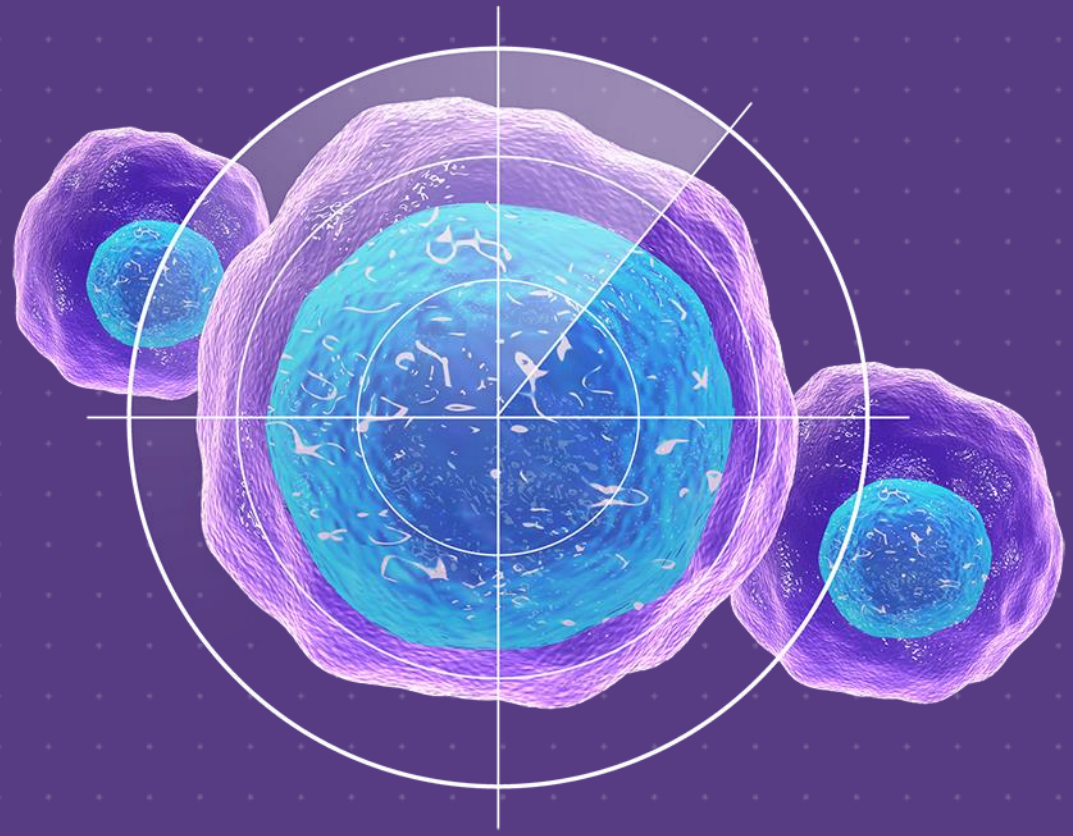
LymphomaHub

VIRTUAL SATELLITE SYMPOSIUM

How I treat relapsed/refractory disease – DLBCL and CLL

November 8, 2020



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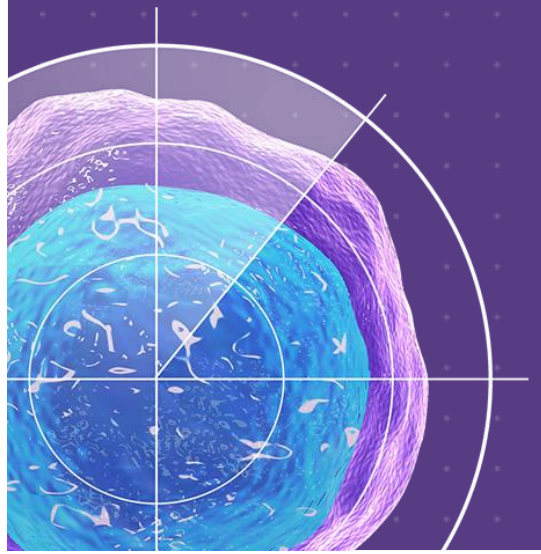
Case 2:
Management of R/R CLL — Latin American perspective

