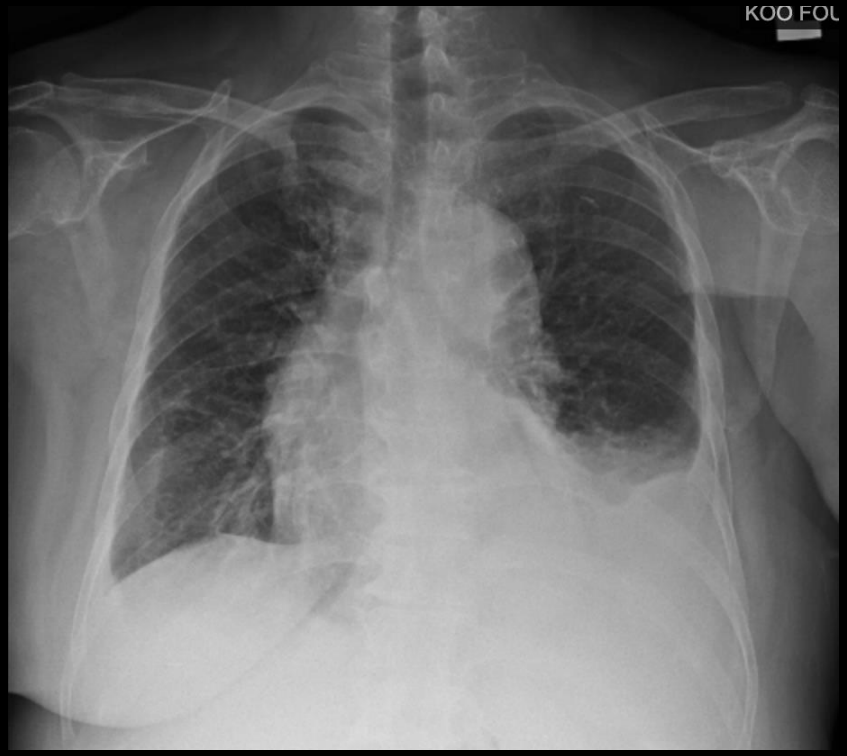
Treatment approach to metastatic hormone positive breast cancer

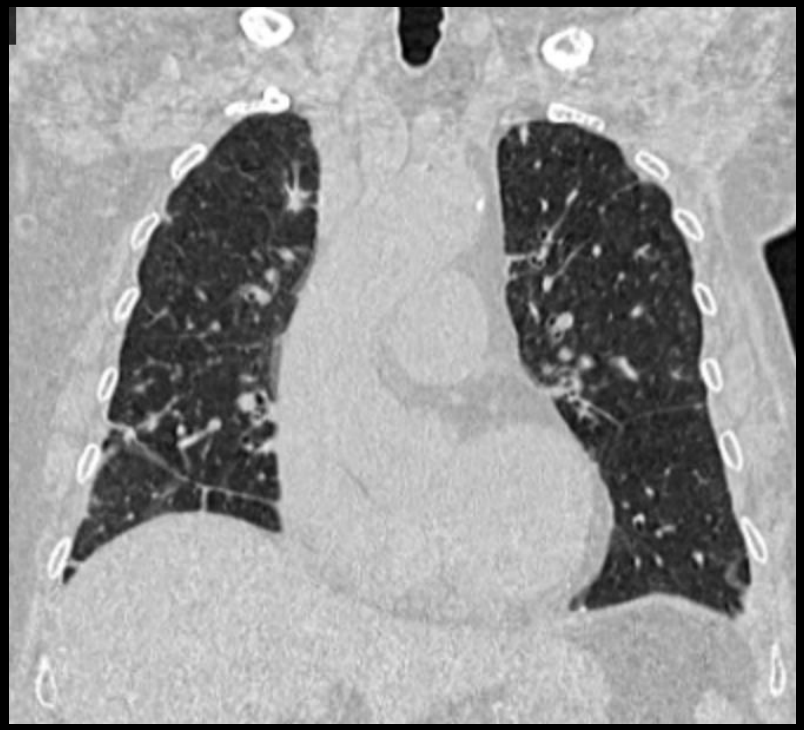
Peng Yu Chen
Hematology and Medical Oncology
KFSYSCC

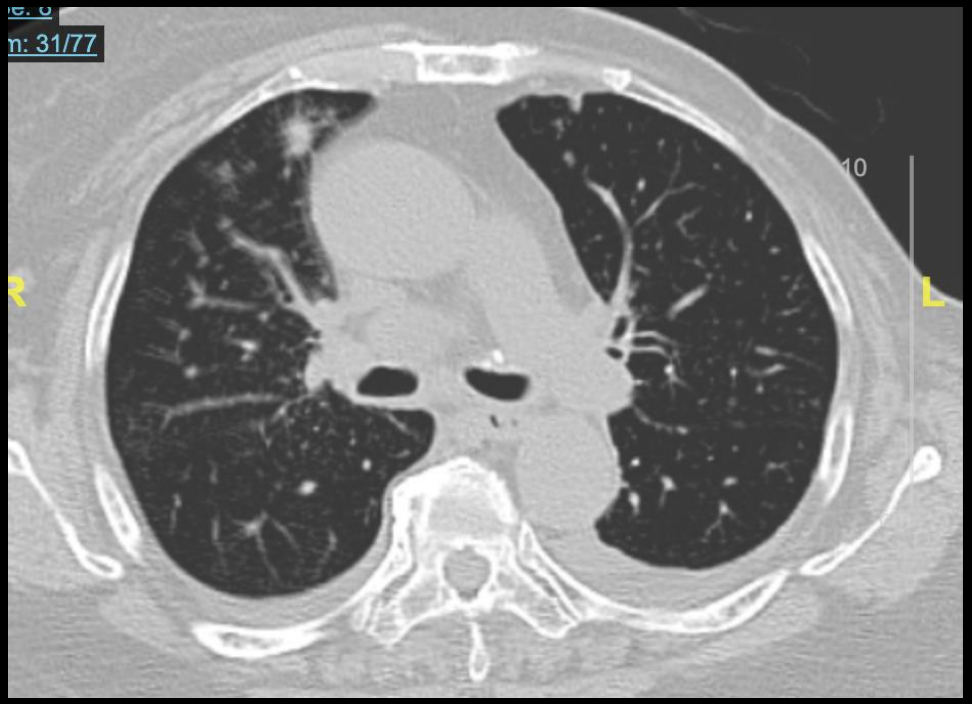
Case Sharing 01

Miss Chen, 79 y/o woman, living in Beitou

- 1997
  - Left breast cancer s/p MRM, pT2N3, refused chemotherapy, refused RT
- 1997-2002, Tamoxifen
- 2012/5
  - Left axillary recurrence, s/p en block ALND,
  - invasive ductal carcinoma, ER(8)PR(2)HER2(0)
- 2012-2017, Femara
- 2018/5
  - Dyspnea, pleural effusion
  - (refused chemotherapy)
  - Restart Femara, poor response



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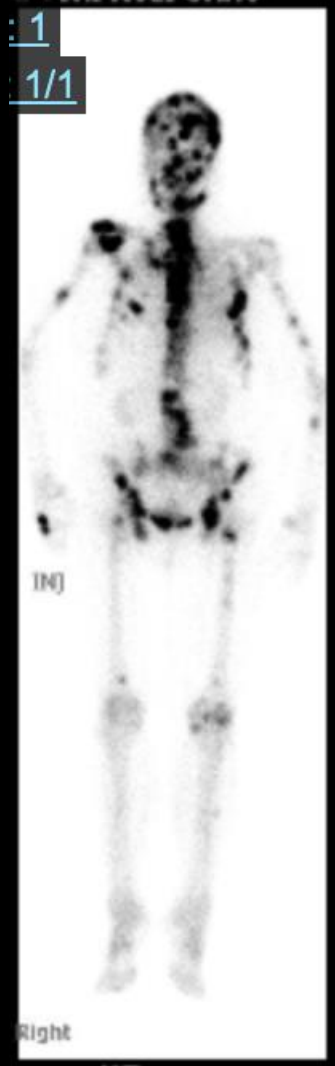

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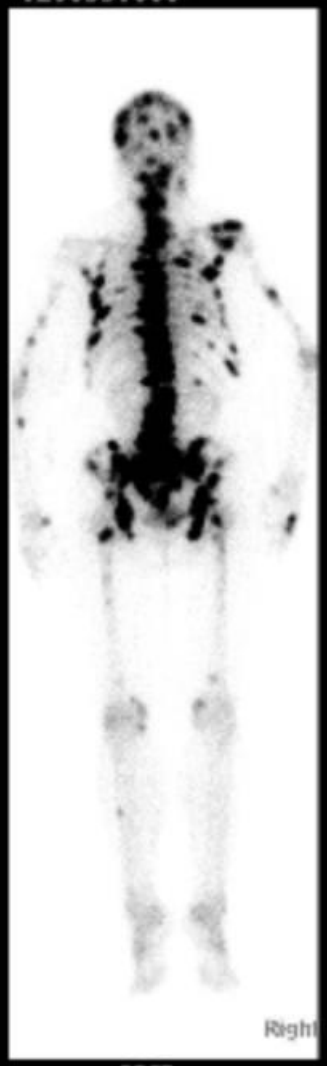
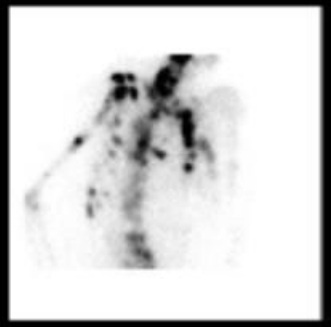
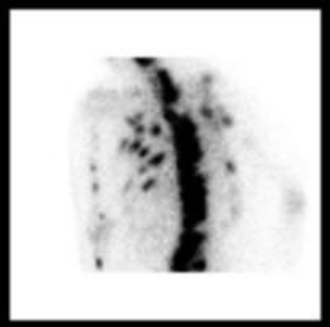


POST


RT SKULL


LT SKULL


RAO CHEST


LPO CHEST

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- **2018/7**
  - **79 y/o woman with advanced breast cancer, multiple lung, pleura, and bone mets**
  - **Hesitated for chemotherapy**

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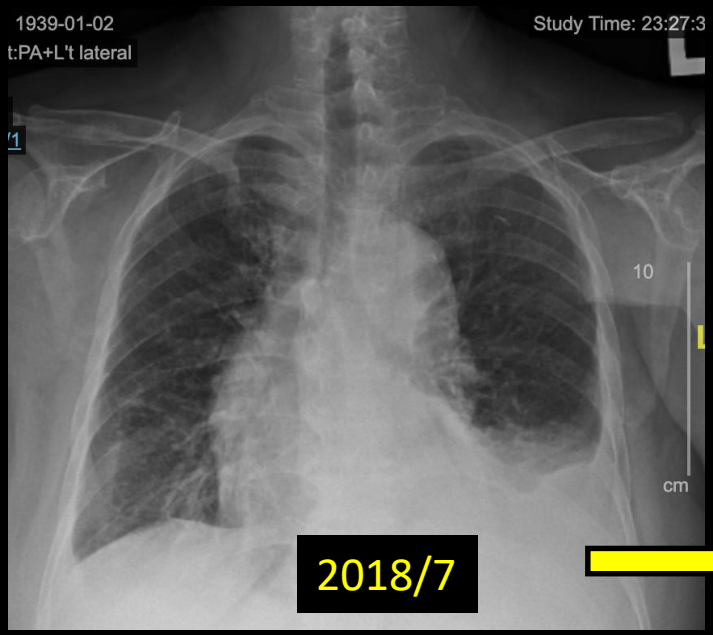
→ Start CDK 4/6 inhibitor (Palbociclib + Aromasin)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t:PA+L't lateral
Study Time: 23:27:3
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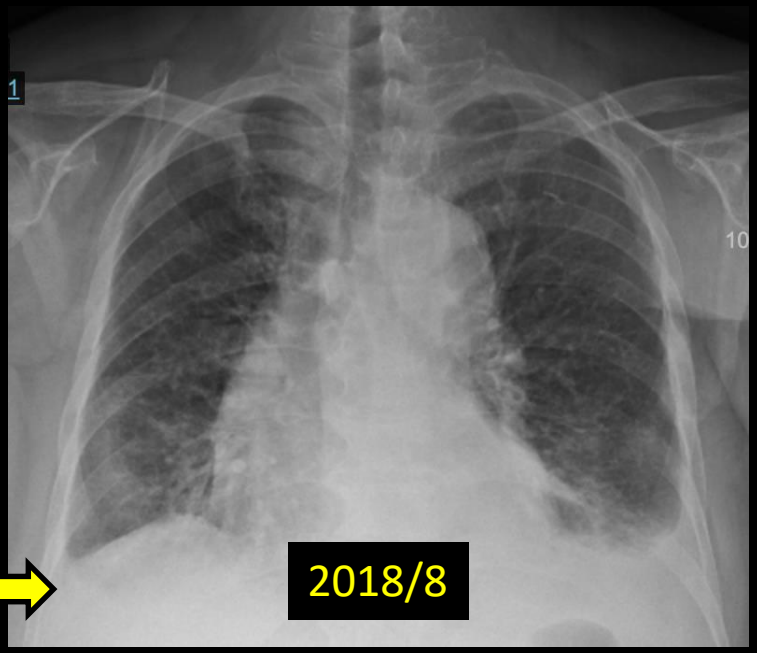
cm
2018/7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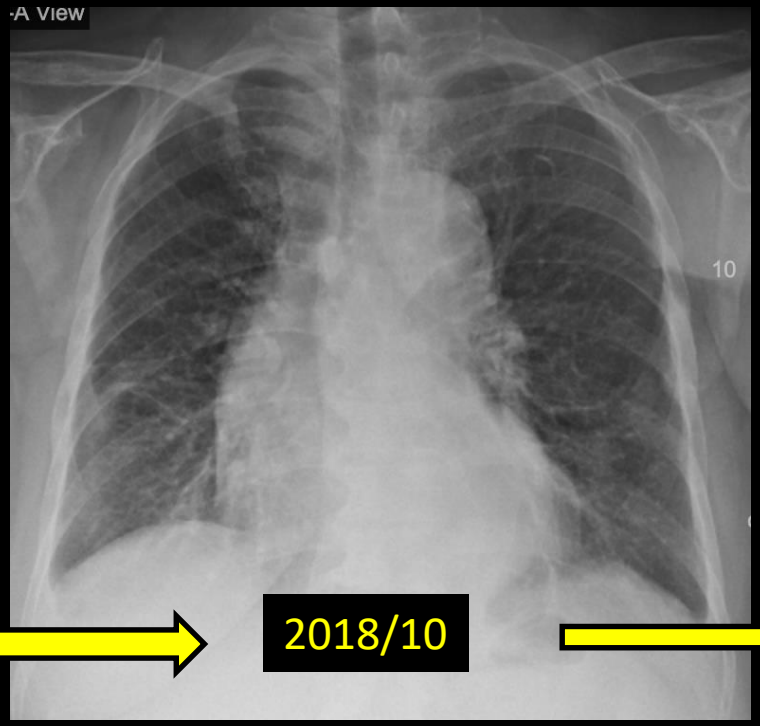
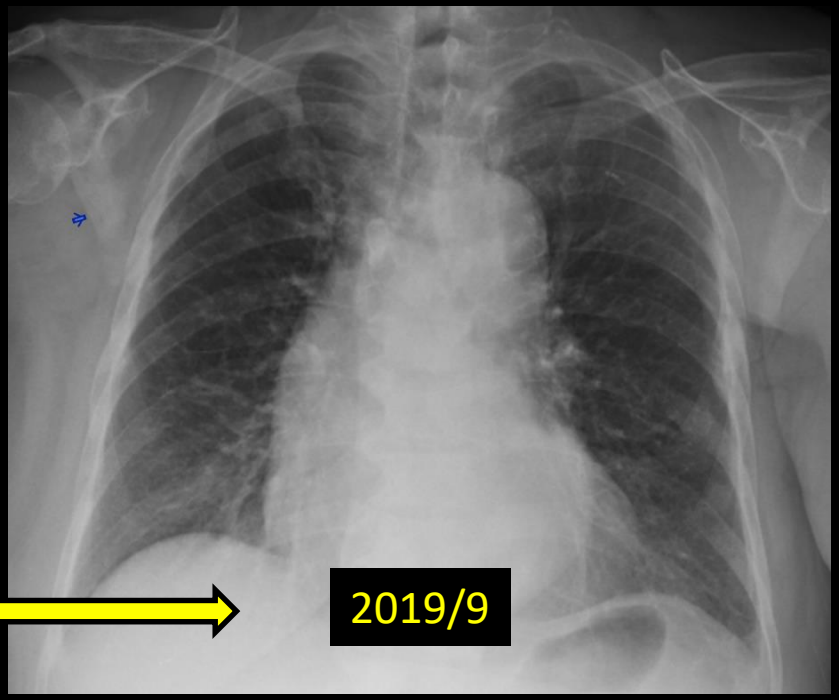
2018/8


-A View
10
2018/10


2019/9

Treatment approach in Hormone Positive mBC

NCCN Guidelines Version 3.2014
Invasive Breast Cancer

NCCN Guidelines Index
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SUBSEQUENT ENDOCRINE THERAPY FOR SYSTEMIC DISEASE

Premenopausal patients with ER-positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

Postmenopausal Patients

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolimus[1]
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2014
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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
Invasive Breast Cancer

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ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal Patients
- **Selective ER modulators (tamoxifen or toremifene) or ovarian ablation or suppression plus endocrine therapy as for postmenopausal women**

Postmenopausal Patients
- **Non-steroidal aromatase inhibitor (anastrozole, letrozole)**
- **Steroidal aromatase inactivator (exemestane)**
- **Exemestane + everolimus[1,2]**
- **Palbociclib + letrozole (category 1)[2,3]**
- **Palbociclib + fulvestrant (category 1)[2, 4]**
- **Ribociclib + letrozole (category 1)[2,3]**
- **Selective ER down-regulator (fulvestrant)[5]**
- **Tamoxifen or toremifene**
- **Megestrol acetate**
- **Fluoxymesterone**
- **Ethinyl estradiol**

[1]A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

[2]If there is disease progression while on a CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another palbociclib regimen. Likewise, if there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen.

