LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

UNDER THE AUSPICES OF:

SIE - Società Italiana di Ematologia

EMERGING PROGNOSTIC/PREDICTIVE FACTORS in CHRONIC LYMPHOCYTIC LEUKEMIA

ILARIA DEL GIUDICE

EMATOLOGIA, Sapienza Università di Roma

Dipartimento di Medicina Traslazionale e di Precisione

COI

- Janssen (AB)
- AstraZeneca (lectures)

Outline

- Established predictive markers: IGHV and TP53
- Potential predictive markers: karyotype
- Resistance to BTKi and anti-BCL2

Treatment choice in CLL in 2022

Time = still clinical criteria for disease progression

CLL

TN or R/R

FISH+seq

- TP53 del/mut
- IGHV mut

Patient

- Age
- Performance status
- CIRS
- Creatinine clearance

CONTINUOS

BTKi (+/- antiCD20)

AIM

Disease control

Prolonged PFS

No matter MRD

FIXED duration

FCR (?)

Venetoclax + O

AIM

Disease eradication

Prolonged PFS

Undetectable MRD

Established predictive markers in 1st line therapy choice

Unmutated IGHV → **anti-BCR, anti-BCL2**

***TP53* del/mut** → **anti-BCR, anti-BCL2**

NO *TP53* del/mut; mutated IGHV; fit → **FCR (?)**

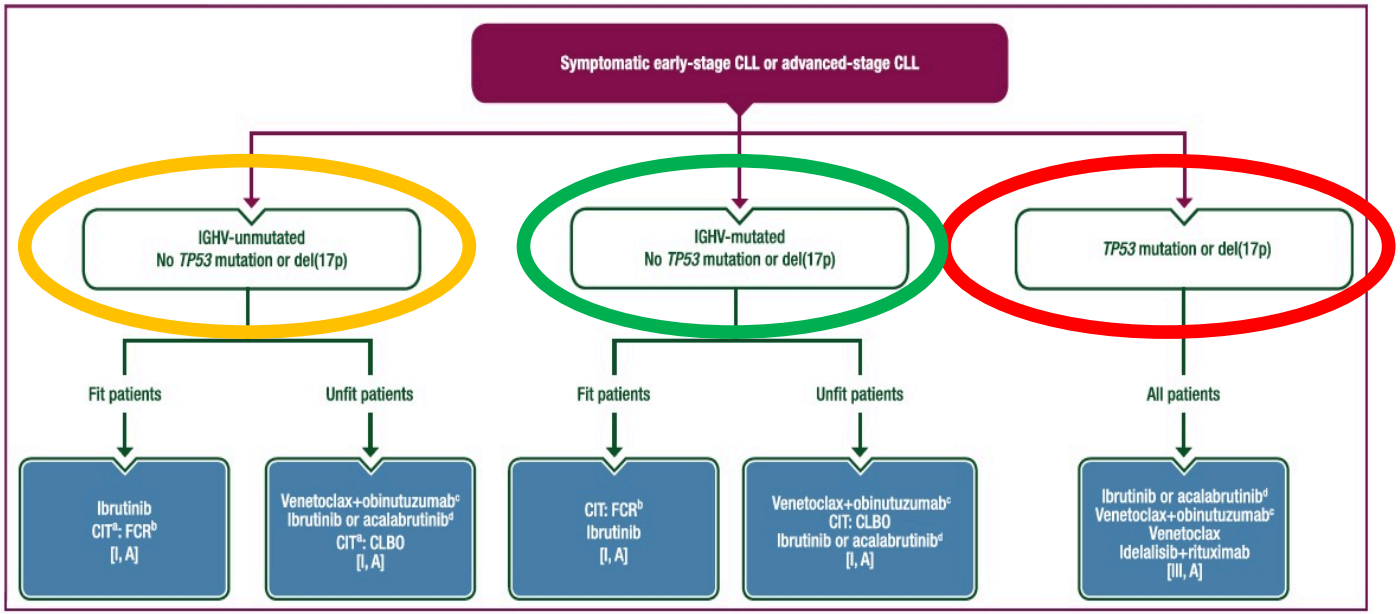


Table 3. Personalised medicine synopsis

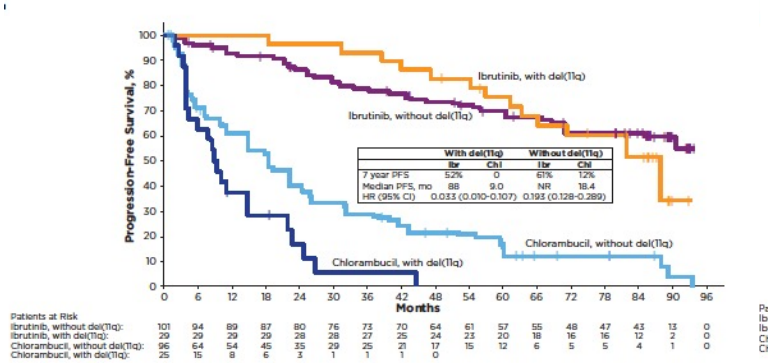
Biomarker	Method	Use	LoE, GoR
TP53 mutation or *del(17p)*	FISH and Sanger or NGS	Strongest prognostic and predictive relevance together with del(17p)	III, A
IGHV	Sanger or NGS	Strong prognostic evidence; predictive evidence for CIT	III, A
Complex karyotype	Chromosome banding	Possible prognostic and predictive relevance but not yet established prospectively	IV, C

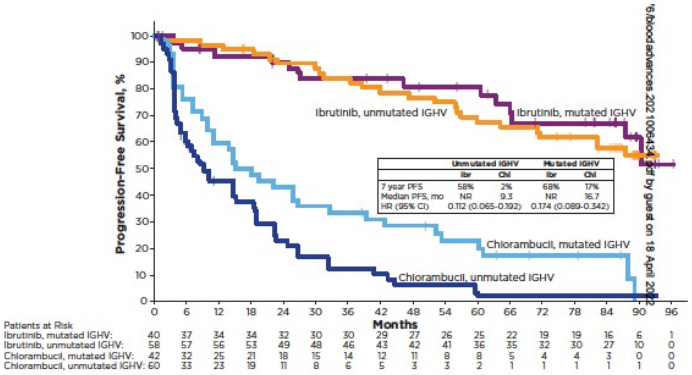
CIT, chemoimmunotherapy; GoR, grade of recommendation; IGHV, immunoglobulin heavy chain variable; LoE, level of evidence; NGS, next-generation sequencing.

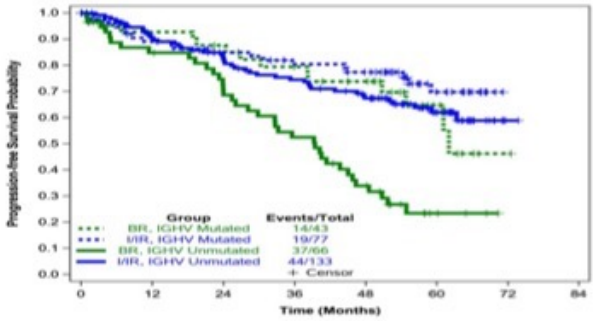
Eichhorst B et al, Ann Oncol 2021
EHA-ESMO guidelines

Ibrutinib is effective both in mutated and unmutated IGHV CLL (elderly TN)

RESONATE-2 Barr, Blood Advances 2022	**ALLIANCE** Woyach, ASH 2021 #639
Elderly ≥ 65y w/o del17p	Elderly ≥ 65y fit
Ibrutinib vs CHL x #12 **7.4 year follow-up**	Ibr+R vs Ibr vs BR (x-over) 55 months follow-up
7y-PFS 59% vs 9%; 7-y OS 78% **58% vs 2% unm IGHV; 68% vs 17% mut IGHV** **52% vs 0% in del11q** **Ibr -> unm = mut**	➢ PFS **Ibr+R -> unm = mut**

