Metastasi ossee e tumore della mammella: l'importanza delle Cicline e impatto sull'osso e sul dolore

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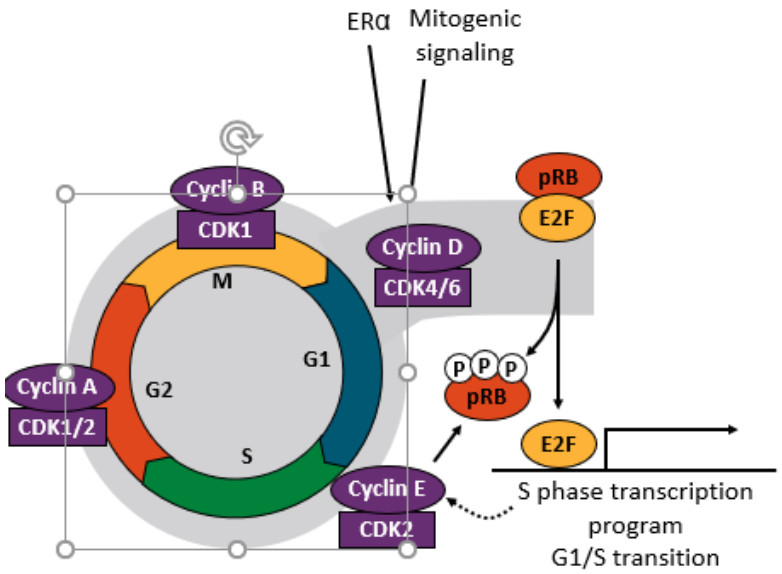
CDK4/6 INHIBITORS…what they are supposed to do ?

Pavia's battle (1525),

Ci-git Monsieur de La Palice. Si il n'était pas mort, il serait encore en vie"
(Qui giace il signore di La Palice. Se non fosse morto, sarebbe ancora in vita)

THE ROLE OF CDK4/6 IN BREAST CANCER



- Cyclin D–CDK4/6 complexes promote cell proliferation through Rb protein phosphorylation.
- Increased CDK4/6 activity is frequently observed in HR+ breast cancer.
- Activation of the cyclin D–CDK4/6–INK4–Rb pathway has been associated with poor response and resistance to endocrine therapy.

The cyclin-dependent kinase (CDK) 4/6 inhibitors drugs that interrupt proliferation of malignant cells by inhibiting progression through the cell cycle.

Asghar. Nat Rev Drug Discov. 2015;14:130. 2. Miller. Cancer Discov. 2011;1:338. 3. Thangavel. Endoc Relat Cancer. 2011;18:333.

CDK4/6 Inhibitors: FDA-Approved Indications in HR+/HER2- MBC

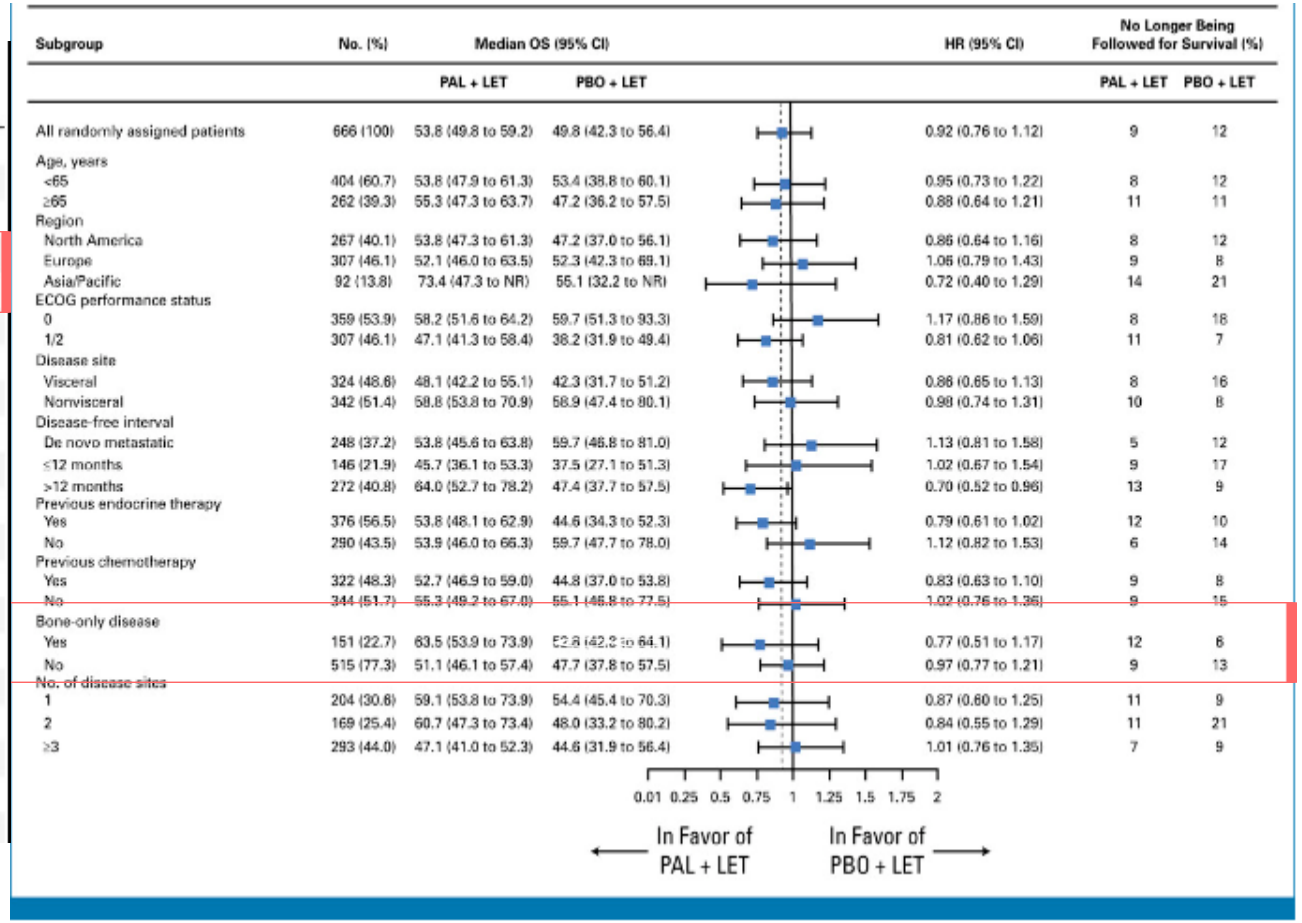
Select Clinical Trials of CDK4/6 Inhibitors for HR+, HER2– ABC[1]		
Ribociclib	**Palbociclib**	**Abemaciclib**
MONALEESA-2 (First-line RIBO + LET in postmenopausal women)	**PALOMA-2** (First-line PAL + LET in postmenopausal women)	**MONARCH-3** (First-line ABE + NSAI in postmenopausal women)
MONALEESA-7 (First-line RIBO + ET + OFS in premenopausal women)	**PALOMA-1** (Phase 2 study of first-line PAL + LET in postmenopausal women)	**MONARCH-2** (ABE + FUL in patients with ≤1 line of ET for ABC)
CompLEEment-1 (First-line RIBO + LET in an expanded patient population)	**PALOMA-3** (PAL + FUL with ≤1 line of ET for ABC)	**MONARCH-1** (Phase 2 study of ABE monotherapy in heavily pretreated patients)
MONALEESA-3 (RIBO + FUL in patients with ≤1 line of ET for ABC)		

CDK4/6i and bone … what we know ?

PALBOCLIB IN BONE ONLY DISEASE
PALOMA 2

b

Baseline Factors	PAL + LET Patients, n (%)	PBO + LET Patients, n (%)	PAL + LET mPFS (95% CI)	PBO + LET mPFS (95% CI)	PAL + LET vs PBO + LET HR (95% CI)	P[a]
All randomized patients, IA	444 (100)	222 (100)	27.6 (22.4–30.3)	14.5 (12.3–17.1)	0.56 (0.46–0.69)	<0.0001
All randomized patients, BICR	444 (100)	222 (100)	35.7 (27.7–38.9)	19.5 (16.6–26.6)	0.61 (0.49–0.77)	<0.0001
Visceral disease	214 (48.2)	110 (49.5)	19.3 (16.4–24.2)	12.3 (8.4–16.4)	0.62 (0.47–0.81)	<0.0005
Nonvisceral disease	230 (51.8)	112 (50.5)	35.9 (27.7–NE)	17.0 (13.8–24.8)	0.50 (0.37–0.67)	<0.0001
Bone-only disease	103 (23.2)	48 (21.6)	36.2 (27.6–NE)	11.2 (8.2–22.0)	0.41 (0.26–0.63)	<0.0001
No bone-only disease[b]	341 (76.8)	174 (78.4)	24.2 (19.4–27.7)	14.5 (12.9–18.5)	0.62 (0.50–0.78)	<0.0001
TFI[c] >12 mo	179 (40.3)	93 (41.9)	30.3 (24.8–NE)	13.8 (8.8–18.2)	0.55 (0.40–0.76)	<0.0005
TFI[c] ≤12 mo	98 (22.1)	48 (21.6)	16.6 (13.9–24.2)	11.0 (5.6–12.9)	0.48 (0.32–0.72)	<0.0005
TFI[c] >2 y	154 (34.7)	77 (34.7)	38.5 (27.5–NE)	16.6 (13.7–23.5)	0.52 (0.36–0.75)	<0.0005
TFI[c] >5 y	90 (20.3)	46 (20.7)	38.6 (27.6–NE)	23.5 (16.3–32.2)	0.60 (0.36–1.00)	<0.05
TFI[c] >10 y	32 (7.2)	23 (10.4)	NR (30.4–NE)	23.5 (16.6–NE)	0.44 (0.19–1.03)	<0.05
De novo metastatic	167 (37.6)	81 (36.5)	27.9 (22.1–33.4)	22.0 (13.9–27.4)	0.61 (0.44–0.85)	<0.005
TFI from prior ET >12 mo	156 (35.1)	78 (35.1)	27.6 (22.2–38.6)	13.8 (8.2–16.6)	0.58 (0.41–0.82)	<0.001
TFI from prior ET ≤12 mo	94 (21.2)	48 (21.6)	16.6 (13.9–24.2)	11.0 (5.6–12.9)	0.49 (0.33–0.73)	<0.0005
Measurable disease	338 (76.1)	171 (77.0)	23.7 (19.3–27.6)	14.5 (12.3–18.5)	0.63 (0.50–0.79)	<0.0001
Nonmeasurable disease[d]	106 (23.9)	51 (23.0)	36.2 (27.6–NE)	16.5 (8.3–19.6)	0.39 (0.25–0.60)	<0.0001
No prior ET with visceral disease	86 (19.4)	47 (21.2)	23.7 (16.8–30.3)	13.9 (10.2–22.2)	0.55 (0.36–0.85)	<0.005
No prior ET without visceral disease	108 (24.3)	49 (22.1)	36.2 (27.9–NE)	27.6 (19.1–35.6)	0.59 (0.38–0.92)	<0.01
Prior ET	250 (56.3)	126 (56.8)	24.2 (18.8–27.6)	11.2 (8.4–14.5)	0.54 (0.42–0.71)	<0.0001
No prior ET	194 (43.7)	96 (43.2)	30.3 (24.5–35.7)	21.9 (15.9–27.4)	0.59 (0.43–0.80)	<0.0005



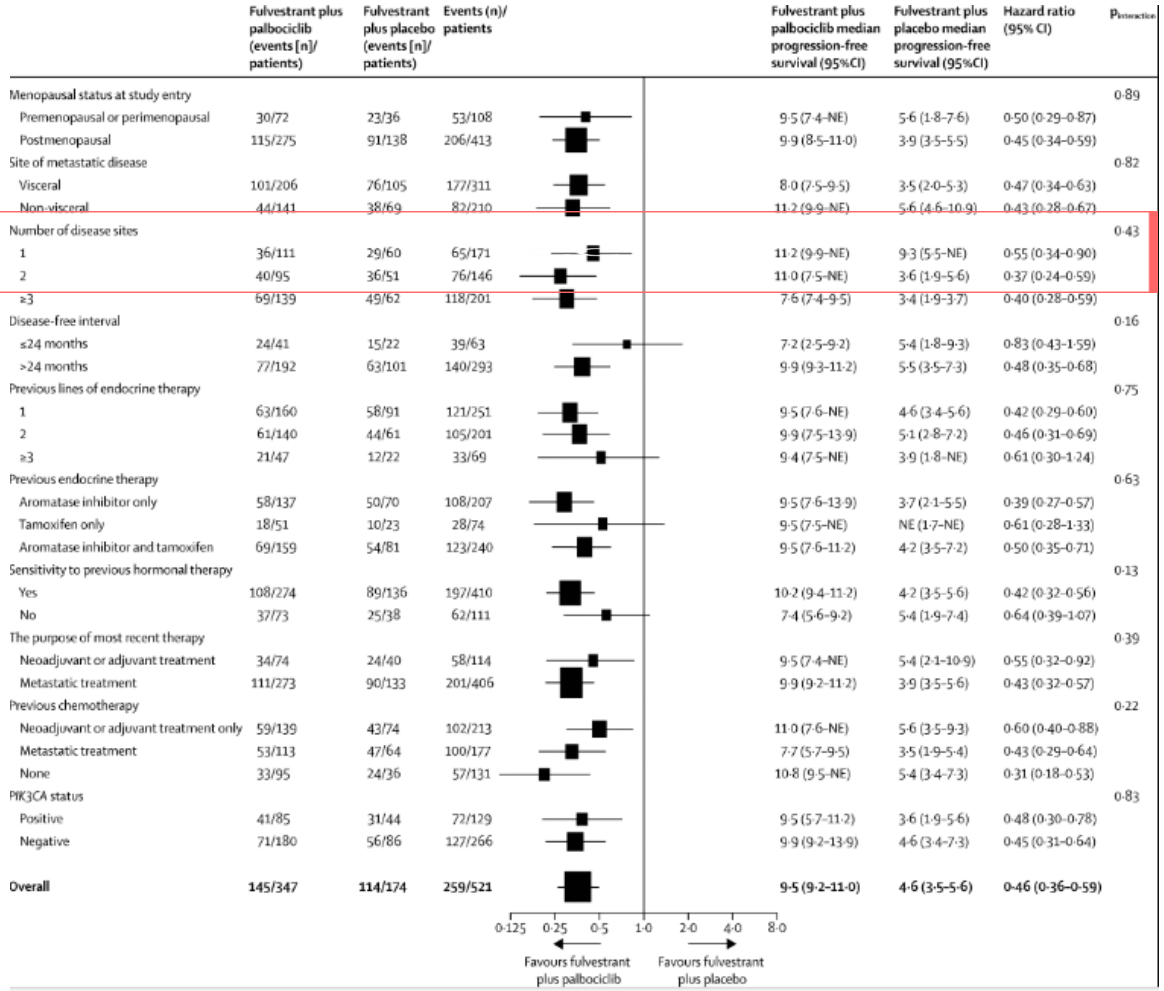
Paloma2: Palbociclib+ letrozolo vs placebo+letrozolo mPFS 36.2mo, HR 0.41 (0.26 - 0.63)

Paloma2: Bone Only Disease mOS 63.5 mo, HR 0,77 (0,51-1,17)

Rugo HS, Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with follow-up. Breast Cancer Res doi: 10.1007/s10549-018-05125-4.

