LYMPHOMA CANADA | LYMPHOME CANADA

ASH 2020 Update Lymphoma

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Disclosures

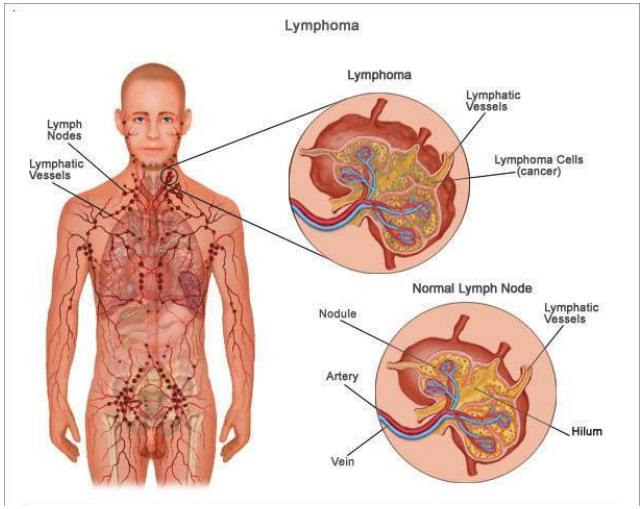
- Ad Boards: Janssen, AbbVie, Amgen, Celgene

Objectives

- To briefly review the current standard of care in:
  - Chronic Lymphocytic Leukemia
  - Indolent Non-Hodgkin's Lymphoma
  - Diffuse Large B cell Lymphoma
- To highlight ASH 2020 updates
- To appreciate future changes in clinical practice

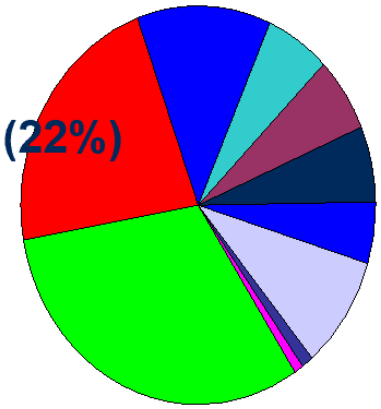
What is Lymphoma?

- Cancers that develop from the immune system
  - Lymphoid tissue, spleen, bone marrow
  - Cells that make Immunoglobulins
- Can exist in the “Leukemic Phase”
  - Chronic Lymphocytic Leukemia



Dr. Michele Berman

Frequency of NHL Subtypes in Adults

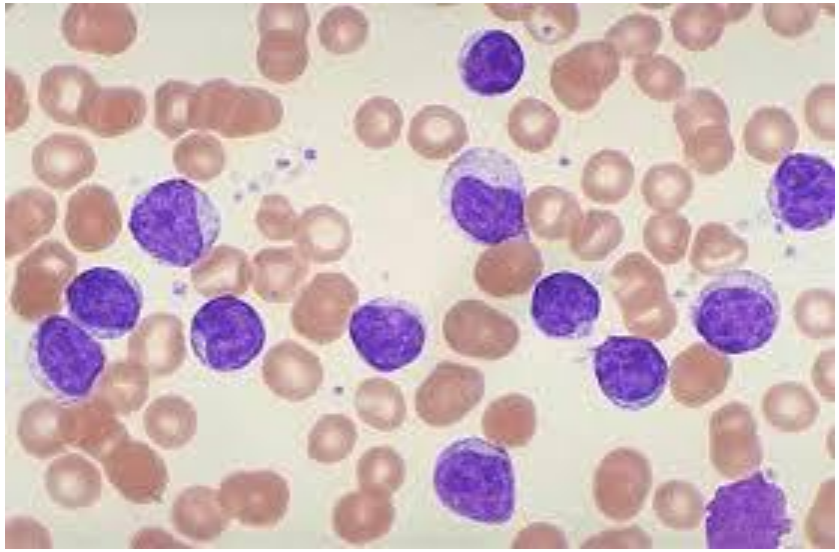


N = 9000 cases / year in Canada

2000 cases/ year CLL in Canada

Armitage *et al. J Clin Oncol* 1998

Chronic Lymphocytic Leukemia



- Average age 72
- Age-adjusted incidence rates are 7.5 to 12 per 100,000 person-years
- B cell lymphocytosis > 5 x 10 9/L
- Flow Cytometry: CD5+, 19+, 23+, dim CD20

The international Prognostic Index for patients with CLL (CLL-IPI): An international meta-analysis

Kutsch N et al. Lancet Oncol 2016

Summary: The CLL-IPI

Variable	Adverse factor	Grading
TP53 (17p)	deleted and/or mutated	4
IGHV status	unmutated	2
B2M, mg/L	> 3.5	2
Clinical stage	Binet B/C or Rai I-IV	1
Age	> 65 years	1
Prognostic Score		0 - 10

Risk Group	Score
Low	0 – 1
Intermediate	2 – 3
High	4 – 6
Very High	7 - 10

PRESENTED AT: ASCO Annual '15 Meeting

N= 3472, 8 Clinical Trials

Lancet Oncol. 2016;S1470-2045:30029-8

CLL-IPI Prognostic Scoring OS Untreated Patients

Risk Category	CLL-IPI Risk Score	5 yr OS	10 yr OS	Hazard Ratio (95% CI)
Low	0-1	93.2%	79%	-
Intermediate	2-3	79.3	39.2	3.5 (2.5-4.8)
High	4-6	63.3	21.9	1.9 (1.5-2.3)
Very High	7-10	23.3	3.5	3.6 (2.6-4.8)

Prospective Validation underway – ? Impact on older patients, targetted therapy

Considerations for Treatment:

- 3 to 27% with 17p del
- 50% unmutated IgHV status

Lancet Oncol. 2016;S1470-2045:30029-8
Dr. Graeme Fraser, CHC Sept 2016

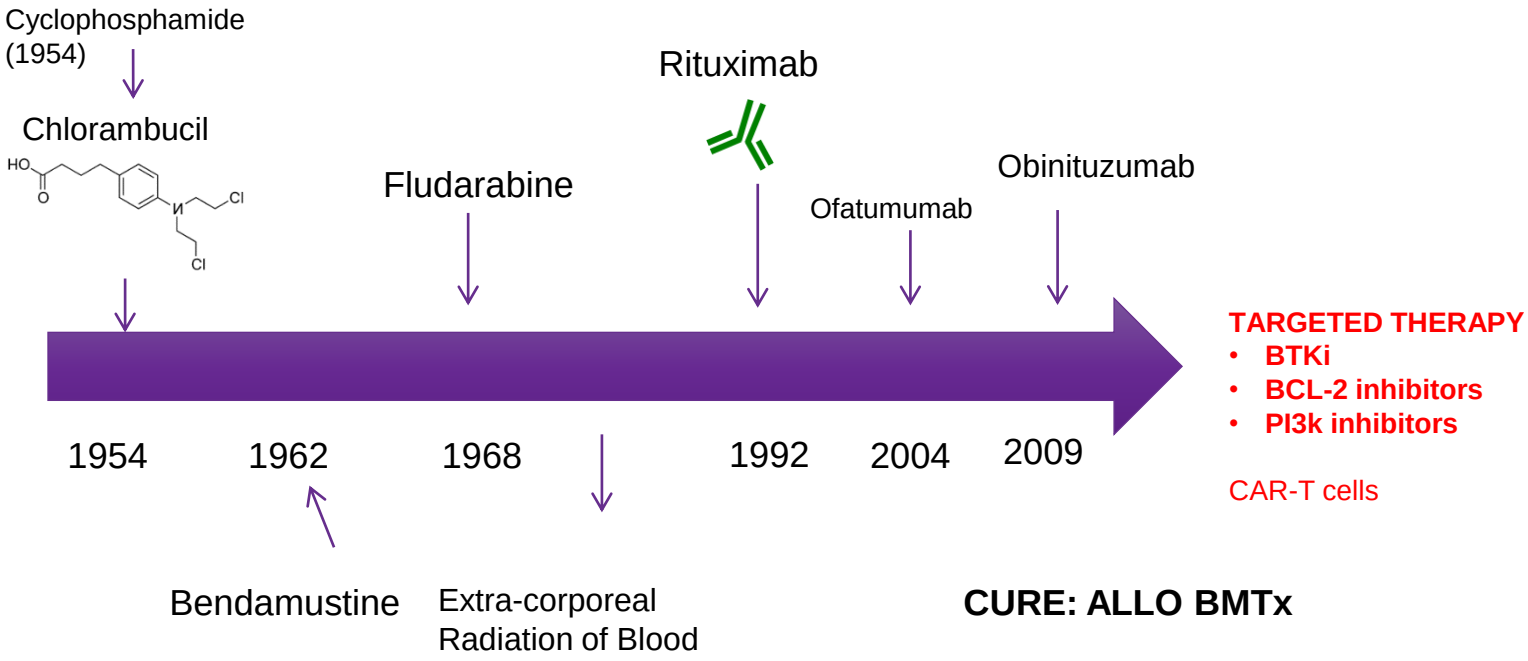
CLL General Considerations
Indications for Cytotoxic Treatment

- Evidence of progressive marrow failure
- Massive, progressive, or symptomatic splenomegaly
- Massive nodes or progressive/symptomatic lymphadenopathy
- Progressive lymphocytosis
  - >50% over a 2-month period
  - Lymphocyte doubling time <6 months*
- Autoimmune anemia and/or thrombocytopenia poorly responsive to standard therapy
- ≥1 of the following disease-related symptoms
  - Unintentional weight loss
  - Significant fatigue
  - Fevers
  - Night sweats

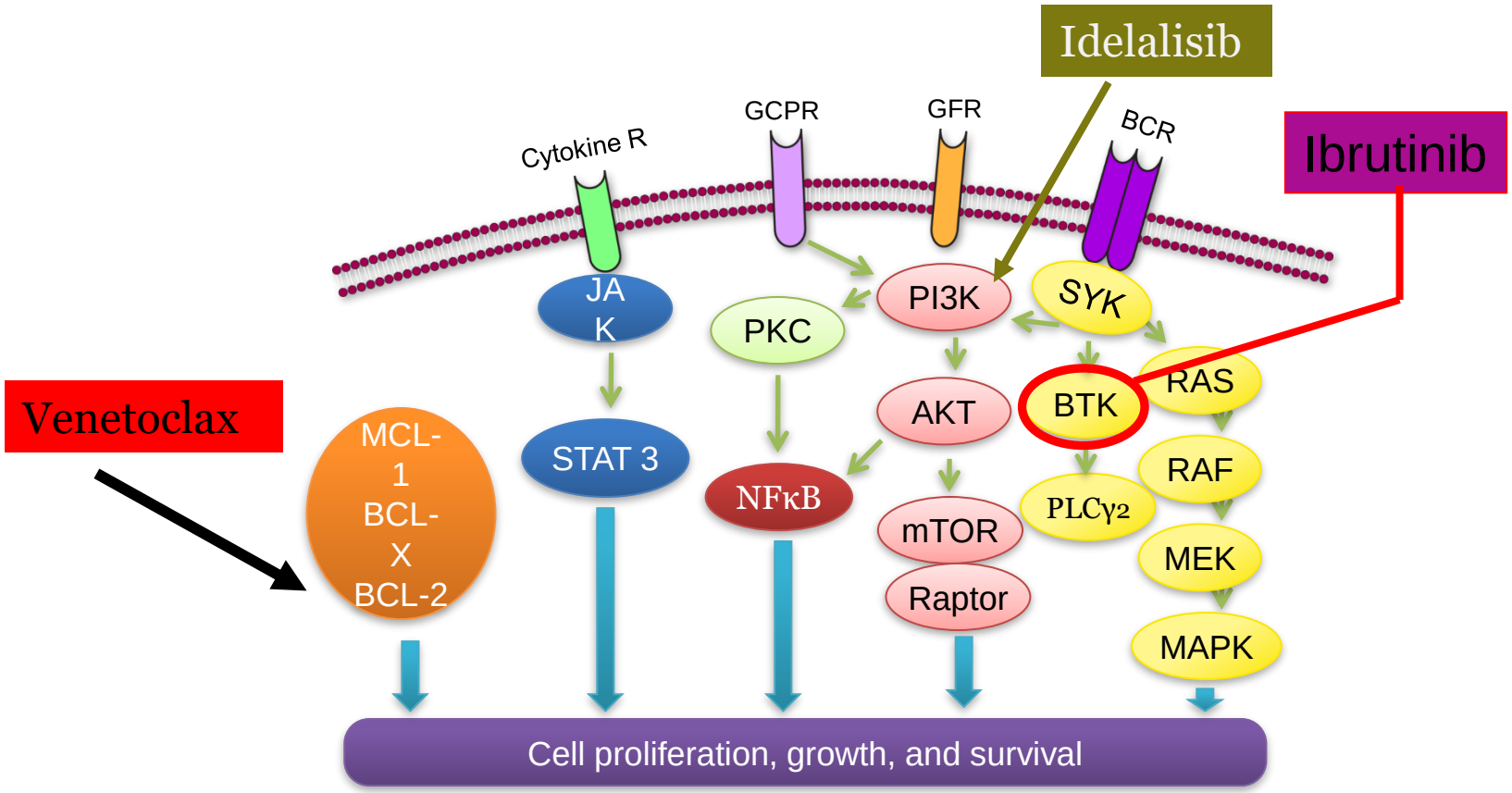
Hallek M, Cheson BD, et al. *Blood.* 2008;111:5446-5456.

*If initial lymphocytes < $30x10^9$/L, lymphocyte doubling time should not be used as a single parameter to define a treatment indication. Factors contributing to lymphocytosis or lymphadenopathy other than CLL should be excluded.

The Evolution of CLL Therapy



Targeted Agents in CLL



Ibrutinib forms a specific and irreversible bond with cystein-481 in BTK and prevents mantel cell migration and adhesion.

Adapted from: Reeder CB, Ansell SM. *Blood*. 2011;117(5):1453-1462.

CLL: Evolution of Chemotherapy Regimens pre 2016

Chemotherapeutic Approach	Typical example	OR (%)	CR (%)	Remission duration
Alkylating agent	Chlorambucil	40–60	<10	~1 year
	C + Obinotuzumab[1]	>78%	20.7%	27 mos
Purine analogue	Fludarabine	60-80	10-20	1.5 - 2 years
Purine analogue and alkylating agent	Fludarabine, Cyclophosphamide (FC)	80-95	20-40	3 - 4 Years
	Fludarabine, Cyclophosphamide, Rituximab (R-FC)[2]	90	44	Median PFS 52 months
Purine analogue-alkylator hybrid	Bendamustine, Rituximab[3]	90	36	Median PFS 44 months

C+O, TTNT 48 mos

Age < 65
IgHV mut
Not 17pdel

1. N Engl J Med. 2014 Mar 20;370(12):1101-10
2. Crump M, et al. *New Evidence in Oncology*. February 2009.
3. Hallek M, et al. Lancet 2010; 376(9747):1164-1174.
4. Eichorst et al. Blood 2013; abstract 526

CR, complete response; OR, overall response.

