POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

Leucemia linfatica cronica: biologia e prognosi

Gianluca Gaidano, M.D., Ph.D.

Division of Hematology
Department of Translational Medicine
Università del Piemonte Orientale
Novara, Italy

DICHIARAZIONE

Gianluca Gaidano

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Abbvie, Astra Zeneca, BeiGene, Incyte, Janssen, Roche)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Agenda

- Prognostic markers in the CLL13 clinical trial
- Prognostic markers in fixed-duration ibrutinib + venetoclax clinical trials
- Novel insights into the biology of Richter syndrome

Agenda

Prognostic markers in the CLL13 clinical trial:

- #345: Eugen Tausch et al., Genetic Markers and Front Line FCR/BR Vs. Rve, Gve and Give Treatment – Outcome Results from the CLL13/GAIA Trial

- #346: Moritz Furstenau et al., High Karyotypic Complexity and Translocations Are Adverse Prognostic Features in Patients with Chronic Lymphocytic Leukemia without TP53 Aberrations Treated with Venetoclax-Based Time-Limited Combinations

CLL13 trial design and primary endopoint

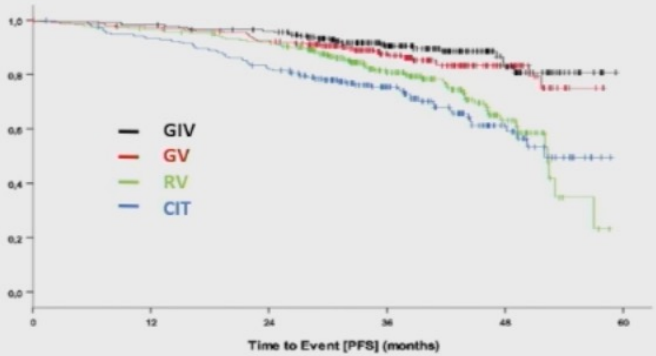
Eligibility

Treatment-naive, fit patients with CLL, **no *TP53*** aberrations (**centrally screened**)

- **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 endpoint analysis, PFS

Data cut 01/22, median OT: 38.8 mo, n=926



GIV vs CIT: **HR 0.32**, 97.5% CI 0.19-0.54, ***p<0.000001***

GV vs CIT: **HR 0.42**, 97.5% CI 0.26-0.68, ***p<0.0001***

RV vs CIT: HR 0.79, 97.5% CI 0.53-1.18, p=0.183

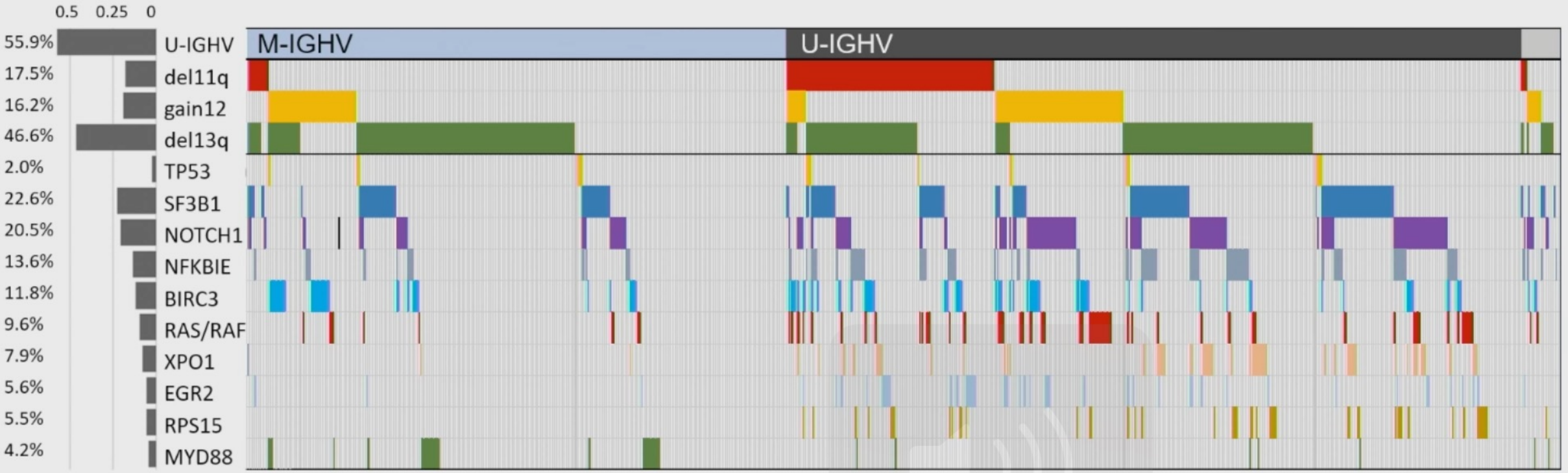
GV and GIV are superior to CIT

Main concept: CIT *versus* pathway inhibitors + anti-CD20

1. Eichhorst B, *et al.* EHA annual meeting 2022

Mutational landscape of patients enrolled in the CLL13 trial

Cytogenetics were assessed via **FISH** in 926/926 (100%) patients,
IGHV with homology threshold of <98% in **925/926 (100%)** cases and
gene mutations via tNGS in **913/926 (98.6%)** of patients for the genes *TP53, NOTCH1, SF3B1, MYD88, BIRC3, XPO1, NFKBIE, EGR2, NRAS, KRAS, BRAF and RPS15.*



- The mutation landscape was as expected based on the clinical trial inclusion criteria (CLL requiring treatment; TP53 wt)
- The few TP53 positivities are due to low sensitivity of local screening procedures

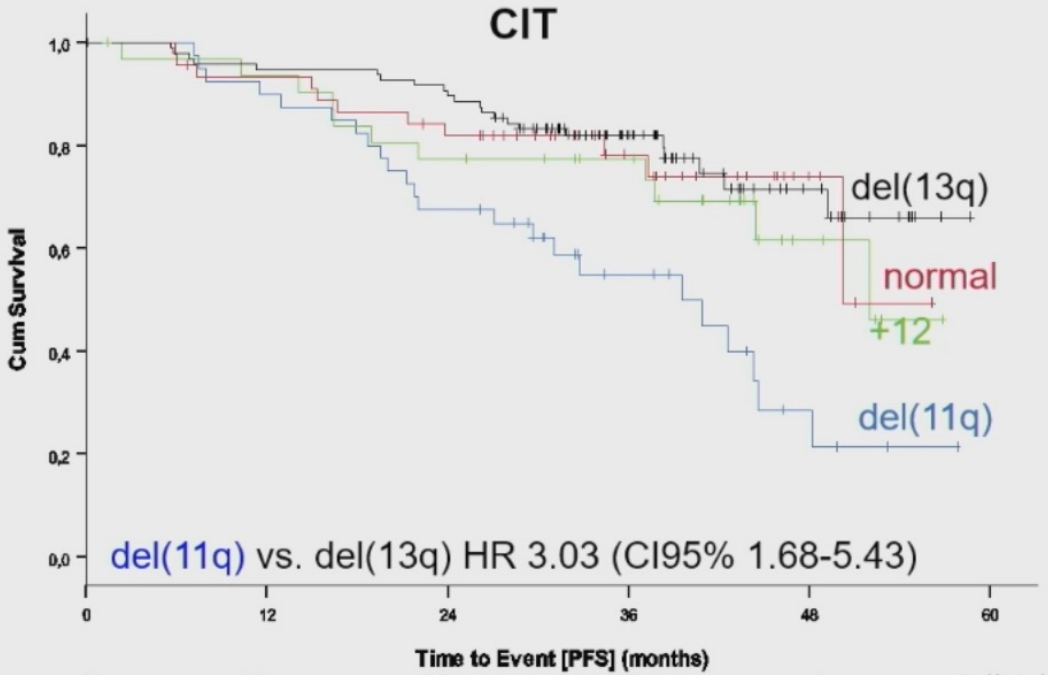
Tausch *et al.*, #345

Prognostic impact of FISH karyotype in the CLL13 trial

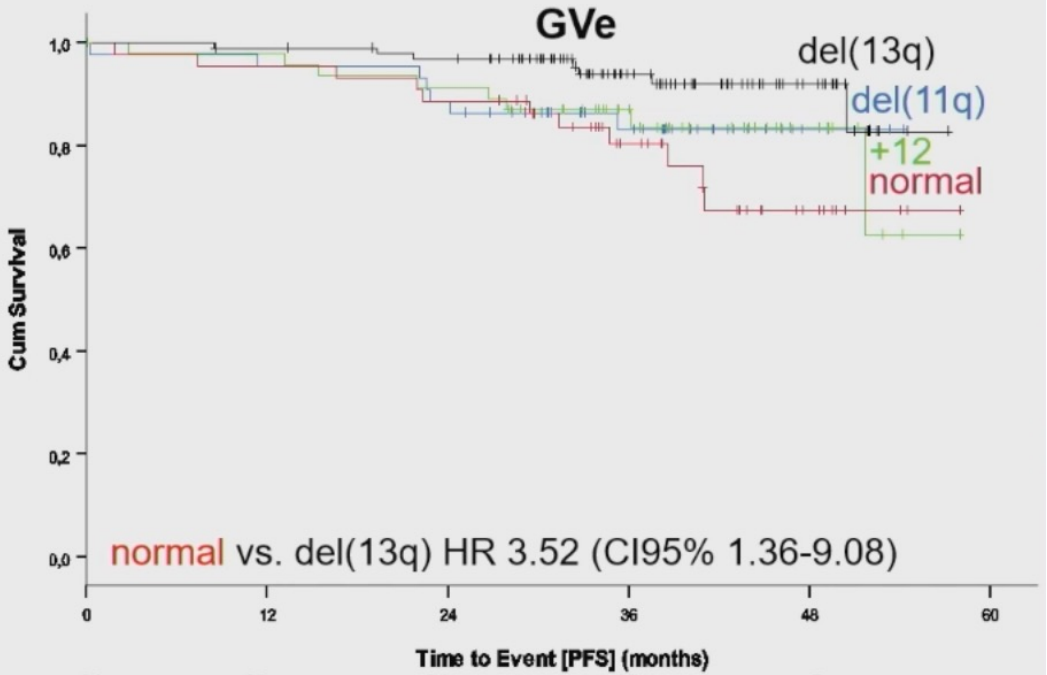
At a median follow up of 38.8 months 188 PFS events were observed.

Del(11q) was only associated with shorter PFS when treated with CIT, but not with RVe/GVe/GIVe.

Del(13q) was associated with signicantly longer PFS with GVe therapy.



