UZ LEUVEN

Trial design in older adults: European perspective

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EORTC *The future of cancer therapy*

SIOG
INTERNATIONAL SOCIETY
OF GERIATRIC ONCOLOGY

Disclosure slide

- **Institutional conflict**:
  - Consulting fees and honoraria to my institute from Abbvie, Amgen, Ariez International, AstraZeneca, Biocartes, DNA Prime, Lilly, Novartis, ORION corporation, Pfizer, PUMA Biotechnology, Roche, Sirtex, TRM Oncology, Vifor Pharma, Daiichi Sankyo.
  - Unrestricted research grant to my institute from Roche.

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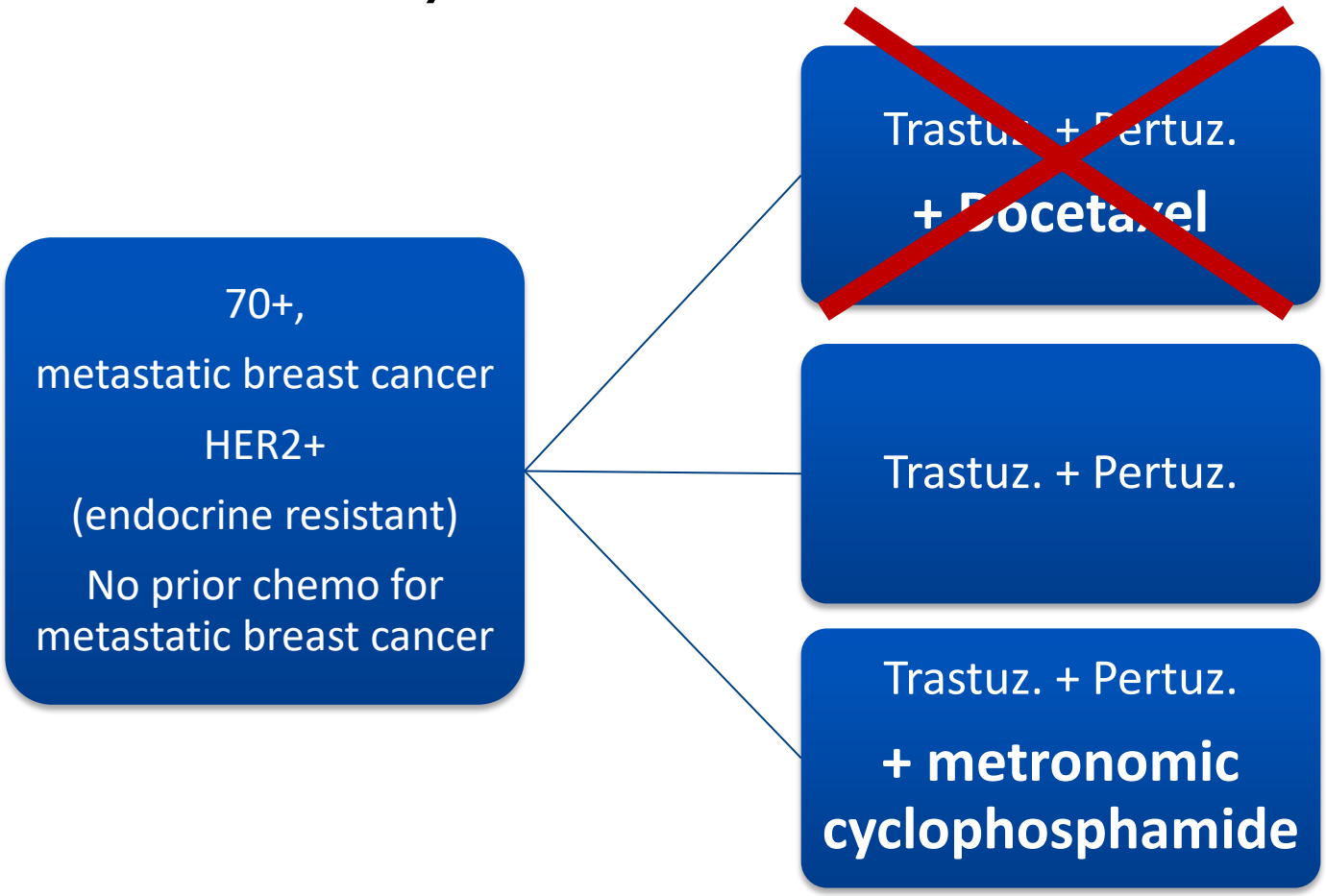
SPECIAL ARTICLE

