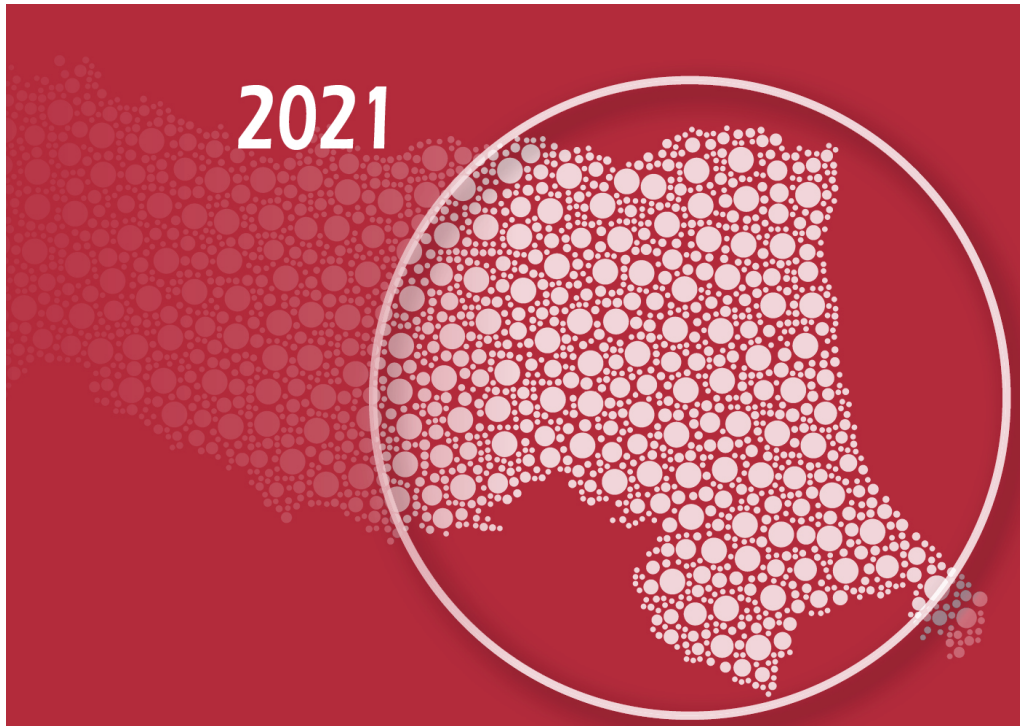


Progetto Ematologia Romagna

Terapia di prima linea: nuove proposte di combinazione di nuovi farmaci

Paolo Ghia

Università Vita-Salute San Raffaele/IRCCS Ospedale San Raffaele

Disclosures

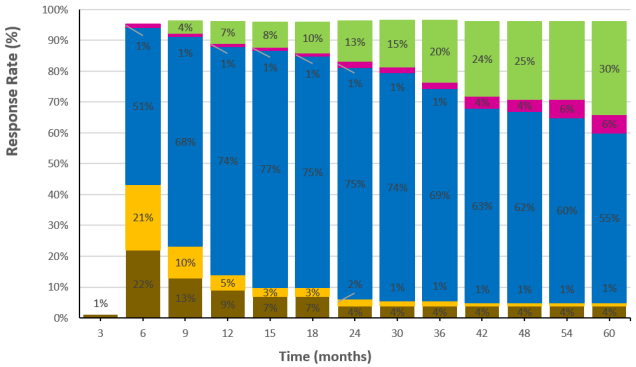
Research Support/P.I.: AbbVie, AstraZeneca, Gilead, Janssen, Novartis, Sunesis

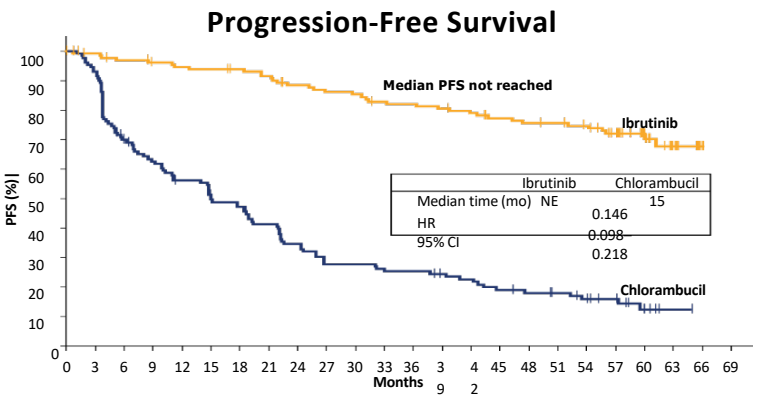
Consultant: AbbVie/PCYC, AstraZeneca, Adapative, ArQule/MSD, BeiGene, Celgene/Juno/BMS, Gilead, Janssen, Loxo/Lilly, Roche

Honoraria: AbbVie, AstraZeneca, Adapative, ArQule/MSD, BeiGene, Celgene/Juno/BMS, Gilead, Janssen, Loxo/Lilly, Roche

Scientific Advisory Board: AbbVie, AstraZeneca, Adapative, ArQule/MSD, BeiGene, Celgene/Juno/BMS, Gilead, Janssen, Loxo/Lilly, Roche

