

Case Report 1

IGHV-unmutated

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REVOLUTIONARY ROAD IN CLL

Innovazione rivoluzionaria nella terapia
della leucemia linfatica cronica

Catania, 28 maggio 2024
Palace Catania UNA Esperienze

In questa slide in relatore dovrà dichiarare il conflitto d'interessi ed indicare:

Il sottoscritto **Innao Vanessa**
in qualità di relatore

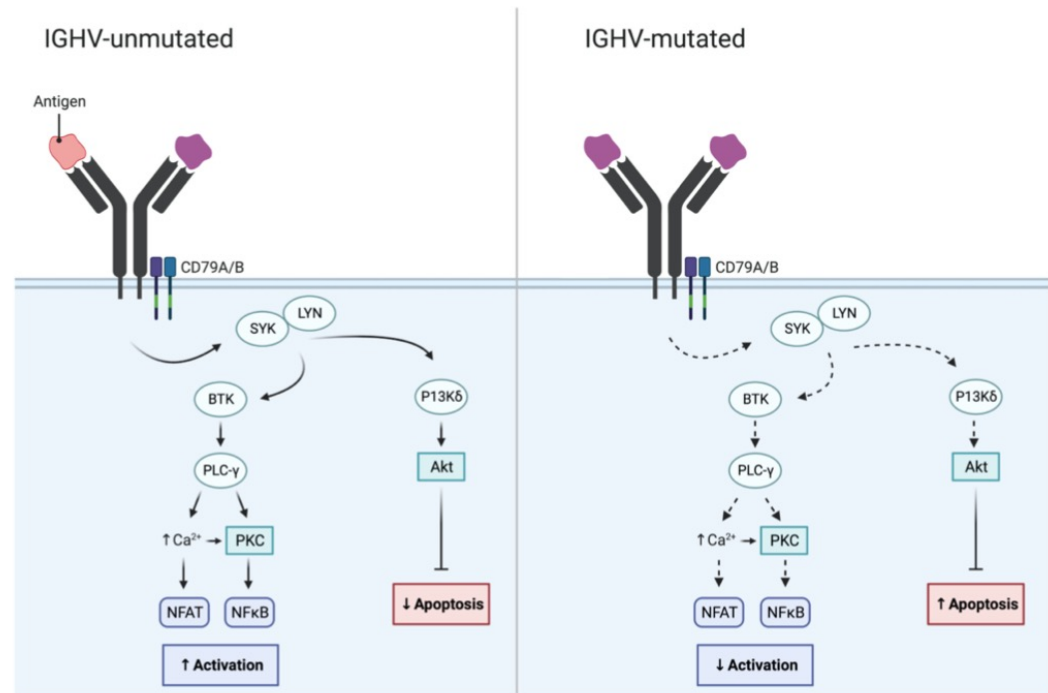
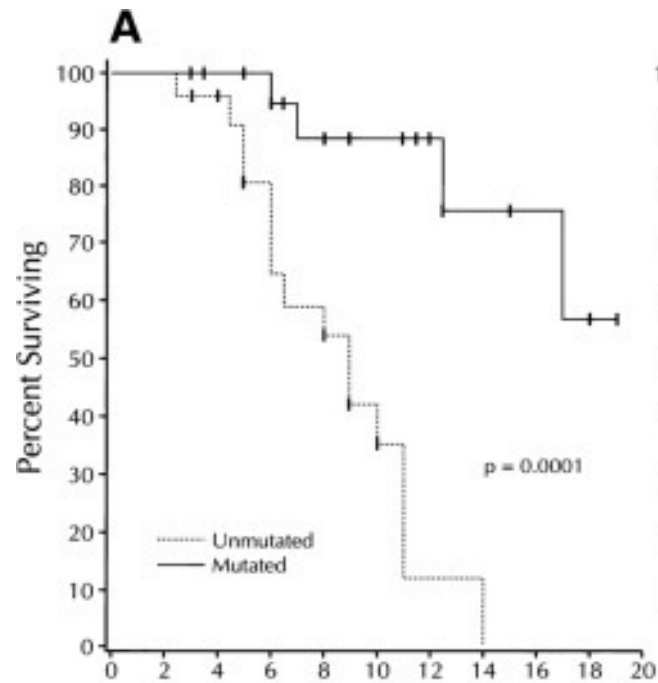
ai sensi dell'art. 76 sul Conflitto di Interessi, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

dichiara

che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Abbvie, Amgen, Astrazeneca, Grifols, GSK, Janssen, Novartis, Sobi.

