Breast Cancer: Critical Review

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Disclosures

Consultant:
Novartis, EliLilly, Astra Zeneca, Tesaro

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Ministry of Health, Veneto Secretary of Health, University of Padova

Early Breast Cancer Outline

- **HR+ EBC: towards an individualized approach for adjuvant endocrine therapy**
  - Impact of clinical risk cathegories on prognosis and prediction of chemoterapy benefit by age and 21-gene recurrence score TAILORx trial
  - Phase III GIM4 trial of extendend adjuvant letrozole after sequential ET
  - Breast Cancer Index for prediction of endocrine benefit in Trans-aTTom trial

- **HER2+ EBC: stepping closer to treatment de-escalation**
  - Phase III KRISTINE trial of neoadjuvant Trastuzumab-Pertuzumab-chemotherapy vs TDM1-Pertuzumab
  - Phase II D-FHCS 14-409 study evaluating HER2 heterogeneity as a predictor of response to neoadjuvant TDM1-Pertuzumab
  - PAM50 analysis in phase III Shorther trial of 9 weeks vs 1 years of adjuvant Trastuzumab combined with CT

- **HER2- EBC: new directions for treatment selection**
  - Randomized phase II GeparOLA trial of neoadjuvant paclitaxel-olaparib vs paclitaxel-carboplatin followed by epirubicin-cyclophosphamide
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GEPs & Guidelines

	ASCO	AIOM	ESMO	NCCN
ONCOTYPE DX	MAY be offered in HR+HER2- N- EBC to guide decision for adjuvant CT SHOULD NOT be offered in HR+HER2- N+ / HER2+ / TN EBC	Multigene molecular prognosic assays for BC not in LEA not refundable	MAY be used in HR+HER2- EBC (IA)	MAY be used in HR+HER2- EBC (I N-, IIA N+)
MAMMAPRINT	MAY be used in HR+HER2- N- EBC in those with HIGH CLINICAL RISK per MINDACT categorization to inform decisions on withholding adjuvant systemic chemotherapy due to its ability to identify a good-prognosis population with potentially limited chemotherapy benefit MAY be used in HR+HER2- N+ EBC in patients (patients should be informed that a benefit of chemotherapy cannot be excluded, particularly in patients with greater than one involved lymph node) SHOULD NOT be used HR+HER2- N+ / HER2+ / TN EBC		MAY be used in HR+HER2- EBC (IA)	MAY be used in HR+HER2- EBC (I)
PAM50 ROR SCORE	MAY be used HR+HER2- N- EBC in conjunction with other clinicopathologic variables, to guide decisions about adjuvant systemic therapy SHOULD NOT be used HR+HER2- N+ / HER2+ / TN EBC		MAY be used in HR+HER2- EBC, include T size and N status in the final score (IB)	MAY be used in HR+HER2- EBC (IIA)
BREAST CANCER INDEX	MAY be offered in HR+HER2- N- EBC to guide decision for adjuvant CT SHOULD NOT be used HR+HER2- N+ / HER2+ / TN EBC		MAY be used in HR+HER2- EBC (IB)	MAY be used in HR+HER2- EBC (IIA)

OUTLINE

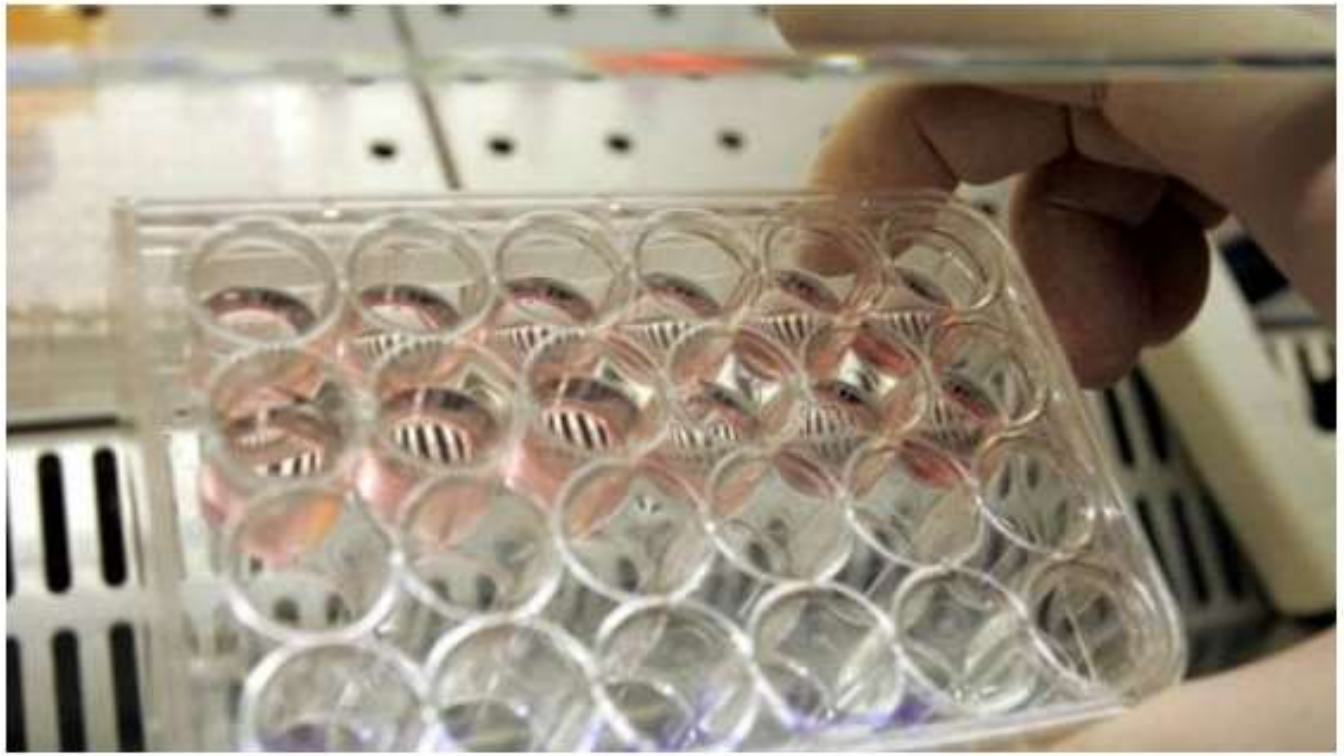
- **ASCO 2019 Data & Guidelines prior ASCO**

