
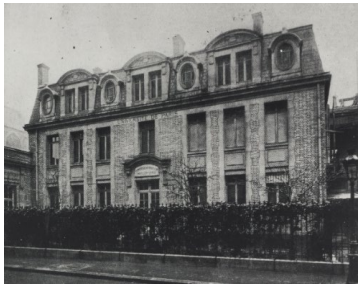

Specific and International Clinical Research for Older Patients with Cancer

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institutCurie

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

EORTC
The future of cancer therapy

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Conflicts of interest

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

Few older adults included in registration studies! Breast cancer as an example

Agent Name	Approval	N	Age ≥ 65	N	Age ≥ 75
Palbociclib	2/2015	37	44%	8	10%
		86	25%		--
Everolimus	7/2012	290	40%	109	15%
Pertuzumab	6/2012	60	15%	5	1%
Eribulin mesylate	11/2010	121	15%	17	2%
Lapatinib	1/2010	34	17%	2	1%
		282	44%	77	12%
Ixabepilone	10/2007	45	10%	3	<1%
		32	13%	6	2.5%

Package Insert, "Geriatric Usage" section

Courtesy to Arti Hurria (adapted)

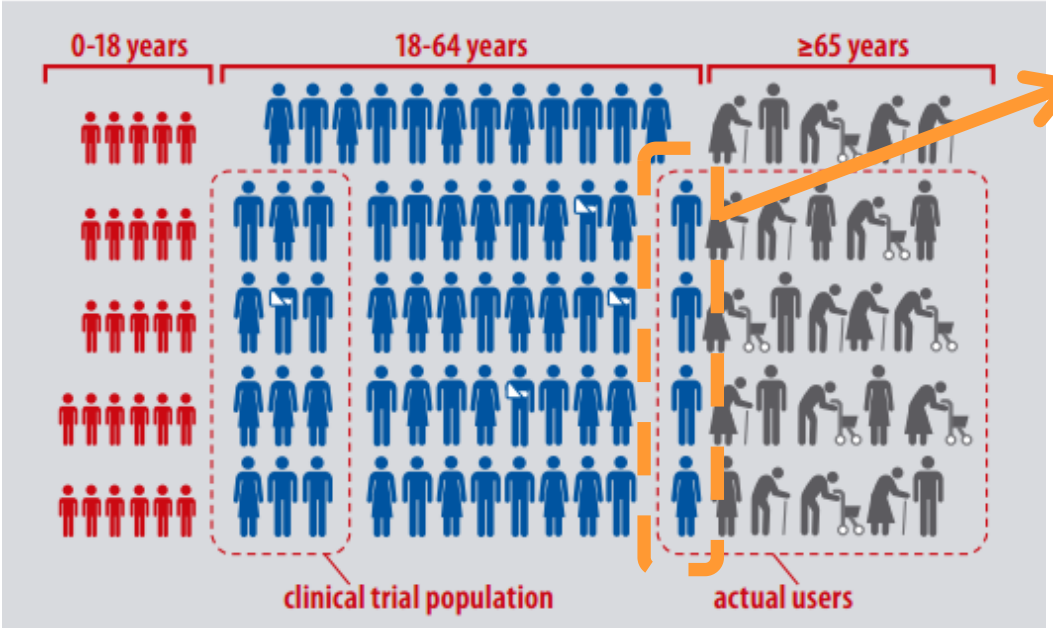
CDK4/6i registration trials for EBC

Study	Design	All N	65+ N	75+ N
monarchE	≥4 pN+ 1-3 pN+ and pT≥5cm, grade III or Ki67≥ 20% Hormonotherapy ± abemaciclib 2 years	5637 *51 yo (44-60)*	850 (15.1%*)	153 (<3%)
PALLAS	Stage II-III Hormonotherapy ± palbociclib 2 years	5761 *52 yo (45-61)*	NR	NR
NATALEE	Stage II-III Hormonotherapy ± ribociclib 3 years	5101 *52 yo (24-90)*	NR	NR

** ~80%< 75 yo*

Johnston JCO 2020, Gnant JCO 2021, Slamon NEJM 2024

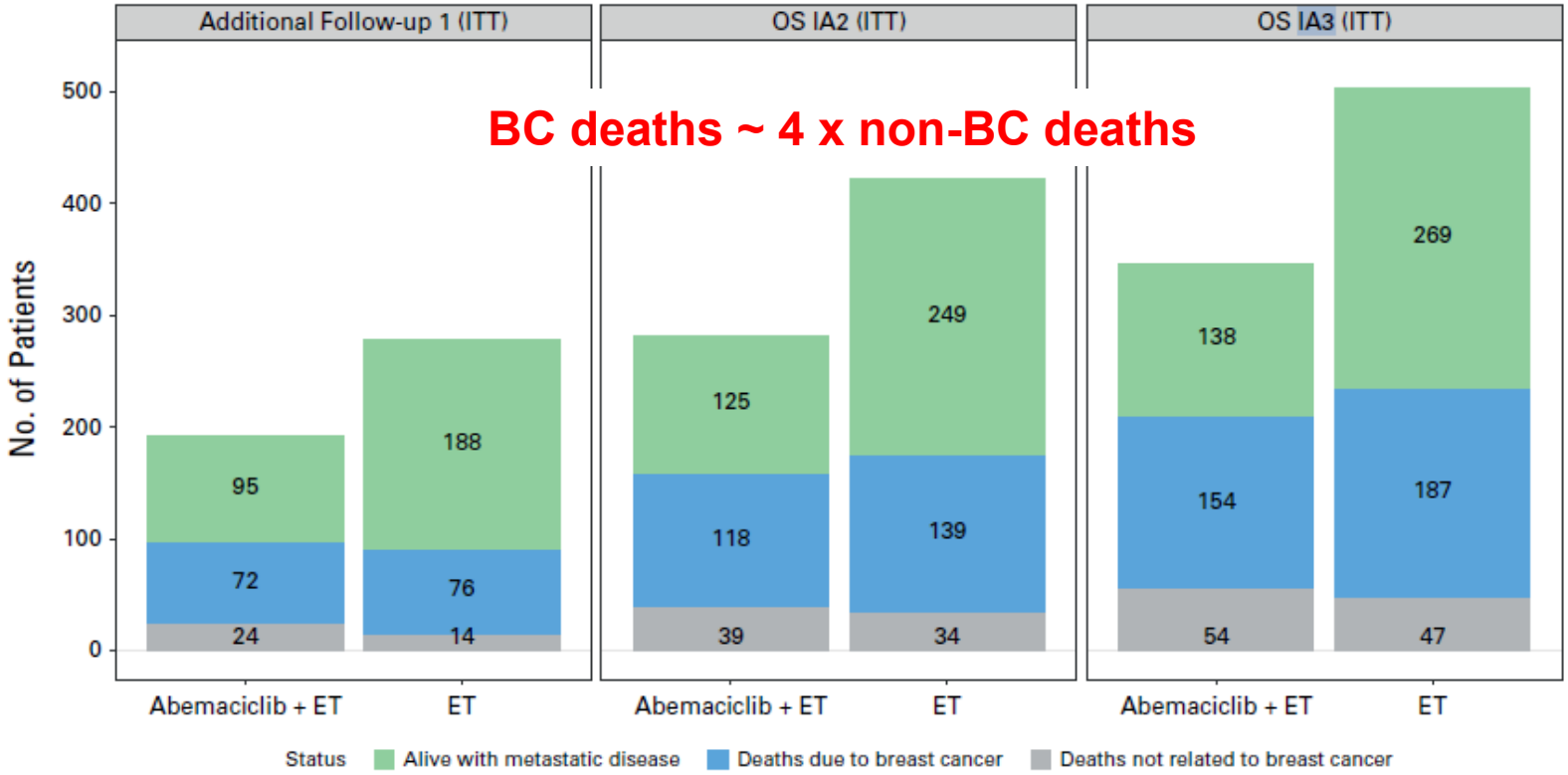
Trial population vs real life?



