bjclub breast Journal Club
20 - 21 APRILE 2023 ROMA
THE HIVE HOTEL

I nuovi farmaci sono un punto di svolta nella creazione di un nuovo algoritmo che vada oltre l'endocrinoresistenza – Provoker

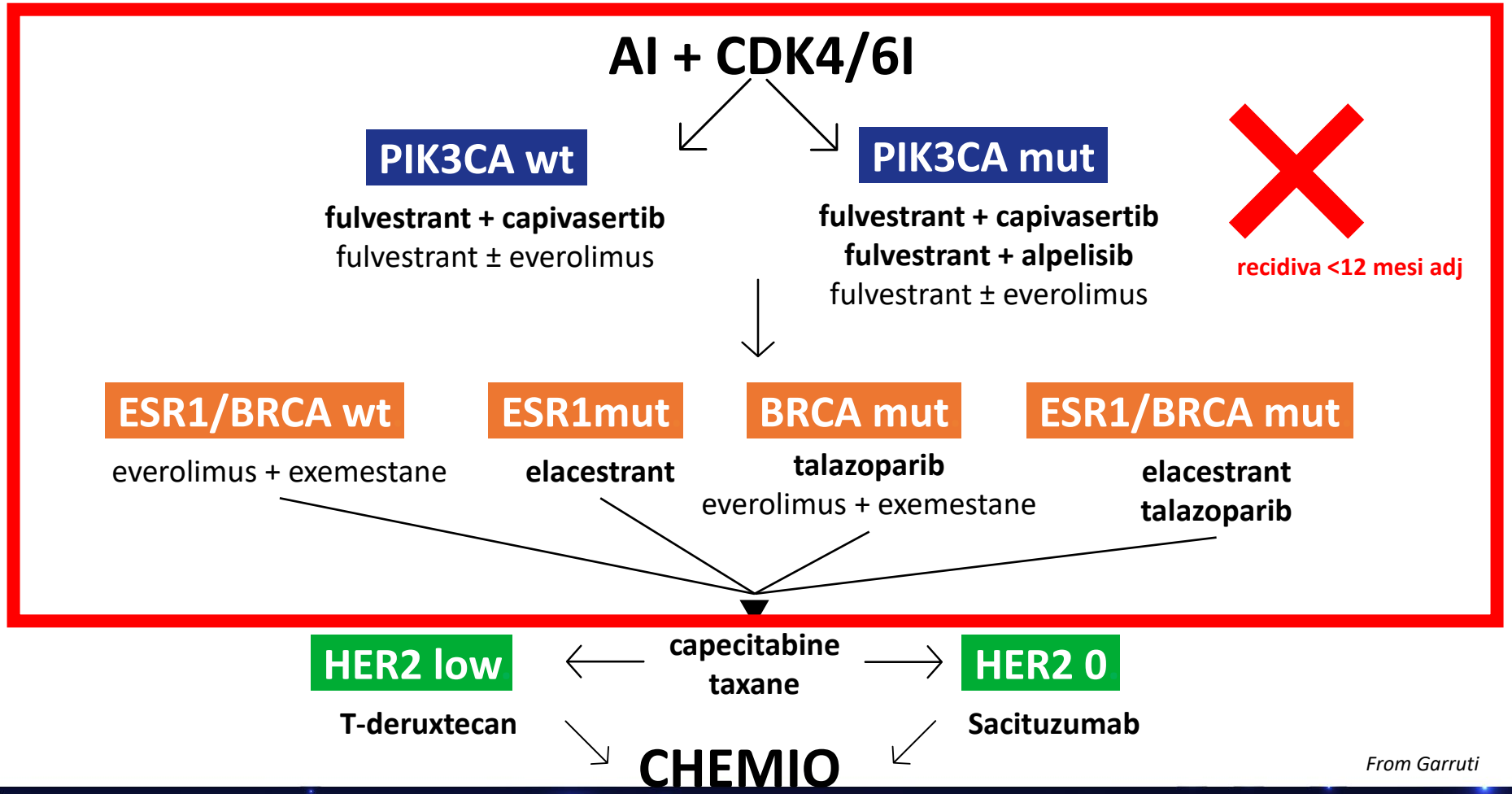
April 21st, 2023

Grazia Arpino, MD PhD
Università di Napoli Federico II

Disclosures

- Consultancy fees/honoraria: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo, Sandoz, AstraZeneca