  ASCO data confirm level 1 evidence for GEPs in HR+/HER2-, N0, EBC

- **ASCO 2019 Data, (new?) Guidelines & Real World Practice**

How to optimize the use in clinical practice?
Patients' selection

Tumore precoce al seno, un test per evitare la chemio nel 70% dei casi

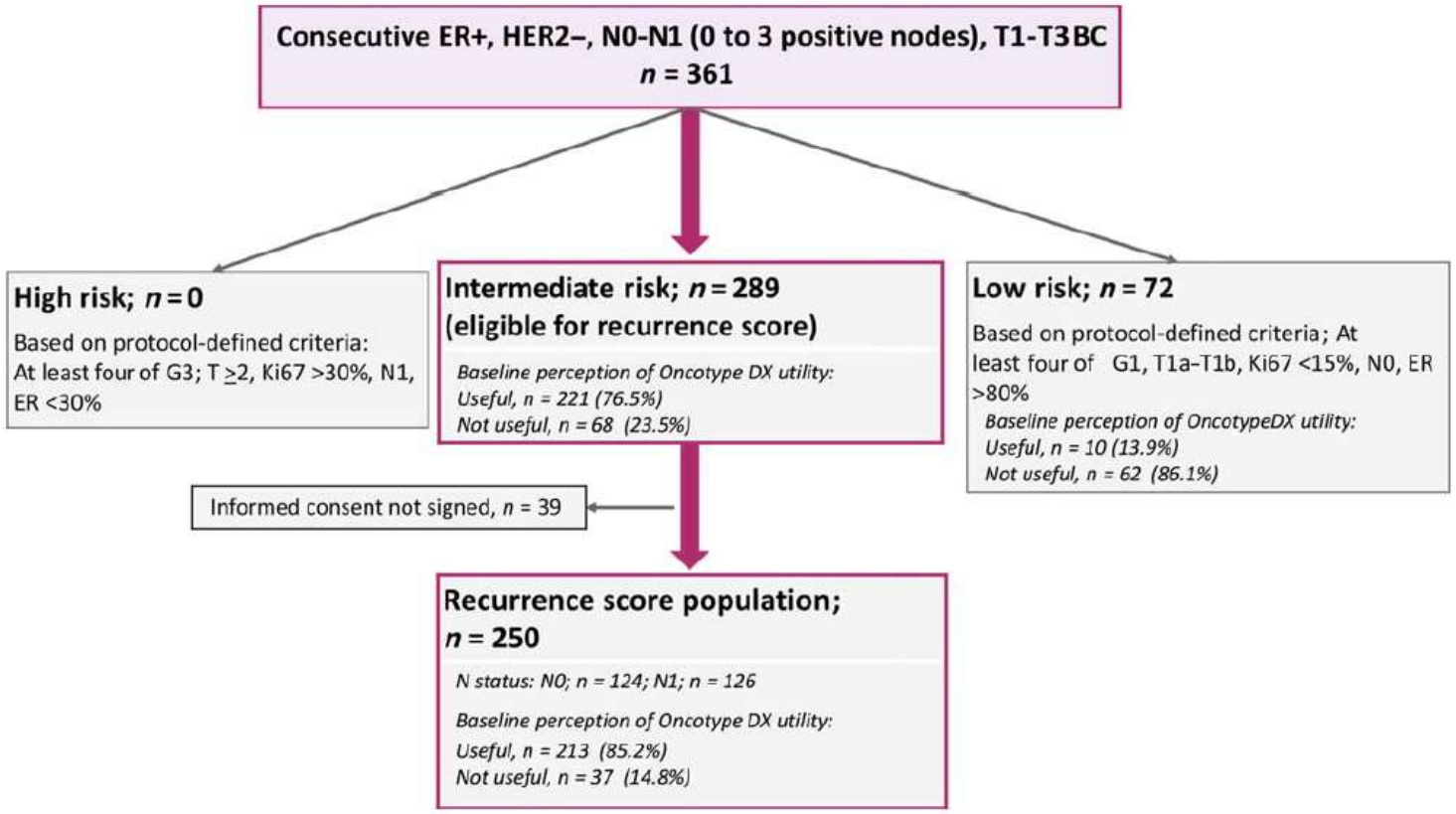


Terapia su misura per le donne con un cancro alle prime fasi grazie allo screening di 21 geni. Sette pazienti su 10 possono essere trattate solo con la terapia ormonale

Sparano JA et al. *N Engl J Med* 2015

Rete Oncologica Veneta
Ricerca, innovazione, assistenza

BREAST-DX Italy Study



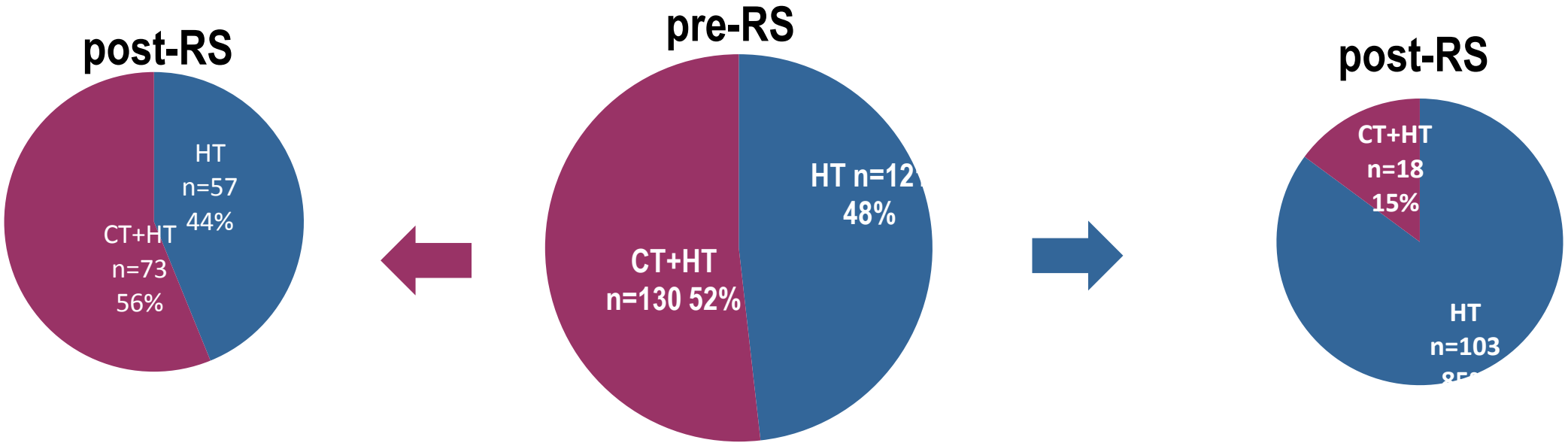
- 52% of these patients were candidate to ET alone
- 16% rate of change in treatment recommendation
- 8% net reduction in CT recommendation

Dieci MV et al, Oncologist 2017

ROXANE:

PRospective multicenter study to assess the impact of the Oncotype DX® Breast Cancer Assay on Resources Optimization and Treatment Decisions for Women with Estrogen Receptor-Positive, Node-Negative and Node-Positive Breast Carcinoma

Rationale:
the impact of RS test on adjuvant treatment decisions in a scenario where, whenever physicians are unsure about treatment recommendation, the test is available



- Overall change in treatment recommendation: **30%** (28% N0, 33% N1)
- **Net CT reduction: 16% (8% N0, 28% N1)**

