Mechanism for targeting CDK4, BTK and PI3K in Mantle Cell Lymphoma

Selina Chen-Kiang, Ph.D.

Weill Cornell Medicine

Goal

To develop mechanism-based therapy in mantle cell lymphoma

- Effective, tolerable, durable
- Mechanism of resistance
- Biomarkers

Bench to Bedside and Back Approach

- Basic science
- Preclinical studies
- Clinical relevance
- Hypothesis-driven combination therapy
- Longitudinal genomics and IHC
    - RNA and exome-sequencing
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    - ATAC (**A**ssay for **T**ransposase-**A**ccesible **C**hromatin)-seq
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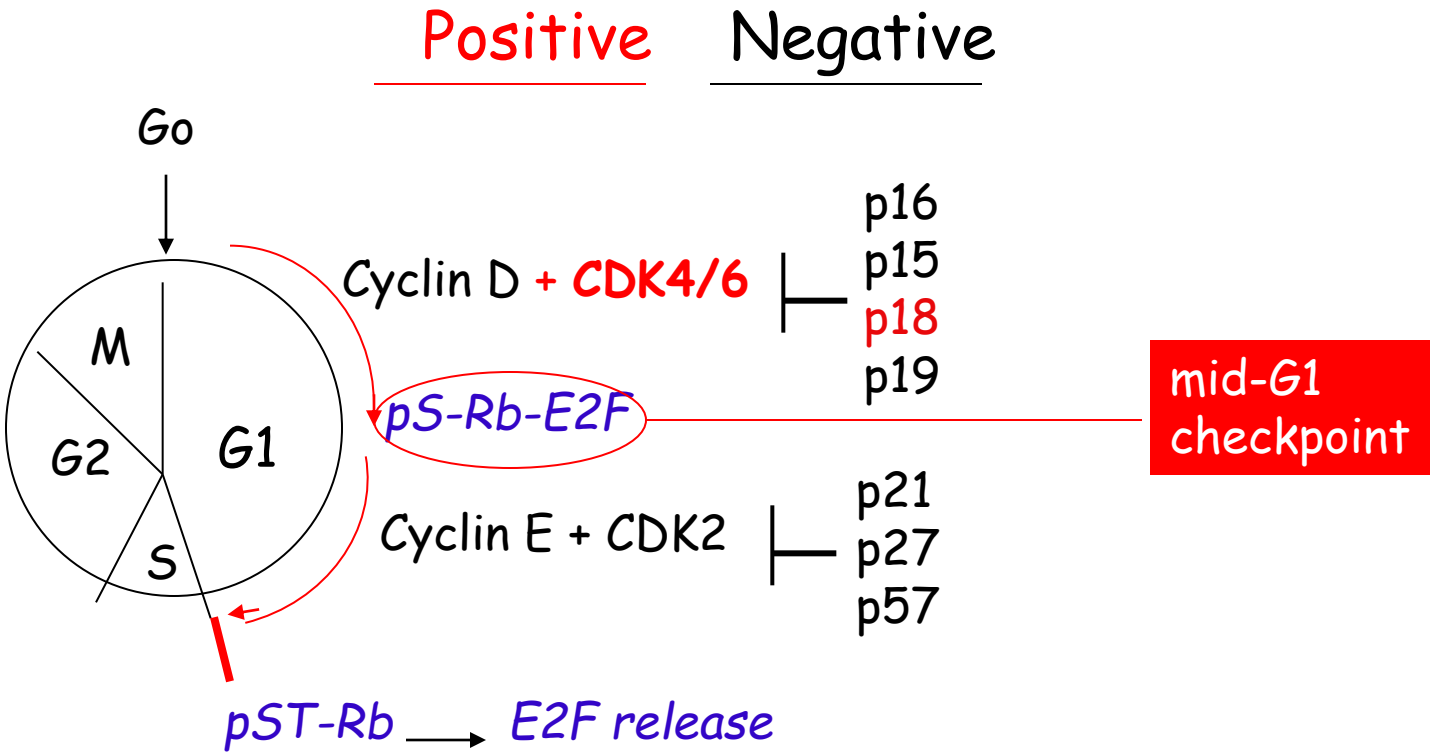
- Mechanism--loss and gain of function studies

Back to bedside!!

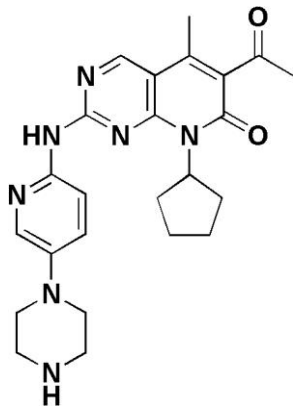
The Cell Cycle



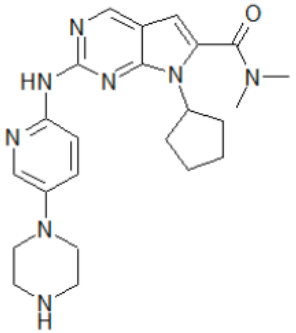
CDK: Cyclin-Dependent Kinase
$p18^{INK4c}$ (*CDKN2C*)

CDK4 and CDK6-Specific Inhibitor

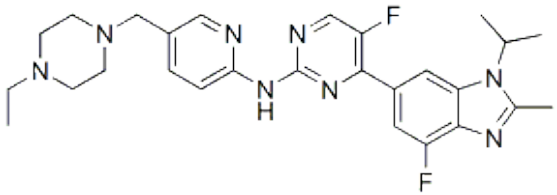
PD 0332991
(palbociclib, Ibrance)

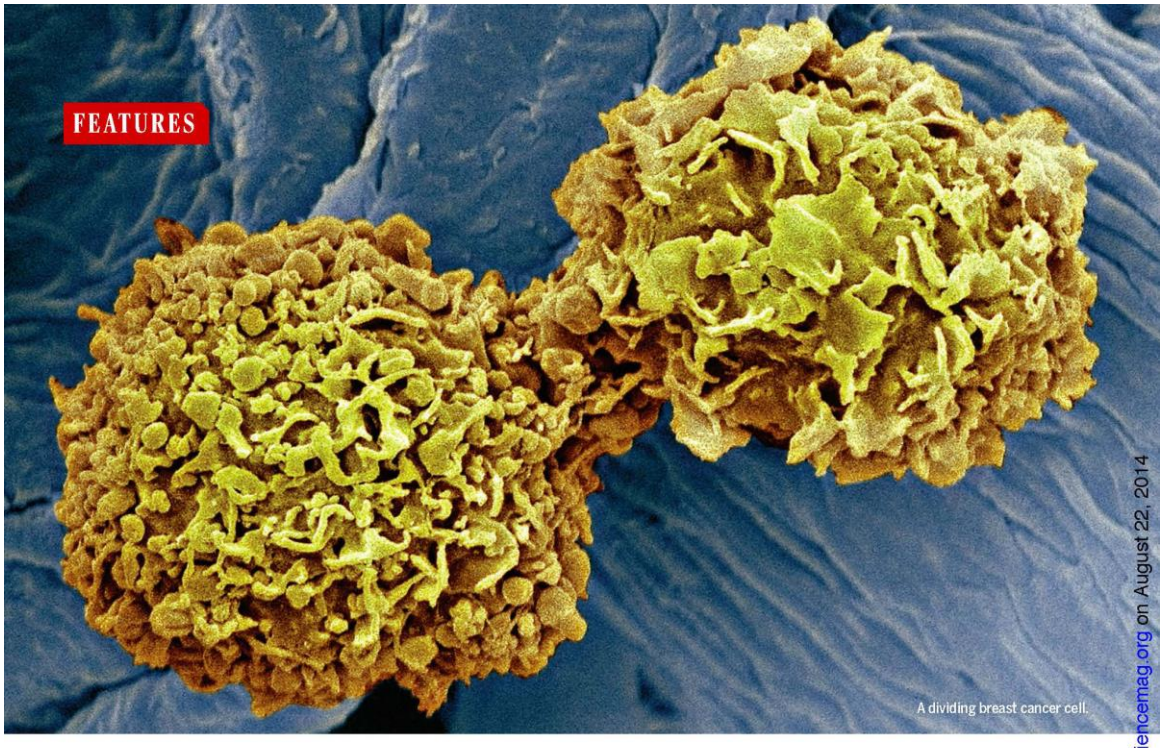


LEE011
(ribociclib)



