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MEETING SUMMARY
ASCO 2019, Chicago, USA

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HIGHLIGHTS ON
CHRONIC LYMPHOCYTIC LEUKEMIA

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EFFECT OF FIXED-DURATION VENETOCLAX PLUS OBINUTUZUMAB ON PFS, AND MRD NEGATIVITY IN PREVIOUSLY UNTREATED PATIENTS WITH CLL AND COMORBIDITIES

Fischer, et al. ASCO 2019 Abstract #7502

CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; PFS, progression free survival

FOURTH GENERATION OF GCLLSG TRIALS

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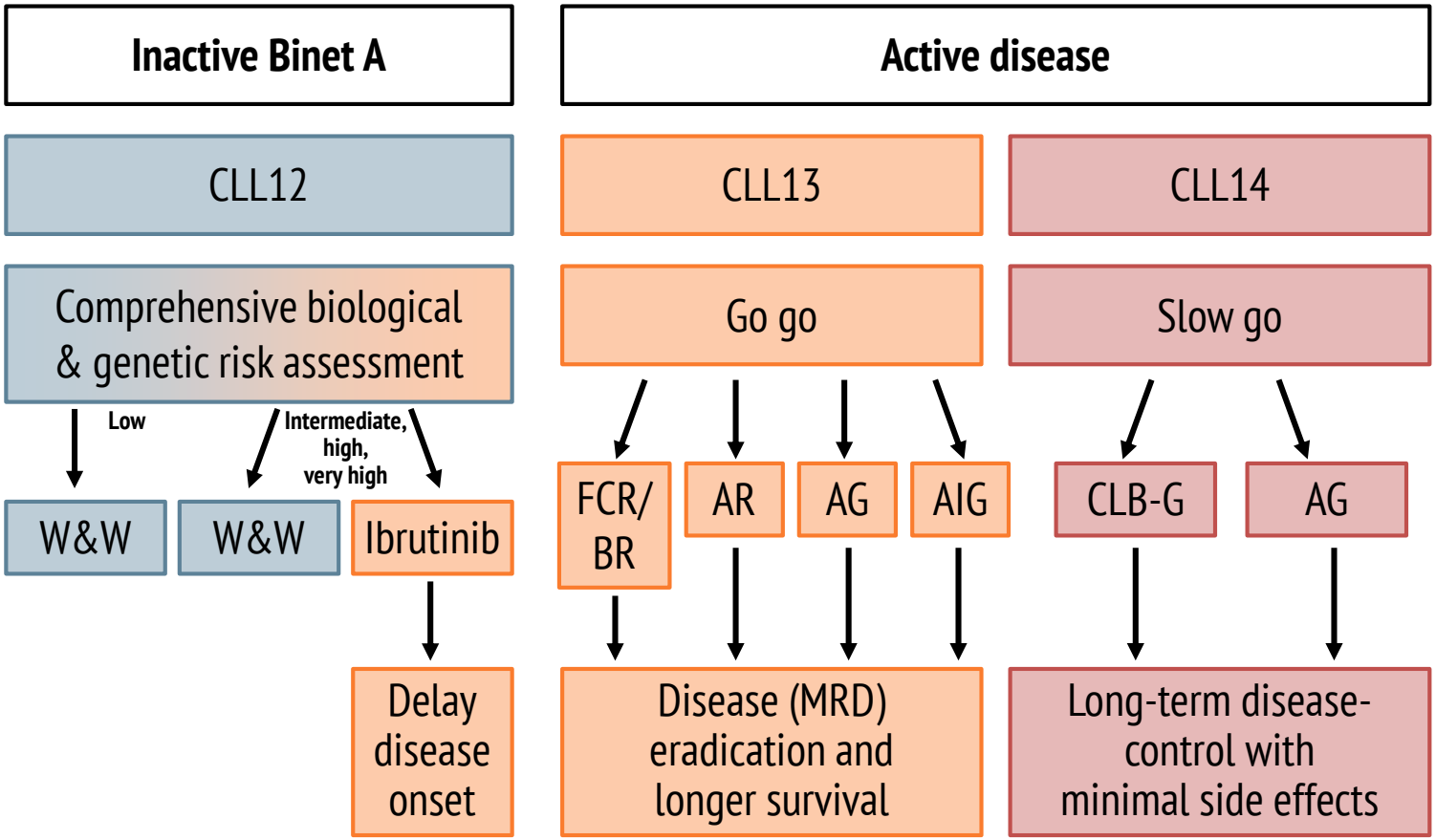
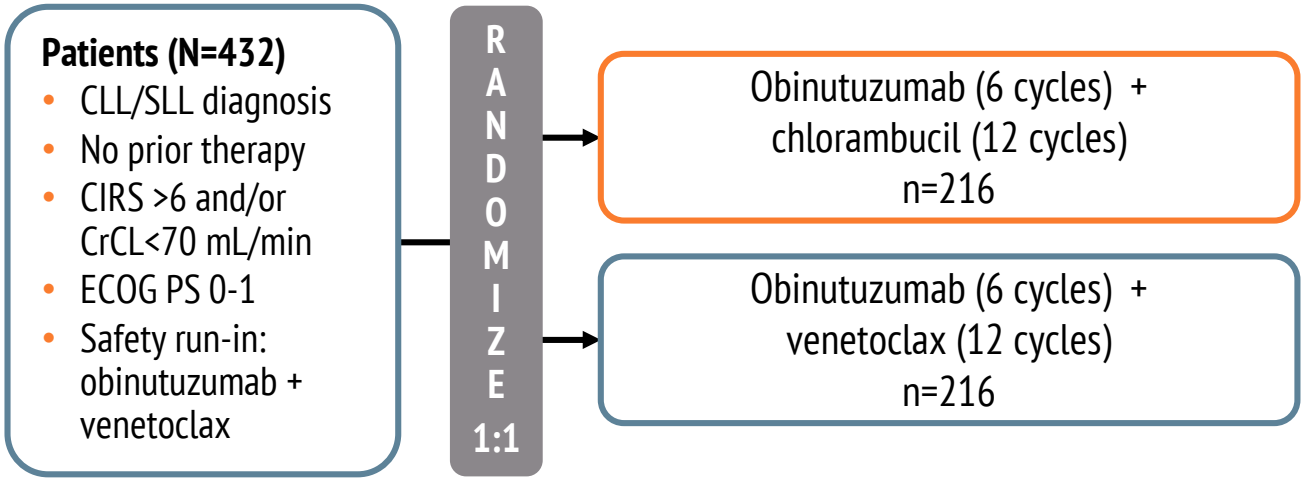
RISK, STAGE AND FITNESS ADAPTED, USING TARGETED AGENTS



