ASSOCIATION OF COMMUNITY CANCER CENTERS

MULTIDISCIPLINARY CHRONIC LYMPHOCYTIC LEUKEMIA CARE

2018 ASH Updates

Brian Koffman, MDCM, FCFP, DABFP, MS Ed
Executive Vice President and Chief Medical Officer
CLL Society, Inc.

ACCC
Association of Community Cancer Centers

CLL/SLL
Chronic Lymphocytic Leukemia
Small Lymphocytic Lymphoma

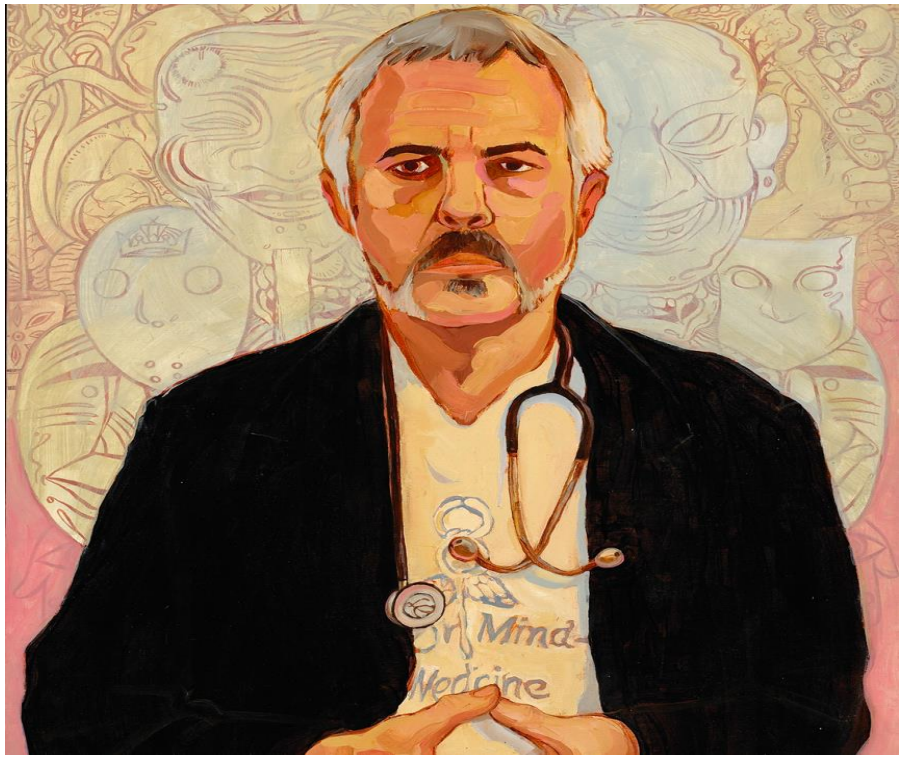
CLL/SLL
ASCO 2015 Cancer Advance of the Year: Transformation of CLL Treatment

CLL/SLL
ASCO 2015 Cancer Advance of the Year: Transformation of CLL Treatment

Has everything changed because of:

1. Predictive/Prognostic Testing
2. Targeted Therapies
3. MRD Testing

Brian Koffman, MDCM, DCFP, FCFP, DABFP, MS Ed
Chief Medical Officer and Executive Vice President
CLL Society (a 501c3 non-profit)



What I have done to beat those odds despite very high-risk disease

- Refusing some treatments and choosing others
- Getting expert on my team
- Becoming an “expert” patient
- Enrolling in clinical trials
- Getting treatments paid for
- Joining a support group

Disclosure

Consulting: Janssen, Novartis, Verastem Oncology

Stocks: AbbVie, AZN, BGNE, BMY, Celgene, GILD, JNJ, MEIP, MGEN, PTLA, SNSS, TGTX, VO

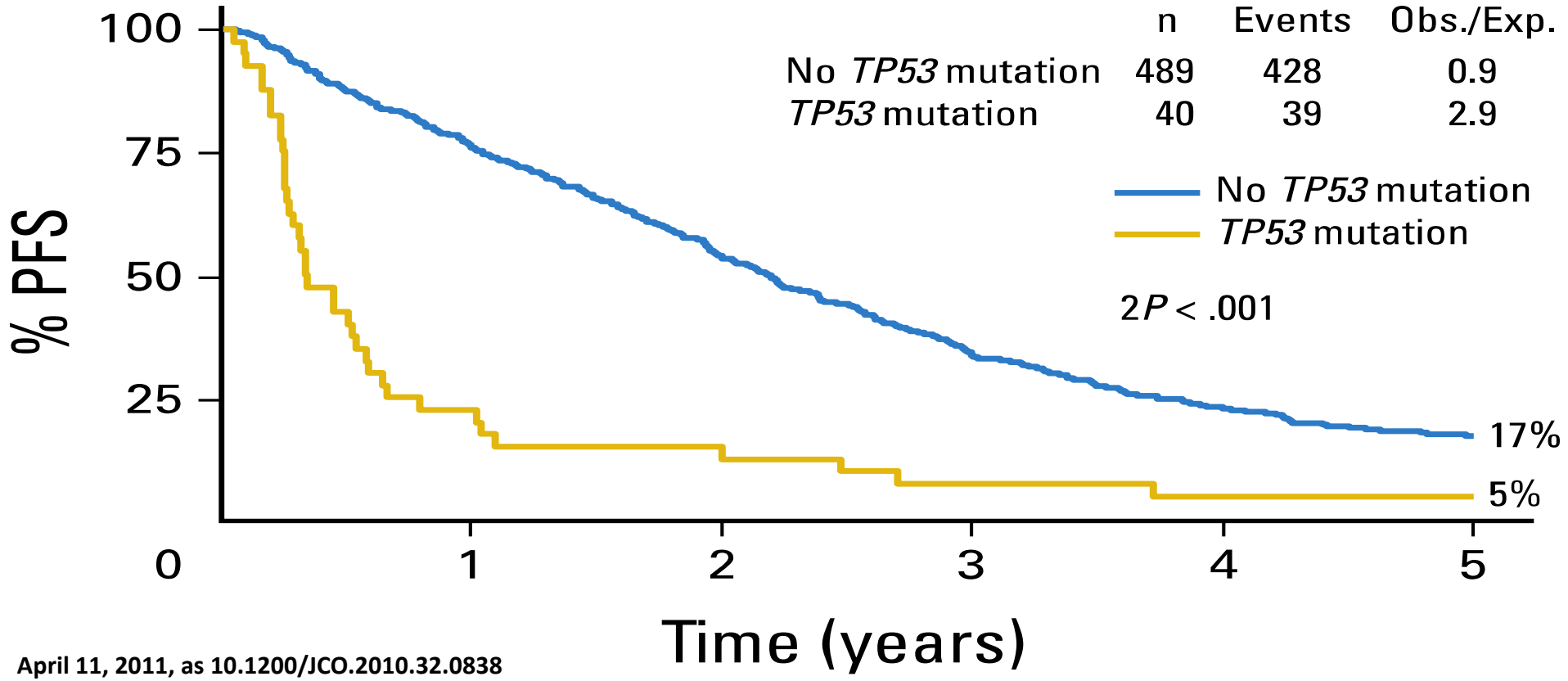
Disclosure

- I am alive and here today because in 2011 I started on a Phase 1 clinical trial of PCI-32765 now known as ibrutinib.
- I have no detectable CLL today in my blood or bone marrow due to a 2nd clinical trial, this time with CAR-T (JCAR-14).
- I have a bias toward novel therapies, clinical trials, and patient involvement.

Prognosis

11q deletion (later 17p deletion), complex karyotype, CD38+, unmutated, ZAP70 +, (now loss of Notch 1, CDKN2A, Dnmt3a, XOP1.

Kaplan Meir Curve (or my 1 in 20 chance of living >5 years)



April 11, 2011, as 10.1200/JCO.2010.32.0838

CLL: Epidemiology, Staging, Prognosis

CLL/SLL: Background

- 20,720 estimated new cases in 2019 in the United States alone.
  - 7% of all NHL are CLL/SLL.
- Median age: 71 yrs; more common in males vs. females.
- SLL and CLL considered the same B-cell malignancy.
  - CLL: > 5000 monoclonal lymphocytes in peripheral blood.
  - SLL: presence of lymphadenopathy and/or splenomegaly and < 5000 monoclonal lymphocytes in peripheral blood.
  - One disease with varied presentation; often termed “CLL/SLL.”
- Historical 5-yr survival: 66% (range: few months to normal life span).
- 15-20% never need treatment.

Siegel RL, et al. CA Cancer J Clin. 2018;68:7-30; CA Cancer J Clin 2019;69:7-34;
http://www.cancer.org. 3. Nabhan C, et al. JAMA. 2014;312:2265-2276.

CLL Epidemiology

- Causes unknown – more genetics than environment.
- Family studies – higher than expected frequency among first-degree family members with CLL/NHL (5-10% of cases).
- No certain environmental risks:
  - No increase in atomic bomb survivors.
  - No evidence for dietary/lifestyle factors.
  - Japanese in Hawaii incidence = Japanese in Japan.
- However, increased incidence of CLL reported among Chernobyl cleanup workers and veterans exposed to Agent Orange
- **US Department of Veterans Affairs has agreed that exposure to Agent Orange is a risk factor for CLL.**
- **Veterans with CLL can claim benefits if they were previously exposed to Agent Orange while in military service.**

Zablotska et al. *Environ Health Perspect.* Jan 2013;121(1):59-65; Hsu et al. *Radiat Res.* Mar 2013;179(3):361-382; Goldin et al. *Haematologica.* May 2009;94(5):647-653; Mescher et al. *Leuk Lymphoma.* Jun 2018;59(6):1348-1355.

CLL Diagnosis (iwCLL)

- Peripheral blood lymphocytosis: ≥5000/µL (≥5 x 10^9/L).
- Flow cytometry: Monoclonal B cells - light chain restriction, CD19, CD20 (dim), CD23 and also the T-cell marker CD5.

Note:

- CLL cells usually have low levels of CD20, lack expression of CD10, and stain poorly, if at all, with the FMC7 a monoclonal antibody, which recognizes specific epitope of CD20.
- CLL cells also express CD200 (also known as OX-2 membrane glycoprotein), which can help to distinguish CLL from mantle cell lymphoma.
- In addition, the CLL cells of >95% of patients express the onco-embryonic surface antigen ROR1.

Blood. 2008;111:5446-5456

Flow Cytometry

Common phenotypes of B-cell cancers

Diagnosis	CD5	CD10	CD19	CD20	CD23	CD79b	FMC-7	CD25	CD11c	CD103
CLL/SLL	+	-	+	+(w)	+	-	-	-/+	+/-	-
Mantle cell lymphoma	+	-	+	+	-	+	+	-	-	-
Follicular lymphoma	-	+	+	+	-/+	+/-	+/-	-	-	-
Marginal zone lymphoma	-	-	+	+	-	+/-	+/-	-/+	+	-
Hairy cell leukemia	-	-	+	+	-	+/-	+/-	+/-	+	+

CLL: Peripheral Blood Smear

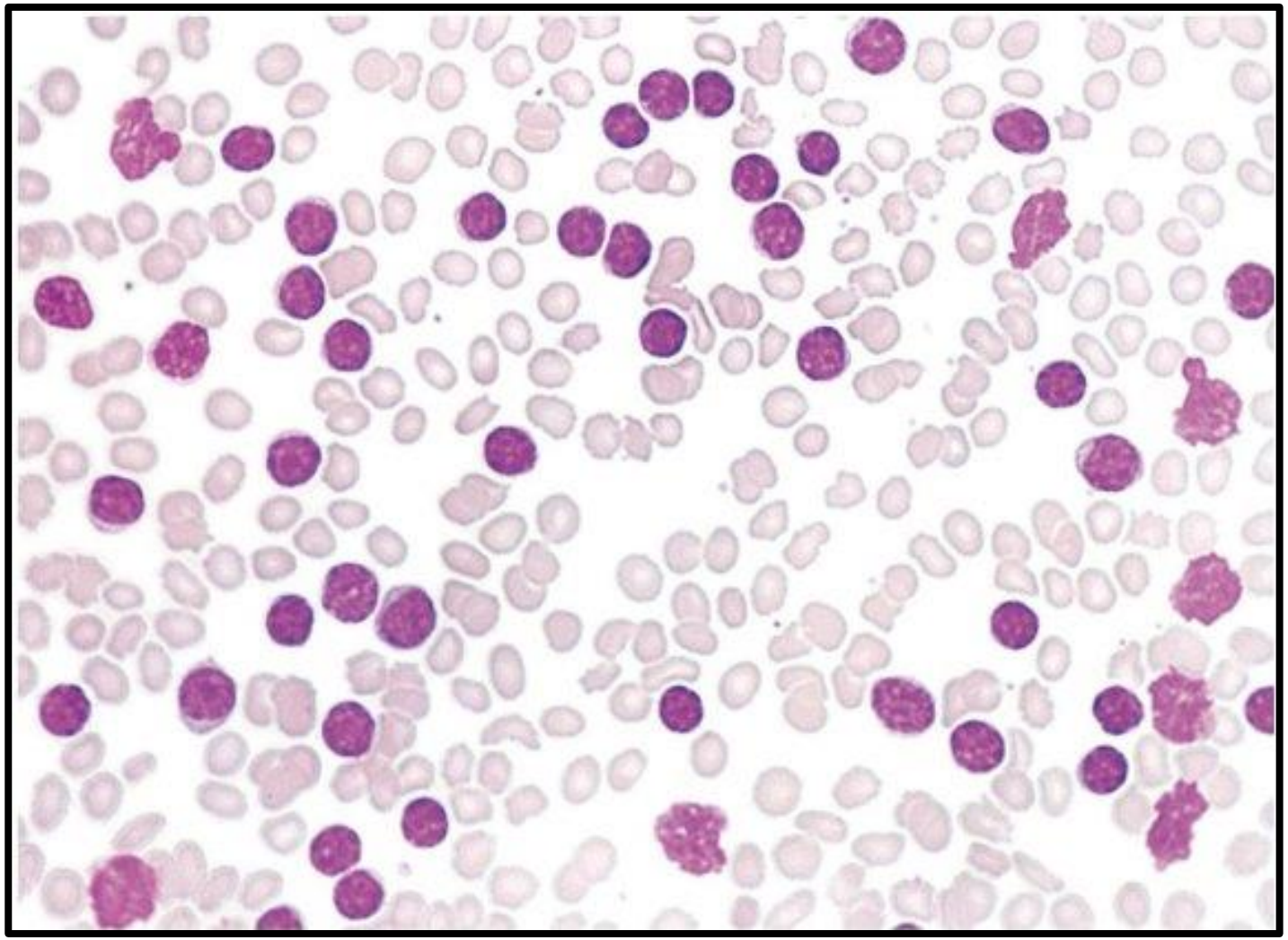


Figure 18.3 Chronic lymphocytic leukaemia: peripheral blood film showing lymphocytes with thin rims of cytoplasm, coarse condensed nuclear chromatin and rare nucleoli. Typical smudge cells are present.

CLL Staging Systems

Rai System[a]

Stage	Description	Risk Status
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow	Low
I	Stage 0 with enlarged node(s)	Intermediate
II	Stage 0-I with splenomegaly, hepatomegaly, or both	Intermediate
III[c]	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%	High
IV[c]	Stage 0-III with platelets <100,000/mcL	High

Binet System[b]

Stage	Description
A	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and <3 enlarged areas
B	Hemoglobin ≥10 g/dL and Platelets ≥100,000/mm^3 and ≥3 enlarged areas
C[c]	Hemoglobin <10 g/dL and/or Platelets <100,000/mm^3 and any number of enlarged areas

A: Blood 1975;46(2):219-243.
B: Cancer 1981;48:198-206.
C: Immune-mediated cytopenias not the basis for these definitions.

Risk Stratification/Prognostic Factors

- Clinical course extremely variable.
- Prognostic factors can help to identify patients who may require therapy relatively soon after diagnosis.
  - Clinical features;
  - Genetics;
  - Molecular; and
  - Biochemical characteristics of the CLL cell.
- Multiple models, nomograms, and prognostic indexes exist – *no single best one.*

Risk Stratification: Prognostic and Predictive Markers

- **Prognostic factors** associated with poorer outcome:
  - Unmutated IgHV ≤ 2% (or VH3.21 even if mutated)
  - ZAP70 expression ≥ 20%
  - CD38 ≥ 30%
  - β2-microglobulin (>3.5 mg per L)
  - Del (17p)/TP53 mutants, Del (11q), complex karyotypes
  - Trisomy 12 (+12) is neutral
  - Male sex
  - Age ≥ 65 years
  - Poor PS from co-morbid conditions

- **Predictive factors:**
  - del17p status
  - TP53 status
  - IgHV mutation status

* Poor prognostic variables still do not impact when to start tx.

Nat Rev Dis Primers, 2017 Jan 19;3:16096; Rossi et al. *Leuk Lymphoma.* Jul 2017;58(7):1548-1560.

