Updates on Breast Cancer in Older patients

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EORTC
The future of cancer therapy

Etienne BRAIN, MD PhD

- Receipt of grants/research supports
  - None
- Receipt of travel supports
  - Daiichi, Gilead, Novartis, Pfizer
- Receipt of honoraria
  - AstraZeneca, Daiichi, Eli Lilly, Incyte, Pfizer, Seagen, Takeda
- Receipt of consultation fees
  - Daiichi, Menarini, Pfizer, Sandoz

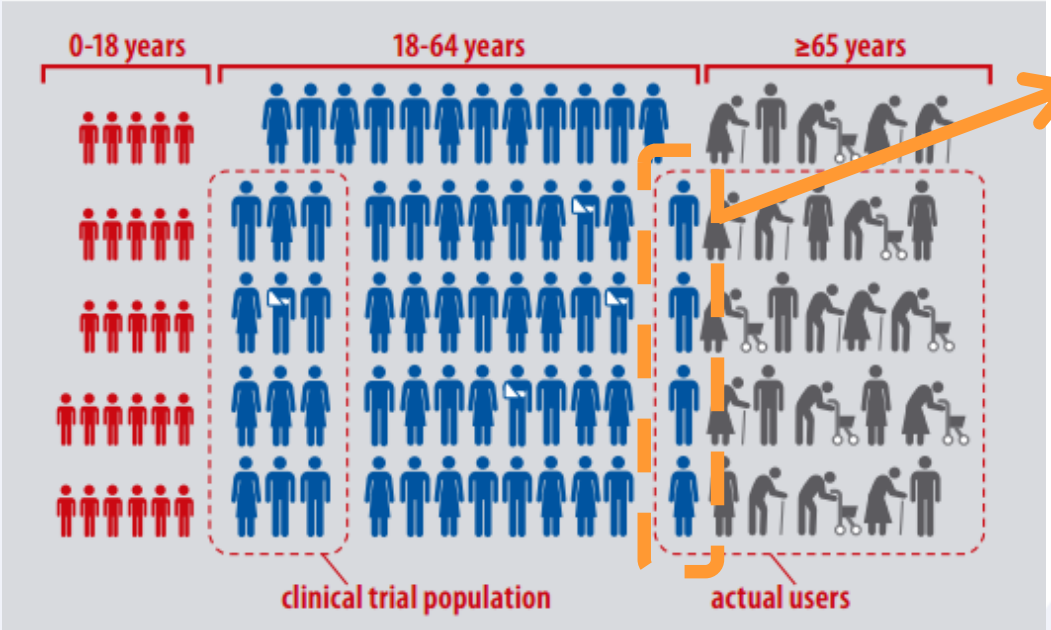
Older patients are systematically excluded from clinical trials

Study	Design	All N	65+ N	75+ N	Reported outcomes
CREATE-X	Capecitabine vs 0	887	NR	0 (0%)	DFS, OS
KATHERINE	T-DM1 vs 0	1486	126 (8.5%)	9 (0.6%)	
ASCENT	Sacituzumab govitecan vs TPC	235	49 (21%)	7 (1.5%)	PFS, OS, RR Compliance, Safety
TROPiCS-02	Sacituzumab govitecan vs TPC	272	73 (27%)	NR	PFS, OS
DESTINY Breast03	T-DXd vs TDM1	261	NR	NR	NR
DESTINY Breast04	T-DXd vs TPC	331	71 (21%)	NR	PFS (Appendix)
KEYNOTE 522	polyCT (Taxol qw + carboplatin + ACdd) ± pembrolizumab	1174 (22-80)	132 (11%)	NR	CR, PFS

Masuda NEJM 2017, von Minckwitz NEJM 2019

Kalinsky ASCO 2021, Rugo JCO 2022 & ESMO 2022, Cortez NEJM 2022, Modi NEJM 2022, Schmid NEJM 2020

Trial population versus real-life



Older ones enrolled in standard explanatory trials are highly selected:

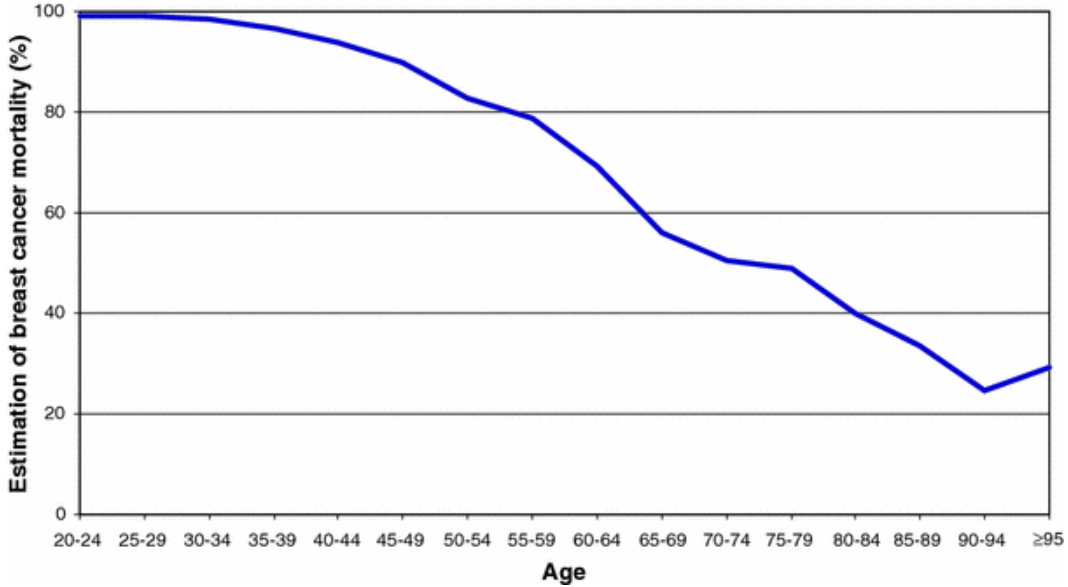
- younger
- w/ less comorbidities
- w/ less organ dysfunctions
- fitter

Competing causes for mortality

A sizeable proportion of elderly with BC die of NON CANCER-related causes

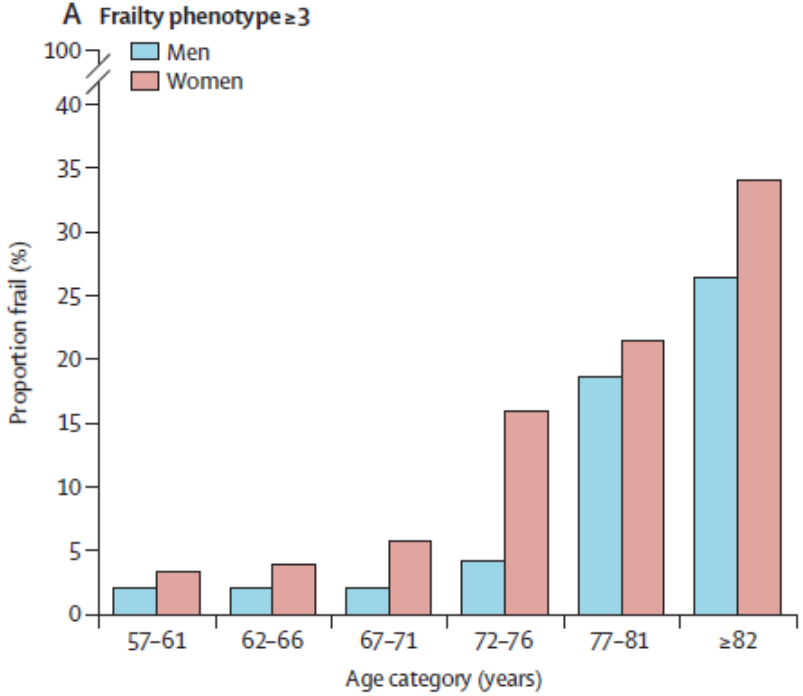
BC mortality as percentage of the total deaths

