Satellite Symposium at
ESH 7th Translational Research Conference – BeiGene
21 October 2023, 13:00-14:00 WEST
Estoril, Portugal

"Working towards precision medicine approaches for CLL"

Satellite Symposium sponsored by BeiGene.

Working towards precision medicine approaches for CLL

Chair & Moderator

Raul Cordoba, MD, PhD, MSc

University Hospital Fundacion Jimenez Diaz
Madrid, Spain

Disclosures

- **Research funding**: Pfizer
- **Advisory boards**: Janssen, Abbvie, Astra Zeneca, Lilly, Beigene, Gilead, Takeda, Incyte, Roche, Regeneron, BMS, Kyowa-Kirin
- **Speakers' bureau**: Janssen, Abbvie, Astra Zeneca, Beigene, Lilly, Gilead, Takeda, Incyte, Roche

The views expressed are those of the speakers and may not necessarily reflect the opinion of BeiGene

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Disclaimers

- The views expressed are those of the speakers and may not necessarily reflect the opinion of BeiGene.
- The following presentation may include data on non-approved indications.
- Zanubrutinib ▼* as monotherapy is indicated in the European Union for the treatment of adult patients with:
  - Waldenström's macroglobulinaemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemoimmunotherapy
  - Chronic lymphocytic leukaemia (CLL)
  - Marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based therapy

  Indications may differ outside of the European Union. Prescribing information may vary depending on local approval in each country. Consult the zanubrutinib prescribing information for the country you practice medicine in for country-specific information.
- Acalabrutinib ▼* is used on its own (monotherapy) in patients with CLL who have had previous treatment. In patients who have not had previous treatment for the condition, acalabrutinib may be used on its own or combined with obinutuzumab.
- Lisocabtagene maraleucel ▼*
- Obinutuzumab is used together with chlorambucil in patients for whom the cancer medicine fludarabine is not recommended.
- Ofatumumab ▼*
- Venetoclax can be used on its own in: 1) patients with particular genetic changes (17p deletion or TP53 mutation) who cannot be treated with medicines known as B-cell receptor pathway inhibitors (ibrutinib and idelalisib) or if these medicines have stopped working; 2) patients who do not have these genetic changes, after treatments with chemotherapy combined with immunotherapy as well as a B-cell receptor pathway inhibitor have both not worked. Venetoclax can be used with obinutuzumab in patients who have not previously been treated for CLL. Venetoclax can be used with rituximab in patients who have received at least one previous treatment.

* ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Learning Objectives

After this session, participants will understand:

- The contemporary treatment landscape for CLL
- How to make individualized treatment choices, especially guided by patient and disease characteristics
- The molecular mapping of CLL and its impact on treatment outcome

Chair and Speakers

Dr Raul Cordoba – University Hospital Fundacion Jimenez Diaz Madrid, Spain

Dr Alessandra Tedeschi – ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

Prof Xose S. Puente – Universidad de Oviedo, Oviedo, Spain

Working towards precision medicine approaches for CLL

Timing (60 minutes)	Topic	Speaker
13.00 – 13.05 h (5 mins)	Welcome & introduction	Raul Cordoba (chair)
13.05 – 13.30 h (25 mins)	Contemporary treatment of CLL – Treatment selection based on patient and disease characteristics	Alessandra Tedeschi
13.30 – 13.45 h (15 mins)	Molecular mapping of CLL and its impact on outcome	Xose Puente
13.45 – 14.00 h (15 mins)	Audience Q&A	Faculty
	Closure & farewell	Raul Cordoba (chair)

Introducing our first Speaker…

Contemporary treatment of CLL – Treatment selection based on patient and disease characteristics

Alessandra Tedeschi, MD, PhD

ASST Grande Ospedale Metropolitano Niguarda
Milan, Italy

Disclosures

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- **Advisory boards:** Janssen SpA, AbbVie, BeiGene, AstraZeneca, Lilly
- **Speakers' bureau:** Janssen SpA, AbbVie, BeiGene, AstraZeneca

CLL – many options, many questions

- Are we ready for personalized treatment in CLL?
- Do biological factors play a role in treatment decision?
- Do patient's age and fitness play a role in treatment decision?
- Do we have enough sequencing data?
- Is there is still a role for cellular therapy in CLL?
- What are the medical needs?

CLL, chronic lymphocytic leukemia.

Factors influencing treatment choice*

Before the introduction of targeted agents (CIT)

Predictive factors:

- Age
- Fitness

- CIRS
- Age
- Surrogate of renal function:

CrCl cut off 70 mL/min

FIT Go Go
UNFIT Slow Go
FRAIL No Go

→ **Chemotherapy intensity**

***Speaker's own view.**

CIRS, cumulative illness rating score, CIT, chemoimmunotherapy; CrCl, creatinine clearance.

Factors influencing treatment choice*

Before the introduction of targeted agents (CIT)

Predictive factors:

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- Fitness

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→ **Chemotherapy intensity**

After the introduction of targeted agents

Disease factors	*Patient factors*	*Other factors*
• Del(17p)/*TP53*	• Comorbidities	• Logistics/caregivers
• *IGHV* mutational status	• Concomitant medications	• Patient preference
• Bulky disease	• Age	• Drug approvals/ reimbursement

→ **Fixed *vs* continuous therapy**

***Speaker's own view.**

CIRS, cumulative illness rating score, CIT, chemoimmunotherapy; CrCl, creatinine clearance; del(17p), deletion of the short arm of chromosome 17; *IGHV*, immunoglobulin heavy chain variable region gene; *TP53*, tumor protein p53.

TN CLL patients: available options

TN CLL

Continuous therapy[1-11]

BTKi (+/- anti-CD20 antibody):

- ***Ibrutinib +/- rituximab***
- ***▼Acalabrutinib +/- obinutuzumab***
- ***▼Zanubrutinib***

Time-limited therapy[12-15]

CIT:

- ***FCR***

BCL2i + anti-CD20 antibody:

- ***Venetoclax + obinutuzumab***

BCL2i + BTKi:

- ***Venetoclax + ibrutinib***

➢ ***RCTs show similar 4-year PFS (approx. 75%) with either approach[1-9,13-15]***
Depends on disease genetic characteristics

BCL2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; CIT, chemoimmunotherapy; FCR, fludarabine, cyclophosphamide and rituximab; PFS, progression-free survival; RCT, randomized clinical trial; TN, treatment naïve.

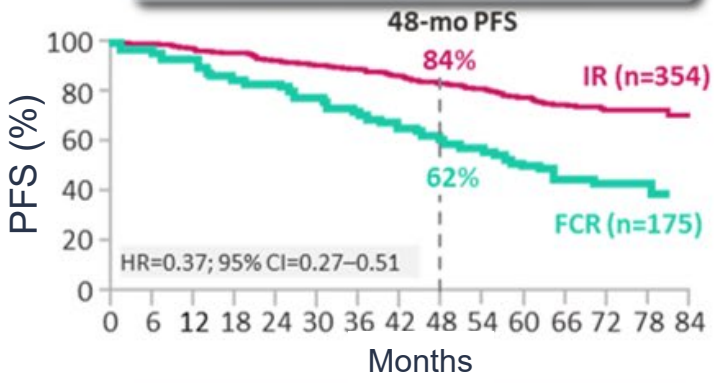
1. Barr PM et al. Blood Adv. 2022;6(11):3440–3450; 2. Ahn IE et al. N Engl J Med. 2020;383:498-500; 3. Woyach JA et al. Blood. 2021;138(1):639–642; 4. Shanafelt TD et al. Blood. 2022;140(2):112–120; 5. Hillmen P et al. ASH 2021; Abstract 642; 6. Shanafelt TD et al. N Engl J Med. 2019;381:432–443; 7. Woyach JA et al. N Engl J Med. 2018;379:2517–2528; 8. Sharman JP et al. ASCO 2022; Poster 7539; 9. Hillmen P et al. EHA 2021; Abstract S145; 10. Tam CS et al. Lancet Oncology. 2022;23(8):1031–1043; 11. Brown JR et al. N Engl J Med. 2023;388:319–332; 12. Al-Sawaf O et al. EHA 2022; Abstract S148; 13. Eichhorst B et al. Blood. 2021;138(1):71; 14. Eichhorst B et al. EHA 2022; Abstract LB2365; 15. Kater AP et al. ASH 2020; Abstract 125.

BTKi continuous therapy: ibrutinib

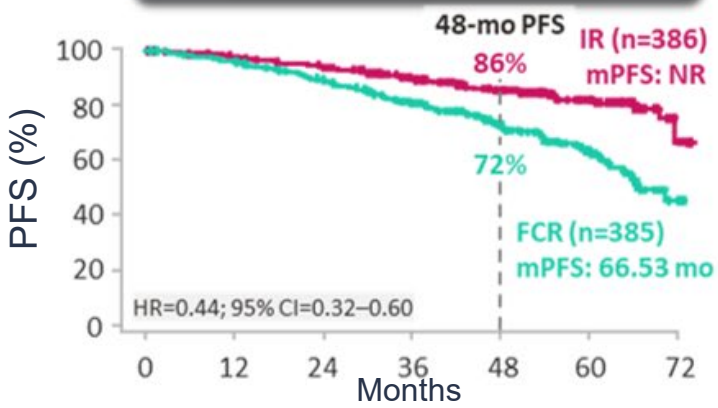
TN CLL

Young/Fit → Elderly/Unfit

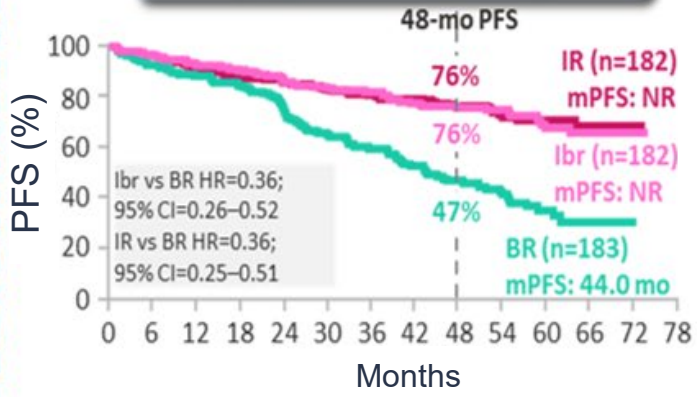
ECOG-1912: INV-assessed[1] PFS
(median follow-up: 70 months)[2]



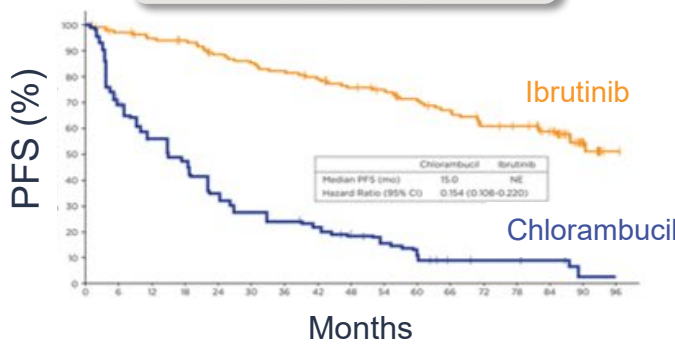
FLAIR: INV-assessed PFS
(median follow-up: 52.7 months)[3]



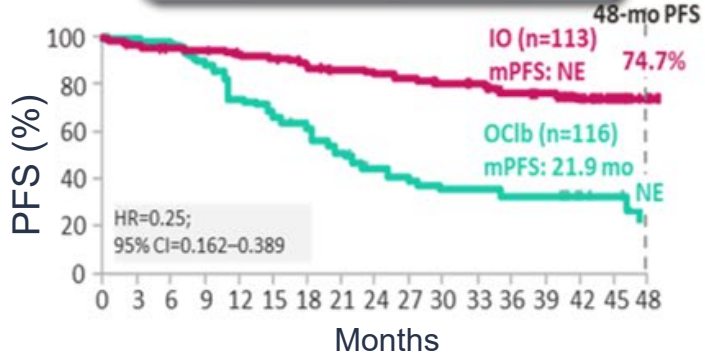
Alliance A041202: INV-assessed PFS[4]
(median follow-up: 55 months)



RESONATE-2[5]
8-year follow-up



iLLUMINATE: INV-assessed PFS[6]
(median follow-up: 45 months)



BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide and rituximab; HR, hazard ratio; Ibr, ibrutinib; INV, investigator; IO, ibrutinib and obinutuzumab; IR, ibrutinib and rituximab; mo, months; (m)PFS, (median) progression-free survival; NE, not evaluable; NR, not reached; OClb, obinutuzumab and chlorambucil.

Figures adapted from 1. Shanafelt TD et al. N Engl J Med. 2019; 381(5):432–443; 2. Shanafelt TD et al. Blood. 2022;140(2):112–120; 3. Hillmen P et al. ASH 2021; Abstract 642; 4. Woyach J et al. Blood. 2021;138(Suppl 1):639; 5. Barr PM et al. Blood Adv. 2022;6(11):3440–3450; 6. Moreno C et al. Haematologica. 2022;107(9):2108–2120.

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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.

BTKi continuous therapy: acalabrutinib

TN CLL

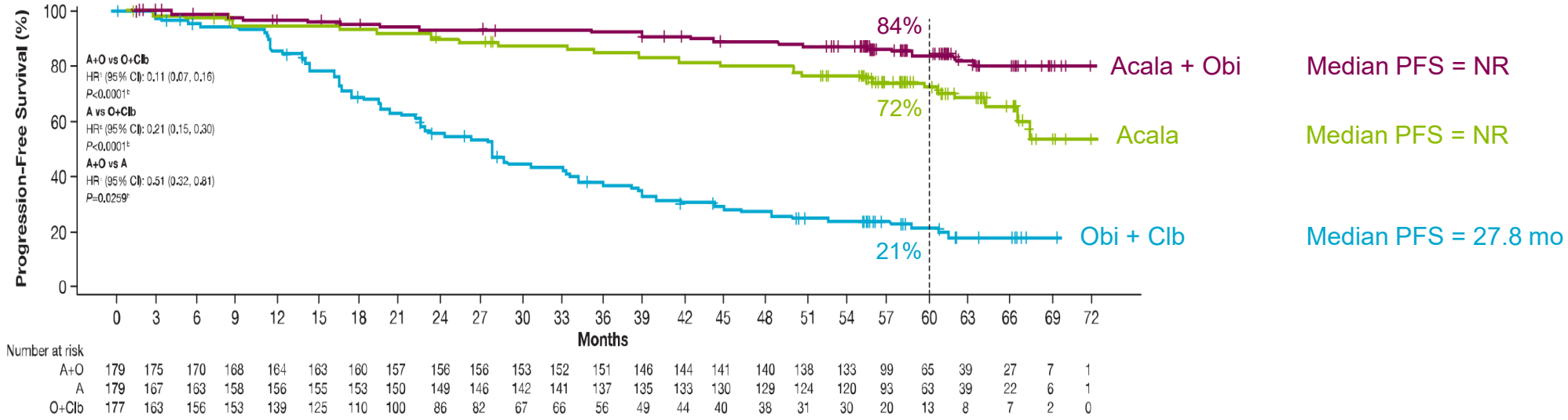
ELEVATE-TN study

Age ≥ 65 years or
< 65 years with coexisting conditions:
- CIRS score > 6, or
- CrCl < 70 mL/min

Randomize

- **Acalabrutinib**
- **Acalabrutinib + obinutuzumab***
- **Chlorambucil* + obinutuzumab***

Median follow-up: 58.2 months



*6 cycles.
Acala, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CIRS, cumulative illness rating score, CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; Clb, chlorambucil; HR, hazard ratio; mo, months; NR, not reached; Obi, obinutuzumab; PFS, progression-free survival; TN, treatment naïve.
Sharman JP et al. ASCO 2022; Poster 7539 (figure adapted).

BTKi continuous therapy: zanubrutinib

TN CLL

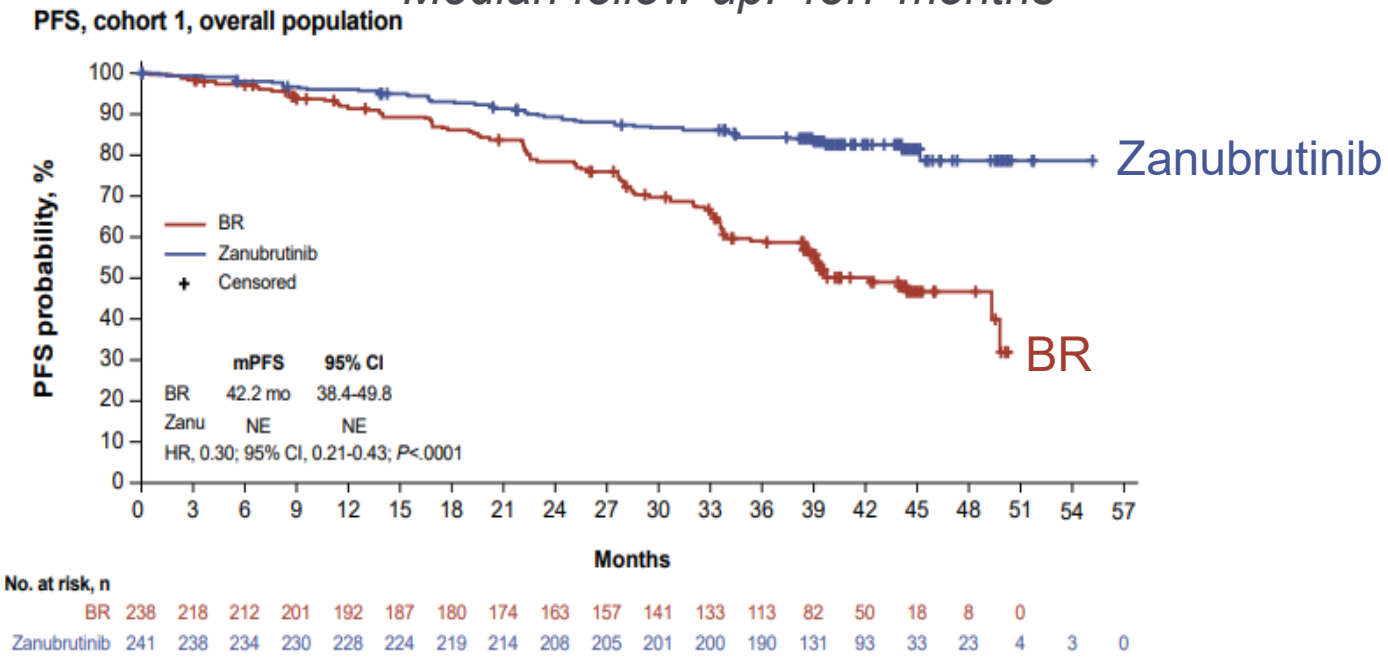
SEQUOIA study Cohort 1

- Untreated CLL/SLL
- ≥ 65 years of age OR unsuitable for treatment with FCR*
- Without del(17p) by central FISH

Randomize

- **Zanubrutinib**
- **Bendamustine + rituximab**

Median follow-up: 43.7 months



*Defined as CIRS >6, CrCl <70 mL/min, or a history of previous severe infection or multiple infections within the last 2 years.

BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CIRS, cumulative illness rating score, CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; del(17p), deletion of the short arm of chromosome 17; FCR, fludarabine, cyclophosphamide and rituximab; FISH, fluorescence in situ hybridization; HR, hazard ratio; mo, months; (m)PFS, (median) progression-free survival; NE, not evaluable; SLL, small lymphocytic leukemia; TN, treatment naïve.

Munir T et al. EHA 2023; Abstract P639 (figure adapted).

Time-limited therapy: venetoclax + obinutuzumab

TN CLL

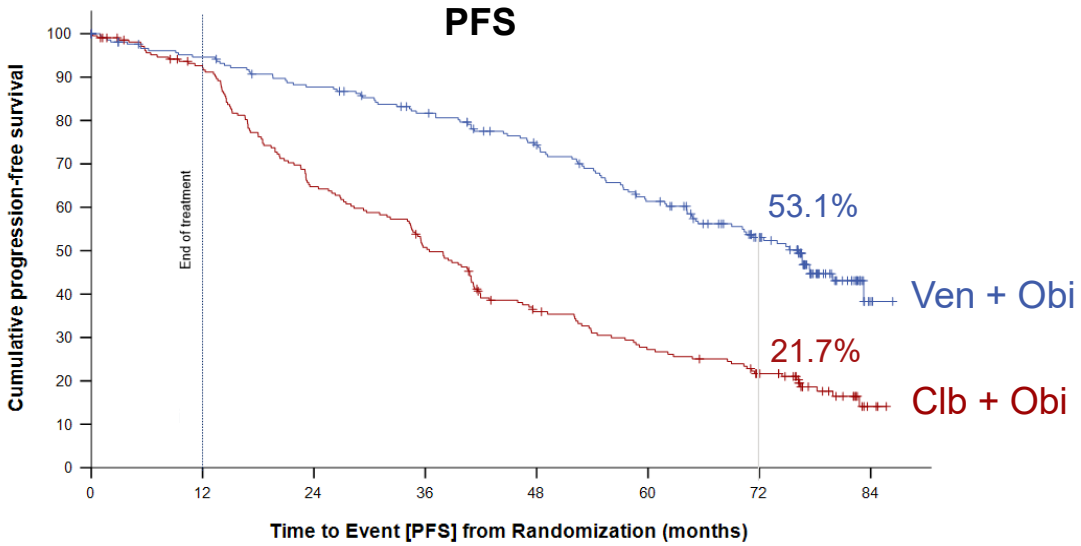
CLL14 study[1]

CIRS score >6
CrCl <70 mL/min

Randomize

- Venetoclax + obinutuzumab
- Chlorambucil + obinutuzumab

Median follow-up: 76.4 months



Ven + Obi uMRD PB: 74% (NGS)

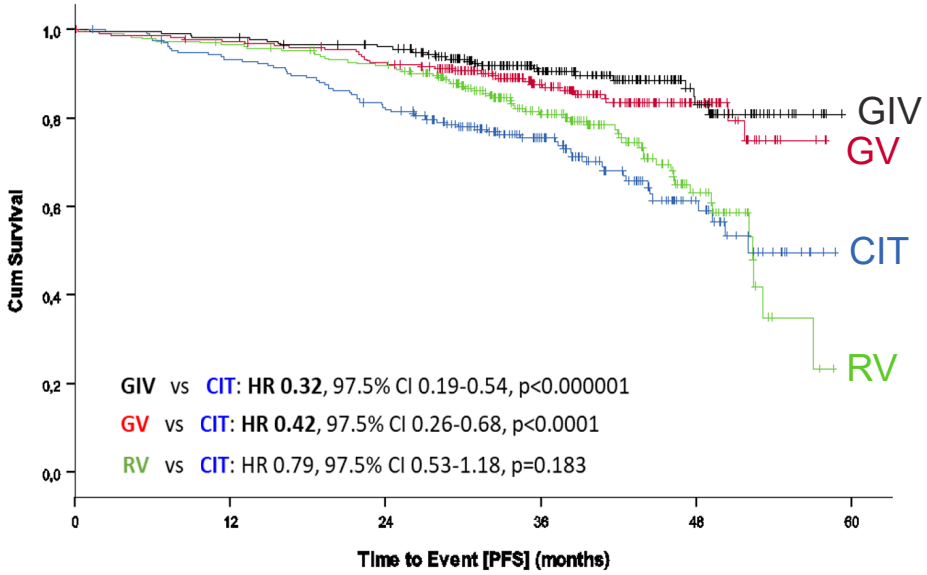
CLL13/GAIA study[2]

Fit patients
No del(17p)/*TP53*mut

Randomize

- GIV: venetoclax + Obi + ibrutinib
- GV: venetoclax + Obi
- RV: venetoclax + rituximab
- CIT: FCR/BR

Median follow-up: 38.8 months



Ven + obi uMRD PB: 86.5% (flow 4c)

BR, bendamustine and rituximab; CI, confidence interval; CIRS, cumulative illness rating score, CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; Clb, chlorambucil; del(17p), deletion of the short arm of chromosome 17; FCR, fludarabine, cyclophosphamide and rituximab; flow 4c, four-color flow cytometry; GIV, venetoclax, obinutuzumab and ibrutinib; GV, venetoclax and obinutuzumab; HR, hazard ratio; mut, mutated; NGS, next-generation sequencing; NR, not reached; Obi, obinutuzumab; PB, peripheral blood; PFS, progression-free survival; RV, venetoclax and rituximab; SCIT, standard chemoimmunotherapy; TN, treatment naïve; *TP53*, tumor protein p53; uMRD, undetectable minimal residual disease.

