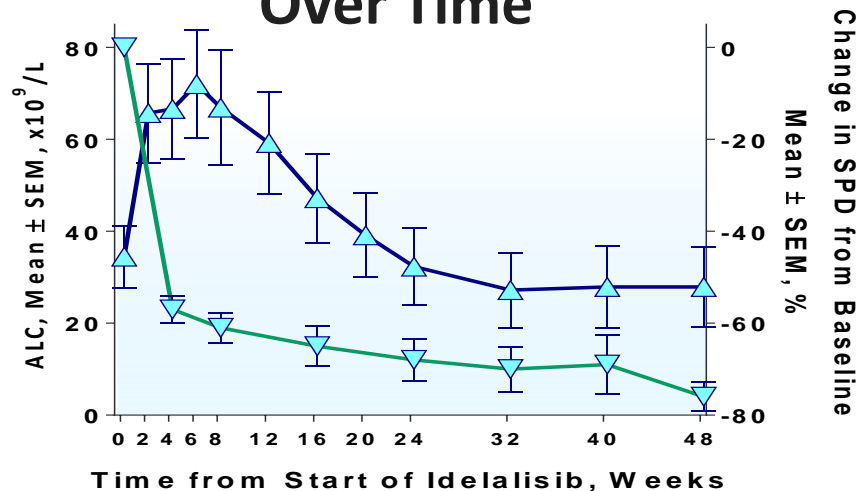
PI3K inhibitors

Idelalisib: Nodal and Overall Response Rate



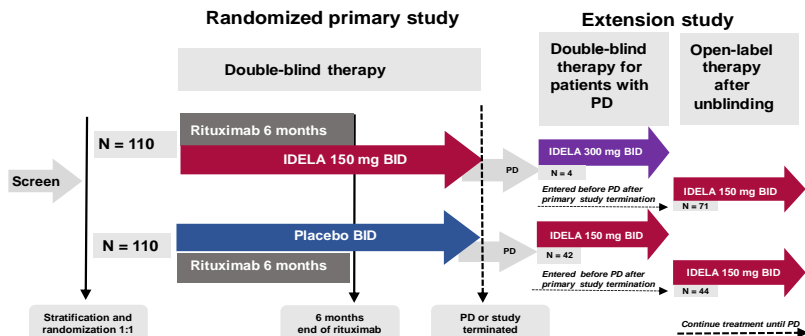
- Decrease by $\geq 50\%$ of nodal SPD
- PR with lymphocytosis (Cheson 2012)
- PR by IWCLL criteria (Hallek 2008)

ALC and Tumor Burden Over Time

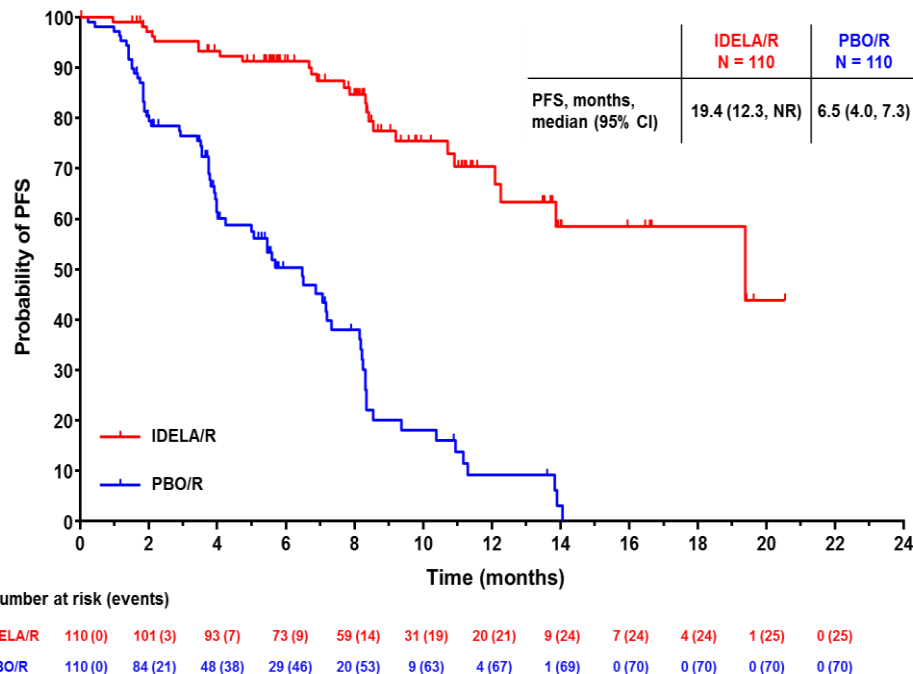


- ALC (N=54)
- SPD (N=51)

Phase III: Rituximab +/- Idelalisib



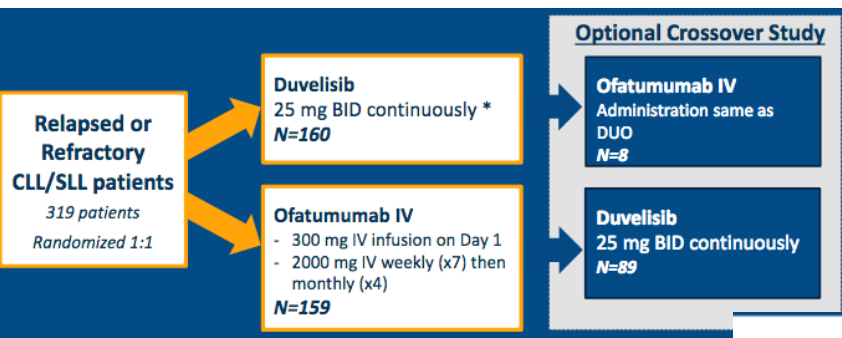
- ORR 83.6%, all PR
- PFS 19mo



Idelalisib: toxicities more common in less heavily pre-treated patients

Toxicity frequency				
	Phase I ¹	Overall relapsed ²	Upfront patients ≥ 65 years ³	Upfront idelalisib and ofatumumab
No patients	54	760	64	24
Median prior therapies	5 (2-14)	≥ 1	0	0
Median age	63 (37-82)	66 (21-91)	71 (65-90)	67.4 (58-85)
Median time on therapy (months)	15 (0.2-48.7)	-	22.4 (0.8-45.8)	7.7 (0.7-16.1)
Grade ≥ 3 transaminitis	1.9%	14%	23%	53%
Grade ≥ 3 colitis/diarrhea	5.6%	14%	42%	13%
Any grade pneumonitis	5.6%	3%	3%	13%