Older ones enrolled in standard explanatory trials are highly selected:

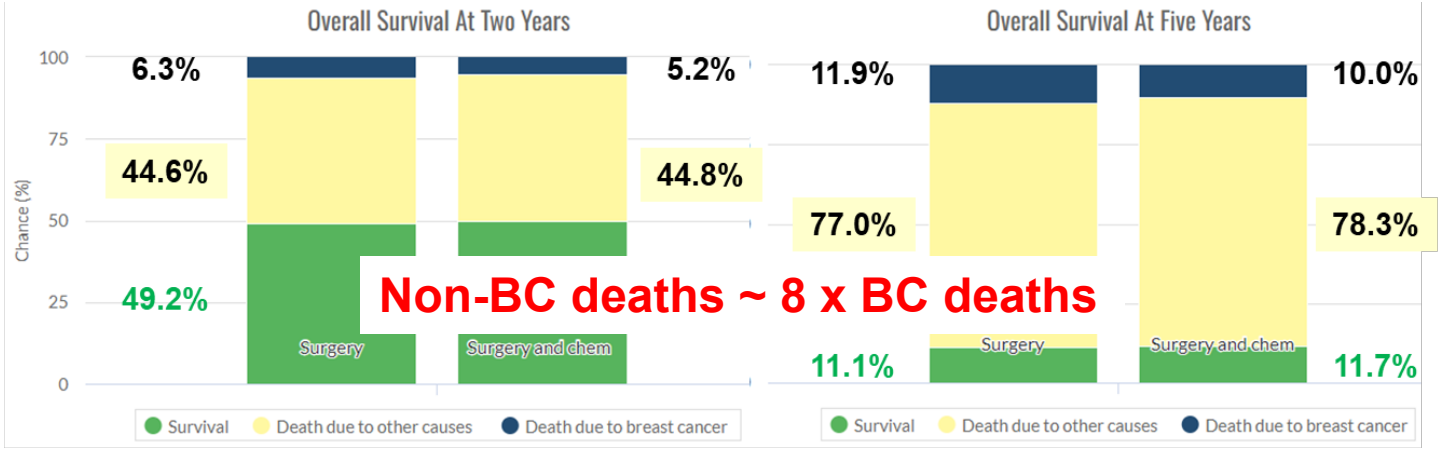
- younger
- w/ less comorbidities
- w/ less organ dysfunctions
- fitter

monarchE



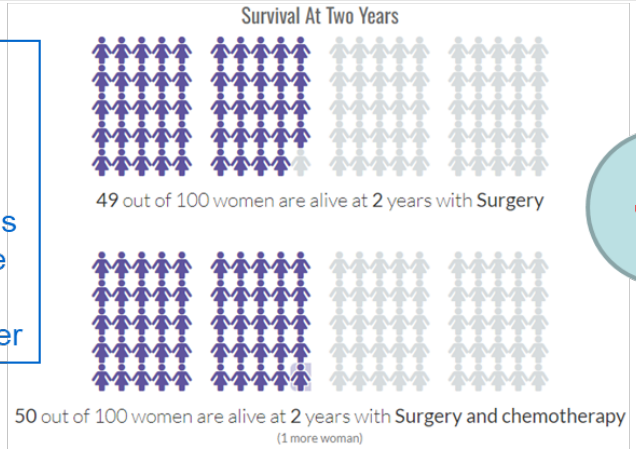
Rastogi JCO 2024

agegap.shef.ac.uk ± adjuvant chemo



Non-BC deaths ~ 8 x BC deaths

80 yo
15 mm grade III
2 pN+
ADL restrictions
Diabetes mellitus
Mild renal failure
Previous non-metastatic cancer



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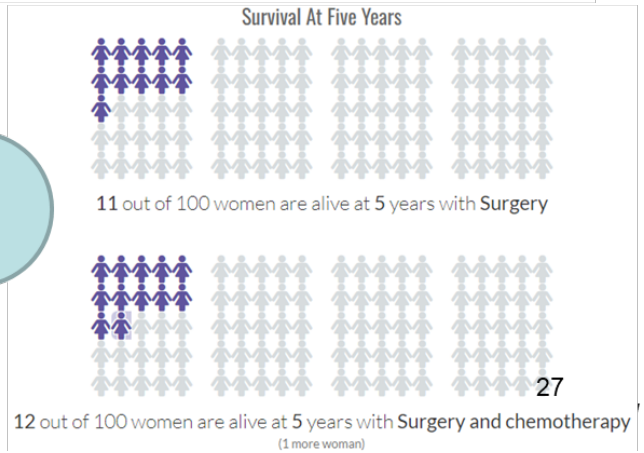


27

Gene expression profiles in 70+

Trial	Age limit	Population 70+
MINDACT	≤ 70	0.8% (56/6.693)
TAILORx	≤ 75	6.8% RS 0-10 (111/1.626) 4.3% RS 11-25 (300/6.897)
RxPONDER	Any	11.6% RS ≤ 25 (581/5.018)

