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PREVALENCE OF *BTK* AND *PLCG2* GENE MUTATIONS IN CHRONIC LYMPHOCYTIC LEUKEMIA PATIENTS RELAPSING ON IBRUTINIB: A EUROPEAN RESEARCH INITIATIVE ON CLL (ERIC) REAL-WORLD STUDY

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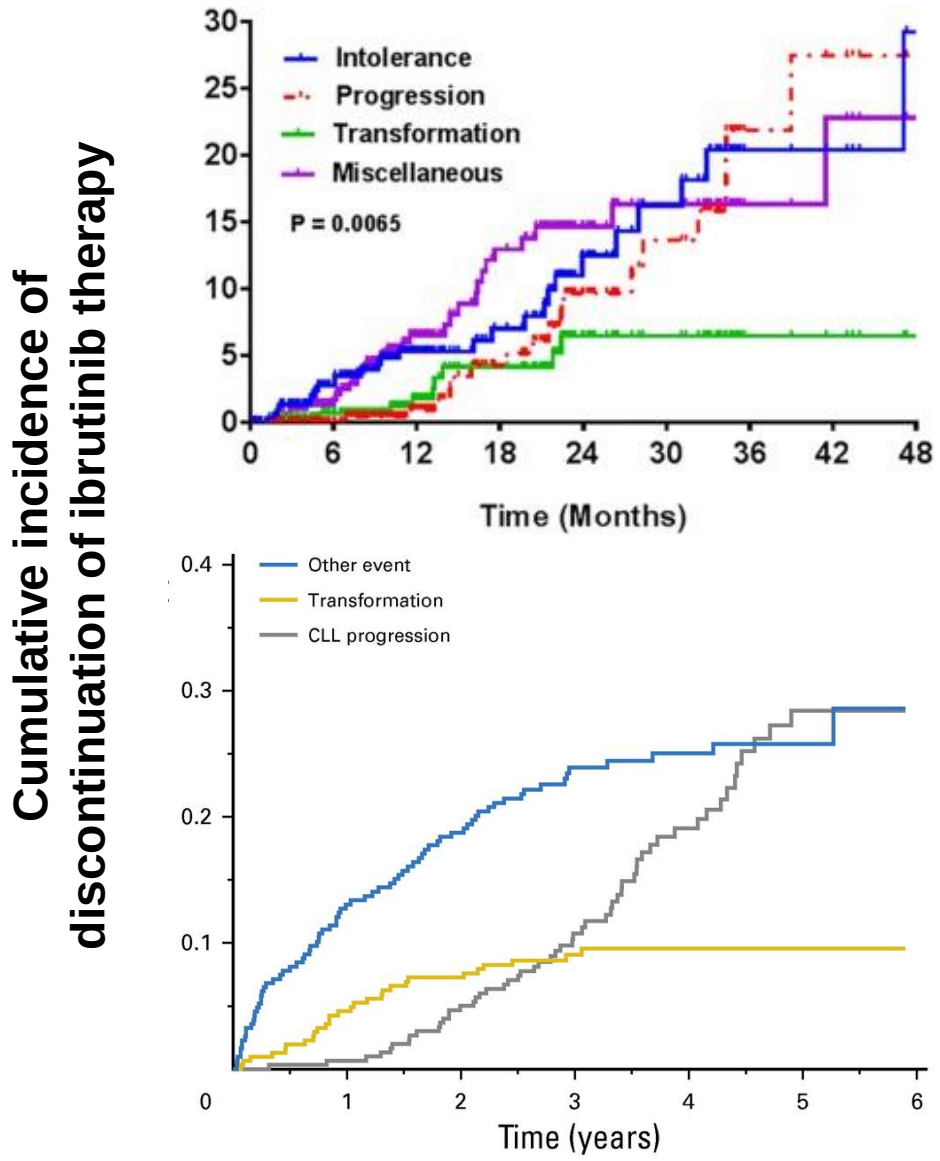
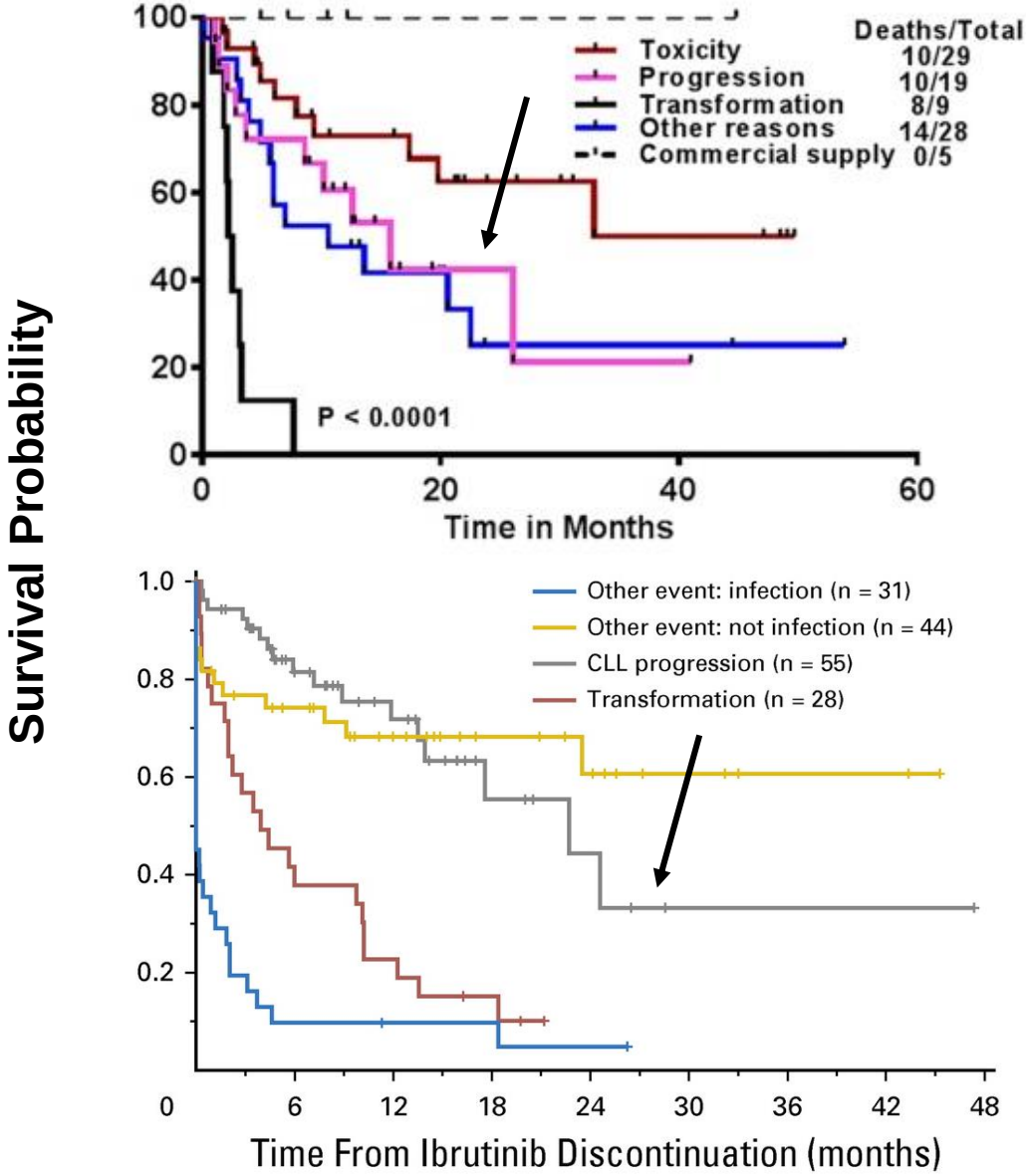
Ibrutinib discontinuation and outcome





