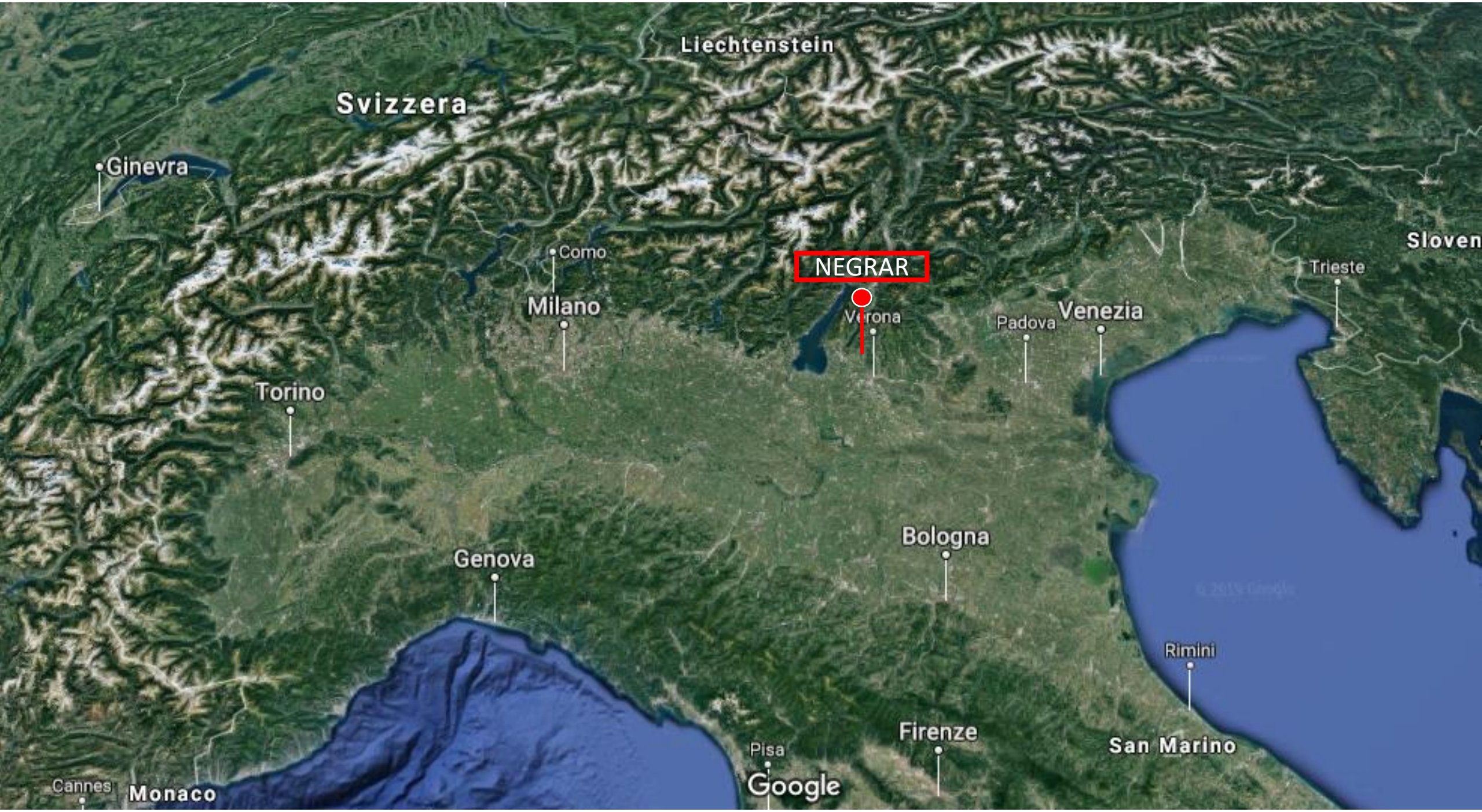
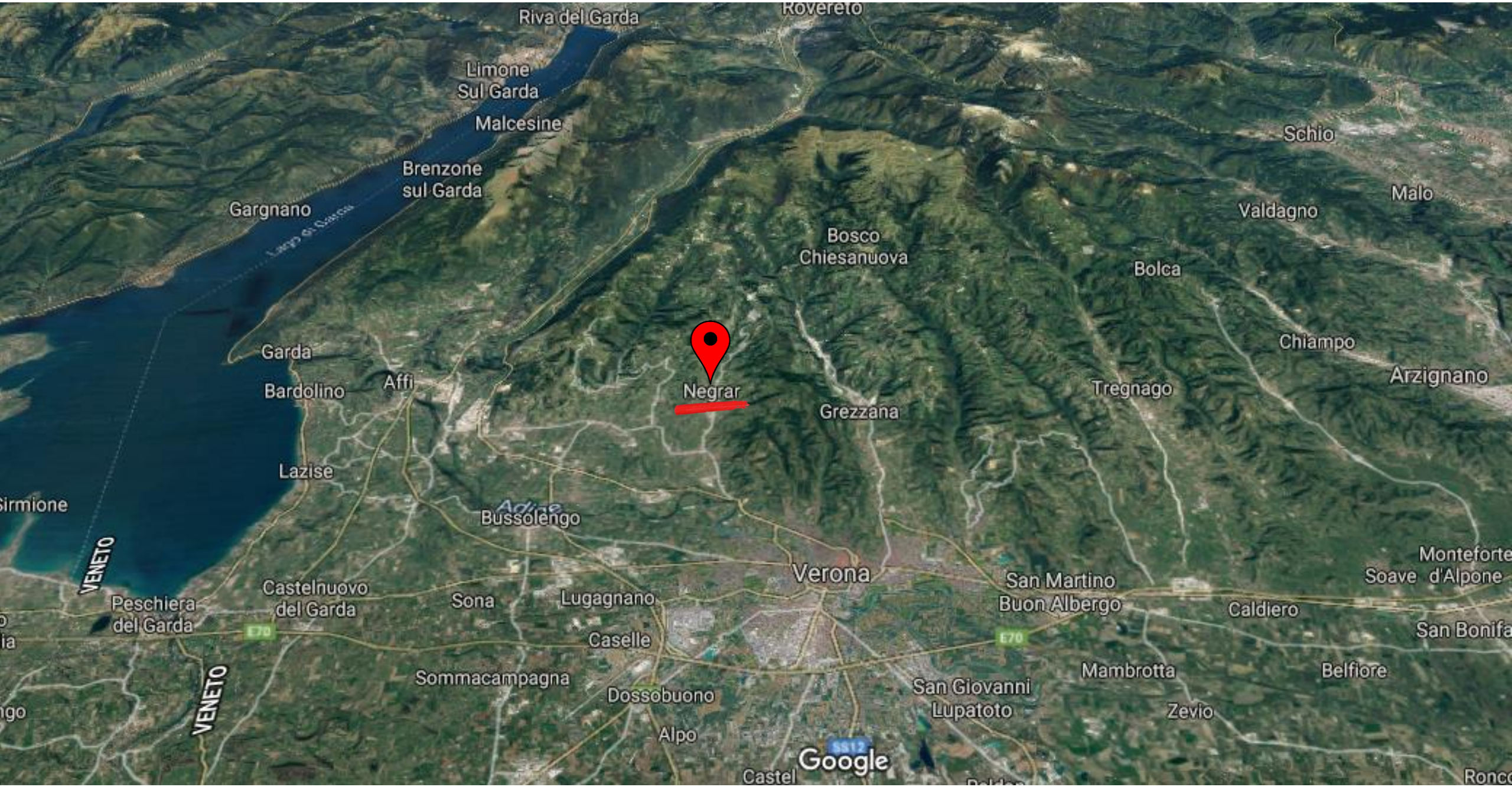
SACRO CUORE
DON CALABRIA
I R C C S

Fabrizio Nicolis

Direttore Sanitario


Liechtenstein
Svizzera
Ginevra
Como
Milano
NEGRAR
Verona
Padova
Venezia
Trieste
Sloven
Torino
Genova
Bologna
Rimini
Firenze
Pisa
San Marino
Cannes
Monaco
Google


Riva del Garda
Rovereto
Limone
Sul Garda
Malcesine
Brenzone
sul Garda
Gargnano
Schio
Malo
Valdagno
Bosco
Chiesanuova
Bolca
Chiampo
Arzignano
Garda
Bardolino
Affi
Negrar
Tregnago
Grezzana
Lazise
Sirmione
Adige
Bussolengo
VENETO
Verona
Monteforte
Soave
d'Alpone
Castelnuovo
del Garda
Peschiera
del Garda
Sona
Lugagnano
San Martino
Buon Albergo
Caldiero
San Bonifa
Caselle
Sommacampagna
Dossobuono
Mambrotta
Belfiore
San Giovanni
Lupatoto
Zevio
Alpo
Google

La Valpolicella


DABURDE
AMARONE
DELLA VALPOLICELLA
CLASSICO
2009

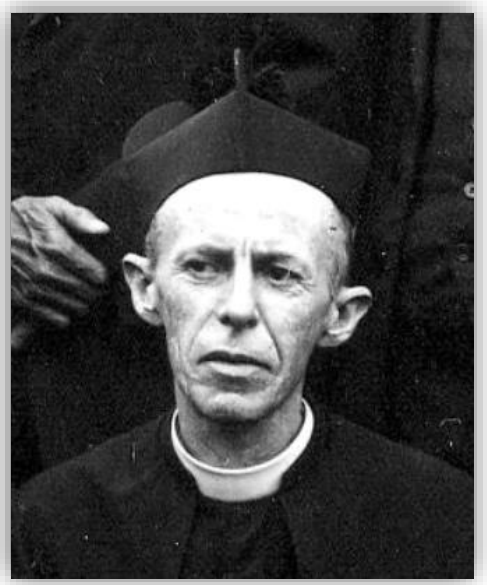
SACRO CUORE
DON CALABRIA

I R C C S

100

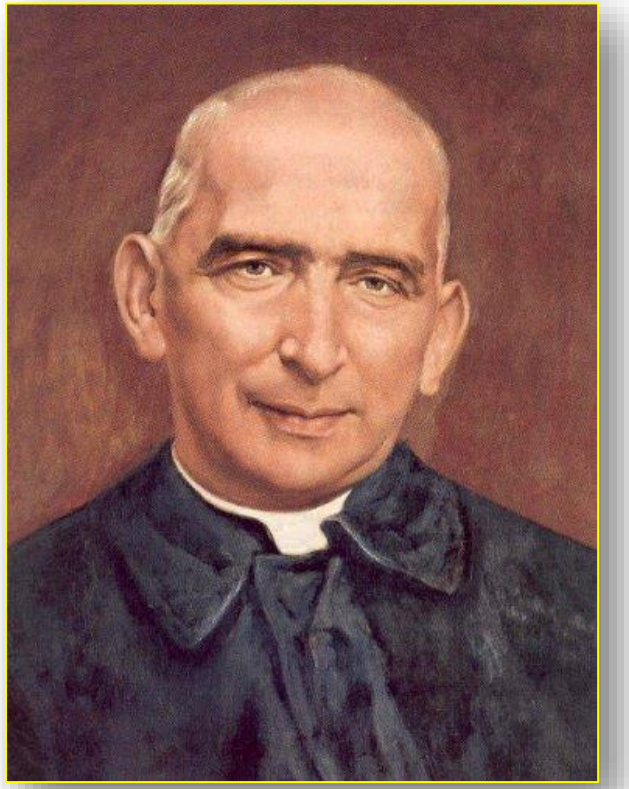
1922 - 2022
SACRO CUORE

1922 – Ricovero Sacro Cuore



don Angelo Sempreboni

San Giovanni Calabria



Verona 8 ottobre 1873
Verona 4 dicembre 1954

La Cittadella della Carità

La Cittadella della Carità

La Cittadella della Carità

La Cittadella della Carità

COMPREHENSIVE HEALTH CENTER

SERIE GENERALE

Anno 159° - Numero 140

GAZZETTA UFFICIALE
DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Martedì, 19 giugno 2018

AVVISO ALLE AMMINISTRAZIONI

SOMMARIO

LEGGI ED ALTRI ATTI NORMATIVI

Ministero dell'economia e delle finanze

DECRETO 3 maggio 2018, n. 70

Regolamento recante attuazione degli articoli 126-vicies semel, 126-vicies bis e 126-vicies quater del decreto legislativo 1° settembre 1993, n. 385 (testo unico bancario), introdotti dal decreto legislativo 15 marzo 2017, n. 37, recante attuazione della direttiva 2014/92/UE, sulla comparabilità delle spese relative al conto di pagamento, sul trasferimento del conto di pagamento e sull'accesso al conto di pagamento con caratteristiche di base. (18G00054) ..... Pag. 1

DECRETI PRESIDENZIALI

DECRETO DEL PRESIDENTE DELLA REPUBBLICA 4 giugno 2018.

Proroga dello scioglimento del consiglio comunale di Scafati. (18A04237) ..... Pag. 6

DECRETO DEL PRESIDENTE DELLA REPUBBLICA 7 giugno 2018.

Scioglimento del consiglio comunale di Canale d'Agordo. (18A04238) ..... Pag. 7

DECRETO DEL PRESIDENTE DELLA REPUBBLICA 7 giugno 2018.

Scioglimento del consiglio comunale di Bussi sul Tirino e nomina del commissario straordinario. (18A04239) ..... Pag. 8

DIRETTIVA DEL PRESIDENTE DEL CONSIGLIO DEI MINISTRI 8 maggio 2018.

Indizione della «Giornata nazionale del fiocchetto lilla dedicata ai disturbi del comportamento alimentare». (18A04218) ..... Pag.

MINISTERO DELLA SALUTE

DECRETO 23 maggio 2018.

Riconoscimento del carattere scientifico nella disciplina «Malattie infettive e tropicali» all'«Ospedale Sacro Cuore - Don Calabria», in Negrar.

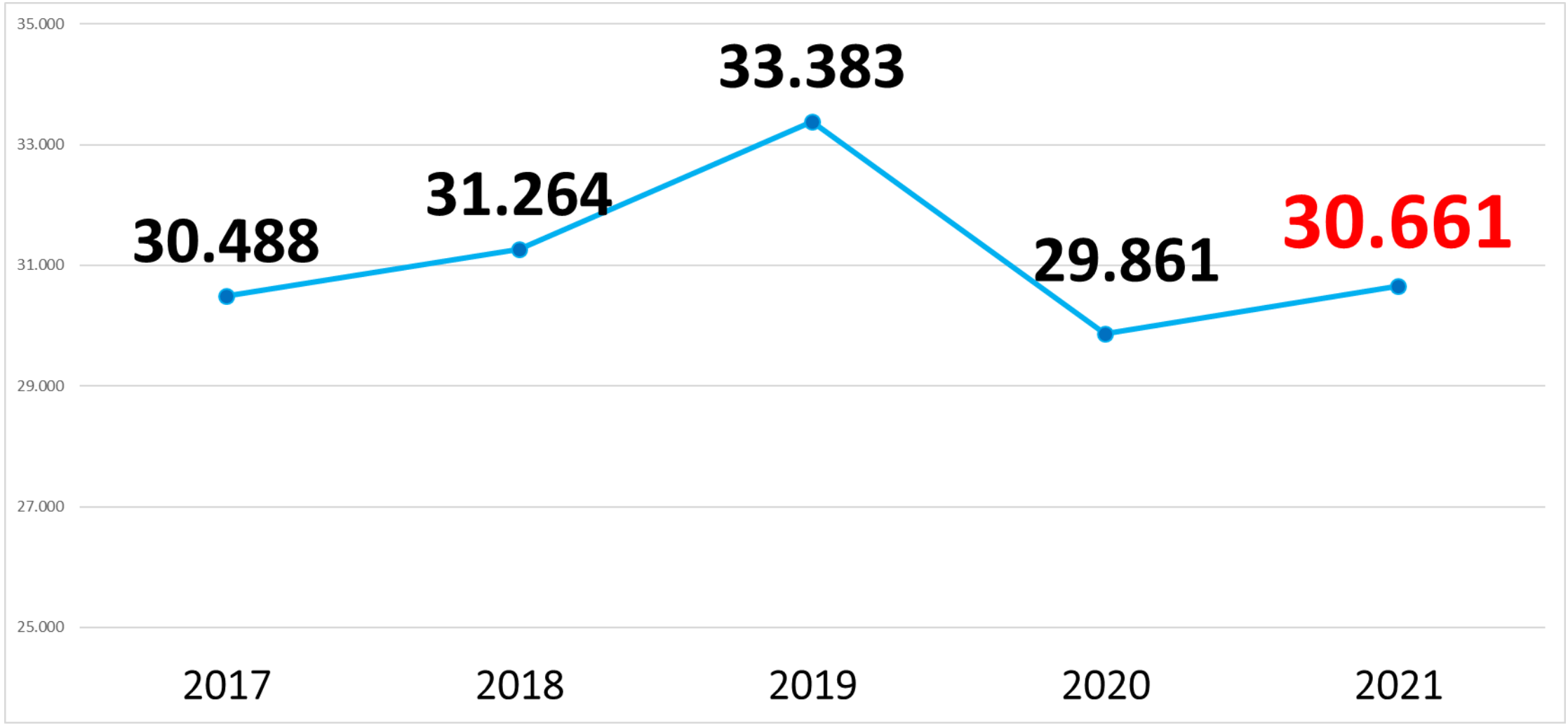
IRCCS Ospedale “Sacro Cuore – Don Calabria”

Schede di dotazione delle Strutture Ospedaliere

DGR n. 614 del 14 maggio 2019

1. Centro di **Riferimento Regionale** per le **Malattie Tropicali**
2. Struttura di **Riferimento Regionale** per la **Riprotesizzazione di ginocchio e anca**
3. Struttura di **Riferimento Regionale** per il trattamento delle **Gravi Patologie Retiniche**
4. Struttura di **Riferimento Regionale** per l’**Endometriosi**
5. Struttura di **Riferimento Regionale** per **Radioterapia**
6. Centro **Hub** per l’attività di **preparazione radiofarmaci** e per attività di terapia radiometabolica

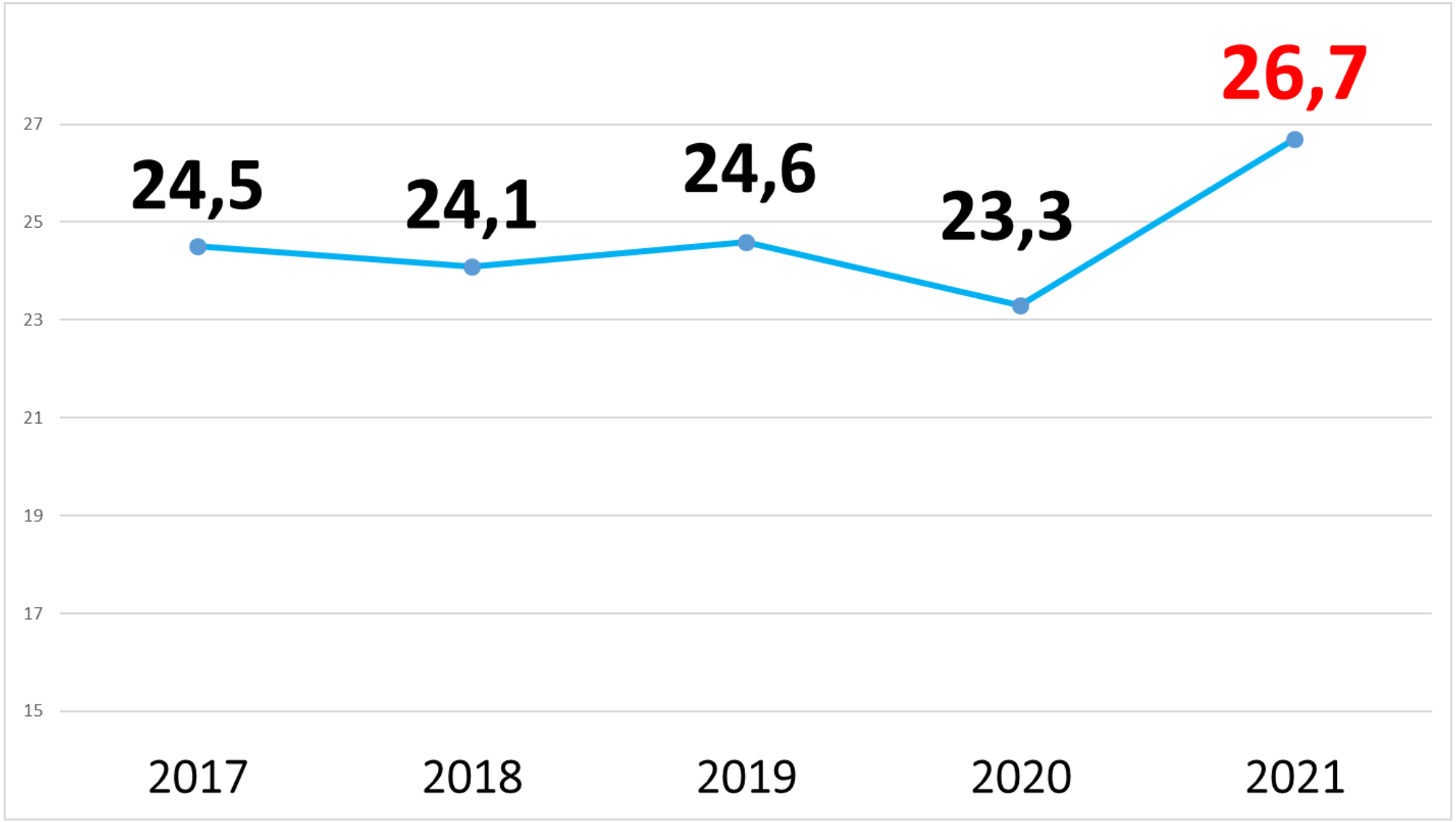
Ricoveri 2017 – 2021



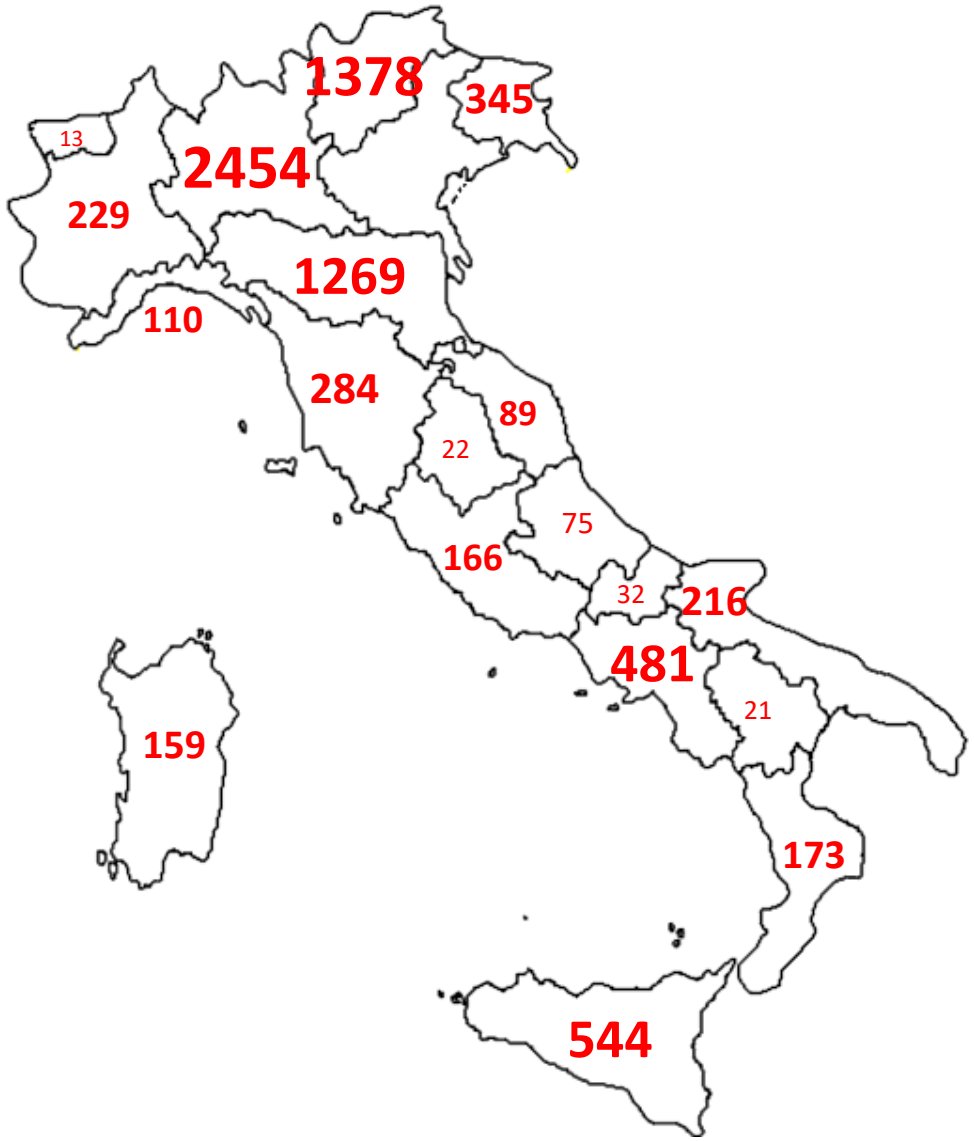
Graduatoria Ospedali per numero di ricoveri Regione Veneto

1	Azienda Ospedaliera di Padova
2	Azienda Ospedaliera di Verona
3	Ospedale di Vicenza
4	Ospedale di Treviso
5	**IRCCS Sacro Cuore Don Calabria**

Attrazione Extraregionale (%)



Attrazione Extraregionale Ricoveri



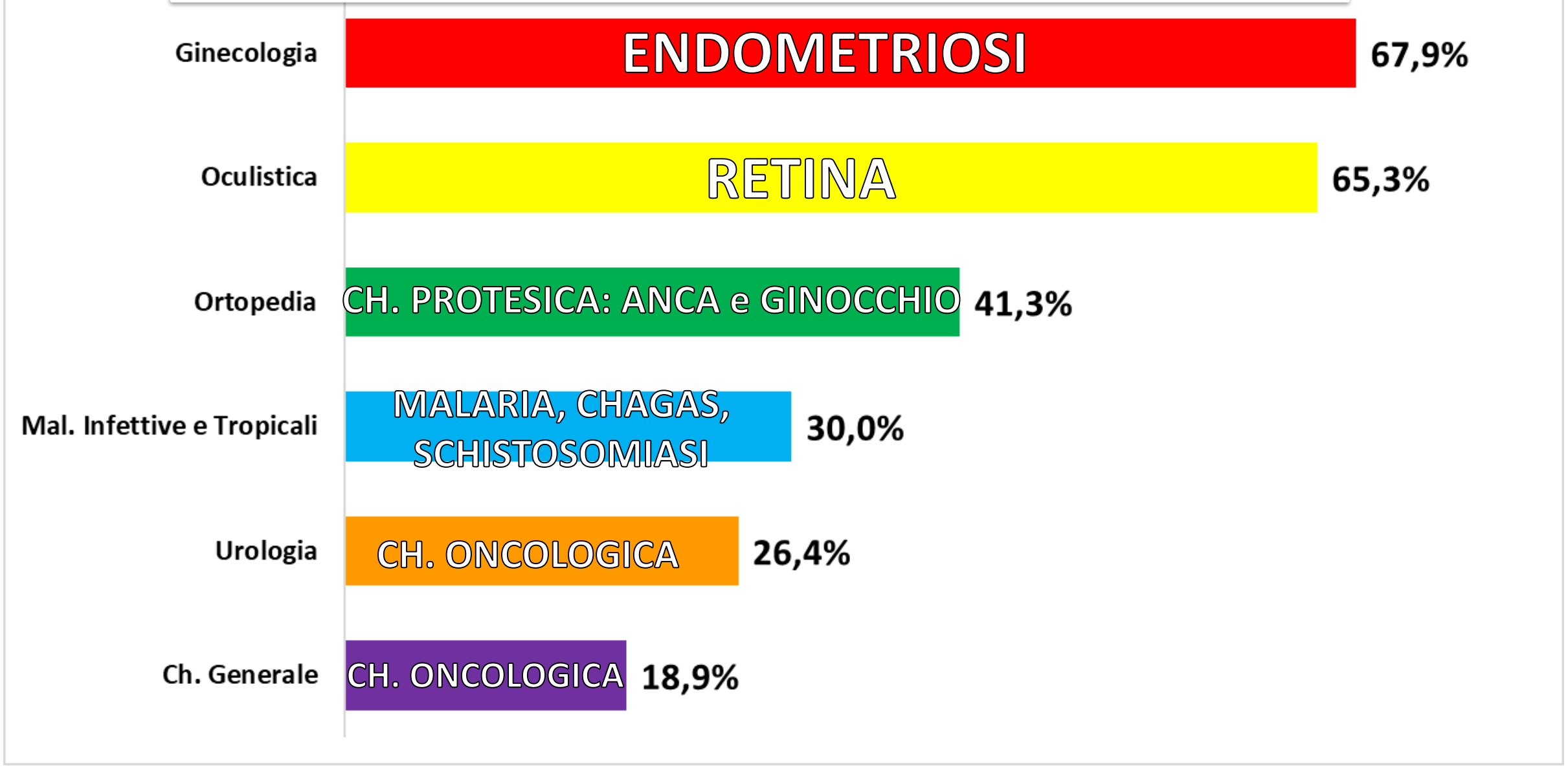
Anno 2021

Totale ricoveri extraregione:

8.060

RICOVERI

Attrazione Extraregionale - % anno **2021**



I nostri investimenti

Radioterapia Oncologica

ADVANCED RADIATION ONCOLOGY DEPARTMENT

- **4 ACCELERATORI LINEARI**
  - TrueBeam (2)
  - ETHOS
  - RM-LINAC UNITY

Prof. Filippo Alongi
Direttore Radioterapia Oncologica

CICLOTRONE con Radiofarmacia

- **19 MeV – 300 µA**

Centro **HUB** per l'attività di **preparazione radiofarmaci**

(DGR n. 614 del 14 maggio 2019)

Dott. Giancarlo Gorgoni

Responsabile Radiofarmacia e Ciclotrone

CORRIERE DELLA SERA
CORRIERE DEL VENETO
22 settembre 2022

MEDICINA

A Negrar nasce l'unica «fabbrica di radiofarmaci» in Italia gestita da un ospedale

La certificazione è giunta a pochi giorni dal meeting sui radiofarmaci che vede in Valpolicella, fino al 23 settembre, i 15 Paesi aderenti al progetto

- **Certificazione AIFA** per la produzione secondo i **criteri GMP** di tutti i **radiofarmaci sperimentali** a base di **Fluoro 18**
- **Unico** ospedale **in Italia** con Radiofarmacia GMP (non gestita da aziende esterne)

Chirurgia Robotica

Unità Operative di Urologia, Chirurgia Generale, Ginecologia e Ortopedia

Biologia Molecolare
Anatomia Patologica

Prof. Giuseppe Zamboni
Direttore Anatomia Patologica

Sequenziatore

Ion GeneStudio™
S5 System

Nuovi laboratori ad alto biocontenimento (BSL 2 e BSL 3)

8 ottobre 2021

Nuova Risonanza Magnetica 3 TESLA

Hospice e Biobanca

Realizzazione Biobanca per l'Oncologia

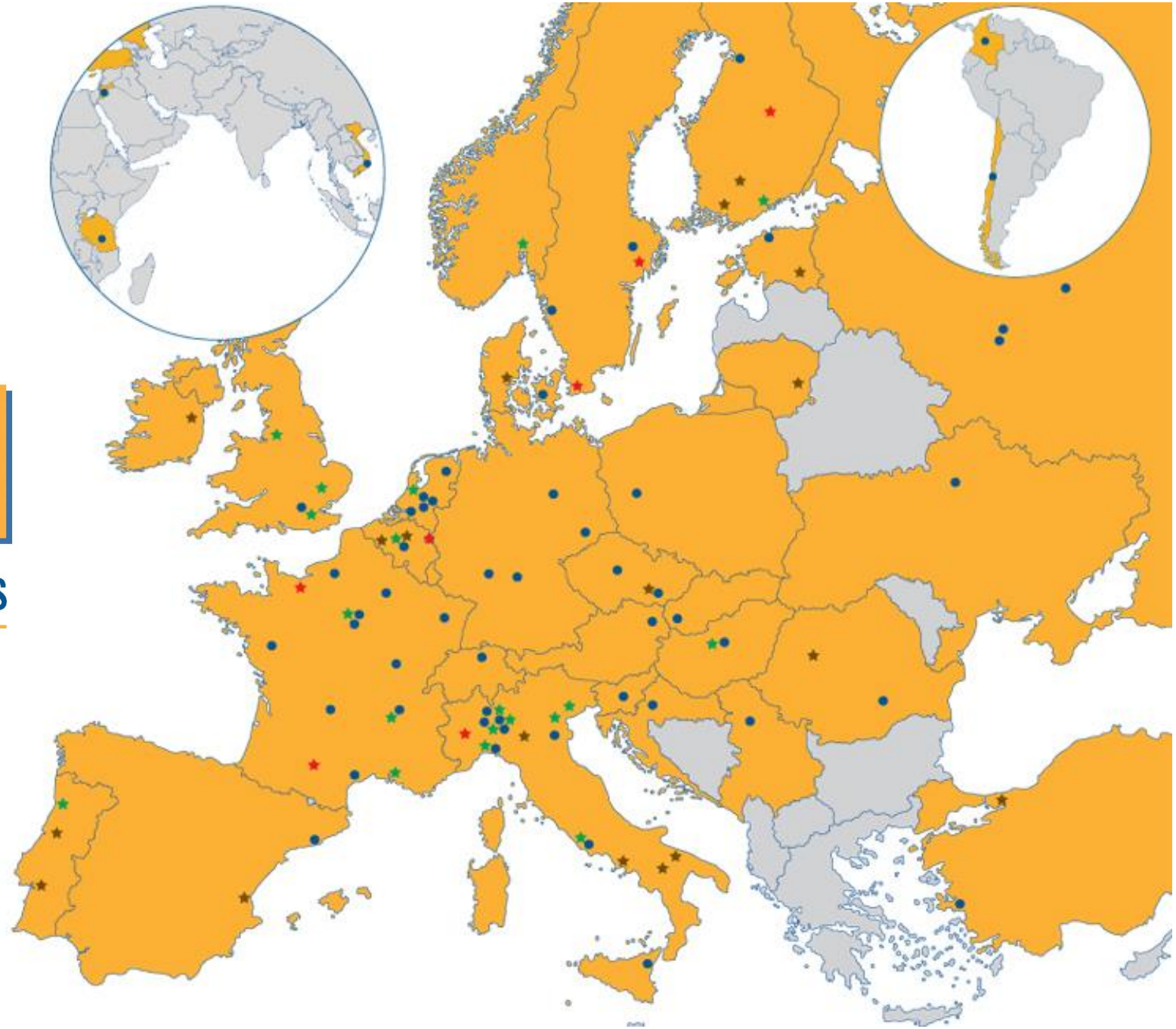
ALLEANZA CONTRO IL CANCRO

34 associati

OECI

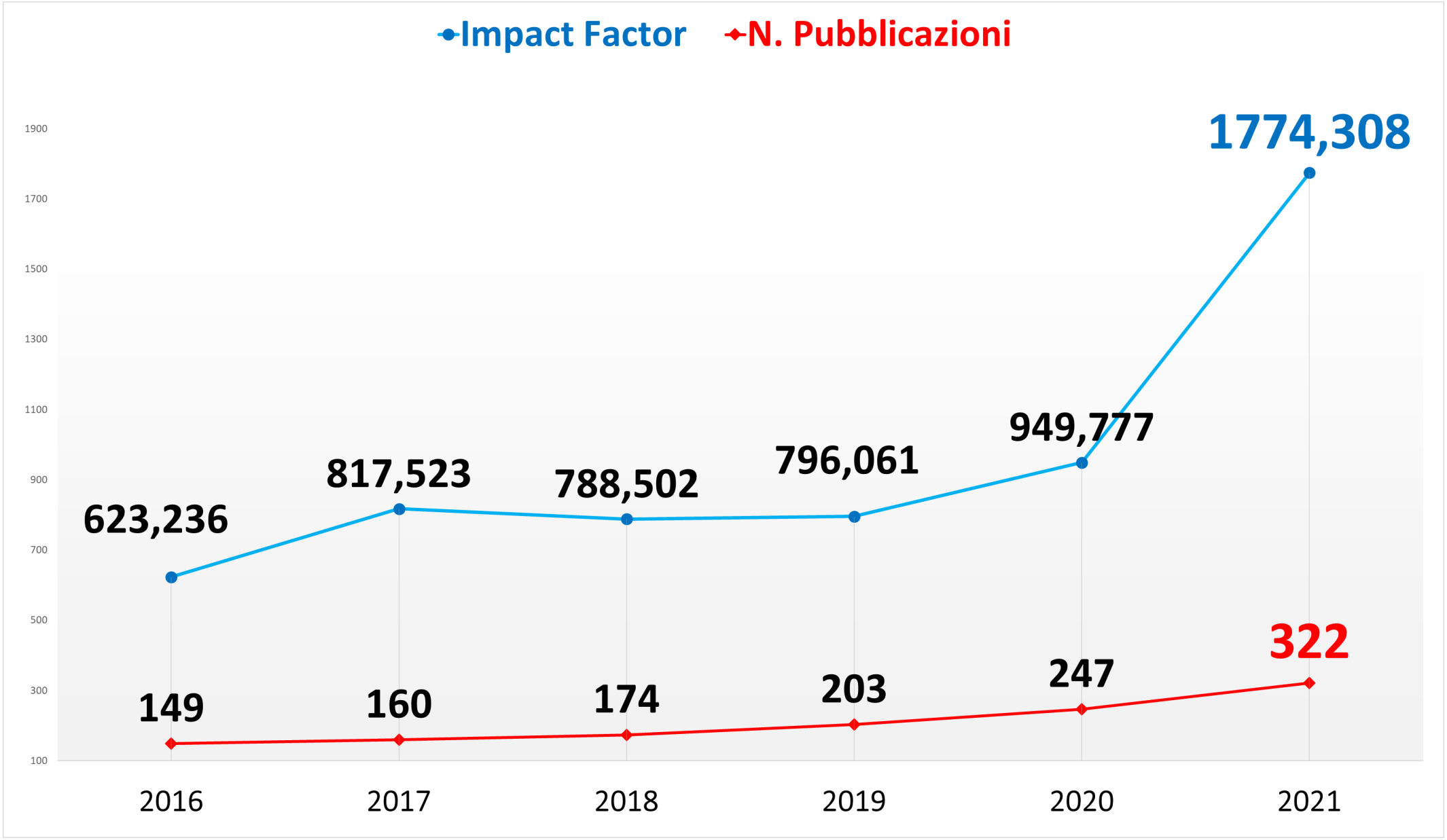
Organisation of European Cancer Institutes

European Economic Interest Grouping



PUBBLICAZIONI SCIENTIFICHE

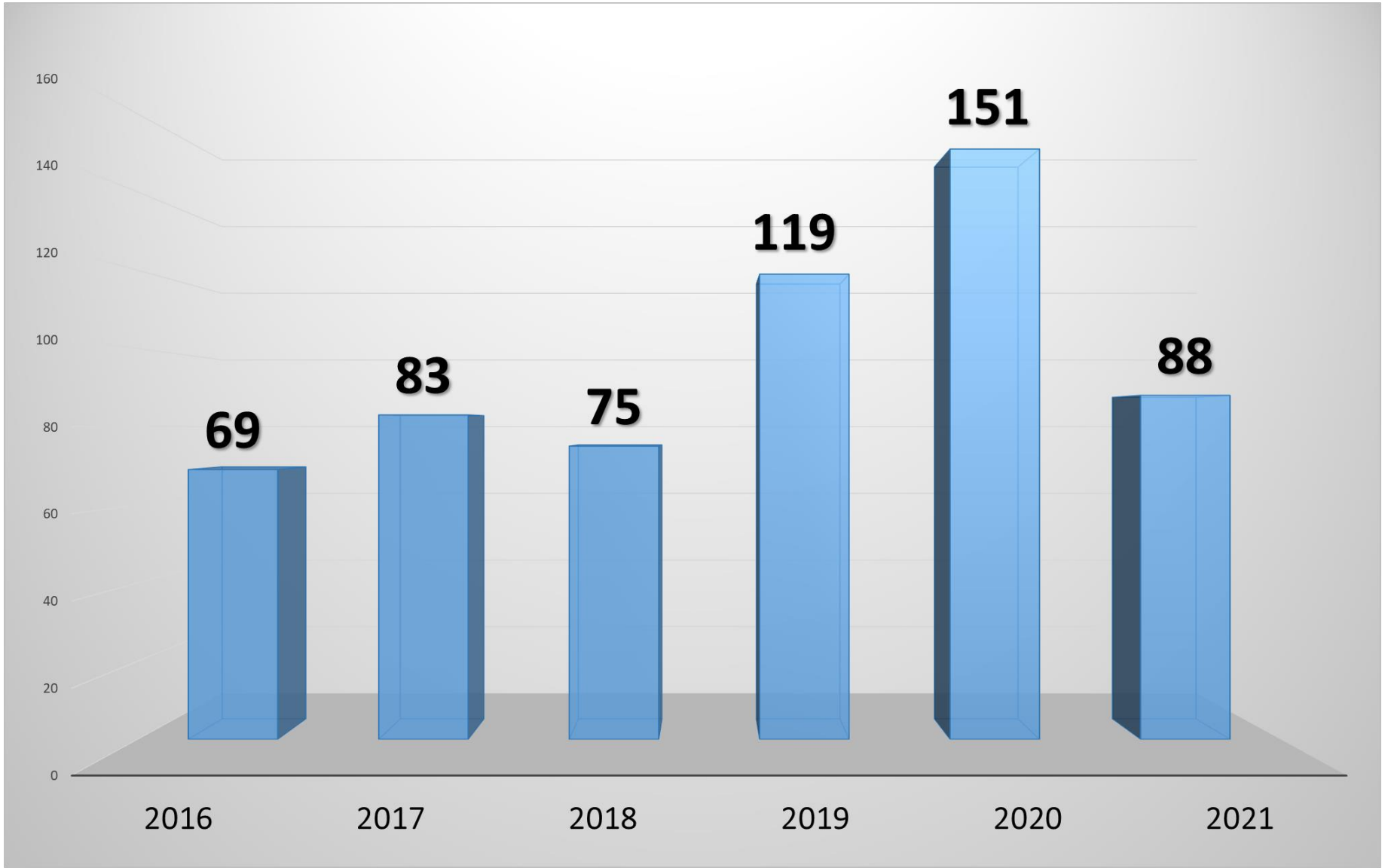
IRCCS Ospedale Sacro Cuore Don Calabria



STUDI CLINICI

(Osservazionali + Sperimentali)

IRCCS Ospedale Sacro Cuore Don Calabria



- **Collaborazioni con Università**

Anno	Scuole di Specialità in rete formativa	Convenzioni attivate extra rete formativa
2019	**21**	**32**
2020	**21**	**31**
2021	**26**	**21**

- **Specializzandi** provenienti da Università

Anno	N. Specializzandi
2019	**82**
2020	**102**
2021	**182**

SACRO CUORE DON CALABRIA IRCCS

LE FRONTIERE DELLA SANITÀ L'ateneo amplia l'offerta formativa. La sede sarà nella cittadella dell'ospedale di Negrar dove, nel giro di due anni, sorgerà un campus

Accordo storico, ci sarà la laurea in Farmacia

Intesa fra Università e Sacro Cuore. Il rettore Nocini: «Strategico nell'identificare vaccini e in interventi d'urgenza». L'ad Piccinini: «Si rafforza una collaborazione trentennale»

Laura Perina

●● L'università di Verona amplia l'offerta formativa con un nuovo corso di laurea dedicato alla formazione dei futuri farmacisti di comunità, ospedalieri e dei professionisti che operano nella ricerca e nell'industria, figure che hanno subìto importanti trasformazioni negli ultimi anni e di cui si avverte in maniera forte il fabbisogno.

«Scienze del farmaco e dei prodotti della salute»: questa la definizione del percorso quinquennale a numero programmato che partirà il prossimo anno accademico 2023/24. I posti disponibili sono 60 e per le aspiranti matricole si aprirà in primavera la possibilità di sostenere l'esame d'ammissione tramite il test online Tolc.

L'iniziativa è frutto di un accordo di collaborazione sottoscritto dall'ateneo con l'Irccs strutture specialistiche e assistenziali di Negrar, compatibilmente con le possibilità ricettive di ciascuna. «Come ha dimostrato anche l'esperienza recente della pandemia, la professione farmaceutica in tutte le sue declinazioni è fondamentale per il miglioramento dell'assistenza sanitaria offerta alla popolazione», afferma il rettore Pier Francesco Nocini.

«La scienza del farmaco ha giocato un ruolo fondamentale, tra la necessità di interventi d'urgenza, la rapidità di ricerca e raccomandazione di soluzioni farmacologiche, la scommessa di una veloce identificazione di vaccini efficaci. Alla luce di queste considerazioni ho proposto all'Irccs Sacro Cuore di mettere insieme forze e risorse per realizzare questo nuovo corso di laurea che il territorio veronese attende da anni».

L'accordo quadro è stato sottoscritto ieri mattina da Nocini e dall'amministratore dele-

I protagonisti Il rettore Pier Francesco Nocini, a sinistra, e l'ad dell'ospedale Sacro Cuore di Negrar, Mario Piccinini

La cerimonia I partecipanti all'incontro a Palazzo Giuliari

SACRO CUORE
DON CALABRIA
I R C C S

Fabrizio Nicolis

Direttore Sanitario

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EIBC

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

FORMAZIONE DI BASE (Core School) - B1 - 1° Modulo

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Con il Patrocinio di

ALLEANZA CONTRO IL CANCRO

AIGOM Associazione Italiana Gruppi Oncologici Multidisciplinari

AIOM Associazione Italiana di Oncologia Medica

Istituto Superiore di Sanità

ROPI Rete Oncologica Pazienti Italia

Università di Verona

AIRO Associazione Italiana Radioterapia e Oncologia clinica

IMN Istituto di Ricerche Farmacologiche Mario Negri - IRCCS

SIAPEC - IAP

AIOM Associazione Italiana Oncologia Medica

AIC Associazione Italiana di Cancerologia

SIUrO Società Italiana di Uro-Oncologia

SIF Società Italiana di Farmacologia

CIPOMO

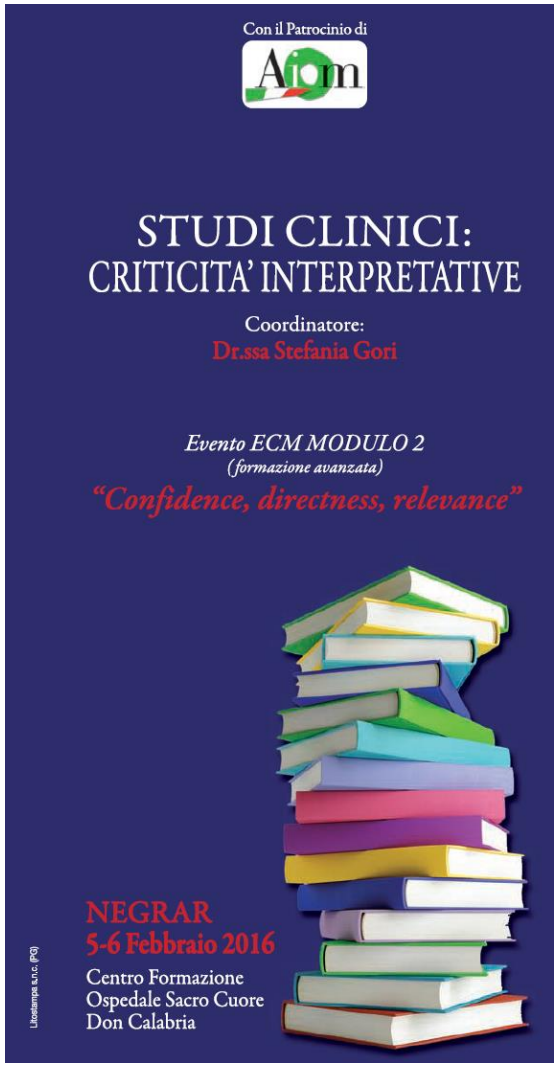
ASSD Associazione Scientifica per la Sanità Digitale

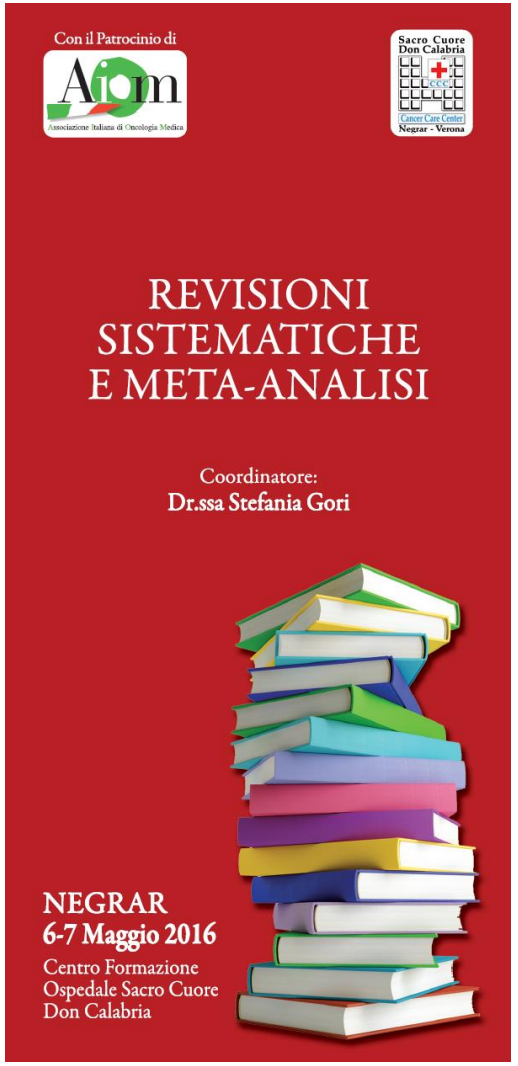
FIGM

SIPO Società Italiana di Psico-Oncologia

FORMAZIONE

.....2016





Scuola Metodologia Studi Clinica- IRCCS Sacro Cuore Don Calabria Negrar-

Edizione 2016

Lavori di gruppo in corso…

Scuola Metodologia Studi Clinica- IRCCS Sacro Cuore Don Calabria Negrar-

VI Edizione-2020

I CORSO – 28/29 Gennaio 2020 (pre-COVID-19)

Numero partecipanti alle 8 edizioni eseguite:

- **oltre 300 nelle prime 5 edizioni (in presenza) + 20 nei Moduli in presenza del 2020 e 2021+ 35 nella 8a edizione 2022 (in presenza)**
- **>90 nei Moduli online della 6a edizione 2020**
- **>90 nei Moduli online della 7a edizione 2021**

2022

SACRO CUORE DON CALABRIA
I R C C S

SCUOLA DI METODOLOGIA CLINICA

IRCCS "Sacro Cuore - Don Calabria" Negrar di Valpolicella

VIII Edizione

NEGRAR DI VALPOLICELLA
28-29 GENNAIO 2022

Scuola Metodologia Studi Clinica- IRCCS Sacro Cuore Don Calabria Negrar-

VIII Edizione-2022

I CORSO – 28/29 Gennaio 2022

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EEIG

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

FORMAZIONE DI BASE (Core School) - B1 - 1° Modulo

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Con il Patrocinio di

ALLEANZA CONTRO IL CANCRO
AIGOM
AIOM
ISTITUTO SUPERIORE DI SANITÀ
ROPI
UNIVERSITÀ di VERONA
AIRO Associazione Italiana Radioterapia e Oncologia clinica
IMN ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI - IRCCS
SIAPEC - IAP
AIC
SIUrO Società Italiana di Uro-Oncologia
SIF SOCIETÀ ITALIANA DI FARMACOLOGIA
CIPOMO
ASSD Associazione Scientifica per la Sanità Digitale
FISM
Società Italiana di Psico-Oncologia

FORMAZIONE DI BASE (Core School)	
B1- LETTURA DI UN TRIAL CLINICO	20-21 gennaio 2023
B2- PREPARAZIONE DI UN PROTOCOLLO DI RICERCA CLINICA	17-18 febbraio 2023
MODULI SPECIALISTICI	
S1- REVISIONI SISTEMATICHE E METANALISI	10-11 marzo 2023
S2-LINEE GUIDA PER LA PRATICA CLINICA	21-22 aprile 2023
S3- I CONFRONTI INDIRETTI	11 maggio 2023
S4- GLI STUDI OSSERVAZIONALI	12-13 maggio 2023

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

Formazione di BASE

LETTURA DI UN TRIAL CLINICO

20 Gennaio 2023

10.00-10.10 Saluti dell'amministratore delegato dell'IRCCS "Sacro Cuore - Don Calabria" Negrar di Valpolicella (VR)
Dr. Mario PICCININI

10.10-10.25 Presentazione ed obiettivi del Corso
Stefania GORI
Giovanni L. PAPPAGALLO

SESSIONE I - NOZIONI DI BASE

10.25-10.45 Etica della ricerca
Fabrizio NICOLIS

10.45-11.45 Quesito clinico di riferimento. Fasi della sperimentazione clinica. Disegni di studio osservazionali ed interventistici
Emilio BRIA

11.45-12.00 Discussione

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: **Cristina MAZZI**

13.00-14.15 Colazione di lavoro

14.15-15.15 Misure di effetto relativo e assoluto
Giovanni L. PAPPAGALLO

15.15-16.15 Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
Cristina MAZZI

16.15-16.30 Discussione

16.30-16.45 Coffee Break

16.45-17.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: **Cristina MAZZI**

17.45 Termine dei lavori della giornata

21 Gennaio 2023

SESSIONE II - VALUTAZIONE DELLE EVIDENZE

09.00-09.45 Rilevanza clinica
Vs significatività statistica
Giovanni L. PAPPAGALLO

09.45-10.15 Trasferibilità delle evidenze al quesito clinico
Giovanni L. PAPPAGALLO

10.15-10.30 Discussione

10.30-10.45 Coffee Break

10.45-11.15 Affidabilità delle prove (rischio di bias, imprecisione degli effetti)
Giovanni L. PAPPAGALLO

11.15-12.00 Dialogo tra clinico e metodologo: "Lettura di uno studio clinico"
Ettore D'ARGENTO
Giovanni L. PAPPAGALLO

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: **Cristina MAZZI**

13.00-13.30 Compilazione questionario ECM

13.30 Conclusione del Corso

PREPARAZIONE DI UN PROTOCOLLO DI RICERCA CLINICA

10 Febbraio 2023

10.15-10.30 Introduzione al Corso
Fabrizio NICOLIS

10.30-11.00 Modalità di svolgimento e presentazione delle proposte di protocollo e formazione dei gruppi di lavoro
Giovanni L. PAPPAGALLO

11.00-11.30 Fattibilità e rilevanza (F.I.N.E.R.) dell'argomento e razionale dello studio
Cristina MAZZI

11.30-12.00 Definizione dell'obiettivo primario e secondari
Giovanni L. PAPPAGALLO

12.00-13.00 Lavoro di gruppo
(valido come prova ECM)
e discussione degli elaborati in corso
Tutors:
Cristina MAZZI
Giovanni L. PAPPAGALLO

13.00-14.15 Colazione di lavoro

14.15-15.00 Definizione del disegno di studio (osservazionale *Vs* interventistico; superiorità *Vs* non inferiorità)
Giovanni L. PAPPAGALLO

15.00-16.00 Lavoro di gruppo
(valido come prova ECM)
e discussione degli elaborati in corso
Tutors:
Cristina MAZZI
Giovanni L. PAPPAGALLO

16.00-16.30 Coffee Break

16.30-17.00 Procedure di assegnazione dei trattamenti
Cristina MAZZI

17.00-18.30 Lavoro di gruppo
(valido come prova ECM)
e discussione degli elaborati in corso
Tutors:
Giovanni L. PAPPAGALLO
Cristina MAZZI

18.30 Termine dei lavori della giornata

11 Febbraio 2023

09.00-10.00 Definizione degli endpoints primario e secondari
Cristina MAZZI

10.00-10.30 Criteri di selezione dei pazienti (e dei Centri)
Giovanni L. PAPPAGALLO

10.30-11.15 Protocollo diagnostico-terapeutico, dimensionamento campionario
Giovanni L. PAPPAGALLO
Cristina MAZZI

11.15-11.30 Coffee Break

11.30-12.30 Lavoro di gruppo
(valido come prova ECM)
e discussione degli elaborati in corso
Tutors:
Cristina MAZZI
Giovanni L. PAPPAGALLO

12.30-13.00 Raccolta modulistica ECM

13.00 Conclusione del Corso

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

MODULI SPECIALISTICI

REVISIONI SISTEMATICHE e METANALISI

10 Marzo 2023

10.30-10.45 Introduzione al Corso
Stefania GORI
Fabrizio NICOLIS
Giovanni L. PAPPAGALLO

10.45-11.30 Tipologia e obiettivi delle Revisioni della Letteratura Scientifica
Michela CINQUINI

11.30-12.00 Strutturazione del quesito clinico e misure di associazione
Giovanni L. PAPPAGALLO

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-14.15 Colazione di lavoro

14.15-15.00 Database bibliografici e ricerca delle informazioni
Veronica Andrea FITTIPALDO

15.00-15.45 Selezione degli sudi; *study flow*
Michela CINQUINI

15.45-16.15 Metodi di valutazione di autori e riviste scientifiche: indici bibliometrici classici e innovativi
Giulio ZUANETTI

16.15-16.30 Coffee Break

16.30-17.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

17.45-18.15 Discussione

18.15 Termine dei lavori della giornata

11 Marzo 2023

09.00-10.00 Valutazione del rischio di bias negli studi selezionati
Ivan MOSCHETTI

10.00-10.15 Discussione

10.15-10.30 Coffee Break

10.30-12.00 *Summary of Findings Tables*
(S.O.F. / Tabelle Sinottiche delle Evidenze)
Ivan MOSCHETTI

12.00-12,45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

12.45-13.00 Compilazione questionario ECM

13.00 Conclusione del Corso

LINEE GUIDA per la PRATICA CLINICA

21 Aprile 2023

10.30-10.45 Introduzione e presentazione del Corso
Fabrizio NICOLIS

10.45-11.00 Metodiche di produzione di linee guida a confronto
Giovanni L. PAPPAGALLO

11.00-11.30 Dal quesito clinico alla raccolta sistematica delle prove
Michela CINQUINI
Giovanni L. PAPPAGALLO

11.30-13.00 La valutazione della qualità delle prove (1): *risk of bias*
Michela CINQUINI
Ivan MOSCHETTI

13.00-14.15 Colazione di lavoro

14.15-16.00 La valutazione della qualità delle prove (2): *imprecision, indirecness*
Michela CINQUINI
Giovanni L. PAPPAGALLO

16.00-16.30 Coffee Break

16.30-17.30 La valutazione della qualità delle prove (3): *inconsistency, publication bias*
Michela CINQUINI
Ivan MOSCHETTI

17.30-18.30 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

18.30 Termine dei lavori della giornata

22 Aprile 2023

09.00-09.30 Tabella Sinottica delle Evidenze
Michela CINQUINI
Ivan MOSCHETTI

09.30-10.30 Esercitazione su GRADE Development Tool (GDT) - GradePro
Michela CINQUINI

10.30-10.45 Coffee Break

10.45-11.45 Dialogo tra clinico e metodologo: "Evidence to Decision Framework e formulazione delle Raccomandazioni
Marco MARUZZO
Giovanni L. PAPPAGALLO

11.45-12.05 Metodiche di valutazione di una Linea Guida e normativa vigente
Michela CINQUINI

12.05-12.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

12.45-13.00 Compilazione questionario ECM

13.00 Conclusione del Corso

SACRO CUORE DON CALABRIA I R C C S

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

MODULI SPECIALISTICI

I CONFRONTI INDIRETTI

11 Maggio 2023

10.30-10.45 Introduzione al Corso
Fabrizio NICOLIS

10.45-11.30 Generalità e requisiti
Giovanni L. PAPPAGALLO

11.30-12.00 *Indirect Treatment Comparison* (Bucher)
Michela CINQUINI

12.00-12.30 *Matching-Adjusted Indirect Comparison* (MAIC) e *Simulated Treatment Comparison* (STC)
Giovanni L. PAPPAGALLO

12.30-13.00 Discussione

13.00-14.15 Colazione di lavoro

14.15-15.45 *Network Meta-Analysis* (NMA)
Michela CINQUINI

15.45-16.45 La valutazione della certezza delle prove
Michela CINQUINI

16.45-17.00 Coffee Break

17.00-18.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

18.00-18.15 Compilazione questionario ECM

18.15 Conclusione del Corso

GLI STUDI OSSERVAZIONALI

12 Maggio 2023

10.15-10.30 Introduzione al Corso
Stefania GORI

10.30-11.00 L'impatto degli studi osservazionali nella pratica clinica
Pierfranco CONTE

11.00-11.15 Classificazione degli studi osservazionali: descrittivi *Vs* analitici
Giovanni L. PAPPAGALLO

11.15-12.00 Studi trasversali: (*cross-sectional*)
Punti di forza/debolezza, metodologie di pianificazione, qualità metodologica, conduzione e analisi
Cristina BOSETTI

12.00-12.45 Studi caso-controllo
Punti di forza/debolezza, metodologie di pianificazione, qualità metodologica, conduzione e analisi
Cristina BOSETTI

12.45-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-14.15 Colazione di lavoro

14.15-15.00 Studi di coorte, con coorte parallela
Punti di forza/debolezza, metodologie di pianificazione, qualità metodologica, conduzione e analisi
Michela CINQUINI

15.00-15.45 Studi di *Real World*
Punti di forza/debolezza, metodologie di pianificazione, qualità metodologica, conduzione e analisi
Oriana NANNI

15.45-16.15 Discussione

16.15-16.30 Coffee Break

16.30-17.30 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13 Maggio 2023

09.00-10.15 Misure di accuratezza diagnostica e validazione di un test
Valter TORRI

10.15-10.30 Discussione

10.30-10.45 Coffee Break

10.45-12.00 Sviluppo e validazione di un modello prognostico
Valter TORRI

12.00-12.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

12.45-13.00 Compilazione questionario ECM

13.00 Conclusione del Corso

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EEIG

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Con il Patrocinio di

ALLEANZA CONTRO IL CANCRO

AIGOM Associazione Italiana Gruppi Oncologici Multidisciplinari

AIOM Associazione Italiana di Oncologia Medica

Istituto Superiore di Sanità

ROPI Rete Oncologica Pazienti Italia

Università di Verona

AIRO Associazione Italiana Radioterapia e Oncologia clinica

IMN Istituto di Ricerche Farmacologiche Mario Negri - IRCCS

SIAPEC - IAP

AIOM Survivorship Italia

AIC Associazione Italiana Infermieri di Camera Operatoria

SIUrO Società Italiana di Uro-Oncologia

SIF Società Italiana di Farmacologia

CIPOMO Collegio Italiano dei Primari Ospedalieri Medici Ospedalieri

ASSD Associazione Scientifica per la Sanità Digitale

FISM

SIPO Società Italiana di Psico-Oncologia

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EEIG

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

FORMAZIONE DI BASE (Core School) - B1 - 1° Modulo

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Programma

20 Gennaio 2023

10.00-10.10 Saluti dell'amministratore delegato dell'IRCCS "Sacro Cuore - Don Calabria" Negrar di Valpolicella (VR)
Dr. Mario PICCININI

10.10-10.25 Presentazione ed obiettivi del Corso
Stefania GORI
Giovanni L. PAPPAGALLO

SESSIONE I - NOZIONI DI BASE

10.25-10.45 Etica della ricerca
Fabrizio NICOLIS

10.45-11.45 Quesito clinico di riferimento. Fasi della sperimentazione clinica. Disegni di studio osservazionali ed interventistici
Emilio BRIA

11.45-12.00 Discussione

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-14.15 Colazione di lavoro

14.15-15.15 Misure di effetto relativo e assoluto
Giovanni L. PAPPAGALLO

15.15-16.15 Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
Cristina MAZZI

16.15-16.30 Discussione

16.30-16.45 Coffee Break

16.45-17.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

17.45 Termine dei lavori della giornata

21 Gennaio 2023

SESSIONE II - VALUTAZIONE DELLE EVIDENZE

09.00-09.45 Rilevanza clinica Vs significatività statistica
Giovanni L. PAPPAGALLO

09.45-10.15 Trasferibilità delle evidenze al quesito clinico
Giovanni L. PAPPAGALLO

10.15-10.30 Discussione

10.30-10.45 Coffee Break

10.45-11.15 Affidabilità delle prove (rischio di bias, imprecisione degli effetti)
Giovanni L. PAPPAGALLO

11.15-12.00 Dialogo tra clinico e metodologo: "Lettura di uno studio clinico"
Ettore D'ARGENTO
Giovanni L. PAPPAGALLO

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-13.30 Compilazione questionario ECM

13.30 Conclusione del Corso

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EEIG

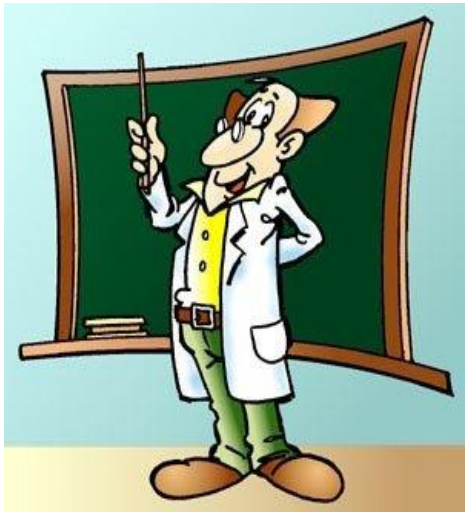
SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

FORMAZIONE DI BASE (Core School) - B1 - 1° Modulo

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"



Liberating Structures® in sintesi

Favorire la creazione di reti tra Colleghi

Ricerca di innovazioni e soluzioni

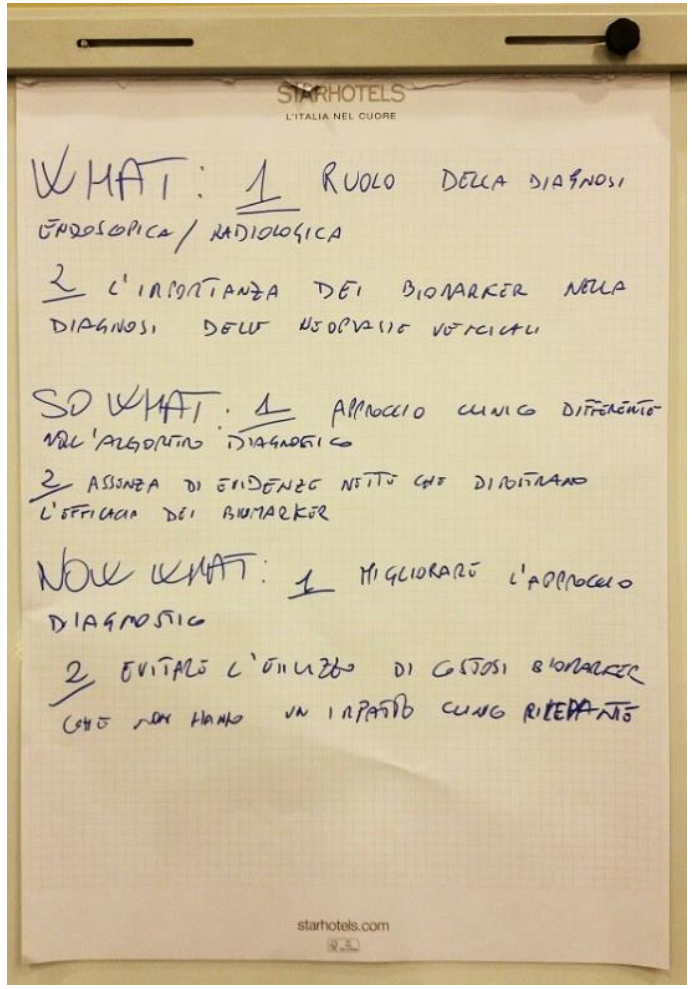
Analisi degli obiettivi

Condivisione di idee

Debriefing (riflessioni e sintesi)

Soluzioni a sfide

What?, So What?, Now What?



Partendo da quanto ascoltato, cosa è emerso di particolar-mente saliente / rilevante?

WHAT?

Per quale motivo le cose emerse sono così rilevanti?

SO WHAT?

Quali ricadute nell'immediato per la mia professione?

NOW WHAT?

SACRO CUORE DON CALABRIA
I R C C S

MEMBER OF ECI
Organisation of European Cancer Institutes - EEIG

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2023 - 9ª EDIZIONE

FORMAZIONE DI BASE (Core School) - B1 - 1° Modulo

NEGRAR DI VALPOLICELLA • 20-21 GENNAIO 2023

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Programma

20 Gennaio 2023

10.00-10.10 Saluti dell'amministratore delegato dell'IRCCS "Sacro Cuore - Don Calabria" Negrar di Valpolicella (VR)
Dr. Mario PICCININI

10.10-10.25 Presentazione ed obiettivi del Corso
Stefania GORI
Giovanni L. PAPPAGALLO

SESSIONE I - NOZIONI DI BASE

10.25-10.45 Etica della ricerca
Fabrizio NICOLIS

10.45-11.45 Quesito clinico di riferimento. Fasi della sperimentazione clinica. Disegni di studio osservazionali ed interventistici
Emilio BRIA

11.45-12.00 Discussione

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-14.15 Colazione di lavoro

14.15-15.15 Misure di effetto relativo e assoluto
Giovanni L. PAPPAGALLO

15.15-16.15 Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
Cristina MAZZI

16.15-16.30 Discussione

16.30-16.45 Coffee Break

16.45-17.45 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

17.45 Termine dei lavori della giornata

21 Gennaio 2023

SESSIONE II - VALUTAZIONE DELLE EVIDENZE

09.00-09.45 Rilevanza clinica Vs significatività statistica
Giovanni L. PAPPAGALLO

09.45-10.15 Trasferibilità delle evidenze al quesito clinico
Giovanni L. PAPPAGALLO

10.15-10.30 Discussione

10.30-10.45 Coffee Break

10.45-11.15 Affidabilità delle prove (rischio di bias, imprecisione degli effetti)
Giovanni L. PAPPAGALLO

11.15-12.00 Dialogo tra clinico e metodologo: "Lettura di uno studio clinico"
Ettore D'ARGENTO
Giovanni L. PAPPAGALLO

12.00-13.00 Lavoro di gruppo
Summing-Up
(metodo: *What? So What? Now What?*)
Tutor: Cristina MAZZI

13.00-13.30 Compilazione questionario ECM

13.30 Conclusione del Corso

- **Etica della ricerca**
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

SACRO CUORE DON CALABRIA

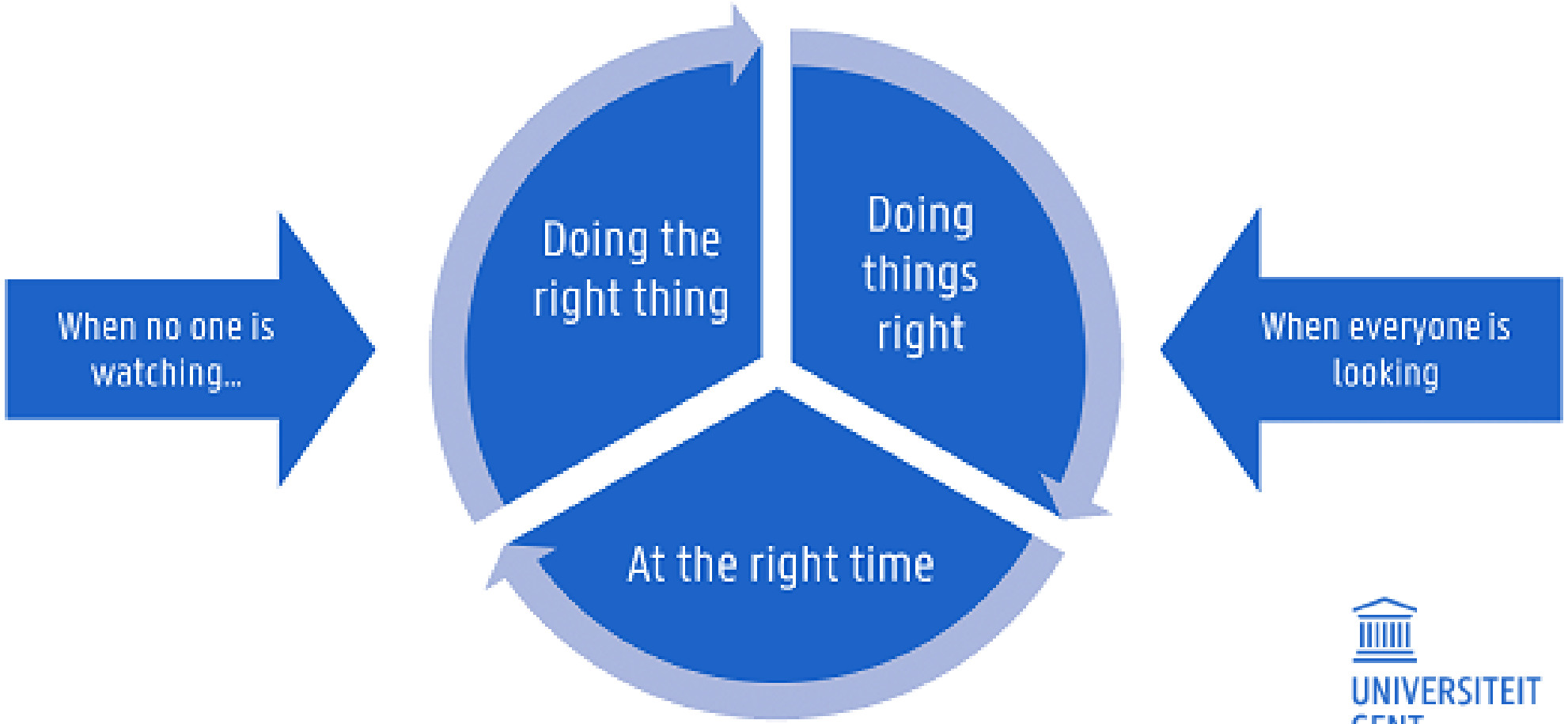
I R C C S

Etica e Integrità della Ricerca

Fabrizio Nicolis

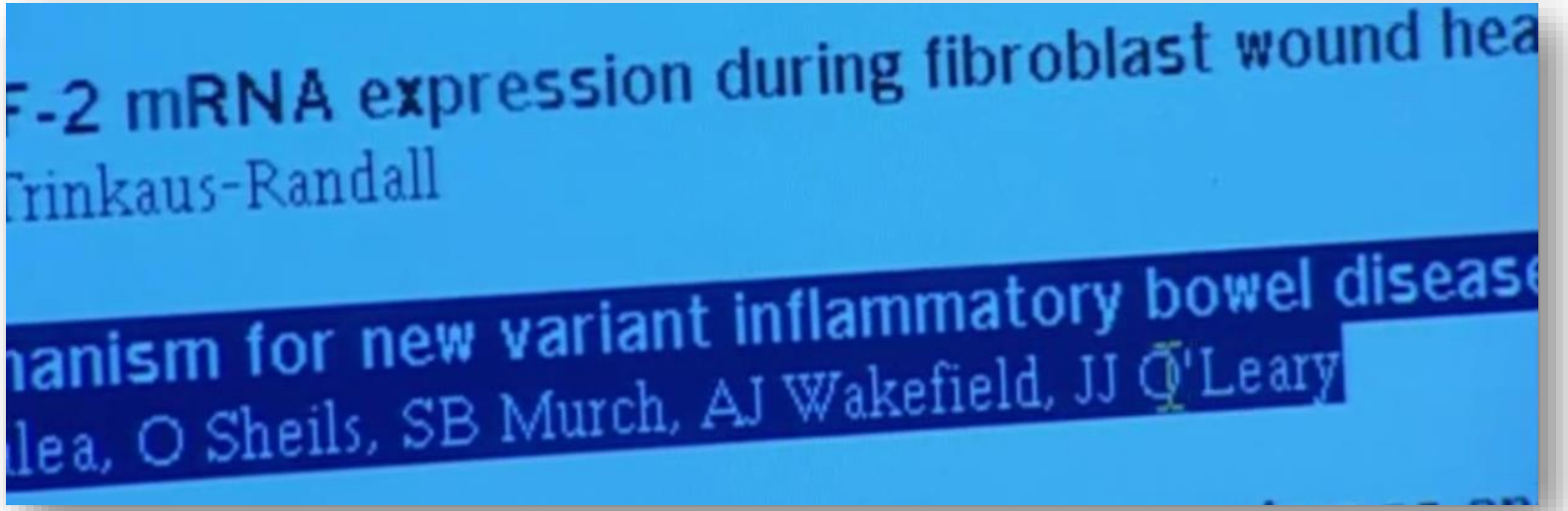
Direttore Sanitario

Research integrity: what is it about?

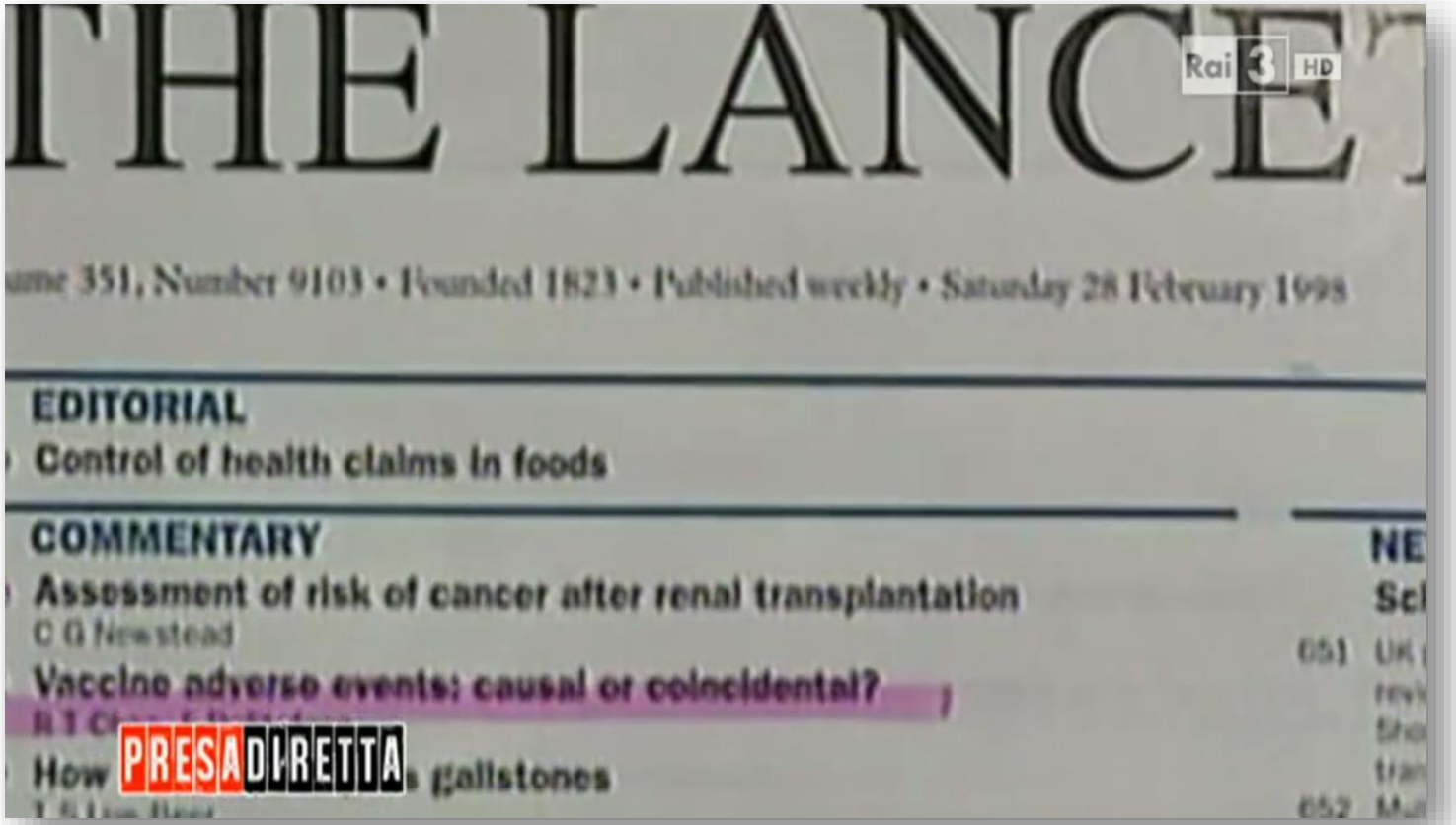


UNIVERSITEIT GENT

La storia di **Andrew Wakefield** inizia nel Royal Free Hospital, importante Ospedale di Londra e grande policlinico universitario pubblico.



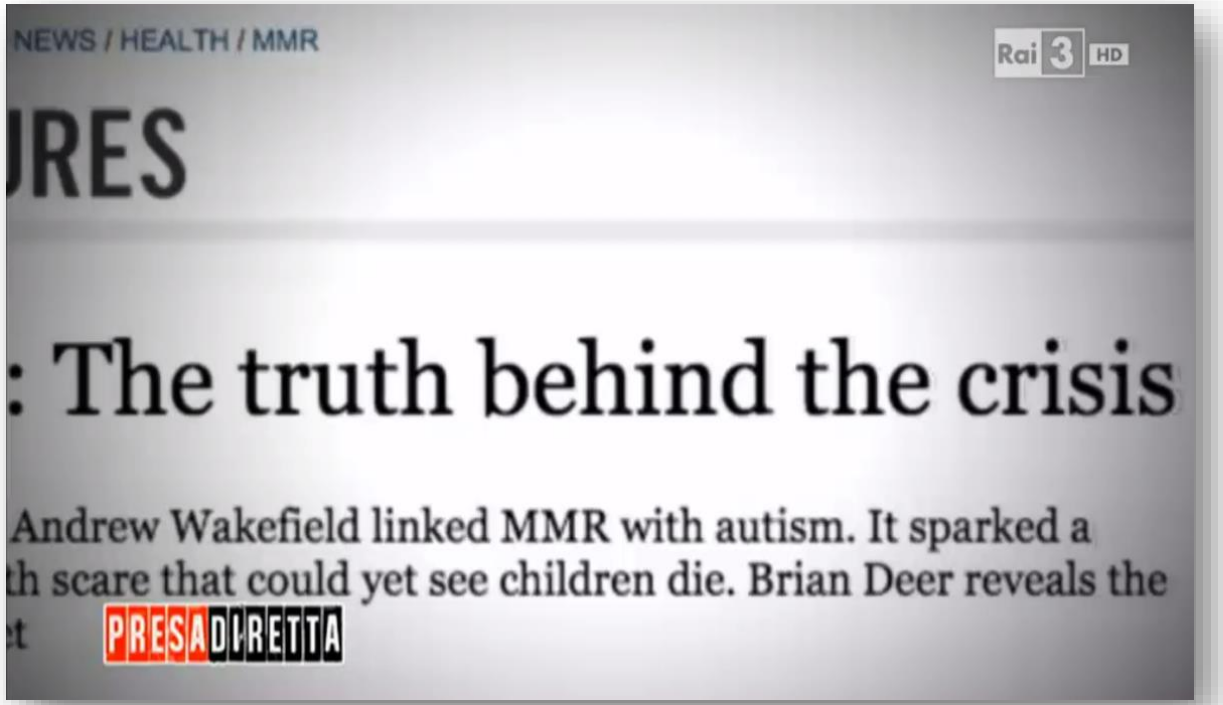
Nel luglio 1997 Wakefield, gastroenterologo, rende pubblica una ricerca che sta conducendo nell'ospedale in cui si ipotizza il legame tra l'assunzione del triplo vaccino MMR e l'insorgenza dell'autismo e del Morbo di Crohn.



I risultati della ricerca condotta su un **campione** di soli **12 bambini** vengono pubblicati 6 mesi dopo nel **febbraio** del **1998** sulla prestigiosa rivista scientifica The Lancet *(Impact Factor 1998: 11,793 – I.F. 2021: 202,731).*

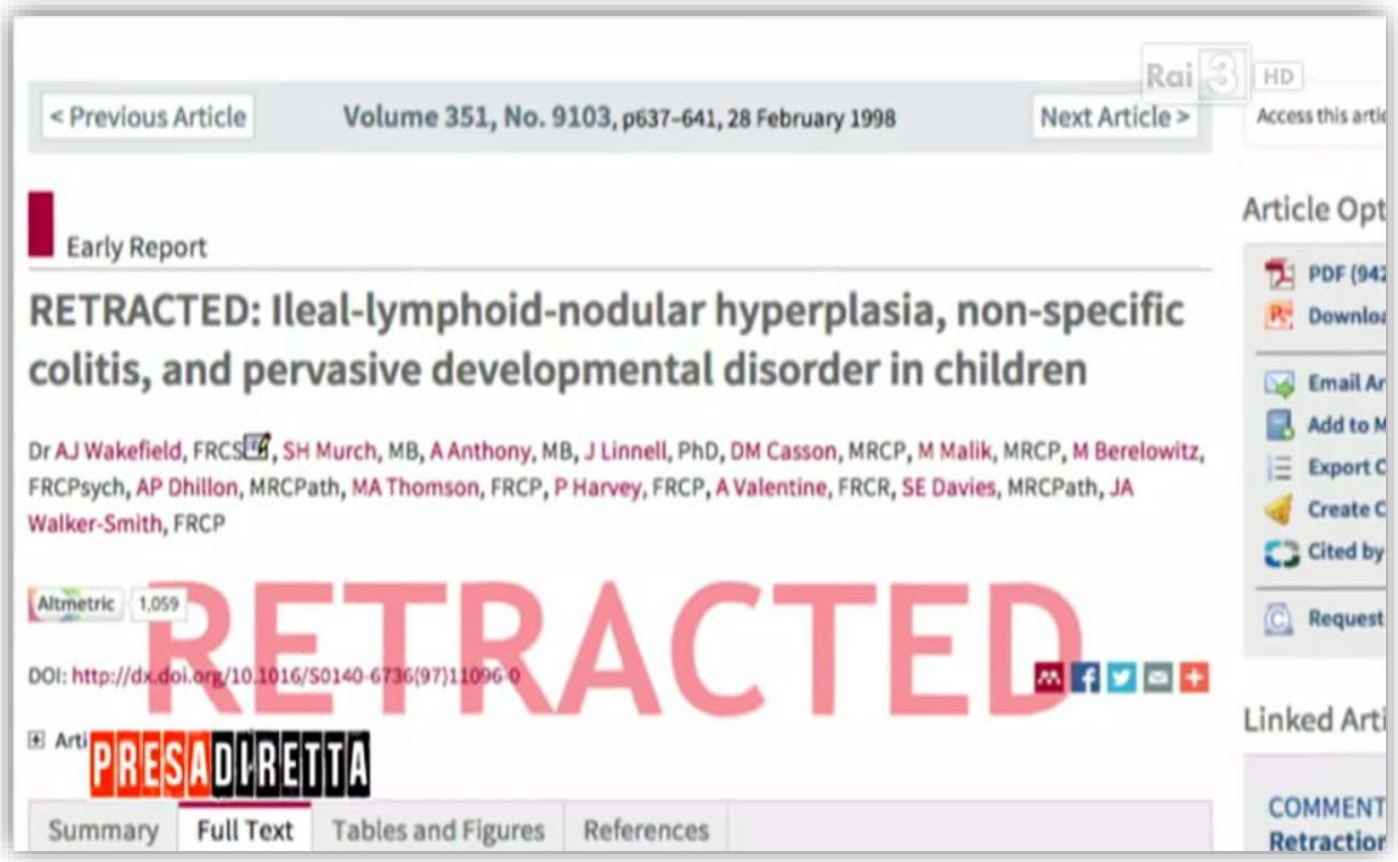
Al primo articolo ne seguono altri su The Lancet, da parte della stessa equipe di ricercatori.

…a Wakefield va tutto bene **fino a dicembre del 2003**



Un’ inchiesta sul **Sunday Times** rivela la presenza di **conflitto di interessi**, sia per Wakefield che per il suo team di medici (relazione con avvocati che convincevano i genitori di bambini autistici a fare causa all’azienda farmaceutica produttrice del vaccino MMR; fondazione di una società privata che vendeva kit diagnostici da usare per i bambini autistici che secondo loro si erano ammalati per colpa dei vaccini).

Si è poi scoperto che la ricerca non reggeva dal punto di vista scientifico: era piena di **gravi errori** nella **scelta dei campioni** analizzati e nelle **procedure di analisi**



Partial retraction:
2004

Fully retraction:
2010

La rivista The Lancet decide di cancellare per sempre l'articolo di Wakefield considerandolo una vera e propria **frode scientifica**

Wakefield è stato radiato nel 2010 dal Consiglio Generale dei Medici Britannici, che lo ha giudicato “disonesto”, “irresponsabile” e in pieno conflitto di interesse nel proprio lavoro di ricerca.