Randomized studies using targeted agents ibrutinib, idelalisib or venetoclax, alone or in combination, as first or second line therapy

Treatment	N	Age[a]	ORR	CR %	PR %	uMRD %	PFS[b]	2y-PFS	2y-OS	Reference
Randomized studies in first line treatment										
Ibrutinib	136	73	86%	4%	82	NA	NR	89%	98%	Burger et al. 2015[107]
Chlorambucil (CLB)	133	72	35%	2%	22	NA	18.9	34%	85%	
Ibrutinib + rituximab	354	58	NA	NA	NA	NA	NA	3 years: 89%	NA	Shanafelt et al. 2018[108]
FCR	175	57	NA	NA	NA	NA	NA	3 years: 73%	NA	
Ibrutinib	182	71	93%	7%	NA	1%	NR	87%	90%	Woyach et al. 2018[109]
Ibrutinib + rituximab	182	71	94%	12%	NA	4%	NR	88%	94%	
BR	183	70	81%	26%	NA	8%	41.0	74%	95%	
Ibrutinib + obinutuzumab	113	70	88%	19%	69%	35%	NR	30 m: 79%	30 m-OS: 86%	Moreno et al. 2019[110]
CLB + obinutuzumab	116	72	73%	8%	66%	25%	19.0	30 m: 31%	30 m-OS: 85%	
Venetoclax + obinutuzumab	216	72	85%	50%	35%	76%	NR	88%	92%	Fischer et al 2019[111]
CLB + obinutuzumab	216	71	71%	23%	48%	35%	NR	64%	93%	
Randomized studies in treatment of relapsed/refractory CLL										
BR + ibrutinib	289	64	83%	10%	72%	26%	NR	18 m: 79%	3y-OS: 82%	Chanan-Khan et al.[112,113]
BR	289	63	68%	3%	65%	6%	13.3	18 m: 24%	3y-OS: 73%	
Venetoclax + rituximab	194	65	92%	8%	84%	62%	NR	85%	92%	Seymour et al. 2018[114]
BR	195	65	72%	4%	69%	13%	17.0	63%	87%	
Idelalisib + rituximab	110	71	81%	0	81%	NA	NR	6 m: 93%	1y-OS: 92%	Furman et al. 2014[115]
Rituximab	110	71	13%	0	13%	NA	5.5	6 m: 46%	1y-OS: 80%	
BR + idelalisib	207	62	70%	1%	69%	NA	20.8	NA	NA	Zelenetz et al. 2017[116]
BR	209	64	45%	0	44%	NA	11.1	NA	NA	

42% discontinuation rate at 5 years (mostly d/t AEs

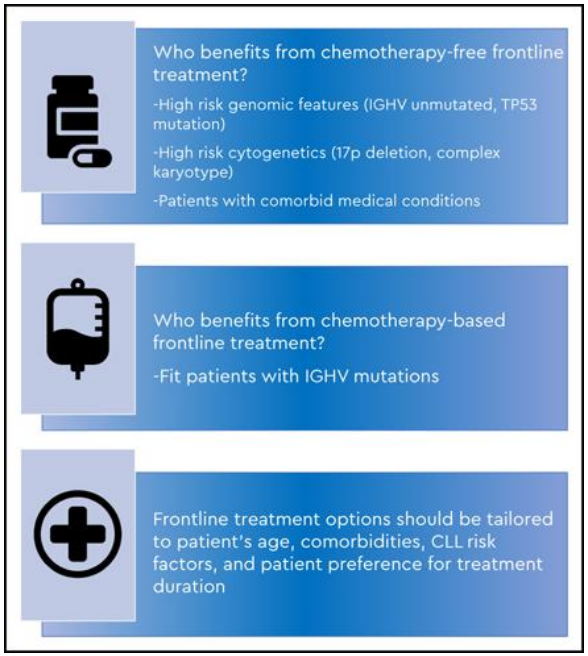
Favors IR for unmut IgHV

No role to adding Ritux to Ibrutinib single agent

ELEVATE TN: Acala + G vs A vs ChlO PFS at 24 months: 93%vs 87% vs 47%

AJH. Nov 2019: 1266-1287

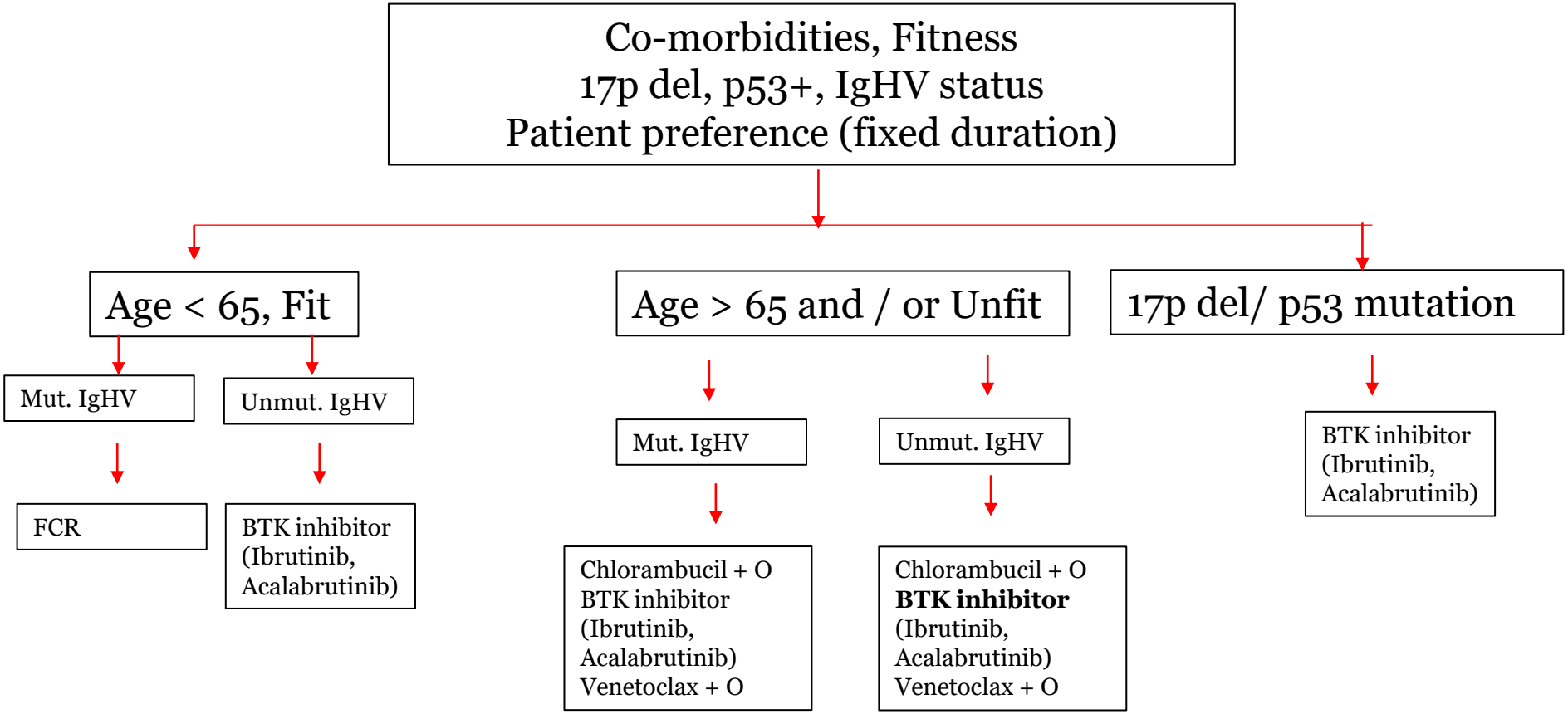
Chemotherapy-free frontline therapy for CLL: is it worth it?



BTKi clinical trial	Arthralgias, %	Atrial fibrillation, %	Bleeding/hemorrhage, %	Hypertension, %	Infection, %
RESONATE-2: ibrutinib[34] (N = 136)	26	16	11	26	12*
A041202					
Ibrutinib[35] (n = 180)	1	17	2*	29*	20*
Ibruitnib-rituximab[35] (n = 181)	2	14	4*	34*	20*
iLLUMINATE: Ibrutinib-Obintuzumab[36] (N = 113)	22	12	NR	17	14*
ECOG E1912: Ibrutinib-rituximab[7] (N = 352)	4.8*	7.4	NR	18.8*	9.4†
ELEVATE-TN					
Acalabrutinib[40] (n = 179)	11.2	3.9	1.7‡	4.5	14†
Acalabrutinib-obinutuzumab[40] (n = 179)	9.5	3.4	2.2‡	7.3	20.8†

Joanna M. Rhodes,Jacqueline C. Barrientos, Chemotherapy-free frontline therapy for CLL: is it worth it?, Hematology Am Soc Hematol Educ Program, 2020,

A basic algorithm for 1L CLL Tx

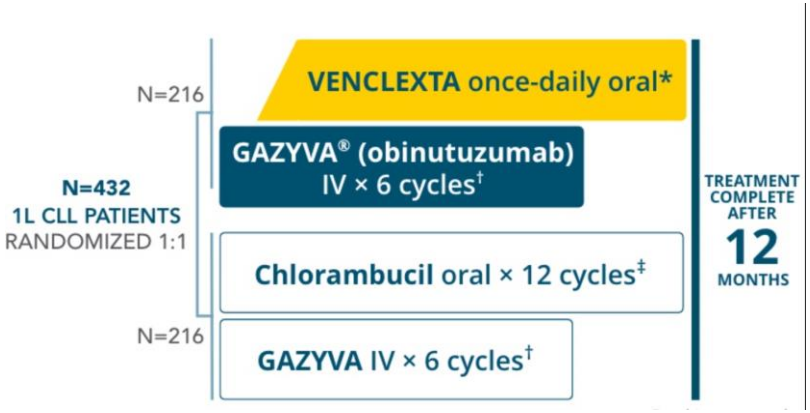


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

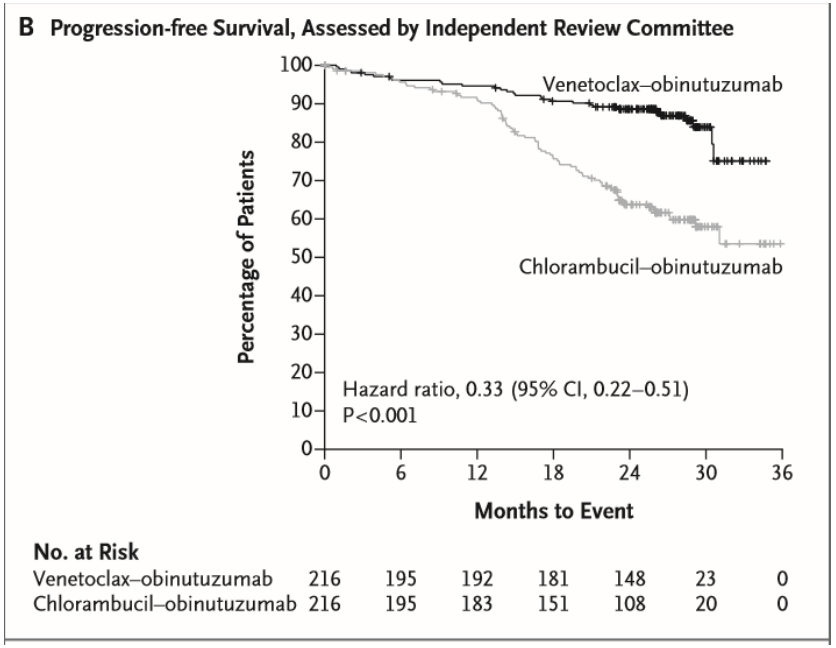
Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions

K. Fischer, O. Al-Sawaf, J. Bahlo, A.-M. Fink, M. Tandon, M. Dixon, S. Robrecht, S. Warburton, K. Humphrey, O. Samoylova, A.M. Liberati, J. Pinilla-Ibarz, S. Opat, L. Sivcheva, K. Le Dû, L.M. Fogliatto, C.U. Niemann, R. Weinkove, S. Robinson, T.J. Kipps, S. Boettcher, E. Tausch, R. Humerickhouse, B. Eichhorst, C.-M. Wendtner, A.W. Langerak, K.-A. Kreuzer, M. Ritgen, V. Goede, S. Stilgenbauer, M. Mobasher, and M. Hallek



CLL14: First upfront Venetoclax Trial

- CIRS score > 6
- 36 month PFS: 82% vs 50%



Abstract #127: Clonal Dynamics after Venetoclax–Obinutuzumab Therapy: Novel Insights from the Randomized, Phase 3 CLL14 Trial

Othman Al-Sawaf et al.

