

The Impact of Biological Ageing on Development and Therapy of Breast Cancer

Dr. Barbara Brouwers

Prof. Dr. Hans Wildiers – Prof. Dr. Diether Lambrechts

Dr. Sigrid Hatse

The Biology of Ageing

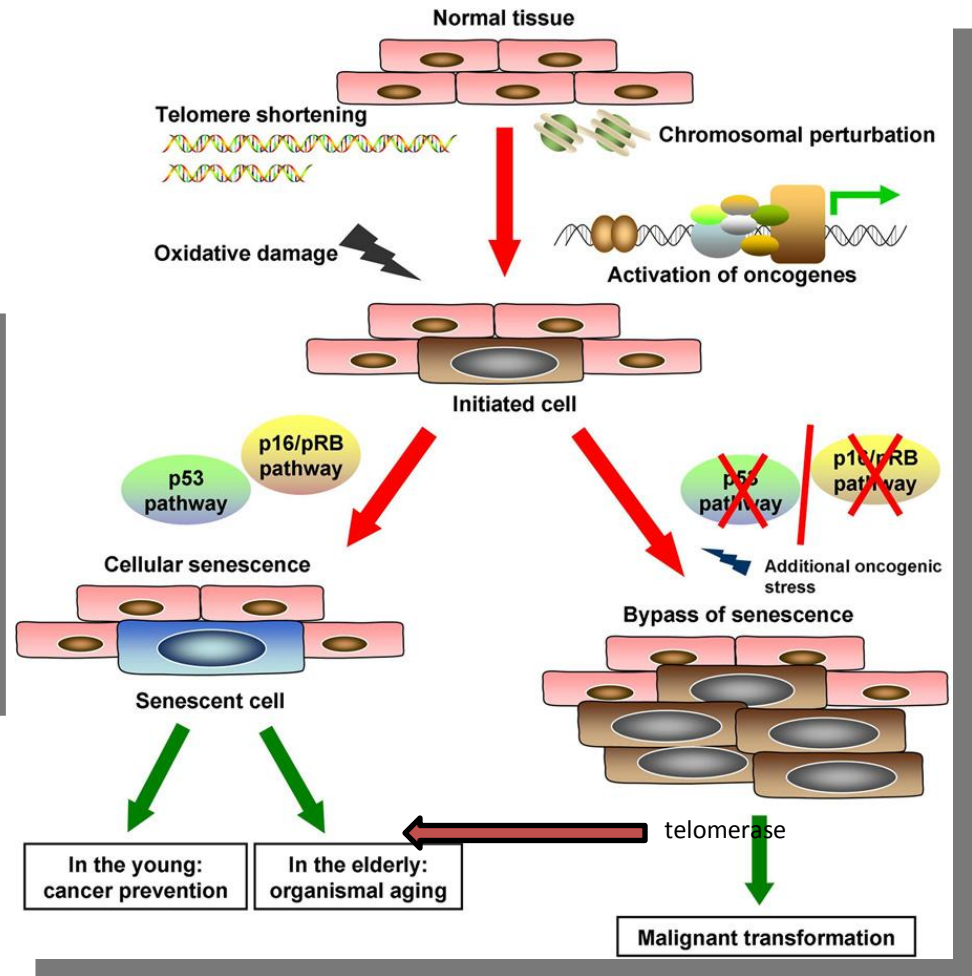
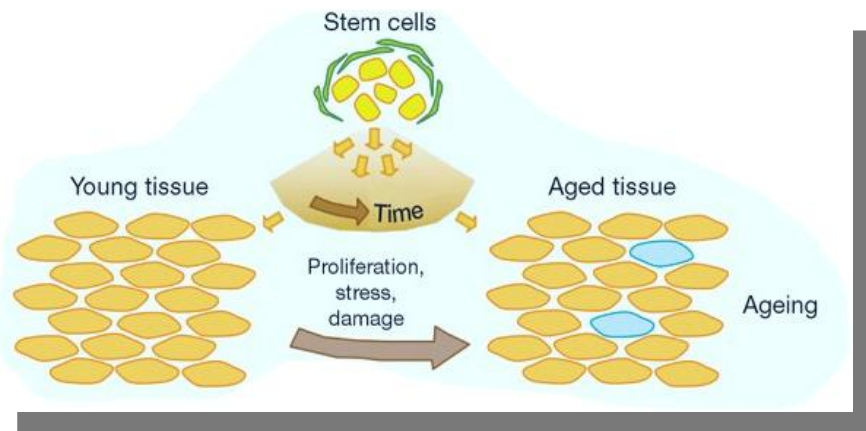


- Genetics
- Environmental Factors
- Diseases/Comorbidities
- ...