New and Emerging Therapies: Clinical Evidence

Question

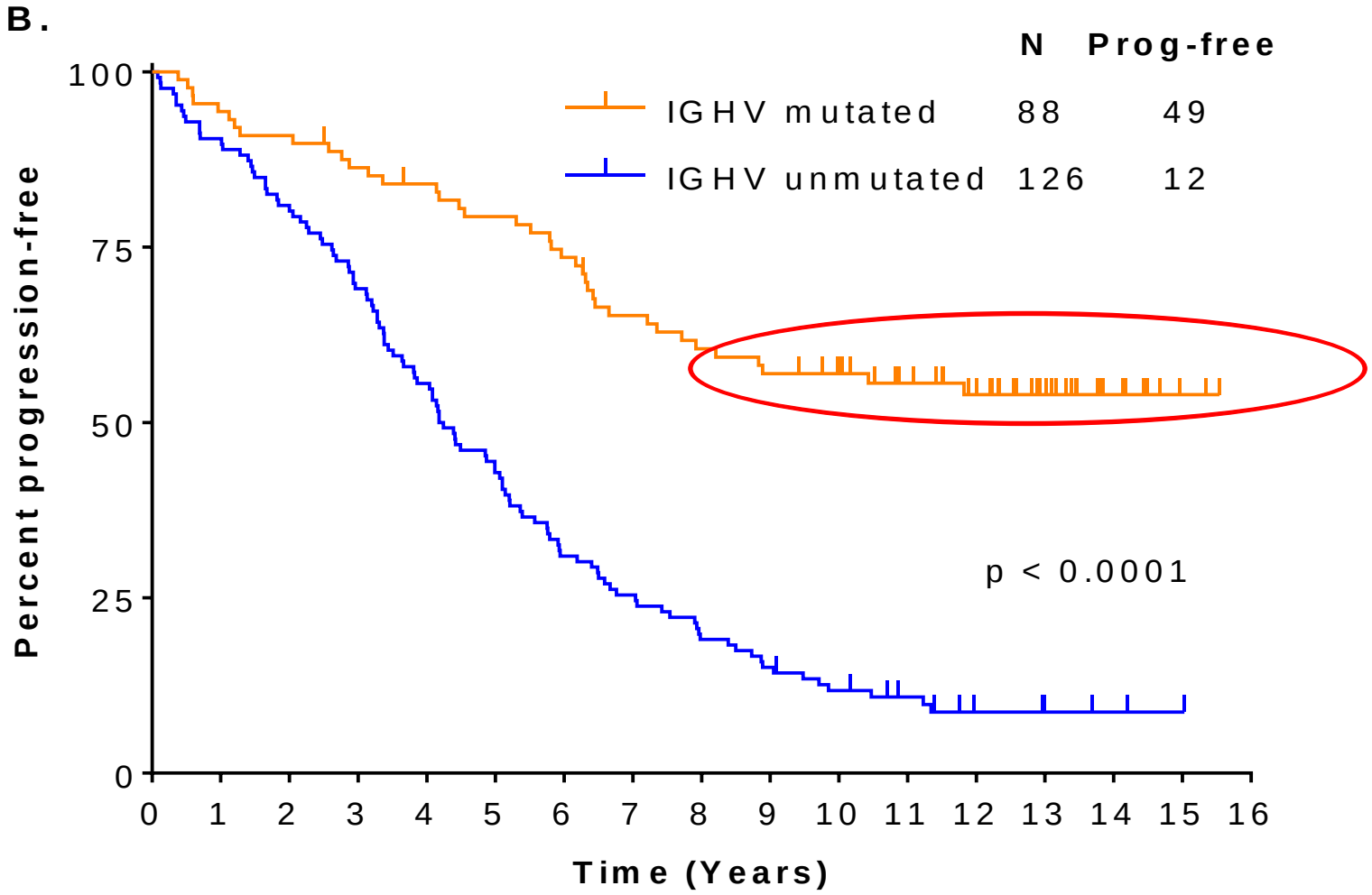
DS is 64-year-old male diagnosed with routine lab with a ALC of 35,000. 18 months later, his ALC is 60,000. He now has multiple 2 x 1.5 cm nodes in both axilla and groin. Otherwise, exam and lab are normal. He asks what symptoms or lab might indicate it is time to treat. You tell him:

1. Unexplained fever >38°C x 2 weeks with no infection
2. Unexplained weight loss >10% over 6 months
3. Drenching night sweats >1 month with no infection
4. Severe fatigue
5. Hgb < 10 or platelets <100,000
6. WBC >100,000
7. All the above
8. 1 – 5

CLL Treatment Indications

- No absolute consensus on when/who to start treatment.
- Indications generally include:
  - Significant disease related symptoms:
    - Fevers, night sweats, weight loss;
    - Severe fatigue.
  - Threatened end-organ function.
  - Progressive bulky disease:
    - Spleen > 6 cm below cm, lymph nodes > 10 cm.
  - Progressive anemia.
  - Progressive thrombocytopenia.
  - Rapid lymphocyte doubling time.
- New(superior) therapies have not changed traditional approach as to when to tx.
- No recent studies indicate that early intervention prolongs survival.
- Presence of del17p does not change approach - ~ 1/3 have indolent course.

Patients with Mutated IGHV Have Prolonged PFS After FCR



Thompson PA et al. *Blood* 2016

Paradigm Shift

CLL Treatment: Targeted Agents

Agent	Indication in CLL
Duvelisib	Third line
Ibrutinib	First or second line
Idelalisib	Second line
Rituximab	First or second line in combination
Obinutuzumab	First line (with chlorambucil or Ibrutinib)
Ofatumumab	First line (with chlorambucil) Second line (with fludarabine and cyclophosphamide) Extended treatment of recurrent or progressive disease
Venetoclax	Second line

Question

6 months later DS's Hgb has dropped to 9.3 grams, his nodes have grown and are bothersome. He complains of severe fatigue. At dx, FISH revealed 11q del, and unmutated IgHV.

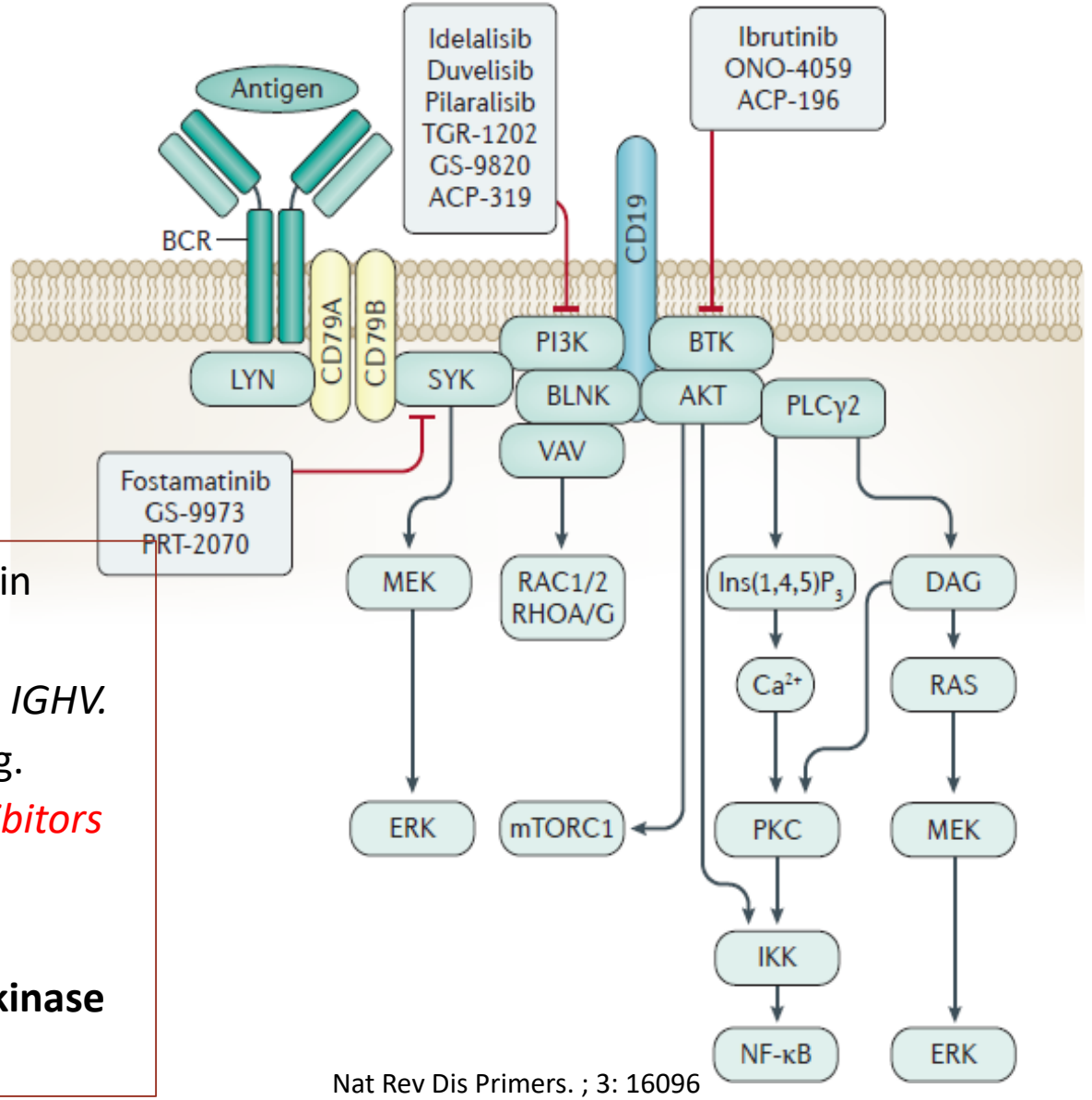
What test(s) do you need consider before starting therapy?

1. Flow Cytometry
2. Bone Marrow Biopsy
3. CT scan
4. FISH
5. TP53 testing
6. IgHV

B-Cell Receptor Signaling Response

- Survival of resting mature B-cells depends on BCR signaling.
- Some B-cell malignancies depend on tonic BCR signaling for tumor expansion and proliferation.
- BTK inhibitors block BCR signaling, induce apoptosis, and inhibit adhesion of malignant B-cells to microenvironment cells.

- Enhanced antigen-independent B-cell activation more common in CLL that expresses unmutated *IGHV.*
- Anergy predominates in most cases of CLL that express mutated *IGHV.*
- Anergic cells less likely to proliferate in response to BCR signaling.
- CLL cells with unmutated *IGHV seem to be more sensitive to inhibitors of BCR signaling than CLL cells with mutated IGHV.*
- **3 main classes of drugs that inhibit BCR signaling have been evaluated: BTK inhibitors, PI3K inhibitors, and spleen tyrosine kinase (SYK) inhibitors.**



Nat Rev Dis Primers. ; 3: 16096

Question

On retesting, DS now has 41% 11q del and 9% 17p del. He has no significant comorbidities. Possible RXs include:

1. FCR (fludarabine, cyclophosphamide, and rituximab)
2. FCG (fludarabine, cyclophosphamide, and obinutuzumab/Gazyva)
3. BR (bendamustine and rituximab)
4. Ibrutinib
5. Idelalisib and rituximab

Ibrutinib

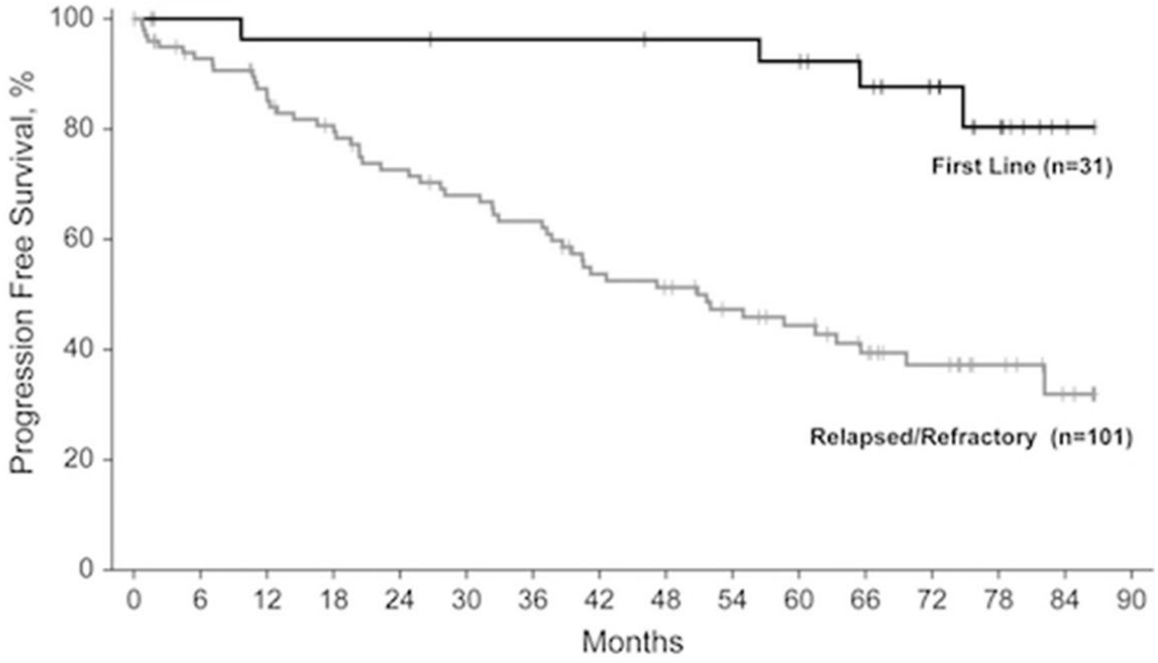
- Oral Bruton's tyrosine kinase inhibitor (BTKi).
- Approved for frontline and relapsed settings.
- Works in patients with or w/o del(17p):
  - No data age < 65 years w/o del(17p) (trial done age >65).
- Increased risk of bleeding (6% severe):
  - ? Mechanism (described as platelet dysfxn);
  - Use with caution or avoid with warfarin/anticoagulation.
- Increased rates of atrial fibrillation.
- Avoid in moderate-to-severe liver disease.
- Lymphocytosis, initially accompanied by a rapid and sustained decrease in lymphadenopathy.
  - Related to inhibition of chemokine receptor signaling, which inhibits migration of CLL cells from blood into lymphoid tissues.
- Secondary resistance develops from binding site mutation – likely also resistant to acalabrutinib.
- Second generation BTKis in clinical trials currently for CLL and approved for MCL/WM.
- Non-covalent binding BTKis in trial for ibrutinib resistance.

- Initial data raised concerns that d/c could lead to worse outcomes.
- New data suggest d/c may be okay, but advice is to continue ibrutinib until next RX in place.

Imbruvica [prescribing information]. Sunnyvale, CA: Pharmacyclics, LLC; 2019

Up to 7 years of follow-up of single-agent Ibrutinib in the Phase 1b/2 PCYC-1102 trial of first line and relapsed/refractory patients with CLL/SLL.

Figure 1. PFS for All-Treated First Line and Relapsed/Refractory Patients with CLL



The primary reason for treatment discontinuation in first line pts was AEs (23%), whereas in R/R CLL it was PD (35%).

Ibrutinib Alone or in Combination with Rituximab Produces Superior Progression Free Survival (PFS) Compared with Bendamustine Plus Rituximab in Untreated Older Patients with Chronic Lymphocytic Leukemia (CLL):

Results of Alliance North American Intergroup Study A041202

Jennifer A. Woyach, Amy S. Ruppert, Nyla Heerema, Weiqiang Zhao, Allison M Booth, Wei Ding, Nancy L. Bartlett, Danielle M Brander, Paul M Barr, Kerry A Rogers, Sameer Parikh, Steven Coutre, Arti Hurria, Gerard Lozanski, Sreenivasa Nattam, Richard A. Larson, Harry Erba, Mark Litzow, Carolyn Owen, James Atkins, Jeremy Abramson, Rich Little, Scott E. Smith, Richard M. Stone, Sumithra Mandrekar, John C. Byrd

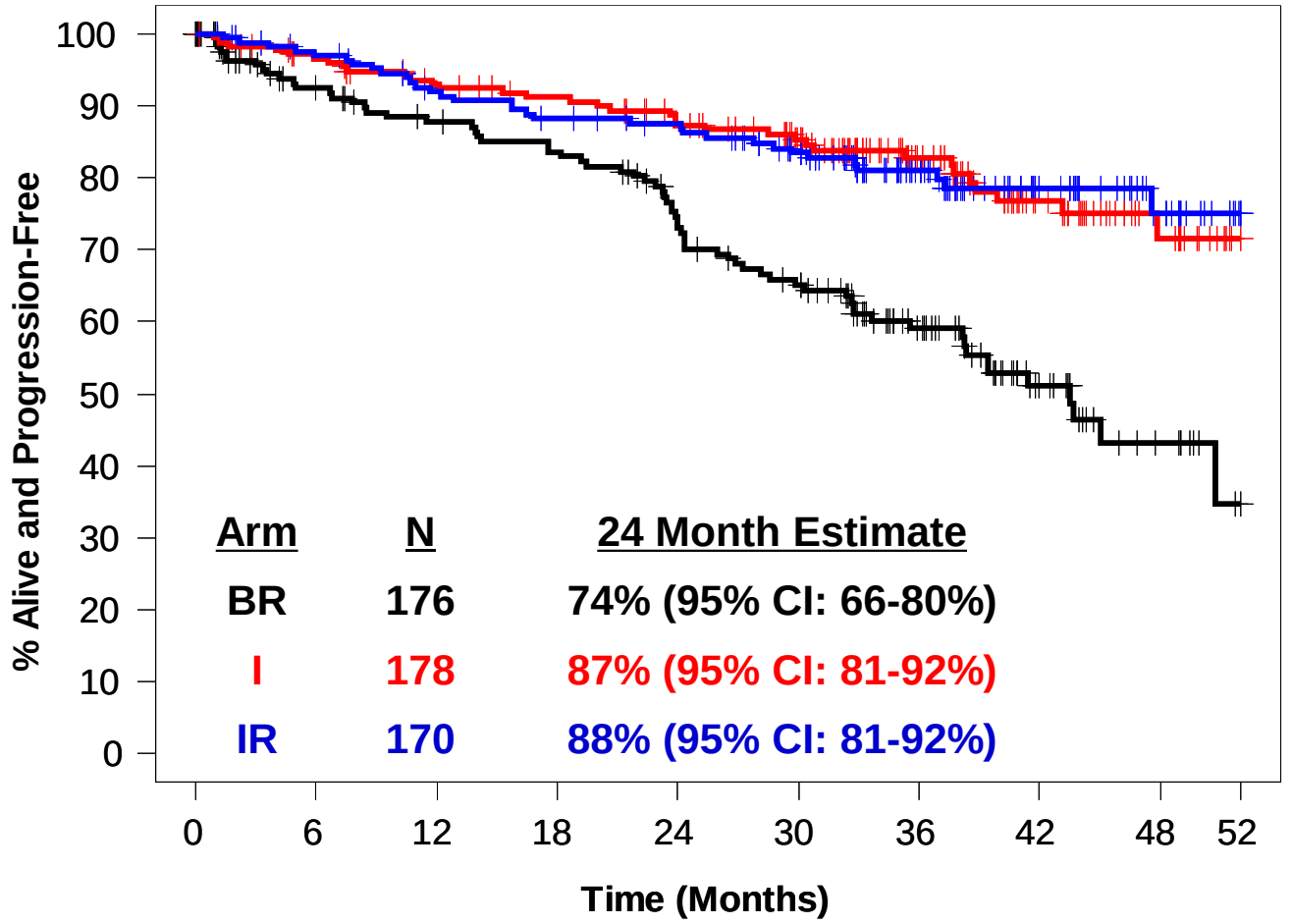
Background

- Older patients are under-represented on CLL clinical trials unless specifically designed.
- Standard therapies for older patients include chlorambucil plus obinutuzumab and bendamustine plus rituximab.
- Despite widespread use, efficacy of ibrutinib vs. standard chemoimmunotherapy has not been investigated.
- Rituximab improves survival with chemotherapy; impact on ibrutinib not established.