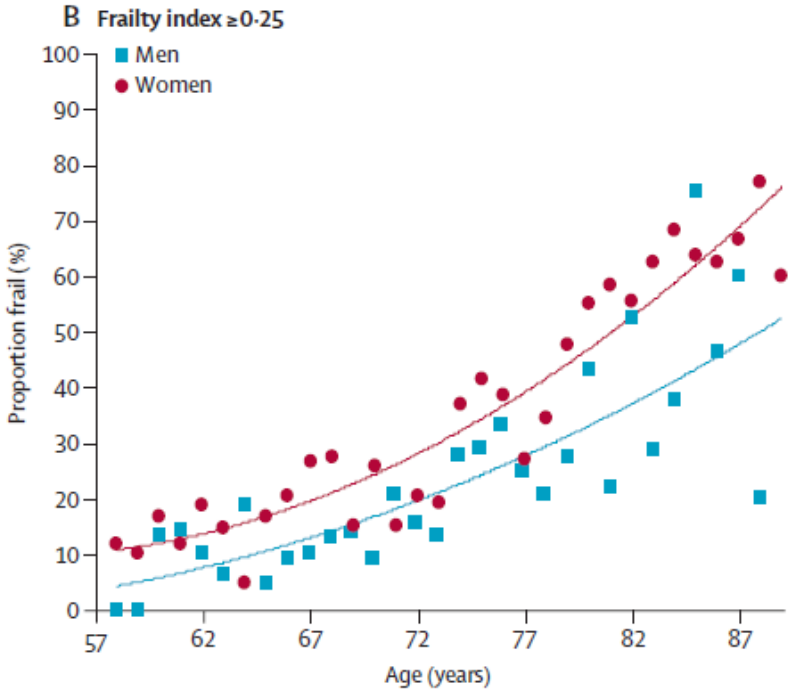
Netherlands Cancer Registry 1995-2005; 127800 patients stage 0-IV; 5y follow-up



Bastiaannet, BCRT 2010

Frailty





G8 ≤ 14: from 40% in adjuvant setting (ASTER 70s) to 70% in MBC (PALOMAGE)

O Hoogendijk Lancet 2019

Trials in older ones

Strategy adjustment question

1. Stepwise dose escalation
2. Replacement/omission of aggressive Tx
3. Better selection of candidates

Methods & solutions

1. RWD
2. Inclusiveness
3. Endpoints and PROs
4. Geriatric interventions

…optimization!

PALOMAGE study design

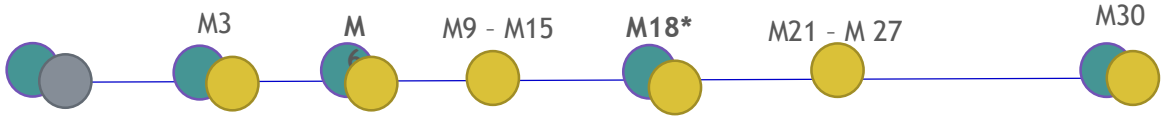
- Patients with HR+ HER2- aBC; age ≥70 yrs (**N=807**)

COHORT A (N=400)
- **ET sensitive and first line treatment for aBC**

COHORT B (N=407)
- **ET resistant and/or with prior aBC treatment**

G8: Geriatric Screening Tool[1]
G-CODE: Geriatric COre Data sEt[2]
EORTC QLQC30 & ELD14: Quality of Life
Compliance: GIRERD (Adherence self-questionnaire)
+ Questions for the investigator

** Only for Cohort A patients*



Start date: Oct. 4, 2018

Follow-up every 3 months and according to clinical practice

Primary endpoint
- Proportion of patients who permanently stopped treatment at 6 months (cohort B) and at 18 months (cohort A) for any reason (toxicity, patient's choice, progression or death)

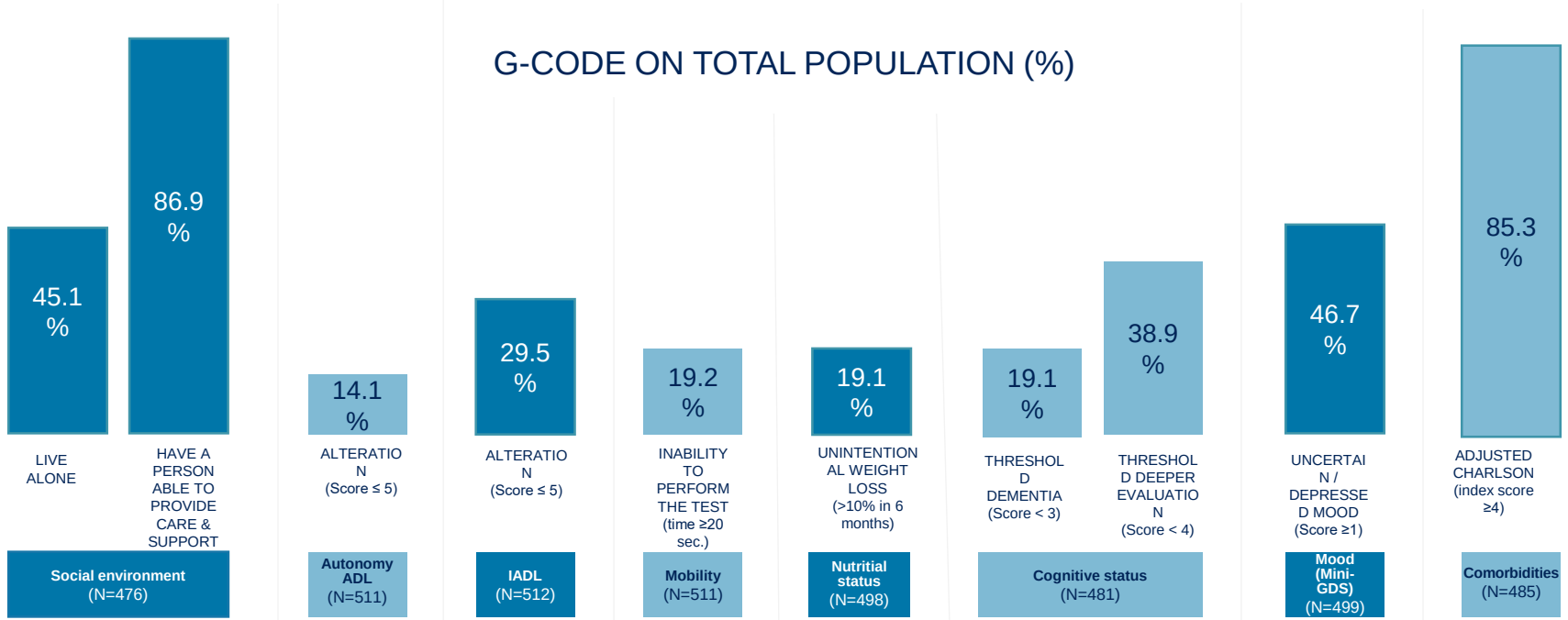
Analysis
- Baseline characteristics (total population)
- Safety evaluation (population with PAL initiation)
  - All AEs/SAEs related or not to the treatment were assessed according to NCI-CTCAE V5.0 criteria at each visit and were described by severity grade

aBC=advanced breast cancer; CTCAE=The Common Terminology Criteria for Adverse Events; EORTC QLQ-30=European Organisation for Treatment of Cancer Quality of Life Questionnaire Core 30; ET=endocrine therapy; HER2-,human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; M=months; PAL=palbociclib.

