

MADRID
2014



Madrid, Spain

26-30 SEPTEMBER 2014

Special symposium: Targeting signalling pathways in haematological malignancies: Are we close to the end of histopathological classification and the chemotherapy era?

Targeting the cyclins

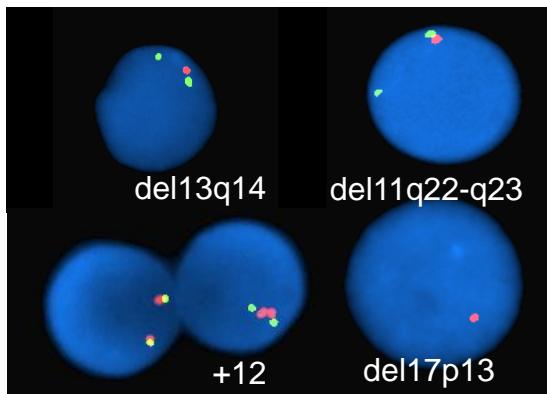
Paolo Ghia



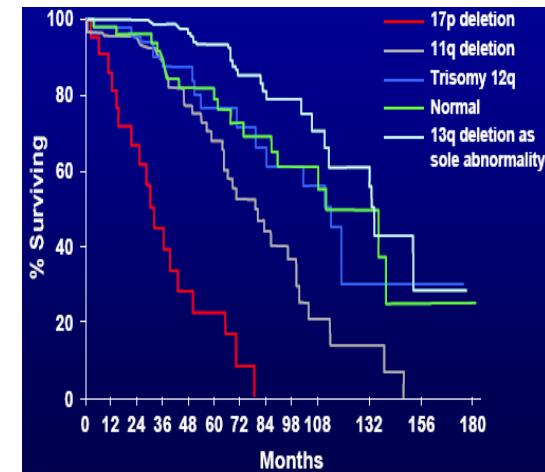
Lab of B Cell Neoplasia - Division of Molecular Oncology
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Istituto Scientifico San Raffaele - Milano



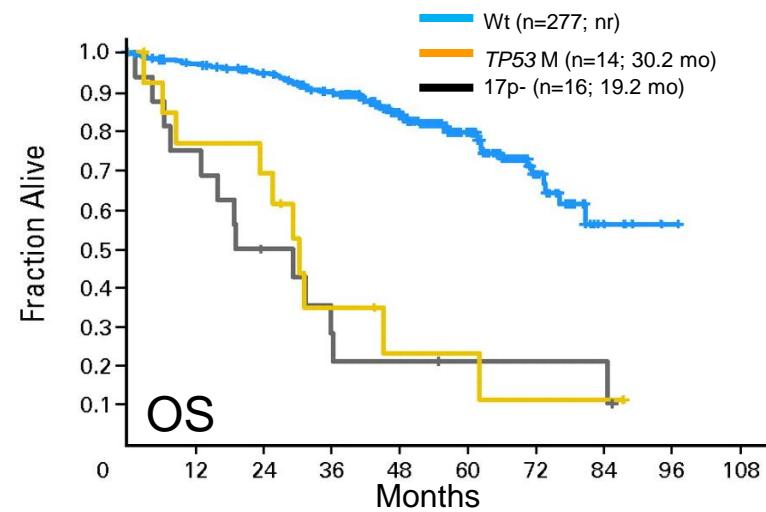
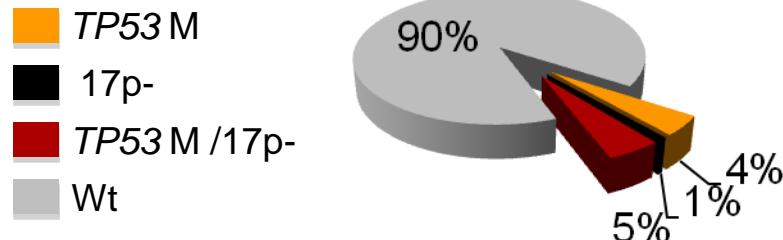
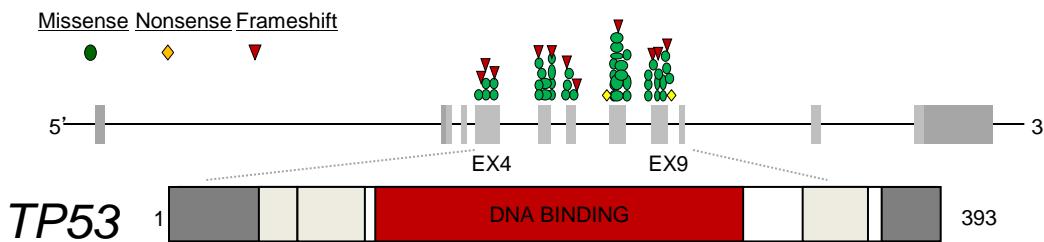
TP53 abnormalities in CLL and chemoresistance



Aberration	Incidence (%)	Median OS (mo)
17p del	3-7	32
11q del	11-25	79
+12	10-16	114
Normal	18-22	111
13q del	33-44	133



Döhner, New Engl J Med 2000

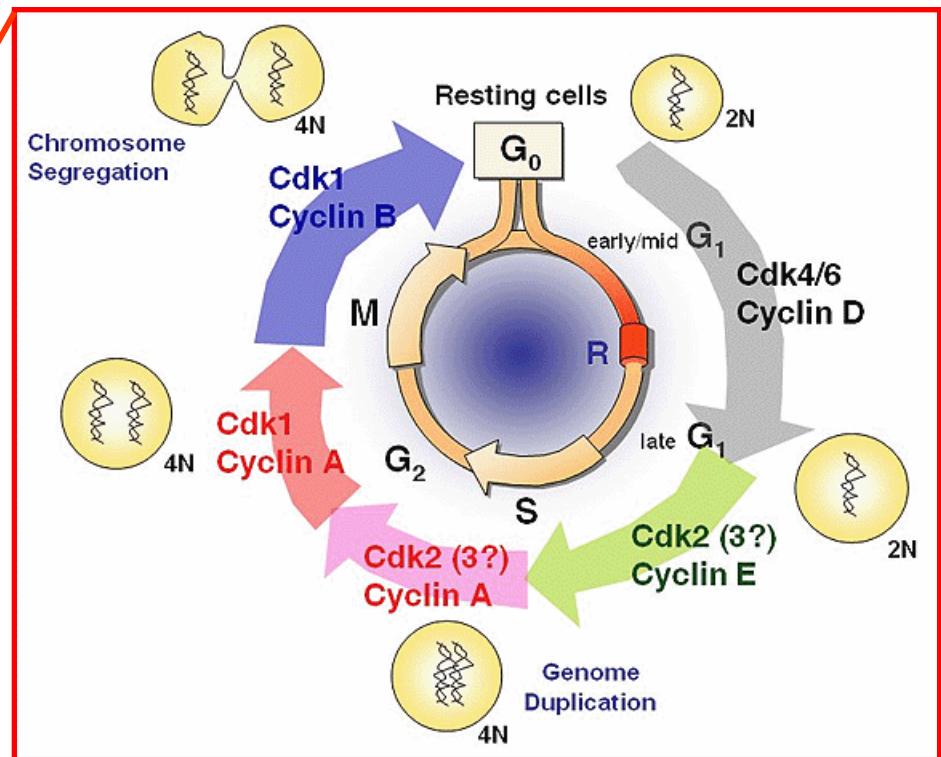
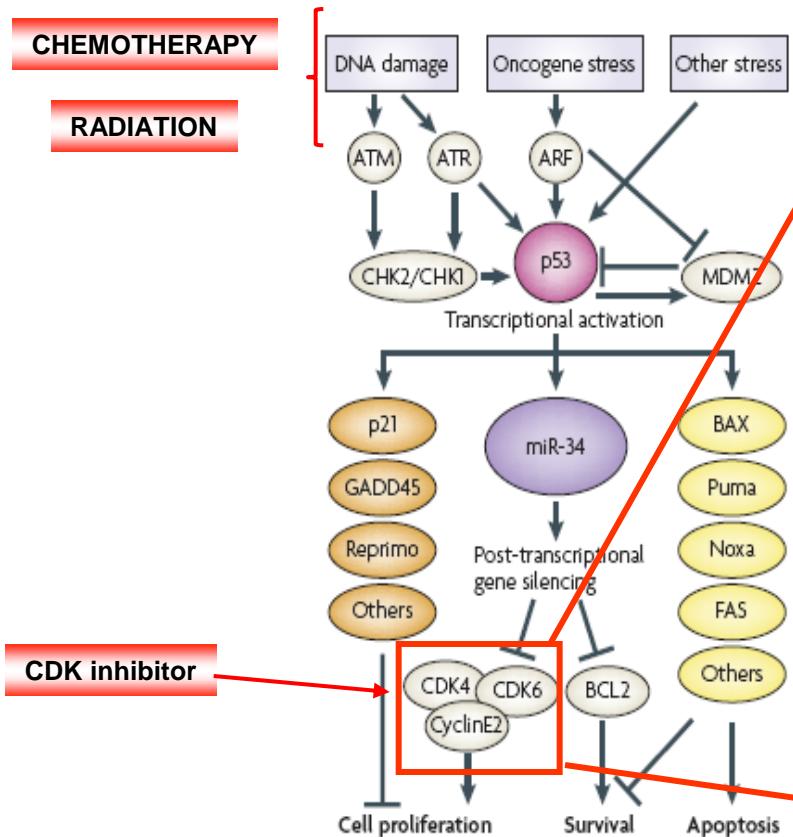


