Ibrutinib

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Phase I/II Ibrutinib in Relapsed CLL
Disease Characteristics

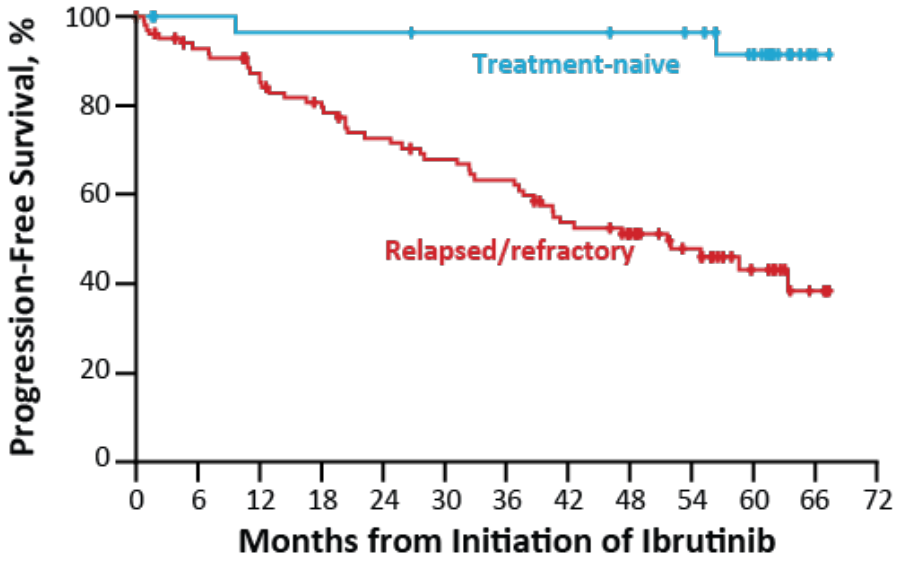
Characteristic	TN 420 n = 27	R/R 420 n = 67
FISH cytogenetic abnormalities Del17p Del11q	 7% 0%	 34% 33%
Any cytopenia	67%	54%
Median ANC, 10^9/L (range) ≤ 1.5 x 10^9/L	4 (0-19) 4%	2.5 (0-14) 27%
Median hemoglobin, g/L (range) ≤ 110 g/L	122 (77-157) 37%	118 (66-176) 33%
Median platelets, 10^9/L (range) ≤ 100 x 10^9/L	113 (32-217) 41%	107 (29-310) 39%
Median age (range)	71 (65-84)	67 (37-82)

Prior Therapies

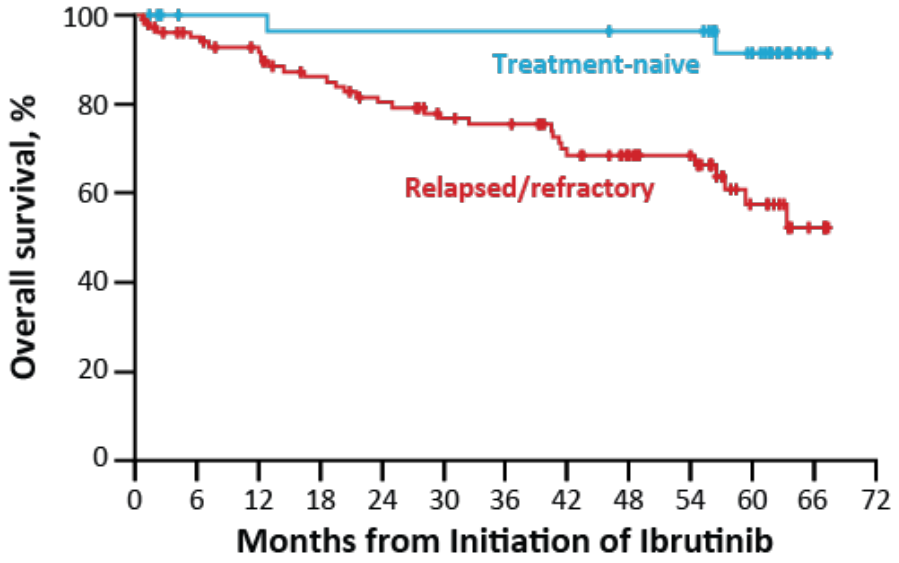
Characteristic	R/R 420 n = 67
Median number of prior therapies (range) 1-2 3 ≥4	4 (1-12) 31% 13% 55%
Type of prior systemic therapy Chemotherapy Nucleoside analog Alkylator (including bendamustine) Any anti-CD20–based therapy Anti-CD20–based chemoimmunotherapy Anti-CD52–based therapy (alemtuzumab) Idelalisib	 100% 94% 90% 99% 97% 24% 6%

Survival Outcomes: Overall Population

Progression-Free Survival



Overall Survival



	Median PFS	5-year PFS
TN (n=31)	NR	92%
R/R (n=101)	52 mo	43%

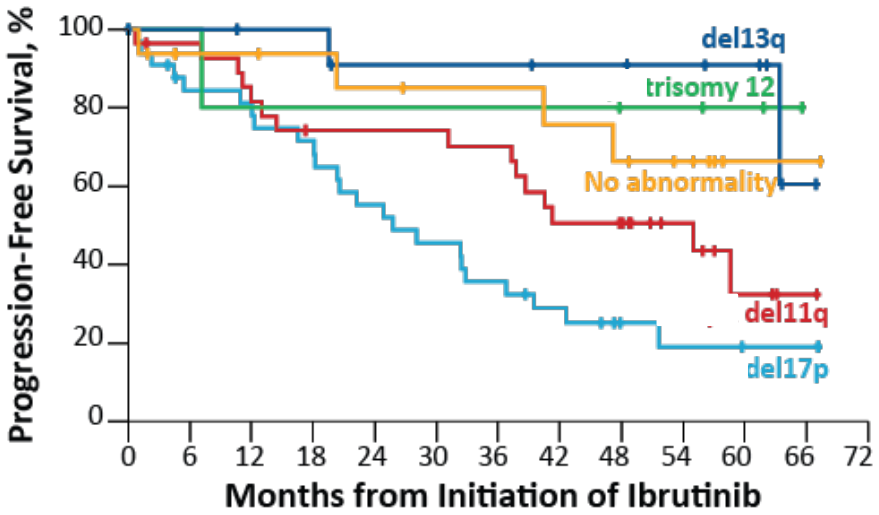
	Median OS	5-year OS
TN (n=31)	NR	92%
R/R (n=101)	NR	57%

NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

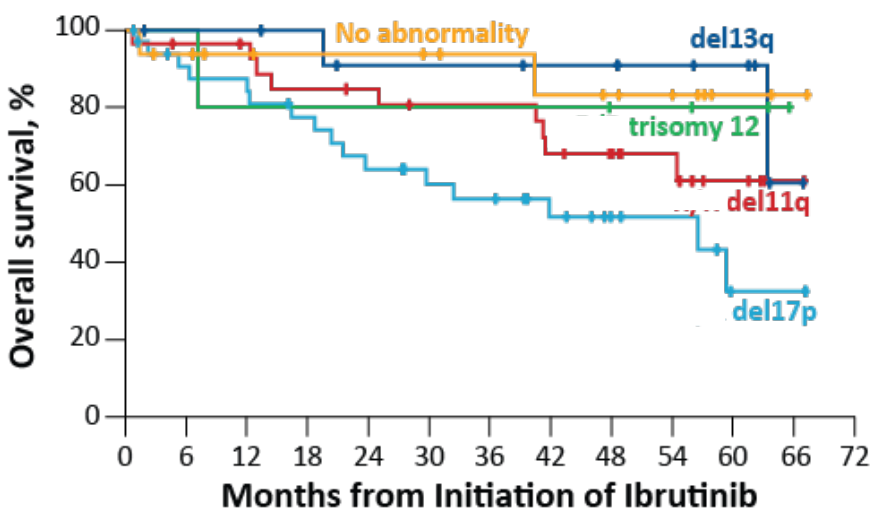
Survival Outcomes by Chromosomal Abnormalities Detected by FISH in R/R Patients*

Progression-Free Survival



	Median PFS	5-year PFS
Del17p (n=34)	26 mo	19%
Del11q (n=28)	55 mo	33%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	66%

Overall Survival



	Median OS	5-year OS
Del17p (n=34)	57 mo	32%
Del11q (n=28)	NR	61%
Trisomy 12 (n=5)	NR	80%
Del13q (n=13)	NR	91%
No abnormality** (n=16)	NR	83%

*Only 2 patients in the TN group showed PD or death. Subgroup analyses, therefore, focused on the R/R population.
**No del17p, del11q, del13q, or trisomy 12; in hierarchical order for del17p, and then del11q
NR, not reached.

ASH 2016, 1102-03 5-year Update; O'Brien et al.

