“GENETIC BIOMARKERS PREDICTING SUSTAINED EFFICACY OF VENETOCLAX-BASED THERAPIES OR CIT IN CHRONIC LYMPHOCYTIC LEUKEMIA: FINAL 5-YEAR ANALYSIS OF THE GAIA/CLL13 TRIAL”

Eugen Tausch, Christof Schneider, Moritz Fürstenau, Sandra Robrecht, Adam Giza, Deyan Yosifov, Billy Chelliah Jebaraj, Christoph Brey, Tamar Tadmor, Patrick Thornton, Michael Gregor, Philipp Staber, Karl-Anton Kreuzer, Matthias Ritgen, Anna-Maria Fink, Kirsten Fischer, Arnon Philip Kater, Carsten Niemann, Michael Hallek, Barbara Eichhorst, Stephan Stilgenbauer

COIs

- Honoraria/speakers bureau: AbbVie, Janssen, Roche, AstraZeneca, BeOne, Lilly
- Research support: AbbVie, Roche
- Travel support: Janssen, AbbVie, BeOne, Lilly

Introduction: CLL13/GAIA study design and results

Eligibility

Treatment-naive, fit patients with CLL,

no TP53 mutation/del(17p) centraly screened via Sanger

- **CIT*** FCR ≤65y, BR >65y
- **RV** rituximab, venetoclax | FD 12 months
- **GV** obinutuzumab, venetoclax | FD 12 months
- **GIV** obinutuzumab, ibrutinib, venetoclax | 12-36 months

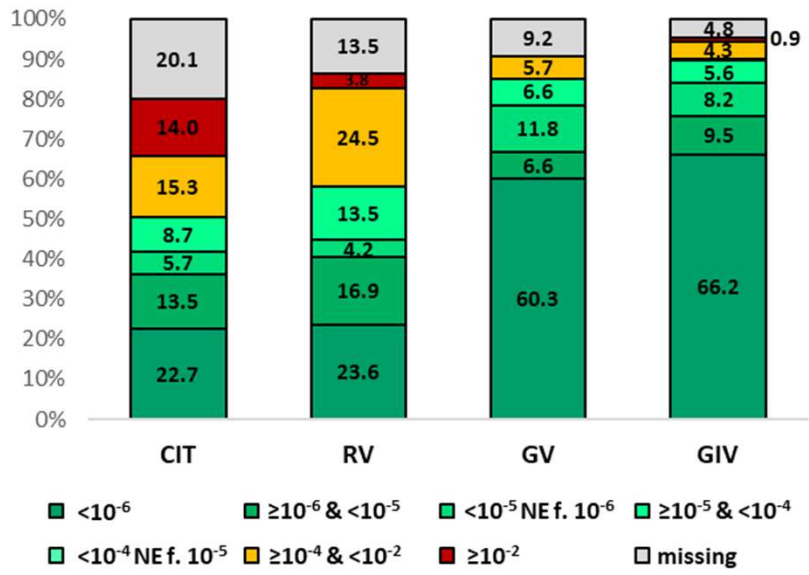
Primary Endpoints

1. uMRD rate at MO15
2. Progression-free survival

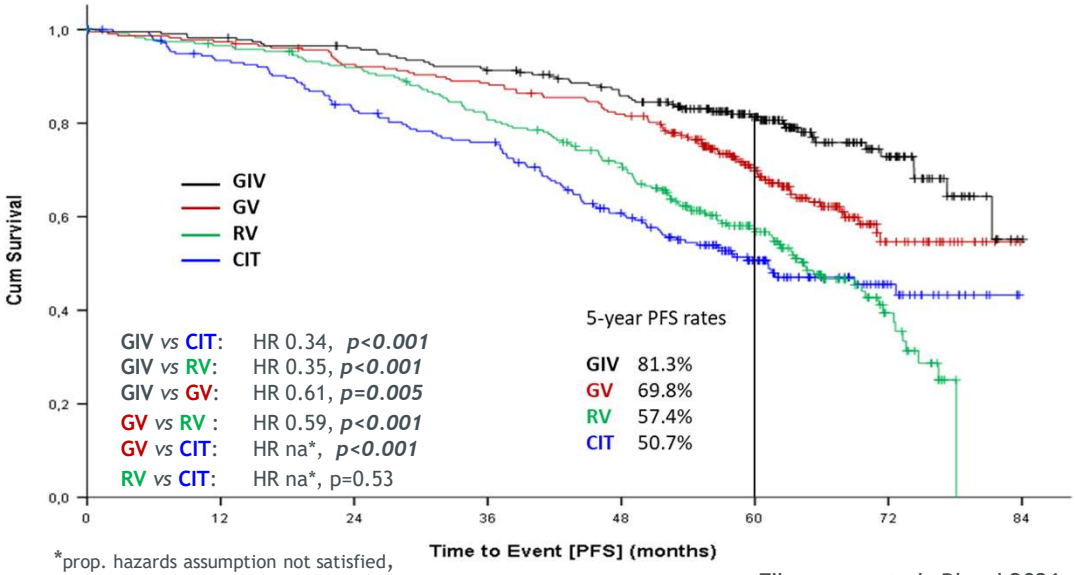
median follow up of 63.8 months

* ≤ 65 years: FCR, > 65 years: BR; [50% FCR / 50% BR] # continuation of ibrutinib up to cycle 36 if MRD detectable