Dennis J. Slamon et al., Overall Survival With Palbociclib Plus Letrozole in Advanced Breast Cancer. JCO 42, 994-1000(2024). DOI:10.1200/JCO.23.00137

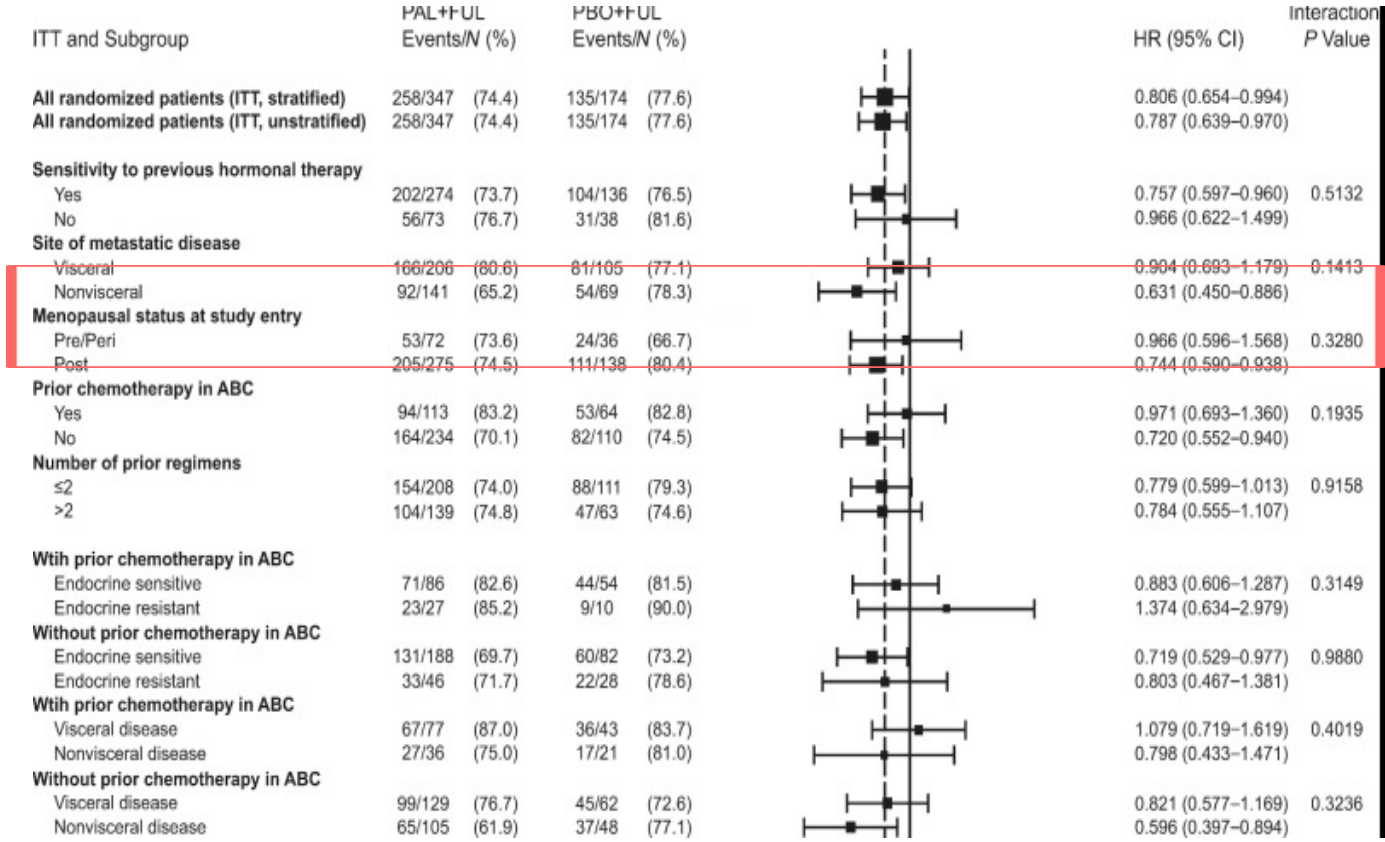
PALBOCLIB IN BONE ONLY DISEASE
PALOMA 3



	Fulvestrant plus palbociclib (events [n]/ patients)	Fulvestrant plus placebo (events [n]/ patients)	Events (n)/ patients	Fulvestrant plus palbociclib median progression-free survival (95%CI)	Fulvestrant plus placebo median progression-free survival (95%CI)	Hazard ratio (95% CI)	$p_{interaction}$
Menopausal status at study entry							0·89
Premenopausal or perimenopausal	30/72	23/36	53/108	9·5 (7·4–NE)	5·6 (1·8–7·6)	0·50 (0·29–0·87)	
Postmenopausal	115/275	91/138	206/413	9·9 (8·5–11·0)	3·9 (3·5–5·5)	0·45 (0·34–0·59)	
Site of metastatic disease							0·82
Visceral	101/206	76/105	177/311	8·0 (7·5–9·5)	3·5 (2·0–5·3)	0·47 (0·34–0·63)	
Non-visceral	44/141	38/69	82/210	11·2 (9·9–NE)	5·6 (4·6–10·9)	0·43 (0·28–0·67)	
Number of disease sites							0·43
1	36/111	29/60	65/171	11·2 (9·9–NE)	9·3 (5·5–NE)	0·55 (0·34–0·90)	
2	40/95	36/51	76/146	11·0 (7·5–NE)	3·6 (1·9–5·6)	0·37 (0·24–0·59)	
≥3	69/139	49/62	118/201	7·6 (7·4–9·5)	3·4 (1·9–3·7)	0·40 (0·28–0·59)	
Disease-free interval							0·16
≤24 months	24/41	15/22	39/63	7·2 (2·5–9·2)	5·4 (1·8–9·3)	0·83 (0·43–1·59)	
>24 months	77/192	63/101	140/293	9·9 (9·3–11·2)	5·5 (3·5–7·3)	0·48 (0·35–0·68)	
Previous lines of endocrine therapy							0·75
1	63/160	58/91	121/251	9·5 (7·6–NE)	4·6 (3·4–5·6)	0·42 (0·29–0·60)	
2	61/140	44/61	105/201	9·9 (7·5–13·9)	5·1 (2·8–7·2)	0·46 (0·31–0·69)	
≥3	21/47	12/22	33/69	9·4 (7·5–NE)	3·9 (1·8–NE)	0·61 (0·30–1·24)	
Previous endocrine therapy							0·63
Aromatase inhibitor only	58/137	50/70	108/207	9·5 (7·6–13·9)	3·7 (2·1–5·5)	0·39 (0·27–0·57)	
Tamoxifen only	18/51	10/23	28/74	9·5 (7·5–NE)	NE (1·7–NE)	0·61 (0·28–1·33)	
Aromatase inhibitor and tamoxifen	69/159	54/81	123/240	9·5 (7·6–11·2)	4·2 (3·5–7·2)	0·50 (0·35–0·71)	
Sensitivity to previous hormonal therapy							0·13
Yes	108/274	89/136	197/410	10·2 (9·4–11·2)	4·2 (3·5–5·6)	0·42 (0·32–0·56)	
No	37/73	25/38	62/111	7·4 (5·6–9·2)	5·4 (1·9–7·4)	0·64 (0·39–1·07)	
The purpose of most recent therapy							0·39
Neoadjuvant or adjuvant treatment	34/74	24/40	58/114	9·5 (7·4–NE)	5·4 (2·1–10·9)	0·55 (0·32–0·92)	
Metastatic treatment	111/273	90/133	201/406	9·9 (9·2–11·2)	3·9 (3·5–5·6)	0·43 (0·32–0·57)	
Previous chemotherapy							0·22
Neoadjuvant or adjuvant treatment only	59/139	43/74	102/213	11·0 (7·6–NE)	5·6 (3·5–9·3)	0·60 (0·40–0·88)	
Metastatic treatment	53/113	47/64	100/177	7·7 (5·7–9·5)	3·5 (1·9–5·4)	0·43 (0·29–0·64)	
None	33/95	24/36	57/131	10·8 (9·5–NE)	5·4 (3·4–7·3)	0·31 (0·18–0·53)	
PIK3CA status							0·83
Positive	41/85	31/44	72/129	9·5 (5·7–11·2)	3·6 (1·9–5·6)	0·48 (0·30–0·78)	
Negative	71/180	56/86	127/266	9·9 (9·2–13·9)	4·6 (3·4–7·3)	0·45 (0·31–0·64)	
Overall	**145/347**	**114/174**	**259/521**	**9·5 (9·2–11·0)**	**4·6 (3·5–5·6)**	**0·46 (0·36–0·59)**	

0·125 0·25 0·5 1·0 2·0 4·0 8·0

Favours fulvestrant plus palbociclib — Favours fulvestrant plus placebo



ITT and Subgroup	PAL+FUL Events/N (%)	PBO+FUL Events/N (%)	HR (95% CI)	Interaction P Value
All randomized patients (ITT, stratified)	258/347 (74.4)	135/174 (77.6)	0.806 (0.654–0.994)	
All randomized patients (ITT, unstratified)	258/347 (74.4)	135/174 (77.6)	0.787 (0.639–0.970)	
Sensitivity to previous hormonal therapy				
Yes	202/274 (73.7)	104/136 (76.5)	0.757 (0.597–0.960)	0.5132
No	56/73 (76.7)	31/38 (81.6)	0.966 (0.622–1.499)	
Site of metastatic disease				
Visceral	166/206 (80.6)	81/105 (77.1)	0.904 (0.693–1.179)	0.1413
Nonvisceral	92/141 (65.2)	54/69 (78.3)	0.631 (0.450–0.886)	
Menopausal status at study entry				
Pre/Peri	53/72 (73.6)	24/36 (66.7)	0.966 (0.596–1.568)	0.3280
Post	205/275 (74.5)	111/138 (80.4)	0.744 (0.590–0.938)	
Prior chemotherapy in ABC				
Yes	94/113 (83.2)	53/64 (82.8)	0.971 (0.693–1.360)	0.1935
No	164/234 (70.1)	82/110 (74.5)	0.720 (0.552–0.940)	
Number of prior regimens				
≤2	154/208 (74.0)	88/111 (79.3)	0.779 (0.599–1.013)	0.9158
>2	104/139 (74.8)	47/63 (74.6)	0.784 (0.555–1.107)	
Wtih prior chemotherapy in ABC				
Endocrine sensitive	71/86 (82.6)	44/54 (81.5)	0.883 (0.606–1.287)	0.3149
Endocrine resistant	23/27 (85.2)	9/10 (90.0)	1.374 (0.634–2.979)	
Without prior chemotherapy in ABC				
Endocrine sensitive	131/188 (69.7)	60/82 (73.2)	0.719 (0.529–0.977)	0.9880
Endocrine resistant	33/46 (71.7)	22/28 (78.6)	0.803 (0.467–1.381)	
Wtih prior chemotherapy in ABC				
Visceral disease	67/77 (87.0)	36/43 (83.7)	1.079 (0.719–1.619)	0.4019
Nonvisceral disease	27/36 (75.0)	17/21 (81.0)	0.798 (0.433–1.471)	
Without prior chemotherapy in ABC				
Visceral disease	99/129 (76.7)	45/62 (72.6)	0.821 (0.577–1.169)	0.3236
Nonvisceral disease	65/105 (61.9)	37/48 (77.1)	0.596 (0.397–0.894)	

Paloma3: mPFS 11.2 mo, HR 0.43 (0.28 - 0.67)

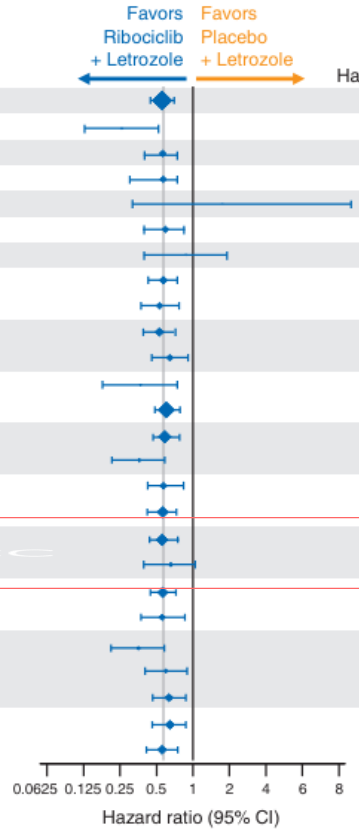
Cristofanilli M et al, Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial, The Lancet Oncology 2016

Paloma3: Non visceral disease mOS , HR 0.63 (0.45 - 0.88)

Cristofanilli M et al, Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer Res. 2022

