Venetoclax in High Risk CLL

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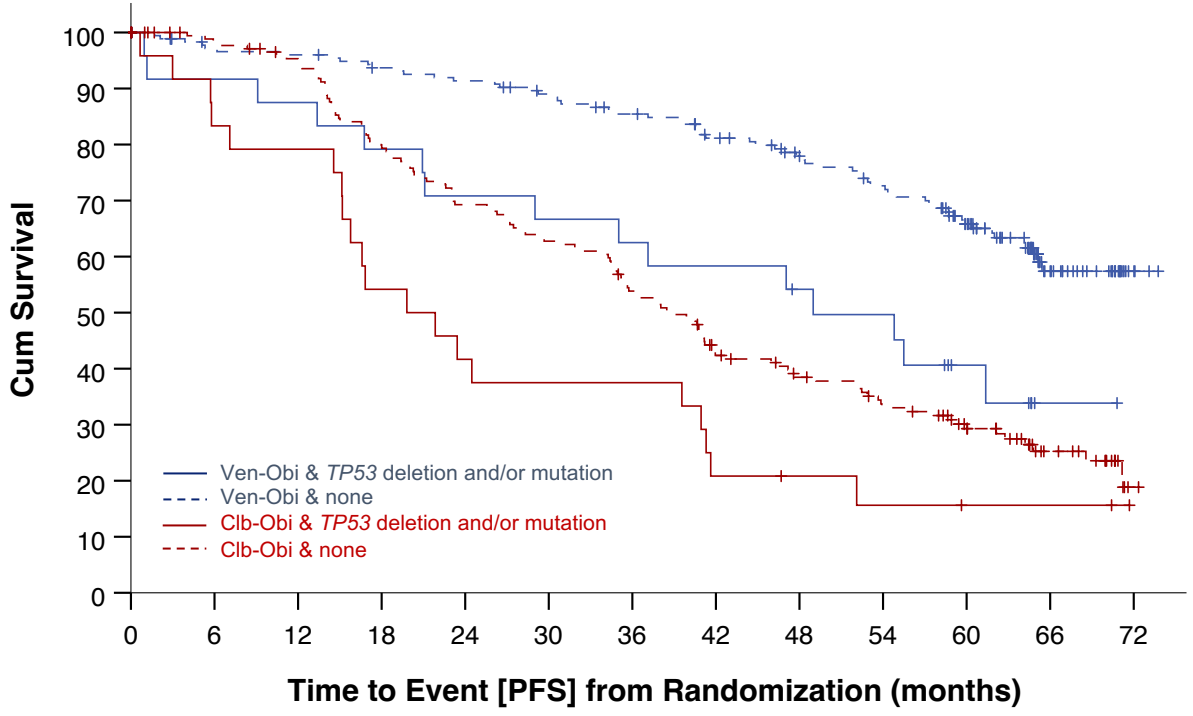
Disclosure of Constantine TAM

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	x					x	
AbbVie	x					x	
BeiGene	x					x	
LOXO						x	
AstraZeneca						x	

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 65.4 months



Ven-Obi & *TP53* del/mut	25	22	21	19	17	16	15	14	12	11	6	1	0
Ven-Obi & none	184	169	167	161	157	150	142	130	119	109	89	33	4
Clb-Obi & *TP53* del/mut	24	20	19	13	10	9	9	5	4	3	2	2	0
Clb-Obi & none	184	169	160	135	117	106	90	68	58	48	36	18	1

