La squadra

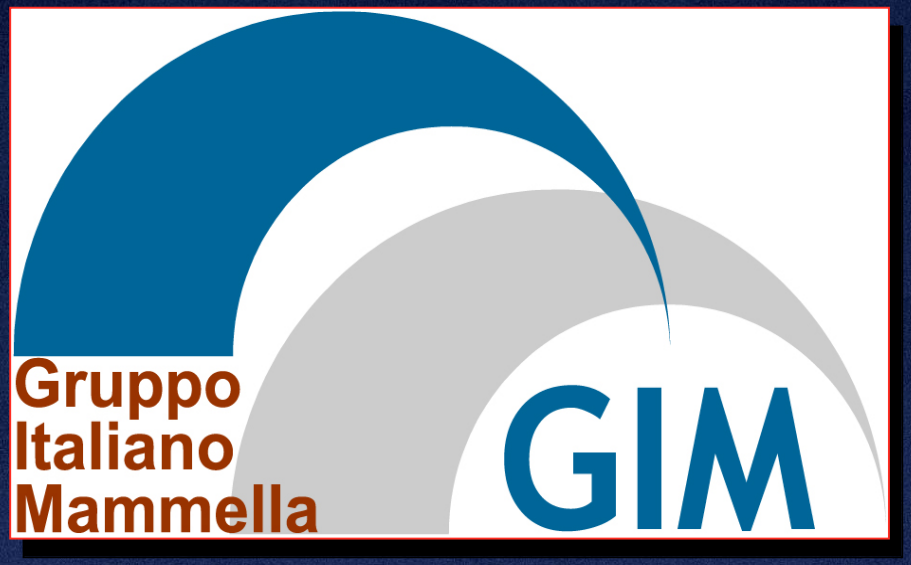
"L'importanza dei gruppi cooperatori"

Gruppo Italiano Mammella GIM

Riunione Annuale
Trieste, 2019

Sabino De Placido

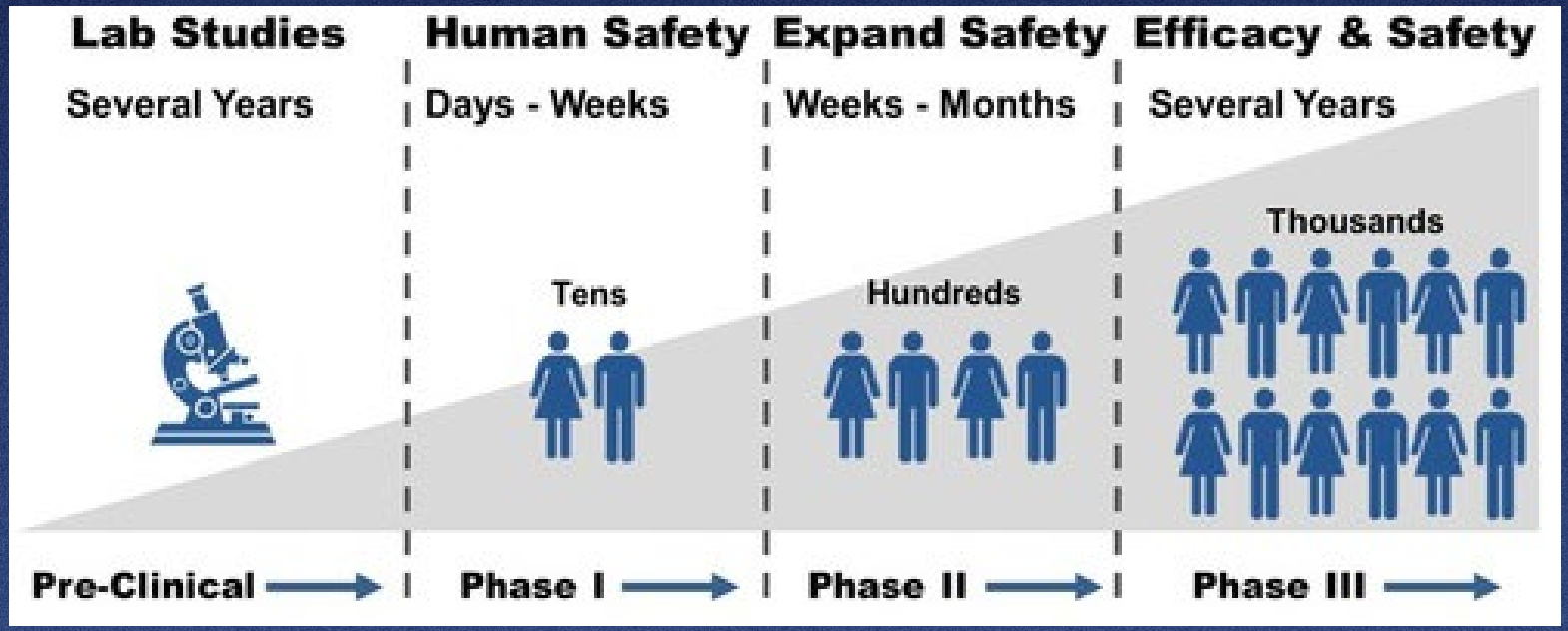
Università degli Studi di Napoli Federico II



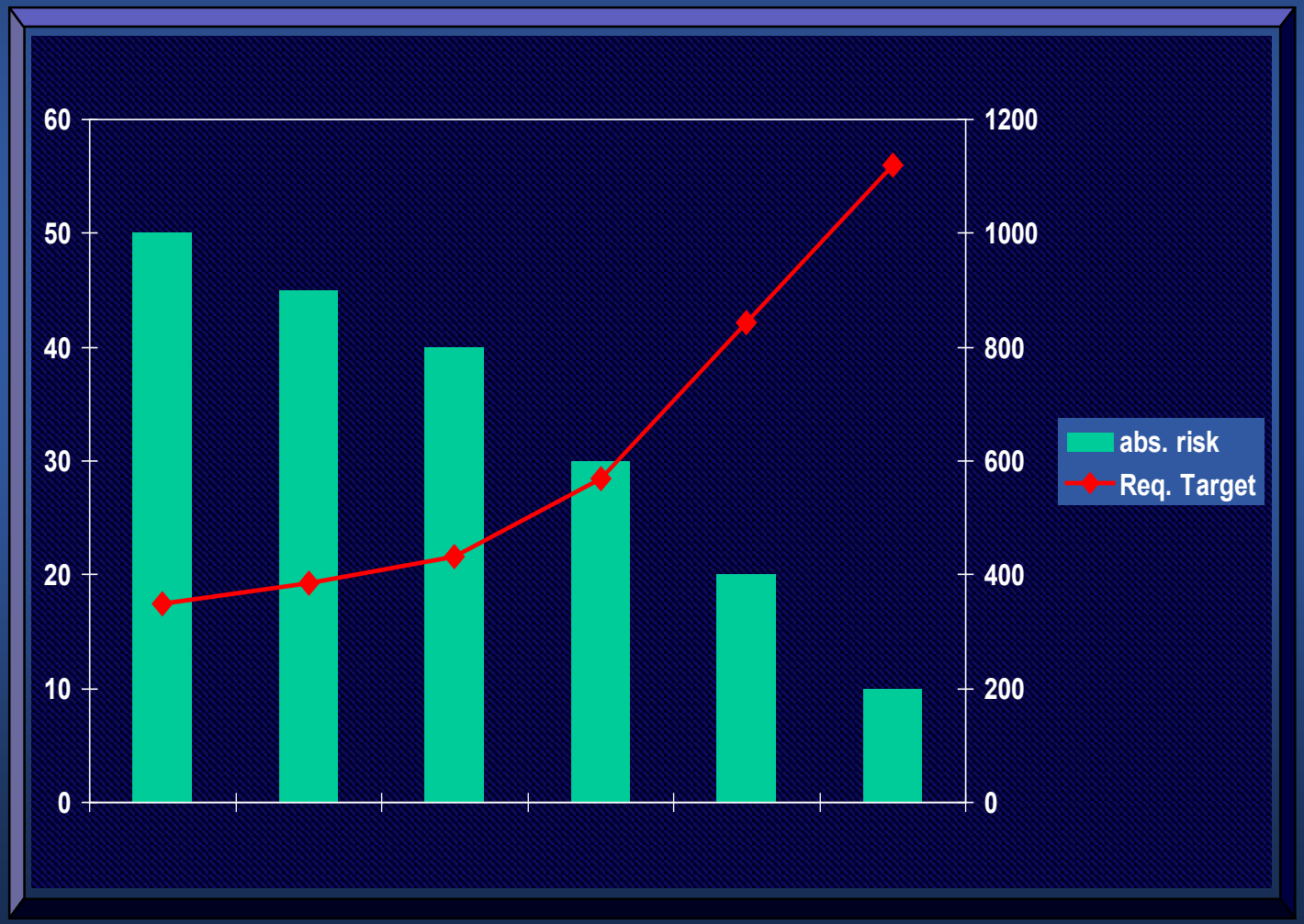
Perchè la ricerca cooperativa ?