Dieci MV et al, Oncologist 2019

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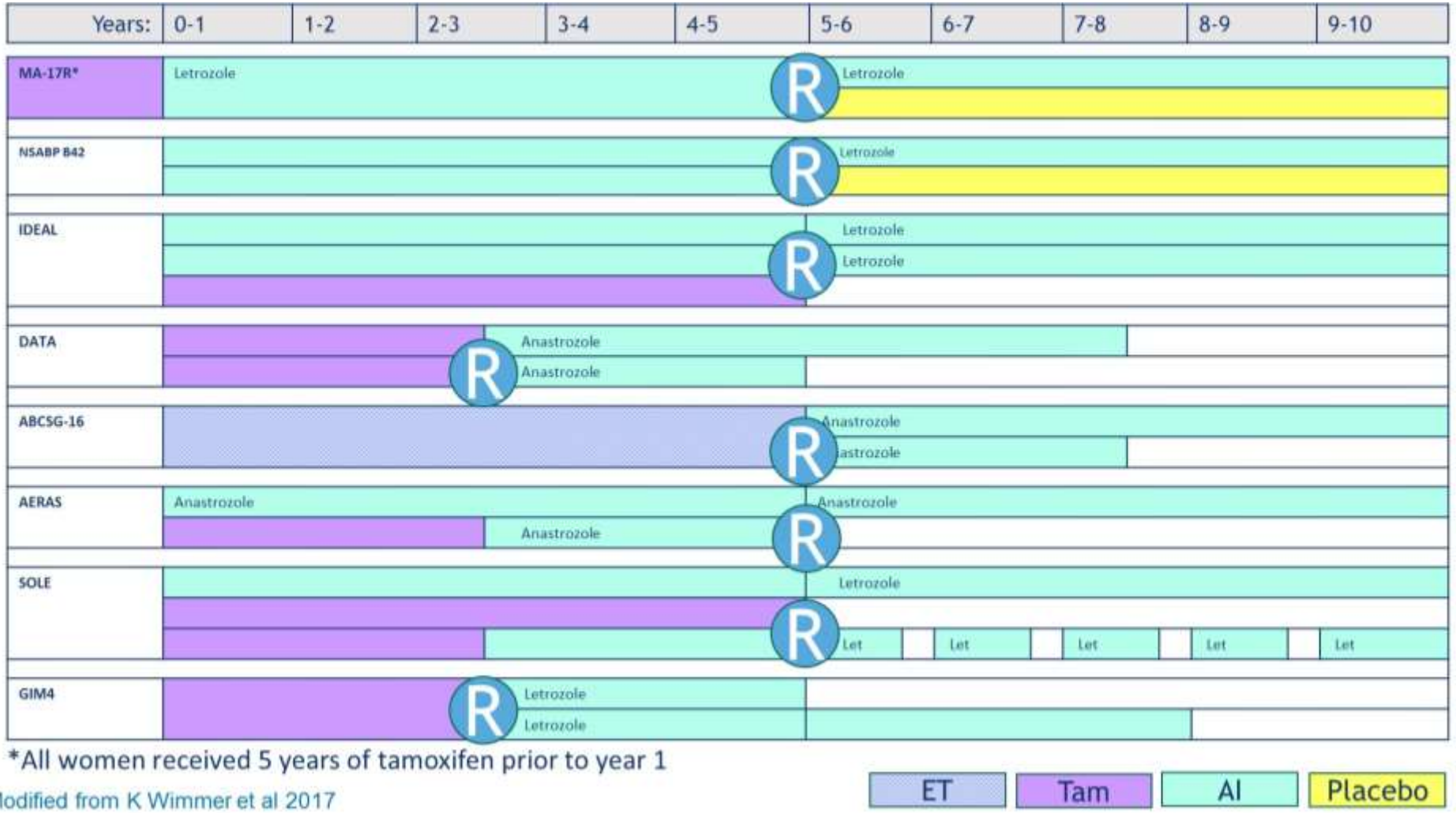
  Use of chemotherapy in HR+/HER2- EBC less common in Italy

  Net chemotherapy reduction induced by OncotypeDx modest in italian clinical practice