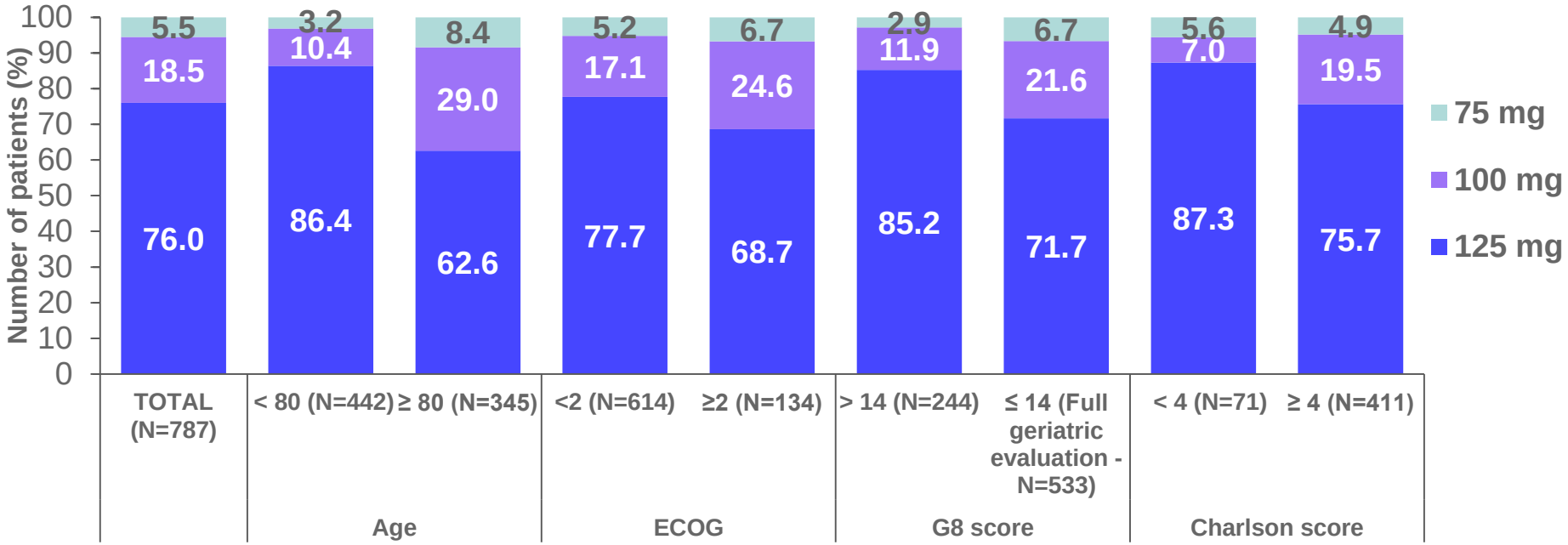
Caillet P, et al. Oral presentation at ASCO 2021

Baseline characteristics: Geriatric Assessment (GA)

- **68,3%** G8 ≤14
- **No difference in GA** between both cohorts



PALOMAGE
Palbociclib initial dose based on frailty factors



Older and frailer (according to ECOG PS, G8 or Charlson scores) patients were more often initiated at a lower dose of palbociclib than younger, less frail patients

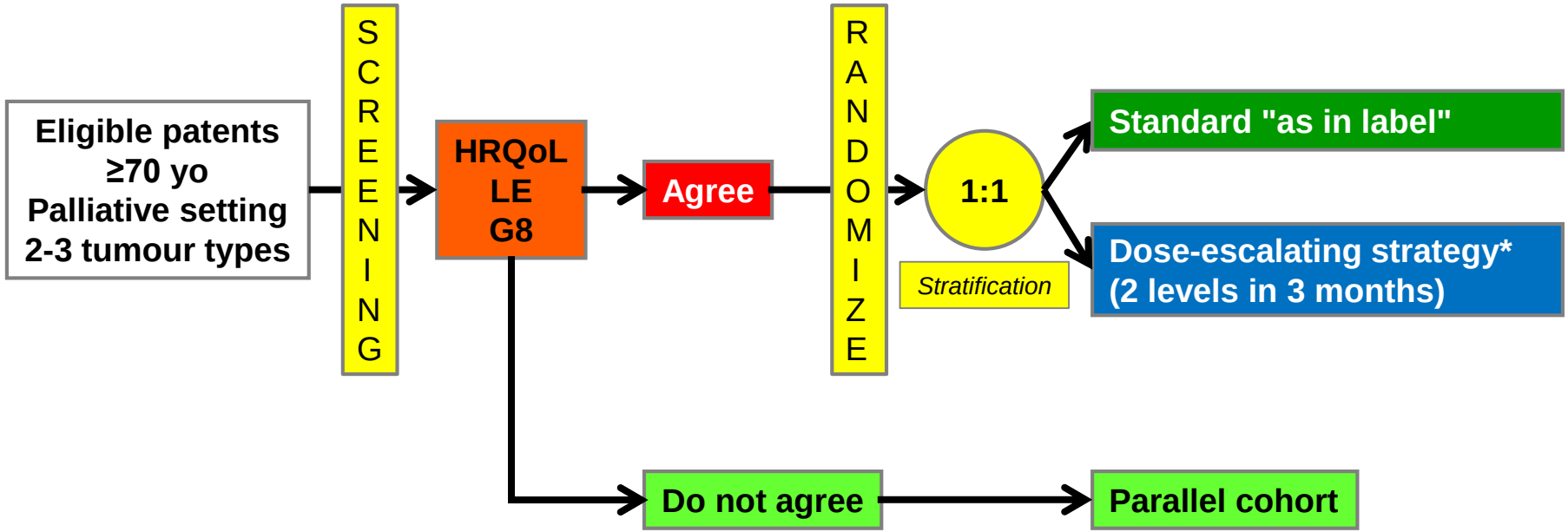
Caillet P, et al. Oral presentation at ASCO 2021.

Project: PlatefoRme EScAlade âGe cancer PRESAGE

Main hypothesis

HRQoL stepwise dose-escalating* > de-escalating strategy

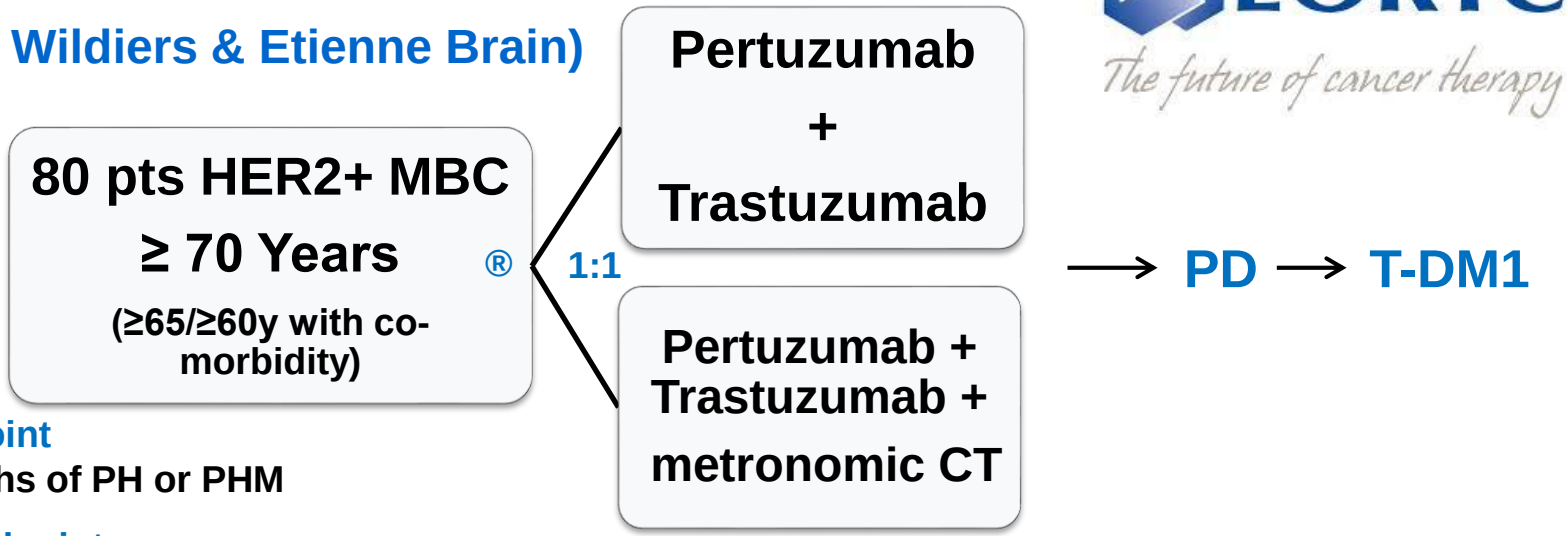
PFS stepwise dose-escalating* = de-escalating strategy



** Treatment intensity escalation (dose escalation or step up strategy)*

EORTC 75111-10114

(Co-PI Hans Wildiers & Etienne Brain)



Primary endpoint
PFS at 6 months of PH or PHM

Secondary endpoints
OS, BCSS, toxicity, RR (RECIST v1.1), HRQoL, evolution of GA during treatment

Stratification: ER/PgR, previous HER2 treatment, G8

Pertuzumab **840 mg loading dose, further 420 mg q3w iv**
Trastuzumab **8 mg/kg loading dose, further 6 mg/kg q3w iv**
Chemotherapy **Metronomic chemotherapy: cyclophosphamide 50 mg/d po continuously**
On progression **Option to have T-DM1** *(3.6 mg/kg iv q3w)* **till progression**