[3]Palbociclib or ribociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[4]For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.

[5]A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

SYSTEMIC THERAPY FOR ER- AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE

HER2-Negative and Premenopausal

See Systemic Treatment of Stage IV (M1) Disease (BINV-20)

HER2-Negative and Postmenopausal or Premenopausal Receiving Ovarian Ablation or Suppression

Preferred regimens:

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective ER down-regulator (fulvestrant, category 1)[a]
- Selective estrogen receptor modulator (tamoxifen or toremifene)
- Steroidal aromatase inactivator (exemestane)
- Aromatase inhibitor + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b,c]
- Fulvestrant + CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) (category 1)[b,c]
- Exemestane + everolimus[b,d]
- Fulvestrant + everolimus
- Tamoxifen + everolimus

Useful in certain circumstances:

- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Ribociclib + tamoxifen (category 1)[e]
- Abemaciclib[b,f]

[a] A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

[b] If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

HER2-Positive and Premenopausal

See Systemic Treatment of Stage IV (M1) Disease (BINV-23)

HER2-Positive and Postmenopausal[g,h]

- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[c] CDK4/6 inhibitor (abemaciclib, palbociclib, or ribociclib) in combination with an aromatase inhibitor (anastrozole, letrozole, or exemestane) or fulvestrant may be considered as a treatment option for first-line therapy for women who are postmenopausal or premenopausal (receiving ovarian suppression or ablation with an LHRH agonist) with hormone-receptor positive, HER2-negative metastatic breast cancer. Fulvestrant has been combined with CDK4/6 inhibitors (ie, palbociclib, ribociclib) in the first-line setting in two randomized trials.

[d] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

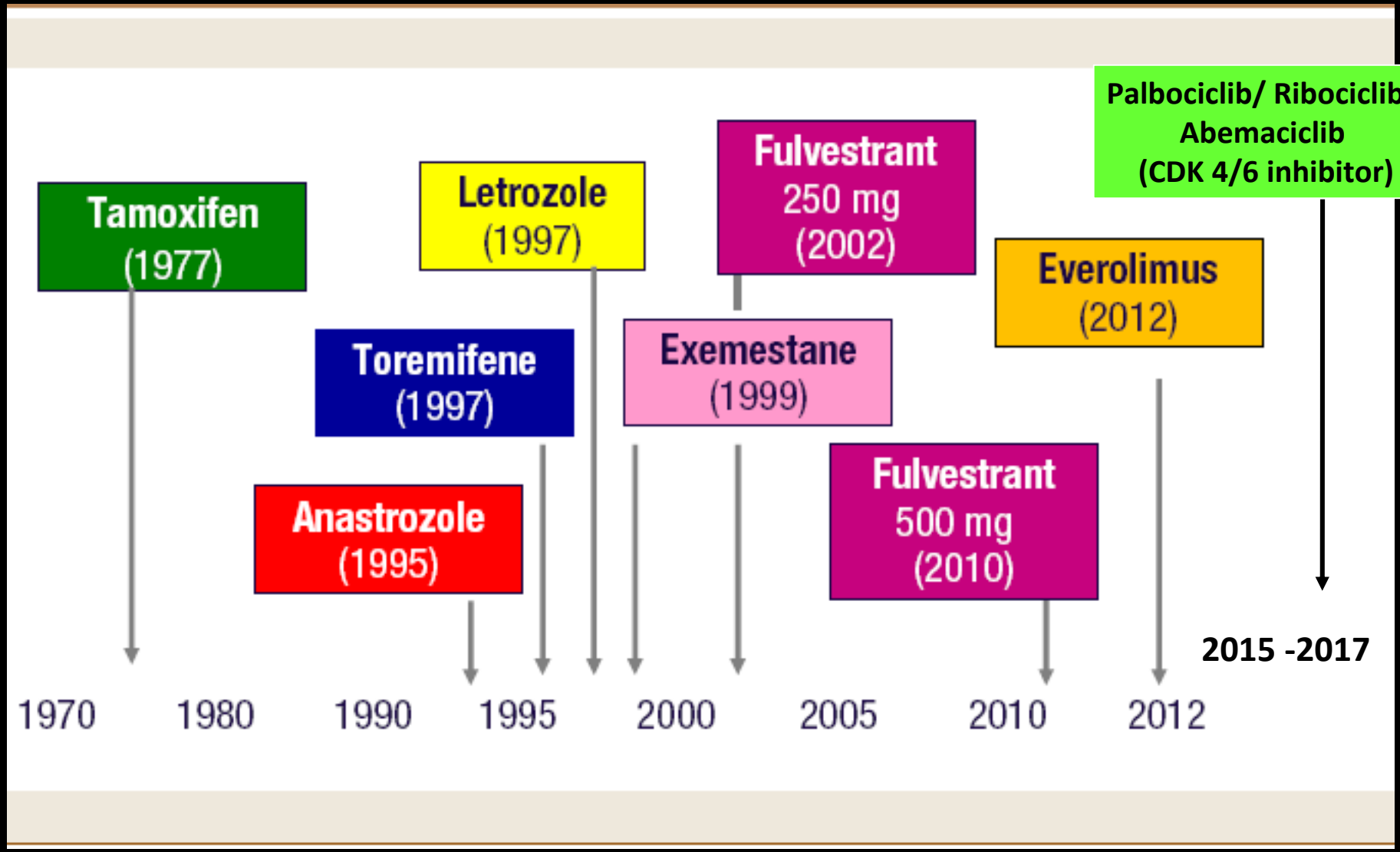
[e] Ribociclib + tamoxifen is not considered a preferred first-line therapy due to QTc prolongation risk but may be considered in certain circumstances as a treatment option for first-line therapy with ovarian suppression or ablation for premenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[f] Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

[g] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.

[h] If treatment was initiated with chemotherapy and trastuzumab + pertuzumab, and the chemotherapy was stopped, endocrine therapy may be added to the trastuzumab + pertuzumab.

Shifting landscape for therapy for ER+ MBC: Timeline of agents for HR-positive advanced breast cancer

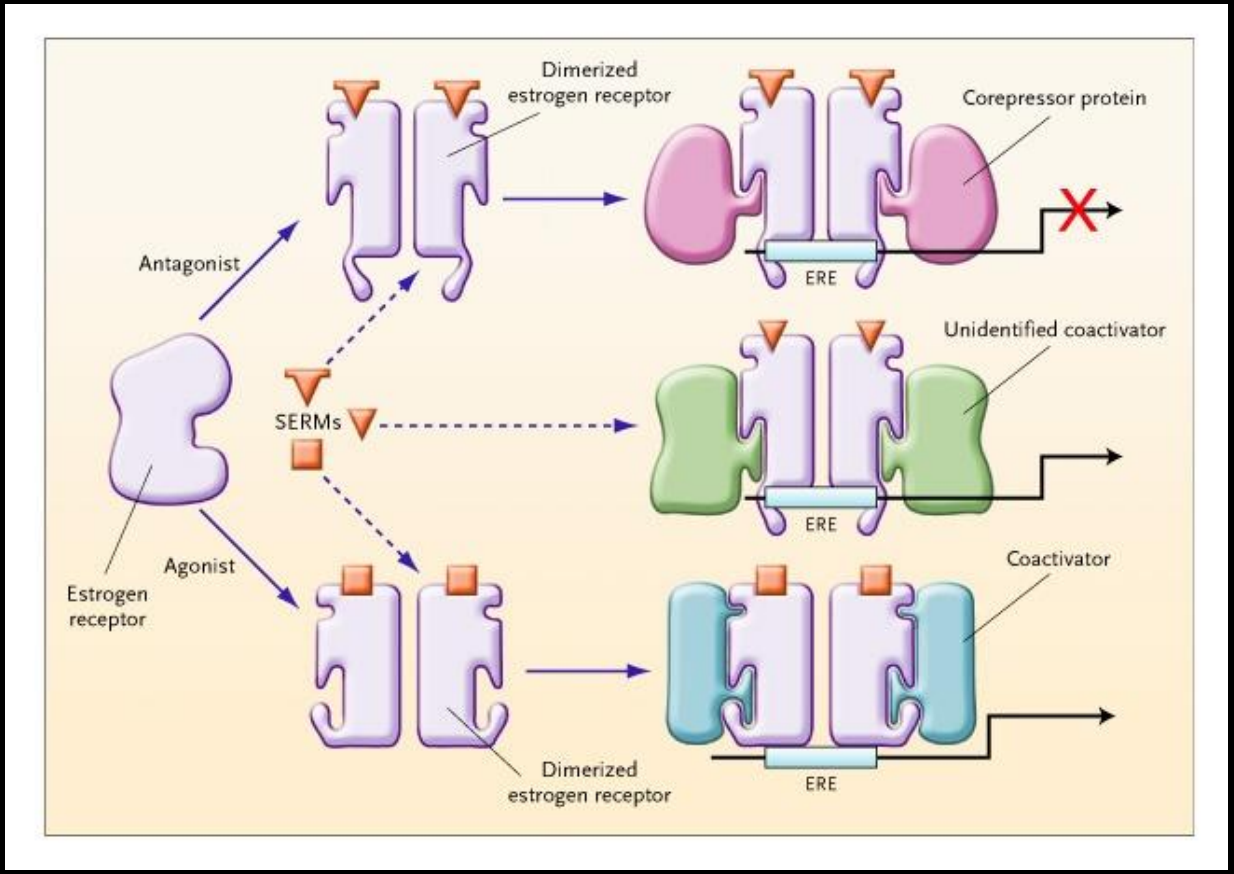


Chlebowski RT. Clinical Breast Cancer 2013, June

SERM vs SERD

SERM (Selective Estrogen Receptor **Modulator**)

Tamoxifen



SERM vs SERD

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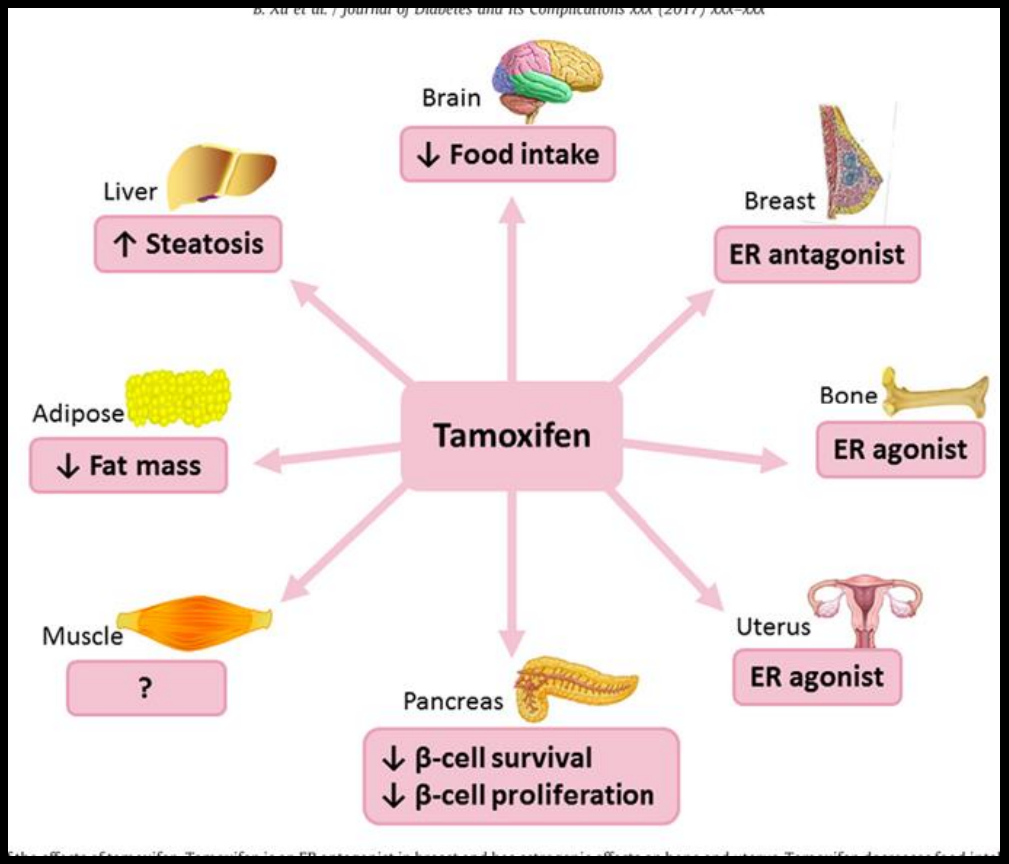
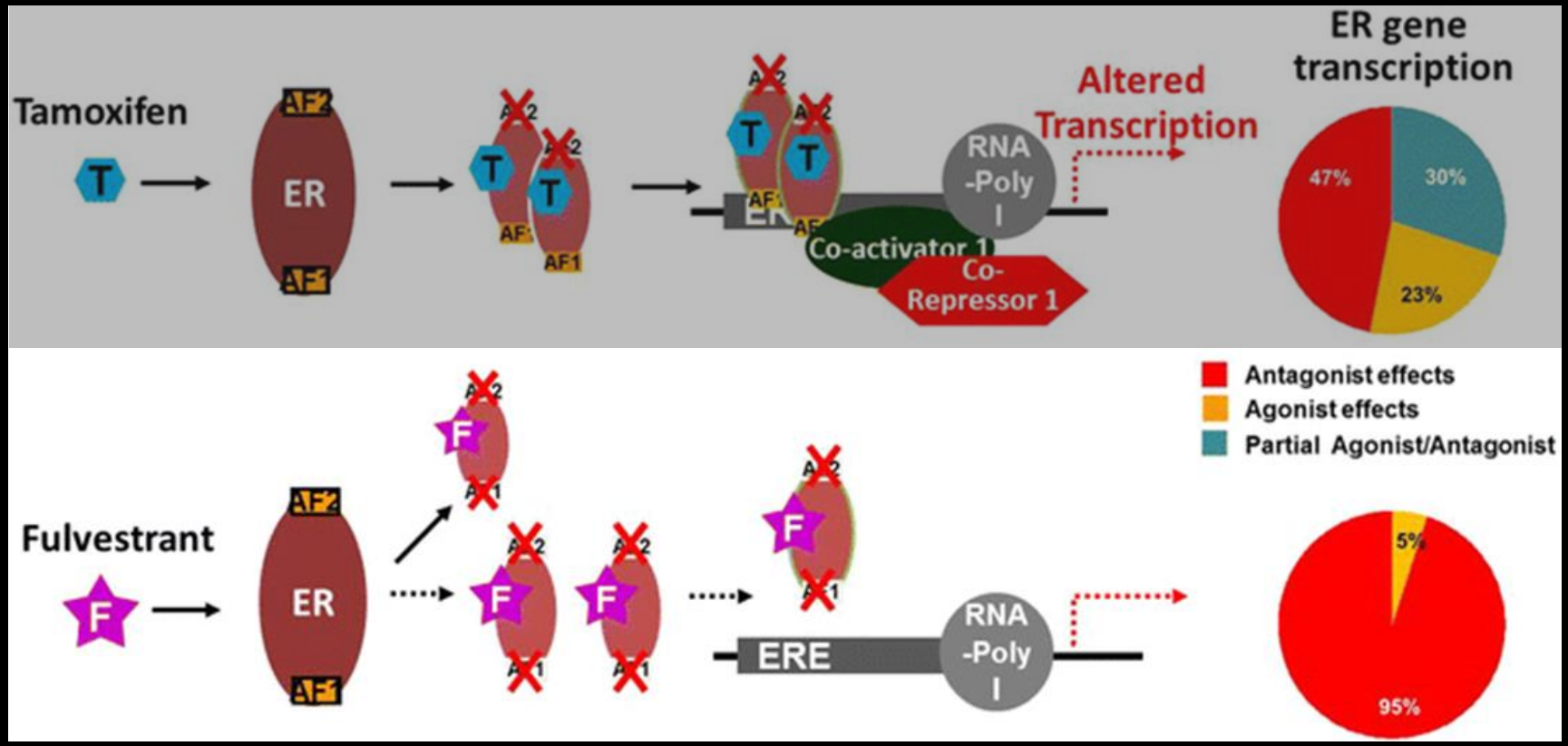


