Chronic Lymphocytic Leukemia: *Putting on a New Face*

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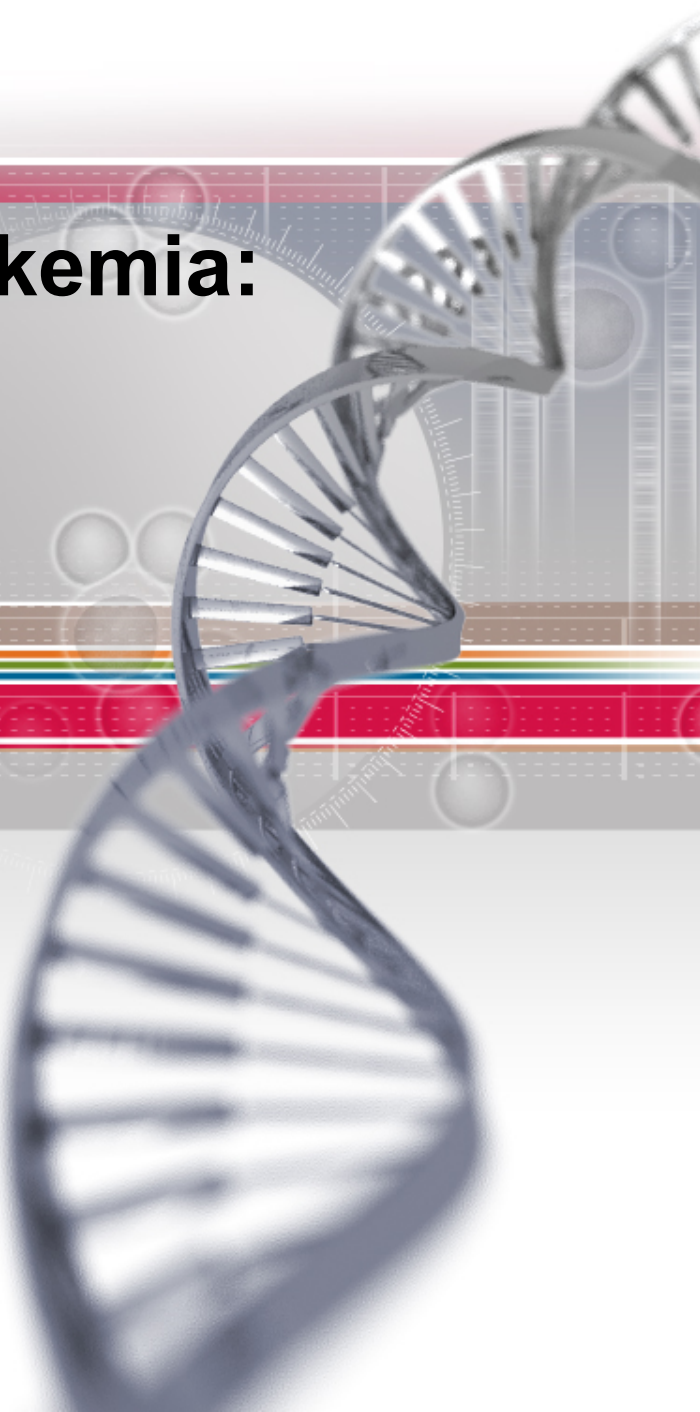


THE OHIO STATE UNIVERSITY The James
Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

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

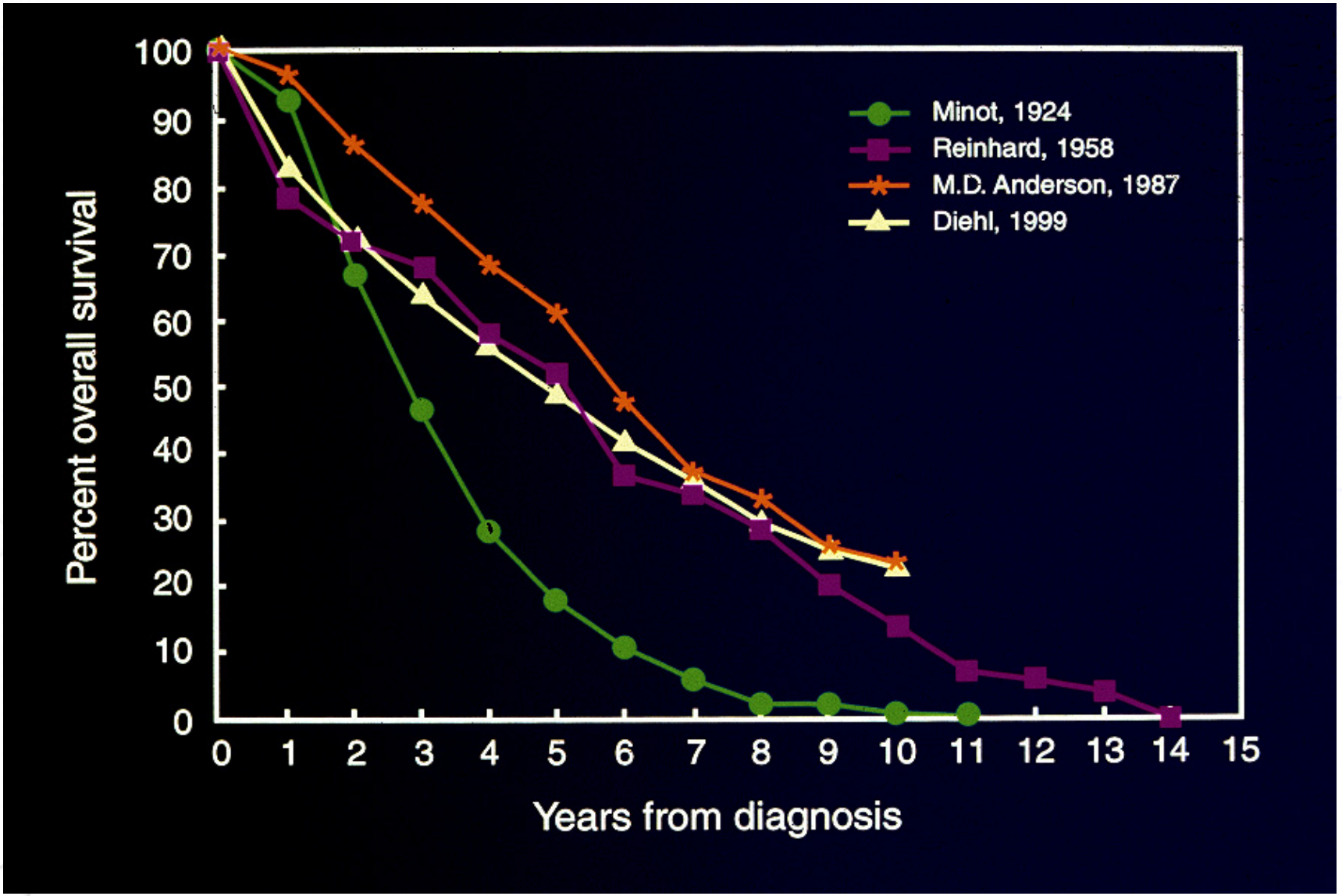
Overview

- **Brief introduction to CLL**
  - Epidemiology and clinical features
  - Genetic risk stratification
- **Current treatment strategies**
  - Standard-of-care chemoimmunotherapy
  - Genetic high-risk disease
  - Elderly patients
- **Emerging agents: the "New Face"**
  - Immunotherapy: monoclonal antibodies and beyond
  - Targeting B-cell receptor signaling with kinase inhibitors

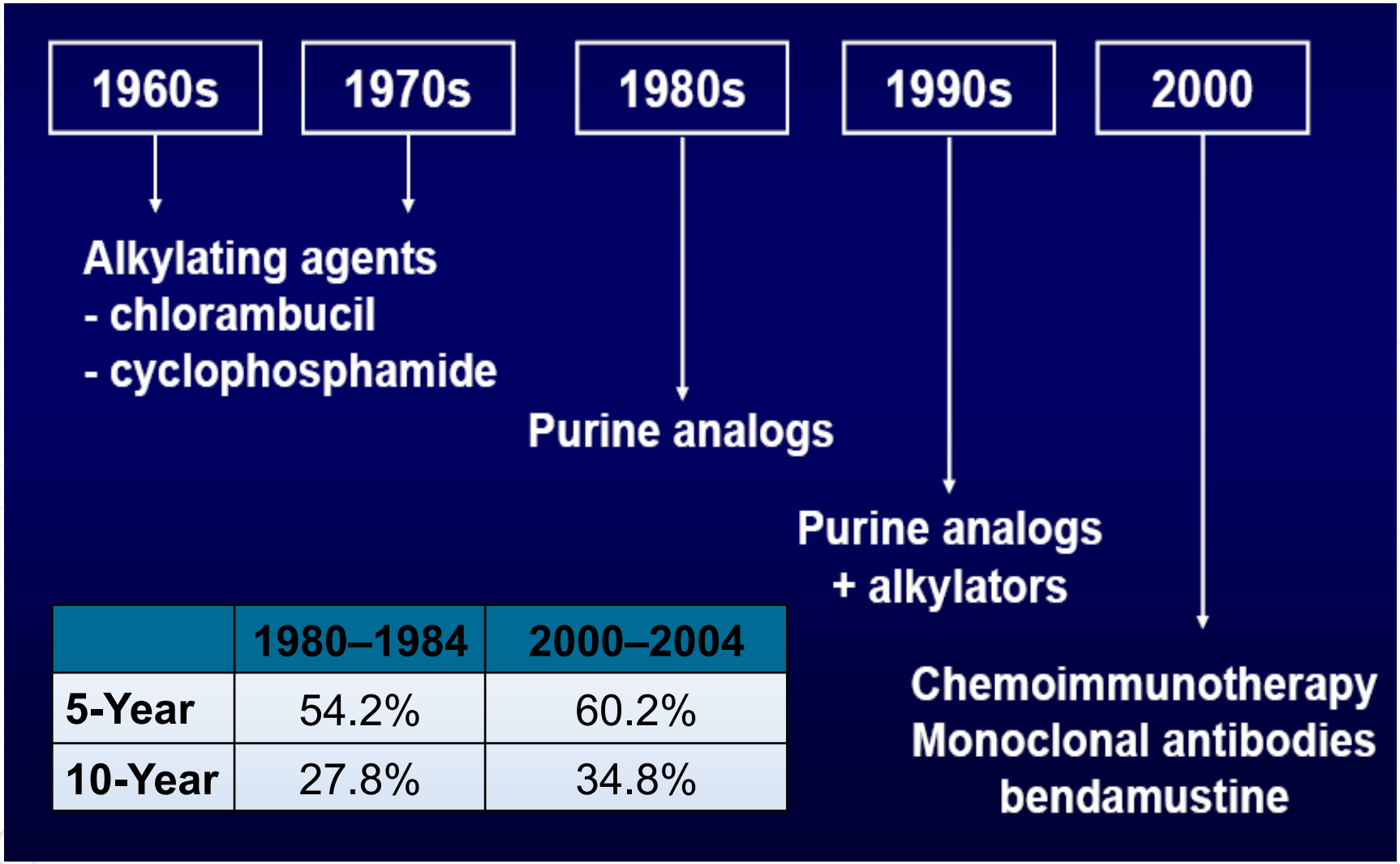
CLL: Epidemiology

- Most common leukemia (~ 15,000 cases per year)
- Disease of older patients, median age at diagnosis 72 years
- Causes ~ 4,400 deaths per year
- Absolute survival has increased during past 2 decades
- 3:2 male-to-female ratio; white > black >>> Asian
- Relatively long median survival makes CLL by far the most prevalent leukemia

American Cancer Society, 2008; Rai et al, 1975; Brenner et al, 2008.


Percent overall survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Years from diagnosis
Minot, 1924
Reinhard, 1958
M.D. Anderson, 1987
Diehl, 1999

CLL: The Changing Face of Survival



	1980–1984	2000–2004
5-Year	54.2%	60.2%
10-Year	27.8%	34.8%

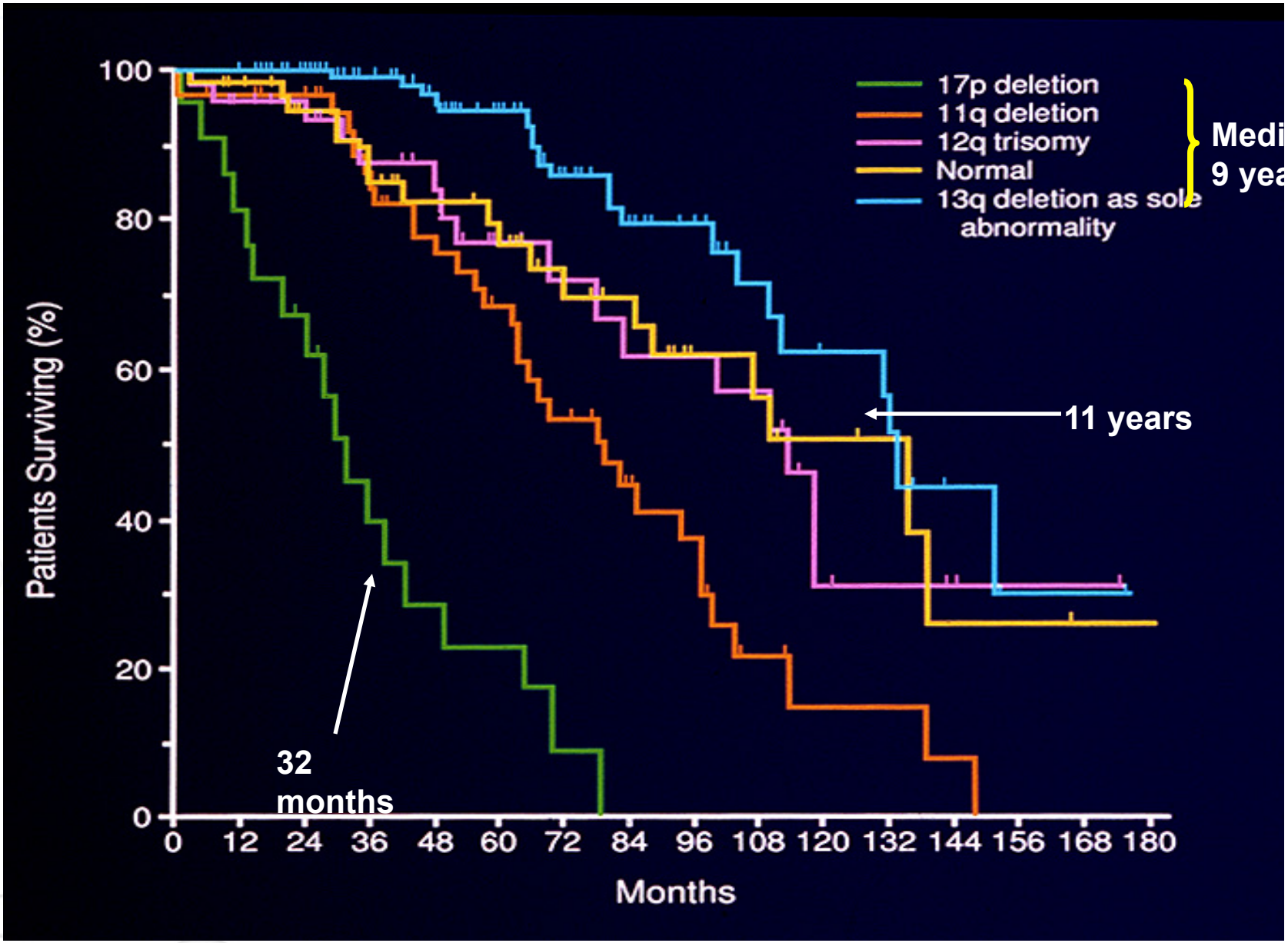
Brenner et al, 2008.

Rai and Binet Staging Systems

Rai	Findings	Survival (mo)
0	Lymphocytosis only	> 150
I	Lymphocytosis + lymphadenopathy	101
II	Lymphocytosis + > spleen and/or liver	71
III	Lymphocytosis + anemia (Hgb < 11.0 g/dL)	19
IV	Lymphocytosis + platelets < 100	19

Binet	Findings	Survival (mo)
A	Hgb ≥ 10, Plts ≥ 100, < 3 involved areas	> 120
B	Hgb ≥ 10, Plts ≥ 100, ≥ 3 involved areas	84
C	Hgb < 10 or Plts < 100	24

Rai et al,1975



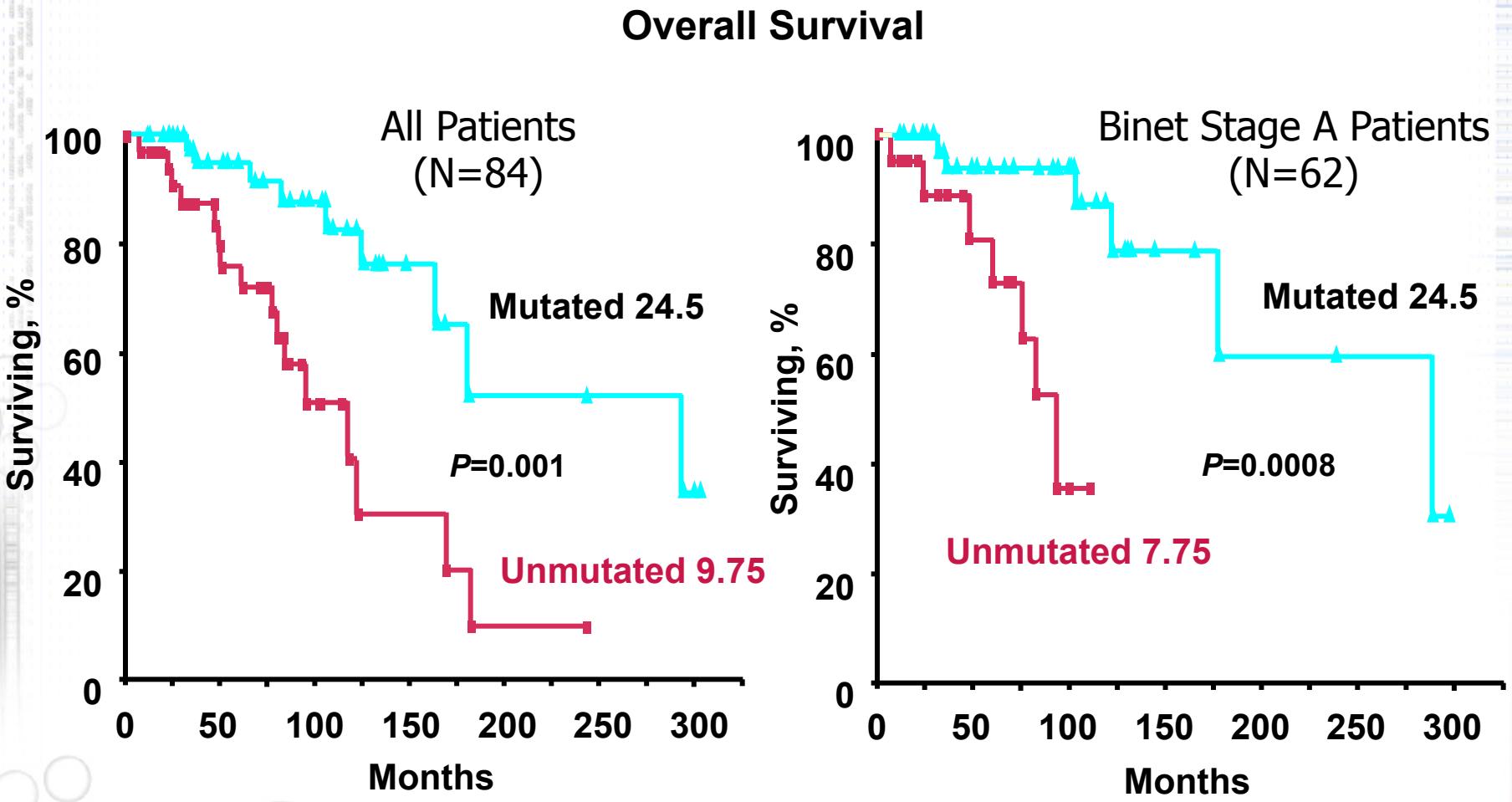
Dohner et al. *NEJM* (2000)