Del(11q)	41	36	27	13	4
Tris 12	34	29	24	20	5
Normal	53	41	35	19	5
Del(13q)	101	91	86	46	14

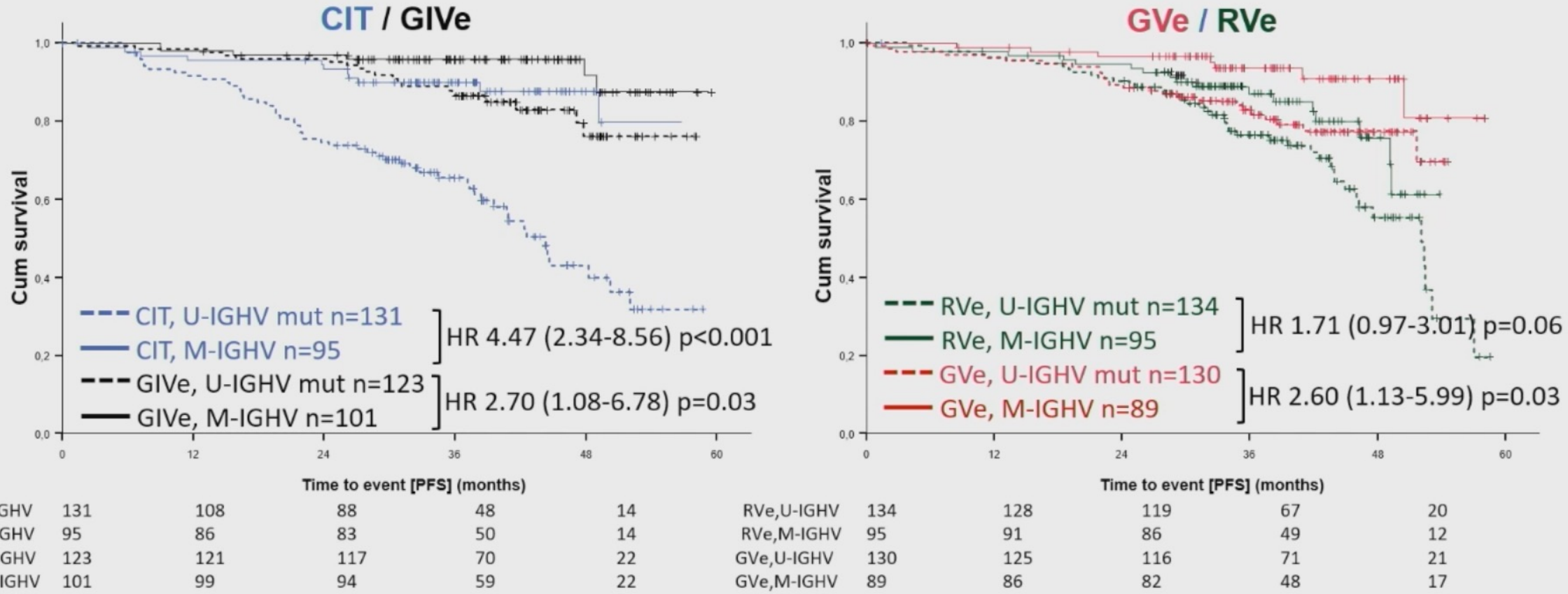


Del(11q)	44	42	39	25	5
Tris 12	47	45	42	26	9
Normal	44	42	39	23	8
Del(13q)	94	92	88	51	20

Tausch *et al.*, #345

Prognostic impact of IGHV in the CLL13 trial

IGHV associated with shorter PFS for all treatment arms with highest difference between U-IGHV and M-IGHV with CIT.



CIT,U-IGHV	131	108	88	48	14
CIT,M-IGHV	95	86	83	50	14
GIVe,U-IGHV	123	121	117	70	22
GIVe,M-IGHV	101	99	94	59	22

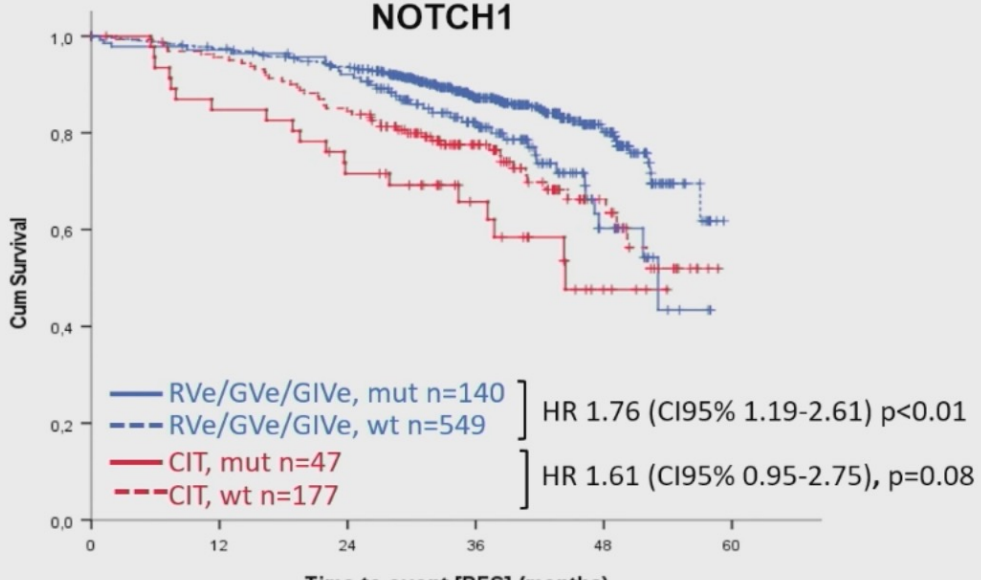
RVe,U-IGHV	134	128	119	67	20
RVe,M-IGHV	95	91	86	49	12
GVe,U-IGHV	130	125	116	71	21
GVe,M-IGHV	89	86	82	48	17

IGHV mutation status maintains its prognostic impact in fixed duration regimens

Tausch *et al.*, #345

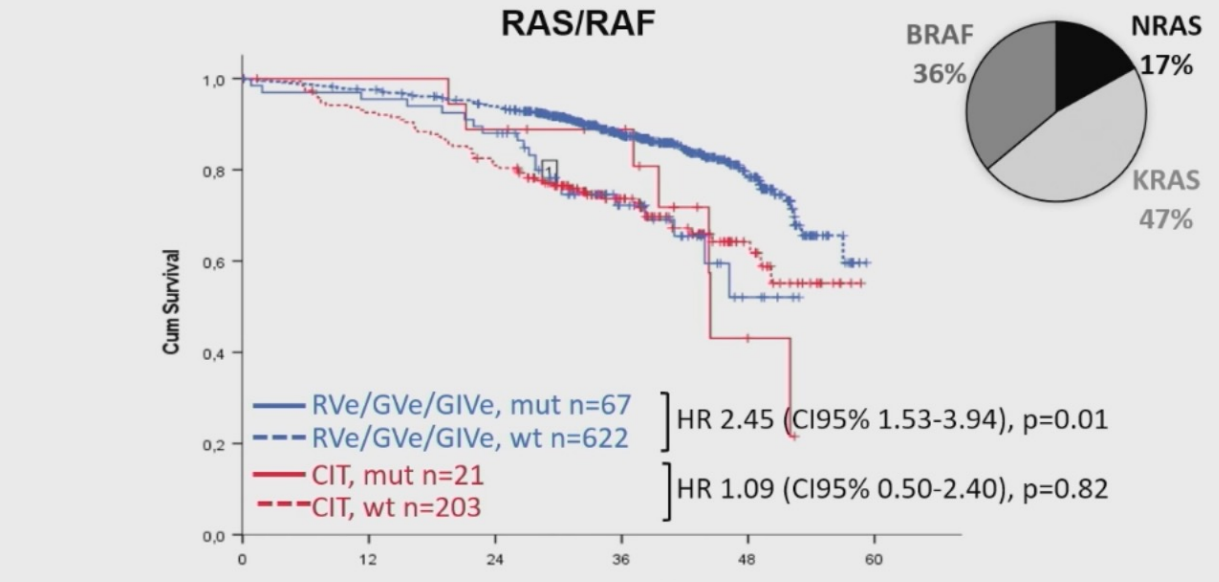
Prognostic impact of *NOTCH1* and *RAS/RAF* mutations in the CLL13 trial

Patients with *NOTCH1* mutation had a shorter PFS with CIT and RVe/GVe/GIVe.



CIT, wt	177	154	136	77	24
CIT, mut	47	39	32	18	4
RVe/GVe/GIVe, wt	549	531	502	296	100
RVe/GVe/GIVe, mut	140	136	128	75	17

Patients with mutations in RAS/RAF had shorter PFS when treated with RVe or GIVe.