LY 2835219
(abemaciclib)





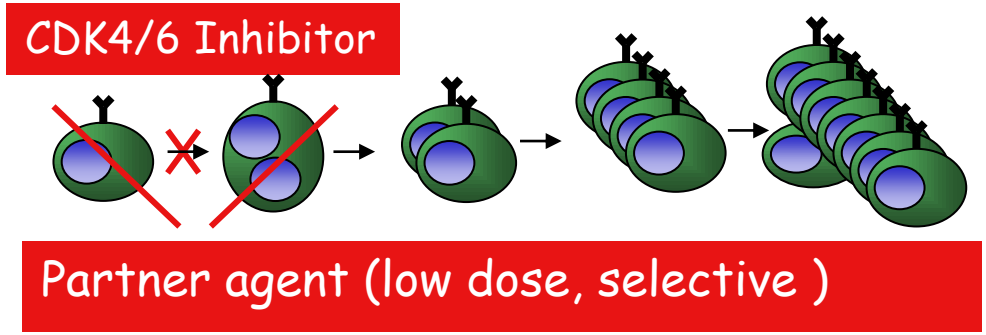
A dividing breast cancer cell.

The cancer drug that almost wasn't

After years in drug development limbo, a compound that interrupts cell division has revitalized a troubled area of cancer research

By **Ken Garber**

Targeting CDK4/CDK6 in lymphoma and myeloma



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Mantle cell lymphoma *Phase I palbocilib*
Multiple Myeloma *Phase I/II palbociclib-bortezomib-Dex*
Mantle cell lymphoma *Phase I palbociclib-bortezomib*

<u>In progress</u>

Mantle cell lymphoma *Phase I palbociclib-Ibrutinib*
Multiple myeloma Phase I palbociclib-Lenalidomide-Dex

<u>3/2017</u>

Mantle cell lymphoma *Phase II palbociclib-Ibrutinib*

Mantle Cell Lymphoma (MCL)

Non-Hodgkin's lymphoma (6%) with an overall poor prognosis.

Incurable due to the eventual development of drug Resistance.

Constitutive cyclin D1 expression due to chromosomal t(11;14) translocation and mutations.

Overexpression of CDK4.

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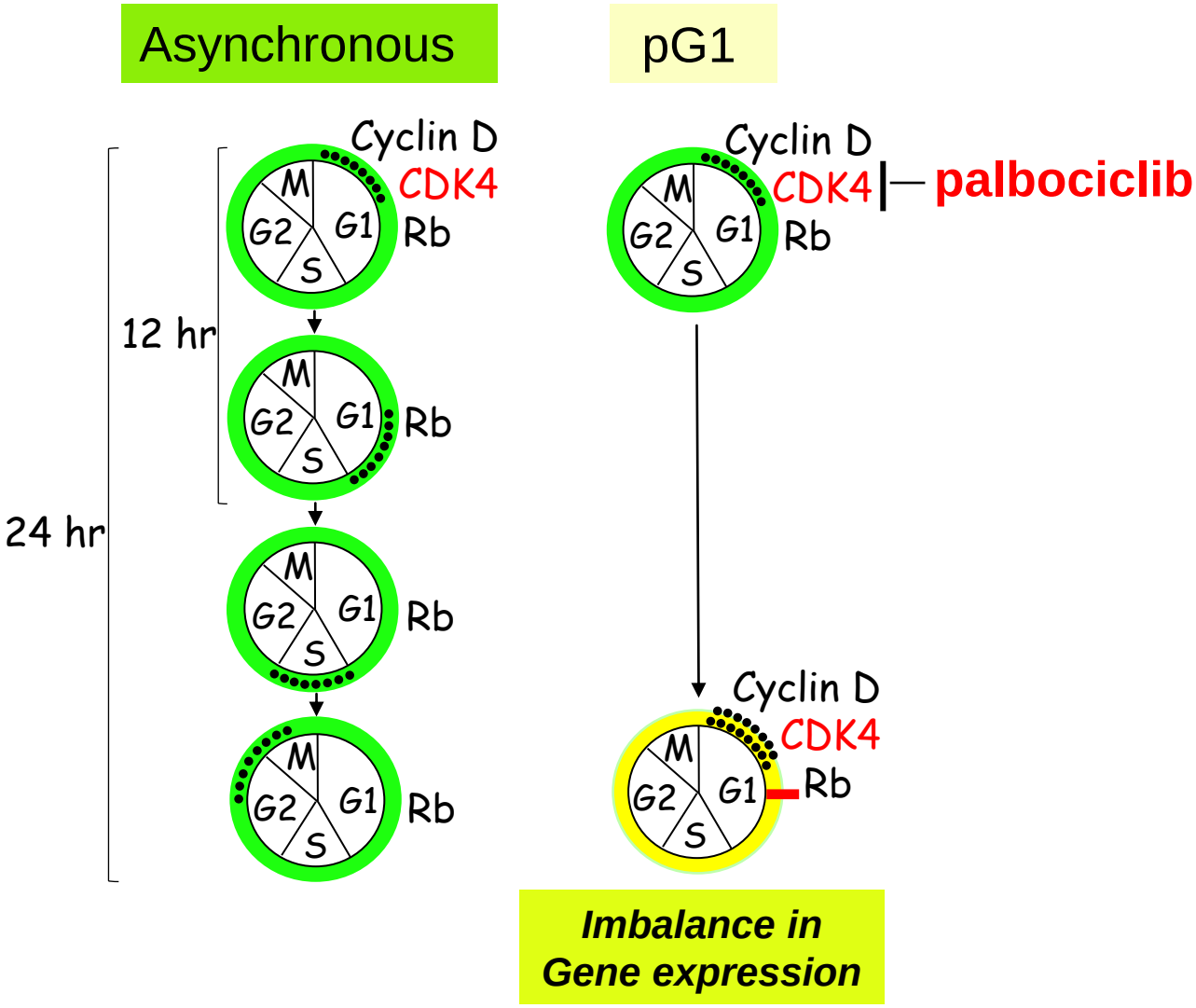
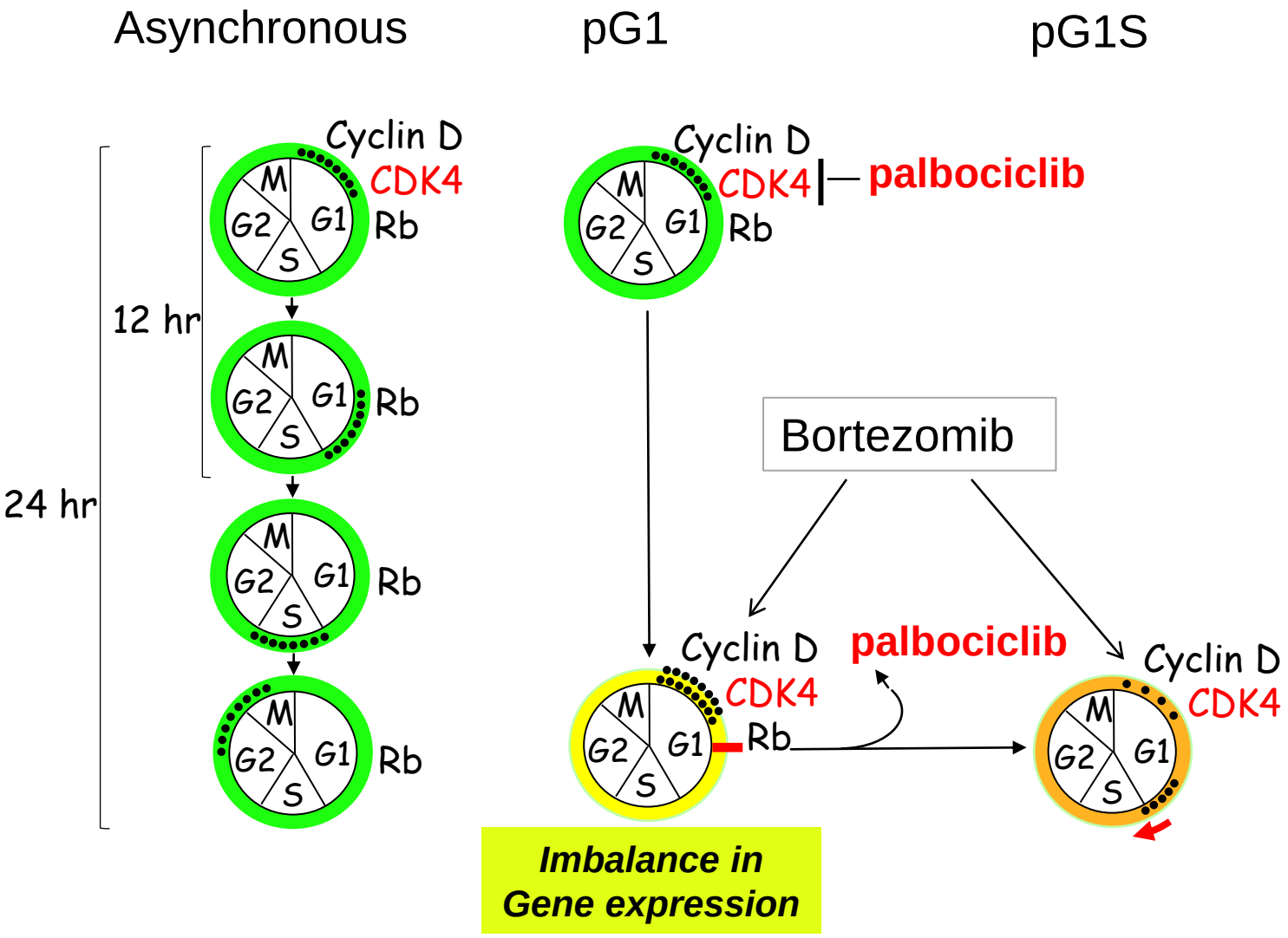
Prolonged Early G1 Arrest (pG1) Hypothesis