Take Home points – Minimal Residual Disease:

1. High uMRD levels are achieved with VO

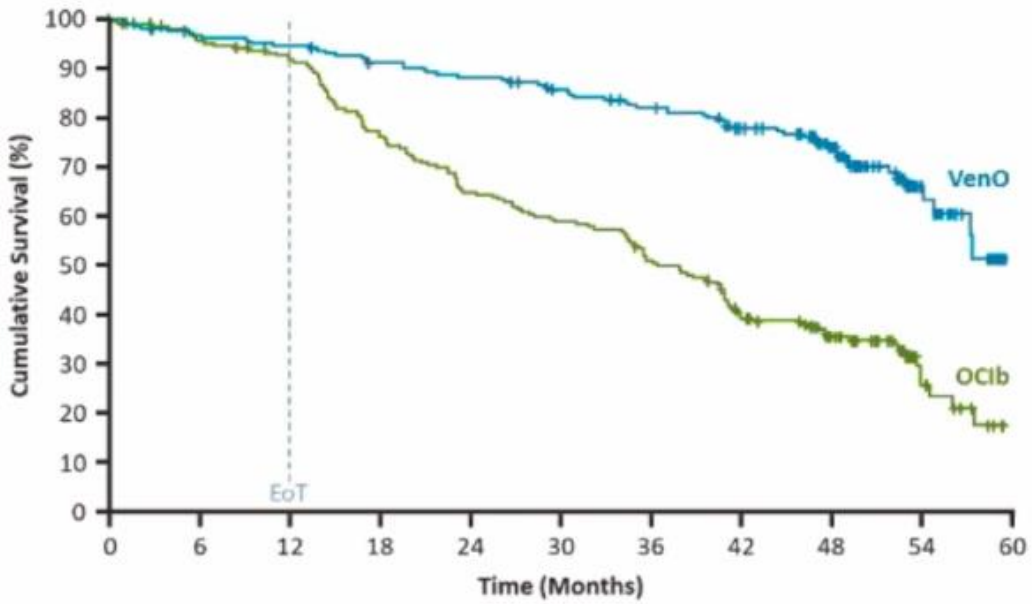
- Two months after treatment completion (follow-up month 3), 40% (7%) of patients in the Ven-Obi arm (Clb-Obi arm) had uMRD levels $<10^{-6}$, 26% (13%) $\geq 10^{-6}$ and $<10^{-5}$
- Patients in the Ven-Obi arm with MRD levels $\leq 10^{-5}$ had a 2-year PFS after EoT of approximately (approx.) 93%, while patients with detectable MRD $>10^{-2}$ had a 2-year PFS of approx. 37%

2. Must continue the full 12 cycles of VO treatment

- In 25% of the Ven-Obi treated patients, MRD response deepened after continuing with 6 cycles of venetoclax monotherapy

Abstract #127: Clonal Dynamics after Venetoclax–Obinutuzumab Therapy: Novel Insights from the Randomized, Phase 3 CLL14 Trial

Othman Al-Sawaf et al.

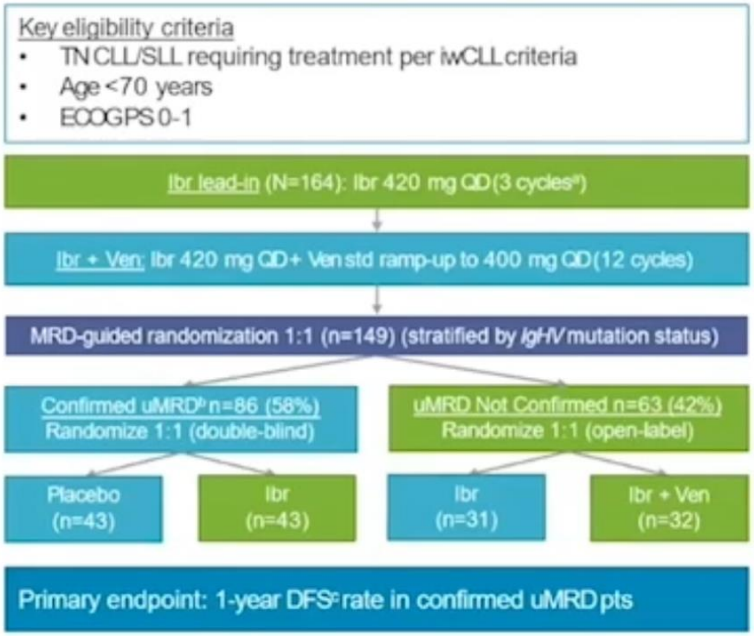


- Median observation time 52.4 months
- All patients off treatment for ≥3 years

	VenO (n=216)	OClb (n=216)
HR (95% CI)	0.33 (0.25–0.45)	
48-month PFS estimate, %	74.0	35.4
Median PFS, months (95% CI)	NR	36.4

Abstract #123: Ibrutinib Plus Venetoclax for First-Line Treatment of CLL/ SLL: 1 yr DFS Results from the MRD Cohort of the Phase 2 CAPTIVATE study

Weirda et al.



Patient Characteristics in MRD Cohort		Confirmed uMRD (n=86)		uMRD Not Confirmed (n=63)	
		Placebo (n=43)	Ibr (n=43)	Ibr (n=31)	Ibr + Ven (n=32)
Median age (range), years		61 (43-69)	56 (34-69)	58 (28-69)	56 (37-69)
Rai stage III/IV disease, n (%)		15 (35)	8 (19)	14 (45)	11 (34)
High-risk Features, n (%)	del(17p)/*TP53* mut	2 (5)	13 (30)	5 (16)	8 (25)
	del(11q)[d]	8 (19)	10 (23)	3 (10)	2 (6)
	Complex karyotype[e]	4(9)	13 (30)	5 (16)	4 (13)
	Unmutated *IgHV*	30 (70)	30 (70)	14 (45)	15 (47)
Any cytopenia, n (%)		19 (44)	6 (14)	13 (42)	14 (44)
LN diameter ≥5 cm , n (%)		18 (42)	10 (23)	7 (23)	11 (34)
Median ALC x 10^9/L (range)		53 (1-235)	56 (2-256)	85 (1-342)	87 (3-419)
ALC≥25 x 10^9/L, n (%)		32 (74)	34 (79)	25 (81)	24 (75)

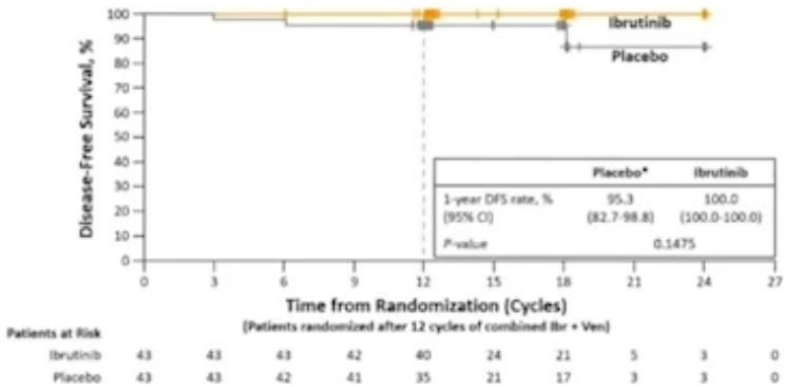
WHU, Mato 2021

[a]28-day cycles. [b]uMRD defined as having uMRD4 serially over at least 3 cycles, and uMRD in both PB and BM. [c]DFS rate: proportion of

WHU, Mato 2021

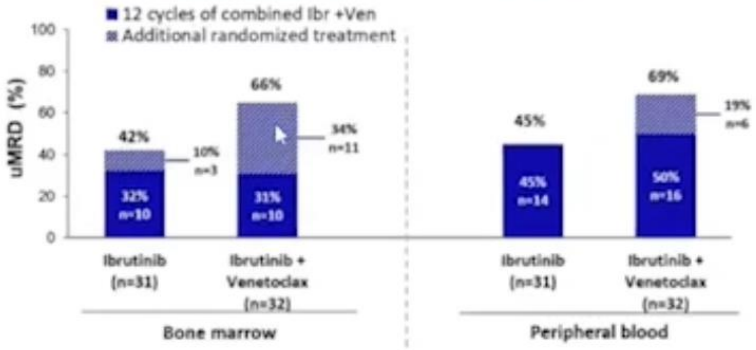
Phase 2 CAPTIVATE Study of Ibrutinib + Venetoclax for 1L Treatment of CLL/SLL: Efficacy in the MRD Cohort

1-year DFS After Randomization in Pts With Confirmed uMRD



Best Overall uMRD Rates in uMRD Not Confirmed Pts

(in pts without confirmed uMRD after 12 cycles of Ibr+Ven, increases in uMRD were great with Ibr+Ven vs Ibr alone)



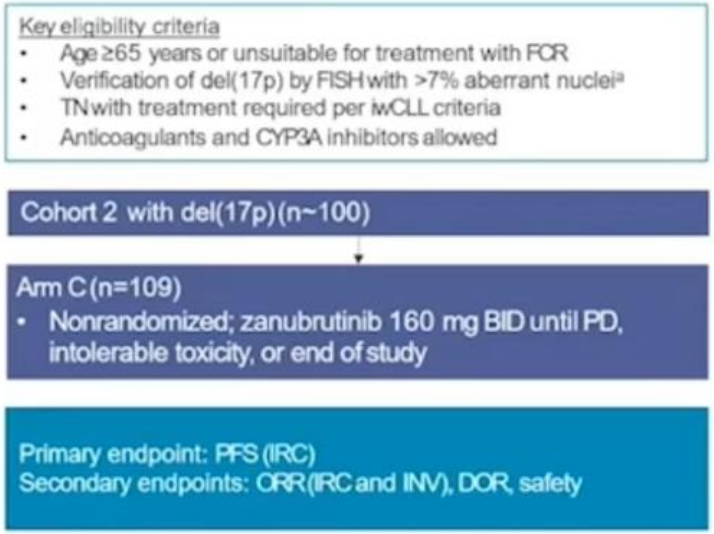
	All Patients	Confirmed uMRD		uMRD Not Confirmed	
	(N=164)	Placebo (n=43)	Ibr (n=43)	Ibr (n=31)	Ibr + Ven (n=32)
30-month PFS, %(95% CI)	95.3 (90.4-98.8)	95.3 (82.7-98.8)	100.0 (100.0-100.0)	95.2 (70.7-99.3)	96.7 (78.6-99.5)

[a]3 DFS events in placebo arm of DFS were PD in 2 pts and MRD relapse in 1 pt.
Median follow-up on study: 31.3 months. Median follow-up post-randomization: 16.6 months.
Wierda WG, et al. ASH 2020. Abstract 123.

WHU, Mato 2021

Abstract #1306: Efficacy and safety of Zanubrutinib in Patients with Treatment-Naïve CLL/SLL with del 17p: Follow-up results from Arm C of the SEQUOIA Trial

Brown et al.



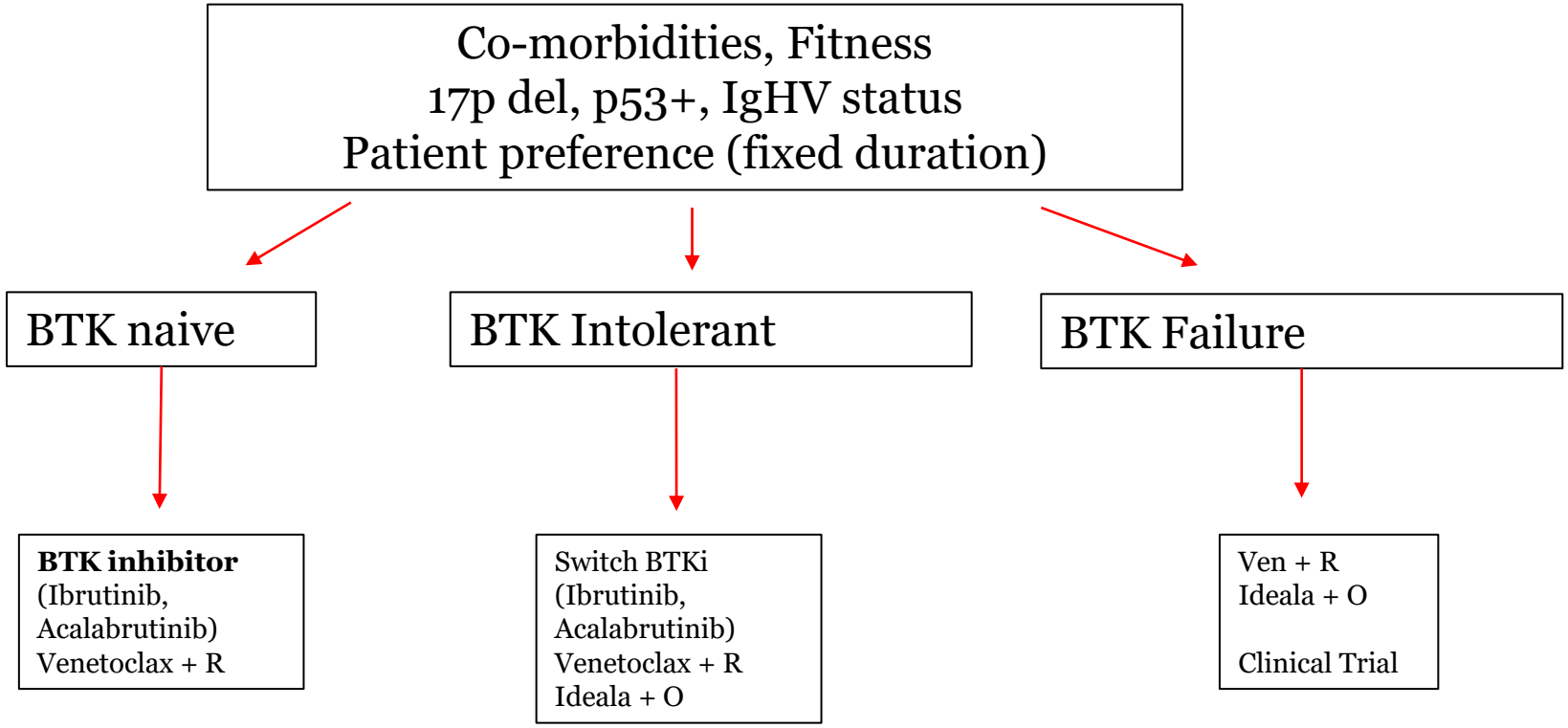
Patient Characteristics			(N=109)
Median age (range), years			70.0 (42-86)
ECOG PS 2, n (%)			14 (12.8)
Median time since diagnosis (Q1-Q3), months			21.62 (7.69-54.77)
SLL, n (%)			10 (9.2)
Binet stage C for CLL, n/N (%)			40/99 (40.4)
del(13q), n (%)			72 (66.1)
del(11q), n (%)			37 (33.9)
IgHV unmutated, n/N (%)			69/104 (66.3)
Bulky disease, n (%)	Any target lesion LDi ≥5 cm		42 (38.5)
	Any target lesion LDi ≥10 cm		11 (10.1)
Karyotype,[b] n (%)	Non-complex (0-2 abnormalities)		54/86 (62.8)
	Complex (abnormalities)	3 or more	32/86 (37.2)
		5 or more	23/86 (26.7)

Table 2: Summary of Efficacy (Best Response)

	TN del(17p) CLL/SLL (n = 90)[a]
Median follow-up, mo (range)	7.0 (2.9-14.5)
Efficacy (best response)	
ORR (CR, PR, or PR-L), n (%) [95% CI][b]	83 (92.2) [84.6-96.8]
CR	0 (0.0)
PR	68 (75.6)
PR-L	15 (16.7)
SD	6 (6.7)
PD	1 (1.1)