CLL, chronic lymphocytic leukemia; GCLLSG, German CLL study group; MRD, minimal residual disease; W&W, watch & wait

CLL14 STUDY DESIGN



- Primary end point: PFS
- Secondary end points: MRD, ORR, OS, safety
- Median follow-up on study: 29 months
- MRD analyzed from C4 every 3 months by allele-specific oligonucleotide polymerase chain reaction assay (ASO-PCR; cut-off, 10^{-4}) and by next generation sequencing (NGS; cut-offs, 10^{-4}, 10^{-5},10^{-6}).

CLL, chronic lymphocytic leukemia; CrCL, creatinine clearance; ECOG, eastern cooperative oncology group; N, number; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression free survival SLL, small lymphocytic lymphoma

Fischer, et al. Presented at ASCO 2019. Abstract #7502

CLL14: RESULTS

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- Superior PFS with VenG vs ClbG
  - (HR 0.35; 95% CI 0.23–0.53; P<0.0001)

MRD	VenG (n=216)	ChlG (n=216)
MRD– by ASO-PCR 3 mo after treatment, PB,%	76	35
MRD– by ASO-PCR 3 mo after treatment, BM,%	57	17
MRD– by ASO-PCR 12 mo after treatment, PB,%	81	27
MRD– rates by NGS, % ($<10^{-4}$,$<10^{-5}$,$<10^{-6}$)	78, 35, 31	34, 15, 4

