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

Trattamento di prima linea

Paolo Ghia
Università Vita-Salute San Raffaele

DICHIARAZIONE

Paolo Ghia

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 **(AbbVie, Astrazeneca, BeiGene, BMS, Janssen, Lilly/LoxoOncology, MSD, Roche)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(AbbVie, AstraZeneca, BMS, Janssen)**
- Partecipazione ad Advisory Board **(AbbVie, Astrazeneca, BeiGene, BMS, Janssen, Lilly/LoxoOncology, MSD, 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

CLL treatments

Continuous BTKi

Pros of Fixed duration:

- **Limits Adverse events**
- **Reduces clonal evolution/resistance**
- **Decreases financial costs**

Ven+O

Ven+O?

Cons of Fixed duration:

- **Shorter PFS in *TP53*-aberrant cases**
- **Limited data on retreatment**
- **Logistical burden – Infusion**

ASH Highlights: combined treatment with Ibrutinib + Venetoclax

- Treatment outcomes after undetectable MRD with first-line ibrutinib plus venetoclax: fixed duration treatment (placebo) versus continued ibrutinib with up to 5 years median follow-up in the CAPTIVATE study
  Allan et al., Abstract 92; Saturday, December 10, 2022

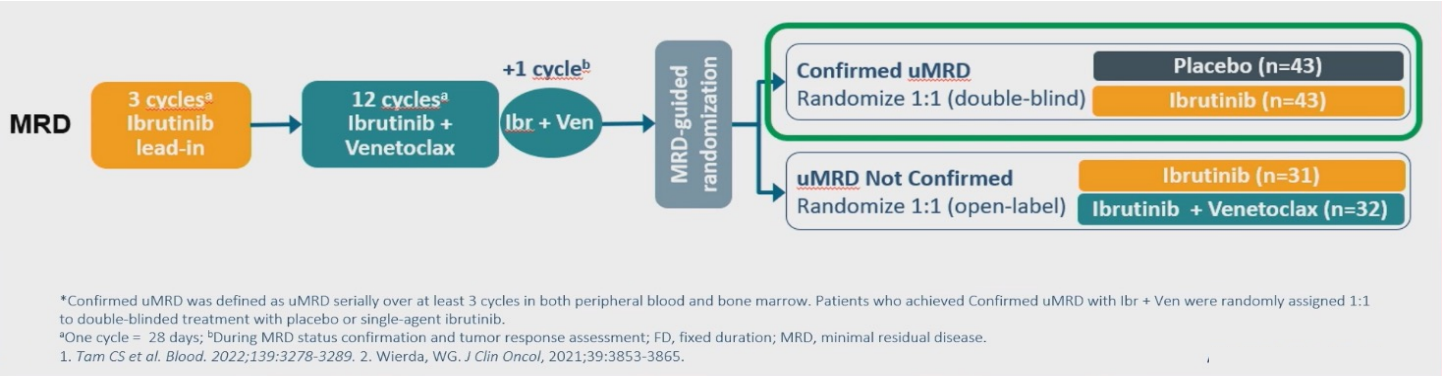
- Residual disease kinetics among patients with high-risk factors treated with first-line fixed-duration ibrutinib plus venetoclax versus chlorambucil plus obinutuzumab (Clb+O): The GLOW Study
  Niemann et al., Abstract 93; Saturday, December 10, 2022

- Combination of ibrutinib plus venetoclax with MRD-driven duration of treatment results in a higher rate of MRD negativity in IGHV unmutated than mutated CLL: updated interim analysis of FLAIR study
  Munir et al., Abstract 94; Saturday, December 10, 2022

- Combined ibrutinib and venetoclax for first-line treatment of patients with CLL: 4-year follow-up data
  Nitin Jain, et al., Abstract 95; Saturday, December 10, 2022

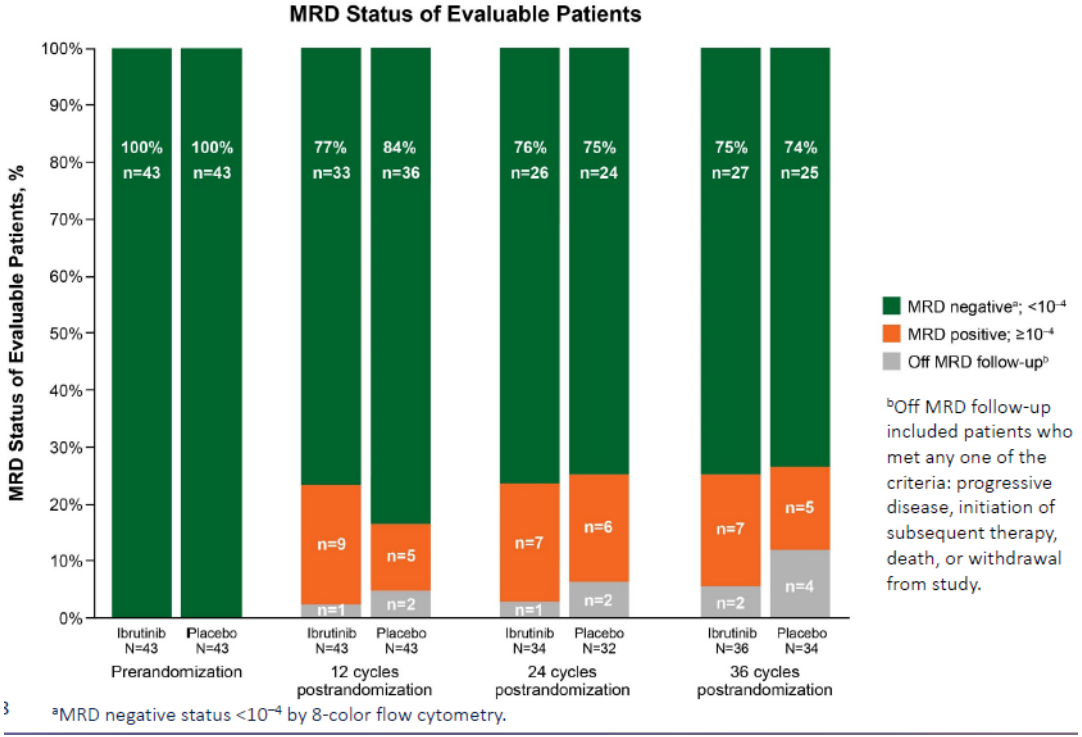
CAPTIVATE phase 2 study: first-line ibrutinib plus venetoclax

