Update in CLL/Lymphoma 2024

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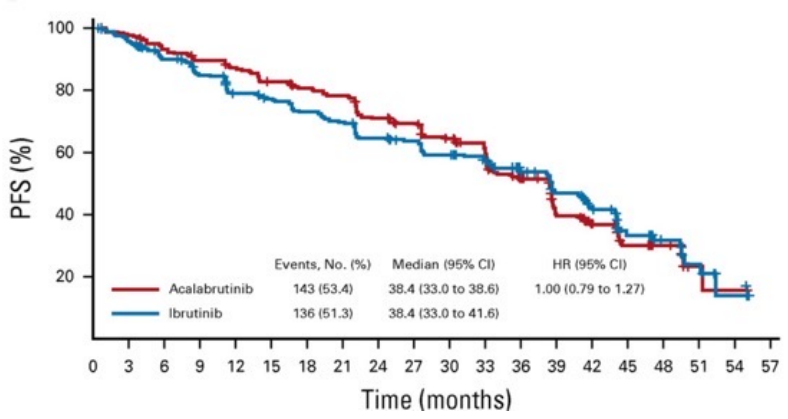
CLL

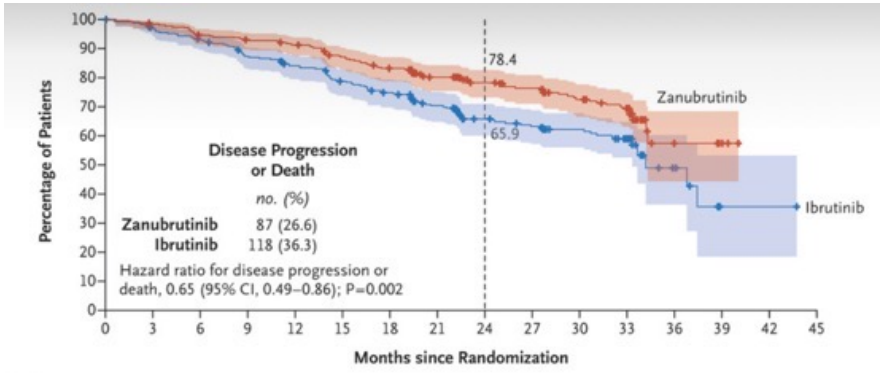
- Watch and Wait still best strategy until findings, counts or symptoms dictate therapy
- Vitamin D levels supplement immunity and may delay progression of CLL to treatment (Blood Adv 2024)
- Vaccinate patients

Approved BTK inhibitors CLL

Name	Other Disease Indication	Binding	Selectivity	Administration
Ibrutinib	WM	1st generation, irreversible covalent Cys481	Moderate	420/560/840 mg, QD
Acalabrutinib	MCL	2nd generation, irreversible covalent Cys481	High	100 mg BID
Zanubrutinib	MCL, MZL, WM, FL	2nd generation, irreversible covalent Cys481	High	160 mg BID or 320 QD
Pirtobrutinib: Received at least 2 lines including BTK and Bcl-2 inhibitor	MCL	3rd generation, reversible non-covalent to both WT BTK and Cys481	High	200 mg QD

Second generation superior





ELEVATE-RR Trial
(Acalabrutinib vs Ibrutinib)
JCO 39:3441, 2021
Non-inferior to ibrutinib for PFS
Less AF, HTN
Higher proportion of TP53 deletion and heavily treated than ALPINE

ALPINE Trial
(Zanubrutinib vs Ibrutinib, phase 3, not blinded)
NEJM 388:319, 2023
Non-inferior to ibrutinib for PFS and ORR (PFS persists at 39 months ASH Ab 202)
Less AF, cardiac events

Pirtobrutinib: BRUIN large phase I

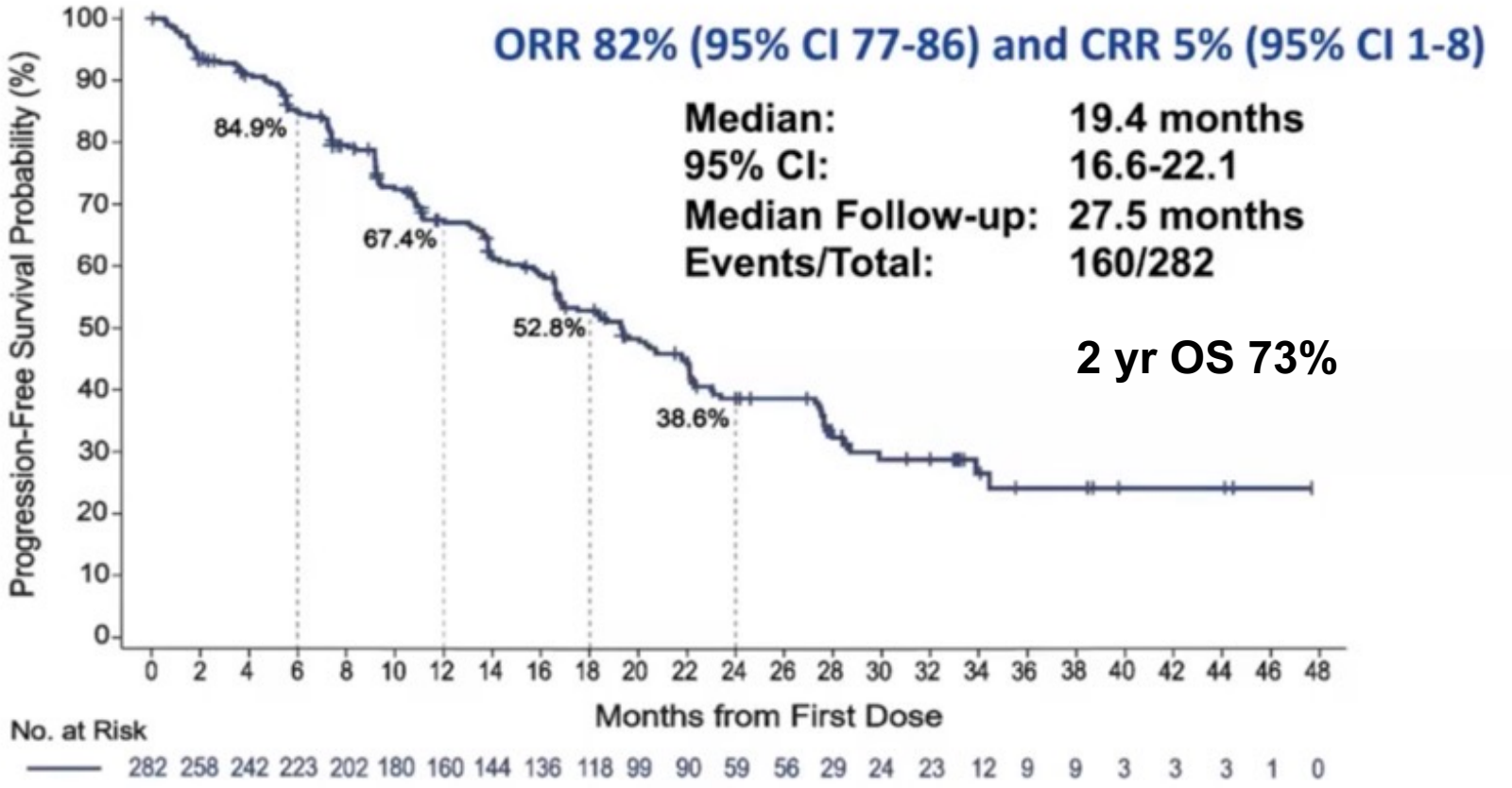
Sick patients, median 4 prior, all received BTK prior
Many received chemotherapy (no longer relevant)
About 46% with resistance mutation

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

30 month follow up BRUIN



ASH 2023 Ab 326 updated from NEJM 389:33, 2023

Pirtobrutinib may be considered in patients who fail covalent BTK inhibitor (or intolerant to both) or Bcl-2 inhibitor

CLL Strategy

Time limited up front, infusion	Go to failure up front, all oral
Venetoclax/Obinutuzumab (Can retreat especially if over a year)	2nd Generation BTK inhibitor (Can switch between for side effects)
2nd Generation BTK inhibitor (Can switch between for side effects)	Venetoclax/Obinutuzumab (Can retreat especially if over a year)
Pirtobrutinib (after failure of BTK and Venetoclax)	
CarT (Lisocabtagene Maraleucel approved 3/2024 based on TRANSCEND CLL 004 study for same indication as Pirtobrutinib but CR rate 20% with duration at least 1 year) vs PI3Kdelta inhibitor vs clinical trial (at any time)	

BOVen Trial

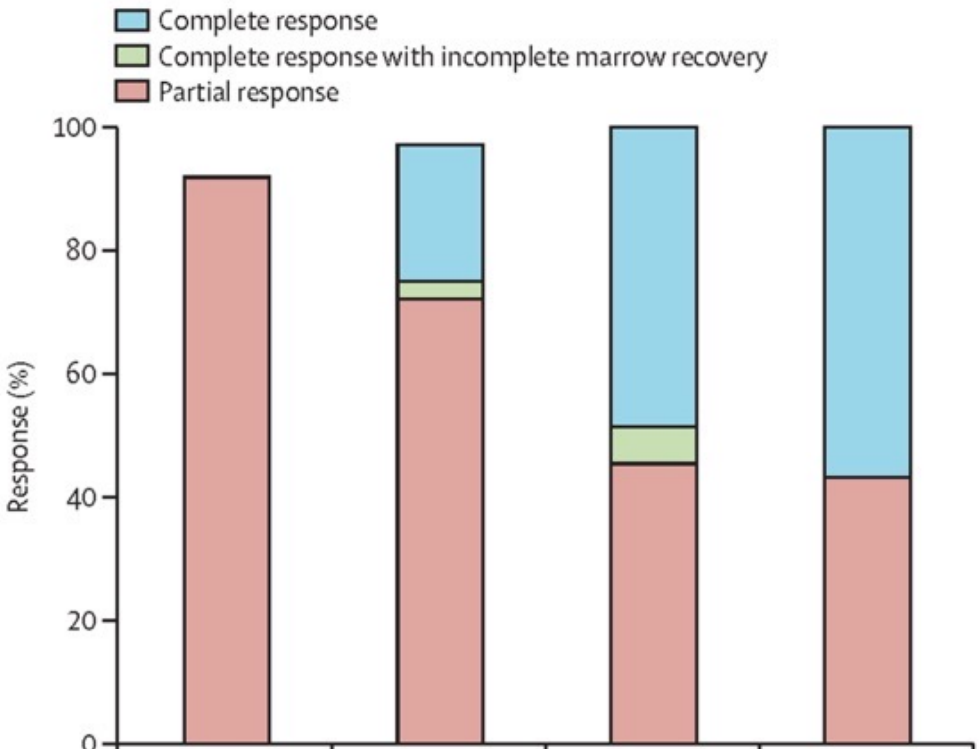
	Patients (n=39)
Age, years	62 (52–70)
Sex	
Female	9 (23%)
Male	30 (77%)
Race and ethnicity	
White and non-Hispanic	35 (90%)
Unknown	4 (10%)
Median lymphocyte count (per μL)	43 400 (20 450–103 300)
Immunoglobulin heavy-chain variable region unmutated	28 (72%)
Chronic lymphocytic leukaemia with high-risk or very-high-risk CLL-IPI	26 (67%)
17p deletion or *TP53* mutation	5 (13%)
17p deletion	2/39 (5%)
TP53 mutation	5/38 (13%)
NOTCH1 mutation	6/38 (16%)
SF3B1 mutation	5/38 (13%)
Fluorescence in-situ hybridisation (hierarchical)	
17p deletion	2 (5%)
11q deletion	6 (15%)
Normal	17 (44%)
Trisomy 12	5 (13%)
13q deletion	9 (23%)

Up front triplet therapy with end-point based on achievement of MRD by ClonSeq (10^{-4})

Lancet Haematol 8:e879, 2021

BOVen Trial

-Well tolerated
-Achieved uMRD ($<10^{-4}$) in blood (96%) and marrow (92%)
-Median duration of therapy was 10 months
Durable PFS
-MRD-free ($<10^{-4}$) survival about 30 months