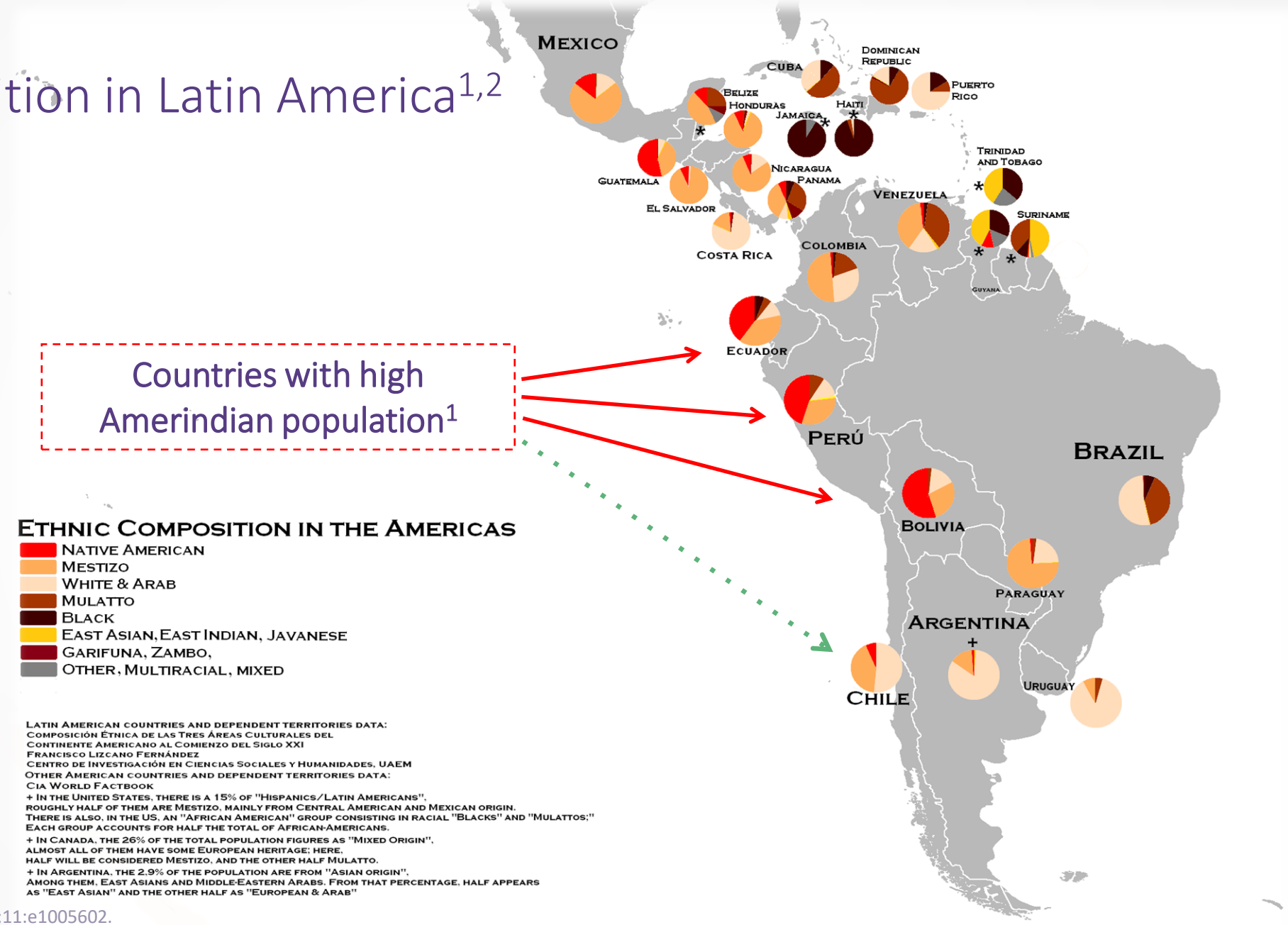
Doctor Astrid Pavlovsky

FUNDALEU

Buenos Aires, AR



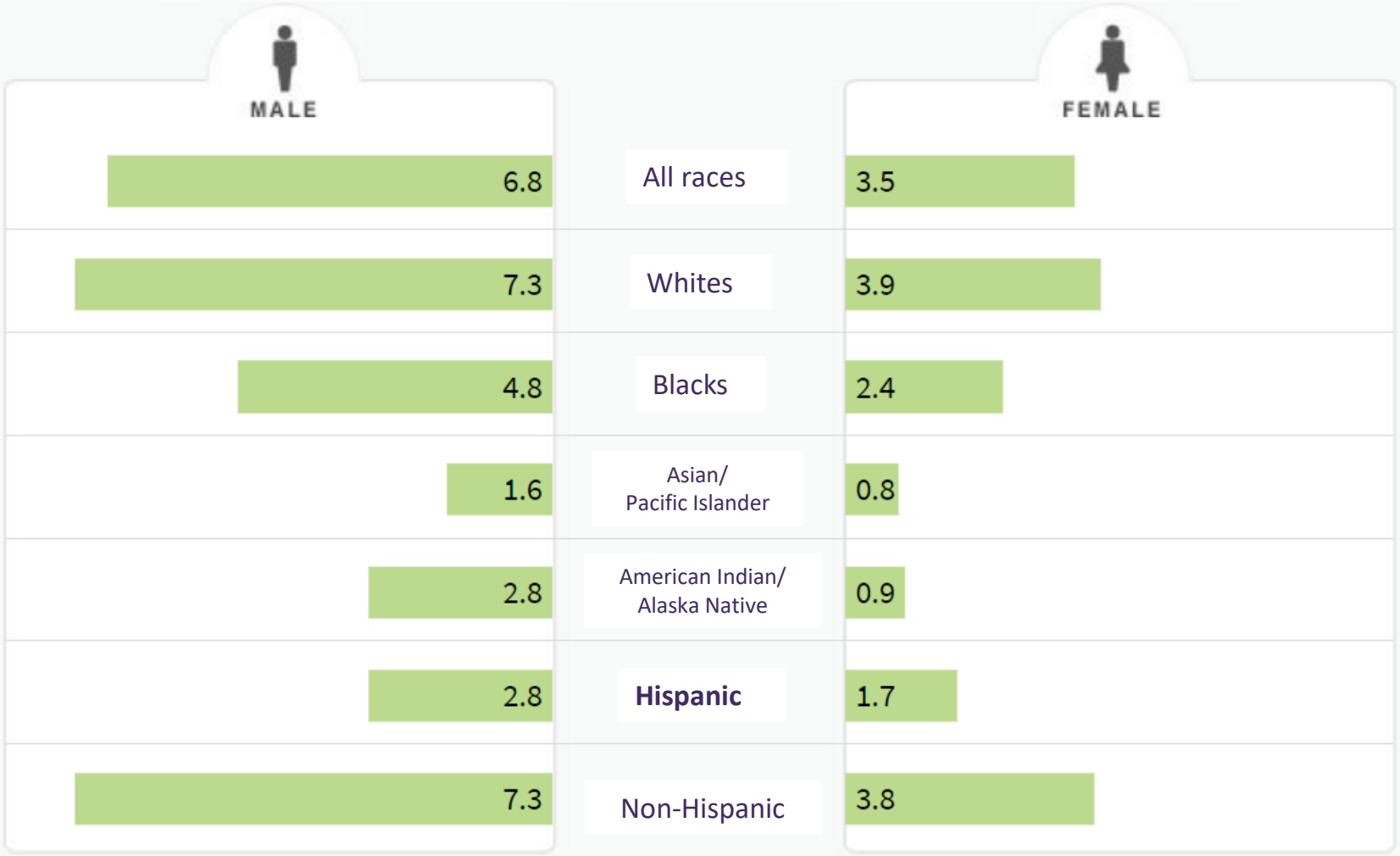
Ethnic composition in Latin America[1,2]



1. Homburger JR, *et al. PLoS Genet.* 2015;11:e1005602.

2. Ethnic composition of the Americas according to Lizcano and the CIA World Factbook. https://en.wikipedia.org/wiki/File:Ethnic_Composition_of_the_Americas.PNG (Accessed Oct 6, 2020).

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex Chronic Lymphocytic Leukemia (USA)[1]



1. Surveillance and Epidemiological, and End Results (SEER) 21 2013 – 2017, Age Adjusted. https://seer.cancer.gov/statfacts/html/clyl.html (Accessed Oct 5, 2020).