Up to 5 years median follow-up



- Median time on study was **56 months** (ibrutinib arm range, 25–68 months; placebo arm range, 40–65 months), with a median of 41 months post-randomization

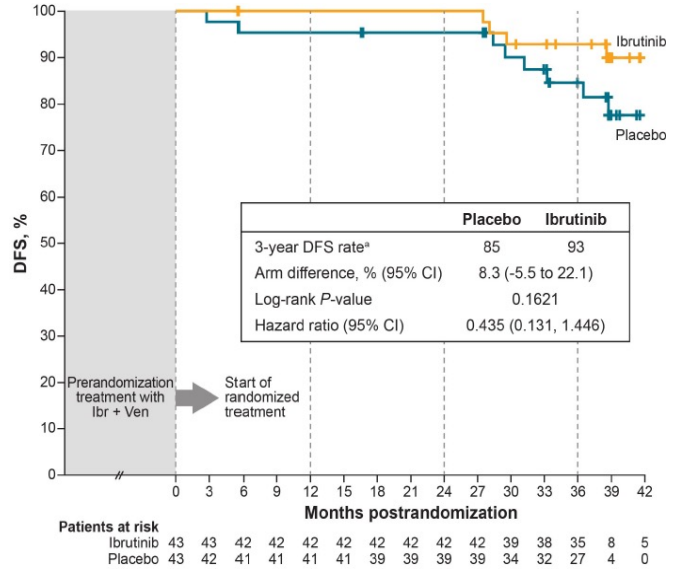
CAPTIVATE: MRD negativity rates were sustained 3-years post-randomization and similar in patients randomized to placebo vs continued ibrutinib



The sustainability of MRD negativity in the ITT population was comparable to that observed in the evaluable population

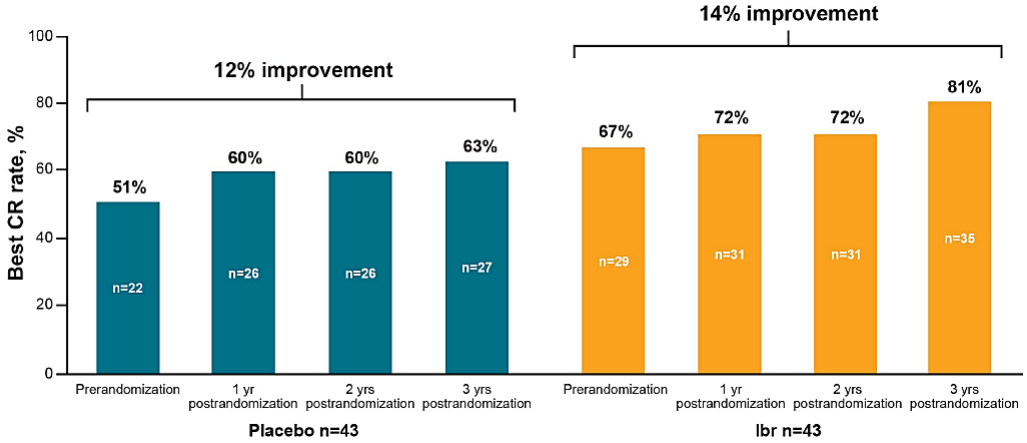
- Ibrutinib arm (ITT): 77% (33/43), 60% (26/43) and 63% (27/43) at 12, 24, and 36 cycles postrandomization, respectively
- Placebo arm (ITT): 84% (36/43), 56% (24/43), and 58% (25/43) at 12, 24, and 36 cycles postrandomization, respectively

3-year disease-free survival (DFS)[a] rates remain not significantly different between confirmed uMRD treatment arms



A median 41 months after stopping treatment, the 3-year DFS rate in the placebo arm remains similar to that in the ibrutinib arm (85% vs 93%)

Complete response rates were steady or increased with an additional year of follow-up

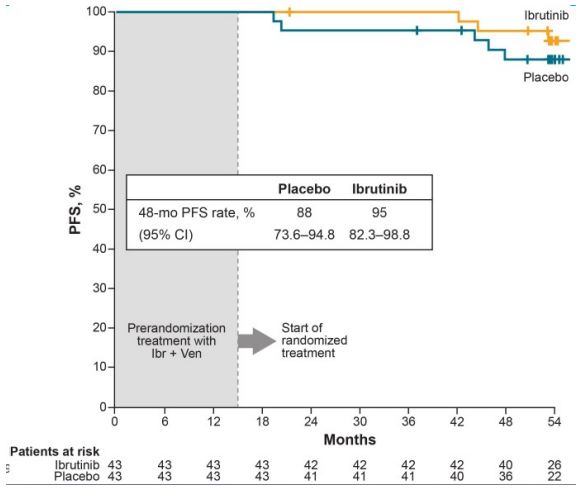


CRs were durable, with no significant difference in duration of CR between treatment arms at 42 months of follow-up

[a]DFS was defined as time from randomization to MRD relapse, PD per investigator assessment, or death, whichever occurred first

Allan et al., ASH 2022; Abstract 92

Progression-free survival (PFS)