Che cos'è un Trial Clinico?

- ***Definizione***: studio farmacologico, biomedico o salute-correlato sull'uomo, che segue dei protocolli predefiniti.
- ***Scopo***: rispondere ad una domanda scientifica e verificare che una nuova terapia/procedura sia sicura, efficace e migliore di quella normalmente impiegata e correntemente somministrata.
- ***Le fasi della ricerca clinica:***



Role of cooperative groups in clinical research

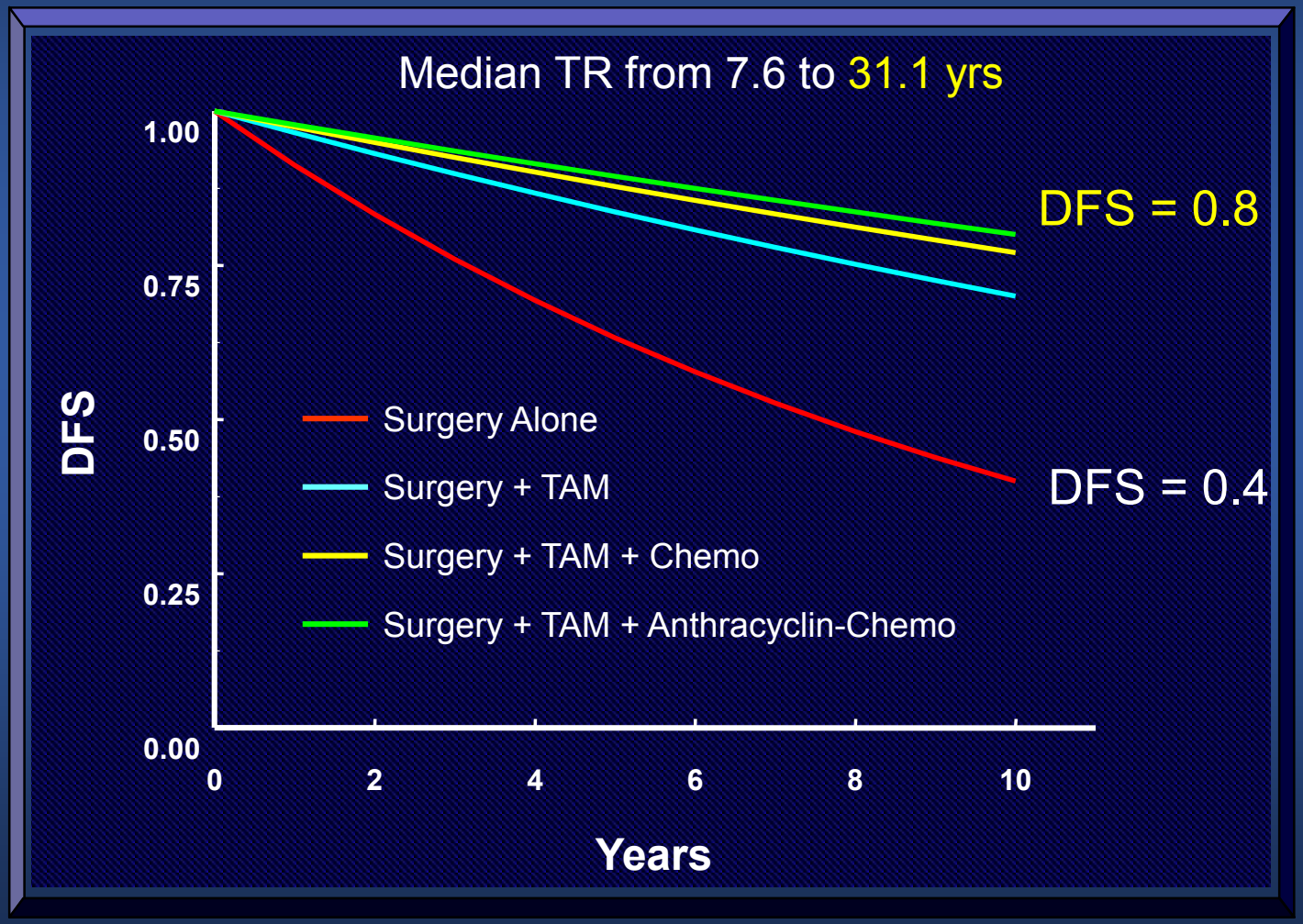


Adjuvant Therapy Effect Simulation

DFS, patient N+, ER+, <50aa

Adjuvant Therapy State of the Art

"Treatment evolutin yield additional proportional reduction in relapse rate "



Estimates from EBCTCG Overview; Exponential Survival

The New England
Journal of Medicine

Volume 332 APRIL 6, 1995 Number 14

ADJUVANT CYCLOPHOSPHAMIDE, METHOTREXATE, AND FLUOROURACIL IN NODE-POSITIVE BREAST CANCER

The Results of 20 Years of Follow-up

GIANNI BONADONNA, M.D., PINUCCIA VALAGUSSA, B.S., ANGELA MOLITERNI, M.D., MILVIA ZAMBETTI, M.D., AND CRISTINA BRAMBILLA, M.D.

CMF vs Surgery

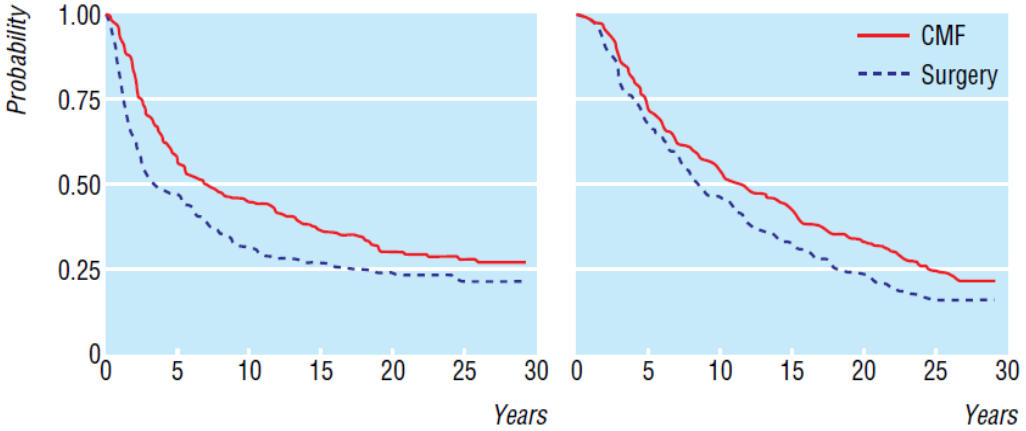


Fig 1 Treatment outcome in the first randomised CMF study after a median observation of 28.5 years. Left: Relapse free survival after surgery alone (179 patients) *v* CMF (207 patients). Univariate analysis: hazard ratio 0.71 (95% confidence interval 0.56 to 0.91; P=0.005). Right: Overall survival after surgery alone (179 patients) *v* CMF (207 patients). Univariate analysis: hazard ratio 0.79 (0.63 to 0.98; P=0.04)

Bonadonna et al.

Twenty-year Results of the Naples GUN Randomized Trial: Predictive Factors of Adjuvant Tamoxifen Efficacy in Early Breast Cancer[1]

Sabino De Placido, Michelino De Laurentiis, Chiara Carlomagno, Ciro Gallo, Franco Perrone, Stefano Pepe, Angela Ruggiero, Alfredo Marinelli, Clorindo Pagliarulo, Luigi Panico, Guido Pettinato, Giuseppe Petrella, and Angelo Raffaele Bianco[2]

