Patient evaluation and risk stratification

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Disclosures

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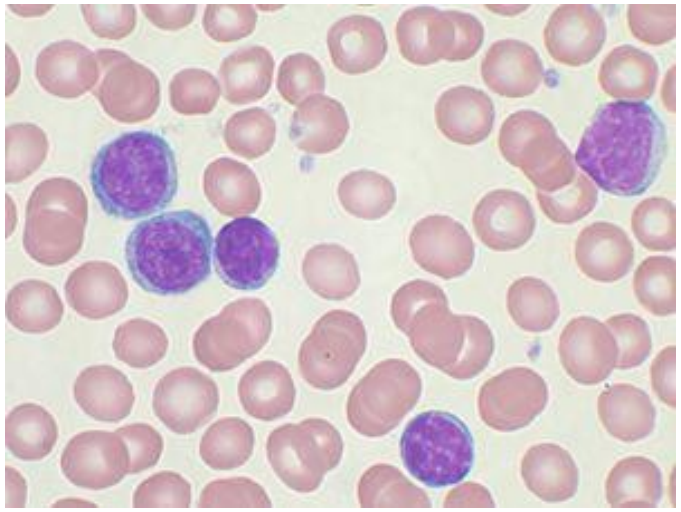
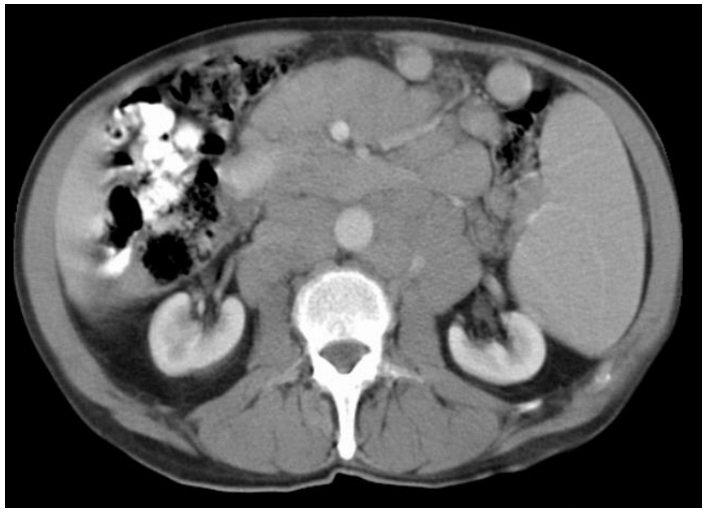
BMS, Bristol Myers Squibb; CTI, Cell Therapeutics, Inc.

Diagnosis of CLL





Monoclonal B-cell lymphocytosis
(CD5+, CD19+, CD20-/+, CD23+)

≤5,000/µL

>5,000/µL

Lymphadenopathy
Spleen / liver enlargement
Anemia / thrombocytopenia

Yes

No

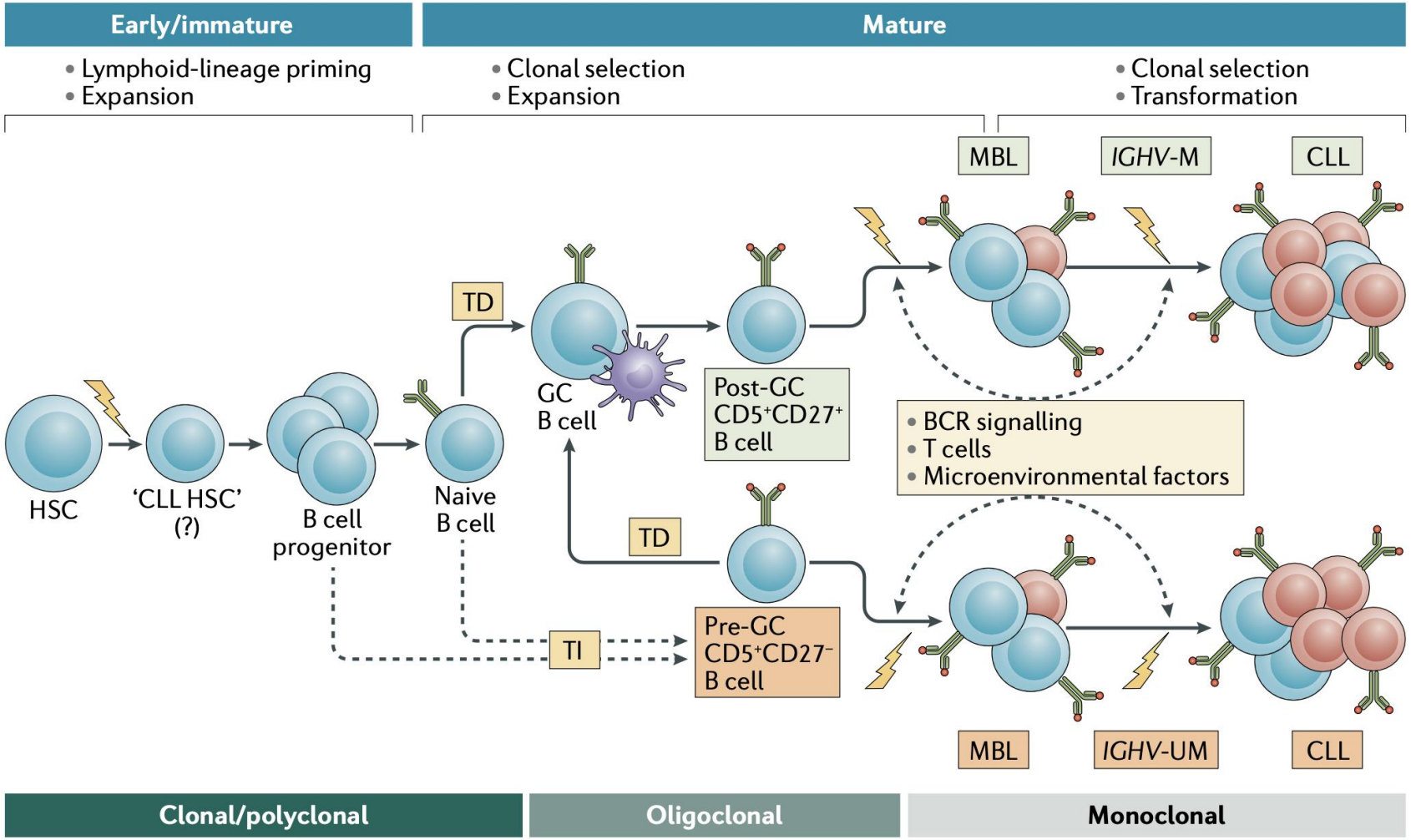
SLL

MBL

CLL

CLL, chronic lymphocytic leukemia; MBL, monoclonal B lymphocytosis; SLL, small lymphocytic lymphoma.
Rawstron AC *et al*. *N Engl J Med* 2008; 359 (6): 575–583.

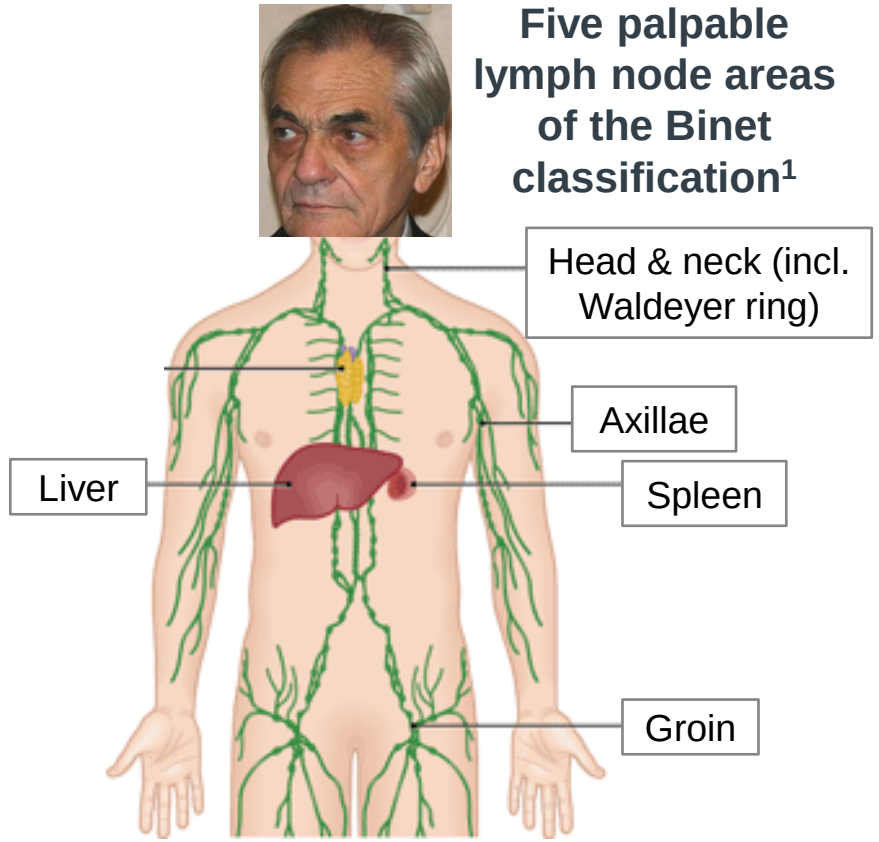
Cellular origin and pathogenesis of CLL



CLL, chronic lymphocytic leukemia; GC, germinal centre; HSC, hematopoietic stem cells; MBL, monoclonal B lymphocytosis; TD, T cell-dependent antigen; TI, T cell-independent antigen.
Bosch F *et al*. *Nat Rev Clin Oncol* 2019; 16 (11): 684–701.

Staging: Binet and Rai classifications

Risk group[1,2]	Binet classification[1]	Rai stage[2]	Median survival[3]
Low	• **Binet A**: Hb ≥10.0 g/dL, platelets ≥100 ×10^9/L, and <3 lymph node areas	• **Stage 0**: Lymphocytosis (>40% lymphoid cells in the bone marrow)	>10 years
Intermediate	• **Binet B**: Hb ≥10.0 g/dL, platelets ≥100 ×10^9/L, and ≥3 lymph node areas	• **Stage I**: Lymphadenopathy • **Stage II**: Splenomegaly and/or hepatomegaly	>8 years
High	• **Binet C**: Hb <10.0 g/dL and/or Plt: <100 ×10^9/L	• **Stage III**: Hb: <11.0 g/dL or hematocrit <33% • **Stage IV**: Plt: <100 × 10^9/L	~7.5 years



Hb, hemoglobin; plt, platelets.

1. Binet JL *et al*. *Cancer* 1981; 48 (1): 198–206. 2. Rai KR *et al*. *Blood* 1975; 46 (2): 219–234. 3. Pflug N *et al*. *Blood* 2014; 124 (1): 49–62.