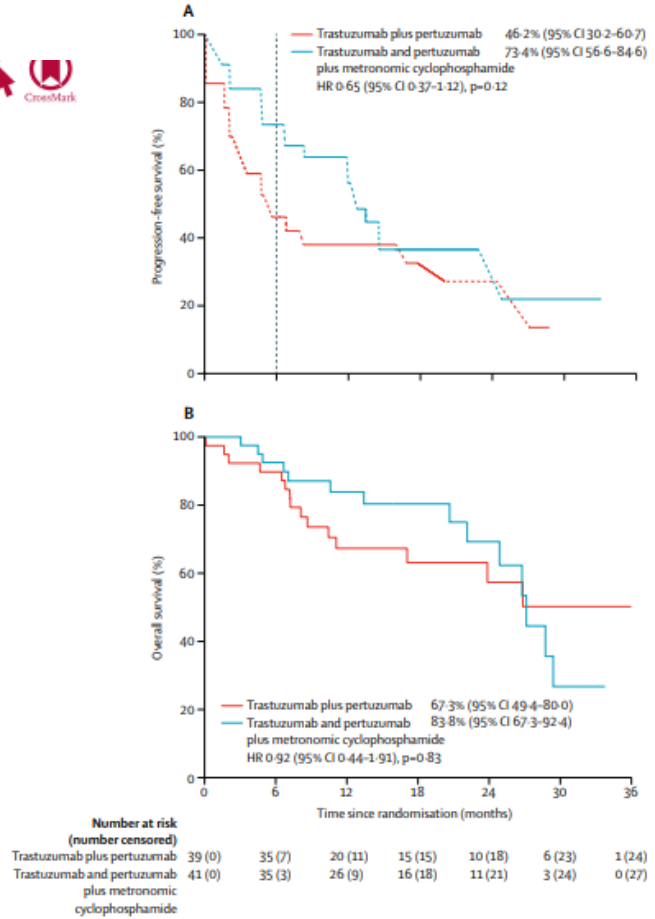
Wildiers Lancet Oncol 2018

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

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

EORTC
The future of cancer therapy

Older/frail patients with HER2+ MBC
TP + metronomic chemo > TP
(7-month longer, median PFS 12.7 vs 5.6 months)
Very acceptable safety profile
T-DM1 active at progression



Wildiers Lancet Oncol 2018

rapid communicatio

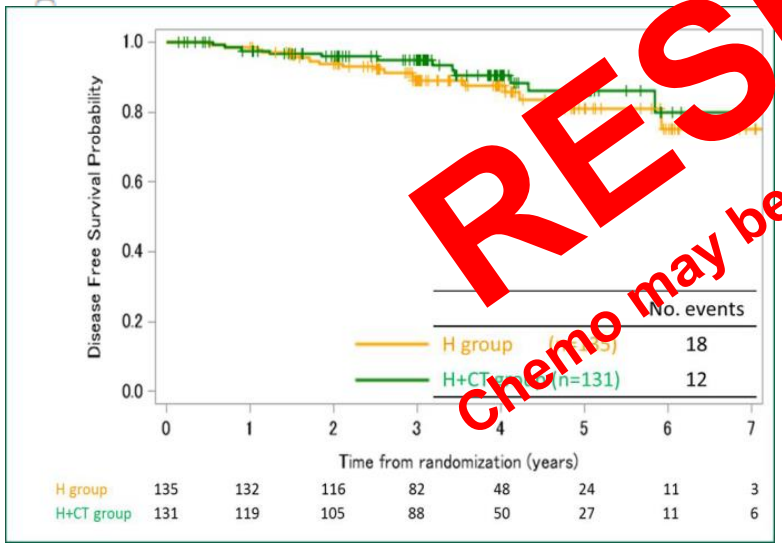
Randomized Controlled Trial of Trastuzumab Wi or Without Chemotherapy for HER2-Positive Early Breast Cancer in Older Patients

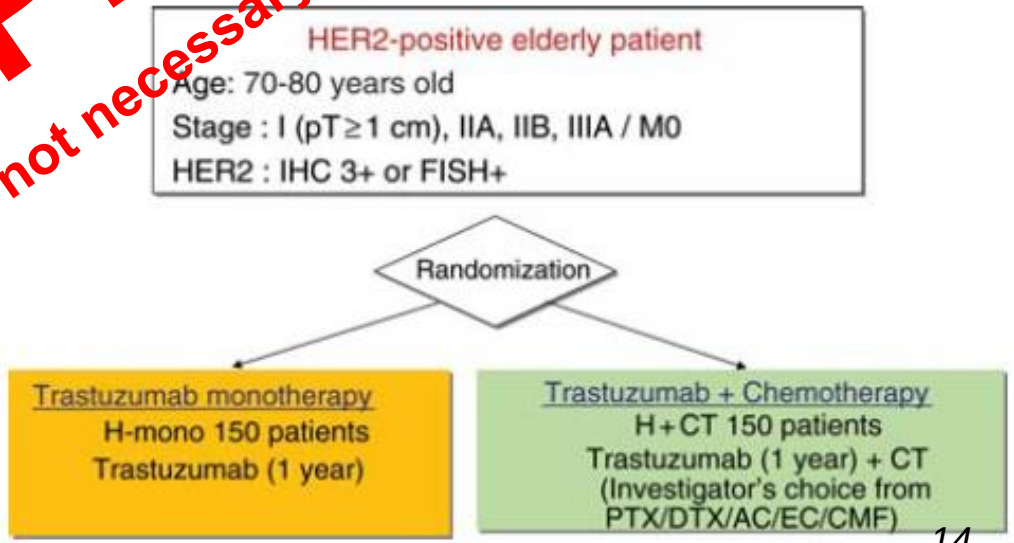
Masataka Sawaki, MD, PhD[1]; Naruto Taira, MD, PhD[2]; Yukari Uemura, PhD[3]; Tsuyoshi S to, PhD[4]; nichi Baba, MD[5]; Kokoro Kobayashi, MD[6]; Hiroaki Kawashima, MD, PhD[7]; Michiko Tsuneizumi, MD, ; Noriko eawa D, PhD[9]; Hiroko Bando, MD, PhD[10]; Masato Takahashi, MD, PhD[11]; Miki Yamaguchi, MD, [12]; omu Ta shima, MD, PhD[13]; Takahiro Nakayama, MD, PhD[14]; Masahiro Kashiwaba, MD, PhD[5]; Toshiro PhD[15]; taka Yamamoto MD, PhD[16]; Hiroji Iwata, MD, PhD[1]; Takuya Kawahara, PhD[17]; Yasuo Ohashi, PhD[18]; Hiro ni M i, PhD[19], for the RESPECT study group

RESPECT!

Chemo may be not necessary at anytime?

275 patients
2009-2014
Non-inferiority
HR 1.22-1.69 β 20%
Follow-up 4.1 years (0.3-8)





Sawaki JCO 2020

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

Hans Wildiers, Etienne Brain, Kevin Punie

EORTC
The future of cancer therapy

BIG
Breast International Group

Non-comparative randomized (2:1) phase II study

EORTC The future of cancer therapy BIG Breast International Group

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

adjuvant chemotherapy required according to treating physician and patient

1:2

- Adjuvant chemo -> AI
- AI + Palbo 2 years

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

06/2019-09/2022
9 countries, 60 sites
372/366 patients randomized
α 5% 1-sided, β 20%

Adjuvant chemo choice:
- 4 TC + G-CSF
- 4 EC or AC + G-CSF
- 12 taxol weekly

Primary endpoint
3y DRFI *(distant metastases or death from breast cancer)* for AI+Palbo arm
- 3-year DRFI of <88% is unacceptable.
- 3-year DRFI of ≥93% is success

Pros:
- Easy endpoint, clinically relevant
- Feasible numbers
- Similar endpoint in 1 arm was used in Mindact and Tolaney study (both NEJM)
- If study is + (88% not included in CI), the conclusion and consequences can be similar as for Mindact and Tolaney study: new standard
- QoL and OS/BCSS can be compared to chemo as secondary