SERM vs SERD

SERD (Selective Estrogen Receptor **Down-regulator**)

Fulvestrant



SERM vs SERD

Tamoxifen vs Fulvestrant

	AF-1 ACTIVITY	AF-2 ACTIVITY	ESTROGEN LEVELS	ERα LEVELS	ESTROGEN-DEPENDENT ERα SIGNALLING	ESTROGEN-INDEPENDENT ERα SIGNALLING
AI	no effect	⇩	⇩	no effect	⇩	no effect
SERM Tamoxifen	⇧	⇩	no effect	no effect	⇩	no effect
SERD Fulvestrant	⇩	⇩	no effect	⇩	⇩	⇩

Adapted from Osborne CK et al., Br J Cancer 200414

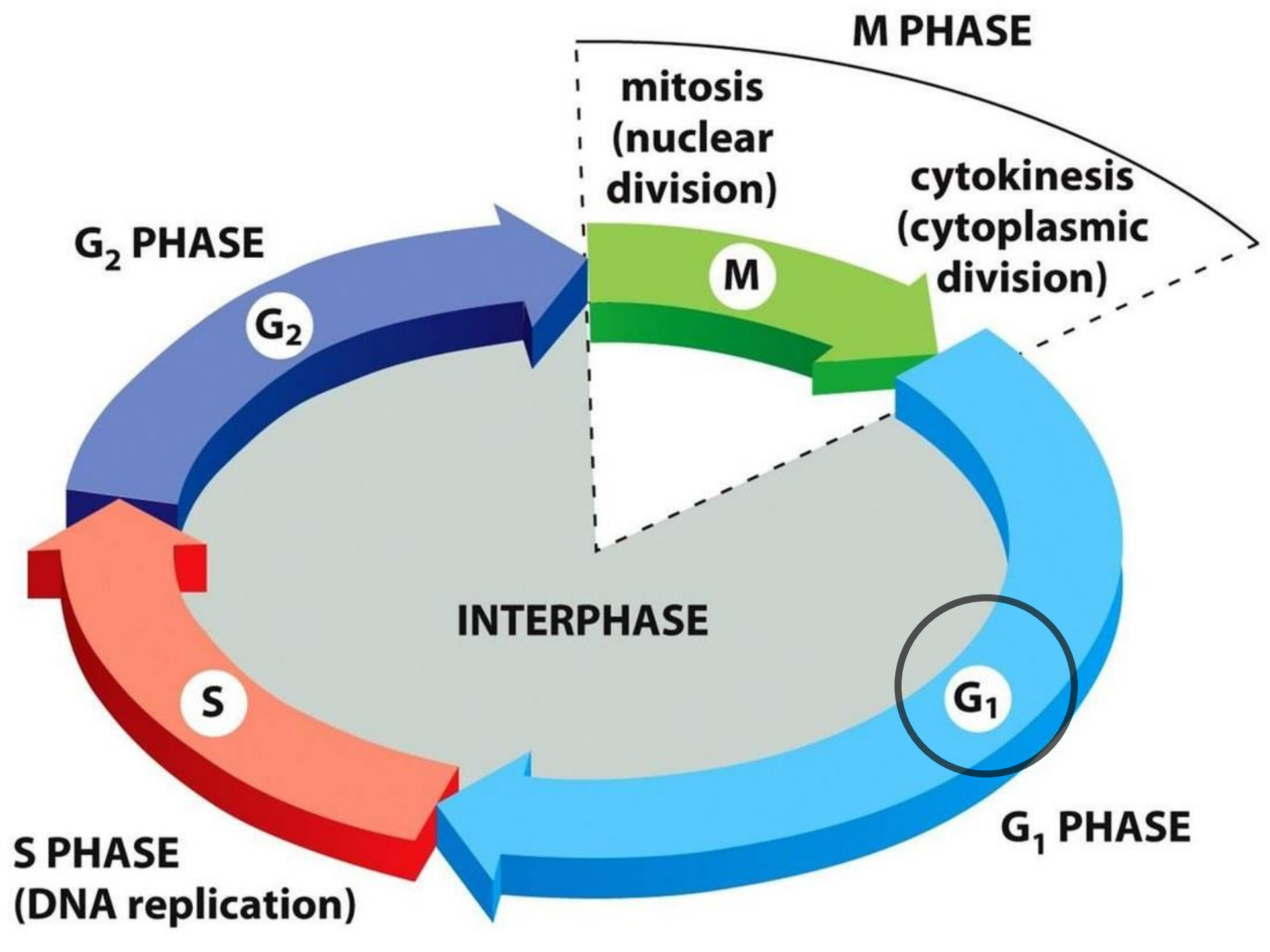
CDK4/6 inhibitor

What is its mechanism ?

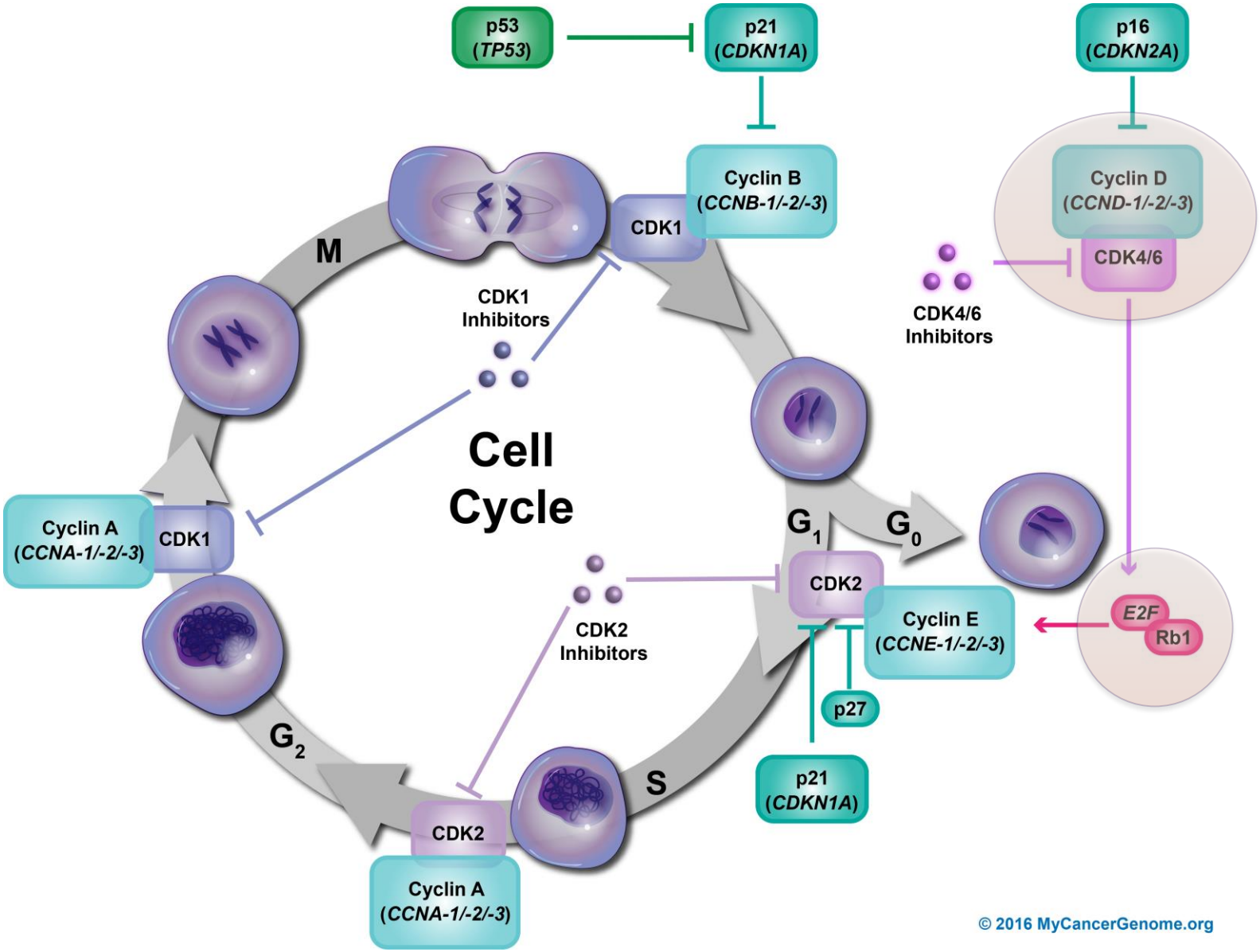
When to give ?

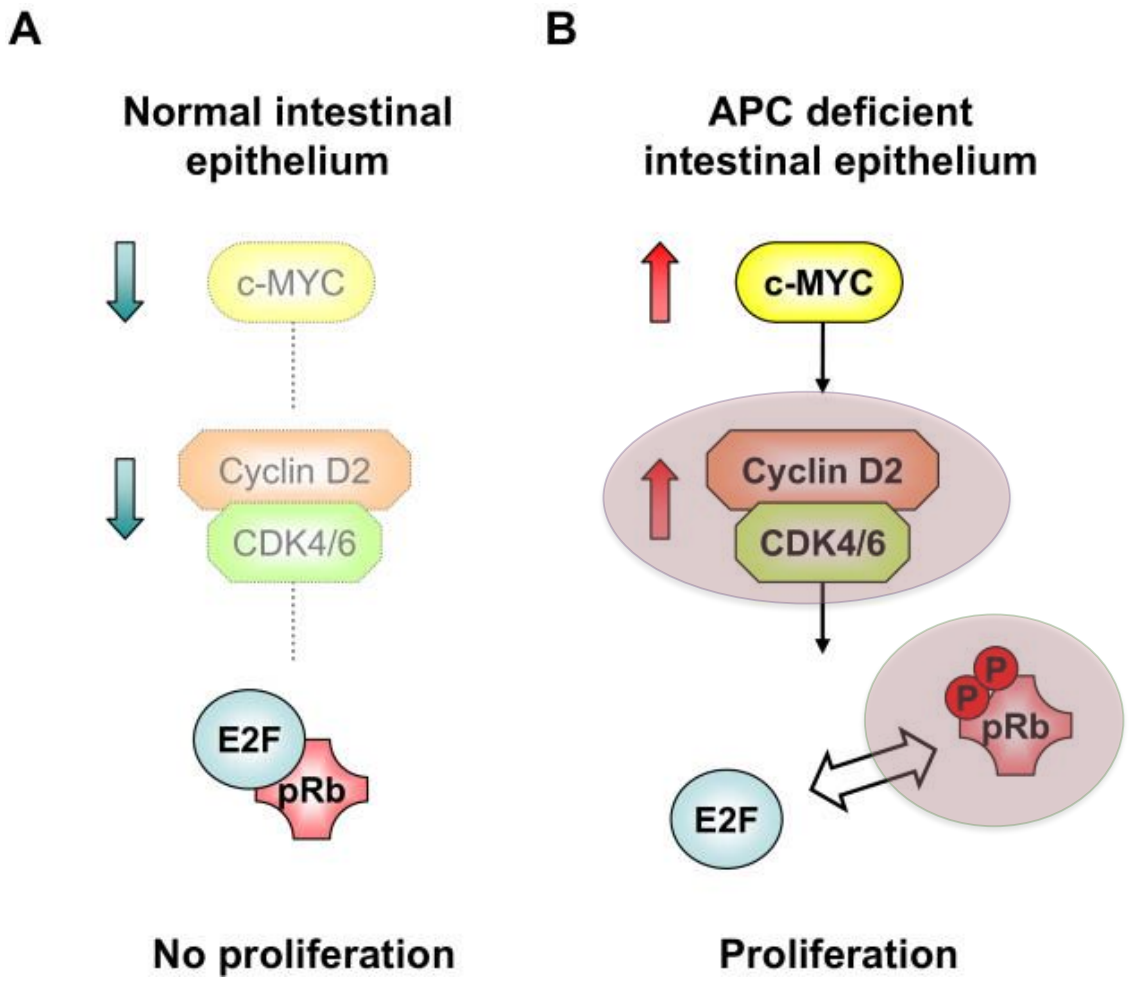
How to give ?

Side effects management ?


M PHASE
mitosis (nuclear division)
cytokinesis (cytoplasmic division)
G2 PHASE
G2
M
INTERPHASE
S
G1
S PHASE (DNA replication)
G1 PHASE

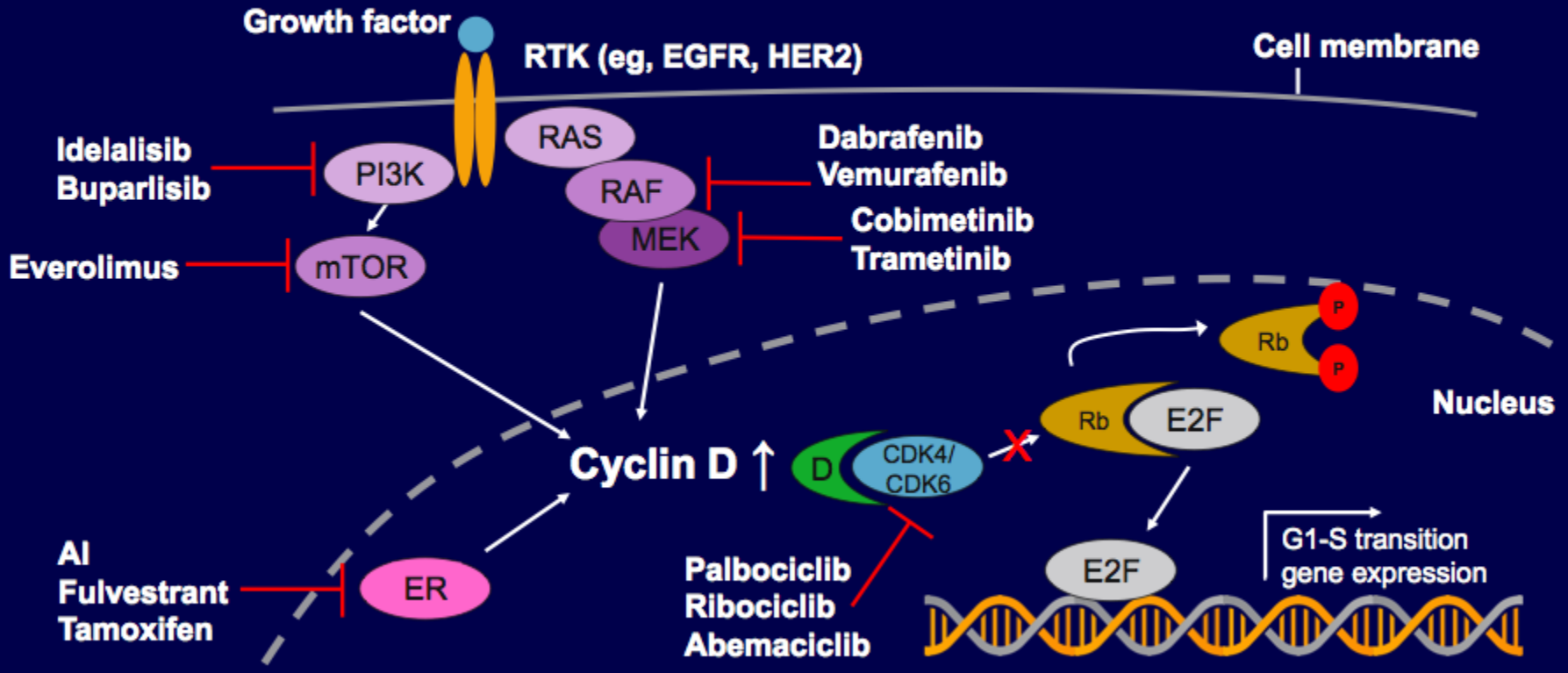
CDK: cyclin dependent kinase





- **CDK4/6 complex phosphorylates Retinoblastoma protein**
- Release of E2F and DP transcription factors → Transition into S phase

Combination Therapy: Rationale



O'Leary B, et al. Nat Rev Clin Oncol. 2016;13:417-430.

Slide credit: clinicaloptions.com


Pfizer
Ibrance®
(palbociclib)
capsules
75 mg
21 Capsules
Rx only
Pfizer
Ibrance®
(palbociclib)
capsules
100 mg
21 Capsules
Rx only
Pfizer
NDC 0069-0189-21
Ibrance®
(palbociclib)
capsules
125 mg
21 Capsules
Rx only


Kisqali®
(ribociclib)
tablets
600 mg daily dose
(three 200 mg tablets)
NDC 0078-0874-21
Rx only
TO OPEN:
PRESS & HOLD HERE
NOVARTIS


Verzenios® 150 mg
Filmtabletten
Abemaciclib
Zum Einnehmen
安健藥業
HEALTH PEACE LIMITED

Comparison of three CDK4/6 Inhibitors

	Palbociclib	Ribociclib	Abemaciclib
Preferential inhibition of CDK4 vs CDK6[25]* IC_{50} (μM)	**x1**	**x8**	**x6**
Free drug concentration (fold difference)[24†]	**x1**	**x22**	**x1**

†Based on preclinical activity. Preclinical activity does not necessarily correlate with clinical outcomes. The data above is not presented to discuss the efficacy and safety information of the mentioned products.

