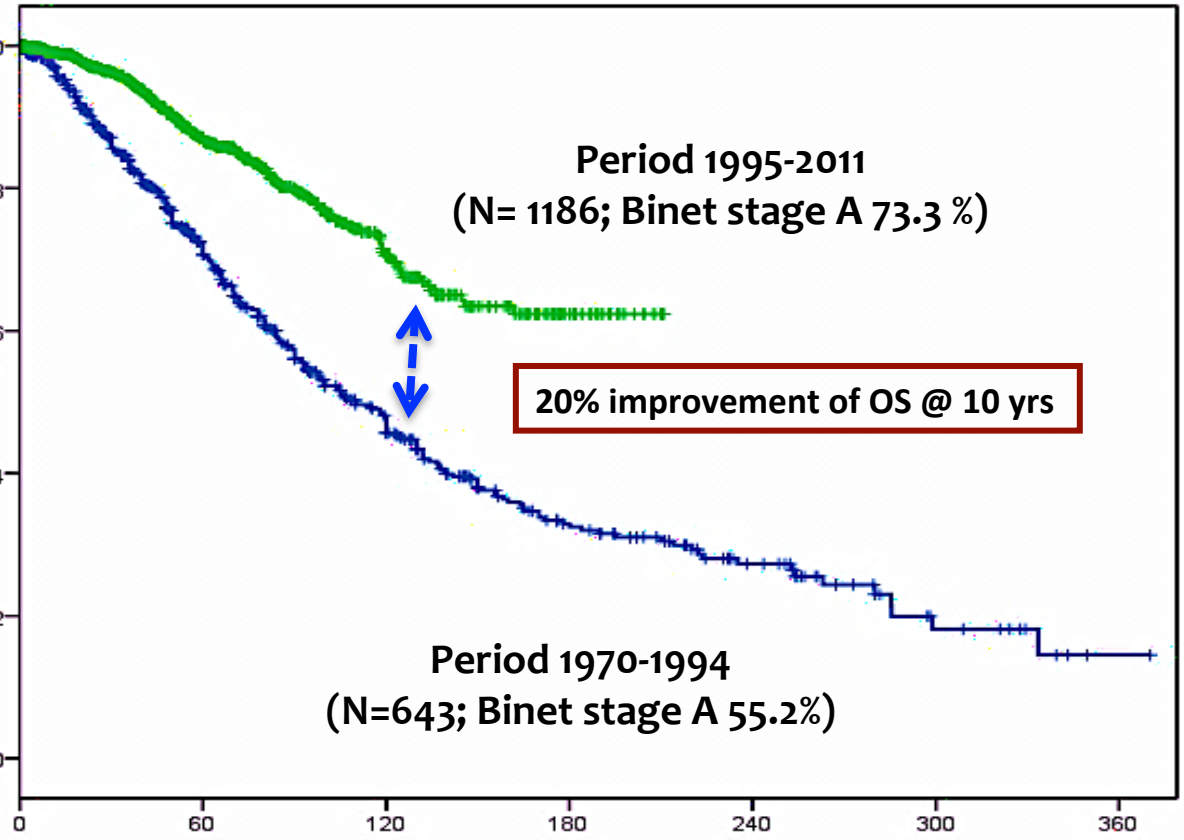
Rimini 16 aprile 2016

Leucemia Linfatica Cronica: Discutendo di nuovi farmaci

Stefano Molica

Survival curves of patients with CLL (Calabria, 1970-2011)

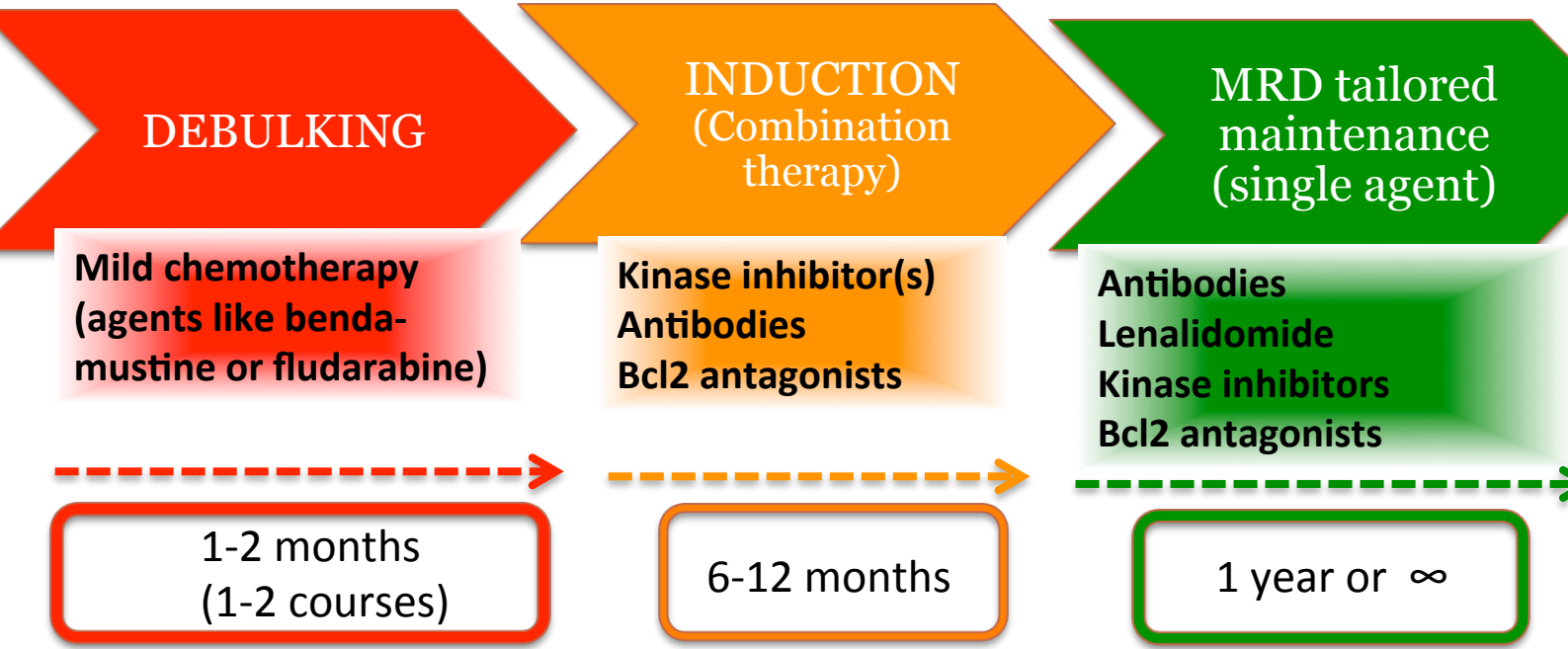


	1970-1994 (n=643)	1
A	355 (55.2%)	
B	153 (23.8%)	
C	135 (21%)	

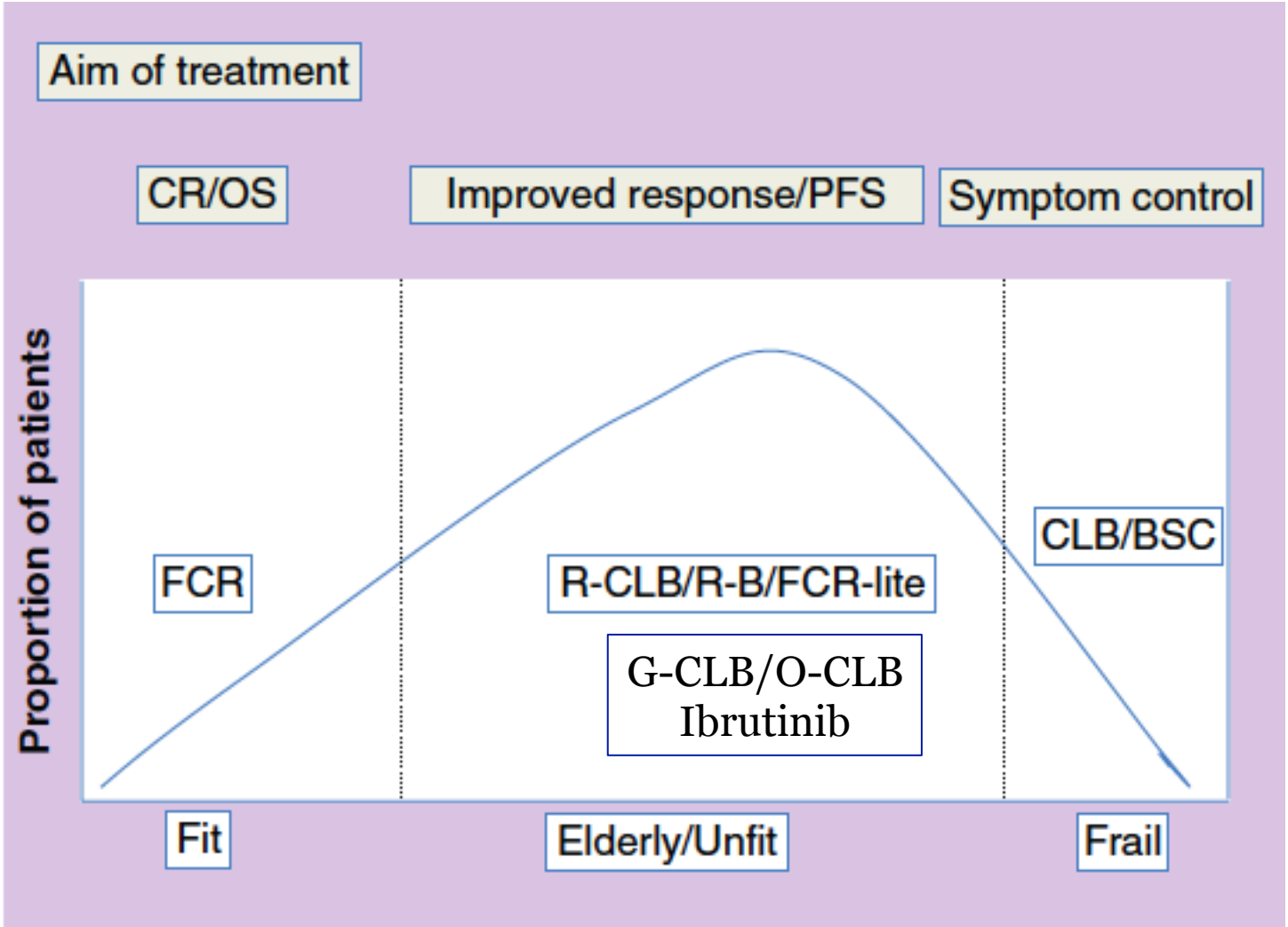
ASH 2015 Oral Preser

Chronic Lymphocytic Leukemia: A New Treatment Era is Born

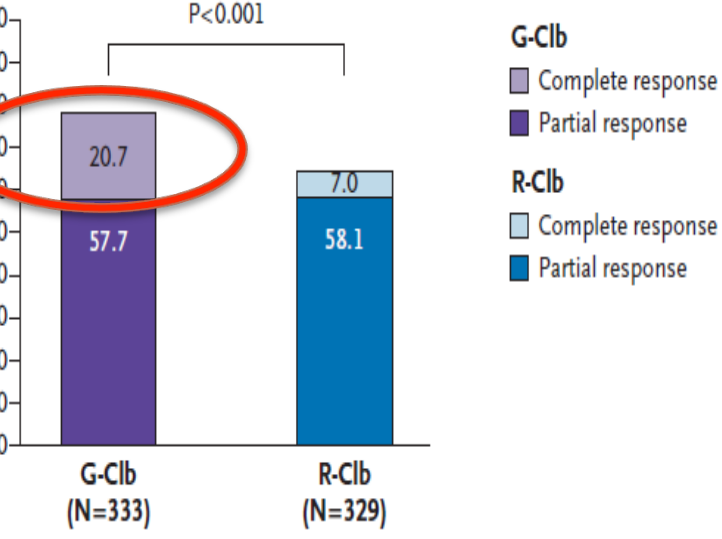
Potential future strategies to achieve long-term control of CLL
***"sequential triple T"*: tailored, targeted, total eradication of MRD**



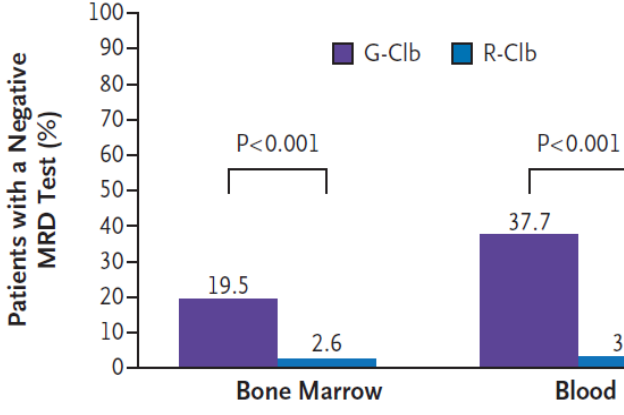
unmet clinical need



CLL11 stage II Response Rate



CLL11 stage II MRD negativi



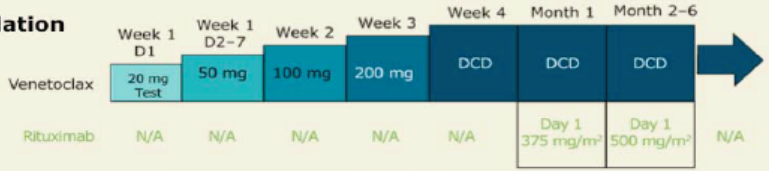
No. of Patients	26/133	3/114	87/231	

COMPLEMENT-1 (O-CLB vs CLB)

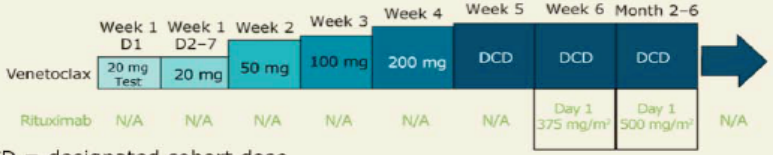
EGATIVE MRD Assessment	CHL		O+CHL	
	N	MRD^{neg} n (%)	N	MRD^{n} n (%
l Subjects (irrespective of response or sample availability)	226	8 (4)	221	26 (1
MRD^{neg} in PB or BM at 3M post treatment	226	4 (2)	221	19 (9
MRD^{neg}in BM at 3M or MRD^{neg} at 6M in PB	226	5(2)	221	17 (8
bjects with IRC-assessed CR or CRi	3	0	32	12 (3
bjects with IRC-assessed PR or nPR	152	7 (5)‡	150	14 (9

More than 50% of CR/CRi subject remained MRD negative in PB for >12 months, 4 subjects were M
egative in BM (out of 8 BM samples)

Final Escalation Strategy:



OR: if one or more electrolytes meet Cairo-Bishop criteria and/or if there is ≥30% decrease in ALC with first dose



D = day; DCD = designated cohort dose
Protocol amendment permits 20 mg for first week, as needed

- The MTD was not identified.
- Selection of 400 mg for assessment in the safety expansion dose was based on trends of higher toxicities at doses >400 mg and informed by data from other studies.

With permission from Roberts AW et al. *Proc ASH* 2014;Abstract 325.

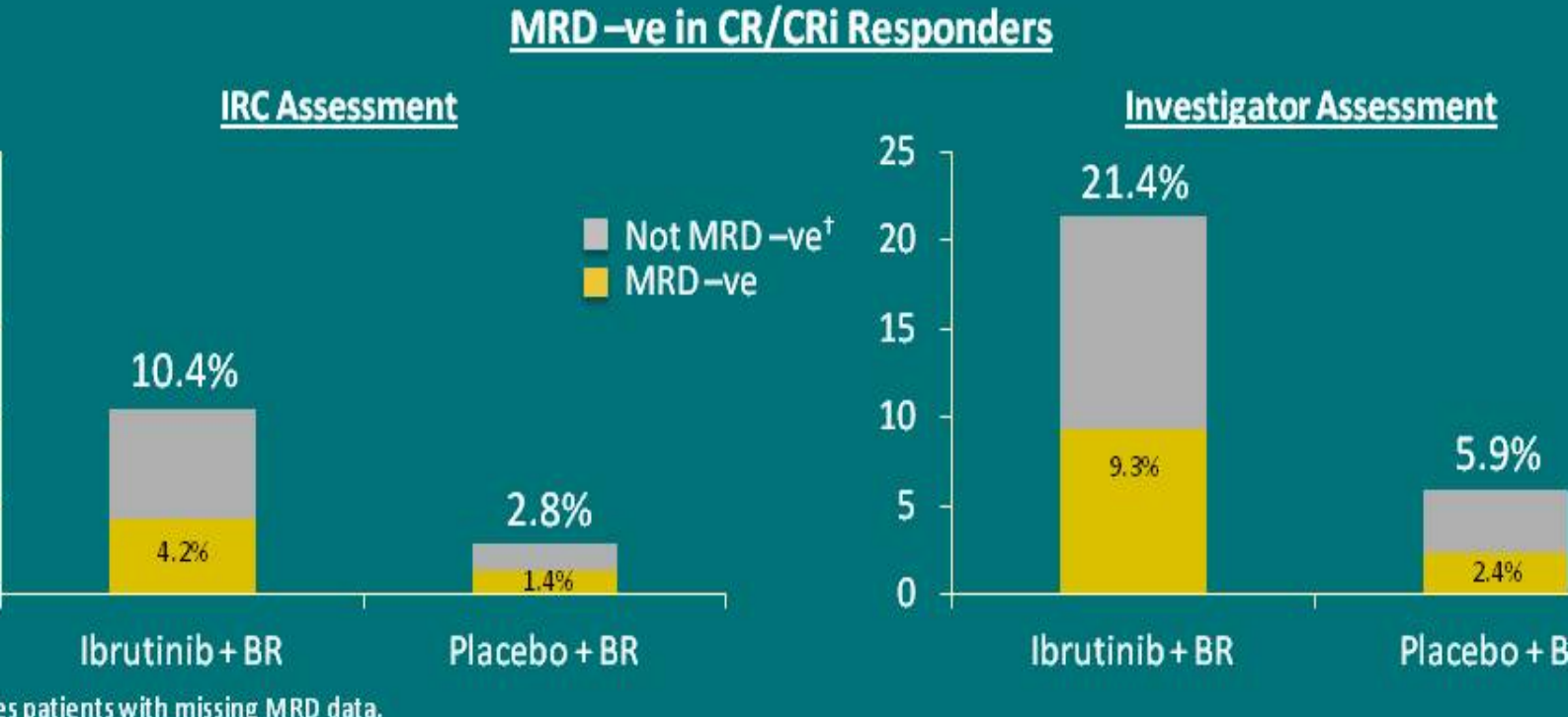
Research To Practice®

Response	MRD-negative	MRD-positive	Comments
CR (n = 15)	9	6	1/6 became MRD-negative at 14 months
PR (n = 22)	8*	14	4/8 MRD-negative patient have 1 remaining lymph node of >1.5 cm as the

RD Negativity

ITT Population	Ibrutinib + BR (N = 289)	Placebo + BR (N = 289)	P-va
ve response*, n (%)	37 (12.8)	14 (4.8)	0.00

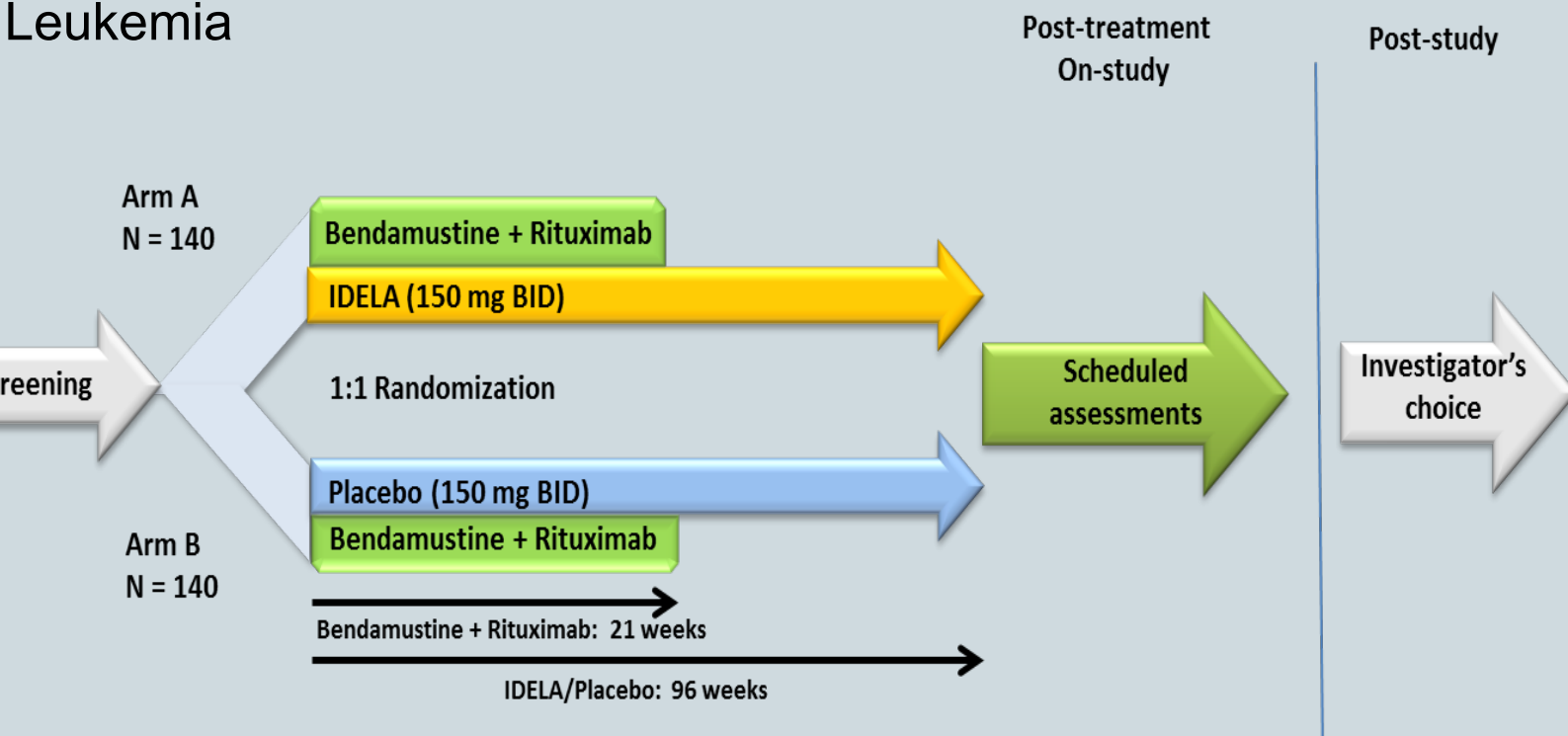
e status , < 1 CLL cell/10,000 leukocytes; 120 and 57 patients had MRD assessed in the ibrutinib + BR and placebo + BR arms, respecti



es patients with missing MRD data.