WHU, Mato 2021

A basic algorithm for 2L CLL Tx



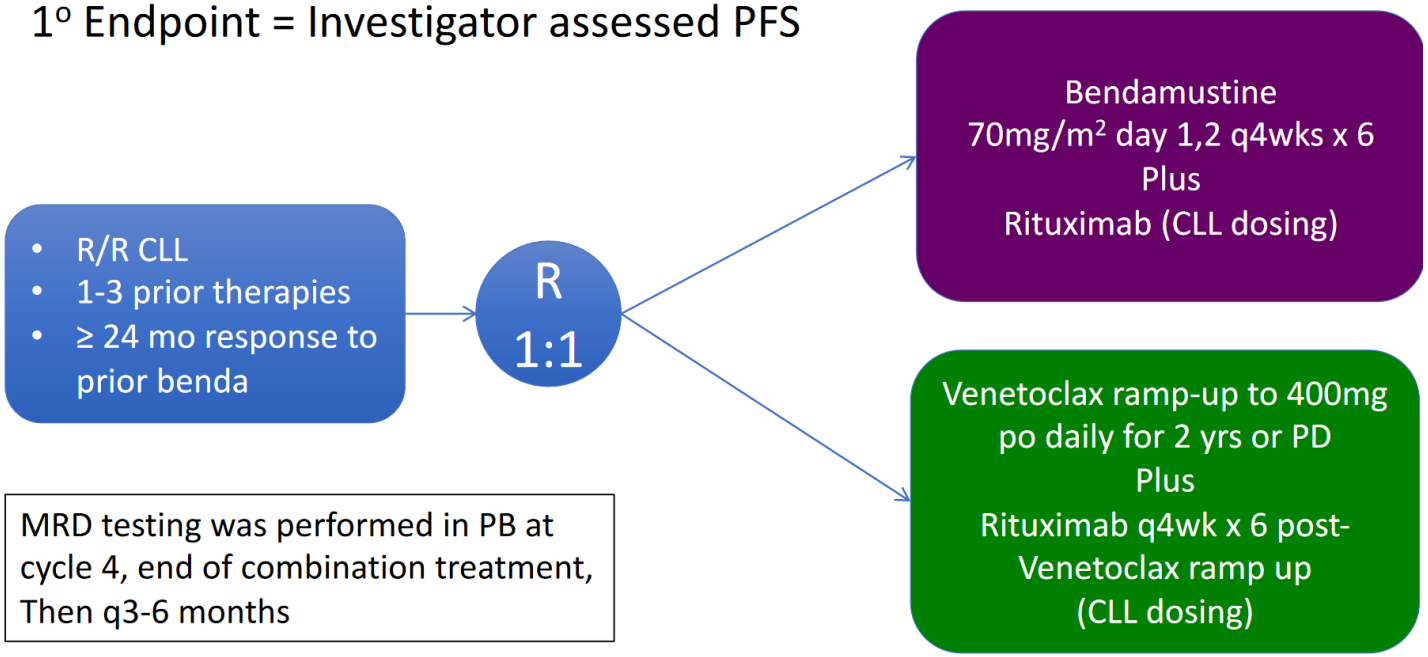
- There is no data to support which is better in BTK naïve patient… Await CLL17

Abstract #125: Five-Year Analysis of Murano Study Demonstrates Enduring Undetectable Minimal Residual Disease (uMRD) in a Subset of Relapsed/Refractory Chronic Lymphocytic Leukemia (R/R CLL) Patients (Pts) Following Fixed-Duration Venetoclax-Rituximab (VenR) Therapy (Tx)

Kater A et al.

N = 389

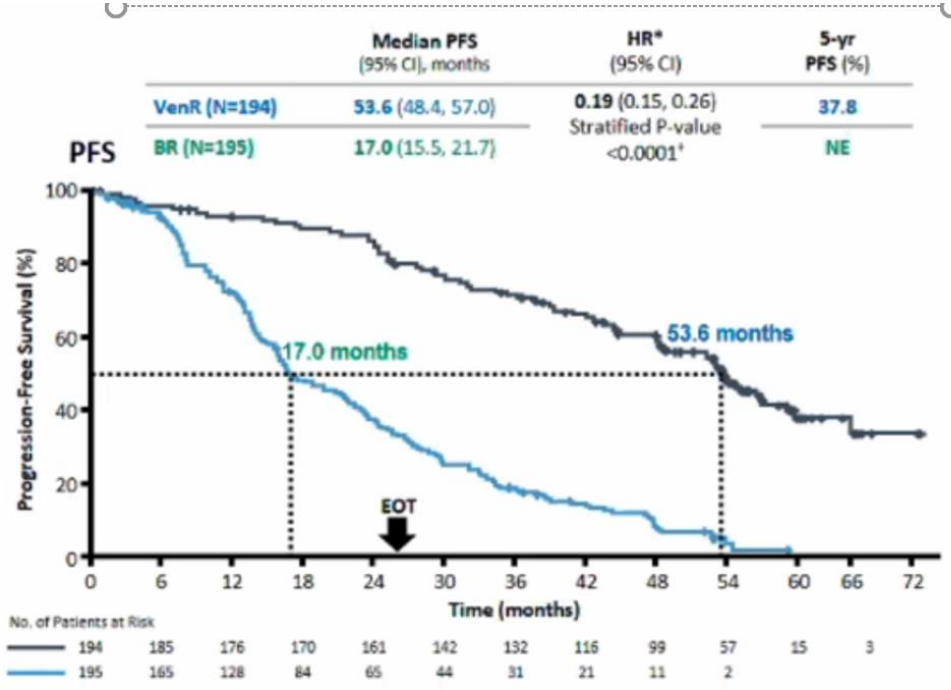
1° Endpoint = Investigator assessed PFS

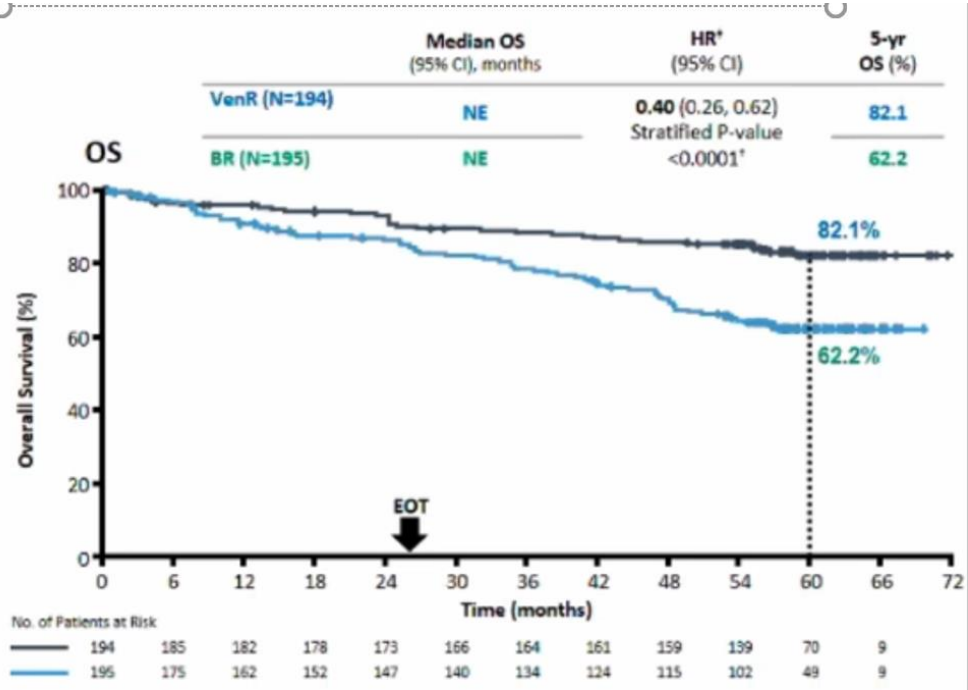


Pts were categorized by MRD status as previously reported, using $<10^{-4}$ threshold for uMRD

MURANO Trial Update: How does VR compare in RR CLL population?

* Median time to next tx is approximately 5 years post 2 years post fixed VR





Dr. Carolyn Owen, BofOnc

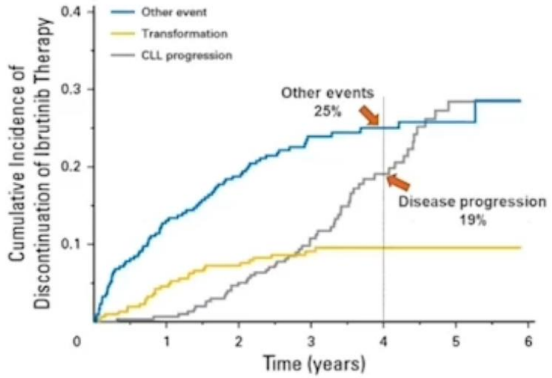
Take Home Points:

- Median PFS was 53.6 (95% CI: 48.4-57.0) mos for VenR and 17.0 (95% CI: 15.5-21.7) mos for BR
  - 5-yr OS estimates of 82.1% (95% CI: 76.4-87.8) for VenR and 62.2% (95% CI: 54.8-69.6) for BR
- MRD conversion was 19 – 24 months before CLL progression

What's the future?: Loxo305 is a novel non-covalent BTKi (overcome the resistance of binding to the BTK)

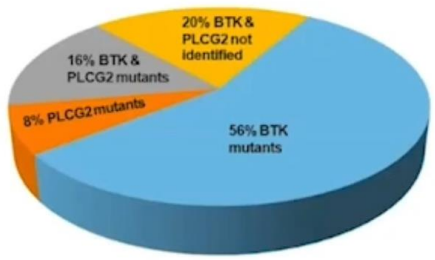
Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib discontinuation from 4 prospective studies[1]



- Ibrutinib discontinuation rates at 5 years
  - Front line = 41%[3]
  - Relapsed/refractory = 54%[1]

Ibrutinib acquired resistance in patients with progressive CLL[2]



- BTK C481 mutations are the dominant reason for progressive CLL after covalent BTK inhibitors[1-8]
- BTK C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

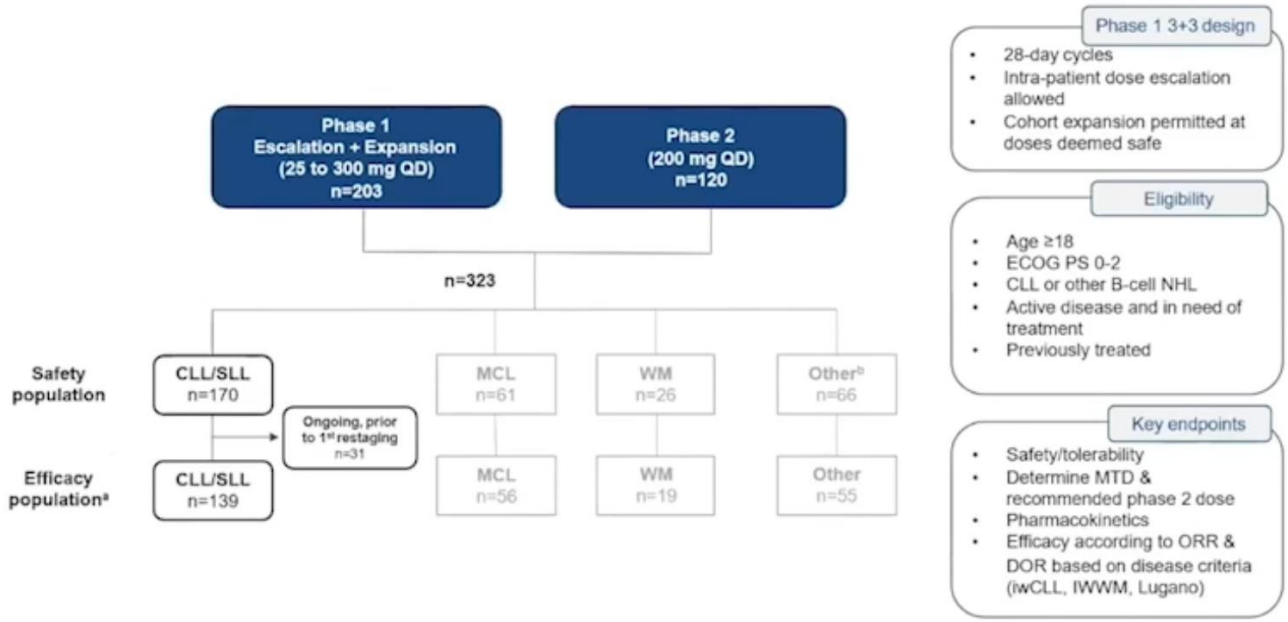
[1]Woyach et al. *J Clin Oncol.* 2017;35:1437-43. [2]Lampson et al. *Expert Rev Hematol.* 2018;11:185-94. [3]Burger et al. *Leukemia.* 2020;34:878-789. [4]Byrd et al. *N Engl J Med.* 2016;374:323-32. [5]Hershkovitz-Rokah et al. *Br J Haematol.* 2018;181:306-19. [6]Woyach et al. *N Engl J Med.* 2014;370:2286–94. [7]Woyach et al. *Blood.* 2019;134(Suppl 1):504. [8]Xu et al. *Blood.* 2017;129:2519–25.

Abstract #542: LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/ SLL: Results from the Phase I/II Bruin Study

Mato A et al.