Extended Adjuvant Endocrine Therapy & Guidelines

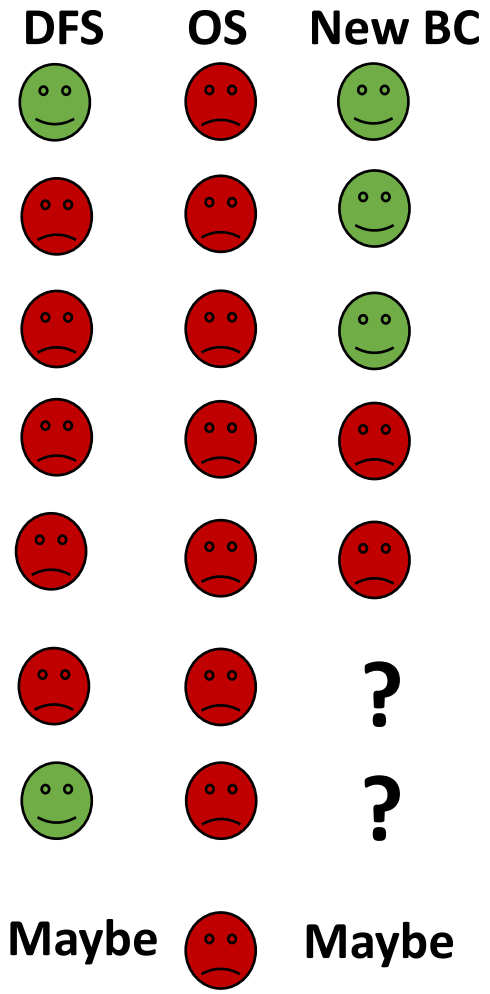
	ASCO	AIOM	ESMO	NCCN
TAM 5y + 5y	The strategies of either continuing tamoxifen for a total of 10 years or extending therapy by switching to an AI are both associated with a reduced risk of breast cancer recurrence. Based on these findings, the Expert Panel recommends either of these approaches for women who have proven tolerant of adjuvant endocrine therapy and are at substantial residual risk for late recurrence	MAY be considered in pre or peri-menopausale HR+ EBC	Extended ET should be discussed with all patients, except those with a very low risk of relapse [I, A], but the optimal duration and regimen of adjuvant ET is currently unknown. There is only a minimal benefit for the use of AIs for more than 5 years [I, C].	After 5 y of initial ET for pts who are post-menopausal at that time the panel recommends considering extended ET with AI for up to 5 y or considering tamoxifene for additional 5 y For pts who remain pre-menopausal after the initial 5 y of tamoxifene the panel recommends considering up to 10 y of tamoxifene
TAM 5y + AI 5y		MAY be considered in pts with HR+ EBC who become post-menopausal during CT or ET risk-benefit balance should be carefully considered		

Extended adjuvant endocrine therapy

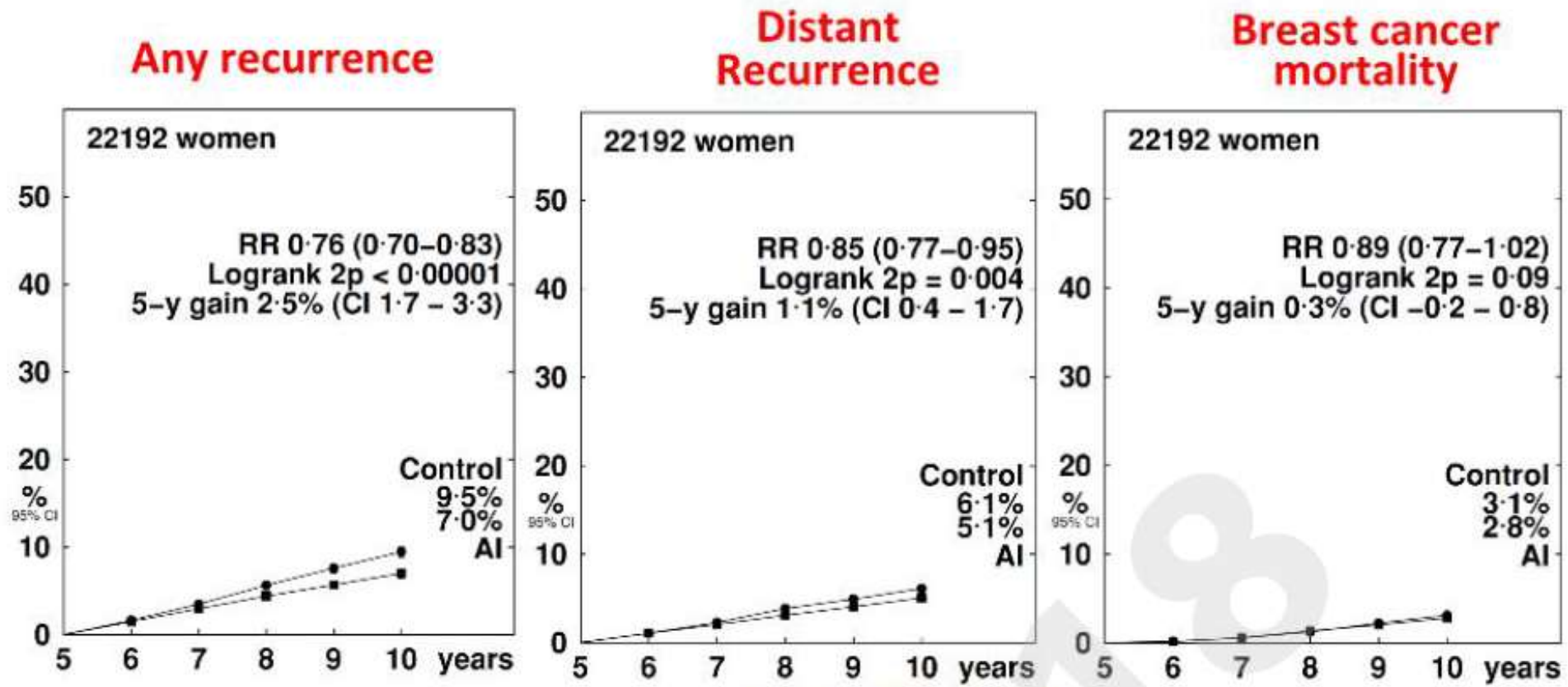


*All women received 5 years of tamoxifen prior to year 1

Modified from K Wimmer et al 2017



Combined results from all trials of Extended AI following 5-10 years of any prior endocrine therapy