Indications for treatment
iwCLL guidelines

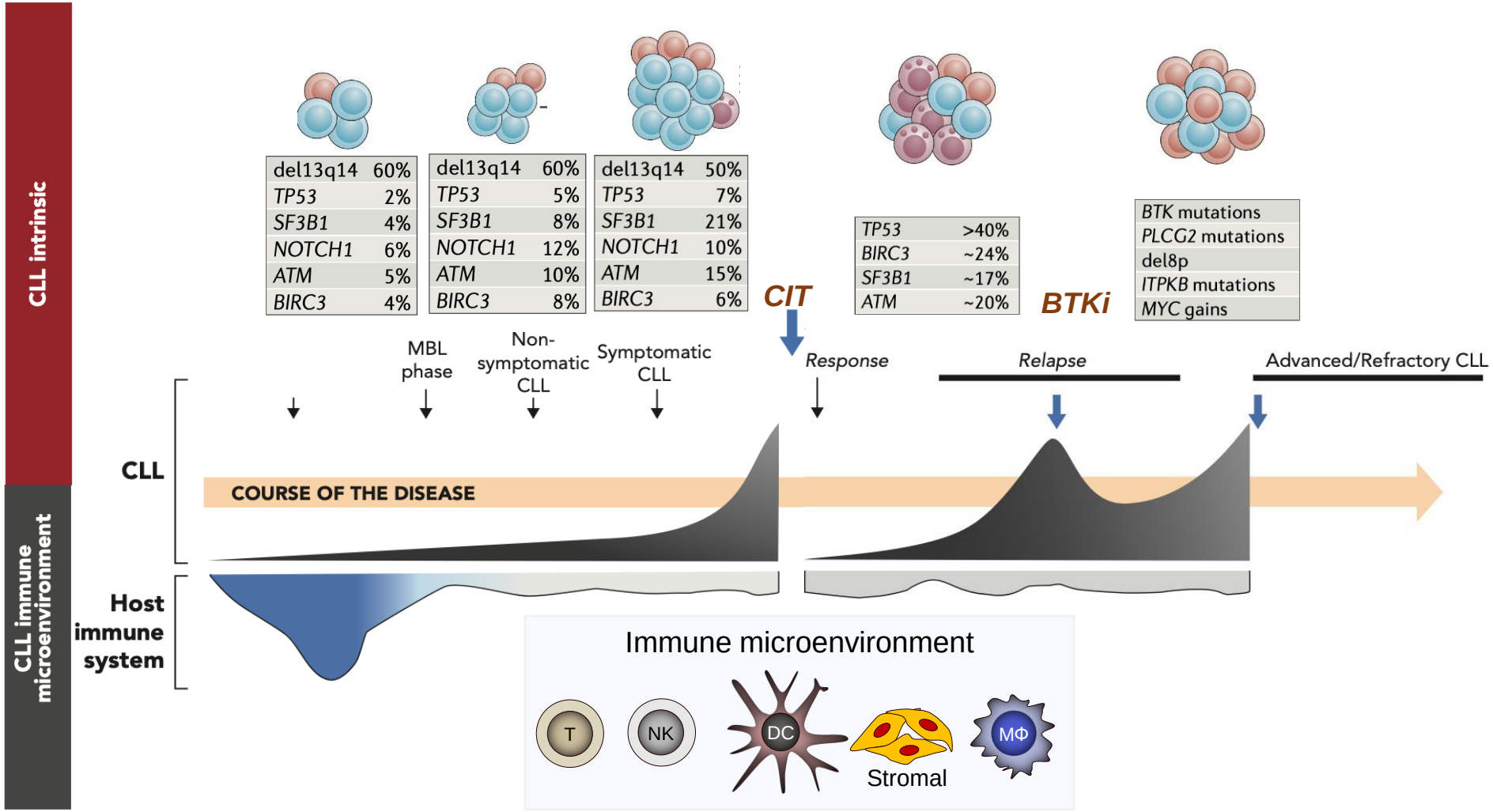
1. Binet C (evidence of progressive marrow failure)

Binet B / A + symptoms:

2. Splenomegaly (≥6 cm below the left costal margin or progressive or symptomatic)
3. Lymphadenopathy (>10 cm or progressive or symptomatic)
4. Lymphocyte doubling time <6 months; ≥50% increase in lymphocytes in <2 months
   - Minimum initial blood lymphocyte count: 30 g/L
5. Autoimmune cytopenias
6. Symptomatic extranodal involvement
7. Disease-related symptoms: Weight loss (≥10%), fatigue, fevers, night sweats

iwCLL, International Workshop on Chronic Lymphocytic Leukemia.
Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.

CLL disease course and coevolution with host immunity



BTKi, BTK inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; DC, dendritic cell; del, deletion; MΦ, macrophage; NK, natural killer cell; T, T cell.
Adapted from Bosch F *et al*. *Nat Rev Clin Oncol* 2019; 16 (11): 684–701 and Nagler A *et al*. *Blood* 2023; 141 (4): 369–379.

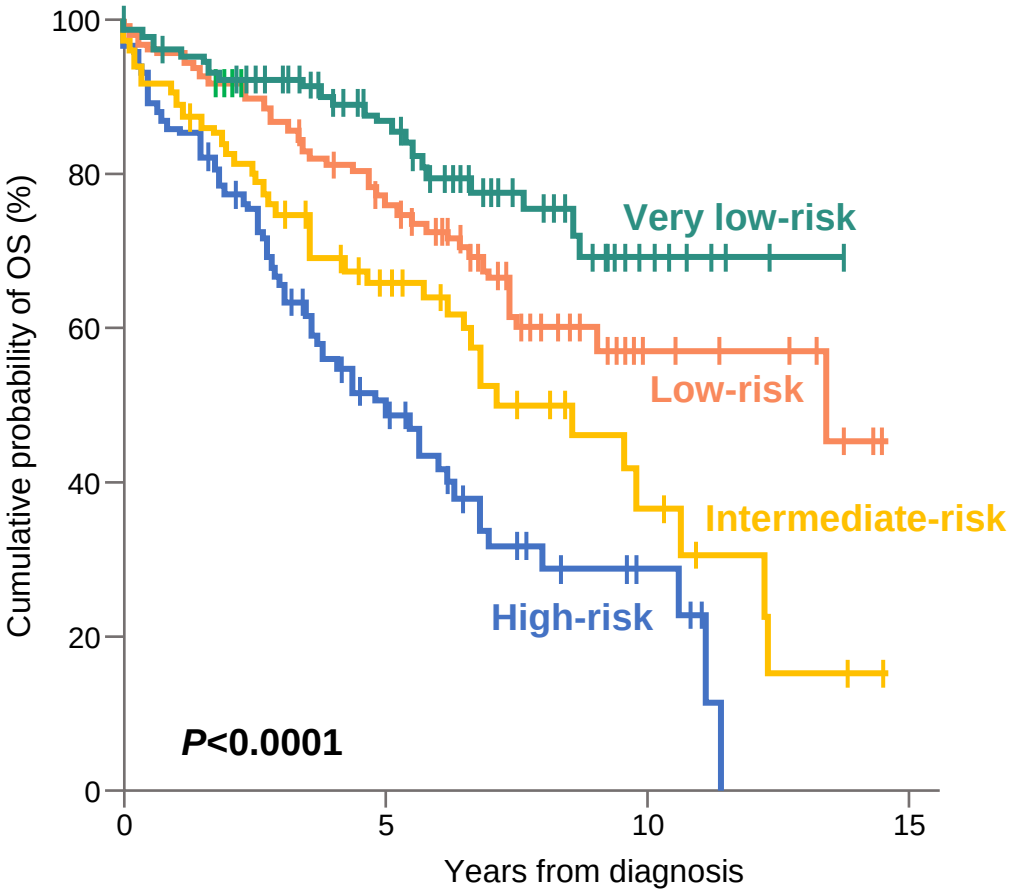
Impact of cytogenetics

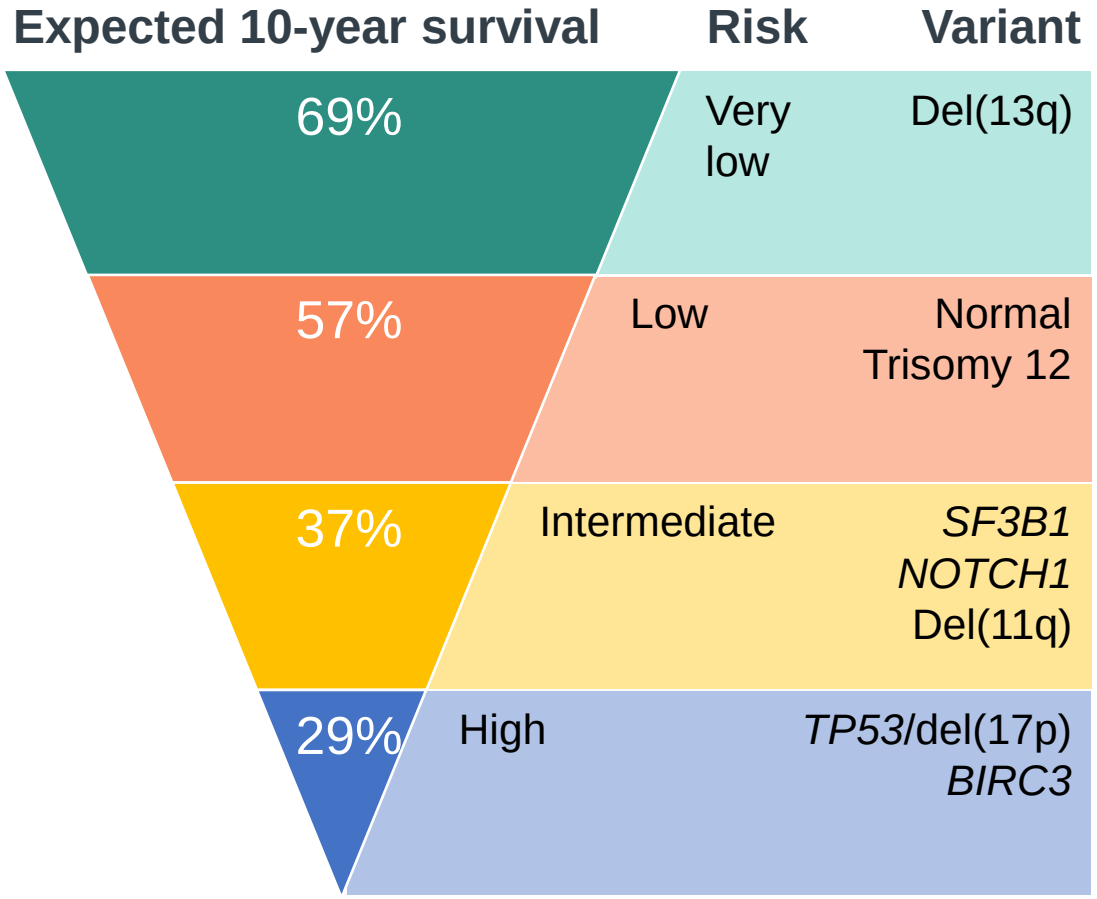
Abnormality	Patients, %	Median time to treatment, months	Median OS, months
Del(17)(p13.1)	7	9	32
Del(11)(q22.3)	18	13	79
Trisomy 12	16	33	114
Del(13)(q14)	55	49	133
None detected	18	92	111

Del, deletion; OS, overall survival.

Döhner H *et al*. *N Engl J Med* 2000; 343 (26): 1910–1916.

Impact of cytogenetics





Rossi D *et al*. Blood 2013; 121 (8): 1403–1412.

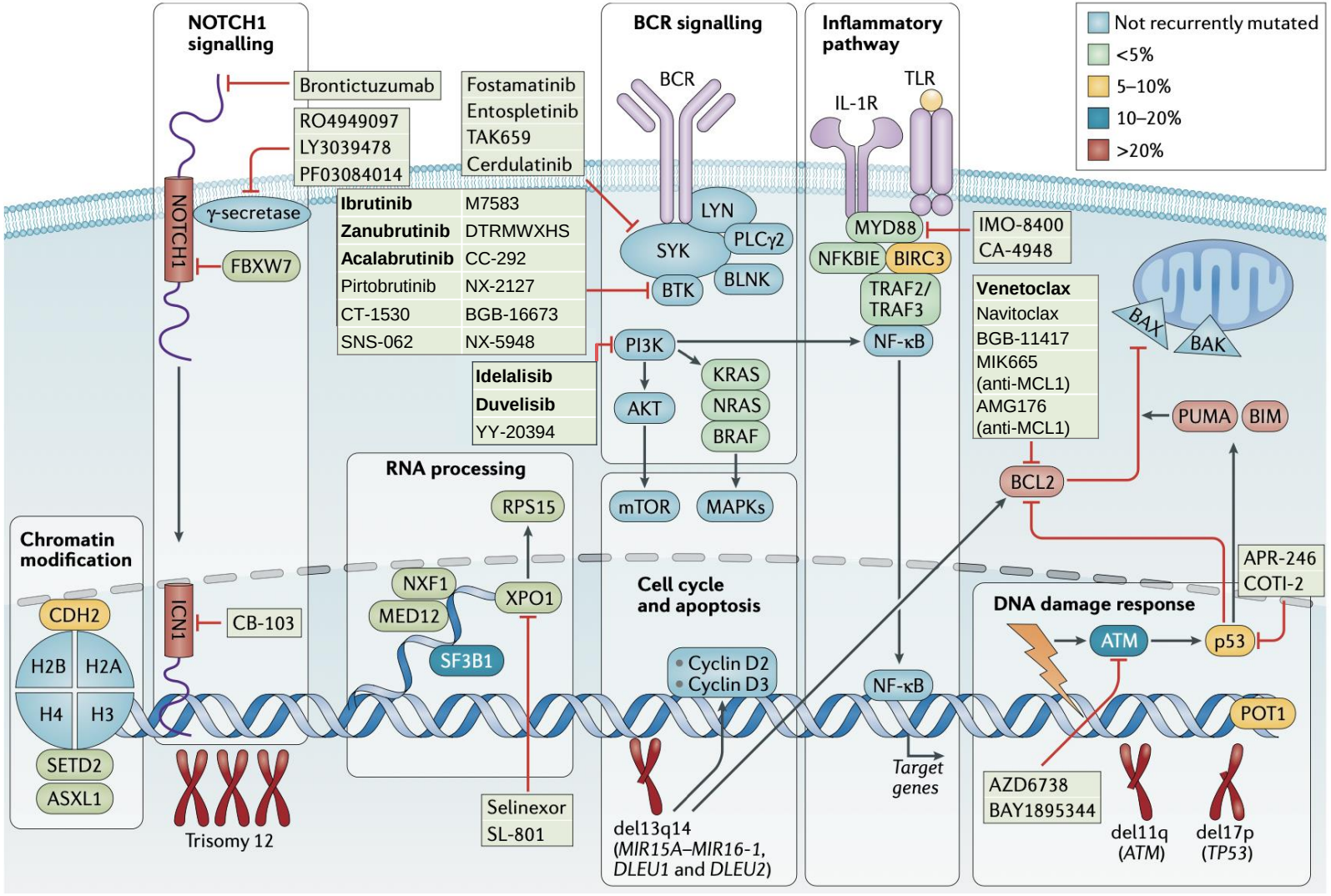
Evaluation of patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI*	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound	Possible	NGI

*Before BCL2i for TLS evaluation.