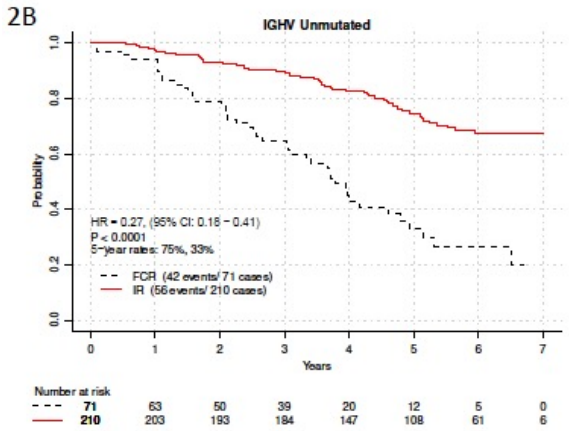


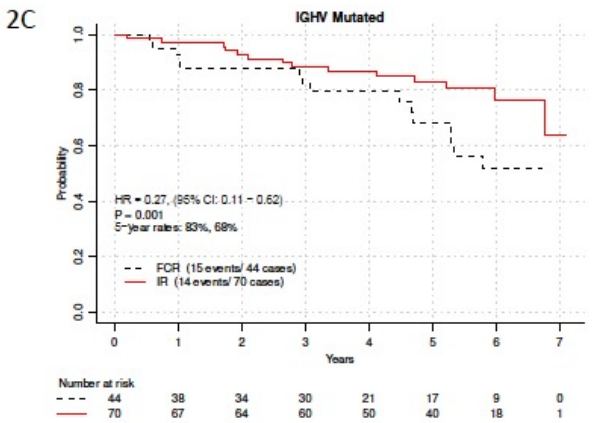


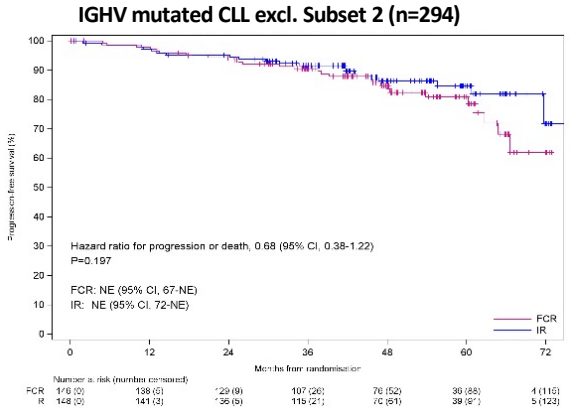


Ibrutinib is effective both in mutated and unmutated IGHV CLL (young)

ECOG1912 Shanafelt, NEJM 2019 Shanafelt, Blood 2022	**FLAIR (interim)** Hillmen, ASH 2021 #642
≤ 70y Fit for FCR, w/o del17p	≤ 75y w/o >20% del17p
Ibr +R vs FCR 70 months follow-up	Ibr+R (up to PB uMRD or 6 y) vs FCR 52.7 months follow-up
6y-PFS also for mut IGHV IR > FCR in PFS IR improved PFS relative to FCR in both IGHV mutated (HR: 0.27; P < 0.001) and IGHV unmutated patients (HR: 0.27; P < 0.001). A statistically significant advantage in OS was observed for IGHV UM patients (HR=0.35, 95% CI 0.15-0.80; p=0.01) but not for IGHV mutated patients (HR=0.72; 95% CI 0.15-3.47, p=0.68).	**For Mut IGHV IR = FCR**

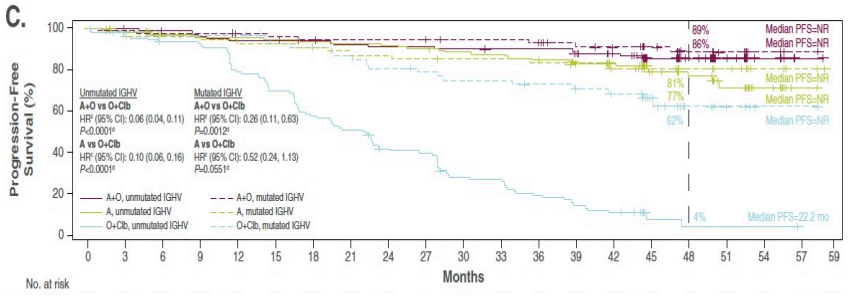


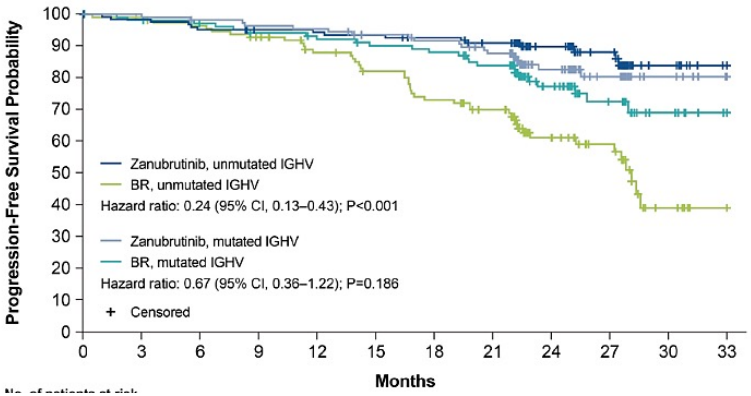




New BTKi are effective both in mutated and unmutated IGHV CLL

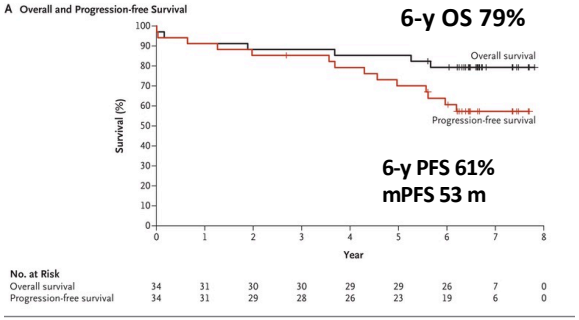
ELEVATE-TN Sharman, Leukemia 2022	**SEQUOIA** Tam, ASH 2021 #396
Elderly ≥ 65y <65y + comorbidities	Elderly ≥ 65y or unfit for FCR w/o del17p
Aca +O vs A vs CHL+O x #6 (x-over)	Zanubrutinib vs BR x #6 (cohort 1)
4-year follow-up	26.2 months
4y-PFS Unm 77.1% (A) , Unm 85.7% (A+O) **Aca -> unm = mut**	➢ 24m-PFS **Zanu -> Unm = mut** **For MUT IGHV, zanu = BR**