EBCTCG, SABCS 2018

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  Approx 50% of relapse are loco-regional or 2nd primaries; no OS gain

  Suboptimal adherence to extended adjuvant ET (might be even worse in RW)

  Risk/benefit of extended ET may be positive for High Risk (BCI?), well motivated patients

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De-escalated adjuvant treatment for HER2+ EBC & Guidelines

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De-escalated adjuvant treatmenst for HER2+ EBC	Chemotherapy plus one year trastuzumab	Chemotherapy plus one year trastuzumab	A duration of one year remains the standard, although in highly selected low-risk patients, who receive anthracycline/taxane-based ChT, shortening trastuzumab duration to 6 months may be discussed [I, B].	Chemotherapy plus one year trastuzumab

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  Chemo-free regimen not as good as chemo plus dual antiHER2 blockade

  HER2 disease is heterogeneous

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  Biomarker-driven de-escalated treatments are lacking

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HER2 disease is heterogeneous
HRD score does not predict efficacy of PARPi or Platinum

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RW HER2+ patients are at lower risk of relapse and higher risk of toxicity (guidelines are appropriate for «trial» patients)
Biomarker-driven de-escalated treatments are lacking
HRD score not ready for clinical used; BRCA mutations (germline or somatic) only predictors of PARPi efficacy

MBC: old & new paradigms after ASCO 2019

- **ET preferred upfront treatment for HR+/HER2- disease (PEARL trial)**
- **PPFS can still be used to justify lack of OS gain in first line? (MONALEESA 7 trial)**
- Successful targeting of AKT/PI3K pathway in HR+/HER2- disease; biomarker-independent (everolimus in bolero 2); biomarker- dependent (alpelisib in solar 1); biomarker independent? (capivasertib in faktion)
- Patient selection and trial end point are crucial for IOC (Impassion 130 trial)
- ADCC is an important component of antiHER2 treatments (SOPHIA trial)
- Genotyping can select patients more likely to develop ADCC (SOPHIA trial)
- New antiHER2 TKIs are available (NELA trial, PHENIX trial); increased CNS control? Diahrrea may be an issue

Treatment Guidelines:
ET is the Treatment of Choice in HR^+ ABC

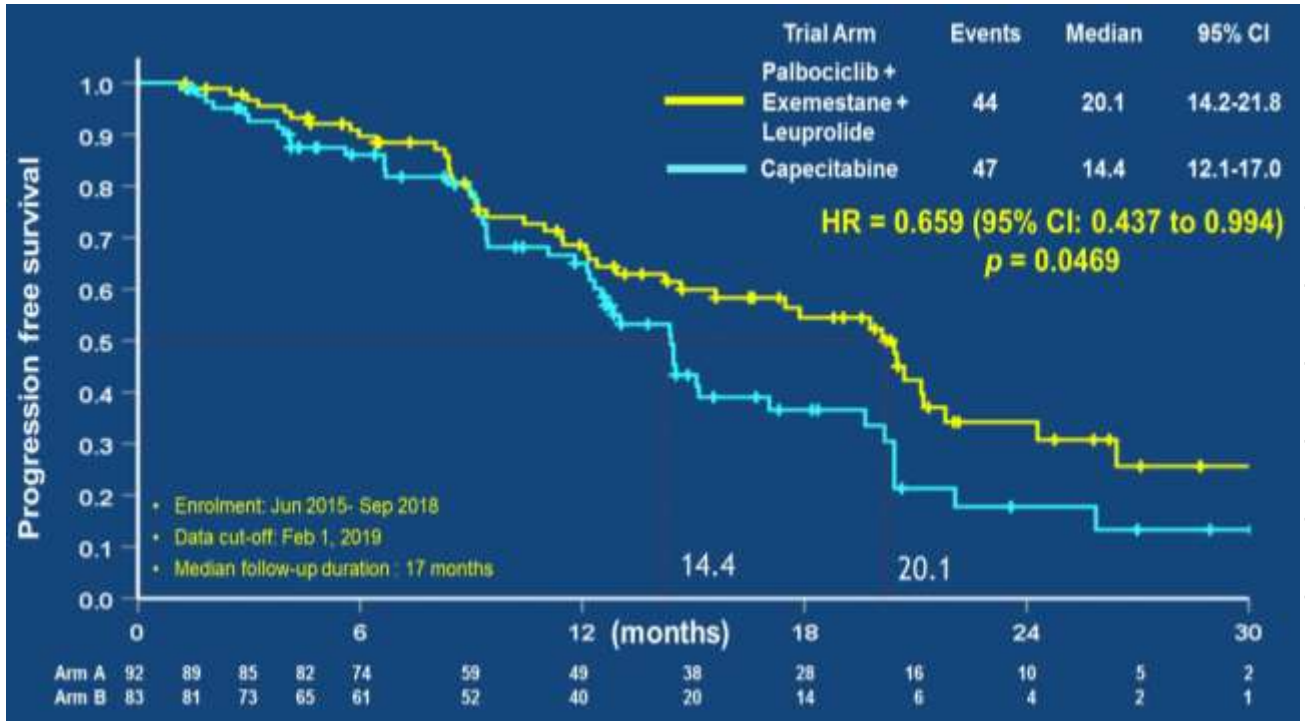
- **NCCN Guidelines:**
  Many women with hormone-responsive breast cancer benefit from sequential use of ET at disease progression. Therefore, women with breast cancers who respond to ET with either tumor shrinkage or long-term disease stabilization should receive additional ET at disease progression[1]