Ibrutinib continuous therapy: long term follow-up





- PFS @ 18 mo: 90% ➔PFS @ 60 mo: 70%
- PFS benefit across all sub-groups
- (Fit patients: median PFS FCR➔ 55 mo; BR➔ 42 mo)

Resonate-2: 6.5 years follow-up

Barr et al poster presentation
ASCO 2021

Median follow-up of 74.9 mo (up to 7y)

Estimated 78-mo PFS rates:
Ibrutinib: 61%
Chlorambucil: 9%

No differences between mutated and unmutated IGHV

Increase in CR to 34%

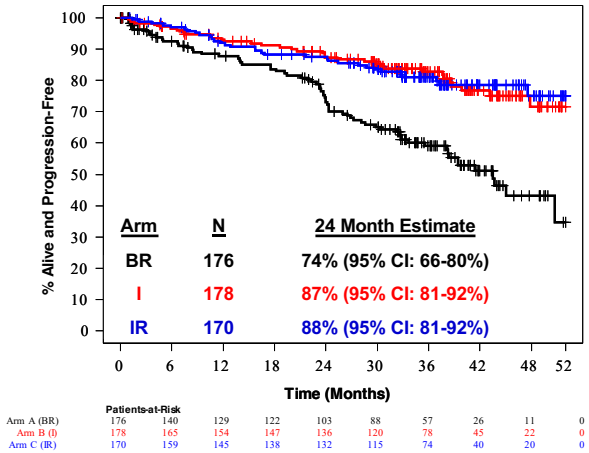
47% of patients remain on ibrutinib

Burger J.A:, et al; Leukemia 2020
To be updated at ASCO 2021

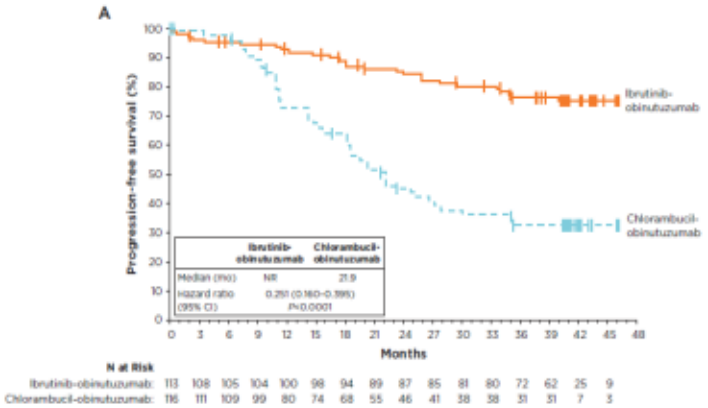
IE Ahn et al. N Engl J Med 2020;383:498-500

BTK inhibitors + anti-CD20 antibodies: any future?

Alliance 041202:
Ibrutinib +/- rituximab versus Bendamustine + rituximab



iLLUMINATE (IRC):
Ibrutinib + obinutuzumab versus chlorambucil + obinutuzumab



ELEVATE TN (IRC):
Acalabrutinib ± obinutuzumab versus chlorambucil + obinutuzumab

Sharman et al poster presentation ASCO 2021

Median follow-up of 46.9 mo (or 4y)

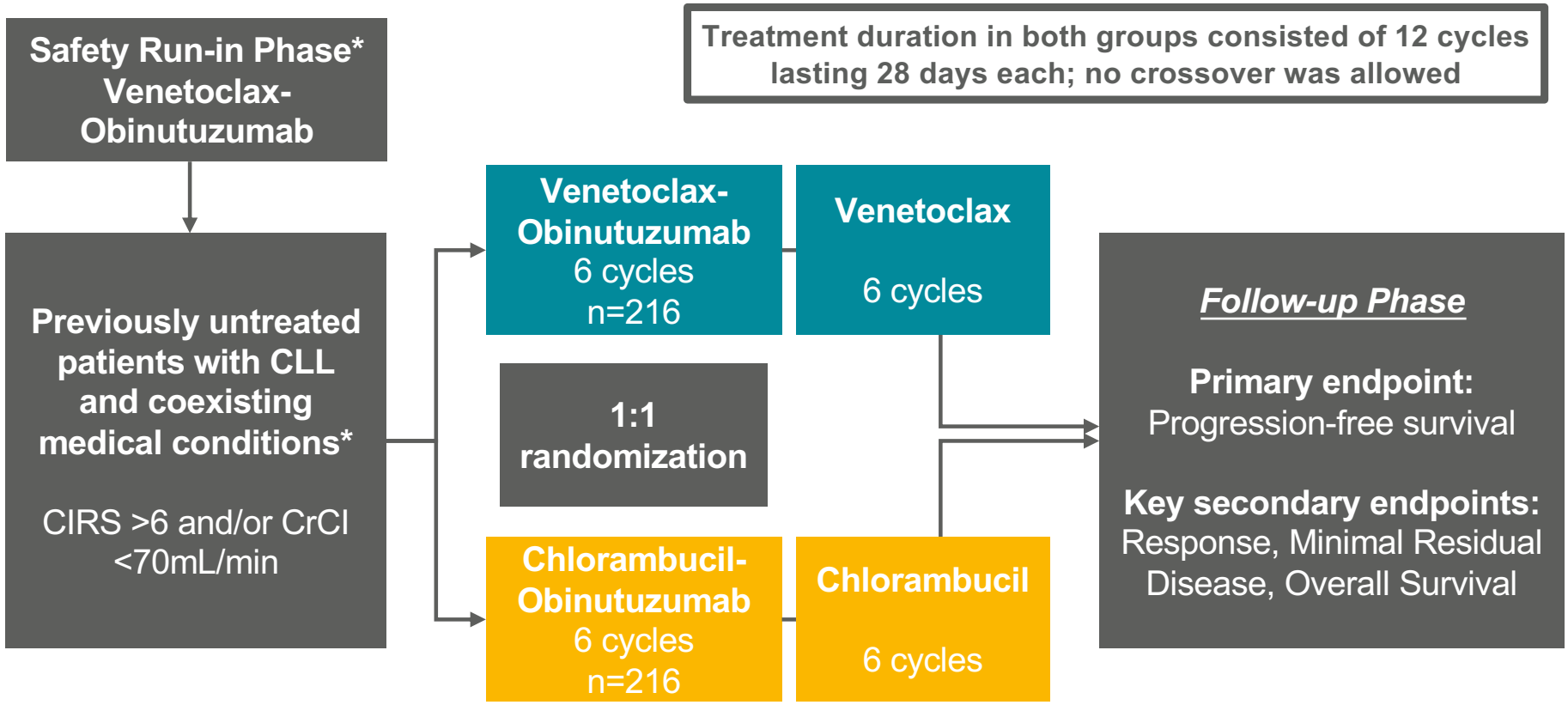
Estimated 48-mo PFS rates:
A+O: 87%
A: 78%
O+Clb: 25%