Loxo-305 is a selective, non-covalent BTKi able to inhibit wild type BTK and the C481 BTK mutant equally in vitro

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment

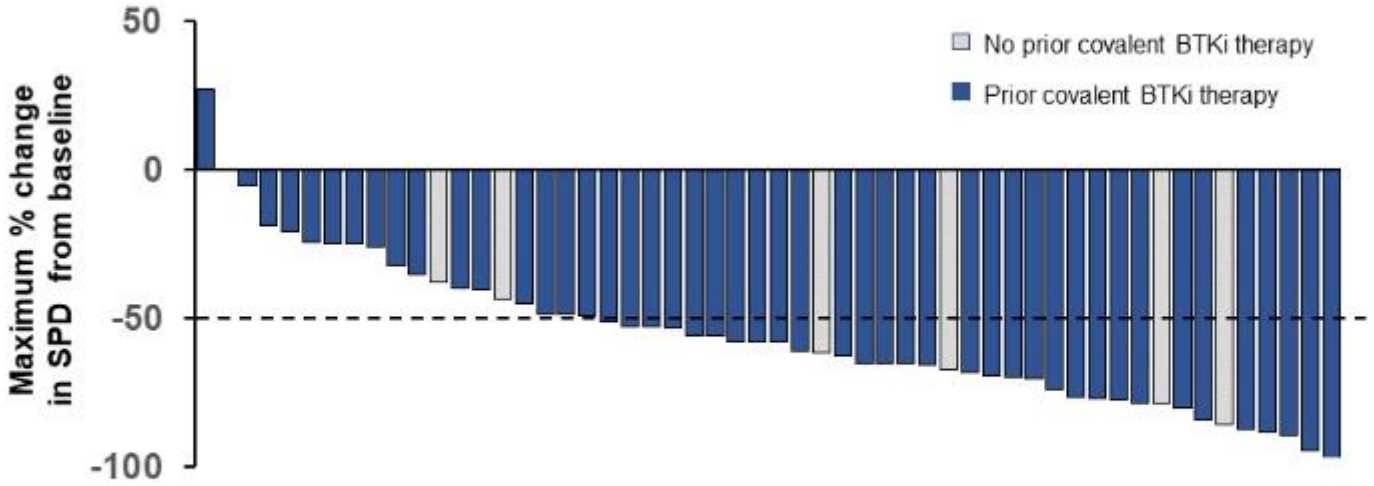


Data cutoff date of 27 September 2020. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]Other includes DLBCL, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, and other transformation. All response data presented based on investigator assessment.

Abstract #542: LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/ SLL: Results from the Phase I/II Bruin Study

Mato A et al.

Figure: Waterfall plot of the maximum % change in SPD from baseline*



* 11 efficacy-evaluable pts are not included in the waterfall plot, including 1 pt who discontinued prior to first response assessment, and 10 pts (4 pts with PR/PR-L and 6 pts with SD) with incomplete tumor lesion measurement data at the time of data cut

Abstract #542: LOXO-305, A Next Generation, Highly Selective, Non-Covalent BTK Inhibitor in Previously Treated CLL/ SLL: Results from the Phase I/II Bruin Study

Mato A et al.

LOXO-305 Safety Profile

	All doses and patients (n=323)						
	Treatment-emergent AEs, (≥10%), n (%)[a]					Treatment-related AEs, n (%)	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	40 (12%)	22 (7%)	3 (1%)	-	65 (20%)	2 (<1%)	27 (8%)
Diarrhea	45 (14%)	10 (3%)	-	-	55 (17%)	-	28 (9%)
Contusion	37 (12%)	5 (2%)	-	-	42 (13%)	-	29 (9%)
AEs of special interest[b,c]							
Bruising	48 (15%)	5 (2%)	-	-	53 (16%)	-	37 (12%)
Rash	30 (9%)	5 (2%)	-	-	35 (11%)	-	18 (6%)
Arthralgia	13 (4%)	3 (1%)	-	-	16 (5%)	-	5 (2%)
Hemorrhage	10 (3%)	4 (1%)	1 (<1%)[d]	-	15 (5%)	-	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	-	15 (5%)	-	4 (1%)
Atrial fibrillation/flutter	-	2 (<1%)[e]	-	-	2 (<1%)	-	-

No DLTs reported and MTD not reached
5 of 323 patients (1.5%) discontinued due to treatment-related AEs
200mg QD selected as recommended Phase 2 dose

Data cutoff date of 27 September 2020. Total % may be different than the sum of the individual components due to rounding. [a]The AEs listed are the most common that occurred at any grade in at least 10% of the patients, regardless of attribution. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Bruising includes contusion, petechia, ecchymosis and increased tendency to bruise. Hemorrhage includes hematoma, epistaxis, rectal hemorrhage, subarachnoid hemorrhage, upper gastrointestinal hemorrhage, vitreous hemorrhage and wound hemorrhage. Rash includes rash maculo-papular, rash, rash macular, rash erythematous, rash popular, rash pruritic and rash pustular. [d]Subarachnoid bleed sustained during a bicycle accident, considered by investigator as unrelated to LOXO-305. [e]Both events considered by

Future Questions in CLL…

- Head to head trial of Ibrutinib vs Acalabrutinib in 1L CLL currently accruing
  - Retrospective data for RR CLL show that acalabrutinib treatment are superimposable on Resonate 2 curves (Ib vs Ofatumumab)
    - Considerations of AEs and QoL in treatment choice
- Which drugs may overcome BTKi resistance (Loxo 305)
- How to use MRD testing in CLL patients?
  - MRD + conversion precludes clinical symptoms by 25 months
  - 17p del or complex cytogenetics patients progress faster
- It is still unclear if Unmut IgHV patients need targeted agents vs CIT
- New combination therapies with time limited exposures

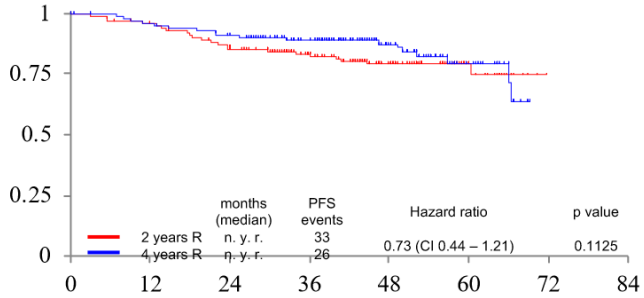
Indolent NHL

First Line Treatment: Follicular Lymphoma

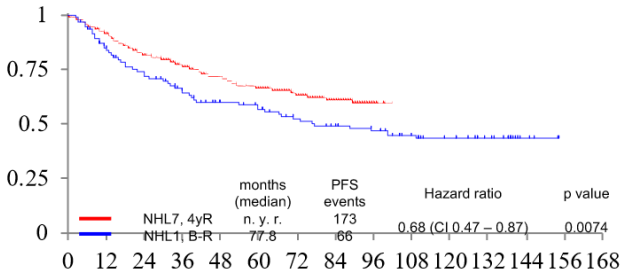
Regiment	Progression Free Survival	Toxicities
StiL Trial: Bendamustine + Rituximab R-CHOP *No maintenance	69.5 months (HR 0.58) 31.2 months	Myelotoxicity, skin reaction Neuropathy, Allopecia
PRIMA: R-FCM + R R-CHOP + R R-CVP + R	3-year PFS 74 % with maintenance rituximab (HR 0.55) vs 58% *73 months f/u: 6-year PFS was 42.7% in the observation arm vs 59.2% in the rituximab maintenance arm	Infusion reactions (24%) Infection (39%)
Gallium Trial: O+Chemo + Maintenance R+Chemo + Maintenance	3-year PFS was 81.9% (95%CI: 77.9-85.2%) vs. 77.9% (95%CI: 73.8-81.4%), respectively, HR: 0.71 *Short median f/u of 34.5 months	Grade ≥3 infusion reactions: obinutuzumab 74.6% vs rituximab 67.8%
Relevance Trial: Revlimid + Ritux + Maintenance R+Chemo + Maintenance	3 year PFS: 77% vs 78%	Grade ¾ neutropenia: 34% vs 50%

StiL NHL 7-2008 MAINTAIN trial: previous results

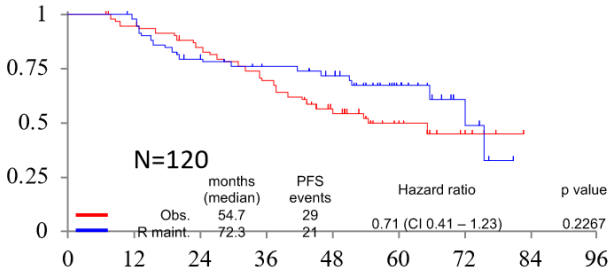
Follicular Lymphoma: B-R + 2 years R vs. B-R + 4 years R



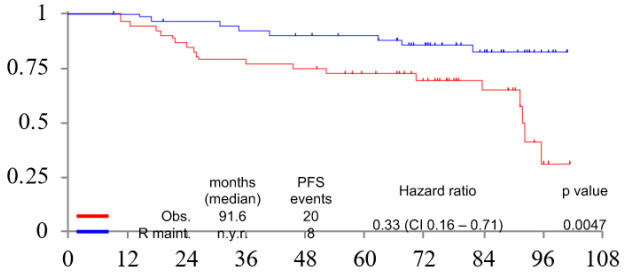
Follicular Lymphoma: B-R (NHL1) vs B-R + R (NHL7)



Mantel Cell Lymyphoma: B-R vs. B-R + 2 years R

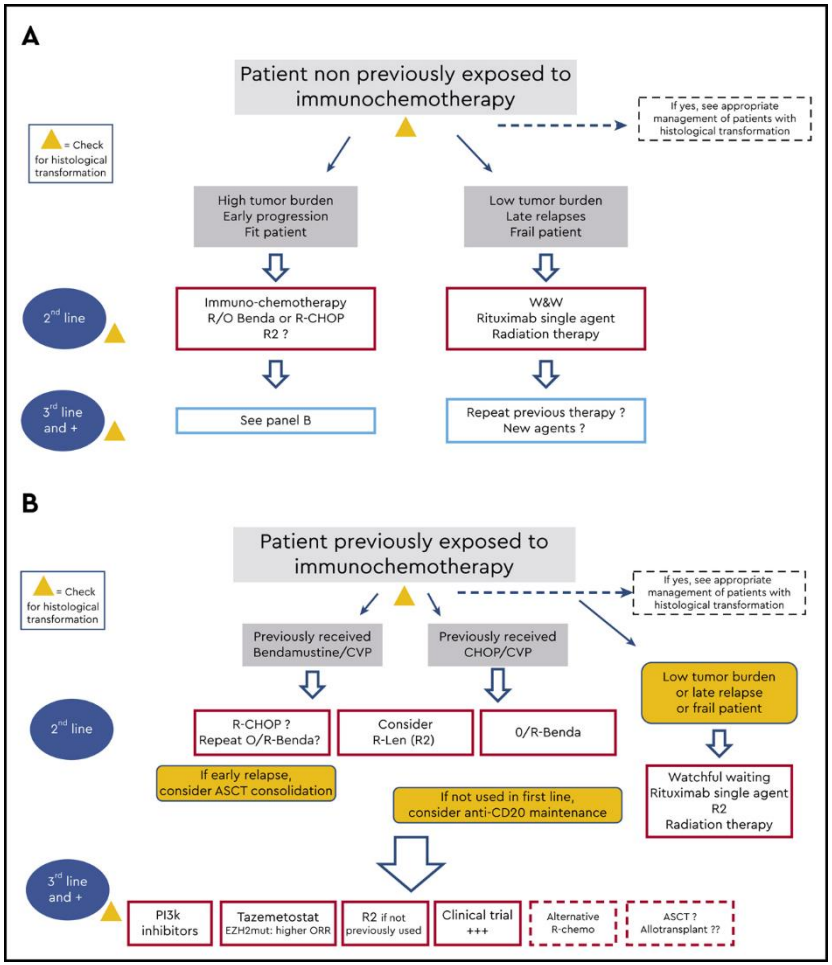


Marginal Zone Lymyphoma: B-R vs. B-R + 2 years R



ASH 2019: Waldenstrom's Macroglobulinemia: Ritux maintenance of no benefit

How do I sequence therapy for follicular lymphoma?



Gilles Salles, How do I sequence therapy for follicular lymphoma?, Hematology Am Soc Hematol Educ Program, 2020,

Options for Relapsed-Refractory Follicular Lymphoma

Drug	Disease characteristics	Number of patients (total/follicular)	ORR	CRR	PFS, median (mo)	DOR, median (mo)	2-y OS	Most common grade 3-4 adverse events (present in ≥5% of patients)*
Idelalisib[27,28]	Double refractory to rituximab and alkylating agents	72/125	66%+	14%+	11 (11+)	12 (11+)	70%+	Neutropenia (27%) ALT elevation (13%) Diarrhea (13%) Pneumonia (7%) Thrombocytopenia (6%)
Duvelisib[14]	Double refractory to rituximab and alkylating agents	129/83	42%+	1%+	10	10	~60%‡	Neutropenia (25%) Diarrhea (15%) Anemia (15%) Thrombocytopenia (12%) Febrile neutropenia (9%) Lipase increased (7%) ALT elevation (5%) Pneumonia (5%) Colitis (5%)
Copanlisib[29]	Relapsed or refractory after 2 lines of therapy	142/104	59%+	20%+	13	14	69% augment	Hyperglycemia (40%) Hypertension (24%) Neutropenia (24%) Pneumonia (11%) Diarrhea (9%) Anemia (5%) Thrombocytopenia (5%)

Studies	Number of patients	ORR	CRR	Main adverse events
Bispecific antibodies				Cytokine release syndrome and ICANS (essentially grade 1-2), cytopenias (20%-25% grade ≥3)
Mosunetuzumab[36]	82	63%	43%	
Glofitamab[37]	24	68%	50%	
Chimeric antigen receptor T cells	80	95%	81%	Cytokine release syndrome (7% grade ≥3), ICANS (15% grade ≥3), cytopenias
Axicabtagene ciloleucel[38]				

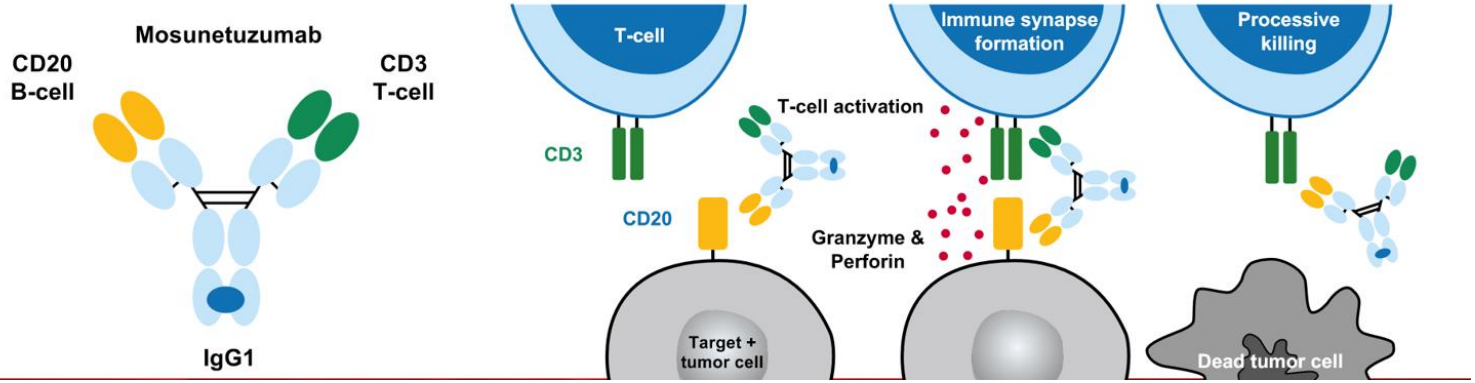
Gilles Salles, How do I sequence therapy for follicular lymphoma?, Hematology Am Soc Hematol Educ Program, 2020,

Abstract #702: Mosunetuzumab Shows Promising Efficacy in Patients with Multiply Relapsed Follicular Lymphoma: Updated Clinical Experience from a Phase I Dose-Escalation Trial

Assouline S et al.