CLL Outcome from Diagnosis by Interphase FISH Abnormalities

Abnormality	% Patients	Median time to Treatment	Median Overall Survival
Del(17p13.1)	7	9	32
Del(11q22.3)	18	13	79
Trisomy 12	16	33	114
Del(13q14)	55	49	133
None detected	18	92	111

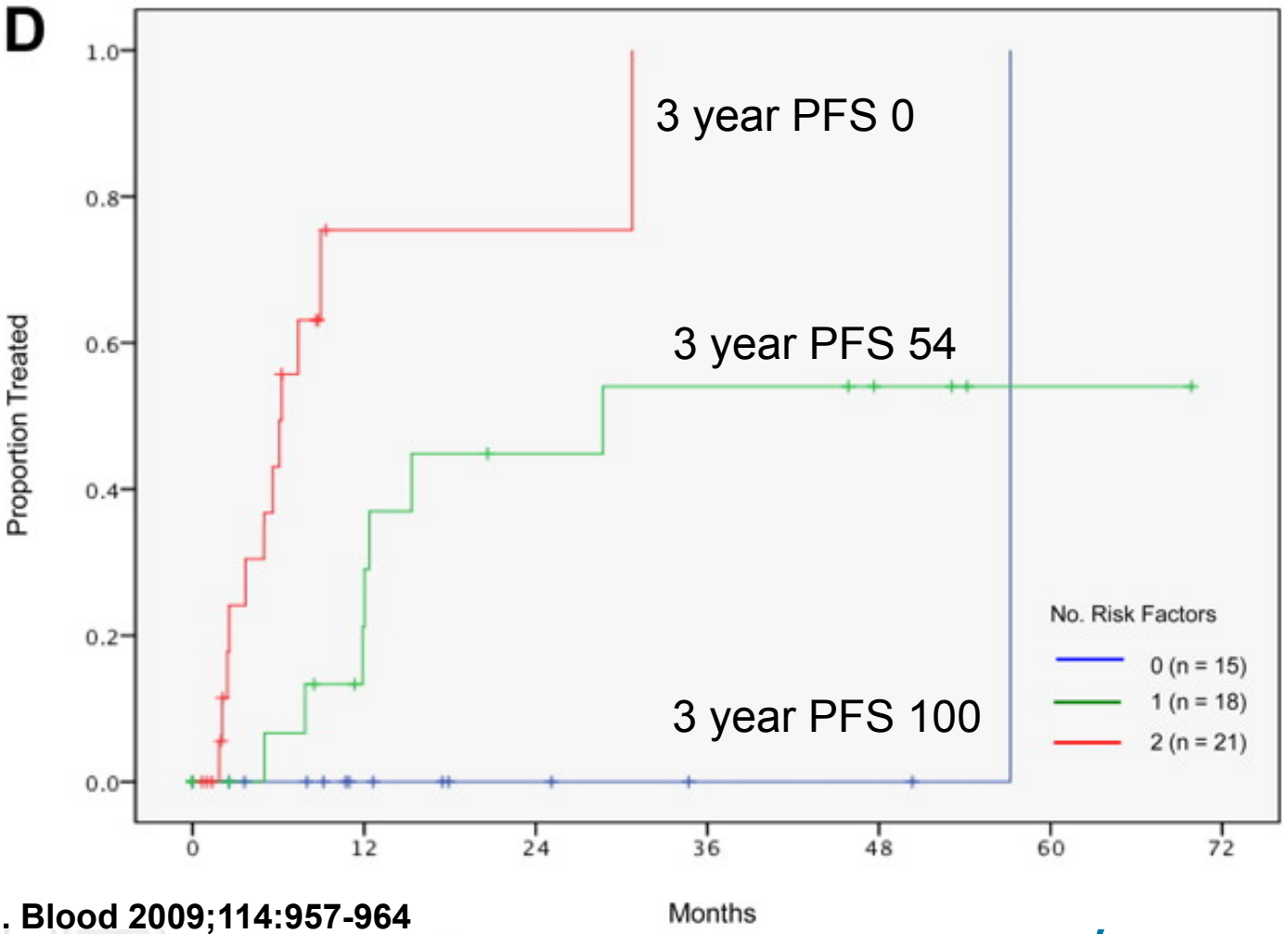
Dohner et al. *NEJM* (2000)

CLL Prognostic Markers
Mutated vs Unmutated IgV_H Genes



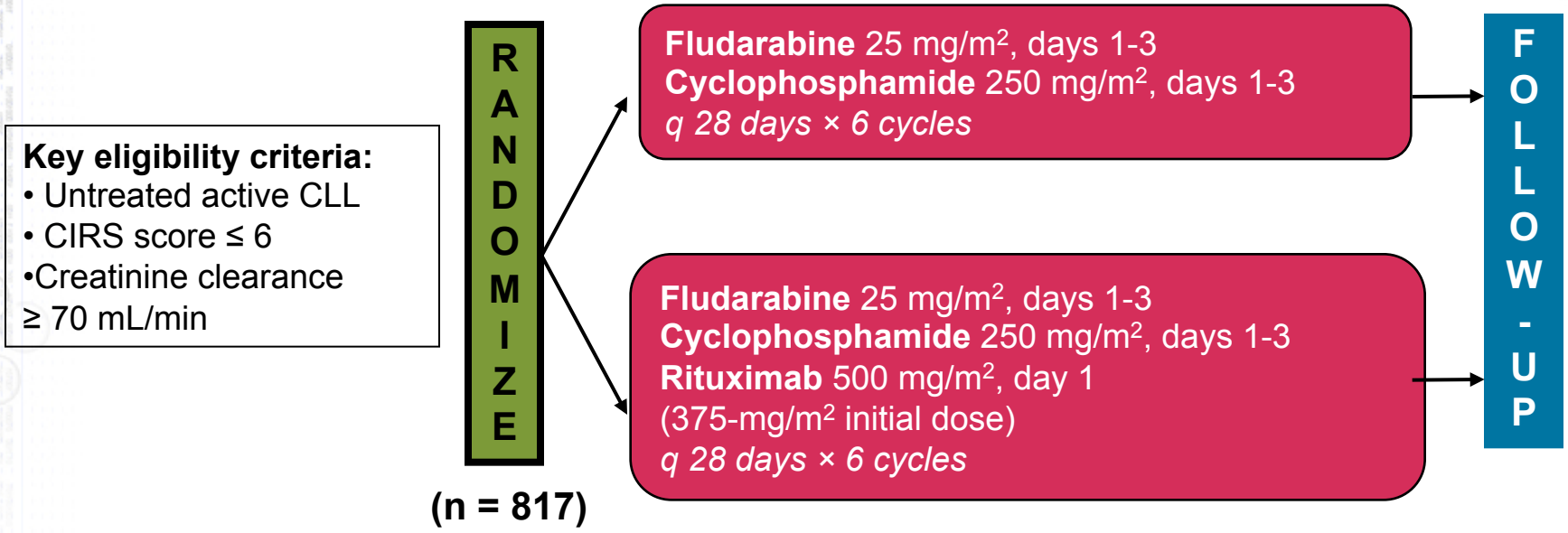
Hamblin TJ, et al. *Blood.* 1999;94:1848-1854.

Deletion 17p does not always portend rapid disease progression



Tam C S et al. Blood 2009;114:957-964

Phase III CLL8 Trial of FC With or Without Rituximab in Untreated CLL: Study Design



- **Primary endpoint: PFS**
- **Secondary endpoints: OS, response, safety**

Hallek et al. ASH 2008; abstract 325.
Hallek et al. ASH 2009; abstract 535.

CLL8 FC v. FCR in Untreated CLL: Efficacy

	FCR (n = 388)	FC (n = 371)	HR	*P* Value
ORR	95%	88%	NA	< .01
CR	44%	22%	NA	< .01
PR	51%	67%	NA	NA
SD	4%	8%	NA	< .01
Median PFS	51.8 months (n = 401)	32.8 months (n = 389)	0.563	< .001
3-Year OS	87% (n = 408)	82.5% (n = 409)	0.664	.012

- **Median observation time: 37.7 months**
- **FCR significantly improved the CR rate in the patients with del(11q), del(13q), trisomy 12, and unmutated *IGHV* (*P* < .001) but not in those with del(17p) (*P* = 0.3)**
- **The patients achieving a CR had the longest survival**

Hallek et al. *The Lancet* (2010)

CLL8 FC v. FCR: 6 year follow-up

Second malignancies

- FC arm, 12%; FCR arm, 10% (*P* = NS)
  - Solid tumors, 5.7%
  - Richter transformation, 4.1% 1.5%
  - MDS or AML, 1.5%
- Mean time to onset, 2.4 y after end of treatment
- No significant difference between arms in rates of any type of second malignancy

Late neutropenia (grade 3/4 neutropenia 2 mo or longer after end of treatment)

- FC arm, 9%; FCR arm, 17% (*P* = .007)
- Occurred predominantly during first 12 mo after end of FCR treatment
- No significant difference between arms at 1 y after end of treatment

Fischer et al. *2012 ASH Annual Meeting* Abstract #435

Chemoimmunotherapy as Initial Treatment for Patients with Chronic Lymphocytic Leukemia

Outcome	CLL8[1] R-FC	MDACC[2,3] R-FC	CALGB[4,5] FR	Mayo[6] PCR	CLL BR
% CR	44	72	47	41	33
% OR	95	95	90	91	91
PFS, mo	52	80	42	34	NR

1. Hallek M, et al. Blood 2009;114: Abstract 535.
2. Keating MJ, et al. J. Clin Oncol. 2005;23(18):4079-4083.
3. Tam CS, et al. Blood 2008;112(4):975-908.
4. Byrd JC, et al. Blood 2003;101:6-14;
5. Byrd et al. Blood 2005;105:49-53.
6. Kay NE, et al. Blood 2007;109(2):405-411.
7. Fischer et al. JCO 2012; 30:3209-16

Chemoimmunotherapy yields suboptimal results for del (17p) CLL

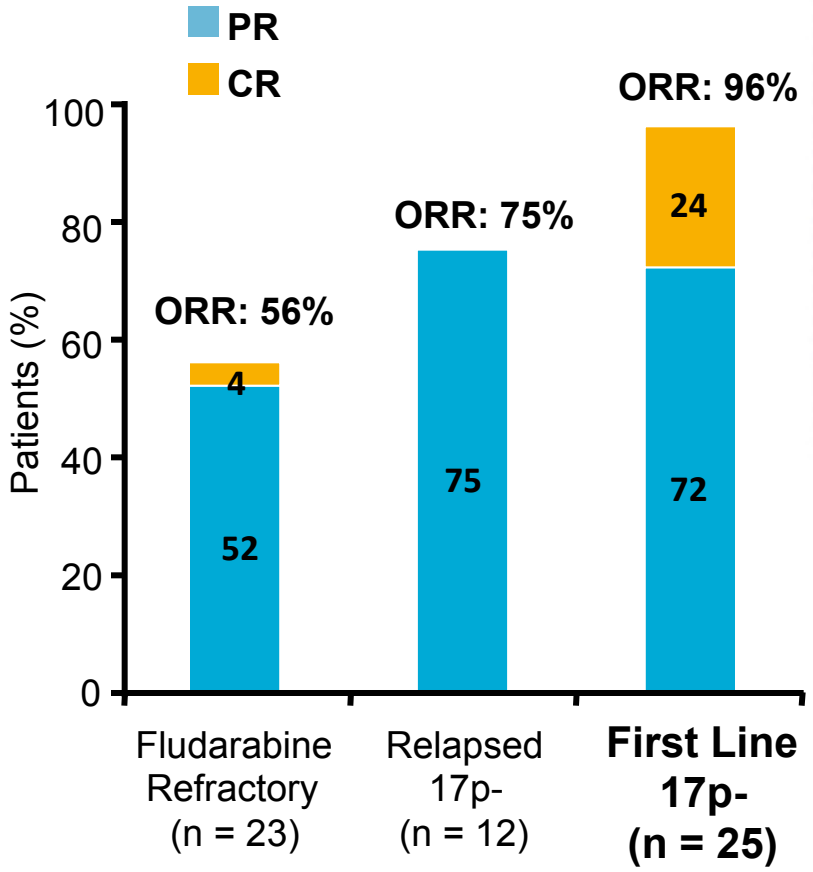
Regimen	N	ORR (%)	CR (%)	Median PFS (months)
FCR-MDA[2,3]	20	70	20	21
FCR-CLL8[1]	21	71	5	11.3
BR[4]	7	43	0	<6

1. Hallek M, et al. Blood 2009;114: Abstract 535.
2. Keating MJ, et al. J. Clin Oncol. 2005;23(18):4079-4083.
3. Tam CS, et al. Blood 2008;112(4):975-908.
4. Fischer et al. JCO 2012; 30:3209-16

CLL20 : Alemtuzumab + Dex Followed by Alemtuzumab or Allo-SCT

- 60 patients evaluable for response
- Median follow-up: 11 mo

Patient Subgroup
Fludarabine refractory (n = 25)
Relapsed 17p- (n = 14)
First line 17p- (n = 25)



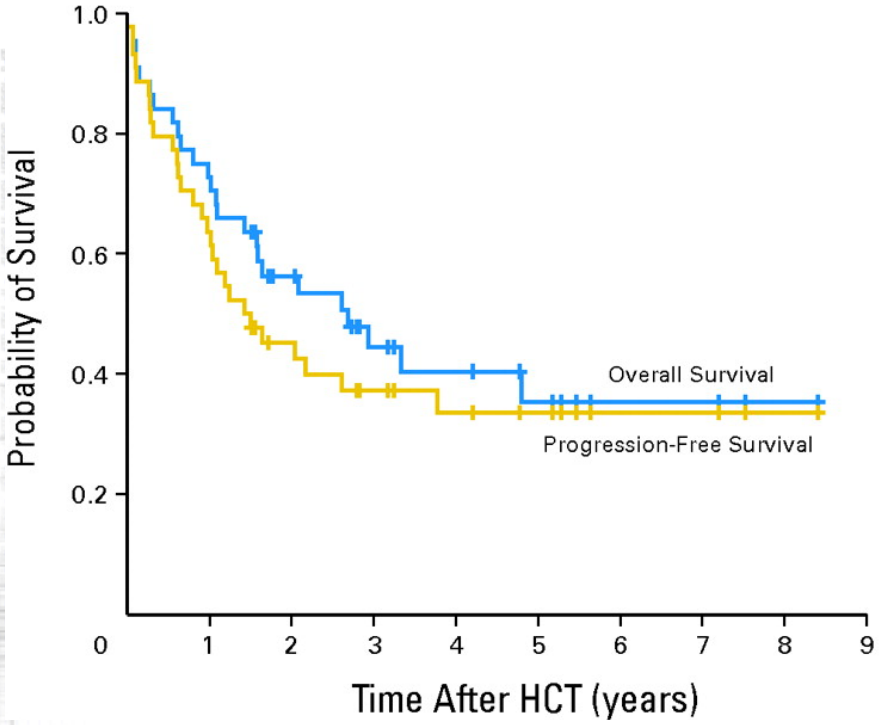
Stilgenbauer S, et al. ASH 2010. Abstract 920.

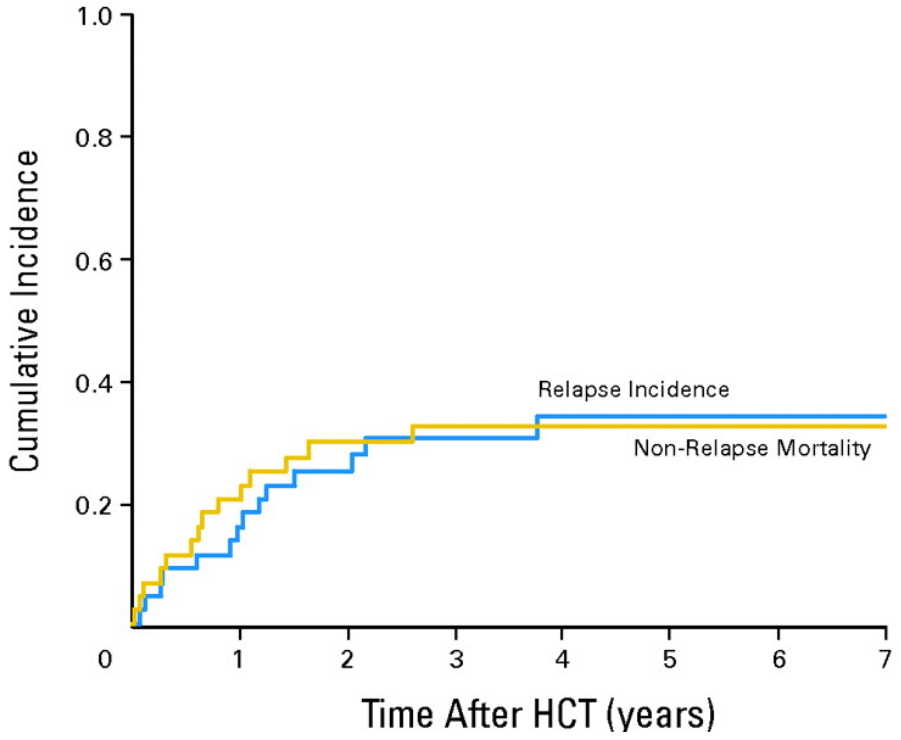
Chemoimmunotherapy for del (17p) CLL

Regimen	N	ORR (%)	CR (%)	Median PFS (months)
Alemtuzumab	11	n/a	64	10.7
Alemtuzumab + dexamethasone	22	100	23	n/a
Alemtuzumab + methylprednisolone	17	88	65	18.3
Rituximab + methylprednisolone	14	100	25	n/a

1. **Hillmen et al. *JCO* 25: 5616 (2007)**
2. **Stilgenbauer S, et al. ASH 2010. Abstract 920.**
3. **Pettitt et al. JCO 2012; 30:1647-1655**
4. **Castro et al. Leukemia 2008; 10:1779-89.**

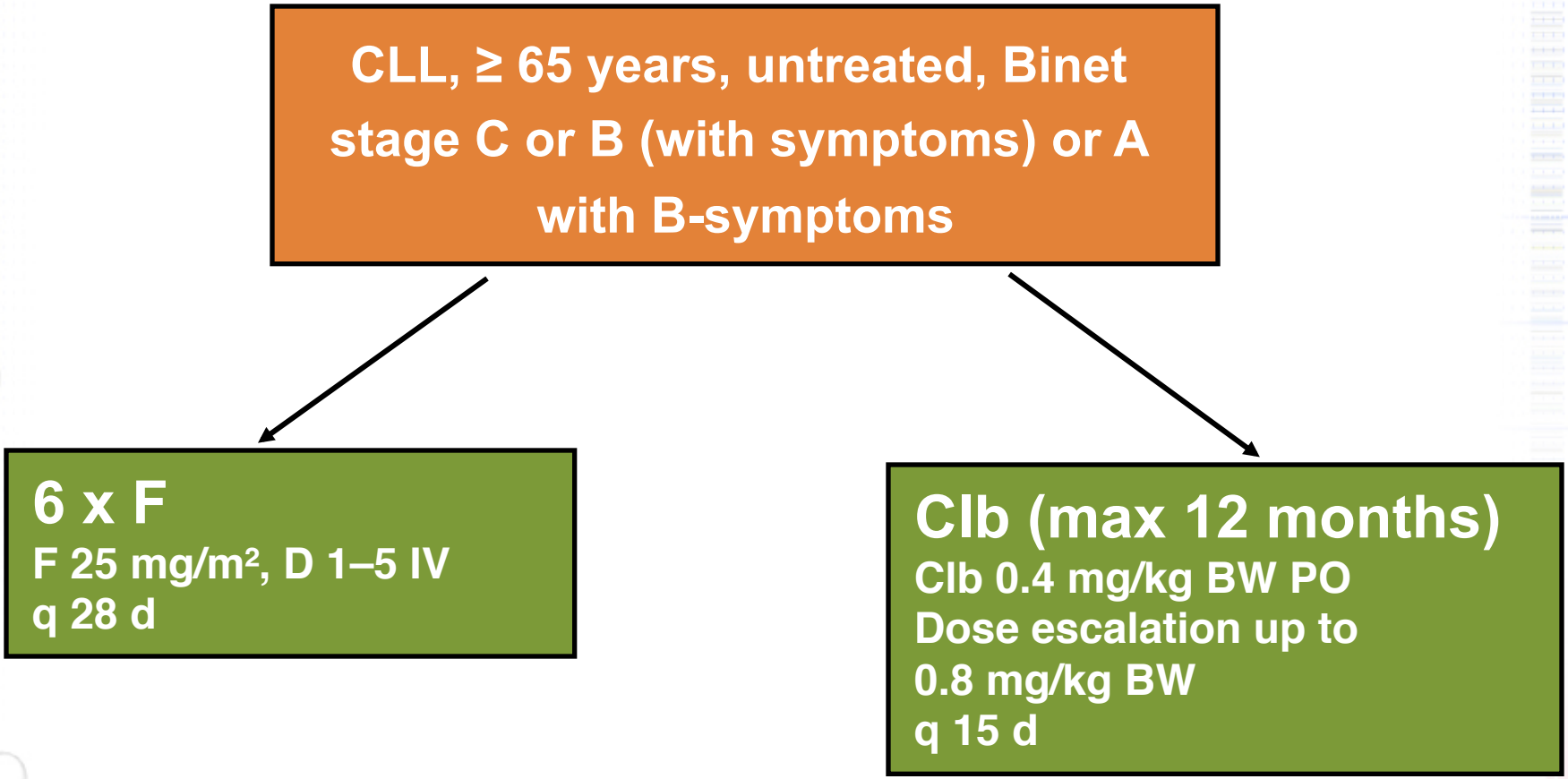
Outcome after allo HCT for del (17p) CLL