Distribution of common B-cell non-Hodgkin lymphoma types in Central and South America[1]*

	Argentina, %	Brazil %	Chile %	Guatemala %	Peru %	CSA total %	North America %
Diffuse large B cell lymphoma	25.9	40.6	38.9	45.1	50.6	40.0	29.2
Follicular lymphoma	34.1	19.8	25.4	10.4	11.6	20.4	33.8
Marginal zone B cell lymphoma, MALT	5.9	9.4	10.4	4.1	4.3	6.9	6.3
Mantle cell lymphoma	8.1	3.6	5.7	6.2	0.6	5.0	6.8
Chronic lymphocytic leukemia/ small lymphocytic lymphoma	**5.4**	**6.3**	**3.6**	**1.6**	**1.8**	**3.8**	**4.8**
Burkitt lymphoma	1.6	2.1	2.1	6.7	1.8	2.9	0.8
Marginal zone B cell lymphoma	4.3	2.1	1.6	2.1	3.0	2.6	1.8

1. Laurini JA, *et al. Blood.* 2012;120(24):4795-4801.
CSA, Central and South America; MALT, mucosa-associated lymphoid tissue.
*Proportions shown as a percentage of 1028 cases of B-cell and T-cell non-Hodgkin lymphoma

Prognostic test availability in South American public and private health systems[1]*

		del17p	*TP53* mut	IGVH
Argentina	Public	+/–	+/–	+/–
	Private	Yes	Yes	Yes
Brazil	Public	+/–	+/–	+/–
	Private	OPE/Pharma	OPE/Pharma	OPE/Pharma
Bolivia	Public	NO	NO	NO
	Private	NO	NO	NO
Chile	Public	+/–	+/–	+/–
	Private	Yes	Yes	Yes
Colombia	Public	Yes	Yes	NO
	Private	Yes	Yes	NO

		del17p	*TP53* mut	IGVH
Ecuador†	Public	NO	NO	NO
	Private	NO	NO	NO
Paraguay	Public	NO	NO	NO
	Private	NO	NO	NO
Peru	Public	NO	Yes	Yes
	Private	NO	Yes	Yes
Uruguay	Public	Yes	+/–	Yes
	Private	Yes	+/–	Yes
Venezuela	Public	NO	NO	NO
	Private	NO	NO	NO

1. Latin American Group on CLL (LAG-CLL), 2019. Unpublished data.
del17p, 17p deletion; IGVH, immunoglobulin variable heavy-chain gene mutation; OPE/Pharma, out-of-pocket expense/pharma support; *TP53* mut, *TP53* mutation.
*Not all data is official; †Some tests are available in SOLCA, Guayaquil, EC.

Prognostic test availability in South American public and private health systems*

		del17p	*TP53* mut	IGVH
Argentina	Public	+/–	+/–	+/–
	Private	Yes	Yes	Yes
Brazil	Public	+/–	+/–	+/–
	Private	OPE/Pharma	OPE/Pharma	OPE/Pharma
Bolivia	Public	NO	NO	NO
	Private	NO	NO	NO
Chile	Public	+/–	+/–	+/–
	Private	Yes	Yes	Yes
Colombia	Public	Yes	Yes	NO
	Private	Yes	Yes	NO
Ecuador[†]	Public	NO	NO	NO
	Private	NO	NO	NO
Paraguay	Public	NO	NO	NO
	Private	NO	NO	NO
Peru	Public	NO	Yes	Yes
	Private	NO	Yes	Yes
Uruguay	Public	Yes	+/–	Yes
	Private	Yes	+/–	Yes
Venezuela	Public	NO	NO	NO
	Private	NO	NO	NO

1. Latin American Group on CLL (LAG-CLL), 2019. Unpublished data.
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*Not all data is official; [†]Some tests are available in SOLCA, Guayaquil, EC

No tests in almost 50% of countries

New Therapies for CLL in South America

Ibrutinib — Approval and availability in different countries[1]*

Countries	R/R CLL	1L CLL	Public health system	Private health system
Argentina	Approved	Approved	Yes	Yes
Brazil	Approved	Approved	NO	Yes (R/R del17p)
Bolivia	Approved	Approved	NO	NO
Chile	Approved	Approved	NO	Yes
Colombia	Approved	Case by case	Yes	Yes
Ecuador	Approved	Approved	NO	OPE
Paraguay	Approved	Approved	NO	Yes
Peru	Approved	Approved	Yes (3L)	Yes
Uruguay	Approved	del17p	Yes (1L del17p)	Yes (1L del17p)
Venezuela	No information	No information	NO	NO

1. Janssen Pharmaceutical Companies of Johnson & Johnson, personal communication, Sept 2020.

CLL, chronic lymphocytic leukemia; Del17p, 17p deletion; OPE, out-of-pocket expense; R/R, relapsed/refractory; 1L, first-line; 3L, third-line.

*Not all data is official.

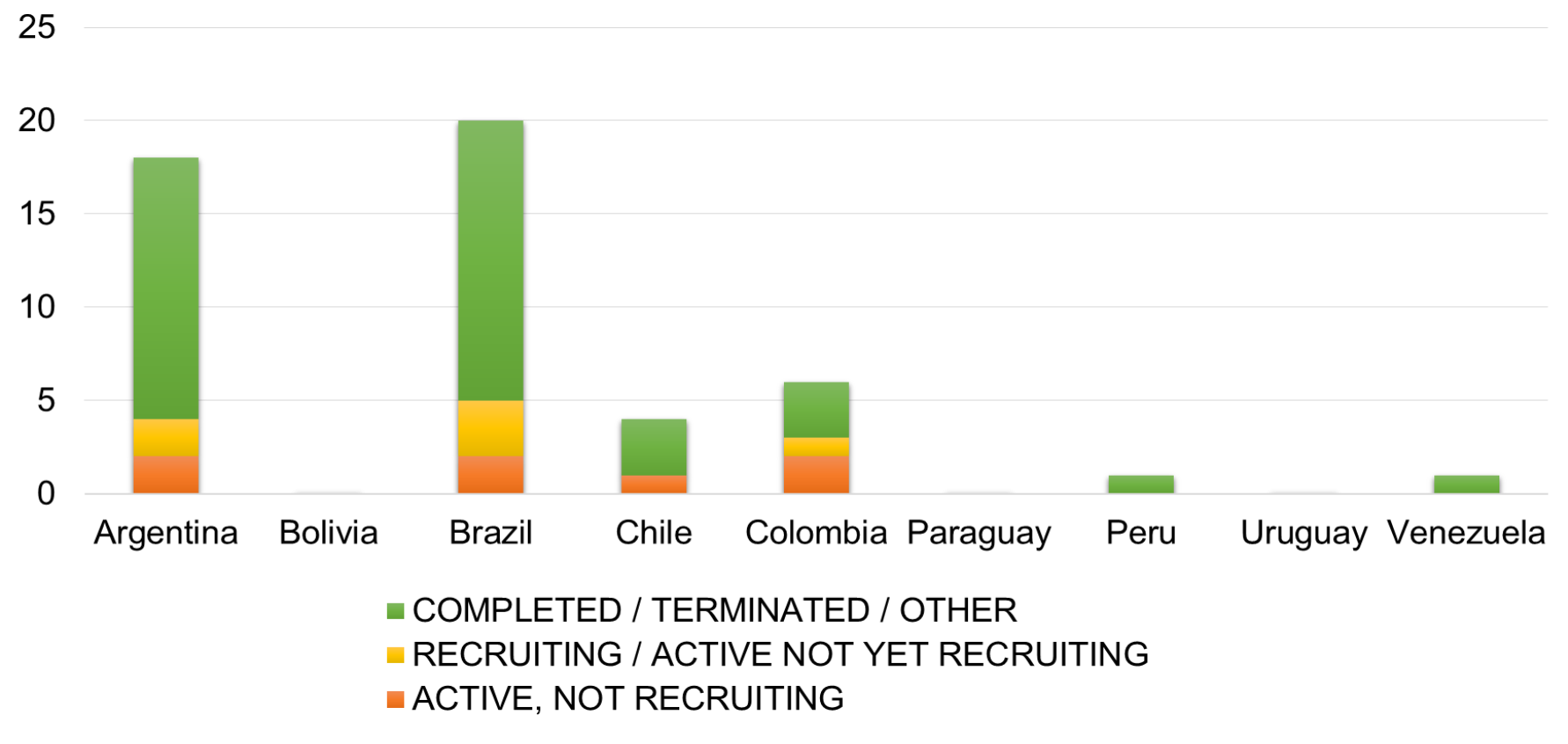
Venetoclax — Approval and availability in different countries[1]