1. Al Sawaf O et al. EHA 2023; Abstract S145 (figure adapted); 2. Eichhorst B et al. N Engl J Med. 2023;388(19):1739-54 (figure adapted).

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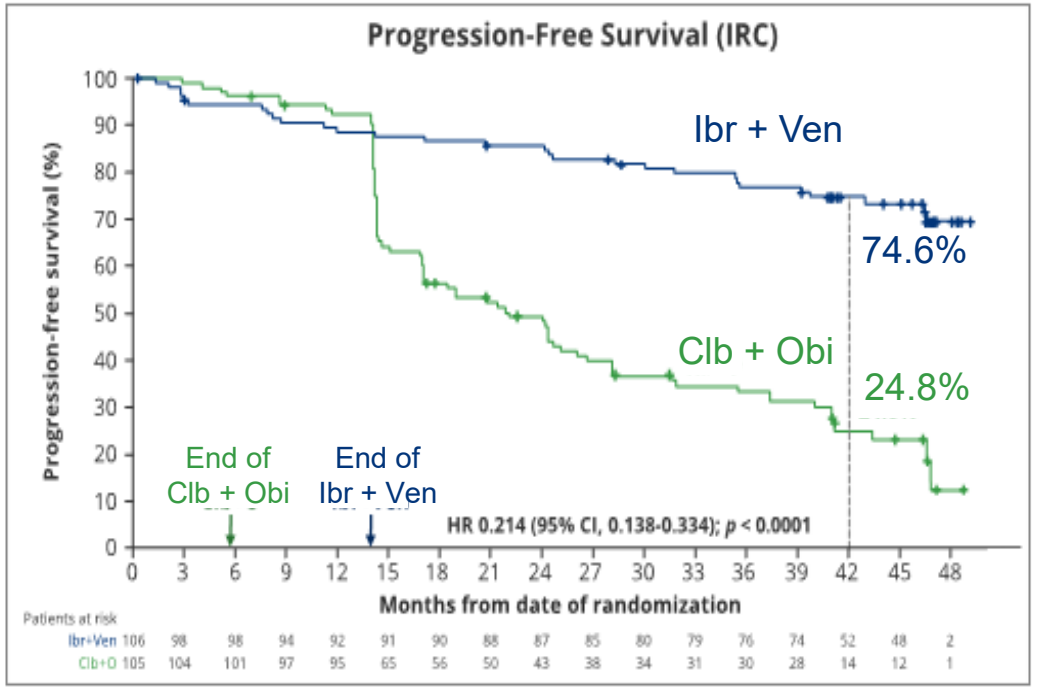
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

Time-limited therapy: venetoclax + ibrutinib

TN CLL

GLOW study[1]: Ibr + Ven *vs* Clb + Obi

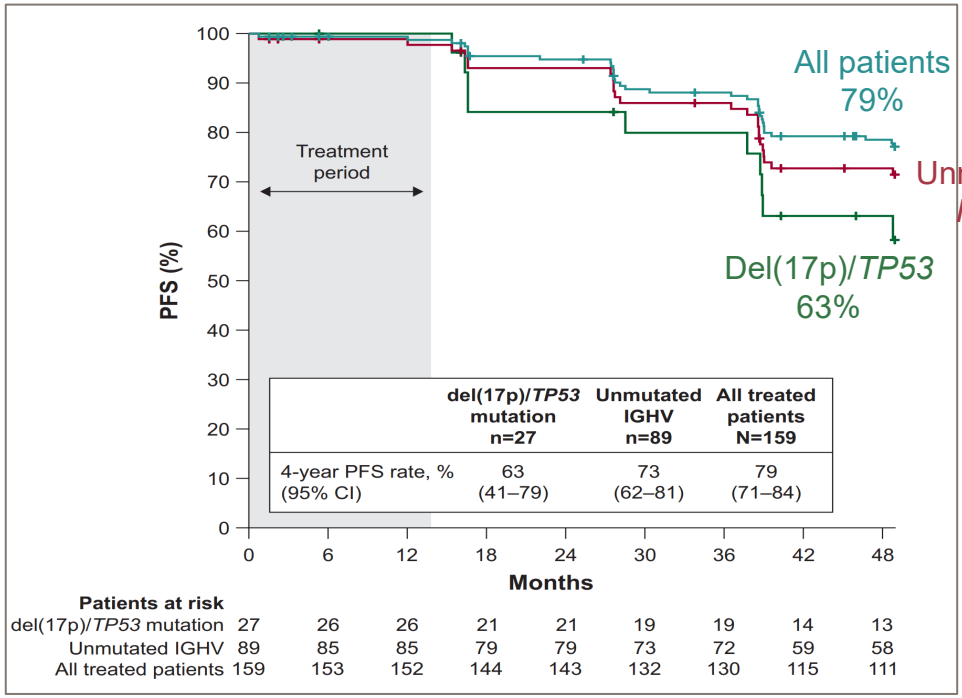
Patients ≥ 65 years or unfit (no del[17p])



uMRD PB: 54.7% (NGS)

CAPTIVATE study[2] (FD cohort): Ibr + Ven

Patients ≤ 70 years



uMRD PB: 57% (flow 8c)

CLL14: Ven + Obi:
4-year PFS: 74%
uMRD PB: 74% (NGS)

CI, confidence interval; CLL, chronic lymphocytic leukemia; Clb, chlorambucil; del(17p), deletion of the short arm of chromosome 17; FD, fixed duration; flow 8c, eight-color flow cytometry; HR, hazard ratio; Ibr, ibrutinib; *IGHV*, immunoglobulin heavy chain variable region gene; IRC, independent review committee; mut, mutated; NGS, next-generation sequencing; Obi, obinutuzumab; PB, peripheral blood; PFS, progression-free survival; TN, treatment naïve; *TP53*, tumor protein p53; uMRD, undetectable minimal residual disease; Ven, venetoclax.

1. Niemann CU et al. ASH 2022; Abstract 642 (figure adapted); 2. Tedeschi A et al. EHA 2023; Poster P617 (figure adapted).

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.

Disease factors that may influence treatment choice (1/3)

TN CLL

CLL14 study

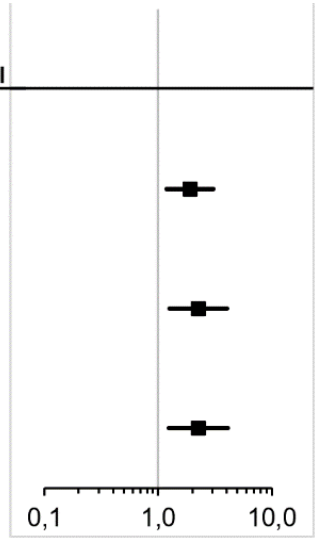
In the context of venetoclax + obinutuzumab[1]:

- **max. lymph node size ≥ 5 cm**
- **unmutated *IGHV***
- ***TP53* del/mutation**

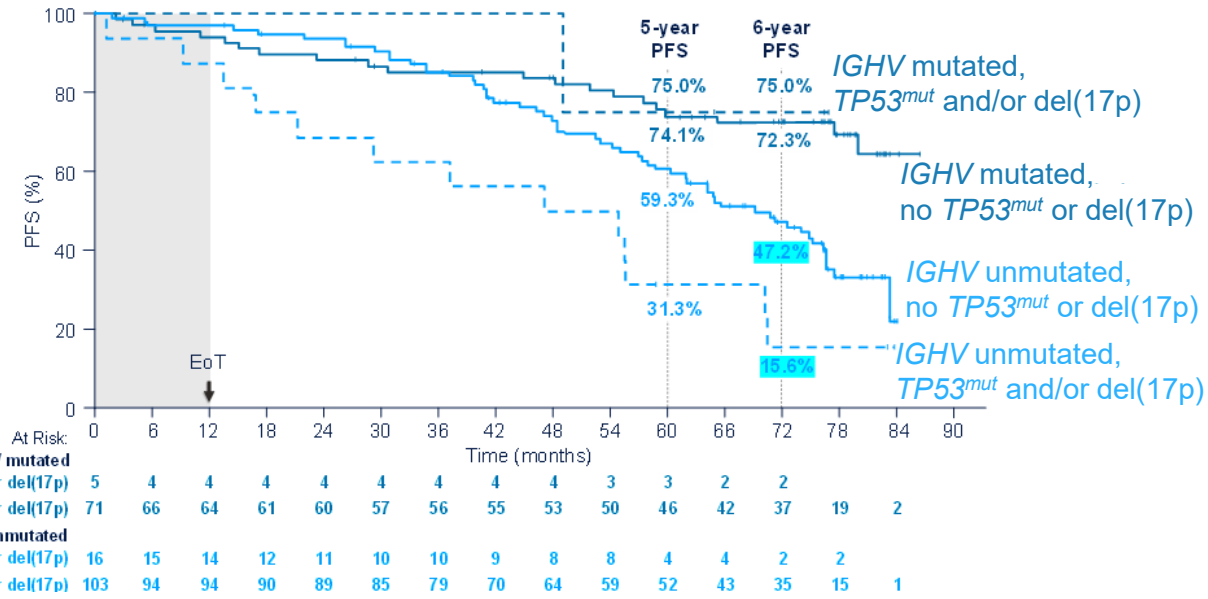
are independent negative prognostic factors for PFS

Negative prognostic factors for PFS[1]

COX regression PFS	Univariate comparison	Hazard ratio	95% Wald CI
Lymph node size			
≥ 5 cm	vs. < 5 cm	1.916	1.189-3.088
IGHV mutational status			
unmutated	vs. mutated	2.258	1.268-4.021
***TP53* deletion/mutation**			
Deleted and/or mutated	vs. none	2.262	1.242-4.120



Ven + Obi: PFS according to *IGHV* and del(17p)/*TP53*[2]



CI, confidence interval; CLL, chronic lymphocytic leukemia; del, deletion; del(17p), deletion of the short arm of chromosome 17; *IGHV*, immunoglobulin heavy chain variable region gene; Obi, obinutuzumab; PFS, progression-free survival; TN, treatment naïve; *TP53*, tumor protein p53; Ven, venetoclax.

1. Al Sawaf O et al. ICML 2023; Abstract 025 (figure adapted); 2. Al Sawaf O et al. EHA 2023; Abstract S145 (figure adapted).

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Disease factors that may influence treatment choice (2/3)

TN CLL

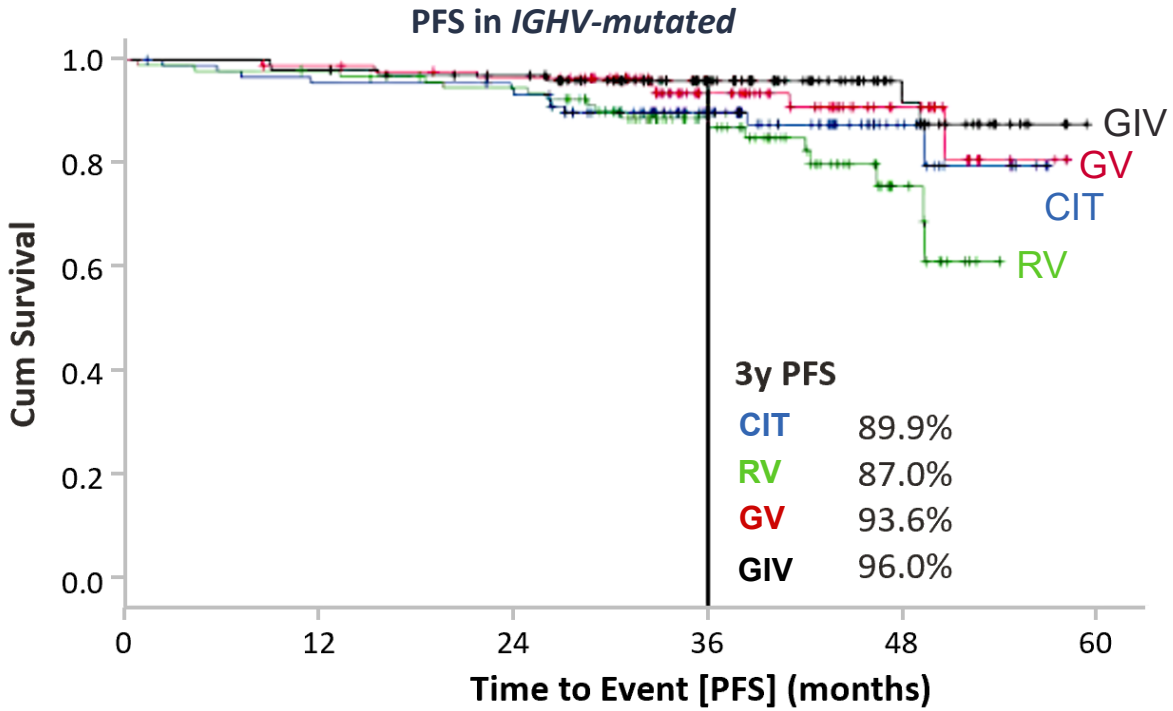
Fixed-duration treatment according to *IGHV*

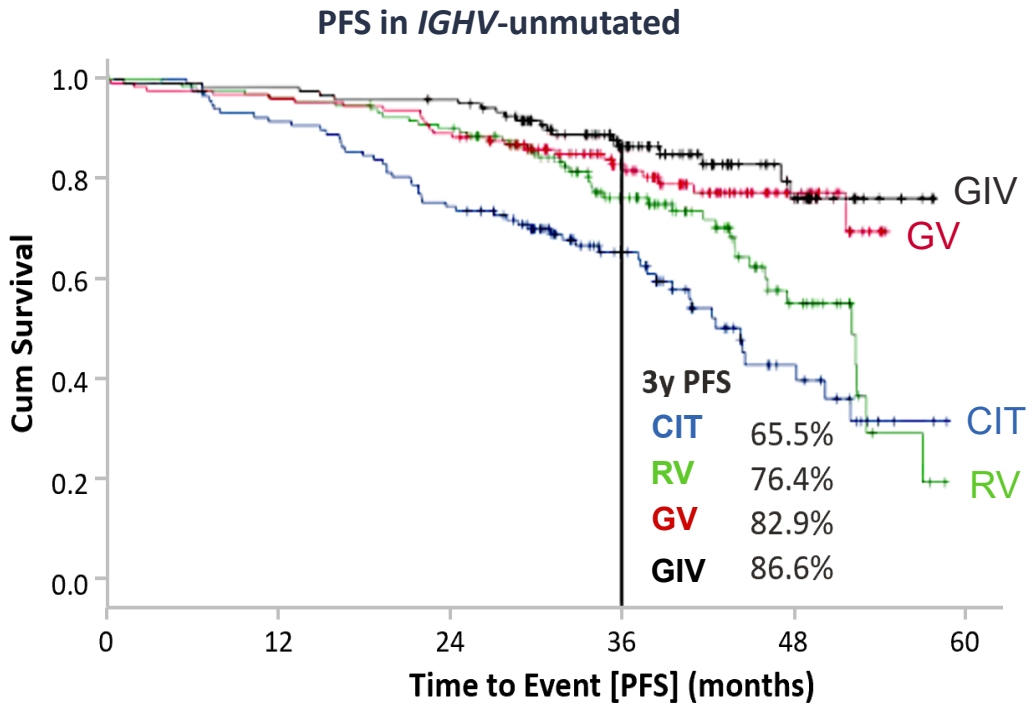
CLL13 study (GAIA)

Fit patients
No del(17p)/*TP53*mut

Randomize

- GIV: venetoclax + Obi + ibrutinib
- GV: venetoclax + Obi
- RV: venetoclax + rituximab
- CIT: FCR/BR





BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; cum, cumulative; del(17p), deletion of the short arm of chromosome 17; FCR, fludarabine, cyclophosphamide and rituximab; GIV, venetoclax, obinutuzumab and ibrutinib; GV, venetoclax and obinutuzumab; *IGHV*, immunoglobulin heavy chain variable region gene; mut, mutated; Obi, obinutuzumab; PFS, progression-free survival; RV, venetoclax and rituximab; SCIT, standard chemoimmunotherapy; TN, treatment naïve; *TP53*, tumor protein p53; y, year.

Eichhorst B et al. N Engl J Med. 2023;388(19):1739-54 (figures adapted).

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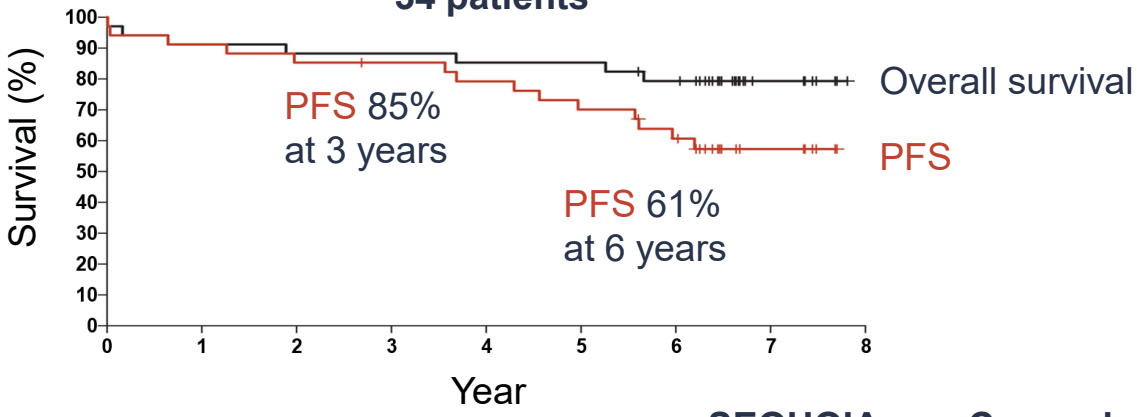
Disease factors that may influence treatment choice (3/3)

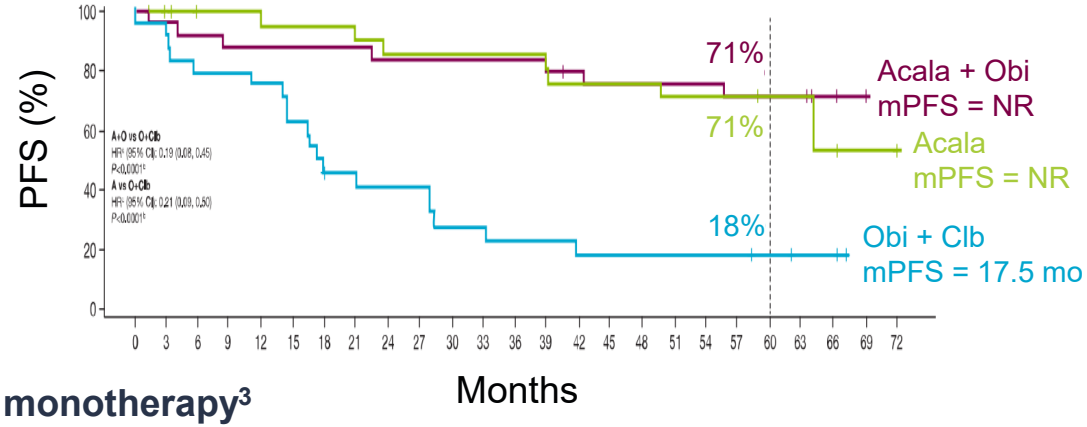
TN CLL

BTKi in del(17p)/*TP53*

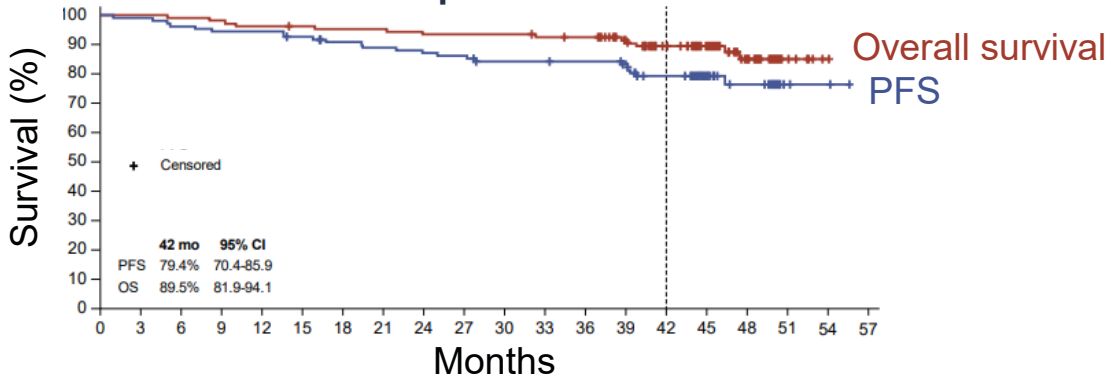
NHLBI Phase II: ibrutinib monotherapy[1]
34 patients



ELEVATE TN: Acala *vs* Acala + Obi *vs* Obi + Clb[2]
23 *vs* 25 *vs* 25 patients



SEQUOIA arm C: zanubrutinib monotherapy[3]
110 patients



Acala, acalabrutinib; BTKi, Bruton's tyrosine kinase inhibitor; Chl, Chlorambucil; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; HR, hazard ratio; mo, months; (m)PFS, (median) progression-free survival; NR, not reached; Obi, obinutuzumab; TN, treatment naïve; *TP53*, tumor protein p53.

Figures adapted from 1. Ahn IE et al. N Engl J Med. 2020;383(5):498–500; 2. Sharman JP et al. ASCO 2022; Abstract 7539; 3. Shadman M et al. EHA 2023; Abstract P639.

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Patient factors influencing treatment choice

TN CLL

Comorbidities[1]

BTKi

Consider cardiovascular risk[1]

BTKis **NOT** recommended for patients with:

- History of ventricular arrhythmia
  - Family history of sudden cardiac death
- Severe, uncontrolled hypertension
- Severe or uncontrolled congestive heart failure (LVEF <30%)

BCL2i

Consider renal impairment

TLS risk

Concomitant medications[2-5]

BTKi

BCL2i

Consider:

- *Strong and moderate CYP3A inhibitors*
- *Strong CYP3A inducers*
- *P-gp inhibitors*

BCL2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CYP3A, cytochrome P4503A; LVEF, left ventricular ejection fraction; P-gp, P-glycoprotein; TLS, tumor lysis syndrome; TN, treatment naïve.

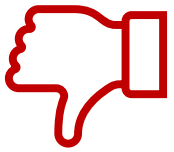
1. Awan FT et al. Blood Adv. 2022;6(18):5516-25; 2. Zanubrutinib. Summary of Product Characteristics. Jul 2023; 3. Venetoclax. Summary of Product Characteristics. Feb 2023; 4. Acalabrutinib. Summary of Product Characteristics. Mar 2023; 5. Ibrutinib. Summary of Product Characteristics. Sep 2023.

