CHRONIC LYMPHOCYTIC LEUKEMIA

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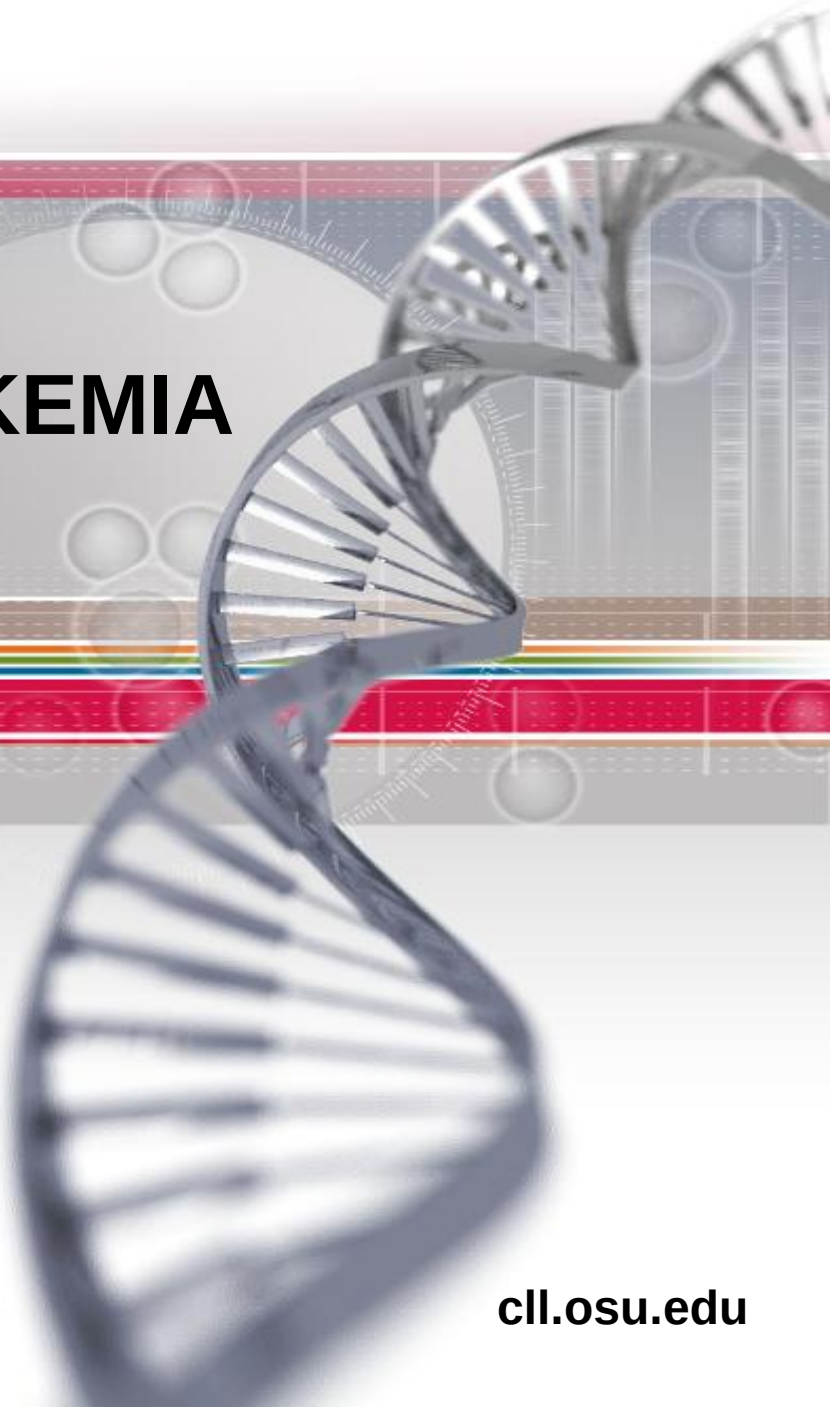
The James
Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

cll.osu.edu



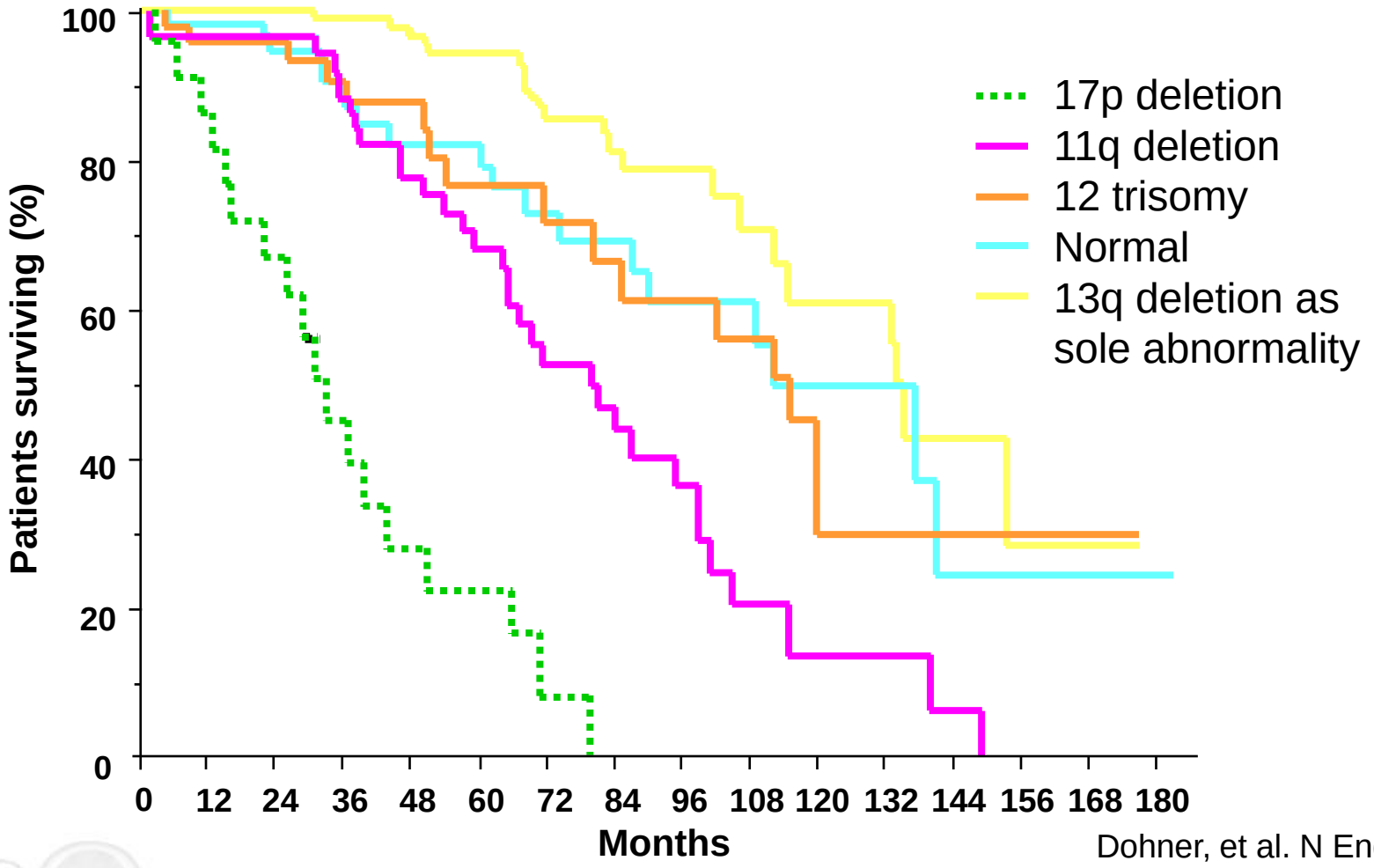
Definition of CLL
IWCLL - 2008

- Small, clones of mature B-cells
- Atleast 5,000/ul B-cells
- Co-express CD5 and CD23

Prognostic Markers

- Interphase cytogenetics and FISH
- IGHV Mutational Status
- CD38
- ZAP-70 methylation