CLL10 Study: FCR VS BR in Front-line CLL

Design

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 ml/min)

Randomization

FCR

Fludarabine 25 mg/m² i.v., days 1-3
Cyclophosphamide 250 mg/m², days 1-3,
Rituximab 375 mg/ m² i.v. day 0, cycle 1
Rituximab 500 mg/m² i.v. day 1, cycle 2-6

BR

Bendamustine 90mg/m² day 1-2
Rituximab 375 mg/m² day 0, cycle 1
Rituximab 500 mg/m² day 1, cycle 2-6

Non-Inferiority of BR in comparison to FCR for PFS:

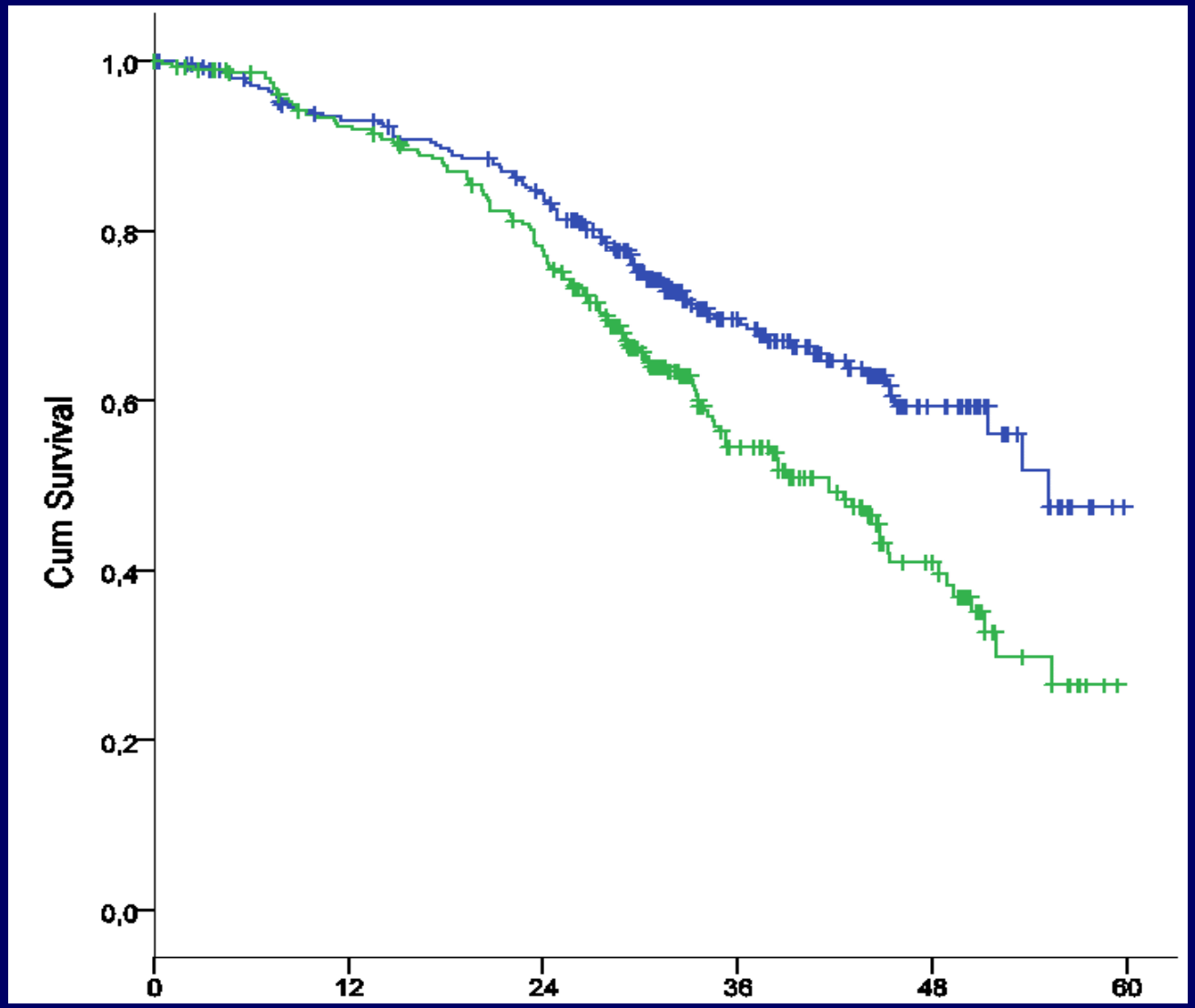
HR (λ BR/FCR) less than 1.388

Eichhorst et al. ASH 2013, Abstract 526

CLL10 Study: FCR VS BR in Front-Line CLL

DEUTSCHE STUDIENGRUPPE

ITT Progression-free Survival = Primary Endpoint



Median PFS

FCR 55.2 months

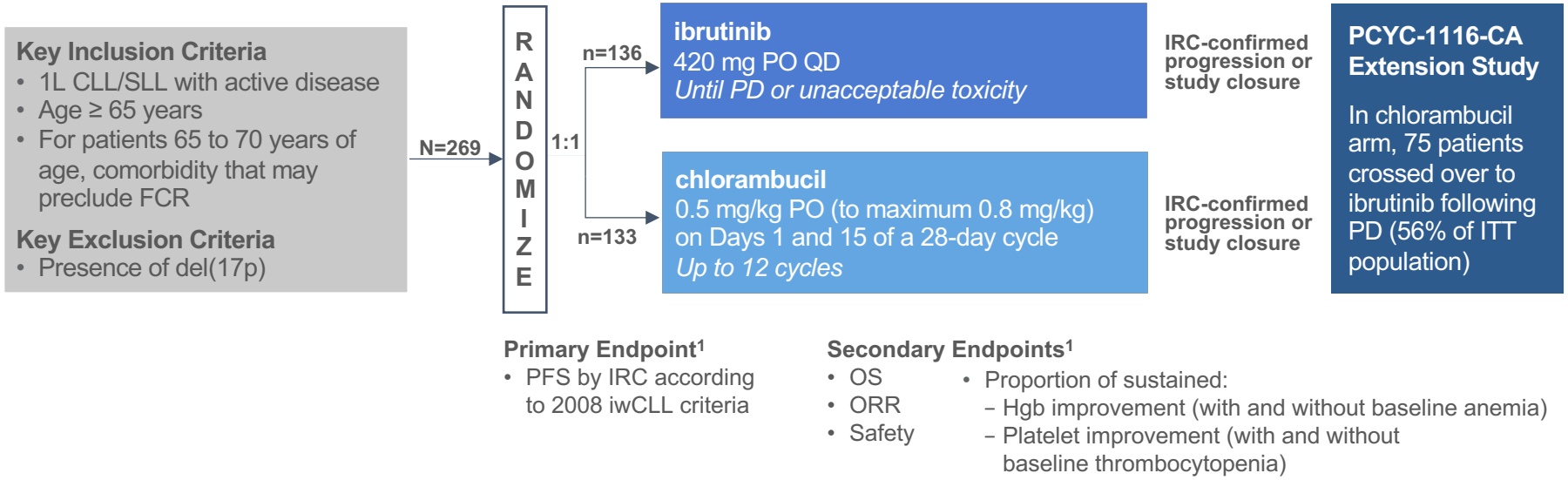
BR 41.7 months

P < 0.001

HR = 1.626 = > 1.388

RESONATE-2: Phase 3 Trial in 1L CLL/SLL

Phase 3 randomized, multicenter, open-label trial of ibrutinib vs chlorambucil in patients ≥65 years of age with 1L CLL/SLL (NCT01722487)



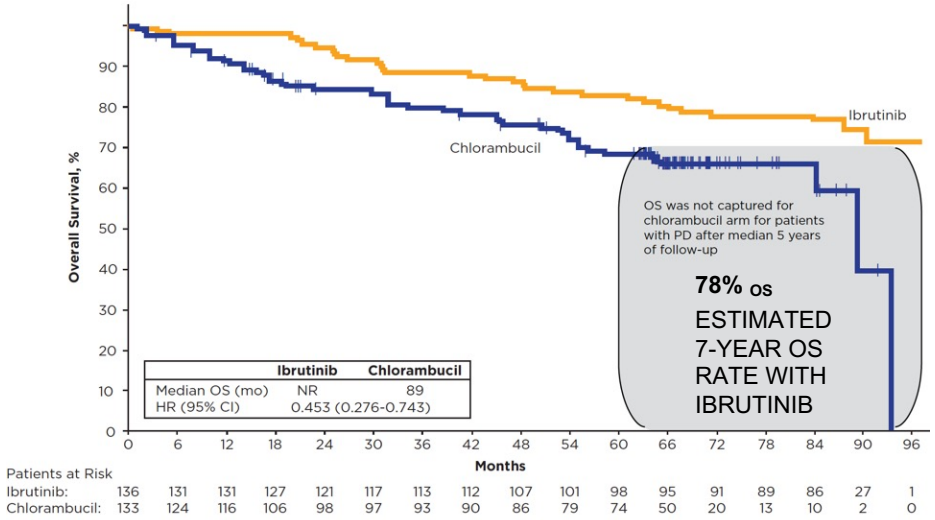
References:

1. Burger JA, Barr PM, Robak T, et al. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. *Leukemia*. 2020;34(3):787-798.