NGS MRD level in PB at MO15



Progression-free survival

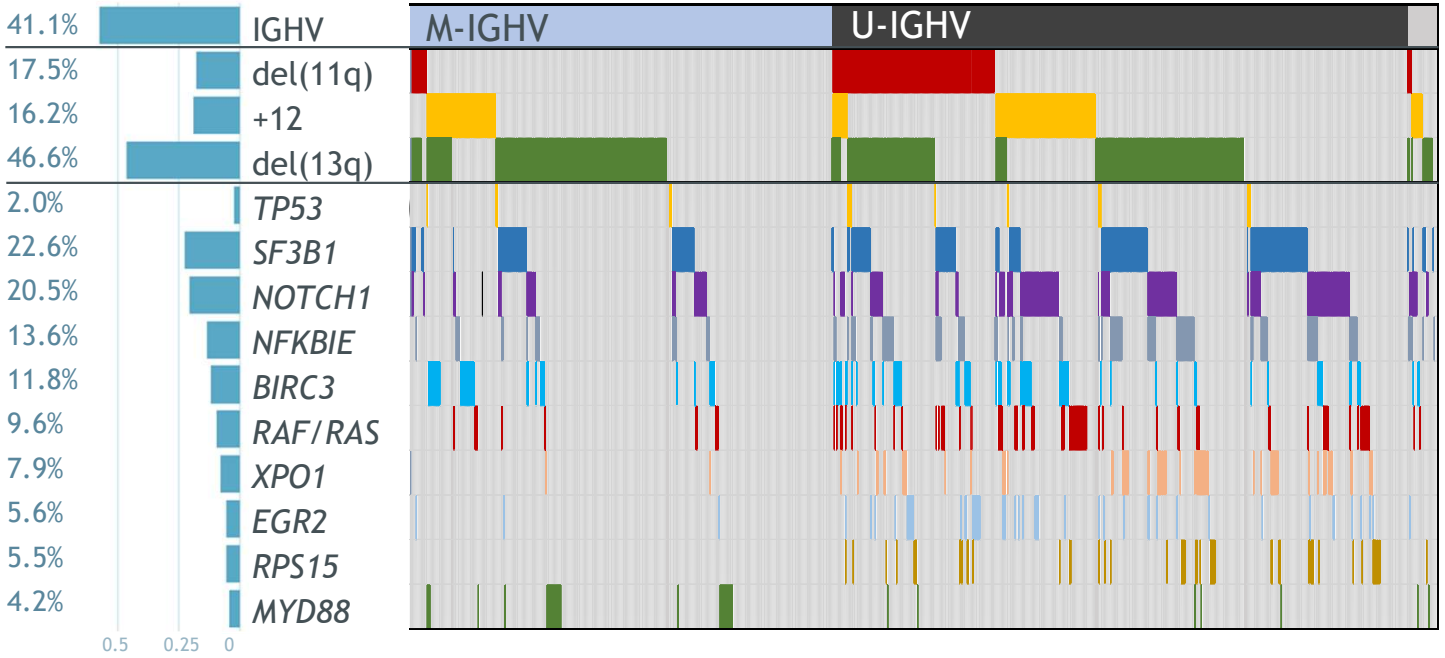


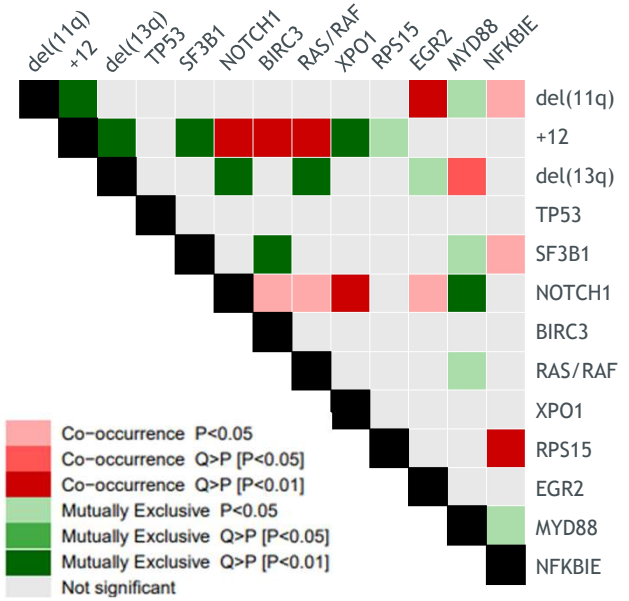
*prop. hazards assumption not satisfied,

Fürstenau et al, Blood 2026

Methods and results: Genetic landscape in CLL13

- **IGHV** with homology threshold of <98% in **925/926 (100%)** cases
- Cytogenetics were assessed via **FISH** in **926/926 (100%)** patients at baseline and **245/328 (75%)** at relapse,
- **Gene mutations via tNGS** in **913/926 (99%)** of patients **at baseline and 235/328 (72%) at relapse** for the genes *TP53*, *NOTCH1, SF3B1, MYD88, BIRC3, XPO1, NFKBIE, EGR2, NRAS, KRAS, BRAF, RPS15, BTK, PLCG2, BCL2 and BCL2 family*.