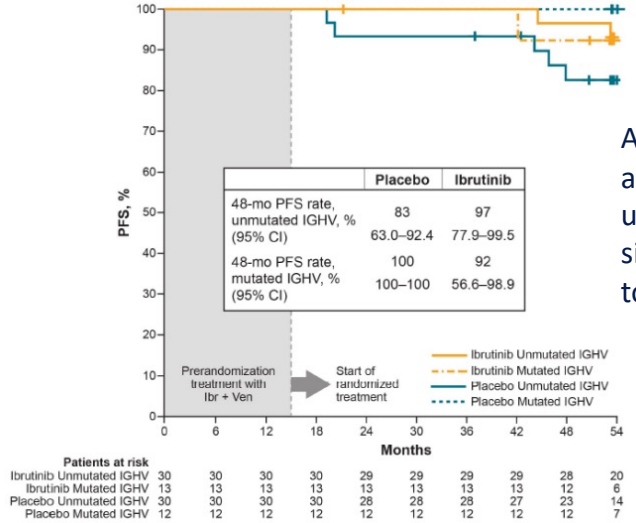


- At 48 months, PFS was 88% (95% CI, 74–95) with placebo and 95% (95% CI, 82–99) with continued ibrutinib

PD and Retreatment Outcomes

- 3 of 7 patients with PD in the placebo arm have initiated retreatment with ibrutinib; all 3 patients had PR
- 2 patients in the ibrutinib arm had PD; none have initiated retreatment

PFS by IGHV mutational status



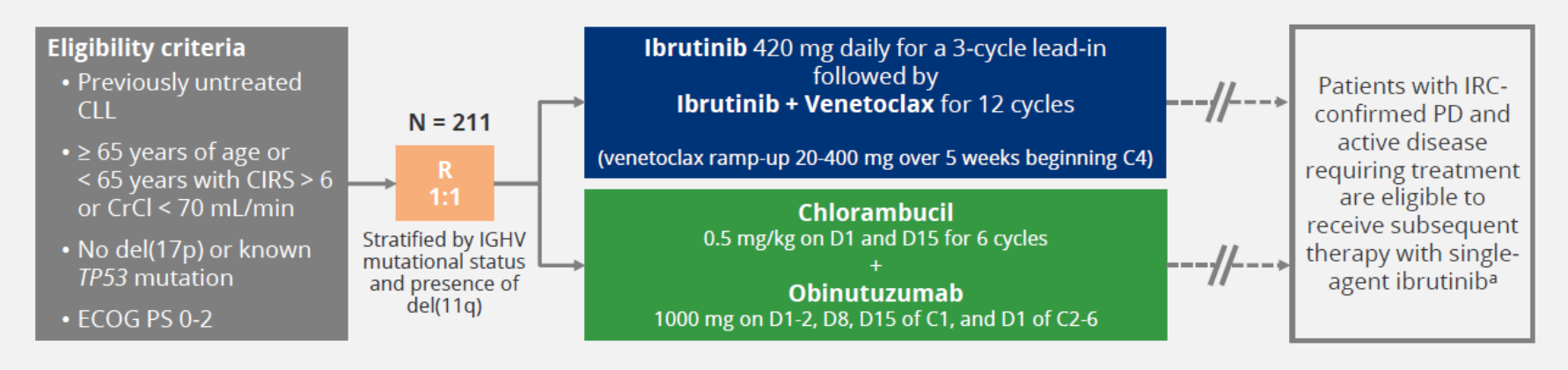
At 48 months, PFS rates among patients with unmutated IGHV were similar to those of the total population

Overall survival:

100% in placebo arm; 98% in ibrutinib arm.

No deaths occurred in either arm during the last 12 months of follow-up

GLOW phase 3 study: first-line ibrutinib plus venetoclax vs chlorambucil plus obinutuzumab (Clb+O)



Primary end point: IRC-assessed PFS

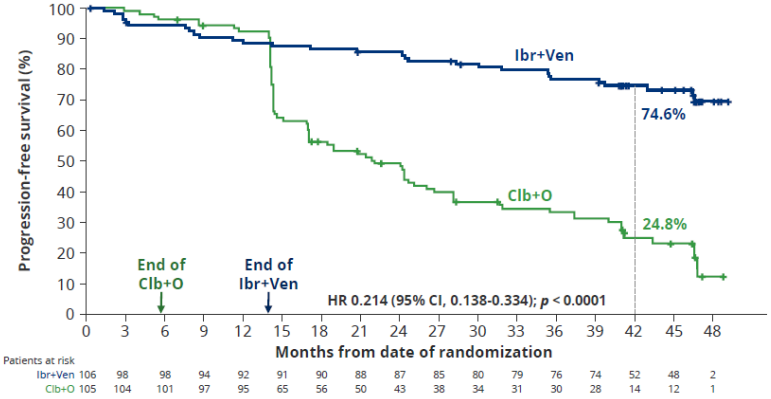
Key secondary end points: uMRD rates, response rates, overall survival, time to next treatment, and safety

- Current analysis
  - Median study follow-up of **46 months** (range, 1.7-51.7)
  - MRD assessed in peripheral blood in responders by NGS

albrutinib provided by the Sponsor to patients from both arms who were eligible to participate in the Subsequent Therapy Phase of the study. C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; NGS, next-generation sequencing; PD, progressive disease; R, randomization.

