SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

AZIENDA OSPEDALIERO-UNIVERSITARIA DI MODENA

GIUSEPPE DOSSETTI:
I VALORI - SVILUPPO E TUTELA DEI DIRITTI
ASSOCIAZIONE CULTURALE ONLUS

La Terapia Personalizzata in Oncologia

Roma, 25-26 Ottobre 2011

Stato dell' arte e prospettive della Target Therapy nei tumori mammari

PierFranco Conte

Department of Oncology, Hematology and Respiratory Diseases
University of Modena and Reggio Emilia, Modena, Italy

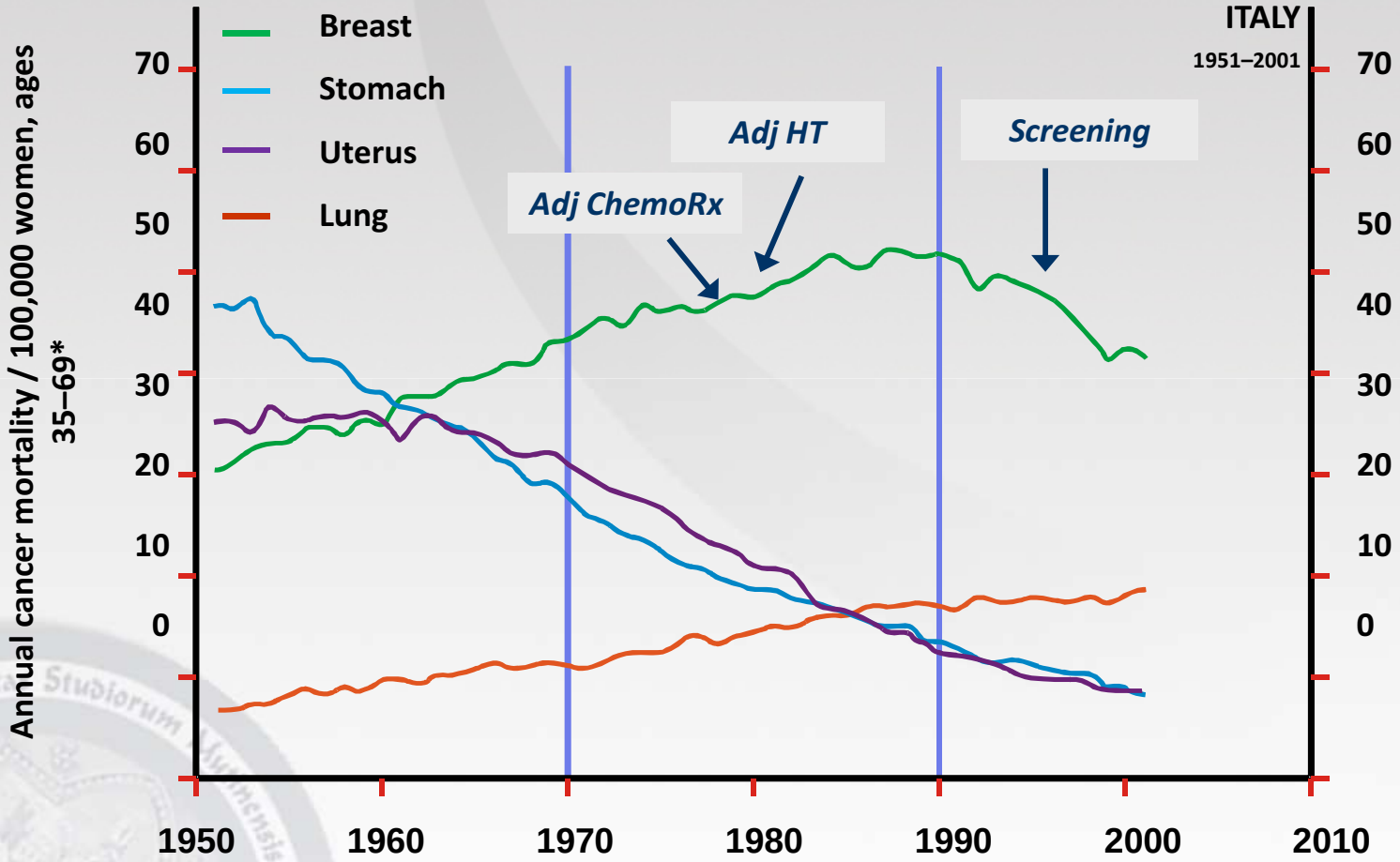
Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

The Conquest of Breast Cancer: a few more steps ahead..

- A successful story ….
- Lessons from a successful story….
- From size to biology:
  - achievements
  - opportunities
  - challenges

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Cancer Mortality in women - Italy



*Mean of annual rates in the component 6-year age groups

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

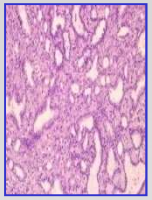
Source: WHO mortality and UN population estimates

The Conquest of Breast Cancer: a few more steps ahead..

- A successful story ….
- Lessons from a successful story….
- From size to biology:
  - achievements
  - opportunities
  - challenges

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

A nice story….