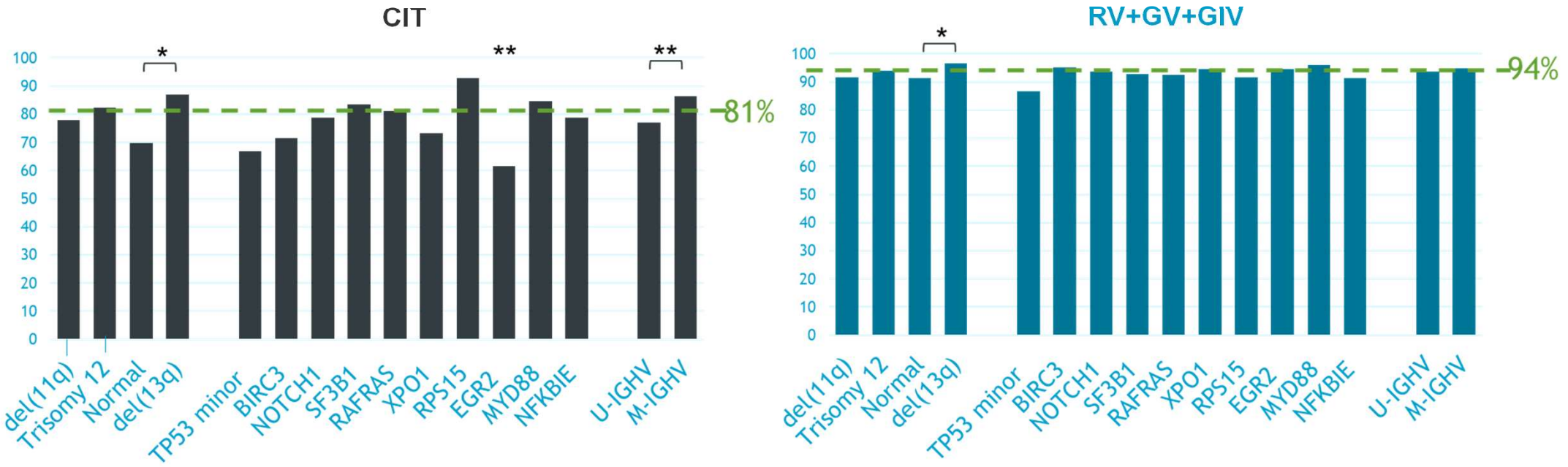




Overall response rate (ORR) at month 15

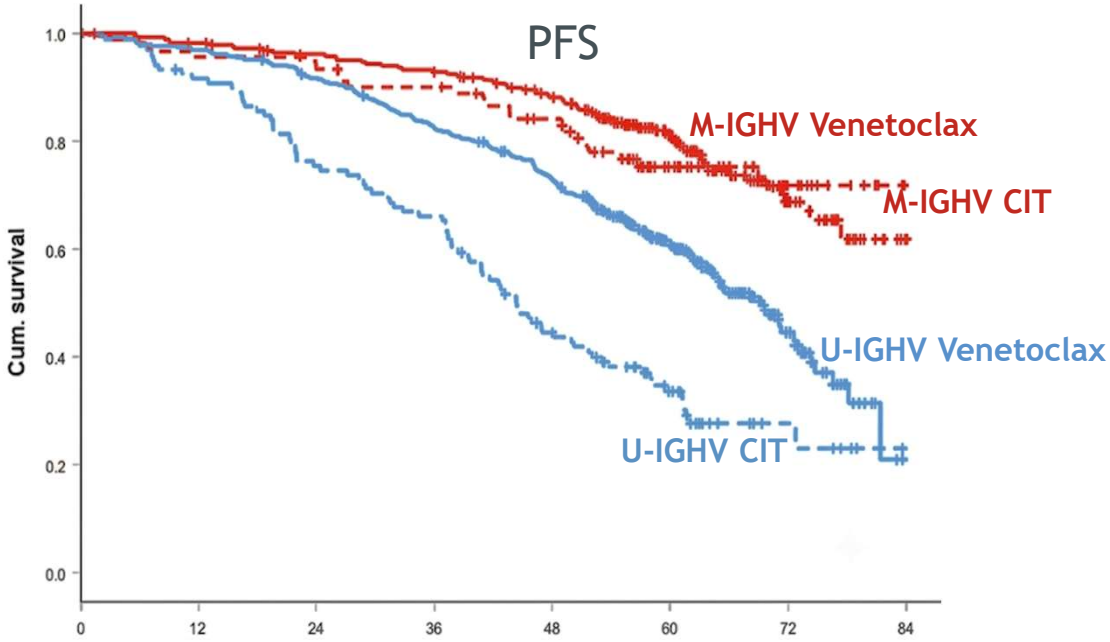
Del(13q) with best ORR in RVe/GVe/GIVe and CIT patients.

U-IGHV (p=0.08) and mutated EGR2 (p=0.08) with non-significant trend for lower ORR with CIT.



