CDK 4/6 Inhibitors: Efficacy and Side Effect Profile

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Cyclin Dependent Kinases (CDKs)

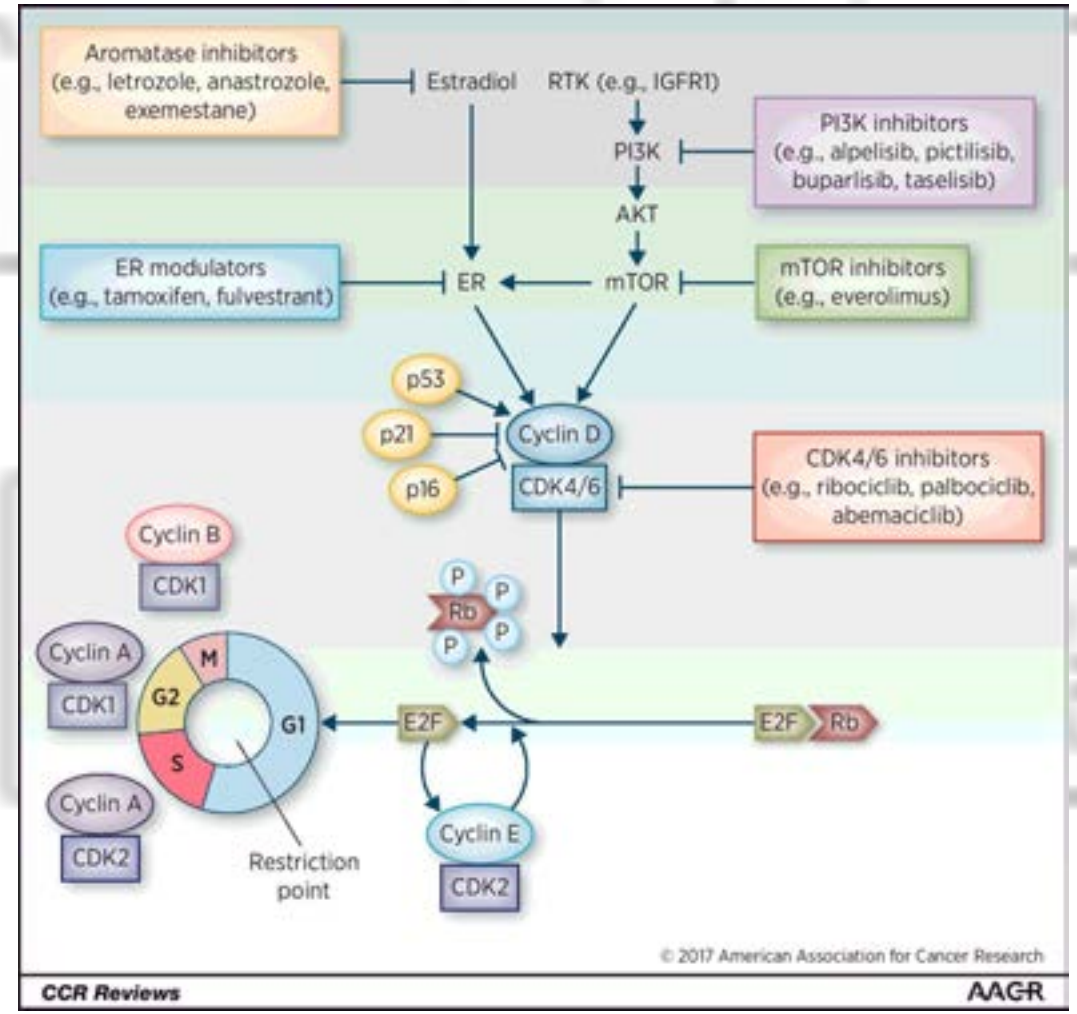
Mechanism of Action

- Subgroup of serine/threonine kinases
- Control cell cycle progression at different checkpoints
- Activity dependent on cyclins (“cyclin-dependent kinases”)
- Activate the catalytic activity of their CDK partners
- Associated cyclins determine effects
    - CDK 4 and 6 associate with cyclin D
    - CDK 2 associates with cyclin E, then A as cell cycle progresses
    - Levels of CDK can also regulate function

Musgrove EA, et al. Nat Rev Cancer. 2011;11(8):558-72; Finn RS et al. Presented at AACR 2014; San Diego, California, USA

Cyclin Dependent Kinases (CDKs)

Key Regulators of Cell Cycle Progression



Cyclin Dependent Kinases (CDKs)