Zenz, J Clin Oncol 2010

CDK inhibition as an anti-leukemic treatment

CHEMOTHERAPY

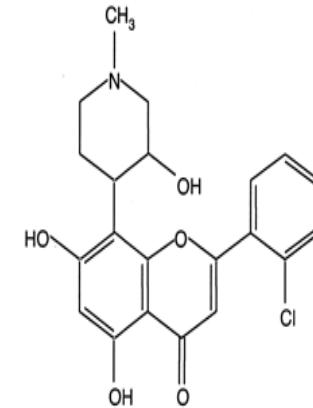
RADIATION



Flavopiridol

Synthetic flavone developed as a tyrosine kinase inhibitor by NCI

- ▶ A broad CDK inhibitor, inhibiting CDK1, CDK2, CDK4, CDK7, and CDK9 → **Inhibition of cell cycle progression**
- ▶ RNA polymerase II inhibitor through inhibition of CDK9 (and potentially CDK7/8) → decreased transcription of anti-apoptotic proteins (e.g., MCL-1 and XIAP) → **Apoptosis**



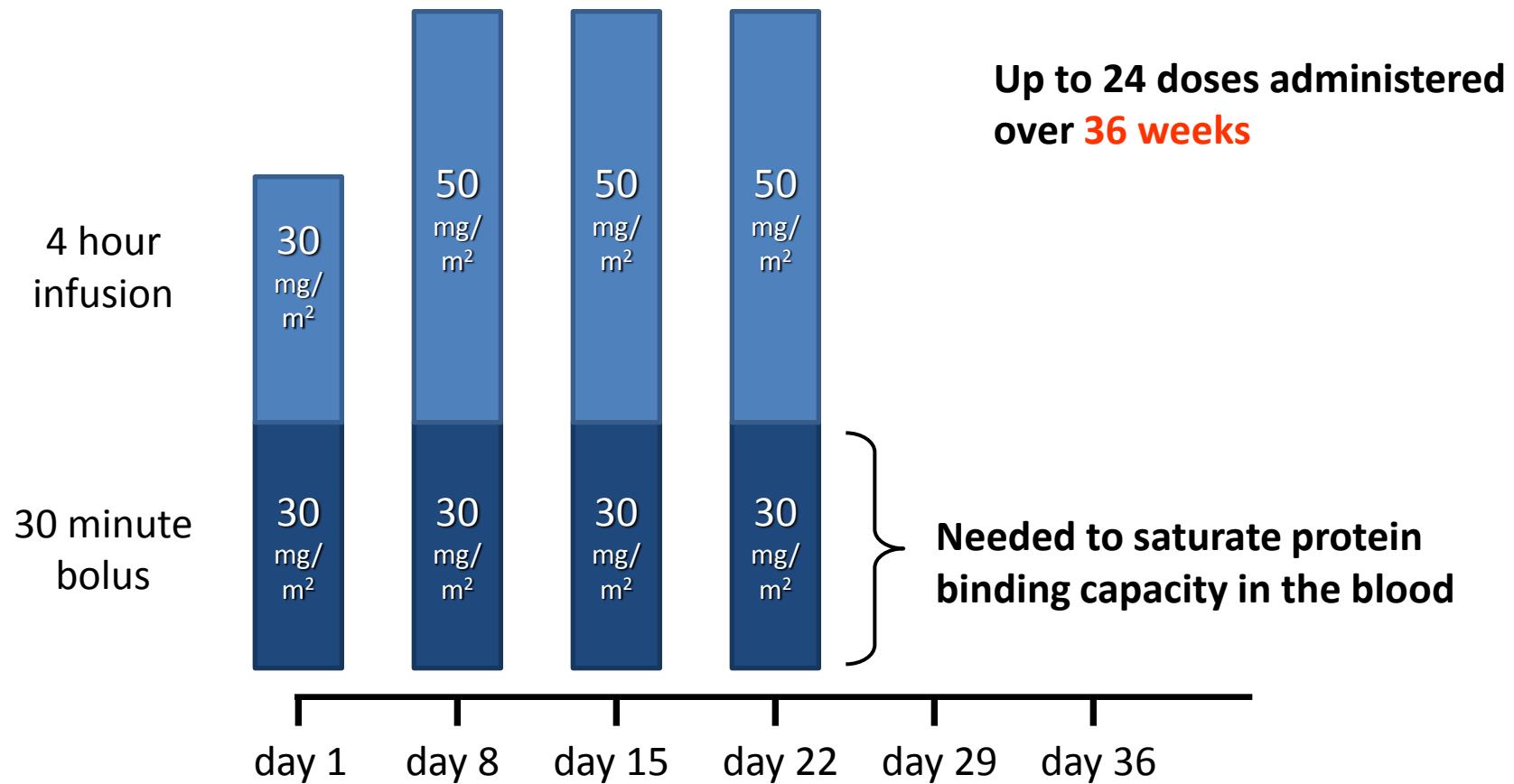
Flavopiridol [MW 438]

(-)-*cis*-5,7-dihydroxy-2-(2-chlorophenyl)-8-[4-(3-hydroxy-1-methyl)piperidinyl]-4*H*-1-benzopyran-4-on, NSC 649890, L86-8275

Flavopiridol Pre-Clinical Studies in CLL

- Induces **apoptosis** in CLL lines and human CLL cells
 - 4 hour LC₅₀ 1.15 uM
 - 24-96 hr LC₅₀ 0.16-0.19 uM
- Induces apoptosis **independent of p53 function**
- Induces apoptosis **independent of IL4**
- Decreases expression of Mcl-1 and XIAP proteins and mRNA *in vitro*

Flavopiridol has important protein-binding capacity



Phase 2 study of Flavopiridol in CLL

ORR, %	NCI 1996 Criteria*	Hybrid Criteria†
Evaluable patients (n = 165) ▪ CR ▪ PR	4 27	2 23
del(17p13.1) (n = 49)	27	14
del(11q22.3) (n = 43)	28	26
Bulky lymphadenopathy (n = 115)	29	25

- Disease progression: 9%**
- Median duration of response: 12.2 mos**

Grade ≥ 3 Adverse Events, %	Patients (n = 165)
Infections	32
Tumor lysis syndrome	39 1 Death
Diarrhea	17
Febrile neutropenia	15

*ORR = CR + PR.