Cattedra di Oncologia Medica, Dipartimento di Endocrinologia ed

THE LANCET

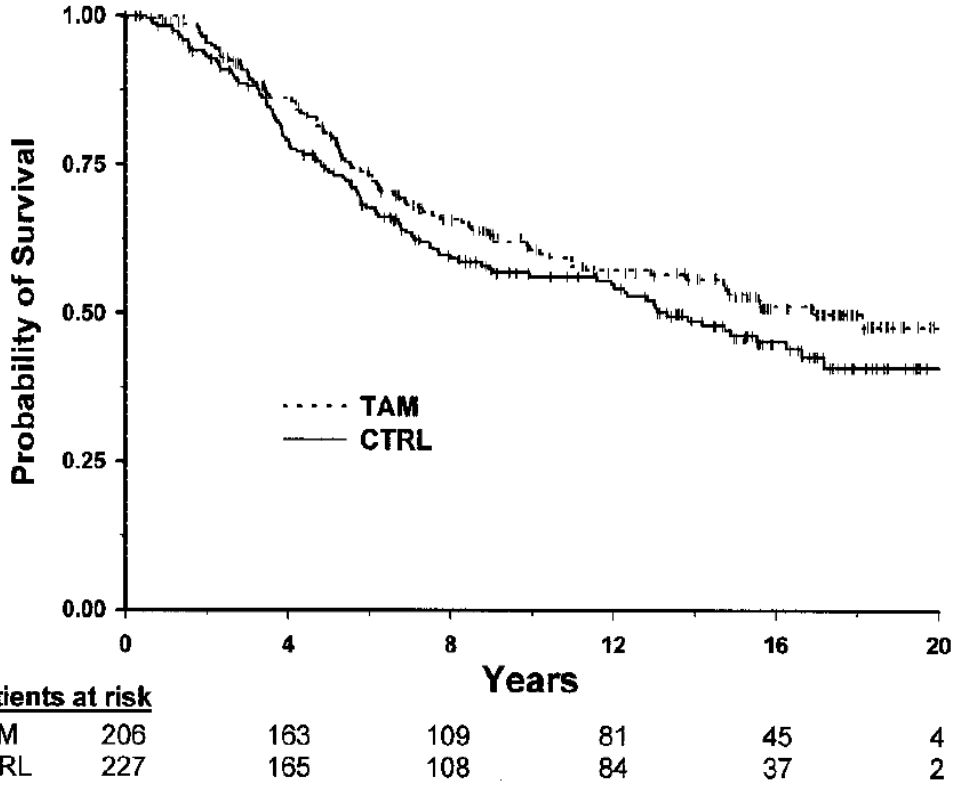


Fig. 2 Survival curves of TAM-treated *versus* control (CTRL) patients.

GIM3-FATA
First Adjuvant Trial on AII aromatase inhibitors in early breast cancer

A phase III study comparing anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen), as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer

S.De Placido, C.Gallo, M.De Laurentiis, G.Bisagni, G.Arpino, M.G.Sarobba, F.Riccardi, A.Russo, L.Del Mastro, A.A.Cogoni, F.Cognetti, S.Gori, A.Frassoldati, D.Amoroso, L.Laudadio, L.Moscetti, F.Montemurro, F.Nuzzo, P.Carlini and F.Perrone
on behalf of the GIM Investigators.

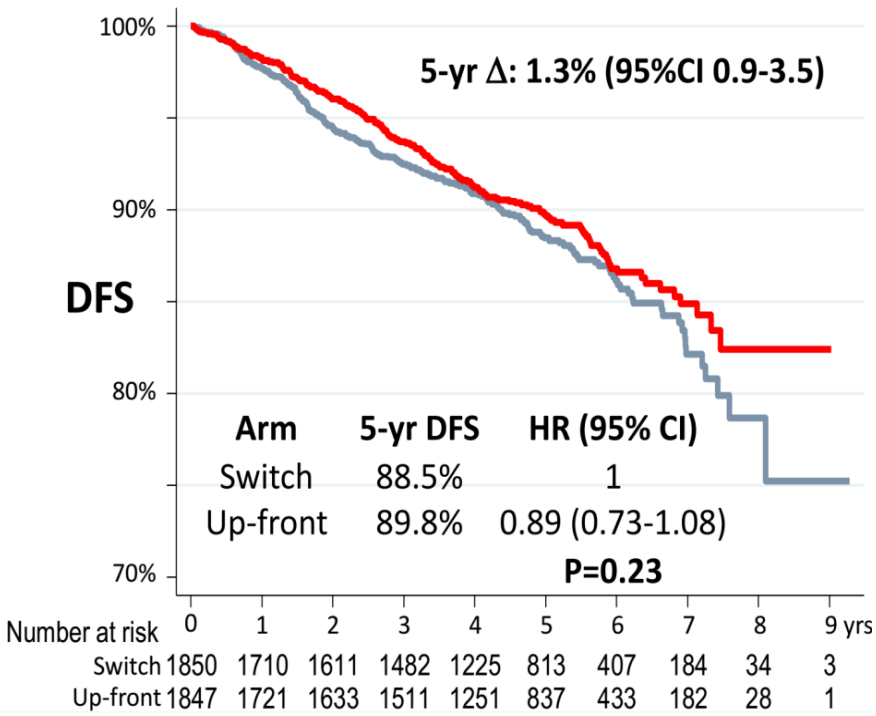
Gruppo Italiano Mammella GIM

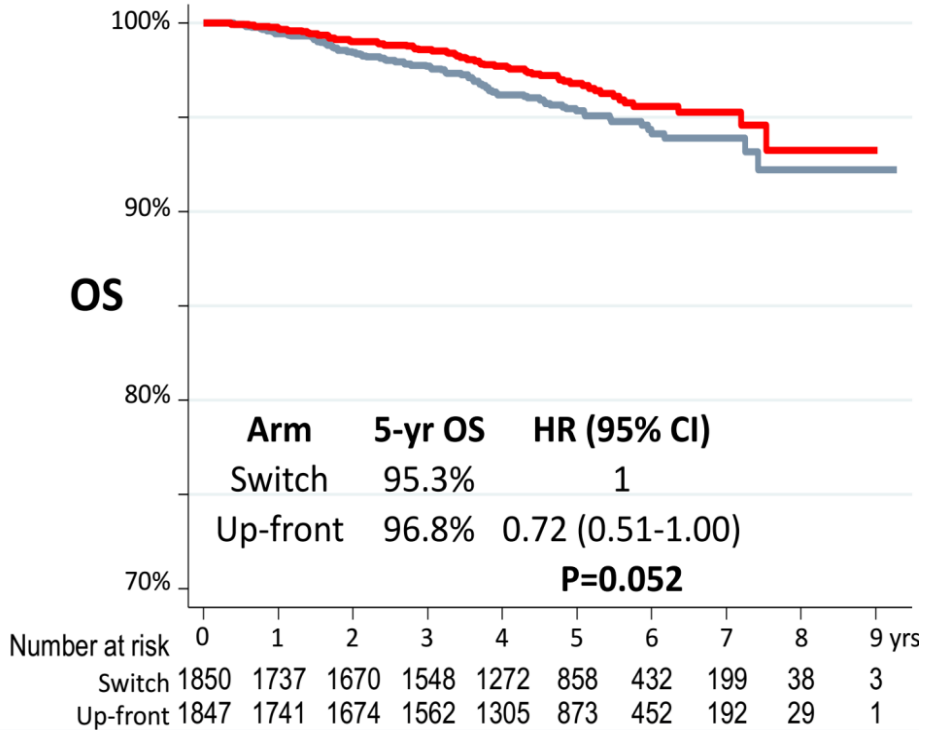
Agenzia Italiana del Farmaco AIFA

EUDRACT number: **2006 – 004018 - 42**

AIFA code: **FARM5K3MEE**

Schedule comparison





Switch Upfront

Adjusted by ER status, HER2 status, Nodal status and Previous Chemotherapy

Perchè è importante partecipare ad un Trial Clinico oncologico?

