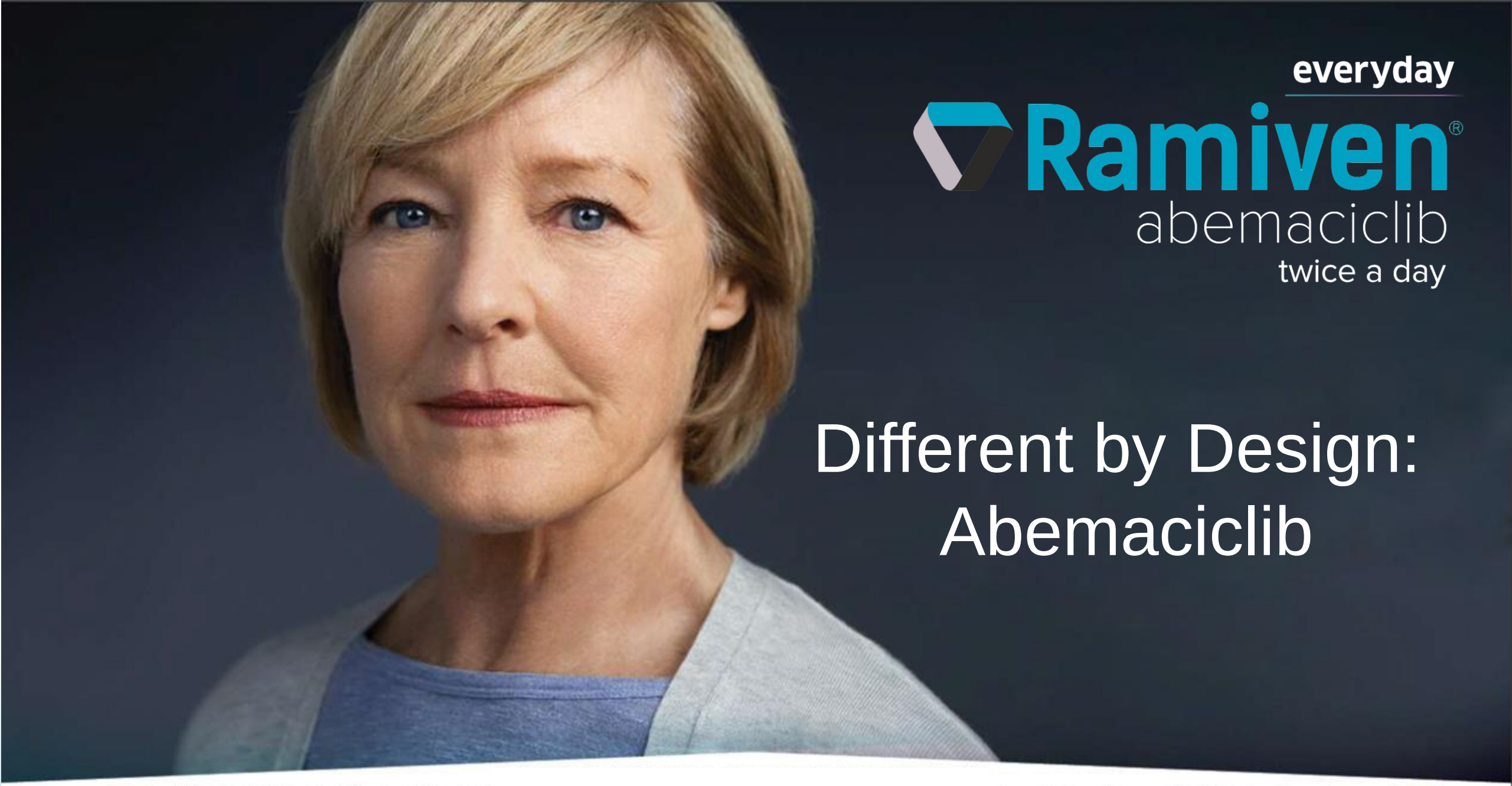

everyday
Ramiven®
abemaciclib
twice a day
Different by Design:
Abemaciclib

PP-AL-IN-0074

Abemaciclib

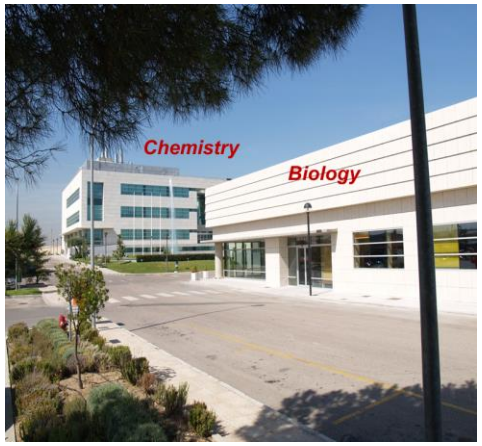
Benchside to Bedside

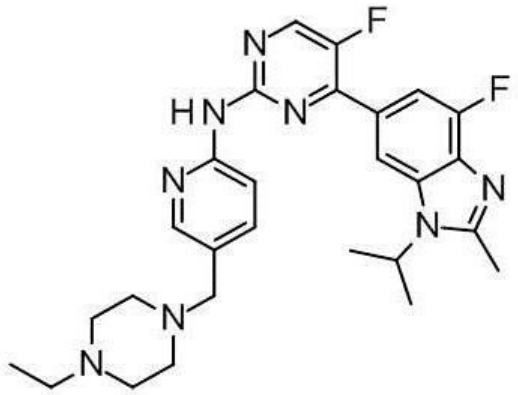
Disclosure

Speaker has been contracted by Lilly for this talk

History of Abemaciclib

- Discovered at Lilly Research Laboratories – Alcobendas, Spain with Indianapolis partners