Conclusion

- Fixed-duration VenG induced deep ($<10^{-6}$ in 1/3 of pts), and long lasting MRD-rates (with a low rate of conversion to MRD+ status 1 year after treatment) in previously untreated pts with CLL and comorbidities, translating into improved PFS

ClbG, chlorambucil-obinutuzumab; CLL, chronic lymphocytic leukemia; CI, confidence interval; HR, hazard ratio; N, number; MRD, minimal residual disease; PFS, progression free survival, SLL, small lymphocytic lymphoma; VenG, venetoclax plus obinutuzumab

Fischer, et al. Presented at ASCO 2019. Abstract #7502

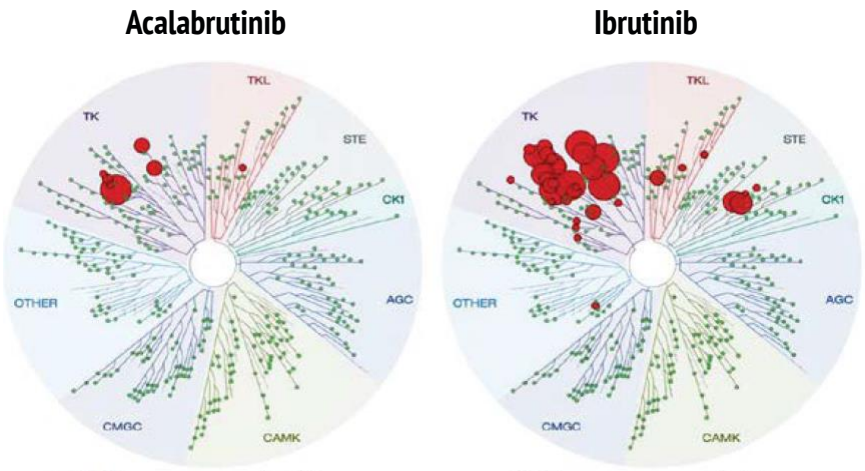
ACALABRUTINIB WITH OBINUTUZUMAB IN TREATMENT-NAIVE AND RELAPSED/REFRACTORY CLL: THREE-YEAR FOLLOW-UP

Woyach, et al. ASCO 2019 Abstract #7500

ACALABRUTINIB

- Acalabrutinib is more selective for BTK with less off-target kinase inhibition compared with ibrutinib in vitro

Kinase Selectivity Profiling at 1 μM



Larger red circles represent stronger inhibition

Kinase Inhibition Average IC_{50} (nM)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	126.0	10.0
ITK	>1000	4.9
BMX	46.0	0.8
TXK	368.0	2.0
EGFR	>1000	5.3
ERBB2	~1000	6.4
ERBB4	16	3.4
BLK	>1000	0.1
JAK3	>1000	32

BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X; BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; ERBB2, erb-b2 receptor tyrosine kinase; ERBB4, erb-b4 receptor tyrosine kinase; IC50, inhibitory concentration of 50%; ITK interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T and X cell expressed kinase.

Barf T, et al. J Pharmacol Exp Ther. 2017;363:240-52; Woyach, et al. Presented at ASCO 2019. Abstract #7500

STUDY DESIGN

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PHASE 1B/2 OF ACALABRUTINIB + OBINUTUZUMAB IN TREATMENT NAÏVE AND RELAPSED REFRACTORY CLL

Patients (19 TN and 26 R/R)
- CLL/SLL diagnosis
- TN or ⩾1 prior therapy
- ECOG PS 0-1
- Measurable nodal disease by CT

→ Acalabrutinib 100 mg BID until PD or unacceptable toxicity
Obinutuzumab 1000mg IV cycles 2–7

Primary end point: ORR
Secondary end points: safety, MRD

Patients	TN (n=19)	R/R (n=26)
Lymph nodes ⩾5 cm, %	53	50
del17p, %	22	19
del11q, %	28	35
Complex karyotype, %	42	56
***IGHV* unmutated, %**	53	65
Follow-up, median (range), mo	36 (1-42)	39 (20-46)
Discontinued, n (%)	2 (11)	7 (27)