Countries	R/R CLL	1L CLL	Public health system	Private health system
Argentina	Approved	Approved	Yes	Yes
Brazil	Approved	Approved	NO	Yes (R/R del17p)
Bolivia	NO	Approved	NO	NO
Chile	Approved	Approved	NO	Yes
Colombia	Approved	Case by case	Yes	Yes
Costa Rica	Approved	NO	NO	OPE
El Salvador	Approved	NO	NO	OPE
Ecuador	NO	Approved	NO	OPE
Paraguay	Approved	Approved	NO	Yes
Peru	Approved	Approved	Yes (3L)	Yes
Uruguay	Approved	del17p	Yes (1L del17p)	Yes (1L del17p)
Venezuela	No information	No information	NO	NO

1. AbbVie, personal communication, Sept 2020.

CLL, chronic lymphocytic leukemia; Del17p, 17p deletion; OPE, out-of-pocket expense; R/R, relapsed/refractory; 1L, first-line; 3L, third-line.

CLL clinical trials in South American countries[1]



1. Latin American Group on CLL (LAG-CLL), unpublished data, Sept 2019.

Regarding our case…

72-year old female, ECOG: 1, mild renal insufficiency unrelated to CLL progression (creatinine 1.6 mg/dL with creatinine clearance of 40 mL/min)

IGVH-mutated, FISH: trisomy 12, *TP53*-mutated

- First-line therapy: Bendamustine – Rituximab
- Second-line therapy: Venetoclax – Rituximab …Now progressing…

- THIS PATIENT WORRIES ME…

CLL, chronic lymphocytic leukemia; ECOG, Eastern Clinical Oncology Group; FISH, fluorescence *in situ* hybridization; IGVH, immunoglobulin variable heavy chain gene mutation.

Risk categories according to the revised high-risk CLL concept[1]

Refractoriness to:	TP53 abnormality present (del17p/*TP53* mut)	High-risk category
CIT only	**Yes**	**I – CIT-resistant** (BTKi- and BCL2i-sensitive)
CIT + BTKi or **CIT + BCL2i** or **BTKi + BCL2i** **(+/– CIT)**	**Yes or No**	**II – CIT- and PI- resistant** (BRKi- and/or BCL2i- refractory)

1. Dreger P, *et al. Blood.* 2018;132(9):892-902.

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; del17p, 17p deletion; PI, pathway inhibitor.

Results of venetoclax in R/R CLL with *TP53* abnormalities

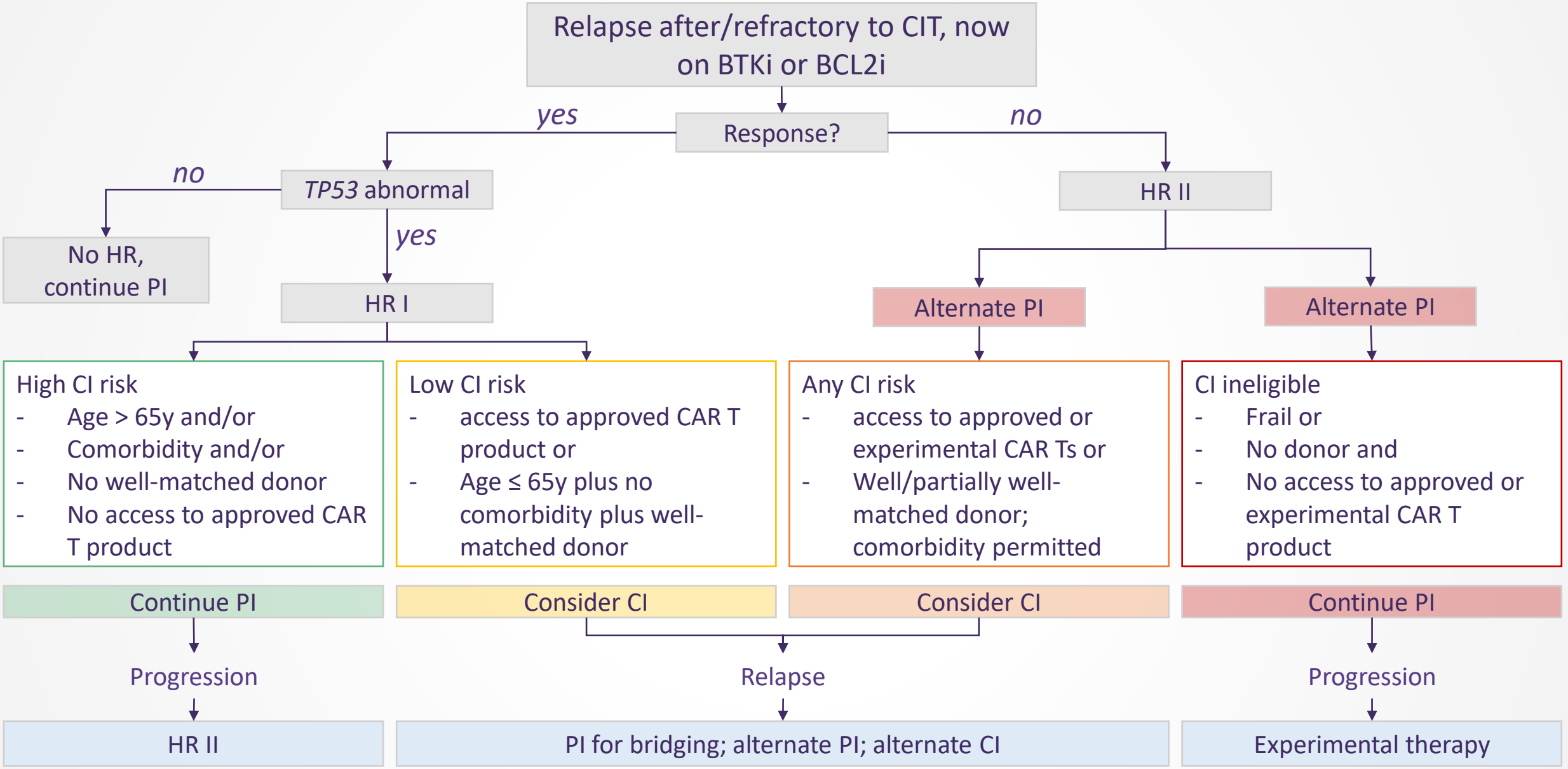
Study type	Aberration	n	ORR (CR/CRi) %	2-year DOR %	2-year PFS %	2-year OS %
Prospective[1]	del17p/ *TP53* mut	153	77 (20)	66	—	73
Pooled prospective[2]	del17p/ *TP53* mut	232	75 (19)*	56†	51	—