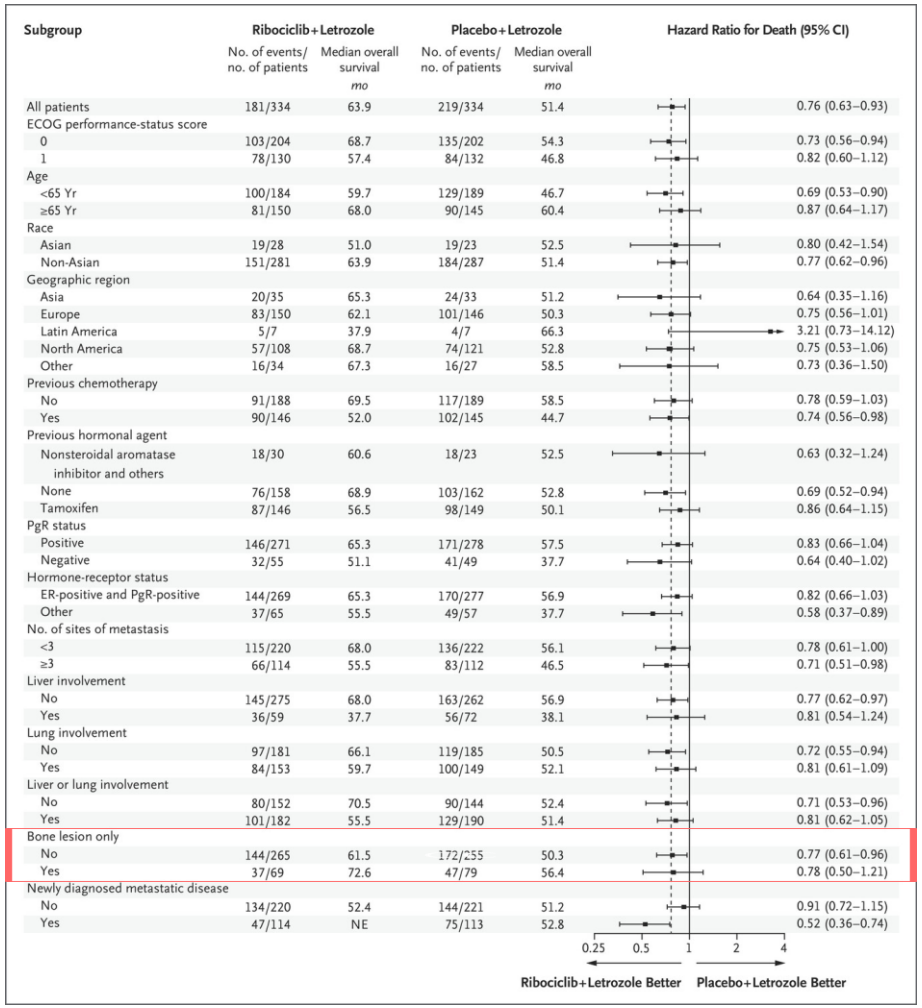
RIBOCICLIB IN BONE ONLY DISEASE
MONALEESA2

Subgroup		Events n/N: Ribociclib + Letrozole	Events n/N: Placebo + Letrozole	Hazard ratio	95% CI
All patients		140/334	205/334	0.568	0.457–0.704
Asia		13/35	27/33	0.265	0.135–0.520
EU		64/150	93/146	0.562	0.407–0.775
US		38/100	63/113	0.527	0.351–0.793
Latin America		4/7	3/7	1.800	0.381–8.504
North America		44/108	67/121	0.608	0.414–0.892
Other regions		15/34	15/27	0.900	0.423–1.915
ECOG PS	0	82/205	123/202	0.581	0.439–0.769
	1	58/129	82/132	0.543	0.385–0.766
Age	<65 years	82/184	127/189	0.518	0.392–0.684
	≥65 years	58/150	78/145	0.658	0.466–0.928
Race	Asian	14/28	19/23	0.370	0.180–0.760
	Non-Asian	121/281	171/287	0.614	0.486–0.775
HR status	ER+ and PgR+	109/269	162/277	0.606	0.475–0.774
	Other	31/65	43/57	0.358	0.217–0.591
Liver or lung metastases	No	59/152	80/143	0.597	0.426–0.837
	Yes	81/182	125/191	0.561	0.424–0.743
Bone-only disease	No	114/265	159/256	0.551	0.432–0.702
	Yes	26/69	46/78	0.642	0.393–1.048
De novo disease	No	97/220	144/221	0.579	0.447–0.749
	Yes	43/114	61/113	0.569	0.384–0.843
Previous endocrine therapy	AI	30/71	48/67	0.375	0.235–0.599
	TAM	47/104	71/105	0.617	0.426–0.894
	None	62/158	86/162	0.651	0.468–0.904
Previous chemotherapy	No	69/188	102/189	0.640	0.470–0.871
	Yes	71/146	103/145	0.501	0.368–0.681



Monaleesa2: Ribociclib + letrozolo vs placebo+letrozolo mPFS HR 0,642 (0,4-1,05)

Rugo, H. S. *et al.*. *Breast Cancer Res. Treat.* **174**, 719–729 (2019)

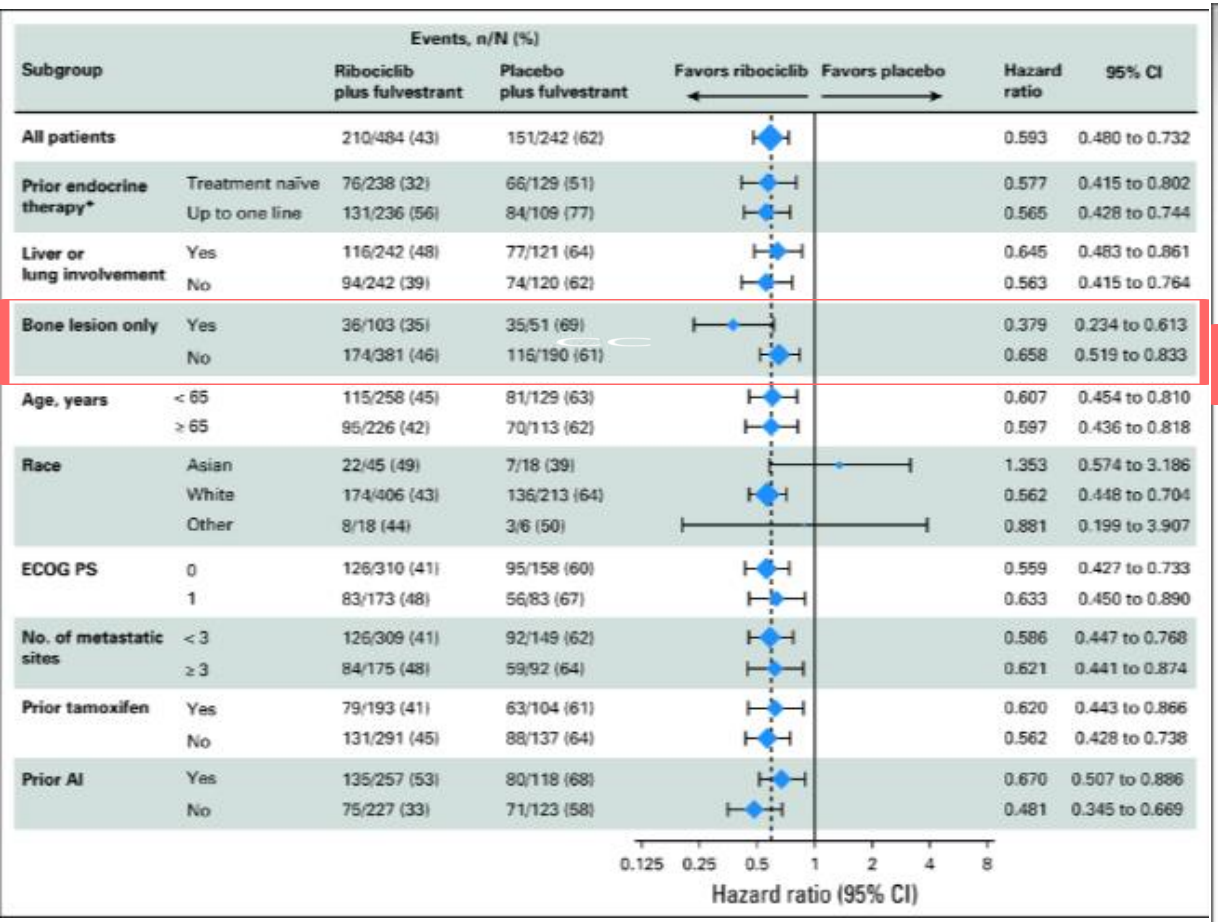


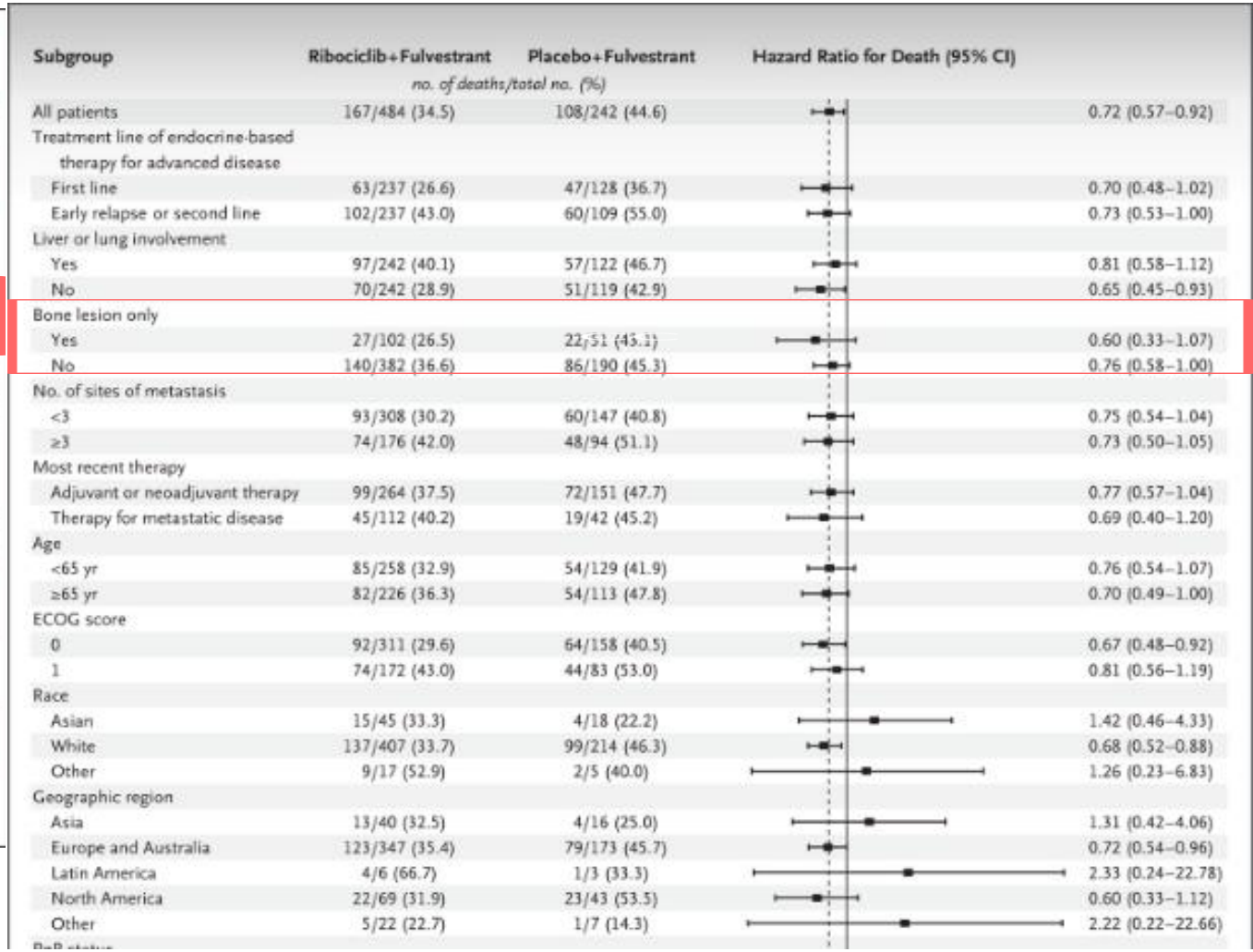
Subgroup	Ribociclib+Letrozole: No. of events/ no. of patients	Ribociclib+Letrozole: Median overall survival (mo)	Placebo+Letrozole: No. of events/ no. of patients	Placebo+Letrozole: Median overall survival (mo)	Hazard Ratio for Death (95% CI)
All patients	181/334	63.9	219/334	51.4	0.76 (0.63–0.93)
ECOG performance-status score					
0	103/204	68.7	135/202	54.3	0.73 (0.56–0.94)
1	78/130	57.4	84/132	46.8	0.82 (0.60–1.12)
Age					
<65 Yr	100/184	59.7	129/189	46.7	0.69 (0.53–0.90)
≥65 Yr	81/150	68.0	90/145	60.4	0.87 (0.64–1.17)
Race					
Asian	19/28	51.0	19/23	52.5	0.80 (0.42–1.54)
Non-Asian	151/281	63.9	184/287	51.4	0.77 (0.62–0.96)
Geographic region					
Asia	20/35	65.3	24/33	51.2	0.64 (0.35–1.16)
Europe	83/150	62.1	101/146	50.3	0.75 (0.56–1.01)
Latin America	5/7	37.9	4/7	66.3	3.21 (0.73–14.12)
North America	57/108	68.7	74/121	52.8	0.75 (0.53–1.06)
Other	16/34	67.3	16/27	58.5	0.73 (0.36–1.50)
Previous chemotherapy					
No	91/188	69.5	117/189	58.5	0.78 (0.59–1.03)
Yes	90/146	52.0	102/145	44.7	0.74 (0.56–0.98)
Previous hormonal agent					
Nonsteroidal aromatase inhibitor and others	18/30	60.6	18/23	52.5	0.63 (0.32–1.24)
None	76/158	68.9	103/162	52.8	0.69 (0.52–0.94)
Tamoxifen	87/146	56.5	98/149	50.1	0.86 (0.64–1.15)
PgR status					
Positive	146/271	65.3	171/278	57.5	0.83 (0.66–1.04)
Negative	32/55	51.1	41/49	37.7	0.64 (0.40–1.02)
Hormone-receptor status					
ER-positive and PgR-positive	144/269	65.3	170/277	56.9	0.82 (0.66–1.03)
Other	37/65	55.5	49/57	37.7	0.58 (0.37–0.89)
No. of sites of metastasis					
<3	115/220	68.0	136/222	56.1	0.78 (0.61–1.00)
≥3	66/114	55.5	83/112	46.5	0.71 (0.51–0.98)
Liver involvement					
No	145/275	68.0	163/262	56.9	0.77 (0.62–0.97)
Yes	36/59	37.7	56/72	38.1	0.81 (0.54–1.24)
Lung involvement					
No	97/181	66.1	119/185	50.5	0.72 (0.55–0.94)
Yes	84/153	59.7	100/149	52.1	0.81 (0.61–1.09)
Liver or lung involvement					
No	80/152	70.5	90/144	52.4	0.71 (0.53–0.96)
Yes	101/182	55.5	129/190	51.4	0.81 (0.62–1.05)
Bone lesion only					
No	144/265	61.5	172/255	50.3	0.77 (0.61–0.96)
Yes	37/69	72.6	47/79	56.4	0.78 (0.50–1.21)
Newly diagnosed metastatic disease					
No	134/220	52.4	144/221	51.2	0.91 (0.72–1.15)
Yes	47/114	NE	75/113	52.8	0.52 (0.36–0.74)

