CORSO SOCIETÀ ITALIANA DI OSTEONCOLOGIA - ISO

23 APRILE 2024 ROMA ISTITUTO DI STORIA DELLA MEDICINA QUALI STRATEGIE TERAPEUTICHE E QUALI NOVITÀ NELLA GESTIONE DELLE METASTASI OSSEE RESPONSABILI SCIENTIFICI: G. LANZETTA - T. IBRAHIM - D. SANTINI



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

Francesco Pantano, MD,PhD, Università Campus Bio-Medico di Roma f.pantano@policlinicocampus.it 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.

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

Select Clinical Trials of	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 (<u>Phase 2</u> 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	MONARCH-1 (Phase 2 study of ABE monotherapy in						
MONALEESA-3 (RIBO + FUL in patients with <1 line of ET for ABC)	of ET for ABC)	heavily pretreated patients)						

CDK4/6i and bone ... what we know ?

PALBOCLIB IN BONE ONLY DISEASE PALOMA 2

)	PAL + LET	PBO + LET	PAL + LET	PBO + LET	PALLIFT		
Baseline Factors	Patient	ts, n (%)	mPFS (95% CI)	HR (9	5% CI)	P°
All randomized patients, IA	444 (100)	222 (100)	27.6 (22.4-30.3)	14.5 (12.3–17.1)	⊢ ∎i	0.56 (0.46-0.69)	<0.000
All randomized patients, BICR	444 (100)	222 (100)	35.7 (27.738.9)	19.5 (16.6–26.6)		0.61 (0.49-0.77)	<0.000
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)	<0.000
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)	<0.000
Bone-only disease	103 (23.2)	48 (21.6)	36.2 (27.6-NE)	11.2 (8.2–22.0)	⊢ ∎−−−i	0.41 (0.26-0.63)	<0.000
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)	<0.000
TFI° >12 mo	179 (40.3)	93 (41.9)	30.3 (24.8-NE)	13.8 (8.8–18.2)	H	0.55 (0.40-0.76)	< 0.000
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)	<0.000
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)	< 0.000
TFI° >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 (30.4NE)	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
TF1 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)	⊢−● −−−1	0.49 (0.33-0.73)	<0.000
Measurable disease	338 (76.1)	171 (77.0)	23.7 (19.3-27.6)	14.5 (12.3–18.5)	⊢ ∎−−1	0.63 (0.50-0.79)	<0.000
Nonmeasurable disease [#]	106 (23.9)	51 (23.0)	36.2 (27.6-NE)	16.5 (8.3–19.6)	H	0.39 (0.25-0.60)	<0.000
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)	<0.000
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)	<0.000

