GIORNATE EMATOLOGICHE VICENTINE

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CLL: ancora spazio per chemio-immunoterapia?

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UOC Ematologia, Verona

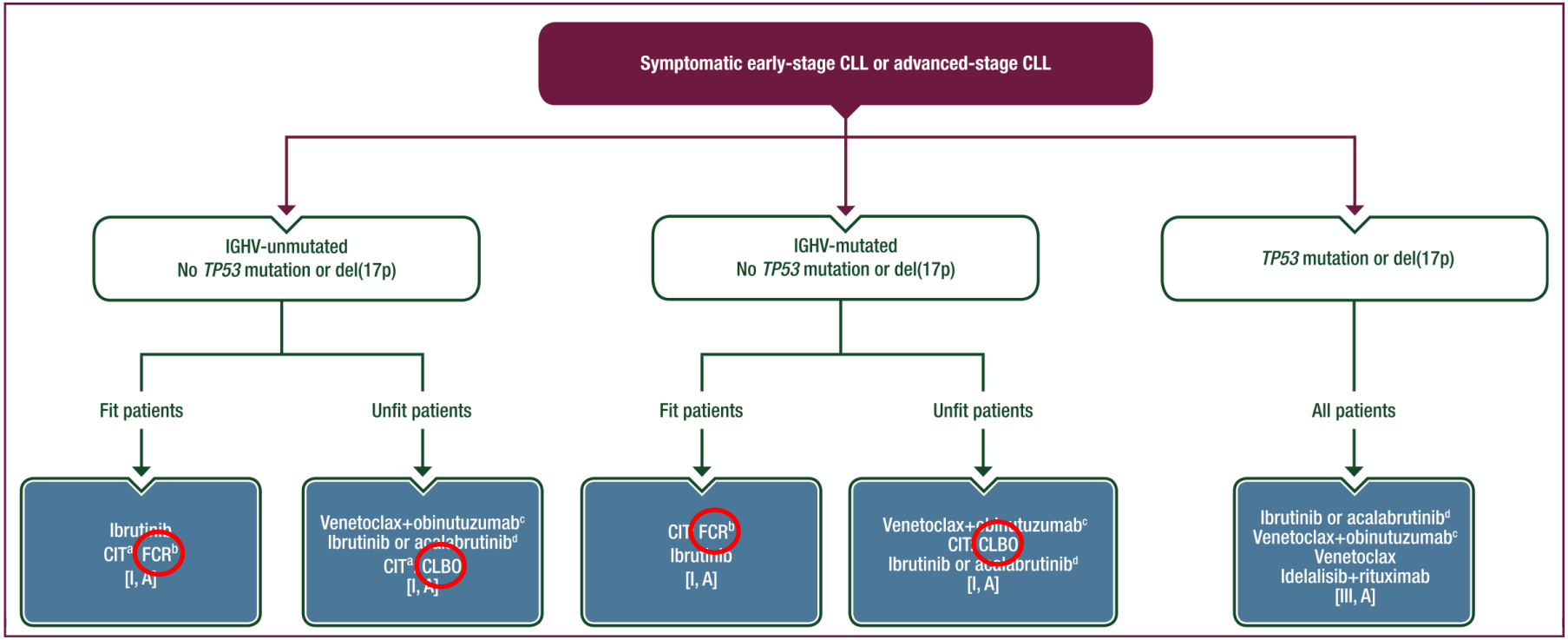
Disclosures of Isacco Ferrarini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	x					x	
Beigene	x					x	
Loxo Oncology	x						

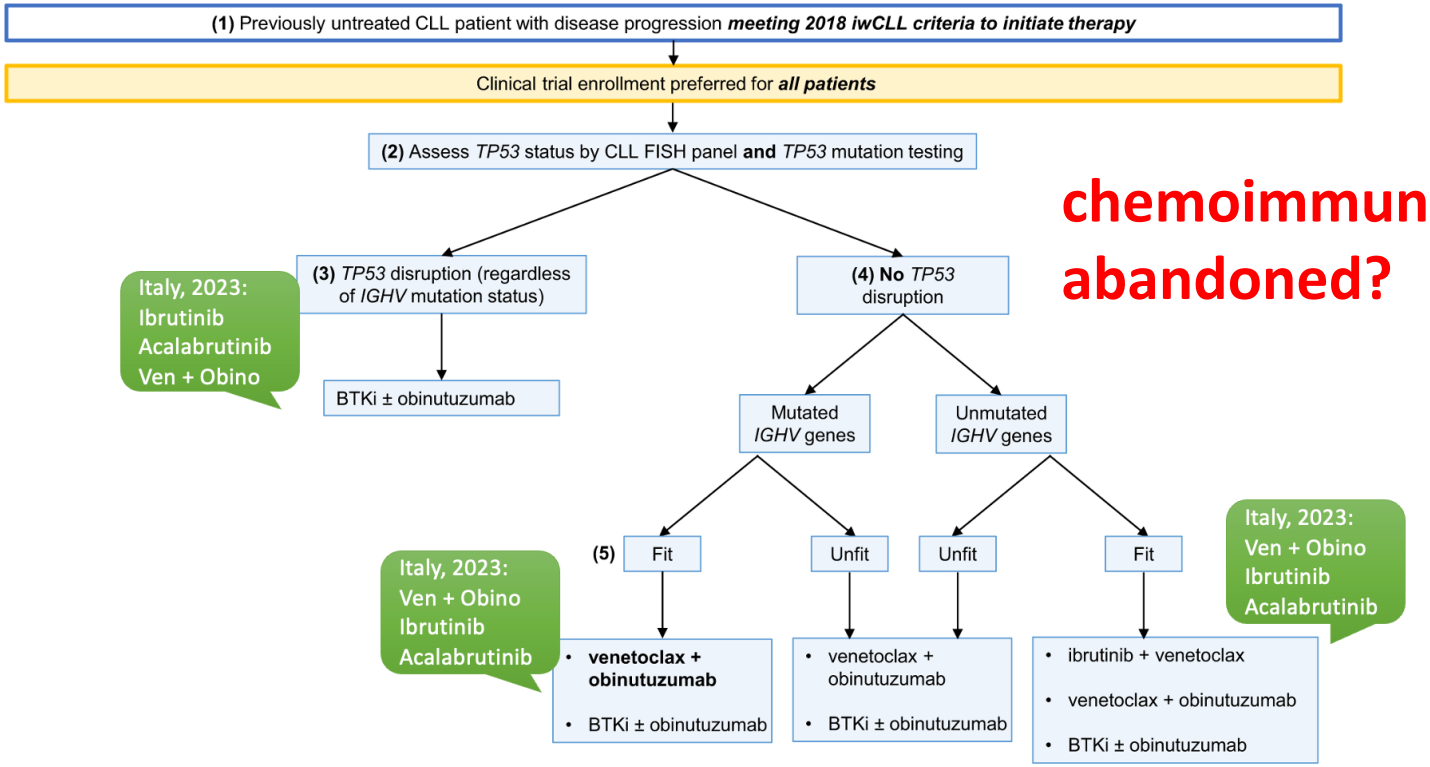
Outline

- Overview of current guidelines for treatment-naive CLL
- Comparison between CIT and BTK inhibitors
- Comparison between CIT and Ven-based regimens
- Hot topics in CLL in October 2023

Treatment-naive CLL: ESMO guidelines 2020



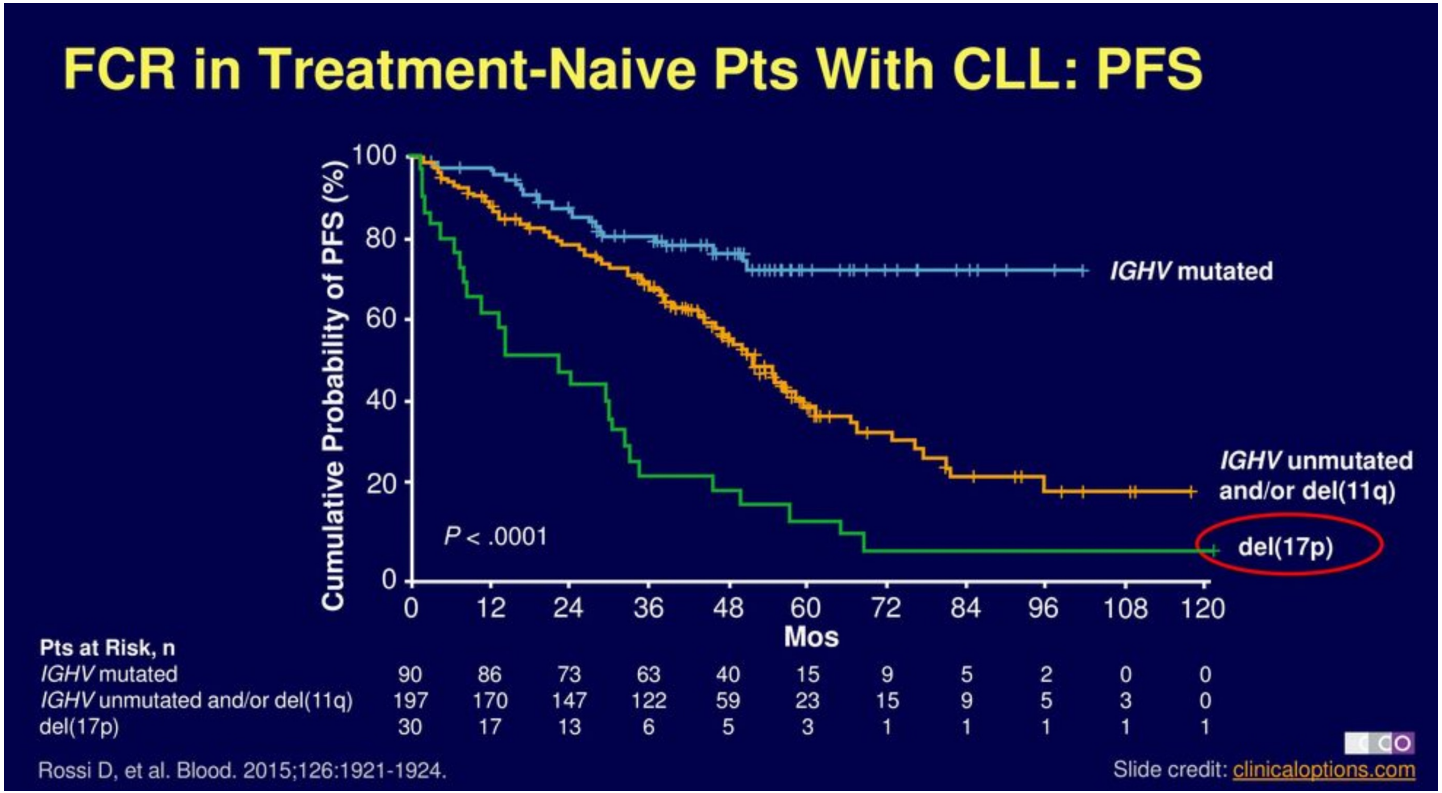
Treatment-naive CLL: Mayo Clinic guidelines 2022



chemoimmunotherapy abandoned?