CBC, complete blood count; CLL, chronic lymphocytic leukemia; CT, computerized tomography; del, deletion; FISH, fluorescence in situ hybridization; IGHV, immunoglobulin heavy chain variable; iwCLL, international workshop on CLL; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography; TLS, tumor lysis syndrome. Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.

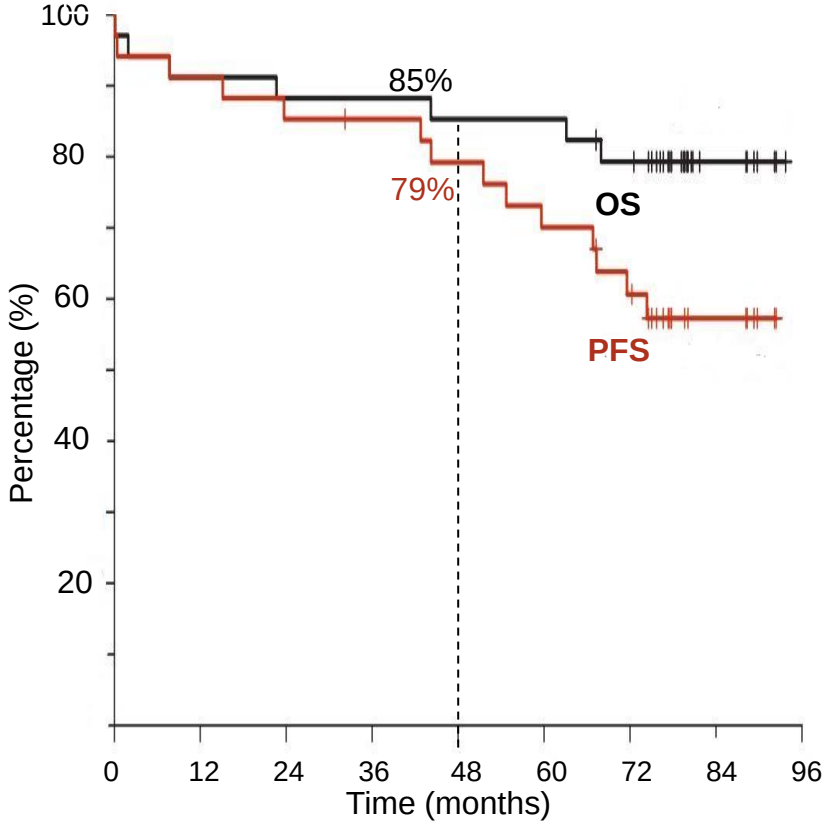
CLL targeted drugs



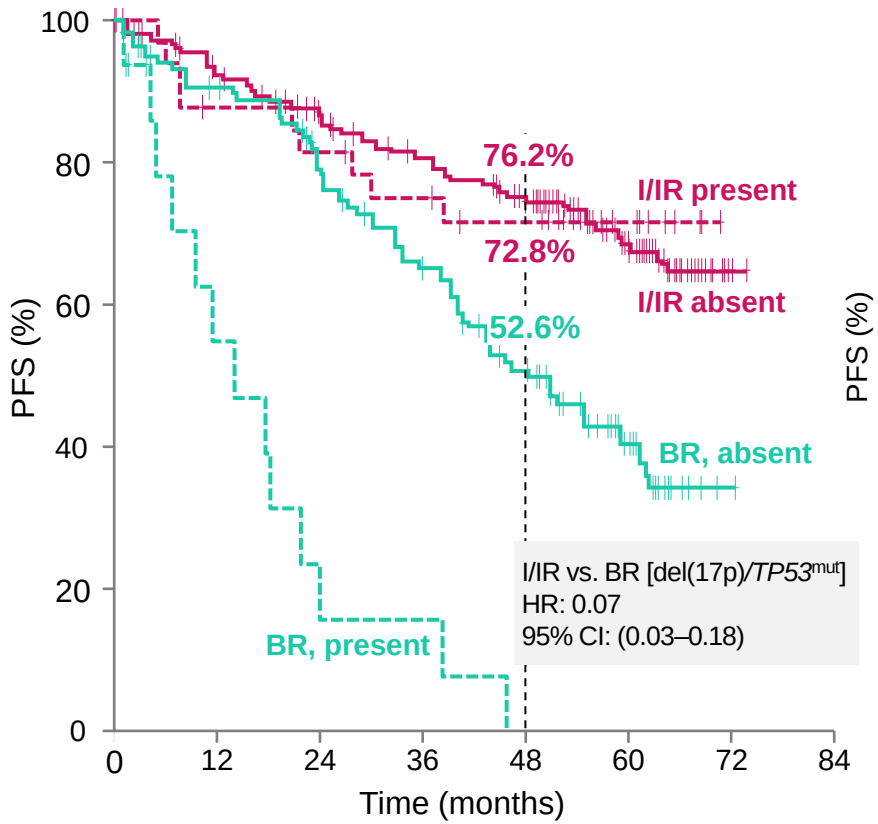
Adapted from Bosch F *et al*. *Nat Rev Clin Oncol* 2019; 16 (11): 684–701.

Del(17p)/*TP53*^{mut} impact on first-line treatment: CIT, BTKi, BCL2i

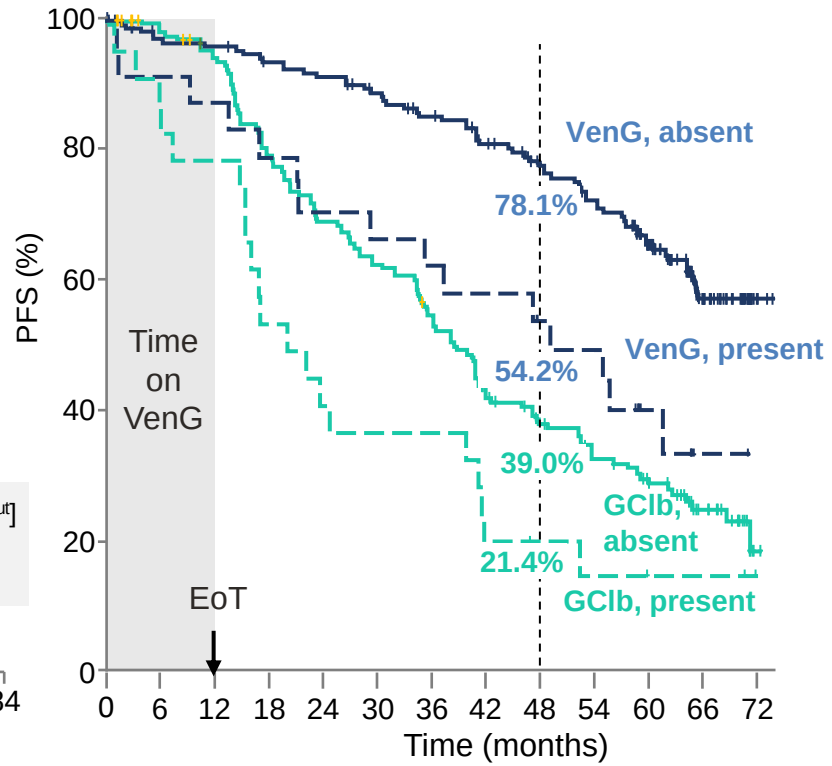
Phase 2 IIT Ibrutinib monotherapy in patients with del(17p)/*TP53*^{mut}*
(median follow-up: 6.5 years)[1]



Alliance A041202 : PFS I/IR vs BR by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 55 months)[2]



CLL14: PFS VenG vs GClb by del(17p)/*TP53*^{mut} status (absent/present)
(median follow-up: 65.4 months)[3]

