

CLINICAL STUDIES IN OLDER PATIENTS: PROBLEMS AND POSSIBILITIES

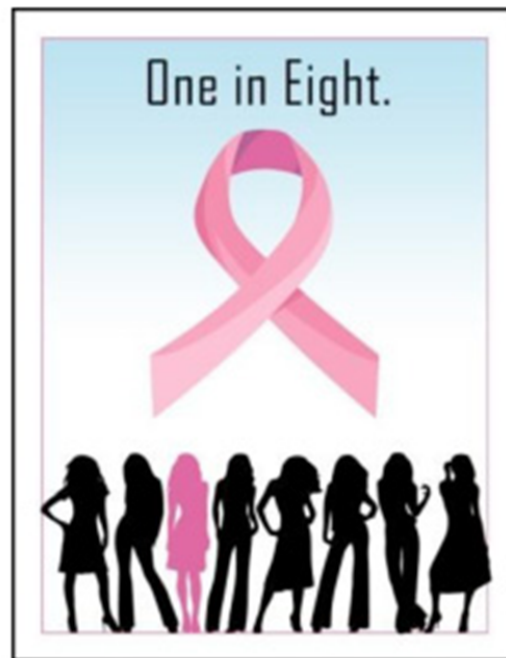
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How we like to think about our patients with breast cancer



How our patient population actually looks like



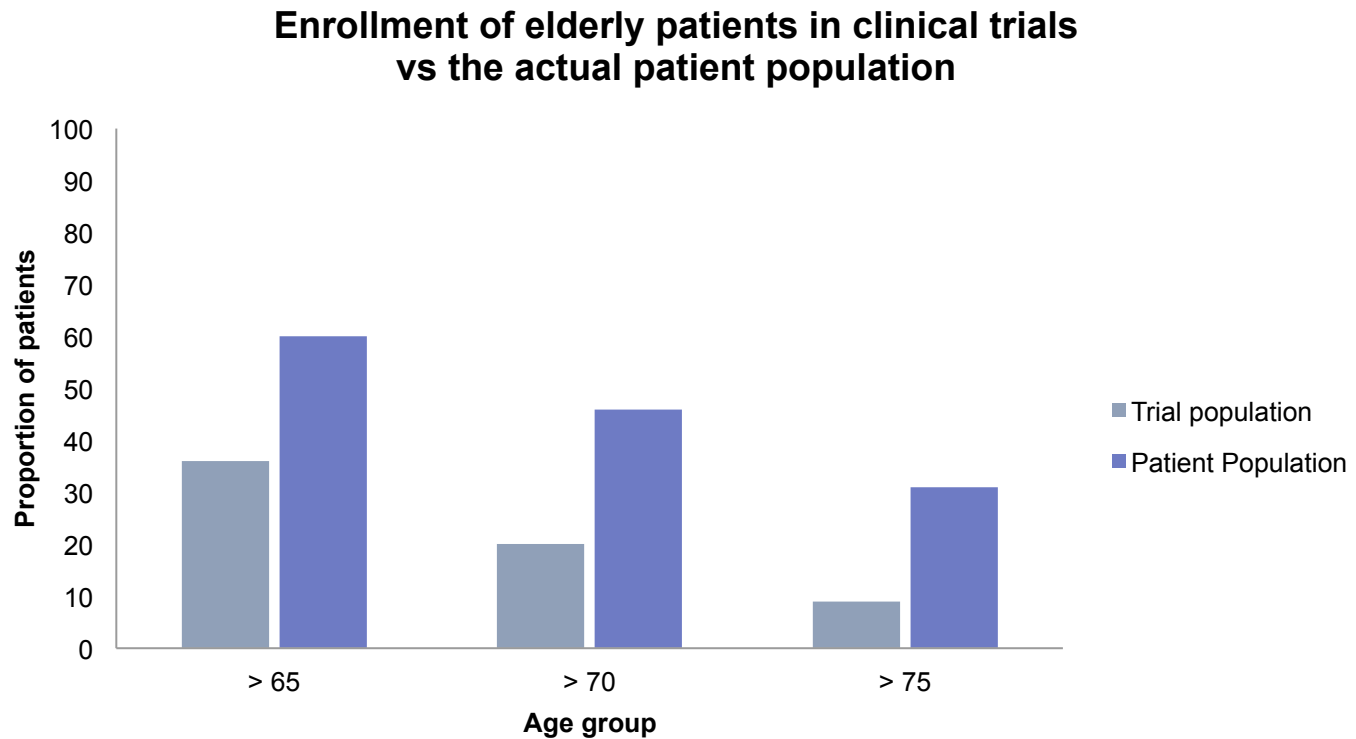
Our perception of patients with breast cancer has translated into our design of clinical trials

"We do not see things as they are, we see things as we are."

Current clinical trials do not fit to the needs of the older population

- Patient population in trials are not representative for the older population
- Focussed on innitiation and intensification of treatment
- Well established end points are not appropriate and relevant for older patients

Underrepresentation of Older Patients with Cancer in Clinical Trials



Trial population of corresponding age is not representative for general population

Older Trial Population



Older General Population



Poor External Validity of a Clinical Trial for older patients

Older Trial population

- Fewer Comorbidities
- Higher socio economic status
- More favourable tumor characteristics
- Lower overall mortality

compared to

Older General Population

Only 4% of current clinical trials for breast cancer are focussed on older patients

Clinical Trials Search Results

Display:

Title

Description with: Locations Eligibility

Full Trial Description

Custom

Hide Search Criteria ^

Cancer Type/Condition: Breast cancer, female

Trial Type: Treatment

Results 1-25 of 359 for your search:

