Rome,
March 23-24 2017

VOI Donna Camilla Savelli Hotel

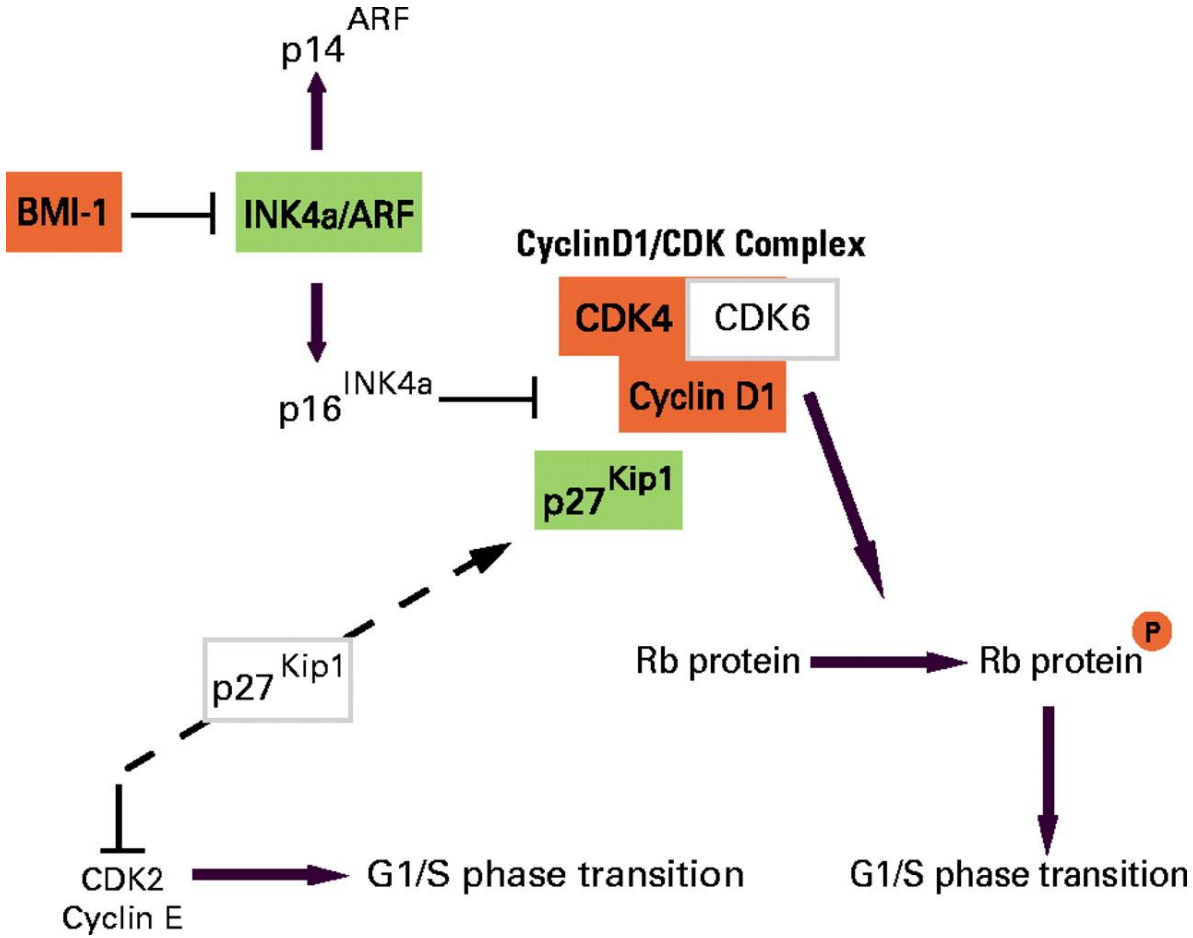
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			X				
Gilead			X				
Celgene			X				
Genentech			X				
Novartis			X				
Pharmacyclics			X				
Verastem			X				

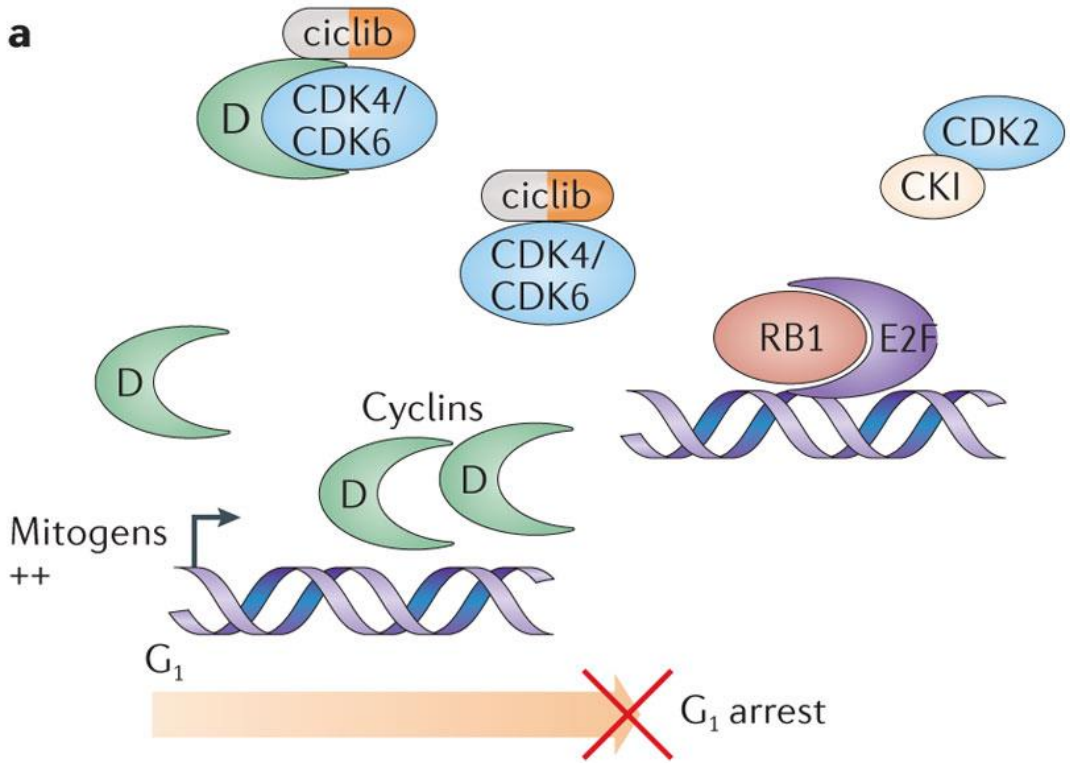
Palbociclib in Previously Treated Mantle Cell Lymphoma