Cardoso NEJM 2016, Sparano NEJM 2018, Kalinsky NEJM 2021

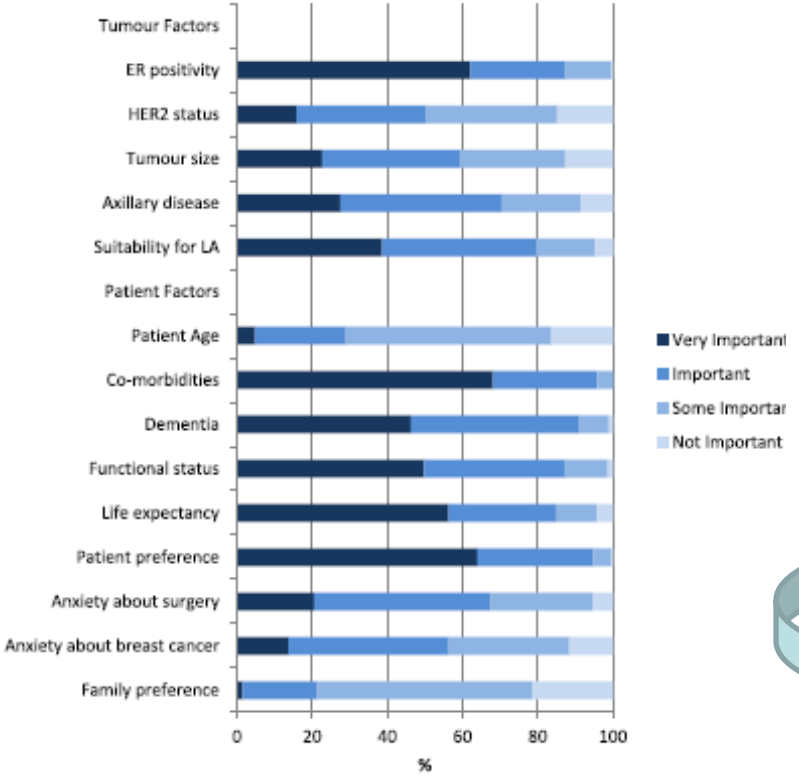
To be addressed in research for older ones

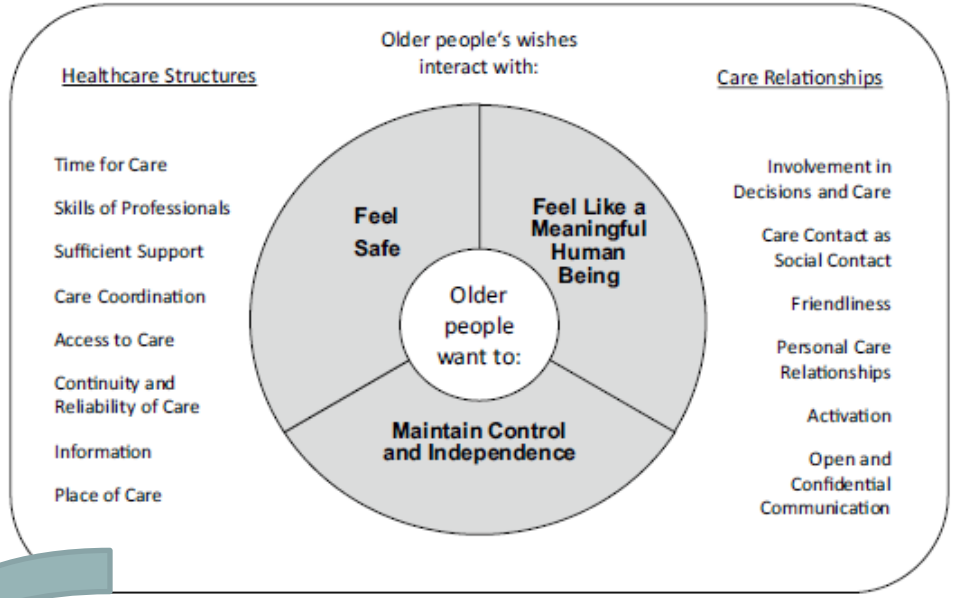
- **Multicomplexity**: usual exclusion if other conditions beyond the disease being studied
- **Settings**: reside in and get care in home, clinic, hospital, nursing home
- **Medical Tx can have both benefits and harms**: safety, harms of overtesting, over Tx, and polypharmacy, benefits of deprescribing
- **Palliative care** needed for many years toward the end of life, not just the 6 mths covered by hospice
- **Caregivers** well-being: include both members of the patient-care partner dyad

Need to move more toward research that abandons reductionism and fully embraces complexity, including webs of causation that incorporate social and environmental determinants of health

Cohen JAMA Internal Med 2024, Covinsky JAMA Internal Med 2024

What counts? HCP vs patient?





Importance of PROMs

International Consortium for Health Outcomes Measurement
ICHOM

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

Acceptability & willingness

West Haven Veterans Affairs

226 patients 60+: attitudes toward burden of Tx, possible outcomes, and likelihood
- Limited life expectancy (cancer, CHF, or COPD)
- Burden of Tx (length of the hospital stay, extent of testing, and invasiveness of interventions)

1. Low-burden Tx (restoring participant's current state of health) vs no Tx resulting in **death**

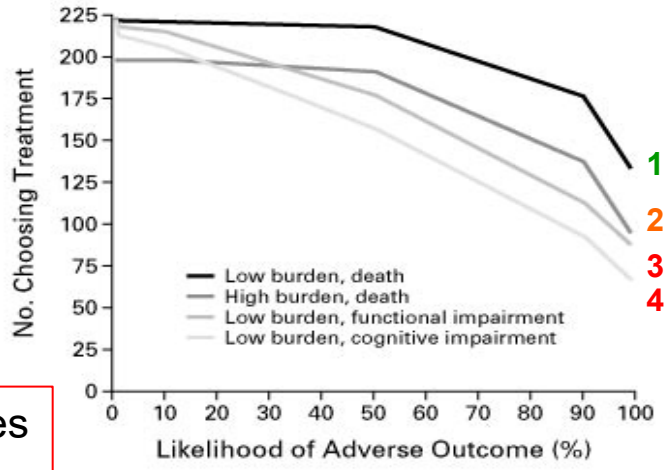
98.7% accept

2. High-burden Tx vs no treatment resulting in **death**

11% decline

3 & 4. Low-burden Tx vs survival w/ **severe functional or cognitive impairment**

