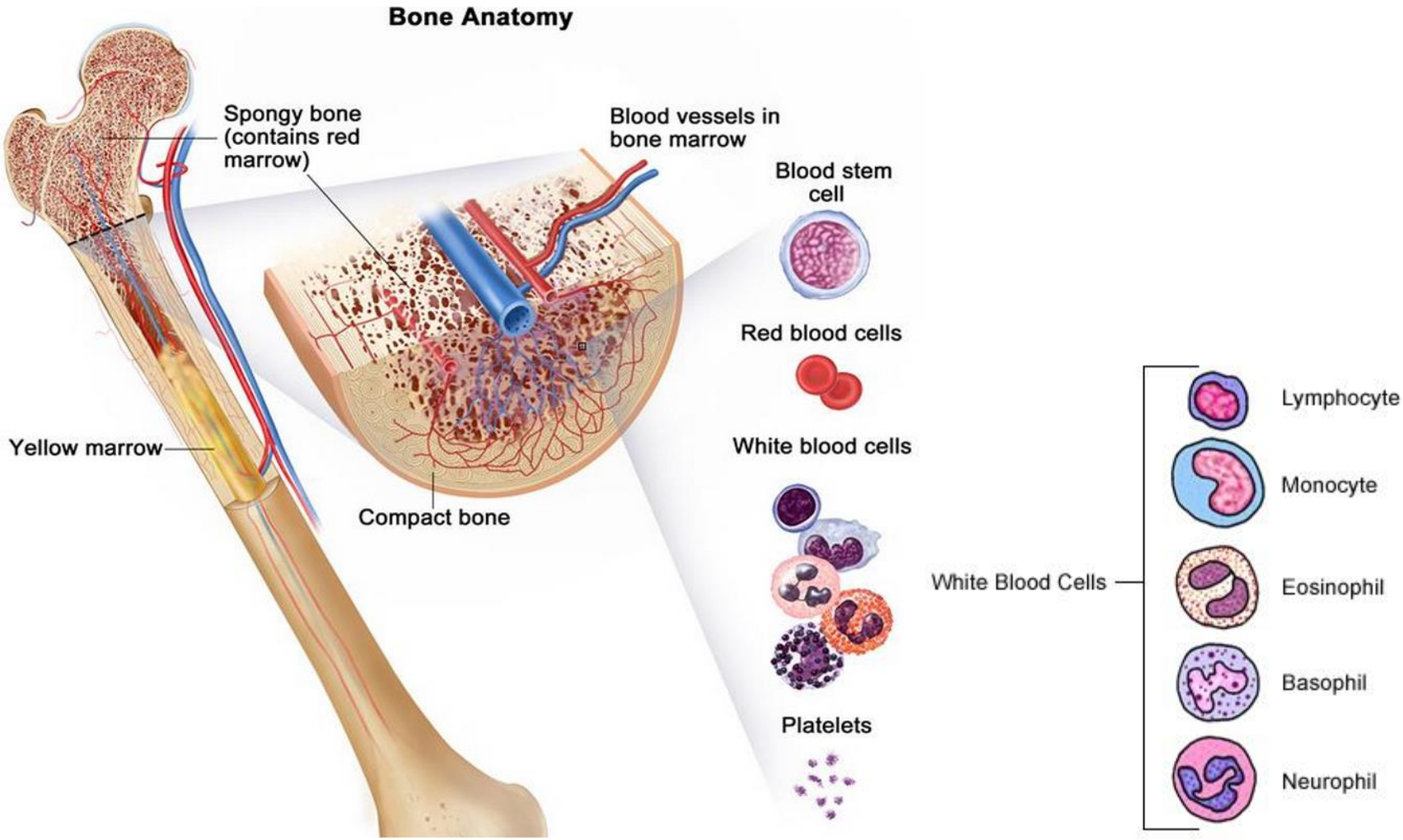
Chronic Lymphocytic Leukemia
Small Lymphocytic Lymphoma
2017 Update

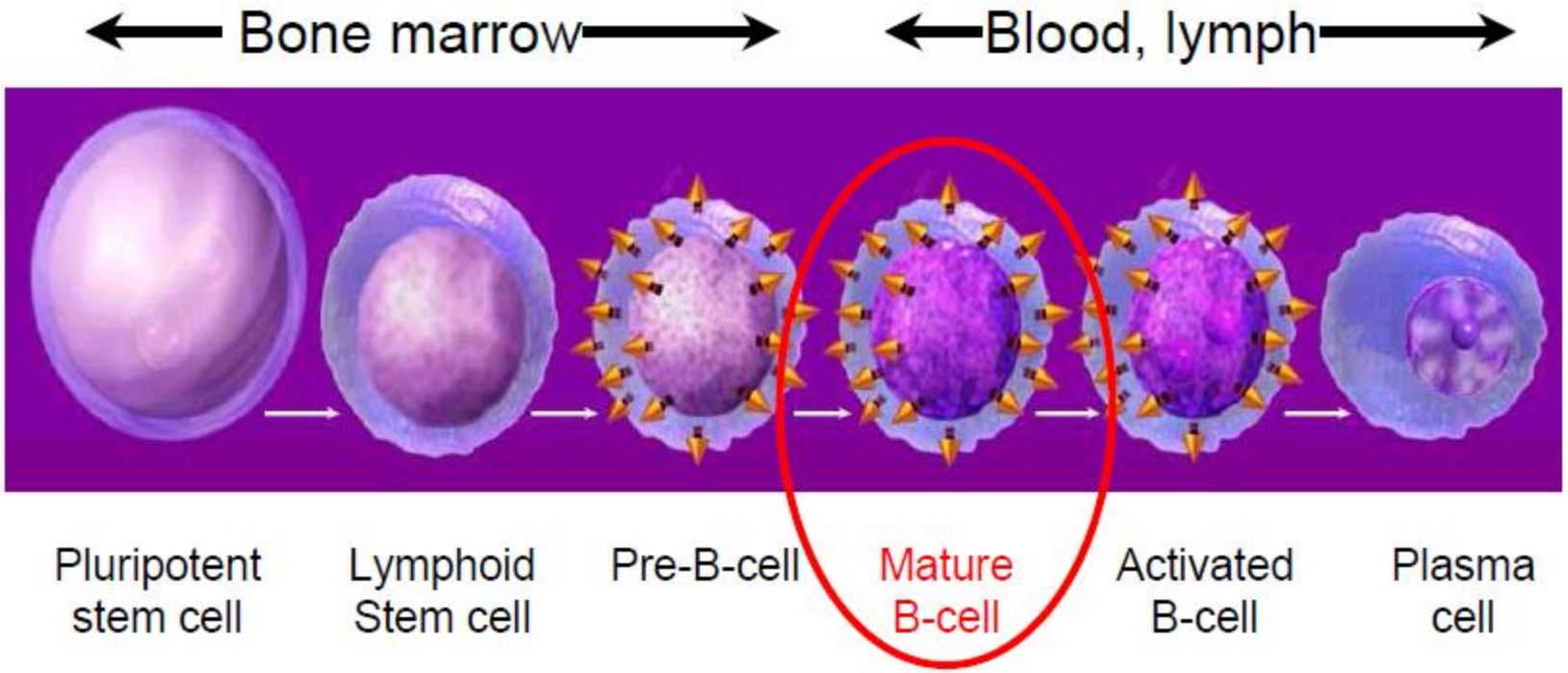
John M Pagel, MD , PhD

Swedish Cancer Institute
Seattle, Washington

What is CLL/SLL?



Newly developed defect in the genetic program of a single mature B-lymphocyte -



CLL vs SLL

- CLL: A blood and bone marrow based disease
  - with progressive accumulation of functionally incompetent lymphocytes in the peripheral blood, bone marrow, spleen and lymph nodes.

- SLL: If absolute lymphocyte count of <5000/microL at the time of diagnosis

CLL

- The most prevalent type of adult leukemia
- Median age of diagnosis of CLL is ~ 72 yrs, with only 10% of patients younger than 50 yrs of age
- More common in men than women (2:1 ratio)
- Environmental predisposition uncertain, although Vietnam veterans with Agent Orange exposure warrant "service-connected status"
- Genetic predisposition present, with ~ 10% of patients having a first-generation relative with CLL

What are the clinical symptoms?

- Often none!
- Non-specific (night sweats, fever, fatigue, weight loss)
- Related to lymph node of spleen enlargement
- Related to bone marrow involvement (cytopenia)
- Infections
- Skin involvement

- High lymphocyte count does NOT cause symptoms

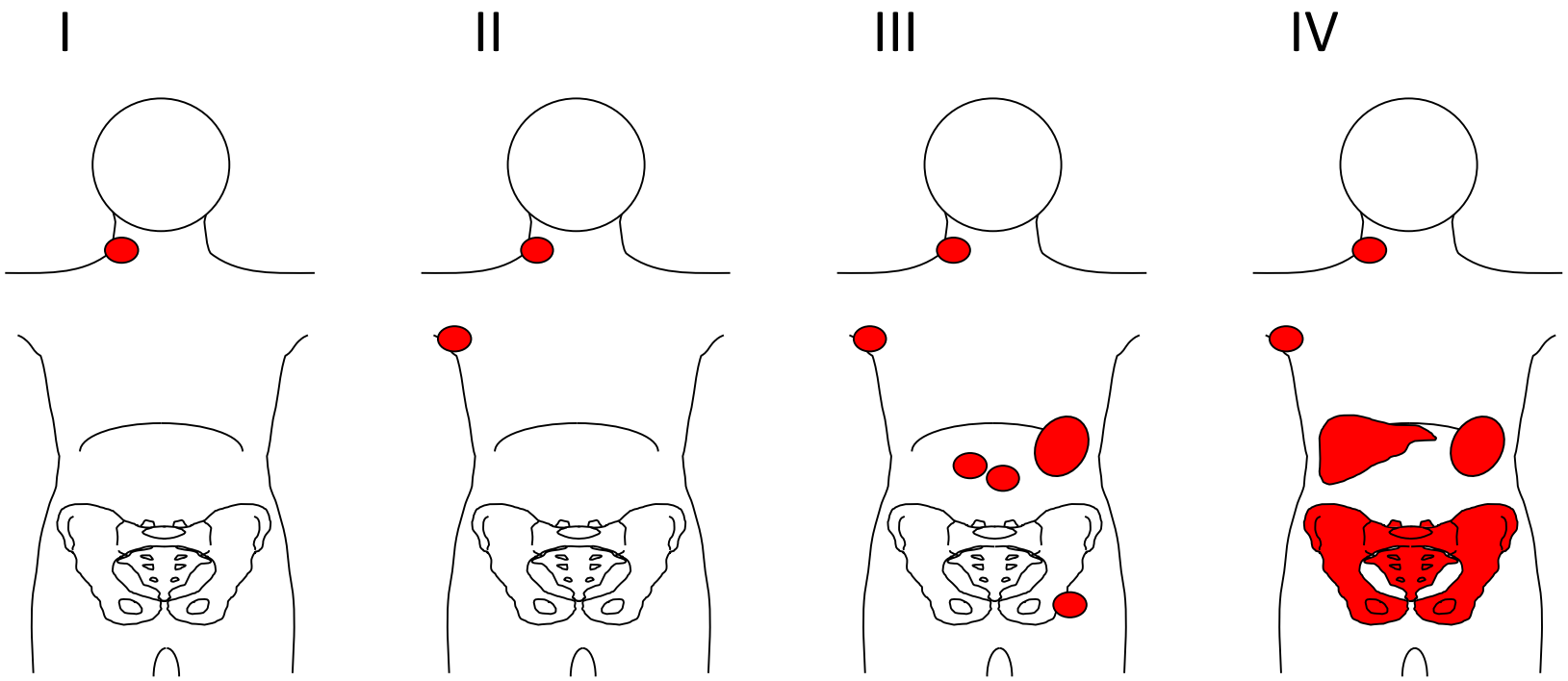
How do we stage CLL?

Rai Staging:

Risk	Stage	Description
Low	0	Lymphocytosis in blood or bone marrow
Intermediate	I	Lymphocytosis + enlarged lymph nodes
	II	Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy
High	III	Lymphocytosis + anemia (Hgb <11 g/dL) with or without enlarged liver, spleen, or lymph lnodes
	IV	Lymphocytosis + thrombocytopenia (platelet count <100,000/microL) with or without anemia or enlarged liver, spleen, or lymph nodes

How do we stage SLL?

Ann Arbor's staging:

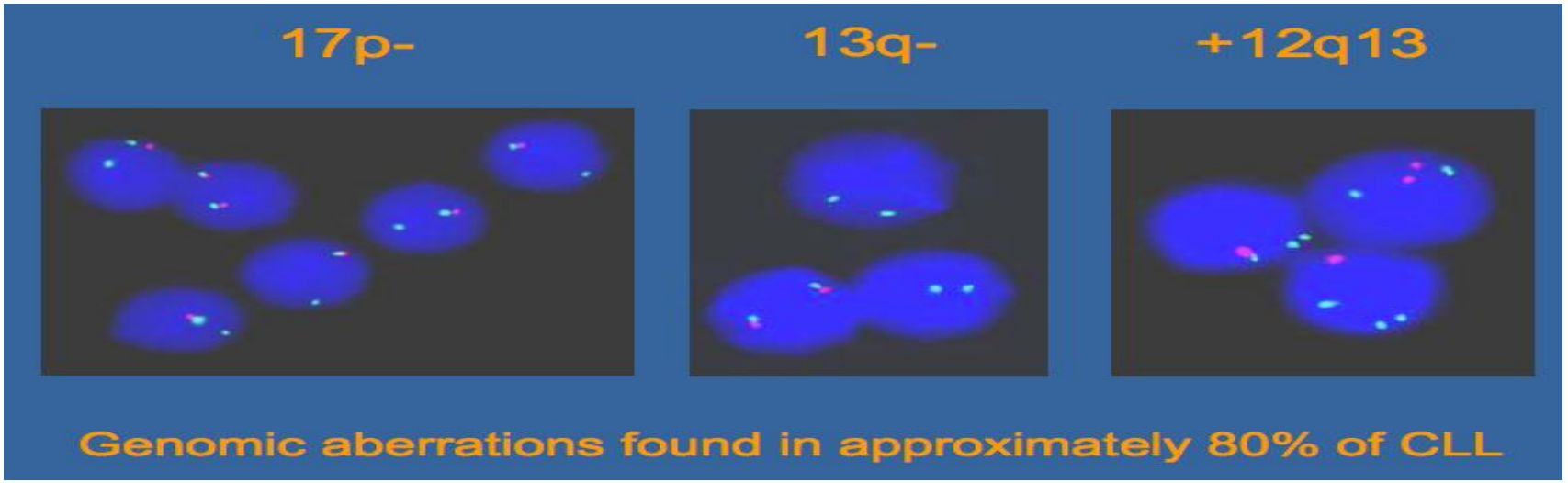


A: No general symptoms

B: General symptoms such as fever, night sweats, weight loss

Prognostic Factors

- FISH defects
  - 17p deletion
  - 11q deletion
  - 12q trisomy
  - Normal
  - 13q deletions



- Immunoglobulin heavy chain variable region (IgV_H)
- CD38 status
- ZAP-70 status
- High serum β2-microglobulin and soluble CD23