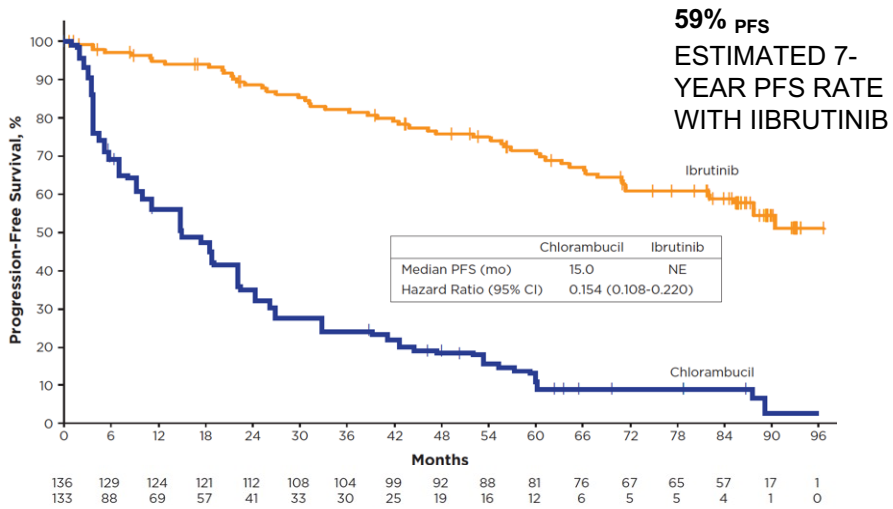
2. Clinicaltrials.gov. Open-label phase 3 btk inhibitor ibrutinib vs chlorambucil patients 65 years or older with treatment-naive cll or sll. https://clinicaltrials.gov/ct2/show/NCT01722487.
Accessed May 2, 2022

Up to 8 Years of Follow-up in RESONATE-2: OS and PFS

Overall Survival



Progression-free Survival

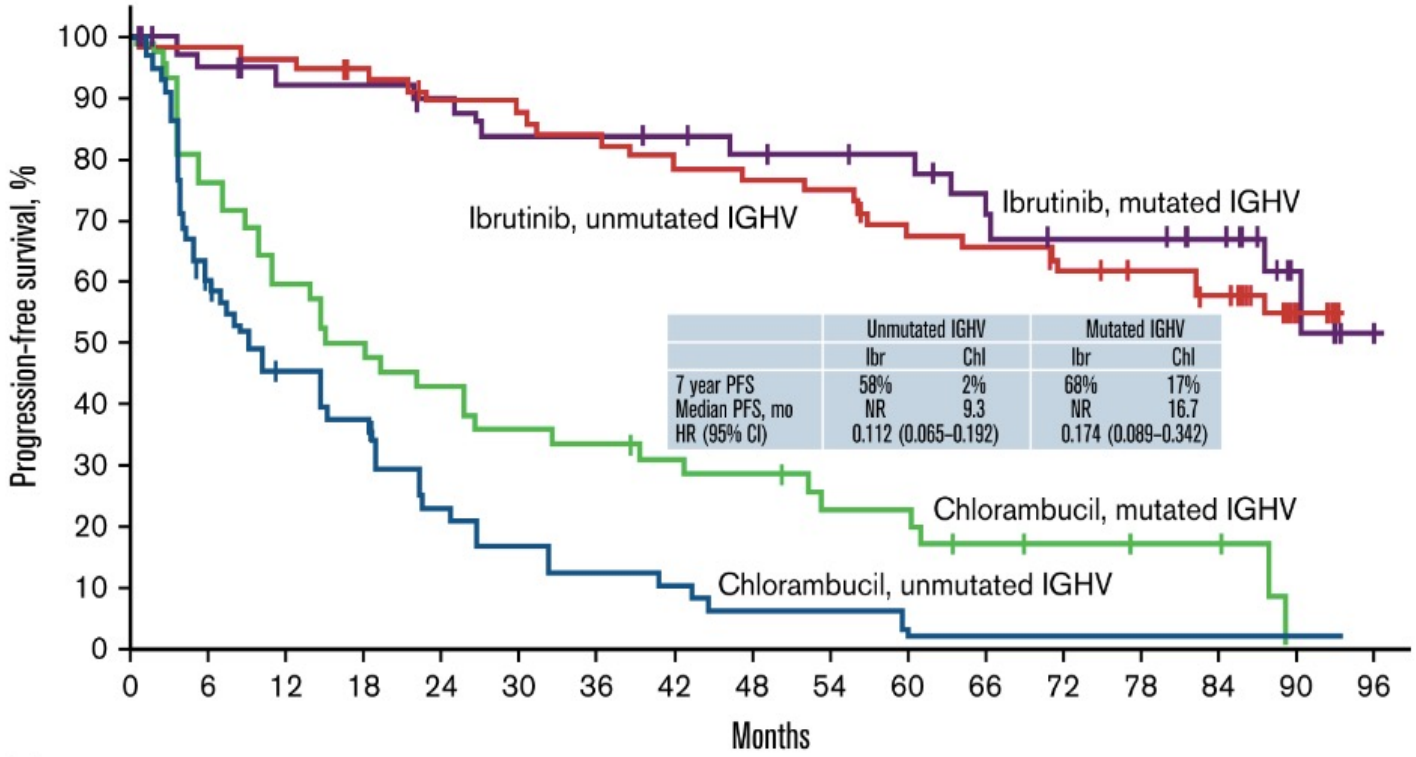


- **78%** taking Ibrutinib were estimated to be alive at 7 years
- **59%** taking Ibrutinib were estimated to be progression-free and alive at 7 years vs 9% of patients taking chlorambucil

Reference:

1. Barr PM, Owen C, Robak T, et al. Up to 8 years follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *Blood Adv*. 2022 Apr 4:bloodadvances.2021006434.doi:10.1182/bloodadvances.2021006434

PFS by Mutation Status



	Unmutated IGHV		Mutated IGHV	
	Ibr	Chl	Ibr	Chl
7 year PFS	58%	2%	68%	17%
Median PFS, mo	NR	9.3	NR	16.7
HR (95% CI)	0.112 (0.065–0.192)		0.174 (0.089–0.342)	

Patients at risk																	
Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

Barr PM, Owen C, Robak T et al Blood Adv 2022 April

Bruton's Tyrosine Kinase and Phospholipase C-Gamma 2 Mutational Profiles in Pooled Analysis of Patients With Chronic Lymphocytic Leukemia Treated With Ibrutinib

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International Workshop on Chronic Lymphocytic Leukemia; October 6–9, 2023; Boston, MA, USA