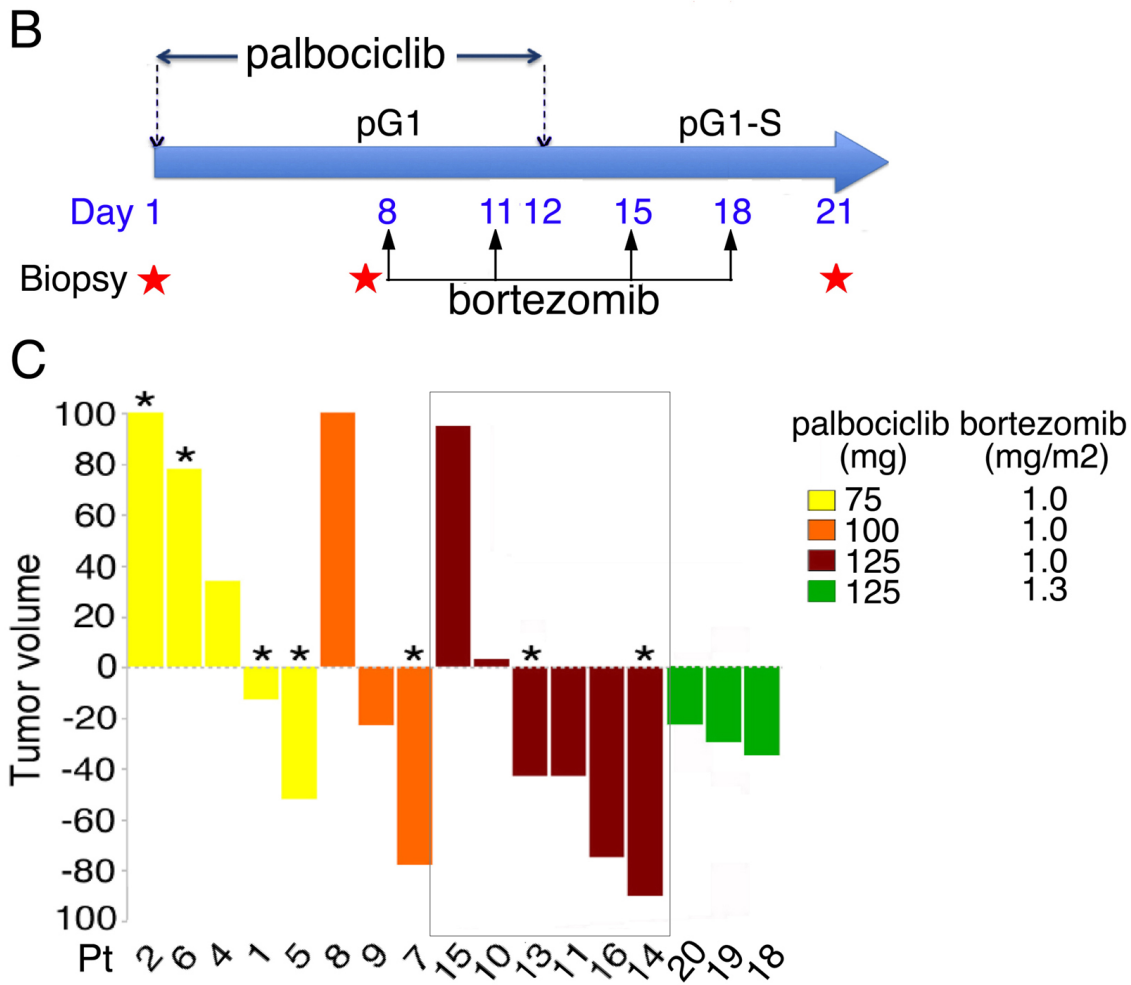
Huang et al., 2012, Blood

Prolonged Early G1 Arrest (pG1) Hypothesis



pG1-S: Release from pG1

Phase I study of palbociclib + bortezomib in patients with recurrent MCL



Martin, Di Liberto, Chiron, Ely, Mason, Leonard, unpublished

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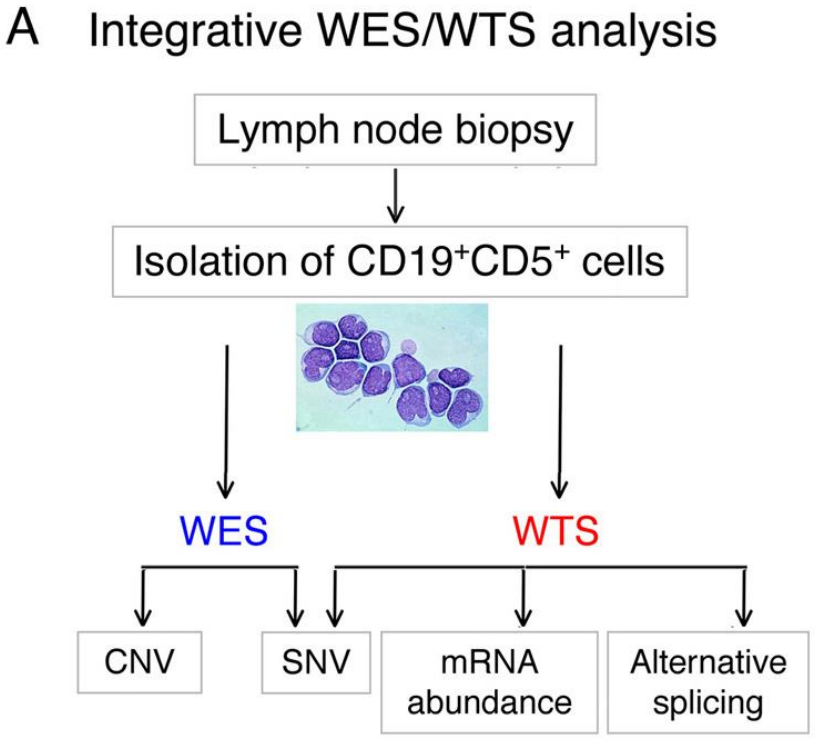