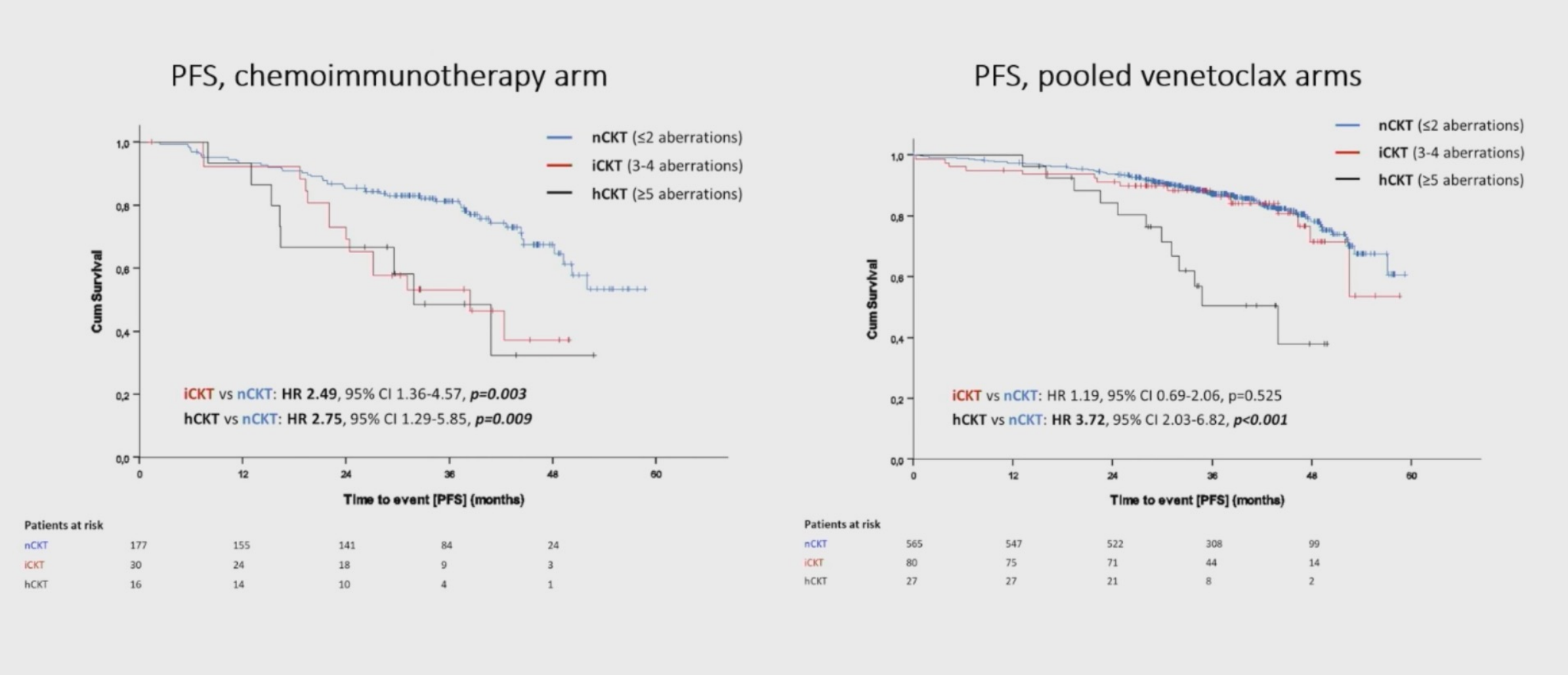


CIT, wt	203	175	152	83	26
CIT, mut	21	18	16	12	2
RVe/GVe/GIVe, wt	622	603	571	343	112
RVe/GVe/GIVe, mut	67	64	59	28	5

- **NOTCH1 and RAS/RAF mutations appear to be prognostic biomarkers in fixed duration therapy**
- **But: which predictive value?**

Tausch *et al.*, #345

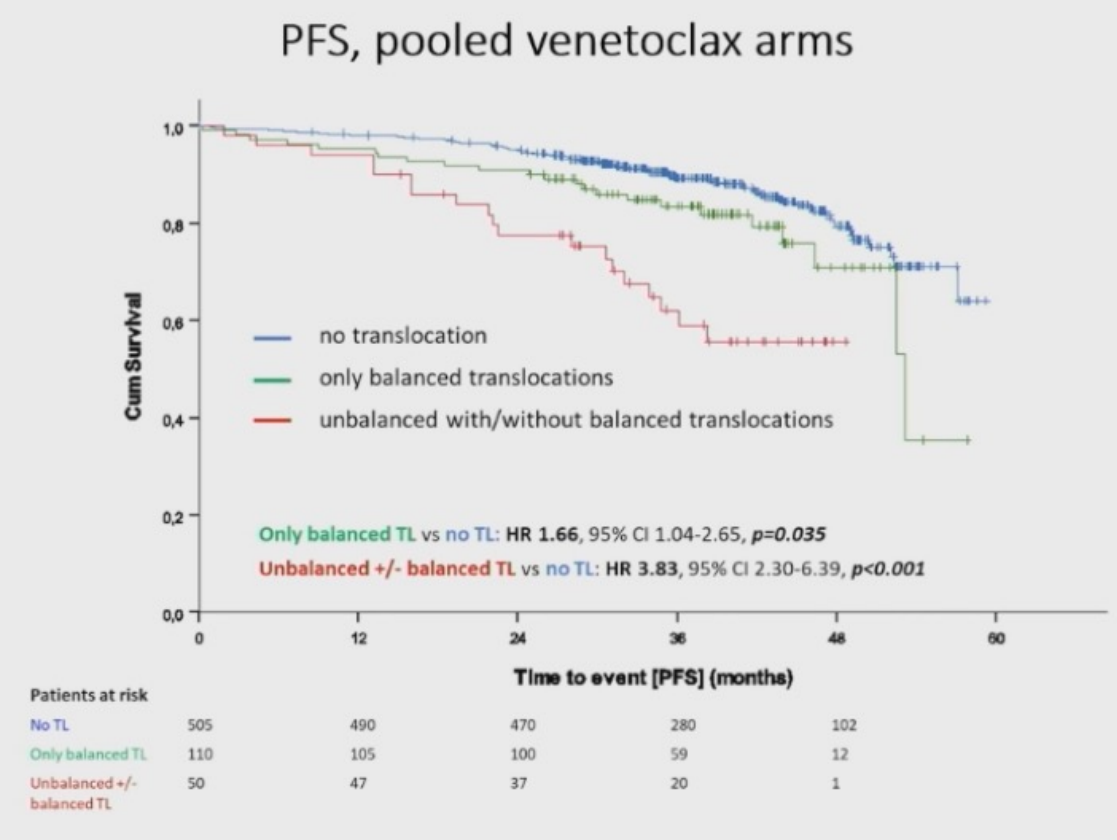
Prognostic impact of complex karyotype in the CLL13 trial

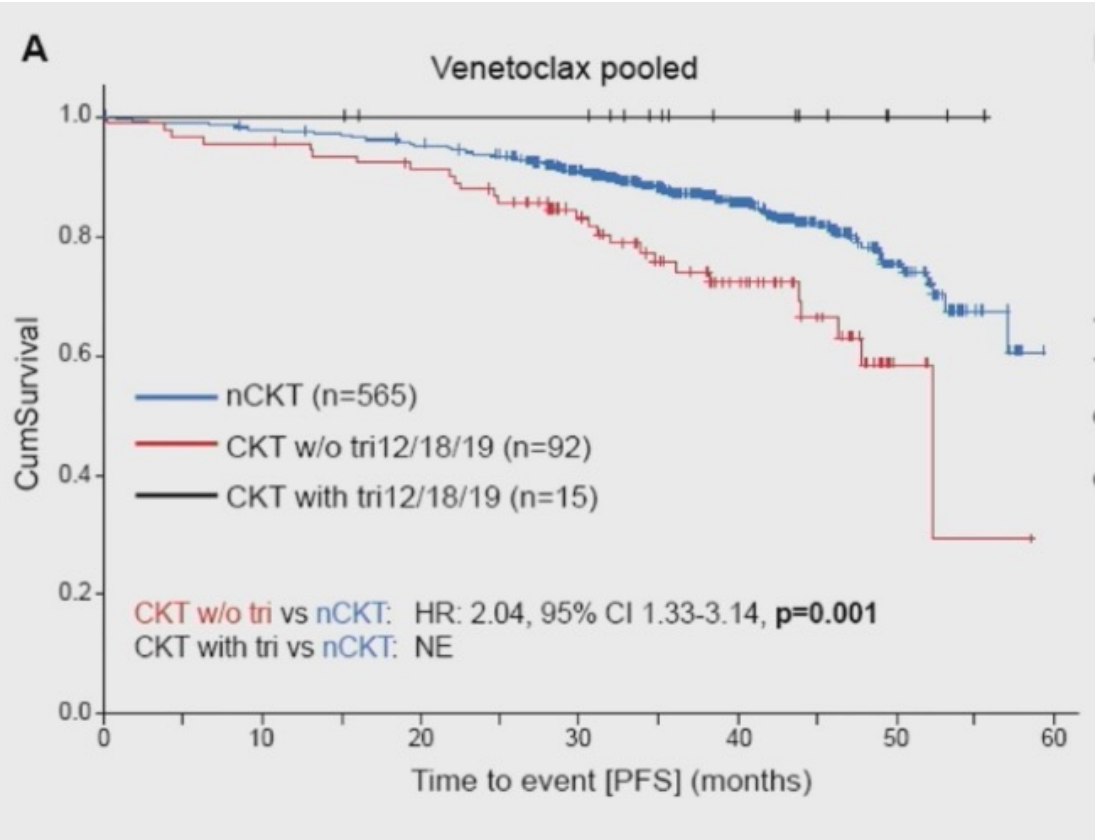


- The evaluation of complex karyotype in the CLL13 trial provides evidence of the clinical impact of complex karyotype beyond *TP53* disruption (exclusion criteria of the trial)
- Compared to the CIT arms in which ≥3 aberrations associated with shorter outcome, in venetoclax arms only patients with ≥5 aberrations are associated with shorter outcome

Furstenau *et al.*, #346

Prognostic impact of translocations/trisomies in the venetoclax arms





- Both balanced and unbalanced translocations are associated with shorter PFS in the pooled venetoclax arms
- **The presence of multiple trisomies (i.e. tris12/18/19) associated with favourable outcomes independent of the presence of complex karyotype in pts treated with venetoclax**

Furstenau *et al.*, #346

Agenda

Prognostic markers in ibrutinib + venetoclax clinical trials:

- #91: Talha Munir et al., MRD4 Eradication at 6 Months and Early Clearance of MRD with Combination of Ibrutinib Plus Venetoclax Results in Sustained Clinical and MRD Responses: Exploratory Analysis of the **Blood Cancer UK TAP Clarity Study**

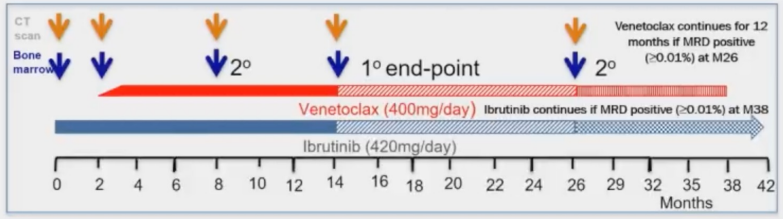
- #92: John Allan et al., Treatment Outcomes after Undetectable MRD with First-Line Ibrutinib (Ibr) Plus Venetoclax (Ven): Fixed Duration Treatment (Placebo) Versus Continued Ibr with up to 5 Years Median Follow-up in the **CAPTIVATE Study**

- #93: Carsten Niemann et al., Residual Disease Kinetics Among Patients with High-Risk Factors Treated with First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): **The Glow Study**