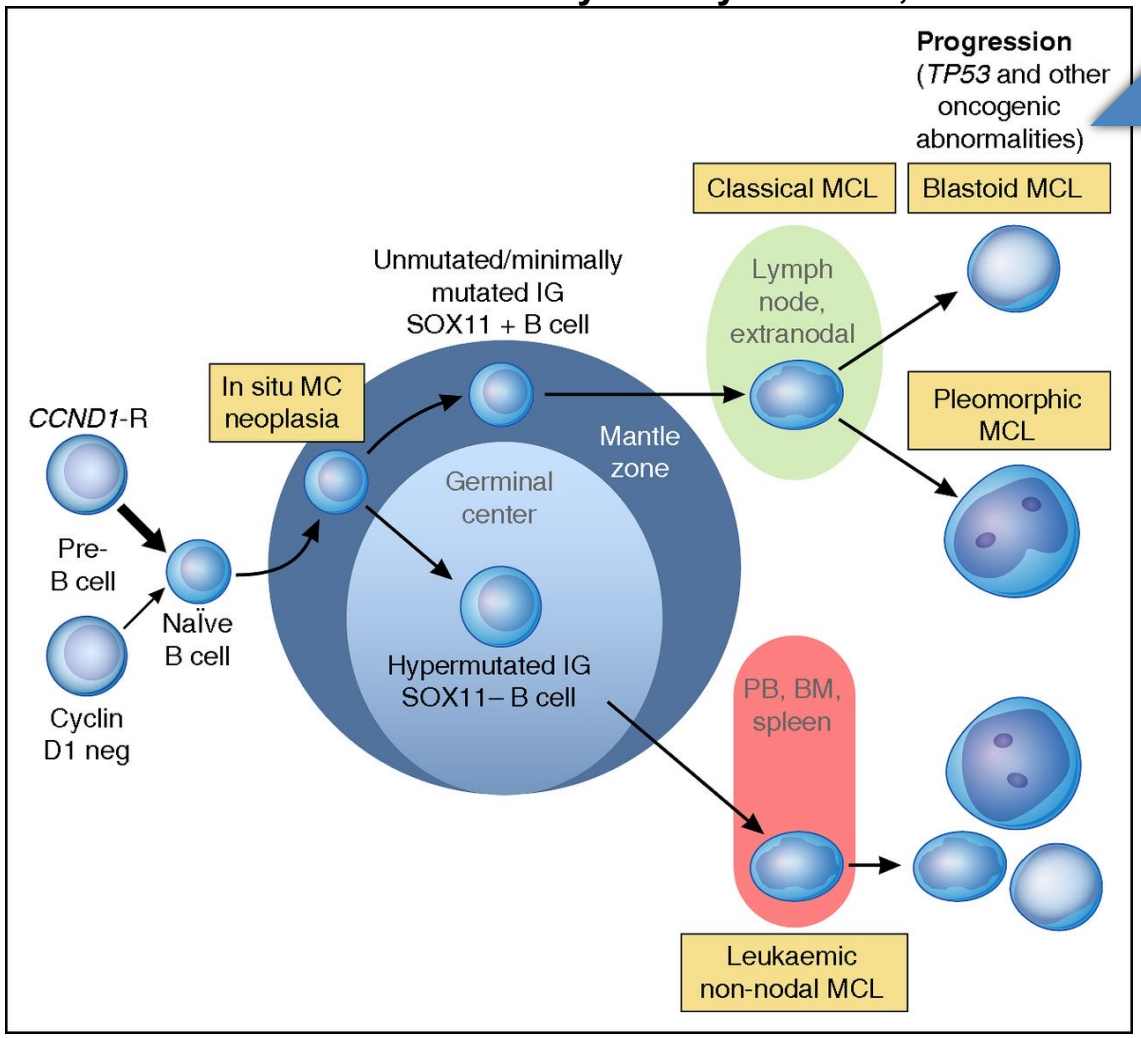


	2 months (n=37)	6 months (n=36)	At treatment discontinuation (n=33)	Best response (n=37)
Overall response (%)	34/37 (92%)	35/36 (97%)	100/100 (100%)	37/37 (100%)
Complete response or complete response with incomplete marrow recovery (%)	0/37 (0%)	9/36 (25%)	18/33 (55%)	21/37 (57%)

Mantle Lymphoma

- Watch and Wait still best strategy until findings, counts or symptoms dictate therapy
- Vaccinate patients
- Spectrum of disease

Proposed model of molecular pathogenesis in the development and progression of major subtypes of MCL. Precursor B cells usually with but sometimes without a CCND1 rearrangement mature to abnormal naïve B cells which may initially colonize, often the inner p...



Aggressivness

Very aggressive
ALL like therapy
Consideration for CarT
vs Allo

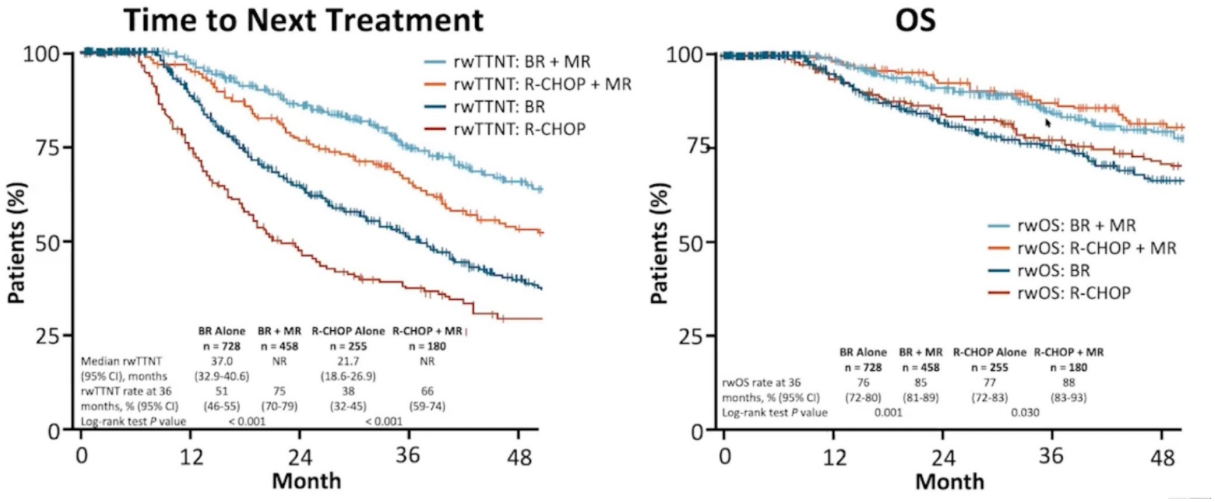
Ki67>30% indicates
More aggressive
Younger/Fit for Txp
?Maintenance

Indolent like CLL
t(11;14) not others
Sox11 neg

Steven H. Swerdlow et al. Blood 2016;127:2375-2390

Fit for Transplant?

Rituximab plus high dose cytarabine based regimen vs BR vs other followed by PBSCT
E1411 did not show advantage of adding bortezomib to BR AND 3-year maintenance rituximab post PBSCT OS advantage (NEJM 2017)



FLATIRON Trial 2021

Can you go directly to maintenance without PBSCT for deep remission patient?

Older/Nonfit

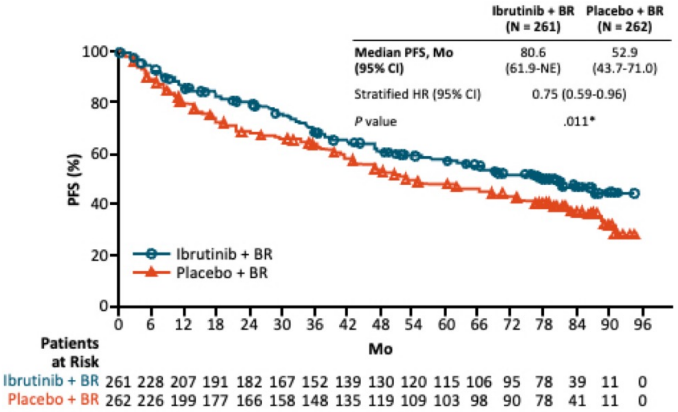
	N	Age	ORR	CR	mPFS
R-CHOP	244	66	89%	42% (CT)	14.4 mo
VR-CAP	243	65	92%	53% (CT)	24.7 mo
BR**	188	70	~90%	~45% (CT)	35-48 mo
RBAC500	57	71	91%	91% (PET)	Not reached

No Maintenance

"R squared": Lenalidomide/Rituximab
NEJM 2015/JCO 2018

Front line, 38 patients, ORR 92%, CR 64%
3y PFS 80%, OS 90%
5y PFS 64%, OS 77%
8/10 patients in CR at 3y are MRD negative
No difference in ORR for MIPI or Ki-67

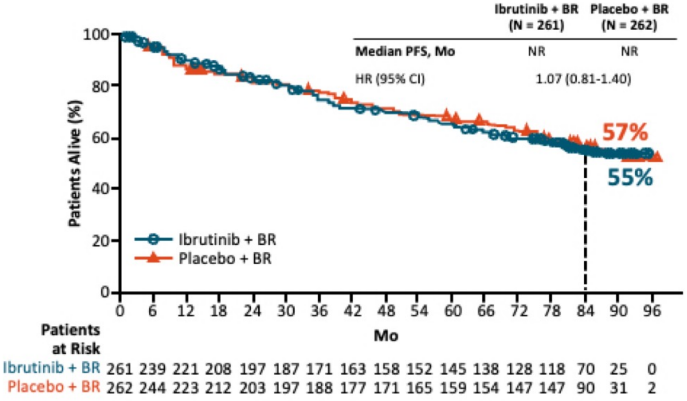
SHINE: Phase III BR vs IBR



Median PFS, Mo	Ibrutinib + BR	Placebo + BR	HR (95% CI)
Patients with blastoid/ pleiomorphic histology	25.6	10.3	0.66 (0.32-1.35)
Patients with *TP53* mutation†	28.8	11.0	0.95 (0.50-1.80)

*In this analysis, there were 19 patients in the ibrutinib plus BR arm and 26 in the BR + placebo arm. †In this analysis, there were 26 patients in the ibrutinib † BR arm and 24 in the BR + placebo arm.

- Median follow-up: 84.7 mo (7.1 yr)
- A 2.3-yr statistically significant and clinically meaningful improvement in median PFS was observed in the ibrutinib arm vs the placebo arm



Deaths due to PD and TEAEs, n (%)*	Ibrutinib + BR (n = 261)	Placebo + BR (n = 262)	HR
Overall	58 (22.2)	70 (26.7)	0.88
▪ PD	30 (11.5)	54 (20.6)	
▪ TEAEs	28 (10.7)	16 (6.1)	

*Exploratory analysis.

- COVID-19–related deaths in 3 patients in the ibrutinib arm during TEAE period and in 2 patients in the placebo arm after TEAE period

Relapsed Mantle?