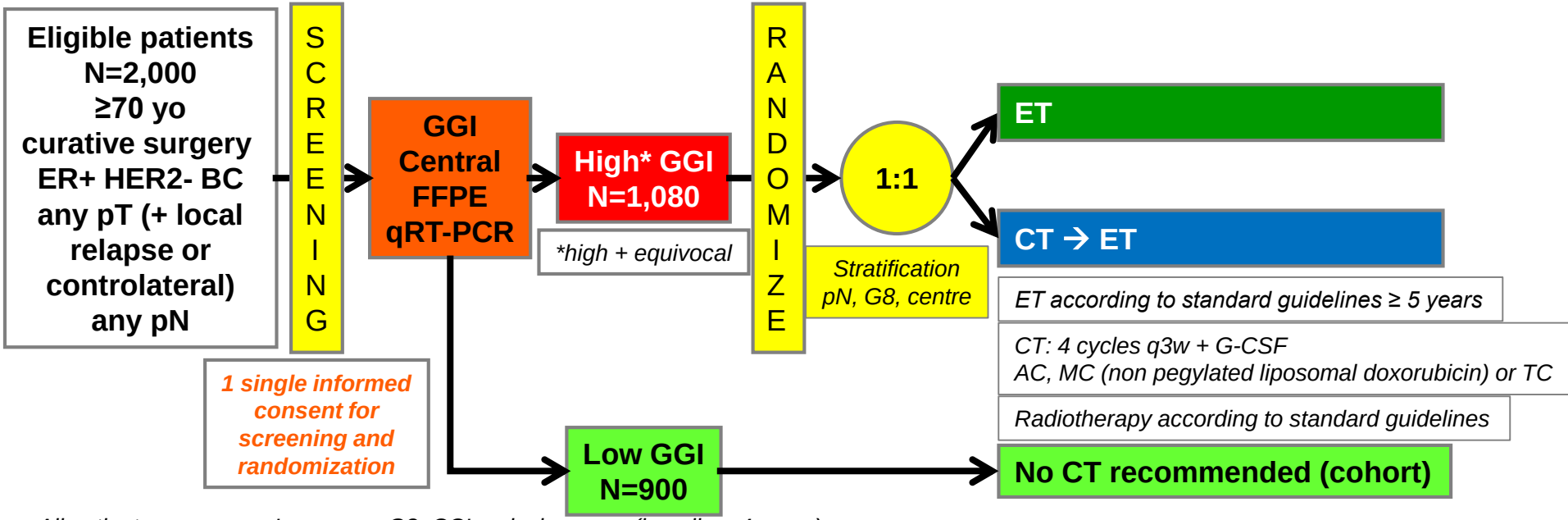
Cons:
- No formal comparison w/ chemo group for primary endpoint
- Less data on QoL/OS/BCSS versus chemo

Gene expression profiles in 70+

Trial	Age limit	Results
MINDACT	≤ 70	0.8% 70+ (56/6.693)
TAILORx	≤ 75	7% 70+ RS 0-10 (111/1.626) 4% 70+ RS 11-25 (300/6.897)
RxPONDER	Any	12% 70-75 yo RS ≤ 25 (581/5.018)

ASTER 70s Study Design

Adjuvant systemic treatment for ER+ HER2- BC in women over 70 according to GGI
Hypothesis: 4-year OS with CT → ET > 4-year OS with ET only if high GGI



All patients — *Lee score, G8, CCI, polypharmacy (baseline, 4 years)*

Randomized patients — *MMSE, IADL, QLQ C30 & ELD15, socioeconomic, willingness, blood & serum (baseline, 3 months, yearly x 4 years)*

ASTER 70s Trial Status

Accrual	12/04/2012-14/04/2016
Data cut-off	April 11, 2022
Median follow-up (randomized patients)	5.94 years (95%CI 5.91-5.98)
Number of OS events	214
Number of French sites **Comprehensive cancer centre** **University hospitals** **General/community hospitals** **Private clinics**	72 23 6 23 20
Number of Belgium sites	12

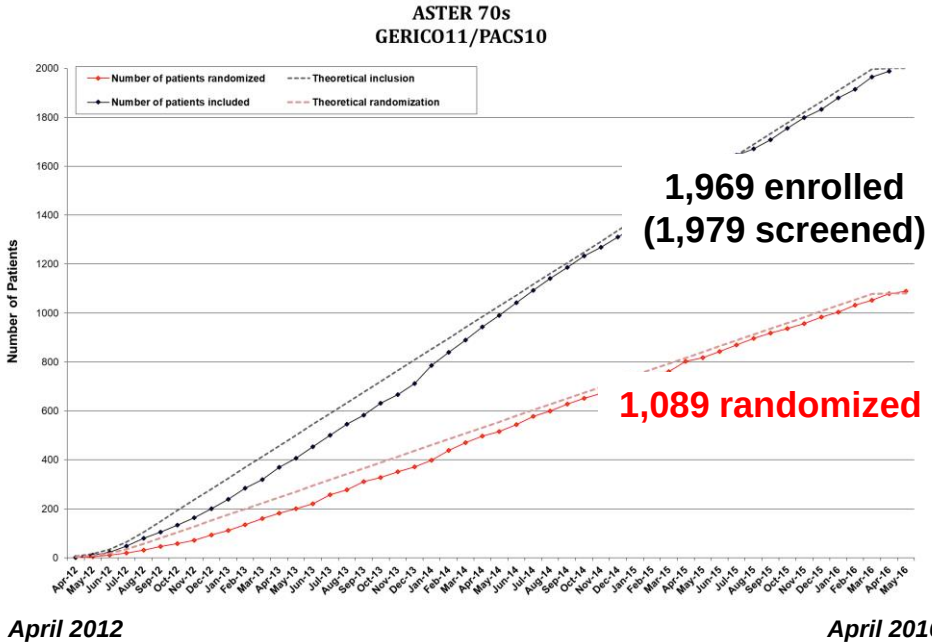
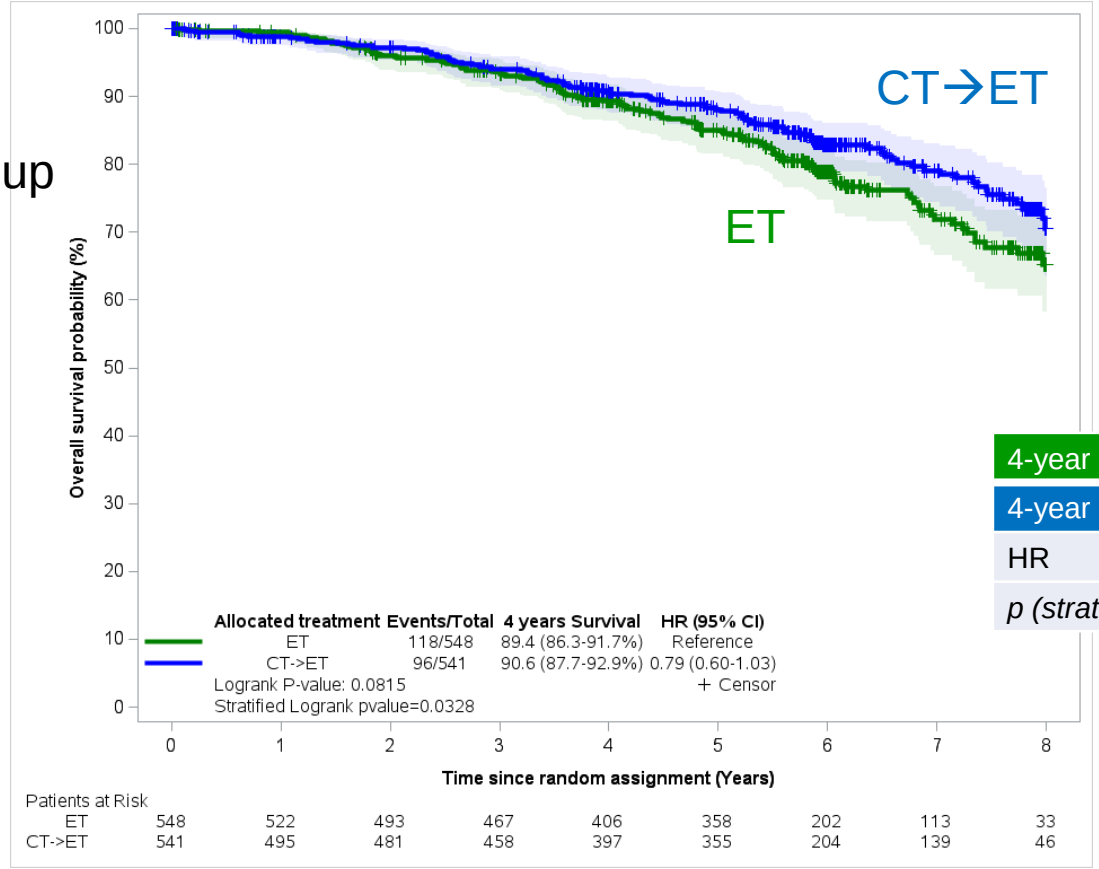


