Quale ormonoterapia di prima linea nelle donne anziane?

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Carcinoma mammario nella donna anziana

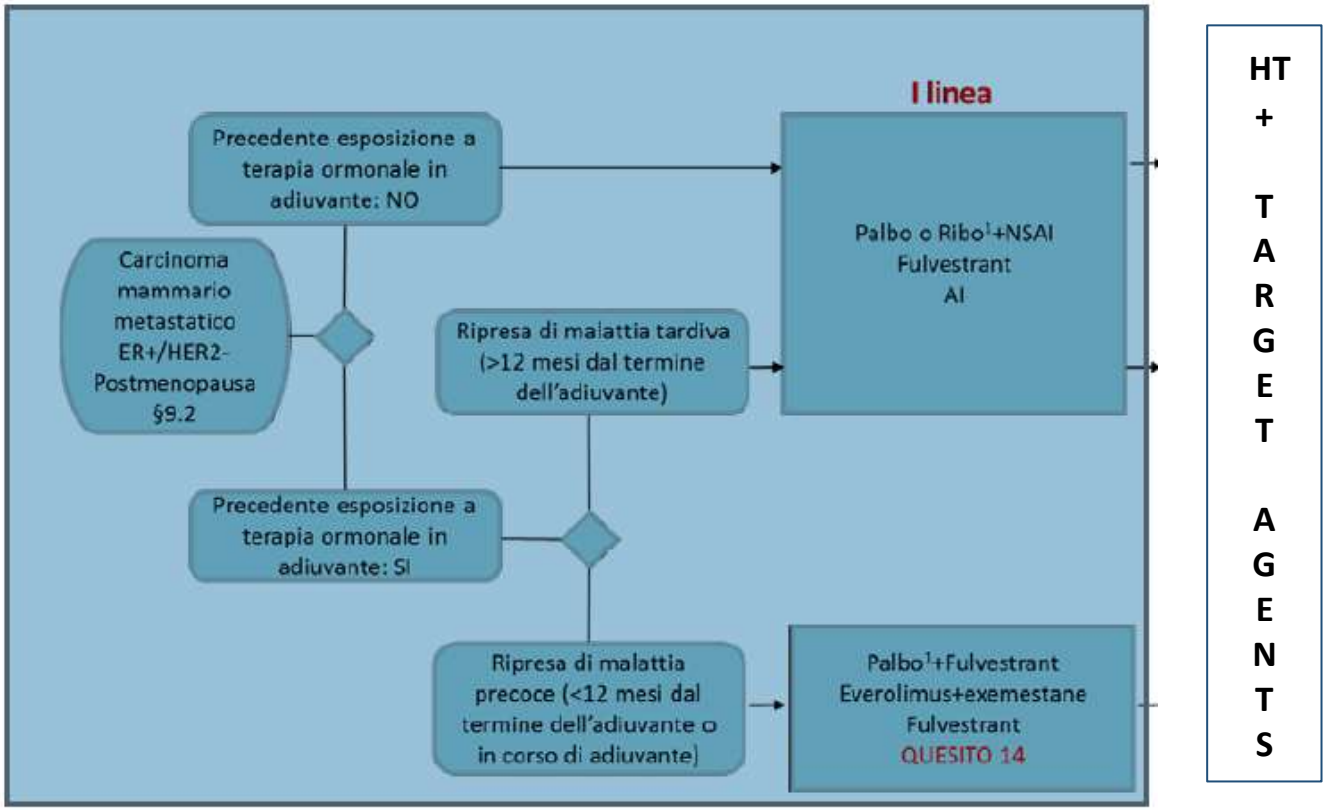
10.5. Terapia sistemica della malattia metastatica

Ormonoterapia

2018 GUIDELINES

La terapia ormonale dovrebbe rappresentare il trattamento di scelta per le pazienti anziane affette da carcinoma mammario metastatico ER-positivo HER2-negativo in assenza di malattia rapidamente evolutiva. La scelta del trattamento segue gli stessi criteri utilizzati nella terapia della paziente più giovane in stato menopausale.