1. Stilgenbauer S, *et al. J Clin Oncol.* 2018;36(19):1973-1980; **2.** Roberts AW, *et al. Blood.* 2016;128(22):3230.
CLL, chronic lymphocytic leukemia; del17p, 17p deletion; *TP53* mut, *TP53* mutation; ORR, overall response rate; CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of response; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.
*Venetoclax alone or with rituximab, n = 211; †n = 175

Cellular immunotherapy is not an option for this patient

- Not a good candidate for allo-SCT (renal disease, 72 years old)
- Experimental CAR T-cells or clinical trials not available in most countries in Latin America

Allo-SCT, allogeneic stem cell transplant.

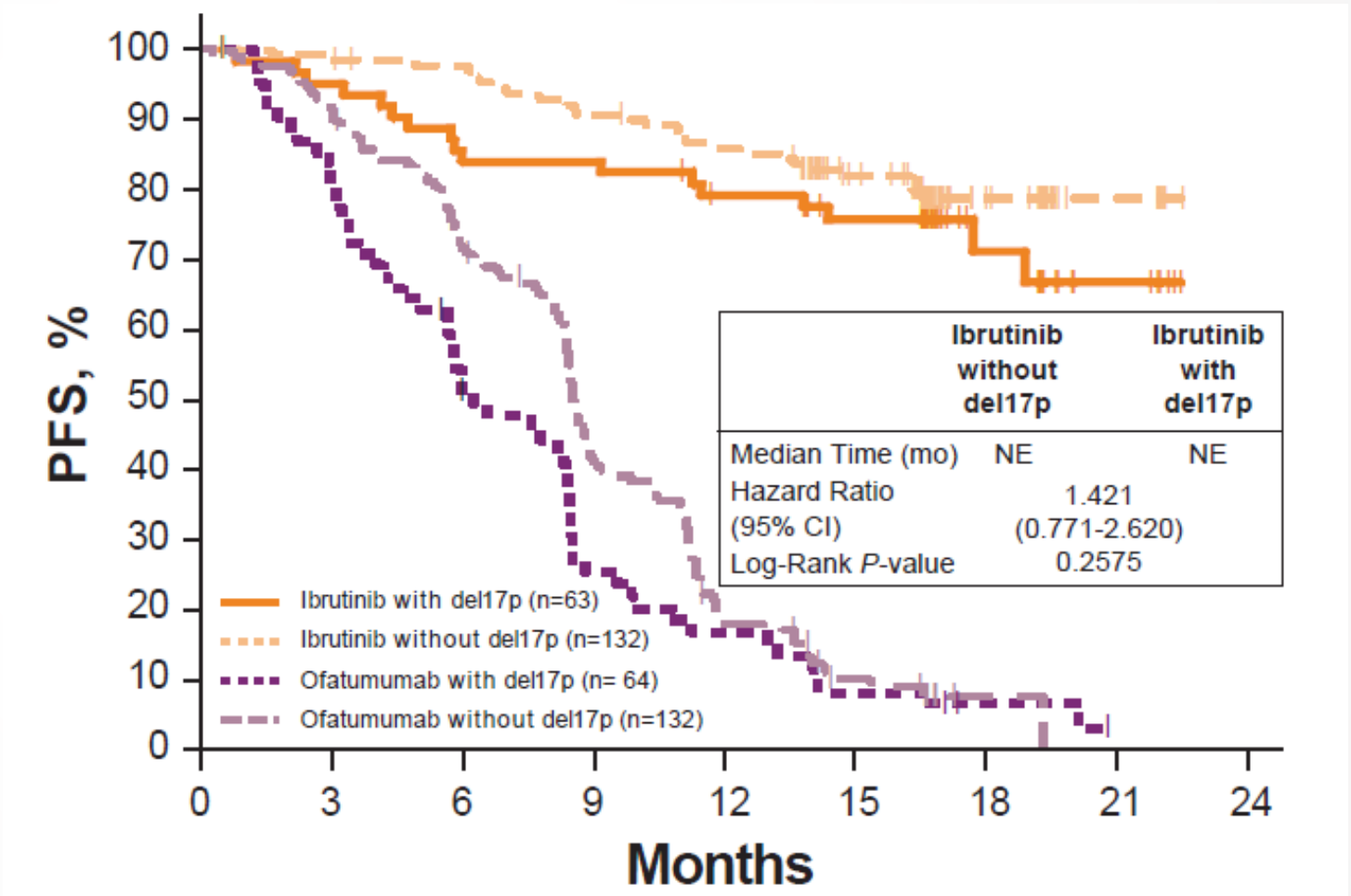


Adapted from Dreger P, *et al. Blood* 2018;132(9):892-902.

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CI, cellular immunotherapy; CIT, chemoimmunotherapy; HR, high-risk category; PI, pathway inhibitor; y, years.