BID, twice daily; CLL, chronic lymphocytic leukemia; CT, computed tomography; ECOG, eastern cooperative oncology group; IV, intravenous therapy; MO, months; MRD, minimal residual disease; n, number of patients; ORR, overall response rate; PD, progressive disease; R/R relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naïve

Woyach, et al. Presented at ASCO 2019. Abstract #7500

SAFETY

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ACALABRUTINIB + OBINUTUZUMAB IN TREATMENT NAÏVE AND RELAPSED REFRACTORY CLL

- Common adverse events (AEs; any grade)
  - Upper respiratory tract infection (71%), increased weight (71%), maculopapular rash (67%), cough (64%), diarrhea (62%), headache (56%), nausea (53%), arthralgia (51%) and dizziness (47%)

- Common grade 3/4 adverse events
  - Decreased neutrophil count (24%), syncope (11%), decreased platelet count, increased weight and cellulitis (9% each)
  - 2 (4%) Gr 3 bleeding events (hematuria, muscle hemorrhage) and 1 (2%) Gr 3 atrial fibrillation event

AEs, adverse events; CLL, chronic lymphocytic leukemia; Gr, grade

Woyach, et al. Presented at ASCO 2019. Abstract #7500

RESULTS

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ACALABRUTINIB + OBINUTUZUMAB IN TREATMENT NAÏVE AND RELAPSED REFRACTORY CLL

	TN (n=19)	R/R (n=26)
ORR (≥ PR), %	95	92
CR, n (%)	6 (32)	2 (8)
PR, n (%)	12 (63)	22 (85)
33-mo response duration rate, % (95% CI)	94 (67, 99)	91 (68, 98)
36-mo PFS rate, % (95% CI)	94 (67, 99)	73 (34, 91)
MRD negative in bone marrow Cycle 12 Day 1, n (%)	5 (26)	4 (15)

Conclusions

- With up to 3 years of follow-up, acalabrutinib + obinutuzumab yielded high response rates that were durable
- The combination remains tolerable with low rates of discontinuation and with no new safety signals

CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; Mo, months; MRD, minimal residual disease; N, number of patients; ORR, overall response rate; PFS, progression free survival; PR, partial response; R/R relapsed/refractory; TN, treatment naïve

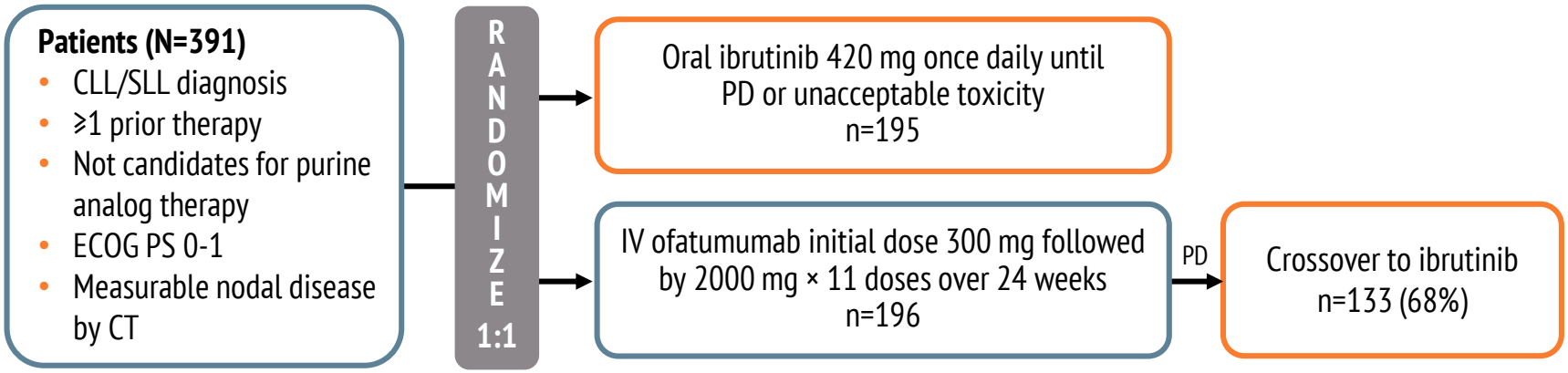
Woyach, et al. Presented at ASCO 2019. Abstract #7500