CDK, cyclin-dependent kinase.
*Free drug concentration is based upon unbound C_{ave} values, determined in human pharmacokinetic studies. Values are normalized to palbociclib.[24,25]

Selective CDK4/6 Inhibitors: Comparison of Key Clinical Characteristics

	Palbociclib	Ribociclib	Abemaciclib
Route	PO	PO	PO
Dose, mg	125 QD	600 QD	200 BID
Schedule	3 wks on/1 wk off	3 wks on/1 wk off	Continuous
Half-life, hr	27	32.6	17-38
ORR (monotherapy), %	6	2.3	19.7
Key grade 3/4 toxicities, %	Neutropenia, 51 Thrombocytopenia, 22	Neutropenia, 28 Thrombocytopenia, 9	Neutropenia, 27 Diarrhea, 20 Fatigue, 13
CNS penetration	Uncertain	No	Yes

DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001. Hamilton E, et al. Cancer Treatment Rev. 2016;45:129-138. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705. Dickler MN, et al. ASCO 2016. Abstract 510. Barroso-Sousa R, et al. Breast Care. 2016;11:167-173.

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Comparative Toxicities of CDK4/6 Inhibitors: Early Phase Trials

Adverse Event (All Grades), %	Palbociclib[1] (N = 37)	Ribociclib[2] (N = 67)	Abemaciclib[3] (N = 173)
Neutropenia	94	46	23
Anemia	70	28	20
Thrombocytopenia	76	34	23
Nausea	24	45	45
Vomiting	5	25	25
Diarrhea	16	27	63
Fatigue	68	33	41
QTc prolongation	No	9	No

1. DeMichele A, et al. Clin Cancer Res. 2015;21:995-1001.
2. Infante JR, et al. Clin Cancer Res. 2016;22:5696-5705.
3. Patnaik A, et al. Cancer Discov. 2016;6:740-753.

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FDA indications for CDK 4/6 inhibitors

	Palbociclib	Ribociclib	Abemaciclib *
FDA approved indication	**Post-M** 1L, combine with AI 2L, combine with Fulv	**Post-M** 1L, combine with AI (TFDA) 1L, Combine with Fulv * 2L, combine with Fulv * **Pre-M** 1L combine wit AI *	**Post-M** 1L, combine with AI * 2L, combine with Fulv * Monotherapy after Chemo and ET *
Food effect	Must be taken with food	With or without food	With or without food
Dose strengths	125/100/75mg	200mg	200/ 150/ 100/ 50mg
Starting dose	125mg OD Intermittently (3 weeks on, 1 week off)	600mg OD Intermittently (3 weeks on, 1 week off)	150/200mg BD continuously (combination/single agent)

This slide was presented by Tseng LM, TJCC 2019

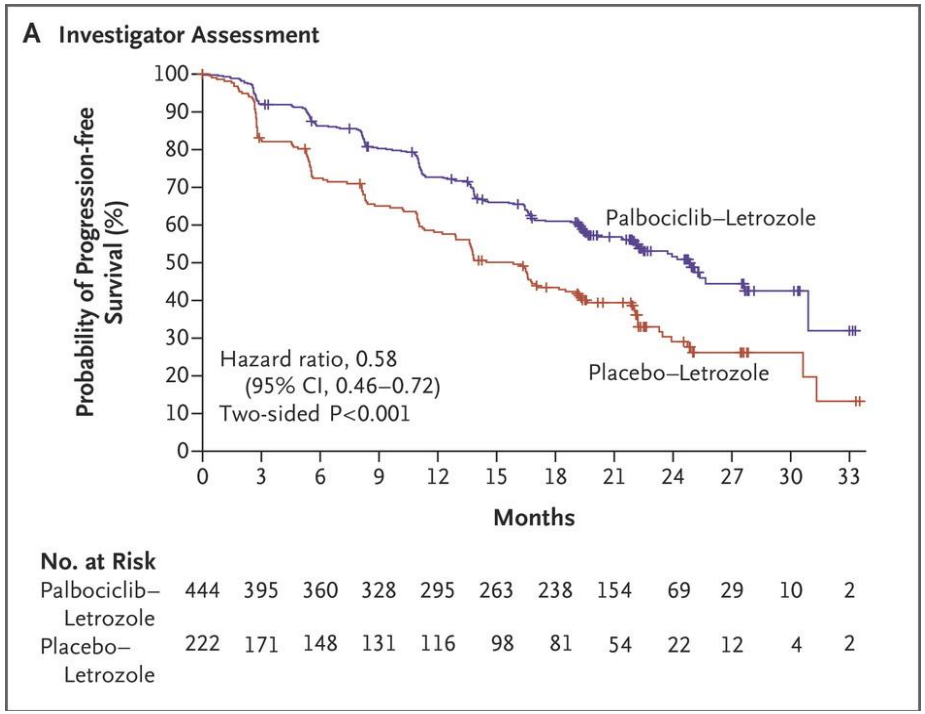
Key phase 3 trials of CDK4/6 inhibitors

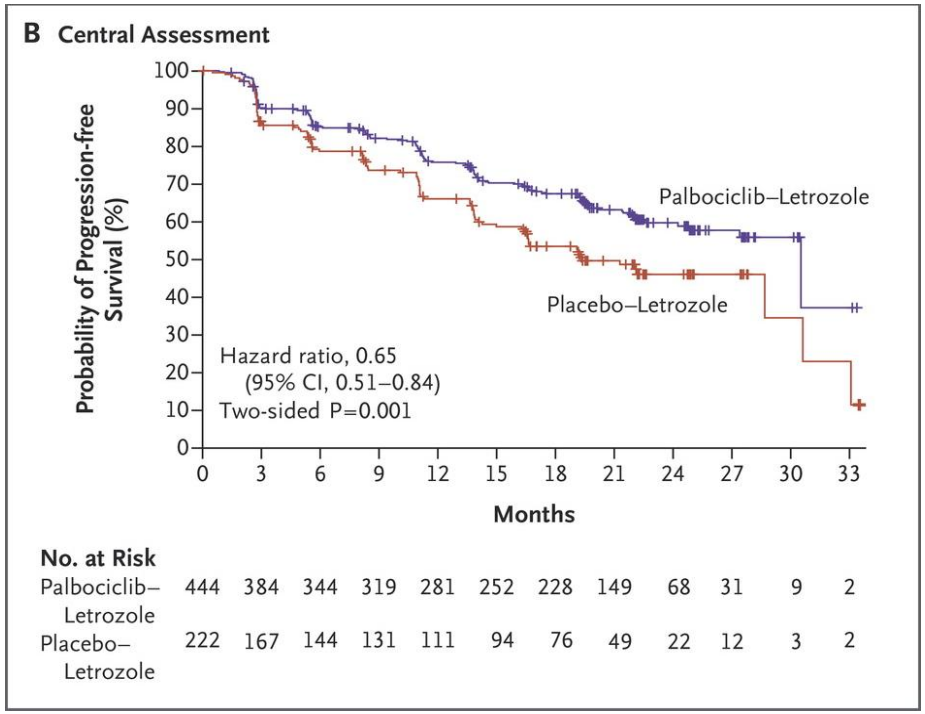
- **Palbociclib**
  - Paloma 2 (1st-line mBC)
  - Paloma 3 (2nd-line mBC)

- **Ribociclib**
  - Monaleesa 2 (1st-line mBC)
  - Monaleesa 7 (1st-line mBC, pre-Menopause)

- **Abemaciclib**
  - Monarch 2 (2nd-line mBC)
  - Monarch 3 (1st-line mBC)

PALOMA 2 Palbo + Letrozole in 1st line mBC



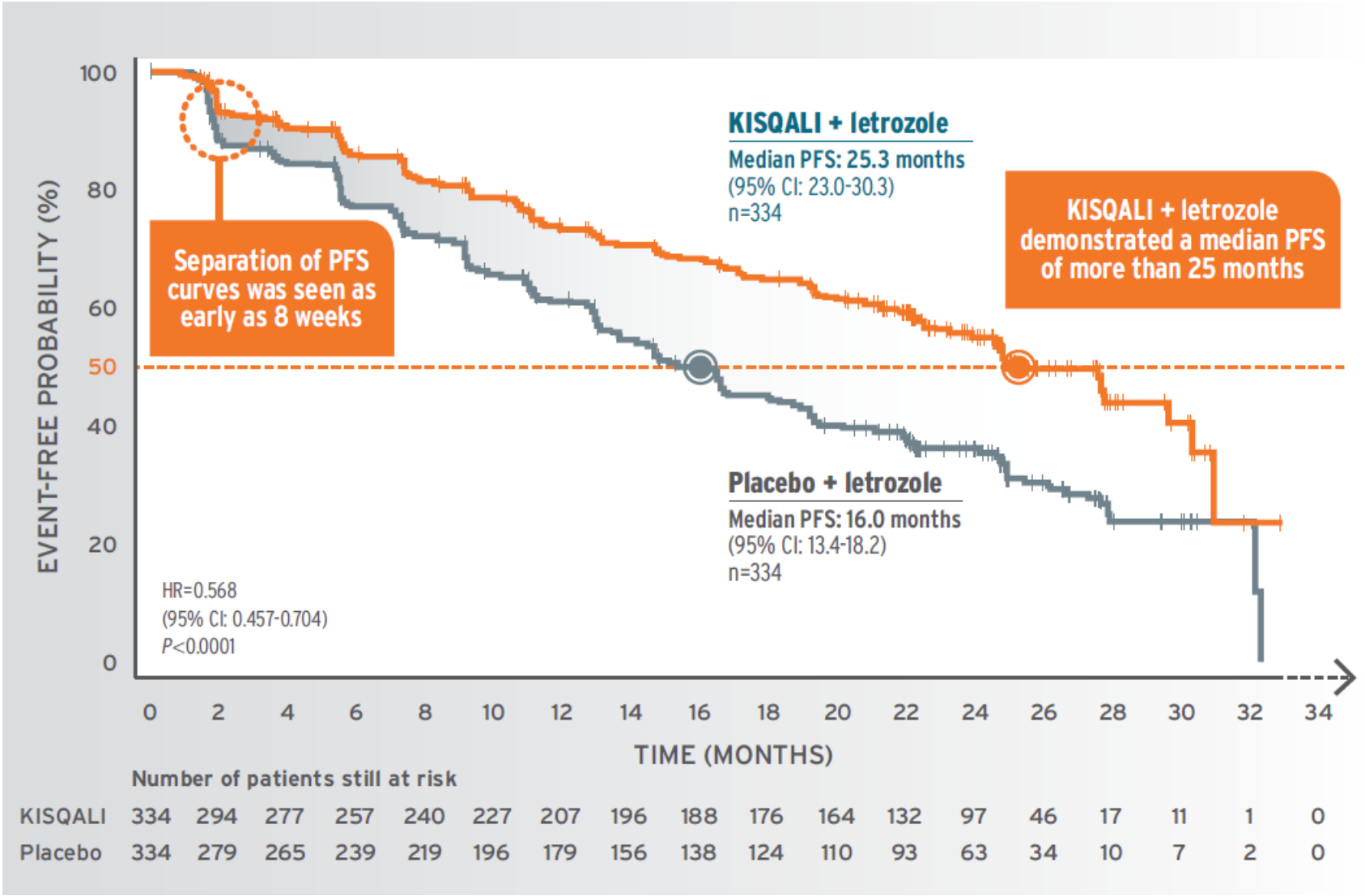


PFS 24.8 m (95% CI, 22.1-NR)
vs 14.5 m (95% CI, 12.9-17.1)

The median duration of follow-up was 23 months.

Finn RS et al. N Engl J Med 2016;375:1925-1936.

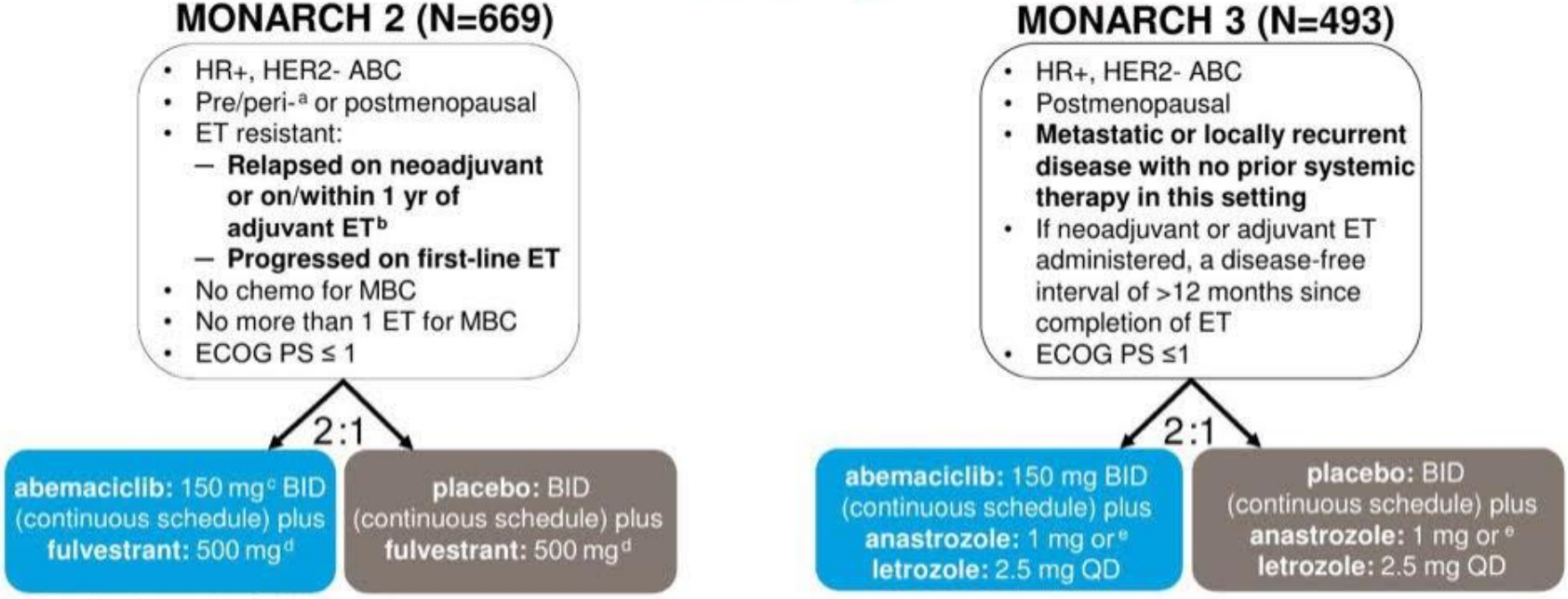
MONALEESA-2 Ribo + Letrozole in 1st line mBC



Hortobagyi et al. MONALEESA-2 Updated PFS Poster presented at ASCO 2017

San Antonio Breast Cancer Symposium
December 5-9, 2017

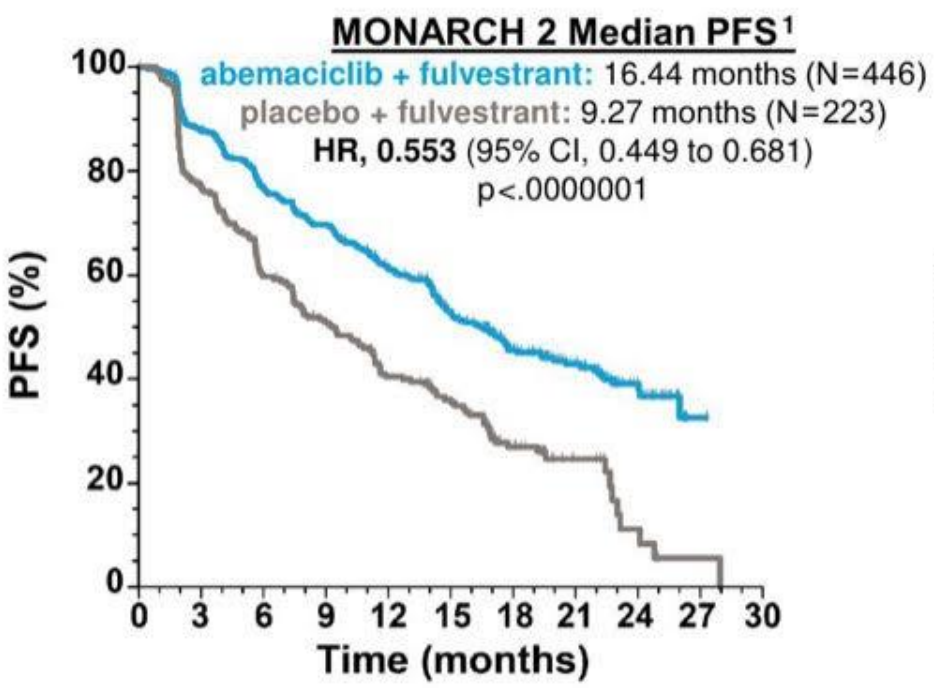
MONARCH 2 and 3 Study Design

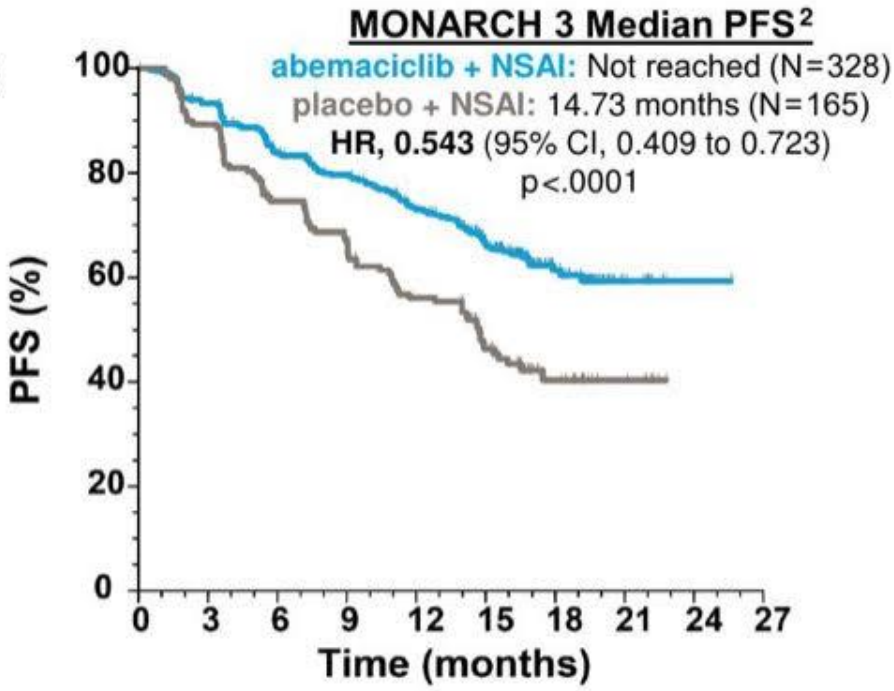


[a] *Required to receive GnRH agonist*
[b] *Most patients entered after progressing while receiving prior ET, with only 8.8% who had disease that progressed within 1 year after completing adjuvant therapy*
[c] *Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled*
[d] *Fulvestrant administered per label*
[e] *Per physician's choice: 79.1% received letrozole, 19.9% received anastrozole*