Niemann et al., ASH 2022; Abstract 93

Progression-free survival (PFS) remained superior for Ibr+Ven versus Clb+O with 4 years of follow up



Median study follow-up: 46 months

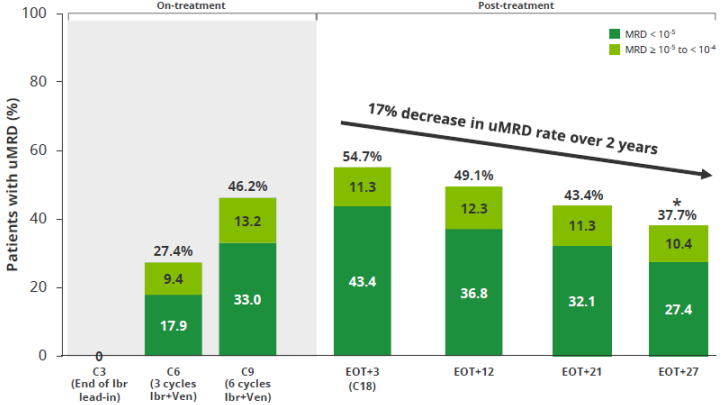
Ibr+Ven reduced the risk of progression or death by 79% versus Clb+O

- HR 0.214 (95% CI, 0.138-0.334); *p*< 0.0001

Estimated 3.5-year PFS rates:

- **74.6%** for Ibr+Ven
- **24.8%** for Clb+O

PB uMRD was attained early during treatment with Ibr+Ven and declined < 10% per year post treatment



On-treatment:

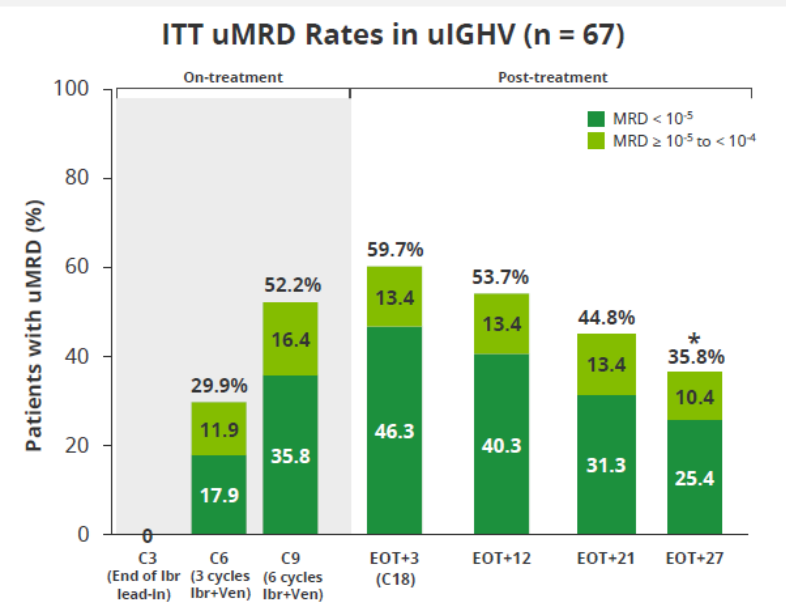
- Most patients who achieved uMRD by EOT+3 did so by C9, after 6 cycles of combined Ibr+Ven

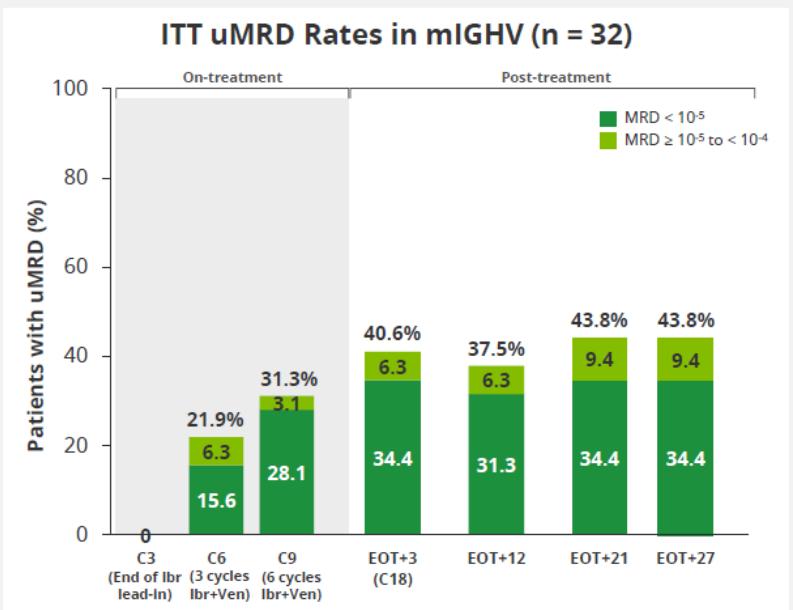
2 years post-treatment:

- Nearly 40% of patients had uMRD, including > 25% with deeper uMRD responses of < 10^{-5}

*8 (7.5%) patients with uMRD (including 6 with uMRD < 10-5) at EOT+21 had missing samples and were considered not uMRD at EOT+27. Numbers may not add up to exact total due to rounding. EOT, end of treatment; EOT+3, end of treatment plus 3 months; ITT, intent to treat; PB, peripheral blood.