Increase in CR since the interim analysis
A+O: 21% to 27%
A: 7% to 11%

Woyach et al., N Engl J Med 2018 379:2517-2528; Moreno C et al, 2018 Lancet Oncol; Sharman JP et al, 2020 Lancet

CLL 14: Venetoclax + obinutuzumab

Study design



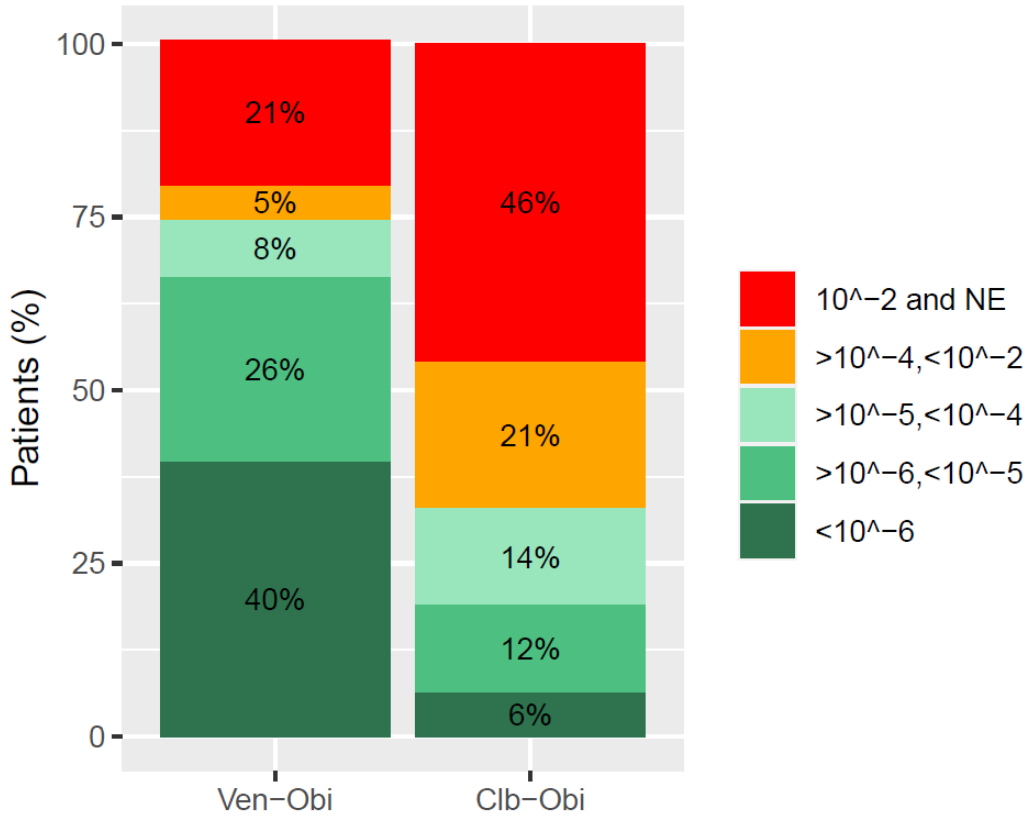
*patients with *TP53* deletion or mutation were enrolled at the investigator's discretion

Fischer et al., ASH 2019; abstract 36; Fischer et al., N Engl J Med 2019; 380:2225-36

CLL 14: Venetoclax + obinutuzumab

MRD results

» **MRD by NGS at EoT**



The CLL14 trial demonstrated very high rates of uMRD *after* **12 cycles of Venetoclax-Obinutuzumab**.