†ORR = CR + PR + nodal response by CT.

EFC6663 interim analysis: Tumor lysis syndrome

	AT Population (n=165)
Number of patients with TLS	39 (25%)
Fatal	1 (1%)
Management	
Dialysis	13 (8%)
Medical	26 (17%)
Onset of TLS episodes	
Cycle 1	37 (23%)
Cycle 2	2 (2%)

Flavopiridol: Risk factors for TLS

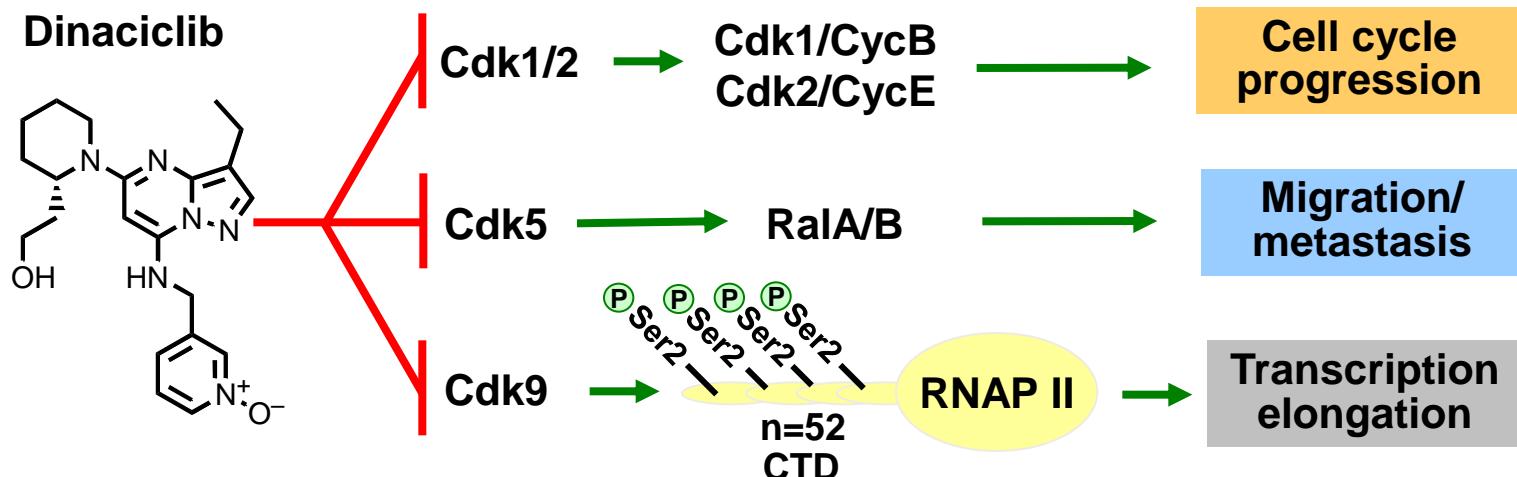
Table 4 Risk factors for TLS in multivariable analysis

Risk factor	Odds ratio*	95% CI	P-value
Female vs. Male	8.6	2.6–27.7	<0.001
Bulky lymphadenopathy $\geq 10\text{ cm}$	3.5	1.1–10.8	0.03
WBC, 50 unit increase	2.0	1.2–3.5	0.01
$\beta 2$ -microglobulin, 1 unit increase	1.6	1.2–2.0	<0.001
Albumin, 1 unit increase	0.3	0.1–0.9	0.04

Abbreviations: TLS, tumor lysis syndrome *An odds ratio >1 (<1) indicates a greater (lesser) odds of TLS for either the first category listed for dichotomous variables or higher values of continuous variables.

SCH 727965 (Dinaciclib): Background

IC ₅₀ Values (nM) for Dinaciclib Against CDK/Cyclin Kinase Complexes							
Cdk2/E	Cdk2/A	Cdk1/B1	Cdk4/D1	Cdk5/p25	Cdk6/D3	Cdk7/H	Cdk9/T
1	1	3	100	1	60	70	4