Immunoglobulin heavy chain variable (*IGHV*) gene mutational status in CLL



Damle RN et al, Blood 1999

Mollstedt J et al, Front Oncol 2023; Rosenquist R et al, Leuk Lymph 2013

REVOLUTIONARY ROAD IN CLL

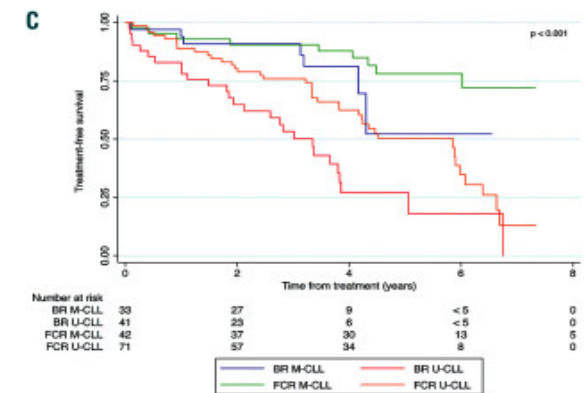
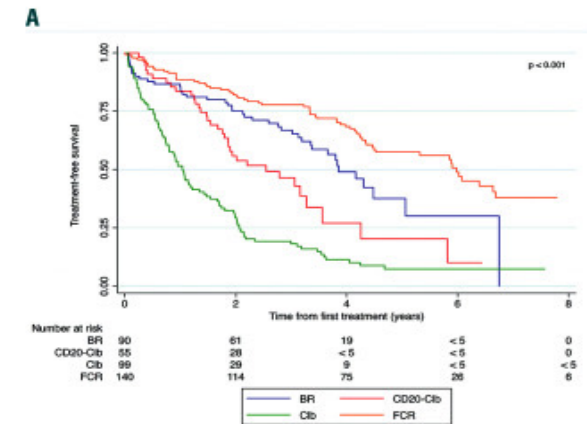
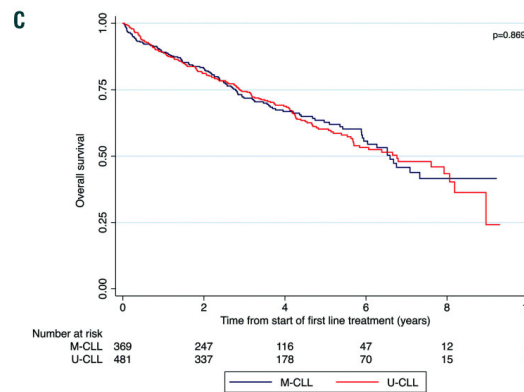
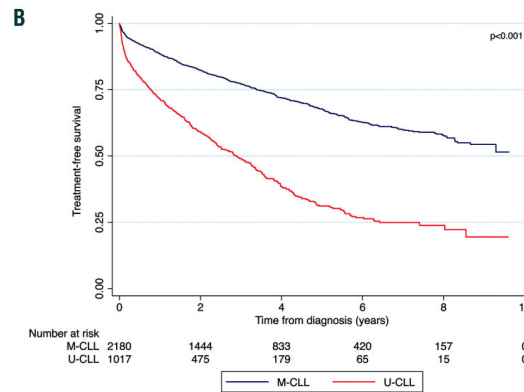
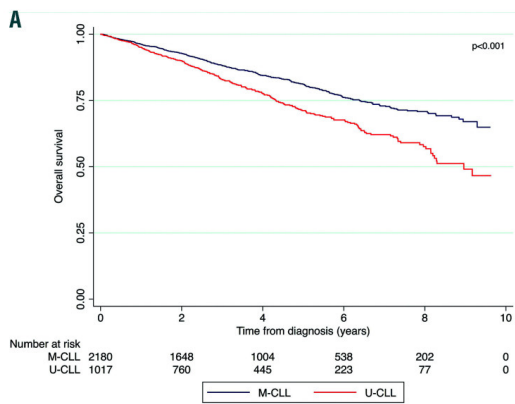
Innovazione rivoluzionaria nella terapia della leucemia linfatica cronica



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IGHV mutational status outcome in CIT era