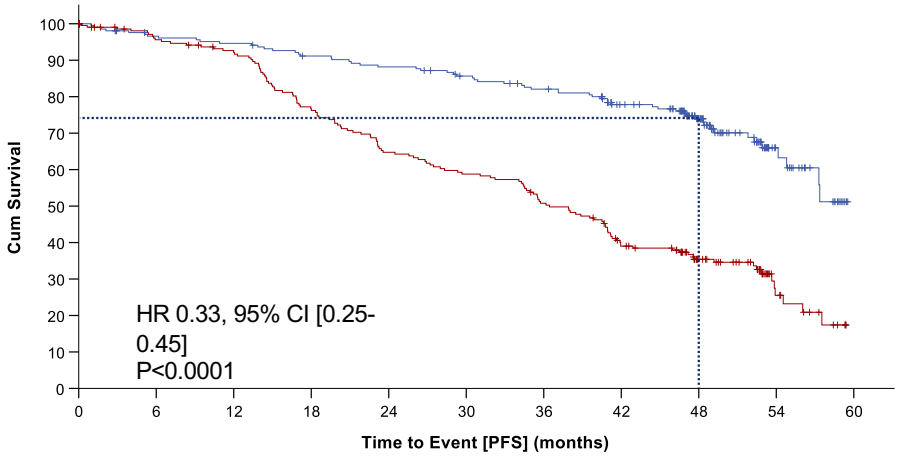
Fischer et al, N Engl J Med, 2019; Al-Sawaf et al, Lancet Oncol, 2020

CLL 14: Venetoclax + obinutuzumab

4-year follow-up

MEDIAN OBSERVATION TIME 52.4 MONTHS

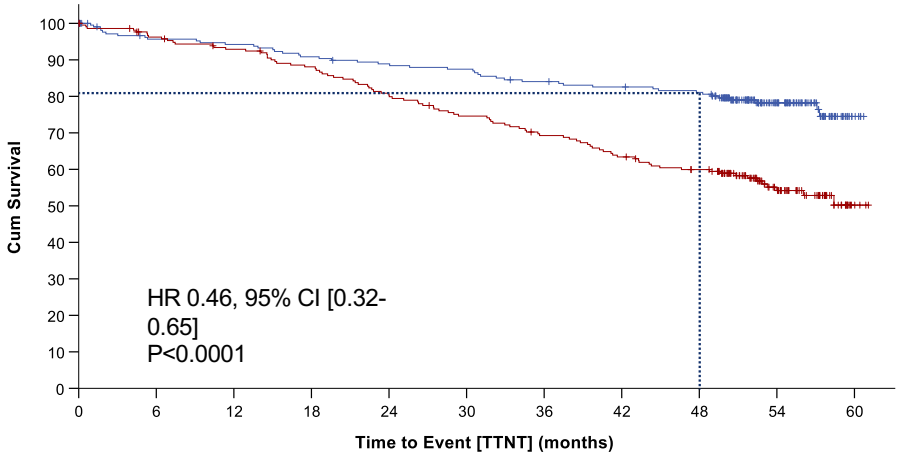
PROGRESSION-FREE SURVIVAL



Median PFS
Ven-Obi: not reached
Clb-Obi: 36.4 months

4-year PFS rate
Ven-Obi: 74.0%
Clb-Obi: 35.4%

TIME TO NEXT TREATMENT



Median TTNT
Ven-Obi: not reached
Clb-Obi: not reached

4-year TTNT rate
Ven-Obi: 81.08%
Clb-Obi: 59.9%

Next anti-leukemic therapy:
Ven-Obi: 35 PDs – 17 NLT
Clb-Obi: 122 PDs – 70 NLT

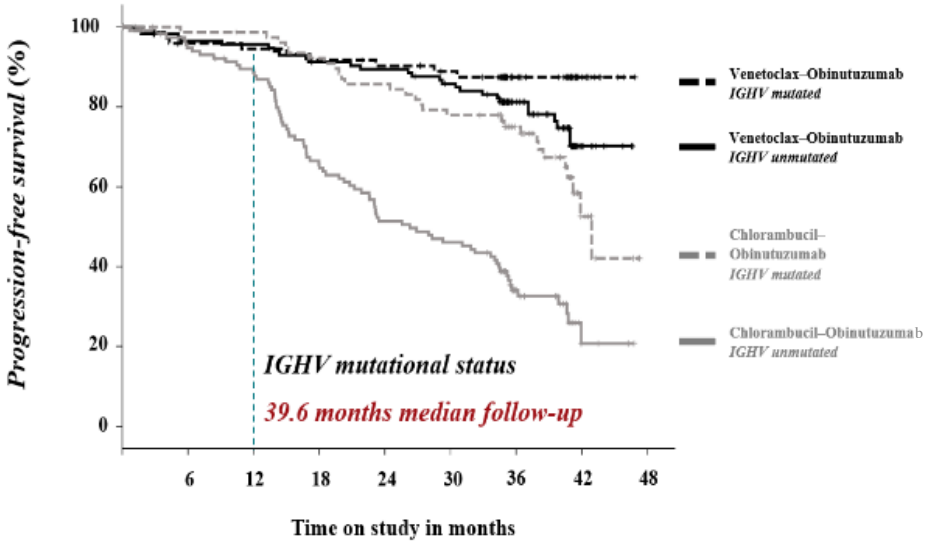
Venetoclax+Obi: si specifica che si fa riferimento ad una indicazioni terapeutica approvata da EMA in data 09/03/2020. Tale indicazione non è ancora rimborsata dal SSN

Al-Sawaf et al., ASH 2020; abstract 127 (oral)