GS-US-312-0120 WALLAMAN: Schematic

A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustin and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia



Correlation of MRD with Progression Free Survival: GCLLSG CLL8

Lower MRD associated with improved PFS (regardless of Tx)

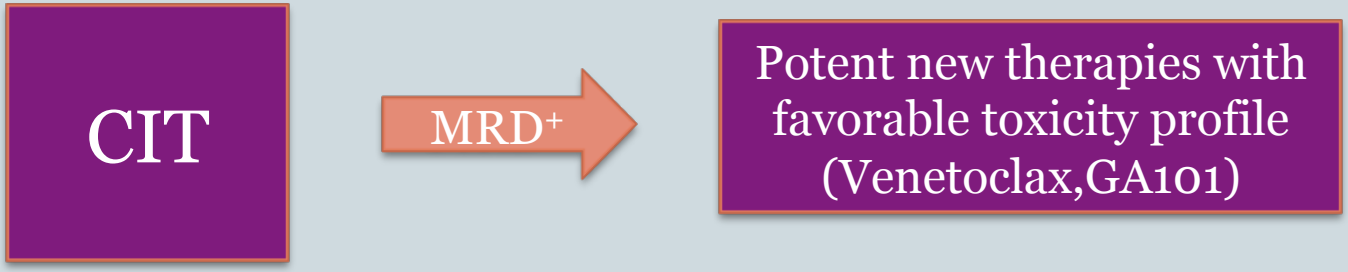
MRD	Median PFS
$< 10^{-4}$	Not reached
$\geq 10^{-4}$ – $< 10^{-3}$	35 months
$\geq 10^{-3}$ – $< 10^{-2}$	33 months
$\geq 10^{-2}$ – $< 10^{-1}$	16 months
$\geq 10^{-1}$	12 months

Lower MRD levels achieved with FCR at 2 months post-treatment

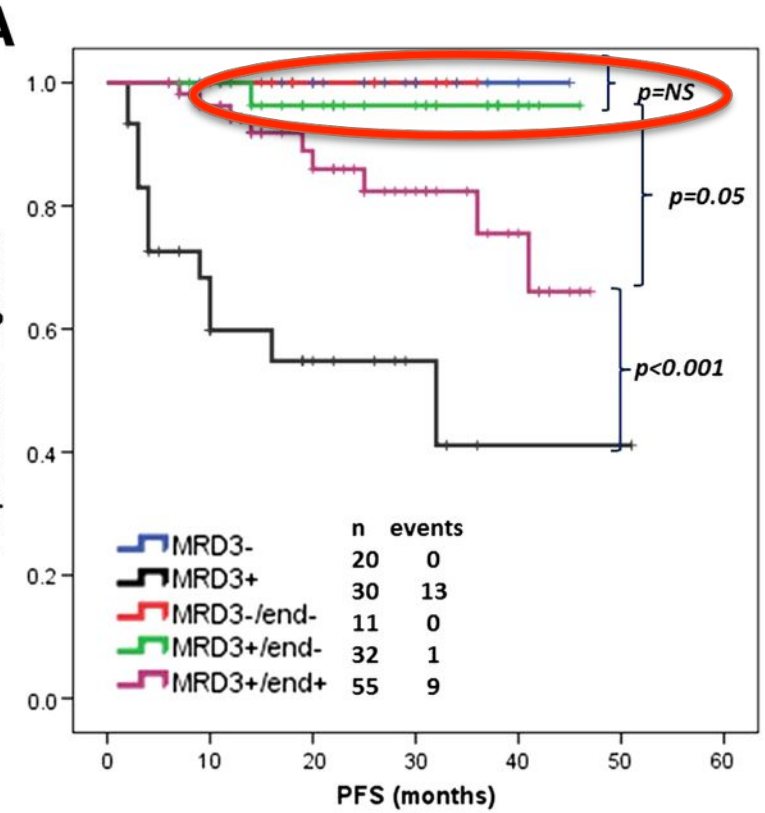
MRD Level Achieved	FCR	FC
$< 10^{-4}$	67%	34%
$\geq 10^{-4}$ – $< 10^{-2}$	23%	50%
$\geq 10^{-2}$	10%	16%

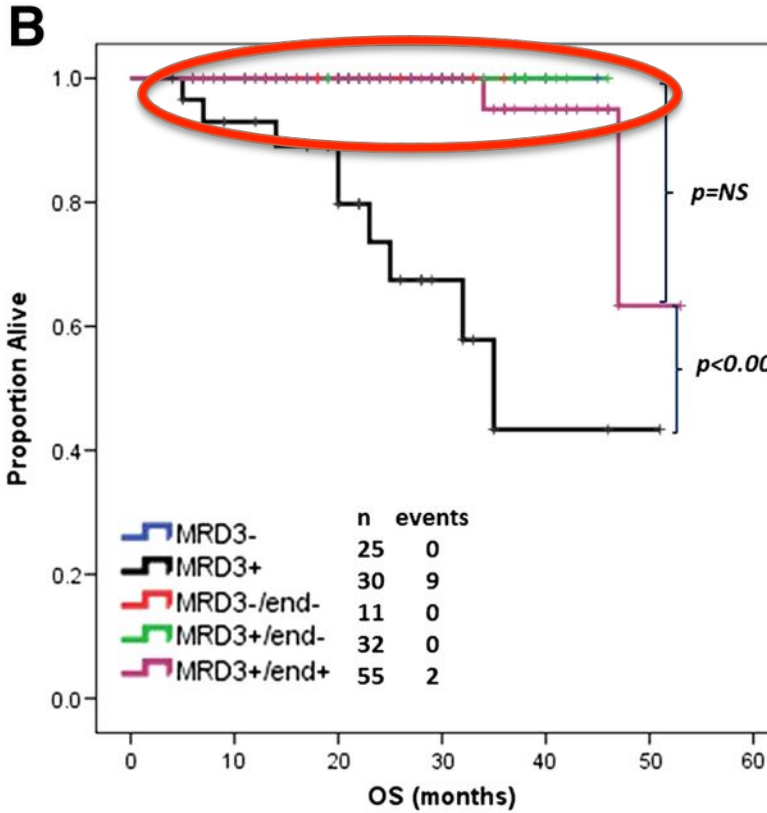
USE OF MRD TO GUIDE TREATMENT DECISIONS

Patients with MRD at final response assessment could be candidate for treatment intensification, consolidation or maintenance strategies.



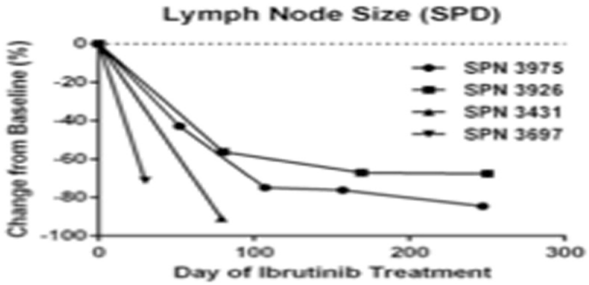
PFS and OS according to MRD/therapy groups.



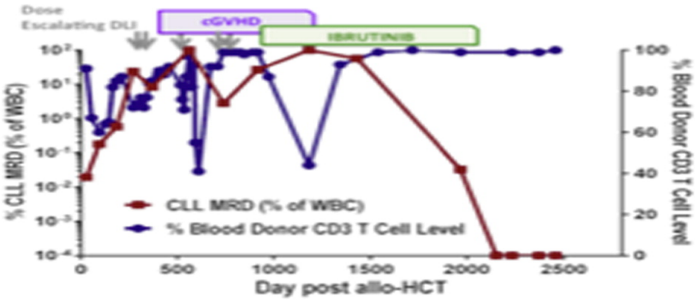


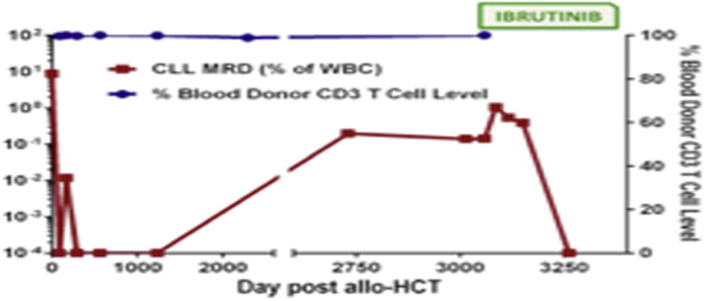
aolo Strati et al. Blood 2014;123:3727-3732

Ibrutinib Treatment of Relapsed CLL Following Allogeneic Transplantation: Sustained Disease Response and Promising Donor Immune Modulation

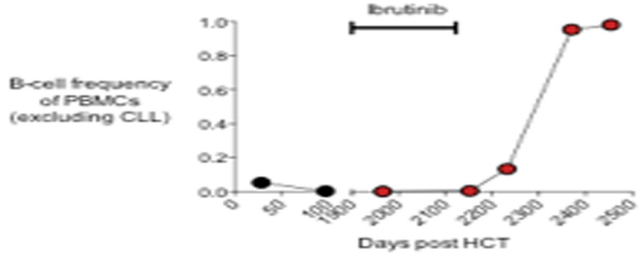


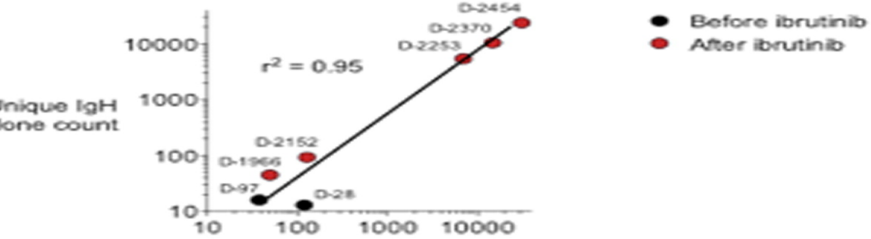
B





D





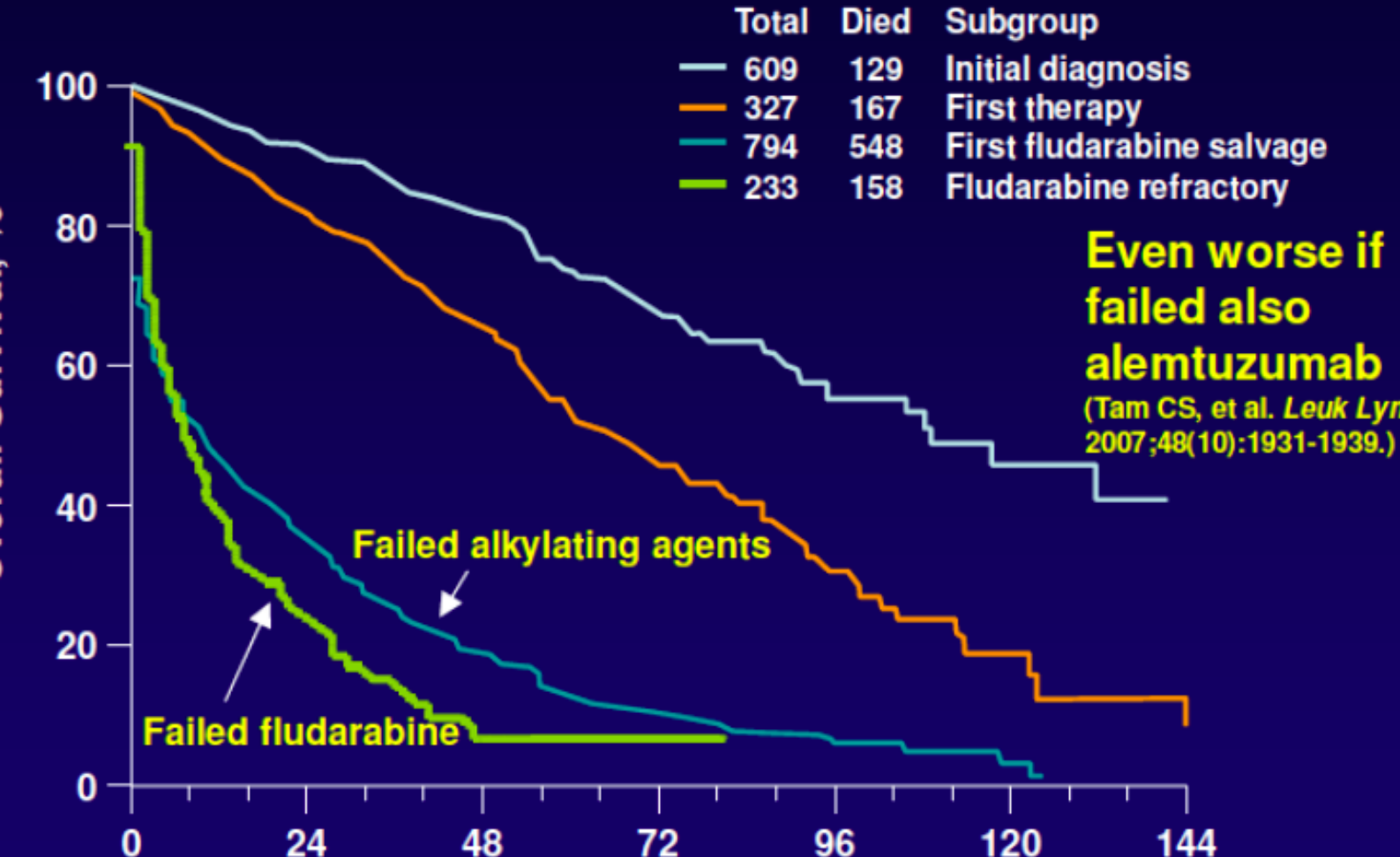
MRD in CLL: Clinical relevance

Minimal residual disease status has been shown to be one of the most powerful predictors not only for PFS but also for OS in patients treated with CIT.

No data on the correlation between MRD and PFS with ibrutinib or idelalisib

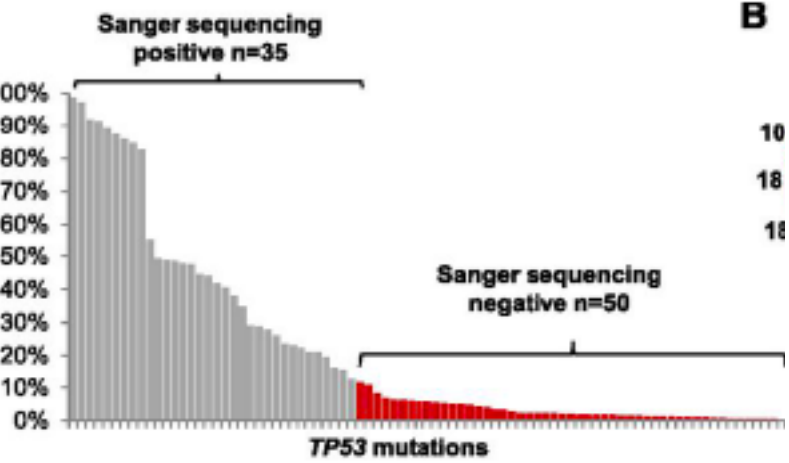
Until now, MRD assessment has been recommende as a tool for clinical trials but not as routine practic

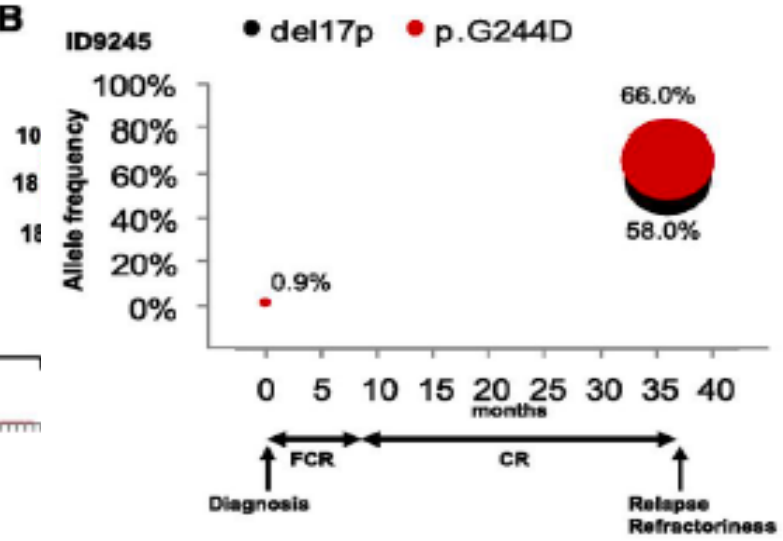
Prognosis of CLL Refractory to Conventional Therapy

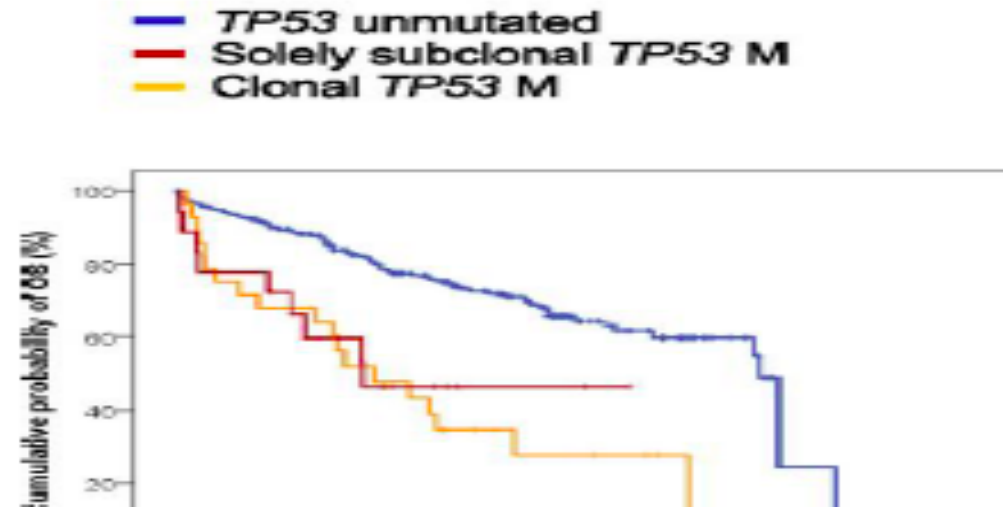


ence of Refractory Disease in patients treated with FCR in up-f
Results of CLL8 trial

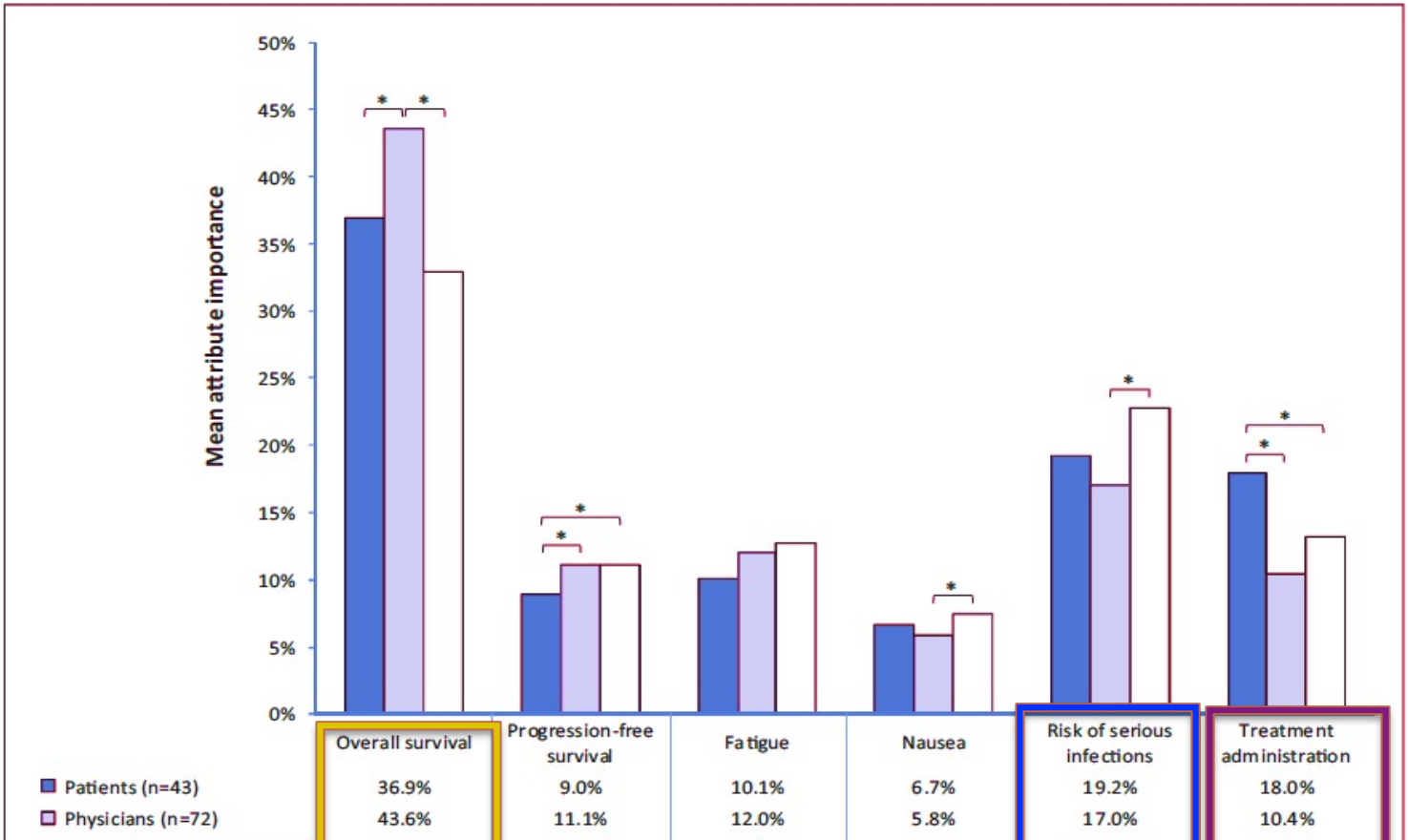
PFS	% pts	OS	17p del	TP53 mut
Less than 6 mo. (refractory)	7.6 %	21.9 mos	34%	44%
Between 6 and 12 mo.	5.6%	21.2 mos	28%	24%
Between 12 and 24 mo.	14.3%	47.3 mos	11%	18%