Danish Register: 850 pts

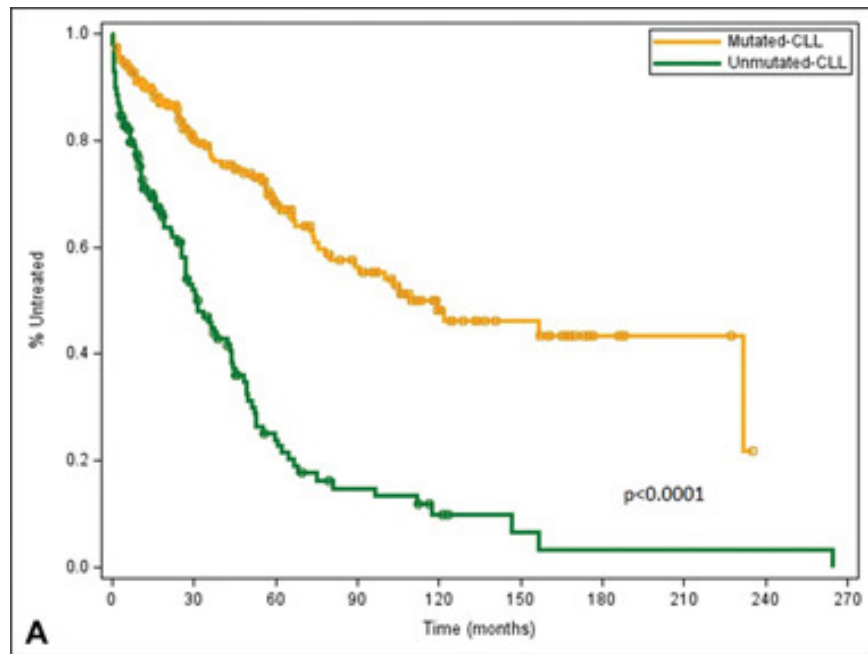


Curovic Rotbain E et al, Haematologica 2020

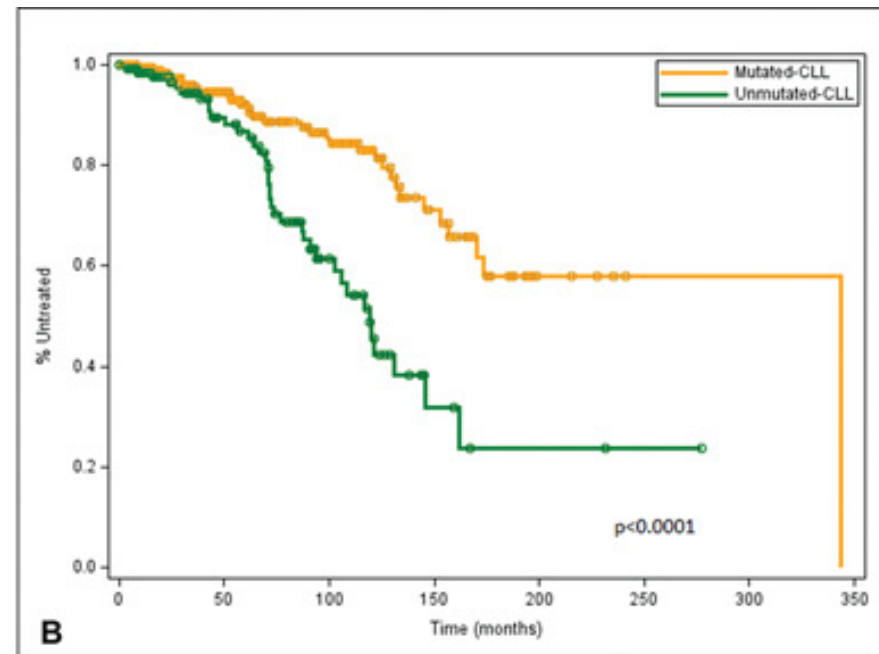
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IGHV mutational status impact



(A) Time to first treatment in CLL patients with mutated and unmutated *IGHV*.



(B) Overall survival in CLL patients with mutated and unmutated *IGHV* gene.