March 26, 2017 pem9019@med.cornell.edu

Weill Cornell Medicine NewYork-Presbyterian

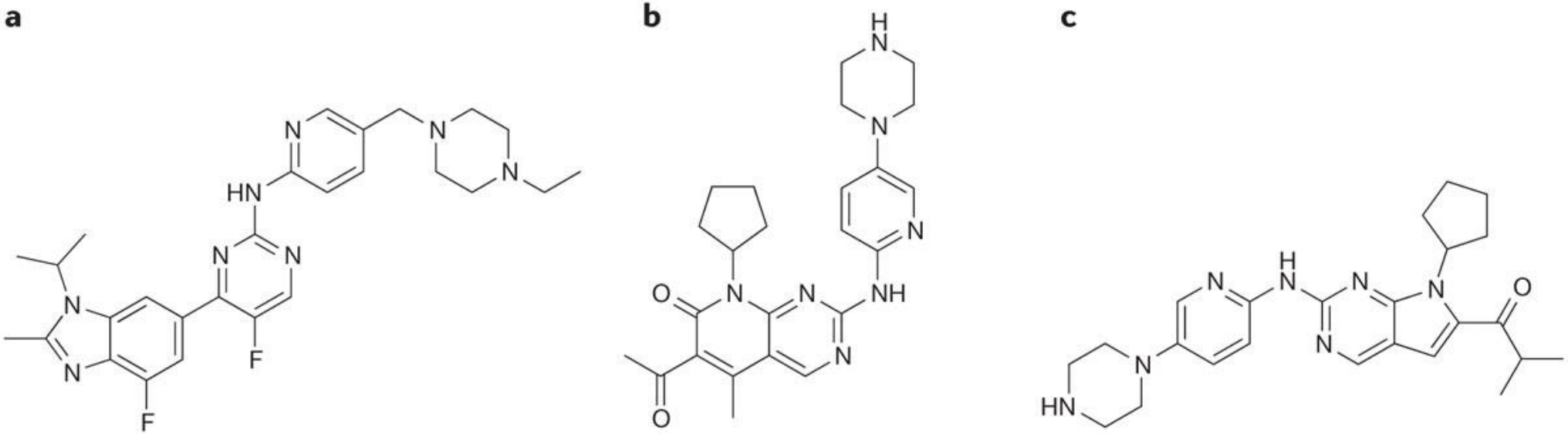
Cell cycle dysregulation and inhibition in mantle-cell lymphoma





Turner, N. C. *et al. Nat. Rev. Clin. Oncol.*.2016.26
Veronica Fernàndez et al. JCO 2005;23:6364-6369

Chemical structure of selective CDK4/6 inhibitors

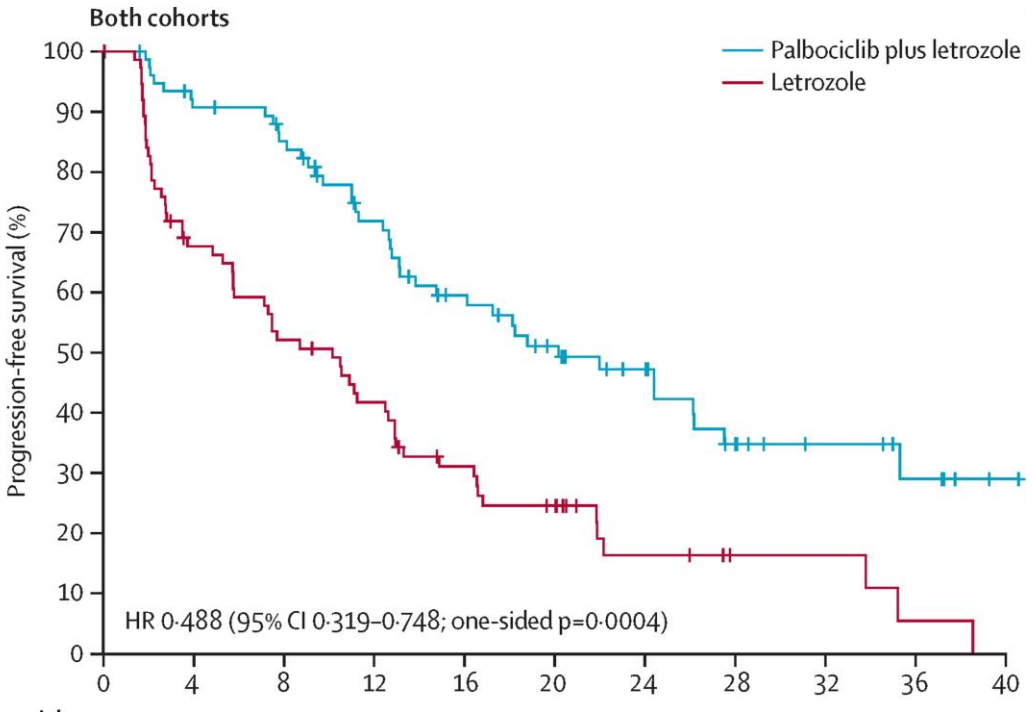


	Abemaciclib (LY-2835219)	Palbociclib (PD-0332991)	Ribociclib (LEE011)
IC_{50}	CDK1: >1 μM	CDK1: >10 μM	CDK1: >100 μM
	CDK2: >500 nM	CDK2: >10 μM	CDK2: >50 μM
	CDK4: 2 nM	CDK4: 9–11 nM	CDK4: 10 nM
	CDK5: ND	CDK5: >10 μM	CDK5: ND
	CDK6: 5 nM	CDK6: 15 nM	CDK6: 39 nM
	CDK7: 300 nM	CDK7: ND	CDK7: ND
	CDK9: 57 nM	CDK9: ND	CDK9: ND