Schetelig J et al. JCO 2008;26:5094-5100

CLL5 Protocol of the GCLLSG for Advanced CLL in Older Patients



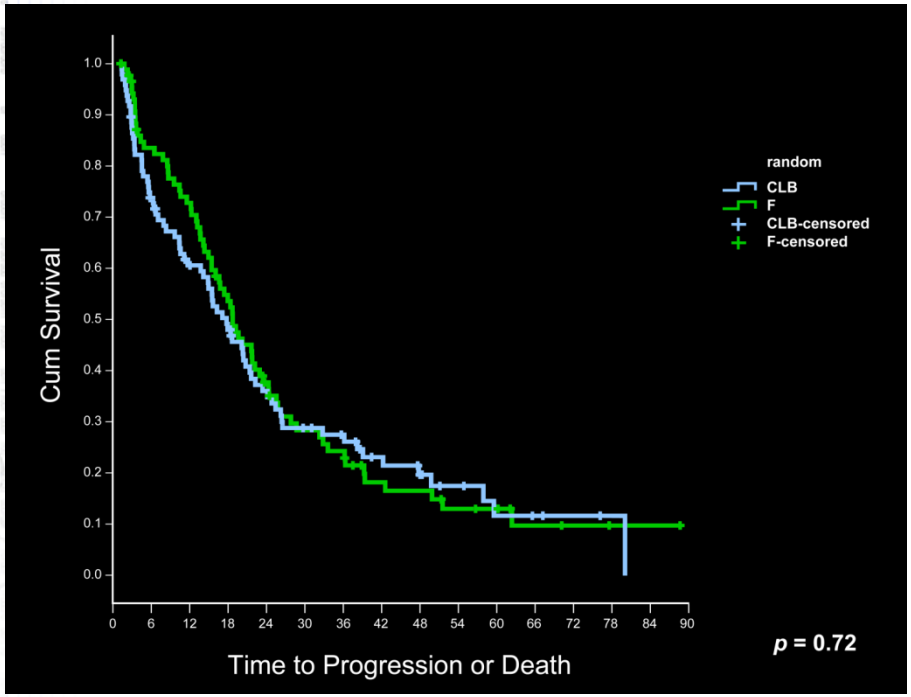
Eichorst et al, Blood 2009.

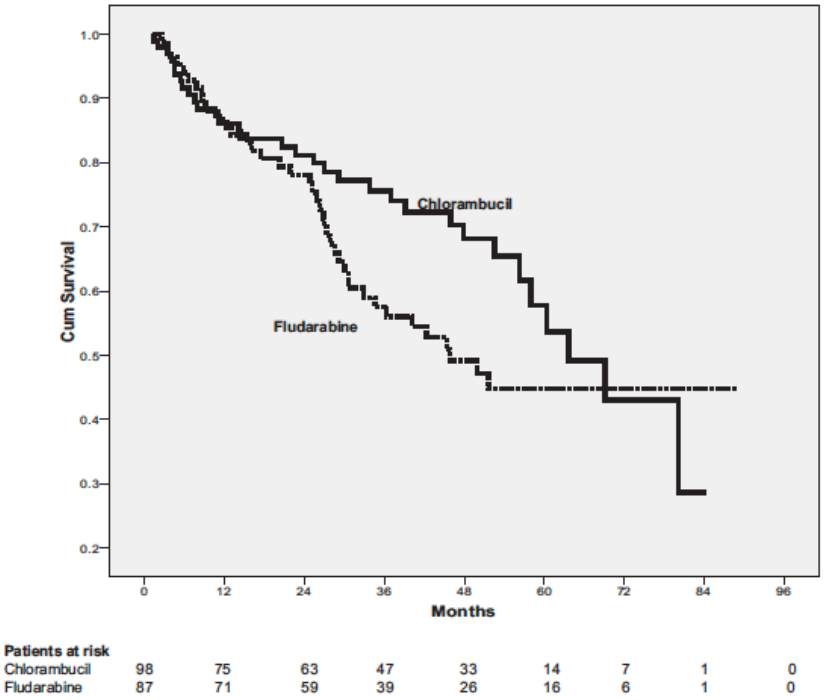
CLL5 Protocol: Response According to NCI Criteria

	Chlorambucil		Fludarabine		
	n	%	n	%	
CR	0	0	6	7	$p = .011$
OR	51	51	67	72	$p < .0013$
NR	49	49	26	28	$p < .001$
Total	100	100	93	100	

Eichorst et al, Blood 2009.

CLL5 Protocol: Survival





Progression defined by the NCI criteria
Median PFS: F 19 months; Clb 18 months

Median observation time = 38 months
Median OS: F 53 months; Clb not reached

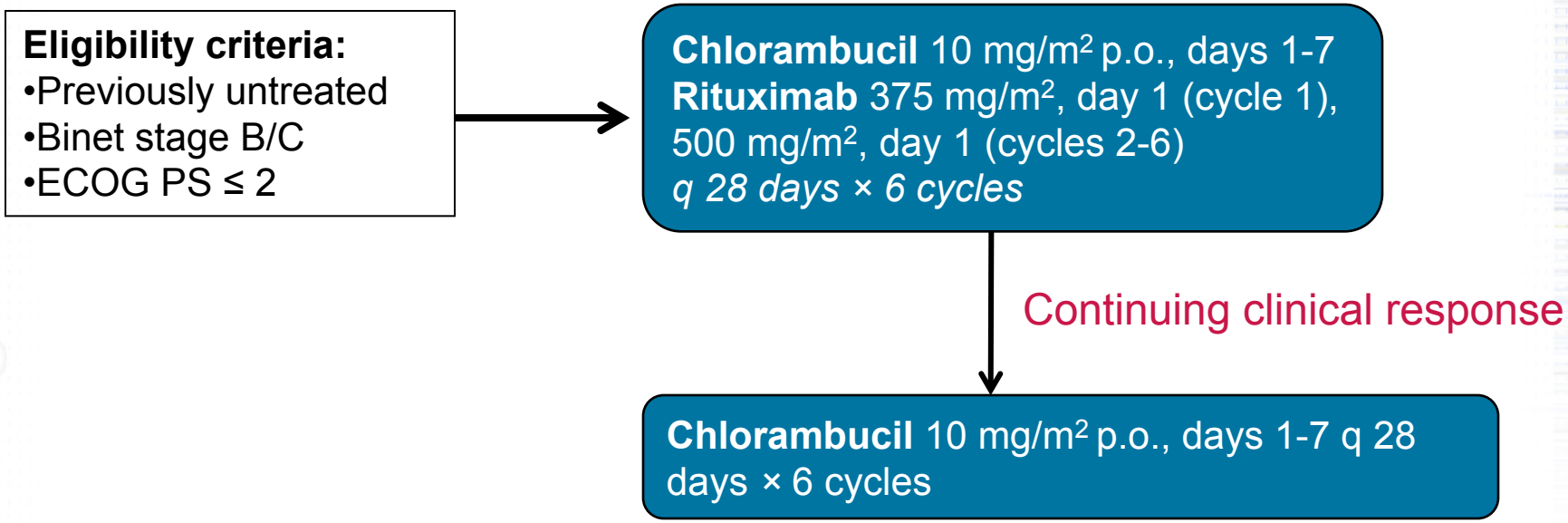
Eichorst et al, Blood 2009.

CALGB data: fludarabine conveys limited benefit to CLL patients >70 yrs

- PFS/OS benefit of fludarabine differs depending on age.
- PFS/OS is not improved with fludarabine versus chlorambucil in patients ≥70 (versus patients ≤70)
- Response rates to FR are dramatically lower among patients ≥ age 70
  - CR: 51% vs. 77%, *P* = 0.02
  - <50% of patients age ≥70 were able to complete the intended six cycles of FR due to toxicity
  - All patients ECOG PS ≤2

Woyach J et al. *JCO* (2013)

Phase II Trial of Chlorambucil Plus Rituximab in Patients With Previously Untreated CLL



- **Primary endpoint: Safety**
- **Secondary endpoints: ORR, PFS, OS, MRD**

Hillmen et al. ASH 2010; abstract 697.

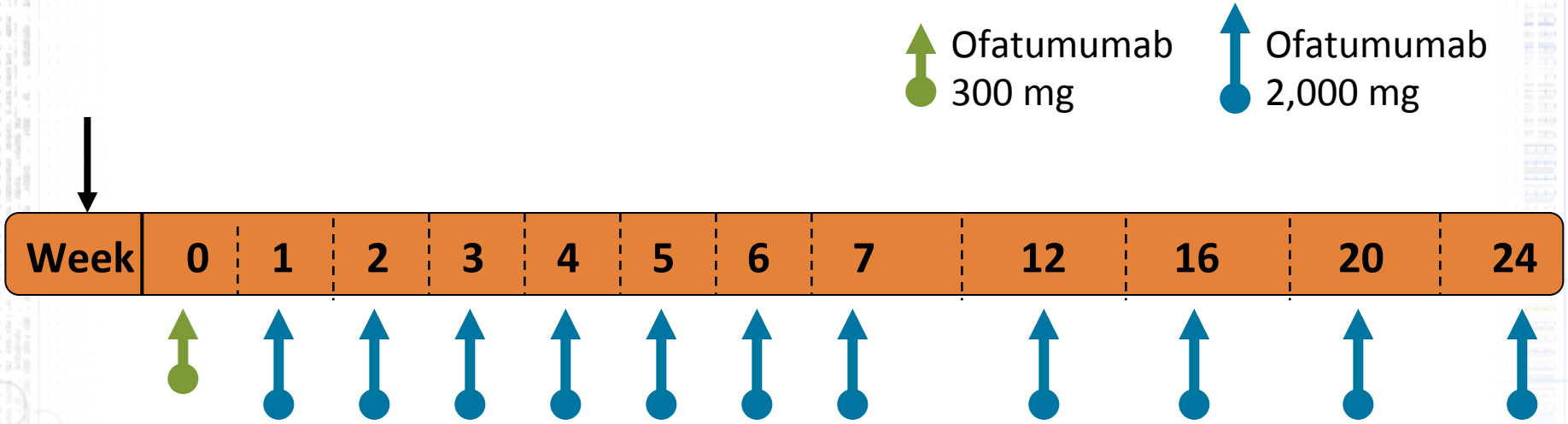
Phase II Trial of Chlorambucil Plus Rituximab in Patients With Previously Untreated CLL

Efficacy	Rituximab/ Chlorambucil (n = 100)	Historical Data on Chlorambucil Alone (n = 200)[a]
Complete Response	12%	6%
Overall Response Rate	80%	66%
Stable Disease/Progressive Disease	17%	30%
Not Evaluable	3%	4%
95% CI for Percentage of Patients Achieving Partial Response or Better	70.8%-87.3%	59.0%-72.5%

- Median PFS: 23.9 months in R-Chl group vs. 18 months in Chl group
- Serious AEs with R-Chl:
  - 57 in 39 patients
  - 13 deaths due to disease progression or treatment-related events

Hillmen et al. ASH 2010; abstract 697.

Ofatumumab in Refractory CLL
Treatment Schedule



Premedication:

- Paracetamol (acetaminophen) 1 g PO or eq
- Antihistamine (cetirizine) 10 mg PO or eq
- Glucocorticoid (prednisolone) 100 mg IV or eq

Median number of infusions: 12 (range, 1–12) for both groups

Wierda et al. *Blood* (2011); Wierda et al. *JCO* (2010)

Ofatumumab in Relapsed CLL
Efficacy

	Fludarabine/ Alemtuzumab-Refractory (n = 95)	Bulky Fludarabine-Refractory (n = 111)
Overall Response Rate[a]	**51%**	**44%**
17p-	**37% (n =27)**	**22% (n =18)**
No 17p-	**56% (n =64)**	**49% (n =89)**
Median PFS	**5.5 months**	**5.5 months**
Median Overall Survival	**14.2 months**	**17.4 months**
Responders	**23 months**	**27.6 months**
Nonresponders	**10.2 months**	**15.5 months**

[a] Independent of age, Rai stage, 11q- status, prior rituximab, and number of prior regimens

Wierda et al. *Blood* (2011); Wierda et al. *JCO* (2010)

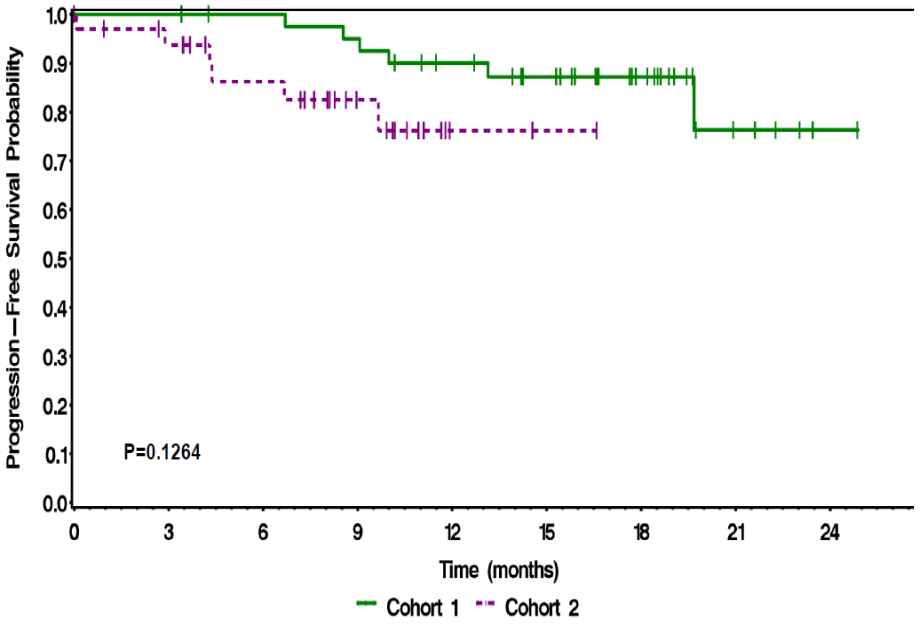
Ofatumumab in Previously Untreated CLL

- Eligibility: age ≥65 years or ineligible/unwilling to receive fludarabine-based therapy
- Treatment plan: 8-weeks induction followed by q2month maintenance x 12 doses
- Cohort 1: 300 mg first dose, 2000 mg subsequent
  Cohort 2: 300 mg first dose, 1000 mg subsequent
- ORR: 62% in cohort 1; 30% in cohort 2
- ORR: del(11q22.3) or del(17p13.1) 33%
- Toxicities were mainly hematologic;
  - G3/4 heme toxicities in 23% of cohort 1 and 21% of cohort 2.
  - G3/4 non-heme toxicities in 16% of cohort 1, 6% of cohort 2

Flinn et al. ASH Annual Meeting 2012. Abstract 719

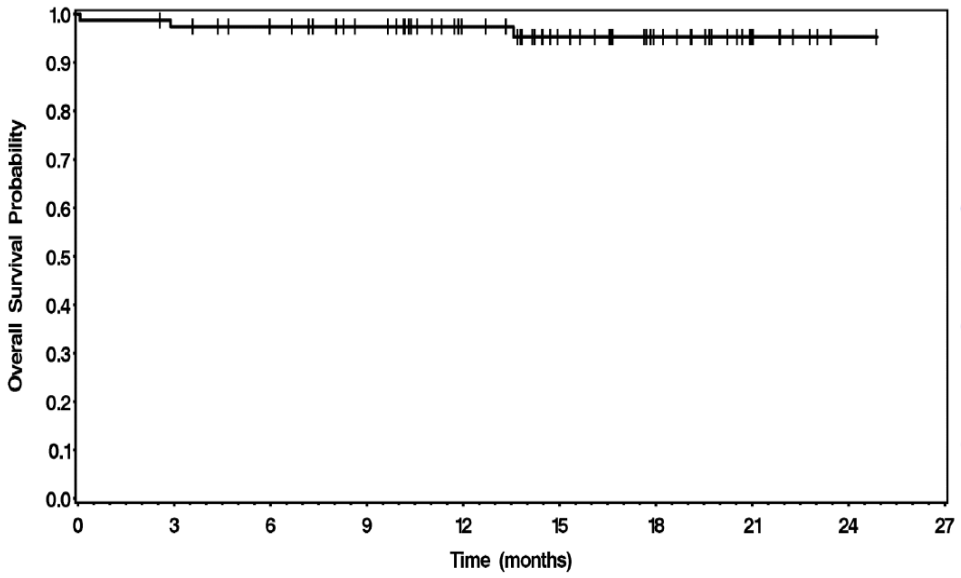
Ofatumumab in Previously Untreated CLL

PFS



12 mo PFS: 90% **Cohort 1**
76% **Cohort 2**

OS



15 mo OS: 96%

Flinn et al. ASH Annual Meeting 2012. Abstract 719

Lenalidomide in CLL Salvage

	RPCI N = 45 (32 evaluable)	MDACC N = 44
Starting dose	25 mg or 5 mg	10 mg
Median dose	TBD[a]	10 mg
Response, %		
CR	6 (18)[b]	3 (7)
nPR		1 (2)
PR	13 (40)	10 (23)
OR	19 (57.5)	14 (32)
SD	5 (14)	11 (25)

Chanan-Khan et al (2007); Ferrajoli et al (2008)