Muñoz-Novas C et al, Glob Med Genet 2024

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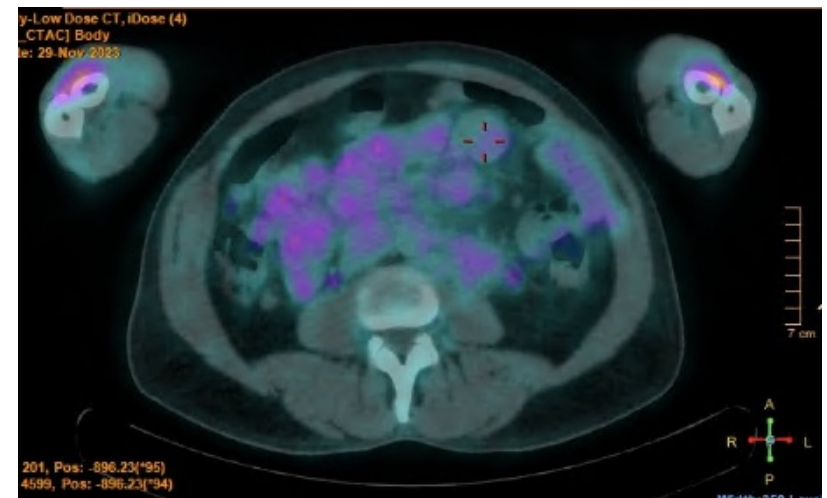
Case Report

M.N., 55-year-old ♂ – ECOG PS 0

- Comorbidity: hypertension, GERD

Hematological history: Aug 2023

- referred lymph nodes appearance in the neck bilaterally, no disease-related symptoms
- **CT scans:** diffused supra- and sub-diaphragmatic lymph nodes up to 13 cm in longest diameter;
- **¹⁸F-FDG PET/CT:** multiple extranodal sites involvement (SUVmax 3.4 in abdomen);
- **CBC:** WBC $8.54 \times 10^3/\mu\text{L}$ (L $4.94 \times 10^3/\mu\text{L}$), Hb 15.6 g/dL, PLT $160 \times 10^3/\mu\text{L}$;
- **Serum Chemistry:** LDH 160 U/L, $\beta 2\text{M}$ 3.88 mg/L, gamma globulins 0.7 g/dL, HBV/HCV/HIV negative;
- **Flow cytometry:** CD5+/CD19+/CD23+/CD20+/CD200+ (MBL, CLL-like);
- **Molecular biology:** absence of del(17p), del(11q), del(13q), and +12, TP53-wt; IGHV unmutated (IGHV 3-11*01, IGHD 3-10*01, IGJ 4*02).



REVOLUTIONARY ROAD IN CLL

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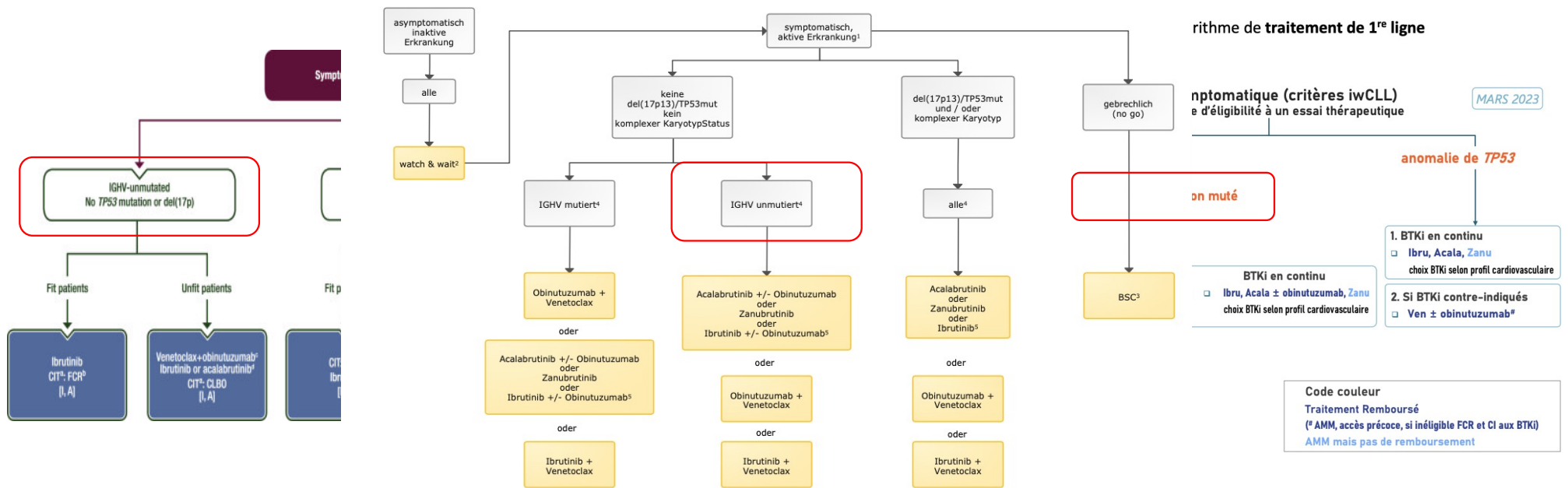
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Case Report