- Support for attending medical conferences from: Novartis, Roche, Eli Lilly, Genetic, Istituto Gentili, Daiichi Sankyo



From Garruti

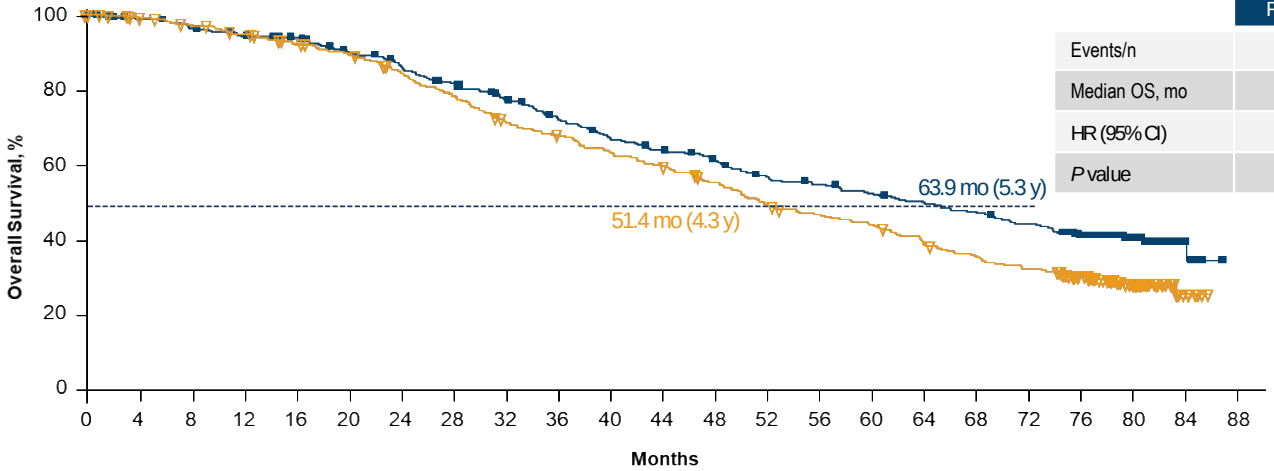
Are new HT based therapies (SERD, pi3K, Akt, PARPi, cdk4/6) GOOD ENOUGH to continue to support target therapies in endocrine resistant AND endocrine sensitive disease???

Is it time to challenge the current treatment algorithm?

From Agostinetto

Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole



	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	0.76 (0.63-0.93)	
P value	.004	

No. at risk

RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

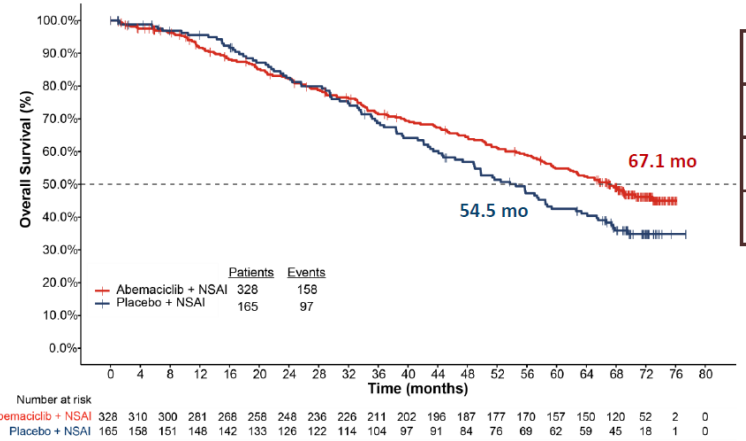
The P value of .004 crossed the prespecified boundary to claim superior efficacy