Prognostic Factors

Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

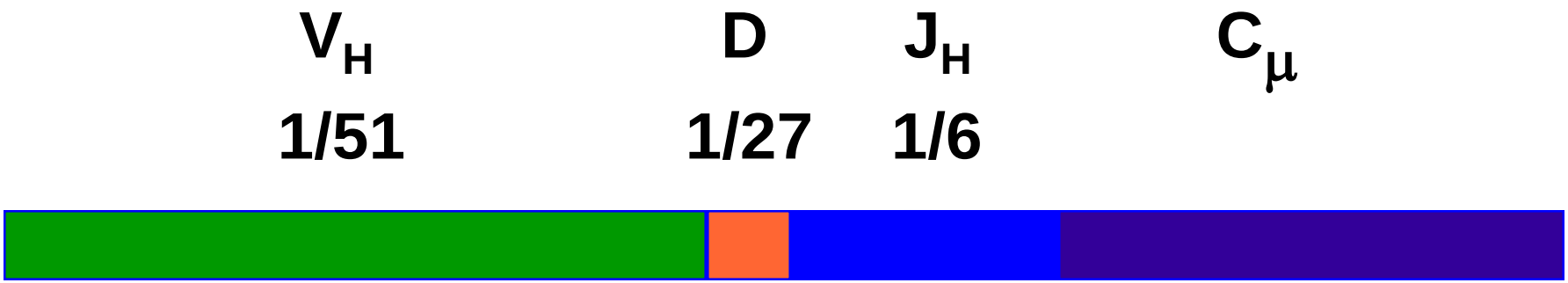
	Outcome Association	
	Favorable	Unfavorable
DNA sequencing[b]		
IGHV	>2% mutation	≤2% mutation
Flow Cytometry		
CD38	<30%	≥30%
Zap 70	<20%	≥20%

Interphase Cytogenetics (FISH)[c]

Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

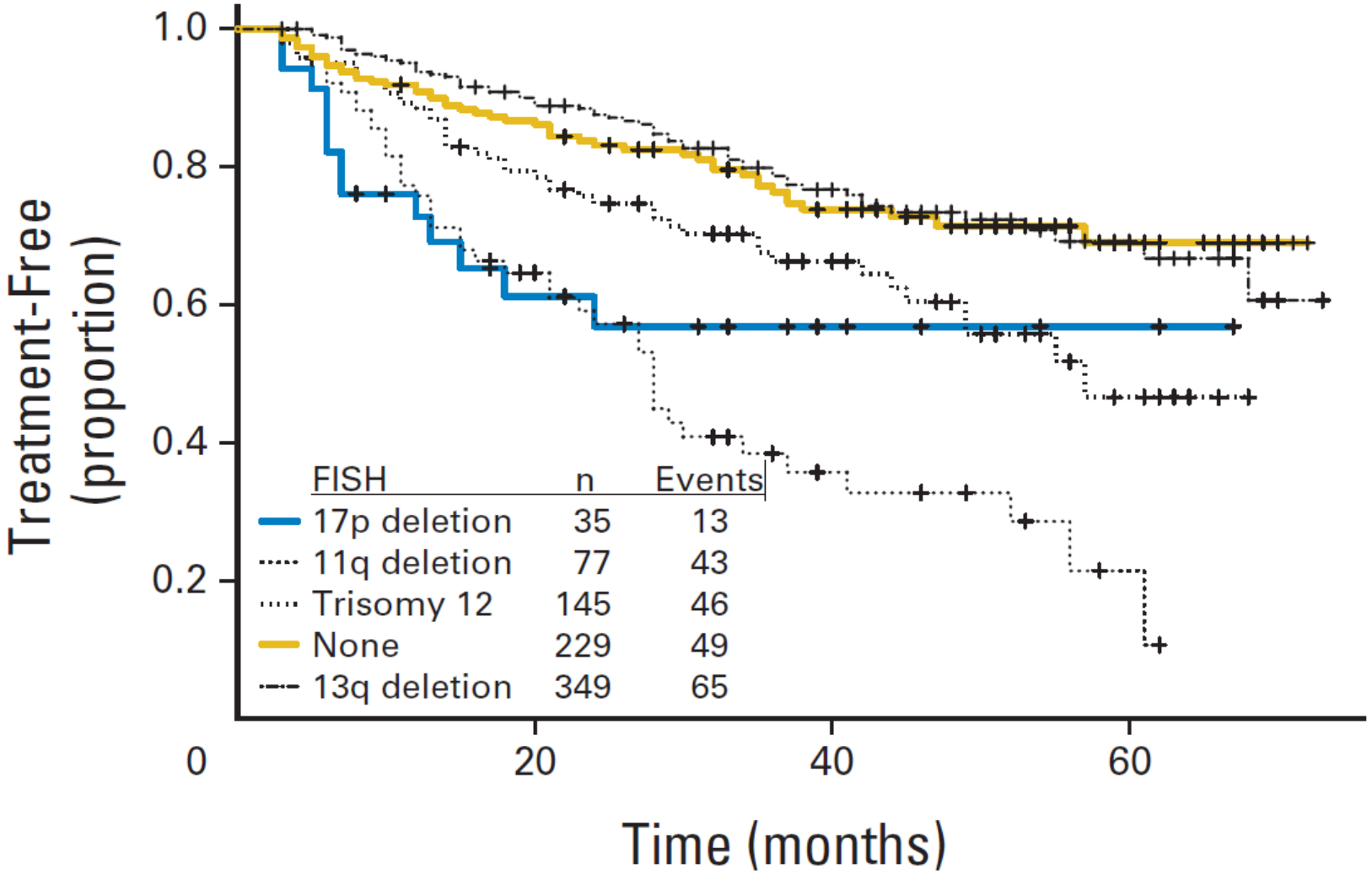
B-Cell Diversity

V_H Rearrangement and Mutation



Somatic mutations

V_H in B-cell chronic lymphocytic leukemia


Treatment-Free (proportion)
1.0
0.8
0.6
0.4
0.2
0
20
40
60
Time (months)
FISH
n
Events
17p deletion 35 13
11q deletion 77 43
Trisomy 12 145 46
None 229 49
13q deletion 349 65

What is the initial work-up for CLL patients?

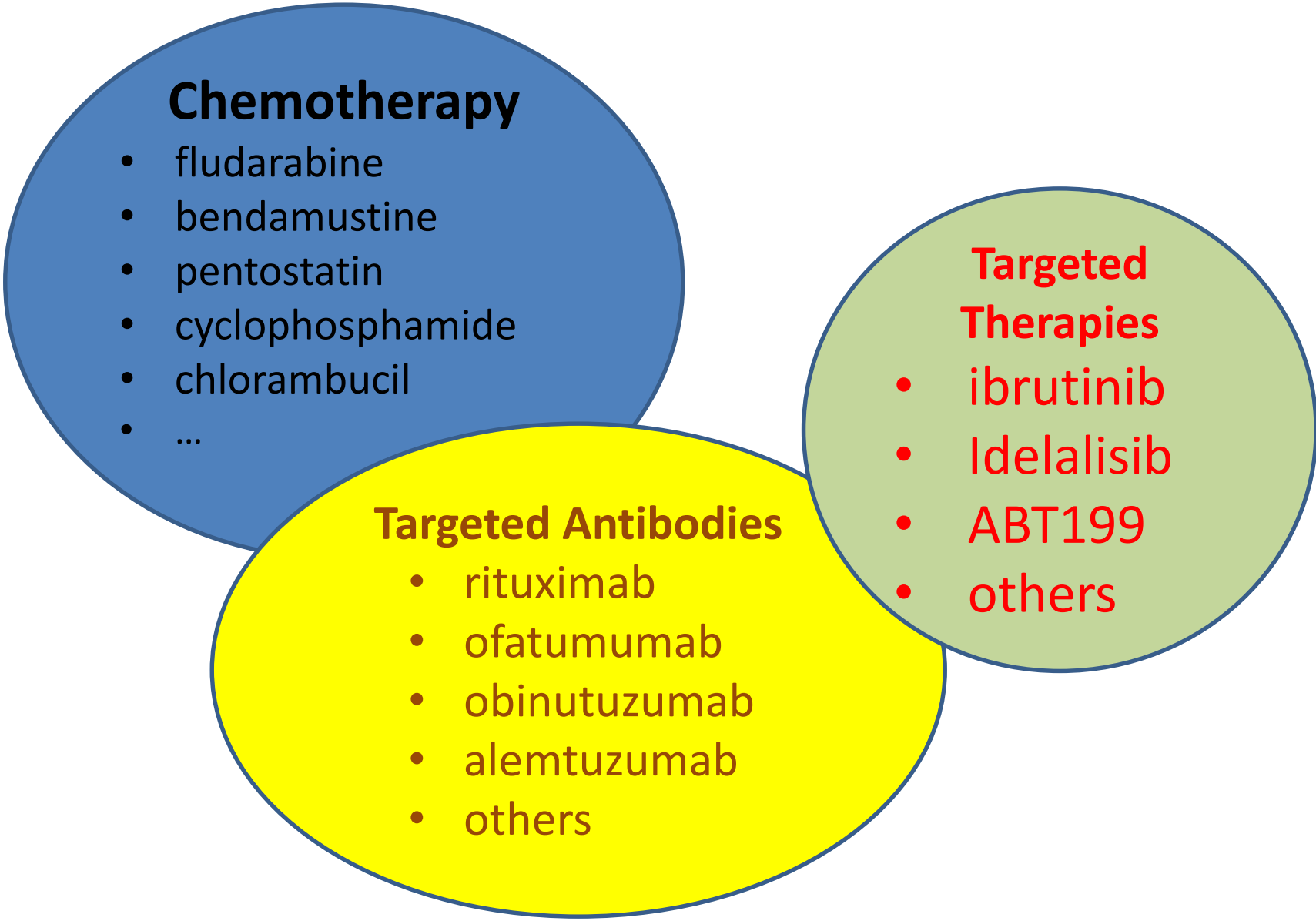
- All patients at diagnosis
  - Flow cytometry to confirm CLL diagnosis
- Informative for prognostic and/or therapy determination
  - Interphase cytogenetics looking for +12, del(13q), del(17)(p13.1), and del(11)(q22.3); del(17p) and del(11q) portend for more aggressive disease
  - Unmutated VH gene status assessment (good lab)
  - ZAP-70 expression by flow cytometry is not recommended outside clinical trial
- β_2-microglobulin
- No CT scan unless symptoms are present; PET scan can be helpful if Richter's suspected
- Bone marrow biopsy and aspirate not necessary in absence of low blood counts

When to start treatment?

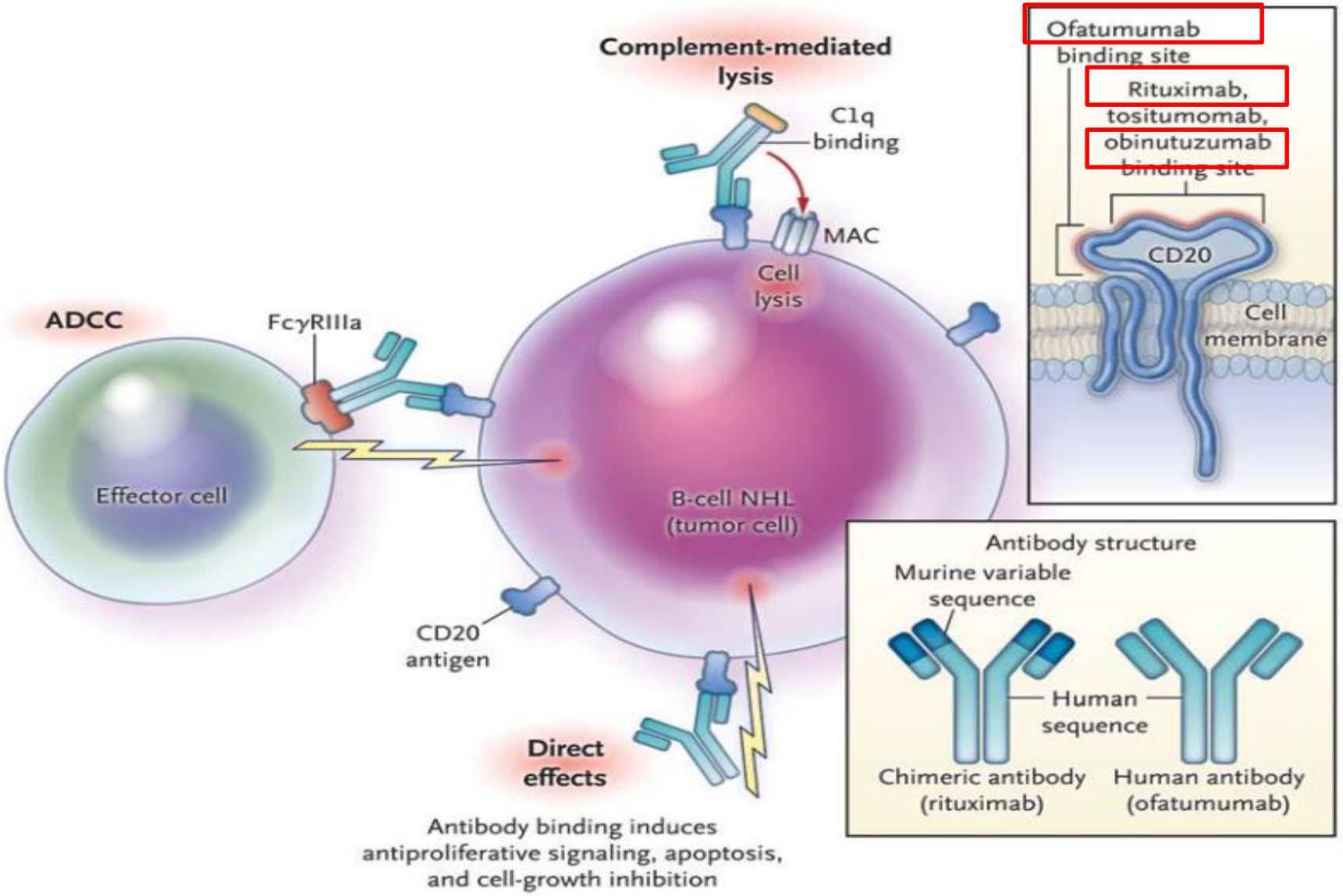
- No advantage to treating CLL until symptoms develop regardless of genomic features

- **IWCLL 2008** criteria for treatment (in primary and relapse)
  - Enlarging, symptomatic lymph nodes (> 10 cm)
  - Enlarging, symptomatic spleen (> 6 cm below costal margin)
  - Cytopenias due to CLL (hemoglobin < 11 g/dL, platelets < 100,000 cells/µL)
  - Constitutional symptoms due to disease (fatigue, B symptoms)
  - Poorly controlled AIHA or ITP
  - Progressive lymphocytosis with an increase of more than 50 percent over a two-month period or LDT of less than six months

What are the treatment options?



Targeted Antibodies



“Standard”Treatment

First line Young/Fit without del 17p

- Chemo + Antibodies
  - FCR (fludarabine +cyclophosphamide +rituximab)
  - BR (bendamustine + rituximab)
  - FR (fludarabine +rituximab)
  - PCR (pentostatin +cyclophosphamide +rituximab)
  - Obinutuzumab + chlorambucil

CLL10, Phase III Interim Analysis: FCR vs BR in CLL

Patients with untreated, active CLL without del(17p) and good physical fitness (CIRS ≤ 6, creatinine clearance ≥ 70 mL/min) (N = 561)

FCR
Fludarabine 25 mg/m^3 IV Days 1-3 +
Cyclophosphamide 250 mg/m^2 Days 1-3 +
Rituximab 375 mg/m^2 IV Day 0, cycle 1 +
Rituximab 500 mg/m^3 IV Day 1, cycles 2-6

BR
Bendamustine 90 mg/m^3 IV Days 1-2 +
Rituximab 375 mg/m^2 Day 0, cycle 1 +
Rituximab 500 mg/m^2 IV Day 1, cycles 2-4

Primary endpoint: noninferiority of BR vs FCR for PFS HR (λBR/FCR) < 1.388

Eichhorst B, et al. ASH 2013. Abstract 526.