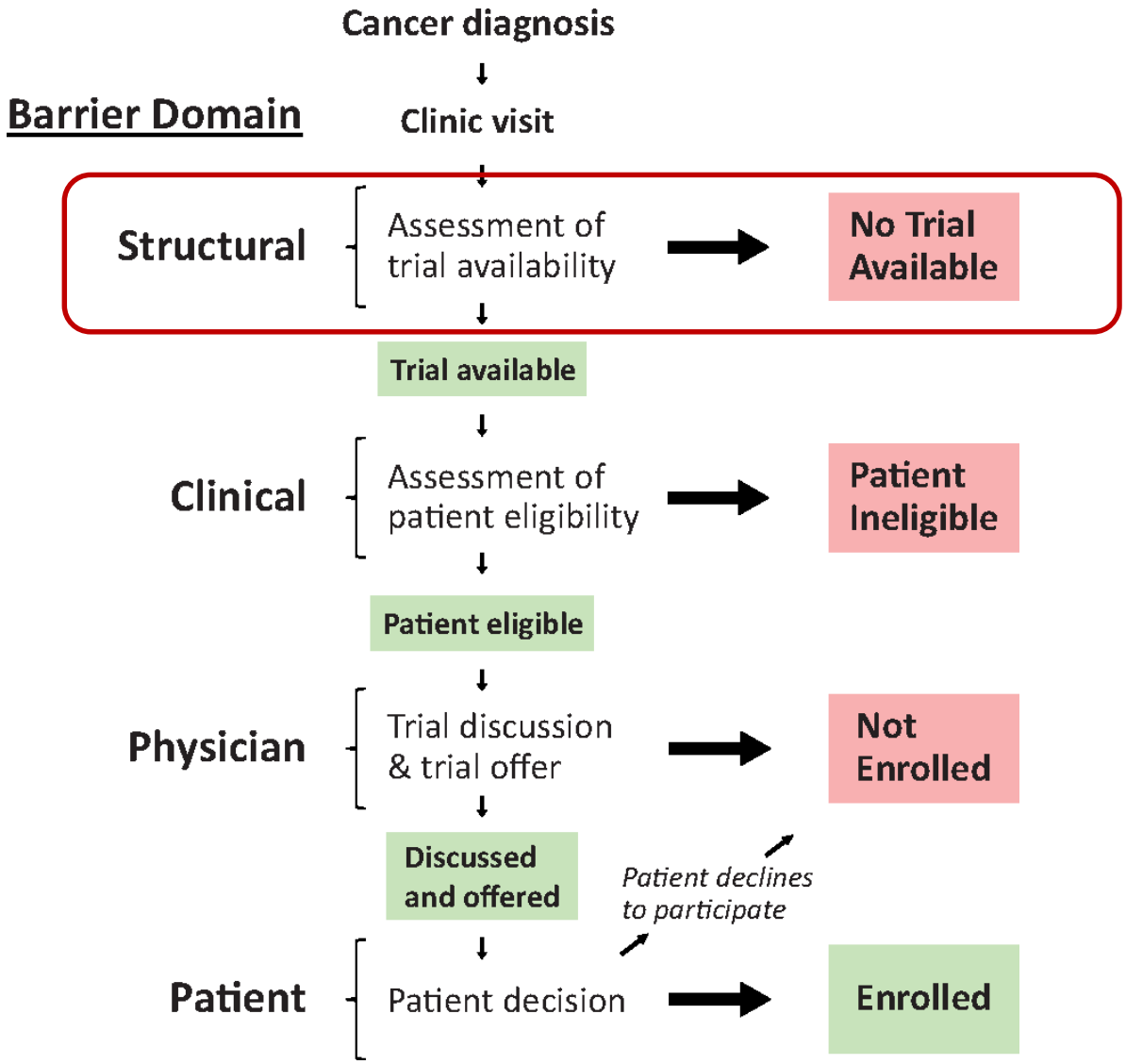
- Sviluppo di nuove strategie terapeutiche che possono incrementare gli outcome clinici dei pazienti oncologici
- Una maggiore partecipazione si traduce in una più veloce ed efficiente conduzione dello studio clinico
- I trial clinici rappresentano una opportunità per i pazienti di accedere a trattamenti innovativi

Quanti pazienti oncologici partecipano ai trail clinicli?

- ≃1/20 pazienti adulti oncologici è arruolato in trial clinici (<5%)
- >70% è propenso o molto favorevole a partecipare ad un trial clinico

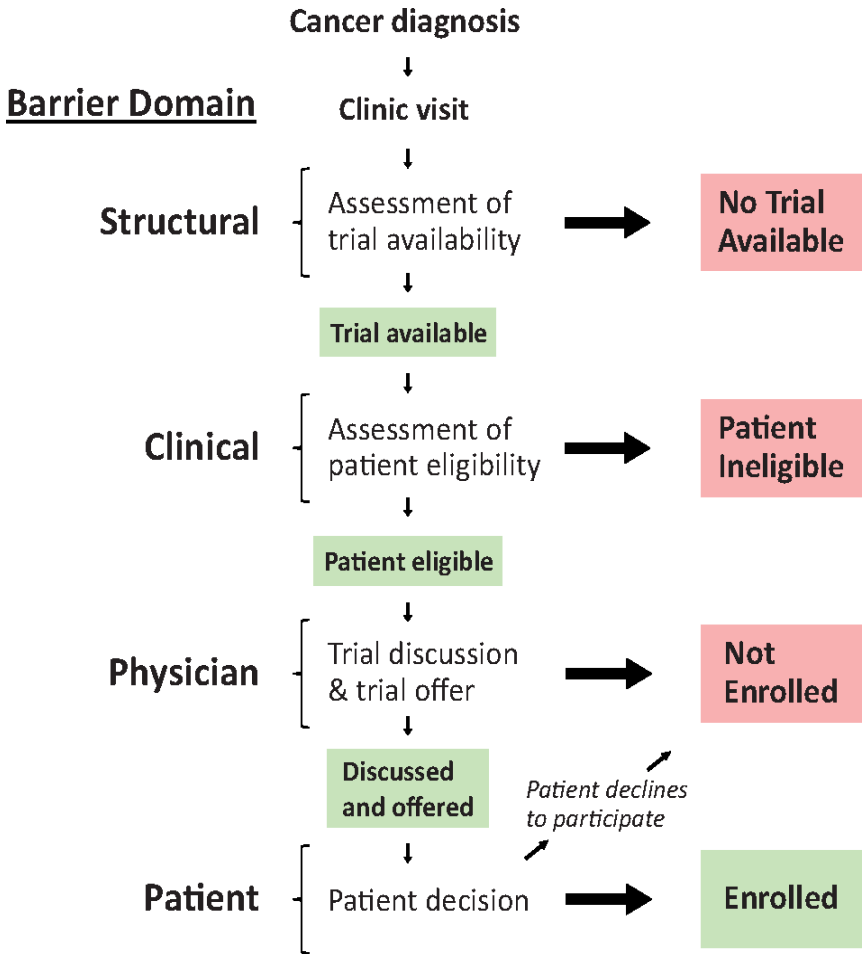
Am Soc Clin Oncol Educ Book. 2016 ; 35: 185–198.

Decision-making framework dei trail clinicli



Unger et al, JNCI 2019

Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation



13 studies evaluated with 8883 patients

55.6% of the time a trial was unavailable for patients at their institution

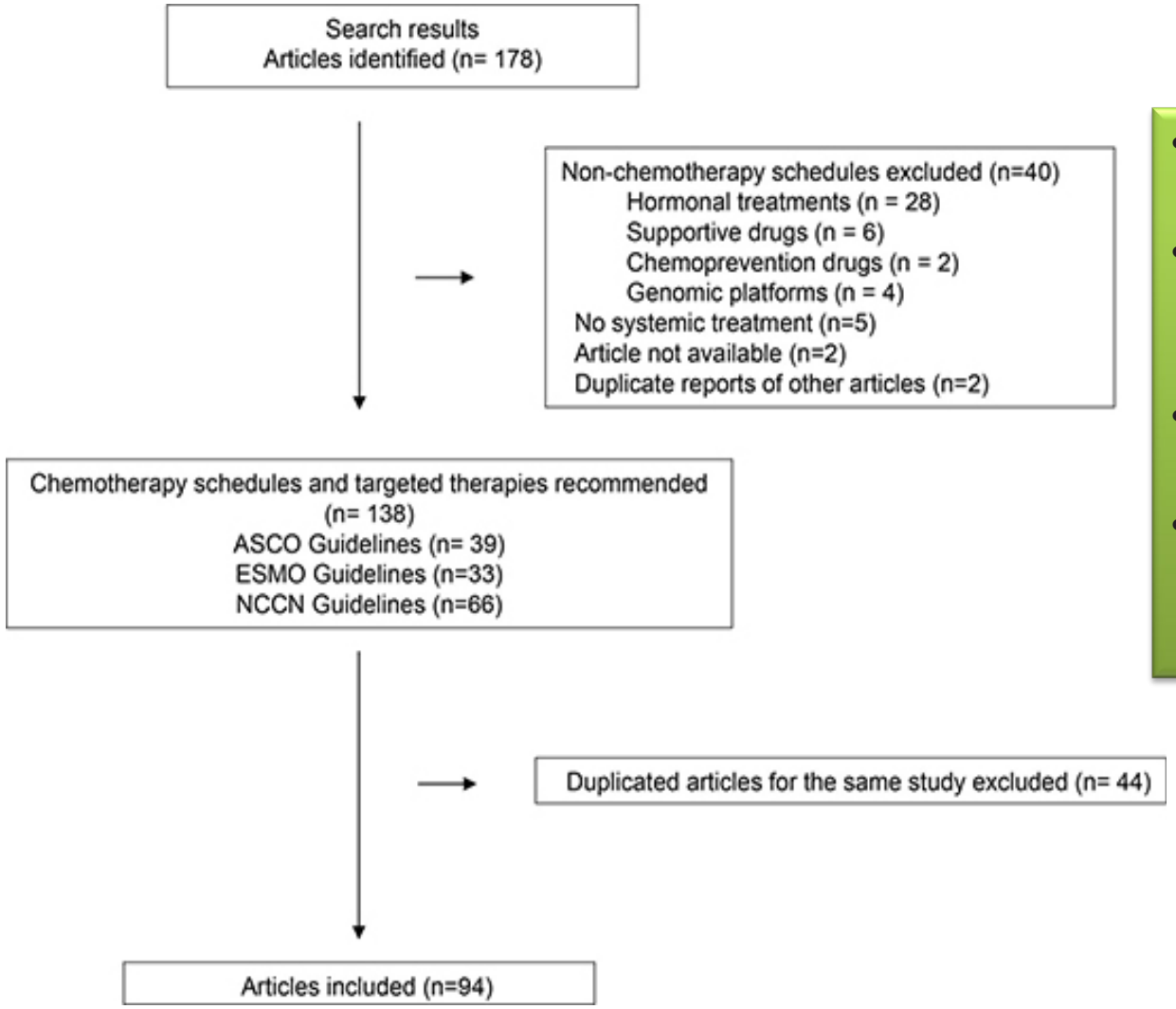
21.5% of patients were ineligible for an available trial