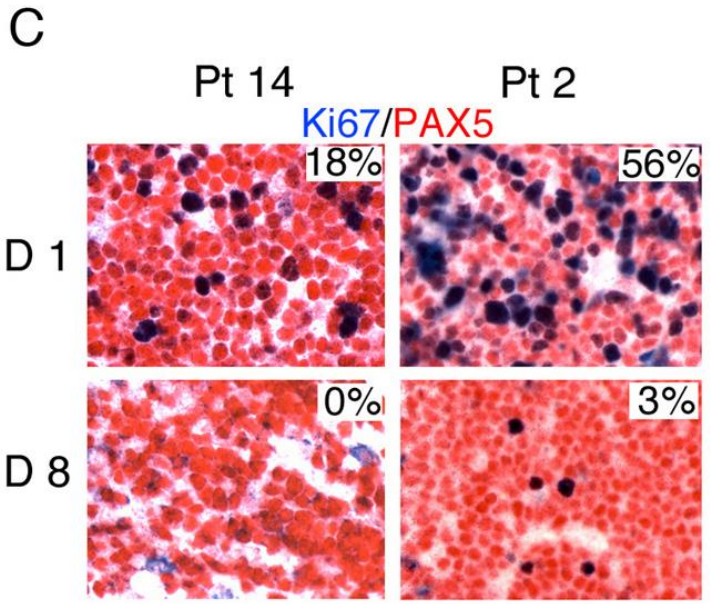
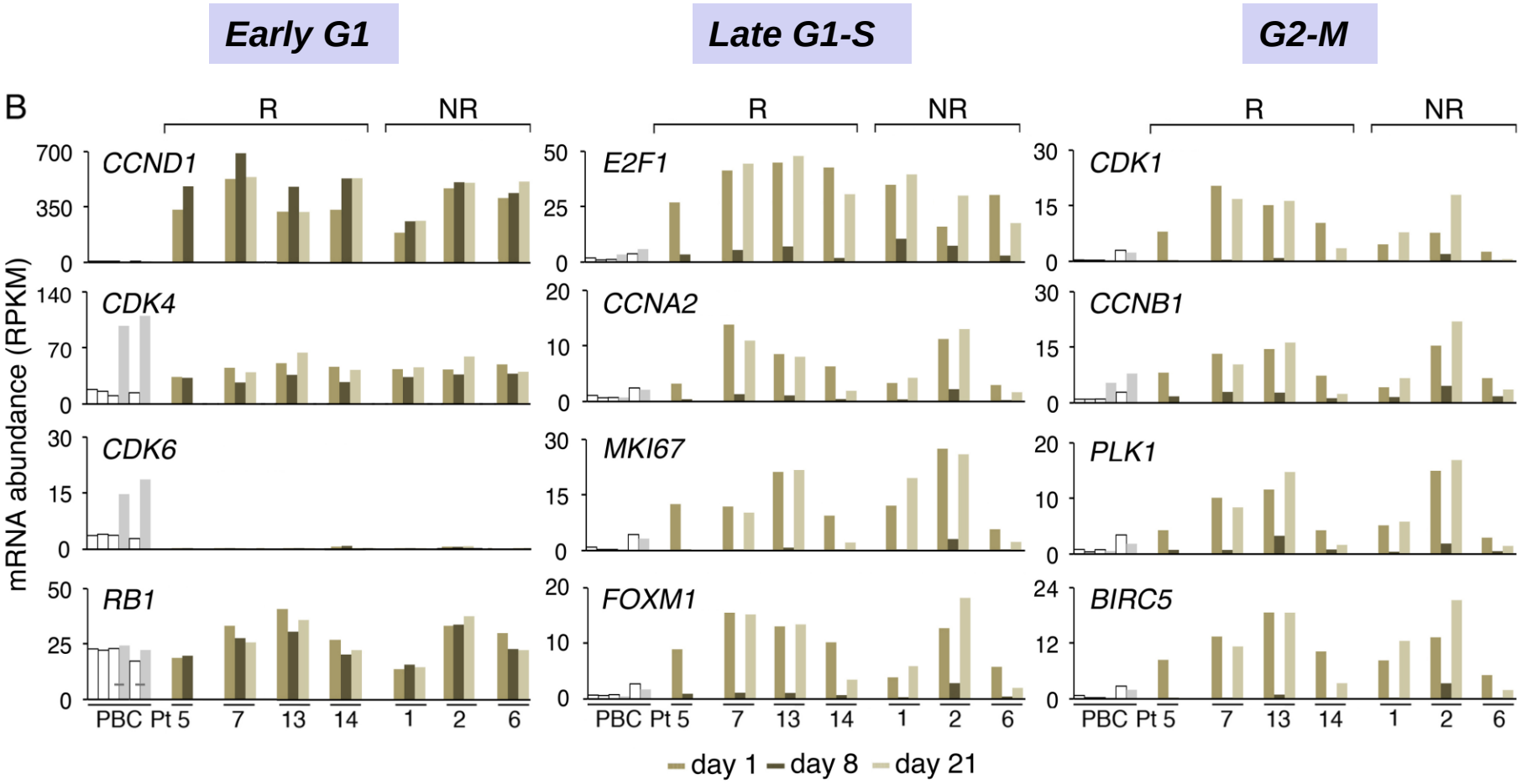
Discovering driver genes that mediate targeting CDK4/6 in lymphoma therapy





Martin, Di Liberto, Chiron, Ely, Mason, Leonard, unpublished

Inhibition of CDK4/6 induces early G1 arrest in all MCL cells *in vivo* initially