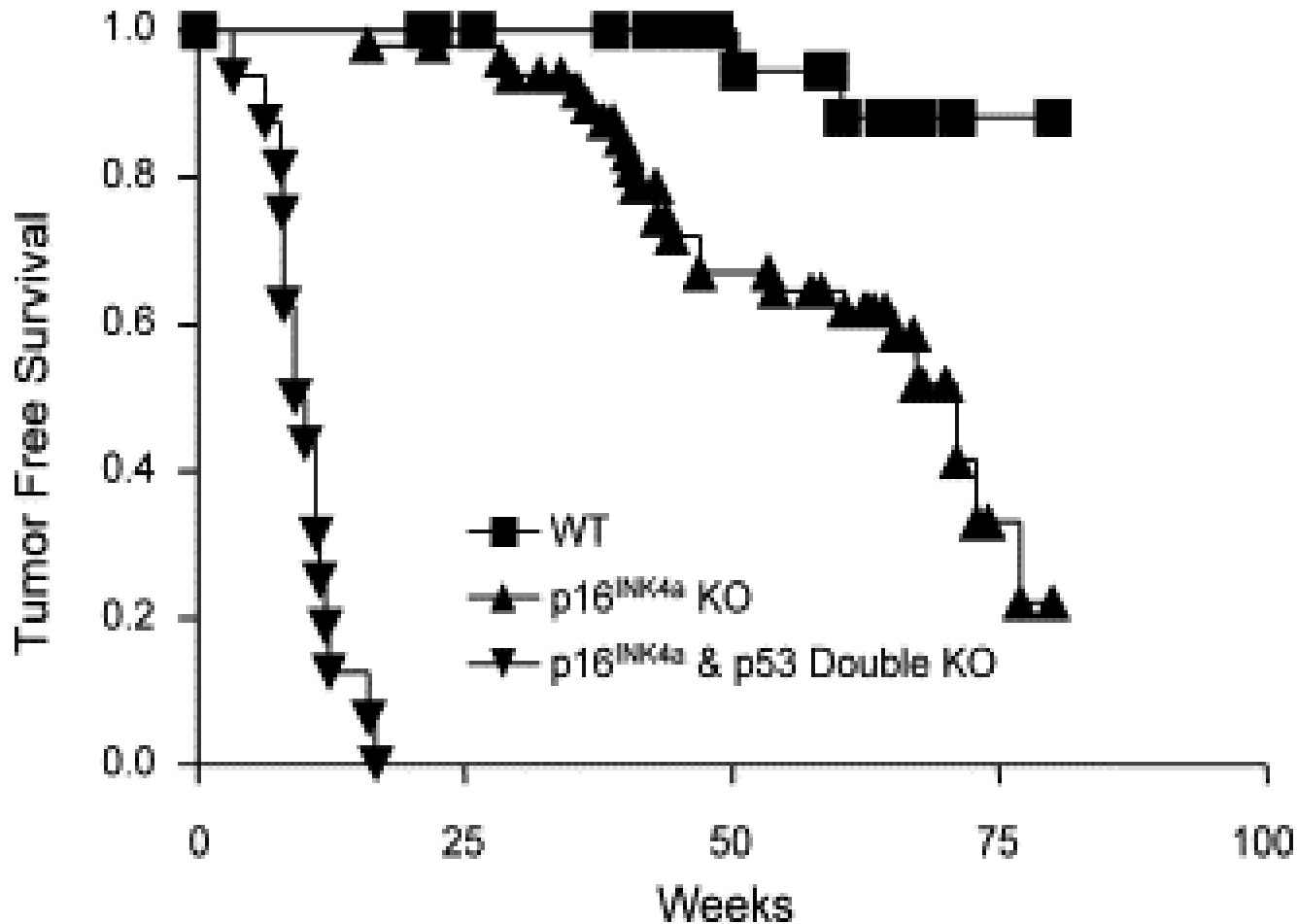


Cellular Senescence

Ageing protects against Cancer

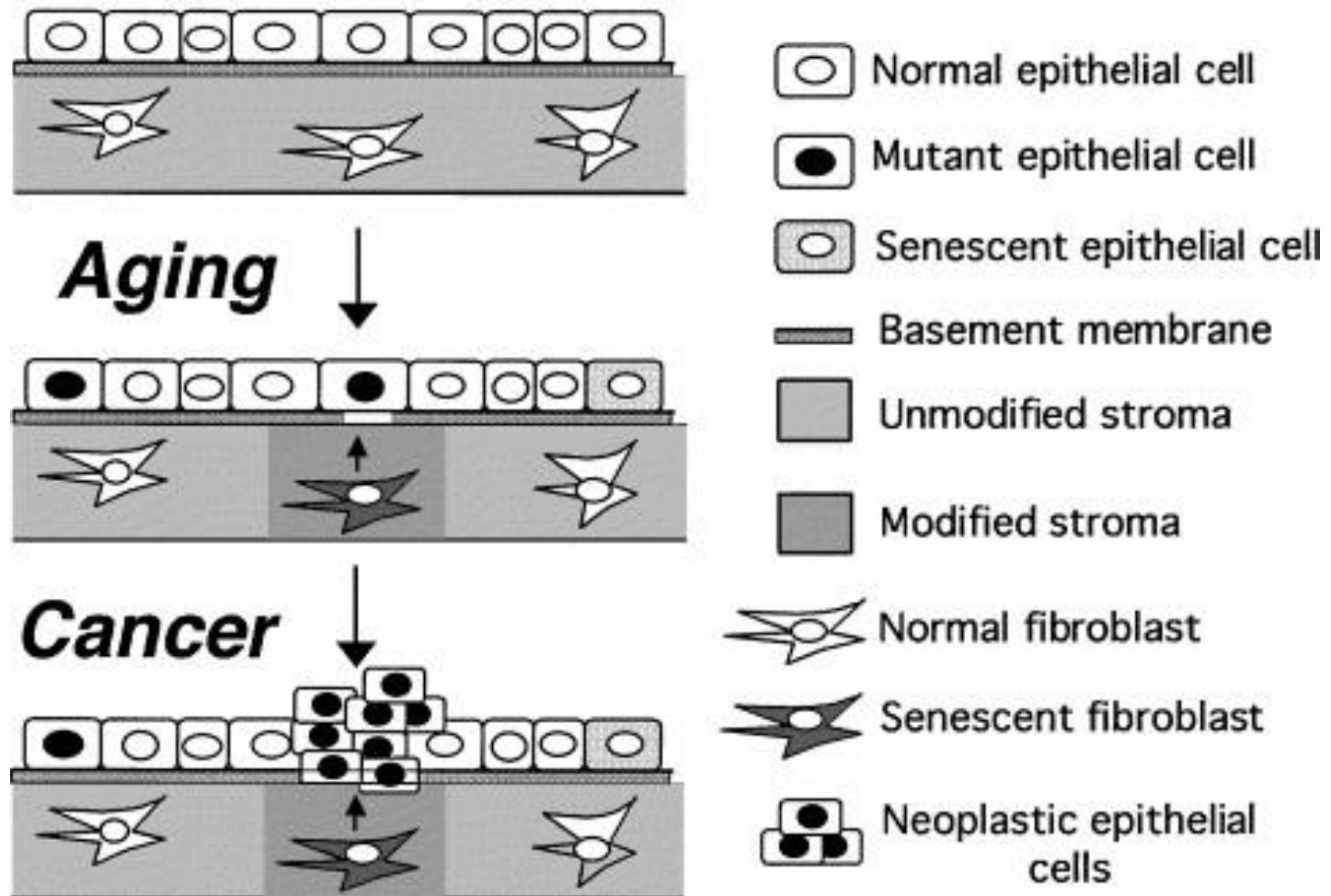


Ageing protects against Cancer

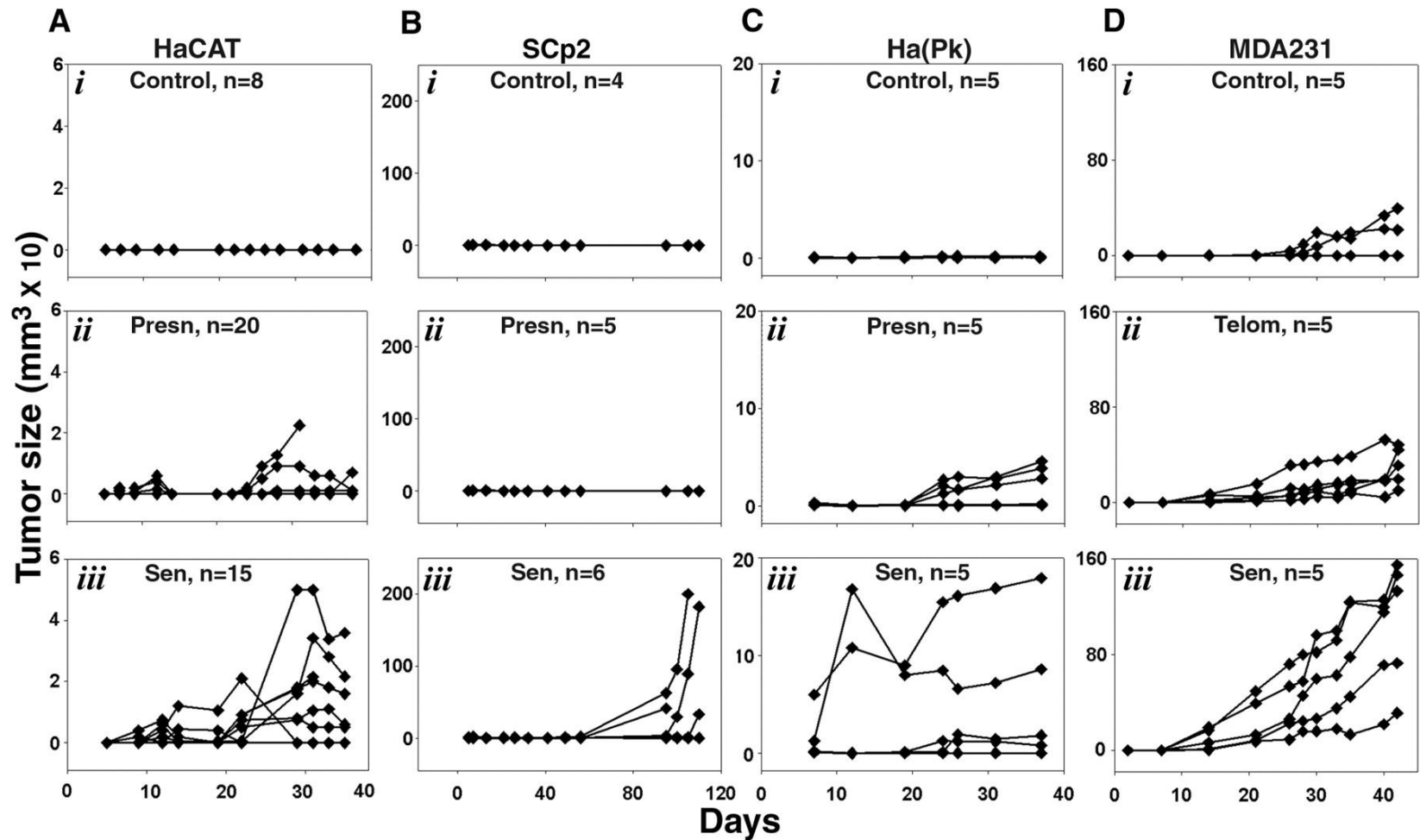


Cellular Senescence

Ageing causes Cancer

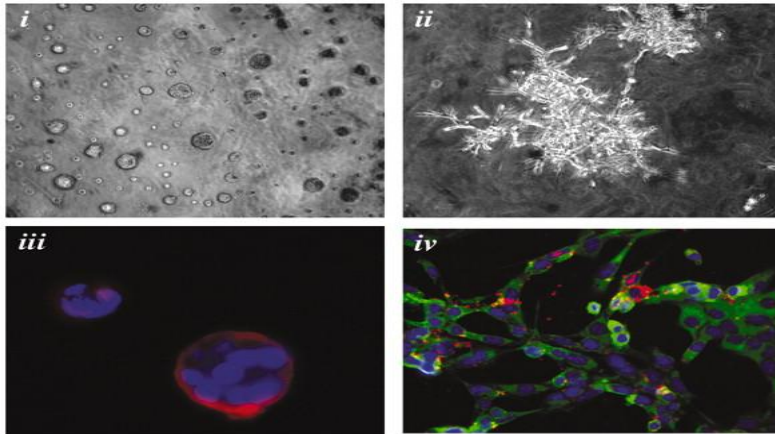


Tumor growth stimulated by fibroblasts.

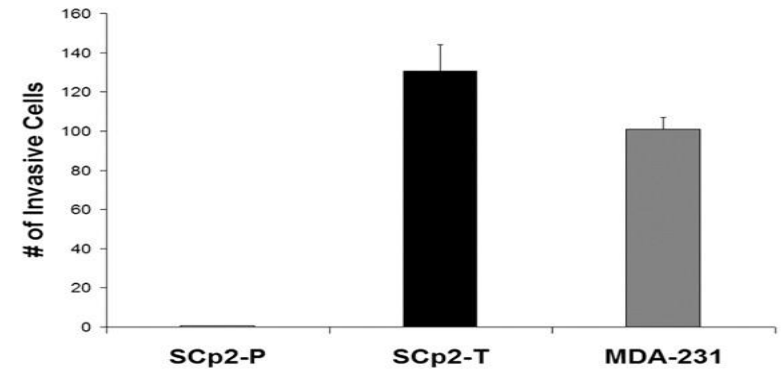


Epithelial tumors stimulated by senescent human fibroblasts progress to full malignancy.

A



B



C

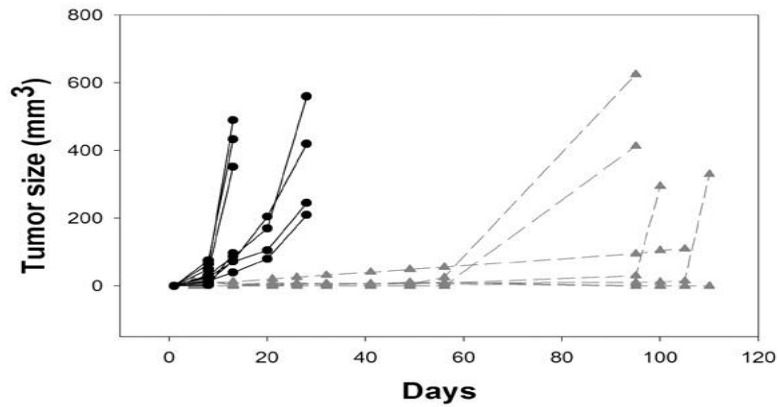
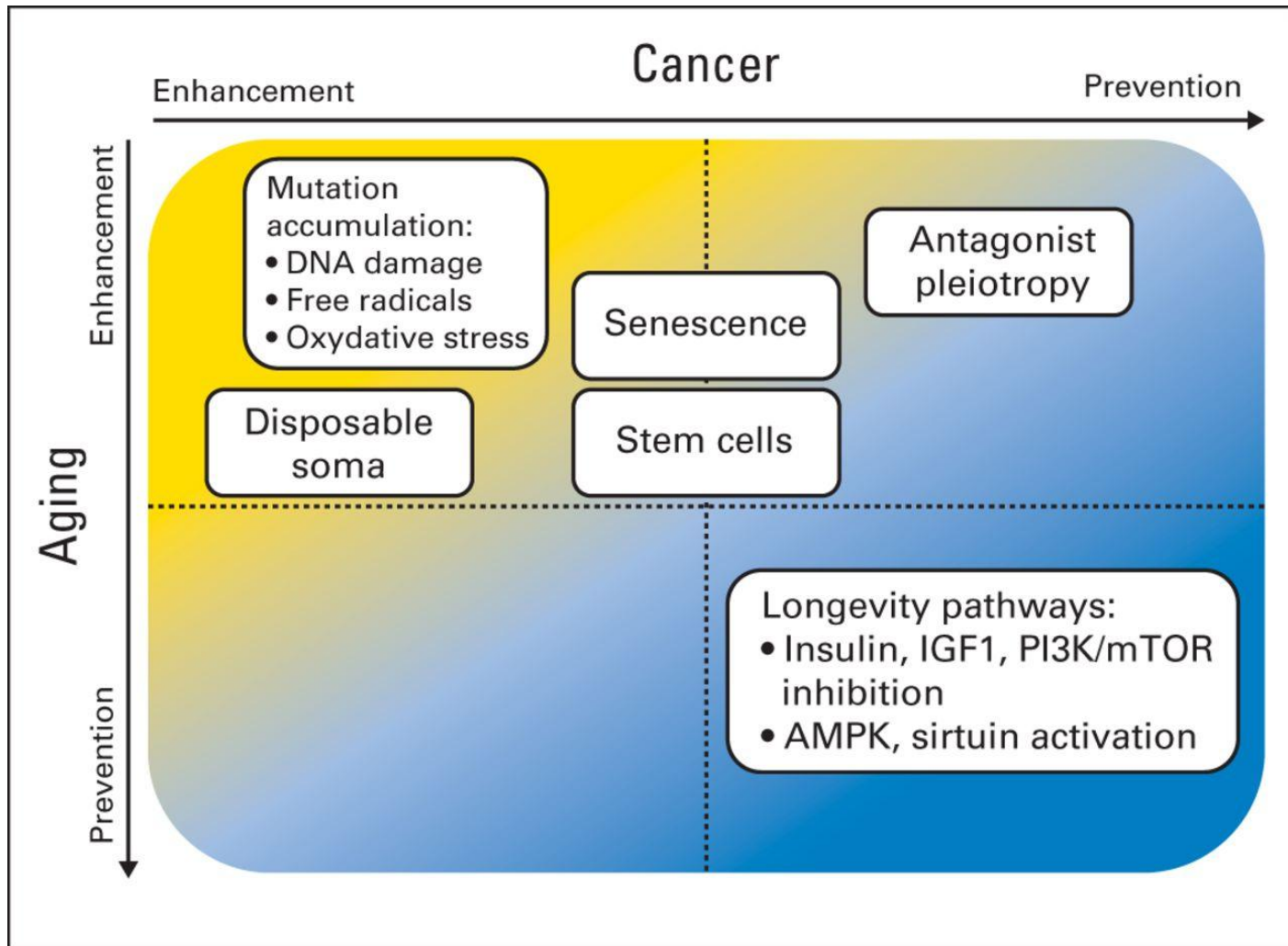


Diagram representing the different positions of the theories of aging on the prevention versus enhancement of aging and cancer.



Falandry C et al. JCO 2014;32:2604-2610

Research Questions

Hypothesis 1

Biological ageing in the host creates a growth- en metastasis stimulating microenvironment

Hypothesis 2

Chemotherapy accelerates biological ageing in the host

- Geriatric Assessment
- Biomarkers of Ageing

B-CGA-1 study
Elderly Biomarker Study

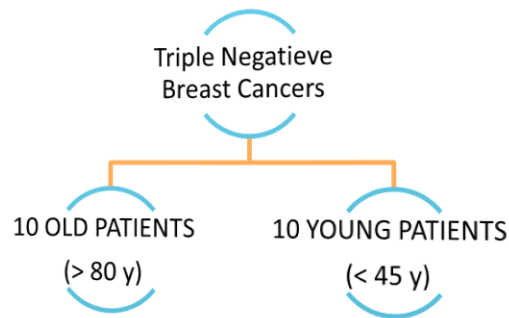
Stromal Gene Expression



Elderly Stromal Gene Expression Study

Materials and Methods

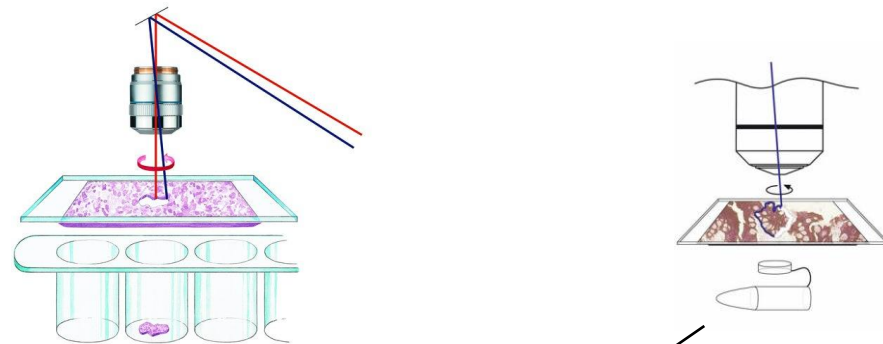
(in cooperation with I.Bordet – D.Fumagalli / C. Sotiriou)