CARCINOMA MAMMARIO METASTATICO ER+/HER2-: terapia ormonale in postmenopausa



Topics

Focus on CDK4/6 inhibitors

- Which data do we have in older patients?
- How can we apply these data to the general older population ?

Transversal data

	Palbociclib	Ribociclib	Abemaciclib
Efficacy	**AGE INDEPENDENT**		
(PFS)	PALOMA 1-2-3[1] 304 pts 65+	MONALEESA 2[2] MONALEESA 3[3] 376 pts 65+	MONARCH 2[4] MONARCH 3[5] 467 pts 65+
	U.S.FDA pooled analysis (registration studies CDK4/6 inh+AI)[6] 884 pts 65+		
PK data	**NO NEED OF DOSE ADJUSTMENT BASED ON AGE**		

[1] Rugo et al. EJC 2018; [2] Sonke et al. Breast Cancer Res Treat 2017; [3]Slamon et al. J Clin Oncol 2018; [4]Goetz et al. J Clin Oncol 2017; [5] Sledge et al. J Clin Oncol 2017; [6]Singh et al. SABCS 2017

Palbociclib

Rugo et al. EJC 2018

AE, n (%)	Palbociclib + endocrine therapy[a]					
	Age <65 y (n = 568)		Age 65–74 y (n = 221)		Age ≥75 y (n = 83)	
	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3
Any AE[c]	561 (98.8)	441 (77.6)	219 (99.1)	172 (77.8)	83 (100)	69 (83.1)
Neutropenia[d]	459 (80.8)	373 (65.7)	170 (76.9)	140 (63.4)	75 (90.4)	61 (73.5)
Leucopenia[d]	272 (47.9)	174 (30.6)	95 (43.0)	52 (23.5)	46 (55.4)	28 (33.7)
Anaemia[d]	140 (24.6)	24 (4.2)	66 (29.9)	10 (4.5)	36 (43.4)	7 (8.4)
Thrombocytopenia[d]	100 (17.6)	11 (1.9)	47 (21.3)	4 (1.8)	21 (25.3)	2 (2.4)
Infections[d]	296 (52.1)	22 (3.9)	138 (62.4)	20 (9.1)	50 (60.2)	6 (7.2)
Fatigue	225 (39.6)	9 (1.6)	91 (41.2)	7 (3.2)	31 (37.3)	6 (7.2)
Nausea	198 (34.9)	1 (0.18)	78 (35.3)	2 (0.90)	25 (30.1)	0
Alopecia	131 (23.1)	0	70 (31.7)	0	26 (31.3)	0
Cough	112 (19.7)	0	68 (30.8)	0	10 (12.0)	0
Stomatitis[d]	170 (29.9)	5 (0.88)	67 (30.3)	1 (0.45)	16 (19.3)	0
Diarrhoea	137 (24.1)	4 (0.70)	63 (28.5)	5 (2.3)	19 (22.9)	0
Arthralgia	156 (27.5)	6 (1.1)	53 (24.0)	1 (0.45)	18 (21.7)	0
Constipation	102 (18.0)	1 (0.18)	49 (22.2)	1 (0.45)	16 (19.3)	0
Back pain	108 (19.0)	6 (1.1)	45 (20.4)	3 (1.4)	18 (21.7)	4 (4.8)
Headache	142 (25.0)	3 (0.53)	45 (20.4)	0	11 (13.3)	0
Decreased appetite	69 (12.1)	4 (0.70)	44 (19.9)	1 (0.45)	23 (27.7)	2 (2.4)
Vomiting	91 (16.0)	4 (0.70)	44 (19.9)	0	16 (19.3)	0
Hot flush	114 (20.1)	0	43 (19.5)	0	10 (12.0)	0
Dyspnoea	71 (12.5)	7 (1.2)	41 (18.6)	2 (0.90)	15 (18.1)	1 (1.2)
Rash[d]	97 (17.1)	3 (0.53)	40 (18.1)	4 (1.8)	9 (10.8)	0
Pain in extremity	74 (13.0)	2 (0.35)	36 (16.3)	0	14 (16.9)	0
Dizziness	75 (13.2)	3 (0.53)	34 (15.4)	0	8 (9.6)	0
Nasopharyngitis	80 (14.1)	0	32 (14.5)	0	7 (8.4)	0
Asthenia	67 (11.8)	9 (1.6)	31 (14.0)	4 (1.8)	15 (18.1)	0
Urinary tract infection	42 (7.4)	1 (0.18)	31 (14.0)	3 (1.4)	15 (18.1)	1 (1.2)
Insomnia	87 (15.3)	1 (0.18)	20 (9.0)	0	5 (6.0)	0