M.N., 55-year-old ♂ – ECOG PS 0

CLL/SLL-B Binet stage B – Rai II with active disease , CLL-IPI 5 (HR)

Abbildung 1: Erstlinientherapie der CLL



Eichhorst B et al, Ann Oncol 2021

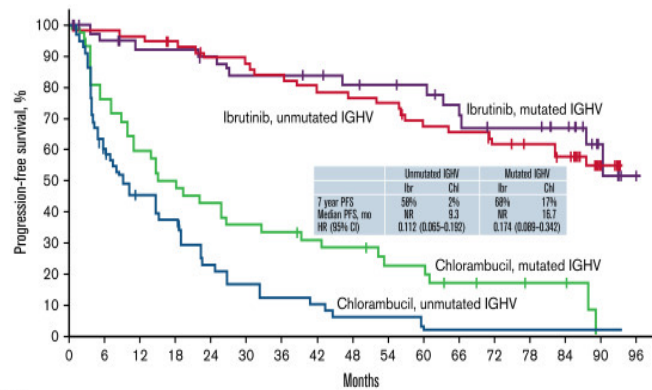
<https://www.filo-leucemie.org/upload/files/texte%20algorithmes%20mars%202023%20def.pdf>

<https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html>

PFS by IGHV Mutation Status in target therapy era: continuous vs fixed duration (1)

ELEVATE – TN

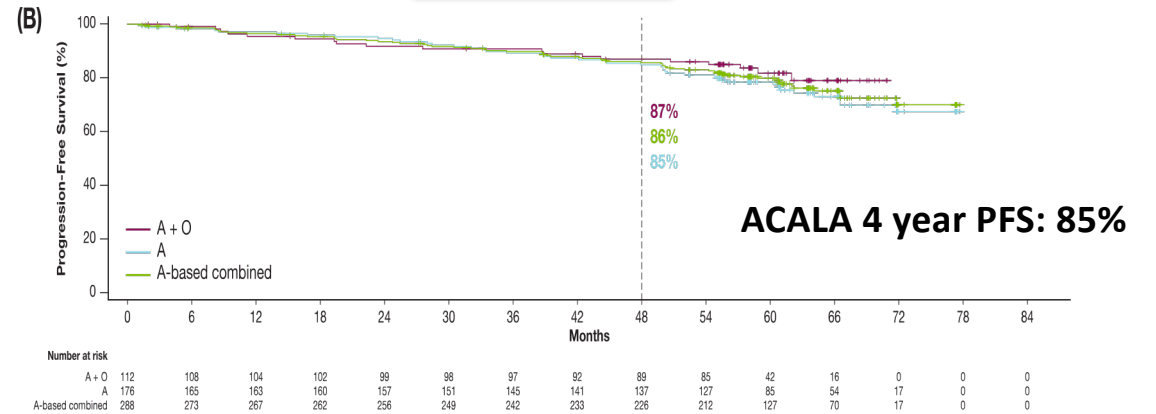
RESONATE-2



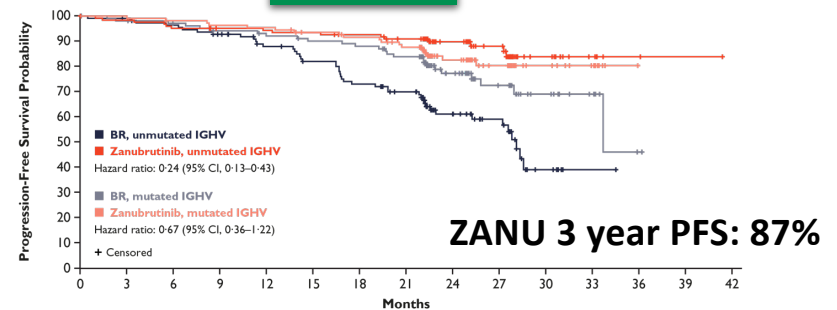
Patients at risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, unmutated IGHV:	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV:	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV:	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