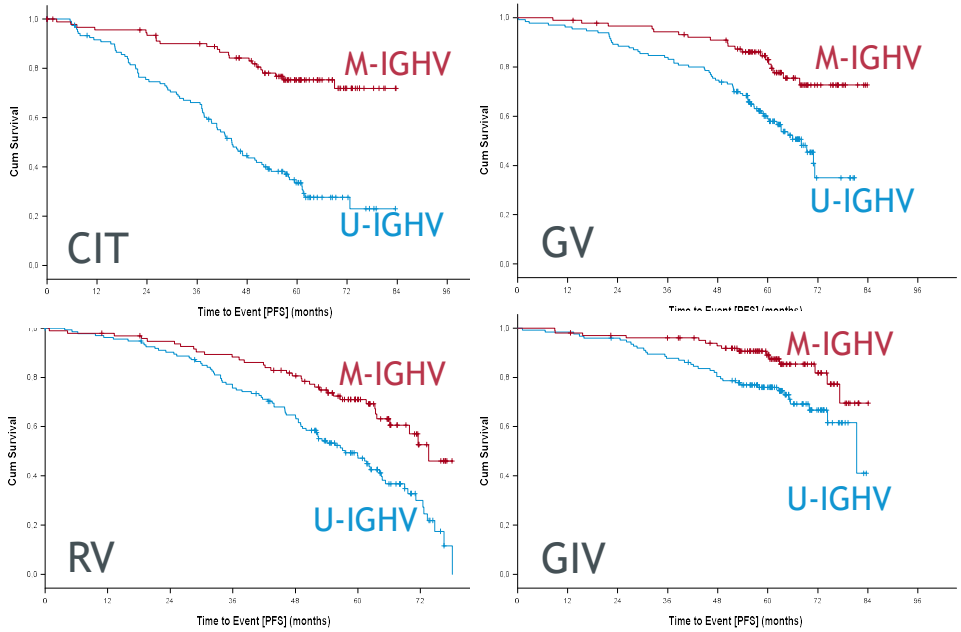
* p<0.05 ** p=0.05-0.1

PFS: U-IGHV is a prognostic factor CIT and RV+GV+GIV



U-IGHV CIT	131	108	89	78	49	27	7	0
U-IGHV Ven	387	374	352	315	276	165	37	0
M-IGHV CIT	95	87	84	80	70	40	14	0
M-IGHV Ven	285	279	268	258	237	148	47	1

Group	5 year PFS (%)	
CIT U-IGHV	33.6%	HR 4.057
CIT M-IGHV	75.3%	
RV+GV+GIV U-IGHV	60.9%	HR 3.048
RV+GV+GIV M-IGHV	81.1%	

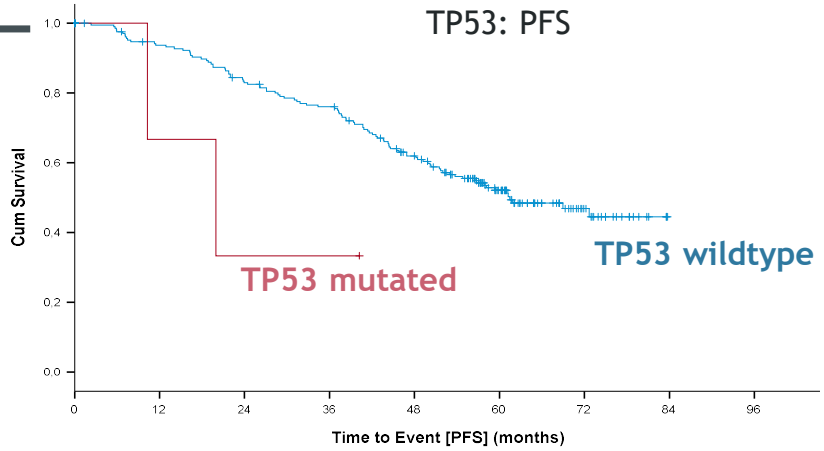


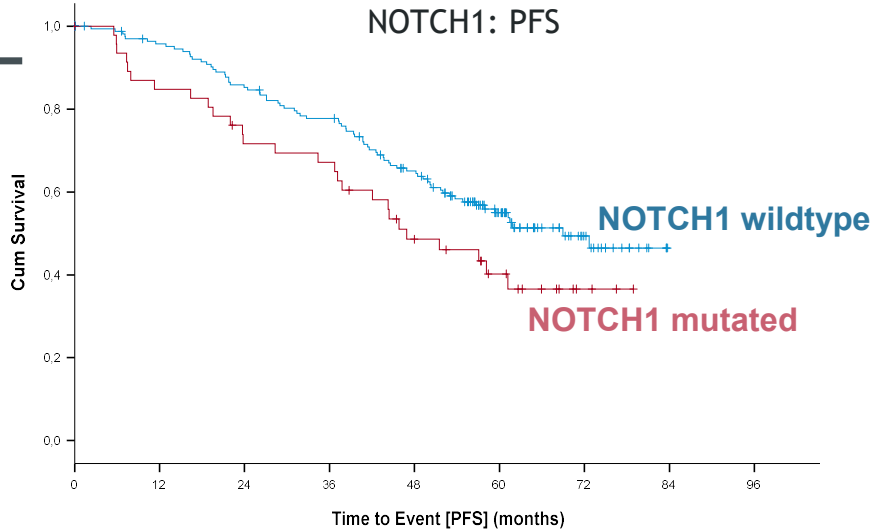
U-IGHV is prognostic for
CIT and Venetoclax based therapies.