Hampel PJ et al, Blood Cancer Journal, 2022

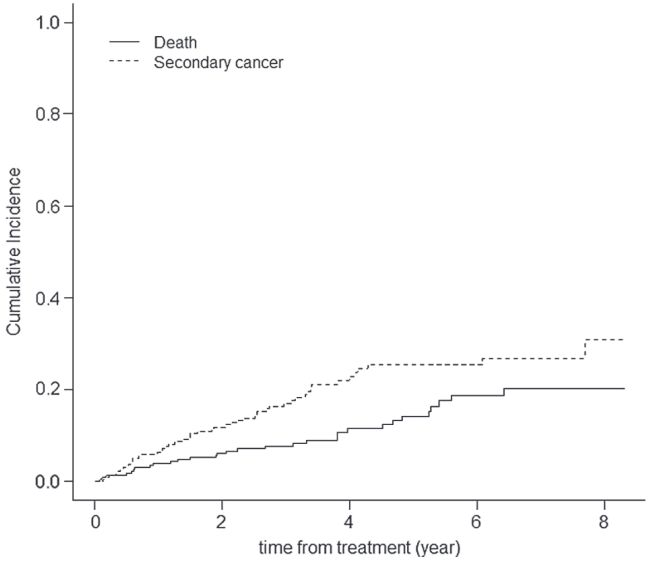
Clinical results of FCR in treatment-naive CLL patients

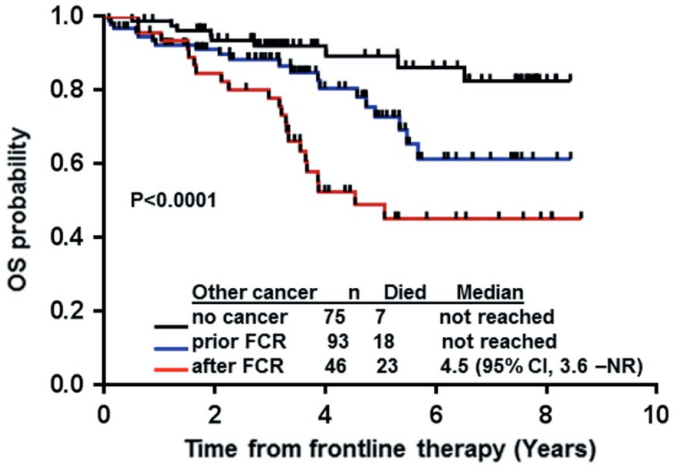


Risk of second cancer after frontline FCR

Table I. Initial characteristics of 234 patients prior to receiving FCR treatment.

Variable	No. of patients	Total patients	%
Age ≥ 60 years	127	234	54
Male sex	171	234	73
Smoking history	81	234	35
ALC ≥ 100×10^9/L	92	232	40
LDH ≥ 1 × normal	110	230	48
β_2-Microglobulin ≥ 3.5 g/dL	133	230	58
Rai stage III/IV	71	234	30
Cytogenetics			
Normal	139	219	64
Abnormal	80	219	36
FISH			
17p deletion	24	215	10
11q deletion	49	215	23
Trisomy 12	34	215	16
Negative	42	215	19
13q deletion	64	215	30
IGHV unmutated	116	181	64
ZAP-70-positive*	112	180	62
CD38-positive	91	234	39
Previous cancers	93	234	40
Previous chemotherapy/radiotherapy	15	93	16
Type of frontline chemotherapy			
FCR†	207	234	88
CFAR	25	234	11
FCMR	3	234	1
Number of FCR cycles			
1–3	38	232	16
4–6	194	232	84





The risk of second cancers was 2.38 times higher than the expected risk in the general population

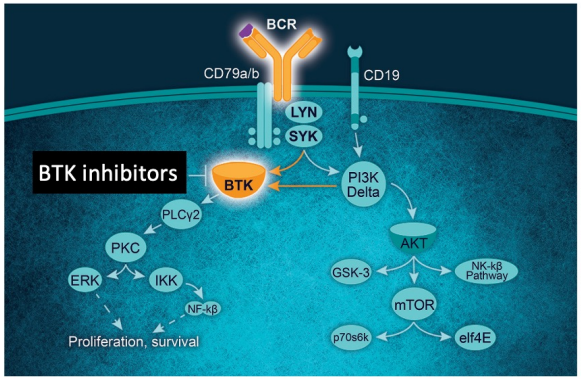
Benjamini O et al, *Leuk & Lymph*, 2015

Major concerns about CIT in CLL

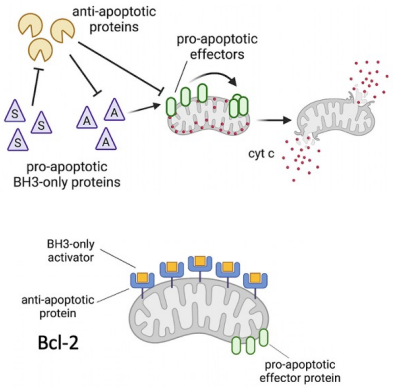
- Suboptimal efficacy in many CLL subsets
- Short and long-term toxicities

Need of novel agents

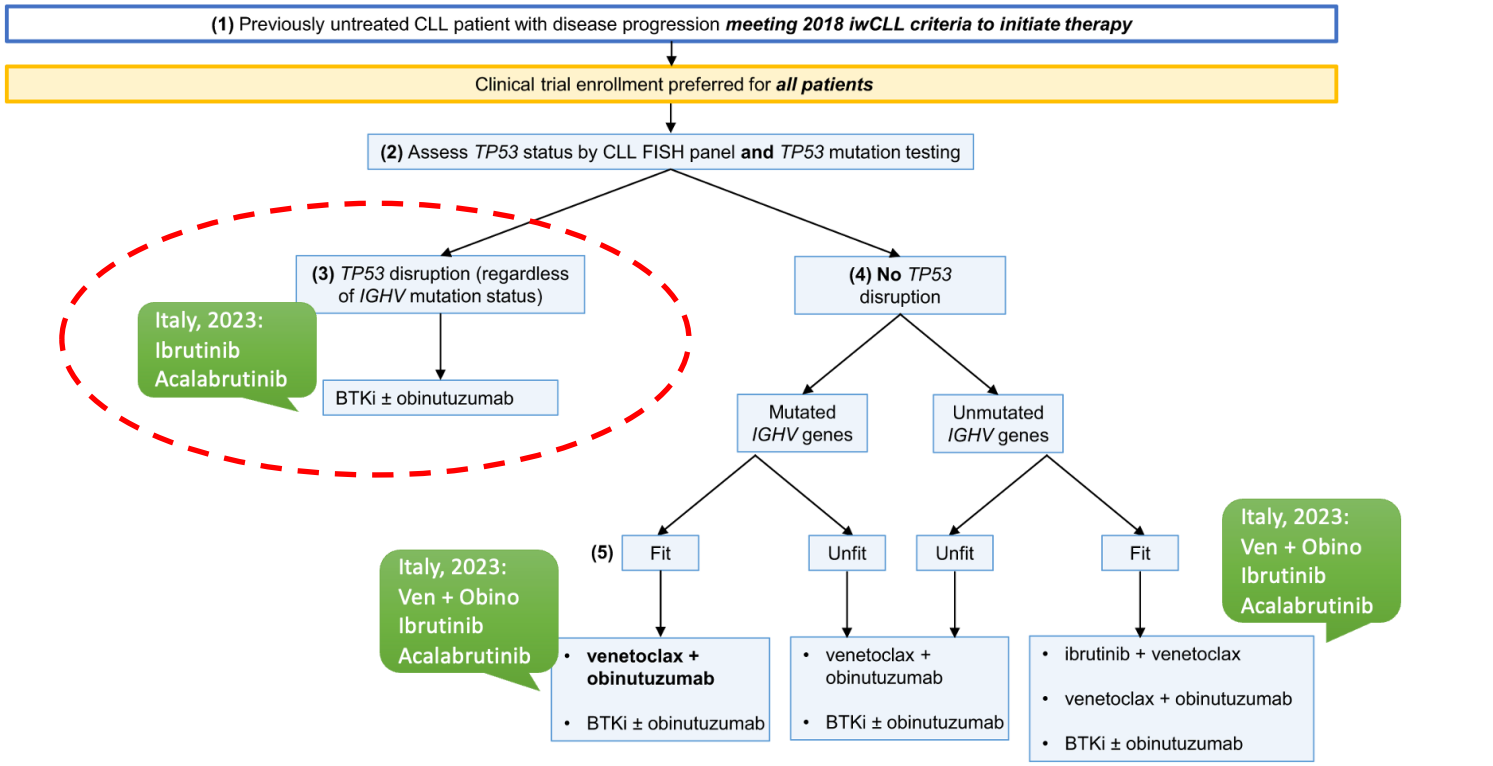
BTK signaling



Bcl-2 dependency



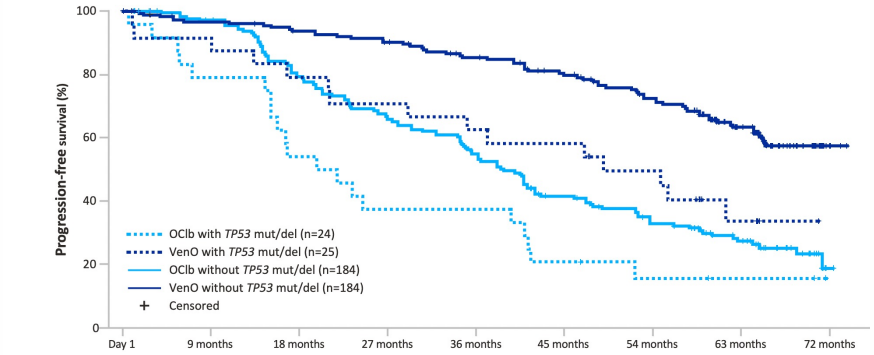
Treatment-naive CLL: Mayo Clinic guidelines 2022



Hampel PJ et al, Blood Cancer Journal, 2022

VenO and BTKi for TP53-disrupted CLL

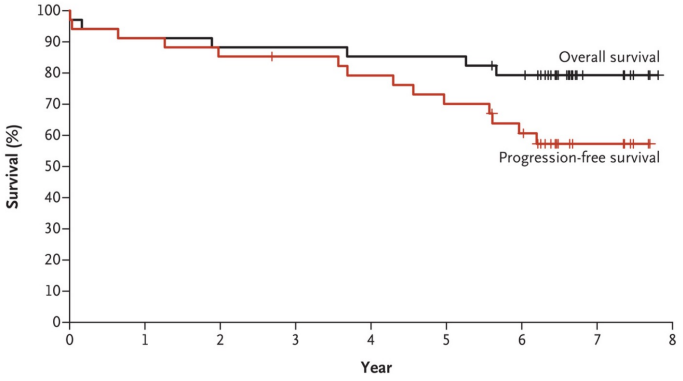
VenO



No. at risk																							
OClb with *TP53* mut/del	24	22	20	19	19	18	13	12	10	9	9	9	9	9	5	5	4	4	3	3	2	2	2	2	
VenO with *TP53* mut/del	25	22	22	22	21	20	19	18	17	17	16	16	15	14	14	14	12	11	11	9	6	5	1	1	
OClb without *TP53* mut/del	184	173	169	166	160	143	135	125	117	112	106	103	90	83	68	65	58	56	48	46	36	30	18	14	1
VenO without *TP53* mut/del	184	173	169	168	167	165	161	159	157	154	150	146	142	140	130	126	119	115	109	106	89	72	33	22	4

Al-Sawaf, et al, *EHA*, 2022

Ibrutinib



No. at Risk									
Overall survival	34	31	30	30	29	29	26	7	0
Progression-free survival	34	31	29	28	26	23	19	6	0