BTKi provide durable responses in TP53 disrupted TN CLL

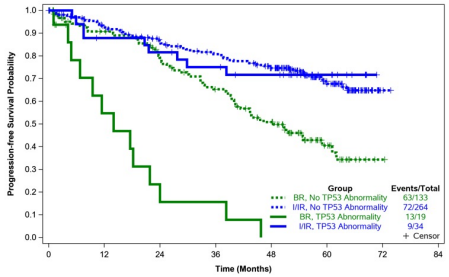
Ibrutinib



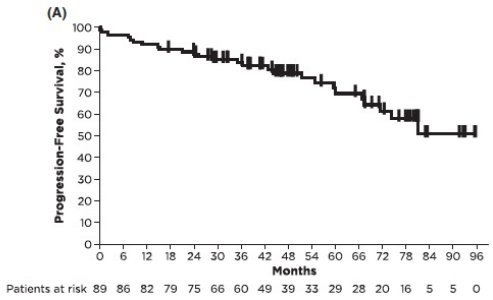
6-y OS 79%

6-y PFS 61%
mPFS 53 m

34 elderly or unfit TP53+ CLL
Ahn et al, NEJM 2020

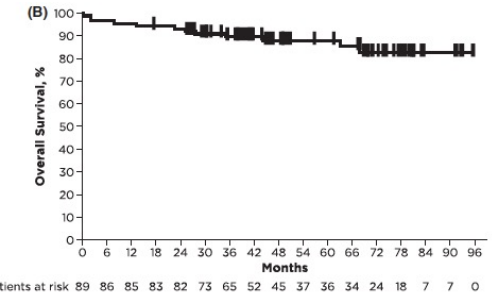


ALLIANCE
Woyach, ASH 2021



89 TN CLL with TP53 disr
4y-PFS 79% - mPFS NR

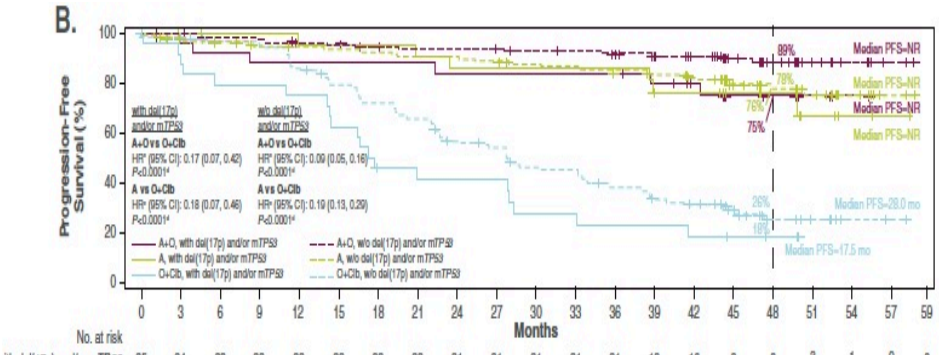
Allan et al, BJH 2022



89 TN CLL with TP53 disr
4y-OS 88%

27 TP53+ CLL - Sivina et al, Blood 2021

ELEVATE: acala +/-O vs CHL+O

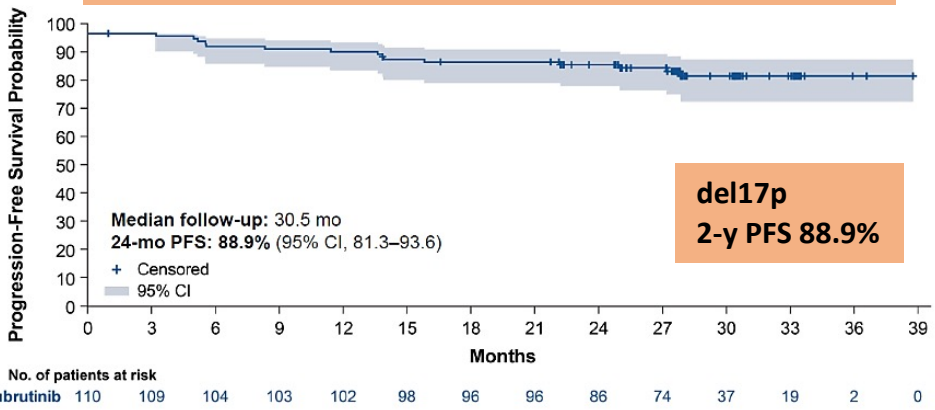


Sharman et al, Leukemia 2022

del17p A
4-y PFS 76.2%

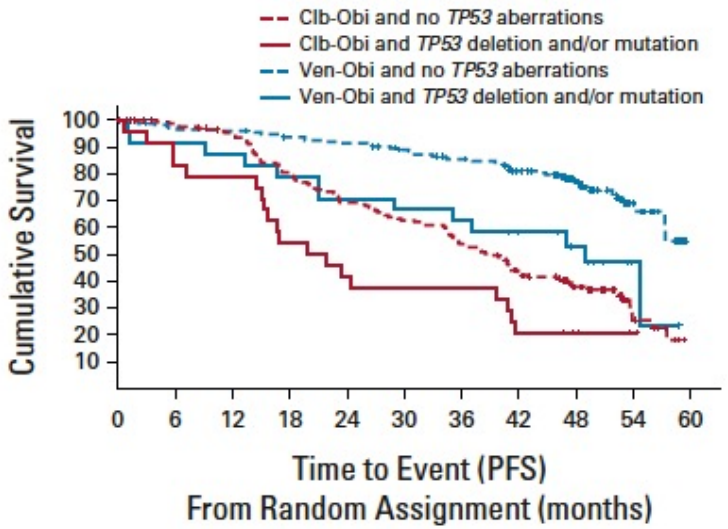
del17p A+O
4-y PFS 74.8%

SEQUOIA (zanubrutinib)
Cohort 2: PFS in 110 patients with del(17p)



del17p
2-y PFS 88.9%

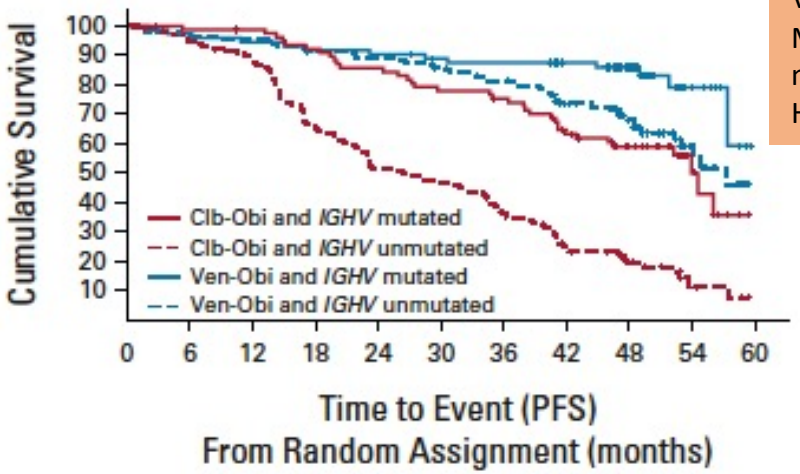
V+O in high risk unfit TN CLL (CLL14)



Ven-O arm
del17p/TP53m
mPFS 49m

Ven-O arm
Del17p/TP53m y/n & PFS
HR 2.50; 95% CI, 1.35-4.63;
p=.004

CLL14 Al-Sawaf, JCO 2021
>18 y, CIRS >6 and/or creat clearance <70 ml/min
Ven + O vs CHL+O FIXED-duration 1 y
52.4 months follow-up
➢ **MVA for PFS in Ven+O del17p**

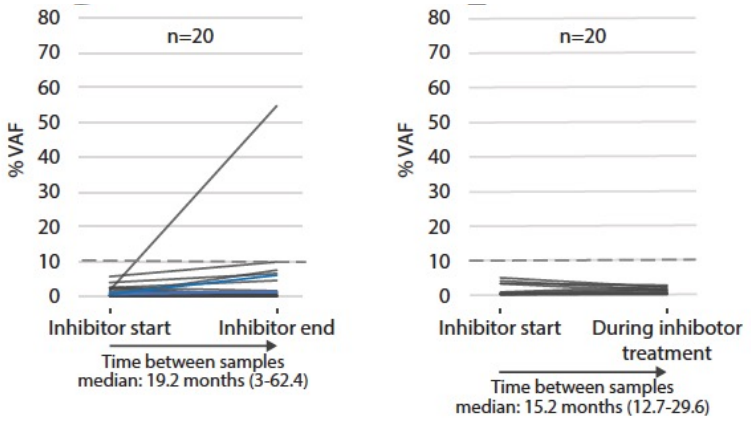


Ven-O arm
Mut IGHV vs unm IGHV
mPFS NR vs 57.3 months
HR 0.47; 95% CI, 0.25-0.87; p=0.02

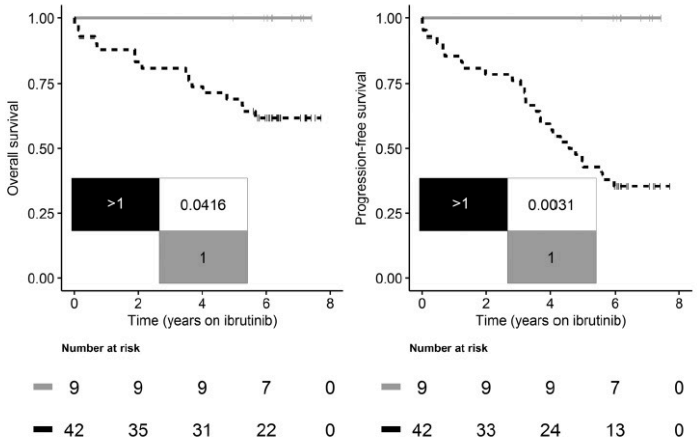
Despite similar rates of uMRD at EOT, analysis of MRD kinetics indicates that the growth dynamics of clones in patients with high-risk disease features are accelerated in these high-risk subgroups.

Tausch et al, Blood 2020
Al-Sawaf et al. JCO 2021

Do minor *TP53* mutations (VAF<10%) matter in the chemo-free era?



Malcikova et al, Blood 2021



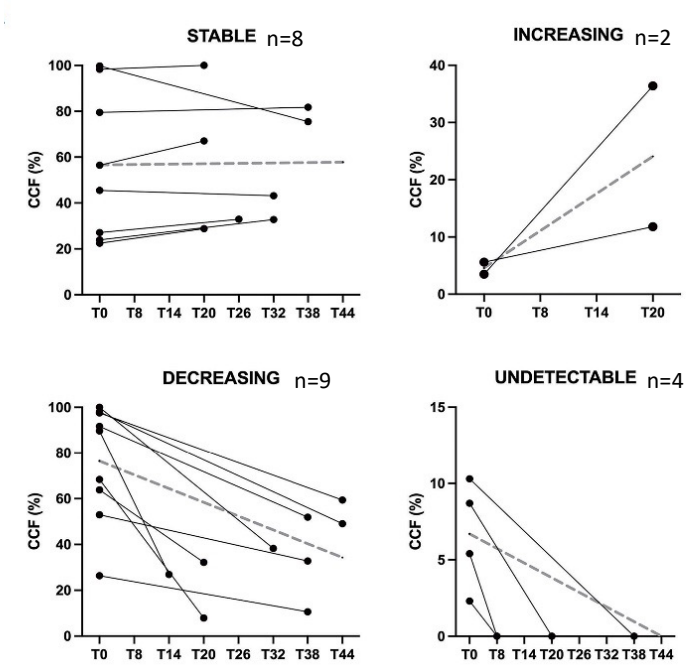
Brieghel et al, CCR 2021

✓ Targeted drugs do not accelerate expansion of TP53 mutated subclones in R/R CLL patients

✓ Multi-hit vs single hit TP53 lesions under ibrutinib **maybe** matter

Ibrutinib treatment **did not** appear to **favor** the selection of **TP53-aberrant clones**
GIMEMA LLC1114

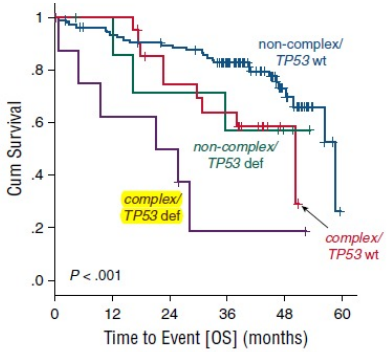
TP53 longitudinal sequencing in 44 TN CLL (17 *TP53* mut) up to >2.5 y of ibrutinib exposure

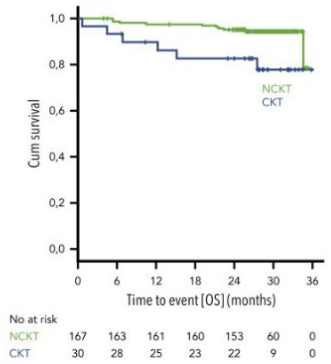


Caffforio et al, Haematologica 2022

Complex Karyotype: a marker of resistance to old and new therapies?