Sanger sequencing
positive n=35
Sanger sequencing
negative n=50
TP53 mutations

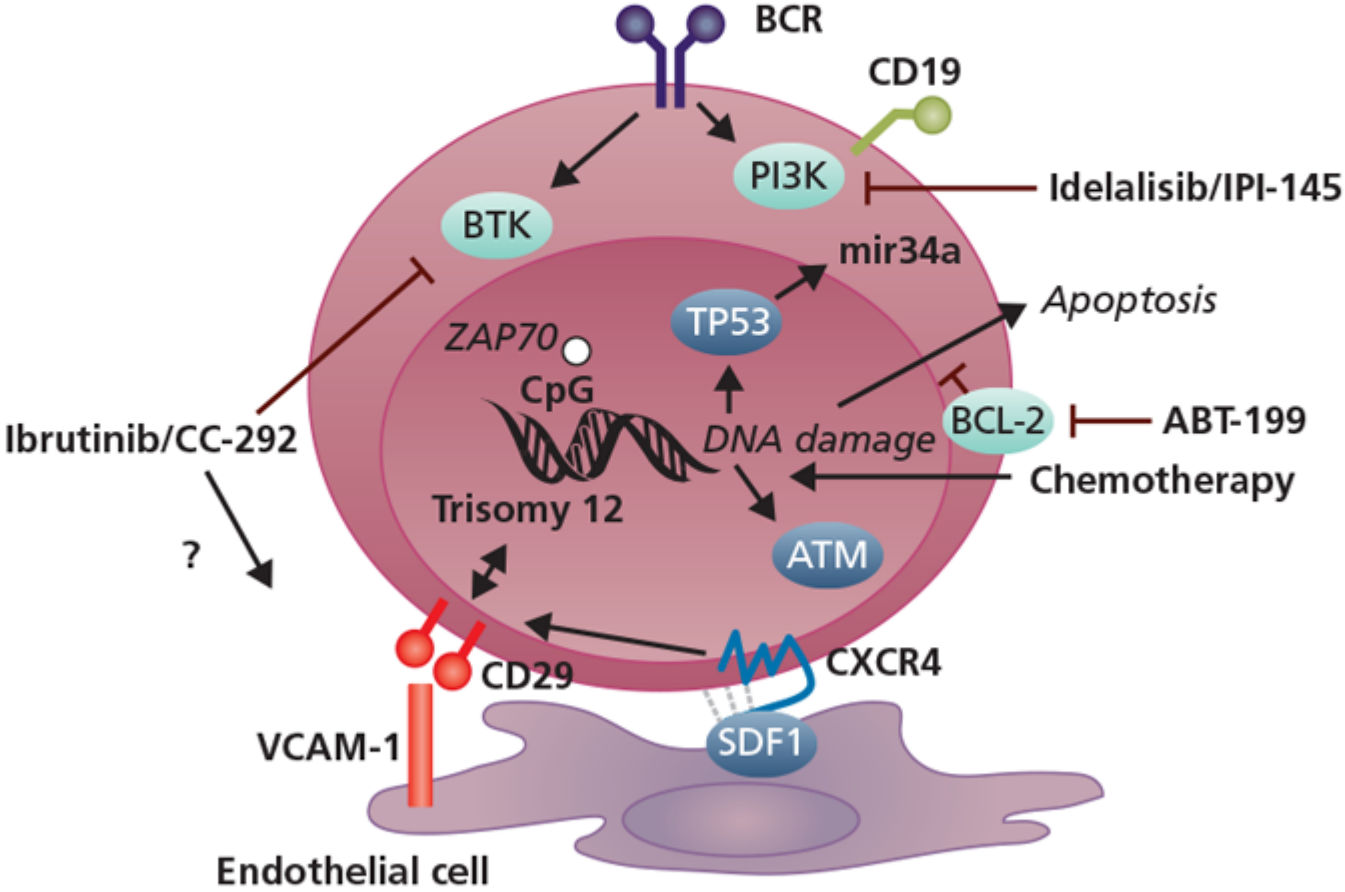

B
ID9245
del17p
p.G244D
Allele frequency
66.0%
58.0%
0.9%
months
FCR
CR
Diagnosis
Relapse
Refractoriness


TP53 unmutated
Solely subclonal TP53 M
Clonal TP53 M

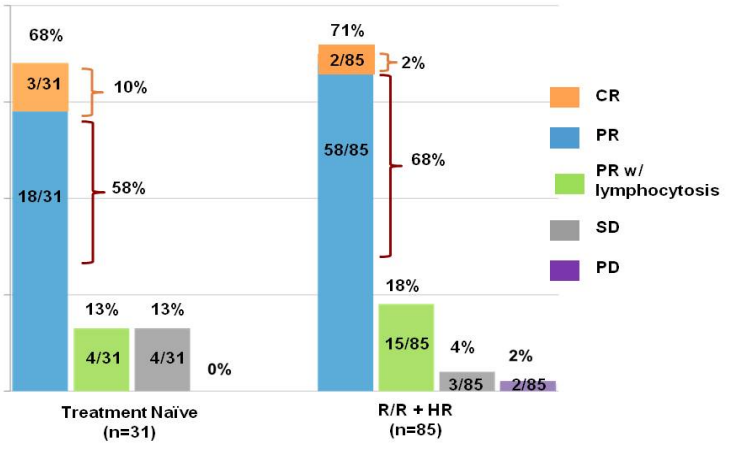
analysis


Mean attribute importance
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Overall survival
Progression-free survival
Fatigue
Nausea
Risk of serious infections
Treatment administration
Patients (n=43)
36.9%
9.0%
10.1%
6.7%
19.2%
18.0%
Physicians (n=72)
43.6%
11.1%
12.0%
5.8%
17.0%
10.4%

Critical Signalling Pathways and New Targeted Agents in B-Cell Malignancies



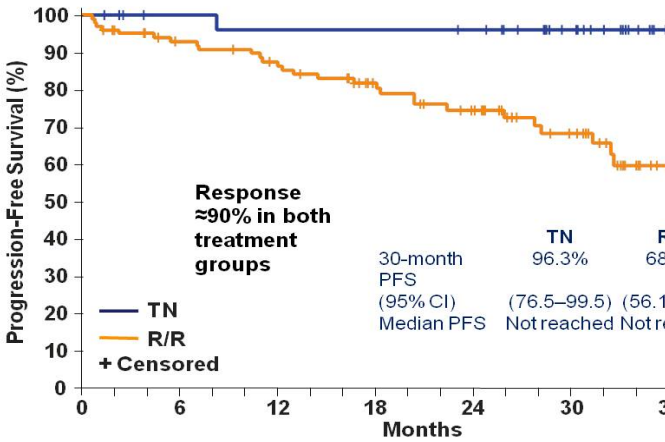
brutinib for CLL: Response



Engl J Med 2013; 369:32-42

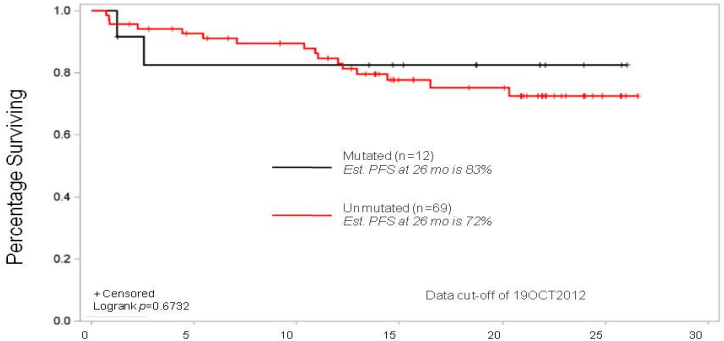
Slide 29

PCYC 1102/1103: Progression-Free Sur



Byrd et al. Blood (2015)

Ibrutinib in Relapsed CLL: PFS by IGHV



ility (n = 144)

- SLL
- nce of del(17p13.1) in
- pheral blood by FISH
- ysis
- sease after 1-4 prior
- s of therapy
- rable nodal disease
- PS 0-1

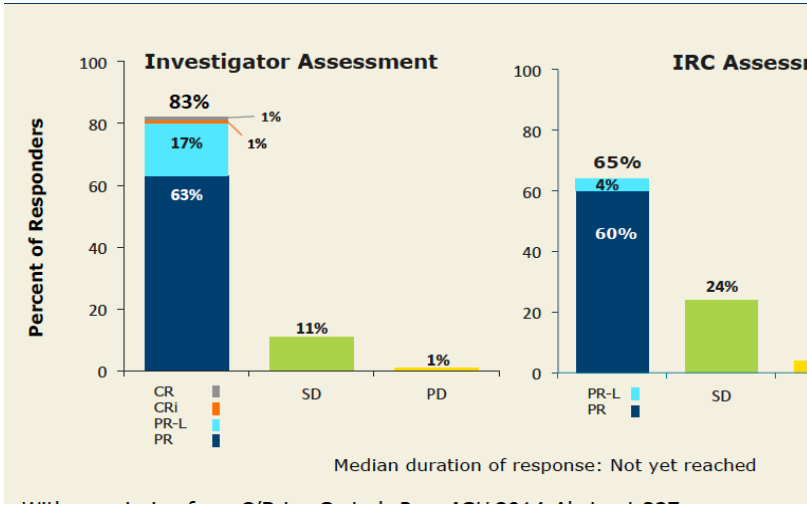
Single-agent ibrutinib
420 mg PO daily
Until unacceptable toxicity
or
disease progression

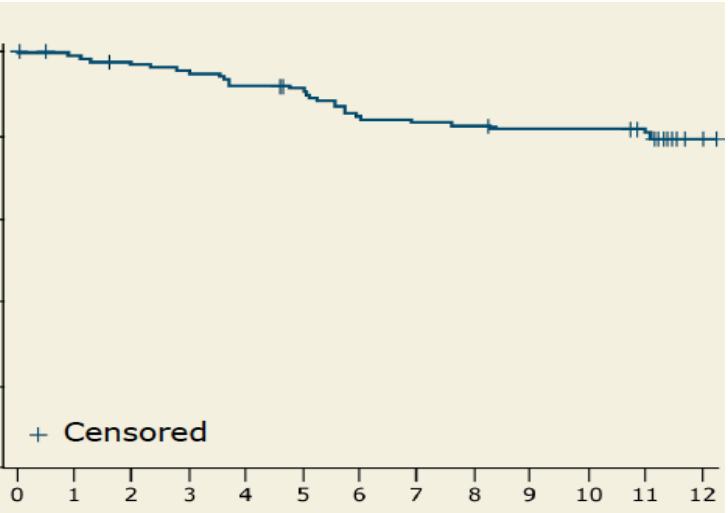
ry analysis was performed 12 months after enrollment of last patient

ary endpoint: Overall response rate (ORR)

ndary endpoints include: Duration of response (DoR), safety and bility

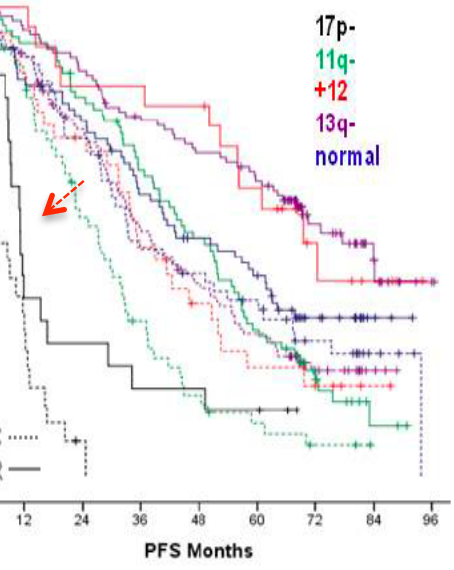
ratory endpoints: PFS and OS



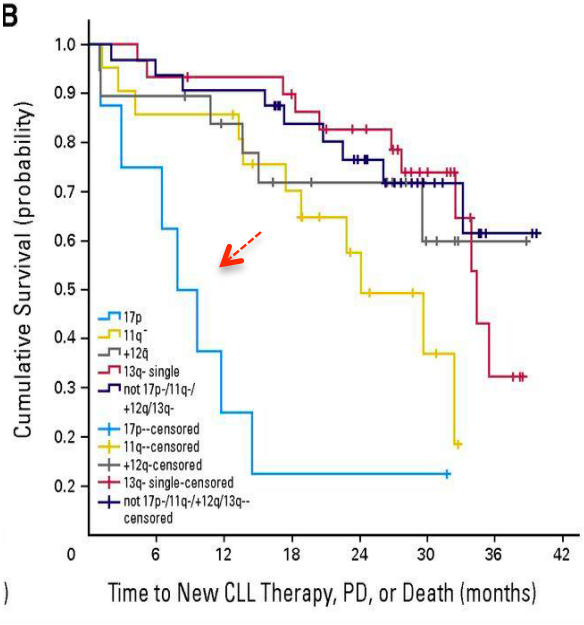


- Atrial fibrillation of any grade occurred in 11 patients
  - Grade 3-4 events = 3.5%; no Grade 5 events
  - 5 patients had a history of atrial fibrillation
  - No treatment discontinuations occurred
- Major bleeding of Grade 2 or 3 occurred in 7 patients
  - Events included intracranial hemorrhage, spontan and traumatic hematomas*, hematuria, hemoptys gastric ulcer and intercostal artery hemorrhages
  - 3 patients were receiving concomitant medication anticoagulants (n = 2), aspirin (n = 1)
  - 1 patient had factor XI deficiency