Phase III: Duvelisib vs Ofatumumab



- ORR 73.8%, 70% in 17p
- 0.6% CR
- PFS 13mo
- PFS 12.7mo in 17p del

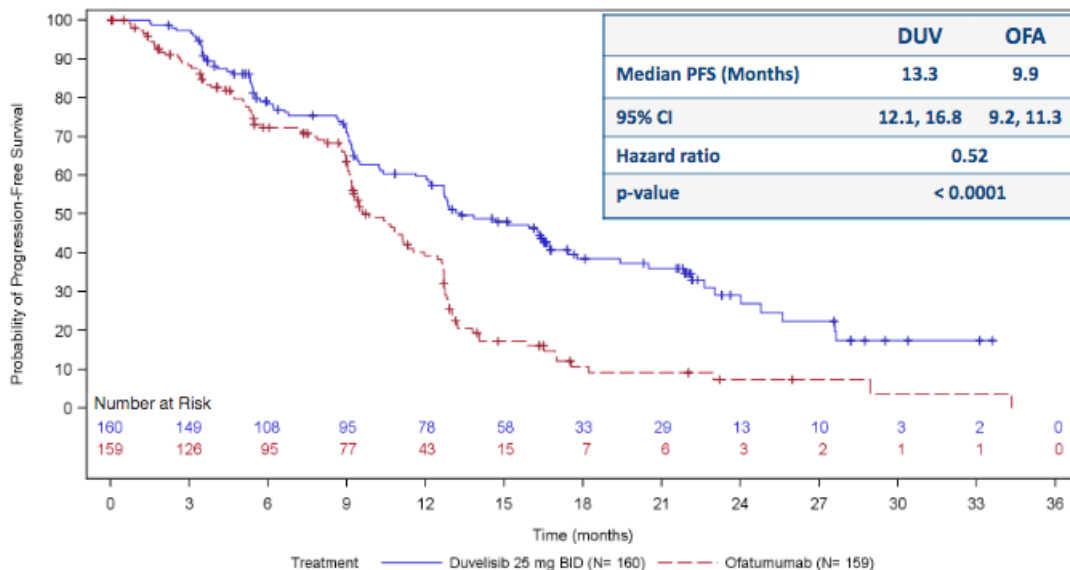


Table 3. Adverse Events in $\geq 10\%$ of Duvelisib-treated Patients

Adverse Event	All Grades		Grade 3 and above	
	Duvelisib	Ofatumumab	Duvelisib	Ofatumumab
	n (%)	n (%)	n (%)	n (%)
Any AE	156 (99)	144 (93)	138 (87)	75 (48)
Hematologic AEs				
Neutropenia	52 (33)	32 (21)	48 (30)	27 (17)
Anemia	36 (23)	16 (10)	20 (13)	8 (5)
Thrombocytopenia	23 (15)	9 (6)	12 (8)	3 (2)
Nonhematologic AEs				
Diarrhea	80 (51)	19 (12)	23 (15)	2 (1)
Pyrexia	45 (29)	16 (10)	4 (3)	1 (1)
Nausea	37 (23)	17 (11)	0	0
Cough	33 (21)	22 (14)	2 (1)	0
Pneumonia	29 (18)	9 (6)	22 (14)	2 (1)
Constipation	26 (17)	13 (8)	1 (1)	0
URTI	25 (16)	12 (8)	0	0
Vomiting	23 (15)	10 (7)	0	0
Bronchitis	21 (13)	13 (8)	5 (3)	1 (1)
Colitis	21 (13)	2 (1)	19 (12)	1 (1)
Fatigue	20 (13)	19 (12)	2 (1)	2 (1)
Decreased appetite	20 (13)	5 (3)	0	1 (1)
Weight decreased	18 (11)	3 (2)	0	0
Asthenia	18 (11)	17 (11)	3 (2)	4 (3)
Abdominal pain	16 (10)	3 (2)	3 (2)	0
Dyspnea	16 (10)	9 (6)	4 (3)	0
Rash	16 (10)	18 (12)	3 (2)	1 (1)

Abbreviations: AE = adverse event; URTI = upper respiratory tract infection.

Adverse Event	Umbralisib	Idelalisib		Duvelisib
	n = 90 CLL	n=125 NHL	n=110 CLL*	n=210 LEUK/LYMPH
Anemia	9%	2%	5%	19%
Neutropenia	13%	27%	42%	32%
Thrombocytopenia	6%	6%	10%	14%
Hepatotoxicity	3-6%	13%	5-9%	19%
Colitis	2%	3%	11%	6%
Diarrhea	3%	13%		11%
Pneumonitis		2%	4%	4%
Dyspnea	4%	3%	2%	11%

* in combination with rituximab

Phase I Umbralisib:

- ORR above the target level
dose of 800mg qd: 85% in CLL
with median PFS of 24mo

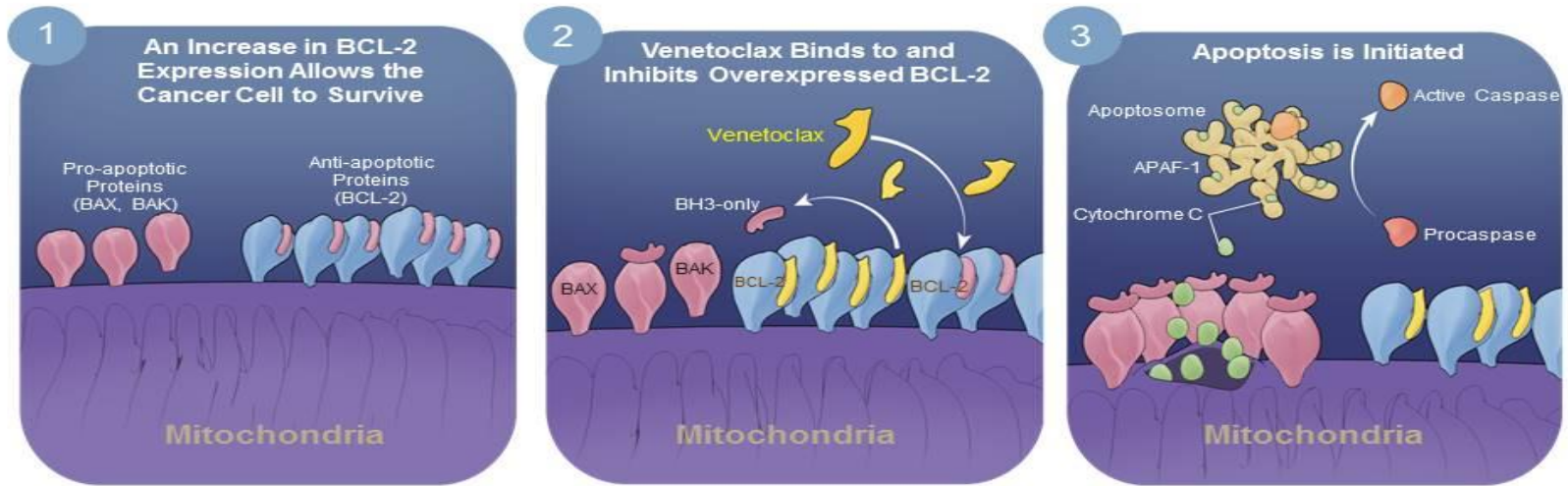
Burris HA, et al. *Lancet Oncology* 2018
Gopal AK, et al. *NEJM* 2014
Furman RR, et al. *NEJM* 2014
Flinn IW, et al. *Blood* 2018

BCL2 inhibitor

Why BCL2 targeting?