Mosunetuzumab: a bispecific antibody targeting CD3 and CD20

- **Full-length humanized IgG1 antibody**
  - Longer half-life than fragment-based drugs
  - PK properties enable once weekly to q3w dosing
- **Mechanism of action**
  - Redirects T-cells to engage and eliminate malignant B-cells
  - Conditional agonist: T-cell activation dependent on B-cell engagement
  - Amino-acid substitution (N297G) to inactivate ADCC and avoid destruction of engaged T cells

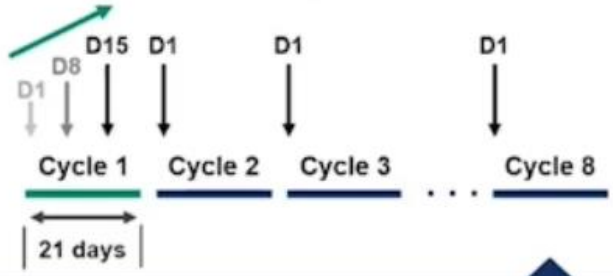


Presented at ASH CARE 2019, Dr. L. Sehn

Phase I/Ib study of mosunetuzumab in R/R B cell lymphomas (GO29781)

Mosunetuzumab dosing schedule*

- **Step-up dosing (IV) during Cycle 1 D1/D8/D15**
- **Cycle 1 D1/D8/D15 dose**: 0.4/1.0/2.8–1/2/13.5mg
- **Cycles 2–8 (D1) dose:** Cycle 1 D15 dose



Treatment duration: CR: 8 cycles

PR or SD: 17 cycles (or progression, toxicity)
Retreatment was permitted for patients with a CR who relapsed

Key inclusion criteria (FL cohort)

- R/R FL (Grades 1–3A; expected to express CD20)
- ≥2 prior systemic therapies
- Age ≥18 years
- ECOG performance status ≤1

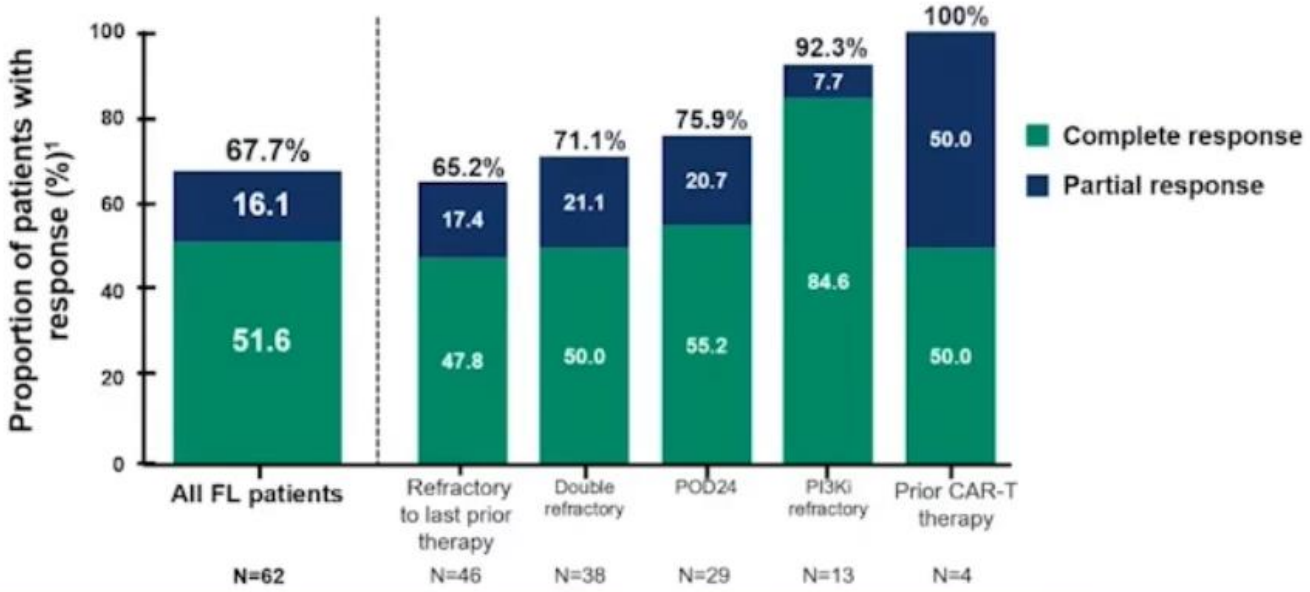
GO29781 primary objectives

- Safety and tolerability
- RP2D
- MTD and DLTs
- Best objective response[1]

*Premedication with steroids (20mg IV dexamethasone or 80mg IV methylprednisolone) required C1–2 and optional C3+.
DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase two dose

1. Cheson BD, et al. J Clin Oncol 2007;25(5):579–86.

Mosunetuzumab response rates (investigator assessed) in patients with R/R FL



High complete response rates were observed across multiple groups according to prior therapy
including those with double refractory disease, POD24, PI3Ki refractory, and those who received prior CAR-T therapy.

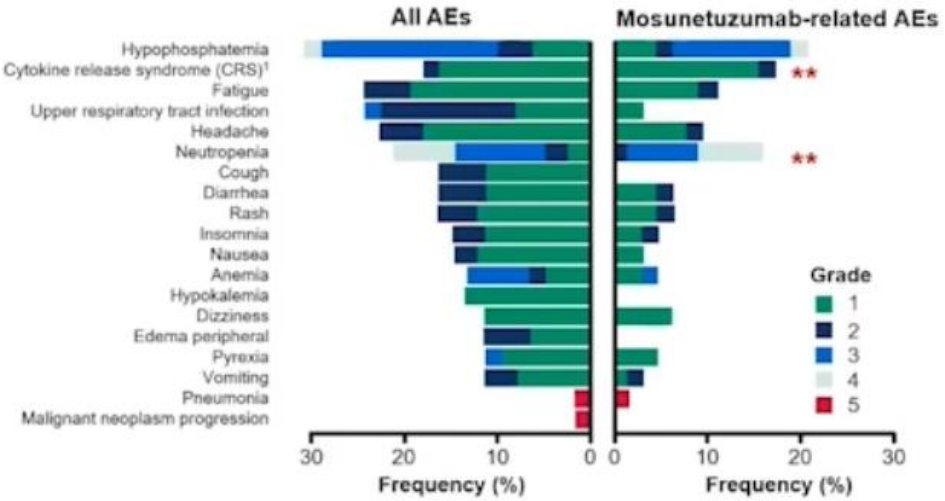
INV, investigator-assessed

1. Cheson BD, et al. J Clin Oncol 2007;25(5):579–86.

Adverse events

Summary of AEs*, n (%)	Safety evaluable patients (N=62)
Any AE	60 (96.8)
Treatment related	45 (72.6)
Serious AE	22 (35.5)
Treatment related	9 (14.5)
Grade ≥3 AE	42 (67.7)
Treatment related	22 (35.5)
Grade 5 AE (excluding disease progression)	1* (1.6)
AE leading to treatment discontinuation	5** (8.1)
Treatment related	4 (6.5)

AEs with an incidence of ≥10% or an NCI-CTCAE Grade of 5



*Grade 5 AE: pneumonia (n=1; onset Day 73)
**AEs leading to treatment discontinuation: pneumonia, atrial flutter (unrelated to treatment), neutropenia, arthritis, alanine aminotransferase increased (n=1 each)

1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25(4):625–38.

Unmet needs Follicular NHL

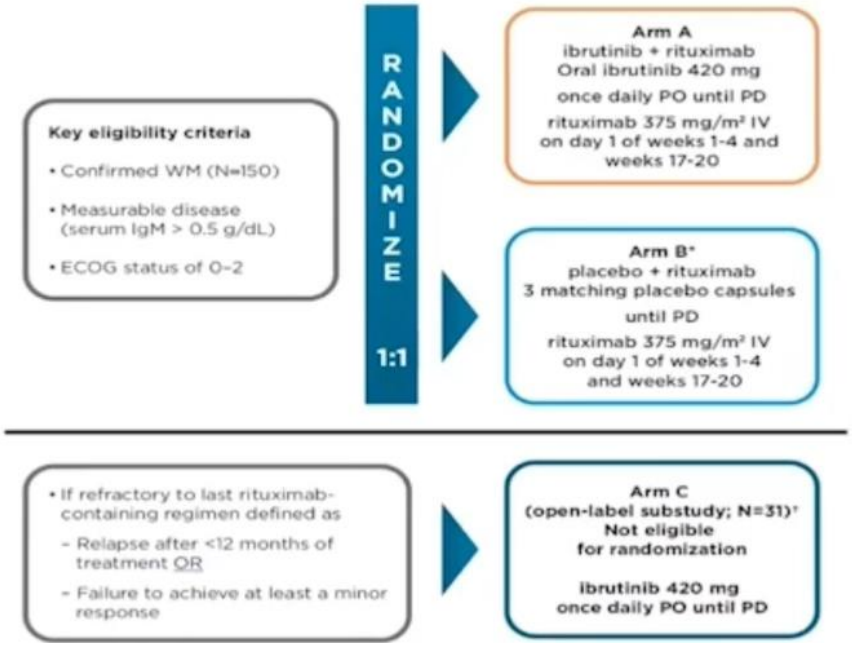
- 2nd Line treatment for Benda naïve: BR
- If treated with BR as first line:
  - No FL registry to clarify which patient population may be better managed by one treatment over another:
    - Retreat with R-chemo (if not POD24)
    - CarT cell tx (Zuma-12)
    - BiTE tx
    - BTKis, revlimid, PI3K inhibitors

Innovate Trial:

Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia

Treon SP et al. NEJM 2015;372:1430-40
Dimopoulos et al. NEJM 2018;378:2399 2410

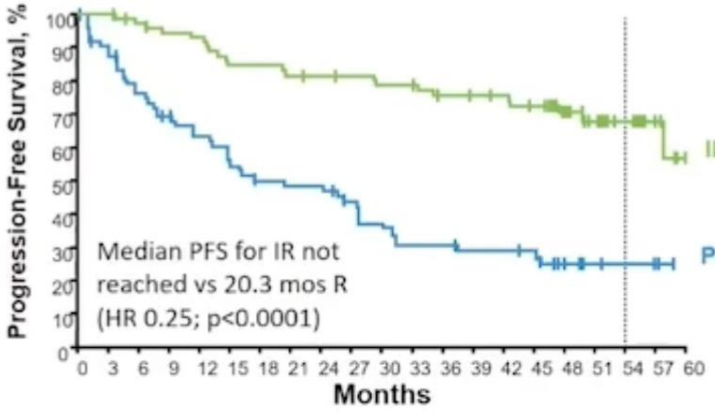
- open-label, international, multicenter, phase 3 study

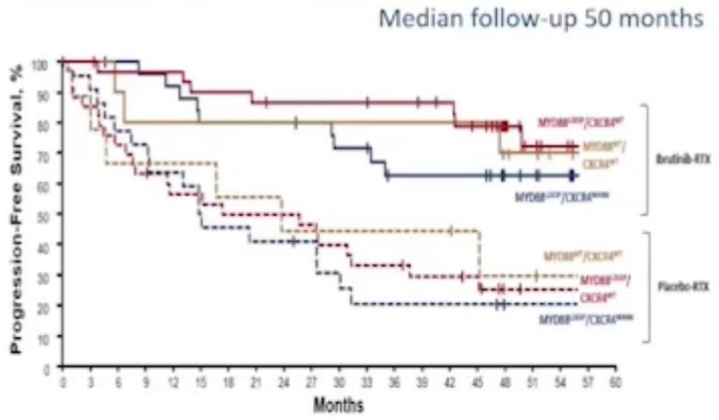


- May 2016 Ibrutinib monotherapy first approved in Canada
- Mar 2019 Ibrutinib + Rituximab approved in Canada
- Frontline and relapsed disease

Abstract # 336: Five-Year Follow-Up of Ibrutinib Plus Rituximab Vs Placebo Plus Rituximab for Waldenstrom's Macroglobulinemia: Final Analysis From the Randomized Phase 3 iNNOVATE™ Study
Buske C. et al.

Abstract #2937: Long-Term Follow-up of Ibrutinib Treatment for Rituximab-Refractory Waldenström's Macroglobulinemia: Final Analysis of the Open-Label Substudy of the Phase 3 iNNOVATE Trial.
Trotman et al.