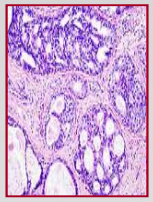
M.R. 62y old - May 2005
Left radical mastectomy + ALND
ILC, pT2 (2.3cm), N2 (14/44 N+),
ER 90%, PgR 80%,
HER2 1+, Ki 67 10%

May-September 2005
dd chemoRx AC x 4 -> Paclitaxel x 4
RT on chest wall and axylla
anastrozole for 5y

December 2010: NED

This tumor is big and lazy

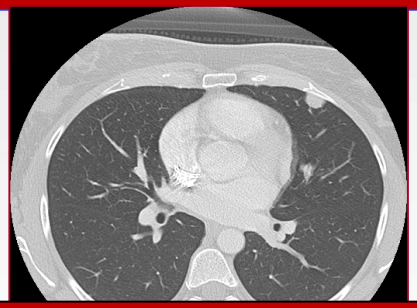
A sad story….



C.B. 44 y old - April 2009
SE quadrantectomy + SN
IDC, pT1c (1.7cm), N0,
ER <1%, PgR 0%,
HER2 0, Ki 67 60%

May-September 2009
ChemoRx TAC x 6
RT on the breast

December 2009: lung mets



This tumor is small and busy

Section of Oncology
University of Modena and Reggio Emilia
Modena

The Conquest of Breast Cancer: a few more steps ahead..

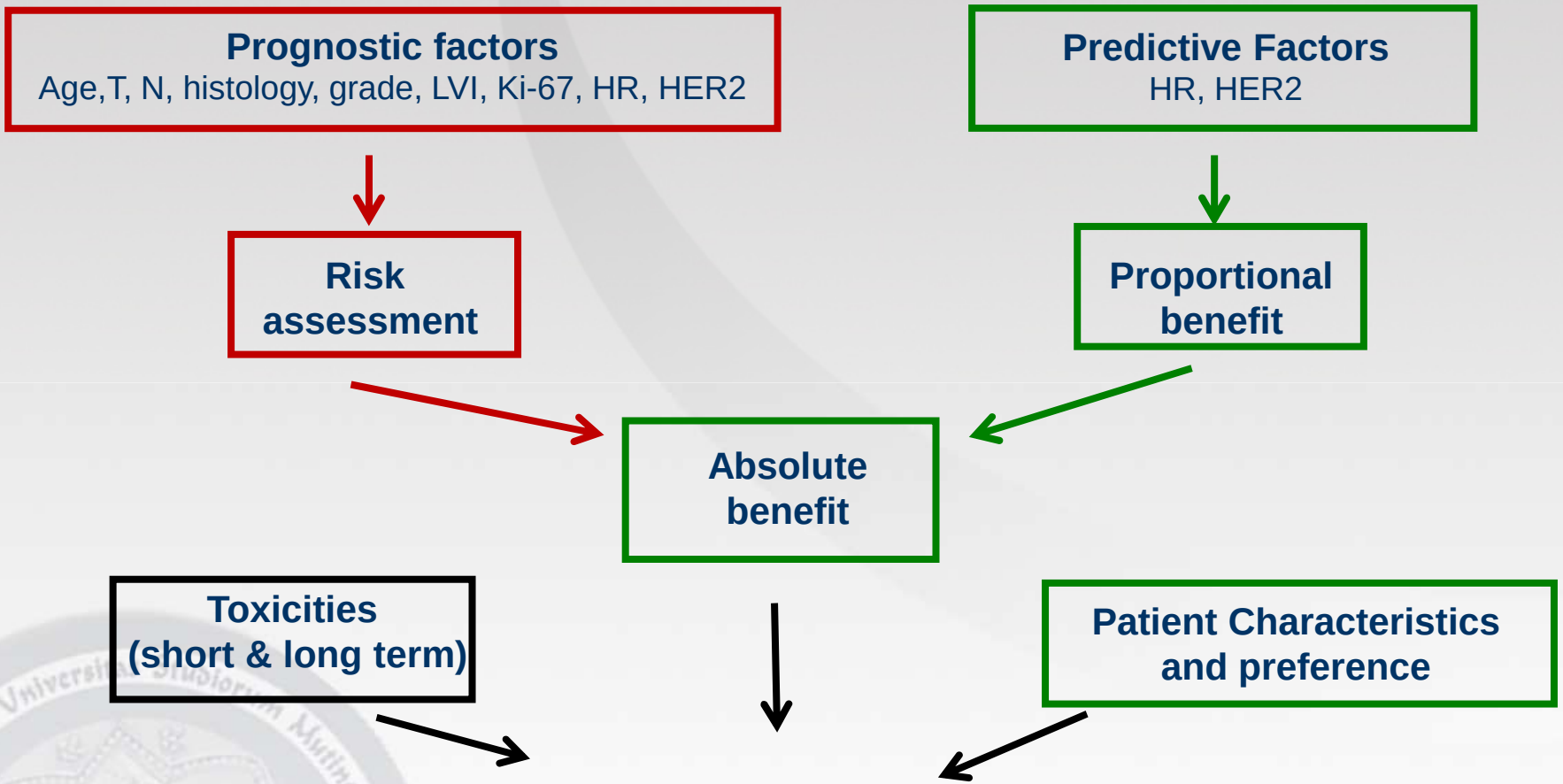
- A successful story ….
- Lessons from a successful story:

lesson # 1: biology can be more important than size

- From size to biology:
  - achievements
  - opportunities
  - challenges

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Adjuvant Rx of EBC - Decision-making Algorithm



Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Number of patients with EBC needed to treat with Adjuvant Therapy to prevent ONE recurrence

Comparison	Absolute Risk Reduction %	NNT
Tamoxifen *vs.* Nil ^	11.8	**8**
Aromatase Inhibitors vs TAM*	3- 5.3	**19 - 33**
Aromatase Inhibitors vs Nil°	**~ 16**	**~ 6**
Polychemo *vs.* Nil (< 50)^	12.3	**8**
Polychemo *vs.* Nil (50+)^	4.2	**23**
Anthra vs CMF^	4.0	**25**
Taxanes *vs.* Anthra§	~ 5	**20**
3rd gen taxane regimen vs Nil°	**~ 23**	**~ 4**
ChemoRx + Trastuzumab vs ChemoRx	6.3 - 18	**6 - 15**
ChemoRx + Trastuzumab vs Nil+	**13 - 35**	**2-3**

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

The Conquest of Breast Cancer: a few more steps ahead..

- A successful story ….

- Lessons from a successful story:

  lesson # 1: biology can be more important than size

  lesson # 2: too many patients are treated to benefit one

  lesson # 3: the “best” Rx is applied to all the patients as we are unable to predict individual treatment sensitivity

- From size to biology:
  - achievements
  - opportunities
  - challenges

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

The quest for personalized cancer medicine….

The Right Dose of
The Right Drug for
The Right Indication for
The Right Patient at
The Right Time

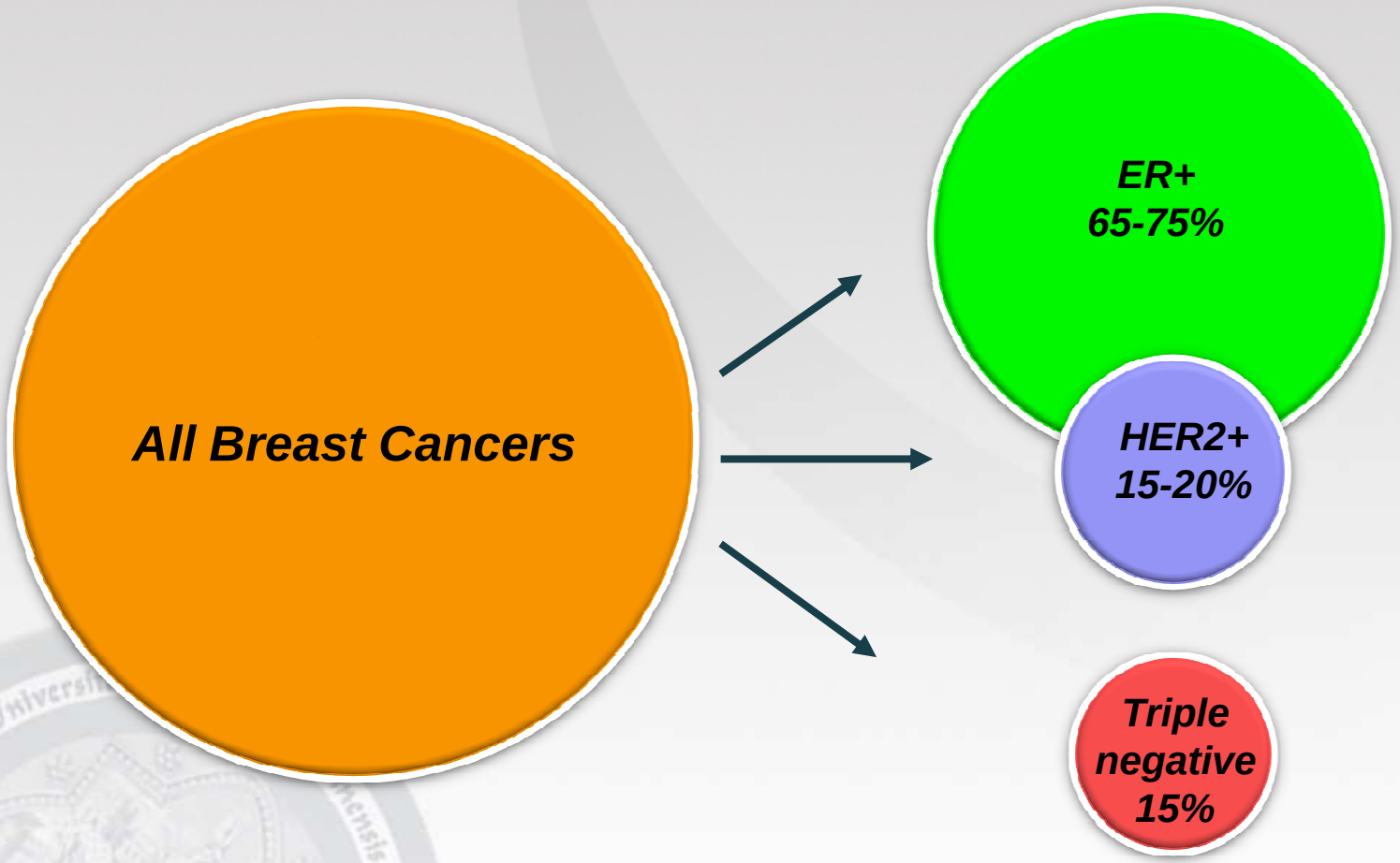
Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

The Conquest of Breast Cancer: a few more steps ahead..