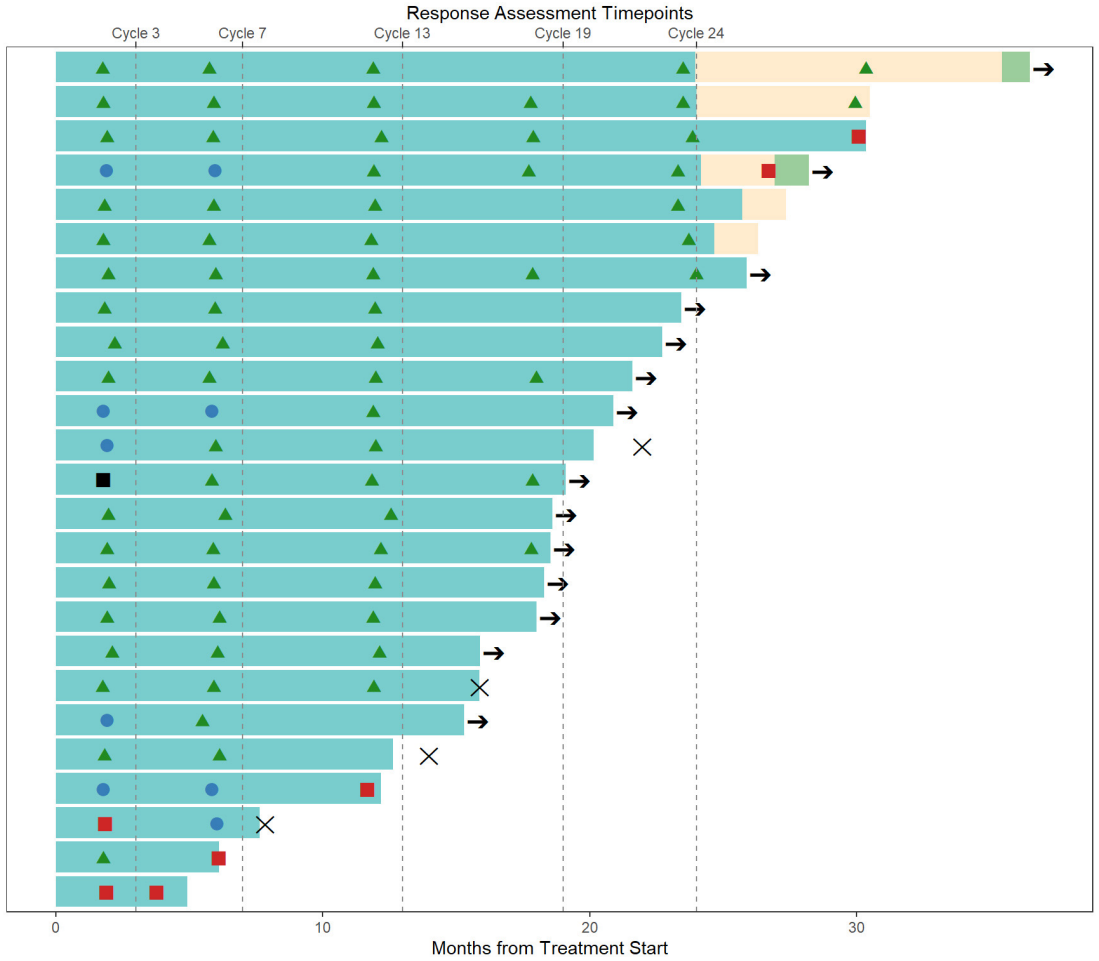
Younger/Fit high risk: Consideration of allo

Older/Other:

Agent	N	Response Rate	mDOR
Bortezomib	155	33%	9.2 months
Temsirolimus	54	22%	7.1 months
Lenalidomide	134	28%	16.6 months
Lenalidomide-rituximab	52	57%	18.9 months
Idelalisib	40	40%	4 months
Ibrutinib	111	68%	17.5 months
Acalabrutinib	124	81%	72% at 12 m
Venetoclax	28	75%	12 months
Ibrutinib-Venetoclax	24	71% (all CR)	80% at 12 m

- Separate indolent and blastoid subsets and for the middle group, especially for Ki-67>30%:
  - High dose therapy still improves depth of remission for transplant eligible patients in the modern age of therapy
  - Question of maintenance based on depth of remission
  - Standard chemotherapy giving way to targeted therapy
  - Acalabrutinib advantages over ibrutinib
  - Venetoclax effective in MCL be mindful of tumor lysis
  - Combination therapies of targeted and immune therapies will increase depth of remission
  - ZUMA-2 published CarT 2020, deep remission, early data

A Multicenter Phase 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Patients with Treatment-Naïve, TP53-Mutant Mantle Cell Lymphoma



2 y PFS 72% (COVID)
2 y OS 79%

Anita Kumar,Jacob Soumerai,Jeremy S. Abramson,Jeffrey A. Barnes,Philip Caron,Maria Chabowska,Mary Devlin,Ahmet Dogan,Lorenzo Falchi,Rayna N. Garcia,Clare Grieve,Emma Haskell,Julie E. Haydu,Patrick Connor Johnson,Ashlee Joseph,Hailey E. Kelly,Alyssa Labarre,Emerald D Littlejohn,Jennifer Kimberly Lue,Joanna Mi,Rosalba Martignetti,Grace McCambridge,Alison Moskowitz,Colette Owens,Sean F. Plummer,Madeline G. Puccio,Gilles Salles,Venkatraman Seshan,Natalie Slupe,Andrew D. Zelenetz, A Multicenter Phase 2 Trial of Zanubrutinib, Obinutuzumab, and Venetoclax (BOVen) in Patients with Treatment-Naïve, TP53-Mutant Mantle Cell Lymphoma, Blood, 2023, Figure 1

Follicular Lymphoma

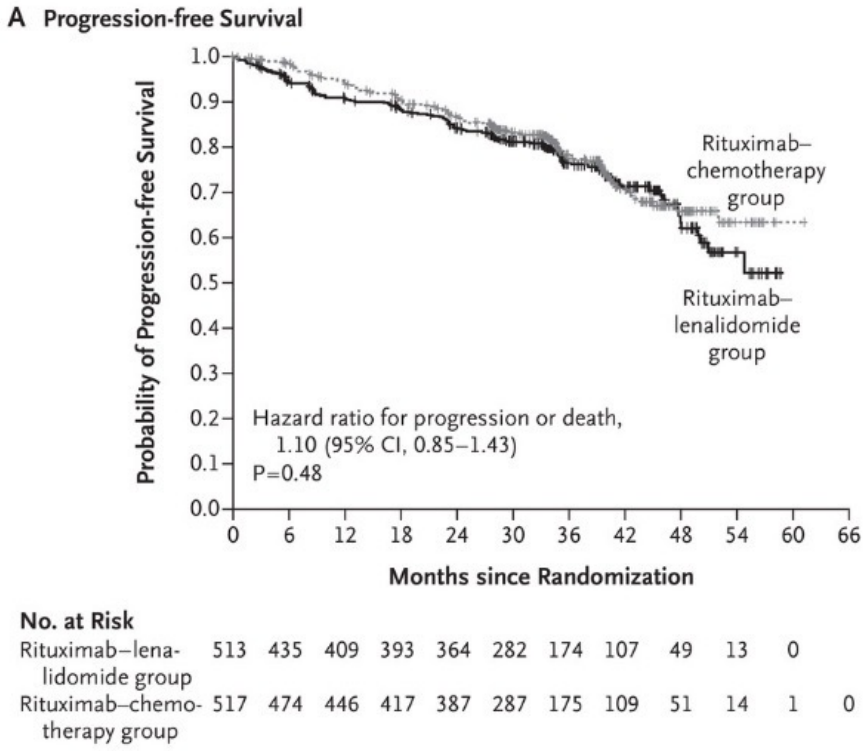
- Median OS of follicular lymphoma is approaching 20 years
- Treatment options for newly diagnosed advanced-stage patients include multiple immunochemotherapy regimens +/- anti-CD20 maintenance therapy, not BTK or PI3KI
- Now with several approved options for relapsed/refractory disease

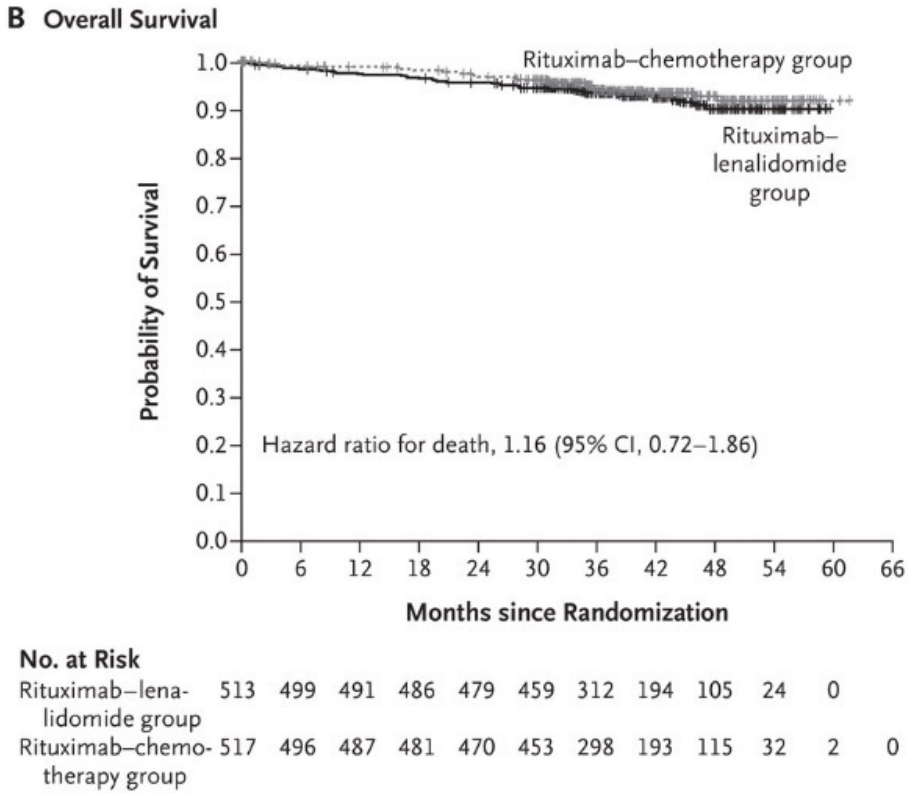
GELF Criteria	BNLI Criteria
High tumor bulk: >7cm mass, ascites/effusions, 3 separate nodes >3cm, Symptomatic splenomegaly, Organ compression	Rapid disease progression 3 months
	Life-threatening organ involvement
	Liver or renal infiltration
Systemic symptoms	Bone lesions
Elevated LDH or Beta-2 microglobin	Systemic symptoms or pruritus
Leukemia or blood cytopenia	Hb<10, WBC<3, Plt<100K 2º marrow

Initial therapy

Chemoimmunotherapy generally first line			R^2 consideration (chemotherapy free)	R maintenance?
StiL, Phase 3 BR vs R-CHOP	BRIGHT, Phase 3 BR vs R-CHOP/R-CVP	GALLIUM, Phase 3 G vs R plus chemo	RELEVANCE, Phase 3 R^2 (lenalidomide/R) vs R-chemo	PRIMA, Phase 3 R maintenance
BR superior to R-CHOP	Trent toward PFS improvement with BR vs R-CHOP/R-CHP	Superior PFS with G but same OS More grade 3-5AE with G G approved 2017 and maintenance	Similar efficacy with R^2 vs R-chemo Less hematologic but more cutaneous toxicity with R^2	Superior PFS and TTF but not OS R approved 2011 maintenance

RELEVANCE Trial



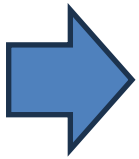


NEJM 379:934, 2018

Initial consideration relapse

BR vs GR (not if previous bendamustine)
R-CHOP vs G-CHOP
R-CVP vs G-CVP
R2
Tazemetostat if EZH2 positive or disease without other alternative