Ahn IE, et al, *NEJM*, 2020

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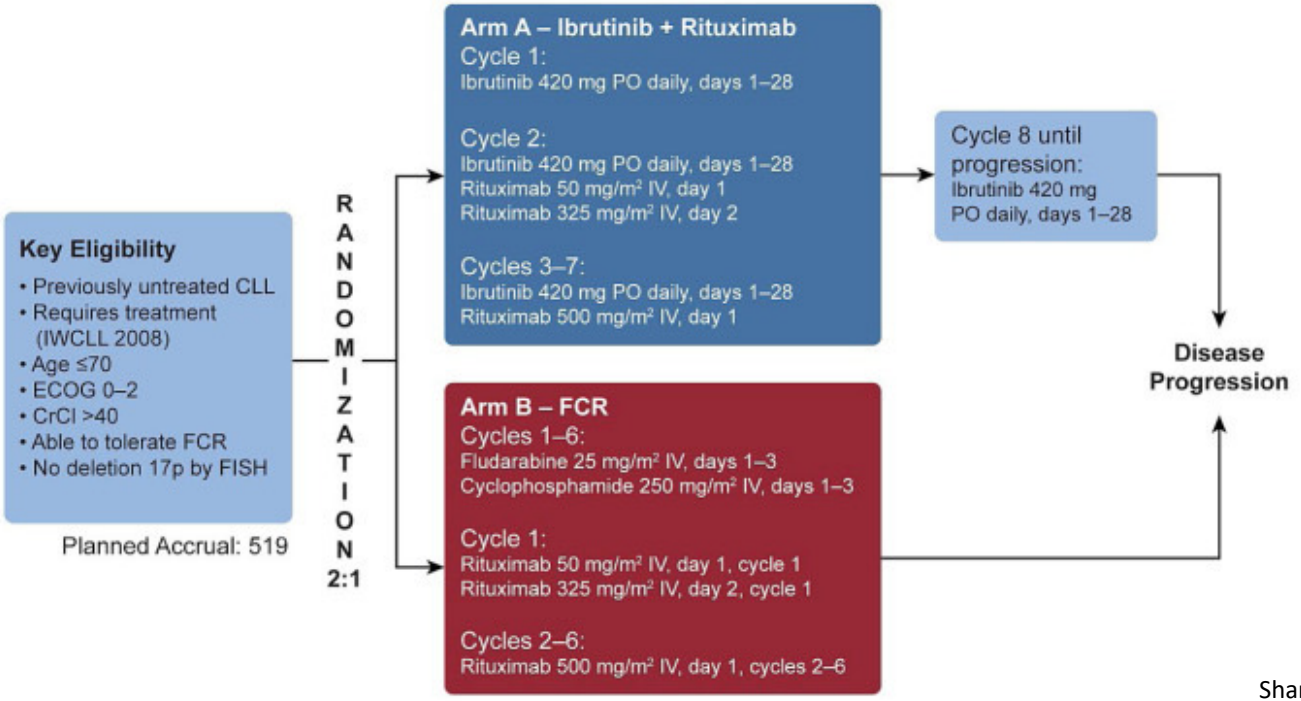
Ibrutinib-Rituximab versus FCR in treatment-naive CLL

ECOG 1912 study



Shanafelt TD et al, *NEJM*, 2019

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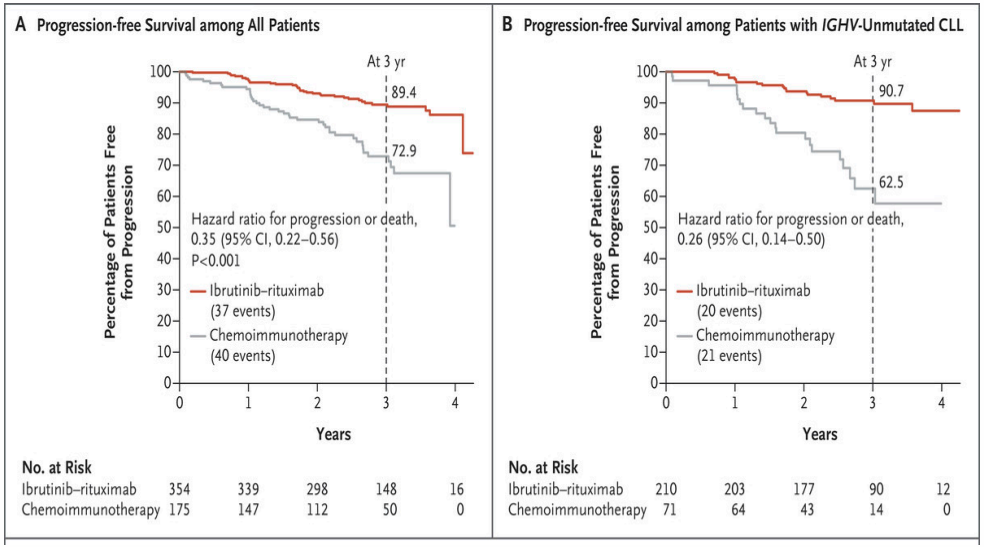

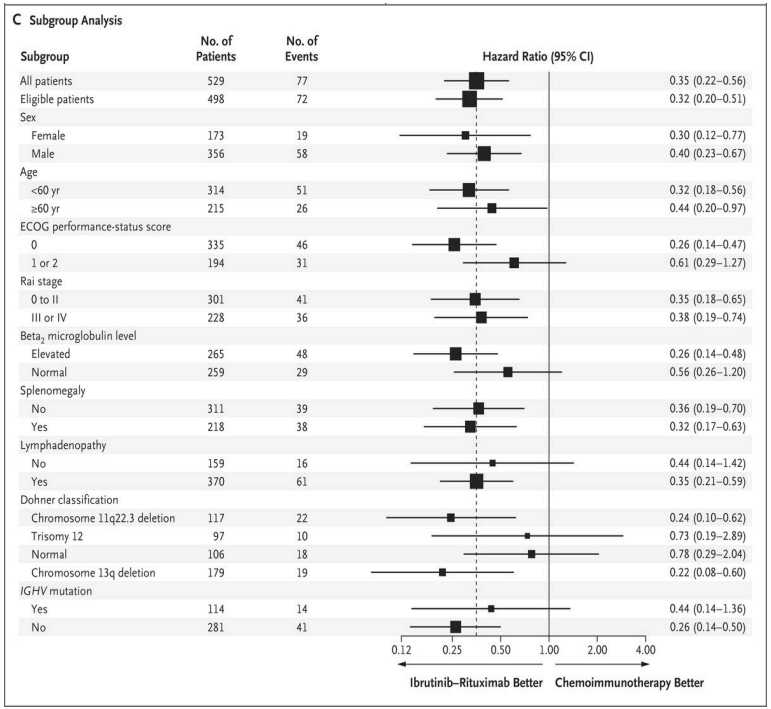

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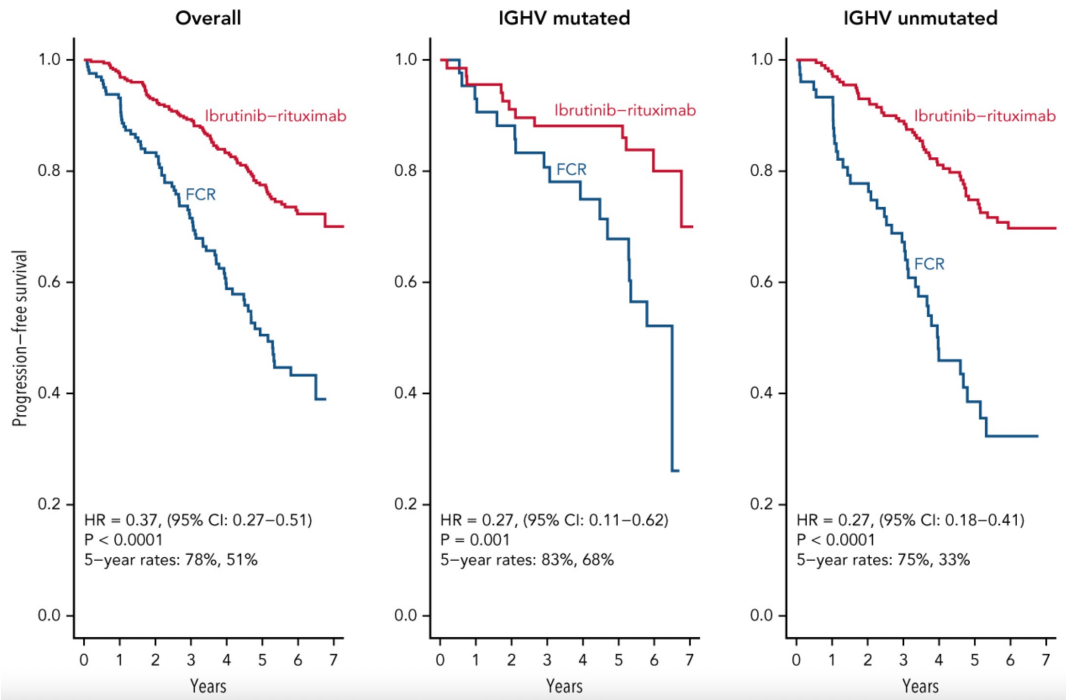
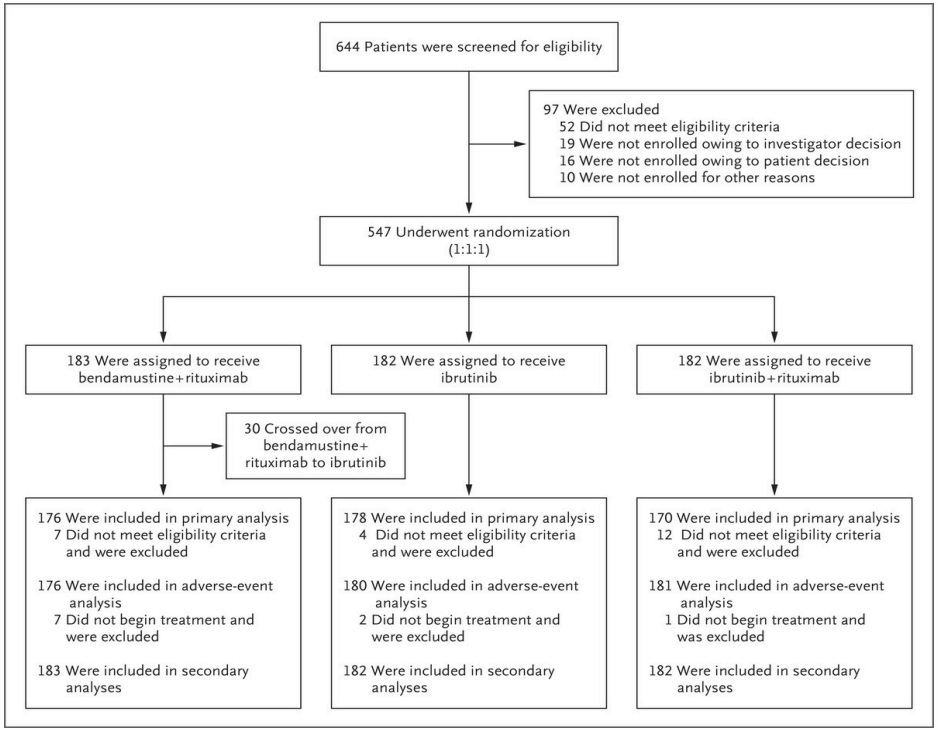