GLOW phase 3 study: uMRD dynamics according to IGHV status

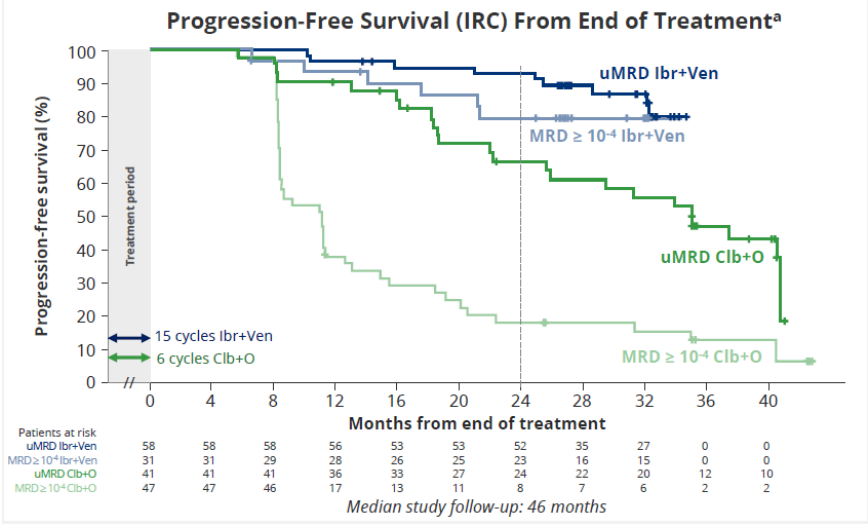


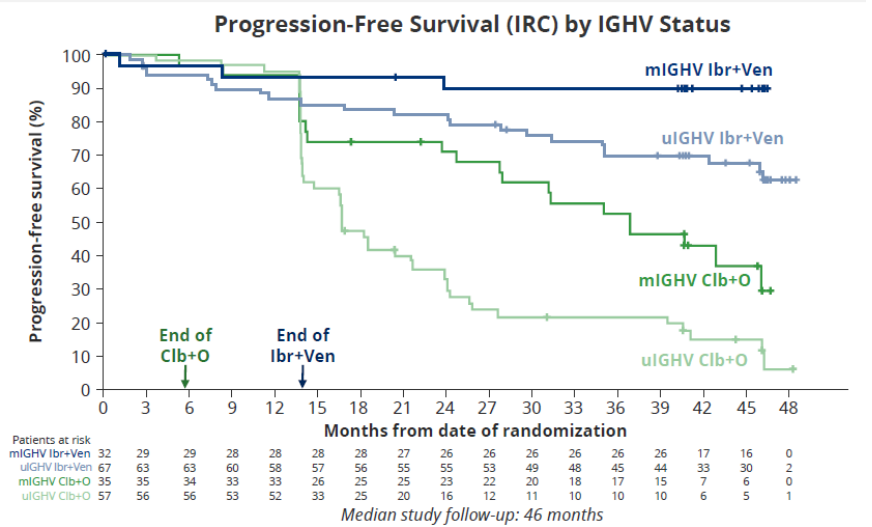


- uMRD rates (including < 10-5) were higher and uMRD was achieved faster in patients with uIGHV versus mIGHV CLL
- uMRDwas better sustained post-treatment in patients with mIGHV CLL

*7 (10.4%) patients with uMRD (including 5 with uMRD < 10-5) at EOT+21 had missing samples and were considered not uMRD at EOT+27.
Numbers may not add up to exact total due to rounding.

GLOW phase 3 study: PFS according to IGHV status





PFS was better sustained with Ibr+Ven versus Clb+O, regardless of MRD status at EOT+3

With Ibr+Ven

- Low impact of EOT+3 MRD status on PFS post-treatment
- PFS rate at 2 years post-treatment remained ≥ 80% regardless of MRD status

PFS at 3.5 years was higher for Ibr+Ven versus Clb+O for both uIGHV and mIGHV CLL

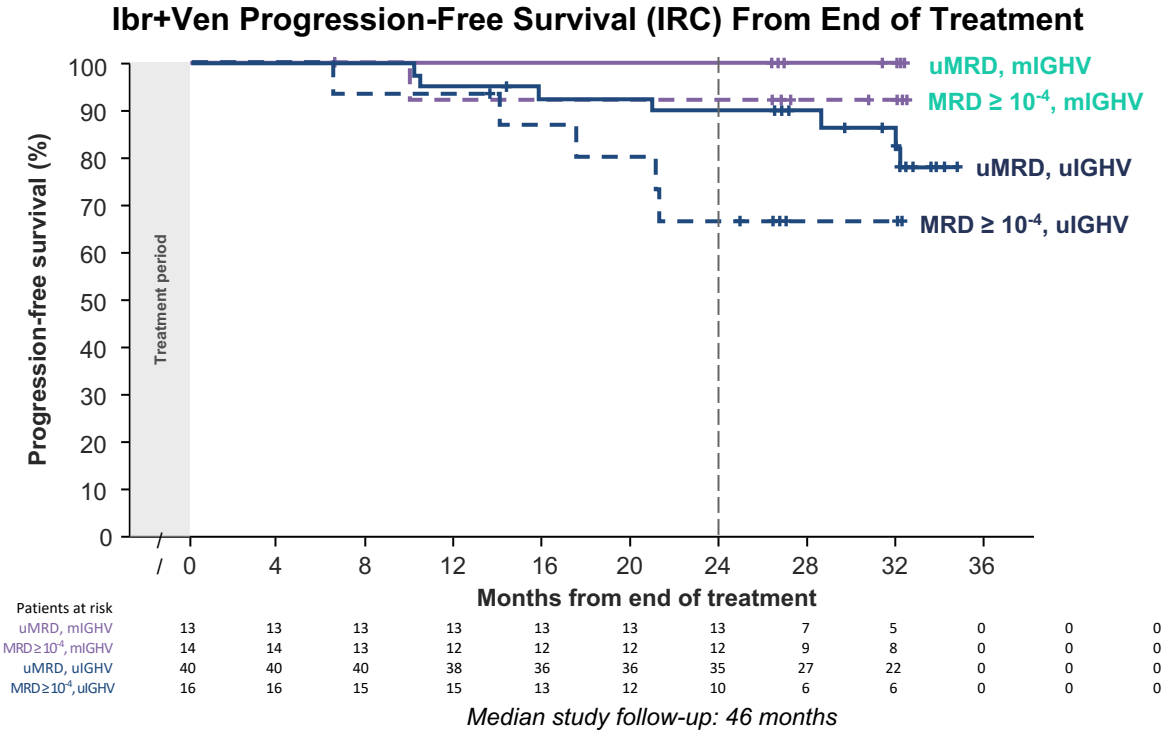
> 90% of patients in the Ibr+Ven arm did not require subsequent treatment at 3.5 years:

- 91.5% for uIGHV; 93.5% for mIGHV

aCurves generated from end of treatment (C15 for Ibr+Ven, C6 for Clb+O), resulting in different durations of post-treatment follow-up.