2021 ESMO congress

Gabriel N. Hortobagyi

HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

OS IA2 for the ITT Population



	abemaciclib + NSAI	placebo + NSAI
Median OS, (months)	67.1	54.5
HR (95% CI; *P* value)	0.754 (0.584-0.974) p-value 0.0301*	
Pre-planned OS IA2 Analysis Data cut: 02 Jul 2021		

*p-value did not reach threshold for statistical significance at this interim

31.5% of patients in the control arm and 10.1% in the abemaciclib arm received a subsequent CDK4 & 6 inhibitor

At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months

- ***IA2 for OS indicates a positive trend also in the subgroup of pts (~50%) with visceral disease (65.1 vs 48.8 mos)***
- ***Final OS analysis expected in 2023***

Goetz MP, ESMO 20

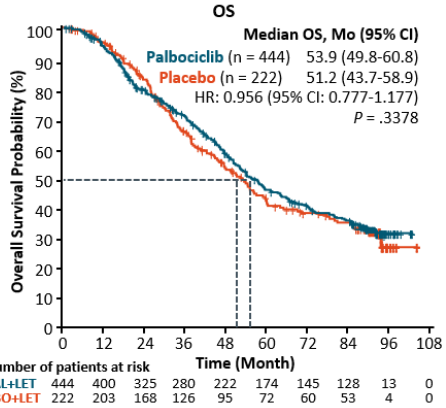
PALOMA-2: OS data with Addition of Palbociclib to First-Line Letrozole in ER+/HER2- ABC

Key Eligibility:
- ER+/HER2- ABC or mBC (postmeno women)
- No prior treatment for advanced disease

R → Palbociclib + Letrozole (N=444)

R → Placebo + Letrozole (N=222)

Statistical Assumptions for OS as Secondary Endpoint:
- Assumption for median OS of 34 to 46 months
- 390 events required to detect a hazard ratio of 0.74 or less (80% power with 1-sided α=0.025)



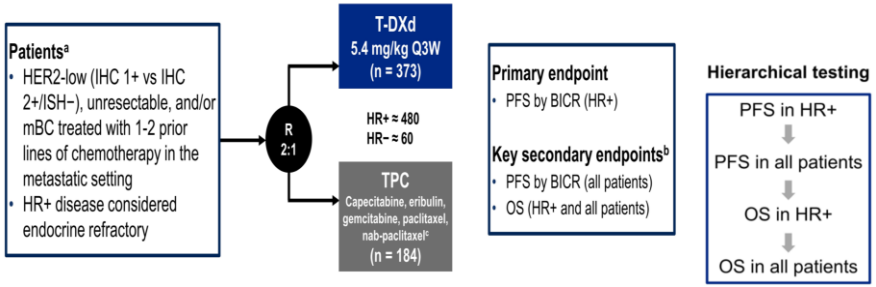
2022 ASCO ANNUAL MEETING

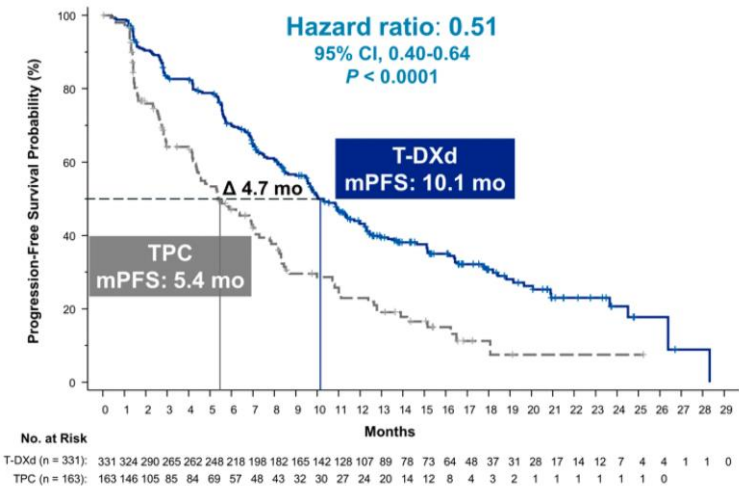
Was lack of OS benefit with palbociclib in PALOMA -2 due to trial related factors or does it represent a true difference?