CLL10 FCR vs BR in CLL: Main Findings

- Median PFS
  - FCR: not reached
  - BR: 44.9 mos
  - *P* = .04
- ORR rates identical, but higher CR rates observed with FCR vs BR
- 2-yr OS
  - FCR: 94.2%
  - BR: 95.8%
  - *P* = .59
- Median observation time: 27.9 mos

Response, %	FCR (n = 274)	BR (n = 273)	*P* Value
CR (CR + CRi)	47.4	38.1	.03
CR	40.1	36.3	
CRi	7.3	1.8	
PR	50.4	59.7	
ORR	97.8	97.8	1

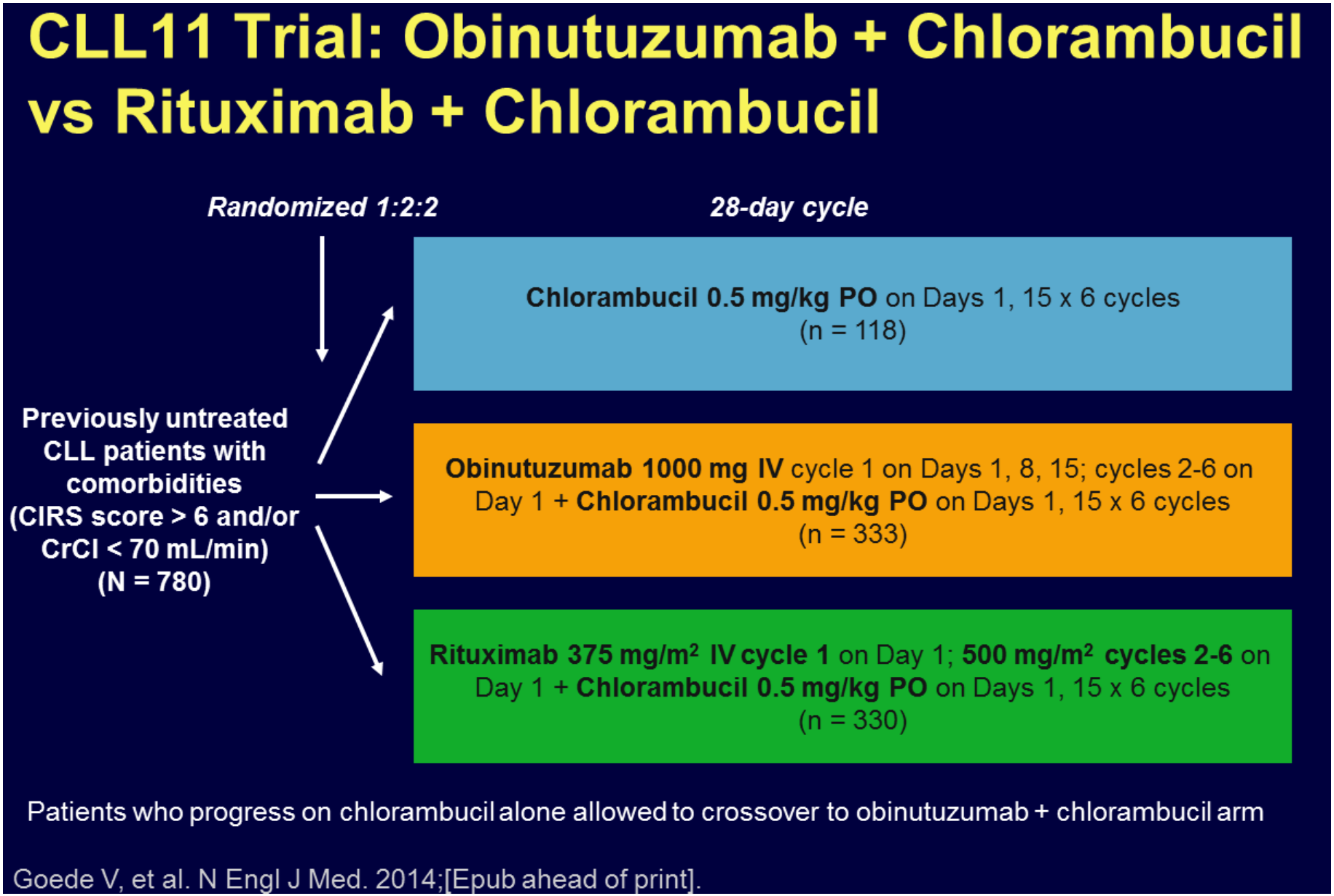
Eichhorst B, et al. ASH 2013. Abstract 526.

Treatment

First line older/unfit without del 17p

- **CLINICAL TRIALS**
- Chemo + Antibodies
  - **BR (bendamustine + rituximab)**
  - **Obinutuzumab + chlorambucil**
  - Rituximab + chlorambucil
  - Rituximab
  - Cladrabine
  - Fludarabine ± rituximab
  - Chlorambucil

Obinutuzumab



Obinutuzumab

CLL11: Response and Toxicity

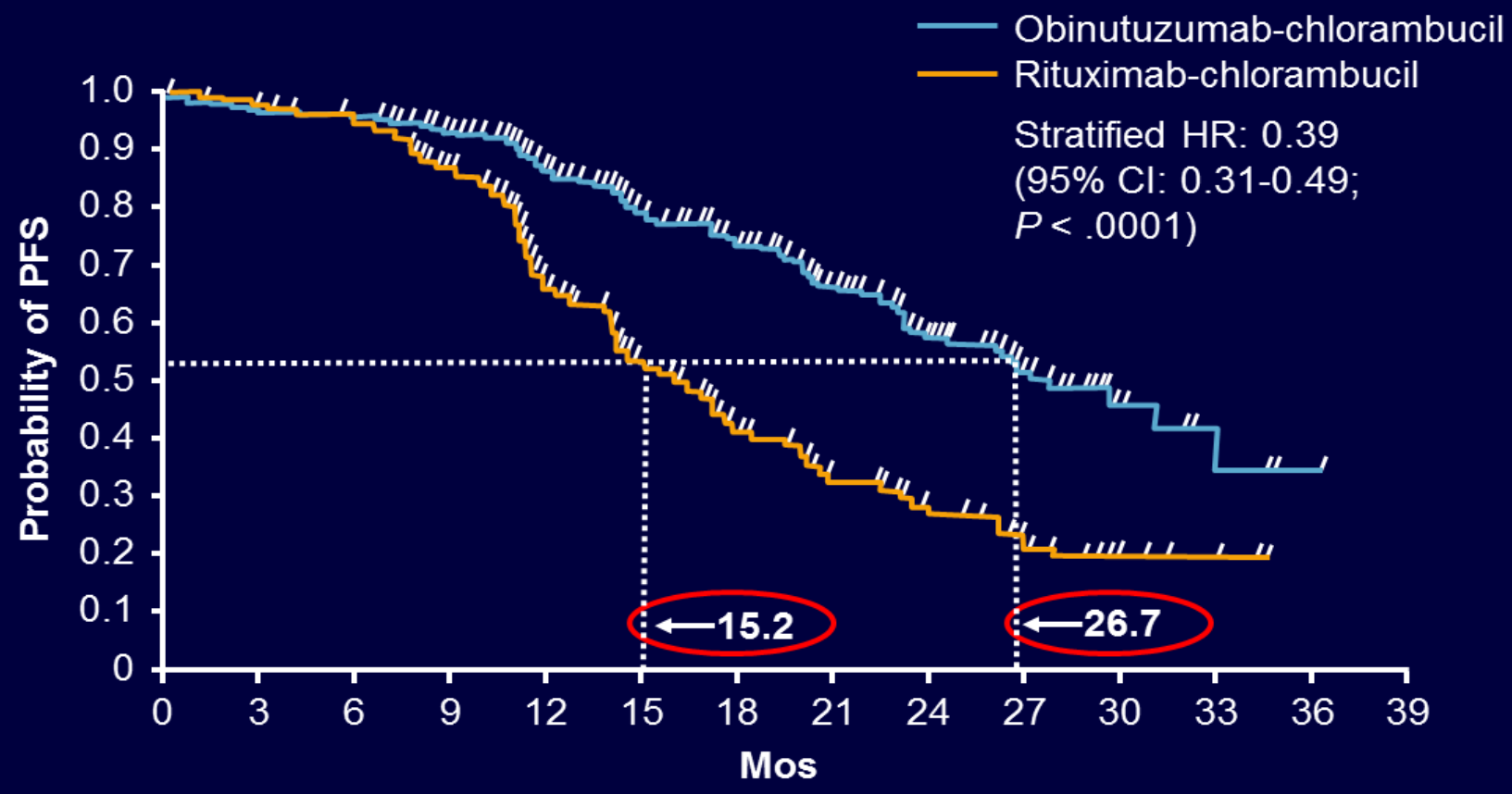
- Response
  - CLB 31% ORR, 0% CR
  - CLB + rituximab 65% ORR, 7% CR ($P < .001$)
  - CLB + obinutuzumab 78% ORR, 21% CR ($P < .001$)
- Toxicity

Grade ≥ 3, %	Obinutuzumab + Chlorambucil (n = 336)	Rituximab + Chlorambucil (n = 321)
Any	73	56
Infusion-related reaction	21	4
Neutropenia	35	27
Anemia	5	4
Thrombocytopenia	11	4
Infection	11	13

Goede V, et al. ASH 2013. Abstract 6.
Goede V, et al. N Engl J Med. 2014;[Epub ahead of print].

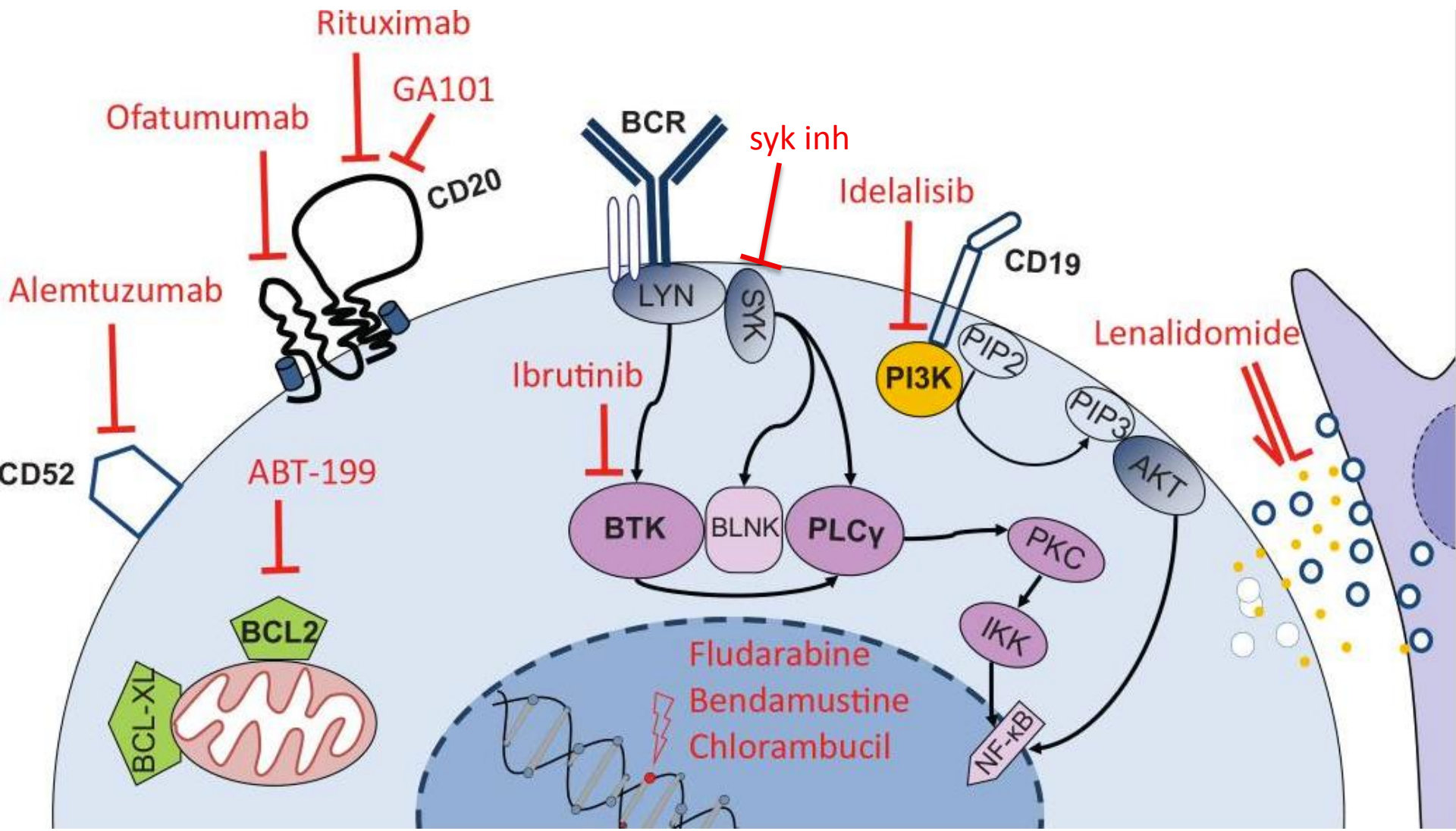
Obinutuzumab

CLL11 Trial: PFS Head-to-Head Comparison



Goede V, et al. N Engl J Med. 2014;[Epub ahead of print].