MONARCH 2 and 3 PFS (ITT)

San Antonio Breast Cancer Symposium
December 5-9, 2017





1. Sledge GW Jr et al. *J Clin Oncol.* 2017;35(25):2875-84
2. Goetz MP et al. *J Clin Oncol.* 2017;35(32):3638-46

Case Sharing 02

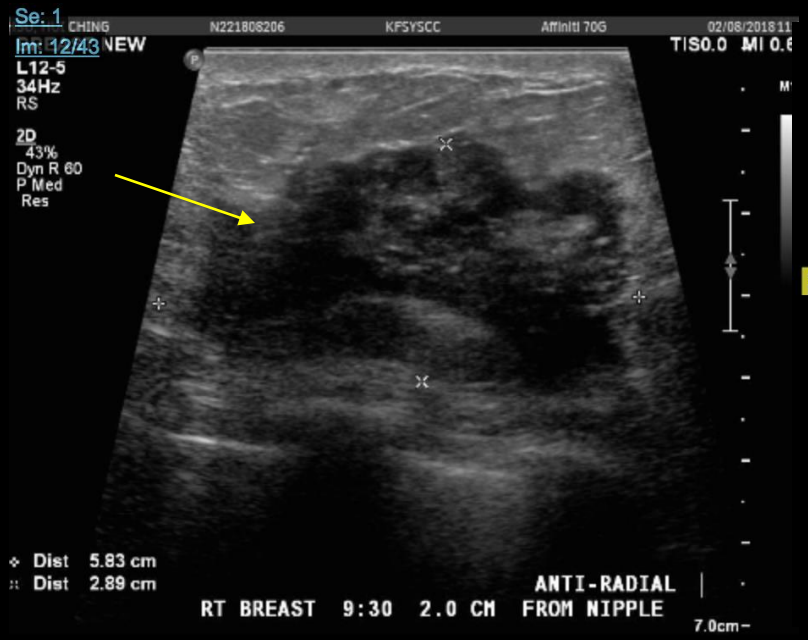
59 y/o woman

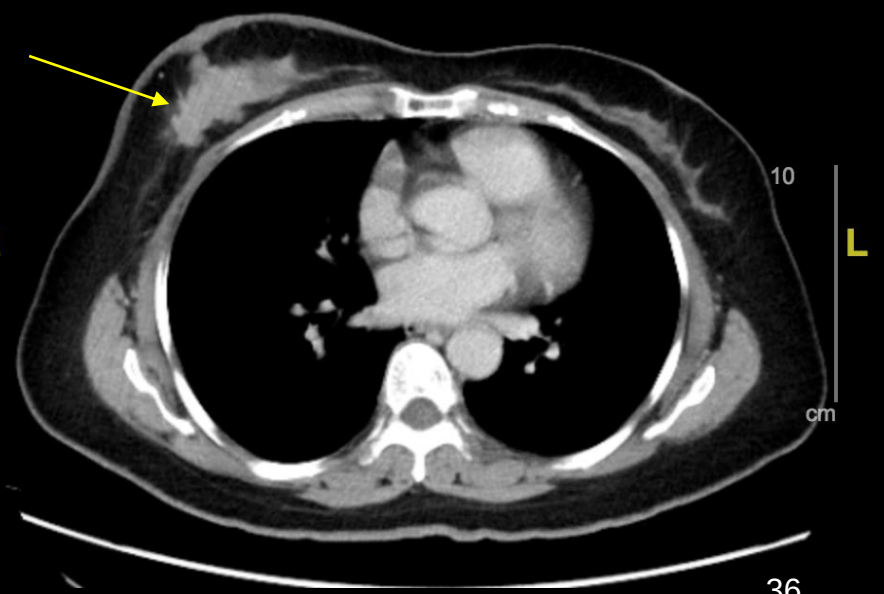
G7P5AA2, menopause at 52 y/o

right breast mass since 2016

2018/2

Right breast mass rapid enlargement, up to 9x8 cm





2018/2, right breast biopsy

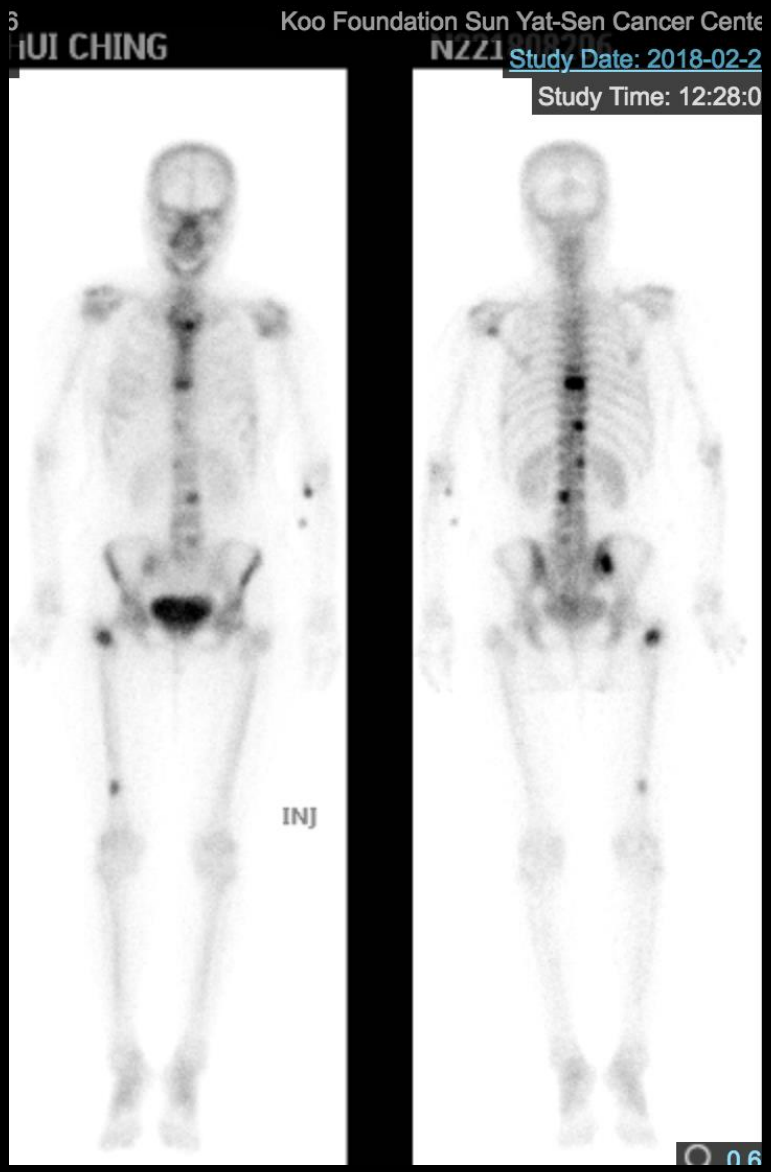
TISSUE ORIGIN: Breast.

PATHOLOGIC DIAGNOSIS:
Right breast, 9.5 o'clock/5 cm from nipple, core biopsy:
·Tumor histology: INFILTRATING DUCTAL CARCINOMA
·Nottingham grade: 3
·Black's nuclear grade in reversed numerical order: 2
·In situ component: present, nuclear grade 2, solid pattern with necrosis
·Microcalcifications: not identified
·Lymphovascular invasion: not identified
·Perineural invasion: not identified

STAINING RESULT(S):
·Estrogen receptor: positive, estimated proportion of tumor cells score 5, average intensity of positive tumor cells score 3, Allred score = 8
·Progesterone receptor: positive, estimated proportion of tumor cells score 4, average intensity of positive tumor cells score 3, Allred score = 7
·HER2: score: 1+ (no overexpression)
·Ki–67: positive, 50% of labeling index

INTERPRETATION:
The invasive cancer cells are positive to ER and positive to PR. There is no overexpression of HER2.

2018/2, bone scan



- Increased uptake of radioactivity in the T7, T8, T11, L1, L3~L5 spines, right iliac bone, sternum, left scapula, right femur, left femoral head, right humerus

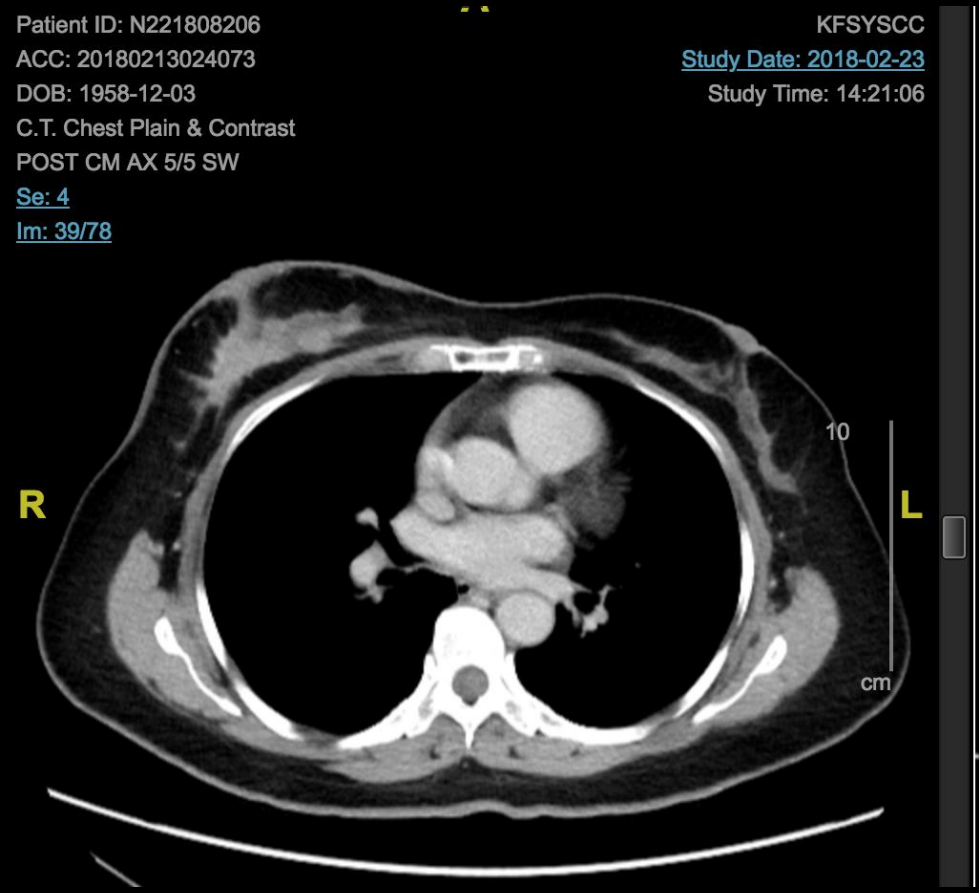
Palbociclib 125mg/day, Femara

	2018/2/27	2018/3/27	2018/4/24					
R.B.C	4.46	3.68	3.41					
HGB	13.9	11.6	11.4					
HCT	41.9	34.1	33.1					
MCV	93.9	92.7	97.1					
MCH	31.2	31.5	33.4					
MCHC	33.2	34	34.4					
RDW	11.9	11.6	16					
PLT	187K	**64K**	**82K**					
W.B.C	6370	**3270**	**3460**					
BAND		1						
SEG		32	30					
LYMPH		40	38					
MONO		3	12					
EO		0	0					
BASO		0	1					
Atyp. Lym		12	10					
ANC		**1046**	**1038**					

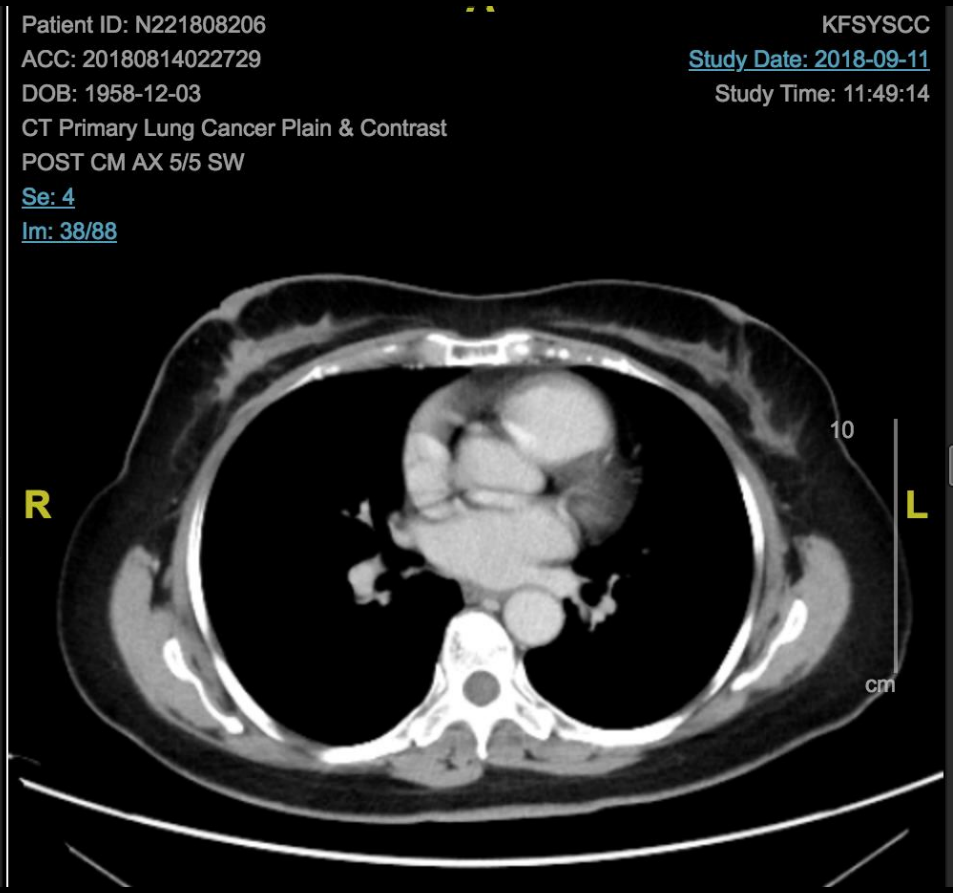
Palbociclib 125mg/day, Femara

	2018/2/27	2018/3/27	2018/4/24	2018/5/15	2018/6/19	2018/7/17	2018/8/14	2018/9/11
R.B.C	4.46	3.68	3.41	3.34	2.93	2.95	2.97	3.16
HGB	13.9	11.6	11.4	11.7	11.1	11.4	11.4	12.1
HCT	41.9	34.1	33.1	33.9	31.8	32.7	32.8	34.1
MCV	93.9	92.7	97.1	101.5	108.5	110.8	110.4	107.9
MCH	31.2	31.5	33.4	35	37.9	38.6	38.4	38.3
MCHC	33.2	34	34.4	34.5	34.9	34.9	34.8	35.5
RDW	11.9	11.6	16	17.4	15.1	13.6	13	12.4
PLT	187K	**64K**	**82K**	**129K**	**103K**	**101K**	**94K**	**117K**
W.B.C	6370	**3270**	**3460**	**3520**	**3110**	**3360**	**3930**	**3870**
BAND		1				1		
SEG		32	30	37	45.3	35	38.2	29.4
LYMPH		40	38	50	43.1	49	50.1	60.2
MONO		3	12	8	9.6	7	10.4	8.8
EO		0	0	0	1	1	0.3	0.3
BASO		0	1	3	1	0	1	1.3
Atyp. Lym		12	10			2		
ANC		**1046**	**1038**	**1302**	**1399**	**1209**	**1493**	**1122**