- The intrinsic apoptotic pathway is universally dysregulated in CLL/SLL and lymphoma due to:
 - overexpression of antiapoptotic proteins such as BCL-2
 - deficiency in functional pro-apoptotic proteins such as TP53 (e.g. in R/R disease)
- Prolonged survival is enabled through evasion of apoptosis, contributing to resistance to cytotoxic agents

Background: Mechanism of Action of Venetoclax (ABT-199/GDC-0199)



- Venetoclax is a selective, potent, orally bioavailable BCL-2 inhibitor that binds BCL-2 with >1000-fold higher affinity than BCL-XL, BCL-W and MCL-1.
- Venetoclax acts as a BH3-mimetic, displacing the BH3-only protein BIM from BCL-2 thereby inducing apoptosis in BCL-2 dependent lymphoid cells

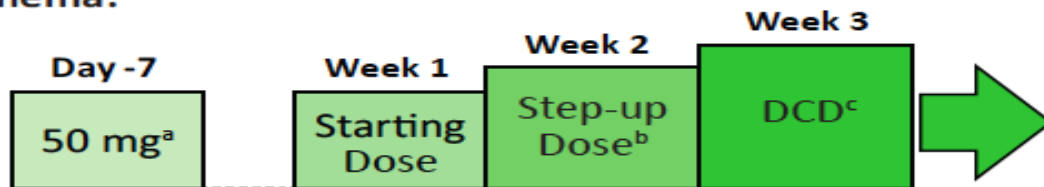
Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

ABT-199 DOSING SCHEMA

- Daily ABT-199 doses increased weekly to the designated cohort dose (DCD).

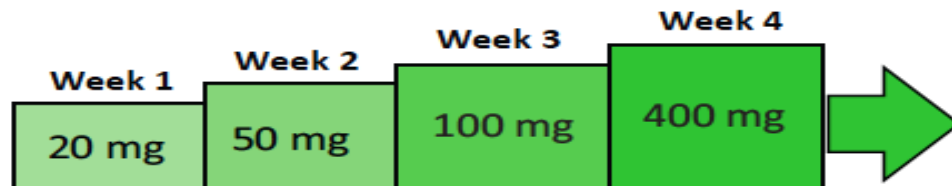
Initial Ramp-Up Schema:

Dose Escalation



Ramp-Up Schema:

Expanded Safety Cohort



^a3 patients (1 each in cohorts 2, 3, & 5) received ABT-199 20 mg as initial dose.

^bStep-up doses range from 100 to 400 mg.

^cDCD ranges from 150 to 1200 mg.

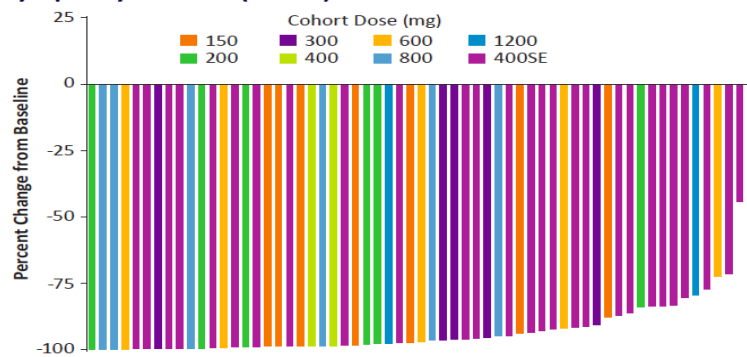
Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

Table 1. Patient Characteristics (n = 105)

Characteristics		All CLL/SLL
Age, y	Median [range]	66 [36-86]
Gender, n (%)	Male	79 (75)
Diagnosis	CLL / SLL	92/13
Lymphocyte count (x 10 ⁹ /L)	Median [range]	6.1 [0.23-243]
	>5 x 10 ⁹ /L, n (%)	60 (57)
Bulky nodes, n (%)	≥5 cm	58 (55)
	≥10 cm	17 (16)
Number of prior therapies	Median [range]	4 [1-11]
<i>IGHV</i> mutation status	Unmutated	36/48 (75)
17p Status	Deleted	23 (28)
	Not Deleted	49 (61)
	Unknown	9 (11)
Fludarabine, n (%)	Prior Treatment	87 (83)
	Refractory	62 (59)
β ₂ -microglobulin, n (%)	>3 mg/L	29 (58)

Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

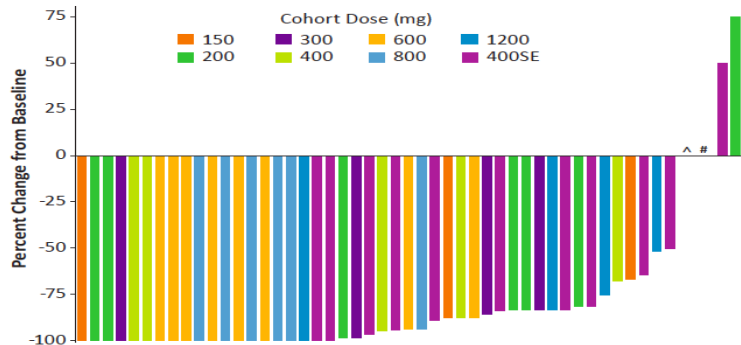
Lymphocyte Count (n = 60)



Data represents patients with lymphocyte count $>5 \times 10^9/L$ at baseline. N = 60 evaluable.
SE = safety expansion.

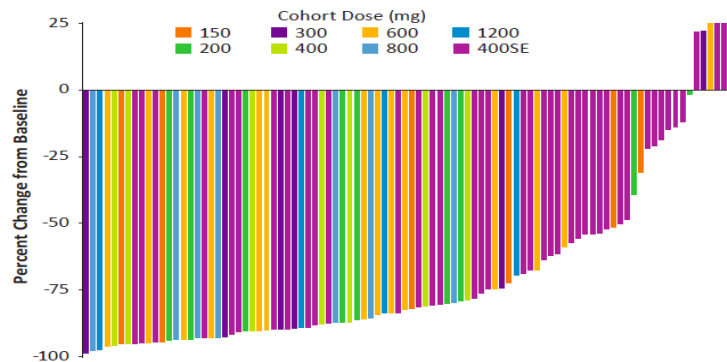
- Median time to 50% reduction: 14 days, range [1-49]

Figure 4. Best Percent Change from Baseline in Bone Marrow Infiltrate (n = 51)



SE = safety expansion
#Patient had 70% infiltrate at baseline and at Week 24.
^Patient did not have CLL infiltrate at baseline.

by CT Scan (n = 93)



SE = safety expansion.