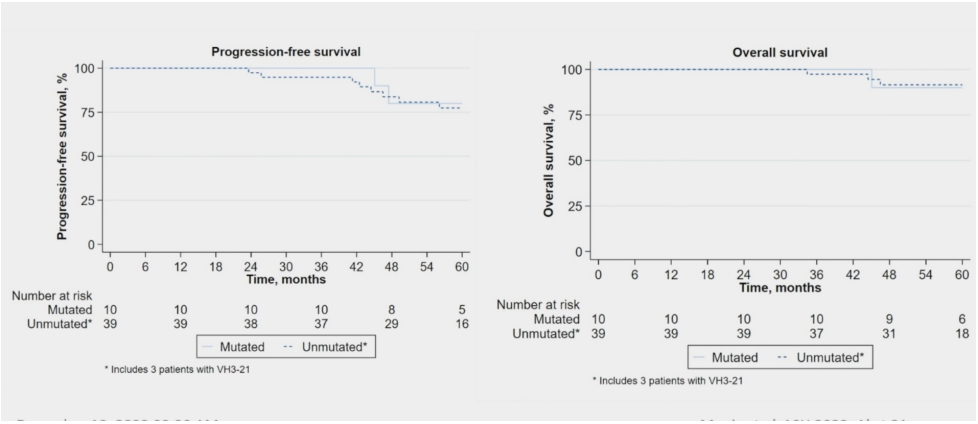
Prognostic impact of IGHV status: evidence from phase 2 clinical trials

TAP Clarity Study

R/R CLL

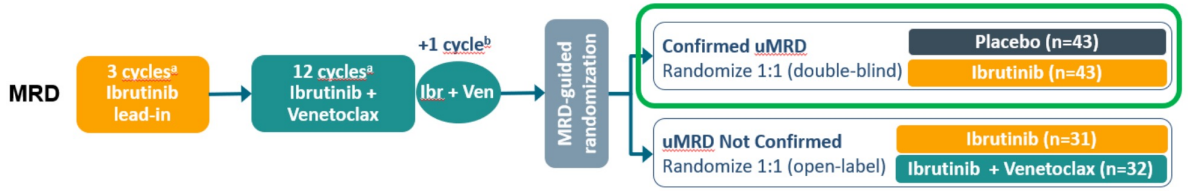


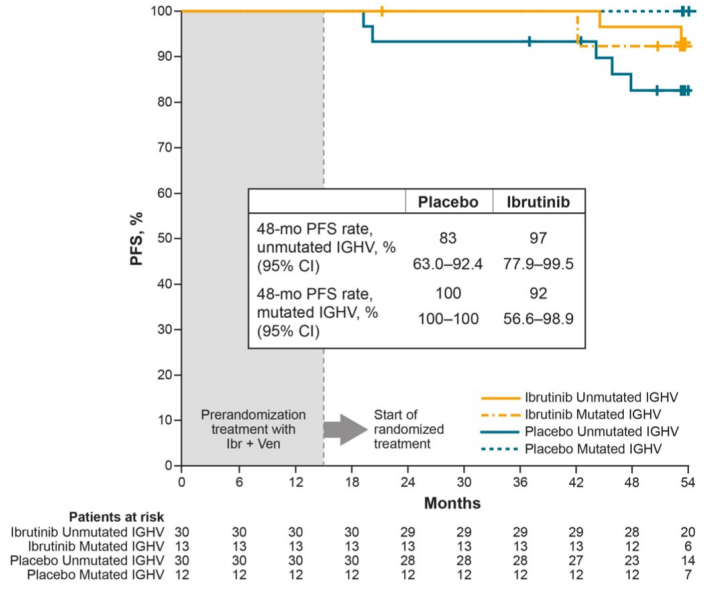
Duration of VEN therapy: 3 consecutive MRD4 (<0.01% CLL) in PB confirmed in BM:
MRD <0.01% at M8 → stop I+V at M14; MRD <0.01% at M14 → stop I+V at M26
MRD negative (<0.01%) at M26 → stop I+V at M26, if MRD positive (≥0.01%) continue IBR till PD
Amendment: if MRD positive (≥0.01%) at M26, Additional Ven for 12 months.



CAPTIVATE trial

1st line CLL <70 years



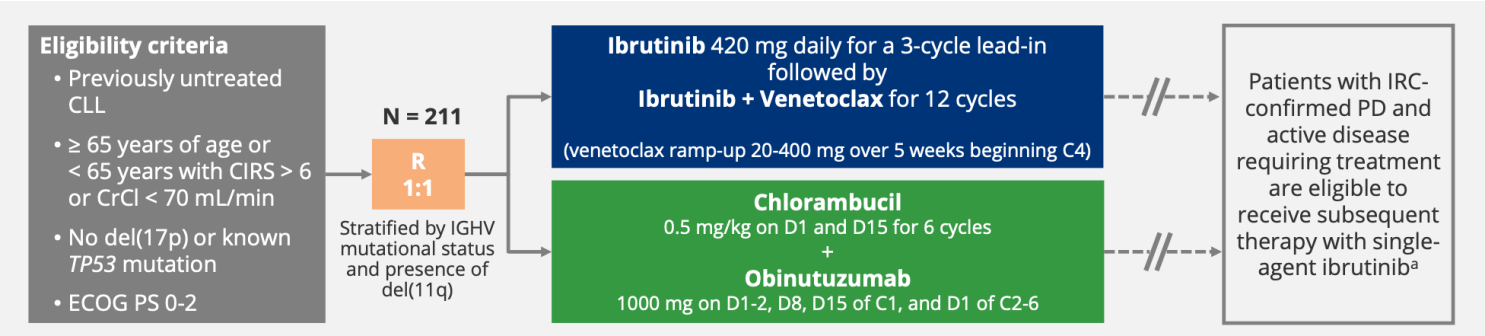


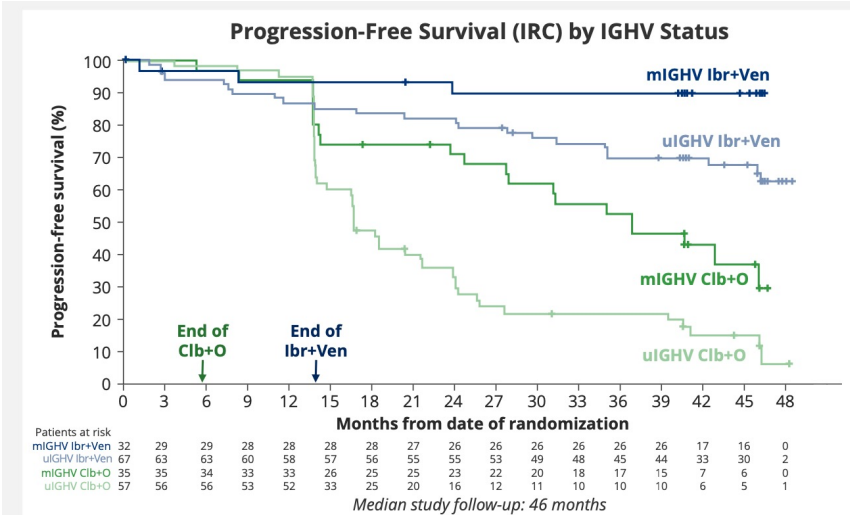
- At 48 months, PFS rates among patients with unmutated IGHV were similar to those of the total population

Fixed duration ibrutinib + venetoclax overcomes the prognostic impact of IGHV status in both R/R CLL patients and in 1st line CLL patients aged <70 years

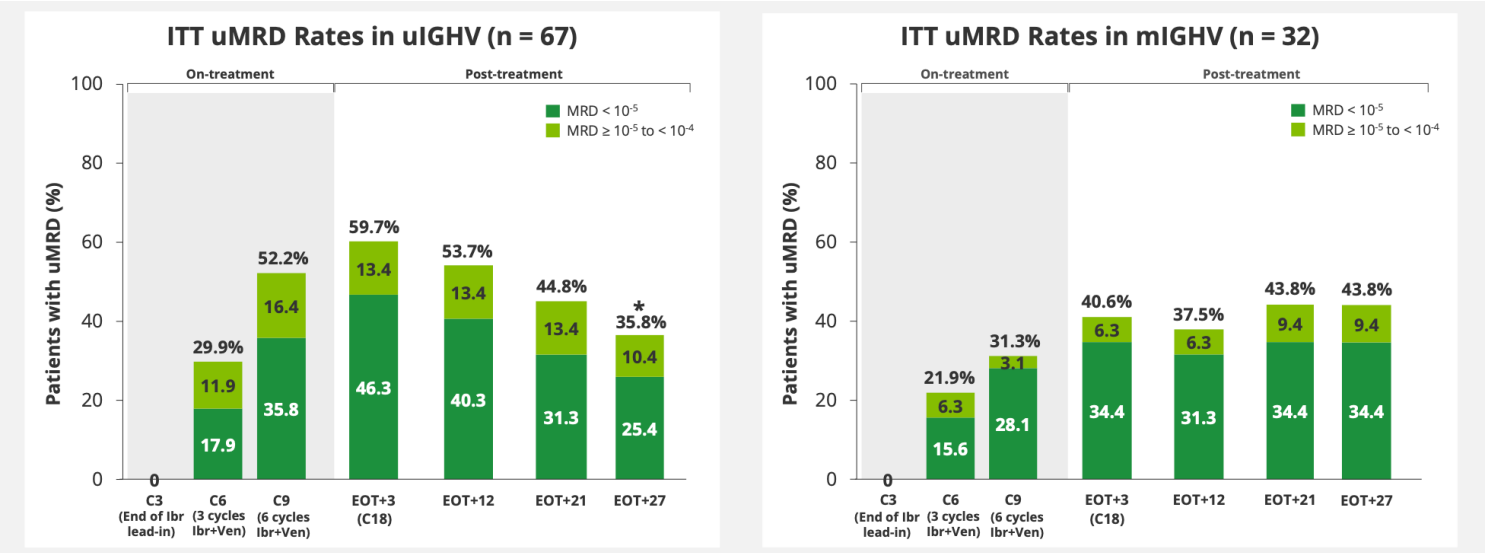
Munir *et al.*, #91; Allan *et al.*, #92

Prognostic impact of IGHV status: evidence from the GLOW phase 3 trial



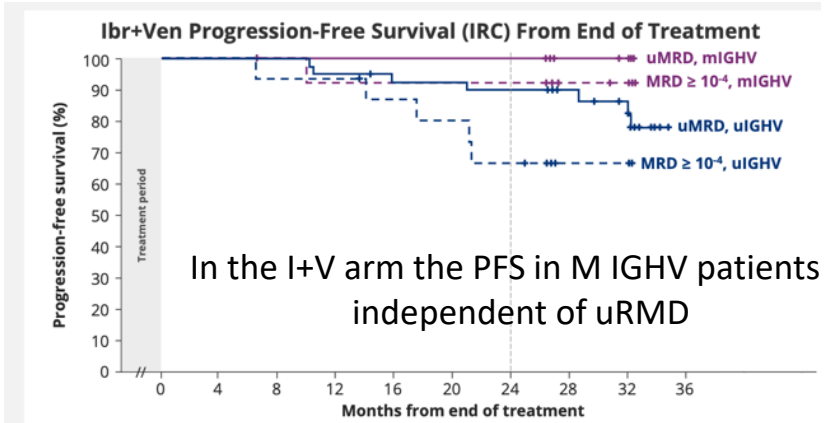


MRD analysis in the I+V arm



- uMRD rates were higher and achieved faster in UM IGHV CLL
- However, uMRD was better sustained post-treatment in M IGHV CLL

- IGHV predict outcomes in both treatment arms but was more pronounced in the Clb+O arm
- However, in the I+V arm the TTNT was similar in UM and M IGHV patients (at 3.5 years 91.5% and 93.5, respectively).