Turner, N. C. *et al.* (2016) Treating cancer with selective CDK4/6 inhibitors
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.26

Nature Reviews | Clinical Oncology

The Paloma 1 trial in Breast Cancer Resulted in Accelerated Approval of Palbocilcib in Feb 2015



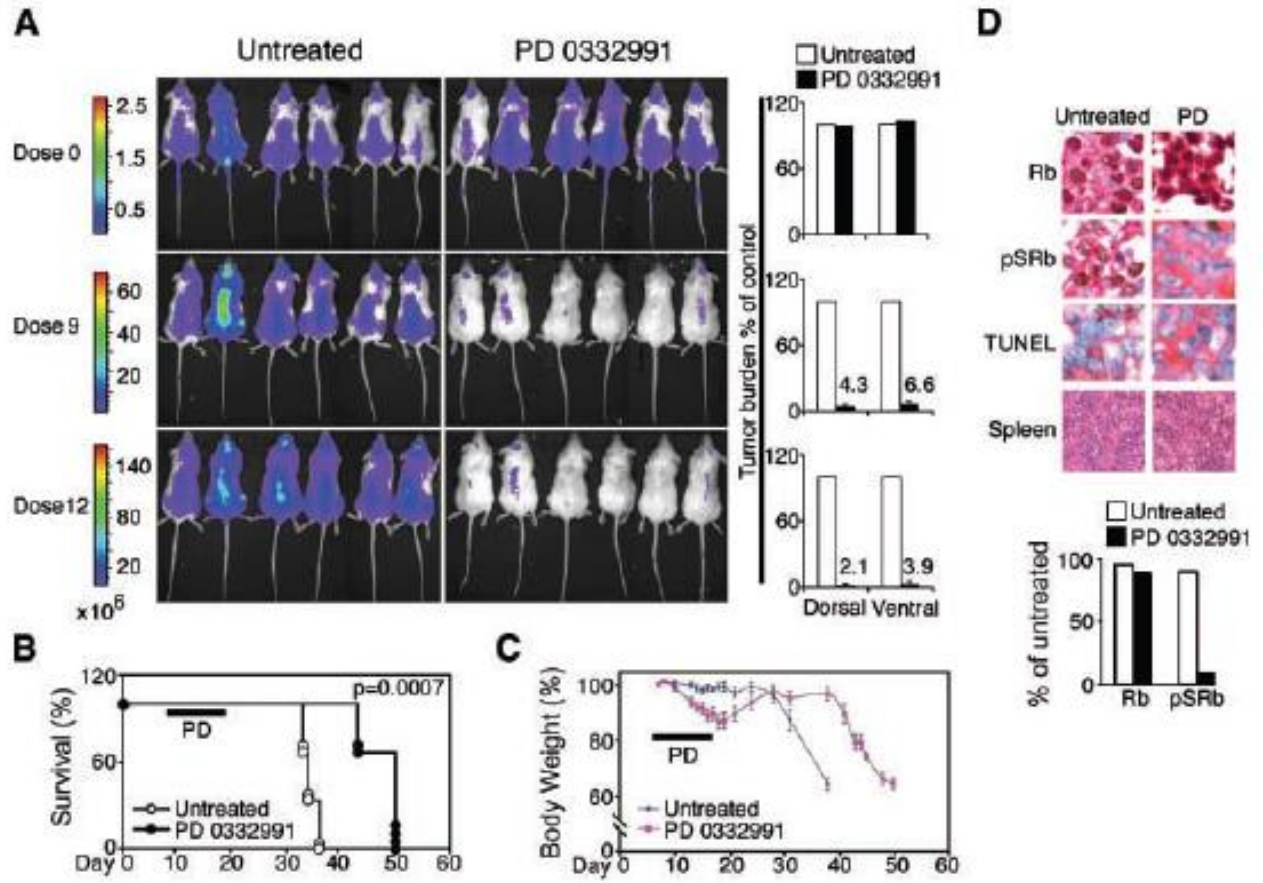
	Palbociclib plus letrozole (n=83)			Letrozole (n=77)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	19 (23%)	49 (59%)	14 (17%)	49 (64%)	16 (21%)	0
Neutropenia	17 (20%)	40 (48%)	5 (6%)	3 (4%)	1 (1%)	0
Leucopenia	20 (24%)	16 (19%)	0	2 (3%)	0	0
Fatigue	30 (36%)	2 (2%)	2 (2%)	17 (22%)	1 (1%)	0
Anaemia	24 (29%)	4 (5%)	1 (1%)	4 (5%)	1 (1%)	0
Nausea	19 (23%)	2 (2%)	0	9 (12%)	1 (1%)	0
Arthralgia	18 (22%)	1 (1%)	0	10 (13%)	2 (3%)	0
Alopecia	18 (22%)	NA	NA	2 (3%)	NA	NA
Diarrhoea	14 (17%)	3 (4%)	0	8 (10%)	0	0
Hot flush	17 (21%)	0	NA	9 (12%)	0	NA
Thrombocytopenia	12 (14%)	2 (2%)	0	1 (1%)	0	0
Decreased appetite	12 (14%)	1 (1%)	0	5 (6%)	0	0
Dyspnoea	11 (13%)	2 (2%)	0	5 (6%)	1 (1%)	0
Nasopharyngitis	13 (16%)	0	0	8 (10%)	0	0
Back pain	11 (13%)	0	1 (1%)	11 (14%)	1 (1%)	0
Headache	12 (14%)	0	0	8 (10%)	0	0
Vomiting	12 (14%)	0	0	2 (3%)	1 (1%)	0
Asthenia	9 (11%)	2 (2%)	0	3 (4%)	0	0

The Lancet Oncology 2015 16, 25-35DOI: (10.1016/S1470-2045(14)71159-3)

A Novel Orally Active Small Molecule Potently Induces G_1 Arrest in Primary Myeloma Cells and Prevents Tumor Growth by Specific Inhibition of Cyclin-Dependent Kinase 4/6