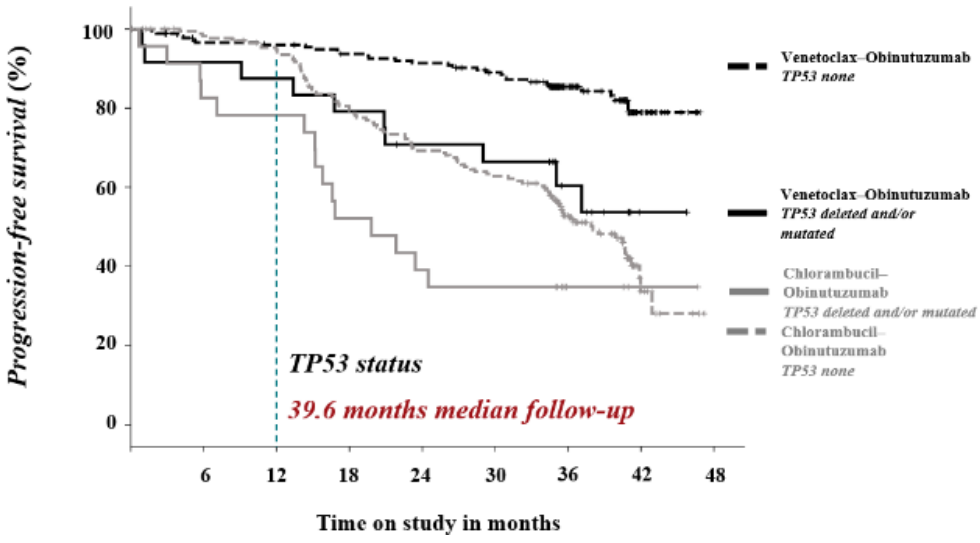
CLL 14: Venetoclax + obinutuzumab

PFS in high-risk patients

PFS by IGHV mutational status



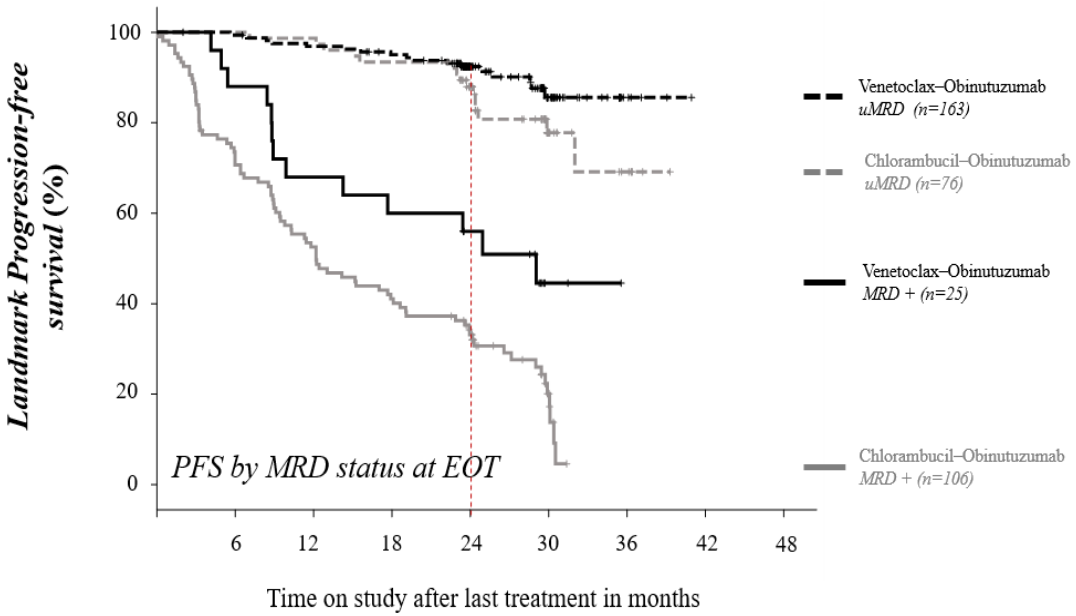
PFS by *TP53* mutational status

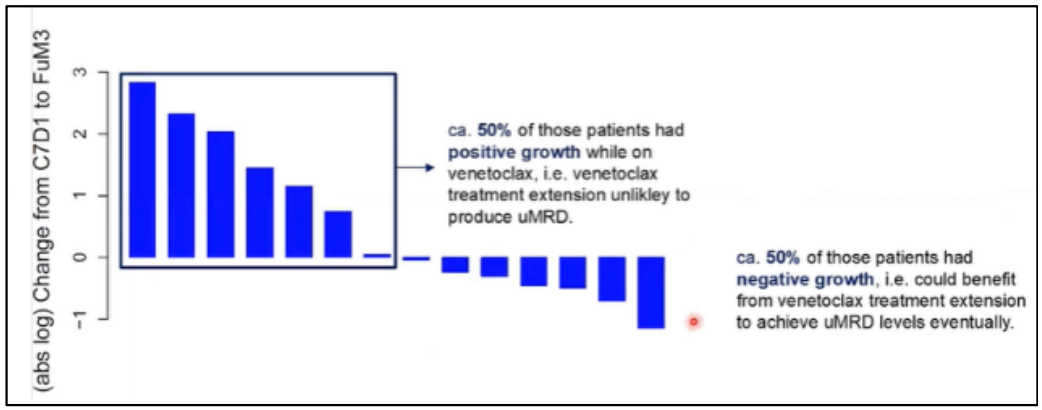


Fischer et al., ASH 2019; abstract 36; Fischer et al., N Engl J Med 2019; 380:2225-36