- 1 of 1,200 compounds tested
  - **Two criteria - continuous dosing and blood brain barrier penetration**
- Date of discovery - February 1, 2008

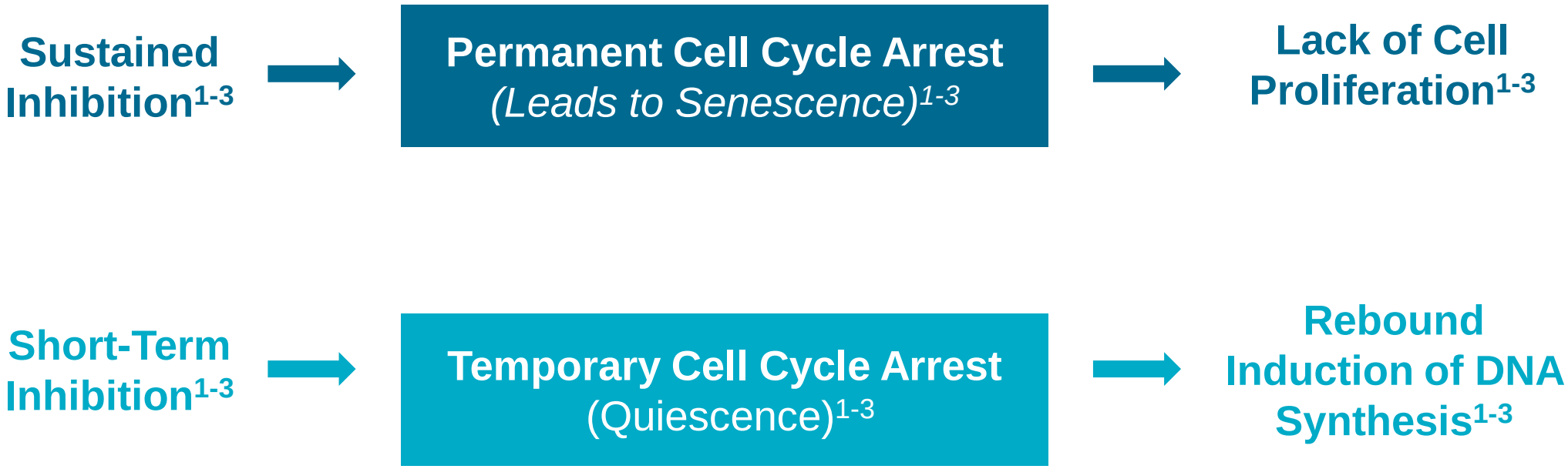




Alcobendas

Lilly

Potential Importance of Sustained Inhibition[1-3]

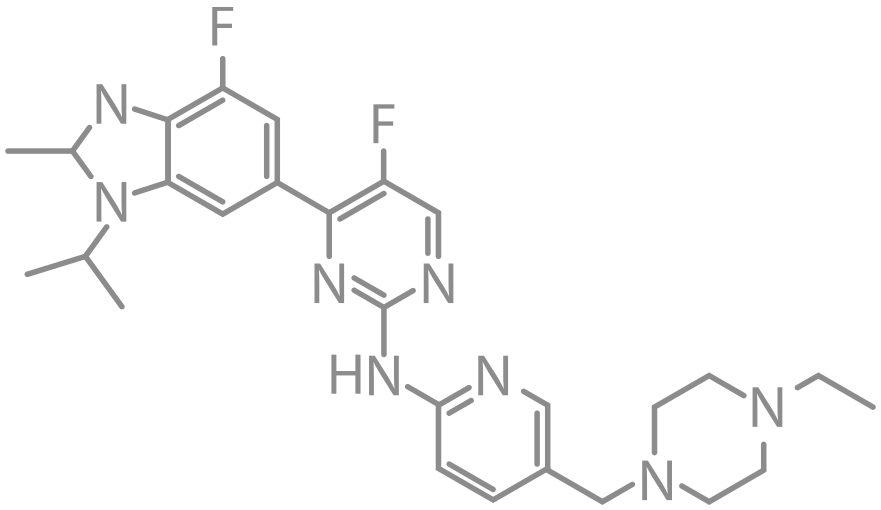


1. Dickler M et al. Clin Ca Res.2017;23(17):5218-24 **2.** Sledge G et al. JCO 2017;35(25):2875-84 **3.** Torres-Guzman et al Oncotarget 2017