Shanafelt TD et al, *NEJM*, 2019

Ibrutinib versus BR in treatment-naive CLL

Alliance study



Woyach et al, *NEJM*, 2018

Ibrutinib versus BR in treatment-naive CLL

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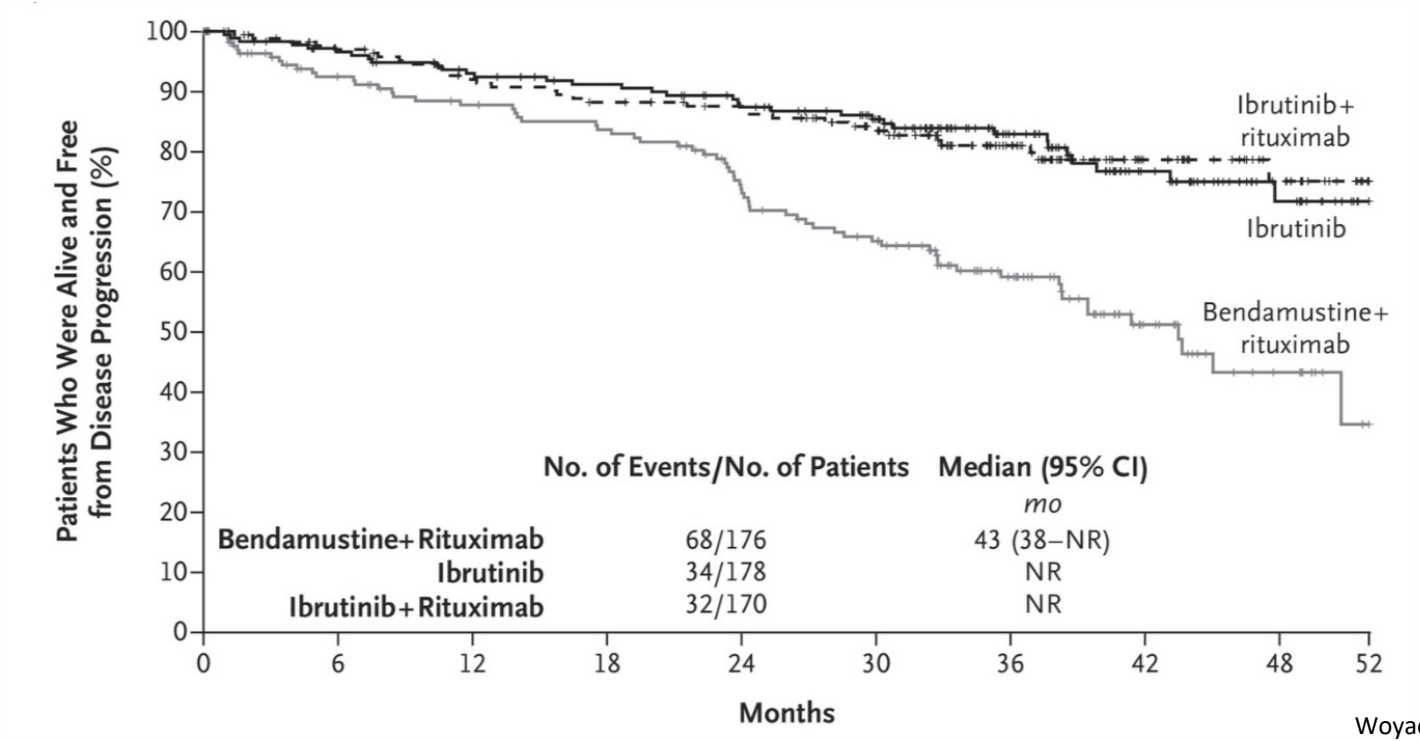
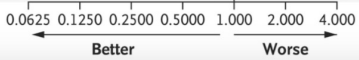


Woyach et al, *NEJM*, 2018

Ibrutinib versus BR in treatment-naive CLL

Subgroup	No. of Patients	No. of Events	Hazard Ratio for Disease Progression or Death (95% CI)
All patients			
Ibrutinib vs. bendamustine+rituximab	365	105	0.37 (0.25–0.56)
Ibrutinib+rituximab vs. bendamustine+rituximab	365	106	0.40 (0.27–0.60)
Ibrutinib+rituximab vs. ibrutinib	364	69	1.06 (0.66–1.70)
Risk category according to modified Rai stage			
Intermediate			
Ibrutinib vs. bendamustine+rituximab	167	53	0.44 (0.25–0.78)
Ibrutinib+rituximab vs. bendamustine+rituximab	168	49	0.32 (0.17–0.59)
Ibrutinib+rituximab vs. ibrutinib	167	32	0.73 (0.36–1.46)
High			
Ibrutinib vs. bendamustine+rituximab	198	52	0.33 (0.18–0.60)
Ibrutinib+rituximab vs. bendamustine+rituximab	197	57	0.50 (0.29–0.85)
Ibrutinib+rituximab vs. ibrutinib	197	37	1.44 (0.75–2.76)
Status with regard to del(17p13.1) or del(11q22.3)			
Absent			
Ibrutinib vs. bendamustine+rituximab	263	70	0.44 (0.27–0.72)
Ibrutinib+rituximab vs. bendamustine+rituximab	265	72	0.50 (0.31–0.80)
Ibrutinib+rituximab vs. ibrutinib	266	52	1.11 (0.65–1.92)
Present			
Ibrutinib vs. bendamustine+rituximab	102	35	0.26 (0.12–0.56)
Ibrutinib+rituximab vs. bendamustine+rituximab	100	34	0.24 (0.11–0.53)
Ibrutinib+rituximab vs. ibrutinib	98	17	0.90 (0.35–2.32)
ZAP70 methylation status			
Unmethylated			
Ibrutinib vs. bendamustine+rituximab	191	61	0.19 (0.11–0.35)
Ibrutinib+rituximab vs. bendamustine+rituximab	191	68	0.31 (0.18–0.51)
Ibrutinib+rituximab vs. ibrutinib	192	35	1.57 (0.80–3.09)
Methylated			
Ibrutinib vs. bendamustine+rituximab	173	43	0.81 (0.45–1.48)
Ibrutinib+rituximab vs. bendamustine+rituximab	173	37	0.58 (0.30–1.12)
Ibrutinib+rituximab vs. ibrutinib	172	34	0.72 (0.36–1.43)



Woyach et al, *NEJM*, 2018

Table 2. Summary of Grade 3, 4, or 5 Adverse Events.*

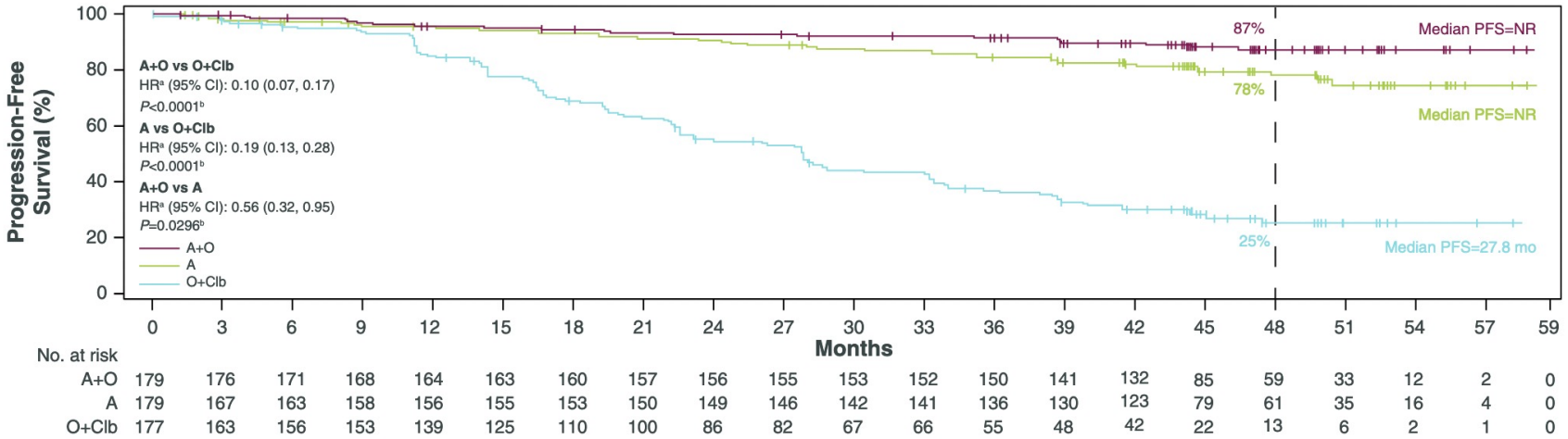
Adverse Event	Bendamustine+ Rituximab (N=176)	Ibrutinib (N=180)	Ibrutinib+ Rituximab (N=181)	P Value†
	number of patients (percent)			
Hematologic				
Any				<0.001
Grade 3	62 (35)	59 (33)	49 (27)	
Grade 4	45 (26)	15 (8)	21 (12)	
Anemia				0.09
Grade 3	22 (12)	20 (11)	11 (6)	
Grade 4	0	1 (1)	0	
Decreased neutrophil count				<0.001
Grade 3	39 (22)	15 (8)	20 (11)	
Grade 4	32 (18)	12 (7)	19 (10)	
Decreased platelet count				0.008
Grade 3	16 (9)	9 (5)	8 (4)	
Grade 4	10 (6)	3 (2)	1 (1)	
Nonhematologic				
Any				0.04
Grade 3	76 (43)	97 (54)	100 (55)	
Grade 4	20 (11)	12 (7)	12 (7)	
Grade 5	15 (9)	24 (13)	22 (12)	
Bleeding‡				0.46
Grade 3	0	2 (1)	3 (2)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	0	0	1 (1)	
Infection§				0.62
Grade 3	17 (10)	29 (16)	28 (15)	
Grade 4	6 (3)	6 (3)	7 (4)	
Grade 5	3 (2)	2 (1)	2 (1)	
Febrile neutropenia				<0.001
Grade 3	13 (7)	3 (2)	1 (1)	
Atrial fibrillation				0.05
Grade 3	5 (3)	15 (8)	10 (6)	
Grade 4	0	2 (1)	0	
Hypertension				<0.001
Grade 3	24 (14)	53 (29)	60 (33)	
Grade 4	1 (1)	0	1 (1)	
Secondary cancer				0.17
Grade 3	6 (3)	5 (3)	13 (7)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	1 (1)	4 (2)	1 (1)	
Unexplained or unwitnessed death				0.24
Grade 5	2 (1)	7 (4)	4 (2)	

- The rate of grade 3, 4, or 5 **hematologic** adverse events was higher with bendamustine plus rituximab (61%) than with ibrutinib or ibrutinib plus rituximab (41% and 39%, respectively)
- The rate of grade 3, 4, or 5 **non hematologic** adverse events was lower with bendamustine plus rituximab (63%) than with the ibrutinib-containing regimens (74% with each regimen)
- Infections occurred in all three treatment groups
- Atrial fibrillation of any grade occurred in 3% of the patients in the bendamustine plus rituximab group, 17% in the ibrutinib group, and 14% in the ibrutinib-plus-rituximab group.
- Grade 3 or higher hypertension occurred in 14%, 29%, and 34%, respectively.