Monaleesa2: Bone only disease Ribociclib + letrozolo vs placebo+letrozolo mOS HR 0,78 (0,5-1,2)

(Gabriel N. Hortobagyi, 2022)

RIBOCICLIB IN BONE ONLY DISEASE
MONALEESA 3





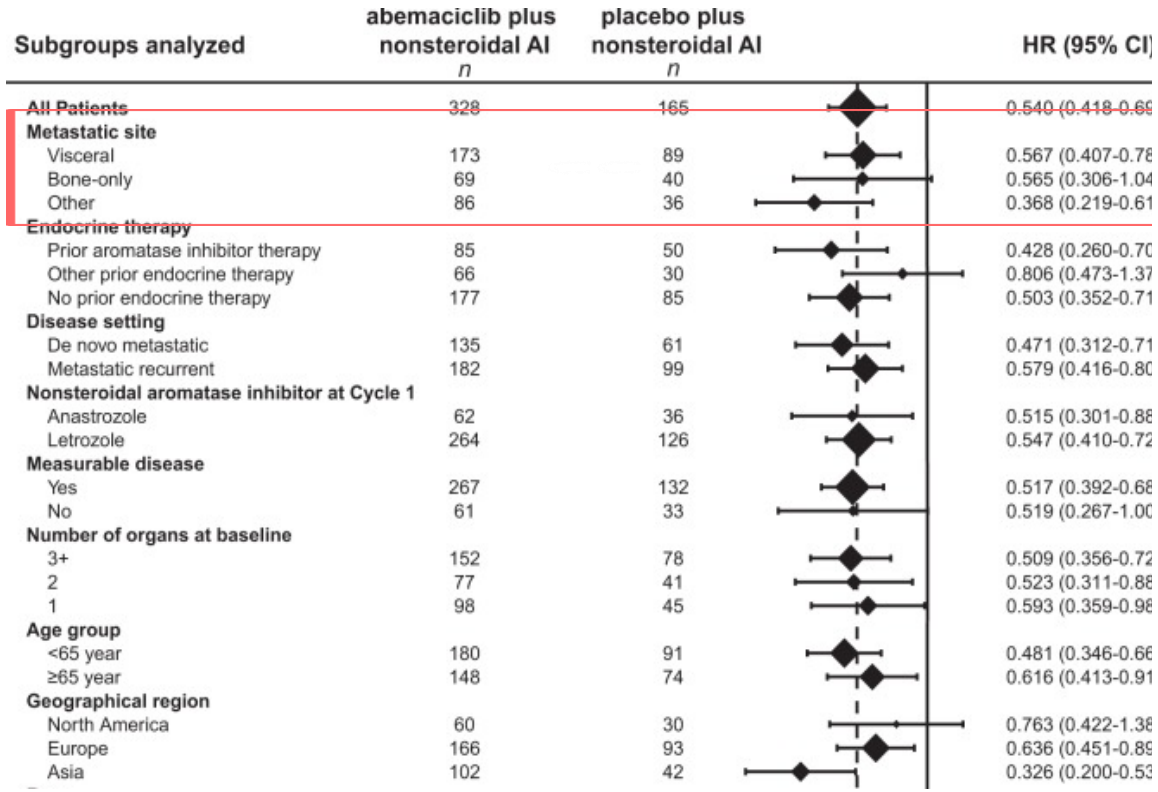
Monaleesa2: mPFS HR 0.37 (0.23 - 0.61)

Monaleesa3 : OS, HR 0.60 (0.33-1.07)

Slamon DJ, Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. J Clin Oncol. 2018 Aug 20;36(24):2465-2472. doi: 10.1200/JCO.2018.78.9909.

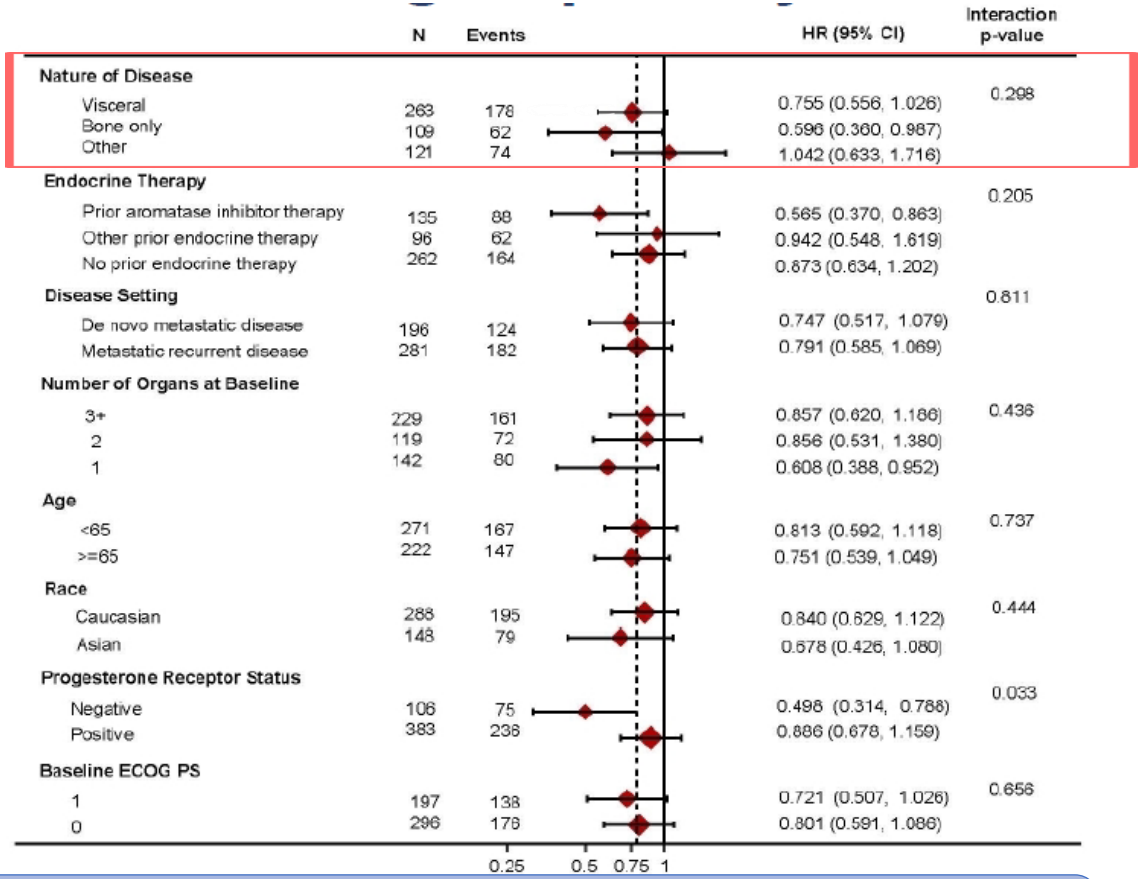
Dennis J. Slamon, Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer, New England Journal of Medicine, 2020. https://www.nejm.org/doi/full/10.1056/NEJMoa1911149

ABEMACICLIB IN BONE ONLY DISEASE
MONARCH 3



Subgroups analyzed	abemaciclib plus nonsteroidal AI *n*	placebo plus nonsteroidal AI *n*	HR (95% CI)
All Patients	328	165	0.540 (0.418-0.69
Metastatic site			
Visceral	173	89	0.567 (0.407-0.78
Bone-only	69	40	0.565 (0.306-1.04
Other	86	36	0.368 (0.219-0.61
Endocrine therapy			
Prior aromatase inhibitor therapy	85	50	0.428 (0.260-0.70
Other prior endocrine therapy	66	30	0.806 (0.473-1.37
No prior endocrine therapy	177	85	0.503 (0.352-0.71
Disease setting			
De novo metastatic	135	61	0.471 (0.312-0.71
Metastatic recurrent	182	99	0.579 (0.416-0.80
Nonsteroidal aromatase inhibitor at Cycle 1			
Anastrozole	62	36	0.515 (0.301-0.88
Letrozole	264	126	0.547 (0.410-0.72
Measurable disease			
Yes	267	132	0.517 (0.392-0.68
No	61	33	0.519 (0.267-1.00
Number of organs at baseline			
3+	152	78	0.509 (0.356-0.72
2	77	41	0.523 (0.311-0.88
1	98	45	0.593 (0.359-0.98
Age group			
<65 year	180	91	0.481 (0.346-0.66
≥65 year	148	74	0.616 (0.413-0.91
Geographical region			
North America	60	30	0.763 (0.422-1.38
Europe	166	93	0.636 (0.451-0.89
Asia	102	42	0.326 (0.200-0.53

Monarch3: mPFS HR 0.565 (0.306-1.044)



	N	Events	HR (95% CI)	Interaction p-value
Nature of Disease				0.298
Visceral	263	178	0.755 (0.556, 1.026)	
Bone only	109	62	0.596 (0.360, 0.987)	
Other	121	74	1.042 (0.633, 1.716)	
Endocrine Therapy				0.205
Prior aromatase inhibitor therapy	135	88	0.565 (0.370, 0.863)	
Other prior endocrine therapy	96	62	0.942 (0.548, 1.619)	
No prior endocrine therapy	262	164	0.673 (0.634, 1.202)	
Disease Setting				0.811
De novo metastatic disease	196	124	0.747 (0.517, 1.079)	
Metastatic recurrent disease	281	182	0.791 (0.585, 1.069)	
Number of Organs at Baseline				0.436
3+	229	161	0.857 (0.620, 1.186)	
2	119	72	0.856 (0.531, 1.380)	
1	142	80	0.608 (0.388, 0.952)	
Age				0.737
<65	271	167	0.813 (0.592, 1.118)	
>=65	222	147	0.751 (0.539, 1.049)	
Race				0.444
Caucasian	288	195	0.840 (0.629, 1.122)	
Asian	148	79	0.678 (0.426, 1.080)	
Progesterone Receptor Status				0.033
Negative	106	75	0.498 (0.314, 0.788)	
Positive	383	238	0.886 (0.678, 1.159)	
Baseline ECOG PS				0.656
1	197	138	0.721 (0.507, 1.026)	
0	296	178	0.801 (0.591, 1.086)	

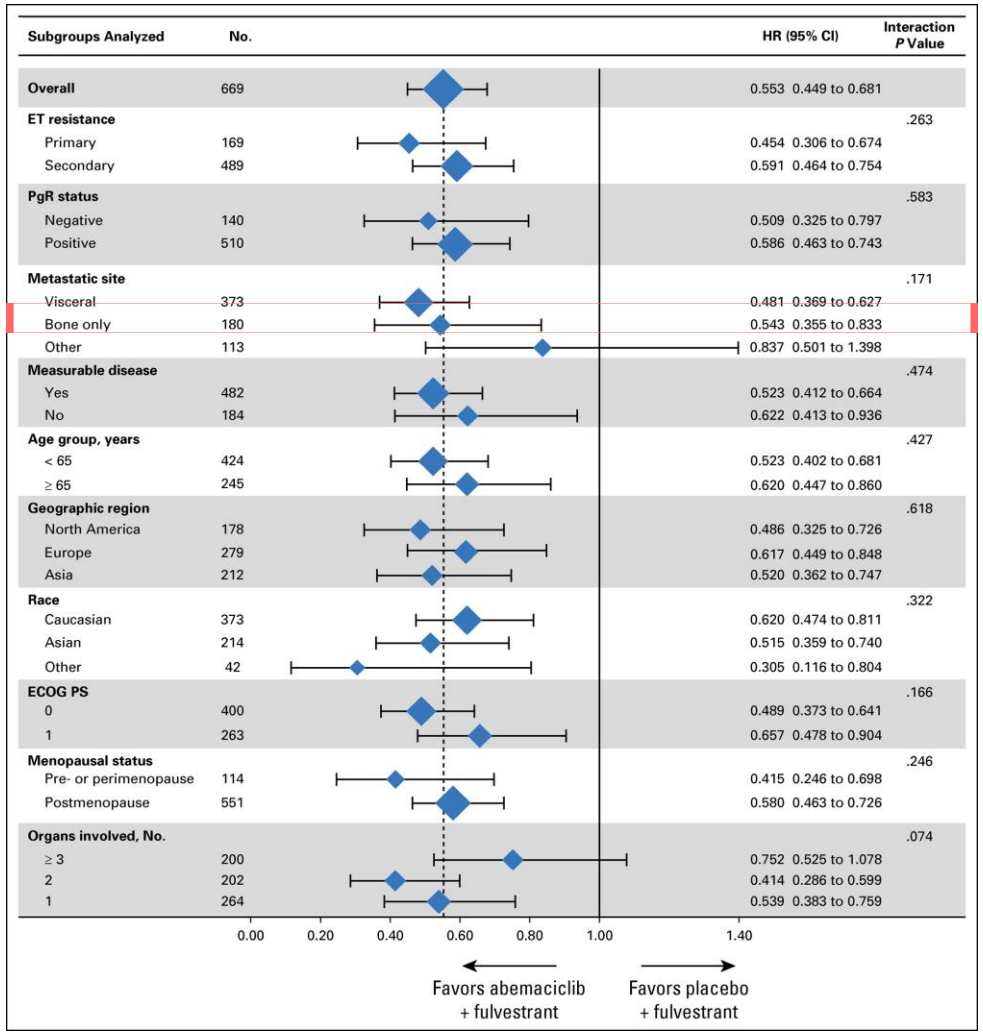
0.25 0.5 0.75 1

Monarch3: mOS HR 0.596 (0.36 - 0.98)

Johnston S, MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. NPJ Breast Cancer. 2019 doi: 10.1038/s41523-018-0097-z