- A successful story ….
- Lessons from a successful story….
- From size to biology:
  - achievements
  - opportunities
  - challenges

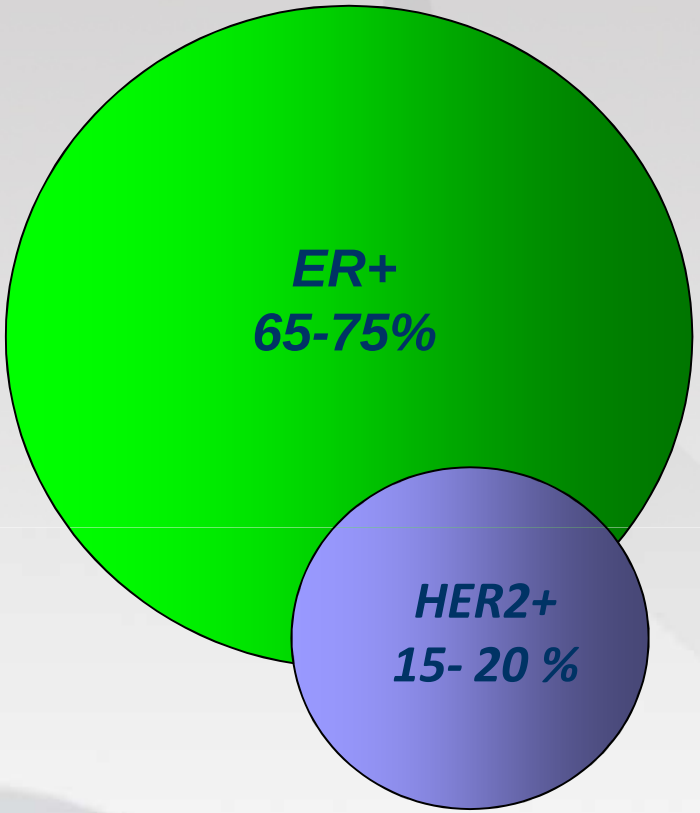
Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Breast Cancer Diseases – 2011



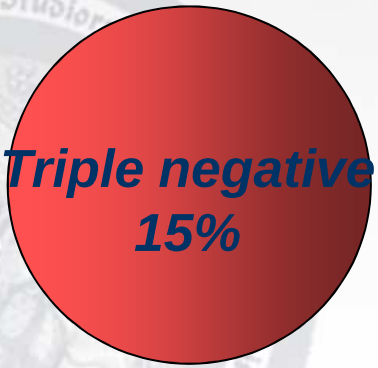
Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

New agents for the breast cancer molecular subtypes



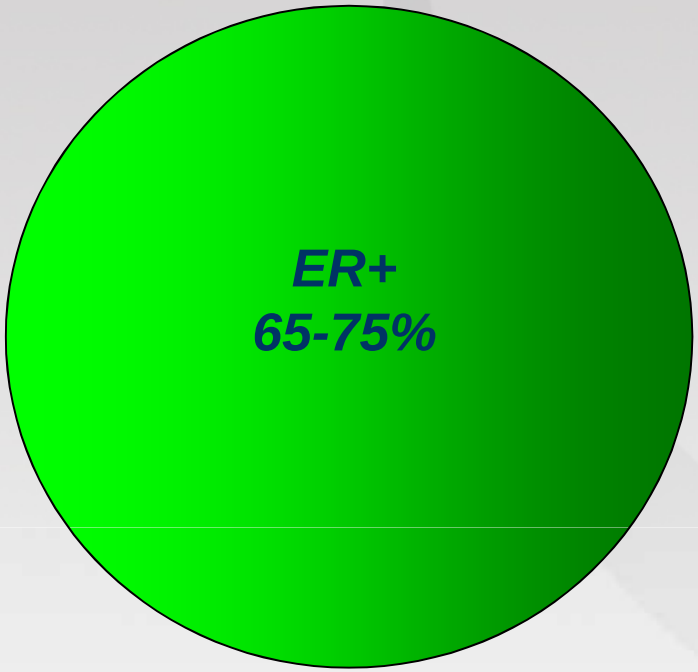
mTOR inhibitors
PI3K inhibitors

Lapatinib
Neratinib
Pertuzumab
TDM-1
AntiHER2 combinations
Trastuzumab + mTORi



New cytotoxics (eribulin, ixabepilone, vinflunine)
Platinum salts
Bevacizumab
PARP inhibitors
AntiEGFR (Cetuximab, erlotinib)
Anti androgens