Phase II Trial of Lenalidomide/Rituximab in Patients With Relapsed CLL: Efficacy

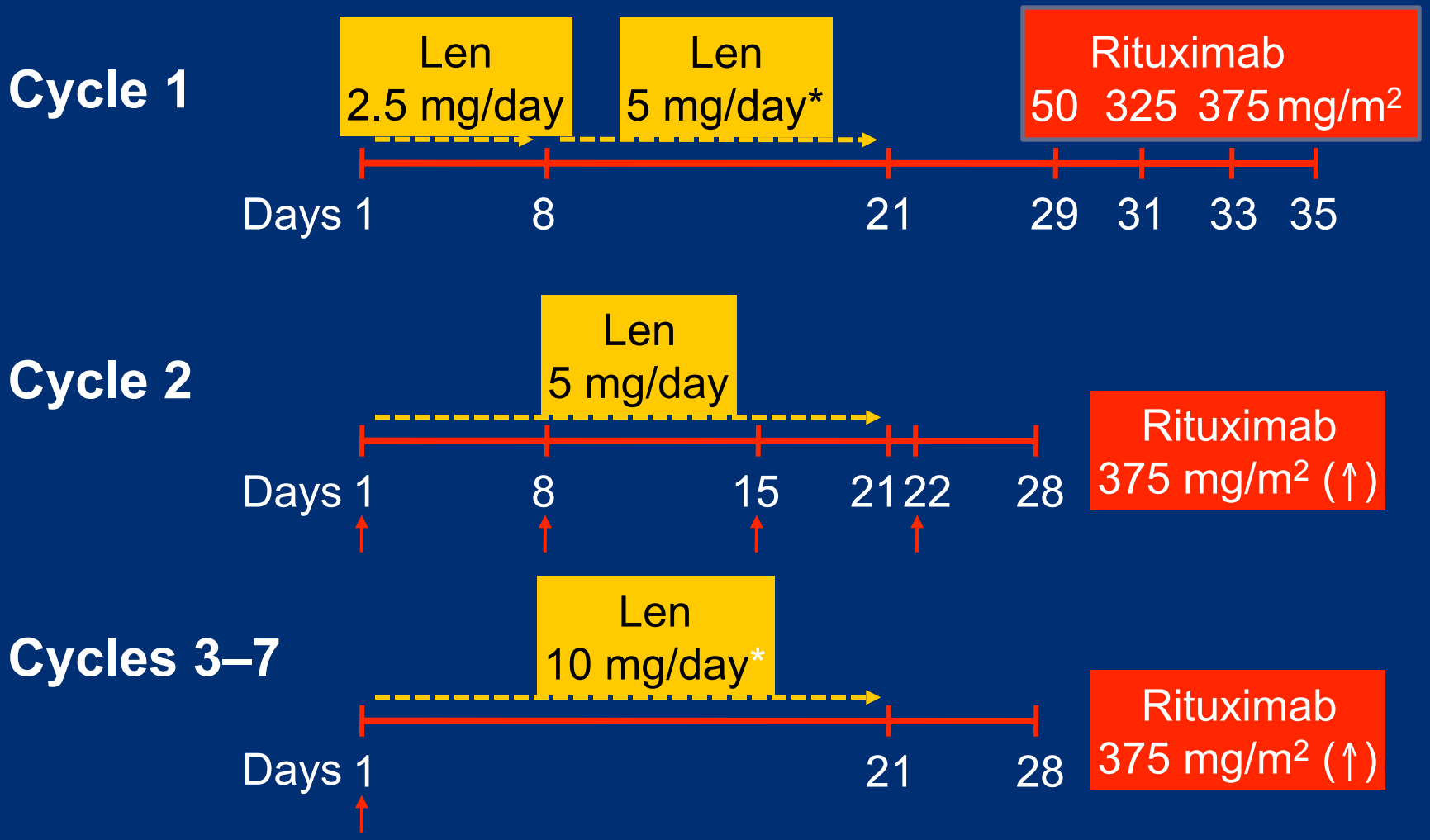
Rituximab: 375 mg/m^2, days 1, 8, 15, 22 (cycle 1); day 1 (cycles 3-12), q 4 weeks

Lenalidomide: 10 mg/day starting on day 9 of cycle 1, continuing until progression

	Cycle 6 (n = 44)	Cycle 12 (n = 22)
ORR	28 (64%)	14 (64%)
CR	0	2 (9%)
nPR	7 (16%)	4 (18%)
PR	21 (48%)	8 (36%)
SD	6 (14%)	1 (4%)

- Median OS: not reached; survival rate: 95%
- Median TTF: 12 months
- All patients received prophylaxis for TLS with allopurinol 300 mg/day on days 1-14 of cycle 1; no antibiotic or antiviral prophylaxis was given.

Treatment Schema

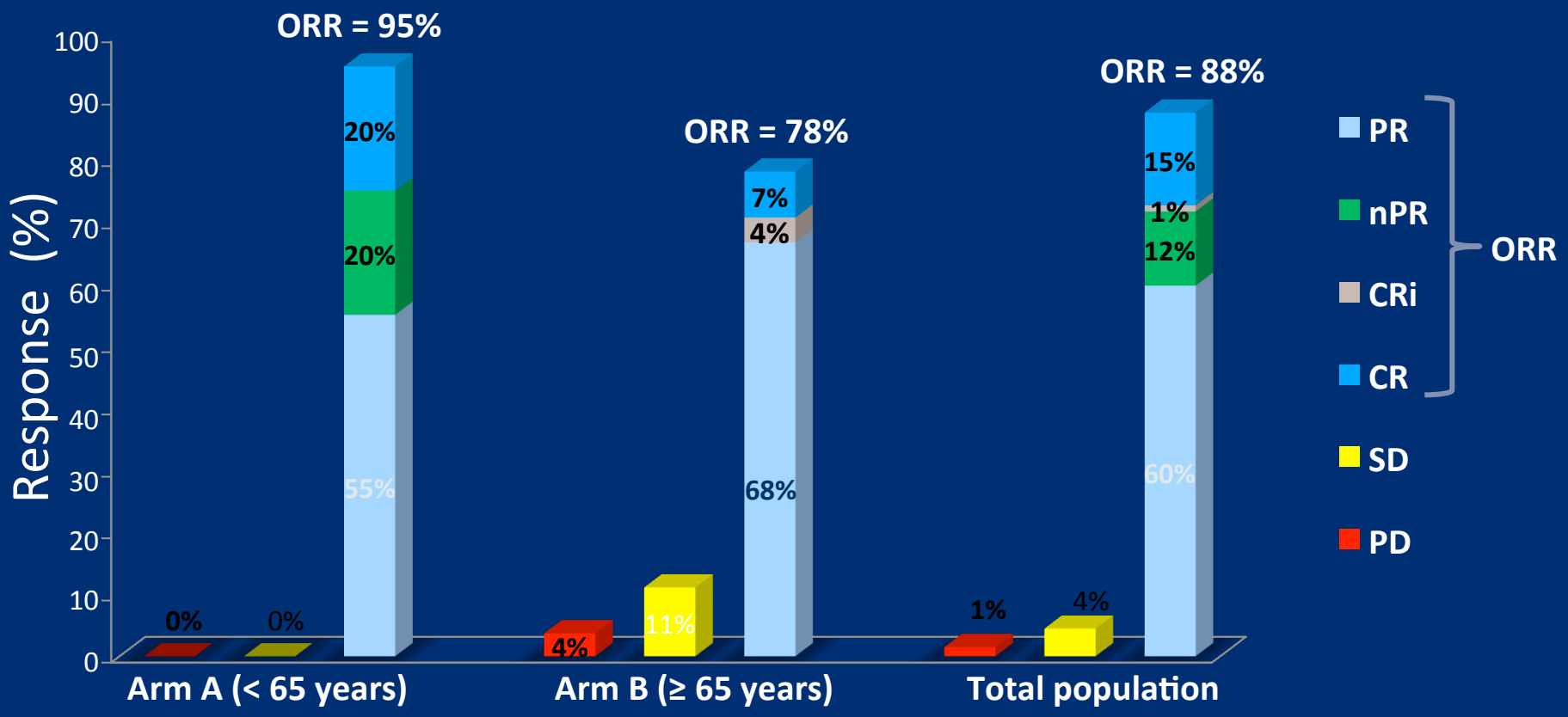


*Len dose increased as tolerated.

James, et al. ASH 2011, Abstract 291

Len, lenalidomide.

Final Response to Therapy



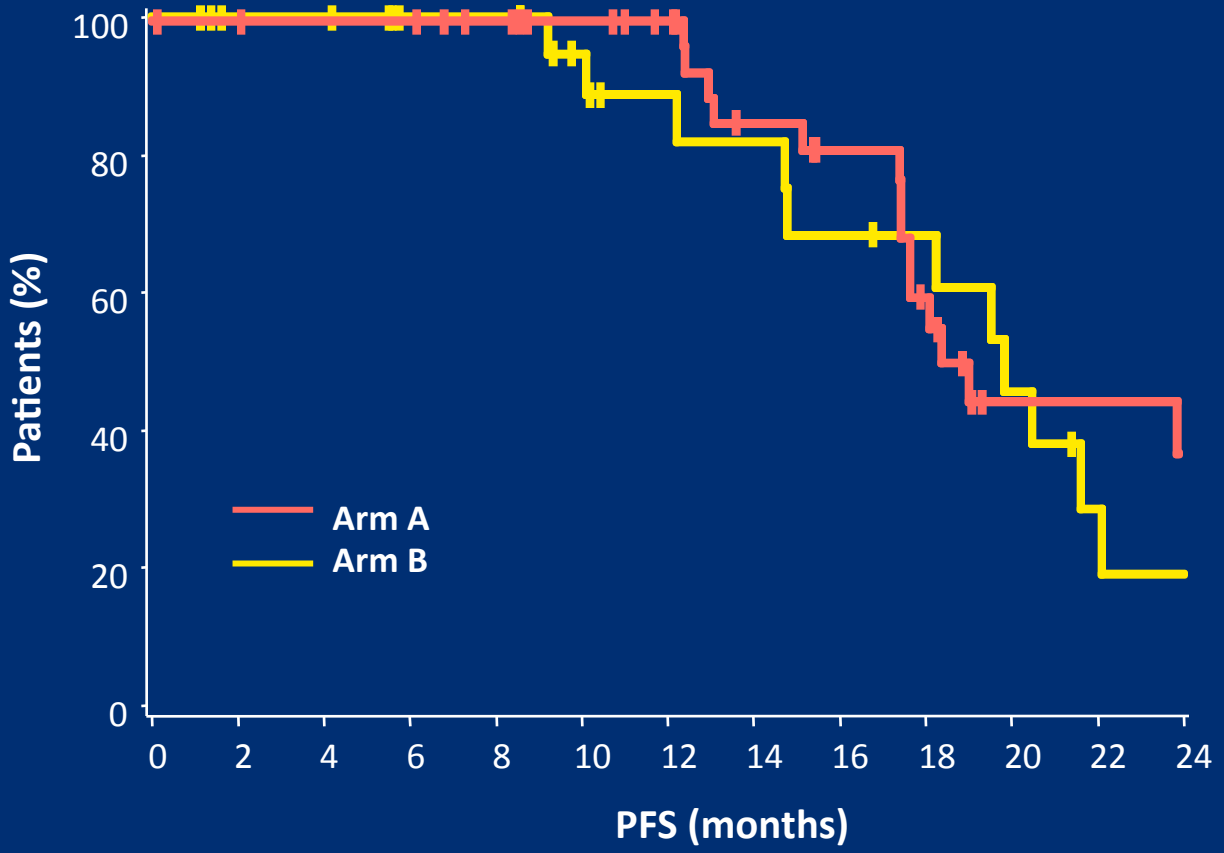
- Arm A (< 65 years)
  - CR: 20% (90% CI 10–33)
  - ORR: 95% (90% CI 85–99)
- Arm B (≥ 65 years)
  - CR: 7% (90% CI 1–22)
  - ORR: 78% (90% CI 61–90)

CRi, CR with incomplete hematopoietic recovery; nPR, nodular PR; PD, progressive disease; PR, partial response; SD, stable disease.

James, et al. ASH 2011, Abstract 291

Lenalidomide + Rituximab in First-line CLL

Progression-free Survival



Arm A (< 65 years)

- n=40 patients
- 16 events
- Median PFS: 19 months
- Median follow-up: 18 months

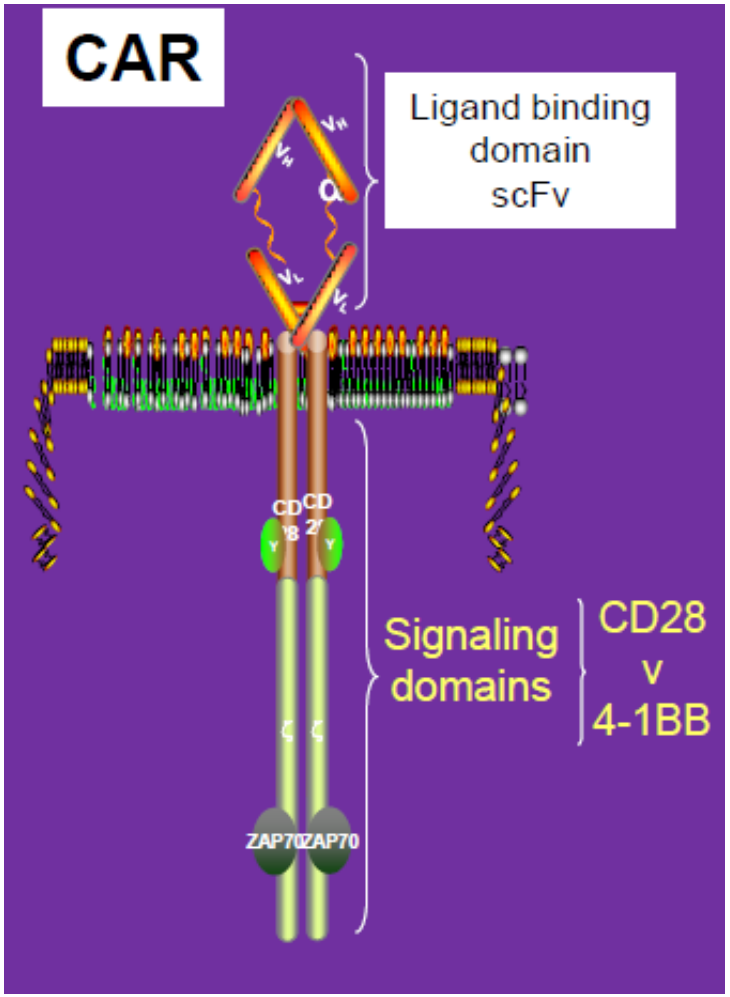
Arm B (≥ 65 years)

- n=29 patients
- 13 events
- Median PFS: 20 months
- Median follow-up: 17 months

James, et al. ASH 2011, Abstract 291

Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

- CAR contains an extracellular domain targeting CD19, CD3 zeta chain, and costimulatory domain containing 4-1BB or CD28



Porter et al. NEJM (2011) 365: 725-733
Kalos et al. ASH 2012, Abstract 756
Porter et al. ASH 2012, Abstract 717
Grupp et al. ASH 2012, Abstract 2604

Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

- N=10; Median age 66
- Chemotherapy 4-7 days pre-infusion
  - FC (1); PC (5) B (4)
- Median dose of CAR cells $1.4x10^8$
- Massive in vivo expansion (1000-10000 fold)
- B cell aplasia
- All responding patients developed cytokine release syndrome
  - IL6, IFNγ, IL2R
  - Treated with steroids, tocilizumab

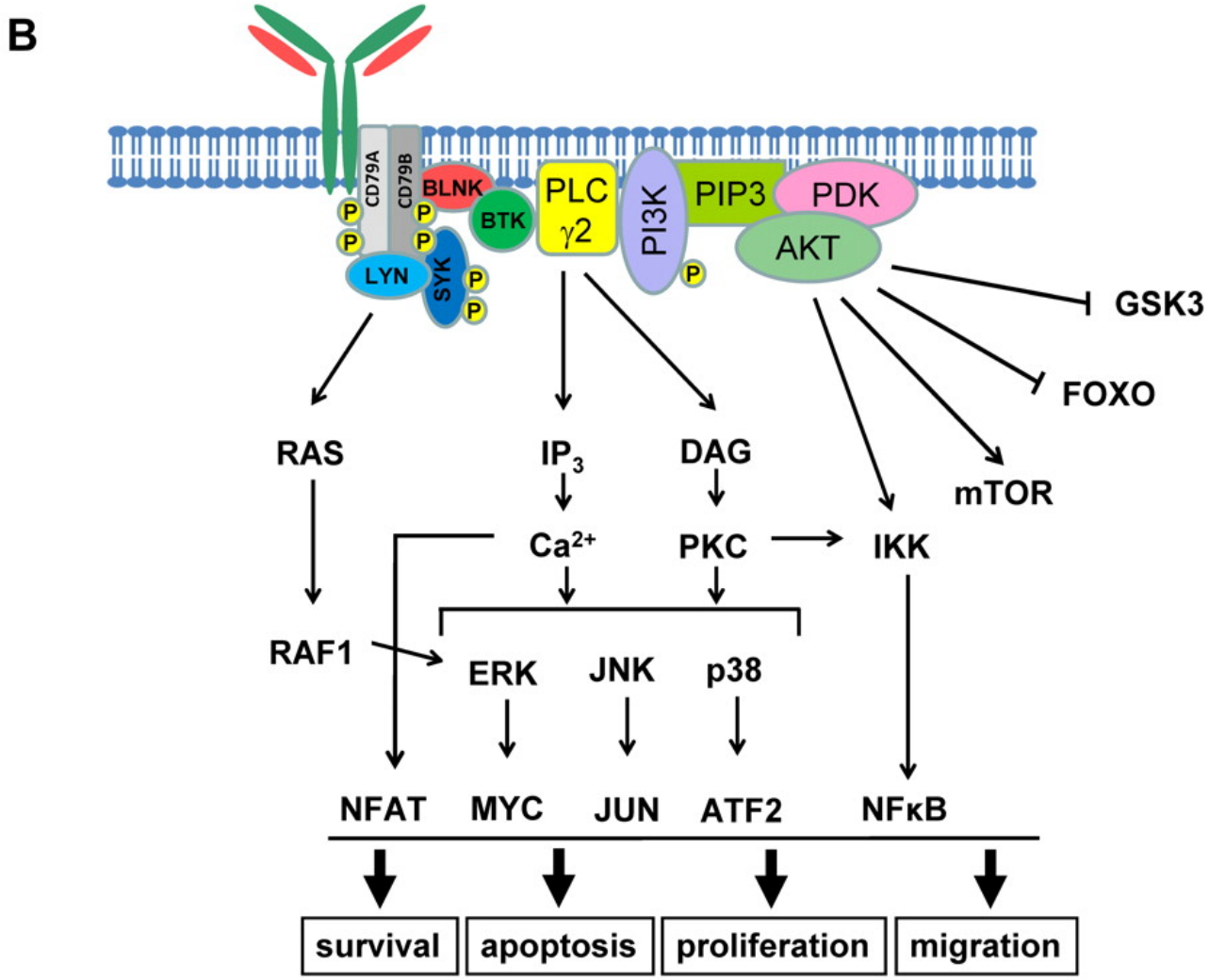
Kalos et al. ASH 2012, Abstract 756; Porter et al. ASH 2012, Abstract 717; Grupp et al. ASH 2012, Abstract 2604

Chimeric Antigen Receptor (CAR) T-Cells in Relapsed/Refractory CLL

UPN	Blood	Marrow	Nodes	Expansion	Comments	Max Resp
01	NED	NED	NED	>3 log	MRD* neg	CR 28 mo+
02	NED	NED	NED	>3 log	MRD* neg	CR 27 mo+
03	PR	PR	PR	2 log		PR 4 mo
04	PR	PR	PR	2 log		PR 4 mo
05	NR	NR	NR	<2 log		NR
06	NR	NR	NR	<2 log		NR
09	NED	NED	NED	>3 log	MRD* neg	CR 7 mo+
10	NED	NED	PR	2 log	Bulky nodes	PR 3 mo +
12	NED	NED	PR	2 log	Bulky nodes	PR 2 mo +
14	ne	ne	ne			ne

