



SINTOMA'24

PARCERIA **soho**
society of hematologic oncology

APOIO
INSTITUCIONAL

bp Educação
e Pesquisa

**QUAIS OS PRINCIPAIS OBJETIVOS
NO TRATAMENTO NA LLC:
DRM, PFS, TEMPO PARA O PRÓXIMO
TRATAMENTO OU A CURA?**

Danielle Leão

Hematologista Titular da BP SP

Pesquisadora clínica



CONFLITOS DE INTERESSE

| <u>Patrocínio para esse evento</u> | “DEUS TE PAGUE” , “ VLW”, “TAMOJUNTO” |
|--|--|
| <u>Instituição</u> | BP - Beneficencia Portuguesa de Sao Paulo |
| <u>Participação em estudos clínicos (Indústria farmacêutica)</u> | Roche, Novartis, GSK, Janssen, Millenium Takeda, ABBVIE, Daichii Sankyo, Pfizer, Celltrion, BMS, AstraZeneca, Viracta, Sandoz, AGIOS, Astellas, MEDAC, Onconova, MSD, Sanofi, Regeneron, Lilly, ADC Therapeutics, Libbs, Beigene |
| <u>Participação em estudos clínicos (ITT, RWE ou registros)</u> | T-Cell Project, HOLA registry, MMyBrave registry, REALITY WW, , Brazilian Group of CLL, Brazilian Group of Multiple myeloma, AML-Brazil, Coalizão COVID Brazil, |
| <u>Palestrante</u> | Janssen, AstraZeneca, Zodiac, Roche, Novartis, Takeda, AMGEN, Roche, Libbs, BMS, Celgene, Pfizer, ABBVIE, Sanofi, Pintfarma, Knight Therapeutics/United Medical |
| <u>Membro de Advisory Board</u> | Kite/Gilead, Knight Therapeutics/United Medical, Janssen, Novartis, AMGEM, Takeda, Roche, BMS, ABBVIE, Libbs, Celgene, Eurofarma |
| <u>Membro de Steering Committee</u> | Janssen |
| <u>Membro de Independent Data Monitoring Committee</u> | Libbs /Mabxscience |
| <u>Afiliação</u> | ASH, EHA, ESO, IMS, CDCN (Castleman disease), ABHH (Associação Brasileira de Hematologia), Coordinator of Clinical Research Committee at ABHH, Myeloma Committee (ABHH), CLL Committee (ABHH), Lymphoma Committee (ABHH) |

COMEÇANDO DO COMEÇO: DEFININDO CONCEITOS

SOBREVIDA LIVRE DE PROGRESSÃO PARA LEIGOS:

- O período de tempo durante e após o tratamento de uma doença (...) que um paciente convive com a doença, mas ela não piora.
- Em estudos clínicos: forma de ver quão bem um novo tratamento funciona.

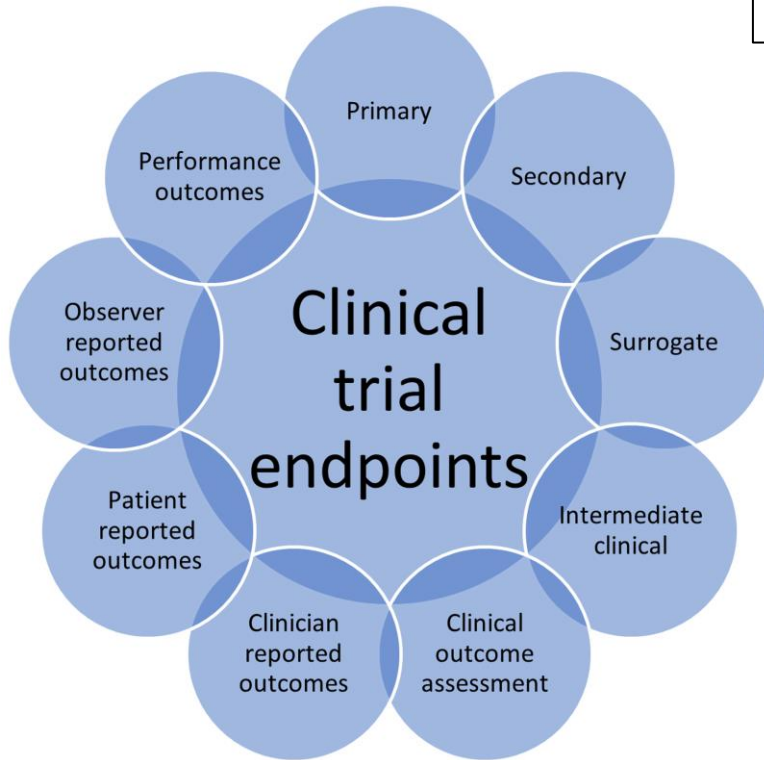


| | |
|--|---|
| Overall survival (OS) | How long people live after treatment |
| Disease free survival (DFS) | The time between treatment aimed at curing cancer, and signs that it has come back |
| Progression free survival (PFS) | The time between treatment aimed at shrinking or controlling cancer, and signs that it has started to grow again |
| Event free survival (EFS) | The time between treatment and having a specific 'event' such as a symptom, type of pain or a fracture, for example |
| Median overall survival | The time from treatment to the point at which half of the patients are living |

Research Question, Objectives, and Endpoints in Clinical and Oncological Research: A Comprehensive Review

Addanki Purna singh • Praveen R. Shahapur • Sabitha Vadakedath • Vallab Ganesh Bharadwaj • Dr Pranay Kumar • Venkata BharatKumar Pinnelli • Vikram Godishala • Venkataramana Kandi ✉

Published: September 25, 2022 DOI: 10.7759/cureus.29575



Objectives in clinical research

Research question

The primary endpoints assess the major research question, secondary endpoints may assess alternative research questions

Hypothesis testing

Intention to treat and per-protocol analysis

Patient-reported outcome measures (PROMs)

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Endpoints in clinical research

The endpoints in clinical research determine whether the clinical trial has been successful in finding out if an intervention/drug has proven beneficial in improving the survival and quality of life of the patient. The endpoints determine the validity of the clinical trial results. There are different types of endpoints like primary endpoints, secondary endpoints, tertiary endpoints, surrogate endpoints (laboratory measurements, physical signs), and others

Endpoints in oncology clinical trials

Cancer clinical trials assume increased significance because the drugs developed against the cancer are intended to increase the survival of the patients. Also, anti-cancer agents are associated with several side effects. Therefore, oncology trials include several endpoints, the primary being the overall survival, and the secondary endpoints include the assessment of other outcomes that indicate the quality of life (QoL), tumor-related endpoints, and others. The disadvantages of oncology clinical trials are the cost associated with the recruitment of a greater number of subjects and long-time follow-up of the patients [32].



surrogate endpoints (laboratory measurements, physical signs),

Tempo desde a randomização ou início do tratamento até a ocorrência de progressão da doença ou morte.

- Endpoint primário mais comum em ensaios clínicos oncológicos
- Desenvolvido para:
 - Fase 2: categorizar os resultados de novos tratamentos contra o câncer
 - Fase 3: facilitar o avanço de terapias promissoras para ensaios de fase 3.

Vários vieses:

- Não mede sobrevida global, qualidade de vida, retorno às atividades do dia a dia
- Medidas arbitrárias
- (acrescento: em doenças indolentes, não está relacionado ao início do novo tratamento!!!)

“Não se destina a informar a prática clínica ou a estabelecer se uma nova terapia proporciona benefícios clinicamente significativos para os pacientes”

“(...)Pode influenciar a prática clínica e as escolhas dos pacientes. Propomos (...)