Treatment Targets

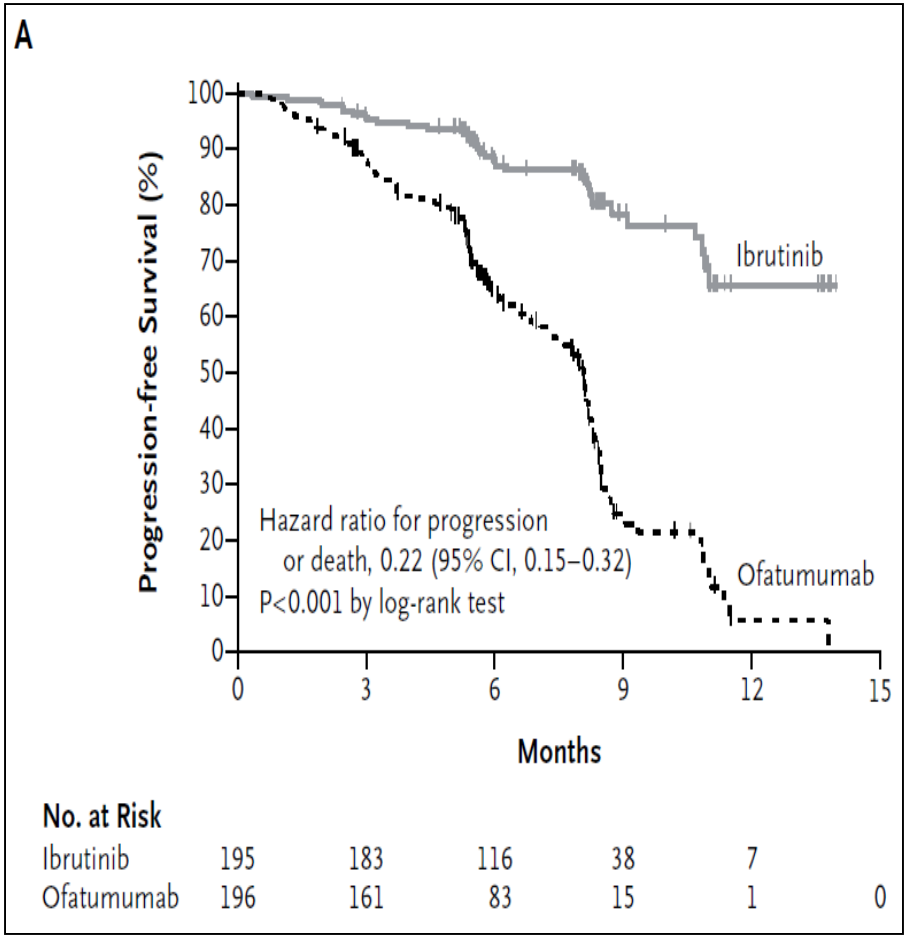


Goals of Novel Therapies

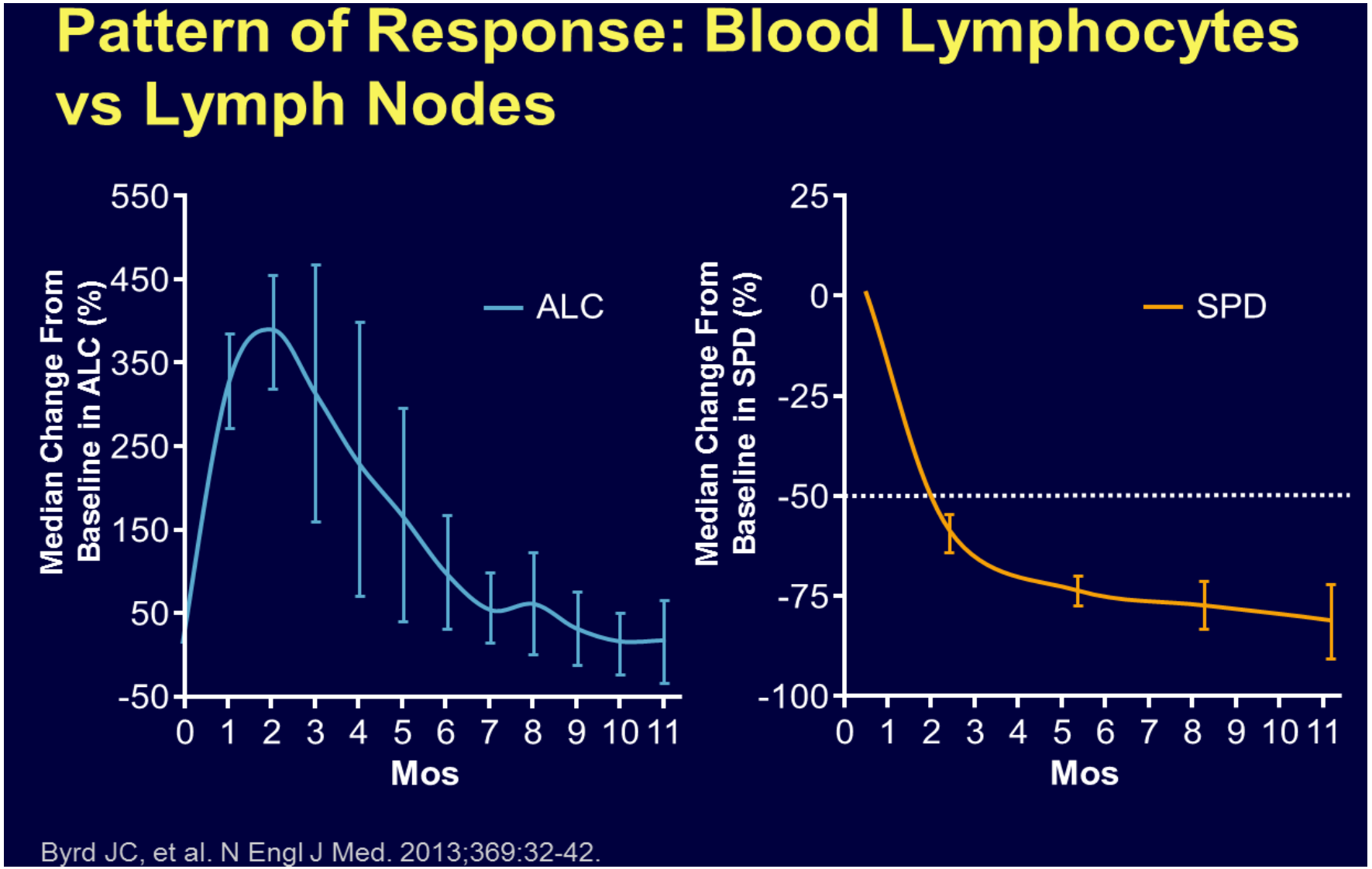
- Harness increasing understanding of biology and technology to improve therapy
- Develop “targeted” treatments selective for malignant cells and less toxic to healthy cells
- Recruit the body’s immune system to fight disease
- Help improve the effects of existing treatments in combination
- Induce longer remissions, and ultimately cure, with fewer side effects

Ibrutinib

- RESONATE study
- Relapsed/Refractory patients
- Ibrutinib vs. ofatumumab
- Primary endpoint : Progression-free survival
- 9.4 months of follow-up



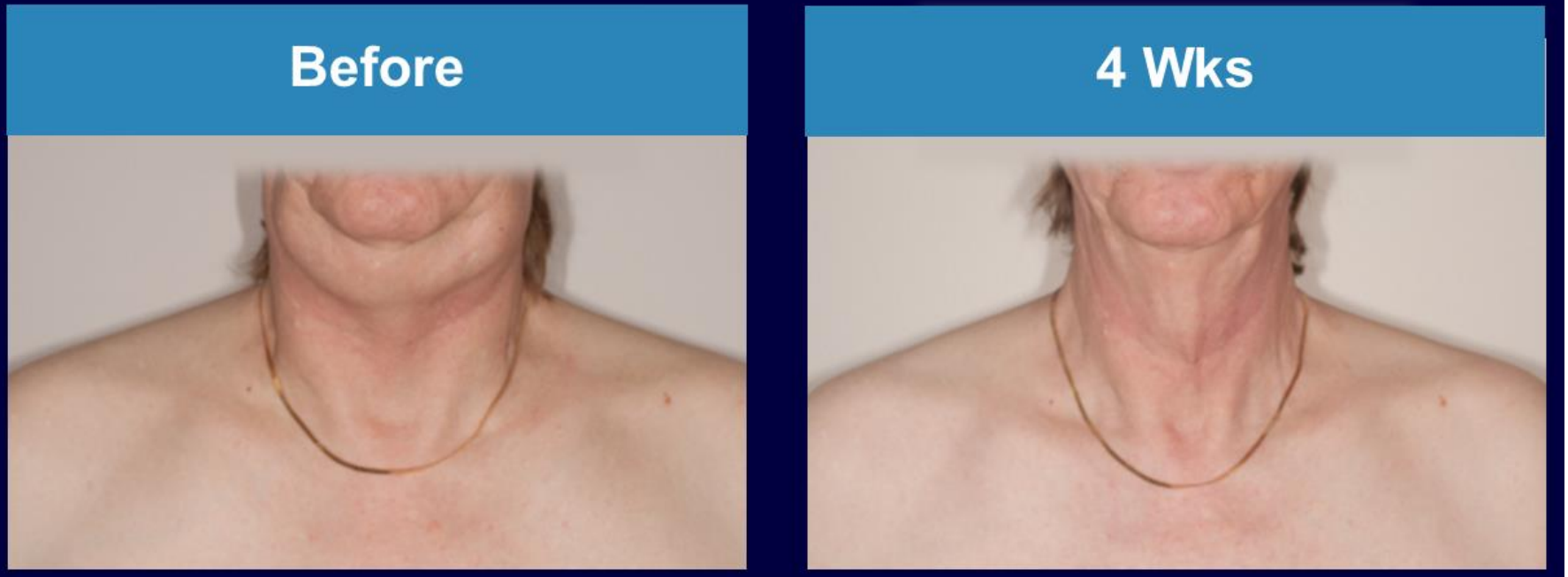
Ibrutinib



Byrd JC, et al. N Engl J Med. 2013;369:32-42.

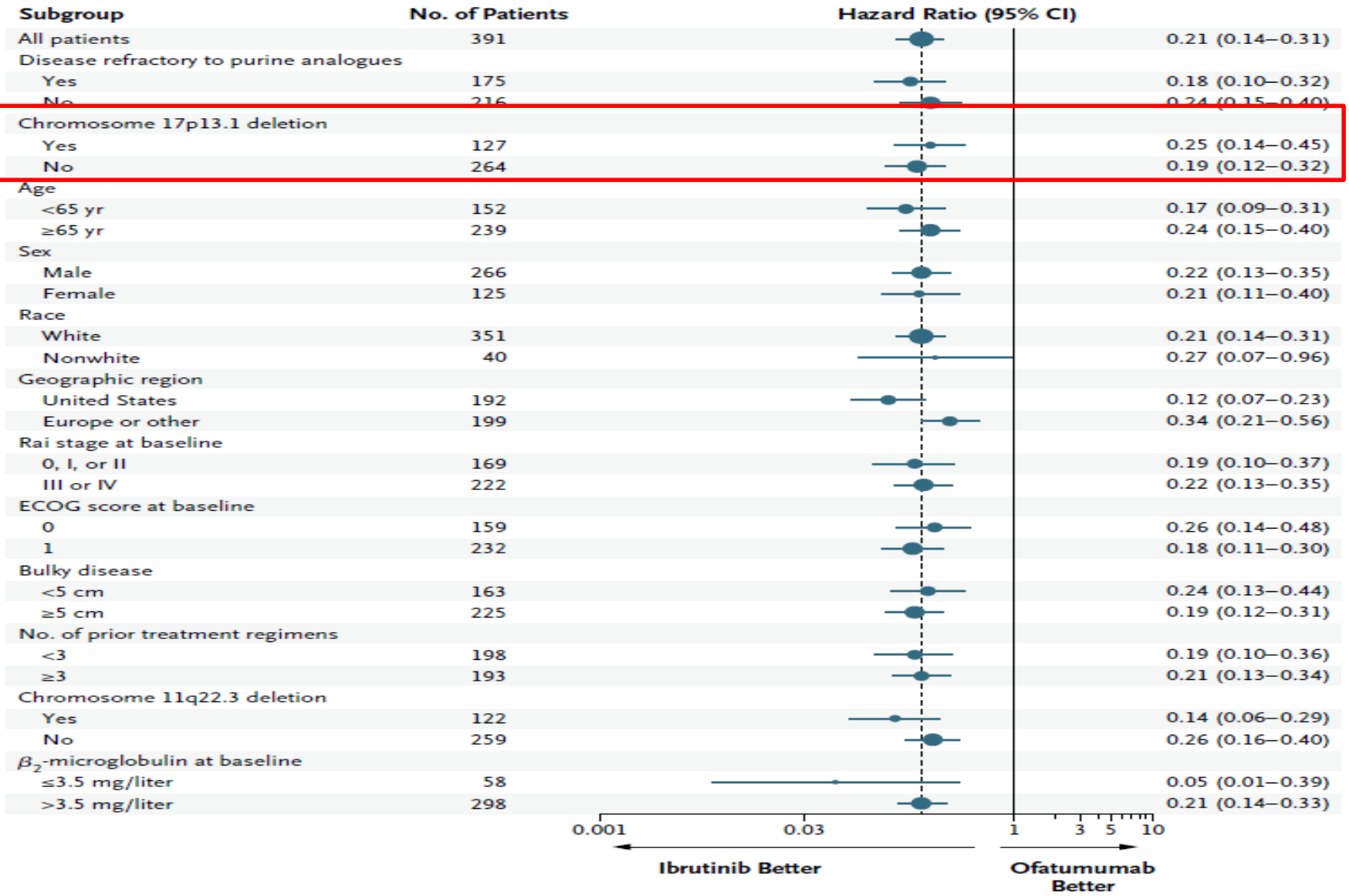
Ibrutinib

Ibrutinib in Refractory CLL With 11q Deletion



Images provided by Susan O'Brien, MD.

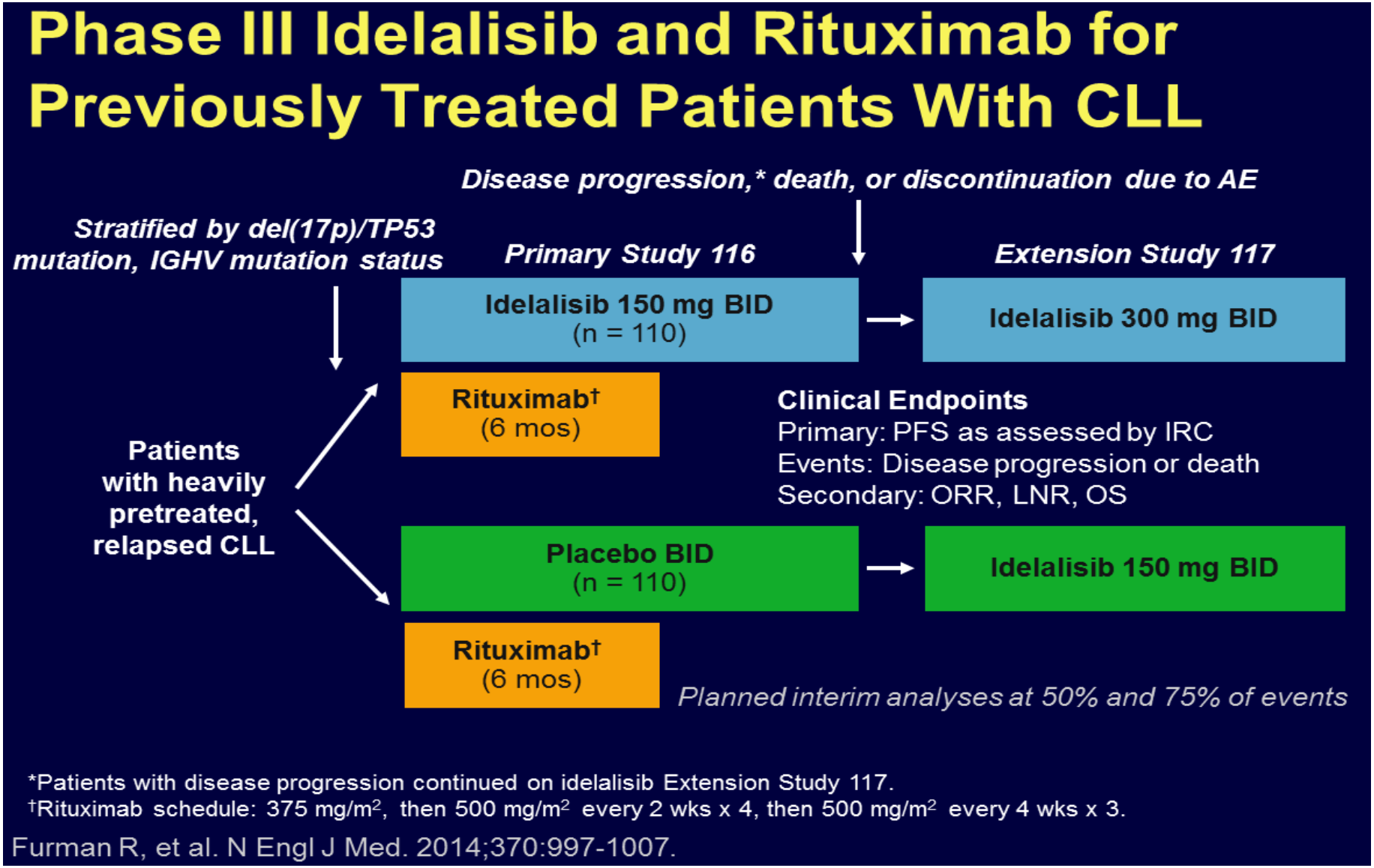
Ibrutinib


Subgroup
No. of Patients
Hazard Ratio (95% CI)
All patients 391 0.21 (0.14–0.31)
Disease refractory to purine analogues
Yes 175 0.18 (0.10–0.32)
No 216 0.24 (0.15–0.40)
Chromosome 17p13.1 deletion
Yes 127 0.25 (0.14–0.45)
No 264 0.19 (0.12–0.32)
Age
<65 yr 152 0.17 (0.09–0.31)
≥65 yr 239 0.24 (0.15–0.40)
Sex
Male 266 0.22 (0.13–0.35)
Female 125 0.21 (0.11–0.40)
Race
White 351 0.21 (0.14–0.31)
Nonwhite 40 0.27 (0.07–0.96)
Geographic region
United States 192 0.12 (0.07–0.23)
Europe or other 199 0.34 (0.21–0.56)
Rai stage at baseline
0, I, or II 169 0.19 (0.10–0.37)
III or IV 222 0.22 (0.13–0.35)
ECOG score at baseline
0 159 0.26 (0.14–0.48)
1 232 0.18 (0.11–0.30)
Bulky disease
<5 cm 163 0.24 (0.13–0.44)
≥5 cm 225 0.19 (0.12–0.31)
No. of prior treatment regimens
<3 198 0.19 (0.10–0.36)
≥3 193 0.21 (0.13–0.34)
Chromosome 11q22.3 deletion
Yes 122 0.14 (0.06–0.29)
No 259 0.26 (0.16–0.40)
β2-microglobulin at baseline
≤3.5 mg/liter 58 0.05 (0.01–0.39)
>3.5 mg/liter 298 0.21 (0.14–0.33)
0.001
0.03
1
3
5
10
Ibrutinib Better
Ofatumumab Better