Median PFS

Ven-Obi & no *TP53*del/mut: NR

Ven-Obi & *TP53*del/mut: 49.0 m

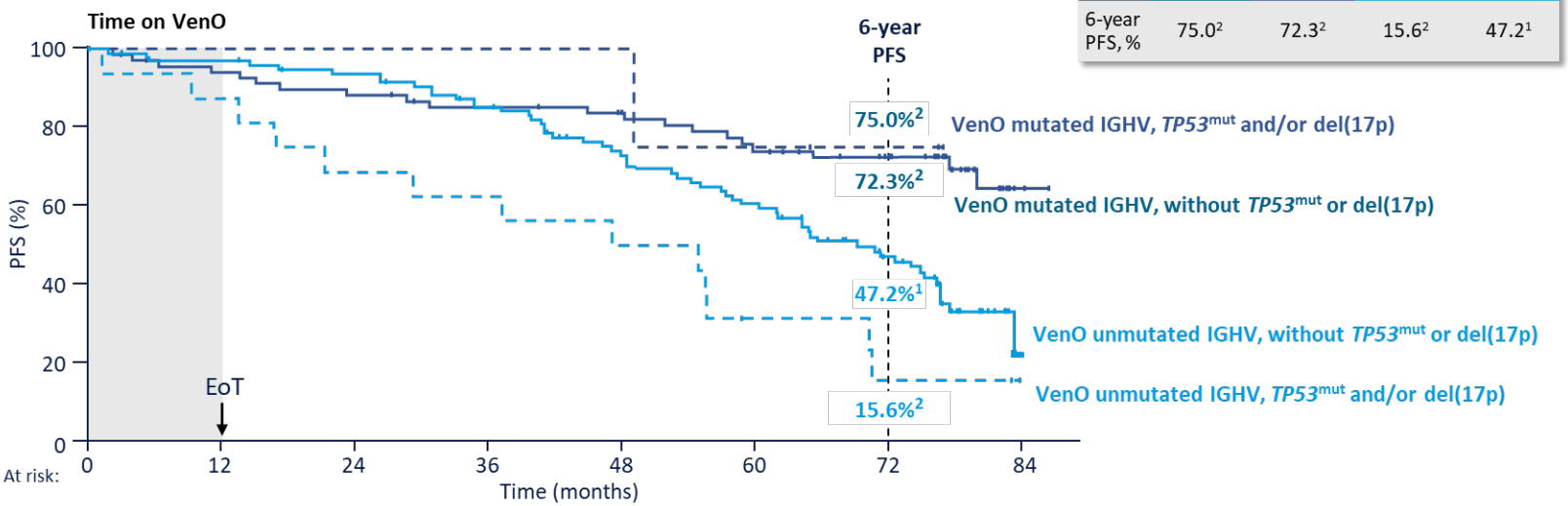
Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 19.8 m

TP53 RISK MAY BE MODULATED BY IGHV STATUS

	VenO mutated IGHV		VenO unmutated IGHV	
	with *TP53*^{mut}/ del(17p) (n=5)	without *TP53*^{mut} or del(17p) (n=71)	with *TP53*^{mut}/ del(17p) (n=16)	without *TP53*^{mut} or del(17p) (n=103)
6-year PFS, %	75.0[2]	72.3[2]	15.6[2]	47.2[1]

VenO arm: Progression-free survival[1]
(median follow-up 76.4 months)

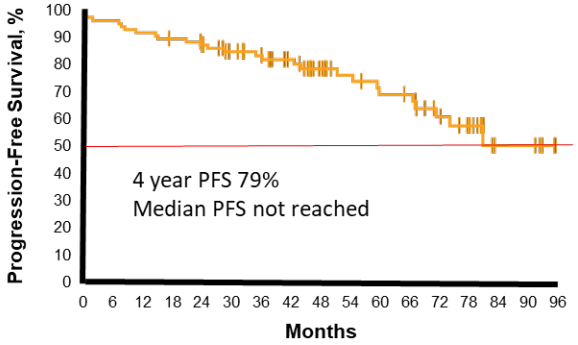


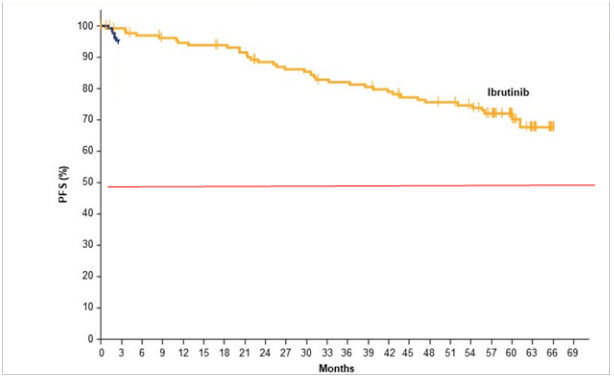
For VenO, PFS was longer for patients with mutated IGHV vs unmutated IGHV, irrespective of *TP53* aberration status.
The 6-year PFS rate was consistent with the overall population in patients with unmutated IGHV and no *TP53* aberration[1,2]

EoT, end of treatment; O, obinutuzumab; Ven, venetoclax.