Resistance to BTKis

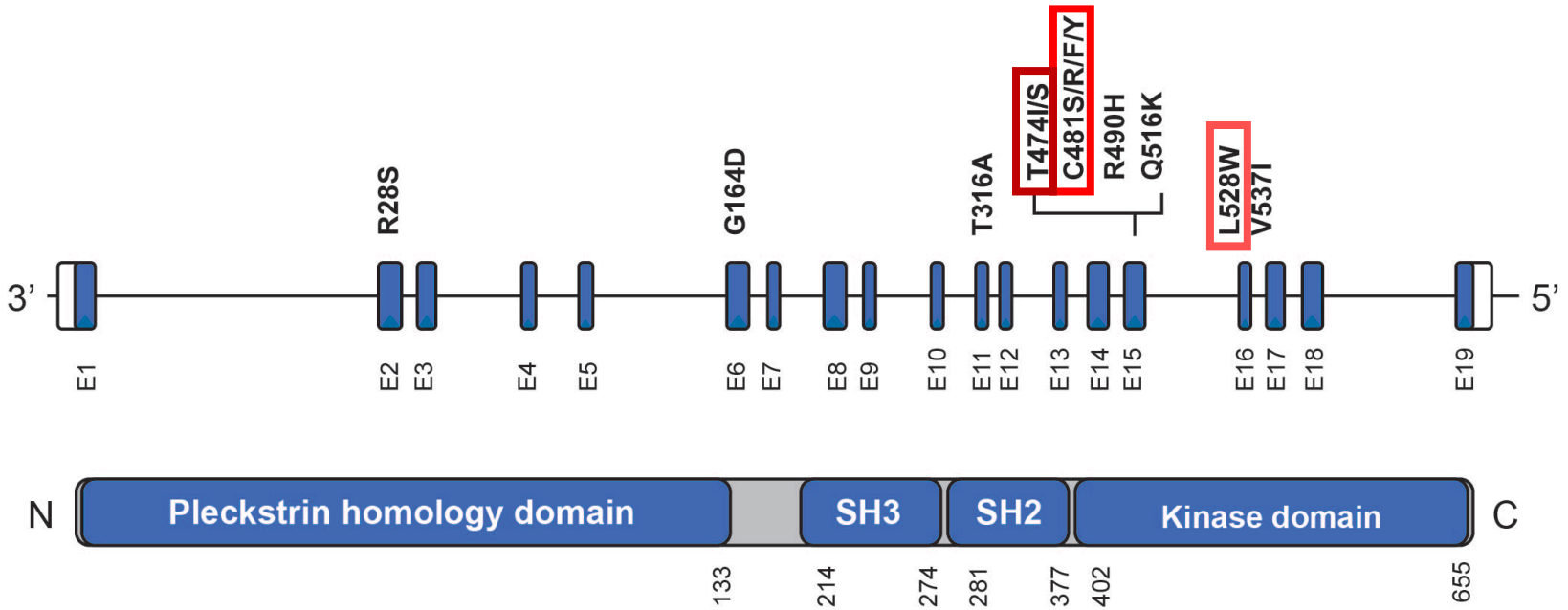


Figure adapted from Sedlarikova L et al. *Front Oncol.* 2020;10:894

- Acquired resistance to BTKis is associated with mutations in *BTK* or *PLCG2*
  - *BTK* C481 mutation: alters binding site of covalent BTKis
  - Non-C481 *BTK* mutations:
    - creates steric hinderance to binding of non-covalent and some covalent BTKis[3–9]
    - preclinical data suggest differential activity of BTK targeting strategies

1L, first-line; *BTK*, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; OS, overall survival; *PLCG2,* phospholipase C-γ2; SLL, small lymphocytic lymphoma.

1. Burger JA et al. *Leukemia.* 2020;34:787–798. 2. Shanafelt T et al. *N Engl J Med.* 2019;381:432–443. 3. Maddocks KJ et al. *JAMA Oncol.* 2015;1:80–87. 4. Handunnetti SM et al. *Blood.* 2019;134(suppl_1):170. 5. Song Y et al. *Br J Haematol.* 2022;198:62–72. 6. Blombery P et al. *Blood Adv.* 2022;6(20):5589–5592. 7. Wang E et al. *N Engl J Med.* 2022;386:735–743. 8. Woyach JA et al. Presented at: International Conference on Malignant Lymphoma; June 13−17, 2023; Lugano, Switzerland. Poster 163. 9. Brown JR et al. Presented at: European Hematology Association Congress; Frankfurt, Germany; June 14–15, 2023. Poster S146.

Assessment of *BTK* and *PLCG2* mutations in 419 patients treated with ibrutinib

All (N=419)				
TN (n=247)			R/R (n=172)	
RESONATE-2[a] N=111	iLLUMINATE N=113	NHLBI Phase 2 N=23	RESONATE N=107	RESONATE-17 N=65

- Time points of sample collection:
  - For patients without PD: last available sample
  - For patients with PD: last available sample before PD and the first available sample at or after PD
- NGS (Ion Torrent) of *BTK/PLCG2* coding regions was performed on DNA extracted from CD19+ enriched PBMCs
  - VAF cutoffs:
    - 0.5% for hotspots (eg, *BTK* C481x and T474I, *PLCG2* R665W, D993H, L845F, S707F)
    - 2.0% for non-hotspots (eg, *BTK* L528W, etc)

[a]PCYC-1115 & PCYC-1116.

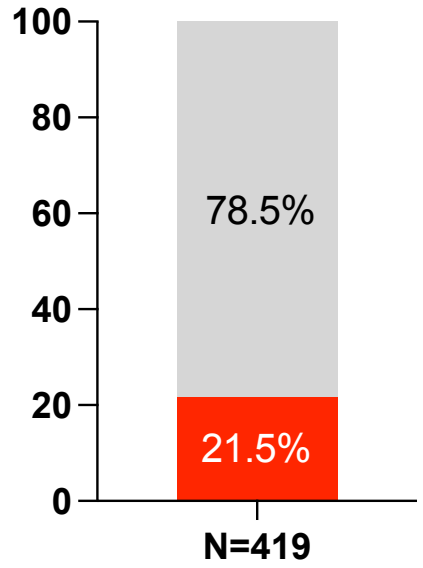
NGS, next-generation sequencing; PD, progressive disease; PMBC, peripheral blood mononuclear cell; R/R, relapsed/refractory; TN, treatment-naive; VAF, variant allele frequency.

Study population

Characteristic	TN n=247	R/R n=172	Total N=419
Median age (range), years	71 (39−89)	65 (44−86)	69 (39−89)
uIGHV, n (% of evaluated)	128 (54)	63 (79)	191 (60)
del(17p) or *TP53* mutation, n (%)	52 (21)	111 (65)	163 (39)
Median follow up (range), months	37 (0.2−77)	48 (2−72)	44 (0.2−77)
PD, n (%)	22 (9)	69 (40)	91 (22)
Death, n (%)	26 (11)	15 (9)	41 (10)
Median PFS, months (95% CI)	NR (NE, NE)	56 (44, 67)	NR (NE, NE)

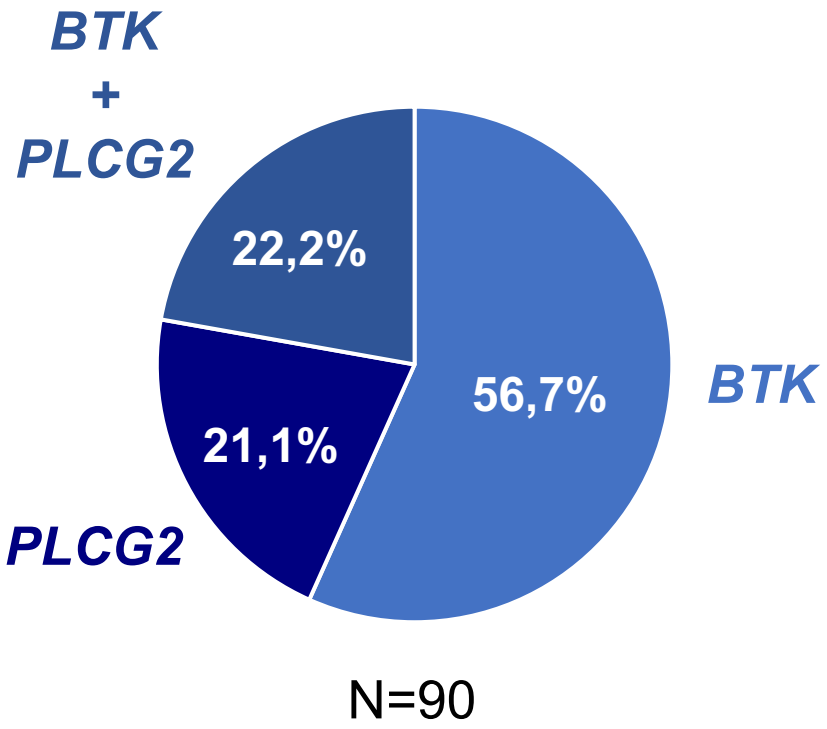
NE, not estimable; NR, not reached; PFS, progression-free survival; uIGHV, unmutated immunoglobulin heavy-chain variable.