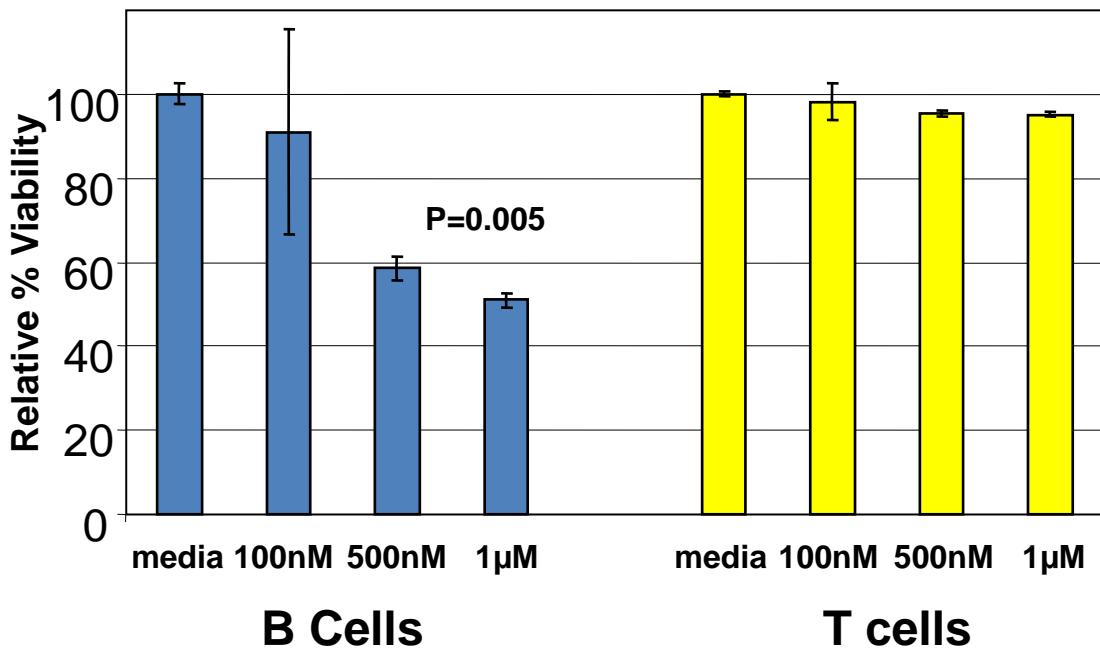
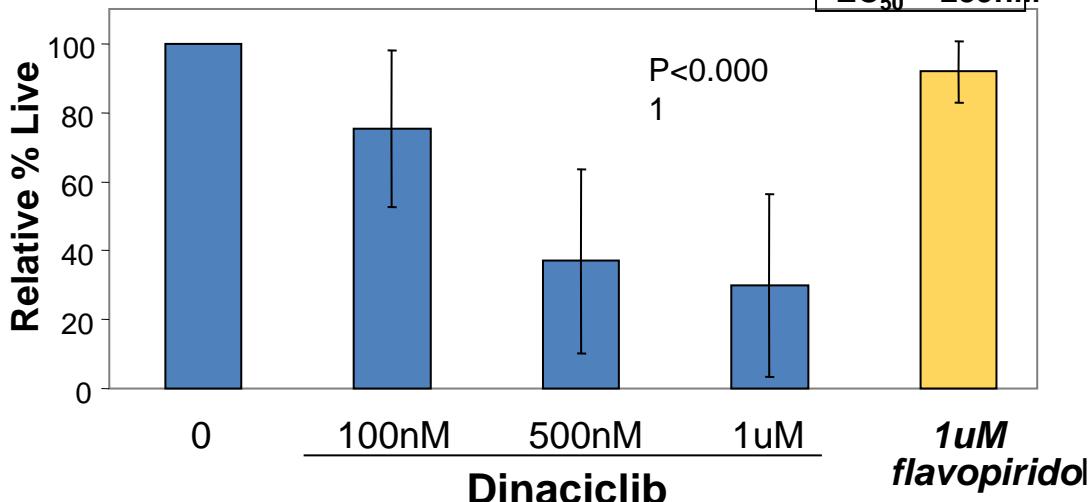
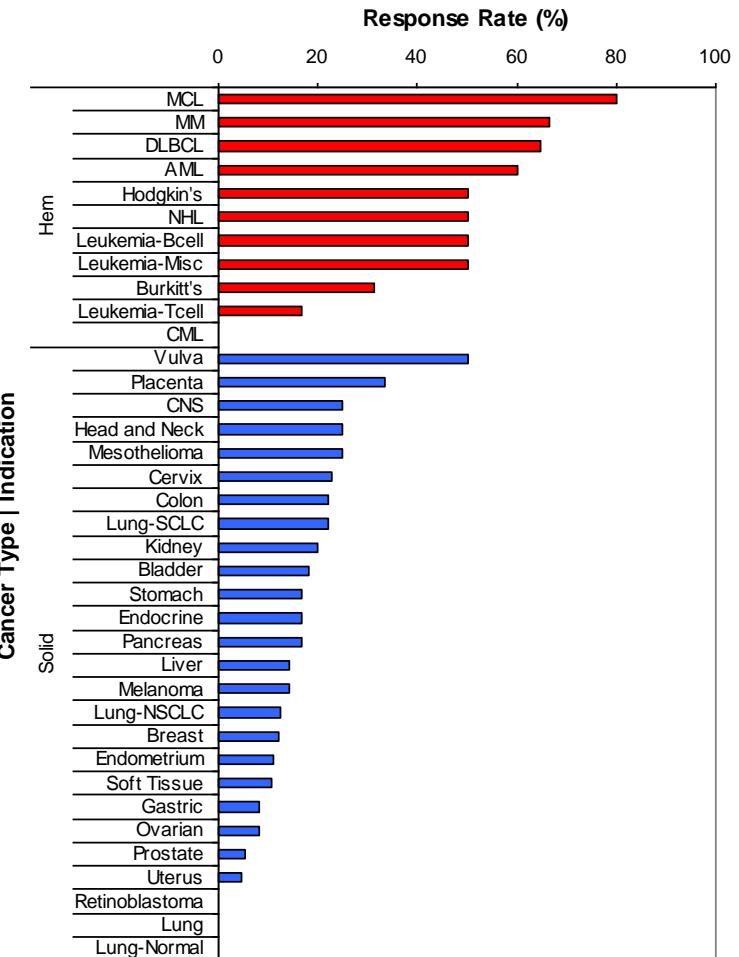


Activity on CDK 9 is believed to be a key component

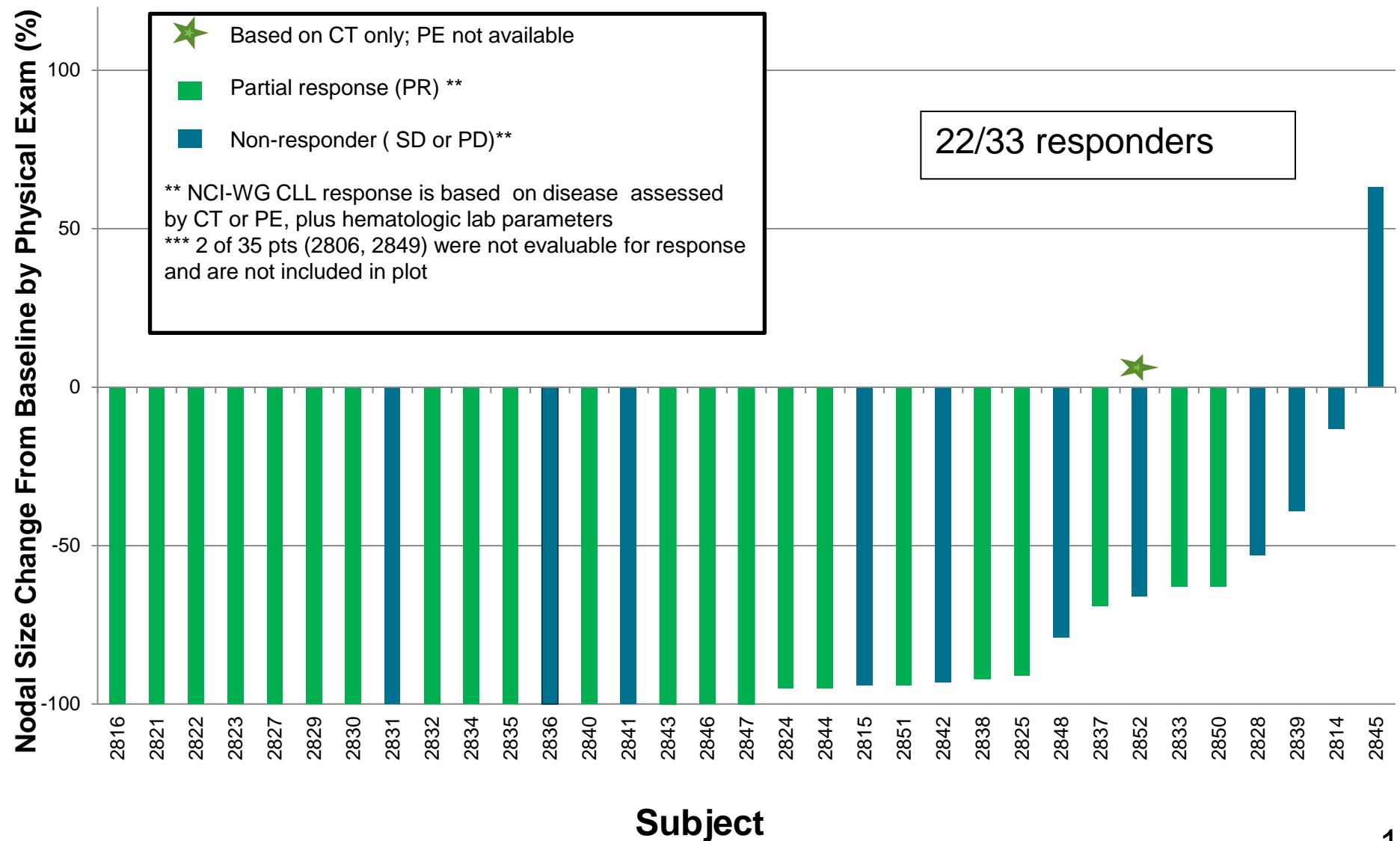
- Dinaciclib has long lasting pro-apoptotic transcriptional effects
- MCL-1 and BCL-XL expression/amplification appear to be predictive biomarkers for response