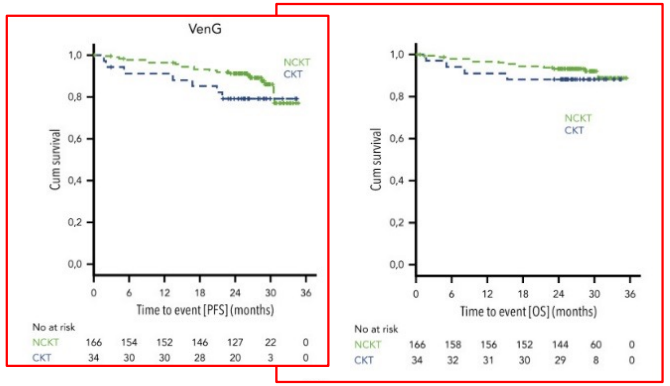
CHL+anti-CD20 Ab





Foà et al, Am J Haematol 2014
Herling, et al. Blood 2016
Al-Sawaf, Blood 2020

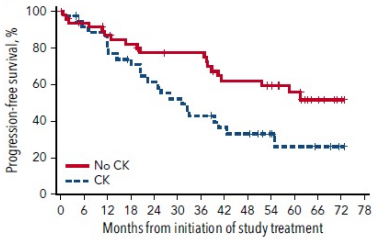
Venetoclax + O in TN CLL (CLL14)

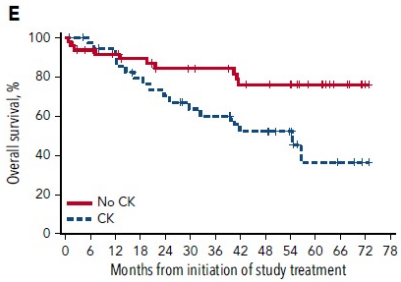


CKT 17% (n=34)
11 with TP53 abn
11 with HCK

No difference in
2y-PFS, 2y-OS,
ORR and uMRD

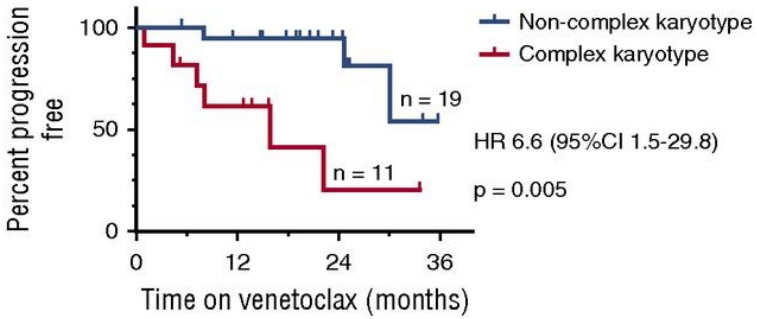
Ibrutinib in R/R CLL





Ibrutinib in TN CLL?
ALLIANCE trial

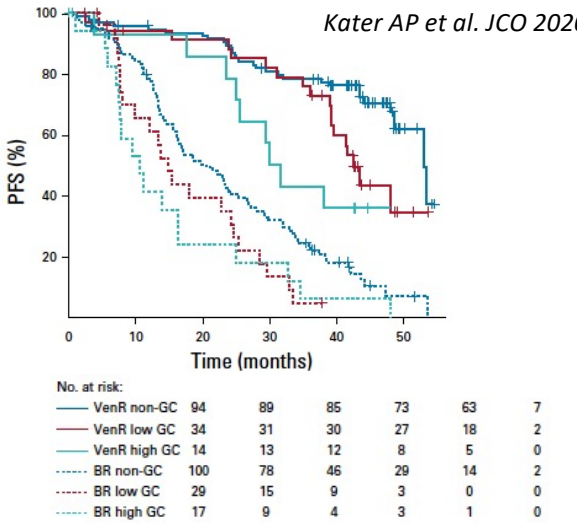
Venetoclax in R/R CLL



Anderson MA, et al. Blood 2017

Venetoclax+R in R/R CLL

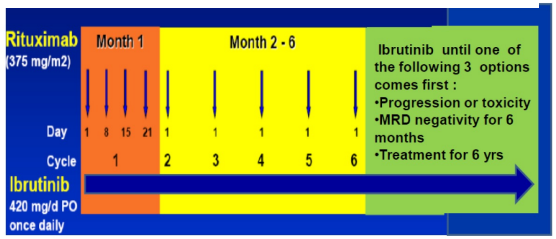
Kater AP et al. JCO 2020



O'Brien et al, Blood 2018 *Woyach, ASH 2021 #639*

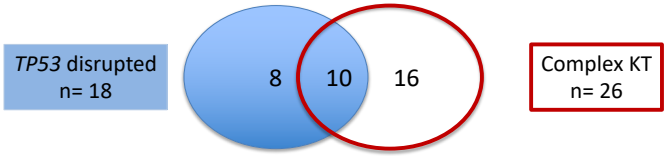
Karyotype in TN unfit CLL patients under ibrutinib + R (GIMEMA LLC1114)

- GIMEMA LLC1114 (NCT02232386) 151 patients*



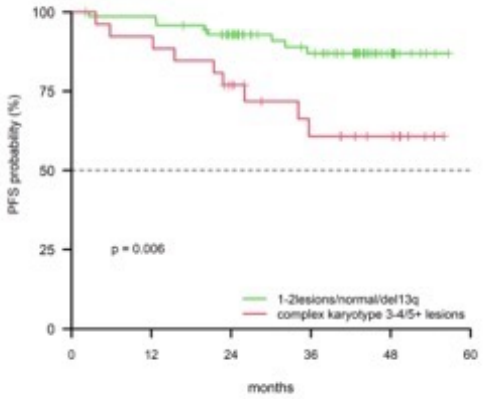
** Mauro et al, Cancers 2021*

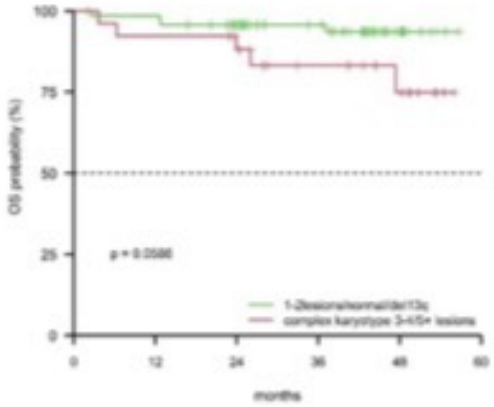
KT was successfully analyzed in 98/121 (81%) available samples.
Complex KT (>3 lesions) = 26/98 cases (27%)
Highly complex KT (≥ 5 lesions) = 10/98
TP53 disruption (17p deletion and/or TP53 mutation) = 18/98 cases (18%)

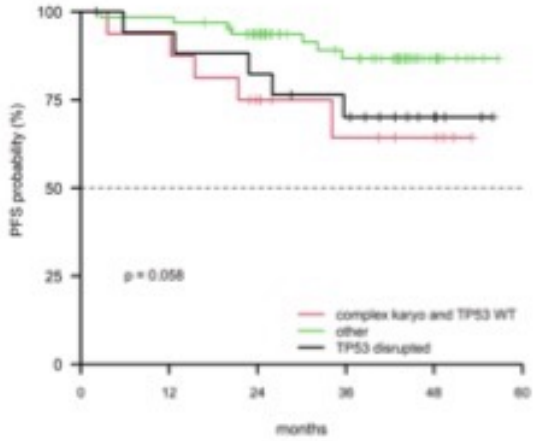


Median follow-up was 42.6 months (range 2.1-56.7)
36-m PFS 79.9 % (95% CI 71.6%-89.1).
36-m OS 92.3% (95% CI 87-98).
In MVA, complex KT was significantly associated with a shorter PFS (p=0.009), beside ECOG PS (p=0.048).

Patients with a complex KT devoid of *TP53* deletions and/or mutations showed the same poor PFS than those with *TP53* disruption .