1. Al-Sawaf O, *et al.* ICML 2023. Abstract 025 (Oral); 2. AbbVie. Data on File. ABVRRTI76440.

IBRUTINIB POOLED RESULTS IN 1L TP53 CLL





PFS TP53 dysfunction

Shanafelt EHA 2020 abstract #2219
ASH 2020 Abstract #2219

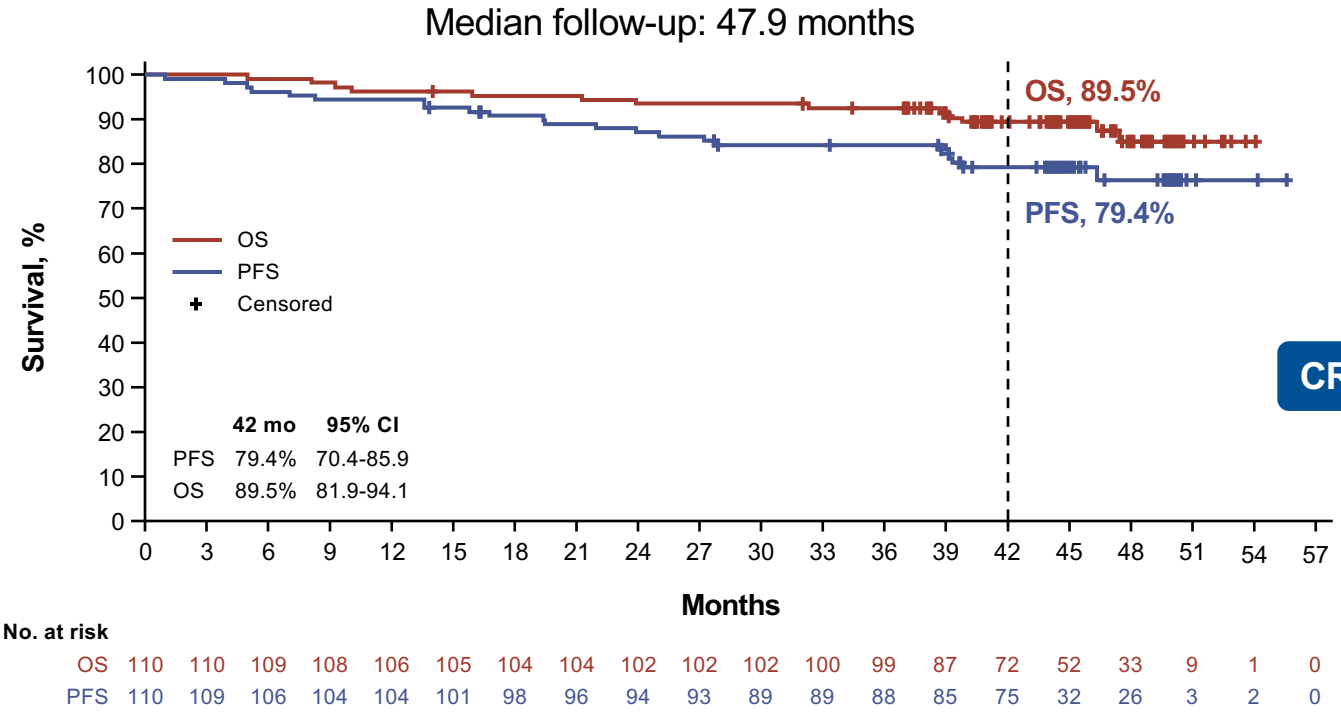
PFS all comers

EHA 2019 RESONATE-2 CLL/SLL Tedeschi
Burger, Barr, Robak et al. Leukemia. 2020 Mar;34(3):787-798

Longer term outcome TP53 dysfunction treated CLL 1L with ibrutinib not clearly worse than all commers longer follow up needed

Burger et al. Leukemia. 2020; 34(3):787-798;
Moreno et al. Lancet Oncol. 2019; 20(1): 43-56;
Shanafelt TD et al. NEJM. 2019; 381(5): 432-43; A
Allan et al. Br J Haematol 2022 Feb; 196(4): 947–953