IBR 7 year PFS: 56%



SEQUOIA



No. of patients at risk (number censored)

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
BR - Unmutated	121 (0)	110 (10)	106 (11)	100 (13)	90 (18)	82 (20)	73 (20)	65 (25)	39 (44)	25 (57)	6 (70)	1 (75)	0 (76)		
Zanubrutinib - Unmutated	125 (0)	121 (2)	117 (2)	114 (5)	113 (5)	112 (5)	109 (7)	104 (10)	68 (45)	44 (68)	14 (96)	6 (104)	2 (108)	1 (109)	0 (110)
BR - Mutated	110 (0)	101 (7)	98 (9)	94 (10)	91 (11)	88 (12)	86 (12)	80 (14)	47 (42)	27 (60)	14 (72)	7 (70)	4 (75)	3 (75)	0 (75)
Zanubrutinib - Mutated	109 (0)	109 (0)	106 (1)	104 (1)	103 (1)	97 (5)	94 (6)	88 (8)	53 (39)	31 (58)	13 (64)	11 (64)	11 (64)	11 (64)	11 (64)

Barr PM et al, Blood Adv 2022; Ghia P et al, Hemasphere 2022; Tam CS et al, Lancet Oncol 2022

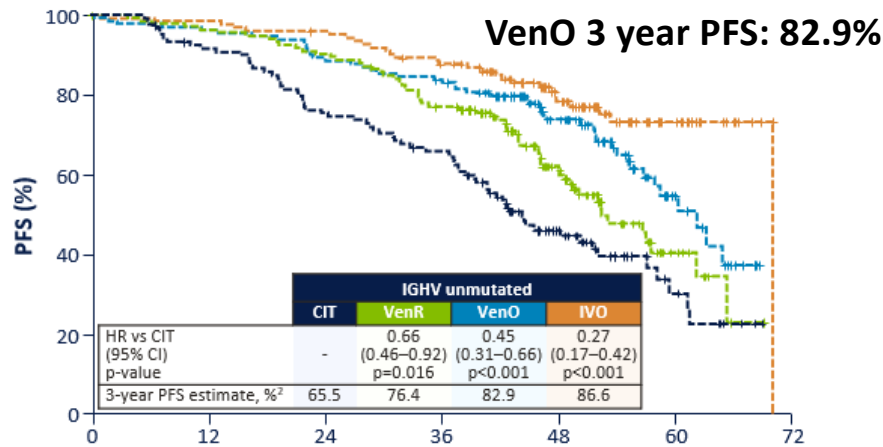
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PFS by IGHV Mutation Status in target therapy era: continuous vs fixed duration (2)

CLL-13

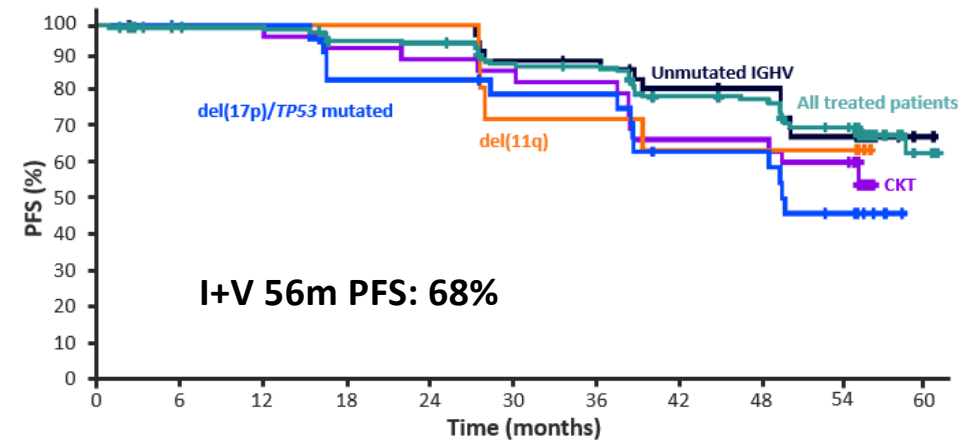
PFS: IGHV unmutated¹
Median follow-up: 50.7 months