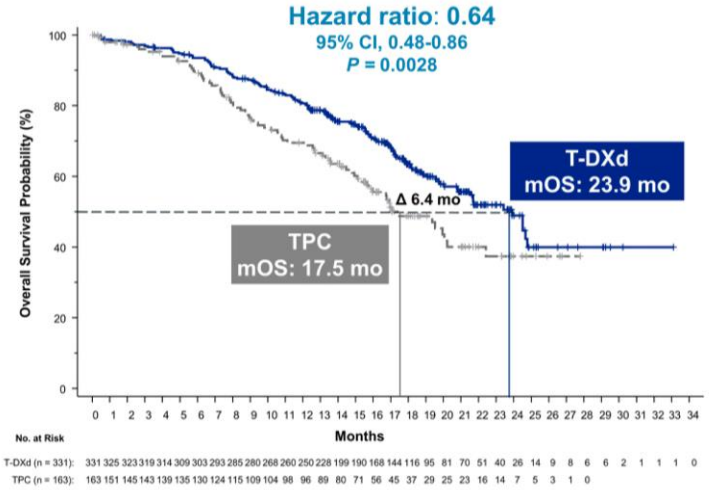
- Inadeguate power to detect an overall survival benefit?
- Missing survival data?
- Inclusion of patients with DFI <12 months?

Finn. ASCO 2022. Abstract LBA1003

DESTINY-Breast04







From Garruti

Modi S et al. NEJM 2022

TROPiCS-02

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

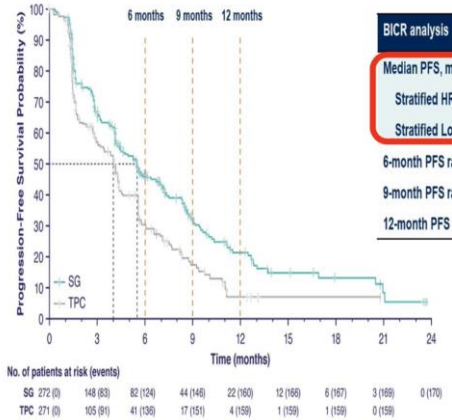
Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Endpoints

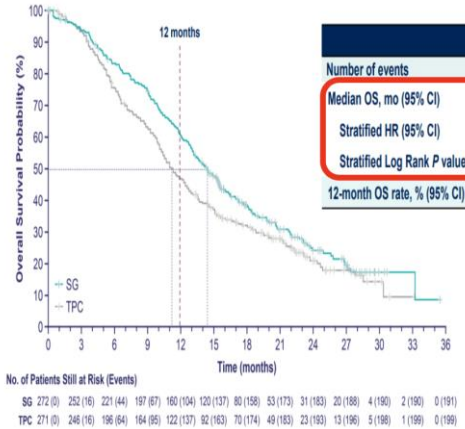
Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	0.66 (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)



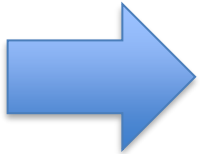
	SG (n=272)	TPC (n=271)
Number of events	191	199
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	0.79 (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)

From Garruti

Rugo H et al. ESMO 2022

Paradigm shift

We need new drugs



We HAVE <u>good</u> drugs but need to further study the BEST sequence based on:

Cost Effectiveness

Predictive Molecular Determinants

Manageable toxicity profile

Thank you for your attention!

bjclub breast Journal Club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

20 - 21 APRILE 2023 ROMA

THE HIVE HOTEL

Via Torino, 6

THE OXFORD DEBATE EDITION