Figure 2A. Kaplan Meier estimation of OS in ITT population according to treatment arm

median follow-up
5.94 years

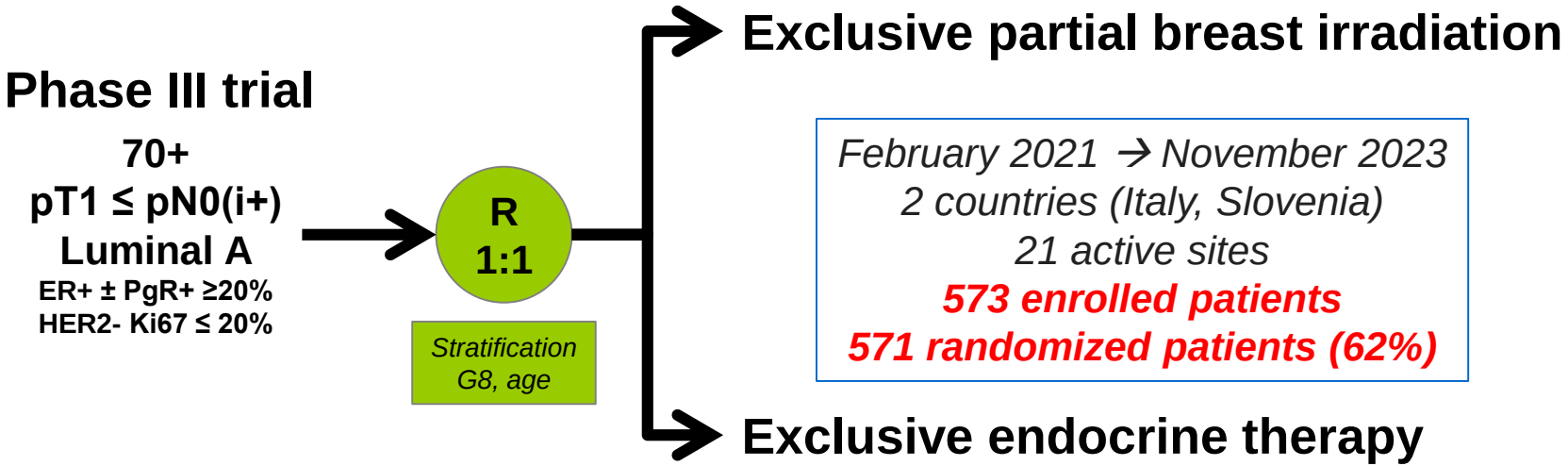


4-year OS	89.4 (86.3-91.7)
4-year OS	90.6 (87.7-92.9)
HR	0.79 (0.60-1.03)
p (stratified logrank)	0.0328

EUROPA NCT04134598 (University of Florence, IT)

ExclUsive endocRine therapy Or Partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (EUROPA): a randomized phase 3 non-inferiority trial

PI Icro Meattini

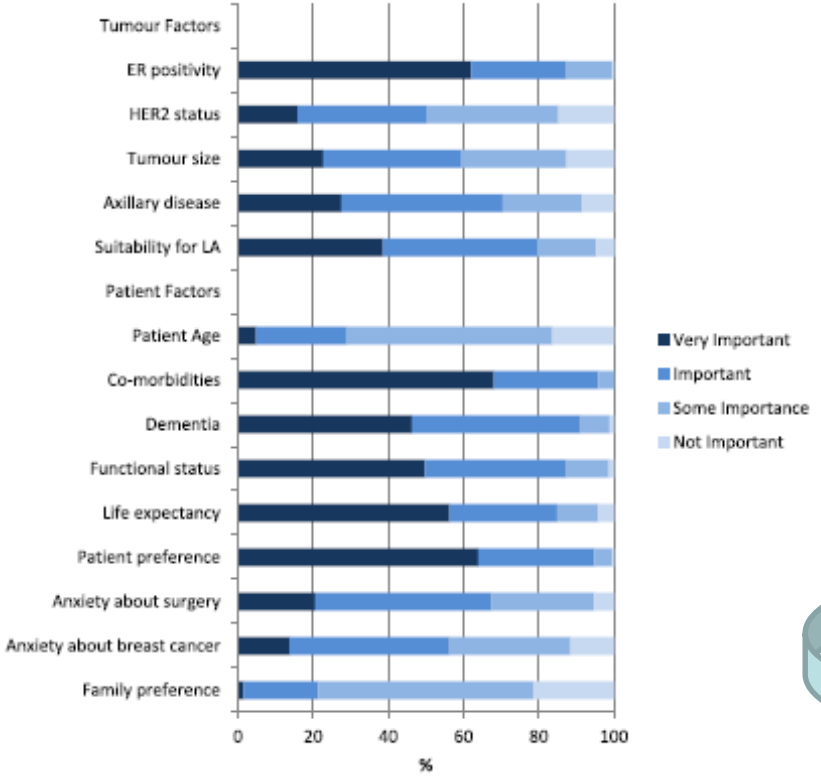


926 patients

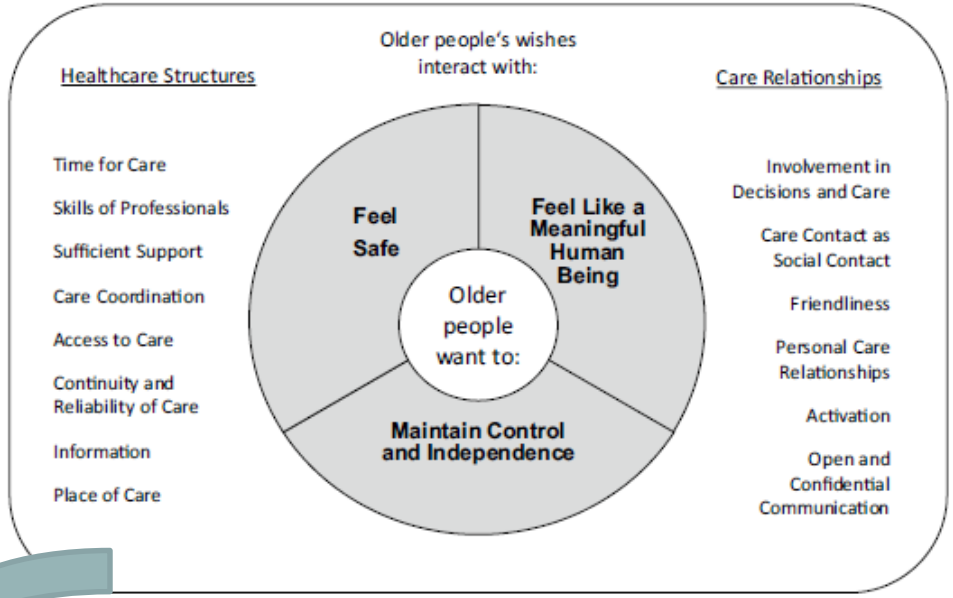
Primary endpoint: 5-year IBTR (4% if ET) + PROMs QoL (QLQ-C30 using GHS at 24 months, 5-points)

1-sided α 0.025%/0.05%, power 80%/90%, non inferiority

What counts? HCP vs patient?



PET vs surgery



Importance of PROMs

International Consortium for Health Outcomes Measurement
ICHOM

Morgan EJSO 2015, Herrler Eur J Ageing 2022, Doolin EJSO 2020

The "Time Toxicity" of Cancer Treatment

Time Toxicity — Time spent coordinating treatments and in-visits to a health care facility (including travel and waiting), seeking urgent/emergent care for side effects, hospitalizations, and follow-up tests and rehabilitation.