End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article

Hans Wildiers, Murielle Mauer, Athanasios Pallis, Arti Hurria, Supriya G. Mohile, Andrea Luciani, Giuseppe Curigliano, Martine Extermann, Stuart M. Lichtman, Karla Balkman, Harvey Jay Cohen, Hyman Muss, and Ulrich Wedding

HER2+ metastatic breast cancer

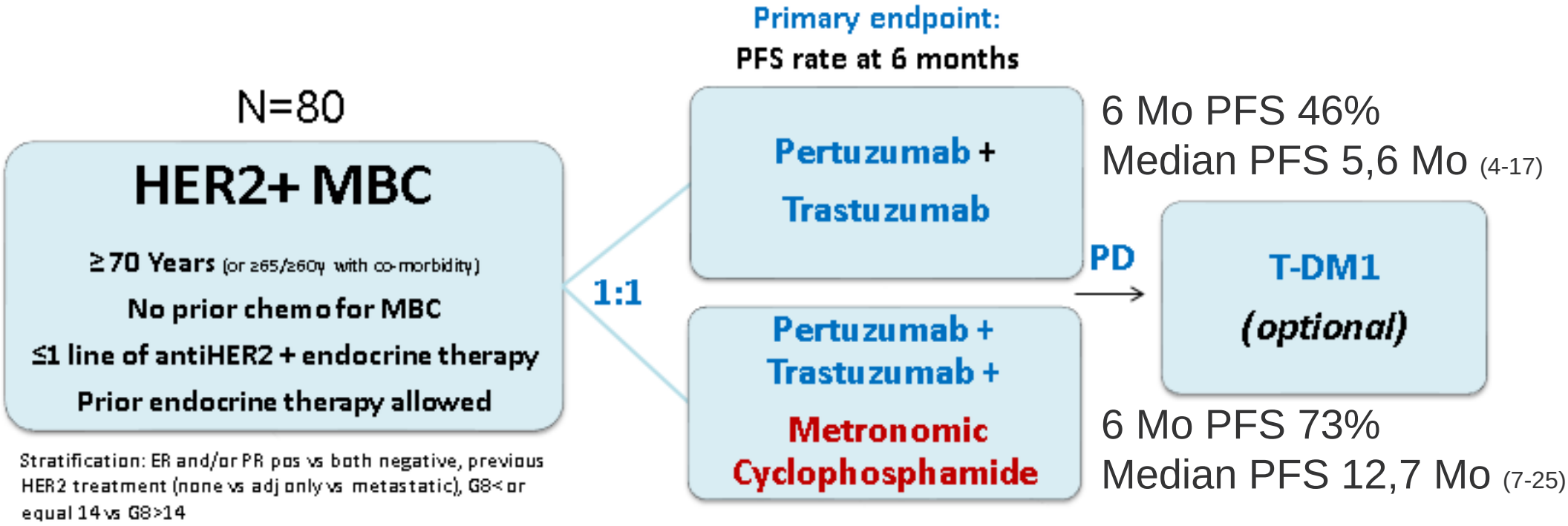
EORTC 75111; HER2+ MBC 1st line therapy



- **Standard arm?**
  Catch 22, docetaxel arm would exclude frail patients

- **Primary endpoint**?
  PFS at 6 months
  (little difference expected for QoL)