Linda B. Baughn,[1] Maurizio Di Liberto,[1] Kaida Wu,[4] Peter L. Toogood,[5] Tracey Louie,[1] Rachel Gottschalk,[3] Ruben Niesvizky,[2] Hearn Cho,[2,3] Scott Ely,[1] Malcolm A.S. Moore,[4] and Selina Chen-Kiang[1,3]

Cancer Res 2006; 66: (15). August 1, 2006



Phase Ib Palbociclib in MCL

Patients and design

- Previously treated MCL
- Palbociclib 3 weeks on/1 week off until progression
- Biopsies on day 1 and 21 of cycle 1

Safety

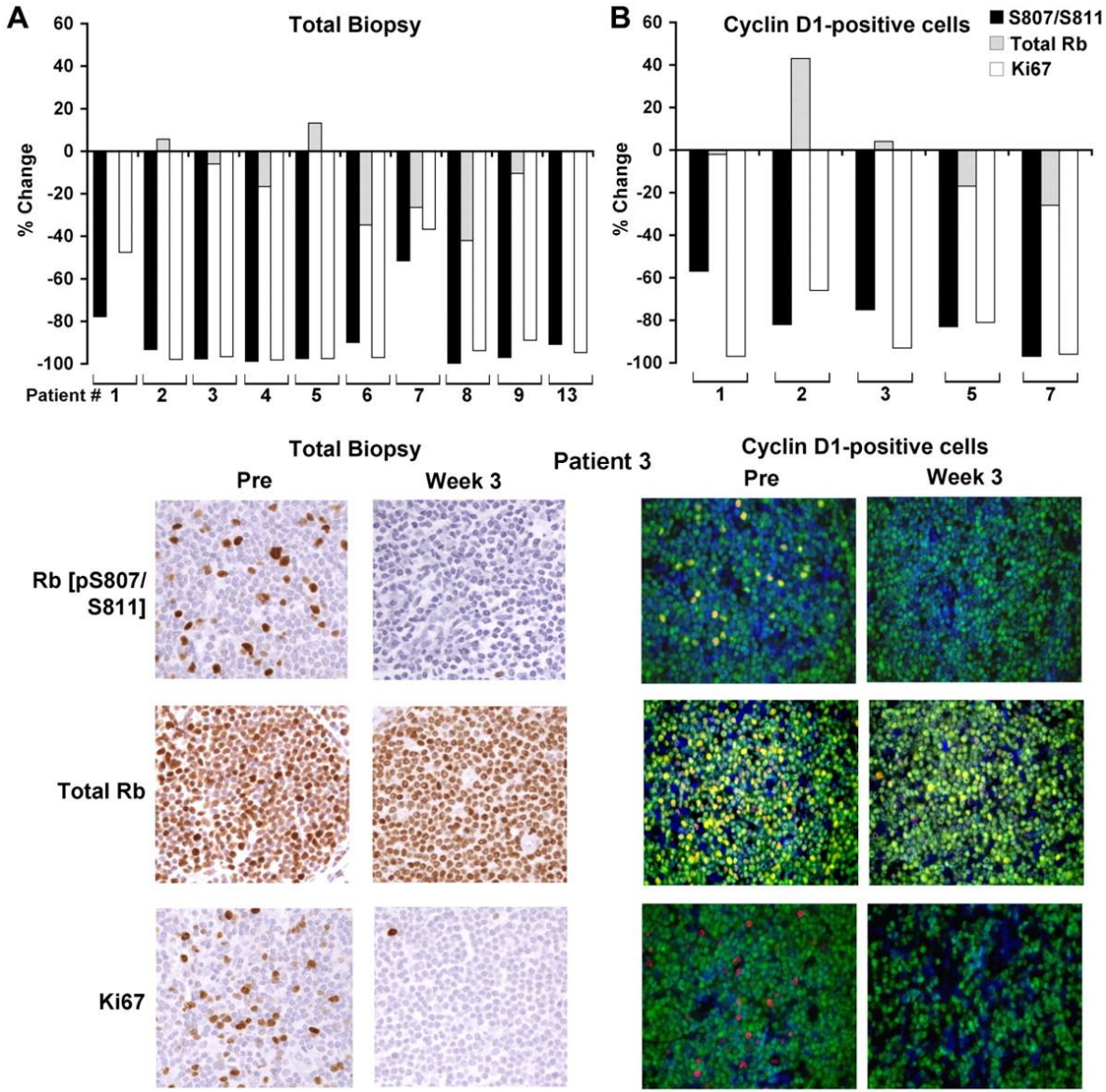
Adverse event, n (%)	Total (n = 17)	Grade 3	Grade 4
Neutropenia	7 (41)	4 (24)	2 (12)
Fatigue	6 (35)	0	0
Thrombocytopenia	5 (29)	3 (18)	1 (6)
Diarrhea	3 (18)	1 (6)	0
Leukopenia	2 (12%)	0	1 (6)
Anemia	2 (12%)	0	0
Nausea	2 (12%)	0	0
Dizziness	2 (12%)	0	0
Headache	2 (12%)	0	0
Hypophosphatemia	2 (12%)	2 (12)	0

Activity

- 16 evaluable
- 1 CR (24+ mo.)
- 2 PR (18.8 mo., 30+ mo.)
- 7 SD
- 6 PD
- Median PFS 4 mo.
- 1-year EFS 29%