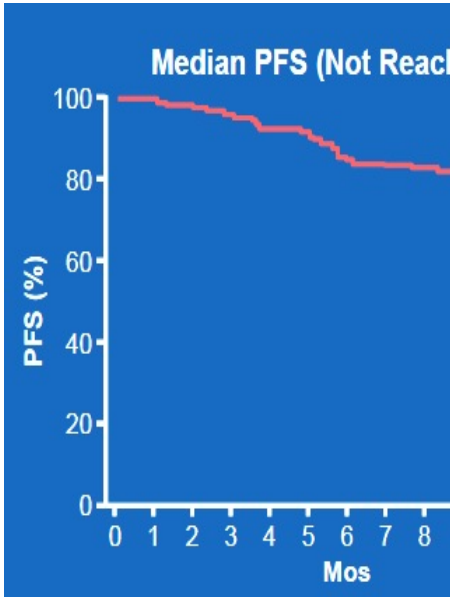
Frontline FCR



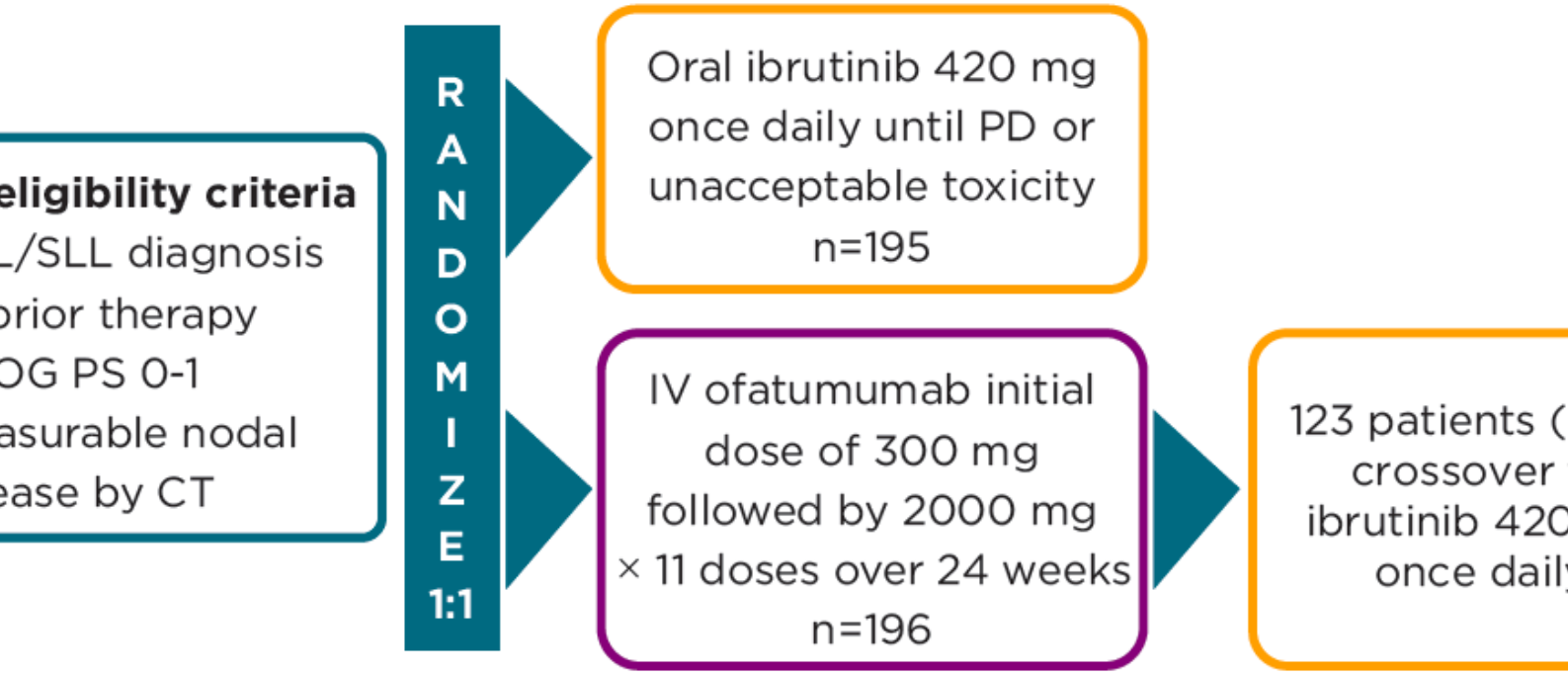
Frontline BR



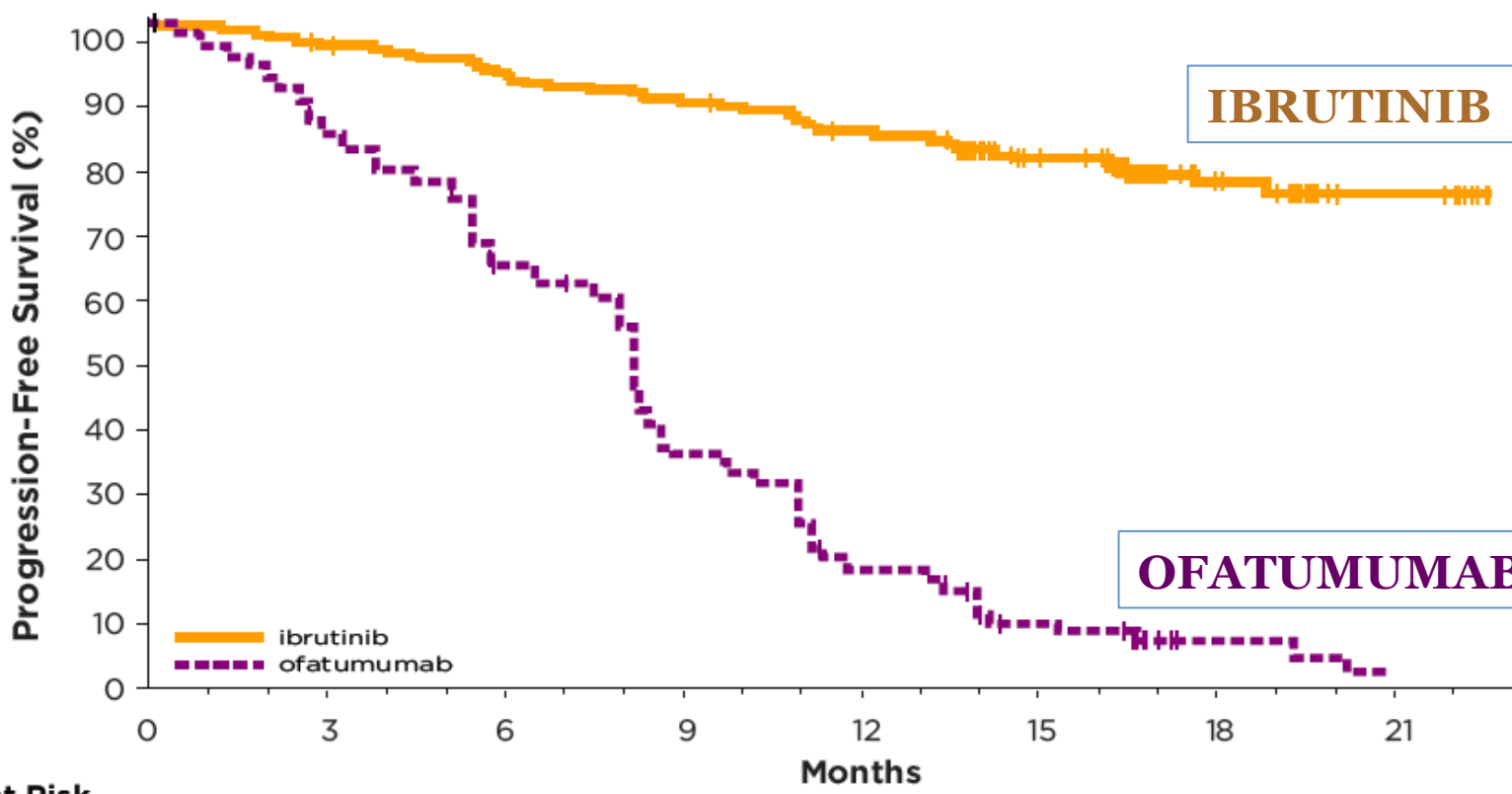
RESONATE-1



re 1. PCYC-1112 (RESONATE™) Study Design



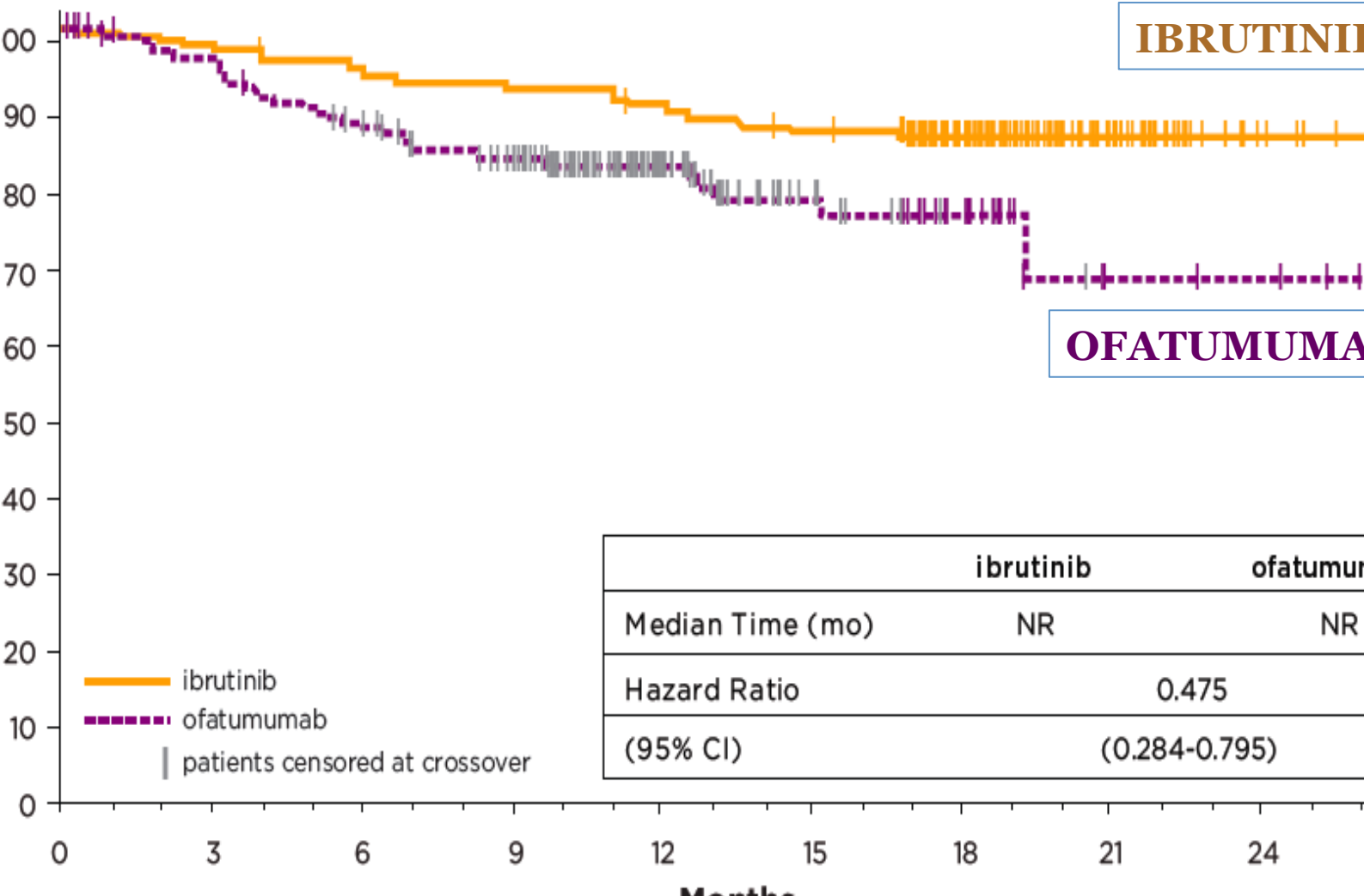
points: PFS, OS, ORR, safety

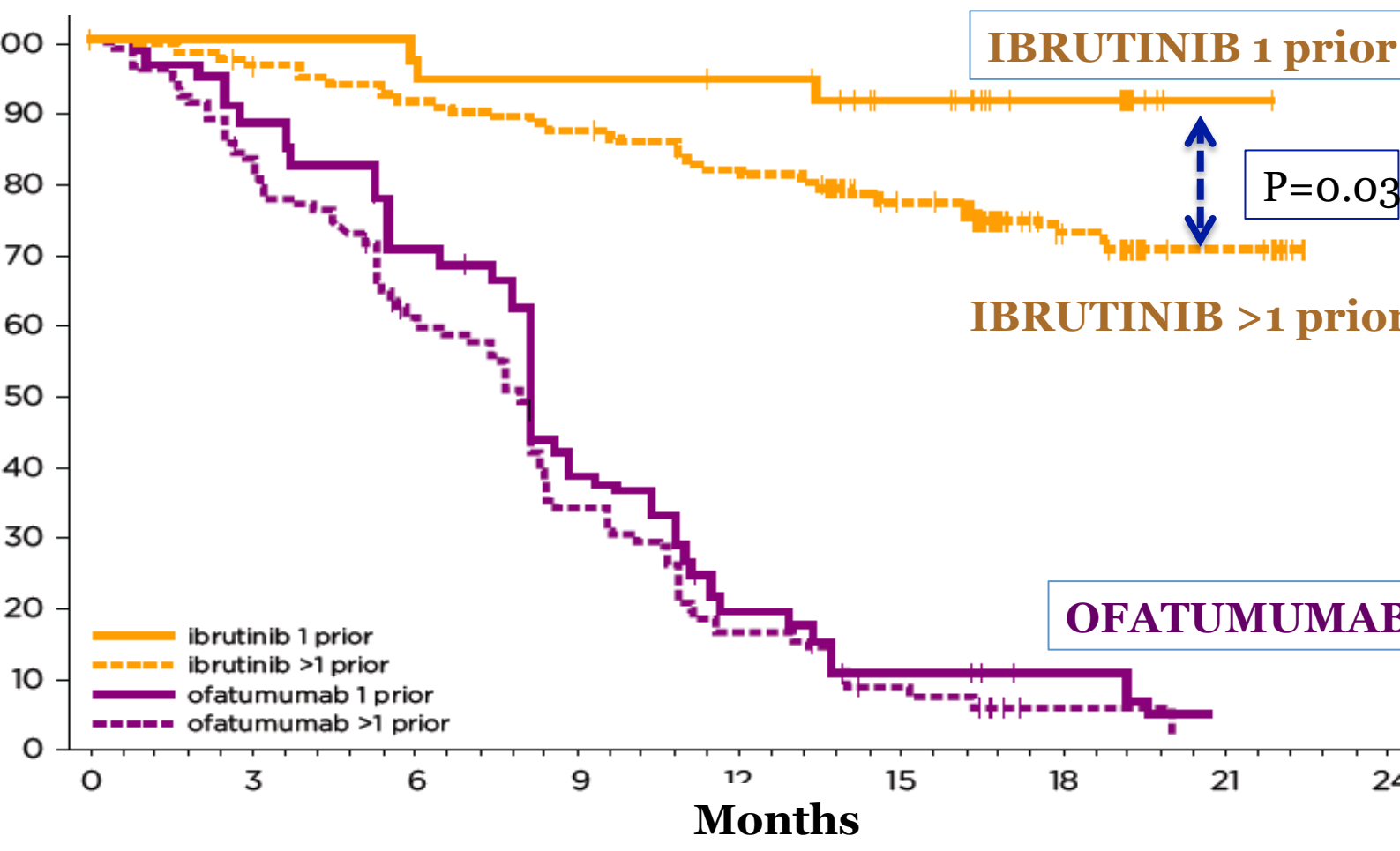


ts at Risk

ibrutinib:	195	187	177	169	158	126	44	14
umumab:	196	158	115	63	31	14	3	

	ibrutinib	ofatumumab
Median Time (mo)	NR	8.1
Hazard Ratio	0.106	


IBRUTINIB
OFATUMUMA
ibrutinib
ofatumumab
patients censored at crossover
ibrutinib
ofatumur
Median Time (mo)
NR
NR
Hazard Ratio
0.475
(95% CI)
(0.284-0.795)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24


IBRUTINIB 1 prior
P=0.03
IBRUTINIB >1 prior
OFATUMUMAB
ibrutinib 1 prior
ibrutinib >1 prior
ofatumumab 1 prior
ofatumumab >1 prior
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
Months

(NCCN V1.2016)

No del (17p)

- without significant comorbidities
- [g] (category 1)
- + rituximab[g,h] (category 1)
- [g]
- mmunotherapy
- [e]
- amustine ± rituximab
- rabine[c,e] + alemtuzumab
- P (rituximab, cyclophosphamide, ubicin, vincristine, prednisone)
- [c] (oxaliplatin, fludarabine,[e] cytarabine
- nab)
- umab
- zumab
- omide[i] ± rituximab
- umab[j] ± rituximab
- rituximab

- Age ≥70 y and younger patients with significant comorbidities
- Ibrutinib[g] (category 1)
- Idelalisib + rituximab[g,h] (category 1)
- Idelalisib [g]
- Chemoimmunotherapy
  - Bendamustine ± rituximab
  - Reduced-dose FCR[c,e]
  - Reduced-dose PCR
  - High-dose methylprednisolone (HDMP) + rituximab
  - Rituximab + chlorambucil
- Ofatumumab
- Obinutuzumab
- Lenalidomide[i] ± rituximab
- Alemtuzumab[j] ± rituximab
- Dose-dense rituximab (category 2B)

del (17p)

Relapsed/Refractory therapy[b]

- Ibrutinib[g]
- Idelalisib + rituximab[g,h] (category
- Idelalisib[g]
- HDMP + rituximab
- Lenalidomide[i] ± rituximab
- Alemtuzumab[j] ± rituximab
- Ofatumumab[k]
- OFAR[c,e]

elalisib + Olatumumab in CLL: Study Desig

Open-label randomized, phase III study

Stratified by del(17p) or TP53 mutation (either vs neither), IGVH mutation (mutated vs unmutated), recurrent disease status (refractory vs relapsed)

r unfit pts with B-cell
L that progressed
mos from completion
f last therapy and
KPS ≥ 60
(N = 261)

IDELA 150 mg BID continuously +
OFA 300 mg Wk 1, then
1000 mg q1w x 7 then q4w x 4
for 12 doses
(n = 174)

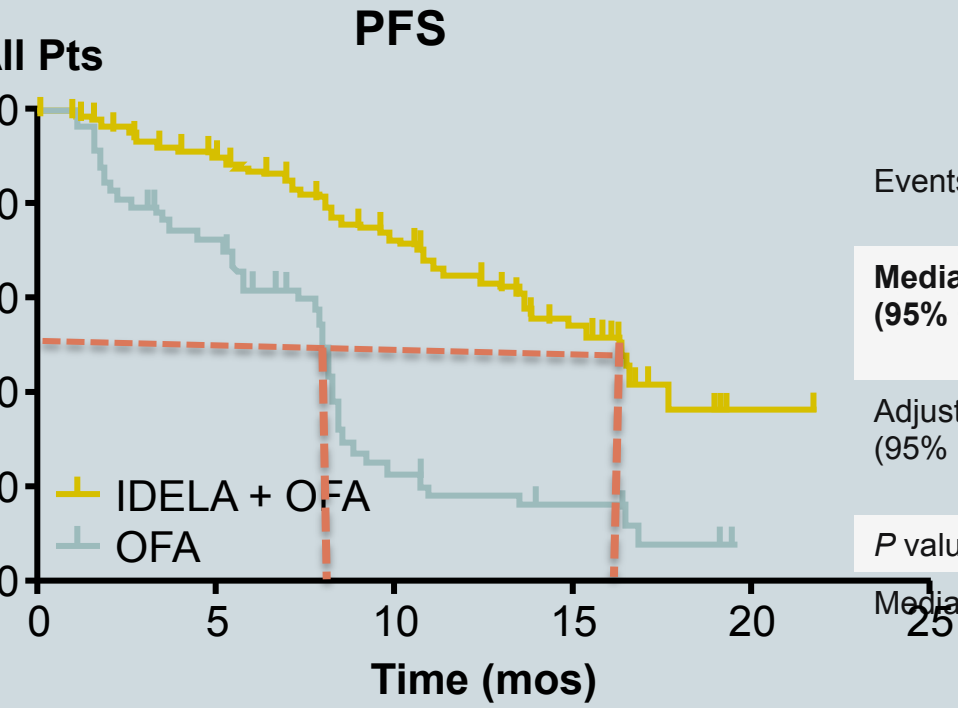
OFA 300 mg Wk 1, then
2000 mg q1w x 7 then q4w x 4
for 12 doses
(n = 87)

Until dis
progression
from any

rimary endpoints: PFS

econdary endpoints: PFS in pts with del(17p)/TP53 mutation, OS, ORR, LNR rate, C
ate

Idelalisib + Ofatumumab in CLL: PFS



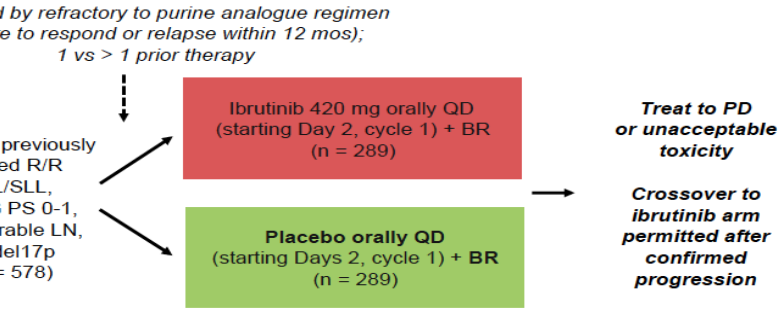
	IDELA + OFA (n = 174)	O (n =
Events, n (%)	76 (44)	54
Median PFS, mos (95% CI)*	**16.3 (13.6-17.8)**	**8 (5.7**
Adjusted HR (95% CI)*	0.27 (0.19-0.39)	
P value†	< .0001	
Median observation, mos	11.1	5

In del(17p)/TP53 subgroup, the median PFS for the IDELA + OFA group was 13.7 mos vs 5.8 for OFA alone (HR 0.32; 95% CI:

Idelalisib + Ofatumumab in CLL: Common Treatment-Related AEs

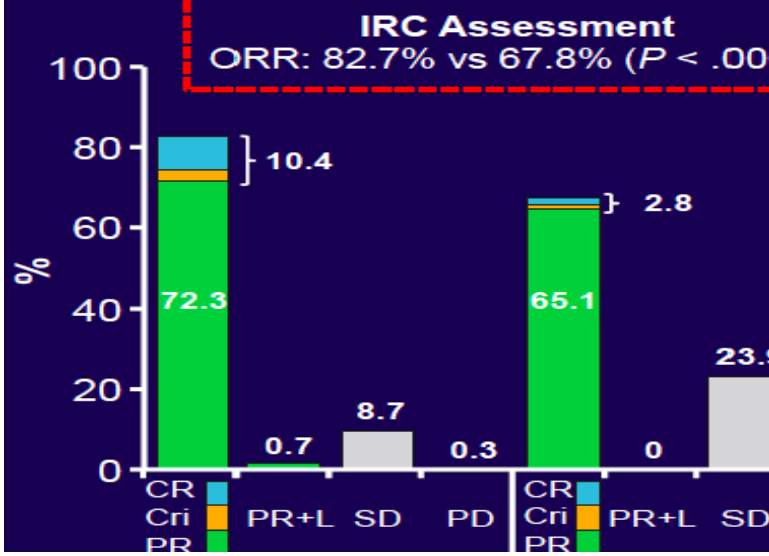
(≥ 18% IDELA + OFA), %	IDELA + OFA (n = 173)		OFA (n = 86)	
	All Grades	Grade ≥ 3	All Grades	Grade ≥
rrhea and/or colitis	49	20	23	1
tropenia	35	34	16	15
exia	32	7	23	2
gue	32	3	28	5
gh	30	< 1	21	0
sea	30	< 1	27	1
h	28	4	11	2
stipation	21	0	15	1
mia	20	12	10	6
dache	19	0	10	0

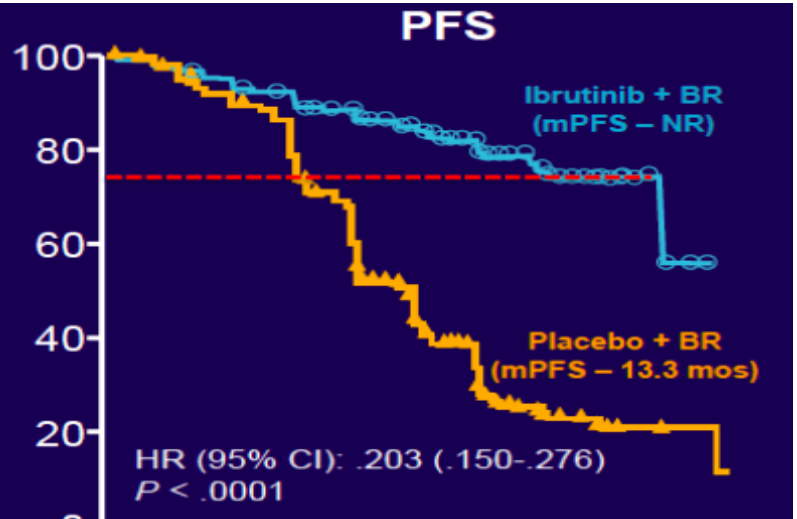
HELIOS: Study Design



ary endpoint: PFS (independent review)

ndary endpoints: ORR (independent review), MRD-negative response rate, safety





Outcome, %	Ibrutinib + BR (n = 289)	Placeb (n =
Treatment discontinuation	29.1	64
▪Progression or relapse	4.8	45
▪AE	14.2	11
Grade 3/4 treatment-emergent AE ≥ 5% of pts	(n = 287)	(n =
▪Neutropenia	53.7	50
▪Thrombocytopenia	15.0	15
▪Anemia	3.5	8.
Any grade bleeding	31.0	14
▪Major hemorrhage	3.8	1

ly 115: Study Design

domized, double-blind, placebo-controlled phase III study

fied by 17p deletion and/or TP53 mutation,
V mutation status, relapsed vs refractory

h measurable
, no history of
sformation or
K/PI3Kδ/SYK
ibitor use
= 416)

Idelalisib 150 mg BID +
Bendamustine 70 mg/m^2 D1,2 Q4W, C1-6 +
Rituximab 375 mg/m^2 C1, 500 mg/m^2 C2-6
(n = 207)

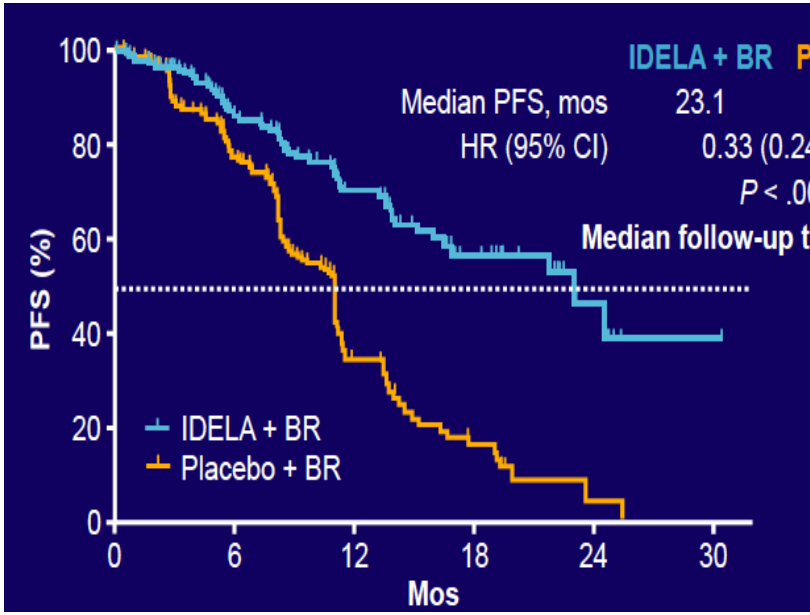
Placebo BID +
Bendamustine 70 mg/m^2 D1,2 Q4W, C1-6 +
Rituximab 375 mg/m^2 C1, 500 mg/m^2 C2-6
(n = 209)

Followed for PD with post-study therapy at investigator's discretion

on < 36 mos from last therapy, requiring treatment, but no progression within 6 mos of last
tine.

ary endpoint: PFS

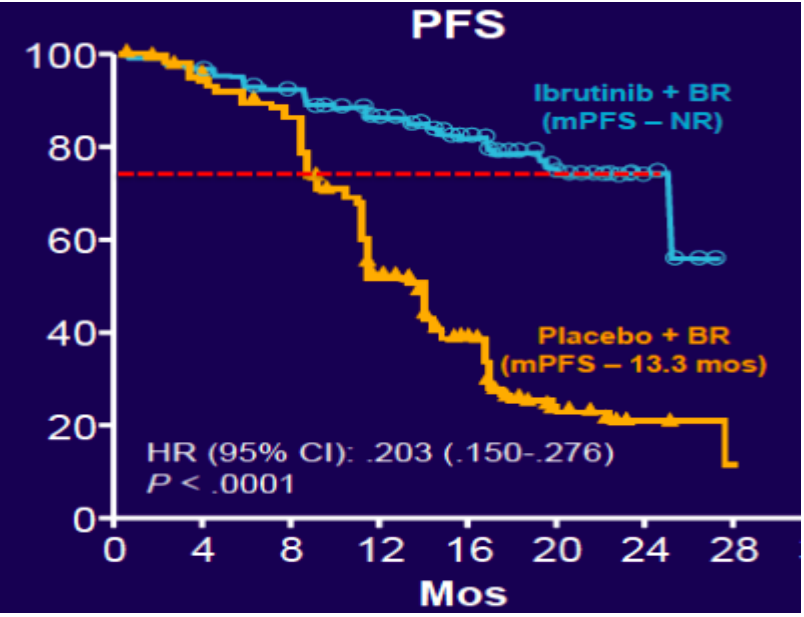
ondary endpoints: ORR, nodal response, CR, OS



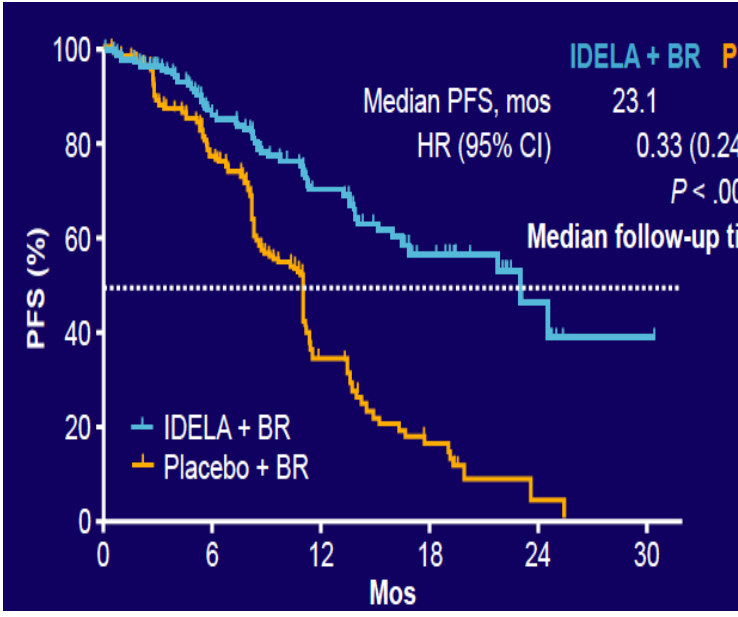
e Parameter, % (95%	IDELA + BR (n = 207)	Placebo + BR (n = 209)
sponse	68 (61-74) 2	45 (38-52) 0
uction in lymph	96 (93-99)	61 (54-68)
egaly response	82 (75-88) 56 (46-66)	57 (49-65) 40 (31-50)
gic response bin	88 (78-95)	70 (58-80)