- 78/93 (84%) evaluable patients had at least a 50% reduction in sum of the product of diameters (SPD) of nodal masses
- The median time to 50% reduction 1.4 months, range [0.65-13.7]. This coincides with first protocol specified CT scan at 6 weeks
- Median time to 50% reduction in BM infiltrate: 5.5mo (1.9-17.4). Coincides with first protocol specified repeat marrow examination at 6 months
- 46/51 (90%) evaluable patients have had at least a 50% reduction
- Anti-tumor activity of ABT-199 was observed in ALL tumor compartments

Objective Responses

Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

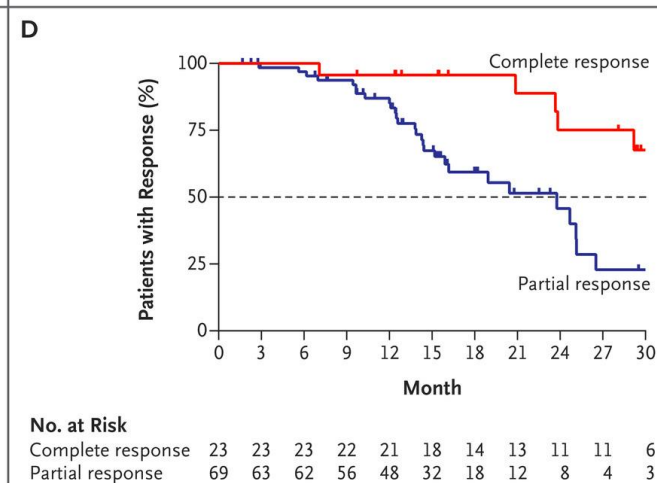
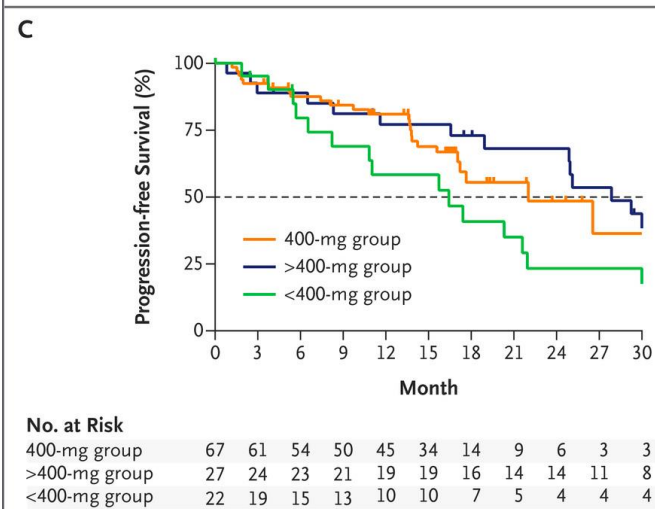
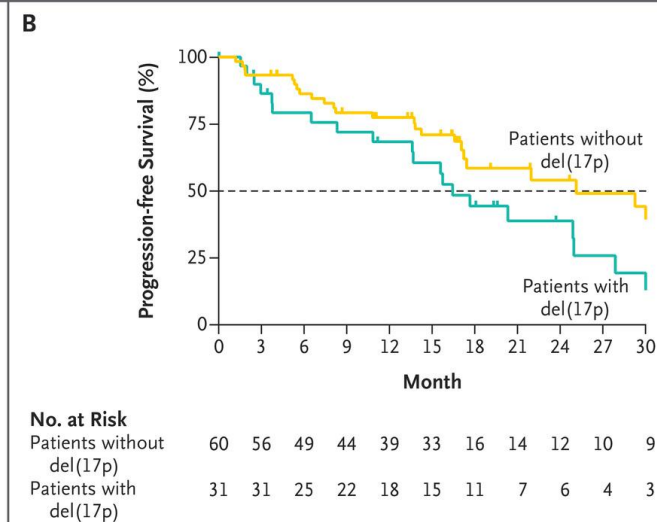
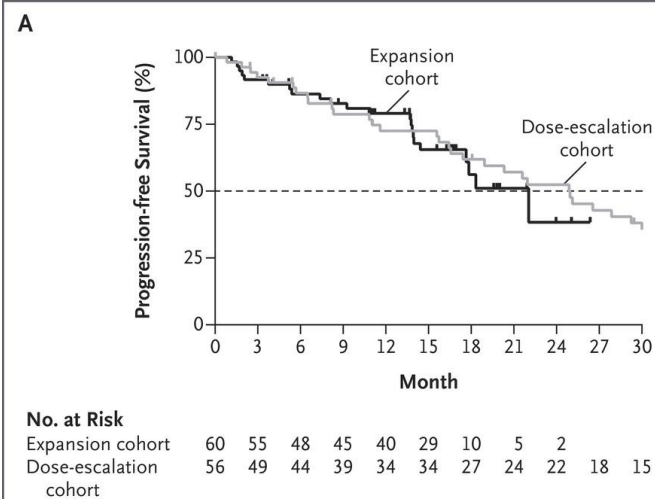
Responses	All n (%) n = 78	del (17p) n (%) n = 19	F-Refractory n (%) n = 41	IGHV Unmutated n (%) n = 24
Overall response	60 (77)	15 (79)	31 (76)	18 (75)
Complete response	18 (23)	5 (26)	9 (22)	7 (29)
Partial response ^a	42 (54)	10 (53)	22 (54)	11 (46)
Stable disease	10 (13)	2 (11)	7 (17)	2 (8)
Disease progression	2 (3)	1 (5)	1 (3)	2 (8)
D/C Prior to first (W6) assessment	6 (8)	1 (5)	2 (5)	2 (8)

Some patients may have more than one high risk marker.

^a 3 patients had confirmatory CT imaging assessments at less than an 8 week interval (5, 6, and 7 weeks).

In the 400-mg expansion cohort, data were mature for the ORR (82%) but less mature for the complete response rate (10% at the time of data cutoff).

The pooled ORR across all doses for all 116 patients was 79%, with a complete response reported in 20% of the patients.



Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

Table 2. Adverse Events (n = 105)

All Grades ≥ 20% of pts	n (%)
Diarrhea	42 (40)
Neutropenia	38 (36)
Nausea	37 (35)
Upper respiratory tract infection	35 (33)
Fatigue	27 (27)
Cough	21 (20)
Grades 3/4 ≥ 5% pts	n (%)
Neutropenia	35 (33)
Anemia	10 (10)
Febrile neutropenia	7 (7)
Thrombocytopenia	7 (7)
Hyperglycemia	7 (7)
Tumor lysis syndrome	7 (7)
Hypokalemia	5 (5)

Phase I Venetoclax (ABT-199/GDC 0199) in R/R CLL

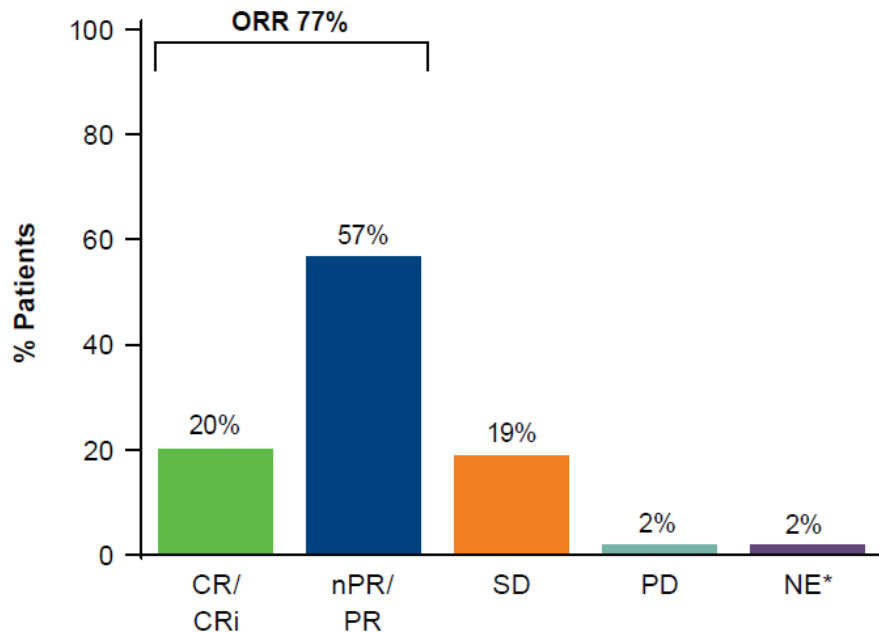
Table 3. Serious Adverse Events Possibly or Probably Related to ABT-199 (n = 105)

SAEs (≥ 2 pts)	n (%)
Febrile neutropenia	4 (4)
Tumor lysis syndrome*	3 (3)

- Other SAEs (n=1): amylase increase, clostridium infection, Escherichia sepsis, fluid overload, influenza, neutropenia, pulmonary embolism, acute renal failure, sepsis, sudden death* (in the setting of TLS), urinary tract infection, viral upper respiratory tract infection, pneumonia, bacterial pneumonia
- More than one event may have occurred in the same patient

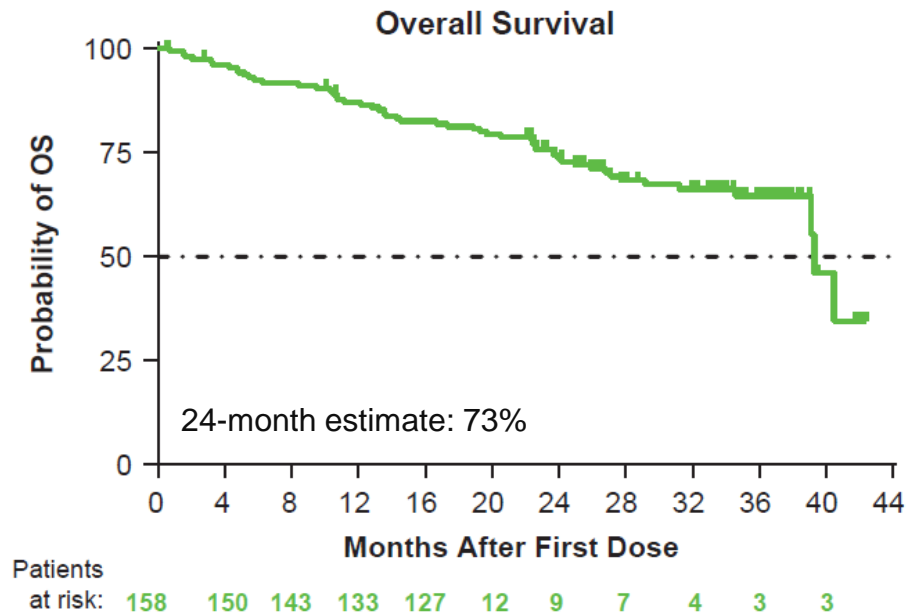
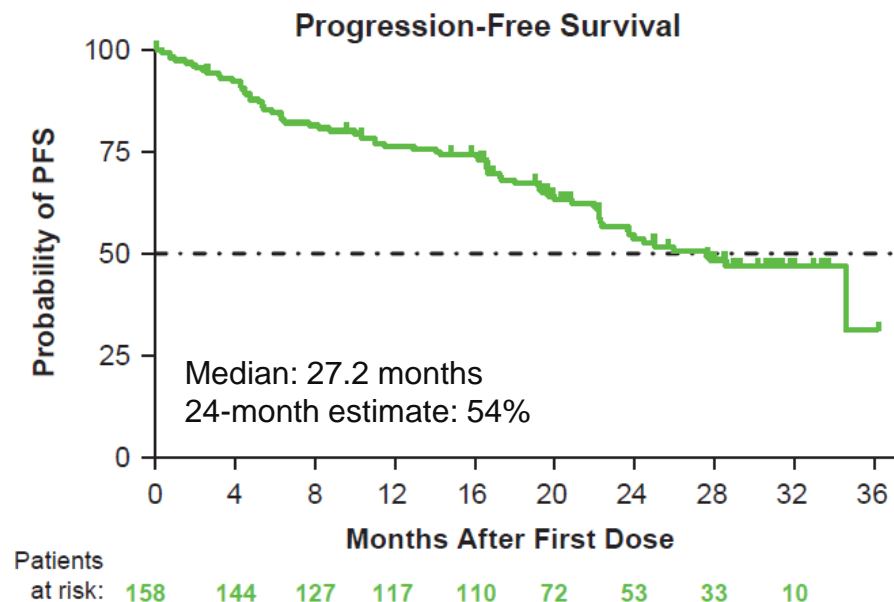
As of April 9, 2014, no additional events of clinical TLS (or SAEs) have been reported since modifications were made to the dose ramp-up scheme as well as the tumor lysis syndrome (TLS) prophylaxis and monitoring schedule.

Phase 2, open-label study: Venetoclax in relapsed/refractory CLL with 17p deletion: response in all patients (n=158)



- Median time to first response was 1 month and time to CR/CRI was 9.8 months
- Among 18 patients who received prior BCRi therapy, ORR was 61% and CR rate was 11%, with 12-month PFS and OS estimates of 50% and 54%, respectively

Venetoclax in relapsed/refractory CLL with 17p deletion: PFS and OS



Venetoclax in relapsed/refractory CLL with 17p deletion: Best MRD status for all patients

	All patients assessed
Peripheral blood	
Number of patients	101
MRD negative	40
MRD positive	61
Bone marrow	
Number of patients	74
MRD negative	18
MRD positive	56

	CR/CRi	nPR	PR
Total peripheral blood negative	20	1	19
Peripheral blood negative and bone marrow negative	14	0	4
Peripheral blood negative and bone marrow positive	3	0	4
Peripheral blood negative and bone marrow not assessed	3	1	11