Niemann et al., ASH 2022; Abstract 93

GLOW phase 3 study: PFS according to uMRD and IGHV status

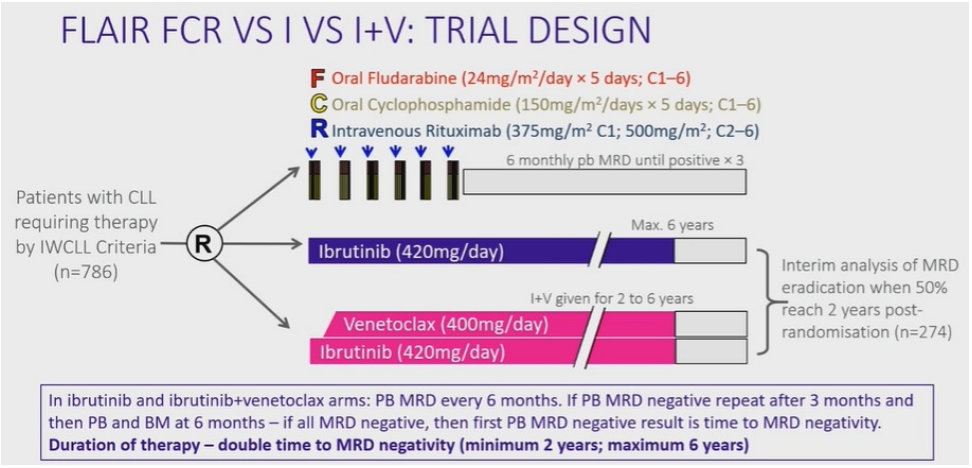


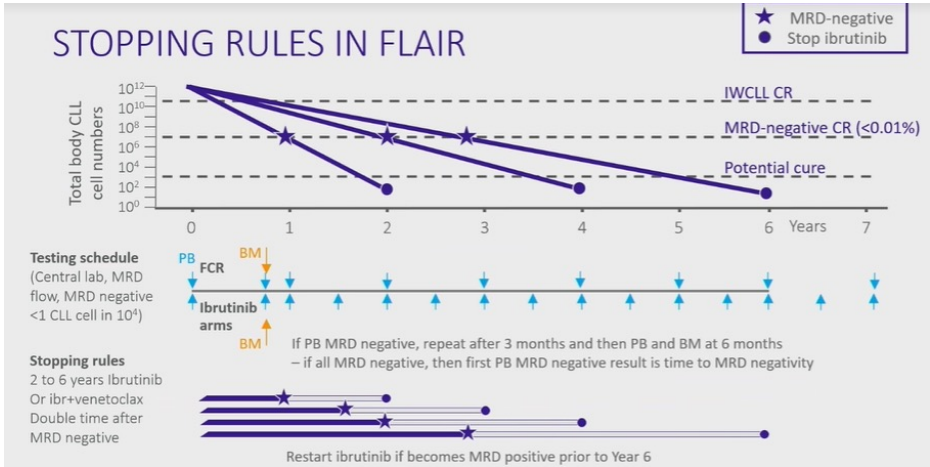
Median study follow-up: 46 months

IRC, independent review committee; uMRD, undetectable minimal residual disease; EOT+3, end of treatment plus 3 months.

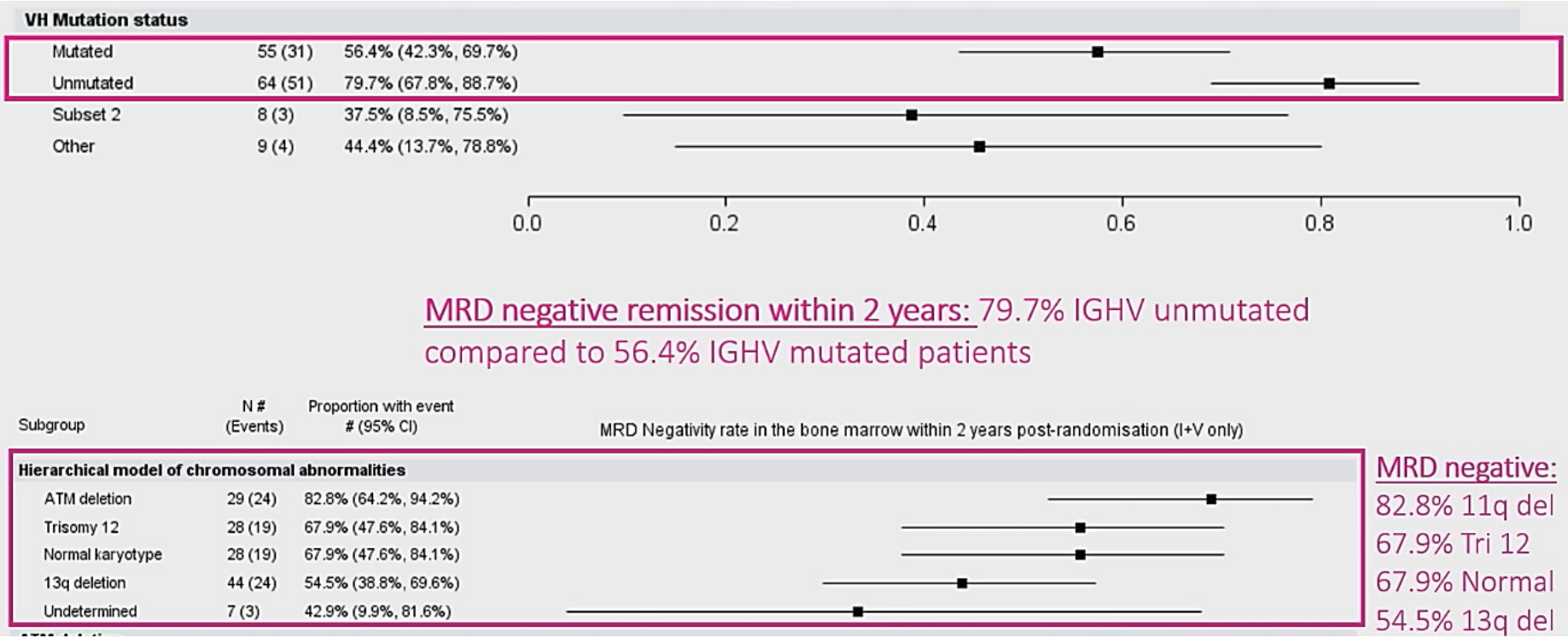
- Estimated PFS at 2 years post-treatment for **mIGHV** CLL:
  - >90% regardless of MRD status at EOT+3
- Estimated PFS at 2 years post-treatment for **uIGHV** CLL:
  - 90% for uMRD at EOT+3 versus 67% for MRD ≥ 10^{-4}