New agents for the breast cancer molecular subtypes



mTOR inhibitors
PI3K inhibitors

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

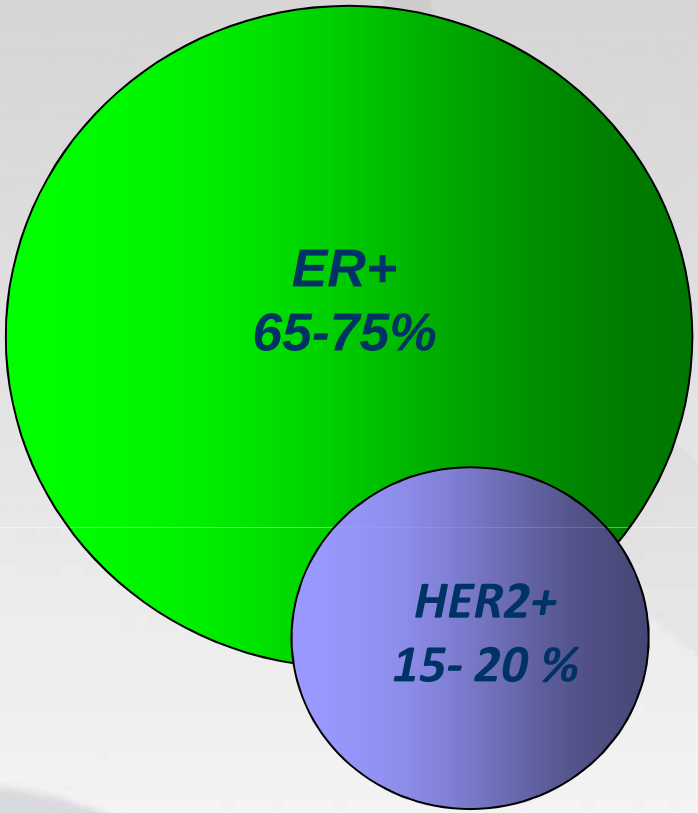
Co-Targeting mTOR and HR in HR+/HER2-ve ABC

	TAMRAD[1] (HR+/HER2-; prior AI)			BOLERO 2[2] (HR+/HER2-; prior Let or Ana)		
	TAM	TAM + everolimus		EXA + placebo	EXA + everolimus	
	57	54		239	485	
CBR %	42.1	**61.1**	**p 0.045**	18.0	**33.4**	**p < 0.0001**
Median PFS (m)	4.5	**8.6**	**HR 0.53**	2.8	**6.9**	**HR 0.43**
Median OS (m)	24	**NR**	**HR 0.32**	NR	**NR**	

[1]Bachelet T et al, SABCS 2010; [2] Baselga J et al, ECCO/ESMO 2011

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

New agents for the breast cancer molecular subtypes



mTOR inhibitors
PI3K inhibitors

AI + antiHER2 agents

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

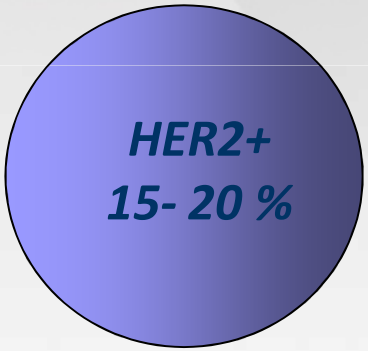
Co-Targeting HER2 and HR in HR+/HER2+ve ABC

	TANDEM[1]			eLEcTRA[2]			Johnston et al [3]		
	ANA	ANA + trastuzumab		LET	LET + trastuzumab		LET + Plac	LET + lapatinib	
Pts #	104	103		31	26		108	111	
ORR %	6.8	**20.3**	**p 0.018**	13.0	**27**	**p 0.3**	15	**28**	**p 0.02**
median PFS (m)	2.4	**4.8**	**HR 0.63**	3.3	**14.1**	**HR 0.67**	3.0	**8.2**	**HR 0.71**
Median OS (m)	23.9	**28.5**	**p 0.32**	NR	**NR**		32.3	**33.3**	**HR 0.74 p 0.1**

[1] Kaufman B, et al. JCO 2009; [2] Huober J et al. The Breast 2011; [3] Johnston S et al. JCO 2009

Section of Oncology
University of Modena and Reggio Emilia
Modena

New agents for the breast cancer molecular subtypes



Lapatinib
Neratinib
Pertuzumab
TDM-1
AntiHER2 combinations
Trastuzumab + mTORi

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

HER2+ EBC
RCTs of PCT + dual antiHER2 blockade

Trial	pts #	Regimen	pCR % (breast&N)
Neo-ALLTO[1]	455	wPac+**T/L/TL**	20 /27.6/**46.9***
NeoSphere[2]	417	**DT/DTP/TP/DP**	21.5/**39.3***/11.2/17.7
CherLob[3]	121	wP-FEC**T/L/TL**	25.7/27.8/**43.1***