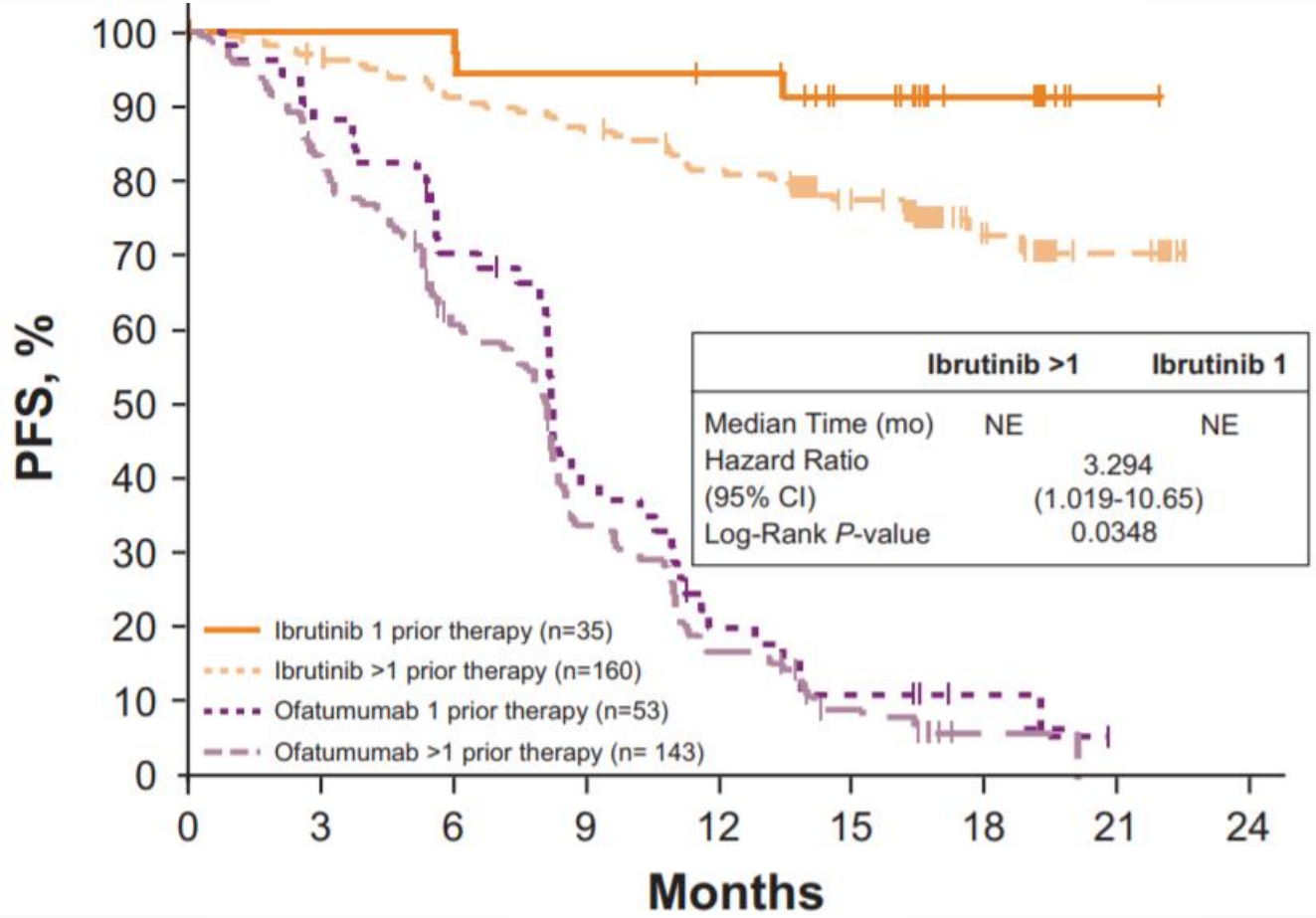
Ibrutinib in high-risk CLL

Deletion or mutation in *TP53* facilitates the development of mutations in *BTK* or *PLCG2* conferring resistance to ibrutinib[1,2]



1. Brown JR, *et al. Leukemia*. 2018;32(1):83-91; **2.** Woyach JA, *et al. J Clin Oncol*. 2017;35(13):1437-1443.

Ibrutinib in high-risk CLL[1]



1. Brown JR, *et al. Leukemia*. 2018;32(1):83-91.

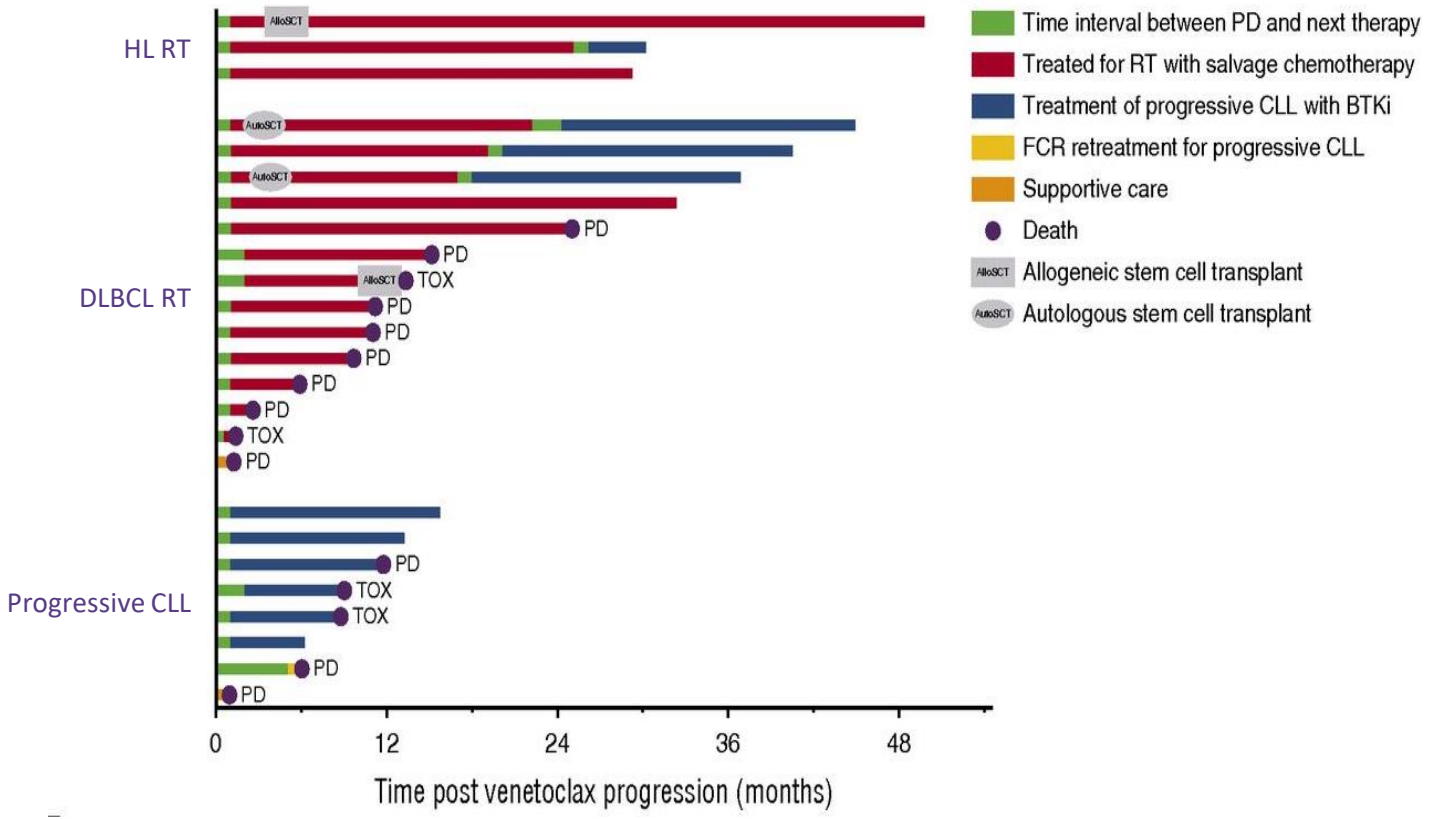
Results of ibrutinib in R/R CLL after venetoclax[1]