Factors influencing treatment choice*

TN CLL

BTKi continuous therapy

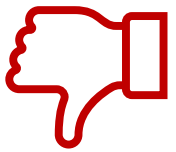
- Easy to deliver
- No intensive early monitoring
- Oral treatment



- Continuous treatment
- Resistance

Time-limited therapy

- Treatment-free period



- Intensive early monitoring
- Care-givers
- Intravenous therapy

- Patient preference
- Cost

***Speaker's own view.**

BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; TN, treatment naïve.

TN patient case

TN CLL

60-year-old male
No concomitant medications/comorbidities
No del(17p)/*TP53*^{mut}
IGHV-mutated

→ **TIME-LIMITED THERAPY**
TARGETED AGENT-BASED

Severe (≥ CTC Grade 3) AEs occurring in ≥5% of patients and AESI independent of incidence

	CIT	Ven + R	Ven + O	Ven + O + Ibr
All patients [SP]	**216**	**237**	**228**	**231**
Anemia	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)
Neutropenia	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)
Thrombocytopenia	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)
Febrile neutropenia	**24 (11.1)**	**10 (4.2)**	**7 (3.1)**	**18 (7.8)**
Infections	**43 (19.9)**	**27 (11.4)**	**32 (14.0)**	**51 (22.1)**
Tumor lysis syndrome*	**9 (4.2)**	**24 (10.1)**	**20 (8.8)**	**15 (6.5)**
Bleeding events	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)
Atrial fibrillation	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)

*Including clinical and laboratory TLS according to Cairo-Bishop criteria
AEs, adverse events; AESI, adverse events of special interest; CIT, chemoimmunotherapy; CTC, common terminology criteria; del(17p), deletion of the short arm of chromosome 17; Ibr, ibrutinib; mut, mutated; *IGHV*, immunoglobulin heavy chain variable region gene; n, number of patients; O, obinutuzumab; R, rituximab; TN, treatment naïve; TP53, tumor protein p53; Ven, venetoclax.
Adapted from Eichhorst B et al. ASH 2021.

TN patient case

TN CLL

76-year-old female
del(17p)/*TP53*^{mut}
IGHV-unmutated

Evaluation of cardiovascular risk → CONTINUOUS BTKi THERAPY

Which BTKi?

	Ibrutinib[1] (N=136)	Acalabrutinib[2] (N=179)	Zanubrutinib[3] (N=240)
Median age, years	73 (65-89)	70 (44-87)	70 (66-75)
Median treatment duration, months	47	45.7	43.7
Ongoing treatment, %	65	69.3	75
Discontinuations due to AE, %	19	12.3	15
Atrial fibrillation, % **All grades**	13*	6	5
Hypertension, % **All grades / Grade ≥3**	21 / 7*	7.3 / 2.8	17.5 / 9.2

These data represent patients without del(17p). This patient case features a patient with del(17p).

*N=135.
AE, adverse event; BTKi, Bruton's tyrosine kinase inhibitor; del(17p), deletion of the short arm of chromosome 17; mut, mutated; *IGHV*, immunoglobulin heavy chain variable region gene; N, number of patients; TN, treatment naïve; *TP53*, tumor protein p53.
Adapted from 1. Burger J et al. EHA 2018; Abstract PF343; 2. Sharman JP et al. EHA 2021; S148; 3. Munir T et al. EHA 2023; Abstract P639.

CLL17: comparing fixed duration with continuous therapy

TN CLL

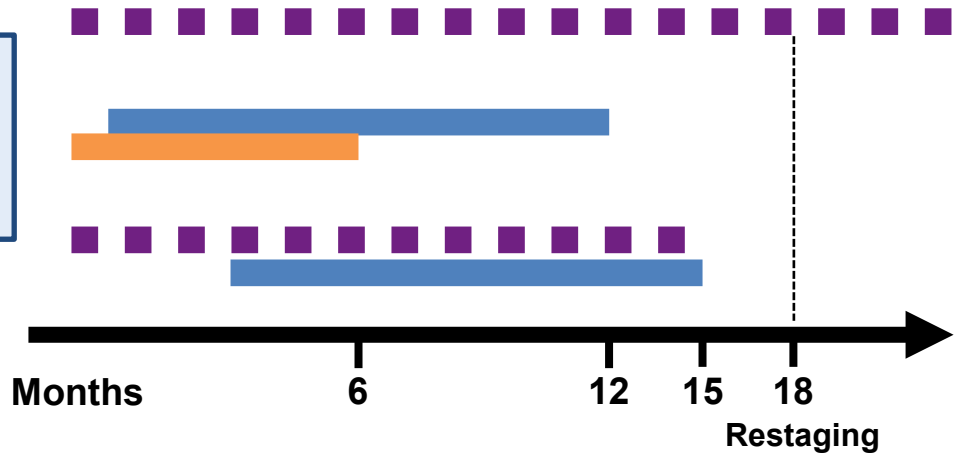
- Unknown which strategy is optimal for adverse prognostic subgroups
- CLL17 should provide insight

CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

- Ibr mono
- Ven + Obi
- Ven + Ibr

Stratification by fitness, del(17p)/*TP53*^{mut}, *IGHV*
RANDOMIZATION[2]



Ibrutinib D1 420 mg PO daily until PD or intolerance

Venetoclax 400 mg PO daily (C1 D22 – C12 D28)
Obinutuzumab 1000 mg IV (C1 D1(2)/8/15, C2–6 D1)

Ibrutinib 420 mg PO daily (C1 D1 – C15 D28)
Venetoclax 400 mg PO daily (C4 D1 – C15 D28)

1L, first-line; C, cycle; CLL, chronic lymphocytic leukemia; D, day; del(17p), deletion of the short arm of chromosome 17; Ibr, ibrutinib; *IGHV*, immunoglobulin heavy chain variable region; IV, intravenous; mono, monotherapy; mut, mutation; Obi, obinutuzumab; PD, progressive disease; PO, oral; TN; treatment naïve; *TP53*, tumor protein p53; Ven, venetoclax.

1. ClinicalTrials.gov. NCT04608318. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04608318 (accessed October 2023); 2. DCLLSG. CLL17 Trial. Available at: https://www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf (accessed October 2023).

R/R CLL patients: available options*

R/R CLL

Continuous therapy

BTKi:

- ***Ibrutinib***
- ***Acalabrutinib***
- ***Zanubrutinib***

BCL2i:

- ***Venetoclax***

Time-limited therapy

BCL2i + anti-CD20 antibody:

- ***Venetoclax + rituximab***

***Speaker's own view.**

BCL2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

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Treatment choice in R/R CLL patients*

R/R CLL

Disease factors

- del(17p)/*TP53*
- *IGHV* mutational status
- Bulky Disease

Patient factors

- Comorbidities
- Concomitant medications

Other factors

- Logistics/caregivers
- Patient preference
- Drug approval/ reimbursement

+

Previous therapy

- Type of initial therapy
- Resistance development
- Toxicities to previous treatments
- Early *vs* late relapse
- Intolerance
- Adequate sequencing

young patients ➡ cellular therapy

***Speaker's own view.**

BCL2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; *IGHV*, immunoglobulin heavy chain variable region; *TP53*, tumor protein p53; R/R, relapsed/refractory.

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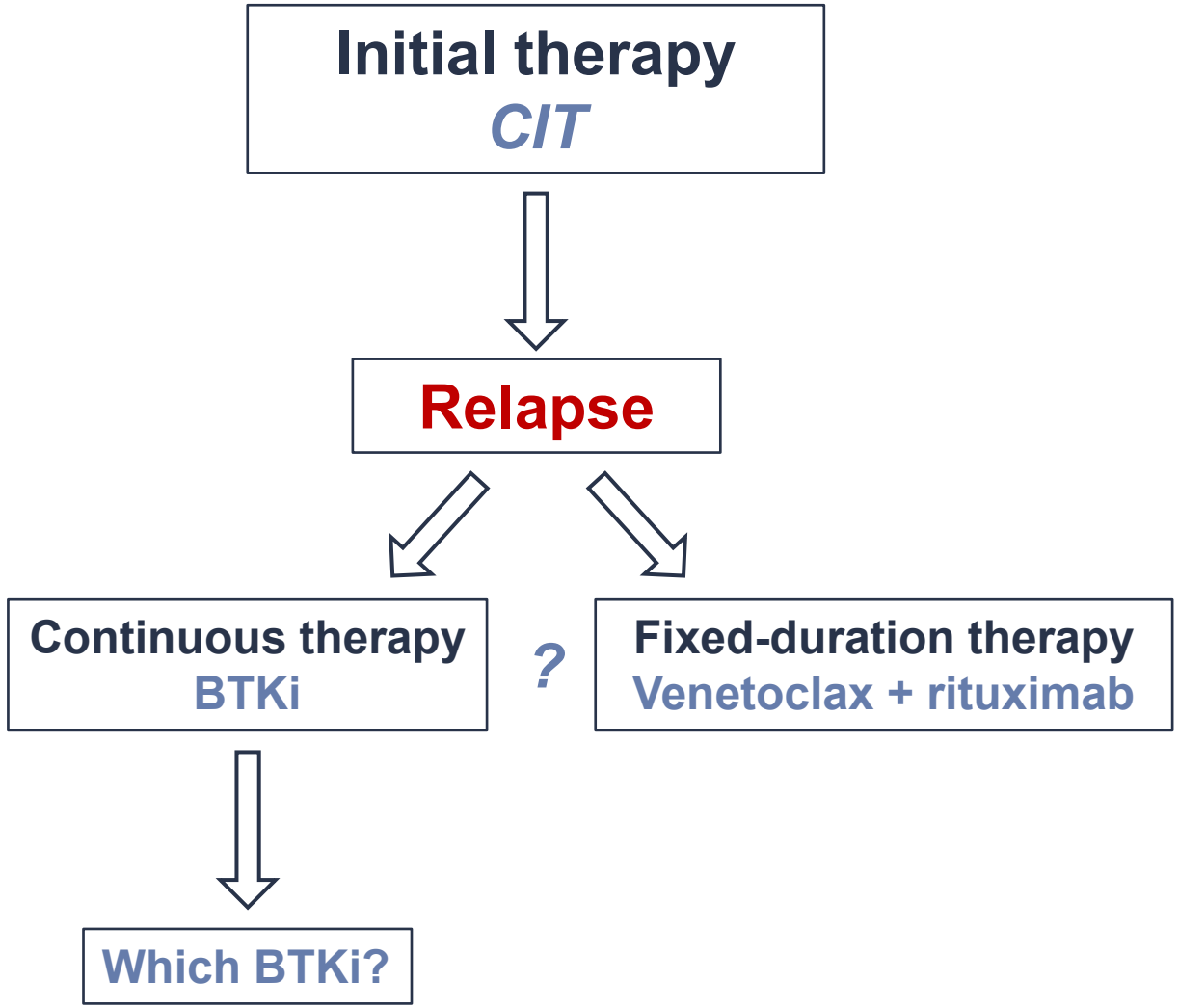
Treatment choice in R/R CLL patients

R/R CLL



No studies comparing:
BTKi vs venetoclax + rituximab

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CIT, chemoimmunotherapy; R/R, relapsed/refractory.

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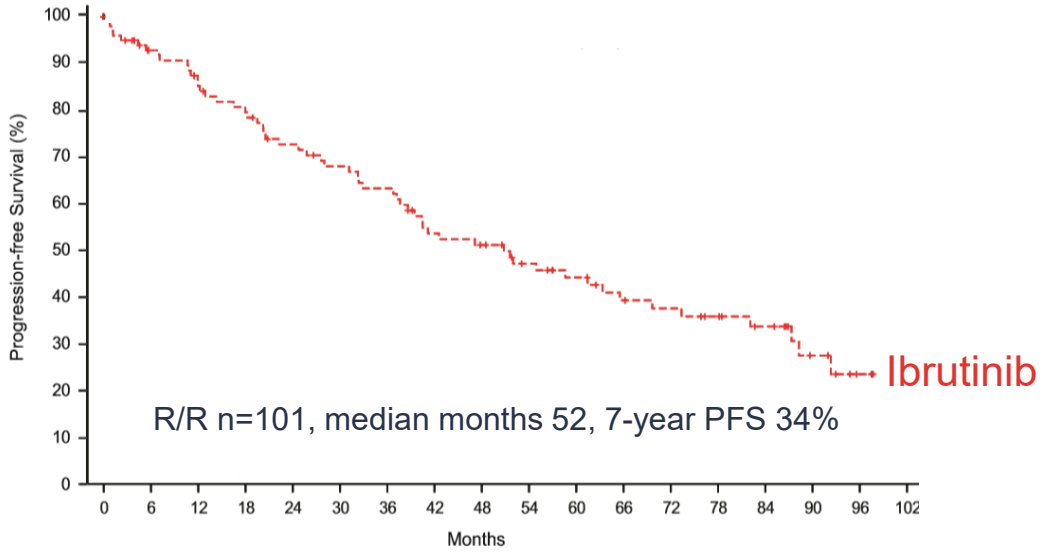
BTKi (ibrutinib) after CIT initial therapy

R/R CLL

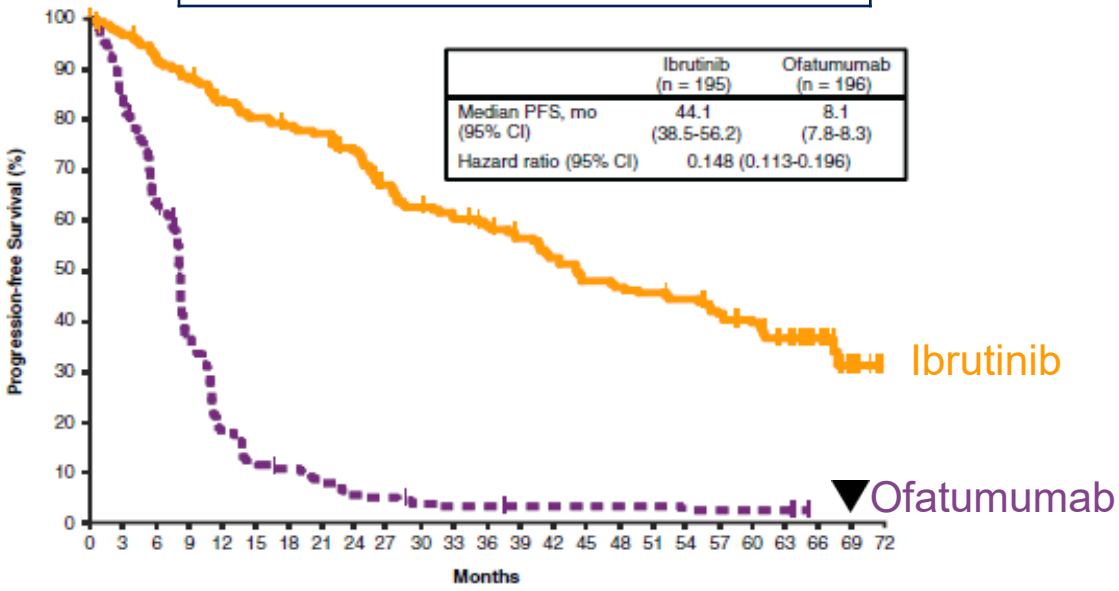
Pivotal Phase Ib/II PCYC-1102 study[1,2] in R/R CLL
Up to 8 years of follow-up

	Ibrutinib n=101
Prior treatments ≥ 4	59%
IGHV^{unmut}	78%
del(17p)	34%



Final analysis from RESONATE study[3,4] in R/R CLL
Up to 6 years of follow-up
Ibrutinib vs ofatumumab

	Ibrutinib n=195
Prior treatments ≥ 3	53%
IGHV^{unmut}	73%
del(17p)	32%
TP53^{mut}	51%



BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; IGHV, immunoglobulin heavy chain variable region; mo, months; mut, mutated; PFS, progression-free survival; TP53, tumor protein p53; unmut, unmutated; R/R, relapsed/refractory.

1. Byrd JC et al. N Engl J Med. 2013;369(1):32-42. 2. Byrd JC et al. Clin Cancer Res. 2020;26(15):3918-27 (figure adapted). 3. Byrd JC et al. N Engl J Med. 2014;371(3):213-23.
4. Munir T et al. Am J Hematol. 2019;94(12):1353-63 (figure adapted).

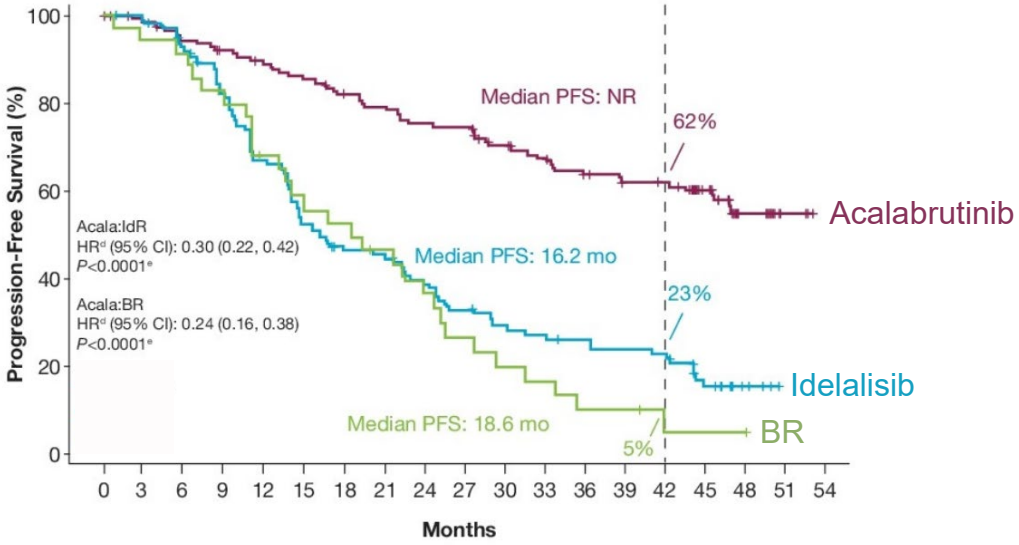
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

BTKi (acalabrutinib) after CIT initial therapy (1/2)

R/R CLL

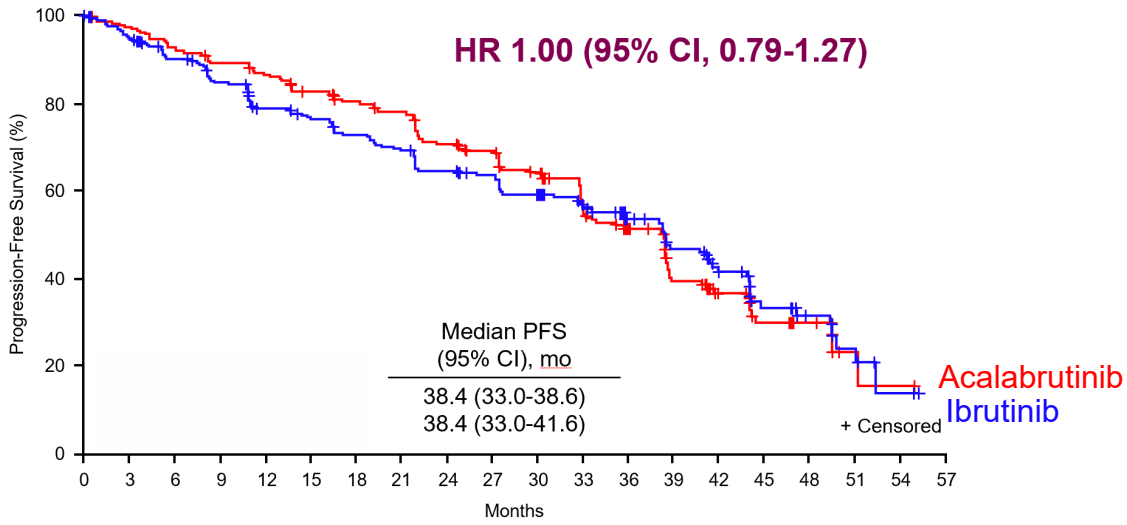
Phase III ASCEND study[1]
Acalabrutinib *vs* idelalisib + rituximab or BR
4 years follow-up

	Acalabrutinib n=101
Median prior Tx	1 (1-8)
IGHV^{unmut}	70.3%
del(17p)	17.4%



Phase III ELEVATE-RR study[2]
Acalabrutinib *vs* ibrutinib – only del(17p) or del(11q)
40.9 months median follow-up

	Acalabrutinib n=268	Ibrutinib n=265
Median prior Tx	2 (1-9)	2 (1-12)
IGHV^{unmut}	82%	89%
del(17p)	45.1%	45.3%



BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(11q), deletion of the long arm of chromosome 11; del(17p), deletion of the short arm of chromosome 17; HR, hazard ratio; *IGHV*, immunoglobulin heavy chain variable region; mo, months; NR, not reached; PFS, progression-free survival; Tx, treatment; unmut, unmutated; R/R, relapsed/refractory.

1. Jurczak W et al. ASCO 2022; Abstract 7538 (figure adapted). 2. Byrd JC et al. J Clin Oncol. 2021;39(31):3441-3452 (figure adapted).

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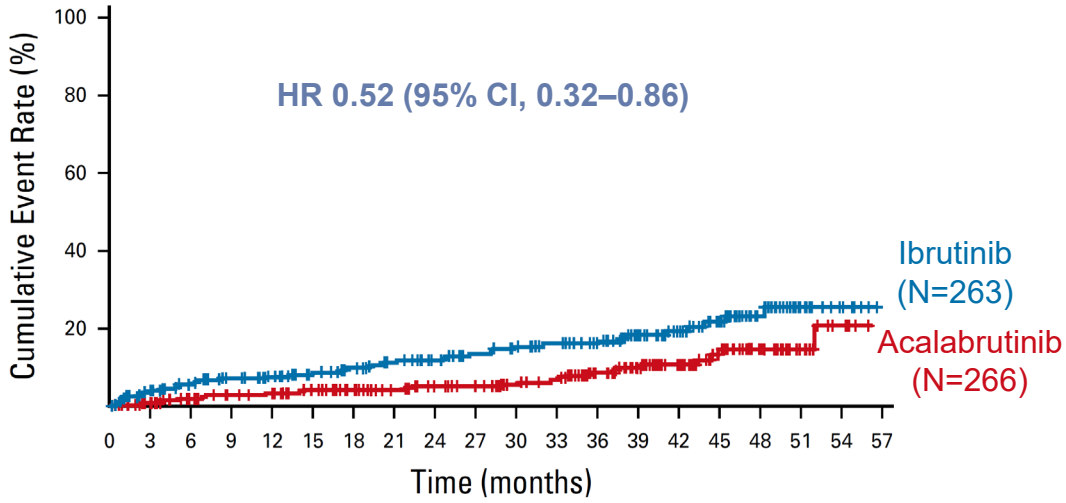
This slide includes data from different clinical trials. These data are meant for demonstration purposes only and are not meant for cross-trial comparison purposes.