74-89% decline



Likelihood of adverse functional and cognitive outcomes of Tx requires explicit consideration in older ones:
Death is not necessarily the most feared outcome

Fried NEJM 2002

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

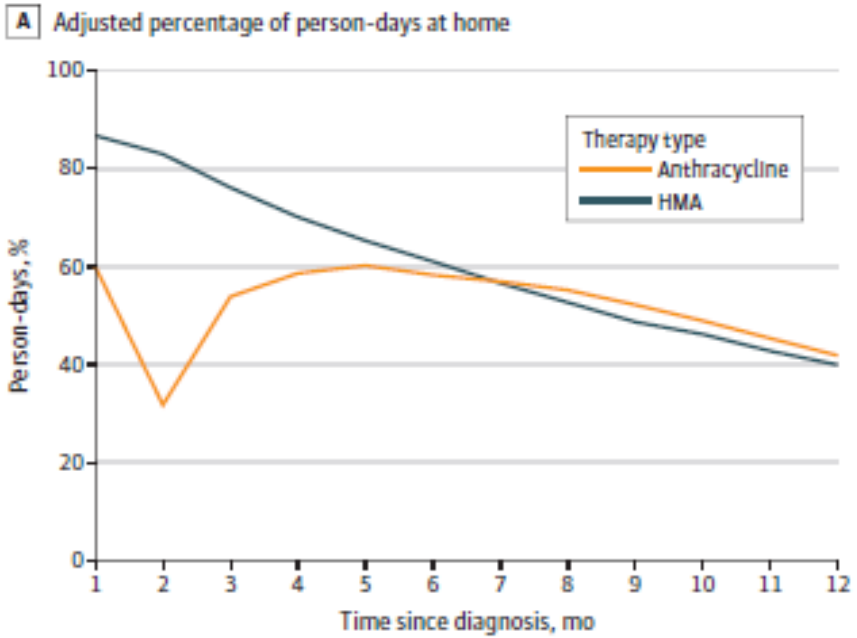
(a 1-hour lab visit = a 6-hour infusion = a 12-hour urgent care visit = an overnight hospitalization; all these are "all-day affairs")

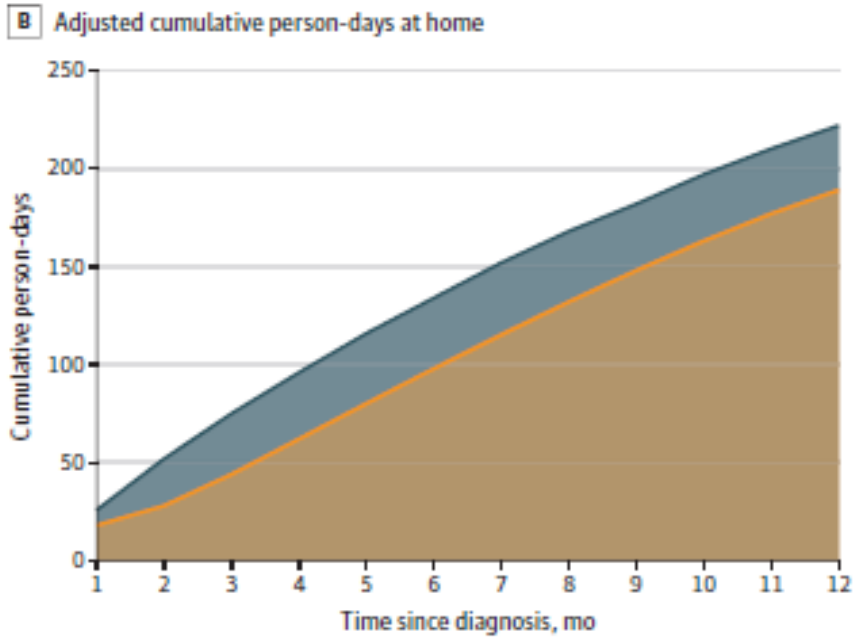
Overall survival = **Days With Physical Health Care System Contact** + **Home Days**

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

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





A, Adjusted person-days at home achieved by patients who received anthracyclines (n = 2824) compared with hypomethylating agents (n = 2542) in the first 12 months following chemotherapy administration. B, The adjusted cumulative person-days achieved by patients who received anthracyclines compared with hypomethylating agents in the first 12 months following chemotherapy.

66+ yo w/ new diagnosis of AML, SEER, 2004-2016

Home time!

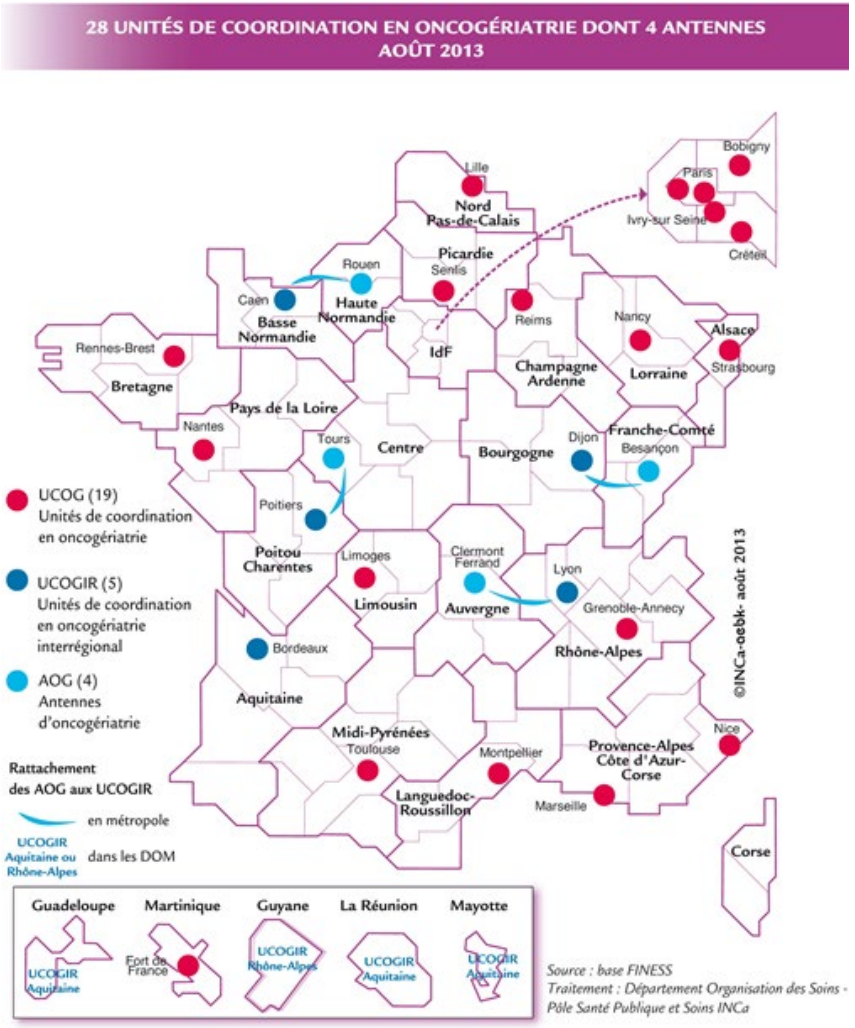
Additional survival afforded by receiving anthracycline-based Tx entirely offset by admission to the hospital or to nursing facilities?