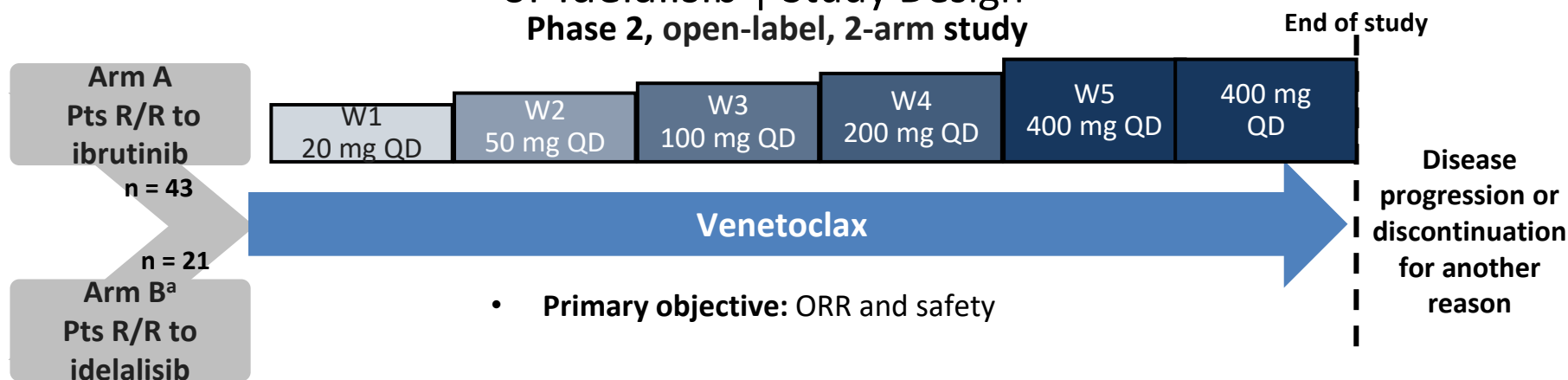
- 30% (48/158) of patients demonstrated blood MRD negativity by flow cytometry and confirmed by NGS in 21/29 who had an evaluable matched time point specimens

Adverse Events of Special Interest

- Laboratory TLS in 5 patients during the ramp-up period
 - 2 with dose interruption (1 day each)
 - No clinical TLS events
- Grade 3/4 neutropenia in 40% of patients
 - 22.4% had baseline neutropenia (any-grade)
 - Manageable: dose interruption/reduction, G-CSF and/or antibiotics
- Infections in 72% of patients (20% grade ≥ 3)
 - Most common (all-grade): URI (15%), nasopharyngitis (14%), and UTI (9%)
- Serious adverse events in 55% of patients
 - Most common: pyrexia (7%), AIHA (7%), pneumonia (6%), and febrile neutropenia (5%)

Venetoclax Monotherapy in Patients Previously Treated With Ibrutinib or Idelalisib | Study Design^{1,2}

Phase 2, open-label, 2-arm study



Characteristic	Ibrutinib Arm n = 43	Idelalisib Arm n = 21
Prior ibrutinib, n (%)	43 (100)	N/A
Time on ibrutinib, median (range), months	17 (1-56)	
Time on venetoclax, median (range), months	13 (0.1-18)	
Prior idelalisib, n (%)	N/A	21 (100)
Time on idelalisib, median (range), months		8 (1-27)
Time on venetoclax, median (range), months		9 (1.3-16)
Refractory to prior ibrutinib or idelalisib, n (%)	39 (91)	14 (67)

QD, once daily; R/R, relapsed/refractory.

^a Arm C (R/R to IDELA or IBR) not presented in this data cut.

Data cutoff: June 10, 2016.

1. Jones J, et al. ASH 2015 [oral presentation 715]; 2. Jones J, et al. ASH 2016 [abstract 637].

Venetoclax Monotherapy in Patients Previously Treated With Ibrutinib or Idelalisib | Key Findings

Efficacy

Response, n (%)	R/R on Ibrutinib (n = 43)		R/R on Idelalisib (n = 21)	
	IRC Assessment	Investigator Assessment	IRC Assessment	Investigator Assessment
ORR	30 (70)	29 (67)	13 (62)	12 (57)
▪CR	0	2 (5)	0	2 (10)
▪CRi	1 (2)	1 (2)	0	1 (5)
▪nPR	0	2 (5)	0	0
▪PR	29 (67)	24 (56)	13 (62)	9 (43)
Nonresponse*	13 (30)	14 (23)	8 (38)	9 (43)
▪SD	--	9 (21)	--	8 (38)
▪PD	--	1 [†] (2)	--	1 [†] (5)
▪Discontinued [‡]	--	4 (9)	--	0

partial response; SD, stable disease.

Incomplete data for 4 patients in Arm A.

IRC-assessed ORRs were 70% for the ibrutinib arm and 48% for the idelalisib arm.

Jones J, et al. ASH 2016 [abstract 637].

- Estimated 12-mo PFS for all pts: 80% (95% CI: 67% to 89%)
- 14/31 (45%) of PB samples were MRD- in Wks 24-48

As of June 10, 2016

Venetoclax Monotherapy in Patients Previously Treated With Ibrutinib or Idelalisib | Key Findings (cont)

Safety

All-Grade AEs (in ≥ 25% patients), %	Total N = 64
Any AE	100
Diarrhea	42
Nausea	41
Neutropenia	36
Anemia	36
Fatigue	31
Decreased platelet count	25

Grade 3/4 AEs (in ≥ 15% patients), %	Total N = 64
Neutropenia	31
Anemia	22
Thrombocytopenia	16

Serious Adverse Events (in ≥ 2 patients), n	Total N = 64
Febrile neutropenia	6
Pneumonia	5
Blood potassium increased	2
Multi-organ failure	2
Septic shock	2

- 2 patients had laboratory TLS without clinical sequelae

TLS, tumor lysis syndrome.

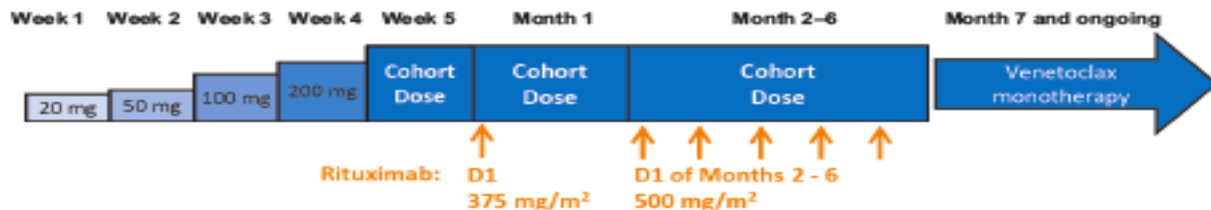
Jones J, et al. ASH 2016 [abstract 637].