14.8% of patients not enroll

8.1% of patients enrolled

Unger et al, JNCI 2019

Role of cooperative groups and funding source in clinical trials supporting guidelines for systemic therapy of breast cancer



- **94 studies identified**
- **Cooperative Groups were involved in 28 (30%) studies**
- **while**
- **Industry either partially or fully sponsored 64 (68%) studies.**

Tibau et al, Oncotarget, 2018

Role of cooperative groups and funding source in clinical trials supporting guidelines for systemic therapy of breast cancer

	n (%)	Cooperative Groups (%)	Non-Cooperative Groups (%)	*P* value
Number	**85 (100%)**	**28 (40%)**	**57 (60%)**	
Number of study subjects				0.015
Mean ± SD	670 ± 1248	1416 ± 2020	384.46 ± 493.94	
Median (range)	292 (22–8381)	448 (77–8381)	284 (28–3384)	
Number of study centres				0.027
Multiple	76 (89%)	28 (100%)	48 (84%)	
Single	9 (11%)	0 (0%)	9 (16%)	
Number of countries of study conduct				0.07
Multiple	48 (56%)	12 (43%)	36 (63%)	
Single	37 (44%)	16 (57%)	21 (37%)	
Type of design				0.018
Randomized	66 (78%)	26 (93%)	40 (70%)	
Single Arm	19 (22%)	2 (7%)	17 (30%)	
Type of study				< 0.0001
Phase III	55 (69%)	25 (93%)	30 (57%)	
Phase II	25 (31%)	2 (7%)	23 (43%)	
Clinical setting				< 0.0001
Metastatic	63 (74%)	14 (50%)	49 (86%)	
Neo/adjuvant	22 (26%)	14 (50%)	8 (14%)	

Tibau et al, Oncotarget, 2018

Role of cooperative groups and funding source in clinical trials supporting guidelines for systemic therapy of breast cancer

Industry funding was associated with higher likelihood of positive outcomes favoring the sponsored experimental arm (*p = 0.013)*

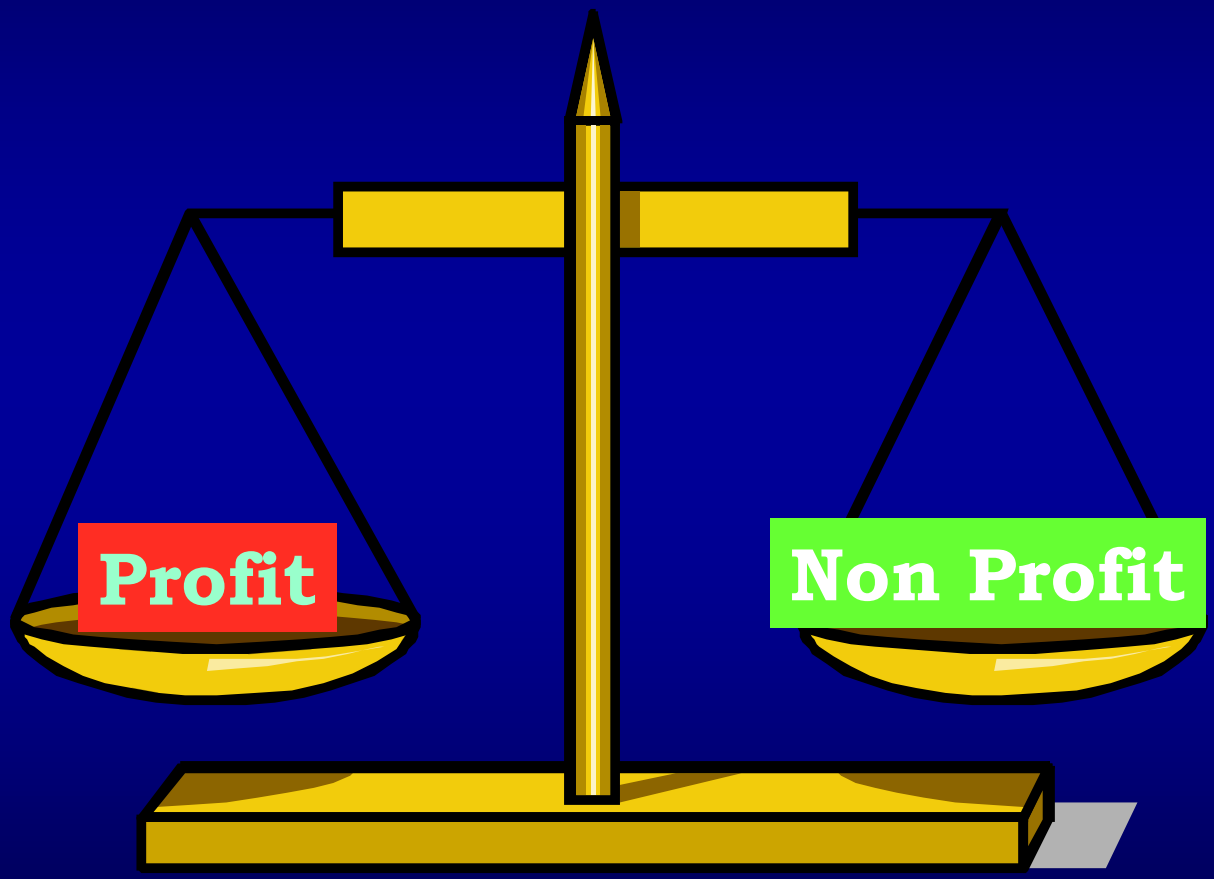
but

this relationship was not seen for CG-sponsored trials (p = 0.53).

Industry funding, but not CG-based funding, was associated with higher likelihood of positive outcomes in clinical studies supporting guidelines for systemic therapy.

