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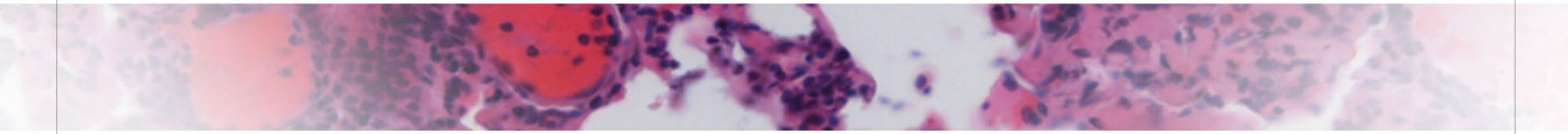

A Clinical Practice Comparison of Patients With CLL/SLL With and Without del(17p) Receiving First-Line Treatment With Ibrutinib

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Introduction

- Deletion 17p (del[17p]) is among the strongest negative prognostic factors for patients with chronic or small lymphocytic leukemia (CLL/SLL)[1-3]
- Ibrutinib monotherapy is effective in treatment-naïve and relapsed/refractory settings,[2,4] but evidence is limited for patients with del(17p), particularly in the first-line (1L) setting[3,5]
- As ibrutinib is now a standard 1L therapy for patients with del(17p),[6] a more in-depth understanding of the impact of del(17p) presence on patient outcomes is needed
- The objective of this retrospective analysis was to evaluate and compare real-world clinical outcomes among patients with CLL/SLL with and without del(17p) receiving 1L ibrutinib monotherapy

1. Fischer K, et al. *Hematol Am Soc Hematol Educ Program*. 2017;2017(1):338-345. 2. Munir T, et al. *Am J Hematol*. 2019;94:1353-1363. 3. O'Brien S, et al. *Blood*. 2018;131(17):1910-1919. 4. Burger JA, et al. *N Engl J Med*. 2015;373(25):2425-2437. 5. Mato AR, et al. *Am J Hematol*. 2018;93:1394-1401. 6. NCCN Guidelines Version 4.2020, CLL/SLL.

Methods

- **Study design:** Observational retrospective data analysis
- **Data source:** Flatiron Health electronic health record–derived database
- **Patient population:** CLL patients received 1L ibrutinib therapy from 1/1/2011 through 12/31/2019
- **Study outcomes (stratified by del 17p status):** Overall survival (OS), time to next treatment (TTNT), time to treatment discontinuation (TTD), and reasons for discontinuation (RFDs)
- **Analyses**
  - Kaplan-Meier method was used to estimate OS, TTNT, and TTD
  - Survival outcomes were compared using Cox proportional hazards modeling; adjustment for covariates was performed
  - RFDs were compared

Inclusion criteria

Age ≥18 years, diagnosed with CLL/SLL (ICD-9 code: 204.1x or ICD-10: C91.1x, C83.0x), with cytogenetic test results (including fluorescence in situ hybridization [FISH]) confirming presence or absence of del(17p); who had ≥2 clinic encounters in the Flatiron Health network; and who received ibrutinib monotherapy as first CLL-directed therapy on/after 1/1/2011

Exclusion criteria

CLL/SLL treatment initiation before entry into the Flatiron Health network

Results: Patient Baseline Characteristics (Table 1)

Patient characteristic		Full cohort, N=1037	del(17p) absent, n=787	del(17p) present, n=250	*P* value
Sex, n (%)	Male	646 (62)	494 (63)	152 (61)	0.628
Age at diagnosis, years	Median (IQR)	69 (62, 77)	69 (61, 76)	71 (62, 78)	0.106
Rai stage at diagnosis, n (%)	0	291 (28)	247 (31)	44 (18)	<0.001
	I	164 (16)	124 (16)	40 (16)	
	II	49 (5)	30 (4)	19 (8)	
	III	62 (6)	40 (5)	22 (9)	
	IV	75 (7)	50 (6)	25 (10)	
	Not documented	396 (38)	296 (38)	100 (40)	
ECOG performance status at index date, n (%)	0	337 (32)	266 (34)	71 (28)	0.190
	1	263 (25)	200 (25)	63 (25)	
	2+	93 (9)	73 (9)	20 (8)	
	Not documented	344 (33)	248 (32)	96 (38)	

Results: Patient Baseline Characteristics (Table 1)