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Primary Endpoint: Progression Free Survival

Eligible Patient Population



Patients-at-Risk

Arm A (BR)	176	140	129	122	103	88	57	26	11	0
Arm B (I)	178	165	154	147	136	120	78	45	22	0
Arm C (IR)	170	159	145	138	132	115	74	40	20	0

Pairwise Comparisons

I vs BR:
Hazard Ratio 0.39
95% CI: 0.26-0.58
(1-sided P-value <0.001)

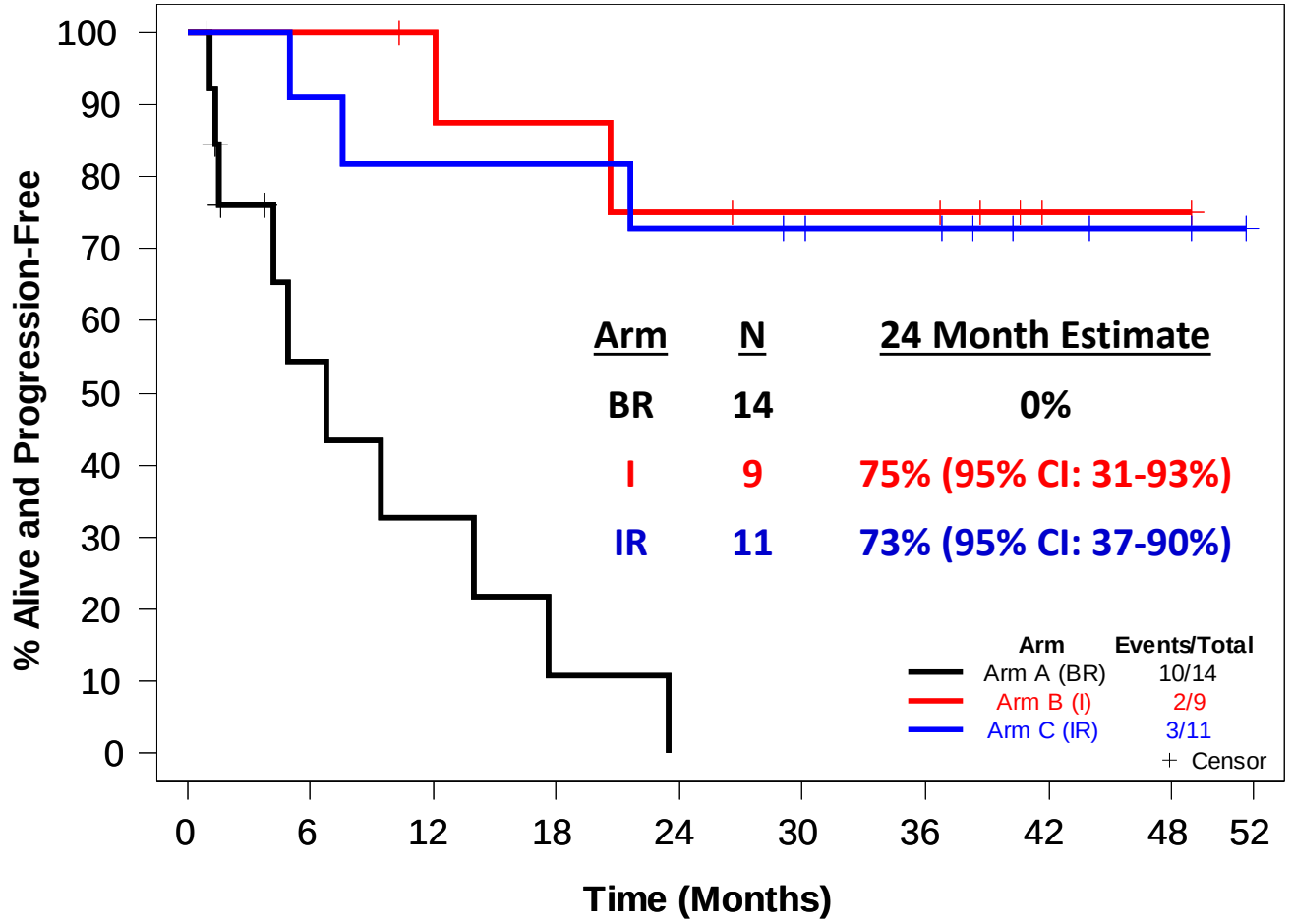
IR vs BR:
Hazard Ratio 0.38
95% CI: 0.25-0.59
(1-sided P-value <0.001)

IR vs I:
Hazard Ratio 1.00
95% CI: 0.62-1.62
(1-sided P-value 0.49)

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Del (17p13.1) Subgroup: Progression Free Survival

Intention-to-Treat Patient Population



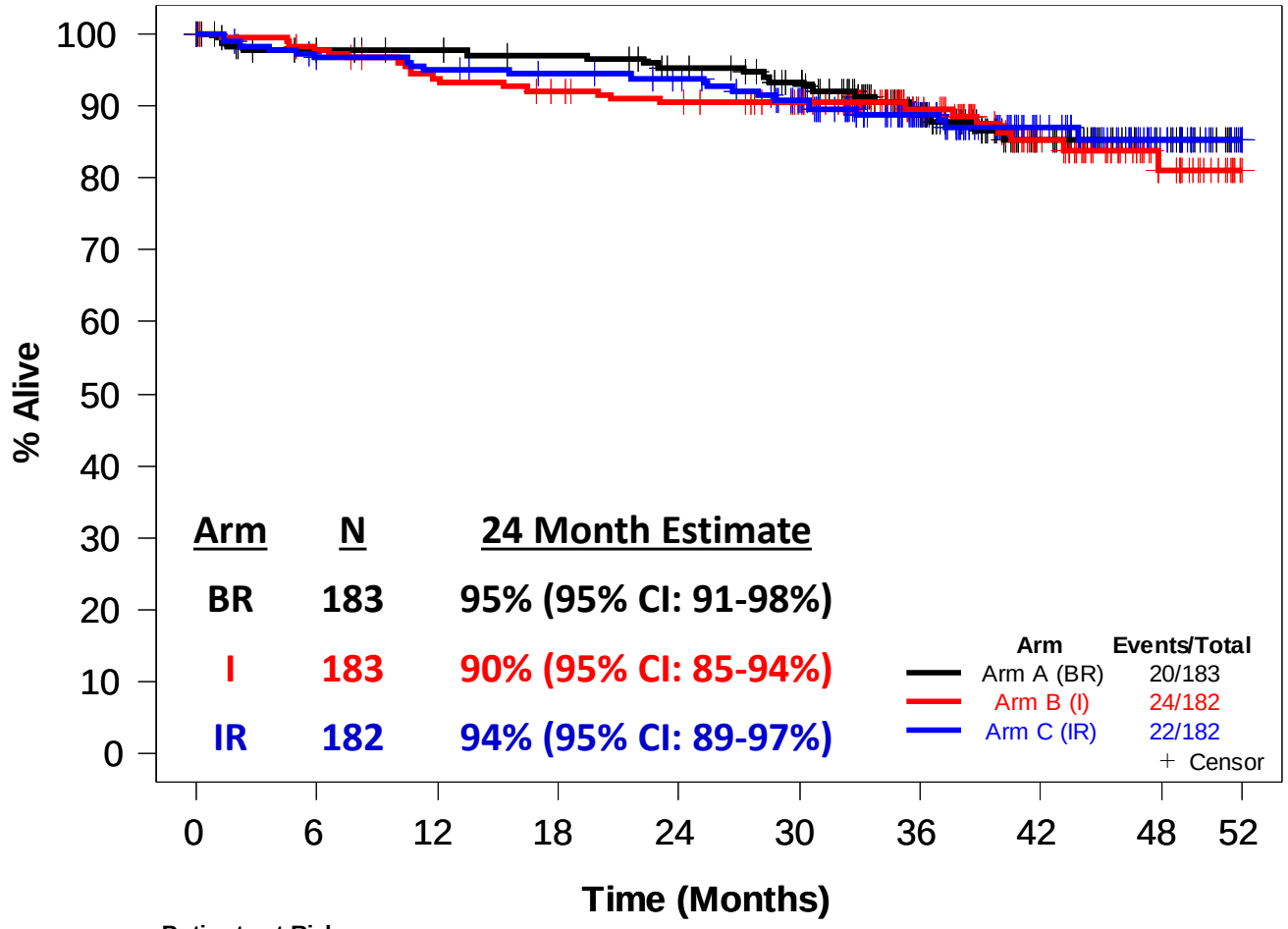
Patients-at-Risk

Arm A (BR)	14	5	3	1	0					
Arm B (I)	9	9	8	7	6	5	5	1	1	0
Arm C (IR)	11	10	9	9	8	7	6	3	2	0

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Overall Survival

Intention-to-Treat Patient Population



Patients-at-Risk										
Arm A (BR)	183	166	163	160	153	143	98	53	23	1
Arm B (I)	182	175	166	161	156	146	100	62	26	1
Arm C (IR)	182	172	169	165	161	147	100	55	24	1

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Conclusions

- Ibrutinib or ibrutinib plus rituximab significantly prolongs PFS compared with BR in the frontline setting for older CLL patients.
- Rituximab does not improve PFS over ibrutinib alone.
- BTK inhibition with ibrutinib is not without significant toxicity in older patients, so close monitoring is still warranted.
  - Strategies to discontinue therapy are of great interest.
- Clinical trials for this patient population are still of high clinical interest; the cooperative group setting remains a reasonable avenue to complete these large studies.
  - A041702 (NCT03737981) and EA9161 (NCT03701282).

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

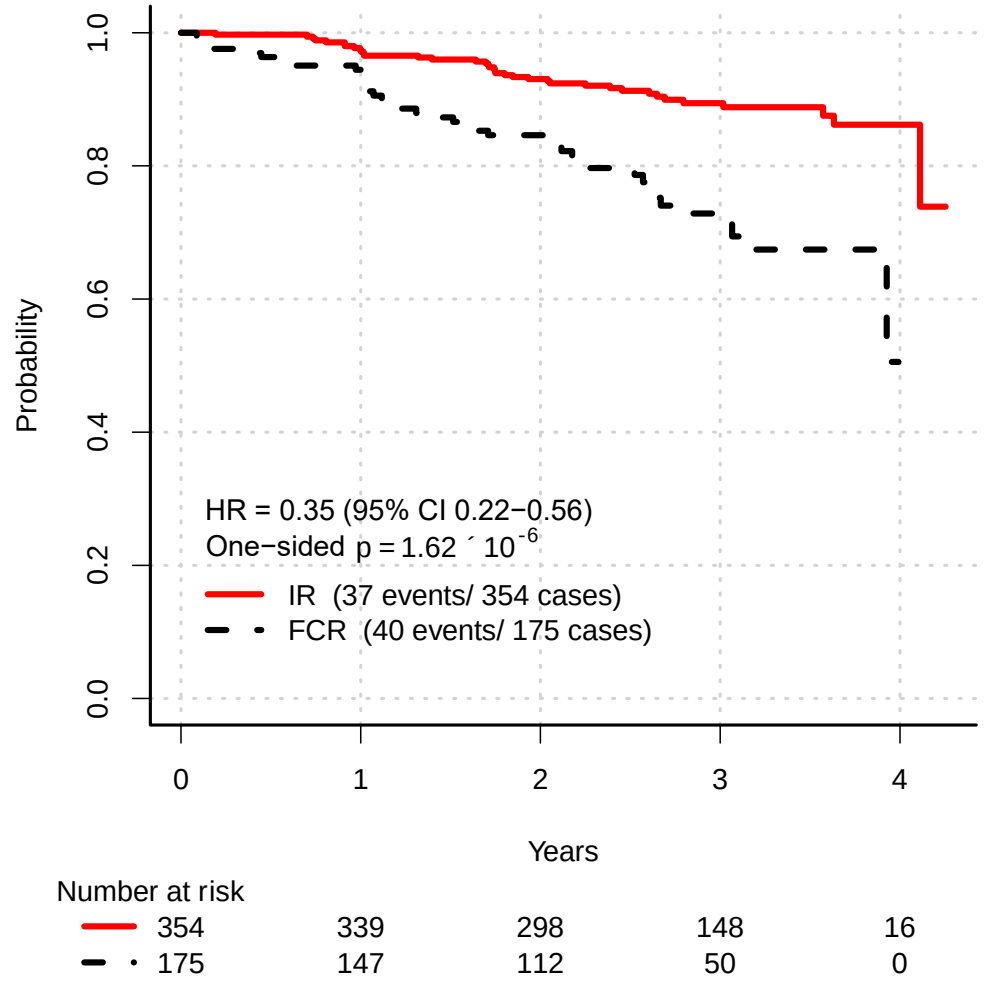
ECOG-E1912: Ibrutinib vs. Fludarabine, Cyclophosphamide, and Rituximab

- 529 treatment-naïve patients aged ≤70 (without del17p).
- Randomized to ibrutinib/rituximab or FCR.
- At median follow-up of 33.4 months:
  - **HR=0.352** (95% CI 0.22-0.5; P<0.001) **for PFS or death** with ibrutinib/rituximab;
  - **HR=0.17** (95% CI 0.05-0.54; P<0.003) **for overall survival** with ibrutinib/rituximab;
  - Similar findings regardless of IgHV mutation status;
  - Grade ≥3 **AEs more common with FCR**: 72% vs. 58%; P=0.0042).

Shanafelt et al. Abstract # LBA-4. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