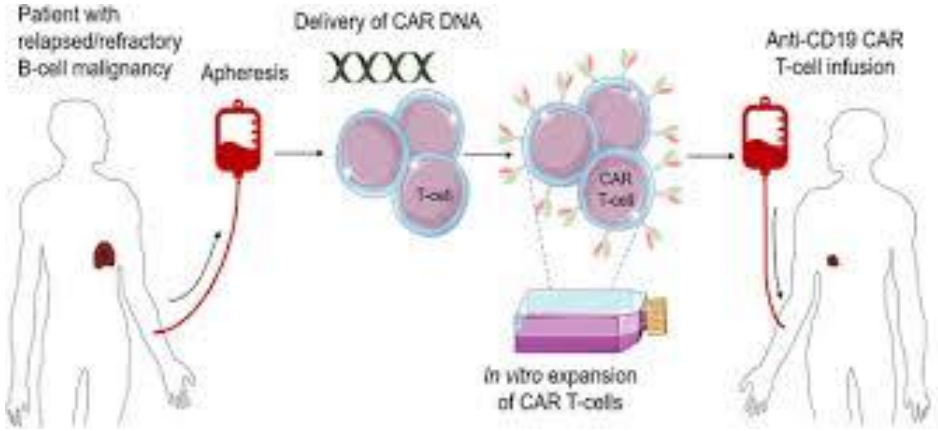




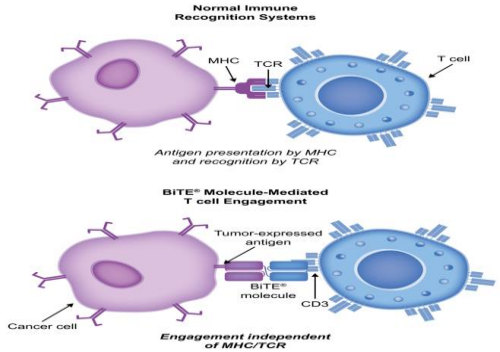
In substudy of heavily pretreated, rituximab-refractory patients:

- Median PFS 39 months much shorter
- PFS influenced by genotype: $MYD88^{MUT}/CXCR4^{WT}$ not reached; $MYD88^{MUT}/CXCR4^{MUT}$ 18 months

Diffuse Large B Cell Lymphoma



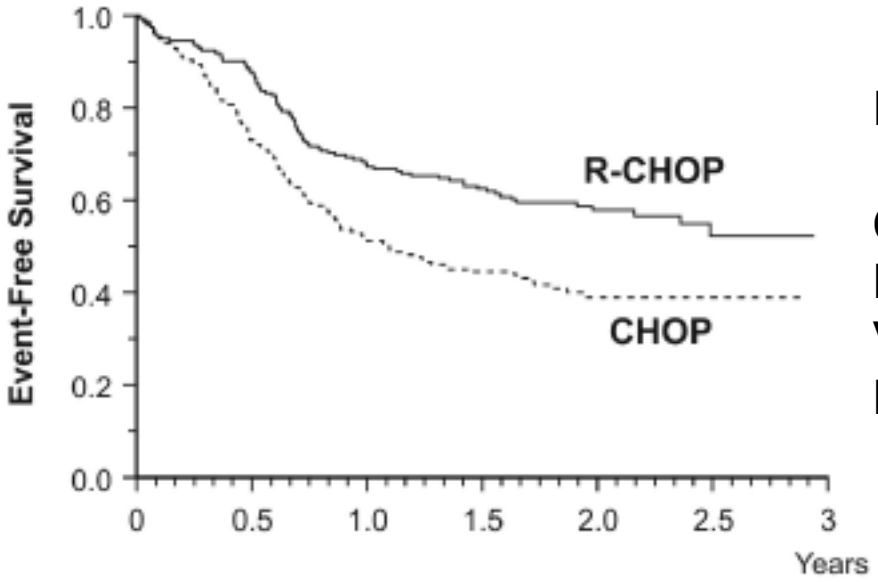
CarT cell Tx



BiTE Tx

Mammalian Genome **volume 29**, pages739–756(2018)

Treatment of 1L DLBCL = R-CHOP



Rituximab: 375 mg/m2

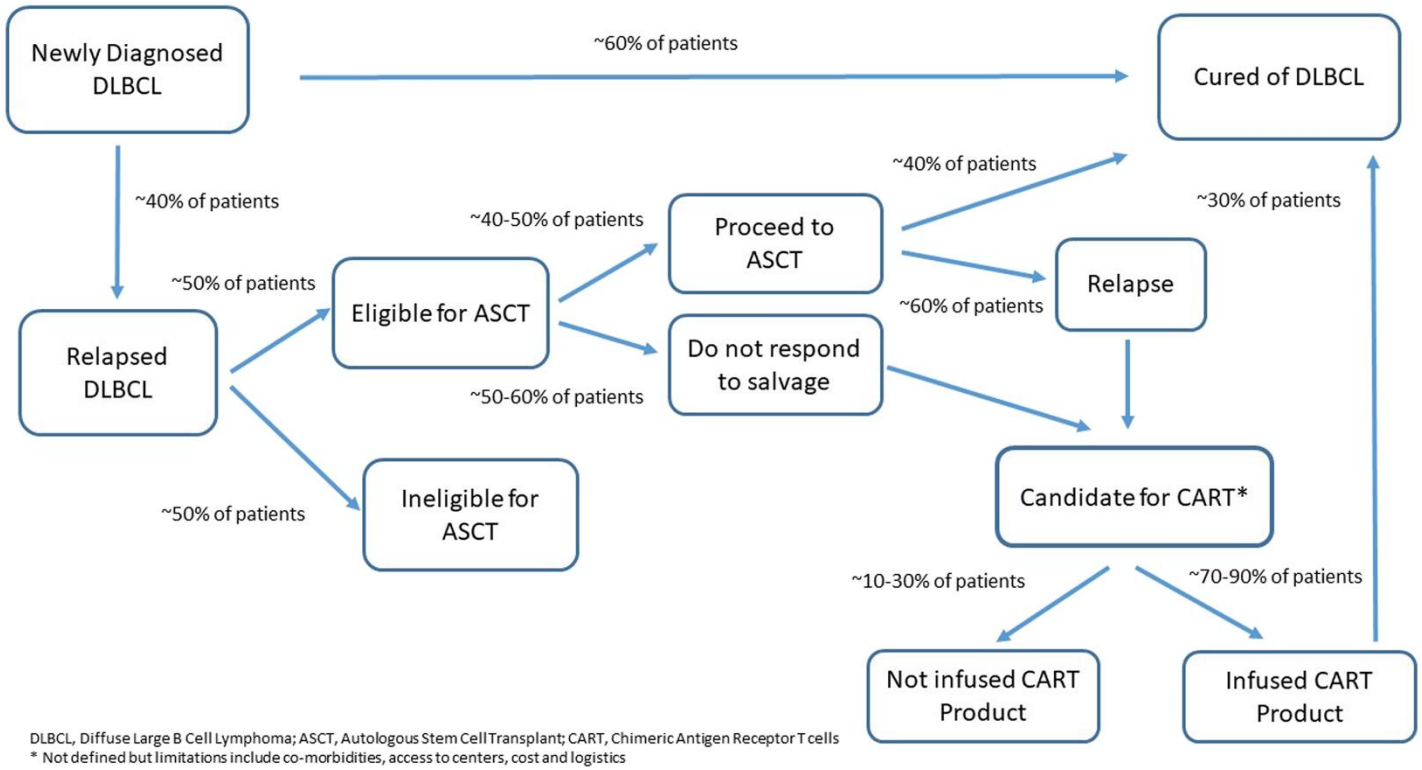
Cyclophosphamide 750 mg/m2
Doxorubin 50 mg/m2
Vincristine 1.4 mg/m2
Prednisone 100 mg po od x 5d

Event-free survival of 399 patients comparing CHOP to R-CHOP (P<0.001)

- The addition of novel therapies to R-CHOP have no shown OS benefit
- POLLARIX Trial results pending (Polatuzumab + RCHP vs RCHOP)
- Trials to start including acalabrutinib to RCHOP

Coiffier et al. **N Engl J Med** 2002; 346: 235-242

Novel targets in Aggressive Lymphoma



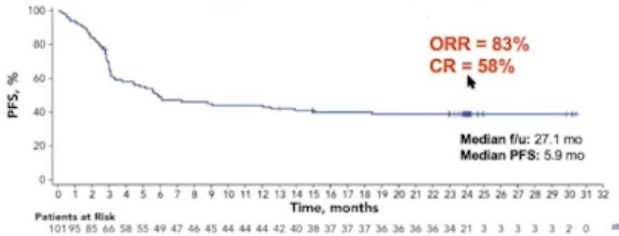
DLBCL, Diffuse Large B Cell Lymphoma; ASCT, Autologous Stem Cell Transplant; CART, Chimeric Antigen Receptor T cells
* Not defined but limitations include co-morbidities, access to centers, cost and logistics

Kami Maddocks, Novel targets in aggressive lymphoma, Hematology Am Soc Hematol Educ Program, 2020, Figure 1.

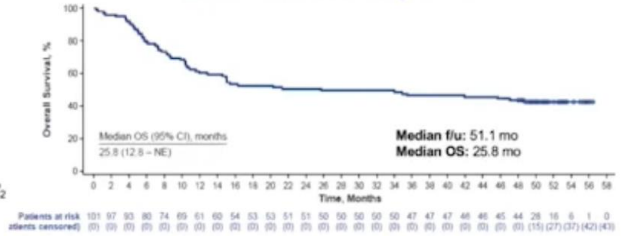
Durable Responses with CART Cell Tx in RR *DLBCL*

ZUMA-1: Axi-cel in r/r large B-cell lymphoma

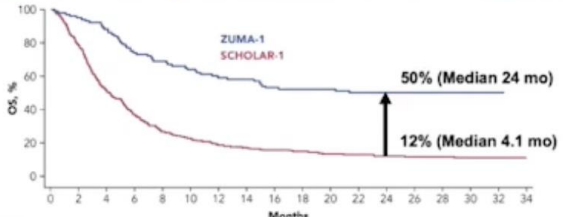
PFS: 39% progression-free at 27.1 mo



OS: 44% alive at 4 years



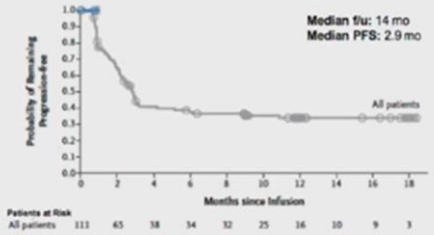
Standardized OS Comparison: ZUMA-1 vs. SCHOLAR-1 (historical)



Neelapu et al. *N Eng J Med* 2017
Locke et al. *Lancet Oncol* 2019
Neelapu et al. ASH 2019
Jacobson et al, ASH 2020

JULIET: PFS with tisagenlecleucel

34% progression-free at 14 mo#



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Schuster et al. *N Eng J Med* 2019

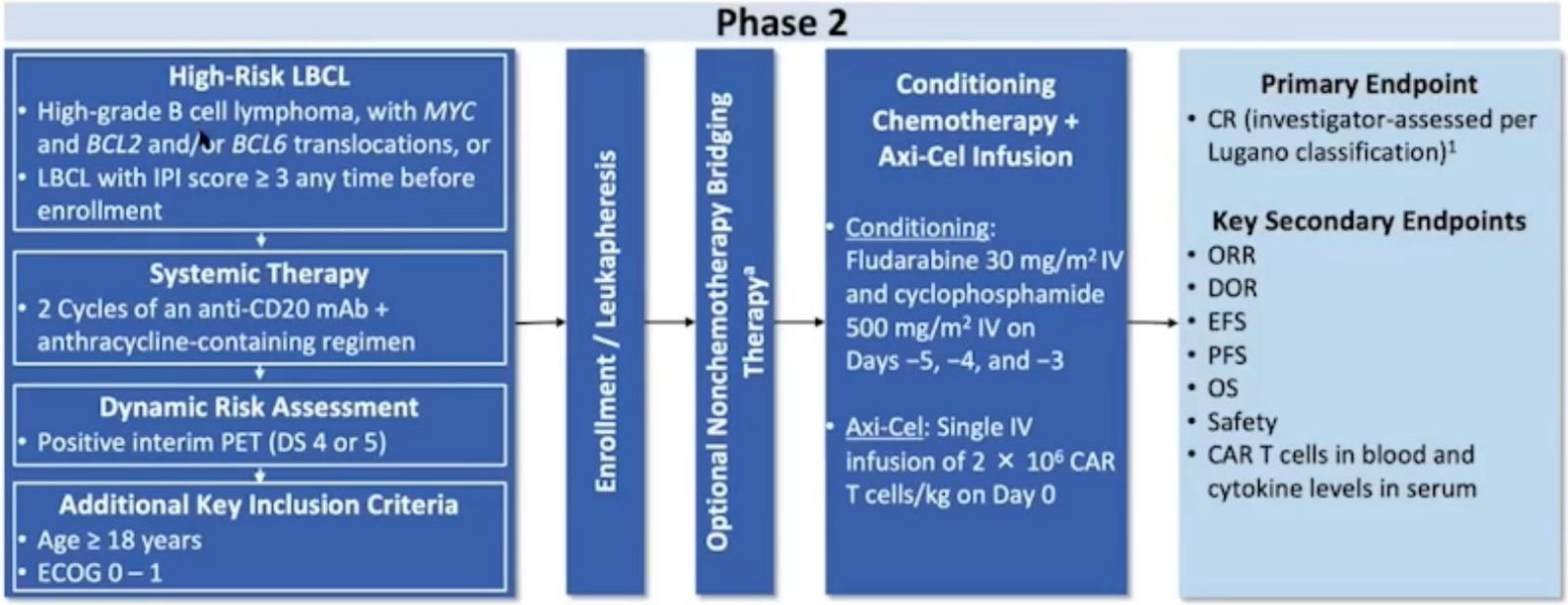
Safety of CART trials in NHL

Safety in multicenter CD19 CAR T trials in adult NHL

Study/Sponsor	Product	N	CRS All Grades	CRS Grade ≥3	NT All Grades	NT Grade ≥3	Toci usage	Steroid usage	Ref
ZUMA1 Kite	CD19/CD3ζ/ CD28	108	92%	11%	67%	32%	45%	29%	Neelapu et al, NEJM 2017
JULIET Novartis	CD19/CD3ζ/ 4-1BB	111	58%	22%	21%	12%	15%	11%	Schuster et al, NEJM 2019
TRANSCEND Juno	CD19/CD3ζ/ 4-1BB	269	42%	2%	30%	10%	20%	21%	Abramson et al, Lancet 2020

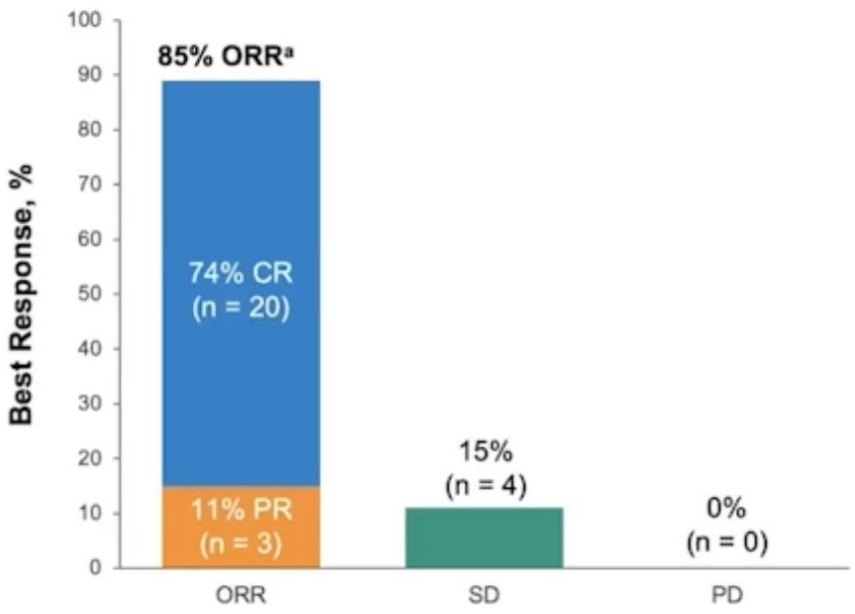
- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA-1
  - 2 related to axi-cel: cardiac arrest, HLH
  - 1 unrelated pulmonary embolism
- 7 deaths on TRANSCEND
  - 4 related to liso-cel: diffuse alveolar damage (DLT), pulmonary hemorrhage, multiple organ dysfunction syndrome, cardiomyopathy
  - 3 unrelated to liso-cel: fludarabine leukoencephalopathy, septic shock, and PML