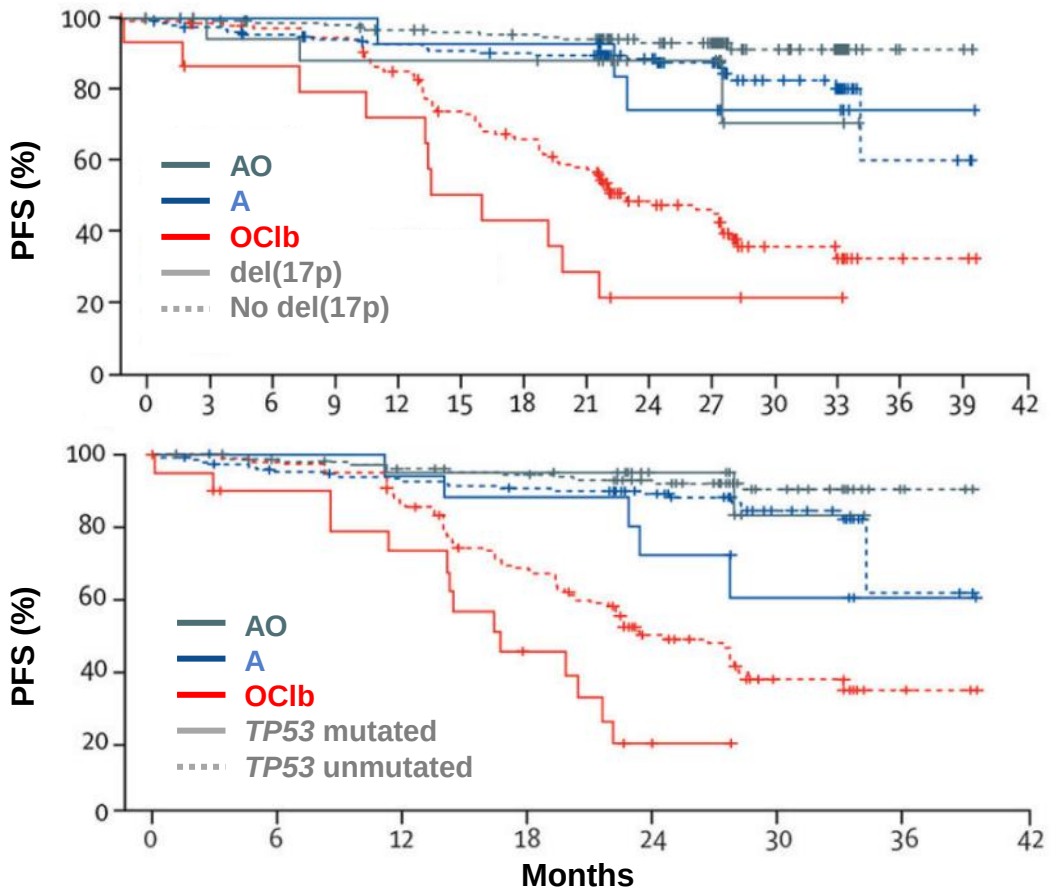


This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

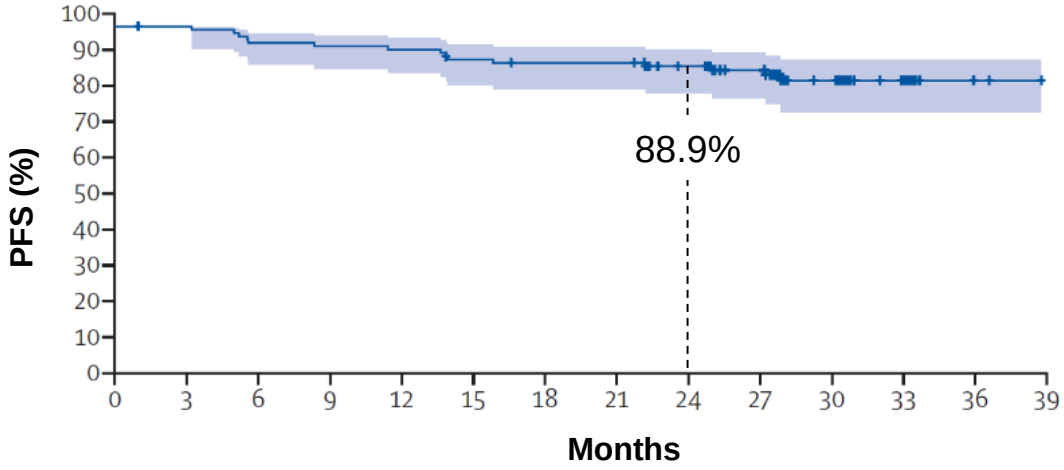
BR, bendamustine plus rituximab; CI, confidence interval; EoT, end of treatment; GClb, obinutuzumab and chlorambucil; HR, hazard ratio; I, ibrutinib; IR, ibrutinib plus rituximab; OS, overall survival; PFS, progression free survival; VenG, venetoclax and obinutuzumab. 1. Ahn IE *et al*. *N Engl J Med* 2020; 383: 498–500; 2. Woyach J *et al*. Oral presentation at ASH 2021; Atlanta, Georgia, USA, December 11–14, 2021 (Abstract 369). 3. Al-Sawaf O *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–12, 2022 (Abstract S148).

Del(17p)/*TP53*^{mut} impact on first-line treatment: Next-gen BTKis

ELEVATE TN: PFS A vs AO vs OClb[1]
(median follow-up: 28 months)



SEQUOIA: PFS Zanubrutinib (Arm C – del[17p])[2]
(median follow-up: 30.5 months)

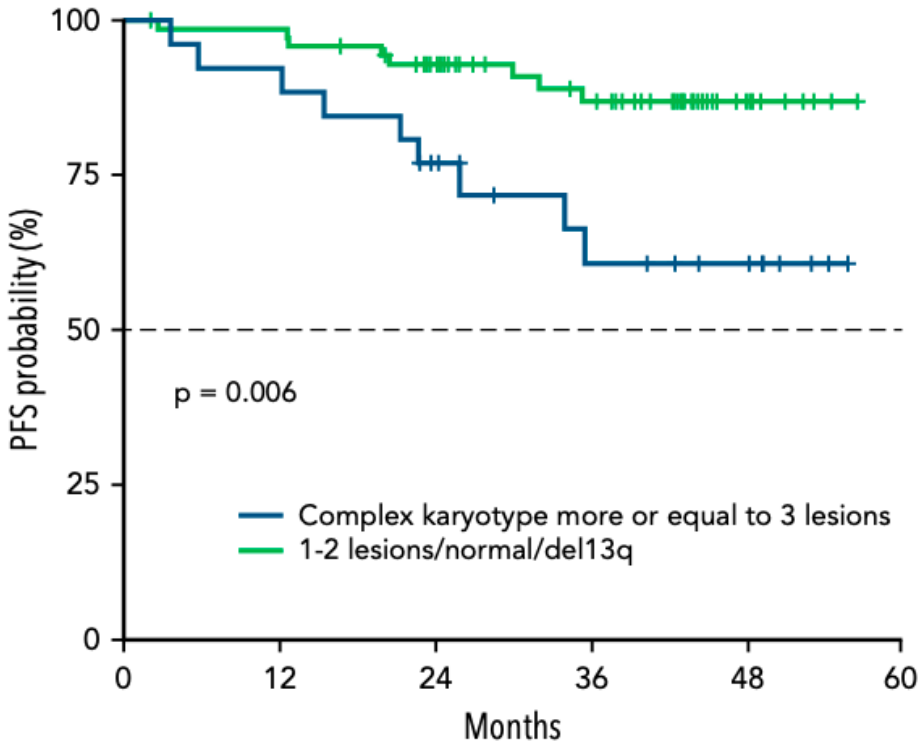


Patients without del(17p) in the SEQUOIA study had a 24-month PFS of 85.5% with zanubrutinib vs. 69.5% with BR*†

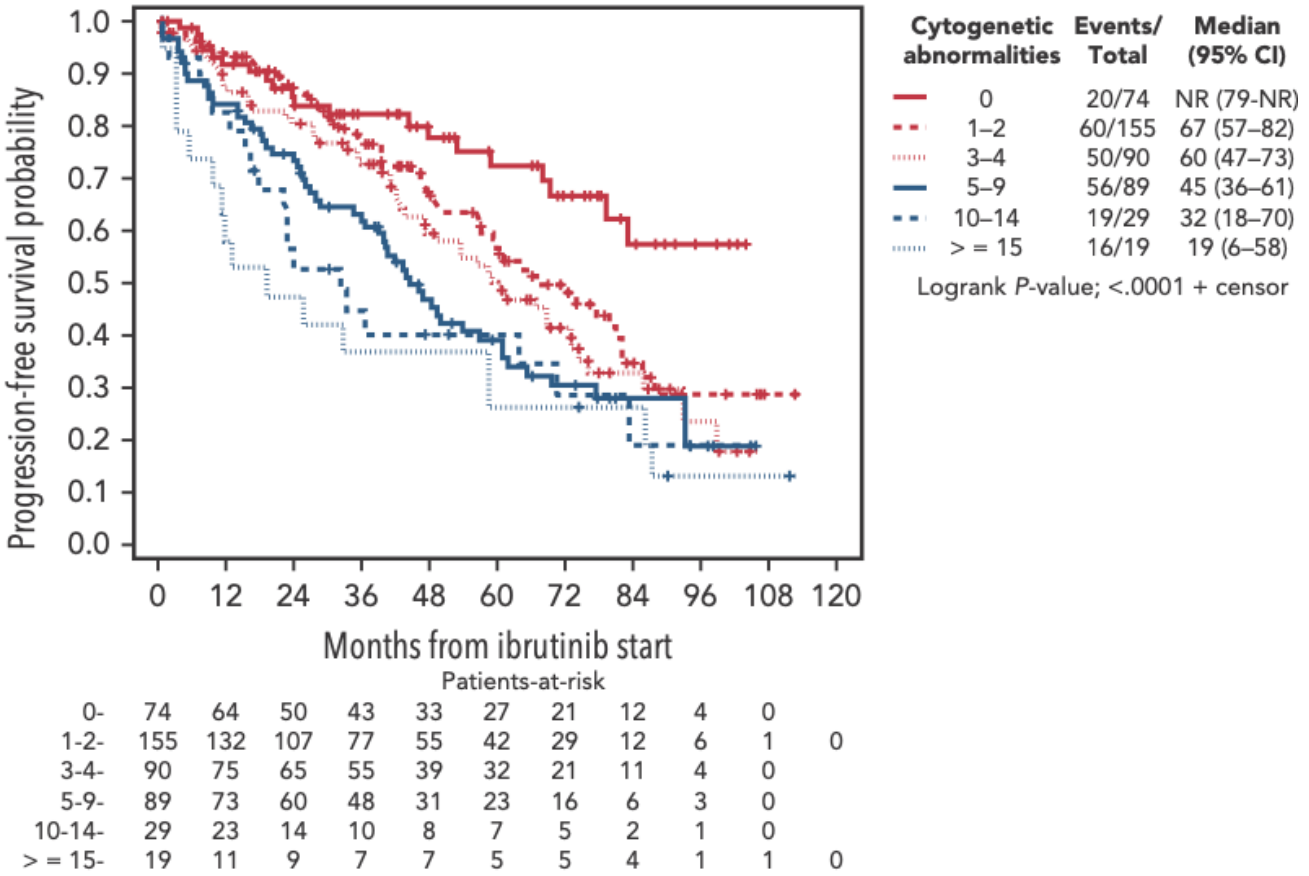
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.
*No significant benefit in the small subgroup of patients with a *TP53* mutation. †6% of patients without del(17p) treated with zanubrutinib or BR were positive for *TP53* mutations.
A, acalabrutinib; AO, acalabrutinb-obinutuzumab; BR, bendamustine and rituximab; BTKi, BTK inhibitor; OClb, obinutuzumab and chlorambucil; PFS, progression-free survival.
1. Sharman JP *et al. Lancet* 2020; 395 (10232): 1278–1291. 2. Tam CS *et al. Lancet Oncol* 2022; 23 (8): 1031–1043.

Karyotypic complexity impact on treatment with ibrutinib

GIMEMA LLC1114 phase 2 study[1]
unfit patients with CLL treated with ibrutinib and rituximab



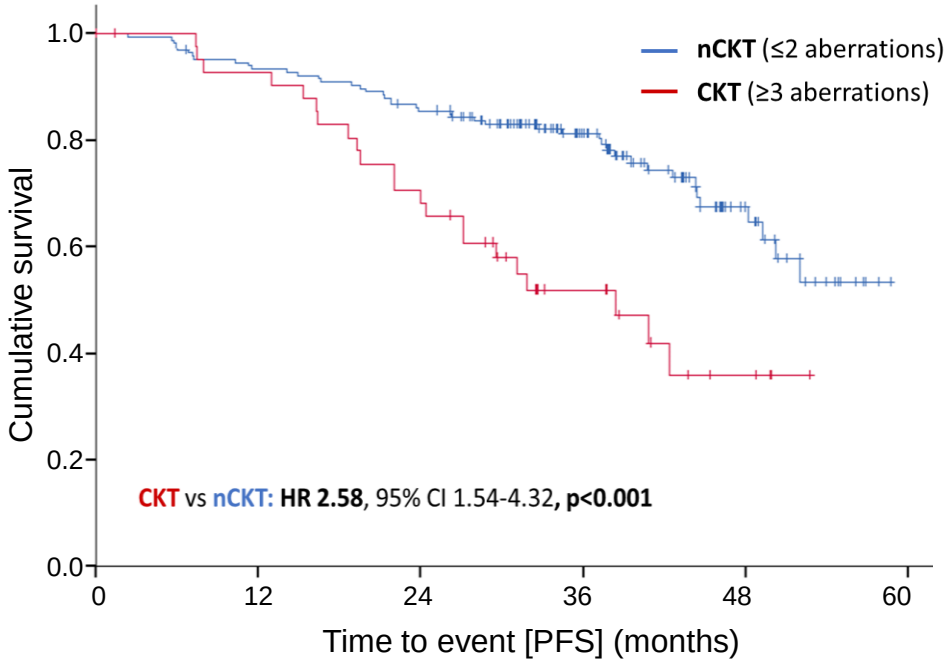
Retrospective institutional study[2]
(Ohio State University, Columbus, OH)



CI, confidence interval; CLL, chronic lymphocytic leukemia; NR, not reached; PFS, progression-free survival.
1. Rigolin GM *et al*. *Blood* 2021; 138 (23): 2372–2382. 2. Kittai AS *et al*. *Blood* 2021; 138 (23): 2372–2382.