Cell Cycle Deregulation in Breast Cancer

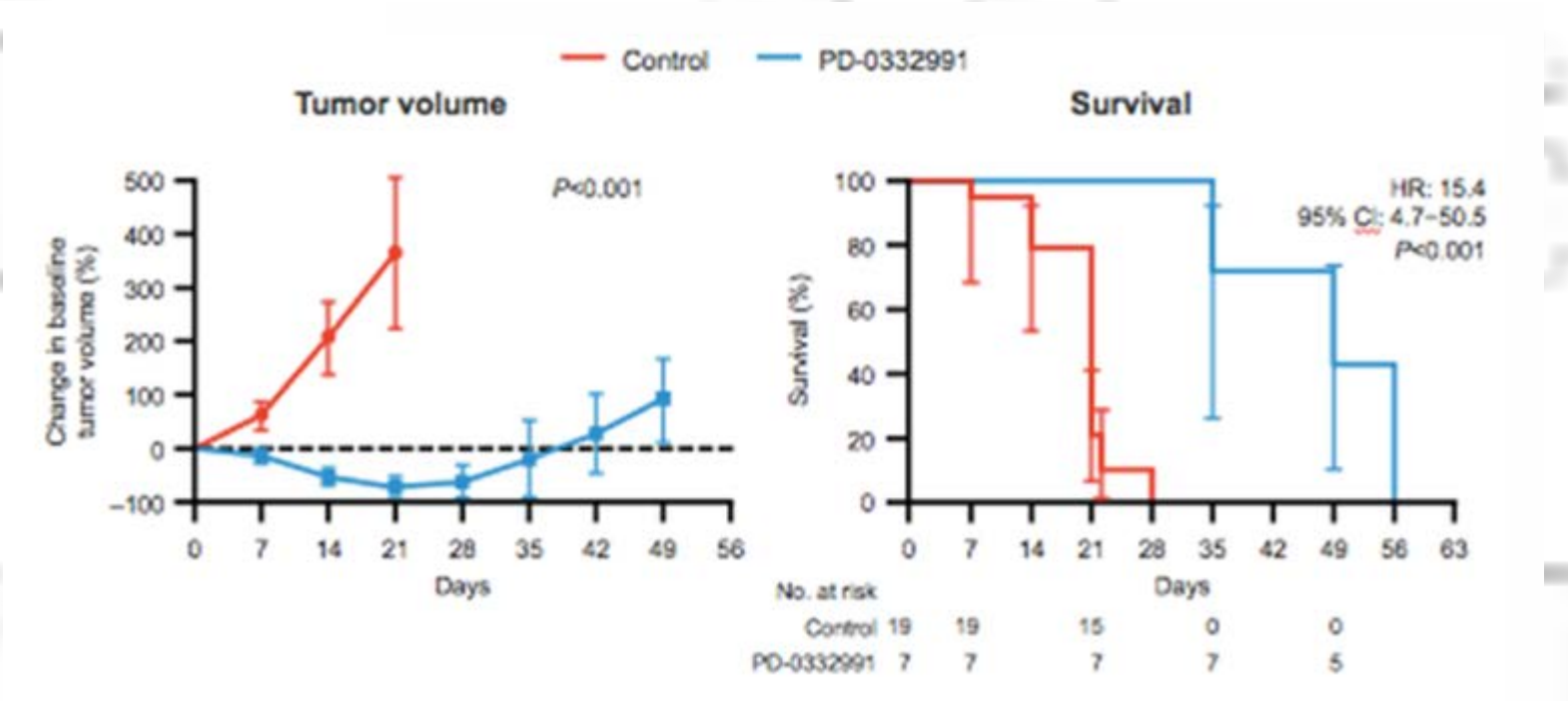
- >90% of human tumors abandon cell G1-S cycle control mechanism through variety of genetic and biochemical alterations:
  - Pathological up-regulaton of CDK4 or CDK6 or Amplification of cyclin D
  - Down-regulation of natural CDK4 inhibitor $p16^{INK4A}$
  - CDK4 mutations that prevent binding of $p16^{INK4A}$ to enzyme
  - Deletion or mutation of Rb
- Alterations result in activation of CDK/Rb and loss of proliferative control through Rb phosphorylation
- ER signaling and cyclin D/CDK4/6 are closely linked

CDK 4/6 Inhibitors

Palbociclib, Ribociclib, Abemaciclib

- Orally active selective inhibitor of CDK4 and CDK6
- Inhibit DNA synthesis and cell proliferation by preventing cell-cycle progression from G1 to S phase
- Highly active in Rb+ cell lines and primary tumors *in vitro*
- Effective in wide range of solid tumors (Inhibits proliferation in cultured and xenografted leukemia, myeloma, breast cancer, colon cancer, and lung cancer cells)