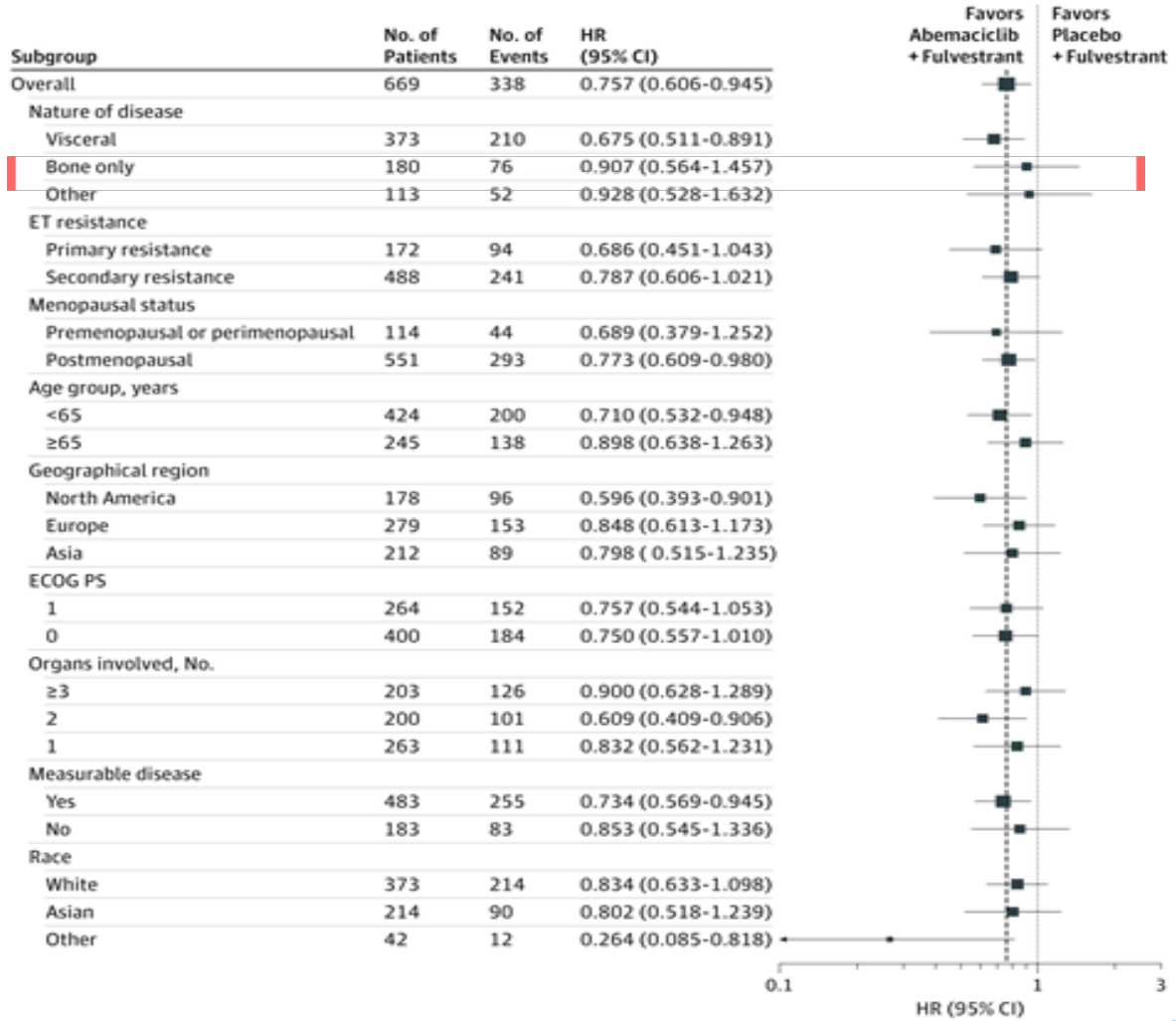
Matthew P Goetz et al, SABCS 2023

ABEMACICLIB IN BONE ONLY DISEASE
MONARCH 2



Monarch2: PFS Abemaciclb + Fulvestrant vs Placebo + Fulvestrant: HR 0,54 (0.355-0,833)

George W. Sledge, Jr. 2017



Monarch2: OS Abemaciclb + Fulvestrant vs Placebo + Fulvestrant: HR 0.907 (0.564-1.457)

(Sledge et al., 2020)

Overall Survival of CDK4/6-Inhibitor–Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis

Francesco Schettini, MD,[1,2,3,*] Fabiola Giudici, MSPH,[4] Mario Giuliano, MD,[1,5] Massimo Cristofanilli, MD,[6] Grazia Arpino, MD,[1] Lucia Del Mastro, MD,[7,8] Fabio Puglisi, MD,[9,10] Sabino De Placido, MD,[1] Ida Paris, MD,[11] Pietro De Placido, MD,[1] Sergio Venturini, PhD,[12,13] Michelino De Laurentis, MD,[14] PierFranco Conte, MD,[15,16] Dejan Juric, MD,[17] Antonio Llombart-Cussac, MD,[3,18] Lajos Pusztai, MD,[19] Aleix Prat, MD,[2,3,20] Guy Jerusalem, MD,[21] Angelo Di Leo, MD,[22] Daniele Generali, MD[2,3,24]

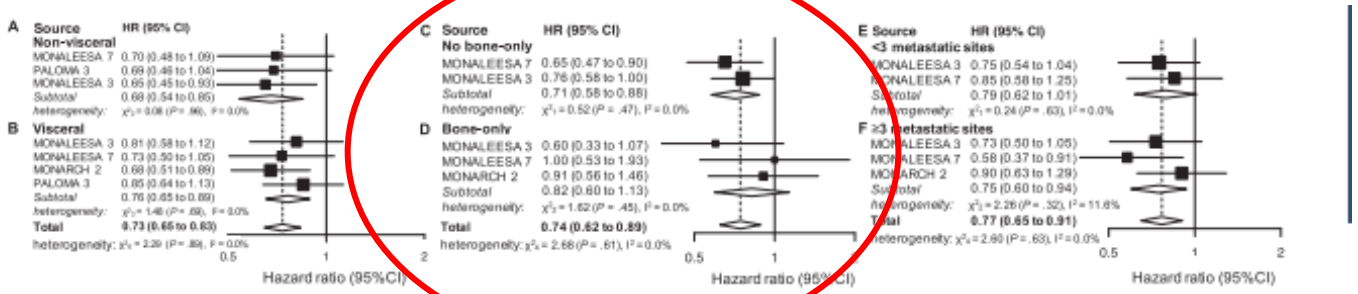
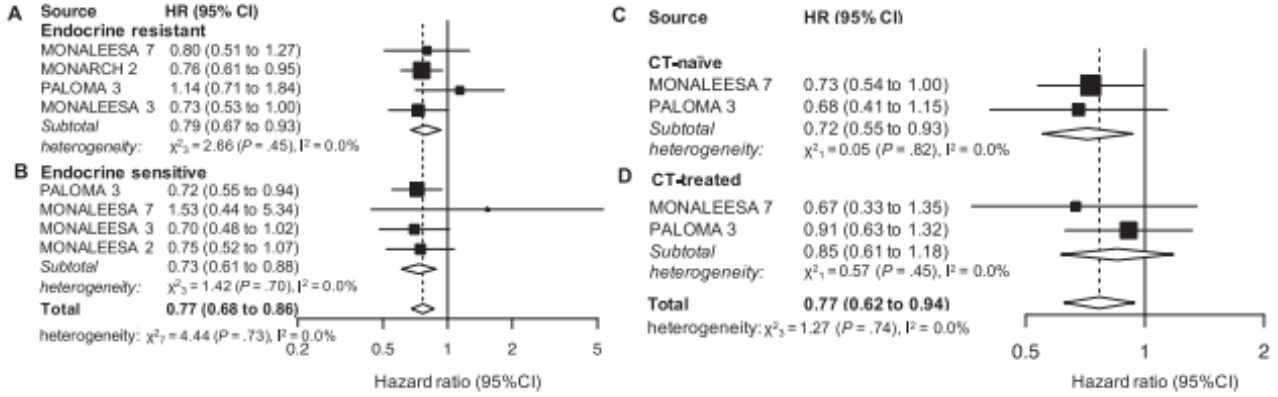


Figure 1. Pooled overall survival (OS) according to metastatic sites and tumor burden. Pooled OS in nonvisceral (A), visceral (B), no bone-only (C), or bone-only (D) disease and in case of less than 3 (E) and 3 or more metastatic sites (F). CI = confidence interval; HR = hazard ratio.



A significant cumulative relative reduction in the riskof death of 24% with cdk4/6 inhibitors + OT vs OT

Reduction of the hazard of dying with CDk4/6 inhibitor of the 29%
HR 0,74(0,62-0,80)

The OS benefit obtained with CDK4/6-inhibitor–based combinations in **bone-only disease** was not statistically significant BUT…
longer follow-up, and more events might be needed to obtain more conclusive results

Schettini F, Giudici F, Giuliano M, et al. Natl Cancer Inst. 2020;112(11):1089-1097.

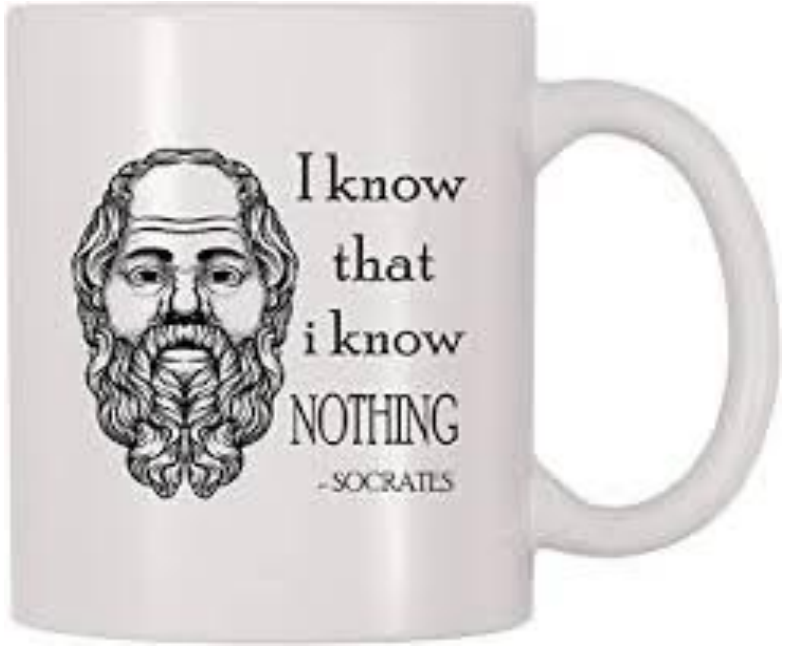
EFFICACY OF CDK 4/6 INHIBITORS IN BONE METASTASES

The combination of CDK4/6 inhibitors and endocrine therapy represents an effective and well-tolerated approach for the first-line treatment of metastatic breast cancer in the BoD setting.

Bone metastasis increase the risk of skeletal-related events (SREs) in cancer patients. In addition to affecting the quality of life, it also increases the medical costs and mortality risk.

To date, there are no studies that comparatively investigate the impact of CDK4 / 6 inhibitors on bone endpoints (Skeletal Related events and Skeletal progression free survival).

CDK4/6i and bone … what we know ?



International Journal of
Molecular Sciences

MDPI

Article

Biological Effects of Cyclin-Dependent Kinase Inhibitors Ribociclib, Palbociclib and Abemaciclib on Breast Cancer Bone Microenvironment

Michele Iuliani [1,*,†], Sonia Simonetti [1,†], Giulia Ribelli [1], Andrea Napolitano [1,2], Umile Giuseppe Longo [3], Bruno Vincenzi [1], Paolo Orsaria [4], Vincenzo Denaro [3], Giuseppe Tonini [1], Daniele Santini [1,‡] and Pantano Francesco [1,‡]

Abstract: The CDK4/6 inhibitors (CDKi) palbociclib, ribociclib, and abemaciclib are currently approved in combination with anti-estrogen therapy for the treatment of advanced and/or metastatic hormone receptor-positive/HER2-neu-negative breast cancer patients. Given the high incidence of bone metastases in this population, we investigated and compared the potential effects of palbociclib, ribociclib, and abemaciclib on the breast cancer bone microenvironment. Primary osteoclasts (OCs) and osteoblasts (OBs) were obtained from human monocyte and mesenchymal stem cells, respectively. OC function was evaluated by tartrate-resistant acid phosphatase assay and real-time PCR; OB activity was assessed by an alizarin red assay. OB/breast cancer co-culture models were generated via the seeding of MCF-7 cells on a layer of OBs, and tumor cell proliferation was analyzed using flow cytometry. Here, we showed that ribociclib, palbociclib, and abemaciclib exerted similar inhibitory effects on the OC differentiation and expression of bone resorption markers without affecting OC viability. On the other hand, the three CDKi did not affect the ability of OB to produce bone matrix, even if the higher doses of palbociclib and abemaciclib reduced the OB viability. In OB/MCF-7 co-culture models, palbociclib demonstrated a lower anti-tumor effect than ribociclib and abemaciclib. Overall, our results revealed the direct effects of CDKi on the tumor bone microenvironment, highlighting differences potentially relevant for clinical practice.