Dinaciclib: in vitro efficacy

$EC_{50} = 239\text{nM}$



CLL: Dinaciclib Monotherapy Activity



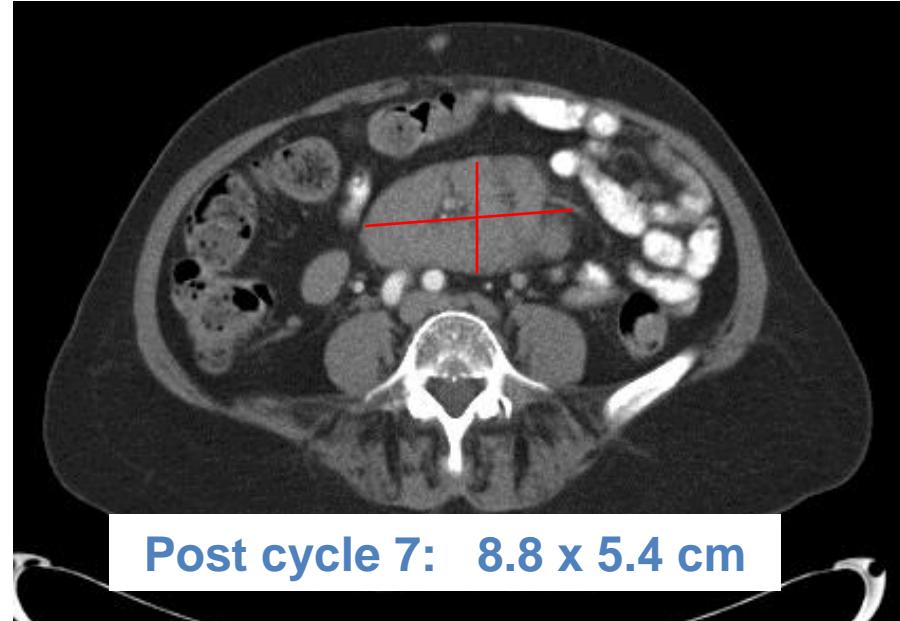
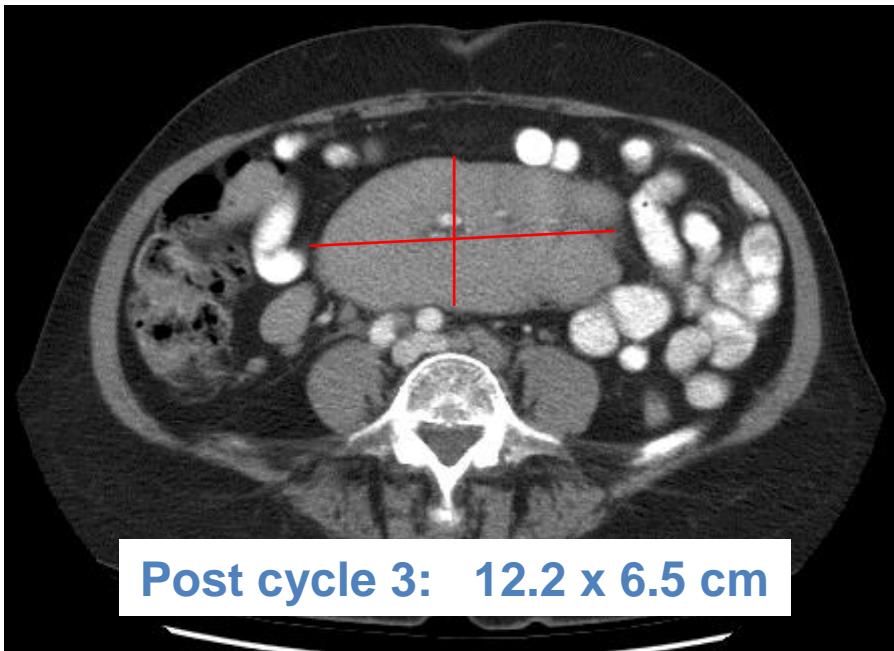
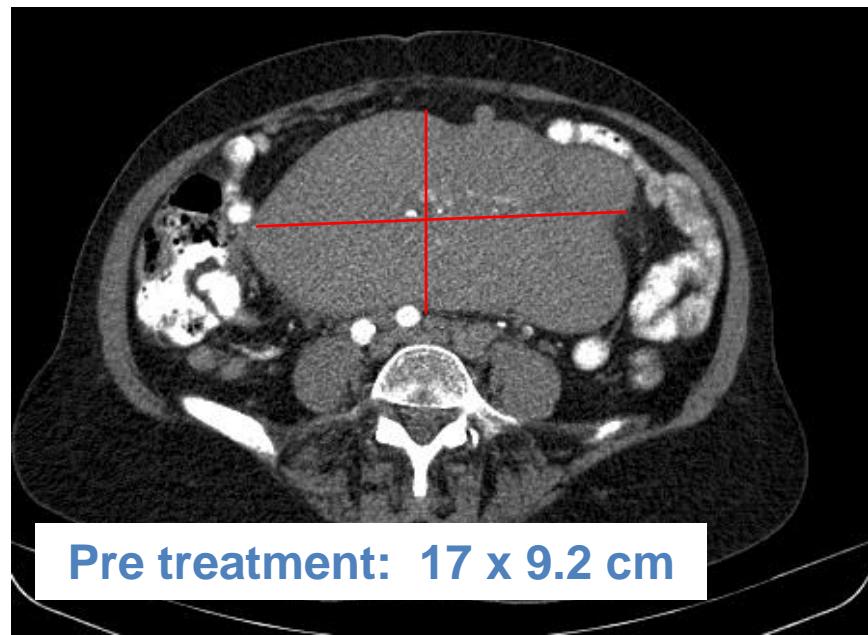
Case Study

Patient with a mesenteric conglomerate lymph node mass

71 year old patient, relapsed CLL, previous response to flavopiridol in 2007 with progressive disease after 8 months off therapy.

The patient was refractory to other biologic therapies. In September 2009, started Dinaciclib.

The patient completed 8 cycles of therapy, and resumed work part time as a home care aide for the elderly.