Febrile neutropenia
1.2% vs 0.9% vs 2.4%

Grade 2?

N.B. grade 2 toxicities could impact on functional status and quality of life of elderly patients

Adverse events (≥ 15% of patients in any arm) regardless of relationship to study drugs in patients aged ≥ 65 and < 65 years

Adverse event, *n* (%)	Age ≥ 65 years (*n* = 294)				Age < 65 years (*n* = 370)			
	Ribociclib + letrozole (*n* = 150)		Placebo + letrozole (*n* = 144[a])		Ribociclib + letrozole (*n* = 184)		Placebo + letrozole (*n* = 186[a])	
Grade	All-grade	Grade 3/4	All-grade	Grade 3/4	All-grade	Grade 3/4	All-grade	Grade 3/4
Total	148 (99)	130 (87)	139 (97)	56 (39)	181 (98)	141 (77)	181 (97)	52 (28)
Neutropenia[b]	111 (74)	90 (60)	7 (5)	0	137 (75)	108 (59)	10 (5)	3 (2)
Nausea	80 (53)	4 (3)	42 (29)	1 (1)	92 (50)	4 (2)	52 (28)	1 (1)
Diarrhea	61 (41)	3 (2)	37 (26)	1 (1)	56 (30)	1 (1)	36 (19)	2 (1)
Fatigue	55 (37)	3 (2)	35 (24)	2 (1)	67 (36)	5 (3)	64 (34)	1 (1)
Vomiting	53 (35)	6 (4)	27 (19)	1 (1)	45 (25)	6 (3)	24 (13)	2 (1)
Alopecia	49 (33)	0	25 (17)	0	62 (34)	0	26 (14)	0
Leukopenia[c]	46 (31)	31 (21)	5 (4)	1 (1)	64 (35)	39 (21)	8 (4)	1 (1)
Anemia[d]	39 (26)	2 (1)	9 (6)	2 (1)	24 (13)	2 (1)	6 (3)	2 (1)
Constipation	38 (25)	2 (1)	23 (16)	0	45 (25)	2 (1)	40 (22)	0
Arthralgia	37 (25)	1 (1)	40 (28)	2 (1)	54 (29)	2 (1)	55 (30)	1 (1)
Decreased appetite	34 (23)	4 (3)	25 (17)	0	28 (15)	1 (1)	25 (13)	1 (1)
Cough	29 (19)	0	28 (19)	0	36 (20)	0	31 (17)	0
Peripheral edema	29 (19)	0	17 (12)	0	22 (12)	0	17 (9)	0
Hypertension	28 (19)	23 (15)	28 (19)	25 (17)	20 (11)	10 (5)	21 (11)	11 (6)
Rash[e]	28 (19)	1 (1)	12 (8)	0	39 (21)	2 (1)	15 (8)	0
UTI[f]	28 (19)	2 (1)	15 (10)	0	21 (11)	0	26 (14)	0
Headache	27 (18)	1 (1)	21 (15)	0	47 (26)	0	42 (23)	1 (1)
Liver enzyme elevation[g]	26 (17)	14 (9)	9 (6)	3 (2)	34 (19)	18 (10)	9 (5)	5 (3)
ALT increased	24 (16)	14 (9)	6 (4)	0	28 (15)	17 (9)	7 (4)	4 (2)
AST increased	22 (15)	6 (4)	7 (5)	3 (2)	28 (15)	13 (7)	5 (3)	1 (1)
Asthenia	25 (17)	2 (1)	21 (15)	2 (1)	18 (10)	1 (1)	17 (9)	0
Back pain	23 (15)	2 (1)	30 (21)	1 (1)	43 (23)	5 (3)	28 (15)	0
Hot flush	22 (15)	1 (1)	27 (19)	0	48 (26)	0	51 (27)	0