Ibrutinib

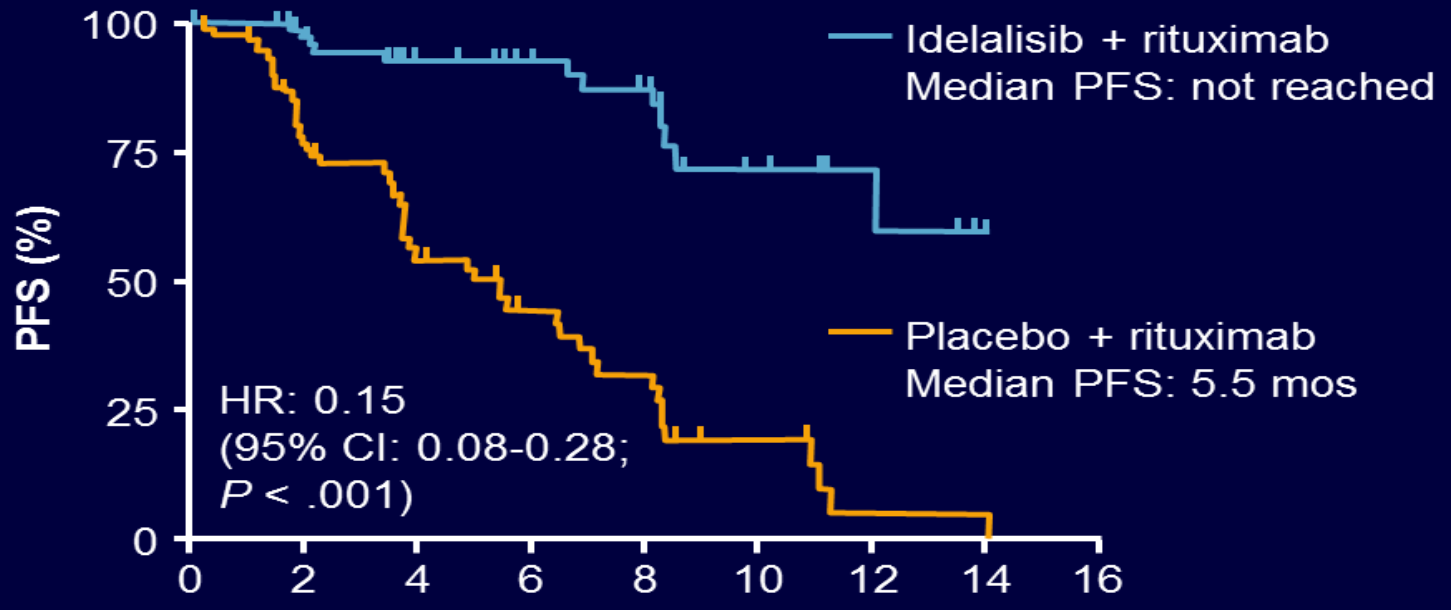
- **Common side effects:**
  - Thrombocytopenia
  - Neutropenia
  - Diarrhea
  - Anemia
  - Fatigue
  - musculoskeletal pain
  - upper respiratory tract infection
  - Rash
  - Nausea
  - Fever

Idelalisib


Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL
Disease progression,* death, or discontinuation due to AE
Stratified by del(17p)/TP53 mutation, IGHV mutation status
Primary Study 116
Extension Study 117
Idelalisib 150 mg BID (n = 110)
Idelalisib 300 mg BID
Rituximab† (6 mos)
Clinical Endpoints
Primary: PFS as assessed by IRC
Events: Disease progression or death
Secondary: ORR, LNR, OS
Patients with heavily pretreated, relapsed CLL
Placebo BID (n = 110)
Idelalisib 150 mg BID
Rituximab† (6 mos)
Planned interim analyses at 50% and 75% of events
*Patients with disease progression continued on idelalisib Extension Study 117.
†Rituximab schedule: 375 mg/m², then 500 mg/m² every 2 wks x 4, then 500 mg/m² every 4 wks x 3.
Furman R, et al. N Engl J Med. 2014;370:997-1007.

Idelalisib

Idelalisib and Rituximab for Previously Treated Patients With CLL: PFS

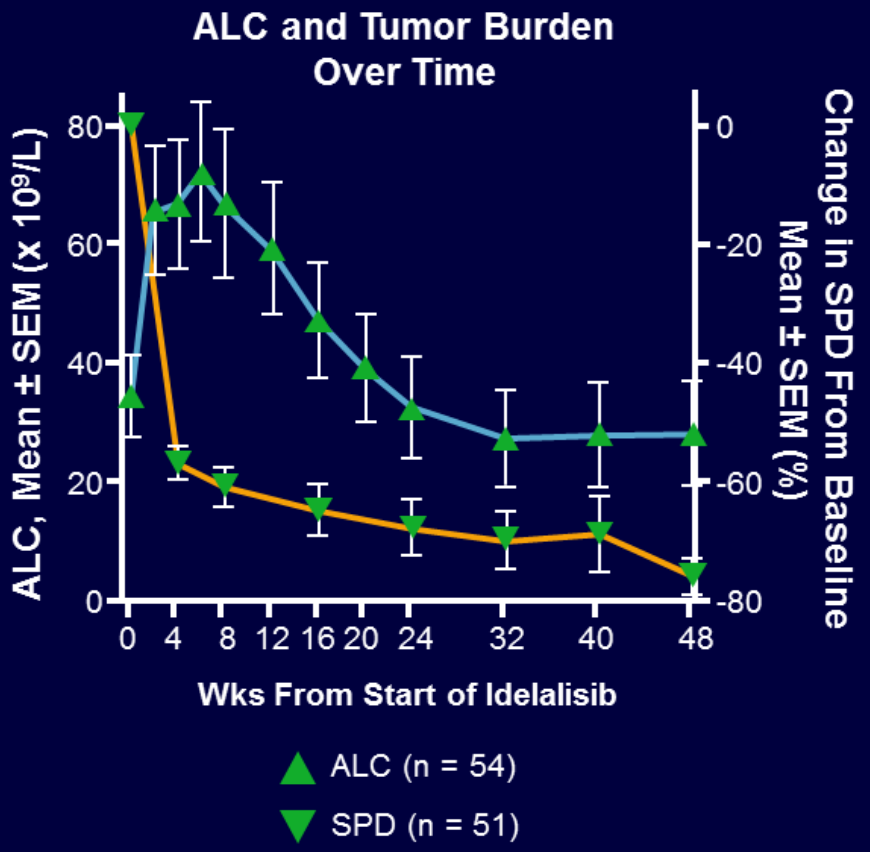


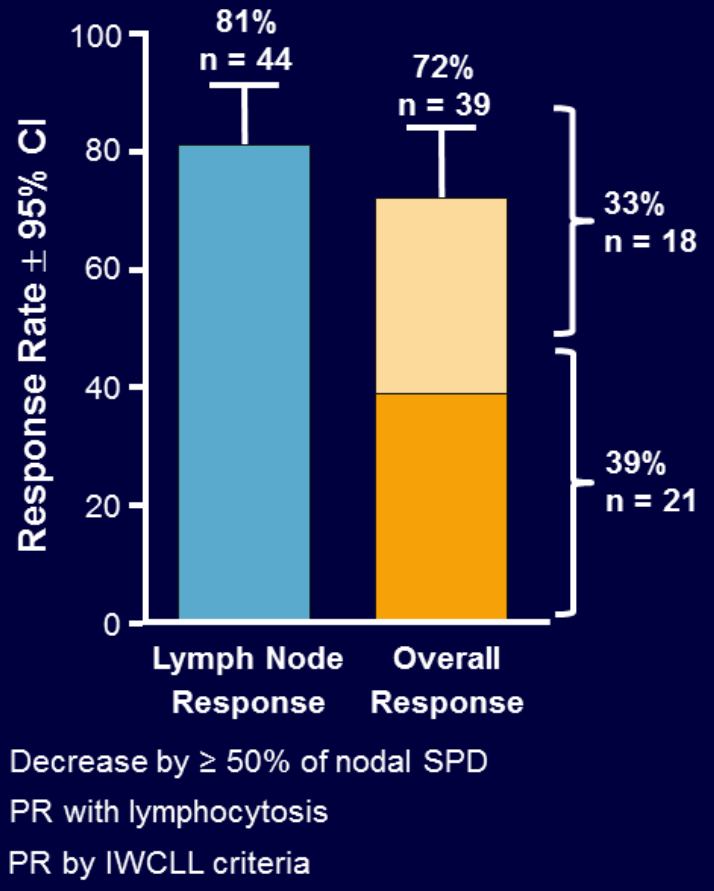
Pts at Risk, n									
Idelalisib + rituximab	110	69	44	34	30	14	6	2	0
Placebo + rituximab	110	62	30	18	13	6	1	1	0

Furman R, et al. N Engl J Med. 2014;370:997-1007.

Idelalisib

Idelalisib: Nodal and ORR

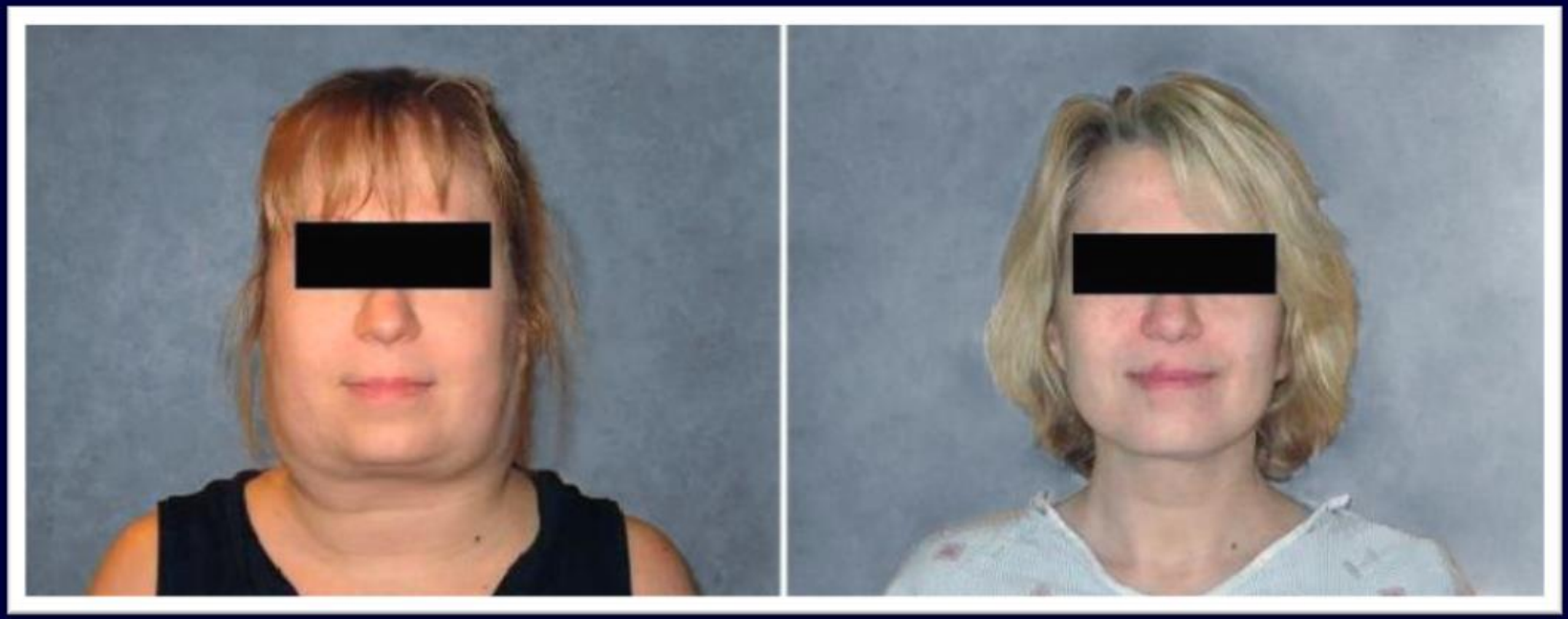




Brown JR, et al. ASCO 2013. Abstract 7003. Hallek M, et al. Blood. 2008;111:5446-5456. Cheson BD, et al. J Clin Oncol. 2012;30:2820-2822.

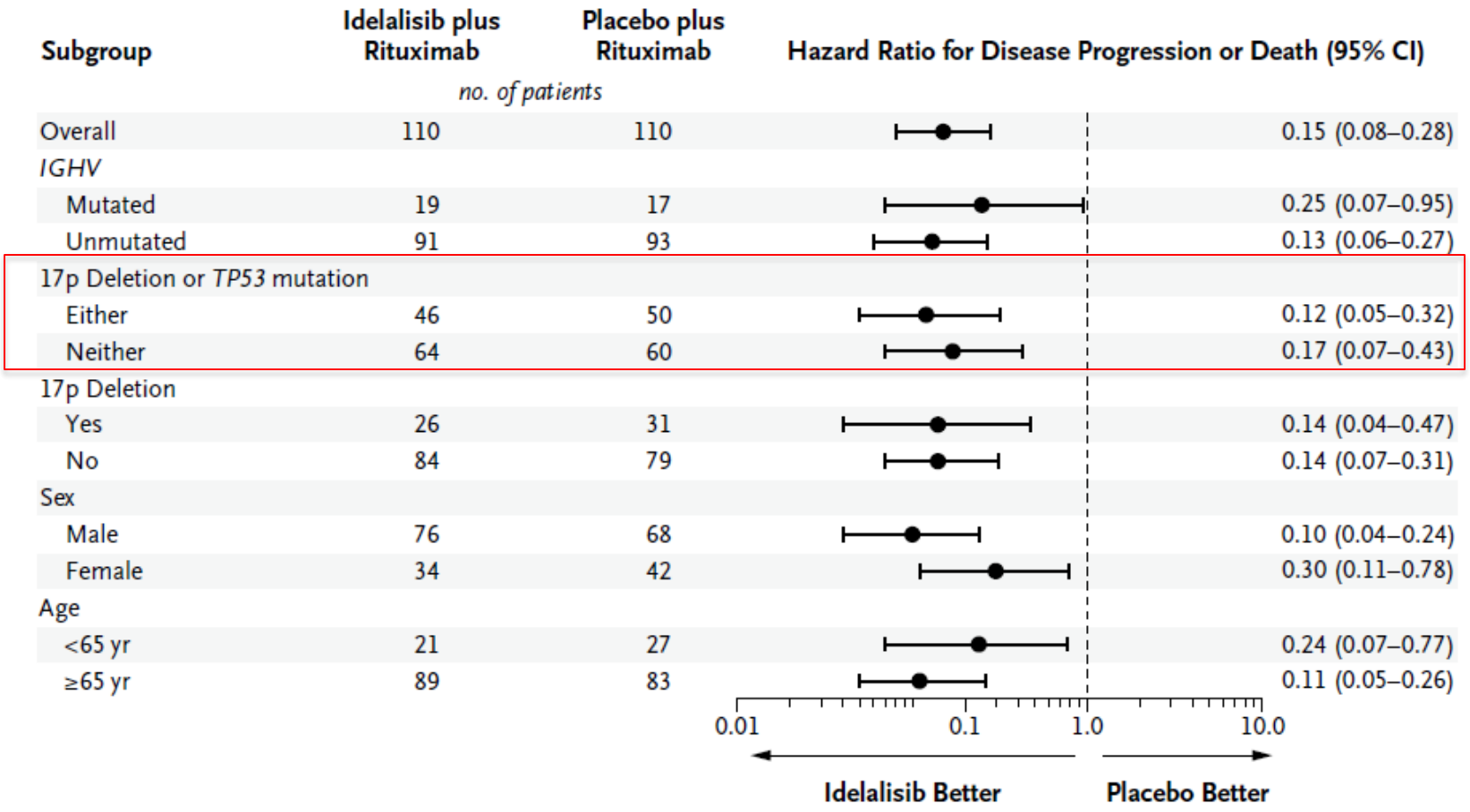
Idelalisib

Marked Reductions in Peripheral Lymphadenopathy With Idelalisib



38-yr-old patient with refractory CLL and 5 previous therapies

Idelalisib


Subgroup
Idelalisib plus Rituximab
Placebo plus Rituximab
Hazard Ratio for Disease Progression or Death (95% CI)
no. of patients
Overall 110 110 0.15 (0.08–0.28)
IGHV
Mutated 19 17 0.25 (0.07–0.95)
Unmutated 91 93 0.13 (0.06–0.27)
17p Deletion or TP53 mutation
Either 46 50 0.12 (0.05–0.32)
Neither 64 60 0.17 (0.07–0.43)
17p Deletion
Yes 26 31 0.14 (0.04–0.47)
No 84 79 0.14 (0.07–0.31)
Sex
Male 76 68 0.10 (0.04–0.24)
Female 34 42 0.30 (0.11–0.78)
Age
<65 yr 21 27 0.24 (0.07–0.77)
≥65 yr 89 83 0.11 (0.05–0.26)
0.01
0.1
1.0
10.0
Idelalisib Better
Placebo Better