Niemann *et al.*, #93

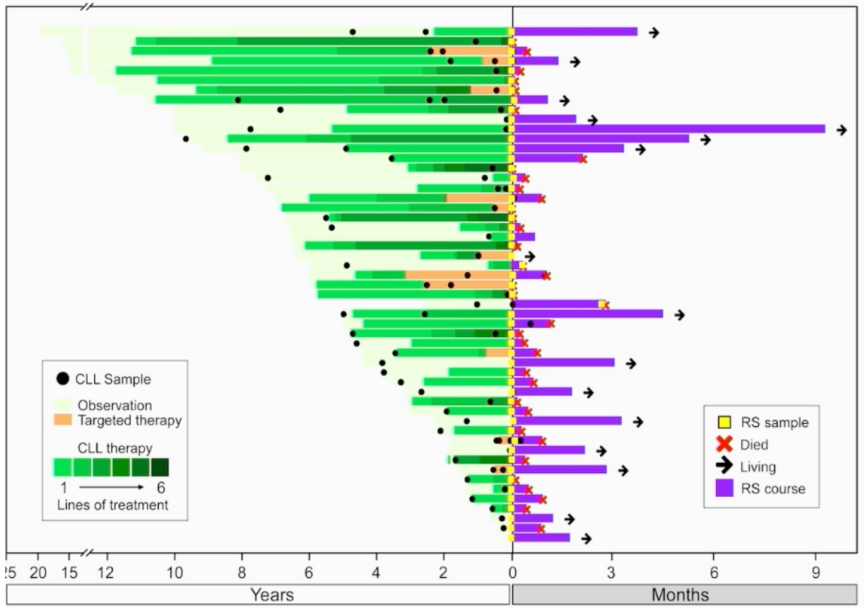
Agenda

Novel insights into the biology of Richter syndrome:

- #633: Erin Parry et al., Evolutionary History of Transformation from Chronic Lymphocytic Leukemia to Richter Syndrome

- #636: Elisa Ten Hacken et al., Immuno-Genetic Changes Underlie Response to Immune Checkpoint Blockade Therapy in Richter's Syndrome Mouse Models

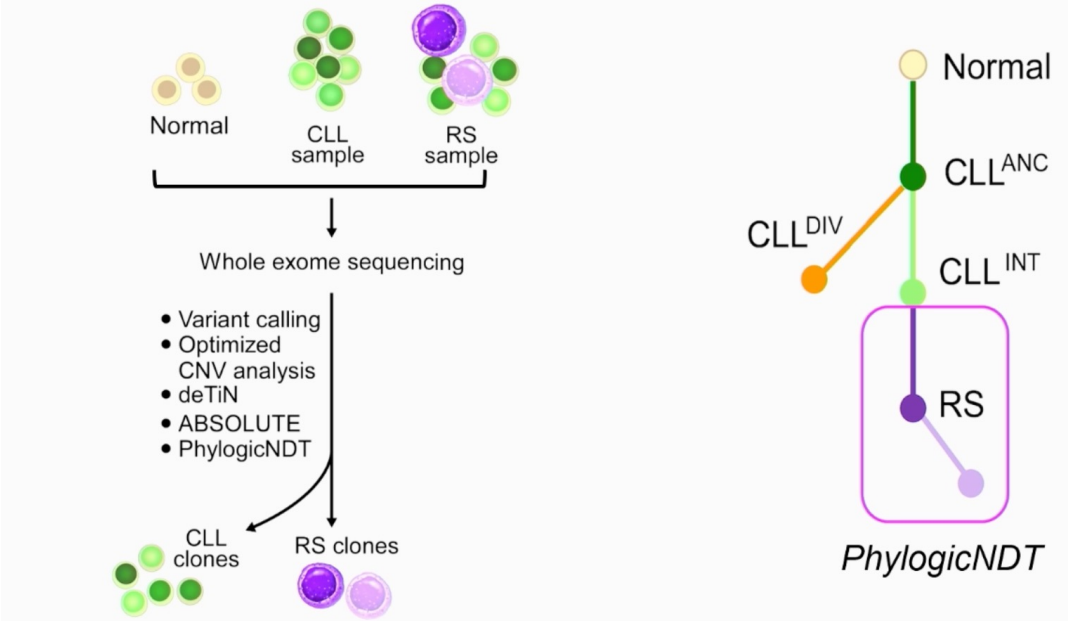
Experimental work-flow



Discovery Cohort **N=53** (WES)
Ulm, Germany
Dana-Farber Cancer Institute
Mayo Clinic
FILO
UCSD
MDACC

Validation Cohort **N=45** (WES/RNA)
FILO

Validation Cohort **N=14** (WGS)
Klintman et al, *Blood* 2021

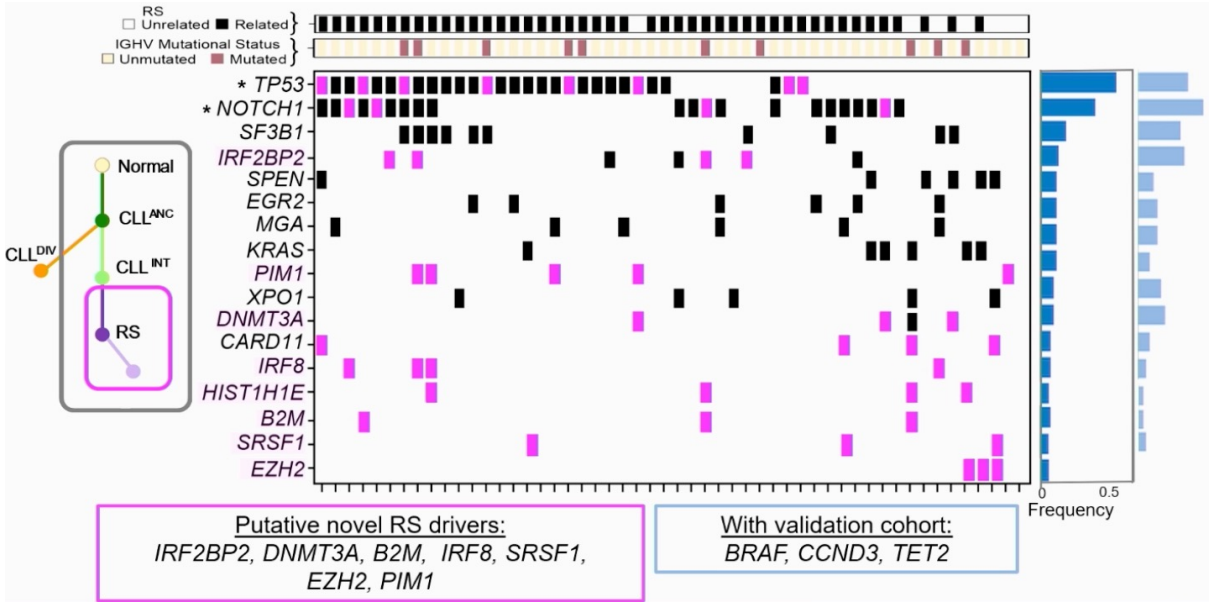


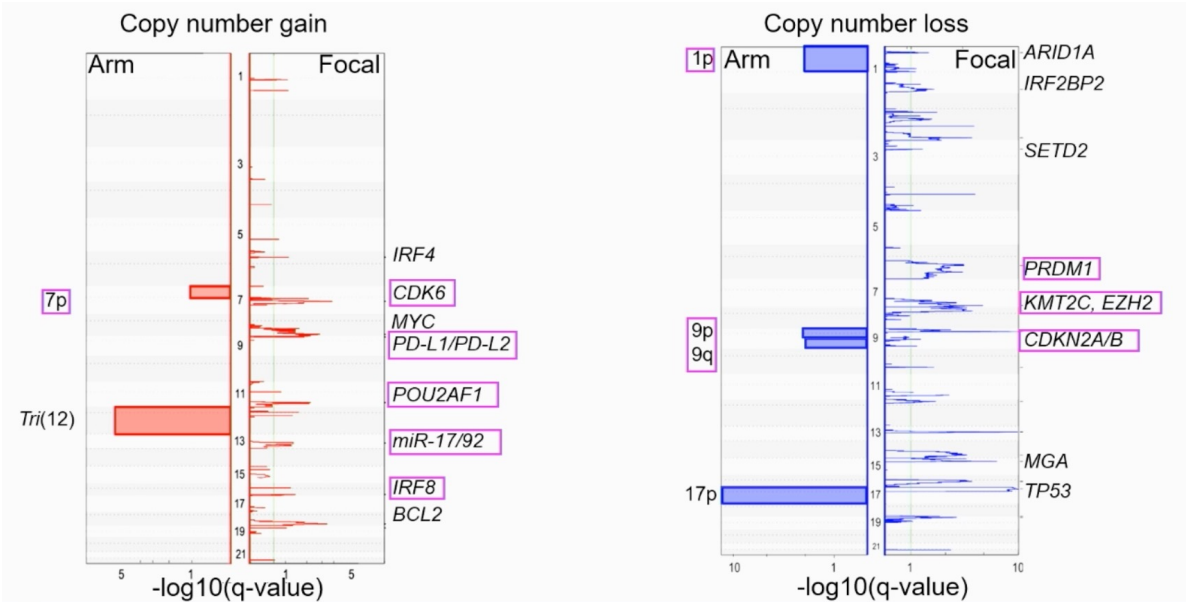
- Multicenter cohorts of CLL patients transformed into RS provided with both phases were analysed with different genomic approaches

- Bioinformatic tools have been applied to deconvolute the different cellular subtypes