INTERVALO LIVRE DE PROGRESSÃO”

Research Question, Objectives, and Endpoints in Clinical and Oncological Research: A Comprehensive Review

Cureus

Part of **SPRINGER NATURE**

Published: September 25, 2022

DOI: 10.7759/cureus.29575

Addanki Purna singh • Praveen R. Shahapur • Sabitha Vadakedath • Vallab Ganesh Bharadwaj • Dr Pranay Kumar • Venkata BharatKumar Pinnelli • Vikram Godishala • Venkataramana Kandi

| Endpoint | Applications | Functions | Drawbacks | | | | | | | | | | | | | | | | | | | | |
|--------------------------------|--|---|---|--|---|--|--|-----------------------------|---|---|--|---|--|---|-----------------------------------|--|---|--|------------------------|--|--|---|---|
| Overall survival | Gold standard primary oncological endpoint | Assesses time from randomization to death, clinical benefit, easily measurable, gives definite results, and eliminates researcher bias | Not effective in slowly progressing diseases, requires quite a high patient number, influenced by cross-over, subsequent therapies, and non-cancer deaths | | | | | | | | | | | | | | | | | | | | |
| Duration of clinical benefit | Primary endpoint | Assesses time from randomization to disease progression or death in patients who achieve a complete response, partial response, or stable disease for 24 weeks or longer | Needs disease-specific validation | | | | | | | | | | | | | | | | | | | | |
| Complete response | A primary endpoint that can also be used as a surrogate endpoint | Assesses time from randomization to survival advantage associated with improved overall survival and prolonged event-free survival | Needs disease-specific validation | | | | | | | | | | | | | | | | | | | | |
| Time to treatment failure | A primary endpoint when used in conjunction with secondary endpoints | Assesses time to treatment failure | <table border="1"> <tr> <td>Disease-free survival</td> <td>A surrogate marker for regular and accelerated approval</td> <td>Assesses time from randomization until evidence of disease recurrence, and requires limited patient number and short follow-up</td> <td>It cannot be statistically validated as a surrogate marker for survival, not definitely measurable, and definitions may differ between studies</td> </tr> <tr> <td>Objective response rate</td> <td>A surrogate marker for regular and accelerated approval</td> <td>Assesses how a specific treatment impacts tumor burden in a patient with a history of solid tumors, needs to be evaluated in single-arm studies, much quicker evaluation as compared with survival studies, and requires much more limited patient number</td> <td>Benefits cannot be measured directly, and detailed measurement of drug activity is unavailable</td> </tr> <tr> <td>Duration of response</td> <td>Used as a surrogate marker</td> <td>Assesses time from randomization to disease progression or death in patients who achieve complete or partial response</td> <td>Needs disease-specific validation</td> </tr> </table> | Disease-free survival | A surrogate marker for regular and accelerated approval | Assesses time from randomization until evidence of disease recurrence, and requires limited patient number and short follow-up | It cannot be statistically validated as a surrogate marker for survival, not definitely measurable, and definitions may differ between studies | Objective response rate | A surrogate marker for regular and accelerated approval | Assesses how a specific treatment impacts tumor burden in a patient with a history of solid tumors, needs to be evaluated in single-arm studies, much quicker evaluation as compared with survival studies, and requires much more limited patient number | Benefits cannot be measured directly, and detailed measurement of drug activity is unavailable | Duration of response | Used as a surrogate marker | Assesses time from randomization to disease progression or death in patients who achieve complete or partial response | Needs disease-specific validation | | | | | | | | |
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| Duration of response | Used as a surrogate marker | Assesses time from randomization to disease progression or death in patients who achieve complete or partial response | Needs disease-specific validation | | | | | | | | | | | | | | | | | | | | |
| Health-related quality of life | Preferred as a secondary clinical endpoint | Assesses status over time | | | | | | | | | | | | | | | | | | | | | |
| Progression-free survival | A surrogate marker for regular and accelerated approval | Assesses of disease number, and evaluation crossover | | | | | | | | | | | | | | | | | | | | | |
| | | Pathological complete response | <table border="1"> <tr> <td>Milestone survival</td> <td>Preferred as a marker</td> <td>Used as a surrogate endpoint/qualitative endpoint</td> <td>Assesses time from randomization to survival probability at a given time point</td> <td>Requires further validation</td> </tr> <tr> <td>Time to progression</td> <td>Clinical benefit</td> <td>Preferred as a surrogate and not a primary endpoint</td> <td>Assesses time from randomization to first evidence of disease progression and effectiveness of targeted therapy</td> <td>Can be adversely affected by patients' disease characteristics</td> </tr> <tr> <td>Event free survival</td> <td>Clinical benefit</td> <td>Preferred as a surrogate and as an alternative to the primary endpoint</td> <td>Assesses time from randomization to disease progression, discontinuation of the treatment, and/or death</td> <td>It needs to be validated for each unique disease/tumor type, treatment, and stage of disease</td> </tr> <tr> <td>Time to next treatment</td> <td></td> <td>Preferred as a surrogate endpoint for incurable diseases</td> <td>Follows up the treatment response until the initiation of next-line therapy</td> <td>Requires validations for specific disease</td> </tr> </table> | Milestone survival | Preferred as a marker | Used as a surrogate endpoint/qualitative endpoint | Assesses time from randomization to survival probability at a given time point | Requires further validation | Time to progression | Clinical benefit | Preferred as a surrogate and not a primary endpoint | Assesses time from randomization to first evidence of disease progression and effectiveness of targeted therapy | Can be adversely affected by patients' disease characteristics | Event free survival | Clinical benefit | Preferred as a surrogate and as an alternative to the primary endpoint | Assesses time from randomization to disease progression, discontinuation of the treatment, and/or death | It needs to be validated for each unique disease/tumor type, treatment, and stage of disease | Time to next treatment | | Preferred as a surrogate endpoint for incurable diseases | Follows up the treatment response until the initiation of next-line therapy | Requires validations for specific disease |
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| Time to next treatment | | Preferred as a surrogate endpoint for incurable diseases | Follows up the treatment response until the initiation of next-line therapy | Requires validations for specific disease | | | | | | | | | | | | | | | | | | | |

Research Question, Objectives, and Endpoints in Clinical and Oncological Research: A Comprehensive Review

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| Duration of clinical benefit | Primary endpoint | Assesses time from randomization to disease progression or death in patients who achieve a complete response, partial response, or stable disease for 24 weeks or longer | Needs disease-specific validation |
| Complete response | | | |
| Endpoint | Applications | Functions | Drawbacks |
| Time to treatment failure | A primary endpoint when used in conjunction with secondary endpoints | Assesses survival from the initiation of chemotherapy intervention to its approval | Assesses how a specific treatment impacts tumor burden in a patient with a history of solid tumors, needs to be evaluated in single-arm studies, much quicker evaluation as compared with survival studies, and requires much more limited patient number |
| Health-related quality of life | Preferred as a secondary clinical endpoint | Assesses patient's quality of life, can directly influence the patient's benefit | Assesses time from randomization to disease progression or death in patients who achieve complete or partial response, independent with a high risk of bias, definitions may differ between studies, and the time definitions may differ between studies |
| Progression-free survival | A surrogate marker for regular and accelerated approval | Assesses duration of response until the first evidence of disease progression or death, requires a limited patient number, short follow-up period, objective and quantitative, cost-effective, and not influenced by crossover | Assesses time from randomization to survival probability at a given time point |
| Pathological complete response | Preferred as a marker | Milestone survival | Assesses time from randomization to complete response, especially in breast cancer tissue and regional lymph nodes |
| Disease control rate | Clinical benefit for survival | Time to progression | Assesses time from randomization to disease progression and effectiveness of targeted therapy |
| Clinical benefit rate | Clinical benefit for survival | Event free survival | Assesses time from randomization to disease progression, discontinuation of the treatment, and/or death |
| Time to next treatment | Preferred as a surrogate endpoint for incurable diseases | | Follows up the treatment response until the initiation of next-line therapy |

QUAIS OS PRINCIPAIS OBJETIVOS

NO TRATAMENTO NA LLC:

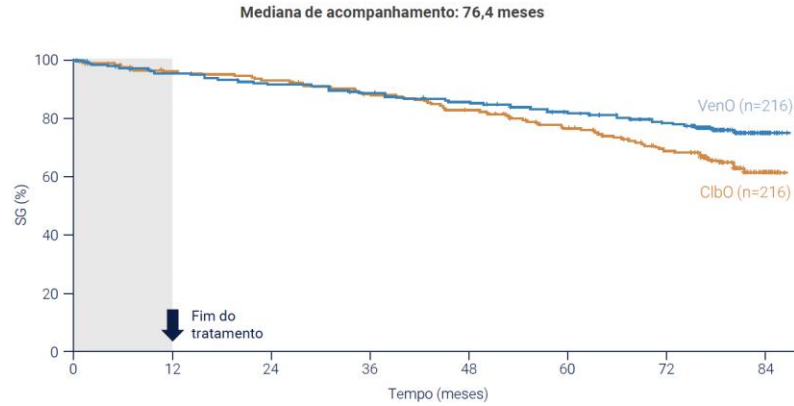
DRM, PFS, TEMPO PARA O PRÓXIMO TRATAMENTO OU A CURA?