Interphase FISH correlates with Survival



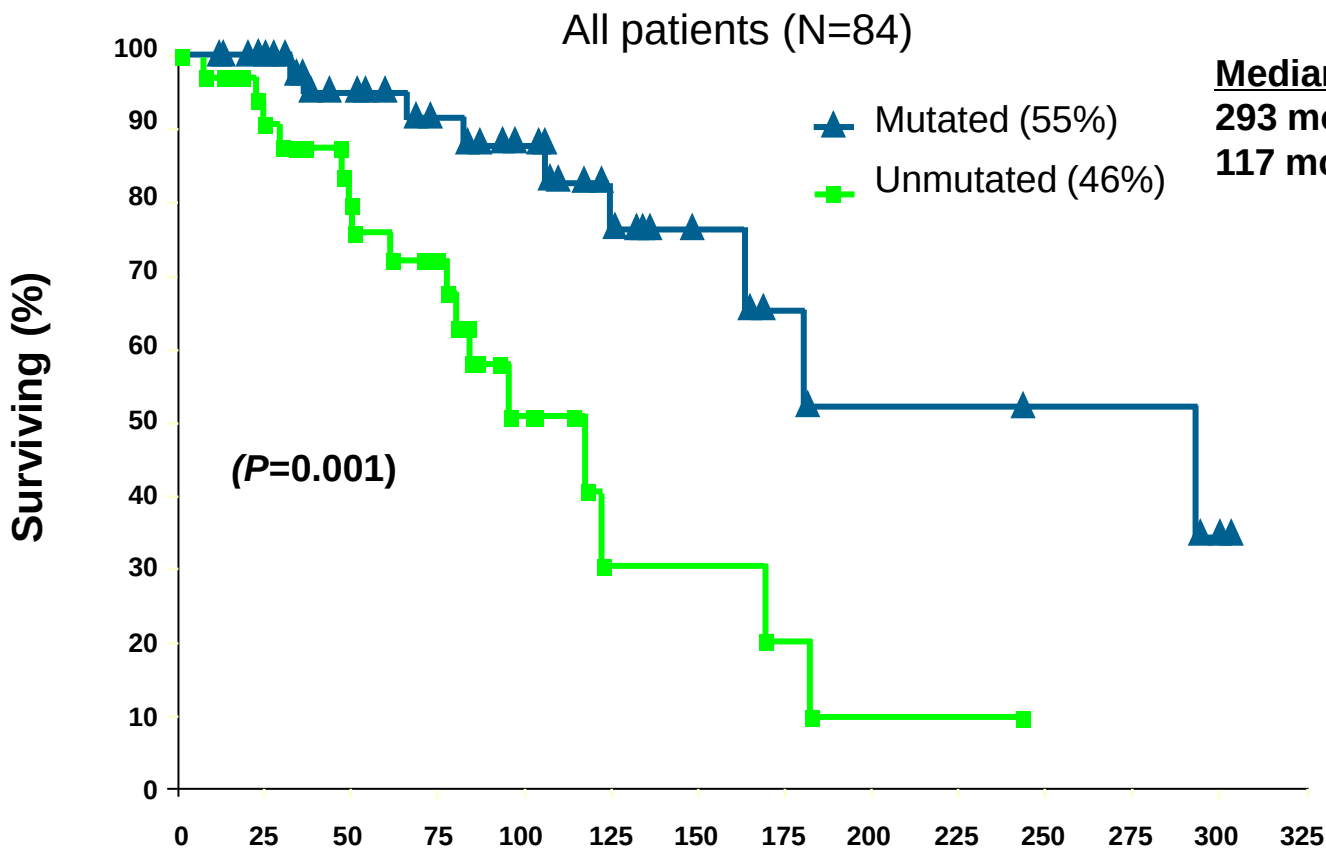
Dohner, et al. N Engl J Med. 2000

Outcome by Interphase FISH Abnormalities

Abnormality detected by FISH	Median Time to Treatment (months)	Median Overall Survival (months)	Percentage of Patients (%)
Del 17p	9	32	7
Del 11q	13	79	18
Trisomy 12	33	114	16
Del 13q	49	133	55
Normal	92	111	18

Dohner, et al. N Engl J Med. 2000

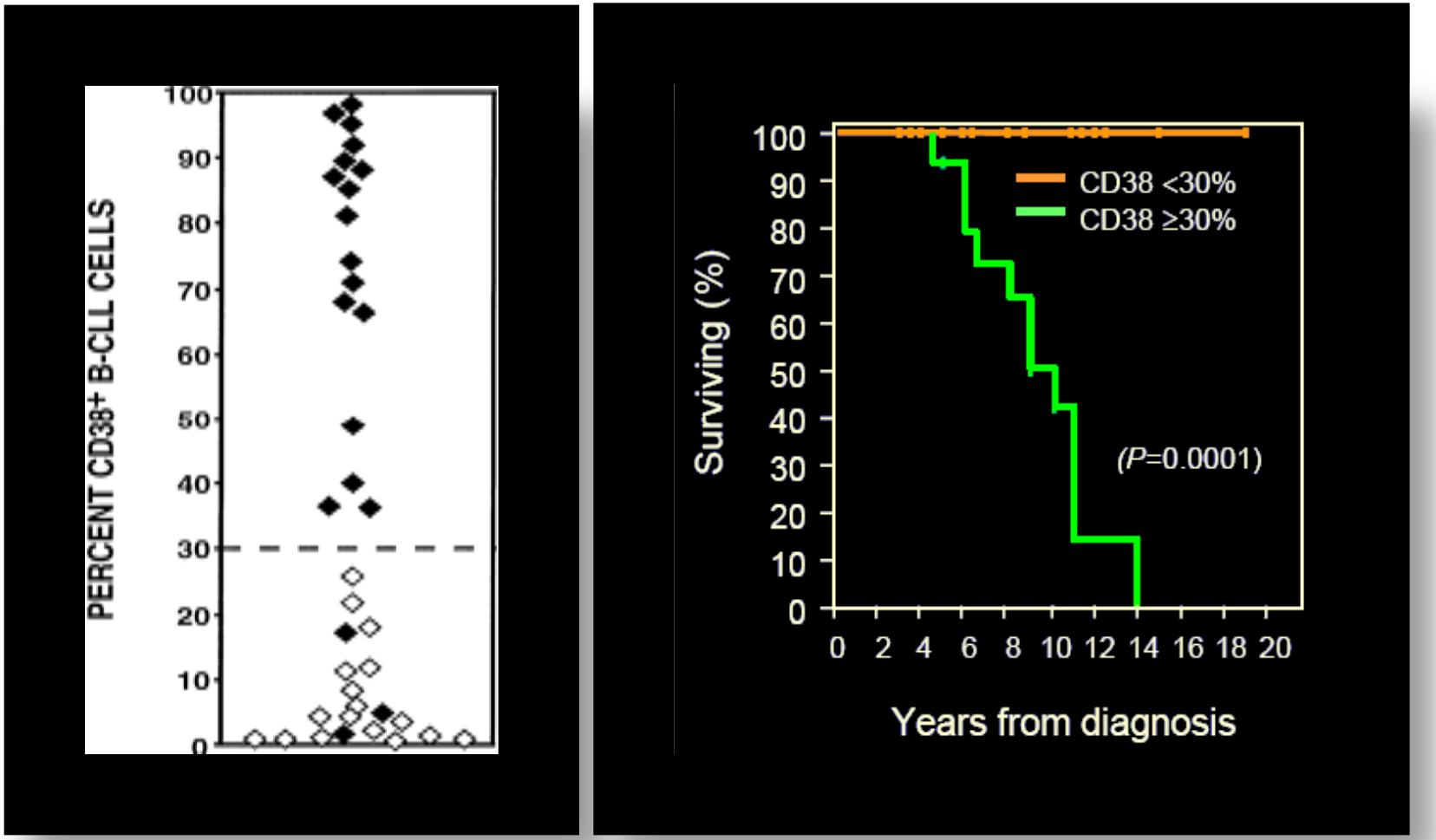
IGHV Mutational Status predicts Survival



Median Survival
293 months (Mutated)
117 months (Unmutated)