FINAL ANALYSIS FROM RESONATE: 6-YEAR FOLLOW-UP IN PATIENTS WITH PREVIOUSLY TREATED CLL OR SLL ON IBRUTINIB

Barr, et al. ASCO 2019 Abstract #7510

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma

RESONATE STUDY DESIGN AND PATIENT DISPOSITION



Primary end point: PFS
Secondary end points: ORR, OS, safety

- Median follow-up on study: 65.3 months (range: 0.3-72) for patients initially assigned to ibrutinib and 65.6 months (range: 0.1-73.9) for patients initially assigned to ofatumumab
  - In total, 133 of 196 patients (68%) in ofatumumab arm crossed over to receive ibrutinib
- Median treatment duration: 41.0 months with ibrutinib and 5.3 months with ofatumumab
  - Among patients initially assigned to ibrutinib, 29% received ibrutinib for >5 years
  - Most common reasons for ibrutinib discontinuation prior to study closure: PD (37%) and AEs (16%)
- Baseline characteristics balanced between ibrutinib vs ofatumumab arms
  - ≥3 prior therapies: 53% vs 46%
  - Genomic high-risk features of del(17p), *TP53* mutation, del(11q) and/or unmutated IGHV: 86% vs 79%

CLL, chronic lymphocytic leukemia; CT, computed tomography; ECOG, eastern cooperative oncology group; IV, intravenous therapy; N= number of patients; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; SLL, small lymphocytic lymphoma

Barr, et al. Presented at ASCO 2019. Abstract #7510

RESULTS

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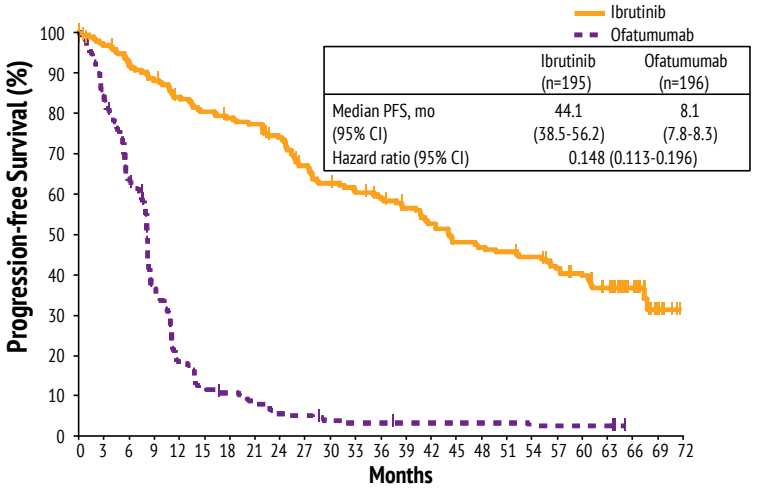
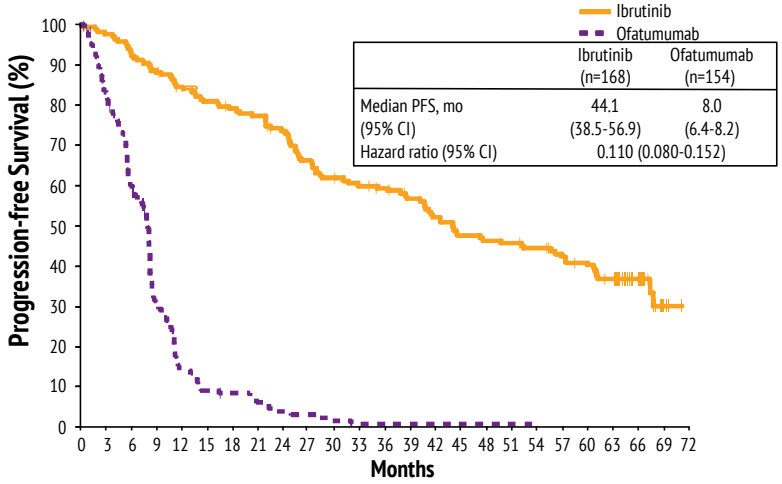
LONG-TERM PFS BENEFIT WITH IBRUTINIB CONSISTENT ACROSS R/R SUBGROUPS DEFINED BY BASELINE CLINICAL AND GENOMIC RISK FACTORS