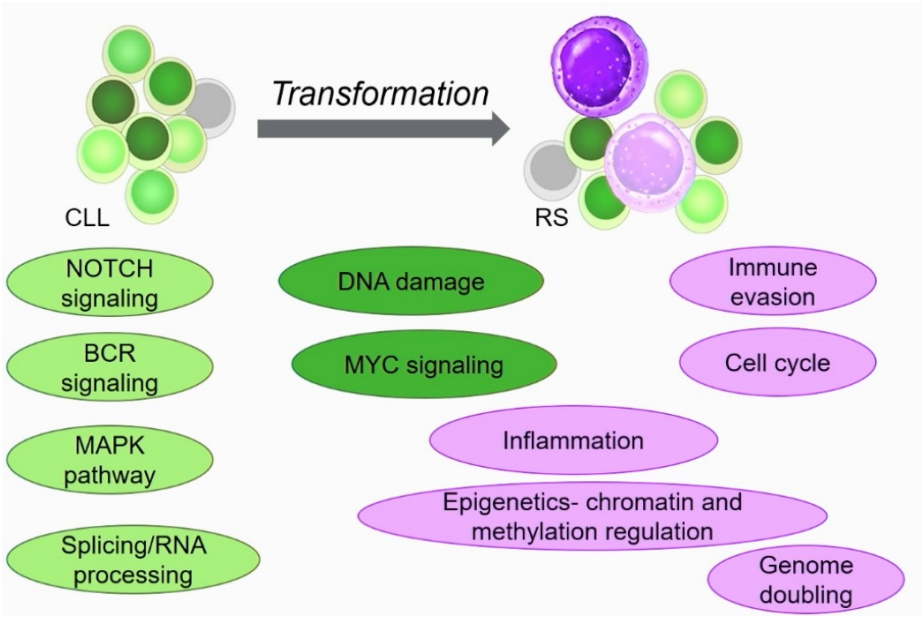
Parry *et al.*, #633

Differences in the genomic and transcriptomic profile between CLL and Richter





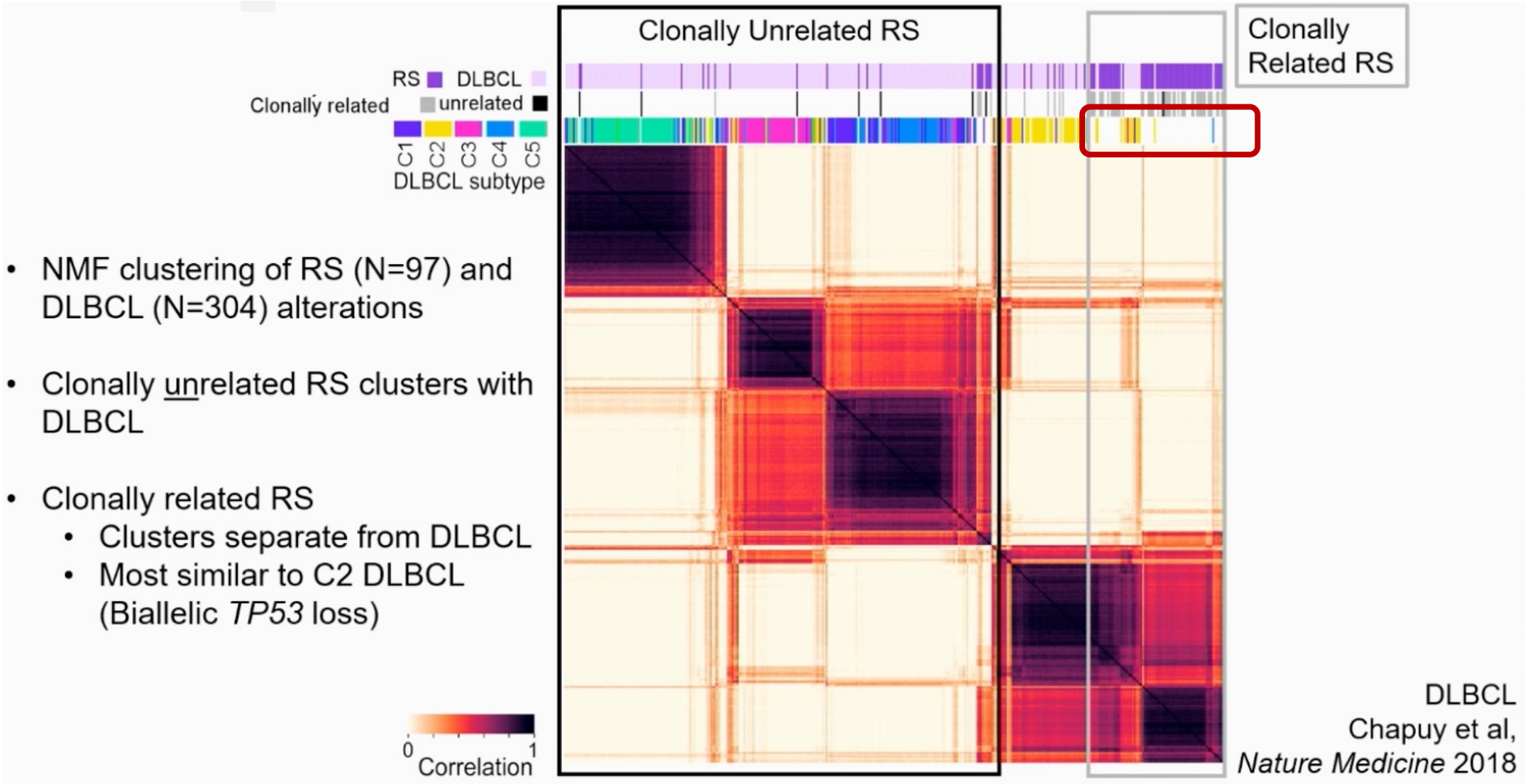
Pathways preferentially involved in CLL



Pathways preferentially involved in Richter

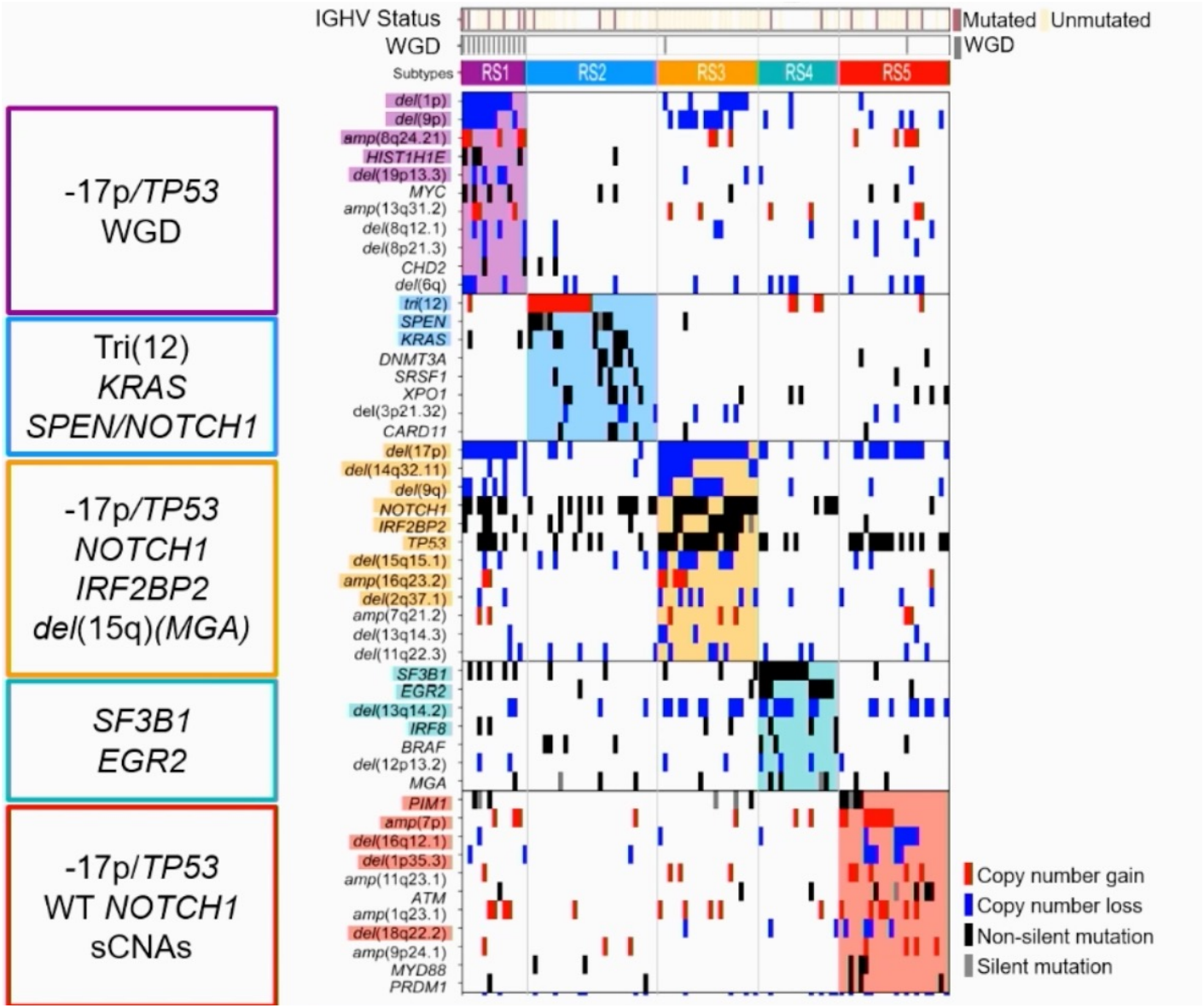
Parry *et al.*, #633

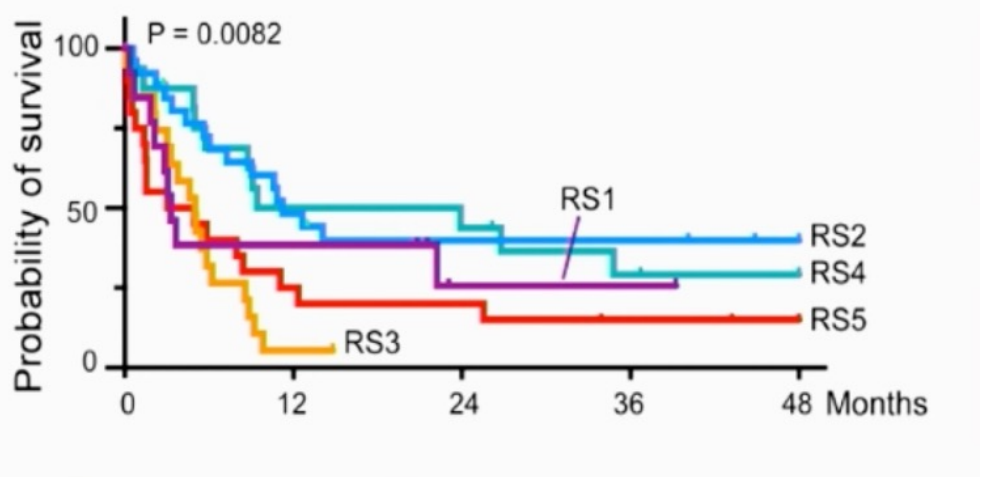
Clonally related RS belongs to different clusters compared to *de novo* DLBCL