2018/2

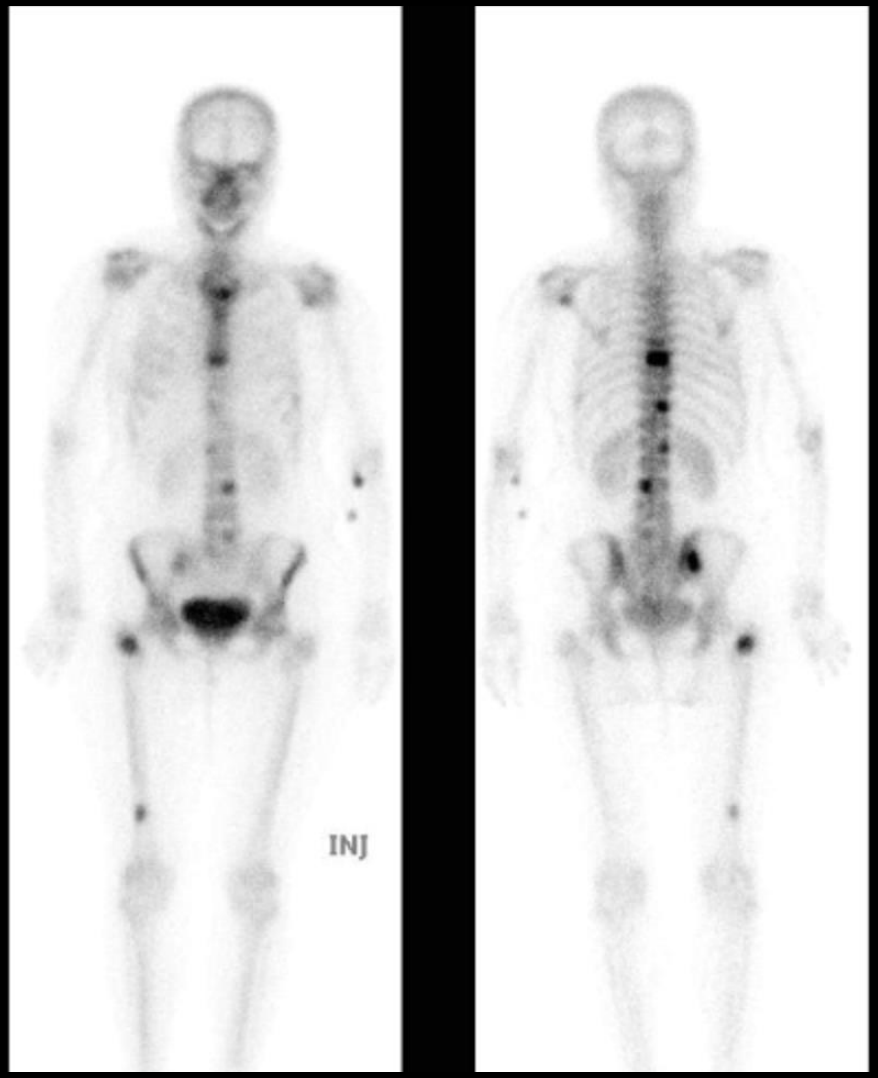


2018/9

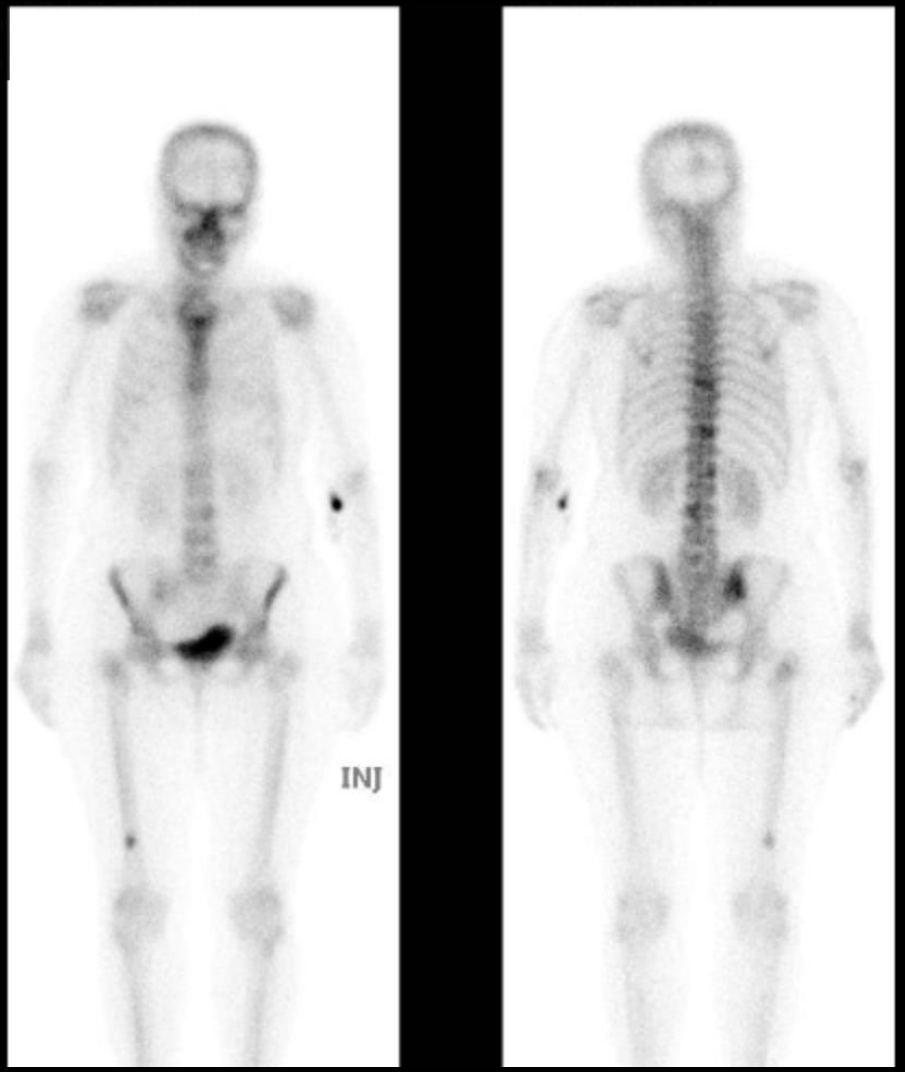


	2018/2/27	2018/3/27	2018/4/24		2018/9/11
Right breast tumor	**9x8cm**	**6x6cm**	**5x5cm**		**Vague**

2018/2



2018/9



- Most of bone lesions became less prominent

報告日期	檢驗名稱	結果值	單位
2018/02/08	CEA	4.55	ng/mL
2018/02/08	CA-153	18.9	U/mL
2018/02/08	HBsAg	4026.1 Positive	S/CO
2018/02/08	Anti-HCV	0.140 Negative	S/CO
2018/02/23	Anti-HBs Ab	0.5 Negative	mIU/mL
2018/02/23	Anti-HBc	10.6 Positive	S/CO
2018/02/23	HBe Ag	0.222 Negative	S/CO
2018/02/23	Anti-HBe	0.010 Positive	S/CO
2018/03/01	HBV PCR	9470	IU/mL

Is HBV prophylaxis necessary for patients undergoing palbociclib ?

Palbociclib 125mg/day
Femara

	2018/2/27				2018/8/14
HBVPCR	9470				undetected

Entecavir 0.5mg/day

Adverse Effects of CDK 4/6 inhibitors

PALOMA-2: Hematological AEs

	PAL + LET (N=444)			PCB + LET (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;375:1925-1936.

PALOMA-2: Non-hematological AEs

	PAL + LET (N=444)			PCB + LET (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]In the palbociclib + letrozole group, 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

[b]Includes MedRA preferred terms for rash AE, adverse event

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

MONALEESA-2: AEs of special interest – QTcF prolongation

QTcF prolongation, n (%)	Ribociclib + Letrozole n=334	Placebo + Letrozole n=330
Average post-baseline QTcF >480 msec (≥Grade 2)	11 (3.3)*	1 (0.3)

- All cases detected by Cycle 2 Day 1; Median time to onset: ~15 days on ribociclib, mean increase 22.9 msec
- In the ribociclib + letrozole arm:
  - There was one case of QTcF >500 msec; the patient had a baseline QTcF of 484 msec (ineligible at study entry)
  - 8/11 patients continued treatment at 600 mg/day
  - Two patients required temporary dose interruption and restarted at 600 mg/day
  - One case of sudden death** occurred in the context of Grade 3 hypokalemia and Grade 2 QTcF prolongation§

*Includes 6 patients with an increase of >60 msec from baseline; and 1 patient with cardiac abnormalities at baseline.
**Patient had administered methadone (known risk of QT prolongation);§Grade ≥2: Average post-baseline QTcF >480 msec.
Hortobagyi GN, *et al. N Engl J Med* 2016;375:1738–1748.

MONALEESA-2: AEs of special interest – Liver enzyme elevations

AE, %	Ribociclib + Letrozole n=334			Placebo + Letrozole n=330		
	Grade 1/2	Grade 3 (>5–20 x ULN)	Grade 4 (>20 x ULN)	Grade 1/2	Grade 3 (>5–20 x ULN)	Grade 4 (>20 x ULN)
Elevated ALT	36	8	2	35	1	0
Elevated AST	37	6	1	31	2	0
	Grade 1/2	Grade 3 (>3–10 x ULN)	Grade 4 (>10 x ULN)	Grade 1/2	Grade 3 (>3–10 x ULN)	Grade 4 (>10 x ULN)
Elevated total bilirubin	4	1	<1	2	<1	0

- Median time to onset for increased LFTs was ~8.1 weeks on ribociclib
- Increased Grade 3/4 ALT or AST led to discontinuation of ribociclib in 4.5% and 2.7% of patients, respectively
- Hy's Law criteria were confirmed in 4 patients in the ribociclib + letrozole arm; liver enzyme levels returned to normal in all patients following ribociclib discontinuation

Hortobagyi GN, *et al. N Engl J Med* 2016;375:1738–1748.

MONARCH 2: Treatment-Emergent AEs

Treatment- Emergent AE Occurring in ≥ 20% in Either Arm, %	Abemaciclib + Fulvestrant (n = 441)		Placebo + Fulvestrant (n = 223)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any	98.6	60.5	89.2	22.8
Diarrhea*	86.4	13.4	24.7	0.4
Neutropenia	46.0	26.5	4.0	1.7
Nausea	45.1	2.7	22.9	0.9
Fatigue	39.9	2.7	26.9	0.4
Abdominal pain	35.4	2.5	15.7	0.9
Anemia	29.0	7.2	3.6	0.9
Leukopenia	28.3	8.8	1.8	0
Decreased appetite	26.5	1.1	12.1	0.4
Vomiting	25.9	0.9	10.3	1.8
Headache	20.2	0.7	15.2	0.4

*Incidence of diarrhea greatly reduced after starting abemaciclib dose amended from 200 mg to 150 mg.

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

Slide credit: clinicaloptions.com

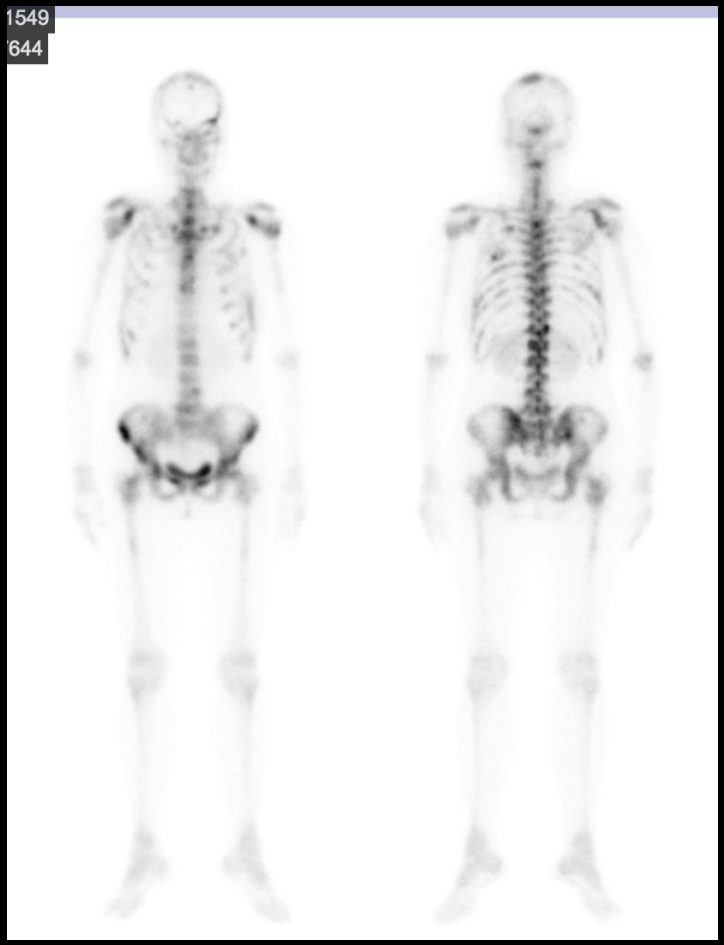
Case Sharing 03

53 y/o woman, G2P2, post-menopause,

Right breast cancer s/p MRM and reconstruction in Sydney in **2000 (36 y/o)** , without adjuvant Tamoxifen or chemotherapy

(2013/6~) Right shoulder pain and disability

(2014/1~) Left breast cancer with multiple bone mets



Increased uptake of radioactivity in the skull, cervical, thoracic and lumbar spines, pelvic bones, sternum, bilateral ribs, scapulae, humeri, femora, right forearm, likely representing bony metastasis.c

2014/2, left breast biopsy

TISSUE ORIGIN: Left breast.

PATHOLOGIC DIAGNOSIS:
Left breast, 3'/3cm, sonoguided core biopsy: INVASIVE CARCINOMA of nuclear grade 2.

GROSS:
The specimen consists of seven linear biopsy cores, measuring from 0.5 cm to 1.1 cm. They are totally submitted in one cassette.

MICROSCOPIC COMMENTS:
Sections show invasive irregular nests through fibrotic stroma, composed of neoplastic ovoid cells displaying mild to moderate degree of nuclear pleomorphism and hyperchromasia. Focal lobular differentiation with cords or indian-file pattern is noted.

IMMUNOHISTOCHEMICAL STUDY:
The section S14-00823 is stained by applying 4 antibodies against E-cadherin (NCH-38), Estrogen receptor (1D5), Progesterone receptor (1A6) and HER2 (polyclonal) respectively.

STAINING RESULT(S):
- E-cadherin: positive
- Estrogen receptor: positive, estimated proportion of tumor cells score 5, average intensity of positive tumor cells score 3, Allred score = 8
- Progesterone receptor: positive, estimated proportion of tumor cells score 5, average intensity of positive tumor cells score 3, Allred score = 8
- HER2: >10% weak and incomplete membranous staining, score: 1+ (no overexpression)

2014/3, bone marrow biopsy for macrocytic anemia

	2010/7/19	2011/8/8	2012/10/13	2013/10/31	2014/2/15	2014/3/4	2014/3/11
R.B.C	4.15	4.27	4.08	3.96	2.8	2.71	2.62
HGB	12.9	13.5	12.8	12.3	**9.6**	**9.3**	**9.1**
HCT	38.9	40.3	38.3	36.5	28.7	29.2	28.4
MCV	93.7	94.4	93.9	92.2	**102.5**	**107.7**	**108.4**
MCH	31.1	31.6	31.4	31.1	34.3	34.3	34.7
MCHC	33.2	33.5	33.4	33.7	33.4	31.8	32
RDW	13.1	13.1	13.1	15.1	23.5	20.7	19.8
PLT	264K	254K	268K	310K	217K	260K	290K
W.B.C	6000	6010	5750	9010	8420	7460	7100

TISSUE ORIGIN: Bone marrow.

PATHOLOGIC DIAGNOSIS:

Bone marrow, site unspecified, biopsy: METASTATIC CARCINOMA, compatible with breast origin.