Richardson JAMA Oncol 2024

From UPCOG to UCOG 2005-2011

INSTITUT NATIONAL DU CANCER

1. Collaboration between oncologists & geriatricians
2. Access
3. Specific research
4. Teaching
5. Information

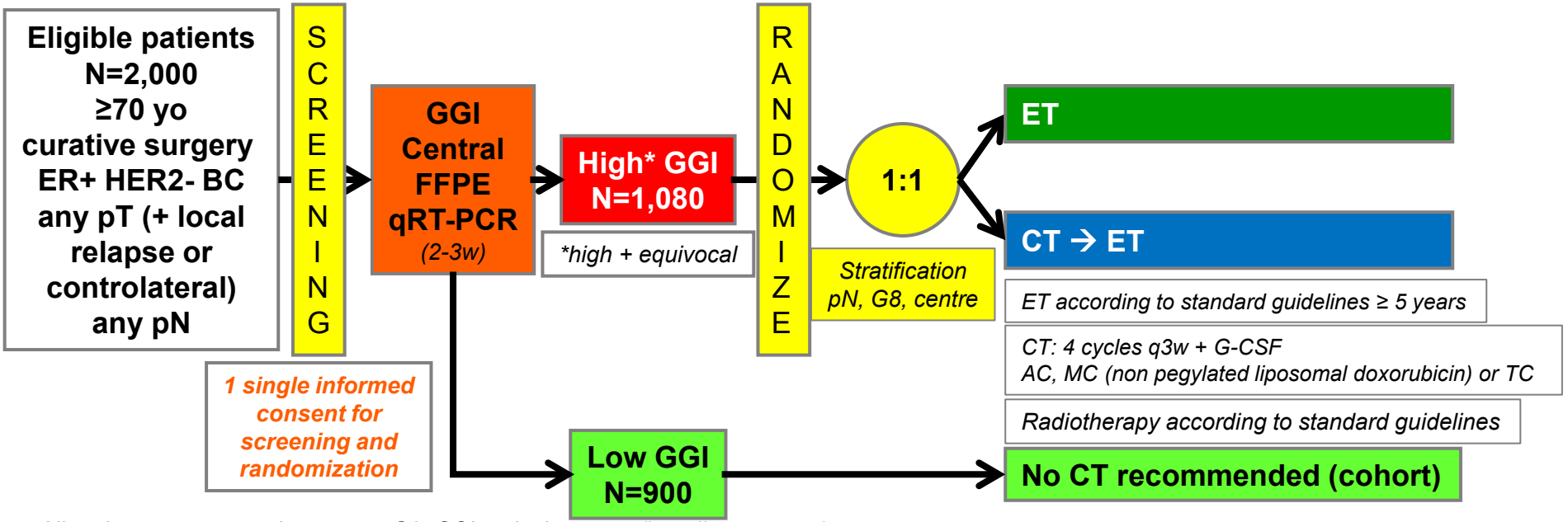


GERICO ≥ 2,500 patients

		Age	Phase	Primary endpoint	N	Ancillary	Publication
2002	**Creation** (F Pein & AC Braud)						
2002	G-01: X+VNR PO breast, lung, prostate	70+	II	ADL	80	PK	CROH 2010
	G-02: CT XELOX CCR M+	70+	II	ADL	60	PK	JGO 2011
2004	G-03: per op brachyXRT breast < 3 cm pN0	70+	II	Feasibility, QoL	40	Cost	Brachy 2013
2005	G-04: CT TxT q2w breast M+	70+	II	IADL	27/60	NA	Poster
	G-05: CT TxT q2w NSCLC M+	70+	II	IADL	5/60	NA	Poster
2006	**G-06**: CT adjuvant anthra (MC) breast ER-	70+	II	ADL	40	Will	CROH 2010
2009	G-09: breast M+ HER2+++ X + lapatinib	70+	II	Composite	4/52	NA	Poster
	Retrospective L1 CT M+ breast (Bergonié)	75+	Cohorte	Description	500	NA	CROH 2001
	DOGMES L1 DXR lipos (GINECO)	70+	II	RR	60	NA	EJC 2012
2010	**G-10/GETUG P-03**: CT TxT prostate + PK	75+	II R	Composite	66/60 :144	PK	Poster
	PRODIGE 20 (G-08): CT ± beva CCR M+	75+	IIR/III	Composite	102	CTC/RX	Pending
2011	**ASTER 70s/G-11/PACS 10**: CT adj breast RH+ HER2- GGI	70+	III	OS (competing risks)	1,080/2,000	TR, cost, acc	Poster, oral
2012	**ELAN** (PAIR ORL, GORTEC/GERICO)	70+	II/III	OS	446	NA	Poster
	SHS (cognition, acceptability, etc.)	70+	SHS	Qualitative res		NA	Poster
2014	**UCGI-30 (G-12)** XRT/CTneo vs XRT rectum **OSAGE** (Besançon)	75+	III I/II	R0 + IADL MTD, RR EOT	420 54	acc	
2016	ASTER 2/3 + EORTC/BIG	70+	III	Outcome + QoL	1,200/2,500	Acc	
2017	MBC, SCSC, STS, palliative XRT						