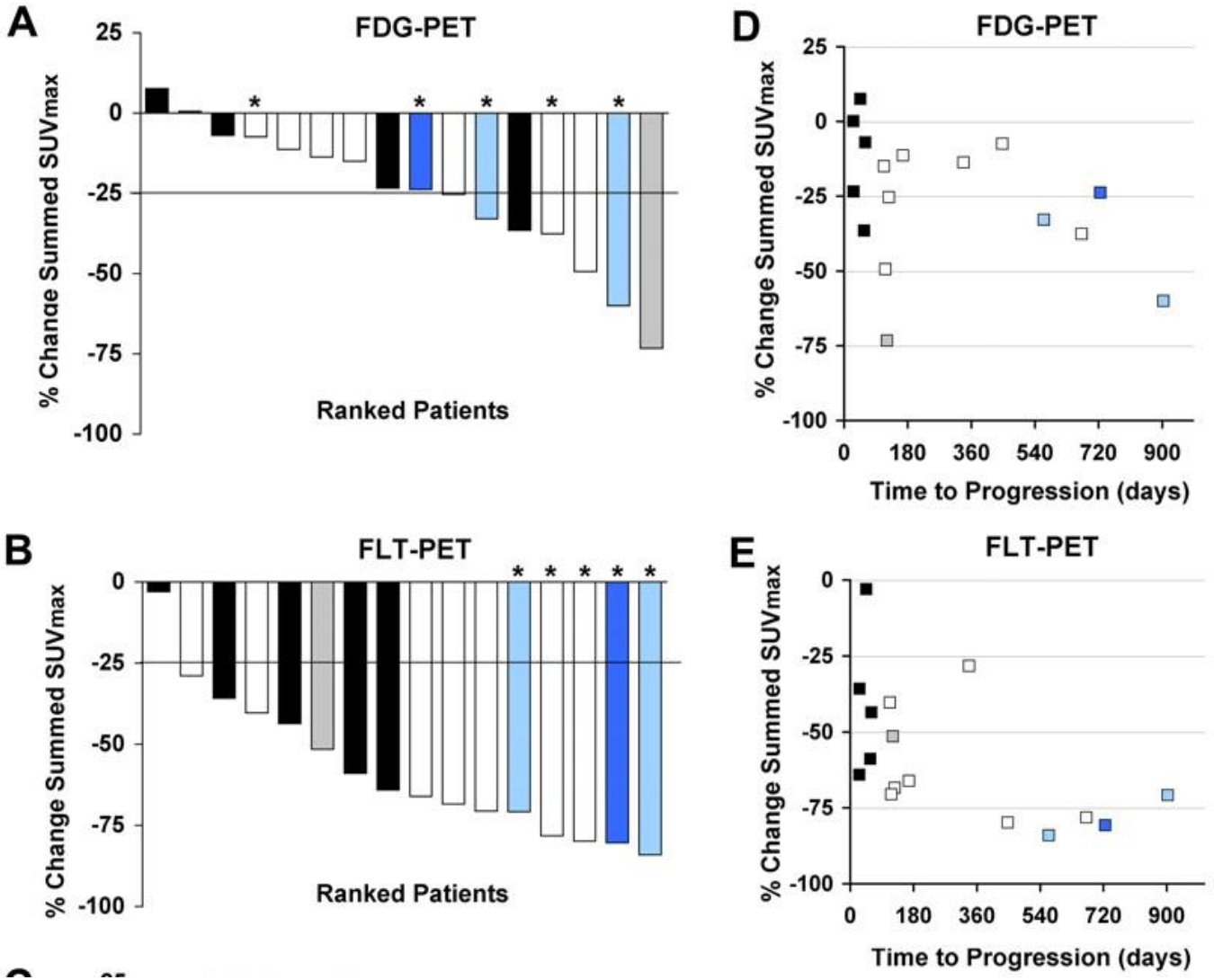
Leonard J P et al. Blood 2012;119:4597-4607

PD0332991-induced changes in Rb phosphorylation and Ki-67 expression in pre- and on-treatment lymph node biopsies.



Leonard J P et al. Blood 2012;119:4597-4607

Quantification of FDG- and FLT-PET changes on PD0332991 and correlation with each other and time to progression.

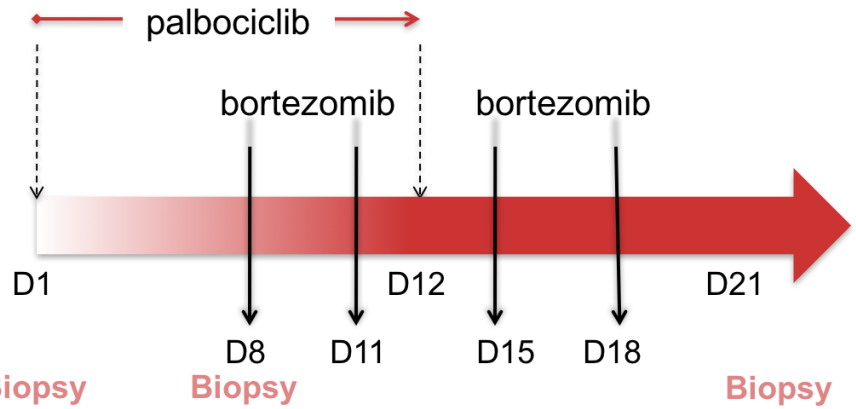


Leonard J P et al. Blood 2012;119:4597-4607

Conclusions

- Palbociclib inhibits CDK4 in all Rb+ MCL cells.
- Change in FLT PET was associated with response duration.
- But degree of CDK4 inhibition is not associated with clinical response. So what determines clinical response?
- Why is there tumor regression with an agent that is presumably cytostatic?
- There is another level of complexity.

Phase I Palbociclib + Bortezomib



Dose level	Palbociclib	Bortezomib
1	75 mg	1.0 mg/m^2
2	100 mg	1.0 mg/m^2
3	125 mg	1.0 mg/m^2
4	125 mg	1.3 mg/m^2