Characteristic, %	IDELA + BR (n = 207)		Placebo + B
	Any Grade	Grade ≥ 3	Any Grade
Any AE	100	93	97
▪Neutropenia	63	60	54
▪Pyrexia	42	7	30
▪Diarrhea	35	7	22
▪Febrile neutropenia	22	20	7
▪Pneumonia	17	11	11
▪Rash	16	3	12
▪ALT elevation	15	11	1
AEs leading to dose reduction	11		6

TRIALS OF CIT versus CIT + BRCi in R/R CLL



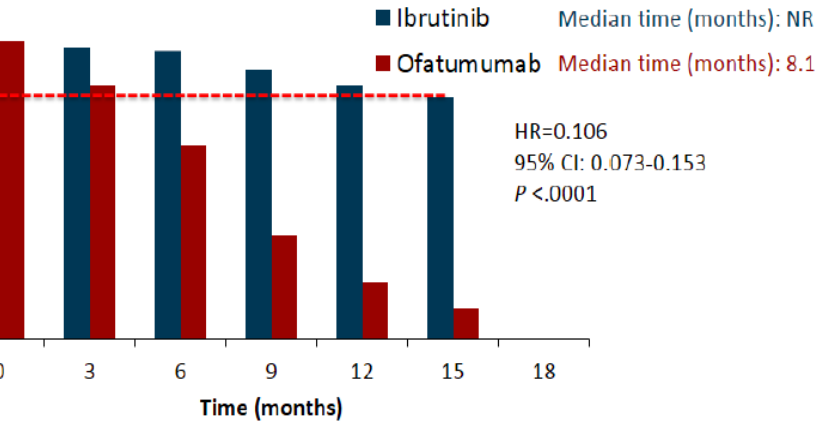
PFS di BR+Ib a 24 mesi 72%
(17p del non inclusi)



PFS di BR+Id a 24 mesi 50%
(17p del inclusi)

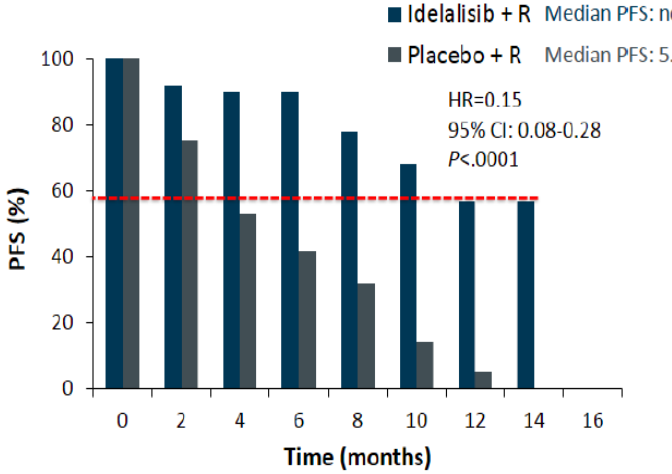
PFS in phase 3 trials of ibrutinib and idelalisib

ted Efficacy Data in the Phase 3 NATE Trial



PFS at 15 months 80%

Phase 3 Trial of Idelalisib + R in R/R PFS—Primary Endpoint



PFS at 14 months 59%

Nello studio IDELA + OFA vs OF

n R/R CLL: All Grades

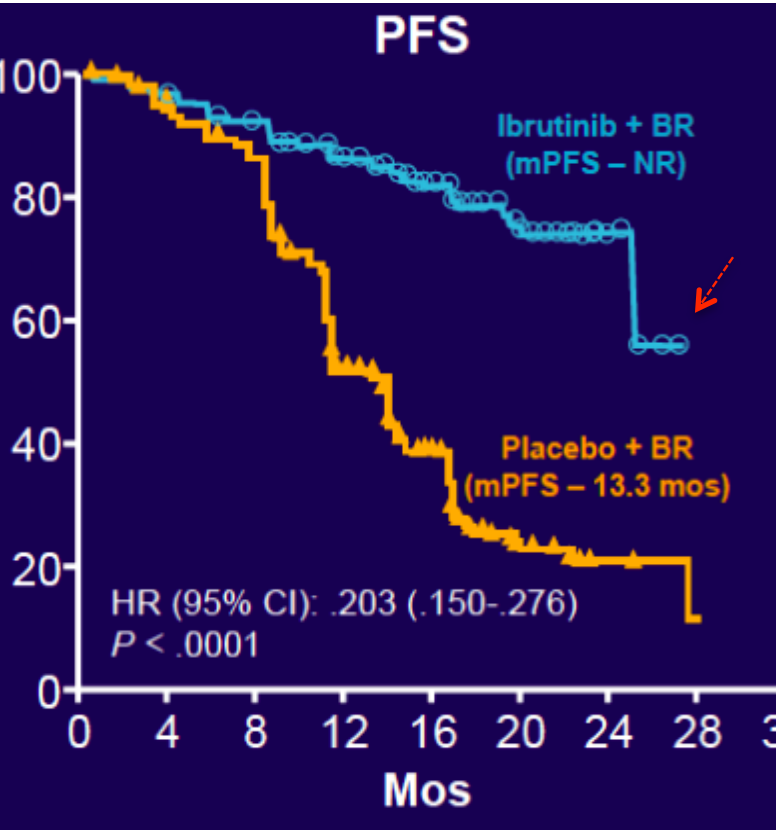
Phase 3 RESONATE Trial[a]

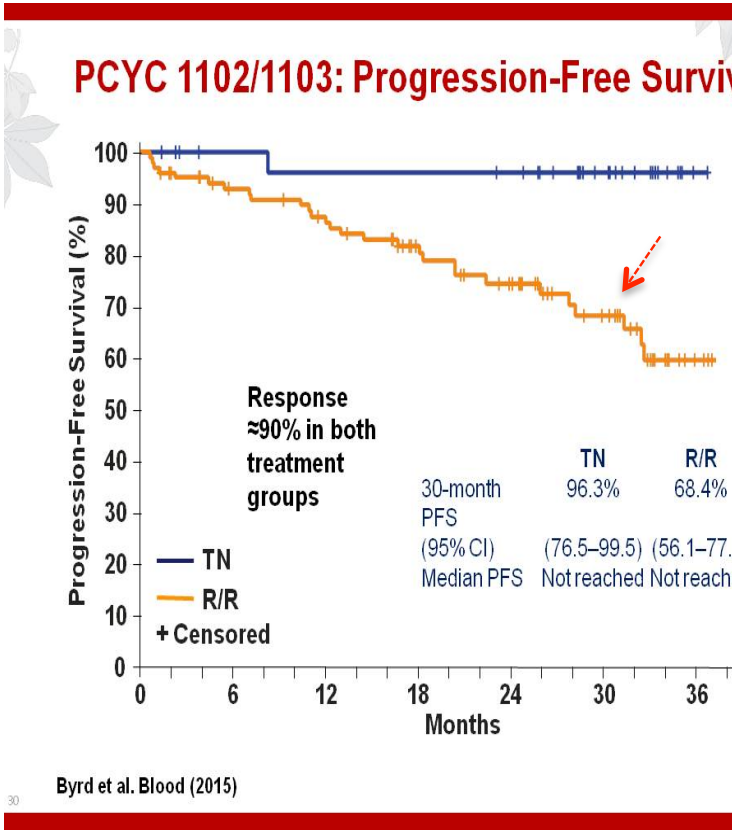
, n (%)	Ibrutinib (n = 195)	Ofatumumab (n = 191)
AE	194 (99)	187 (98)
hea	93 (48)	34 (18)
ea	51 (26)	35 (18)
ia	46 (24)	28 (15)
nia	44 (23)	33 (17)
ropenia	42 (22)	28 (15)
mbocytopenia	33 (17)	22 (12)
algia	34 (17)	13 (7)
	31 (16)	20 (10)
tipation	30 (15)	18 (9)

Phase 3 Idelalisib + R[b]

Event, n (%)	Idelalisib + R (n = 110)	Placebo (n = 1
Any TEAE	100 (91)	101 (9
Pyrexia	32 (29)	17 (1
Nausea	26 (24)	23 (2
Diarrhea	21 (19)	15 (1
IRR	17 (15)	30 (2
SAEs	44 (40)	37 (3
Pneumonia	7 (6)	9 (8
Pyrexia	7 (6)	3 (3
Pneumonitis	4 (4)	1 (1
Diarrhea	3 (3)	1 (1
Neutropenia	60 (55)	52 (4

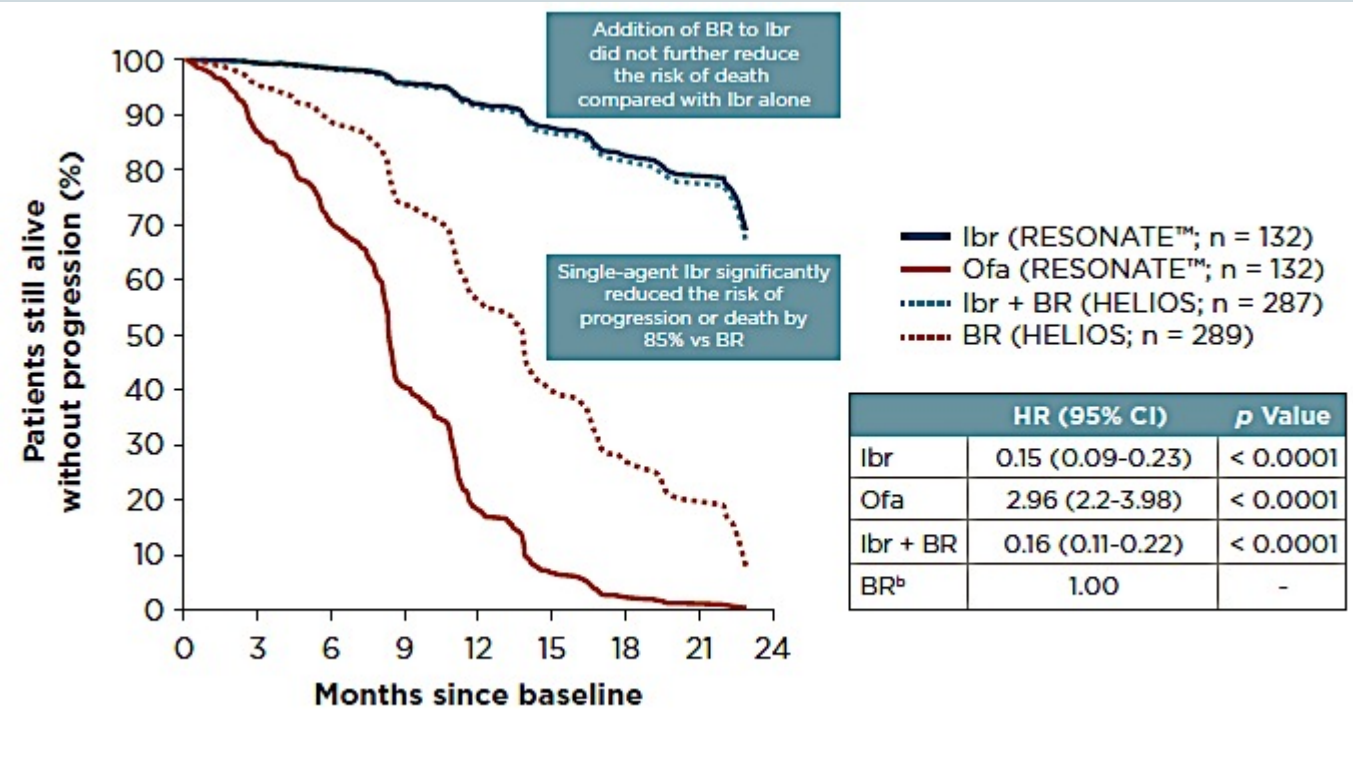
trial.





t 30 months in the I+BR arm 57%

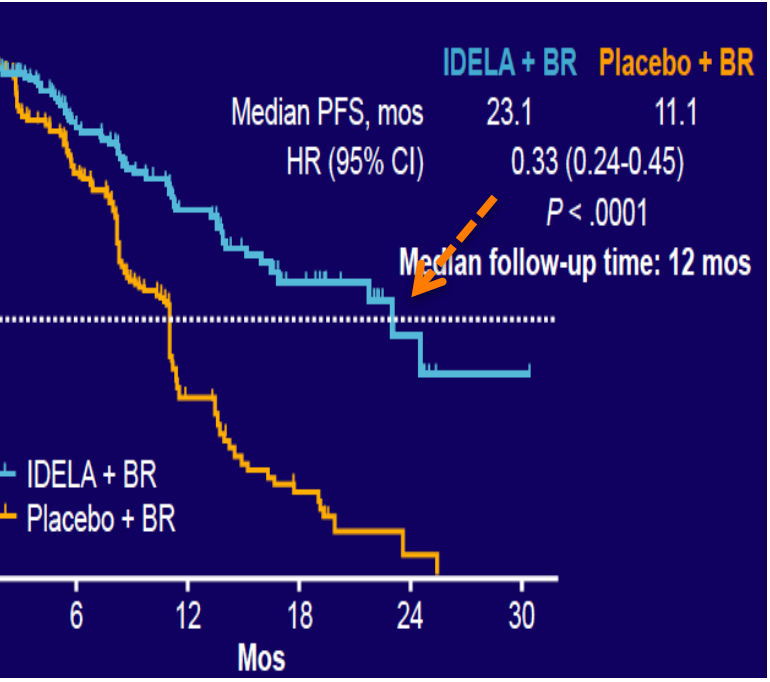
PFS at 30 months for R/R pts



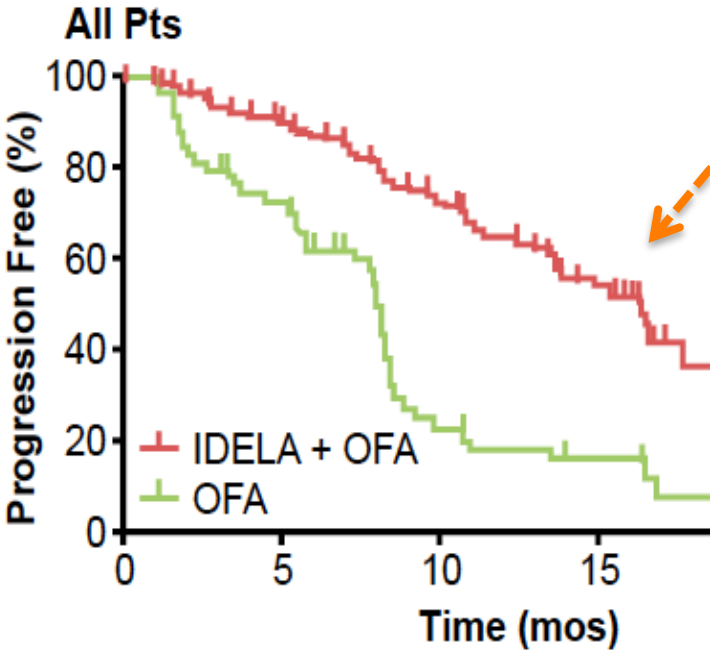
	HR (95% CI)	*p* Value
Ibr	0.15 (0.09-0.23)	< 0.0001
Ofa	2.96 (2.2-3.98)	< 0.0001
Ibr + BR	0.16 (0.11-0.22)	< 0.0001
BR[b]	1.00	-

n the overall CLL/SLL population, PFS and OS were comparable for single-agent ibruti
ersus ibrutinib + BR and were significantly improved for single-agent ibrutinib versus

PFS of patients who received idelalisib + ofatumumab or idelalisib + BR

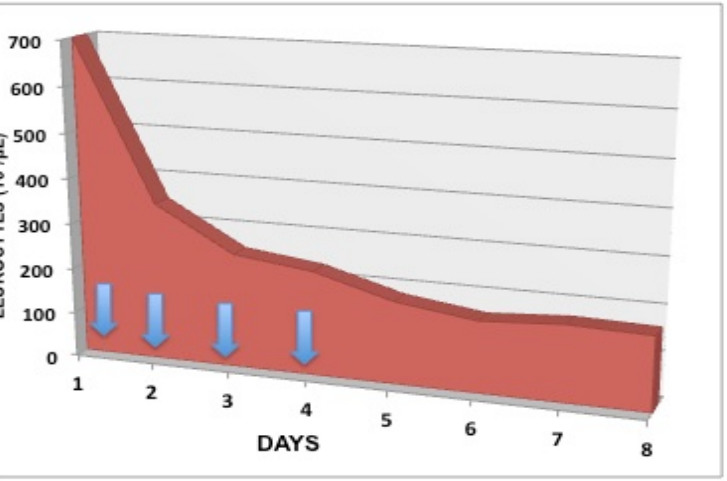


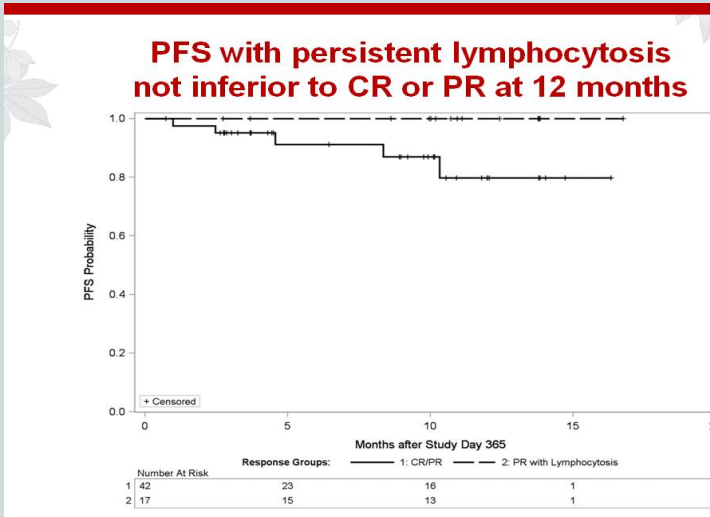
Median PFS 23.1 months



Median PFS 16.3 mon

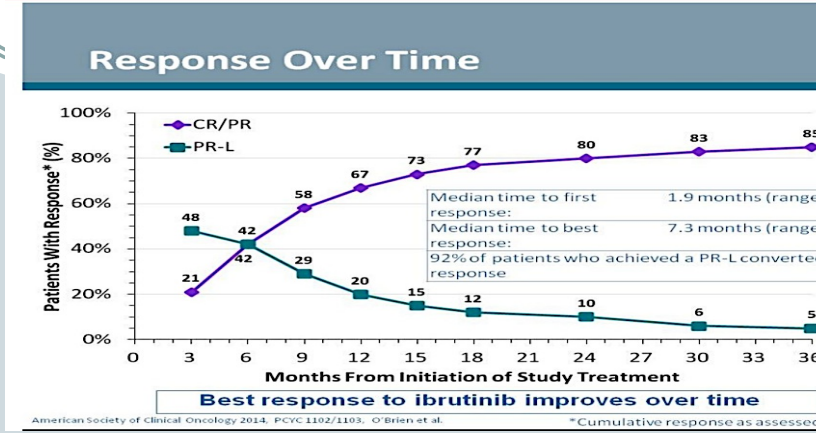
The initial lymphocytosis seen with these agents would result in patients being classified as having progressive disease based on iwCLL criteria, although all other parameters indicate improvement.

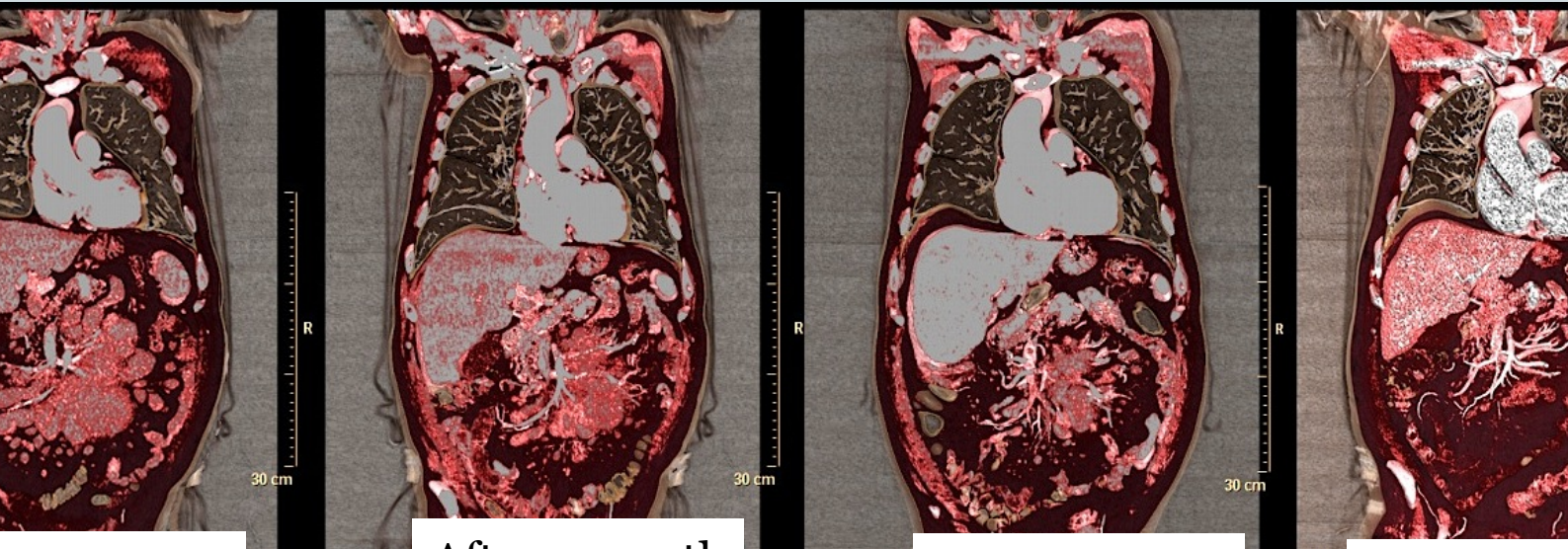




inhibitor treatment

The novel agents are given as continuous therapy and maximal response is often slowly evolving over time.