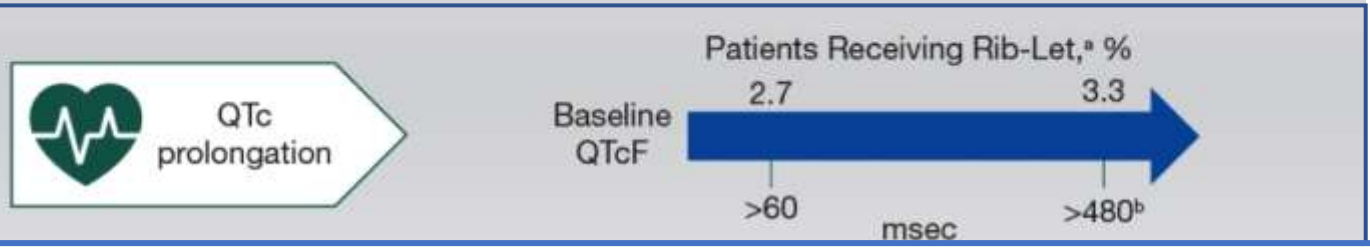
Grade 2?

Ribociclib Sonke et al. Breast Cancer Res Treat 2017

The incidence of both liver enzyme elevations and QT prolongation was similar across subgroups

Ribociclib: transaminitis and QTc prolongation

No ≠ in incidence <65 vs ≥65



L'analisi dei dati preclinici e clinici di ribociclib ha dimostrato che ribociclib prolunga l'intervallo QT in modo concentrazione-dipendente. Inoltre, sulla base della correlazione tra l'esposizione a ribociclib e il ΔQTcF e dell'esperienza clinica ottenuta dagli studi CLEE011A2301 (MONALEESA-2), CLEE011E2301 (MONALEESA-7) e CLEE011F2301 (MONALEESA-3) risulta che la riduzione della dose di ribociclib è una strategia efficace per la gestione della terapia nelle pazienti che manifestano prolungamento del QTcF.
La informiamo pertanto che, in via conservativa, al fine di ridurre il rischio di prolungamento successivo del QTcF nelle pazienti che hanno presentato un primo QTcF compreso tra 481-500 msec, il dosaggio di ribociclib dovrebbe essere ridotto di 1 livello alla prima evidenza di QTcF ≥ 481 msec.

Sotalol (antiarrhytmics, beta blockers), Ibutilide (antiarrhytmics, parenteral, Dofetilide (antiarrhytmics, oral)

Treatment exposure by age

	Palbo[1]	Ribo[2*]	Abema
Rx discontinuation due to AEs	≥75 6% 65-74 5.4% <65 1.6%	65+ 9% <65 7%	-
	[3] ≥70 17%, ≥65 16%, <65 8%		
Relative DI	AGE INDEPENDENT		
	Paloma 1 65+ 99.4% <65 97.1% Paloma 2 65+ 97% <65 98.2% Paloma 3 65+ 97.3% <65 95.6%	65+ 86% <65 90%	

DI, dose intensity

[1] Rugo et al. EJC 2018; [2] Sonke et al. Breast Cancer Res Treat 2017; [3] Singh et al. SABCS 2017,
* data on CompLEEment-1 not reported due a short median exposure to ribociclib of 1.6 mos