Woyach et al, *NEJM*, 2018

Acalabrutinib versus O-Chlorambucil in treatment-naive CLL

Elevate TN study



Sharman JP et al, *Leukemia*, 2022

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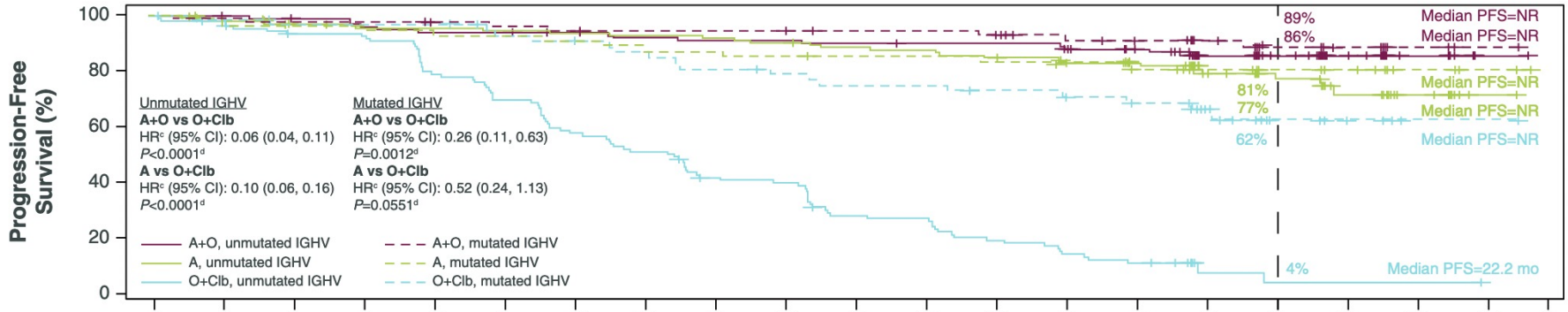
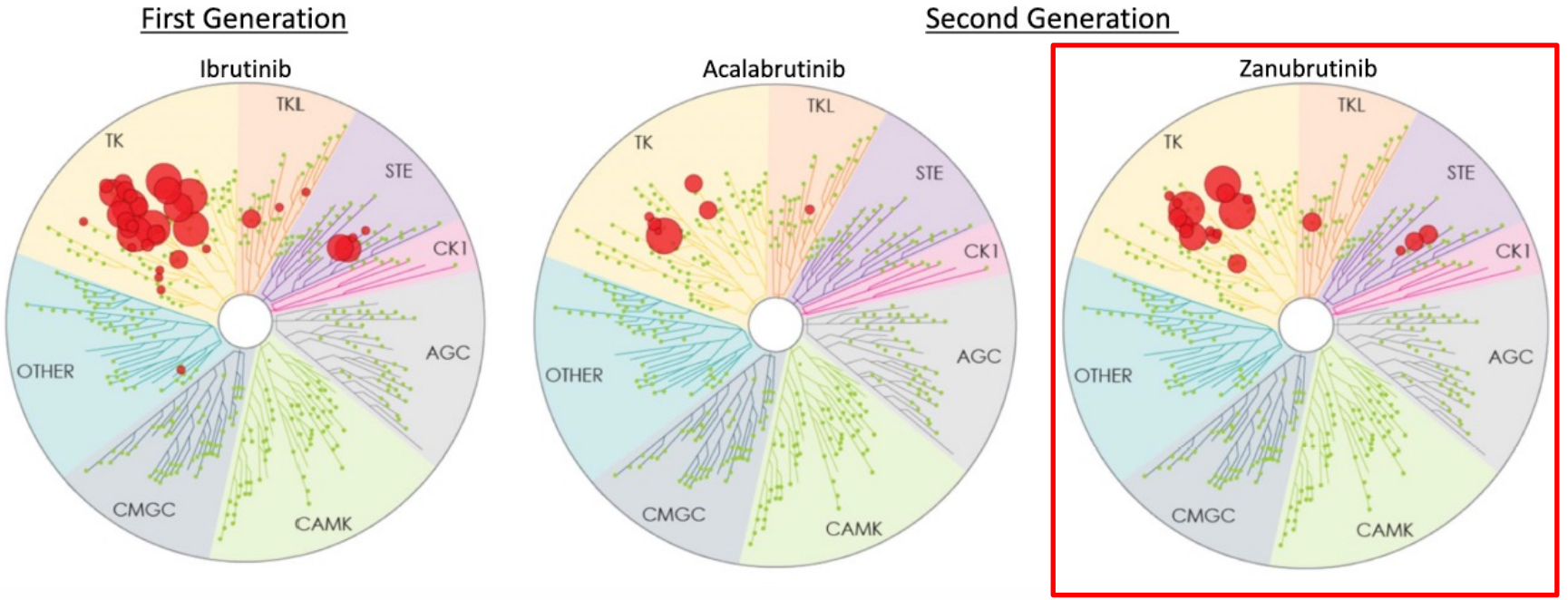


No. at risk																				
A+O, unmutated IGHV	103	102	100	97	95	95	94	92	91	91	90	89	89	84	78	47	35	17	7	1	0
A, unmutated IGHV	119	112	109	107	107	106	105	104	103	101	98	97	93	89	84	52	38	22	11	1	0
O+Clb, unmutated IGHV	116	105	101	99	85	75	62	55	43	41	28	27	19	14	11	2	1	1	1	0	0
A+O, mutated IGHV	74	72	69	69	67	66	64	63	63	62	61	61	59	55	52	36	23	16	5	1	0
A, mutated IGHV	58	53	52	49	47	47	46	44	44	43	42	42	41	40	38	27	23	13	5	3	0
O+Clb, mutated IGHV	59	56	53	52	52	48	46	43	41	39	37	37	35	33	30	19	11	5	1	1	0

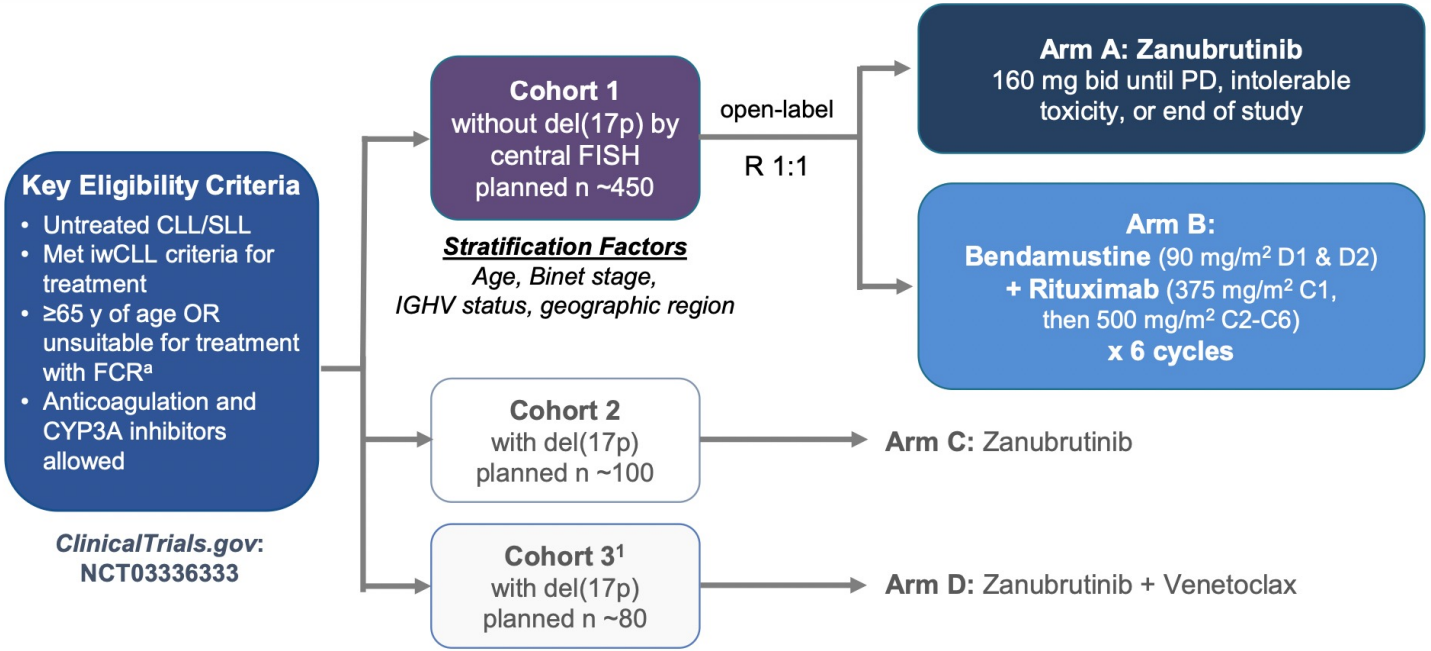
Sharman JP et al, *Leukemia*, 2022

Covalent BTK inhibitors



Zanubrutinib versus BR in treatment-naive CLL

Sequoia study



Tam CS et al, *Lancet Oncol*, 2022

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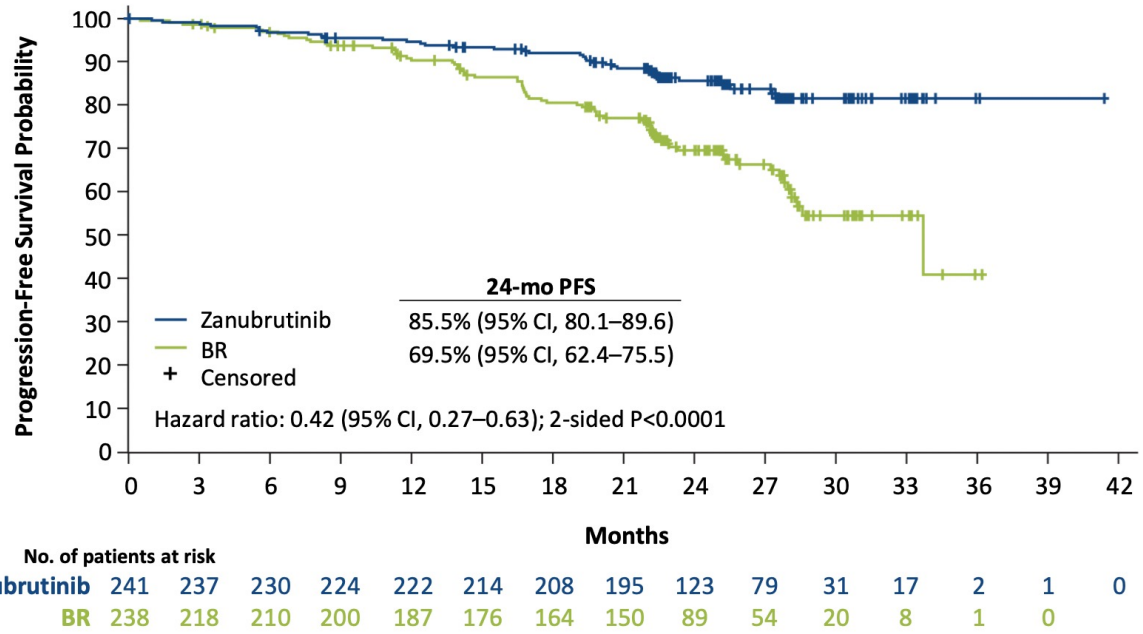

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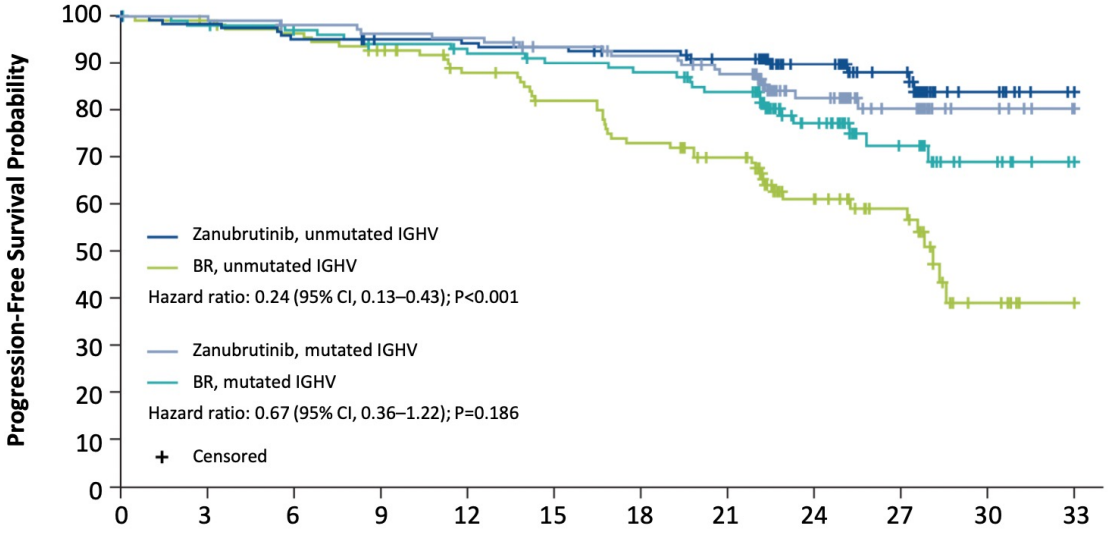

No. of patients at risk												
Zanubrutinib - Unmutated	125	121	117	114	113	112	109	104	68	44	14	6
BR - Unmutated	121	110	106	100	90	82	73	65	39	25	6	1
Zanubrutinib - Mutated	109	109	106	104	103	97	94	88	53	33	15	10
BR - Mutated	110	101	98	94	91	88	86	80	47	27	14	7