At risk:	Time (months)						
	0	12	24	36	48	60	72
CIT 131	108	89	77	34	9		
VenR 134	128	119	100	56	10		
VenO 130	125	116	108	67	15		
IVO 123	121	117	105	65	24		

CAPTIVATE

Investigator-assessed PFS¹
(Median time on study: 56 months)



	FD cohort				
	del(11q)* (n=11)	CKT ⁺ (n=31)	del(17p)/TP53 (n=27)	Unmutated IGHV* (n=40)	All (N=159)
54-month PFS rate, % (95% CI)	64 (30–85)	60 (41–75)	45 (25–64)	68 (50–80)	70 (62–77)

Fürstenau M et al, ASH 2023 Abstract 635 (Oral); Allan JN et al, Clin Cancer Res 2023.

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Case Report

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CLL-B Binet stage B – Rai II with active disease , CLL-IPI 3 (Int), HR TLS

Nov 2023 start 1L treatment: Obinutuzumab + Venetoclax

After C1:

- No AE reported (including IRR and TLS)
- No hematological/extra-hematological toxicity
- Disappearance of lymph nodes at the neck**

Debulky lymphocytosis

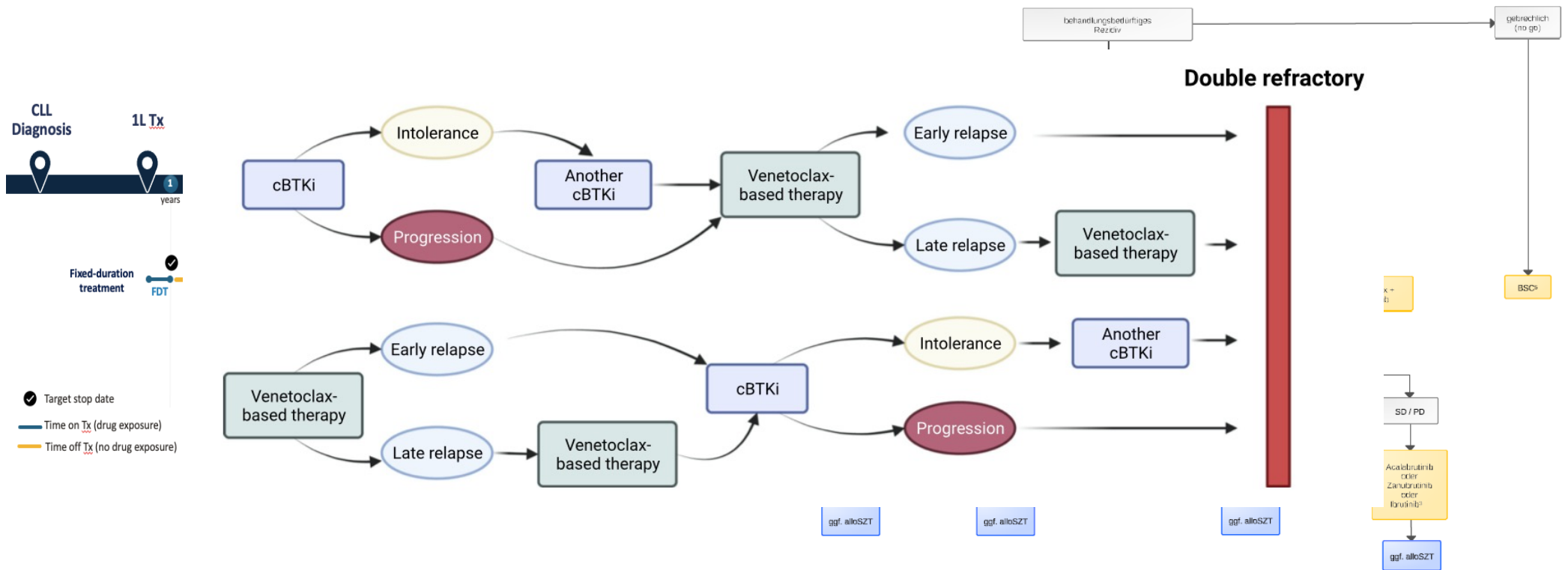
- C1 D1: L $4.9 \times 10^3/\mu\text{L}$
- C1 D2: L $0.4 \times 10^3/\mu\text{L}$