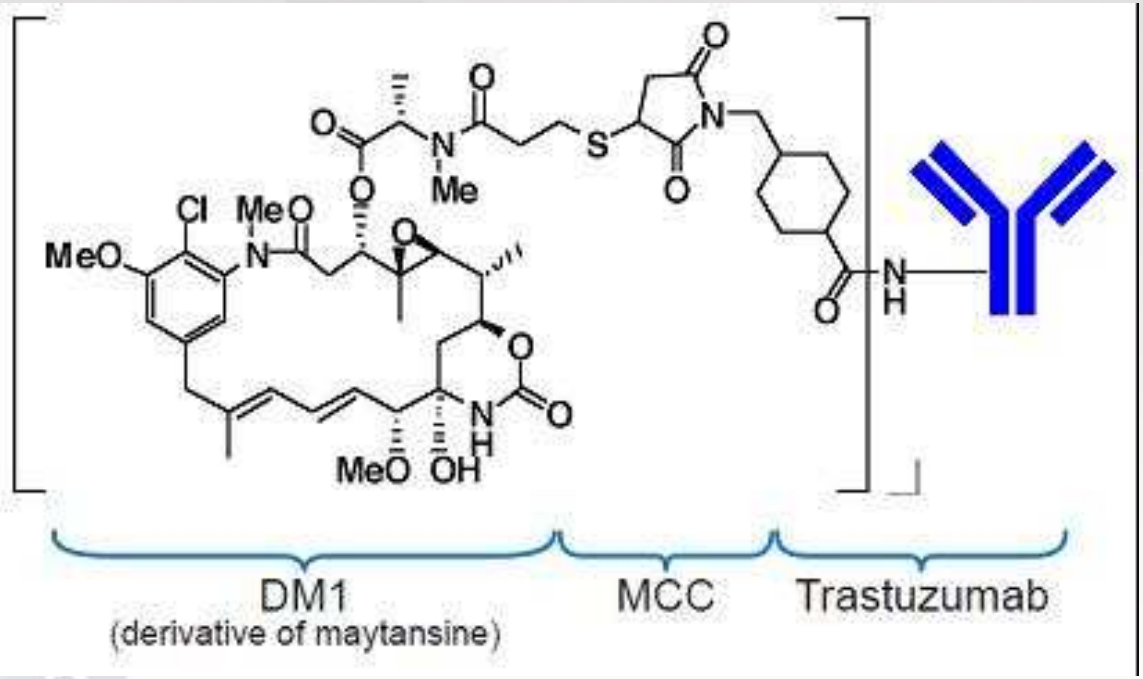
T = trastuzumab; L = Lapatinib; P = Pertuzumab

**** p value < 0.05***

[1]*Baselga J et al, SABCS 2010;* [2]*Gianni L et al, SABCS 2010;* [3]*Guarneri V et al, ASCO 2011*

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

- **Trastuzumab-DM1 (T-DM1) is an anti-HER2 antibody drug–conjugate [1,2]**
  - Combines the HER2-targeting properties of trastuzumab[3] with targeted delivery of a highly potent anti-microtubule derivative, DM1[3-5]
  - After binding to HER2, T-DM1 undergoes receptor-mediated internalization,[6] resulting in intracellular release of DM1



1. Krop I, et al. J Clin Oncol 2008; 2.Burris HA, et al. J Clin Oncol, 2010; 3. Lewis Phillips, et al. Cancer Res. 2008; 4 . Junttila TT, et al. Breast Cancer Res Treat, 2010; 5. Remillard S, et al. Science 1975; 6.Austin CD, et al. 2004. Mol Biol Cell 2004

University of Modena and Reggio Emilia
Modena

Randomized phase II study of TDM-1 vs Trastuzumab/Docetaxel in HER2+ ABC

Outcome	Trastuzumab + Docetaxel	TDM-1	
Patients #	**70**	**67**	
CR %	**4.3**	**10.4**	
PR %	**53.6**	**53.7**	
OR %	**57.9**	**64.1**	
SD %	**33.3**	**19.4**	
median PFS (m)	**9.2**	**14.2**	HR 0.59
G $\geq$ 3 AE %	**89.4**	**46.4**	

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Hurvitz SA, et al. ESMO 2011.

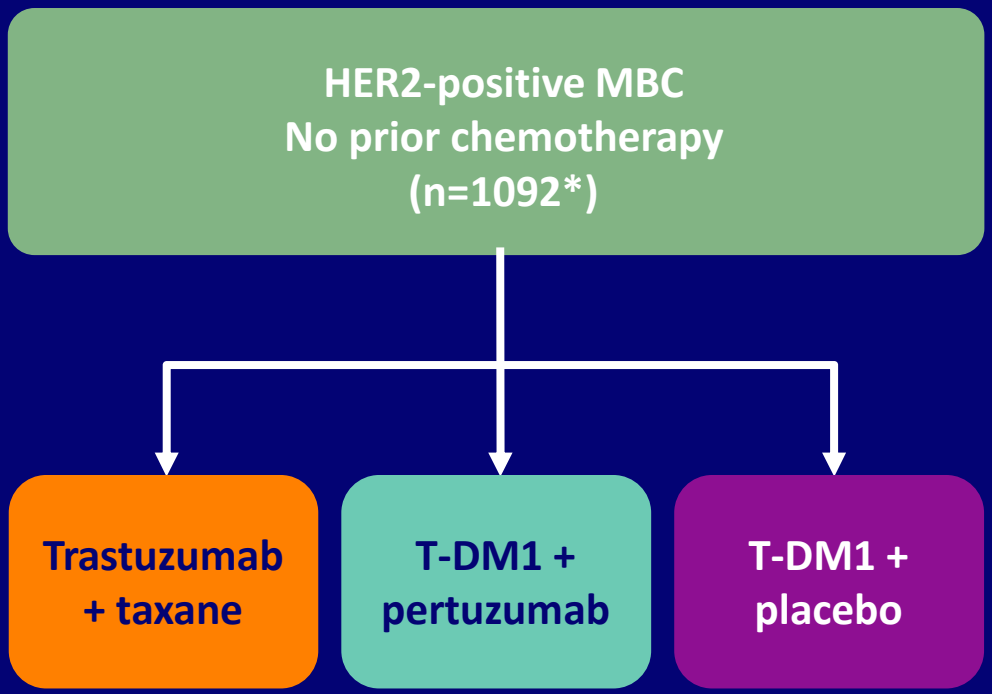
TDM4788g/BO22589 (MARIANNE): a Phase III trial of T-DM1 ± pertuzumab vs trastuzumab + docetaxel in 1st L