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



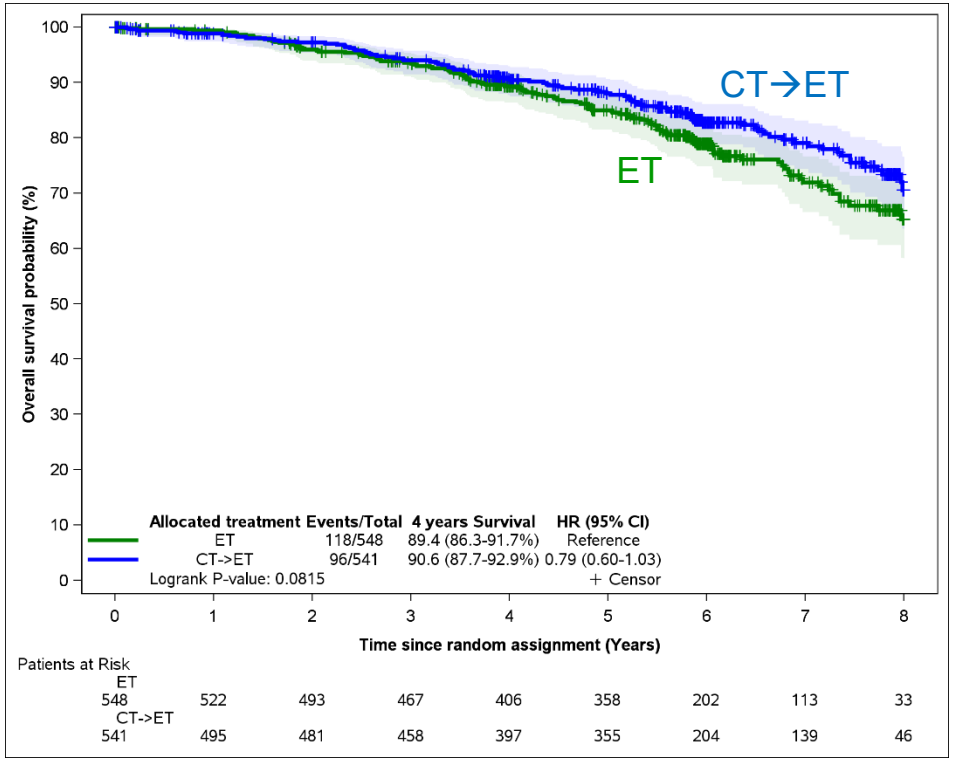
All patients — *Lee score, G8, CCI, polypharmacy (baseline, 4 years)*

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

PRESENTED BY:
Etienne BRAIN

OS: ET — *vs* CT→ET — (intent to treat) (primary endpoint)

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	0.08

PALOMAGE study design

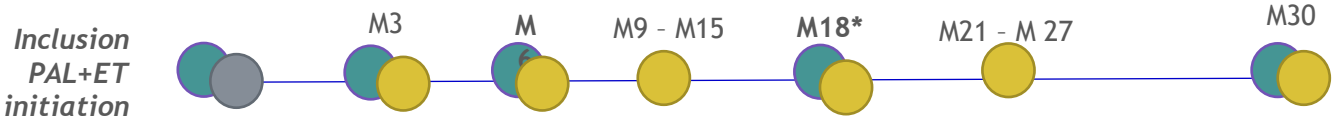
- Patients with HR+ HER2- aBC; age ≥70 yrs (**N=807**)

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

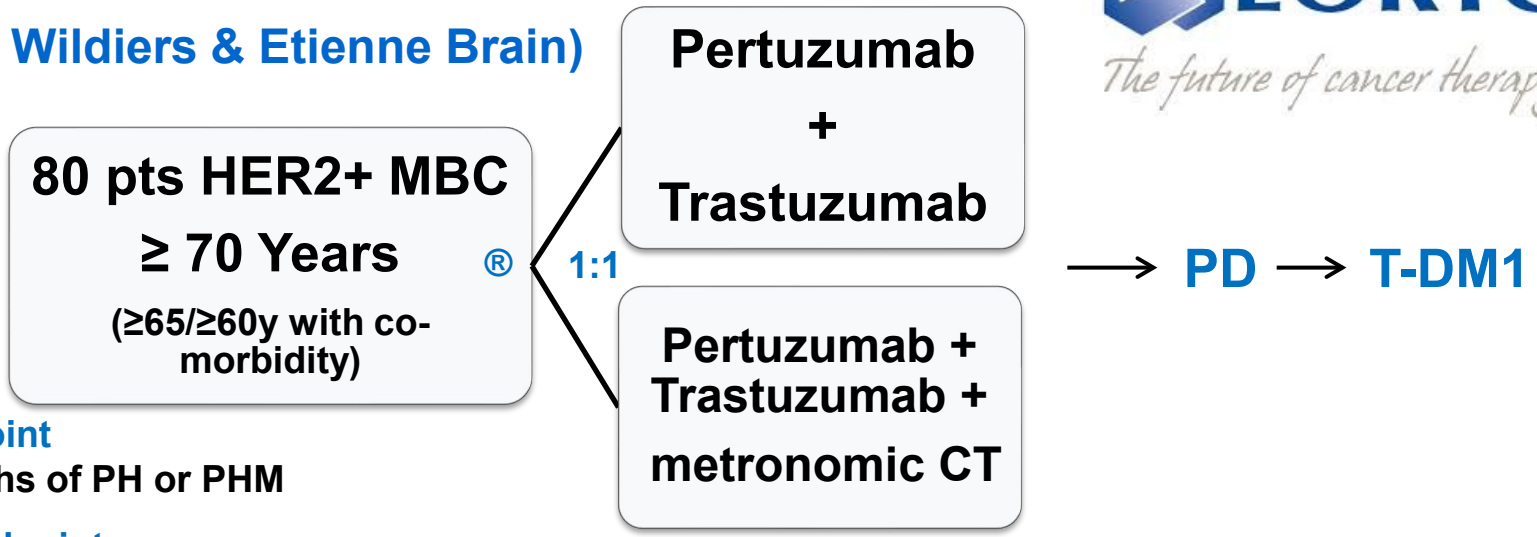
Primary endpoint
- Proportion of patients who permanently stopped treatment at 6 months (cohort B) and at 18 months (cohort A) for any reason (toxicity, patient's choice, progression or death)

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.