FLAIR phase 3 study: updated interim analysis of ibrutinib plus venetoclax with MRD-driven duration of treatment



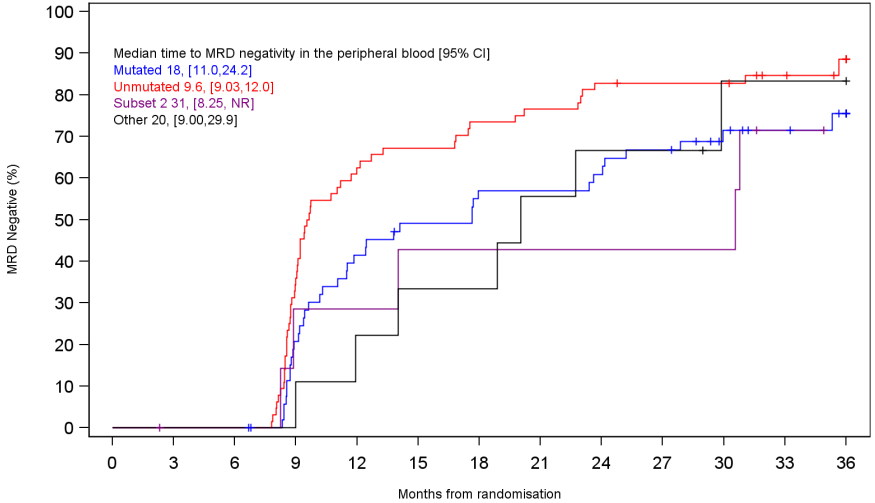


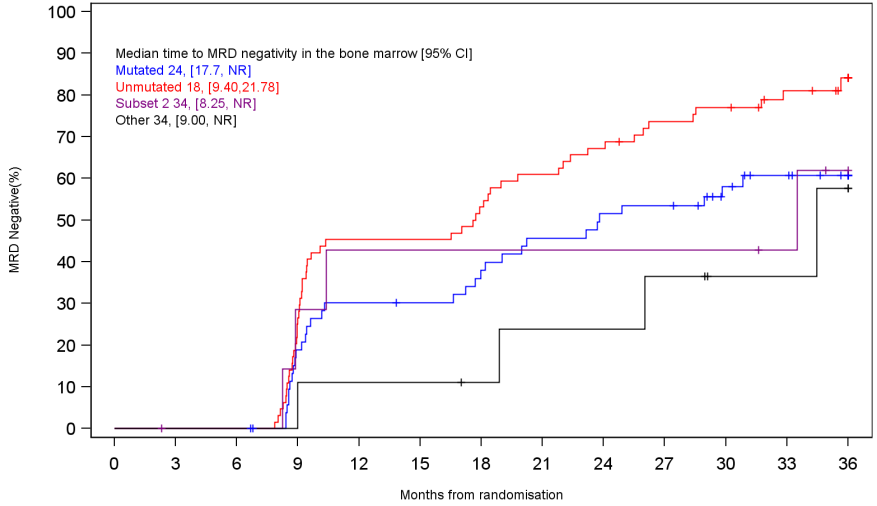
FLAIR phase 3 Study: MRD within 2 years by sub-group



Munir et al., ASH 2022; Abstract 94

FLAIR phase 3 Study: Time to MRD negativity by IGHV mutation status (I+V TREATMENT ONLY)





Ibrutinib and venetoclax for first-line treatment of CLL patients:

4-year follow-up data

	C1	C2	C3	C4 --> 27 (24 cycles of Combined Rx)
Ibrutinib	420mg daily	420mg daily	420mg daily	420mg daily
Venetoclax	-	-	-	20mg daily 1 week; 50mg daily 1 week; 100mg daily 1 week; 200mg daily 1 week; 400mg daily continuous

Duration of therapy: 24 cycles of combined IBR and VEN

Marrow MRD (flow cytometry) at end of cycle 24 of combined Rx
- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥0.01%): Continue 12 additional cycles of IBR + VEN

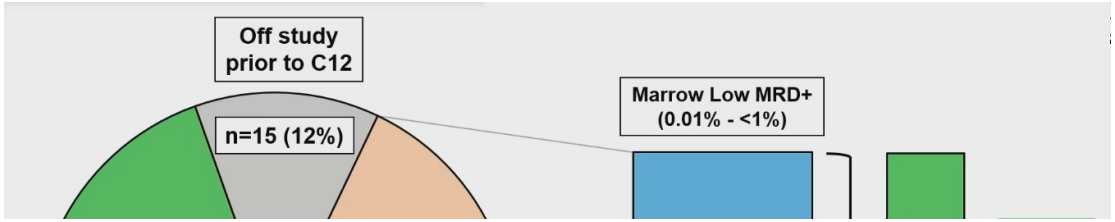
Patients with treatment-naïve CLL/SLL meeting 2008 iwCLL treatment criteria with at least one of the following feature:
- Del(17p) or mutated *TP53*
- Del(11q)
- Unmutated *IGHV*
- Age ≥65 years