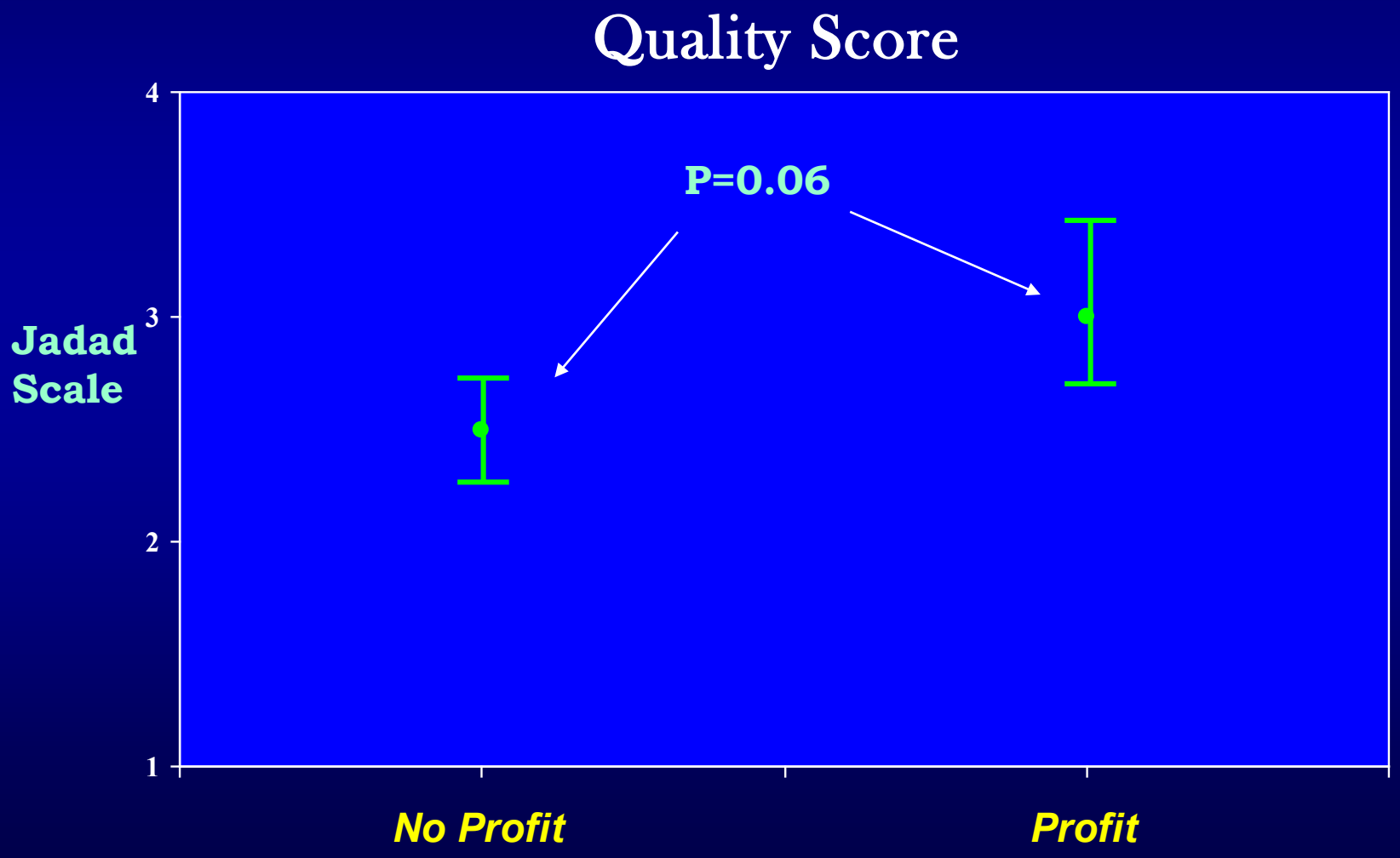
Tibau et al, Oncotarget, 2018

La Qualità delle Sperimentazioni



RCT for Multiple Myeloma

Djulbegovic B, et al: The Lancet, 356: 635-638, 2000



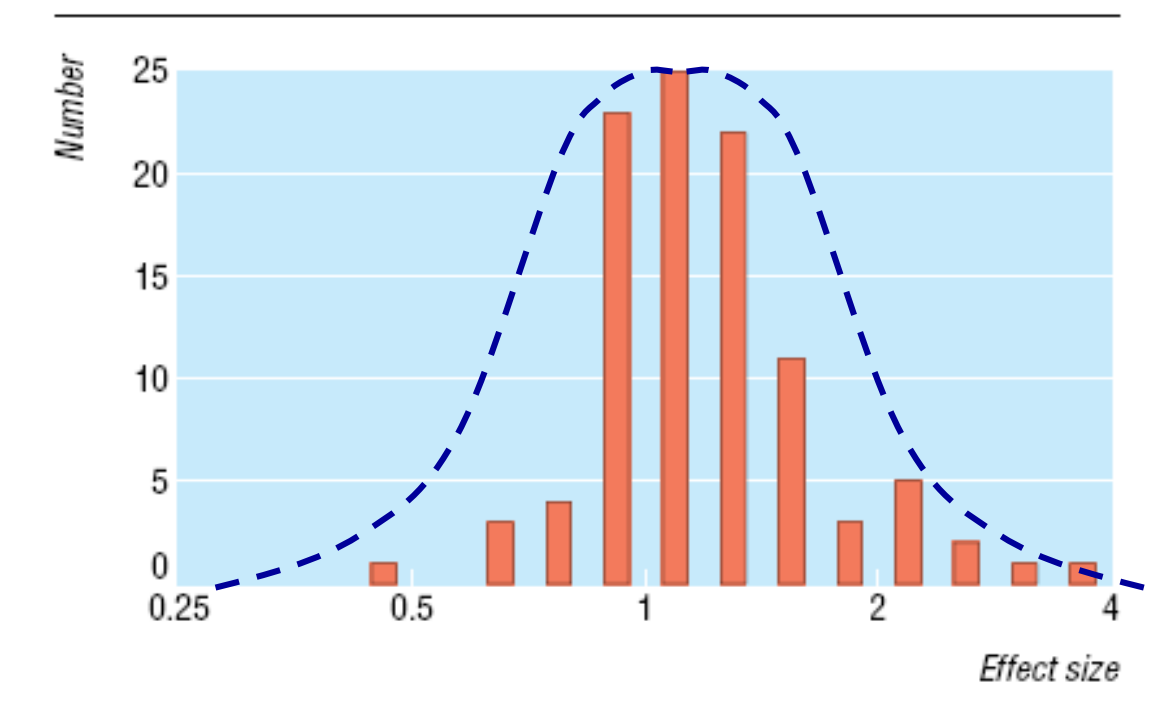
The Uncertainty Principle
"Treatment Equipoise" o "Equal Bet"

Una Sperimentazione Clinica Randomizzata che non segue questo principio è:

- **Metodologicamente Scorretta**
- **Eticamente Scorretta**

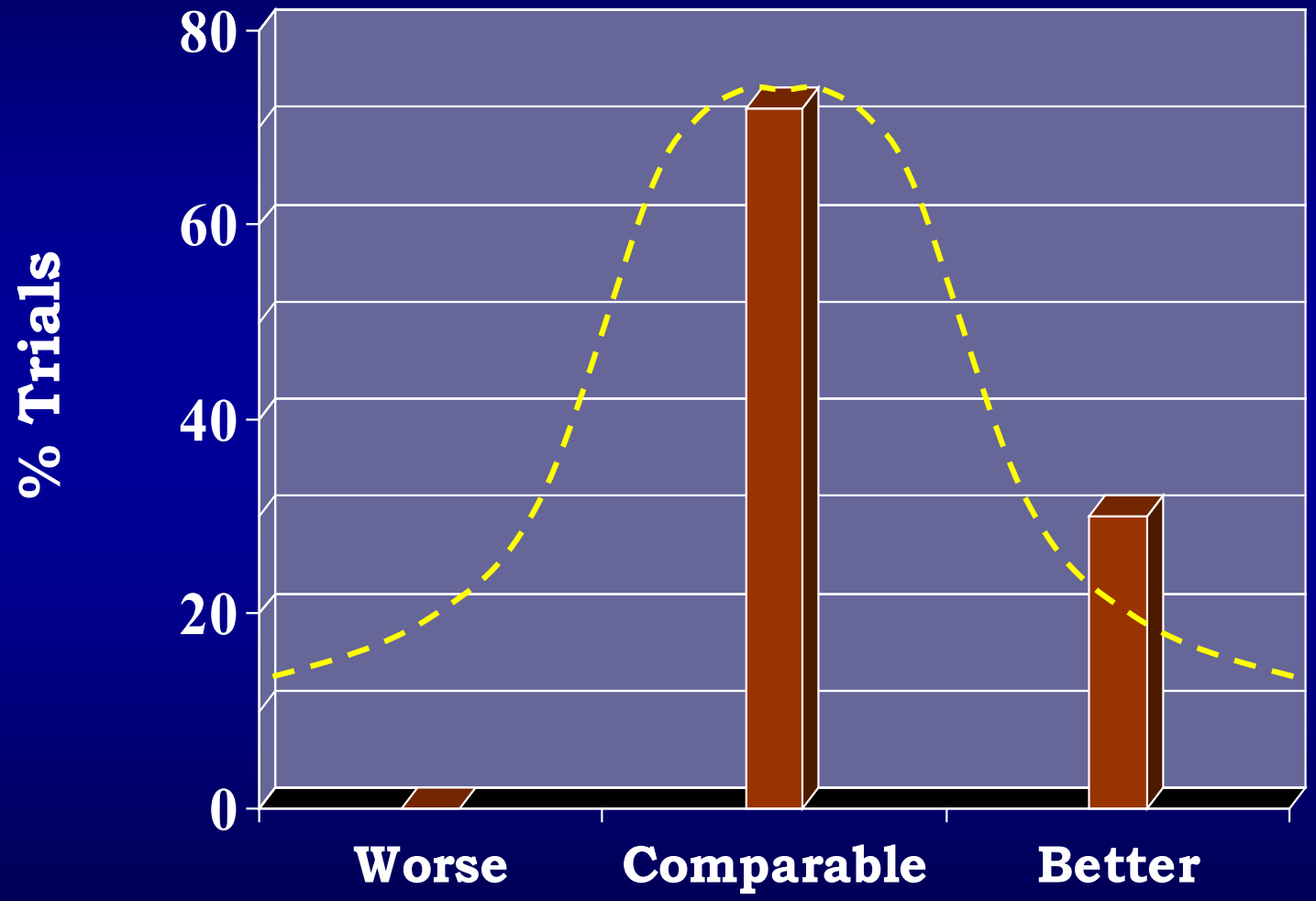
ECOG/CALGB 'No Profit' Trials
Satisfation of Uncertainty Principle

BMJ. 2004 Jun 19;328(7454):1463. Epub 2004 May 26



Distribution of effect sizes among ECOG and CALGB randomised controlled trials, 1981-95. Effect sizes >1 favour experimental treatment; effect sizes <1 favour standard treatment