Tumors are matched for

- Tumor Grade
- Tumor Size
- Nodal Status

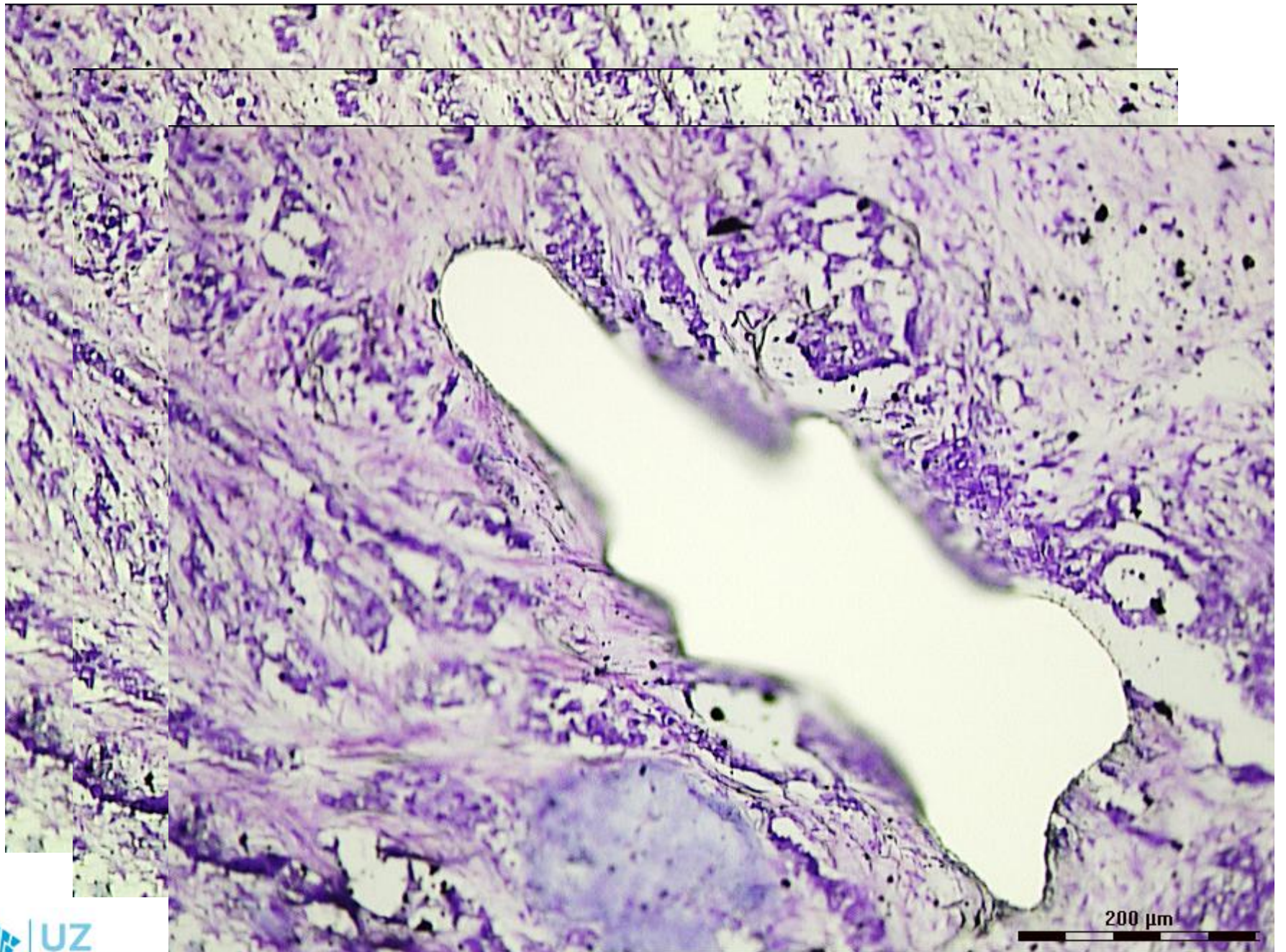
Laser Capture Microdissection of tumor associated stroma

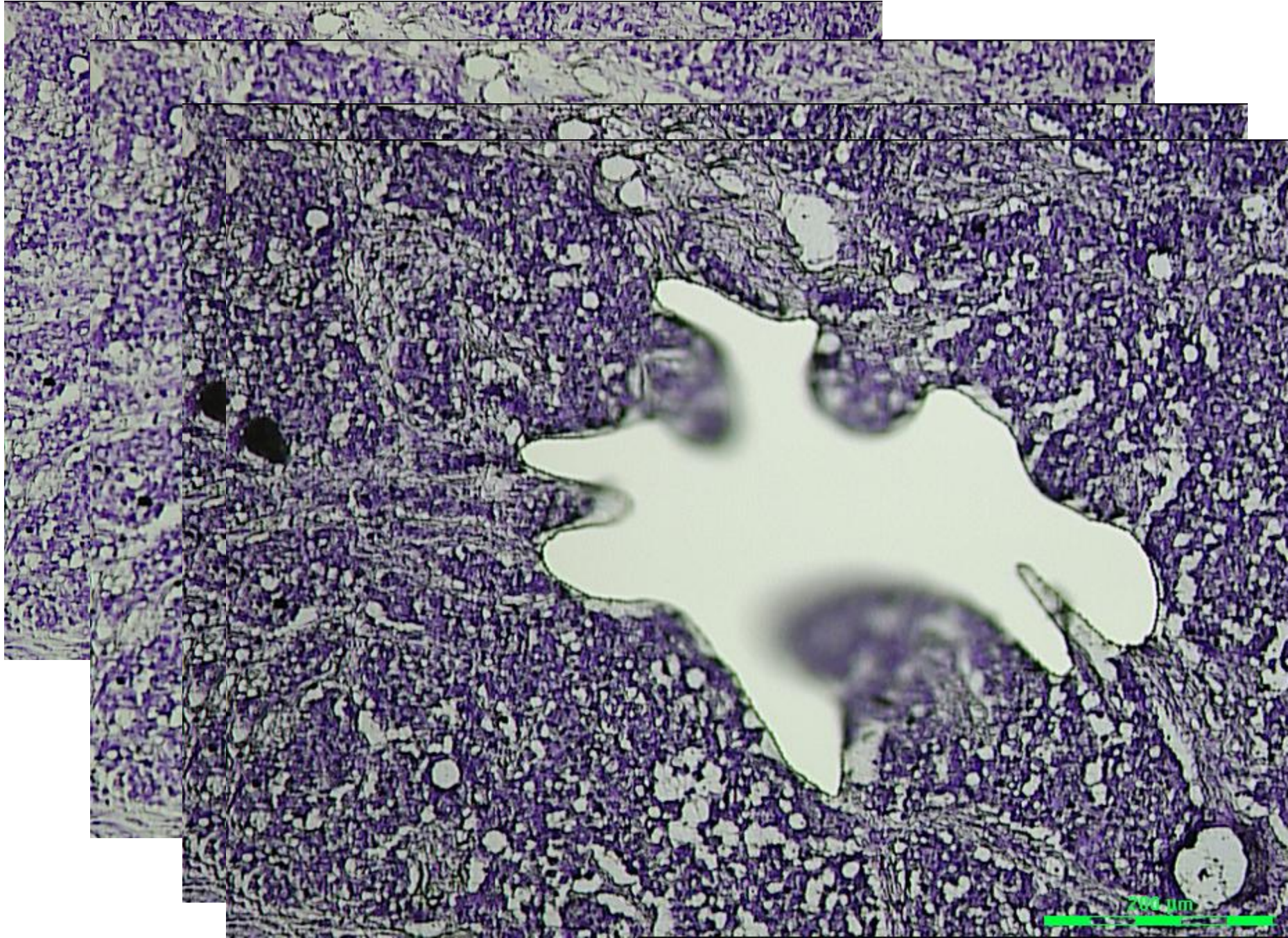


RNA extraction

RNA amplification

Microarray Gene expression Analysis on RNA

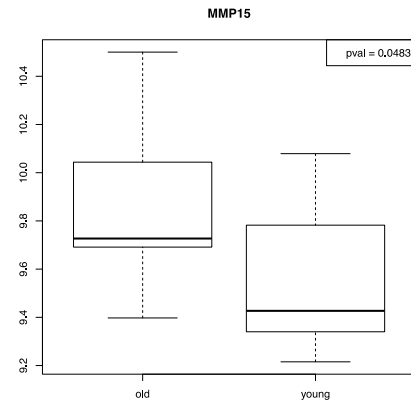
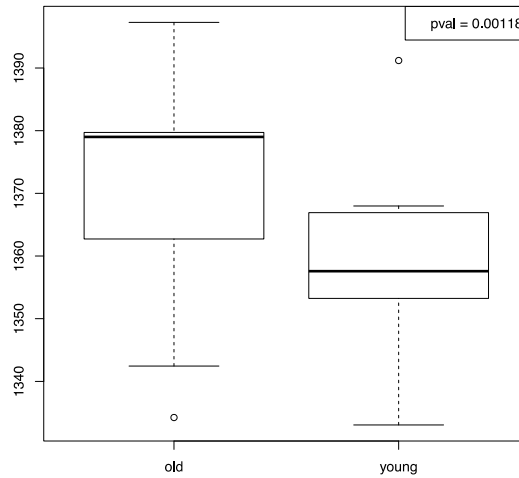
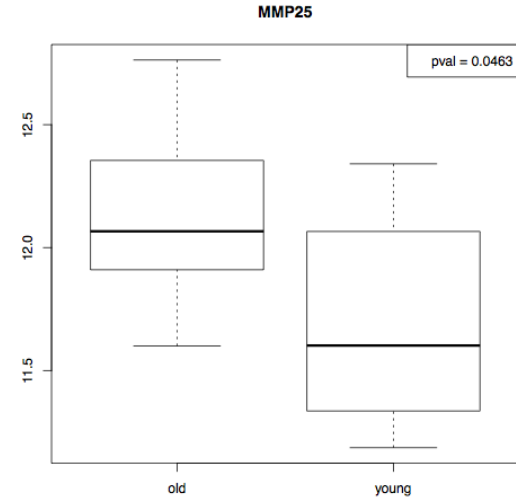
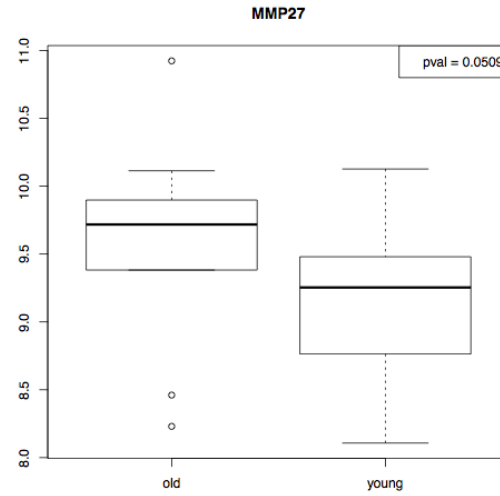
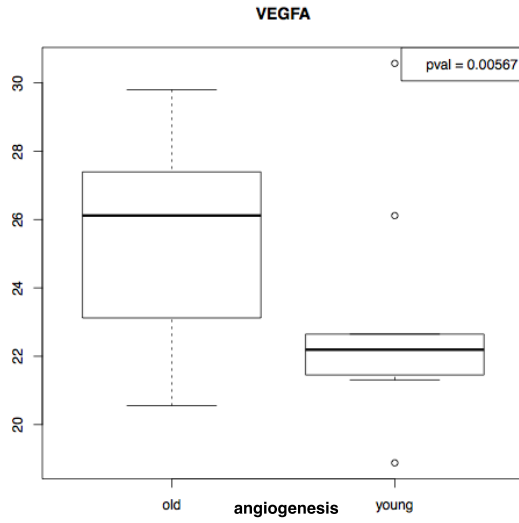