- NMF clustering of RS (N=97) and DLBCL (N=304) alterations
- Clonally unrelated RS clusters with DLBCL
- Clonally related RS
  - Clusters separate from DLBCL
  - Most similar to C2 DLBCL (Biallelic *TP53* loss)

Molecular composition and clinical impact of RS clusters

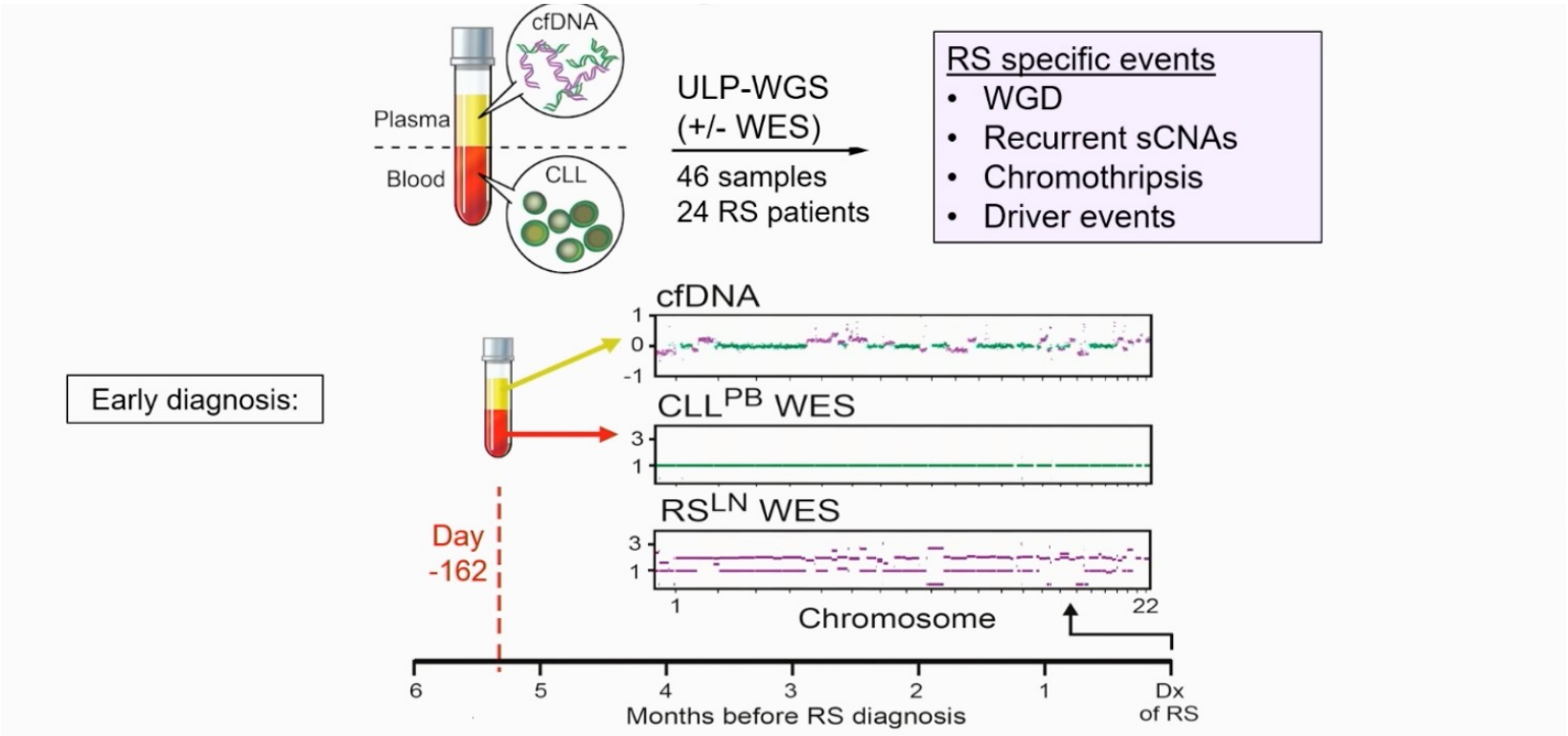




- 5 different RS subtypes have been identified
- 3 clusters are characterised by *TP53* abnormalities (RS1, RS3, RS5) and associated with worse outcome
- 2 clusters are not characterised by *TP53* abnormalities (RS2 and RS4) and associated with better prognosis

Parry *et al.*, #633

Toward early detection of RS?



- cfDNA has been analysed by ultra low pass-WGS

- In patients who will develop RS, molecular abnormalities typical of RS (i.e. whole genome duplication, chromothripsis) were already detectable in plasma several months before RS diagnosis

Parry *et al.*, #633

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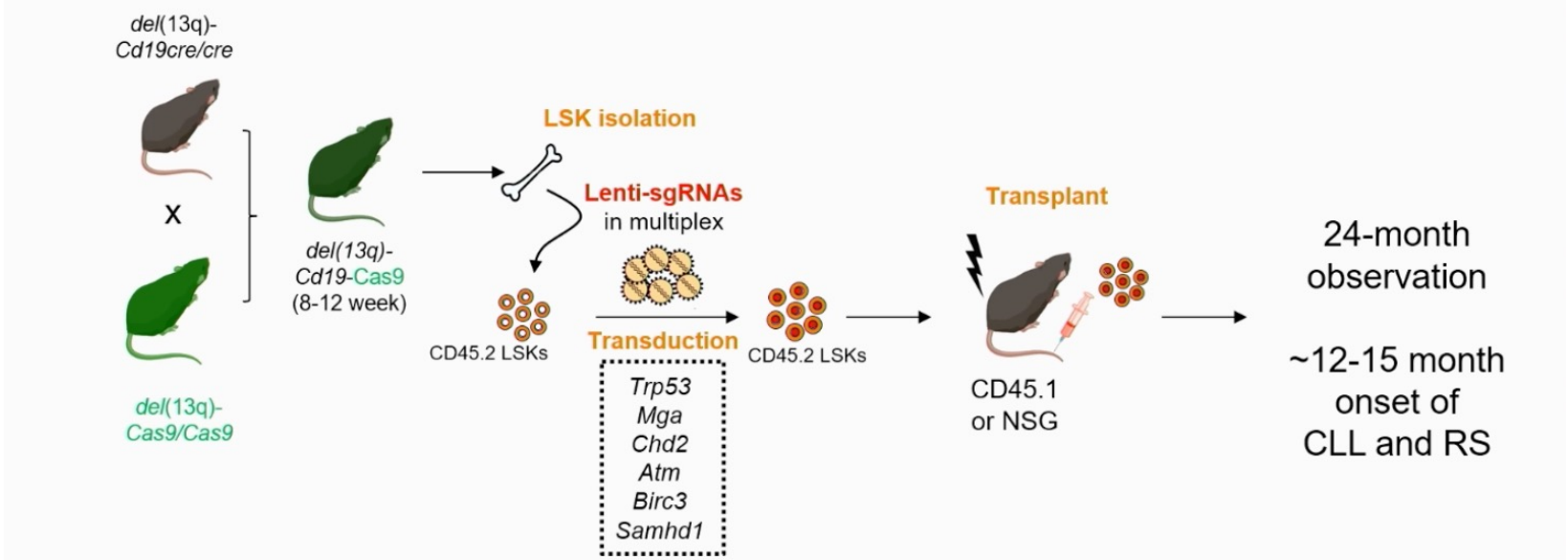
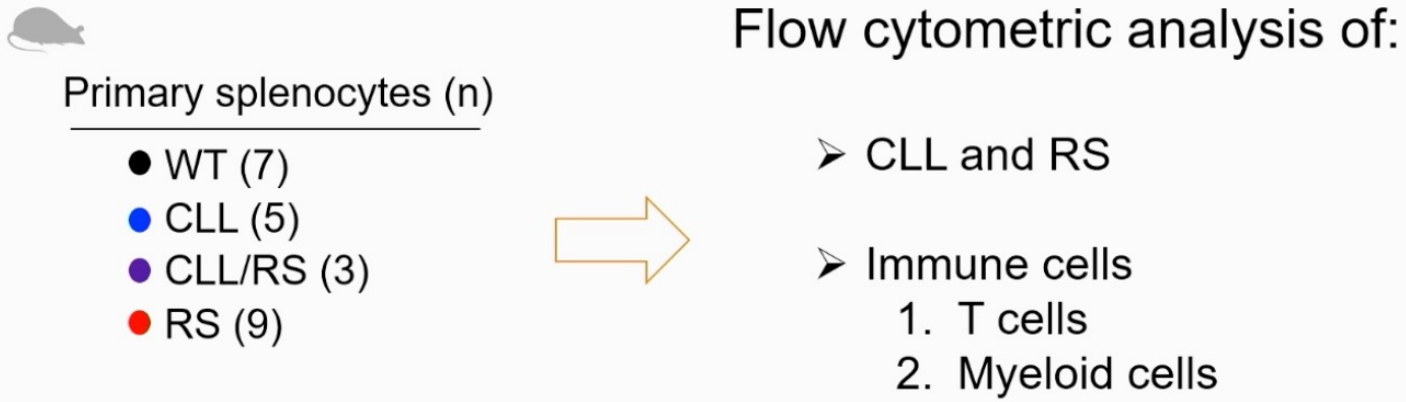
Experimental workflow



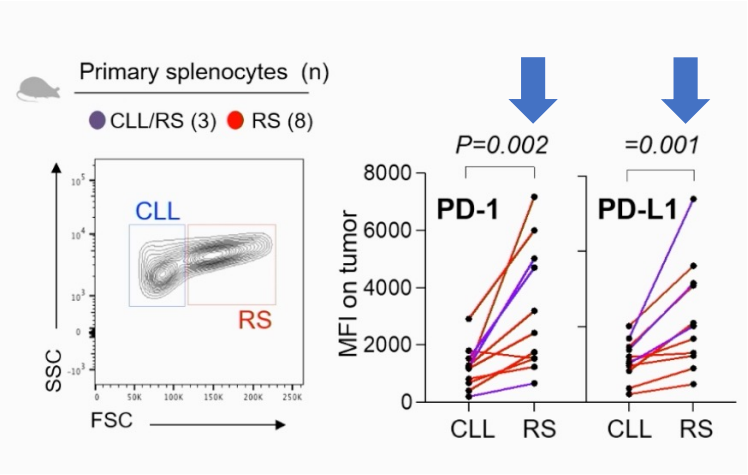


- Generation of mouse models that reflect the CLL transformation into Richter syndrome