R: complete and partial response
NR: progression disease

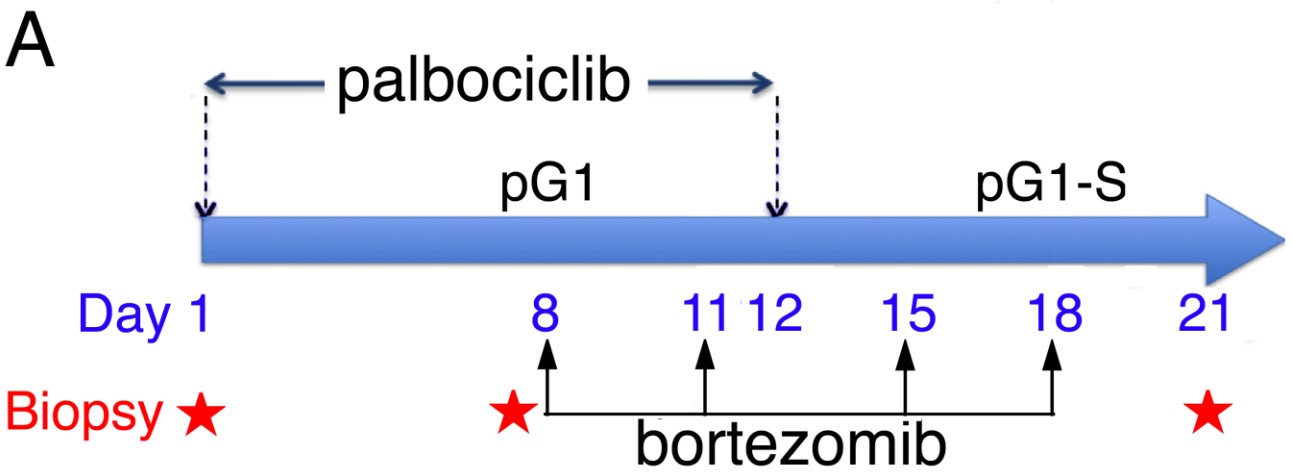
Di Liberto, Chiron, Mason, Martin, Leonard, Ely, unpublished

Inhibition of CDK4/6 induces reversible early G1 arrest in all MCL cells initially.

Can we identify driver genes in pG1(day 8) that discriminate sensitivity from resistance to targeting CDK4 in combination with bortezomib?

Di Liberto, Chiron, Mason, Martin, Leonard, Ely, unpublished

Phase I study of palbociclib + bortezomib (Palbz) in patients with recurrent MCL



Martin, Di Liberto, Leonard, et al, unpublished

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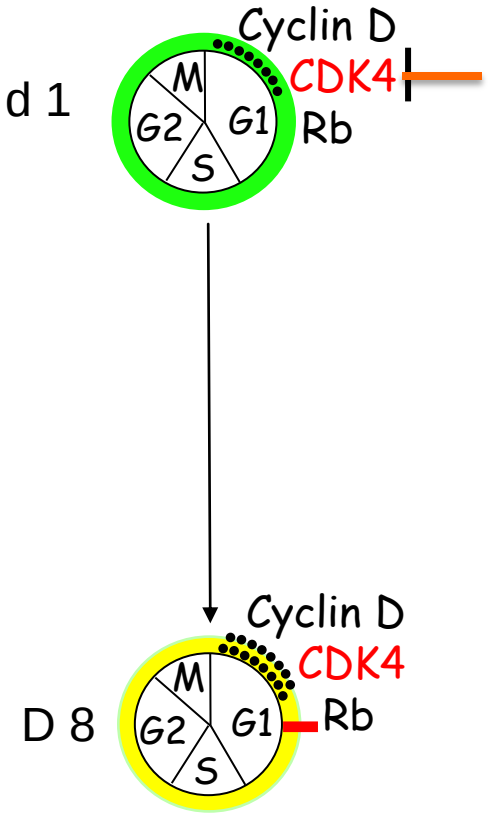
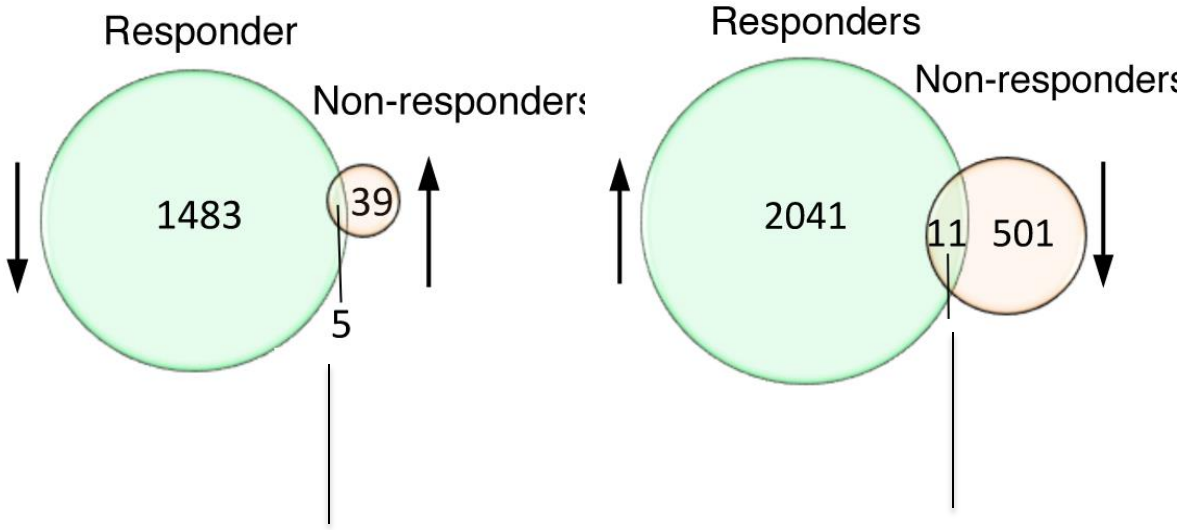
Opposite regulation of genes in pG1 (d8/d1) in responding vs non-responding patients