Il Consiglio lo ha ritenuto colpevole di aver agito contro l’interesse dei propri pazienti, tutti bambini disabili, e di aver mentito all’editore di un’importante rivista scientifica, The Lancet.

OECD

2007

ORGANISATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT
GLOBAL SCIENCE FORUM

Best Practices for Ensuring Scientific Integrity and Preventing Misconduct

The Organisation for Economic Co-operation and Development (OECD) is an **international** organisation that works to build ***better policies for better lives***. Our goal is to shape policies that foster prosperity, equality, opportunity and well-being for all. We draw on 60 years of experience and insights to better prepare the world of tomorrow.

The European Code of Conduct for Research Integrity

REVISED EDITION

- Prima pubblicazione: 2011
- Revisione: 2017

ALLEA
ALL European Academies

ALLEA Member Academies

Albania: Akademia e Shkencave e Shqipërisë; **Armenia**: Գիտությունների ազգային ակադեմիա; **Austria**: Österreichische Akademie der Wissenschaften; **Bielorussia**: Нацыянальная акадэмія навук Беларусі; **Belgio**: Académie Royale des Sciences, des Lettres et des Beaux-Arts de Belgique; Koninklijke Vlaamse Academie van Belgie voor Wetenschappen en Kunsten; Koninklijke Academie voor Nederlandse Taal- en Letterkunde; Académie Royale de langue et de litterature françaises de Belgique; **Bosnia-Erzegovina**: Akademija nauka i umjetnosti Bosne i Hercegovine; **Bulgaria**: Българска академия на науките; **Croazia**: Hrvatska Akademija Znanosti i Umjetnosti; **Repubblica Ceca:** Akademie věd České republiky; Učená společnost České republiky; **Dinamarca**: Kongelige Danske Videnskabernes Selskab; **Estonia**: Eesti Teaduste Akadeemia; **Finlandia**: Tiedeakatemiain neuvottelukunta; **Francia**: Académie des Sciences - Institut de France; Académie des Inscriptions et Belles-Lettres; **Georgia:** საქართველოს მეცნიერებათა ეროვნული აკადემია; **Germania**: Leopoldina - Nationale Akademie der Wissenschaften; Union der deutschen Akademien der Wissenschaften; Akademie der Wissenschaften in Göttingen, Akademie der Wissenschaften und der Literatur Mainz, Bayerische Akademie der Wissenschaften, Berlin-Brandenburgische Akademie der Wissenschaften, Akademie der Wissenschaften in Hamburg, Heidelberger Akademie der Wissenschaften, Nordrhein-Westfälische Akademie der Wissenschaften und der Künste, Sächsische Akademie der Wissenschaften zu Leipzig (membri associati); **Grecia**: Ακαδημία Αθηνών; **Ungheria:** Magyar Tudományos Akadémia; **Irlanda**: The Royal Irish Academy - Acadamh Ríoga na hÉireann; **Israele**: האקדמיה הלאומית הישראלית למדעים; **Italia**: Accademia Nazionale dei Lincei; Istituto Veneto di Scienze, Lettere ed Arti; Accademia delle Scienze di Torino; **Kosovo**: Akademia e Shkencave dhe e Arteve e Kosovës; **Lettonia**: Latvijas Zinātņu akadēmija; **Lituania**: Lietuvos mokslų akademijos; **Macedonia**: Македонска Академија на Науките и Уметностите; **Moldova**: Academia de Ştiinţe a Moldovei; **Montenegro**: Crnogorska akademija nauka i umjetnosti; **Paesi Bassi:** Koninklijke Nederlandse Akademie van Wetenschappen; **Norvegia**: Det Norske Videnskaps-Akademi; Det Kongelige Norske Videnskabers Selskab; **Polonia**: Polska Akademia Umiejętności; Polska Akademia Nauk; **Portogallo**: Academia das Ciências de Lisboa; **Romania**: Academia Română; **Russia**: Российская академия наук (membro associato); **Serbia**: Srpska Akademija Nauka i Umetnosti; **Slovacchia**: Slovenská Akadémia Vied; **Slovenia**: Slovenska akademija znanosti in umetnosti; **Spagna**: Real Academia de Ciencias Exactas, Físicas y Naturales; Reial Acadèmia de Ciències i Arts de Barcelona; Institut d'Estudis Catalans; **Svezia**: Kungl. Vetenskapsakademien; Kungl. Vitterhets Historie och Antikvitets Akademien; **Svizzera**: Akademien der Wissenschaften Schweiz; **Turchia**: Türkiye Bilimler Akademisi; Bilim Akademisi; **Ucraina**: Національна академія наук України; **Regno Unito**: The British Academy; The Learned Society of Wales; The Royal Society; The Royal Society of Edinburgh

ALLEA
ALL European Academies

Italia:

- Accademia Nazionale dei Lincei
- Istituto Veneto di Scienze, Lettere ed Arti
- Accademia delle Scienze di Torino

A) I **PRINCIPI** su cui si fonda l'integrità della ricerca

B) Le **BUONE PRASSI** di ricerca

C) Le **VIOLAZIONI** dell'integrità della ricerca

Numero pagine: **10**

4 FUNDAMENTAL PRINCIPLES OF RESEARCH INTEGRITY

The European Code of Conduct for Research Integrity, 2017

1

RELIABILITY

in ensuring the quality of research, reflected in the design, the methodology, the analysis, and the use of resources.

HONESTY

in developing, undertaking, reviewing, reporting, and communicating research in a transparent, fair, full, and unbiased way.

2

3

RESPECT

for colleagues, research participants, society, ecosystems, cultural heritage, and the environment.

ACCOUNTABILITY

for research, from idea to publication, for its management and organisation, for training, supervision, and mentoring, and for its wider impact.

4

A) I PRINCIPI su cui si fonda l'integrità della ricerca

1- AFFIDABILITÀ

nel garantire la **qualità della ricerca** che si riflette nella progettazione, nella metodologia, nell'analisi e nell'uso delle risorse.

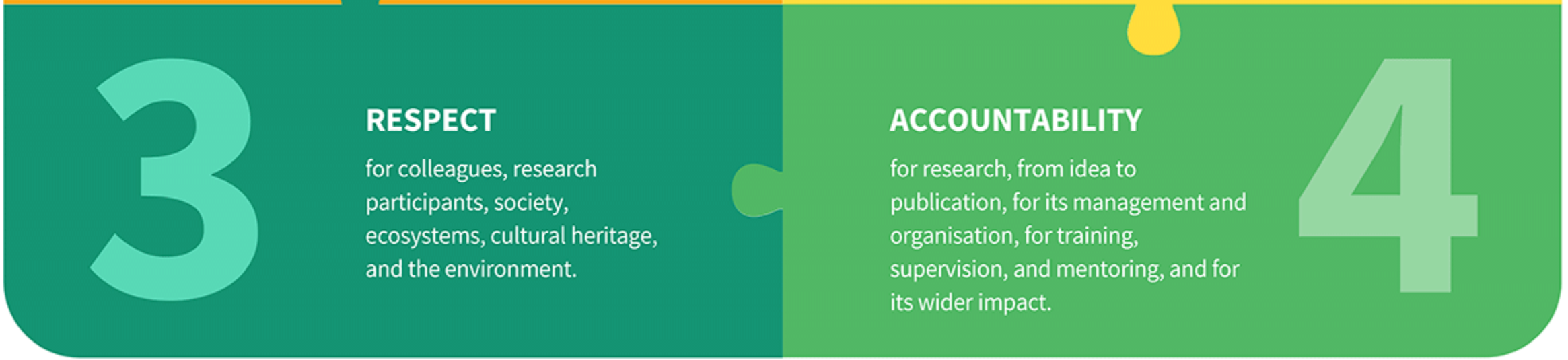
A) I PRINCIPI su cui si fonda l'integrità della ricerca

1- AFFIDABILITÀ

nel garantire la **qualità della ricerca** che si riflette nella progettazione, nella metodologia, nell'analisi e nell'uso delle risorse.

2- ONESTÀ

nello sviluppare, condurre, rivedere, riferire e comunicare la **ricerca** in maniera **trasparente**, **equa**, **completa** e **obiettiva**.



A) I PRINCIPI su cui si fonda l'integrità della ricerca

1- AFFIDABILITÀ
nel garantire la **qualità della ricerca** che si riflette nella progettazione, nella metodologia, nell'analisi e nell'uso delle risorse.

2- ONESTÀ
nello sviluppare, condurre, rivedere, riferire e comunicare la **ricerca** in maniera **trasparente**, **equa**, **completa** e **obiettiva**.

3- RISPETTO per:
colleghi, partecipanti alla ricerca, società, ecosistemi, patrimonio culturale e ambiente

ACCOUNTABILITY

for research, from idea to publication, for its management and organisation, for training, supervision, and mentoring, and for its wider impact.

4

A) I PRINCIPI su cui si fonda l'integrità della ricerca

1- AFFIDABILITÀ
nel garantire la **qualità della ricerca** che si riflette nella progettazione, nella metodologia, nell'analisi e nell'uso delle risorse.

2- ONESTÀ
nello sviluppare, condurre, rivedere, riferire e comunicare la **ricerca** in maniera **trasparente**, **equa**, **completa** e **obiettiva**.

3- RISPETTO per:
colleghi, partecipanti alla ricerca, società, ecosistemi, patrimonio culturale e ambiente

4- RESPONSABILITÀ
dall'idea iniziale alla pubblicazione, per la gestione e organizzazione della ricerca, per la formazione, la supervisione e il tutoraggio, e infine per i suoi impatti più ampi.

B) Le BUONE PRASSI di ricerca

Nei diversi contesti:

- Ambiente di ricerca
- Formazione, supervisione e tutoraggio
- Procedure di ricerca
- Salvaguardie (ambiente, rapporti tra ricercatori, etc.)
- Qualità e gestione dei dati
- Collaborazione
- Pubblicazione e diffusione
- Revisione, valutazione ed editing

C) Le VIOLAZIONI dell'integrità della ricerca

Le situazioni principali in cui si configura una ***frode scientifica***:

- **FABBRICAZIONE**: invenzione di risultati che vengono registrati come se fossero reali
- **FALSIFICAZIONE**: manipolazione di materiali, attrezzature o processi di ricerca, oppure ingiustificata modifica, omissione o soppressione di dati o risultati
- **PLAGIO**: utilizzo dei lavori e delle idee di altre persone senza citare la fonte originaria, violando così i diritti dell'autore o degli autori originari sulla propria produzione intellettuale

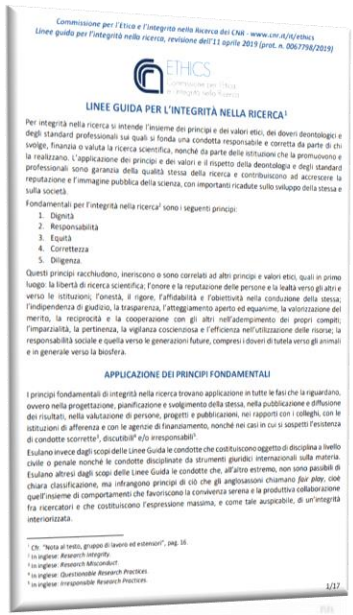
Consiglio Nazionale delle Ricerche

Commissione per l'Etica e l'Integrità nella Ricerca

ETHICS
Commissione per l'Etica
e l'Integrità nella Ricerca

La Commissione per l'Etica e l'Integrità nella Ricerca è presieduta dal Presidente del Cnr. La Commissione è un organismo indipendente con funzioni di consulenza in materia di etica della ricerca, bioetica e biodiritto, inclusi gli aspetti etici, deontologici e giuridici ricompresi nell'ambito della integrità nella ricerca (*Research Integrity*), così come descritta in letteratura scientifica e nelle principali Carte e Convenzioni internazionali nonché nelle "Linee guida per l'integrità nella ricerca" del Cnr, approvate il 10 giugno 2015 e revisionate nel 2019.

Commissione per l'Etica e l'Integrità nella Ricerca del CNR - www.cnr.it/it/ethics
Linee guida per l'integrità nella ricerca, revisione dell'11 aprile 2019 (prot. n. 0067798/2019)


Commissione per l'Etica e l'Integrità nella Ricerca del CNR - www.cnr.it/it/ethics
Linee guida per l'integrità nella ricerca, revisione dell'11 aprile 2019 (prot. n. 0067798/2019)

ETHICS
Commissione per l'Etica e l'Integrità nella Ricerca

LINEE GUIDA PER L'INTEGRITÀ NELLA RICERCA[1]

Per integrità nella ricerca si intende l'insieme dei principi e dei valori etici, dei doveri deontologici e degli standard professionali sui quali si fonda una condotta responsabile e corretta da parte di chi svolge, finanzia o valuta la ricerca scientifica, nonché da parte delle istituzioni che la promuovono e la realizzano. L'applicazione dei principi e dei valori e il rispetto della deontologia e degli standard professionali sono garanzia della qualità stessa della ricerca e contribuiscono ad accrescere la reputazione e l'immagine pubblica della scienza, con importanti ricadute sullo sviluppo della stessa e sulla società.

Fondamentali per l'integrità nella ricerca[2] sono i seguenti principi:

1. Dignità
2. Responsabilità
3. Equità
4. Correttezza
5. Diligenza.

Questi principi racchiudono, ineriscono o sono correlati ad altri principi e valori etici, quali in primo luogo: la libertà di ricerca scientifica; l'onore e la reputazione delle persone e la lealtà verso gli altri e verso le istituzioni; l'onestà, il rigore, l'affidabilità e l'obiettività nella conduzione della stessa; l'indipendenza di giudizio, la trasparenza, l'atteggiamento aperto ed equanime, la valorizzazione del merito, la reciprocità e la cooperazione con gli altri nell'adempimento dei propri compiti; l'imparzialità, la pertinenza, la vigilanza coscienziosa e l'efficienza nell'utilizzazione delle risorse; la responsabilità sociale e quella verso le generazioni future, compresi i doveri di tutela verso gli animali e in generale verso la biosfera.

APPLICAZIONE DEI PRINCIPI FONDAMENTALI

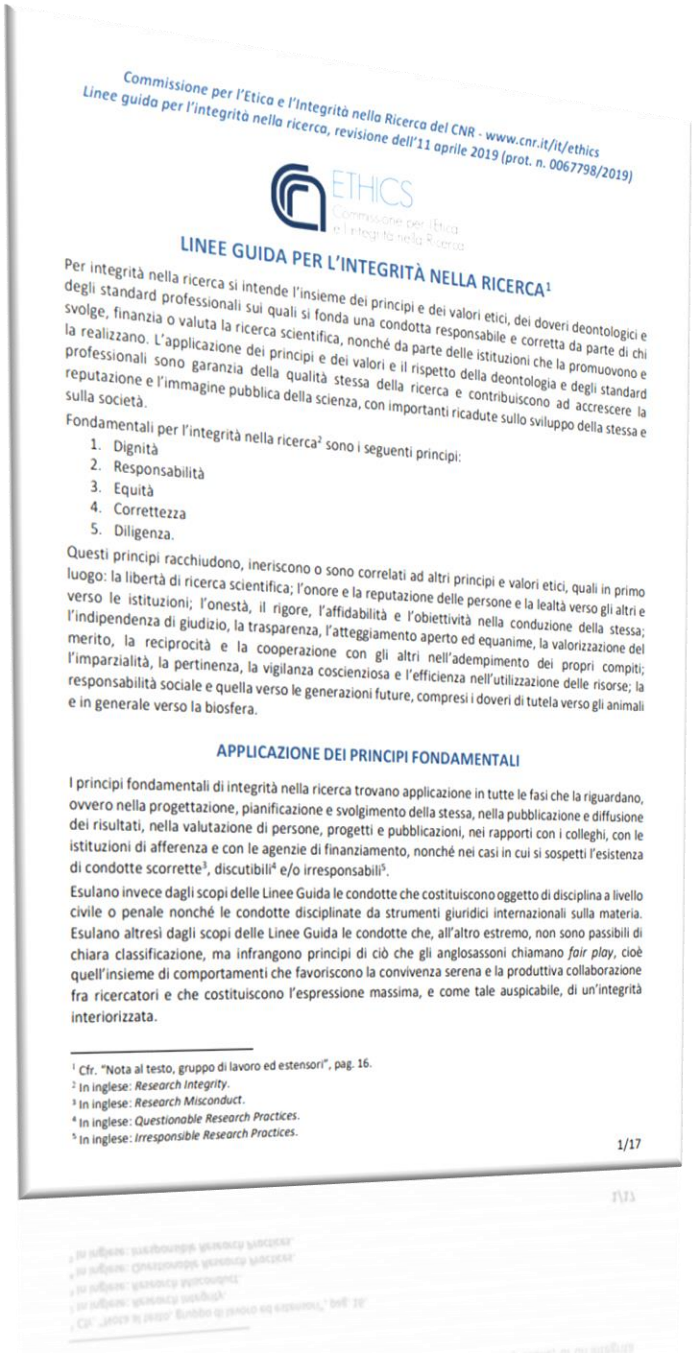
I principi fondamentali di integrità nella ricerca trovano applicazione in tutte le fasi che la riguardano, ovvero nella progettazione, pianificazione e svolgimento della stessa, nella pubblicazione e diffusione dei risultati, nella valutazione di persone, progetti e pubblicazioni, nei rapporti con i colleghi, con le istituzioni di afferenza e con le agenzie di finanziamento, nonché nei casi in cui si sospetti l'esistenza di condotte scorrette[3], discutibili[4] e/o irresponsabili[5].

Esulano invece dagli scopi delle Linee Guida le condotte che costituiscono oggetto di disciplina a livello civile o penale nonché le condotte disciplinate da strumenti giuridici internazionali sulla materia. Esulano altresì dagli scopi delle Linee Guida le condotte che, all'altro estremo, non sono passibili di chiara classificazione, ma infrangono principi di ciò che gli anglosassoni chiamano *fair play*, cioè quell'insieme di comportamenti che favoriscono la convivenza serena e la produttiva collaborazione fra ricercatori e che costituiscono l'espressione massima, e come tale auspicabile, di un'integrità interiorizzata.

[1] Cfr. "Nota al testo, gruppo di lavoro ed estensori", pag. 16.
[2] In inglese: *Research integrity*.
[3] In inglese: *Research Misconduct*.
[4] In inglese: *Questionable Research Practices*.
[5] In inglese: *Irresponsible Research Practices*.

1/17

LINEE GUIDA PER L'INTEGRITÀ NELLA RICERCA[1]



Commissione per l'Etica e l'Integrità nella Ricerca del CNR - www.cnr.it/it/ethics
Linee guida per l'integrità nella ricerca, revisione dell'11 aprile 2019 (prot. n. 0067798/2019)

ETHICS
Commissione per l'Etica e l'Integrità nella Ricerca

LINEE GUIDA PER L'INTEGRITÀ NELLA RICERCA[1]

Per integrità nella ricerca si intende l'insieme dei principi e dei valori etici, dei doveri deontologici e degli standard professionali sui quali si fonda una condotta responsabile e corretta da parte di chi svolge, finanzia o valuta la ricerca scientifica, nonché da parte delle istituzioni che la promuovono e la realizzano. L'applicazione dei principi e dei valori e il rispetto della deontologia e degli standard professionali sono garanzia della qualità stessa della ricerca e contribuiscono ad accrescere la reputazione e l'immagine pubblica della scienza, con importanti ricadute sullo sviluppo della stessa e sulla società.

Fondamentali per l'integrità nella ricerca[2] sono i seguenti principi:

1. Dignità
2. Responsabilità
3. Equità
4. Correttezza
5. Diligenza.

Questi principi racchiudono, ineriscono o sono correlati ad altri principi e valori etici, quali in primo luogo: la libertà di ricerca scientifica; l'onore e la reputazione delle persone e la lealtà verso gli altri e verso le istituzioni; l'onestà, il rigore, l'affidabilità e l'obiettività nella conduzione della stessa; l'indipendenza di giudizio, la trasparenza, l'atteggiamento aperto ed equanime, la valorizzazione del merito, la reciprocità e la cooperazione con gli altri nell'adempimento dei propri compiti; l'imparzialità, la pertinenza, la vigilanza coscienziosa e l'efficienza nell'utilizzazione delle risorse; la responsabilità sociale e quella verso le generazioni future, compresi i doveri di tutela verso gli animali e in generale verso la biosfera.

APPLICAZIONE DEI PRINCIPI FONDAMENTALI

I principi fondamentali di integrità nella ricerca trovano applicazione in tutte le fasi che la riguardano, ovvero nella progettazione, pianificazione e svolgimento della stessa, nella pubblicazione e diffusione dei risultati, nella valutazione di persone, progetti e pubblicazioni, nei rapporti con i colleghi, con le istituzioni di afferenza e con le agenzie di finanziamento, nonché nei casi in cui si sospetti l'esistenza di condotte scorrette[3], discutibili[4] e/o irresponsabili[5].

Esulano invece dagli scopi delle Linee Guida le condotte che costituiscono oggetto di disciplina a livello civile o penale nonché le condotte disciplinate da strumenti giuridici internazionali sulla materia. Esulano altresì dagli scopi delle Linee Guida le condotte che, all'altro estremo, non sono passibili di chiara classificazione, ma infrangono principi di ciò che gli anglosassoni chiamano *fair play*, cioè quell'insieme di comportamenti che favoriscono la convivenza serena e la produttiva collaborazione fra ricercatori e che costituiscono l'espressione massima, e come tale auspicabile, di un'integrità interiorizzata.

[1] Cfr. "Nota al testo, gruppo di lavoro ed estensori", pag. 16.
[2] In inglese: *Research Integrity*.
[3] In inglese: *Research Misconduct*.
[4] In inglese: *Questionable Research Practices*.
[5] In inglese: *Irresponsible Research Practices*.

1/17

A) PRINCIPI FONDAMENTALI per l'integrità nella ricerca

B) CONDOTTE che **PROMUOVONO** l'integrità nella ricerca, in tutte le fasi della ricerca (progettazione, svolgimento, pubblicazione dei risultati, etc.)

C) CONDOTTE LESIVE dell'integrità nella ricerca, in tutte le fasi della ricerca

Numero pagine: **17**

CONDOTTE che **PROMUOVONO** l'integrità nella ricerca

Un esempio

3. Educare all'integrità nella ricerca: le istituzioni scientifiche e chi in esse riveste ruoli di coordinamento o direzione scientifica o amministrativa contribuiscono, nelle forme consentite dal proprio ruolo, a formare i ricercatori riguardo ai principi dell'integrità nella ricerca e in generale alle responsabilità sociali implicate dalle sperimentazioni.

ETHICS
Commissione per l'Etica
e l'Integrità nella Ricerca

LINEE GUIDA PER L'INTEGRITÀ NELLA RICERCA

DECRETO LEGISLATIVO 23 dicembre 2022, n. **200**.

Riordino della disciplina degli Istituti di ricovero e cura a carattere scientifico.

G.U. Serie generale - n. 304, 30-12-2022

Art. 4. Modifiche all'articolo 8 del decreto legislativo 16 ottobre 2003, n. 288

5-bis. Gli Istituti, nel rispetto della legge 31 maggio 2022, n. 62, garantiscono che l'attività di ricerca e cura si conformi ai **principi** della **correttezza**, **trasparenza**, **equità**, **responsabilità**, **affidabilità** e **completezza** riconosciuti a livello internazionale. Essi pubblicano tutti i dati e le fonti della ricerca in modo veritiero e oggettivo, al fine di consentire la verifica e la riproducibilità, con specifico riferimento al mantenimento dei dati utilizzati. A tal fine, per garantire la valutazione dell'attività scientifica, anche con riguardo agli effetti di quest'ultima sulla salute della popolazione, utilizzano indicatori di efficacia ed efficienza della qualità dell'attività di ricerca riconosciuti a livello internazionale. **Gli Istituti adottano e aggiornano periodicamente un codice di condotta per l'integrità della ricerca**. Il personale in servizio presso gli IRCCS è tenuto ad aderire ad un codice di condotta che disciplina prescrizioni comportamentali volte al corretto utilizzo delle risorse e al rispetto di regole di *fair competition (concorrenza leale).*

Organisation of European Cancer Institutes – EEIG

OECI Qualitative Standards

Prevention and detection and handling of scientific misconduct	
Standard 78	
Conduct of research is defined by core principles of research integrity.	
1	There is a code of conduct regarding good research practices, covering the research environment, data practices and management, publication and dissemination, such as those of the European Code of Conduct for Research Integrity.
2.	There is a procedure to deal with violation of research integrity, such as research misconduct.

CONDOTTE che **PROMUOVONO** l'integrità nella ricerca

Un esempio

5. Comunicare con obiettività e responsabilità: nella misura consentita da ciascuna diversa forma e modalità di pubblicazione, i ricercatori forniscono in modo scrupoloso, obiettivo e imparziale la maggior quantità possibile di elementi e informazioni anche su aspetti quali:
    a. la letteratura fondamentale e le conoscenze antecedenti lo studio;
    b. lo scopo originario e i metodi definiti *prima* dello svolgimento della ricerca;
    c. le eventuali modifiche negli obiettivi e nelle metodologie intercorse *dopo* l'avvio della ricerca;
    d. i risultati significativi conseguiti, compresi quelli negativi o nulli;
    e. le possibili interpretazioni, l'ambito di applicabilità e le limitazioni dei risultati conseguiti.

ETHICS
Commissione per l'Etica e l'Integrità nella Ricerca

Research Letter

April 16, 2020

The Use of Not-Negative Conclusions to Describe Results of Formally Negative Trials Presented at Oncology Meetings

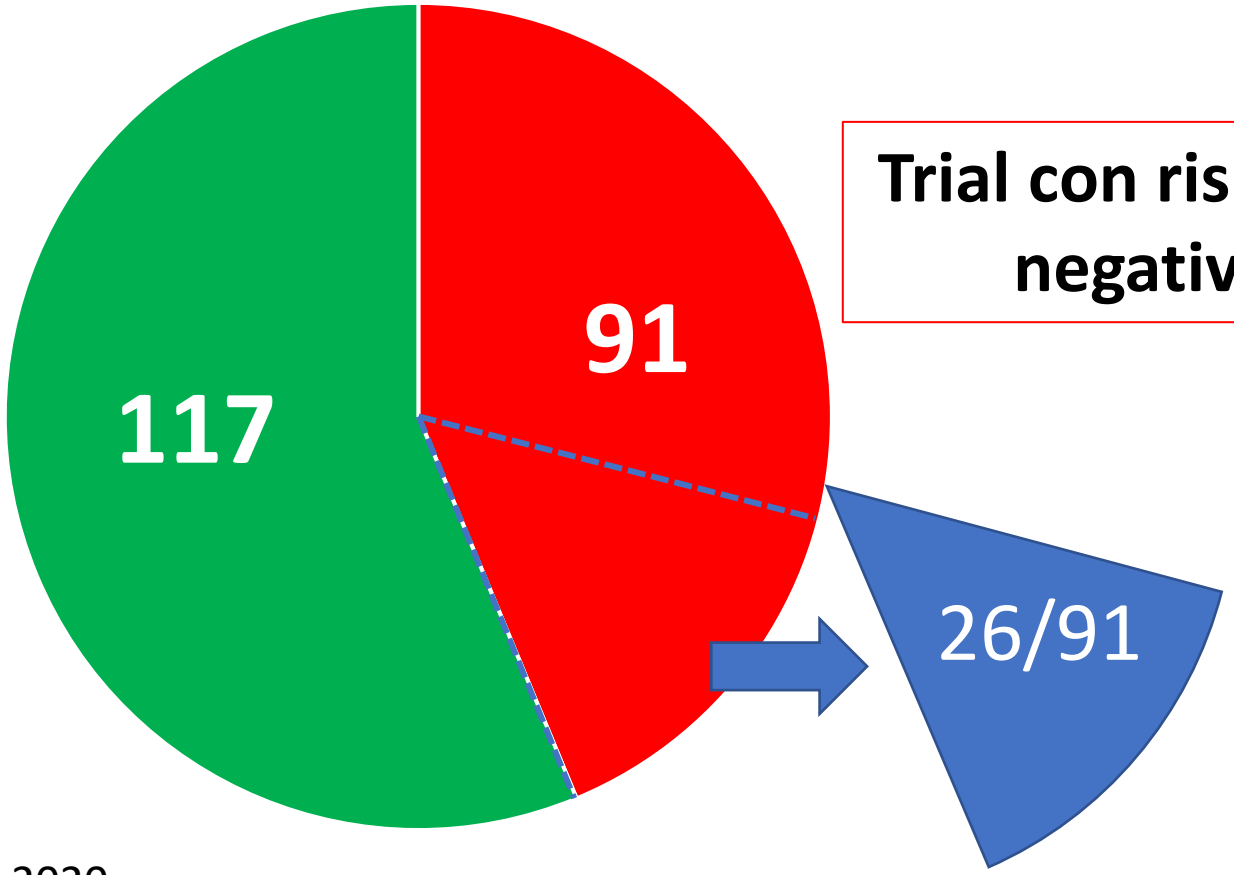
Massimo Di Maio, MD[1,2]; Marco Audisio, MD[1,2]; Claudia Cardone, MD[3,4]; et al

» Author Affiliations | Article Information

JAMA Oncol. 2020;6(6):926-927. doi:10.1001/jamaoncol.2020.0475

Trial Clinici randomizzati di Fase 3
Presentati ai congressi ASCO e ESMO dal 2017 al 2019 (tot=208)

Trial con risultati positivi



Trial con risultati negativi

Trial presentati con CONCLUSIONI NON NEGATIVE: il 29% dei trial con risultati negativi

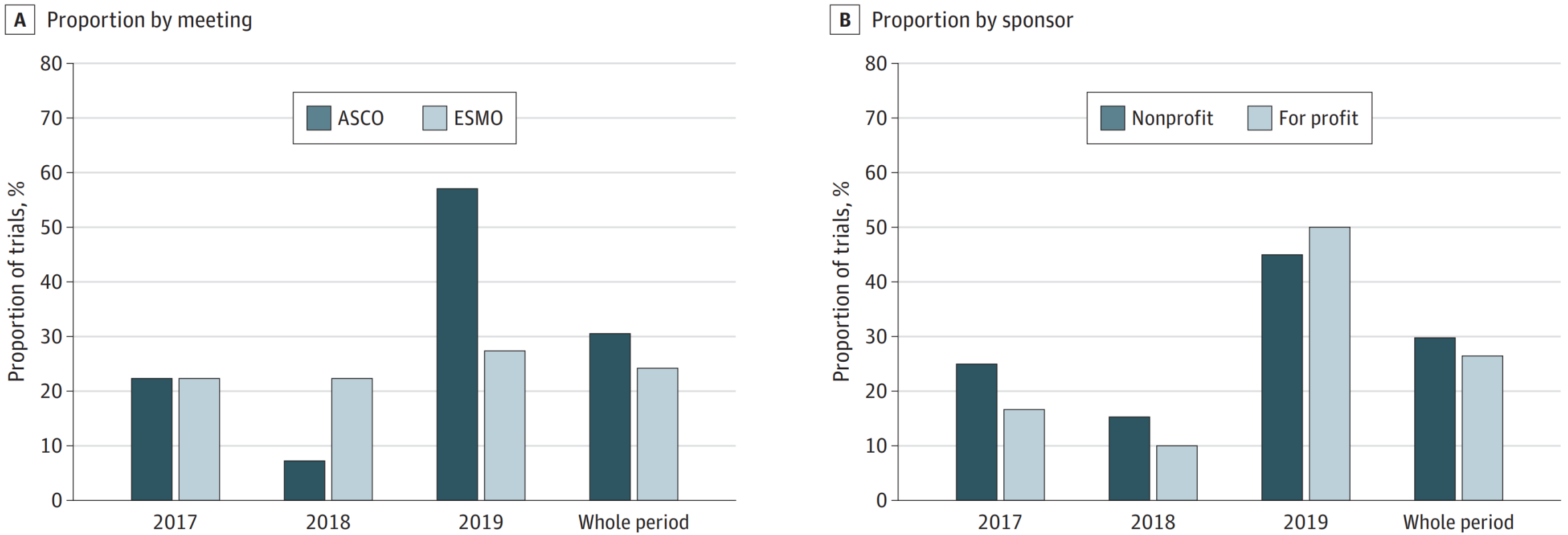
Di Maio M et al., JAMA Oncol. 2020

I Trial con risultati negativi MA presentati con CONCLUSIONI NON NEGATIVE:

- Sono aumentati nel corso degli anni
- Sono risultati essere maggiori ai congressi ASCO vs ESMO
- Sono superiori tra i trial no-profit vs profit

Di Maio M et al., JAMA Oncol. 2020

Figure. Proportion of Formally Negative Trials With Not-Negative Conclusions in Oral Presentations at American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) Meetings From 2017 Through 2019



A, Proportion of trials according to meeting. B, Proportion of trials according to study sponsor.

Di Maio M et al., JAMA Oncol. 2020

NOT-NEGATIVE CONCLUSIONS:

(1) numerically better outcome in the experimental arm, despite a nonsignificant P value,

(2) emphasis on positive subgroup(s),

(3) emphasis on positive secondary end point (s),

(4) noninferiority interpretation of a negative superiority trial

Di Maio M et al., JAMA Oncol. 2020

In conclusion, we believe that more attention should be paid to the statements included in the conclusions of oral presentations at meetings, and the discussants' role is crucial. When the primary end point is not met, the word *negative* should be explicitly used.

Di Maio M et al., JAMA Oncol. 2020

CONDOTTE LESIVE dell'integrità nella ricerca

Un esempio

PRATICHE DISCUTIBILI E/O IRRESPONSABILI:

- ostacolare, rallentare, o sabotare indirettamente e involontariamente il lavoro dei colleghi attraverso la non-condivisione protratta oltre i limiti professionalmente e scientificamente giustificabili, di dati, metodi, risultati negativi di esperimenti, informazioni su errori metodologici o di altro tipo;

World Health Organization

Joint statement on public disclosure of results from clinical trials

18 May 2017 | Departmental news | Reading time: 8 min (2142 words)

Some of the world's largest funders of medical research and international non-governmental organizations agreed on new standards that will require all clinical trials they fund or support to be registered and the results disclosed publicly. Currently, about 50% of clinical trials go unreported, often because the results are negative. These unreported trial results leave an incomplete and potentially misleading picture of the risks and benefits of vaccines, drugs and medical devices, and can lead to use of suboptimal or even harmful products

ABOUTPHARMA

Dicembre 2022-gennaio 2023 | Numero 204 | Euro 9,00 | www.aboutpharma.com | ISSN 2785-6194

Frodi nella ricerca

Quando la scienza trucca le carte

Dicembre 2022

SACRO CUORE DON CALABRIA

I R C C S

Etica e Integrità della Ricerca

Fabrizio Nicolis

Direttore Sanitario

- Etica della ricerca
- **Quesito clinico di riferimento**
- **Fasi della sperimentazione clinica**
- **Disegni di studio osservazionali e interventistici**
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

UNIVERSITÀ CATTOLICA del Sacro Cuore

Comprehensive Cancer Center

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA 2023 - 9ª Edizione

'Lettura di un Trial Clinico' - Sessione I – Nozioni di Base

- Quesito Clinico di Riferimento
- Fasi della Sperimentazione Clinica
- Disegni di Studio Osservazionali ed Interventistici

Emilio Bria

U.O.S.D. Oncologia Toraco-Polmonare,
Comprehensive Cancer Center,
Fondazione Policlinico Universitario Agostino Gemelli IRCCS,
Università Cattolica del Sacro Cuore, Roma
emilio.bria@unicatt.it

Negrar (VR), 20 Gennaio 2023

Disclosures

- Advisory Boards / Speakers' fee:
  - *MSD, Astra-Zeneca, Celgene, Pfizer, Helsinn, Eli-Lilly, BMS, Novartis, Roche*
- Research Support / Grants from:
  - *Università Cattolica del Sacro Cuore (UCSC), Fondazione Policlinico Universitario Agostino Gemelli IRCCS, A.I.R.C. (Associazione Italiana Ricerca sul Cancro), I.A.S.L.C. (International Association for the Study of Lung Cancer), L.I.L.T. (Lega Italiana per la Lotta contro i Tumori), A.I.O.M. (Associazione Italiana di Oncologia Medica), Fondazione Cariverona, Fondazione Roche, AZ Open Innovation*
- Travels / Hospitality:
  - *Roche, Astra-Zeneca, BMS, MSD.*

UNIVERSITÀ CATTOLICA del Sacro Cuore

AIRC

Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

AIOM
Associazione Italiana di Oncologia Medica

IASLC

LILT
LEGA ITALIANA PER LA LOTTA CONTRO I TUMORI
prevenire è vivere

Fondazione Roche

AstraZeneca
openinnovation

FONDAZIONE Cariverona

Topics

- **Quesito Clinico di Riferimento**
- **Fasi della Sperimentazione Clinica**
- **Disegni di Studio Osservazionali ed Interventistici**

‘La Scuola di Atene’ (Particolare, Platone [Leonardo] e Aristotele), Raffaello Sanzio, 1509-1511, Musei Vaticani, Roma

Topics

- **Quesito Clinico di Riferimento**
- Fasi della Sperimentazione Clinica
- Disegni di Studio Osservazionali ed Interventistici

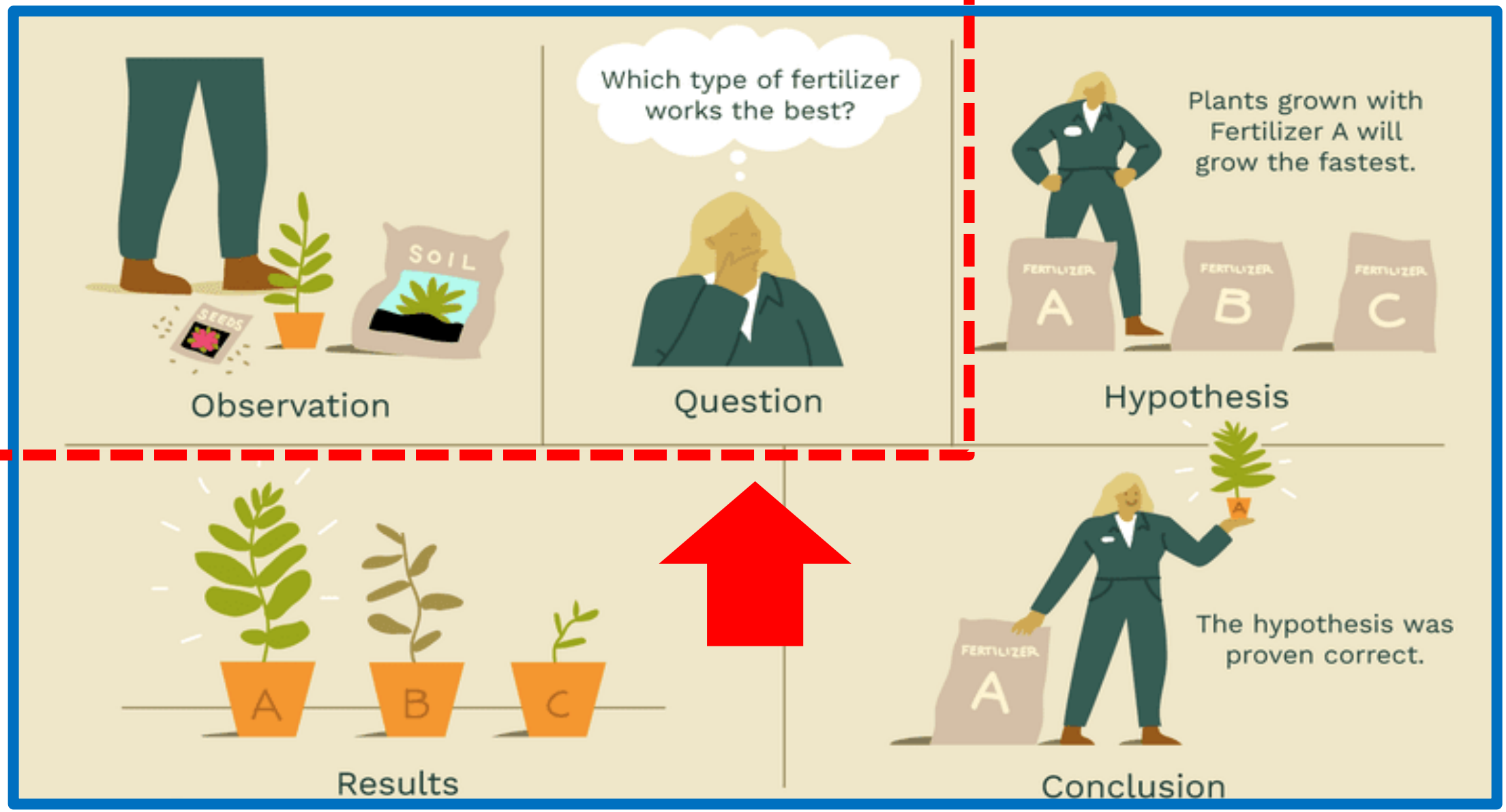
'Madonna dei Pellegrini' (Particolare), Caravaggio, 1604 – 1606, Sant'Agostino in Campo Marzio, Roma

Fattori da prendere in considerazione come primo approccio alla lettura di un articolo riguardante una sperimentazione clinica

1. **Gravità dell'affezione.**
2. **Efficacia/tollerabilità delle terapie disponibili.**
3. ***Unmet need* attuali (efficacia e/o tollerabilità).**
4. **Presumibile superiorità delle terapie sperimentali.**

Bruzzi & Pappagallo, 1987
mod. Pappagallo 2020

Steps of the Scientific Method



Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - **Descrizione dei dati e inferenza statistica**
  - **L'importanza della numerosità campionaria**
  - **La rappresentatività del campione**
  - **La tentazione delle analisi per sottogruppi**

'Sibilla Libica' (Particolare), Michelangelo, circa 1512, Cappella Sistina, Roma

Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - **Descrizione dei dati e inferenza statistica**
  - **L'importanza della numerosità campionaria**
  - **La rappresentatività del campione**
  - **La tentazione delle analisi per sottogruppi**

Una buona ricerca clinica deve essere:

1. **Scientificamente rilevante**
2. **Metodologicamente corretta**
3. **Eticamente accettabile**

La Buona Ricerca Clinica

- **Non è etico ciò che non è rilevante scientificamente:**
  - **Uno studio clinico deve rispondere ad un bisogno reale;**
  - **La domanda deve essere clinicamente e biologicamente giustificata.**
- **Non è etico ciò che non è metodologicamente corretto**
  - **Uno studio clinico metodologicamente non corretto:**
    - **Può portare a conclusioni inutili, sbagliate, potenzialmente dannose;**
    - **Espone a rischi ingiustificati i malati;**
    - **E' uno spreco di risorse!**

La Buona Ricerca Clinica

- **Non è necessariamente etico ciò che è metodologicamente corretto.**

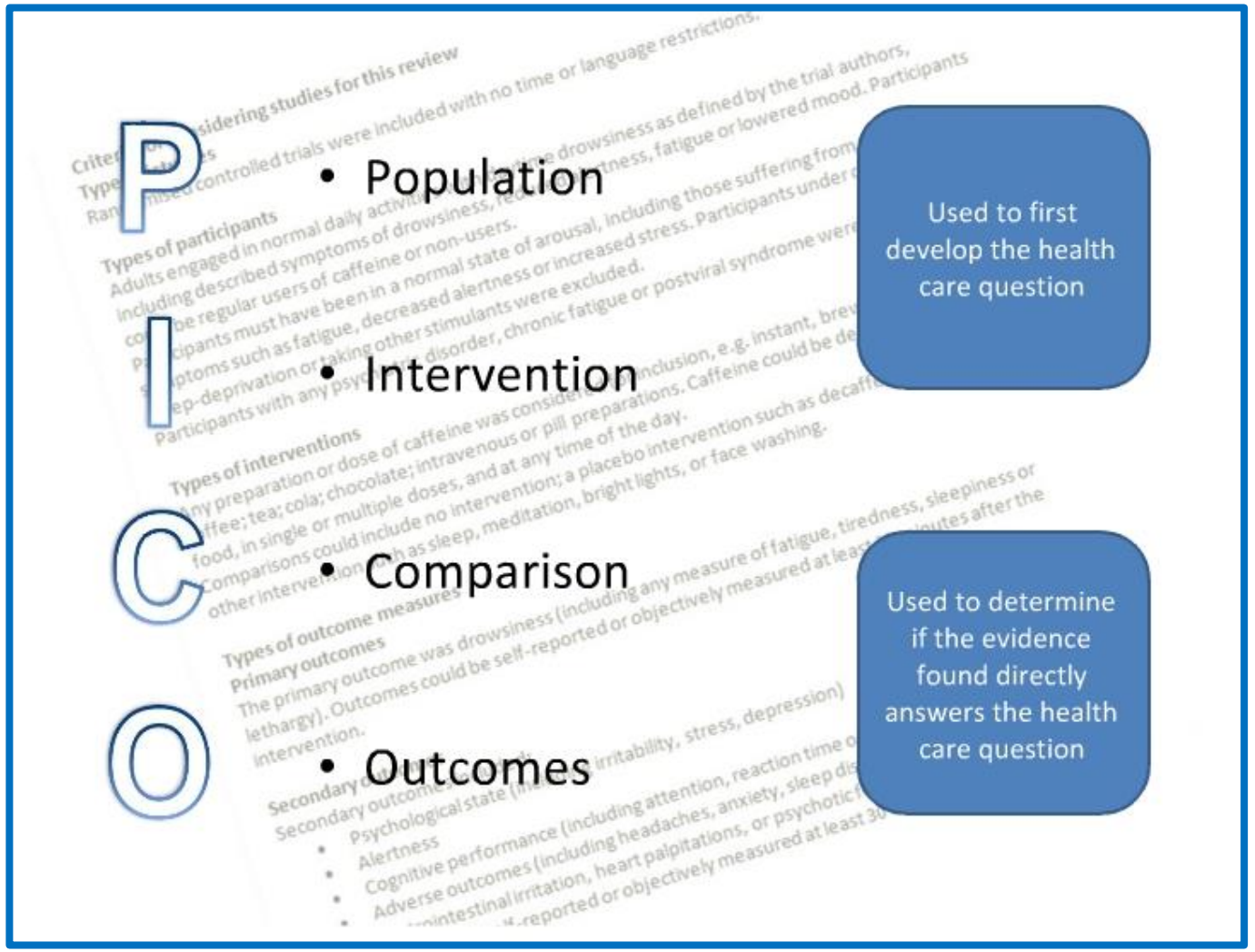
  Esempi:

  - **Quesito sostanzialmente irrilevante**
  - **Rapporto rischi-benefici ingiustificato**
  - **Domanda di *non-inferiorità* ingiustificata**
  - ***Interruzione* dello studio ingiustificata**

'Virtù e la Legge' (Particolare, La Virtù), Raffaello Sanzio, 1511-15, Musei Vaticani, Roma

Lettura di un Trial: P.I.C.O.

Un trial clinico non dovrebbe essere *letto così com'è*, ma avendo come riferimento uno specifico quesito di particolare interesse.



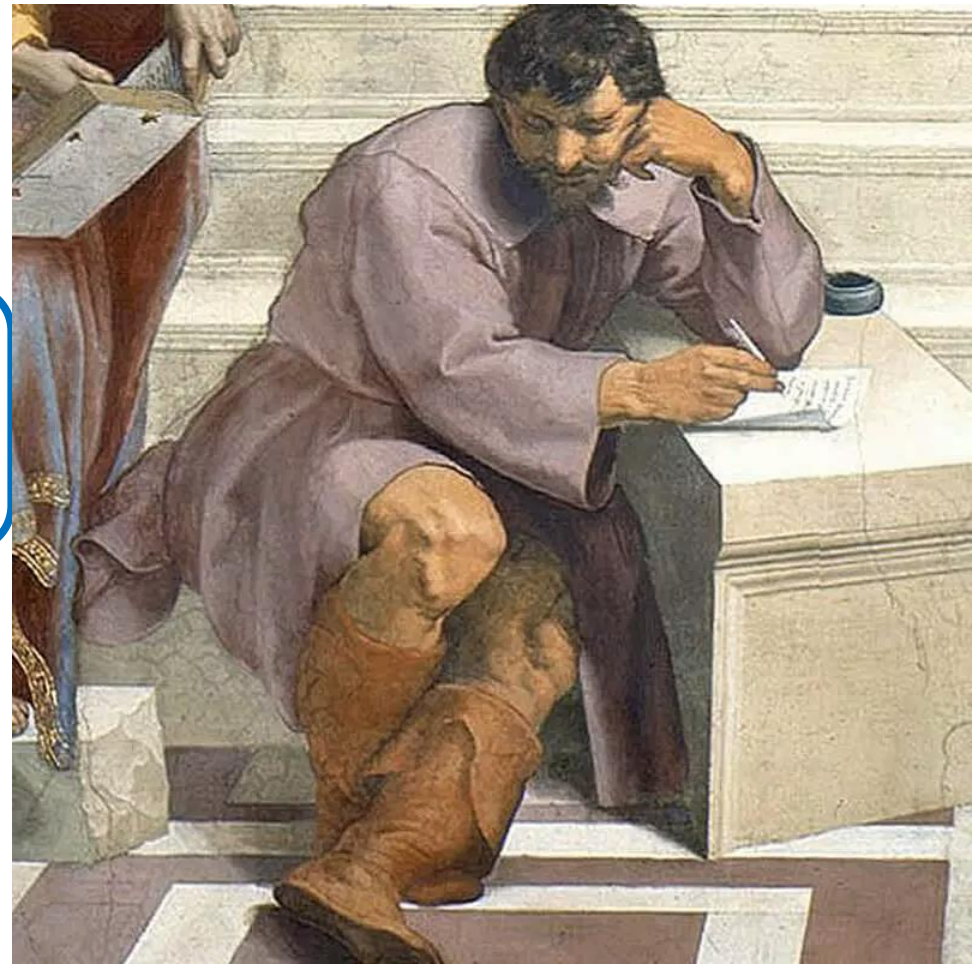
Courtesy of Pappagallo G.

Topics

- Quesito Clinico di Riferimento

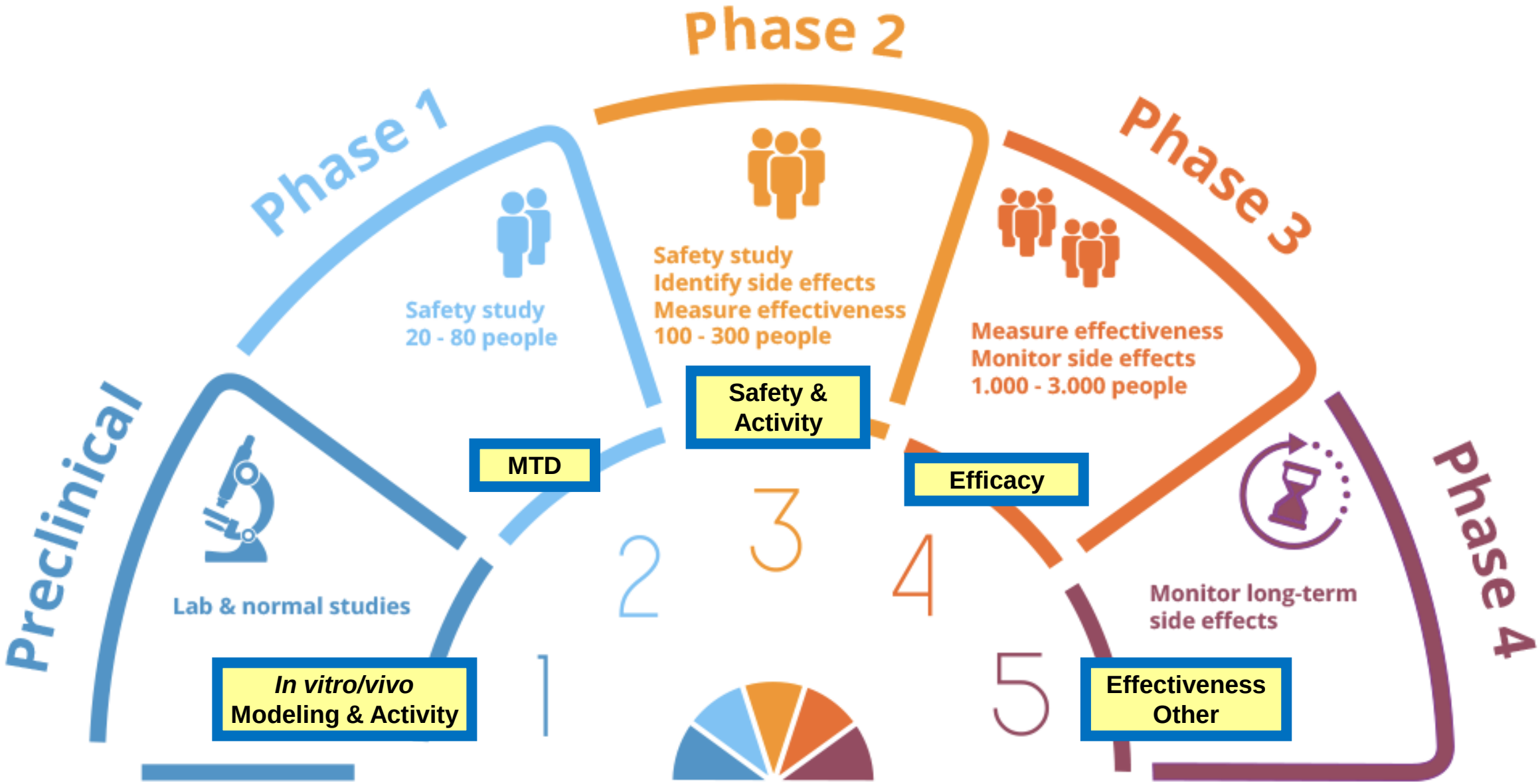
- **Fasi della Sperimentazione Clinica**

- Disegni di Studio Osservazionali ed Interventistici



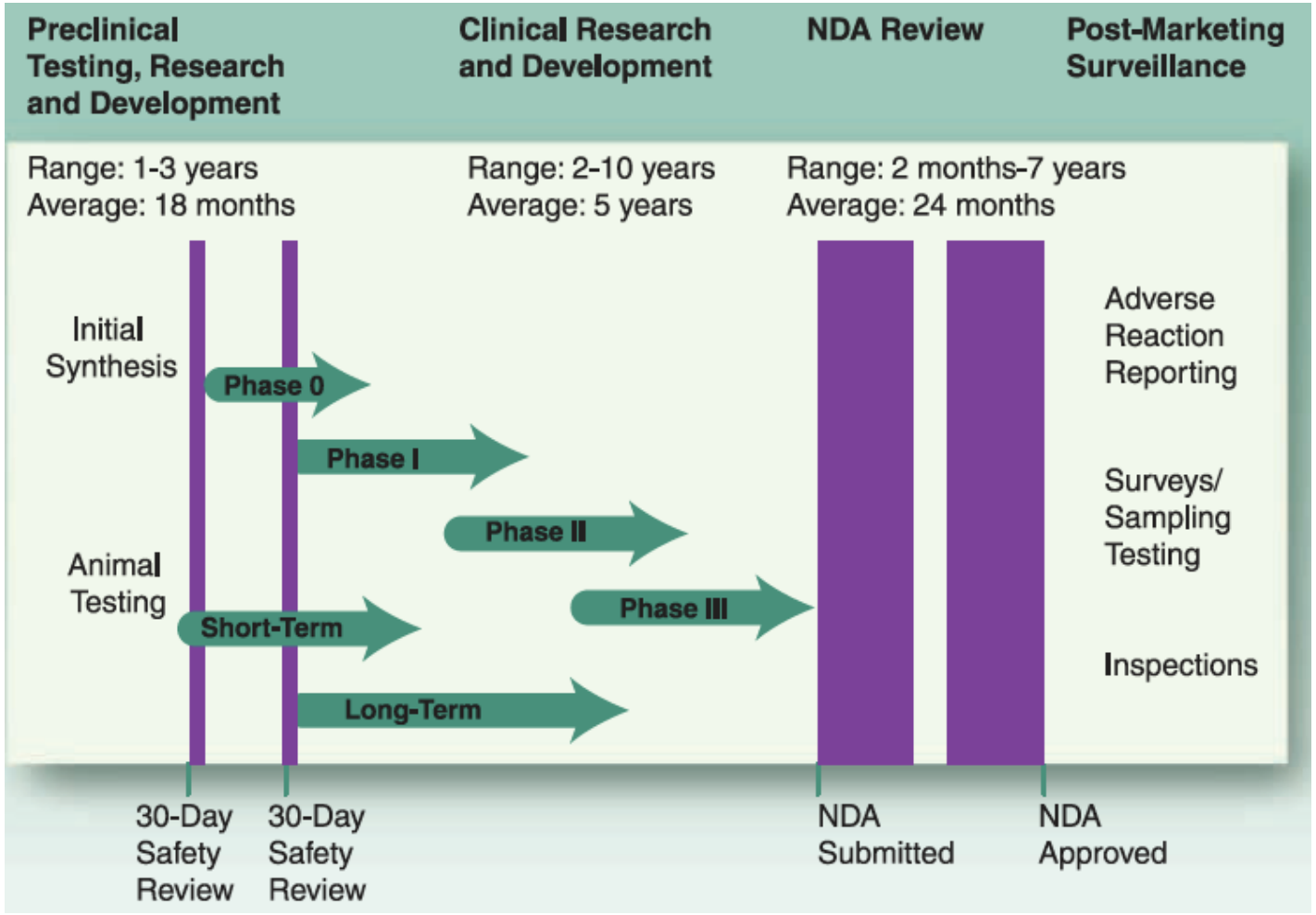
‘La Scuola di Atene’ (Particolare, Michelangelo), Raffaello Sanzio, 1509-1511, Musei Vaticani, Roma

Traditional Drug Developmeng according to Phases & Aims



'*Average*' Duration of Drug Development Process

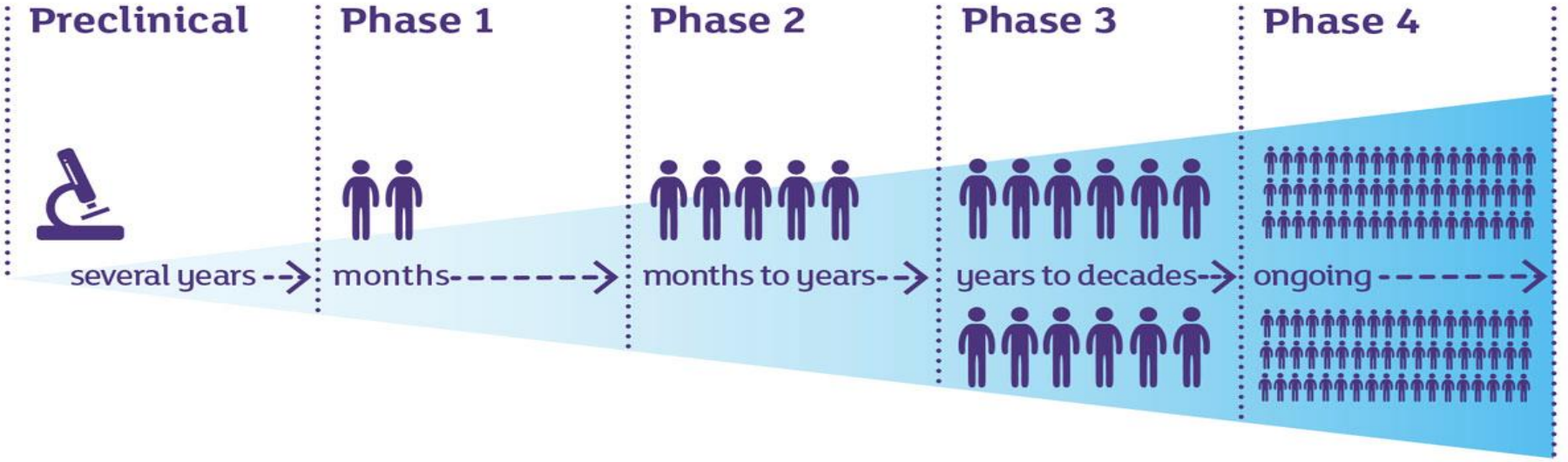
Phase I	What is a safe dose to give for the NEW treatment and with what toxicities?	Dose Toxicities
Phase II	**Is the efficacy of the NEW treatment worthy of direct comparison to STANDARD treatment in the phase III setting?**	**Early efficacy measure E.g. response, 6-month PFS**
Phase III	How does the NEW treatment compare to STANDARD treatment in terms of efficacy?	Survival time

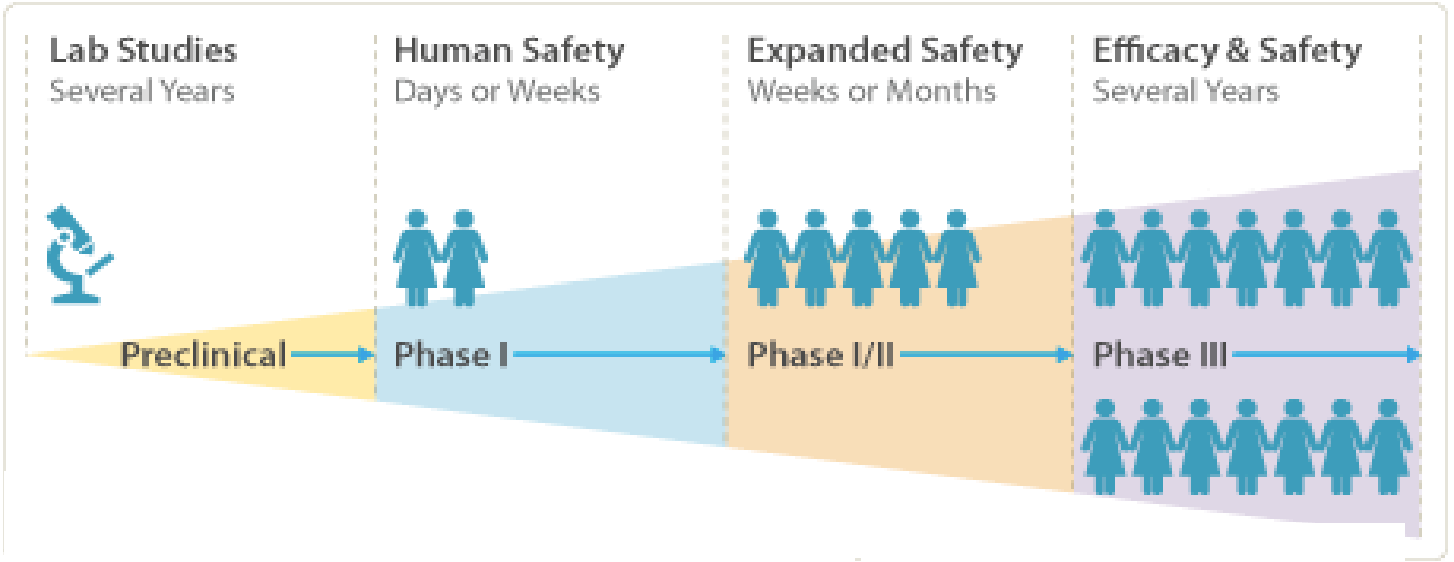


Courtesy of Billingham C, 2008

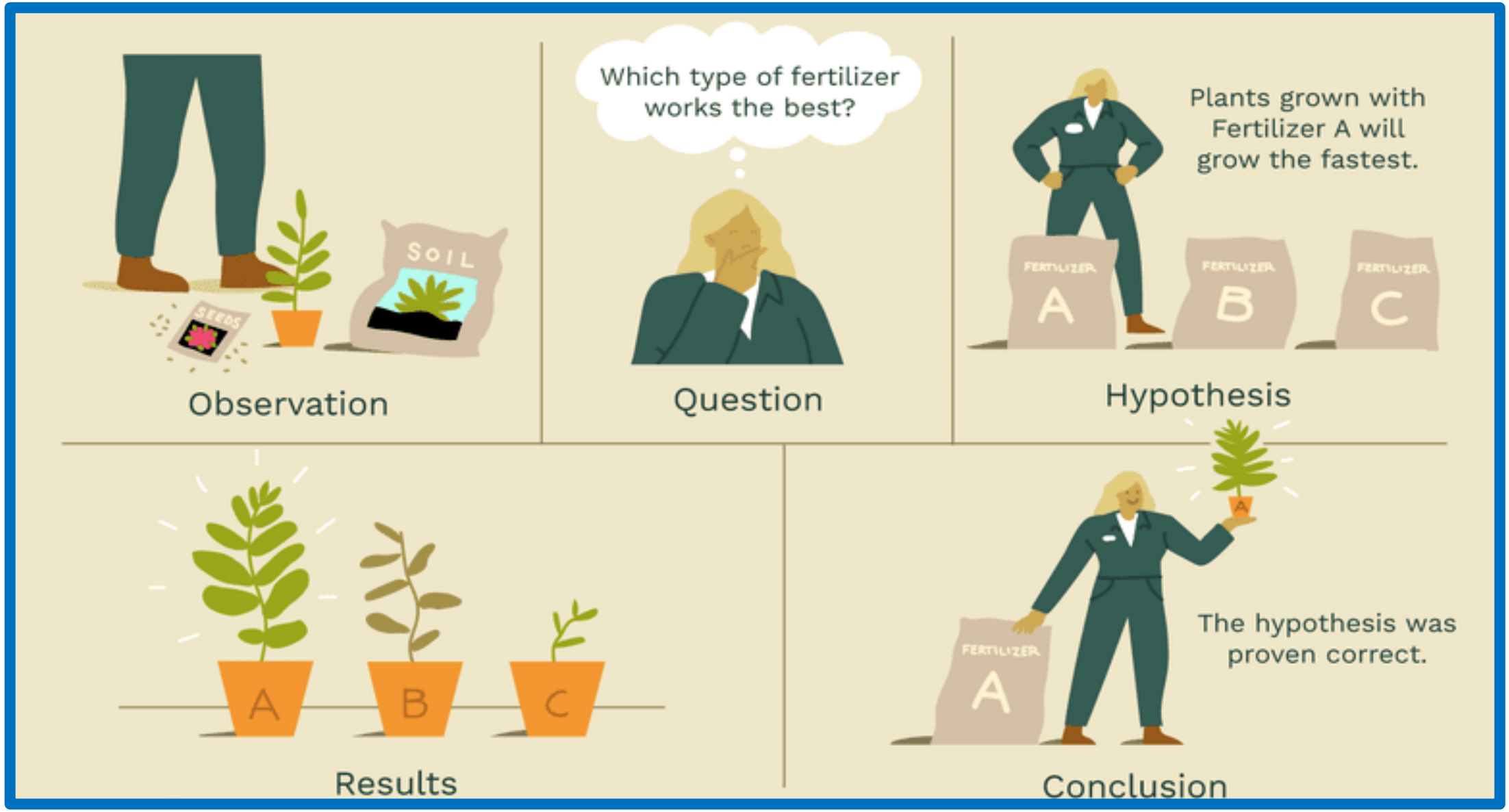
Eliopoulos H et al, Clin Cancer Res 2008

'*Average*' Duration of Drug Development Process





Steps of the Scientific Method



Clinical Trials Methodology

- Objectives/aims of clinical studies are:
  - **–Phase I**
  - –Phase II
  - –Phase III

Clinical Trials Methodology: Topics of Phases

Phase	Objectives and Aims	Subjects	Focused on
I	Pharmacokinetics Safety	Healty Subjects Patients	DRUG
II	Activity Safety	Patient	DISEASE
III	Efficacy	Patients	INDIVIDUAL PATIENT

The Role of ‘Early’ phases (I-II) is CRUCIAL !

- **After preclinical, in the 1-3 yrs of drug development, you can:**
  - **Easily control drug effect**
  - **Monitor either biological and clinical action**
  - **Identify the ‘REAL’ target (if present!)**
- **When the drug enters phase III, only early stopping can be applied (with all related concerns….)**

‘Profeta Isaia’, Raffaello Sanzio, 1511-12, Sant'Agostino in Campo Marzio, Roma

Phase I: *Definition & Pre-requisites*

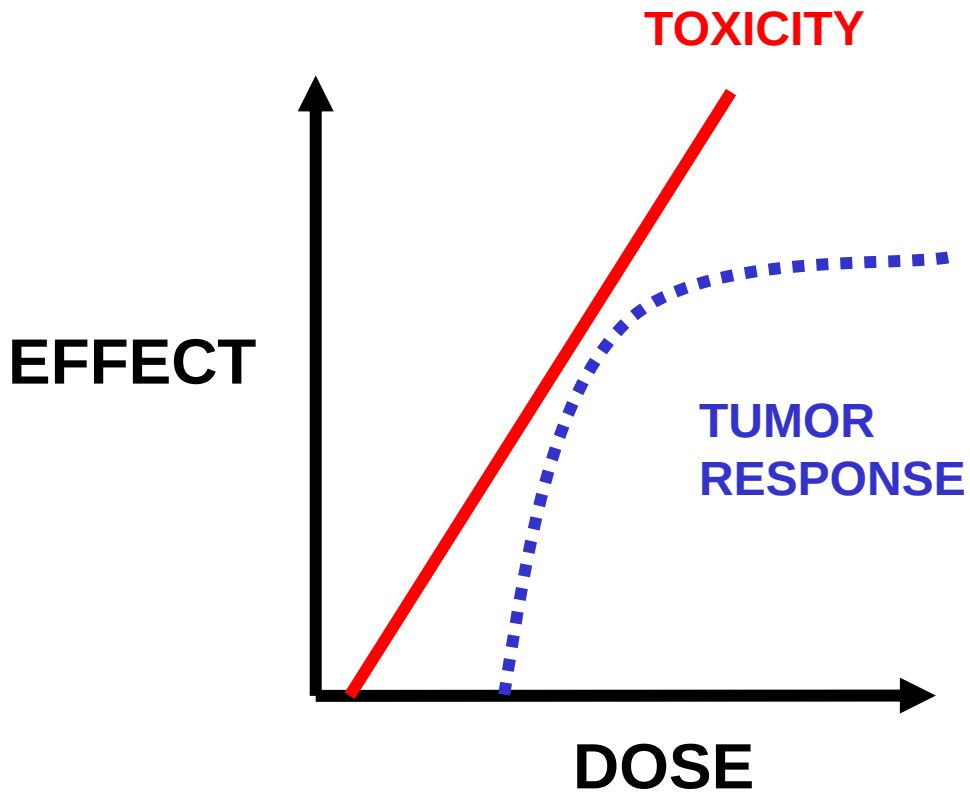
- **1st evaluation of a new cancer therapy in humans**
  - ***Dose-escalation studies***
  - **First-in-human single agent study**
  - **Combination of novel (or approved) agents**
  - **Combination of novel agent and radiation therapy**
- **Which agents deserve to enter Phase I?**
  - **It is *biologically plausible* that the agent may have activity in cancer (target seems valid and agent affects it)**
  - **Preclinical or other evidence of efficacy**
  - **Reasonable expectation of safety (toxicology)**
  - **Sufficient data on which to base a starting dose**

Phase I Trials : Endpoints/Objectives?

- **Primary**
  - **Identify the maximally tolerated dose (MTD) and recommended Phase II dose (RP2D)**
    - ***MTD = level @ DLT (in Europe or Japan)***
    - ***MTD = level below DLT (in US)***
  - **Identify dose-limiting toxicities (DLTs)**
    - ***Unacceptable toxicities for severity/duration, which limit further dose escalation***
- **Secondary**
  - **Pharmacokinetics (PK)**
  - **Pharmacodynamics (PD)**

‘Old-Style’ cytotoxics: Dose-Effect model

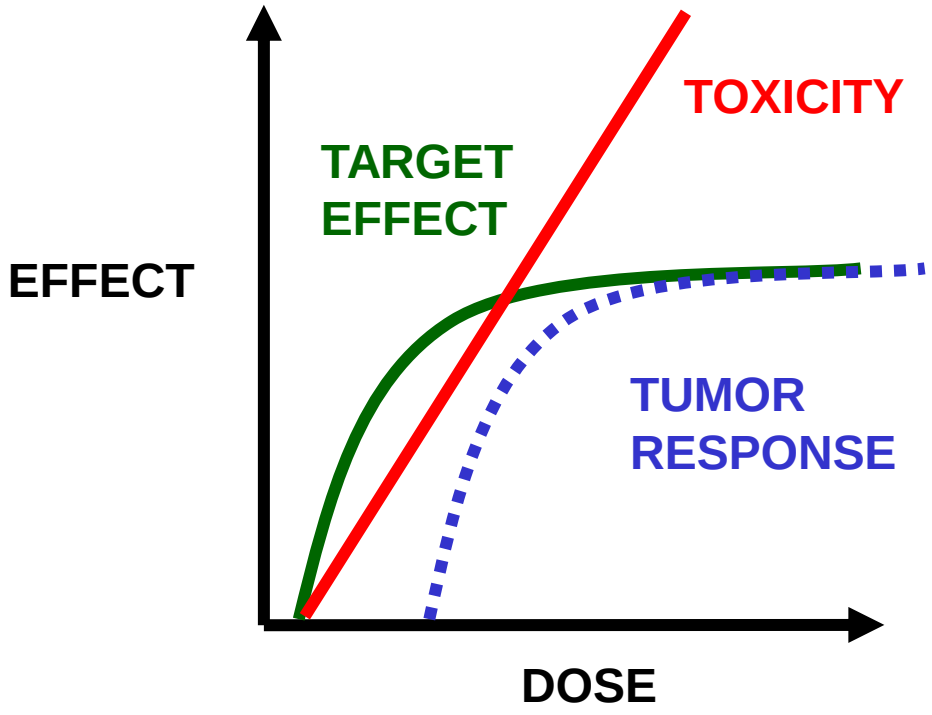
Aim of Phase I: MTD (maximum tolerated dose)

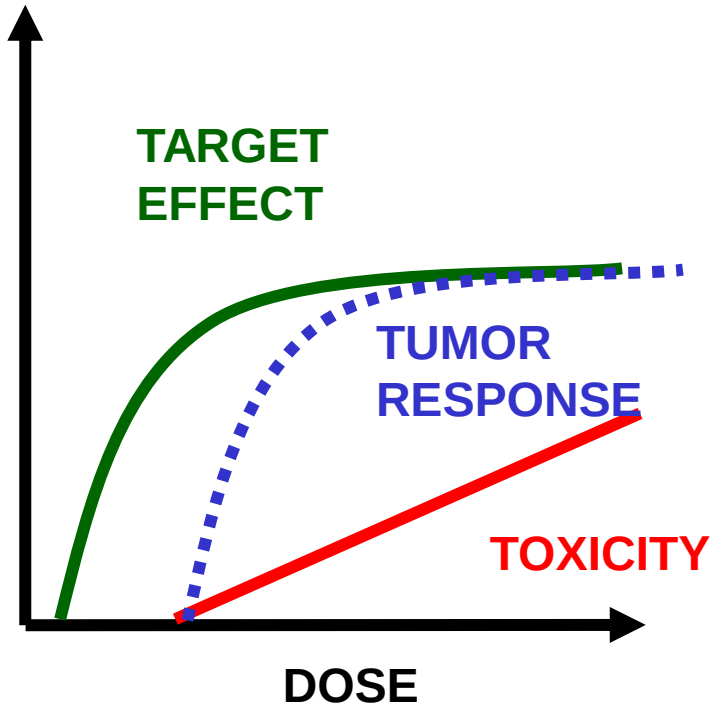


- **Usually have *a direct correlation* between dose and toxicity**
- **Over a threshold, *toxicity limits activity***
- **Phase I aims to find out MTD as conducive to the highest efficacy**

Targeted Agents: Is Dose-Effect model Reliable?

<u>Aim of Phase I</u>: MTD or MTID (minimum target-inhibiting dose)?



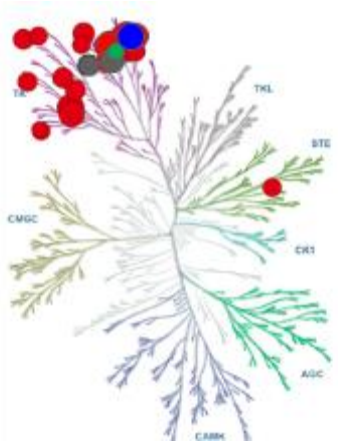


DrugSpecificity: **<u>LOW</u>** **<u>HIGH</u>**

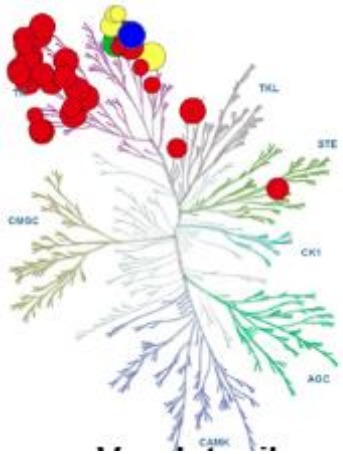
More Selective *RET* Multikinase Inhibitors for *RET*-Rearranged NSCLC

- RET
- KDR/VEGFR2
- FGFR1-3/EGFR
- MET/ALK/ROS
- Other kinases

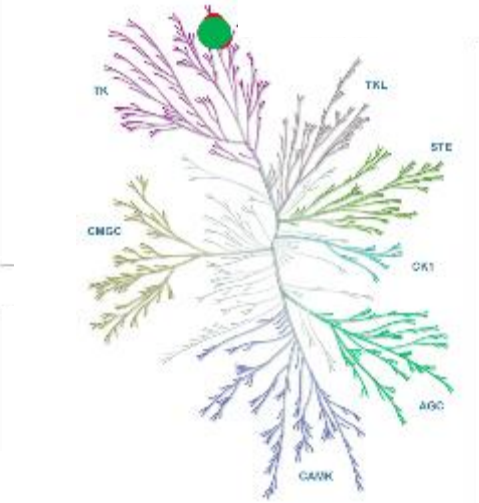
Cabozantinib



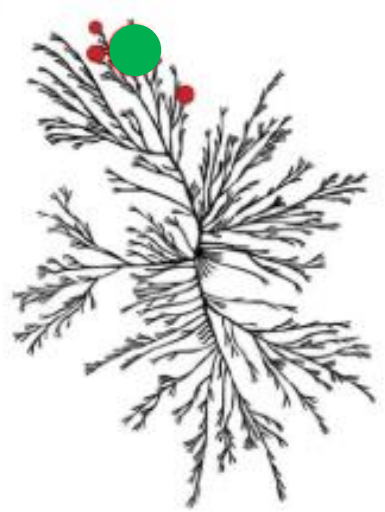
Vandetanib



Selpercatinib (LOXO-292)



Pralsetinib (BLU-667)



Agent	Cabozantinib	Vandetanib	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
IC_{50} RET, nM*	11	4	3	0.4
ORR, %	37	18	68	58
▪ CR	5	0	2	1

*Cell free.

Velcheti. WCLC 2017. Abstr OA 12.07. Gautschi. JCO. 2017;35:1403. Drilon. WCLC 2019. Abstr PL02.08. Gainor. ASCO 2019. Abstr 9008. Rahal. AACR 2017. Abstr B151. Solomon. J Thorac Oncol. 2020;15:541.

Phase I Study Basic Design Principles

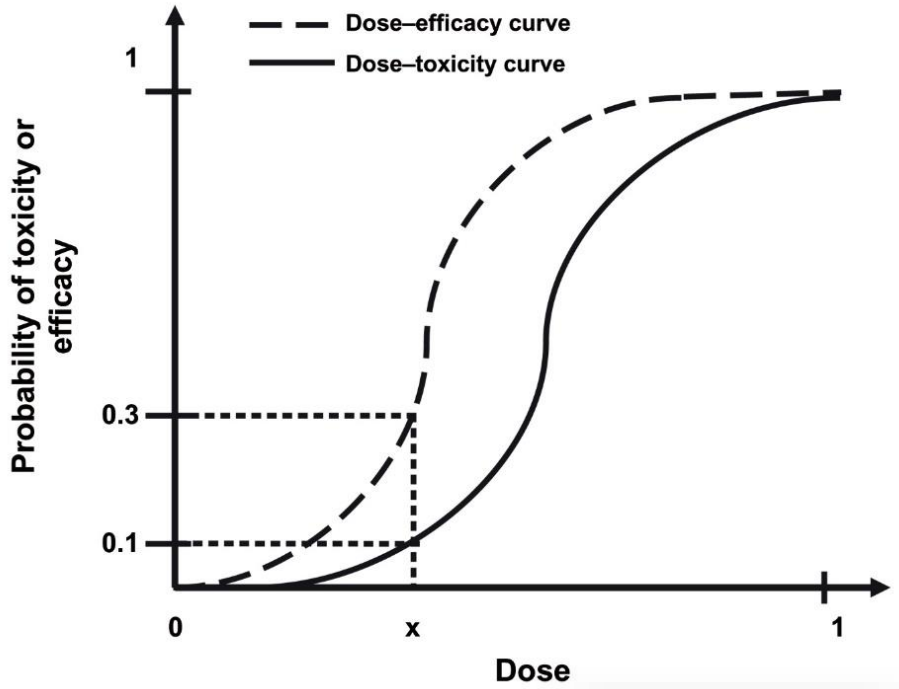
- **Define a recommended dose (*dose-escalation context*):**
  - **SAFELY (minimum # of serious toxicities)**
  - **EFFICIENTLY (smallest possible # of pts)**
  - **RELIABLY (high statistical confidence)**

!SAFETY TRUMPS EVERYTHING ELSE!