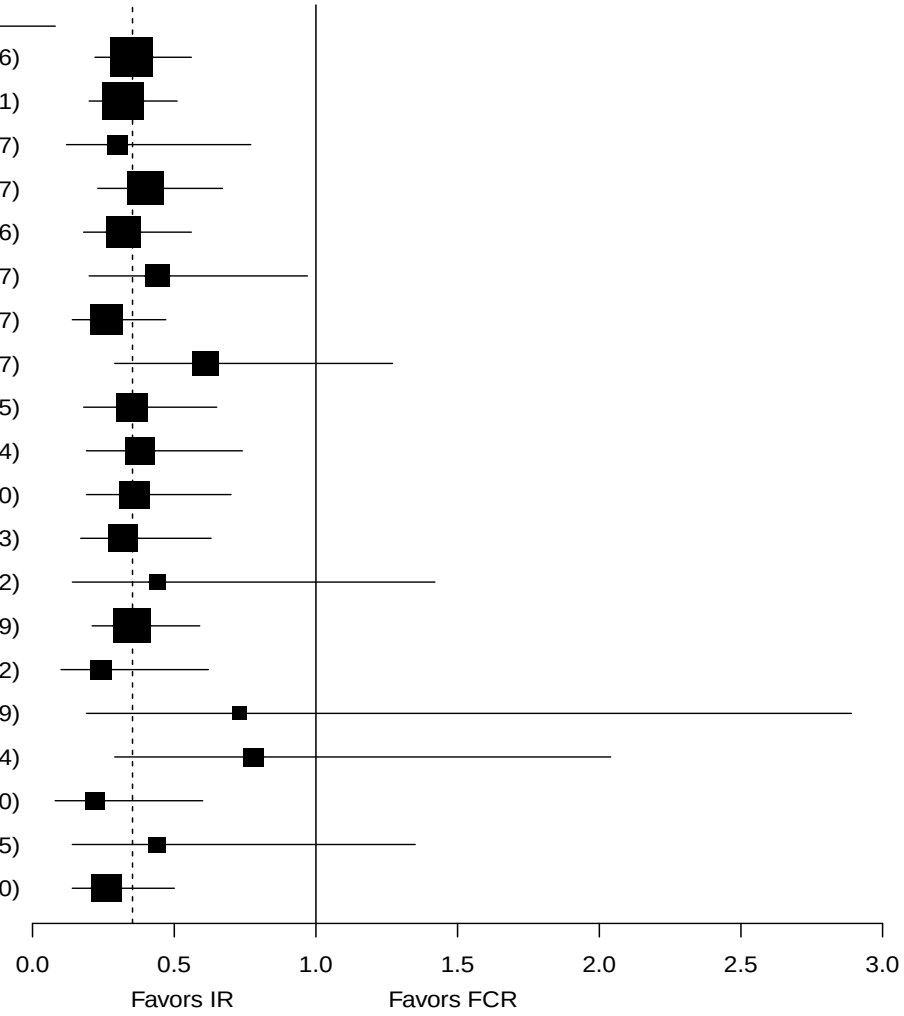
Progression Free Survival

HR = 0.35 (95% CI 0.22-0.5)
One sided p<0.00001

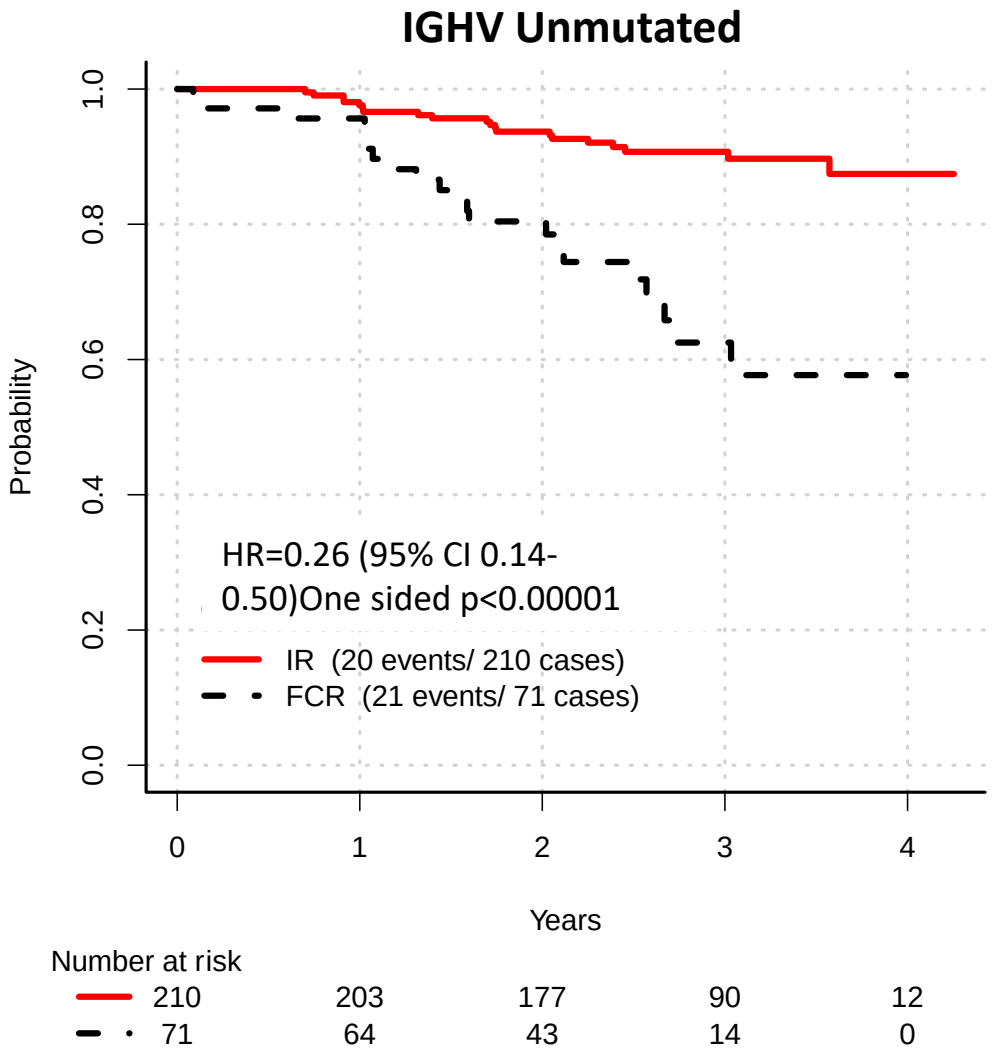


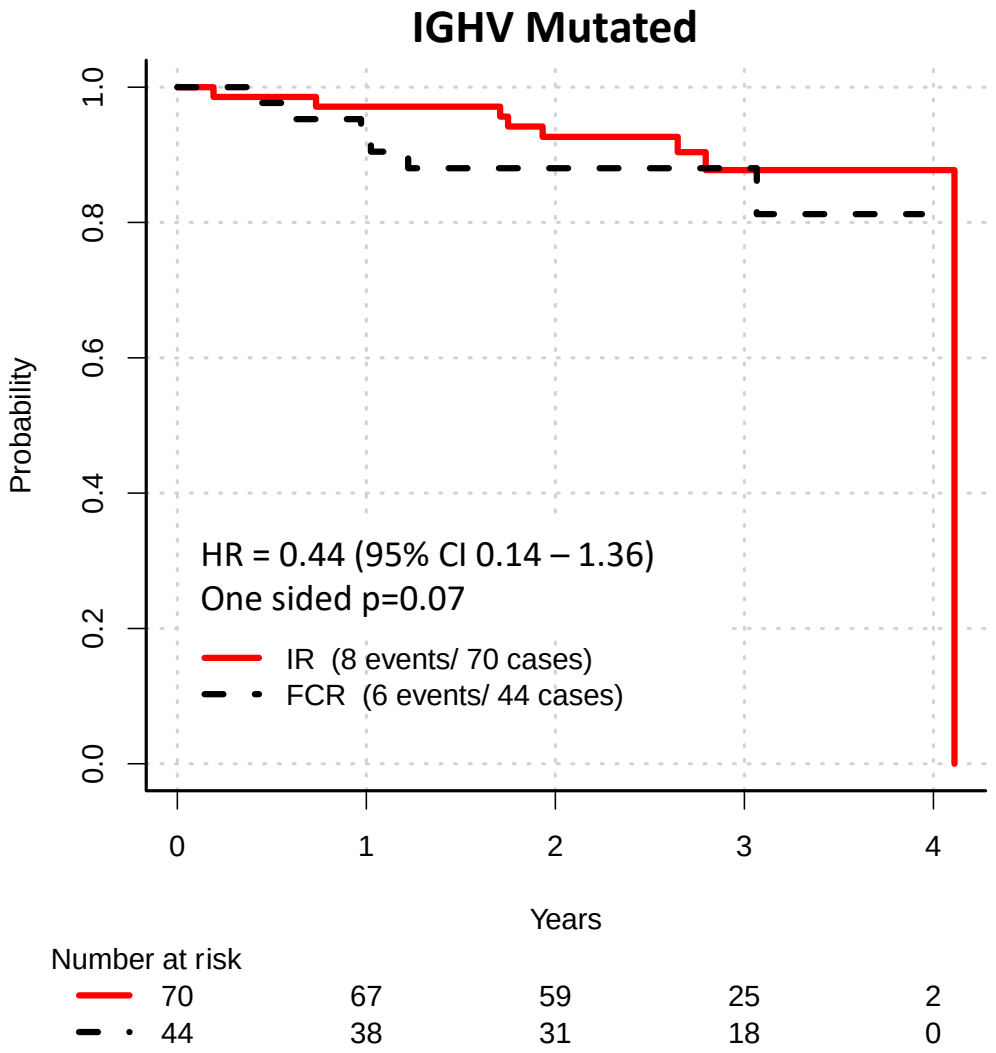
PFS Sub-Group Analysis

Group	N	E	HR	95% CI
All randomized	529	77	0.35	(0.22, 0.56)
Eligible	498	72	0.32	(0.20, 0.51)
Female	173	19	0.30	(0.12, 0.77)
Male	356	58	0.40	(0.23, 0.67)
Age < 60	314	51	0.32	(0.18, 0.56)
Age >= 60	215	26	0.44	(0.20, 0.97)
ECOG PS 0	335	46	0.26	(0.14, 0.47)
ECOG PS 1 or 2	194	31	0.61	(0.29, 1.27)
Rai Stage 0−II	301	41	0.35	(0.18, 0.65)
Rai Stage III−IV	228	36	0.38	(0.19, 0.74)
Splenomegaly No	311	39	0.36	(0.19, 0.70)
Splenomegaly Yes	218	38	0.32	(0.17, 0.63)
Lymphadenopathy No	159	16	0.44	(0.14, 1.42)
Lymphadenopathy Yes	370	61	0.35	(0.21, 0.59)
Dohner Del(11q22)	117	22	0.24	(0.10, 0.62)
Dohner Trisomy 12	97	10	0.73	(0.19, 2.89)
Dohner Normal	106	18	0.78	(0.29, 2.04)
Dohner Del(13q)	179	19	0.22	(0.08, 0.60)
IGHV Mutated	114	14	0.44	(0.14, 1.35)
IGHV Unmutated	281	41	0.26	(0.14, 0.50)

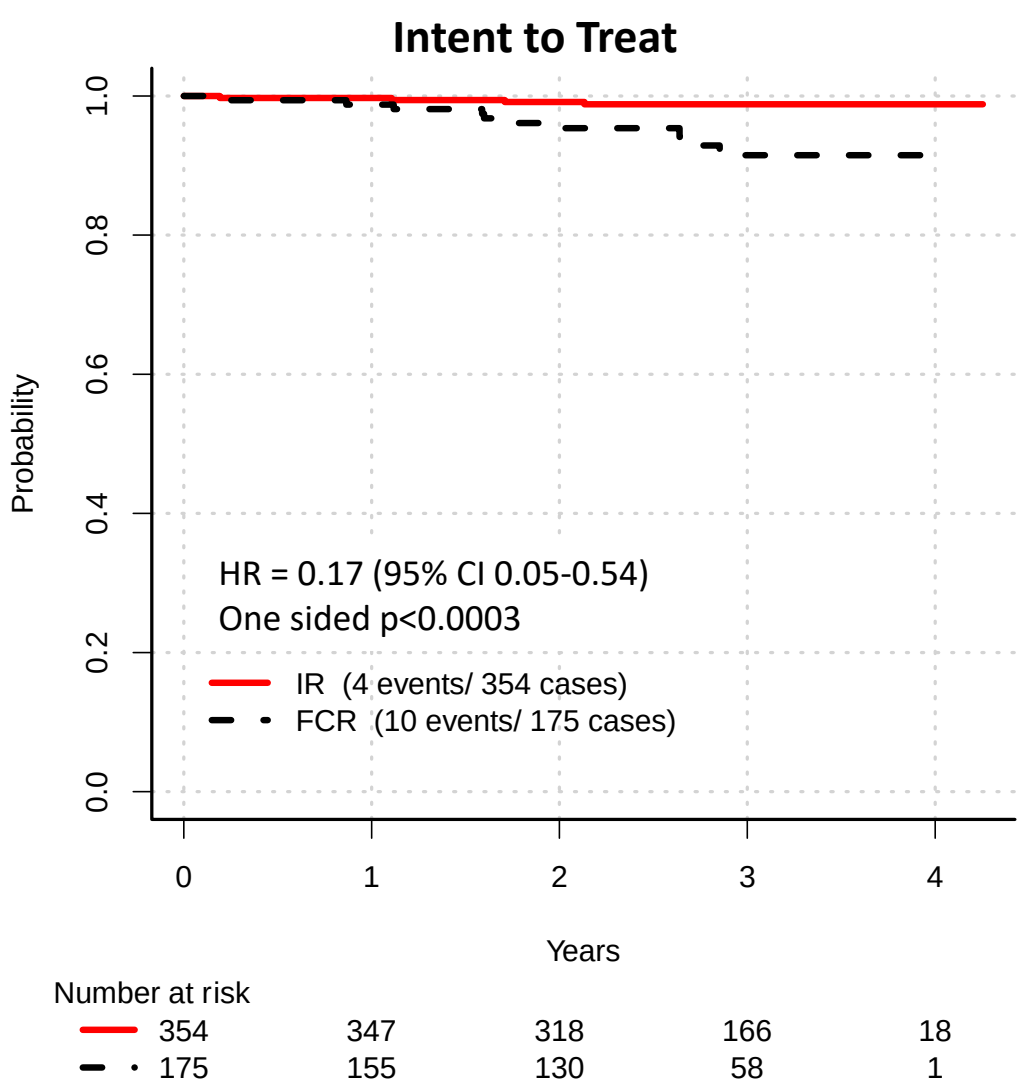


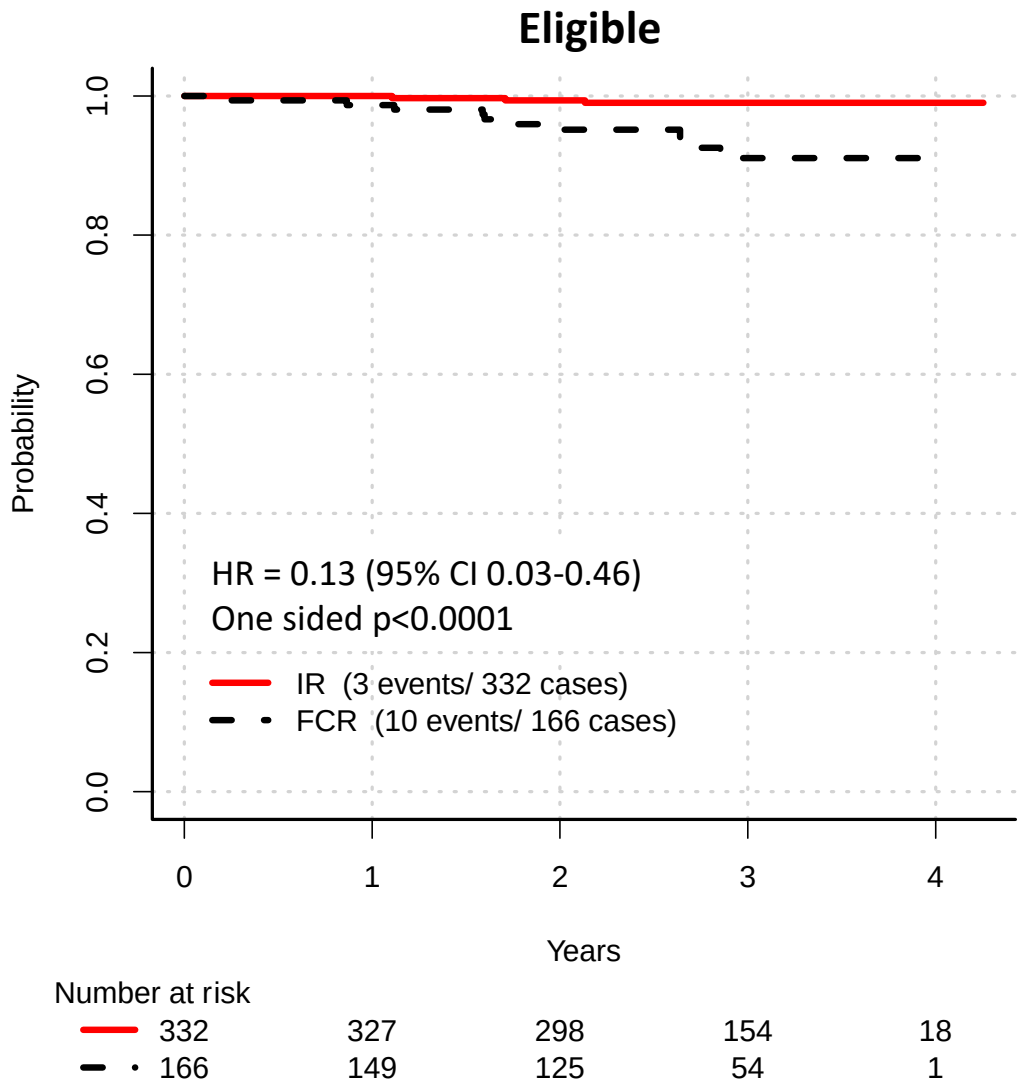
Progression Free Survival: IGHV Status





Overall Survival





Conclusions

- Ibrutinib and rituximab provides superior PFS and OS compared to FCR for patients with previously untreated CLL.
- Ibrutinib and rituximab was well tolerated in patients ≤age 70.
- The need for indefinite therapy should be evaluated in future clinical trials testing novel agent combination therapy.
  - EA9161 (NCT03701282; pts age<70) & A041702 (NCT03737981; pts age>70).

Grade 3, 4, or 5 Adverse Events ALLIANCE

During treatment or follow-up (excluding crossover)

Adverse Event	BR n=176	Ibrutinib n=180	IR n=181	p-value
All Hematologic -- no. (%)	**107 (61)**	**74 (41)**	**70 (38)**	**<0.001**
Anemia	22 (13)	21 (12)	11 (6)	0.09
Neutropenia	71 (40)	27 (15)	39 (22)	<0.001
Thrombocytopenia	26 (15)	12 (7)	9 (5)	0.008
All Non-hematologic -- no. (%)	**111 (63)**	**133 (74)**	**134 (74)**	**0.04**
Bleeding	0 (0)	3 (2)	5 (3)	0.46
Infections	26 (15)	37 (21)	37 (20)	0.62
Febrile neutropenia	13 (7)	3 (2)	1 (1)	<0.001
Atrial fibrillation	5 (3)	17 (9)	10 (6)	0.05
Hypertension	25 (14)	53 (29)	61 (34)	<0.001
Unexplained/unwitnessed death	2 (1)	7 (4)	4 (2)	0.24

- Deaths during active treatment + 30 days: 2 (1%), 13 (7%), 13 (7%).
- Deaths during active treatment + 30 days, up to 6 cycles: 2 (1%), 3 (2%), 6 (3%).