Overview of *BTK* and *PLCG2* mutation status



Undetectable *BTK/PLCG2* mut

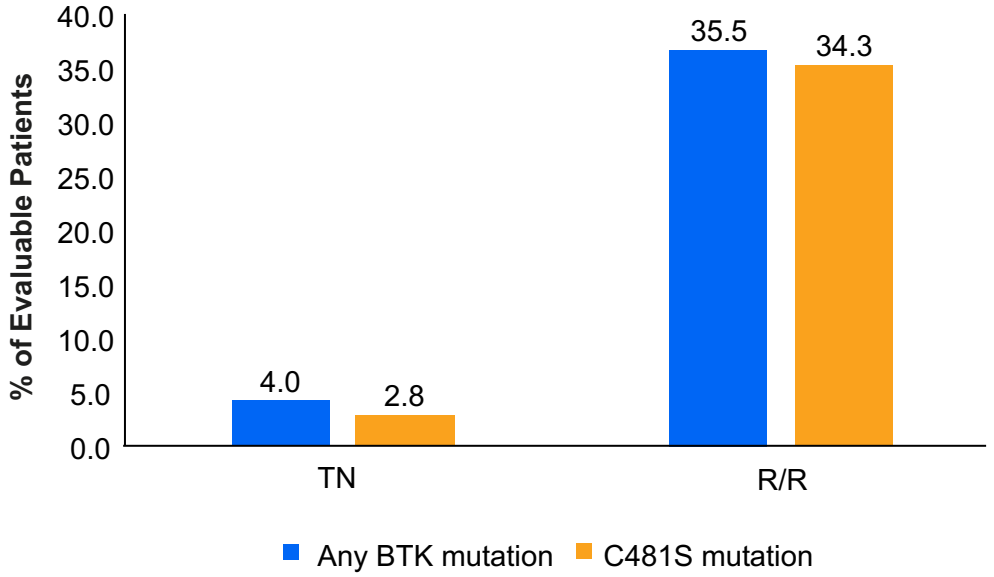
Detectable *BTK/PLCG2* mut

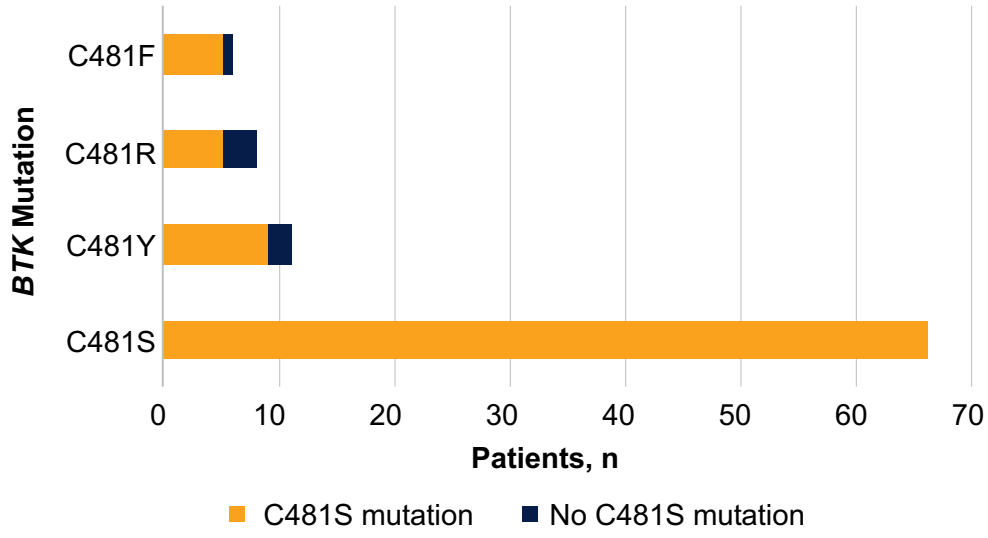


N=90

BTK mutations occurred more frequently in the R/R setting, with C481S being the most common mutation observed

- 17% of evaluable patients had a *BTK* mutation (n=71 of 419, including 10 TN and 61 R/R)
- *BTK* C481S was the most observed mutation (16% [n=66 of 419], including 7 TN and 59 R/R)
  - Of these 66 patients:
    - 58% had del(17p) or *TP53* mutation at baseline[a]
    - 48% had PD, mostly from the R/R CLL group (2 TN; 30 R/R)



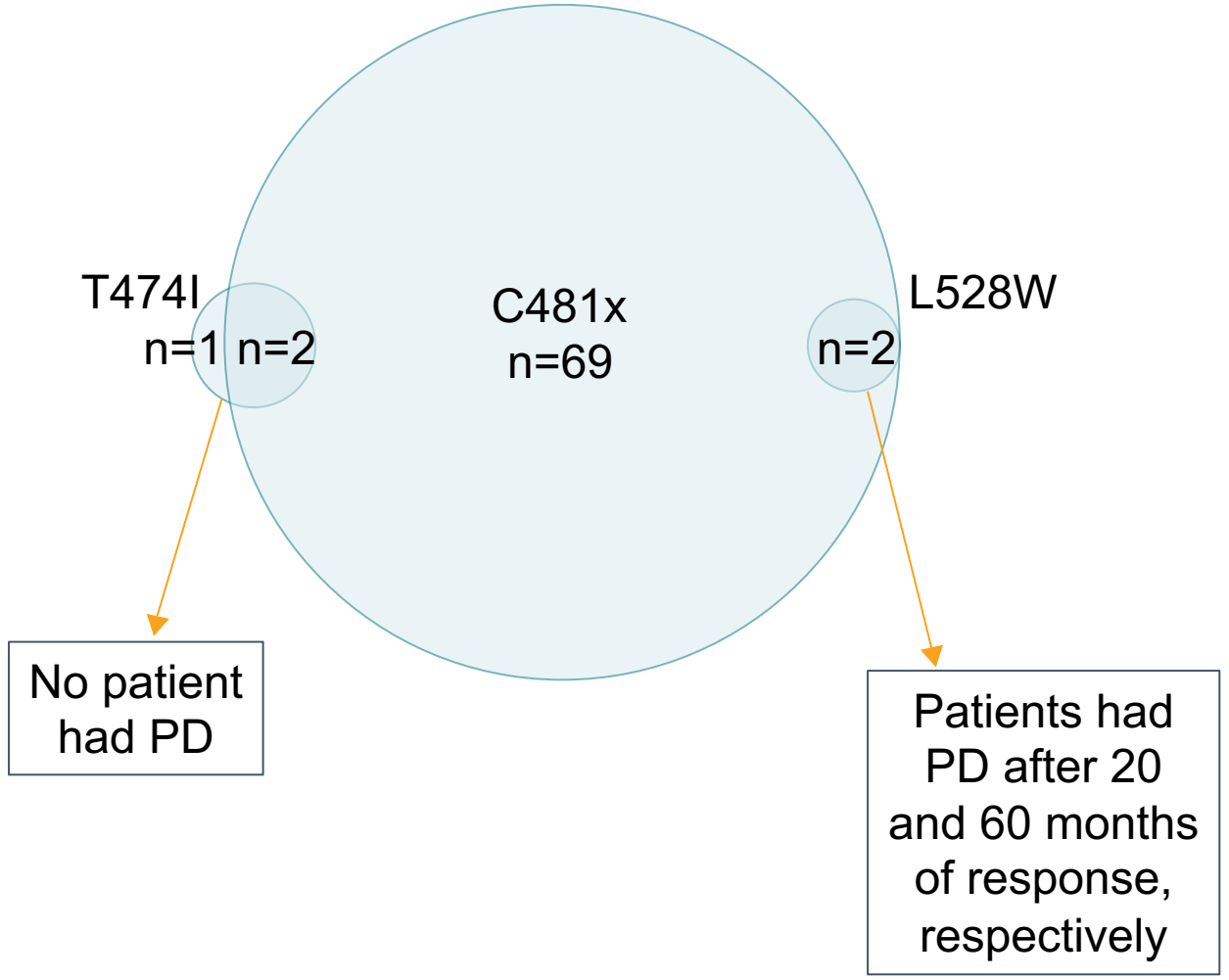


[a]Of 90 patients with either a *BTK* or *PLCG2* mutation, 50 patients had confirmed del(17p) and/or *TP53* at baseline.

T474I and L528W mutations occurred in <1% of patients and co-occurred with C481 mutations

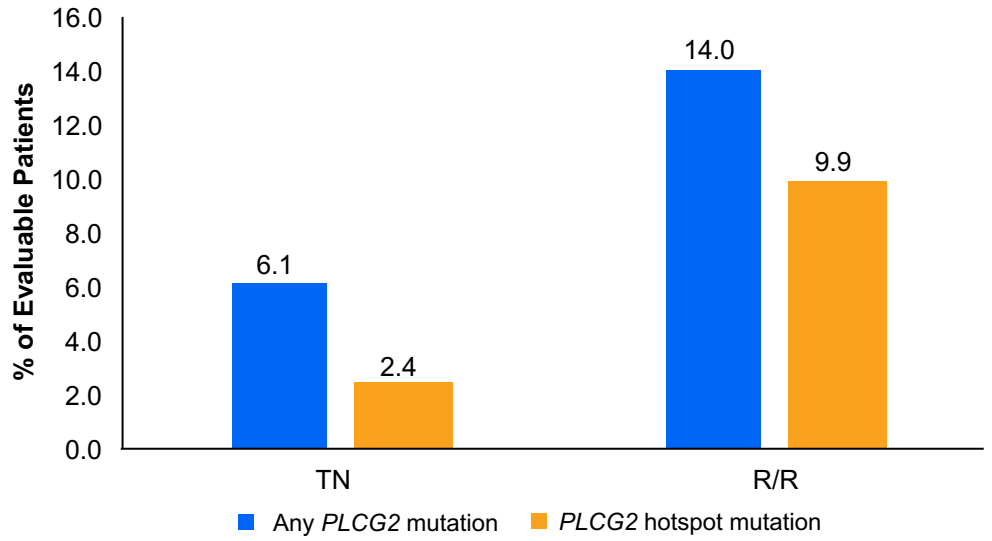
- **0.7%** with *BTK* T474I mutation (n=3 of 419, including 2 TN and 1 R/R)
  - 2 of 3 patients also had C481 mutations
  - 0 of 3 patients had PD