Proposed Metric of Time Toxicity — Days with Physical Health Care System Contact

(a 1-hour lab visit = a 6-hour infusion = a 12-hour urgent care visit = an overnight hospitalization; all these are "all-day affairs")

Overall survival = **Days With Physical Health Care System Contact** + **Home Days**

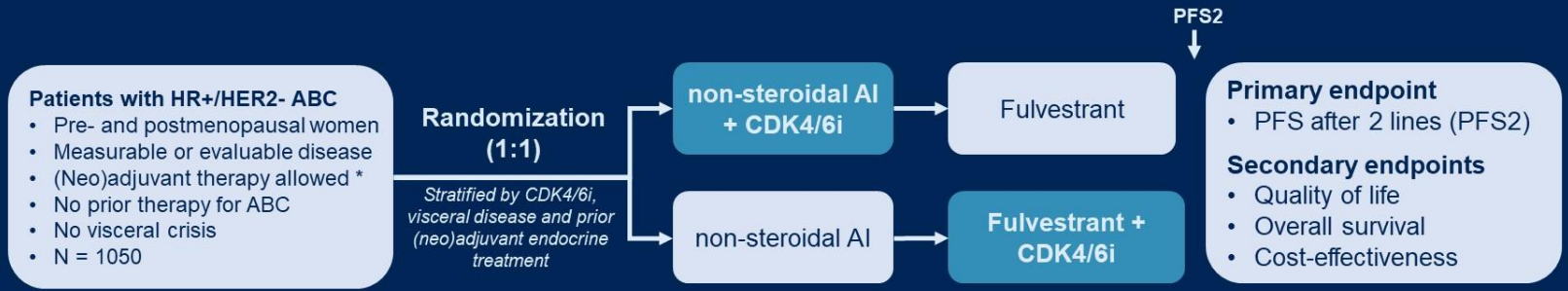
Hypothetical Treatment	Clinical Trajectory	Overall Survival (in days)	Home Days
Option A (Chemotherapy)	Frequent clinic visits; Chemotherapy toxicity, hospitalization, and rehabilitation	150	90
Option B (No cancer-directed treatment)	Short hospitalization for symptom control	120	115

Day 0 — Day 30 — Day 90 — Day 180

With information on **"Time Toxicity"** and **"Home Days"**, a clinician can better guide a patient regarding a treatment strategy that best aligns with the patient's goals.

Gupta J Clin Oncol 2022

SONIA trial design



- Tumor assessments every 12 weeks
- PFS locally assessed per RECIST v1.1
- Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. ClinicalTrials.gov (NCT03425838)
1. Cherny NI, et al. Ann Oncol 2017

Summary of the main findings

SONTA

CDK4/6 inhibition in first-line compared to second-line

- Does not improve Progression-Free Survival
- Does not improve Overall Survival
- Does not improve Quality of Life
- Extends time on CDK4/6i by 16.5 months
- Increases incidence of grade 3-4 toxicity by 42%
- Increases drug expenditure by $200,000 per patient[1]

1. CMS drug prices: CMS.gov, Centers for Medicare & Medicaid Services

Impact of GA on Tx Decision

- Oncological decision before or after “some kind of” geriatric assessment
  - **28-40% modification** of initial Tx plan
  - **66% with less intensive Tx**
  - Potential interventions in **>70%** patients
    - Social
    - Nutrition
    - Polypharmacy
  - Positive effect on Tx completion (x2), toxicity (:2), and HRQoL
  - GAIN, GAP70+, GERICO, INTEGERATE

Hamaker Acta Oncol 2014, J Geriatr Oncol 2018 & 2022
Li JAMA Oncol 2021, Mohile Lancet 2021, Lund BJC 2021, Soo Lancet Health Long 2022

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

CARG Cancer & Aging Research Group

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Practical Geriatric Assessment

To be completed by the patient or caregiver

Patient Name:	Patient DOB:	Date Being Completed:

1 | How many times have you fallen in the last 6 months? _____

2 | Does your health limit you in walking one block?

☐ Not limited at all
☐ Limited a little
☐ Limited a lot

3 | Does your health now limit you in climbing one flight of stairs?

☐ Not limited at all
☐ Limited a little

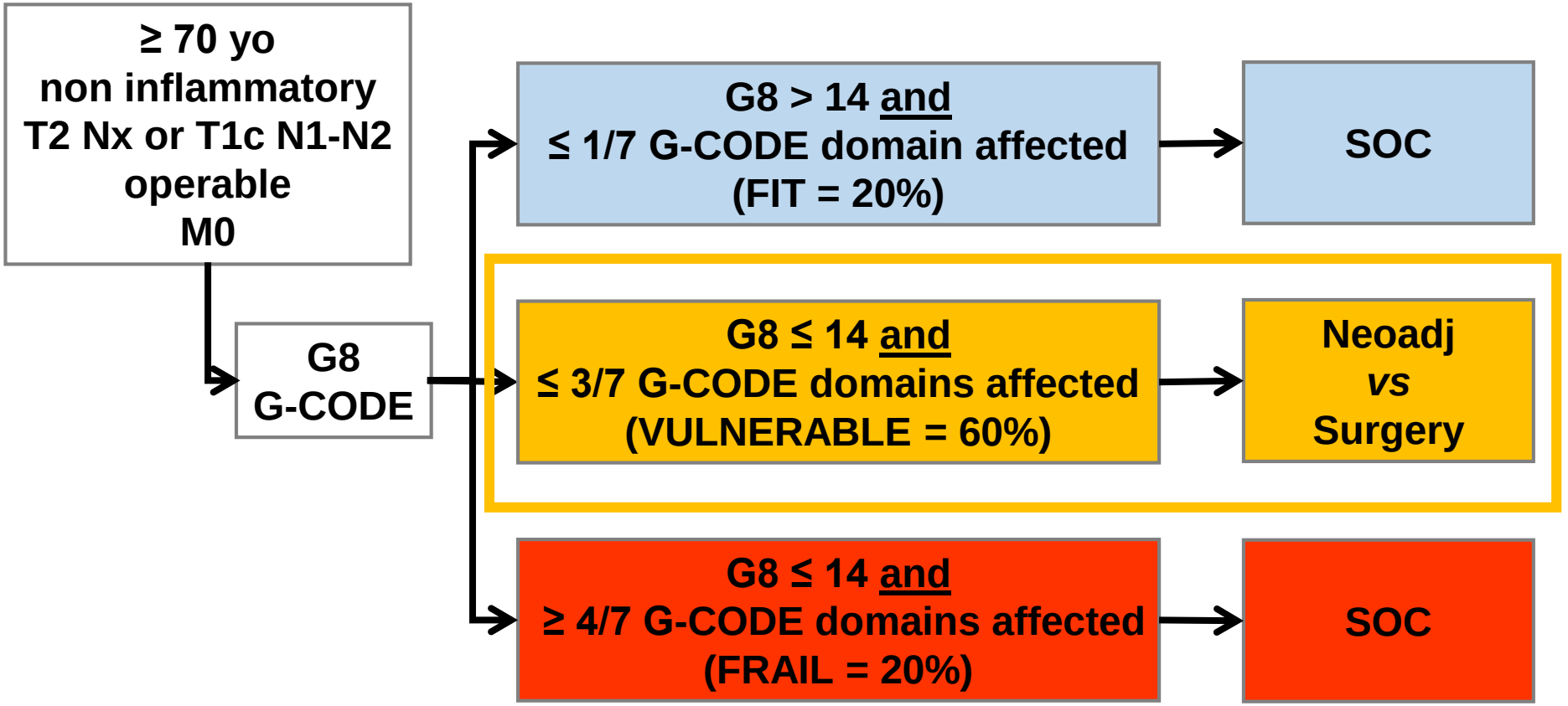
Recommendation	Type	Evidence Quality	Strength
1.1. All patients with cancer age 65 years and older with geriatric assessment (GA)-identified impairments should have GA-guided management included in their care plan. GA-guided management includes using GA results to inform cancer treatment decision making as well as addressing impairments through appropriate interventions, counseling, and/or referrals.	EB	H	S
2.1. A geriatric assessment should include high priority aging-related domains known to be associated with outcomes in older patients with cancer to include measurement of physical and cognitive function, emotional health, comorbid conditions, polypharmacy, nutrition, and social support.	EB	H	S
2.2. The Panel recommends the Practical Geriatric Assessment (PGA) as one option for this purpose. See the PGA tool.	IC	M	W

EB, evidence based; GA, geriatric assessment; H, high; I, intermediate; IC, informal consensus; M, moderate; S, strong; W, weak.