Subgroup	No. (%)	Median O	S (95% CI)		HR (95% CI)	No Long Followed for	ger Being r Survival (%)
		PAL + LET	PBO + LET			PAL + LET	PBO + LET
All randomly assigned patients	666 (100)	53.8 (49.8 to 59.2)	49.8 (42.3 to 56.4)	н ф и	0.92 (0.76 to 1.12)	9	12
Age, years							
<65	404 (60.7)	53.8 (47.9 to 61.3)	53.4 (38.8 to 60.1)		0.95 (0.73 to 1.22)	8	12
265	262 (39.3)	55.3 (47.3 to 63.7)	47.2 (36.2 to 57.5)		0.88 (0.64 to 1.21)	11	11
Region							
North America	267 (40.1)	53.8 (47.3 to 61.3)	47.2 (37.0 to 56.1)	F	0.86 (0.64 to 1.16)	8	12
Europe	307 (46.1)	52.1 (46.0 to 63.5)	52.3 (42.3 to 69.1)		1.06 (0.79 to 1.43)	9	в
Asia/Pacific ECOG performance status	92 (13.8)	73.4 (47.3 to NR)	55.1 (32.2 to NR)		0.72 (0.40 to 1.29)	14	21
0	359 (53.9)	58.2 (51.6 to 64.2)	59.7 (51.3 to 93.3)	H =	1.17 (0.86 to 1.59)	8	18
1/2	307 (46.1)	47.1 (41.3 to 58.4)	38.2 (31.9 to 49.4)	⊢_ ∎÷∔4	0.81 (0.62 to 1.06)	11	7
Disease site							
Visceral	324 (48.6)	48.1 (42.2 to 55.1)	42.3 (31.7 to 51.2)	⊢∎i∔-ı	0.86 (0.65 to 1.13)	8	16
Nonvisceral	342 (51.4)	58.8 (53.8 to 70.9)	58.9 (47.4 to 80.1)		0.98 (0.74 to 1.31)	10	8
Disease-free interval							
De novo metastatic	248 (37.2)	53.8 (45.6 to 63.8)	59.7 (46.8 to 81.0)	H-H-B	1.13 (0.81 to 1.58)	5	12
≤12 months	146 (21.9)	45.7 (36.1 to 53.3)	37.5 (27.1 to 51.3)		1.02 (0.67 to 1.54)	9	17
>12 months	272 (40.8)	64.0 (52.7 to 78.2)	47.4 (37.7 to 57.5)		0.70 (0.52 to 0.96)	13	9
Previous endocrine therapy							
Yes	376 (56.5)	53.8 (48.1 to 62.9)	44.6 (34.3 to 52.3)	⊢ ∎÷ł	0.79 (0.61 to 1.02)	12	10
No	290 (43.5)	53.9 (46.0 to 66.3)	59.7 (47.7 to 78.0)	H	1.12 (0.82 to 1.53)	6	14
Previous chemotherapy							
Yes	322 (48.3)	52.7 (46.9 to 59.0)	44.8 (37.0 to 53.8)		0.83 (0.63 to 1.10)	9	8
No	344 (51.7)	55.3 (49.2 to 67.0)	55.1 (46.8 to 77.5)		1.02 (0.76 to 1.36)	9	15
Bone-only disease							
Yes	151 (22.7)	63.5 (53.9 to 73.9)	52.8 (42.2 to 64.1)		0.77 (0.51 to 1.17)	12	6
No	515 (77.3)	51.1 (46.1 to 57.4)	47.7 (37.8 to 57.5)		0.97 (0.77 to 1.21)	9	13
No. of disease sites							-
1	204 (30.6)	59.1 (53.8 to 73.9)	54.4 (45.4 to 70.3)		0.87 (0.60 to 1.25)	11	9
2	169 (25.4)	60.7 (47.3 to 73.4)	48.0 (33.2 to 80.2)		0.84 (0.55 to 1.29)	11	21
≥3	293 (44.0)	47.1 (41.0 to 52.3)	44.6 (31.9 to 56.4)		1.01 (0.76 to 1.35)	7	9
			0.01 0.	25 0.5 0.75 1 1.25 1.	5 1./5 Z		
			In	Favor of In Fa	avor of		
			ф _{рл}	LIFT PRO	I+LET →		

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

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.

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

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

	palbociclib (events [n]/ patients)	plus placebo (events [n]/ patients)	patients			palbociclib median progression-free survival (95%CI)	placebo median progression-free survival (95%CI)	(95% CI)	Patteraction
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)	
			0-12	5 0.25 0.5 1.0	2-0 4-0	8-0			
				Favours fulvestrant F plus palbociclib	avours fulvestrant plus placebo				

Fulvestrant plus Fulvestrant Events (n)/

	PAL+F	UL	PRO+F	UL			Interaction
TT and Subgroup	Events	/N (%)	Events	W (%)	11	HR (95% CI)	P Value
II randomized patients (ITT, stratified)	258/347	(74.4)	135/174	(77.6)	⊢⊷	0.806 (0.654-0.994)	
II randomized patients (ITT, unstratified)	258/347	(74.4)	135/174	(77.6)	⊢ ₩-1	0.787 (0.639-0.970)	
ensitivity to previous hormonal therapy					i l		
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)	
ite 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)	⊢_∎_ i	0.631 (0.450-0.886)	
lenopausal status at study entry					il		2
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)	
rior 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)	
lumber 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)	
Vtih prior chemotherapy in ABC							
Endocrine sensitive	71/86	(82.6)	44/54	(81.5)	⊢_i∎ i	0.883 (0.606-1.287)	0.3149
Endocrine resistant	23/27	(85.2)	9/10	(90.0)	i ii	1.374 (0.634-2.979)	
Vithout prior chemotherapy in ABC					i l		
Endocrine sensitive	131/188	(69.7)	60/82	(73.2)	⊢ =+-4	0.719 (0.529-0.977)	0.9880
Endocrine resistant	33/46	(71.7)	22/28	(78.6)	⊢	0.803 (0.467-1.381)	
Vtih 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)	
Vithout prior chemotherapy in ABC							
Visceral disease	99/129	(76.7)	45/62	(72.6)	⊢ ₽ 1 1	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