RESULTS

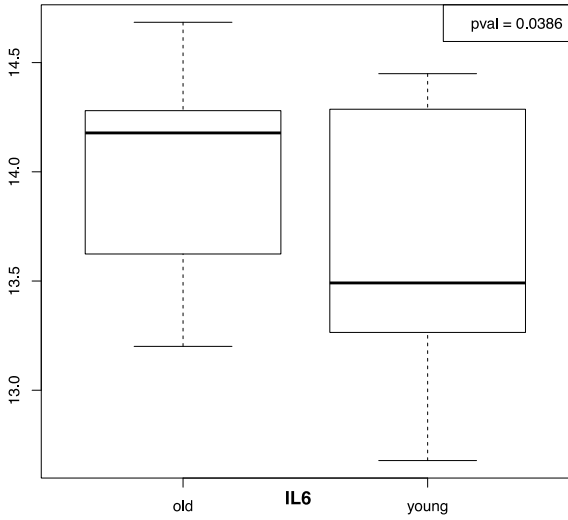
Angiogenesis

Matrix Remodelling

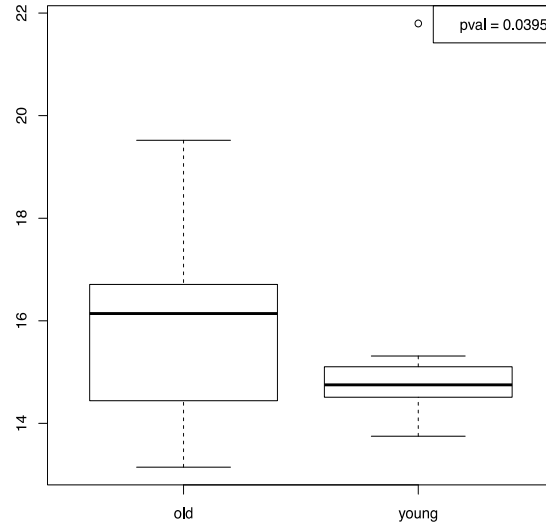


RESULTS cytokines

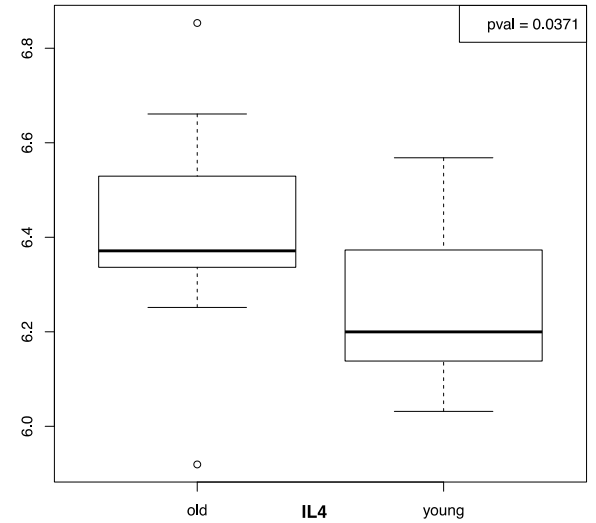
IL34



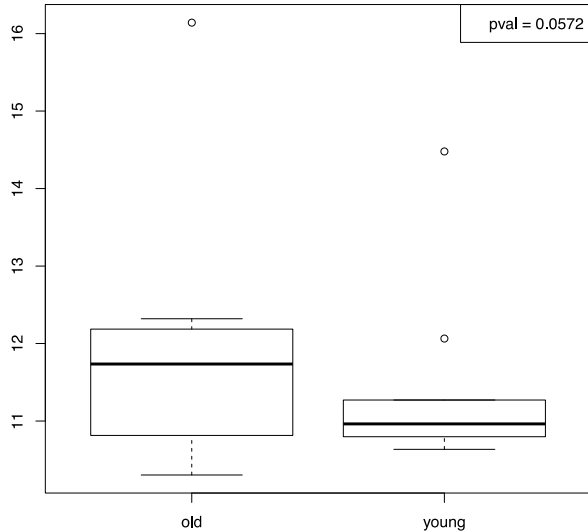
IL33



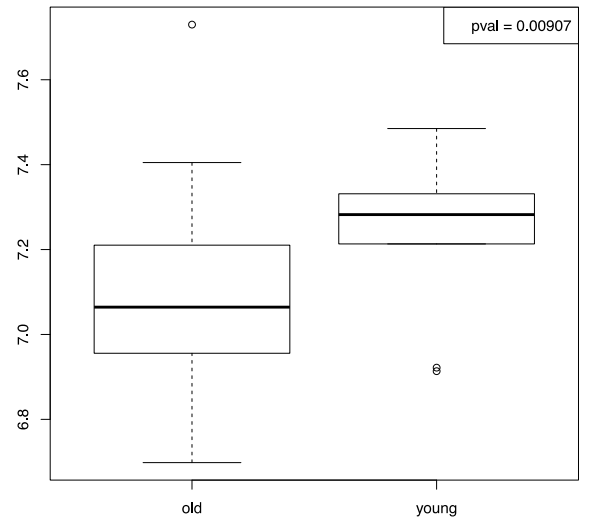
IL26



IL6

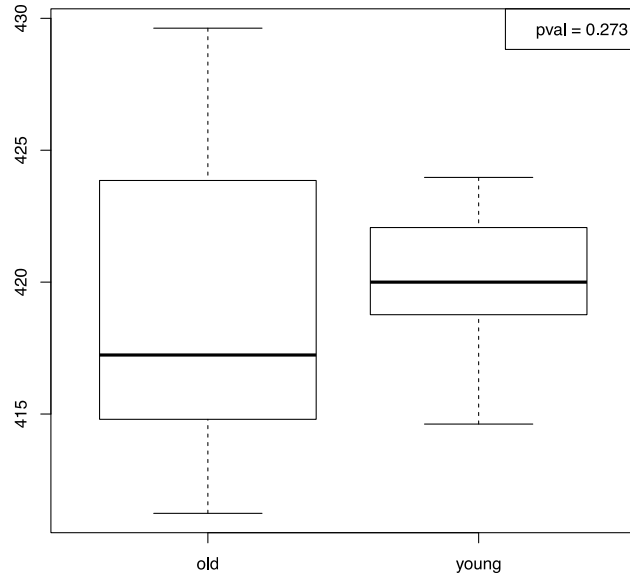


IL4

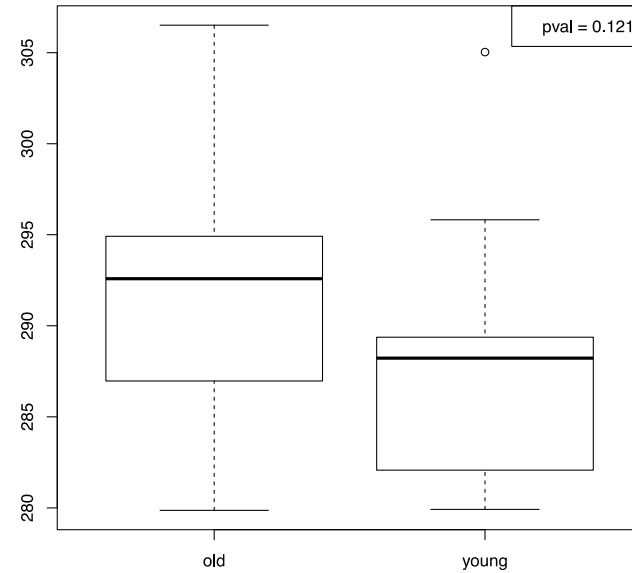


RESULTS autophagy/senescence transition

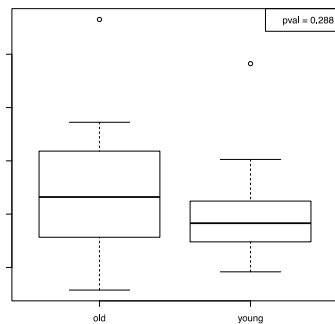
autophagy



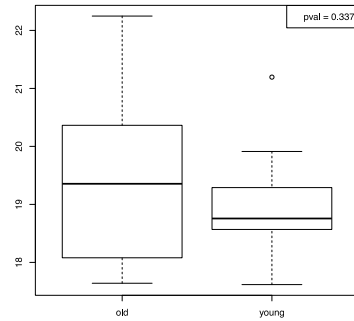
glycolysis



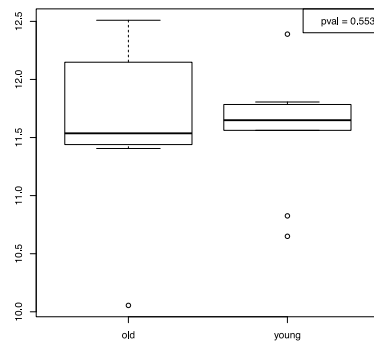
BNIP3



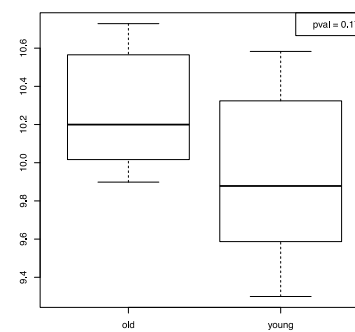
BNIP3L



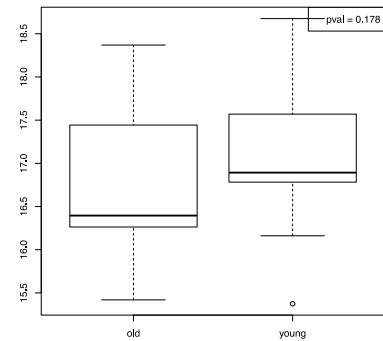
BECN1



ATG16L1

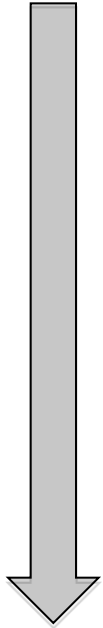


CAV1





2. Chemotherapy → ↑ Biol Ageing? How to measure biological age?



1. Clinical Measures

- Calendar Age?
- CGA items
- Classification of Balducci
 - FIT
 - VULNERABLE
 - FRAIL
- Better way of using the information of geriatric assessment?

2. Biomarkers of Ageing

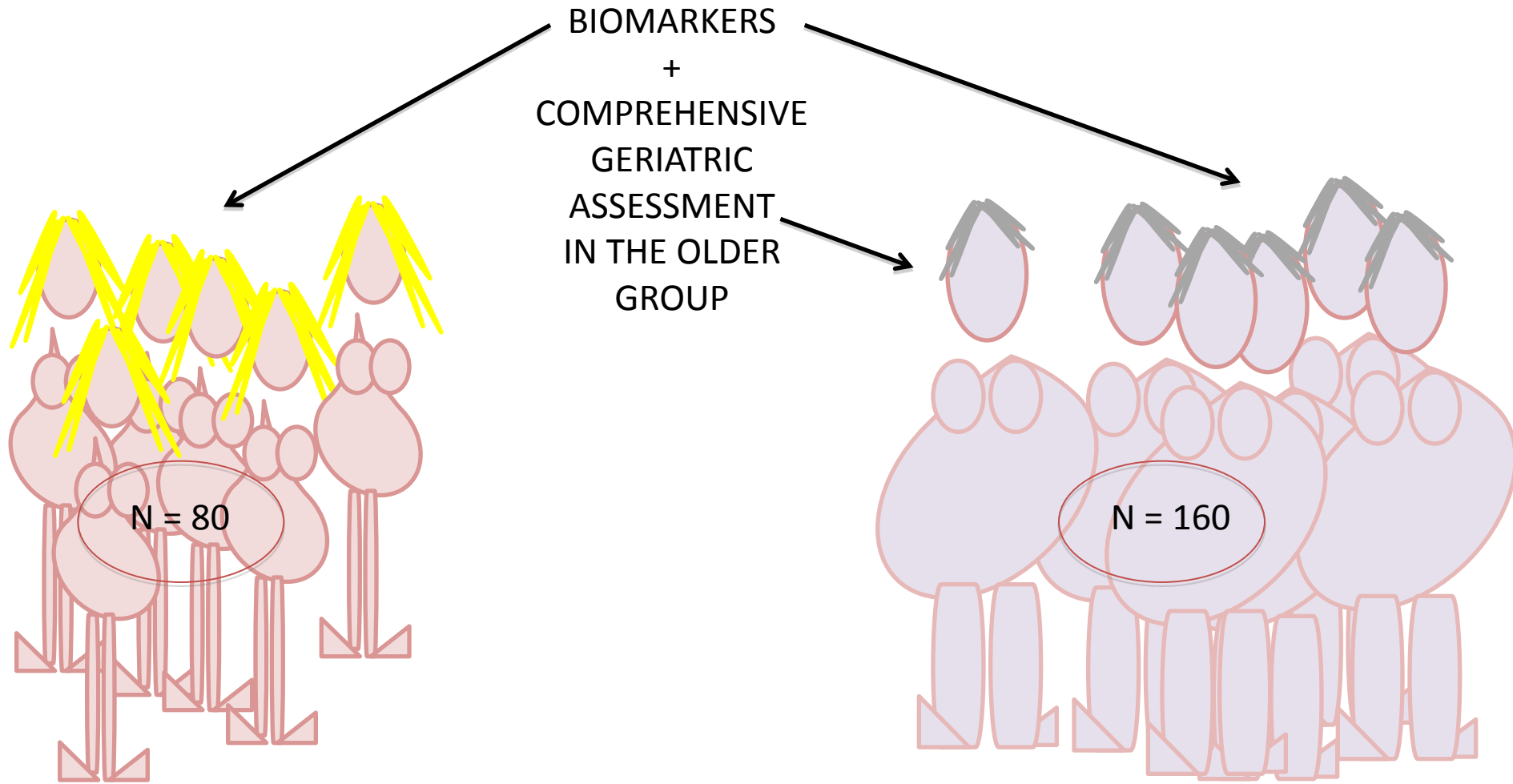
- Telomere length in WBC
- Cytokines/Chemokines circulating in the blood
- Endocrine markers/Growth Factors (eg. IGF-1)
- Phenotype profile of circulating WBC subsets