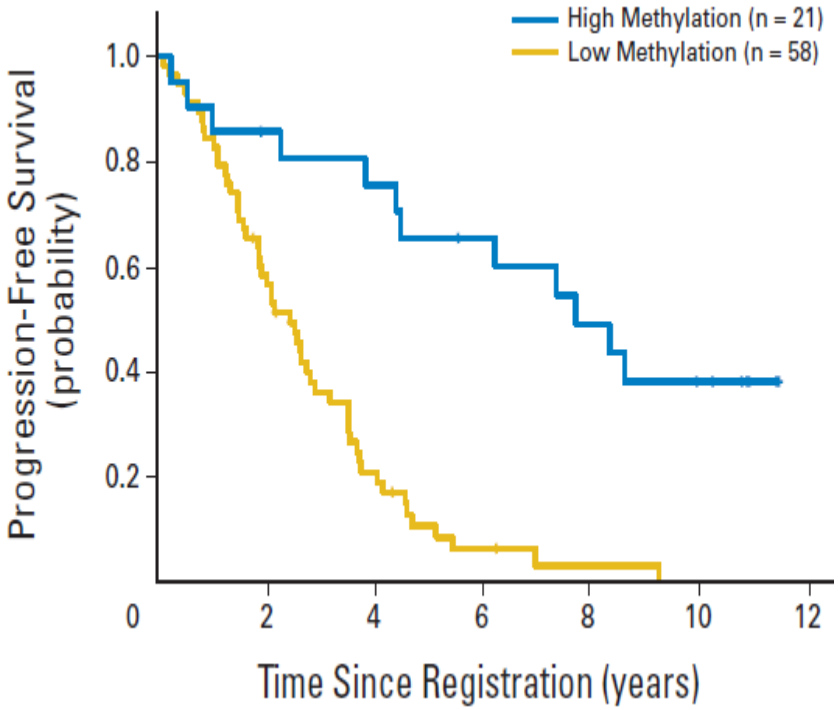
Hamblin et al. Blood. 1999

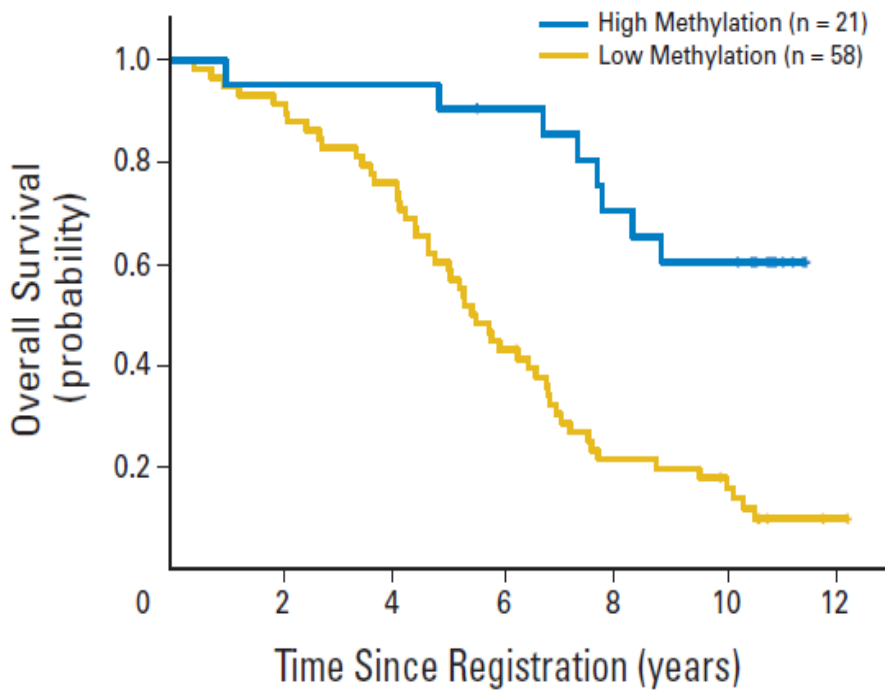
CD38 expression correlates with IGHV mutational status



Damle, et al, Blood, 1999

ZAP-70 Methylation





- loss of methylation at a specific single CpG dinucleotide in the ZAP-70 5' regulatory sequence is a highly predictive and reproducible biomarker of poor prognosis in this disease

Claus et al. J Clin Oncol 2012

Other Prognostic Markers

	Favorable Outcome	Un-Favorable Outcome
LDH	Low or Normal	Elevated
Lymphocyte Doubling Time	> 12 months	< 12 months
Thymidine Kinase Activity	Low or Normal	Elevated
Beta-2 Microglobulin	Low or Normal	Elevated

Prognostic factors in CLL: Summary

- Interphase-FISH cytogenetic analysis is standard of care
- Chromosomal abnormalities may change with time
- IGHV status does not change with time
- CD38 and ZAP-70 methylation correlates with IGHV

So is stage of the cancer important in CLL

- Rai/Binet Staging system has been used for a long time
- Newer molecular methods are much more useful

What do we do at Initial Presentation?

- **All patients undergo**
  - History and Physical
  - CBC with diff
  - CMP
  - Direct Anti-Globulin Test*
  - Quantitative Immunoglobulins
  - Infectious Serology*
  - Peripheral Blood Flow cytometry
  - +/- CT scan CAP*
  - +/- Bone Marrow Biopsy*

What do we do at Initial Presentation?

- **Prognostic Markers**
  - Interphase FISH
  - Conventional karyotyping
  - IGHV mutational analysis
  - ZAP-70 Methylation
  - Beta-2 microglobulin
  - LDH
  - Lymphocyte doubling time

Timing of Therapy

- Constitutional symptoms – **How you feel**
  - Unintentional weight loss of >10% within the previous 6 mos
  - significant fatigue (ECOG PS 2 or worse)
  - fevers >100.5˚ F for >2 wks without other evidence of infection
  - night sweats for >1 month without evidence of infection

NCI-IWCLL recommendations, Blood, 2008

Timing of Therapy

- Worsening or steroid resistant anemia and/or thrombocytopenia
- Spleen >6cm below the left costal margin
- Lymph Nodes >10cm
- Lymphocyte doubling time (LDT) of <6 months

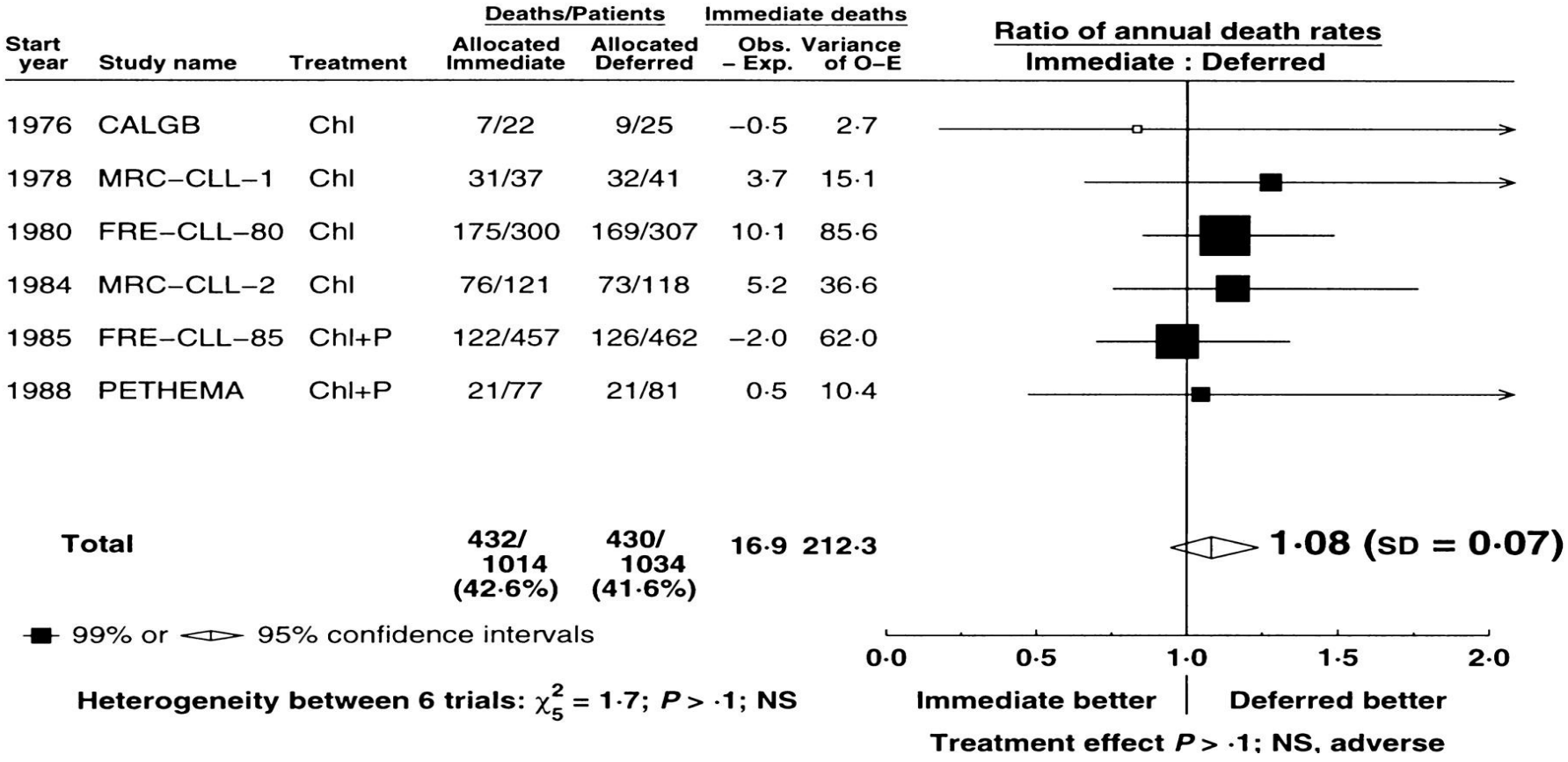
NCI-IWCLL recommendations, Blood, 2008

Don’t Treat

- Hypogammaglobulinemia
- Monoclonal or oligoclonal paraproteinemia
- **Elevated leukocyte count**

NCI-IWCLL recommendations, Blood, 2008

Early Treatment Does not improve Survival



J Natl Cancer Inst, 1999

But treatments have changed ……

- Early treatment can be considered if
  - treatment is well tolerated
  - doesn't have too many side effects
  - and works well

- Early intervention trial of ibrutinib available at OSU soon for patients who don't need treatment per conventional criteria

Infectious Complications

- Infections are the leading cause of death in CLL
- Most common infections are sinus, throat and chest
- It generally results from low immunoglobulin levels and defective immune system

- Intravenous immunoglobulins (IVIg) can help in some patients

How to prevent infections?