HER2+ metastatic breast cancer



Metronomic CT (chemotherapy): cyclophosphamide 50 mg/d po continuously

On progression: Option to have T-DM1 *(3.6 mg/kg iv q3w)* till progression

Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group Lancet oncol 2018

Hans Wildiers, Konstantinos Tryfonidis, Lissandra Dal Lago, Peter Vuylsteke, Giuseppe Curigliano, Simon Waters, Barbara Brouwers, Sevilay Altintas, Nathan Touati, Fatima Cardoso, Etienne Brain

	N (%)
Age (years) – Median (Range)	77 (61 - 91)
WHO PS 2-3	19 (23.8)
ER and/or PgR positive	55 (68.8)
No prior anti-HER2 therapy for MBC	72 (91.1)
Prior adjuvant endocrine therapy	24 (30.4)
Visceral involvement	74 (93.3)
G8 score at baseline G8 ≤ 14	56 (70.9)
Frail (SPPB ≤ 7)	37 (52.9)

Adjuvant CDK4/6i in Luminal breast cancer

1. Randomized phase III ; non-inferiority

70+, surgery for stage II-III EBC ER pos, HER2 neg

adjuvant chemotherapy required according to treating physician and patient

Stratification for clinical frailty: (G8 >14 vs ≤ 14) and stage

Adjuvant chemo choice:
- 4 TC + G-CSF
- 4 EC or AC + G-CSF
- 12 taxol weekly if 3-weekly regimen not desired

Adjuvant chemo -> AI

AI + CDK4/6i

Pros:
- Most clean design
- Best comparison for DDFS, and QoL

Cons:
- Large numbers and cost
- Realistic?

Coprimary endpoint:
- 3y-DDFS (90%): non-inferior
- QoL: superior

Adjuvant CDK4/6i in Luminal breast cancer

2. Randomized phase III ; superiority

70+, surgery for stage II-III EBC ER pos, HER2 neg

adjuvant chemotherapy required according to treating physician and patient

Stratification for clinical frailty: (G8 >14 vs ≤14) and stage

Adjuvant chemo choice:
- 4 TC + G-CSF
- 4 EC or AC + G-CSF
- 12 taxol weekly if 3-weekly regimen not desired

Adjuvant chemo -> AI

AI + CDK4/6i

Pros:
- Superiority design requires less numbers
- Both QoL decline and distant relapse are relevant
- Feasible numbers