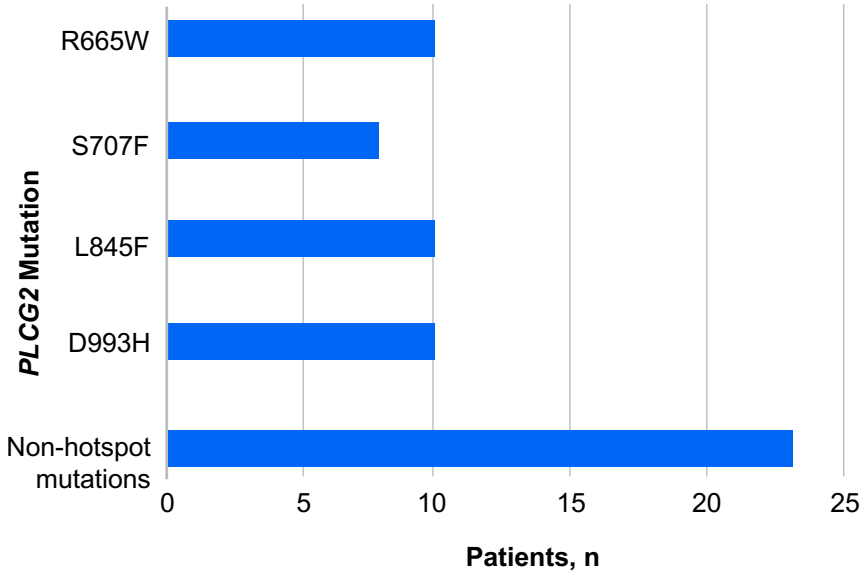
- **0.5%** with *BTK* L528W mutation (n=2 of 419, including 2 TN and 0 R/R)
  - 2 of 2 patients also had C481 mutations
  - 2 of 2 patients had PD
    - 1 patient had a *BTK* L528W mutation detectable prior to PD (VAF 4%) that was no longer detectable at PD



Mutational hotspots of *PLCG2* are dispersed across the gene

- 9% of evaluable patients had a *PLCG2* mutation (n=39 of 419, including 15 TN and 24 R/R)
- Hotspot *PLCG2* mutations were observed in 5% patients (n=23 of 419, including 6 TN and 17 R/R)
  - Co-occurrence of *PLCG2* hotspot mutations was common (43%)
  - Of these 23 patients:
    - 65% had del(17p) or *TP53* mutation at baseline[a]
    - 39% had PD, mostly from the R/R CLL group (1 TN; 8 R/R)
- 5% of evaluable patients had co-occurring *BTK* and *PLCG2* mutations (n=20 of 419, including 3 TN and 17 R/R)
  - Of these 20 patients:
    - 65% had del(17p) or *TP53* mutation at baseline[a]
    - 50% had PD, mostly from the R/R CLL group (1 TN; 9 R/R)





[a]Of 90 patients with either a *BTK* or *PLCG2* mutation, 50 patients had confirmed del(17p) and/or *TP53* at baseline.

Differential preclinical BTKi activity on *BTK* mutations: Clinical implications

- BTKi activity was evaluated in vitro on TMD8 cells expressing WT and mutant *BTK* (CRISPR-Cas9)
- Cells were treated with BTKi for 3 days prior to testing of cell viability (CellTiter-Glo; control: no treatment)

- Acalabrutinib and zanubrutinib have the least-potent cell-killing activity against *BTK* C481S
- Ibrutinib has the most-potent cell-killing activity against *BTK* T474I
- Zanubrutinib and pirtobrutinib have the least-potent cell-killing activity against *BTK* L528W
- These data may have implications on the duration of continued treatment benefit after mutation emergence

3-day EC_{50} (nM)	*BTK*			
	WT	**C481S**	**T474I**	**L528W**
Ibrutinib	0.6	414.0	1.9	181.4
Acalabrutinib	3.9	2973.8	43.3	3.5
Zanubrutinib	0.7	2322.0	11.7	3000.0
Pirtobrutinib	8.2	12.6	2727.5	3000.0

Most-potent cell-killing activity

Least-potent cell-killing activity

EC_{50}, half maximal effective concentration; WT, wild-type.

Conclusions

BTK C481S and hotspot *PLCG2* mutations were the most common mutations observed, most frequently in the R/R setting. *BTK* mutations affecting the L528 and T474 loci are rare occurrences with ibrutinib (<1%)

<50% of patients with *BTK* C481S or hotspot *PLCG2* mutations had progressive disease, suggesting that patients with these mutations may continue to benefit from ibrutinib treatment

It is critical to continue to generate data on the emerging mutational profiles of covalent BTKis because this may have implications for effective treatment sequencing with noncovalent BTKis in the future

Initiating First-Line Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL) Improves Overall Survival Outcomes to Rates Approximating an Age-Matched Population ≥ 65 Years

Paolo Ghia, MD, PhD[1]; Carolyn Owen, MD[2]; Jacqueline C. Barrientos, MD, MS[3]; Paul M. Barr, MD[4]; Anthony R. Mato, MD, MSCE[5]; Chunxue Shi, MS[6]; Anita Szoke, MD[7]; Christopher Abbazio, PharmD[7]; Gabriel S. Krigsfeld, PhD[7]; Jan A. Burger, MD, PhD[8]

[1]Division of Experimental Oncology, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [2]Tom Baker Cancer Centre, University of Calgary and Alberta Health Services, Calgary, Canada; [3]Columbia University Division of Hematology/Oncology at Mount Sinai Medical Center, Miami, FL, USA; 4Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [5]CLL program, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Biostatistics, Everest Clinical Research, Owings Mills, MD, USA; [7]AbbVie Inc, North Chicago, IL, USA (Pharmacyclics LLC, an AbbVie Company, South San Francisco, CA, USA); [8]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

OBJECTIVE

- The objectives of this study are 1) To compare pooled OS of previously untreated patients with CLL who received ibrutinib to that of the available age-matched general population and 2) To compare the pooled characteristics and OS results with ibrutinib vs CT/CIT across three phase 3 studies.

KEY TAKEAWAYS

- OS benefit has been proven across age and fitness with 1L ibrutinib.
- Dose modification for 1L Ibr-treated pts with CLL was effective in resolving AEs for the majority of patients, allowing them to remain on treatment.
- This study demonstrates that ibrutinib prolonged survival of previously untreated patients with CLL to the extent that it may be comparable to an age-matched general population, whereas CT/CIT did not.

INTRODUCTION

- CLL OS rates have improved over the last 20 years, starting with the use of CT/CIT, then with the introduction of novel agents such as ibrutinib, a once-daily BTKi.[1–5]
  - 1L ibrutinib has shown superiority to standard CT/CIT across a range of previously untreated patient populations, with demonstrated significant OS benefit in multiple randomized phase 3 studies.
  - Recent 8-year follow-up data from RESONATE-2 demonstrated that 59% of previously untreated unfit patients remain progression-free.[5]
- The ideal goal of any therapeutic regimen is to cure patients of their disease, but the first step is to provide enough effective therapeutic options to allow patients to live with their disease.[5-7]
  - Continuous treatment with ibrutinib is possible without toxicity limiting its ongoing use in most patients.
  - Dose management for AEs allows patients to continue to benefit from ibrutinib.
- Given the size of the program and the length of follow-up, there is a unique opportunity to assess whether the initiation of 1L ibrutinib could essentially remove the survival hazard associated with CLL vs the general population.

METHODS

- Data for previously untreated CLL/SLL patients were pooled across 3 studies: ECOG-ACRIN E1912 (NCT02048813),[2] RESONATE-2 (NCT01722487),[8] and iLLUMINATE (NCT02264574).[9]

- Pooled data compared OS outcomes in pts treated with ibrutinib and ibrutinib + aCD20 (ibrutinib + rituximab; ibrutinib + obinutuzumab, or single-agent ibrutinib) to those treated with CT/CIT (fludarabine + cyclophosphamide + rituximab; chlorambucil + obinutuzumab, or single-agent chlorambucil).

- AEs leading to dose modifications in a pooled population were evaluated.

- Study design, patient characteristics, and clinical efficacy and safety outcomes for the individual studies were previously described.

- OS of pooled ibrutinib and CT/CIT-treated patients were compared with OS of the age-matched general population. Survival estimates for the general population age-matched to the ibrutinib and CT/CIT cohorts were obtained from the survival probability from life tables published by the CDC for total US population in 2019 (https://www.cdc.gov/nchs/products/life_tables.htm).

- OS was estimated using Kaplan-Meier methodology.

RESULTS

Table 1. Baseline Characteristics of Pooled Ibrutinib and CT/CIT-Treated Patients

- A total of 603 and 424 patients with previously untreated CLL/SLL received ibrutinib and CT/CIT treatment, respectively, across the 3 pooled studies (**Table 1**).