ITT population



	Ibrutinib (n=195)	Ofatumumab (n=196)
Median PFS, mo (95% CI)	44.1 (38.5-56.2)	8.1 (7.8-8.3)
Hazard ratio (95% CI)	0.148 (0.113-0.196)	

Genomic high-risk population (del(17p), *TP53* mutation, del(11q), and/or unmutated *IGHV*)



	Ibrutinib (n=168)	Ofatumumab (n=154)
Median PFS, mo (95% CI)	44.1 (38.5-56.9)	8.0 (6.4-8.2)
Hazard ratio (95% CI)	0.110 (0.080-0.152)	

- With median study follow-up of 65.4 months, continued PFS benefit was observed with ibrutinib with median PFS of 44 months in both ITT and genomic high-risk populations

CI, confidence interval; ITT, intention-to-treat; Mo, months; N, number; PFS, progression free survival; R/R relapsed/refractory

Barr, et al. Presented at ASCO 2019. Abstract #7510

RESULTS

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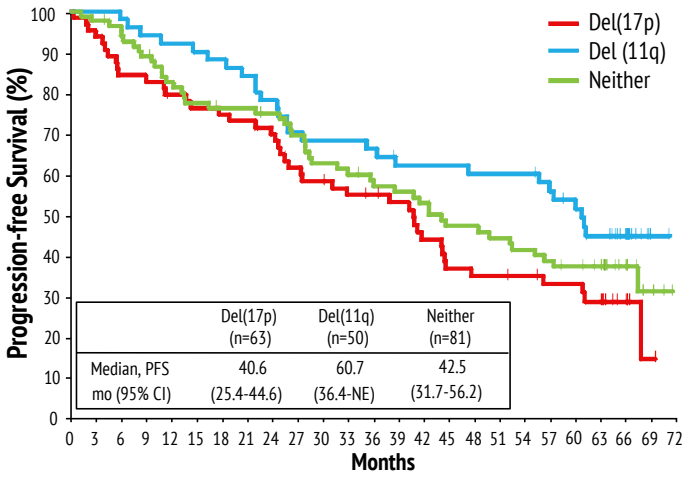
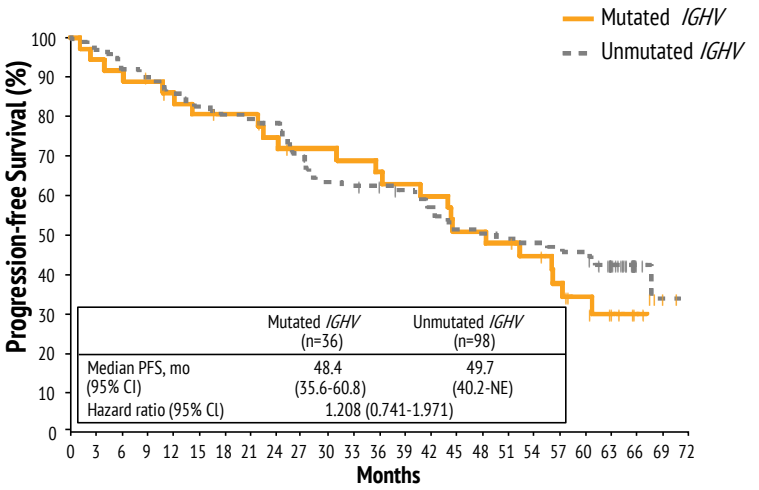
LONG-TERM PFS BENEFIT WITH IBRUTINIB CONSISTENT ACROSS R/R SUBGROUPS DEFINED BY BASELINE CLINICAL AND GENOMIC RISK FACTORS

By chromosomal deletion (ibrutinib arm)