Idelalisib

- **Common side effects:**
  - Fever
  - Fatigue
  - Nausea
  - Chills
  - Diarrhea
  - Thrombocytopenia
  - Neutropenia
  - Anemia
  - Liver enzyme abnormalities

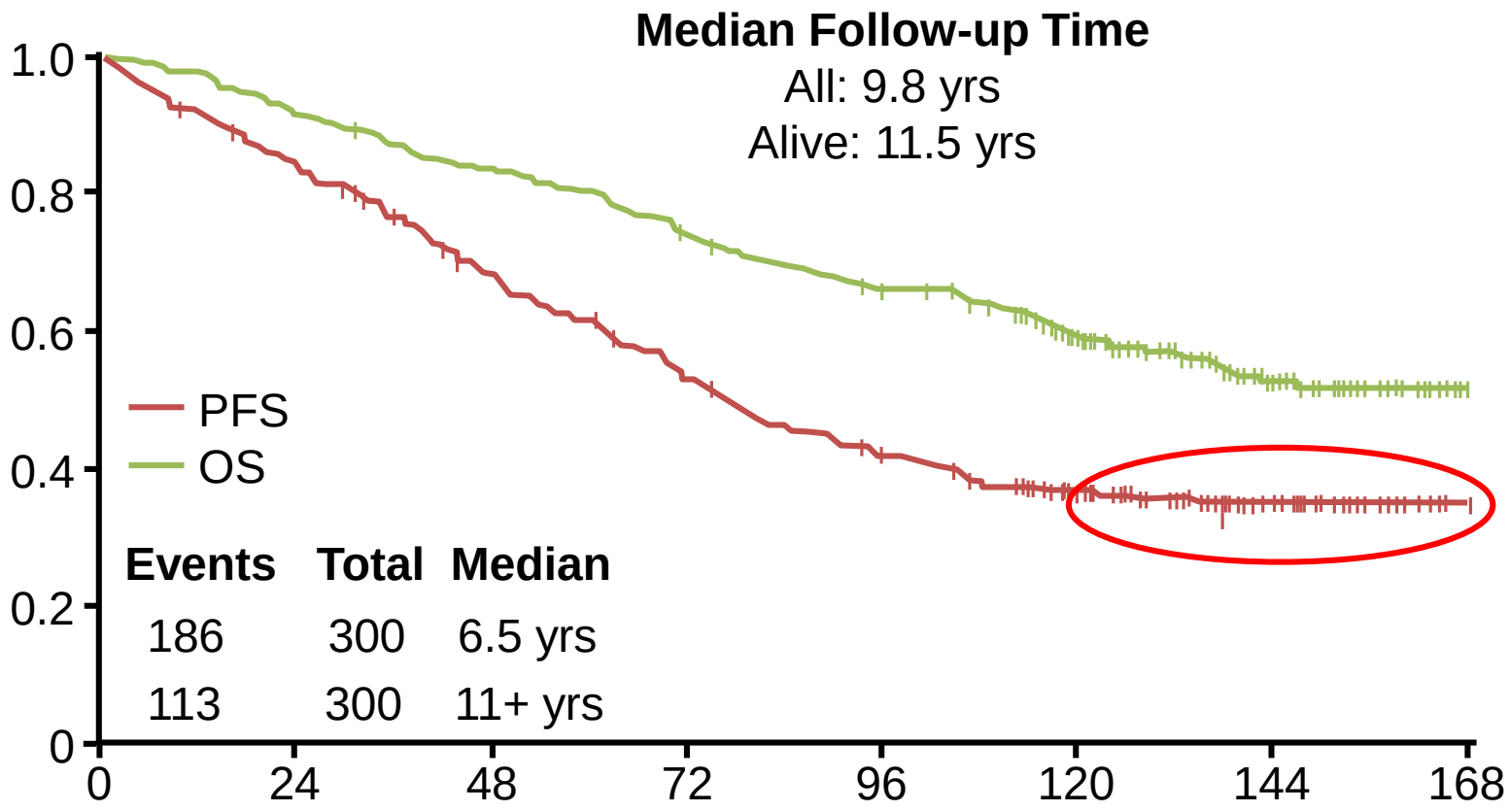
Venetoclax Monotherapy in Rel/Ref CLL and SLL

- Small molecule, orally bioavailable
- High affinity for Bcl-2

Response, %	Evaluable Patients (n = 56)	del(17p) (n = 17)	Fludarabine Refractory (n = 27)
ORR	84	82	89
CR	23	12	22
PR	61	71	67
SD	7	6	7
PD	2	6	--
Discontinue prior to first assessment	7	6	4

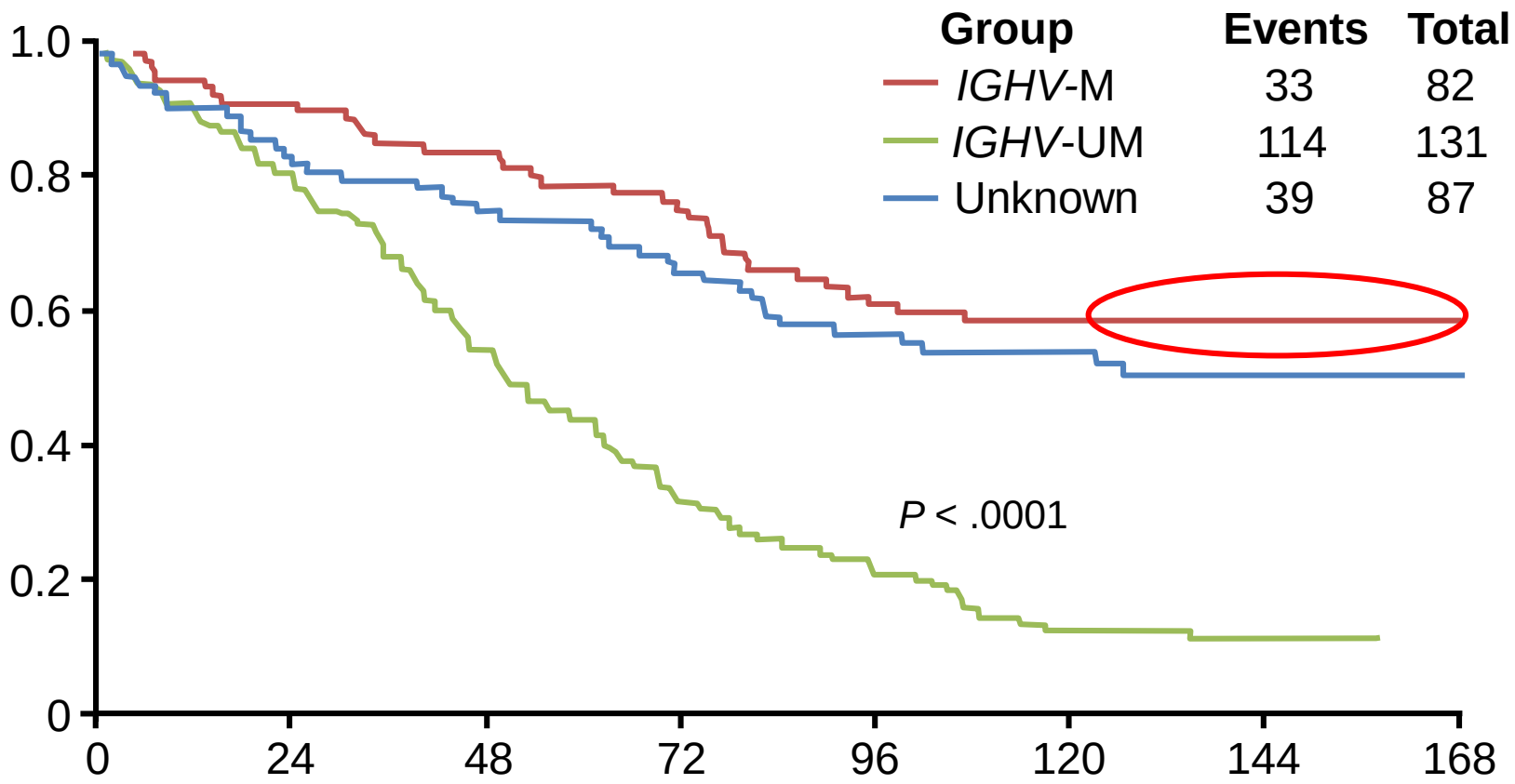
Should New Effective Single Agents Replace Chemotherapy as Frontline Therapy in CLL?

FCR300: PFS and OS



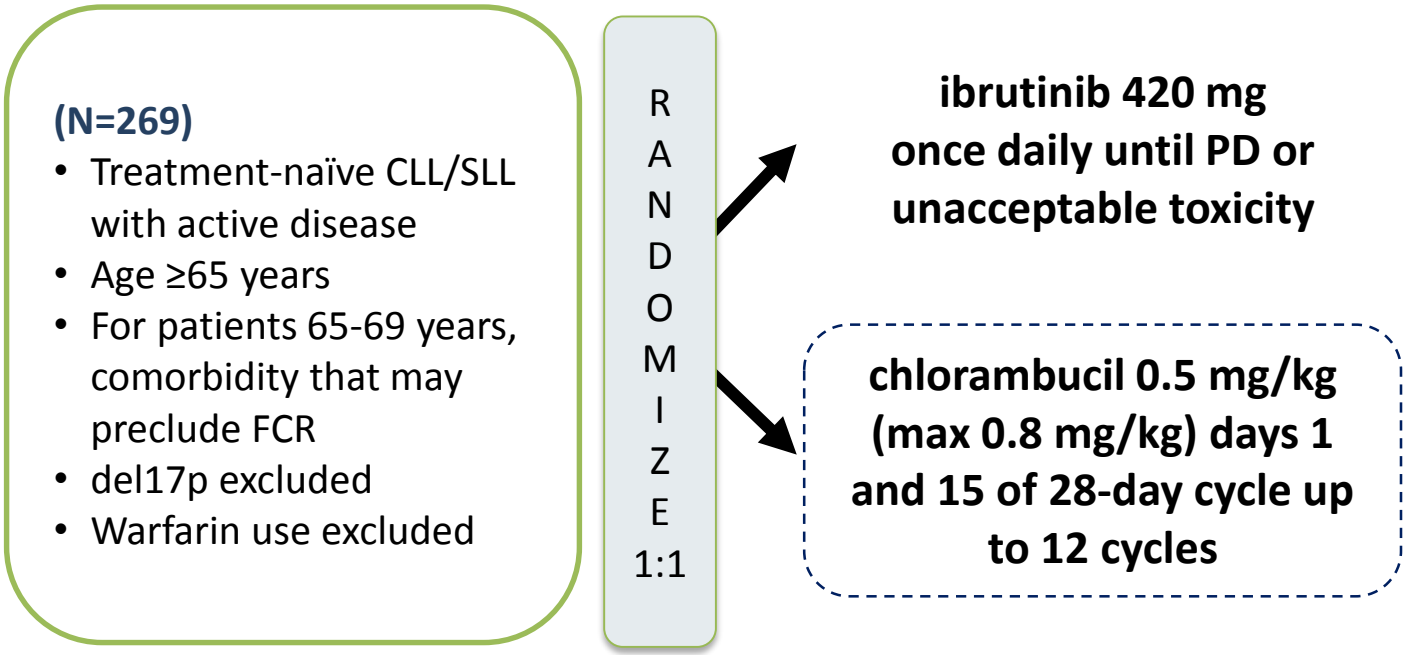
Wierda WG, et al. iWCLL 2013. Abstract 5.21.

FCR300: PFS by *IGHV* Mutation Status



Wierda WG, et al. iWCLL 2013. Abstract 5.21.

Results from the International, Randomized Phase 3 Study of Ibrutinib Versus Chlorambucil in Patients 65 Years and Older with Treatment-Naïve CLL/SLL (RESONATE-2)

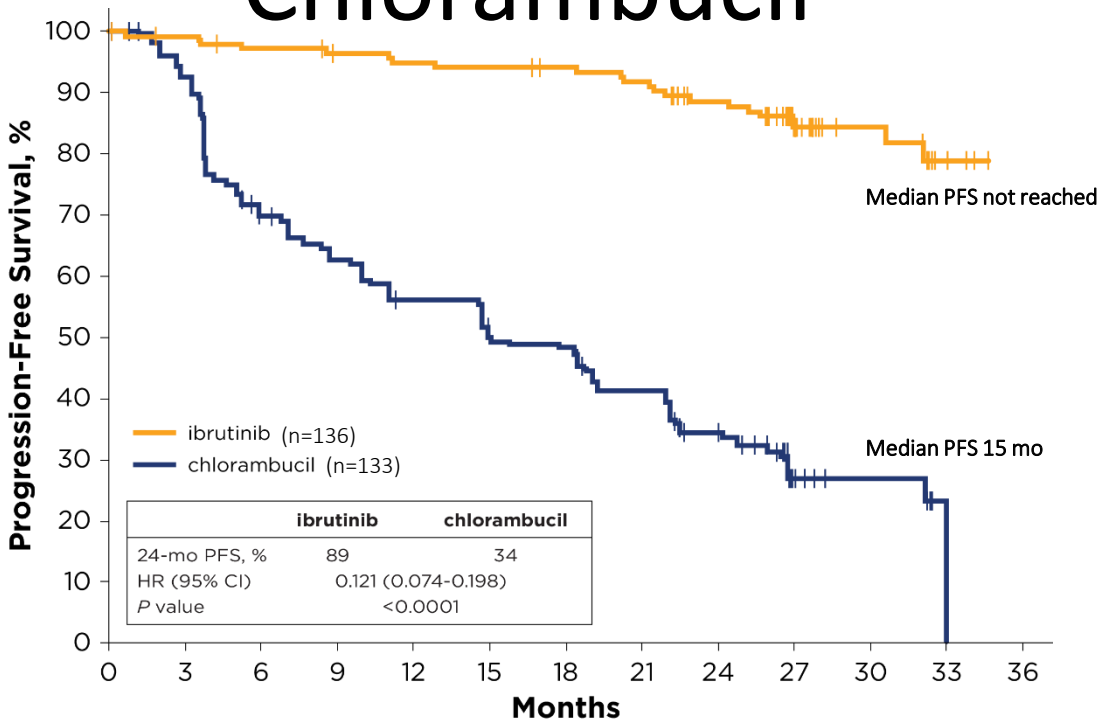


- Phase 3, open-label, multicenter, international study
- **Primary endpoint**: PFS as evaluated by IRC (2008 iwCLL criteria)
- **Secondary endpoints**: OS, ORR, hematologic improvement, safety