- **ABC1 Guidelines:**
  ET is the preferred option for HR^+ disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response[2]

- **ESMO Guidelines:**
  ET is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding endocrine responsiveness of the tumor[3]

1. NCCN Clinical Practice Guidelines: Breast Cancer; v3.2012; 2. Cardoso F, et al. *Breast*. 2012; 3. Cardoso F, et al. *Ann Oncol*. 2011.

Young PEARL Trial

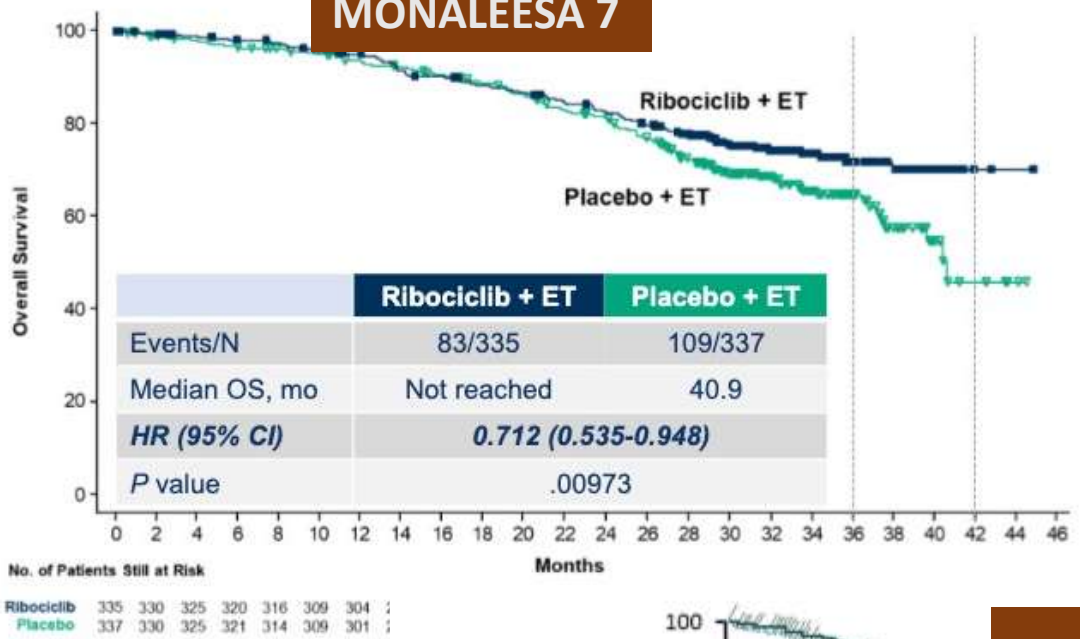


	Palbo+Exe+LHRH	capecitabine
ORR %	50.8	44.8
CBR %	80.4	69.9
Neutropenia ≥ 3/4	**75.0**	16.3
Arthralgia (all G)	**21.7**	5.8
Nausea (all G)	12.0	**34.9**
Diarrhea	12.0	**38.4**
Hand-foot	1.1	**76.7**

First evidence that Guidelines recommending ET vs Chemo are still valid with CDK 4/6i