As of June 10, 2016

Phase Ib Rituximab and Venetoclax in R/R CLL

Study Overview

- M13-365 (NCT01682616):⁷ Phase 1b, open-label, dose-escalation trial of venetoclax plus rituximab in patients with R/R CLL/SLL
- Most patients were ramped up to the cohort target daily dose (200–600 mg daily venetoclax)



Inclusion criteria:

- Indication for treatment by 2008 iwCLL criteria⁸
- ECOG performance score ≤ 1
- ANC $\geq 1000/\mu\text{L}$, hemoglobin ≥ 9 g/dL, platelets $\geq 50,000/\text{mm}^3$
- AST/ALT $\leq 3 \times \text{ULN}$
- CrCl ≥ 50 mL/min

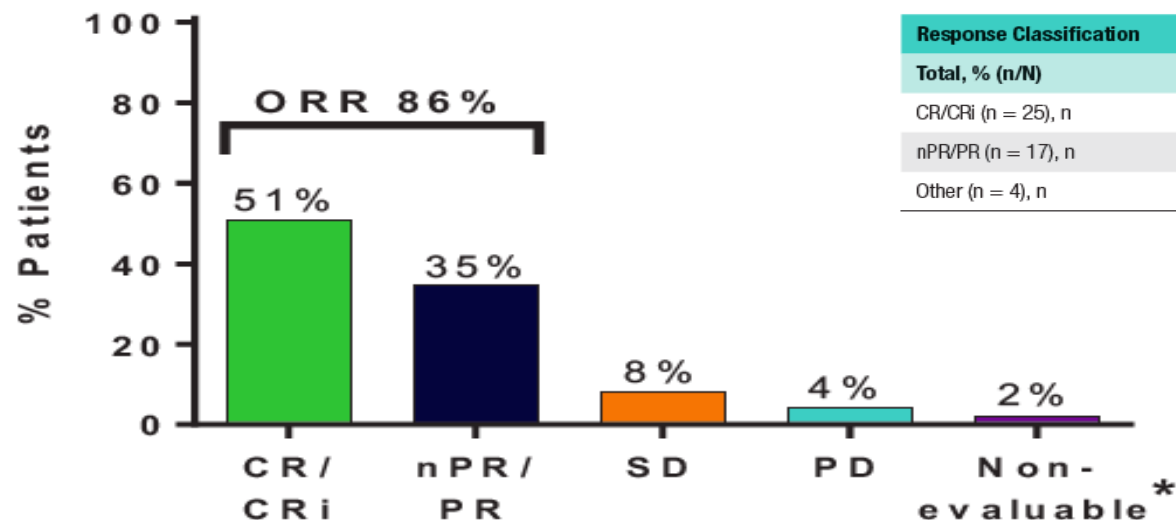
Exclusion criteria:

- Active and uncontrolled autoimmune cytopenias
- Prior autologous or allogeneic stem cell transplant
- >3 prior myelosuppressive regimens

Phase Ib Rituximab and Venetoclax in R/R CLL

Overall Safety and Efficacy

- All patients experienced AEs and the most common were upper respiratory tract infection, neutropenia, and mild GI issues
- Grade 3/4 AEs were reported for 37 (76%) patients, with the most common being neutropenia (53%), thrombocytopenia (16%), and anemia (14%)
- Best objective response:



Best Observed Bone Marrow MRD Evaluation

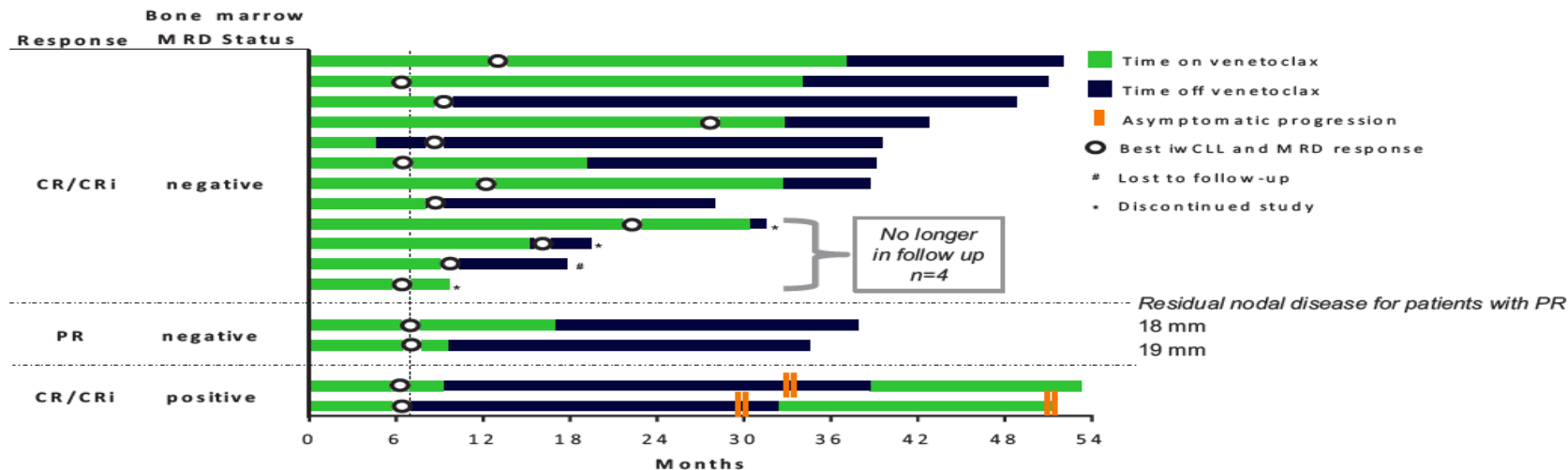
Response Classification	MRD-negative	MRD-positive	Not Evaluable
Total, % (n/N)	59% (29/49)	29% (14/49)	12% (6/49)
CR/CRi (n = 25), n	21	4	0
nPR/PR (n = 17), n	8	9	3*
Other (n = 4), n	0	1†	3‡

*1 patient was not evaluable due to a fatal TLS event that was previously reported.
As of 5Apr2017.