Rigolin GM, Del Giudice I et al. Blood 2021

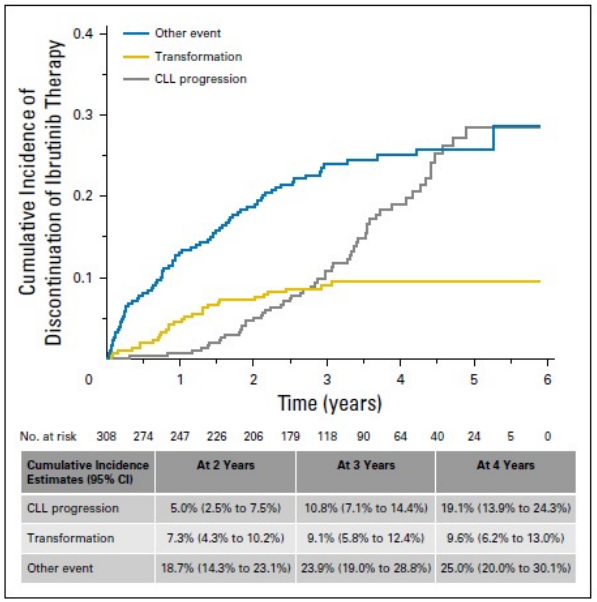
Resistance to ibrutinib: *BTK* & *PLCg2* mutations in clinical trials

308 R/R CLL pts from 4 ibrutinib-based trials (40% del17p)

Predictive markers of ibrutinib-failure:
complex KT, *TP53*-del, age <65 years

BTK/PLCg2-mut retrospectively identified in 85% of 46 relapsed cases **up to 9.3 months (7.6-11.7) before clinical relapse**

112 CLL patients followed prospectively every 3 months: 8 relapsed, all with *BTK/PLCg2*-mut pre-relapse; 8 show *BTK/PLCg2*-mut but not (yet) relapsed

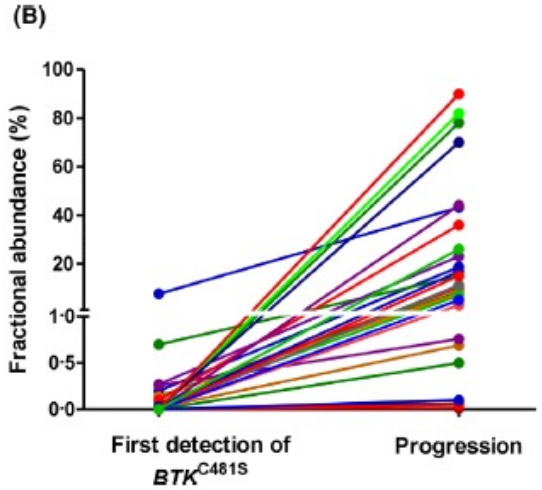


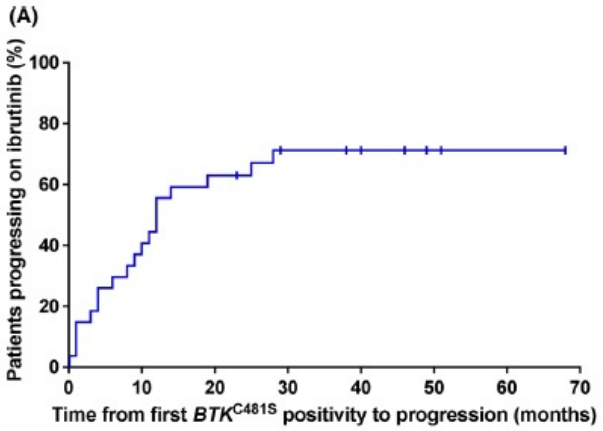
Cumulative Incidence Estimates (95% CI)	At 2 Years	At 3 Years	At 4 Years
CLL progression	5.0% (2.5% to 7.5%)	10.8% (7.1% to 14.4%)	19.1% (13.9% to 24.3%)
Transformation	7.3% (4.3% to 10.2%)	9.1% (5.8% to 12.4%)	9.6% (6.2% to 13.0%)
Other event	18.7% (14.3% to 23.1%)	23.9% (19.0% to 28.8%)	25.0% (20.0% to 30.1%)

- BTK C481 loss of drug binding
- PLCg2 gain-of-function mutations (SH2 autoinhibitory domain)
- Linear or branching evolution
- Others [del(8p) (TRAIL-R) + ITPKB mutations]

Burger J, et al. Nat Commun 2016
Ahn IE, et al. Blood 2017; JCO 2020
Woyach JA, et al, JCO 2017
Ladau DA, Nat Communic 2017

Resistance to ibrutinib: *BTK* & *PLCg2* mutations in the real-life





83 R/R CLL treated with ibrutinib

(median 36 m, range 13-68)

Follow-up 40 m (13-69)

- 44 relapsed
- 12 relapsed with BTK WT
- 32 relapsed with BTK C481S

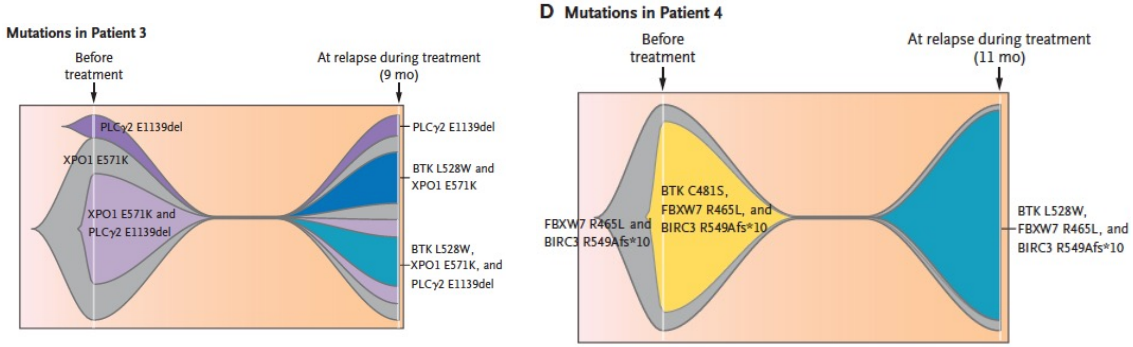
BTK C481S by ddPCR

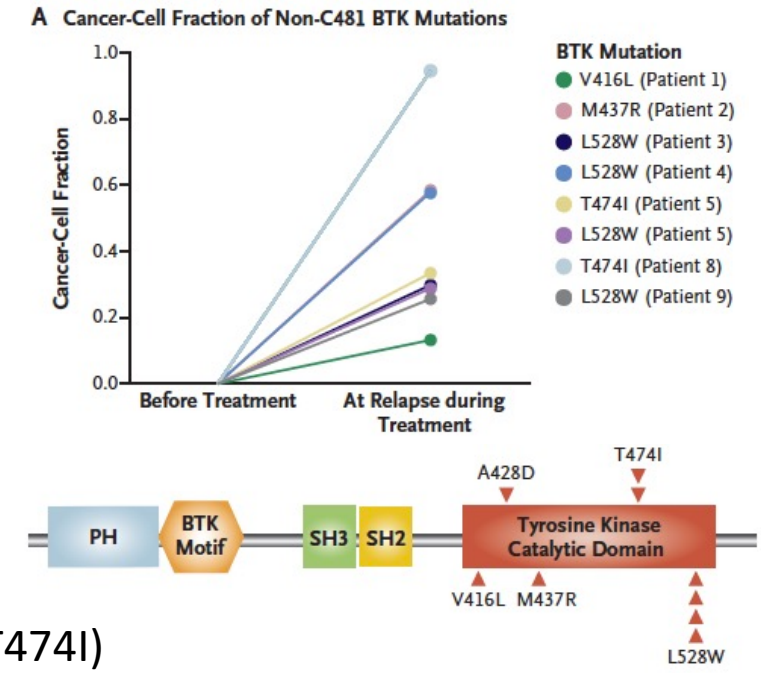
- 48.2% (n=40/83)
- 80% (32/40) relapse with a FA 10.6% (0.01%-90%)
- 20% (8/40) no relapse with a FA 0.69% (up to 20%), in 3 disappeared

Time to relapse: **9 months (7.6-11.7)**

Bödör et al. Br J Haematol. 2021
Quinquenel et al: a FILO group study. Blood. 2019