Park YH, ASCO 2019

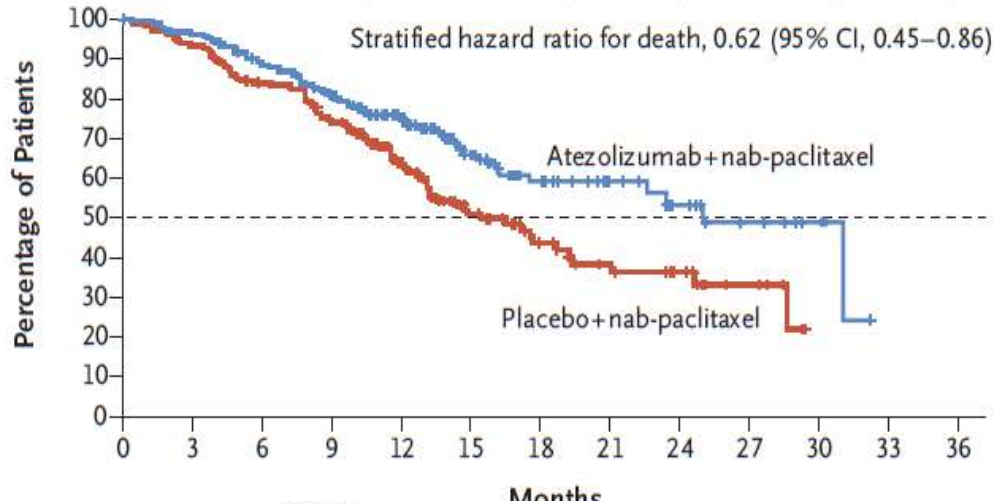
HR+/HER2- MONALEESA 7



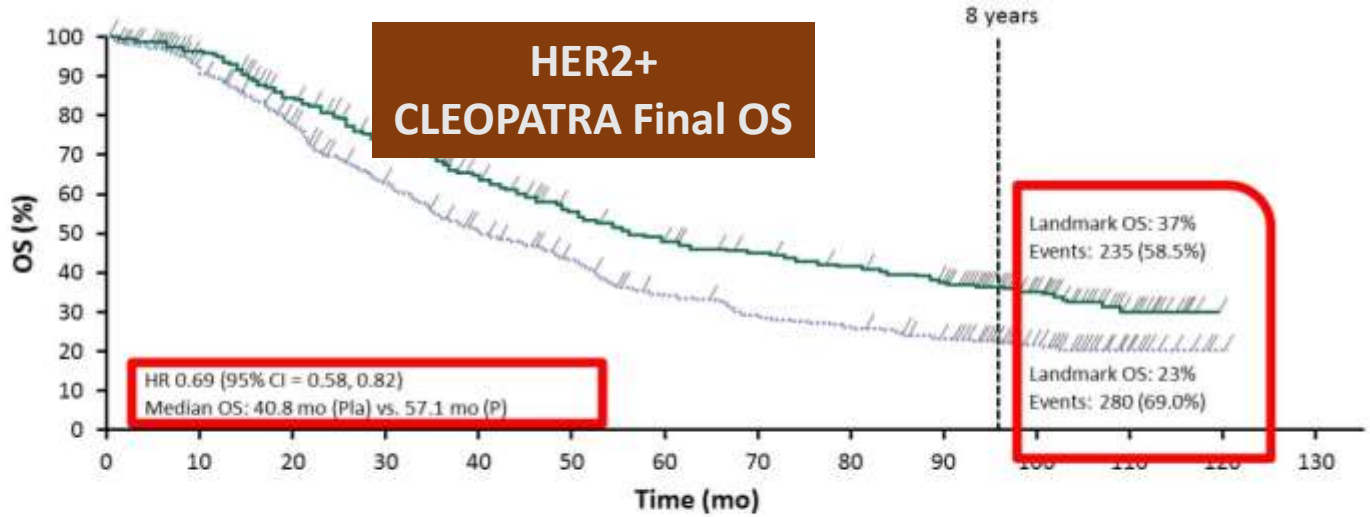
	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

TN PDL1+ IMPASSION 130

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



HER2+ CLEOPATRA Final OS



Number at risk

P + H + D	402	371	318	269	228	188	165	150	137	120	71	20	0	0
Pla + H + D	406	350	289	230	181	149	115	96	88	75	44	11	1	0

PFS is still an acceptable End Point for MBC ?
Monaleesa OS gain: chance? Drug effect? Class effect?

	Data maturity	Median FU	ET+CDK476i Median OS	ET+placebo Median OS	HR (95%CI)	p
PALOMA-3 *Turner N, NEJM 2018*	Final OS analysis, death occured in 60% of pts	44.8	34.9	28.0	**0.81 (0.645-1.03)**	0.09
MONALEESA-7 *Im SA, NEJM 2019*	Second interim, 75% of total events (189/252)	34.6	NR	40.9 (37.8-NR)	**0.71 (0.54-0.95)**	0.00973
MONALEESA-2 *Hortobagyi G, Ann Oncol 2018*	~25% of events reached (116/4009	26.4	NR	33.0 (33.0-NR)	**0.75 (0.52-1.08)**	NR