Baseline characteristics (n=120)

		n (%) or median [range]
Age, years		64.5 [26-88]
	≥65	60 (50)
	≥70	35 (29)
Gender, M		87 (73)
ALC, K/μL		76.3 [1.14-366]
PLT, K/μL		140 [28-334]
HGB, g/dL		12.0 [7.7-18.4]
B2M, mg/L		3.6 [1.7-13.7]
FISH	Del(17p)	20 (17)
	Del(11q)	31 (26)
	Trisomy 12	23 (19)
	Negative	19 (16)
	Del(13q)	27 (22)
IGHV status (n=116)	Unmutated	100 (86)
Cytogenetics (n=115)	Complex	15 (13)
Mutations (n=119)	*TP53*	19 (16)
	NOTCH1	35 (29)
	SF3B1	26 (22)
	BIRC3	10 (8)
Del(17p) / *TP53*-m		27 (23)

Jain et al., ASH 2022; Abstract 95

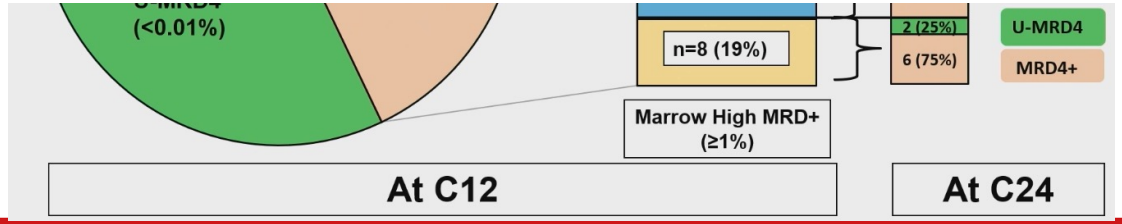
Ibrutinib and venetoclax for first-line treatment of CLL patients: Impact of 2nd year of treatment

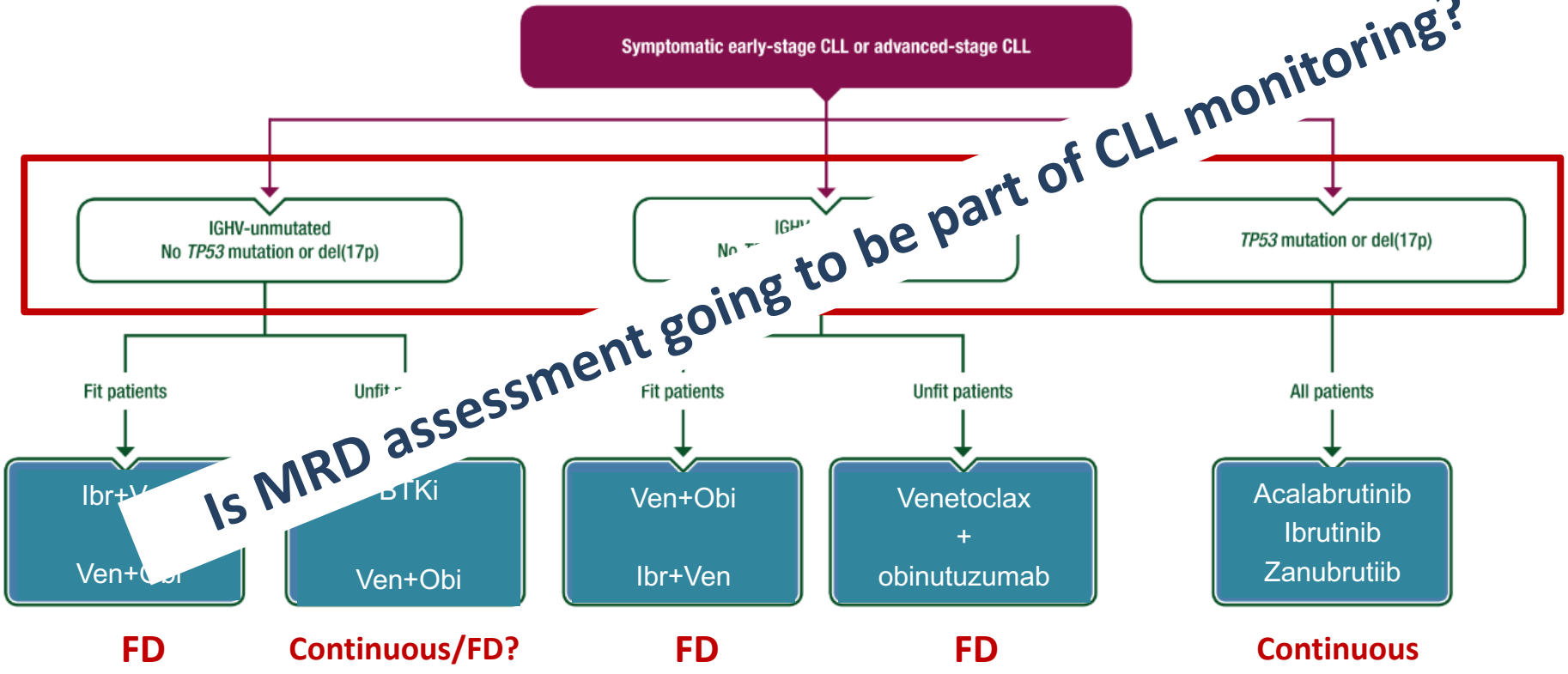


With a trial amendment, MRD+ pts after C24 could get 12 additional cycles of IBR + VEN combination

18/23 pts resumed combination for 12 additional cycles

11/18 (61%) pts achieved U-MRD remission during the third year of combined Rx





Is MRD assessment going to be part of CLL monitoring?

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