By *IGHV* mutation status (ibrutinib arm)



- Among patients treated with ibrutinib, median PFS trended longest for patients with del(11q)
  - Median PFS was similar between patients with del(17p) and those without del(11q) or del(17p) abnormalities
  - In further exploratory analysis, median PFS in patients with del(17p) and/or TP53 mutation was 41 months; median PFS in patients with del(11q) was 57 months, and was not reached in those without any of these abnormalities
- PFS was comparable irrespective of *IGHV* mutation status

CI, confidence interval; ITT, intention-to-treat; Mo, months; N, number; PFS, progression free survival; R/R relapsed/refractory

Barr, et al. Presented at ASCO 2019. Abstract #7510

RESULTS

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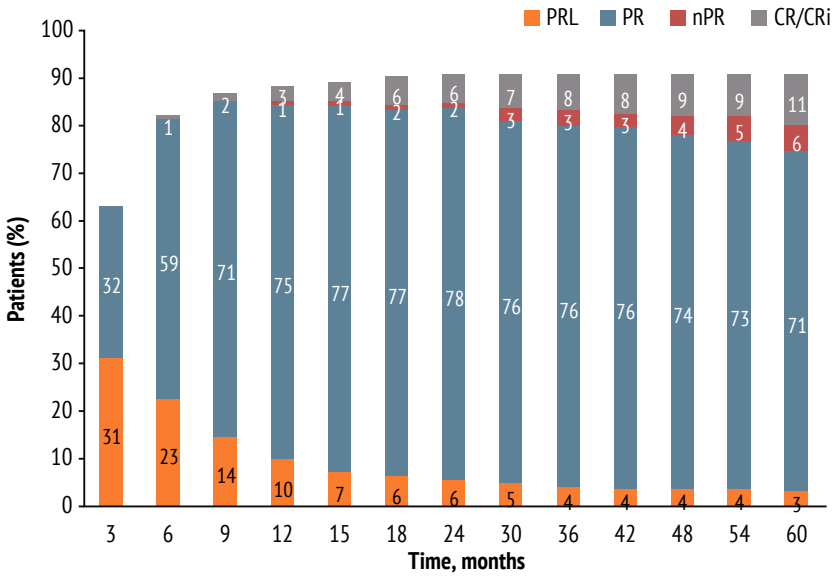
DEPTH OF RESPONSE IMPROVED OVER TIME WITH CONTINUOUS IBRUTINIB TREATMENT

Cumulative best response over time with ibrutinib



- ORR of 91% with long-term follow-up on ibrutinib
- Increase in CR/CRi rates over time to 11%

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; Mo, months; N, number; OS, overall survival

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RESULTS

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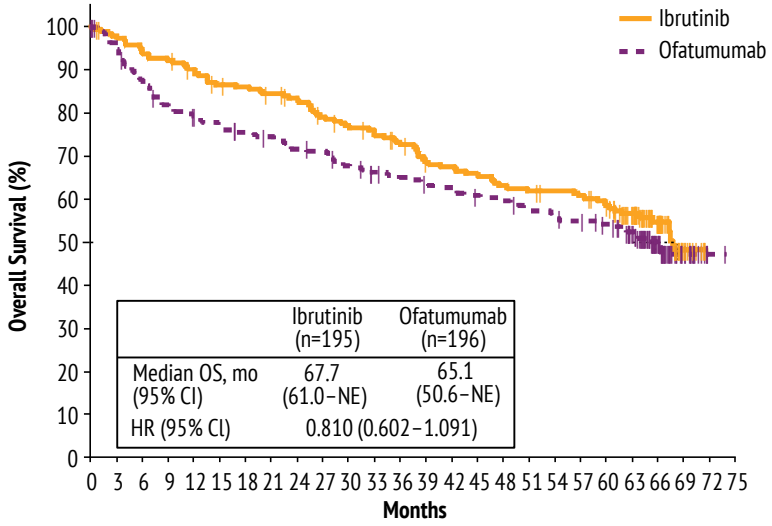
DEPTH OF RESPONSE IMPROVED OVER TIME WITH CONTINUOUS IBRUTINIB TREATMENT