After 6 months → no AEs to date, reevaluation CT show a CR

Possible next therapeutic scenarios (1)

Figure 2: Therapy of CLL in case of relapse and Refractory



Hayama M et al, Onco Targets Ther 2024

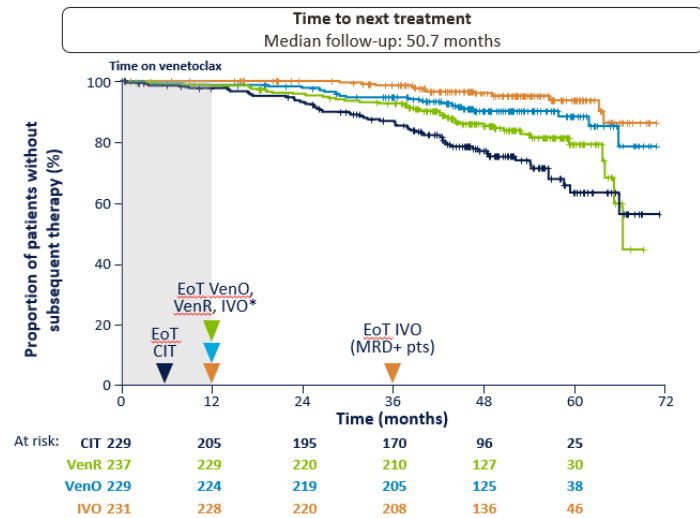
<https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll/@@guideline/html/index.html>

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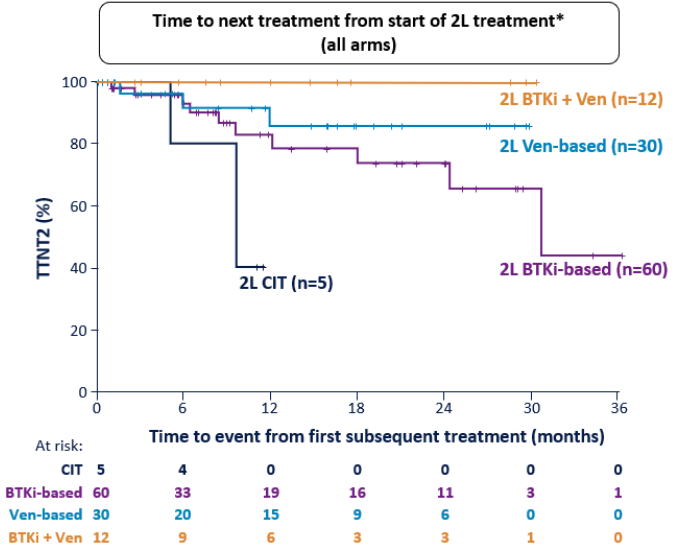
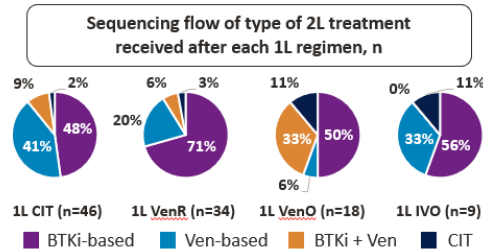
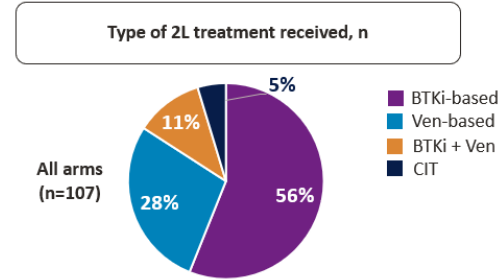
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Possible next therapeutic scenarios (2)

CLL13: TTNT at the 4-year analysis



	CIT	VenR	VenO	IVO
HR vs CIT	-	0.62	0.34	0.17
(97.5% CI)	-	(0.39-1.00)	(0.20-0.60)	(0.09-0.36)
p-value	-	p=0.023	p<0.001	p<0.001
4-year TTNT, %	77.2	86.2	90.4	96.0



BTKi post-VEN: ORR 86.2%

And after
olive harvest ...



... drug holiday
... with VEN