CLL 14: Venetoclax + obinutuzumab

MRD rates and impact on PFS





Al-Sawaf et al., ASH 2020; abstract 127 (oral) ; Fischer et al. ASH 2019 Abstract 36

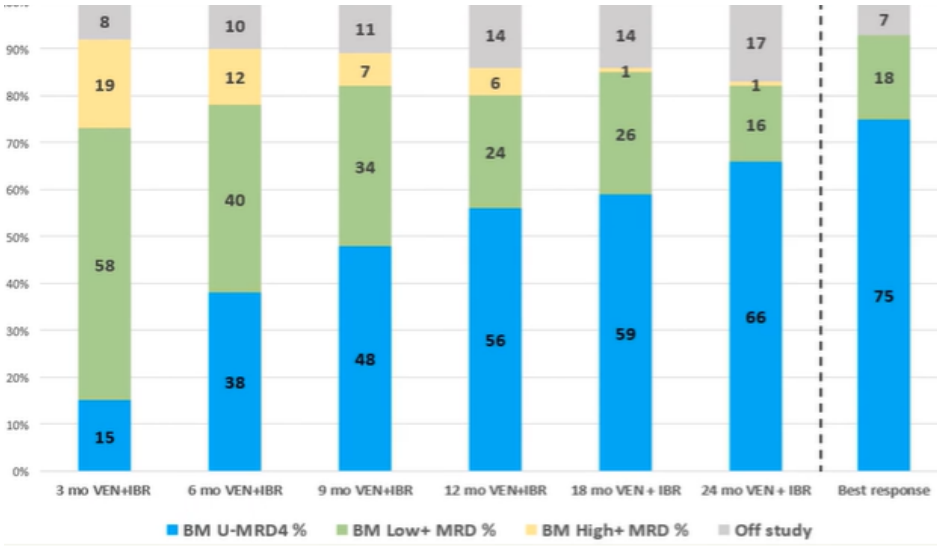
MDACC: Ibrutinib-Venetoclax combination in frontline

80 patients enrolled with a median follow-up of 36.3 months

Baseline characteristics

		n (%) or median [range]
Age, years		65 [26-83]
	≥65	43 (54)
	≥70	24 (30)
Gender, M		57 (71)
ALC, K/µL		75.6 [1.14-338]
PLT, K/µL		130 [28-334]
HGB, g/dL		11.6 [7.7-15.8]
B2M, mg/L		3.5 [1.7-13.7]
FISH	Del(17p)	14 (18)
	Del(11q)	20 (25)
	Trisomy 12	17 (21)
	Negative	10 (12)
	Del(13q)	19 (24)
IGHV status (n=76)	Unmutated	63 (83)
Cytogenetics (n=78)	Complex	12 (15)
	Diploid	32 (41)
Mutations (n=79)	*TP53*	11 (14)
	NOTCH1	22 (28)
	SF3B1	18 (23)
	BIRC3	5 (6)

Marrow MRD response at serial time points (n=80)



Marrow U-MRD4 % (ITT)

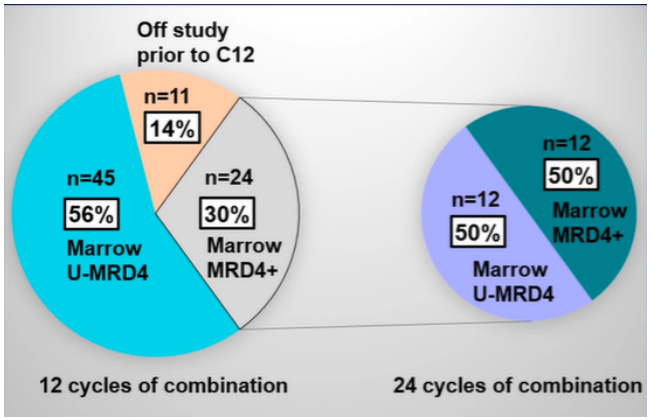
- At 12 months = 56%
- At 24 months = 66%
- Best response = 75%

92% of patients had either unmutated IGHV , TP53 aberration or del(11q)

Jain et al., 2019; N Engl J Med 380: 2095-2103; Jain et al., ASH 2020; Abstract 3138

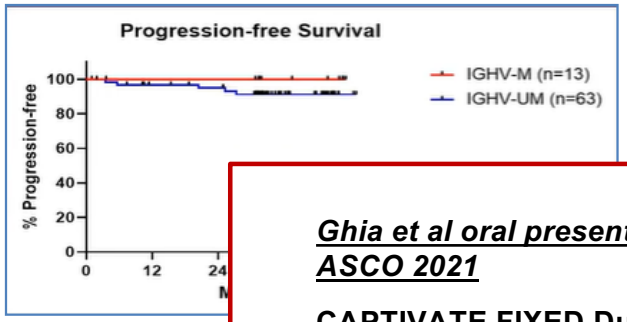
MDACC: Ibrutinib-Venetoclax combination in frontline