Select All on Page

Sort by: Phase of Trial

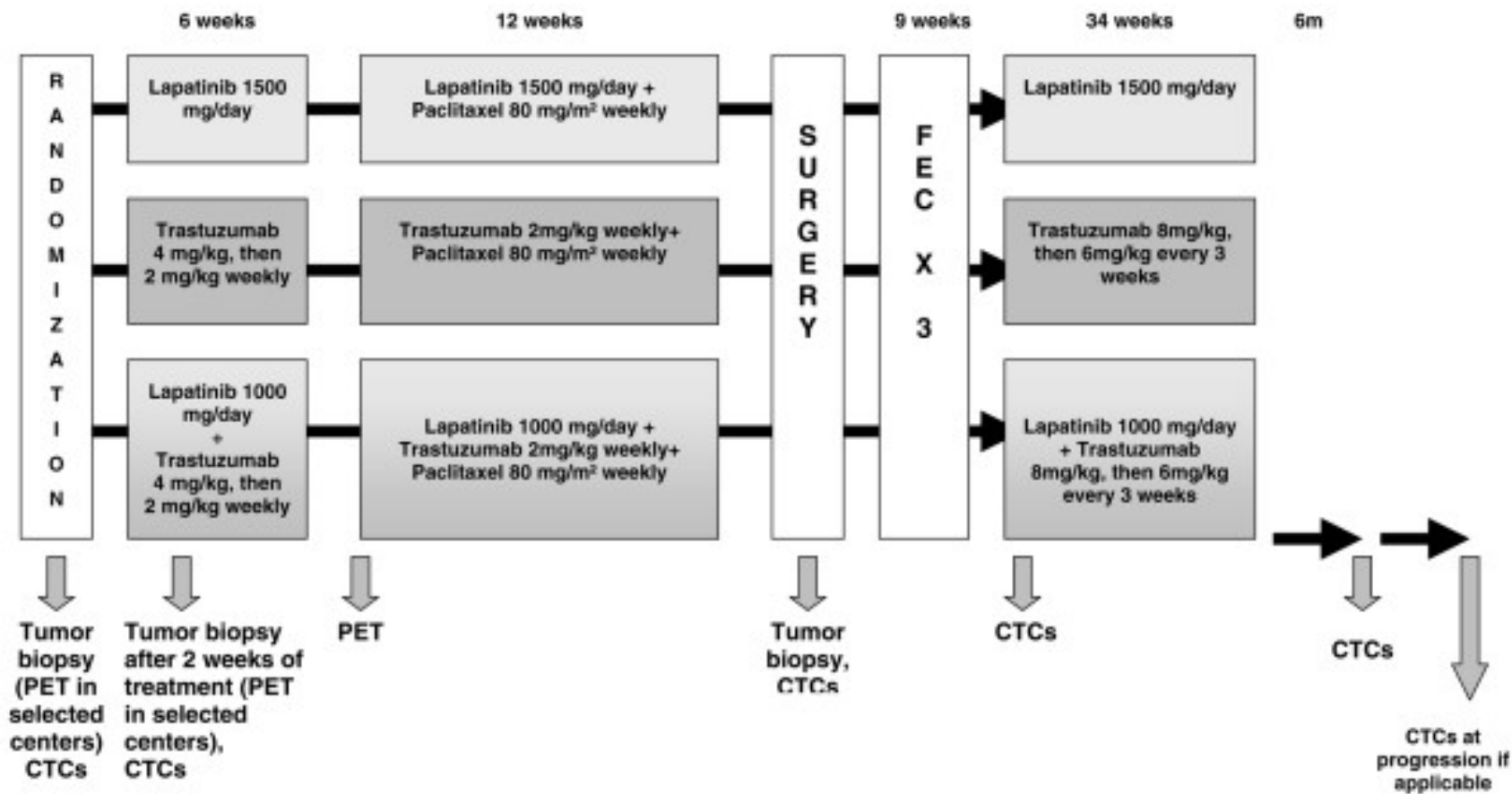
Show 25

Results per Page

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Trial designs



Omission of therapy might be a more clinically relevant question

Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial

Ian H Kunkler, Linda J Williams, Wilma J L Jack, David A Cameron, J Michael Dixon, on behalf of the PRIME II investigators

Summary

Background For most older women with early breast cancer, standard treatment after breast-conserving surgery is adjuvant whole-breast radiotherapy and adjuvant endocrine treatment. We aimed to assess the effect omission of whole-breast radiotherapy would have on local control in older women at low risk of local recurrence at 5 years.

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Adjuvant Chemotherapy in Older Women with Early-Stage Breast Cancer

Hyman B. Muss, M.D., Donald A. Berry, Ph.D., Constance T. Cirrincione, M.S., Maria Theodoulou, M.D., Ann M. Mauer, M.D., Alice B. Kornblith, Ph.D., Ann H. Partridge, M.D., M.P.H., Lynn G. Dressler, Ph.D., Harvey J. Cohen, M.D., Heather P. Becker, Patricia A. Kartscheske, B.S., Judith D. Wheeler, M.P.H., Edith A. Perez, M.D., Antonio C. Wolff, M.D., Julie R. Gralow, M.D., Harold J. Burstein, M.D., Ph.D., Ahmad A. Mahmood, M.D., Gustav Magrinat, M.D., Barbara A. Parker, M.D., Ronald D. Hart, M.D., Debjani Grenier, M.D., Larry Norton, M.D., Clifford A. Hudis, M.D., and Eric P. Winer, M.D., for the CALGB Investigators*

Current clinical trials do not fit to the needs of the older population

- Patient population in trials are not representative for the older population
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- Well established end points are not suitable and relevant for older patients