- Pneumococcal vaccine every 2-5 years (PCV13)
- Flu vaccine every year

- Avoid live virus vaccines including
  - Shingles
  - Nasal flu
  - Oral polio
  - Yellow fever

Secondary Cancers

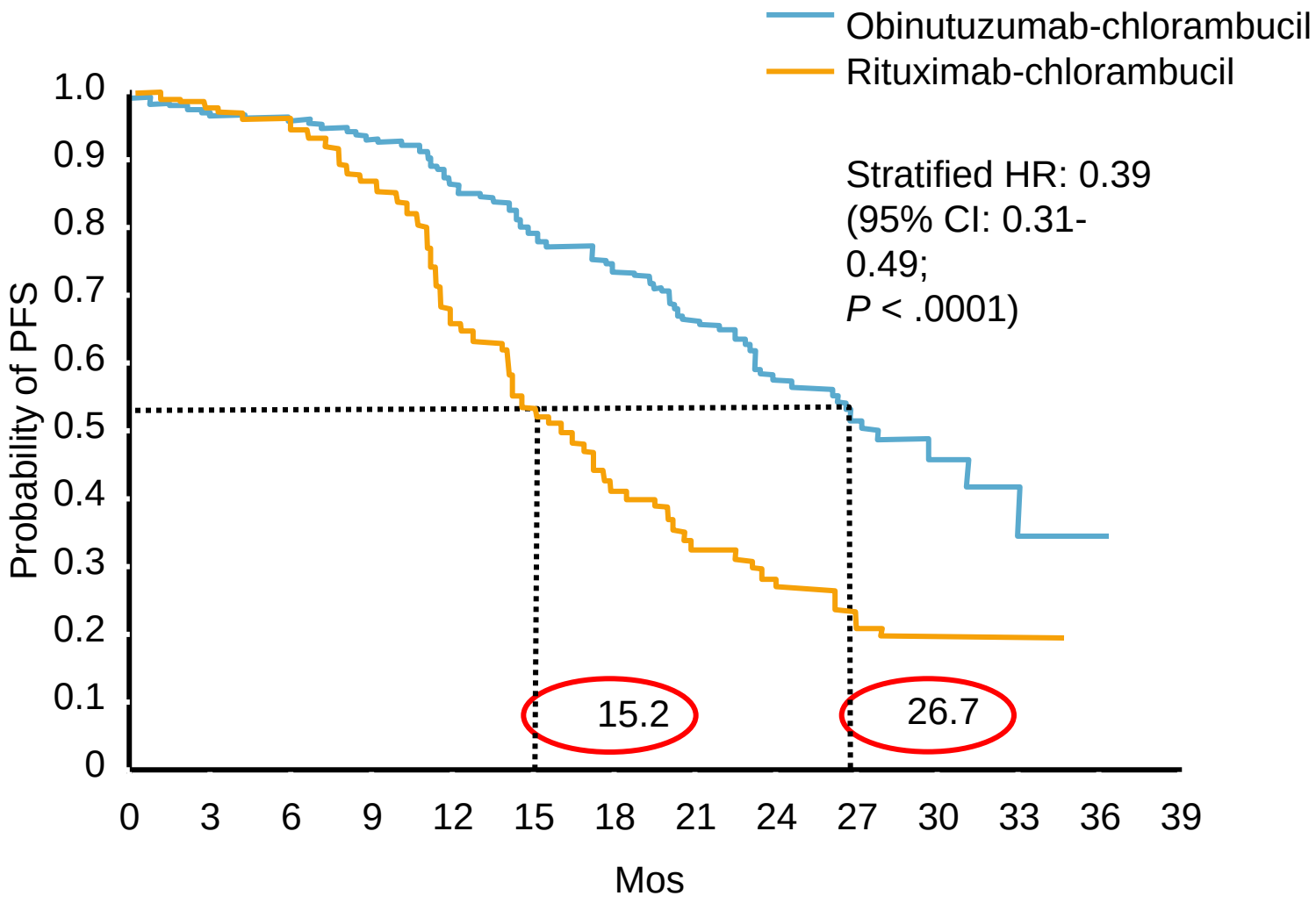
- Patients with CLL are at a high risk of getting secondary cancers
  - Colonoscopy every 5 years
  - Skin exam by dermatologist every year
  - Mammogram every year
  - Pap smear every year
  - PSA every year

Issues with Supplements

- Metabolism uncertain
- Side effects not well characterized
- Efficacy not proven in clinical trials
- Interaction with other drugs not known

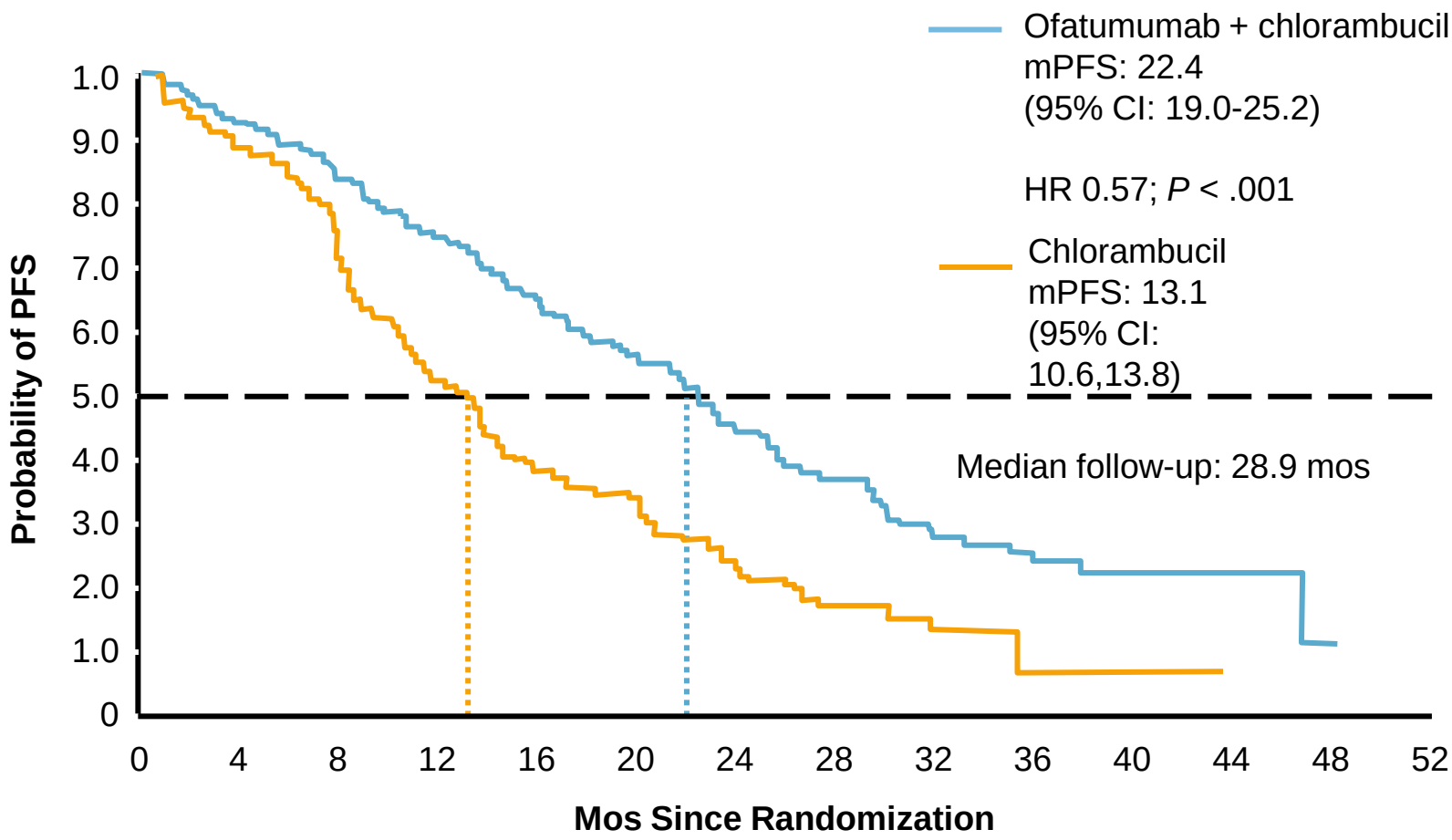
- Please tell your doctor about the type of supplement that you take