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

Ibrutinib Adverse Events: ECOG 1912

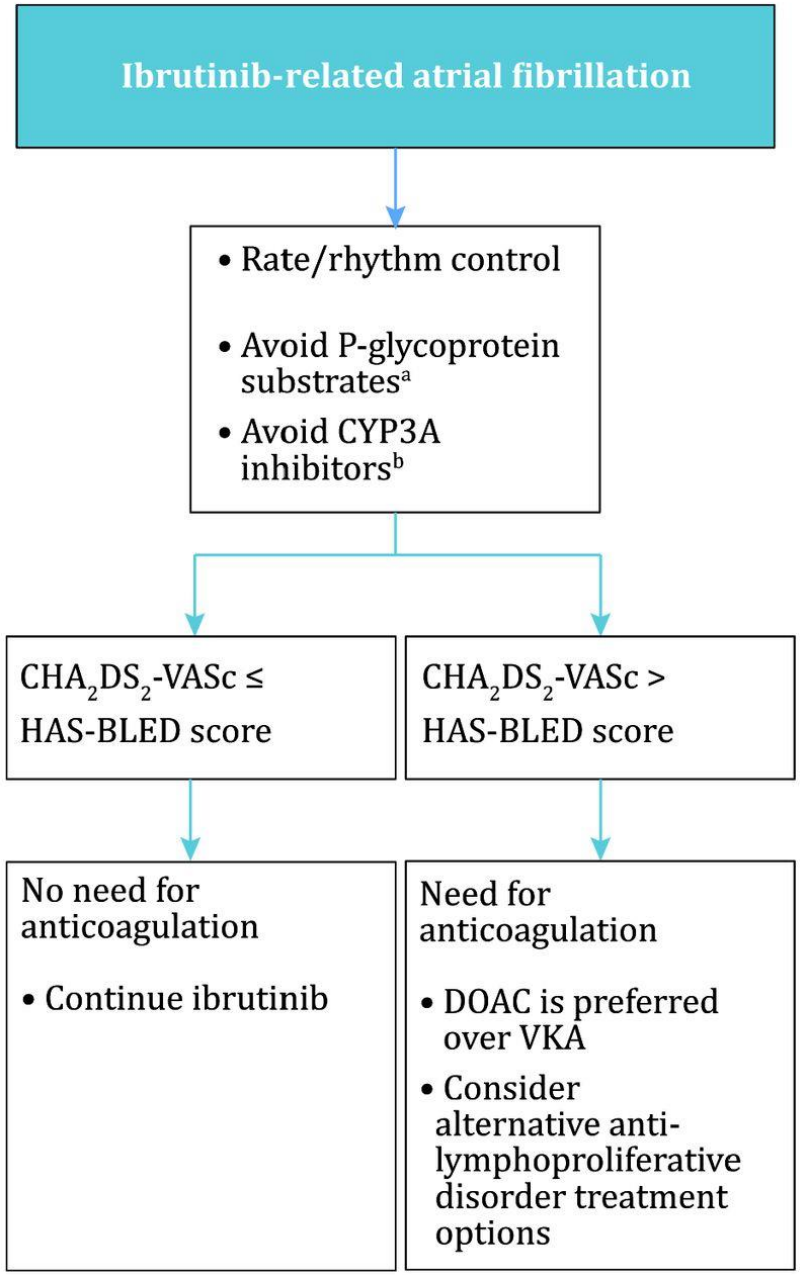
Randomized Phase III frontline young patients (I *vs.* I-R vs. FCR)

TABLE 1. Grade ≥3-5 Treatment-Related Adverse Events

Adverse Event	Ibrutinib plus Rituximab (n=352)	Fludarabine, Cyclophosphamide, Rituximab (n=158)	p Value
Neutropenia	22.7%	43.7%	<0.001
Anemia	2.6%	12%	<0.001
Thrombocytopenia	2.9%	13.9%	<0.001
Infection	7.1%	19%	<0.001
Atrial fibrillation	2.9%	0%	0.04
Bleeding	1.1%	0%	0.32
Hypertension	7.4%	1.9%	0.01
Diarrhea	2.6%	0.6%	0.19

Shanafelt et al. Abstract # LBA-4. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

Flowchart for Management of Atrial Fibrillation During Ibrutinib Use



Iris de Weerdt et al. Haematologica 2017;102:1629-1639

Summary of Relevant Issues Relating to Bleeding and Anticoagulation During Ibrutinib Treatment

Ibrutinib and bleeding

- Cessation of ibrutinib 3-7 days before and after invasive procedures
- Bruising is very common and does not herald major bleeding
- Concomitant antiplatelet therapy does not seem to increase major bleeding
- Concomitant anticoagulation does not seem to increase major bleeding
- Very limited experience with concomitant vitamin K antagonists
- Avoid combined anticoagulation and antiplatelet treatment during ibrutinib use

Iris de Weerdt et al. Haematologica 2017;102:1629-1639

BCL-2 Inhibitor: Venetoclax

- Orally available, selective, small molecule inhibitor of BCL2:
  - BH3 mimetic: Mimics Bcl-2 homology 3 (BH3) domains of the pro-apoptotic Bcl-2 family members, which neutralize these proteins by binding to their surface hydrophobic grooves.
- FDA approved for relapsed del(17p) disease only:
  - Multicenter, open label phase 2;
  - ORR 79%, 8% CR;
  - 12-month PFS was 72%, OS 87%;
- TLS! – Assess risk, use hypouricemic agents, monitor:
  - High-risk patients require hospitalization.

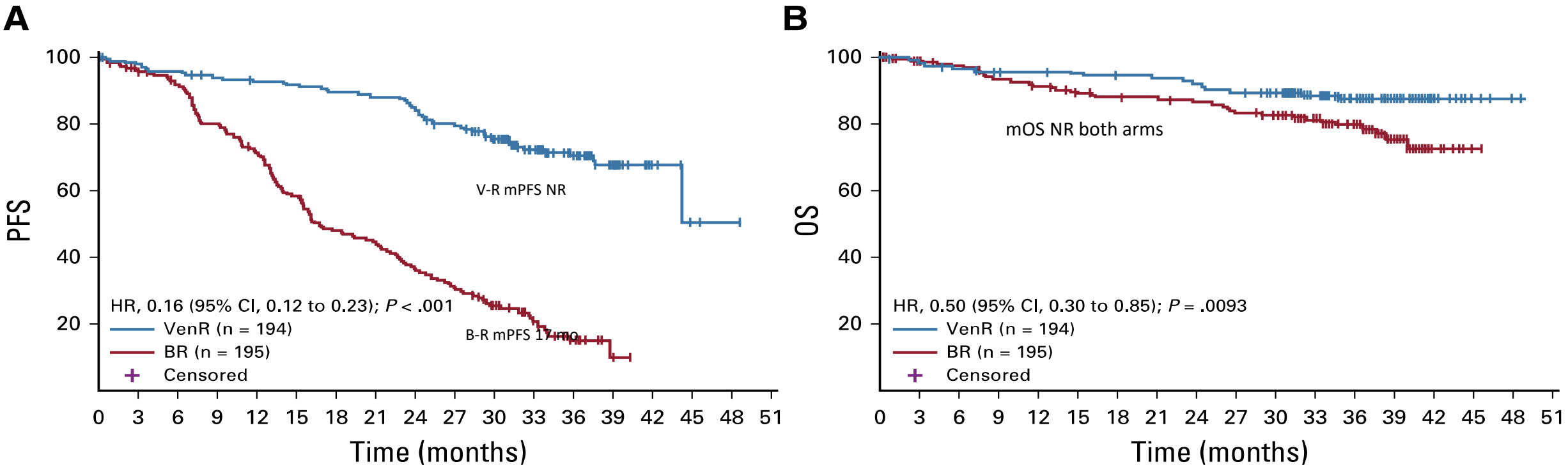
Lancet Oncol. 17, 768–778 (2016)

Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study

Patients with R/R CLL after 1-3 previous lines of therapy

Venetoclax 5-wk titration, 400 mg PO QD for C1-6 + **rituximab** (n = 194) vs **bendamustine** + **rituximab** (n = 195) for 6 cycles

ORR: 93.3% with venetoclax/R vs 67.7% with BR. Estimated 3-year mPFS 71.4% vs 15.2%



No. at risk:

VenR	194	190	185	179	176	174	170	167	161	150	135	99	61	21	6	2	1
BR	195	178	164	142	128	103	84	79	65	55	41	26	10	2			

No. at risk:

VenR	194	190	185	183	182	179	178	176	173	168	163	128	87	39	13	4	2
BR	195	181	175	167	162	155	152	150	147	141	136	111	76	34	9	1	

J Clin Oncol 37:269-277

CAPTIVATE: Efficacy (I+V)

Outcome, %	6 Cycles of I+V (n = 30)	9 Cycles of I+V (n = 14)	12 Cycles of I+V (n = 14)
Blood MRD			
▪ < 0.01% (undetectable)	77	86	93*
▪ 0.01% - < 1.0%	13	7	7
▪ ≥ 1.0%	10	NE	--
Bone marrow MRD†			
▪ < 0.01% (undetectable)	--	--	86
▪ 0.01% - < 1.0%			14
ORR			100 (n = 11)
▪ CR			36
▪ CRi	--	--	18
▪ nPR			9
▪ PR			36

***79% with confirmed undetectable MRD. †Assessed only after 12 cycles I + V.**

Wierda WG, et al. ASCO 2018. Abstract 7502.

Venetoclax Toxicity

- Tumor lysis syndrome (TLS) is the most important potential early complication.
- Slow, stepped-up dosing and preventive measures can nearly eliminate this risk.
- The most common single agent toxicities include neutropenia, diarrhea, nausea, URI, anemia, fatigue, thrombocytopenia, musculoskeletal pain, edema, and cough.
- Similar toxicity with higher rates when combined with rituximab (MURANO).

TLS adverse reactions and relevant common (≥10%) new or worsening laboratory abnormalities occurring at ≥5% (any grade) or ≥2% (grade 3 or 4) higher incidence with VEN+R compared with BR

Parameter	VEN+R (n=194)		BR (n=188)	
	All Grades§ (%)	Grade 3 or 4 (%)	All Grades§ (%)	Grade 3 or 4 (%)
TLS	3	3	1	1
Laboratory Abnormality				
Hypocalcemia	62	5	51	2
Hyperuricemia	36	36	33	33
Hyperkalemia	24	3	19	2

rxabbvie.com/pdf/venclexta.pdf

Murano Toxicity Data Summary

SUMMARY OF ADVERSE REACTIONS REPORTED WITH INCIDENCE OF ≥10% AND ≥5% HIGHER FOR ALL GRADES OR ≥2% HIGHER FOR GRADE 3 OR 4 IN PATIENTS TREATED WITH VEN+R COMPARED WITH BR

Adverse Reaction by Body System	VEN+R followed by single agent VENCLEXTA® (n=194)		BR (n=188)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood & lymphatic system disorders				
Neutropenia*	65	62	50	44
Gastrointestinal disorders				
Diarrhea	40	3	17	1
Infections & infestations				
Upper respiratory tract infection*	39	2	23	2
Lower respiratory tract infection*	18	2	10	2
Musculoskeletal & connective tissue disorders				
Musculoskeletal pain*	19	1	13	0
Metabolism & nutrition disorders				
Tumor lysis syndrome	3	3	1	1

*Includes multiple adverse reaction terms.

rxabbvie.com/pdf/venclexta.pdf

Venetoclax TLS Risk Assessment

STEP 1: **ASSESS**
PRIOR TO TREATMENT

- Assess Tumor Burden
- Assess Renal Function and Comorbidities
- Assess & Correct Baseline Blood Chemistries

STEP 2: **PREPARE**
2-3 DAYS PRIOR TO FIRST DOSE

- Begin Administering Anti-hyperuricemics 2-3 Days Prior
- Initiate Oral and/or IV Hydration 2 Days Prior*

STEP 3: **INITIATE**
FIRST 5 WEEKS OF TREATMENT

- 5-Week Dose Ramp-up†
- Blood Chemistry Monitoring‡

rxabbvie.com/pdf/venclexta.pdf

Venetoclax TLS Management

Tumor Burden Assessment	STEP 2: PREPARE (2-3 DAYS PRIOR TO FIRST DOSE) Anti-hyperuricemics*	Hydration†	STEP 3: INITIATE (FIRST 5 WEEKS OF TREATMENT) Blood chemistry monitoring‡§
LOW TUMOR BURDEN All LN <5 cm **AND** ALC <25 x 10^9/L	Allopurinol	Oral (1.5-2 L)	**Outpatient** • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
MEDIUM TUMOR BURDEN Any LN 5 cm to <10 cm **OR** ALC ≥25 x 10^9/L	Allopurinol	Oral (1.5-2 L) Consider additional IV	**Outpatient** • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with CrCl <80 mL/min; see below for monitoring in hospital
HIGH TUMOR BURDEN Any LN ≥10 cm **OR** Any LN ≥5 cm **AND** ALC ≥25 x 10^9/L	Allopurinol Consider rasburicase if baseline uric acid is elevated	Oral (1.5-2 L) **AND** IV (150-200 mL/hr as tolerated)	**In hospital** • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12, and 24 hours **Outpatient** • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

rxabbvie.com/pdf/venclexta.pdf.

PI3K Inhibitor: Idelalisib

- Oral inhibitor of phosphoinositide 3'-kinase (PI3K) delta.
- Approved in relapsed setting in combination with rituximab:
  - I-R superior to placebo-R (ORR 81% vs 13%; mOS 20.8 mo vs NR);
  - Works in all subsets del(17p)/TP53, IGHV mutations.
- Also causes lymphocytosis initially (peaks at week 2, resolves by week 12).
- AE: Transaminitis, pneumonitis, colitis (can be severe and occur > 6 months after initiating tx) – **black box warnings.**
- Prophylaxis for varicella, PCP, test HBV, monitor CMV.

N Engl J Med 2014; 370:997-1007; Zydelig [prescribing information]. Foster City, CA: Gilead Sciences, Inc.; 2014

Toxicity: Idelalisib

Table 2. Adverse events reported during idelalisib use.

	Previously untreated [79]	Previously treated [12, 13, 76-78]
Total (number)	64	393
Diarrhea and/or colitis, any grade	64	14-43
Grade ≥3	42	4-18
Fatigue, any grade	31	24-36
Grade ≥3	0	2-3
Cough, any grade	33	13-29
Grade ≥3	2	0-4
URTI, any grade	NR	14-20
Grade ≥3	NR	0
Pneumonia, any grade	28	11-22
Grade ≥3	19	6-20
Pneumonitis, any grade	3	2
Grade ≥3	3	2
AST and/or ALT increased, any grade	67	24-60
Grade ≥3	23	2-20
Neutropenia, any grade	53	30-57
Grade ≥3	28	10-43
Anemia, any grade	23	23-37
Grade ≥3	3	2-11
Thrombocytopenia, any grade	14	17-30
Grade ≥3	2	5-17
Febrile neutropenia, any grade	5	3-11

Values represent percentage of patients affected. URTI: upper respiratory tract infection; AST: aspartate transaminase; ALT: alanine transaminase; NR: not reported.

Idelalisib: Summary of Common Adverse Events

- Diarrhea occurs in 2 forms: self-limiting and severe:
  - Self-limiting: usually early onset and responds to common antidiarrheal agents.
  - Severe: responds poorly to antimotility agents but appears to be responsive to budesonide and/or systemic corticosteroids.
- ALT/AST elevations are generally reversible with idelalisib dose interruptions:
  - 74% of patients were able to be retreated with idelalisib without recurrence.
- Pulmonary symptoms should be evaluated for pneumonitis:
  - Discontinue idelalisib with any severity of symptomatic pneumonitis.
  - Some patients were treated with discontinuation of corticosteroids in addition to continuing antibiotics if pneumonitis did not improve.

Coutre S, et al. Leuk Lymphoma. 2015;56:2779-2786.

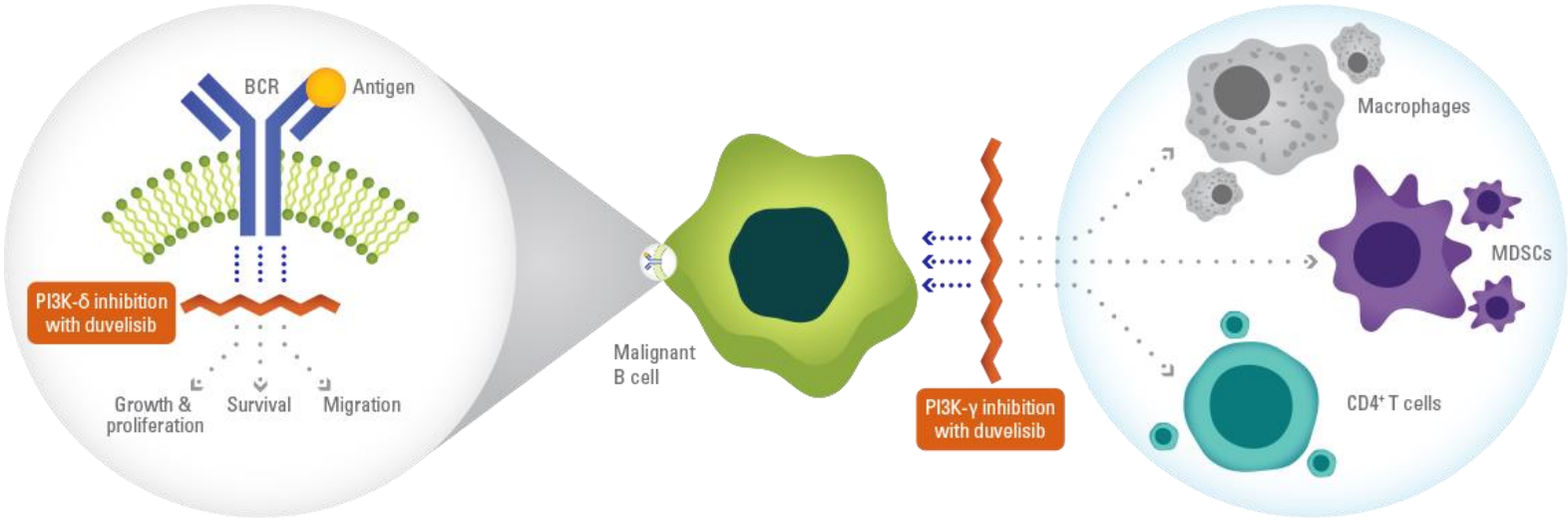
Duvelisib

- **Duvelisib is a first-in-class, oral dual inhibitor of PI3K-δ,γ approved by the US FDA for treatment of adult patients with:**
  - relapsed/refractory CLL or SLL after ≥ 2 prior therapies.[1]
  - relapsed/refractory FL after at least ≥ 2 prior systemic therapies.[1]

    Note: This indication is approved under accelerated approval based on overall response rate (ORR); continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

PI3K-δ (delta) inhibition predominantly restricts malignant B-cell growth and survival.[1]

PI3K-γ (gamma) inhibition helps modulate the tumor microenvironment, a network of nonneoplastic cells essential to malignant B-cell survival and proliferation.[1,2]



Prohibit proliferation and reduce viability in malignant B cells with PI3K-δ inhibition.