SOBREVIDA GLOBAL

Com aproximadamente 6 anos de acompanhamento,
dados para SG permanecem imaturos

Sobrevida global

CLL14 – EHA 2023



ACOMPANHAMENTO DE 6 ANOS

SG mediana

VenO: NA vs ClbO: NA

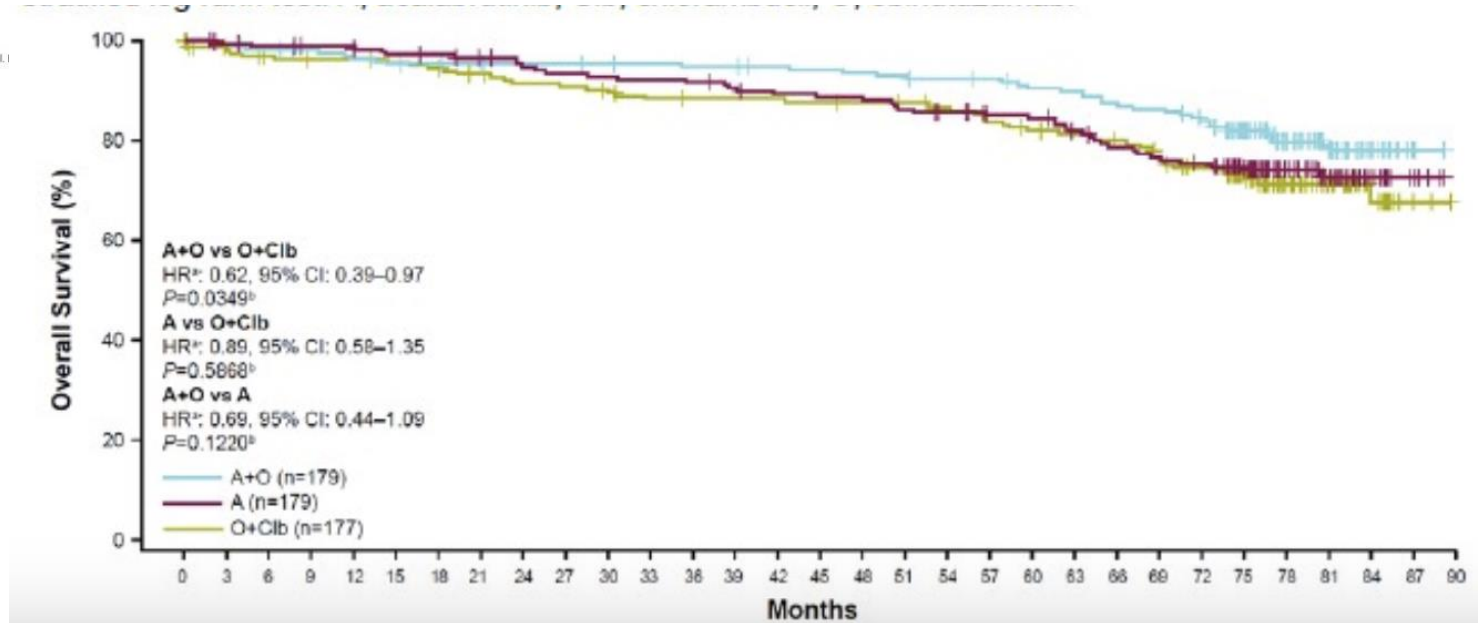
Taxa SG - 6 anos

VenO: 78,7% vs ClbO: 69,2%

HR de 0,69, IC 95% [0,48-1,01]
p=0,052*

*Descritivo: ClbO: clorambucil + obinutuzumabe; HR: hazard ratio; IC: intervalo de confiança; NA: não atingida; SG: sobrevida global; VenO: VENCLEXTA® (venetoclax) + obinutuzumabe. 1. Al-Sawaf O, et al.

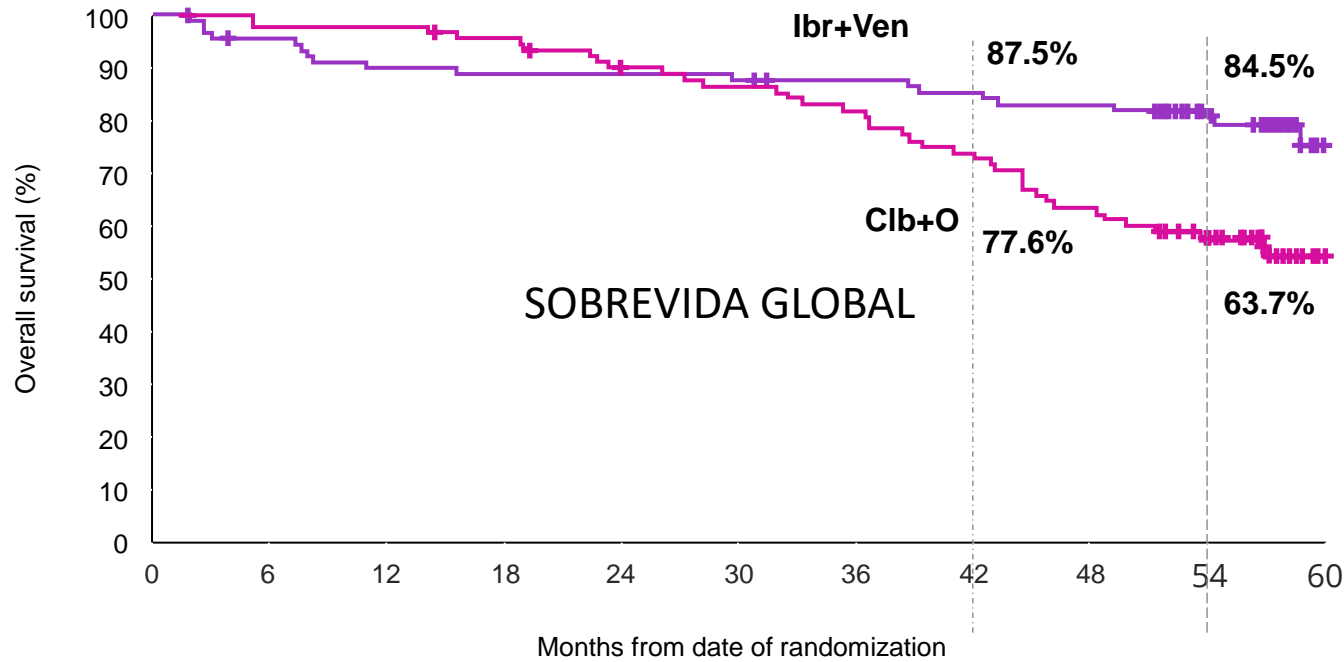
ELEVATE-TN – ASH 2023



SOBREVIDA GLOBAL

GLOW – ASH 2023

Overall Survival (ITT)



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
 - HR 0.453 (95% CI, 0.261–0.785);
p = 0.0038
- Estimated 54-month OS rates:
 - **84.5%** for patients treated with Ibr+Ven
 - **63.7%** for patients treated with Clb+O

| Patients at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 | 60 |
|------------------|-----|-----|-----|-----|----|----|----|----|----|----|----|
| Ibr+Ven | 106 | 100 | 95 | 94 | 94 | 93 | 91 | 89 | 87 | 74 | 19 |
| Clb+O | 105 | 103 | 103 | 100 | 93 | 90 | 86 | 79 | 70 | 57 | 17 |

p value is nominal.

CI, confidence interval; Clb, chlorambucil; HR, hazard ratio; Ibr, ibrutinib; ITT, intent-to-treat; O, Obinutuzumab; OS, overall survival; Ven, venetoclax.
Moreno C, et al. ASH 2023. Abstract #634.