Karyotypic complexity impact on first-line treatment: CLL13 data

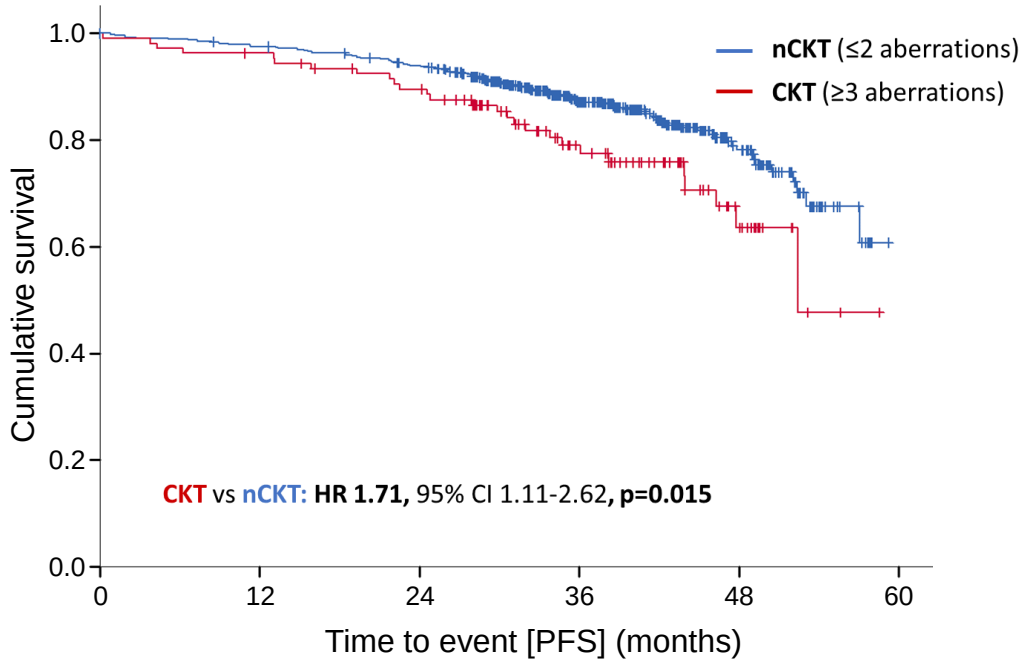
PFS, chemoimmunotherapy arm



Patient at risk

nCKT	177	155	141	84	24
CKT	46	38	28	13	4

PFS, pooled venetoclax arms

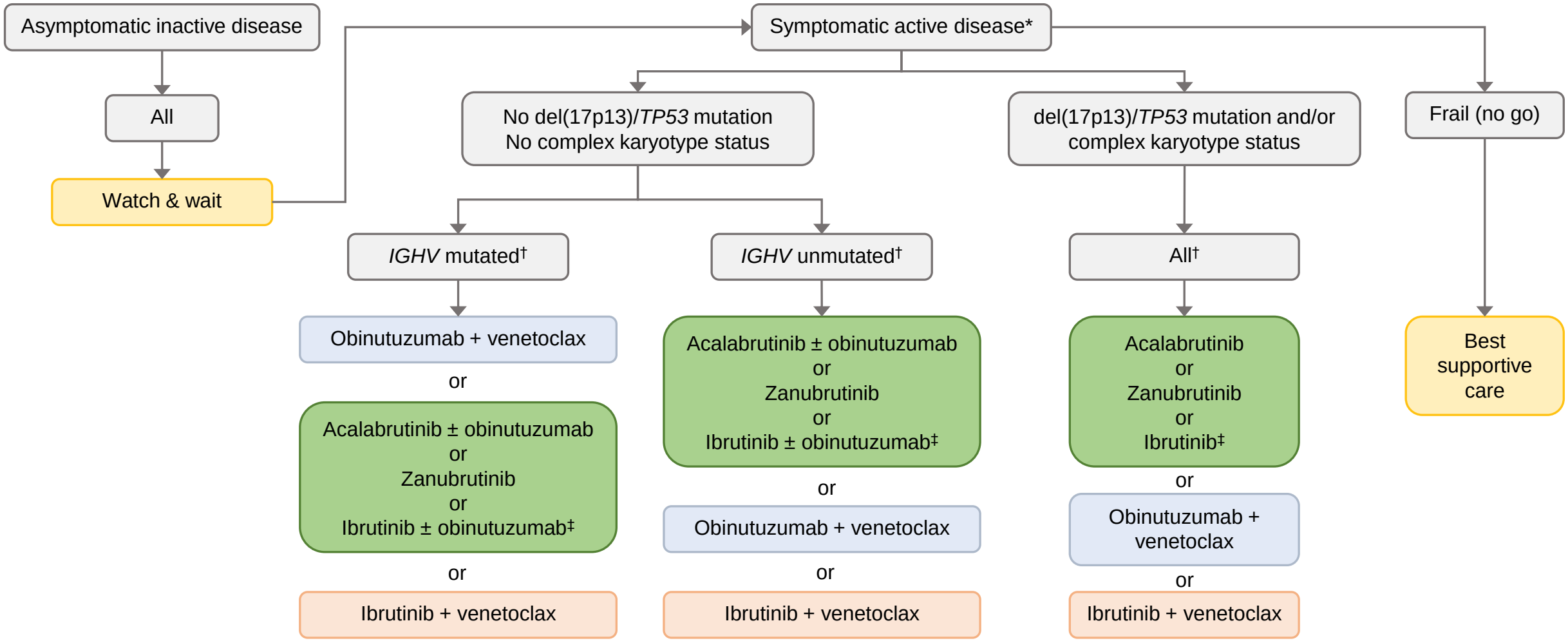


Patient at risk

nCKT	565	547	522	308	99
CKT	107	102	92	52	16

CI, confidence interval; CKT, complex karyotype; HR, hazard ratio; nCKT, non-CKT; PFS, progression-free survival.
Furstenau M *et al*. Oral presentation at ASH 2022; New Orleans, LA, USA, December 10–13, 2022 (Abstract 346).

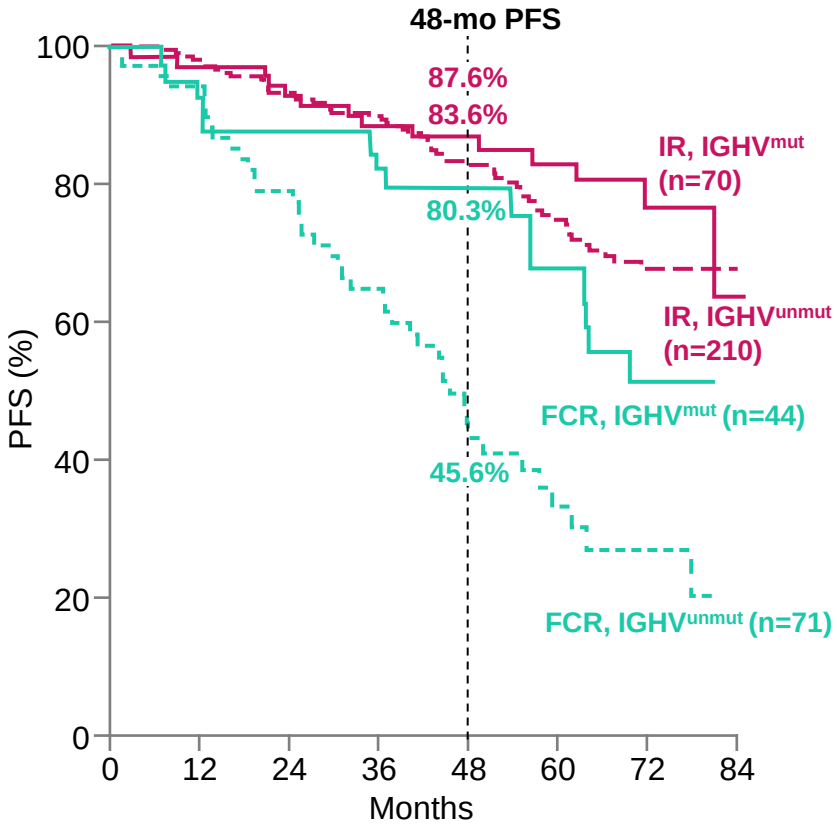
First-line treatment recommendations based on risk factors



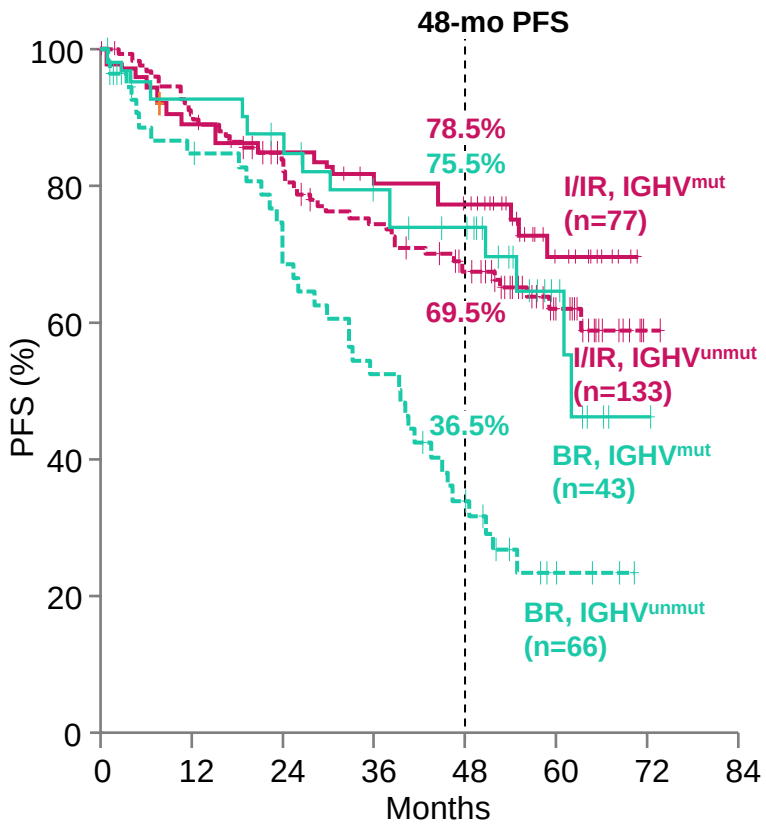
*Active disease according to the iwCLL 2018 criteria; †The sequence of therapies represents one possibility. ‡If acalabrutinib or zanubrutinib are contraindicated or not available, ibrutinib (± obinutuzumab) remains a therapy option, taking into account an increased risk of cardiac side effects. Acalabrutinib and zanubrutinib have not been systematically evaluated in younger/fit patients as first-line therapy.
Adapted from the Onkopedia guidelines: Chronic Lymphocytic Leukemia (CLL), 2023. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll

IGHV impact on first-line treatment: CIT, BTKi

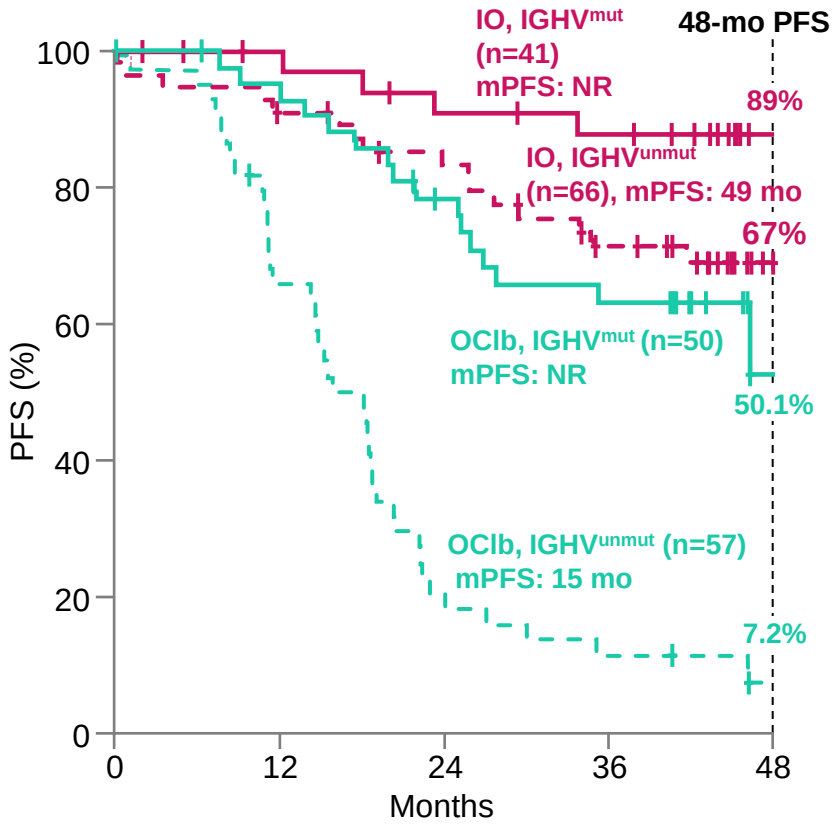
ECOG 1912: PFS IR vs FCR
(median follow-up: 70 months)[1]