Phase Ib Rituximab and Venetoclax in R/R CLL

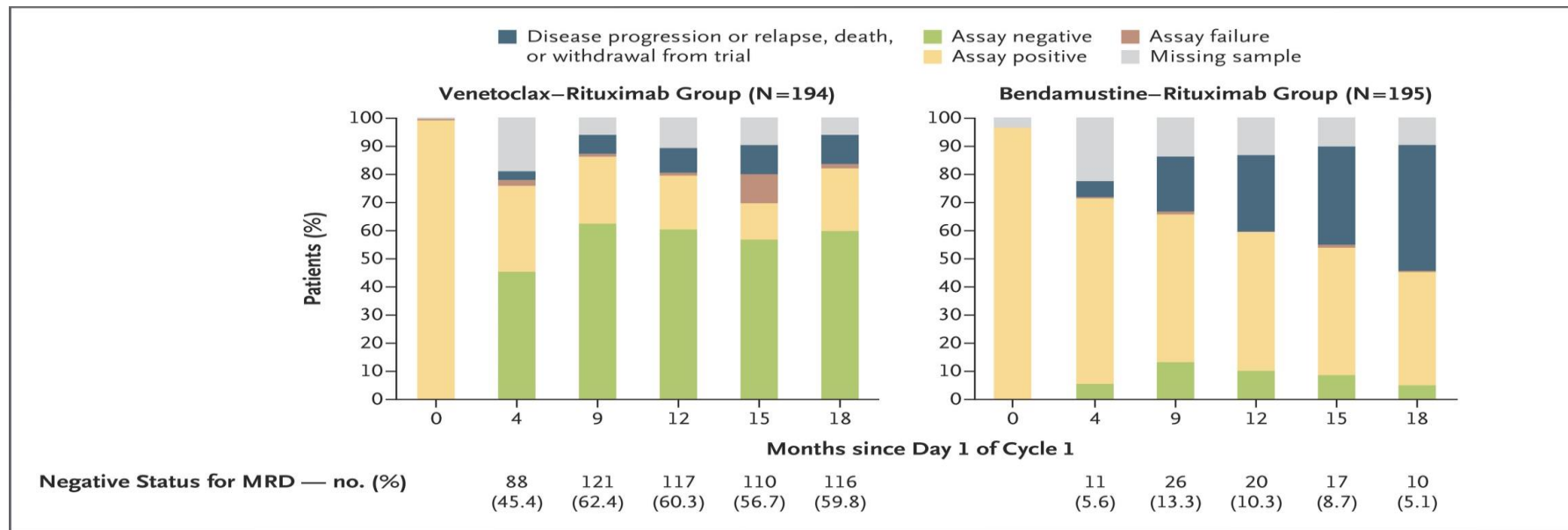
Current Status for Patients Who Stopped Therapy After Response

- Prior to stopping therapy, median time on therapy was 16 months (range: 5–38)
- 10/12 active patients remain progression-free off therapy after a median of 20 months (6–40)



- ORR of 86% (51% CR/CRi) and 59% of pts achieved marrow MRD-neg
- Pts who continued on therapy have durable responses (min 31mo)
- 12 pts had durable remissions after elective treatment cessation, 10 ongoing
- None of the pts who achieved marrow MRD-neg had POD (median time off therapy of 20 months)
- Two pts who had MRD-pos CR/CRi had asymptomatic POD ≥ 24 months off tx and were re-treated:
 - one pt achieved PR then POD after 19 months of re-tx
 - the other achieved CR at 14 months of re-treatment and is active on study

MURANO: MRD Clearance in PB over Time

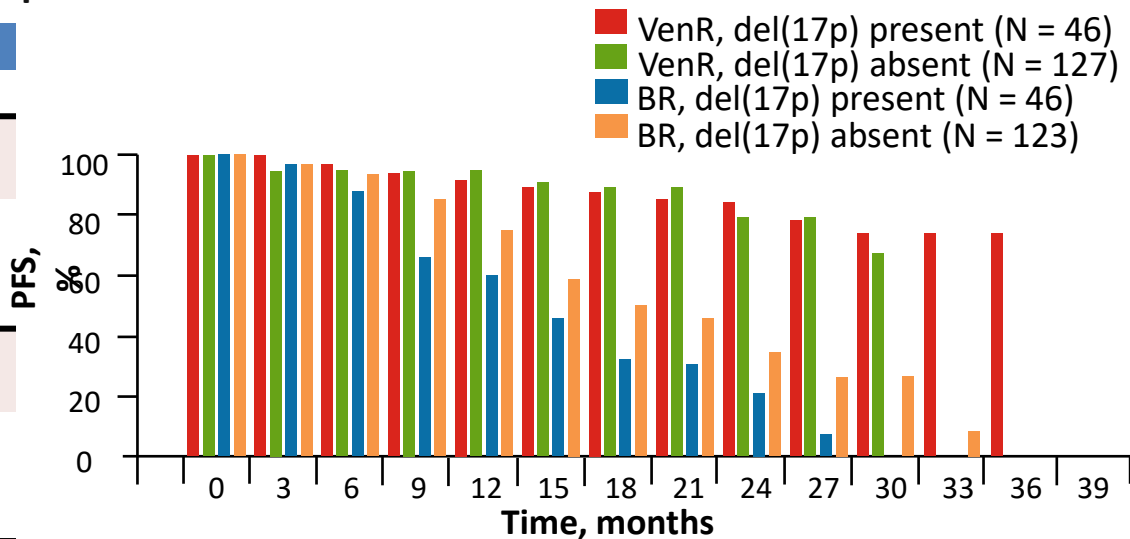


MURANO: VenR in High Risk Subgroups

Presence/absence of del(17p), *TP53*, and *IGHV* mutation does not affect benefit of VenR vs BR

Median PFS (months) in High-Risk Subgroups

Subgroup	VenR	BR	HR (95% CI)
del(17p)			
Absent	NR	21.4	0.19 (0.12, 0.32)
Present	NR	15.4	0.13 (0.05, 0.29)
<i>TP53</i> mutation			
Unmutated	NR	21.2	0.15 (0.09, 0.25)
Mutated	NR	12.9	0.19 (0.10, 0.36)
<i>IGHV</i> mutation			
Unmutated	NR	15.7	0.16 (0.10, 0.26)
Mutated	NR	22.9	0.11 (0.04, 0.31)



Combination Approaches

A Potential Pathway to Fixed-Duration Therapy?

Front-line

- CAPTIVATE: ibrutinib + venetoclax^[a]
- GLOW: ibrutinib + venetoclax vs chlorambucil + obinutuzumab^[b]
- AVO: acalabrutinib, venetoclax, and obinutuzumab^[c]
- Phase 1 study of ibrutinib/venetoclax/obinutuzumab^[d]
- ELEVATE CLL TN: acalabrutinib + obinutuzumab vs obinutuzumab + chlorambucil vs acalabrutinib^[e]

Relapsed/refractory

- Ibrutinib + venetoclax: high CR and MRD-negative rates^[g]

a. Weirda W, et al. *J Clin Oncol*. 2018;36:7502; b. ClinicalTrials.gov. NCT02910583; c. ClinicalTrials.gov. NCT03580928; d. Rogers KA, et al. *Blood*. 2017;130:431; e. ClinicalTrials.gov. NCT02475681; f. ClinicalTrials.gov. NCT02950051; g. Jain N, et al. *Blood*. 2017;130:429.

Future Thoughts

- Optimal management of CLL should be tailored to the patient based on **comorbidities, fitness, and quality of life**
- Ongoing issues:
 - determination of optimal sequencing
 - duration of and compliance with treatment
 - short- and long-term tolerability
 - emergence of resistance
 - role of MRD negativity in the era of novel agents
 - Cost
- ***Major clinical trials comparing TKI vs CIT will be presented soon***
- What will be the role of combination strategies?

Thank you very much for your attention
Questions? jbarrientos@northwell.edu