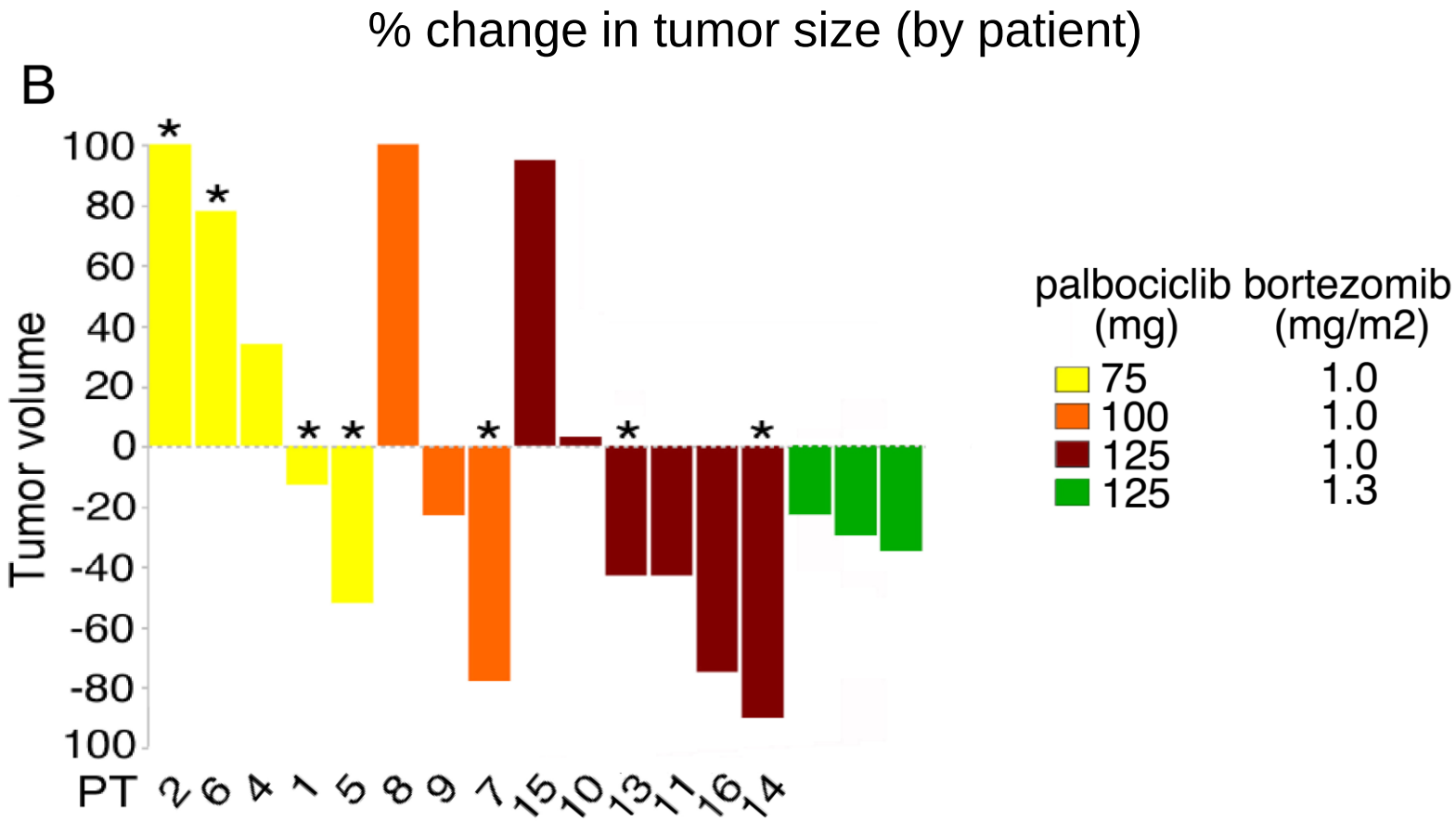
Restaging
-After cycles 2, 5, 8, 12, then q4 cycles

Duration of therapy
-Until progression, toxicity, withdrawal of consent

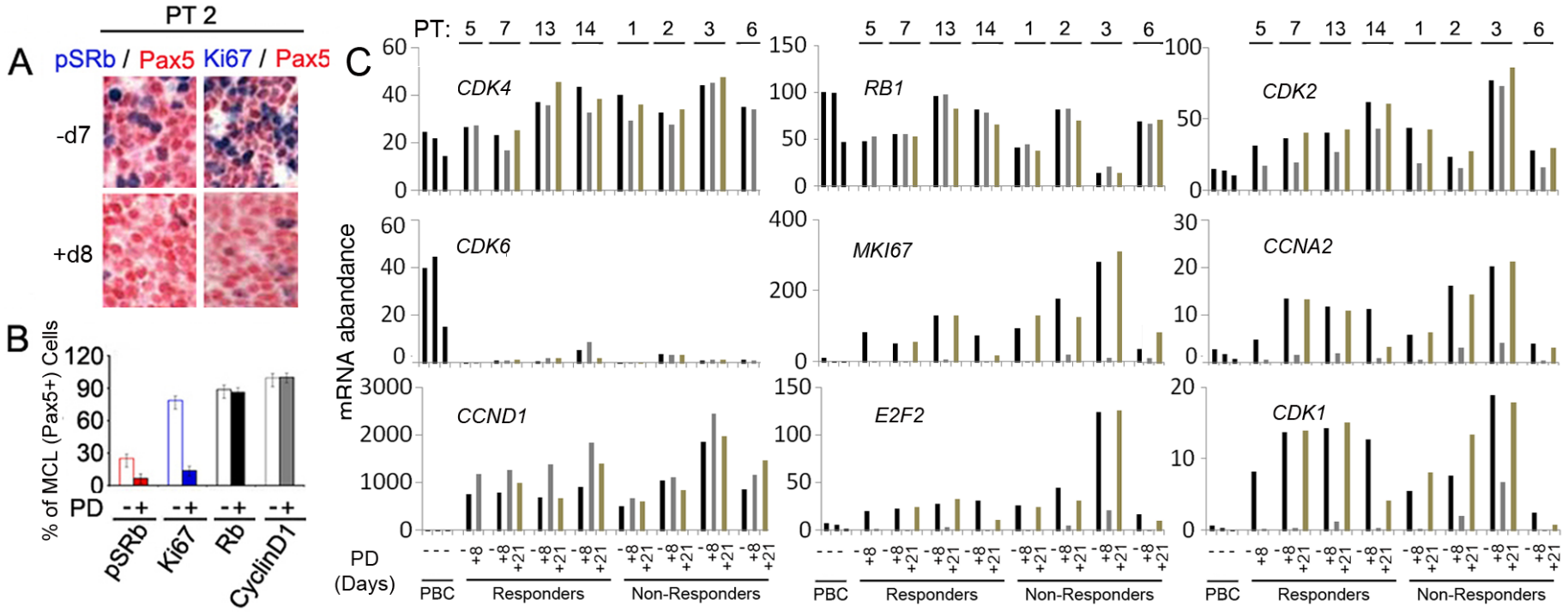
Concomitant medications
-HSV prophylaxis rec.
-GCSF permitted after cycle 1