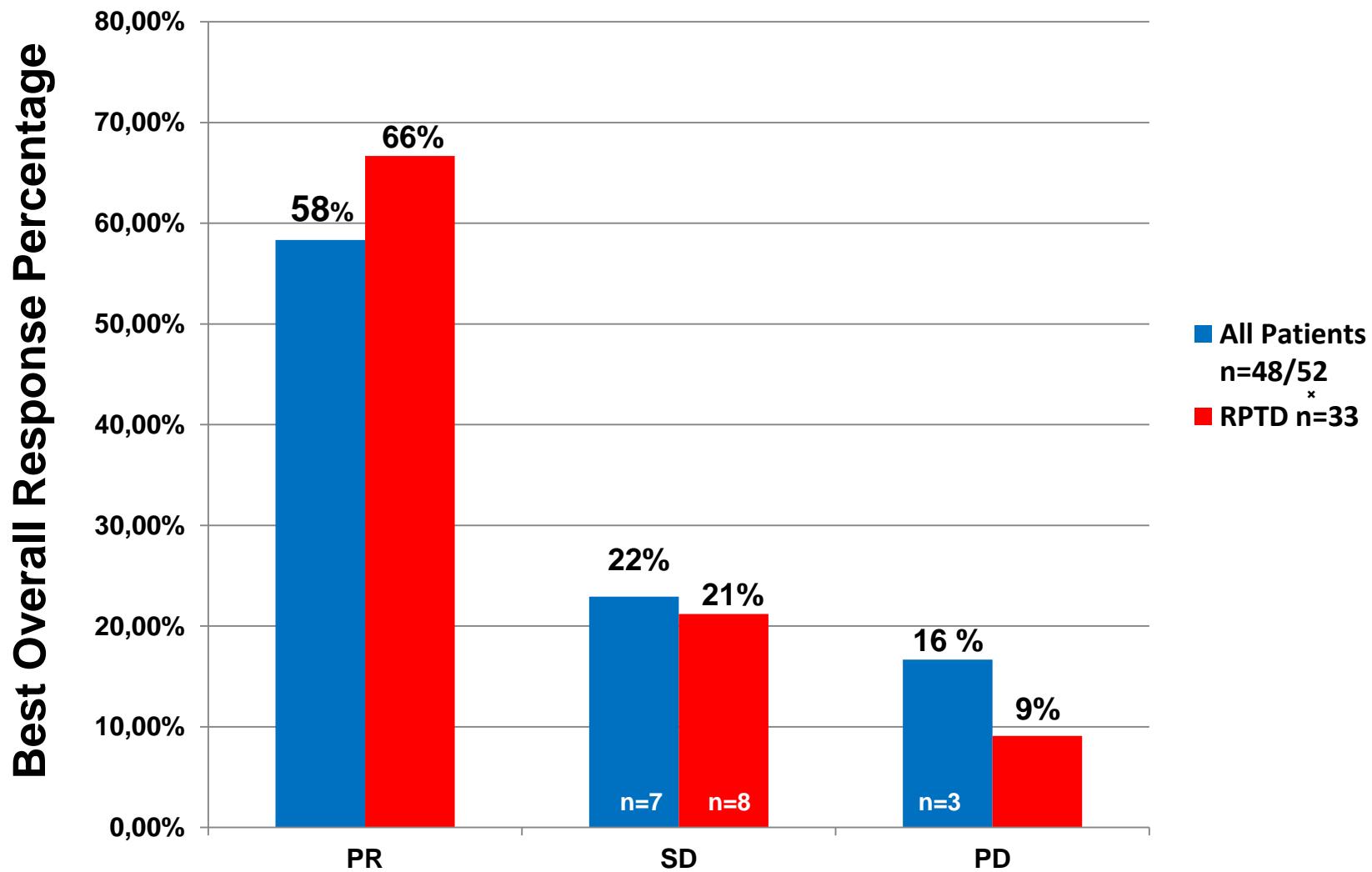
Efficacy of Dinaciclib in CLL

Dose (mg/m ²)	Number of Subjects	Number of DLT's	Description of DLTs
5	4	0	
7	6	1	sepsis (fatal)
10	3	0	
14	16+19	4+3	Tumor Lysis Syndrome requiring dialysis
17	4	2	Tumor Lysis Syndrome requiring dialysis; pneumonia

Tumor Lysis Syndrome

Dose (mg/m ²)	N	TLS Events / Dialysis	Description of TLS Events
14	16	4 / 1	<ul style="list-style-type: none">■ C1D1; dose reduced to 10 mg/m²■ C1D1; dose reduced to 10 mg/m²■ C1D1; continued same dose■ C1D1 requiring HD; dose reduced
10>14	6	2 / 0	<ul style="list-style-type: none">■ C1D1; dose reduced to 7mg/m²■ C2D1; dose reduced to 10mg/m²
7>10>14	13	1 / 1	<ul style="list-style-type: none">■ C1D8 requiring HD; dose reduced to 7 mg/m² and experienced 2nd TLS C2D1; off-study d/t AE of TLS
17	4	1 / 1	<ul style="list-style-type: none">■ C1D1 requiring dialysis; dose reduced

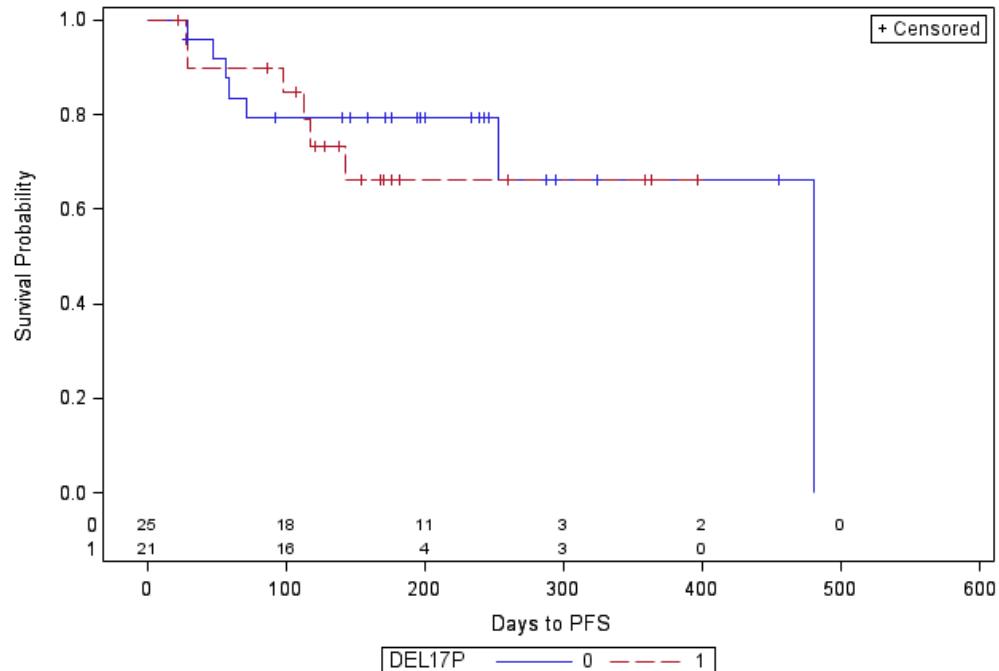
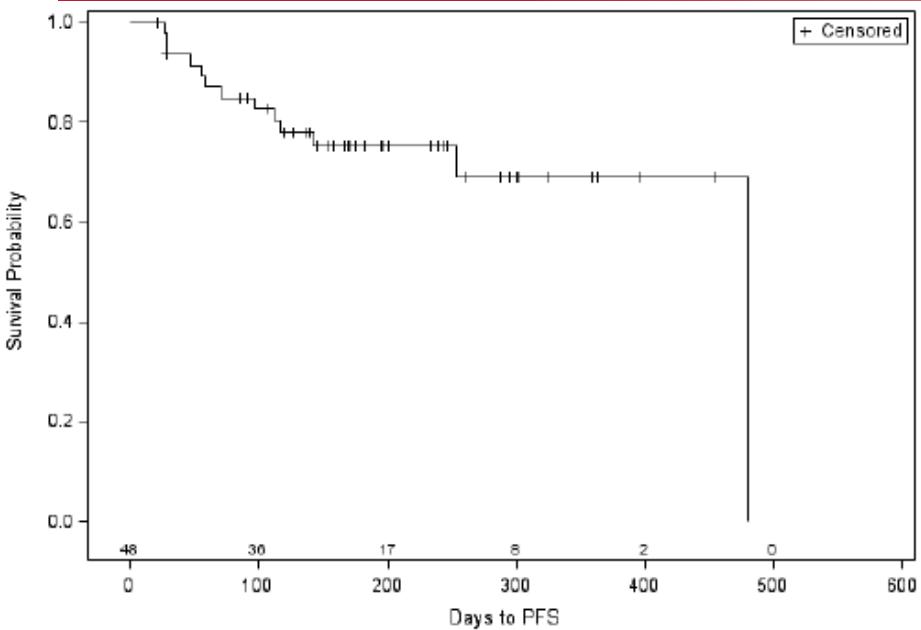
Overall Response Assessment NCI-WG criteria