PD-0332991 Monotherapy Has Antitumor Activity in a CDK4/6-dependent Murine Model of Breast Cancer



Rb-competent MMTV-c-neu mice treated with palbociclib (100mg/kg/day)
for 21 days showed marked reduction in tumor volume and improved median
survival vs. controls

Roberts, P. J. et al. J Natl Cancer Inst 2012;104:476-487

CDK 4/6 Inhibitors in Clinical Development

IC_{50} Values of Available Compounds

Table 1. IC_{50} Values of CDK 4/6 Inhibitors.			
	IC_{50} (nM)		
	Palbociclib (Fry *et al.*, 2004)	**Ribociclib** (Kim *et al.*, 2013)	**Abemaciclib** (Gelbert *et al.*, 2014)
CDK4-cyclin D1	11	10	2
CDK6-cyclin D1/2/3	16	39	10
CDK1-cyclin B	>10,000	113,000	1627
CDK2-cyclin A/E	>10,000	76,000	504
CDK9-cyclin T	NR	NR	57
NR, not reported.			

CDK 4/6 Inhibitors
Clinical Trials in mBC

	Palbociclib (PD-0332991; Pfizer)			Ribociclib (LEE-011; Novartis)			Abemaciclib (LY2835219; Eli Lilly)		Fulvestrant (AZ)
Study	**PALOMA-2**	**PALOMA-3**	**PEARL**	**MONALEESA-2**	**MONALEESA-3**	**MONALEESA-7**	**MONARCH-2**	**MONARCH-3**	**FALCON**
Setting	1st line	1st or later line	Later line	1st line	1st or 2nd line	1st line	1st or 2nd line	1st line	1st line
Menopausal status	Post	Pre and Post	Post	Post	Post	Pre	Pre and Post	Post	Post
Target No. Patients	650	521	348	667	660	660	630	450	524
Endocrine Partner	Letrozole	Fulvestrant	Exemestane or Fulvestrant	Letrozole	Fulvestrant	Anastrozole or letrozole, or tamoxifen	Fulvestrant	Anastrozole or letrozole	Fulvestrant + placebo vs. anastrozole + placebo
Primary Endpoint	PFS	PFS	PFS	PFS	PFS	PFS	PFS	PFS	PFS

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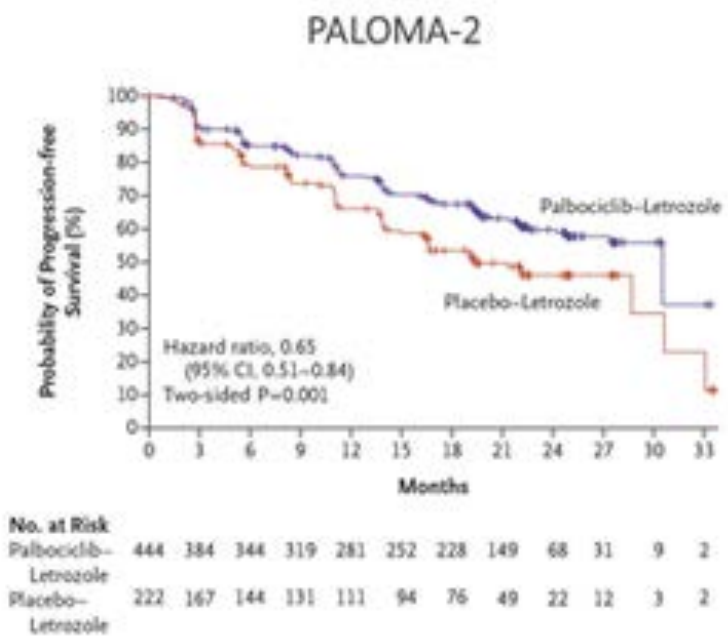
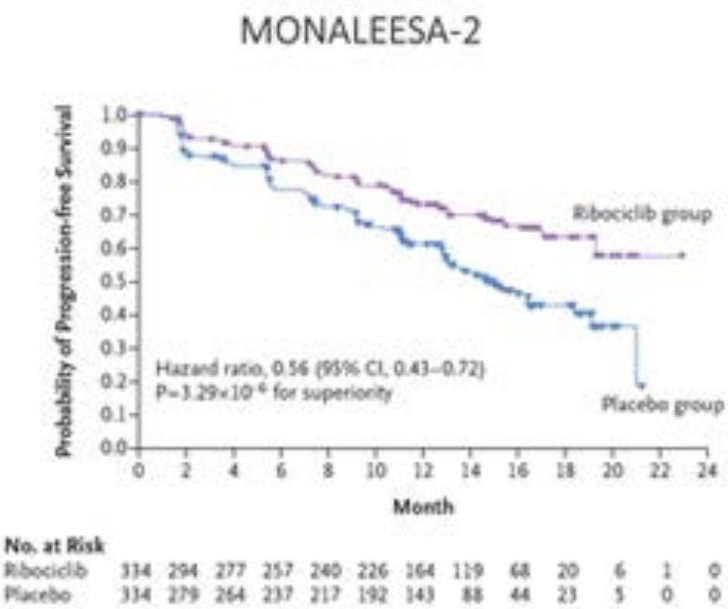
CDK4/6 Inhibition