Characteristic	Pooled Ibr or Ibr + aCD20 treatment[a] N=603	Pooled CT/CIT treatment[a] N=424
Median age at randomization (range), years	63 (31–89)	67 (28–90)
Median age at initial diagnosis (range), years	60 (30–87)	63 (28–90)
Median time from initial diagnosis to randomization (range), months	24 (0–342)	28 (0–480)
Sex, n (%)		
Male	391 (65)	280 (66)
Female	212 (35)	144 (34)
Age group at randomization, n (%), years		
<65	333 (55)	179 (42)
65-75	191 (32)	156 (37)
≥75	79 (13)	89 (21)
Ibr treatment, n (%)		
Ibr + rituximab	354 (59)	NA
Ibr	136 (23)	NA
Ibr + obinutuzumab	113 (19)	NA
CT/CIT treatment, n (%)		
Fludarabine + cyclophosphamide + rituximab	NA	175 (41)
Chlorambucil	NA	133 (31)
Chlorambucil + obinutuzumab	NA	116 (27)
Baseline ECOG performance, n (%)		
0	344 (57)	213 (50)
1	233 (39)	189 (45)
2	26 (4)	22 (5)
CIRS score category, n (%)		
≤6	481 (80)	320 (76)
>6	93 (15)	85 (20)
Rai stage, n (%)		
0–II	319 (53)	229 (54)
III/IV	284 (47)	195 (46)
Del11q, n (%)		
No	474 (79)	320 (76)
Yes	121 (20)	92 (22)
IGHV, n (%)		
Mutated	150 (25)	135 (32)
Unmutated	334 (55)	188 (44)
Del(17p) or *TP53* mutation, n (%)		
No	482 (80)	308 (73)
Yes	56 (9)	31 (7)

[a]*Percentage totals over/under 100% due to rounding.*

RESULTS (CONTINUED)

Table 2. Study Treatment Disposition and Treatment Exposure

	Pooled Ibr or Ibr + aCD20 treatment N=603	Pooled CT/CIT treatment N=424
Median treatment duration (range), months	39 (0-97)	5 (0-12)
Overall median follow-up (range), months	41 (0-97)	40 (0-93)
ECOG-ACRIN E1912	38 (0-52)	33 (0-51)
RESONATE-2	86 (0-97)	64 (0-93)
iLLUMINATE	43 (0-52)	41 (1-52)
Study treatment disposition, n (%)		
Ongoing	334 (55)	NA
Discontinued	266 (44)	NA
Discontinued early	NA	144 (34)
Reason for treatment discontinuation, n/N (%)[a]		
AEs	95/266 (36)	77/144 (54)
Progressive disease	36/266 (14)	9/144 (6)
Withdrawal by patient	23/266 (9)	15/144 (10)
Death	19/266 (7)	1/144 (1)
Investigator and physician decision	10/266 (4)	38/144 (26)

[a]*Denominator is patients who discontinued the treatment*

RESULTS (CONTINUED)

Figure 1. Improved OS for Pooled 1L Ibrutinib vs CT/CIT-Treated Patients

- OS estimates (3- and 5- year) were significantly improved with long term treatment with ibrutinib compared with CT/CIT treatment (**Figure 1**).

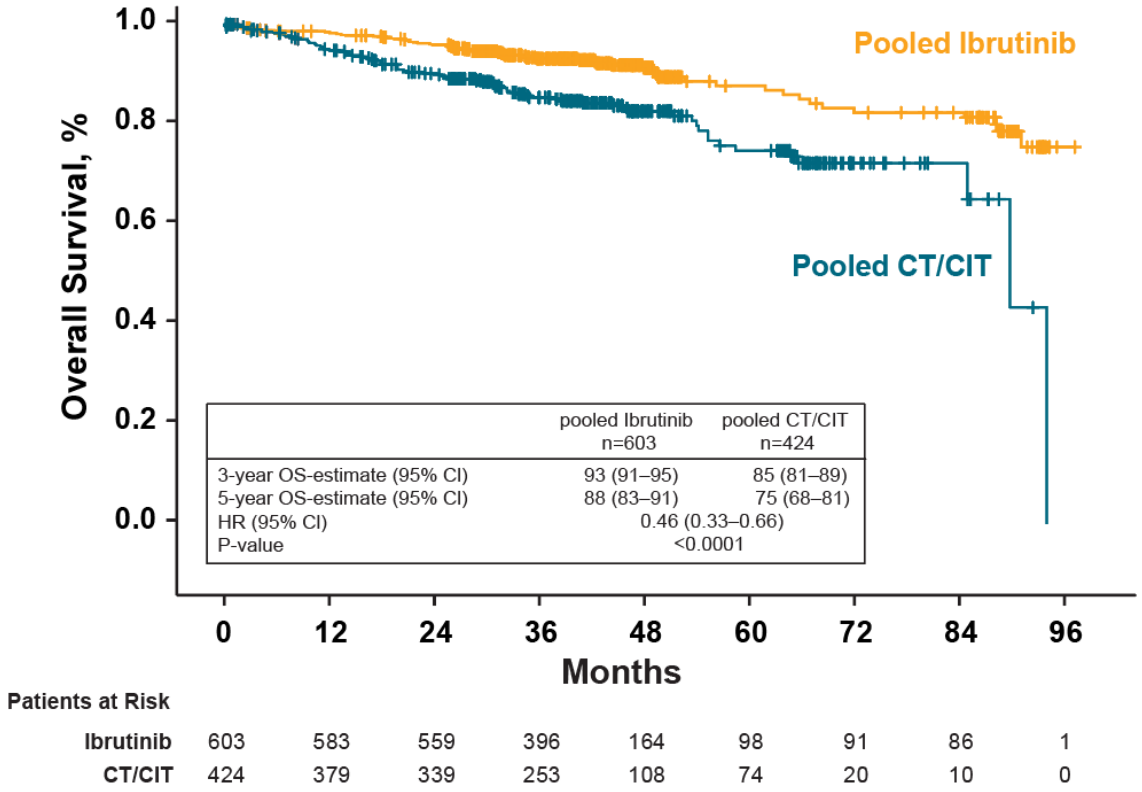
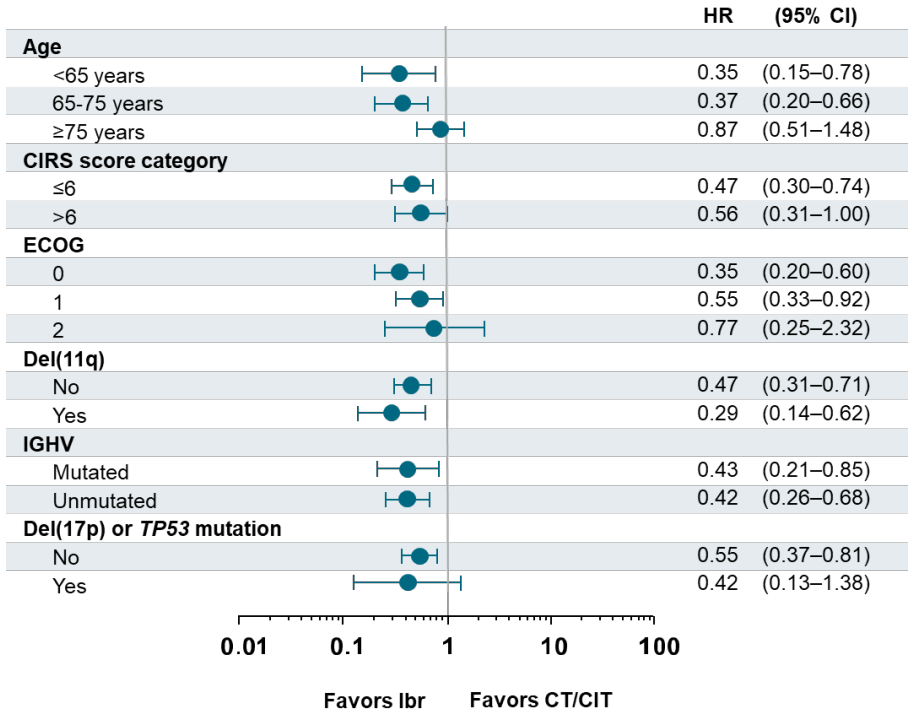


Figure 2. Improved OS With Ibrutinib vs CT/CIT Treatment Across Prespecified Patient Subgroups