Pre-clinical Data

Abemaciclib Structure and Kinase Inhibition Profile

Abemaciclib is an ATP-competitive CDK 4 and CDK 6 inhibitor



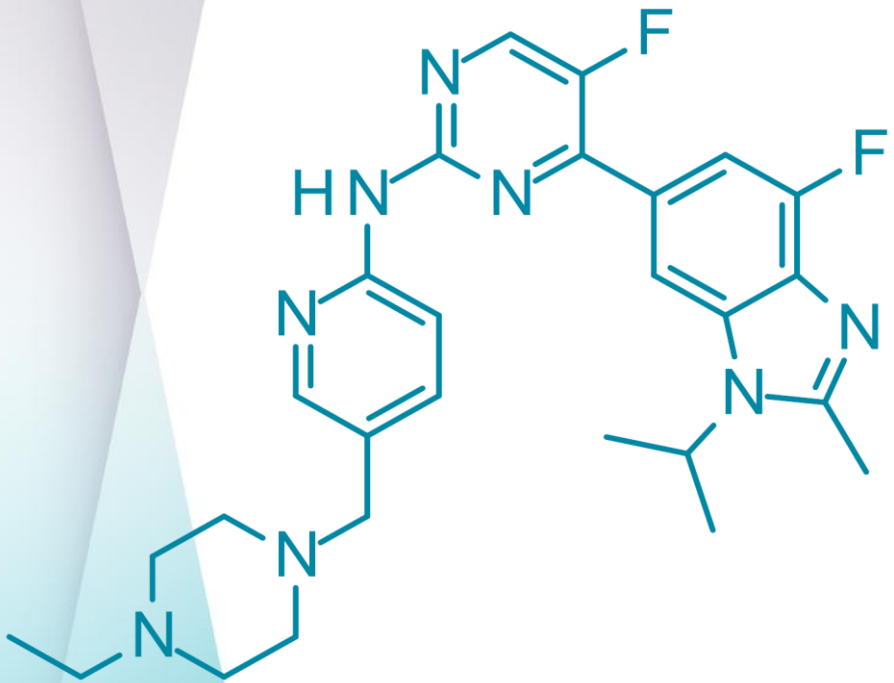
Adapted from: Gelbert et al. Invest New Drugs. 2014; 32(5):825-37

Biochemical Assay[a]	Ki [ATP] (nM)
CDK 4 / cyclin D1	0.6 ± 0.3
CDK 6 / cyclin D3	8.2 ± 1.1
Ratio CDK 6/CDK 4	14x

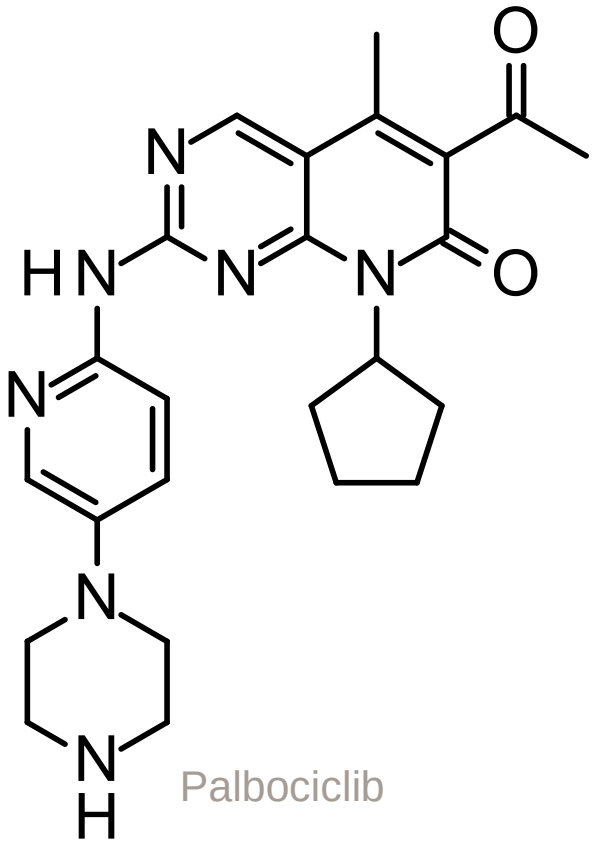
Torres-Guzmán et al. *Oncotarget*. 2017; 8(41):69493-69507

[a]Data obtained using the mesylate salt form and reported in nmol/L; Ki data reported as average of two independent determinations (n=2) ± standard deviation