Endocrine therapy + CDK4/6 inhibitors

- The efficacy of the combination is age independent
- Preliminary safety data on palbociclib and ribociclib are reassuring, but more data are warranted in a less selected elderly population (ie. possible drug interactions, reduced compliance, etc)
- Limited data in patients 75+ and unfit patients
- Need to increase the relevance of data in older patients

FACILE: FeAsibility of first-line riboCIclib in oLdEr patients with advanced breast cancer

- Phase II, multicenter (20 italian centers), single arm trial

N= 194 patients; study duration= 36 months

- **Patient population**: men and women aged ≥70 years, with HR+, HER2 negative ABC who have not received any prior systemic treatment for advanced disease (1° line).

- **Primary objective**: to assess the feasibility of first line ribociclib in combination with a non steroidal aromatase inhibitor in elderly patients with HR+/HER2 neg ABC

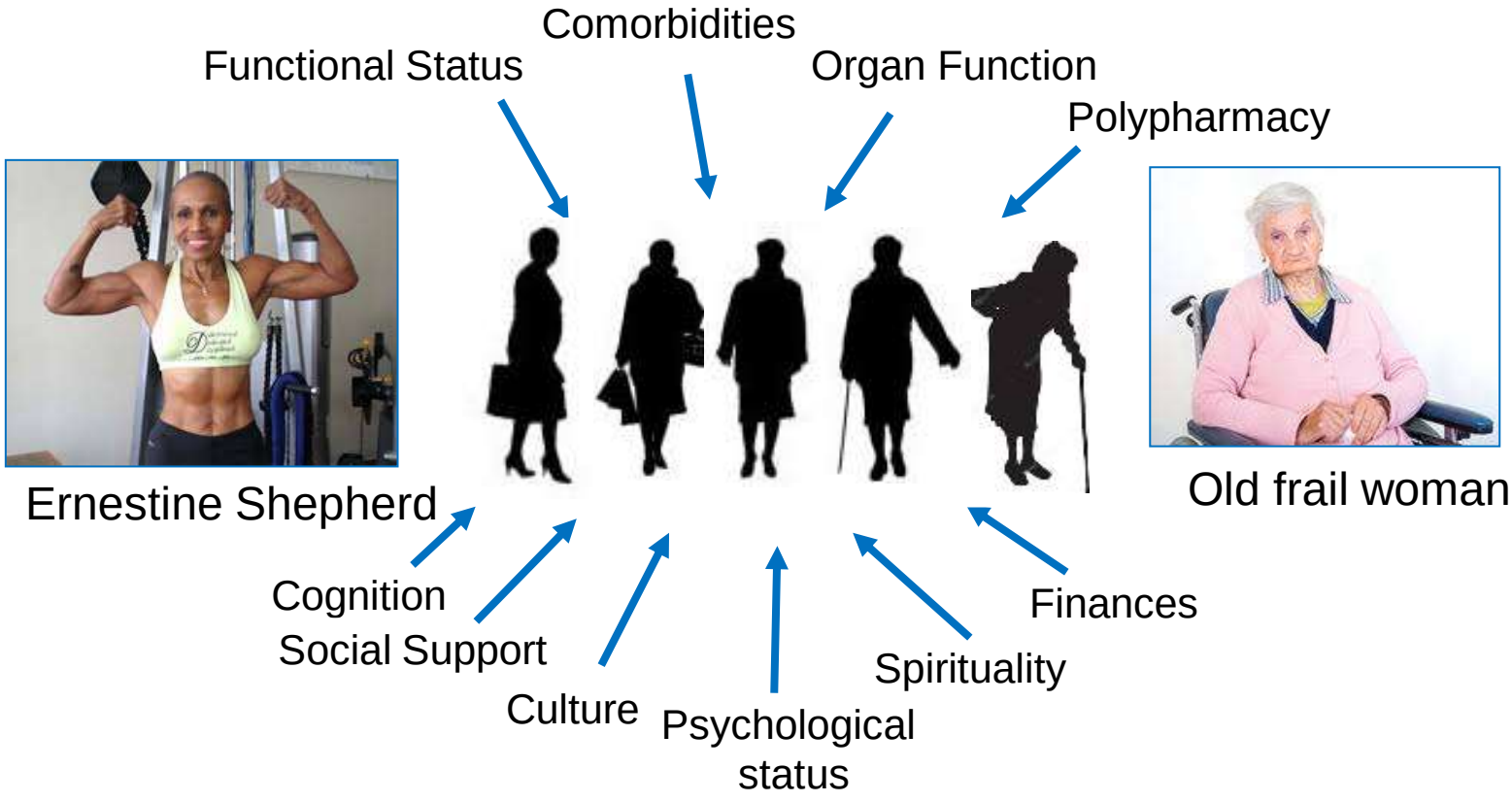
- The **treatment feasibility** will be evaluated as the proportion of patients not having experienced disease progression (PD), still on treatment with ribociclib plus NSAI 6 months after the first drug administration