STAINING RESULT(S):

- Estrogen receptor: positive, estimated proportion of tumor cells score 4, average intensity of positive tumor cells score 1, Allred score = 5
- Progesterone receptor: positive, estimated proportion of tumor cells score 4, average intensity of positive tumor cells score 1, Allred score = 5
- HER2: >10% weak and incomplete membranous staining, score: 1+ (no overexpression)
- GATA-3: positive

Case No.2

53 y/o woman, G2P2, post-menopause,

(2014/1~) Left breast cancer with multiple bone mets, extensive bone marrow involvement

(2014/4~ 2014/7) CAF x6

(2014/8/14~2015/8) Femara

(2015/8/13~2015/12) Taxotere/Xeloda

(2015/12~2016/9) Arimidex ~

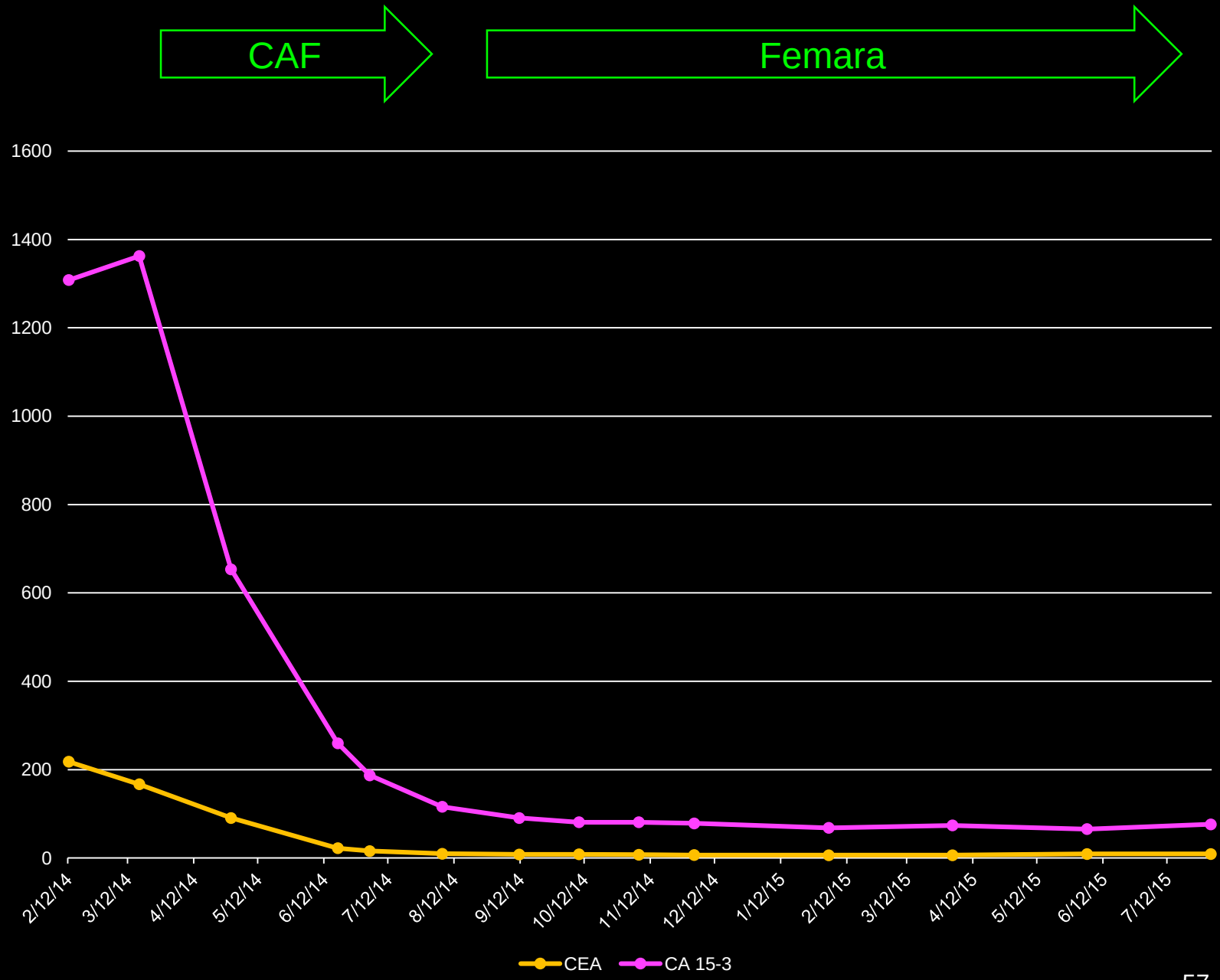
(2016/9/20~2016/12) Taxotere/Xeloda

(2016/12~2017/2) Aromasin/Afinitor (complicated with interstitial pneumonitis)

(2017/3/16~2017/8) Fulvestrant/femara

(2017/9~ 2017/12) Paclitaxel/Gemcitabine

(2017/12~2018/3) Femera


CAF
Femara
1600
1400
1200
1000
800
600
400
200
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2/12/14
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4/12/14
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6/12/14
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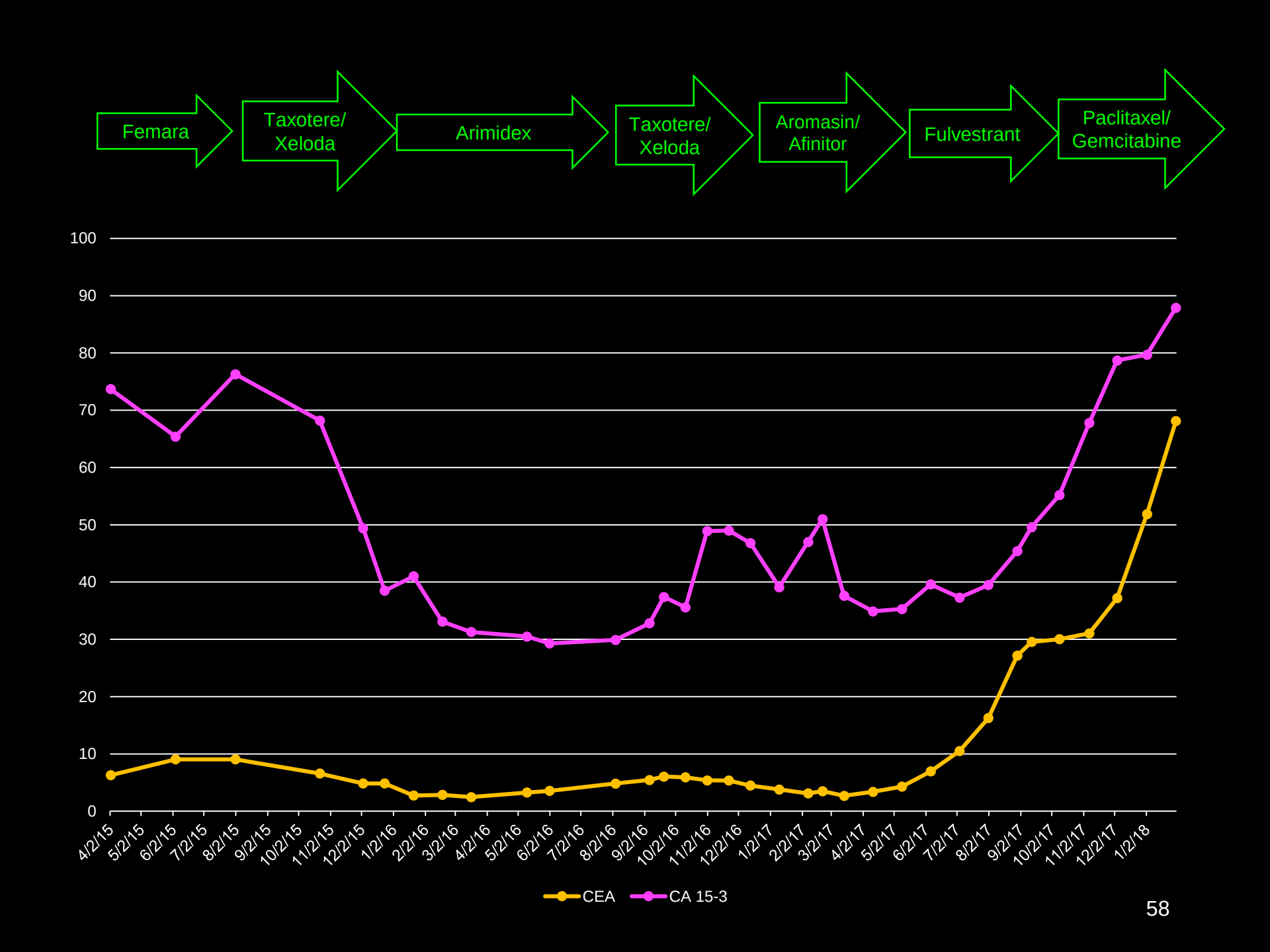
CEA
CA 15-3


Femara
Taxotere/ Xeloda
Arimidex
Taxotere/ Xeloda
Aromasin/ Afinitor
Fulvestrant
Paclitaxel/ Gemcitabine
100
90
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60
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8/2/17
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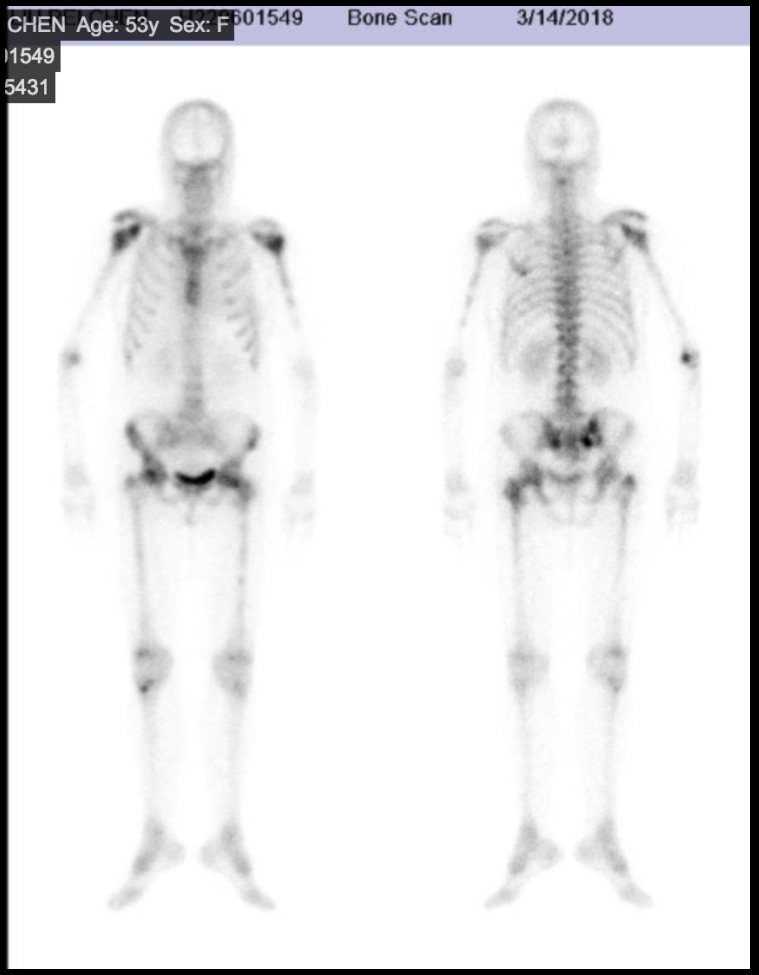
10/2/17
11/2/17
12/2/17
1/2/18
CEA
CA 15-3

2018/3

- Rising tumor markers
  - CA 153: 87.9
  - CEA: 68.1
- Restaging work-up
  - Bone metastasis only,
  - No evidence of visceral organ mets



Multiple active bony lesions, more prominent in the right humeral, bilateral femoral and tibial lesions

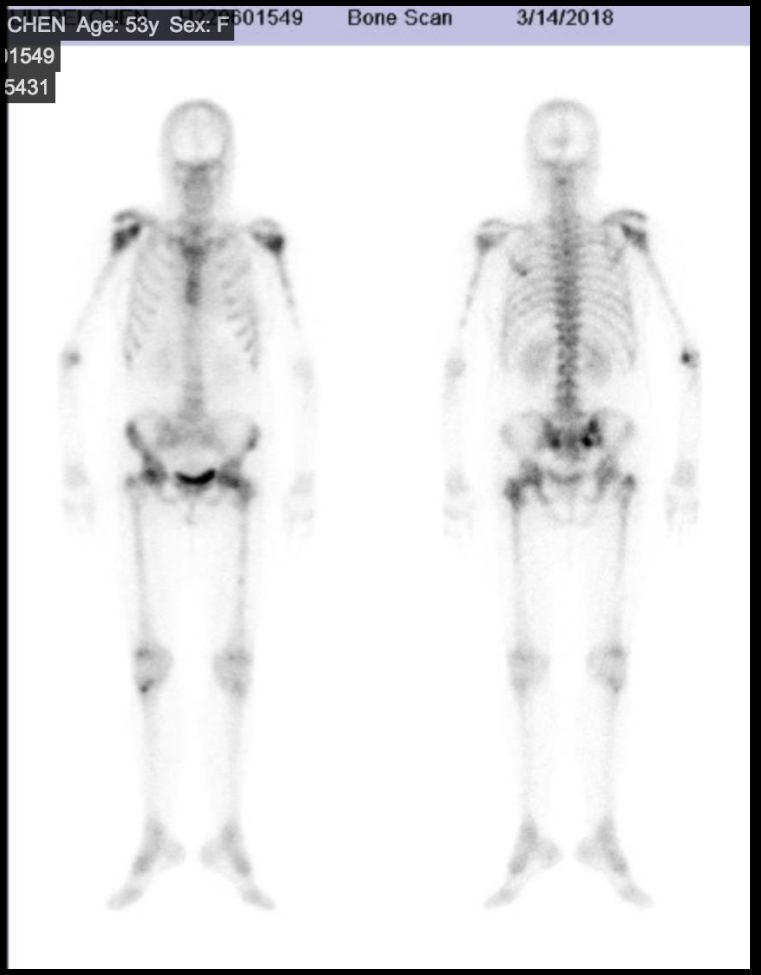
2018/3

- Rising tumor markers
  - CA 153: 87.9
  - CEA: 68.1

- Bone metastasis
- No evidence of visceral organ mets.

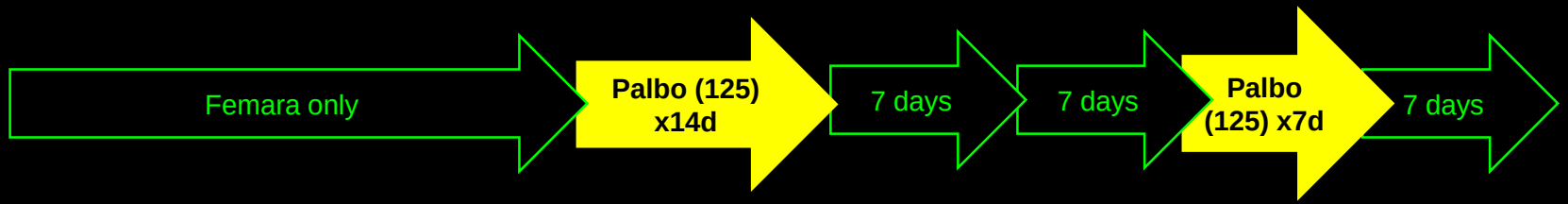
Treatment options

- CDK 4/6 inhibitors + AI
  - Palbociclib
  - Ribociclib
- Chemotherapy
  - Eribulin
  - Vinorelbine

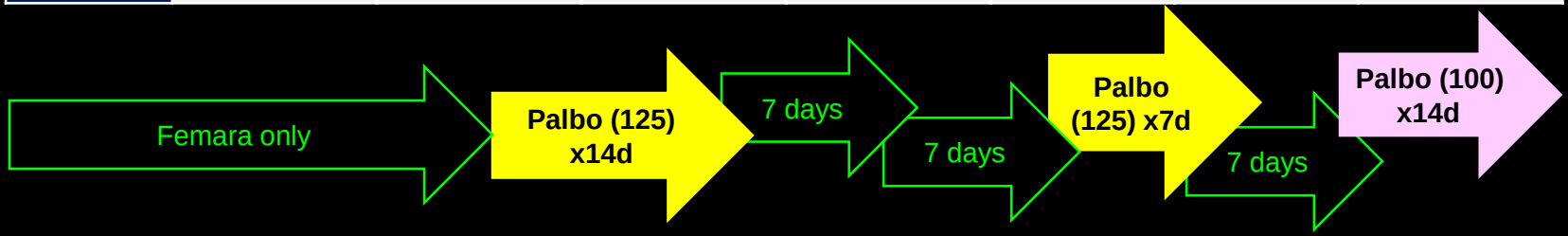


Multiple active bony lesions, more prominent in the right humeral, bilateral femoral and tibial lesions