- In clb arm, n=43 crossed over to ibrutinib

Tedeschi et al. ASH 2015 Abstract 495

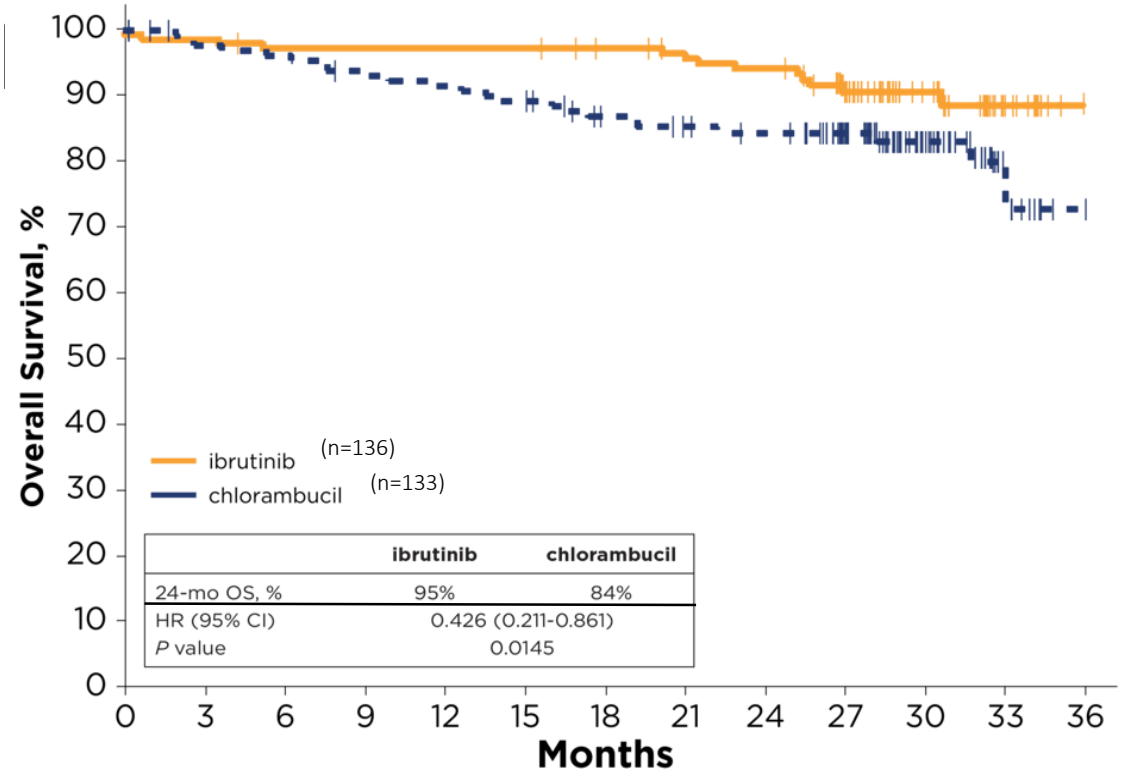
Ibrutinib Prolonged PFS Over Chlorambucil



- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

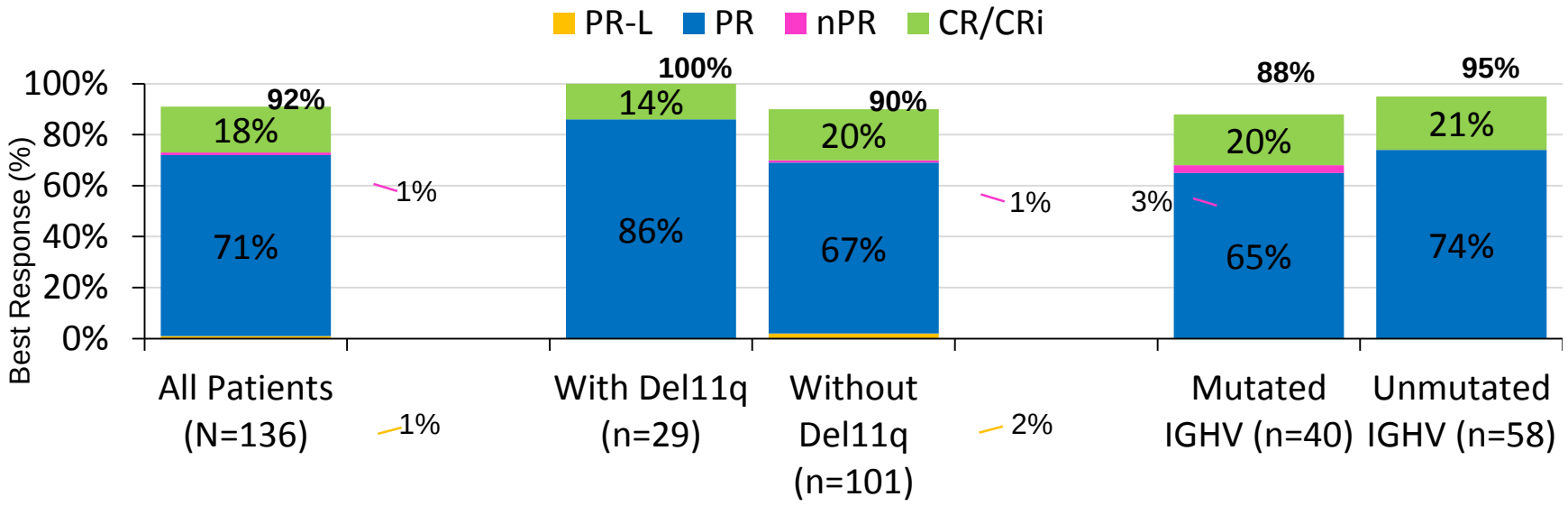
Barr et al. Abstract #234, ASH 2016.

Ibrutinib Continues to Demonstrate OS Benefit Over Chlorambucil With Longer



Barr et al. Abstract #234, ASH 2016.

ORR in the Ibrutinib Arm



- Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months.

**Response rates with chlorambucil are the same as in the original report (Burger NEJM 2015)*

Barr et al. Abstract #234, ASH 2016.

What is next?

Acalabrutinib Monotherapy in Patients With Ibrutinib Intolerance: Results From the Phase 1/2 ACE-CL-001 Clinical Study

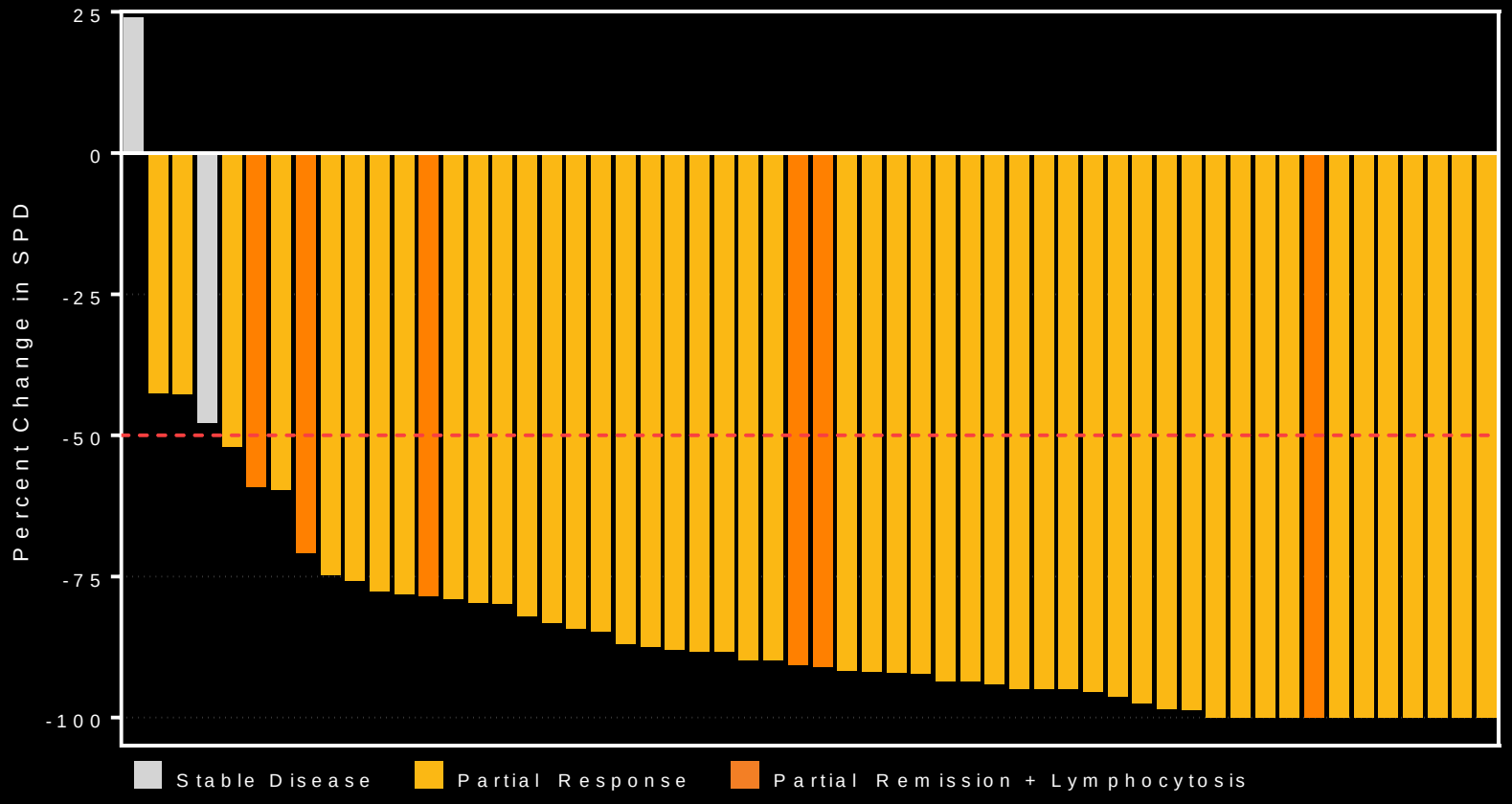
- Acalabrutinib is a highly selective, potent BTK inhibitor
- Minimal off-target effects on TEC, EGFR, or ITK signaling in vitro

Kinase Inhibition IC50 (nmol/L)

Kinase	Acalabrutinib	Ibrutinib
BTK	5.1	1.5
TEC	93	7.0
BMX	46	0.8
TXK	368	2.0
ERBB2	~1000	6.4
EGFR	>1000	5.3
ITK	>1000	4.9
JAK3	>1000	32
BLK	>1000	0.1

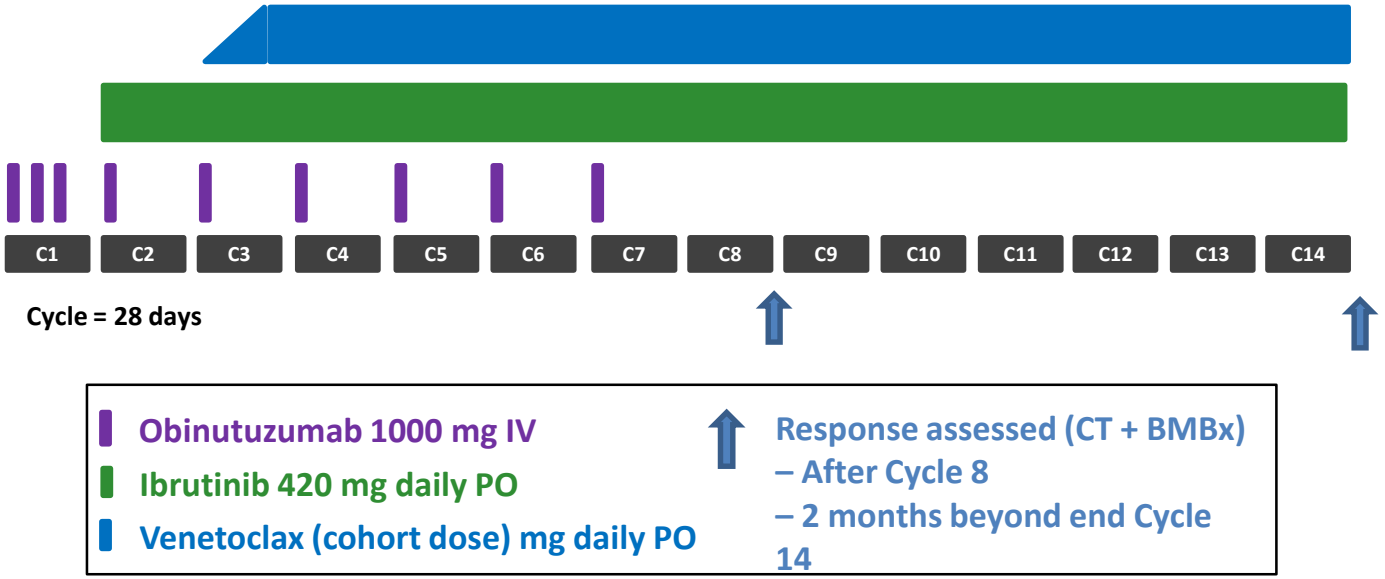
Awan F et al. Abstract 638, ASH 2016

Change in Lymphadenopathy (CT Scan)



Byrd et al. ASH 2015. Abstract 831

Phase 1b Results of a Phase 1b/2 Study of Obinutuzumab, Ibrutinib, and Venetoclax in Relapsed/Refractory CLL



Jones et al. Abstract #639, ASH 2016

What about supportive care?

- Recurrent sinus or lung infections:
  - IgG levels
  - Monthly IVIG
- Antibiotic prophylaxis
  - Viral and bacterial
- Vaccination
  - Annual influenza vaccine
  - Pneumococcal vaccine every 5 years
  - Avoid all live vaccines including Zoster

- Autoimmune anemia

- Transfusion

The practice of oncology is undergoing a transformation

- Paradigm shift in Oncology
  - What cures people
- The next five years – How to get to 100%
  - “Thinking outside the box”

New Paradigm

- The immune system is the “agent” that improves outcome and *CURES* people with systemic cancer.

- Fundamental shift in our understanding of cancer.