ZUMA-12: Multicenter phase 2 study of axi-cel as part of first-line therapy in patients with high-risk LBCL



Neelapu et al, ASH 2020, Abstract 405

ZUMA-12 interim analysis: Efficacy



	Response Evaluable N = 27[b]
Median follow-up (range), months	9.3 (0.9 – 18.0)
Patients with ≥ 6-month follow-up, n (%)	19 (70)
Patients with ongoing response as of data cutoff	19 (70)
Median time to response (range), months	
Initial objective response	1.0 (0.9 – 3.1)
CR	1.0 (0.9 – 6.4)
Patients converted from PR / SD to CR, n (%)	5 (19)
PR to CR	4 (15)
SD to CR	1 (4)

Neelapu et al, ASH 2020, Abstract 405

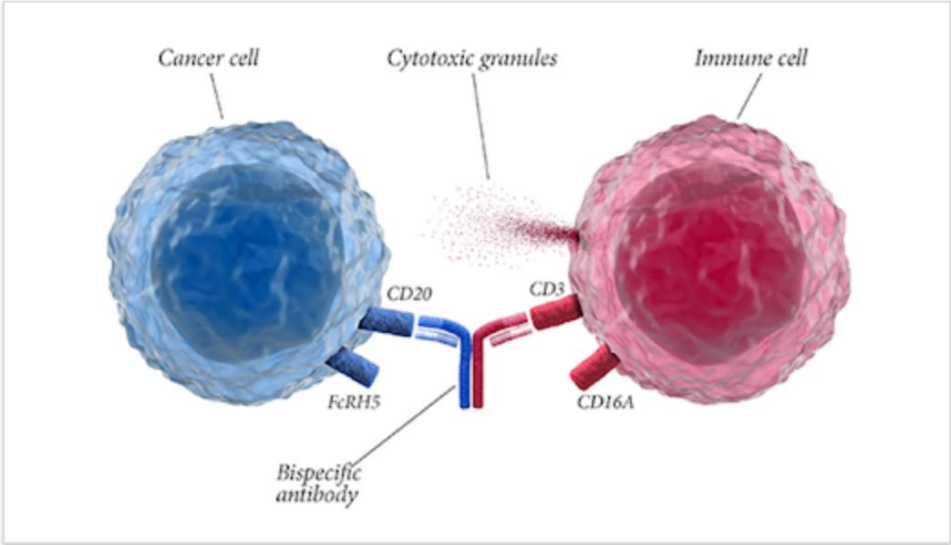
Abstract #405: Interim Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) as First-Line Therapy in Patients with High-Risk Large B Cell Lymphoma
Neelapu et al.

- Adults > 18 met 2 criteria for high risk LBCL:
  - Double or Triple Hit Lymphoma by FIST or IPI > 3
  - Positive interim PET after 2 cycles of R-chemo
- Primary endpoint: investigator assessed CR rate of 74%, 85% ORR
- Axi-cel appears to be safe and effective in DLBCL not responding to early frontline R-chemotx
  - Approved in Canada for DLBCL in 3rd line
  - The future: Zuma-7 (Second line ASCT eligible results pending)

Bi-specific T cell engagers

- Not yet FDA approved

- Mosunetuzumab
- Gliofitamab
- Odronextamab
- Epcoritamab
- Plamotamab



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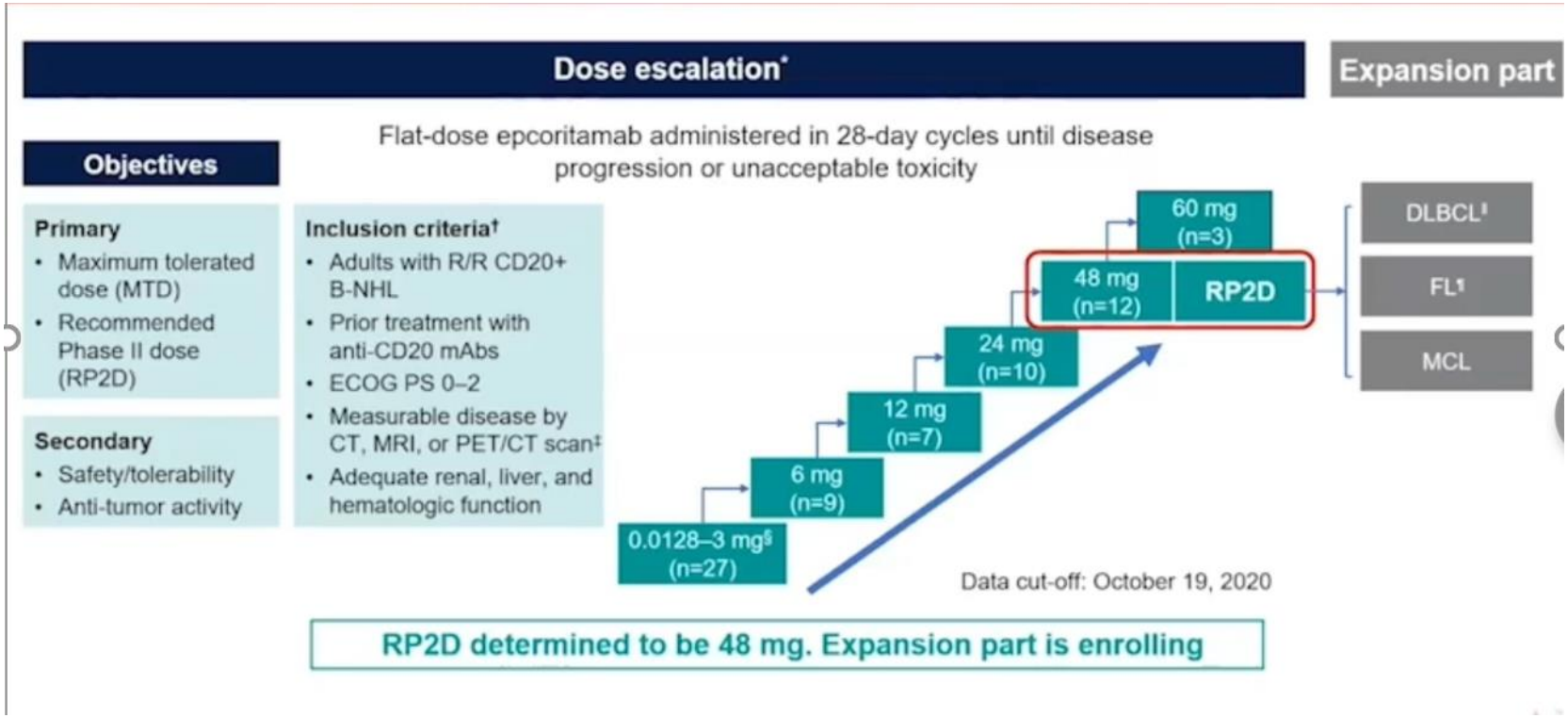
Abstract # 402: Subcutaneous Epcoritamab Induces Complete Responses with an Encouraging Safety Profile across Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma Subtypes, Including Patients with Prior CAR-T Therapy: Updated Dose Escalation Data

Hutchings M, et al.



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Characteristic	All histologies* (N=68)	DLBCL (n=46)	FL (n=12)
Median age, years (range)	68 (21–84)	68 (21–82)	73 (35–84)
Male, n (%)	45 (66)	30 (65)	8 (67)
Median time since most recent relapse or progression, months (range)	1.6 (0–88)	1.5 (0–88)	1.6 (1–17)
Prior lines of therapy, median (range)	3 (1–18)	3 (1–6)	5 (1–18)
Prior therapies, n (%)			
Anti-CD20 mAb	68 (100)	46 (100)	12 (100)
Anthracyclines	62 (91)	46 (100)	9 (75)
Alkylating agents	67 (99)	46 (100)	12 (100)
Autologous stem cell transplantation	7 (10)	5 (11)	1 (8)
CAR-T cell therapy	6 (9)	5 (11)	0 (0)
Refractory to, n (%)			
Most recent systemic therapy	59 (87)	42 (91)	10 (83)
Alkylating agents	56 (82)	40 (87)	9 (75)
CD20 mAbs	60 (88)	42 (91)	10 (83)
ECOG PS,† n (%)			
0	35 (52)	23 (50)	6 (50)
1	29 (43)	21 (46)	4 (33)
2	3 (4)	2 (4)	1 (8)

Patients were heavily pretreated; most patients were refractory to anti-CD20 therapy

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Response*	DLBCL (n=46)		FL (n=12)		MCL‡
	12–60 mg (n=23)	48–60 mg† (n=12)	0.76–48 mg (n=11)	12–48 mg (n=5)	0.76–48 mg (n=4)
Evaluable patients, n	22§	11§	10‖	5	4**
ORR, n (%)¶	15 (68)	10 (91)	9 (90)††	4 (80)	2 (50)
CR	10 (46)	6 (55)	5 (50)	3 (60)	1 (25)
PR	5 (23)	4 (36)	4 (40)	1 (20)	1 (25)
Stable disease, n (%)	1 (5)	0	0	0	1 (25)
Progressive disease, n (%)	5 (23)	0	1 (10)	1 (20)	0

Abstract # 626: Glofitamab Step-up Dosing Induces High Response Rates in Patients with Hard-to-Treat Refractory or Relapsed Non-Hodgkin Lymphoma
Hutchings M, et al.

- Phase I/Ib, dose-escalation, dose-expansion trial
- Patients (pts) with relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL)
- Obino given day -7 to avoid CRS

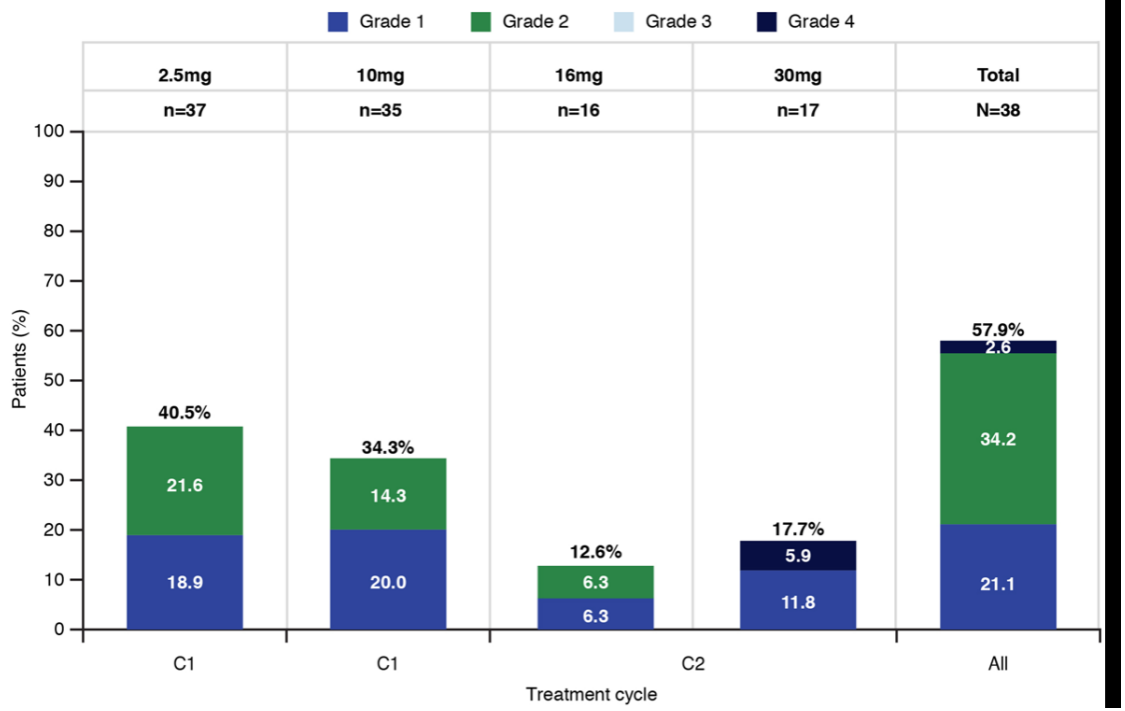
Patient Demographics

Table: Patient demographics and baseline disease characteristics

	All patients (N=38)
Age — year	
Median	68
Range	(52–85)
Male sex — no. (%)	22 (57.9)
ECOG PS — no. (%)	
0	23 (60.5)
1	15 (39.5)
2	0
Ann Arbor stage at study entry — no. (%)	
Number of evaluable patients*	38 (100)
Stage I	1 (2.6)
Stage II	4 (10.5)
Stage III	7 (18.4)
Stage IV	26 (68.4)
Aggressive non-Hodgkin lymphoma— no. (%)	28 (73.7)
Diffuse large B-cell lymphoma	12 (31.6)
Transformed follicular lymphoma	5 (13.2)
Mantle cell lymphoma	5 (13.2)
Richter's transformation	5 (13.2)
Follicular lymphoma (Grade 3B)	1 (2.6)
Indolent non-Hodgkin lymphoma — no. (%)	10 (26.3)
Follicular lymphoma (Grade 1–3A)	10 (26.3)

CRS rates and ORRs

Figure: The incidence of cytokine release syndrome in the cohorts of patients receiving step-up doses of glofitamab by treatment cycle and Lee Grade.



After a median follow-up of 2.8 months, across all efficacy-evaluable pts (n=32) the overall response rate (ORR) and complete metabolic response (CMR) rate was 62.5% and 40.6%, respectively.

Conclusions

- ASH 2020 highlights that treatment of Lymphomas continue to evolve
  - Targeted therapies, New combinations
  - Manipulation of the Immune system in RR disease
- There is no ‘one size fits all’ approach
- Translates into improved life expectancies

ASH 2020

QUESTIONS