Trial outcomes

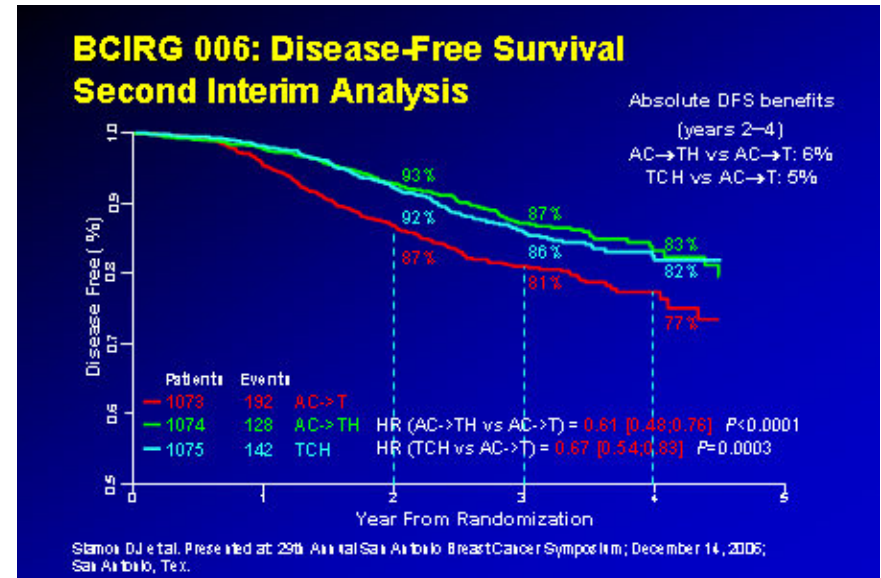
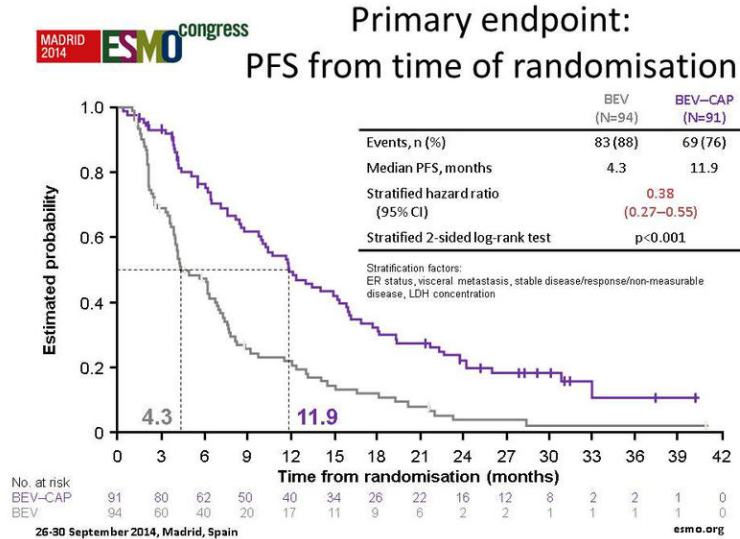
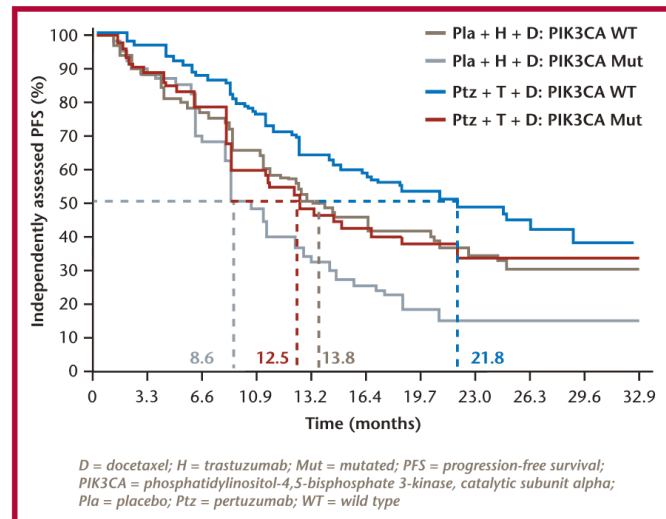


Figure 2. Progression-free survival by PIK3CA status



Clinical trials are focussed on cancer related outcomes

- Disease free survival: time to disease recurrence or death due to any cause
- Recurrence free survival: time to disease recurrence or death due to breast cancer
- Progression free survival: time to progression
- Treatment Failure Free Survival: time to early treatment discontinuation because of any reason other than death due to other cause

Using these endpoints in the older population

- Cancer related endpoints are influenced by competing causes of death
- Defining cause of death is challenging in older patients:
 - Some cancer treatments might also influence non–cancer-related deaths
 - Misclassification of cause of death in older patients
- But most of all: does it really matter to patients how they die?

If level A evidence is not helping us...

Use Level B!

Observational Data

- Advantages specifically for the older population:
 - Population based evidence
 - Survival analysis does not rely on cause of death
- Relative Survival = excess mortality due to breast cancer

$$\frac{\text{Overall survival of population with breast cancer}}{\text{Overall survival of matched background population}}$$

- Includes both death directly from breast cancer as well as treatment related death

An example



Treatment patterns and relative survival for older patients with non-metastatic breast cancer

An international comparison using the EURECCA database

Aim of the study



To compare **locoregional and systemic treatment strategies** between European countries in patients aged 70 years and older with non-metastatic breast cancer