SEQUOIA “Arm C” – Zanubrutinib in 17p- CLL

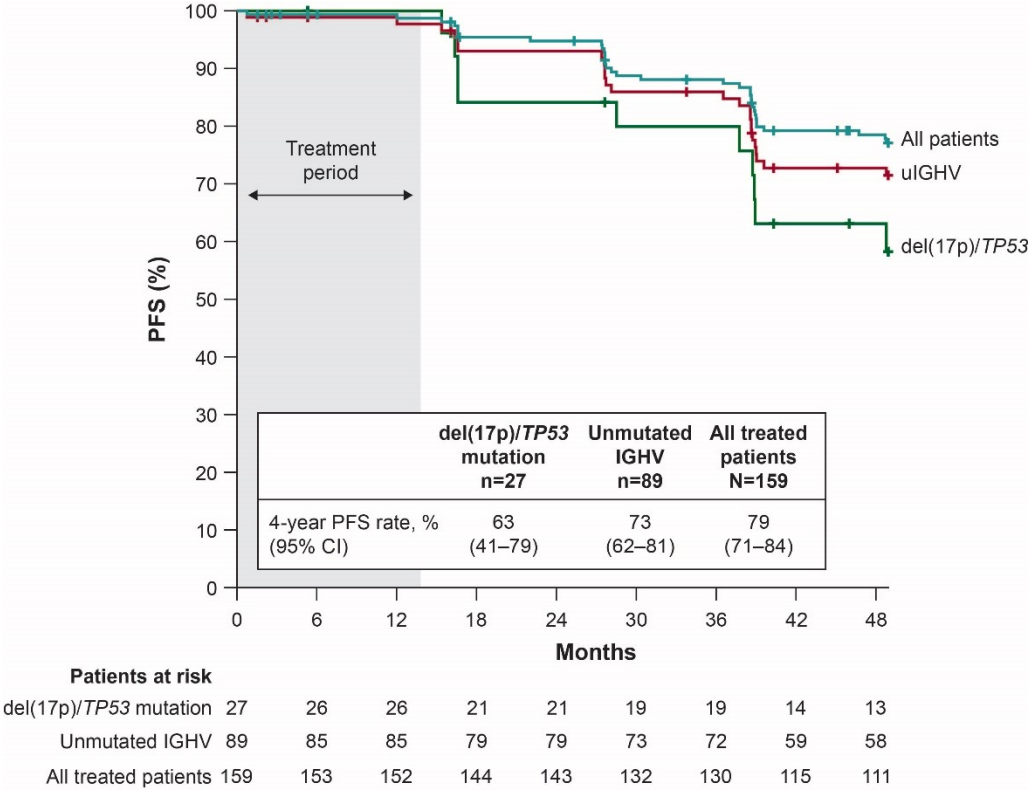


CR/CRi rate, 14.5%

CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Is Time Limited Therapy Possible for 17p- CLL?

CAPTIVATE FIXED-DURATION COHORT (12 MONTHS)