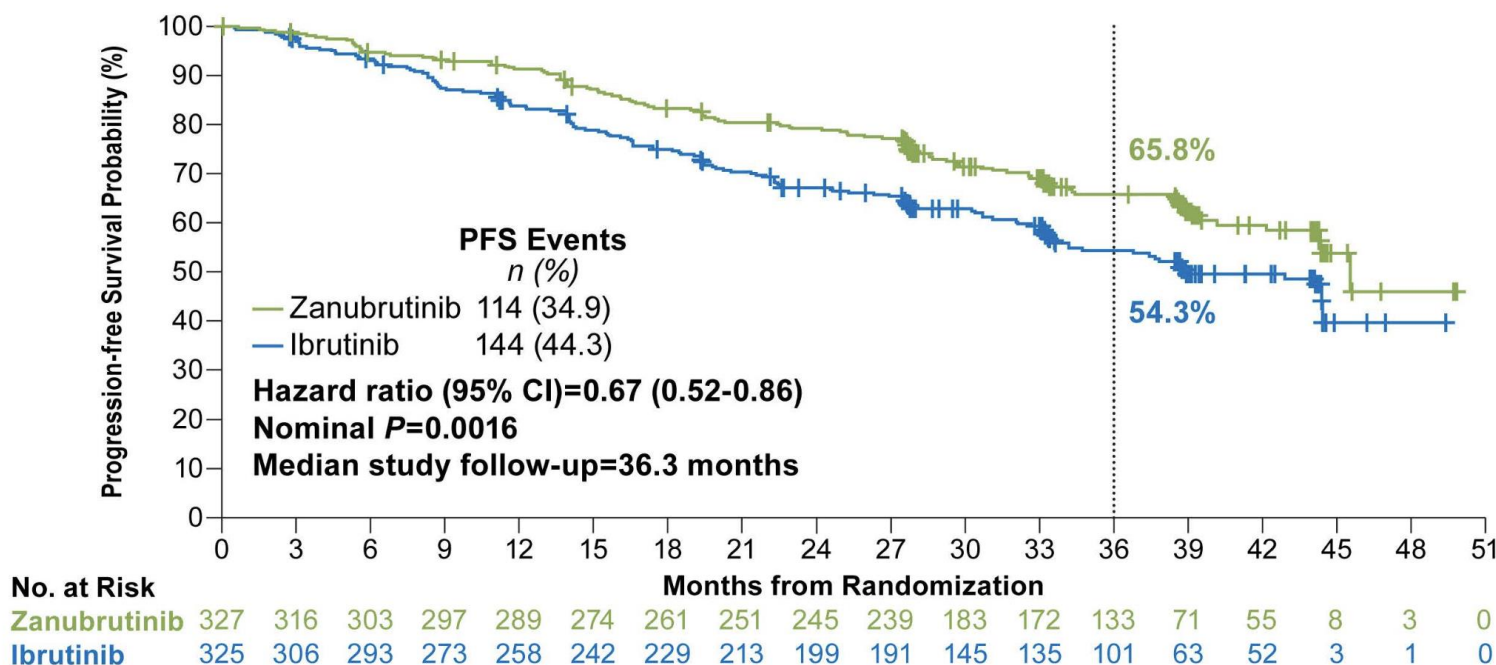
202 Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Jennifer R. Brown, MD, PhD¹, Barbara F. Eichhorst, MD et al.

SEGUIMENTO: 3 anos

• ALPINE– ASH 2023

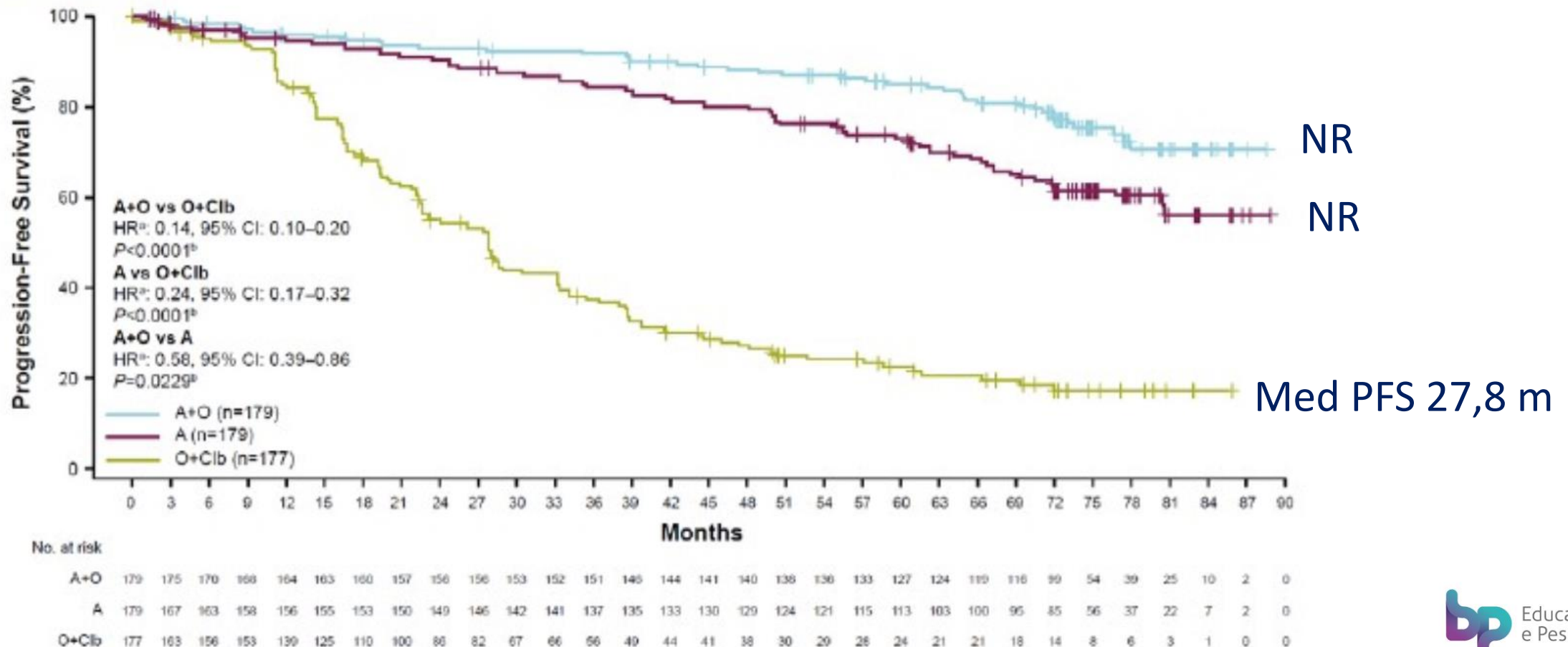
Figure 1. Investigator-Assessed Progression-Free Survival (ITT Population)



• ELEVATE-TN – ASH 2023

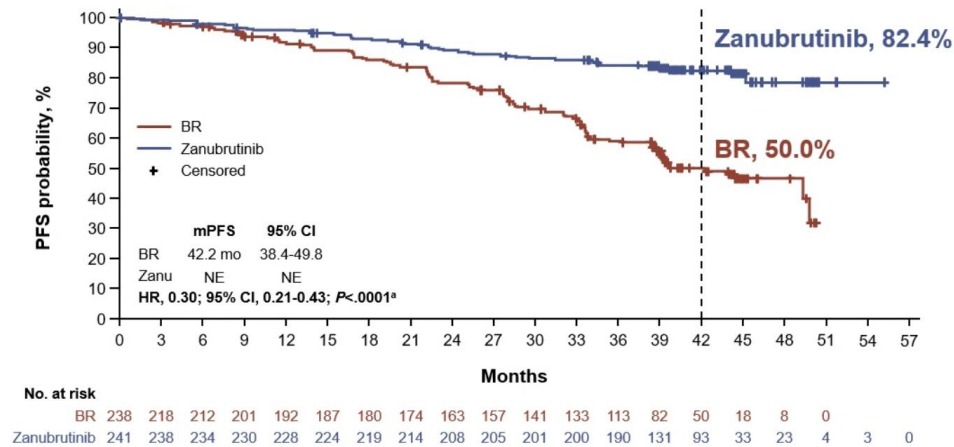
636 Acalabrutinib ± Obinutuzumab Vs Obinutuzumab + Chlorambucil in Treatment-Naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of Elevate-TN

Jeff P. Sharman et al.



Cohort 1: PFS in Patients Without del(17p)

Median follow-up: 43.7 months

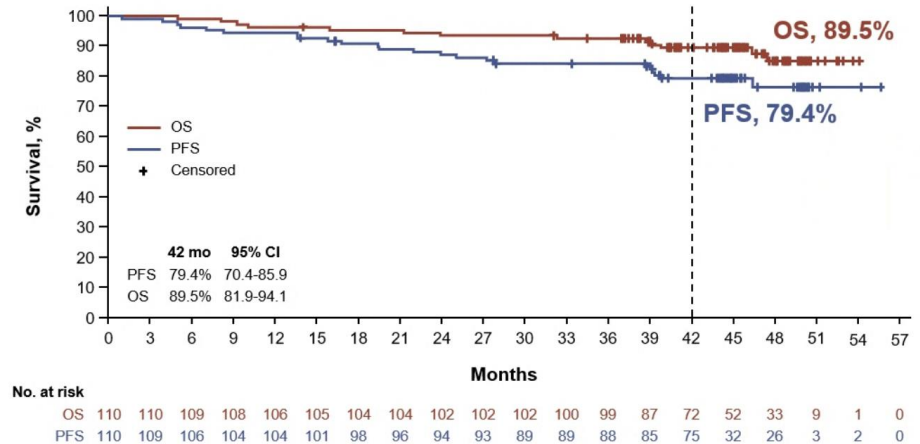


BR, bendamustine plus rituximab; CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; zanu, zanubrutinib.
^a Descriptive P value.