Patients with U-IGHV have strongest benefit from Ven-based therapies compared to CIT

PFS in CIT: Univariate analysis of genetic subgroups

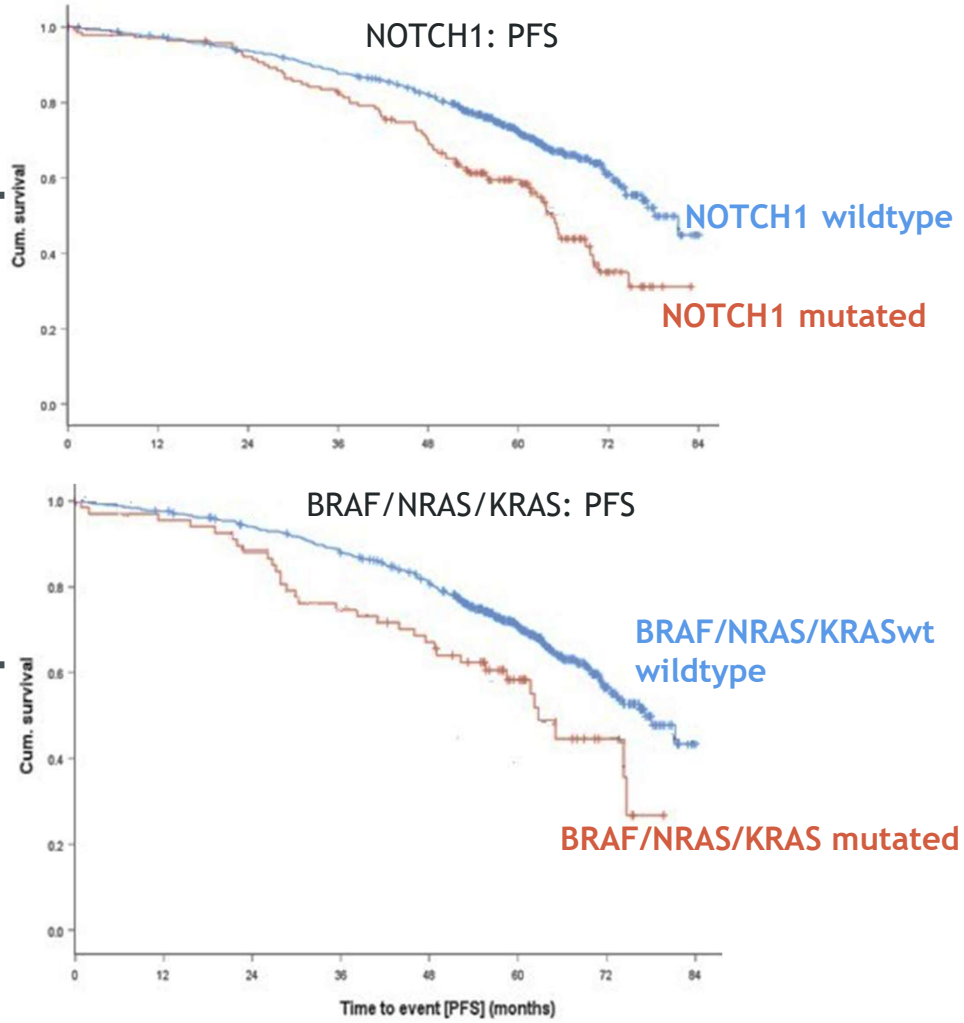
TP53 minor	HR 3.733	CI95: 0.91-15.33	p=0.068
BIRC3	HR 1.363	CI95: 0.78-2.40	p=0.282
NOTCH1	HR 1.936	CI95: 0.99-2.38	p=0.058
SF3B1	HR 0.854	CI95: 0.54-1.36	p=0.507
RAF/RAS	HR 1.234	CI95: 0.66-2.31	p=0.51
XPO1	HR 1.595	CI95: 0.83-3.07	p=0.162
RPS15	HR 1.587	CI 5: 0.8-3.15	p=0.187
EGR2	HR 1.615	CI95: 0.784- 3.33	p=0.193
MYD88	HR 0.417	CI95: 0.13-1.32	p=0.14
NFKBIE	HR 1.383	CI95: 0.83-2.30	p=0.21
del(11q)	HR 2.242	CI95% 1.46-3.45	**p<0.001**
+12	HR 1.321	CI95% 0.81-2.15	p=0.262
del(13q)	HR 0.813	CI95% 0.55-1.20	p=0.294





PFS in RV+GV+GIV: Univariate analysis of genetic subgroups

TP53 minor	HR 1.107	CI95% 0.49-2.49	p=0.805
BIRC3	HR 1.321	CI95% 0.92-1.89	p=0.126
NOTCH1	HR 1.813	CI95% 1.38-2.39	**p<0.001**
SF3B1	HR 1.357	CI95% 1.03-1.79	**p=0.032**
RAF/RAS	HR 1.715	CI95% 1.19-2.48	**p=0.004**
XPO1	HR 1.734	CI95% 1.19-2.53	**p=0.004**
RPS15	HR 0.840	CI95% 0.46-1.54	p=0.571
EGR2	HR 1.956	CI95% 1.27-3.01	**p=0.002**
MYD88	HR 0.801	CI95% 0.40-1.62	p=0.538
NFKBIE	HR 1.315	CI95% 0.93-1.86	p=0.121
del(11q)	HR 1.643	CI95% 1.23-2.20	**p<0.001**
+12	HR1.091	CI95% 0.79-1.51	p=0.596
del(13q)	HR 0.758	CI95% 0.59-0.97	**p=0.028**



PFS: Multivariable Analysis for CIT and RV+GV+GIV:

CIT

COX regression PFS	Univariable comparison	Hazard ratio	95% Confidence Interval		P value
			Lower	Upper	
Age (years)					
> 65	***vs.*** ≤ 65	2.162	1.433	3.261	< 0.001
IGHV mutational status					
Unmutated	***vs.*** Mutated	3.551	2.195	5.745	< 0.001
Complex karyotype					
CKT	***vs.*** NCKT	1.686	1.088	2.610	0.019
Bulky disease					
With	***vs.*** Without	1.545	1.008	2.370	0.046