Immunotherapy



R vs G maintenance

Autologous SCT

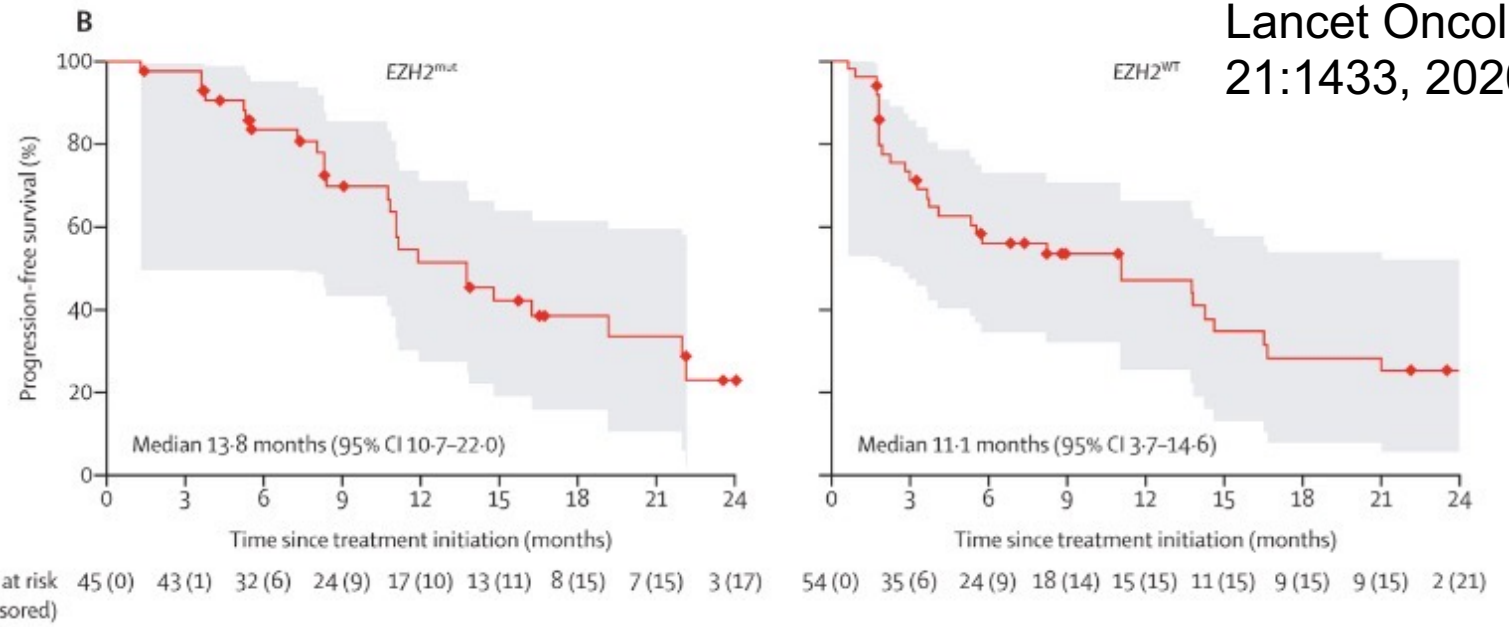
Allogeneic SCT

Immunotherapy

Keep in mind the effect and timing of chemotherapy for immunotherapy

EZH2:Tazemetostat oral inhibitor

EZH2 mutations lock B-cell in germinal state and pathway relevant in follicular lymphoma; 20% of patients have activating mutation
Alone effective (approved 2020) and now being combined with rituximab, anti-CD20 and immune therapies

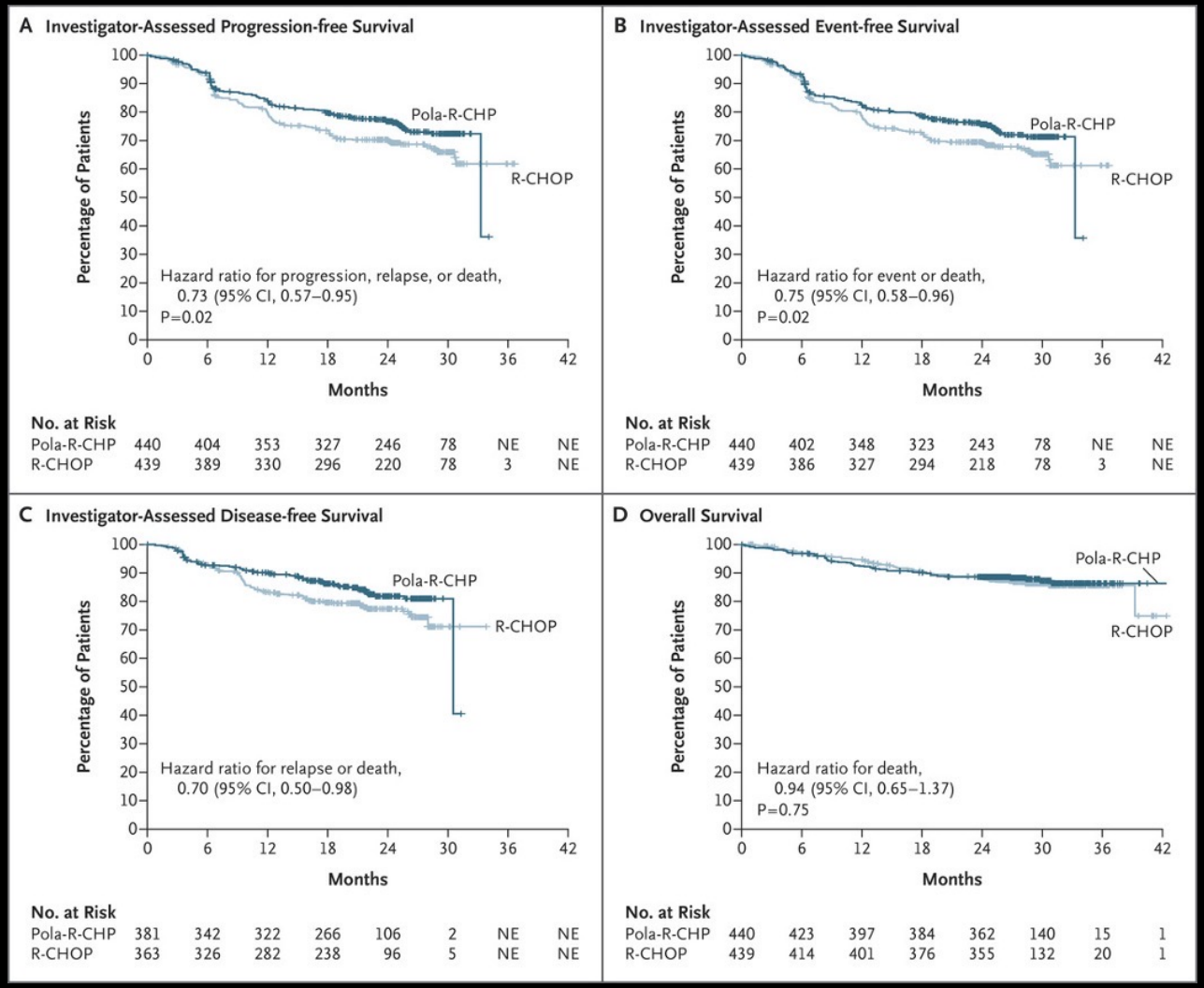


Lancet Oncol 21:1433, 2020

Large Cell Lymphoma

- Up front therapy with R-CHOP vs Pola-R-CHP
- Second line: PBSCT vs Tafasitamab-Lenalidomide vs CarT
- Third line: Pola-BR vs Loncastuximab tesirine vs Car-T

POLARIX: Overall results

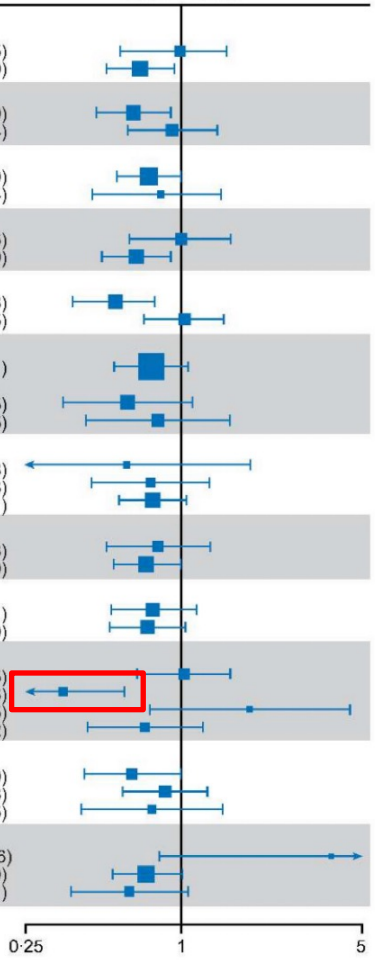


H Tilly et al. N Engl J Med 2022;386:351-363.

The NEW ENGLAND JOURNAL of MEDICINE

POLARIX: Subsets

Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



H Tilly et al. N Engl J Med 2022;386:351-363.

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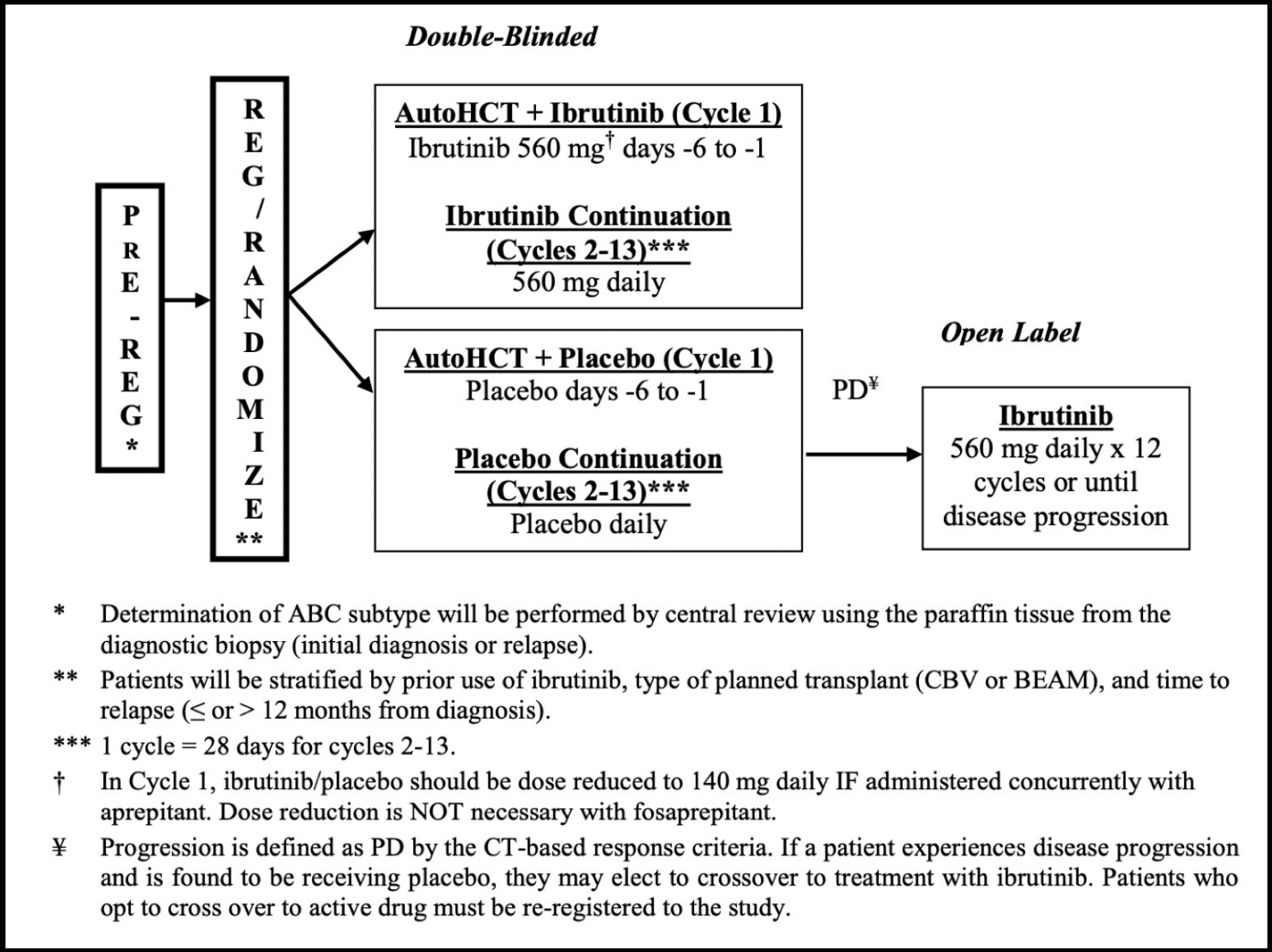
Activated B: A051301



* Determination of ABC subtype will be performed by central review using the paraffin tissue from the diagnostic biopsy (initial diagnosis or relapse).