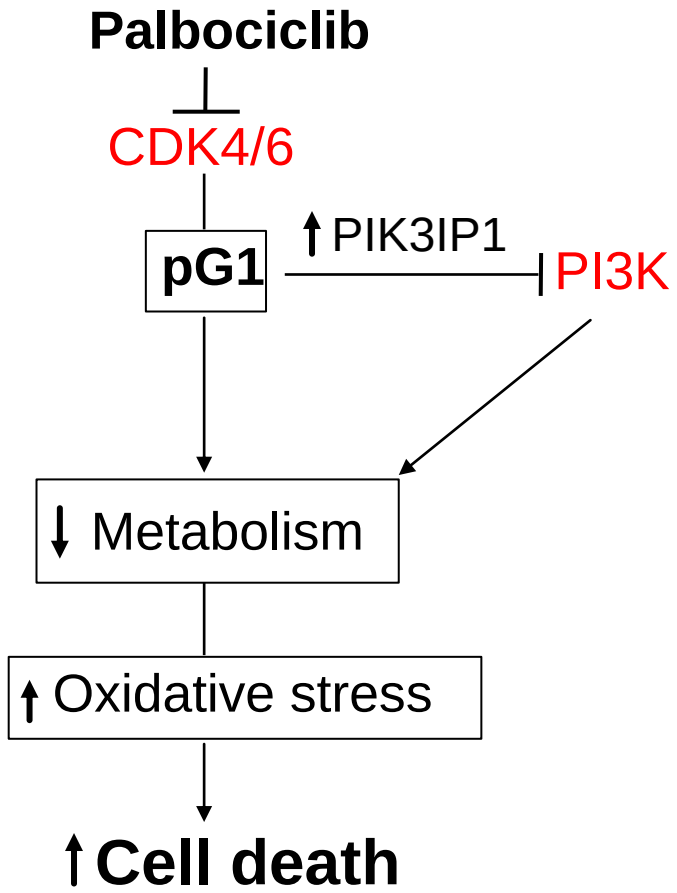
Imbalance in Gene expression



Metabolism
Redox homeostasis
PI3K activation

Di Liberto, Martin, Huang, et al, unpublished

pG1 reprogramming of MCL cells by CDK4 inhibition



Chiron, Di Liberto, Martin et al, Cancer Discovery, 2014

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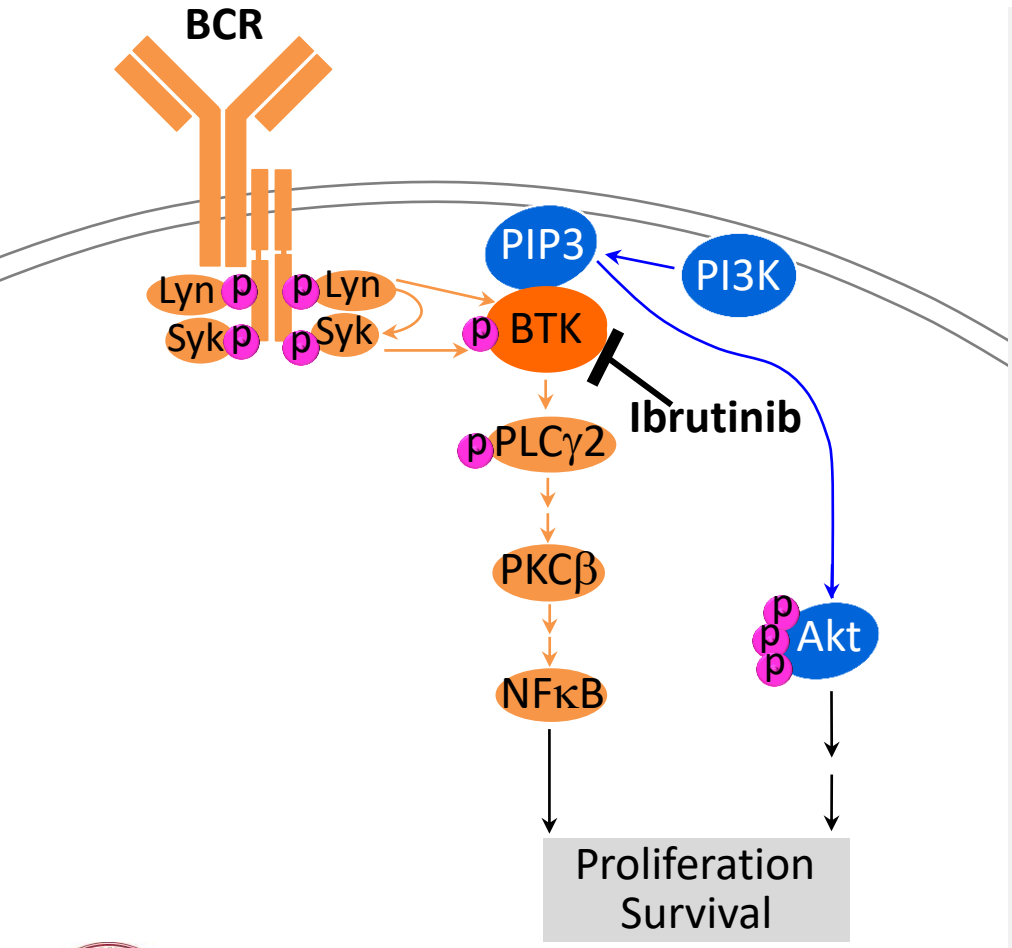
Overriding ibrutinib resistance By targeting CDK4/6 in Combination therapy

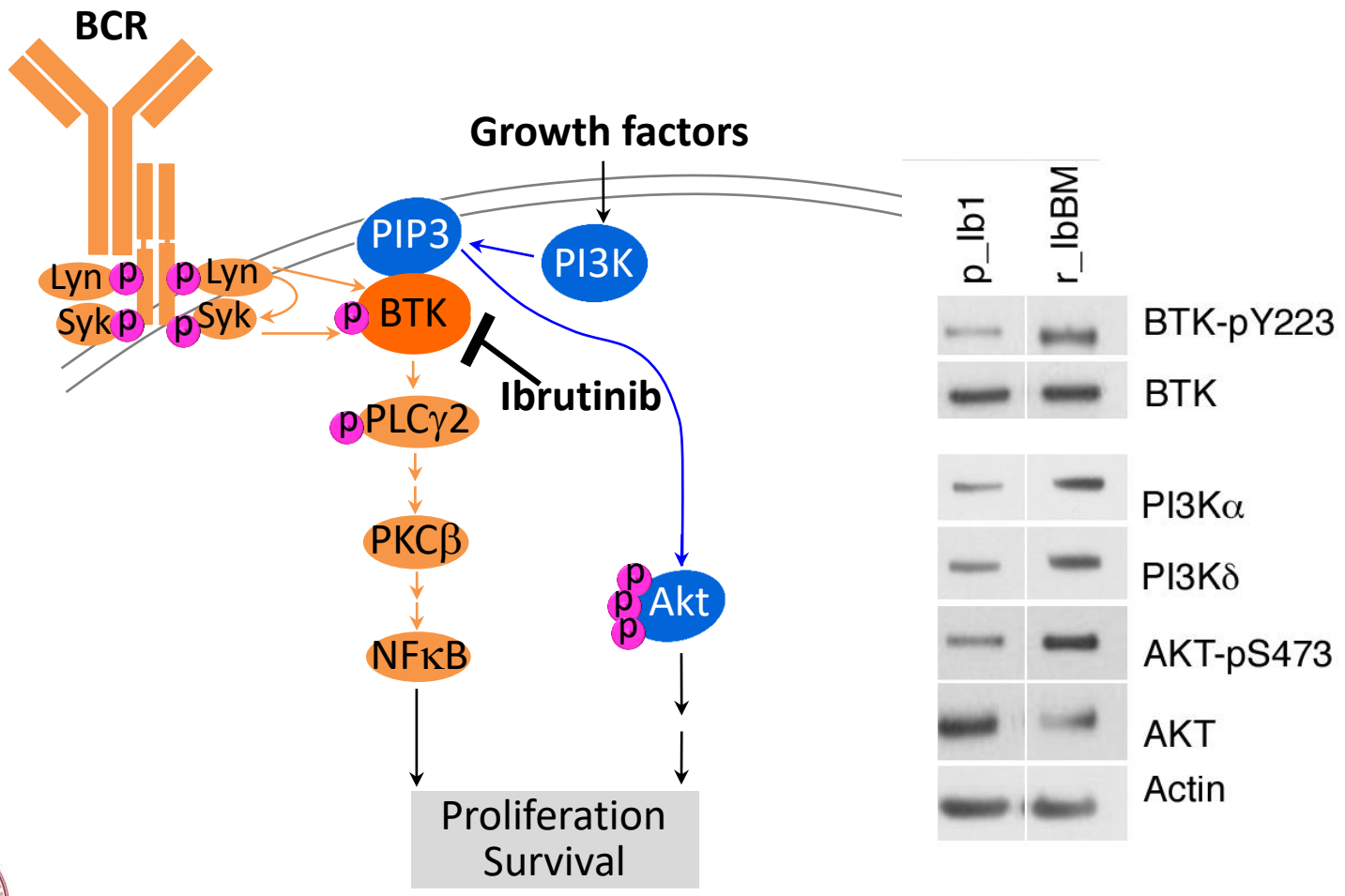
Targeting Bruton Tyrosine Kinase (BTK) by Ibrutinib in MCL