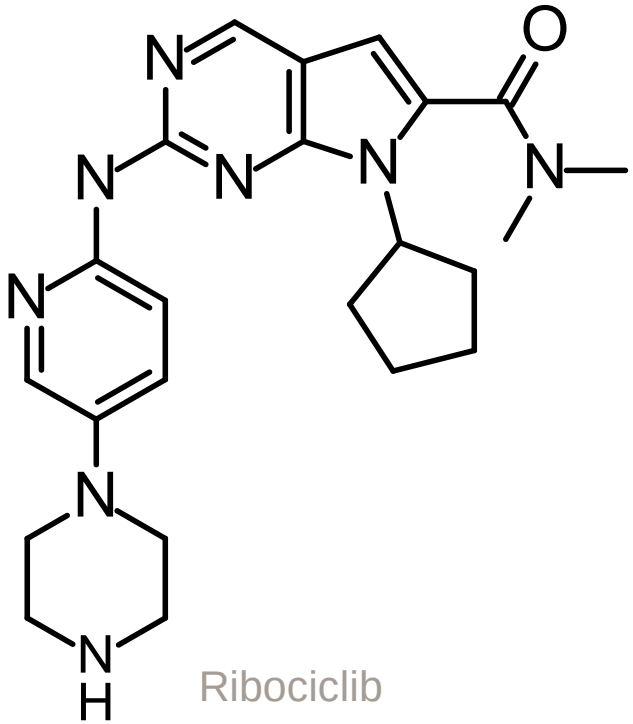
Abemaciclib is structurally distinct



Abemaciclib



Palbociclib



Ribociclib

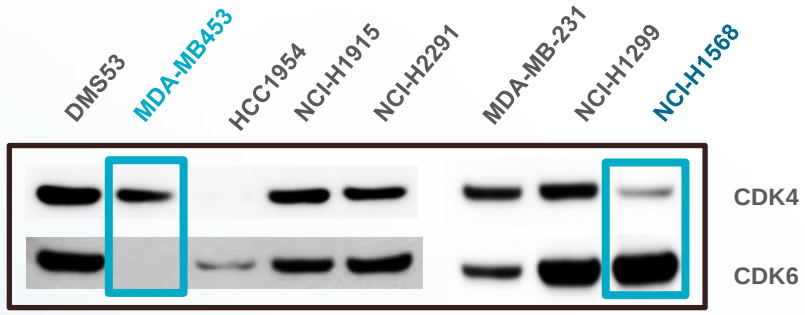
1. Abemaciclib [package insert]. Indianapolis, IN: Eli Lilly and Company; 2018. 2. Palbociclib [prescribing information]. New York, NY: Pfizer Inc.; 2015. 3. Ribociclib [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2017.

Abemaciclib is a more potent inhibitor of CDK4 than CDK6

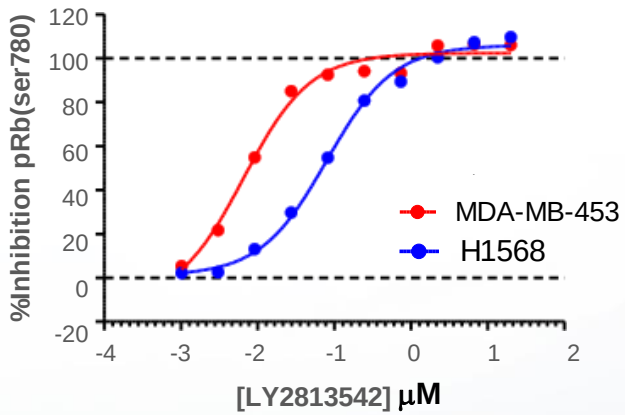
Method	Ki [ATP] c(nM)	
Compound	Abema	Palbo
CDK4/CyclinD1	0.6	2.9
CDK6/cyclinD3	8.2	4.0
Ratio	**14X**	**1.4X**
	CDK4>CDK6	**CDK4≈CDK6**

- Abemaciclib is about 14X more selective for CDK4/cyclinD1 vs. CDK6/cyclinD3 in biochemical assays.
- Palbociclib is a nearly equipotent inhibitor of CDK4/cyclinD1 and CDK6/cyclinD3.