- **Start with a safe dose**
  - ***1/10th of the LD10 in rodents, or 1/3rd of the minimal toxic dose in large animals expressed as mg/m^2***
- **Minimize # of pts treated at sub-toxic/therapeutic doses**
- **Escalate dose rapidly in the absence of toxicity**
- **Escalate dose slowly in the presence of toxicity**
- **Expand patient cohort at recommended phase II dose**

Dose Escalation Methods

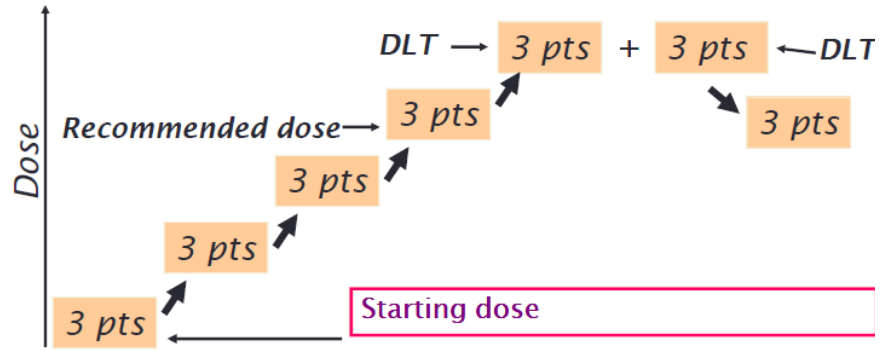
- **Rule-Based Designs**
  - **Traditional 3+3 Design**
  - **Accelerated Titration Design**
  - **Pharmacologically Guided Dose Escalation**
- **Model-Based Designs**
  - **Modified Continual Assessment Method**



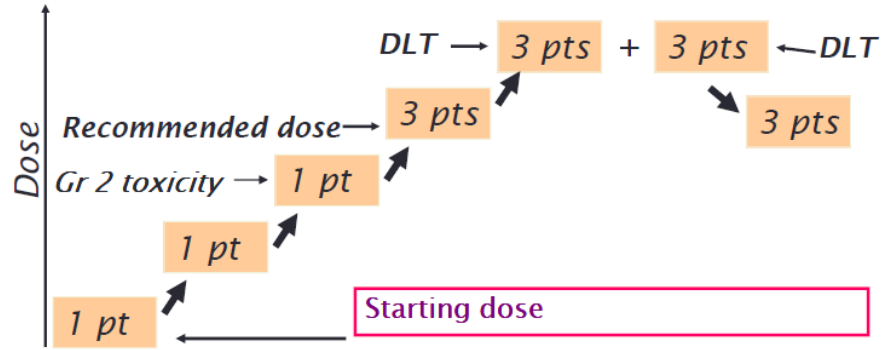
"Escalation in decreasing steps" , L. Fibonacci, 13th century

Le Tourneau C, et al. JNCI 2009

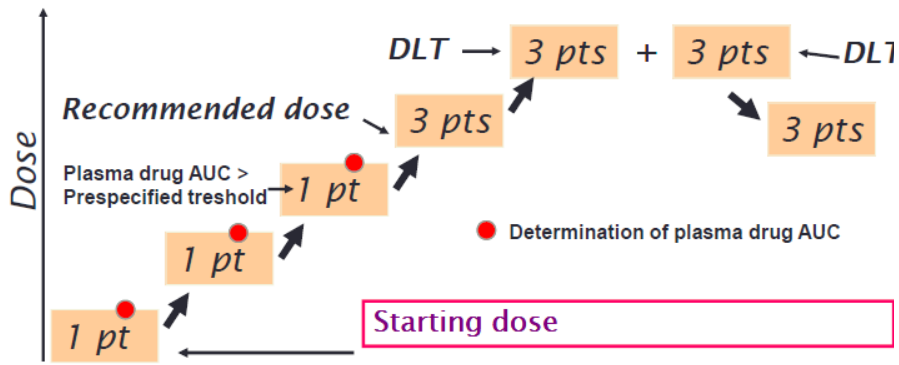
Phase I "Standard" 3 + 3 Design



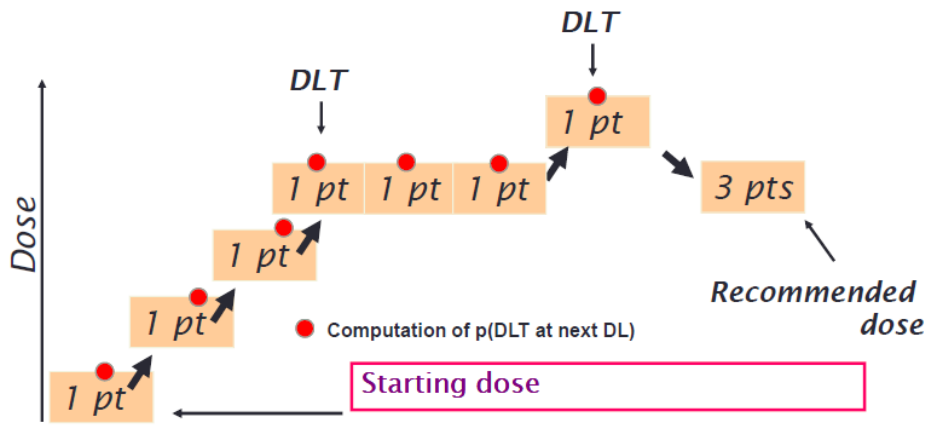
Accelerated Titrated Design



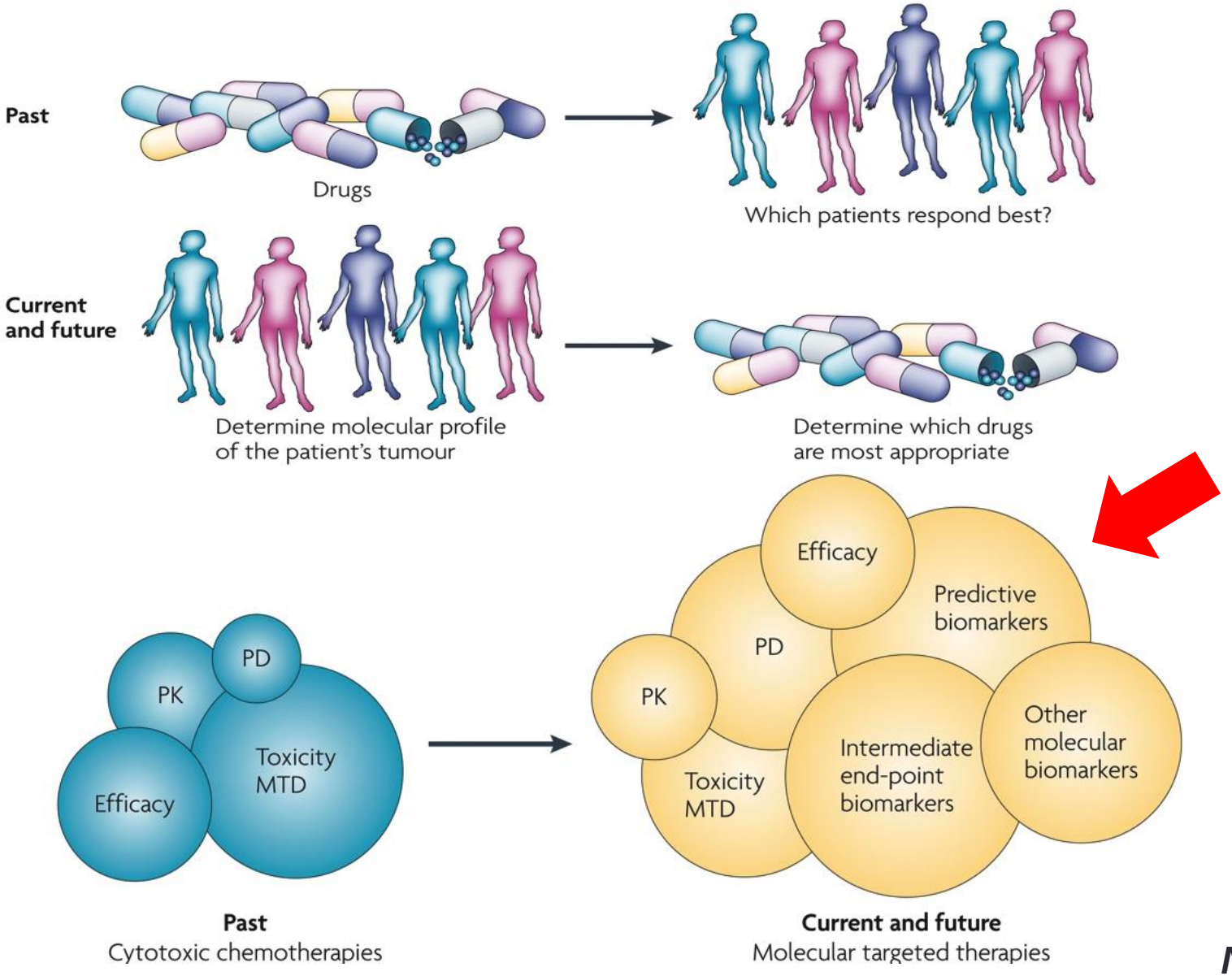
Pharmacologically Guided Dose Escalation



Model-Based Phase I Design: Modified Continual Assessment Method



Phase Is: A Changing Paradigm Overtime



Yap TA, et al.
Nat Rev Cancer 2010

Predictive Biomarkers

Together with corresponding PK data should confirm target modulation and help to identify the *biologically active dose range*

- **Advantages**
  - **Decrease the number of patients receiving ineffective treatments**
  - **Minimize the need for retrospective subgroup analysis in later phase trials**
- **Drawbacks**
  - **Might not be applicable to broad-spectrum inhibitors**
  - **Regulatory issues**
  - **Difficulties in recruiting**
  - **Potential benefit in unselected population could be missed - prevalence**

Recent examples:

- EML4-ALK fusion – ALK/MET inhibitors *Crizotinib, Alectinib, other*
- V600E BRAF mutation – BRAF inhibitor *(Dabrafenib + Trametinib)*

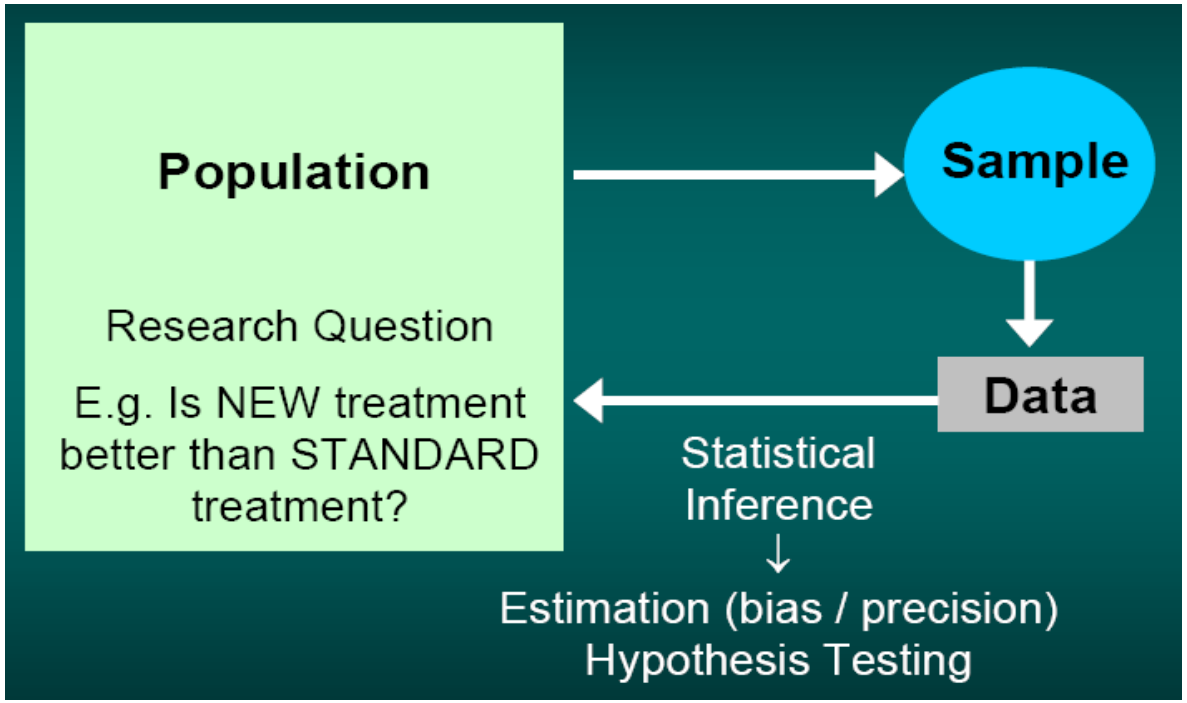
Clinical Trials Methodology

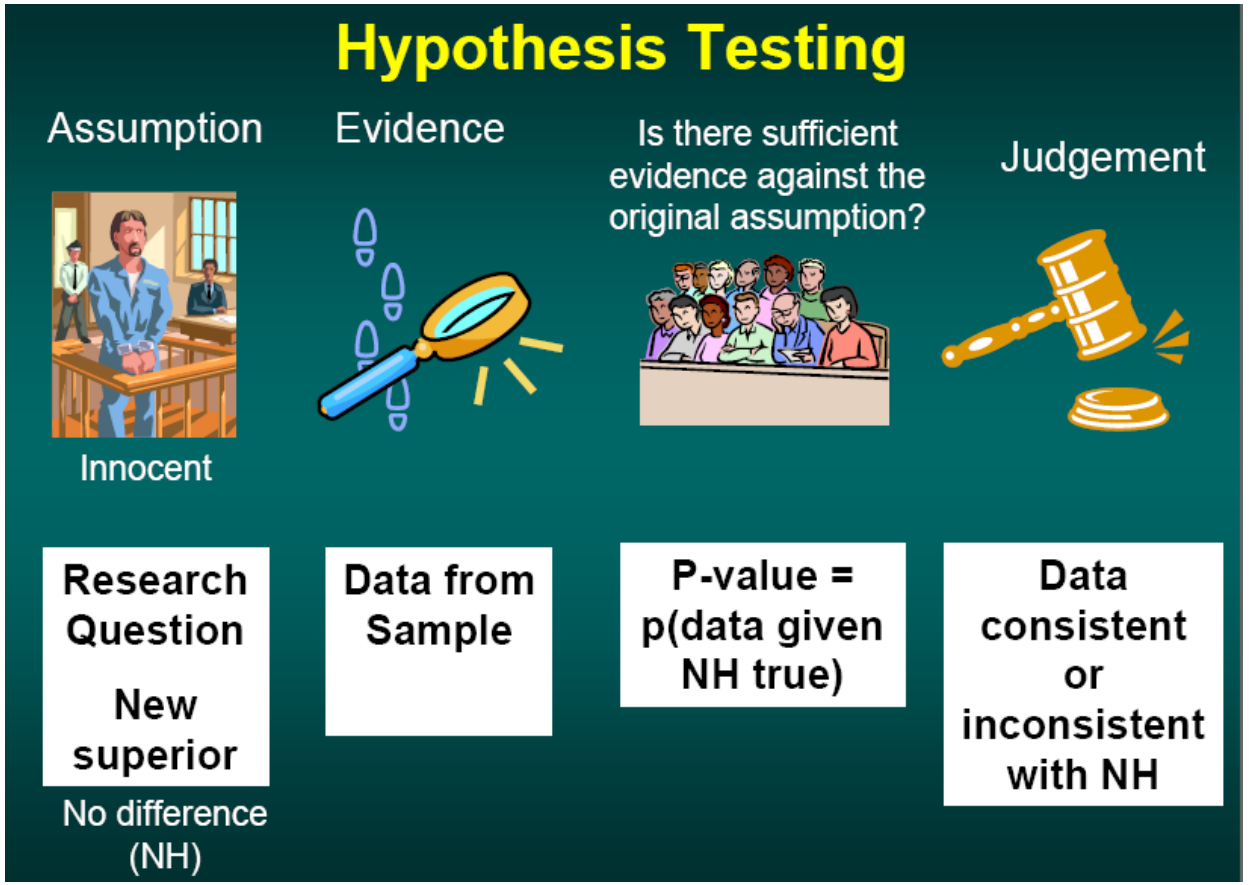
- Objectives/aims of clinical studies are:
  - –Phase I
  - **–Phase II**
  - –Phase III

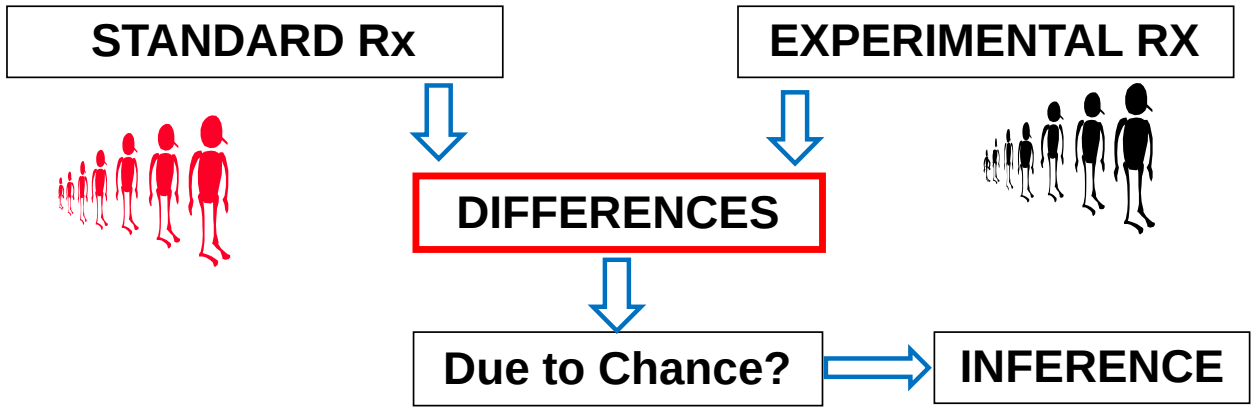
Clinical Trials Methodology: Topics of Phases

Phase	Objectives and Aims	Subjects	Focused on
I	Pharmacokinetics Safety	Healty Subjects Patients	DRUG
II	**Activity** **Safety**	**Patients**	**DISEASE**
III	Efficacy	Patients	INDIVIDUAL PATIENT

Why Do We Need Statistics?







Aim of Statistical Analysis: Search for the Truth!

Courtesy of Billingham C, 2008

What do we assess in clinical trials?

- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[Phase IV?]**

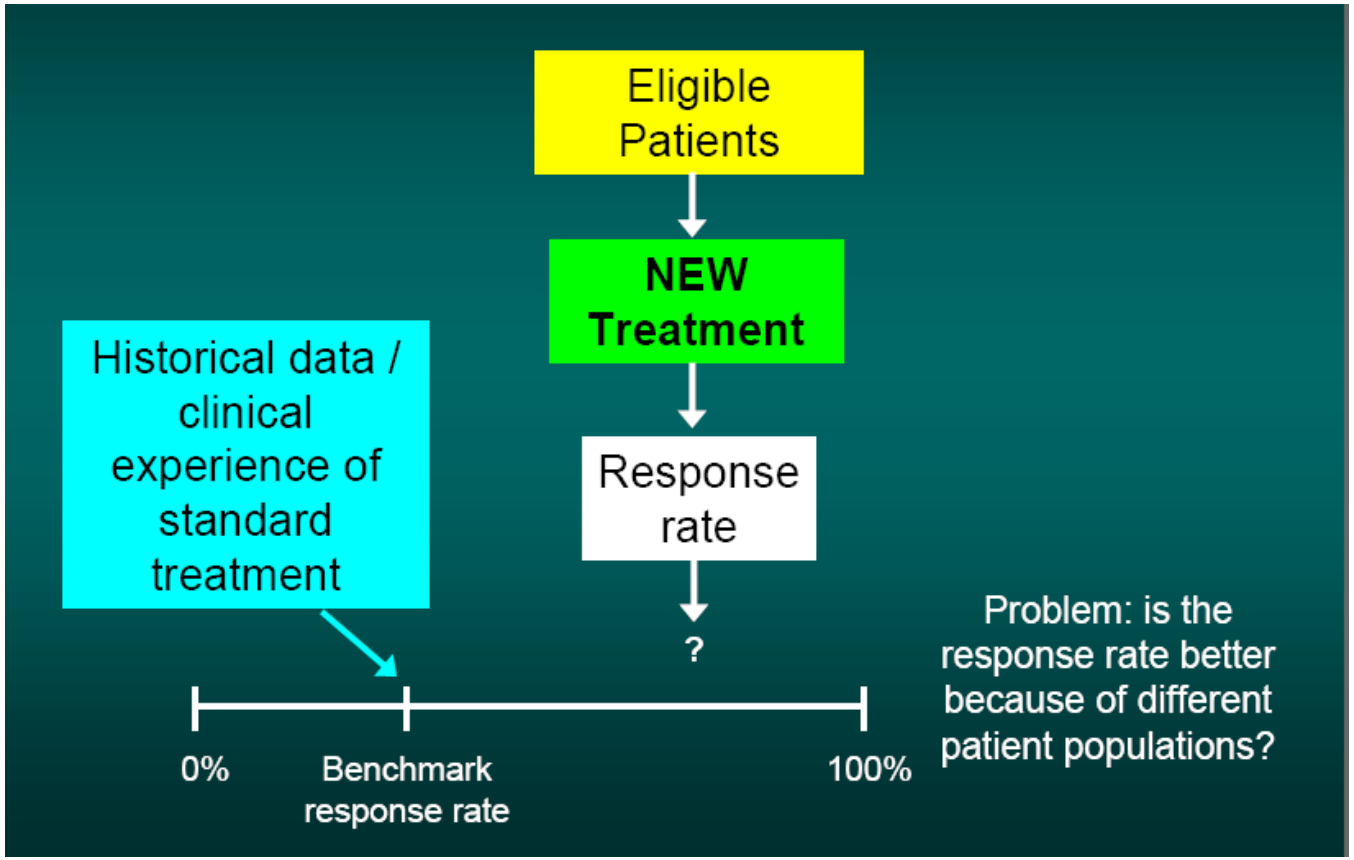
Attività *vs.* Efficacia

Trattamento	Attività	Efficacia
Diuretico	Riduzione P.A.	Riduzione Malatt. C.V.
Antidiab. Orale	Riduz. Glicemia	Riduz. Mortalità
A.Infiammat.	Az. A.Aggregante	Riduzione Malatt. C.V.
Citotossico	Riduz. Tumorale	Riduz. Mortalità
Citostatico	Controllo Malattia	Riduz. Mortalità
Fatt. Di Crescita	Stimolo Crescita	Riduz. Complicanze

Courtesy of Pappagallo G.

Single-Arm Phase II: Pros and Cons

Single-Arm Phase II Study



Setting the Bar in Phase II Studies

Citation of historical data	Number	Conclusions		Results	
		Unclear	Clear	Reject alternative (agent not worthy of further study)	Reject null (agent worthy of further study)
No historical data cited	32	3	29	6 (21%)	23 (79%)
Historical data cited					
Did not meet criteria	29	2	27	4 (15%)	23 (85%)
Met criteria	9	0	9	6 (67%)	3 (33%)

- **Studies that met the criteria for appropriate citation of prior data were significantly less likely to reject the null (33%) than those cited that did not meet the criteria (85%) *p=0.006***

Courtesy of Billingham C, 2008

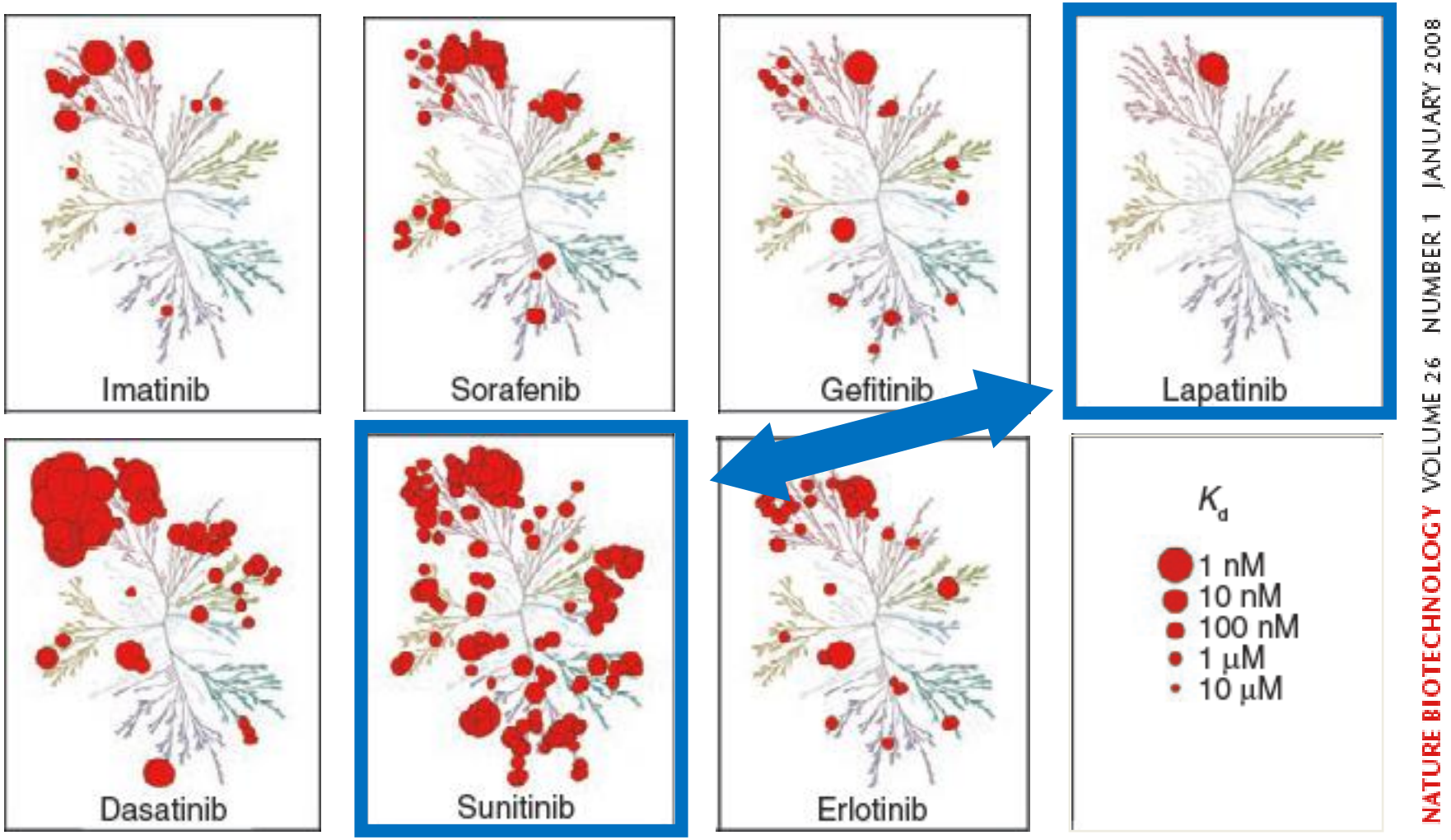
Vickers AJ et al, Clin Cancer Res 2007

Targeted Agents – 'MYTHS'

1. **Conversely to Classical cytotoxics, Targeted agents selectively hit a specific molecule/enzyme**
   - **their functional/clinical effects are directly related to the level of target inhibition**
2. Targeted agents are 'cytostatic' in nature:
   - they will slow down growth, but seldom shrink pre-existing tumor masses

Modified - Courtesy of Milella M, ESMO 2008

‘Targeted’ agents, particularly ATP-competitive kinase inhibitors, frequently hit multiple targets



NATURE BIOTECHNOLOGY VOLUME 26 NUMBER 1 JANUARY 2008

Modified - Courtesy of Milella M, ESMO 2008

Targeted Agents – ’MYTHS’

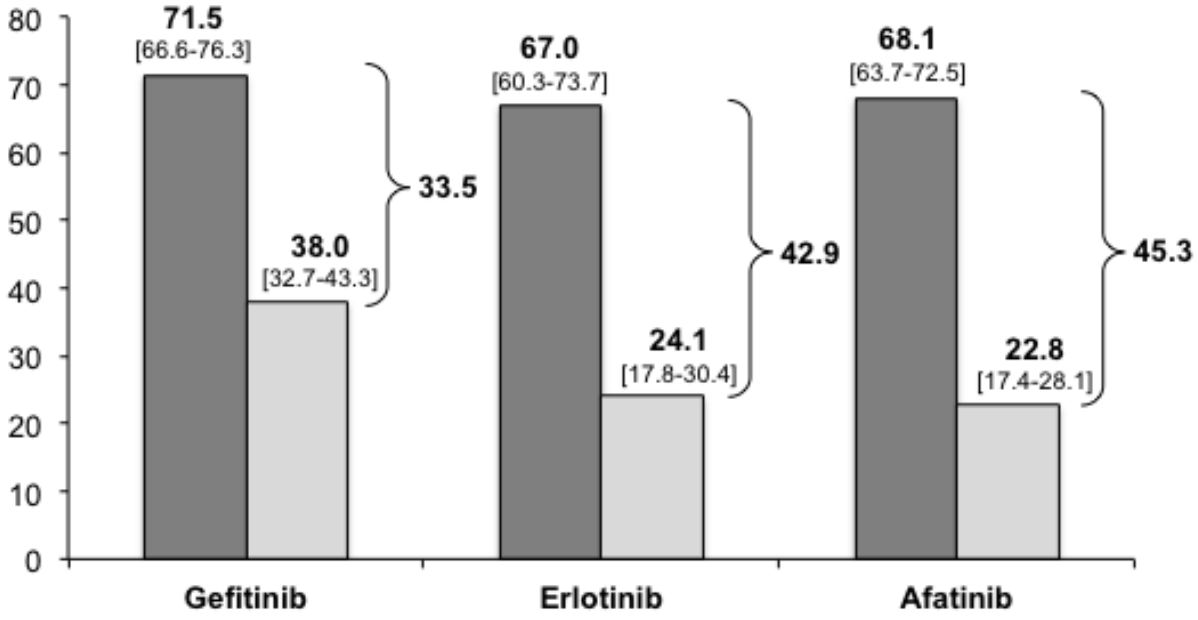
1. Conversely to Classical cytotoxics, Targeted agents selectively hit a specific molecule/enzyme
   - their functional/clinical effects are directly related to the level of target inhibition

2. **Targeted agents are ‘cytostatic’ in nature:**
   - **they will slow down growth, but seldom shrink pre-existing tumor masses**

Modified - Courtesy of Milella M, ESMO 2008

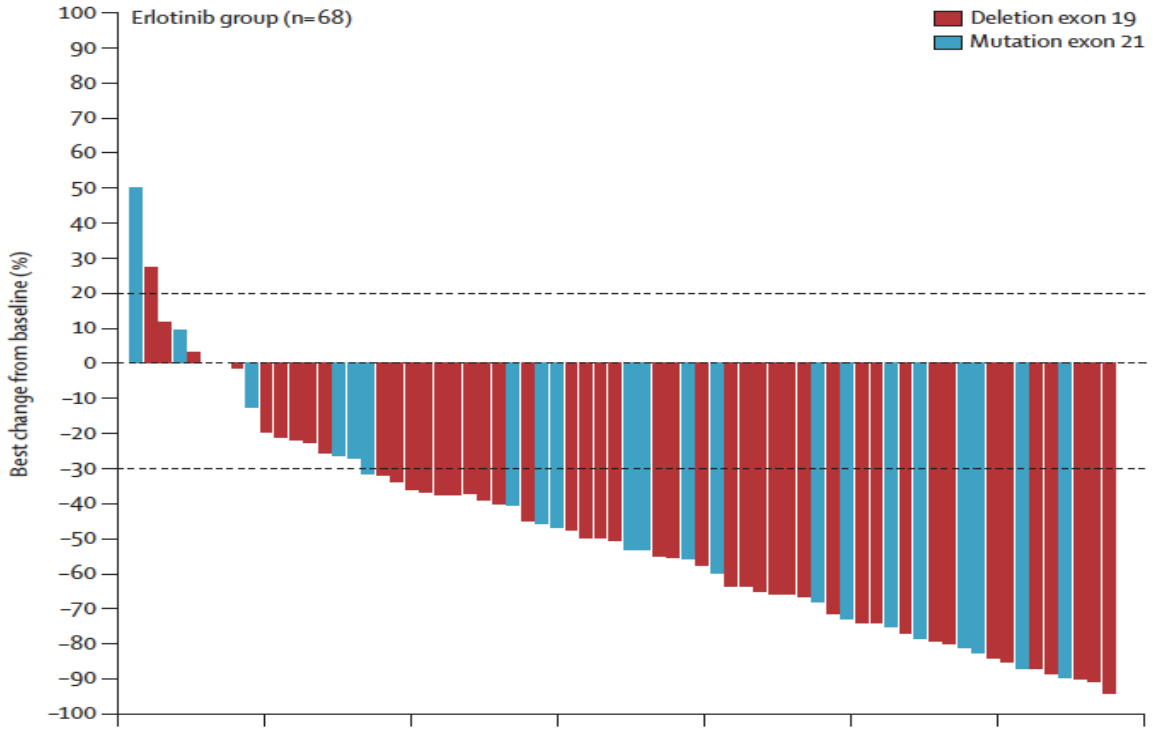
EGFR De-addiction as a treatment goal!

Overall Activity
(Overall Response Rate (ORR), RECIST)
RCTs of TKIs *vs.* Firs-Line Chemo



Pilotto S et al, Crit Rev Oncol Hem 2014

Example: EURTAC (Erlotinib *vs.* Chemo)
Watefall Plot



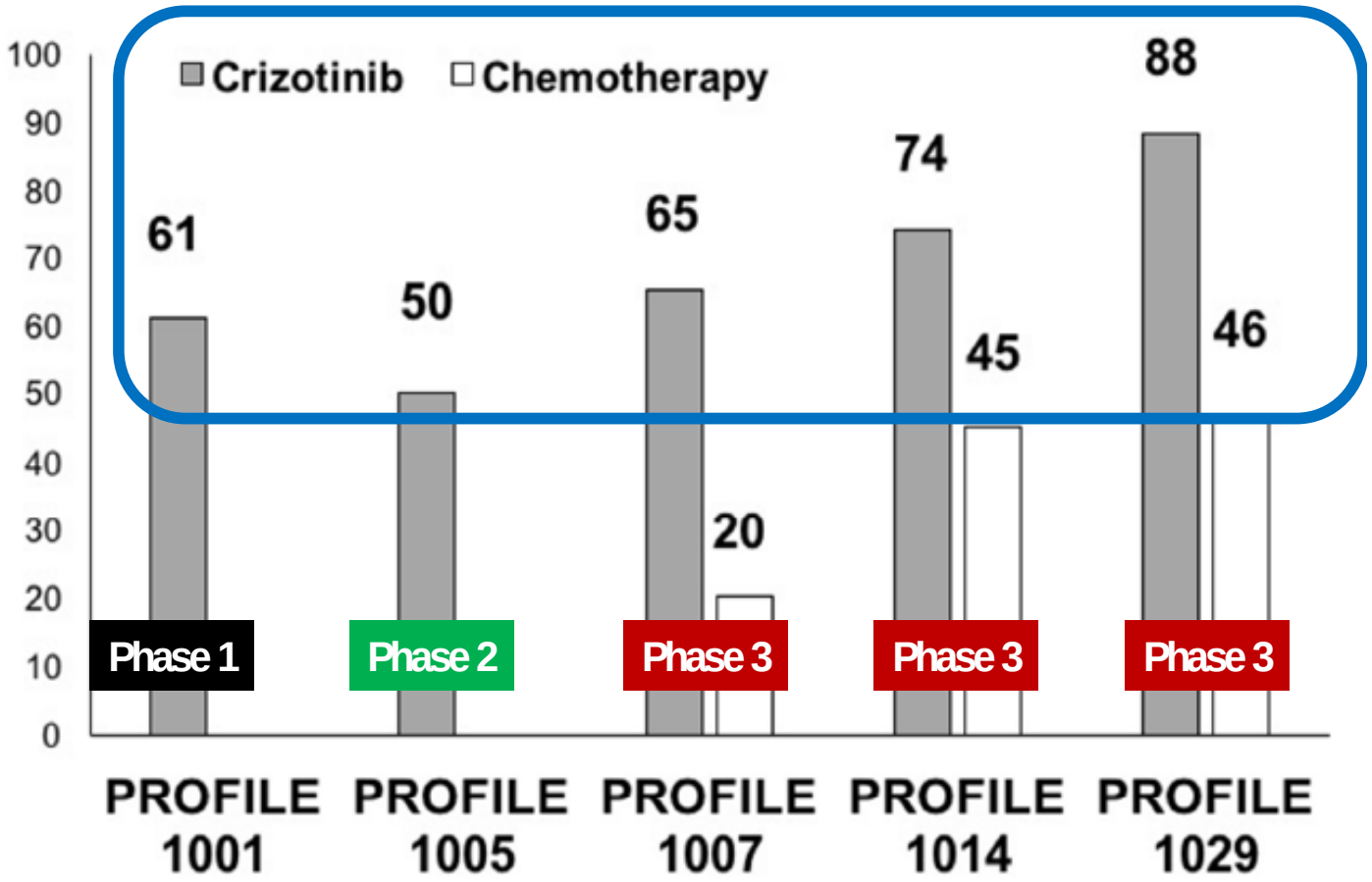
Rosell R et al, Lancet Oncol 2012

Definition of DE-ADDICTION: less than 10% of primary resistance

Besse B, WCLC 2017

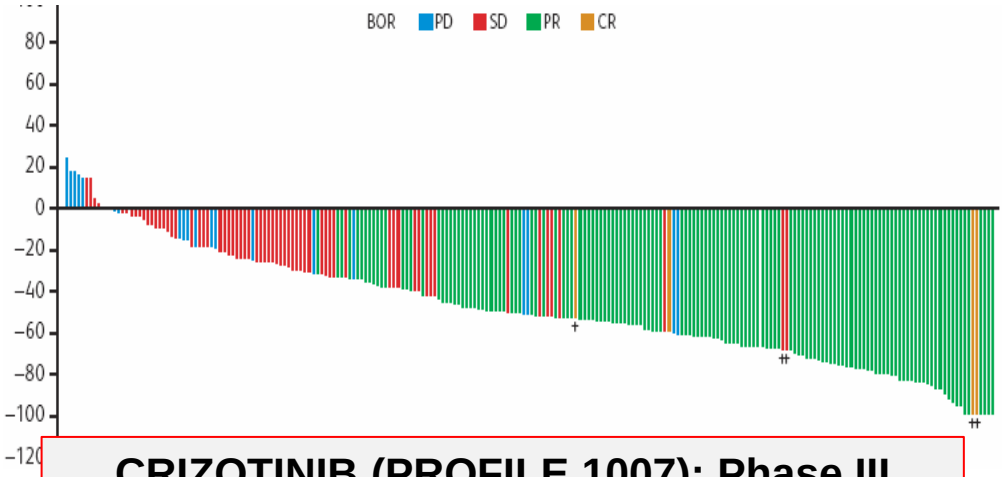
ALK De-addiction as a treatment goal!

Consistent Activity of Crizotinib (ORR) Across Developmental Phases (from Phase 1 to 3)

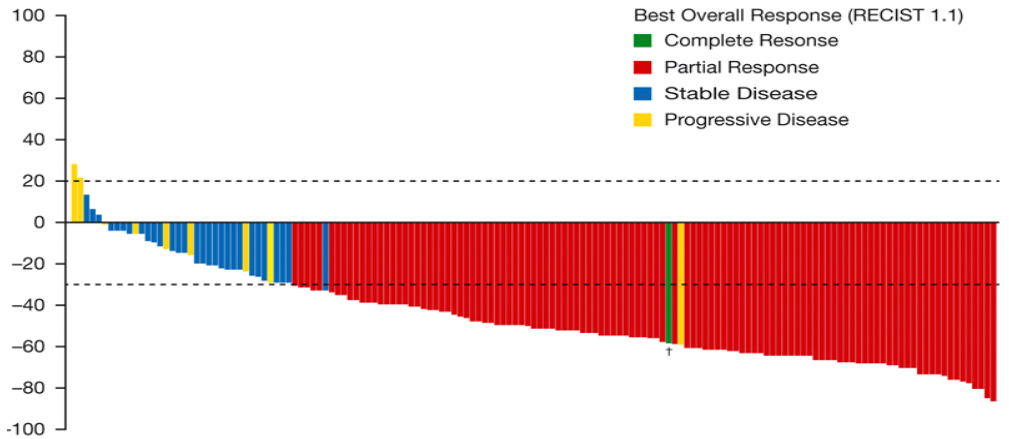


Caccese M et al, Exp Opinion Pharm 2016

CRIZOTINIB (PROFILE 1005): Phase II



CRIZOTINIB (PROFILE 1007): Phase III



Kim et al, ASCO 2014, Blackhall F et al, ESMO-Open 2018
Shaw A et al, NEJM 2013

Relationship between Blood Biomarkers and Activity: BFAST

- Unresectable, stage IIIB or IV NSCLC
- *ALK*+ by centralised blood screening only
- Treatment naïve
- ECOG PS 0–2

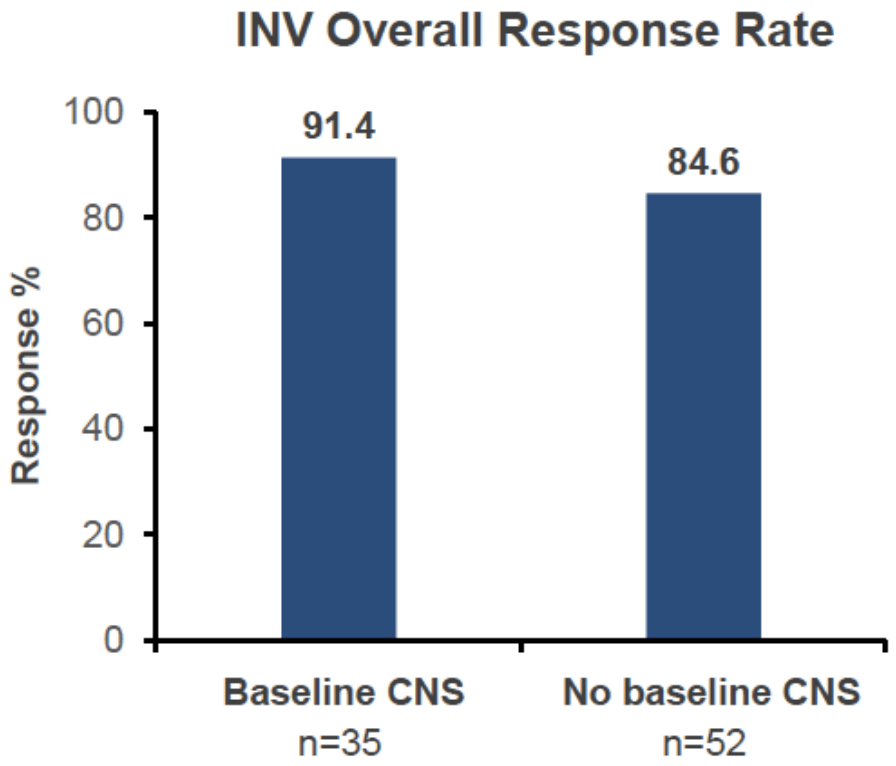
→ **Alectinib 600mg BID** → **Until PD, toxicity, withdrawal or death**

Primary endpoint
Confirmed ORR by investigator

Exploratory endpoint
Confirmed ORR by investigator for patients with baseline CNS metastases

- 83.9% — N=73 ***EML4***
- 3.4% — N=3 **Not identified**
- 2.3% — N=2 ***CLIP4***
- 1.4% — N=1 ***ERCC8*** ***DCTN1*** ***STRN*** ***ETV6*** ***AAK1*** ***TMEM178*** ***KIF5B*** ***PGM2*** ***EPS8***

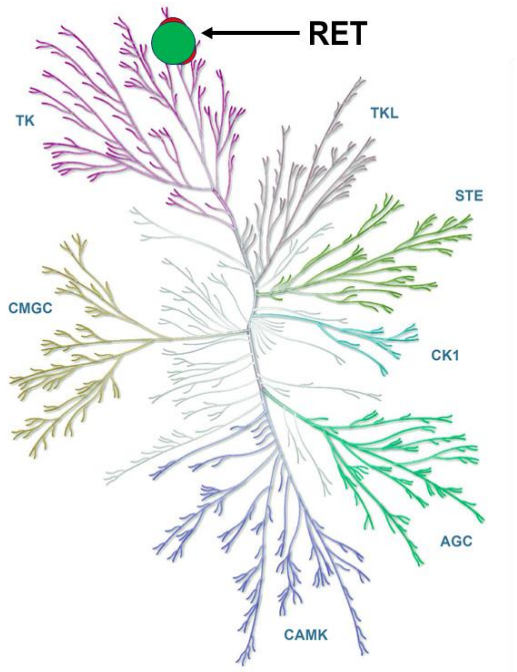
- The **5.4%** (119 of 2219) prevalence of *ALK* in the screening population is close to the expected rate of 5%[1]
- 38/87 (43.7%) patients had a ***TP53*** mutation
- **Median bTMB** at baseline was **two mutations** (range: 0 to 21)
  - 3/87 (3.4%) patients had bTMB ≥ 16 mutations

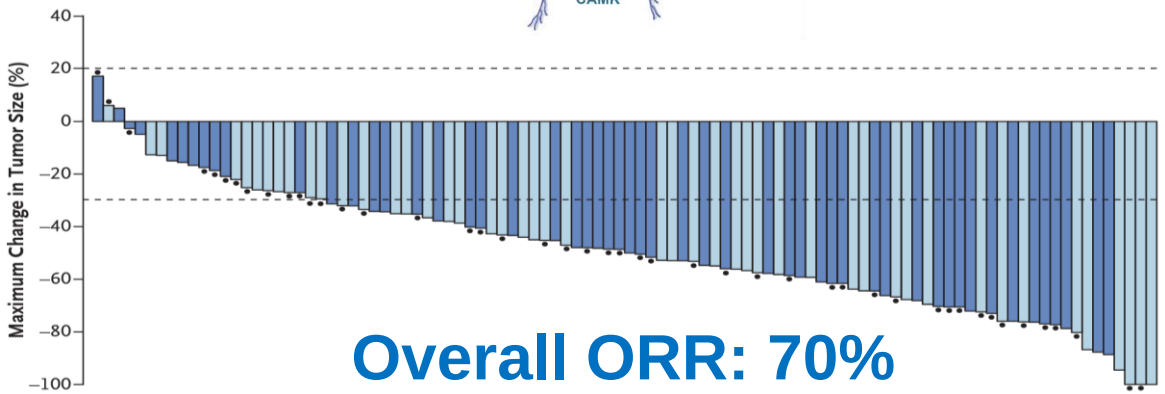


Gadgeel S et al, ESMO 2019

RET-Driven NSCLC: TKI Specificity and Activity

Selpercatinib (LOXO-292)

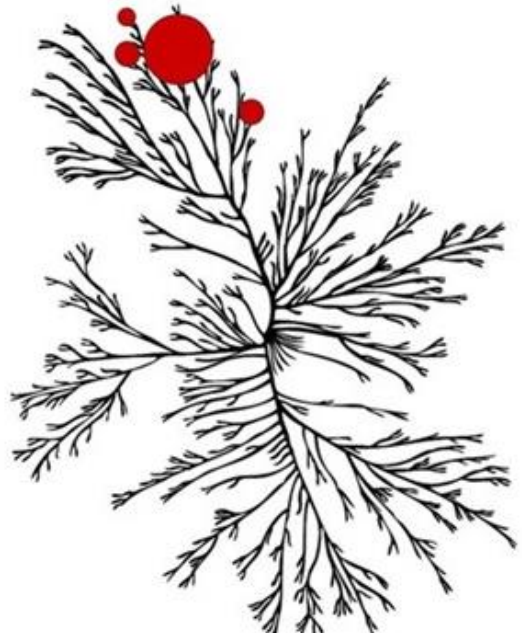


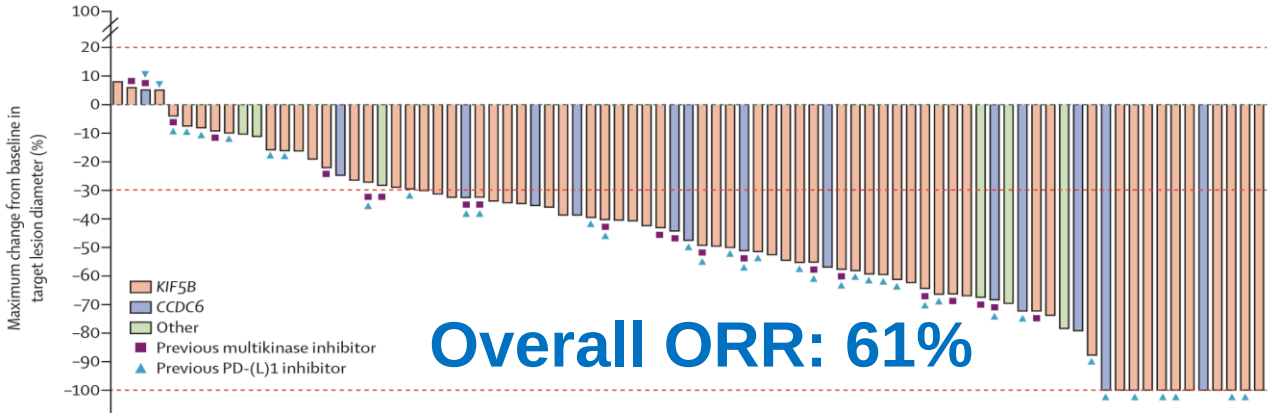


Overall ORR: 70%

Drilon A et al, WCLC 2019
Drilon A et al, NEJM 2020

Pralsetinib (BLU-667)

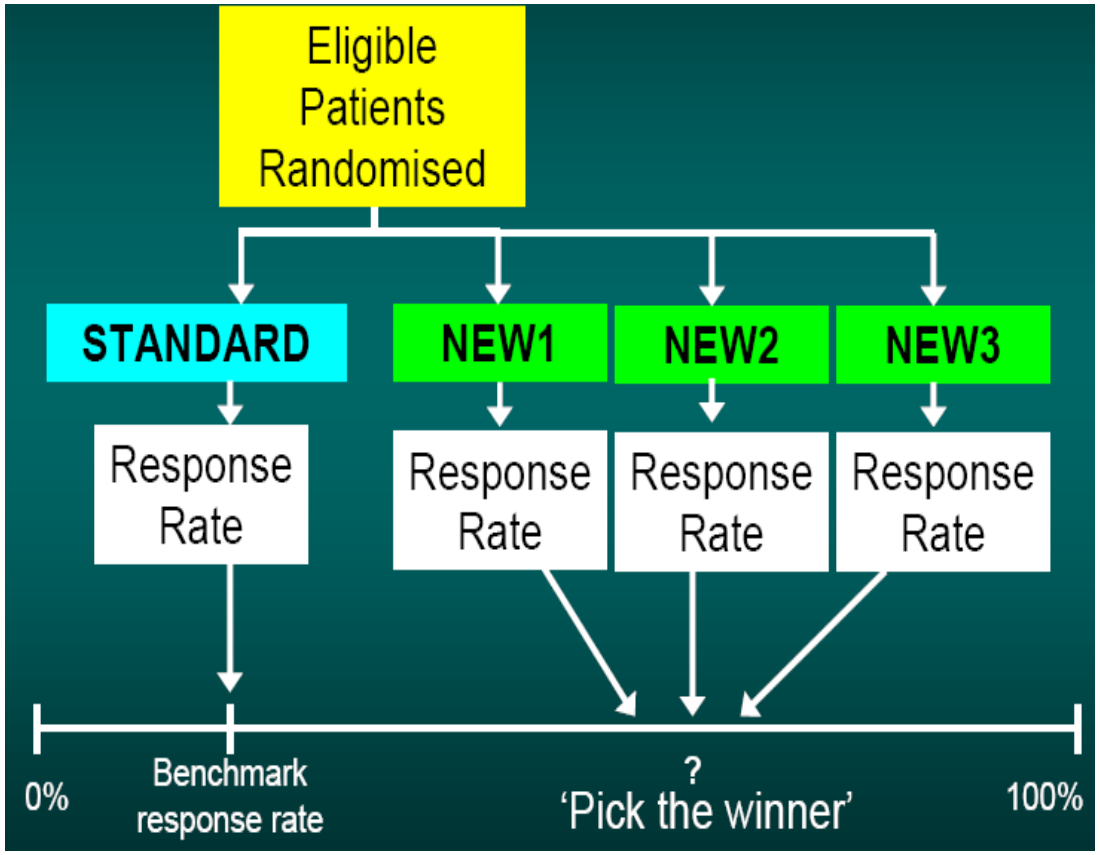




Overall ORR: 61%

Gainor J et al, ASCO 2019
Gainor J et al, Lancet Oncol 2021

Pros & Cons (Random. Phase II): Overinterpretation



***Comparative means*:**
The winner enters the Phase III fashion

Pros	Cons
• Control of selection bias • Simultaneous testing of several new treatments, combinations, doses, etc. • Generally preferable: some degree of control is better than none!	• NOT a statistical comparison between randomized groups • The randomized Phase II trials DO NOT replace phase III trials • Over-interpretation of comparative results from small sized randomized Phase II trials

Courtesy of Billingham C, 2008

Dafni U, WCLC 2019

Clinical Trials Methodology

- Objectives/aims of clinical studies are:
  - –Phase I
  - –Phase II
  - **–Phase III**

Classification by Objective

Phase III: Compare new treatment to standard therapy or placebo.

http://www.msra.org.au/next-20-article-clinical-trials-phase-1

Dafni U, WCLC 2019

Clinical Trials Methodology: Topics of Phases

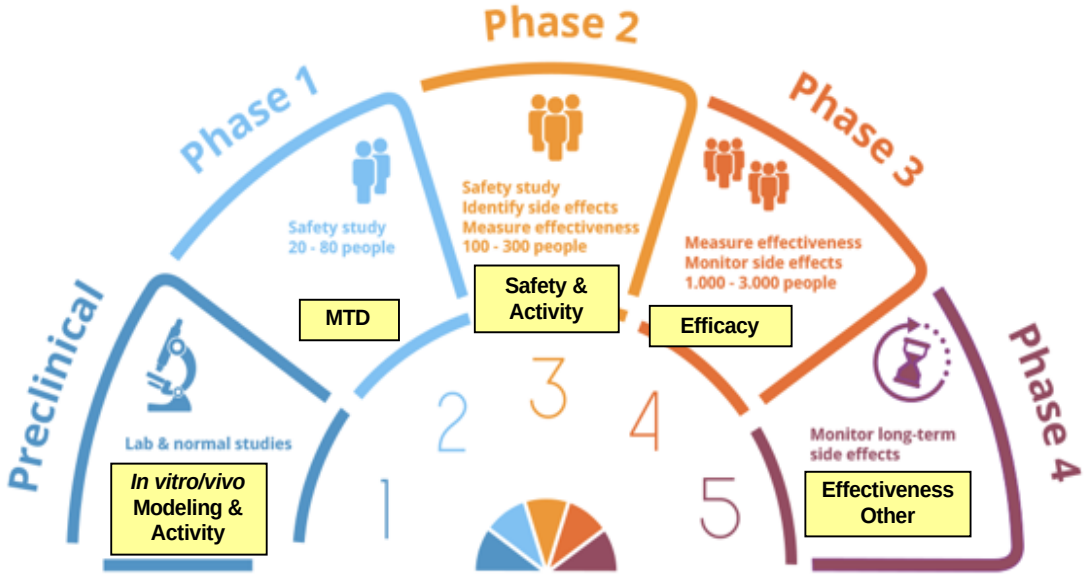
Phase	Objectives and Aims	Subjects	Focused on
I	Pharmacokinetics Safety	Healty Subjects Patients	DRUG
II	Activity Safety	Patients	DISEASE
III	**Efficacy**	**Patients**	**INDIVIDUAL PATIENT**

What do we assess in clinical trials?

- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[Phase IV?]**

Gold Standard: RCTs

- **Phase III clinical trials are the gold standard for evaluating therapeutic interventions.**
- **Randomization:**
  - **Provides a treatment assignment that is independent of outcome and patient/disease features, thus balancing treatment groups on known and unknown factors associated with outcome.**
  - **The intention-to-treat (ITT) analysis approach is the gold standard for all phase III) randomized, controlled clinical trials: analyzes all patients in the treatment groups as randomized without regard to treatment actually received.**



Riwani and Hilsenbeck, J Clin Oncol 2012

Dafni U, WCLC 2019

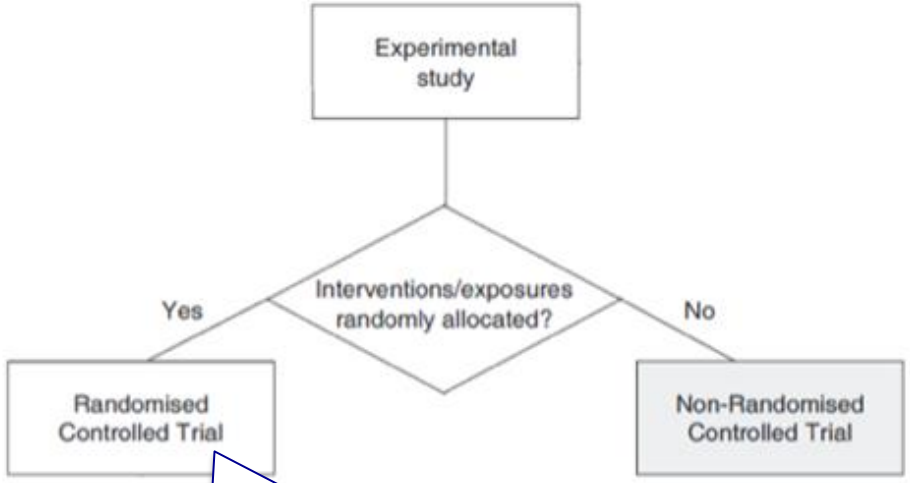
Phase III trials: Randomization

- Assignment of subjects to groups compared according to a random sequence
- Why to randomize? To avoid:
  - **Selection bias**
  - **Performance bias**
  - **Detection bias**
  - **Attrition bias**

Jüni P. et al. BMJ 2001

Phase III trials: Randomization

- **Assegnazione casuale** dei pazienti al gruppo sperimentale o di controllo, al fine di assicurare che tutti i fattori prognostici (noti e sconosciuti) si distribuiscano omogeneamente nei due gruppi.
- Tutti i requisiti della randomizzazione hanno lo scopo di assicurare che il **processo con cui vengono creati i due gruppi a confronto segua le leggi del caso**, e che **nessun fattore possa interferire** con la sua casualità.



Minimizes allocation bias, balancing both known and unknown prognostic factors, in the assignment of treatments.

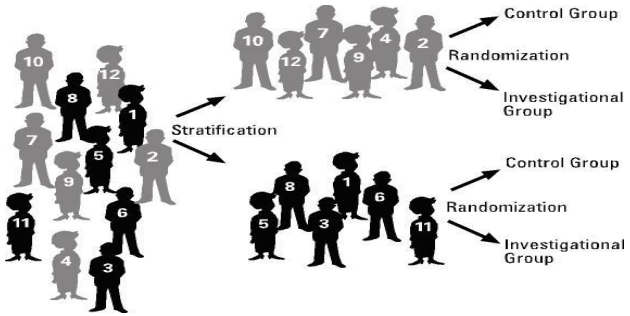
Lachin, 2000

Phase III trials: Randomization

RANDOMIZZAZIONE STRATIFICATA

Allestimento di liste di randomizzazione separate per una o più caratteristiche pre-trattamento:

- ✓ misura atta a evitare sbilanciamenti fra i trattamenti a confronto per specifici fattori prognostici;
- ✓ possibili vantaggi di tipo gestionale e organizzativo (es. stratificazione per Centro);
- ✓ considerare solo fattori di stratificazione oggettivamente definibili.



MASCHERAMENTO (BLINDING)

- **Insieme delle procedure atte a prevenire distorsioni dovute al fatto che il Paziente, il Medico o il Valutatore sono a conoscenza del trattamento ricevuto dal Paziente:**
  - **Paziente = singolo cieco**
  - **Paziente + Medico = doppio cieco**
  - **Paziente + Medico + Valutatore = triplo cieco**
- **Necessità connessa agli obiettivi dello studio e al tipo di variabile di effetto utilizzata**

Design Elements and Ethics

Sample Size Determination

- Experiments with **more patients** than needed violate the individual human rights of the specific patients
- Experiments with **less patients** than needed violate human rights of the whole society
- **ETHICAL to use appropriate sample size**

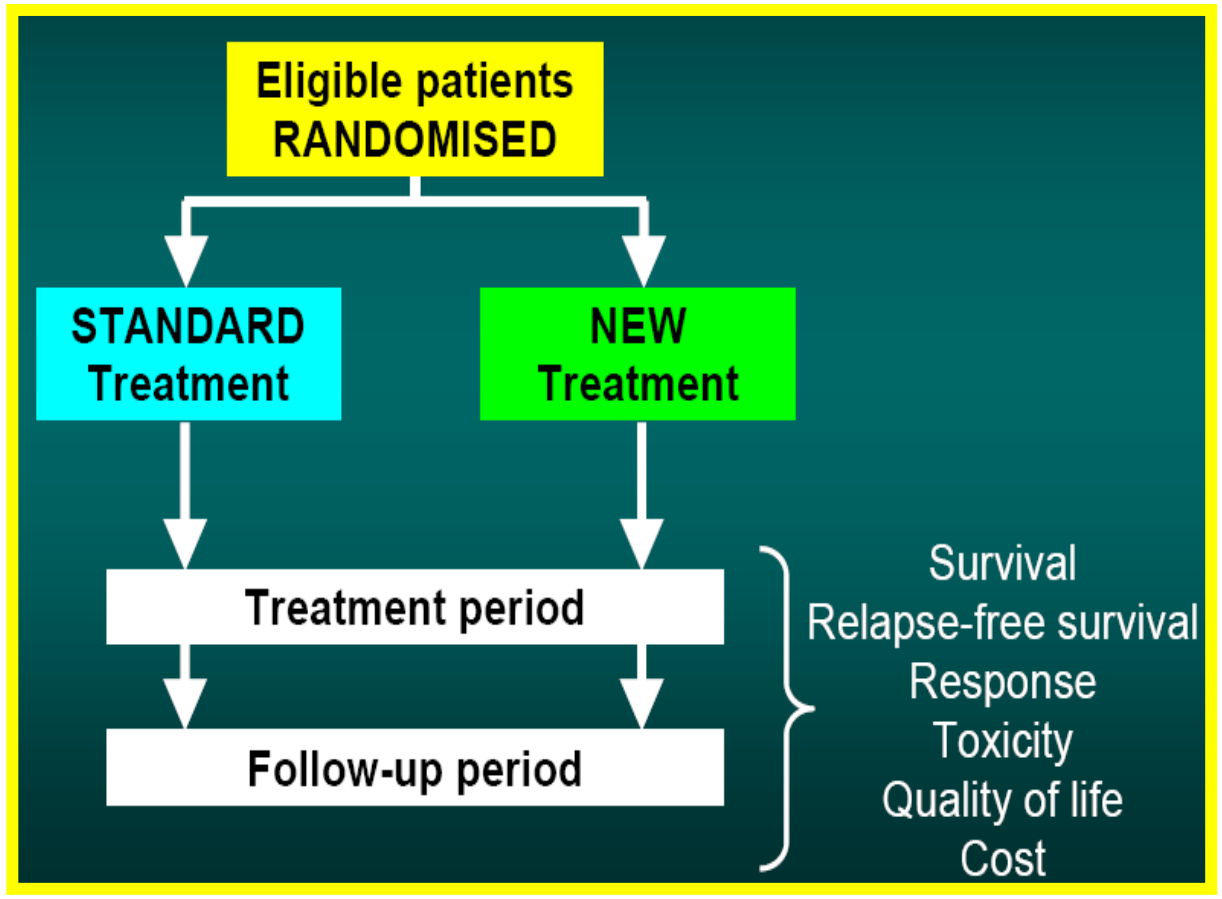
Bias, Variability & Generalizability

- To **address Bias** of the estimate, the design needs to include at least:
  - **Randomization**
- To **address Variability** of the estimate, the design needs to include:
  - **Adequate Sample Size**
- To **address Generalizability** of the results, the design needs to include:
  - **Inclusion of diverse subgroups (eg. older age, female gender)**

Declaration of Helsinki:
http://oss-sper-clin.agenziafarmaco.it/normativa/direttive_OsSC-000122-000000.pdf

Dafni U, WCLC 2019

Randomized Phase III Clinical Trials

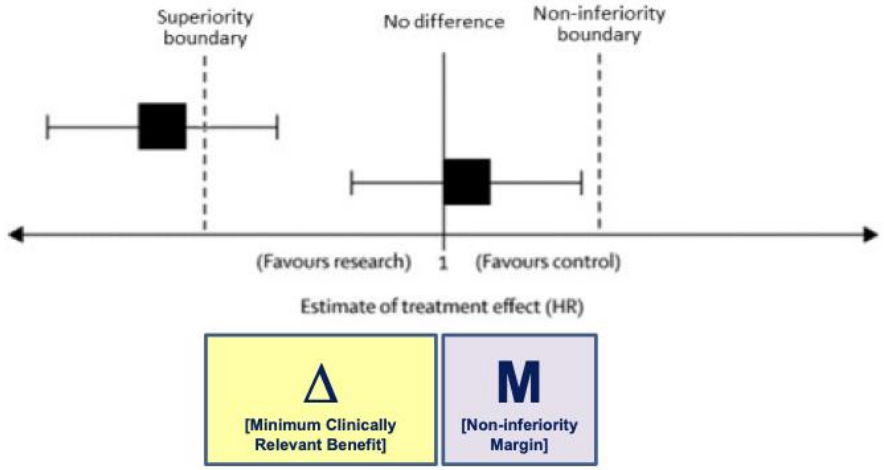


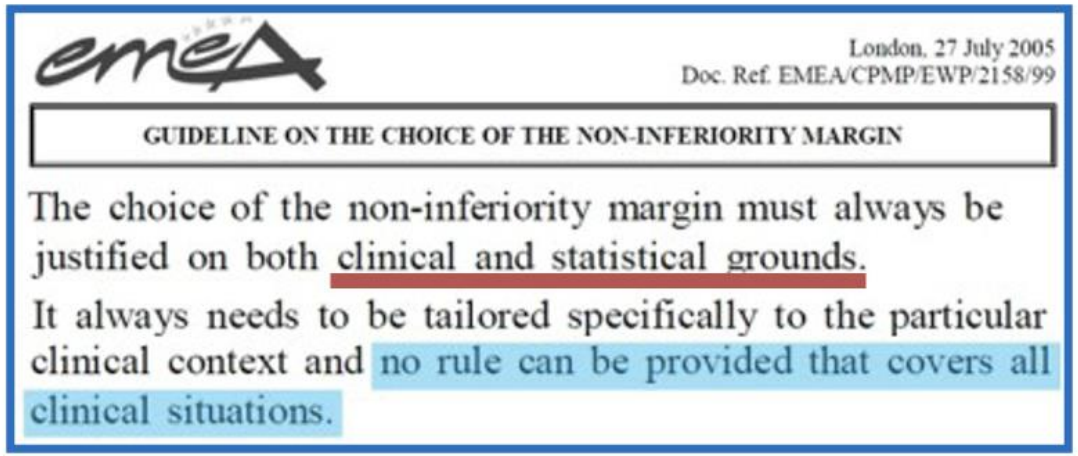
- **The new drug is more effective than other drugs?**
  - **Superiority trial (is 'statistically' relevant?)**
- **The new drug is as effective as other drugs but with fewer side effects (or minor discomfort or lower costs)?**
  - **Non-inferiority trial**
- **The use of the new drug determines a therapeutic benefit for patients?**
  - **Amount of the benefit (is 'clinically' relevant?)**
- **What categories of patients may derive more benefit from the new drug?**
  - **Subgroups analysis**

Sizing a trial (A [Exp.] *vs.* B [Control]) For…

- **Superiority**:
  - **A** is better than **B** in terms of the primary outcome, and ***this expected difference must be clinically relevant [Minimum Clinically Relevant Benefit: ∆]***
- **Non-inferiority**:
  - **A** is ***inferior*** to **B** in terms of the primary outcome, but ***not lower than a clinically pre-specified 'margin' [M] which is considered clinically relevant***.
    - **Ex. You can accept a small degree of lower benefit, if patients experience better tollerability**

Superiority & Non-inferiority





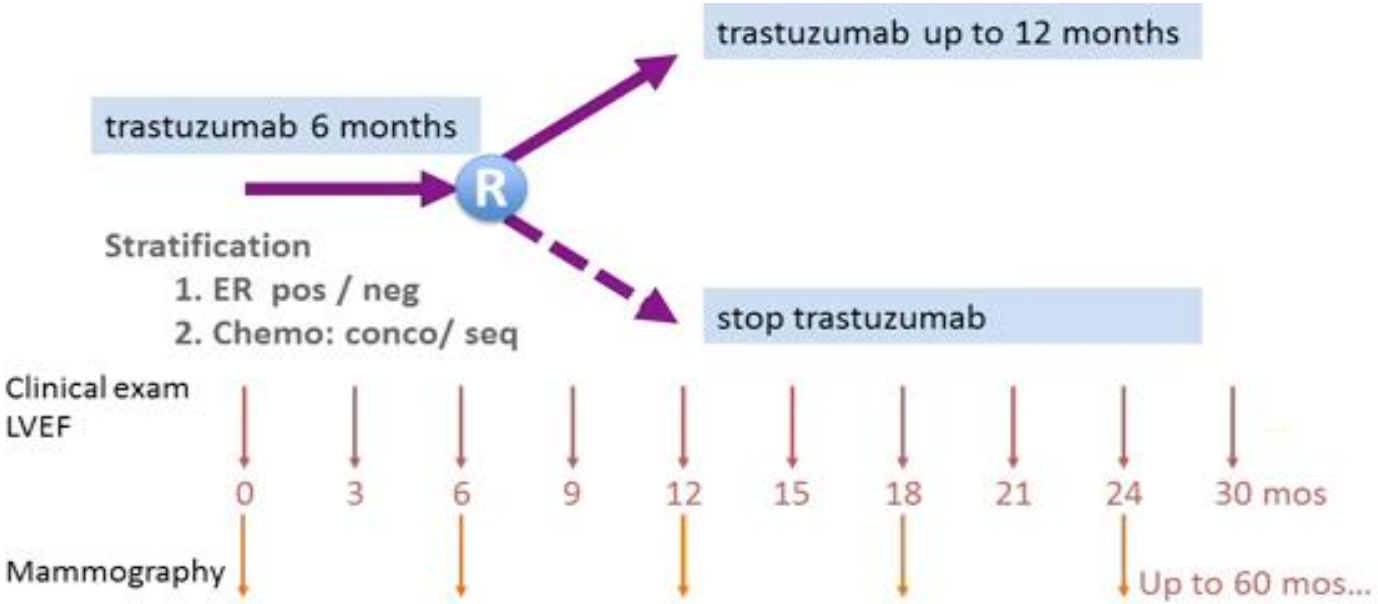
London, 27 July 2005
Doc. Ref. EMEA/CPMP/EWP/2158/99

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

The choice of the non-inferiority margin must always be justified on both clinical and statistical grounds.

It always needs to be tailored specifically to the particular clinical context and no rule can be provided that covers all clinical situations.

Non-Inferiority in Breast Cancer: Trastuzumab De-Escalation

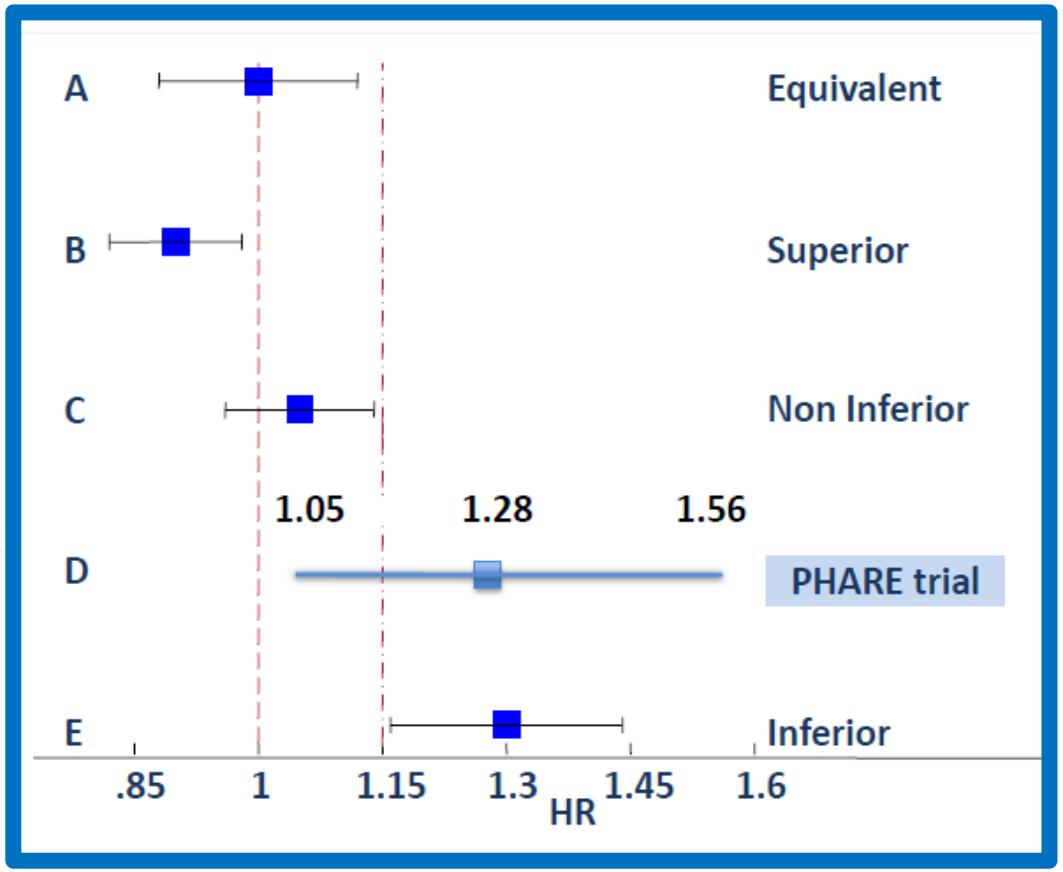


- **Non inferiority randomized trial**
  - 2% variation in terms of absolute difference of recurrence
  - The 95% CI HR margins should not cross the 1.15 boundary
  - 1040 DFS events required for 80% power at 5% level

  or

  4 years of accrual and at least 2 years of follow-up
  - HR were estimated from the stratified Cox model

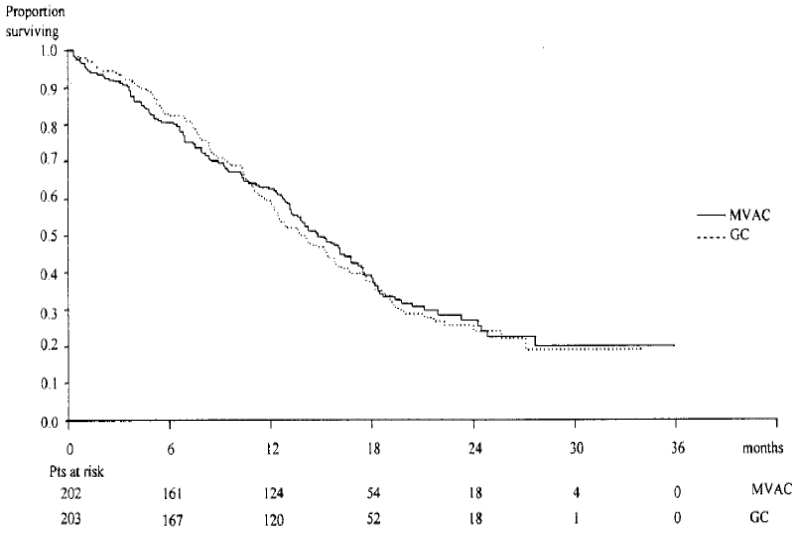
- **Accrual target: 3400 patients**



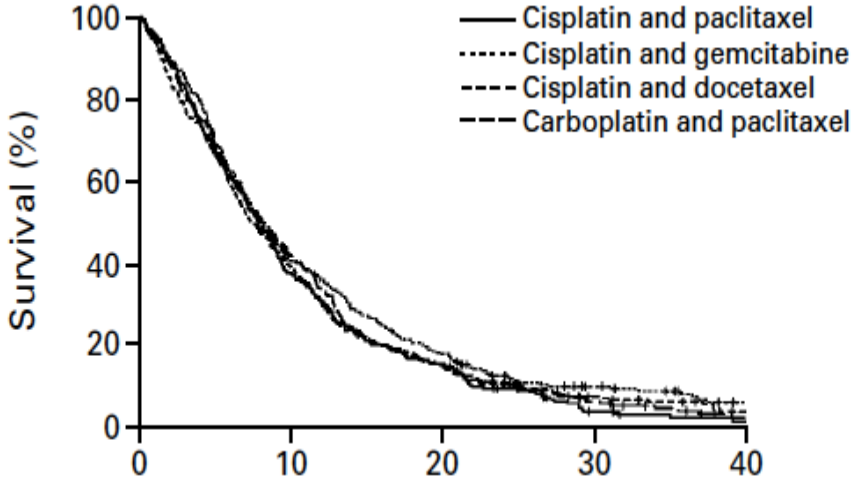
Pivot X et al, ESMO 2012

Key Examples of Mis-intepretation of SUPERIORITY RCTs with Relevant Implication for Clinical Practice

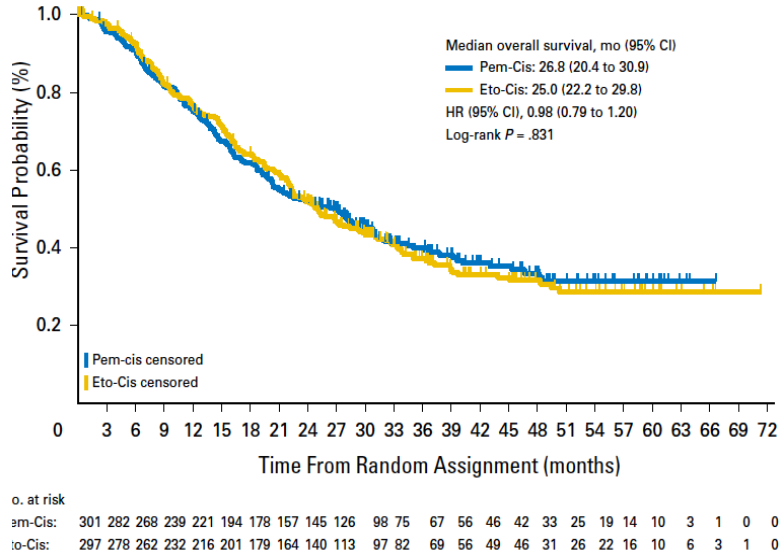
Bladder [Stage IV-Advanced]: Testing SUPERIORITY of CIS-GEM *vs.* MVAC



NSCLC [Stage IIIB-IV - ECOG 1594]: Testing SUPERIORITY of One *vs.* Other(s)



NSCLC [Stage III – PROCLAIM] Testing SUPERIORITY of CIS-PEM *vs.* CIS-VP-16



Non-Inferiority & Equivalence MUST be Pre-Specified and Powered! Beware of Wrong Conclusions for Clinical Practice!

Van De Maase H et al, JCO 2000

Schiller J et al, NEJM 2002

Senan S et al, J Clin Oncol 2015

Superiority Trials: Principles and ASCO/ESMO Advices

- **Aim:** To demonstrate the superiority of a new therapy compared to an established therapy or placebo
- **Sample Size**: To estimate the sample size one needs to consider
  - the ***Clinical significance (Δ)***: By how much should the new therapy be better than the established?
  - the ***Power (1-β)***: the probability of correctly showing a benefit (usually ≥ 80%)
  - the ***Significance level (α)***: the probability of wrongly concluding that a benefit exists (usually ≤5%)

- **ASCO: Recommended Targets for Meaningful Trial Goals**
- **ESMO: Development of the Magnitude of Clinical Evaluation Scale**

- ***Ellis et al. 2013. JCO. American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes***
- ***ASCO 2014, 2015, ESMO 2014, ECCO 2015; Annals of Oncology 2015***

Modified by Dafni U, WCLC 2019

Recommended Targets for Meaningful Trial Goals

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

- HR ≤ 0.8, with an improvement in median OS 2.5 to 6 months:
- Minimum incremental improvement over standard therapy that would define a clinically meaningful outcome.

Ellis et al. 2013. JCO. American Society of Clinical Oncology Perspective:

Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Dafni U, WCLC 2019

What do we assess in clinical trials?

- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[are Phase IV, 'Real World' Data]**

Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - Descrizione dei dati e inferenza statistica
  - L'importanza della numerosità campionaria
  - **La rappresentatività del campione**
  - La tentazione delle analisi per sottogruppi

'Liberazione di San Pietro' (Particolare), Raffaello Sanzio, 1513-1514, Musei Vaticani, Roma

Generalizability of Data from RCTs

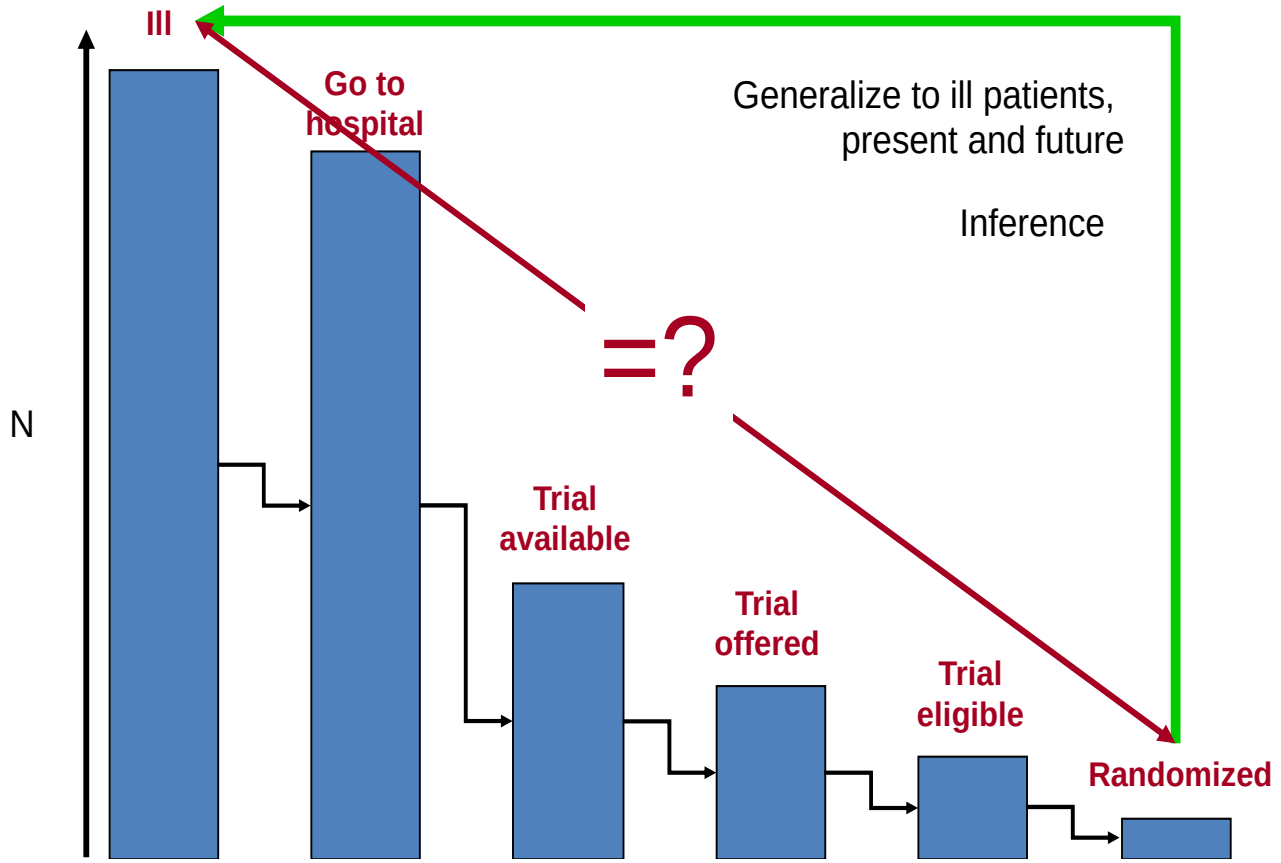
Problems that Might Limit Intepretation of RCTs

Some randomised controlled trials might:

- Ask questions of commercial rather than clinical interest
- Be based on inadequate preclinical and early clinical studies
- Use surrogate endpoints that do not reflect patient benefit (ie, duration or quality of survival)
- Fail to assess or inadequately assess health-related quality of life or patient-reported outcomes even though the goals of treatment are palliative
- Show statistically significant but clinically irrelevant results
- Be analysed and reported prematurely
- Underestimate the toxicity of new treatments
- Be subject to biased reporting, both in the primary publication and by the media
- Select patients who do not represent those seen in everyday practice

Tannock I et al, Lancet Oncology 2016

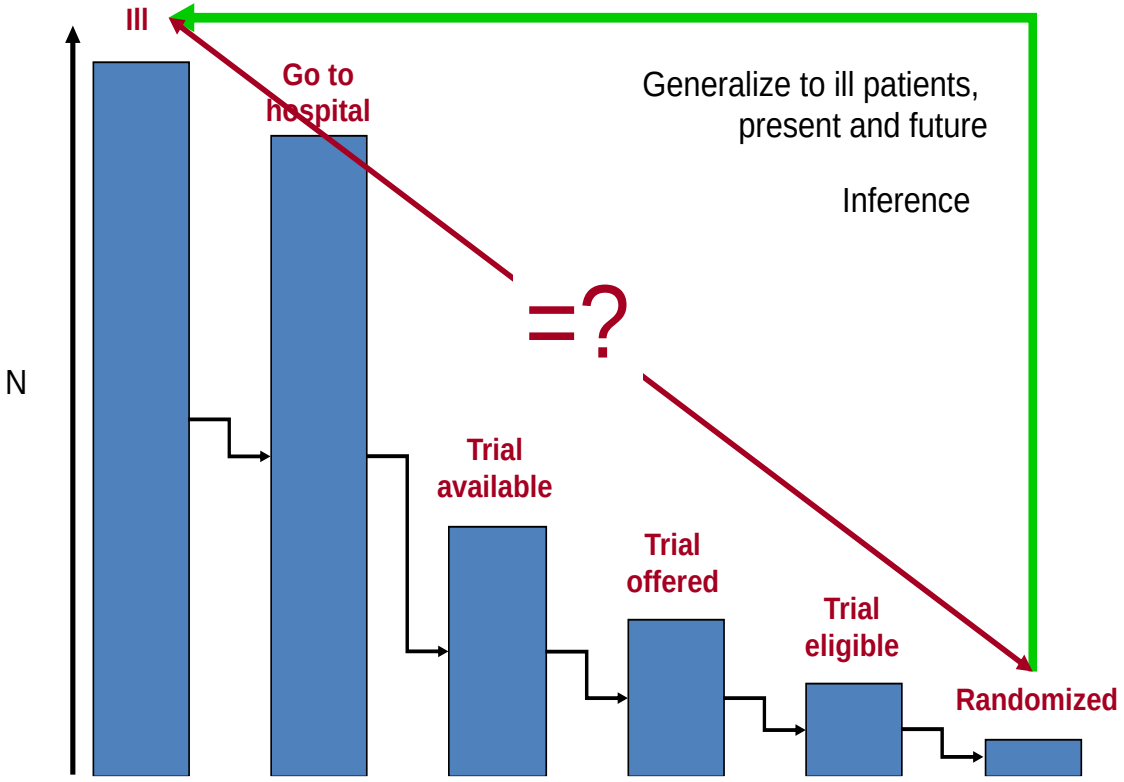
External Validity?



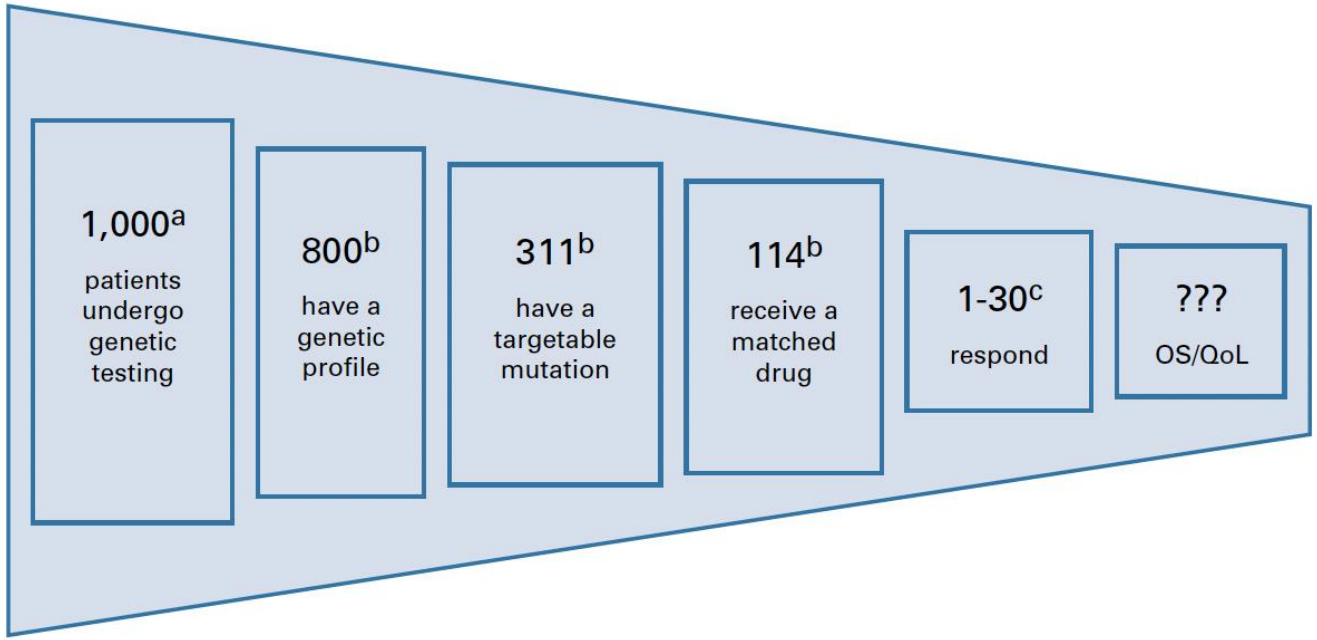
Courtesy of Di Maio M & Perrone F

Generalizability of Data from RCTs/Basket & PM Trials

External Validity?



'The shrinking denominator'



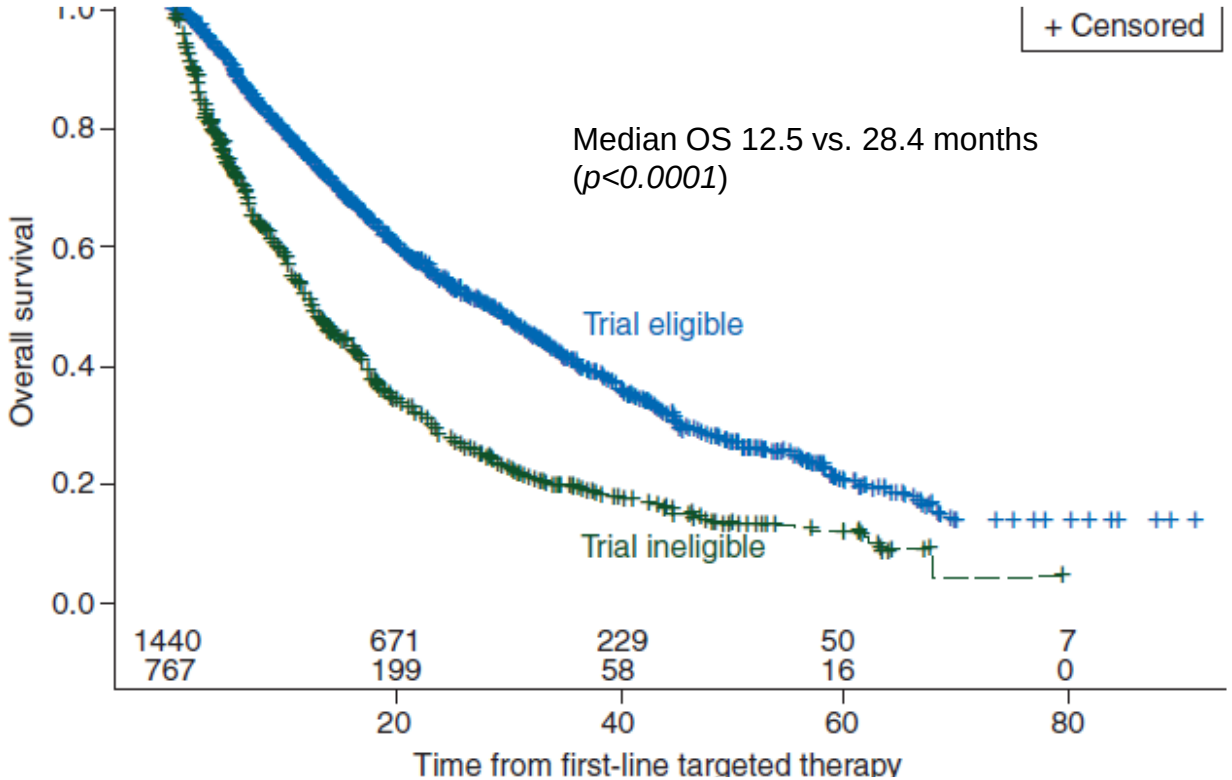
Representative results derived from a large series of patients who have undergone genetic testing and where an attempt has been made to treat with a drug targeting a genetic mutation.