Tam CS et al, *Lancet Oncol*, 2022

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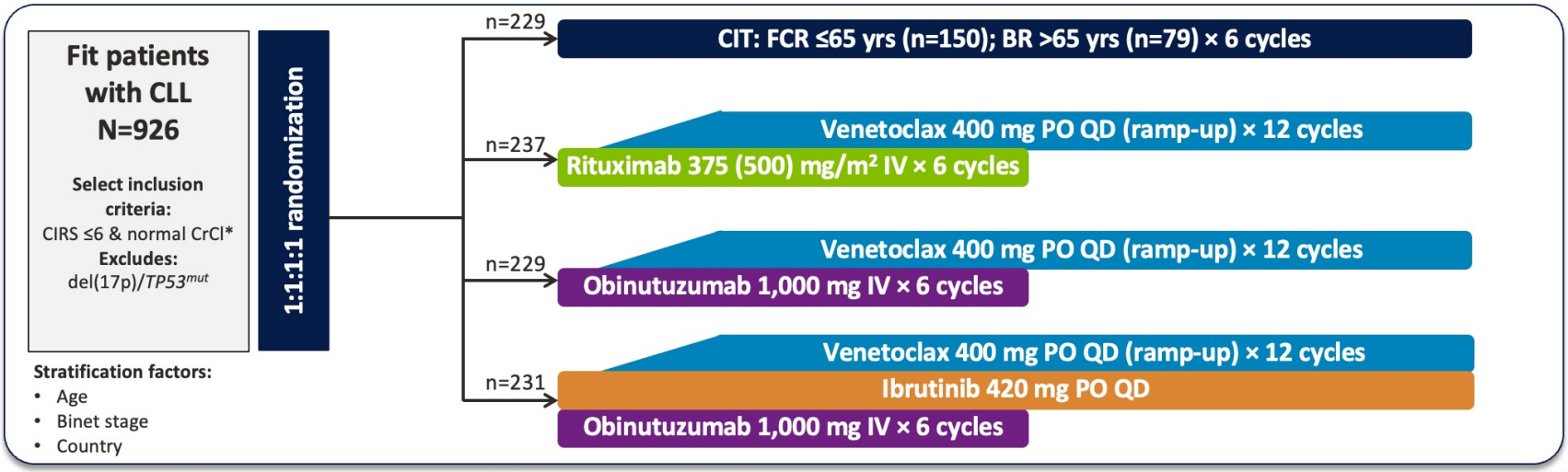
CLL13 study design



Co-Primary Endpoints:

- uMRD ($<10^{-4}$) in PB at month 15 (VenO vs CIT)
- PFS (IVO vs CIT)

Key Secondary Endpoints:

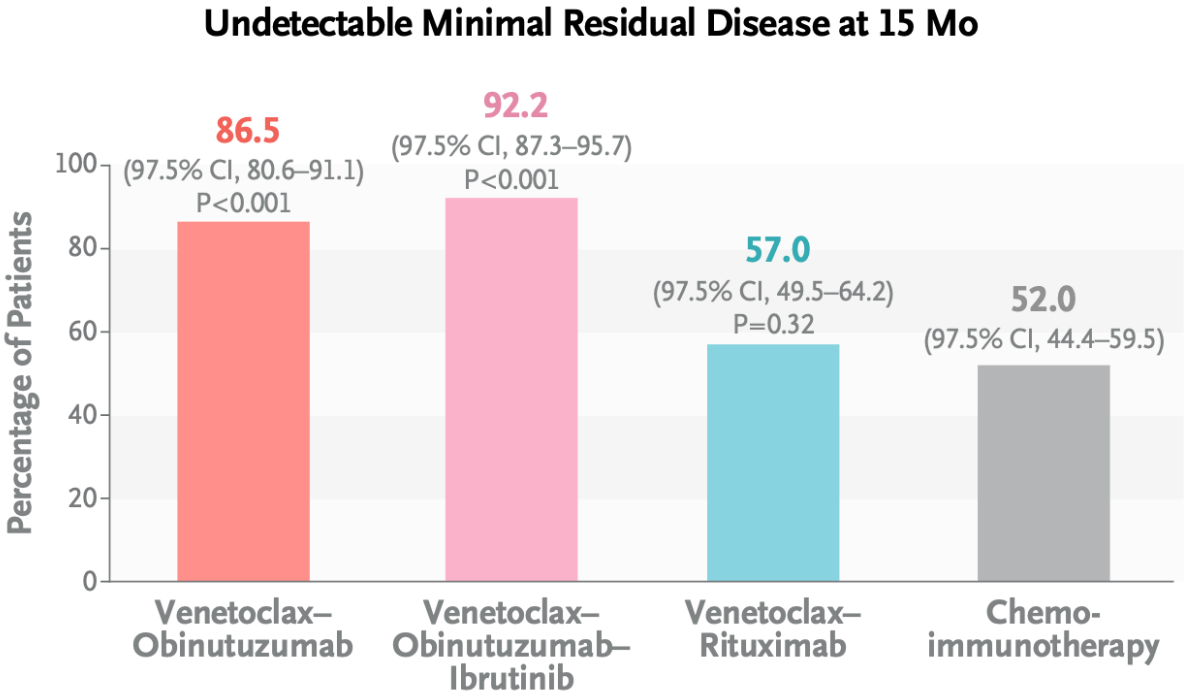
- MRD in PB at month 15 (all other comparisons)
- MRD in BM at final restaging
- PFS (all other comparisons)
- ORR
- CR/CRi rate

Analyses: Interim analysis: 138 PFS events; PFS interim analysis postponed to Q1 2022 due to low number of events

* Normal CrCl defined as ≥70 mL/min; 28-day cycles; Data cut for first co-primary endpoint analysis: February 28, 2021.
BM, bone marrow; BR, bendamustine + rituximab; CIRS, cumulative illness rating scale; CIT, chemoimmunotherapy; CrCl, creatinine clearance; EFS, event-free survival; FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; PB, peripheral blood.

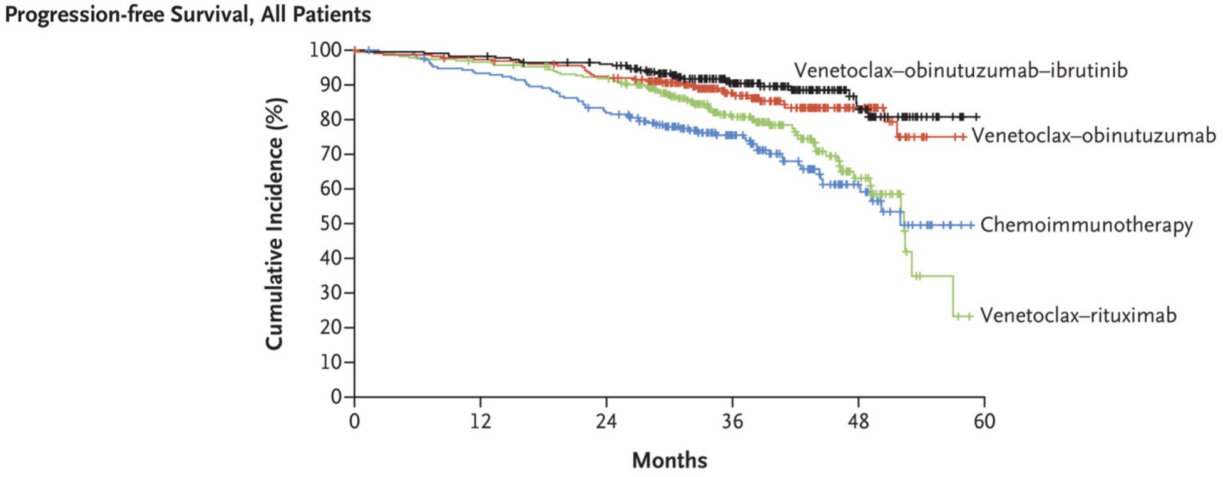
ClinicalTrials.gov: http://clinicaltrials.gov/ct2/show/NCT02950051 (accessed December 2021);
Eichhorst B, *et al.* ASH 2021. Abstract 71 (Oral).

CLL13 trial



The percentage of patients with undetectable minimal residual disease was significantly higher in the venetoclax–obinutuzumab group and the venetoclax–obinutuzumab–ibrutinib group than in the CIT group (P<0.001 for both comparisons), but it was not significantly higher in the venetoclax–rituximab group (P=0.32).

CLL13 trial



No. at Risk

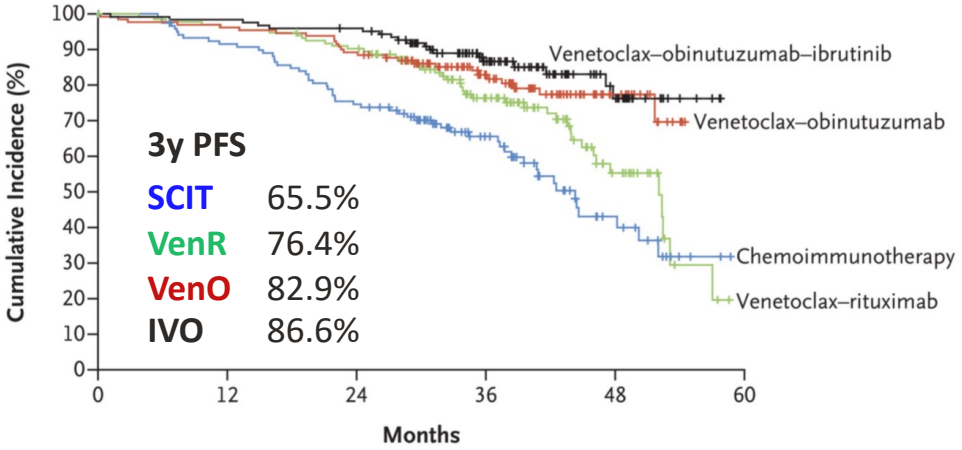
Chemoimmunotherapy	229	197	172	98	28	0
Venetoclax–rituximab	237	226	212	119	32	0
Venetoclax–obinutuzumab	229	221	208	125	42	0
Venetoclax–obinutuzumab–ibrutinib	231	227	217	132	44	0

Treatment arm	3-yr PFS, %
SCIT	75.5
VenR	80.8
VenO	87.7
IVO	90.5

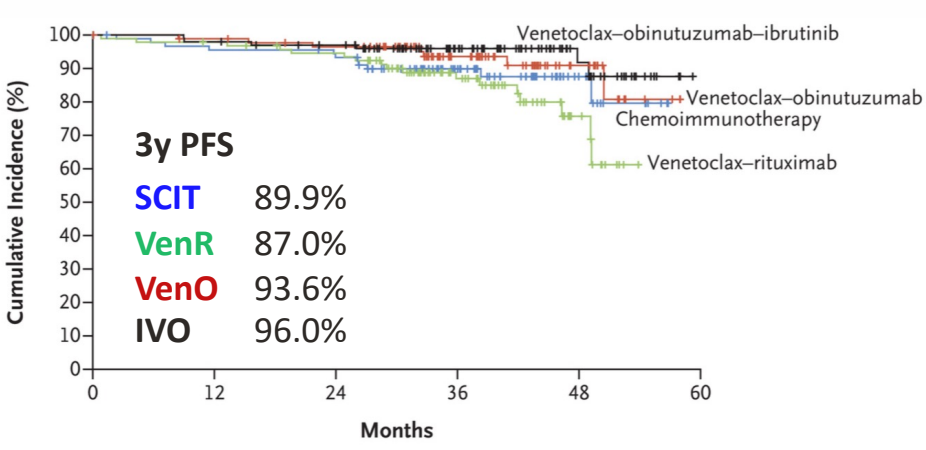
Eichhorst et al, *NEJM*, 2023

CLL13 trial

PFS, U-IGHV



PFS, M-IGHV



Eichhorst et al, *NEJM*, 2023

While chemoimmunotherapy is being abandoned,

new questions emerge about CLL treatment…

Boston, iwCLL 2023

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a. Treatment of intermediate-risk (WT TP53 and U-IGHV) patients?
b. Choice of BTK inhibitor?
c. Treatment of double-resistant CLL patients?
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Outline