		Total N=19	Level 1 N=6	Level 2 N=3	Level 3 N=7	Level 4 N=3
Median age	(range)	64 (42-83)	61	75	64	71
Sex	M:F	11:8	3:3	2:1	6:1	2:1
Prior therapies	(range)	2 (1-7)	2.5 (1-7)	3 (2-5)	4 (1-7)	1 (1-2)
Prior bortezomib		7	1	3	1	2
LDH	ULN=192	209	190	224	225	130
WBC	x 109	4.8	4.8	6.9	4.8	4.3
ECOG	0-1	18	5	3	7	3
	2	1	1	0	0	0
MIPI	low	6	2	1	2	1
	Int.	11	4	0	7	2
	high	2	0	2	0	0

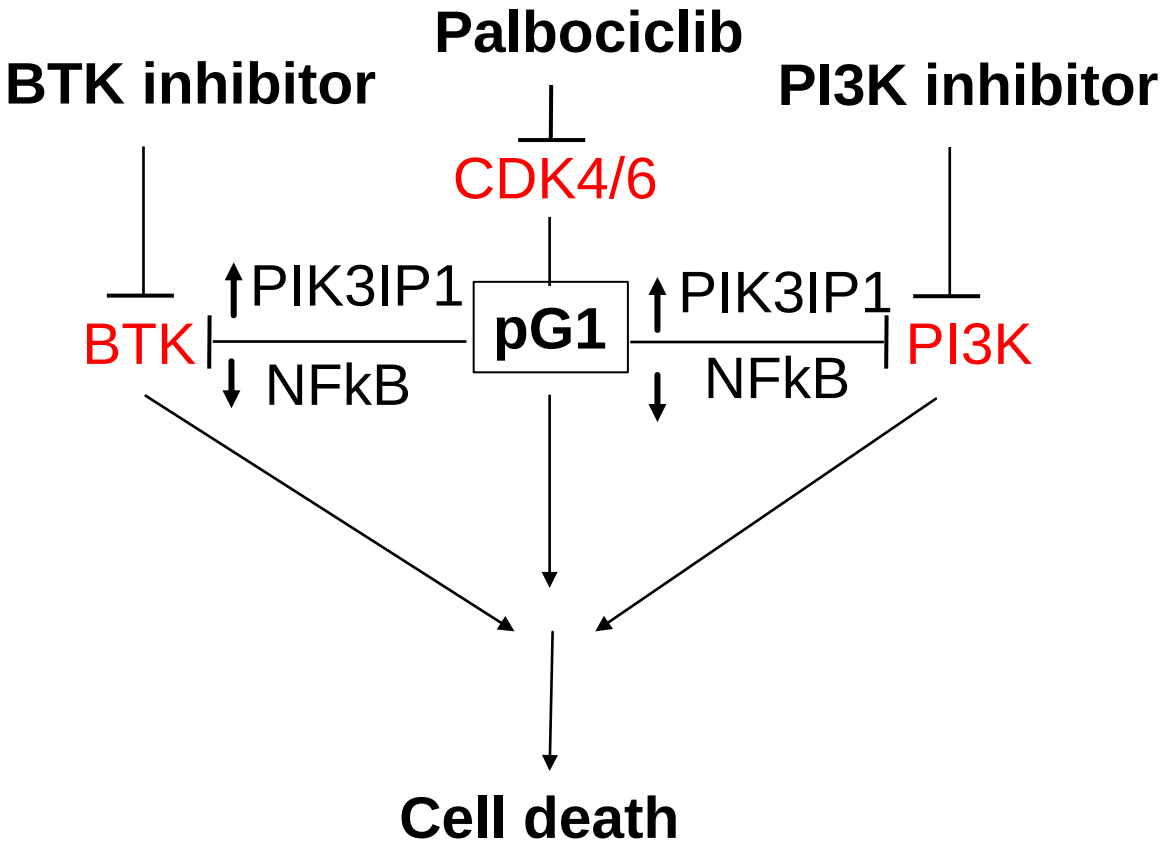
Phase I Palbociclib + Bortezomib: Efficacy



Palbociclib Induces Reversible Cell Cycle Arrest



Prolonged inhibition of CDK4 reprograms MCL cells for greater killing by BTK or PI3K inhibition



Dose level	Ibrutinib	PD 0332991 (palbociclib)
1	280 mg	75 mg x 21 days
2	420 mg	75 mg x 21 days
3	420 mg	100 mg x 21 days
4	560 mg	100 mg x 21 days
5	560 mg	125 mg x 21 days

DLT (cycle 1)
- Grade 3 or 4 non-heme tox., N/V/D ≥ grade 3 >48h
- Grade 4 ANC > 7 days, or ANC < 750 cells/mL with fever or sepsis
- Grade 4 plts >5 days or grade ≥3 with bleeding

Patients seen D1, 2, 8, 14 during cycle 1, then on D1 of each cycle

Response evaluated after cycle 3, cycle 6, then every 6 cycles
- CR confirmed by PET/CT, BMBx (if involved), endoscopy (if involved)

Treatment continues until progression or unacceptable toxicity

Figure courtesy of Selina Chen-Kiang

Weill Cornell Medicine NewYork-Presbyterian

Di Liberto, Huang, et al, unpublished
Chiron et al, Cancer Discovery, 2014

Dose-limiting toxicity, notable adverse events, and infections

Dose level	# of DLT	DLT
1	0/3	--
2	0/3	--
3	1/6	Grade 4 platelets > 5 days
4*	0/6	--
5	2/5	Grade 3 rash (n=2)

*DL4 was established as the MTD

Notable Adverse Events (n=1)

- Grade 3 pneumonitis
- Grade 3 decreased LVEF
- Grade 4 bleeding
- Grade 4 increased ALT/AST
- Grade 4 ARDS

Grade 3-4 infections (n=1)