Jain et al. Cancer 2017; Woyach et al. JCO 2017

BTK and *PLCG2* mutations in CLL patients relapsed on ibrutinib

Ref.	Pts with mut/total	Analytical Method	*BTK* mutations	VAF %	*PLCG2* mutations	VAF %
Woyach, 2014	6/6	WES	C481S	17-60	R665W; L845F S707Y	8-38
Ahn, 2017	8/10	High sensitivity NGS; ddPCR	C481S C481R	1.6-78.2 15.8	6nt del; R665W P664S; S707Y; L845F	0.1-18.3
Woyach, 2017	40/46 (retrospective); 8/8 (prospective)	Targeted Deep Sequencing	C481S C481R C481F C481A	0.2-94.8 18.1 1.1-100 45.3	R665W; S707P; S707F; S707Y; L845F; D993Y; L845/846del	3.6-44
Burger, 2016	2/4	WES; ddPCR	C481S	NR	M1141R; S707F; M1141K; D993H	12.0-35.0 (CCF)
Landau, 2017	5/7	Targeted Deep Sequencing	C481S	2.2-78.2	R665W; S707Y; L845F	0.2-4.7
Kadri, 2017	1/3	Targeted Deep Sequencing	C481S C481R	8.5-90.0 2.5	NR	NR
Kanagal-Shamanna, 2019	16/23	Targeted Deep Sequencing	C481S; C481F C481R; C481Y V537I	11(1-91)	None	NA

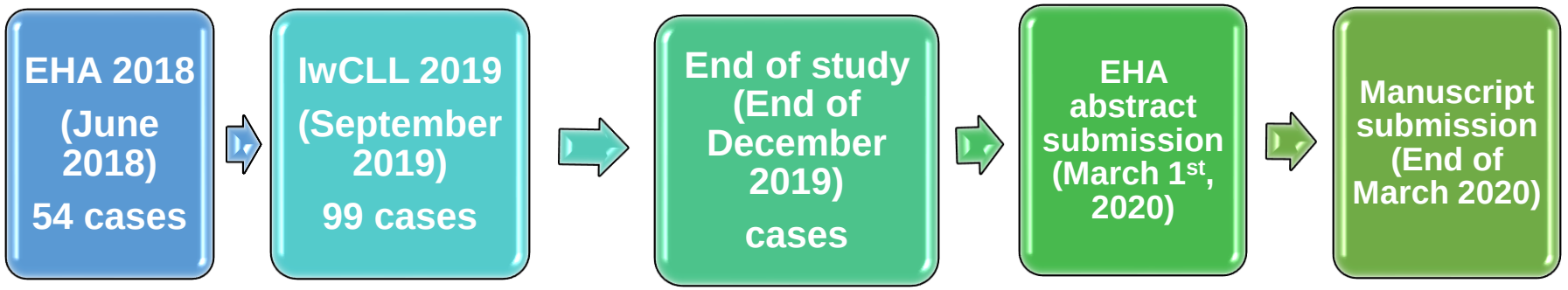
Participating Sites

Up to 21 sites

Country	Number of sites (Site IDs)
Italy	7 (OSR MI, Policlinico MI, Torino, UniTo, Padova, Novara, Modena, Niguarda MI)
UK	4 (Southhampton, Bournemouth, Cambridge, RMH London)
Greece	2 (Athens, Thessaloniki)
Australia	2 (Melbourne, Sidney)
Sweden	1 (KI Stockholm)
Argentina	1 (Buenos Aires)
Croatia	1 (Zagreb)
Hungary	1 (Budapest)
France	1 (Toulouse)
Russia	1 (Saint Petersburg)

Update (2Dec2019)

# patients	Batch 1&2	Batch 3	Batch 4	Batch 5	TOTAL
relapsed	22	6	21	(12)	49 + (12)
sensitive (>1y)	32	17	1	0	50
TOTAL	54	23	22	(12)	99-111



Study Design

International, retrospective, observational, multicenter study

20 ERIC participating sites:

- **Italy (7)**
- **UK (3)**
- **Greece (2)**
- **Australia (2)**
- **Sweden (1)**
- **Croatia (1)**
- **Argentina (1)**
- **Hungary (1)**
- **France (1)**
- **Russia (1)**

PRIMARY OBJECTIVE:

To determine the prevalence of *BTK* and *PLCG2* mutations in CLL patients relapsing or responding to ibrutinib in a real-world setting