			181	Envore	Equara		
		Even	ts n/N	Bibociclib	Placebo		
		Ribociclib	Placebo	+ Letrozole	+ Letrozole		
5	Subgroup	+ Letrozole	+ 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
JS		38/100	63/113			0.527	0.351-0.793
atin 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
	0	82/205	123/202	H+1		0.581	0.439-0.769
2000 F5	1	58/129	82/132	H-1		0.543	0.385-0.766
100	<65 years	82/184	127/189	H+1		0.518	0.392-0.684
Age	≥65 years	58/150	78/145	⊢ •−1		0.658	0.466-0.928
2000	Asian	14/28	19/23			0.370	0.180-0.760
hace	Non-Asian	121/281	171/287	· • • •		0.614	0.486-0.775
ID atatua	ER+ and PgR+	109/269	162/277	• • •		0.606	0.475-0.774
in status	Other	31/65	43/57			0.358	0.217-0.591
iver or lung	No	59/152	80/143	H		0.597	0.426-0.837
netastases	Yes	81/182	125/191			0.561	0.424-0.743
lone only diese	No	114/265	159/256	H++		0.551	0.432-0.702
sone-only disea	Yes	26/69	46/78	H-+-		0.642	0.393-1.048
De neuro dieces	No	97/220	144/221	H F F		0.579	0.447-0.749
<i>Je novo</i> diseas	e Yes	43/114	61/113			0.569	0.384-0.843
Provinces	AI	30/71	48/67	—		0.375	0.235-0.599
revious	TAM	47/104	71/105			0.617	0.426-0.894
endocrine thera	Py None	62/158	86/162			0.651	0.468-0.904
Previous	No	69/188	102/189			0.640	0.470-0.871
hemotherapy	Yes	71/146	103/145			0.501	0.368-0.681
						—	
			(0.0625 0.125 0.25 0.5 1	2 4 6	8	

Hazard ratio (95% CI)

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

Subgroup	Ribociclib-	- Letrozole	Placebo+	Letrozole	Hazard Ratio f	or Death (95% CI)
	No. of events/ no. of patients	Median overall survival	No. of events/ no. of patients	Median overall survival		
		mo		mo		
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	h <mark>1</mark>	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	18/30	60.6	18/23	52.5		0.63 (0.32-1.24)
inhibitor and others	18/50	00.0	10/25	52.5		0.05 (0.52-1.24)
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	87/140	50.5	50/145	50.1		0.00 (0.01 1.12)
Positive	146/271	65.3	171/278	575		0.83 (0.66-1.04)
Negative	22/55	51.1	41/49	37.5		0.64 (0.40-1.02)
Hormone-receptor status	52/55	51.1	41/45	51.7		0.01 (0.10 1.02)
ER-positive and PaR-positive	144/260	65.2	170/277	56.0		0.82 (0.66-1.03)
Other	27/65	55.5	40/57	27.7		0.52 (0.37 0.89)
No of sites of metastasis	37/03	33.5	49/37	37.7		0.58 (0.57-0.85)
~3	115/220	69.0	126/222	56.1		0.78 (0.61 1.00)
-3	115/220	68.0	130/222	56.1		0.78 (0.01-1.00)
≥J	66/114	33.5	85/112	40.5		0.71 (0.31-0.98)
Liver involvement	1 15 10 75	60.0	1 62 10 62			0.77 (0.62, 0.07)
NO	145/2/5	68.0	163/262	56.9		0.77 (0.62-0.97)
fes	36/59	37.7	56/72	38.1		0.81 (0.54–1.24)
Lung involvement						0.70 (0.55 0.00)
NO	97/181	66.1	119/185	50.5		0.72 (0.55-0.94)
res	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 disea	se					
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)
				0.25	5 0.5 1 2	4
				-		-