Courtesy of Di Maio M & Perrone F

Chan KKW et al, J Clin Oncol 2021

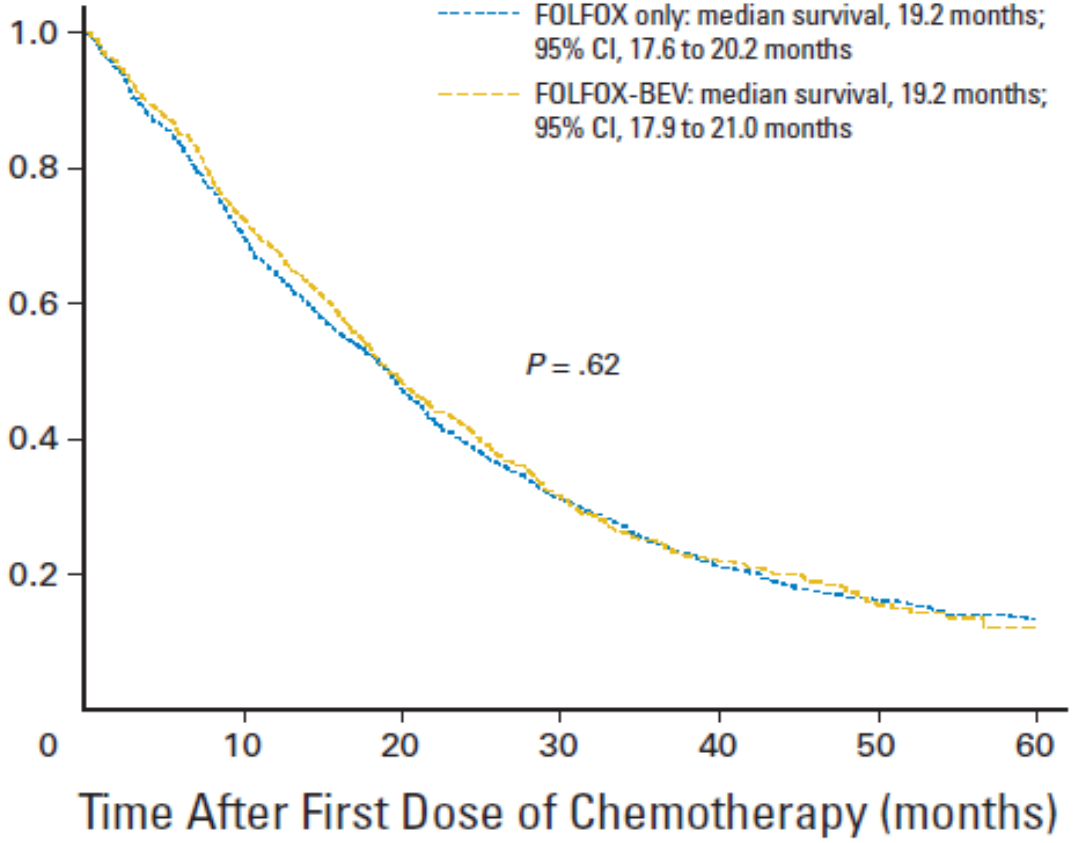
Targeted Therapy Performance in the '*Real World*'

Trials' *Ineligible* Pts vs. *Eligible* (all receiving targeted agents)



Deng DY et al, Ann Oncol 2014

Addition of Bevacizumab to FOLFOX, '*Registry*' Context



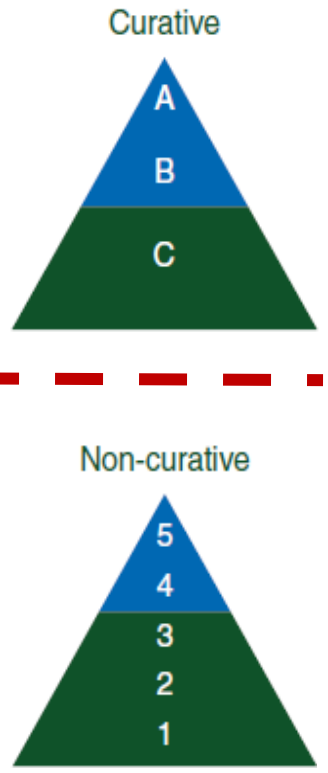
Meyerhardt T et al, JCO 2012

ESMO & ASCO are aiming to add Quantity to Quality

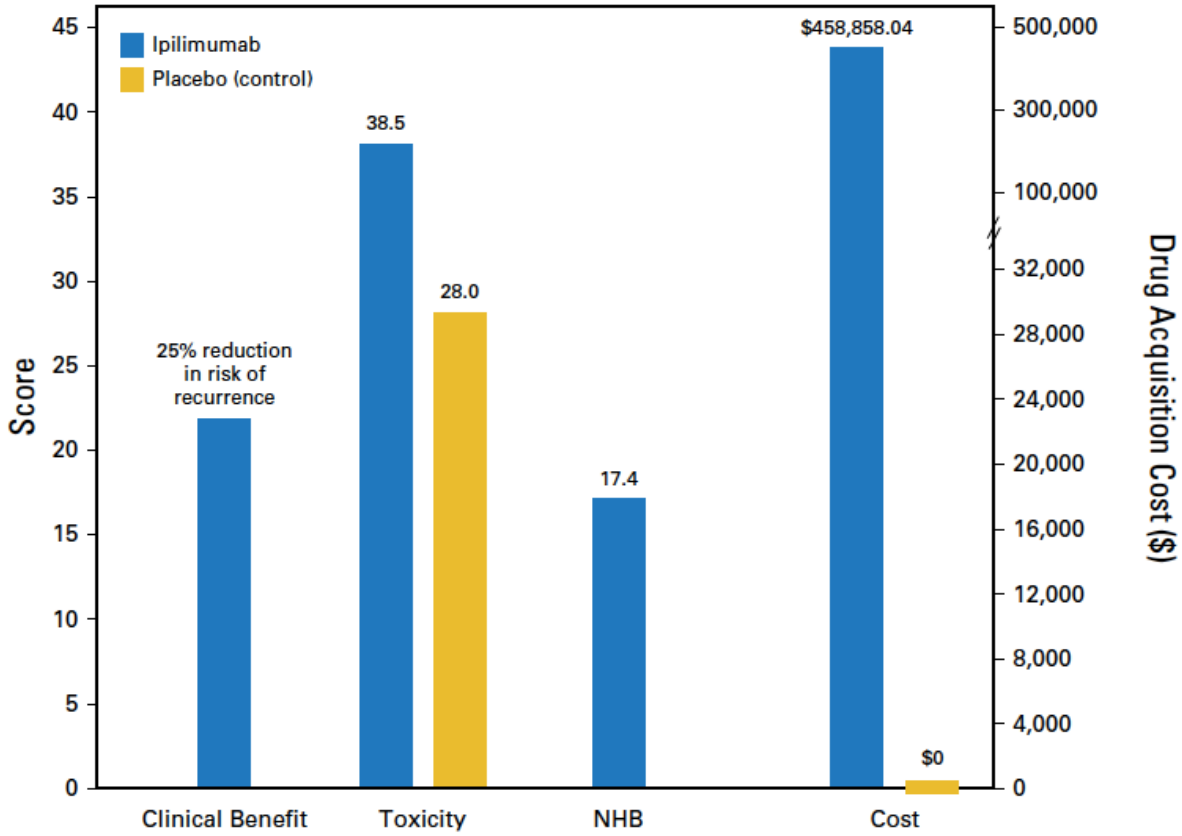
MCBS: Magnitude of Clinical Benefit Score

Table 2. Maximal preliminary scores

Treatments with curative intent (form 1)
>5% improvement of survival at ≥3-year follow-up
Improvements in DFS alone HR <0.60 (primary end point) in studies without mature survival data
Treatments with non-curative intent (form 2)
Primary outcome OS (form 2a)
Control ≤12 months
HR ≤0.65 *AND* gain ≥3 months *OR*
Increase *in* 2-year survival alone ≥10%
Control >12 months
HR ≤0.70 *AND* gain ≥5 months *OR*
Increase *in* 3-year survival alone ≥10%
Primary outcome PFS (form 2b)
Control ≤6 months
HR ≤0.65 *AND* gain ≥1.5 months
Control >6 months
HR ≤0.65 *AND* gain ≥3 months



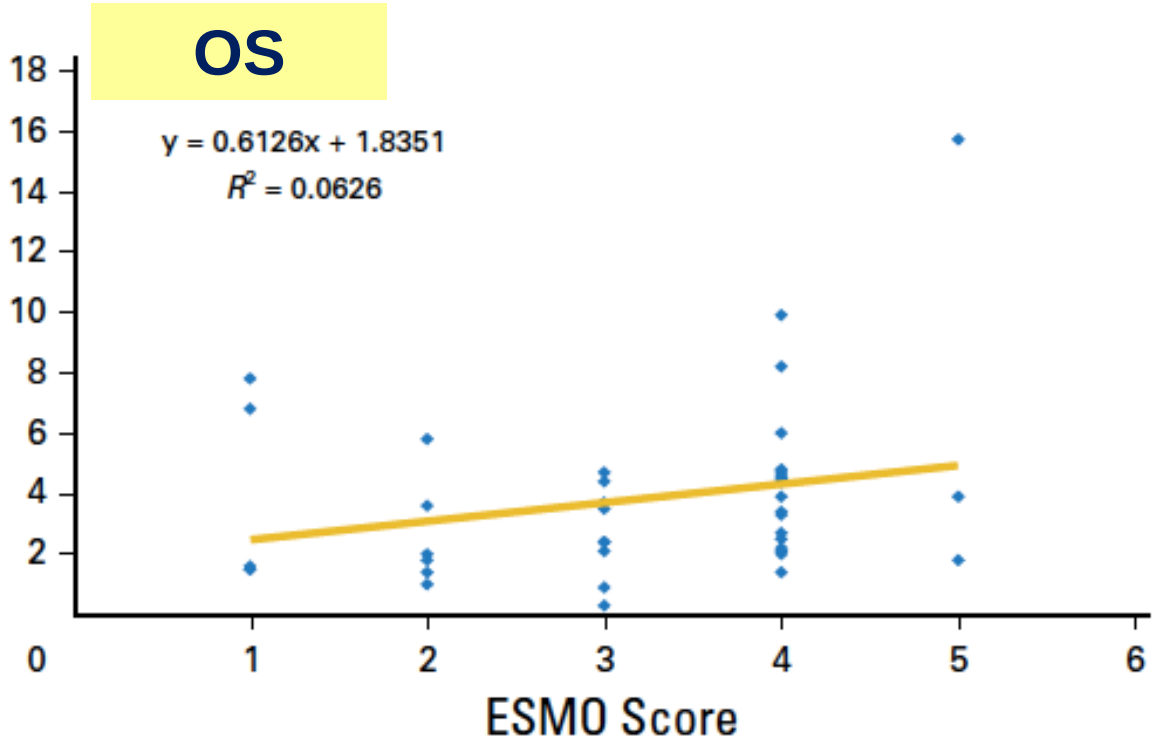
NHB: Net Health Benefit (NHB)

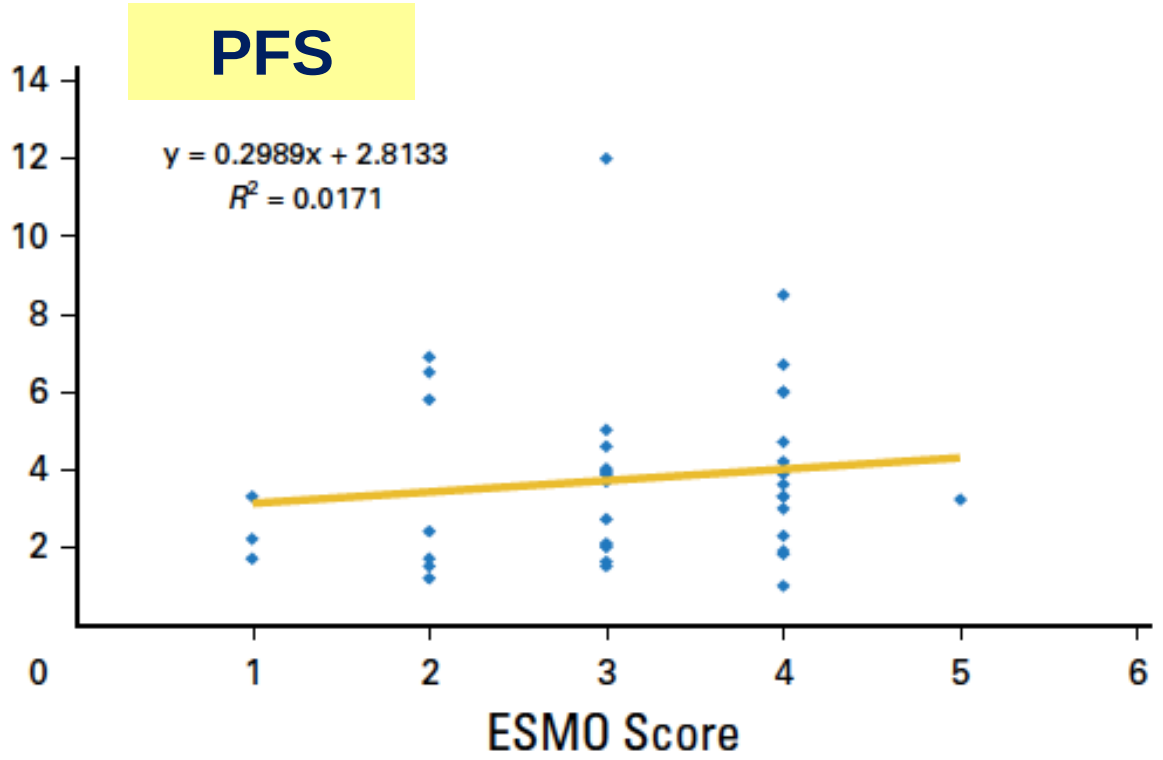


Cherny NI, et al, Ann Oncol 2015

Schnipper LE, et al, JCO 2016

Do we really add Quantity to Quality?

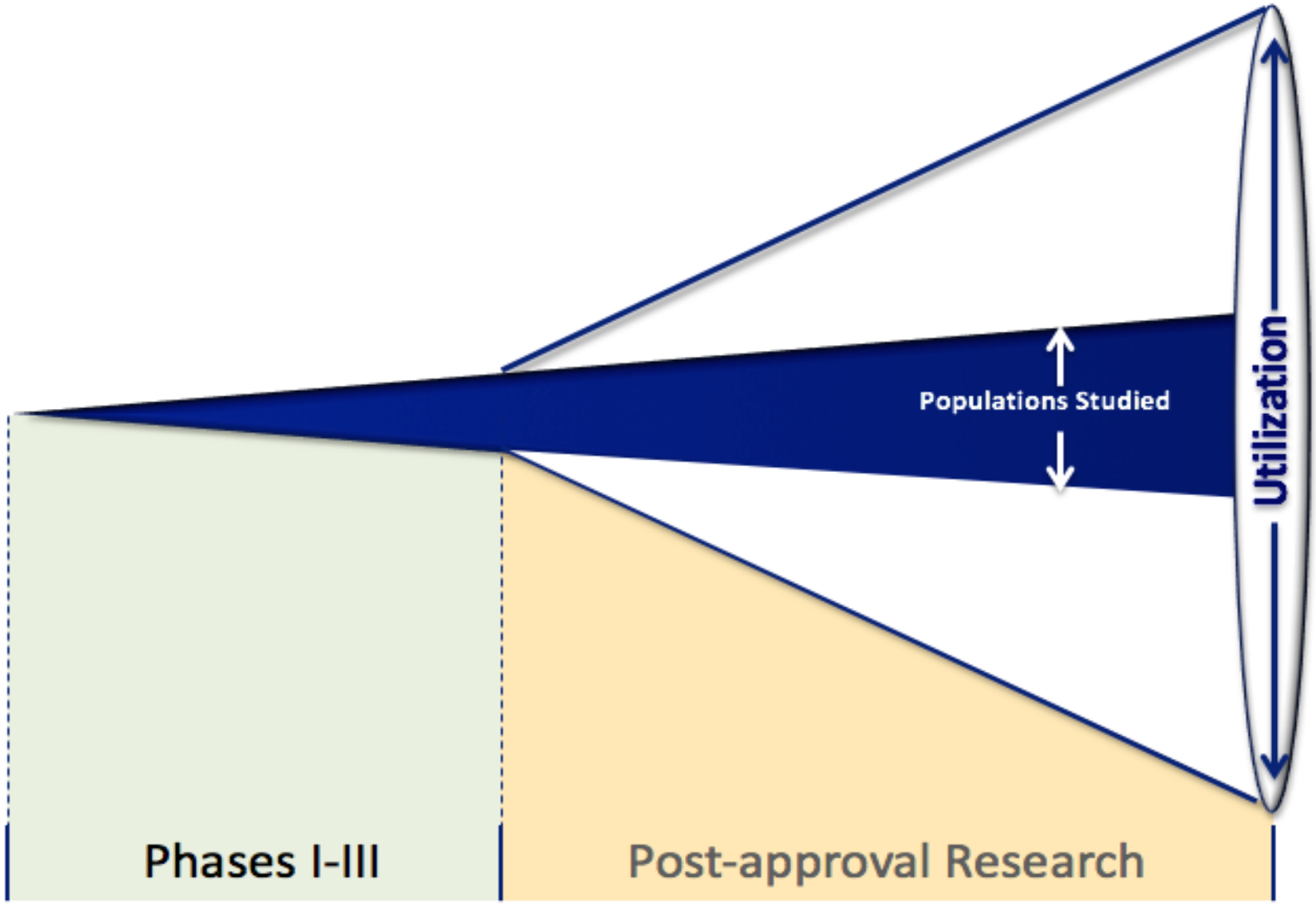




- **ESMO MCSB:**
  - **Poor correlation between outcome and scores**
  - **Decision criterion different from HTAs in the last 20 years.**
- **ASCO Value Framework:**
  - **Not possible to estimate**

Messori A et al, JCO 2017

The ‘Pyramid’ of Evidence is Evolving



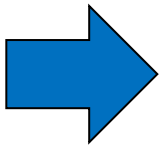
Variances in populations utilizing technology versus the populations studied

- Differing age groups (elderly, pediatrics)
- Race, ethnicity & gender variances
- Unstudied co-morbid conditions
- Differing concomitant drugs (including OTC)
- Lifestyle variances including smoking, dietary habits
- Differences in disease severity
- Varying levels of compliance

Modified from Di Maio M

What do we assess in Ph. IV/Post-Marketing/RWD clinical studies?

- **Activity:**
  - ability of the treatment to induce modifications of the disease thanks to which it is assumed that the patient may have a benefit **[Phase II]**
- **Efficacy:**
  - ability of the treatment to induce a clinical benefit in patients who are administered ***in an experimental context*** **[Phase III]**
- **Effectiveness:**
  - ability of a treatment to be effective in a ***non-experimental, concrete and coincident with the clinical practice*** **[Phase IV?]**



FDA U.S. FOOD & DRUG ADMINISTRATION

Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural

https://www.fda.gov/media/124795/download

How to measure ‘Real Life’ Effectiveness

Real life effectiveness data can be collected in a number of ways:

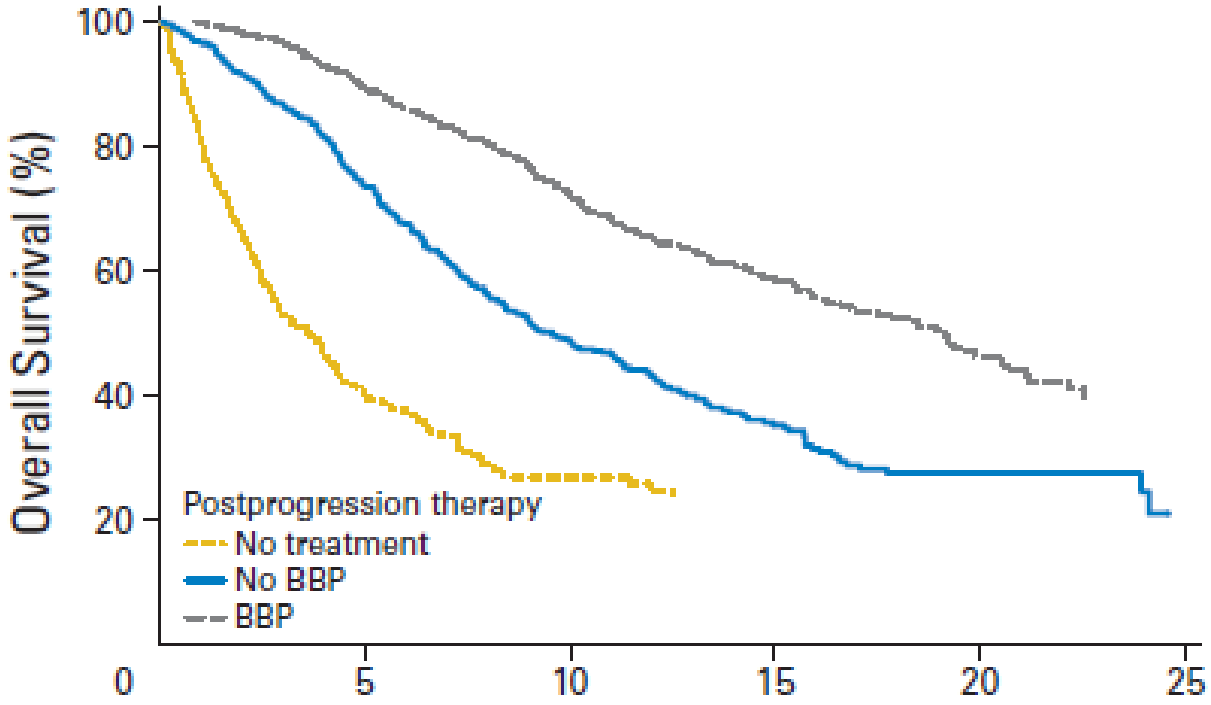
- **Databases;**
- **Patient and population surveys;**
- **Patient chart reviews;**
- **Observational data from cohort studies;**
- **Pragmatic clinical trials;**
- **Registries.**

	Efficacy study (*clinical trials*)	Effectiveness study (*observational studies*)
Question	**Does the intervention work under IDEAL circumstances?**	**Does the intervention work in REAL-LIFE practice?**
Setting	**Resource-intensive IDEAL setting**	**REAL-LIFE everyday clinical setting**
Population	**Highly selected, homogeneous population; many exclusion criteria**	**Heretogeneous population; few exclusion criteria**
Providers	**Highly experienced and training**	**Representative, usual providers**
Intervention	**Strictly enforced and standardized; no concurrent interventions**	**Applied with flexibility; concurrent interventions permitted**

Annemans L. «Real-life data: a growing need». ISPOR 2007

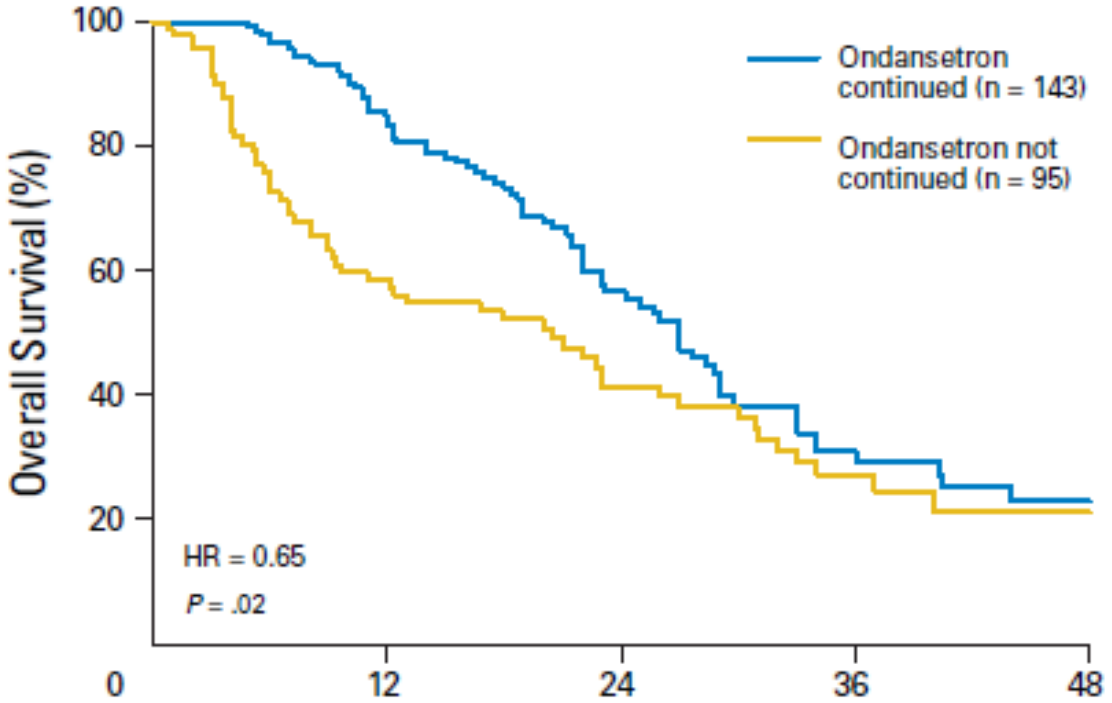
Hidden Biases in Observational Studies

BRITE Trial [Large, Observational]: Bevacizumab Beyond Progression, Advanced CRC [HR 0.46]



Grothey A et al, J Clin Oncol 2008

Second Line Advanced CRC Patients' Series: Fluorauracil Beyond Progression [HR 0.72]

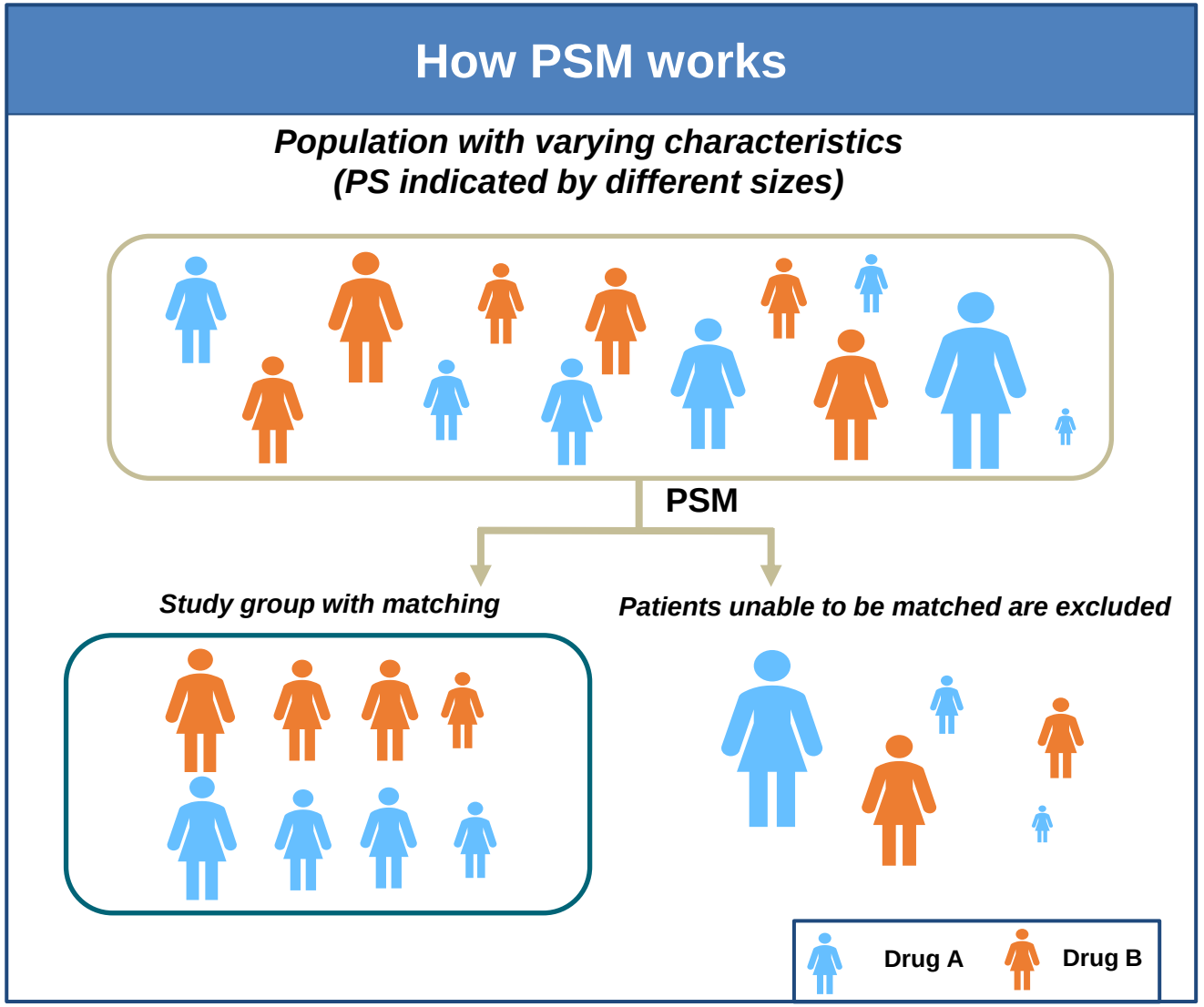


Kopetz S et al, J Clin Oncol 2009

Propensity Score Matching (PSM)

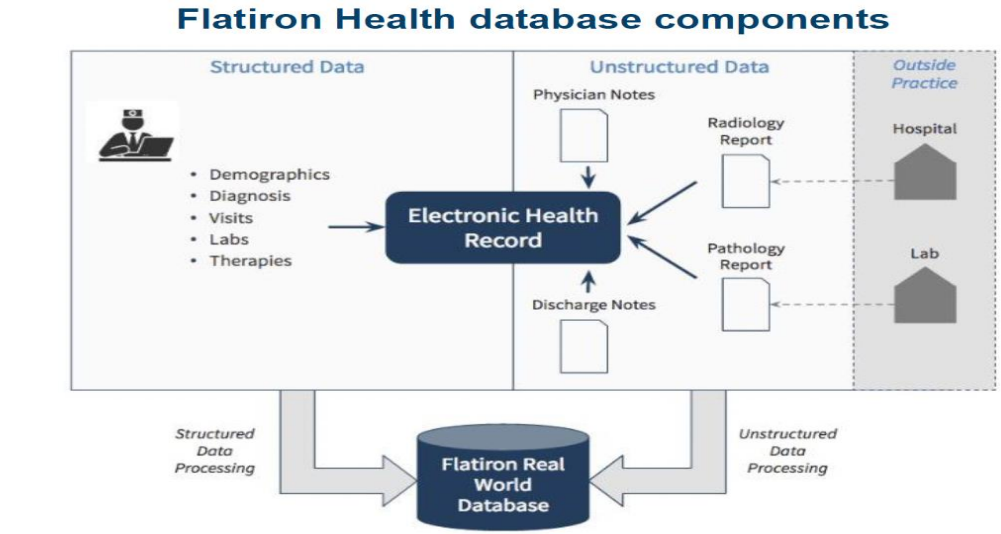
- **PSM is a statistical matching technique that attempts to eliminate or reduce any bias in real-world studies that are caused by the lack of randomisation**

- **The propensity score (PS) is the probability of a subject being assigned to a particular treatment given a set of observed key covariates (e.g. age or performance status) that may impact on this treatment decision**



Austin PC, Multivariate Behav Res 2011

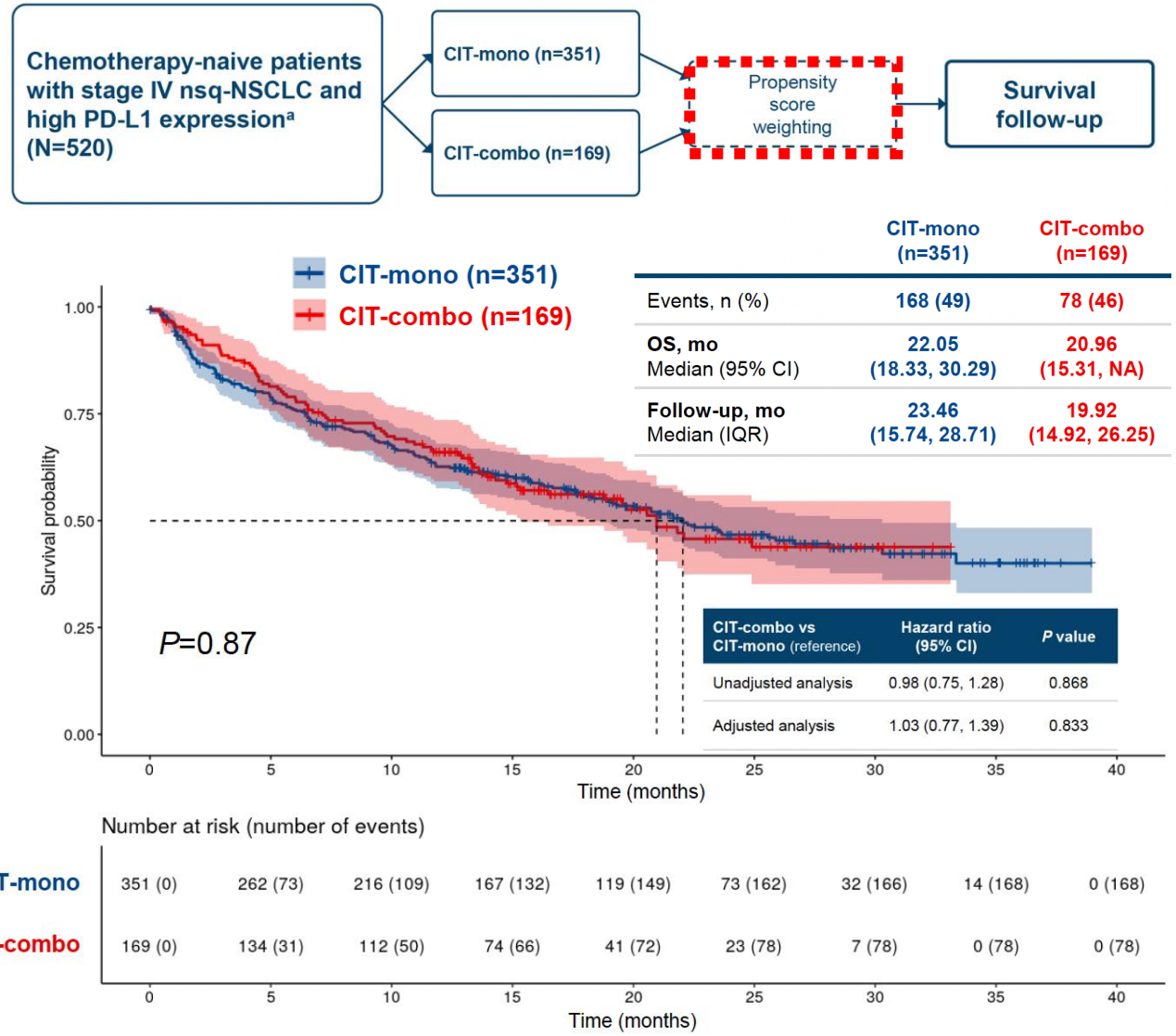
RWD: Effectiveness of IO(CT) for Advanced NSCLC



Patients diagnosed with NSCLC with ≥2 visits in the FH network on or after 1 Jan 2011 (N=246,400) → Probabilistic sample (n=141,013) → Advanced diagnosis after 24 Oct 2016 (n=24,075) → De novo stage IV (n=14,635); Relapse after initial diagnosis stage I-III (n=9440)

Attrition step	De novo stage IV NSCLC	Initial diagnosis stage I-III NSCLC
Receipt of CIT-mono or CIT-combo[a]	5168	2125
Relevant line of therapy started before 28 Feb 2019	3132	1271
Normal laboratory values	2756	1104
ECOG performance status, 0-1	1508	642
PD-L1 ≥1%	975	379
No evidence of ALK, EGFR, ROS1, BRAF	930	352
No structured activity gap	905	347
Evidence of metastatic diagnosis	905	253
Random sample	774	–
Confirmed receipt of treatment in 1L	764	191
Non-squamous histology	594	134
PD-L1 ≥50%	428	92

N=520



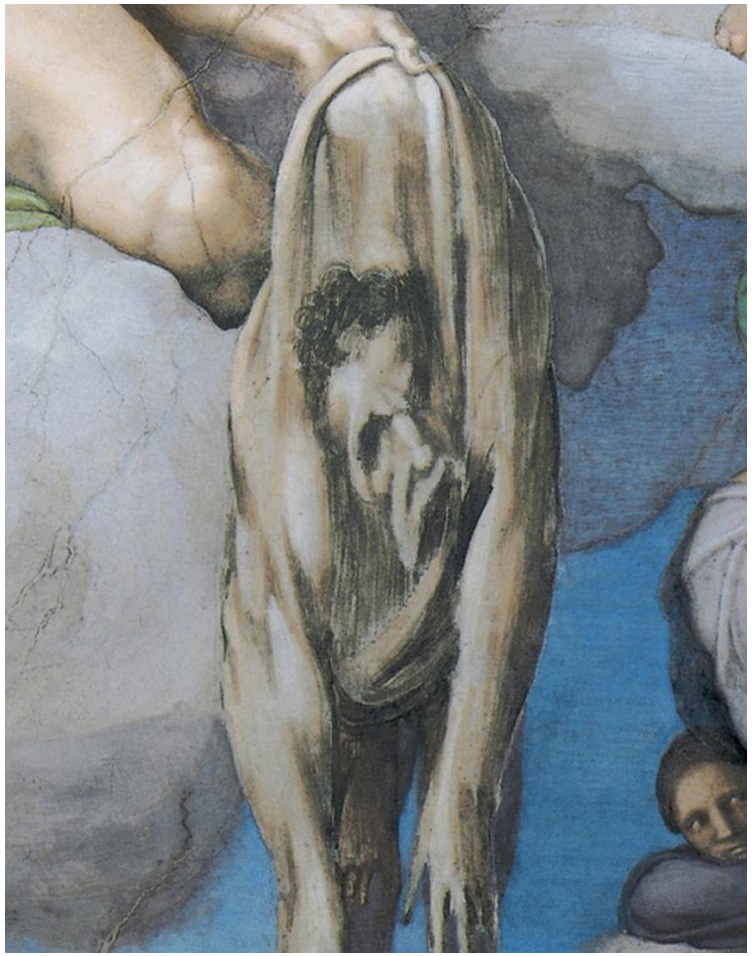
	CIT-mono (n=351)	CIT-combo (n=169)
Events, n (%)	168 (49)	78 (46)
OS, mo Median (95% CI)	22.05 (18.33, 30.29)	20.96 (15.31, NA)
Follow-up, mo Median (IQR)	23.46 (15.74, 28.71)	19.92 (14.92, 26.25)

CIT-combo vs CIT-mono (reference)	Hazard ratio (95% CI)	*P* value
Unadjusted analysis	0.98 (0.75, 1.28)	0.868
Adjusted analysis	1.03 (0.77, 1.39)	0.833

Peters S et al, ESMO Virtual Plenary, March 2021

Topics

- Quesito Clinico di Riferimento
- Fasi della Sperimentazione Clinica
- **Disegni di Studio Osservazionali ed Interventistici**



'Giudizio Universale' (Particolare, Autoritratto?), Michelangelo, 1535 - 1541, Cappella Sistina, Roma

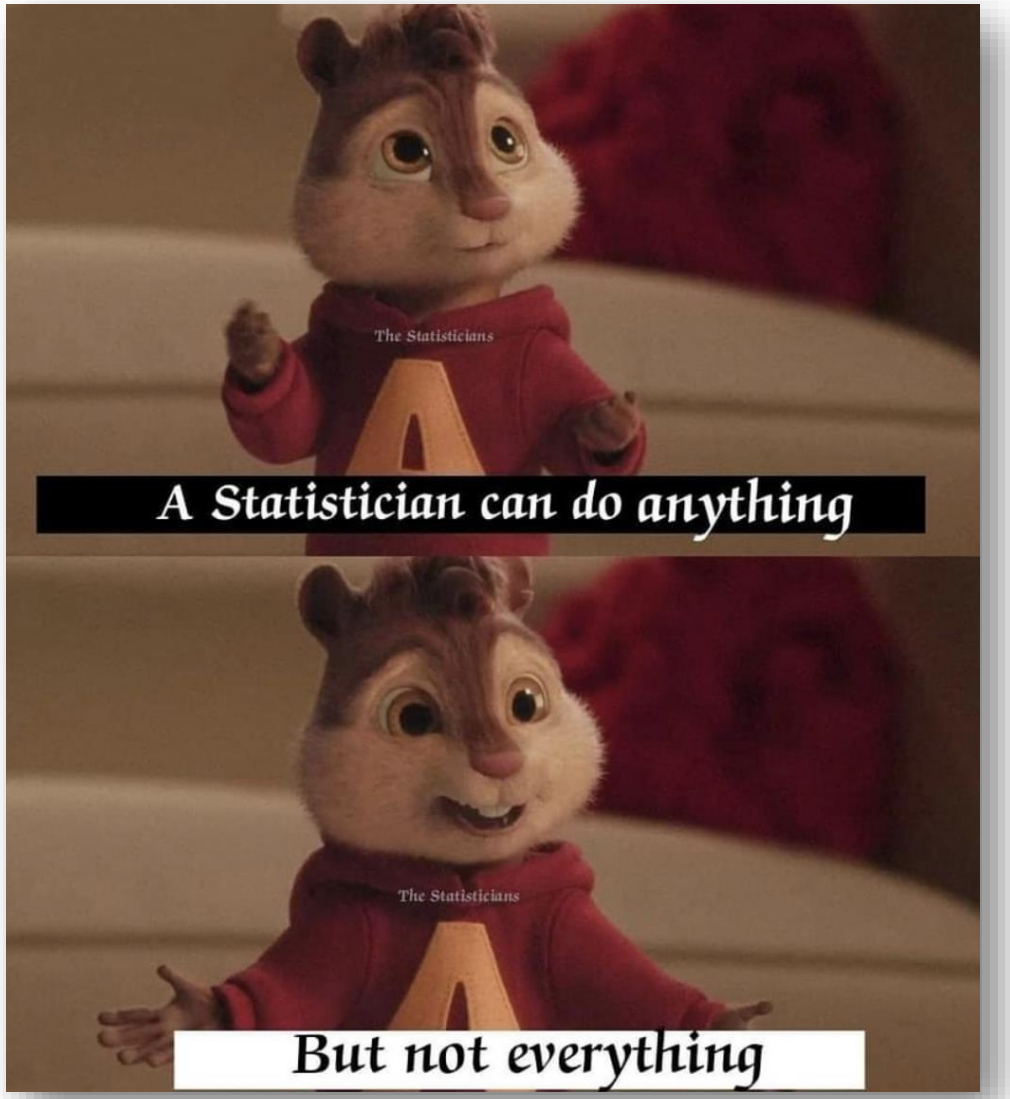
Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza <u>del disegno di studio</u>**
  - Descrizione dei dati e inferenza statistica
  - L'importanza della numerosità campionaria
  - La rappresentatività del campione
  - La tentazione delle analisi per sottogruppi

E' la struttura operativa dello studio, che permette di giungere a risultati:

1. **Credibili**
2. **Riproducibili**
3. **Generalizzabili**

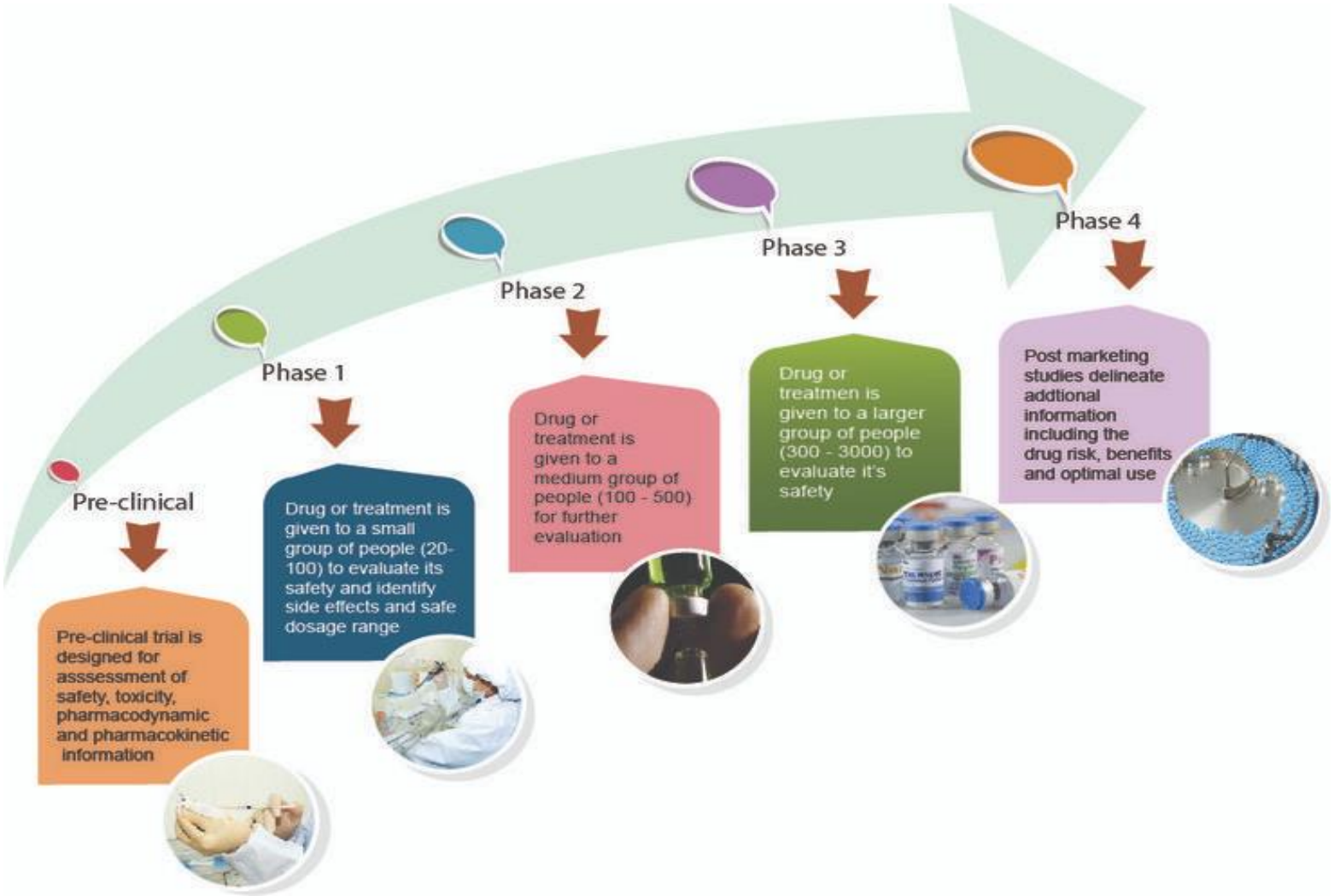
L'analisi Dovrebbe Essere Coerente Con Il Disegno Dello Studio!



'If you torture your data long enough, they will tell you whatever you want to hear'

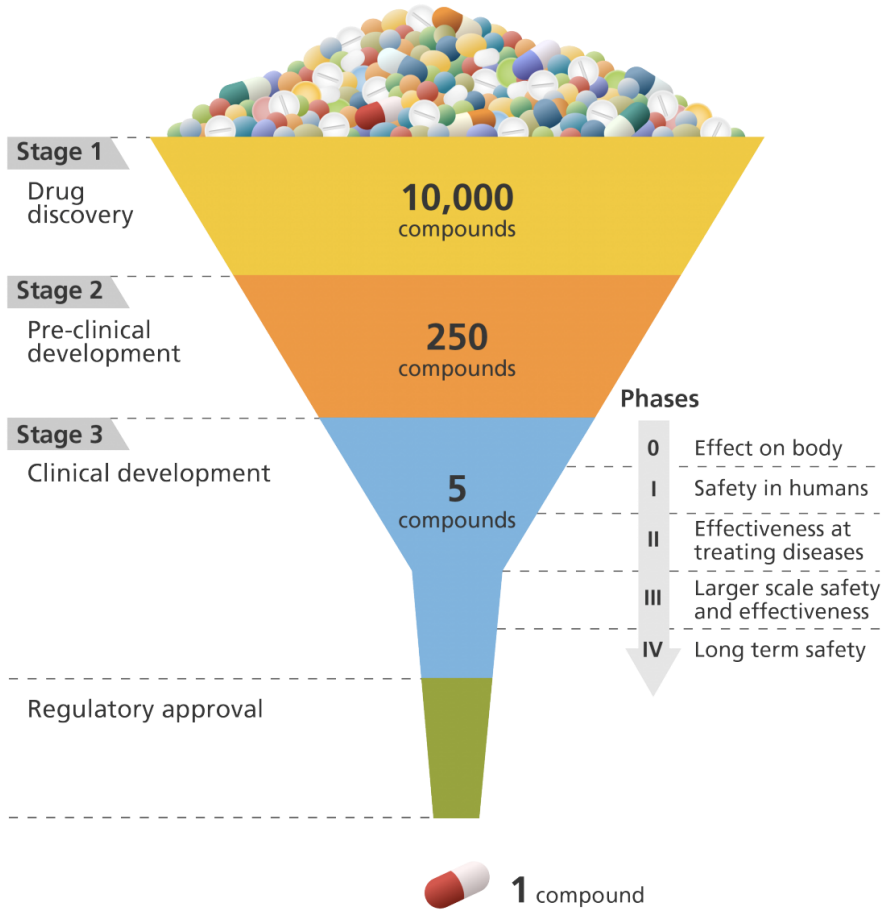
Mills, N Engl J Med 1993

Il programma di ricerca clinica



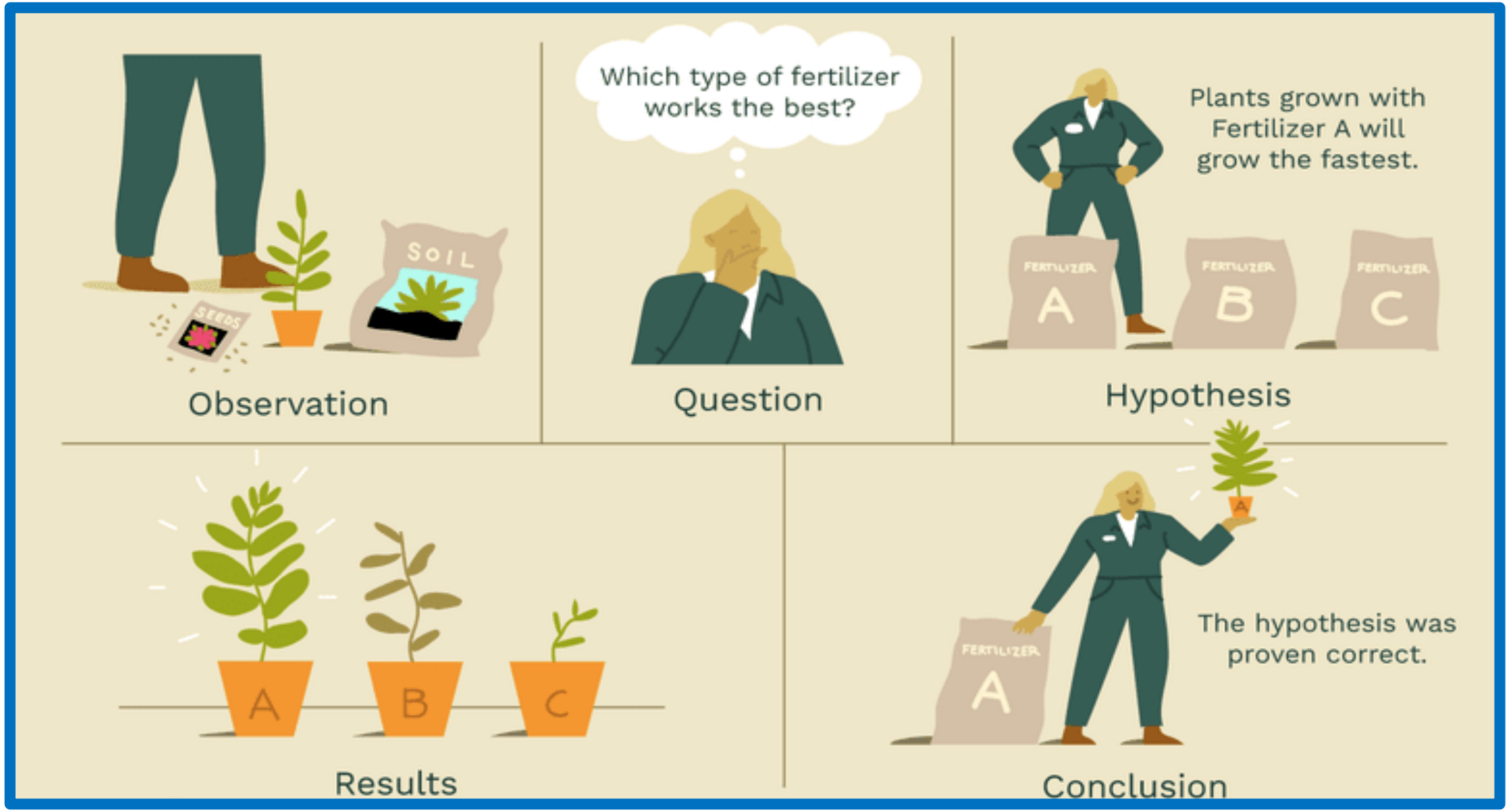
Source: www.pinterest.it/excaliburhealth

Drugs' Attrition: One out of 10,000 Coumpound!



Source: Genome Research Limited

Steps of the Scientific Method



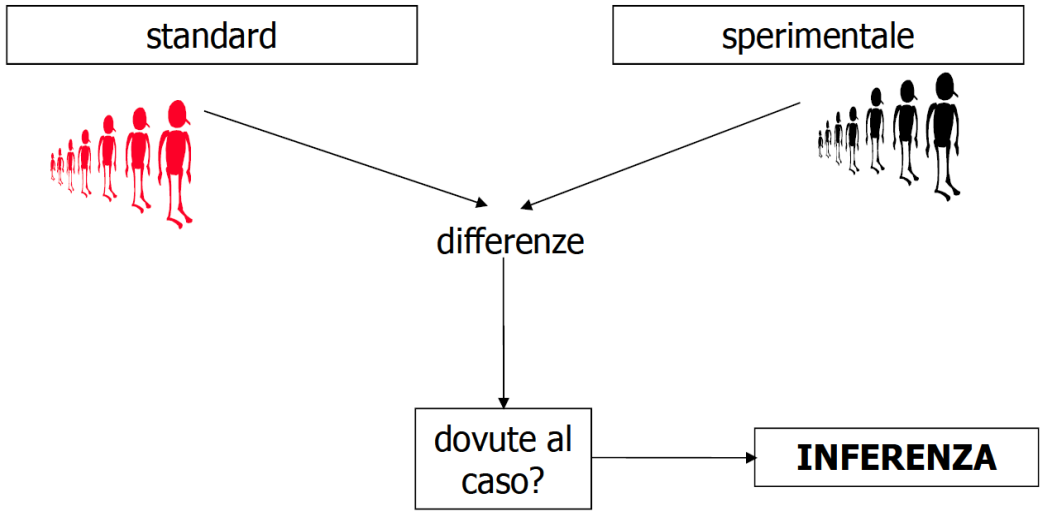
Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - **Descrizione dei dati e inferenza statistica**
  - L'importanza della numerosità campionaria
  - La rappresentatività del campione
  - La tentazione delle analisi per sottogruppi

- **Statistica descrittiva**: prende in considerazione gli aspetti di presentazione (es. tabelle e grafici) dei dati
- **Statistica inferenziale**: deriva conclusioni riguardanti le popolazioni a partire dallo studio di un campione

Courtesy of Valter Torri

Inferenza Statistica



Ipotizziamo che in un campione di pazienti la % risposte del trattamento A sia migliore rispetto a quella di B

Come interpretiamo questa differenza?

3 possibili ipotesi per giustificare la diversità osservata:

1. **Il confronto è viziato perché qualche fattore non considerato è responsabile della differenza osservata**
2. **La differenza è dovuta alla variabilità campionaria**
3. **A è effettivamente più attivo di B**

L'ipotesi 1 può essere esclusa disegnando bene l'esperimento

L'ipotesi 2 può essere esclusa applicando un test di significatività statistica

Soltanto dopo avere escluso le ipotesi 1 e 2 possiamo concludere che A è migliore di B

Studi Osservazionali *vs.* Studi Sperimentali

- An observational study draws inferences from a sample to a population where the independent variable is not under the control of the researcher.

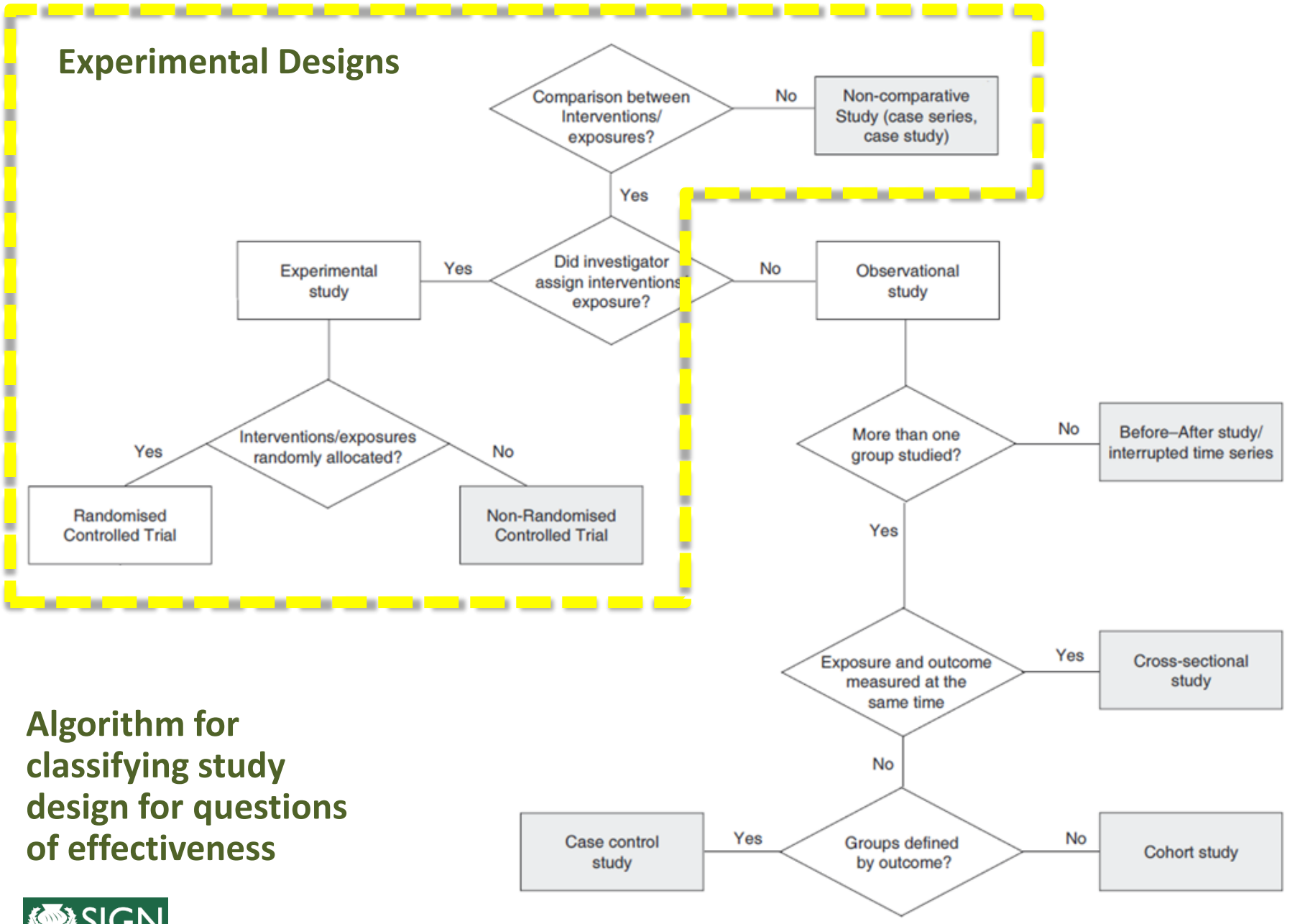
- The term observational study covers a wide range of study designs, a common feature of which is that they are non-interventional, in the sense that the study protocol does not determine the precise features of any therapy given to the participants in the study.

Studi non controllati

Studi controllati non randomizzati

Studi controllati randomizzati

Experimental Designs



Algorithm for classifying study design for questions of effectiveness

SIGN
Scottish Intercollegiate Guidelines Network

Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

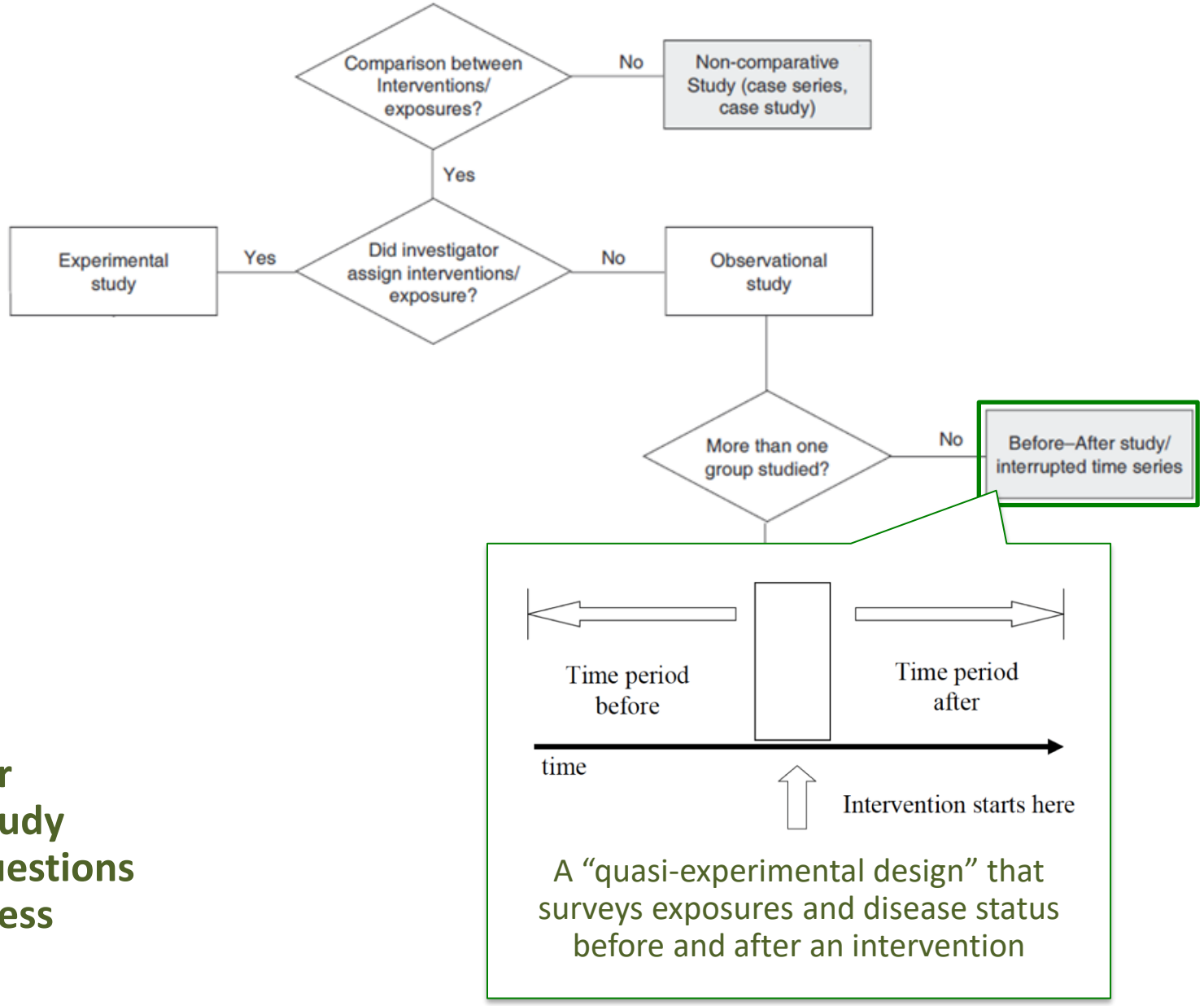
Identify the incidence of a particular outcome over time

Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions



Algorithm for classifying study design for questions of effectiveness

SIGN
Scottish Intercollegiate Guidelines Network

Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

Identify the incidence of a particular outcome over time

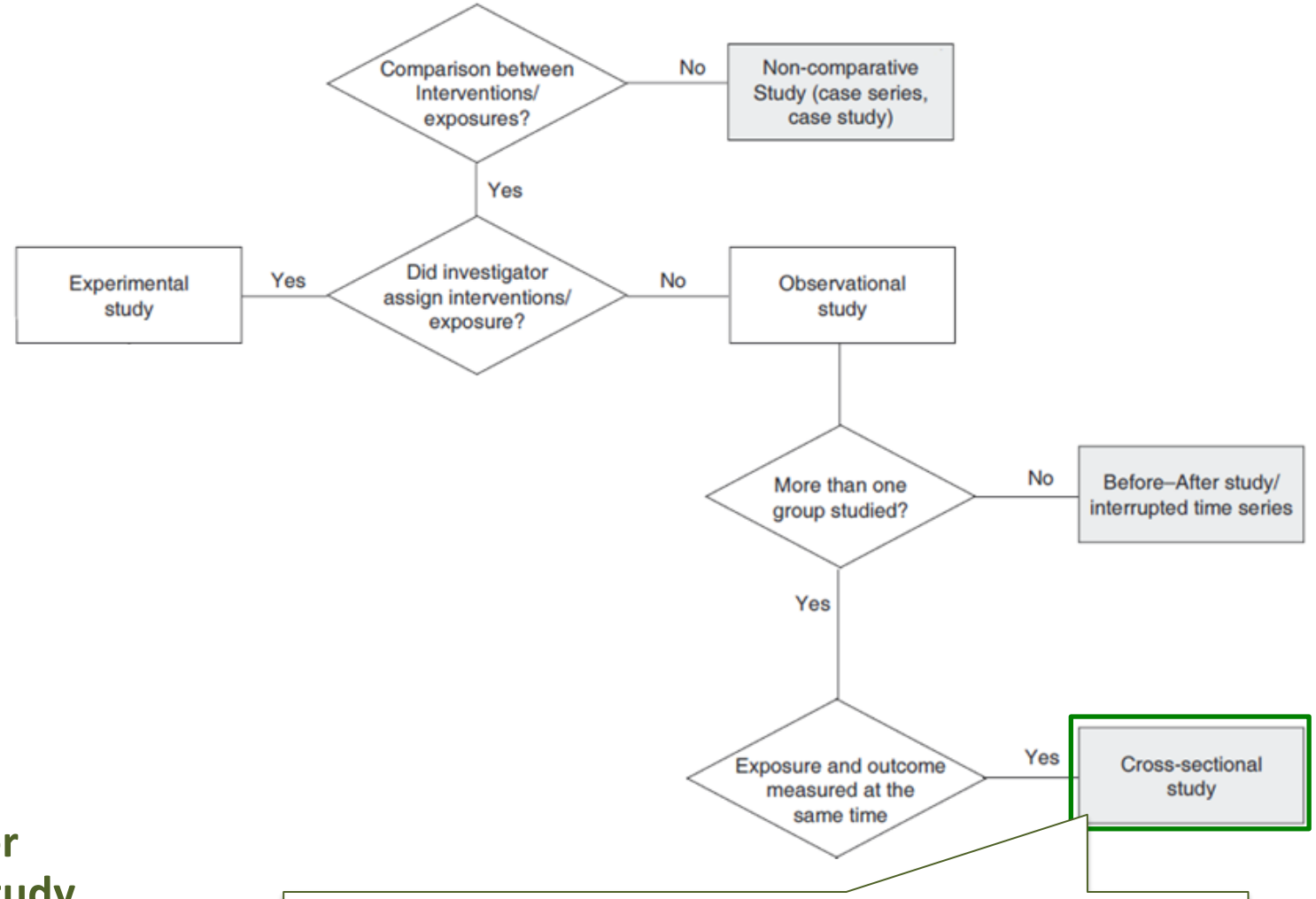
Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Algorithm for classifying study design for questions of effectiveness



Subjects selected irrespective of the presence or absence of the characteristics of interest. Similar to a case series, except that the purpose of the analysis is to record associations between variables, rather than merely to report frequencies of their occurrence

SIGN
Scottish Intercollegiate Guidelines Network

Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

Identify the incidence of a particular outcome over time

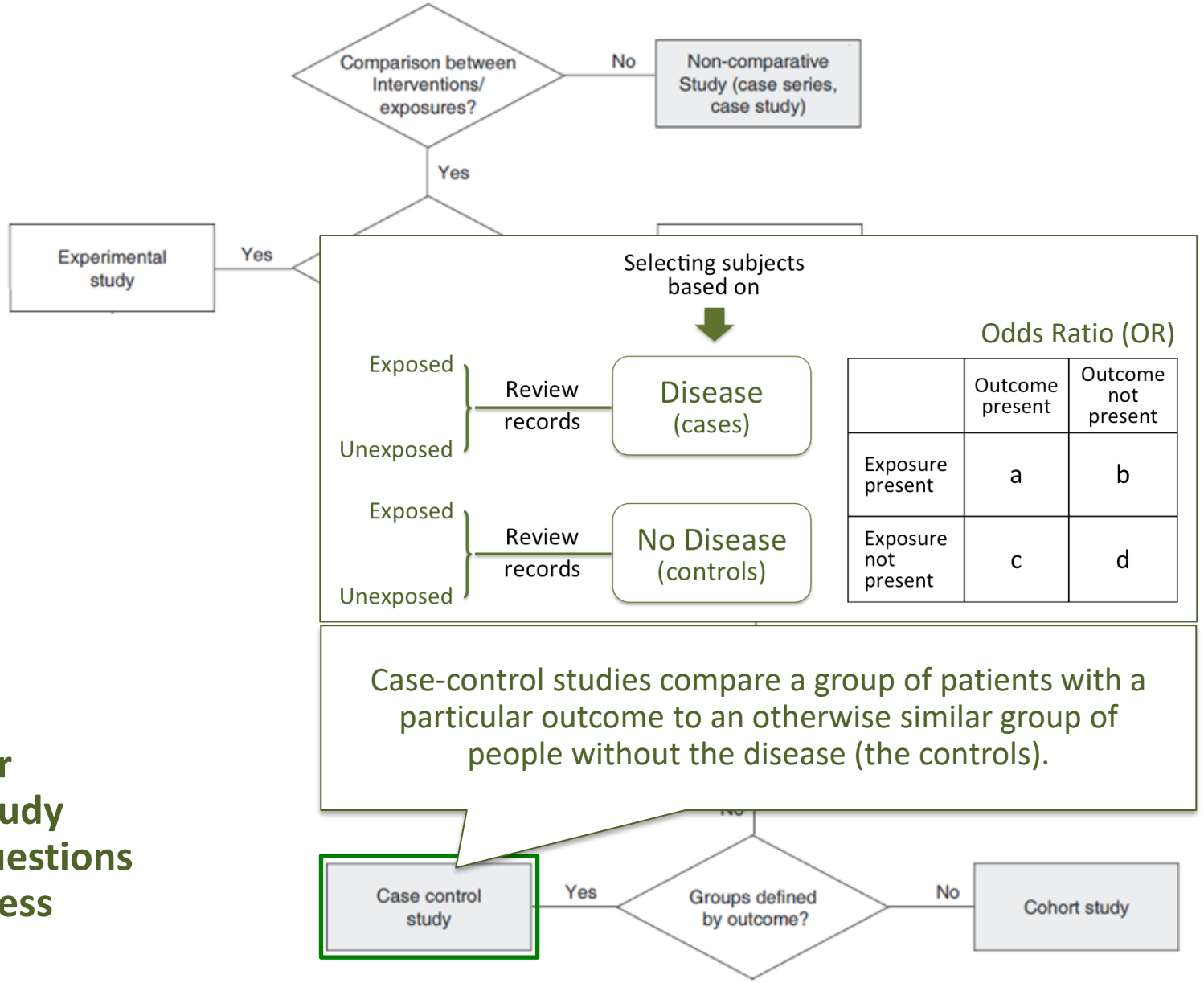
Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Algorithm for classifying study design for questions of effectiveness



Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

Identify the incidence of a particular outcome over time

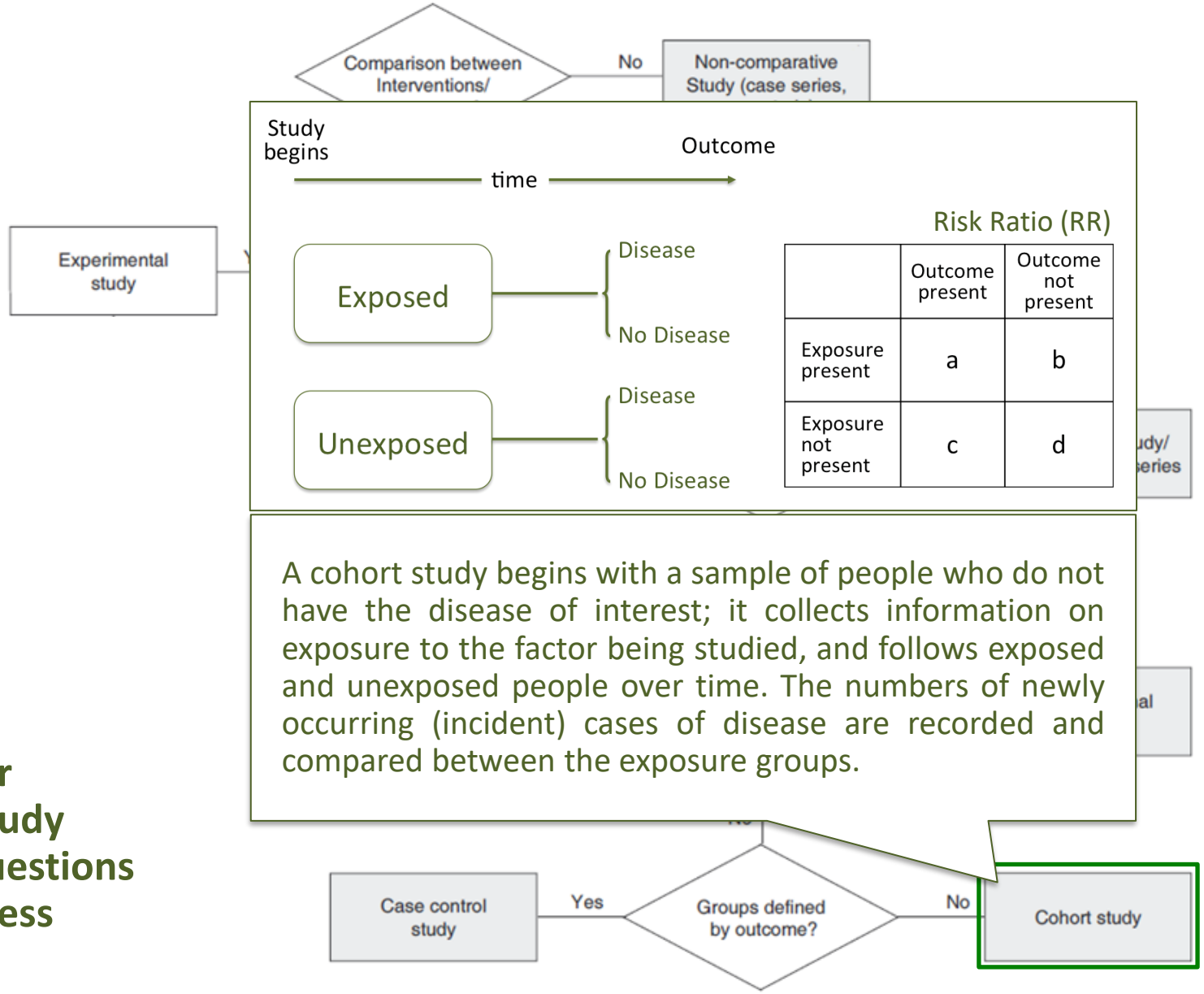
Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Algorithm for classifying study design for questions of effectiveness



SIGN
Scottish Intercollegiate Guidelines Network

Time matters…

Cross-Sectional Studies
(exposure and outcome measured at the same time)

Case-Control Studies
(groups defined by the outcome)

Cohort Studies
(groups not defined by the outcome)

Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particular outcome

Cohort

Identify the incidence of a particular outcome over time

Non-comparative case series

Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Observational Studies

“EPIDEMIOLOGIC” Vs “THERAPEUTIC”

Before-After

Surveys disease status before and after an intervention

Cross-Sectional

Provide information on prevalence of a particular condition at a single time point (time window)

Case-Control

Identify predictors of a particu outcome

Cohort

Identify the incidence of a particular outcome over time

Non-comparative case series

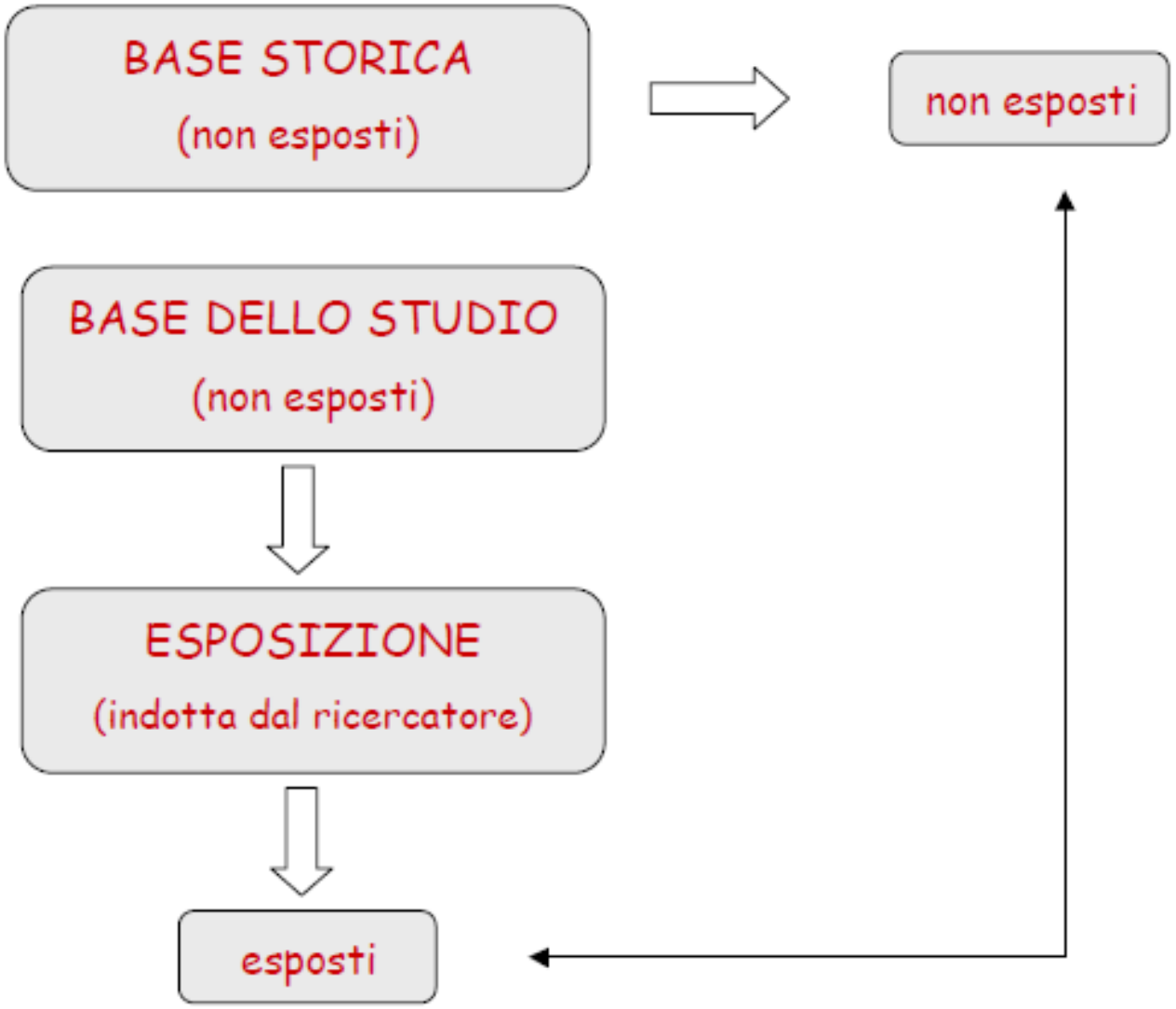
Report outcomes of patients who received a specific intervention

Comparative case series

Compare outcomes between patients who received different interventions

Any observed difference between the outcomes of study arms may be attributable to baseline differences rather than to a true treatment effect.

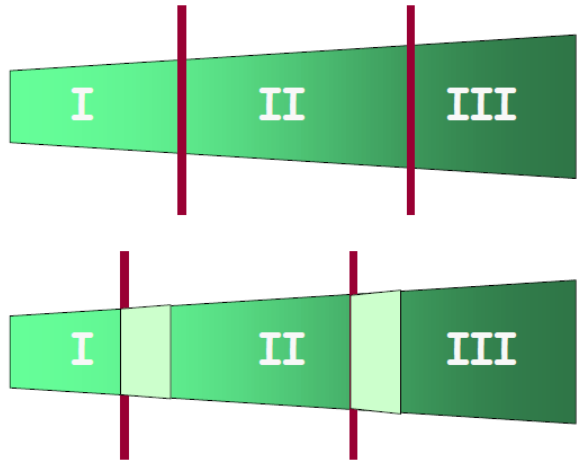
Studi non controllati (*es. controlli storici*)



Problemi

- Variabilità del decorso
- Selezione della popolazione
- Effetto “placebo”

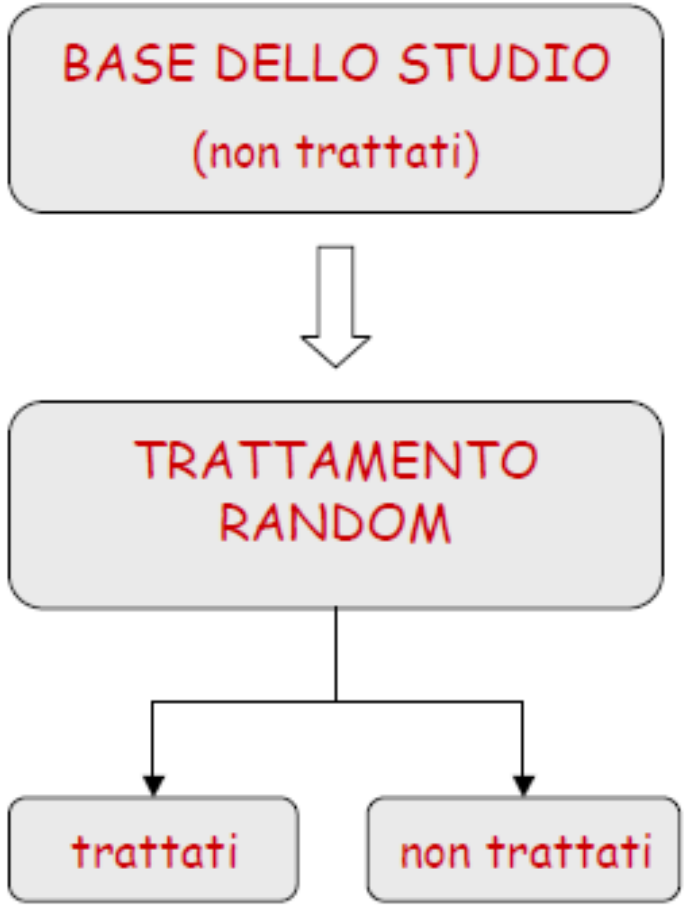
La migrazione di stadio: il fenomeno di Will Rogers



Studi Controllati

Studi con controlli paralleli

Studi randomizzati



Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - **Descrizione dei dati e inferenza statistica**
  - **<u>L'importanza della numerosità campionaria</u>**
  - **La rappresentatività del campione**
  - **La tentazione delle analisi per sottogruppi**

La Precisione della Stima

Numeri assoluti	Proporzione Osservata	Intervallo di confidenza 95%
2/10	20%	0.1% - 44.8%
4/20	20%	2.5% - 37.5%
6/30	20%	5.7% - 34.3%
8/40	20%	7.6% - 32.4%
10/50	20%	8.9% - 31.1%
12/60	20%	9.9% - 30.1%
14/70	20%	10.6% - 29.4%
16/80	20%	11.2% - 28.8%
18/90	20%	11.7% - 28.3%
20/100	20%	12.2% - 27.8%
50/250	20%	15.0% - 25.0%

Fattori che influenzano la numerosità del campione in una sperimentazione clinica

Importanza della Numerosità Campionaria

- Immaginiamo di voler verificare la superiorità di un trattamento sperimentale rispetto allo standard
- Fissati il rischio di risultato falso positivo (5%) e la potenza (80%), il numero di eventi necessari dipende dall'entità dell'impatto prognostico che ipotizziamo (**Hazard Ratio**)

Hazard Ratio (HR)	Numero di eventi necessari
0.80	631
0.70	247
0.60	121
0.50	66
0.40	38
0.30	22
0.20	13
0.10	6

Numero di eventi	Potenza
20	20%
30	28%
40	36%
50	44%
60	51%
70	57%
80	63%
90	68%
100	72%
110	76%
120	80%

Objectives and End-points

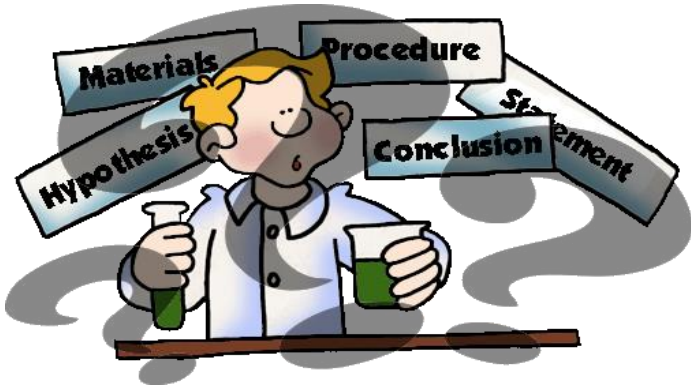
- The selection of endpoints in a clinical trial is extremely important and requires a marriage of:
  - Clinical relevance
  - Statistical reasoning.
- The motivation for every clinical trial begins with a scientific question.

- The primary objective of the trial is to address the scientific question by collecting appropriate data.
- The selection of the primary endpoint is made to:
  - Address the primary objective of the trial.

Evans SR, J Exp Stroke Transl Med 2011

Objectives and End-points

- The primary end-point should be:
  - Clinically relevant
  - Interpretable
  - Sensitive to the effects of intervention
  - Practical and affordable to measure
  - Ideally measured in an unbiased manner
- Endpoints can generally be categorized by their scale of measurement.

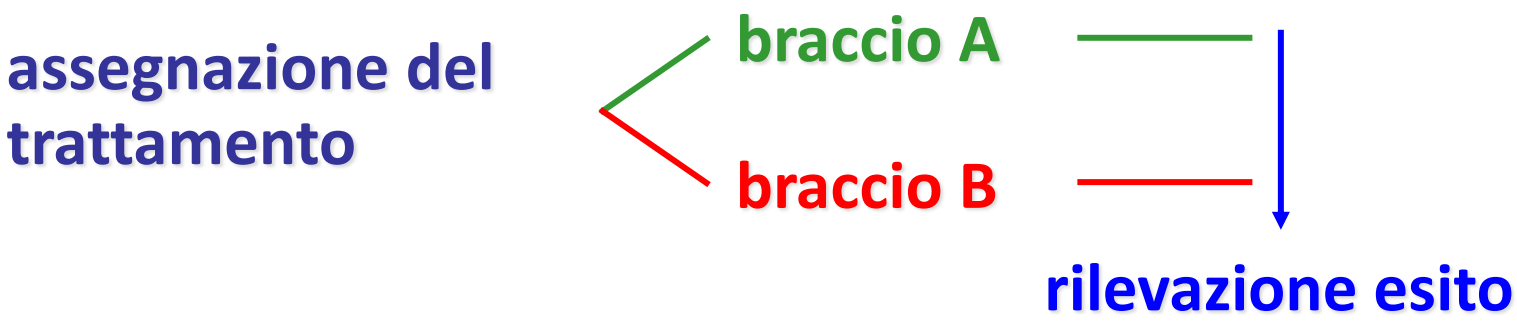


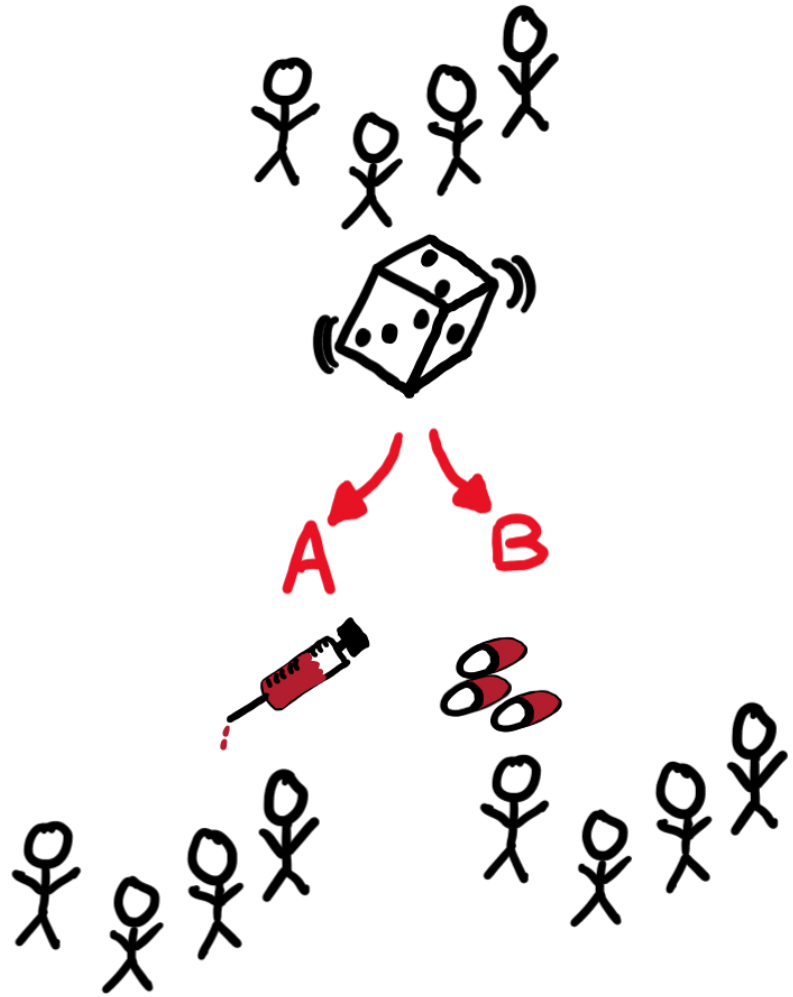
- The 3 most common types of endpoints in clinical trials are:
  - Continuous endpoints (ex. Pain-VAS),
  - Categorical (ex. binary, response vs. no response)
  - Event-time endpoints (ex. time to death)
- The scale of the primary endpoint impacts:
  - Analyses
  - Trial power
  - Costs

Evans SR, J Exp Stroke Transl Med 2011

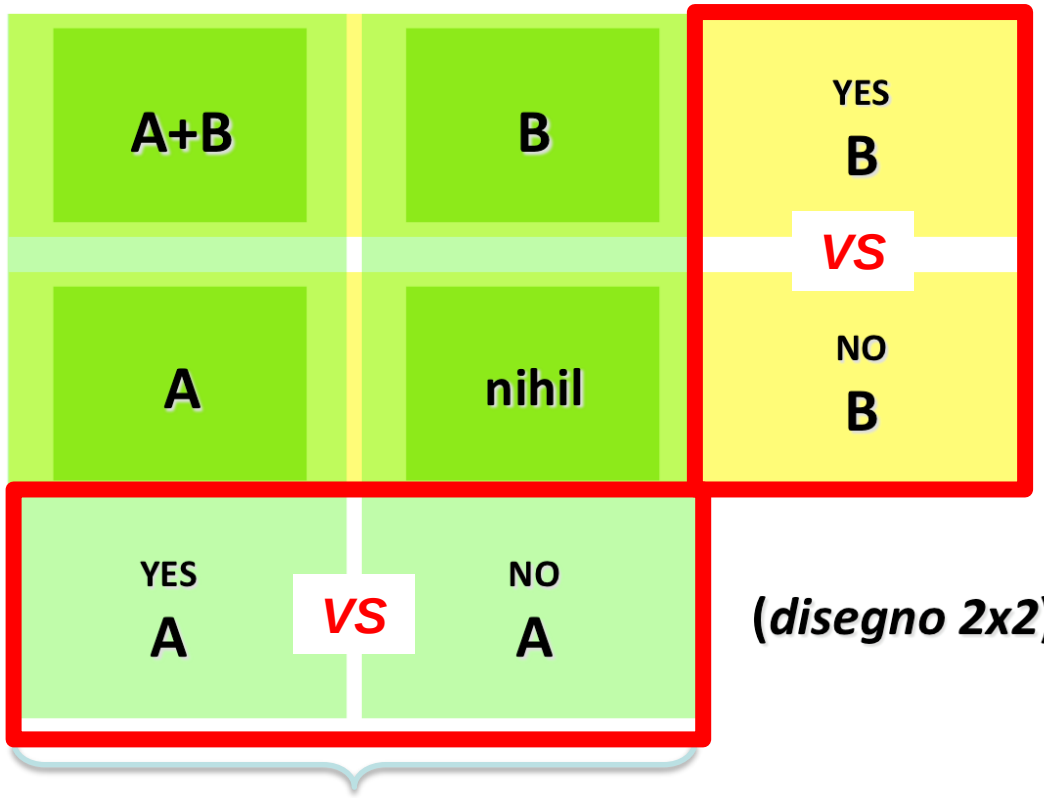
Disegno a Bracci Paralleli

Assegnazione del paziente a un gruppo di trattamento, al quale si appartiene per l'intera durata dello studio:





Disegno Fattoriale



Valuta l'efficacia di B

(*disegno 2x2*)

Valuta l'efficacia di A

Prerequisito: non interazione tra gli effetti degli interventi ("righe Vs colonne")

Factorial Design for RCTs

- The sample size of the factorial design is based on a non-interaction assumption between the two aimed questions.
- The application of factorial design allows two independent questions to be answered using the same patients:
  - In other words, it is a simple way to conduct two trials in one.
- If a significant interaction is expected, or it emerges during the trial (ex. other evidence), it should be kept in mind that its occurrence could make the primary result of the trial practically useless, and the unique useful information could come from secondary, less powered analyses.