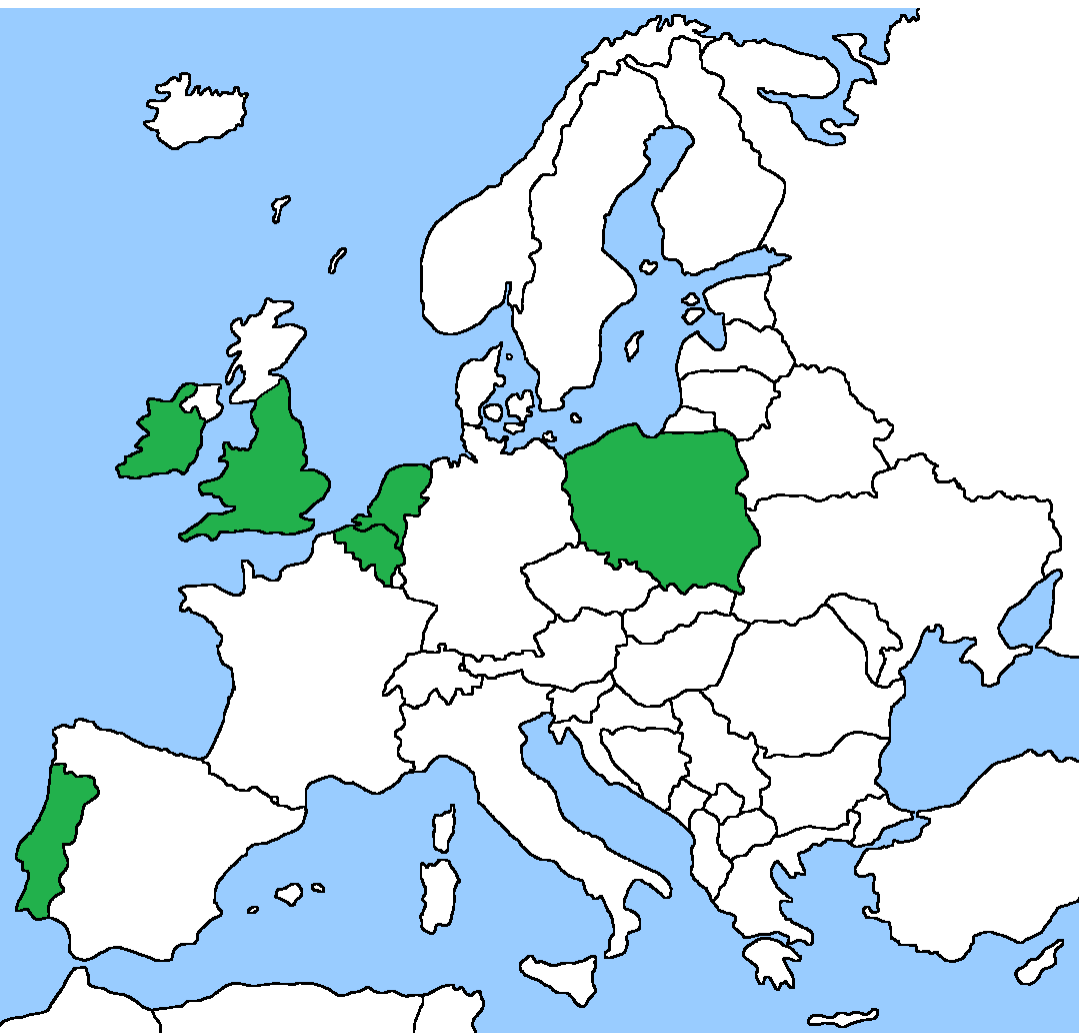
To compare **relative survival** between European countries in patients aged 70 years and older with non-metastatic breast cancer

- Data selection
 - Population based national or regional data registry
 - Incidence years 2000 and onwards
 - Breast cancer TNM stage I-III
 - Women aged ≥ 70 years and older

- Comparing treatment strategies
 - Stratification according to stage of disease
 - Proportion of treatment (%) using descriptive statistics and chi-square test

- Comparing relative survival
 - Stratification according to stage of disease
 - Incidence years 2000-2010
 - Five year relative survival
 - Relative Excess Risk (RER)
 - Adjusted for age, incidence year, grade, morphology

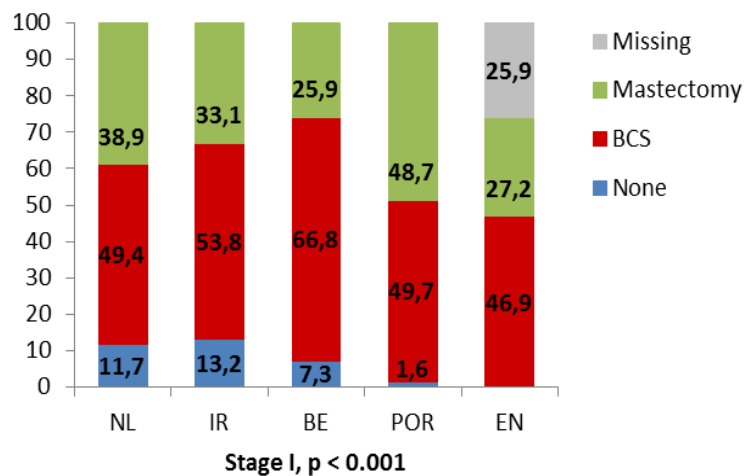
Data Registries



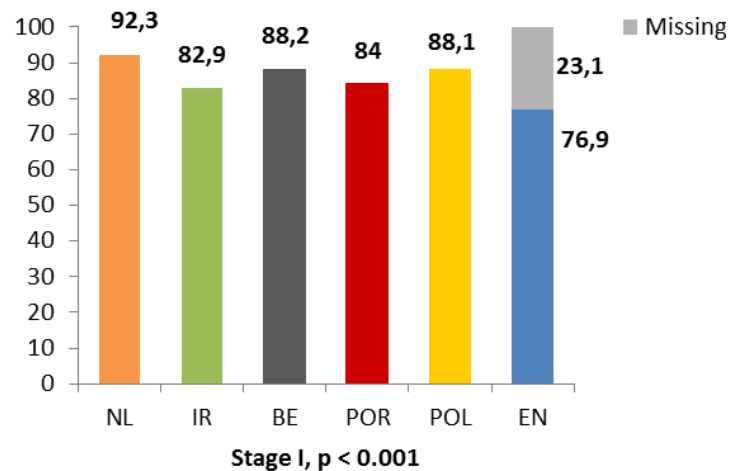
Country	Data	Incidence years	<i>n</i>
The Netherlands	National	2000-2010	39 704
Belgium	National	2003-2009	5 156
Ireland	National	2007-2008	3 931
Portugal North	Regional	2006-2010	654
Poland	Regional	2011-2014	516
England	National	2000-2014	69 164
Total			119 125