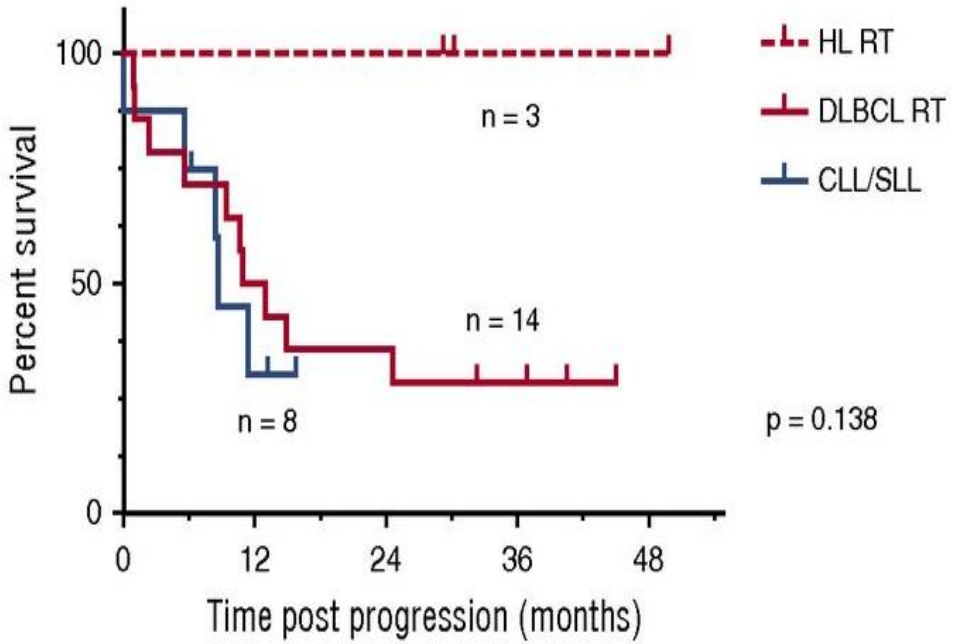
2nd PI	N	del17p, n (%)	Progression on therapy, n (%)	Type of progression (%)
Ibrutinib	67	27 (40)	25 (37)	Progressive CLL (32) Richter transformation (68)

1. Anderson MA, *et al. Blood.* 2017;129(25):3362-3370.

CLL, chronic lymphocytic leukemia; del17p, 17p deletion; PI, pathway inhibitor; R/R, relapsed/refractory.

Progression under venetoclax therapy[1]





1. Anderson MA, *et al. Blood.* 2017;129(25):3362-3370.

Pathway inhibitor treatment considerations for specific patient populations

Population	Ibrutinib	Idelalisib	Venetoclax
Elderly (≥ 65 years)	No dose adjustment required		
Renal impairment	Mild/moderate: no dose adjustment required		
	Severe (< 30 mL/min CrCl): • Treat if benefit outweighs risk • Monitor closely for toxicity	Severe (< 30 mL/min CrCl): • No dose adjustment required	< 80 mL/min CrCl: • Consider more intensive prophylaxis & closer monitoring Severe (< 30 mL/min CrCl): • Treat if benefit outweighs risk • Monitor closely for toxicity
Hepatic impairment	Mild: • recommended dose is 140 mg/day	Mild/moderate: • No dose adjustment but intensified monitoring of AEs recommended	
	Severe: • Not recommended	Severe: • Caution recommended	Severe: • Not recommended

IMBRUVICA SmPC Jun 2017. https://www.ema.europa.eu/en/documents/product-information/imbruvica-epar-product-information_en.pdf. Accessed Oct 7, 2020; Zydelig SmPC Dec 2016. https://www.ema.europa.eu/en/documents/product-information/zydelig-epar-product-information_en.pdf. Accessed Oct 7, 2020; Venclyxto SmPC May 2017. https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf. Accessed Oct 7, 2020.

AEs, adverse events; CrCl, creatinine clearance.

Other options …

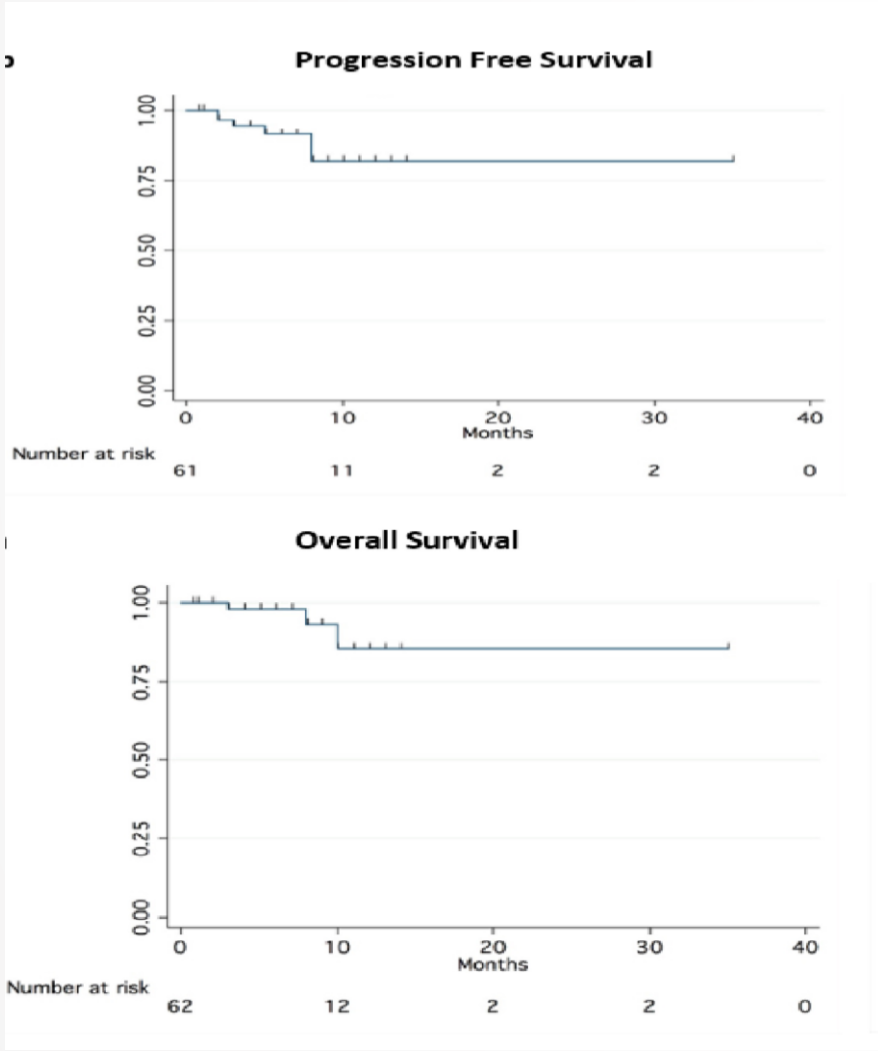
- Ibrutinib is a well established and potent treatment for CLL; however, **discontinuation due to intolerance** precludes a significant number of patients in clinical practice from long-term benefit of this targeted therapy