Obinutuzumab plus Chlorambucil



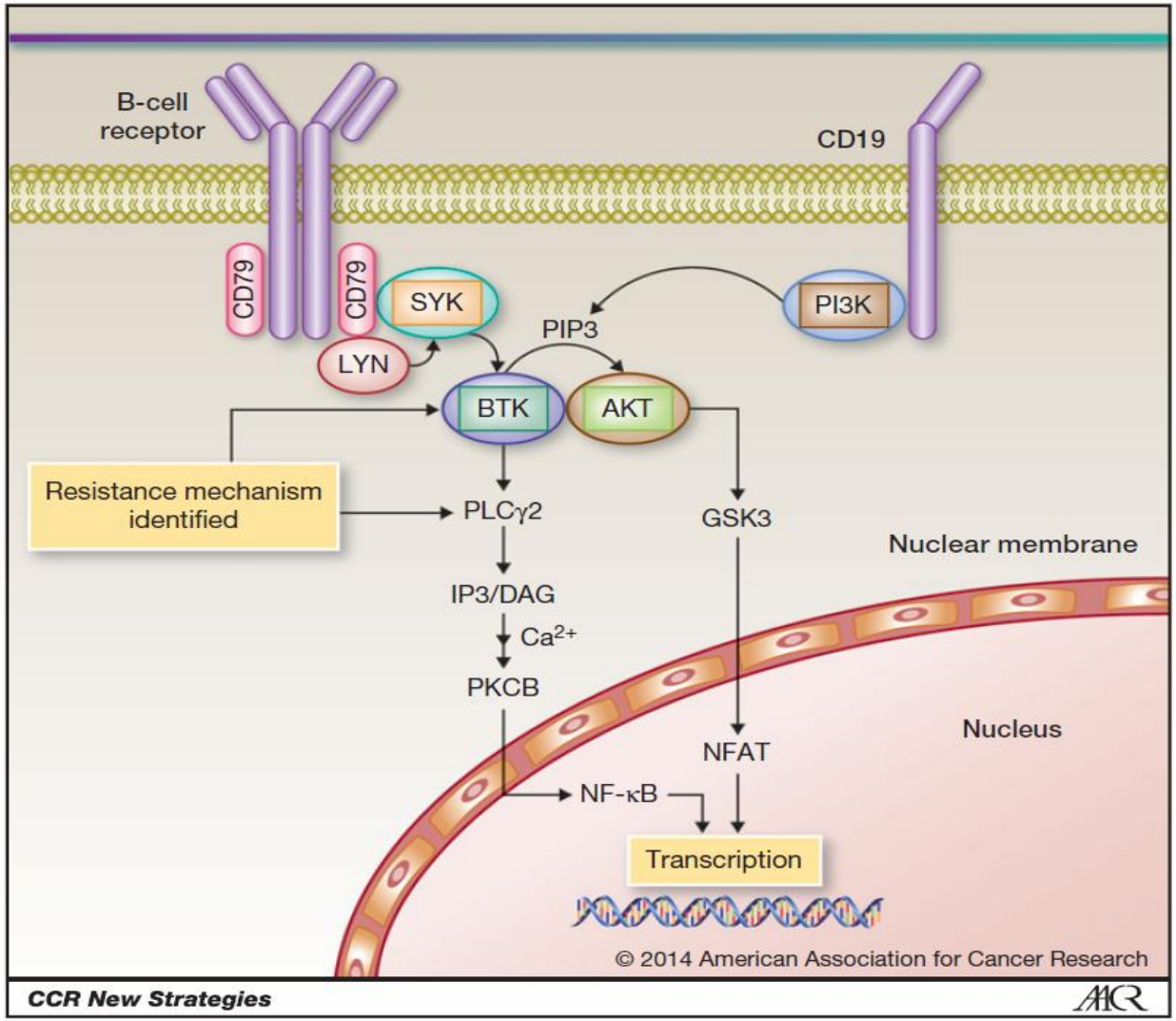
Goede, et al. Nejm 2014

Ofatumumab plus Chlorambucil



Hillmen P, et al. ASH 2013. Abstract 528.

Targeting kinases in CLL



Awan F, et al, CCR 2014

Ibrutinib

- Forms a specific bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC_{50} = 0.5 nM
- Orally administered with once-daily dosing resulting in 24-hr target inhibition
- No cytotoxic effect on T cells or NK cells
- Promotes apoptosis and inhibits migration and adhesion in CLL cells

PCYC-1102-CA: Phase IB/II in CLL/SLL

PCYC-1102-CA

Total enrollment 117 patients

Dates enrolled
20th May 10 –
27th Jul 11

Relapsed/Refractory
420 mg/d (n=27)
Median follow-up 17.5 months

Treatment Naïve ≥ 65 yrs
420 mg/d (n=26)
Median follow-up 14.4 months

Relapsed/Refractory
840 mg/d (n=34)
Median follow-up 13.8 months

High-risk Relapsed/Refractory
420 mg/d (n=25)
Median follow-up 7.4 months

Treatment Naïve ≥ 65 yrs
840 mg/d (n=5)
Median follow-up 7.4 months

Co-leaders: J Byrd and S O'Brien

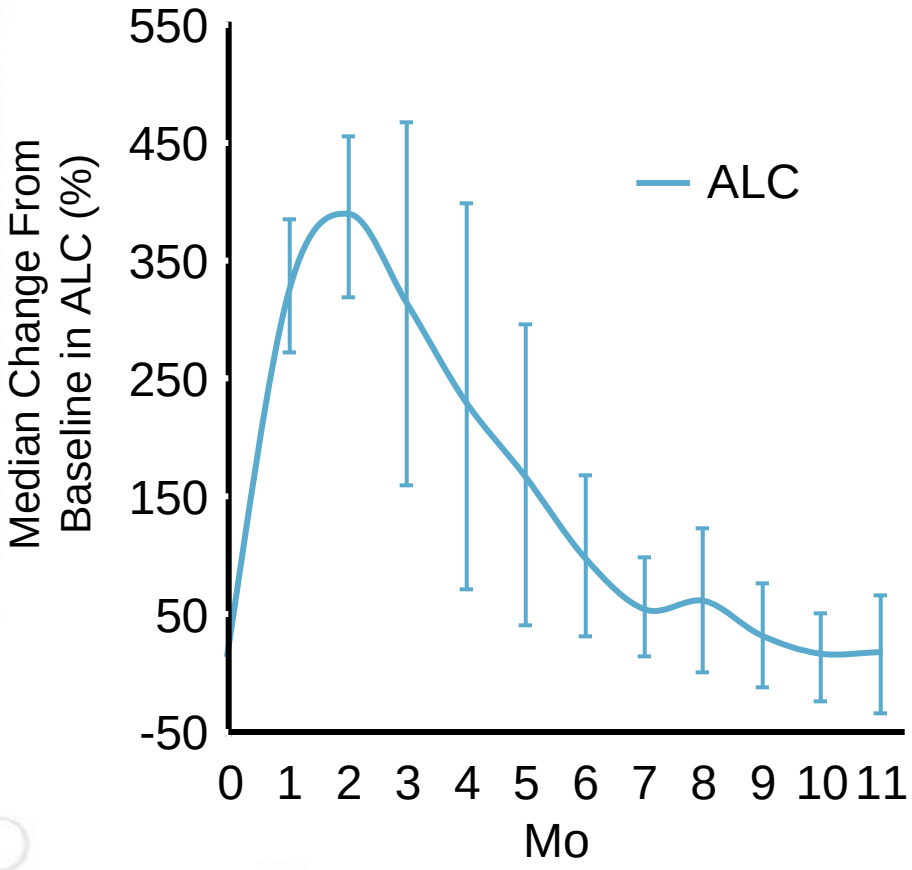
Phase II CLL Patient Characteristics

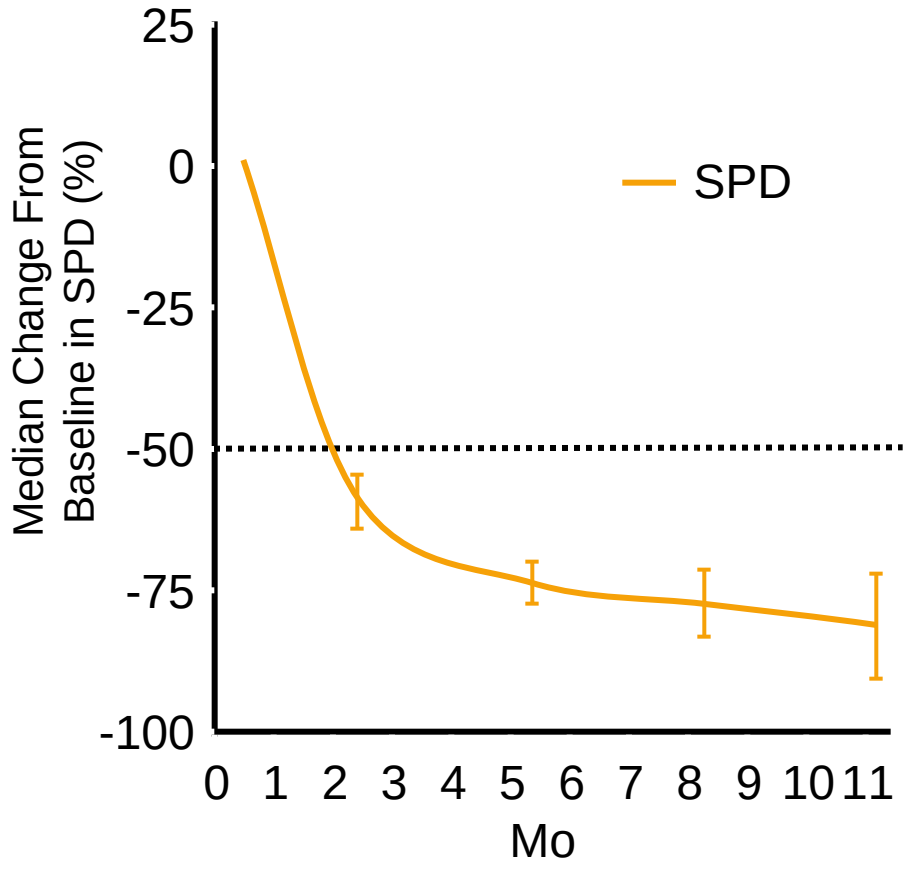
	TN ≥65 yrs (N=31)	R/R + HR (N=85)
Age, years ≥ 70 years, (%)	74%	35%
ECOG Status 0, 1, 2 Median Prior Therapies	74%, 26%, 0% N	41%, 56%, 2% 4 (1-12)
Rai Stage III/IV at Baseline	48%	65%
Prognostic Markers, % IGHV unmutated del(17p13.1) del(11q22.3)	 55% 7% 3%	 85% 35% 39%