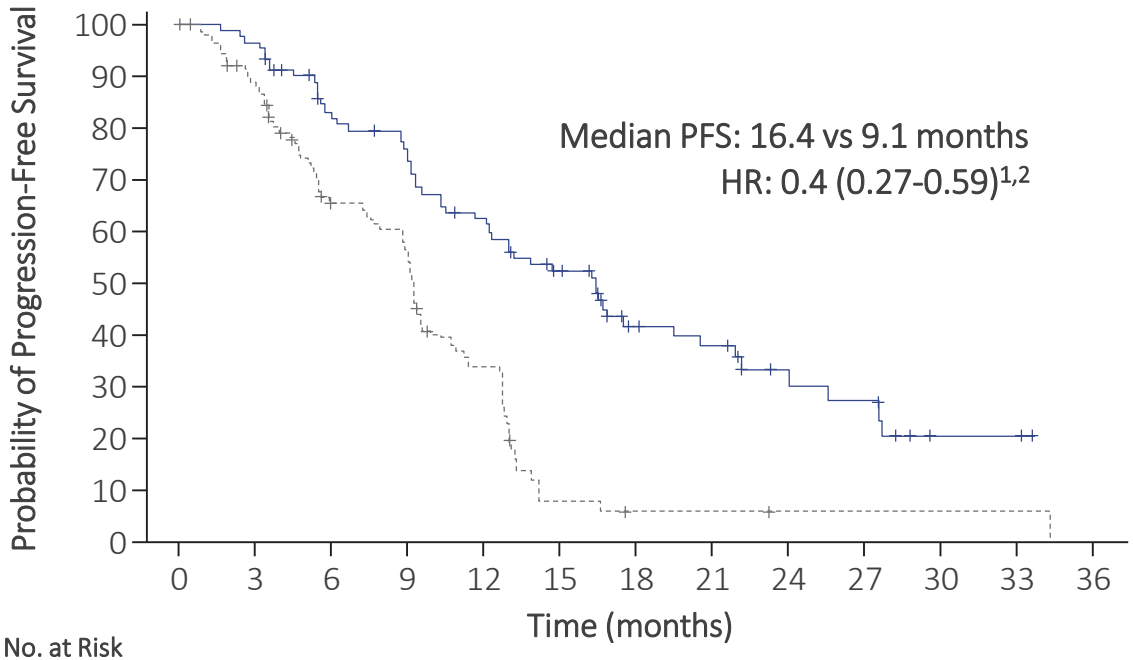
Block CXCL12-induced T-cell migration and M2 macrophage polarization with PI3K-inhibition (based on pre-clinical studies).

1. COPIKTRA Prescribing Information, Verastem, Inc.
2. Nicholas NS, et al. *Biochim Biophys Acta*. 2016;1863(3):471-482

DUO Patients ≥2 Prior Lines of Therapy:

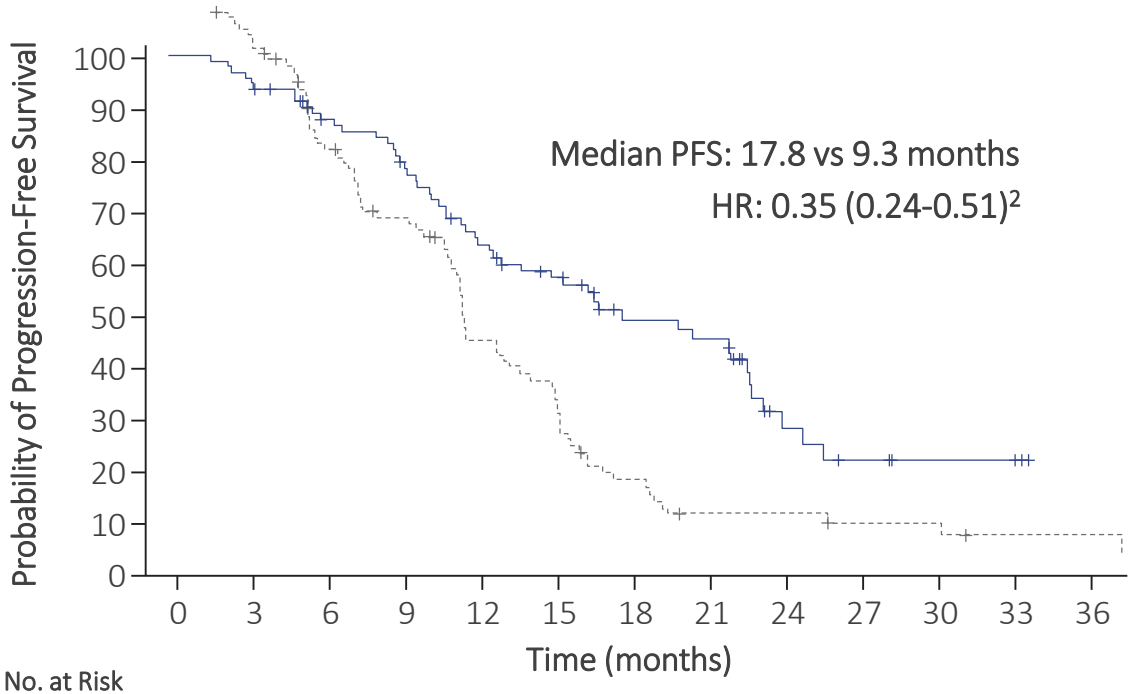
Duvelisib Demonstrated >7-month Median PFS Advantage vs Ofatumumab*

Progression-Free Survival per IRC[1]



No. at Risk													
Duvelisib	95	88	69	60	50	39	13	19	11	9	2	2	0
Ofatumumab	101	78	52	39	22	4	2	2	1	1	1	1	0

Progression-Free Survival per Investigator[2]



No. at Risk													
Duvelisib	96	89	74	67	53	42	26	24	10	6	4	3	0
Ofatumumab	101	83	55	45	27	12	5	5	3	3	1	1	0

+ Censored — Duvelisib 25 mg BID (N=95) ----- Ofatumumab (N=101)

*Kaplan-Meier estimate.
BID, twice a day; HR, hazard ratio; IRC, Independent Review Committee; PFS, progression-free survival

1. Copiktra (duvelisib) [prescribing information]. Needham, MA: Verastem, Inc.; 2018. 2. Flinn IW, et al. Presented at ICHM. February 28th – March 3rd, 2019. Miami, Florida. Abstract 810.

Duvelisib Warnings and Precautions:

Incidence of Serious (Including Fatal) Adverse Experiences and Time to Onset

Adverse Experience n= 442	Serious (including fatal)	Fatal	Median Onset (all grades)	Range of Onset	75% of Events Occurred By	Median Event Duration and Range
Infections	31%	18/442, 4%	3 months	1 day to 32 months	6 months	Not reported
Diarrhea or Colitis	18%	1/442, <1%	4 months	1 day to 33 months	8 months	Duration: 0.5 months Range: 1 day to 29 months, 75th Percentile: 1 month
Cutaneous Reactions*	5%	2/442, <1%	3 months	1 day to 29 months	6 months	Duration: 1 month Range: 1 day to 37 months, 75th Percentile: 2 months
Pneumonitis	5%	1/442, <1%	4 months	9 days to 27 months	9 months	Duration: 1 month 75% resolve by 2 months

*Included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN).

The most common serious infections were pneumonia, sepsis, and lower respiratory tract infections. Serious, including fatal, Pneumocystis jirovecii pneumonia (PJP) occurred in 1% of patients. CMV reactivation/infection occurred in 1% of patients.

Current Treatment Landscape in CLL

First-line Treatment Options

With *del(17p)/TP53* mutations	**No *del(17p)/TP53* mutations**
Ibrutinib	FCR
Obinutuzumab	BR
Clinical trial	Ibrutinib
(*if contraindications to ibrutinib*)	Chlorambucil + obinutuzumab

Second-line Treatment Options

With *del(17p)/TP53* mutations	**No *del(17p)/TP53* mutations**
Ibrutinib	Ibrutinib
Venetoclax + rituximab	Venetoclax + rituximab
Idelalisib + rituximab	Idelalisib + rituximab
Duvelisib (after 2 prior lines tx)	Duvelisib (after 2 prior lines tx)
Other options:	Other options:
Acalabrutinib (*off label*)	Acalabrutinib (*off label*)
High-dose methylprednisolone + CD20 mAb	Alternate chemotherapy not used first line?
	High-dose methylprednisolone + CD20 mAb

Three KIs are available:

Ibrutinib (BTKi), idelalisib (PI3Kδi), and duvelisib (PI3Kδ/γi)

Also BCL-2 inhibitor: Venetoclax (BCL2i)

Current Treatment Landscape in CLL

First-line Treatment Options

With *del(17p)/TP53* mutations
- Ibrutinib
- Obinutuzumab
- Clinical trial
- (*if contraindications to ibrutinib*)

No *del(17p)/TP53* mutations
- FCR
- BR
- Ibrutinib
- Chlorambucil + obinutuzumab

Second-line Treatment Options

With *del(17p)/TP53* mutations
- Ibrutinib
- Venetoclax + rituximab
- Idelalisib + rituximab
- Duvelisib (after 2 prior lines tx)

Other options:
- Acalabrutinib (*off label*)
- High-dose methylprednisolone + CD20 mAb

No *del(17p)/TP53* mutations
- Ibrutinib
- Venetoclax + rituximab
- Idelalisib + rituximab
- Duvelisib (after 2 prior lines tx)

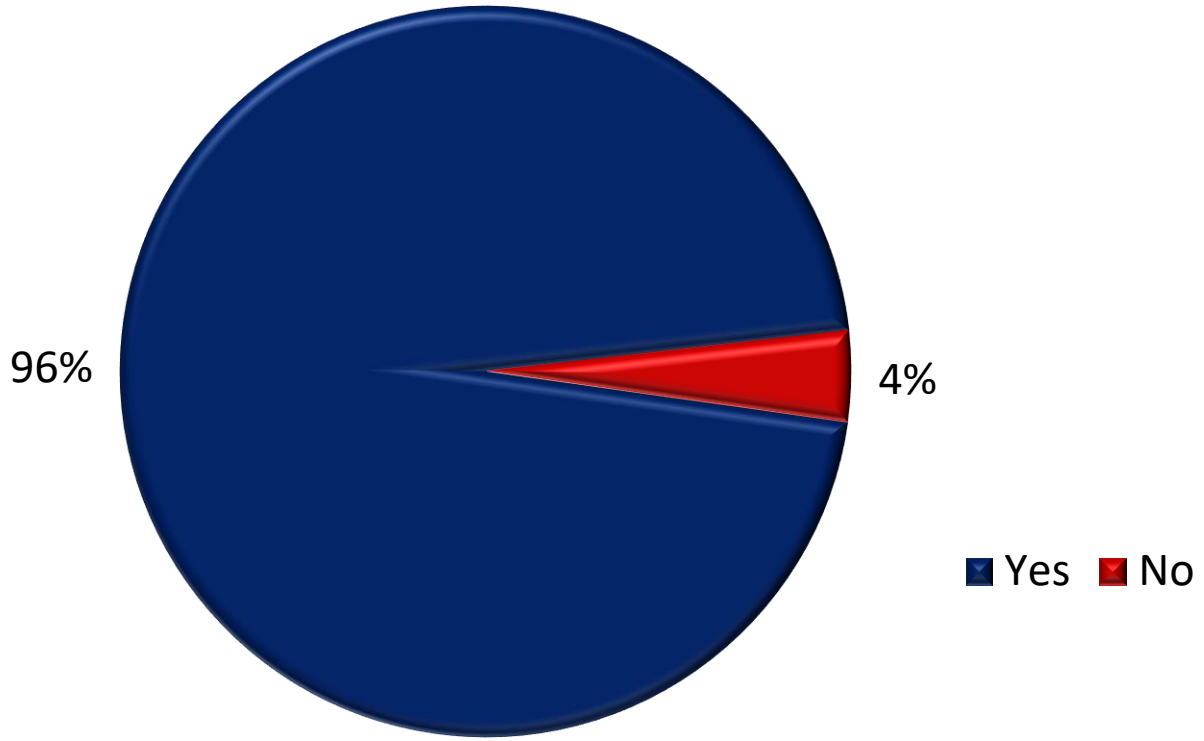
Other options:
- Acalabrutinib (*off label*)
- Alternate chemotherapy not used first line?
- High-dose methylprednisolone + CD20 mAb

Three KIs are available:

Ibrutinib (BTKi), idelalisib (PI3Kδi), and duvelisib (PI3Kδ/γi)

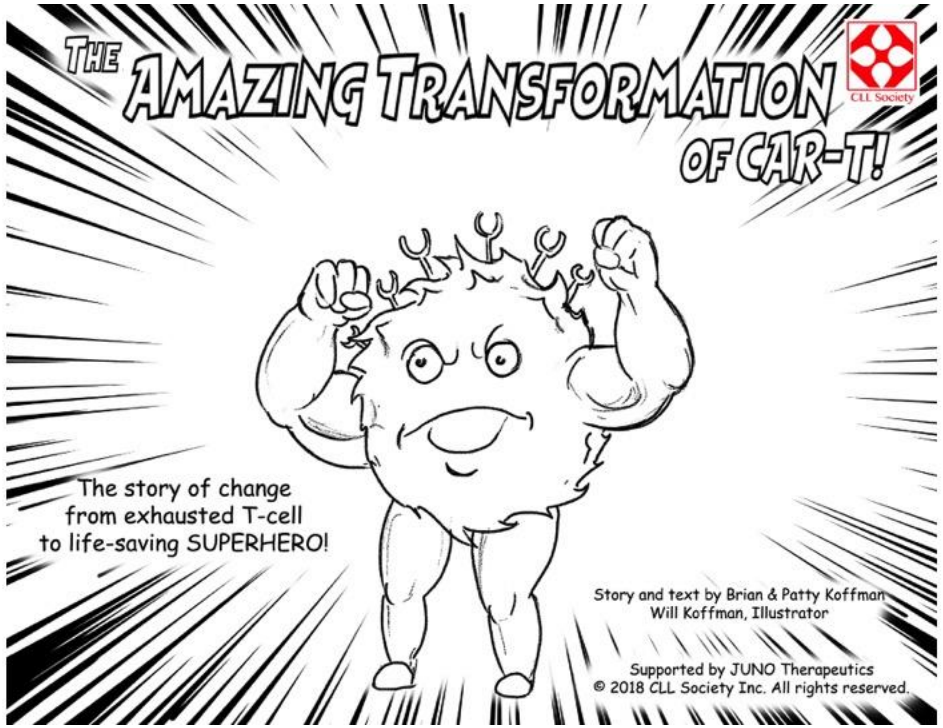
Also BCL-2 inhibitor: Venetoclax (BCL2i)

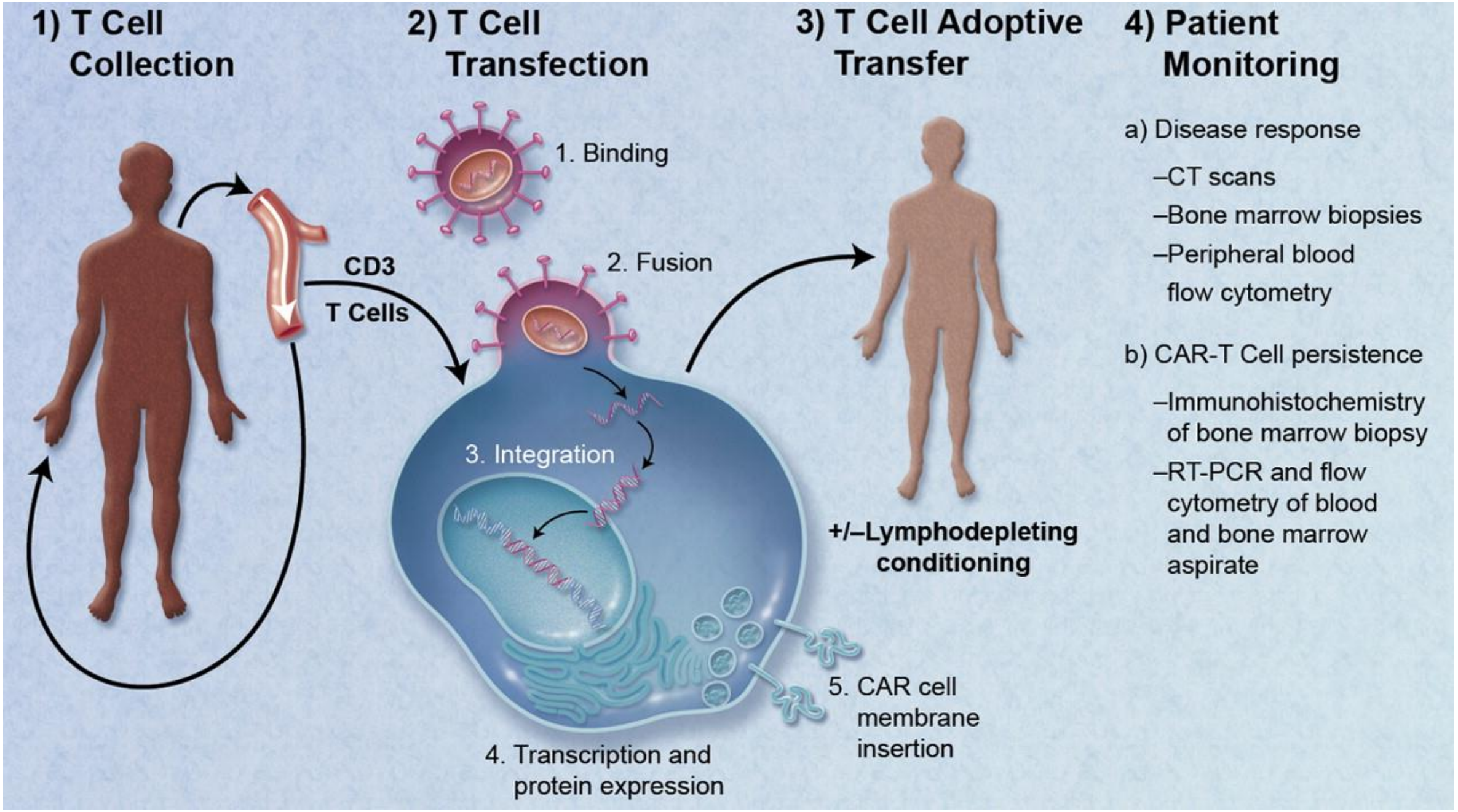
2016 Treatment Selection Survey
Willingness to Take Lifelong Therapy for Long-Term Control Without Potential for Cure