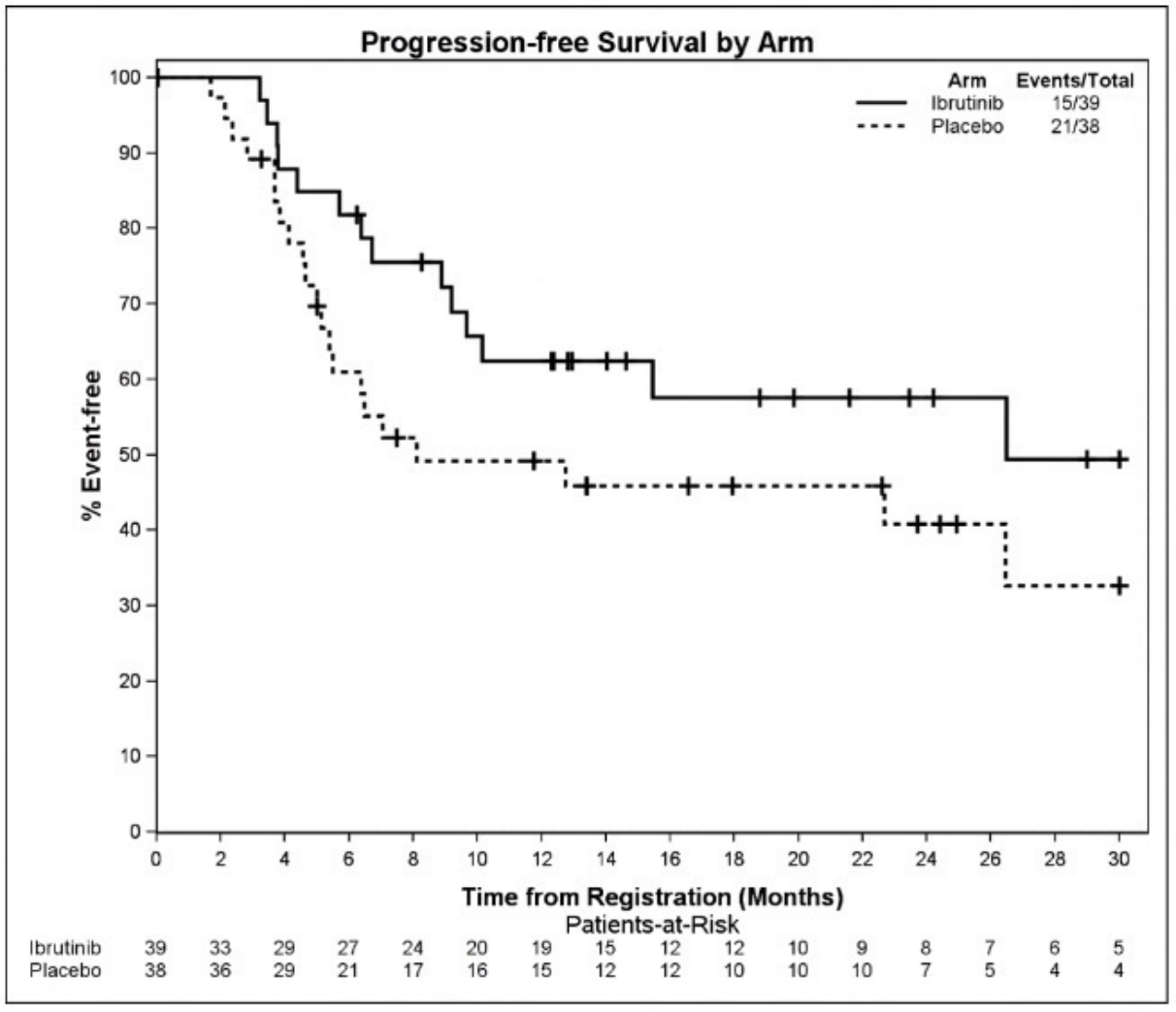
** Patients will be stratified by prior use of ibrutinib, type of planned transplant (CBV or BEAM), and time to relapse (≤ or > 12 months from diagnosis).

*** 1 cycle = 28 days for cycles 2-13.

† In Cycle 1, ibrutinib/placebo should be dose reduced to 140 mg daily IF administered concurrently with aprepitant. Dose reduction is NOT necessary with fosaprepitant.

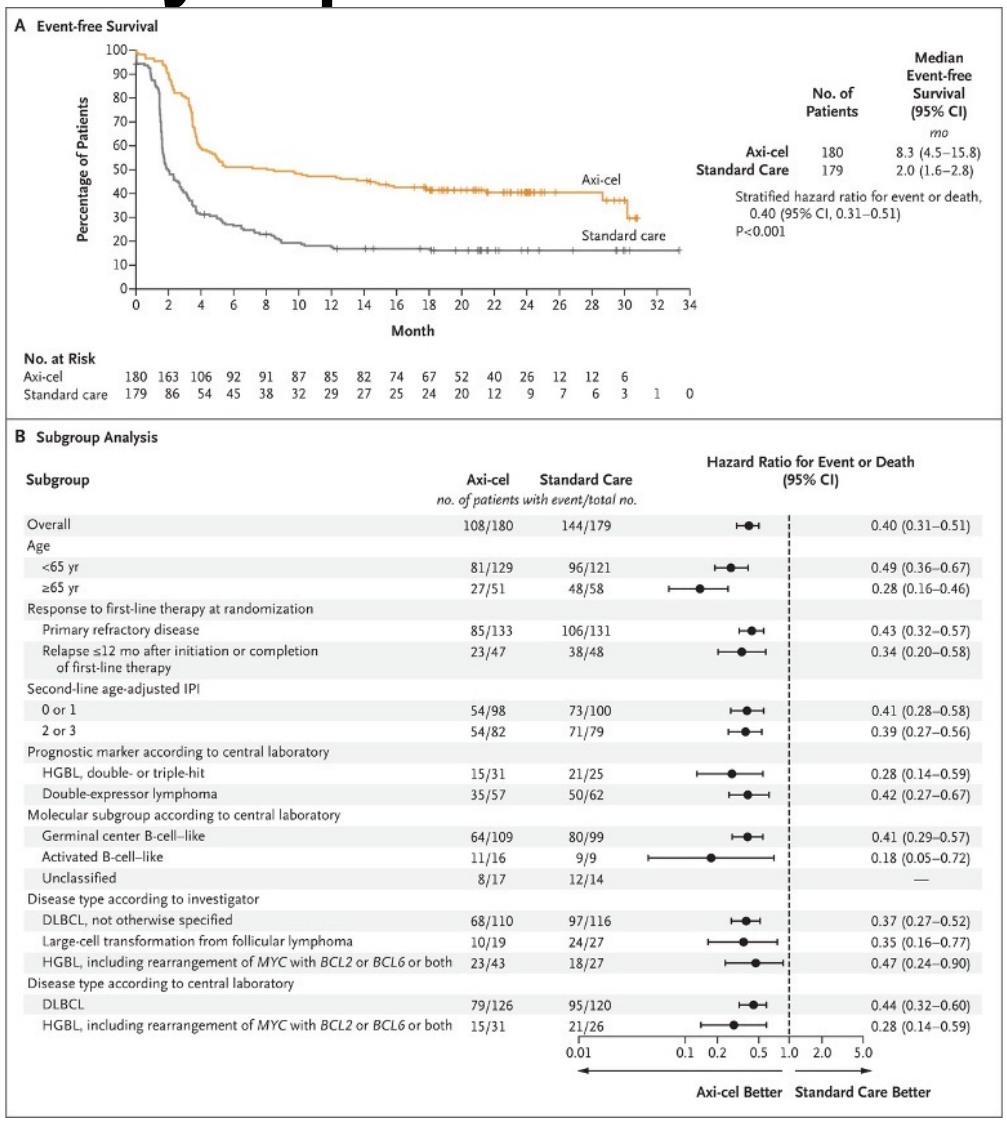
¥ Progression is defined as PD by the CT-based response criteria. If a patient experiences disease progression and is found to be receiving placebo, they may elect to crossover to treatment with ibrutinib. Patients who opt to cross over to active drug must be re-registered to the study.

Activated B: A051301



ASH 2023
Ab 437

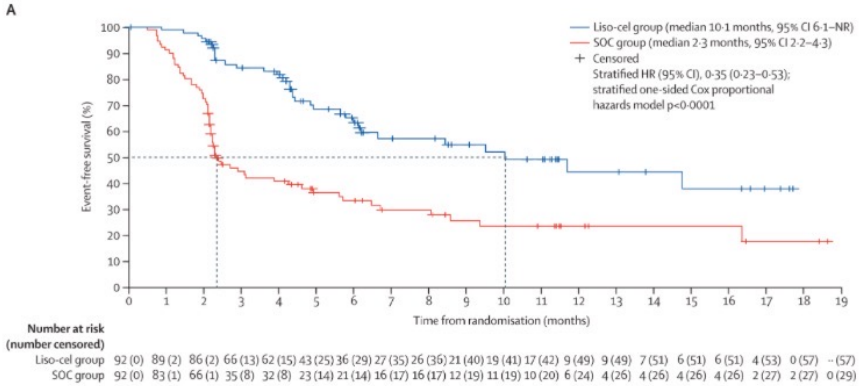
Axi-cel 2nd line aggressive lymphoma ZUMA-7

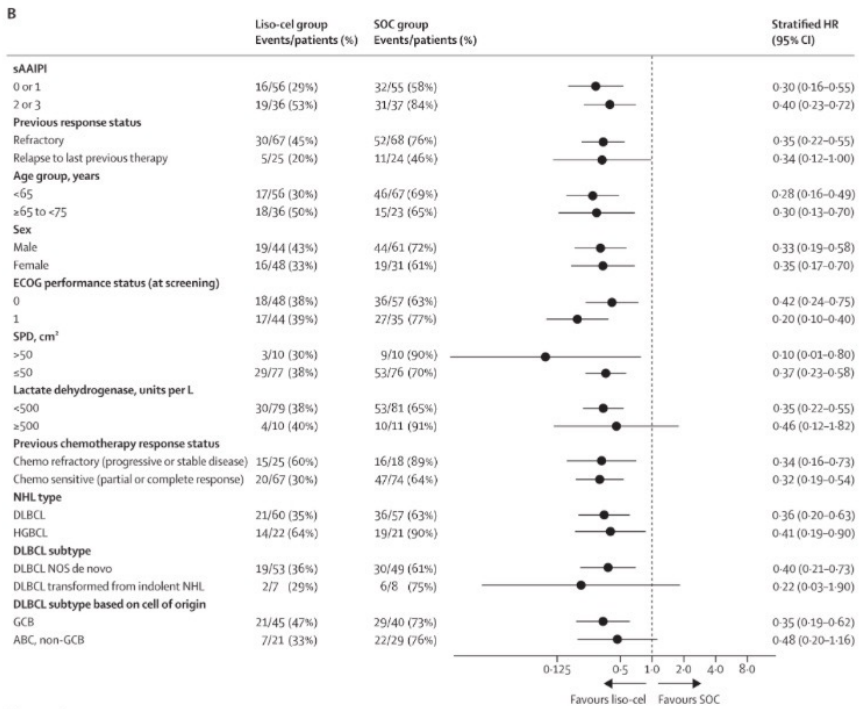


- Only glucocorticoids allowed for bridging and impending organ compromise not allowed
- 36% went on to PBSCT; only 7% with activated B-cell
- Ab 7565: Durable responses better in tumors with better expression of B-cell antigens (CD19,20, BCMA)