Modest toxicity in phase II study similar to phase I study

NEJM 2013
Lancet Oncology

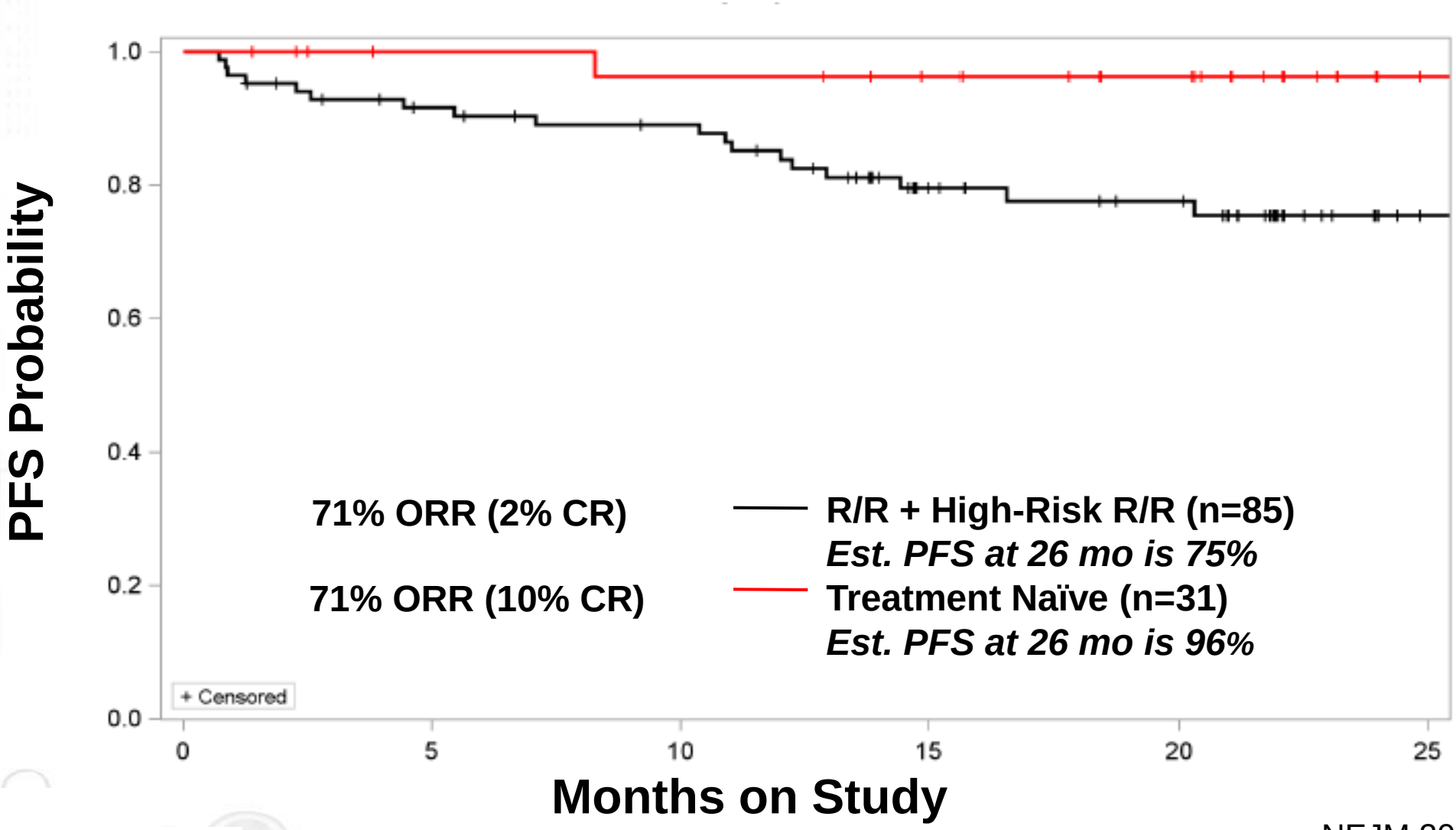
Pattern of Response: Blood Lymphocytes vs Lymph Nodes





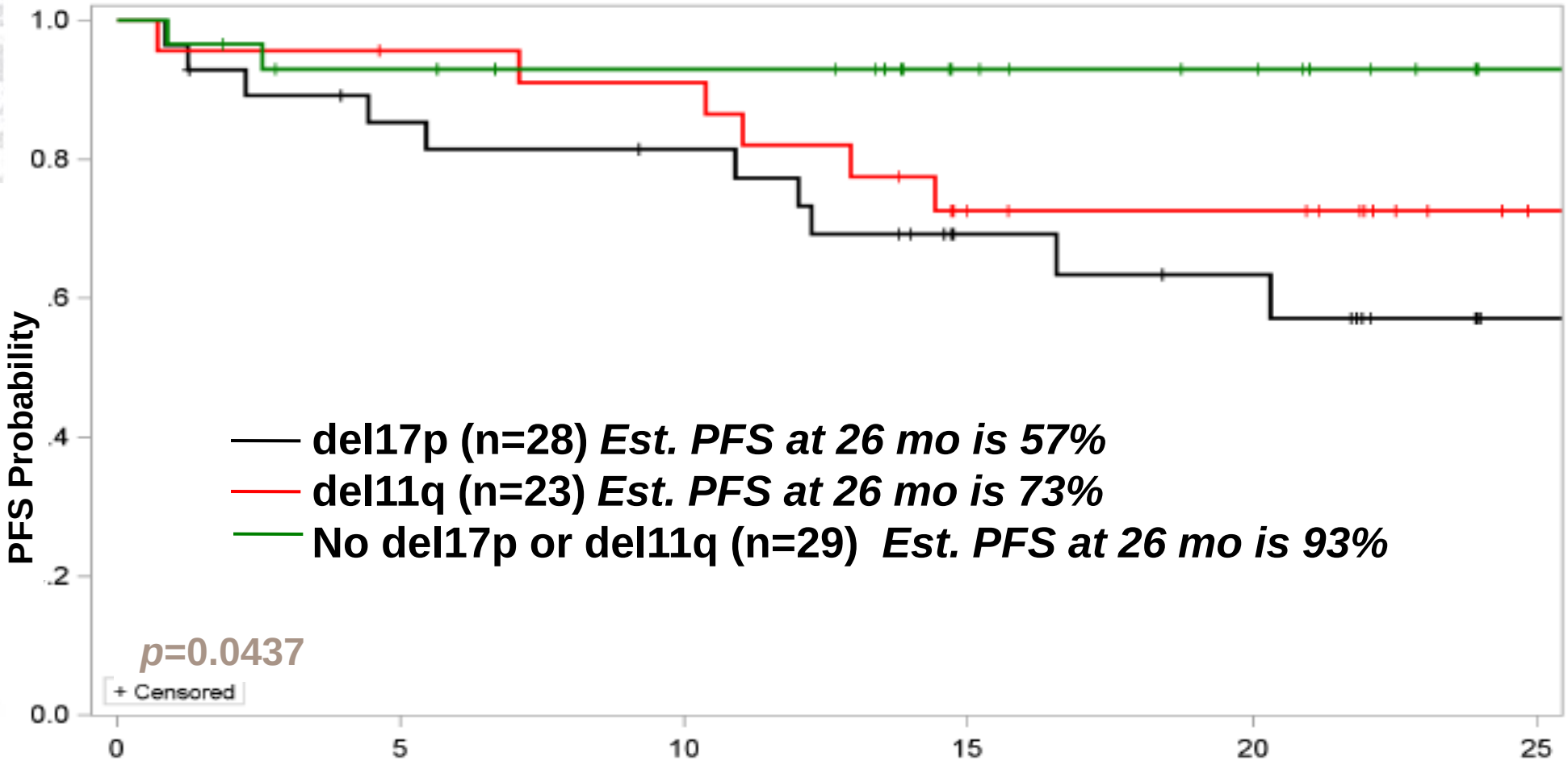
Byrd JC, et al. N Engl J Med. 2013;369:32-42.