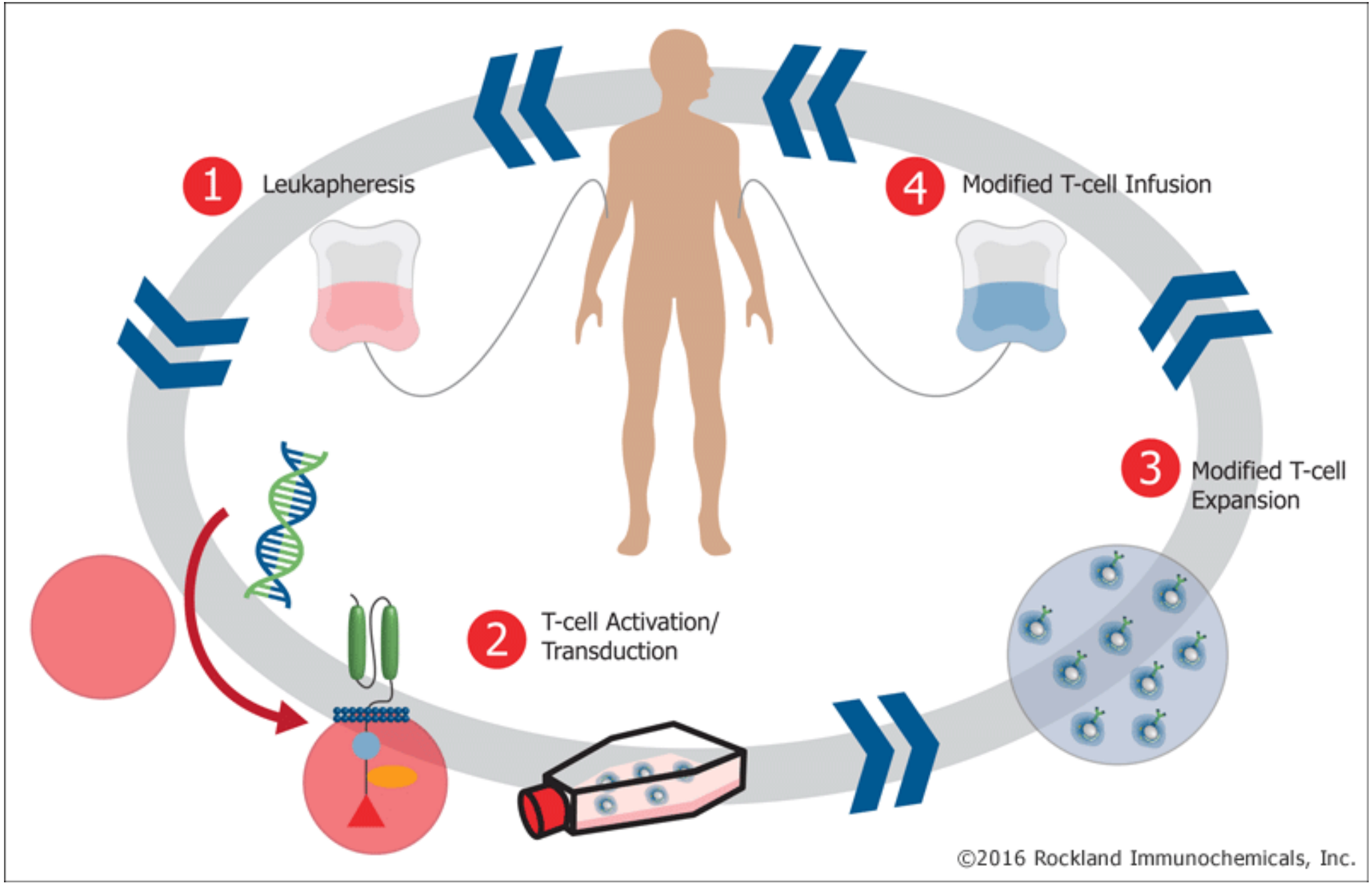


CLL SOCIETY

CAR-T Cell Therapy
Role in CLL




1) T Cell Collection
2) T Cell Transfection
3) T Cell Adoptive Transfer
4) Patient Monitoring
CD3
T Cells
1. Binding
2. Fusion
3. Integration
4. Transcription and protein expression
5. CAR cell membrane insertion
+/–Lymphodepleting conditioning
a) Disease response
–CT scans
–Bone marrow biopsies
–Peripheral blood flow cytometry
b) CAR-T Cell persistence
–Immunohistochemistry of bone marrow biopsy
–RT-PCR and flow cytometry of blood and bone marrow aspirate


1 Leukapheresis
4 Modified T-cell Infusion
3 Modified T-cell Expansion
2 T-cell Activation/ Transduction
©2016 Rockland Immunochemicals, Inc.

Why CARs?

- Best of both worlds of the immune system:
  - B cell specificity;
  - T cell cytotoxicity without presentation.
- Form of Adoptive T cell therapy.
- Synthetically engineered receptors designed to overcome immune tolerance/tumor evasion.
- Targets surface molecules in their native confirmation.
- Engage target independent of antigen presenting cell (APC) and MHC complex.

Ideal CAR Target…

- Tumor specific.
- Universally expressed on only tumor cells.
- Cell surface molecule.
- CD 19:
  - Found on B cell malignant cells (NHL, CLL, ALL, etc.);
  - Expressed on early B cells but NOT stem cells.

Complications of CAR T Cells

- **Cytokine Release Syndrome (CRS)**
  - Typically within 5 days and CRP best predictor.
  - Exponential T cell proliferation leads to IL2, IL6, IFN.
  - Can lead to macrophage activation syndrome and shock/ organ failure.
    - Treated with IL6 monoclonal antibodies (Tocilizumab) and steroids.

- **B Cell Aplasia**
  - Immunoglobulin replacement required to keep Ig > 5g/L.

- **Encephalopathy**
  - Unclear pathogenesis.
  - Self limiting.
  - No long-term complications.
  - CAR T cells in CSF in all patients.

Maude et al. Blood May 2015

Challenges of CAR-T Cell Therapy

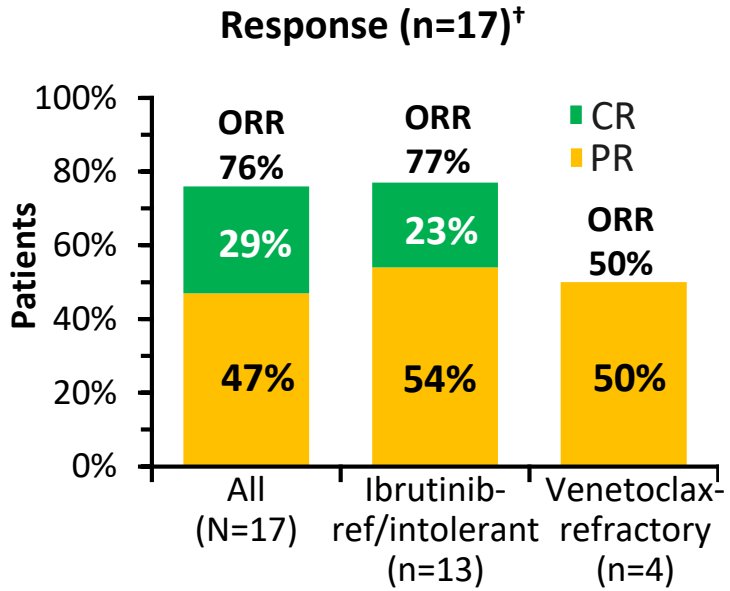
- Unclear how well it will work against solid tumor or even large nodes.
  - Problem of T cells entering tumor site.
- Will tumors lose target antigen and develop resistance?
- Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient.
- Exhaustion of transferred T cells:
  - Use CRISPR gene editing to delete PD-1 from T cells;
  - Increased risk of autoimmune reactions from endogenous TCRs;
  - Use CRISPR to delete TCRs;
  - Result is PD-1- T cells expressing tumor-specific CAR.

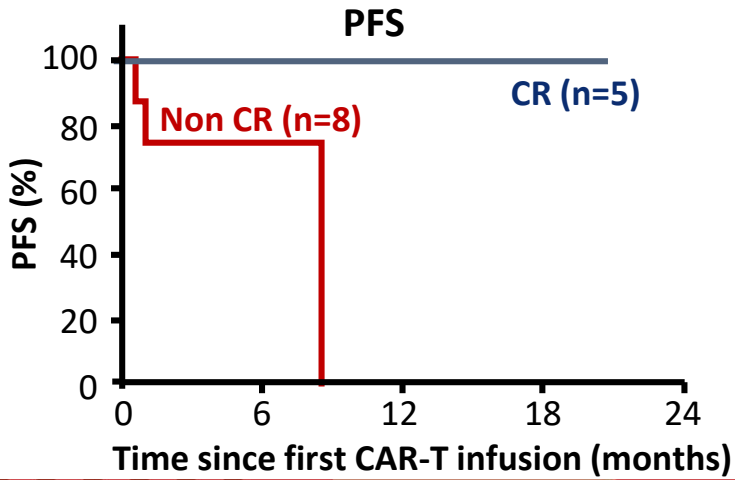
CD19-Targeted CAR-T Therapy in Patients with Ibrutinib-Refractory CLL

Characteristics	All Patients (n=18)
Median age, years (range)	60 (40–73)
Prior fludarabine + R regimen, %	18 (100)
Prior ibrutinib	18 (100)
Ibrutinib-refractory, n (%)	11 (61)
Ibrutinib-intolerant, n (%)	3 (17)
Venetoclax-refractory, n (%)	4 (22)
Complex karyotype, n (%)	12 (67)
del(17p), n (%)	11 (61)
Median abnormal B-cells in BN, % (range)	77 (0.4–96)

At day 28, 11/13 (85%) of patients who received Cy/Flu lymphodepletion and $2x10^6$ CAR-T cells/kg had complete elimination of marrow disease*

* By flow cytometry; † 4 weeks after last CAR-T infusion.





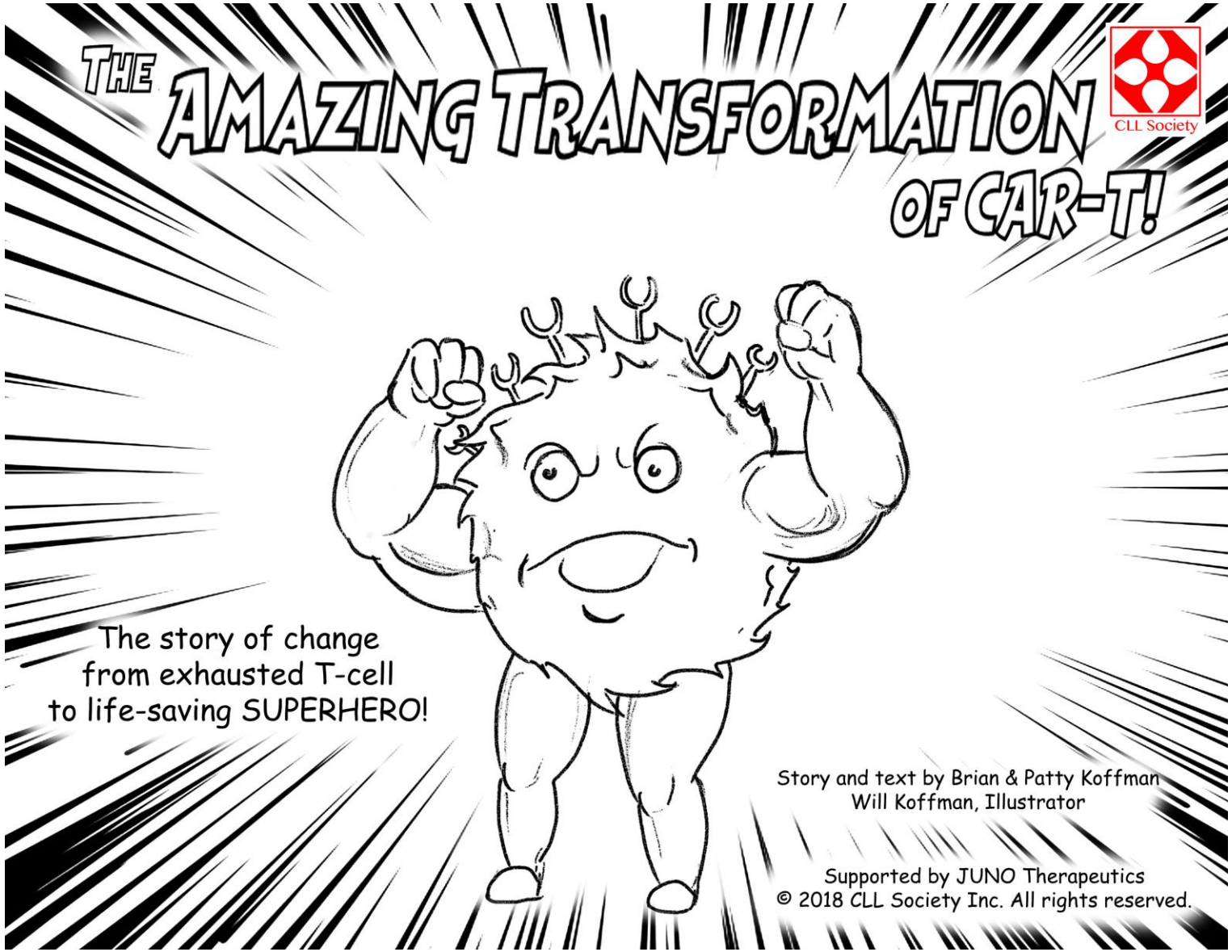
Turtle CJ, *et al. Blood* 2016; **128**:Abstract 56.

Transcend CLL 004 Phase 1 Study: Lisocabtagene Maraleucel (LISO-CEL; JCAR017) CD19-Targeted Defined Cell Product

- **Liso-cel demonstrated promising activity in a heavily pretreated patient population with high-risk CLL, all of whom had received prior ibrutinib.**
- Liso-cel toxicities were manageable at both dose levels tested – Low rates of grade 3 CRS (6.3%) and neurologic events (18.8%).
- High best ORR (81.3%) and a CR/CRi rate (43.8%).
  – Responses have deepened over time at 3- and 6-month follow-up – CR continues in 5 of 6 patients with at least 3 months of follow-up.
- Early uMRD4 responses were observed in a majority of patients (73.3%) and were maintained at 3 and 6 months.

Conclusions

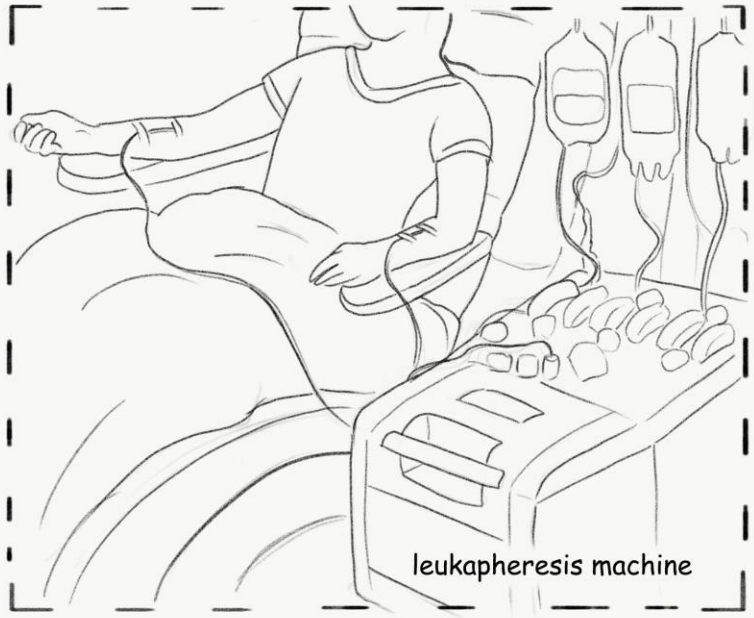
- CAR-T cells are exciting addition to our ability to treat CLL and other cancers.
- The quality of CARs is improving and further data is accumulating.
- However, long-term data (Persistence of CARs) is lacking.
- The cause of toxicity is not clear.
- More questions than answers at presence. Where/when/how to use them.


THE AMAZING TRANSFORMATION OF CAR-T!
CLL Society
The story of change
from exhausted T-cell
to life-saving SUPERHERO!
Story and text by Brian & Patty Koffman
Will Koffman, Illustrator
Supported by JUNO Therapeutics
© 2018 CLL Society Inc. All rights reserved.