2 projects to answer these questions

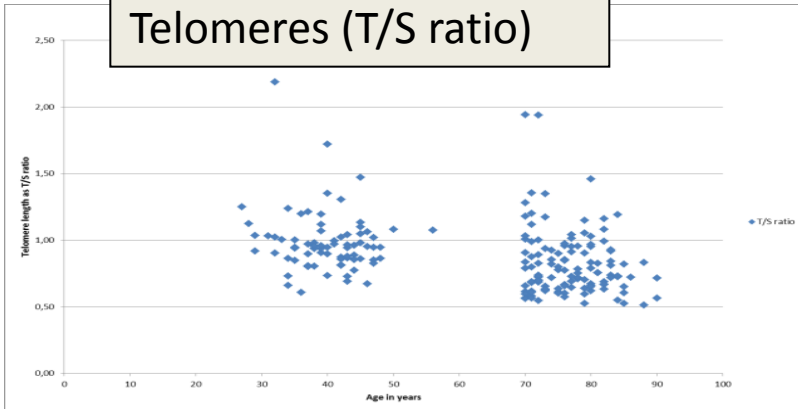
- Value of different clinical and biological markers in reflecting biological age and the relationship between each other
 - **B-CGA-1 study** (retrospective)
- Use of these different markers in studying the effect of chemotherapy on the ageing process
 - **EBS** (prospective)

2.1 B-CGA-1 Study RETROSPECTIVE

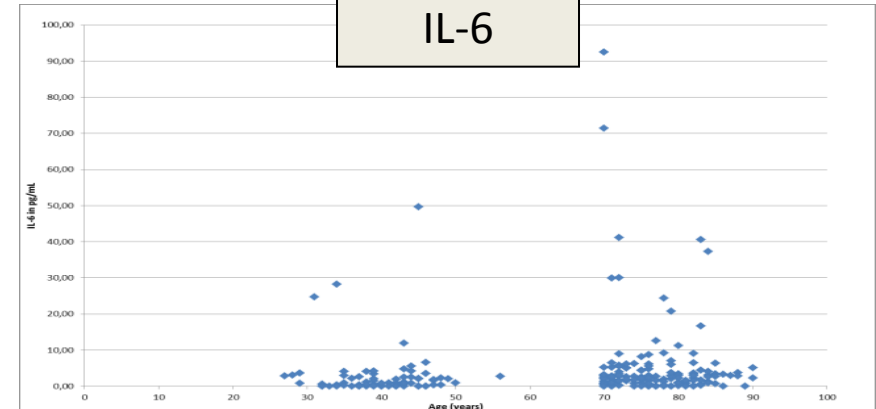


Biomarkers \sim Calendar Age

Telomeres (T/S ratio)

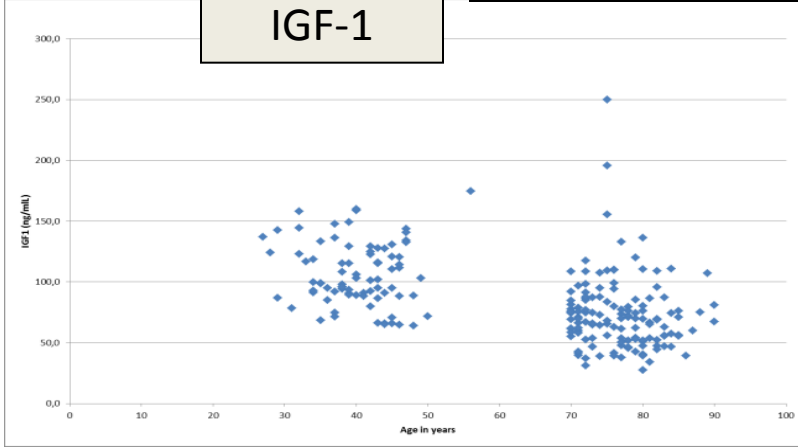


IL-6

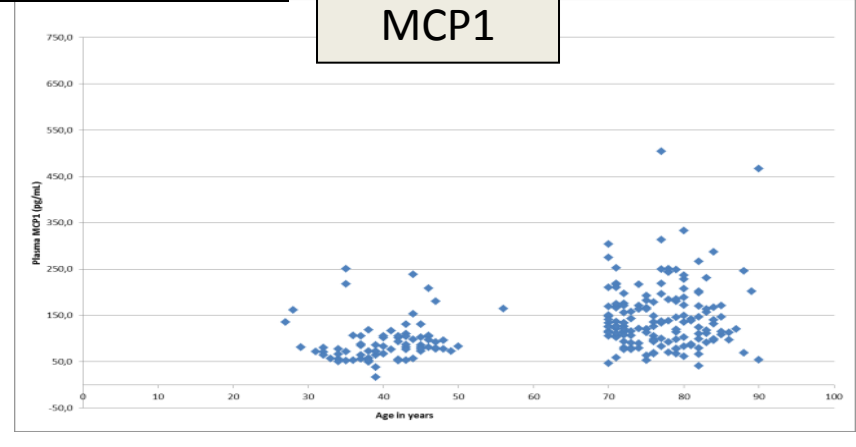


| Biomarker | N | Spearman | P |
|-----------------|-----|----------|--------|
| Telomere Length | 196 | -0.396 | <.0001 |
| IL-6 | 238 | 0.272 | <.0001 |
| IGF-1 | 213 | -0.529* | <.0001 |
| MCP-1 | 238 | 0.412 | <.0001 |
| RANTES | 238 | -0.106 | 0.1032 |

IGF-1



MCP1

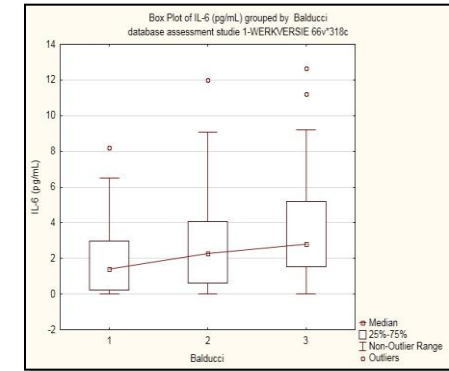


Biomarkers ~ Frailty/Clinical Ageing

SUBSCORES IN GERIATRIC ASSESSMENT

| | IGF-1 | | | IL-6 | | |
|----------|-------|----------------|--------|------|----------------|--------|
| | N | Spearman Corr. | P | N | Spearman Corr. | P |
| ECOG | 127 | -0.094 | 0.2937 | 149 | 0.244 | 0.0028 |
| GRP | 132 | -0.016 | 0.8537 | 157 | 0.078 | 0.3288 |
| G8 | 118 | 0.041 | 0.6628 | 137 | -0.129 | 0.1320 |
| ADL24 | 123 | -0.139 | 0.1243 | 145 | 0.205 | 0.0134 |
| IADL8 | 123 | 0.073 | 0.4211 | 141 | -0.202 | 0.0163 |
| MMSE | 130 | 0.071 | 0.4192 | 152 | -0.093 | 0.2525 |
| GDS_15 | 130 | -0.026 | 0.7653 | 152 | 0.028 | 0.7329 |
| MNA14 | 118 | 0.096 | 0.2995 | 137 | -0.118 | 0.1691 |
| MNA30 | 51 | 0.089 | 0.5327 | 65 | -0.368 | 0.0026 |
| Charlson | 133 | -0.195 | 0.0248 | 158 | 0.154 | 0.0539 |

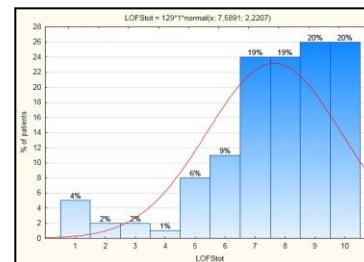
BALDUCCI



IL-6
 N= 158
 Fit : 1.4 - Vulnerable : 2.3 - Frail : 2.8 (pg/ml)
 p-value = 0.019

Leuven Oncogeriatric Frailty Score

LOFS



IL-6
 N= 129
 Spearman coeff -0.218
 p-value = 0.0131

0

10

FRAIL

VULNERABLE

FIT

Conclusions of B-CGA-1 study

- **IL-6** most strongly correlated with frailty status
- **Other markers** not clearly correlated with frailty, but do significantly change with calendar age
- → do in some way still reflect part of the ageing process
- **LOFS** could be an optimal way of summarizing CGA data for an individual patient

2.2 Elderly Biomarker Study

CHEMOTHERAPY

N = 62

4 * Docetaxel - Cyclophosphamide



CONTROL

N = 57

Aromatase Inhibitor

BIOMARKERS AGEING

- Telomere Length
- IL-6, IL-10, TNF- α
- RANTES, MCP-1
- IGF-1
- (p16)
- Subsets of circulating WBC (immunageing)

POPULATION

≥ 70 years

Operated for Early Breast cancer

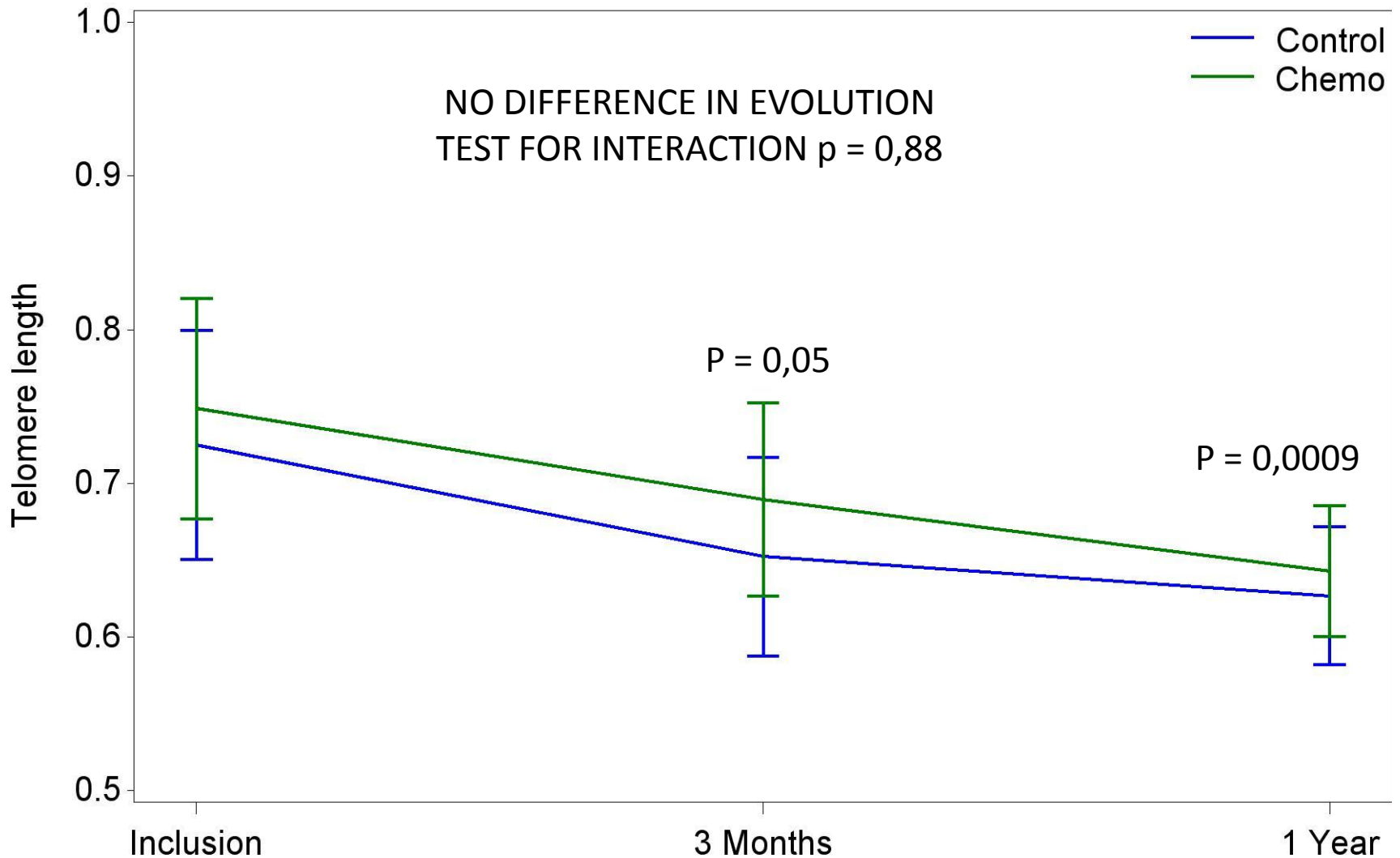
Assigned adjuvant chemotherapy or hormonal therapy