Shadman et al ICML 2023

Cohort 2: PFS and OS in Patients With del(17p)

Median follow-up: 47.9 months

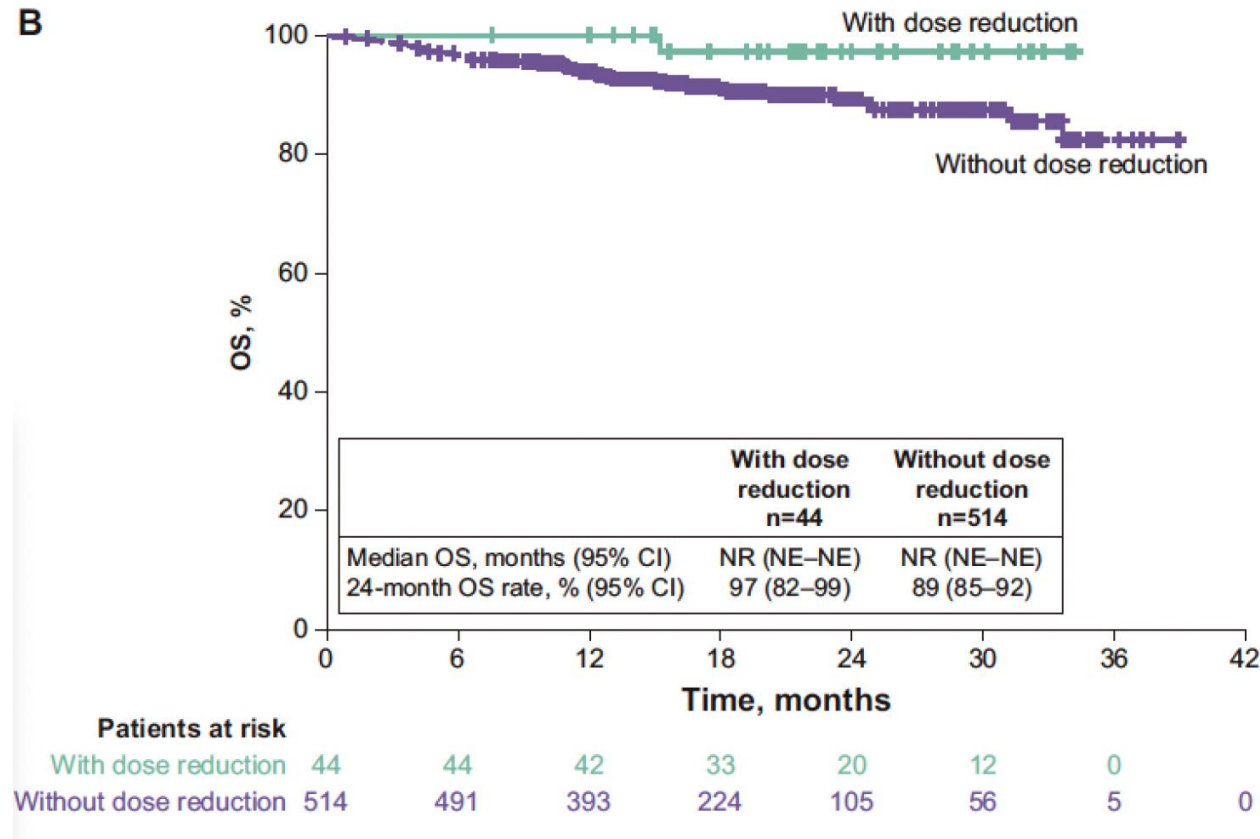


CI, confidence interval; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; del(17p), deletion in chromosome 17p; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Shadman et al IMCL 2023

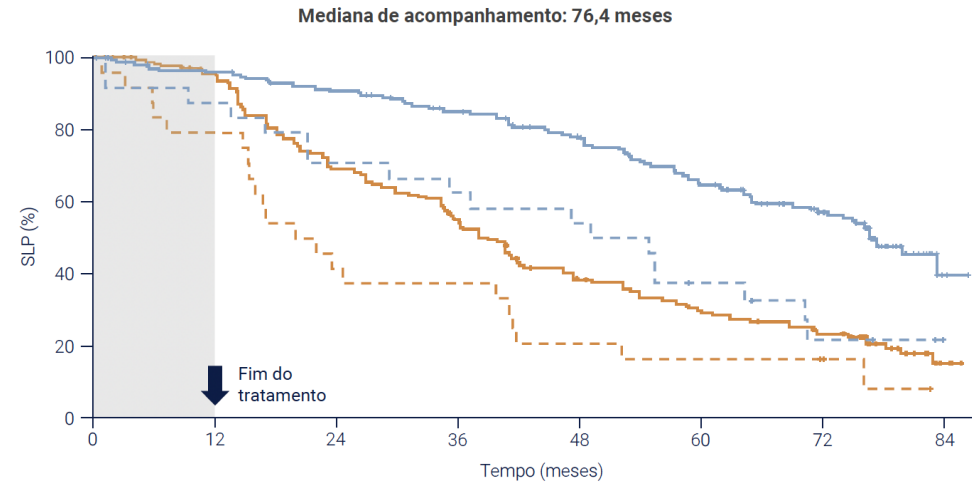
SITUAÇÕES EM QUE PFS É ANALISADA DE OUTRAS FORMAS

Ibrutinib Dose Modifications for Management of Cardiac Adverse Events in Patients With B-Cell Malignancies: Pooled Analysis of 10 Clinical Trials
 EHA 2023. Deborah M. Stephens et al. Poster 644



EHA 2023 – CLL14

Sobrevida livre de progressão - status de TP53 e/ou del(17p)



ACOMPANHAMENTO DE 6 ANOS

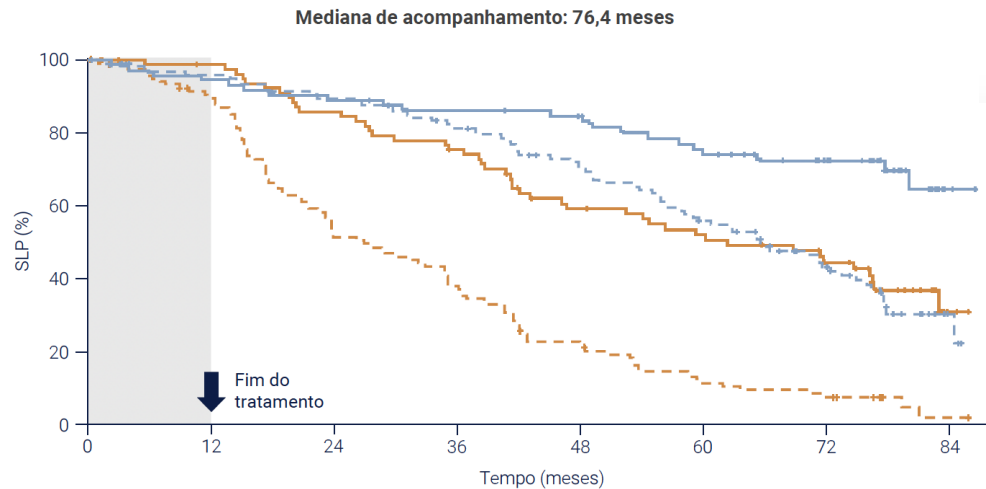
SLPm - TP53^{mut} e/ou del(17p)

VenO: 51,9 m vs ClbO: 20,8 m

SLPm - sem TP53^{mut} ou del(17p)

VenO: 76,6 m vs ClbO: 38,9 m

Sobrevida livre de progressão - status IGHV



— VenO, sem TP53^{mut} ou del(17p) - - - VenO TP53^{mut} e/ou del(17p) — ClbO, sem TP53^{mut} ou del(17p) - - - ClbO TP53^{mut} e/ou del(17p)

ClbO: clorambucil + obinutuzumabe; del: deleção; mut: mutação; NA: não atingida; SLP: sobrevida livre de progressão; VenO: VENCLEXTA® (venetoclax) + obinutuzumabe. 1. Al-Sawaf O, et al. EHA 2023. Resumo S145 (Oral).