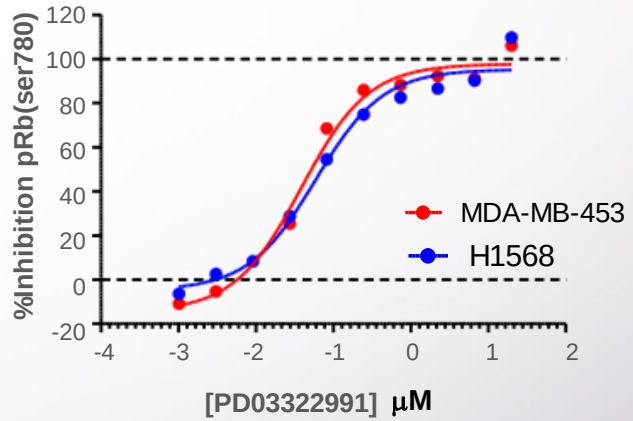
Relative expression of CDK4 vs. CDK6



abemaciclib



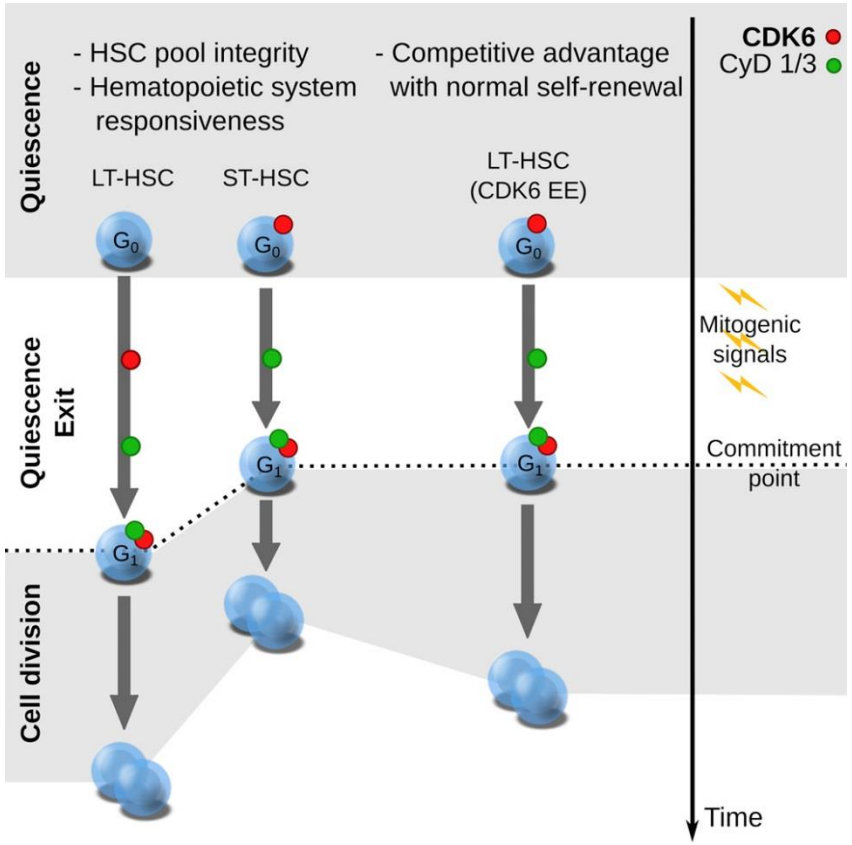
palbociclib



Pre-clinical Data

Adapted from: Beckmann, et al. Characterization of the mechanism of action for abemaciclib with antiestrogen combined therapy in human breast cancer cell lines. http://cancerres.aacrjournals.org/content/76/14_Supplement/2836. Accessed May 06, 2019

CDK6 Regulator of Hematopoietic Stem Cell Activation



From Laurenti et al. Cell Stem Cell 16, 302–313, March 5, 2015

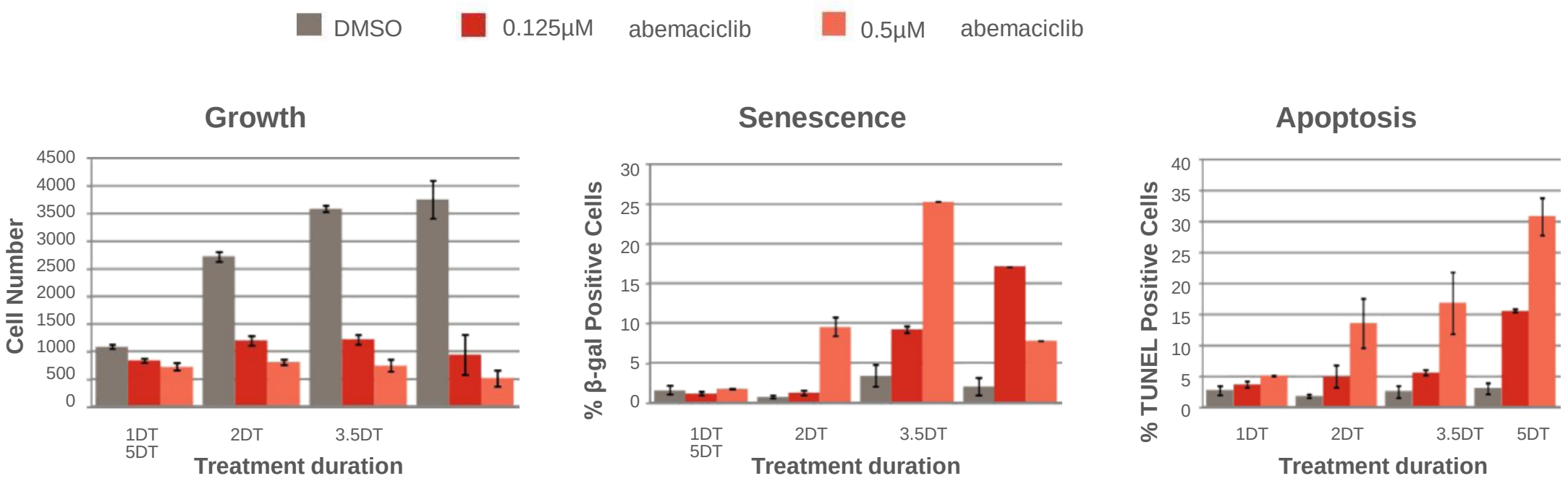
- CDK6 Levels Regulate Quiescence Exit in Human Hematopoietic Stem Cells[1]
- CDK6 acts as a transcriptional regulator to suppress Egr1 in hematopoietic stem cells (HSC), allowing their activation and proliferation[2]
- CDK6 deficiency is characterized by defects in the hematopoietic system[3]