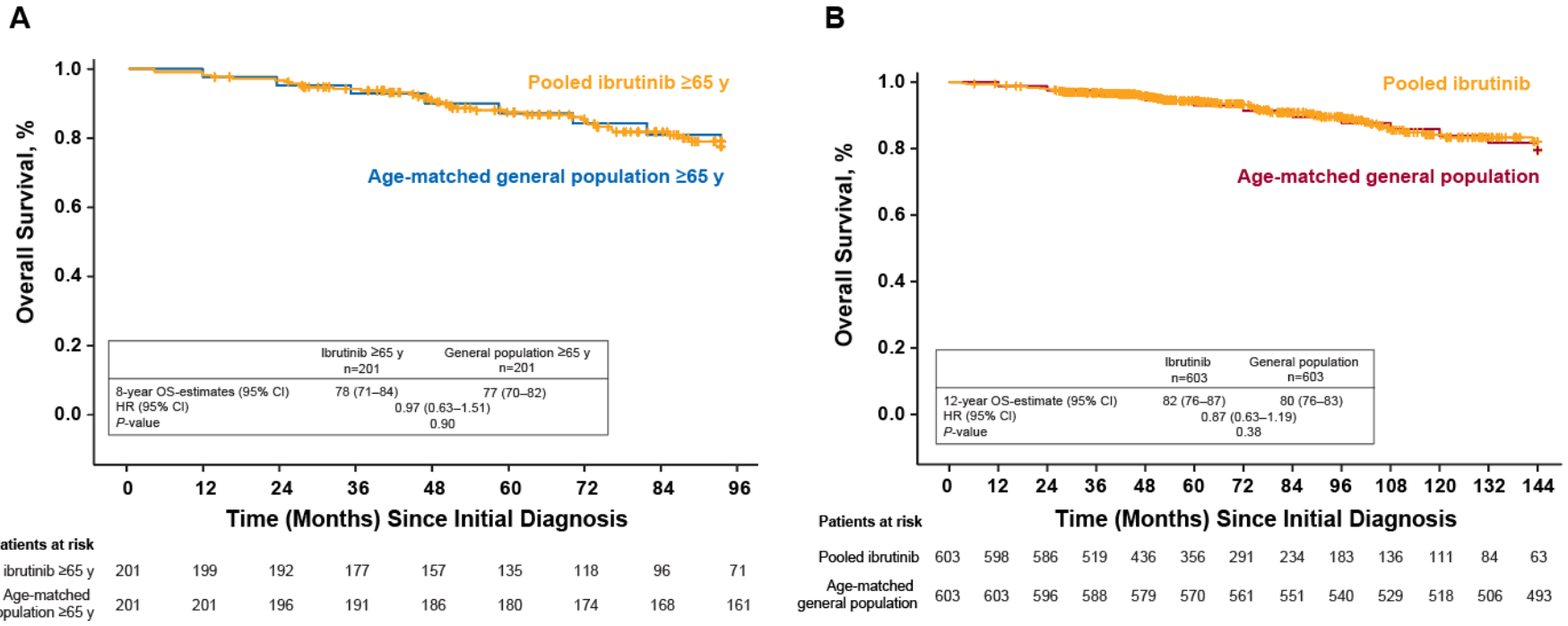
- OS outcomes with ibrutinib were improved compared to CT/CIT treatment across all prespecified patient subgroups, including those with high-risk features such as mutated del(11q), unmutated IGHV, and del(17p) or *TP53* mutation (**Figure 2**).
  - Notably, patients with mutated IGHV treated with ibrutinib has significantly improved OS vs patients treated with CT/CIT (**Figure 2**).



[a]*Hazard ratios (ibrutinib vs CT/CIT) were obtained using cox proportional hazards regression model. The hazard ratios < 1 indicate lower fatal risk occurring in ibrutinib-treated patients compared CT/CIT-treated patients.*

Figure 3. Similar OS Estimate for Pooled Ibrutinib-Treated Patients ≥65 years[a] (A) and Overall Pooled Ibrutinib-Treated Patients[b] (B) vs Age-Matched General Population Population

- 201 ibrutinib-treated patients ≥65 years were included in the analysis; median time on treatment was 44 months, with a median follow-up from initial diagnosis of 6.8 years.
  - OS estimate (8-year) was comparable for the ibrutinib-treated patients ≥65 years vs age-matched general population (**Figure 3A**).
- We also conducted the analysis in the total pooled population of 603 ibrutinib-treated patients; median time on treatment was 39 months, with a median follow-up from initial diagnosis of 5.9 years.
  - OS estimate (12-year) was also comparable for the overall ibrutinib-treated vs age-matched general population (**Figure 3B**).



[a]*Data after 96 months is not represented in the KM curve;* [b]*Data after 144 months is not represented in the KM curve*

RESULTS (CONTINUED)

Table 3. Any AEs Leading to Dose Reductions in Pooled Ibrutinib-Treated Patients

AEs leading to dose reduction	Pooled Ibr-treated pts N=248
Pts with an AE leading to dose reduction, n (%)	48 (19)
Outcome of first AE leading to dose reduction, n/N (%)[a]	
Initial AE resolved	45/48 (94)
No recurrence or recurred at lower grade	31/48 (65)
Recurred at same or higher grade	17/48 (35)
AEs of interest by SOC, n (%)[b]	
Hematologic	13 (5)
Dermatologic	7 (3)
Infection	7 (3)
Cardiac	5 (2)
Gastrointestinal	4 (2)
Musculoskeletal	3 (1)
Grade of AE leading to dose reduction, n (%)[b]	
Grade 1	12 (5)
Grade 2	19 (8)
Grade 3	23 (9)
Grade 4	5 (2)

[a]Denominator is patients with any AEs leading to dose reductions; [b]The same patient may be counted in more than one category due to multiple events.

- Remaining on active treatment with ibrutinib may be a contributing factor to maximizing overall survival benefit. Active dose management for the prevention of AE recurrence or worsening (through dose reductions and dose holds) may allow patients to remain on ibrutinib, thereby contributing to an overall survival benefit.
- Dose reductions and dose holds were assessed in a pooled safety population of 248 patients from the RESONATE-2 and iLLUMINATE studies; ECOG-ACRIN E1912 patients were excluded due to limitations in details of AE data collection.
- Ibrutinib dose reductions were used for AE management in 48/248 patients (19%) (**Table 3**).
  - The median duration of treatment with ibrutinib at a reduced dose was 31 months (range, 0-84+).
  - Following dose reduction, 45/48 patients (94%) had resolution of the initial AE.
  - AEs did not recur or recurred at a lower grade for 31/48 pts (65%).
  - The frequency of AEs leading to dose reductions was highest in the first 0–2 years and lower in subsequent years (**Supplemental Figure 2A**).
- The frequency of ibrutinib dose holds of ≥7 days used for AE management generally decreased over time (**Supplemental Table 1 and Supplemental Figure 2B**).

RESULTS (CONTINUED)

Table 4. AEs with Recommended Dose Reductions in Pooled Ibrutinib-Treated Patients per Ibrutinib USPI[a]

AEs with recommended dose reductions per USPI[a]	Pooled Ibr-treated pts N=248
Pts with an AE leading to dose reduction, n (%)	21 (9)
Dose reduced to, n (%)[b]	
420 mg to 280 mg	16 (7)
420 mg to 140 mg	1 (0.4)
280 mg to 140 mg	4 (2)
Outcome of first AE leading to dose reduction, n/N (%)[c,d,e]	
Initial AE resolved	20/21 (95)
No recurrence or recurred at lower grade	16/21 (76)
Recurred at same or higher grade	5/21 (24)

- For AEs with recommended dose reductions per USPI[a] (revised version, August 2022), AEs did not recur or recurred at a lower grade in 16/21 patients (76%) (**Table 4**).

[a]AEs for which dose reductions are recommended in the USPI (grade 2 cardiac failure, grade 3 cardiac arrythmia, grade 3-4 non-hematological AEs (excluding cardiac failure and cardiac arrythmia), grade 3-4 neutropenia with infection or fever, and grade 4 hematological AEs)[10]; [b]One patient had dose reduction to 280 mg which occurred for 1 week before re-escalation to 420 mg; [c]Denominator is patients with AEs for which dose reductions are recommended in the ibrutinib USPI; [d]Two patients that had two different AESIs that led to dose reduction, for one subject neither recurred, for the other, one did not recur, and the other (rash maculo-papular) recurred at a lower grade; [e]Five patients had AEs that recurred at the same grade (grade 3 atrial fibrillation [n=1], grade 3 diarrhea [n=1], grade 3 headache [n=1], grade 4neutropenia [n=1], and grade 3 pleural effusion [n=1] that all resolved without further dose reduction).

CONCLUSIONS

- This pooled analysis suggests treatment with 1L ibrutinib improves OS vs traditional CT/CIT regardless of age and fitness and may eliminate the need for CT/CIT in some patients.

- Active management of AEs through dose reductions resulted in AE resolution (>90%) and prevention of AE recurrence or worsening (65%) in the majority of patients, allowing patients to remain on ibrutinib treatment, potentially maximizing OS benefit.

- This study is the first demonstration to our knowledge that patients who initiate ibrutinib have similar survival estimates as age-matched patients in the general population.