- BTK is required for survival of lymphoma cells;
- Targeting BTK with Ibrutinib is highly effective in MCL[1];
- However, relapse is virtually universal--aggressive proliferation and poor prognosis[2]

1. *Wang et al. N Engl J Med 2014.*
2. *Martin et al. Blood 2016.*

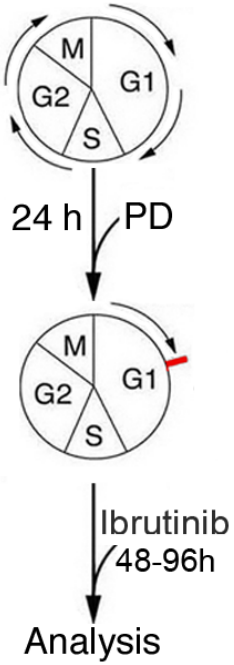
Ibrutinib resistance is concurrent with PI3K activation

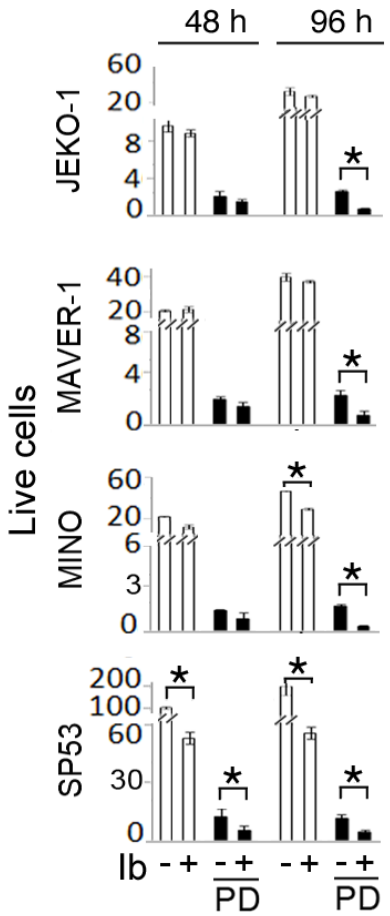


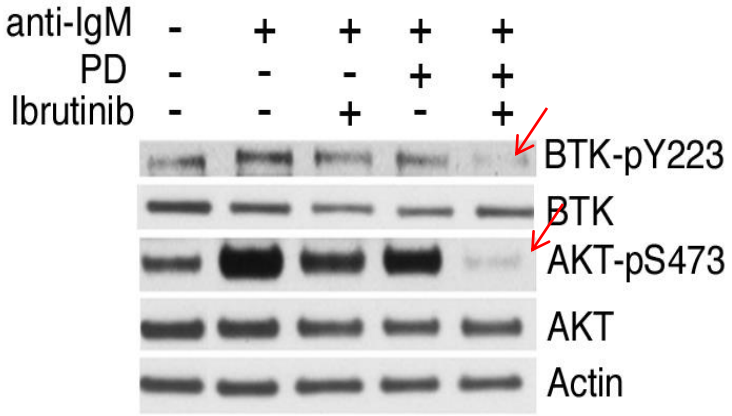
Chiron, Di Liberto, Martin et al, Cancer Discovery, 2014

Prolonged CDK4 inhibition reprograms MCL cells for ibruitinib killing by inhibiting both BTK and AKT

B

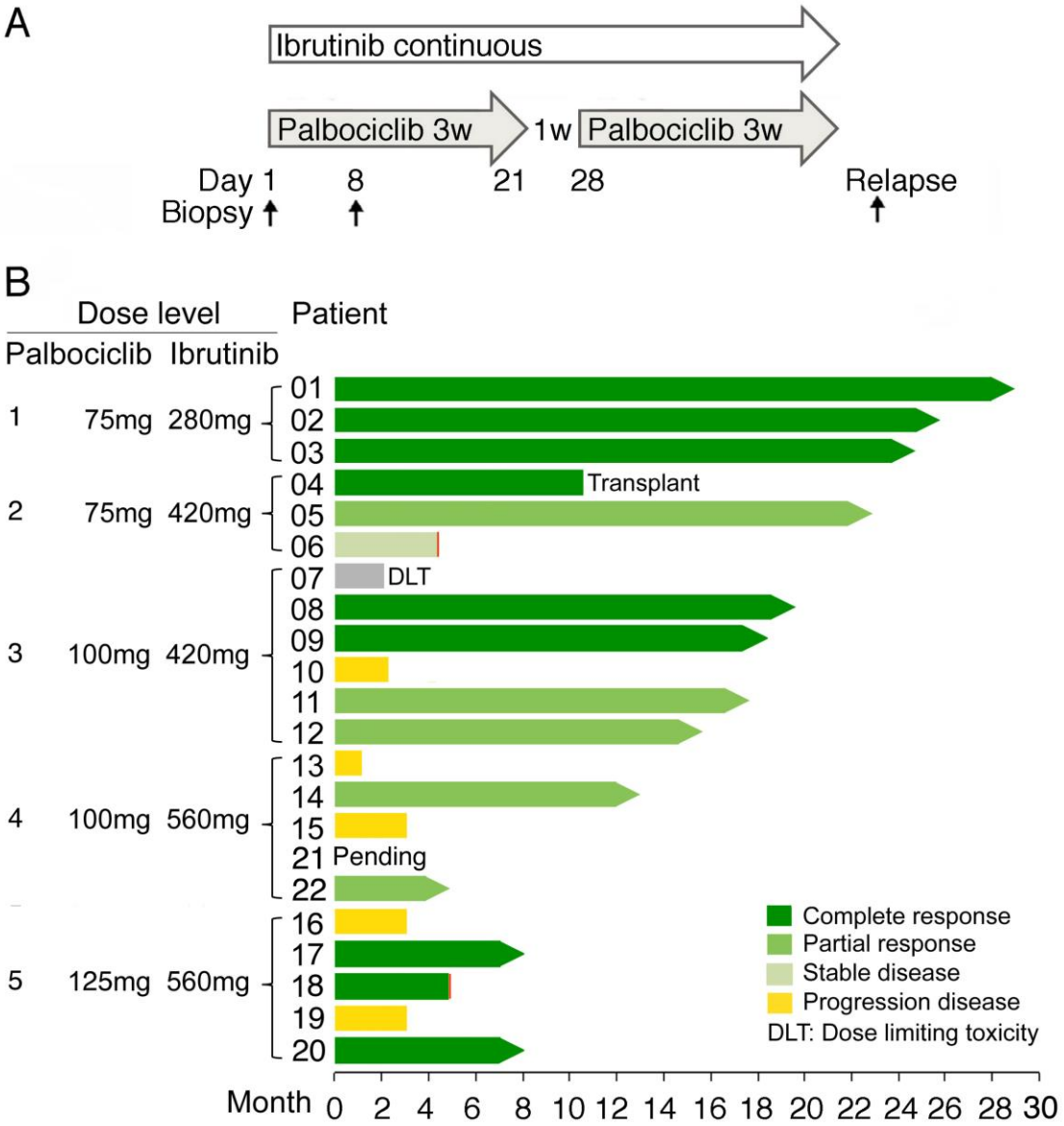






Chiron, Di Liberto, Martin et al, Cancer Discovery, 2014

Phase I clinical trial of palbociclib + Ibrutinib in recurrent MCL



Abstract #150
Martin et al.
A Phase I Trial of Ibrutinib Plus PD 0332991 (Palbociclib) in Patients with Previously Treated Mantle Cell Lymphoma

Phase I clinical trial of palbociclib + Ibrutinib in recurrent MCL

	Palbociclib + Ibrutinib	Ibrutinib	Palbociclib
Overall response	64%	68%	18%
Complete response	43%	21%	5%
Partial response	21%	47%	