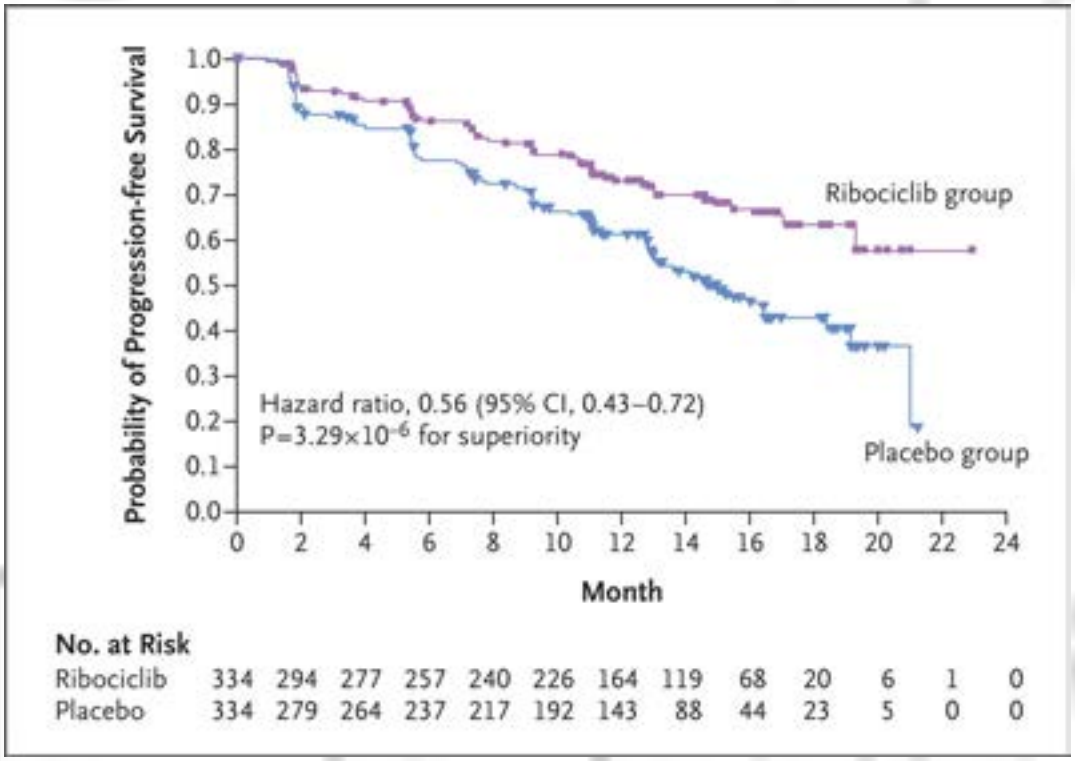
PFS in PALOMA-2 and MONALEESA-2

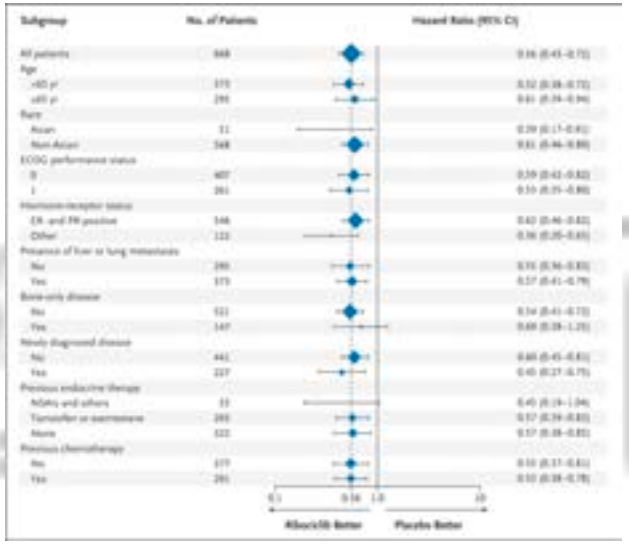




CDK4/6 Inhibition by Ribociclib

MONALEESA-3





CDK4/6 Inhibition by Palbociclib

Non-haematological AEs (>15%) in PALOMA-2

	Palbociclib + letrozole (N=444)			Placebo + letrozole (N=222)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Any AE (%)	98.9	62.2	13.5	95.5	22.1	2.3
Fatigue	37.4	1.8	0	27.5	0.5	0
Nausea	35.1	0.2	0	26.1	1.8	0
Arthralgia	33.3	0.2	0	33.8	0.5	0
Alopecia[a]	32.9	0	0	15.8	0	0
Diarrhea	26.1	1.4	0	19.4	1.4	0
Cough	25.0	0	0	18.9	0	0
Back pain	21.6	1.4	0	21.6	0	0
Headache	21.4	0.2	0	26.1	1.8	0
Hot flush	20.9	0	0	30.6	0	0
Constipation	19.4	0.5	0	15.3	0.5	0
Rash[b]	17.8	0.9	0	11.7	0.5	0
Asthenia	16.9	2.3	0	11.7	0	0
Vomiting	15.5	0.5	0	16.7	1.4	0
Pain in extremity	15.3	0.2	0	17.6	1.4	0
Stomatitis	15.3	0.2	0	5.9	0	0

[a] 30% patients had grade 1 alopecia and 3% had grade 2 alopecia in the placebo + letrozole group; 15% patients had grade 1 alopecia and 1% had grade 2 alopecia

Finn RS, et al. *N Engl J Med* 2016 Nov 17;375(20): 1925–1936

CDK4/6 Inhibition by Palbociclib
Haematological AEs (>15%) in PALOMA-2

	Palbociclib + letrozole (N=444)			Placebo + letrozole (N=222)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any AE, %	98.9	62.2	13.5	95.5	22.1	2.3
Neutropenia[a]	79.5	56.1	10.4	6.3	0.9	0.5
Leukopenia[a]	39.0	24.1	0.7	2.3	0	0
Anemia[a]	24.1	5.2	0.2	9.0	1.8	0