Patient characteristic		Full cohort, N=1037	del(17p) absent, n=787	del(17p) present, n=250	*P* value
Deletion 17p, n (%)	Present	250 (24)	0 (0)	250 (100)	<0.001
Deletion 11q, n (%)	Present	187 (8)	144 (18)	43 (17)	<0.001
Deletion 13q, n (%)	Present	487 (47)	368 (47)	119 (48)	0.024
Trisomy 12, n (%)	Present	274 (26)	224 (28)	50 (20)	<0.001
***IgHV* status, n (%)**	Mutated Unmutated Unknown	170 (16) 257 (25) 610 (59)	141 (18) 193 (25) 453 (58)	29 (12) 64 (26) 157 (63)	0.024

Kaplan-Meier Curves for OS and Time to Discontinuation (TTD)

Figure 1. Kaplan-Meier Curves for OS

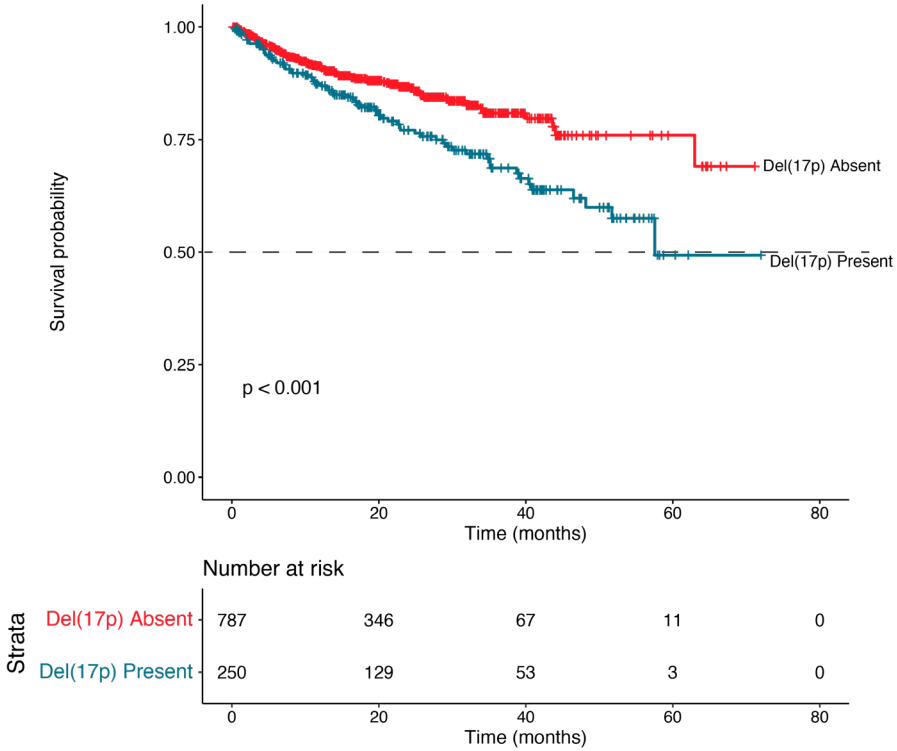
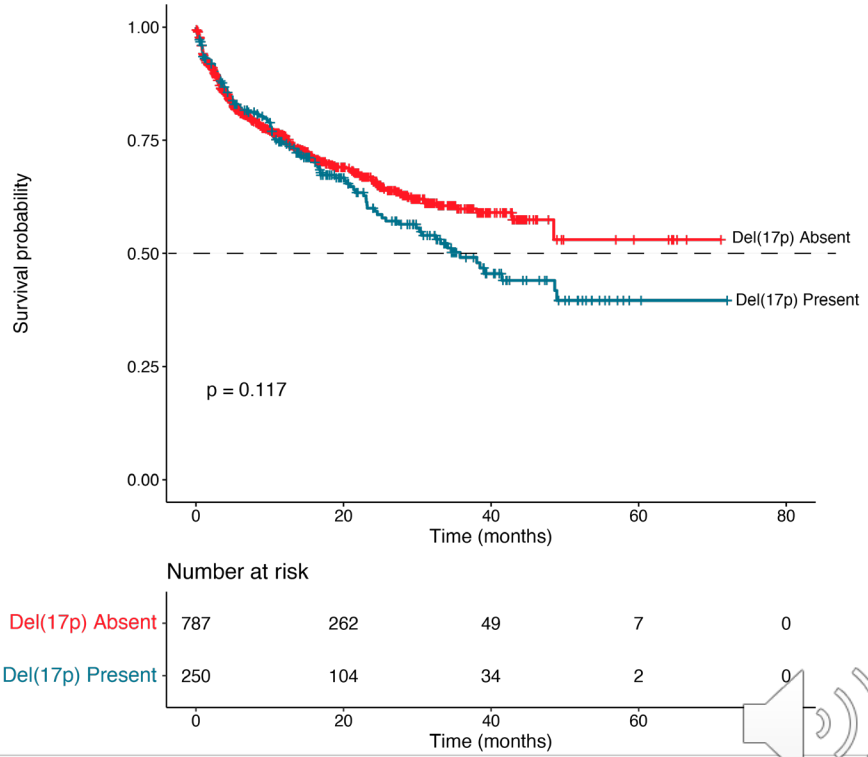