1. Laurenti et al. Cell Stem Cell 16, 302–313, March 5, 2015 **2.** Scheicher et al. Blood 2015 125:90-101 **3.** Malumbres et al. Cell 2004 Vol 118:493-504

Abemaciclib Induces Senescence and Apoptosis

Sustained target inhibition contributes to higher levels of senescence and apoptosis

MCF-7



Pre-clinical Data

Adapted from: Torres-Guzmán et al. Oncotarget. 2017; 8(41):69493-69507

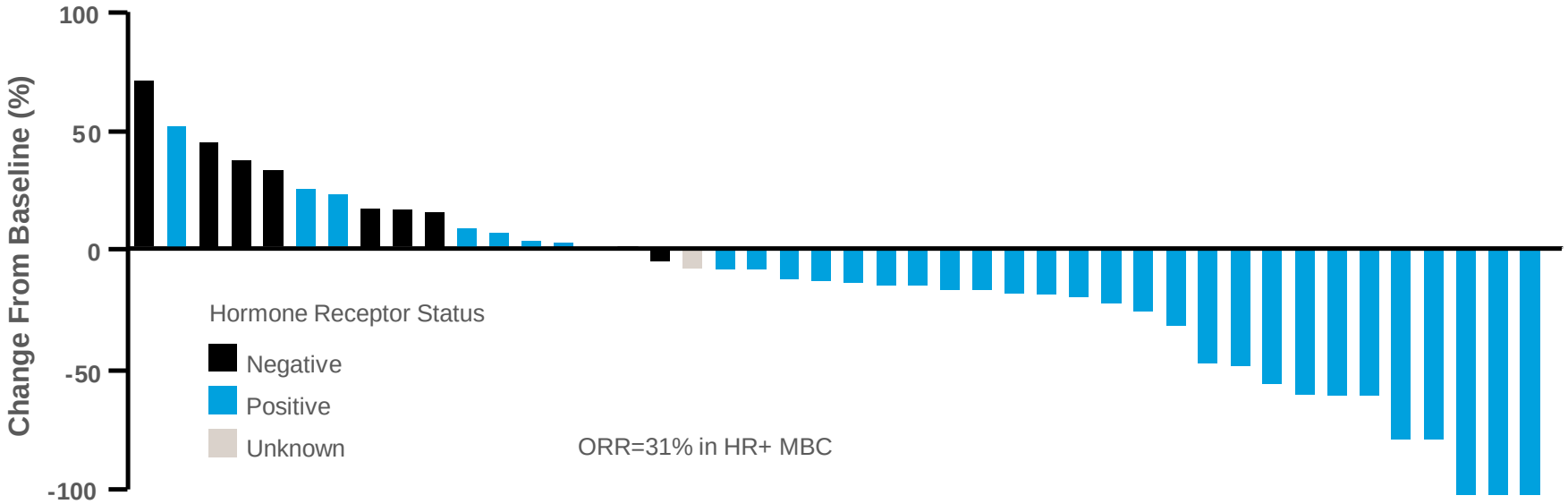
PP-AL-IN-0074

Abemaciclib Phase 1 Study

Neutropenia not dose limiting toxicity - continuous dosing feasible

Phase 1 trial of abemaciclib

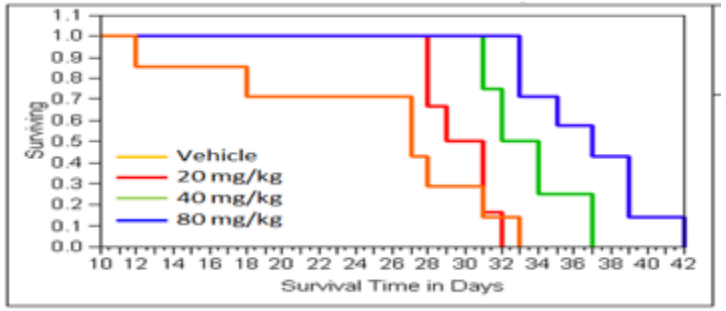
- Single agent activity was observed in a subgroup of heavily pretreated patients with HR+ MBC
  - Neutropenia was not a dose limiting toxicity (DLT) and continuous dosing was feasible – DLT was fatigue



Adapted from: Patnaik A et al. Cancer Discov 2016;6:740-53

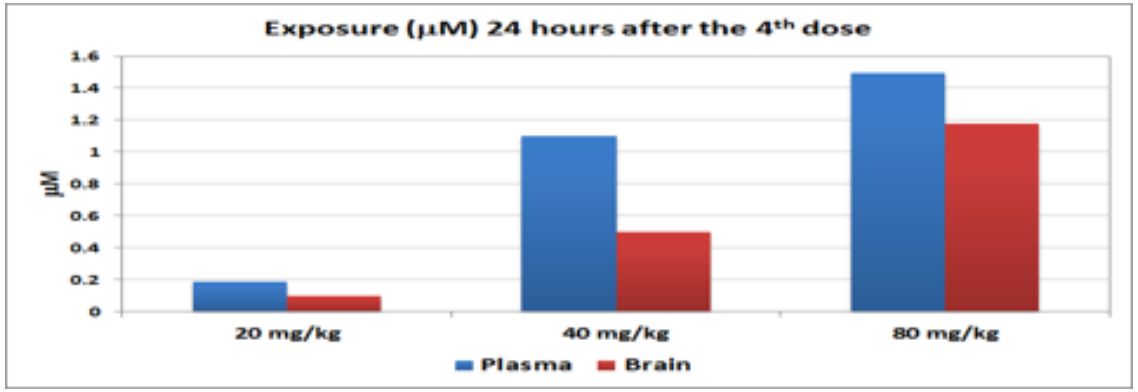
Abemaciclib Effectively Distributes into CNS