Thrombocytopenia[a]	15.5	1.4	0.2	1.4	0	0

- Grade 3/4 febrile neutropenia was reported in 1.8% of patients in the palbociclib + letrozole arm vs. 0% in the placebo + letrozole arm

[a]Includes clustered Medical Dictionary for Regulatory Activity (MedDRA) preferred terms
AE, adverse event

Finn RS, et al. *N Engl J Med* 2016 Nov 17;375(20): 1925–1936

CDK4/6 Inhibition durch Palbociclib

Adverse Events (>10%) in PALOMA-3

AEs,* n (%)	Palbociclib + fulvestrant (n=345)			Placebo + fulvestrant (n=172)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	56 (16)	189 (55)	34 (10)	5 (3)	0	1 (1)
Anemia	86 (25)	10 (3)	0	16 (9)	3 (2)	0
Leukopenia	76 (22)	93 (27)	2 (1)	5 (3)	1 (1)	1 (1)
Thrombocytopenia	65 (19)	6 (2)	2 (1)	0	0	0
Infections	137 (40)	6 (2)	1 (<1)	47 (27)	5 (3)	0
Fatigue	127 (37)	8 (2)	0	47 (27)	2 (1)	0
Nausea	112 (32)	0	0	46 (27)	1 (1)	0
Headache	78 (23)	2 (1)	0	33 (19)	0	0
Diarrhea	74 (21)	0	0	31 (18)	1 (1)	0
Constipation	66 (19)	0	0	27 (16)	0	0
Alopecia	58 (17)	0	0	11 (6)	0	0
Vomiting	57 (17)	1 (<1)	0	24 (14)	1 (1)	0
Hot flush	53 (15)	0	0	28 (16)	1 (1)	0
Decreased appetite	49 (14)	3 (1)	0	13 (8)	1 (1)	0
Rash	50 (14)	2 (1)	0	9 (5)	0	0
Back pain	47 (14)	4 (1)	0	26 (15)	3 (2)	0
Cough	51 (15)	0	0	22 (13)	0	0
Arthralgia	48 (14)	1 (<1)	0	27 (16)	0	0
Pain in extremity	43 (12)	0	0	18 (10)	3 (2)	0
Stomatitis	41 (12)	2 (1)	0	4 (2)	0	0
Dizziness	40 (12)	1 (<1)	0	16 (9)	0	0
Dyspnea	39 (11)	0	1 (<1)	12 (7)	2 (1)	0
Pyrexia	37 (11)	1 (<1)	0	9 (5)	0	0