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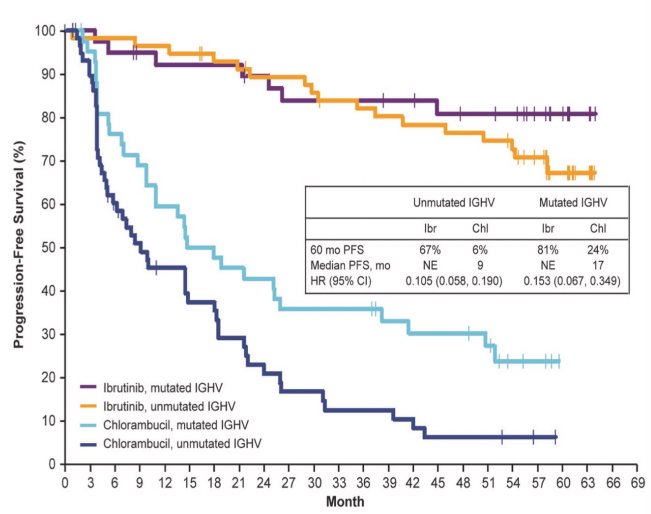
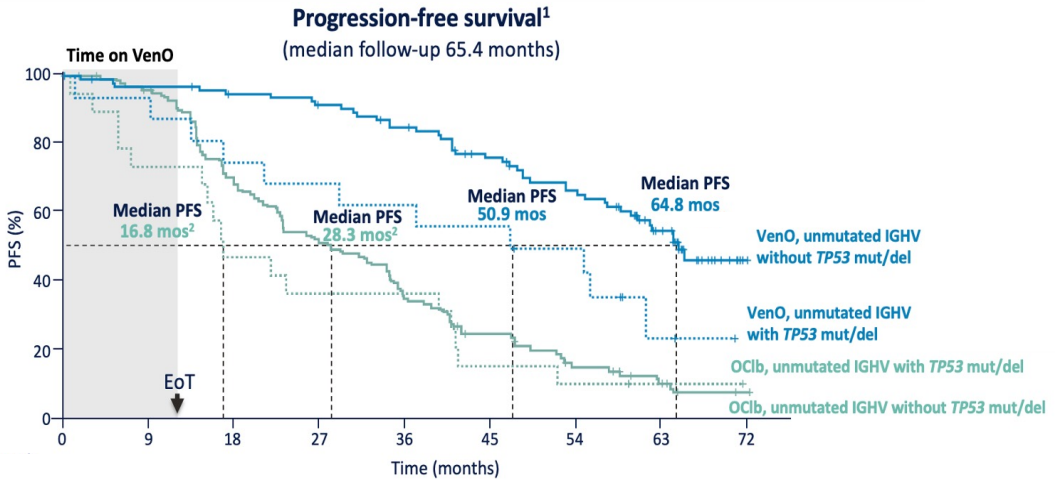
Treatment of intermediate-risk (WT TP53 and U-IGHV) patients
Continuous or fixed duration treatment?

ibrutinib



Burger JA et al, *Leukemia*, 2020

G-Ven



Al-Sawaf O et al, *Nat Comm*, 2023

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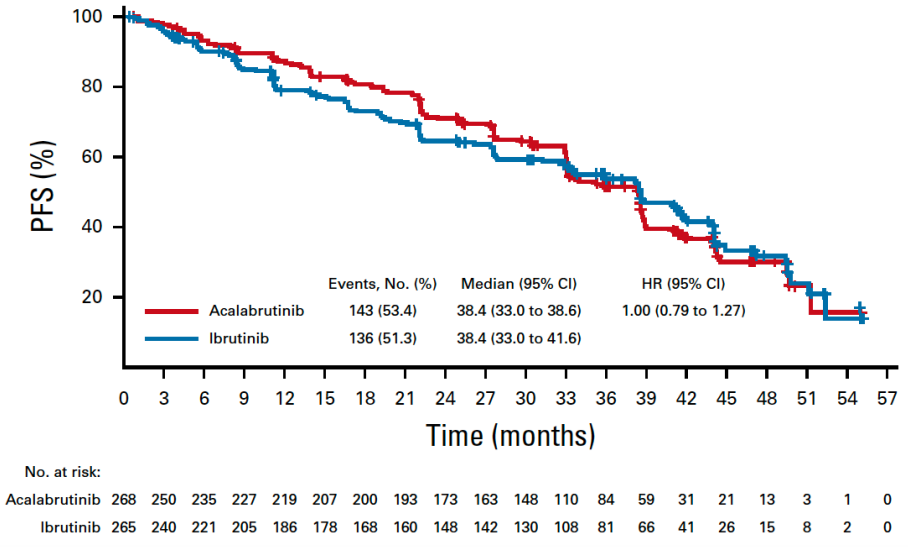
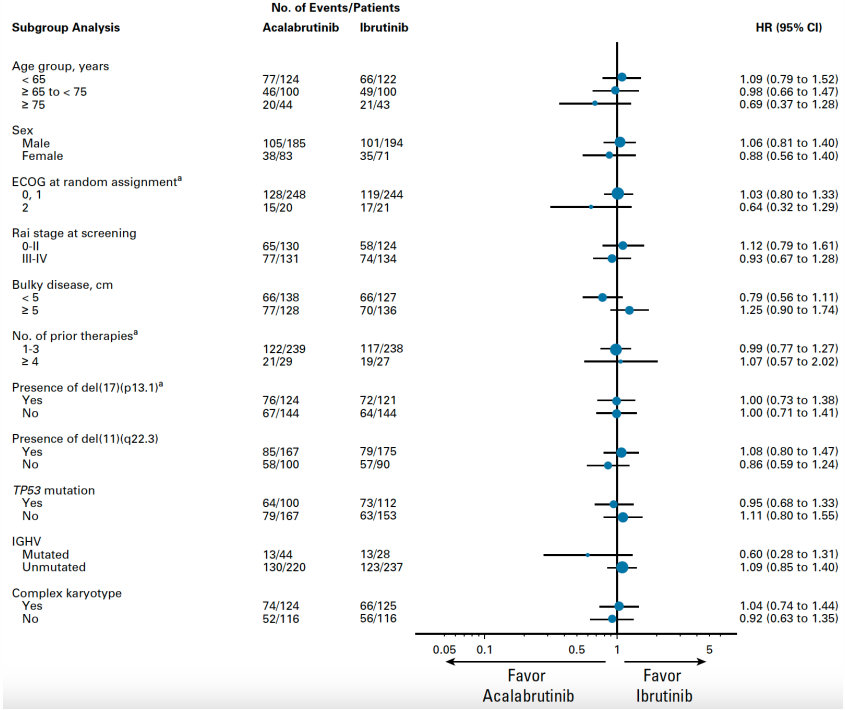
Acalabrutinib versus Ibrutinib in del17p and del11q R/R CLL

ELEVATE R/R study

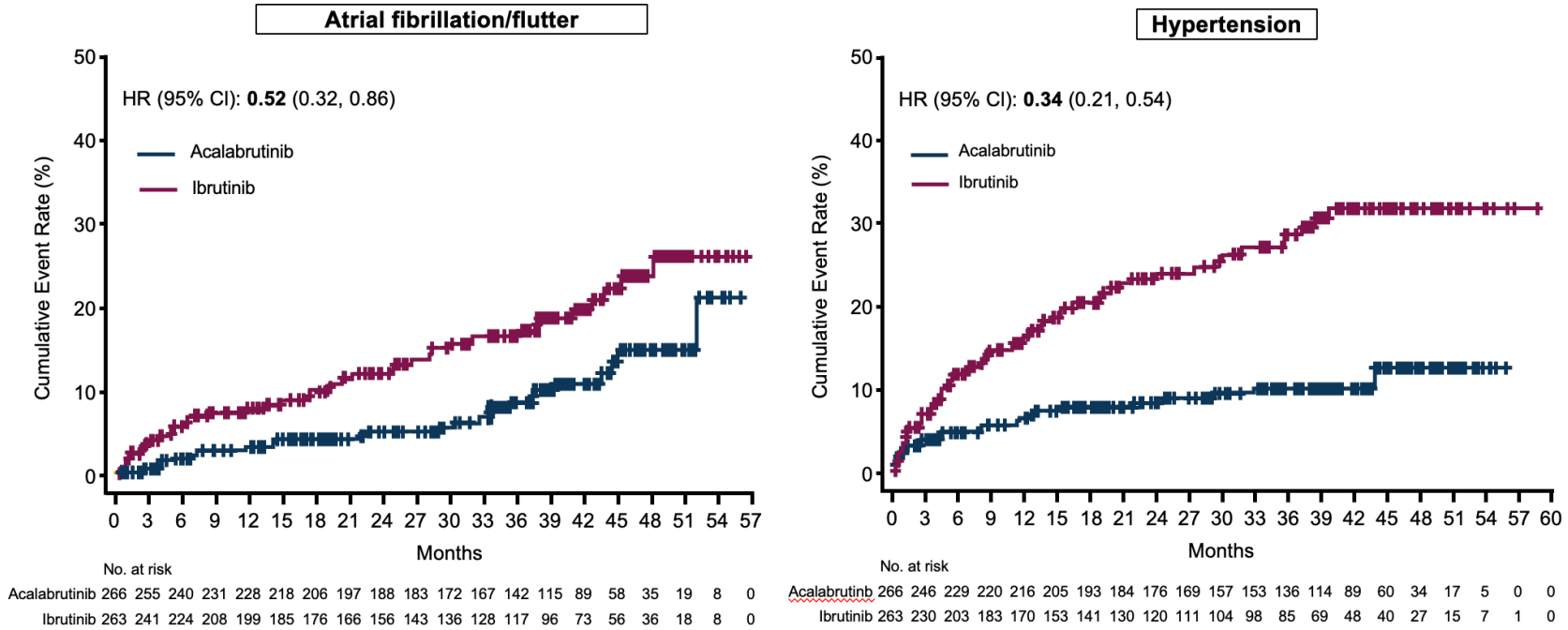




Byrd JC et al, *JCO*, 2021

Safety: Atrial fibrillation/flutter and Hypertension

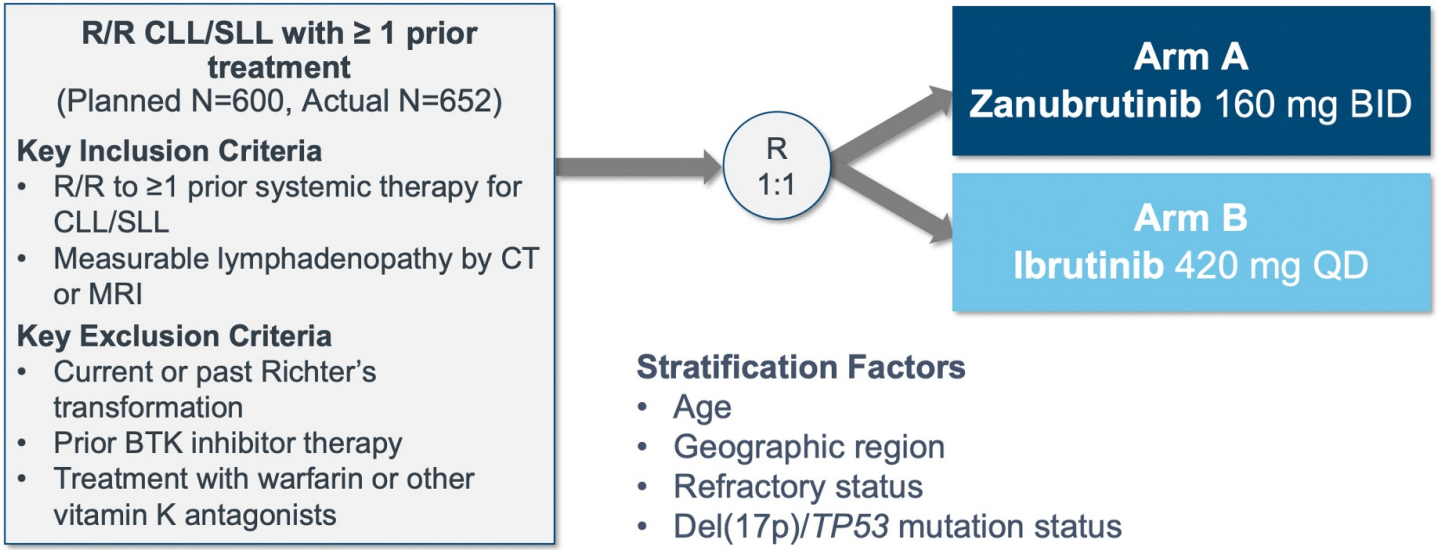
- Lower cumulative incidences of any grade atrial fibrillation/flutter and hypertension with acalabrutinib