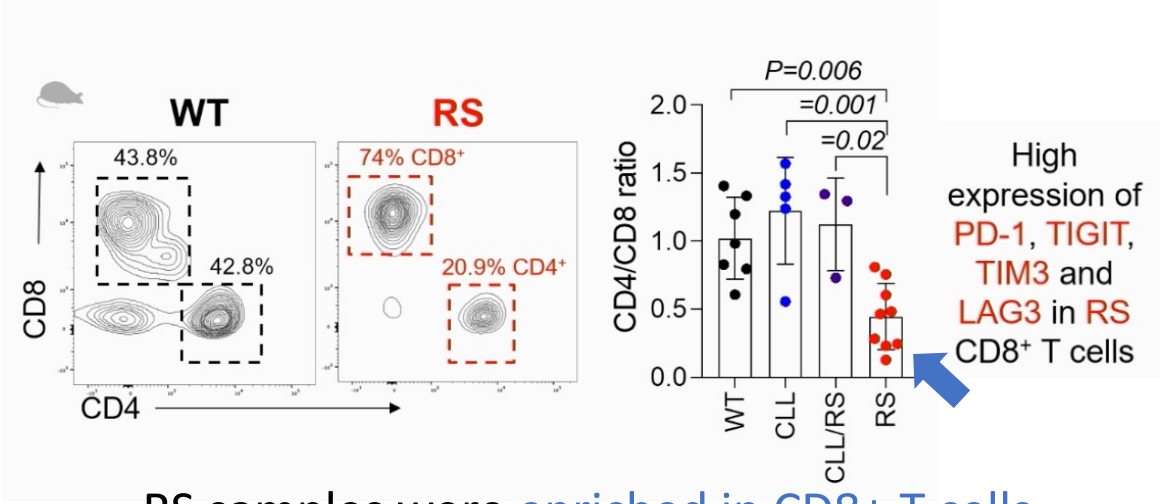
- Flow cytometry analysis on mice splenocytes to evaluate the potential impact of checkpoint blockade therapy

Ten Hacken *et al.*, #636

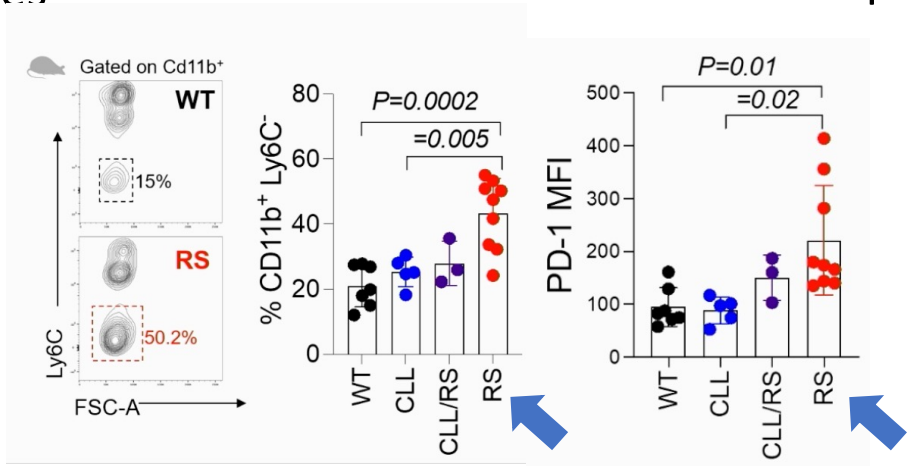
Differences between RS and CLL



RS samples were enriched in PD-1 and PD-L1 expression, indicative of immune evasion, compared to CLL samples



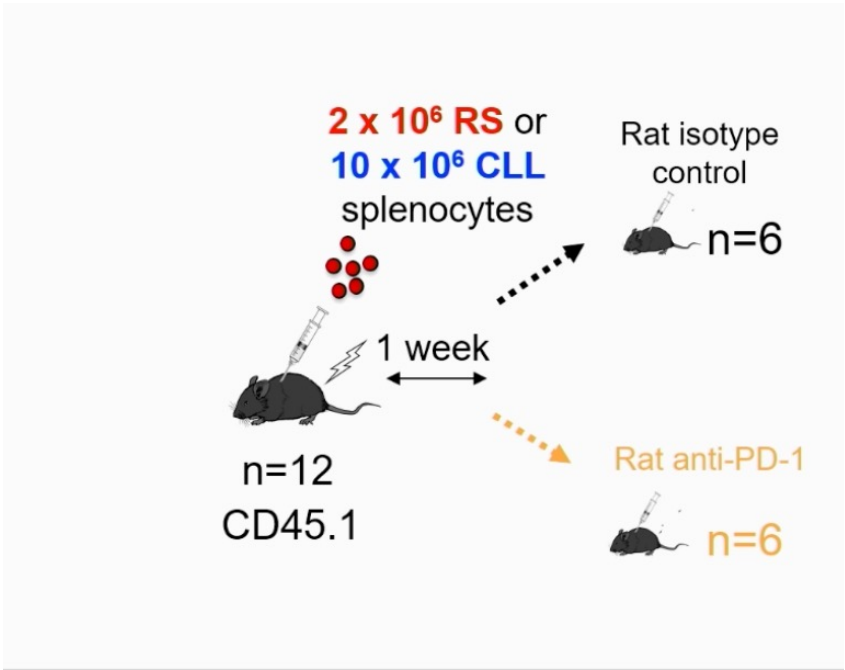
RS samples were enriched in CD8+ T cells that express markers of exhaustion compared to CLL samples

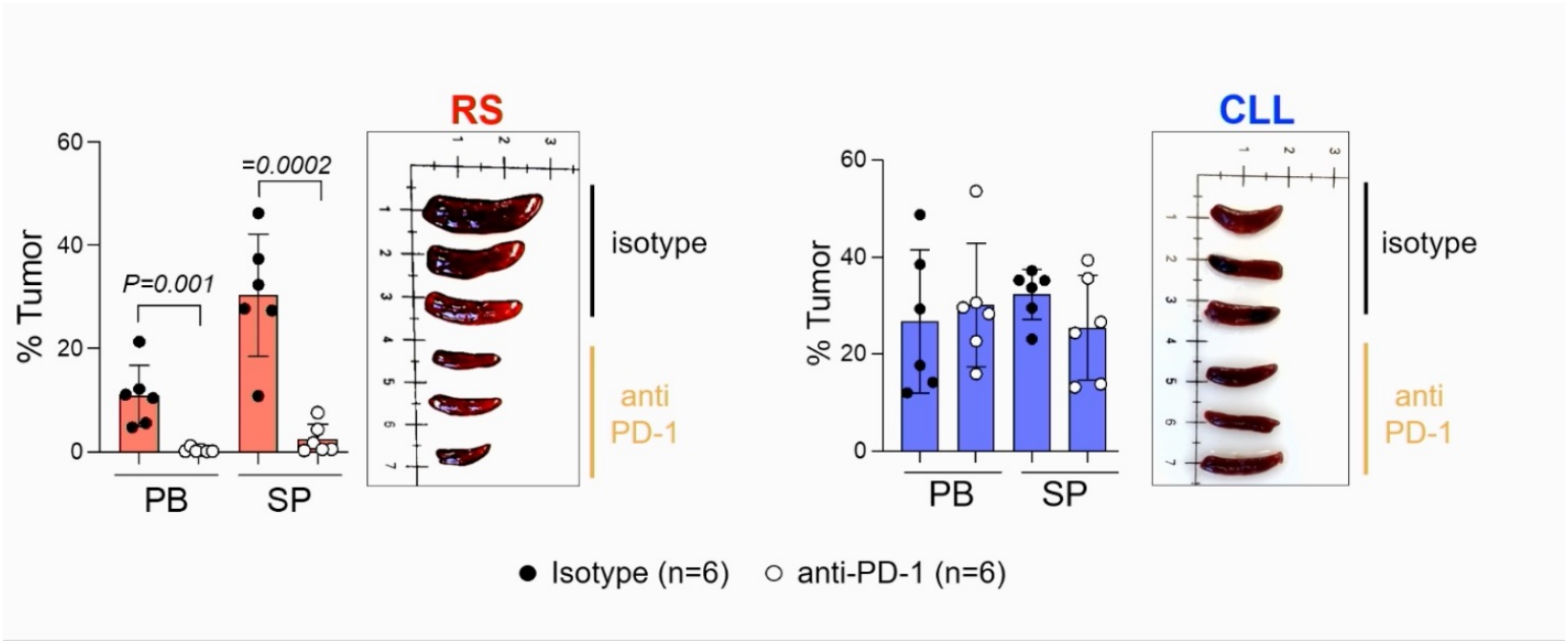


RS samples were enriched in tissue associated macrophages that express higher levels of PD-1 compared to CLL samples

Ten Hacken *et al.*, #636

Anti PD-1 therapy is active in mice injected with RS but not with CLL





Ten Hacken *et al.*, #636

Conclusions

Prognostic markers in the CLL13 clinical trial

- UM IGHV genes and *NOTCH1* mutations are prognostic both in CIT and in venetoclax arms
- *BRAF/NRAS/KRAS* mutations associated with shorter PFS in venetoclax arms
- hCKT (≥5 aberrations) but not CKT (≥3 aberrations) associated with shorter PFS

Prognostic markers in ibrutinib + venetoclax clinical trials:

- Fixed duration ibrutinib + venetoclax seems to overcome the prognostic impact of IGHV mutational status
- UM IGHV patients are characterised by faster/higher level of MRD negativity but MRD rapidly reappears after treatment cessation compared to M IGHV patients.

Novel insights into the biology of Richter syndrome

- Clonally related RS is molecularly distinct from *de novo* DLBCL and the novel molecular subtypes of RS harbor prognostic significance
- cfDNA analysis is a potential tool for non-invasive and early diagnosis of RS
- RS mice models show high expression of PD-1/PD-L1 exhausted CD8+ T cells and increased PD1+ TAM
- Immune check point-inhibitors are active in RS but not in CLL