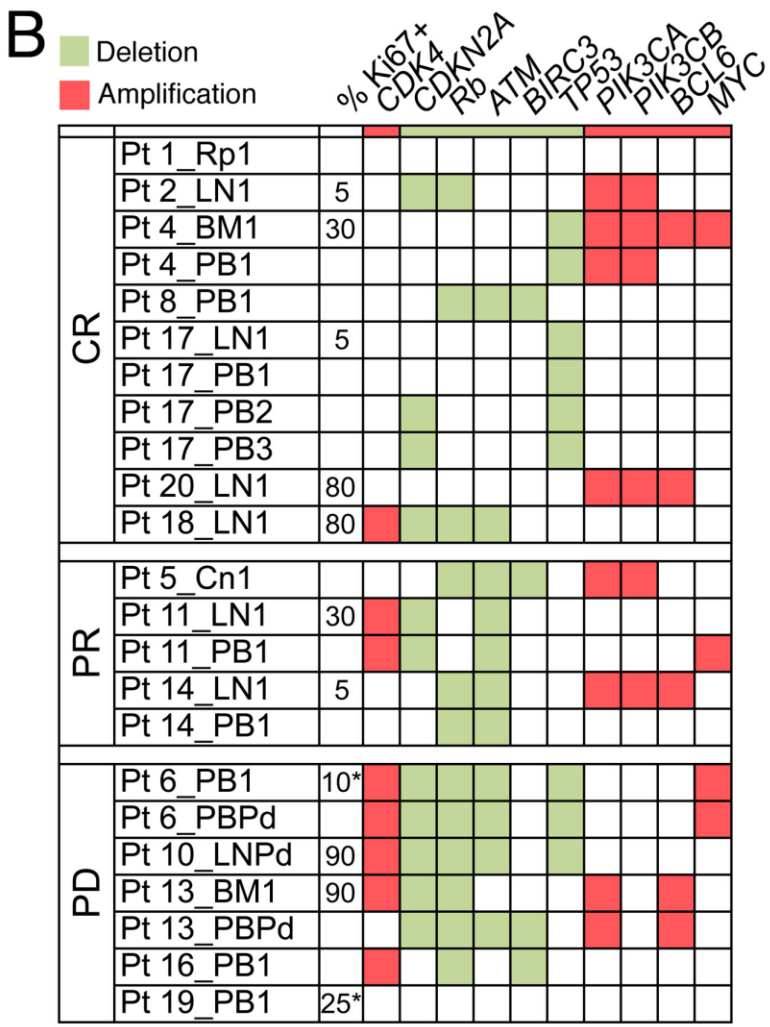
Durable—only one CR patient progressed
Well tolerated

Phase II

Clinical Trial is planned for early 2017

Concurrent loss of Rb and p16 and CDK4 amplification in resistance to palbociclib-Ibrutinib therapy

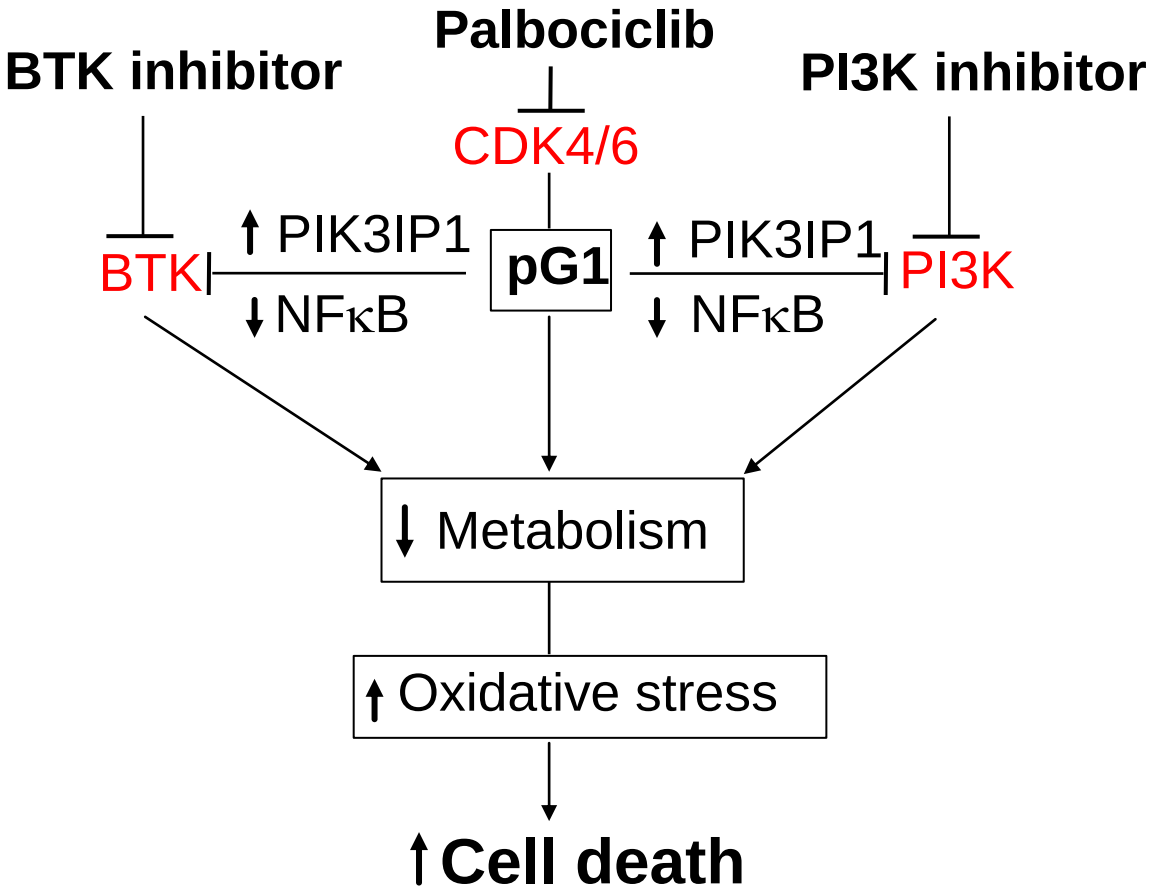
Copy *number* variation (CNV) of MCL cells



- Frequent monoallelic deletion of *Rb1* (9/15), *CDKN2A/B* (7/15), *ATM (*7/15) and *TP53* (4/15), and amplification of *CDK4* (6/15) and *PIK3CA/B* (6/15)
- CR and PR despite these CNVs or aggressive proliferation (KI67>50%)
- CR and PR despite concurrent *CDK4* amplification and *CDKN2A/B* deletion
- PD was associated with concurrent *CDK4* amplification and *Rb* deletion in 4/5 patients, and additional *CDKN2A/B, ATM* or *BIRC3* deletion in 3/5 patients.

Di Liberto, Huang, Martin, Elemento, unpublished

Inhibition of CDK4 reprograms MCL cells for vulnerability to BTK or PI3K inhibition



Promises and Challenges in targeting CDK4/6

- Mechanism of therapeutic targeting of CDK4/6
  - Chromatin remodeling
  - Reprogramming of gene expression
  - Cancer cell metabolism
- Mechanism-based combination therapy
  - Selection of partners - cell cycle specificity
  - Node of integration
  - Sequence, toxicity
- Mechanism of resistance
  - Tumor intrinsic and extrinsic
- Identification of biomarkers
  - longitudinal integrative WES/WTS
  - scRNA-seq, ATAC-seq, ctDNA analysis
- Disease specificity

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