Byrd JC et al, *JCO*, 2021

Zanubrutinib in R/R CLL/SLL

Alpine Study *– phase III randomized study of zanubrutinib vs ibrutinib*



Hillmen P et al, *BSH*, 2022

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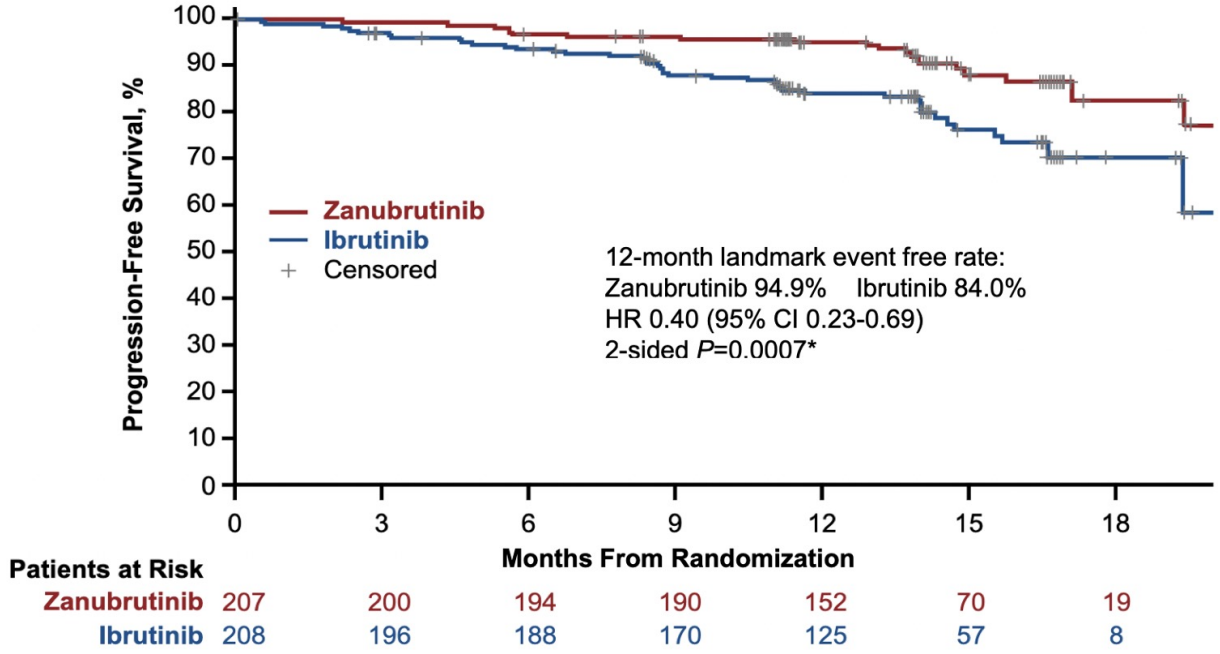

Hillmen P et al, *BSH*, 2022

Choice of BTK inhibitor

IBRUTINIB

- Longer follow-up
- QD administration schedule
- Experience with dose reduction
- Higher incidence of AF

ACALABRUTINIB

- Reduced incidence and different timing of AF
- Reduced incidence of hypertension
- Headache
- (PPI discontinuation)

ZANUBRUTINIB

- Reduced incidence of AF
- Better efficacy?
- Higher incidence of hypertension
- Neutropenia

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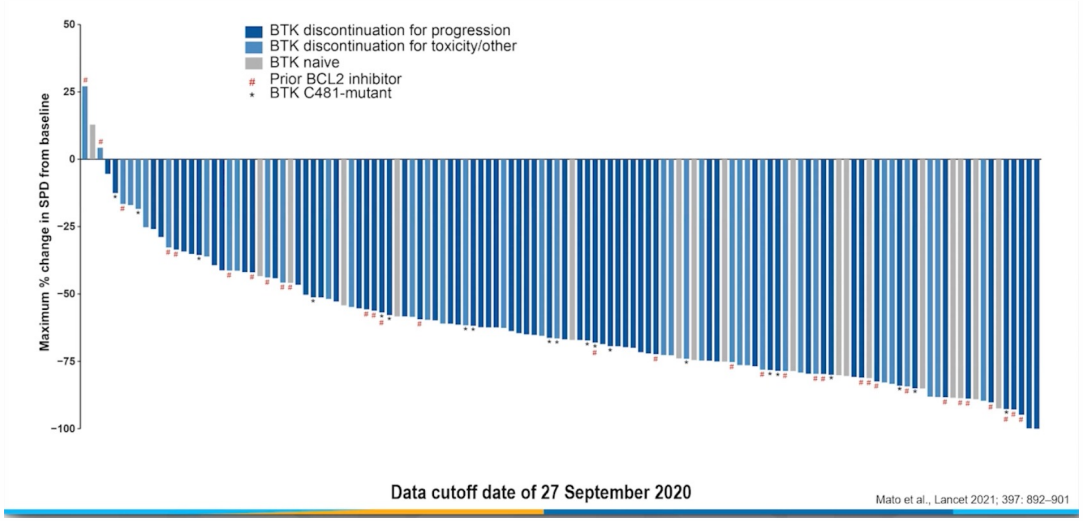
Survival of double-R CLL

Pirtobrutinib in R/R CLL/SLL



Aronson JH et al, *Am J Hematol*, 2022; Mato AR et al, *Lancet*, 2021

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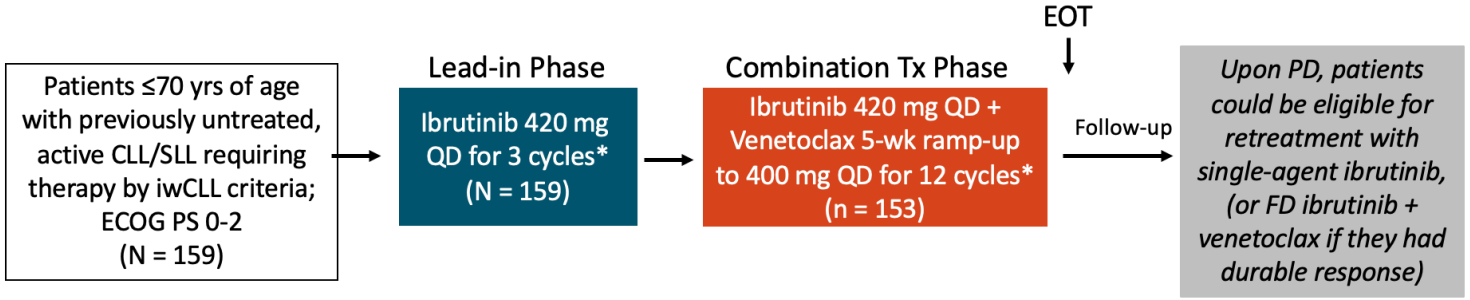
Venetoclax + Ibrutinib in TN CLL

CAPTIVATE Study (phase II) – Fixed duration cohort



Primary endpoint: CR/Cri rate in patients without del(17p)
Secondary endpoints: ORR, DoR, uMRD rates, PFS, OS

Tam C, et al, Blood, 2022

Venetoclax + Ibrutinib in TN CLL

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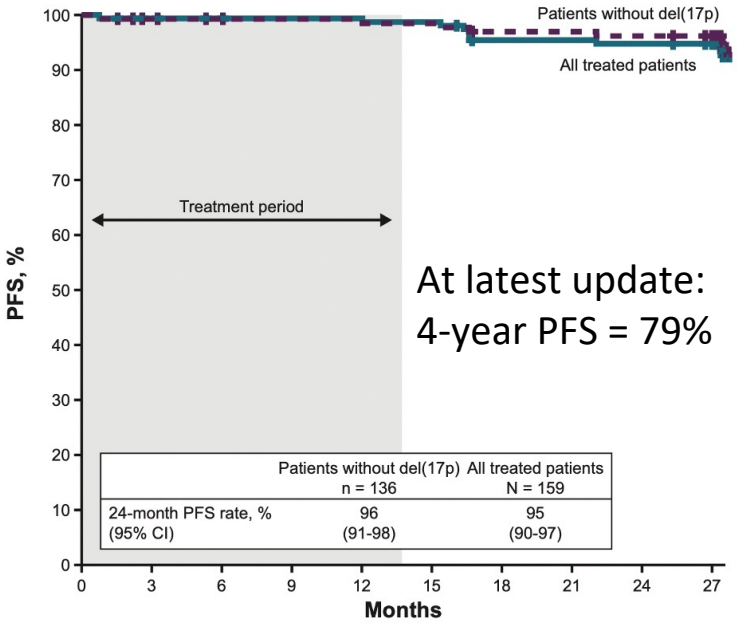

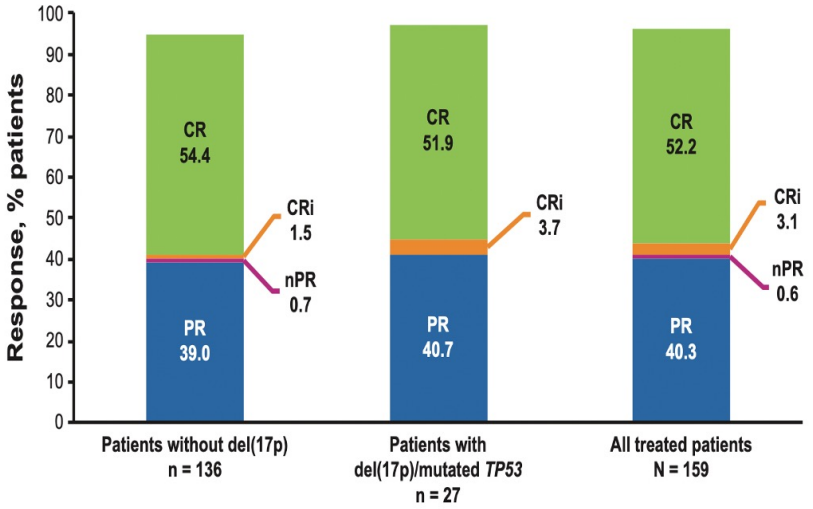

Tam C et al, *Blood*, 2022

Conclusion and Discussion

- As demonstrated by multiple clinical trials, BTK inhibitors and venetoclax-based regimens outperform CIT in first and subsequent lines of treatment
- Efficacy of novel agents over CIT is more evident in intermediate and high-risk CLL
- Also low-risk patients benefit from novel agents by virtue of their efficacy and lower/different short and long-term toxicity
- Among novel regimens, treament choice must be individualized based on biological features, patient's age and comorbidities, hospital access, etc.
- Optimal choice and sequencing of novel regimens is still matter of clinical investigation
- Re-treatment after fixed duration therapy?

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X edizione

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Palazzo Bonin Longare - Vicenza

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