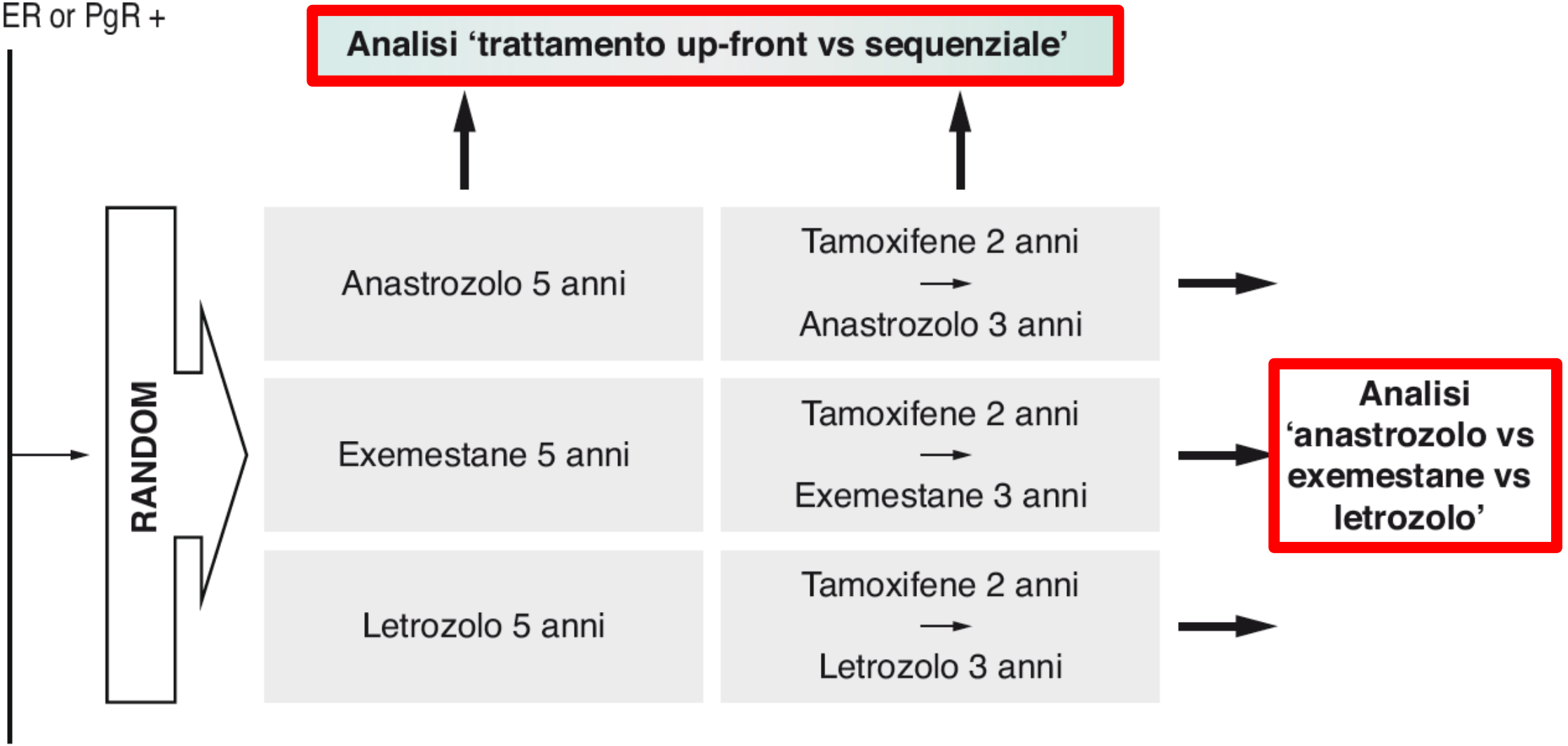
Bria E et al, Ann Oncol 2016

Gruppo Italiano Mammella (GIM) Studies

Source: Trial Sponsors > Index > G > Gruppo Italiano Mammella (GIM)

Pazienti

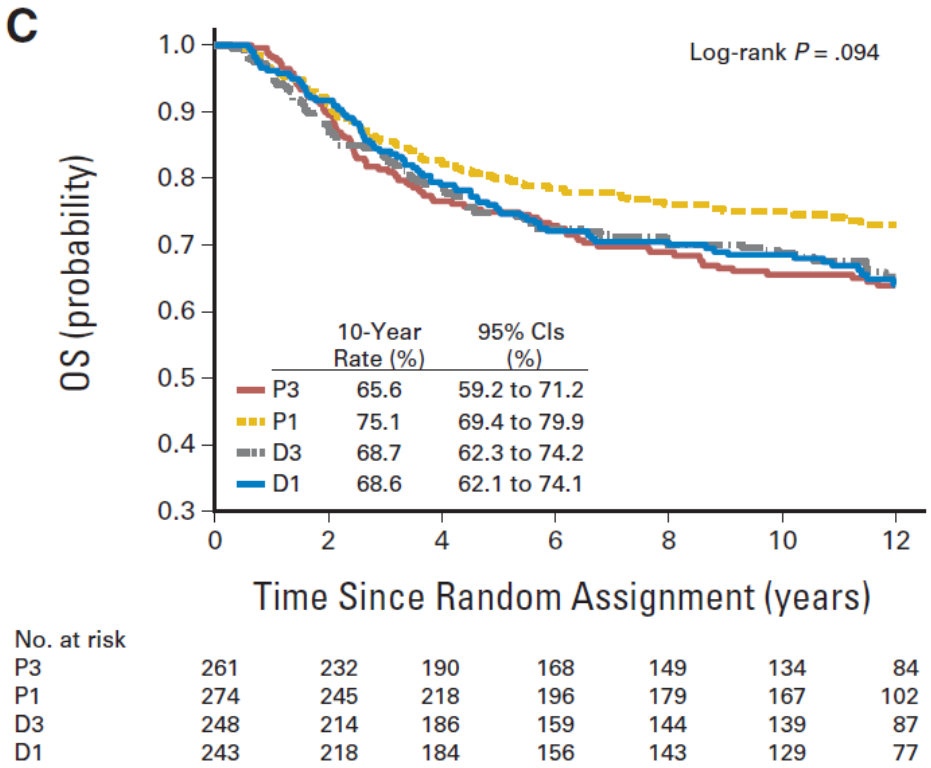
- Carcinoma mammario operato
- Postmenopausa
- ER or PgR +



Paclitaxel in TNBC

Weekly Paclitaxel	Weekly Docetaxel	WEEKLY
		vs
3-Weekly Paclitaxel	3-Weekly Docetaxel	3-WEEKLY
PACLITAXEL *vs*	DOCETAXEL	

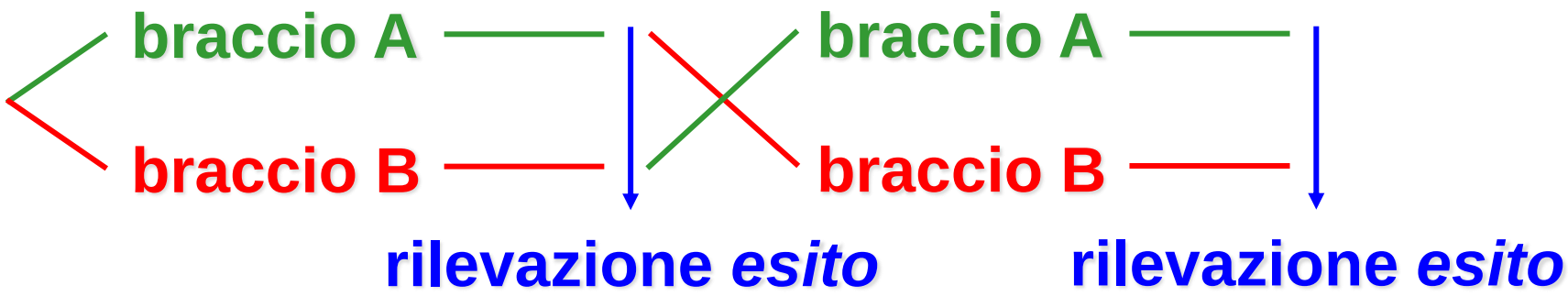
E1199 Trial, TNBC subgroup (SEE LATER!!!!)



Sparano JA et al, J Clin Oncol 2015

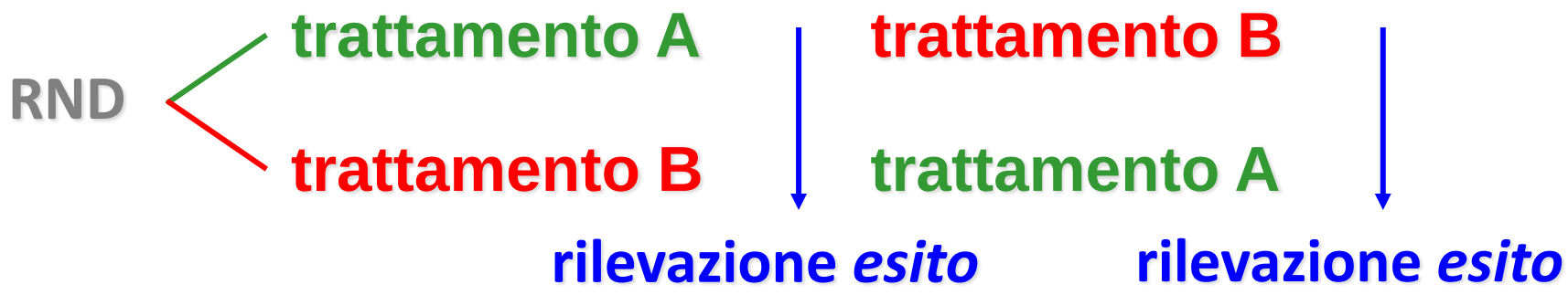
Disegno Crossover

Ciascun paziente riceve entrambi i trattamenti oggetto di sperimentazione clinica (*within patient* vs *between patient*):

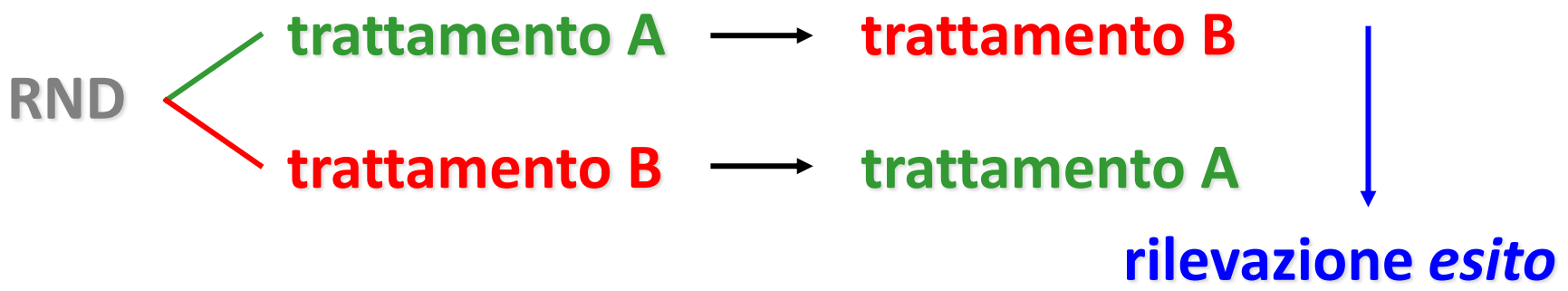


Viene "sottratta" dal confronto dei trattamenti l'influenza delle caratteristiche del paziente, le quali possono influire sull'indicatore di effetto → dimensione campionaria minore rispetto a uno studio a bracci paralleli.

ATTENZIONE A NON CONFONDERE UN DISEGNO CROSSOVER…



…CON UN DISEGNO A BRACCI PARALLELI DI TIPO SEQUENZIALE

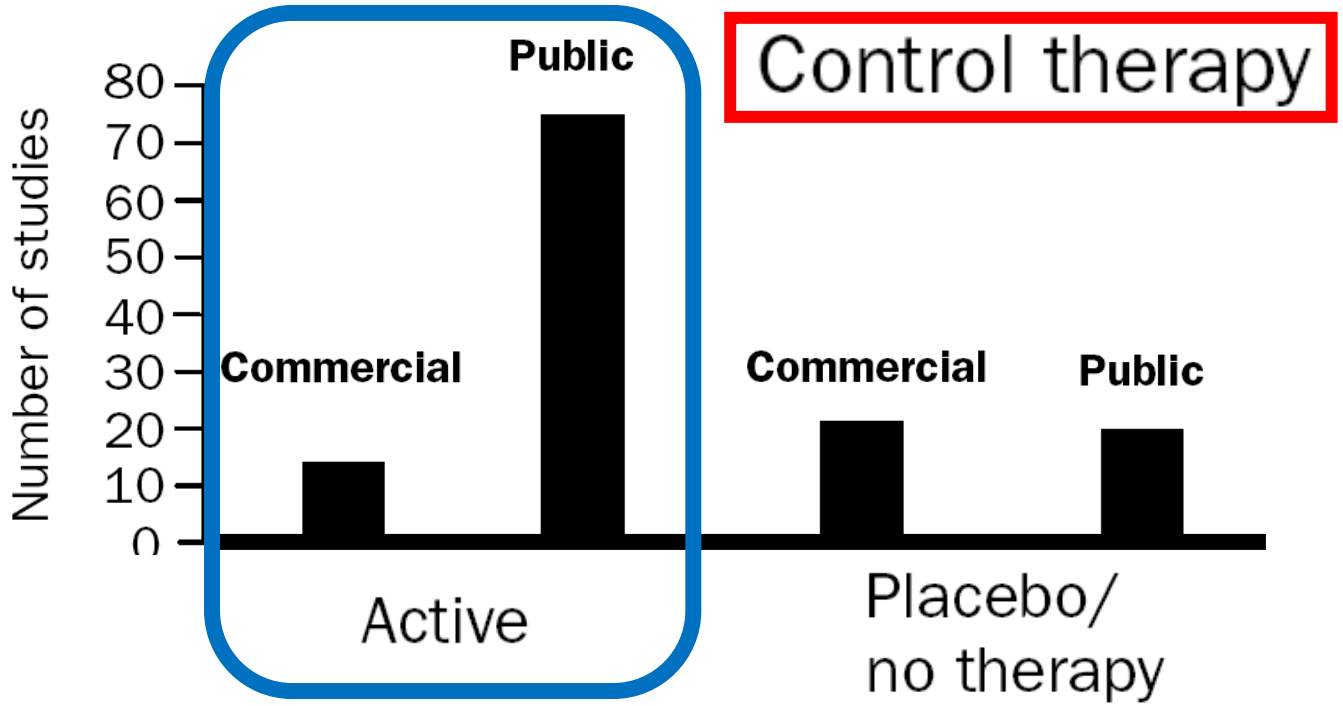


Do not forget the Choice/Performance of the Control Arm!

The uncertainty principle and industry-sponsored research

Choice of Control Group

- The selection of an appropriate control group is a critical decision which impacts on the scientific validity and ethical acceptability of a clinical investigation.
- The proper control group allows for discrimination between patient outcomes caused by the test treatment, and outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.



- **Active Control adopted in <20% of COMMERCIAL trials vs >80% of PUBLIC**

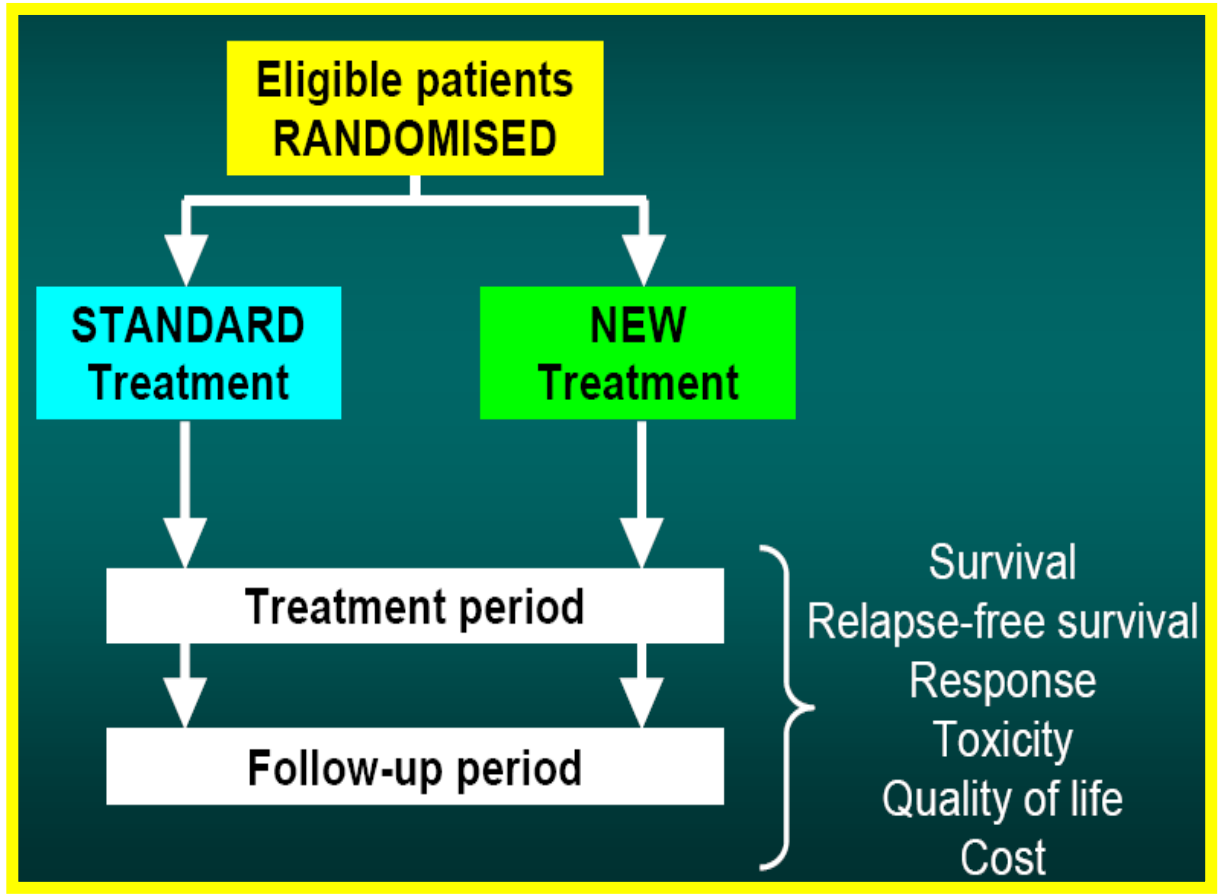
Djulbegovic B et al, Lancet 2000

Dall'Ipotesi al Disegno di una Sperimentazione Clinica

- **Premessa: la buona ricerca clinica**
- **L'importanza del disegno di studio**
  - Descrizione dei dati e inferenza statistica
  - L'importanza della numerosità campionaria
  - La rappresentatività del campione
  - **La tentazione delle analisi per sottogruppi**

'San Matteo e L'angelo' (Particolare), Caravaggio, 1602, San Luigi dei Francesi, Roma

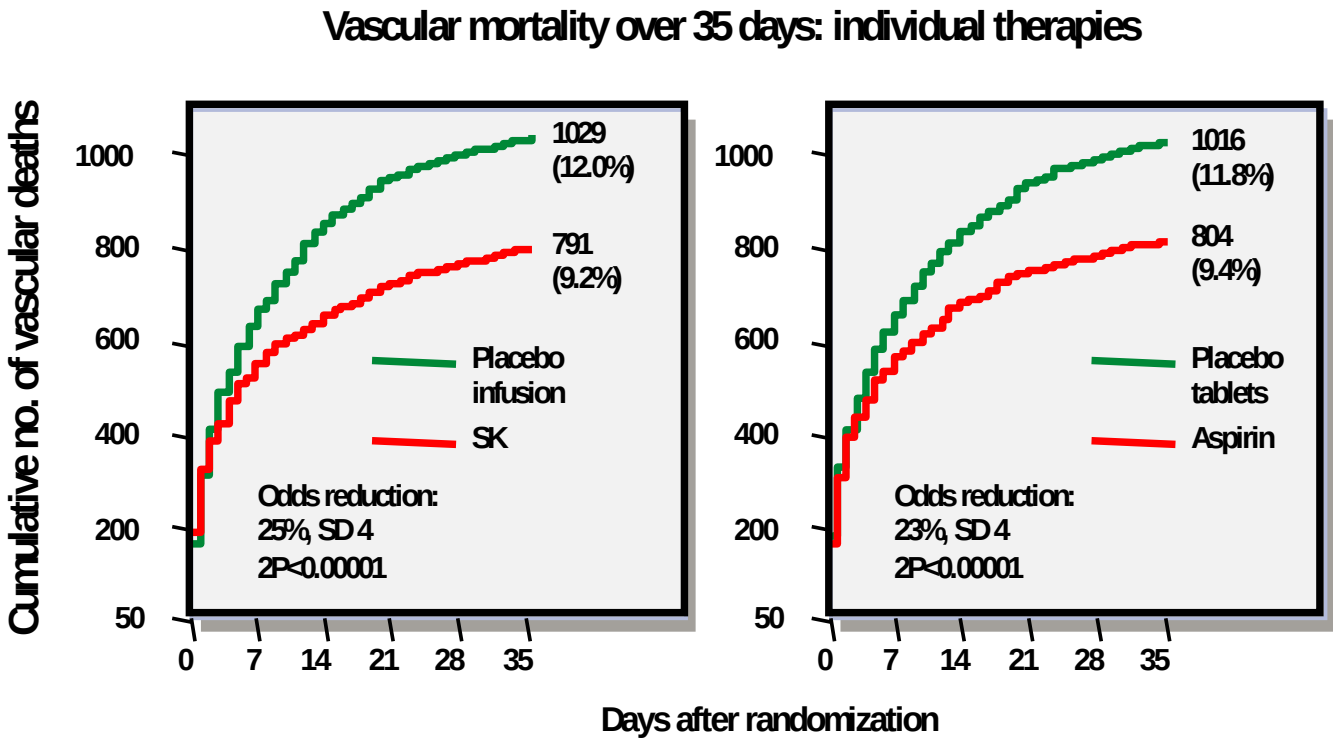
Issues with Randomized Ph. III Clinical Trials

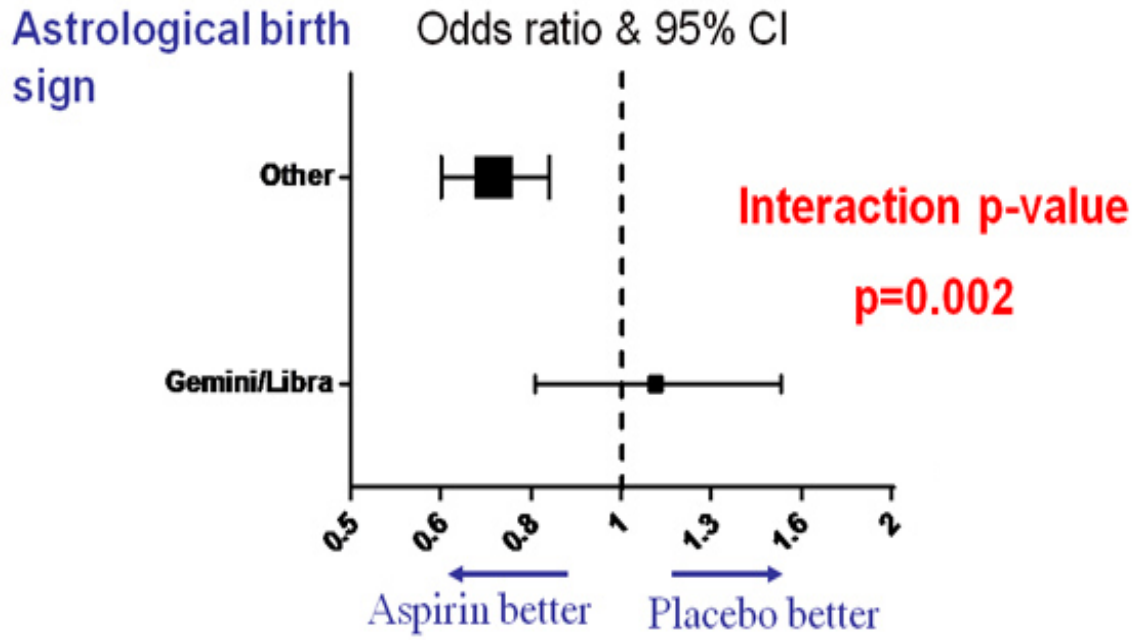


- **The new drug is more effective than other drugs?**
  - **Superiority trial (is 'statistically' relevant?)**
- **The new drug is as effective as other drugs but with fewer side effects (or minor discomfort or lower costs)?**
  - **Non-inferiority trial**
- **The use of the new drug determines a therapeutic benefit for patients?**
  - **Amount of the benefit (is 'clinically' relevant?)**
- **What categories of patients may derive more benefit from the new drug?**
  - **Subgroup analysis**

Subgroup Analyses:
The Case of '*Gemini & Libra*' in ISIS2 Trial

ISIS-2: aspirin vs control - effects on vascular death in 17,187 patients with acute myocardial infarction (Peto et al, Lancet 1988)

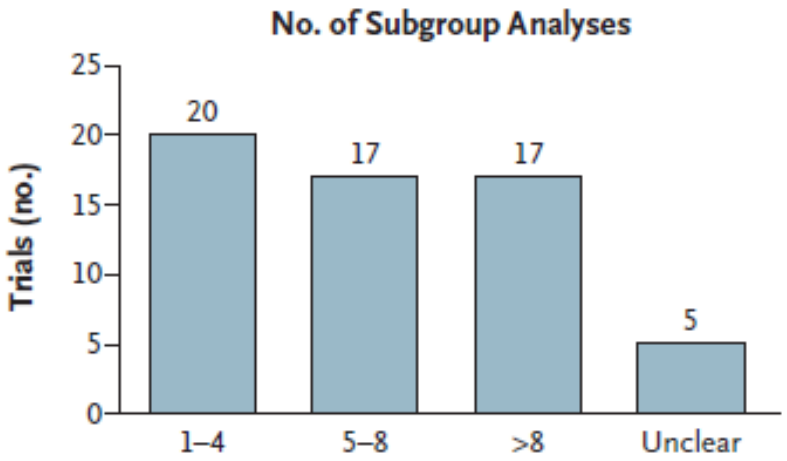


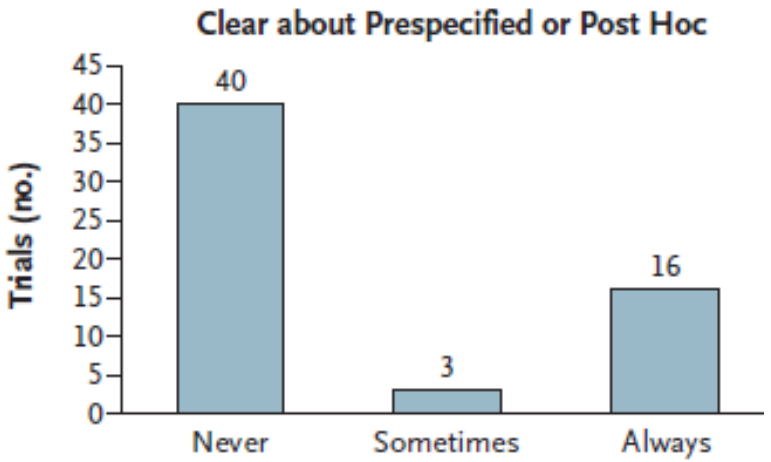


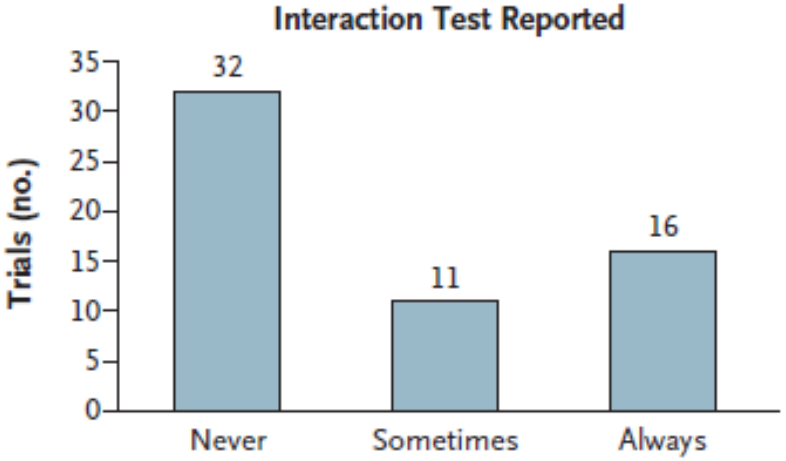
The ISIS-2 Collaborative Group. Lancet 1988

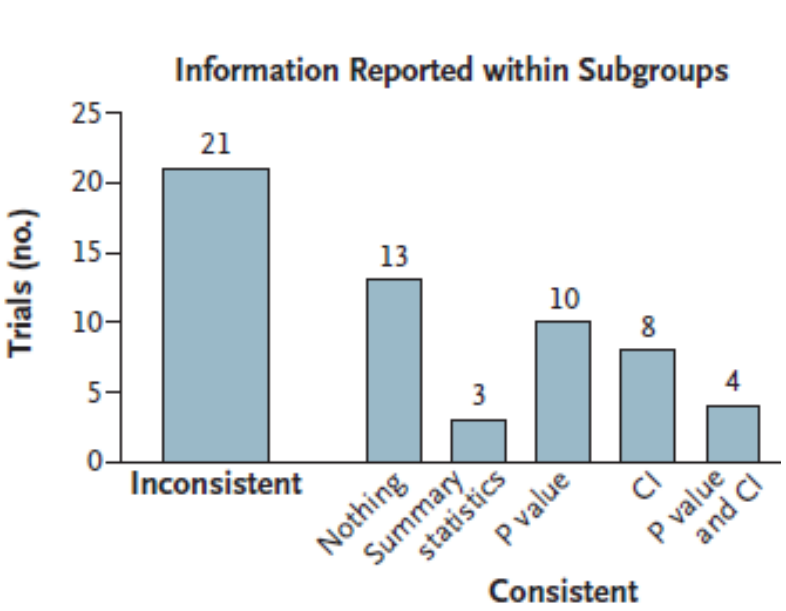
Courtesy of Michiels S, ESMO 2008

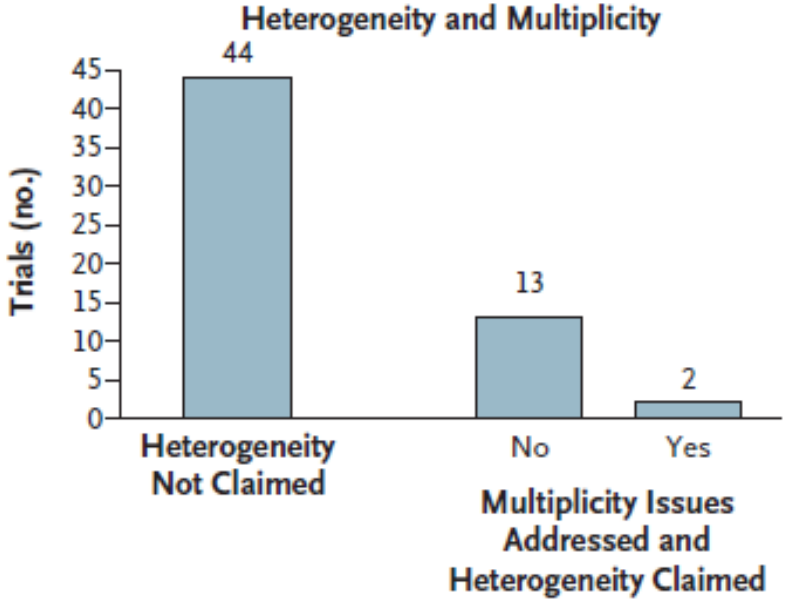
Reporting of Subgroup Analyses in Clinical Trials

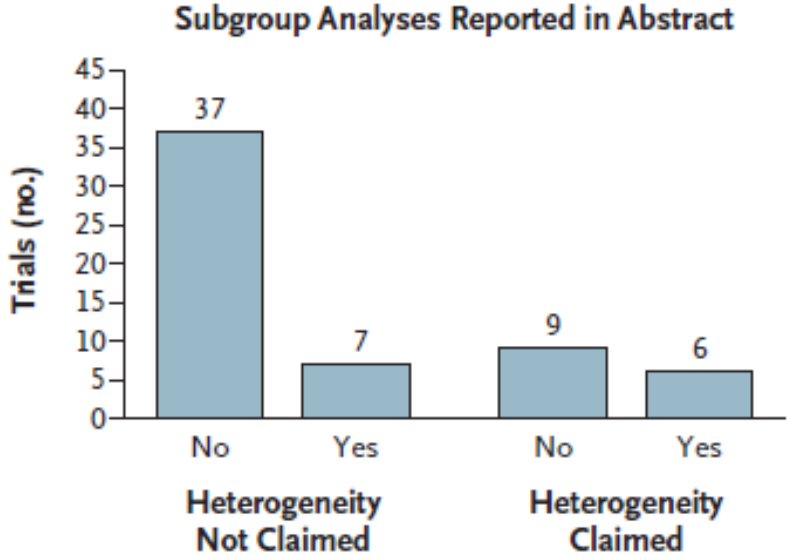










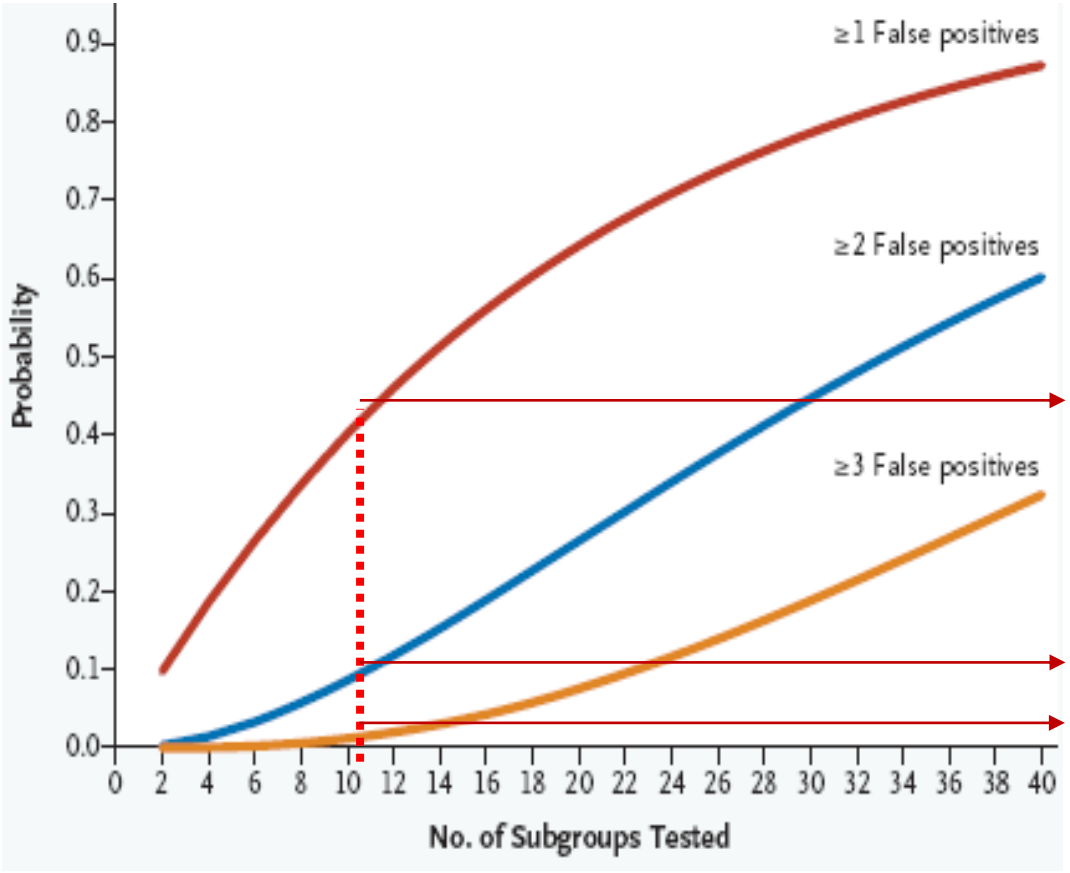


Wang R ey al, NEJM 2007

False Positive (F.P.) Risk when Testing Subgroups in RCTs

Ex.: if you test 10 subgroups, your F.P. chance is:

The Challenge of Subgroup Analyses — Reporting without Distorting



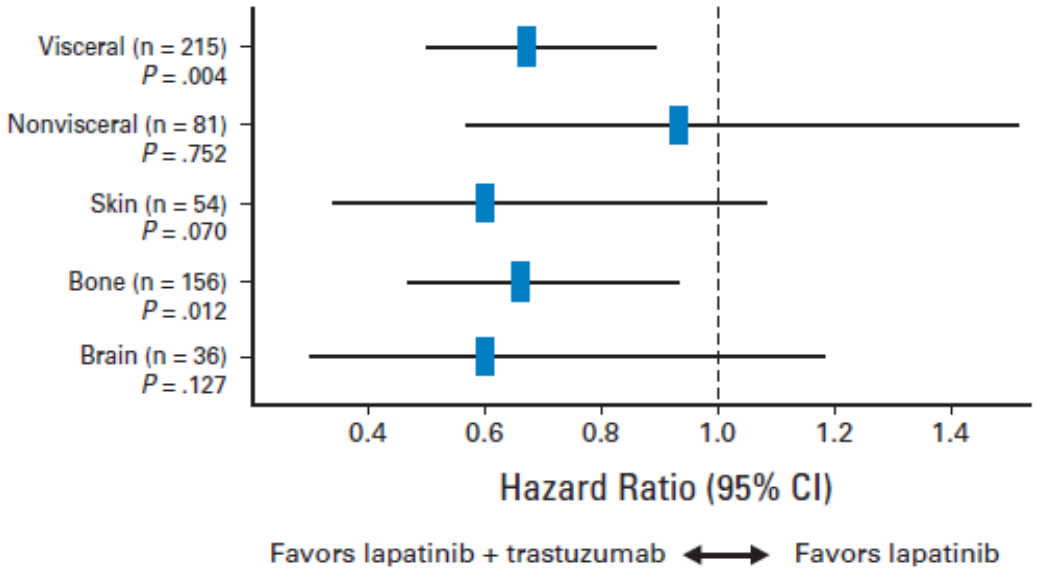
Probability That Multiple Subgroup Analyses Will Yield at Least One (Red), Two (Blue), or Three (Yellow) False Positive Results.

Souglakos et al, NEJM 2006

HER2+ ABC: Subgroup Analyses with anti-HER2 agents

LAP vs. LAP-trast

……Patients presenting with visceral or bone disease at baseline experienced a longer PFS if treated with the combination therapy……



No significant Interaction!

Blackwell KL et al, JCO 2010

PER + TRAS-Doc vs. TRAS-DOC

PFS

No significant Interaction!

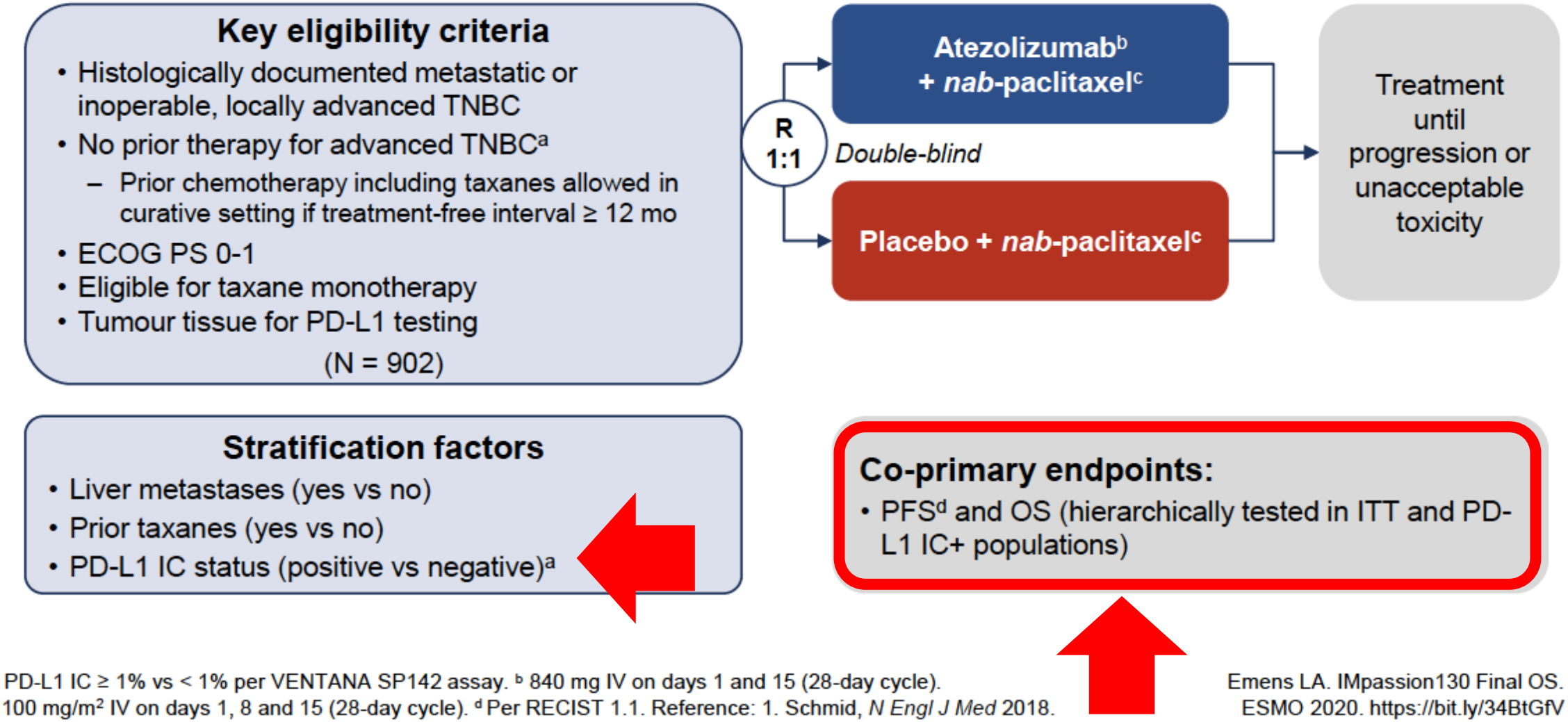
OS

Significant Interaction!

Unfortunately, these data are not highlighted in the paper, and the curve according to disease type is NEVER report in *ANY* paper!

Swain S et al, NEJM 2015

IMpassion 130: Study Design



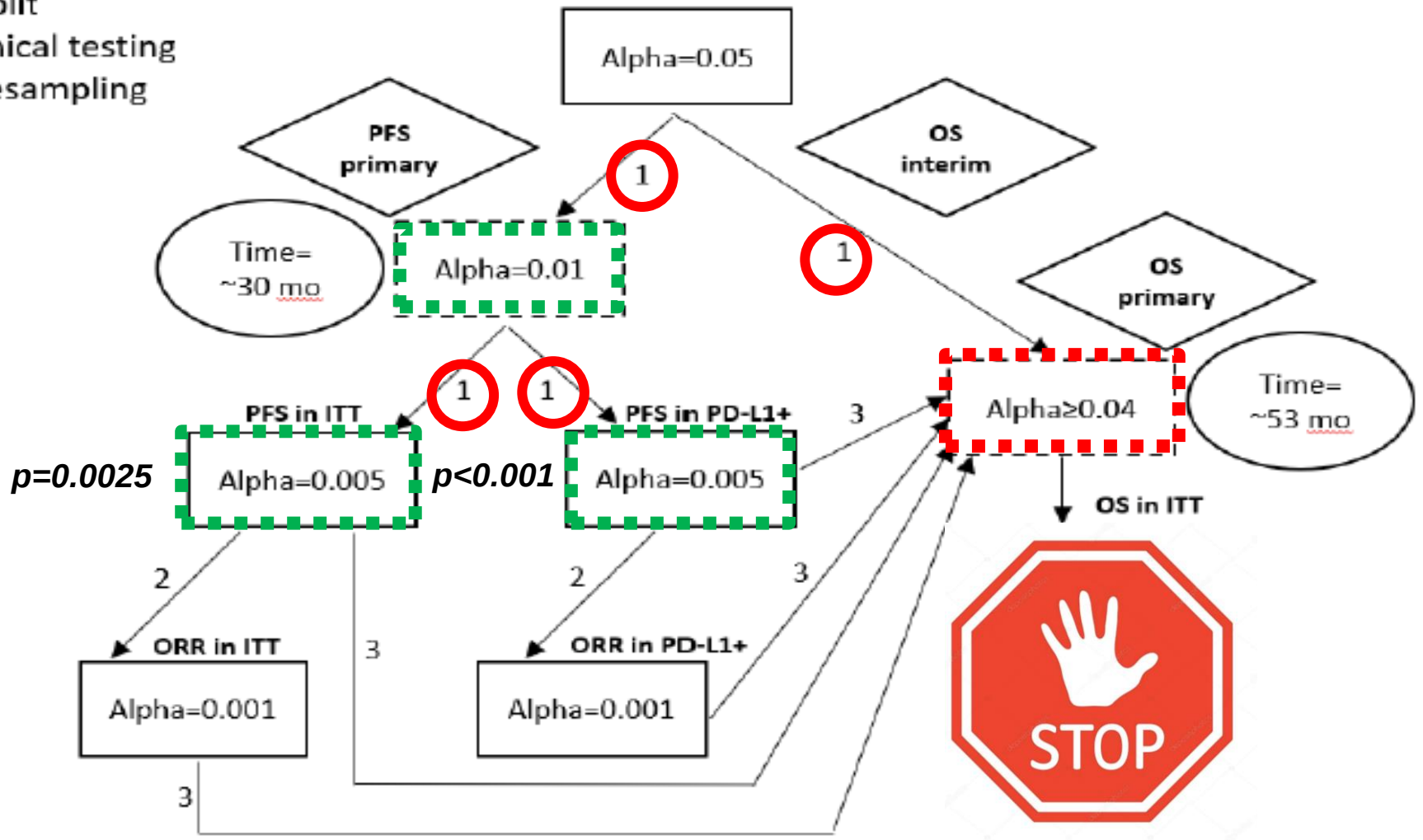
[a] PD-L1 IC ≥ 1% vs < 1% per VENTANA SP142 assay. [b] 840 mg IV on days 1 and 15 (28-day cycle).
[c] 100 mg/m² IV on days 1, 8 and 15 (28-day cycle). [d] Per RECIST 1.1. Reference: 1. Schmid, *N Engl J Med* 2018.

Emens LA. IMpassion130 Final OS. ESMO 2020. https://bit.ly/34BtGfV

Emens LA et al, ESMO 2020

IMpassion 130: Study Design & Stat. Assumptions

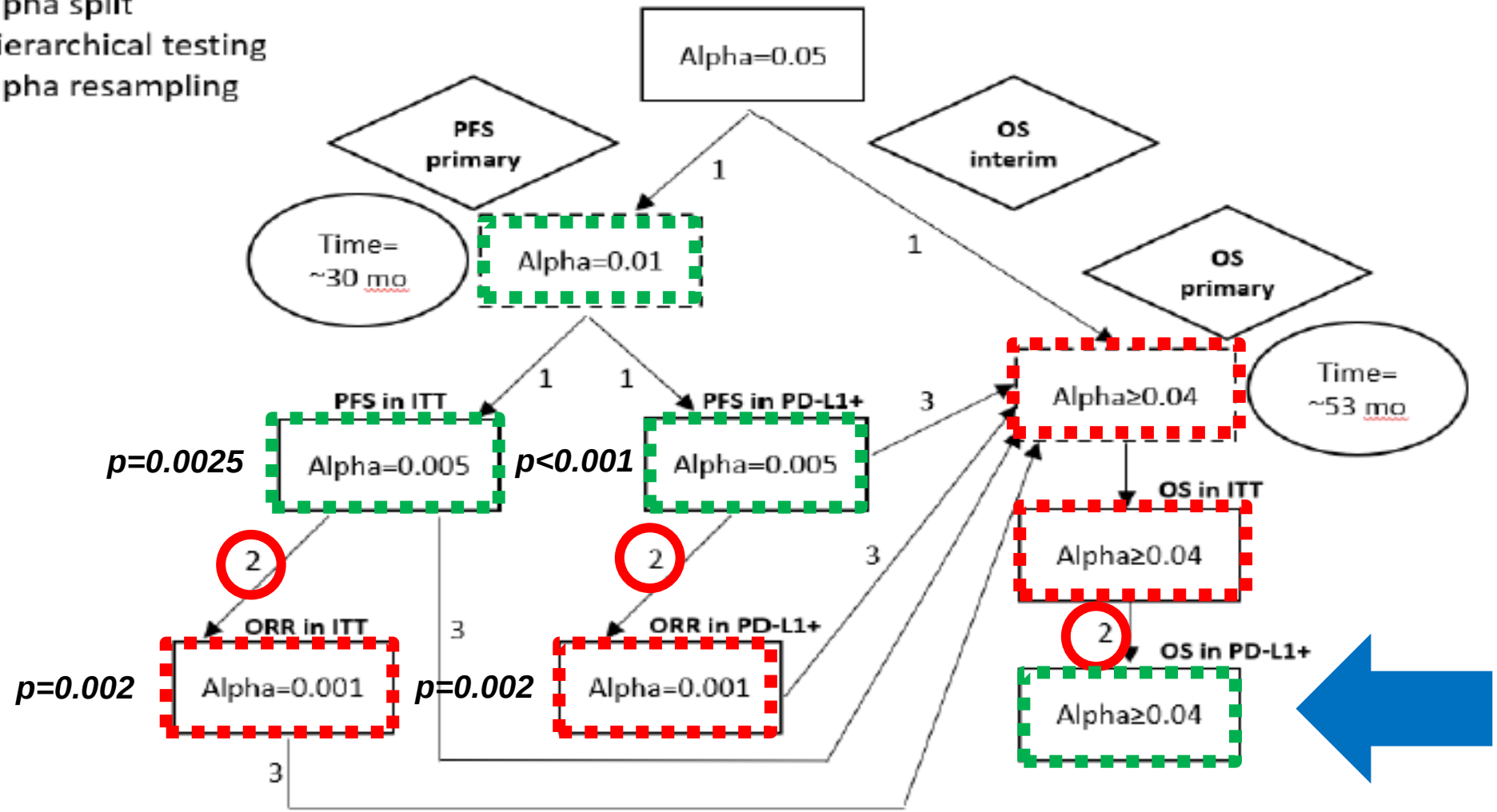
Type I error control:
1 = alpha split
2 = hierarchical testing
3 = alpha resampling



Shmid et al NEJM 2018

IMpassion 130: Study Design & Stat. Assumptions

Type I error control:
1 = alpha split
2 = hierarchical testing
3 = alpha resampling

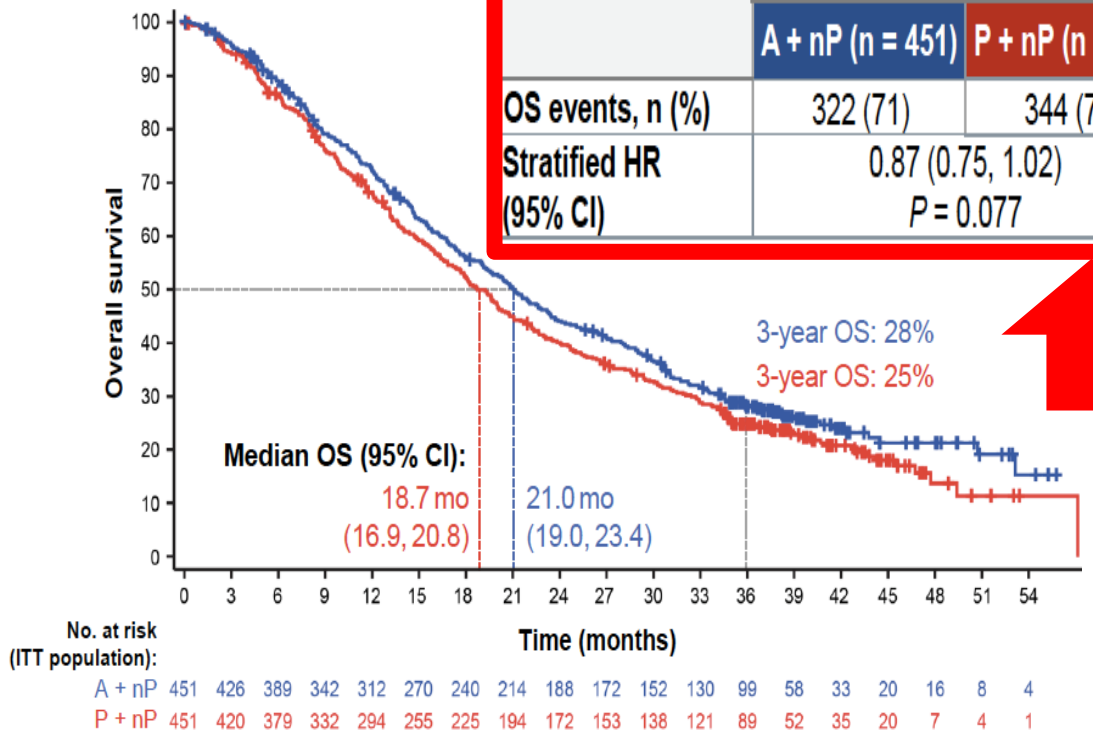


Shmid et al NEJM 2018

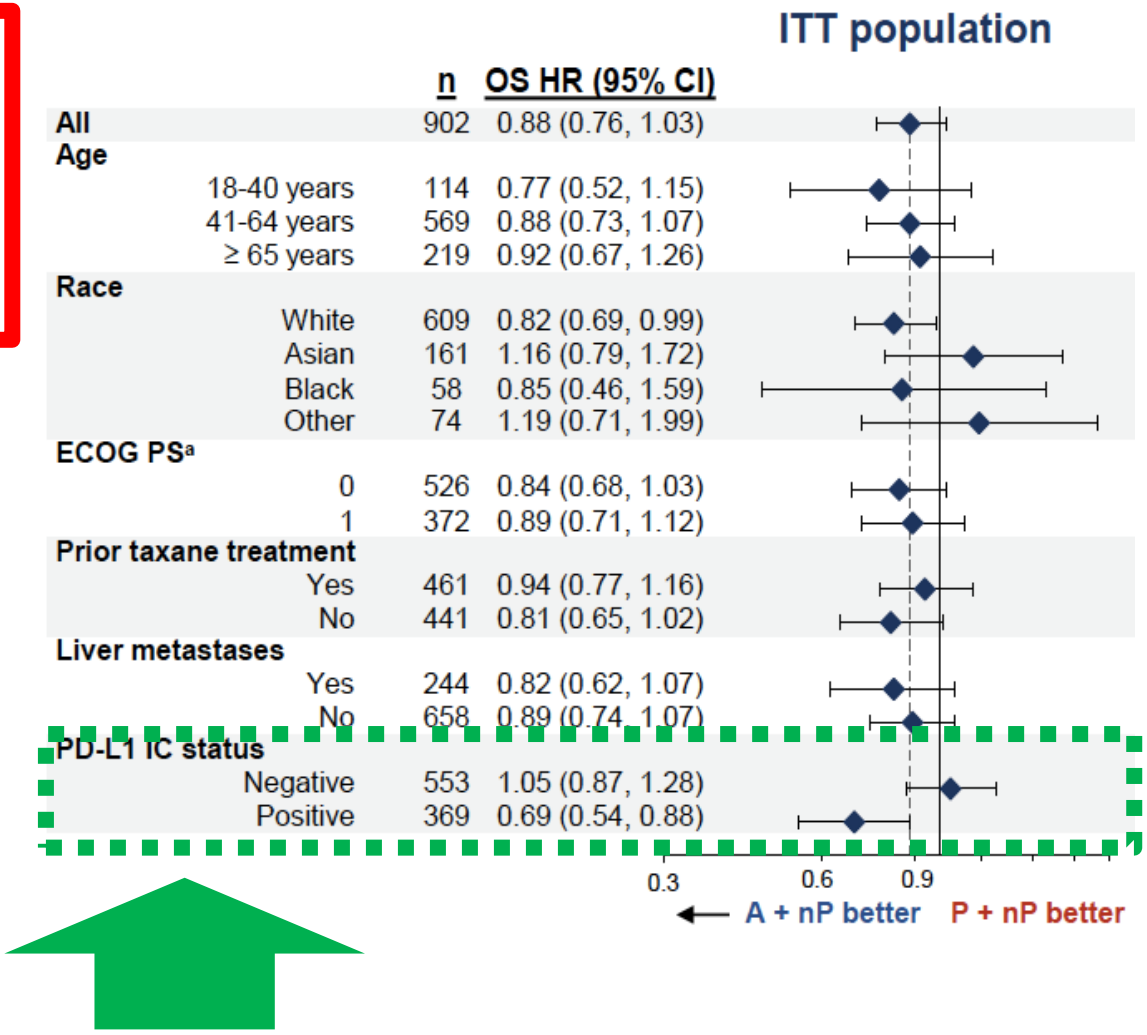
IMpassion 130: Co-Primary End-Point (OS-ITT)

Overall Survival (OS): ITT

	ITT population	
	A + nP (n = 451)	P + nP (n = 451)
OS events, n (%)	322 (71)	344 (76)
Stratified HR (95% CI)	0.87 (0.75, 1.02) *P* = 0.077	



OS: Subgroups



Emens LA et al, ESMO 2020

Emens LA et al, ESMO 2020

Subgroup Analyses and Interactions

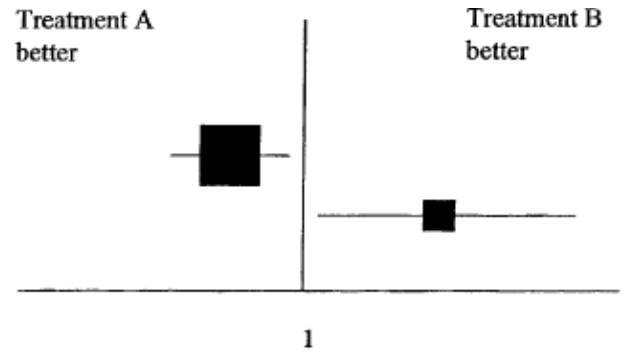
Subgroup analyses in RCTs: risk of subgroup-specific analyses

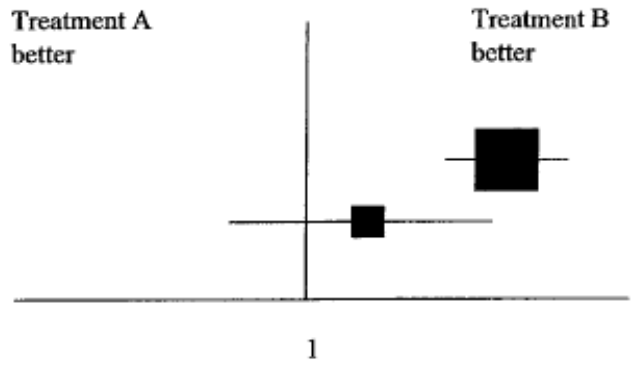
- A test for interaction between treatment and subgroup is the appropriate way to examine whether treatment effects differ between subgroups.
- This approach tests and estimates the difference between treatment effects across subgroups directly.
- It involves 1 statistical test irrespective of the number of subgroups, whereas subgroup specific analyses involve 2 or more.

Brookes ST el, J Clin Epid 2004

Type of Interactions

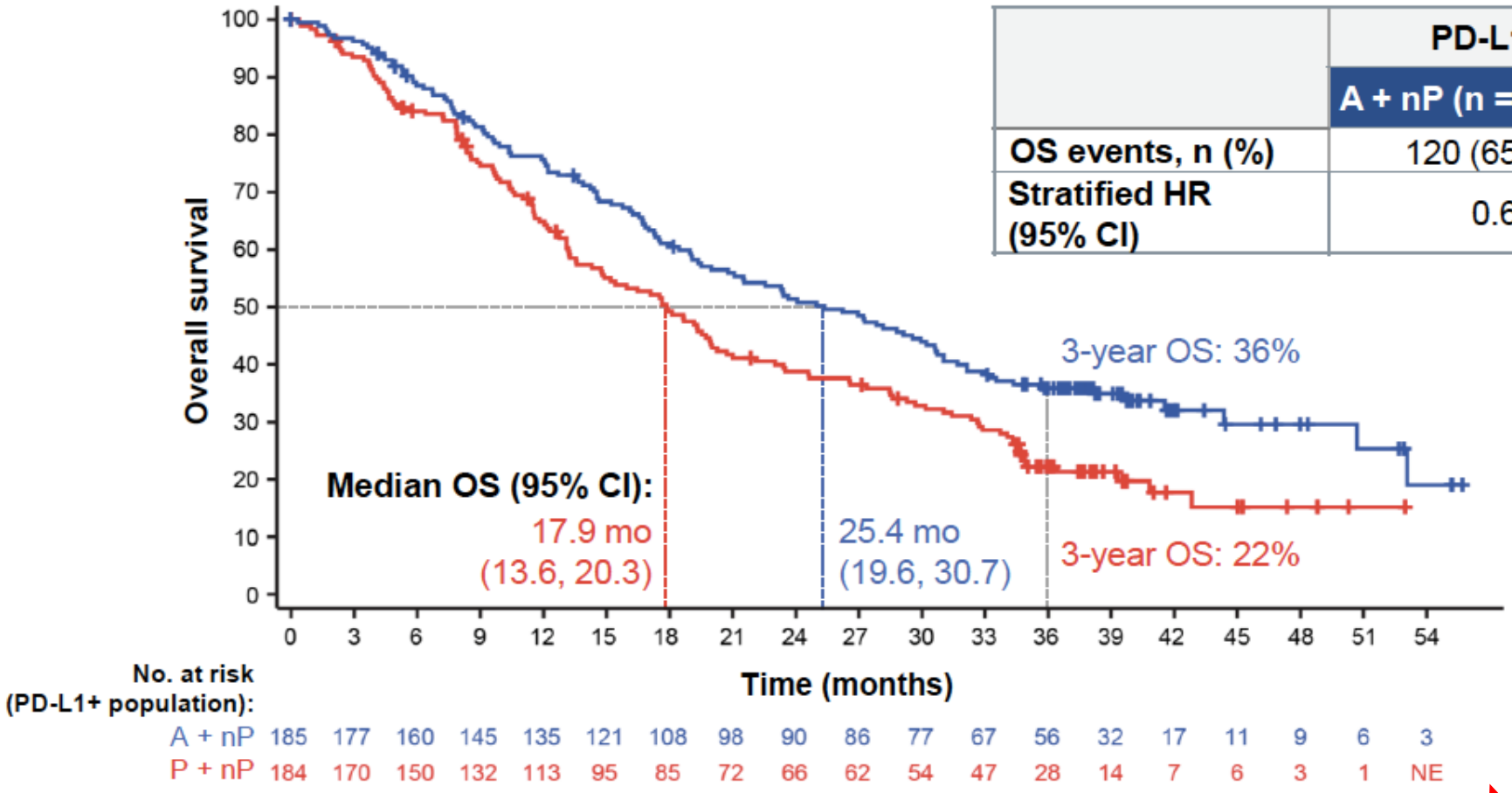
- **Qualitative Interaction: the direction of true treatment differences varies among subsets of patients**
  - **also called *crossover interaction***
- **Quantitative Interaction: variation in the magnitude but NOT direction of treatment effects among patient subgroups – also called a *non-crossover interaction***





Modified - Amy Wagaman, 2008

IMpassion 130: OS (PD-L1 positive)



	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

So What? FDA claims for a Confirmatory Trial to verify such 'potential' benefit

i.e. Prospective Phase III testing ATEZO benefit in PD-L1 positive patients

Emens LA et al, ESMO 2020

IMpassion 131: Study Design & Stat. Assumptions

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Stratification:
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

Primary endpoint: PFS (investigator assessed)

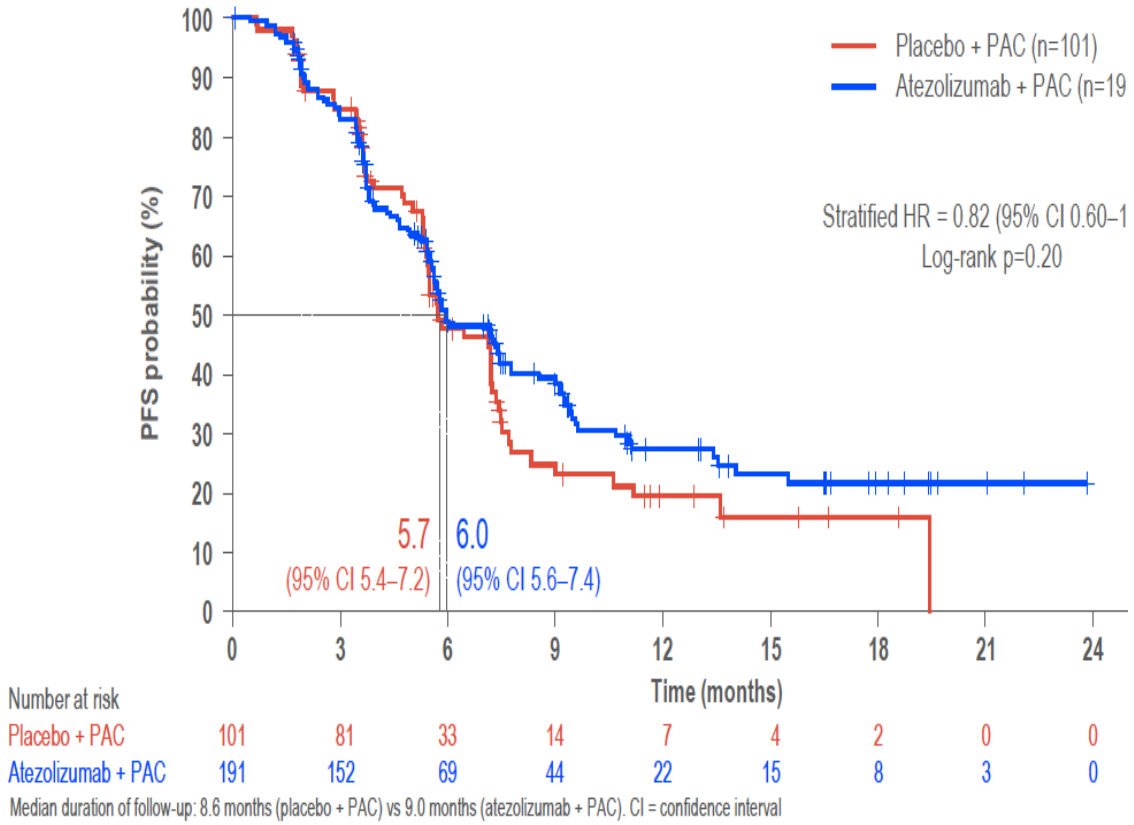
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

- Hierarchical testing informed by results from IMpassion130[1]
- Primary endpoint: Investigator-assessed PFS
  - Tested first in PD-L1+ population (defined as IC ≥1%)
  - Target HR 0.62 (median PFS 5.0 → 8.0 months); 5% 2-si[illegible] alpha and 80% power; 155 PFS events in PD-L1+ population
  - If significant in PD-L1+, PFS tested in the ITT population

Miles D et al, ESMO 2020

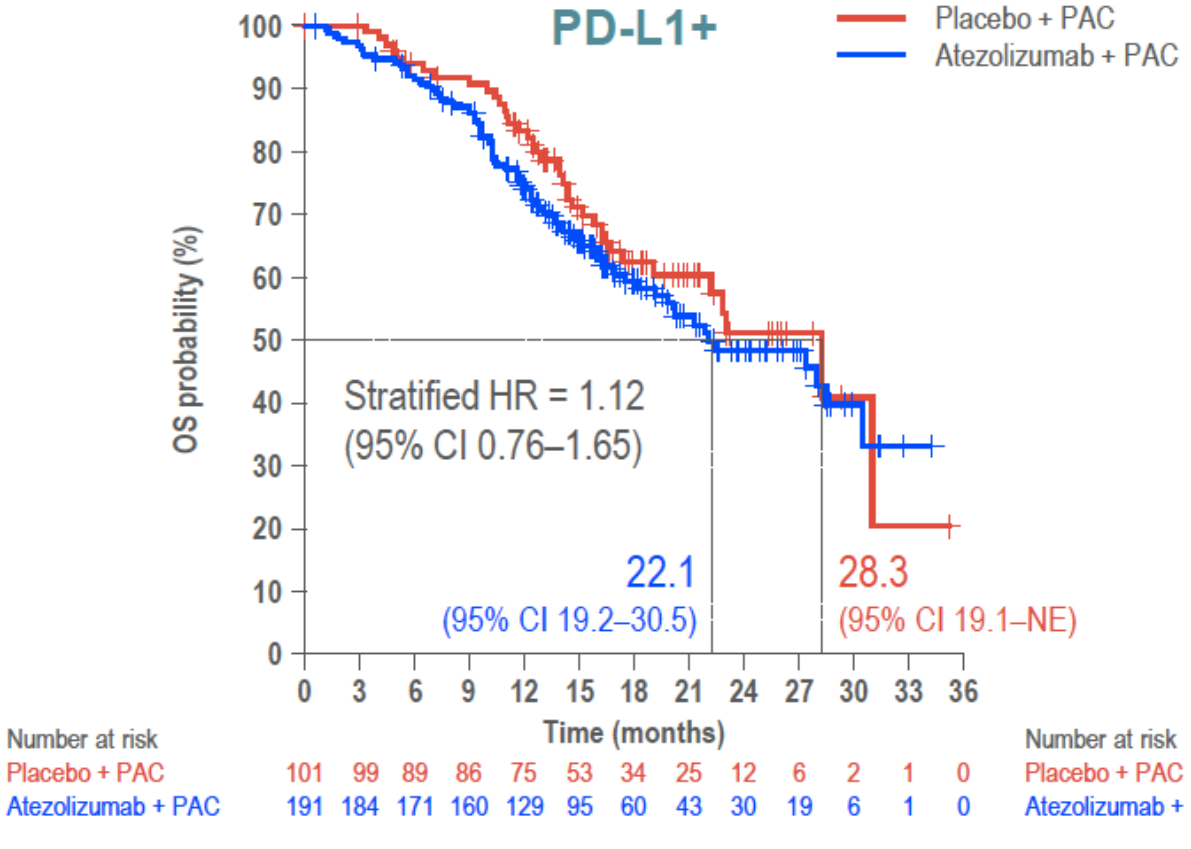
IMpassion 131: PFS and OS (PD-L1 positive)

PFS (PD-L1 Positive)



Median duration of follow-up: 8.6 months (placebo + PAC) vs 9.0 months (atezolizumab + PAC). CI = confidence interval

OS (PD-L1 Positive)



Miles D et al, ESMO 2020

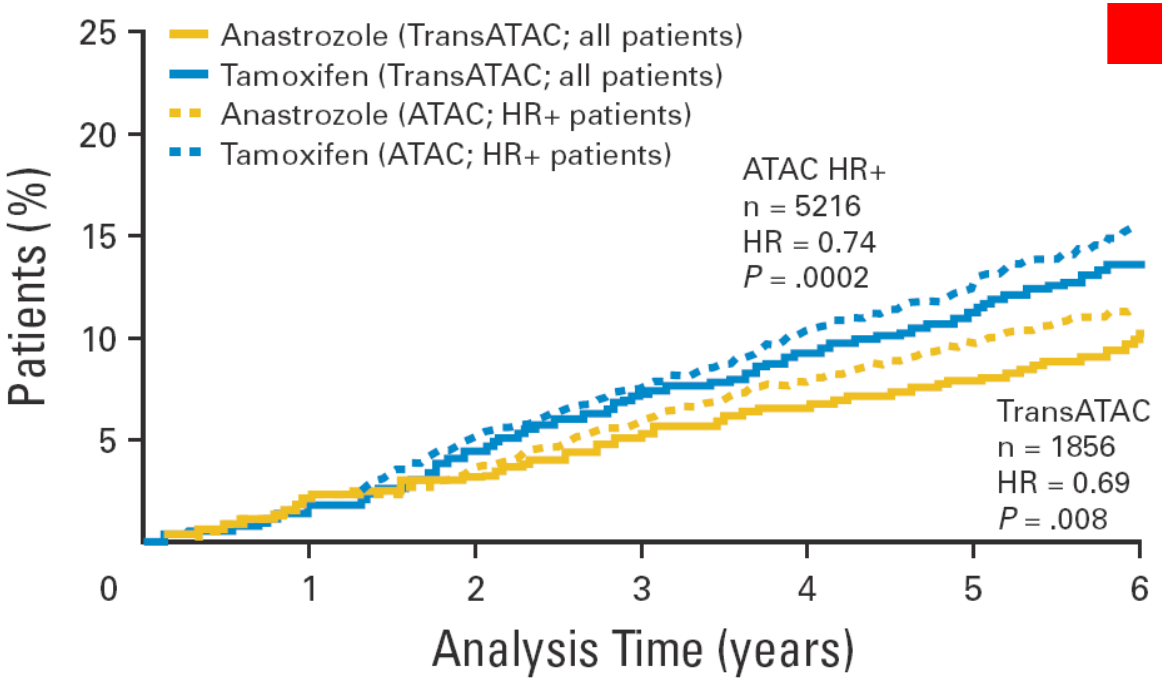
Roche provides update on Tecentriq US indication for PD-L1-positive, metastatic triple-negative breast cancer

Basel, 27 August 2021 - Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the company has made the decision to voluntarily withdraw the US accelerated approval for Tecentriq® (atezolizumab) in combination with chemotherapy (Abraxane®, albumin-bound paclitaxel; nab-paclitaxel) for the treatment of adults with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) whose tumours express PD-L1, as determined by a US Food and Drug Administration (FDA)-approved test. Roche made this decision following consultation with the US FDA, based on the agency's assessment of the current mTNBC treatment landscape and in accordance with the requirements of the accelerated approval programme. This decision only impacts the mTNBC indication in the US. It does

https://www.roche.com/media/releases/med-cor-2021-08-27.htm

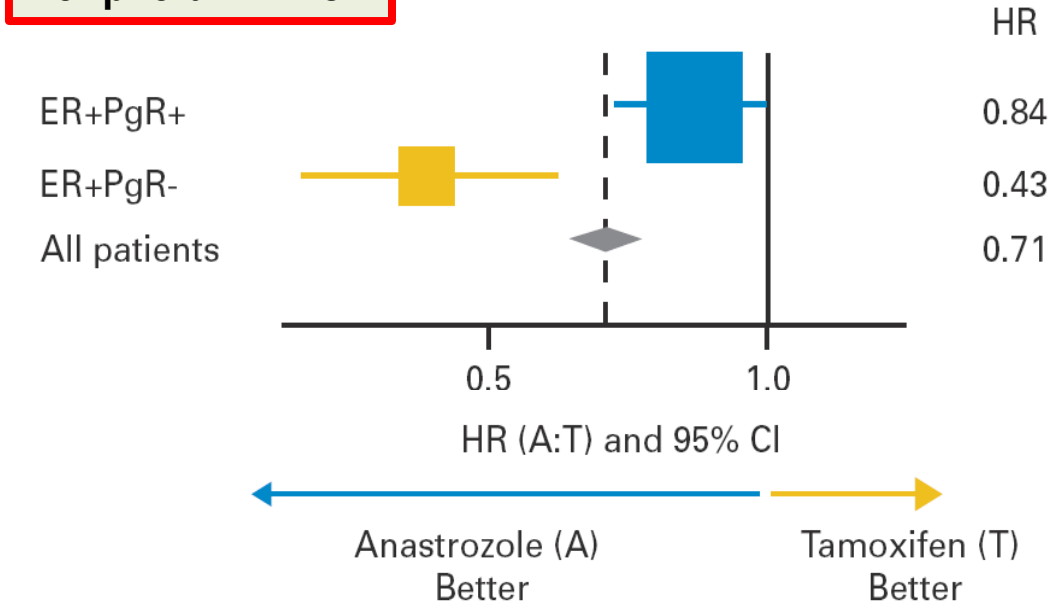
ATAC *vs.* TRANS-ATAC: Subgroups of Interests

Time-To-Recurrence: Similar Overall Benefit of Anastrozole *vs.* Tamoxifen (HR 0.74 *vs.* HR 0.69)



Subgroup Analysis: Significant Interaction, the Hypothesis that a differential effect according to PgR status is generated

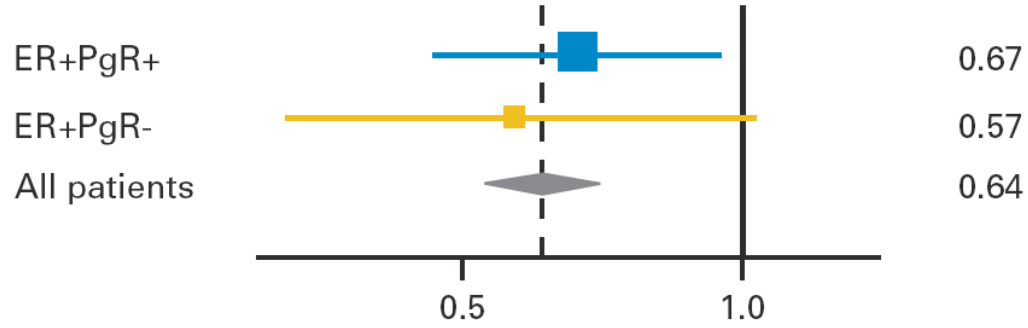
Peripheral ATAC



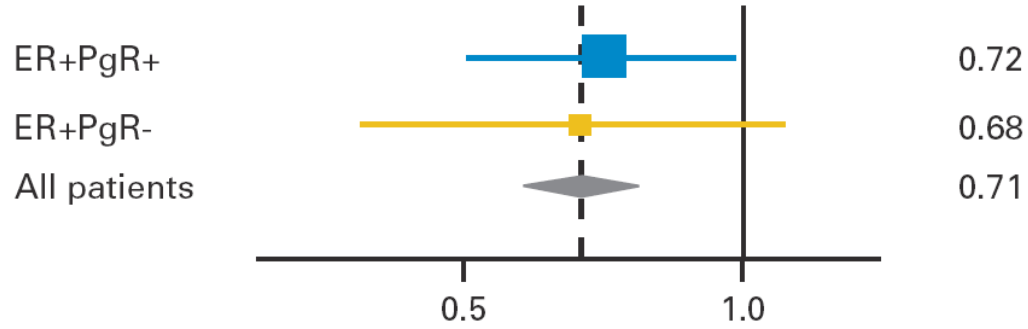
Dowsett M et al, J Clin Oncol 2008

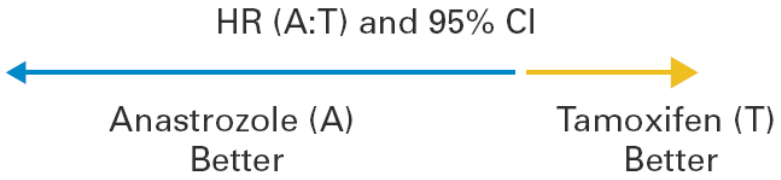
ATAC *vs.* TRANS-ATAC: Subgroups of Interests

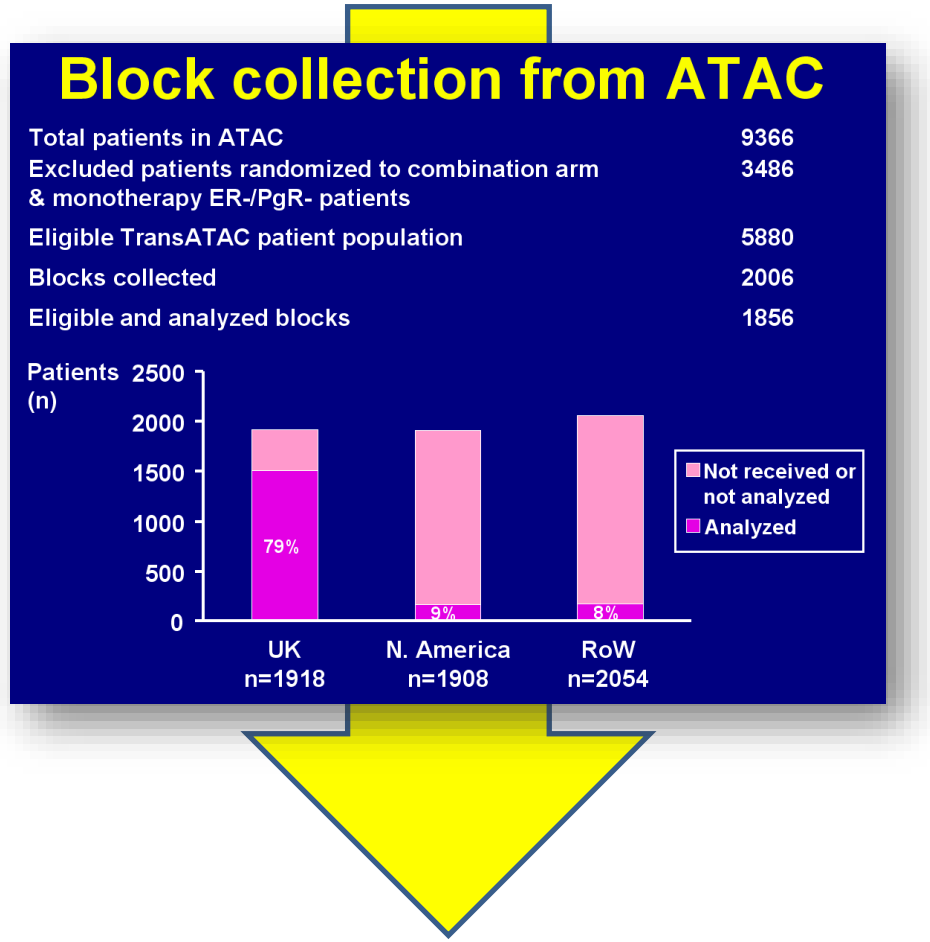
Peripheral TRANS-ATAC



Centralized TRANS-ATAC







Attrition Rate of 19.8% (of total pts.) and 31.5% (of eligible Trans-ATAC)

Dowsett M et al, J Clin Oncol 2008

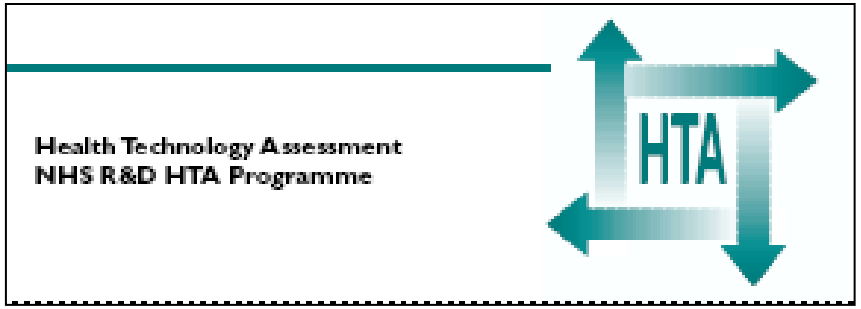
Recommendations for Subgroup Analyses

Interpretation

- Subgroup analyses **should**, as far as possible, **be restricted to those proposed before data collection**…….
- Trials should ideally be **powered** with subgroup analyses in mind……
- Subgroup-specific analyses are unreliable and affected by many factors.
- These analyses should always be **based on formal tests of interaction** although even these should be interpreted with caution.
- Unless there is strong supporting evidence, they are best viewed as a **hypothesis-generation exercise**.

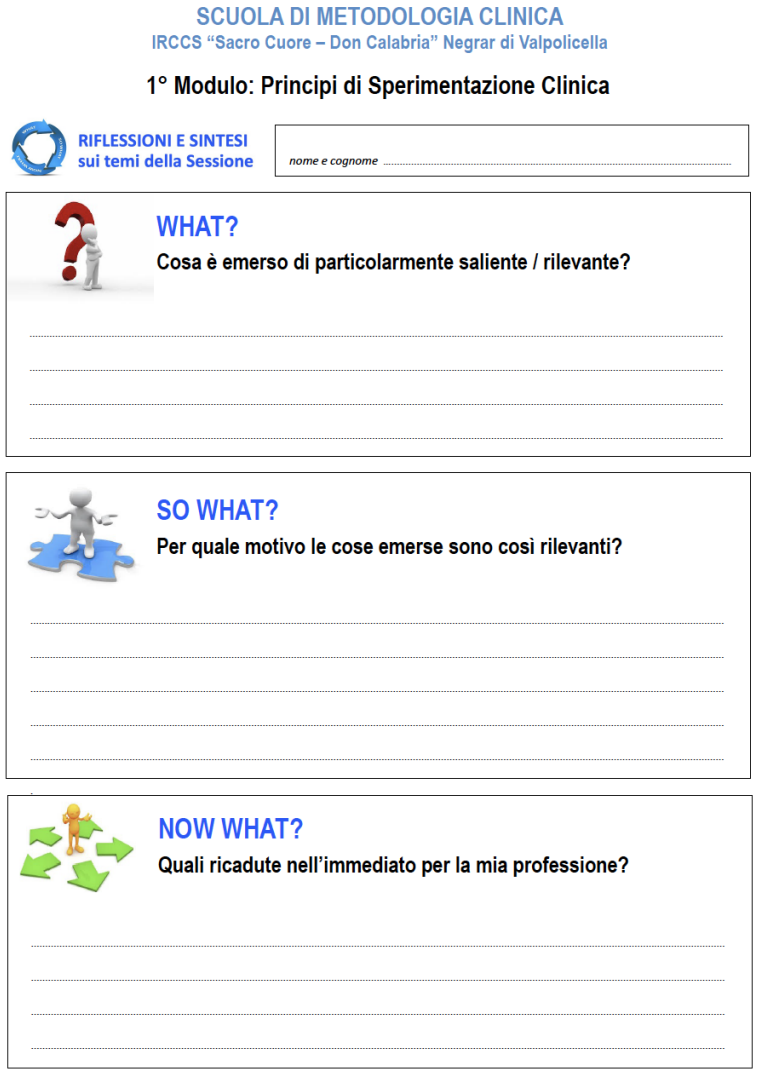
Research

- The implications of **considering confidence intervals** rather than p-values could be considered.
- The same approach as in this study could be applied to contexts other than RCTs, such as observational studies and meta-analyses.