Abemaciclib Prolongs Survival in an Intracranial U87MG GBM Model[1]



Treatment	Median Survival (days)	SE
Vehicle	25.14	2.82
20 mg/kg	29.83	0.70
40 mg/kg	33.50*	1.32
80 mg/kg	36.86*	1.28

*p<0.05



- Functional evidence for CNS penetration by abemaciclib[1]
- Abemaciclib is a potent and selective oral CDK4 and CDK6 inhibitor that crosses the blood-brain barrier and inhibits the growth of intracranial human brain tumour xenografts[2]

1. De Dios A et al. Presented at AACR, 2016
2. Gelbert LM et al. Invest New Drugs. 2014:32;825-837.

MONARCH Clinical Development Program

Researching treatment across the breast cancer continuum

MONARCH 3[3]

MONARCH 2[2]

MONARCH 1[1]

1. Dickler M, et al. Clin Cancer Res 2017;23:5218–24; **2.** Sledge GW Jr, et al. J Clin Oncol 2017;35:2875–84; **3.** Goetz MP, et al. J Clin Oncol 2017;35:3638–46;

MONARCH 1: Study Design

Inclusion Criteria

- ER+ (ER and/or PR+), HER2- MBC
- Measurable disease
- ECOG PS 0/1
- Progressed on or after prior ET
- Prior treatment with 1 or 2 chemotherapy regimens in MBC
- Included treatment with taxane in adjuvant or metastatic setting