Figure 2. Kaplan-Meier Curves for TTD



Results: Adjusted Hazard Ratios (Table 2)

- Cox proportional hazard analyses were consistent with Kaplan-Meier findings, with OS significantly different between del(17p) and non-del(17p) groups, at *P*=0.009
- Results for TTNT and TTD were shorter but were not statistically significant in the del(17p) population

		Median (months)	Adjusted analyses*		
Outcome			**Event rate, %**	**Hazard ratio**	***P* value**
Overall survival (OS)	del(17p) present	57.5	26.0	1.59	***0.009***
	del(17p) absent	Not reported	12.6	(reference)	
Time to next treatment (TTNT)	del(17p) present	50.2	33.6	1.20	0.209
	del(17p) absent	Not reported	22.2	(reference)	
Time to discontinuation (TTD)	del(17p) present	35.8	41.2	1.11	0.435
	del(17p) absent	Not reported	29.9	(reference)	

*Adjustment for covariates was performed for sex; age at index date; practice type; Rai stage at diagnosis; Eastern Cooperative Oncology Group status; year of index date; status of deletions 11q, 13q, and trisomy 12; and *IgHV* mutation status. No multiplicity adjustments were made among the analyses.

Results: Reasons for Discontinuation (RFDs) (Table 3)

- RFDs were analyzed using updated data from Flatiron Health (N=1069) and the same inclusion/exclusion criteria
- No statistically significant differences in RFDs were noted between groups, except for disease progression

Reasons for first discontinuation of ibrutinib episodes*, n (%)	Full cohort N=1069	del(17p) absent n=815	del(17p) present n=254	*P* value
Discontinued for any reason	**320 (30)**	**235 (29)**	**85 (33)**	**0.1595**
Toxicity†	174 (54)	135 (57)	39 (46)	0.0666
Progression	40 (13)	17 (7)	23 (27)	***<0.0001***
Patient request	21 (7)	19 (8)	2 (2)	0.0761
Financial burden	4 (1)	3 (1)	1 (1)	1.0000
Disease-related symptoms not due to therapy	9 (3)	9 (4)	0 (0)	0.1190
Completion of treatment	1 (0)	1 (0)	0 (0)	1.0000
Other	88 (28)	66 (28)	22 (26)	0.6967
Unknown	3 (1)	3 (1)	0 (0)	0.5680

*Patients could have multiple reasons for discontinuation. First discontinuation episode was used to define time to discontinuation.
†Toxicity of therapy was greater in the del(17p) absent group, but this finding was not statistically significant.

Conclusions

- Data on ibrutinib use in patients with del(17p) vs those without del(17p) in the frontline setting are limited[1,2]
- This real-world study strengthens evidence that CLL/SLL patients with del(17p) receiving ibrutinib in the frontline setting have inferior survival outcomes compared to patients without del(17p)
- Limitations inherent to real-world data include missing information and unmeasured confounders
- Del(17p) remains associated with inferior outcomes for patients with CLL/SLL despite the advent of ibrutinib; this reflects an ongoing unmet need for more efficacious therapy among patients with del(17p)

1. O'Brien S, et al. *Blood*. 2018;131(17):1910-1919. 2. Mato AR, et al. *Am J Hematol*. 2018;93:1394-1401.

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Disclosures

- **BT** is currently employed by and is a current equity holder in BeiGene, Ltd.
- **SA** is currently employed by and is a current equity holder in BeiGene, Ltd.
- **KY** is currently employed by and is a current equity holder in BeiGene, Ltd.
- **JCS** is currently employed by and is a current equity holder in BeiGene, Ltd.
- **EH** was employed by BeiGene, Ltd., at the time of the analysis and is a current equity holder in BeiGene, Ltd.
- **JH** is currently employed by, is a current equity holder in, and receives travel accommodations and expenses from BeiGene, Ltd.; is a current equity holder in and ended employment in the last 24 months for Agios Pharmaceuticals Inc.; and is a current equity holder in Vertex
- **JPS** provides consultancy for and receives research funding from Genentech, AstraZeneca, Pharmacyclics LLC (an AbbVie Company), Pfizer, AbbVie, TG Therapeutics, Acerta, Roche, Celgene, and BMS; and receives research funding from BeiGene, Ltd.