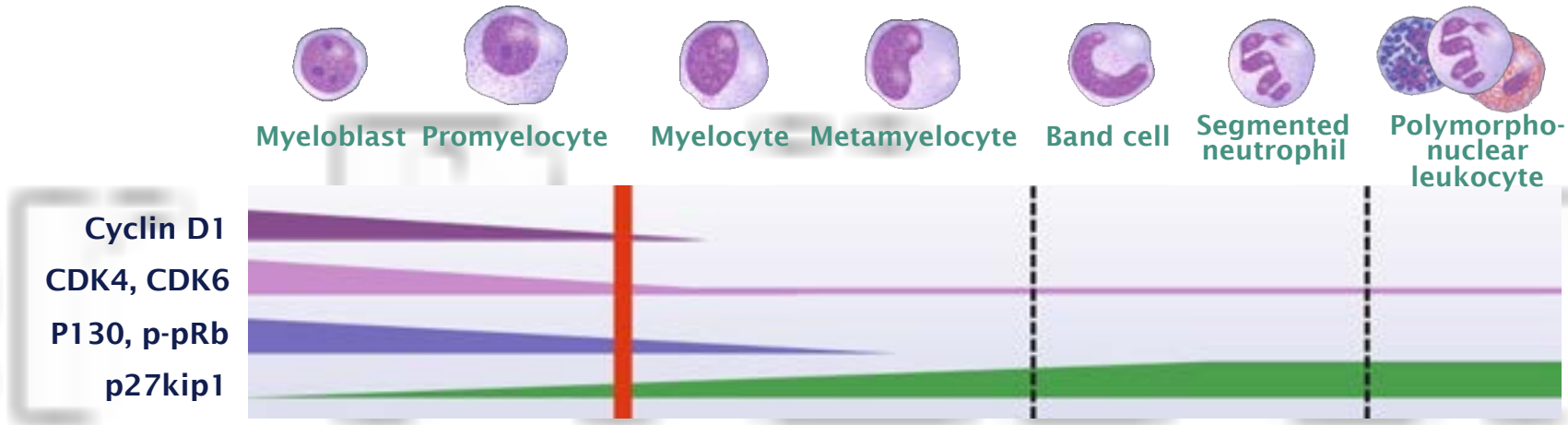
AE, adverse event; *Graded in accordance with the maximum Common Terminology Criteria for Adverse Events Grade, Version 4.0, and the Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0.
No Grade 5 AEs were observed. Full AE data is presented in Cristofanilli M, et al. Lancet Oncol 2016.

Cristofanilli M, et al. Lancet Oncol 2016 [Published online 2 March 2016; http://dx.doi.org/10.1016/S1470-2045(15)00613-0]

Proliferating Early Neutrophil Precursors Depend on Cyclin D–CDK4/6 Activity

- Hematopoietic stem cells and early neutrophil precursors depend on cyclin D–CDK4/6 activity to enter and traverse the cell cycle and proliferate[1–3]
- Non-dividing mature neutrophils, not dependent on cyclin D–CDK4/6, show down-regulation of cyclin D, CDK 4/6, and Rb proteins and up-regulation of CDK inhibitor p27kip1[1,2]

Cell cycle proteins during granulopoiesis[1]



p130, Rb-like protein 2; p-pRb, phosphorylated retinoblastoma protein; p27kip1, CDK inhibitor

1. Klausen P, et al. *J Leukoc Biol*. 2004;75:569–78; 2. Kumar S, Fillippi M-D. In Gabrilovich D, ed. *The Neutrophils.* 3rd ed. London: Imperial College Press; 2013:1–41; 3. Roberts PJ, et al. *J Natl Cancer Inst.* 2012;104:476–87.

Graphic adapted from: Klausen P, et al. *J Leukoc Biol*. 2004;75:569–78.

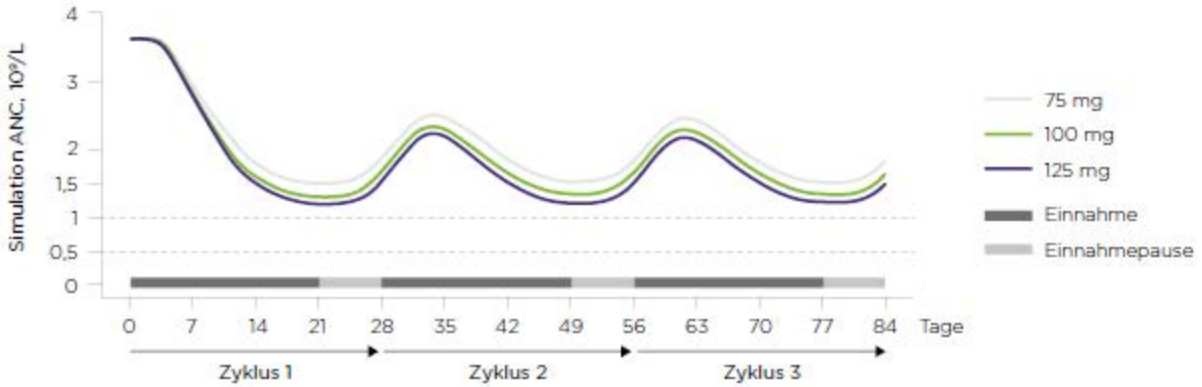
Wissenswertes

zur Palbociclib-induzierten Neutropenie (PIN)