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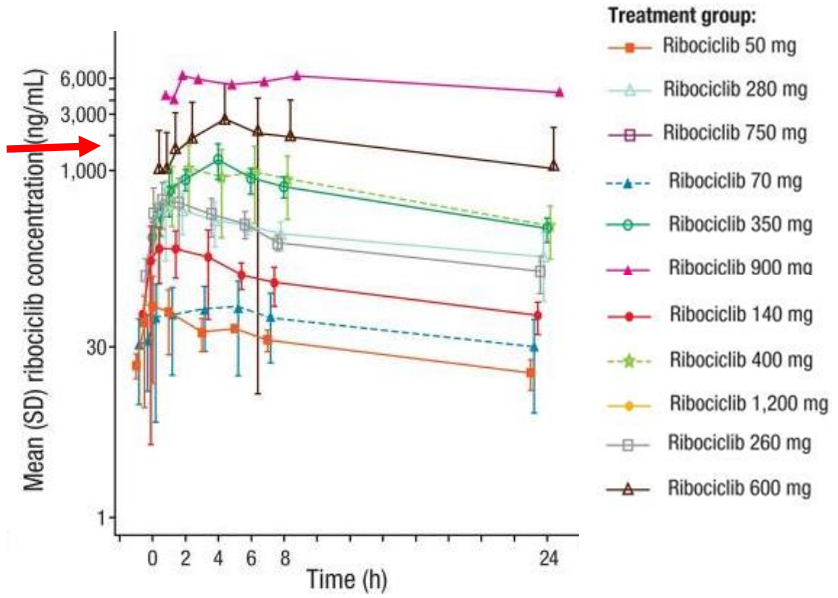
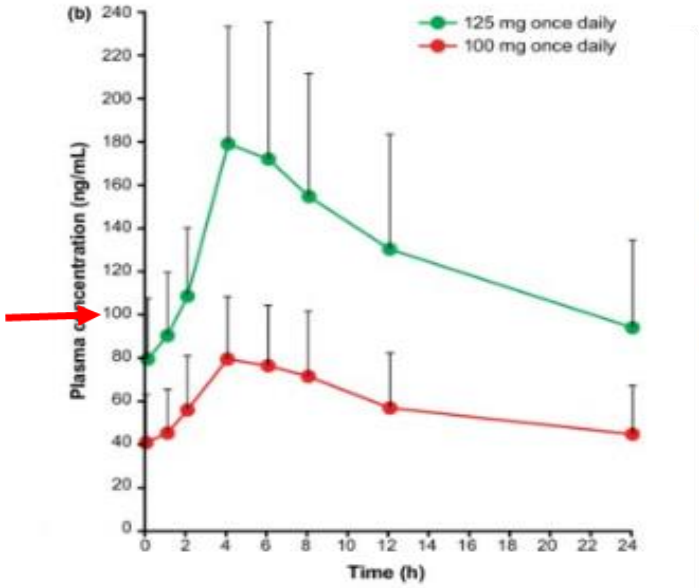
Accepted: 22 February 2022
Published: 24 February 2022

The choice of cdki drug concentrations: pharmacokinetic considerations

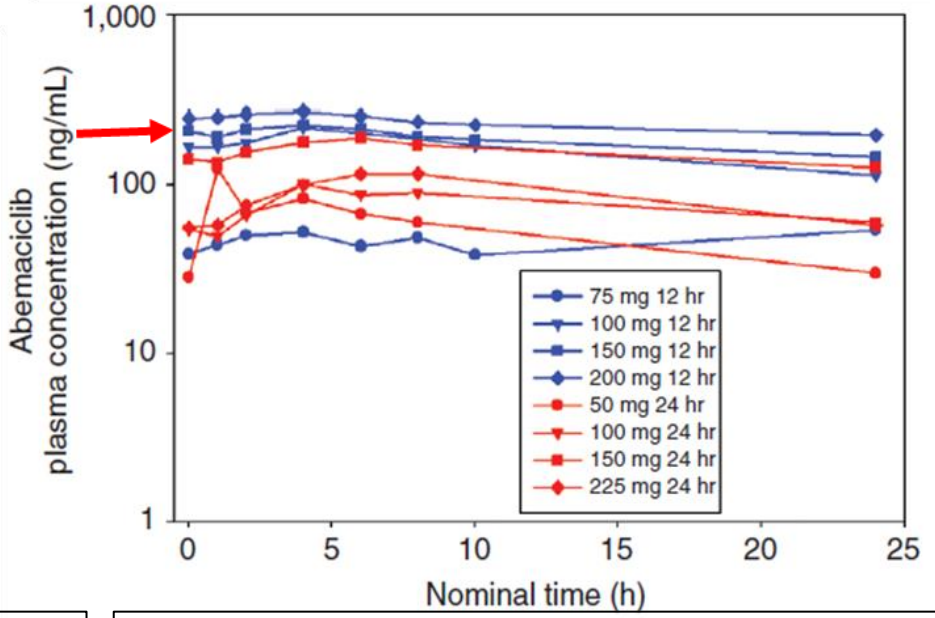
Ribociclib



Palbociclib



Abemaciclib



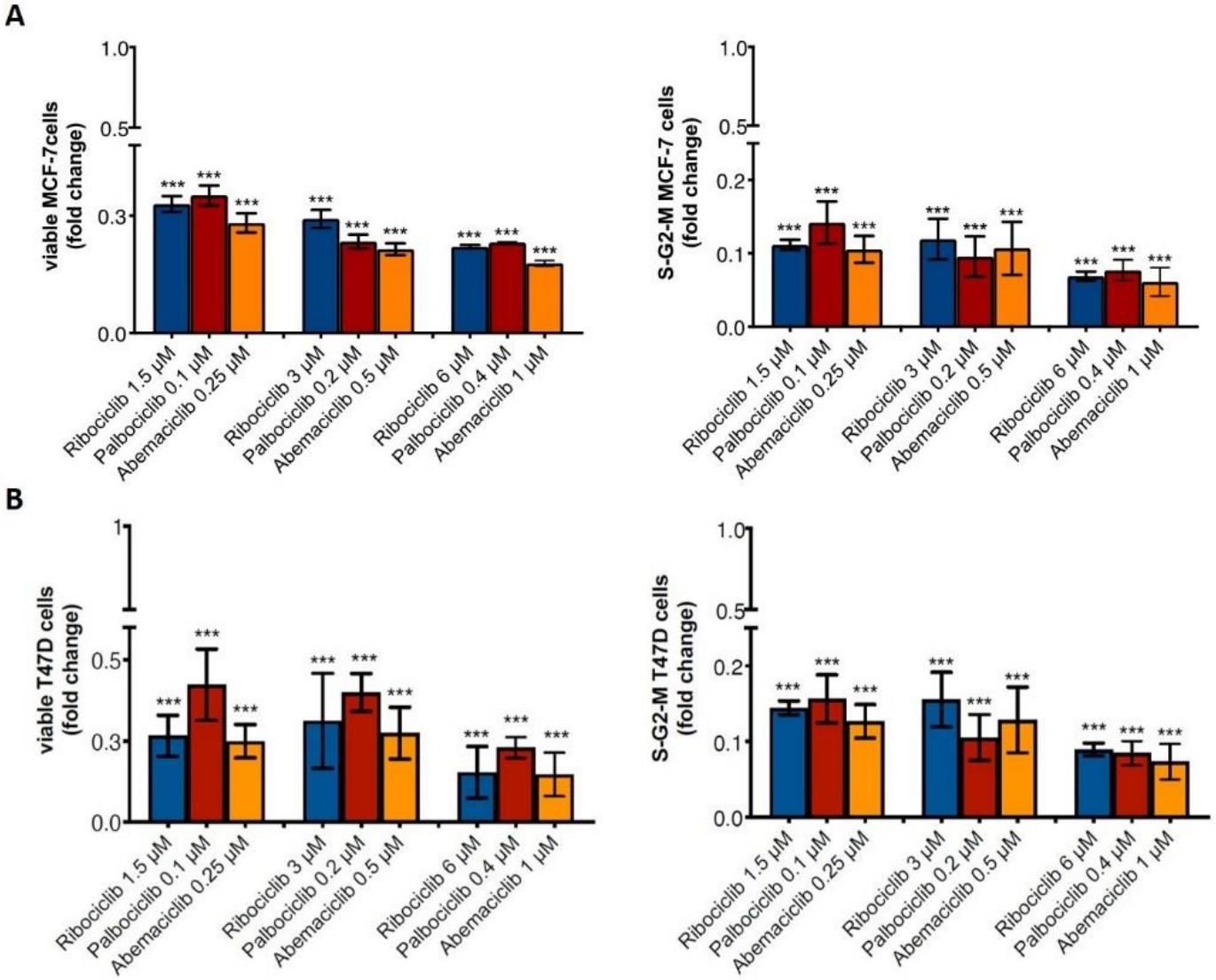
Ribociclib Mean plasma concentration ~ 1500 ng/ml = **3 µM**

Palbociclib Mean Plasma Concentration:~ 100 ng/ml = **0,2 µM**

Abemaciclib Mean Plasma Concentration: ~ 300 ng/ml = **0,5 µM**

Drug concentrations used in *in vitro* experiments

The choice of CDKi drug concentrations: in vitro validation



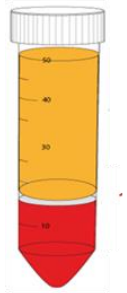
The three CDKi showed a similar anti-tumor effect on the two hormone-sensitive breast cancer cells

The choice of concentrations was appropriated!!

Human primary in vitro osteoclast generation

immediately

PBMC isolation



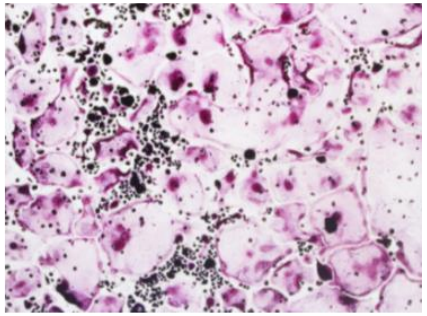
immediately

CD 14 monocyte sorting

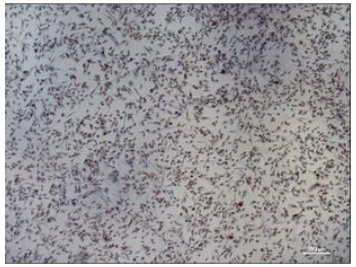
14 dd

+ RANKL
+ MCFS

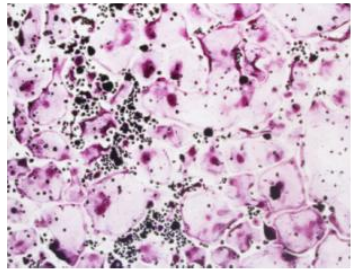
Mature osteoclasts



DIFFERENTIATION (TRAP ASSAY)

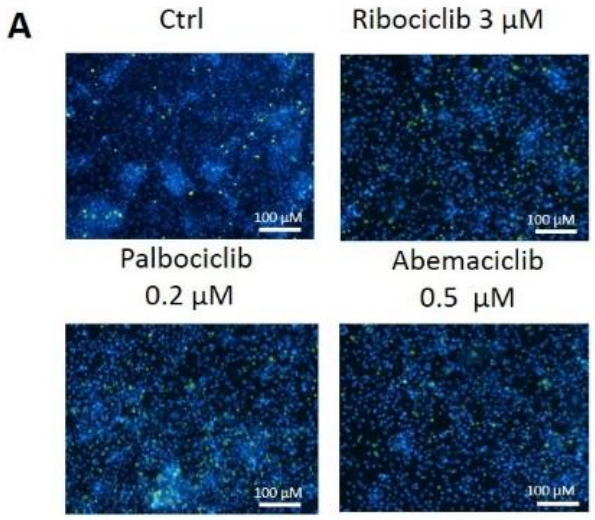


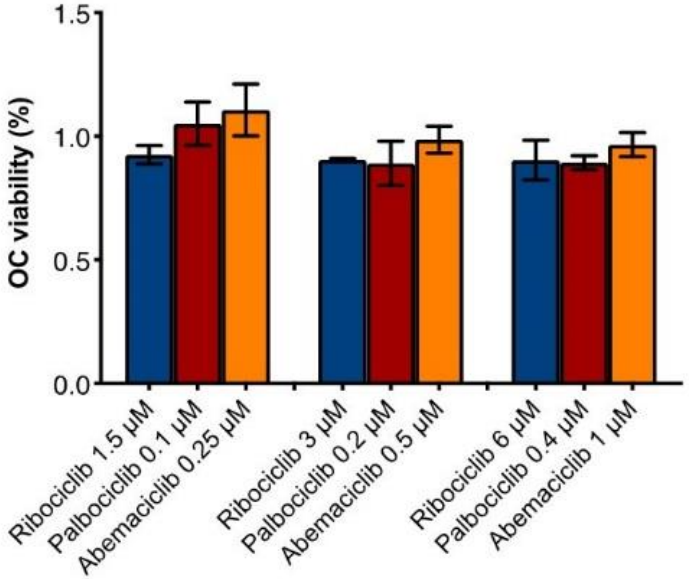
UNDIFFERENTIATED

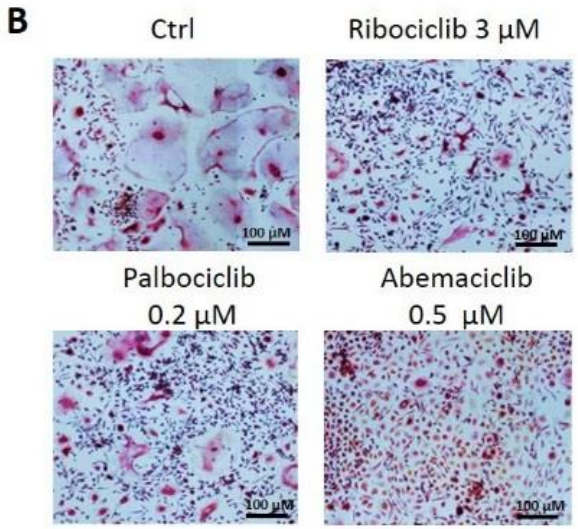


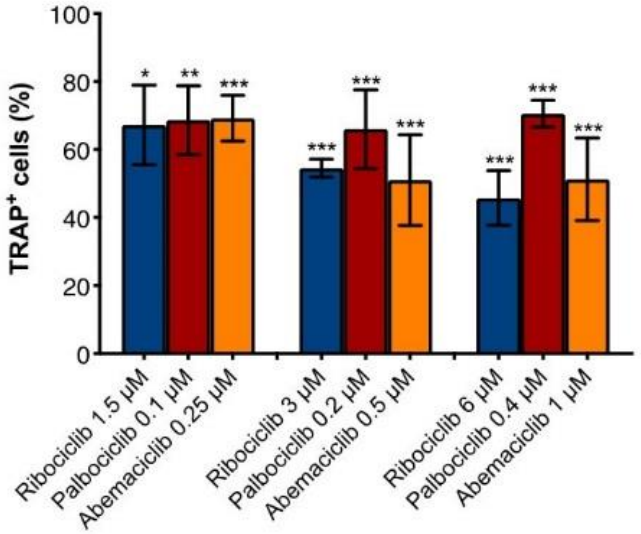
DIFFERENTIATED

CDKi effects on osteoclast differentiation







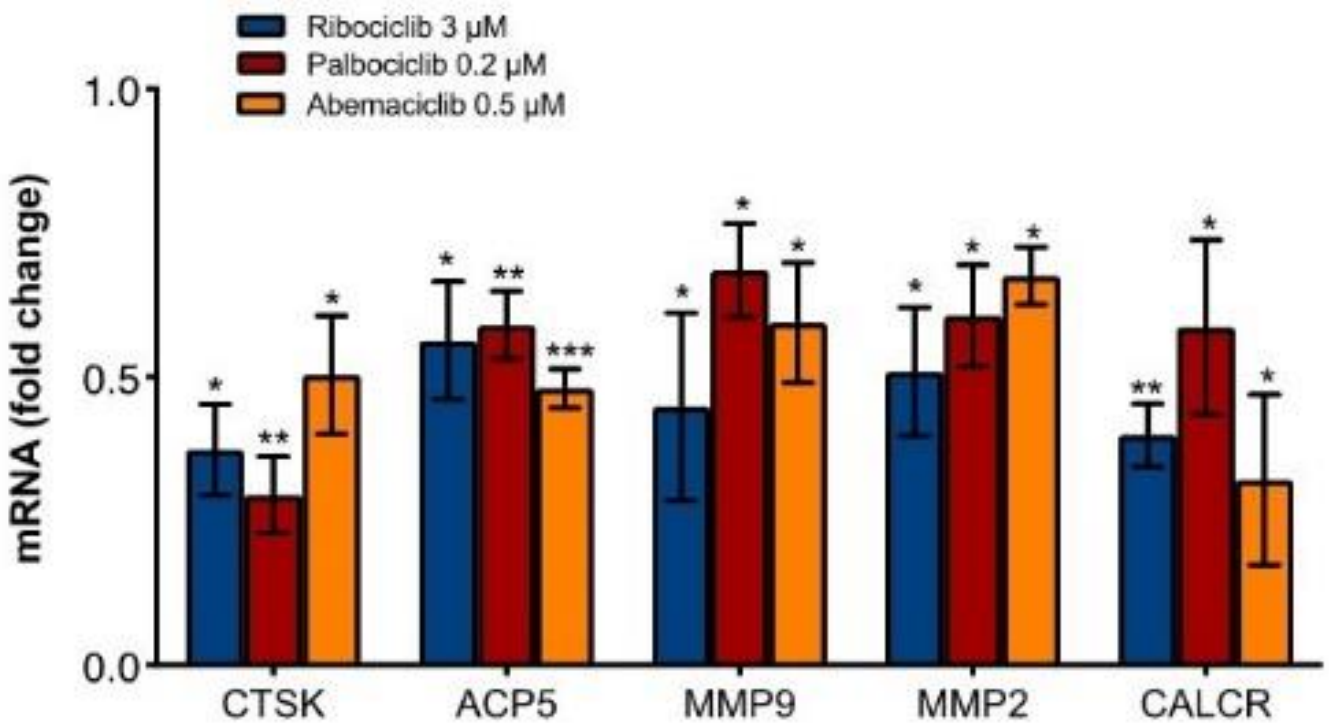


The three CDKi inhibited osteoclast differentiation without affecting osteoclast viability