N Engl J Med 386:640, 2022

Liso-cel 2nd line aggressive lymphoma TRANSFORM

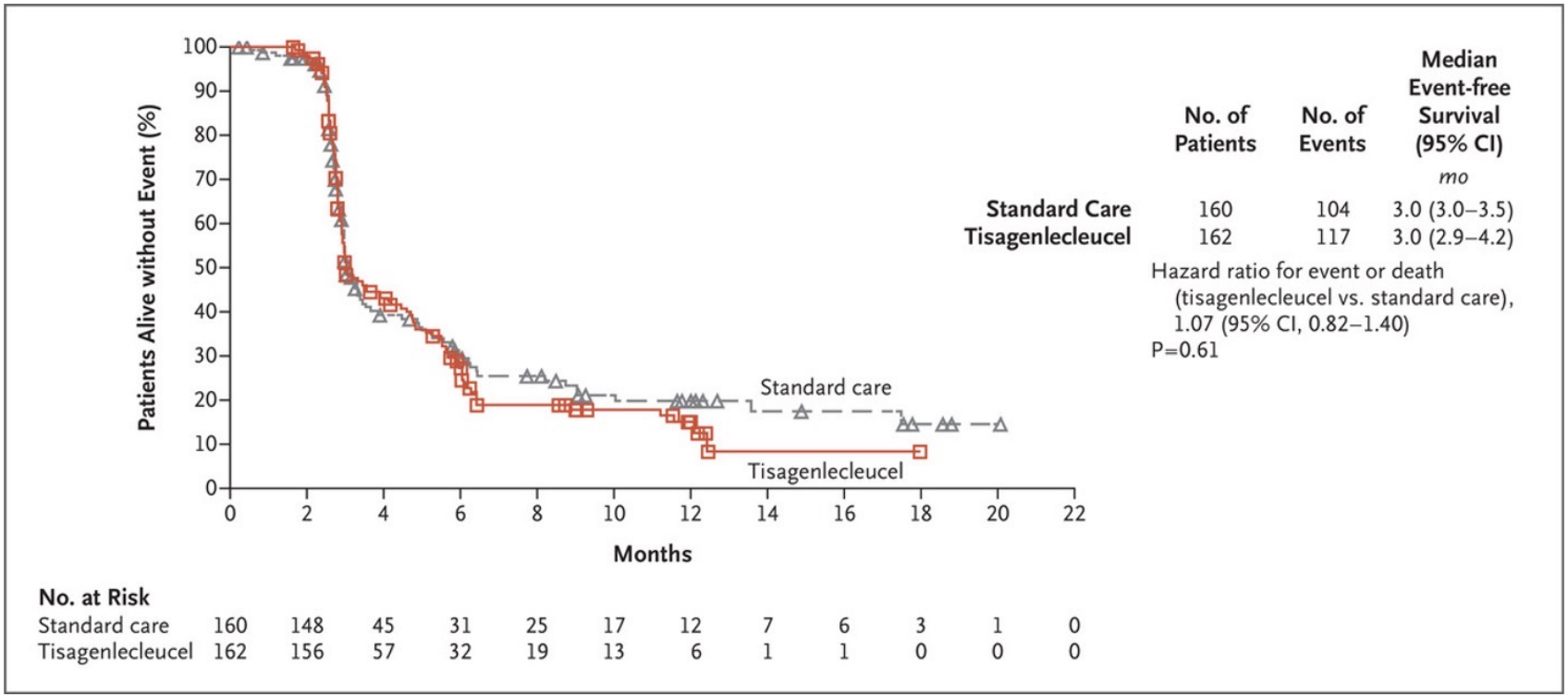




- 4x improved EFS 2.5x improved PFS in this phase 3 study
- Better in all subgroups and potentially better OS (immature at publication)
- Good safety profile

Lancet 399:2294, 2022

Tisagenlecleucel 2nd line aggressive lymphoma



- Impending organ system dysfunction allowed and 83% received bridging chemotherapy
- 32% went on to PBSCT

N Engl J Med 2022;386:629-639

Axi-Cel Vs Tisagenlecleucel

	Axicabtagene ciloleucel	Tisagenlecleucel
Co-stim Domain	CD28	4-1BB
Retrovirus	Retrovirus	Lentivirus
Production turnaround	Rapid	Slower
Early trials	Similar efficacy and toxicity	

- Axicabtagene ciloleucel might be considered over PBSCT for steroid controlled without organ compromise

Phase II Glofitamab BiTE

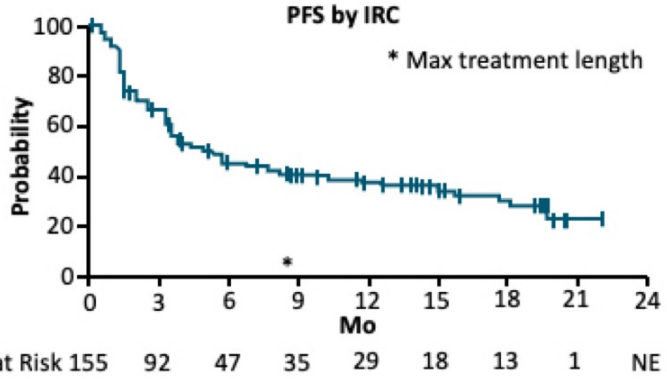
Patients with DLBCL NOS, HGBCL, transformed FL, or PMBCL; ECOG PS 0-1 and ≥2 prior therapies, including anti-CD20 and anthracycline (N = 155)

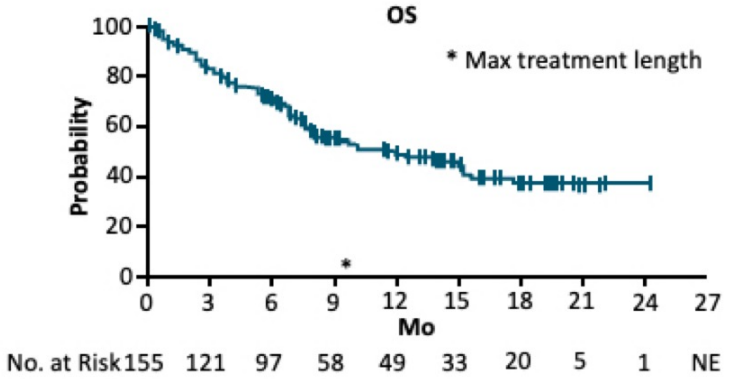
Cycle 1 (21 Days)

D1: Obinutuzumab pretreatment (1 x 1000 mg)
D8: Glofitamab IV 2.5 mg, monitoring after first dose
D15: Glofitamab IV 10 mg

Cycles 2+ (21 Days), Up to 12 Cycles

D1: Glofitamab IV 30 mg





Outcome, % (95% CI)	Glofitamab (N = 155)
Median PFS, mo (95% CI)	4.9 (3.4-8.1)
6-mo PFS rate	45.5 (37.2-53.8)
12-mo PFS rate	37.1 (28.5-45.8)
Median OS, mo (95% CI)	11.5 (7.9-15.7)
12-mo OS rate	49.8 (41.1-58.5)

40% CR, CRS low grade, first BiTE with meaningful outcome

Careful with Bendamustine ahead of T-cell collection (follicular, etc)

Tisagenlecleucel

•For adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).
•For young adult patients up to age 25 with relapsed or refractory acute lymphoblastic leukemia (ALL).
•Follicular lymphoma (failing 2 lines, ELARA, better tolerated, curative for some?)

Brexucabtagene autoleucel

•For patients with relapsed or refractory mantle cell lymphoma.
•For adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Axicabtagene ciloleucel

•For patients with the following conditions that have either not responded to or have relapsed following two or more lines of systemic therapy:

- Diffuse large B-cell lymphoma (DLBCL)
- Primary mediastinal B-cell lymphoma
- High grade B-cell lymphoma
- DLBCL that results from follicular lymphoma
- Follicular lymphoma (failing 2 lines, ZUMA-5, curative for some?)

Careful with Bendamustine ahead of T-cell collection (follicular, etc)

Lisocabtagene maraleucel

•For adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including:

- Diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma)
- High-grade B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Follicular lymphoma grade 3B and

- Relapsed/refractory follicular lymphoma failing 2 prior lines (5/15/24)
- Relapsed/refractory mantle cell lymphoma failing 2 prior lines (5/30/24)
- CLL failing 2 lines with BTK and Bcl2 inhibitors

Third line agents no transplant no CarT (Major question is whether these treatments cure as we think sometimes happens for CarT; no clear plateau at 12 months)

Antibody-drug conjugates

- Polatuzumab vedotin
  - Pola-BR vs BR (phase II data approval)
- Loncastuximab tesirine (third line)
  - LOTUS2 (single arem phase 2, 25-30% CR-70% at 2 year for CR. Q3weeks for one year. Effusions/photosensitivity

Tafasitamab-Lenalidomide (second line and beyond)

- LMINE Phase II

CD20 Bispecific Antibodies (CRS usually low grade, step up dosing, admission still recommend for first dose; first month at primary treatment center for potential grade 3 patients). Both B cell and T cell depletion through redirection (infectious prophylaxis needs)

•Glofitamab: IV, fixed duration (first step up dose cycle 1 day 8 highest risk CRS, less than 5% by cycle 3)

- Diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma)
- High-grade B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Follicular lymphoma grade 3B
- Relapsed/refractory follicular lymphoma failing 2 prior lines (5/15/24)
- Relapsed/refractory mantle cell lymphoma failing 2 prior lines (5/30/24)

Epcoritamab: subcutaneous, treat until relapse (first targeted dose cycle 1 day 15 highest risk CRS, less than 5% cycle 3)

Mosunetuzumab: Follicular

CD20xCD3 in trial follicular NHL

	Phase	N	ORR%	SAE%	Grade 3 AE
Mosunetuzumab	1/2	90	78.9	CRS 44	Neutropenia Hyponatremia
Glofitamab	1/2 with G	171	65.7	CRS 50 Fever 46	Neutropenia Infections
Plamotamab	1	53	43.4	CRS 63	
Epcortimab	1/2	68	68	CRS 59 Fever 69	Neutropenia, Anemia, Pneumonia, Low PO4
Odronextamab	1	145	51	CRS 61 Fever 73	Anemia, neutropenia, thrombocytopenia, Low PO4

Management of BiTE Toxicity

CD3:CD20 BiTE: Blood 143:1565, 2024
CRS: Higher lymphoma burden→higher risk
Tumor flare in 3-7% with increased pain (steroids)
Cytopenias: lowest levels 2-4 months (skip dose)
Infections: previous higher mortality during COVID in trials. Vaccinate (VZV, COVID, Pneumo, Influenza), Pre-test (Hep B/C, HIV, CMV/EBV), prophylactic abx and measure Ig levels (replace)
ICANS: Rare compared to CarT, mostly grade 1-2 (steroids, anti-epileptic drugs)