BTKi (acalabrutinib) after CIT initial therapy (2/2)

R/R CLL

Phase III ELEVATE-RR CLL

ITT Population	Acalabrutinib (N=266)	Ibrutinib (N=263)	Difference in TEAE Incidence Rates [A-I], %	*P*-value†
Atrial fibrillation/flutter, all grades, n (%) **95% CI***	25 (9.4) (6.4, 13.5)	42 (16.0) (12.0, 20.9)	−6.6 (−12.2, −0.9)	0.0228
Infections, grade ≥3, n (%) **95% CI***	82 (30.8) (25.6, 36.6)	79 (30.0) (24.8, 35.8)	+0.8 (−7.1, +8.6)	0.8777
Richter's transformation, n (%) **95% CI***	10 (3.8) (2.1, 6.8)	13 (4.9) (2.9, 8.3)	−1.2 (−4.7, +2.3)	0.5131



N (%)	Acalabrutinib (N=266)	Ibrutinib (N=263)
AF/flutter	**25 (9.4)**	**42 (16.0)**
Events/100 person-months	0.366	0.721
Time to onset, median (range), months	28.8 (0.4–52.0)	16.0 (0.5–48.3)
Leading to treatment discontinuation	0	7 (16.7)
Subgroup analysis		
Patients without prior history of AF/flutter	15/243 (6.2)	37/249 (14.9)
AF/flutter events at 24 months, %	4.5	10.3

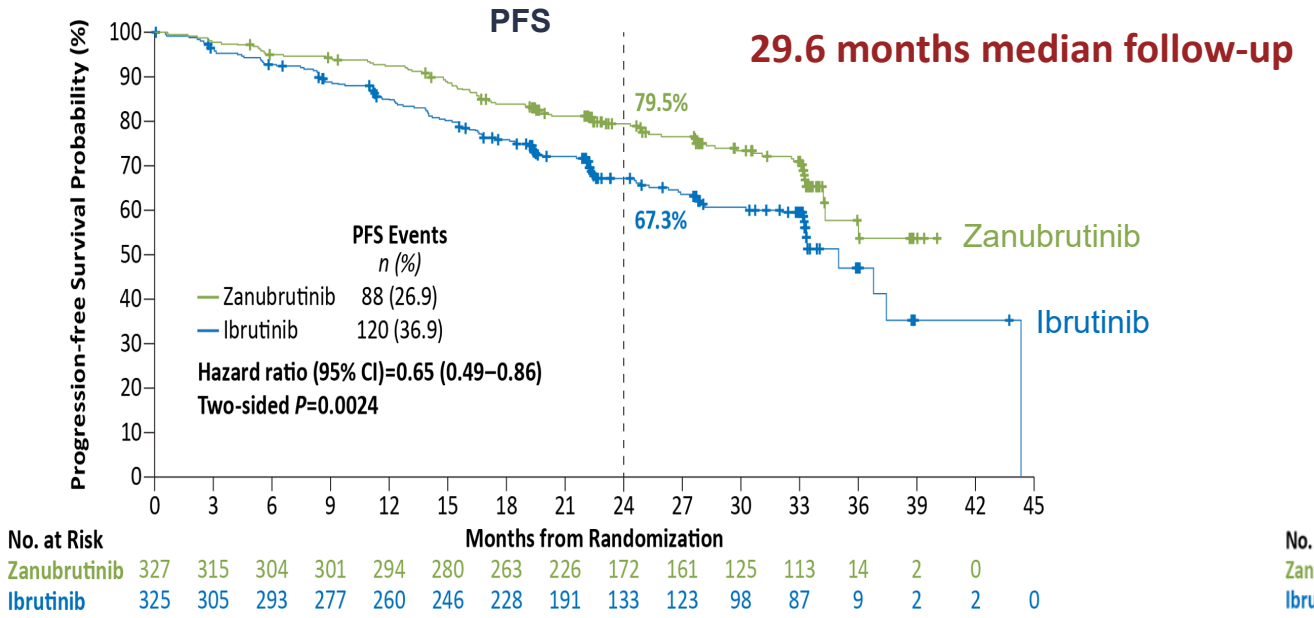
*95% CI based on Normal approximation (with use of Wilson's score). †Based on Cochran-Mantel-Haenzel test stratified by del(17p) status (yes *vs* no) and number of prior therapies (1-3 *vs* ≥4).
AF, atrial fibrillation; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; HR, hazard ratio; ITT, intention to treat; N, number of patients in each treatment arm; n, number of patients; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
Byrd JC et al. J Clin Oncol. 2021;39(31):3441-3452 (figure adapted).

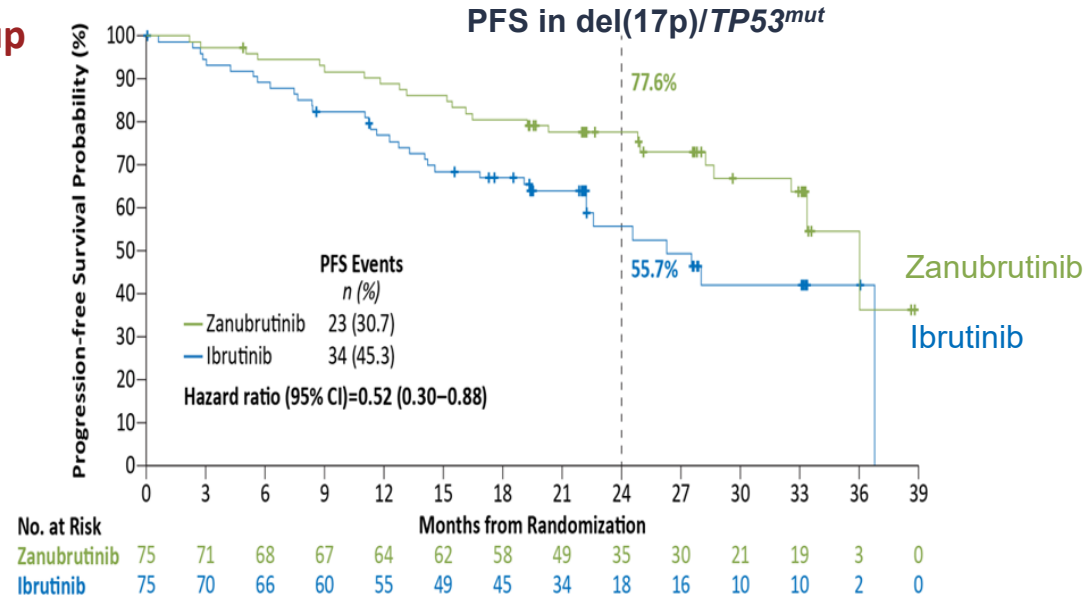
BTKi (zanubrutinib) after CIT initial therapy (1/2)

R/R CLL

Phase III ALPINE study: zanubrutinib *vs* ibrutinib

	Zanubrutinib n=327	Ibrutinib n=325
Median prior Tx	1 (1-6)	1 (1-12)
IGHV^{unmut}	73.1%	73.5%
del(17p) and/or *TP53*^{mut}	22.9%	23.1%





BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; *IGHV*, immunoglobulin heavy chain variable region; mut, mutated; n, number of patients; PFS, progression-free survival; *TP53*, tumor protein p53; Tx, treatment; unmut, unmutated; R/R, relapsed/refractory.

Brown JR et al. N Engl J Med. 2023;388:319–32 (figures adapted).

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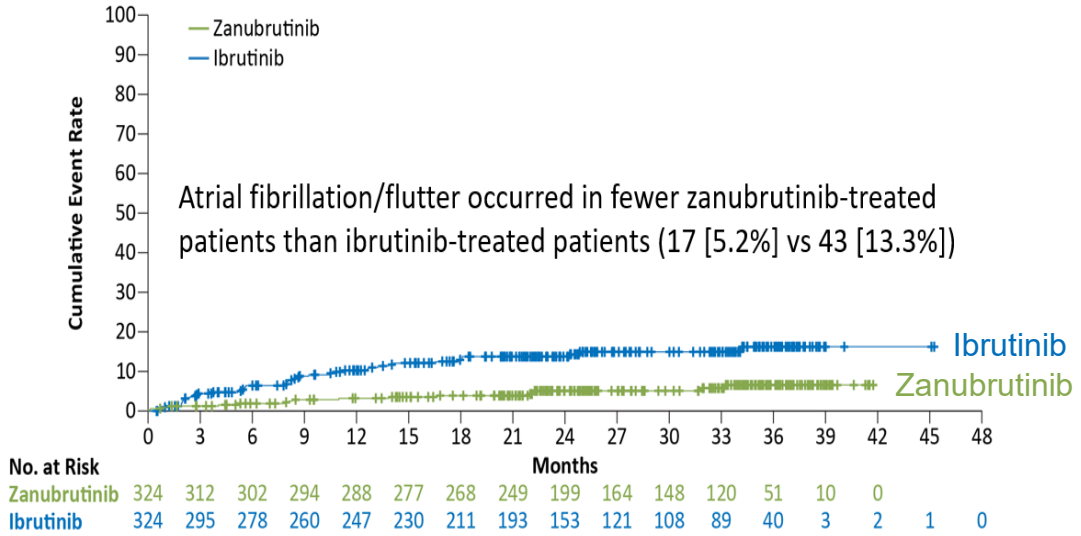
BTKi (zanubrutinib) after CIT initial therapy (2/2)

R/R CLL

Phase III ALPINE study: zanubrutinib *vs* ibrutinib

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**



AESI, adverse events of special interest; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; n, number of patients; R/R, relapsed/refractory.
Brown JR et al. N Engl J Med. 2023;388:319–32 (figure adapted).

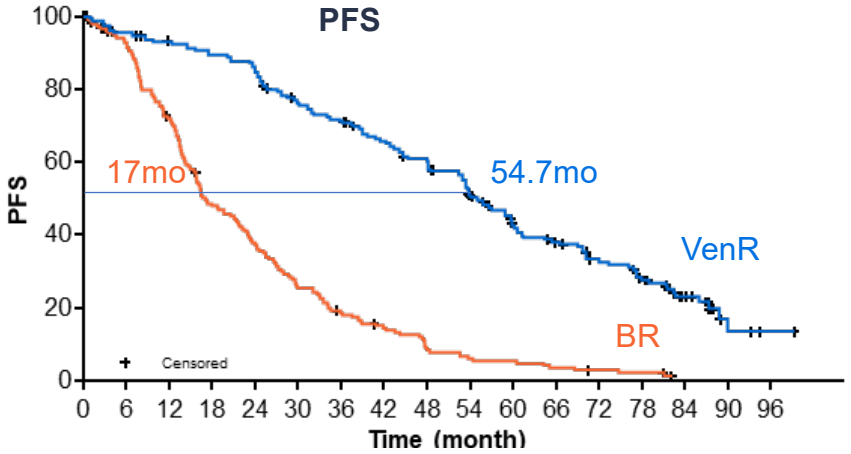
Venetoclax + rituximab after CIT initial therapy

R/R CLL

Phase III MURANO study: venetoclax + rituximab *vs* BR

	VenR n=194	BR n=195
Median prior Tx	1	1
IGHV^{unmut}	68.3%	68.3%
del(17p) / *TP53*^{mut}	26% / 25%	27.2% / 27.7%

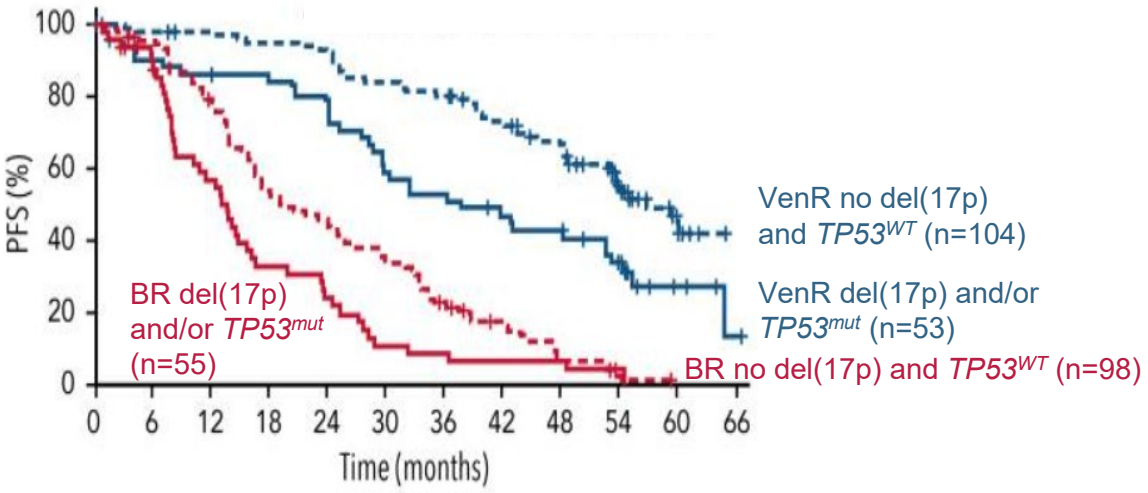
7 years follow-up[1]



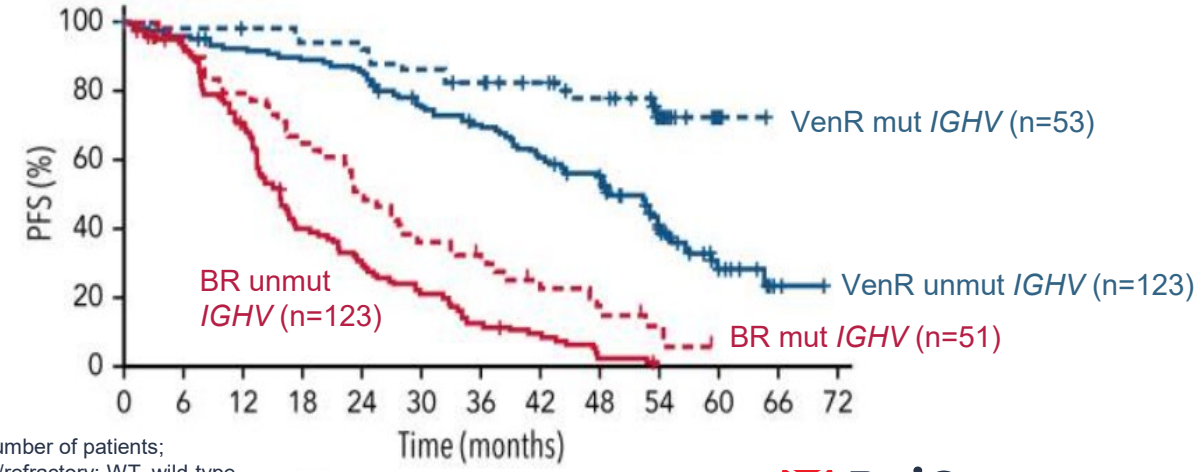
	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE

59.2 months follow-up[2]

PFS according to del(17p)/*TP53*



PFS according to *IGHV*



BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio; *IGHV*, immunoglobulin heavy chain variable region; mo, months; mut, mutated; n, number of patients; NE, not evaluable; PFS, progression-free survival; *TP53*, tumor protein p53; Tx, treatment; unmut, unmutated; R/R, relapsed/refractory; WT, wild-type.

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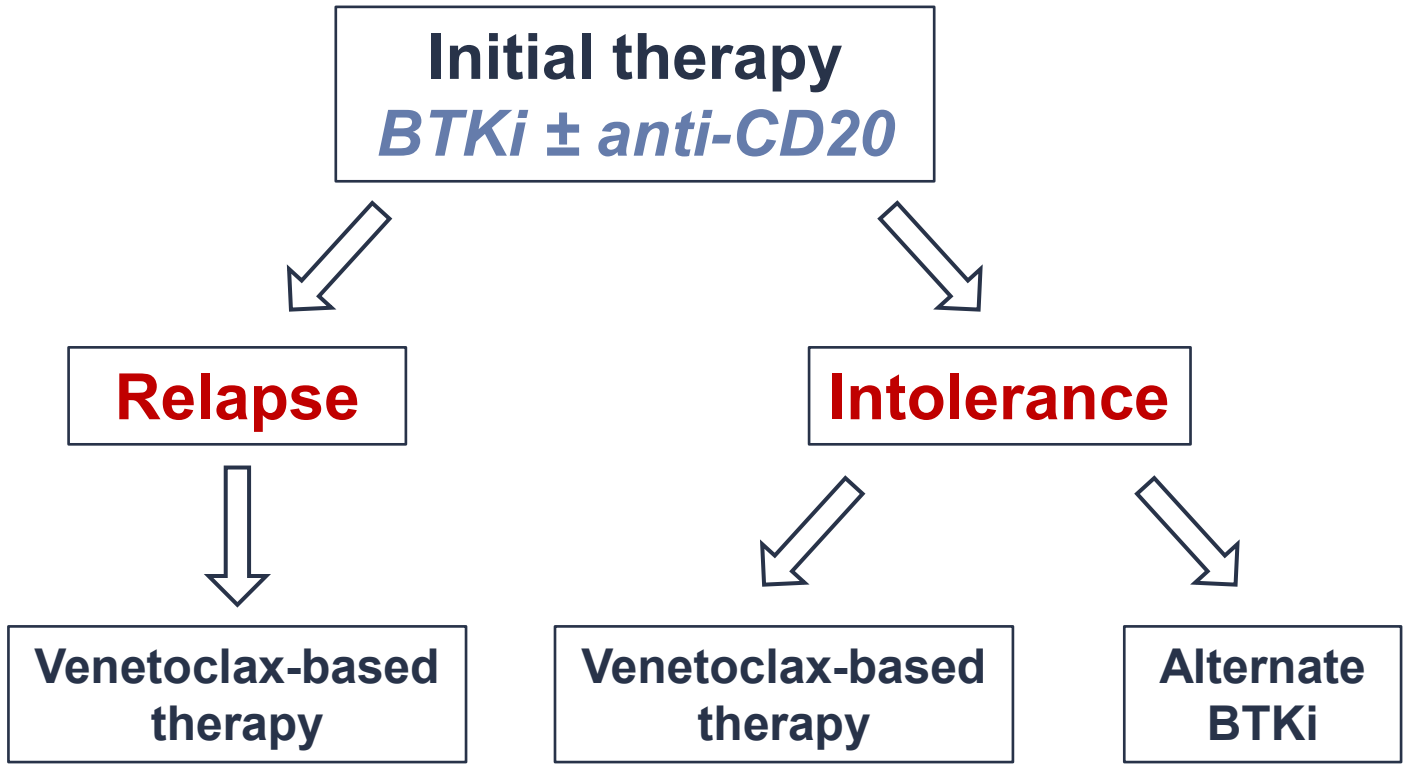
1. Kater AP et al. EHA 2023; Abstract S201 (figure adapted); 2. Seymour JF et al. Blood. 2022; 140(8):839-850 (figures adapted).

Treatment choice in R/R CLL patients*

R/R CLL



***Speaker's own view.**

BTKi, Bruton's tyrosine kinase inhibitor; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; R/R, relapsed/refractory.

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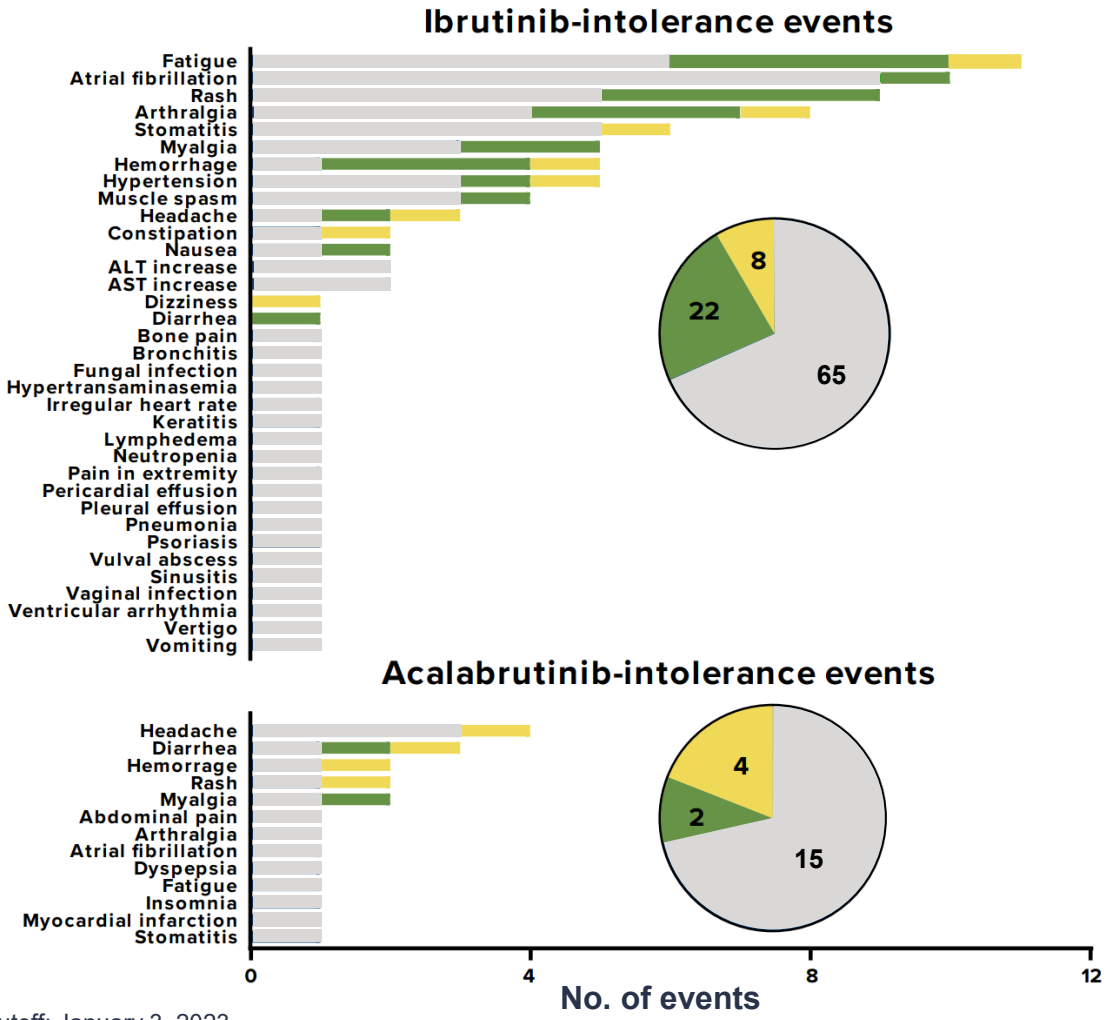
Zanubrutinib in patients intolerant to acalabrutinib or ibrutinib

Phase II trial: zanubrutinib in previously treated B-cell lymphoma patients intolerant of prior BTKi



Data cutoff: January 3, 2023.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTKi, Bruton's tyrosine kinase inhibitor.
Shadman M et al. ICML 2023; Poster 345.