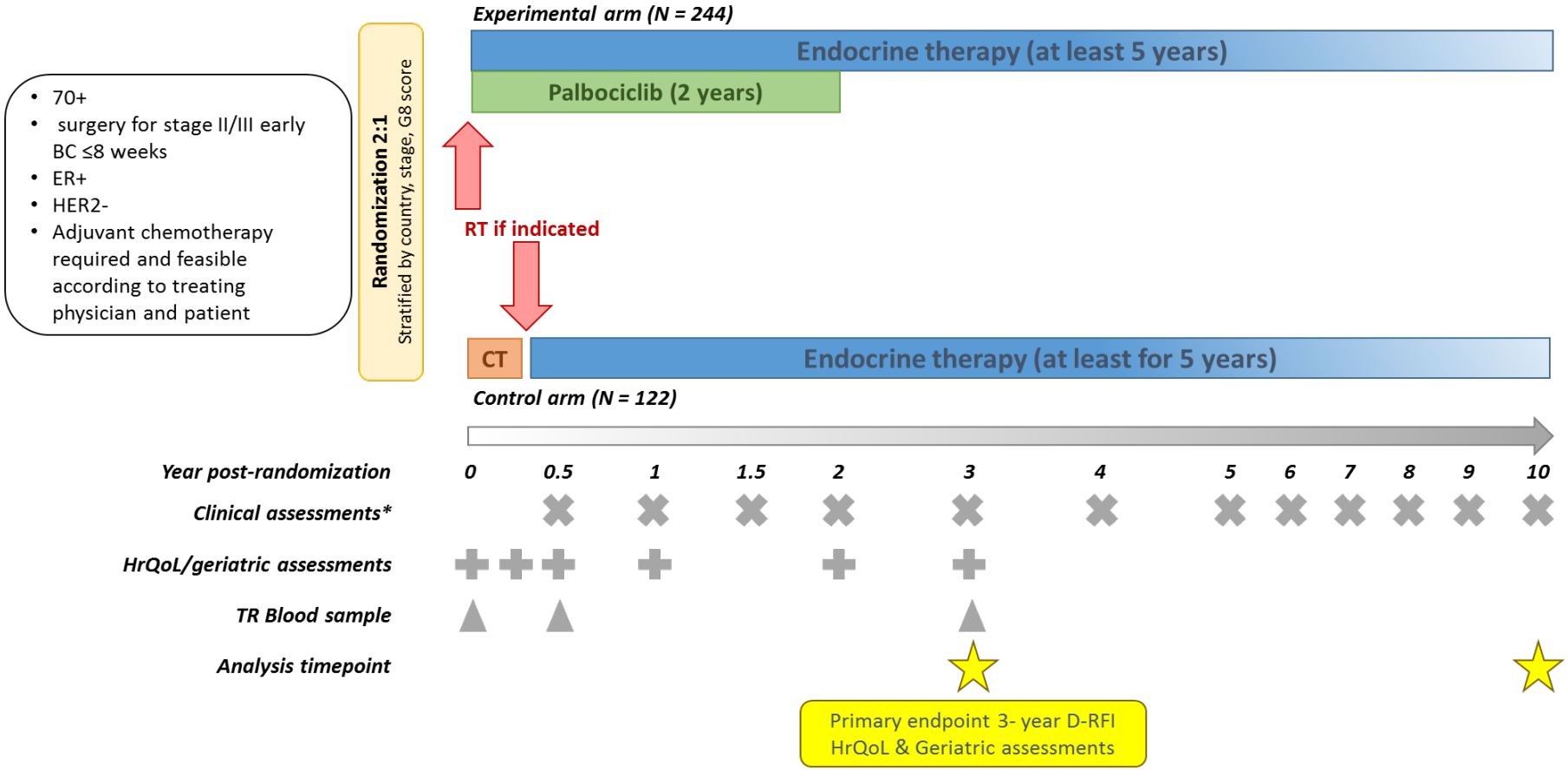
Cons:
- How acceptable is the composite? QoL decline versus death
- QoL decline much more frequent than relapse/death: relevant composite?
- Attempts to find better composite for adjuvant setting failed so far (in metastatic it is easier)

Composite endpoint: time to deterioration
- distant relapse
- death rate without relapse
- HRQOL (health related quality of life) decline

Adjuvant CDK4/6i in Luminal breast cancer

3. Randomized (2:1) non-comparative phase II study

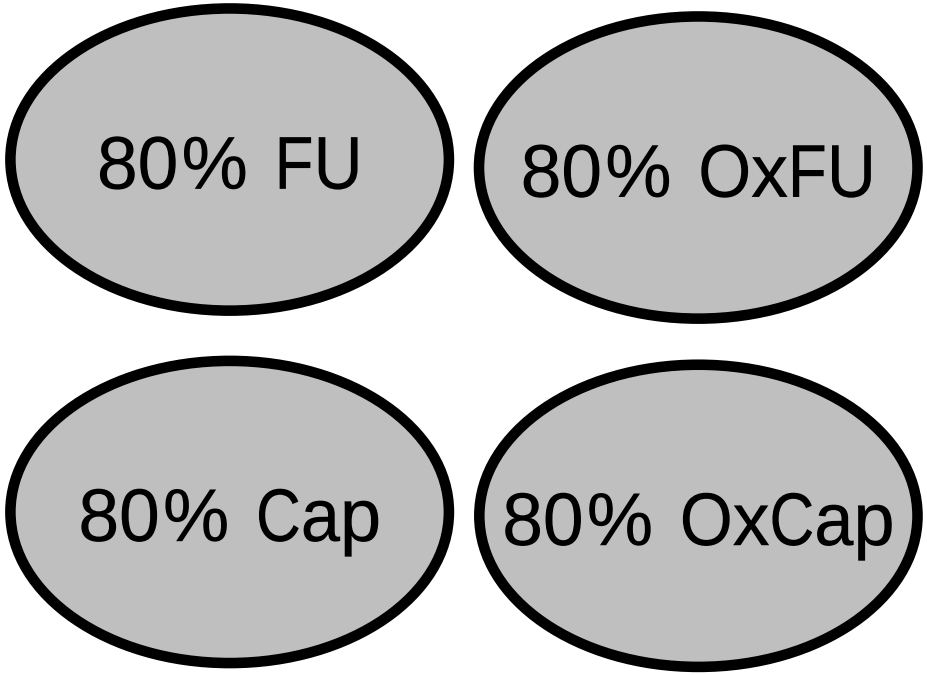
EORTC–ETF-BCG STUDY 1745 (APPALACHES): A PHASE II STUDY OF ADJUVANT PALBOCICLIB AS AN ALTERNATIVE TO CHEMOTHERAPY IN ELDERLY PATIENTS WITH HIGH-RISK ER+/HER2- EARLY BREAST CANCER