Alliance A041202: PFS I/IR vs BR
(median follow-up: 55 months)[2]



iLLUMINATE: PFS IO vs OClb
(median follow-up: 45 months)[3]



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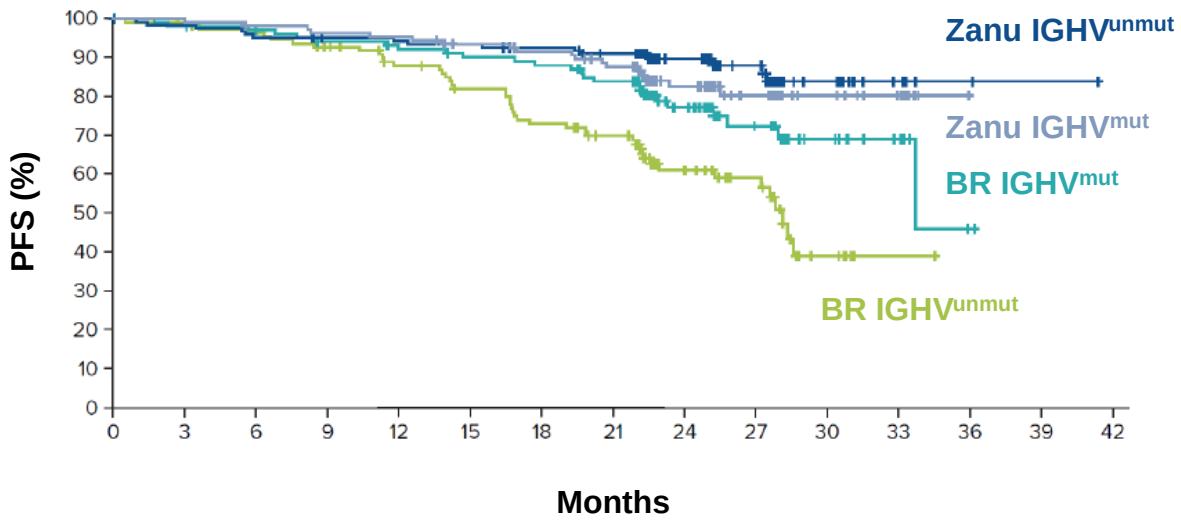
BR, bendamustine and rituximab; BTKi, BTK inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; HR, hazard ratio; I, ibrutinib; IO, ibrutinib and obinutuzumab; IR, ibrutinib and rituximab; mo, month; mPFS, median progression-free survival; mut, mutated; NR, not reached; OClb, obinutuzumab and chlorambucil; PFS, progression-free survival; unmut, unmutated.

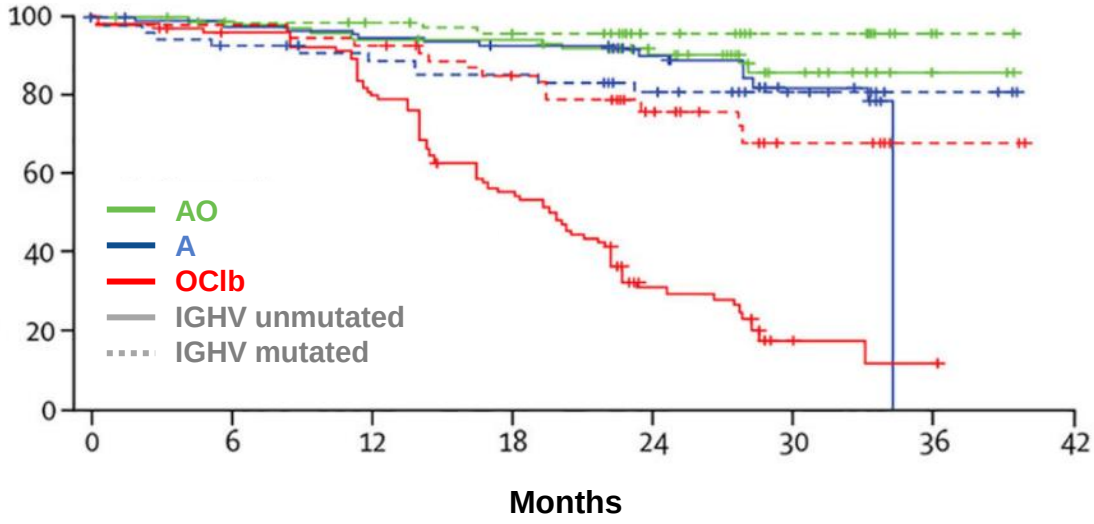
1. Shanafelt TD *et al. Blood* 2022; 140 (2): 112–120. 2. Woyach J *et al*. Oral presentation at ASH 2021; Georgia, USA, December 11–14, 2021 (Session 642). 3. Moreno C *et al*. *Haematologica* 2022; 107 (9): 2108–2120.

IGHV impact on first-line treatment: Next-gen BTKis

SEQUOIA: PFS Zanubrutinib vs BR[1,2]
(median follow-up: 26 months)



ELEVATE TN: PFS A vs AO vs OClb[3]
(median follow-up: 28 months)



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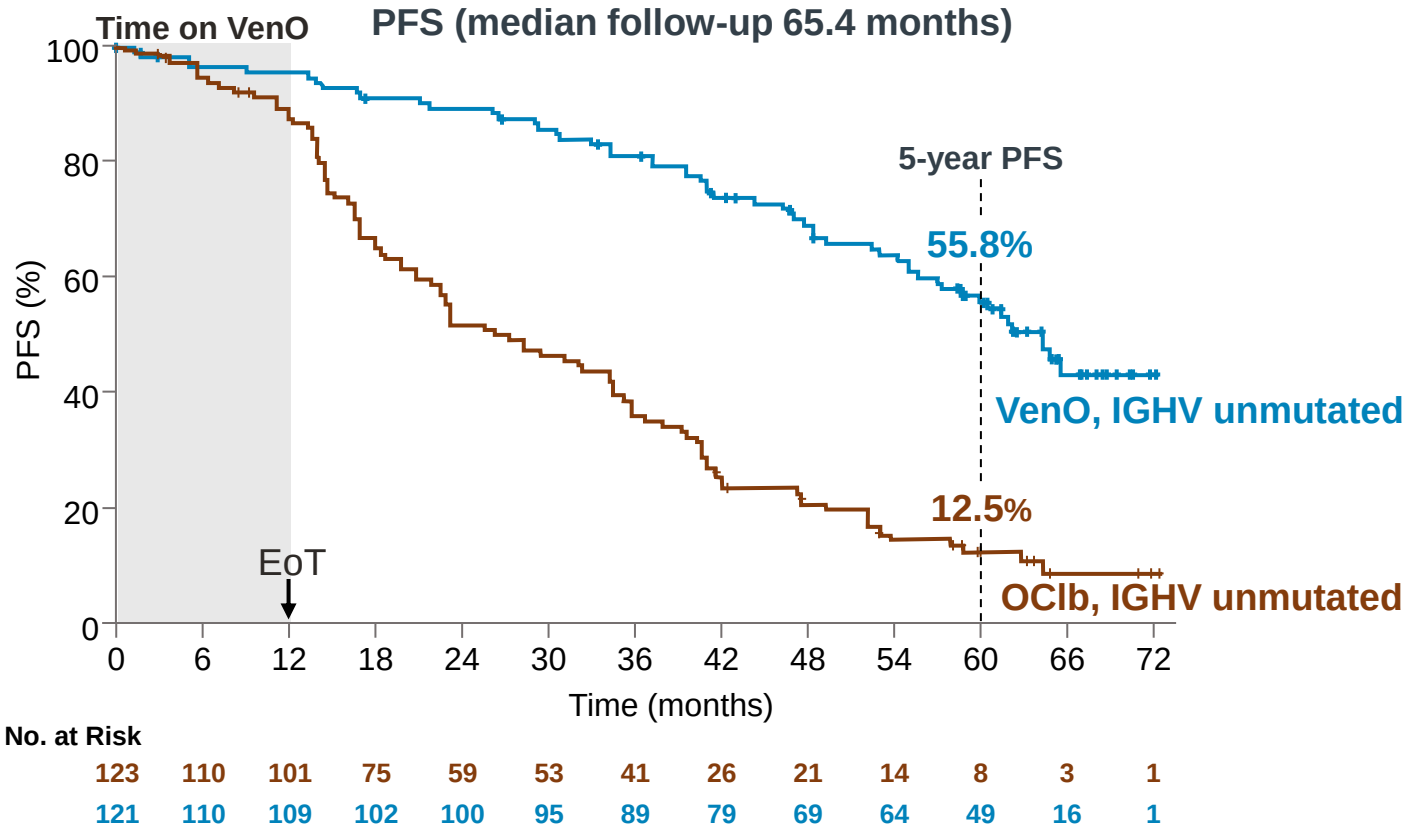
A, acalabrutinib; AO, acalabrutinb-obinutuzumab; BR, bendamustine and rituximab; BTKis, BTK inhibitors; IGHV, immunoglobulin heavy chain variable region; mut, mutated; OClb, obinutuzumab and chlorambucil; PFS, progression-free survival; unmut, unmutated; Zanu, zanubrutinib.

1. Tam CS *et al. Lancet Oncol* 2022; 23 (8): 1031–1043. 2. Tam CS *et al. Lancet Oncol* 2022; 23 (8): 1031–1043 (supplementary figure 3). 3. Sharman JP *et al. Lancet* 2020; 395 (10232): 1278–1291.

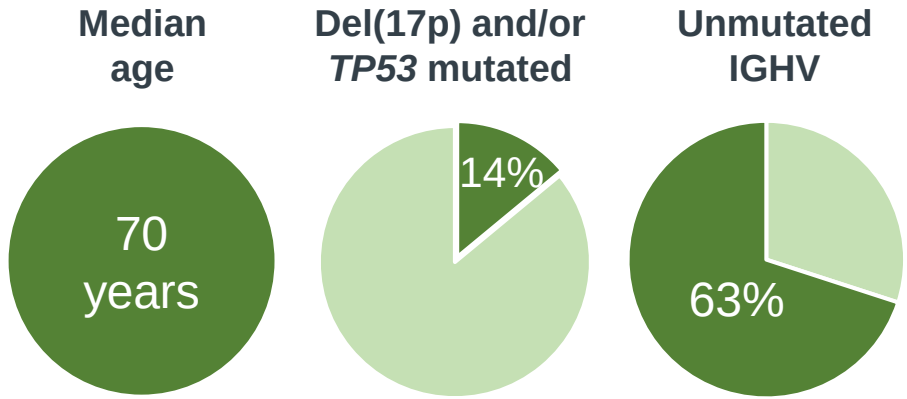
IGHV impact on first-line treatment: CIT, BTKi, BCL2i