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

RIBOCICLIB IN BONE ONLY DISEASE MONALEESA 3

		Events,	n/N (%)				
Subgroup		Ribociclib plus fulvestrant	Placebo plus fulvestrant	Favors ribociclib	Favors placebo	Hazard ratio	95% CI
All patients		210/484 (43)	151/242 (62)	r 🔶		0.593	0.480 to 0.732
Prior endocrine therapy*	Treatment naïve Up to one line	76/238 (32) 131/236 (56)	66/129 (51) 84/109 (77)			0.577 0.565	0.415 to 0.802 0.428 to 0.744
Liver or lung involvement	Yes No	116/242 (48) 94/242 (39)	77/121 (64) 74/120 (62)			0.645 0.563	0.483 to 0.861 0.415 to 0.764
Bone lesion only	Yes No	36/103 (35) 174/381 (46)	35/51 (69) 116/190 (61)	L H		0.379 0.658	0.234 to 0.613 0.519 to 0.833
Age, years	< 65 ≥ 65	115/258 (45) 95/226 (42)	81/129 (63) 70/113 (62)			0.607 0.597	0.454 to 0.810 0.436 to 0.818
Race	Asian White Other	22/45 (49) 174/406 (43) 8/18 (44)	7/18 (39) 136/213 (64) 3/6 (50)	- H		1.353 0.562 0.881	0.574 to 3.186 0.448 to 0.704 0.199 to 3.907
ECOG PS	0 1	126/310 (41) 83/173 (48)	95/158 (60) 56/83 (67)			0.559 0.633	0.427 to 0.733 0.450 to 0.890
No. of metastatic sites	<3 ≥3	126/309 (41) 84/175 (48)	92/149 (62) 59/92 (64)	H		0.586 0.621	0.447 to 0.768 0.441 to 0.874
Prior tamoxifen	Yes No	79/193 (41) 131/291 (45)	63/104 (61) 88/137 (64)			0.620 0.562	0.443 to 0.866 0.428 to 0.738
Prior Al	Yes No	135/257 (53) 75/227 (33)	80/118 (68) 71/123 (58)			0.670 0.481	0.507 to 0.886 0.345 to 0.669
			0.1:	25 0.25 0.5 Hazard rat	1 2 4 io (95% CI)	8	