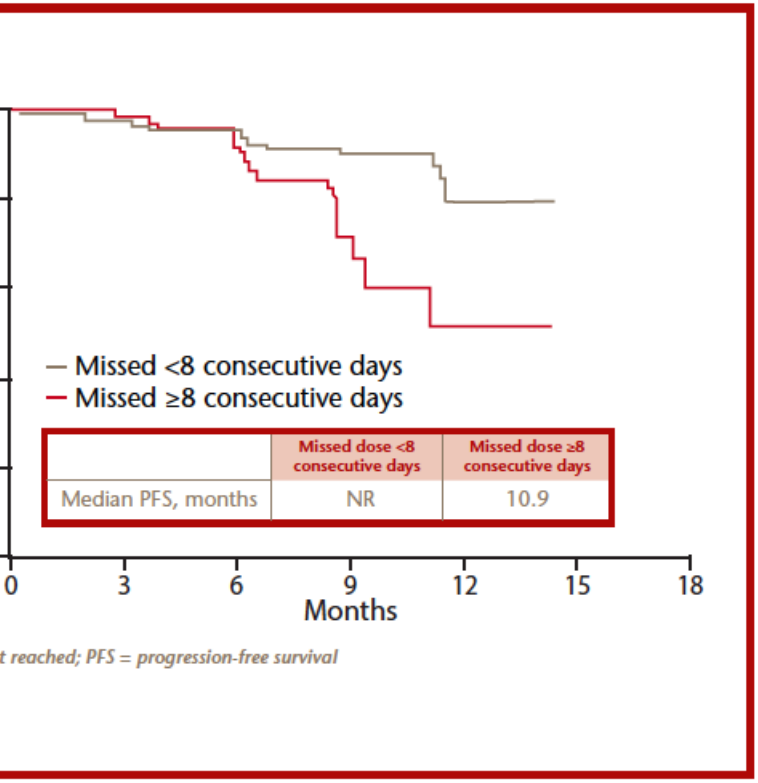




inhibitor treatment

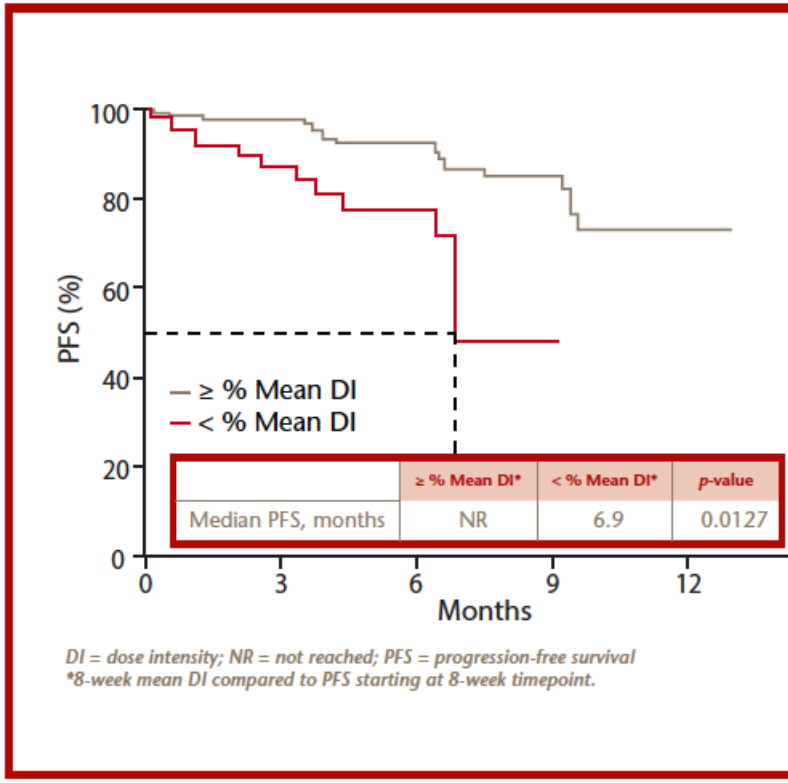
- Adherence to Ibrutinib is predictive of PFS: A sub-analysis of RESONAT

. Progression-free survival by missed dose
ecutive days



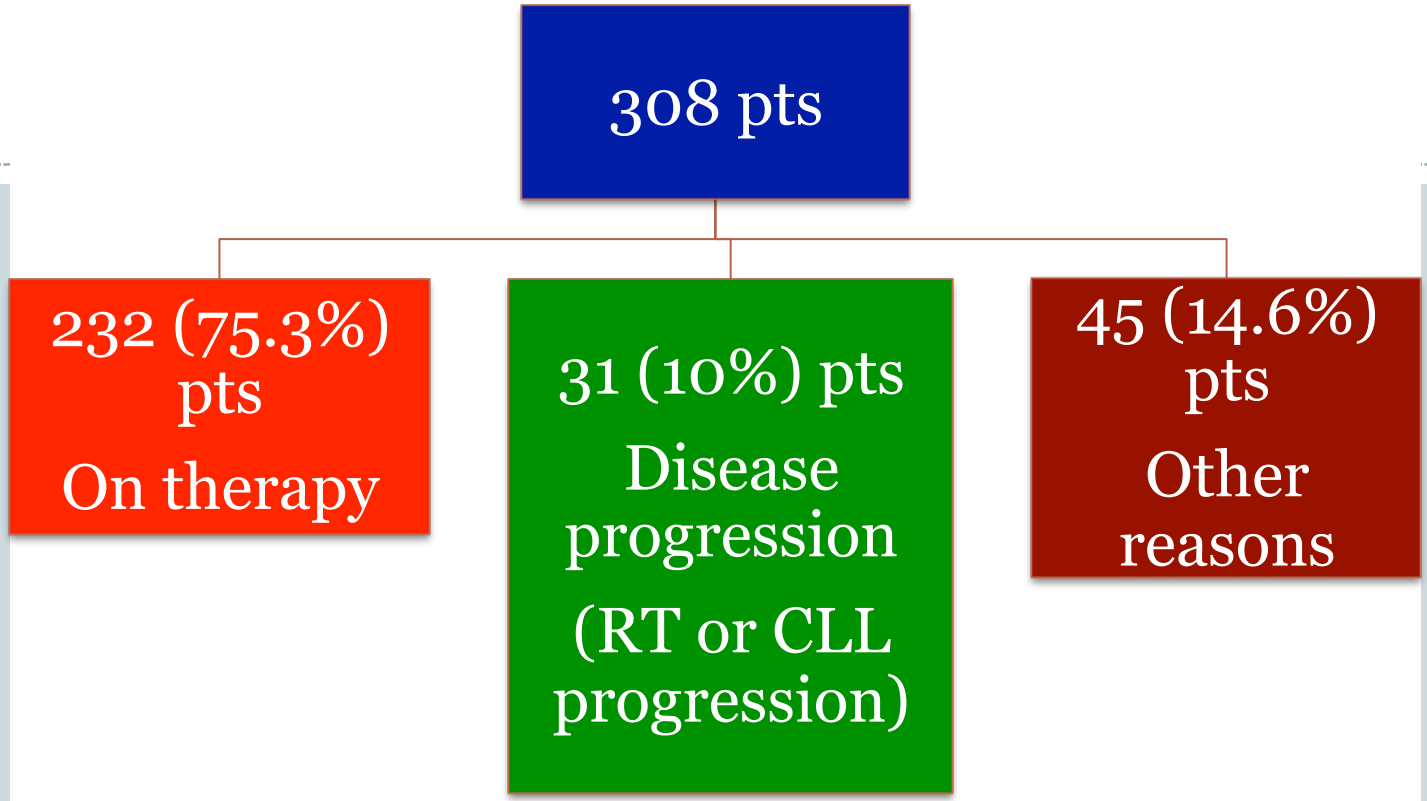
t reached; PFS = progression-free survival

Figure 2. Progression-free survival by mean dose int



DI = dose intensity; NR = not reached; PFS = progression-free survival
*8-week mean DI compared to PFS starting at 8-week timepoint.

Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia



Median follow-up 20 months

Outcomes Post-RI Discontinuation in CLL: Study Design

Multicenter, retrospective analysis of CLL pts (N = 178) who discontinued ibrutinib- or idelalisib-based therapies

- 143 ibrutinib-based therapy
- 35 idelalisib-based therapy

ason, %	Ibrutinib	Idelalisib
icity	51	52
progression	28	31
nter's nsformation	8	6
/CAR-T	2	0
elated death or er	11	11

Most Common Toxicities for Discontinuation, %

Ibrutinib (n = 66)

- Atrial fibrillation
- Infection
- Hematologic
- Bleeding
- Pneumonitis

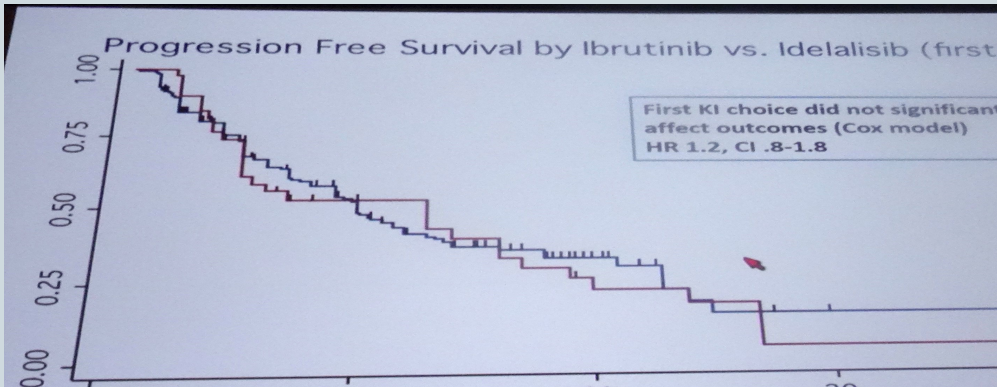
Idelalisib (n = 18)

- Pneumonitis
- Colitis
- Rash
- Transaminitis

Outcomes Post KI Discontinuation in CLL: Response to Alternate Treatments

esponse, %	Alternate KI (n = 38)	BCL2-i (CT) (n = 13)	CITs (n = 12)	CD20 Tx (n = 11)
R	50	76	25	36
	0	7	17	9
	50	69	8	27
	30	16	33	45
	20	8	42	19

direct comparisons performed.



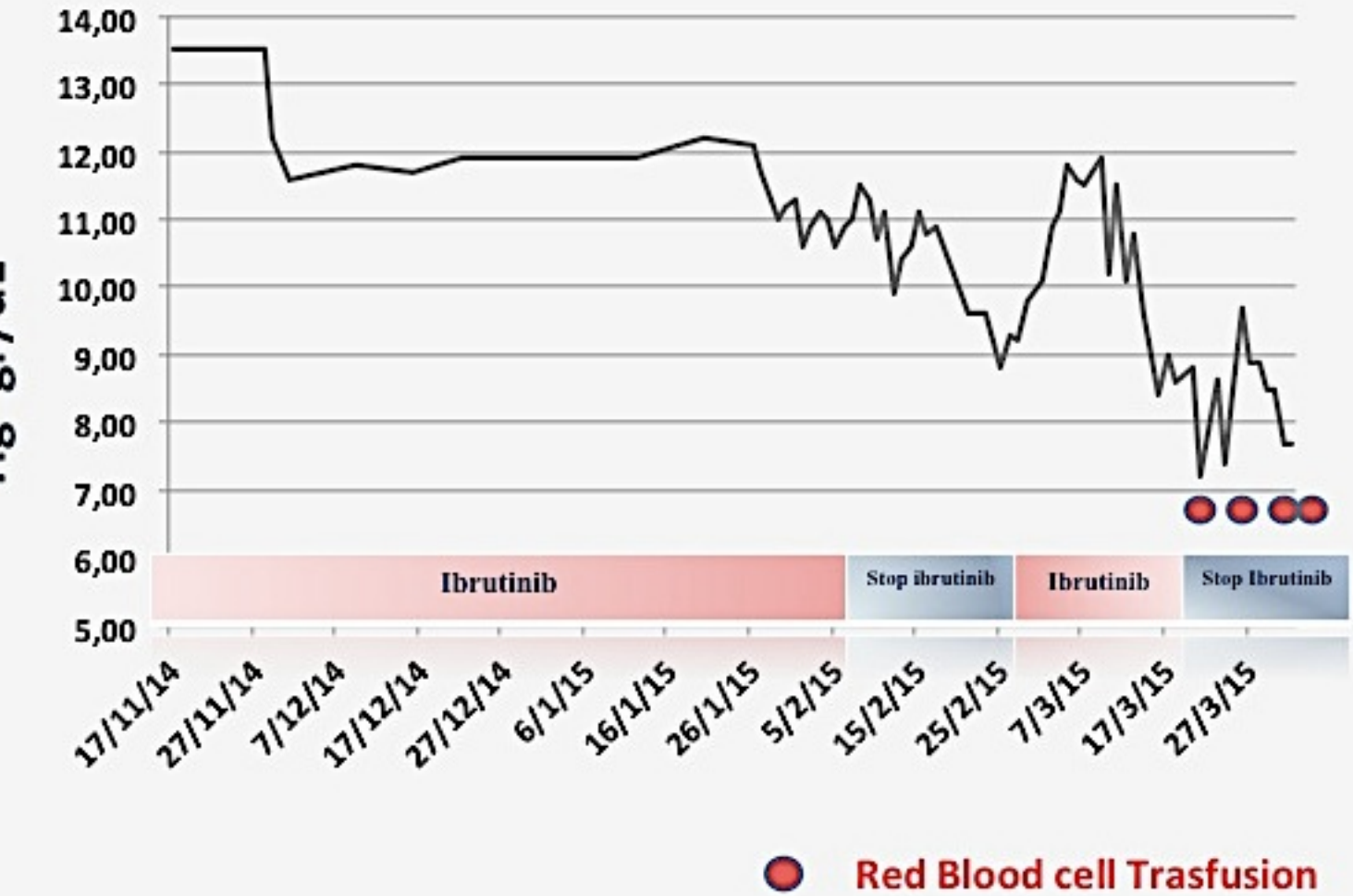

14,00
13,00
12,00
11,00
10,00
9,00
8,00
7,00
6,00
5,00
Ibrutinib
Stop ibrutinib
Ibrutinib
Stop Ibrutinib
17/11/14
27/11/14
7/12/14
17/12/14
27/12/14
6/1/15
16/1/15
26/1/15
5/2/15
15/2/15
25/2/15
7/3/15
17/3/15
27/3/15
Red Blood cell Trasfusion

Table 1

Relationship between treatment with ibrutinib and incidence autoimmune hemolytic anemia (AHIA) in chronic lymphocytic leukemia (CLL).

Source	N. pts.	History of AHIA	Ibrutinib-emergent AIHA	Ibrutinib-relapsed AIHA	Ibrutinib-controlled AIHA
RESONATE-Trial[4]	195	29	0	0	1
PYC-102/PYC-1109/OSU 11133[5]	271	42	2	1	0
Case reports[7-8]*	3	3	0	1	2

4.03)

Grade 1

Atrial Fibrillation, Asymptomatic, intervention not indicated

Grade 2

Atrial Fibrillation, Non-urgent medical intervention indicated

Grade 3

Atrial Fibrillation, Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)

Grade 4

Atrial Fibrillation, Life-threatening (e.g., arhythmia associated with CHF, hypotension, syncope, shock)

Atrial Fibrillation in CLL/SLL Patients on Ibrutinib

Phase II trial (NCT01500733) that enrolled TN and rel/ref pts (n. 86)
≥ 65 yo without del 17p (n=35);
≥ 18 yo with presence of del 17p (n=51)

median follow-up of 28 mo

14 *(16%)* of 86 patients were
nd to have A fib while on study
9 (10%) first episode)

The median time
to the first event on study
was *18.24 (IQR: 10.8-26.0) mo*

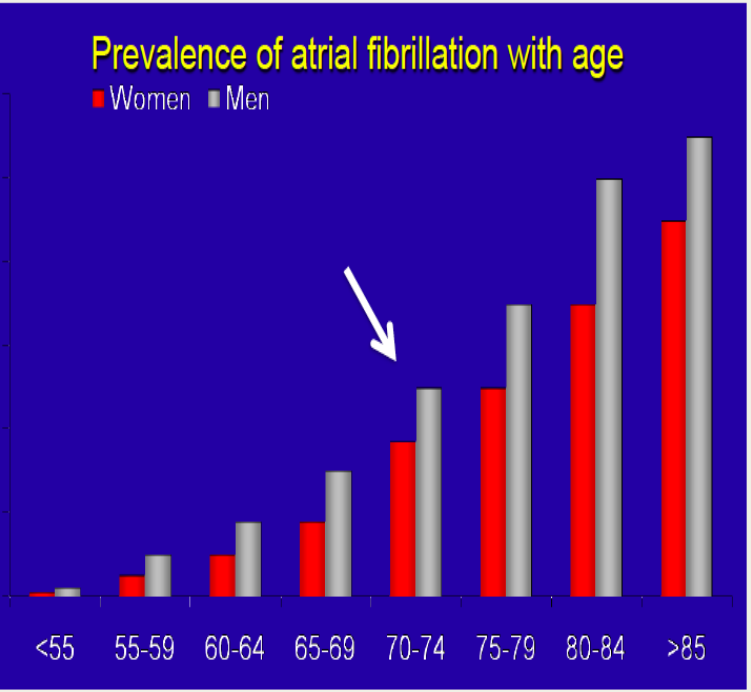
3/14 patients had grade 3 AF

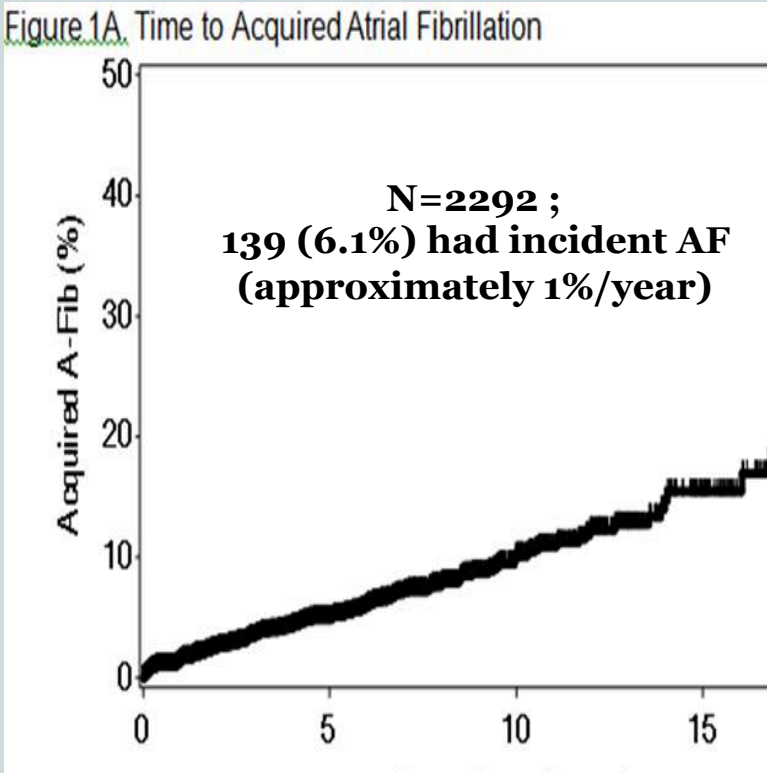
Restared ibrutinib at 280 mg
ASA (1) ASA+sotalol (1); apixaban (1)

11/14 patients had grade 2 AF

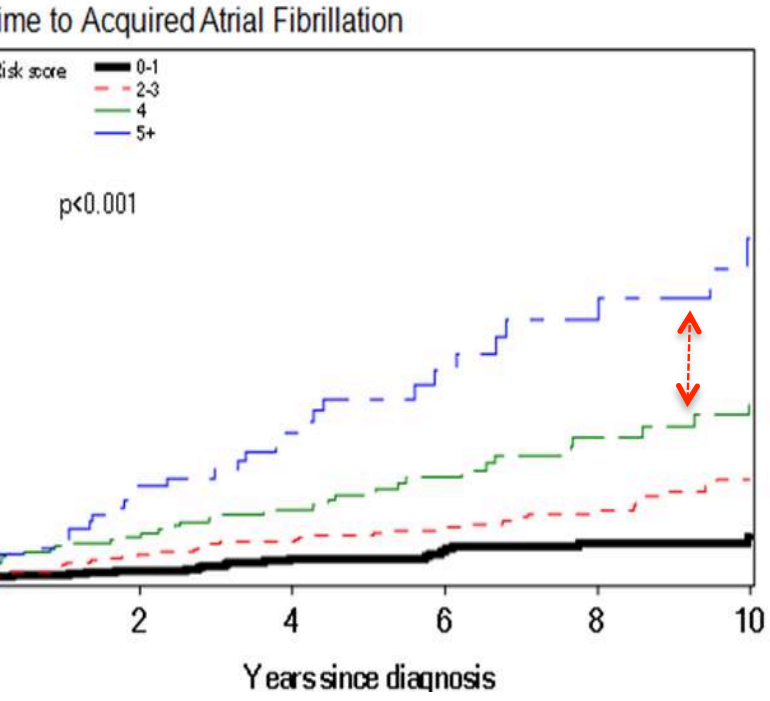
Restared ibrutinib at 420 mg
ASA (7); apixaban (4)

course of the natural history of CLL.





2950 - Atrial Fibrillation in Patients with Chronic Lymphocytic Leukemia (CLL)



Factors associated with an increased risk of developing AF

Factor	Hazard Ratio
Age ≥ 75 years	3.6
Gender (male)	1.8
Valvular heart disease	2.4
Hypertension	1.5

Changing Clinical Practice in CLL

The incidence of AF increases with age and over the course of the natural history of CLL.

It is reasonable to consider ibrutinib even in patients with risk factors for atrial fibrillation.

It is imperative that clinicians understand the risk and educate patients on the symptoms of this adverse event.