Resistance to pirtobrutinib: *BTK* & *PLCg2* mutations





9 CLL pts who failed pirtobrutinib for progressive disease (RS in 3)

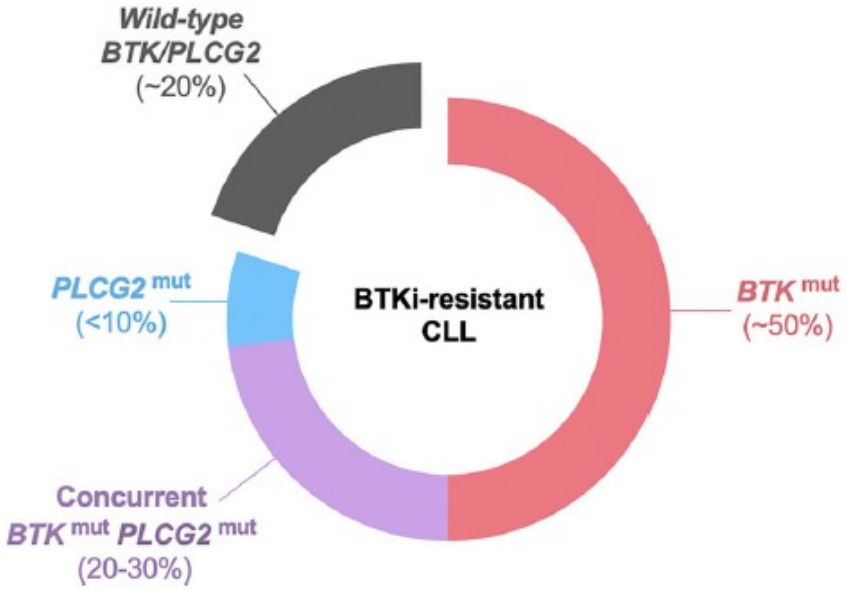
7 acquired non-C481 BTK mutations (V416L, A428D, M437R, L528 W, T474I)
2 persisting PLGg2 mutations

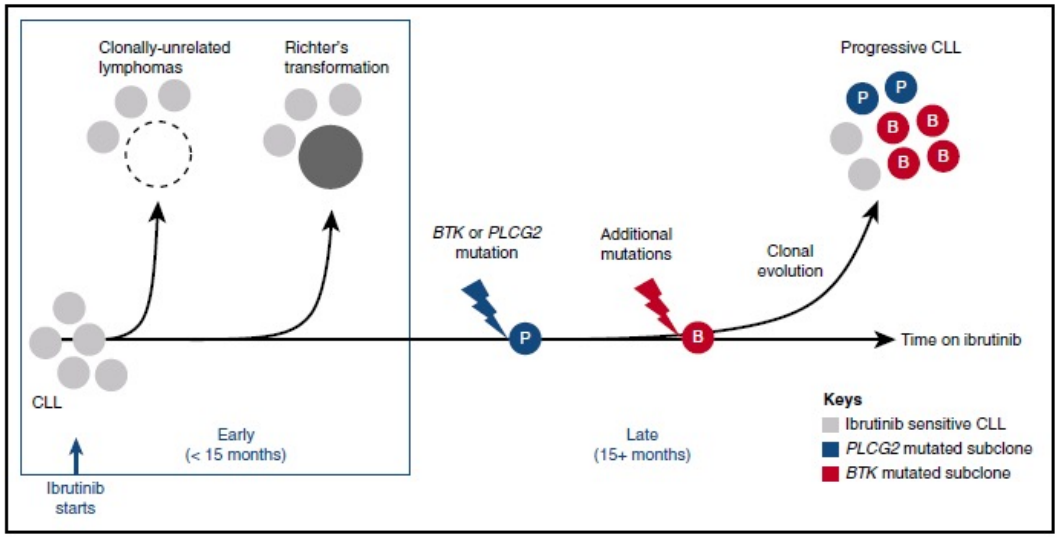
In 4 patients with preexisting BTK C481 mutations, BTK C481 clones were suppressed by pirtobrutinib in 2 patients, followed by acquisition of new non-C481 BTK mutations associated with clinical resistance to pirtobrutinib

These mutations also interfered with the ability of covalent BTK inhibitors to block BTK enzymatic activity

Wang et al, NEJM 2022

Resistance to ibrutinib: *BTK* & *PLCg2* mutations





BTK and PLCG2 may occur and be detected several months before clinical progression in R/R CLL

Can they be proposed as predictive biomarkers of relapse?

At present there is no evidence that treatment interventions before a clinical progression have significant benefits

Thus, they do not provide actionable information to the clinicians when taking decisions on the management or treatment of individual patients.

They should be prospectively analyzed in clinical trials.

Resistance to venetoclax in R/R CLL

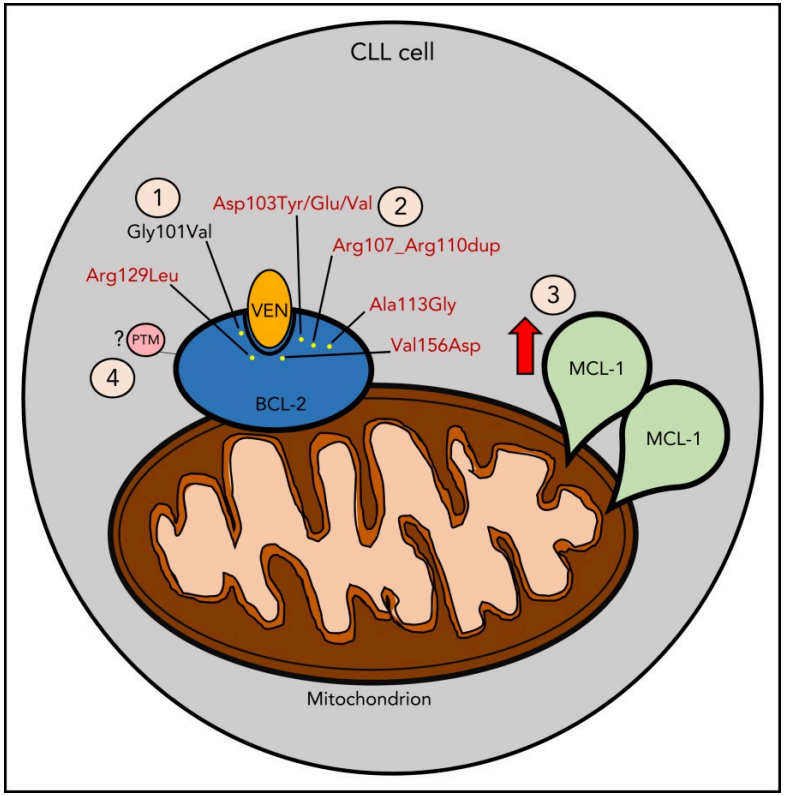
8 pretreated CLL cases (all *TP53*-del/mut): 6 PR and 2 SD
Resistant to venetoclax after 15.4 months (4-22 m)
4 developed RS

✓ *BTG1*-mut in 2 cases
Homozygous deletion *CDKN2A/B* in 3 cases
***BRAF*-mut** in 1 case
Amplification *CD274* (PD-L1) in 1 case

✓ ***NOTCH1* mut, *TP53*** del/mut

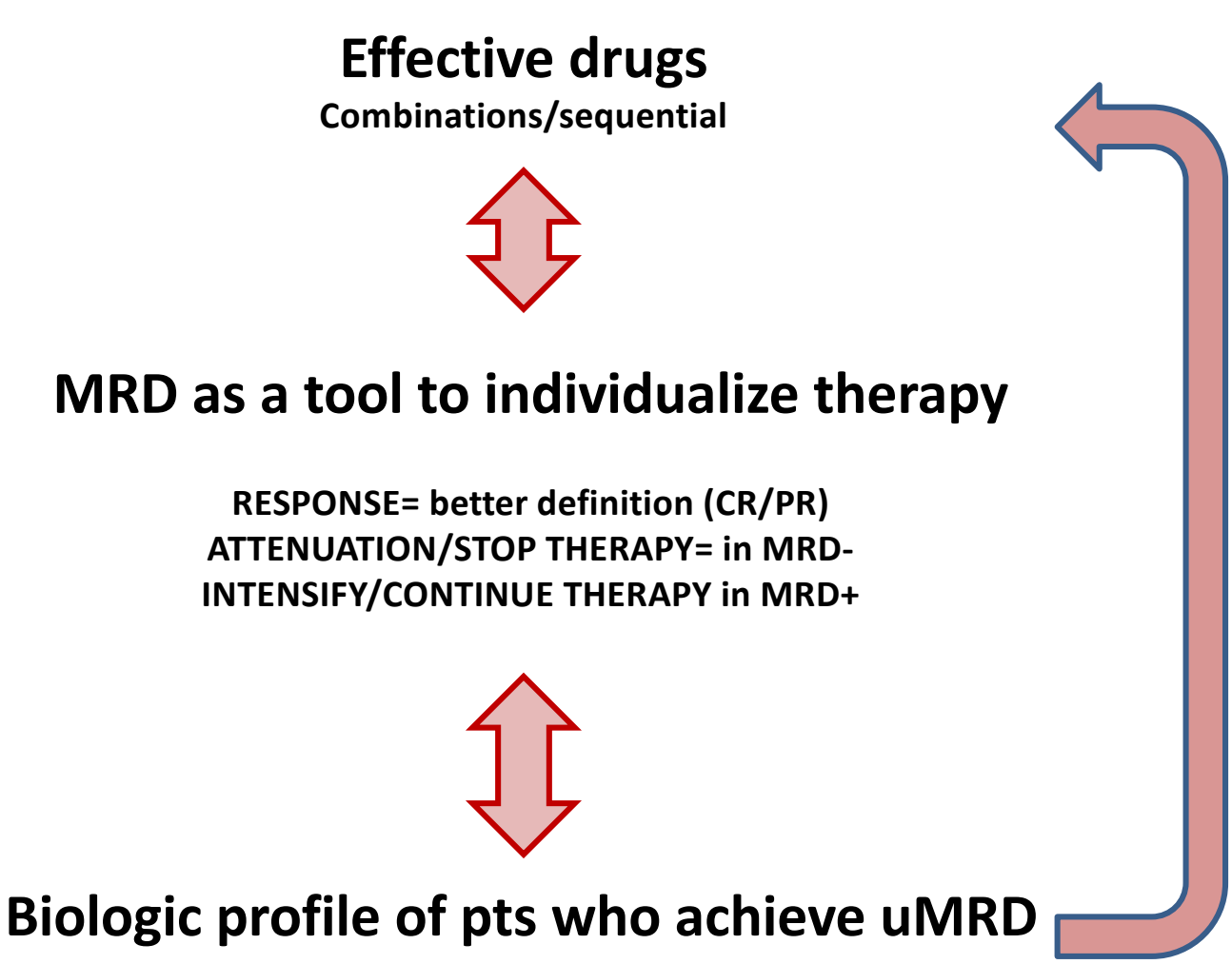
✓ In 7/21 PD under venetoclax
BCL2 Gly101Val and other mutations