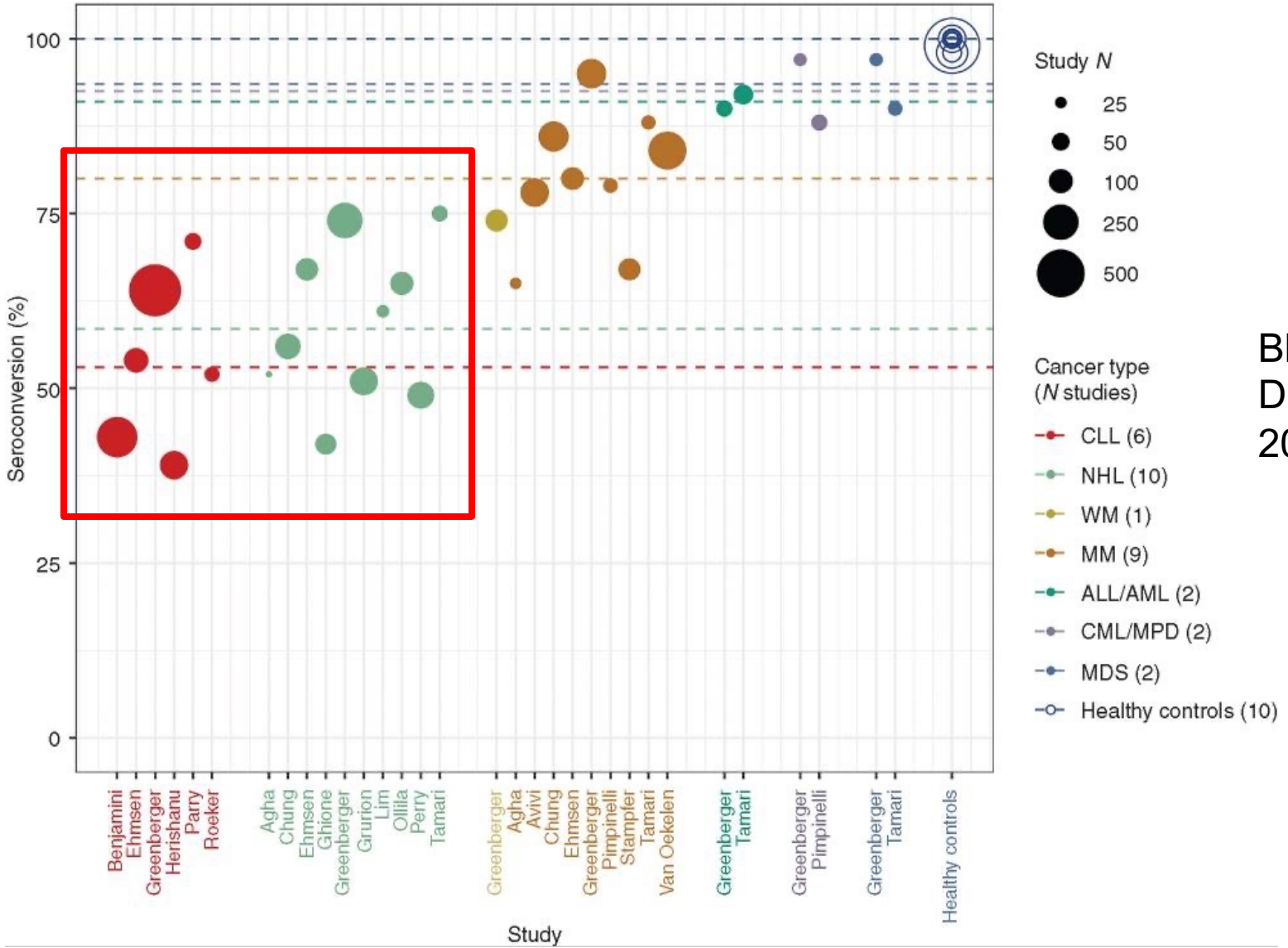
Immunotherapy in Community

Bottom line is to work with your transplant/cellular therapy center for CarT and initial treatment BiTE and become familiar with later potential SAE as these therapies mature. Immune based therapies are moving earlier in treatment.

Oncologist as Immunologist

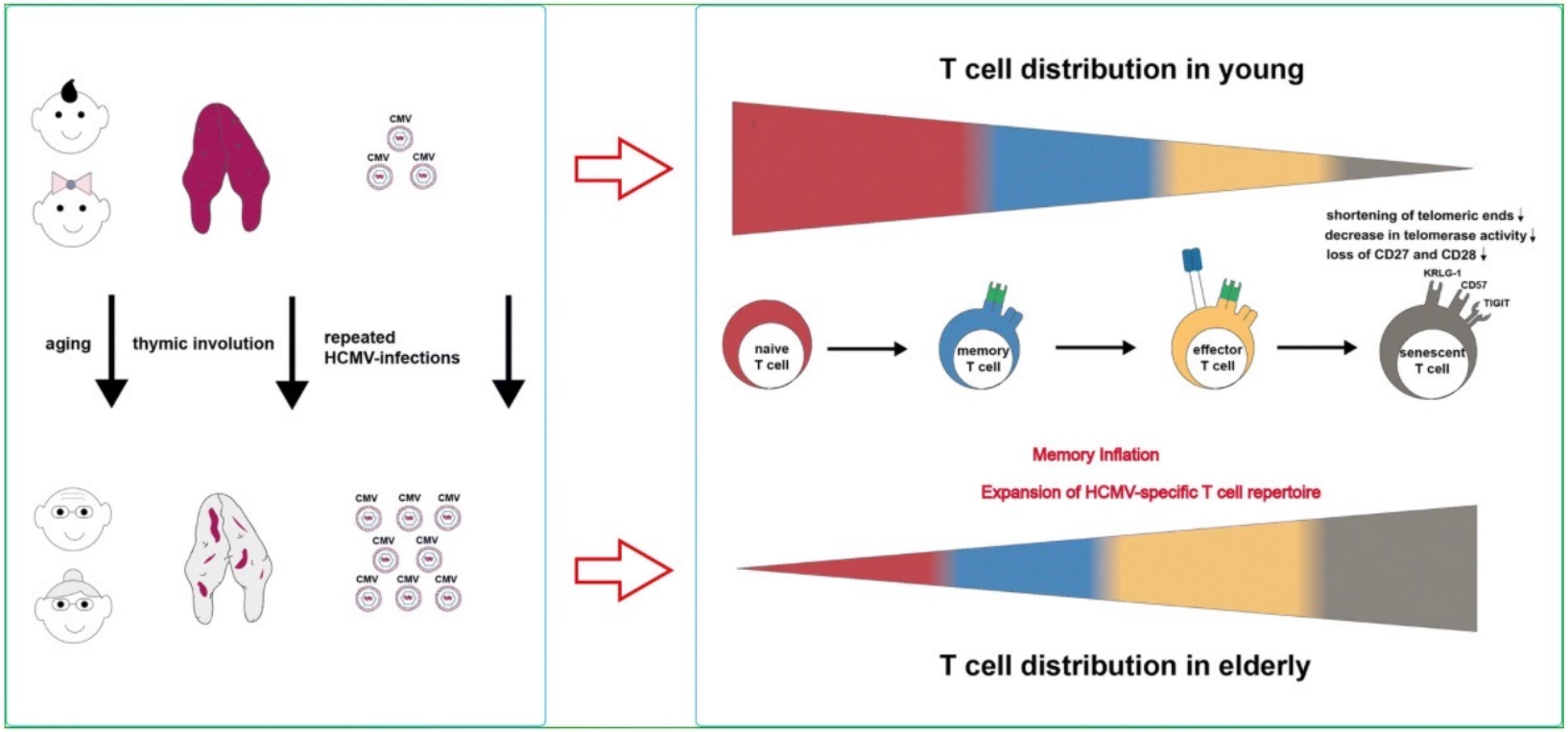
Optimization and planning for inevitable immune based therapy

Rates of Anti COVID IgG



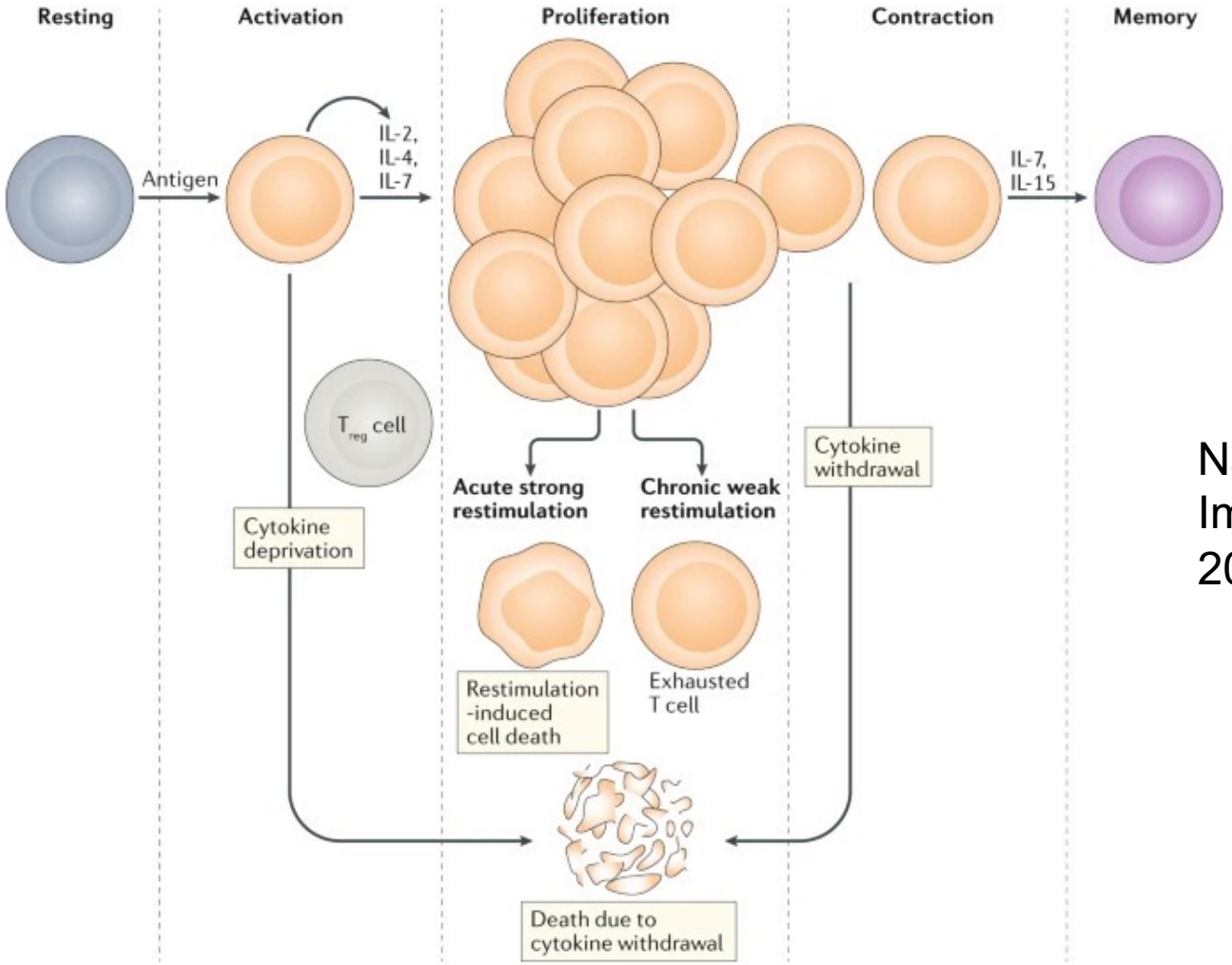
Blood Cancer Discov 2:562, 2021

T-cell exhaustion



J of Hematology & Oncology 11:91, 2018

T-cell physiology



Natrure Rev Immunol 20:651, 2020

Figure 1.- CAR T-cell composition at peak expansion after infusion according to previous bendamustine exposure.