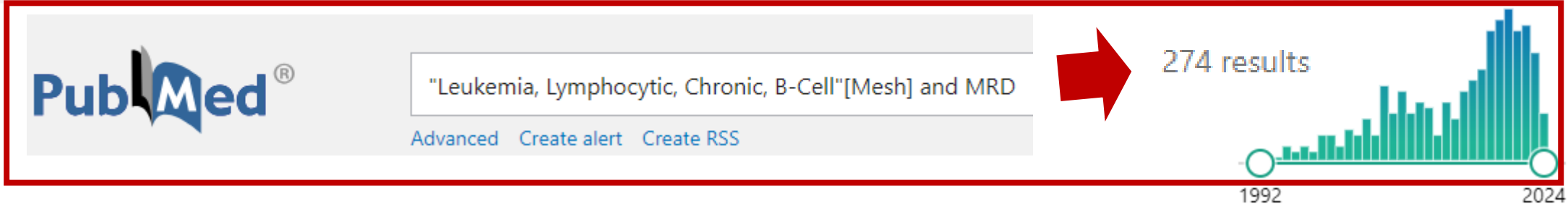
SLPm - IGHV mutado

VenO: NA vs ClbO: 62,2 m

SLPm - IGHV não mutado

VenO: 64,8 m vs ClbO: 26,9 m

— Ven-Obi e IGHV mutado - - - Ven-Obi e IGHV não mutado — Clb-Obi e IGHV mutado - - - Clb-Obi e IGHV não mutado



BRIEF REPORT | DECEMBER 15, 2016

BRIEF REPORT | DECEMBER 15, 2016

Minimal residual disease is an independent predictor for 10-year survival in CLL

[Clinical Trials & Observations](#) [Brief Report](#)

Marwan Kwok, Andy C. Rawstron, Abraham Varghese, Paul A. S. Evans, Sheila J. M. O'Connor, Chi Doughty, Darren J. Newton, Paul Moreton, Peter Hillmen



The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2024;390:326-337

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease

Munir T et al. DOI: 10.1056/NEJMoa2310063

PubMed®

"Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh] and MRD

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274 results

1992 2024

[Front Oncol.](#) 2023; 13: 1112616.

PMCID: PMC9971803

Published online 2023 Feb 14. doi: [10.3389/fonc.2023.1112616](https://doi.org/10.3389/fonc.2023.1112616)

PMID: [36865804](https://pubmed.ncbi.nlm.nih.gov/36865804/)

Measurable residual disease in chronic lymphocytic leukemia

[Giulia Benintende](#),^{1,*} [Federico Pozzo](#),² [Idanna Innocenti](#),³ [Francesco Autore](#),³ [Alberto Fresa](#),³ [Giovanni D'Arena](#),⁴ [Valter Gattei](#),² and [Luca Laurenti](#)¹

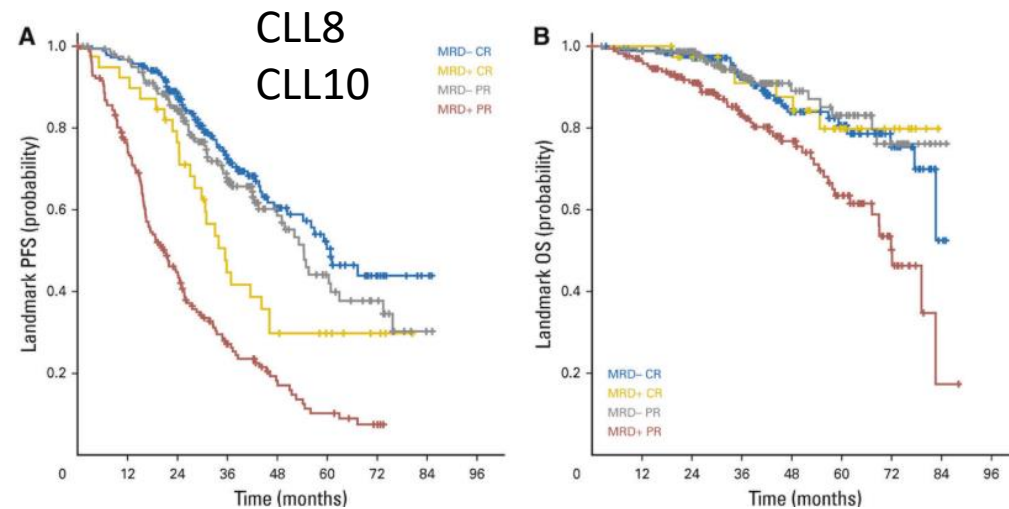
Leukemia (2021) 35:3059–3072

<https://doi.org/10.1038/s41375-021-01241-1>

Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations

William G. Wierda¹ · Andrew Rawstron² · Florence Cymbalista³ · Xavier Badoux⁴ · Davide Rossi⁵ · Jennifer R. Brown⁶ · Alexander Egle⁷ · Virginia Abello⁸ · Eduardo Cervera Ceballos⁹ · Yair Herishanu¹⁰ · Stephen P. Mulligan¹¹ · Carsten U. Niemann¹² · Colin P. Diong¹³ · Teoman Soysal¹⁴ · Ritsuro Suzuki¹⁵ · Hoa T. T. Tran¹⁶ · Shang-Ju Wu¹⁷ · Carolyn Owen¹⁸ · Stephan Stilgenbauer¹⁹ · Paolo Ghia²⁰ · Peter Hillmen²¹

- Altamente sensível
- Células patológicas residuais
- Desfecho substituto : SLP e SG



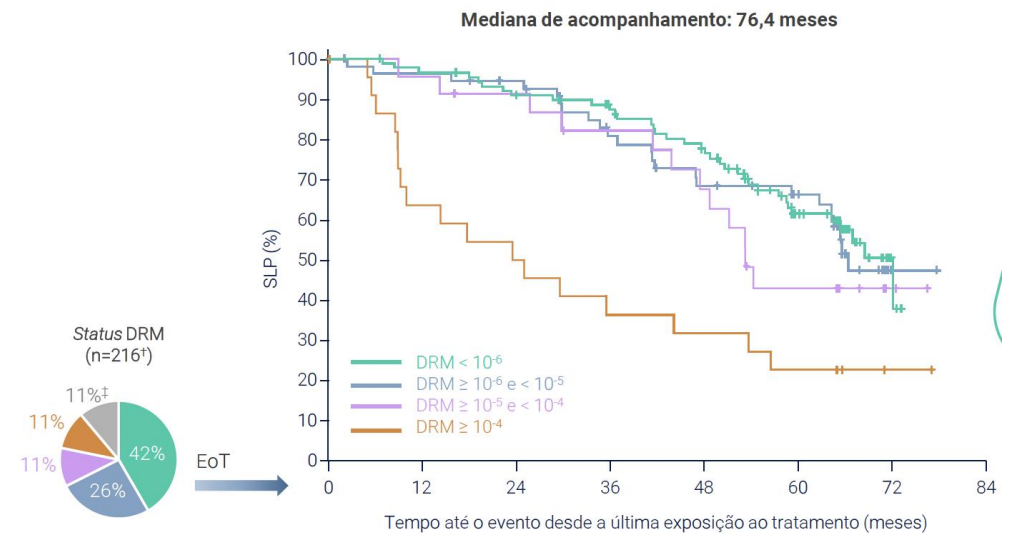
Acta Haematologica 2024, Vol. 147, No. 1

| Study name | Timing, compartment | Method |
|-------------------|---------------------|---------|
| MURANO [51] | EOCT, PB | ASO-PCR |
| | EOT, PB | ASO-PCR |
| CLARITY [55] | At 14 mo, PB | FLC |
| CLL14 [52] | 3 mo post-EOT, PB | ASO-PCR |
| GLOW [56] | 3 mo post-EOT, PB | NGS |
| CAPTIVATE FD [57] | 3 mo post-EOT, PB | FLC |
| NCT02756897 [58] | 24 mo, BM | FLC |
| CLL13 [59] | 3 mo post-EOT, PB | FLC |

EHA 2023 – CLL14

SLP após VenO de acordo com o *status* de DRM

Avaliação de DRM por NGS em sangue periférico no final do tratamento com VenO



[†]População com intenção de tratar. As porcentagens podem não ser iguais a 100% devido ao arredondamento; [‡]Ausente. DRM: doença residual mínima; DRM: doença residual última geração; SLP: sobrevida livre de progressão; VenO: VENCLEXTA® (venetoclax) + obinutuzumabe. 1. Al-Sawaf O, et al. EHA 2023. Resumo S145 (Oral).

[Front Oncol.](#) 2023; 13: 1112616.