✓ MCL1 overexpression



Herling et al. Nat Communic 2018
Roberts et al. Blood 2019
Blombery et al. Cancer Disc 2019
Blombery et al. Blood 2020

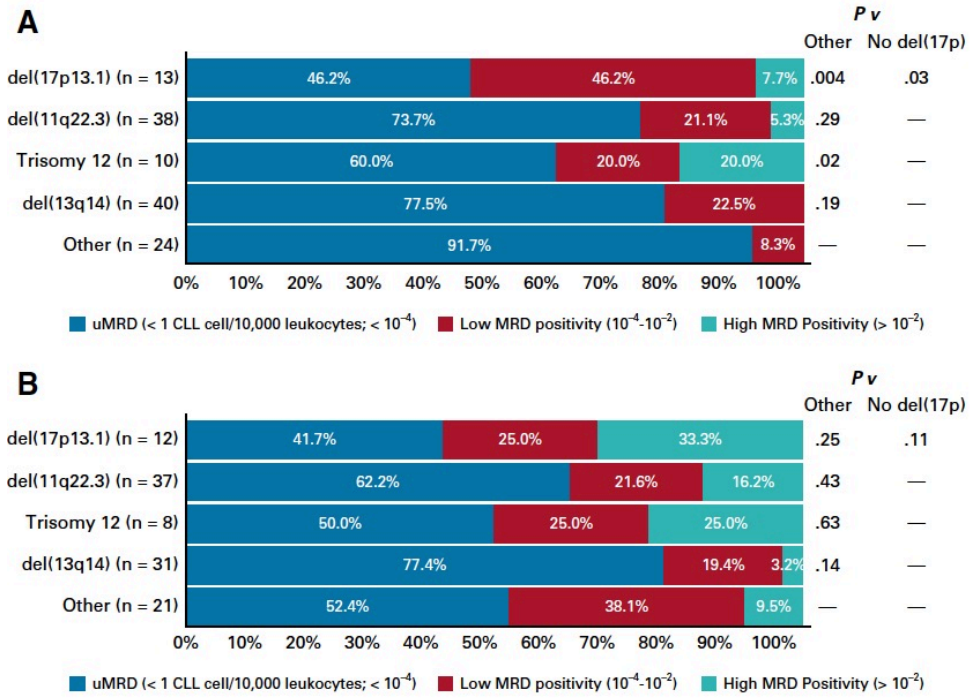
Measurable residual disease (MRD) in CLL: clinical implications in the near future

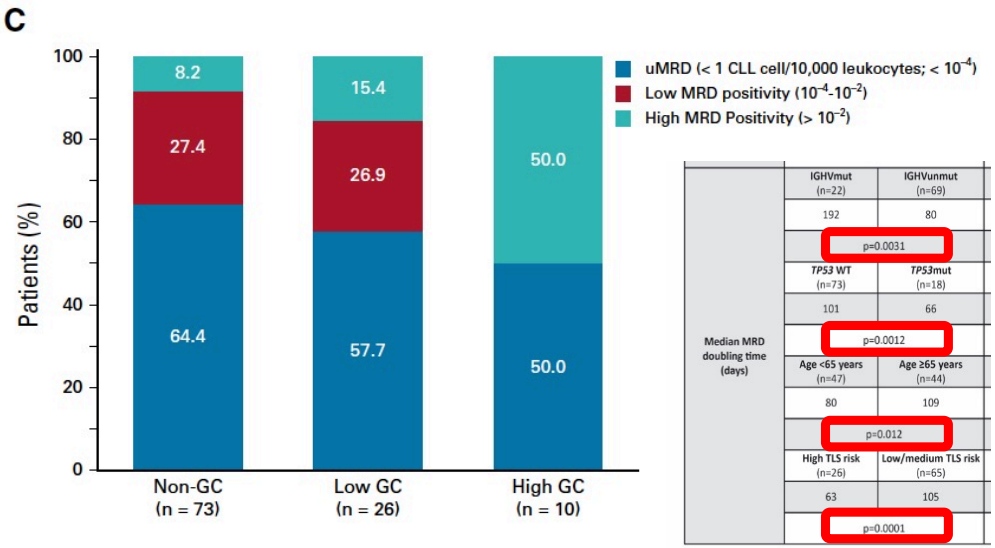


TRIALS to maximize uMRD (fixed duration)
COMBO x2 // x3
GAIA
GLOW
CLL17
……MANY

TRIALS with MRD as a decision tool
Phase II Captivate (Ibrutinib + Venetoclax 1stL)
CLARITY (Ibrutinib + Venetoclax R/R)
IMPROVE

Prediction of uMRD with venetoclax+R in R/R CLL (MURANO)





Kater et al. JCO 2019
Kater et al. JCO 2020

At m+9 **[EOCT]:**
PB uMRD = 62.4%
BM uMRD 27.3%

PB at m +24 **[EOT]**
uMRD4 (<10^{-4}) = 64% (at 9.9 months, PD: 2.4%)
low-MRD (>10-4-<10-2) = 18% (PD: 13%)
high-MRD (≥10^{-2}) at EOT: high risk subgroup (PD: 79%)

EOCT= higher MRD positivity rates in pts with:
- 17p- and +12
- BIRC3 and BRAF mutations

EOT= higher MRD positivity rates in pts with:
- TP53, NOTCH1, XPO1, and BRAF mutations
- Genetic complexity (5 or more CNV)

Conclusions

- Established predictive markers:

TP53 disruption is still a high risk subgroup (continuous better than fixed?)

Mutated IGHV: ibrutinib+R better than FCR?

- Potential predictive markers: karyotype

Need to be largely assessed in TN patients treated with BTKi or anti-BCL2 to become an established predictive marker

- Resistance to BTKi and anti-BCL2

Clinical trials

SAPIENZA
UNIVERSITÀ DI ROMA

Grazie!

FIL MRD NETWORK

FONDAZIONE ITALIANA LINFOMI

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

AIL Roma
Vanessa Verdecchia • ODV
ROMAIL • ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE - LINFOMI E MIELOMA

AIRC

Richter's syndrome (DLBCL)

CDKN2A deletion ~50% TP53 disruption c-Myc activation (gain, ampl)	Trisomy 12 ~30% NOTCH1 mutation	~20% Heterogeneous Genomic aberrations

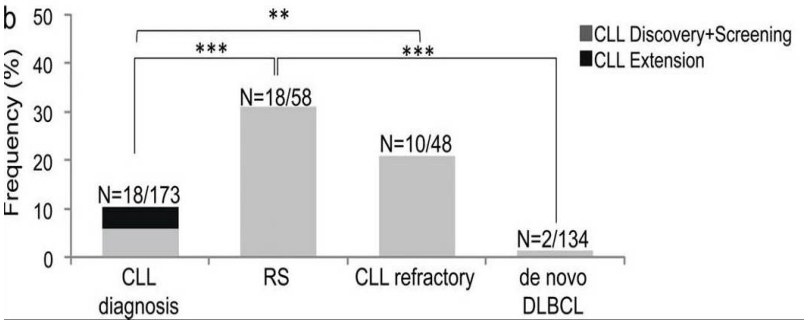
Subset #8 IGHV4-39/IGHD6-13/IGHJ5/IGKV1-39

Increased risk of transformation in RS (17-fold)
5-y probability = 70%
Biology: IgG switched & trisomy 12

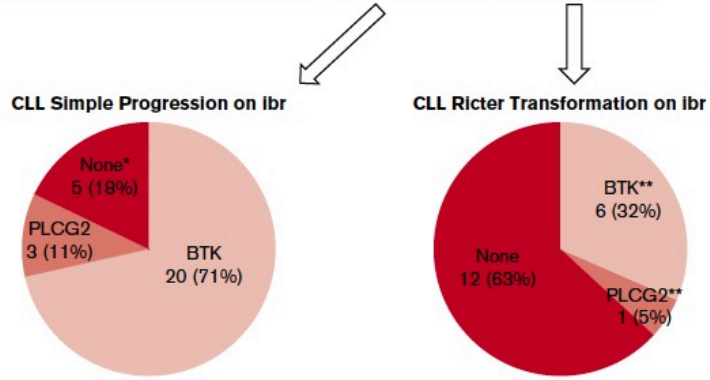
Rossi et al. Clin Cancer Res 2009

***NOTCH1* mutations**

11% at diagnosis, 21% chemorefractory CLL,
31% Richter Syndrome (all DLBCL).