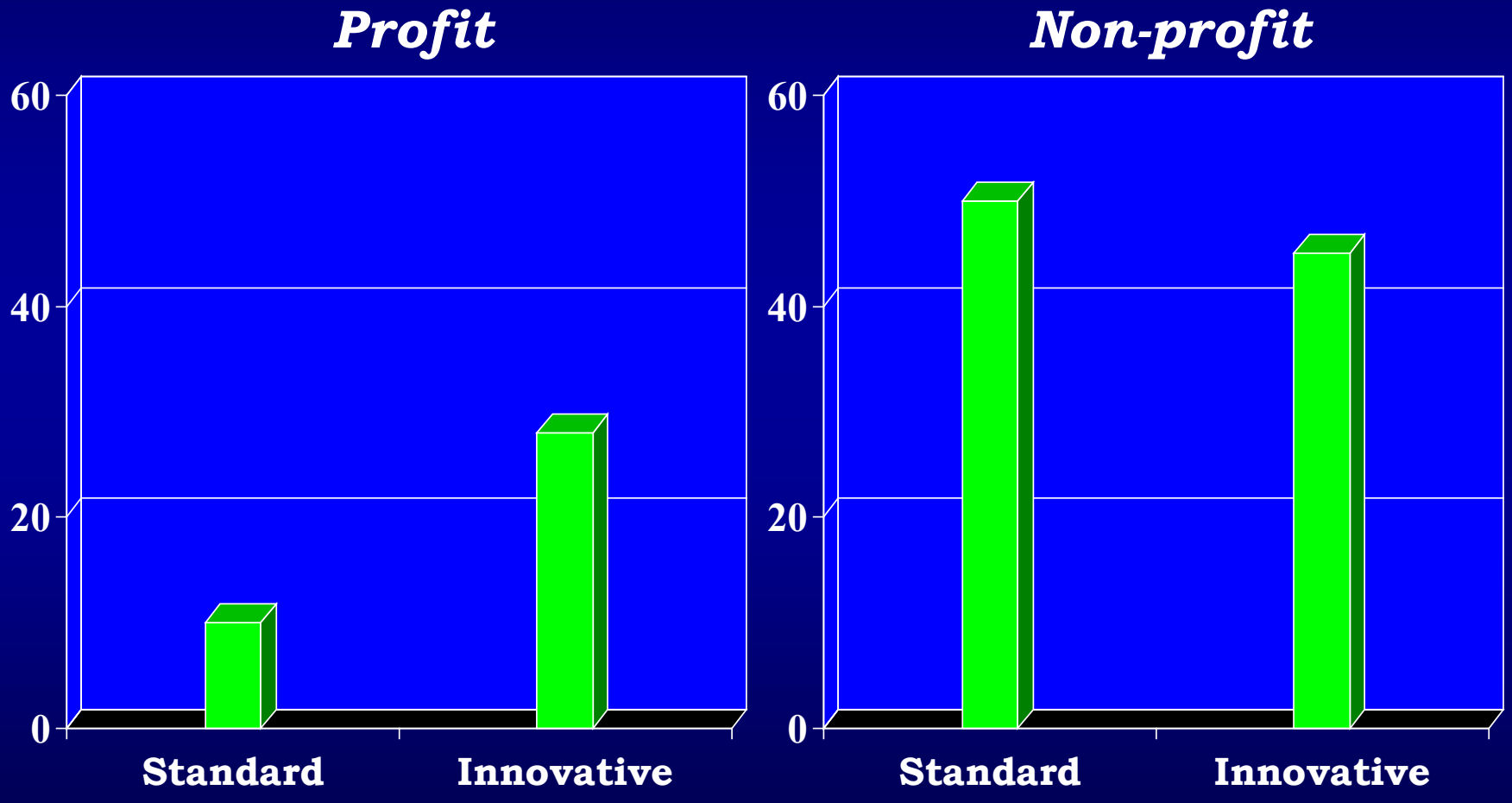
Efficacy Outcome of Manufacturer-Associated vs Comparison Drug (NSAID)



Rochon PA, et al: Arch Intern Med, 154: 157-163, 1994

Effect of funding source on Trial Outcome

136 RCT for Multiple Myeloma



Djulbegovic B, et al: The Uncertainty Principle and industry-sponsored research
The Lancet, 356: 635-638, 2000

The Uncertainty Principle Violation

Possible Causes

- **Trial Design**
  - Inadequate standard
  - Inadequate methodology
- **Data Analysis**
  - Inadequate End-Points
  - Inadequate Population
- **Publication**
  - Selective publication
  - Delayed publication
  - Ghost writing / Emphatic writing

Bodenheimer T: Uneasy Alliance. Clinical Investigators and the Phamaceutial Industry New Engl J Med, 342: 1539-1543, 2000

Gruppo Italiano Mammella

- Anno di fondazione: 2002
- Oncologi fondatori:
  - Marco Venturini
  - Francesco Cognetti
  - Sabino De Placido

- Sponsor studi GIM:

- *Consorzio ONCOTECH è un consorzio pubblico-privato dedicato alla ricerca clinica, alla formazione, alla divulgazione e comunicazione scientifica ed all'informatica medica in campo oncologico, costituendo una realtà unica in Italia per struttura, ampiezza di aree d'interesse e rilevanze di progetti in corso.*

CLINICAL TRIALS condotti dal GIM

TRIAL	TYPE OF STUDY	ACCRUAL TIME	N°PATIENTS	STATUS
GIM1	Fase III Adiuvante CT, N-	2003 - 2010	1.636	COMPLETED
GIM2	Fase III Adiuvante CT, N+	2003 - 2006	2.091	COMPLETED
GIM3 - FATA	Fase III Adiuvante HT, postmenopausa	2007 – 2012	3.707	COMPLETED
GIM4 - LEAD	Fase III Adiuvante HT, postmenopausa	2005 - 2010	2.056	COMPLETED
GIM5 - CYPLEC	Traslazionale , HT postmenopausa	2005 – 2008	488	COMPLETED
GIM6 - PROMISE	Fase III Conservazione della fertitiltà	2003 – 2008	282	COMPLETED
GIM7 - DOT	Fase III, Terapia mirata su malattia metastatica	2008 –2011	31	EARLY STOP
GIM8 - OVER	Fase III, HT + terapia mirata su malattia metastatica	2008 - 2013	348	COMPLETED
GIM9 – NEO-ADIXERN	Fase II, neoadiuvante	2008 –2010	47	COMPLETED
GIM10 - CONSENT	Fase III, adiuvante, postmenopausa	2013 – 2019	1.014	COMPLETED
GIM11 - BERGI	Fase II, II° linea, Her2 -, pz. mts Bevacizumab + Eribulina	2014 – 2016	61	COMPLETED
GIM15 - NEPA	Fase II, adiuvante, CT Terapia di supporto con Netupitant + CT	2016 – 2016	150	COMPLETED
GIM18 - FUMANCE	Fase III, randomizzato, Her2 -, postmenopausa, terapia di mantenimento dopo 1° linea di CT con Faslodex	2016 – 2017	12	EARLY STOP

Ongoing CLINICAL TRIALS

TRIAL	TYPE OF STUDY	ACCRUAL START	PLANNED/ ACTUAL ACCRUAL
PREFER 1	Osservazionale, prospettico sulla preservazione della fertilità nelle pazienti ca mammario invasivo	29/11/2012	Non definito da protocollo/402
PREFER 2	Osservazionale, prospettico sul trattamento ca mammario in gravidanza e sul follow-up delle donne che hanno avuto una gravidanza dopo trattamento ca mammario	25/03/2014	Non definito da protocollo/70
GIM12 – TYPHER	Fase II, randomizzato, Her2 +, mts Lapatinib + Trastuzumab vs Trastuzumab + CT	26/02/2015	154 / 59
GIM13 - AMBRA	Osservazionale, mts, Her2 – Osserva la 1° linea di CT e successive	06/05/2015	1.500 / 921
GIM14 - BIO-META	Osservazionale, mts Osserva la durata e il n° di linee di OT, ter. Biol. e CT	Nov. 2015	2.500 / 2361
GIM16 - FEVEX	Fase III, randomizzato, ca localmente avanzato/mts, ER,Pgr+, Her2 - , pz. già trattate con IA Fulvestrant →Everolimus + Exemestane Exemestane + Everolimus→Fulvestrant	16/12/2015	745 / 142
GIM19 - STAR	Osservazionale, ca mammario adiuvante, neoadiuvante e mts, Er, Pgr +. Pz che hanno assunto IA generico e brandes	11/05/2016	2.144 / 929
GIM20 – CitoHer2	Osservazionale, prospettico, neoplasia mammaria metastatica HER2- positiva, per analisi del profilo citochinomico in pz. che ricevono T-DM1	18/07/2018	132 / 16