Brookes ST et al, Health Technology Assessment 2001

1. Riflettete da soli per 10 min. e compilate il form →
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso



SCUOLA DI METODOLOGIA CLINICA

IRCCS "Sacro Cuore – Don Calabria" Negrar di Valpolicella

1° Modulo: Principi di Sperimentazione Clinica

RIFLESSIONI E SINTESI sui temi della Sessione

nome e cognome .....

WHAT?

Cosa è emerso di particolarmente saliente / rilevante?

SO WHAT?

Per quale motivo le cose emerse sono così rilevanti?

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?

- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- **Misure di effetto relativo e assoluto**
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk) OR (odds ratio)	RD (risk difference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	tempo a evento	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

VARIABILE DI RISPOSTA

- di tipo **qualitativo (nominale)**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- di tipo **quantitativo**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- del tipo **“tempo a evento”**
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	**nominale**	**RR (relative risk / relative rate)** **OR (odds ratio)**	RD (risk / rate differencedifference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	tempo a evento	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence

number of new events during the specified period

number of persons at risk during the specified period

  - person-time = incidence rate)
  - ncidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence estimates
- Rate (based on events per person-time = incidence rate)
  - Rate Ratio = ratio of 2 incidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

Risks, Rates, and Odds

number of new events during the specified period

time each person was observed, totaled for all persons

- Risk (proportion with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence estimates
- Rate (based on events per person-time = incidence rate)
  - Rate Ratio = ratio of 2 incidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence estimates
- Rate (based on events per person-time = incidence rate)
  - Rate Ratio = ratio of 2 incidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = e estimates
- Rate (based on events p
  - Rate Ratio = ratio of
  - Rate Difference = ab
- Odds (number of events / numbe ion events)
  - Odds Ratio = ratio of 2 odds

Odds Ratios are used to compare the occurrence of the outcome of interest (e.g. disease or unfavourable event), given exposure to the variable of interest (e.g. health characteristic, or intervention).

Most commonly used in **case-control studies**

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	**nominale**	RR (relative risk / relative rate) OR (odds ratio)	**RD (risk difference / rate difference)**
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	tempo a evento	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

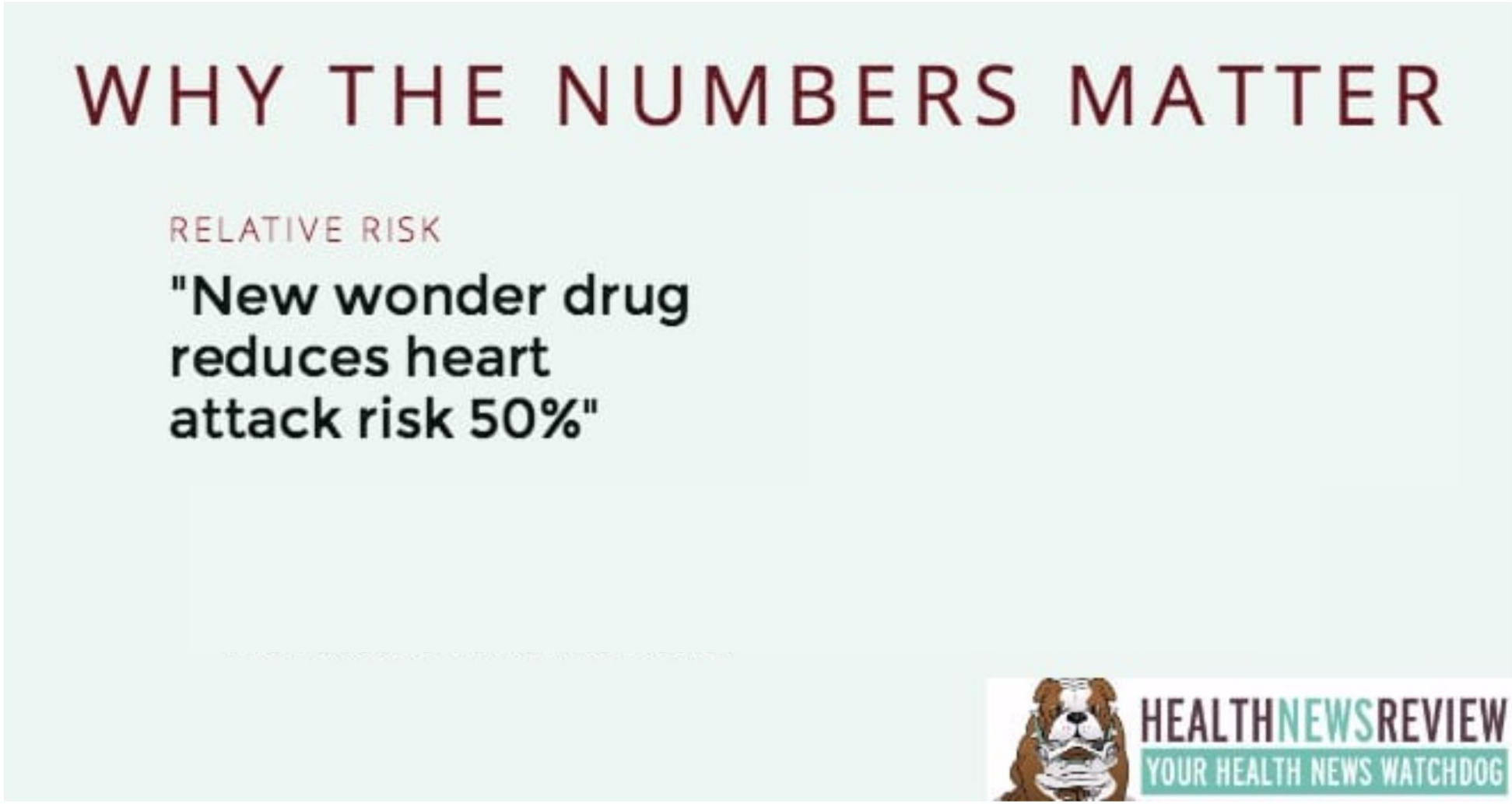
Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence estimates
- Rate (based on events per person-time = incidence rate)
  - Rate Ratio = ratio of 2 incidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

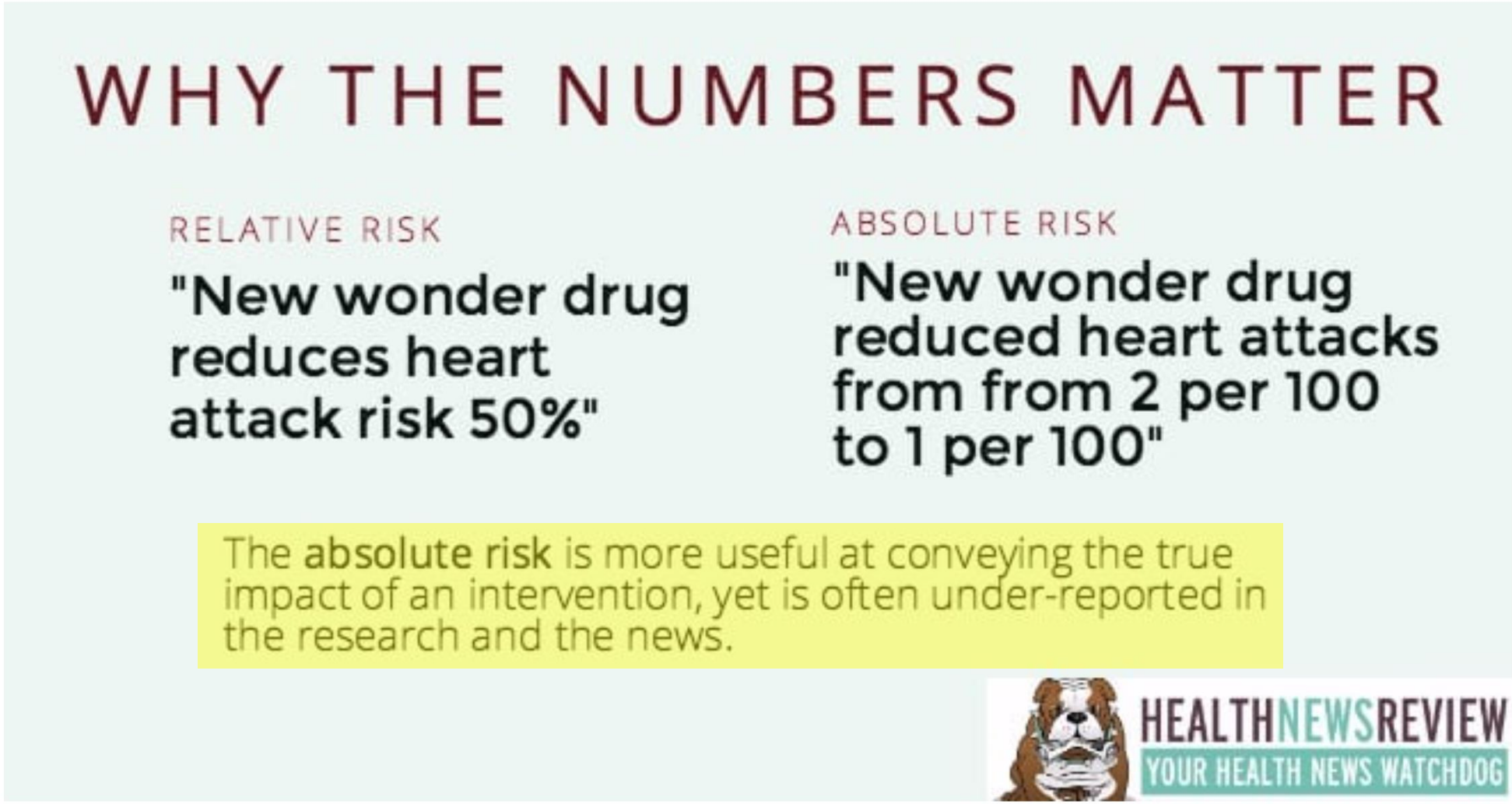
Risks, Rates, and Odds

- Risk (proportion of persons with disease = cumulative incidence)
  - Risk Ratio = ratio of 2 cumulative incidence estimates = Relative Risk
  - Risk Difference = absolute difference of 2 cumulative incidence estimates
- Rate (based on events per person-time = incidence rate)
  - Rate Ratio = ratio of 2 incidence rates = Relative Rate
  - Rate Difference = absolute difference of 2 incidence rates
- Odds (number of events / number of non events)
  - Odds Ratio = ratio of 2 odds

Beneficio RELATIVO (RR, OR , HR) o ASSOLUTO (RD)?



Beneficio RELATIVO (RR, OR , HR) o ASSOLUTO (RD)?



VARIABILE DI RISPOSTA

- di tipo **qualitativo (nominale)**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- di tipo **quantitativo (intervallare)**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- del tipo **“tempo a evento”**
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

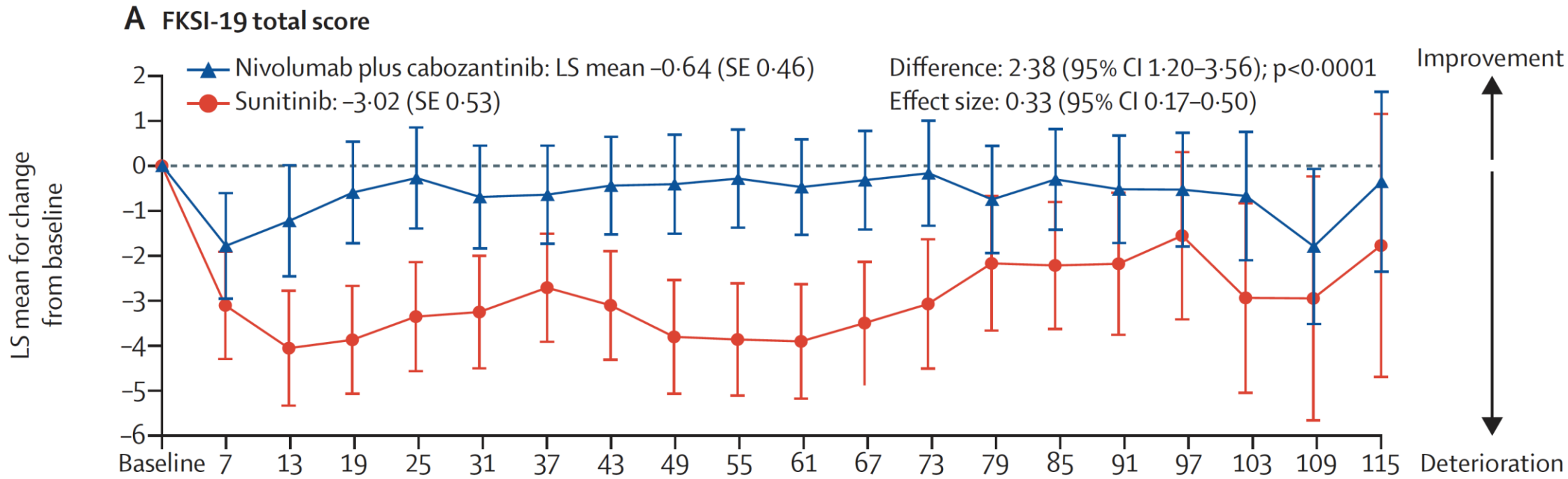
Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk / relative rate) OR (odds ratio)	RD (risk difference / rate difference)
Punteggi di qualità di vita	**intervallare**	-	**MD (mean difference)**
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	tempo a evento	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial

David Cella, Robert J Motzer*, Cristina Suarez, Steven I Blum, Flavia Ejzykowicz, Melissa Hamilton, Joel F Wallace, Burcin Simsek, Joshua Zhang, Cristina Ivanescu, Andrea B Apolo, Toni K Choueiri*

Lancet Oncol **2022; 23: 292–303**



VARIABILE DI RISPOSTA

- di tipo **qualitativo (nominale)**
  - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- di tipo **quantitativo (intervallare)**
  - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- del tipo “**tempo a evento**”
  - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk / relative rate) OR (odds ratio)	RD (risk difference / rate difference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	**tempo a evento**	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

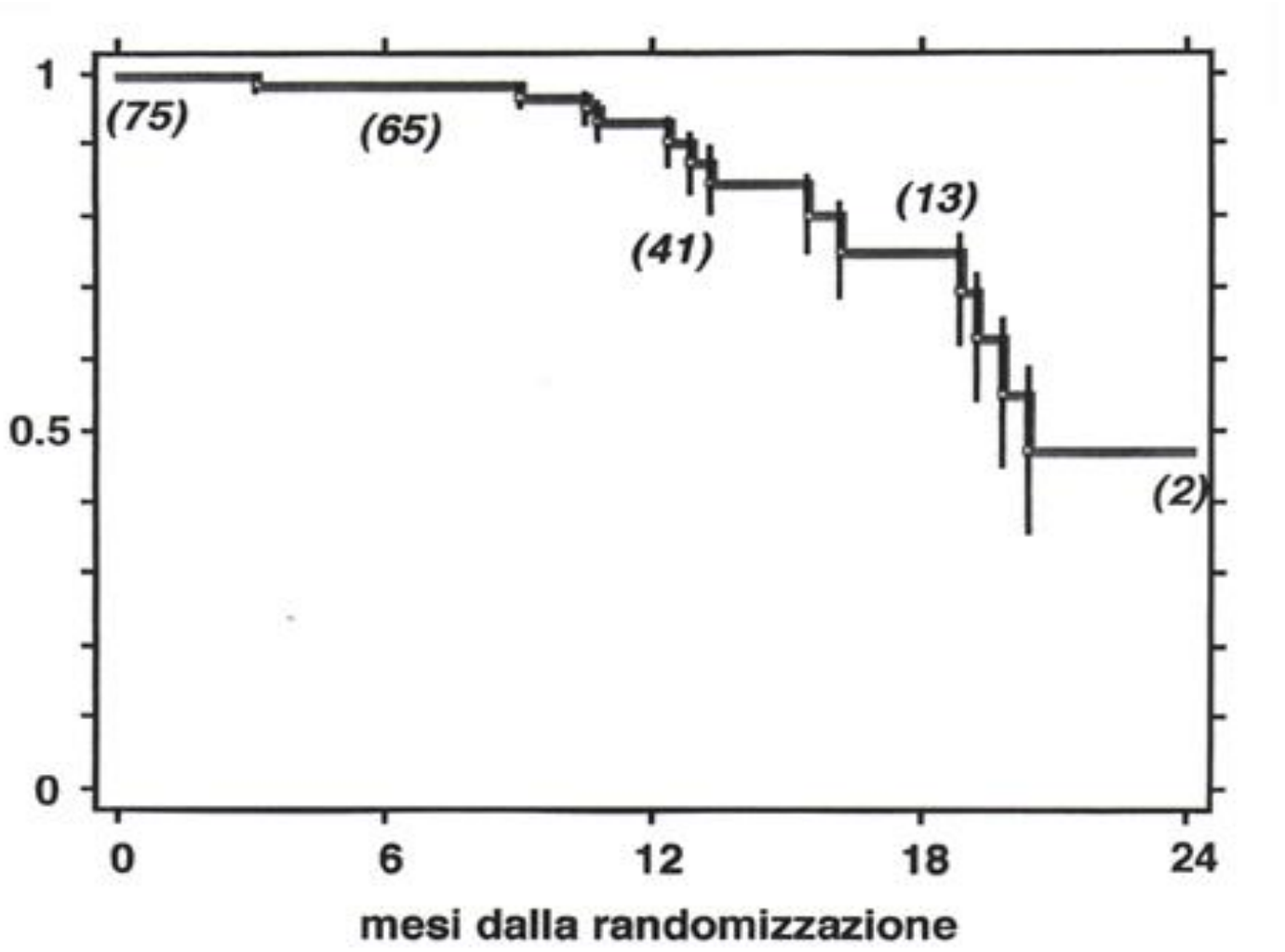
Variabile tempo-a-evento

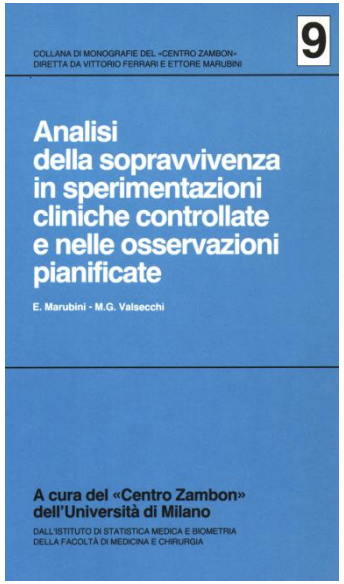
- Apparentemente assimilabile a una variabile di tipo quantitativo (intervallare)…
- …ma il verificarsi o meno di un evento la rende assimilabile a una variabile di tipo qualitativo (nominale)

Metodo di Kaplan-Meier

Stima della probabilità di sopravvivere in corrispondenza di ciascuno dei tempi in cui si verifica almeno un evento

CURVA DI SOPRAVVIVENZA

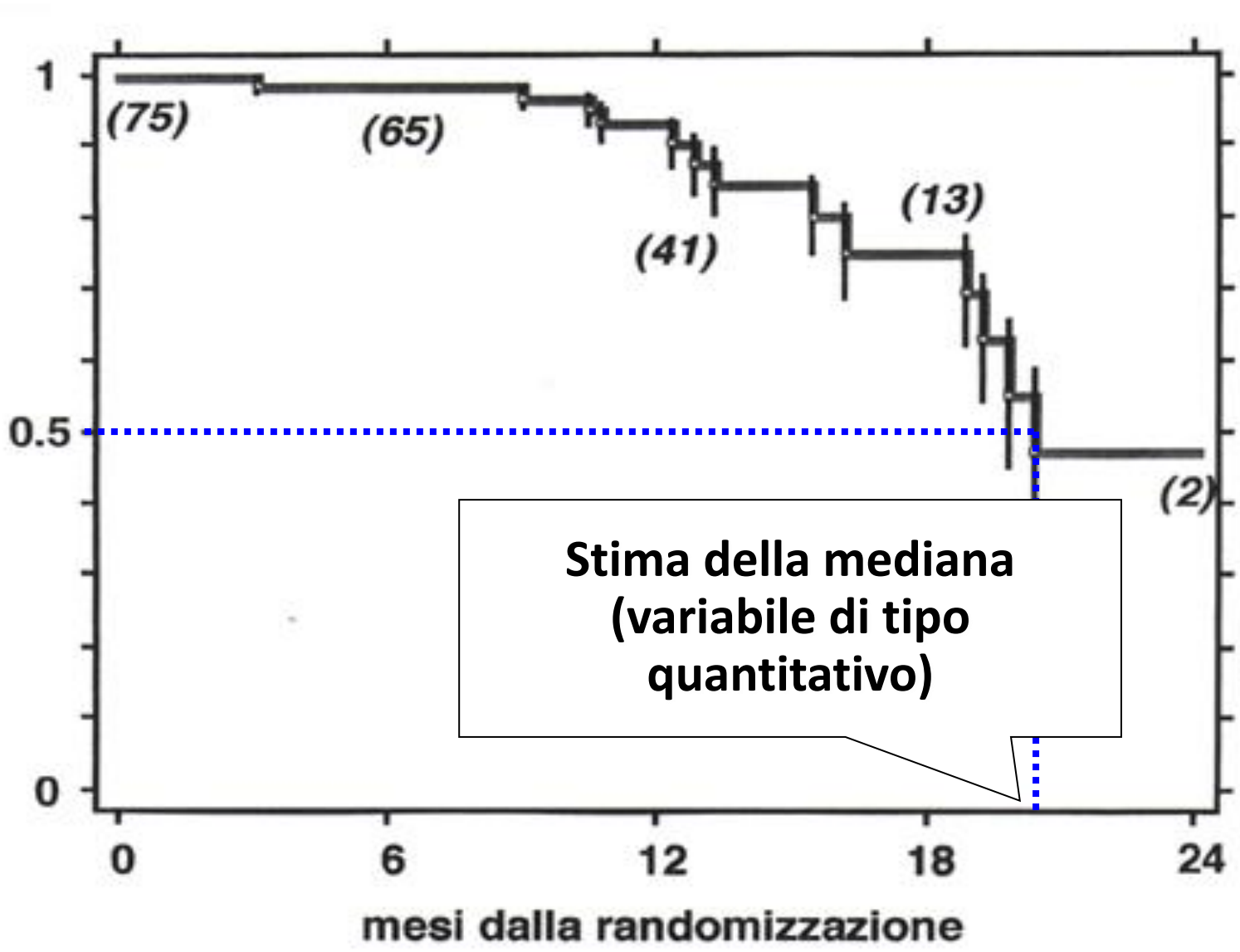


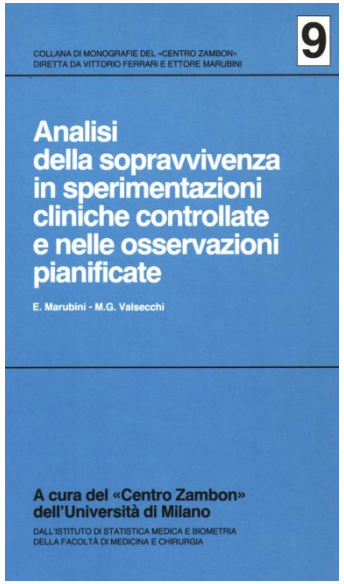


Tempi di risposta $t_{(j)}$	Tempi troncati* t^*	N° soggetti esposti a rischio n_j	N° eventi terminali d_j	Rischio istantaneo di "morte" $\hat{\lambda}(t_{(j)})$	Probabilità cumulativa di sopravvivere $t_{(j)}$ $\hat{P}_j$
9		20	1	1/20 = .050	(1 – 1/20) × 1 = .9500
13		19	1	1/19 = .053	(1 – 1/19) × .9500 = .8996
20		18	1	1/18 = .055	(1 – 1/18) × .8996 = .8501
26		17	1	1/17 = .059	(1 – 1/17) × .8501 = .7999
27		16	1	1/16 = .062	(1 – 1/16) × .7999 = .7503
28		15	1	1/15 = .067	(1 – 1/15) × .7503 = .7000
30		14	1	1/14 = .071	(1 – 1/14) × .7000 = .6503
32		13	2	2/13 = .154	(1 – 2/13) × .6503 = .5502
75		11	1	1/11 = .091	(1 – 1/11) × .5502 = .5001
79		10	1	1/10 = .100	(1 – 1/10) × .5001 = .4501
91		9	1	1/9 = .111	(1 – 1/9) × .4501 = .4001
	177*	8	0	0/8 = .0	(1 – 0/8) × .4001 = .4001
193		7	1	1/7 = .143	(1 – 1/7) × .4001 = .3429
541		6	1	1/6 = .167	(1 – 1/6) × .3429 = .2856
1129		5	1	1/5 = .200	(1 – 1/5) × .2856 = .2285
	1499*	4	0	0/4 = .0	(1 – 0/4) × .2285 = .2285
1585		3	1	1/3 = .333	(1 – 1/3) × .2285 = .1524

TABELLA 10.
Calcolo secondo Kaplan e Meier della curva di sopravvivenza del rene trapiantato nei pazienti di tabella 6.

CURVA DI SOPRAVVIVENZA

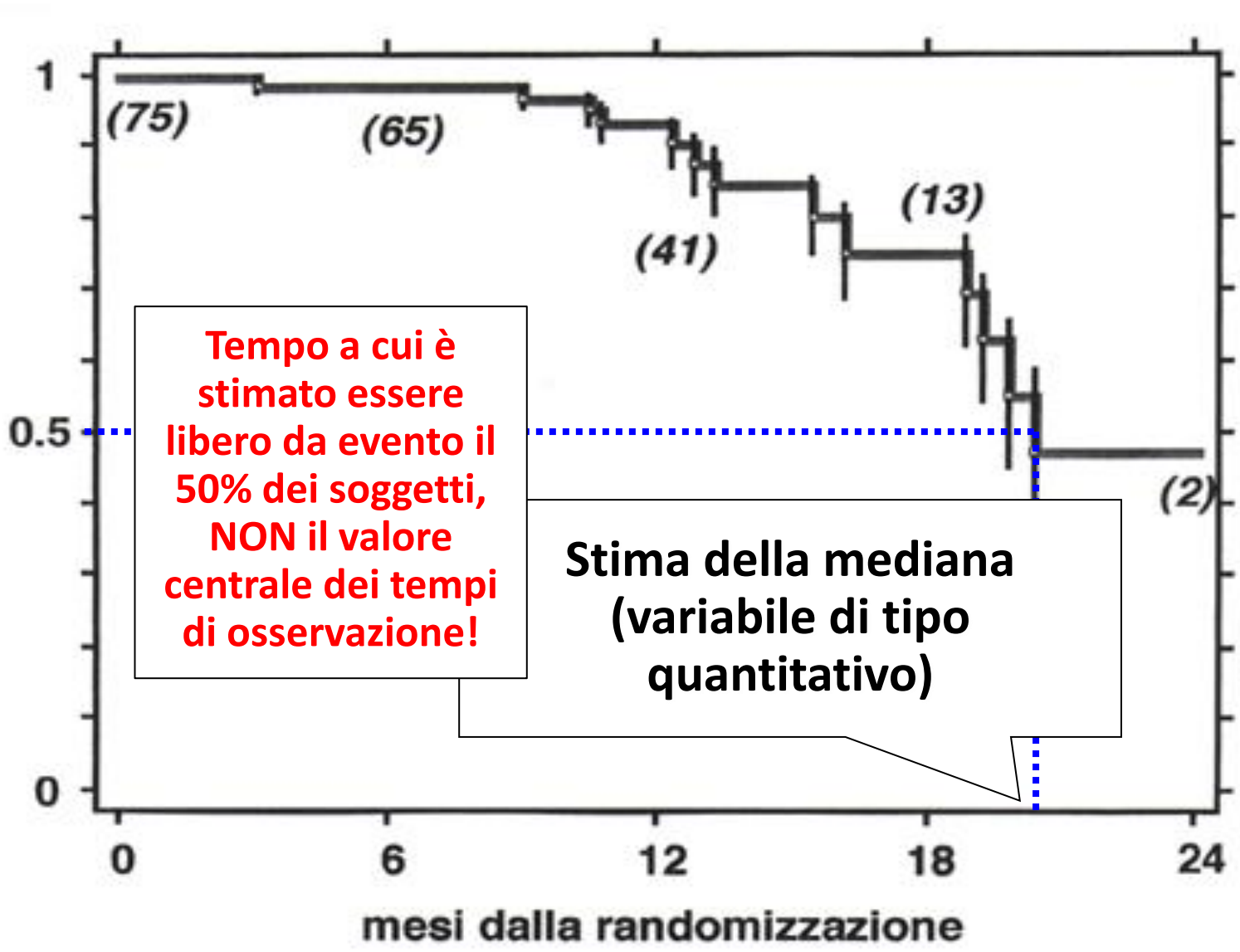




Tempi di risposta $t_{(j)}$	Tempi troncati* t^*	N° soggetti esposti a rischio n_j	N° eventi terminali d_j	Rischio istantaneo di "morte" $\hat{\lambda}(t_{(j)})$	Probabilità cumulativa di sopravvivere $t_{(j)}$ $\hat{P}_j$
9		20	1	1/20 = .050	(1 – 1/20) × 1 = .9500
13		19	1	1/19 = .053	(1 – 1/19) × .9500 = .8996
20		18	1	1/18 = .055	(1 – 1/18) × .8996 = .8501
26		17	1	1/17 = .059	(1 – 1/17) × .8501 = .7999
27		16	1	1/16 = .062	(1 – 1/16) × .7999 = .7503
28		15	1	1/15 = .067	(1 – 1/15) × .7503 = .7000
30		14	1	1/14 = .071	(1 – 1/14) × .7000 = .6503
32		13	2	2/13 = .154	(1 – 2/13) × .6503 = .5502
75		11	1	1/11 = .091	(1 – 1/11) × .5502 = .5001
79		10	1	1/10 = .100	(1 – 1/10) × .5001 = .4501
91		9	1	1/9 = .111	(1 – 1/9) × .4501 = .4001
	177*	8	0	0/8 = .0	(1 – 0/8) × .4001 = .4001
193		7	1	1/7 = .143	(1 – 1/7) × .4001 = .3429
541		6	1	1/6 = .167	(1 – 1/6) × .3429 = .2856
1129		5	1	1/5 = .200	(1 – 1/5) × .2856 = .2285
	1499*	4	0	0/4 = .0	(1 – 0/4) × .2285 = .2285
1585		3	1	1/3 = .333	(1 – 1/3) × .2285 = .1524

TABELLA 10.
Calcolo secondo Kaplan e Meier della curva di sopravvivenza del rene trapiantato nei pazienti di tabella 6.

CURVA DI SOPRAVVIVENZA



Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

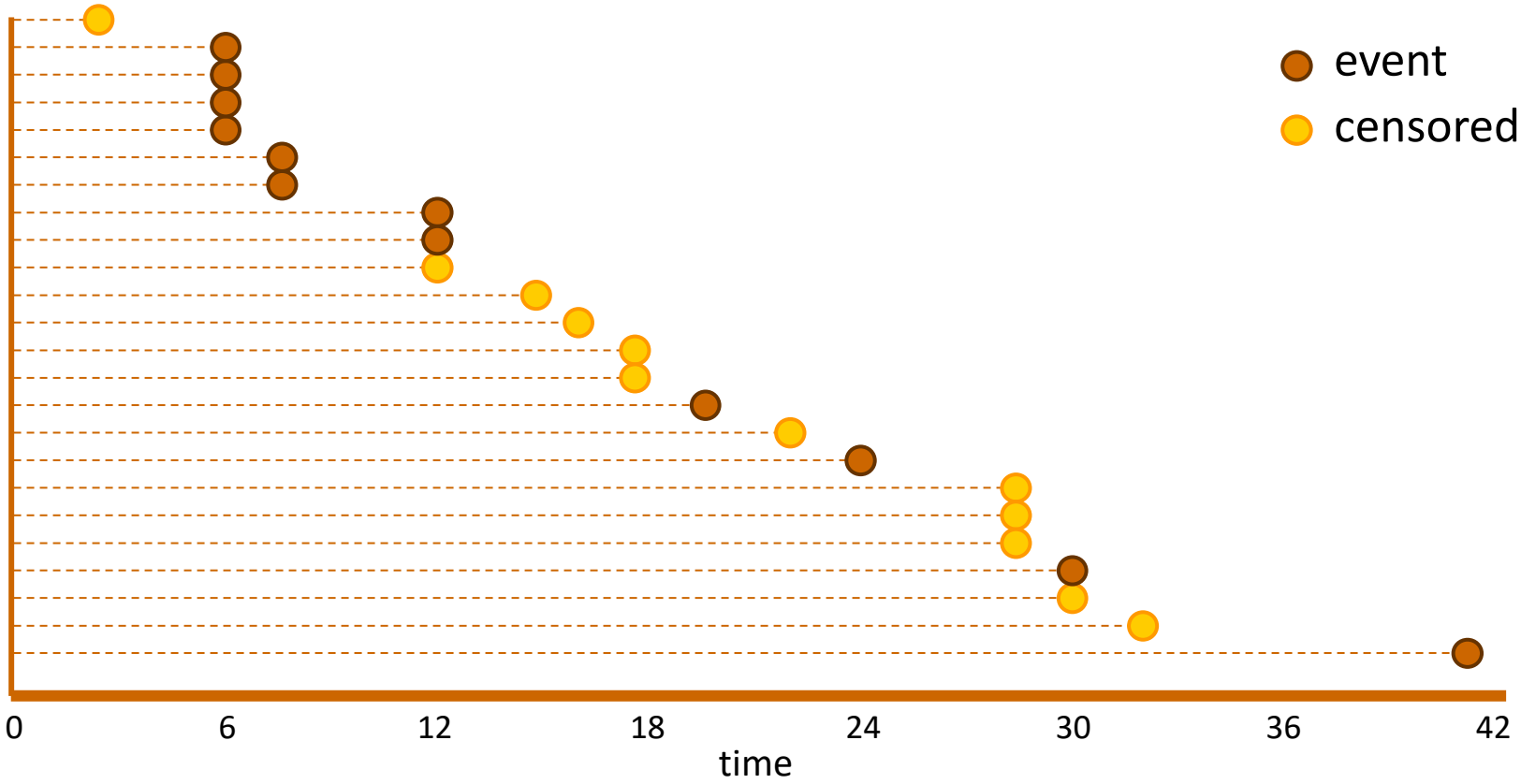
Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk / relative rate) OR (odds ratio)	RD (risk difference / rate difference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	**tempo a evento**	**HR (hazard ratio)** - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) RD (risk difference)

Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

$$\lambda = \frac{d}{f + F}$$

d = number of events
f = sum of follow-up times for patients with event
F = sum of follow-up times for patients with no event (censored)



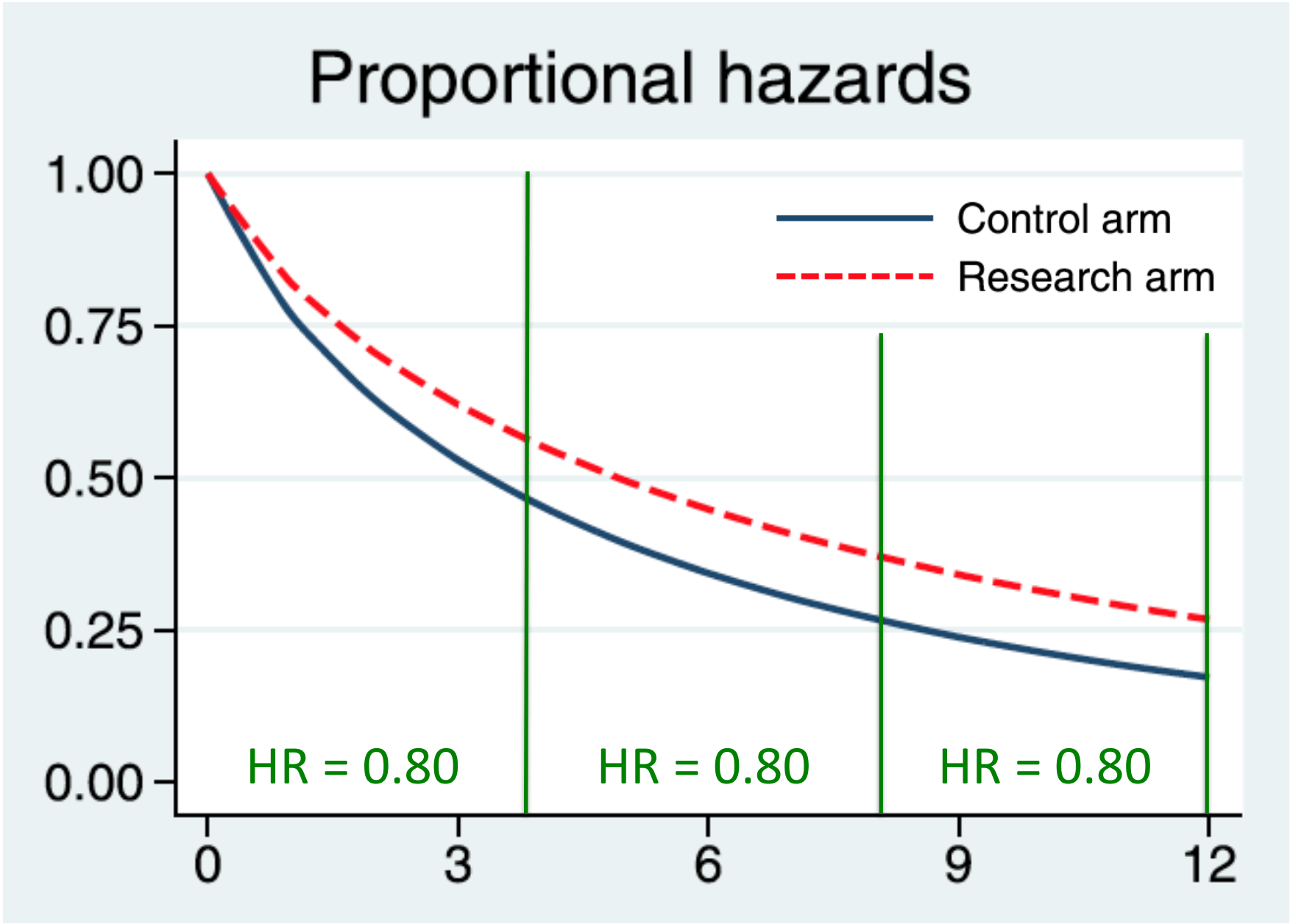
d = 12
f = 6+6+6+6+8+8+12+12+20+24+30+42 = 180
F = 3+12+15+16+18+18+22+28+28+28+30+33 = 251

$$\lambda = \frac{12}{431} = 0.0278$$

R. D'Amico 2009, modif.

Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

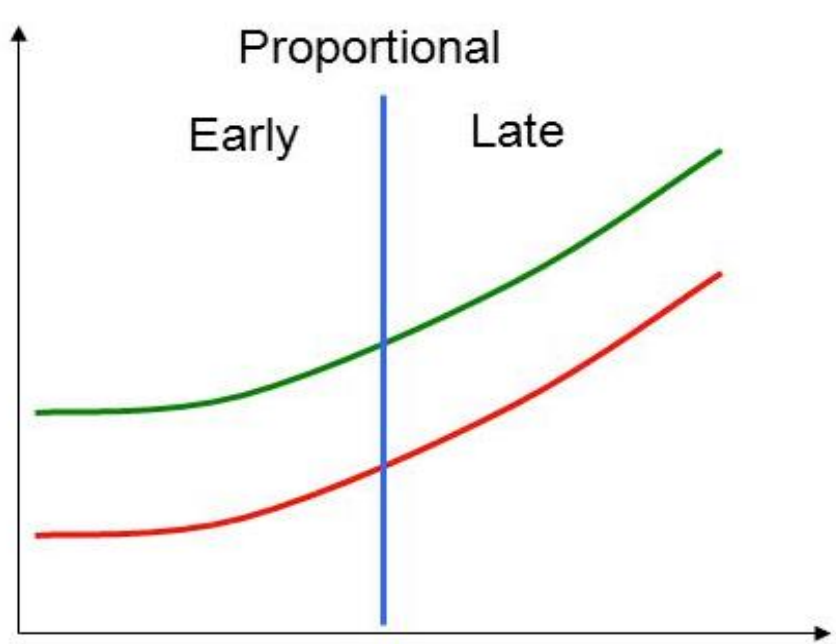

Proportional hazards
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
HR = 0.80
HR = 0.80
HR = 0.80

Defining a Hazard Ratio (HR)

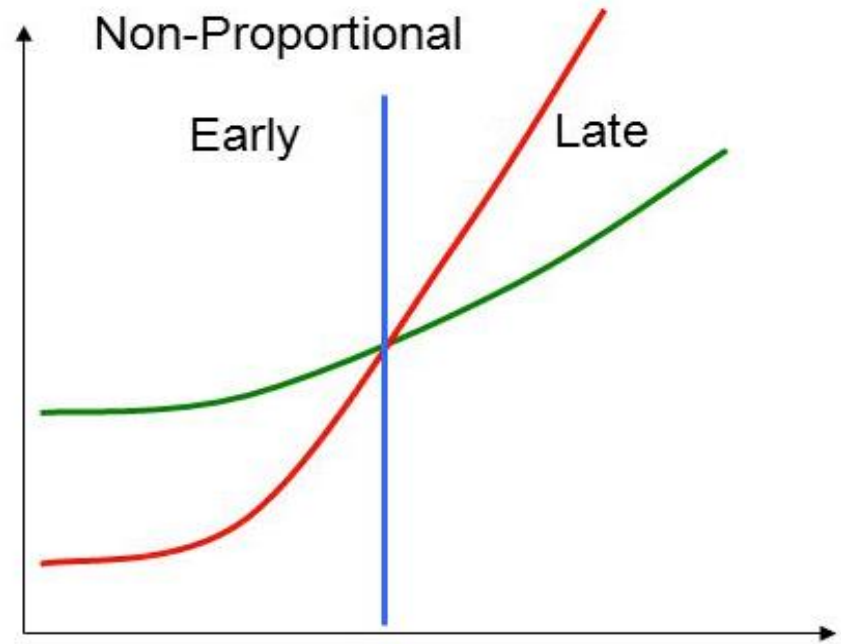
- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

Proportional Hazard Assumption

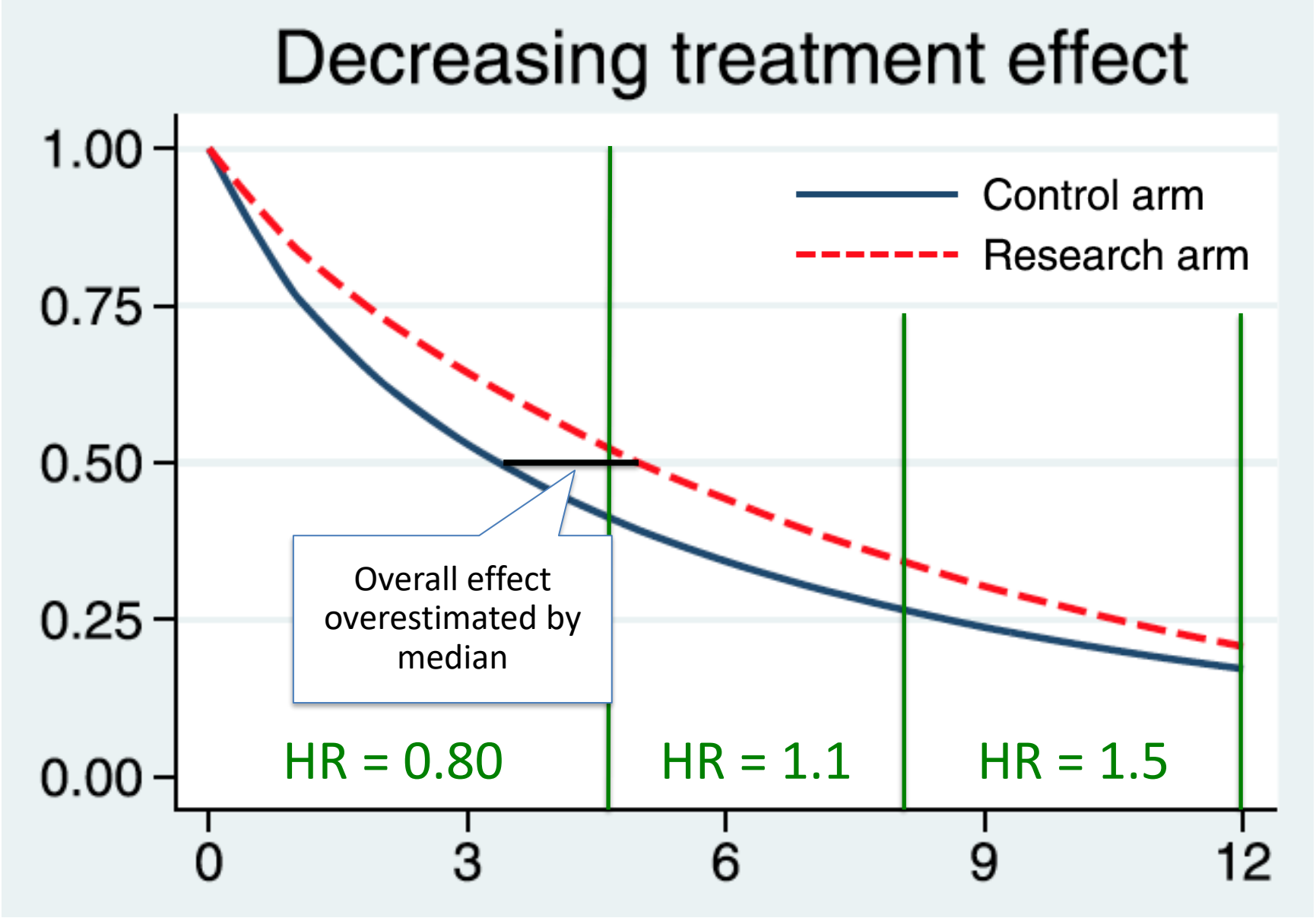
If we are comparing a new treatment with the standard treatment, it is assumed that the ratio of the hazard for an individual on a new treatment to that for an individual on the standard treatment remains constant over time

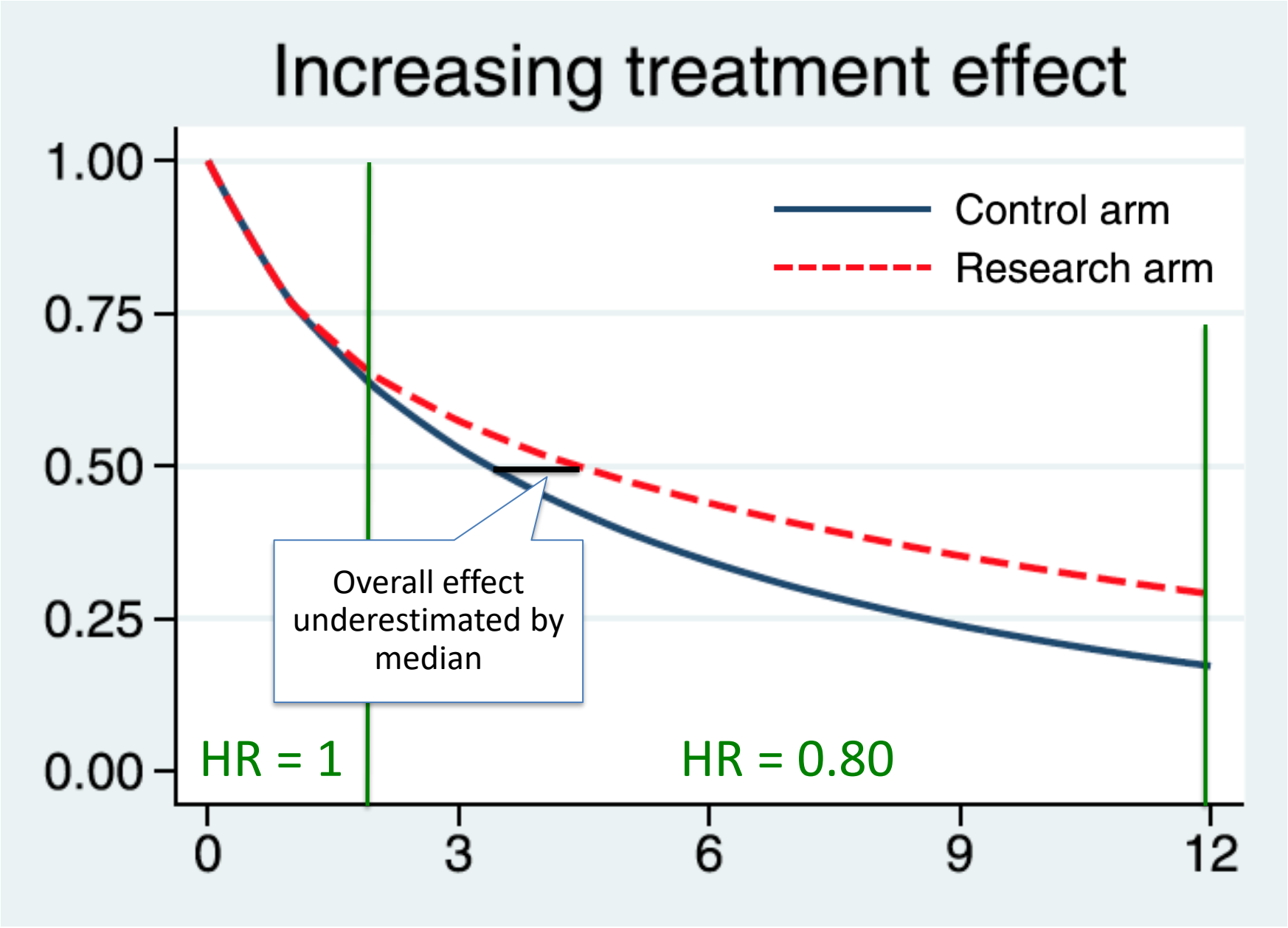


Here, the effect is the same in both time periods



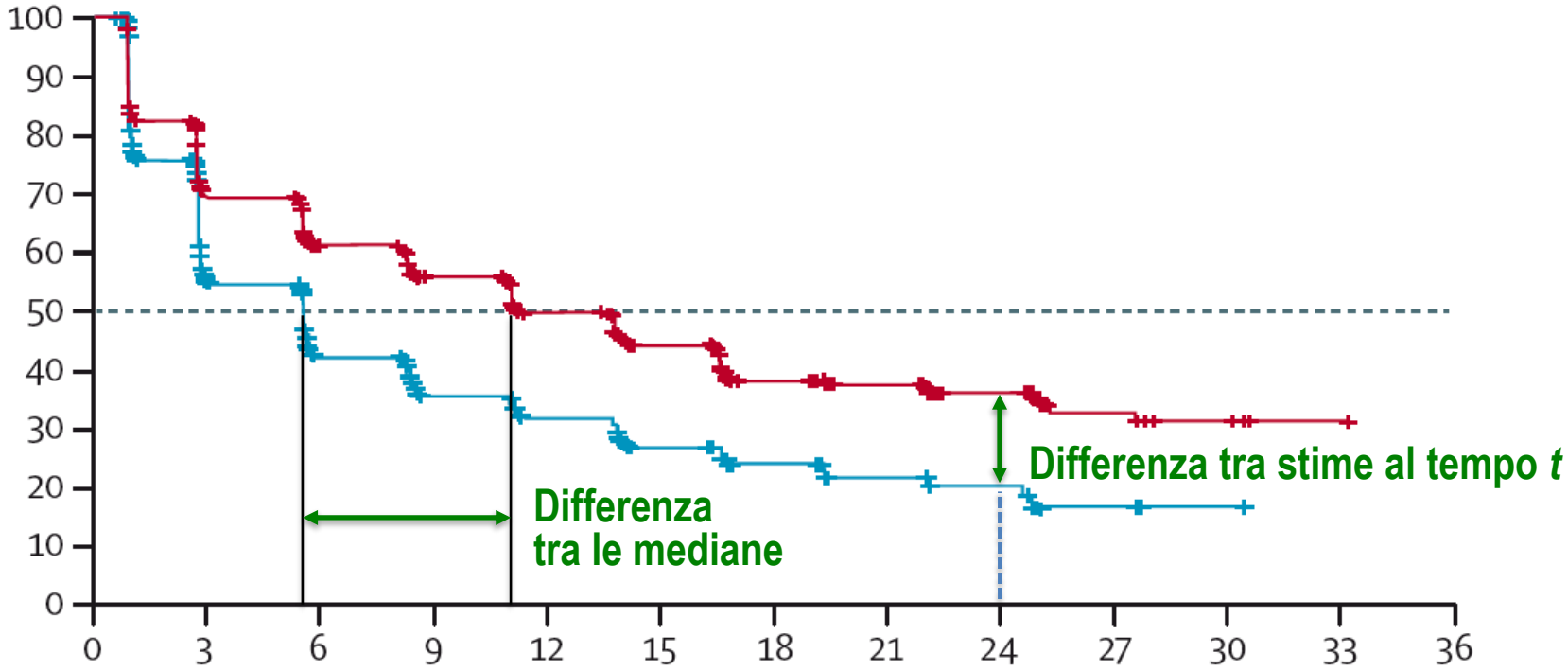
Here, the effect is negative in the early period and positive in the late period

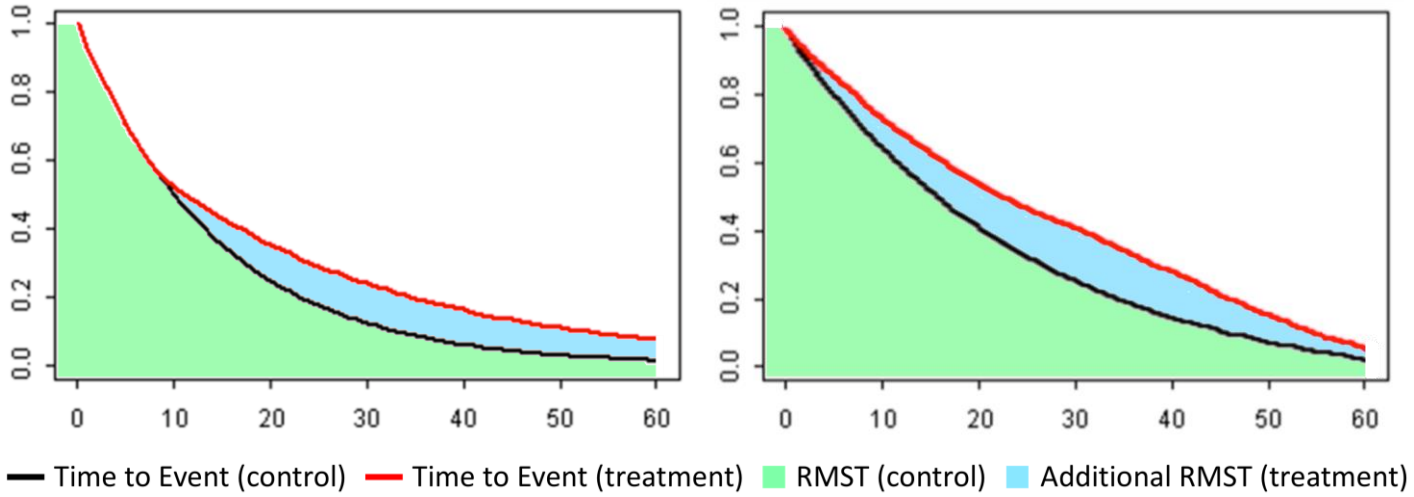

Decreasing treatment effect
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
Overall effect overestimated by median
HR = 0.80
HR = 1.1
HR = 1.5


Increasing treatment effect
1.00
0.75
0.50
0.25
0.00
0
3
6
9
12
Control arm
Research arm
Overall effect underestimated by median
HR = 1
HR = 0.80

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk / relative rate) OR (odds ratio)	RD (risk difference / rate difference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	**tempo a evento**	HR (hazard ratio) - - -	**differenza tra mediane** **differenza tra stime al tempo t…** **RMST (restricted mean survival time)** RD (risk difference)





Restricted Mean Survival Time (differenza tra le aree sotto la curva)

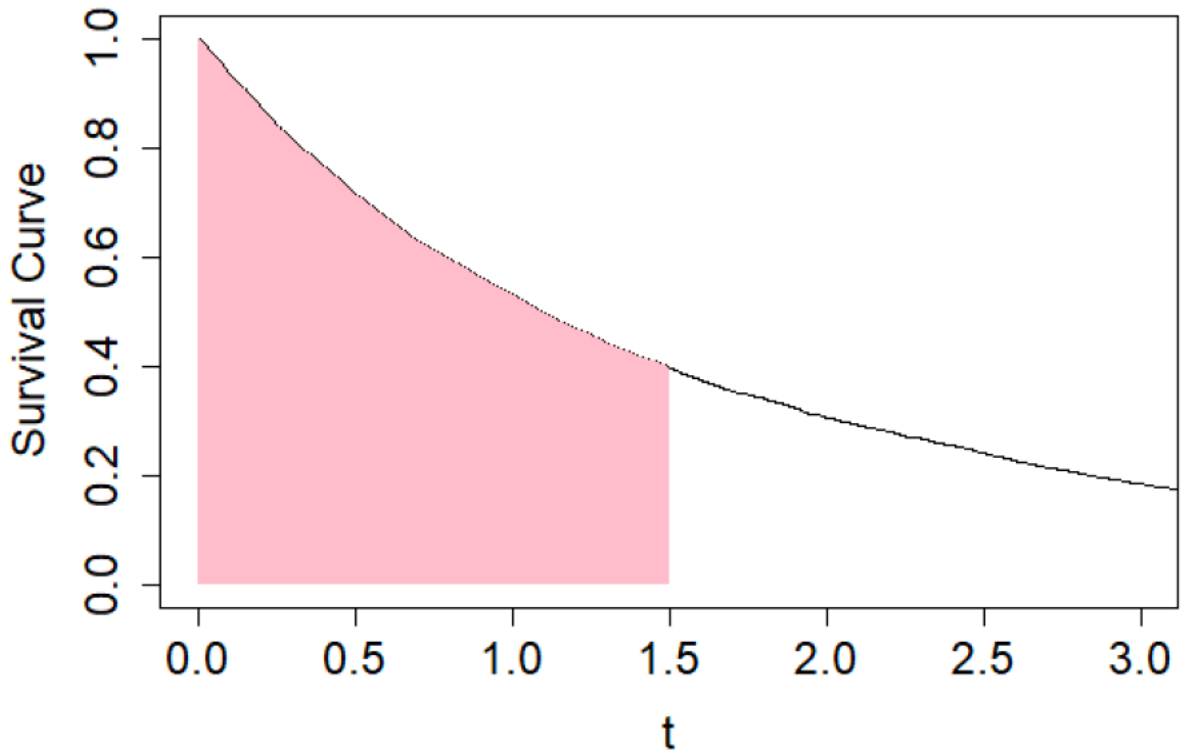
Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
  - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH),* i.e. the risk does not depend on time, that is, "risk is constant over time"
  - If non PH is present, the HR is actually time-dependent and the estimated HR that is obtained is some type of average over the event times
  - The *restricted mean survival time* is as a possible alternative tool in the analysis of these trials

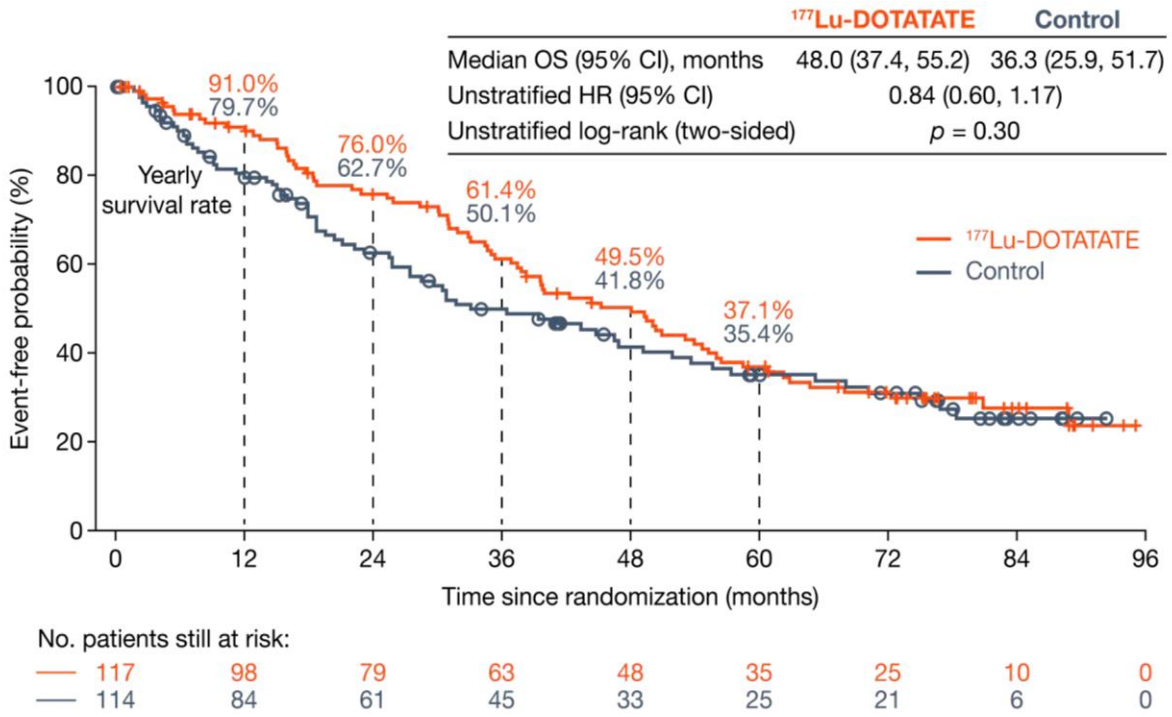
Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome

Patrick Royston* and Mahesh KB Parmar

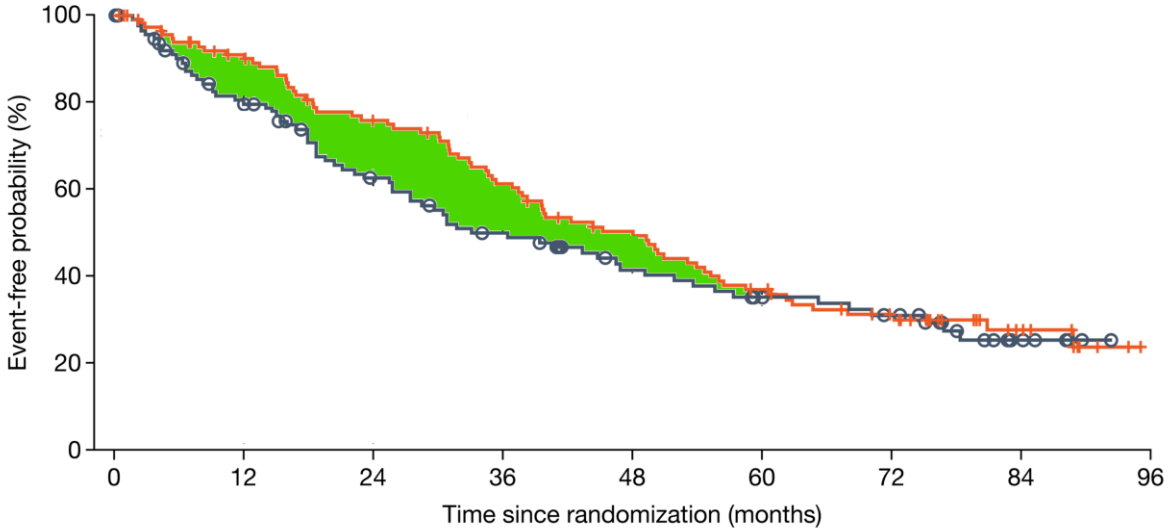
BMC Medical Research Methodology 2013, **13**:152



The phase 3 NETTER-1 study of 177Lu-DOTATATE in patients with midgut neuroendocrine tumours: further survival analyses



Deaths, n (%)	65 (55.6)	63 (55.3)
RMST, months (95% CI)	41.2 (37.6, 44.9)	36.1 (31.9, 40.4)
Difference, months (95% CI)	**5.1 (–0.5, 10.7)**	



Ruszniewski PB, et al. ESMO 2021

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

Endpoint	Tipo di variabile statistica	Indicatore comparativo di effetto	
		relativo	assoluto
Attività (CR, PR, SD, ecc.) Tossicità (eventi avversi)	nominale	RR (relative risk / relative rate) OR (odds ratio)	RD (risk difference / rate difference)
Punteggi di qualità di vita	intervallare	-	MD (mean difference)
OS (overall survival) PFS (progression-free survival DFS (disease-free survival) TTD (time to deterioration…)	**tempo a evento**	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t… RMST (restricted mean survival time) **RD (risk difference)**

Journal of Clinical Epidemiology 118 (2020) 124–131

GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles

Nicole Skoetz[a,*], Marius Goldkuhle[a], Elvira C. van Dalen[b], Elie A. Akl[c], Marialena Trivella[d], Reem A. Mustafa[e], Artur Nowak[f], Philipp Dahm[g], Holger Schünemann [h], Ralf Bender[i], GRADE Working Group

Absolute effect estimates (i.e., risk difference, the number needed to treat) provide important supplementary information to relative effect estimates by considering the control event rate over a given time period. As they take into account the underlying baseline risk for the event of interest in the study groups, absolute effect estimates are less vulnerable to exaggerated effect interpretation than relative effect estimates and allow a more appropriate assessment of the clinical relevance of effects.

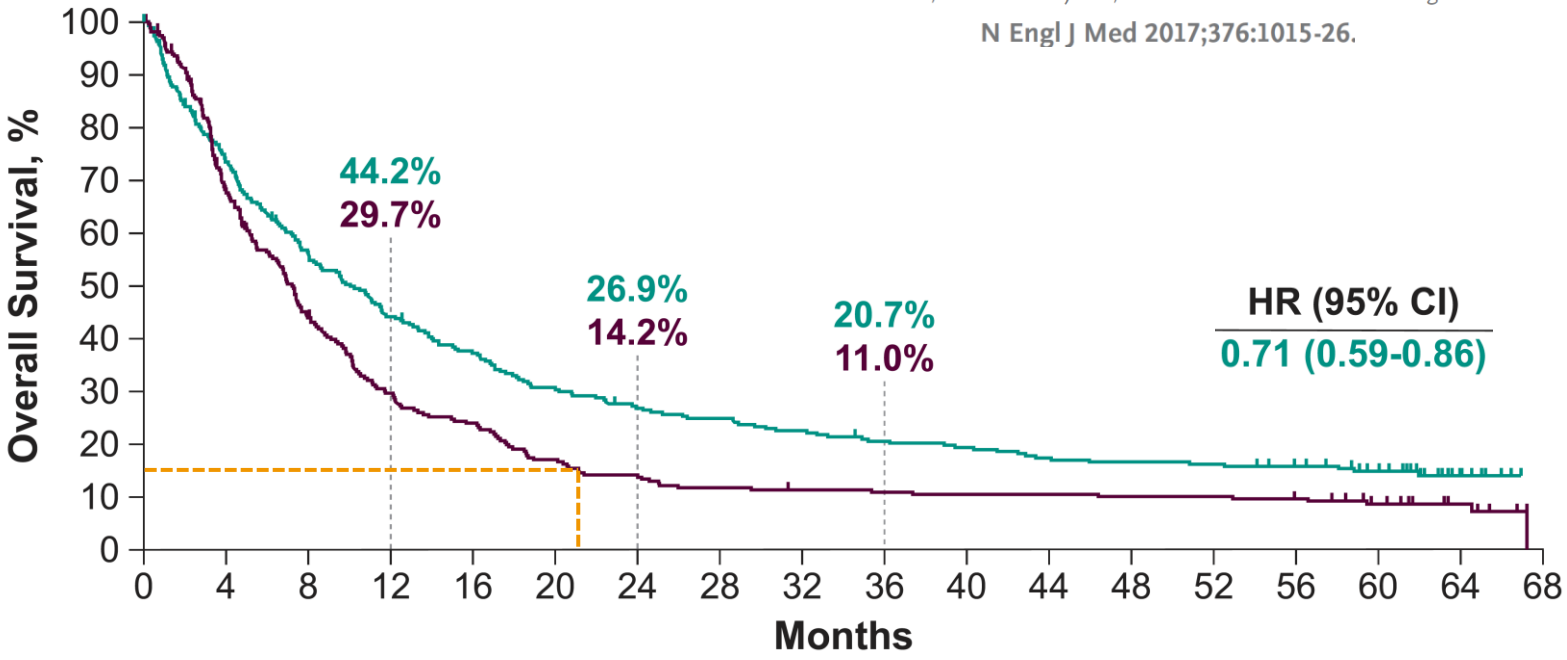
…

Data from Kaplan-Meier survival curves from the control groups of the trials included in the analysis may be used to estimate the baseline risk.

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

N Engl J Med 2017;376:1015-26.

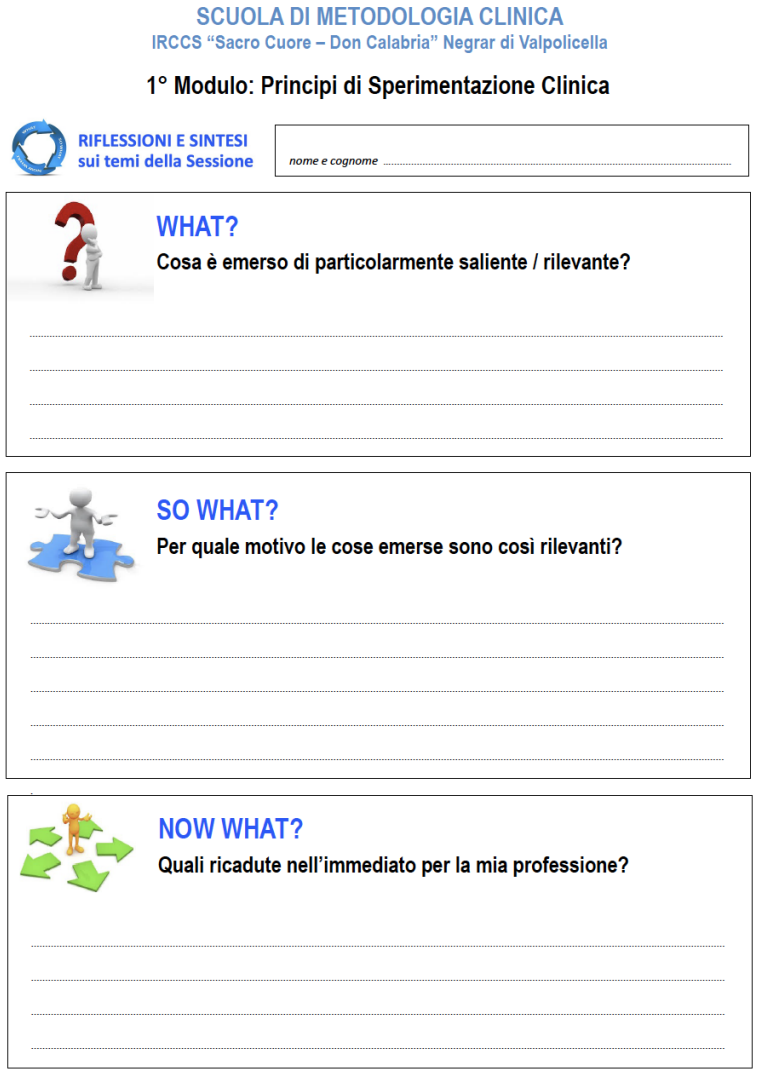


- Median f.u.: 21.1 months
- Basal risk* at median f.u.: 85%
- **Risk Difference: 11 events lower / 100 pts (95%CI: 18 lower to 5 lower)**
- NNT = 9

** J Clin Epidemiol 118 (2020) 124-131*

- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- **Principi di statistica medica (errori statistici, verifica di ipotesi, dimensiona-mento campionario)**
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

1. Riflettete da soli per 10 min. e compilate il form →
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso



SCUOLA DI METODOLOGIA CLINICA

IRCCS "Sacro Cuore – Don Calabria" Negrar di Valpolicella

1° Modulo: Principi di Sperimentazione Clinica

RIFLESSIONI E SINTESI sui temi della Sessione

nome e cognome .....

WHAT?

Cosa è emerso di particolarmente saliente / rilevante?

SO WHAT?

Per quale motivo le cose emerse sono così rilevanti?

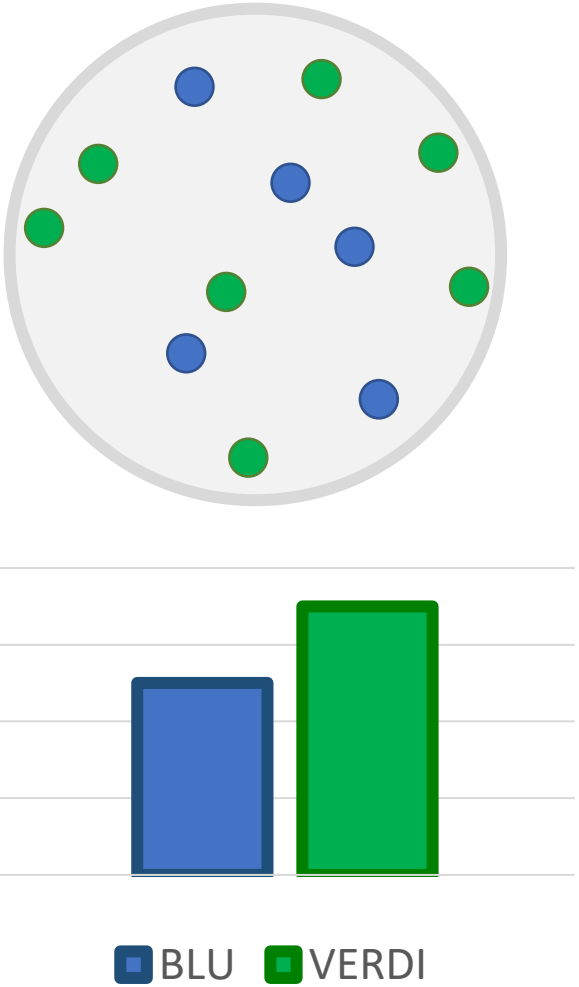
NOW WHAT?

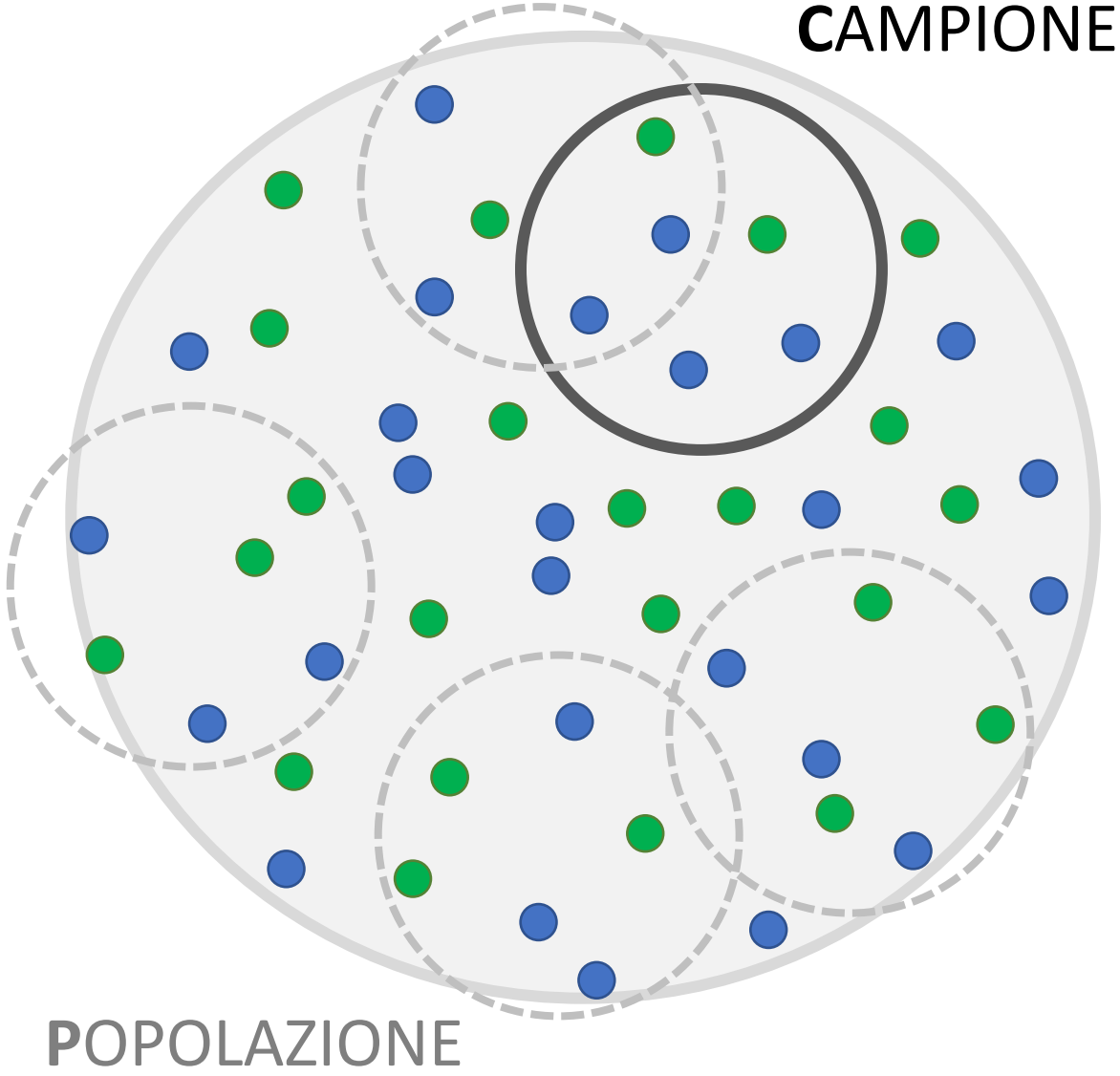
Quali ricadute nell'immediato per la mia professione?

PRINCIPI DI STATISTICA MEDICA:
ERRORI STATISTICI,
VERIFICA DI IPOTESI,
DIMENSIONAMENTO CAMPIONARIO

> “we can be blind to the obvious, and we are also blind to our blindness.”
>
> — **Daniel Kahneman**

STATISTICA DESCRITTIVA VS. INFERENZIALE





STIMA PUNTUALE VS. STIMA INTERVALLARE

Stima puntuale
Singolo valore che mira al parametro della popolazione.

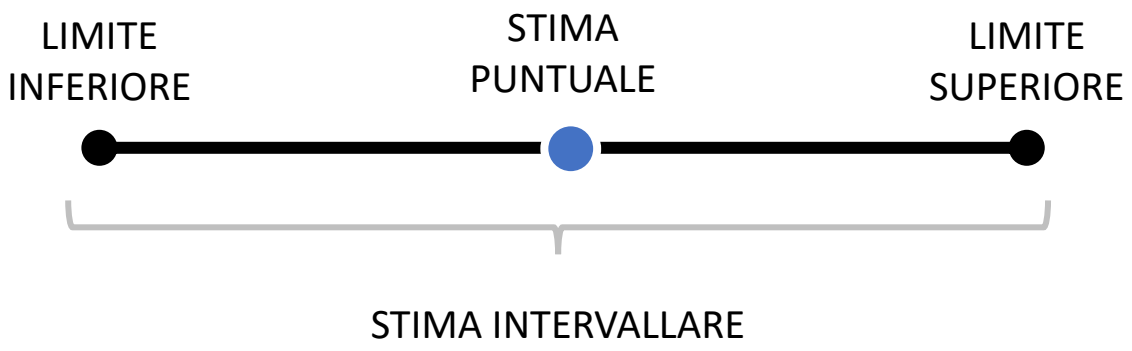
Stima intervallare
Specifica un intervallo di valori che contiene il parametro della popolazione. Solitamente viene costruito tenendo conto di una probabilità del 95%.

Se riportiamo un intervallo di valori plausibili, abbiamo buone probabilità di cogliere il parametro.

INTERVALLI DI CONFIDENZA

Qual è la cosa che ha il 95% di probabilità di accadere?
Circa **il 95% degli intervalli costruiti** seguendo la procedura di estrazione del campione e di stima conterrà il vero parametro di popolazione.

Il nostro intervallo costruito dal campione osservato conterrà o non conterrà il parametro, non lo sappiamo.



TEST D'IPOTESI

In un **tribunale**:
l'imputato è considerato innocente se non diversamente dimostrato.

L'obiettivo del pubblico ministero è di trovare delle **evidenze** che dimostrino la colpevolezza dell'imputato.

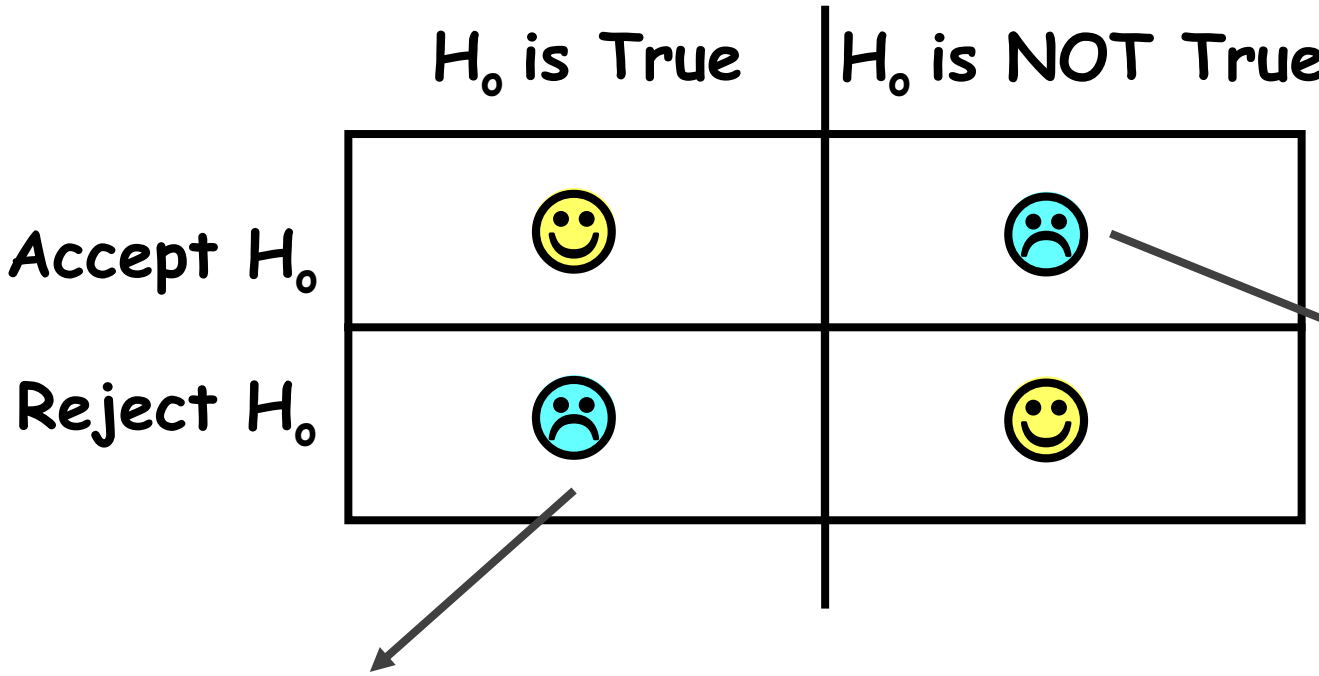
Ma quanto siamo disposti a considerare certe le evidenze che definiranno la colpevolezza dell'innocente?

		Verità	
		INNOCENTE	COLPEVOLE
Verdetto	INNOCENTE	Corretto	Errore
	COLPEVOLE	Errore	Corretto

TEST D'IPOTESI

In tribunale	In uno studio clinico
Innocente	Non esiste differenza tra i trattamenti (H0)
Colpevole	Esiste una differenza tra i trattamenti (H1)

TEST D'IPOTESI



Errore di II tipo (β)
Accetto un'ipotesi che non è vera

Errore di I tipo (α)
Rifiuto un'ipotesi vera

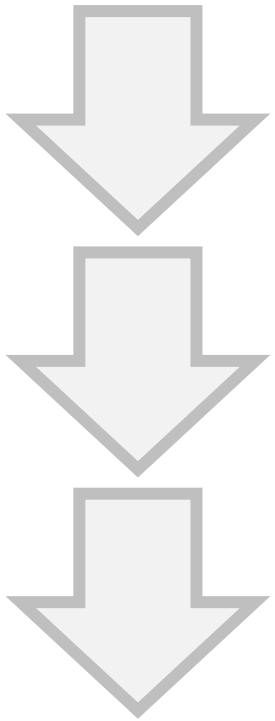
G.L. Pappagallo - S. Hilsenbeck, SABCS 2007 (modif. CM)

TEST D'IPOTESI

In tribunale	In uno studio clinico
Innocente	Non esiste differenza tra i trattamenti (H0)
Colpevole	Esiste una differenza tra i trattamenti (H1)
Assolvo l'innocente	Corretta accettazione di H0
Condanno il colpevole	Corretto rifiuto di H0
Condanno l'innocente	Errore di I tipo
Assolvo il colpevole	Errore di II tipo

G.L. Pappagallo - S. Hilsenbeck, SABCS 2007 (modif. CM)

VERIFICA D'IPOTESI



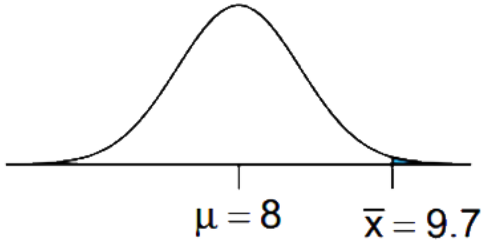
1. Impostare le ipotesi:
   - H0 : $\mu 0 - \mu 1 = 0$ (Non esiste differenza tra i trattamenti)
   - H1 : $\mu 0 - \mu 1 \neq 0$ (Esiste differenza tra i trattamenti)
2. Calcolare il valore del test e il corrispettivo **pvalue** (p)
3. Prendere una decisione:
   - Se il valore di $p < \alpha$, rifiutare H0
   - Se il valore di $p > \alpha$, non rifiutare H0

P-VALUE

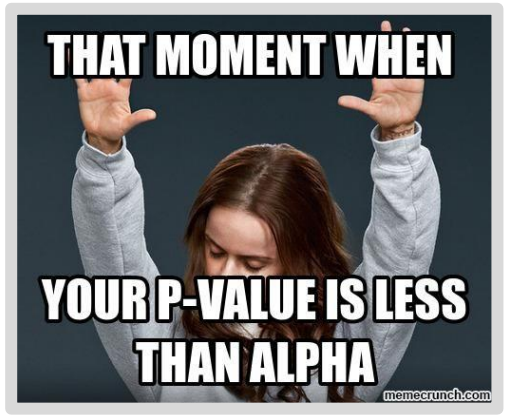
Il p-value è la probabilità che il parametro che voglio stimare, sotto l'ipotesi H0, abbia un valore uguale o più estremo di quello che ho osservato.

Ipotesi: H0: $\mu = 8$

Campione: $\bar{X} = 9.7$



$$p\text{-value} = P(\bar{x} > 9.7 \mid \mu = 8) = P(Z > 2.50) = 0.0062$$



P-VALUE

Non possiamo concludere da un P-value piccolo, se è presente un rapporto di causa effetto o se le nostre conclusioni possono essere generalizzate ad una popolazione più ampia.

Questo perché i p-value non possono dirci se il disegno di uno studio è stato impostato correttamente o se i dati sono stati raccolti in modo appropriato

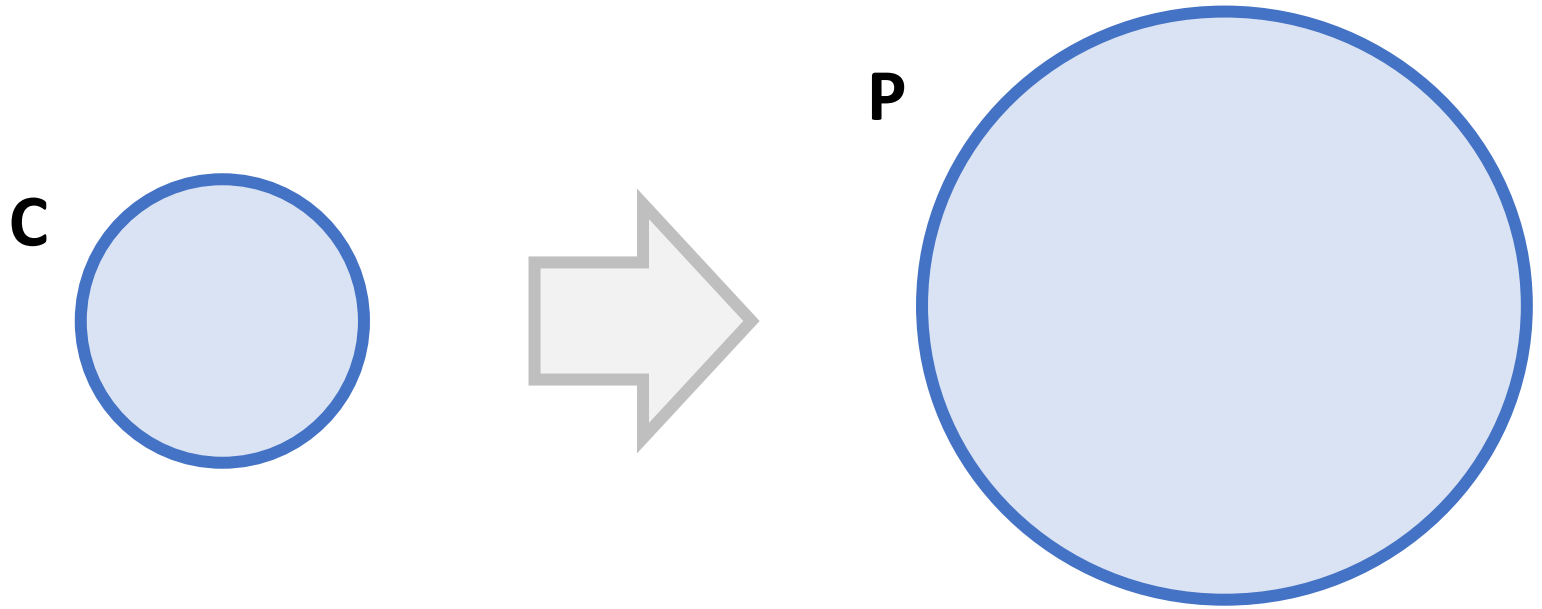
Garbage In → Garbage Out

Inoltre, il p-value non ci da alcuna informazione sulla rilevanza degli effetti che abbiamo osservato. **Rilevanze statistica non implica rilevanza clinica**.