Stage I – Locoregional treatment

% Most extensive surgery

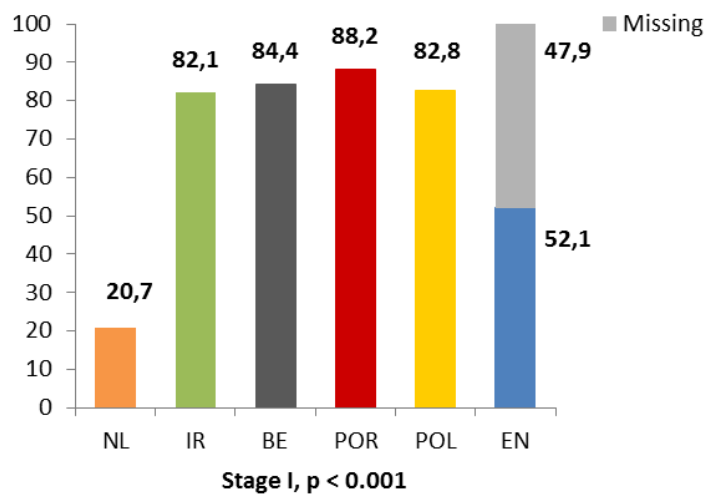


% Radiotherapy after BCS

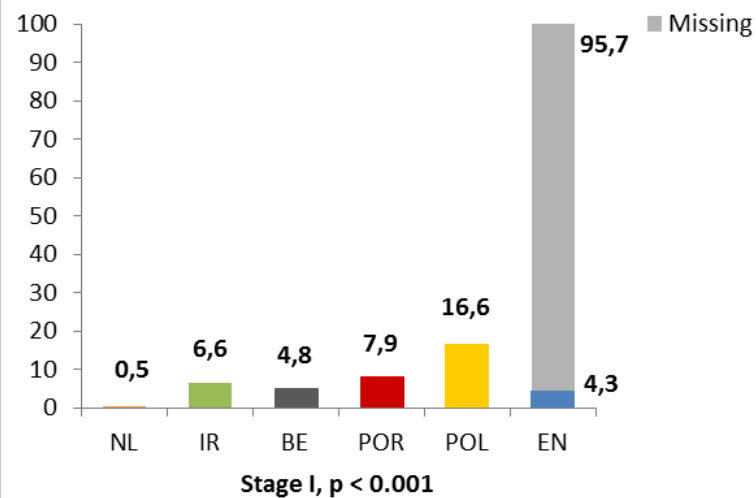


Stage I – Systemic treatment

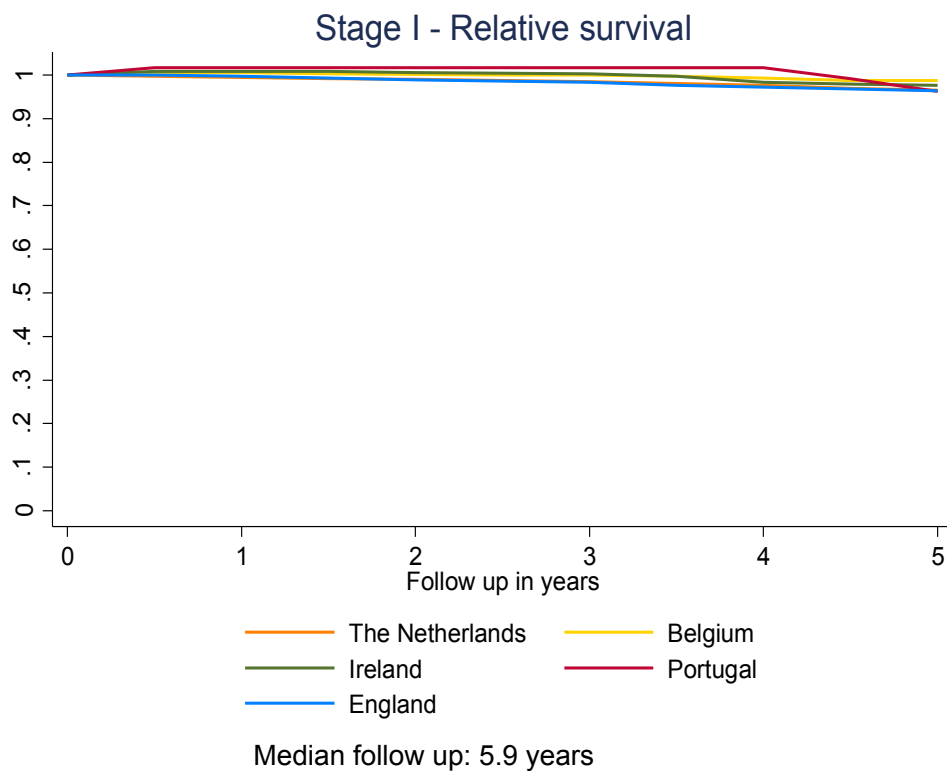
% (neo) Adjuvant endocrine therapy



% (neo) Adjuvant chemotherapy

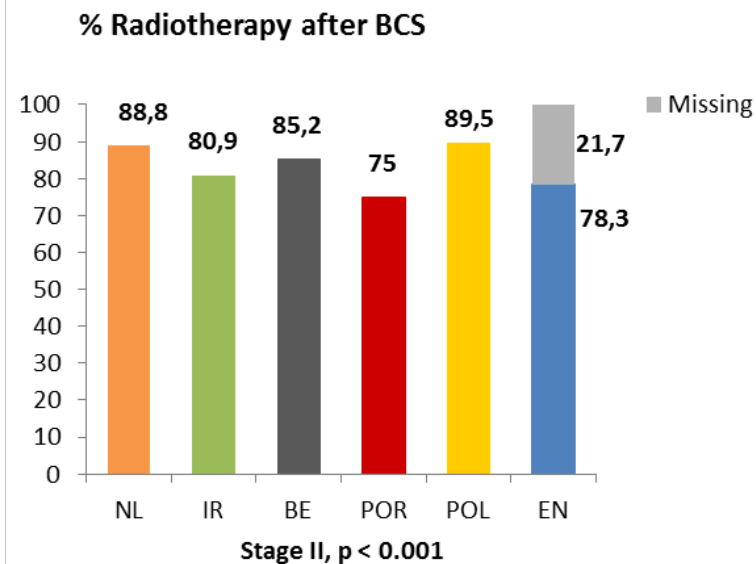