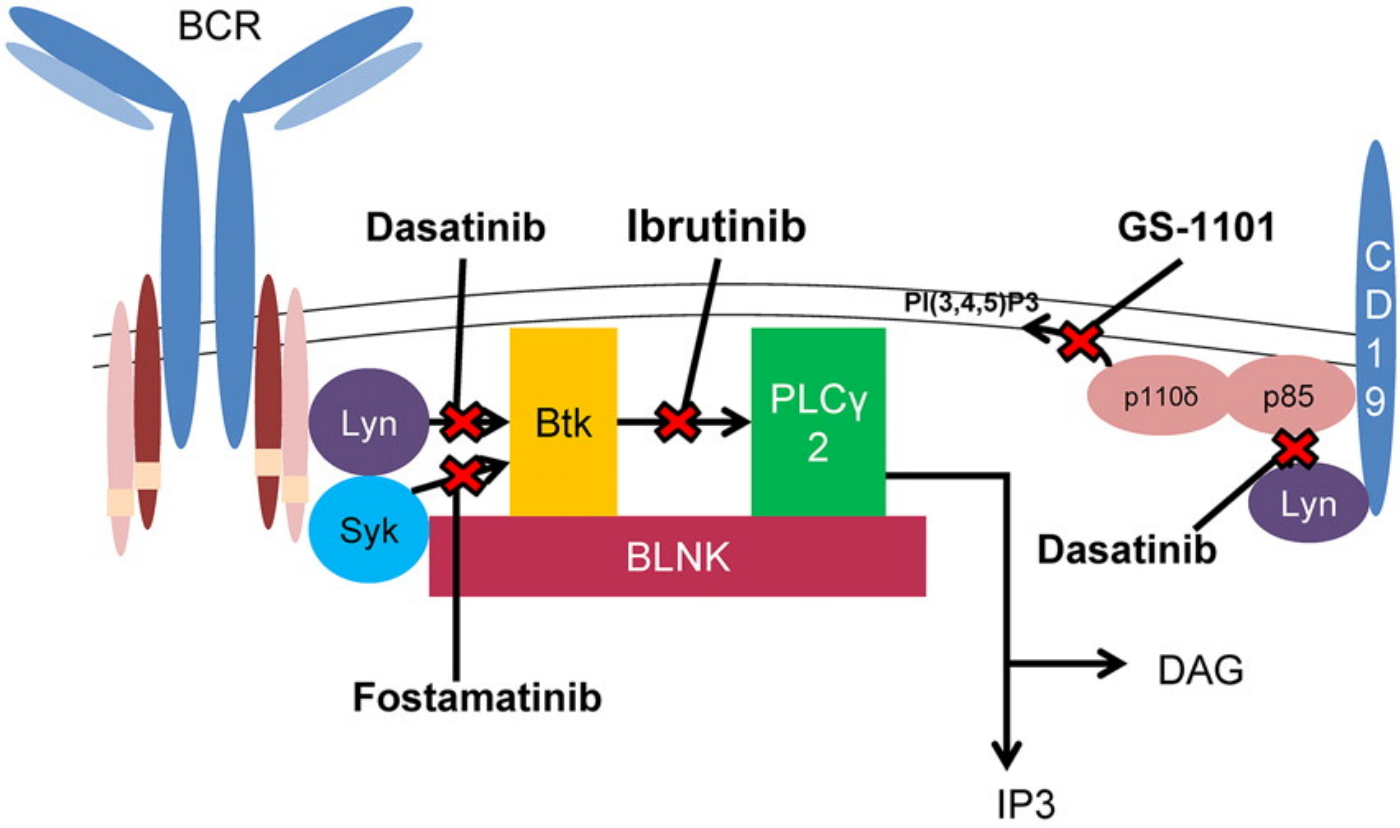
Porter et al. ASH Annual Meeting 2012, Abstract 717

B-cell receptor signalling in CLL



Stevenson F K et al. Blood 2011;118:4313-4320

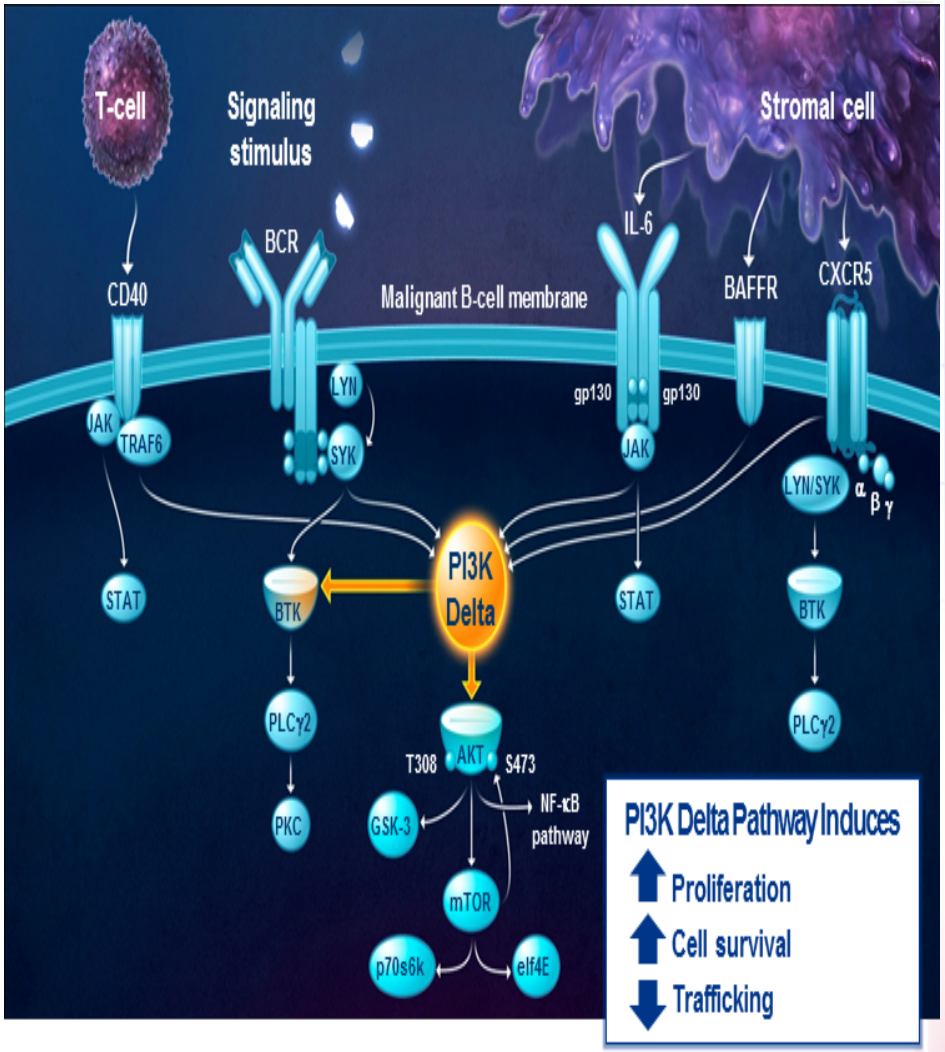
Kinase inhibitors in CLL



Woyach J A et al. Blood 2012;120:1175-1184

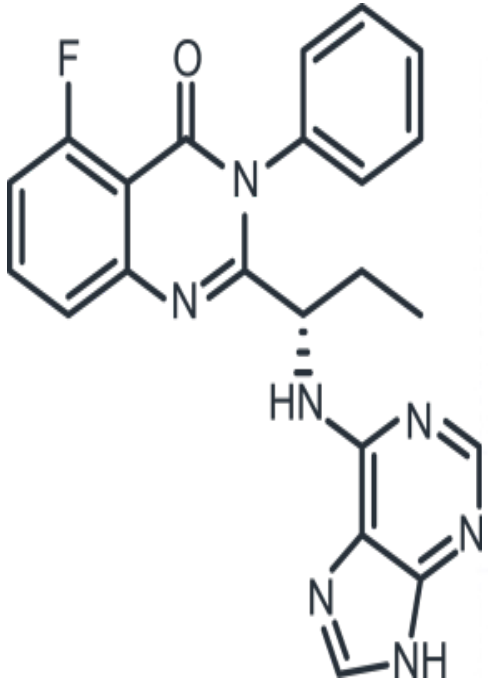
Rationale for Targeting PI3K-δ in CLL

- PI3K-δ knock out has B-cell phenotype
- PI3-kinase ↑ in CLL vs normal B-cells
- PI3K-δ inhibition in CLL cells promotes
  - ↑ Apoptosis
  - ↓ Proliferation
  - ↓ Chemokines
  - ↓ Microenvironment response



Herman S et al: Blood 2010
Lanutti B, et al: Blood 2011

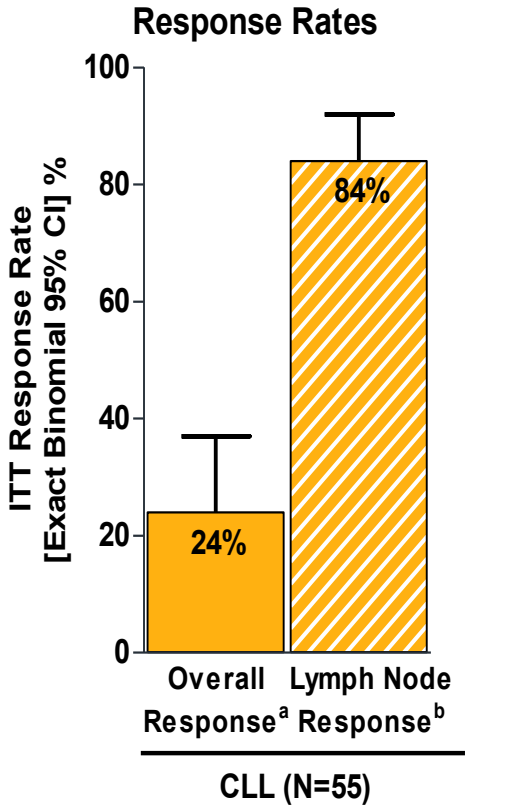
CAL-101/GS-1101



- Selective orally available PI3K-δ inhibitor
- Finding eventual dose (150 mg BID) in CLL
- No definitive DLT identified in CLL but transient, reversible transaminitis early in therapy most problematic in NHL

Herman S et al: Blood 2010
Lanutti B, et al: Blood 2011

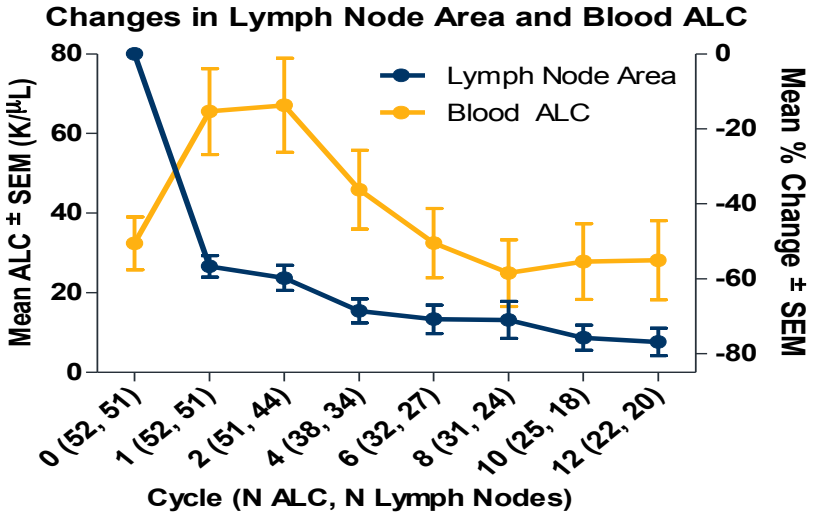
GS-1101 Response in CLL

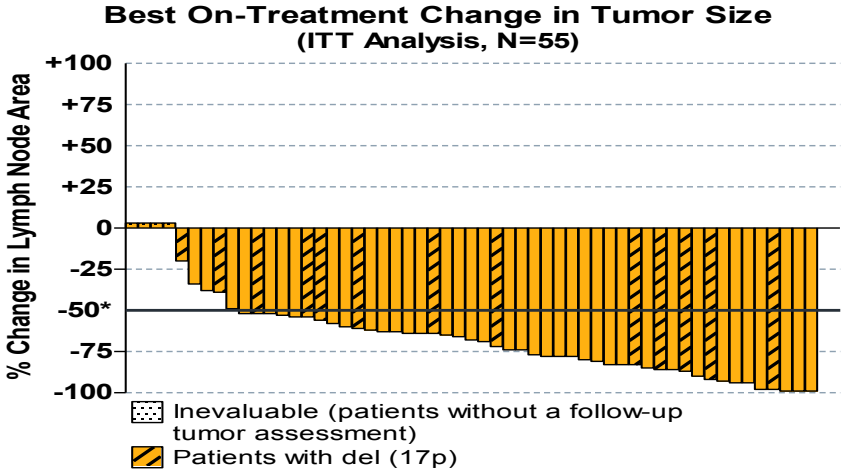


[a] IWCLL response criteria

[b] Decrease by 50% in the nodal SPD

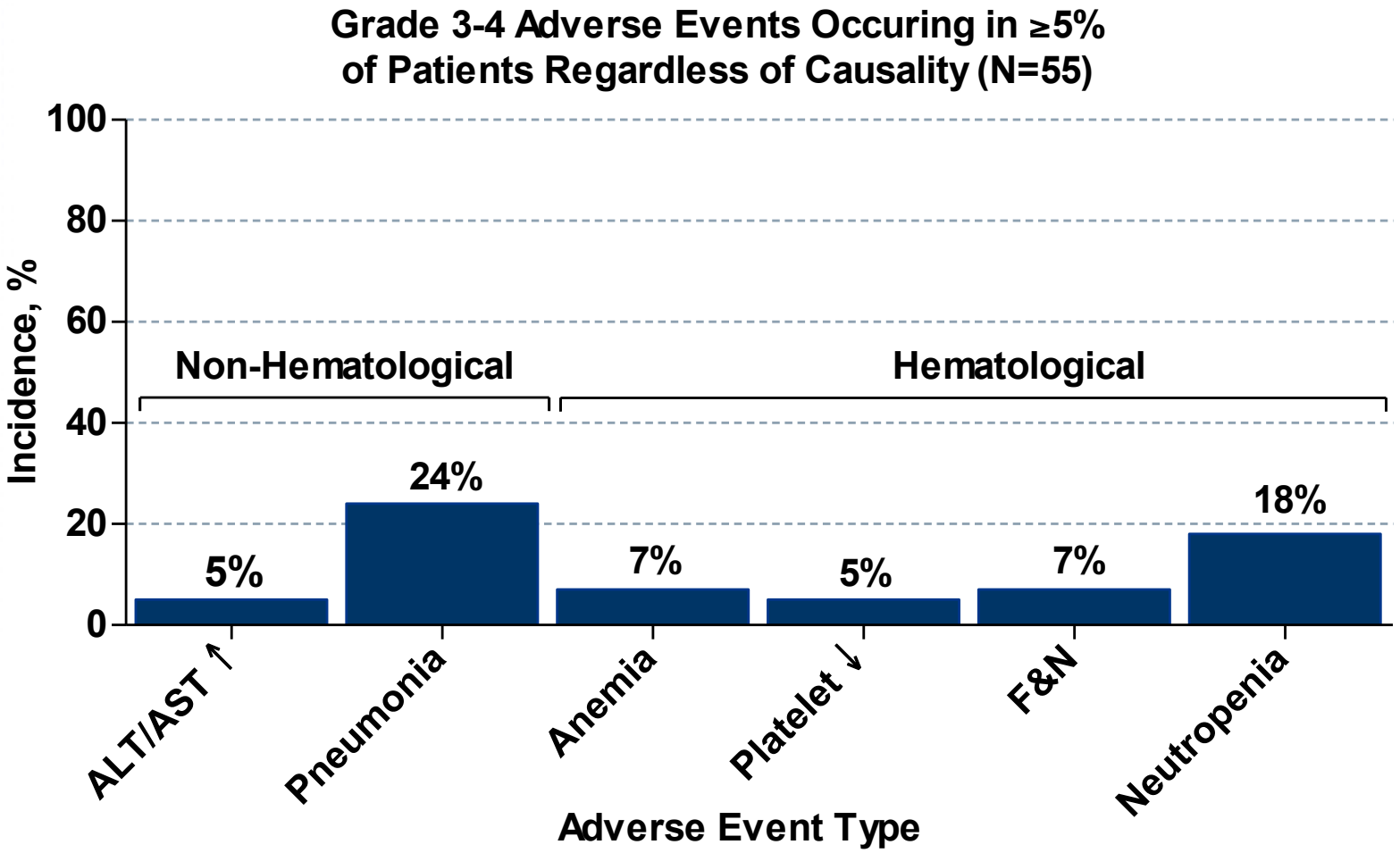
Hallek, Blood June 2008





Coutre S, et al: ASCO 2011

GS-1101 Grade 3-4 Toxicity



Coutre S, et al: ASCO 2011

CAL-101 (GS-1101) Has Been Evaluated as Monotherapy and Combination Therapy in Patients with Previously Treated CLL

Phase 1b
Single-agent Study

GS-1101
50 to 350 mg
BID

Phase 1b
Combination Study

GS-1101
100 or 150 mg
BID
+
Rituximab
375 mg/m^2
weekly
x 8 weeks

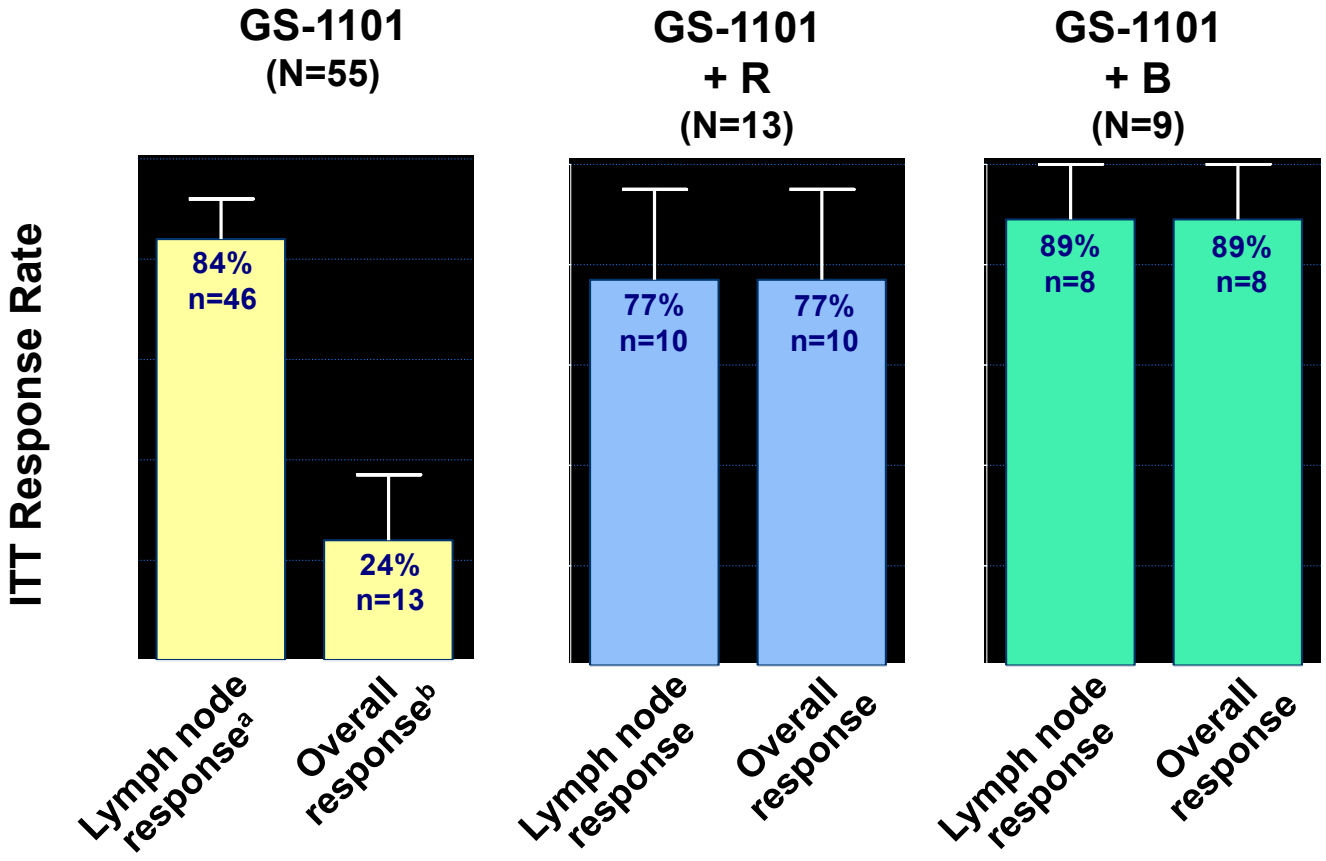
GS-1101
100 or 150 mg
BID
+
Bendamustine
90 mg/m^2
Days 1,2 Q 4 weeks
x 6 cycles