GERIATRIC ASSESSMENT

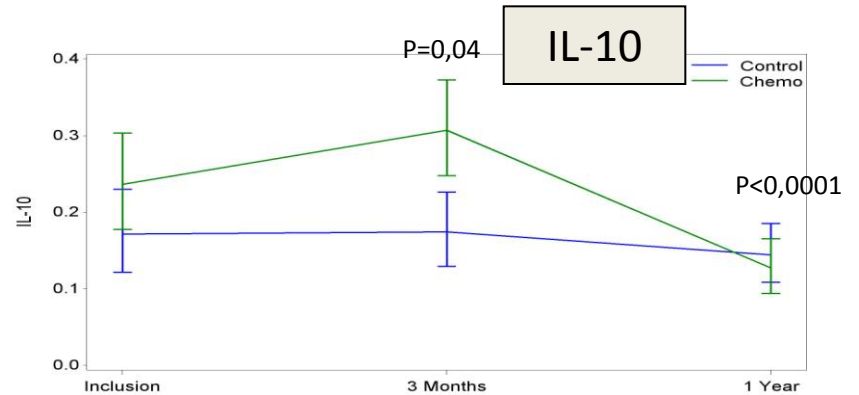
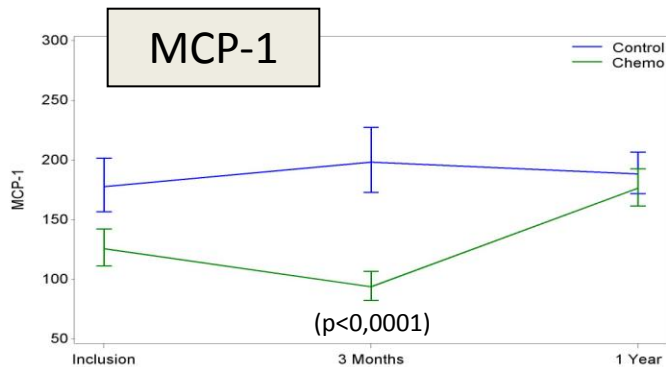
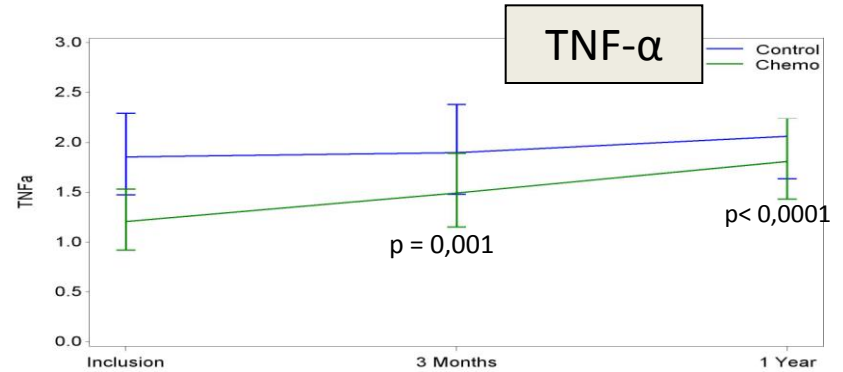
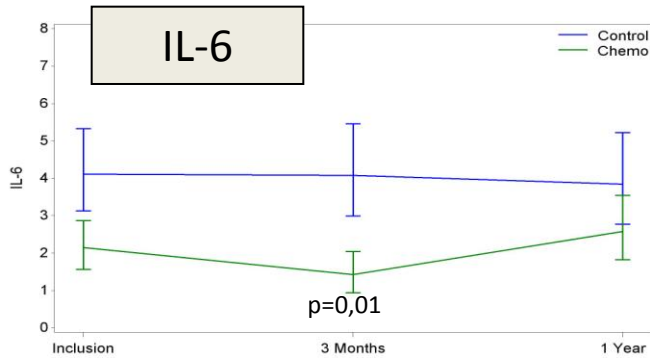
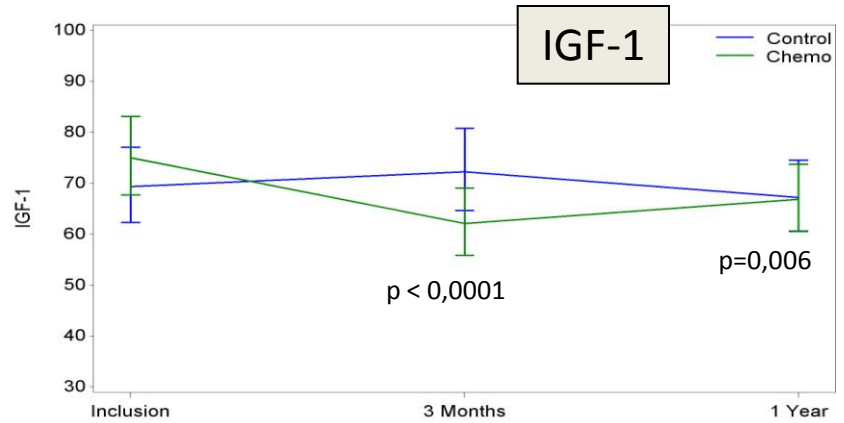
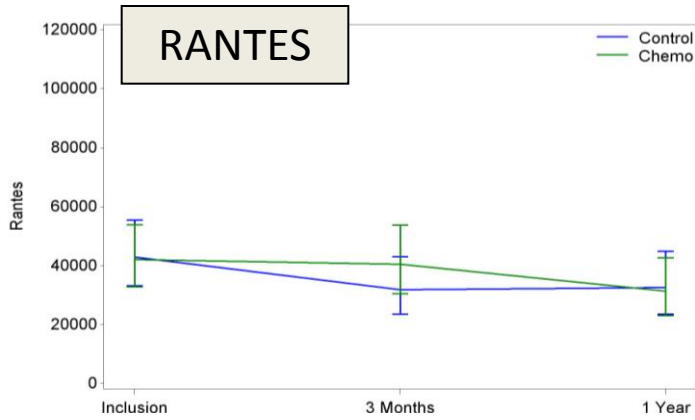
- G8 (geriatric screening test)
- ADL/iADL
({instrumental}Activities of Daily Life)
- Fear of Falls Questionnaire
- EORTC QoL
- MMSE-30
- MNA-SF (Mini Nutritional Assessment, SHORT FORM)
- Charlson Co-morbidity

Index

Primary Endpoint : Telomere Evolution



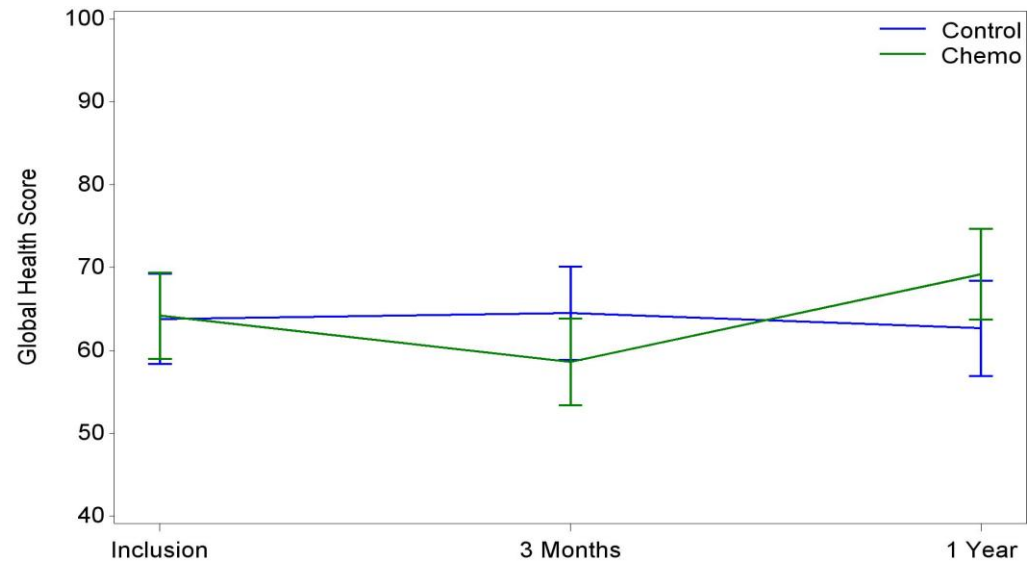
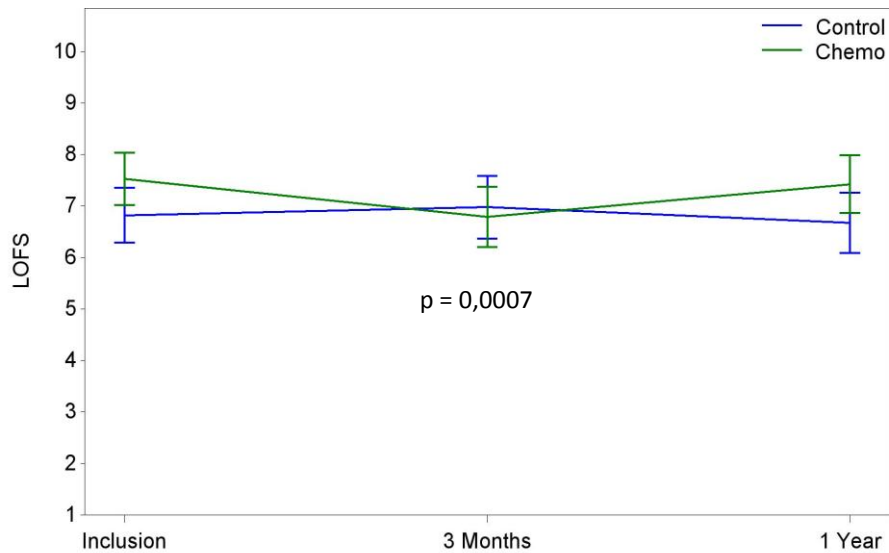
Other Biomarkers



Evolution Clinical Parameters

LOFS
Leuven
Oncology
Frailty Score

Global Health
Status



Correlations

- **IL-6** and **TNF- α** correlated most strongly with **chronological age**

| Marker | Spearman correlation | P-value | N observations |
|--------------|----------------------|---------|----------------|
| T/S | -0.109 | 0.3198 | 86 |
| IL-6 | 0.318 | 0.0008 | 108 |
| IL-10 | -0.028 | 0.7796 | 101 |
| IGF-1 | -0.096 | 0.3298 | 106 |
| TNF-a | 0.342 | 0.0003 | 108 |
| MCP-1/CCL-2 | 0.179 | 0.0652 | 107 |
| RANTES/CCL-5 | -0.014 | 0.8836 | 107 |

- **IL-6** correlated most strongly with **LOFS** (spearman -0,209, p=0,0313)
- In Chemo cohort, **MCP-1** and **RANTES** were associated with **functional** decline (iADL ≥ 1 point decline at 1y)
- **No biomarkers were associated with QoL decline and grade II-III-IV toxicity**

Conclusion

- **Breast cancer micro-environment** in older patients :
 - Higher angiogenesis
 - More Matrix Remodeling
 - More pro-inflammatory cytokines
 - More autophagy/senescence transition could not be confirmed
- **IL-6** most strongly correlates with **frailty status**
- Other markers do not clearly correlate with frailty, but do significantly change with **calendar age**
- **Biomarker evolution during chemotherapy** did not differ significantly when compared with a control group at a timepoint of 1 year after start of adjuvant treatment
- Neither was there a difference in evolution of **geriatric assessment results**

Many Thanks to ...

- All patients participating in the study and all patients consenting for the MBC blood bank
- Prof. Dr. Hans Wildiers, Prof. Dr. Diether Lambrechts
- Dr. S Hatse – Bruna S. Dalmasso – K Corthouts
- Cindy Kenis – Sanne De Coster – Britt Leys
- Dr. D. Fumagalli, Prof. Dr. C. Sotiriou, S. Brohée
- Pathology Department of UZ Leuven – Prof. Dr. G. Floris

- All other members of LEO & ExpRT as well as physicians, nurses (and others) of the hospital supporting and helping with the Elderly Biomarker Study
- Research Funds : Vlaamse Liga tegen Kanker, Stichting tegen Kanker, Fonds voor Wetenschappelijk Onderzoek Vlaanderen

Oncology, fellowship and networking

Evandro de Azambuja, MD, PhD

Department of Medicine, BrEAST Data Centre

Institut Jules Bordet

Brussels, BE

5th

International Congress
of Breast Disease Centers

2015

About me...