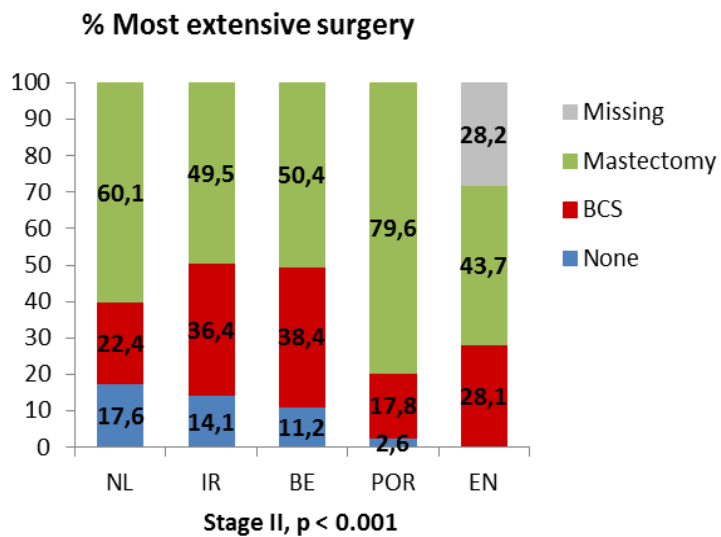


Stage I – Relative survival



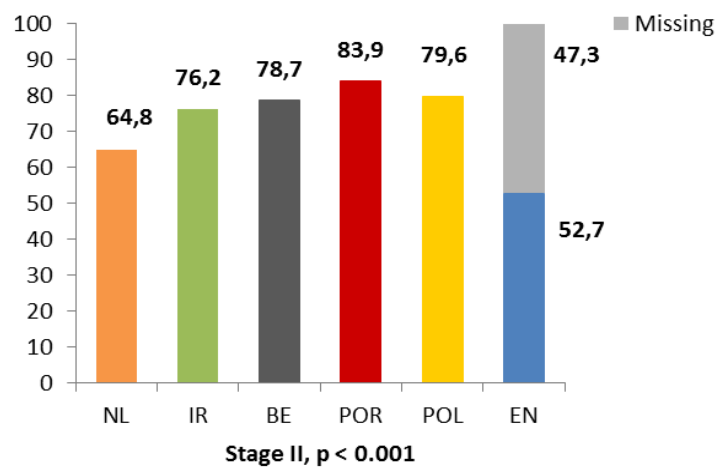
	5 year RS	95% CI	Adj RER	95% CI	p-value
NL	0.96	(0.95-0.97)	ref		
BE	0.99	(0.96-1.01)	0.31	(0.10-0.93)	0.04
IR	0.98	(0.93-1.02)	0.27	(0.02-3.88)	0.33
POR	0.99	(0.91-1.05)	1.02	(0.20-5.34)	0.98
EN	0.97	(0.96-0.98)	1.31	(1.10-1.58)	0.003