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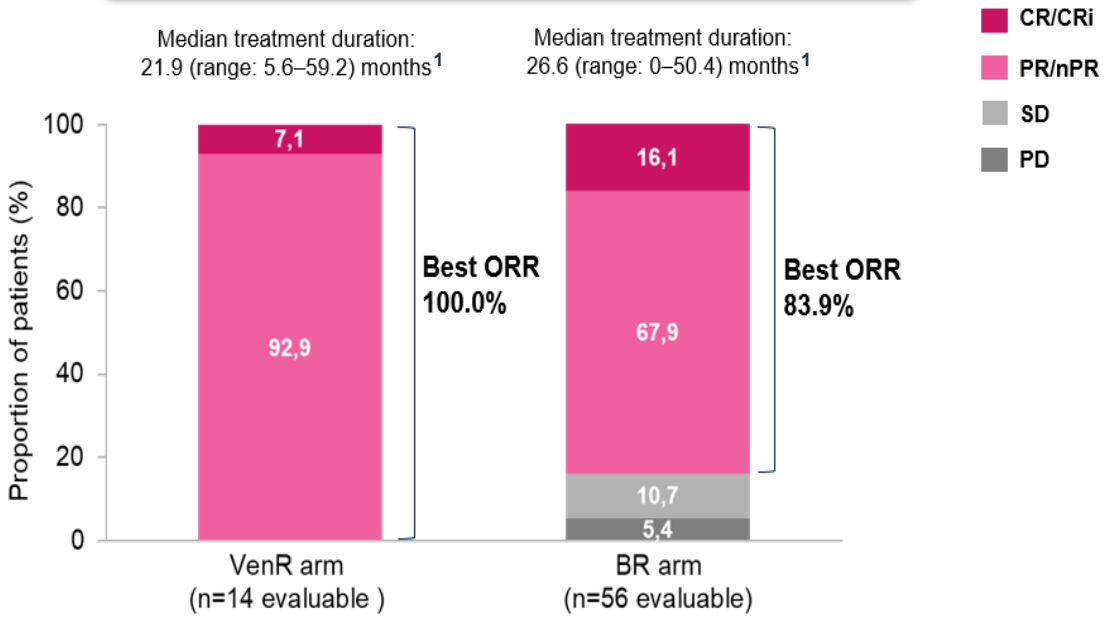
BTKi after venetoclax-based therapy

R/R CLL

MURANO: Best ORR to subsequent BTKi therapy
(median follow-up: 59 months)



BCRi treatment after venetoclax: Real-world experience – summary[2-7]

Analyses of ibrutinib regimens post-venetoclax regimen	Treatment	ORR
Ibr post-Ven, in 4 US centers	Ibr post-Ven (n=25) All patients were Ibr-naive	14 (56%)

Analysis of BTKi/BCRi regimens post-venetoclax regimen	Treatment	ORR
BTKi post-Ven/VenR, in 2 Australian centers	Ibr (n=21) or zanubrutinib (n=2) post-Ven All patients were BCRi-naive	91%
BCRi post-Ven regimen (CORE Registry, US centers, EU/UK centers) (67% treated in real-world setting)	BTKi post-Ven in BTKi-naive (n=44)	83.9%
	BTKi post-Ven in BTKi-exposed (n=30) - BTKi-intolerant/-resistant	53.4% 70%/50%
	Pi3Ki post-Ven in BTKi-exposed (n=17)	46.9%
BCRi, CT/CIT, or other after Ven regimen (CORE Registry)	Next regimen post-Ven (n=23, including n=9 Ibr and n=4 other BCRi)	60.8% (Ibr: 5/9)

BCL2i, B-cell lymphoma-2 inhibitor; BCRi, B cell antigen receptor inhibitor; BR, bendamustine and rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CIT, chemoimmunotherapy; CR, complete response; CRi, complete response with incomplete marrow recovery; CT, chemotherapy; EU, European Union; Ibr, ibrutinib; nPR, nodular partial remission; ORR, overall response rate; PD, progressive disease; PI3Ki, phosphoinositide 3-kinases; PR, partial response; R, rituximab; R/R, relapsed/refractory; SD, stable disease; UK, United Kingdom; US, United States; Ven, venetoclax.

1. Harrup R et al. ASH 2020; Abstract 3139. 2. Brown JR et al. ASH 2019; Abstract 4320. 3. Mato AR et al. Haematologica. 2018;26:3589–3596; 4. Lin VS et al. Blood. 2020;135:2266–2270; 5. Mato AR et al. Clin Cancer Res. 2020;26:3589–3596; 6. Mato AR et al. ASH 2019; Abstract 1756. 7. Seymour JF et al. ASH 2019: Abstract 355.

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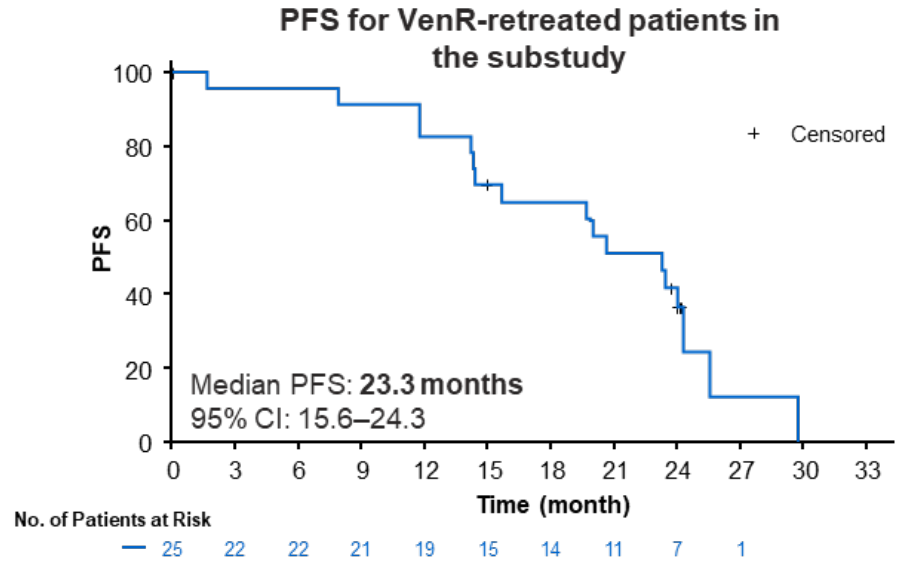
Venetoclax re-treatment

R/R CLL

MURANO study: patient outcomes with venetoclax re-treatment

	Patients retreated with VenR (n=25)
Median age, years (range)	**66 (49–82)**
Median prior therapies	**2**
del(17p) and/or *TP53* mutation	
Yes/No/unknown	**32%/20%/40%**



Phase II ReVenG study: Ven + Obi re-treatment in patients with relapsed CLL Ongoing!

CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; Obi, obinutuzumab; PFS, progression-free survival; R, rituximab; R/R, relapsed/refractory; *TP53*, tumor protein p53; Ven, venetoclax.
Kater AP et al. EHA 2023; Abstract S201.

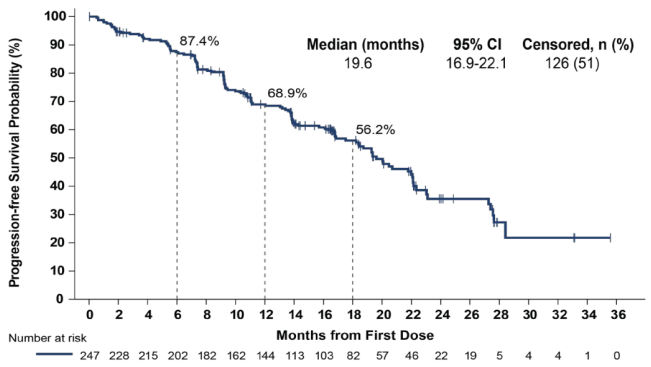
Double-refractory patients

R/R CLL

Phase I/II BRUIN study: pirtobrutinib in cBTKi pre-treated R/R CLL/SLL

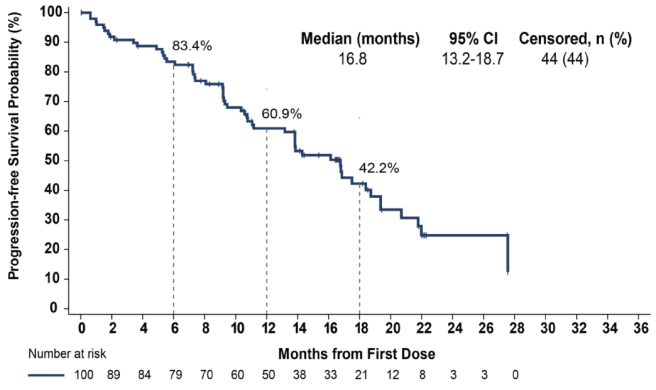
	Patients retreated with pirtobrutinib (n=247)
Median age, years (range)	66 (49–82)
Previous BTKi	100%
Previous BCL2i	41%
del(17p) and/or *TP53* mutation	47%

All prior BTKi patients
Median prior lines = 3



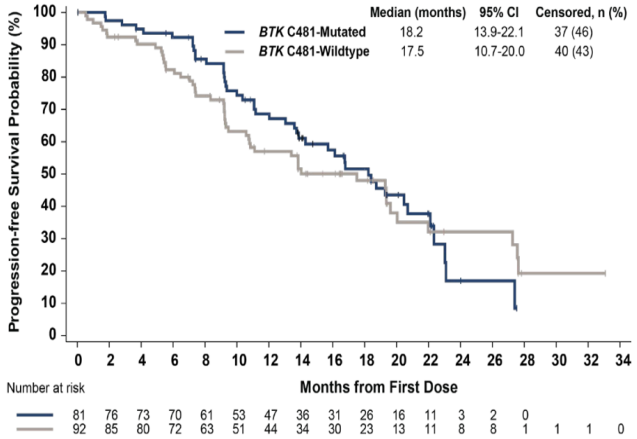
- Median follow-up of 19.4 months for patients who received prior BTKi

Prior BTKi and BCL2i patients
Median prior lines = 5



- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

***BTK* C481 mutation status[a,b]**



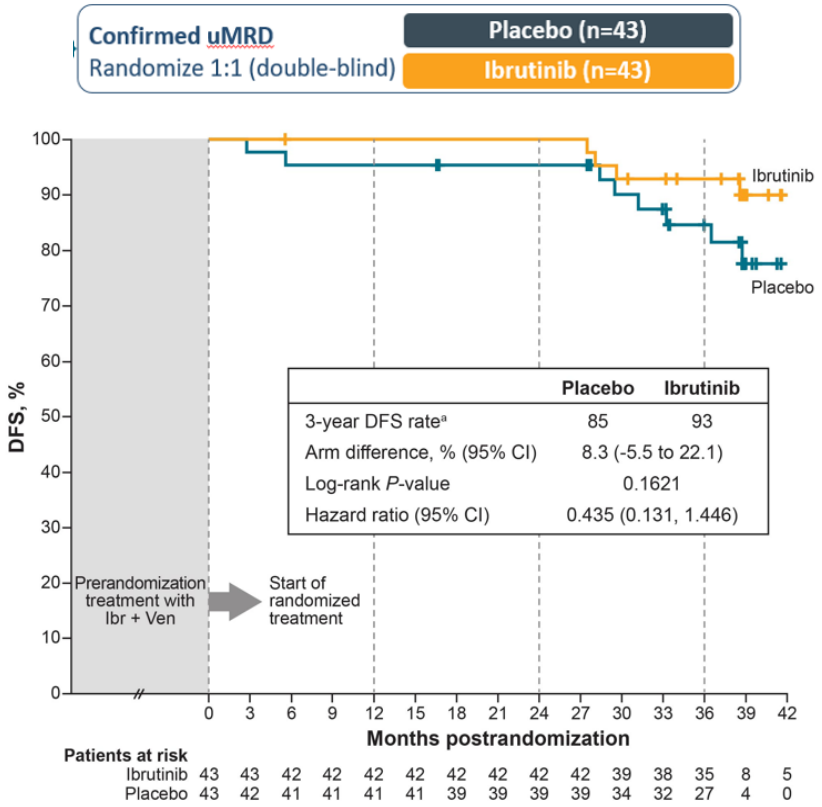
BCL2i, B-cell lymphoma-2 inhibitor; (c)BTKi, (covalent) Bruton's tyrosine kinase inhibitor; CI, confidence interval; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; n, number of patients; R/R, relapsed/refractory; SLL, small lymphocytic leukemia; *TP53*, tumor protein p53.
Woyach JA et al. Blood. 2022;140(Supplement 1):12427-28.

A look at the future

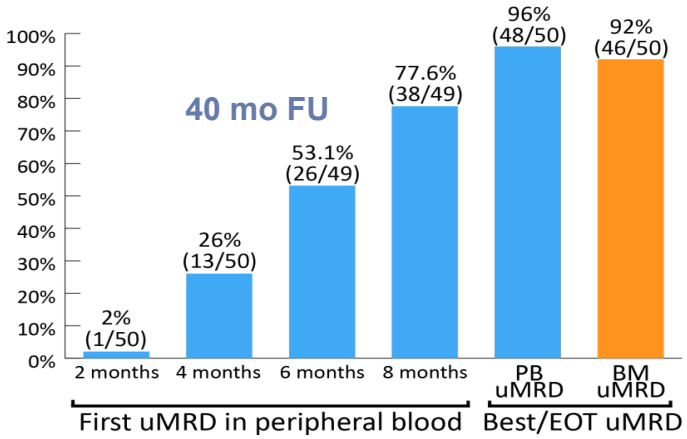
Doublets or triplets? MRD-guided treatment?

TN CLL

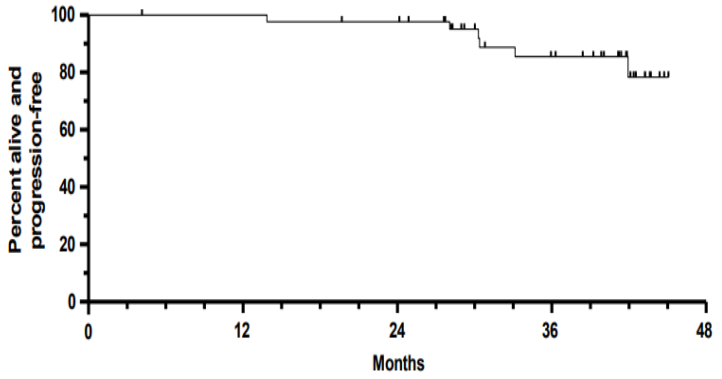
Phase II CAPTIVATE study[1]:
ibrutinib + venetoclax
5 years FU



Phase II BOVen study[2]:
zanubrutinib + obinutuzumab + venetoclax



Tx stop at a median of 10 mo



Median MRD FS 29.8 mo

CI, confidence interval; CLL, chronic lymphocytic leukemia; DFS, disease-free survival; EOT, end of treatment; FS, free survival; FU, follow-up; Ibr, ibrutinib; mo, months; Tx, treatment; (u)MRD, (undetectable) minimal residual disease; n, number of patients.

1. Allan JN et al. ASH 2022; Abstract 92 (figure adapted); 2. Soumerai JD et al. ICML 2023 (figures adapted).

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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.

A look at the future

R/R CLL

CAR-T

- ▼Lisocabtagene maraleucel TRANSCEND CLL 004 study[1]
  - Double refractory: ORR 43%, CR 18%

BTK degrader

- NX-2127-001 Phase 1 study[2]
  - Prior BTKi treatment: objective response rate 33%
- BGB-16673-101 Phase 1 study[3]
- BGB-16673-102 Phase 1 study[4]

BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; R/R, relapsed/refractory.

1. Siddiqi T et al. ASCO 2023; Abstract 7501; 2. Mato A et al. ASH 2022. 3. Clinicaltrials.gov. NCT05006716. Available at: https://clinicaltrials.gov/ct2/show/NCT05006716 (accessed October 2023); 4. Clinicaltrials.gov. NCT05294731. Available at: https://clinicaltrials.gov/ct2/show/NCT05294731 (accessed October 2023).

Conclusions*…….still many questions

*Speaker's own view

CLL treatment decision strictly depends on:

- **patient and disease characteristics**
- **AE profile of target agents**
- **patient preference/logistics**

BTKi

- **more effective in high-risk patients**
- **easy to deliver**
- **resistance development**
- **zanubrutinib more effective than ibrutinib in R/R, better tolerated**
- **acalabrutinib better tolerated than ibrutinib in R/R, same efficacy**

BCL2i

- **strict monitoring**
- **benefit of treatment-free period**

CIT

- **no further role (toxicities, secondary MDS/AML)**

Importance of adequate program from the start of therapy

- **importance of sequencing**

Importance of age

- **age *per se* is not a limitation to receive a targeted agent**
- **young high-risk patients ➡ allogeneic transplant**

Unmet clinical needs

- *No randomized trials yet on FD vs continuous Tx (CLL17 results)*
- *MRD-oriented therapy?*
- *Lack of clinical trials on sequencing*
- *Mostly real-life data/small populations*
- *Lack of knowledge on the impact of genetics beyond TP53/IGHV/del(17p) on the outcomes of current therapies?*
- *CAR-T role*

AE, adverse event; AML, acute myeloid leukaemia; BCL2i, B-cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T cells; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; FD, fixed duration; *IGHV*, immunoglobulin heavy chain variable region; MDS, myelodysplastic syndrome; MRD, minimal residual disease; R/R, relapsed/refractory; *TP53*, tumor protein p53; Tx, treatment.

Molecular mapping of CLL and its impact on outcome

Xose S. Puente, PhD

Universidad de Oviedo
Oviedo, Spain

Disclosures

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- **Advisory boards**: None
- **Speakers' bureau**: None
- **Other**: None

The views expressed are those of the speakers and may not necessarily reflect the opinion of BeiGene.

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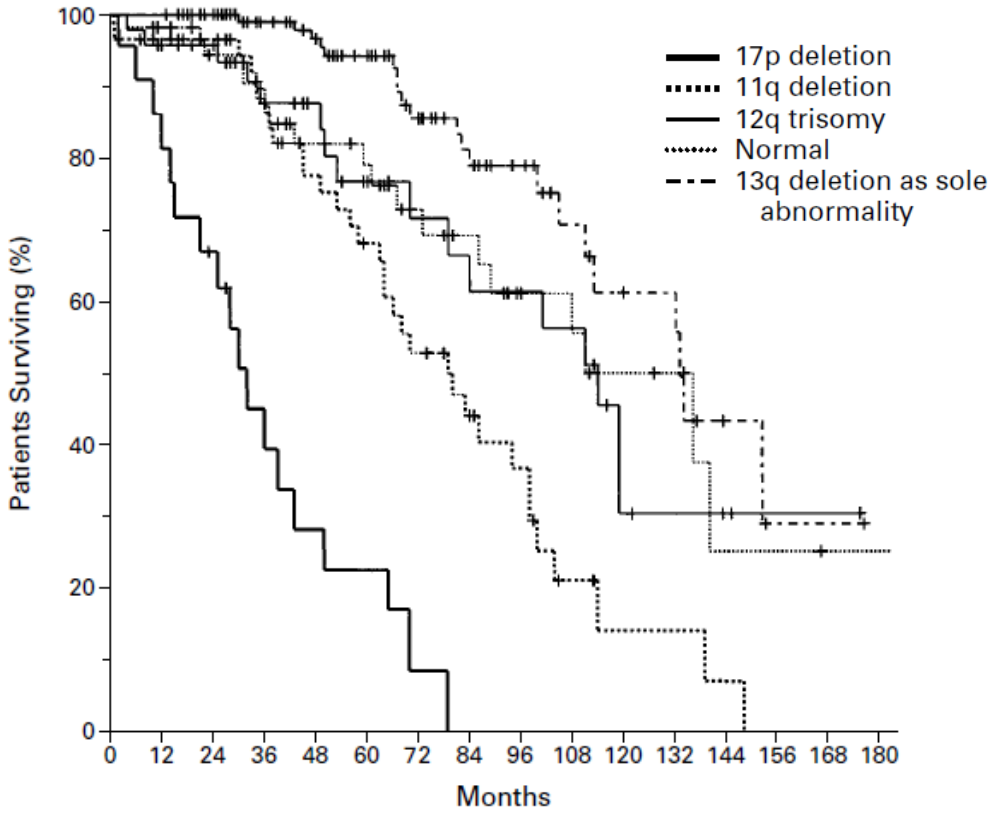
Introduction (Speaker's own view)

- New treatments for CLL have become available in past years, like the BTKis
- Such treatments have been improved by next generation versions of these drugs
- First steps towards personalization of CLL therapy are being made, for example based on *TP53*^{mut} / del(17p)
- Current research shows that CLL genetics is more complex than *TP53*^{mut} / del(17p) / *IGHV* status, and it impacts outcomes
- These new insights may provide new "handles" to further personalize CLL treatment

BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17; *IGHV*, immunoglobulin heavy chain variable region; mut, mutated; *TP53*, tumor protein p53

Genomic aberrations and CLL progression



No. at Risk																
17p deletion	23	18	13	8	5	4	1	0	0	0	0	0	0	0	0	0
11q deletion	56	53	47	43	33	27	20	15	10	4	2	2	1	0	0	0
12q trisomy	47	44	41	29	24	17	14	13	12	11	4	3	2	1	1	0
Normal	57	51	45	37	30	27	20	17	12	11	6	5	2	2	1	1
13q deletion as sole abnormality	117	117	106	91	80	63	45	36	24	16	12	11	3	1	1	0

17p deletion → *TP53*

11q deletion → *ATM*

13q deletion →*miR-15/16*

Chromosome 12 trisomy

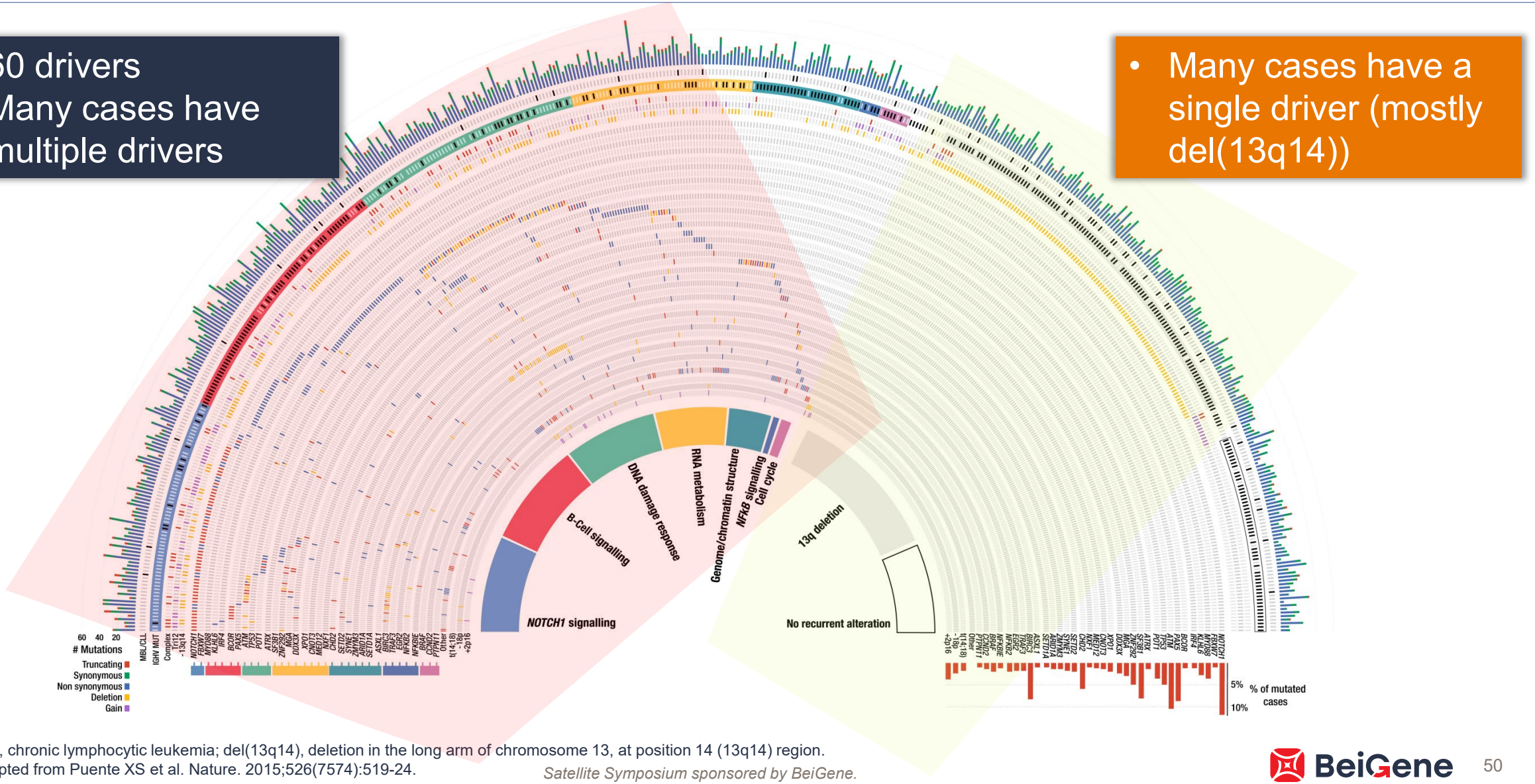
ATM, ataxia-telangiectasia mutated (gene); CLL, chronic lymphocytic leukemia; 11q deletion, deletion of the long arm of chromosome 11; 13q deletion, deletion of the long arm of chromosome 13; 17p deletion, deletion of the short arm of chromosome 17; *miR*, microRNA tumor suppressor located at 13q14 region deleted in CLL; *TP53*, tumor protein p53.