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

rapid communicatio

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

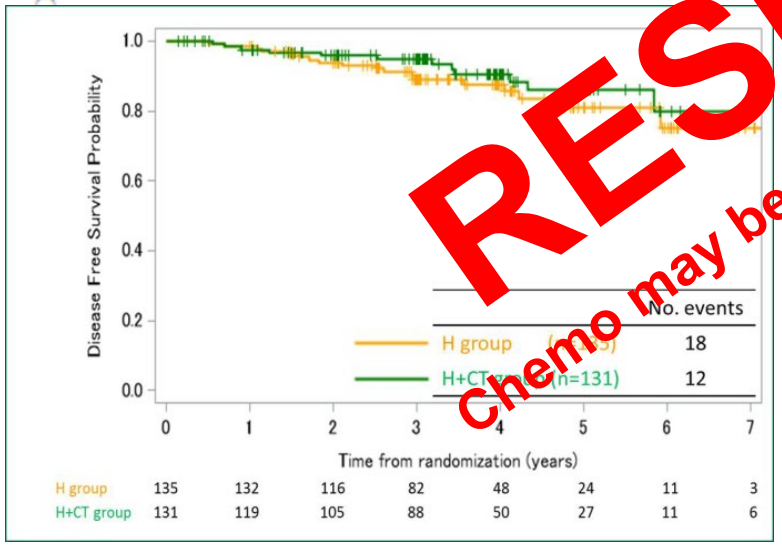
Masataka Sawaki, MD, PhD[1]; Naruto Taira, MD, PhD[2]; Yukari Uemura, PhD[3]; Tsuyoshi S to, PhD[4]; nichi Baba, MD[5]; Kokoro Kobayashi, MD[6]; Hiroaki Kawashima, MD, PhD[7]; Michiko Tsuneizumi, MD, ; Noriko eawa D, PhD[9]; Hiroko Bando, MD, PhD[10]; Masato Takahashi, MD, PhD[11]; Miki Yamaguchi, MD, ; omu Ta hima, 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

Check f update

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)



HER2-positive elderly patient
Age: 70-80 years old
Stage : I (pT≥1 cm), IIA, IIB, IIIA / M0
HER2 : IHC 3+ or FISH+

Randomization

Trastuzumab monotherapy
H-mono 150 patients
Trastuzumab (1 year)

Trastuzumab + Chemotherapy
H+CT 150 patients
Trastuzumab (1 year) + CT
(Investigator's choice from PTX/DTX/AC/EC/CMF)

Sawaki JCO 2020

pcori PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Funding Opportunities | Research & Related Projects | Engagement in Research | Implementation of Evidence

Explore Our Portfolio

Research | In progress; Not yet recruiting

Comparing Oral Drug Dosing Strategies in Older Patients with Metastatic Breast Cancer to Maximize Tolerance and Reduce Discontinuation: The CDK4/6 Inhibitor Dosing Knowledge (CDK) Study

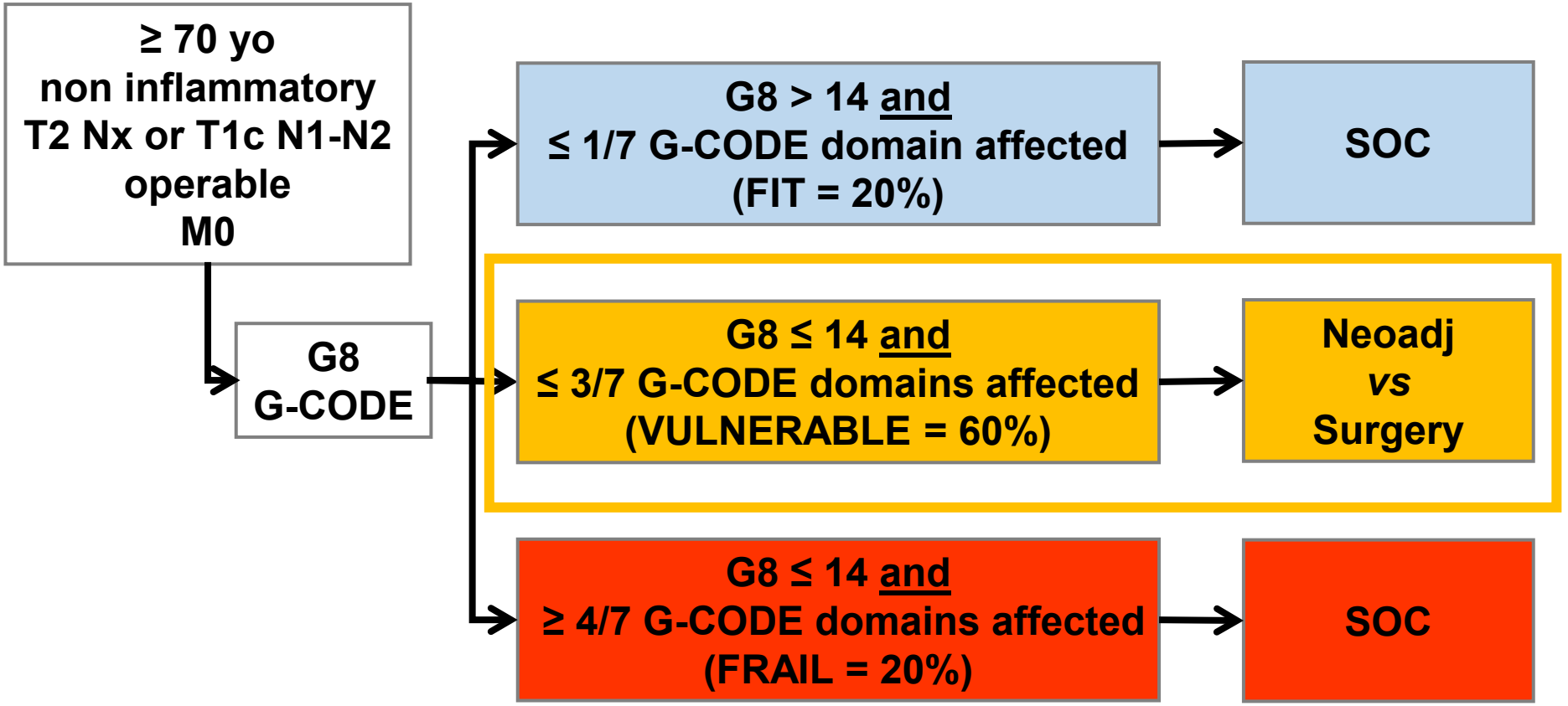
500 patients ≥ 65 yo
HR+/HER2- MBC
planned use of CDK4/6i (PAL or RIB) + ET
1st time in metastatic setting