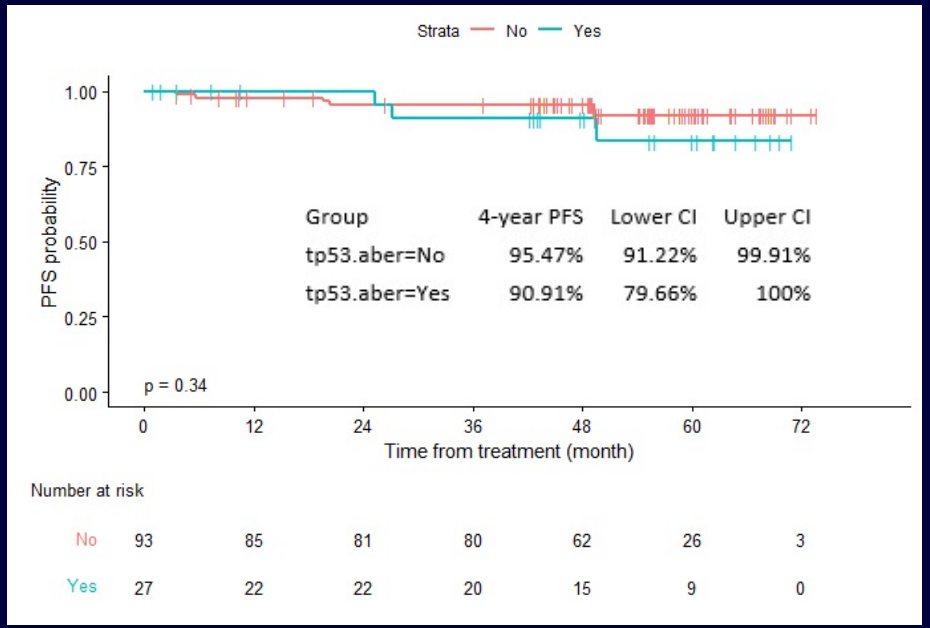


Time to Next Treatment

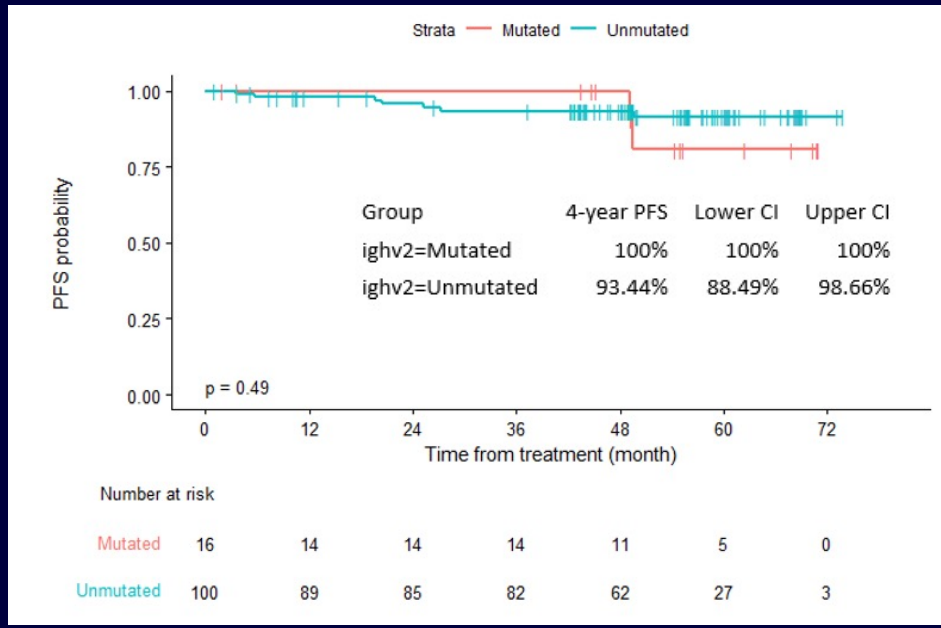
- Median TTNT was not reached (n=28; range 1–53 months)
- Landmark estimate of the proportion of patients who had not started a next treatment at 4 years was 84% (95% CI 77–89)

IGHV, immunoglobulin heavy chain variable region gene; PFS, progression-free survival; uMRD, undetectable minimal residual disease.

MD ANDERSON PHASE 2 IBR-VEN (24 MONTHS)



TP53 aberrant status



IGHV mutation status

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

CAPTIVATE MRD-DRIVEN COHORT

Efficacy outcomes, % (95% CI)	All treated Placebo (N=43)	All treated Ibrutinib (N=43)	Del(17p), TP53 mut, or CK Placebo (n=6)	Del(17p), TP53 mut, or CK Ibrutinib (n=20)
DFS (3-year)	85 (69–93)	93 (80–98)	100 (100–100)	95 (70–99)
PFS (4-year)	88 (74–95)	95 (82–99)	100 (100–100)	95 (70–99)
OS (4-year)	100 (100–100)	98 (84–100)	100 (100–100)	100 (100–100)

- Outcomes were consistent with the total population, although sample size is small in the placebo arm

[a]In ibrutinib arm, 20 high-risk: 13 del(17p)/*TP53* + 7 CK without del(17p)/*TP53*. In the placebo arm, 6 high-risk: 2 del(17p)/*TP53* + 4 CK without del(17p)/*TP53*.

ASH 2022; Allan JN et al.

CONCLUSIONS

- Ven-O outcomes inferior in patients with TP53 aberrancy
- Not clear if Ibrutinib-Venetoclax is able to overcome the requirement for BTK maintenance
- If time-limited Ibr-Ven : ideally longer exposure (24 months) or MRD-driven