Phase II Response and Progression-free Survival



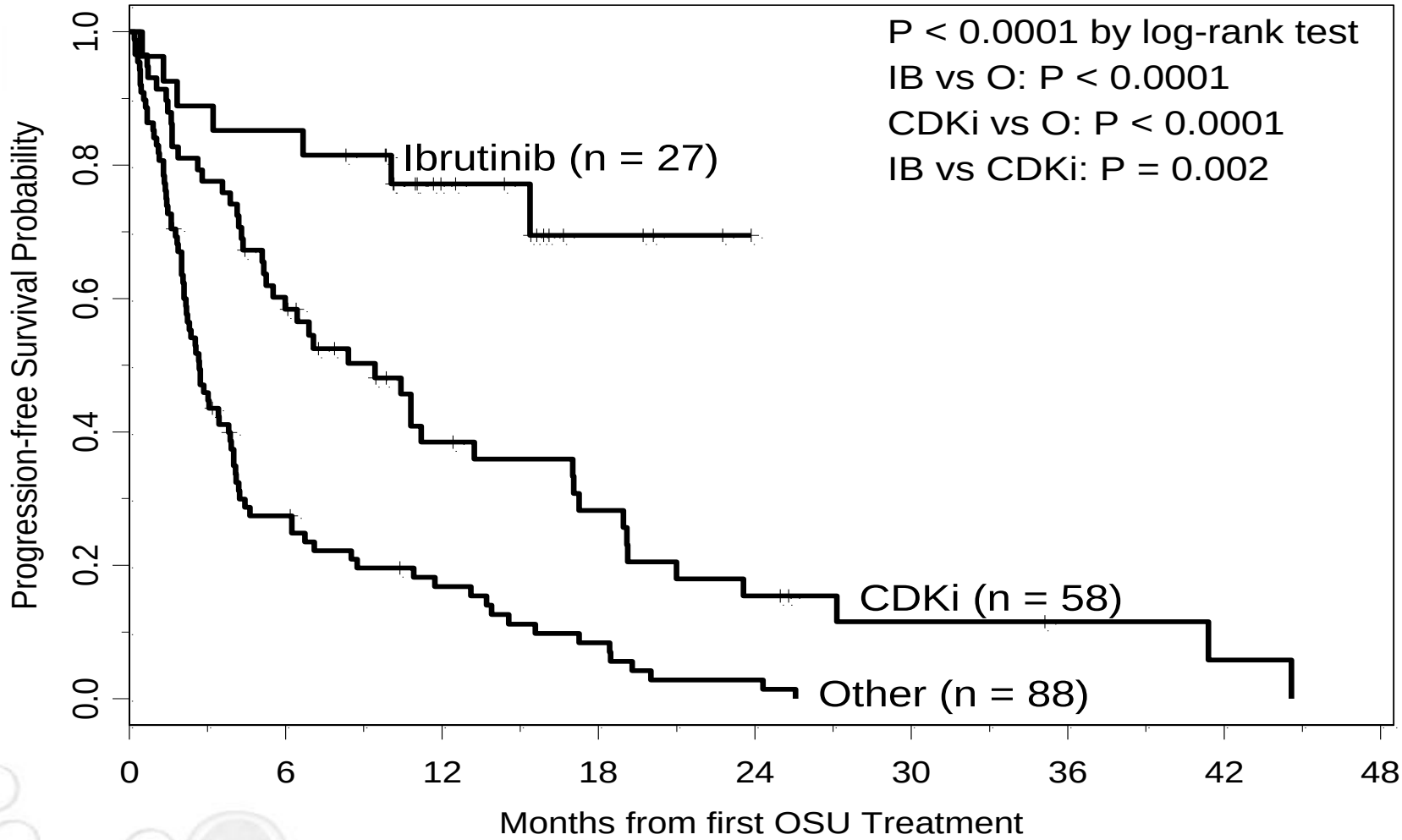
NEJM 2013

PFS by FISH: Relapse Cohort

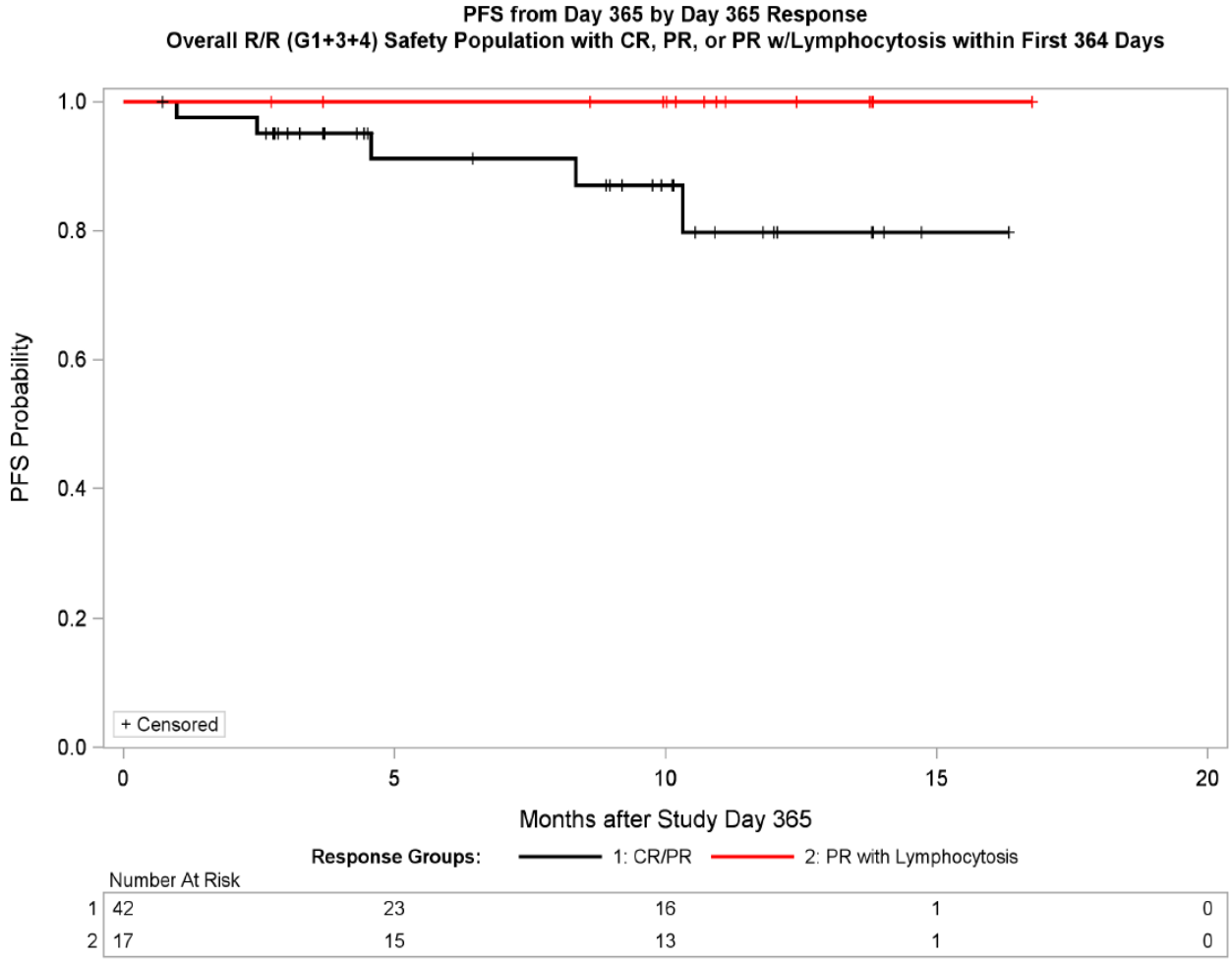


Months on Study

Early Results Of Impact: Outcome of Treatment of del(17p13.1) CLL at OSU

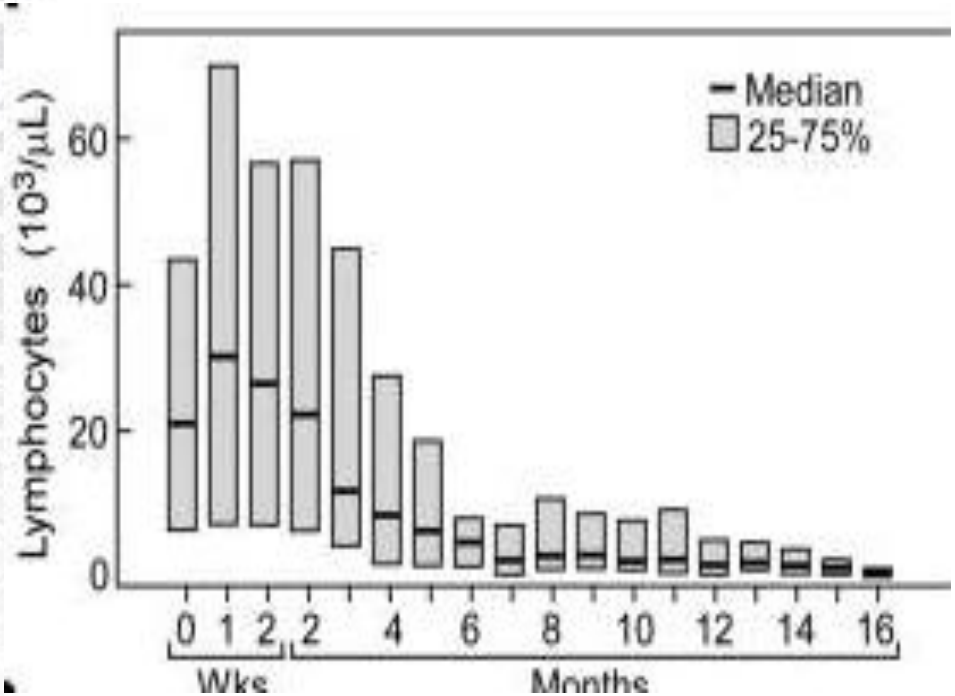


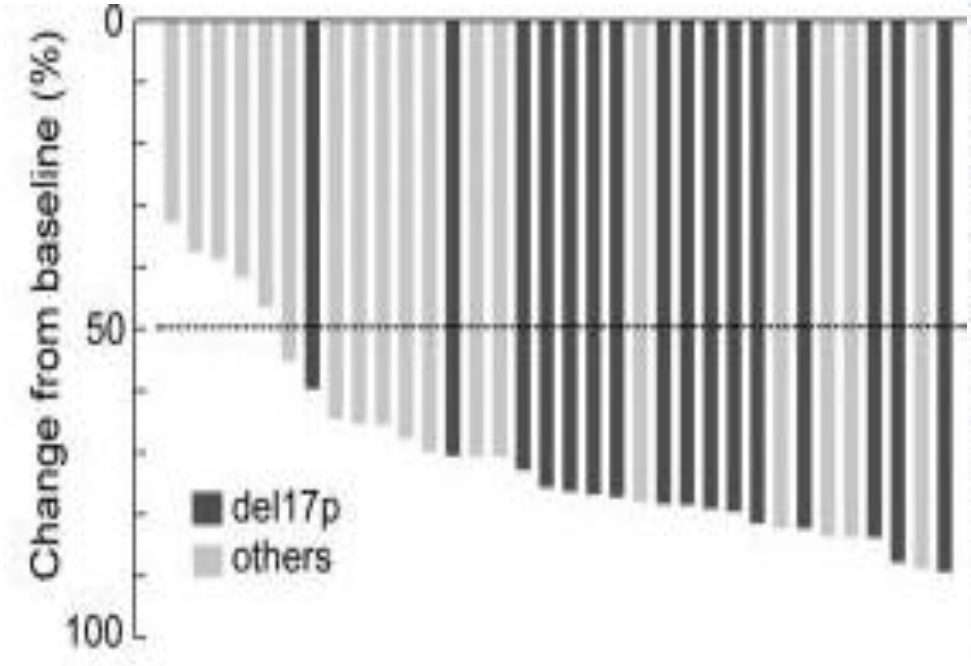
PR-L is not associated with inferior PFS compared with PR/CR at 12 months



Woyach J et al: Blood 2014

Ibrutinib and Rituximab



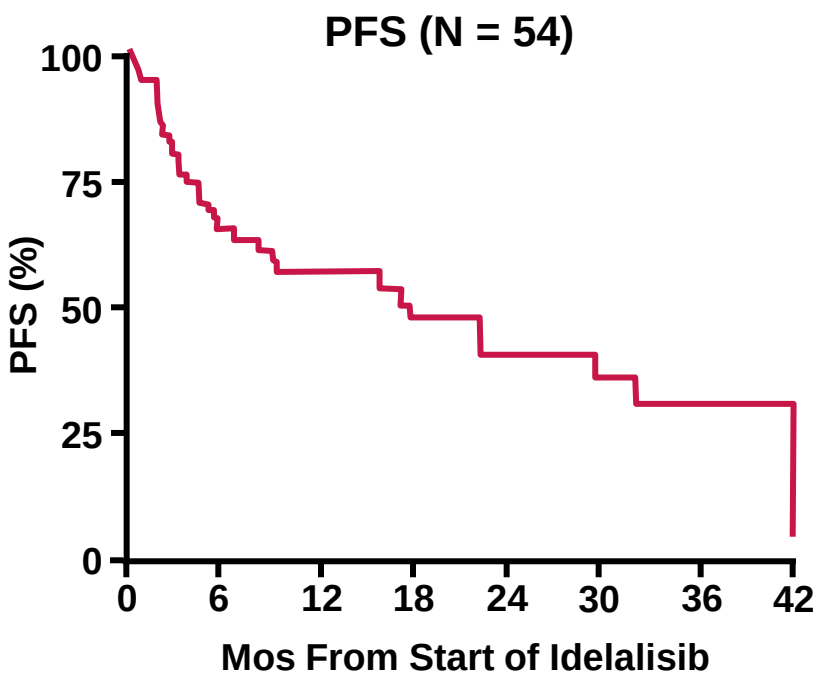


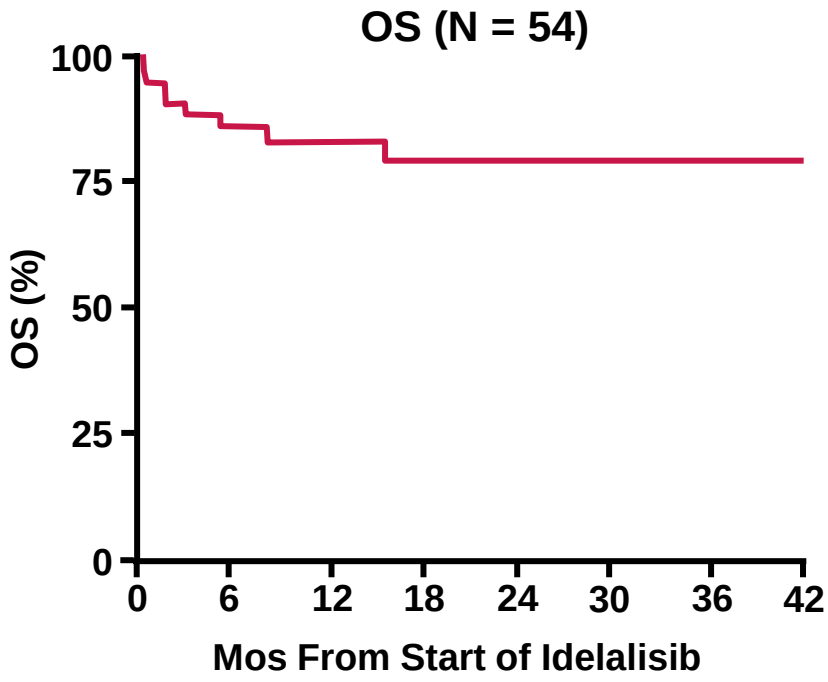
Burger J et al: Lan Onc 2014

Idelalisib

- Selective PI3-K delta inhibitor