Primary endpoints

- PFS (independent assessment)
- Safety

Secondary endpoints

- ORR (independent assessment)
- OS
- 1-year survival
- PFS
- ORR (investigator assessment)
- CBR
- TTF
- DoR
- Safety and tolerability



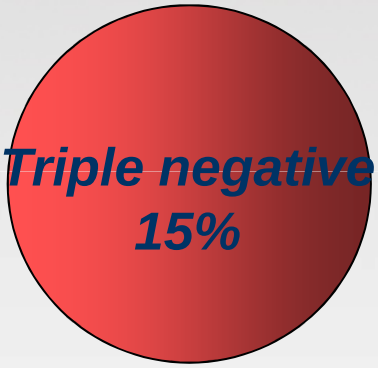
FPI Jul 2010

Estimated completion: 2012
Estimated date of data availability: 2012

332 centres in 40 countries

Clinicaltrials.gov

New agents for the breast cancer molecular subtypes



New cytotoxics (eribulin, ixabepilone, vinflunine)
Platinum salts
Bevacizumab
PARP inhibitors
AntiEGFR (Cetuximab, erlotinib)
Anti androgens

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

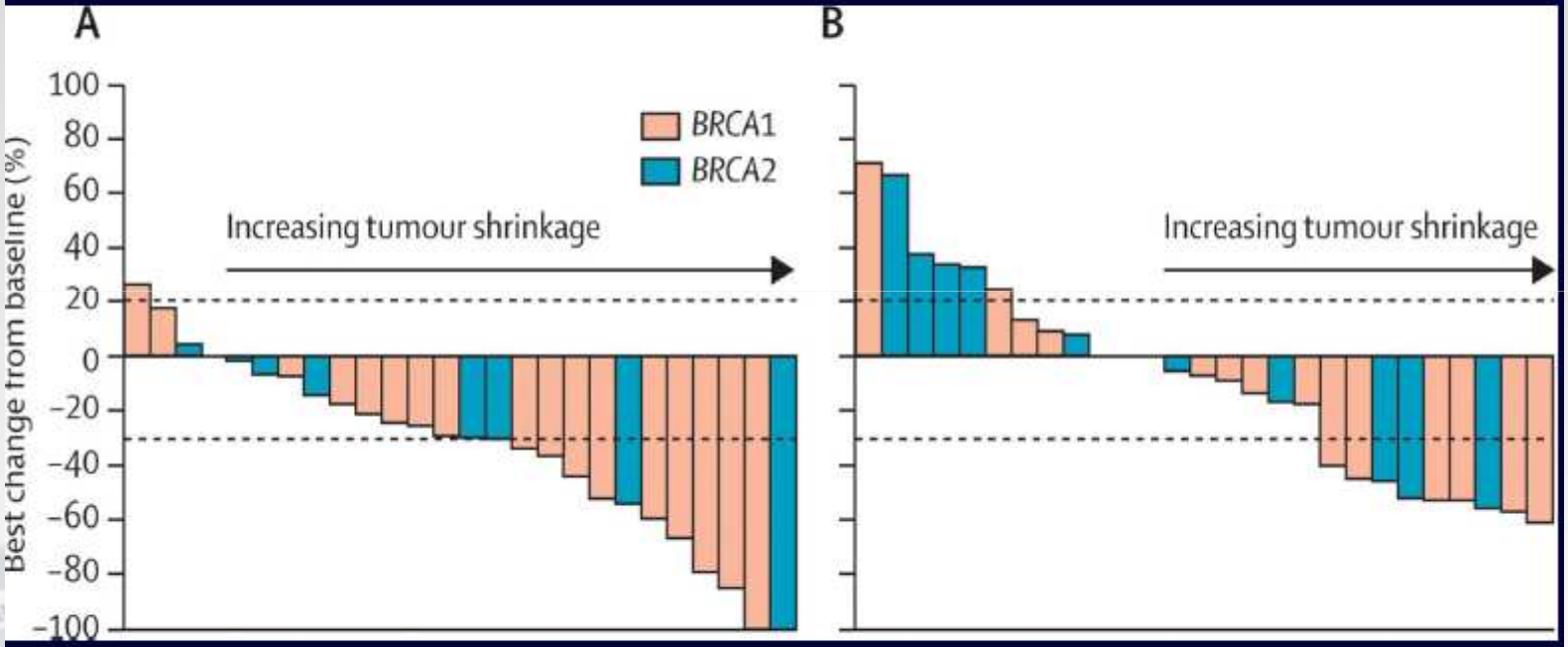
DNA repair is essential for cell survival

DNA lenght per cell	**2 meters**
Cells per human	2×10^{13}
DNA lenght per human	4×10^{13} meters
Distance from the Earth to the Sun	1.49×10^{11} meters
Number of return trips to the Sun	134
DNA damage/cell/day	**10,000-30,000**
Number of DNA damage pathways	5 (2 alleles)