Wait a minute…

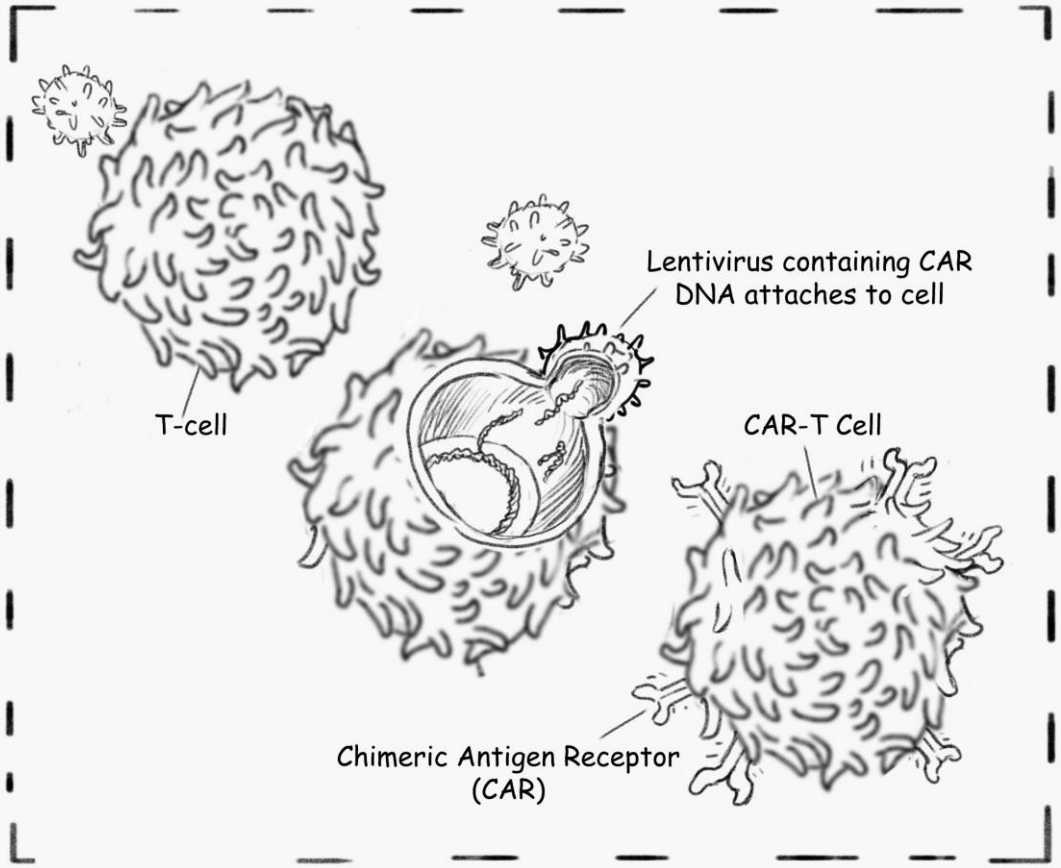
I am being pulled out of my person.

Now I'm being spun around like crazy!

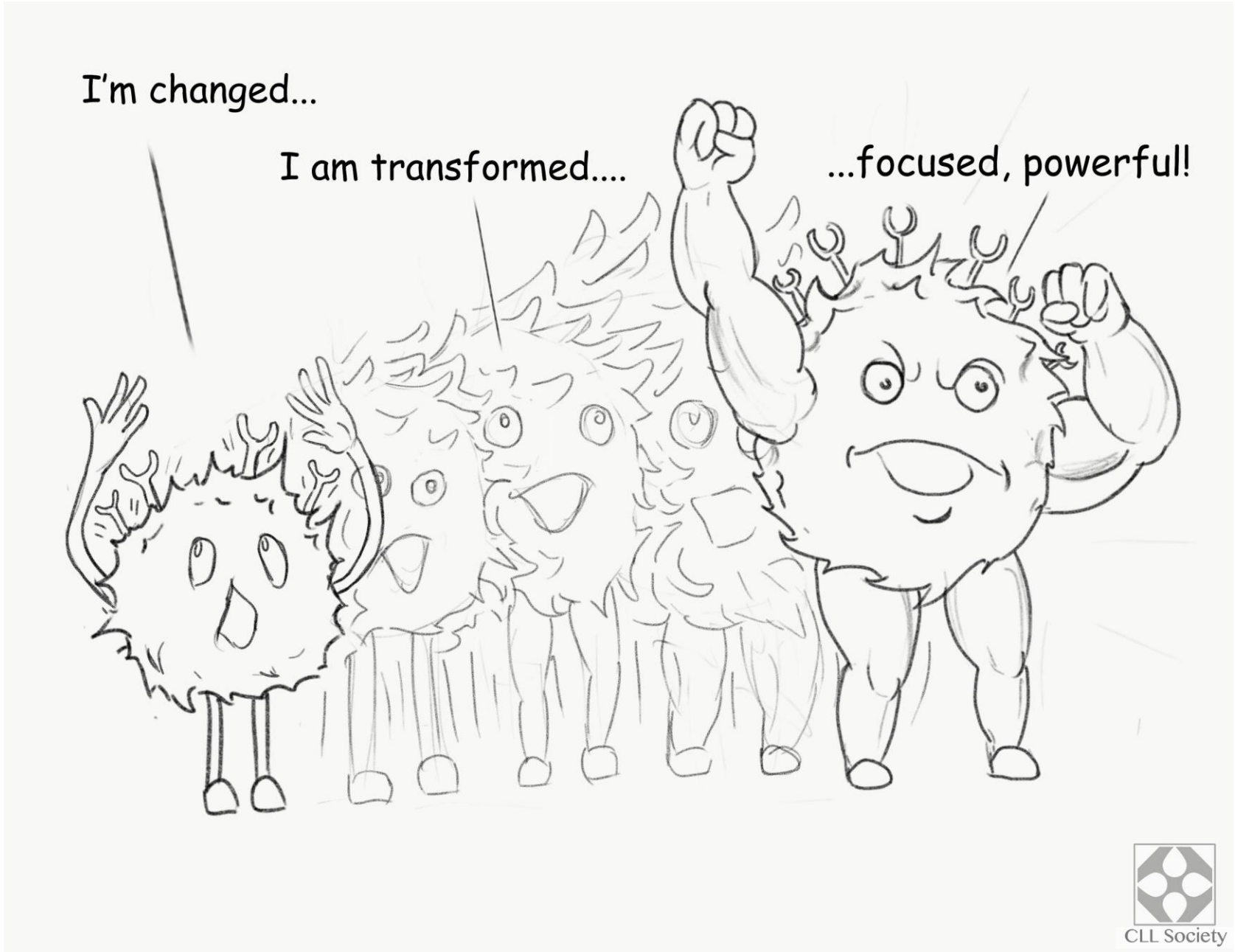


CLL Society

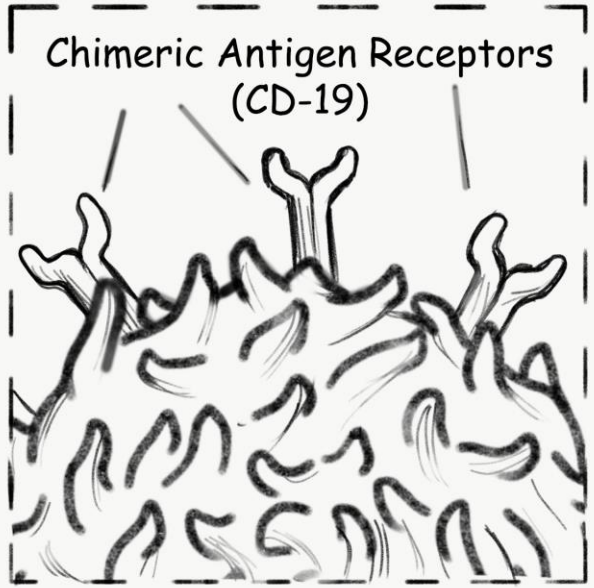
And to add insult to injury, I'm being attacked by viruses that are inserting new messages into my DNA, my instructional code.



CLL Society


I'm changed...
I am transformed....
...focused, powerful!
CLL Society

I am part me, part another creature, like the ancient mythical chimera that was part lion, part goat and part snake. In my case it's part human and part virus. The virus is helping me to build a new receptor to recognize a marker on the surface of B-cells - CD-19. I am a Chimeric Antigen Receptor-T cell, a **CAR-T** or **Car-ty** as I like to be called.



My new CAR has a target element, spacer, transmembrane domain, co-stimulatory domain and signaling domain to supercharge me!

CLL Society

Understanding U-MRD

Undetectable Minimal Residual Disease (U-MRD) CLL

- Complete eradication of leukemia is desired end point.
- Sensitive multicolor flow cytometry, PCR or NGS, can detect MRD in many patients with complete clinical response.
- Substantial evidence that therapies able to eradicate MRD usually lead to improved clinical outcome.
- Techniques for assessing MRD have become well-standardized.
- 6-color flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive to < 1 CLL cel /10,000 leukocytes.
- Typical flow cytometry–based assay: 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81) increasingly commercially available.

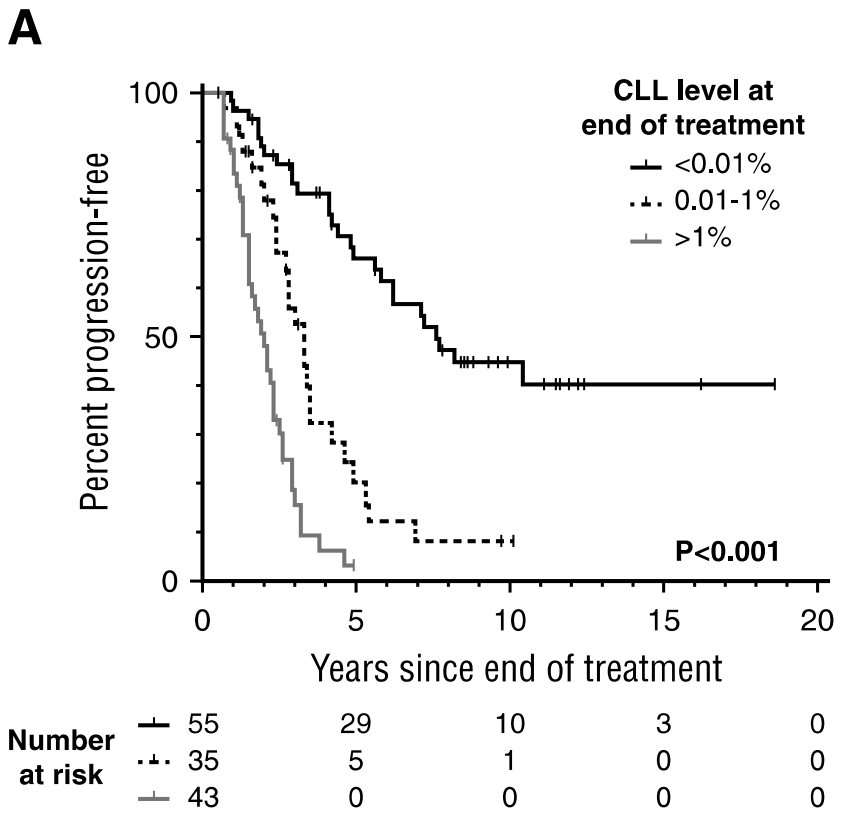
Blood. 2018;131(25):2745-2760

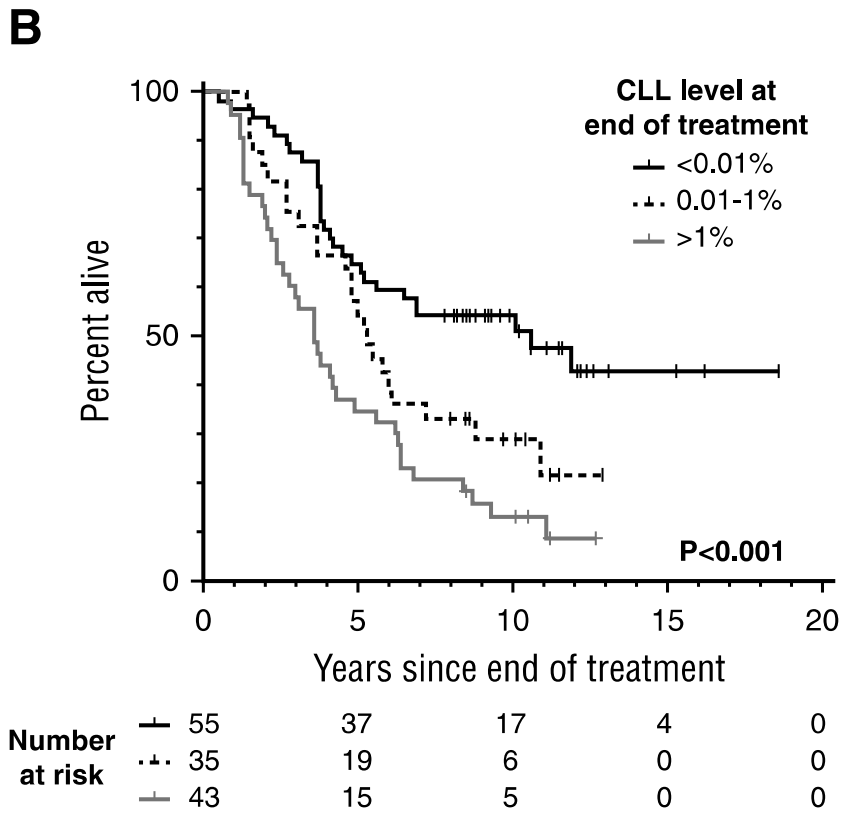
Undetectable Minimal Residual Disease (U-MRD) CLL, Cont'd

- **Patients have undetectable MRD (U-MRD) if blood or marrow <1 CLL cell/10,000 leukocytes.**
- Peripheral blood generally used for assessment; marrow will have detectable CLL when also found in peripheral blood.
- Some therapies preferentially clear blood but not marrow (such as monoclonal antibodies); therefore, may be important to confirm that marrow is MRD-neg when blood is MRD-neg.
- Preferred term now is U-MRD.

Blood. 2018;131(25):2745-2760

Minimal Residual Disease (MRD) Is Independent Predictor of 10-year Survival in CLL



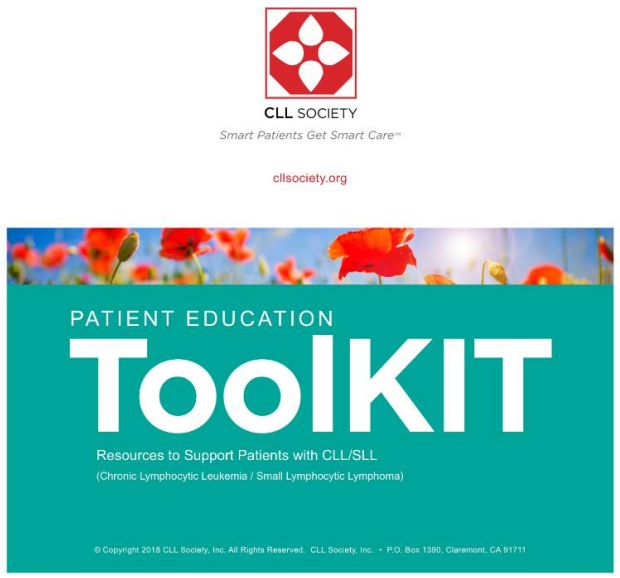


Retrospective analysis of bone marrow MRD status after various therapies in UK 1996-2007

Upfront MRD(-) vs. MRD (+): 10-year PFS 65% vs 10%, 10-year OS 70% vs 30%

Blood, 2016 128;24.

CLL Patient Education Toolkit



The CLL Toolkit provides health care providers with CLL-specific educational materials to supplement the education that is taking place verbally in their physician-patient dialogue.

- Binder format;
- Just-in-time handouts on various topics;
- Meets the patient where they are in the CLL journey;
- Supplemental online materials for updates, re-orders, and surveys.

CLL SOCIETY

SIGN UP FOR A FREE COPY TODAY!

cllsociety.org/kit

The CLL Society, Inc.

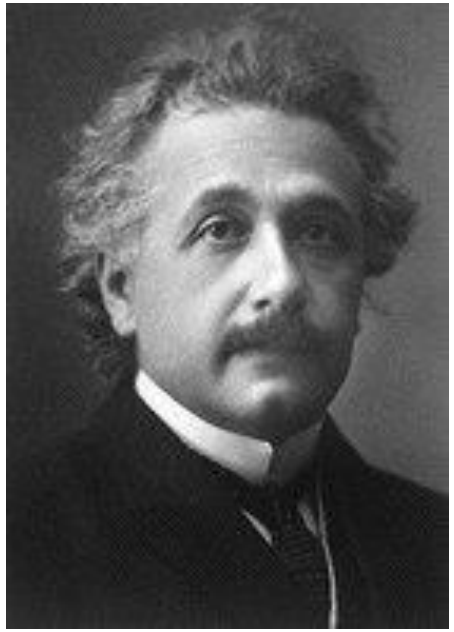
- 501C3 non-profit founded by family physician and CLL patient and his CLL caregiver.
- Focus on patient and caregiver education, support, and research.
- Dedicated to addressing the unmet needs of the CLL and related blood cancer communities.
- The primary source of reliable CLL-specific information:
  - Over 1.3 Million website visits since 2015;
  - ~ 5000 patients and caregivers on mailing list;
  - > 800 original articles with conference coverage including ASH, ASCO & EHA;
  - Research presented at ASCO, ASH and EHA including the largest survey of CLL patients.
- World-renowned CLL physicians on our Medical Advisory Board.

CLL SOCIETY

CLL/SLL
ASCO 2015 Cancer Advance of the Year: Transformation of CLL Treatment

Has everything changed because of:

1. Predictive/Prognostic Testing YES
2. Targeted Therapies YES
3. MRD Testing Not Yet



If I had an hour to solve a problem and my life depended on the solution, I would spend the first 55 minutes determining the proper question to ask.
Albert Einstein (1879 - 1955) Physicist & Nobel Laureate

Thank You

Brian Koffman, MDCM, FCFP, DABFP, MS Ed
Executive Vice President and Chief Medical Officer
CLL Society, Inc.

CLL SOCIETY