Designs: Phase 1-2 dose-ranging trials

Endpoints: Recommended dosing regimen, safety, antitumor activity

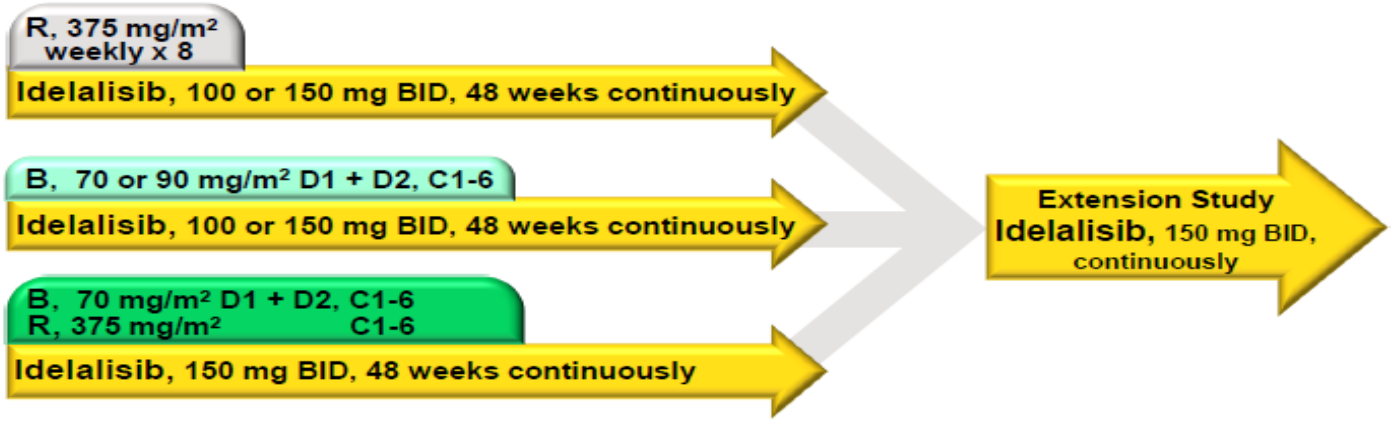
Follow-up: After 48 weeks, patients who continue to benefit can continue GS-1101 single-agent therapy on an extension study

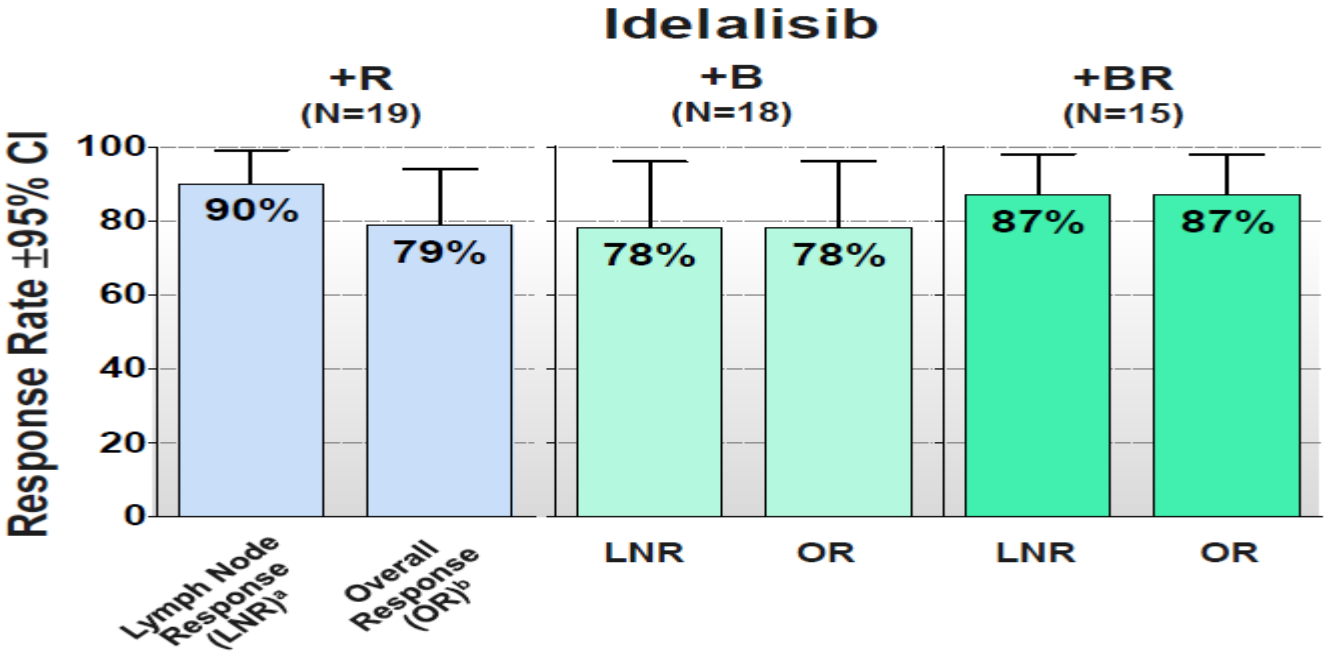
Combinations of GS-1101 with Rituximab or Bendamustine Significantly Increased Overall Response



[a] Decrease by ≥50% in the nodal SPD
[b] Response by IWCLL criteria [Hallek 2008]

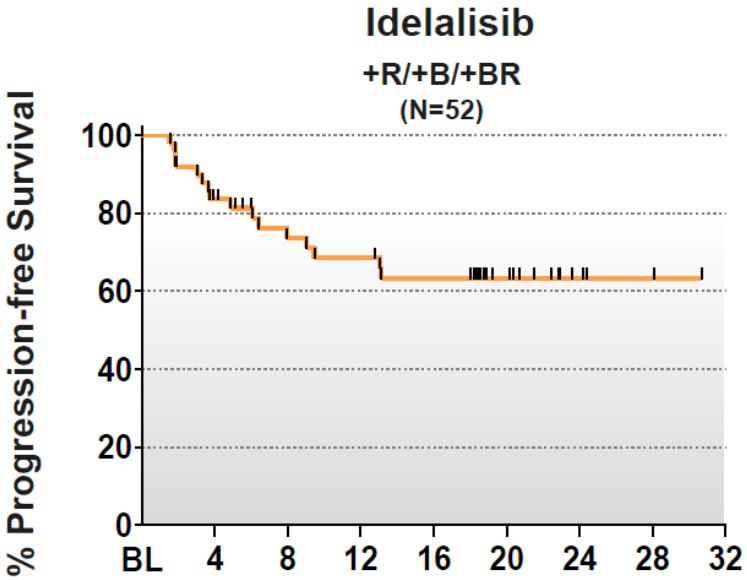
Idelalisib Combinations in Relapsed CLL





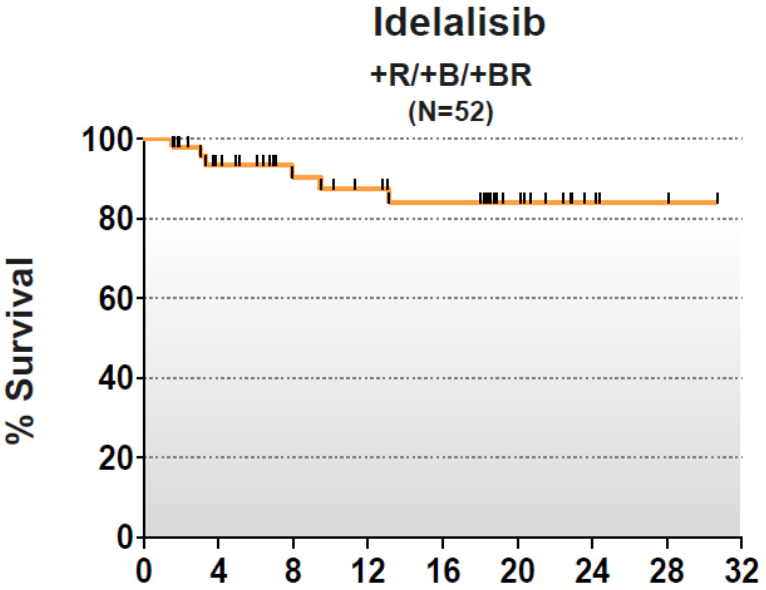
Coutre et al. ASH Annual Meeting 2012, Abstract 191

GS-1101 (Idelalisib; CAL-101) in Relapsed/Refractory CLL



PFS

Median PFS not yet reached
PFS 2 years: 63.4%

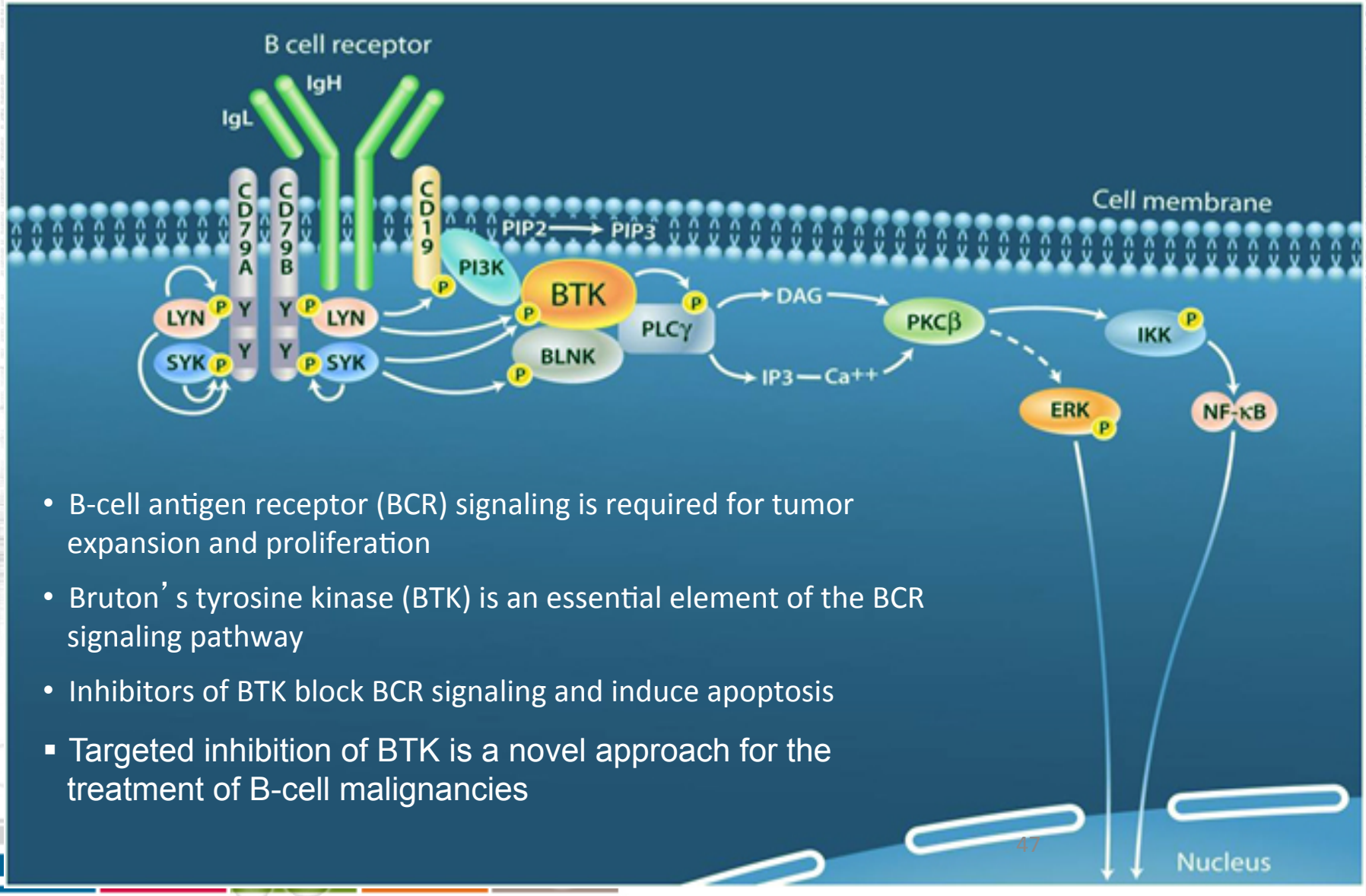


OS

Median OS not yet reached
OS 2 years: 84.0%

Coutre et al. ASH Annual Meeting 2012, Abstract 191

Bruton's Tyrosine Kinase (BTK)
A critical kinase for lymphoma cell survival and proliferation



- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- Bruton's tyrosine kinase (BTK) is an essential element of the BCR signaling pathway
- Inhibitors of BTK block BCR signaling and induce apoptosis
- Targeted inhibition of BTK is a novel approach for the treatment of B-cell malignancies

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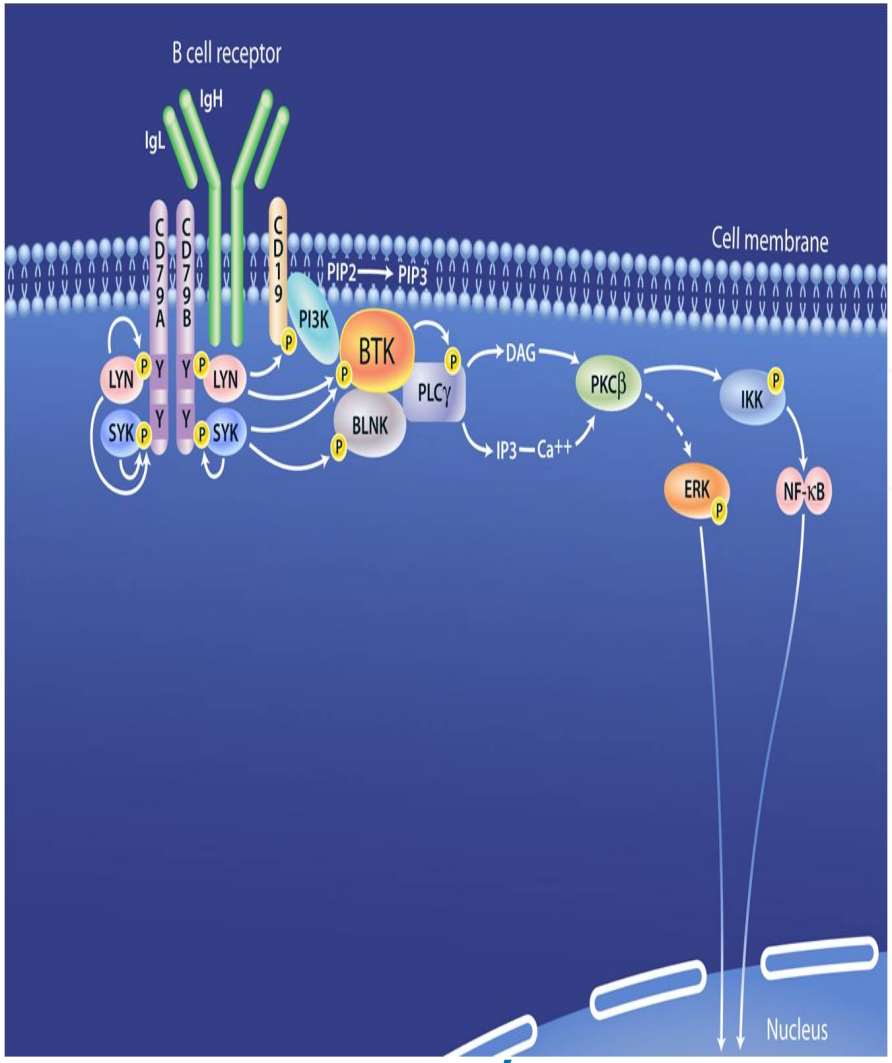
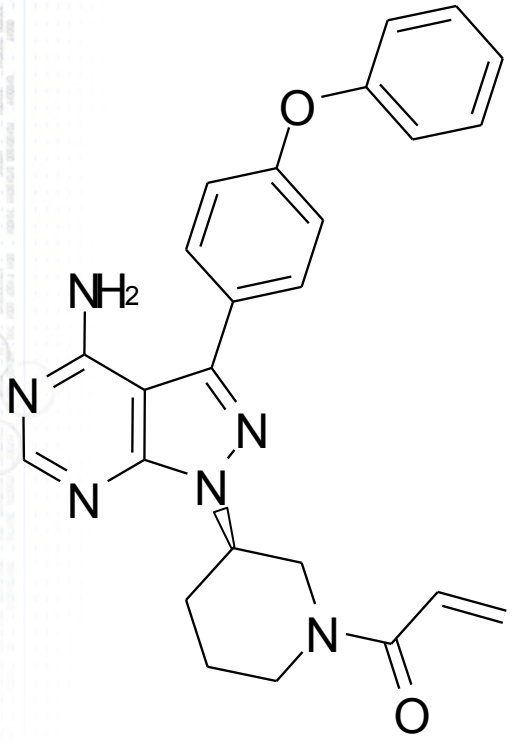
Rationale for Targeting BTK in CLL

- Loss of BTK has B-cell specific phenotype in mice & humans
- Inhibition of BTK inhibits PI3K, MAPK, and NF-kB
- BTK inhibition in CLL cells promotes
  - ↑ Apoptosis
  - ↓ Proliferation
  - ↓ Chemokines
  - ↓ Microenvironment response



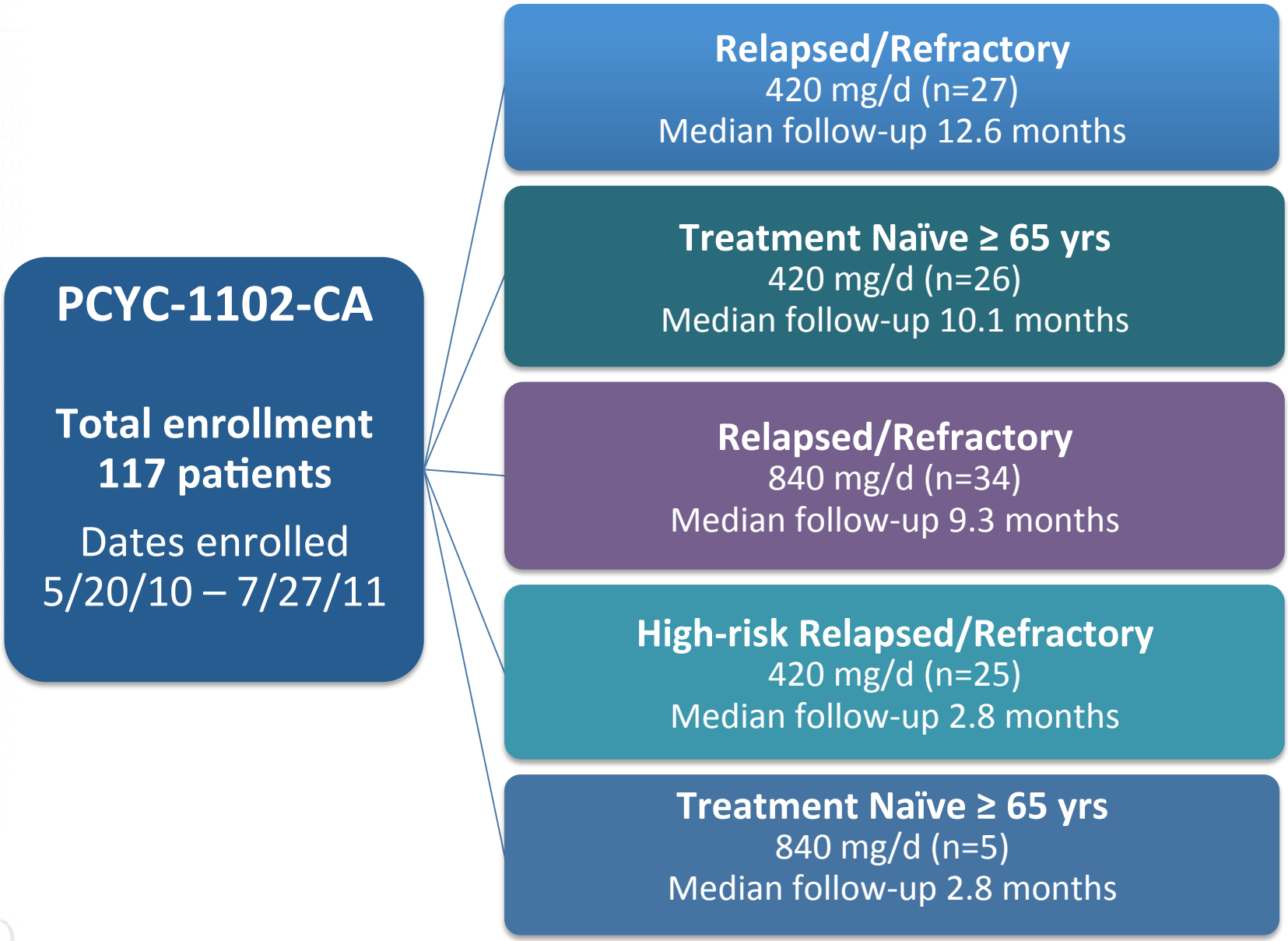
Herman S, et al: Blood 2011
Ponader S, et al: Blood 2012
de Rooij MF, et al: Blood 2002