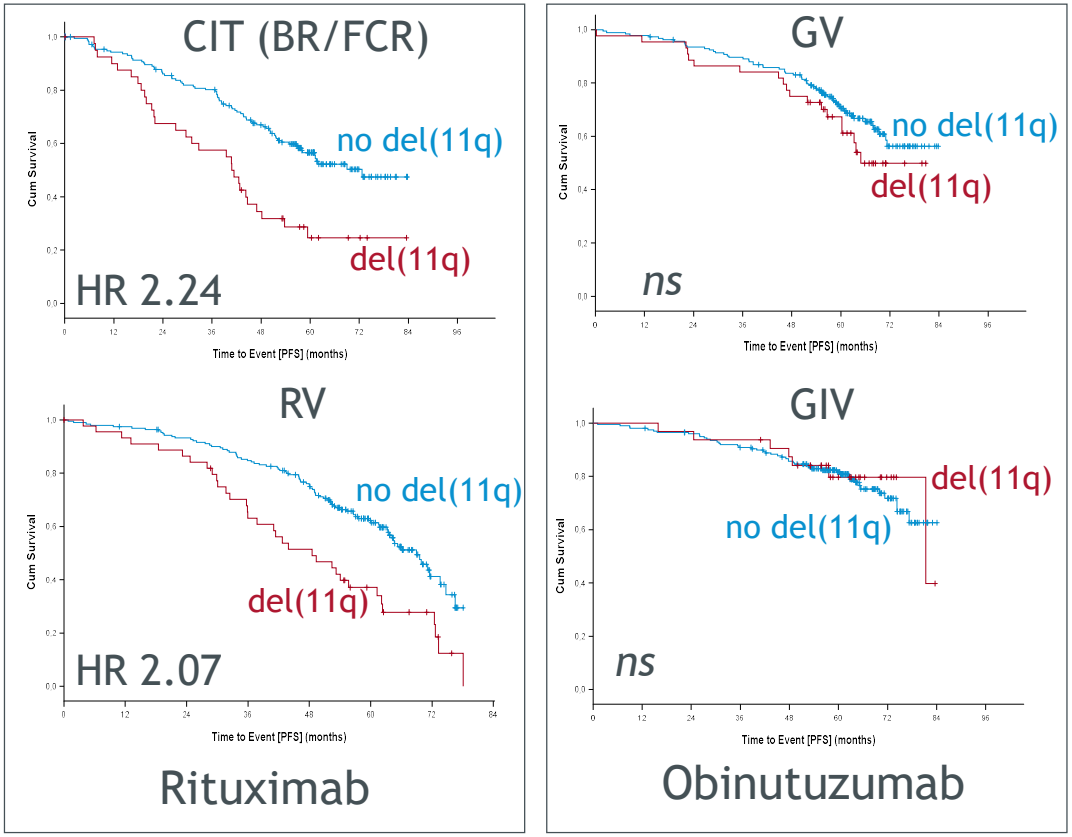
For CIT U-IGHV was the strongest independent prognostic factor followed by age, bulky disease and CKT (≥3 aberrations)

RV+GV+GIV

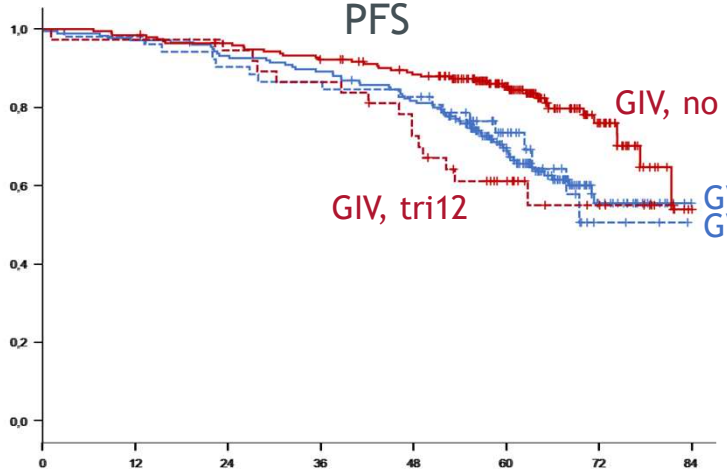
COX regression PFS	Univariable comparison	Hazard ratio	95% Confidence Interval		P value
			Lower	Upper	
IGHV mutational status					
Unmutated	***vs.*** Mutated	2.010	1.497	2.698	< 0.001
Complex karyotype					
CKT	***vs.*** NCKT	1.926	1.412	2.627	< 0.001
NOTCH1					
Mutated	***vs.*** Unmutated	1.563	1.164	2.100	0.003
EGR2					
Mutated	***vs.*** Unmutated	1.613	1.032	2.520	0.036

For Ven-based therapies mutated NOTCH1 and EGR2 were confirmed as independent prognostic factors for RV+GV+GIV in addition to CKT and U-IGHV

PFS: Single arm comparison reveals predictive impact in genetic subgroups



GV vs. GIV



GV - No tri12	177	172	163	156	142	87	22	0
GIV - No tri12	194	191	184	175	163	110	37	1
GV - tri12	52	51	47	45	43	22	3	0
GIV - tri12	37	36	35	32	26	16	7	0

Del(11q) with shorter PFS with Rituximab (CIT, RV), but not with Obinutuzumab (GV, GIVe).