Döhner H et al. N Engl J Med. 2000;343:1910-1916.

Genomic aberrations and CLL progression

- 60 drivers
- Many cases have multiple drivers

- Many cases have a single driver (mostly del(13q14))

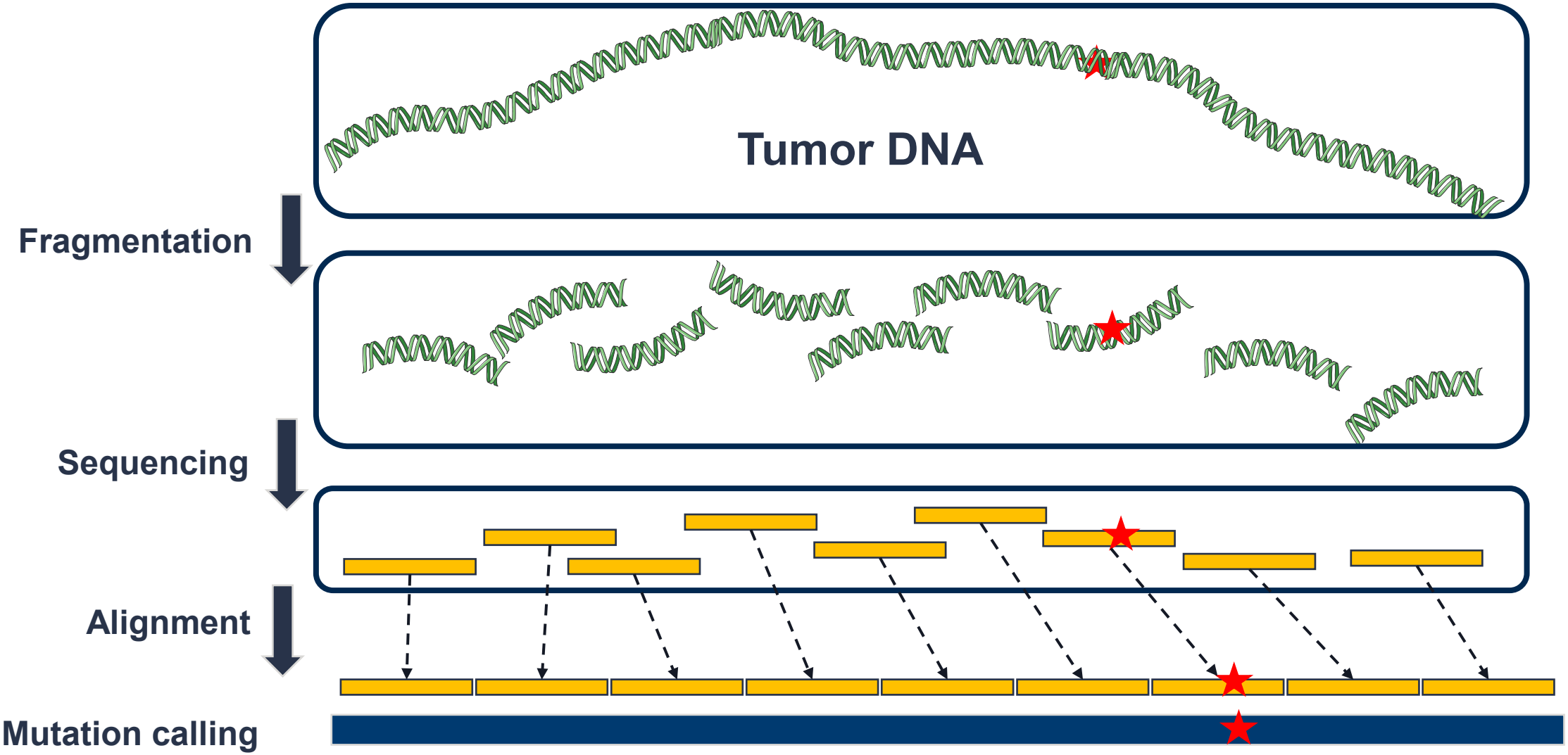


CLL, chronic lymphocytic leukemia; del(13q14), deletion in the long arm of chromosome 13, at position 14 (13q14) region.
Adapted from Puente XS et al. Nature. 2015;526(7574):519-24.

10% of cases are driver-less tumors / 1

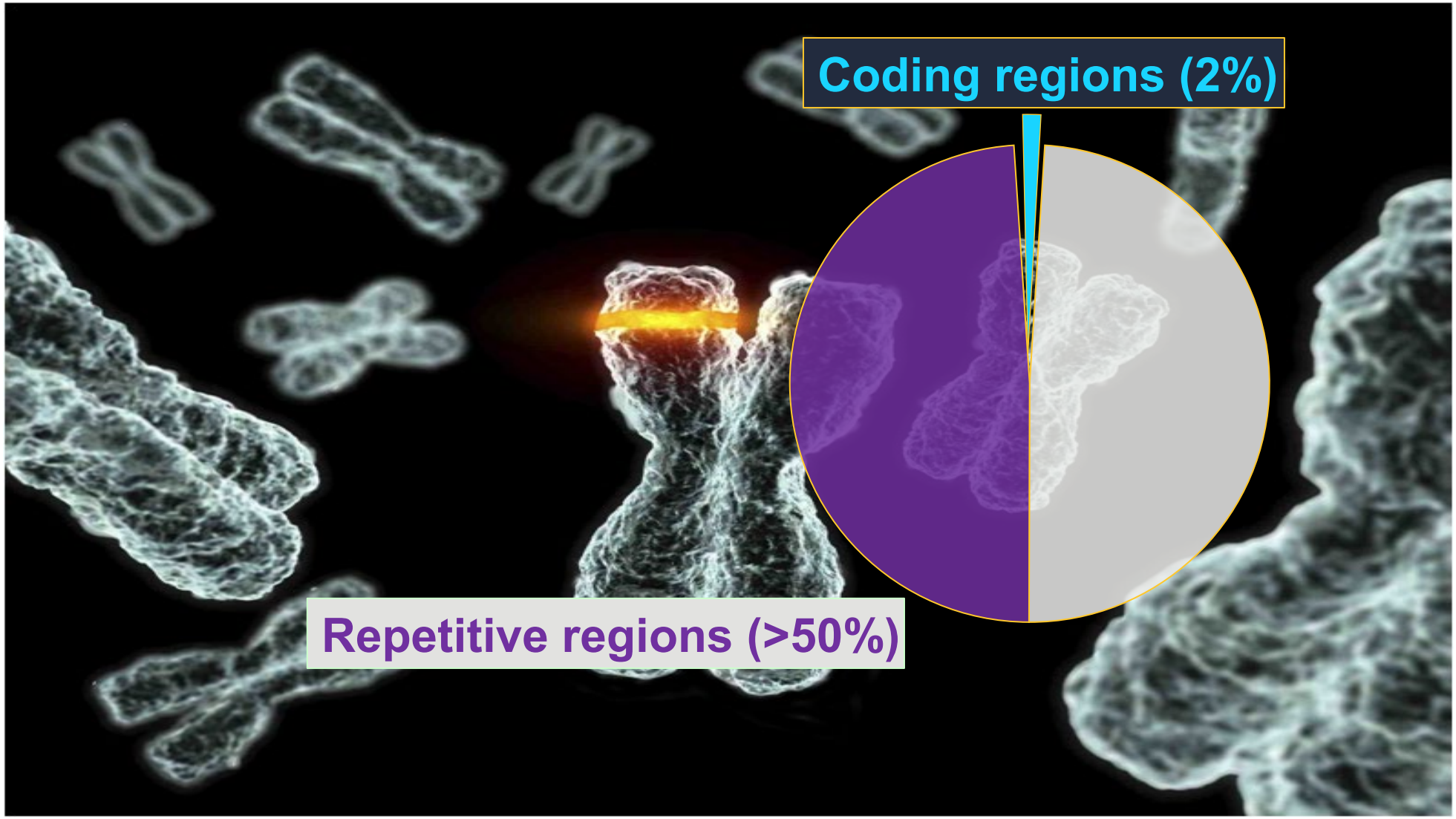
Adapted from Puente XS et al. Nature. 2015;526(7574):519-24.

Identification of somatic mutations from short reads



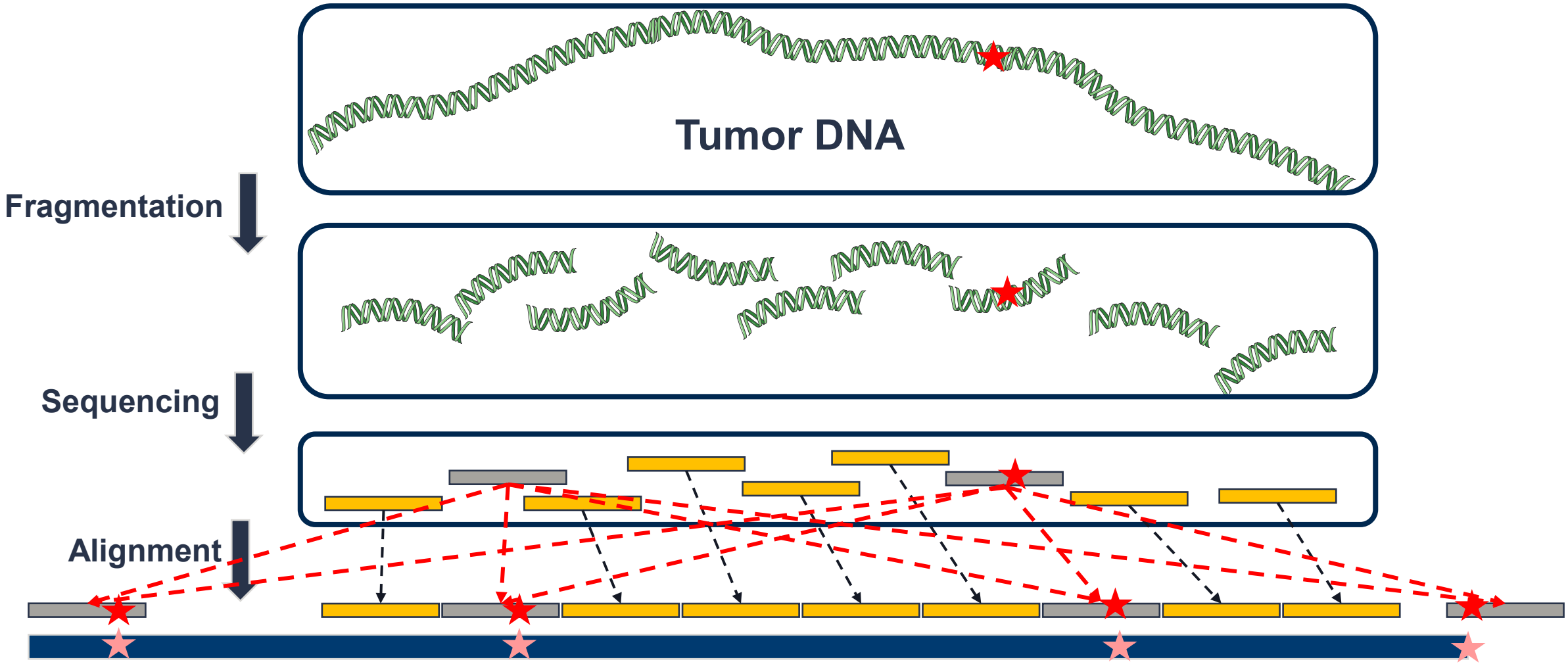
DNA, deoxyribonucleic acid.
Slide courtesy of Dr XS Puente.

How much of the genome is visible?



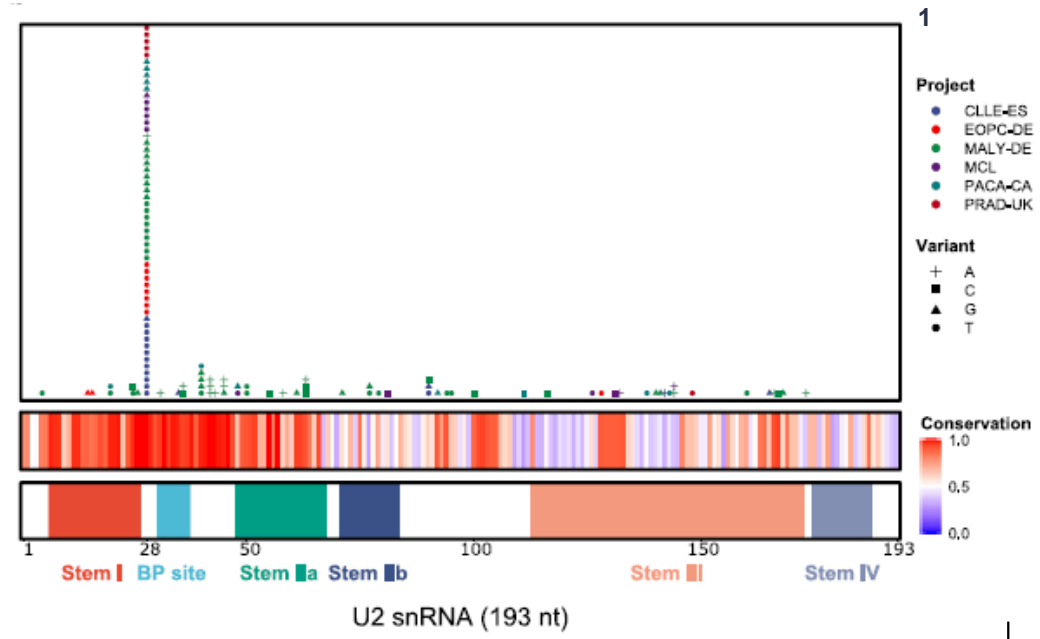
Slide courtesy of Dr XS Puente.

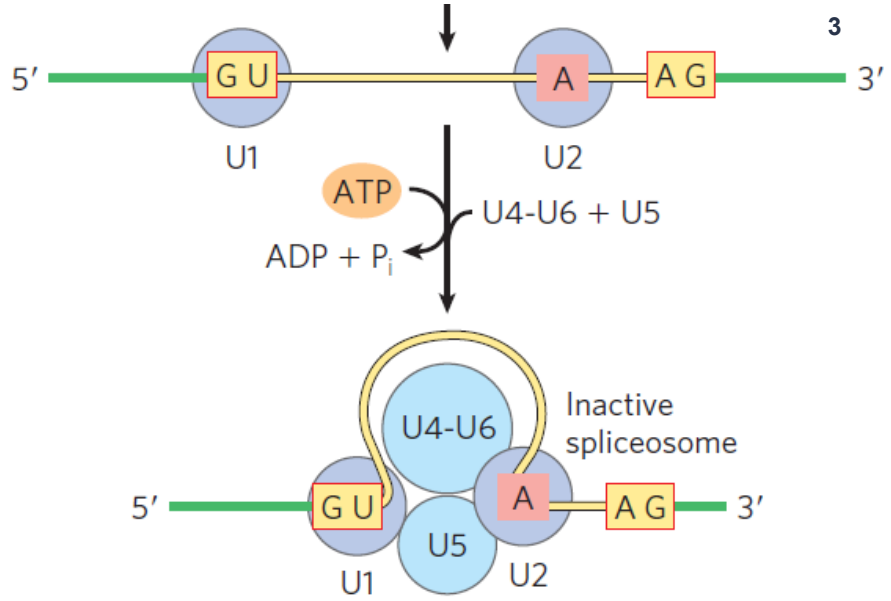
Identification of somatic mutations from short reads: repetitive elements

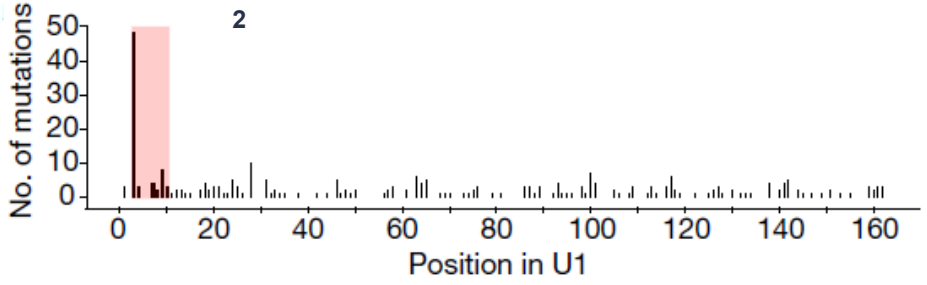


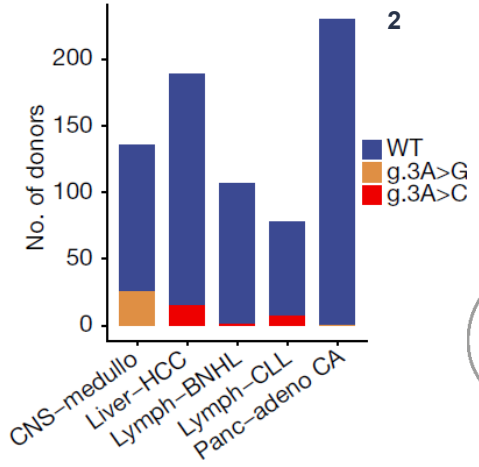
DNA, deoxyribonucleic acid.
Slide courtesy of Dr XS Puente.

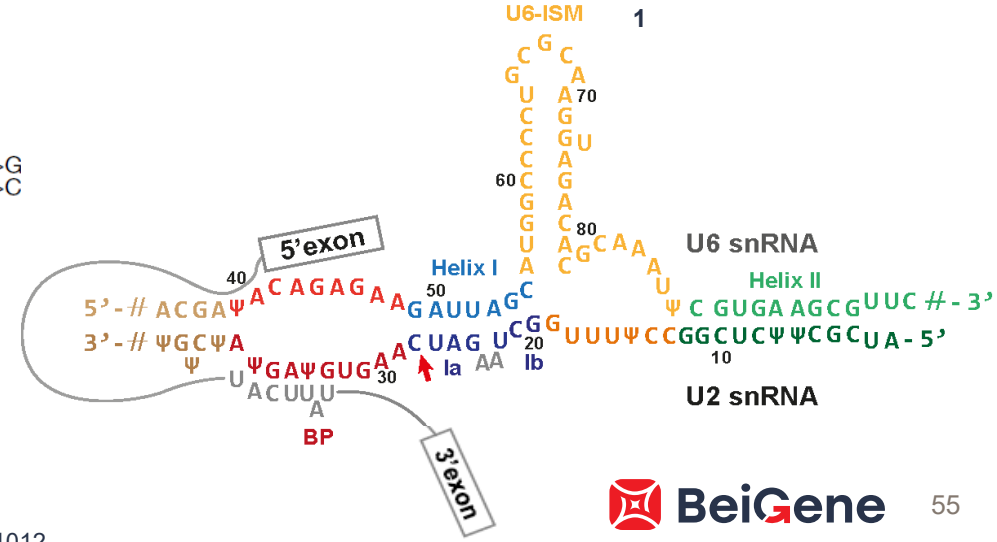
Recurrent mutations in repetitive small nuclear RNAs (U1 and U2)





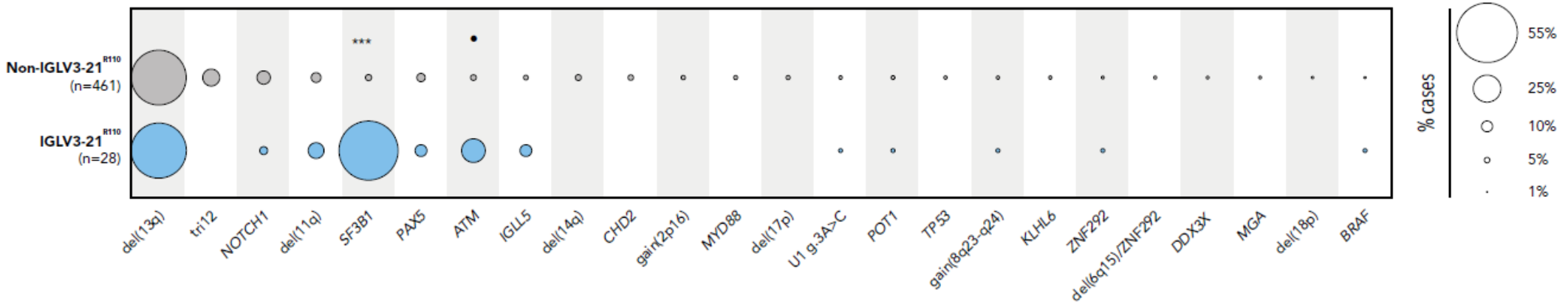






1) Bousquets-Muñoz P et al. npj Genome Med. 2022;7:19 (bottom right figure adapted).
2) Shuai S et al. Nature. 2019;574(7780):712-716.
3) Adapted from Nelson DL and Cox MM. Principles of Biochemistry. 4th Ed. London: Palgrave Macmillan; 2008. Chapter 26, p. 1012.

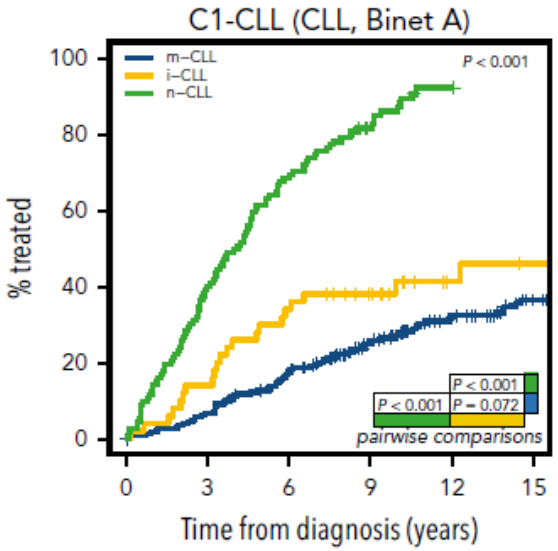
IGLV3-21^{R110}: unfavorable prognosis

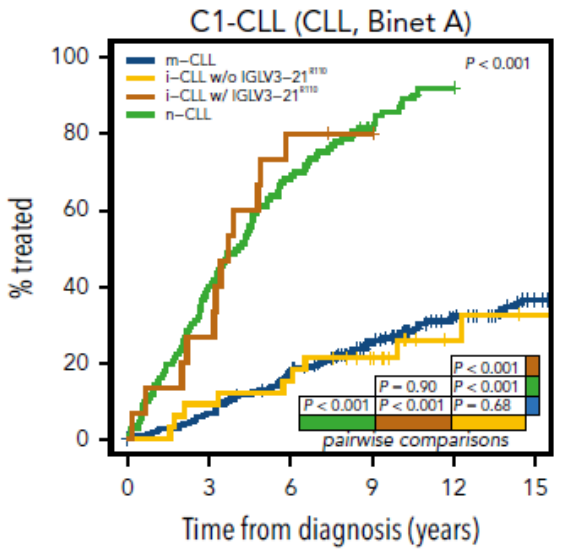


3 epigenetic CLL subtypes (correlate with IGHV mutational status and patient outcome):

- m-CLL: memory-like CLL (good prognosis)
- i-CLL: intermediate CLL (intermediate prognosis)
- n-CLL: naïve-like CLL (poor prognosis)

- IGLV is repetitive
- IGLV3-21^{R110} enriched in intermediate CLL (38%)
- i-CLLs with 21^{R110} behave as n-CLL





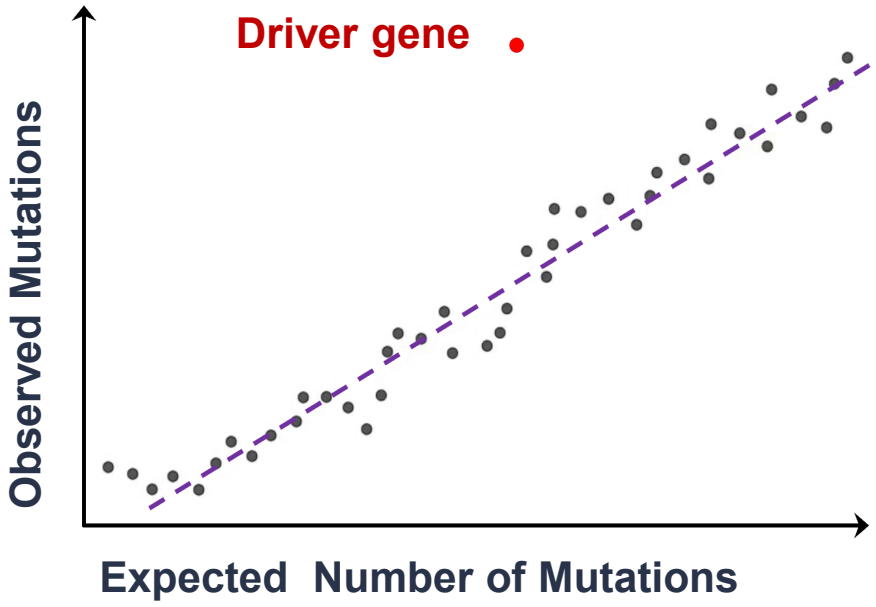
CLL, chronic lymphocytic leukemia; IGLV, immunoglobulin lambda variable chain.
Nadeu F et al. Blood. 2021;137(21):2935-2946.