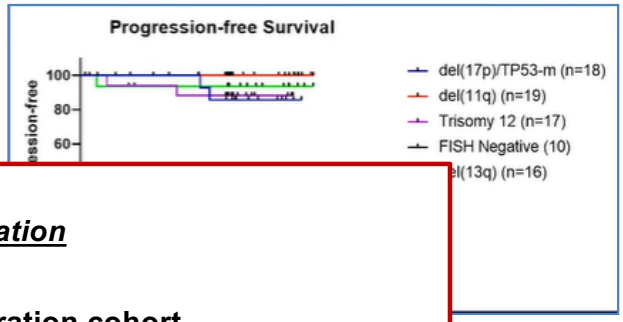
50% of marrow MRD+ at cycle 12 achieved marrow uMRD at cycle 24 with ongoing IV



- At the end of C12, 24 patients were BM MRD+
- 12/24 achieved BM uMRD at the end of C24
- Based on this data the trial has been amended to allow 12 additional cycles of IV for those who are marrow MRD+ at C24

PFS by IGHV, FISH and TP53 status





Ghia et al oral presentation
ASCO 2021

CAPTIVATE FIXED Duration cohort

Phase 2 study: Ibrutinib + venetoclax for 12 cycles (preceeded by 3 cycles of ibrutinib)

Median follow-up of 27.9 mo

CR rate: 55%, consistent in all genetic subgroups

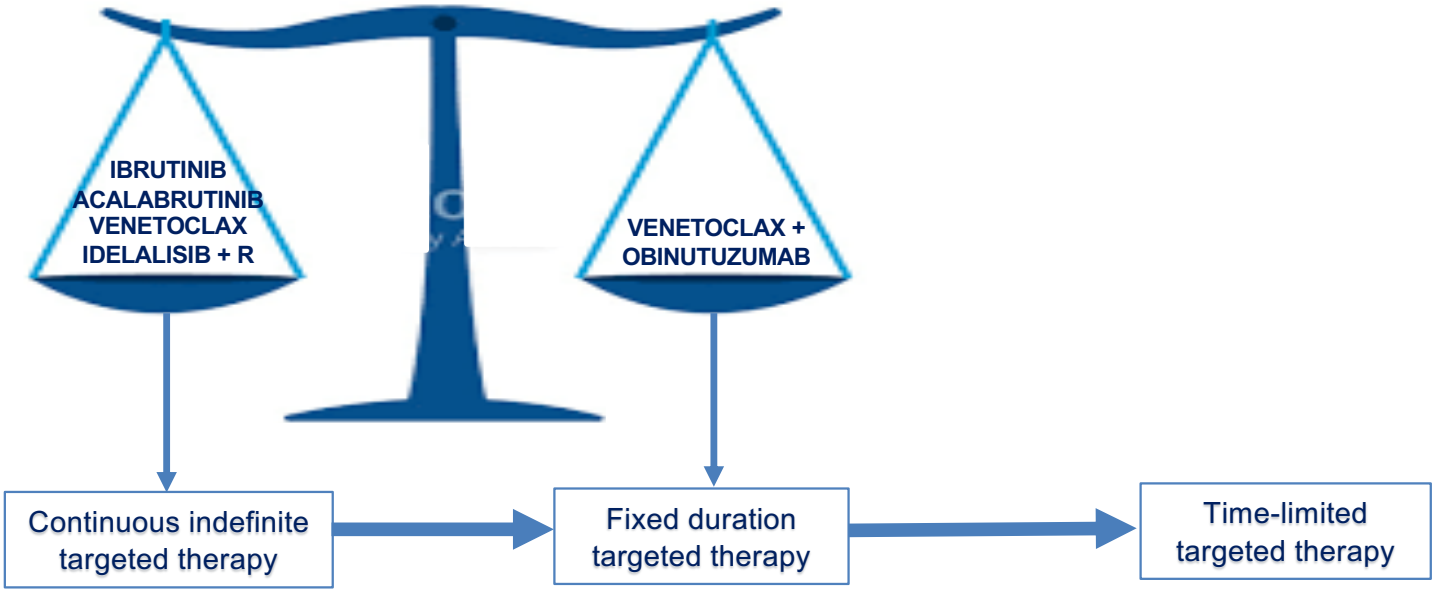
Best uMRD: 77% in PB; 60% in BM
Estimated 24-mo PFS rates: 95%

Outcomes for patients with del(17p)/TP53 mutation

- Of 13/18 patients with TP53-abberation who completed C24, BM uMRD at C12: 69%; at C24: 77%.
- 3 patients were marrow MRD+ at C24, one had Richter's transformation

Jain et al., 2019; N Engl J Med 380: 2095-2103; Jain et al., ASH 2020; Abstract 3138

The future of treatment: MRD-driven?