No significant PFS benefit from GIV vs. GV for

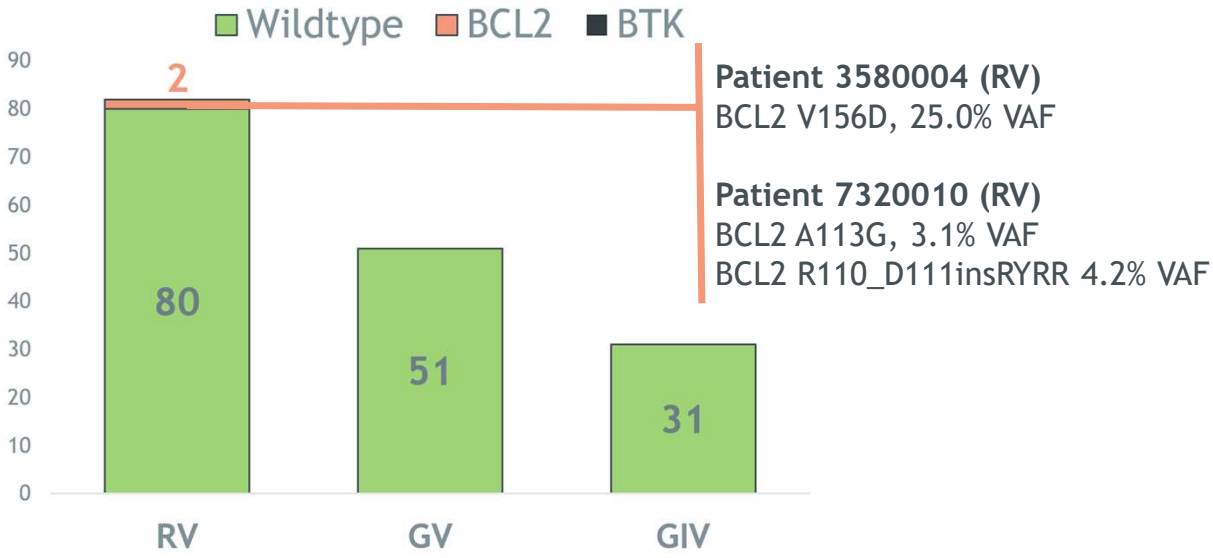
Subgroup	HR (GIV vs. GV)	CI95%
Trisomy 12 (tri12)	1.29	0.64-2.58
BIRC3 mutated	1.84	0.74-4.59
BRAF/NRAS/KRAS mutated	1.43	0.64-2.56

Acquired resistance mutations and genetic alterations at relapse

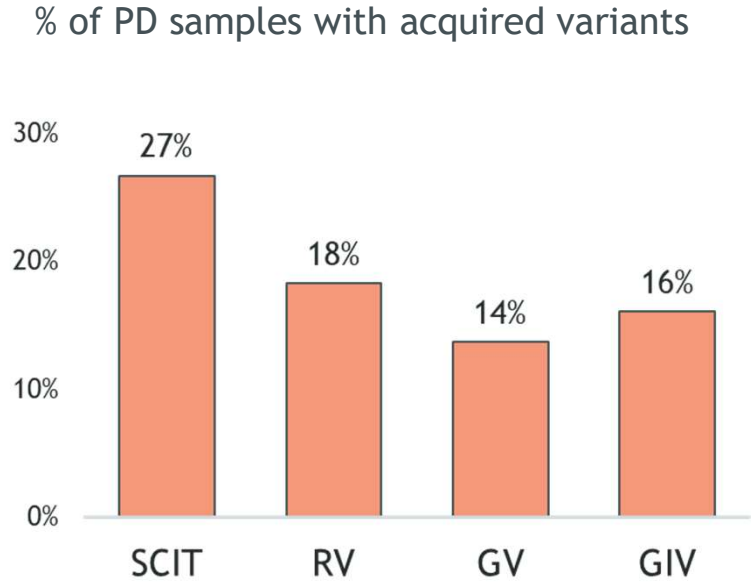
235 relapse samples analysed for acquired mutations

3 acquired BCL2 mutations in 2 relapses after RV (1.2%)