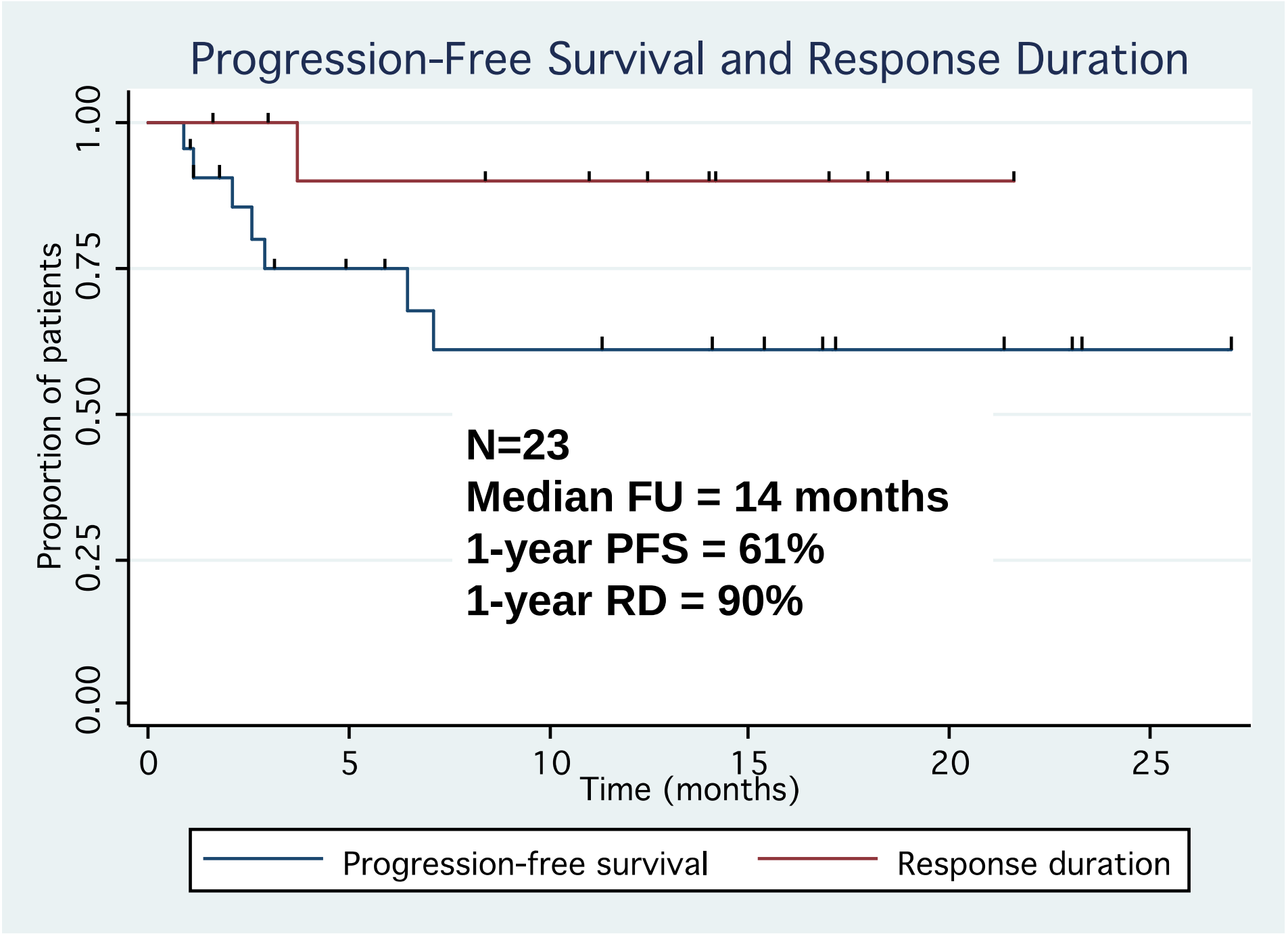
- Grade 3 diverticulitis
- Grade 3 VZV encephalitis
- Grade 3 febrile neutropenia
- Grade 3 C. diff
- Grade 4 PCP pneumonia

Best response – Intent to treat

Response	Total n=22	DL 1 n=3	DL 2 n=3	DL 3 n=6	DL 4 n=4	DL 5 n=5
CR[#]	9 (41%)	3	1	2		3
PR[$]	5 (23%)		1	2	2	
SD	1 (5%)		1			
PD	5 (23%)			1	2	2
NE*	2 (9%)			1	1	

[#] - Median time to CR was 3 cycles
[$] - 3 PR are CR by PET with residual microscopic marrow/GI involvement.
* - Two NE patients stopped treatment due to adverse events (platelets).
* - Three NE patients are currently receiving ongoing treatment and have not yet been assessed for response.

Characteristic	Response
Ki67 (n=13)	
< 50%	6/8 (75%)
> 50%	3/5 (60%)
Response to prior therapy (n=18)	
Refractory	2/6 (33%)
Responder	10/12 (83%)
Number of prior therapies (n=21)	
< 4	11/18 (61%)
≥ 4	2/3 (67%)
MIPI (n=21)	
Low	5/7 (71%)
Intermediate	5/8 (62.5%)
High	3/6 (50%)


Progression-Free Survival and Response Duration
Proportion of patients
0.00
0.25
0.50
0.75
1.00
0
5
10
15
20
25
Time (months)
N=23
Median FU = 14 months
1-year PFS = 61%
1-year RD = 90%
Progression-free survival
Response duration

Conclusion

- The MTD was ibrutinib 560 mg daily plus palbociclib 100 mg x 21/28 days.
- Toxicity is primarily myelosuppression.
- Rash occurred in 39%
  - Grade 3 rash (DLT) in 2 patients at DL5.
- ORR 64%; CR rate 43%
  - Median time to CR of 3 months
  - Responses occurred at all levels of Ki67.
- Estimated one-year PFS 61%.
- Estimated one-year RD 90%.
  - Only one responding patient has progressed
- A single-arm phase II multi-center clinical trial to evaluate time to progression is planned.

Acknowledgements

Clinical Groups

WCM

John Leonard

Jia Ruan

Amelyn Rodriguez

Scott Heese

OSU

Kristie Blum

Kami Maddocks

Wash U

Nancy Bartlett

UNC

Steven Park

Basic Science

Chen-Kiang Lab

Selina Chen-Kiang

Maurizio Di Liberto

Xiangao Huang

Bioinformatics

Olivier Elemento

Pathology

Giorgio Inghirami

NIH/NCI

Pamela Harris

Funding Sources

NIH/NCI

LRF

V Foundation

Our Patients

&

Their Families

Weill Cornell Medicine