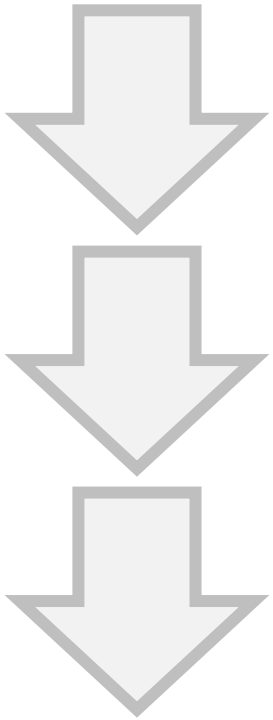
P-VALUE

Il campione deve essere **rappresentativo** per permettere l'inferenza

e **casuale** per essere rappresentativo.



DALL'IPOTESI ALLA NUMEROSITÀ

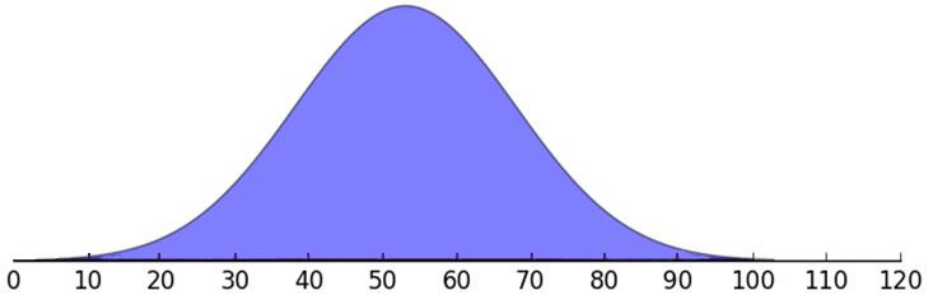


- **Obiettivo primario.**
- Definizione del **disegno di studio.**
- Scelta dei **criteri di inclusione** dei soggetti e metodi di selezione del campione.
- Definizione dell'**endpoint** corrispondente.
- Calcolo della **numerosità campionaria.**

ENDPOINT

Gli endpoints o **outcome** sono **misure di efficacia** scelte per valutare il raggiungimento degli obiettivi.

Devono essere validi, appropriati e clinicamente rilevanti.



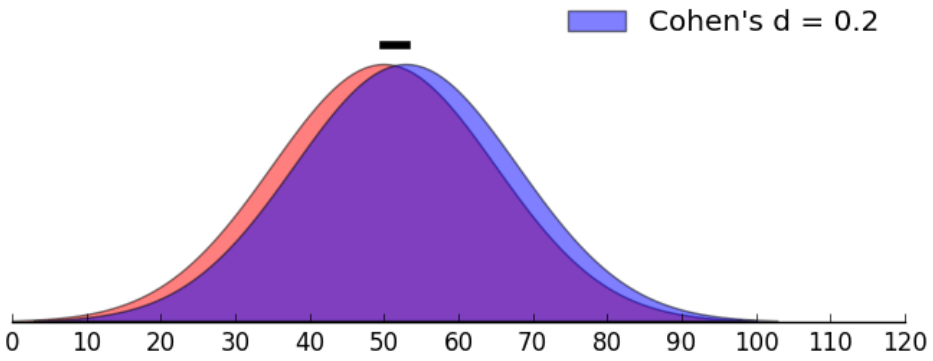
EFFECT SIZE

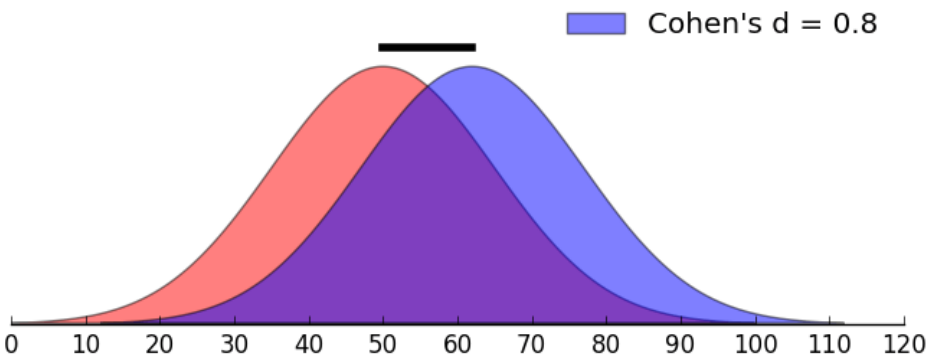
L'effect size è la misura quantitativa della forza di un fenomeno.

Esprime la **grandezza** (size) della differenza o relazione indagata.

Esempio:

$$\boldsymbol{d}_{Cohen} = \frac{differenza\ media}{standard\ deviation}$$



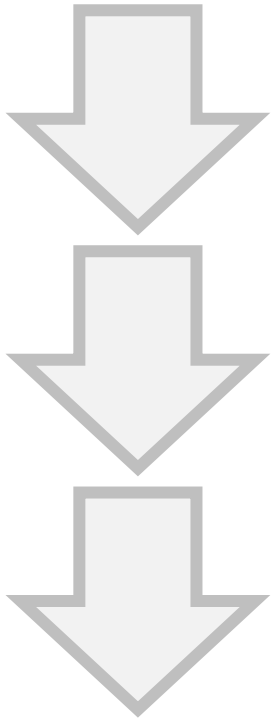


SAMPLE SIZE

Un trial clinico è un esperimento che coinvolge persone. L'arruolamento di un numero adeguato di soggetti ha anche una rilevanza **etica**. Il numero di soggetti dovrebbe essere sufficiente affinché si riesca a rispondere adeguatamente agli obiettivi prefissati.

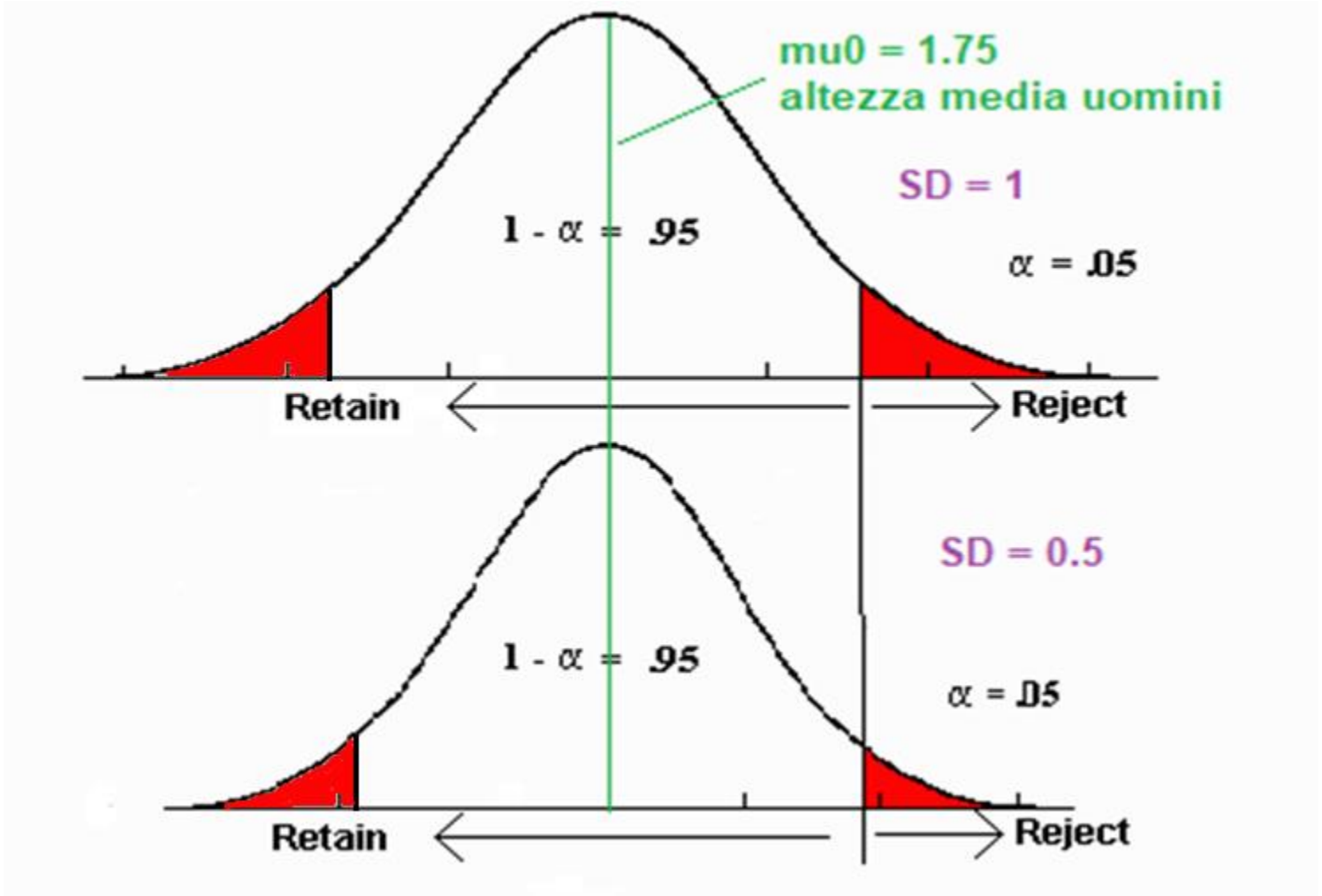
Sottodimensionare o sovradimensionare uno studio ha anche implicazioni **economiche**.

ELEMENTI DEL SAMPLE SIZE

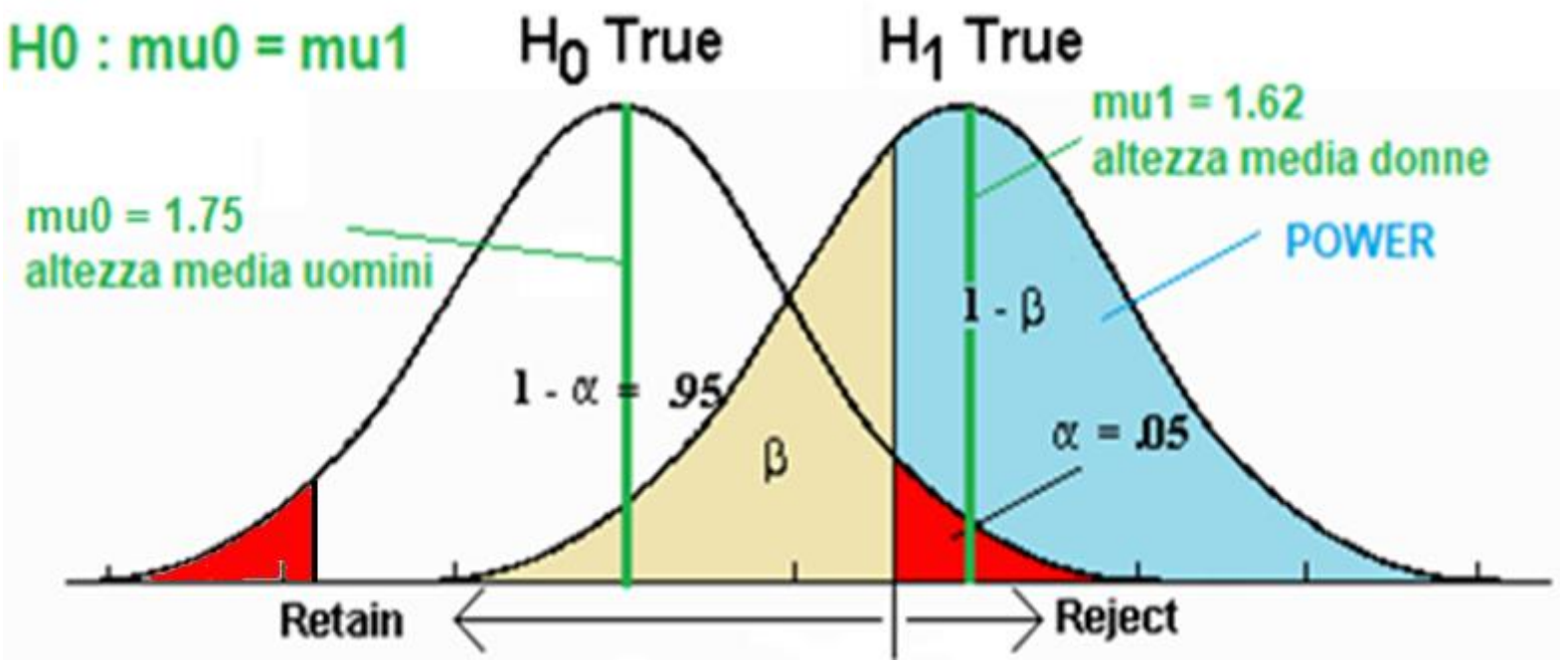


- **Effect size**: misura dell'effetto (assoluta o relativa).
- **Variabilità.**
- Errore di primo tipo (**α**).
- Errore di secondo tipo (β) o **POTENZA** (**1- β**).
- **Grandezza** campione.

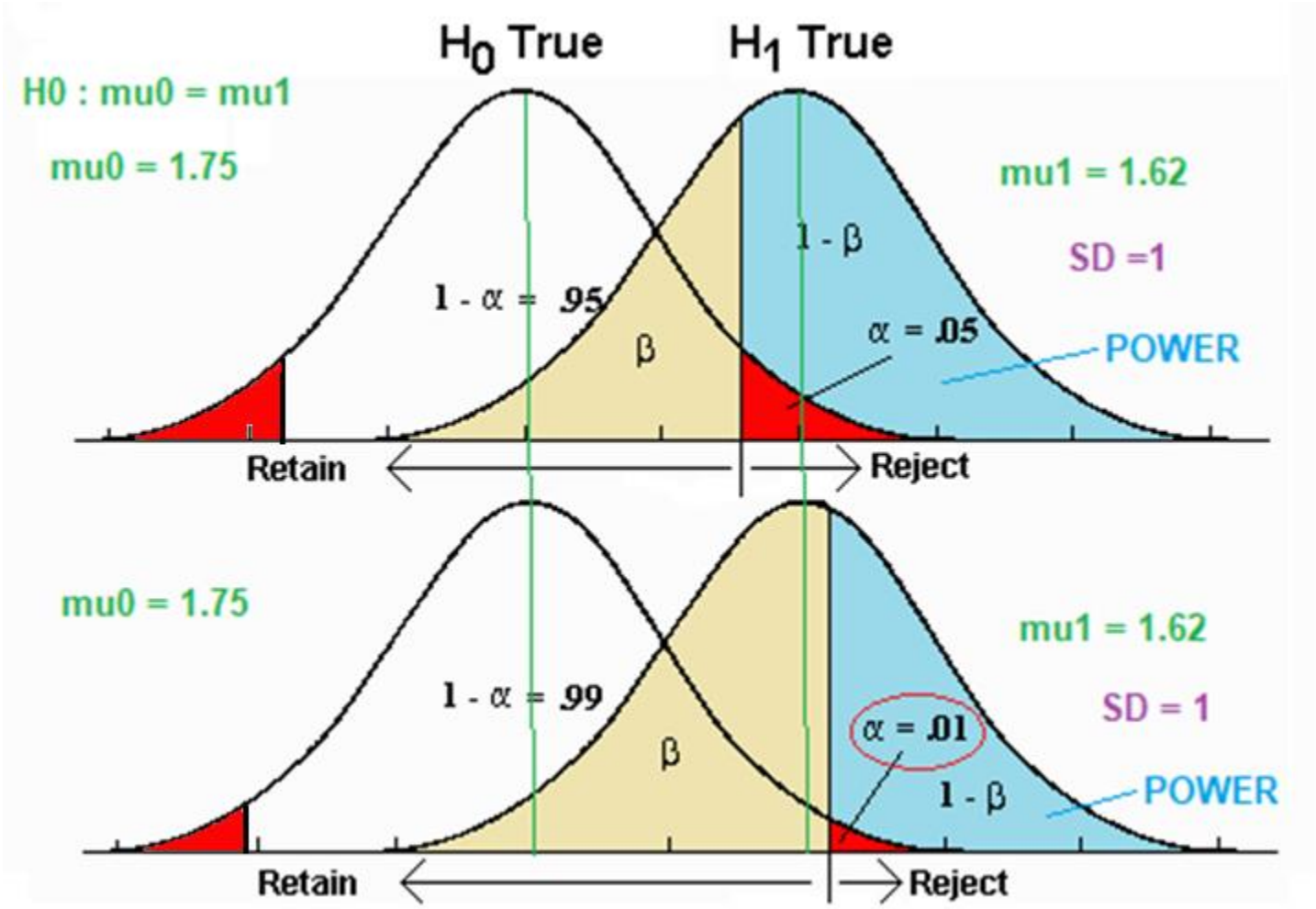
L'OUTCOME PRIMARIO E LA SUA DISTRIBUZIONE



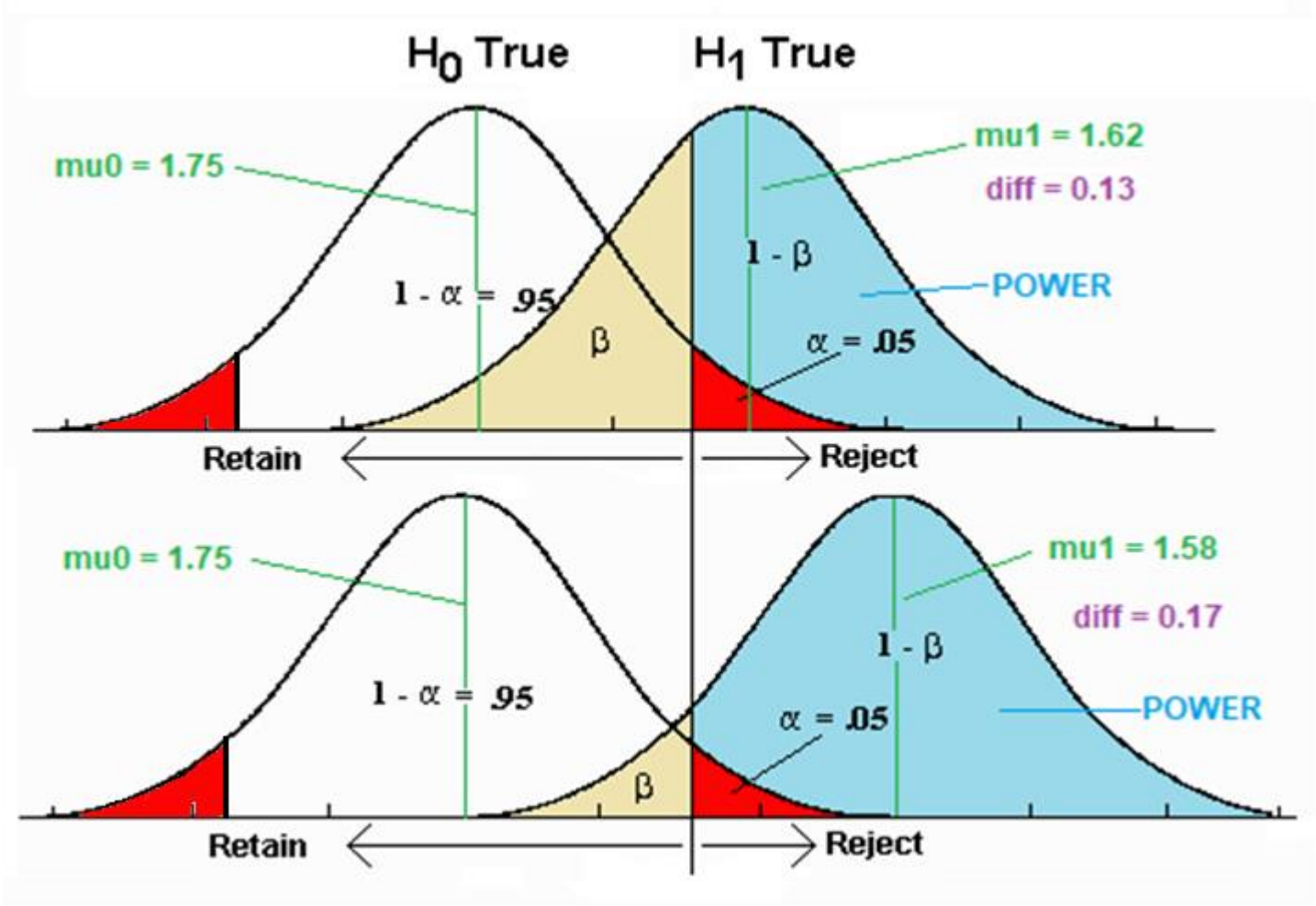
L'OUTCOME PRIMARIO E LA SUA DISTRIBUZIONE NEI DUE GRUPPI



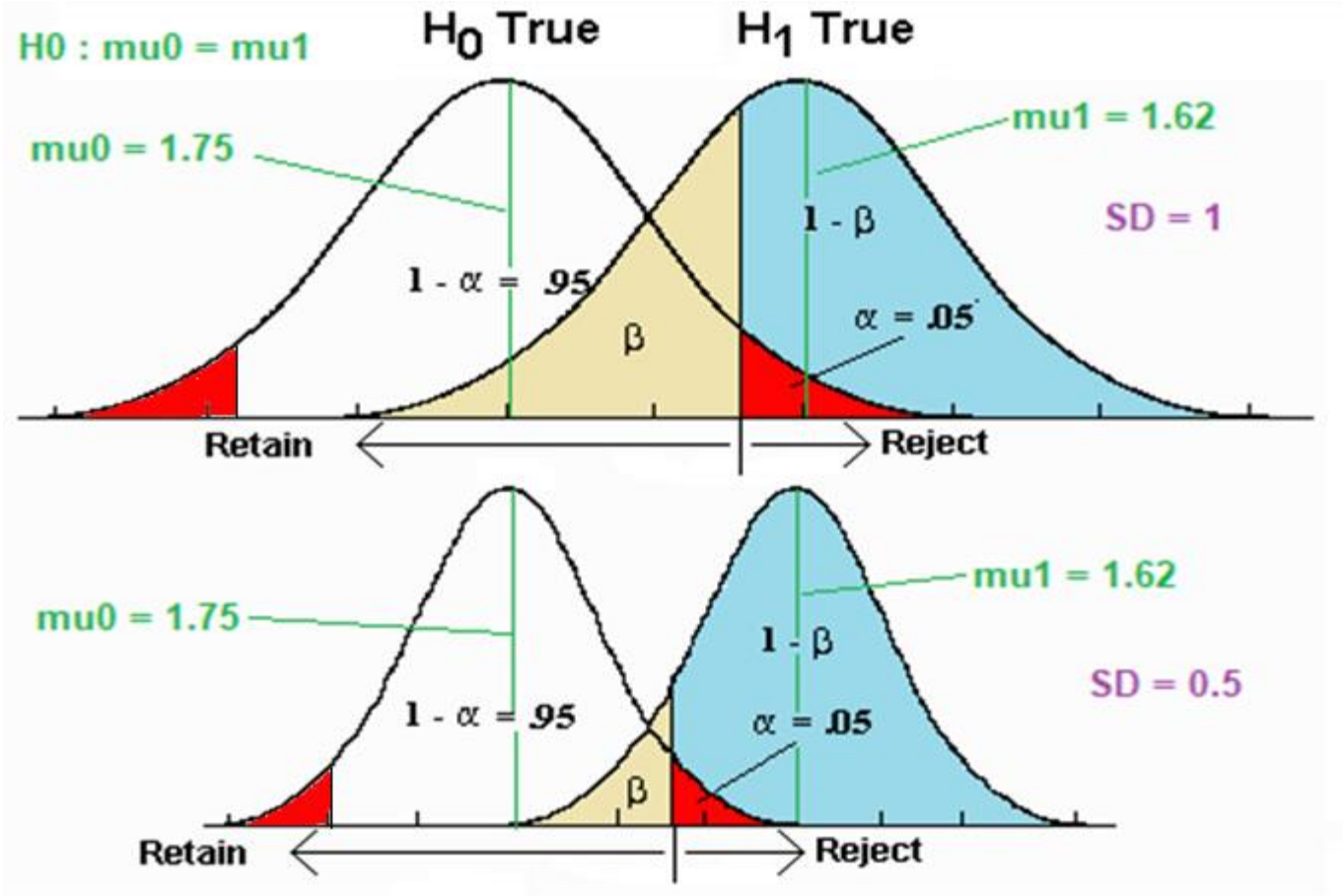
COME VARIA LA POTENZA AL VARIARE DELL'ERRORE DI PRIMO TIPO



COME VARIA LA POTENZA AL VARIARE DELLA DIFFERENZA ASSOLUTA



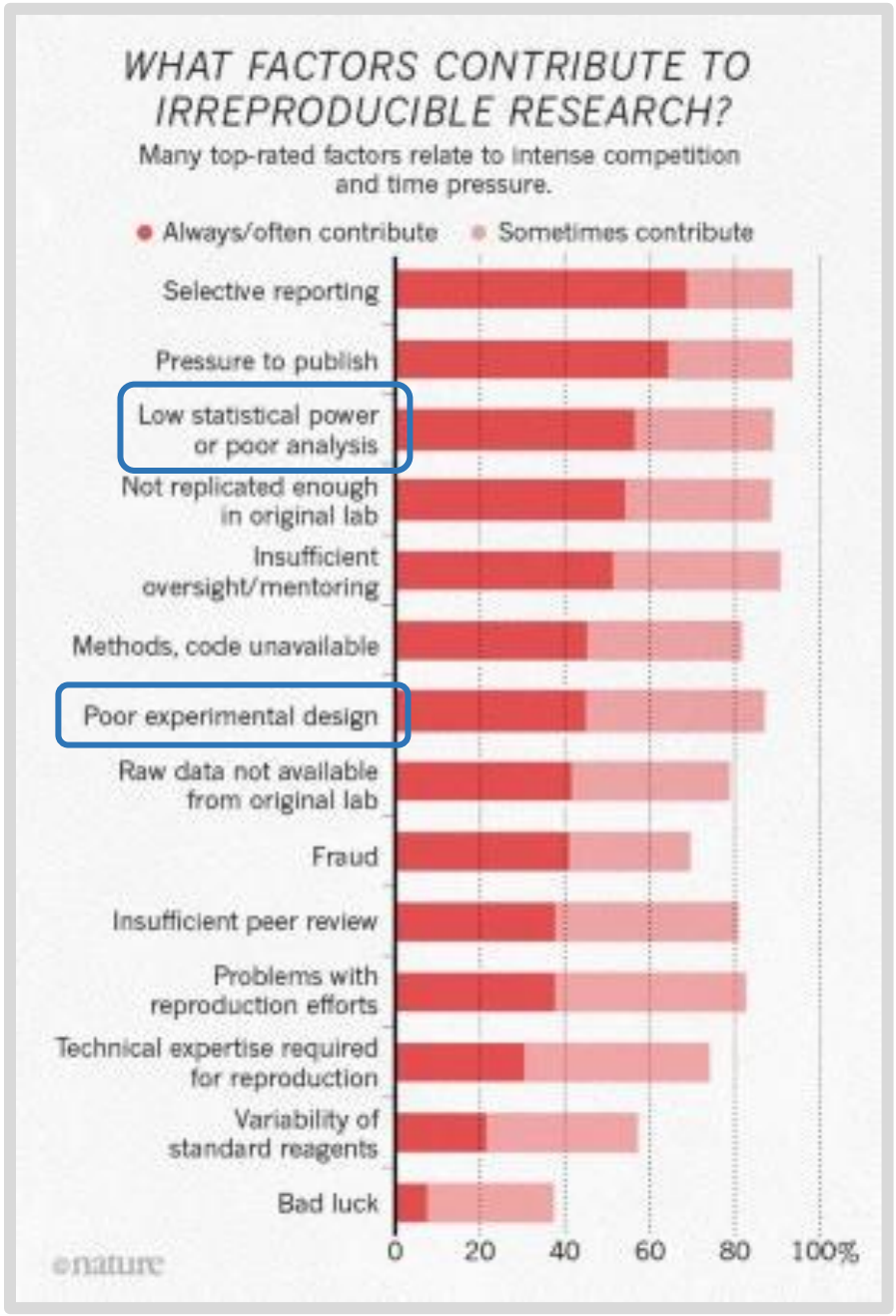
COME VARIA LA POTENZA AL VARIARE DELLA DEVIAZIONE STANDARD



PRINCIPI FONDAMENTALI

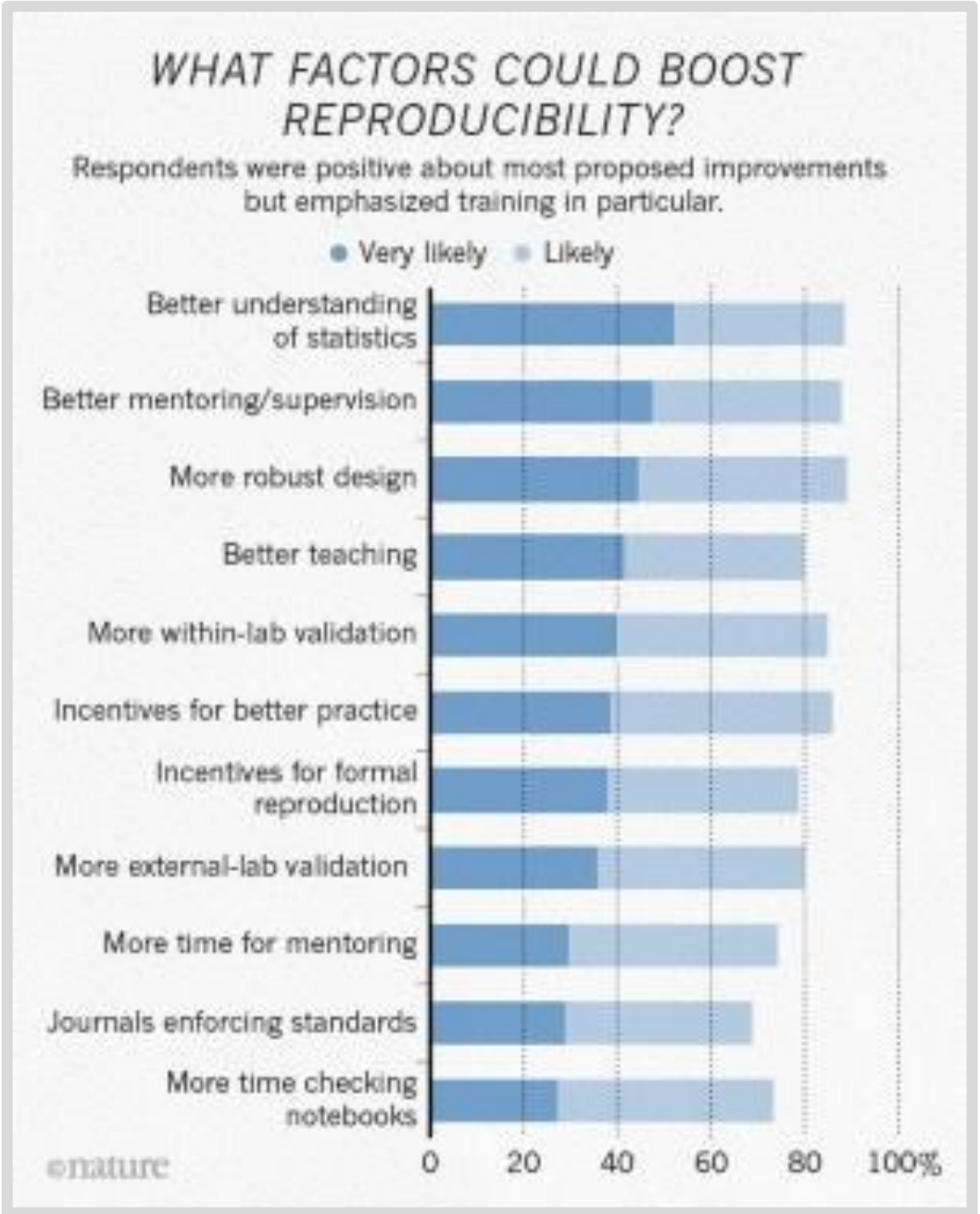
1,500 scientists lift the lid on reproducibility.

Baker, Nature, 2016



1,500 scientists lift the lid on reproducibility.

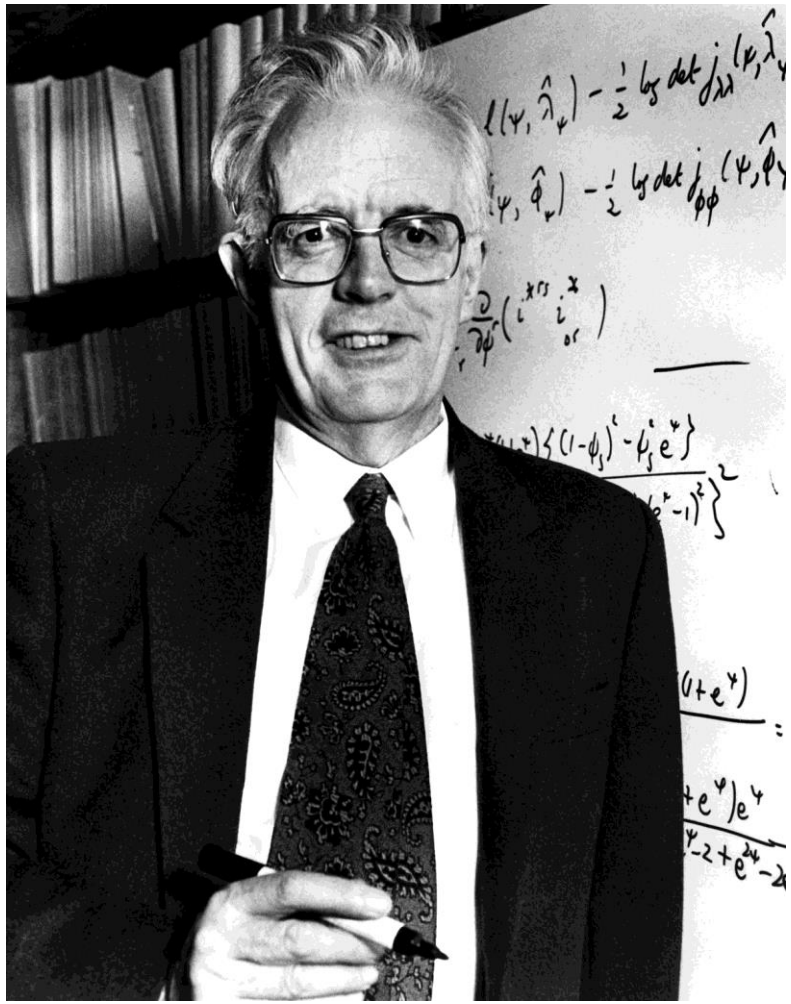
Baker, Nature, 2016



MY TWO CENTS…

STATISTICO VS. STATISTA

Sir David Cox



Presidente Sergio Mattarella

DIALOGHI CON STATISTICI, COSA EVITARE:

- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- **Rilevanza clinica Vs significatività statistica**
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

Statistical Vs Clinical Significance

- **Statistical Significance**

  "Is an observed difference **likely to be real**"

  ✓ dependent on the magnitude of the number of patients
  NOT on whether the difference is meaningful for patients

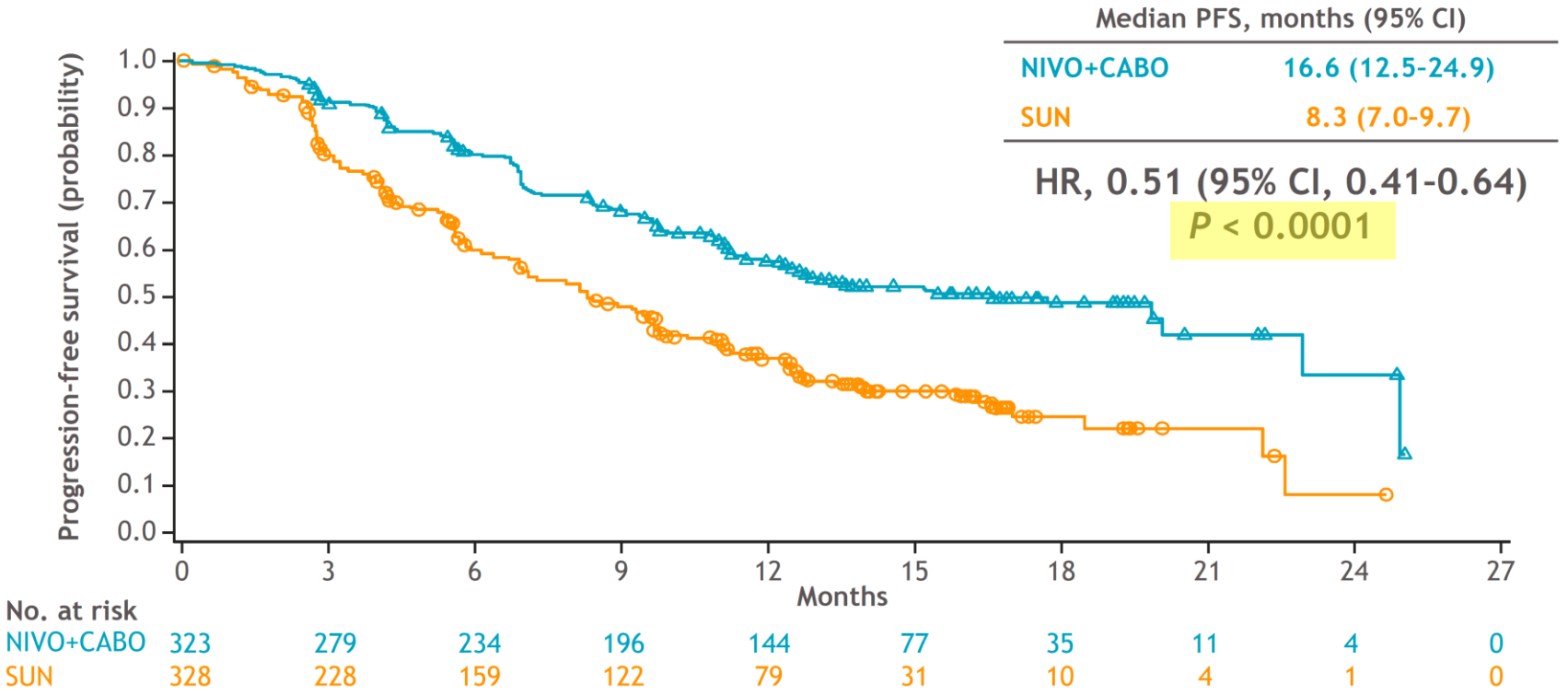
- quando il valore di **p** risultante dal test di significatività è più piccolo del valore soglia (usualmente 5%), si considera lo studio (statisticamente) positivo;
- se il valore di **p** è maggiore del 5%, si considera lo studio (statisticamente) negativo

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

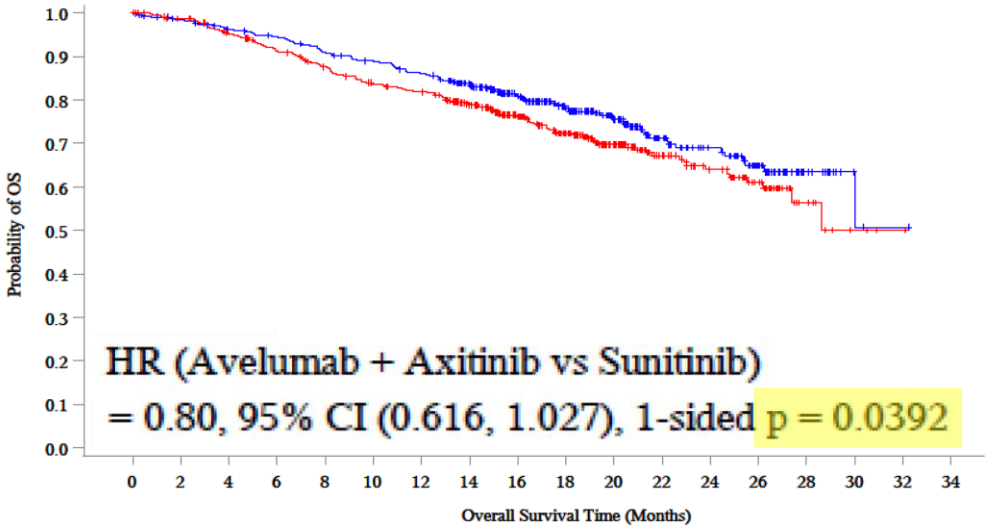
Progression-free survival per BICR



It was estimated that ~350 progression or death events would result at least 95% power to detect a hazard ratio of 0.68

P-value is a measure of the probability that an observed difference could have occurred just by random chance.

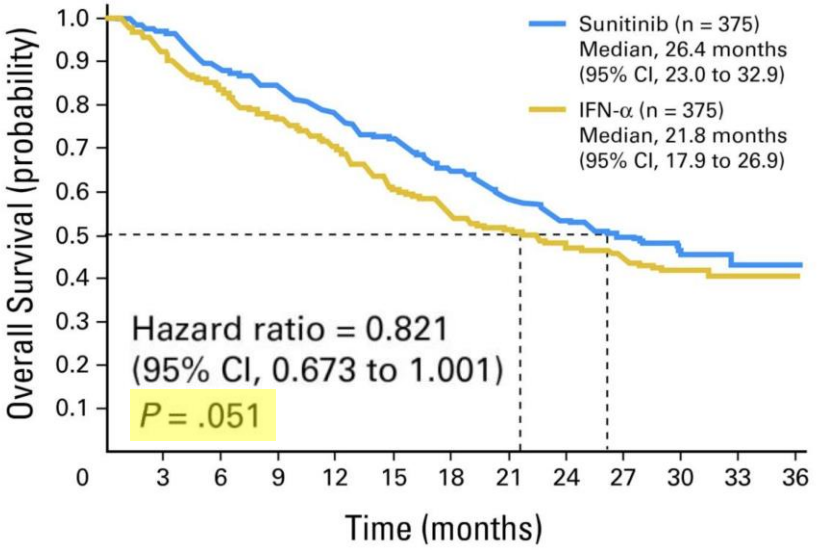
- Don't base your conclusions solely on whether an association or effect was found to be "statistically significant".



Motzer R, et al. N Engl J Med. 2019 Mar 21;380(12):1103-1115.

P-value is a measure of the probability that an observed difference could have occurred just by random chance.

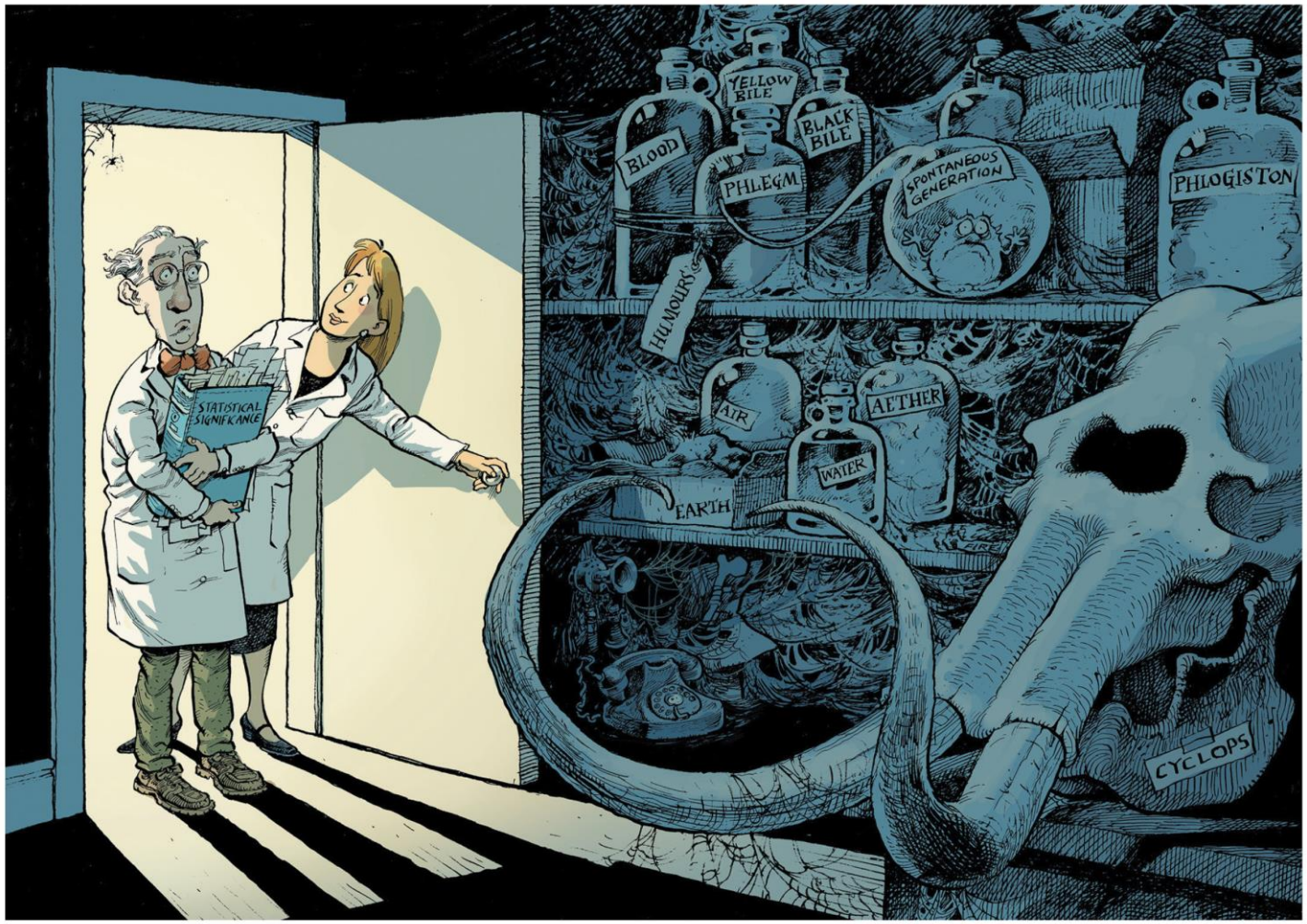
- Don't base your conclusions solely on whether an association or effect was found to be "statistically significant".
- Don't believe that an association or effect is absent just because it was not statistically significant.



Motzer R, et al. N Engl J Med. 2007 Jan 11;356(2):115

P-value is a measure of the probability that an observed difference could have occurred just by random chance.

- Don't base your conclusions solely on whether an association or effect was found to be "statistically significant".
- Don't believe that an association or effect is absent just because it was not statistically significant.
- Don't conclude anything about scientific or practical importance based on statistical significance (or lack thereof).



Retire statistical significance

Valentin Amrhein, Sander Greenland, Blake McShane and more than 800 signatories call for an end to hyped claims and the dismissal of possibly crucial effects.

21 MARCH 2019 | VOL 567 | NATURE | 305

The fragility of phase 3 trials supporting FDA-approved anticancer medicines: a retrospective analysis

Joseph C Del Paggio, Ian F Tannock

***Lancet Oncol* 2019; 20: 1065–69**

Fragility Index (FI) = the minimum number of changes from non-events to events resulting in loss of statistical significance in a RCT

FI≤2 in 59% of trials

	Control group (n=362)	Experimental group (n=360)	
Number of events	157	129	p=0·040
Number of non-events	205	231	
Number of events	157	129+1=130	p=0·048
Number of non-events	205	231–1=230	
Number of events	157	129+2=131	p=0·058
Number of non-events	205	231–2=229	

Statistical Vs Clinical Significance

- **Statistical Significance**

  "Is an observed difference likely to be real"

  ✓ dependent on the magnitude of the number of patients and/or the **magnitude of the difference** NOT on whether the difference is meaningful for patients

- **Clinical Significance**

  "Is an observed difference likely **to be meaningful for patients**"

  ✓ dependent on the magnitude of the difference NOT the number of patients

J Natl Cancer Inst 2011;103:16–20

When Are "Positive" Clinical Trials in Oncology Truly Positive?

Alberto Ocana, Ian F. Tannock

What Constitutes a Positive Clinical Trial in Oncology?

We would define a positive trial as one in which the predefined value of δ represents a clinically important difference in an end-point that directly reflects benefit (mainly OS or quality of life) to patients and for which the results provide a best estimate of the difference that exceeds that predefined value of δ.

Obiettivi di uno studio comparativo

Si ritiene che il trattamento in esame "A" abbia le potenzialità per migliorare il trattamento standard "B" almeno di una quantità Δ

studio di superiorità

A > B di una quantità Δ di interesse clinico

studio di non inferiorità

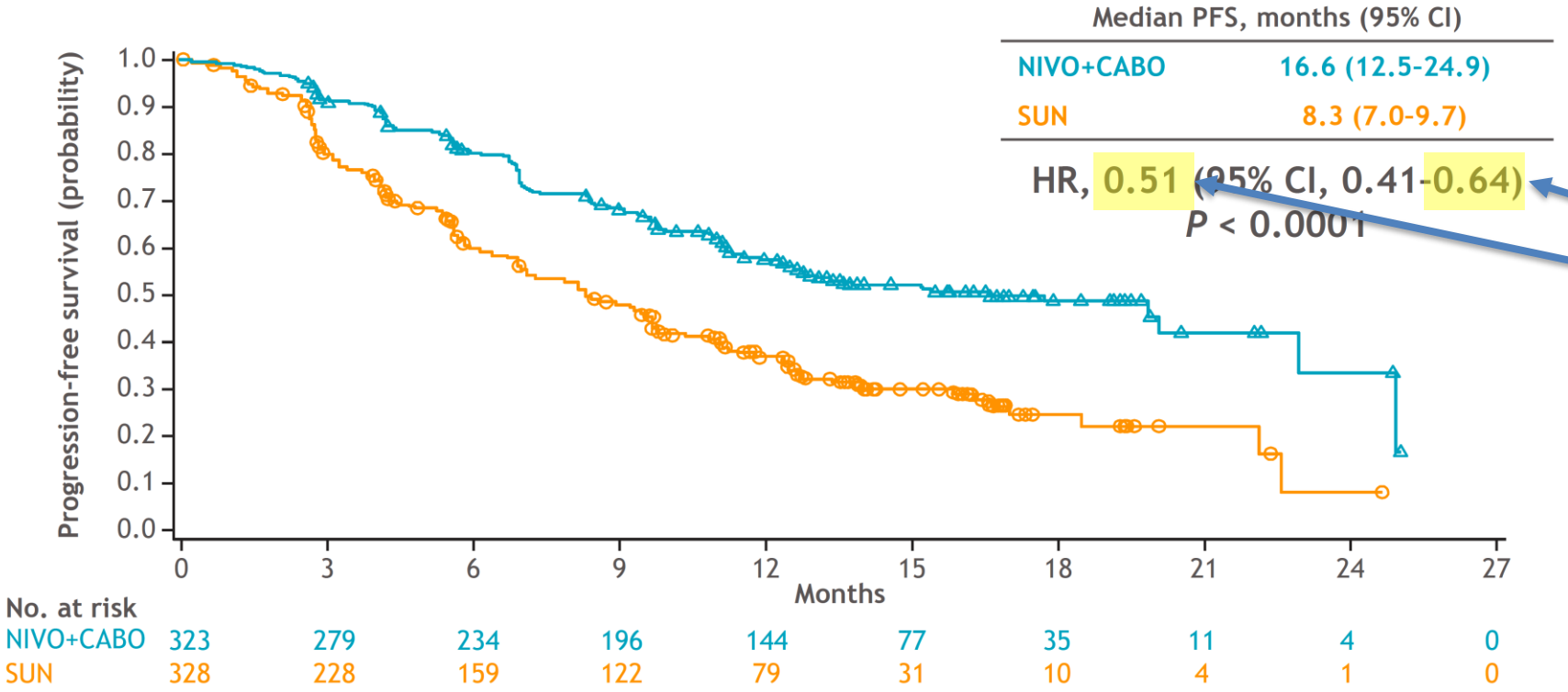
A < B non oltre una quantità M di rilevanza clinica

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

Progression-free survival per BICR



It was estimated that ~350 progression or death events would result at least 95% power to detect a hazard ratio of 0.68

Symptom Endpoints (Patient-Reported Outcomes)

- Blinding is often difficult
- Data are often missing or incomplete
- Clinical significance of small changes unknown
- Few validated instruments

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

N Engl J Med 2013;369:722-31

Table 2. Change in Health-Related Quality of Life during the First 6 Months for 927 Patients Treated in the Study.*

Instrument	Pazopanib	Sunitinib	Difference in Mean Change from Baseline Score with Pazopanib vs. Sunitinib†	P Value§	Drug Favored According to Significant Difference¶	Effect Size‖
	number of patients					
FACIT-F**	377	403	2.32	<0.001	Pazopanib	0.24
FKSI-19**						
Treatment side effects	351	382	0.31	0.03	Pazopanib	0.14
Disease-related physical symptoms	378	407	0.78	0.03	Pazopanib	0.13
Disease-related emotional symptoms	370	402	–0.05	0.41	Neither	–0.04
Functional well-being	378	403	0.31	0.10	Neither	0.09
Total score	377	408	1.41	0.02	Pazopanib	0.14

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

N Engl J Med 2013;369:722-31

Table 2. Change in Health-Related Quality of Life during the First 6 Months for 927 Patients Treated in the Study.*

Instrument	Pazopanib	Sunitinib	Difference in Mean Change from Baseline Score with Pazopanib vs. Sunitinib†	P Value§	Drug Favored According to Significant Difference¶	Effect Size‖
	number of patients					
FACIT-F**	377	403	2.32	<0.001	Pazopanib	0.24
FKSI-19**						
Treatment side effects	3			0.03	Pazopanib	0.14
Disease-related physical symptoms	3			0.03	Pazopanib	0.13
Disease-related emotional symptoms	3			0.41	Neither	–0.04
Functional well-being	378	403	0.31	0.10	Neither	0.09
Total score	377	408	1.41	0.02	Pazopanib	0.14

Rilevanza dell'effetto da rapportare alla M.I.D. specifica

Minimal (Clinical) Interesting Difference (MID / MCID)

the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management

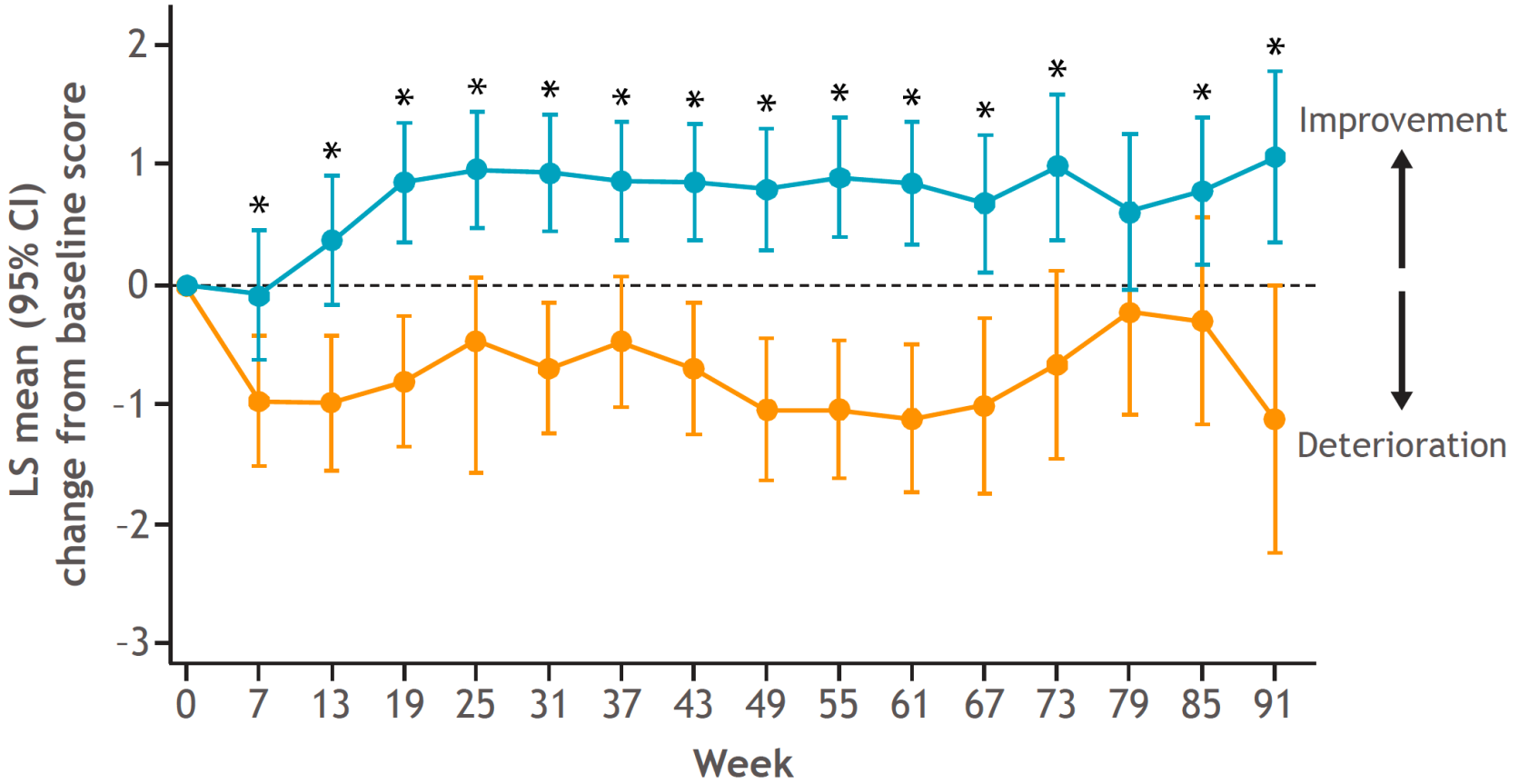
- it’s easily understood by clinicians as a key concept in the interpretability of PRO scores;
- will inform judgments about the success-fulness of an intervention;

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

FKSI: Disease-Related Symptom Subscale



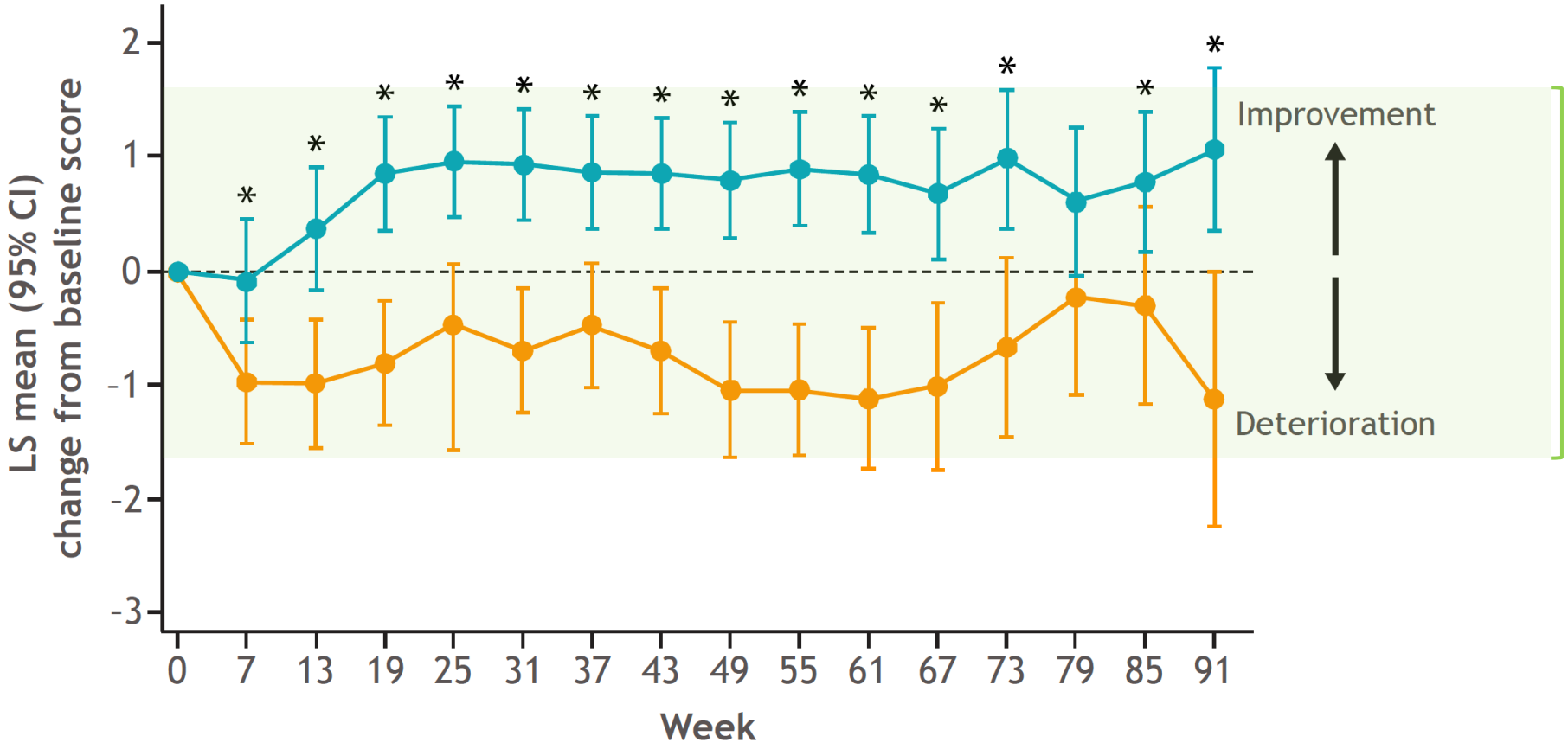
*Between-arm difference was statistically significant at this timepoint ($P < 0.05$)

VIRTUAL 2020 ESMO congress

Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial

Toni K. Choueiri,[1] Thomas Powles,[2] Mauricio Burotto,[3] Maria T. Bourlon,[4] Bogdan Zurawski,[5] Víctor Manuel Oyervides Juárez,[6] James J. Hsieh,[7] Umberto Basso,[8] Amishi Y. Shah,[9] Cristina Suarez,[10] Alketa Hamzaj,[11] Carlos Barrios,[12] Martin Richardet,[13] David Pook,[14] Yoshihiko Tomita,[15] Bernard Escudier,[16] Joshua Zhang,[17] Burcin Simsek,[17] Andrea B. Apolo,[18] Robert J. Motzer[19]

FKSI: Disease-Related Symptom Subscale



Castellano D, et al. Annals of Oncology 20: 1803–1812, 2009

*Between-arm difference was statistically significant at this timepoint ($P < 0.05$)

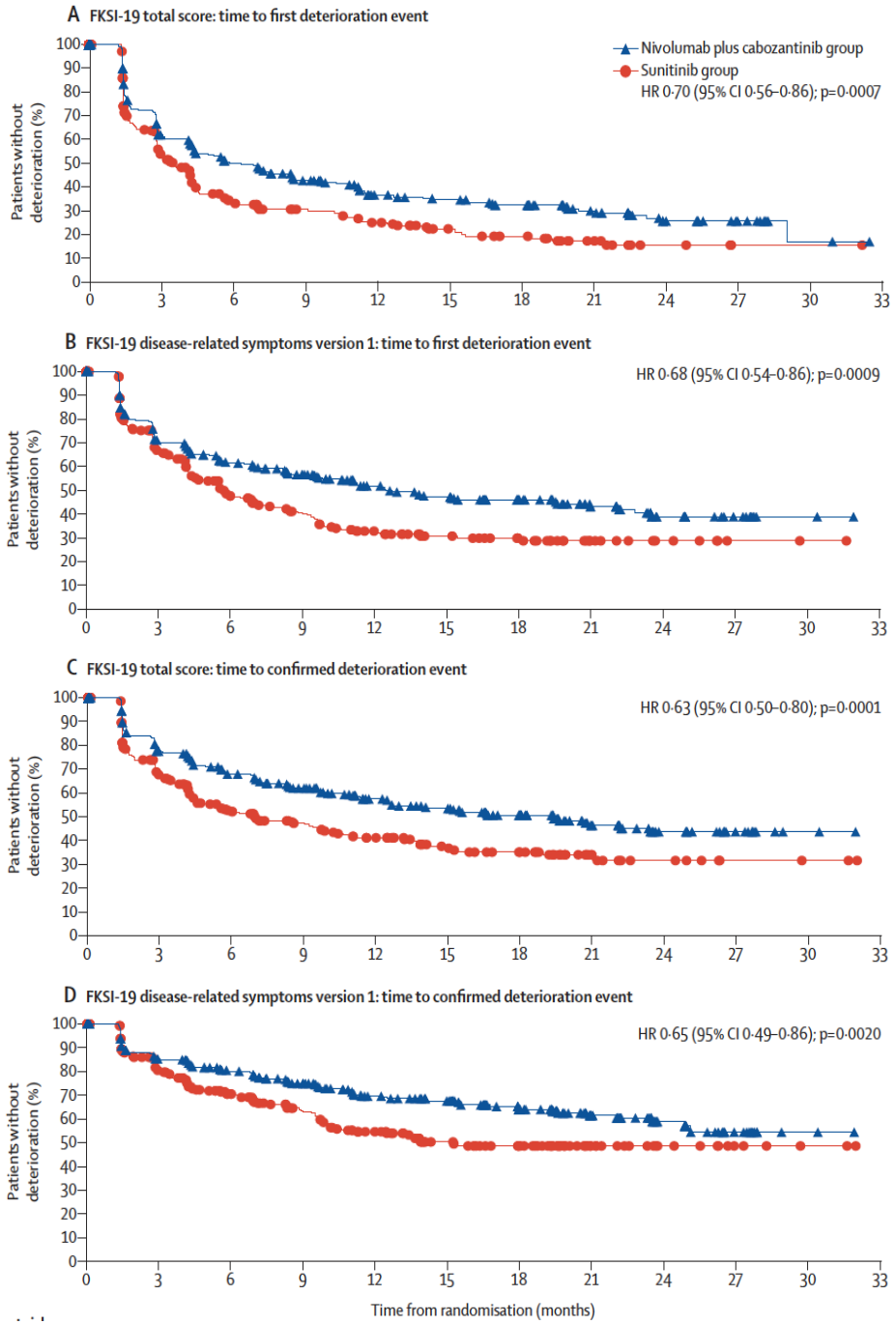
Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial

David Cella*, Robert J Motzer*, Cristina Suarez, Steven I Blum, Flavia Ejzykowicz, Melissa Hamilton, Joel F Wallace, Burcin Simsek, Joshua Zhang, Cristina Ivanescu, Andrea B Apolo, Toni K Choueiri

Lancet Oncol 2022; 23: 292–303

Time to first deterioration and time to confirmed deterioration were assessed for FKSI-19 and EQ-5D-3L. Time to first deterioration was defined as the time from randomisation to the first date that a patient had a change from baseline meeting or exceeding the prespecified primary meaningful change threshold for the scale.

Death or progression were not considered deterioration events.



Parliamo di Maturità di uno Studio Clinico

$$\frac{\text{numero di eventi osservati}}{\text{numero di pazienti arruolati}} \quad Vs \quad \frac{\text{numero di eventi osservati}}{\text{numero degli eventi previsti}}$$

For trials with a well-designed interim-monitoring plan, stopping at 50% or greater information has a negligible impact on estimation.

Freidlin & Korn. Clinical Trials 2009; 6: 119–125

Nivolumab plus Cabozantinib versus Sunitinib for Advanced Renal-Cell Carcinoma

T.K. Choueiri, T. Powles, M. Burotto, B. Escudier, M.T. Bourlon, B. Zurawski, V.M. Oyervides Juárez, J.J. Hsieh, U. Basso, A.Y. Shah, C. Suárez, A. Hamzaj, J.C. Goh, C. Barrios, M. Richardet, C. Porta, R. Kowalyszyn, J.P. Feregrino, J. Żołnierek, D. Pook, E.R. Kessler, Y. Tomita, R. Mizuno, J. Bedke, J. Zhang, M.A. Maurer, B. Simsek, F. Ejzykowicz, G.M. Schwab, A.B. Apolo, and R.J. Motzer, for the CheckMate 9ER Investigators*

N Engl J Med 2021;384:829-41.

	Nivo+Cabo N = 323	Sunitinib N = 328
PFS per BICR		
Events, n (%)	144 (44.6)	191 (58.2)

It was estimated that ~350 progression or death events would result at least 95% power to detect a hazard ratio of 0.68

335 events observed / 350 planned: I.F. 95.7%

arativo

Vista la migliore tollerabilità del trattamento in esame “A”, si è disposti ad accettarne una eventuale minore efficacia rispetto al trattamento standard “B” purché questa non vada oltre un margine M

studio di superiorità

A > B di una quantità Δ di interesse clinico

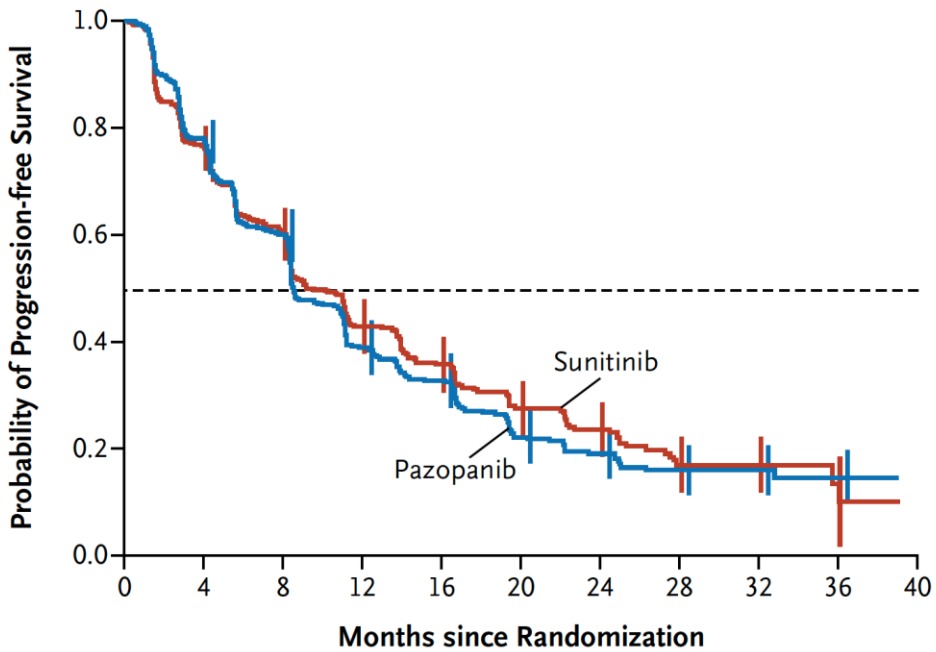
studio di non inferiorità

A < B non oltre una quantità M di rilevanza clinica

Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma

Robert J. Motzer, M.D., Thomas E. Hutson, D.O., David Cella, Ph.D., James Reeves, M.D., Robert Hawkins, M.B., B.S., Ph.D., Jun Guo, Ph.D., Paul Nathan, M.B., B.S., Ph.D., Michael Staehler, M.D., Paul de Souza, M.B., B.S., Ph.D., Jaime R. Merchan, M.D., Ekaterini Boleti, M.D., Ph.D., Kate Fife, M.D., Jie Jin, M.D., Robert Jones, Ph.D., Hirotsugu Uemura, M.D., Ph.D., Ugo De Giorgi, M.D., Ulrika Harmenberg, M.D., Ph.D., Jinwan Wang, M.D., Cora N. Sternberg, M.D., Keith Deen, M.S., Lauren McCann, Ph.D., Michelle D. Hackshaw, Ph.D., Rocco Crescenzo, D.O., Lini N. Pandite, M.D., and Toni K. Choueiri, M.D.

N Engl J Med 2013;369:722-31



STATISTICAL ANALYSIS

We calculated that 631 disease-progression events were required for the study to have 80% power to reject the null hypothesis of an increased risk in the hazard of disease progression with pazopanib (hazard ratio, ≥1.25).

hazard ratio 1.05 (95% CI, 0.90 to 1.22)

Studi di non-inferiorità:
Analisi ITT *Vs* analisi PP

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use
London, 27 July 2000 CPMP/EWP/482/99

IV.2.3 Choice of analysis set

In a superiority trial the full analysis set, based on the ITT (intention-to-treat) principle, is the analysis set of choice, with appropriate support provided by the PP (per protocol) analysis set. In a non-inferiority trial the full analysis set and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation.

Guidance for Industry
Non-Inferiority Clinical Trials

March 2010
Clinical/Medical

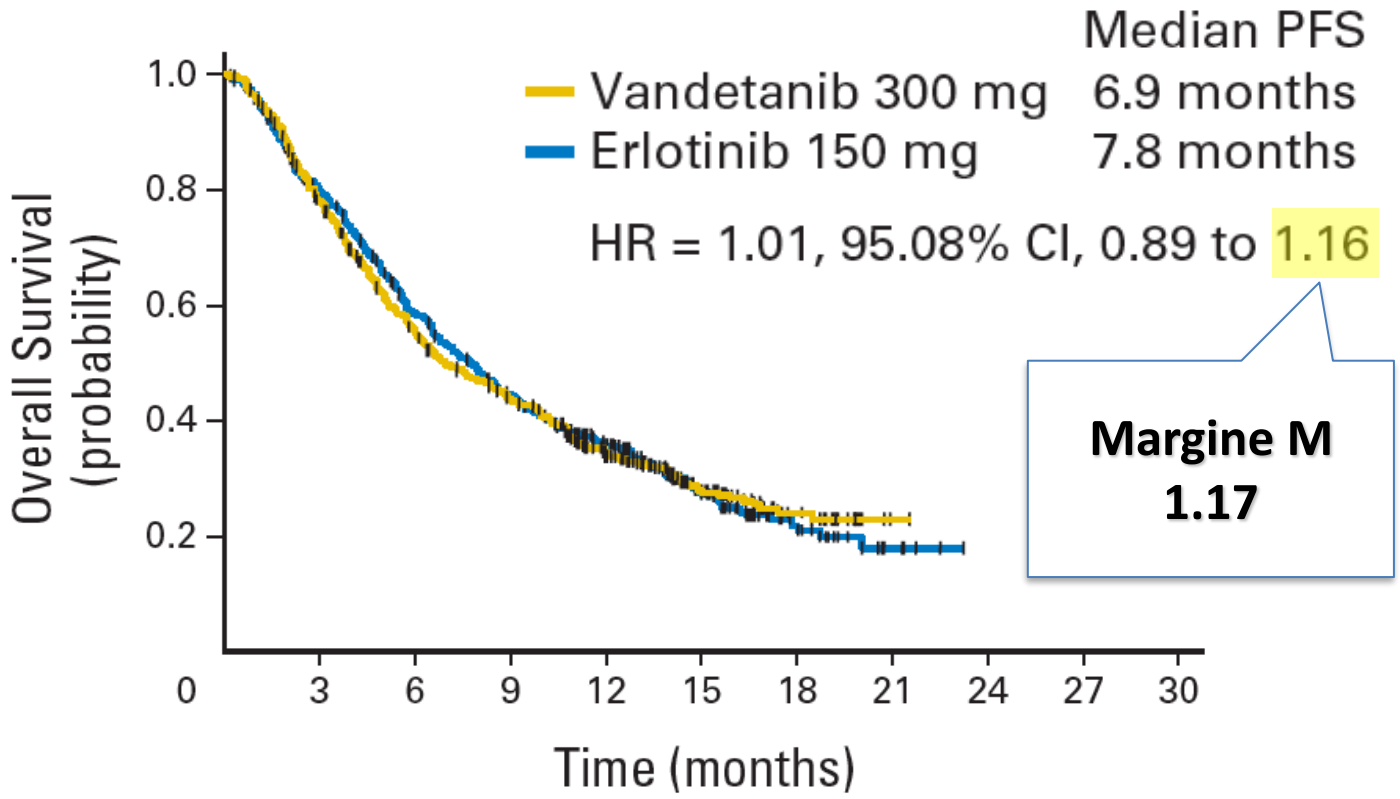
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

Although an "as-treated" analysis is therefore often suggested as the primary analysis for NI studies, there are also significant concerns with the possibility of informative censoring in an as-treated analysis. It is therefore important to conduct both ITT and as-treated analyses in NI studies.
Differences in results using the two analyses will need close examination.

Phase III Trial of Vandetanib Compared With Erlotinib in Patients With Previously Treated Advanced Non–Small-Cell Lung Cancer

Ronald B. Natale, Sumitra Thongprasert, F. Anthony Greco, Michael Thomas, Chun-Ming Tsai, Patrapim Sunpaweravong, David Ferry, Clive Mulatero, Robert Whorf, Joyce Thompson, Fabrice Barlesi, Peter Langmuir, Sven Gogov, Jacqui A. Rowbottom, and Glenwood D. Goss

J Clin Oncol 29:1059-1066. © 2011 by American Society of Clinical Oncology

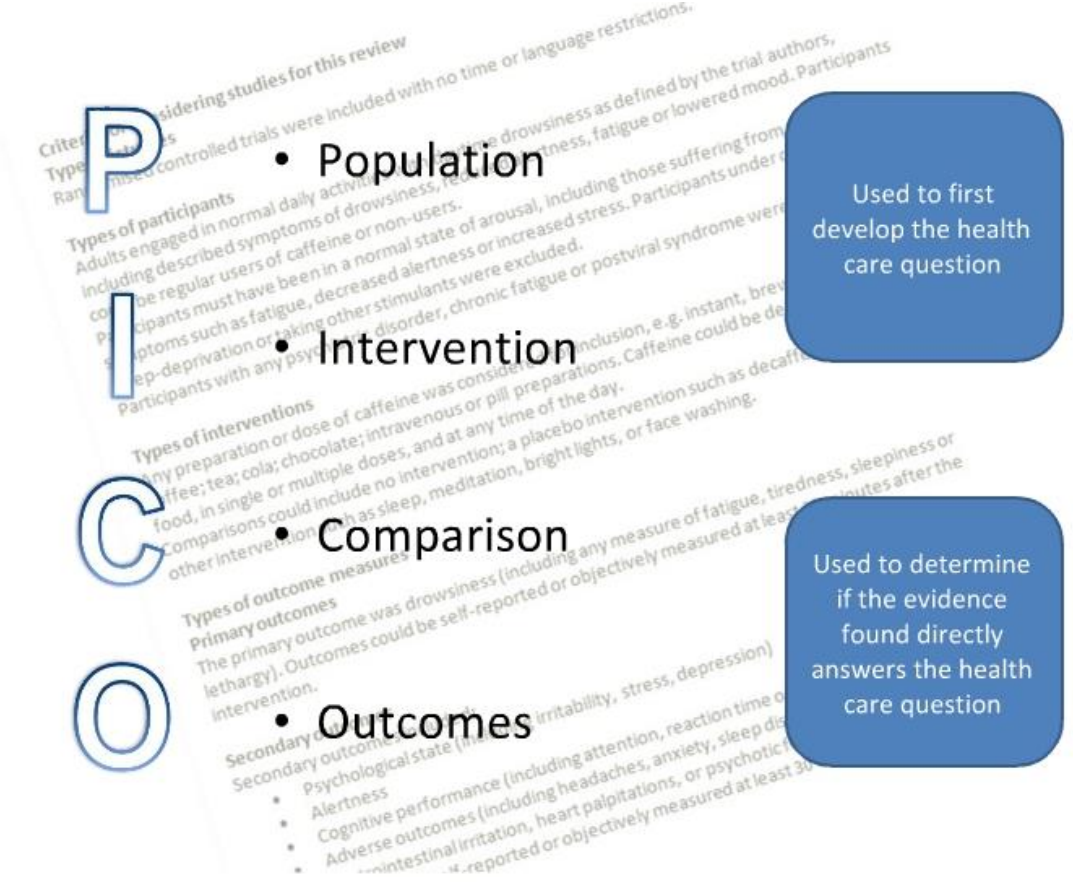


The overall incidence of grade ≥ 3 AEs was higher with vandetanib than erlotinib (50% *v* 40%, respectively)

- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- Rilevanza clinica Vs significatività statistica
- **Trasferibilità delle evidenze al quesito clinico**
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

PREMESSA

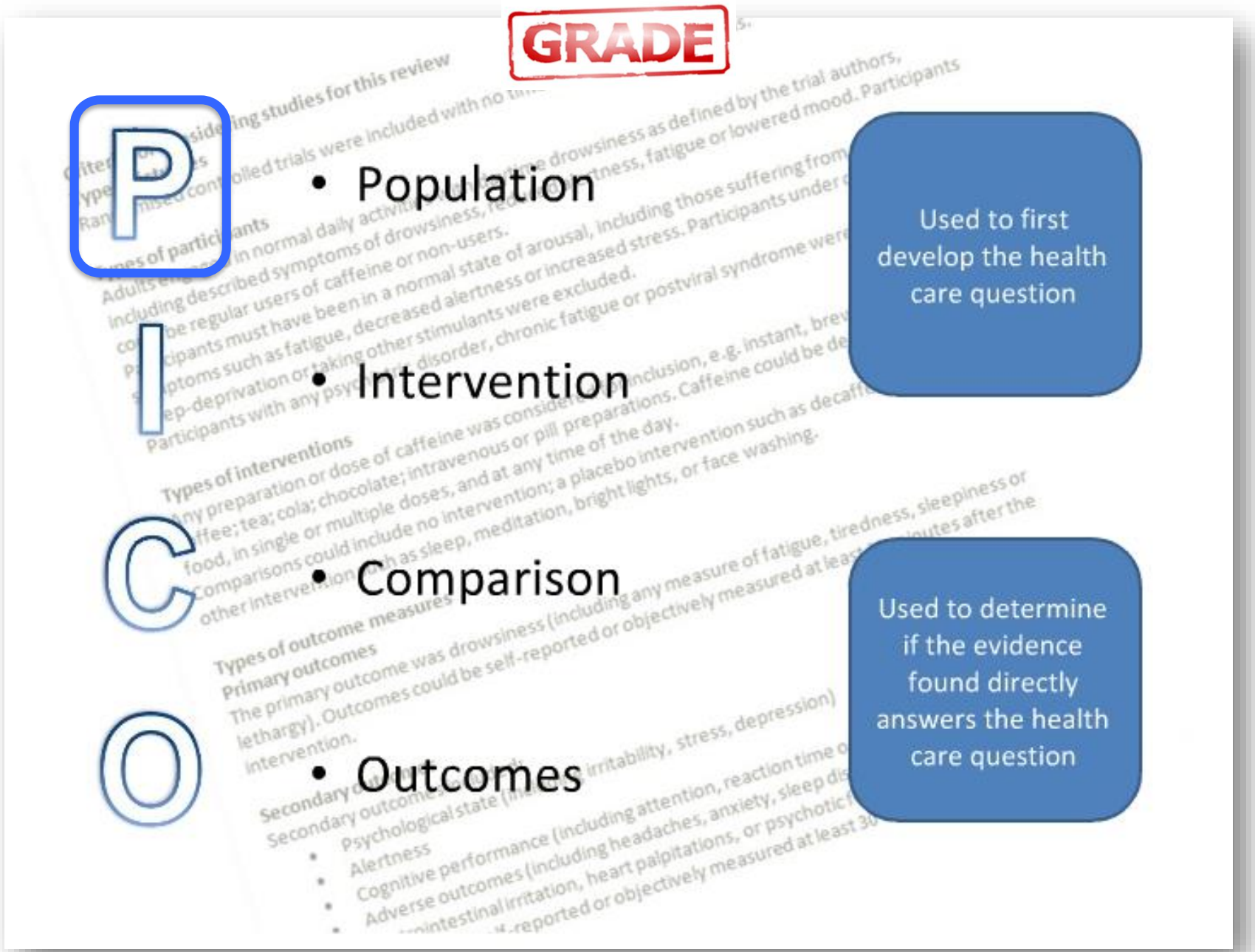
Un trial clinico non dovrebbe essere *letto così com'è*, ma avendo come riferimento uno specifico quesito di particolare interesse.



Direct evidence…

…comes from research that:

- is conducted in the **Population** that we are providing answers for;
- includes the **Intervention** that we are interested in…
- …and compares these interventions with the appropriate **Alternatives**;
- measures the **Outcomes** in which we are interested

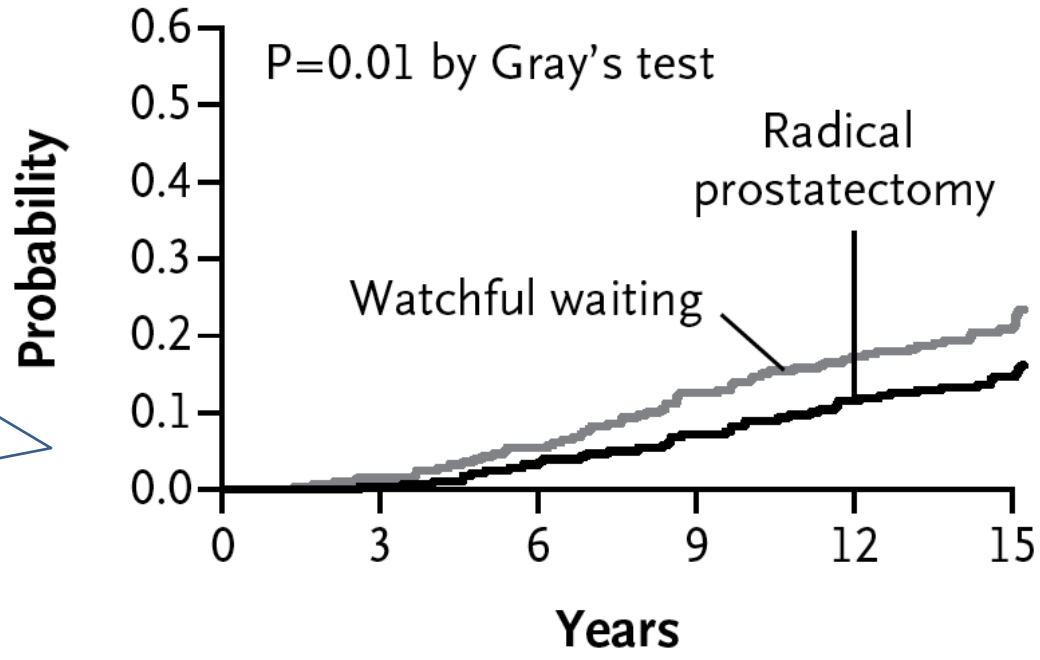

GRADE
P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

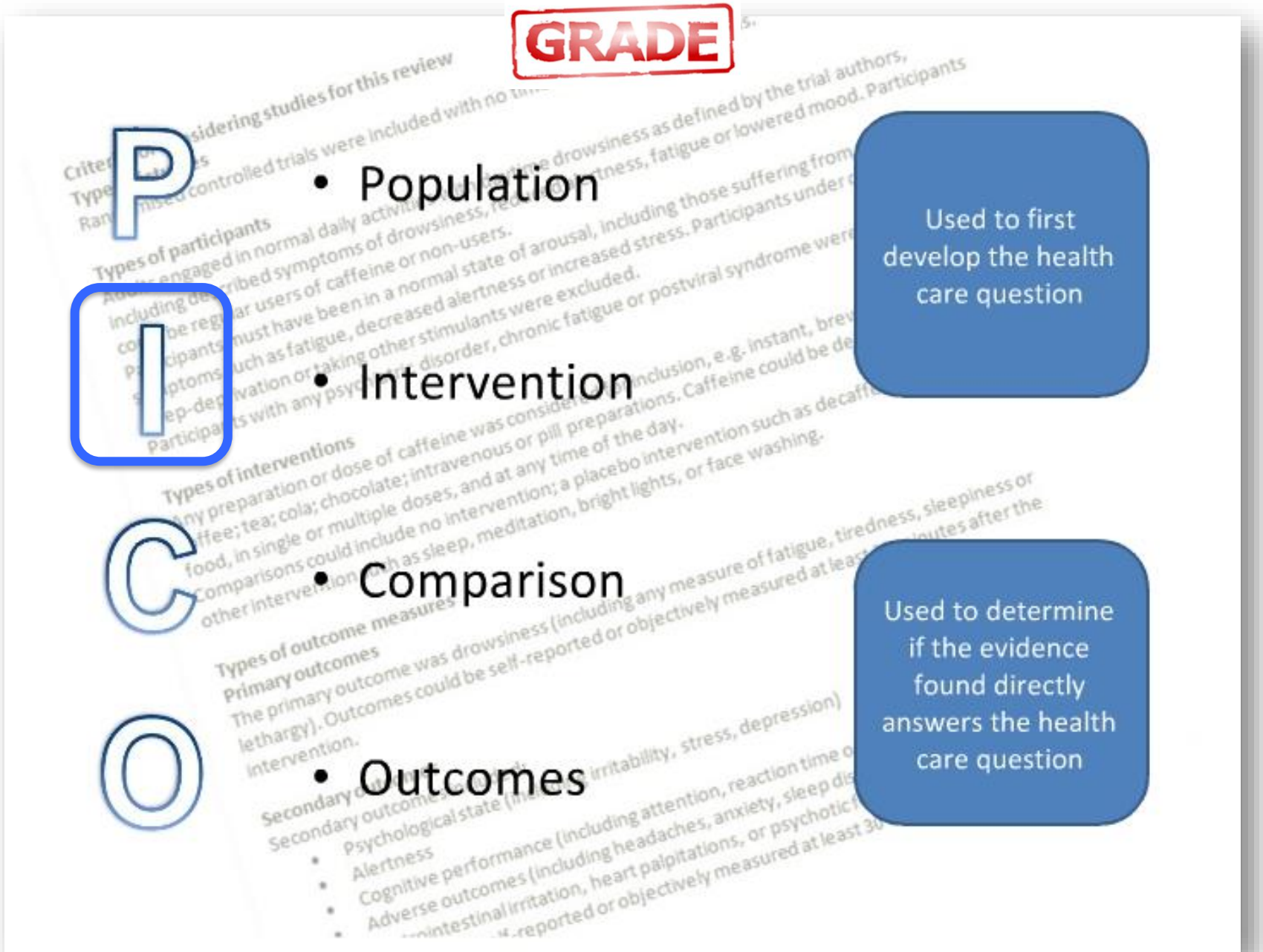
Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D., Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D., Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D., Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D., Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D., Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., for the SPCG-4 Investigators*

N Engl J Med 2011;364:1708-17.