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Modified from H Calvert

Olaparib Phase II in Breast Cancer
Best % change from baseline in target lesions by genotype



400 mg twice daily

100 mg twice daily

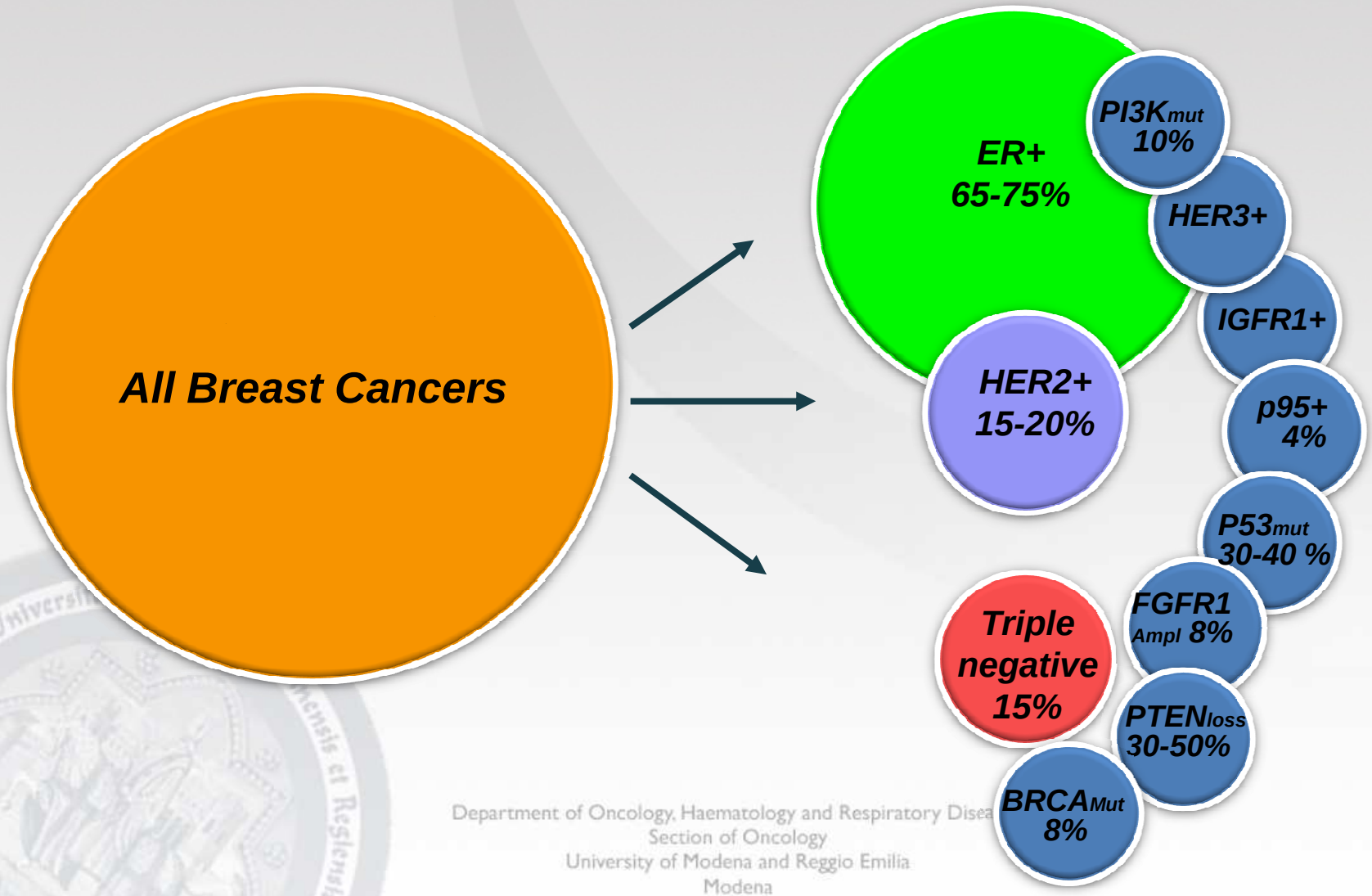
Tutt et al. Lancet 376:235, 2010

Section of Oncology
University of Modena and Reggio Emilia
Modena

From clinical excellence
... to breakthrough ...



Breast Cancer Diseases – 201…



Department of Oncology, Haematology and Respiratory Disea
Section of Oncology
University of Modena and Reggio Emilia
Modena

BC subtypes: an orphan designation ?

- Breast cancer incidence in Italy: 137.8×10^5
- Breast Cancer Prevalence in Italy: 520.000
- Definition of Rare Disease:
  - 1/1,500 people (USA)
  - 1/2,000 people (EU)
  - 1/2,500 people (Japan)

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena

Predictive Biomarkers in Oncology:
the slippery path from EBM to Personalized Medicine

- Our standards of care are based on EBM
- EBM provides the best approach for the average population

The molecular characterization of human tumors

  - New study design
  - Registration, Reimbursement, Accessibility

Department of Oncology, Haematology and Respiratory Diseases
Section of Oncology
University of Modena and Reggio Emilia
Modena