Stage II – Locoregional treatment

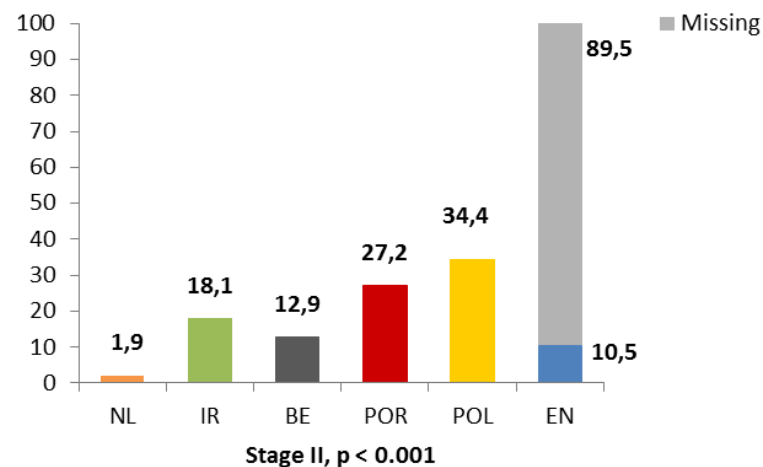


Stage II – Systemic treatment

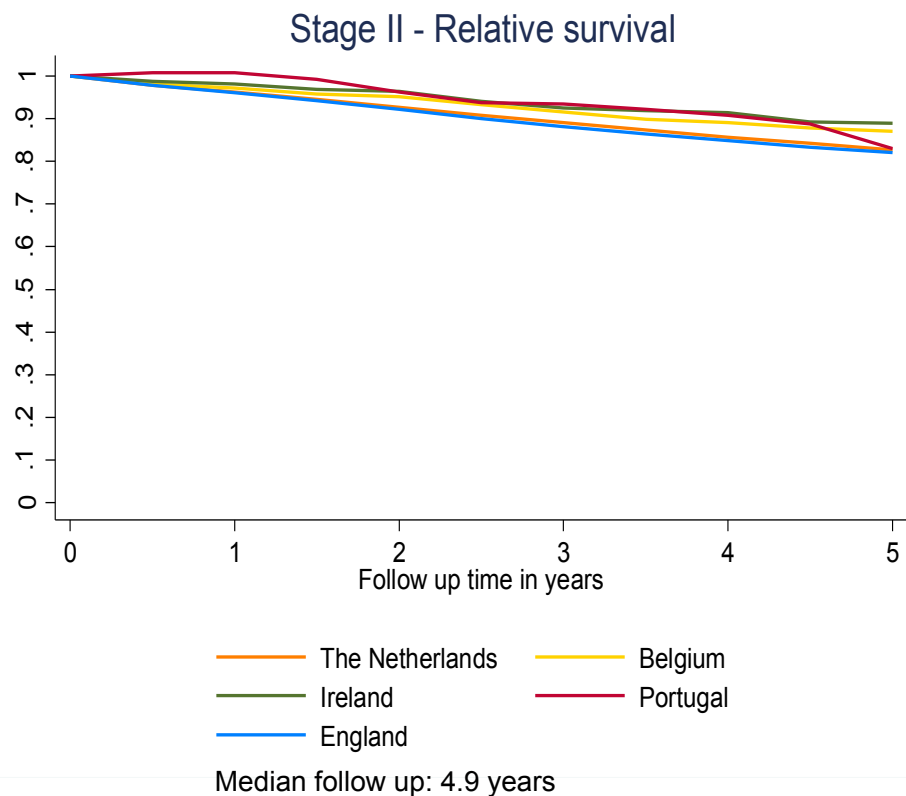
% (neo) Adjuvant endocrine therapy



% (neo) Adjuvant chemotherapy

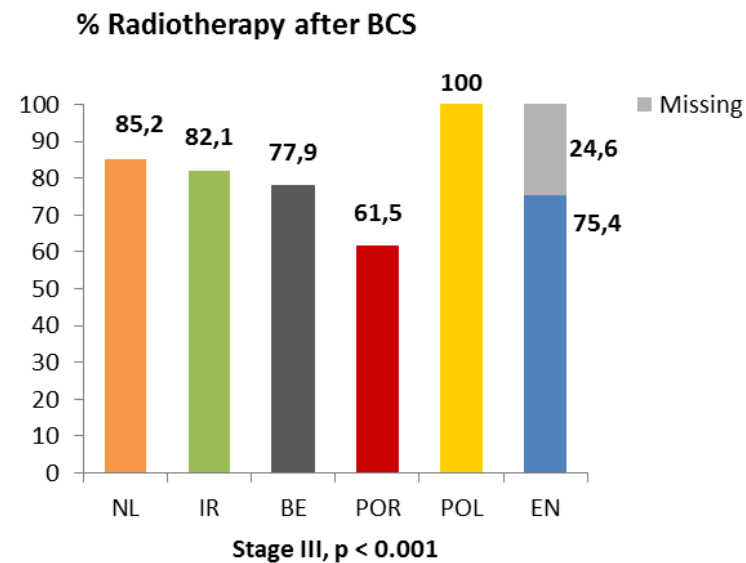
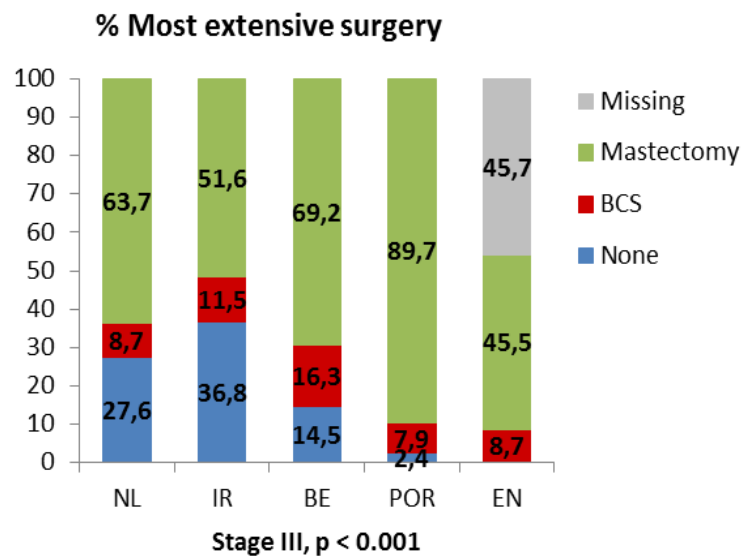


Stage II – Relative survival



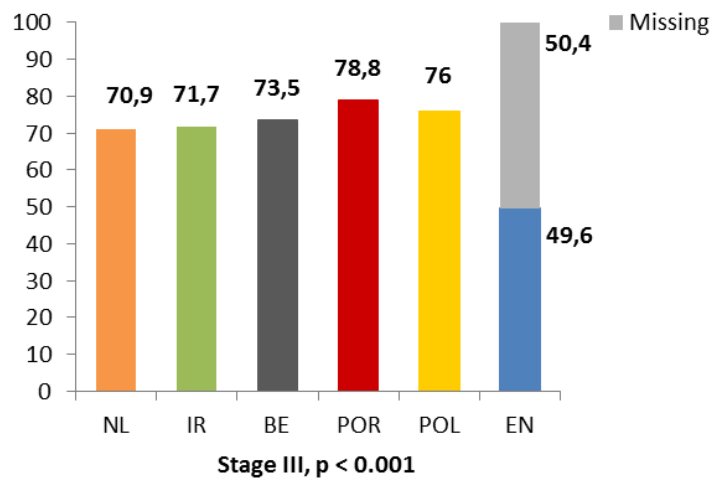
	5 year RS	95% CI	Adj RER	95% CI	p-value
NL	0.83	(0.82-0.85)	Ref		
BE	0.88	(0.85-0.90)	0.72	(0.58-0.90)	0.004
IR	0.89	(0.85-0.92)	0.80	(0.61-1.06)	0.12
POR	0.89	(0.81-0.96)	1.07	(0.64-1.79)	0.80
EN	0.83	(0.82-0.84)	1.20	(1.11-1.30)	< 0.001