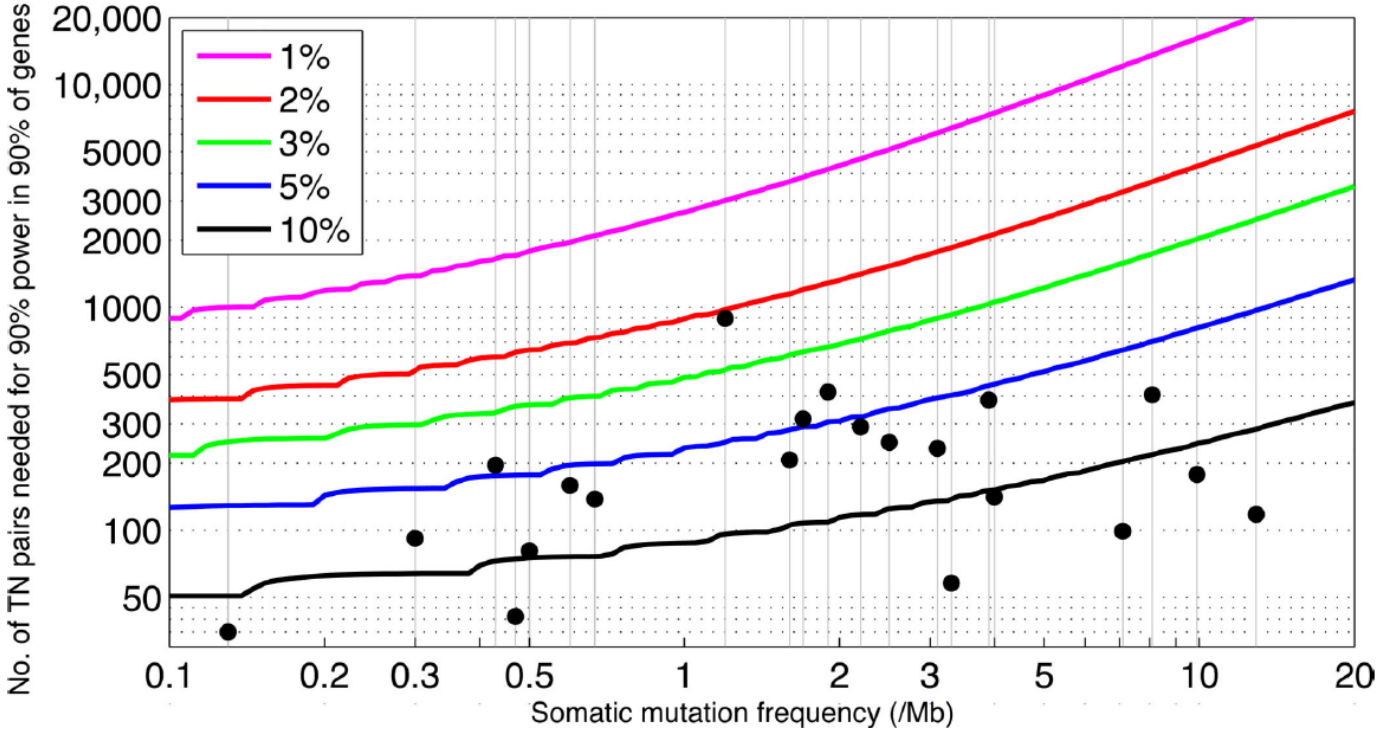
10% of cases are driver-less tumors / 2

Adapted from Puente XS et al. Nature. 2015;526(7574):519-24.

CLL 500: are we identifying all driver genes?

- Driver genes are identified using statistics
- If a gene/alteration frequency is higher than by chance, there is selection
- Power to detect drivers depends on mutation burden and number of cases

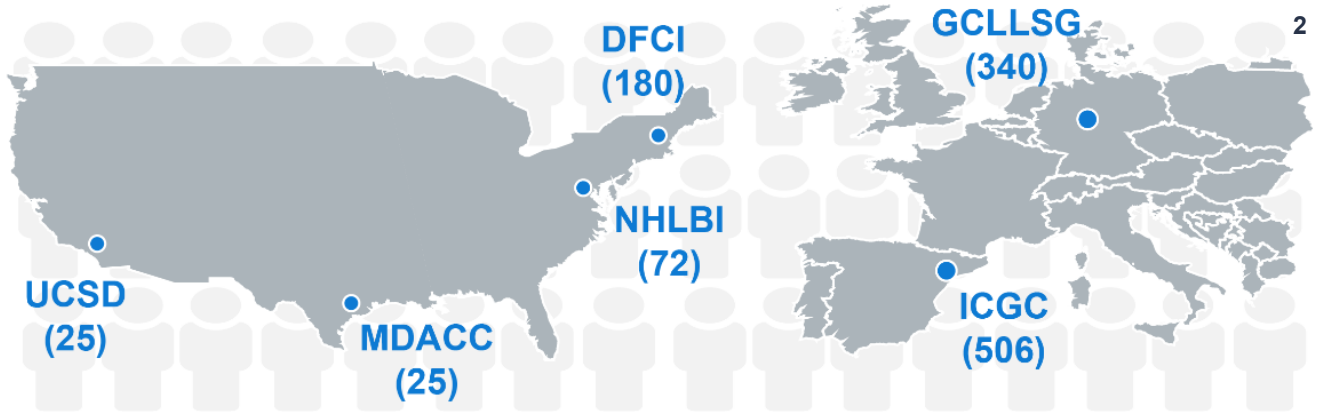




CLL, chronic lymphocytic leukemia.
Left hand graphic: speaker's own; right hand graphic: Lawrence MS et al. Nature. 2014;505:495-501.

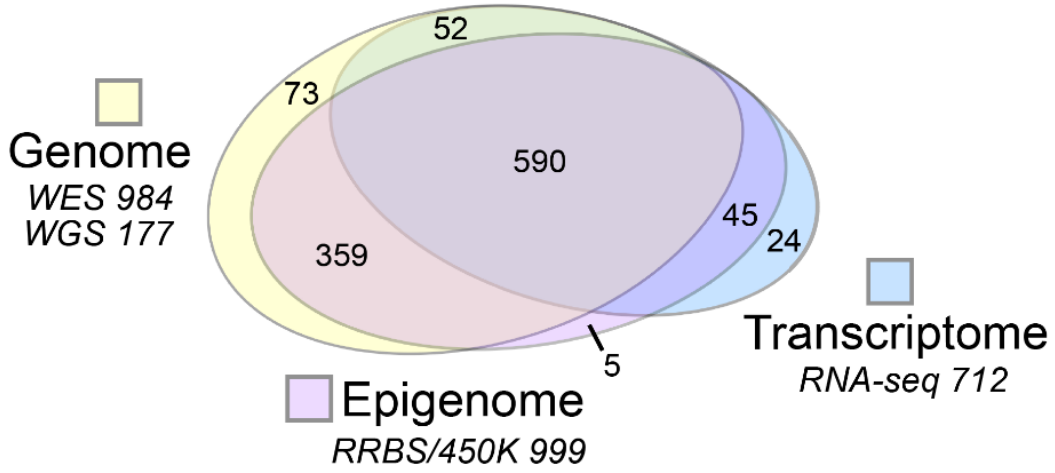
The CLL-1100 project[1]

- Joined ICGC cohort:
  - ICGC-CLL
  - Dana Farber Cancer Institute
  - German CLL Study Group
  - NHLBI, MDACC, UCSD



Multiomic data from 1148 CLL patients

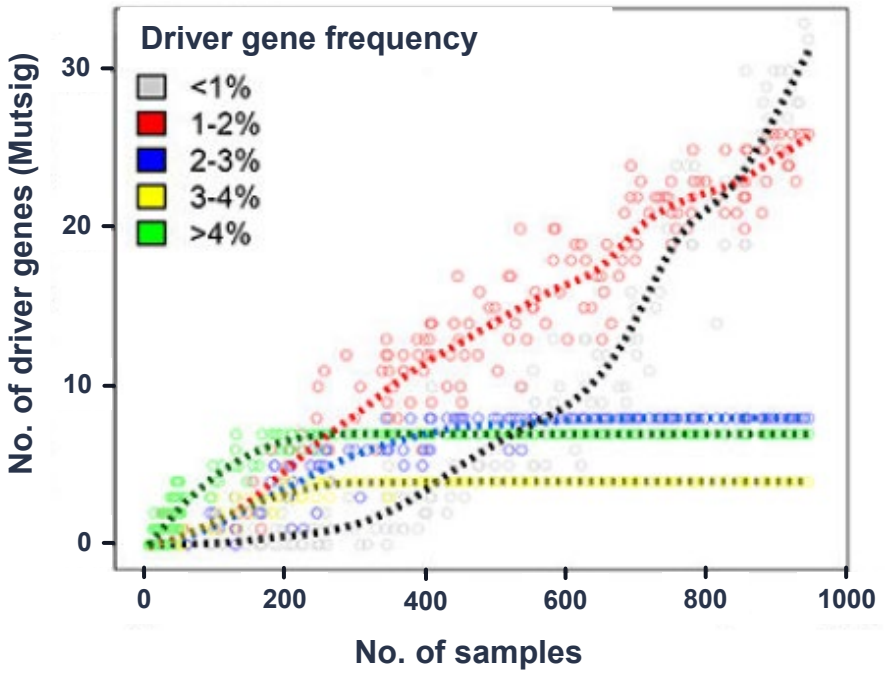
Mutation calling
Genetic drivers
(pan-CLL and per subtype)
Structural variation
Evolutionary trajectories

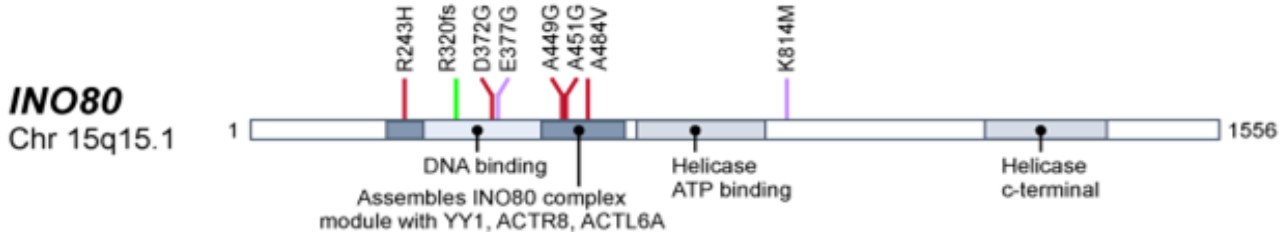


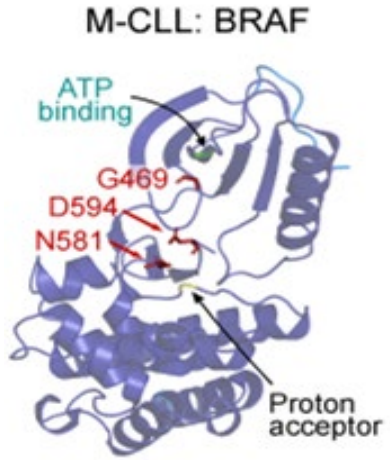
CLL, chronic lymphocytic leukemia; DFCI, Dana Farber Cancer Insititute; GCLLSG, German CLL Study Group; ICGC, International Cancer Genome Consortium; MDACC, MD Anderson Cancer Center; NHLBI, National Heart, Lung, and Blood Institute; UCSD, University of California San Diego; WES, whole-exome sequence; WGS, whole-genome sequence.

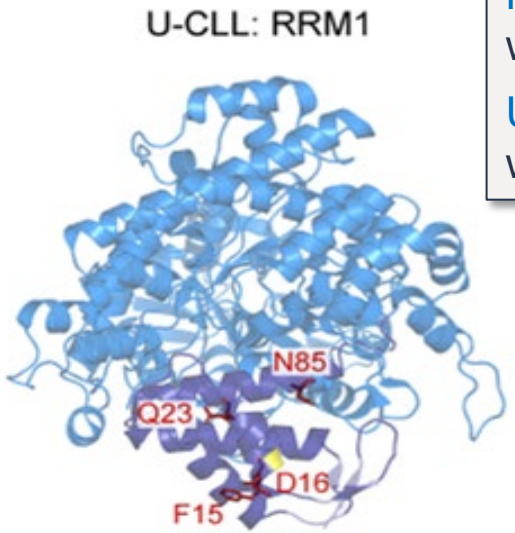
(1) Knisbacher BA et al. Blood. 2020;136(1):3; (2) cllmap.org (last access: October 2023).

Increased ability to detect driver events









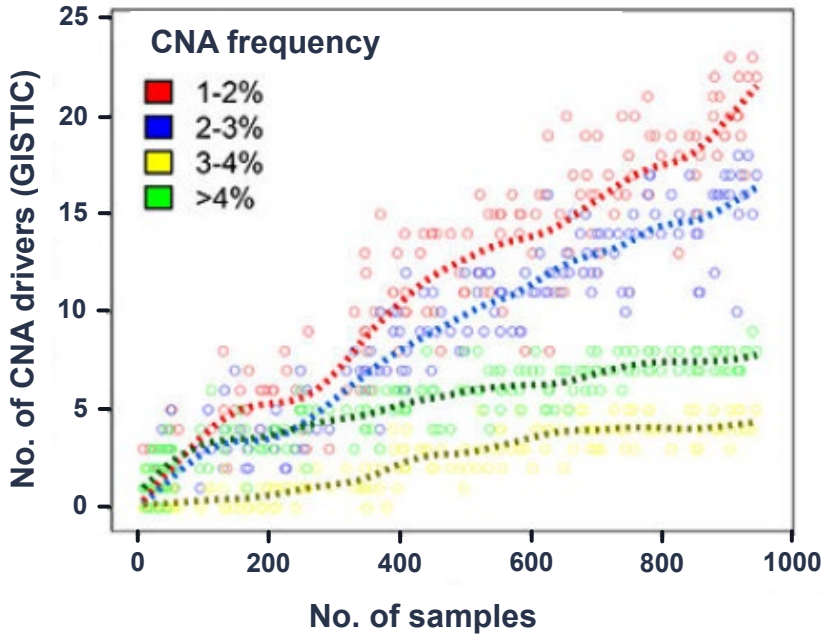
M-CLL = CLL with *IGHV*^{MUT}

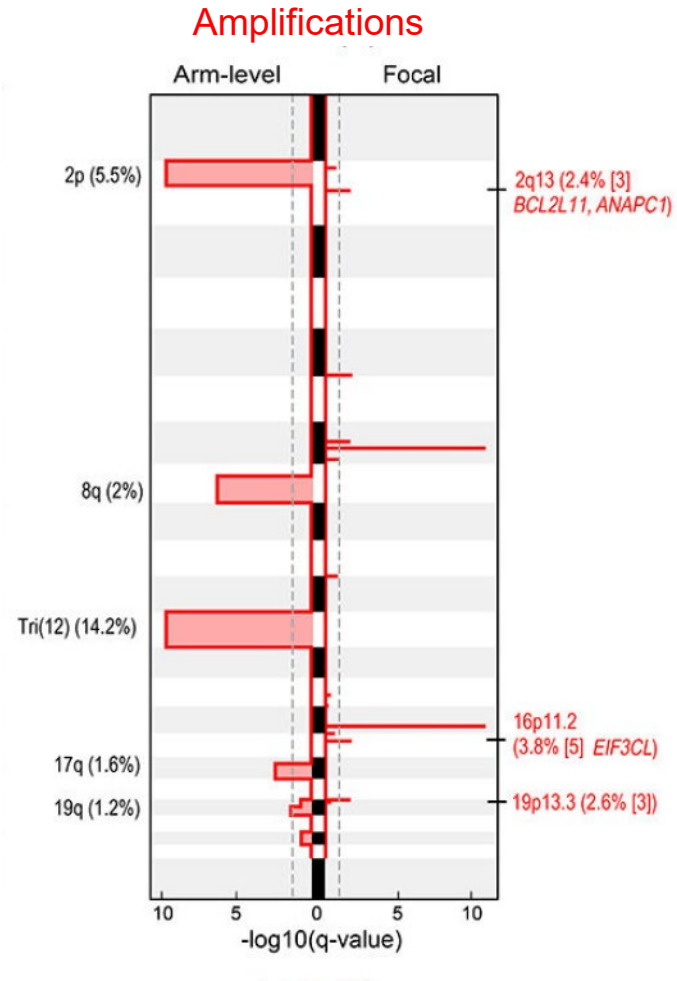
U-CLL = CLL with *IGHV*^{UNMUT}

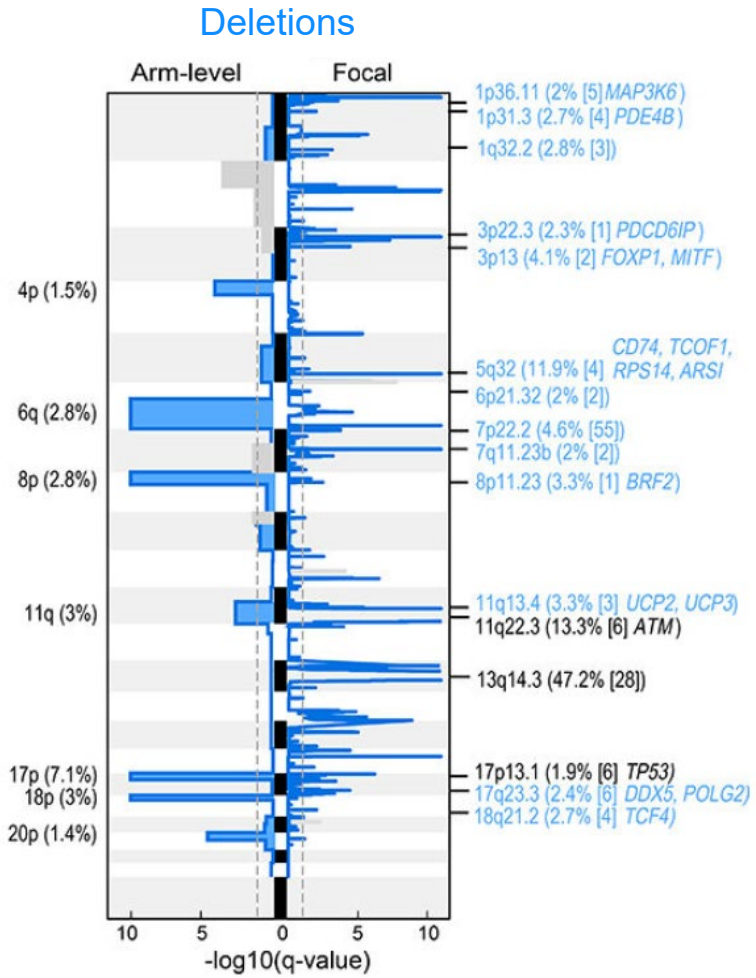
- Saturation for detecting driver genes at >2% frequency
- Detection of additional drivers based on spatial clustering of mutations
- 46 out of 88 driver genes were new in CLL

CLL, chronic lymphocytic leukemia; M-CLL, CLL with mutated *IGHV*; RRM1, ribonucleoside-diphosphate reductase large subunit; U-CLL, CLL with unmutated *IGHV*.
Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

Increased ability to detect driver events





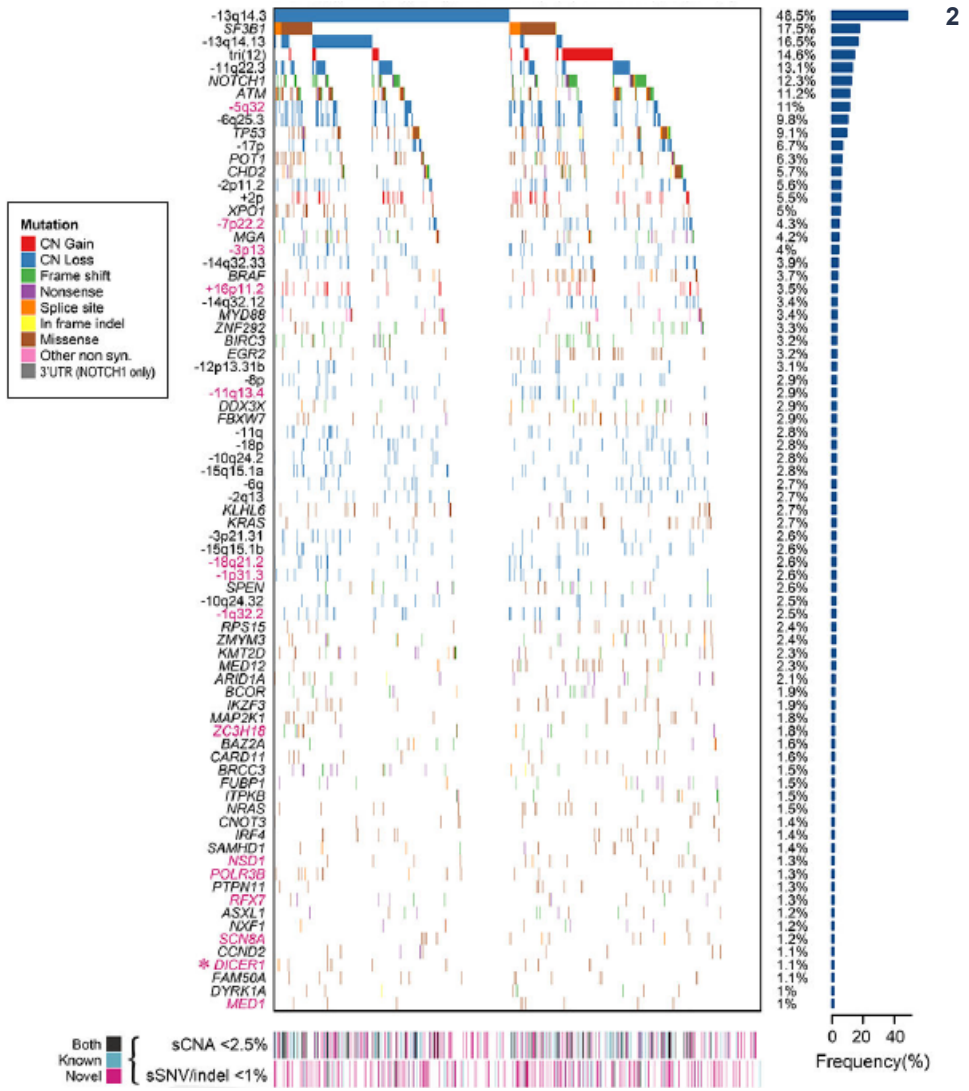


- CNA saturation at >3% frequency
- Higher sensitivity for detection of focal events