Subgroup	Ribociclib+Fulvestrant	Placebo+Fulvestrant	Hazard Ratio for Death (95% CI)	
	no. of deaths	/tatal na. (%)		
All patients	167/484 (34.5)	108/242 (44.6)		0.72 (0.57-0.92)
Treatment line of endocrine-based			1	
therapy for advanced disease				
First line	63/237 (26.6)	47/128 (36.7)		0.70 (0.48-1.02)
Early relapse or second line	102/237 (43.0)	60/109 (55.0)	+ + +	0.73 (0.53-1.00)
Liver or lung involvement			1	
Yes	97/242 (40.1)	57/122 (46.7)		0.81 (0.58-1.12)
No	70/242 (28.9)	51/119 (42.9)		0.65 (0.45-0.93)
Bone lesion only				
Yes	27/102 (26.5)	22/51 (43.1)		0.60 (0.33-1.07)
No	140/382 (36.6)	86/190 (45.3)		0.76 (0.58-1.00)
No. of sites of metastasis			1	
<3	93/308 (30.2)	60/147 (40.8)		0.75 (0.54-1.04)
>3	74/176 (42.0)	48/94 (51.1)		0.73 (0.50-1.05)
Most recent therapy				
Adjuvant or neoadjuvant therapy	99/264 (37.5)	72/151 (47.7)		0.77 (0.57-1.04)
Therapy for metastatic disease	45/112 (40.2)	19/42 (45.2)		0.69 (0.40-1.20)
Age			1	
<65 yr	85/258 (32.9)	54/129 (41.9)		0.76 (0.54-1.07)
≥65 yr	82/226 (36.3)	54/113 (47.8)		0.70 (0.49-1.00)
ECOG score				
0	92/311 (29.6)	64/158 (40.5)	+ + +	0.67 (0.48-0.92)
1	74/172 (43.0)	44/83 (53.0)		0.81 (0.56-1.19)
Race			i l	
Asian	15/45 (33.3)	4/18 (22.2)	····	1.42 (0.46-4.33)
White	137/407 (33.7)	99/214 (46.3)		0.68 (0.52-0.88)
Other	9/17 (52.9)	2/5 (40.0)	· · · · · · · · · · · · · · · · · · ·	1.26 (0.23-6.83)
Geographic region				
Asia	13/40 (32.5)	4/16 (25.0)	· · · · · ·	1.31 (0.42-4.06)
Europe and Australia	123/347 (35.4)	79/173 (45.7)		0.72 (0.54-0.96)
Latin America	4/6 (66.7)	1/3 (33.3)		- 2.33 (0.24-22.78)
North America	22/69 (31.9)	23/43 (53.5)		0.60 (0.33-1.12)
Other	5/22 (22.7)	1/7 (14.3)		- 2.22 (0.22-22.66)
B-B-11	1 1 1 A		1	

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.

Monaleesa2: mPFS HR 0.37 (0.23 - 0.61)

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 Al n	placebo plus nonsteroidal Al 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	a contra de la contra de		
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		4	2 10 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2
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	I I	•
Anastrozole	62	36	0.515 (0.301-0.88
Letrozole	264	126 🛏	0.547 (0.410-0.72
Measurable disease		1	
Yes	267	132 🛏	0.517 (0.392-0.68
No	61	33	0.519 (0.267-1.00
Number of organs at baseline			10.000 (20.000)))))))))))))))
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		í	
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	Evente	-		Interaction
	N	Events		111 (00% 01)	p-value
Nature of Disease					0.009
Visceral	263	178	· · · · · · · · · · · · · · · · · · ·	0.755 (0.556, 1.026)	0.285
Bone only Other	109	62		0.596 (0.360, 0.987)	
Galei	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		0.873 (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					
3+	229	161		0.857 (0.620, 1.186)	0.436
2	119	72	· · · · · · · · · · · · · · · · · · ·	0.856 (0.531, 1.380)	
1	142	80	· • • • •	0.608 (0.388, 0.952)	
Age					
<65	271	167		0.813 (0.592, 1.118)	0.737
>=65	222	147		0.751 (0.539, 1.049)	
Race					
Caucasian	288	195	· • •	0.840 (0.629, 1.122)	0.444
Asian	148	79	·+	0.678 (0.426, 1.080)	
Progesterone Receptor Status					0.000
Negative	106	75 н	_	0.498 (0.314, 0.788)	0.033
Positive	383	236	⊢	0.886 (0.678, 1.159)	
Baseline ECOG PS					
1	197	138	• • • •	0.721 (0.507, 1.026)	0.656
0	296	176		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