Ven-O:[1]
5-year PFS in uIGHV: Ven + O: 55.8%
Clb + O: 12.5%



Acalabrutinib:[2]
5-year PFS in uIGHV: A + O: 82%
A : 72%
Clb + O: 6%

A total of 535 patients (A+O, n=179; A, n=179; O+Clb, n=177) were randomized

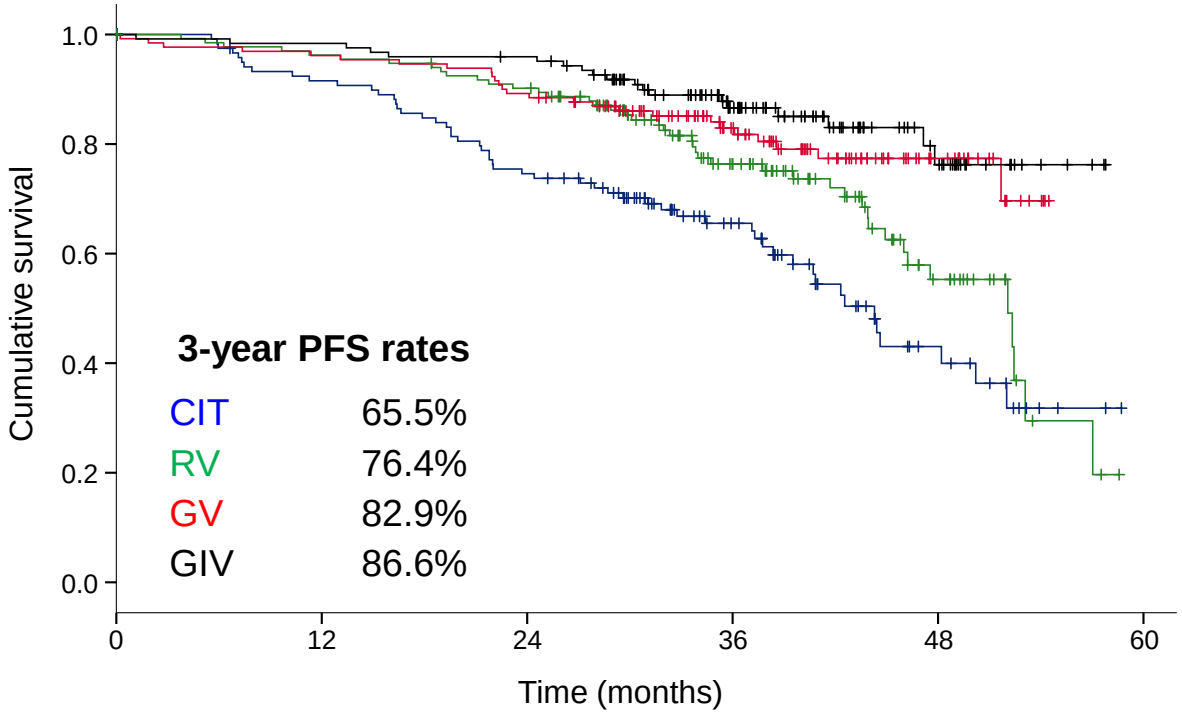


A, acalabrutinib; Clb, chlorambucil; EoT, end of treatment; O, obinutuzumab; PFS, progression-free survival; uIGHV, unmutated IGHV; Ven, venetoclax.

1. Al Sawaf O *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–17, 2022 (Abstract S148). 2. Sharman JP *et al*. Poster presentation at EHA 2022; Vienna, Austria, June 9–17, 2022 (Abstract P666).

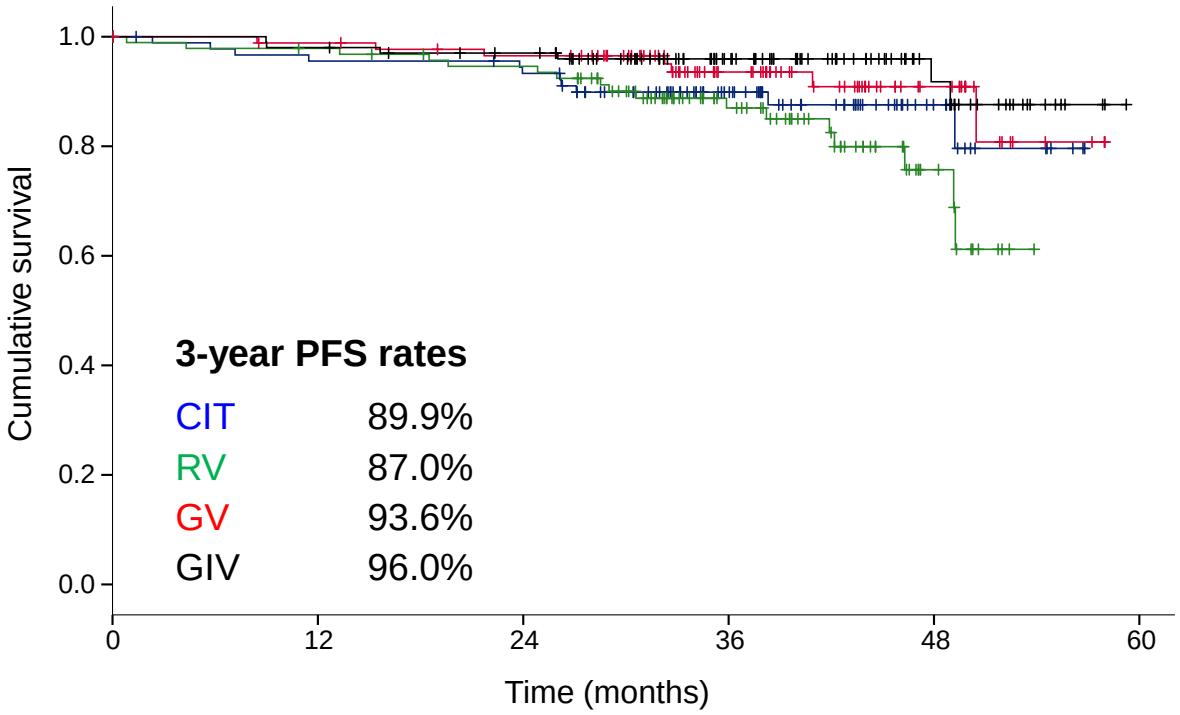
IGHV impact on first-line treatment: CIT, BTKi, BCL2i

Unmutated IGHV



CIT	131	108	88	48	14
RV	134	128	119	67	20
GV	130	125	116	71	21
GIV	123	121	117	70	22

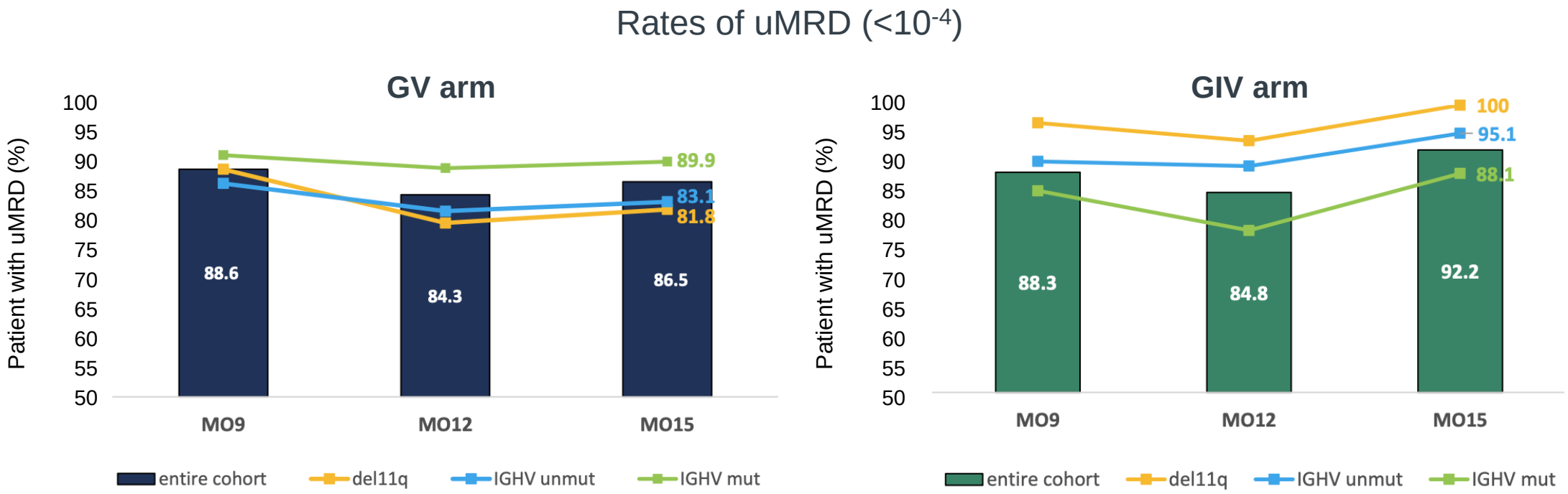
Mutated IGHV



CIT	95	86	83	50	14
RV	95	91	86	49	12
GV	89	86	82	48	17
GIV	101	99	94	59	22

BCL2i, BCL2 inhibitor; BTKi, BTK inhibitor; CIT, chemoimmunotherapy; GIV, obinutuzumab, ibrutinib, and venetoclax; GV, obinutuzumab and venetoclax; PFS, progression-free survival; RV, rituximab and venetoclax.
Eichhorst B *et al*. Oral presentation at EHA 2022; Vienna, Austria, June 9–17, 2022 (Abstract LB2365).

Who benefits from the addition of a BTKi to venetoclax and obinutuzumab?

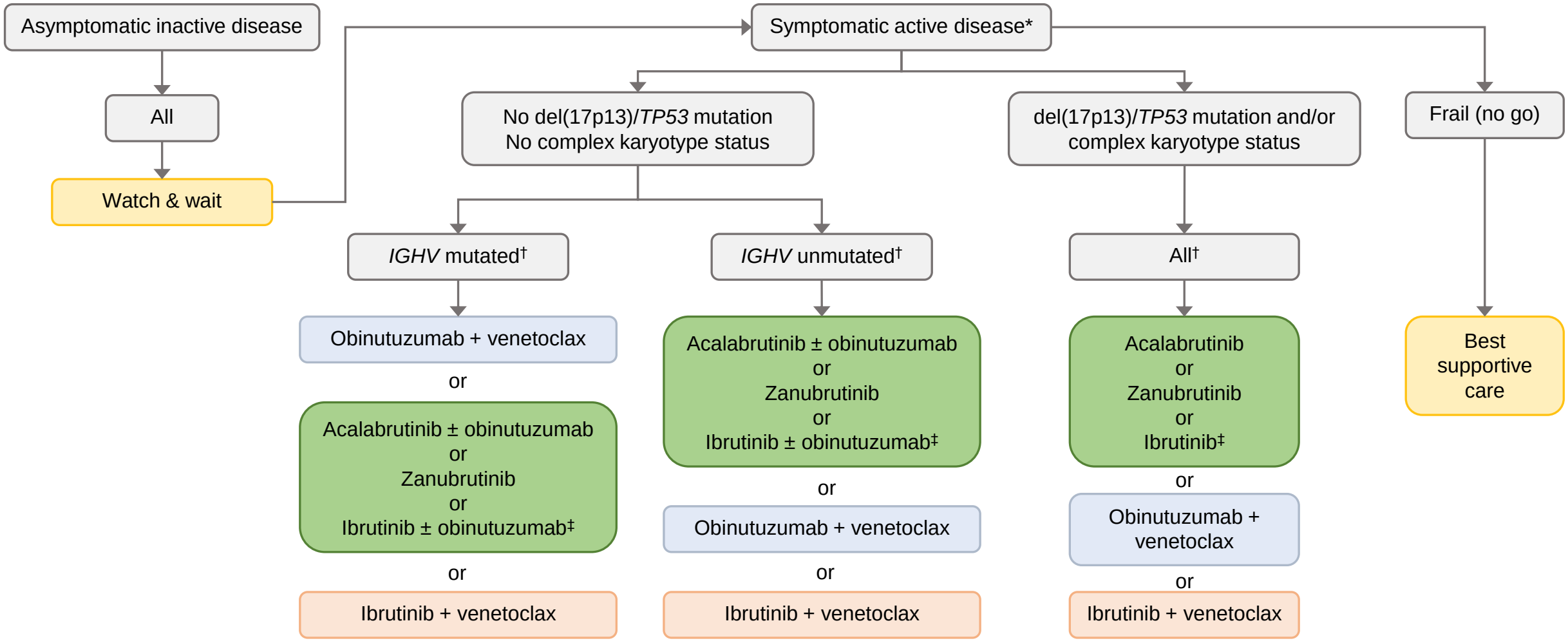


Based on uMRD (<10^{-4}) outcomes, patients who benefit from the addition of BTKi to venetoclax and obinutuzumab have…

- Unmutated IGHV
- Del(11q)