Published online 2023 Feb 14. doi: [10.3389/fonc.2023.1112616](https://doi.org/10.3389/fonc.2023.1112616)

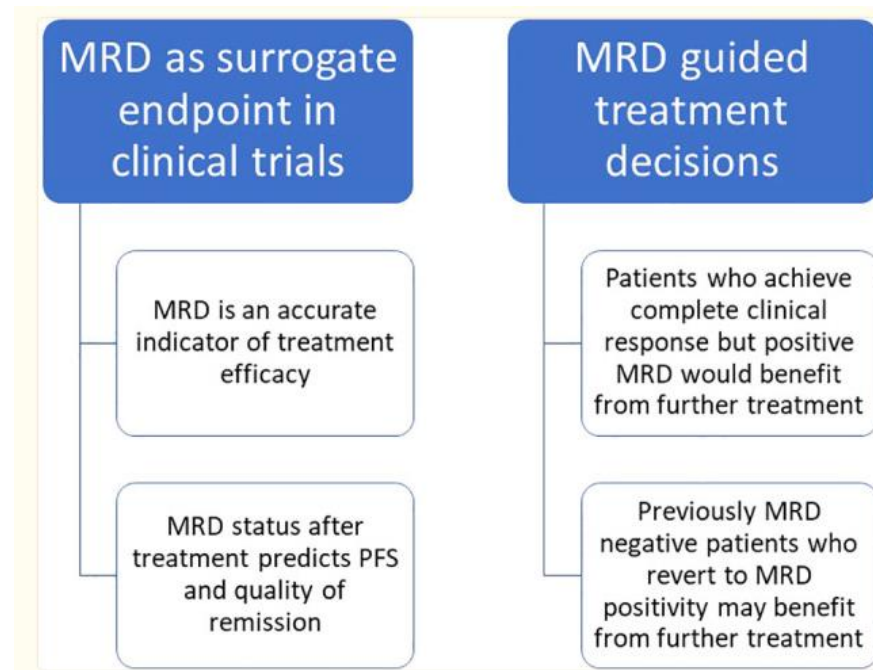
PMCID: PMC9971803

PMID: [36865804](https://pubmed.ncbi.nlm.nih.gov/36865804/)

Measurable residual disease in chronic lymphocytic leukemia

[Giulia Benintende](#),¹ * [Federico Pozzo](#),² [Idanna Innocenti](#),³ [Francesco Autore](#),³ [Alberto Fresa](#),³ [Giovanni D'Arena](#),⁴
[Valter Gattei](#),² and [Luca Laurenti](#)¹

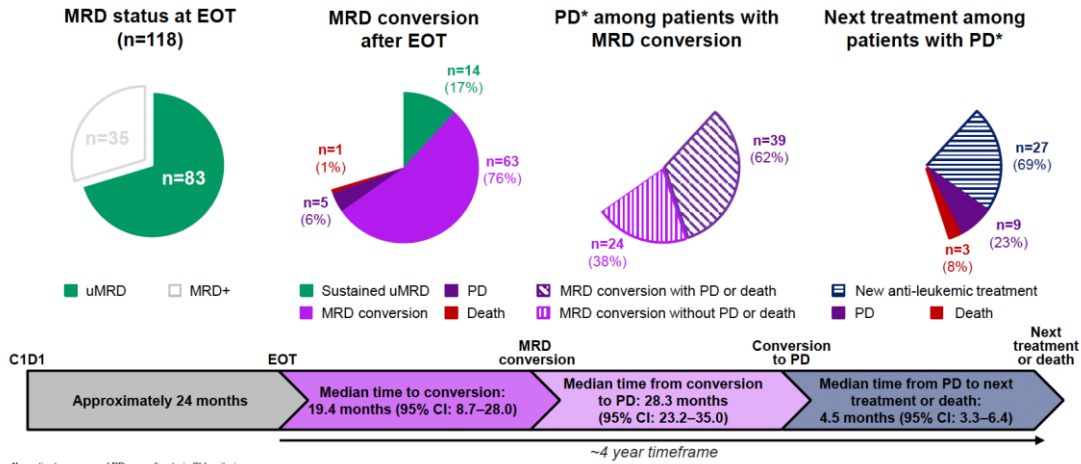
IwCLL e ERIC:
<1 célula / 10.000 leucócitos



ALCANÇAR DRM E MANTÊ-LA!

1. Seymour JF, et al. Blood 2022;140(8):839–50.

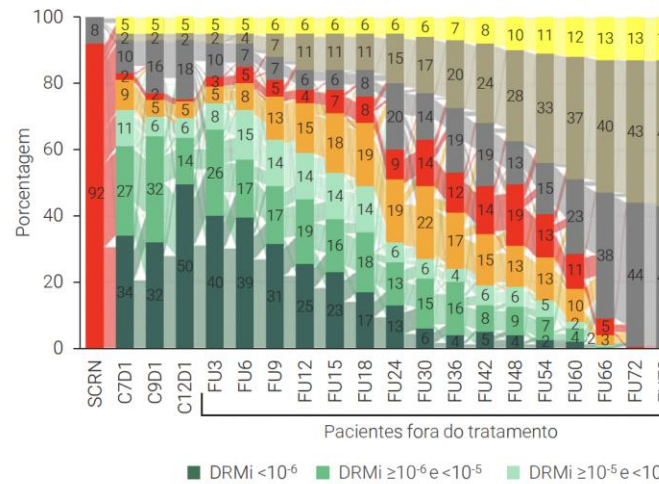
Most patients who received the full 2 years of VenR treatment had uMRD at EOT; generally MRD conversion with subsequent PD did not occur until ~4 years post EOT



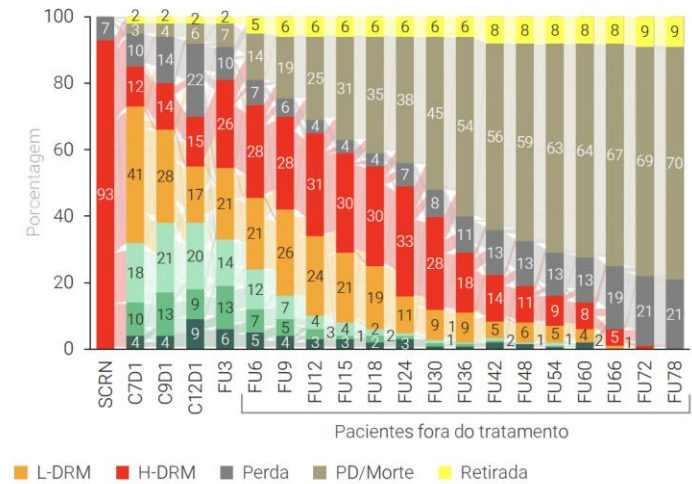
EHA 2023 – CLL14

Cinco anos após o término do tratamento, as respostas profundas foram mantidas com VenO

VenO: Taxas de DRMi ao longo do tempo por NGS (n=216)



C1b0: Taxas de DRMi ao longo do tempo por NGS (n=216)



5 anos após o tratamento, 7,9% dos pacientes mantiveram DRMi <math><10^{-4}</math> com VenO versus 1,9% dos pacientes com C1b0

C1b0: clorambucil + obinutuzumabe; DRM: doença residual mínima; DRMi: doença residual mínima indetectável; H-DRM: alta DRM; L-DRM: baixa DRM; NGS: sequenciamento de última geração; PD: progressão da doença; VenO: VENCLEXTA® (venetoclax) + obinutuzumabe. 1. Al-Sawaf O, et al. EHA 2023. Resumo S145 (Oral).

MRD-directed therapy in CLL: ready for prime time?

Joanna M. Rhodes ✉, Carlos A. Lopez, Jacqueline C. Barrientos



Hematology Am Soc Hematol Educ Program (2023) 2023 (1): 413–420.

Current Experience with Measurable Residual Disease (MRD) in CLL

Prognostic for PFS and time to next treatment with some fixed-duration regimens

PFS correlated with U-MRD Rate:
 CLL14 (VO vs CO)
 CAPTIVATE (IV → IV VS I)
 CLL13 (CIT → VR vs VO vs VOI)
 MURANO (VR vs BR)
 TRANSCEND (CAR-T)

PFS Benefit Irrespective of U-MRD:
 GLOW (IV vs CO)
 ELEVATE-TN (A vs AO vs CO)
 E1912 (IR vs FCR)

Currently, no evidence that MRD-guided approach should be used outside of clinical trials

Key Questions to be Answered for "Prime Time" use of MRD in CLL

Timing for testing? Ideal compartment to test? Method for Testing?