(HBV-DNA > 20000 UI/mL)

Fig 1

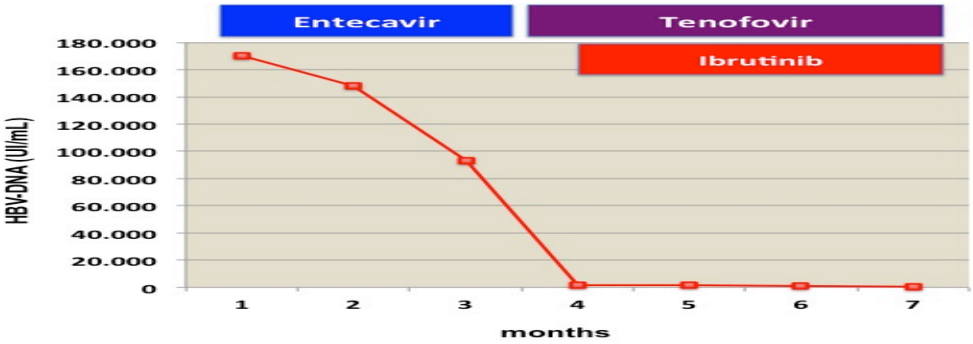
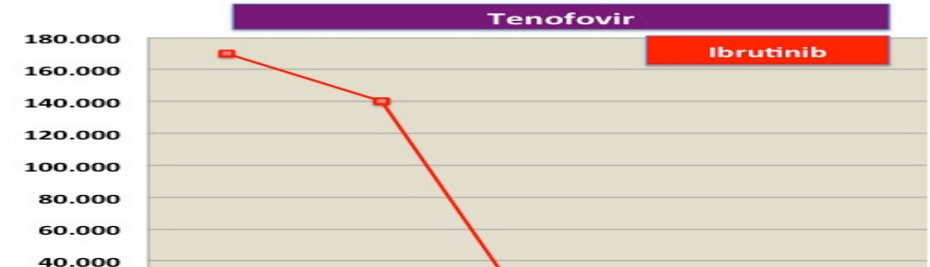
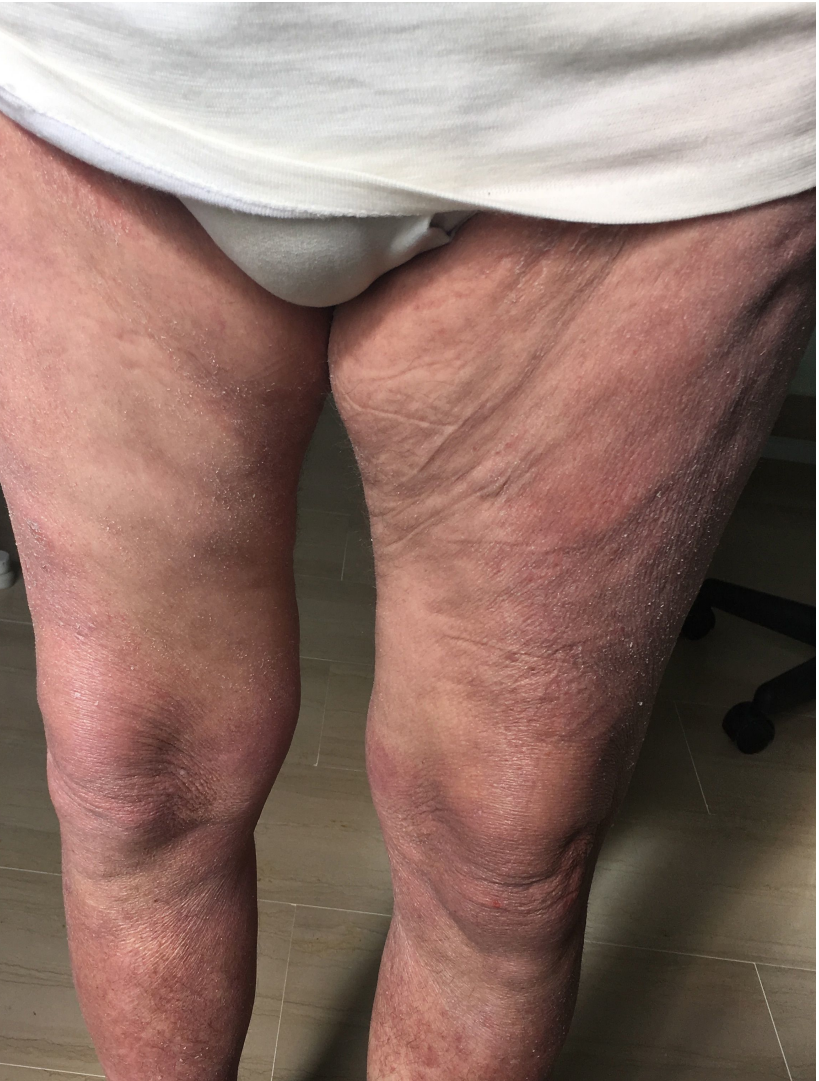
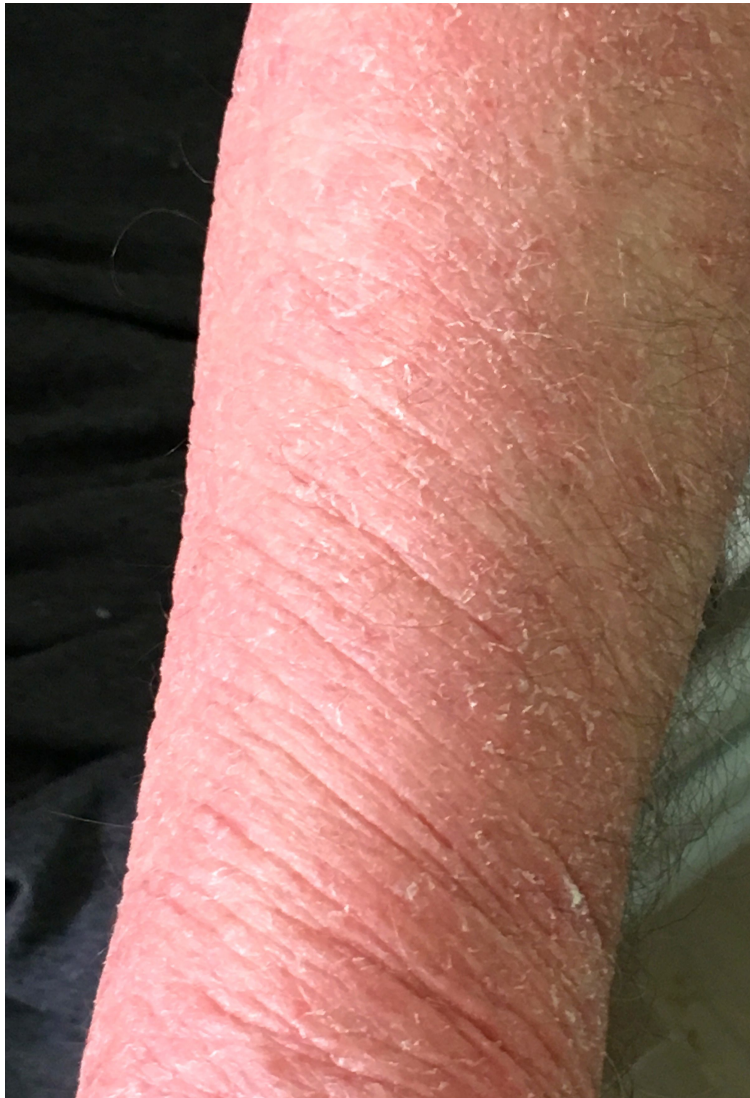
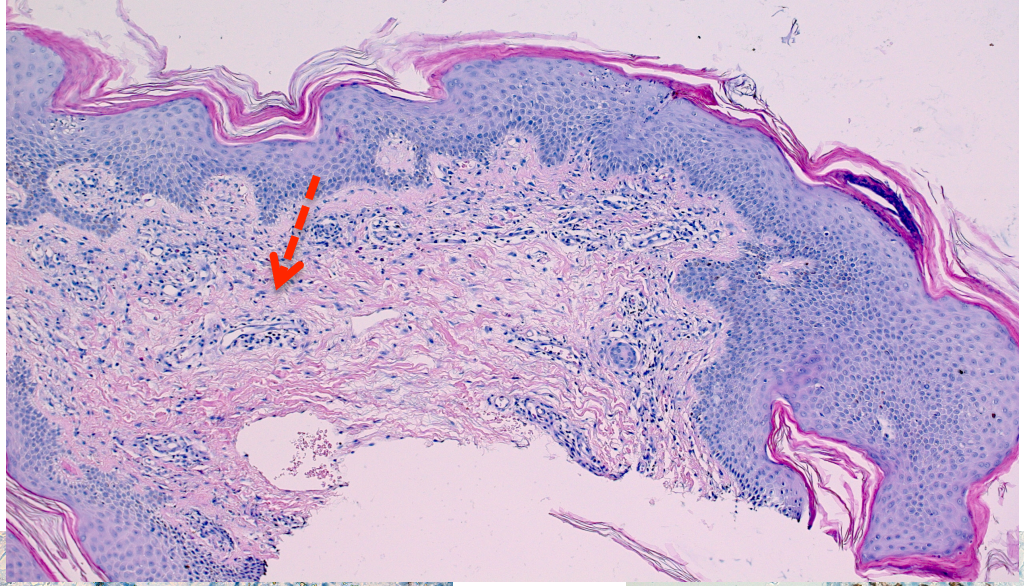


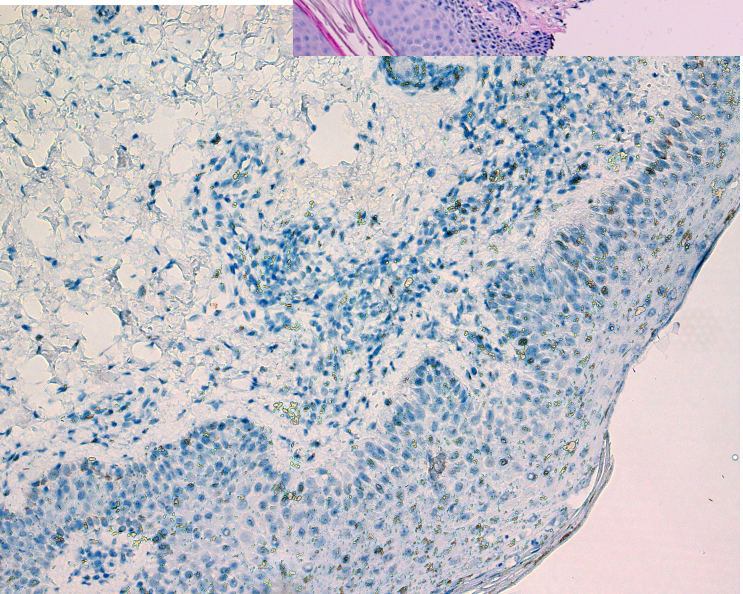
Fig 1 B

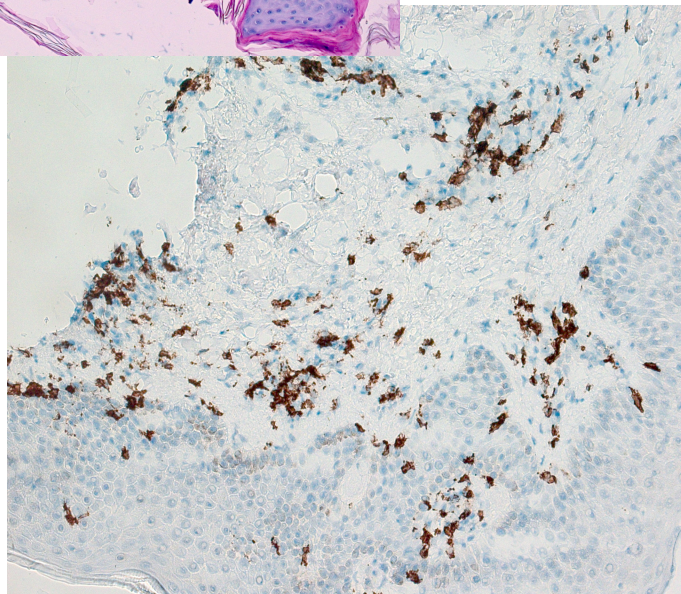


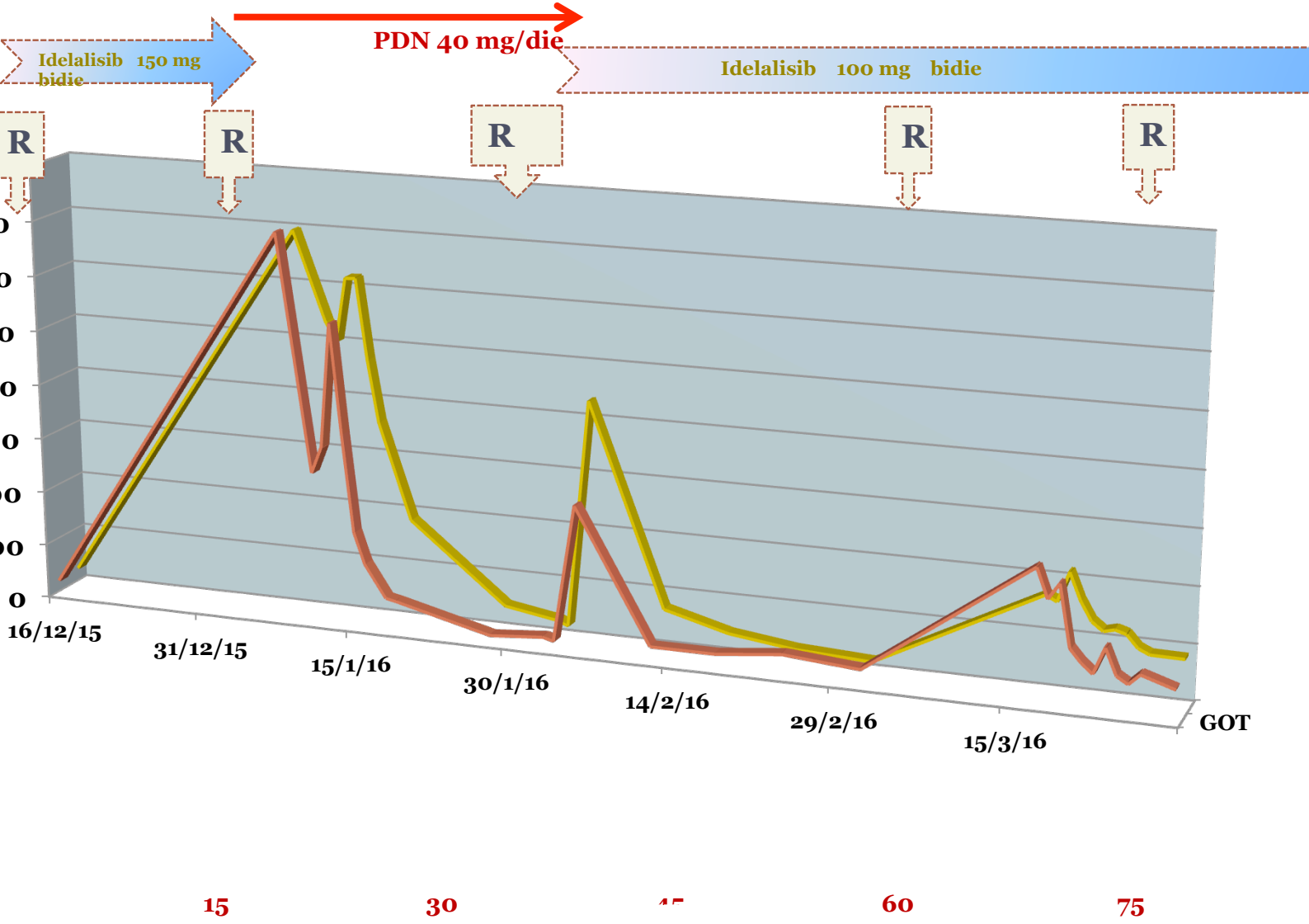











Idelalisib 150 mg bidie
PDN 40 mg/die
Idelalisib 100 mg bidie
R
R
R
R
R
16/12/15
31/12/15
15/1/16
30/1/16
14/2/16
29/2/16
15/3/16
GOT

15 30 60 75

Study Design

Single-arm, multicenter phase II study

CLL with del(17p);
COG PS 0-2;
o major organ
sfunction,* prior
oSCT, RT, other
halignancy, or
ncontrolled AI
cytopenia
(N = 107)

→

Venetoclax
20 mg QD Day 1†
50 mg QD Days 2-7
100 mg QD Wk 2
200 mg QD Wk 3
400 mg QD Wk 4+

→

Response assess
iwCLL 2008 criter

Risk-based TLS prophylaxis used

Primary endpoint: ORR (IRC assessment)

Secondary endpoints: CR/PR, time to first response, DoR, PFS, OS, safety

Exploratory endpoint: MRD

Best Responses

sponse, %	Investigator	IRC
erall response	73.8	79.4
CR or CRi	15.9	7.5
nPR	3.7	2.8
PR	54.2	69.2
response	26.2	20.6
Stable disease	22.4	NA

25/48 pts (52%) had no evidence of CLL in bone marrow by IHC

18/45 pts assessed (40%) were MRD negative in peripheral blood samples

Among 87 pts with baseline lymphocytosis, only 4 failed to normalize ALC count to < 4 x 10^9/L

- Median time to normalization: 22 days (range: 2-122)

Among 96 pts with baseline lymphadenopathy, 89 had ≥ 50% reduction in nodal size of the largest target lesion (by SPD)

- Median time to ≥ 50% reduction: 2.7 mos (range: 0.7-8.4)

Response Duration and Survival

rameter	
CLL response, median mos (range)	
Time to first response	0.8 (0.1-8.1)
Time to CR/CRi	8.2 (3.0-16.3)
ration of response: 12-mo estimates, % (n = 85)	
All responders	84.7
CR/CRi/nPR	100
MRD negative	94.4
rvival rates: 12-mo estimates, % (95% CI) (n = 107)	
PFS	72 (61.8-79.8)
OS	86.7 (78.6-91.9)

Venetoclax in R/R CLL With del(17p): AEs

atment-Emergent AE,*	Any Grade	Grade 3/4
	96	76
tropenia	43	40
rrhea	29	0
sea	29	1
mia	27	18
gue	22	0
exia	20	1
ombocytopenia	19	15
erphosphatemia	16	1
niting	15	1
ction	72	20
Upper respiratory	15	2
Nasopharyngitis	14	NR
UTI	9	NR

- Neutropenia
  - Baseline (any grade): 22.4%
  - Manageable with dose interruption or reduction, G-CSF, and/or antibiotics
- 5 pts with laboratory TLS duri dose escalation
  - 2 dose interruptions (1 day ea but no clinical TLS
- Serious AEs in 55% of pts
  - Most common SAEs: pyrexia, 7%; AIHA, 7%; pneumonia, 6% febrile neutropenia, 5%

Relapsed/Refractory CLL

First-in-human study of second-generation BTK inhibitor acalabrutinib (ACP-196)

R/R CLL/SLL; ECOG PS 0-2; no prior BTK inhibitors* (N = 61†)

Acalabrutinib Dose Escalation (Phase I)
100 mg QD (n = 9†)
175 mg QD (n = 8)
250 mg QD (n = 7)
400 mg QD (n = 6)

Acalabrutinib Dose Expansion (Phase II)
100 mg BID
(n = 31)

or BCL-2 or PI3Kδ inhibitors, pancytopenia, and prior BMT allowed.
t discontinued prior to 28-day DLT review.

Tumor assessments at BL and end of cycles 2, 4, 6, 9, 12, 15, 18, 21, and 24 (day cycles)

Primary objective: safety, MTD

Secondary objectives: PK, PD, tumor response, PFS

Response

ponse, %	All Cohorts (n = 60*)	100 mg QD (n = 8)	175 mg QD (n = 8)	250 mg QD (n = 7)	400 mg QD (n = 6)	100 BI (n =
	85	100	75	100	100	77
lymphocytosis	10	0	25	0	0	1
	5	0	0	0	0	10
	0	0	0	0	0	0

dified iwCLL 2008 best overall response assessment.

At median follow-up of 14.3 mos:

- ORR (n = 60): 95%
- del(17p) ORR (n = 18): 100%

Best responses over time: PR increases, PR + lymphocytosis decreases

Reduced lymphocytosis and lymphadenopathy by CT (56/57 pts with BL assessments) over time

Acalabrutinib in R/R CLL: Safety

Median follow-up: 14.3 mos

s, % (N = 61)	Grade 1/2	Grade 3
atment related, % of pts		
adache	20	--
reased bruising	12	--
techiae	12	--
arrhea	10	--
chymosis	8	--
atment emergent, 0% of pts		
adache	43	--
arrhea	38	2
eight gain	25	2
rexia	20	3
per respiratory tract ction	23	--
tigue	18	3
ripheral edema	21	--

Serious AEs, %	Pt (N =
Treatment related, all pts	
▪Febrile neutropenia, grade 4	2
Treatment emergent, ≥ 2% of pts	
▪Pneumonia, grades 3-5	10
▪AIHA, grade 3	3
▪Pyrexia, grade 2/3	3

*1 unrelated fatal pneumonia.

- No major bleeding events or atrial fibrillation reported
- 8 discontinuations: CLL progression (fatal pneumonia (1); investigator or p decision (2); diarrhea (1), dyspnea (1 gastritis (1), active AIHA requiring treatment (1)

16 relapsed/refractory CLL patients including 5 RS patients were enrolled.

4 out of 5 RS patients had responded to therapy.

3 RS patients who had responded to therapy had decreased or stable sPD-L1 levels

The 4th RS and two CLL had increased sPD-L1 levels an had not demonstrated clinical response.

Experiences in clinical practice seem to confirm in terms of efficacy and safety results of clinical als.

Use of an alternate BCRi following discontinuation of another BCRi is efficacious in > 50%.