Eligibility Criteria

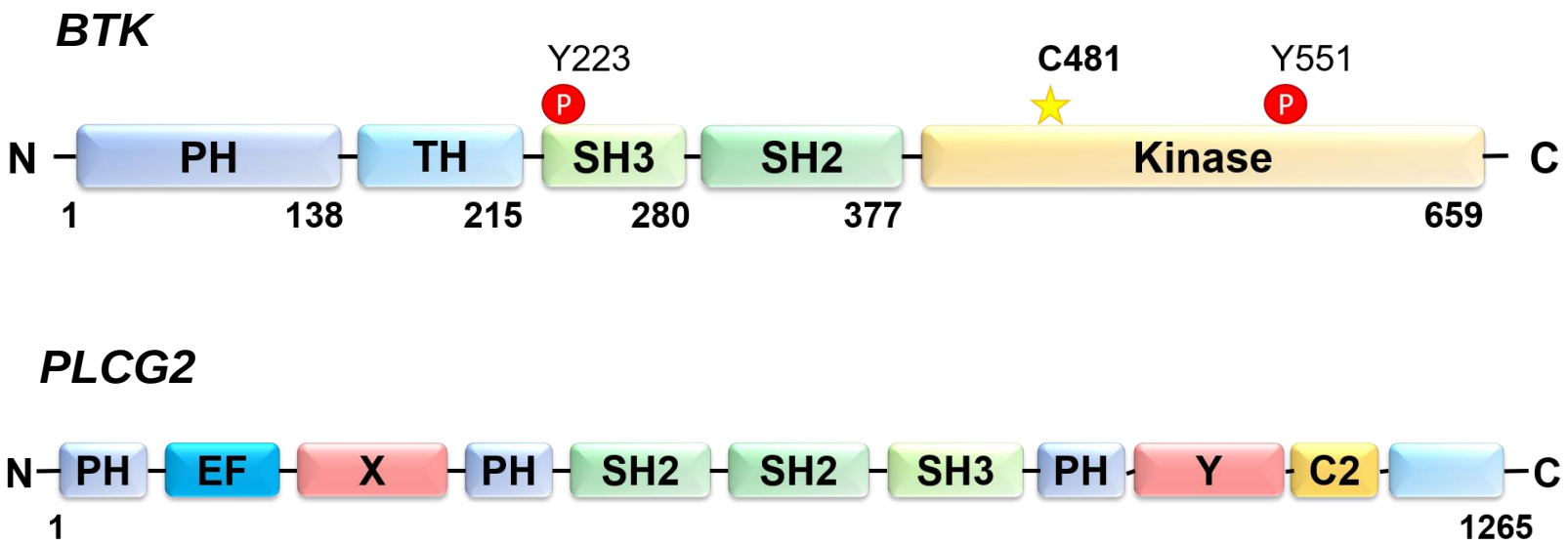
CLL patients who received ibrutinib treatment at full dose without >14 days interruption

- ***Relapsed cases*: relapse on ibrutinib according to the modified IwCLL 2008 criteria**
- ***Responders*: responding to ibrutinib according to the modified IwCLL 2008 criteria and have samples collected after at least 1 year of treatment**

Patients with Richter Transformation were excluded

Methods

- DNA extraction from purified B cells
- Agilent HaloPlexHS kit (*BTK* and *PLCG2* all exons)
- Paired-end sequencing (NextSeq Illumina)
- Variant allelic frequency (VAF) cutoff of 1% (Targeted deep sequencing)



Patient cohort (n = 99)

Characteristics	Relapsed n = 49	Responsive n = 50	Overall n = 99
Median age, y (range)	64 (48-86)	71 (46-85)	67 (46-86)
Gender (M:F)	1.87	1.78	1.81
# prior therapies (0/1/≥2)	0/6/37	9/12/29	9/18/66
del(17p) (n= 88)	45.2%	34.8%	39.8%
TP53 Mutations	58.2%	48%	53.1%
IGHV Unmutated (n=42)	74.2%	68.3%	70.8%
Duration of ibrutinib treatment (months)	25 (3-57)	35 (8-73)	33 (3-58)
Best Response to ibrutinib CR/PR or nPR	4/34	12/38	16/72

Concluding Summary

- We analyzed **49 relapsed** and **50 responding CLL** patients treated with **ibrutinib**
- **Around 50%** of cases **relapsing** on ibrutinib had ***BTK*$^{C481S/R}$** mutations
- ***PLCG2* mutations** were **rare** overall: 6 relapsed cases with *BTK*$^{C481S/R}$ mutations and only 1 with isolated *PLCG2* mutations
- These results indicate the **outgrowth of several resistant clones** during ibrutinib treatment
- It remains to **be established** the **mechanisms** leading to **resistance** in cases **without *BTK/PLCG2* mutations** (ddPCR, WES, RNA-seq)

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