- Acalabrutinib inhibits BTK more selectively than ibrutinib, and while demonstrating impressive activity, may result in **significantly less off-target adverse events.**

  The pivotal trial included patients with creatinine clearance > 30 mL/min

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia.

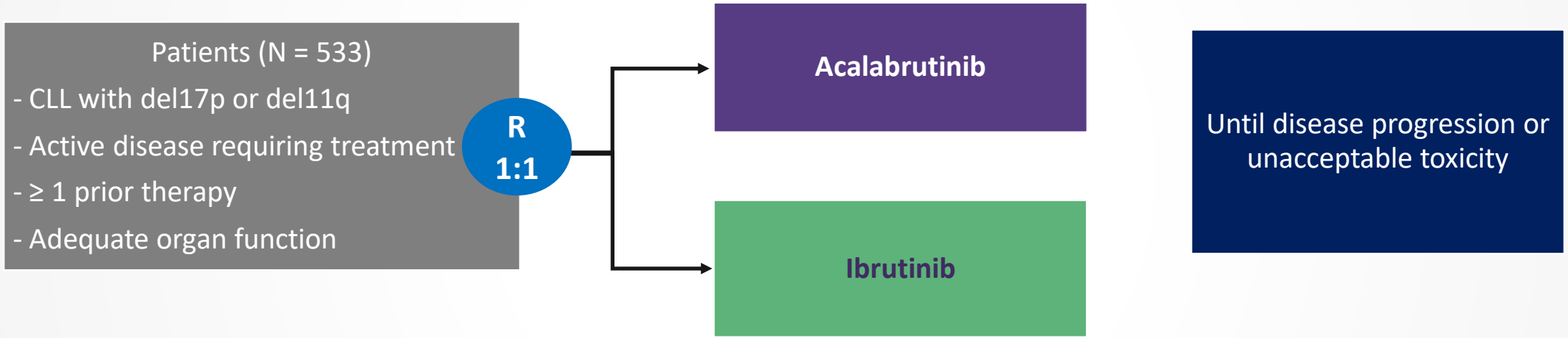
Acalabrutinib: A retrospective analysis of real-world patients[1]



Total number of patients	69	Number tested
Median age at receiving acalabrutinib (range)	70 (51–89)	69
Sex (%, n)	Female 41%, 28 Male 59%, 41	69
del17p (+)	22%, 13	59
del17p (+)	43%, 26	60
P53 mutation (+)	24%, 13	53
Complex karyotype (+)	31%, 17	54
IGVH mutated (%, n)	25%, 11	43

1. Yazdy S, *et al. Blood.* 2019;134(Supplement_1):4311.

Elevate CLL R/R
Acalabrutinib *vs* ibrutinib in previously treated high-risk CLL



Primary outcome: PFS (noninferiority)

Secondary outcomes: Grade ≥ 3 infections; Richter transformation; AF; OS

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477696. Updated Dec 5,2019. Accessed Oct 9, 2020.

AF, atrial fibrillation; CLL, chronic lymphocytic leukemia; OS, overall survival; PFS, progression-free survival, R/R, relapsed/refractory.

Other options…

Combination therapies:

- Most include venetoclax plus anti-CD20
- Other options not yet approved

Abbreviations

Regarding our case…

72 year-old female, ECOG: 1, mild renal insufficiency

IGVH-mutated, FISH: trisomy 12, *TP53*-mutated

- First-line therapy: Bendamustine – Rituximab
- Second-line therapy: Venetoclax – Rituximab …Now progressing…

- THIS PATIENT WORRIES ME…

- **I would suggest ibrutinib as third-line therapy**
- **Consider acalabrutinib if available**

Abbreviations

Second-line treatment algorithm for patients with CLL

Response to 1L therapy	Fitness	Therapy
Refractory or progress within 3 years	Go go	Change to one of the following options: Ibrutinib, idelalisib + R, venetoclax + rituximab, chemoimmunotherapy (FCR or BR), lenalidomide (+R), alemtuzumab + dexamethasone. Discuss consolidation with allogeneic SCT
	Slow go	Change to one of the following options: Ibrutinib, idelalisib + R, venetoclax + rituximab, alemtuzumab + dexamethasone, chemoimmunotherapy (chlorambucil + rituximab or obinutuzumab, BR, FCR-lite), lenalidomide (+R), high-dose rituximab
Progress after 3 years	All	Repetition of 1L therapy is possible

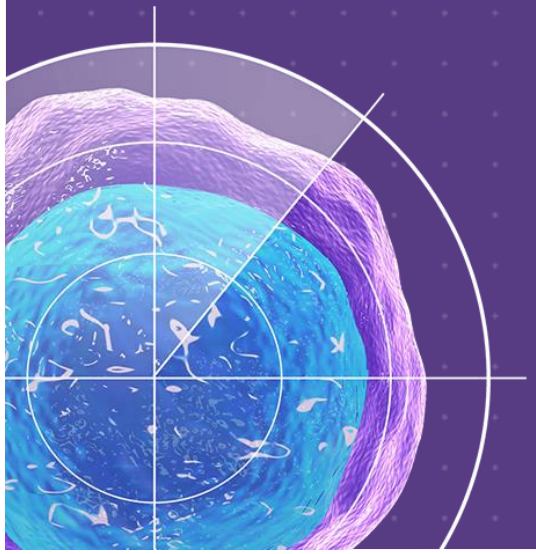
Adapted from Hallek M, *et al. Am J Hematol.* 2019;94(11):1266-1287.
BR, bendamustine + rituximab; FCR, fludarabine, cyclophosphamide, rituximab; R, rituximab; SCT, stem cell transplant; 1L, first-line.

Management of R/R CLL — Latin American perspective

Thank you for your attention!

LymphomaHub

Thank you



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