CLL, chronic lymphocytic leukemia; CNA, copy number alterations.
Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

CLL map with 1100 cases[1]

- 202 candidate drivers (109 new)
- Most of them in fewer than 3% of patients



CLL, chronic lymphocytic leukemia.
(1) Knisbacher BA et al. Blood. 2020;136(1):3; (2) Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

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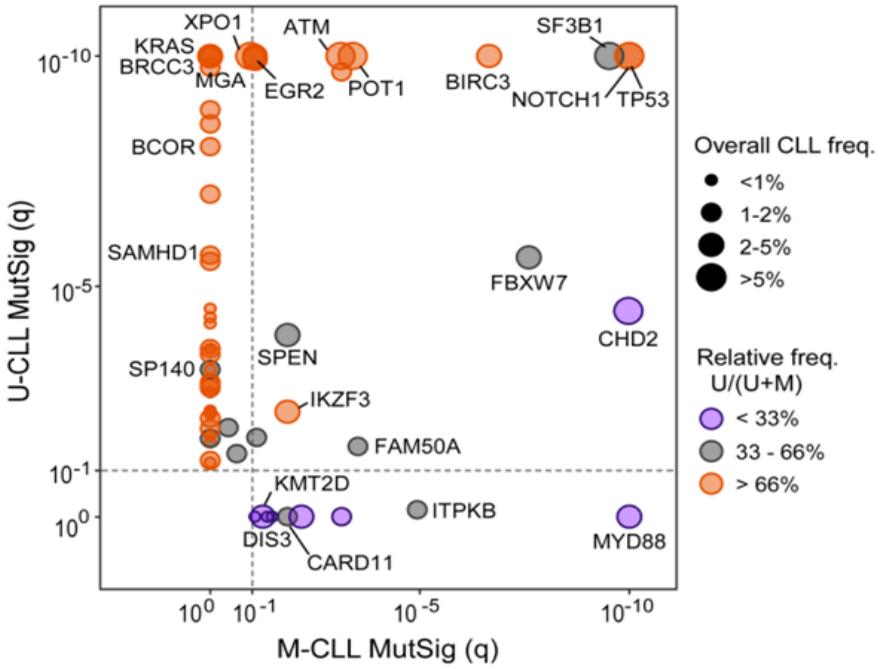
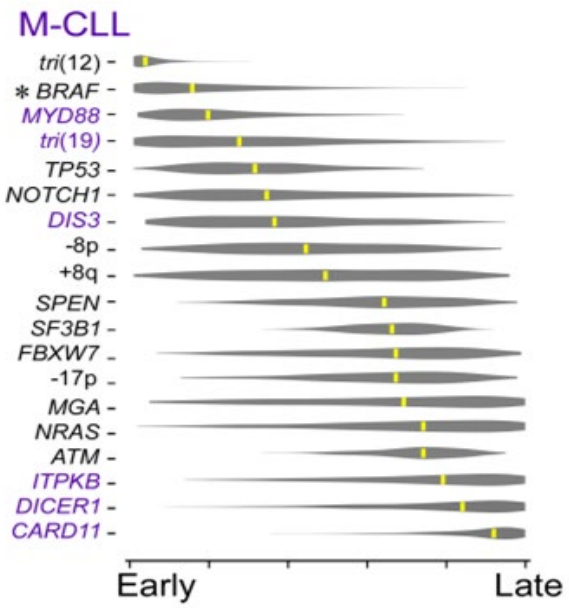
Differences between U-CLL and M-CLL

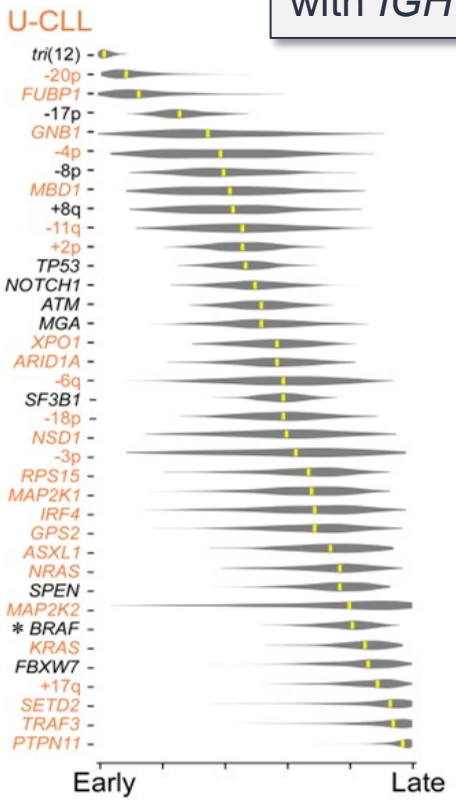
- 76% of driver genes were either specific or more frequent in U-CLL
- 3.8% patients lacked drivers (6.6% M-CLL vs. 0.6% U-CLL)
- >85% of drivers were subclonal (late events) → impact on diagnosis

M-CLL = CLL with *IGHV*^{MUT}

U-CLL = CLL with *IGHV*^{UNMUT}

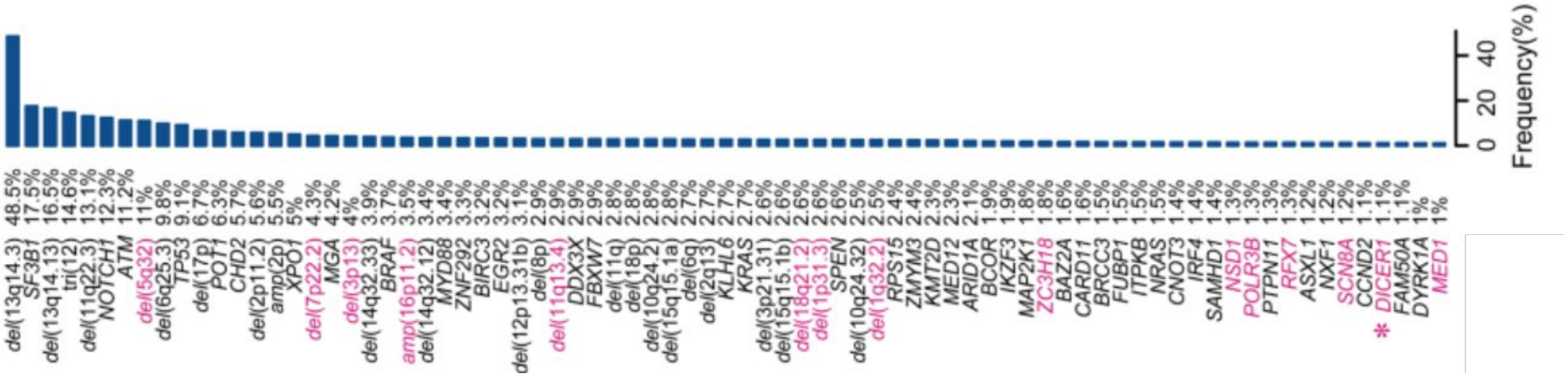






CLL, chronic lymphocytic leukemia; M-CLL, CLL with mutated *IGHV*; U-CLL, CLL with unmutated *IGHV*.
Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

Long tail of drivers at very low frequency

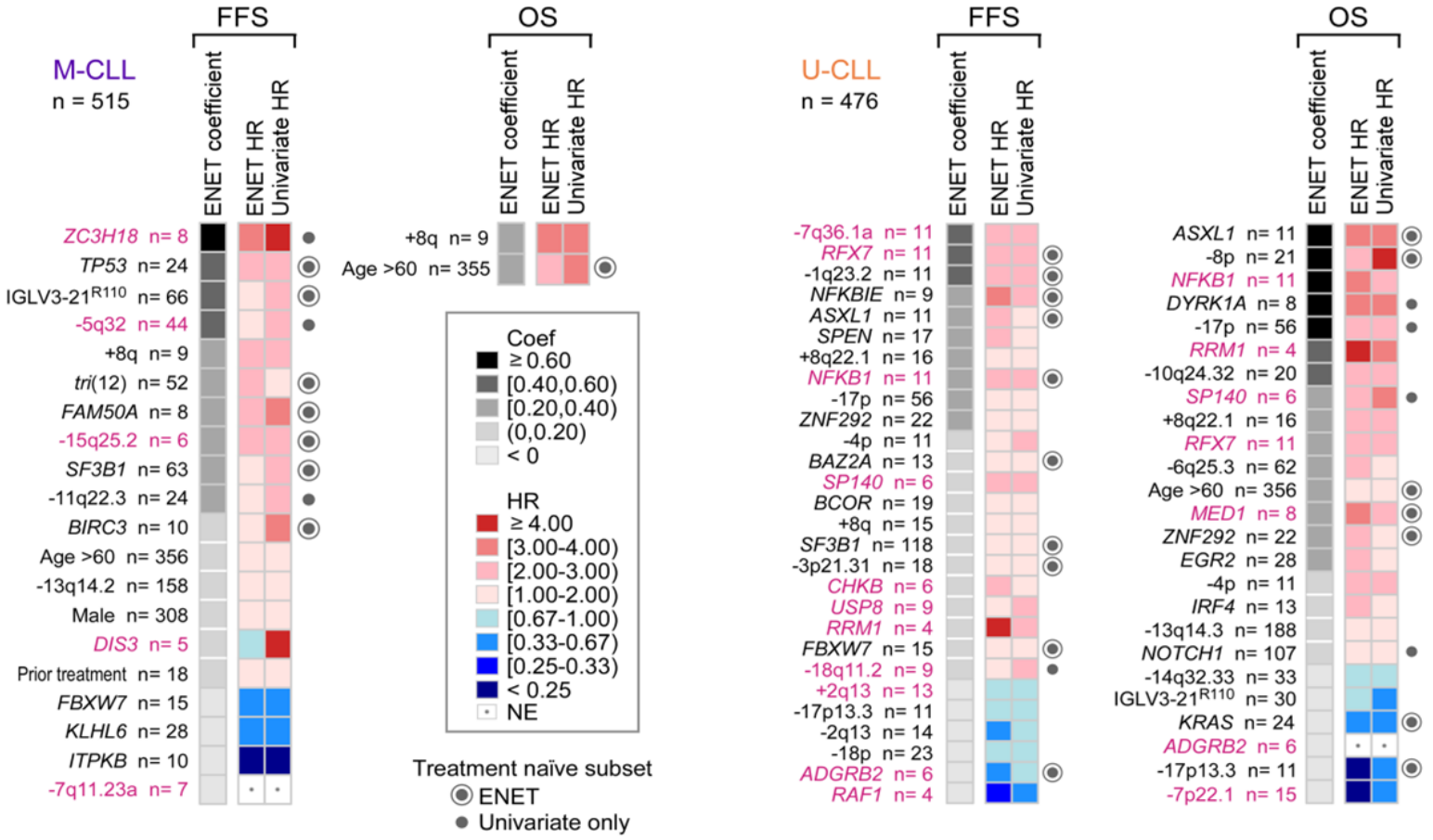


- Highly heterogeneous pathology

Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

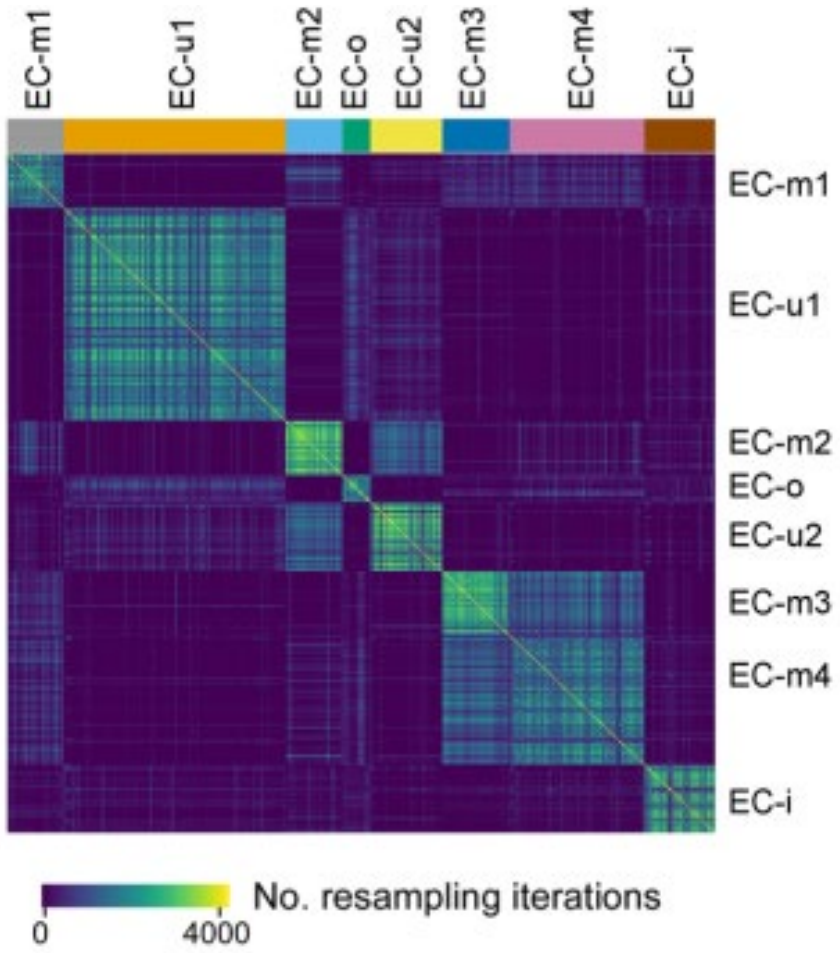
Clinical impact

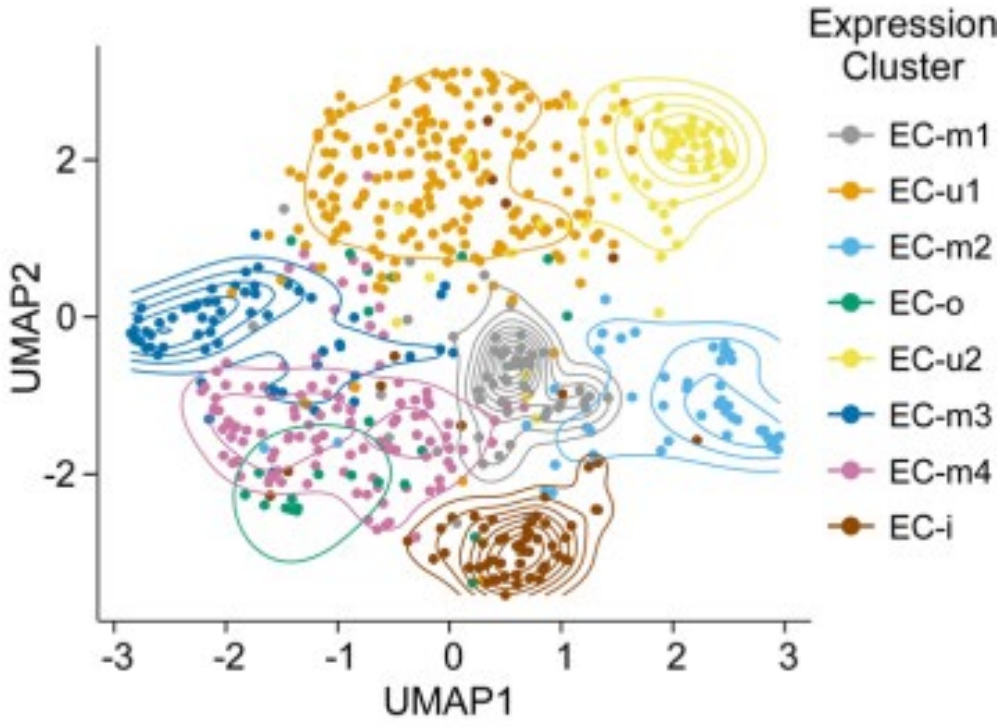
- U-CLL had more genes with impact on failure-free or overall survival than M-CLL (41 vs. 18)
- *TP53* mutation in absence of 17p loss is not associated with adverse outcome



CLL, chronic lymphocytic leukemia; del(17p), deletion of the short arm of chromosome 17 M-CLL, CLL with mutated *IGHV*; *TP53*, tumor protein p53; U-CLL, CLL with unmutated *IGHV*.
Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

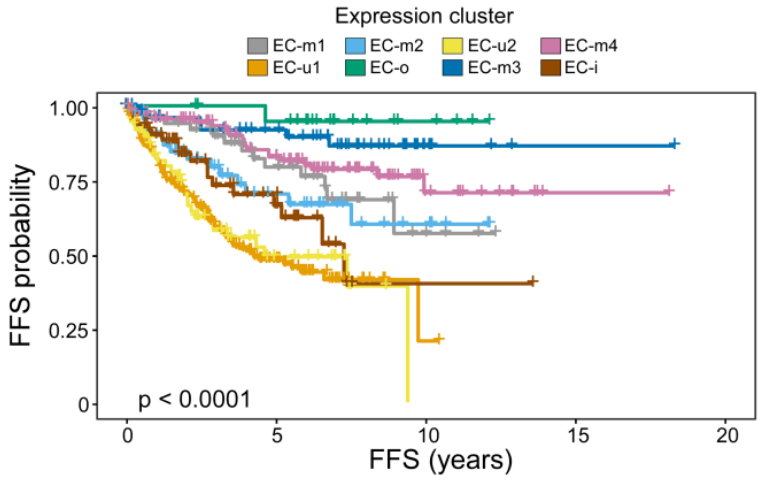
Expression analysis defines 8 expression clusters





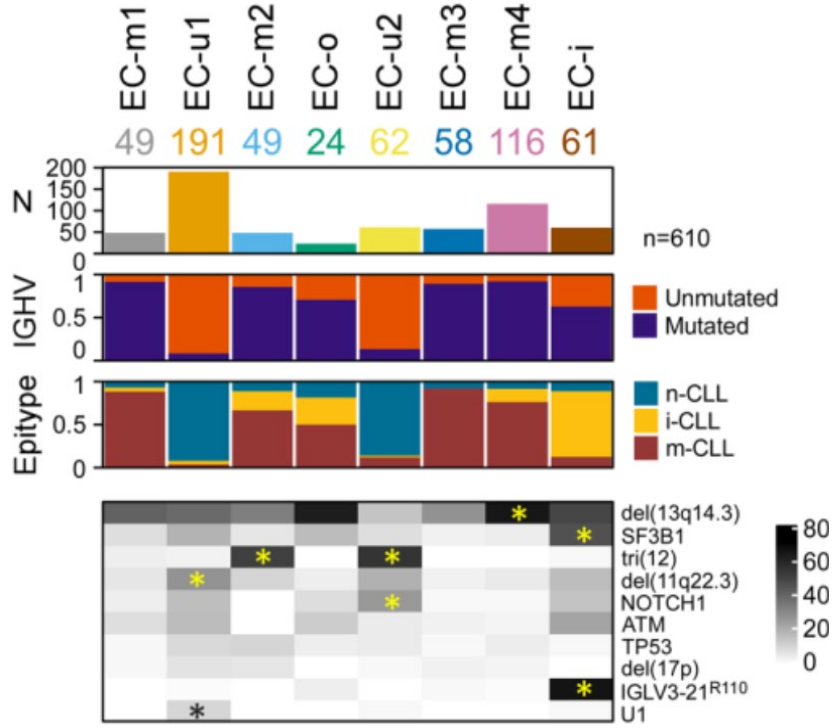
EC, expression cluster; UMAP, uniform manifold approximation and projection.
Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

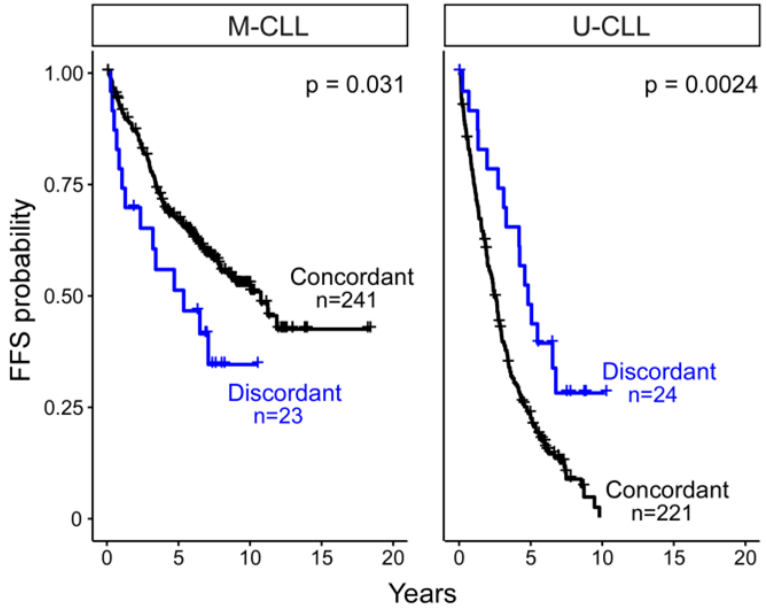
Expression clusters are associated with *IGHV*-status, driver mutations and progression



FFS without blacklisted participants, n=603

EC-m1	53	28	3	0	0
EC-u1	188	43	1	0	0
EC-m2	48	20	6	0	0
EC-o	21	18	4	0	0
EC-u2	64	13	0	0	0
EC-m3	54	38	3	1	0
EC-m4	113	68	13	1	0
EC-i	62	17	1	0	0





- 8% of samples are in expression clusters not corresponding to the major *IGHV* mutation group (i.e., M-CLLs in EC-u groups)
- Discordant cases have different FFS than concordant

CLL, chronic lymphocytic leukemia; EC, expression clusters; FFS, failure free survival; *IGHV*, immunoglobulin heavy chain variable region; M-CLL, CLL with mutated *IGHV*; U-CLL, CLL with unmutated *IGHV*.

Adapted from Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

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Summary (speaker's own)

- **Number of driver alterations expanded to 202:**
  - >96% of CLL tumors have at least one driver alteration
- **Most alterations are present in <2% of cases:**
  - Many have clinical impact (mostly in U-CLL, i.e., CLL with *IGHV*^{UNMUT})
- **8 Expression Clusters define subtypes of patients:**
  - Different prognosis
  - *IGHV*-subtype prognosis affected by expression cluster

CLL, chronic lymphocytic leukemia; *IGHV*, immunoglobulin heavy chain variable region; U-CLL, CLL with unmutated *IGHV*.

Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674.

Conclusion and future implications

- This research refines our current disease paradigm and establishes a new spectrum of events contributing to leukemogenesis that may have implications beyond prognostication[1].
- The driver mutations identified in this study will allow the design of specific gene panels for[2]:
  - Better patient stratification
  - Understanding differences in response to therapy, and
  - Identifying molecular targets that might benefit specific subgroups of patients
- In future, this molecular foundation may allow for better prediction of response to therapy or provide the basis for rational combination of novel agents[1].

1) Knisbacher BA et al. Nat Genet. 2022;54(11):1664-1674; 2) speaker's own.

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Closure and farewell

Overall session summary (Speaker's own)

- CLL treatment choice is driven by multiple patient, disease and drug factors.
- Various new continuous and fixed duration therapy options are emerging.
- Treatment sequencing must be considered from the beginning.
- There is a growing understanding of CLL genetics and its clinical impact.
- These exciting developments are driving increasing personalization of therapy, with the goal of better clinical outcomes, for CLL patients.

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