Overall survival (ITT population)



- Median OS: 67.7 months with ibrutinib vs 65.1 months with ofatumumab, without censoring or adjustment for crossover (in 68%) from ofatumumab to ibrutinib (hazard ratio: 0.810)

Response to next-line therapy following ibrutinib discontinuation

- Responses noted in 10 of 27 patients receiving next-line therapy after ibrutinib; responses seen with venetoclax, idelalisib + rituximab, HDMP + alemtuzumab, and investigational agents

CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; Mo, months; N, number; OS, overall survival

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CONCLUSIONS

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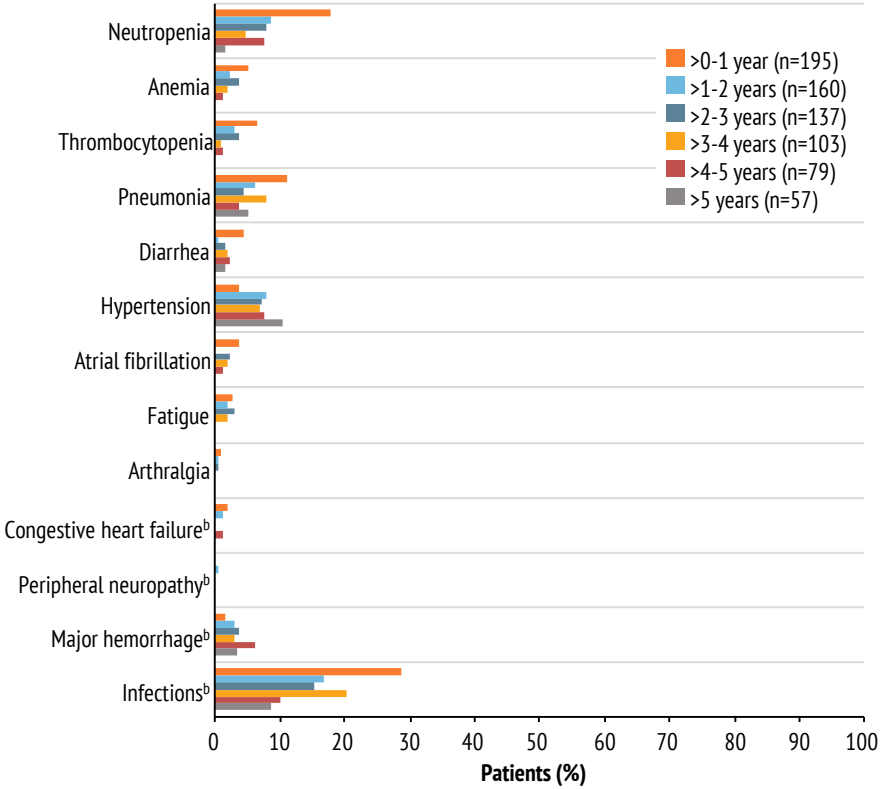
PREVALENCE OF MOST GRADE ≥3 AES OF CLINICAL INTEREST WITH IBRUTINIB DECREASED OVER TIME

Prevalence of grade ≥3 AEs of clinical interest over time for the ibrutinib arm (ITT population)[a]



Conclusions

- With up to 6 years of follow-up, extended ibrutinib treatment showed sustained efficacy in patients with relapsed/refractory CLL/SLL, with similar efficacy in patients with high-risk genomic features
- Safety remained acceptable with low rates of discontinuation due to AEs, and with no new safety signals over long-term therapy
- These results further establish long-term benefit and tolerability for continuous ibrutinib treatment in patients with relapsed/refractory CLL/SLL

[a]Prevalence was determined by the proportion of patients with a given AE (existing event or new onset of an event) during each yearly interval. Multiple onsets of the same AE term within a specific yearly interval were counted once, and the same AE term continuing across several yearly intervals was counted in each of the intervals.
[b]Combined terms.

AE, adverse events; CLL, chronic lymphocytic leukemia; ITT, intention-to-treat; SLL, small lymphocytic lymphoma

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