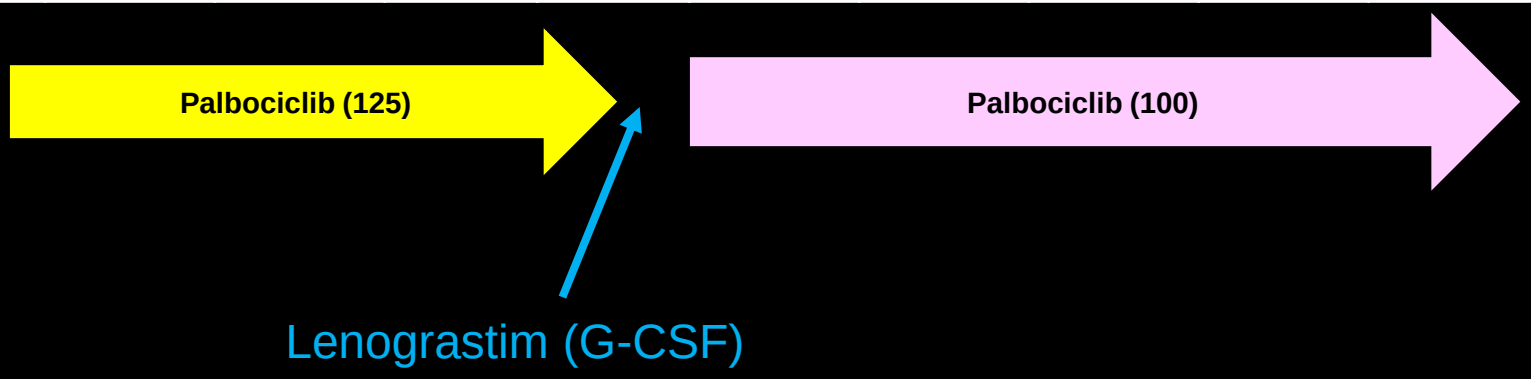
	2018/1/30	2018/3/6	2018/3/20	2018/3/27	2018/4/3	2018/4/17
HGB	11.5	11.8	11.5	11.1	11.1	11.3
PLT	198K	206K	184K	109K	209K	275K
W.B.C	**9650**	**7320**	**3090**	**3220**	**4240**	**3800**
SEG	**66.1**	**52.7**	**20**	**24.6**	**31**	**22**
LYMPH	27.4	39.2	54	65.5	40	44
ANC	**6379**	**3858**	**618**	**792**	**1314**	**836**
CEA	**68.1**	**89.3**		**98.2**		**132.6**
CA 15-3	**87.9**	**82.4**		**74.7**		**81.6**



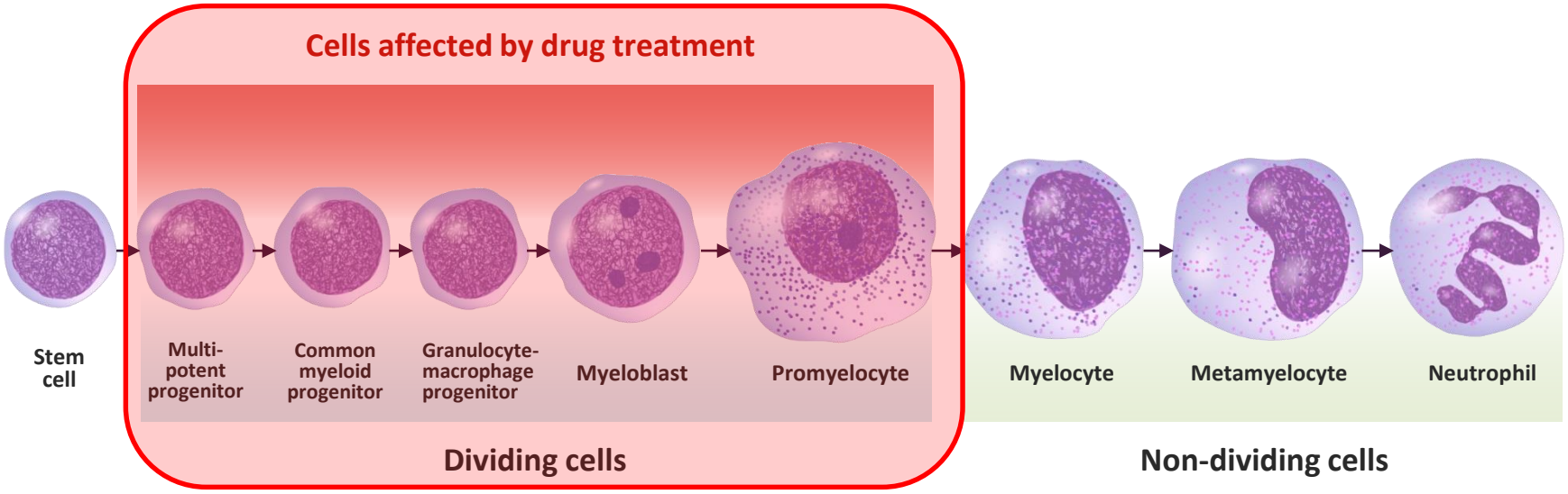
	2018/1/30	2018/3/6	2018/3/20	2018/3/27	2018/4/3	2018/4/17	2018/5/1
HGB	11.5	11.8	11.5	11.1	11.1	11.3	
PLT	198K	206K	184K	109K	209K	275K	
W.B.C	**9650**	**7320**	**3090**	**3220**	**4240**	**3800**	
SEG	**66.1**	**52.7**	**20**	**24.6**	**31**	**22**	
LYMPH	27.4	39.2	54	65.5	40	44	
ANC	**6379**	**3858**	**618**	**792**	**1314**	**836**	
CEA	**68.1**	**89.3**	**-**	**98.2**	**-**	**132.6**	**-**
CA 15-3	**87.9**	**82.4**	**-**	**74.7**	**-**	**81.6**	**-**



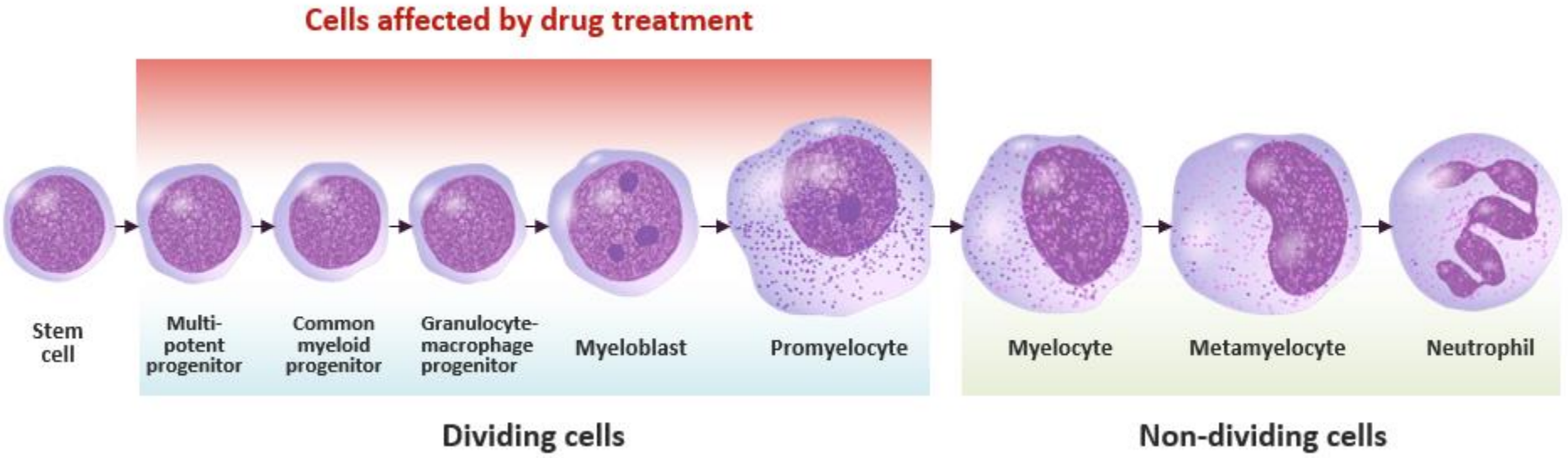
	2018/3/6	2018/3/20	2018/3/27	2018/4/3	2018/4/17	2018/5/15	2018/6/12	2018/7/10	2018/8/7	2018/9/3
HGB	11.8	11.5	11.1	11.1	11.3	10.8	10.8	10.9	9.8	9.4
PLT	206K	184K	109K	209K	275K	201K	158K	161K	136K	130K
W.B.C	**7320**	**3090**	**3220**	**4240**	**3800**	**4770**	**3310**	**2230**	**2220**	**2300**
SEG	52.7	20	24.6	31	22	38	21	28	32	23
LYMPH	39.2	54	65.5	40	44	50	28	37	34	43
ANC	**3858**	**618**	**792**	**1314**	**836**	**1812**	**695**	**847**	**710**	**529**



Normal Neutrophil Differentiation in the Bone Marrow Comprises Dividing and Quiescent Cells



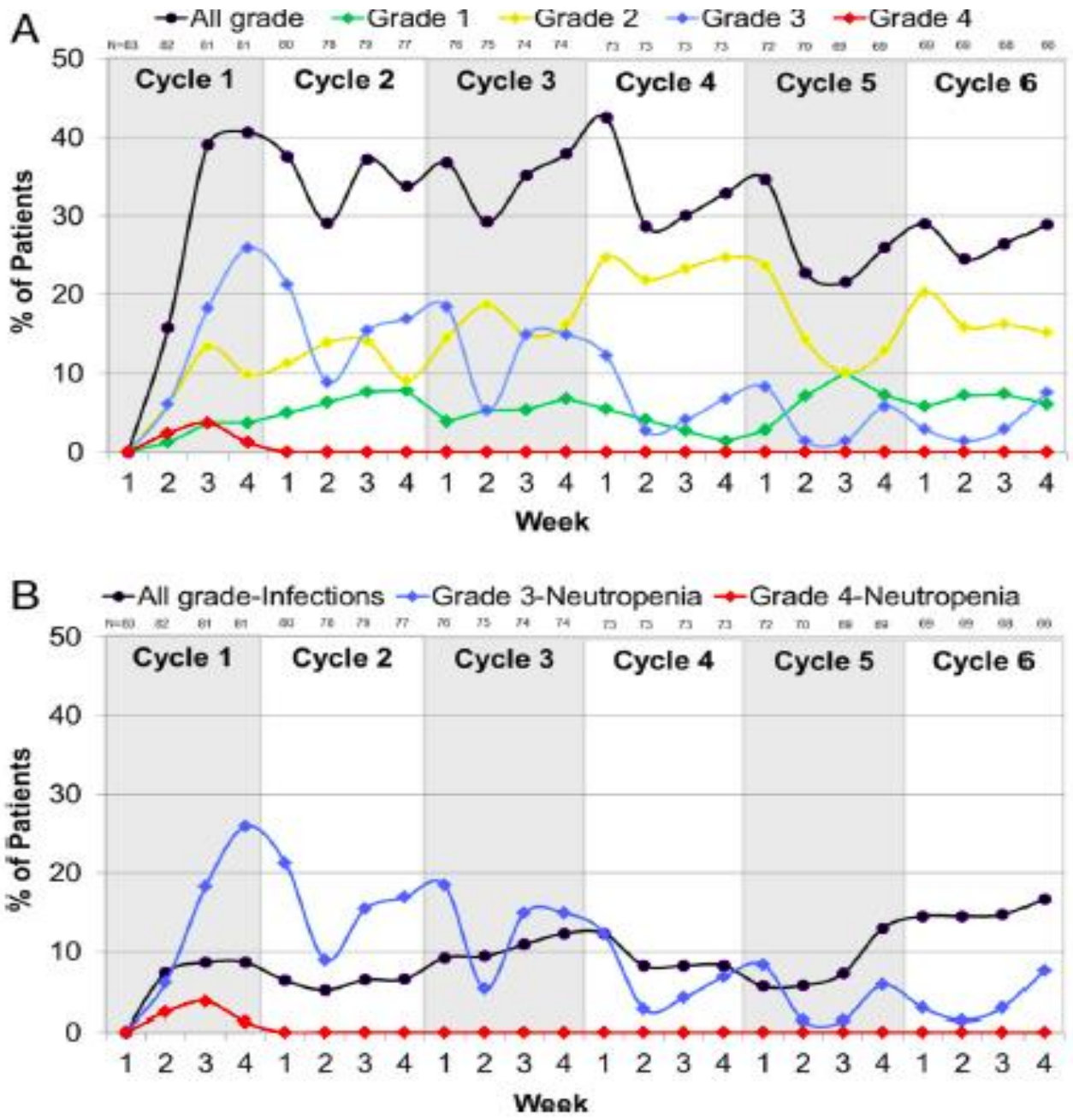
	Palbociclib-induced neutropenia[1,2]	Chemotherapy-induced neutropenia[2-4]
Mechanism	Cell cycle arrest but no death of proliferating neutrophil precursors	DNA damage and apoptosis of proliferating neutrophil precursors
Reversibility	Rapid recovery	Delayed recovery



- The least differentiated and most rapidly proliferating cells
- Most dependent on cyclin D–CDK4/6 activity

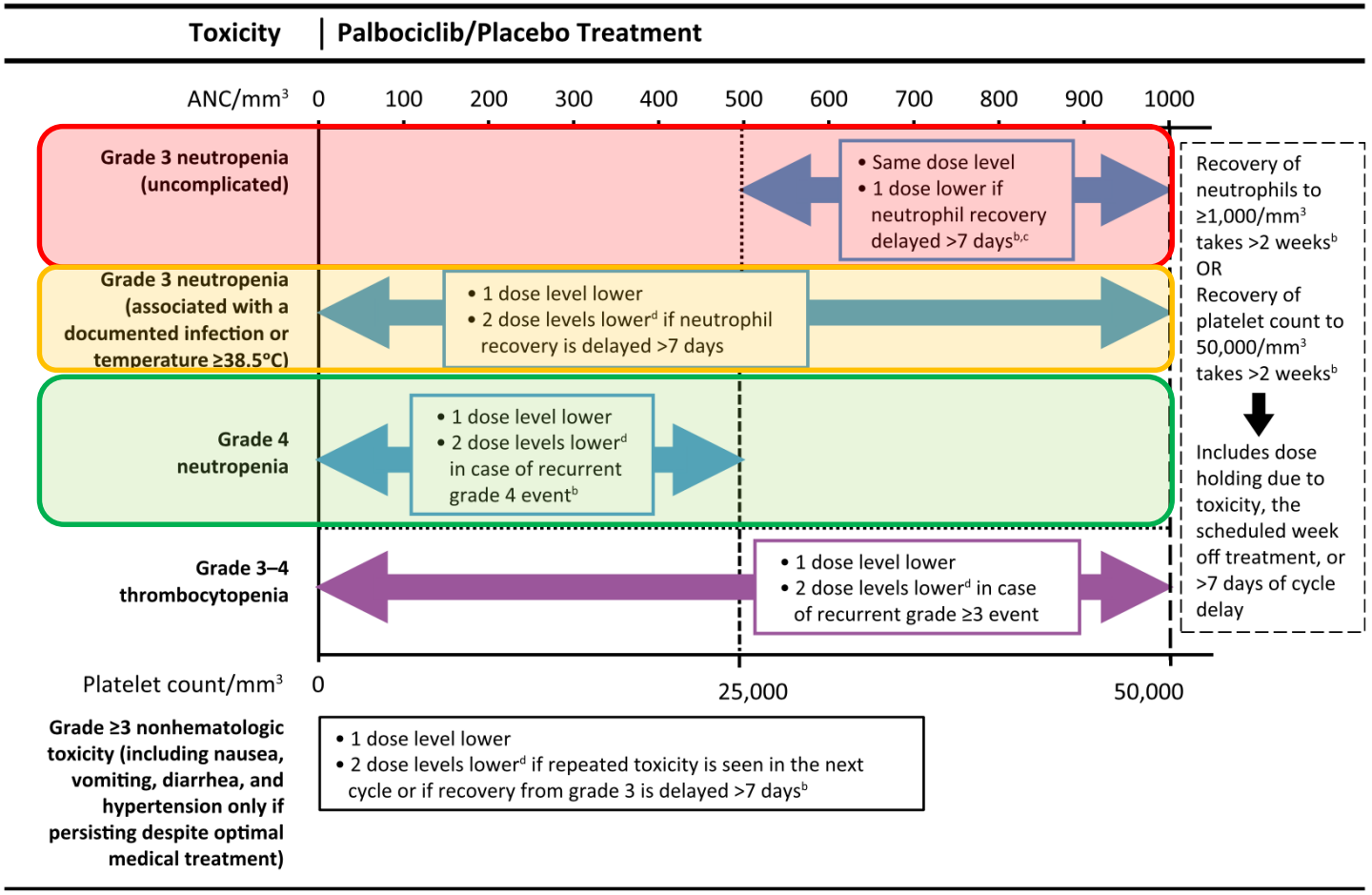
- Palbociclib has no effect on non-dividing mature neutrophils

Frequency of neutropenia in PALOMA 1



Finn RS. Breast Cancer Res. 2016 Jun 28;18(**1**):67

Palbociclib Dose Adjustment



Monitoring in the first 6 cycles

PALBOCICLIB

Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
Day 1	Day 14	Day 1	Day 14					
CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC
-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-
-	-	-	-	-	-	-	-	-

RIBOCICLIB

Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
Day 1	Day 14	Day 1	Day 14					
CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC	CBC
ECG	ECG	ECG	-	-	-	-	-	ECG
SE	-	SE	SE	SE	SE	SE	SE	SE
LFT	LFT	LFT	LFT	LFT	LFT	LFT	LFT	LFT

ABEMACICLIB

Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Clinically indicated
Day 1	Day 14	Day 1	Day 14					
CBC	CBC	CBC	CBC	CBC	CBC	-	-	CBC
LFT	LFT	LFT	LFT	LFT	LFT	-	-	LFT

- Additional warning and precaution to be taken with respect to diarrhoea management on first sign of loose stools with antidiarrhoeal treatment, and
- Monitoring for signs and symptoms of thrombosis and pulmonary embolism
- Monitoring for serum creatinine levels

Summary

- **CDK 4/6 inhibitors for hormone positive metastatic breast cancer**
  - Provide better response, PFS
  - Well manageable AEs
  - Improve QoL (as compared with chemotherapy)

Thank you