* Excludes 4 inevaluable patients

*

Progression-free Survival: All Patients



Kind courtesy of Jones J, OSU 2014

Phase 3: Dinaciclib vs Ofatumumab

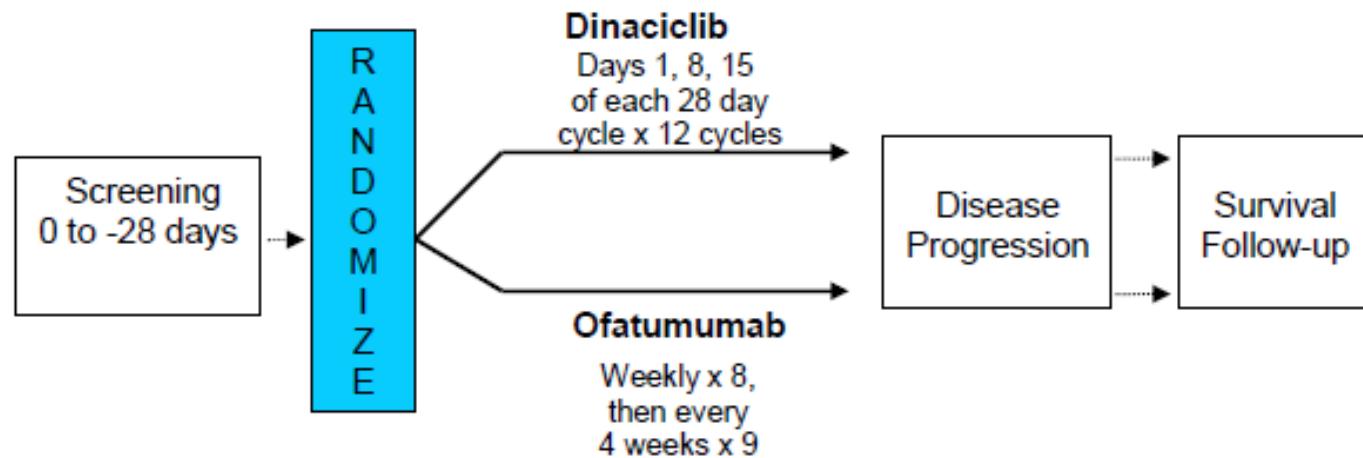
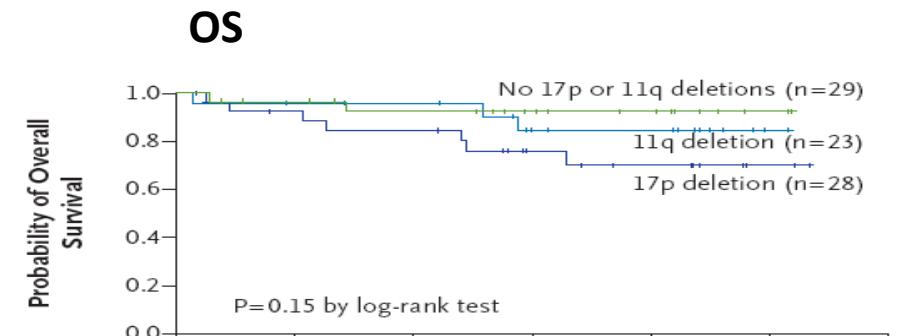
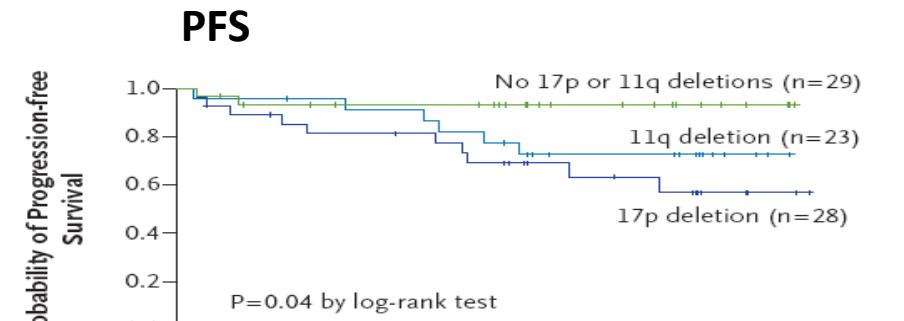
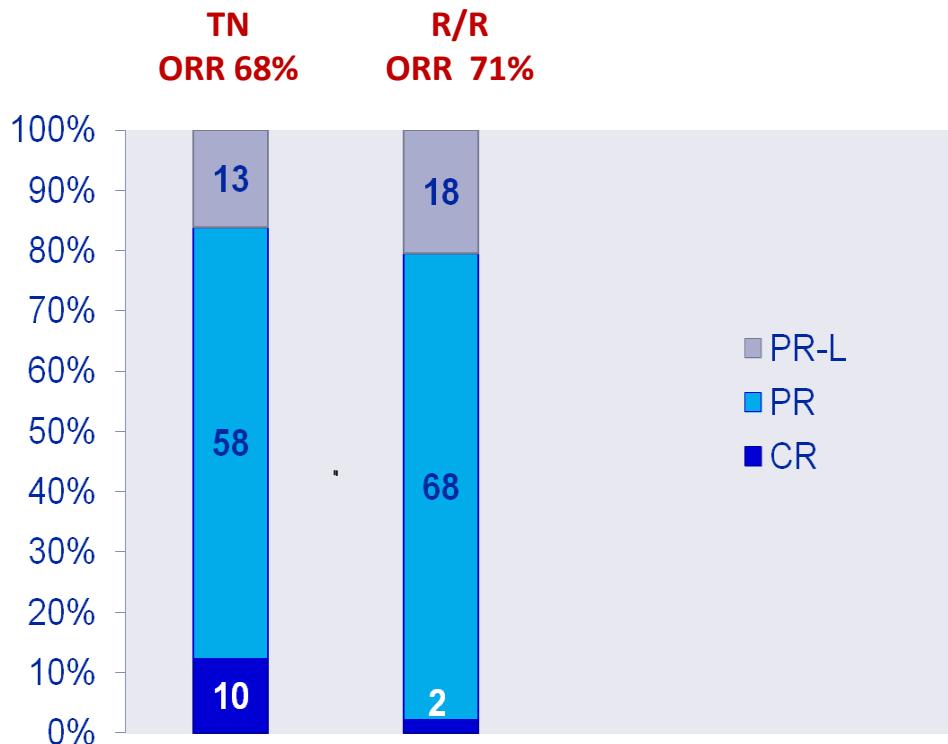