Source: The New York Times, Los Angeles Times

20 December 2013 | $10

Science

Breakthrough of the Year

Cancer Immunotherapy

T cells on the attack

AAAS

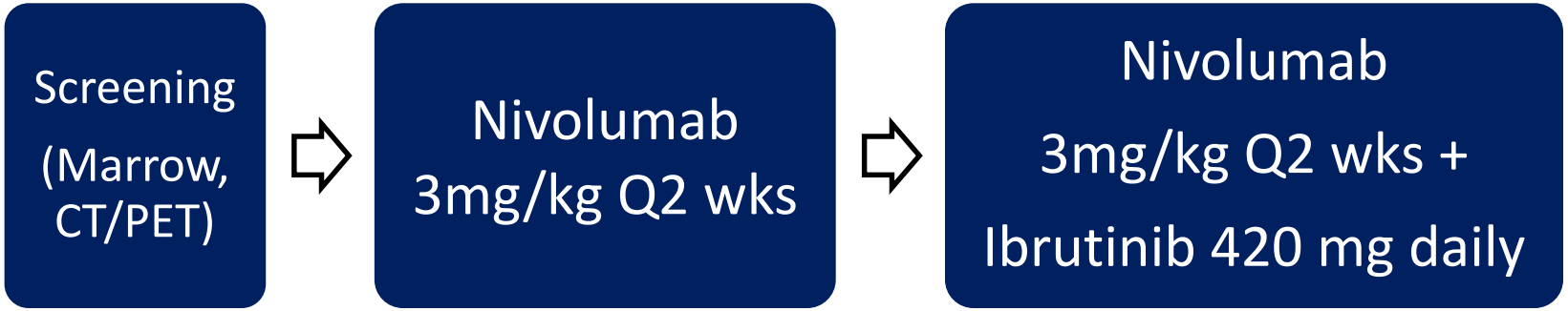
Rationale for Immunotherapy

- Immune dysregulation in CLL
  - result of overexpression of checkpoint receptors by T cells and respective ligands on CLL cells
- Checkpoint inhibition may result in correction of immune dysregulation and an anti-leukemia effect
  - GVL is a powerful approach in CLL
    - Success of allogeneic HCT

Castro JE, Kipps TJ. Best Pract Res Clin Haematol. 2016 Mar;29(1):15-29
van Gelder M,Bone Marrow Transplant. 2016 Dec 12

Nivolumab Combined with Ibrutinib for CLL and Richter Transformation - A Phase II Trial

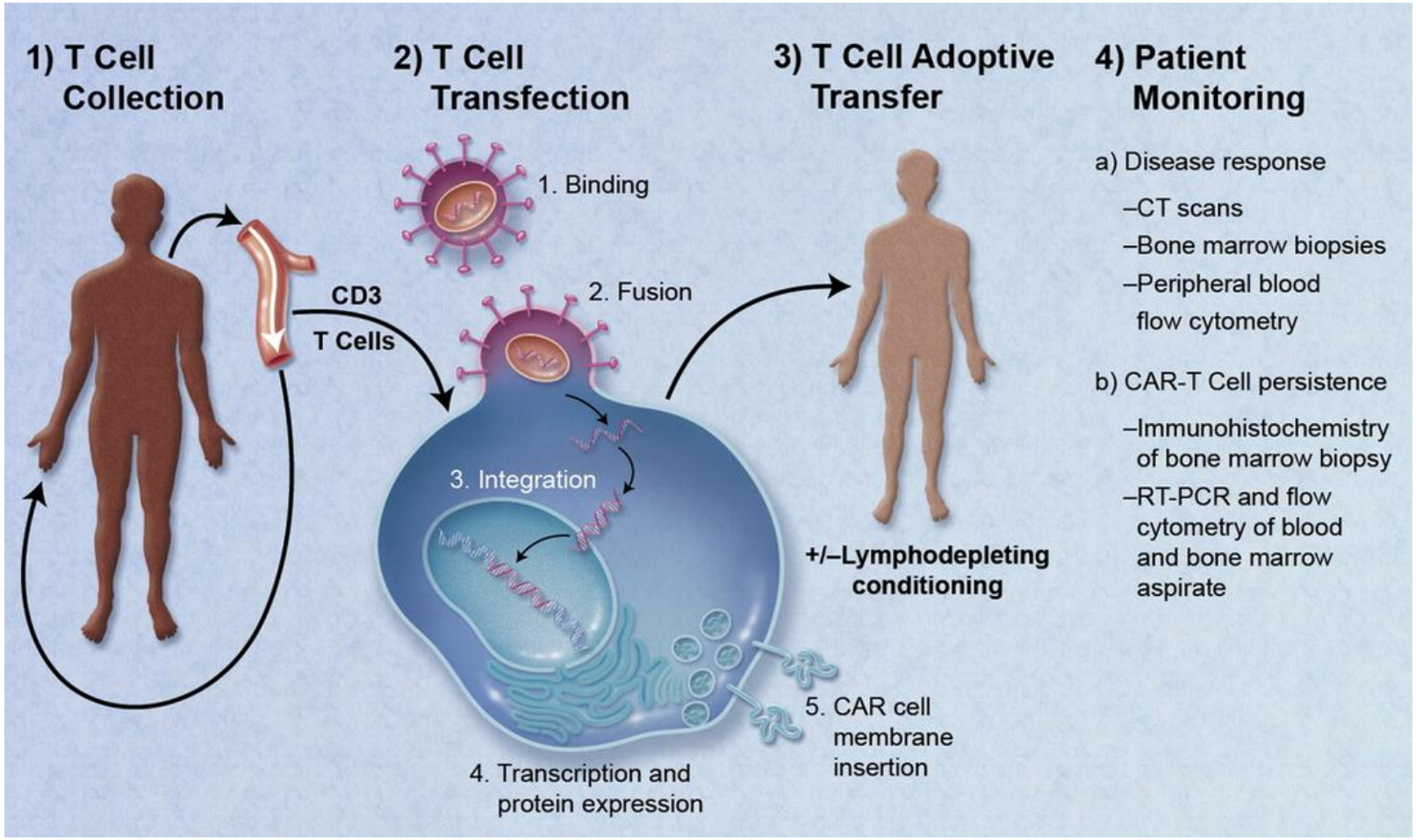
Cohort 1: Relapsed CLL/SLL, or RT



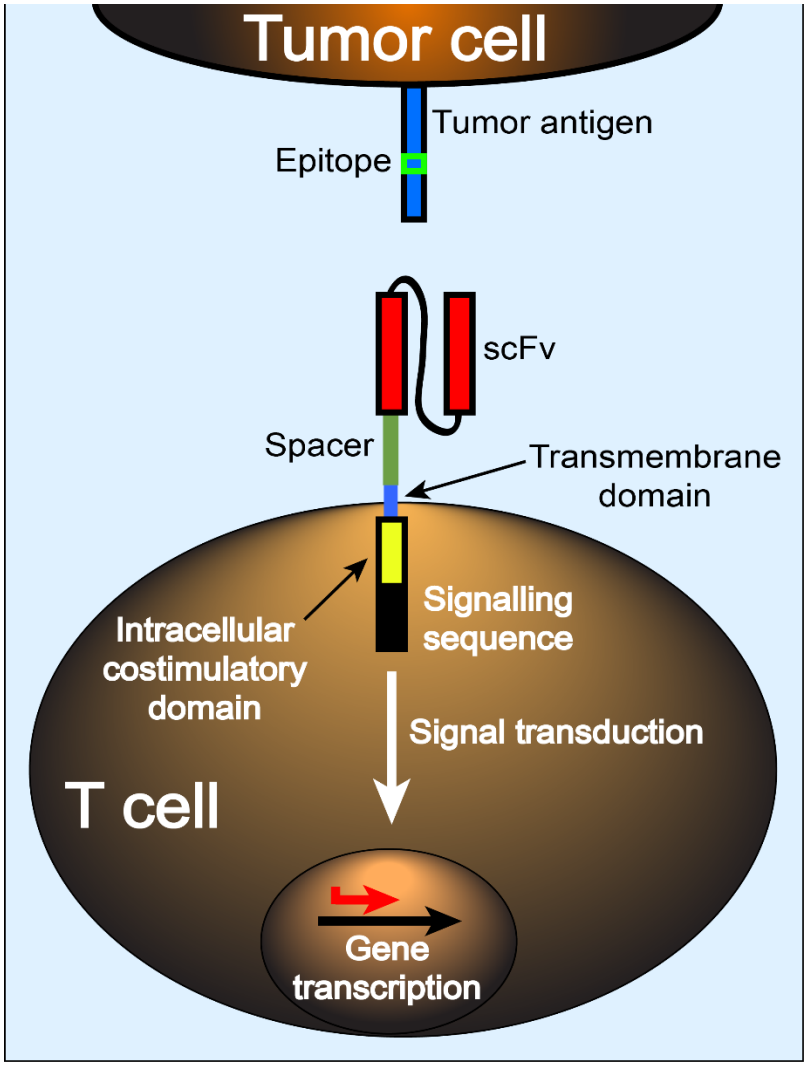
- Response Evaluation (bone marrow and imaging)
  - After C1, C3, C6, C9, C12, then Q6 months

Jain et al. Abstract #59, ASH 2016

What about CAR- T cell therapy?



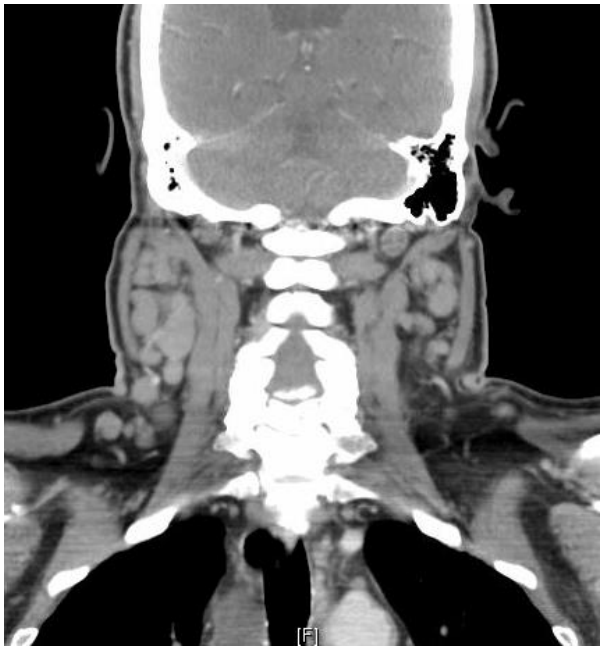
Chimeric antigen receptors



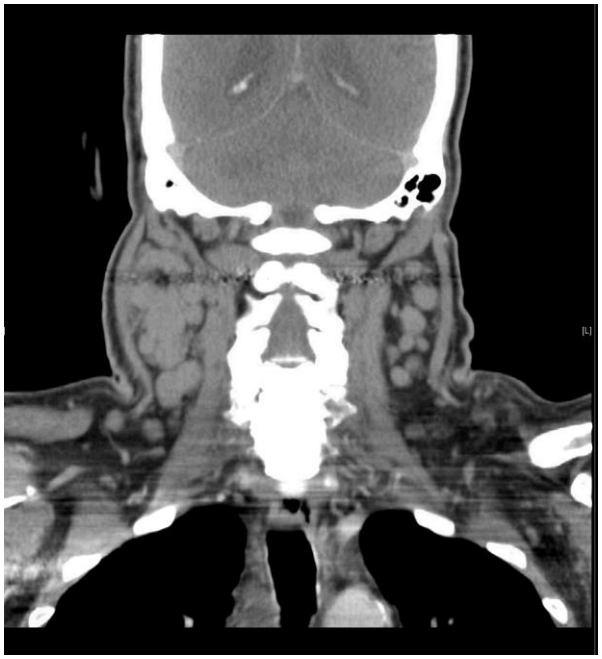
- CARs and CAR-T cells
  - Target surface molecules
  - Enables redirection of engineered T cell subsets to a specified target antigen

Turtle et al, Curr Opin Immunol, 2013

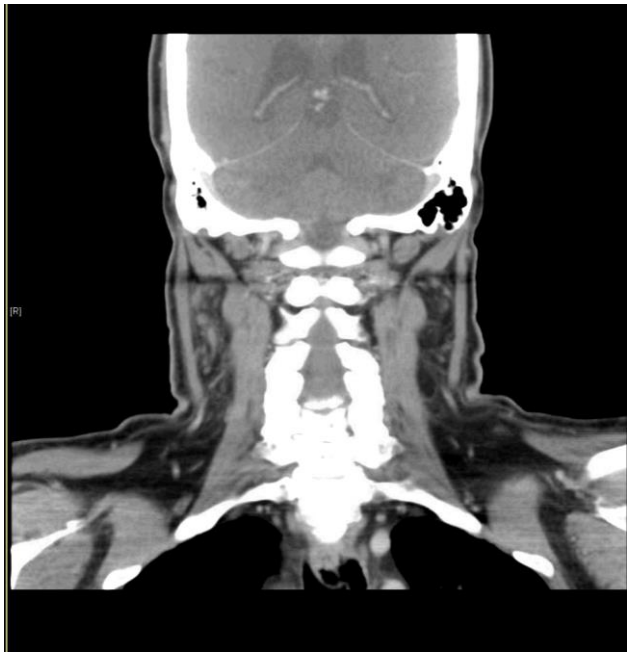
Relapsed after auto HCT



Before RICE

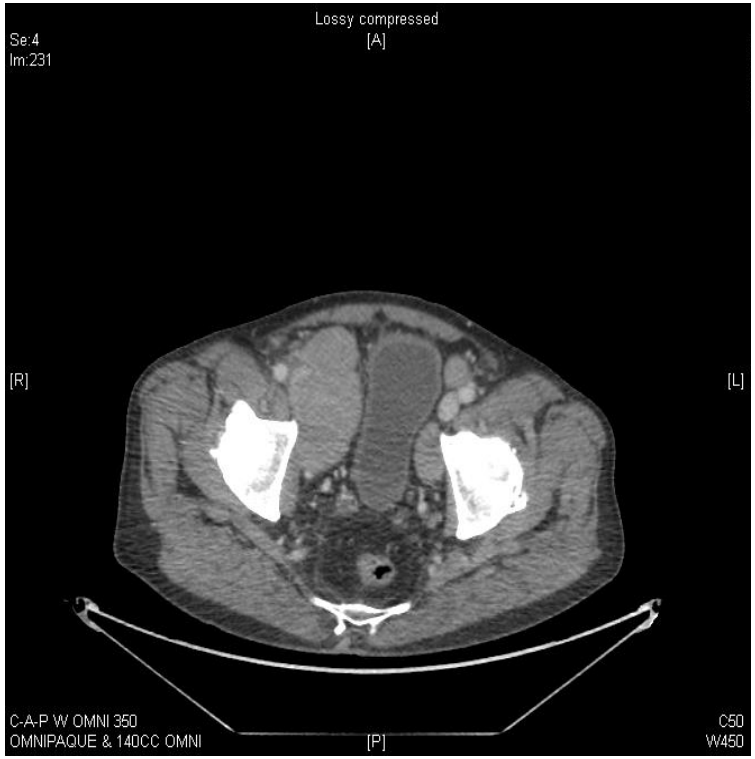


Before CED and CD19 CAR-T cells

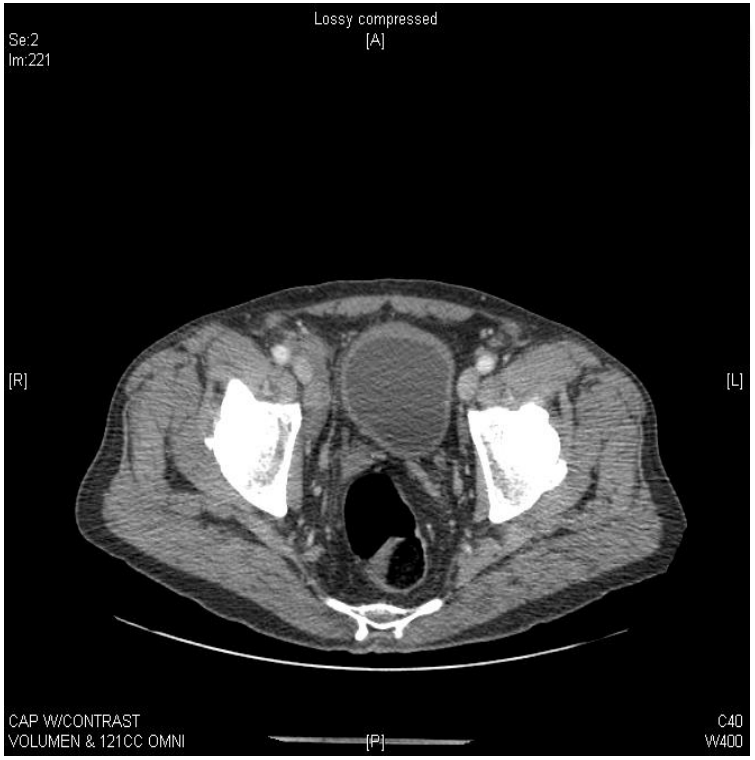


Day 28 after CED and CD19 CAR-T cells

Relapsed after HCT



Before CED and CD19 CAR-T cells



Day 27 after CED and CD19 CAR-T cells

Promising Immunotherapy Conclusions

- Several exciting new approaches
  - approved and in clinical trials
- More selective than chemotherapy Is this the beginning of the end for chemotherapy?

Take home messages

- Take advantage of the recent advancements
- Making the wise choice
- Some of the “older” treatments may still be the best option for you

- Several exciting new agents in clinical trials
  - More selective than chemotherapy but not without toxicity
  - Already second-generation PI3K and BTK inhibitors in clinical trials as well as SYK inhibitors, etc

Questions?

John.pagel@swedish.org