- **Geriatric evaluation** will be performed before study enrolment:
  - G8 questionnaire (G8)
  - Activity of Daily Living (ADL); Instrumental ADL (IADL)
  - Cumulative Illness Rating Scale (CIRS-G)
  - Classification as fit, vulnerable or frail using the Balducci criteria

HR+, homone receptor positive;
ABC, advanced breast cancer

What to do waiting for older patients-focused data?

Heterogeneity of the older population



Clinical case

12/2015 lumpectomy + axillary lymph nodes dissection: infiltrating ductal carcinoma pT1c (1,7 cm)pN1a (1 ln) G2, ER80%, PgR50%, Ki67 20%, HER2-
→ Non steroidal aromatase inhibitor (AI)+ radiotherapy

1/2019 the patient reported bone pain; bone scan and CT scan revealed several lesions on spine and long bones (osteoblastic) and minimal liver involvement (3 lesions max size 1,5 cm)
Liver biopsy confirmed metastases consistent with original breast cancer and HER2-negative HR positive disease
Started therapy with Zometa; pain was well controlled by pain killers

Therapeutic options

- Endocrine therapy alone
- Endocrine therapy + targeted agent

➢ **Fulvestrant + CDK 4/6 inhibitor**

Different pt's related scenarios

75 y.o. patient	75 y.o. patient	85 y.o. patient
Limited but not worrisome safety data in 75+ Evaluate possible substitution of carbamazepine (strong CYP3A inducer should be avoided with CDK 4/6 inhibitors use). If possible … **Fulvestrant + CDK 4/6 inhibitor**	Multimorbid pt & Polypharmacy → not represented in clinical trials No life-threatening comorbidities CGA (targeted interventions?) If presence of caregiver and easy access to the hospital **Fulvestrant + CDK 4/6 inhibitor** Close monitoring and proactive management of side effects	Not represented in clinical trials Life expectancy ≈ 8 years CGA (important to define the physiological functional reserve) If presence of caregiver and easy access to the hospital and substitution of carbamazepine **Fulvestrant + CDK 4/6 inhibitor might be an option** Close monitoring and proactive management of side effects
ECOG PS 0	ECOG PS 1	ECOG PS 0
Active, taking care of her house	Can make light housework	Active, taking care of her house

Quale ormonoterapia di prima linea nelle donne anziane?

Conclusions

- First-line endocrine therapy + CDK 4/6 inhibitors is a standard of care in patients with ER+HER2 metastatic breast cancer
- First-line endocrine therapy + CDK 4/6 inhibitors is a standard of care also in older FIT patients
- Waiting for *ad hoc* data in a less selected patients' population, in the absence of life threatening AEs, the combination can be considered also in unfit (exclude frail) patients if a close monitoring of AEs is assured

THANK YOU

FOR YOUR ATTENTION