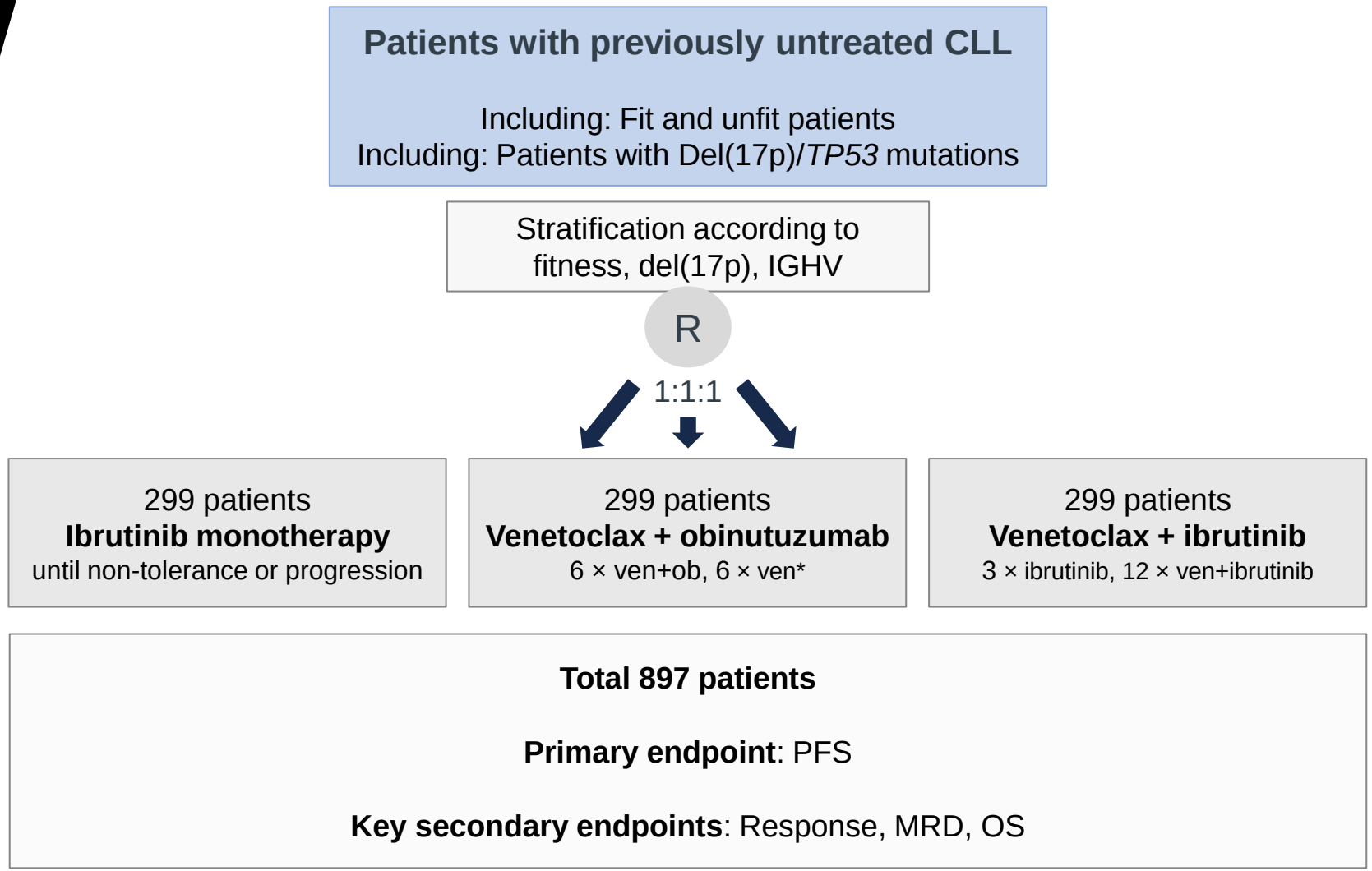
BTKi, BTK inhibitor; Del, deletion; GIV, obinutuzumab, ibrutinib, and venetoclax; GV, obinutuzumab and venetoclax; mut, mutated; uMRD, undetectable minimal residual disease; unmut, unmutated.
Fürstenau M *et al*. Oral presentation at ASH 2021; Atlanta, Georgia, USA, December 11–14, 2021 (Abstract 72).

First-line treatment recommendations based on risk factors



*Active disease according to the iwCLL 2018 criteria; †The sequence of therapies represents one possibility. ‡If acalabrutinib or zanubrutinib are contraindicated or not available, ibrutinib (± obinutuzumab) remains a therapy option, taking into account an increased risk of cardiac side effects. Acalabrutinib and zanubrutinib have not been systematically evaluated in younger/fit patients as first-line therapy.

Onkopedia guidelines: Chronic Lymphocytic Leukemia (CLL), 2023. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll



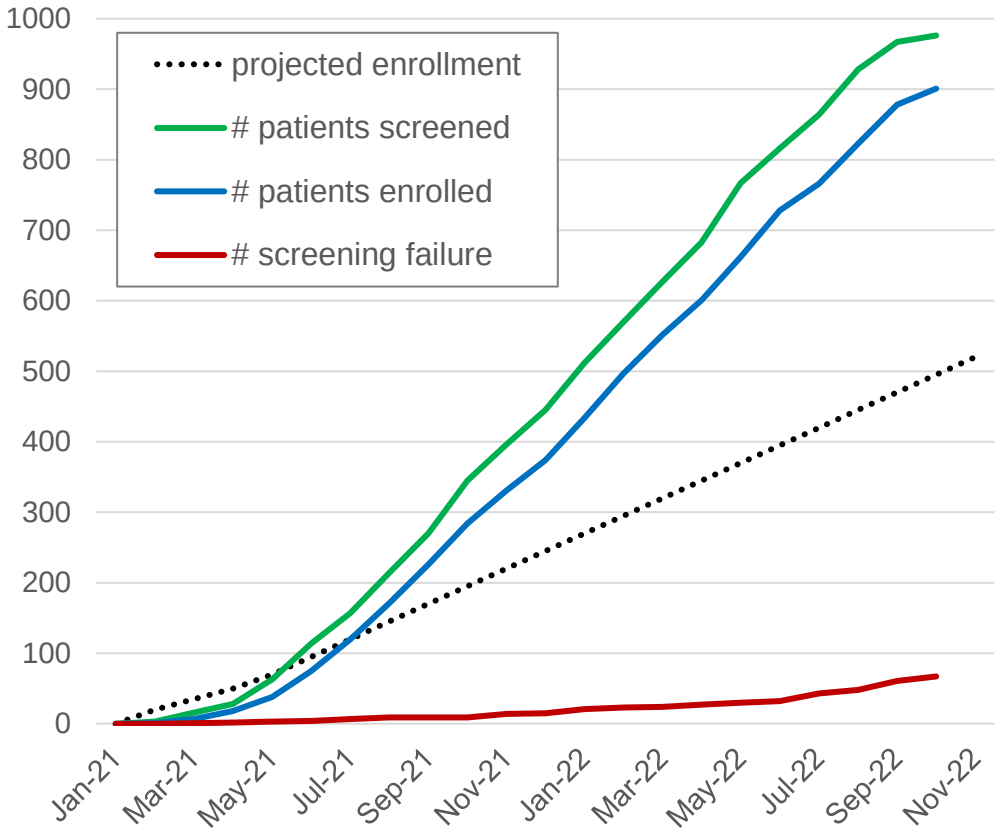
CLL, chronic lymphocytic leukemial; MRD, minimal residual disease; ob, obinutuzumab; OS, overall survival; PFS, progression-free survival; ven, venetoclax.
Al-Sawaf O. Oral presentation at the XIIIth International Workshop of the German CLL Study Group; Cologne, Germany, September, 2022.

CLL17

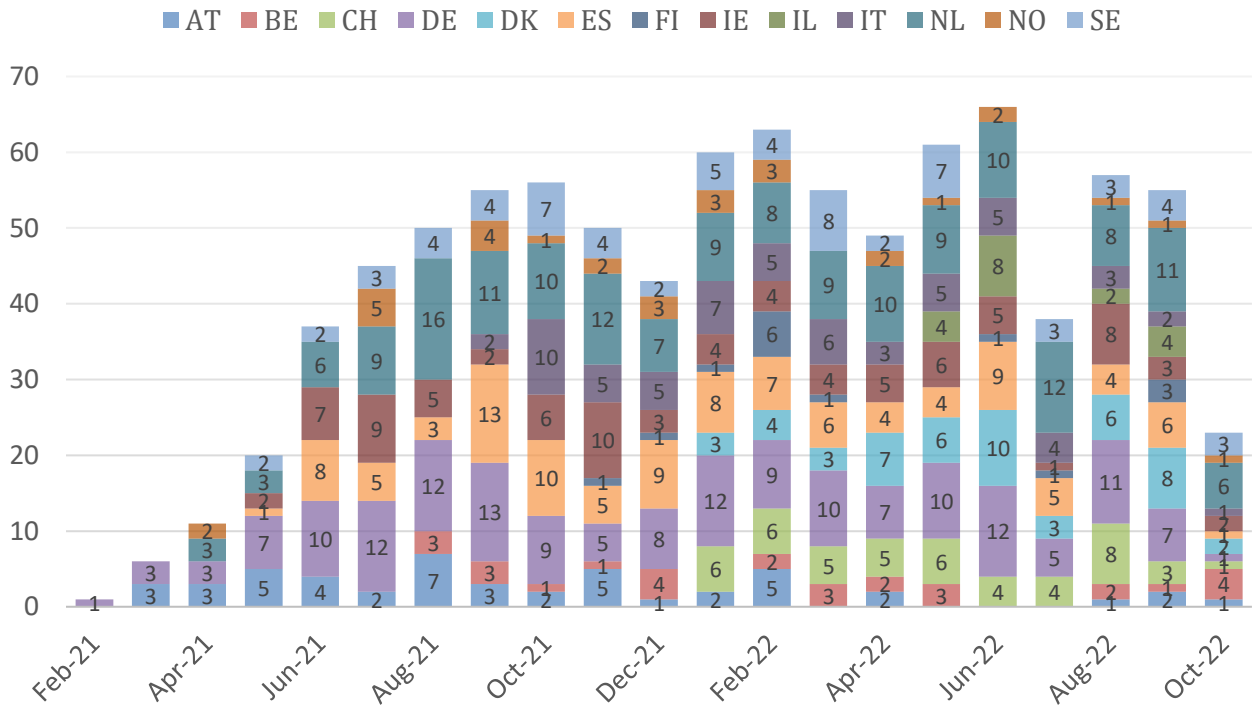
End of recruitment: 14 month ahead of schedule

patients screened: 976
patients enrolled: 901 (99.3%) of 907
screening failure: 67
patients screening ongoing: 8

Global patient enrollment



Patient enrollment per month and country



AT, Austria; BE, Belgium; CH, Switzerland; DE, Germany; DK, Denmark; ES, Spain; FI, Finland; IE, Ireland; IL, Israel; IT, Italy; NL, Netherlands; SE, Sweden.
Al-Sawaf O. Oral presentation at the XIIIth International Workshop of the German CLL Study Group; Cologne, Germany, September, 2022.

Summary

- The Binet (predominant in Europe) and Rai staging systems remain the cornerstone of CLL staging, identifying three subgroups with distinct clinical outcomes[1,2,3]
  - In general, patients with low-risk disease (Binet A, Rai Stage 0) should be followed by watch and wait unless there is evidence of disease progression or disease-related symptoms[4]

- The most important biomarkers to evaluate before selecting first-line therapy are:[5]
  - Del(17p)/*TP53*^{mut}
  - Karyotype complexity (</≥3 aberrations)
  - IGHV status

- The CLL17 trial will provide important insights into the relative benefits of BTKi-, BCL2i- or doublet-based treatment for high genetic risk CLL[6]

1. Binet JL *et al*. *Cancer* 1981; 48 (1): 198–206. 2. Rai KR *et al*. *Blood* 1975; 46 (2): 219–234. 3. Pflug N *et al*. *Blood* 2014; 124 (1): 49–62. 4. Hallek M *et al*. *Blood* 2018; 131 (25): 2745–2760.
5. Onkopedia guidelines: Chronic Lymphocytic Leukemia (CLL), 2023. Available at: https://www.onkopedia.com/de/onkopedia/guidelines/chronische-lymphatische-leukaemie-cll.
6. Al-Sawaf O. Oral presentation at the XIIIth International Workshop of the German CLL Study Group; Cologne, Germany, September, 2022.