ABEMACICLIB IN BONE ONLY DISEASE MONARCH 2

Subgroups Analyzed	No.					HR (95% CI)	Interaction P Value
Overall	669	F	-		р	0.553 0.449 to 0.681	
ET resistance			1				.263
Primary	169	⊢	<u> </u>			0.454 0.306 to 0.674	l I
Secondary	489	F		4		0.591 0.464 to 0.754	l I
PgR status							.583
Negative	140		<u>م ا</u>	-		0.509 0.325 to 0.797	,
Positive	510	F		ł		0.586 0.463 to 0.743	3
Metastatic site							.171
Visceral	373					0.481 0.369 to 0.627	,
Bone only	180			_		0.543 0.355 to 0.833	3
Other	113		H	-		0.837 0.501 to 1.398	3
Measurable disease			1				.474
Yes	482	⊢				0.523 0.412 to 0.664	ļ.
No	184	⊢				0.622 0.413 to 0.936	6
Age group, years							.427
< 65	424	H				0.523 0.402 to 0.681	
≥ 65	245	H				0.620 0.447 to 0.860)
Geographic region							.618
North America	178					0.486 0.325 to 0.726	3
Europe	279	H	+			0.617 0.449 to 0.848	3
Asia	212			1		0.520 0.362 to 0.747	,
Race							.322
Caucasian	373	ŀ		-		0.620 0.474 to 0.811	
Asian	214	H				0.515 0.359 to 0.740)
Other	42	⊢	P**			0.305 0.116 to 0.804	
ECOG PS							.166
0	400	\vdash	÷-1			0.489 0.373 to 0.641	
1	263	1				0.657 0.478 to 0.904	1
Menopausal status							.246
Pre- or perimenopause	114	⊢				0.415 0.246 to 0.698	3
Postmenopause	551	F				0.580 0.463 to 0.726	5
Organs involved, No.							.074
≥ 3	200		H			0.752 0.525 to 1.078	3
2	202	⊢ _				0.414 0.286 to 0.599)
1	264			4		0.539 0.383 to 0.759)
	0.00	0.20 0.40	0.60	0.80 1.0	00 1.4	40	
			-		\rightarrow		
			Favors ab	emaciclib	Favors placeb	0	
			+ fulve	estrant	+ fulvestrant		

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

			Favors	Favors	
ubaroup	No. of Patients	No. of Events	HR (95% CI)	Abemaciclib + Fulvestrant	Placebo + Fulvestrant
overall	669	338	0.757 (0.606-0.945)	-	- Turescruit
Nature of disease				T	
Visceral	373	210	0.675 (0.511-0.891)		
Bone only	180	76	0.907 (0.564-1.457)		
Other	113	52	0.928 (0.528-1.632)		
ET resistance					
Primary resistance	172	94	0.686 (0.451-1.043)		-
Secondary resistance	488	241	0.787 (0.606-1.021)		
Menonausal status	100		0.000 (0.000 1.011)		
Premenopausal or perimenopausal	114	44	0.689 (0.379-1.252)		
Postmenopausal	551	293	0.773 (0.609-0.980)	_	
Age group, years		200	0.779 (0.005 0.000)	T	
<65	424	200	0.710 (0.532-0.948)	_	
>65	245	138	0.898 (0.638-1.263)		
Geographical region					
North America	178	96	0.596 (0.393-0.901)		
Europe	279	153	0.848 (0.613-1.173)		
Asia	212	89	0.798 (0.515-1.235)		
ECOG PS					
1	264	152	0.757 (0.544-1.053)		-
0	400	184	0.750 (0.557-1.010)	i	
Organs involved. No.					
≥3	203	126	0.900 (0.628-1.289)		
2	200	101	0.609 (0.409-0.906)		
1	263	111	0.832 (0.562-1.231)		
Measurable disease					
Yes	483	255	0.734 (0.569-0.945)		
No	183	83	0.853 (0.545-1.336)		
Race					
White	373	214	0.834 (0.633-1.098)		-
Asian	214	90	0.802 (0.518-1.239)		
Other	42	12	0.264 (0.085-0.818) +		
			0.1		1 3
				HR (95% CD)	

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

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

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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). Cl = 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 CDK4/6inhibitor-based combinations in **boneonly disease** was not statistically significant BUT... longer follow-up, and more events might be needed to obtain more conclusive results

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 ?





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.

Received: 12 January 2022 Accepted: 22 February 2022 Published: 24 February 2022

The choice of cdki drug concentrations: pharmacokinetic considerations



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



DIFFERENTIATION (TRAP ASSAY)



UNDIFFERENTIATED



DIFFERENTIATED

CDKi effects on osteoclast differentiation





dollo 24M 54M

icito 3 µM

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palbooline 1. 1. M. S. M.

dicite 1.5 mm

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



В

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



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









Survival: HR (95% CI, p-value)

Overall Survival









Data Not Published . Confidential

Survival Probabilities

CDKInhibitor

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+/HER2e metastasi ossee.