PIN and CIN werden durch verschiedene Mechanismen hervorgerufen und unterscheiden sich daher in ihrer Schwere und den auftretenden Komplikationen.

	Palbociclib-induzierte Neutropenie (PIN)[3,4]	Chemotherapie-induzierte Neutropenie (CIN)[4-6]
Mechanismus	Zellzyklus-Arrest, aber kein Zelltod von proliferierenden neutrophilen Vorläuferzellen	DNA Schäden und Apoptose von proliferierenden neutrophilen Vorläuferzellen
Reversibilität	Rasche Erholung	Verzögerte Erholung
Febrile Neutropenie	< 2% in PALOMA-2 Studie	10-50% bei soliden Tumoren[5]

Simulierte durchschnittliche ANC-Zeitprofile für verschiedene Dosierungen von Palbociclib (Dosierschema: 3 Wochen Einnahme / 1 Woche Pause)[8]



Palbociclib-associated Neutropenia

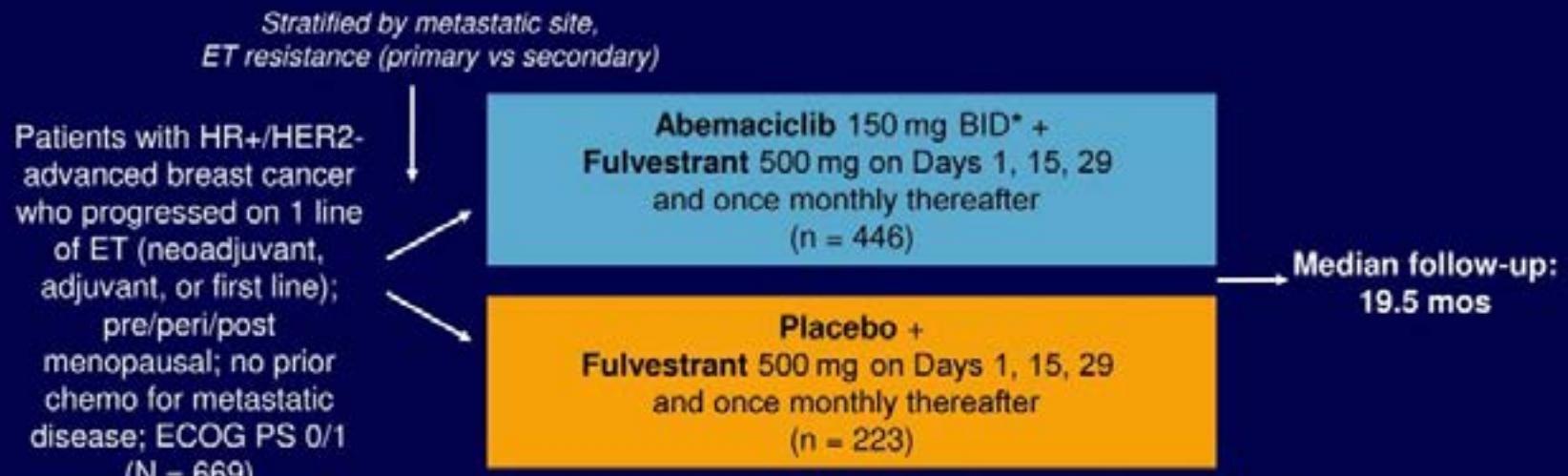
Dose Modification

CTCAE Grade (v4.0)	Dose modifications
Grade 1 or 2 neutropenia	No dose adjustment is required
Grade 3 neutropenia	**Day 1 of cycle:** withhold palbociclib, repeat CBC monitoring within 1 week. When recovered to ≤Grade 2, start the next cycle at the *same dose* **Day 14 of first 2 cycles:** Continue palbociclib at current dose to complete cycle. Repeat CBC on day 21 Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia in subsequent cycles
Grade 3 neutropenia[b] with fever ≥38.5°C and/or infection	Withhold palbociclib until recovery to Grade ≤2 Resume at *next lower dose*
Grade 4 neutropenia	Withhold palbociclib until recovery to Grade ≤2 Resume at *next lower dose*