Pazienti in era pre-PSA




GRADE
P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

Long-term oncologic outcomes of postoperative adjuvant versus salvage radiotherapy in prostate cancer: Systemic review and meta-analysis of 5-year and 10-year follow-up data

Ja Yoon Ku[1], Chan Ho Lee[1], Hong Koo Ha[1,2]

Korean J Urol 2015;56:735-741.

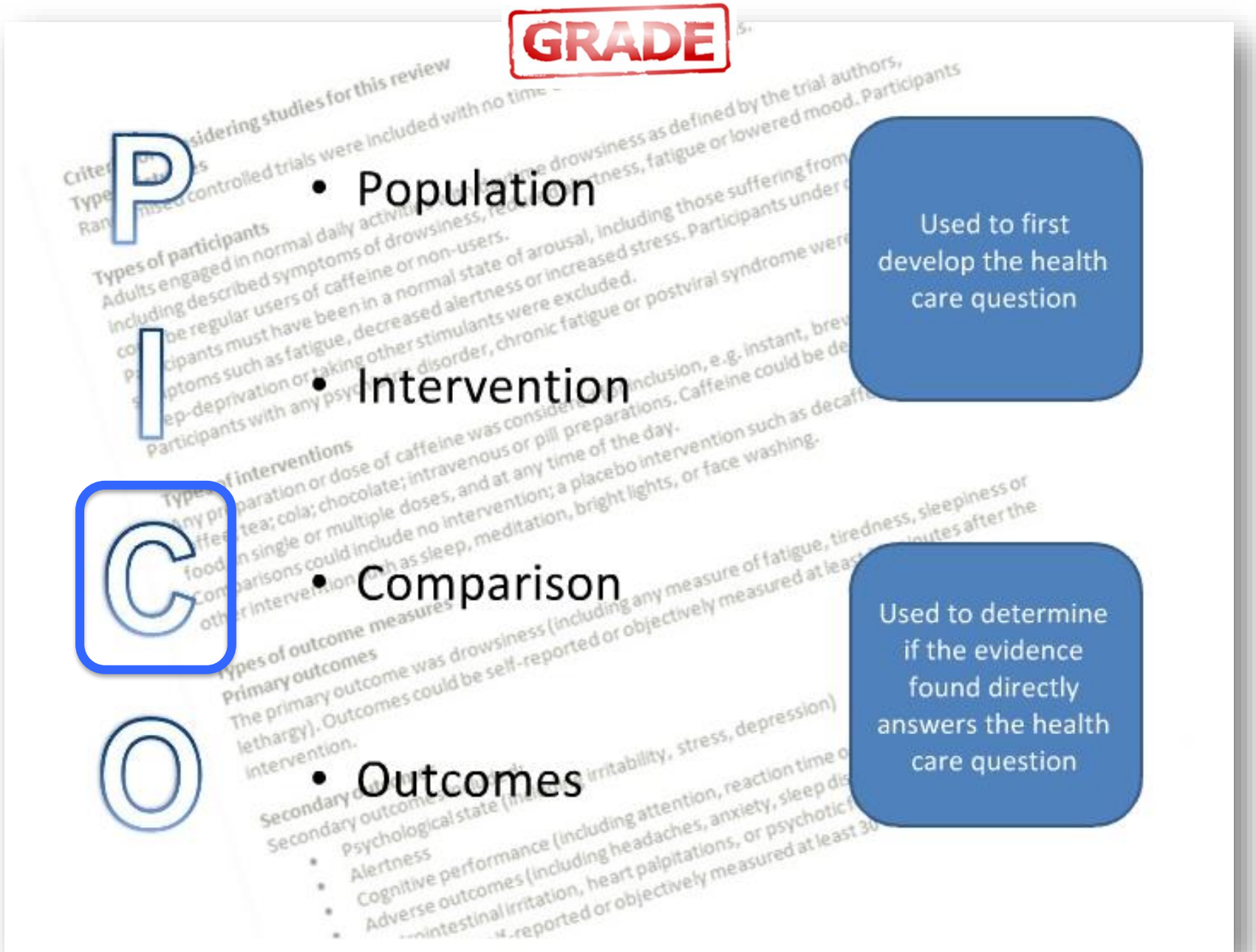
The present systemic review has the following limitations that must be taken into account.

The first limitation is that we heterogeneously recruit randomized controlled studies and retrospective studies: in retrospective studies, the initiation timing of radiotherapy is somewhat different in each study.

The second limitation is that there is a difference in dose and modality (2-dimensional, 3-dimensional, or intensity modulated radiation therapy) of radiation compared to recent practice, which may alter oncologic outcomes.

The third limitation [illegible] were different in eac[illegible] of long-term outcome be[illegible]

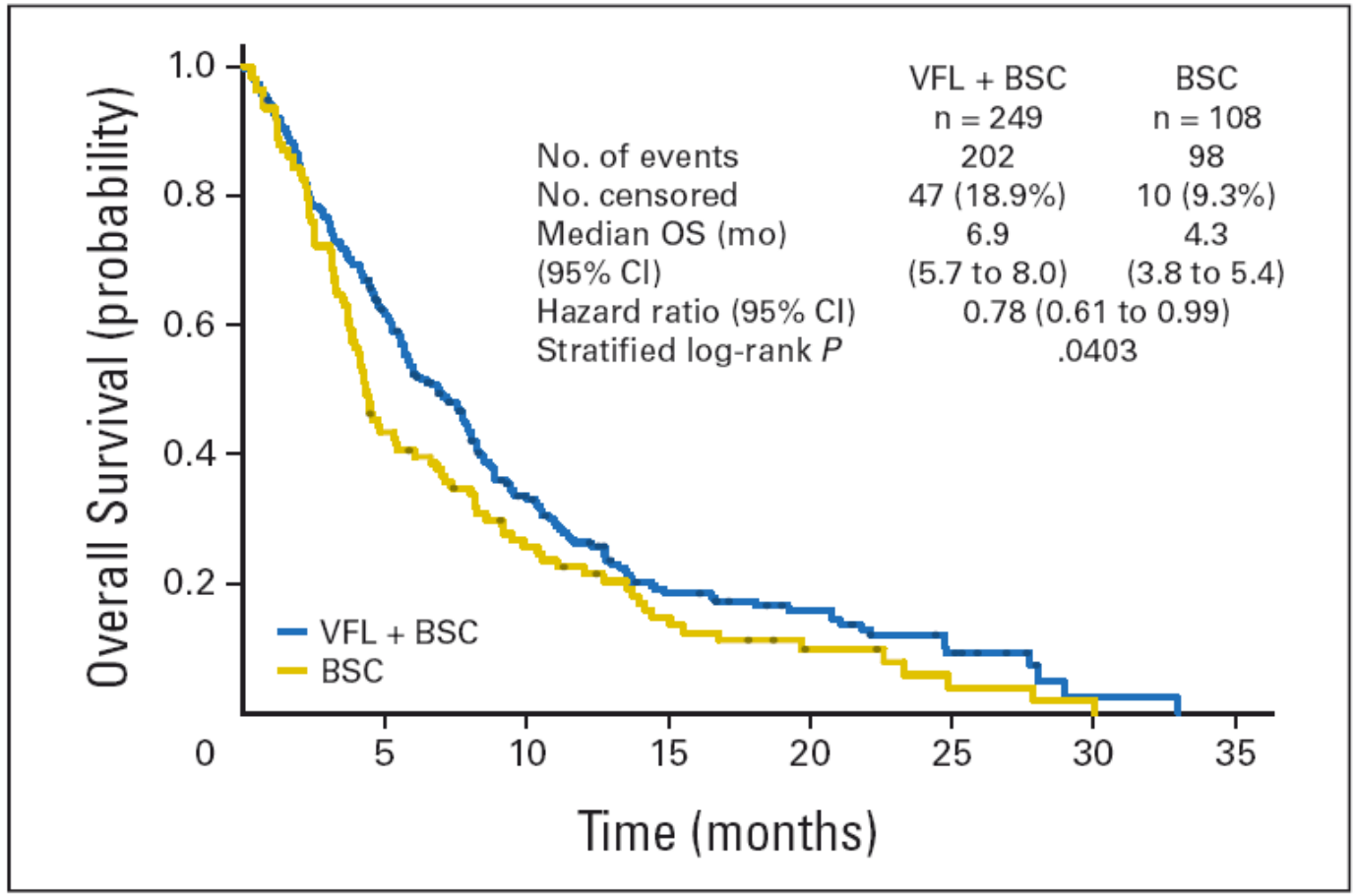
Indirectness per I. (di P.I.C.O.)


GRADE
P
I
C
O
• Population
• Intervention
• Comparison
• Outcomes
Used to first develop the health care question
Used to determine if the evidence found directly answers the health care question

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

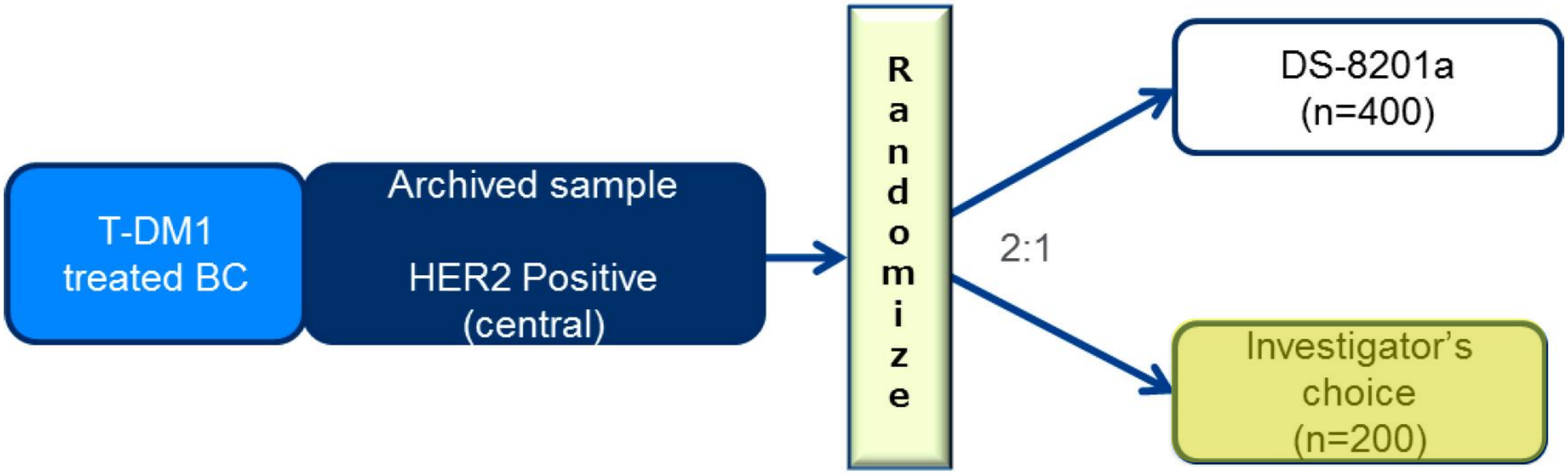
Joaquim Bellmunt, Christine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Armelle Caty, Joan Carles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, Patrick Hurteloup, Eric Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

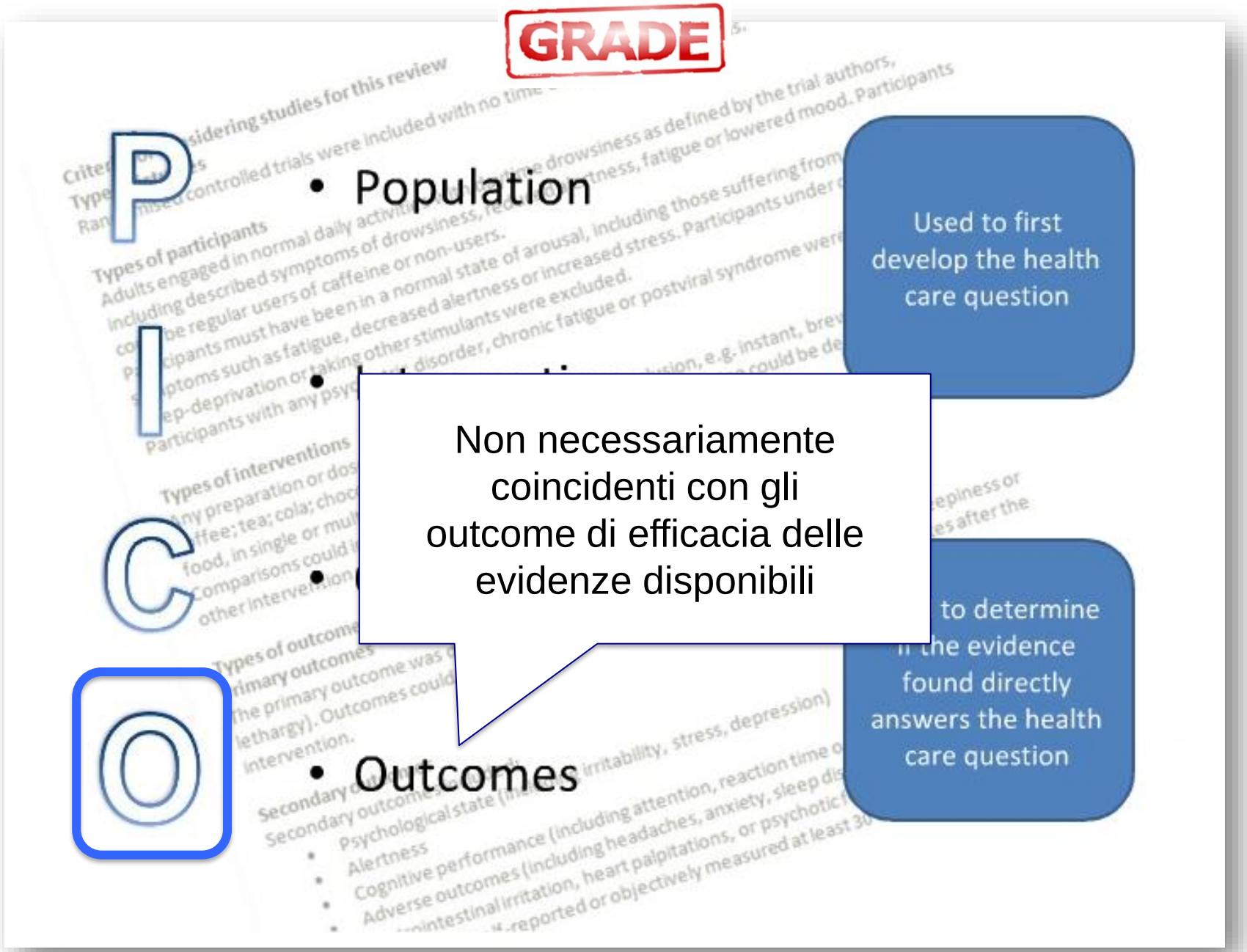
J Clin Oncol 27:4454-4461. © 2009 by American Society of Clinical Oncology



A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, ACTIVE-CONTROLLED STUDY OF DS-8201A, AN ANTI-HER2-ANTIBODY DRUG CONJUGATE, VERSUS TREATMENT OF INVESTIGATOR'S CHOICE FOR HER2-POSITIVE, UNRESECTABLE AND/OR METASTATIC BREAST CANCER SUBJECTS PRETREATED WITH PRIOR STANDARD OF CARE HER2 THERAPIES, INCLUDING T-DM1

DS8201-A-U301




GRADE
P
I
C
O
• Population
• Outcomes
Used to first develop the health care question
Non necessariamente coincidenti con gli outcome di efficacia delle evidenze disponibili
to determine if the evidence found directly answers the health care question

Surrogate outcome markers in research and clinical practice

Scott Twaddell

(Aust Prescr 2009;32:47–50)

Table 1

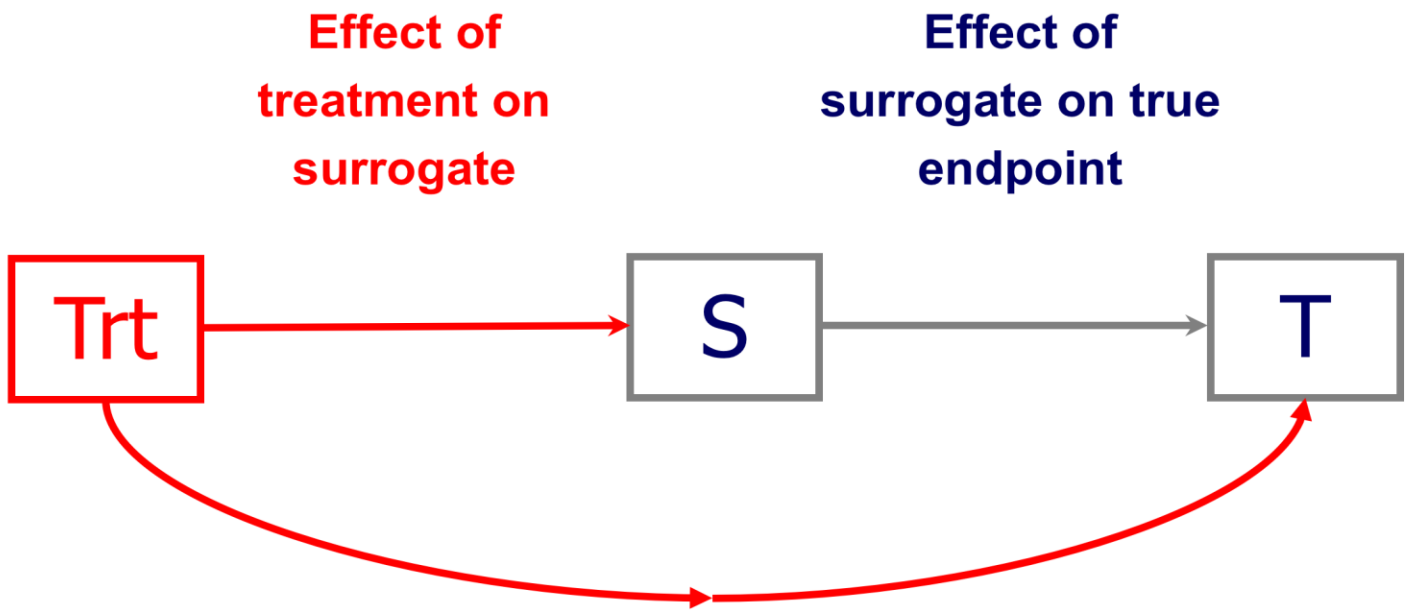
Surrogate markers often used in clinical practice

Generally accepted as valid		Doubt still exists about validity	
Surrogate marker	**Predicts**	**Surrogate marker**	**Predicts**
HbA1c	Diabetic microvascular complications	HbA1c	Diabetic macrovascular complications
FEV_1	Mortality in chronic obstructive pulmonary disease	Bone mineral density	Fracture risk
Blood pressure	Primary and secondary cardiovascular events	Prostate specific antigen	Prognosis of prostate cancer
Viral load	Survival in HIV infection	Suppression of arrhythmia	Long-term survival
Cholesterol concentration	Primary and secondary cardiovascular events	Carotid intima-media thickness	Coronary artery disease
Intraocular pressure	Visual loss in glaucoma	Albuminuria	Cardiovascular events

HbA1c glycated haemoglobin

FEV_1 forced expiratory volume in one second

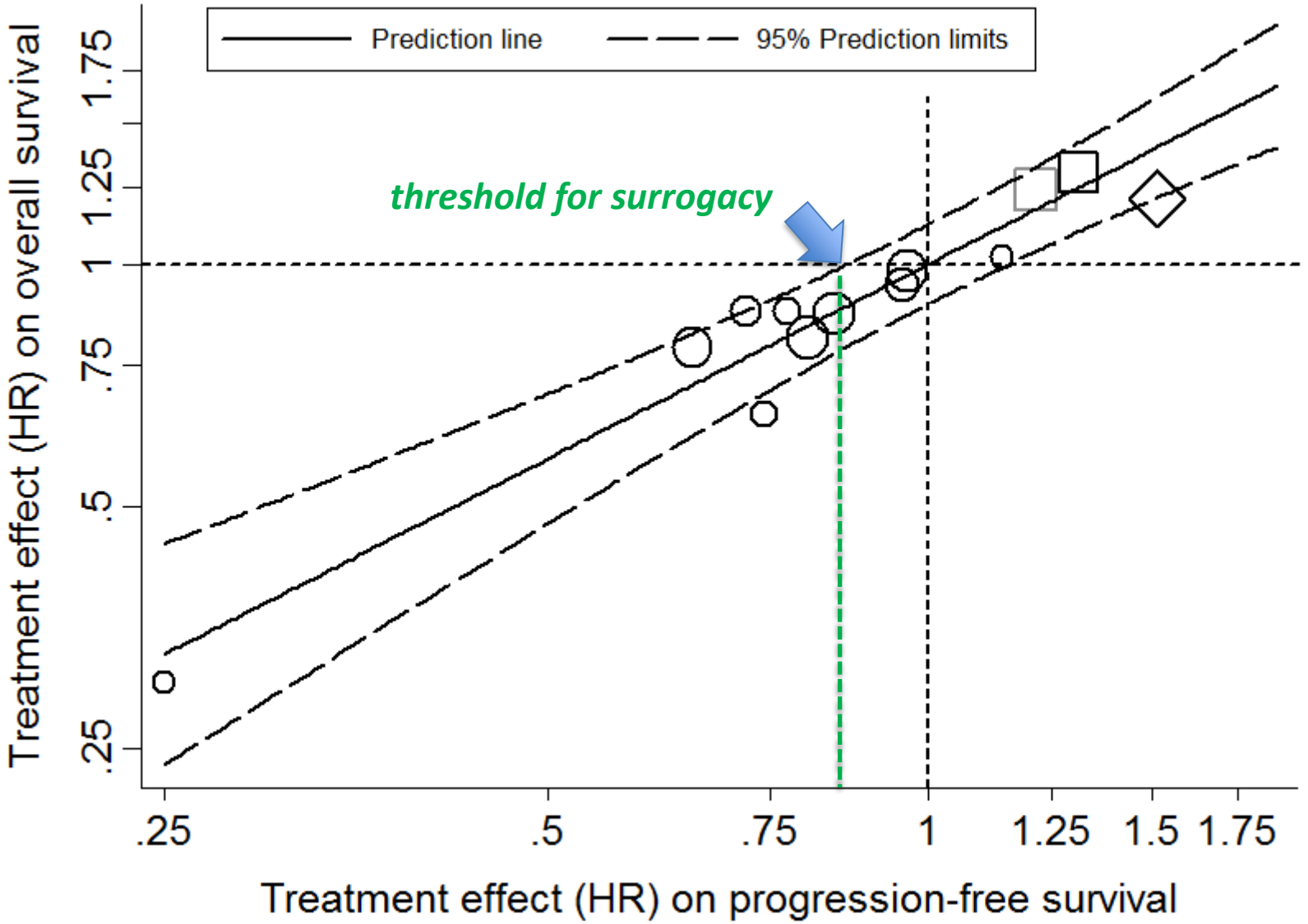
VALIDATION OF SURROGATE ENDPOINTS: "FULL CAPTURE OF EFFECT"



Effect of treatment on true endpoint must be fully captured by surrogate

*Prentice, Statist Med 1989;**8**:431.*

TRIAL LEVEL CORRELATION BETWEEN EFFECTS

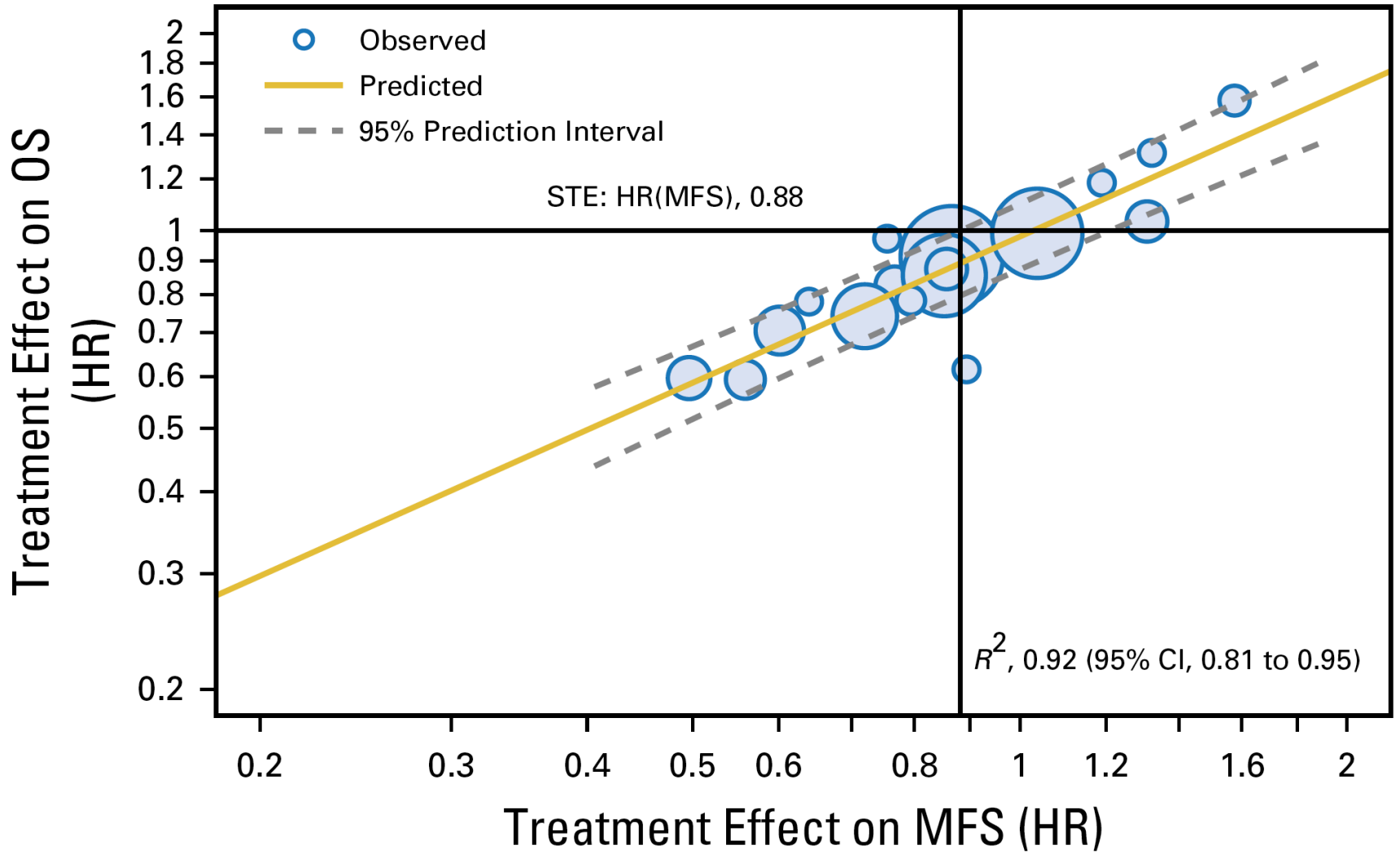


Burzykowski and Buyse, Pharmaceutical Statist 2006;5:173

Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

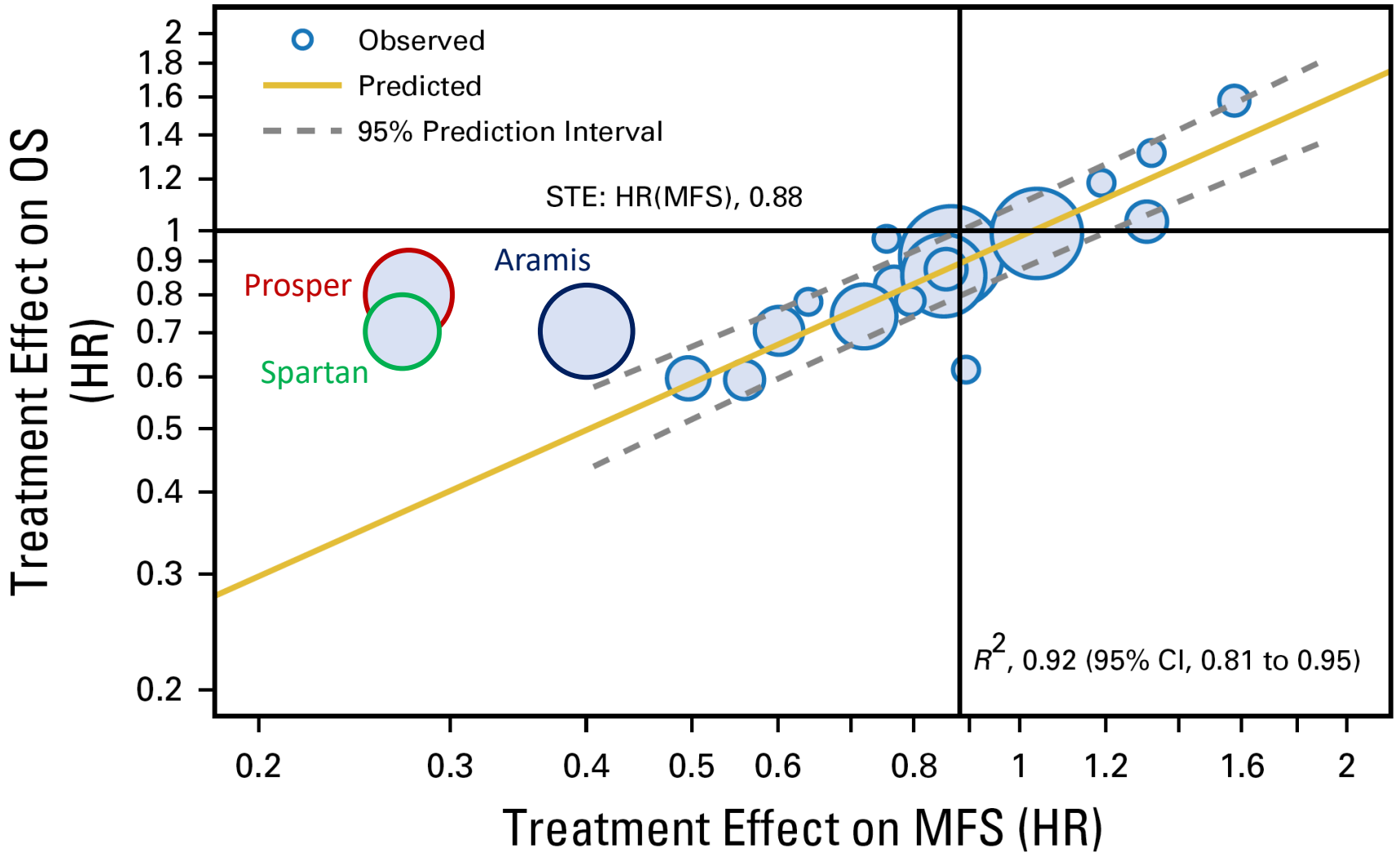
J Clin Oncol 35:3097-3104.



Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer

Wanling Xie, Meredith M. Regan, Marc Buyse, Susan Halabi, Philip W. Kantoff, Oliver Sartor, Howard Soule, Noel W. Clarke, Laurence Collette, James J. Dignam, Karim Fizazi, Wendy R. Paruleker, Howard M. Sandler, Matthew R. Sydes, Bertrand Tombal, Scott G. Williams, and Christopher J. Sweeney, on behalf of the ICECaP Working Group

J Clin Oncol 35:3097-3104. © 2017 by American Society of Clinical Oncology



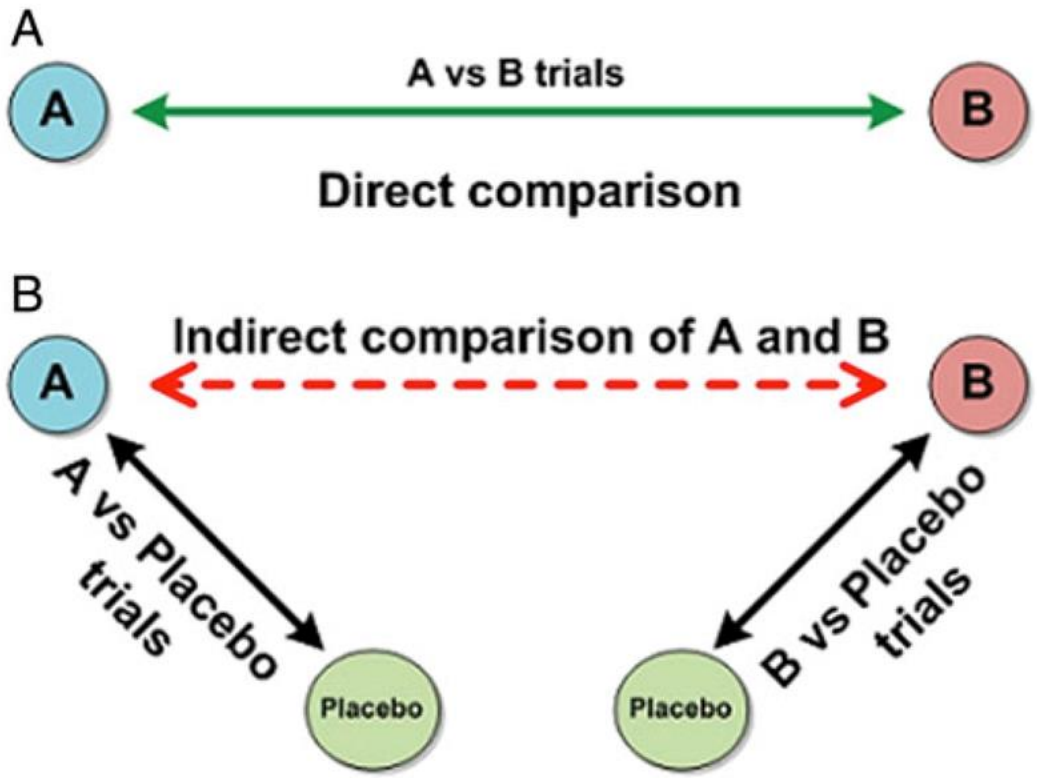
Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

HTA

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.



through a

Common Comparator

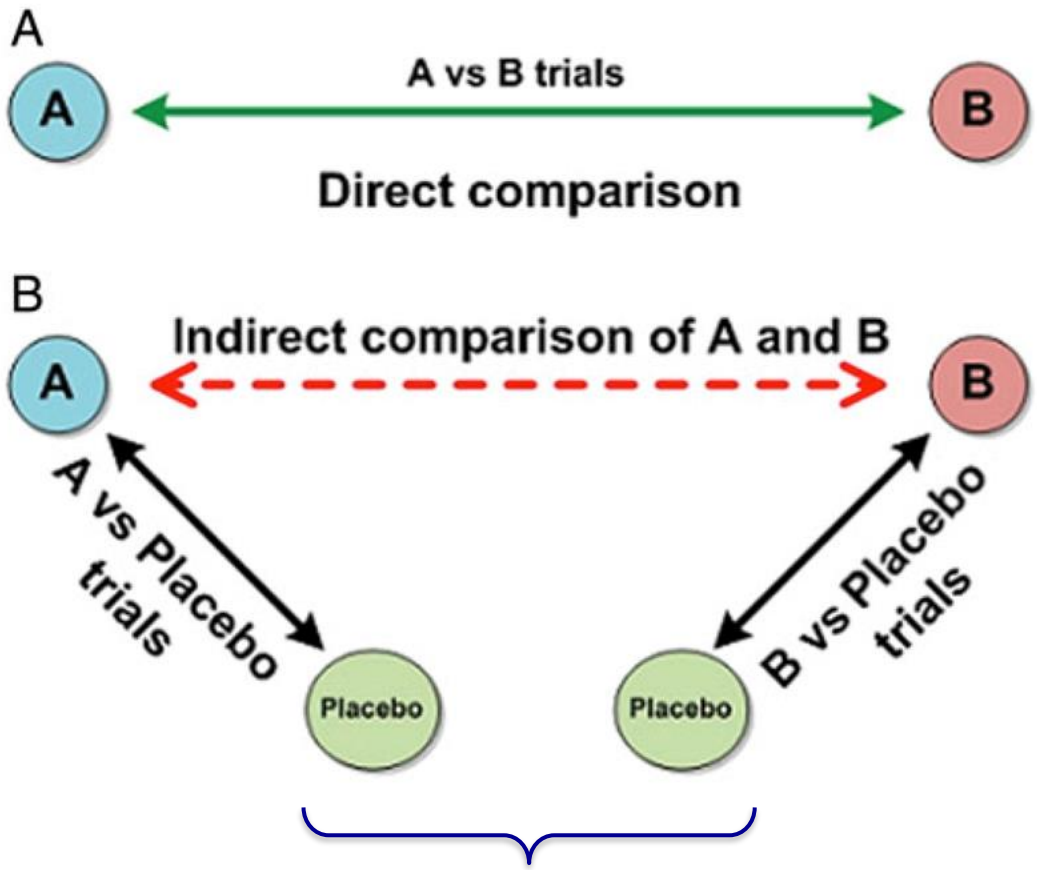
Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

HTA

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.



Similarity Assumption

trials must be comparable on effect modifiers to obtain an unbiased pooled estimate.

Indirect comparisons of competing interventions

AM Glenny,[1*] DG Altman,[2] F Song,[3] C Sakarovitch,[2] JJ Deeks,[2] R D'Amico,[2] M Bradburn[2] and AJ Eastwood[4]

Health Technology Assessment 2005; Vol. 9: No. 26

HTA

When conducting systematic reviews to evaluate the effectiveness of interventions, direct evidence from good-quality RCTs should be used wherever possible. If little or no such evidence exists, it may be necessary to look for indirect comparisons from RCTs. The reviewer needs, however, to be aware that the results may be susceptible to bias.

- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensionamento campionario)
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- **Affidabilità delle prove (imprecisione degli effetti, rischio di bias)**
- Dialogo tra clinico e metodologo (lettura di uno studio clinico)

Caso Vs Bias

CASO

Errore Random

Risultati Imprecisi

Errore in diminuzione con l'aumentare delle dimensioni del campione

BIAS

Errore Sistematico

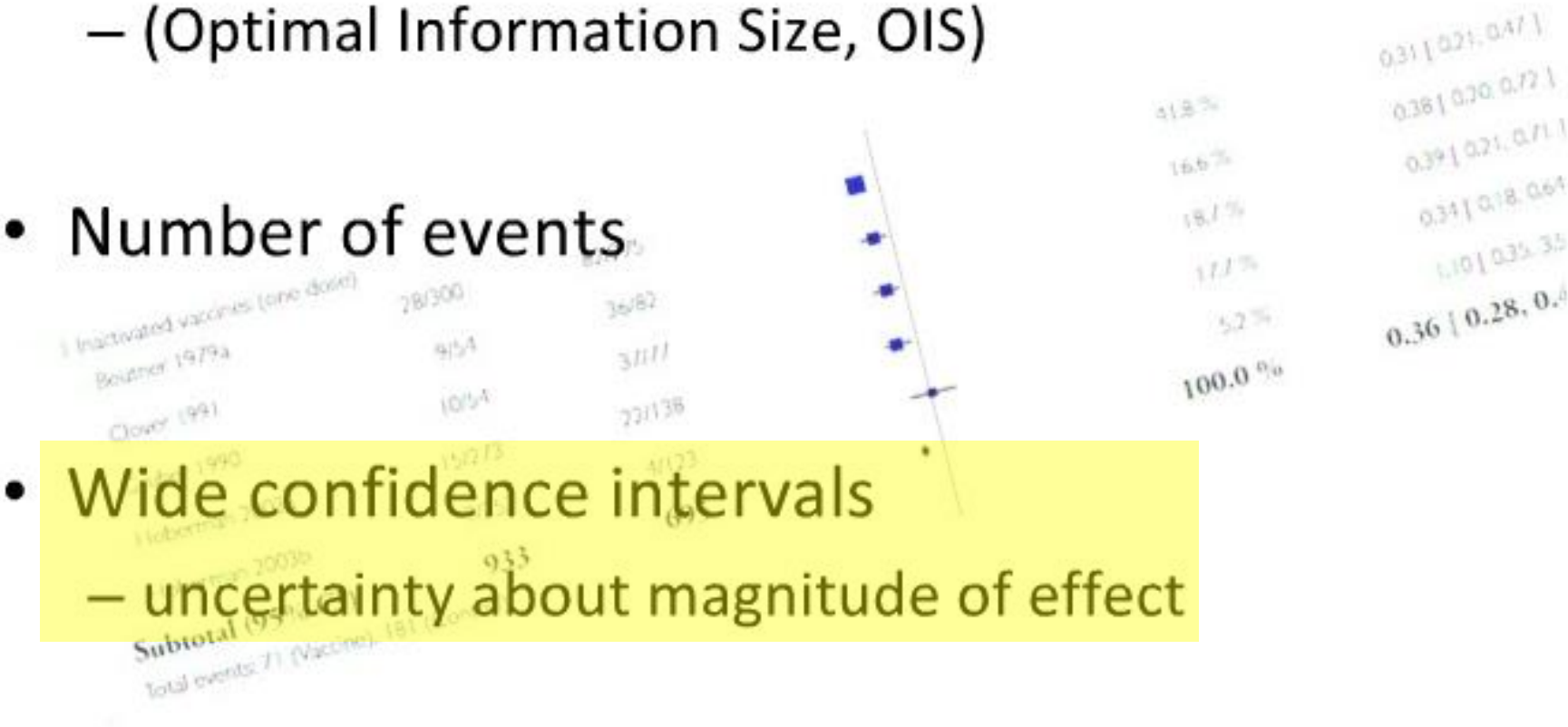
Risultati Inesatti

Errore non influenzato dalle dimensioni del campione

When are results precise enough?

Consider

- Small sample size
  - (Optimal Information Size, OIS)
- Number of events
- Wide confidence intervals
  - uncertainty about magnitude of effect



Journal of Clinical Epidemiology 64 (2011) 1283–1293

GRADE guidelines 6. Rating the quality of evidence—imprecision

Gordon H. Guyatt[a,b,*], Andrew D. Oxman[c], Regina Kunz[d,e], Jan Brozek[a], Pablo Alonso-Coello[f], David Rind[g], PJ Devereaux[a], Victor M. Montori[h], Bo Freyschuss[i], Gunn Vist[c], Roman Jaeschke[b], John W. Williams Jr.[j], Mohammad Hassan Murad[h], David Sinclair[k], Yngve Falck-Ytter[l], Joerg Meerpohl[m,n], Craig Whittington[o], Kristian Thorlund[a], Jeff Andrews[p], Holger J. Schünemann[a,b]

Key Points

- GRADE's primary criterion for judging precision is to focus on the 95% confidence interval (CI) around the difference in effect between intervention and control for each outcome.

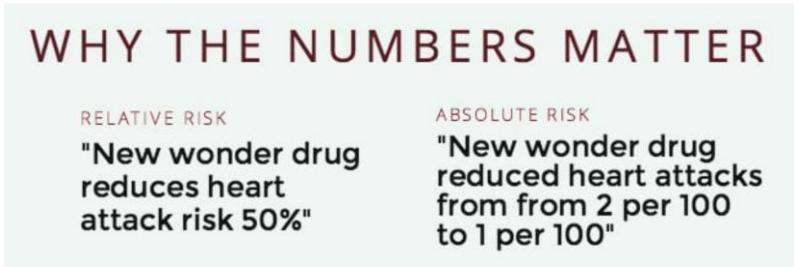
Journal of Clinical Epidemiology 64 (2011) 1283–1293

GRADE guidelines 6. Rating the quality of evidence—imprecision

Gordon H. Guyatt[a,b,*], Andrew D. Oxman[c], Regina Kunz[d,e], Jan Brozek[a], Pablo Alonso-Coello[f], David Rind[g], PJ Devereaux[a], Victor M. Montori[h], Bo Freyschuss[i], Gunn Vist[c], Roman Jaeschke[b], John W. Williams Jr.[j], Mohammad Hassan Murad[h], David Sinclair[k], Yngve Falck-Ytter[l], Joerg Meerpohl[m,n], Craig Whittington[o], Kristian Thorlund[a], Jeff Andrews[p], Holger J. Schünemann[a,b]

Key Points

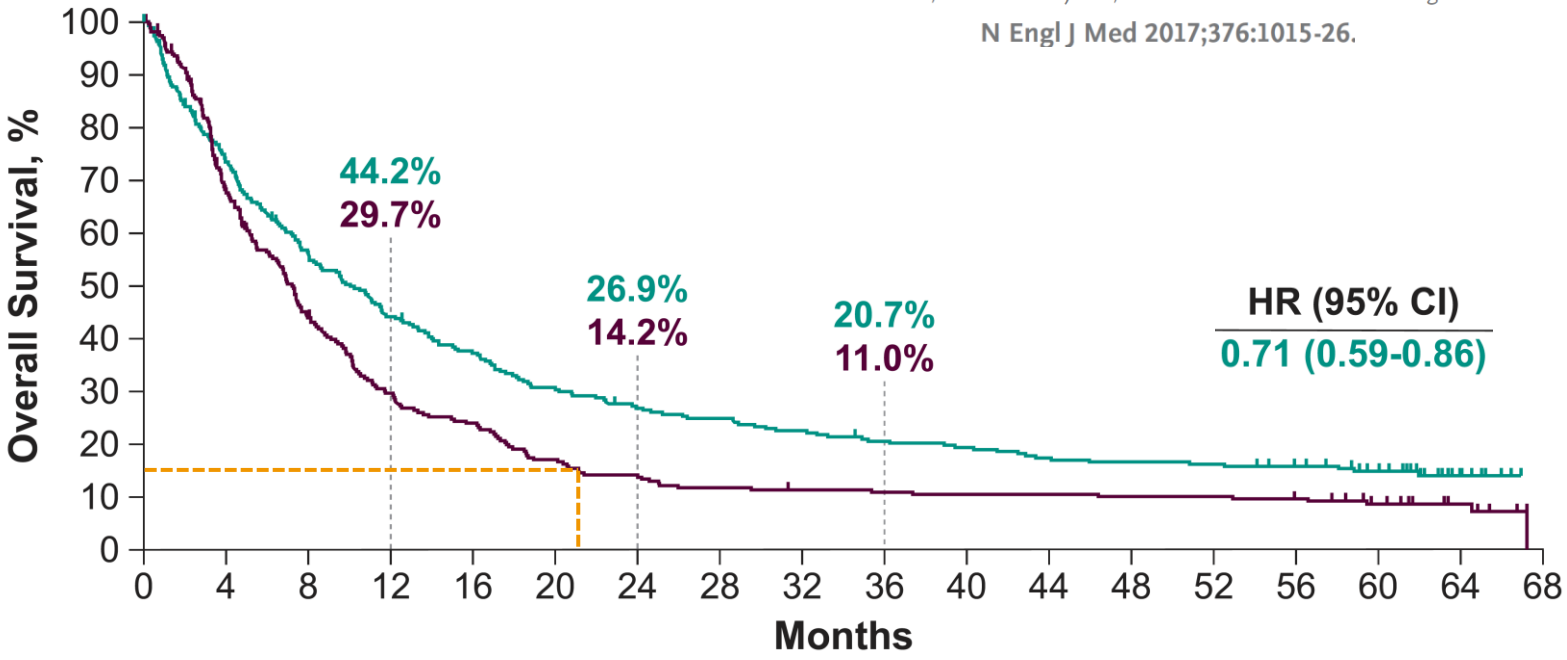
- GRADE's primary criterion for judging precision is to focus on the 95% confidence interval (CI) around the difference in effect between intervention and control for each outcome.
- In general, the CIs to consider are those around the absolute, rather than the relative effect.



Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

N Engl J Med 2017;376:1015-26.



LC95% consistenti con una rilevante efficacia (↓18 eventi decesso / 100 paz.) e con un beneficio marginale (↓5 eventi decesso / 100 paz.)

NON seria imprecisione

- Median f.u.: 21.1 months
- Basal risk* at median f.u.: 85%
- **Risk Difference**: 11 events lower / 100 pts (**95%CI: 18 lower to 5 lower**)
- NNT = 9

** J Clin Epidemiol 118 (2020) 124-131*

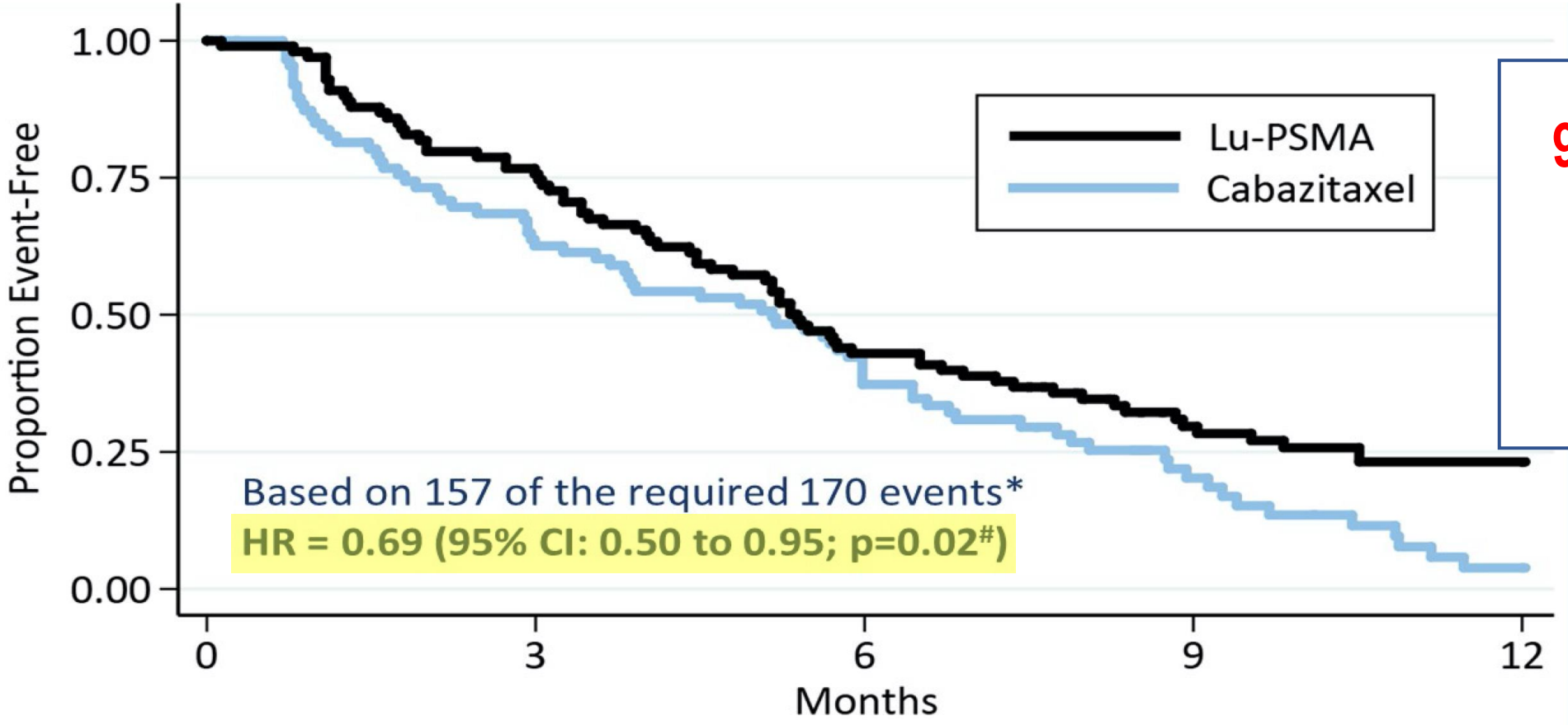
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 #TheraP

A randomised phase II trial of ^{177}Lu-PSMA-617 (Lu-PSMA) theranostic versus cabazitaxel in metastatic castration resistant prostate cancer (mCRPC) progressing after docetaxel: Initial results

TheraP (ANZUP 1603)

Michael Hofman, Louise Emmett, Shahneen Sandhu, Amir Iravani, Anthony Joshua, Jeffrey Goh, David Pattison, Hsiang Tan, Ian Kirkwood, Siobhan Ng, Roslyn Francis, Craig Gedye, Natalie Rutherford, Alison Zhang, Margaret McJannett, Martin Stockler, John Violet, Scott Williams, Andrew Martin, Ian Davis

- median follow-up: 13.3 months
- baseline risk: 95.1%
- absolute risk: 8 events fewer (95%CI: 1 fewer to 17 fewer)



95%CI of absolute effect consistent with opposite interpretations

NON Imprecisione Clinica anche in presenza di valore di P ≥0.05

M.I.D. EORTC QLQ-C30 GHS: **10 punti**

Scale	Cabazitaxel	Lu-PSMA	Diff.
	Pred. Mean (SE) {95% CI}	Pred. Mean (SE) {95% CI}	Pred. Mean (SE) {95% CI} [p-value]
Global health status / QoL	60.4 (1.8) {56.9 to 63.9}	63.4 (1.6) {60.3 to 66.5}	3.0 (2.3) {-1.6 to 7.5} [0.202]

IC95% dell'effetto assoluto compreso nel *range* di non rilevanza clinica (<10 punti)

NON Imprecisione

Lancet 2021; 397: 797–804

Caso Vs Bias

CASO

↓

Errore Random

↓

Risultati Imprecisi

Errore in diminuzione con l'aumentare delle dimensioni del campione

BIAS

↓

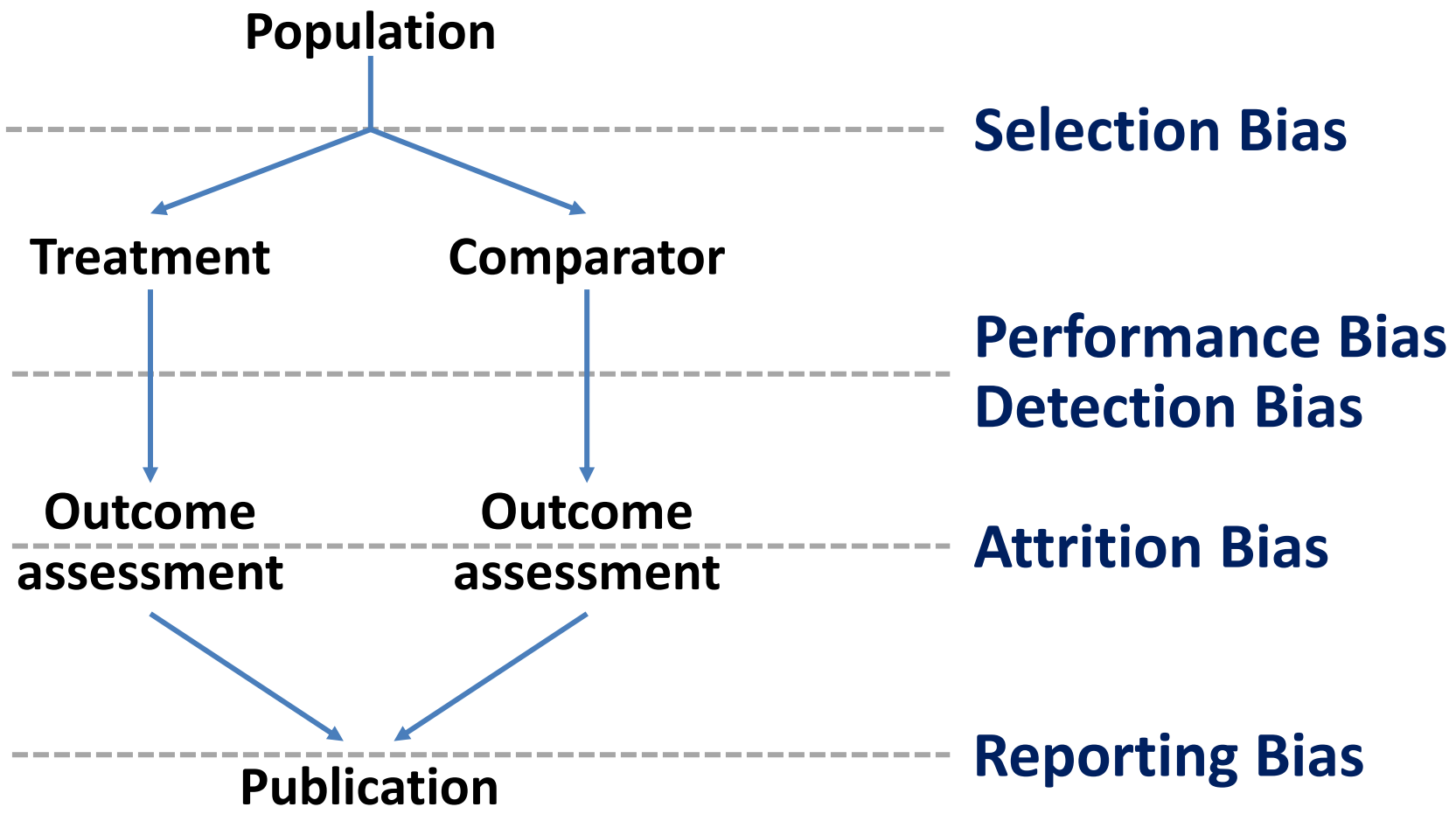
Errore Sistematico

↓

Risultati Inesatti

Errore non influenzato dalle dimensioni del campione

Study Flow & Risk of Bias…



SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

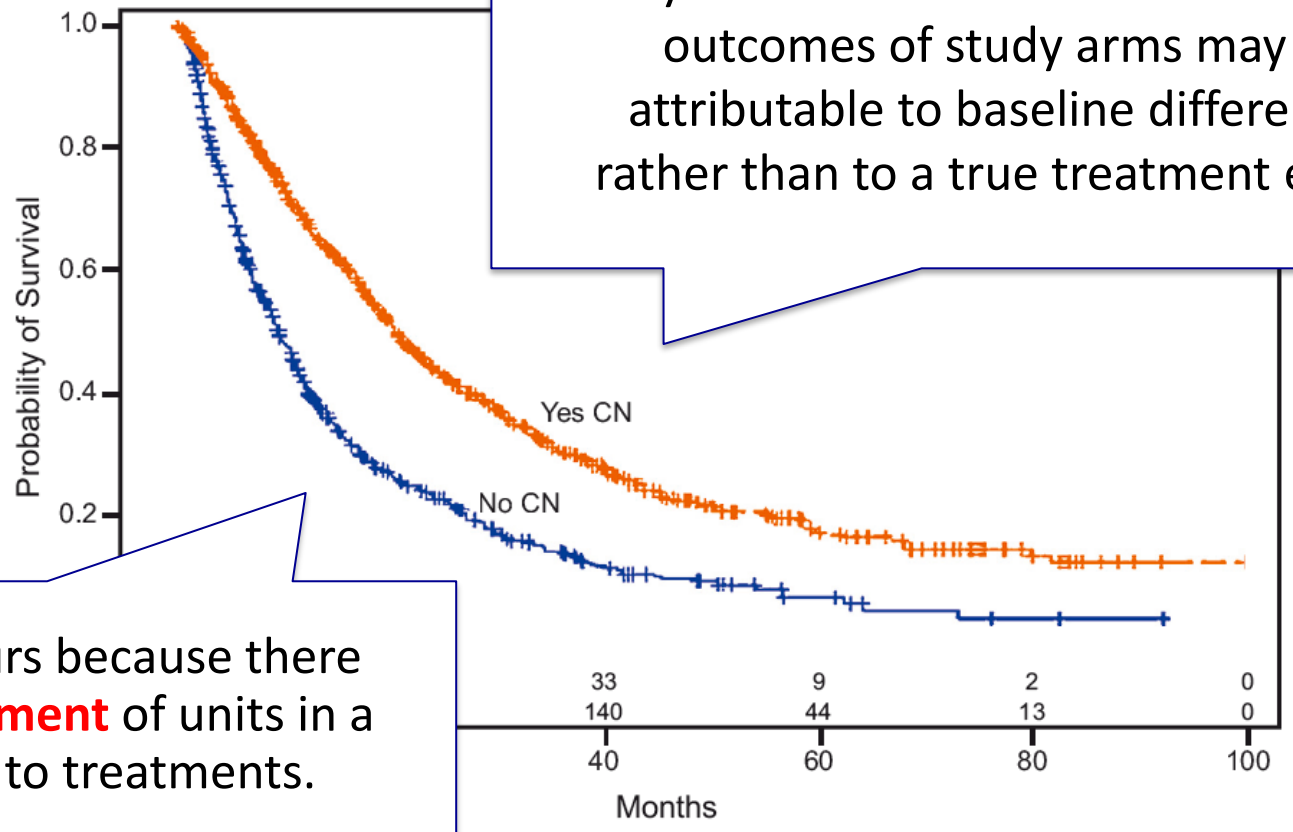
Version 5.1.0

Cytoreductive Nephrectomy in Patients with Synchronous Metastases from Renal Cell Carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium

Daniel Y.C. Heng[a,,†], J. Connor Wells[a,†], Brian I. Rini[b], Benoit Beuselinck[c], Jae-Lyun Lee[d], Jennifer J. Knox[e], Georg A. Bjarnason[f], Sumanta Kumar Pal[g], Christian K. Kollmannsberger[h], Takeshi Yuasa[i], Sandy Srinivas[j], Frede Donskov[k], Aristotelis Bamias[l], Lori A. Wood[m], D. Scott Ernst[n], Neeraj Agarwal[o], Ulka N. Vaishampayan[p], Sun Young Rha[q], Jenny J. Kim[r], Toni K. Choueiri[s]*

EUROPEAN UROLOGY 66 (2014) 7

Any observed difference between the outcomes of study arms may be attributable to baseline differences rather than to a true treatment effect.



A possible **bias** occurs because there is **no random assignment** of units in a target population to treatments.

Reconciling the Use of Cytoreductive Nephrectomy in the Targeted Therapy Era

Stephen H. Culp *

EUROPEAN UROLOGY 66 (2014) 711–712

Although retrospective, the results of this study are strengthened by the number of patients examined, inclusion of patients from institutions around the world, and lack of patient exclusion based on RCC histology or type of targeted agent.

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

Joaquim Bellmunt, Christine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Armelle Caty, Joan Carles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, Patrick Hurteloup, Eric Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

J Clin Oncol 27:4454-4461. © 2009

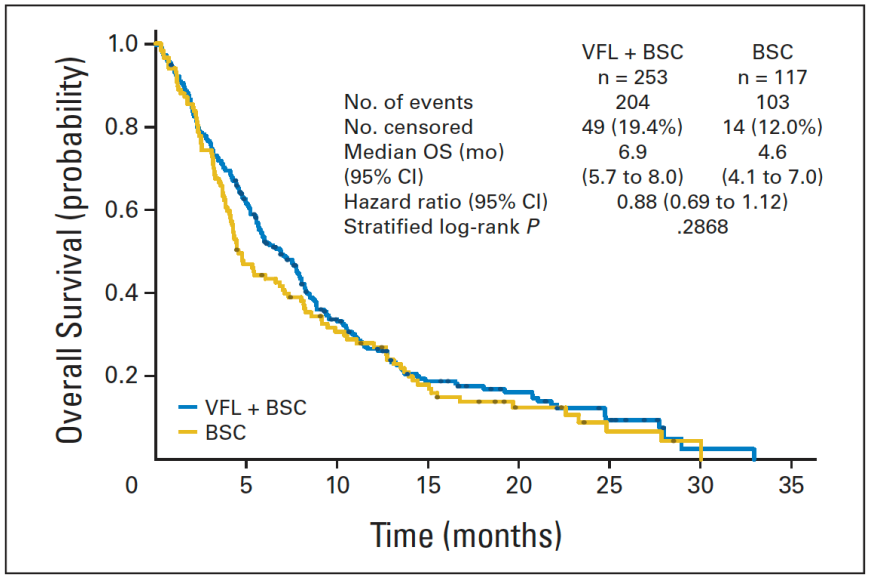


Fig 2. Overall survival (OS) in the intent-to-treat population (n = 370). VFL, vinflunine; BSC, best supportive care.

Although the objective of the median 2-month survival advantage favoring VFL BSC versus BSC was achieved (6.9 v 4.6 months, respectively), this difference was not statistically significant (P .287; Fig 2).

Phase III Trial of Vinflunine Plus Best Supportive Care Compared With Best Supportive Care Alone After a Platinum-Containing Regimen in Patients With Advanced Transitional Cell Carcinoma of the Urothelial Tract

Joaquim Bellmunt, Christine Théodore, Tomasz Demkov, Boris Komyakov, Lisa Sengelov, Gedske Daugaard, Armelle Caty, Joan Carles, Agnieszka Jagiello-Gruszfeld, Oleg Karyakin, François-Michel Delgado, Patrick Hurteloup, Eric Winquist, Nassim Morsli, Yacine Salhi, Stéphane Culine, and Hans von der Maase

J Clin Oncol 27:4454-4461. © 2009

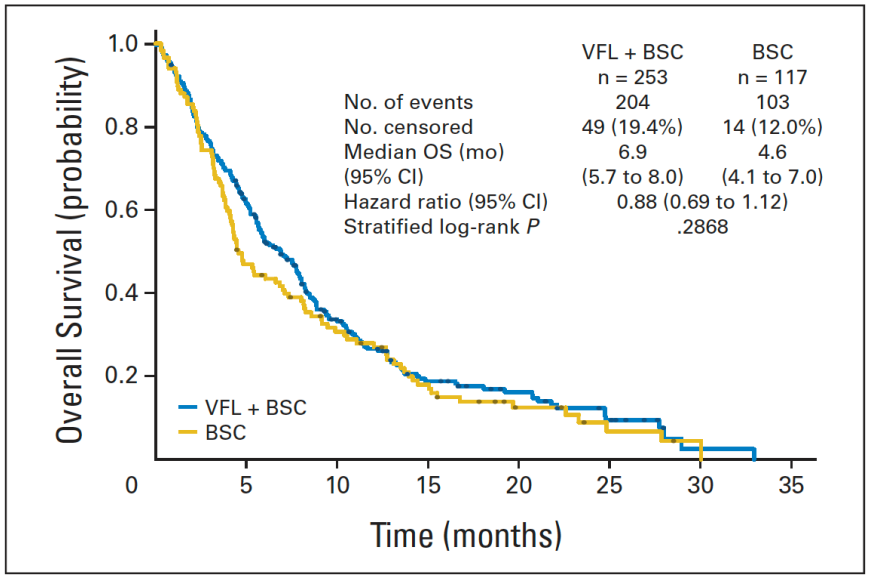


Fig 2. Overall survival (OS) in the intent-to-treat population (n = 370). VFL, vinflunine; BSC, best supportive care.

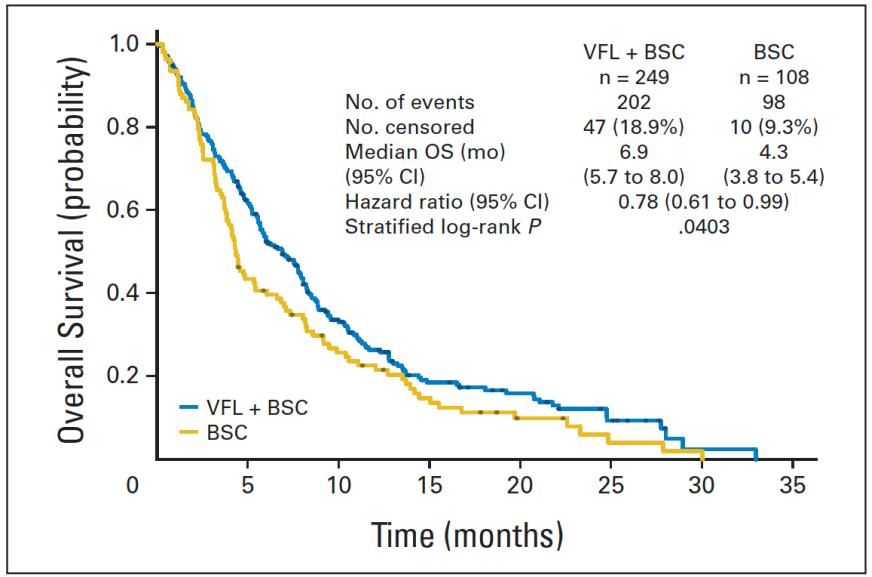


Fig 3. Overall survival (OS) in the eligible population (n = 357; 96.5% of intent-to-treat population). VFL, vinflunine; BSC, best supportive care.

Although the objective of the median 2-month survival advantage favoring VFL BSC versus BSC was achieved (6.9 v 4.6 months, respectively), this difference was not statistically significant (P .287; Fig 2).

In the eligible population (Fig 3), the objective of achieving a 2-month survival difference in OS between the VFLBSC and BSC arms was met (6.9 v 4.3 months, respectively), and this difference is statistically significant (P. 040).

What is Selective Crossover?

- Special case of *non-adherence to a randomized treatment* following the report of *positive trial results*: control group patients selectively cross over to the experimental treatment
- *Disturbs the randomized comparison* in updated analyses performed subsequent to the first results

BIG 1-98 Monotherapy Update

Median Follow-up 76 months

	Hazard Ratio	Events Letrozole N=2463	Events Tamoxifen N=2459	Hazard Ratio (95% CI)	ITT P-value
Disease-free Survival					
Intent-to-treat*		509	565	0.88 (0.78–0.99)	0.03
Censored				0.84 (0.74–0.95)	
Overall Survival					
Intent-to-treat		303	343	0.87 (0.75–1.02)	0.08
Censored				0.81 (0.69–0.94)	
Time to distant recurrence					
Intent-to-treat		257	298	0.85 (0.72–1.00)	0.05
Censored				0.81 (0.68–0.96)	

0.5 0.75 1.0 1.25 1.5

Favors Letrozole Favors Tamoxifen

International Breast Cancer Study Group
IBCSG SABCS 2008

*Let:Tam: breast cancer events, 321:363
second (non breast) malignancy, 101:115
deaths without prior cancer event, 87:87

BIG
BREAST INTERNATIONAL GROUP

SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

If no patient blinding was performed…

… were they **unbiased** when filling the QoL questionnaire?

If no physician blinding was performed…

TREATMENT A

Not at risk of renal impairment

TREATMENT B

Renal impairment as common adverse event

Same frequency of creatinine testing?

SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

If no evaluator blinding was performed…

… was he (totally) **unbiased** when evaluating the scan?

Rischio di bias legato all'assenza di mascheramento

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to documented disease progression (as evaluated by independent central review by radiologists who were unaware of the treatment assignments) or death from any cause. Secondary end points included the objective response rate, overall survival (defined as the time from randomization to death from any cause), safety, and the side-effect profile.

Basso rischio di Detection Bias
(valutazione indipendente in cieco)

Alto rischio di Detection Bias

Alto rischio di Performance & Detection Bias

Basso rischio di Detection Bias
(per caratteristica intrinseca dell'outcome)

Lancet 2021; 397: 797–804

SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

CONSORT

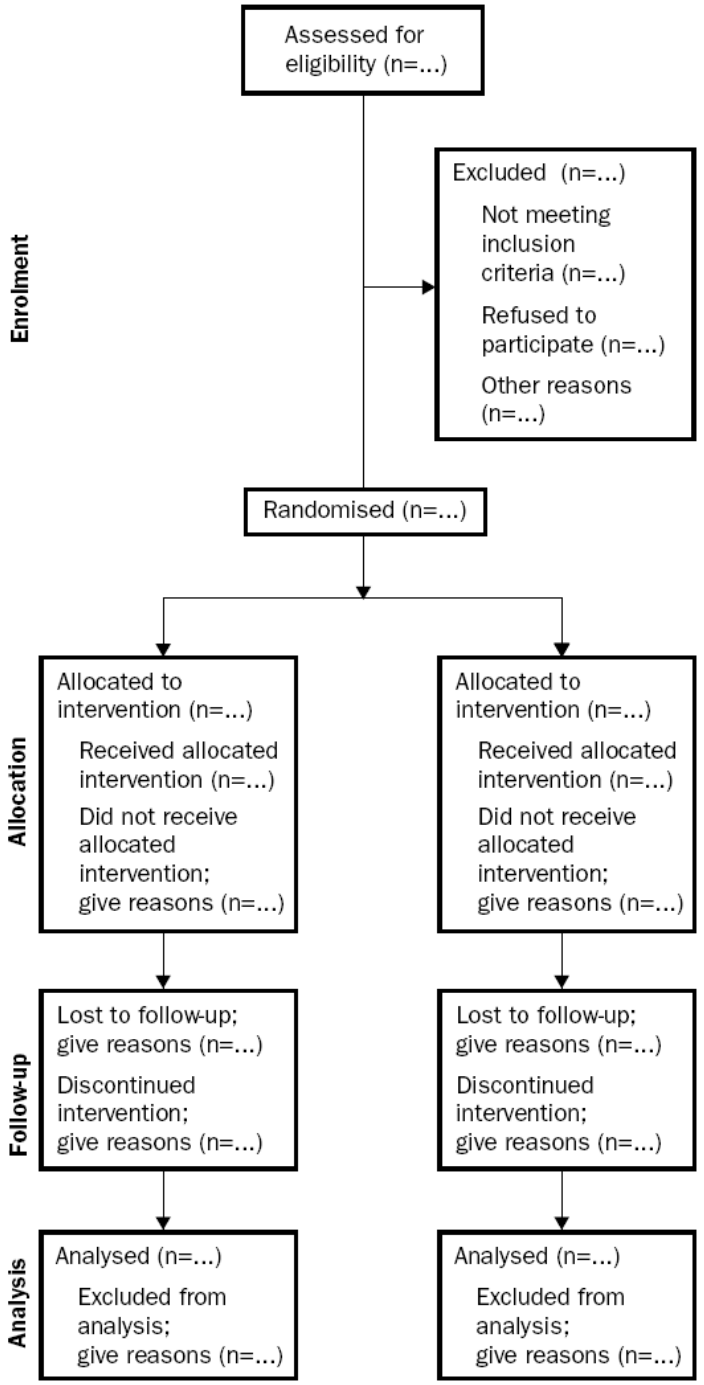
TRANSPARENT REPORTING of TRIALS

The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials

*David Moher, Kenneth F Schulz, Douglas G Altman, for the CONSORT Group**

Lancet 2001; **357:** 1191–94

A ciascuno studio è richiesto di dare conto del flusso di pazienti nelle fasi di arruolamento, assegnazione del trattamento, follow-up e analisi



Can trial quality be reliably assessed from published reports of cancer trials: evaluation of risk of bias assessments in systematic reviews

Claire L Vale *senior research scientist*, Jayne F Tierney *senior research scientist* , Sarah Burdett *senior research scientist*

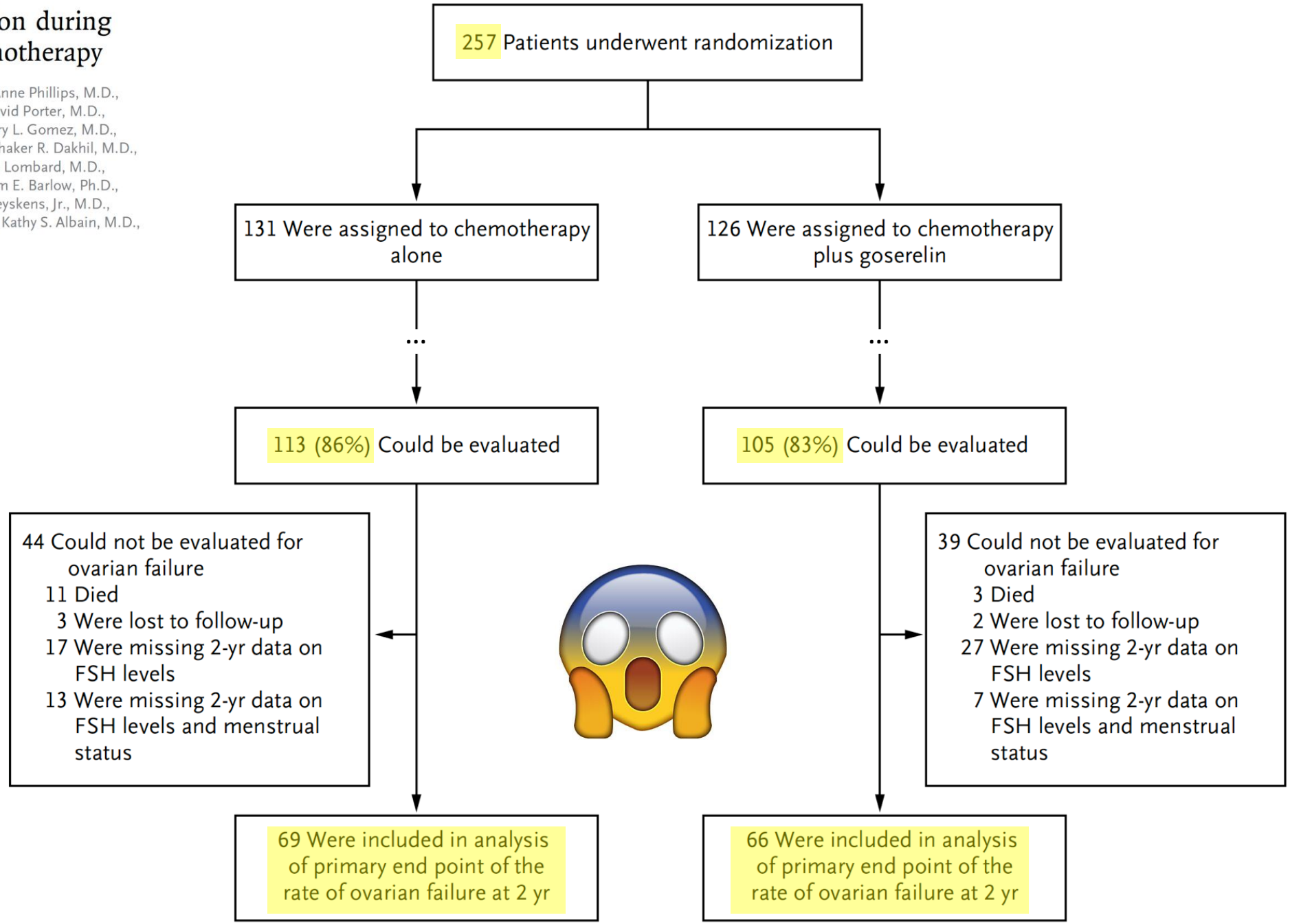
BMJ 2013;346:f1798 doi: 10.1136/bmj.f1798 (Published 22 April 2013)

To evaluate attrition bias, on the basis of whether the outcome data were incomplete or not, the authors had to establish a rule of thumb to ensure consistency between assessments. Trials were assessed as low risk of bias if less than 10% of patients were excluded overall and if similar proportions were excluded from both arms. Trials were judged as high risk of bias if there were considerable imbalances between arms or if more than 10% of randomised patients were excluded from the analysis.

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

Halle C.F. Moore, M.D., Joseph M. Unger, Ph.D., Kelly-Anne Phillips, M.D., Frances Boyle, M.B., B.S., Ph.D., Erika Hitre, M.D., David Porter, M.D., Prudence A. Francis, M.D., Lori J. Goldstein, M.D., Henry L. Gomez, M.D., Carlos S. Vallejos, M.D., Ann H. Partridge, M.D., M.P.H., Shaker R. Dakhil, M.D., Agustin A. Garcia, M.D., Julie Gralow, M.D., Janine M. Lombard, M.D., John F. Forbes, M.B., B.S., Silvana Martino, D.O., William E. Barlow, Ph.D., Carol J. Fabian, M.D., Lori Minasian, M.D., Frank L. Meyskens, Jr., M.D., Richard D. Gelber, Ph.D., Gabriel N. Hortobagyi, M.D., and Kathy S. Albain, M.D., for the POEMS/S0230 Investigators

N Engl J Med 2015;372:923-32.



SOURCES OF BIAS IN CLINICAL TRIALS

Type of bias	Description	
Selection bias.	Systematic differences between baseline characteristics of the groups that are compared.	• Sequence generation. • Allocation concealment.
Performance bias.	Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest.	• Blinding of participants and personnel. • Other potential threats to validity.
Detection bias.	Systematic differences between groups in how outcomes are determined.	• Blinding of outcome assessment. • Other potential threats to validity.
Attrition bias.	Systematic differences between groups in withdrawals from a study.	• Incomplete outcome data
Reporting bias.	Systematic differences between reported and unreported findings.	• Selective outcome reporting

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

Instances of SRB

* Selective omission of outcomes from reports
* Selective choice of data for an outcome
* Selective reporting of analyses using the same data
* Selective reporting of subsets of the data
* Selective under-reporting of data

The Cochrane Handbook, 2011

A METHODS GROUP OF

THE COCHRANE COLLABORATION®

Quality of Life in Patients With Metastatic Renal Cell Carcinoma Treated With Sunitinib or Interferon Alfa: Results From a Phase III Randomized Trial

David Cella, Jim Z. Li, Joseph C. Cappelleri, Andrew Bushmakin, Claudie Charbonneau, Sindy T. Kim, Isan Chen, and Robert J. Motzer

J Clin Oncol 26:3763-3769. © 2008 by American Society of Clinical Oncology

Instruments	Difference in Least Squares Means		
FKSI-DRS (primary endpoint)	1.98*	MID = 2 points	✗
FKSI-15	3.27*	MID = 3 points	✓
FACT-G	5.58*	MID = 5 points	✓
PWB	1.42*	MID = 2 points	✗
SFWB	1.20*	MID = 2 points	✗
EWB	0.787*	MID = 2 points	✗
FWB	1.98*	MID = 2 points	✗
EQ-5D Index	0.0364*	MID = 0.09	✗
EQ-VAS	4.74*	MID = 8	✗

*Results were statistically significant at critical $P = .05$

Patients receiving sunitinib reported higher FKSI-15 and FACT-G scores at each cycle than those receiving IFN-α, per pre-established clinically meaningful thresholds.

Riassumendo:

- **selezione dei soggetti da assegnare a uno specifico trattamento, rimozione di alcuni pazienti dall'analisi, analisi non preordinata su sottogruppi di pazienti (*selection bias*)**

  ***rimedio:* randomizzazione (e stratificazione)**

- **conoscenza da parte del paziente/medico/valutatore del trattamento in atto (*performance/detection bias*)**

  ***rimedio:* mascheramento**

- **perdita dei pazienti alla valutazione di uno specifico outcome di interesse (*attrition bias*)**

  ***rimedio:* disegno di studio e procedure di follow-up**

- **selezione dei risultati da comunicare a mezzo presentazione/pubblicazione (*reporting bias*)**

  ***rimedio:* database degli studi clinici in corso**

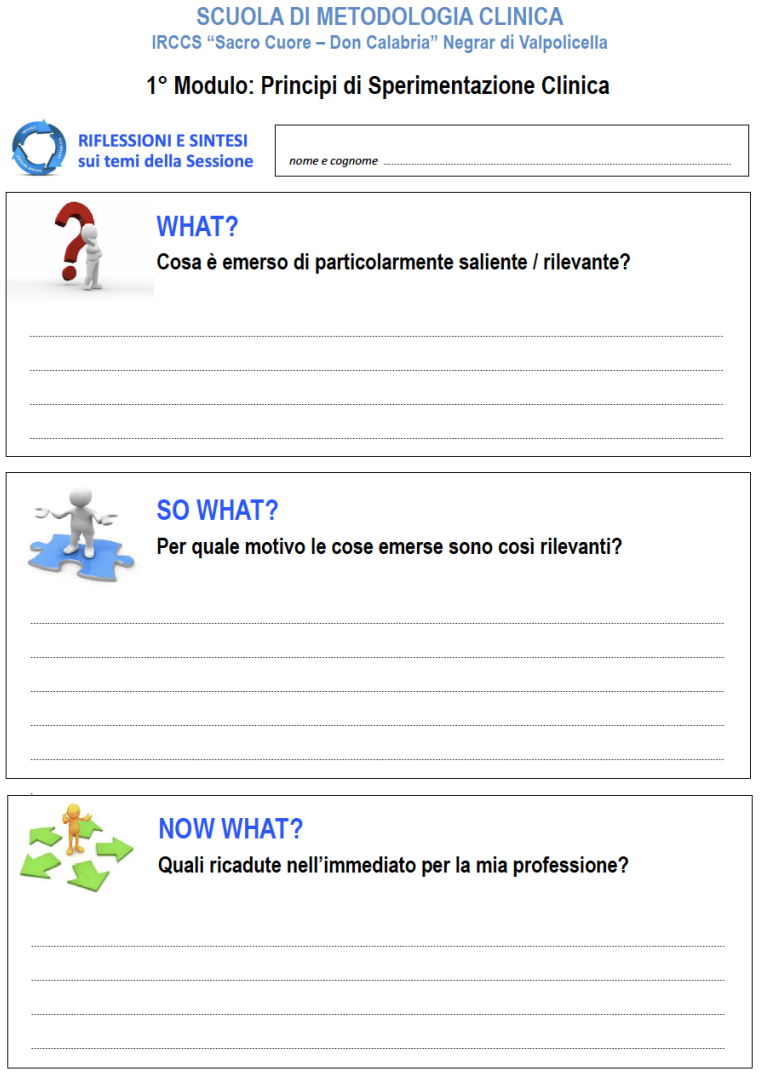
- Etica della ricerca
- Quesito clinico di riferimento
- Fasi della sperimentazione clinica
- Disegni di studio osservazionali e interventistici
- Misure di effetto relativo e assoluto
- Principi di statistica medica (errori statistici, verifica di ipotesi, dimensiona-mento campionario)
- Rilevanza clinica Vs significatività statistica
- Trasferibilità delle evidenze al quesito clinico
- Affidabilità delle prove (imprecisione degli effetti, rischio di bias)
- **Dialogo tra clinico e metodologo (lettura di uno studio clinico)**

Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial

Mary O'Brien, Luis Paz-Ares*, Sandrine Marreaud, Urania Dafni, Kersti Oselin, Libor Havel, Emilio Esteban, Dolores Isla, Alex Martinez-Marti, Martin Faehling, Masahiro Tsuboi, Jong-Seok Lee, Kazuhiko Nakagawa, Jing Yang, Ayman Samkari, Steven M Keller, Murielle Mauer, Nitish Jha, Rolf Stahel, Benjamin Besse†, Solange Peters†, on behalf of the EORTC-1416-LCG/ETOP 8-15 – PEARLS/KEYNOTE-091 Investigators‡*

Lancet Oncol **2022; 23: 1274–86**

1. Riflettete da soli per 10 min. e compilate il form →
2. Confrontatevi con i Colleghi del Vostro tavolo per 15 min., declinate un W^3 condiviso e delegate un portavoce
3. Riportate sulla lavagna il Vostro W^3 condiviso su almeno due aspetti ritenuti rilevanti e impattanti sulla professione (in 5 min.)
4. Presentate ai Colleghi degli altri tavoli il Vostro W^3 condiviso



SCUOLA DI METODOLOGIA CLINICA

IRCCS "Sacro Cuore – Don Calabria" Negrar di Valpolicella

1° Modulo: Principi di Sperimentazione Clinica

RIFLESSIONI E SINTESI sui temi della Sessione

nome e cognome .....

WHAT?

Cosa è emerso di particolarmente saliente / rilevante?

SO WHAT?

Per quale motivo le cose emerse sono così rilevanti?

NOW WHAT?

Quali ricadute nell'immediato per la mia professione?