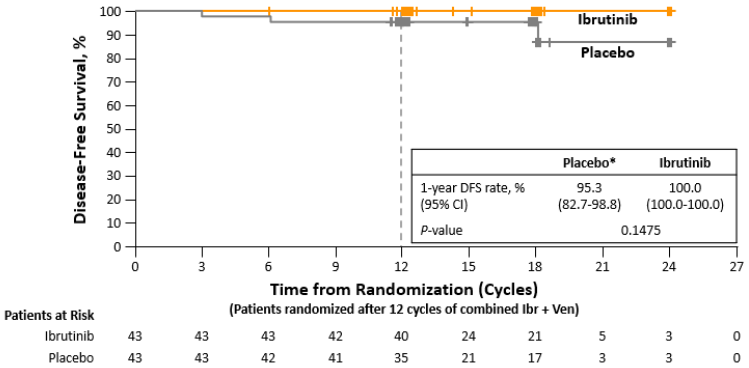


Modified from original of S. Molica

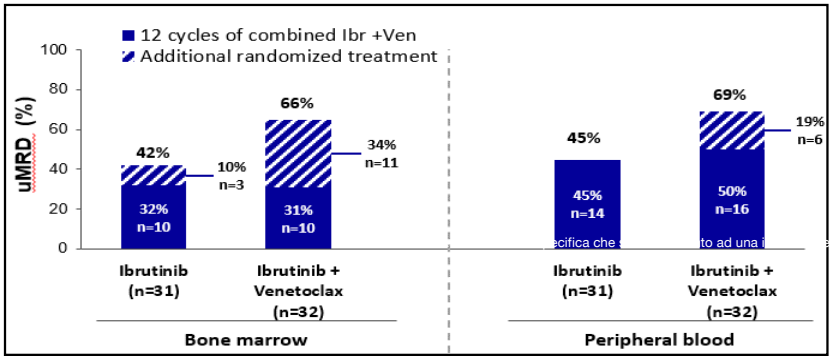
CAPTIVATE: Ibrutinib plus venetoclax

1-year disease-free survival from the MRD cohort

Primary Endpoint: 1-year DFS after randomization in patients with confirmed uMRD (Randomized, double-blind: Ibr vs Pbo)



In patients with not confirmed uMRD (Randomized: Ibr vs Ibr + Ven)



All Four Arms: Median follow-up on study: 31.3 months

	Confirmed uMRD		uMRD Not Confirmed	
	Placebo (n=43)	Ibrutinib (n=43)	Ibrutinib (n=31)	Ibrutinib + Venetoclax (n=32)
30-month PFS (95% CI)	95.3 (82.7–98.8)	100.0 (100-100)	95.2 (70.7–99.3)	96.7 (78.6–99.5)

- **Prevalence of AEs was generally highest during the first 6 months of ibrutinib + venetoclax and decreased over time**
- **Most common gr 3/4 AEs (≥5% of pts): Neutropenia (36%), hypertension (10%), thrombocytopenia (5%), diarrhea (5%)**

- 1L ibr + ven is an all-oral, once-daily, chemotherapy-free regimen with high rates of PB and BM uMRD, and a 90% reduction in high-risk TLS monitoring
- 1-yr DFS in pts randomized to placebo after ibr + ven combination was similar to that of pts continuing ibr, supporting a fixed-duration treatment that offers treatment-free remissions
- Depth of response achieved with this regimen is reflected in the 30-mo PFS rate of ~95% across all treated pts
- Safety profile of ibr + ven was consistent with known AEs for ibr and ven, and no new safety signals emerged

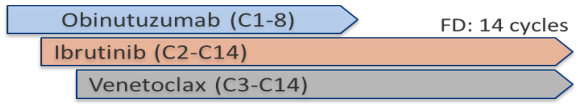
Wierda et al., ASH 2020; abstract 123 (oral)

2021

Are Triplet Combinations the Future in 1L?

I + V + G (n=25): 14 mos Fixed

Median f/u: 41.1 mos



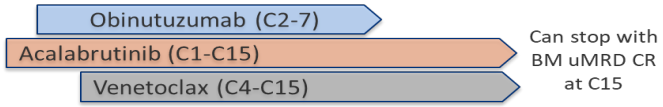
- **28% uMRD CR** at EOT
- **32% CR/CRi**
- **uMRD: 67% PB and BM** (EOT)

- 36-mos PFS and OS: 95%
- Gr 3+ decreased neutrophil (56%), decreased platelets (40%)

*Study also has R/R cohort (n=25)

A + V + G (n=44): MRD-guided

Median f/u: 19 mos

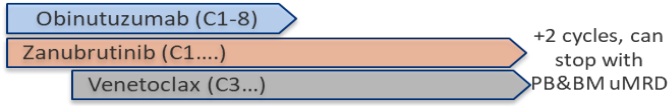


- **31% BM uMRD CR** at C16
- **43% CR/CRi**
- **uMRD: 84% PB, 77% BM** (C16)

- 11/36 pts stopped for uMRD
- Gr 3+ neutropenia (34%), thrombocytopenia (23%)
  - 11% received G-CSF

Z + V + G (n=39): MRD-guided

Median f/u: 14 mos



- uMRD CR not reported
- **49% CR/CRi**
- **uMRD: 92% PB, 84% BM** (best)

- 29 pts stopped for uMRD (~8 cycles ZVG)
- Gr 3+ neutropenia (15%), thrombocytopenia (5%)
  - 23% received G-CSF
- ZG lead-in reduced TLS risk

- IVG triplet has longest follow-up at 3 years, including post-treatment outcomes
- CR rate no higher than 50%. High uMRD rates.
- Gr 3+ neutropenia/hematological toxicity are common, requiring GF support

Rogers et al. JCO 2020; Roger et al., ASH 2020; abstract 1305 (Poster) ***Davids et al., ASH 2020; abstract 2216 (Poster)*** ***Soumerai et al., ASH 2020; abstract 1307 (Poster)***

Personalized treatment in CLL

IRCCS Ospedale San Raffaele
Division of Experimental Oncology

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