Indicated dose (start high, deescalate if needed)
versus (1:1)
titrated dose (start low, escalate if tolerated)

Primary objective = time to discontinuation of CDK4/6i

https://www.pcori.org/, https://clinicaltrials.gov/study/NCT06377852

Screening for EORTC BCG 2338



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

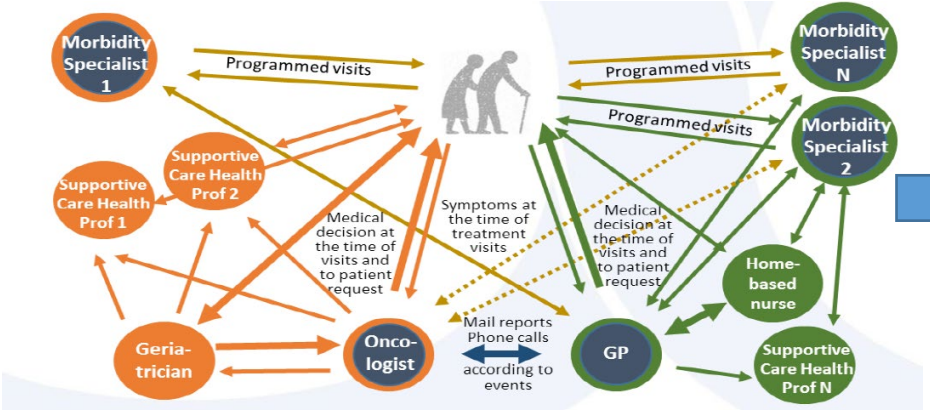
Tools for research in older ones

- **Measuring outcomes and consider factors important in older persons**: not just on maximizing the lifespan but also the health span (i.e. years free of disease and disability)
- **Data science and IA**, but most valuable information about patients (goals, preferences, life circumstances, social and psychological determinants) often missing from data sources
- **Real-time tracking of enrollment and representativeness**

Box. Core Concepts That Define Aging Research
Focus on maximizing function and quality of life
Falls, mobility, and physical function
Cognitive function and delirium
Multimorbidity
Person-centered outcomes and goals for care
Care across settings
Prevention and avoidance of overtreatment (eg, less is more, avoidance of polypharmacy, deprescribing, patient safety)
Palliative care
Well-being of caregivers
Social context of care

Cohen JAMA Internal Med 2024, Covinsky JAMA Internal Med 2024

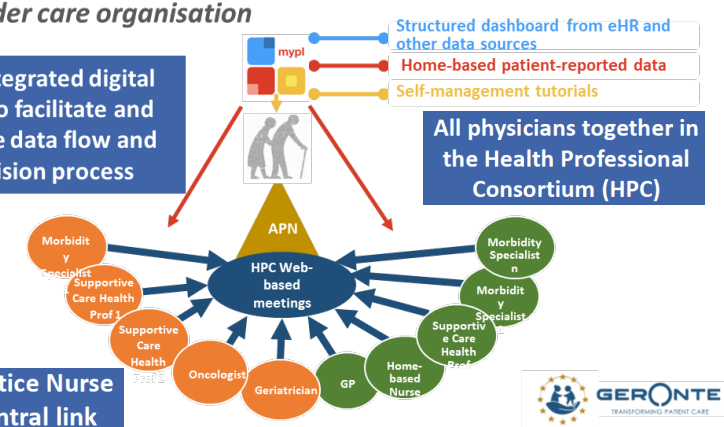
≥ 70 yo & ≥ 1 moderate/severe multimorbidity



GERONTE patient-centred management

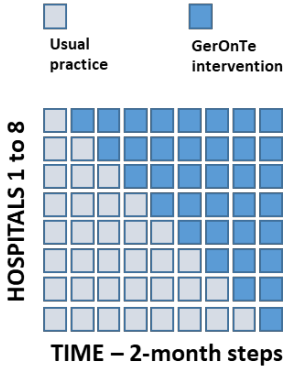
Reconsider care organisation

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
Breast, colorectal, prostate, lung
90/site, 10 q2m, 30 mths

GERONTE TRANSFORMING PATIENT CARE

Geriatric COre DatasEt (G-CODE)

(Delphi/RAND + Consensus Methods)

DIALOG
Gerico · Ucog

1. **Social environment**: Q1 “do you live alone?” + Q2 “do you have a person or caregiver able to provide care and support?”
2. **Autonomy**: Activities of Daily Living (ADL) (abnormal if <6/6) and 4-Instrumental ADL (IADL) (abnormal if <4/4)
3. **Mobility**: Timed Up and Go test (TUG) (abnormal if >20 sec)
4. **Nutrition**: unintentional weight loss (>10% in 6 months) and BMI (< 21)
5. **Cognitive status**: Mini-Cog (abnormal if <4/5)
6. **Mood**: Mini-Geriatric Depression Scale (Mini-GDS) (abnormal if ≥ 1/4)
7. **Comorbidities**: updated Charlson index score

→ National & International validation

DIALOG = GERICO + UCOG
(intergroup of clinical research in GO labeled by INCa in 2014-2017-2022)

Paillaud Eur J Cancer 2018

Today

Community

SoFOG
SOCIÉTÉ FRANCOPHONE D'ONCO-GÉRIATRIE

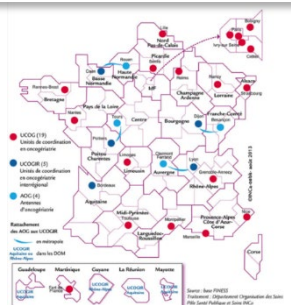
Scientifc Committee

INSTITUT NATIONAL DU CANCER

DIALOG
Gerico · Ucog

unicancer

GERICO
unicancer



UCOG national network

Conclusions

- Age is not a contra-indication to treatment for…
  …nor to clinical trials!
- Age is an independent predictor of adverse outcomes associated with treatment for…
  … especially when relying on results from trials run in younger adult population

- Clear information and consideration are crucial (semantic)
- No age-agnostic prognostic/predictive tool!
- Goals & preferences shift with time flow and life experience

SIOG
INTERNATIONAL SOCIETY OF GERIATRIC ONCOLOGY

2024
MONTREAL
CANADA
17–19 OCT



Shabbir Alibhai
NATIONAL COORDINATOR, SIOG 2024 SCIENTIFIC PROGRAMME COMMITTEE

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

Supriya Mohile
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Optimising treatment in older cancer patients is precision medicine too!

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