Table 1 Treatment Overview

	Cycle 1				Cycle 2				Cycle 3				Cycles 4 - 12				
	D 1	D 8	D 1	D 5	D 2	D 1	D 8	D 1	D 2	D 1	D 8	D 1	D 2	D 1	D 8	D 1	D 2
Dinaciclib	x	x	x			x	x	x		x	x	x		x	x	x	
Ofatumumab	x	x	x	x	x	x	x	x					x				

Merck-sponsored phase 3 study (ofatumumab v. dinaciclib) discontinued as of fall 2013

Efficacy of Ibrutinib in Relapsed CLL



ABT-199 monotherapy phase I in CLL

	All CLL N=55 ^a n (%)	del(17p) N=16 ^a n (%)	Flu-Refractory N=18 ^b n (%)
Best Response			
Overall response rate			
Complete response	All Grades ≥ 20% of pts		n (%)
CR with incomplete marrow recovery	Diarrhea		42 (40)
Partial response	Neutropenia		38 (36)
Stable disease	Nausea		37 (35)
Disease progression	Upper respiratory tract infection		35 (33)
	Fatigue		27 (27)
	Cough		21 (20)
	Grades 3/4 ≥ 5% pts		n (%)
	Neutropenia		35 (33)
	Anemia		10 (10)
	Febrile neutropenia		7 (7)
	Thrombocytopenia		7 (7)
	Hyperglycemia		7 (7)
	Tumor lysis syndrome		7 (7)
	Hypokalemia		5 (5)

Is there any future for CDK inhibition?



***Uncertain* future but *certain* clinical interest**

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Responses by Dose Level

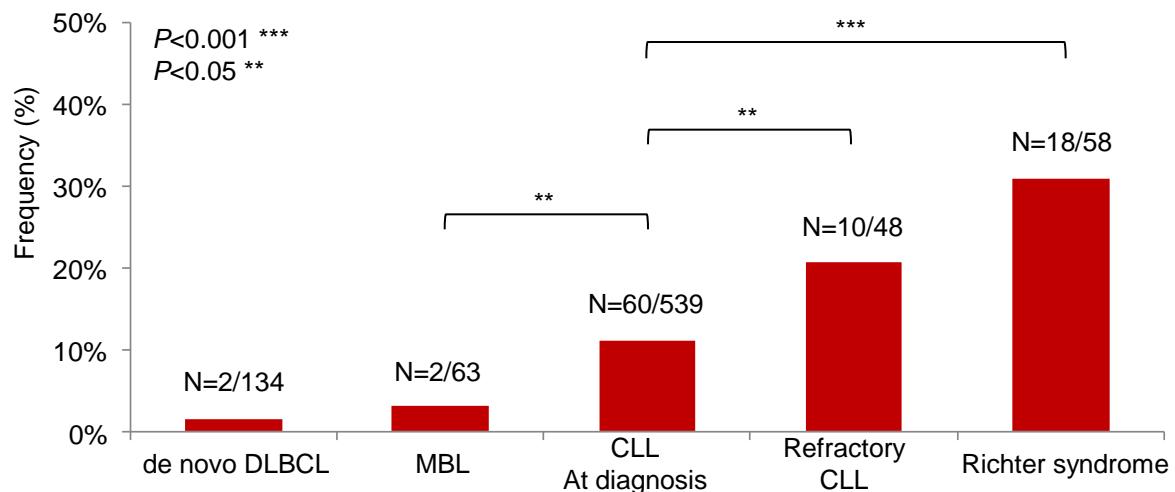
Dose Level (mg/m ²)	No Patients	Responders No. (%)
5	4	1 (25)
7	5	1 (20)
10	3	2 (67)
14	16	11 (69)
17	4	1 (25)
10→14	6	4 (67)
7→10→14	13	7 (53)
Total	52	28 (54)

Flavopiridol, Fludarabine, and Rituximab (FFR)

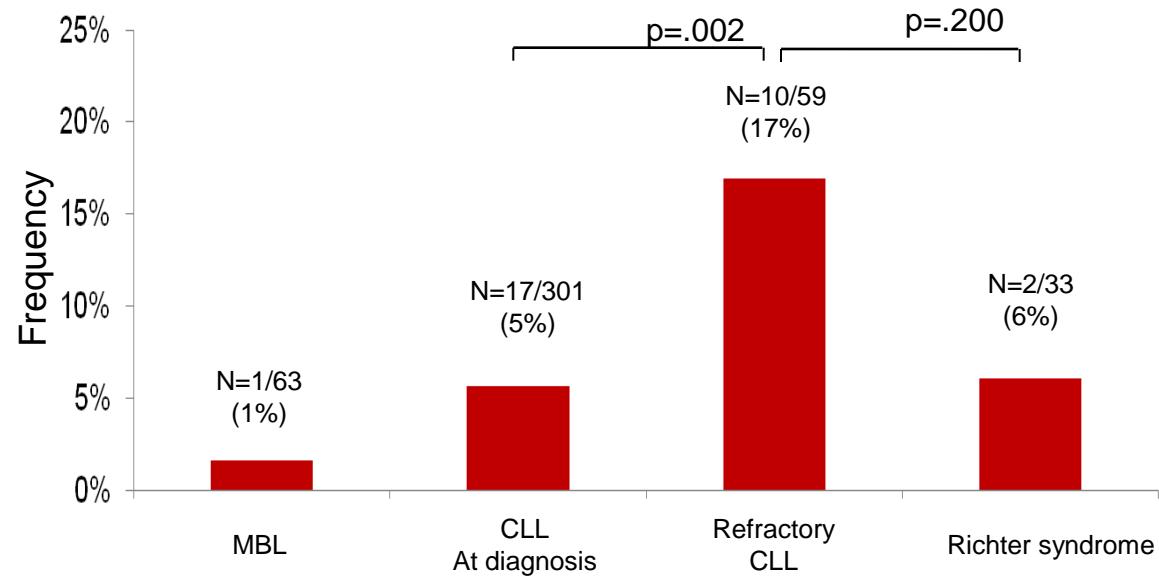
Group	N	OR n (%)	CR* n (%)	PR n (%)	Median PFS months
All patients	38	31 (82)	21 (55)	10 (26)	28.5
MCL	10	8 (80)	7 (70)	1 (10)	32.3
FL	9	9 (100)	7 (78)	2 (22)	25.6
CLL/SLL	14	11 (79)	7 (50)	4 (29)	25.1
Untreated	22	18 (82)	12 (55)	6 (27)	not reached
Relapsed	16	13 (81)	9 (56)	4 (25)	26.7
1-hr dosing	21	18 (86)	14 (67)	4 (19)	27.6
Hybrid dosing	17	13 (76)	7 (41)	6 (35)	29.3

Gene mutations associate with refractory CLL

NOTCH1 mutations across different CLL clinical phases



SF3B1 mutations across different CLL clinical phases



B Cell Receptor (BCR)

A signaling complex composed of an antigen-recognition unit (surface IgM) and a signaling unit (Igα/Igβ chain heterodimer)