- Medical oncologist fully trained in Porto Alegre, Brazil
- Specialization in Internal Medicine and Medical Oncology
- Master degree in Medical Sciences
- PhD in Medical Sciences



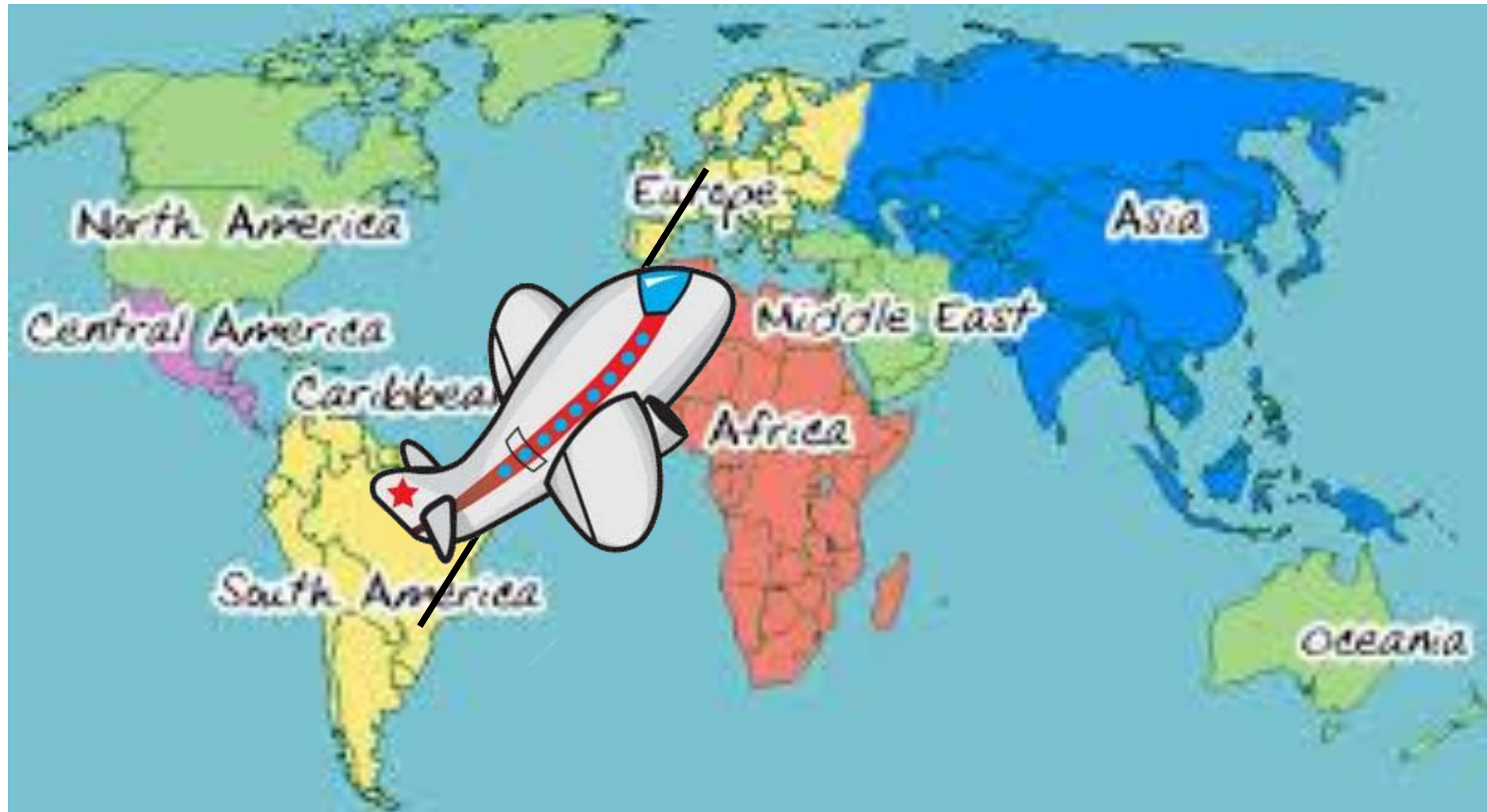
How everything changed...

ASCO®

2003

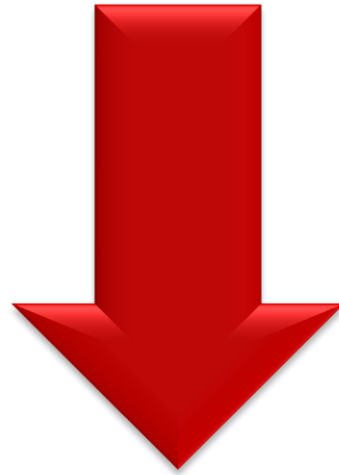


A few months later..



My first take home message...

Identify a good mentor



And do not be afraid of making contacts

But why was I looking for a change?

- To acquire skills in clinical research
- To acquire skills in developing and running international clinical trials
- To have an international experience in clinical work
- To open my mind to new techniques, drugs, etc...

What did I learn between 2003-2015?

- Networking
- Research cannot stand alone: there is a need for collaboration
- You have to work hard if you want to achieve your goals
- Pass on your knowledge: do not be afraid of sharing/discussing information, ideas, etc...
- Dedicate some time to think

How ESMO played a role in this?

ESMO: 2005-2015

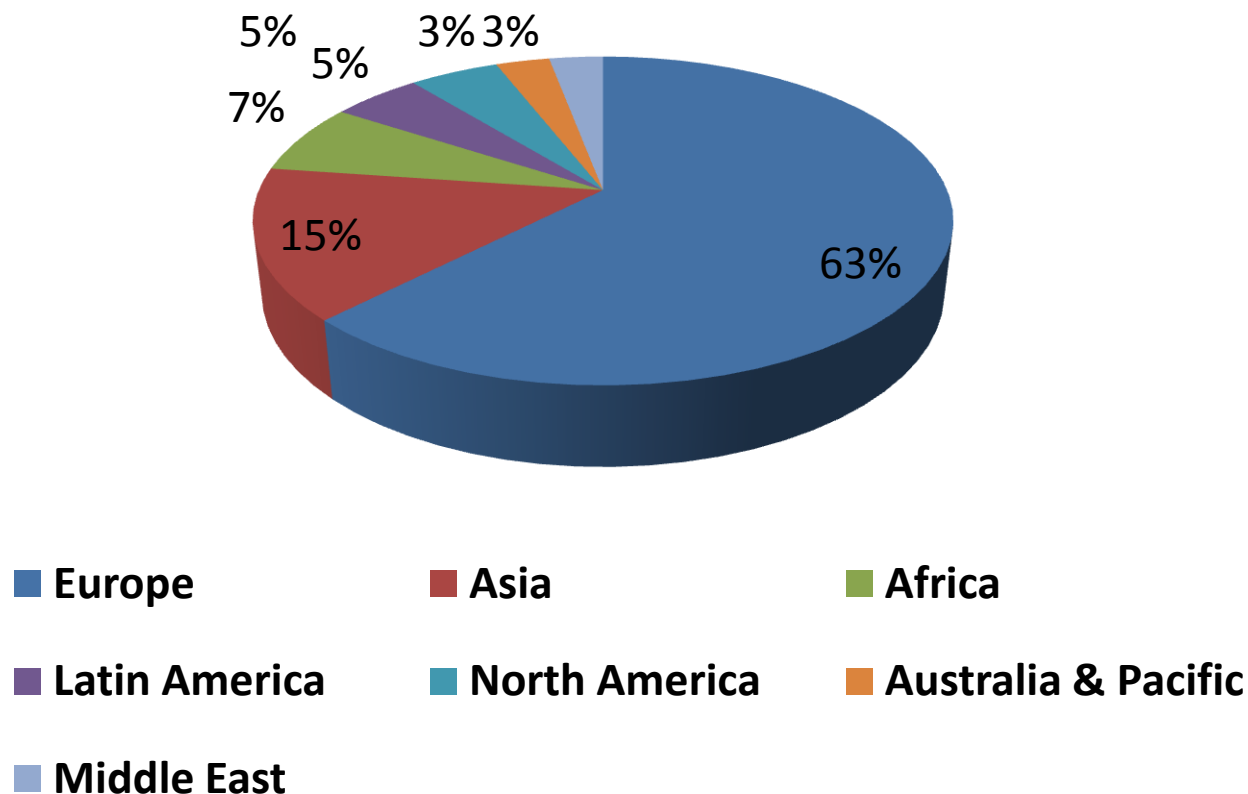
- Member since 2005
- Member of the **ESMO Young Oncologist Committee**
2009-2013
- Member of the **ESMO Press Release Committee** since
July 2011

ESMO: 2005-2015

- Co-chair of the **Young Oncologist Track for ECCO-ESMO** conference 2013 (Amsterdam)
- Chair of the **Early Breast Cancer track ESMO** conference 2014 (Madrid)
- **Editor-in-chief for the Daily News** at the ESMO Conference 2014 (Madrid)

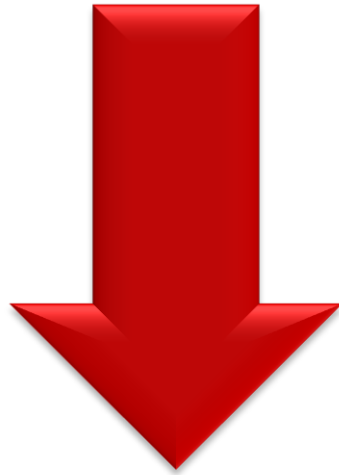
Young Oncologists: the leaders for tomorrow

37% of ESMO active members are younger than 40 years old



My second take home message...

To invest time in committees and societies



Be committed, reliable and share your vision

**What were the other
opportunities I had?**

Benefiting from opportunities

- Innovators in breast cancer (NYC)
- Innovators in breast cancer UK
 - Mentorship
 - Collaboration
 - Leadership



- European Science Communication Network (ESConet)

ASCO Experience



2014 Oncology Literature Reviews

Updates in Breast Cancer

Third Quarter

Evandro de Azambuja, MD, PhD
Jules Bordet Inst
Brussels, Belgium



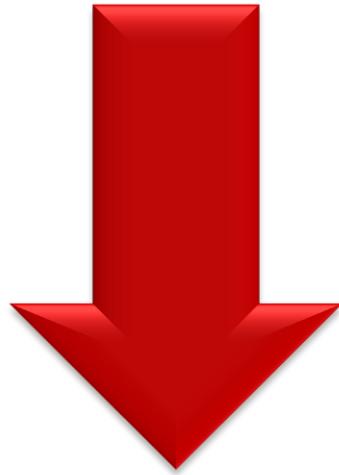
Planning Group
Aditya Bardia, MD
Massachusetts
General Hospital
Cancer Institute
Cambridge, MA



Turn your speakers on!

My third take home message...

To interact with knowledgeable people



They are people like you!

Why can research not stand alone?



What is BIG?

- **International** non-profit organisation
- **Network** of **academic** breast cancer research **groups / data centres**
- **Founded** in **1999** by European opinion leaders in breast cancer
- **55** members tied to **several thousand hospitals** worldwide
- **>30 clinical trials** ongoing or under development
- Member group **data centres** manage trials
- **Brussels-based headquarters** provides support services

What is BIG vision & mission?

We will find a cure for breast cancer through global research and collaboration

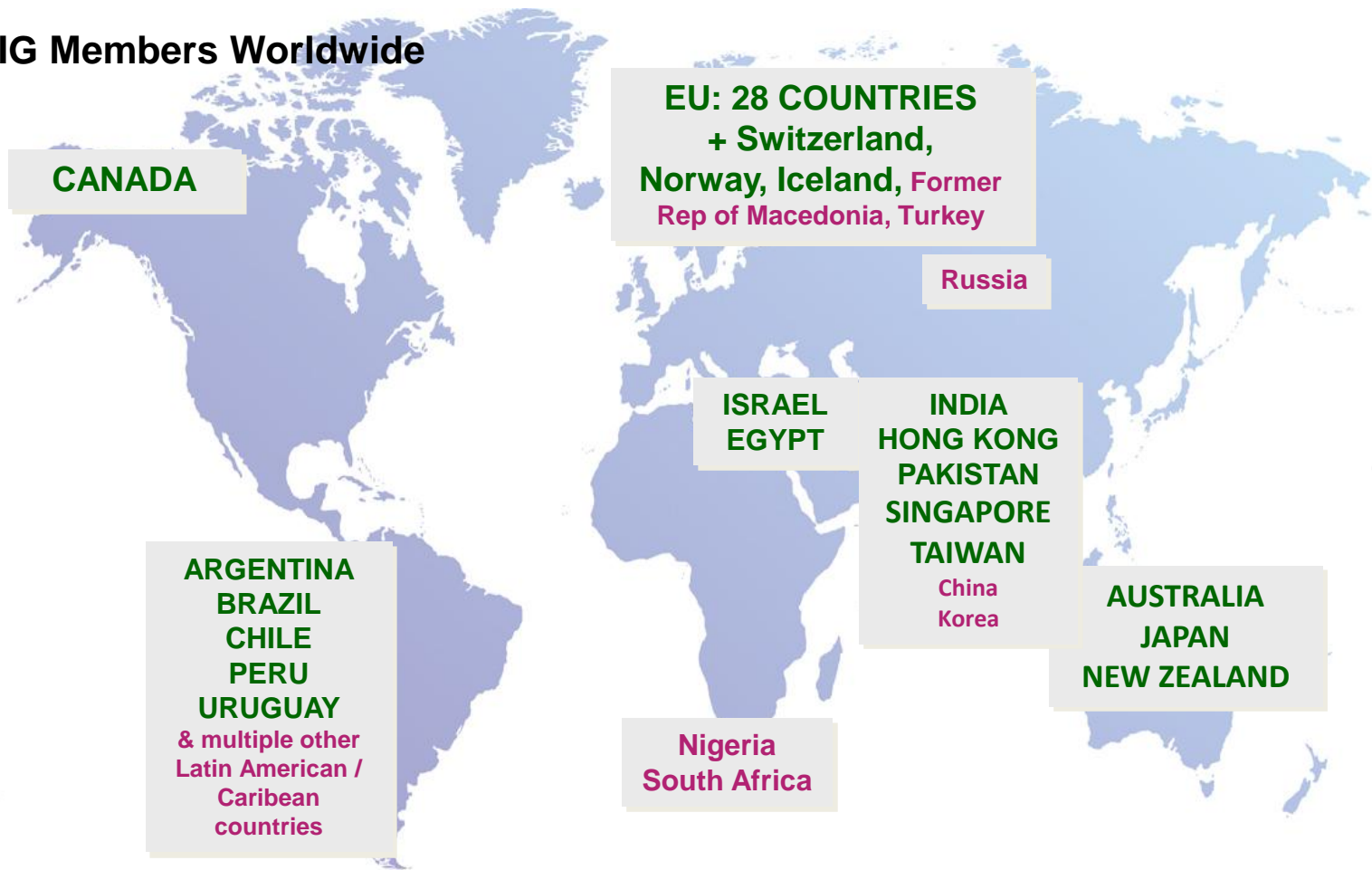
Facilitating breast cancer research internationally