Domain	Measure
Physical function / performance	Falls Physical function 4-meter gait speed
Functional status	IADL
Nutrition/weight loss	From G8/MNA
Social support	MOS social support 8 item
Psychological	PROMIS Anxiety 4 item GDS 5
Comorbidity	Comorbidity Hearing, vision
Cognitive function	Mini-Cog
GA screening tool	G8
Risk of chemo tox	CARG

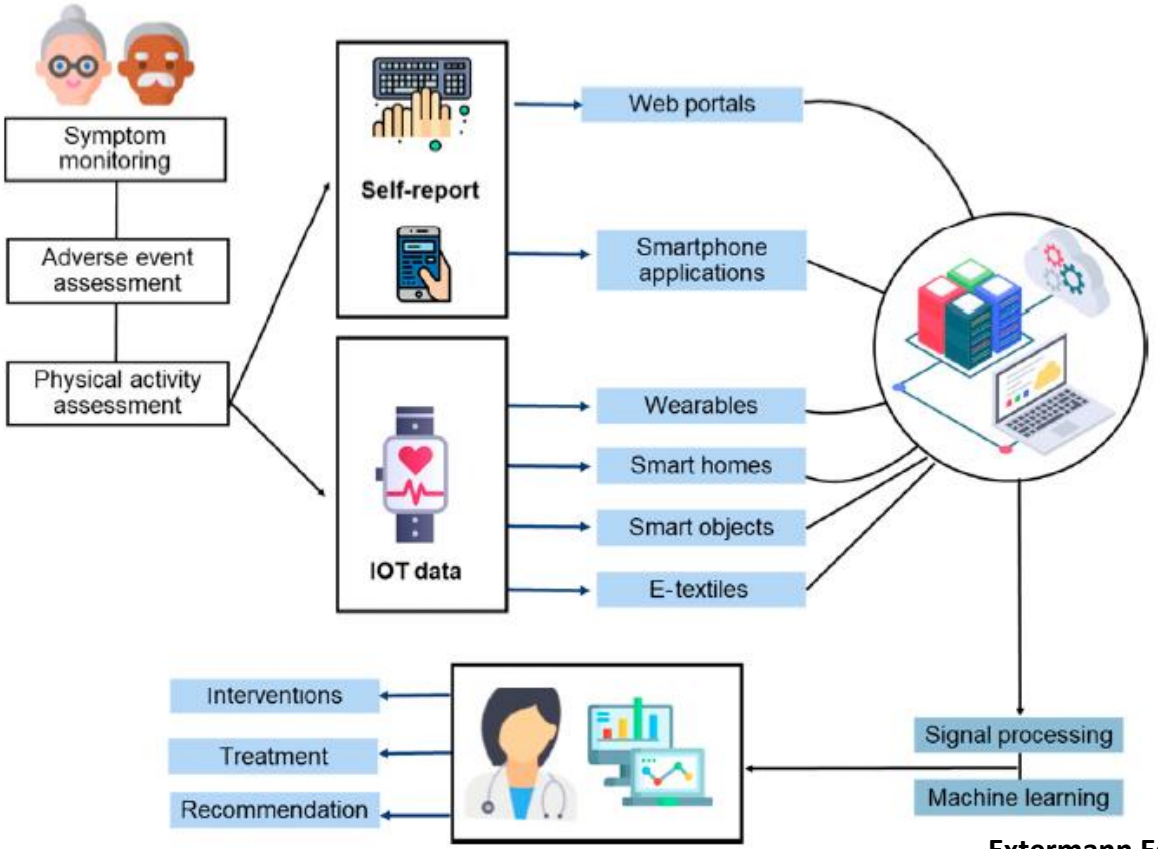
Dale J Clin Oncol 2023, Grants JOP 2023

Screening for EORTC BCG 2338



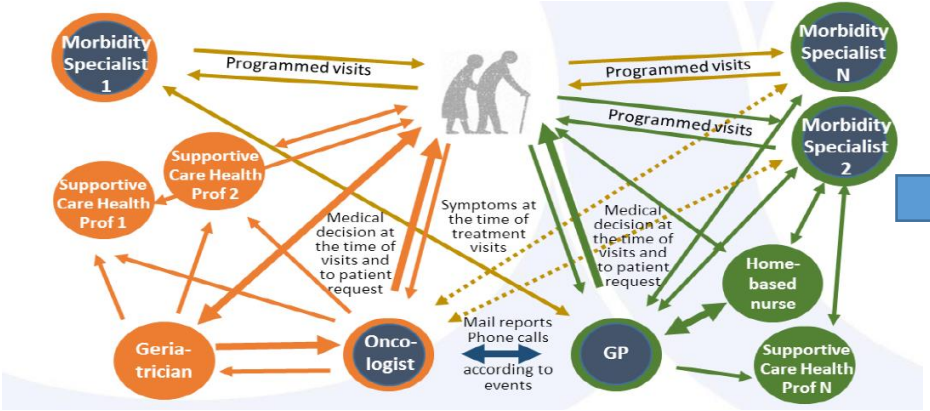
* *G8 score > 14 and >1/7 G-CODE domain affected are not plausible options*

Potential Uses of Self-Report and the Internet of Things for the Monitoring and Follow-up of Older Adults With Cancer



Extermann Educational book ASCO 2022

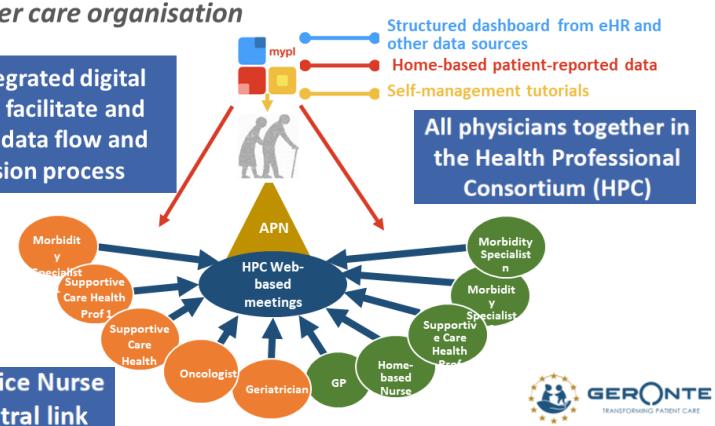
≥ 70 yo & ≥ 1 moderate/severe multimorbidity



GERONTE patient-centred management

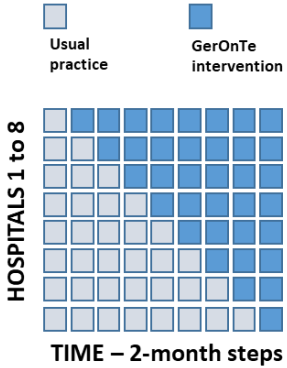
Reconsider care organisation

An integrated digital tool to facilitate and secure data flow and decision process



Advanced Practice Nurse (APN) as a central link with patients

Stepped wedge design



- **Two trials**
  - *France and Belgium/Netherlands*
  - *8 centres per trial*
  - *>634 patients per trial*
- **Investigating centers**
  - *Three Referral Centers per trial*
  - *Five Community Hospitals per trial*
- **Centers enter intervention arm by randomization**
  - *Until the end of the trial*
  - *Known from baseline*
- **Financial compensation at the end of the trial**

Primary endpoint
Improve patient 6-month HRQoL

720 patients & 8 sites
90/site, 10 q2m, 30 mths

Age is not a contraindication to treatment for…

… nor to clinical trials!

Age is an independent predictor of adverse outcomes associated with treatment for…

… especially when relying on trial results run in younger adult population

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NATIONAL COORDINATOR, SIOG 2024 SCIENTIFIC PROGRAMME COMMITTEE

Martine Puts
CONFERENCE CO-CHAIR, SIOG 2024 SCIENTIFIC PROGRAMME COMMITTEE

Supriya Mohile
CONFERENCE CO-CHAIR, SIOG 2024 SCIENTIFIC PROGRAMME COMMITTEE

Optimising treatment in older cancer patients is precision medicine too!

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GERIATRIC ONCOLOGY
ADVANCED COURSE
TREVISO, ITALY
JULY 3-5, 2024

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10th edition
September 2024