Ongoing CLINICAL TRIALS

TRIAL	TYPE OF STUDY	ACCRUAL START	PLANNED/ ACTUAL ACCRUAL
NEOGENE	Test genomici mirati ad identificare mutazioni "actionable" in pazienti con tumore della mammella recettori ormonali negativi/her2 positivo o triplo negativo: fattibilità e perfezionamento (delle tecniche.) Studio osservazionale prospettico retrospettivo	04/11/2018	200 / 16
GIM21 – LiqERBcept	Interventistico, non farmacologico, neoplasia mammaria metastatica HER2- positiva, su biopsia liquida per intercettazione di traiettorie mutazionali in pz. che ricevono T-DM1	07/11/2018	45 / 13
GIM22 – ERICA	Fase II, randomizzato, carcinoma mammario metastatico. Seconda linea di eribulina seguita da capecitabina oppure sequenza inversa	30/07/2018	150 / 22
GIM23 – POSTER	Osservazionale prospettico sul trattamento ormonale adiuvante delle pz. con ca mammario operato in premenopausa con recettori ormonali positivi	Ott. 2019 (stima primo paziente)	STARTUP
GIM24 – PALBO-PB	Fase II, ca localmente avanzato/mts, HR+, Her2 –con Palbociclib+Fulvestrant in pz. pre e post menopausa progredite ad un trattamento con terapia ormonale + un inibitore CDK4/6	Ott. 2019 (stima primo paziente)	STARTUP
GIM25 - CAPT	Fase II, ca mammario, Atezolizumab+Carboplatin+Paclitaxel in 1° linea mts, PD-L1 triplo negativo	Dic. 2019 (stima primo paziente)	STARTUP

I risultati del GIM

- Centri partecipanti:100
- Arruolamento pazienti
  - 16.874 pazienti (dal 2002 al 2019)
  - 1.055 pazienti/anno
  - 168,8 pazienti/centro

I risultati del GIM

Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2 × 2 factorial, randomised phase 3 trial

GIM2

Lucia Del Mastro, Sabino De Placido*, Paolo Bruzzi, Michele De Laurentiis, Corrado Boni, Giovanna Cavazzini, Antonio Durando, Anna Turletti, Cecilia Nistico, Enrichetta Valle, Ornella Garrone, Fabio Puglisi, Filippo Montemurro, Sandro Barni, Andrea Ardizzoni, Teresa Gamucci, Giuseppe Colantuoni, Mario Giuliano, Adriano Gravina, Paola Papaldo, Claudia Bighin, Giancarlo Bisagni, Valeria Forestieri, Francesco Cognetti, for the Gruppo Italiano Mammella (GIM) Investigators†*

Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial

GIM3

Sabino De Placido, Ciro Gallo*, Michelino De Laurentiis, Giancarlo Bisagni, Grazia Arpino, Maria Giuseppa Sarobba, Ferdinando Riccardi, Antonio Russo, Lucia Del Mastro, Alessio Aligi Cogoni, Francesco Cognetti, Stefania Gori, Jennifer Foglietta, Antonio Frassoldati, Domenico Amoroso, Lucio Laudadio, Luca Moscetti, Filippo Montemurro, Claudio Verusio, Antonio Bernardo, Vito Lorusso, Adriano Gravina, Gabriella Moretti, Rossella Lauria, Antonella Lai, Carmen Mocerino, Sergio Rizzo, Francesco Nuzzo, Paolo Carlini, Francesco Perrone*, on behalf of the GIM Investigators†*

I risultati del GIM

Effect of the Gonadotropin-Releasing Hormone Analogue Triptorelin on the Occurrence of Chemotherapy-Induced Early Menopause in Premenopausal Women With Breast Cancer

A Randomized Trial

JAMA. 2011;306(3):269-276

Lucia Del Mastro, MD
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Emanuela Magnolfi, MD
Tiziana Scotto, MD
Carlo Vecchio, MD
Marco Venturini, MD

GIM6

Original Investigation

Ovarian Suppression With Triptorelin During Adjuvant Breast Cancer Chemotherapy and Long-term Ovarian Function, Pregnancies, and Disease-Free Survival

A Randomized Clinical Trial

Matteo Lambertini, MD; Luca Boni, MD; Andrea Michelotti, MD; Teresa Gamucci, MD; Tiziana Scotto, MD; Stefania Gori, MD; Monica Giordano, MD; Ornella Garrone, MD; Alessia Levaggi, MD; Francesca Poggio, MD; Sara Giraudi, MD; Claudia Bighin, MD; Carlo Vecchio, MD; Mario Roberto Sertoli, MD; Paolo Pronzato, MD; Lucia Del Mastro, MD; for the GIM Study Group

L'impatto sulla pratica clinica

Selection of Optimal Adjuvant Chemotherapy Regimens for Human Epidermal Growth Factor Receptor 2 (HER2) –Negative and Adjuvant Targeted Therapy for HER2-Positive Breast Cancers: An American Society of Clinical Oncology Guideline Adaptation of the Cancer Care Ontario Clinical Practice Guideline

Neelima Denduluri, Mark R. Somerfield, Andrea Eisen, Jamie N. Holloway, Arti Hurria, Tari A. King, Gary H. Lyman, Ann H. Partridge, Melinda L. Telli, Maureen E. Trudeau, and Antonio C. Wolff

J Clin Oncol 34:2416-2427. © 2016

Acceptable Adjuvant Chemotherapy Regimens for Patients With Higher-Risk Early Breast Cancer

These adjuvant chemotherapy regimens can be used for patients with early breast cancer:

- Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3 (superior to fluorouracil-epirubicin-cyclophosphamide × 6)
- Doxorubicin-cyclophosphamide × 4 → docetaxel × 4 (superior to doxorubicin-cyclophosphamide × 4)
- Docetaxel-doxorubicin-cyclophosphamide × 6 (superior to fluorouracil-doxorubicin-cyclophosphamide × 6)
- Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week
- Dose-dense doxorubicin-cyclophosphamide → paclitaxel administered once every 2 weeks
- Dose-dense epirubicin 90mg/m^2, cyclophosphamide 600mg/m^2 every 2 weeks 4 cycles → paclitaxel 175mg/m^2 every 2 weeks for 4 cycles

L'impatto sulla pratica clinica

Tailoring therapies—improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015

Young women — LHRH agonist therapy during chemotherapy proved effective to protect against premature ovarian failure and preserve fertility in young women with ER-negative breast cancer undergoing chemotherapy [5, 112].

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Invasive Breast Cancer

FERTILITY AND BIRTH CONTROL

- **Randomized trials have shown that ovarian suppression with GnRH agonist therapy administered during adjuvant chemotherapy in premenopausal women with ER-negative tumors may preserve ovarian function and diminish the likelihood of chemotherapy-induced amenorrhea.**

Fertility Preservation in Patients With Cancer: ASCO Clinical Practice Guideline Update

Kutluk Oktay, Brittany E. Harvey, Ann H. Partridge, Gwendolyn P. Quinn, Joyce Reinecke, Hugh S. Taylor, W. Hamish Wallace, Erica T. Wang, and Alison W. Loren

J Clin Oncol 36. © 2018

Recommendation 3.5 (updated). Ovarian suppression: There is conflicting evidence to recommend GnRHa and other means of ovarian suppression for fertility preservation. The Panel recognizes that, when proven fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRHa should not be used in place of proven fertility preservation methods.

Conclusioni

The cancer clinical research landscape is rapidly changing ……

- The cancer clinical research landscape is rapidly changing, and all Independent Research Centers need to urgently adapt in order to offer patients effective and affordable cancer care

- Clinical and translational research are the backbone in establishing scientific advances as novel treatments and advancing progress to the benefit of patients.

- Effective treatment of cancer remains one of the biggest medical challenges in the world, due to the large diversity in the spectrum of mutations in individual cancer patients.

- To tackle this problem, cancer research will need to be performed at a larger scale than is currently possible within single cancer institutes.

The cancer clinical research landscape is rapidly changing ……

The prerequisites for joint translational and clinical research programs are very demanding.

These require:

1. **The creation of a virtual single ‘e-hospital’ and a powerful translational platform that integrates all patient files using a common software platform that federates the databases from each of the centres.**

2. **Intercompatible clinical molecular profiling laboratories with a robust underlying computational biology pipeline.**

3. **Standardised functional and molecular imaging.**

The cancer clinical research landscape is rapidly changing ……

These require:

4. **Commonly agreed SOPs for liquid and tissue biopsy procurement, storage and processing, for molecular diagnostics, 'omics', functional genetics, immunemonitoring etc.**

5. **Big Data analysis**

6. **A culture of data collection and data storage that provides complete longitudinal data sets to allow for: effective data sharing and common database building, and to achieve a level of completeness of data that is required for conducting innovative outcome research.**