PCI-32765: A Potent Btk Inhibitor

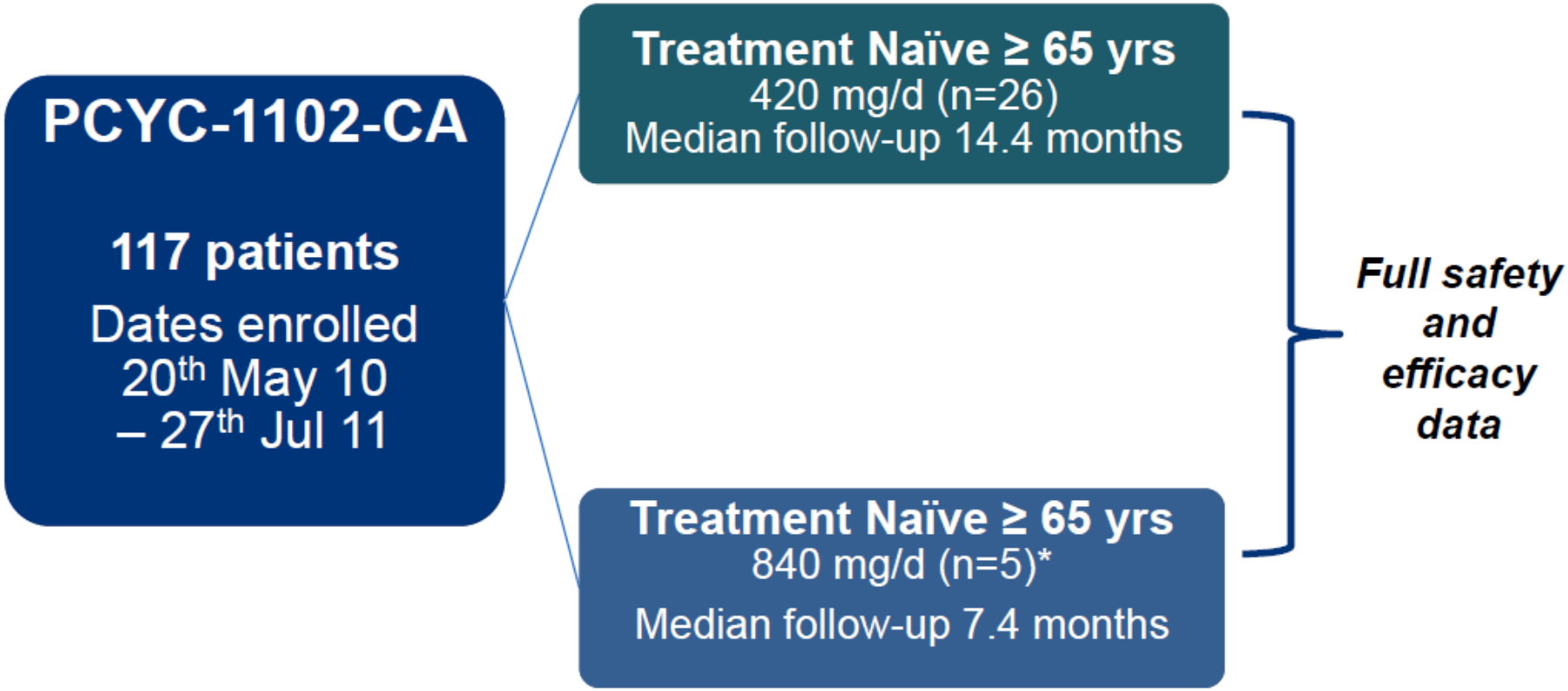


- Forms a specific and irreversible bond with cysteine-481 in Btk
- Potent irreversible Btk inhibition with IC_{50} = 0.5 nM
- Inhibits BCR signaling and active in spontaneous canine model of lymphoma
- Orally available
- Once daily dosing results in 24-hr sustained target inhibition

Honigberg LA et al: Proc Natl Acad Sci U S A.107:13075-80, 2010


PCYC-1102-CA
Total enrollment
117 patients
Dates enrolled
5/20/10 – 7/27/11
Relapsed/Refractory
420 mg/d (n=27)
Median follow-up 12.6 months
Treatment Naïve ≥ 65 yrs
420 mg/d (n=26)
Median follow-up 10.1 months
Relapsed/Refractory
840 mg/d (n=34)
Median follow-up 9.3 months
High-risk Relapsed/Refractory
420 mg/d (n=25)
Median follow-up 2.8 months
Treatment Naïve ≥ 65 yrs
840 mg/d (n=5)
Median follow-up 2.8 months

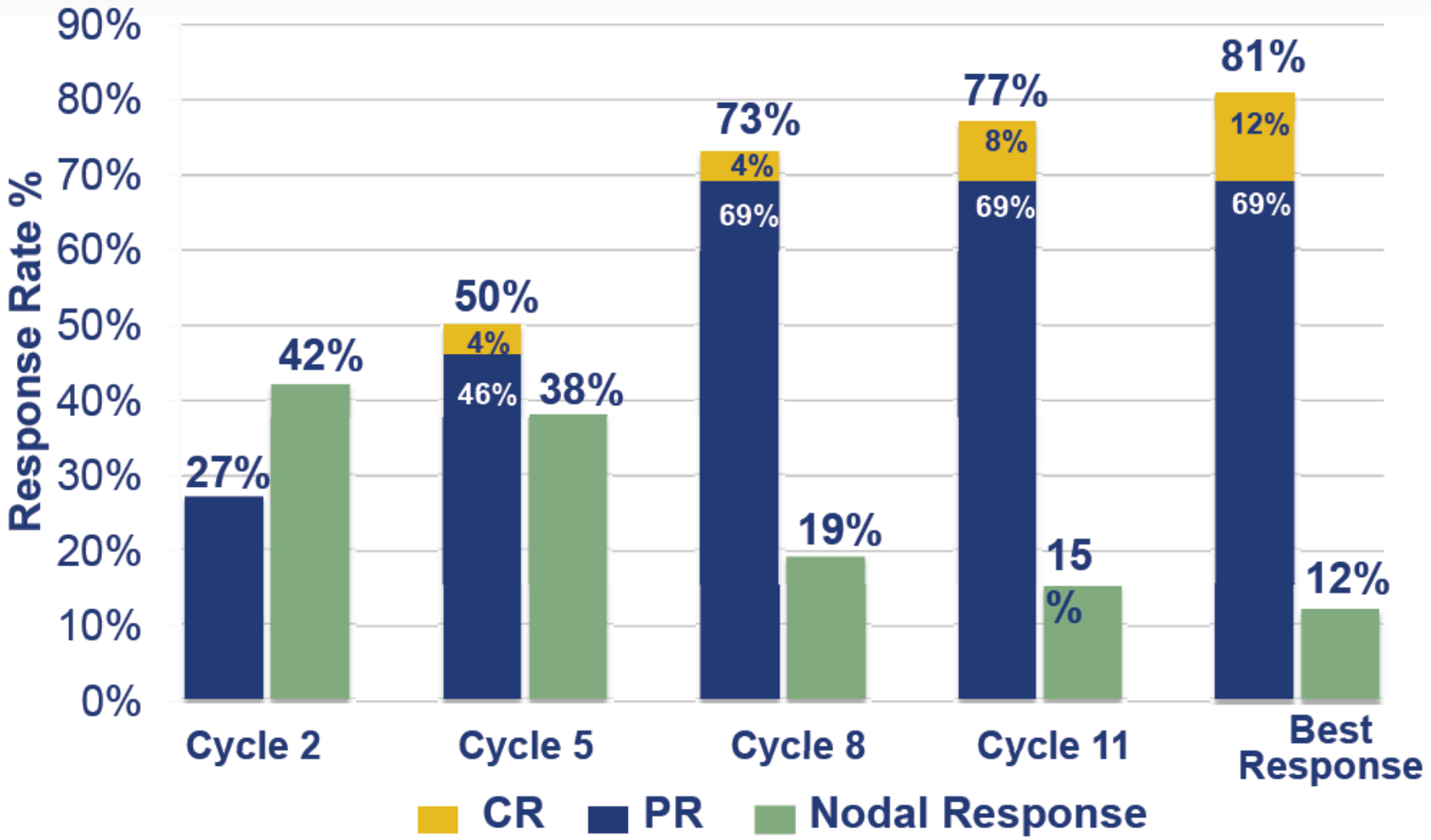
Ibrutinib in Treatment-Naïve CLL



**The 840mg TN cohort was terminated after comparable activity and safety between doses was shown in R/R patients. One patient in this cohort received only 420 mg daily.*

Cumulative Best Response

420 mg/day N=26, Median Follow-up=14.4 mos



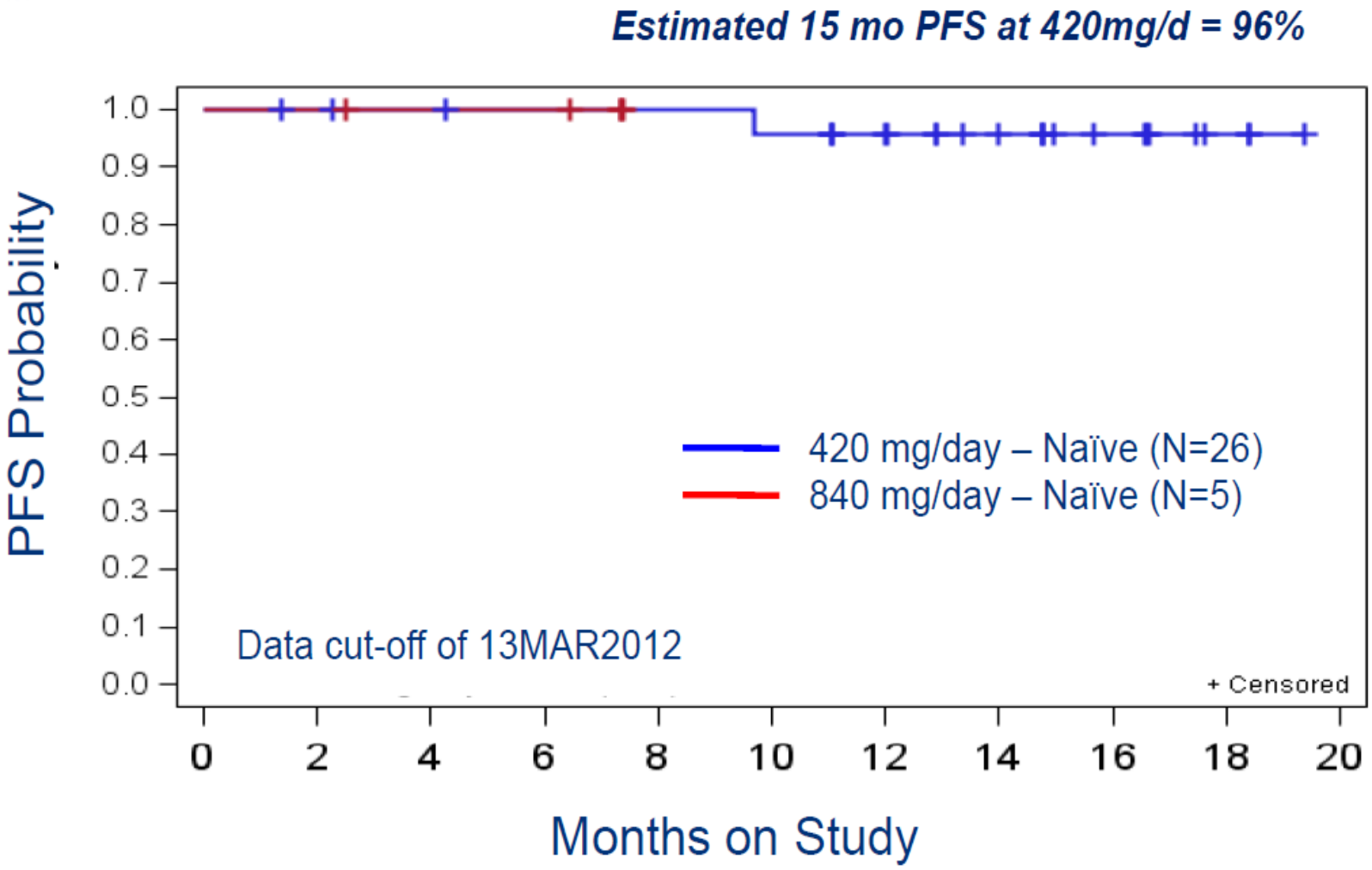
O'Brien et al. ASCO Annual Meeting 2012, Abstract 6515

Cumulative Best Response by Risk Feature

	N	ORR % (n)	CR % (n)
All Patients	31	**74** (23)	**10** (3)
≥ 70 years age	23	**70** (16)	**13** (3)
Hgb < 11 g/dL or PLT < 100K/µL at screening	19	**79** (15)	**11** (2)
IgVH unmutated	13	**92** (12)	**15** (2)
Del17p present	2	**100** (2)	**0** (0)
β2 Microglobulin > 3mg/L	7	**86** (6)	**29** (2)

O'Brien et al. ASCO Annual Meeting 2012, Abstract 6515

Ibrutinib in Treatment-Naïve CLL
Estimated Progression-Free Survival



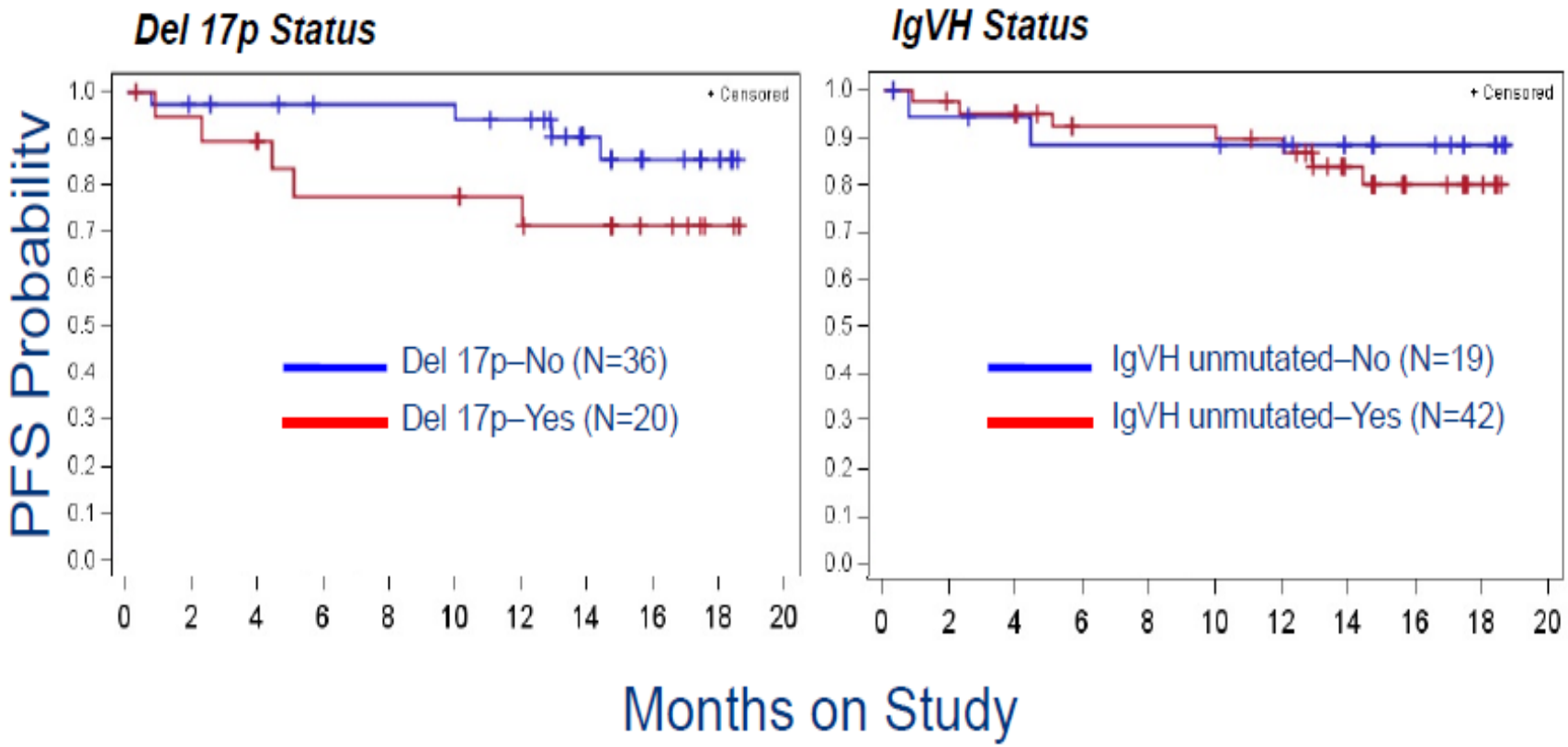
O'Brien et al. ASCO Annual Meeting 2012, Abstract 6515

Marked Response in Rel/Ref CLL
Best Response by Risk Features

	n/N	ORR %
All Patients	**41/61**	**67**
≥ 70 years age	13/19	68
Bulky disease ≥ 5 cm	24/33	73
Bulky disease ≥ 10 cm	7/10	70
Hgb < 11 g/dL or PLT < 100K/µL at screening	22/36	61
IgVH unmutated	31/42	74
Del 17p	13/20	65
Del 11q	16/22	73
β2 Microglobulin > 3mg/L	19/29	66
Purine Analog Refractory (< 12 mos from any purine analog to next therapy)	17/28	61