No acquired BTK or PLCG2 mutations

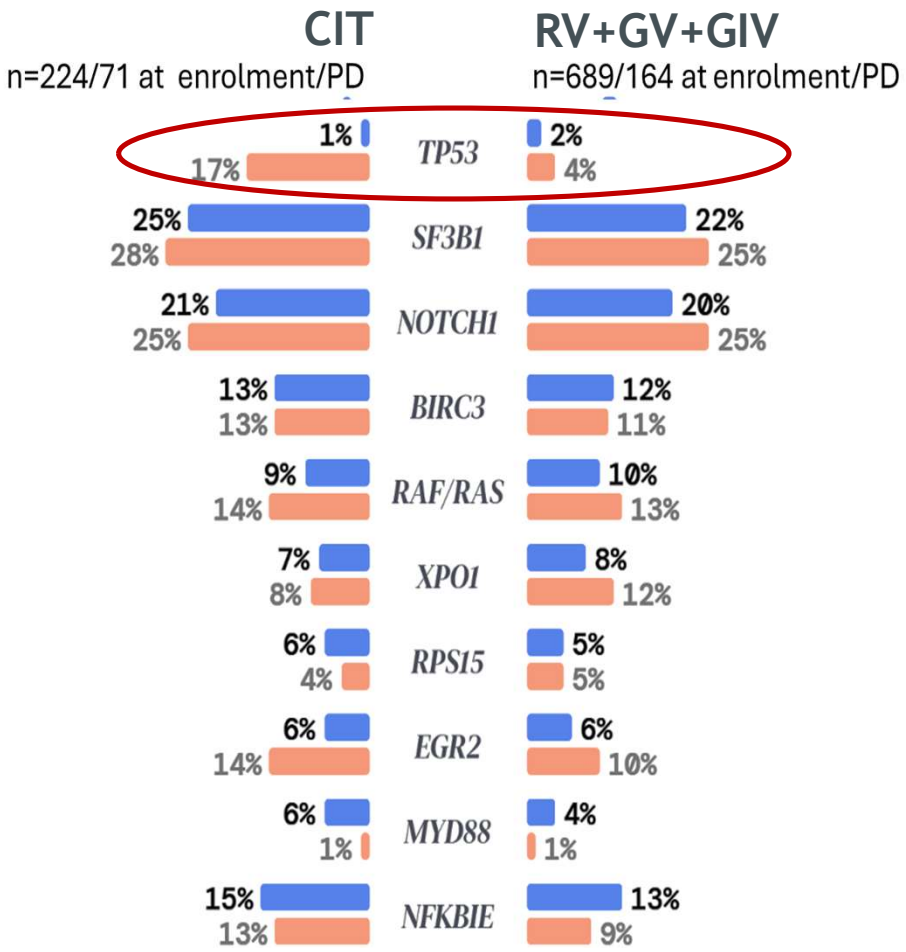


48 of 235 patients (20%)
with acquired mutations at disease progression

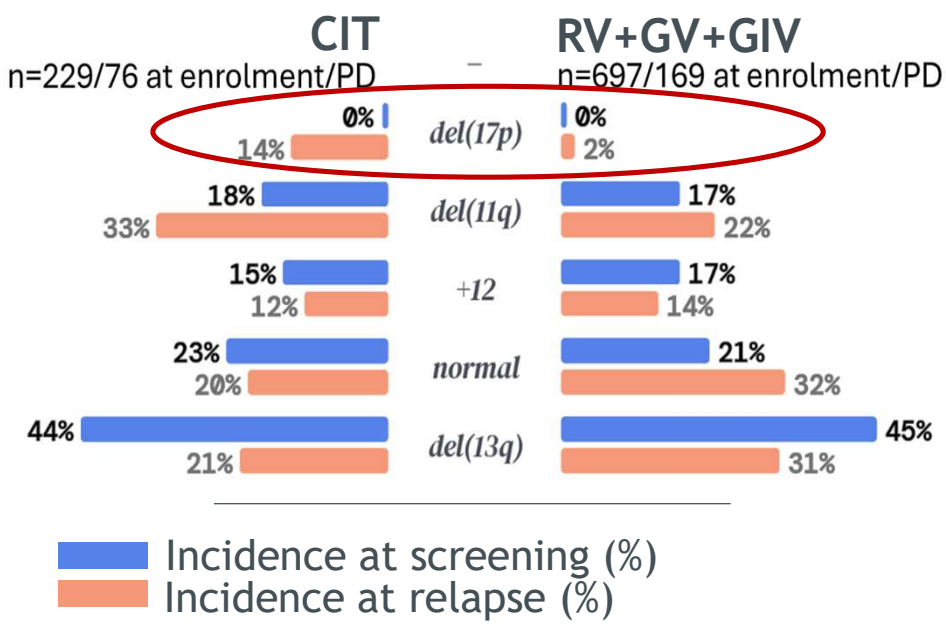


Gene mutation frequency at enrolment (blue) and progression (orange)

Molecular Genetics



Cytogenetics



TP53 mutation / del(17p) incidence increased to 17%/14% after CIT and 4%/2% after RV+GV+GIV

Summary

Beyond U-IGHV and complex karyotype, *NOTCH1* and *EGR2* mutations emerge as novel independent adverse prognostic factors for PFS in venetoclax-treated CLL.

Del(11q) confers significant PFS benefit from obinutuzumab-based regimens.

Clonal evolution of del(17p) and *TP53* mutations occurs markedly less frequently with venetoclax-based therapy compared to CIT.

Acquired resistance mutations at progression are rare – at 1% for BCL2 and absent for BTK/PLCG2 - supporting venetoclax retreatment strategies.

Acknowledgements

ulm university universität ulm

Stephan Stilgenbauer
Christof Schneider
Billy Jebaraj
Deyan Yosifov
Armin Riecke

HOVON · Nordic CLL Study Group · cancer trials ireland

Arnon Kater
Karsten Niemann
Patrick Thornton
Michael Gregor
Tamar Tadmor
Philipp Staber

Patients of the CLL13/GAIA trial and their families

UNIVERSITÄTS KLINIKUM ulm

DEUTSCHE STUDIENGRUPPE

Barbara Eichhorst
Moritz Fürstenau
Paula Cramer
Petra Langerbeins
Julia v. Tresckow
Kirsten Fischer
Othman Al-Sawaf
Anna Fink
Sandra Robrecht
Adam Giza
Rudy Ligtvoet
Michael Hallek
GCLLSG Central lab
Matthias Ritgen
Anke Schilhabel
Karl-Anton Kreuzer