[a]Table applies to all hematologic adverse events except lymphopenia (unless associated with clinical events, e.g opportunistic infections);
[b]Absolute neutrophil count (ANC); Grade 1: ANC<lower limit of normal –1500/mm^3; Grade 2: ANC 1000–<1500/mm^3;
Grade 3: ANC 500–<1000/mm^3; Grade 4: ANC<500/mm^3

1. Ibrance prescribing information, 2016.

MONARCH 2: Study Design



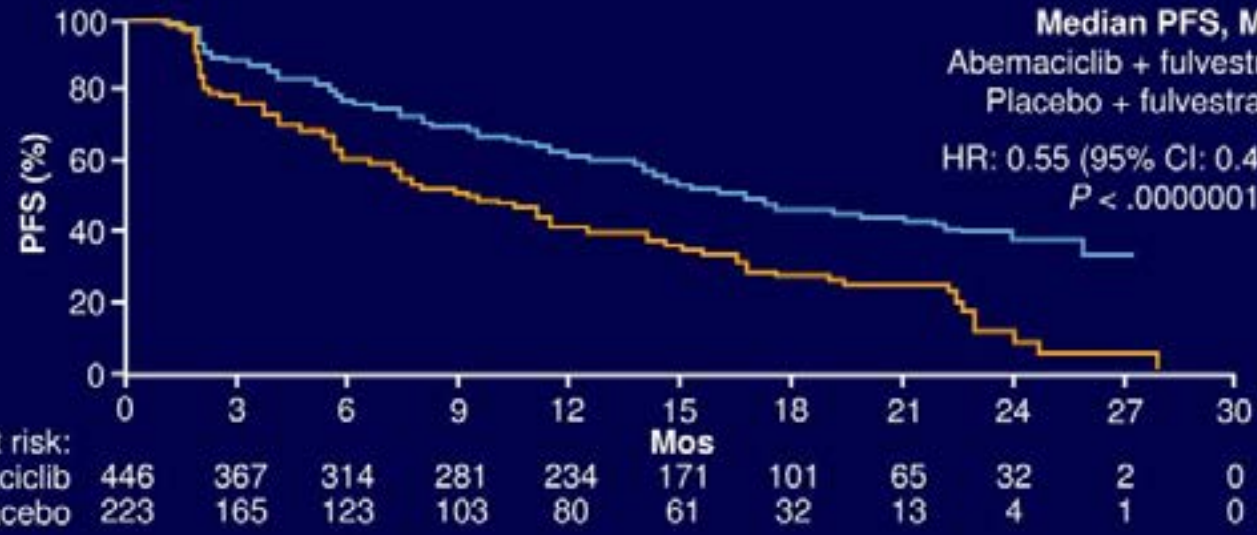
*Dose reduced from 200 mg to 150 mg after 178 pts enrolled.

- Pts enrolled at 142 centers in 19 countries
- Primary endpoint: PFS (investigator assessed)
- Secondary endpoints: OS, ORR, clinical benefit rate, safety

Sledge GW, et al. ASCO 2017. Abstract 1000.

Slide credit: clinicaloptions.com

MONARCH 2: PFS



Median PFS, Mos
Abemaciclib + fulvestrant: 16.4
Placebo + fulvestrant: 9.3
HR: 0.55 (95% CI: 0.449-0.681; *P* < .0000001)

Patients at risk:											
Abemaciclib	446	367	314	281	234	171	101	65	32	2	0
Placebo	223	165	123	103	80	61	32	13	4	1	0

- PFS benefit with addition of abemaciclib to fulvestrant observed across all pt subgroups, except those with nonvisceral soft tissue metastases
- ORR, abemaciclib cohort vs placebo cohort: 35.2% vs 16.1%

Sledge GW, et al. ASCO 2017. Abstract 1000. Reproduced with permission.

CDK4/6 Inhibition by Abemaciclib

Adverse Events (>10%) in MONARCH-2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain*	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections*	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia*	46	24	3	4	1	<1
Anemia*	29	7	<1	4	1	0
Leukopenia*	28	9	<1	2	0	0
Thrombocytopenia*	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue*	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	3	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

CDK 4/6 Inhibitors
Conclusions

- Highly effective in advanced breast cancer when combined with endocrine therapy
- Can prolong chemo-free interval
- State-of-the-Art treatment in first and second line setting
- Side effect profile consequence of Mode of Action
- Neutropenia, QT-time (Ribo), and diarrhea (Abe) Aes of concern
- AE can be managed but needs to be followed along treatment course