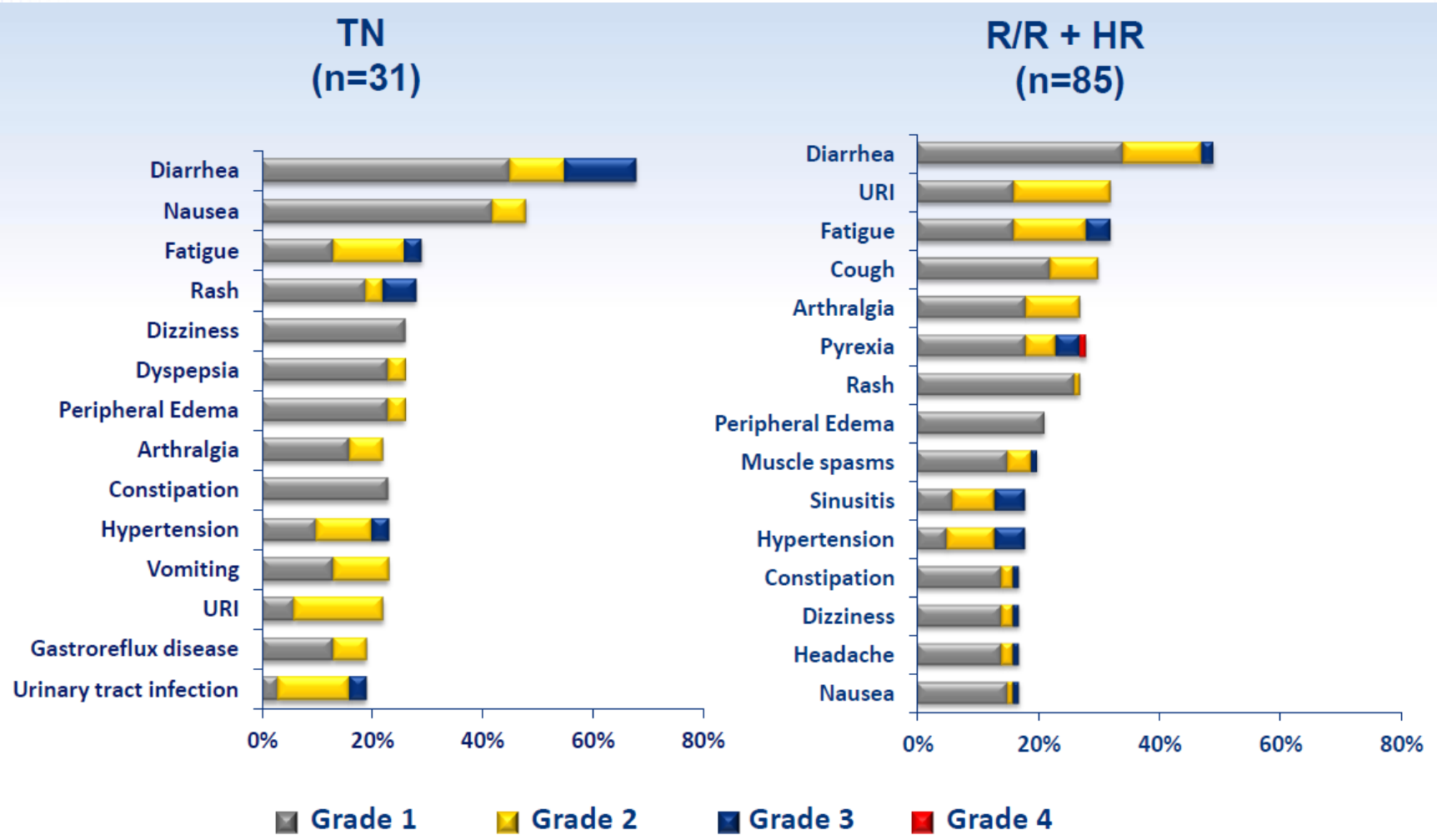
Byrd et al. ASH Annual Meeting 2012, Abstract 189

Ibrutinib Phase Ib Relapsed/Refractory:
PFS by Genetic Risk Feature



Byrd et al. ASH Annual Meeting 2012, Abstract 189

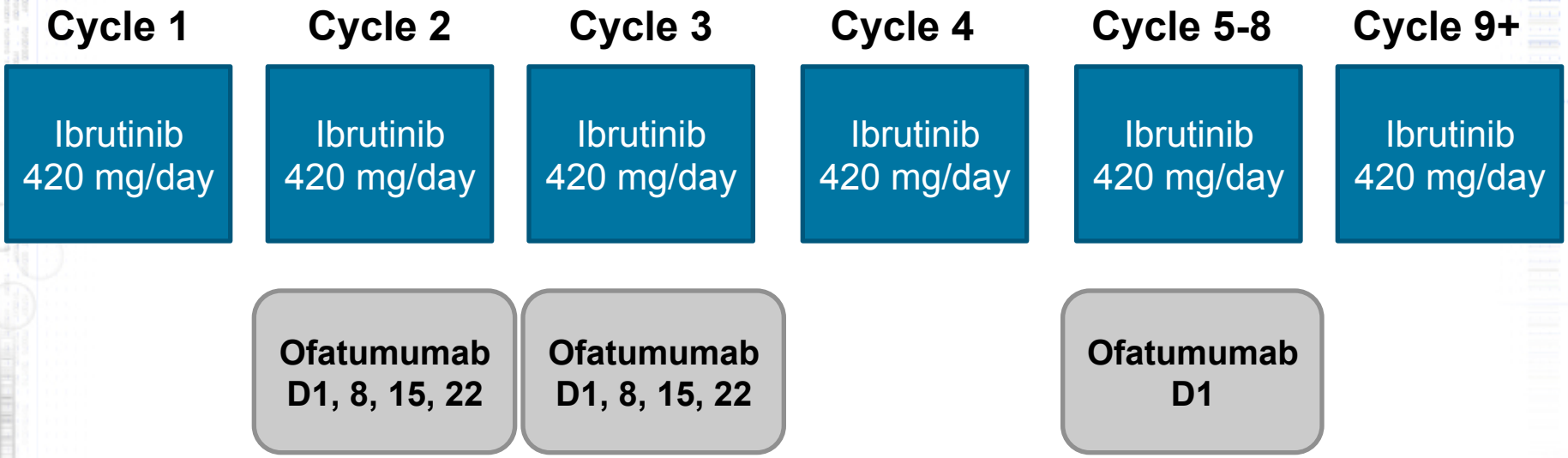
Ibrutinib in CLL -- Safety



Byrd et al. ASH Annual Meeting 2012, Abstract 189

OSU 10053: Ibrutinib + Ofatumumab

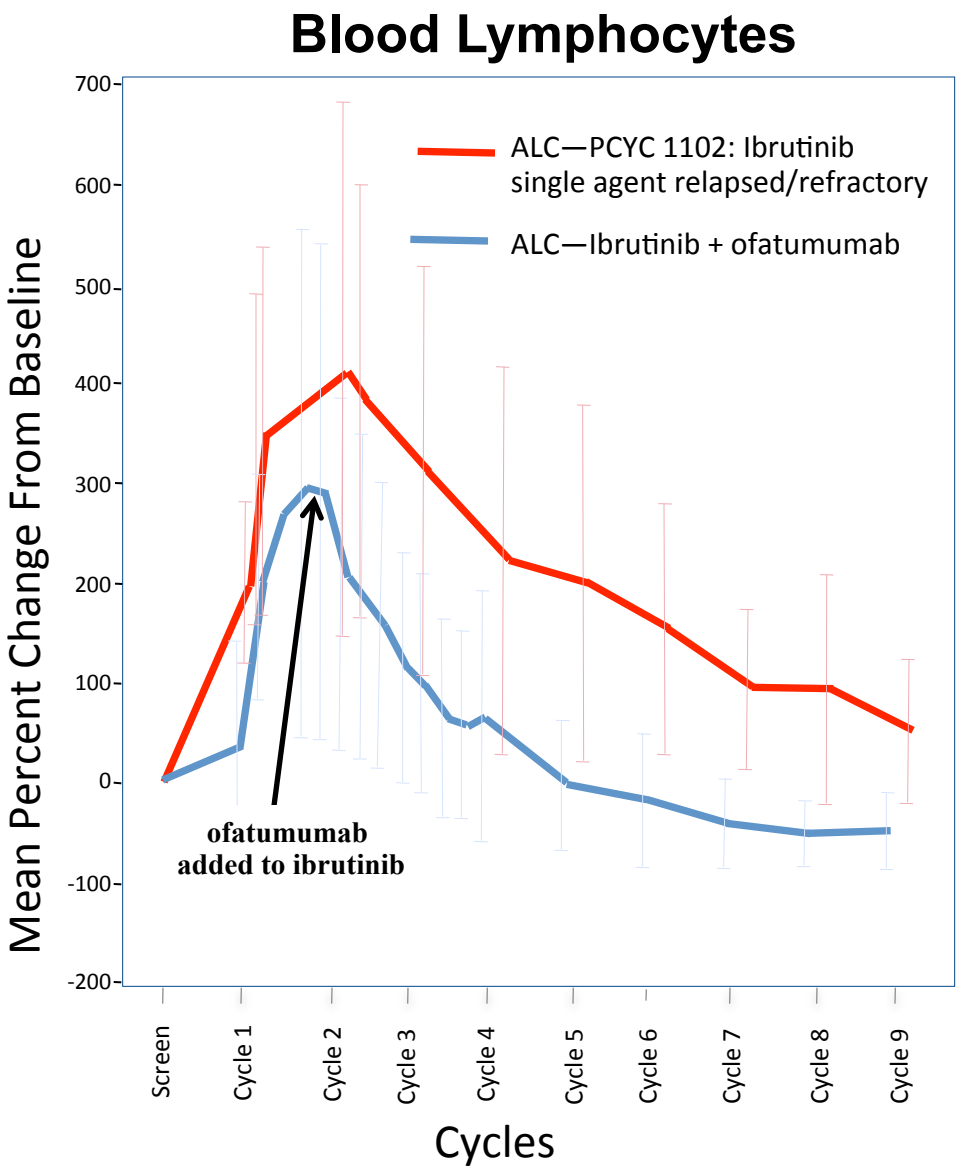
Eligibility: **Relapsed/Refractory CLL**
≥2 priors (including nucleoside analog
CD20+ >10%

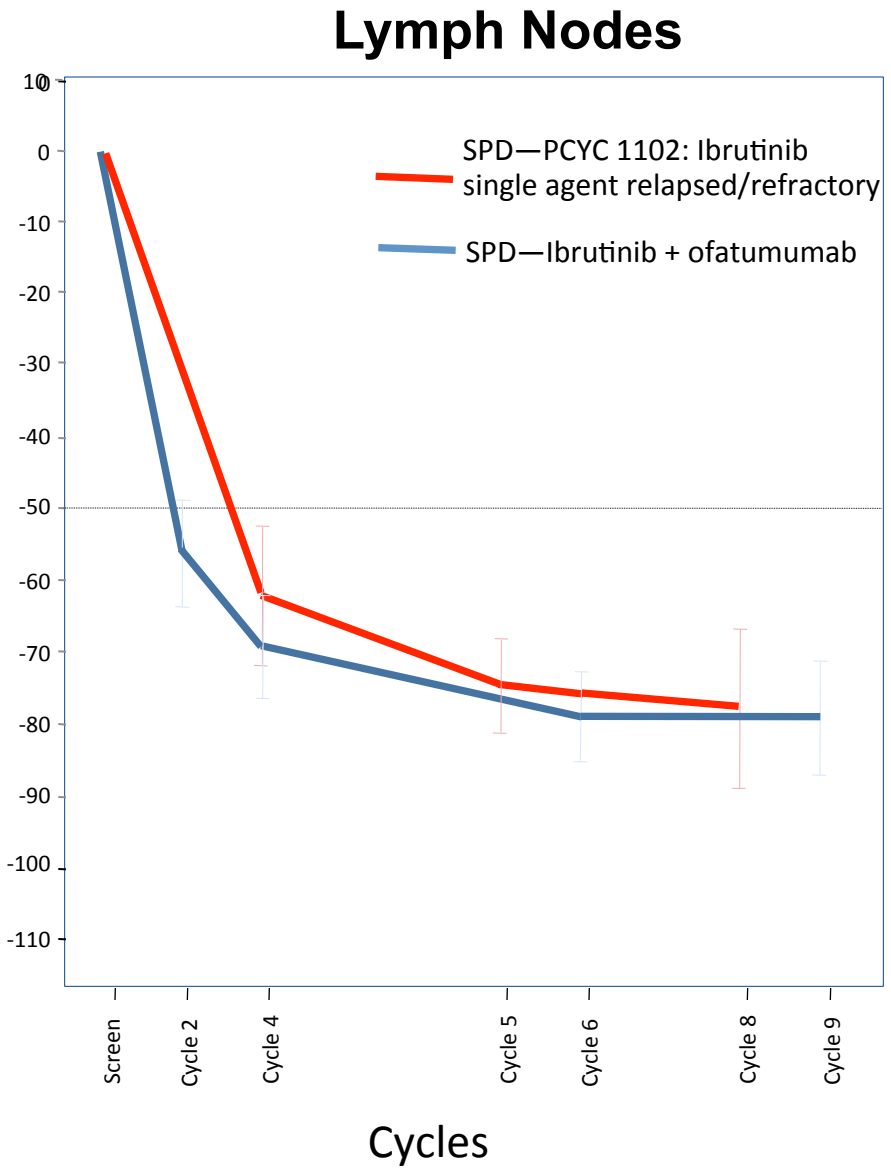


Cycle Length = 28 days

Jaglowski et al. ASCO Annual Meeting 2012, Abstract 6508

Ibrutinib Mediates Transient Rise in Lymphocyte Count that is Diminished in Combination with ofatumumab





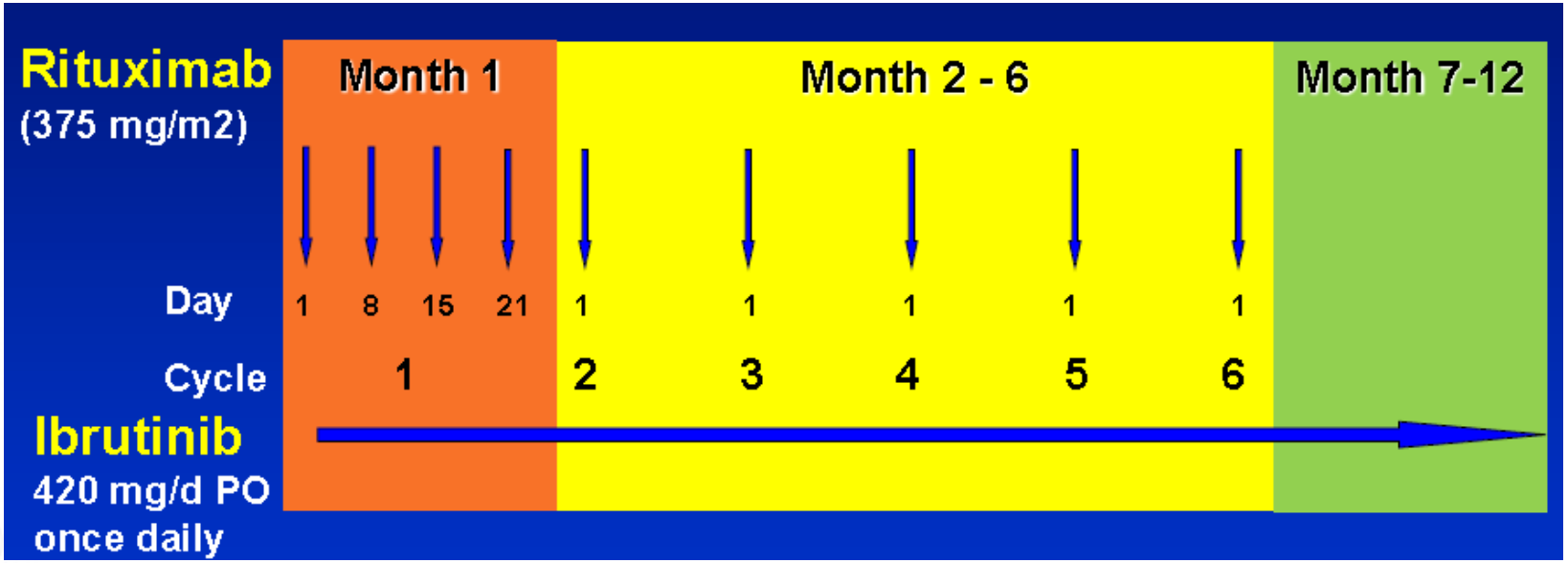
OSU 10053: Best Response

	CLL/SLL/PLL (N=24)	Richter's (N=3)
	# (%)	# (%)
CR	1 (4)	0
PR	23 (96)	2 (67)
ORR	**100 %**	**67%**
SD	0	1 (33)
PD	0	0
NE	0	0

Median Follow-up = 9.8 months (5.2 – 12.9 months)
24 (89%) patients remain on study
3 Patients have discontinued:
1 allo HSCT, 1 death (Richter's), 1 PD (Richter's)

Jaglowski et al. ASCO Annual Meeting 2012, Abstract 6508

Ibrutinib + Rituximab in High-risk CLL

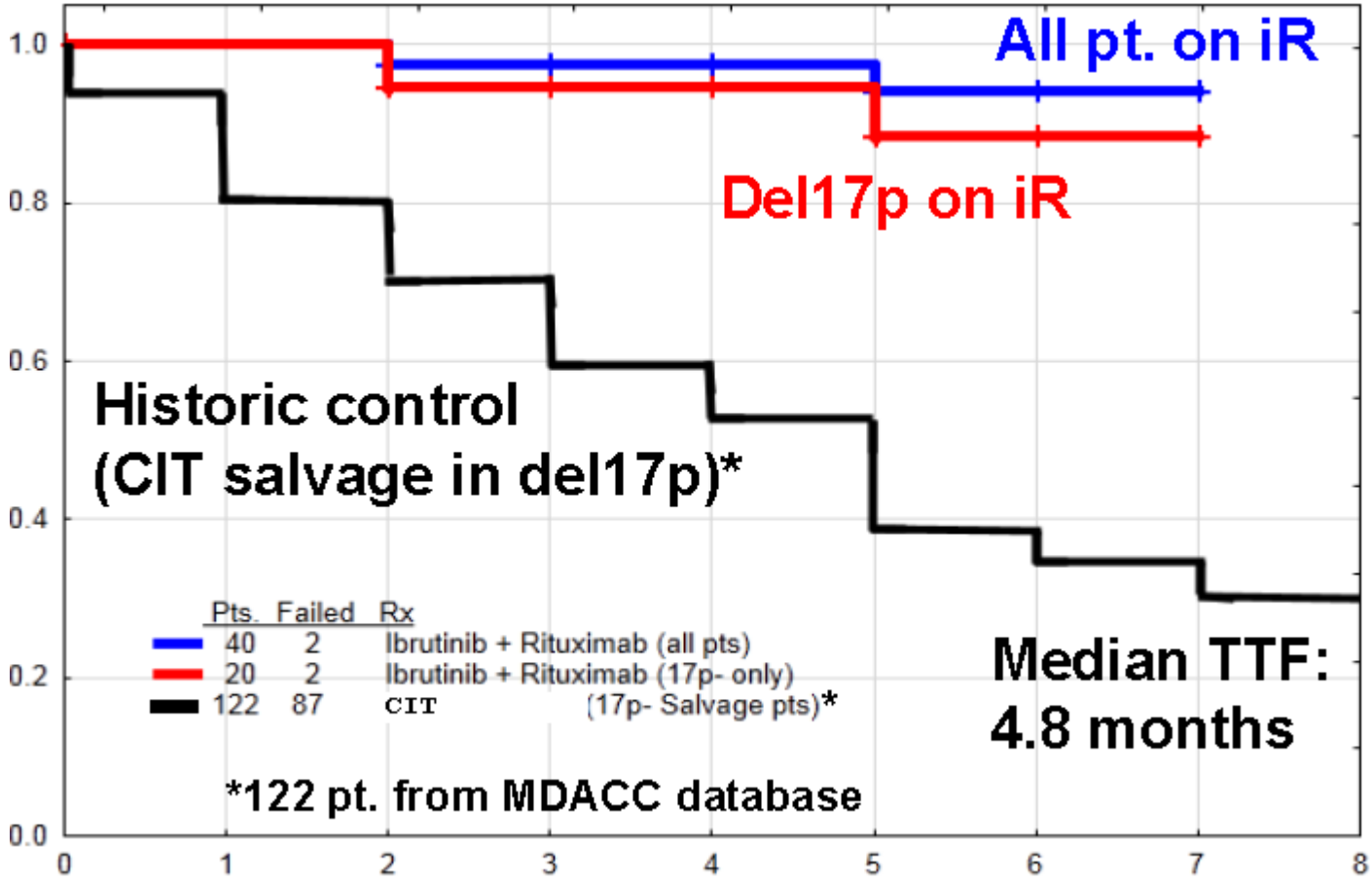


High-risk disease (del17p or *TP53* mutation [treated or untreated], or PFS < 36 months after frontline FCR, or relapsed del11q CLL

- **median age of 65 (range 35–82); median of 2 prior therapies**
- **31 patients unmutated *IGHV*, 1patient mutated *IGHV***
- **19 del17p or TP53 mutation (4 without prior tx), 13 del11q**

Burger et al. ASH Annual Meeting 2012, Abstract 187

Ibrutinib + Rituximab in High-Risk CLL



Burger et al. ASH Annual Meeting 2012, Abstract 187

Creating a cancer-free world. *One person, one discovery at a time.*