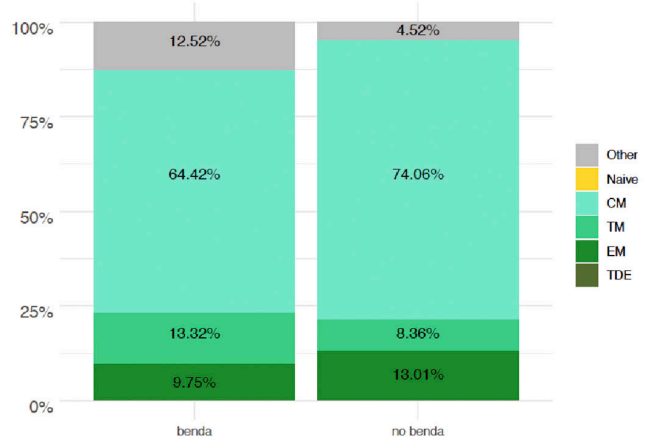


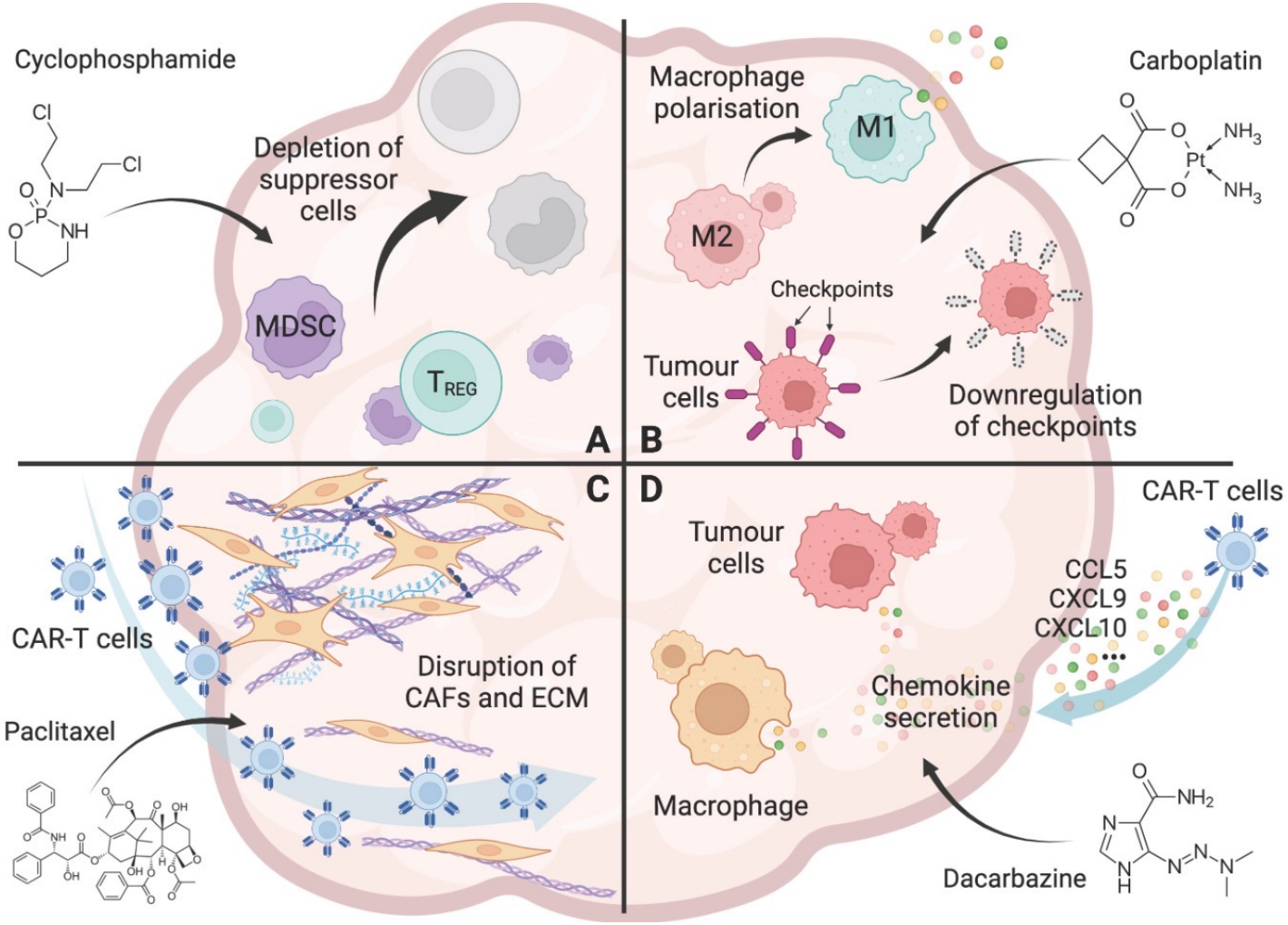
Figure 2.- Best response achieved after CAR T-cell therapy depending on the use and timing of previous bendamustine.

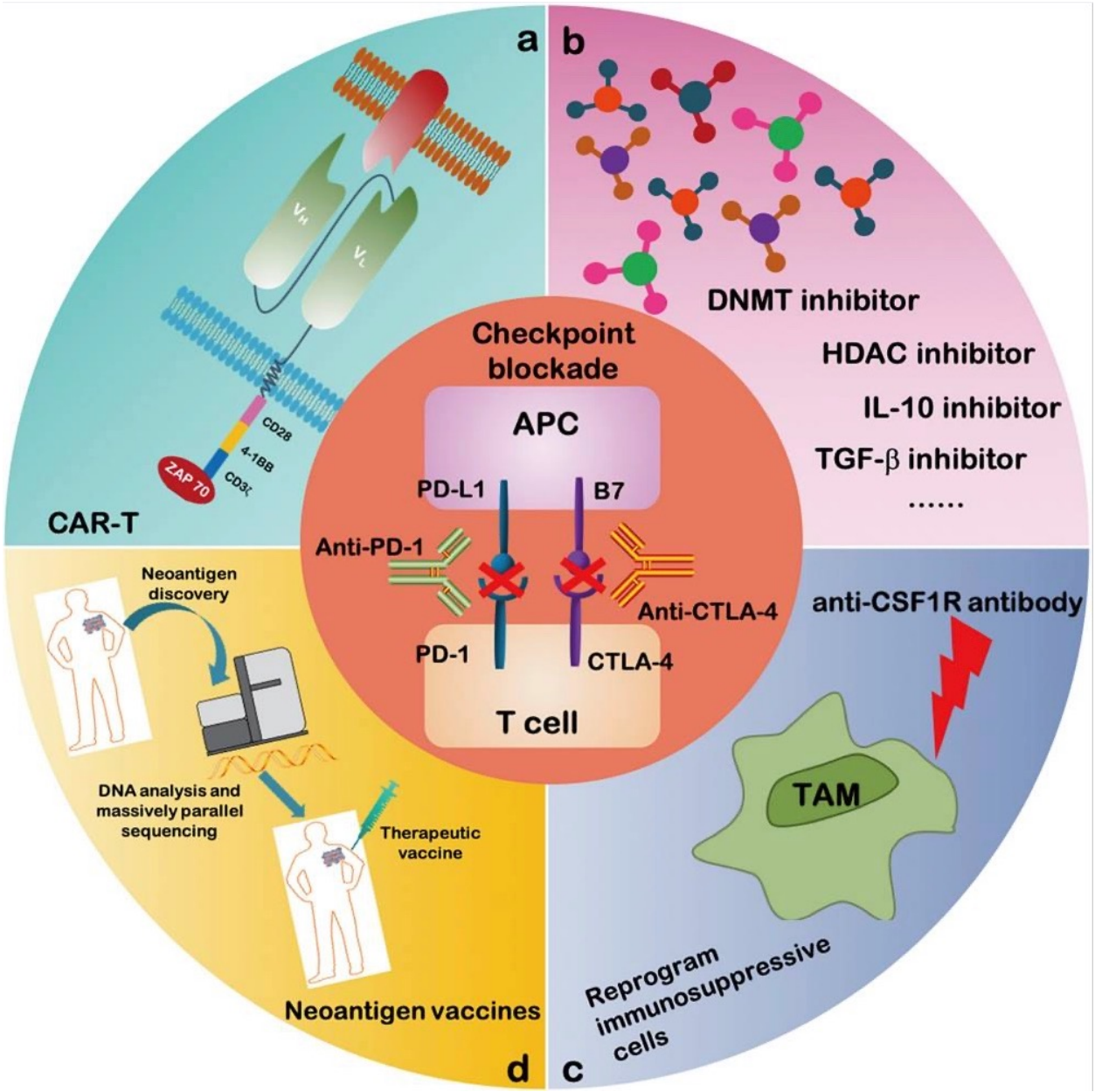
Figure abbreviations: CM central memory, TM transitional memory, EM, effector memory, TDE terminal effector, CR complete response, PR partial response, SD stable disease, PD progressive disease

Gloria Iacoboni et al. Recent Bendamustine Treatment before Apheresis Has a Negative Impact on Outcomes in Patients with Large B-Cell Lymphoma Receiving Chimeric Antigen Receptor T-Cell Therapy, Blood, 2022, Figure 1

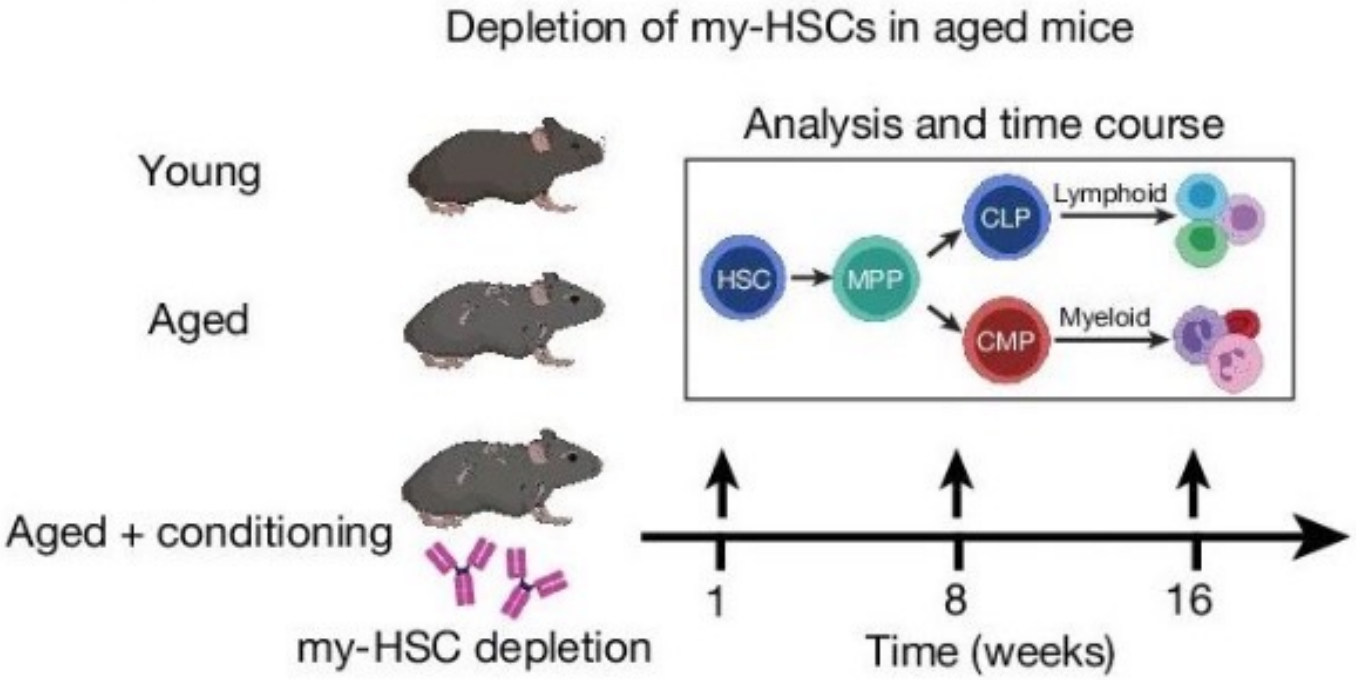
Chemotherapy Helpful?

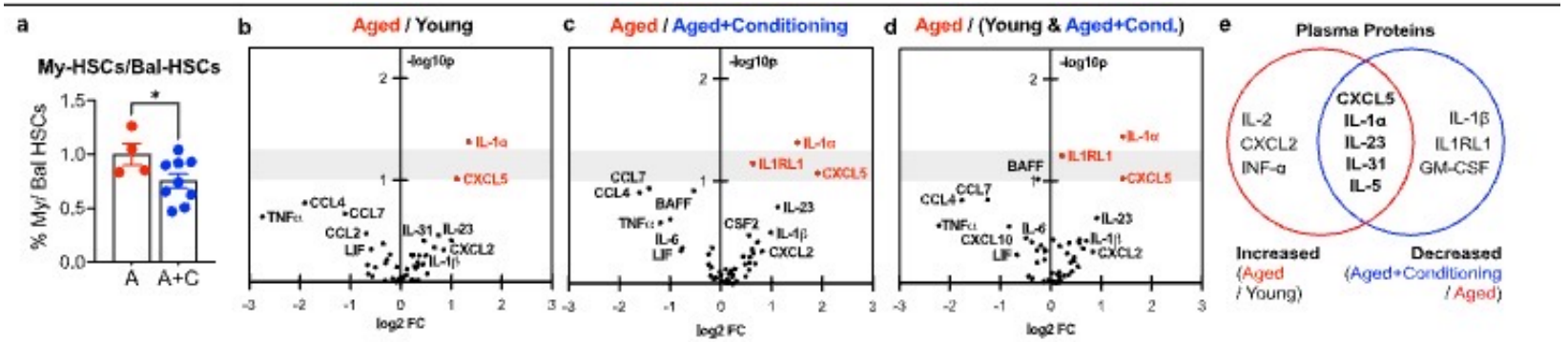
https://doi.org/10.3389/fimmu.2023.1140541





doi: 10.3389/fcell.2020.00017





Nature 628:162, 2024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Home of the Dunbar CAR T-Cell Program

Questions?