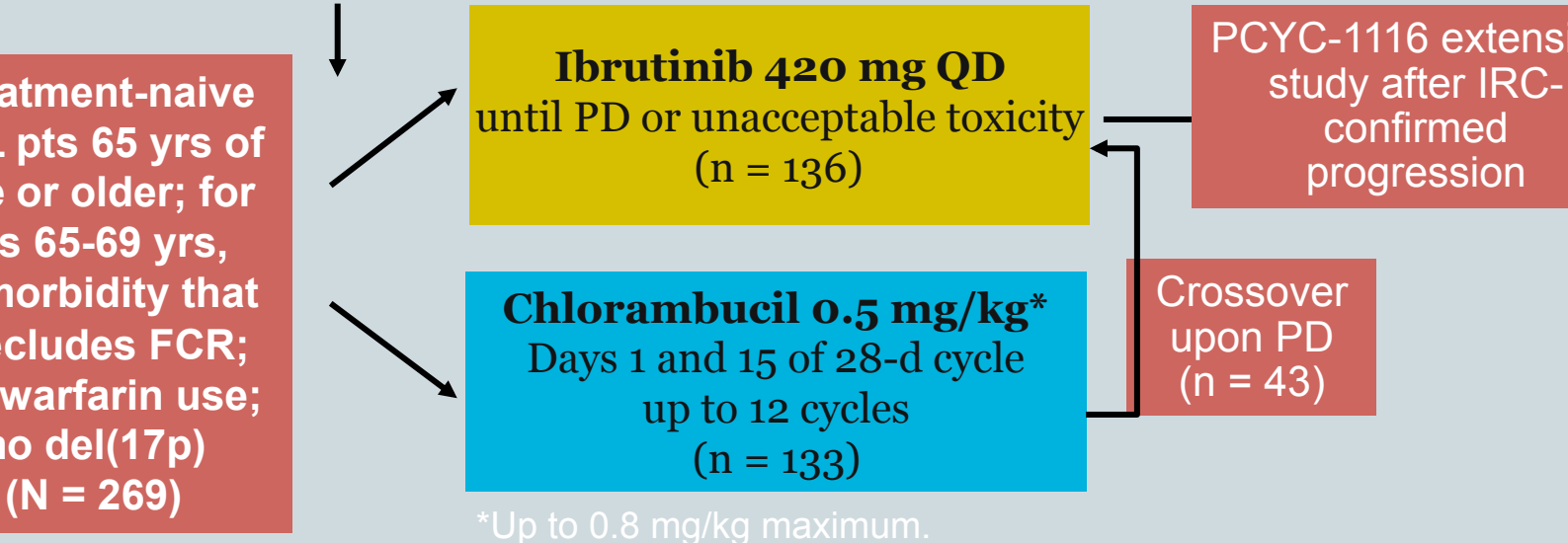
The association of BCRi with CIT should be reserve only to patients included in clinical trial.

	action		
Duvelisib	PI3K-δ, ɣ inhibitor		Duvelisib vs Ofatumuma (phase III) Duvelisib/Obinutuzuma after BTK inhibitor
Acalabrutinib (ACP-196)	BTK inhibitor	Acalabrutinib alone vs Acalabrutinib plus Obinutuzumab vs Obinutuzumab Plus Chlorambucil (phase III)	Acalabrutinib vs Ibrutin (phase III)
Pembrolizumab	PD-1 Inhibitor		Relapsed/refractory CL (phase II)
CAR T cells	Adoptive T-cell therapy		Relapsed/refractory CL (phase I /II)

Ibrutinib vs Chlorambucil in Tx-Naïve Elderly Pts With CLL (RESONATE-2)

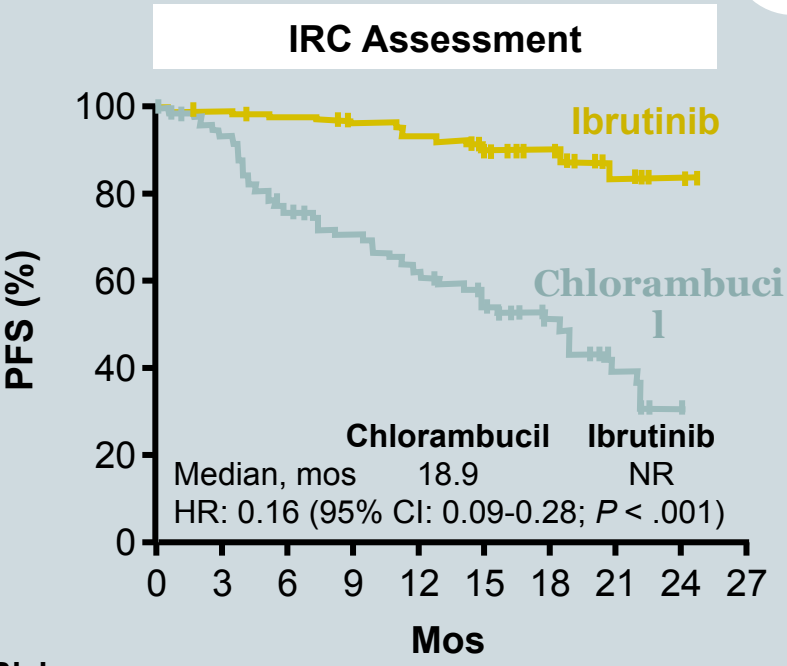
Open-label, randomized phase III trial

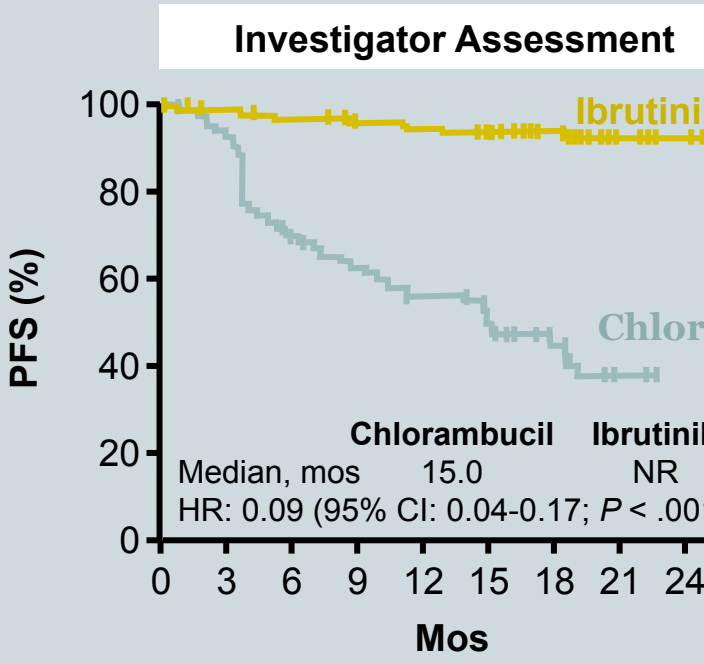
Primary endpoint: IRC-evaluated PFS
Secondary endpoints: OS, ORR, hematologic improvement, safety



*Up to 0.8 mg/kg maximum.

RESONATE 2: PFS (Primary Endpoint)





Risk, n
brutinib 136 133 130 126 122 98 66 21 2 0
mbucil 133 121 95 85 74 49 34 10 0 0

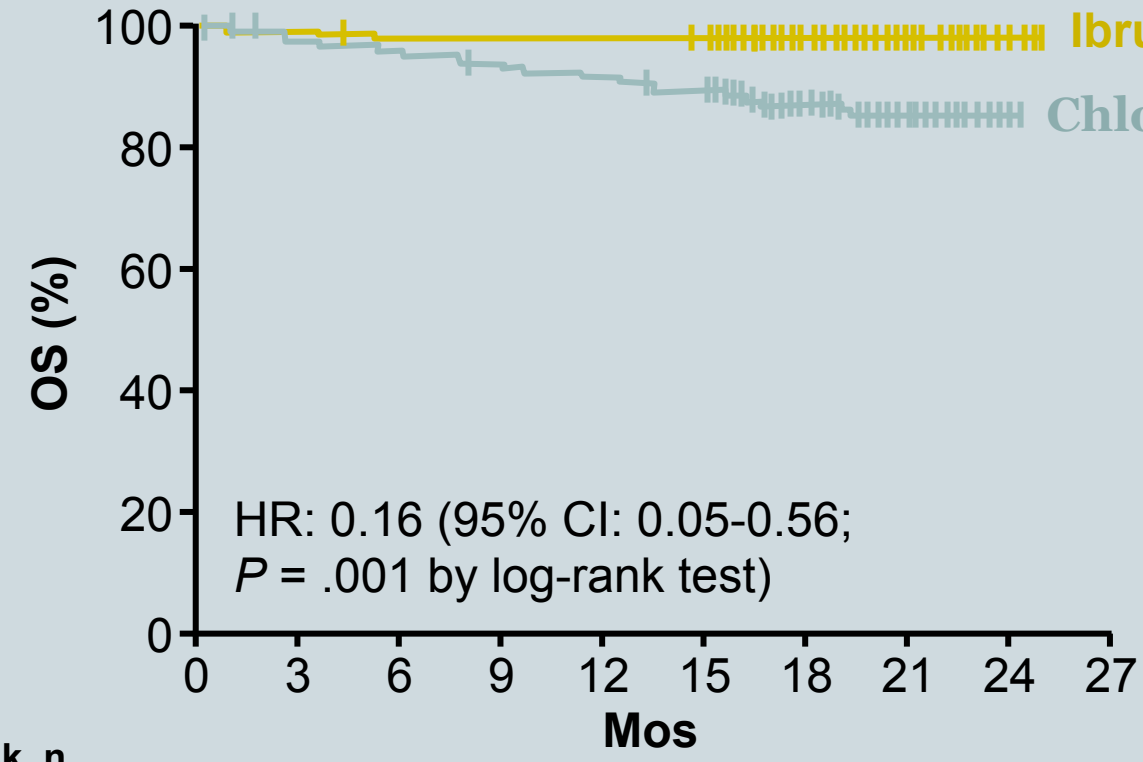
Pts at Risk, n
Ibrutinib 136 133 129 125 123 104 69 22 2
Chlorambucil 133 121 88 88 69 46 31 10 0

PFS results not dependent on age, Rai stage, ECOG PS, or bulky disease

1 Richter's transformation in chlorambucil arm; none on ibrutinib arm

RESONATE-2: OS

84% reduction in risk of death with ibrutinib



Pts at Risk, n										
Ibrutinib	136	134	131	131	131	129	74	32	4	0
Chlorambucil	133	127	125	121	118	113	62	24	1	0

RESONATE-2: Adverse Events

rameter	Ibrutinib (n = 136)	Chlorambucil (n = 133)
dian duration of study treatment, mos nge)	17.4 (0.7-24.7)	7.1 (0.5-11.7)
ected AEs, %		
Hypertension	14	0
Atrial fibrillation	6	1
Major hemorrhage	4	2

Pts with grade 3 HTN (n = 6) managed with anti-HTN drugs, did not require dose reduction of ibrutinib; 4 had history of HTN

Among pts with atrial fibrillation (n = 8), 2 discontinued ibrutinib

- 7 of 8 with history of HTN, CAD, and/or myocardial ischemia

Among pts with major bleeding (n = 6), 3 discontinued ibrutinib

- 3 of 6 on concomitant aspirin or low-molecular-weight heparin

(Study 115): Study Design

Randomized, double-blind, placebo-controlled phase III study

tratified by 17p deletion and/or TP53 mutation, IGHV mutation status, relapsed vs refractory

LL* with measurable isease, no history of LL transformation or rior BTK/PI3Kδ/SYK inhibitor use (N = 416)

Idelalisib† 150 mg BID + **Bendamustine** 70 mg/m² D1,2 Q4W, C1-6 + **Rituximab** 375 mg/m² C1, 500 mg/m² C2-6 (n = 207)

Placebo† BID + **Bendamustine** 70 mg/m² D1,2 Q4W, C1-6 + **Rituximab** 375 mg/m² C1, 500 mg/m² C2-6 (n = 209)

Followed fo with post-st therapy a investigato discretio

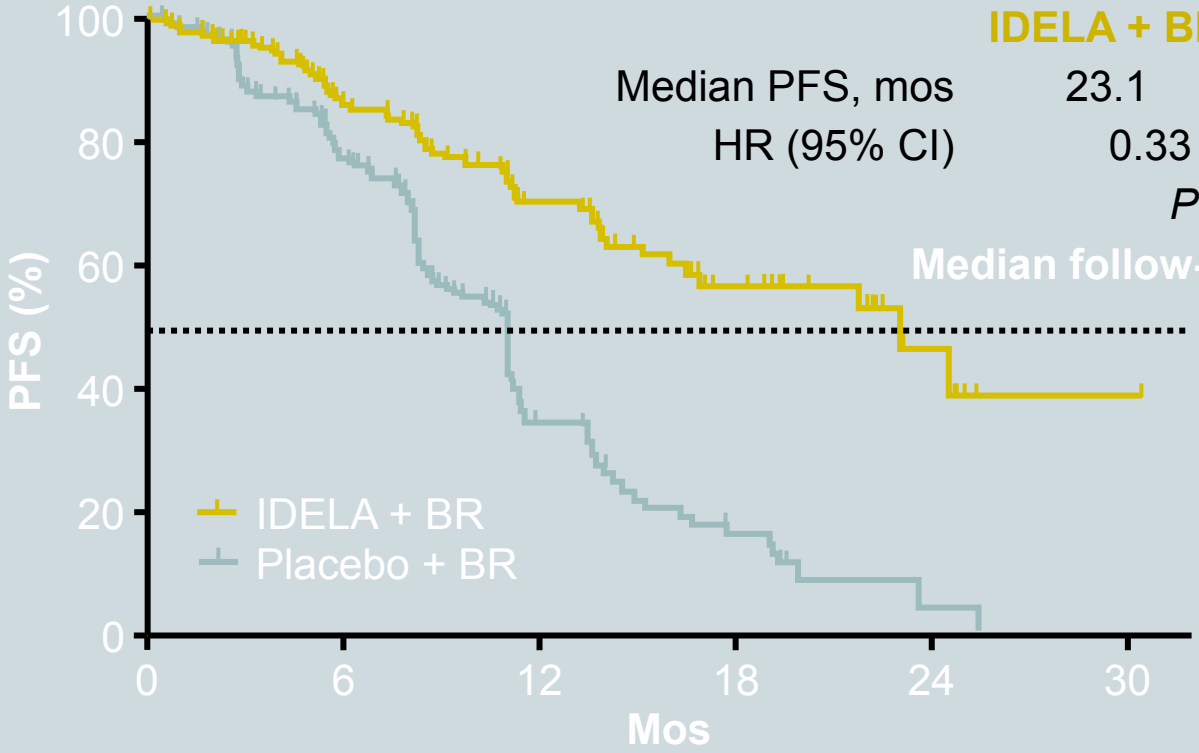
ogression < 36 mos from last therapy, requiring treatment, but no progression within 6 mos of las damustine.

utinib and placebo until progression or intolerance

Primary endpoint: PFS

Secondary endpoints: ORR, nodal response, CR, OS

Study 115: PFS



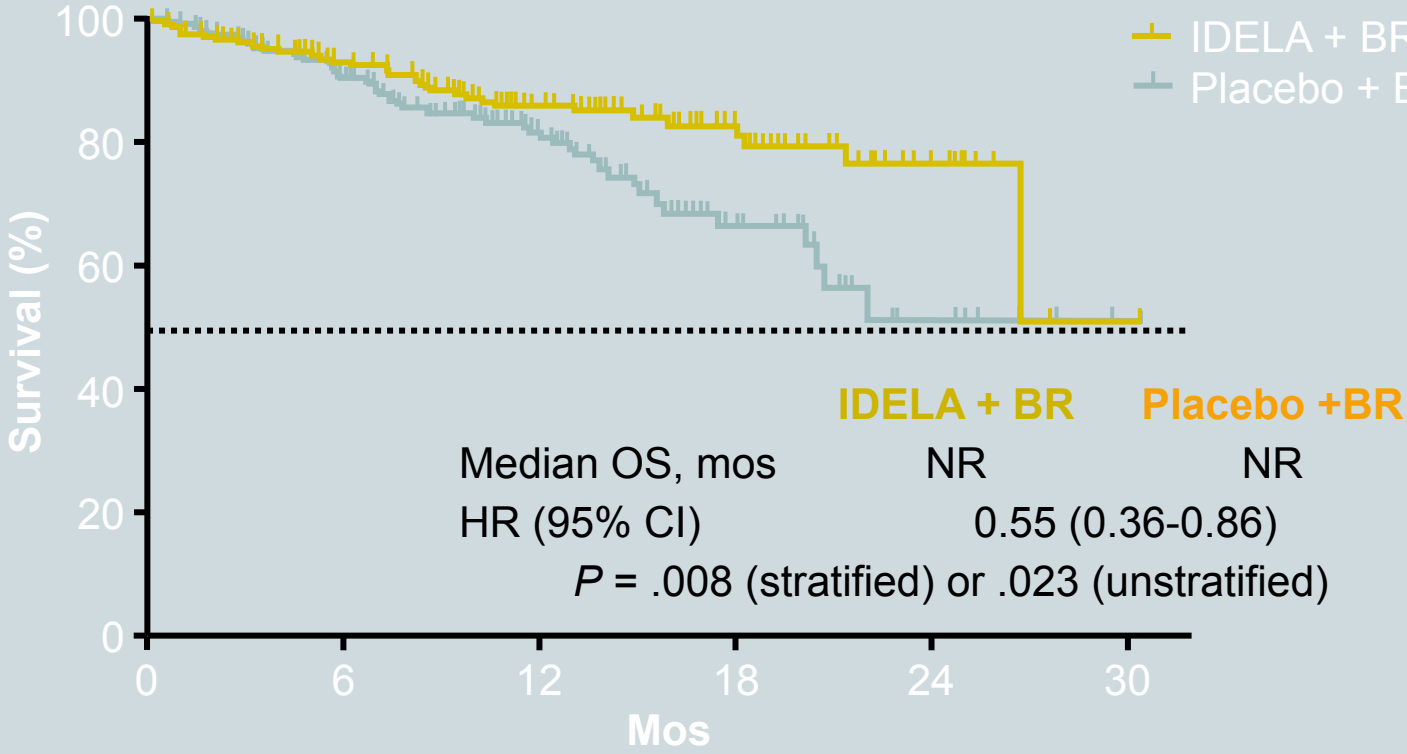
	IDELA + BR	Placebo +
Median PFS, mos	23.1	11.1
HR (95% CI)	0.33 (0.24-0.45)	
	P < .0001	

Median follow-up time: 12

at risk, n (events)

LA + BR	207 (0)	154 (25)	74 (51)	27 (61)	6 (63)	1 (64)
ebo + BR	209 (0)	145 (46)	36 (111)	11 (126)	1 (131)	0 (132)

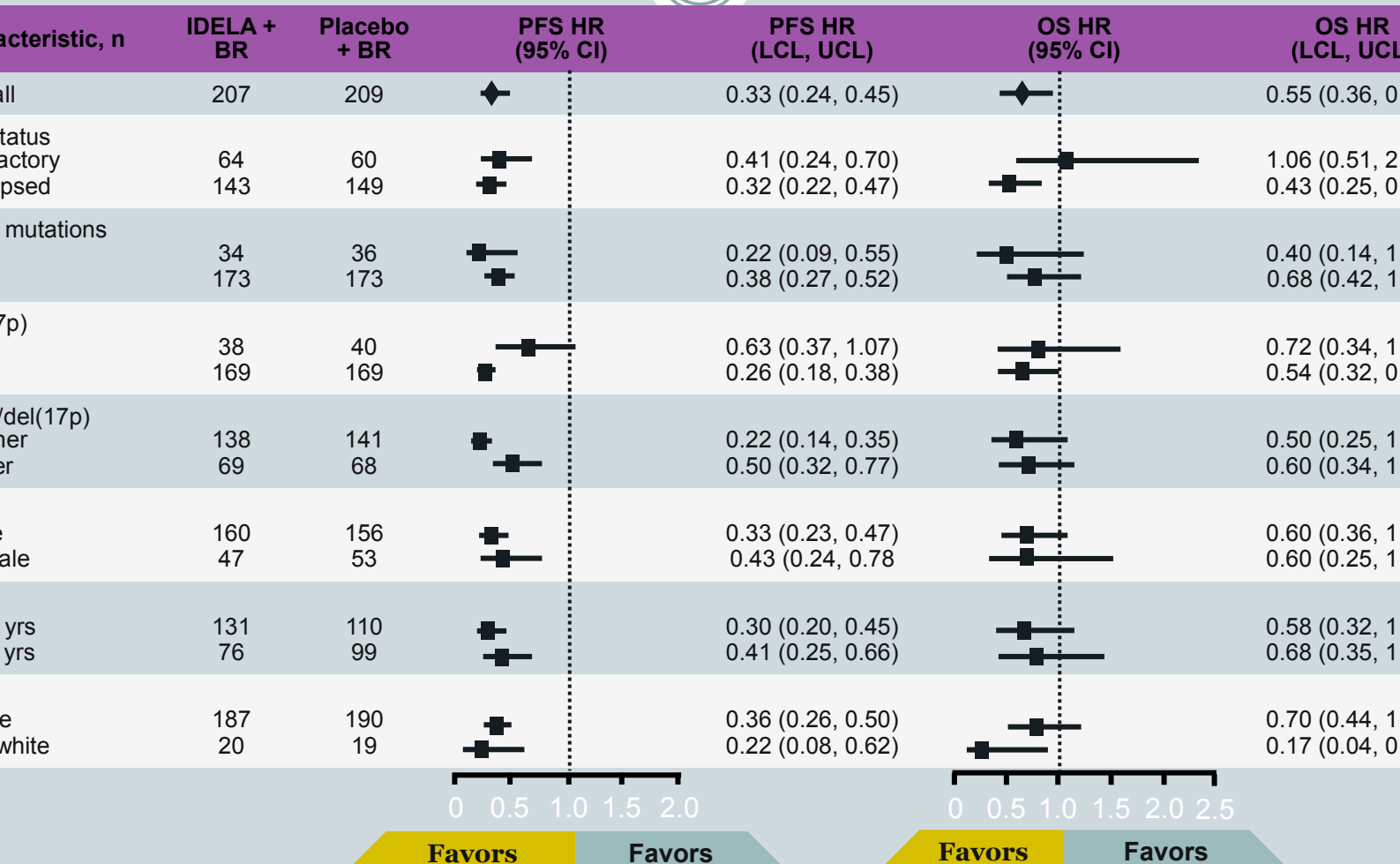
Study 115: OS



at risk, n (events)

LA + BR	207 (0)	181 (14)	104 (27)	52 (30)	13 (33)	1 (34)
ebo + BR	209 (0)	180 (20)	93 (35)	33 (47)	8 (51)	0 (51)

Study 115: PFS and OS by Subgroup



Study 115: Safety

aracteristic, %	IDELA + BR (n = 207)		Placebo + BR (n = 20	
	Any Grade	Grade ≥ 3	Any Grade	Grade
y AE	100	93	97	76
eutropenia	63	60	54	46
yrexia	42	7	30	3
arrhea	35	7	22	2
brile neutropenia	22	20	7	6
neumonia	17	11	11	6
ash	16	3	12	0
LT elevation	15	11	1	< 1
s leading to dose reduction	11		6	
s leading to discontinuation	26		13	
aths	10		7	

CLL Summary

- Ibrutinib is highly active in previously untreated elderly pts with CLL/SLL
- The combination of idelalisib with bendamustine/rituximab is active in R/R CLL
  - Associated with increased toxicity compared with BR
- Switching to ibrutinib or idelalisib after failure of the alternative kinase inhibitor appears active and may be a reasonable approach

CLL Summary

- Venetoclax is active with deep responses in R/R CLL with del(17p)
  - Tumor lysis syndrome may occur and pts should be carefull monitored
- Acalabrutinib, a second-generation BTK inhibitor, i highly active in R/R CLL
  - Phase III study comparing ibrutinib vs acalabrutinib for previously treated CLL under way