Stage III – Locoregional treatment

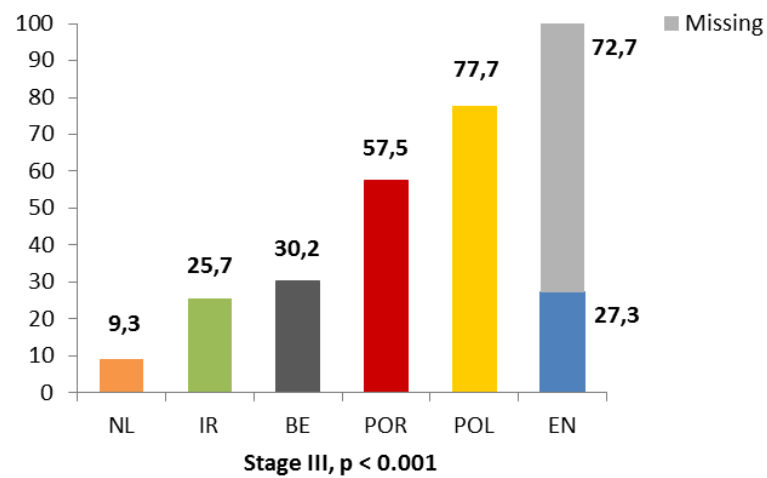


Stage III – Systemic treatment

% (neo) Adjuvant endocrine therapy

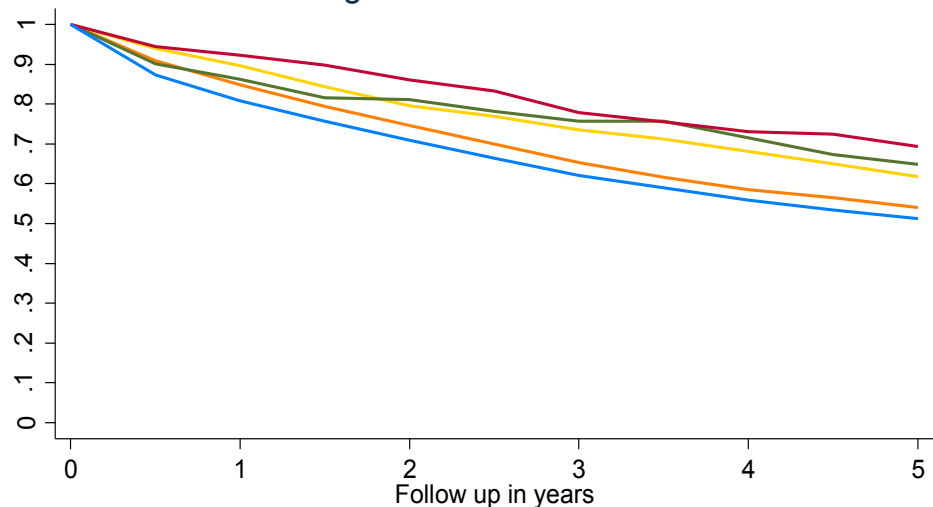


% (neo) Adjuvant chemotherapy



Stage III – Relative survival

Stage III - Relative survival



— The Netherlands — Belgium
— Ireland — Portugal
— England

Median follow up: 3.1 years

	5 year RS	95% CI	Adj RER	95% CI	p-value
NL	0.56	(0.54-0.58)	ref		
BE	0.65	(0.61-0.69)	0.78	(0.66-0.92)	0.004
IR	0.67	(0.59-0.74)	0.81	(0.64-1.02)	0.08
POR	0.72	(0.62-0.82)	0.78	(0.52-1.16)	0.222
EN	0.53	(0.52-0.55)	1.27	(1.17-1.37)	< 0.001

Highlights

Stage I

- Higher proportion of endocrine therapy is associated with improved survival

Stage II

- Higher proportion of systemic therapy (both chemotherapy and endocrine therapy) is associated with improved survival

Stage III

- High proportion of no surgery is not associated with decreased survival
- High proportion of chemotherapy is associated with improved survival

Limitations in data

- International differences in healthcare
- Regional data (selection) versus national data
- Missing data

Limitations in analysis

- Uncertainty regarding causality of the association between treatment strategies and survival outcomes

Findings from this study

Treatment strategies

- Large international differences in treatment strategies for older patients
- Most striking differences in systemic treatment

Survival outcomes

- International differences in five year relative survival outcomes for older patients
- Most striking difference in five year relative survival in stage III

Overall

- Higher proportion of systemic treatment is linked with improved five year relative survival
- Causal relation?

Final remarks

- Future clinical trials should be specifically designed for older patients:
 - Clinically relevant intervention for this population
 - Use overall survival and quality of life as primary endpoints
- Optimize the possibilities of observational data from cancer registries
 - More representative for the older population
 - Use international differences in treatment and survival as indications for optimization of existing treatment possibilities
 - Instrumental variable analysis as a pseudo randomization to directly assess treatment effects

Thank you for your attention