- Single agent response rate of 72%
- 39% PR and 33% PR+L
- Penumonitis, colitis, transaminitis

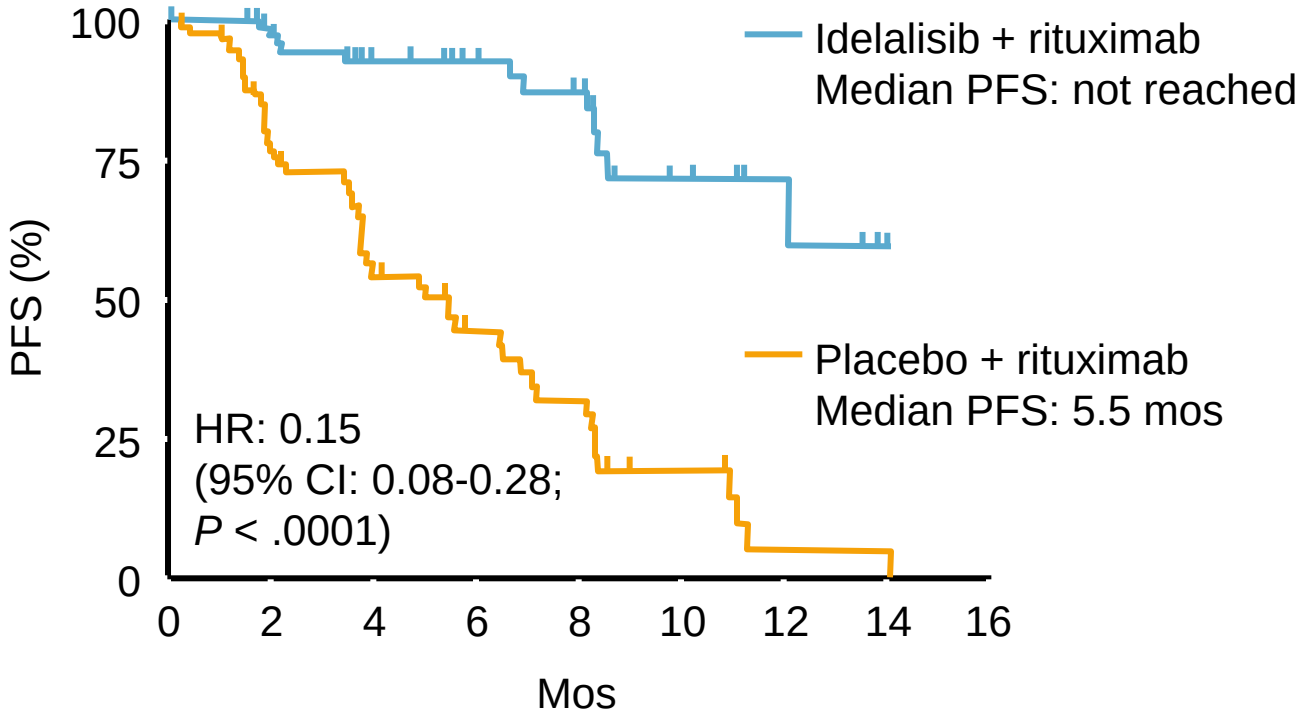
Idelalisib in relapsed/refractory CLL





Brown JR, et al. Blood. 2014 May 29;123(22):3390-7

Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL



Furman R, et al. N Engl J Med. 2014

Summary

- CLL is a disease with varied presentation
- Comprehensive diagnostic and prognostic workup is important for optimal management at the time of diagnosis
- Multiple treatment options exist including chemotherapy and non-chemotherapy approaches
- Prognosis is generally excellent and improving every day