10 Key Principles of Research Conduct

1. Advance knowledge → Serve patients
2. Retain independence
3. Database control / statistical leadership
4. Steering Committee
5. Independent Data Monitoring Committee
6. Trial monitoring
7. Presentations / publications – academic standards
8. GCP / regulatory standards
9. Biological specimen collection for future research
10. Long-term follow-up of patients

Who is in BIG?

55 BIG Members Worldwide



National GROUPS or
International GROUPS / **centres**



Large multinational trials
e.g. HERA, MINDACT, (Neo)ALTTO, APHINITY

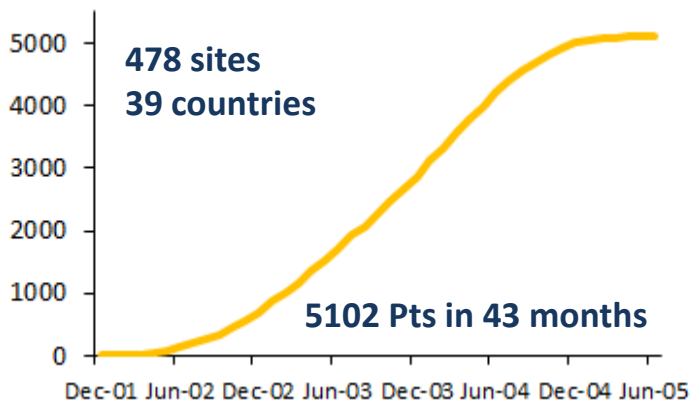
The BIG experience: activating clinical trials and recruiting patients

Single HER2 blockade vs observation

Dual HER2 blockade vs single HER2 blockade

Trastuzumab

HERA

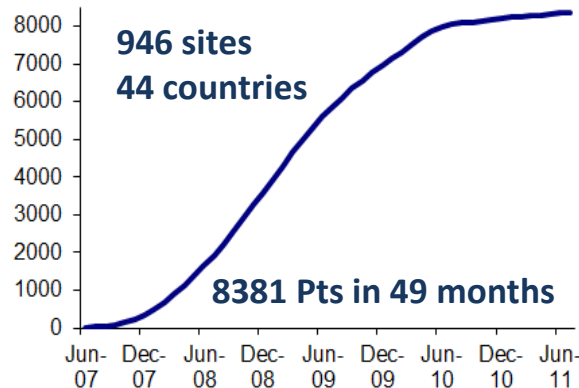


Europe
North America
South America
Australasia

3850 (75%)
160 (3%)
284 (6%)
808 (16%)

Trastuzumab ± Lapatinib

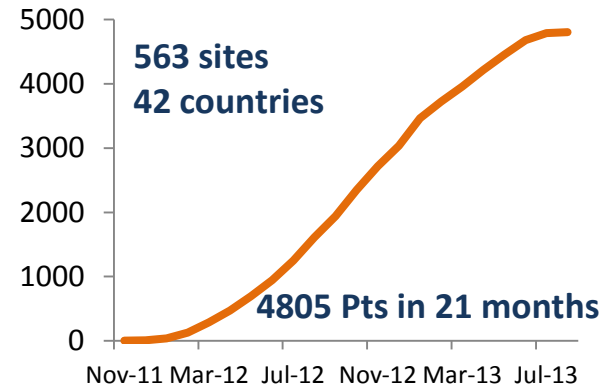
ALTO



4470 (54%)
959 (11%)
444 (5%)
2508 (30%)

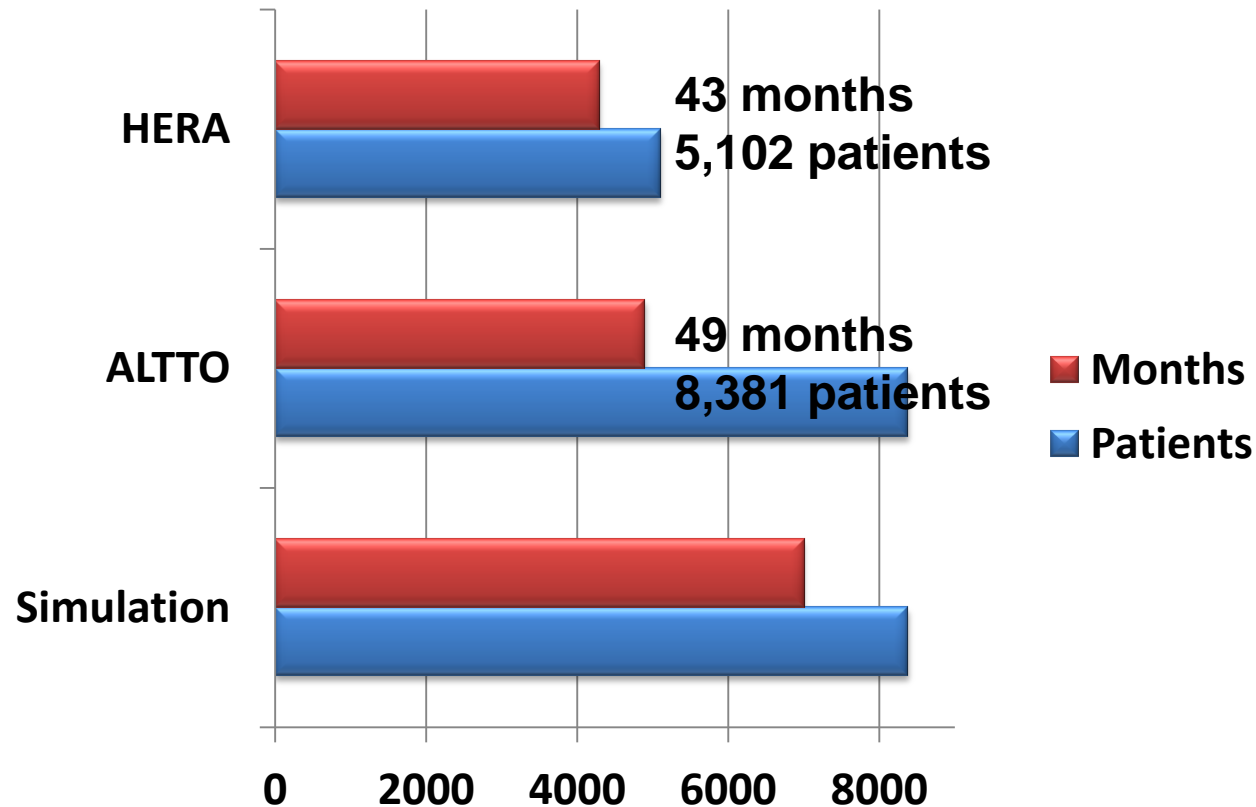
Trastuzumab ± Pertuzumab

APHINITY



2721 (57%)
700 (15%)
124 (3%)
1259 (26%)

What if ALTT0 had a similar accrual as HERA?



50% sites and similar # of countries
Based on HERA monthly accrual
42% longer accrual and delay in results!

Fellowship: the best way of networking!



**36 fellows, colleagues, collaborators and
friends in 15 countries**

My fourth take home message...

Collaboration is crucial



Publication opportunities

Long-Term Benefit of High-Dose Epirubicin in Adjuvant Chemotherapy for Node-Positive Breast Cancer: 15 Efficacy Results of the Belgian Multicentre Study

Evandro de Azambuja, Marianne Paesmans, Marc Beauduin, Anisa Vindevoghel, Nathalie Co Claude Fines, Fernand Ries, Marie Thérèse Closon-Dejardin, Joseph Kerger, Philippe Gobert, C Alain Tagnon, Stella Dolci, Jean M. Nogares, Angelo di Leo, and Marline J. Piccart-Gebhart



European Journal of Heart Failure (2011) 13, 1–10
doi:10.1093/eurjhf/hfq213

POSITION STATEMENT

Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology

1*, Thomas Force², Michael S. Ewer³, Gilles W. de Keulenaer⁴, Stefan D. Anker^{6,7}, Metin Avkiran⁸, Evandro de Azambuja⁹, Dirk L. Brutsaert⁴, Gianluigi Condorelli¹¹, Arne Hansen¹, Joseph A. Hill¹³, Emilio Hirsch¹⁴, Denise Hilfiker-Kleiner¹⁵, Sven de Jong¹⁷, Gitte Neubauer¹⁸, Burkert Pieske¹⁹, Junir Pirmohamed²¹, Mathias Rauchhaus^{22,23}, Douglas Sawyer²⁴, Johann Wojta²⁶, Faiez Zannad²⁷, and Ajay M. Shah^{8*}

➔ Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial

Luca Gianni, Umeko Dafny, Richard D Gelber, Evandro de Azambuja, Suresh Murthy, Anwar Galal, Michael Untch, Ian Smith, Joseph Sparano, Christian Jackisch, David Cameron, Marc Mans, Josell Loh-Pedro, Anshu Veronesi, C Edward Hudis, Michael J Fisher, Zhenzhou Shen, George Skolaros, Marlon Pritchard, for the Herceptin Adjuvant (HERA) Trial Study Team

clinical practice guidelines

The Lancet Oncology Commission

by chemotherapy,
for ESMO Clinical

Annals of Oncology 23 (Supplement 7): vi155–vi166, 2012
doi:10.1093/annonc/mds293

Planning cancer control in Latin America

Paul E Goss, Brent Brantley, Tanja Budimir-Crojevic, Kathrin Brummer-Wippel, Yanina Chavez-Karlo Unger-Saldivia, Mayra Fernandez, Mónica Delgado, Pedro E. El-Jedidi, Diego Taura, Gustavo Claudio Paredes, Eduardo Canogo, Carlos Vallejos, Alejandro Mohar, Felicia Kraus, Hector Ari Richard Guillen, Dianne Finlayson, Sergio Simon, Carlos Barrios, Rebecca Kightlinger, Andres S. Sotgiu-Slijepci, Marcelo Blaya, Fabiano de Figueiredo, Pradip K. Santona Santos, Alberto Castro Andon-Felipe Cardoso Zanillo, Noel Mordillo, Jose Jimenez, Helen Tsou, Anshu Cavaliere, Carlos R Alfonso-Sanchez-Gonzalez, Dennis Sgroi, Mauricio Goffo, Rodrigo Fresno, Rui Manuel Reis, Guilherme Roubini, Gustavo Inesati, Eduardo Rosenthal, Bettina Roth, Lucia Villa, Angella Lara-Sokone, Alfredo Cosmopolita-Correa, Anshu Hemdani, Mariana Bertolini, Gilberto Schwarzbauer, Sa Marciano, Henry Gomez, Marc Humbert, Alessandra Durkin, Gustavo Azeiteiro

Luminal B Breast Cancer: Molecular Characterization, Clinical Management, and Future Perspectives

Feipei Aides, Dimitrios Zardavas, Ivana Bozovic-Spasojevic, Lina Pugliano, Debora Fumagalli, Evandro de Azambuja, Giuseppe Viale, Christos Sotiriou, and Marline Piccart

My fifth take home message...

Good quality writing



Acknowledgments (I)



Acknowledgments (II)