- Defined based on randomization date regardless of treatment administration, delays or interruptions.

BC = Breast cancer; CT = chemotherapy; D-RFI = Distant Relapse Free Interval; HrQoL = Health-related Quality of Life; RT = radiotherapy; TR = Translational Research

Metastatic colorectal cancer: FOCUS2



1. Does the addition of oxaliplatin improve PFS? NO

2. Does oral capecitabine improve QoL compared with IV 5FU? NO

Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial

Matthew T Seymour, Lindsay C Thompson, Harpreet S Wasan, Gary Middleton, Alison E Brewster, Stephen F Shepherd, M Sinead O'Mahony, Timothy S Maughan, Mahesh Parmar, Ruth E Langley, on behalf of the FOCUS2 Investigators and the National Cancer Research Institute Colorectal Cancer Clinical Studies Group*

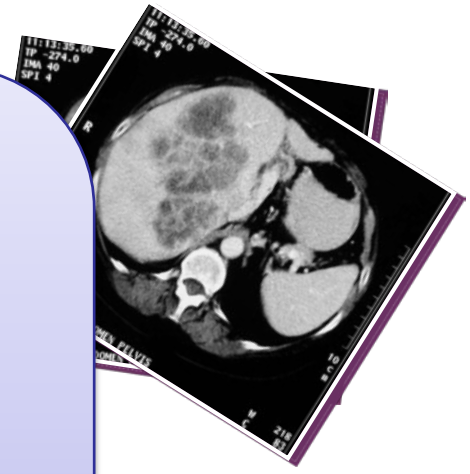
Lancet 2011, 377:1749-59

Metastatic colorectal cancer: FOCUS2

Overall Treatment Utility (OTU)

patient's view:

did it have an



OTU at 3 months
=
With the benefit of hindsight:

- am I (the patient) glad I decided to have the treatment?
- am I (the doctor) glad I decided to give the treatment?

benefit?

toxicity?

Good example of composite endpoint

Metastatic colorectal cancer: FOCUS2

after 12 weeks:

good OTU

all of:

- cli… efit'

a…

41%

an…

- no major toxicity

intermediate OTU

either

- clinician 'no benefit', but patie… d no ma…

or

- clin… but pa… appy or major toxicity

32%

poor OTU

- clinician 'no benefit'

and eith…

- pati…

or

- ma…

27%

or

- patient has died

Anticancer drugs are NOT well tolerated in all older patients with cancer

Hans Wildiers, Nienke A de Glas

Lancet Healthy Longev 2020; 1: e43–47

Panel: Reports on new anticancer drugs lack evaluation of frailty

- Many scientific publications conclude that new anticancer drugs are well tolerated by and feasible for older patients (aged 70 years or older) with cancer
- Most reports do not recognise that the older population enrolled in trials does not reflect the general older population, in which frailty is a common issue
- Incorporating measurements of frailty in clinical trials is important because these individuals have an increased risk of worse outcomes
- Tolerance of new anticancer agents should be evaluated in older frail patients before concluding that the treatment is well tolerated in all older patients