N=132

Abemaciclib 200 mg PO Q12H

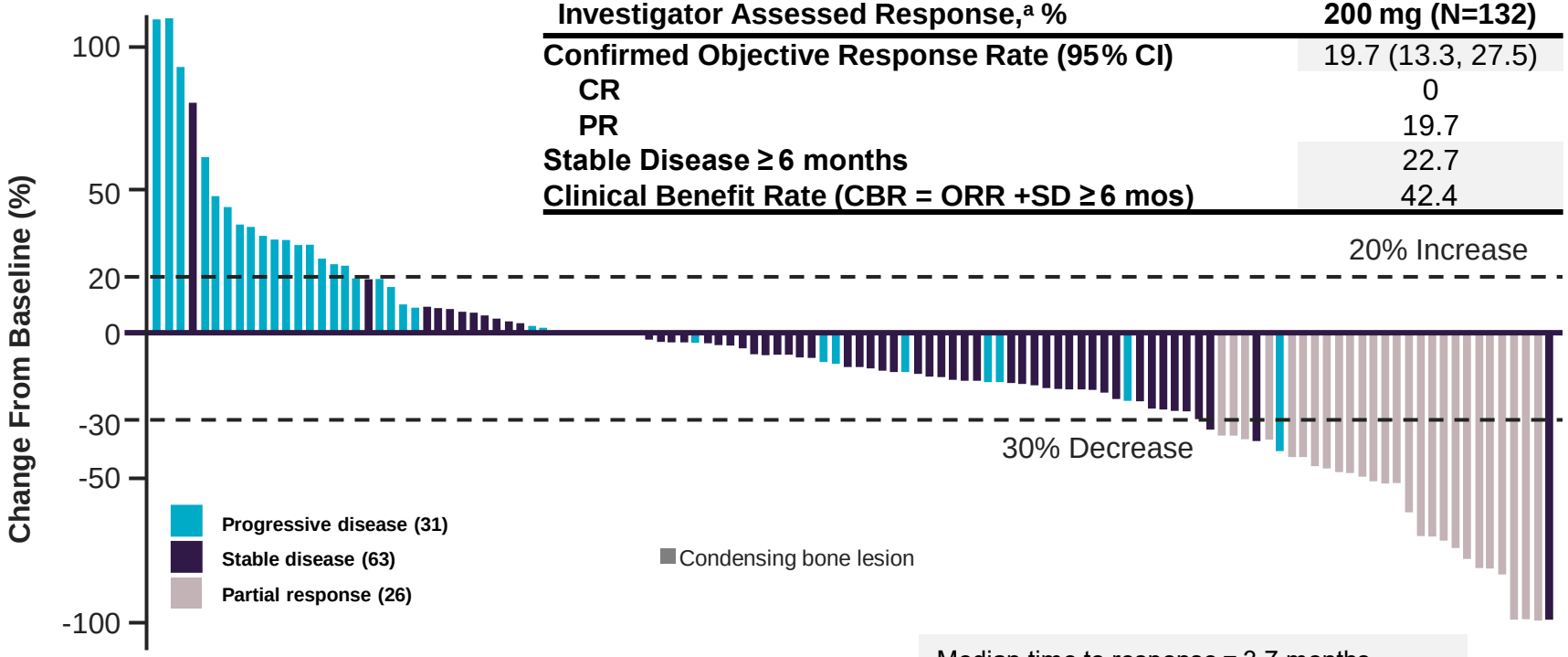
Primary Endpoint: ORR

- Phase 2, single arm, open-label study
- Overall, this patient population was heavily pre-treated and had a poor prognosis
- Study population at baseline:
  - 100% of women received ET and 1–2 chemotherapy regimens in the metastatic setting
  - Majority (90%) of patients with visceral disease
  - Liver (71%) and bone were most common metastatic sites
  - 51% of women had 3 or more metastatic sites
  - Median of 3 (range 1–8) lines of systemic therapy
  - Median of 1 (range 1–3) lines of chemotherapy
  - Median of 2 (range 1–6) lines of ET

Dickler M, et al. *Clin Cancer Res* 2017;23:5218–24.

MONARCH 1 (JPBN): 18-Month Response Summary[1]

Investigator Assessed Response,[a] %	Abemaciclib 200 mg (N=132)
Confirmed Objective Response Rate (95% CI)	19.7 (13.3, 27.5)
CR	0
PR	19.7
Stable Disease ≥ 6 months	22.7
Clinical Benefit Rate (CBR = ORR +SD ≥ 6 mos)	42.4



Median time to response = 3.7 months

Median DoR = 8.9 months[a]

[a] Assessments based on independent review were comparable

Dickler M et al. *Clin Cancer Res* 2017;23:5218–24.

1. Dickler MN et al. Presented at ASCO 2016. Abstract #510

Summary

- Abemaciclib is a potent and selective CDK4&6i, with a greater inhibitory potency (14x) to CDK4 than CDK6[1]
- In ER+ BC cell lines, sustained target inhibition by abemaciclib induced cell cycle arrest leading to senescence and apoptosis[3]
- Phase 1 clinical study demonstrated a safety profile of Abemaciclib which allows continuous dosing - while neutropenia occurred, it was not the dose limiting toxicity[2]
- Abemaciclib is the only CDK4&6i approved as
  -Monotherapy
  -Dosed continuously (twice-daily)

1. Beckmann, et al. Characterization of the mechanism of action for abemaciclib with antiestrogen combined therapy in human breast cancer cell lines. http://cancerres.aacrjournals.org/content/76/14_Supplement/2836. Accessed May 06, 2019; **2.** Patnaik A et al. Cancer Discov 2016;6:740-53; **3.**Torres-Guzmán et al. Oncotarget. 2017; 8(41):69493-69507; **4.** Gelbert et al. Invest New Drugs. 2014; 32(5):825-37; **5.** Dickler M, et al. Clin Cancer Res 2017;23:5218–24.

Concluding Remarks

- CDK4/6 inhibitors have revolutionized the treatment of patients with HR-positive, HER2-negative MBC
- Endocrine therapy in combination with CDK4/6 inhibitors is a cornerstone of treatment
- Abemeciclib, Palbociclib and ribociclib inhibitors are appropriate treatment options regardless of line of treatment or menopausal status
- Toxicities associated with each of the CDK4/6 inhibitors are manageable with dose interruptions and reductions

Speaker's opinion

API

Abridged Pack Insert- Abemaciclib (Ramiven®)

Product description
Abemaciclib (Ramiven®)
Film coated tablets [available in 50mg, 100mg, 150mg and 200mg]

Indication and Usage
(i) Ramiven® is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.
• In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

(ii) As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Dose and method of administration
The recommended dose of Abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Recommended starting dose in combination with fulvestrant or an aromatase inhibitor: 150 mg twice daily.
Recommended starting dose as monotherapy: 200 mg twice daily orally.
Method of Administration
For Oral use, the dose can be taken with/ or without food.
Contra-indications
Hypersensitivity to the active substance or to any of the excipients.
Undesirable effects
The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, anaemia, fatigue, nausea, vomiting and decreased appetite.
Overdose
In the event of an abemaciclib overdose, fatigue and diarrhea may occur. General supportive care should be provided.
Special warning and precaution:
Neutropenia: Neutropenia was reported in patients receiving abemaciclib. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia. Fatal events occurred in <1% of patients.
Infections/infestations: Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1% of patients. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.
Venous thromboembolism: Venous thromboembolic events were reported in 5.3% of patients treated with abemaciclib plus fulvestrant or aromatase inhibitors, compared to 0.8% of patients treated with placebo plus fulvestrant or aromatase inhibitors. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.
Increased aminotransferases: Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification.
Diarrhoea: Diarrhoea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3).
Diarrhoea can be associated with dehydration. Patients should start treatment with antidiarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop >Grade 2 diarrhoea.
Concomitant use of inducers of CYP3A4: Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib.
Visceral crisis: There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.
Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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PP-AL-IN-0022