Ribociclib and Abemaciclib exerted an higher osteoclast inhibitory effect compared to Palbociclib

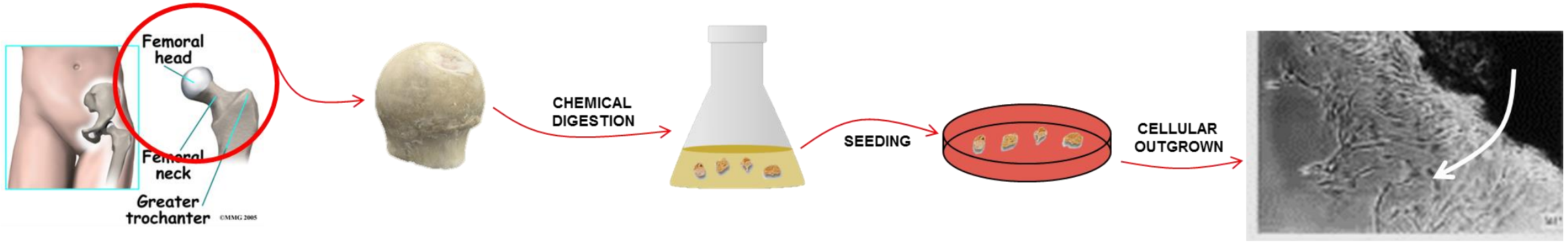
Osteoclasts were cultured in steroid deprivated media

CDK inhibitors effects on bone resorption

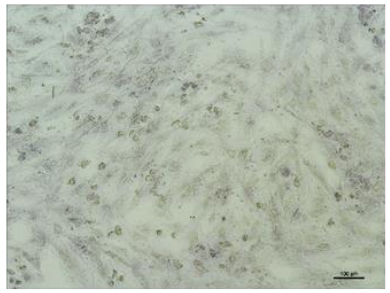


CDK inhibitors reduced the expression of genes involved in bone resorption

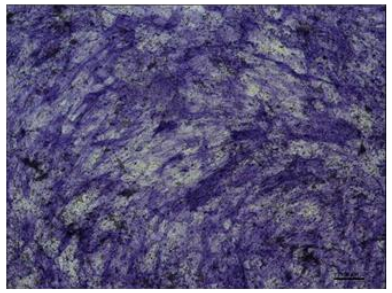
Human primary in vitro osteoblast generation



DIFFERENTIATION (ALP ASSAY)



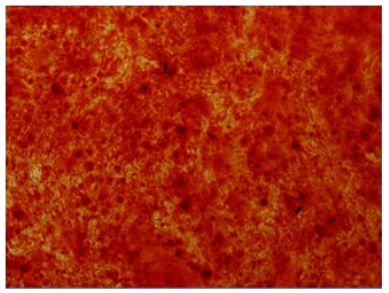
UNDIFFERENTIATED



DIFFERENTIATED

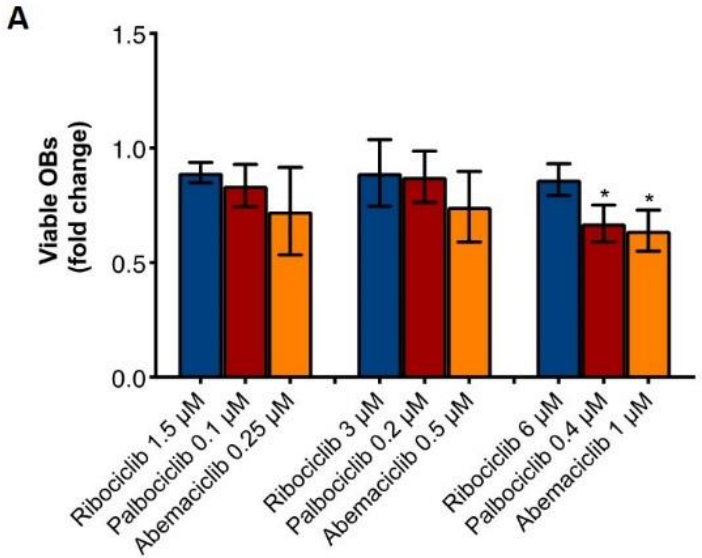
ACTIVITY (ALIZARIN RED ASSAY)

UNDIFFERENTIATED

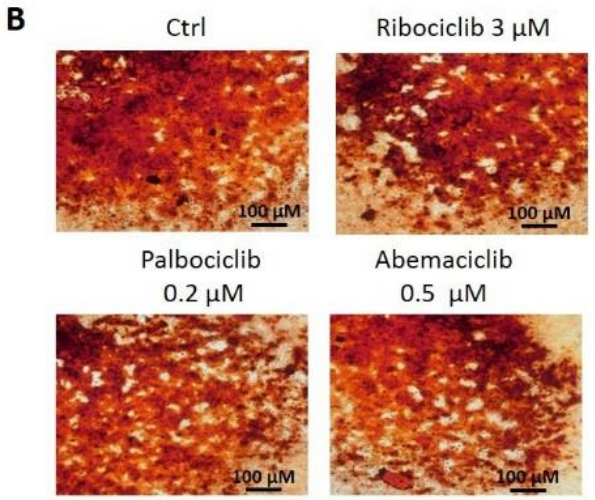


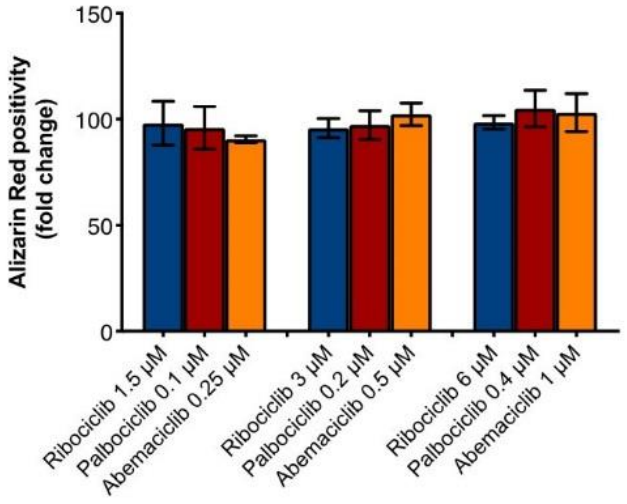
DIFFERENTIATED

CDKi effects on osteoblast differentiation



The higher concentrations of palbociclib and abemaciclib reduced osteoblast viability

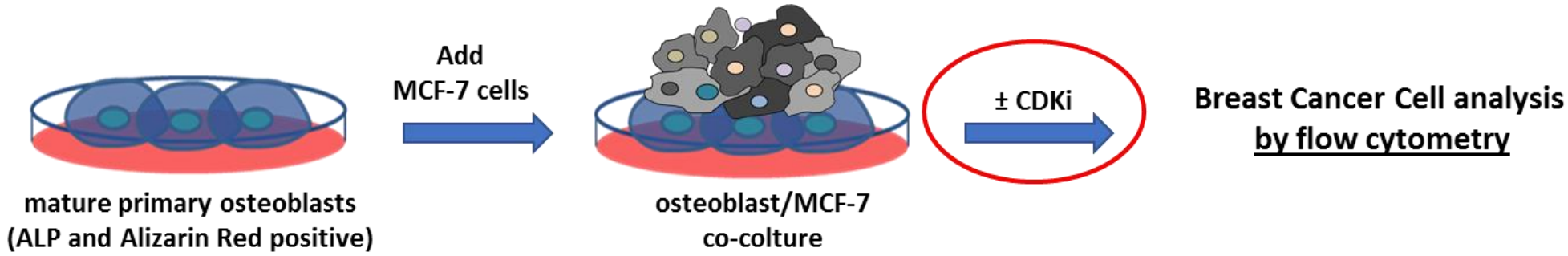


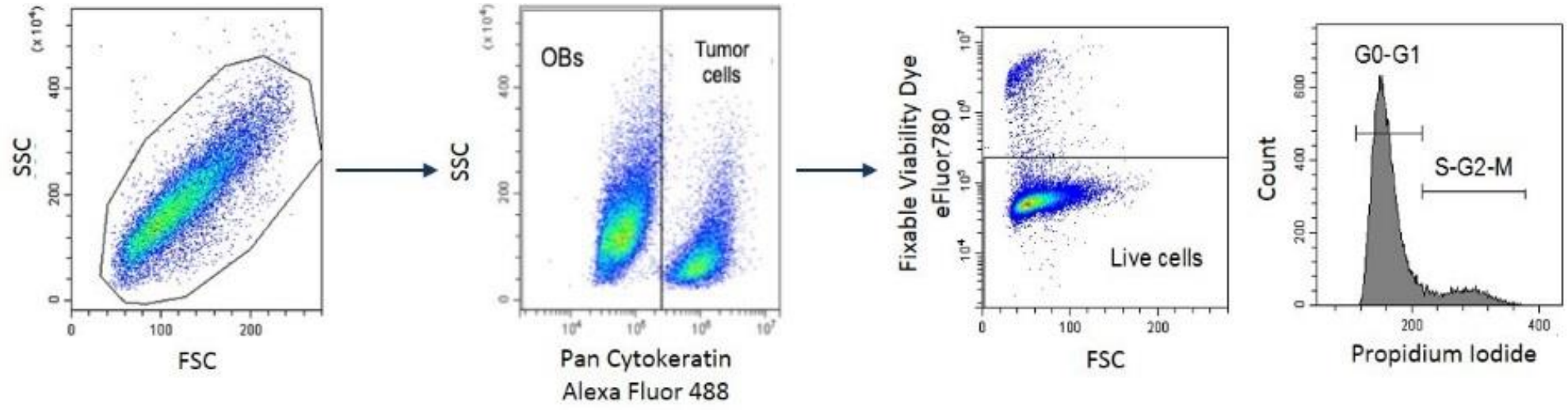


CDKi did not affect the ability of osteoblasts to produce bone matrix

Osteoblasts were cultured in steroid deprivated media

Breast cancer bone metastatic model co-culture generation and flow cytometry analysis

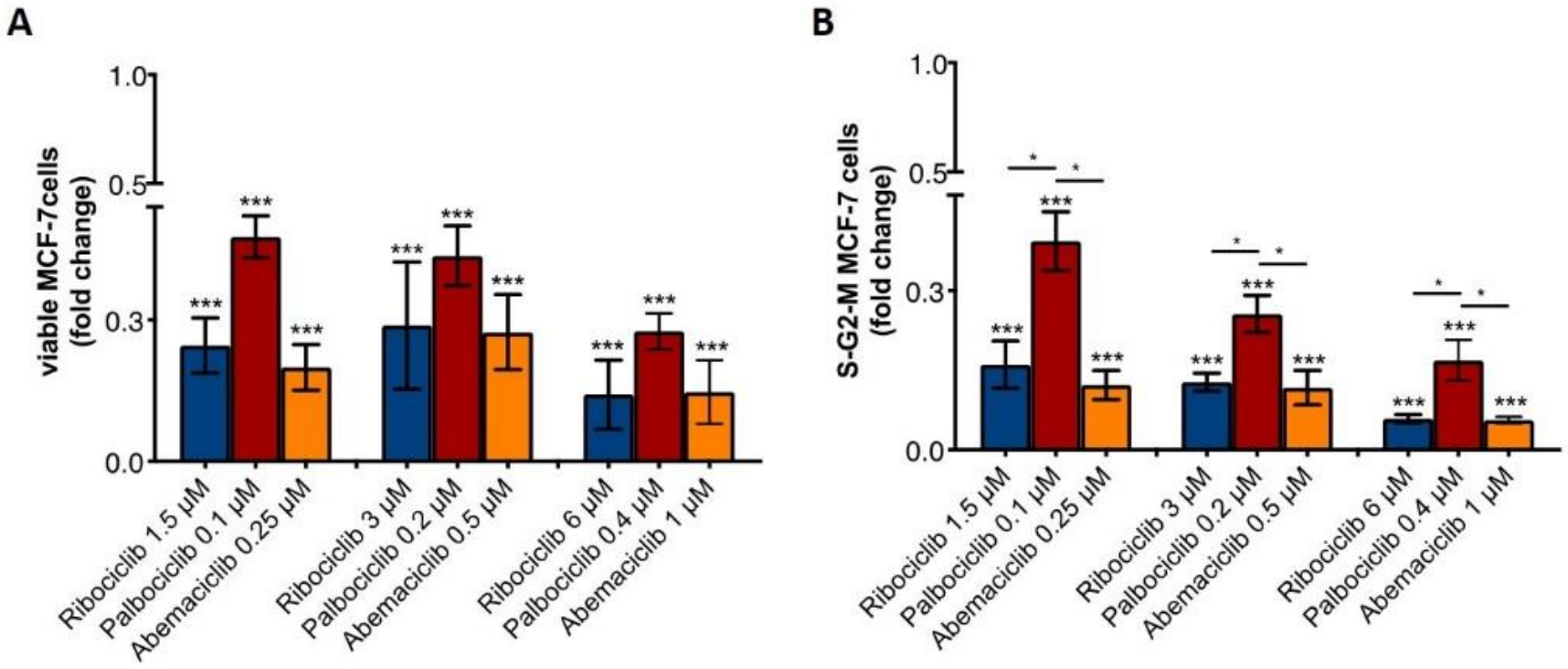




Pan-Cytokeratin staining allows to discriminate between breast cancer cells and osteoblasts
(Pan-Cytokeratin negative)