Which MRD endpoints to target to guide treatment duration?

Which patients benefit most from MRD-adapted treatment?

Factors Confounding "Ideal" U-MRD Target

Time after Treatment

Testing too early or with too insensitive a method might underestimate utility of U-MRD to predict PFS

Some continuous regimens (e.g. FLAIR) can take longer to achieve UMRD

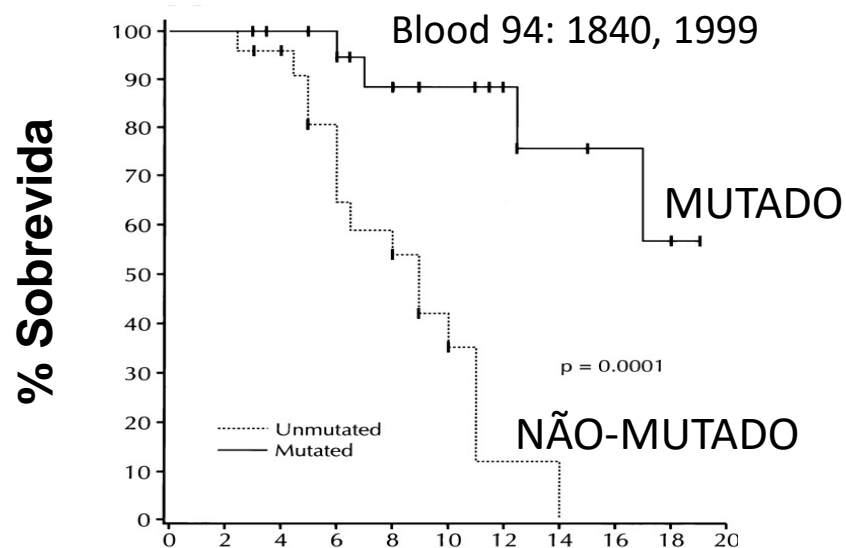
Currently, no evidence that MRD-guided approach should be used outside of clinical trials

MRD: Measurable Disease; CLL: Chronic Lymphocytic Leukemia; PFS: Progression-Free Survival; VO: venetoclax + obinutuzumab; CO: chlorambucil + obinutuzumab; IV: Ibrutinib + Venetoclax; I: Ibrutinib; CIT: Chemoimmunotherapy; VR: Venetoclax + Rituximab; VOI: venetoclax + obinutuzumab + ibrutinib; BR: Bendamustine + rituximab; CART: Chimeric antigen receptor T-cell Therapy; CR: Complete Remission; U-MRD: undetectable MRD; A: acalabrutinib; AO: acalabrutinib + obinutuzumab; IGHV μ : IGHV unmutated

This image was created with Biorender

E A CURA??

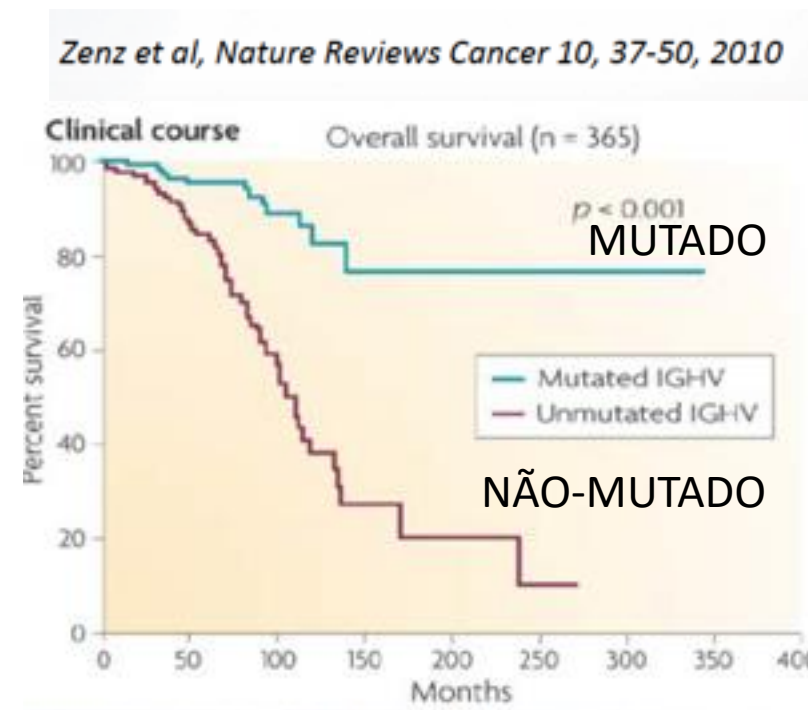
SOBREVIDA EM FCR



Anos após o diagnóstico

**MUTADO:
Sobrevida mediana >24 anos**

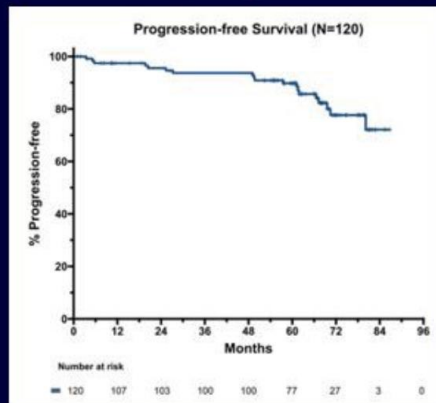
**NÃO MUTADO:
Sobrevida mediana:9 anos**



SOBREVIDA EM FCR X NOVOS TRATAMENTOS

I + V Regimen Comparisons, ASH 2023

MDACC, I+V 24 cycles

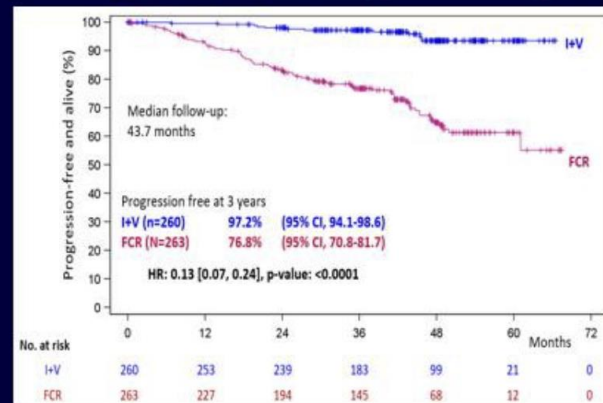


N=120
 Median age = 64.5 yrs
 IGHV-UM = 86%
 Del(17p) / TP53-m = 23%

5 yr PFS = 89.8%

Jain, ASH 2023

FLAIR, UK, I+V 2-6 years

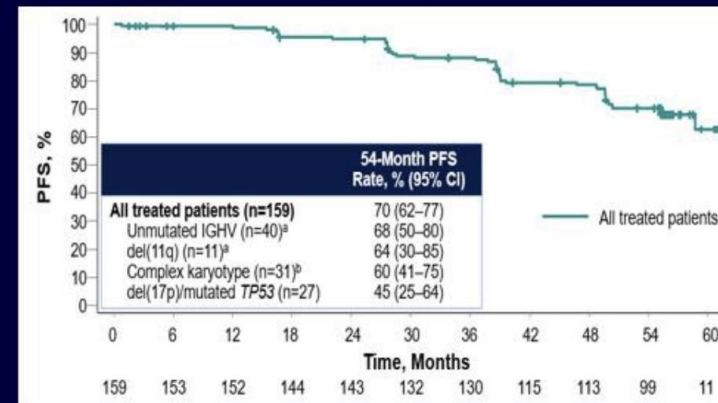


N=260
 Median age = 62 yrs
 IGHV-UM = 48%
 Del(17p) = excluded

3 yr PFS = 97.2%

Hillmen, ASH 2023

CAPTIVATE, I+V 12 cycles



N=159
 Median age = 60 yrs
 IGHV-UM = 56%
 Del(17p) / TP53-m = 17%

4.5 yr PFS = 70%

Ghia, ASH 2023

@NitinJainMD Jan 4, 2024



Hospital BP Paulista

OBRIGADA!

DANIELLE LEÃO

***Instagram: [danielleleao.hemato](https://www.instagram.com/danielleleao.hemato)**

LinkedIn: [linkedin.com/in/danielle-leao](https://www.linkedin.com/in/danielle-leao)

danileao10@gmail.com

OBRIGADA!

*Instagram: [danielleleao.hemato](https://www.instagram.com/danielleleao.hemato)

LinkedIn: [linkedin.com/in/danielle-leao](https://www.linkedin.com/in/danielle-leao)

danileao10@gmail.com



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