	Total pt	CLLPD	RT
Maddocks[6]	20	11	9
Burger[18]	5	5	0
Ahn[43]	12	9	3
Current study	9	3	6
Total	46	28	18



Kadri, et al. Blood Adv 2017
Condoluci A, Front Oncol 2022

Ibrutinib in TN or R/R patients: 4 factor score

•The US National Institutes of Health, from 804 CLL patients treated with ibrutinib in 6 clinical trials, predictive of PFS and OS in both TN and R/R cases (60%).

•Recently validated in an Italian study including 586 ibrutinib treated patients, mostly R/R (Morabito et al, 2021).

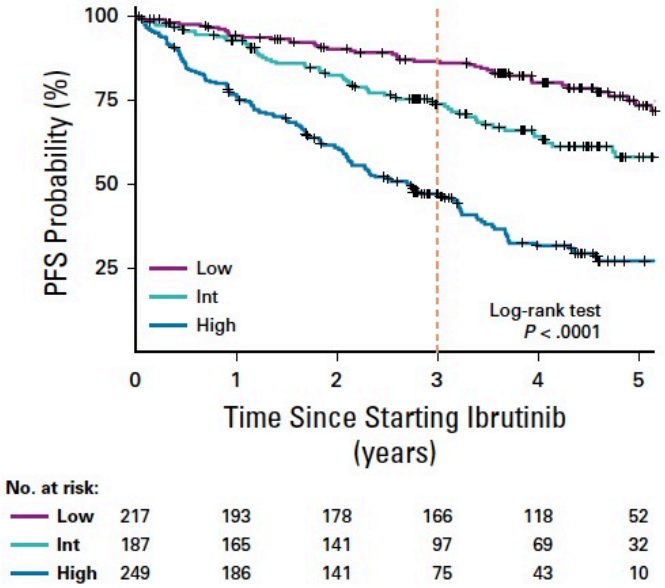
Parameter	***Risk score***
Disease status (R/R vs TN)	1
LDH > 250 U/L	1
β2-microglobulin $\geq$5 mg/L	1
Del(17p)/ mutations *TP53*	1

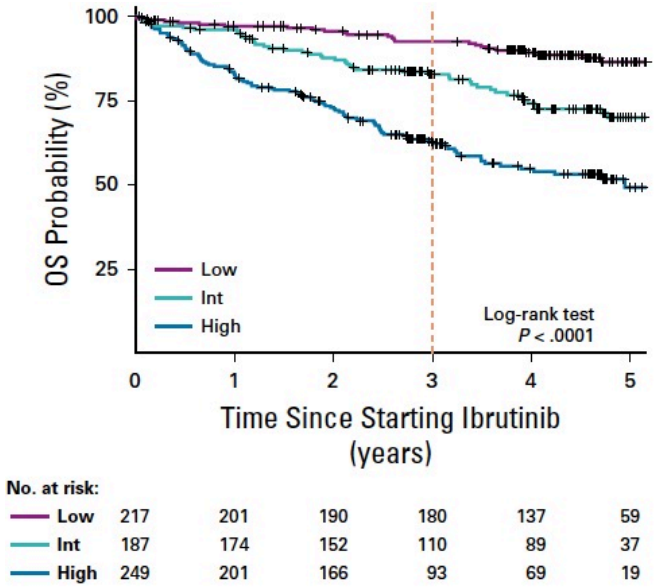
Three categories with a different 3-year PFS and OS:

- *Low-Risk (0-1 point), Intermediate-risk (2 points), High-risk (3-4)*

Anhn et al, *JCO 2021*

Ibrutinib in TN or R/R patients: 4 factor score





3y-PFS: 87% Low, 74% Int, 47% High

3y-OS: 93% Low, 83% Int, 63% High

At 3 years:

- *Low-Risk 13% had progressed/died vs 53% high-risk*
- *PLCg and BTK mutations more frequent in high risk group (50%, 40%, 17%)*
- *RS more frequent in high risk group (17% , 5%, 0%)*

Anhn et al, *JCO 2021*

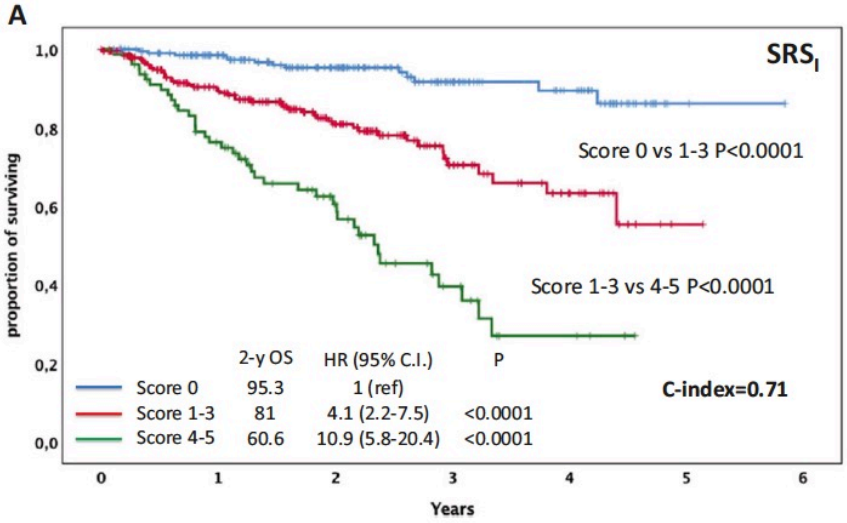
Ibrutinib in R/R patients: SRSi

- Italian study, 541 R/R CLL receiving ibrutinib outside clinical trial
- Previous lines of therapy: 2 (range 1-9)

Parameter	*Risk score*
Anemia <11/<12 g/dl	2
LDH > ULN	2
β2-microglobulin ≥5 mg/L	1

Three categories with a different OS:

- *Low-Risk (0 factor),*
- *Intermediate-risk (1-3 factors),*
- *High-risk (4-5)*



2y-OS:
95.3% Low, 81% Int, 60.6% High

Gentile et al, Leukemia 2021

Ibrutinib in R/R patients: CLL3 score

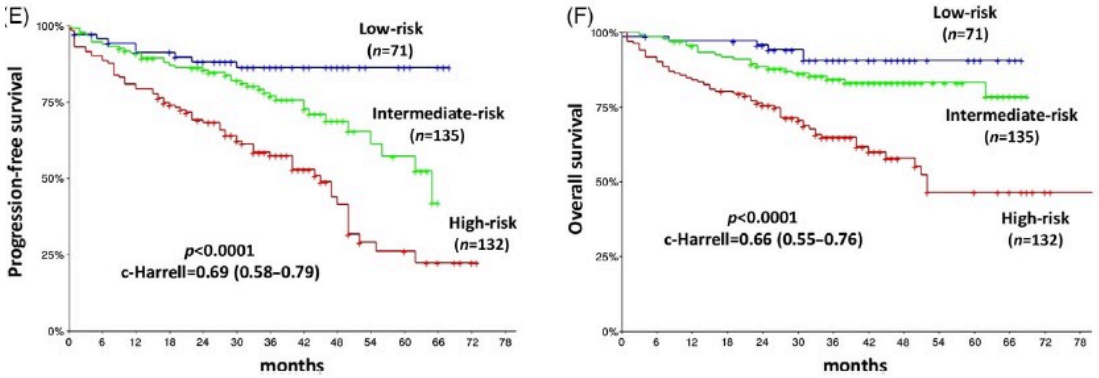
- Italian study, 338 CLL receiving ibrutinib outside clinical trial (80% R/R)
- Previous lines of therapy: 2 (range 1-9)

Parameter	*Risk score*
Stage III/IV	1
LDH > ULN	1
Early-POD (<24 m)	1

Three categories with a different PFS & OS:

- *Low-Risk (0 factor), (21%)*
- *Intermediate-risk (1 factor), (40%)*
- *High-risk (2-3) (39%)*

CLL3 score (LDH, Rai stage, and time from the start of last therapy)



3y-PFS:
86.4% Low, 77% Int, 57.6% High

3y-OS:
91% Low, 84% Int, 65% High

Molica et al, Am J Hematol 2022