Brest cancer/osteoblasts were cultured in steroid deprivated media

CDK inhibitors effect on breast cancer cells in bone microenvironment



The three CDKi reduced cell viability and cancer cell proliferation in breast cancer/osteoblasts co-culture models

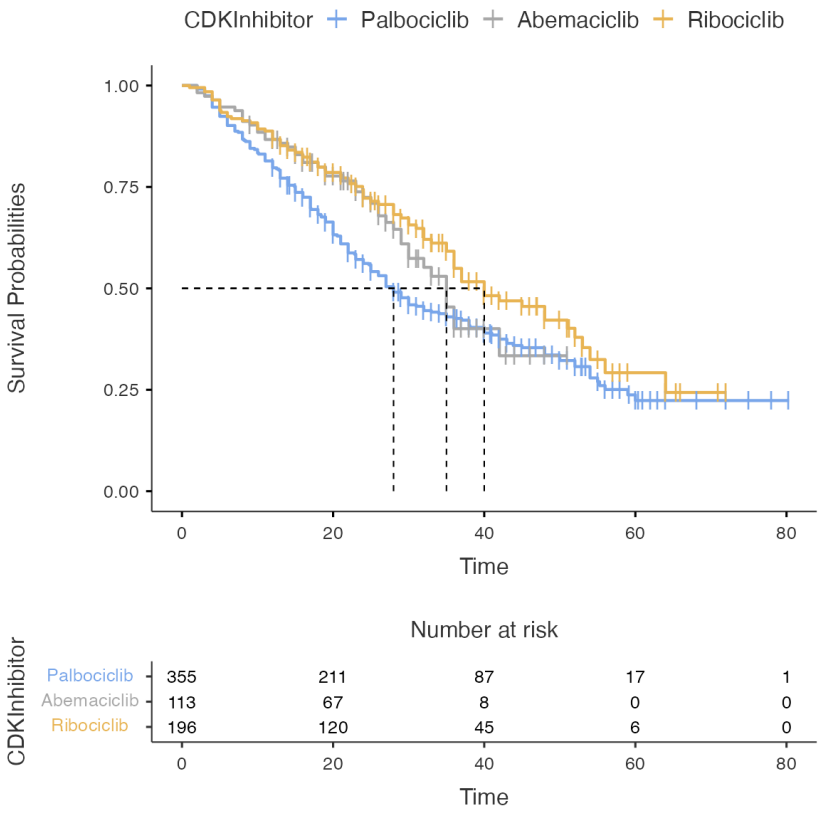
Ribociclib and abemaciclib exerted a higher anti-tumor effect compared to Palbociclib

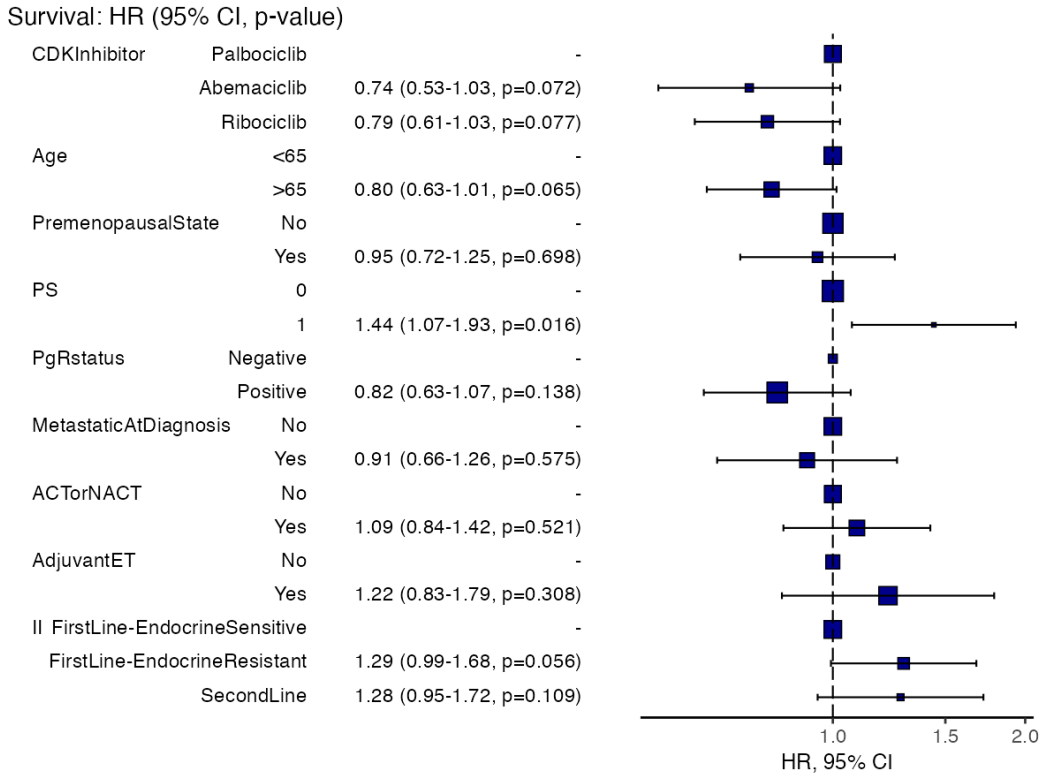
Real World Comparative Evidence about efficacy and toxicity of CDK4/6 Inhibitors

- 1284 ECOG PS0-1 patients treated with bone metastases as first or second line of treatment with at least 12 months of follow up were collected from 26 Italian Insitutions

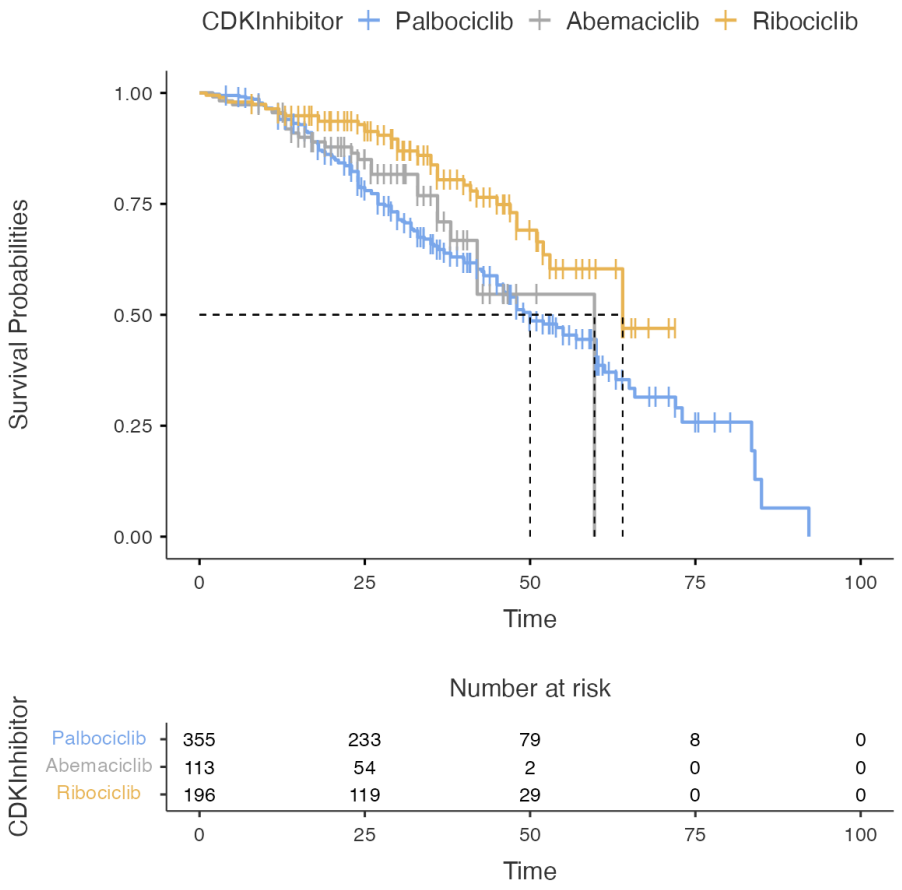
665 pts bone *only disease*

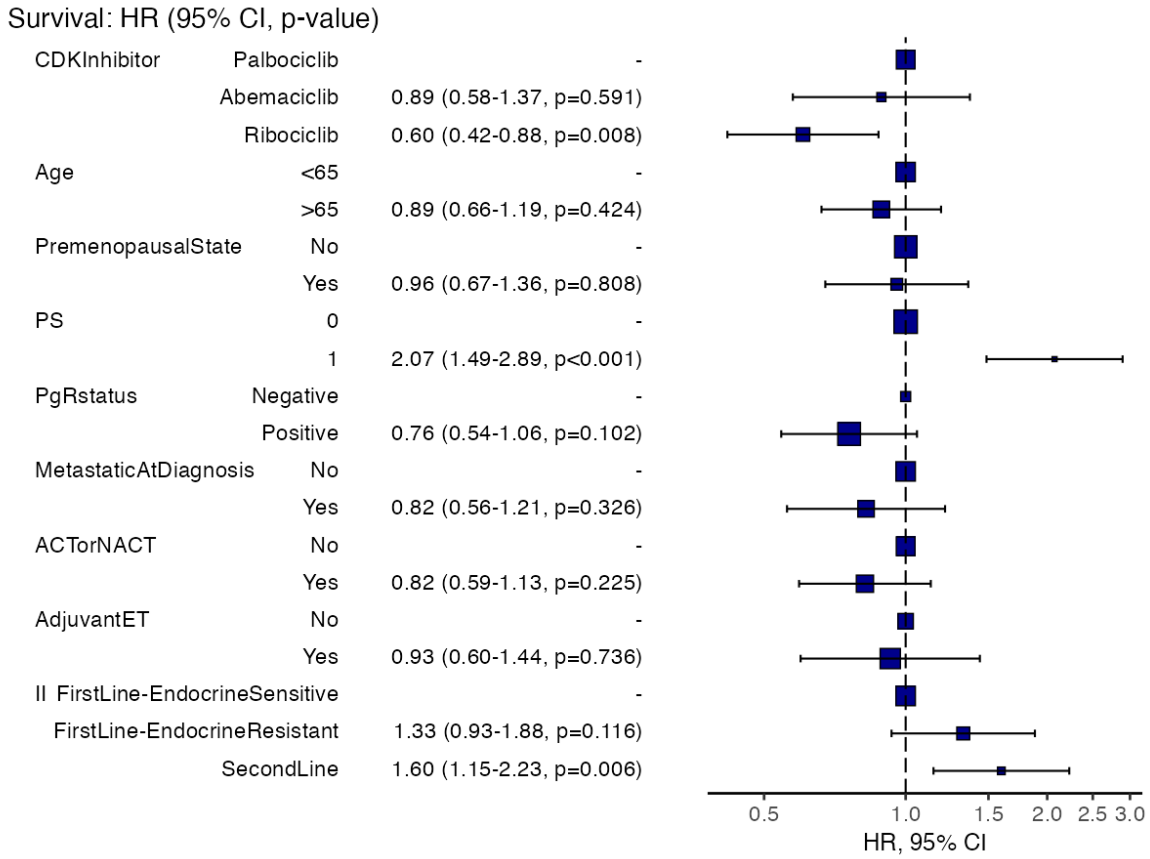
Progression Free Survival





Overall Survival





Data Not Published . Confidential

Conclusions

Osteoclasts:

- The three CDKi inhibited osteoclast differentiation and activity
- The comparative analysis shows that Ribociclib and Abemaciclib exerted an higher osteoclast inhibitory effect compared to Palbociclib

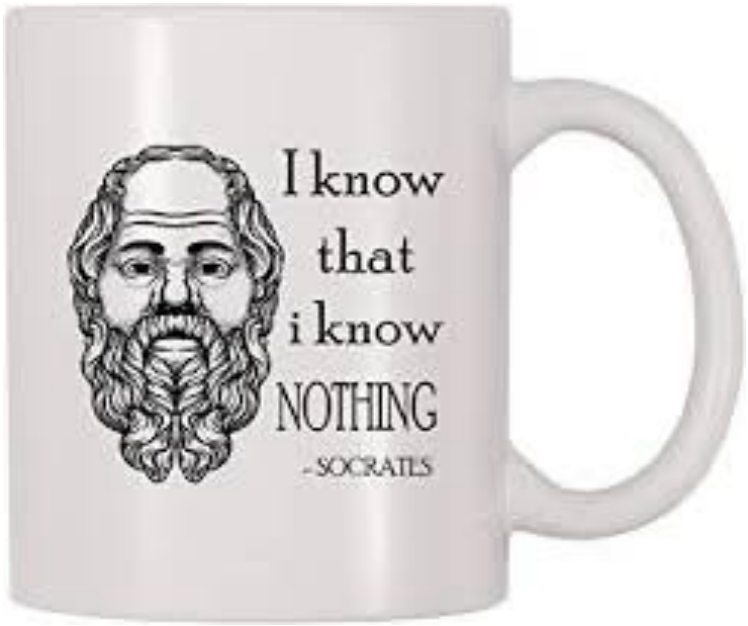
Osteoblasts:

- The three CDKi did not affect the ability of **osteoblasts** to produce bone matrix
- The comparative analysis shows that the higher concentrations of palbociclib and abemaciclib reduced **osteoblast** viability

Breast cancer bone metastatic models:

- The three CDKi reduced cell viability and cancer cell proliferation in breast cancer/osteoblasts co-culture models
- The comparative analysis shows that Ribociclib and abemaciclib exerted a higher anti-tumor effect compared to Palbociclib

The three CDKi exert a direct effect on the tumor bone microenvironment, but with differences potentially relevant for clinical practice



- **Bone health in CDK4/6 inhibitors: real world experience.**
- Studio retrospettivo osservazionale multicentrico di real life di Palbociclib, Ribociclib e Abemaciclib in combinazione con inibitori dell'aromatasi o Fulvestrant in pazienti con ca mammella HR+/HER2- e metastasi ossee.