Sesión paralela 3. Nuevos Paradigmas en investigación clínica

Nuevos diseños en ensayos clínicos de fase temprana

XI Conferencia Anual de las Plataformas Tecnológicas de Investigación Biomédica: Medicamentos Innovadores, Nanomedicina Tecnología Sanitaria y Mercados Biotecnológicos

Nuevos paradigmas ante innovaciones biomédicas disruptivas

Barcelona, 5 y 6 de Marzo de 2018

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Disclosures

The views expressed are the personal views of the presenter and may not be understood as being made on behalf of or reflecting the position of EMA, its committees/WP, or the AEMPS

My DoI is publicly available at EMA website

Fases del desarrollo tradicional de medicamentos

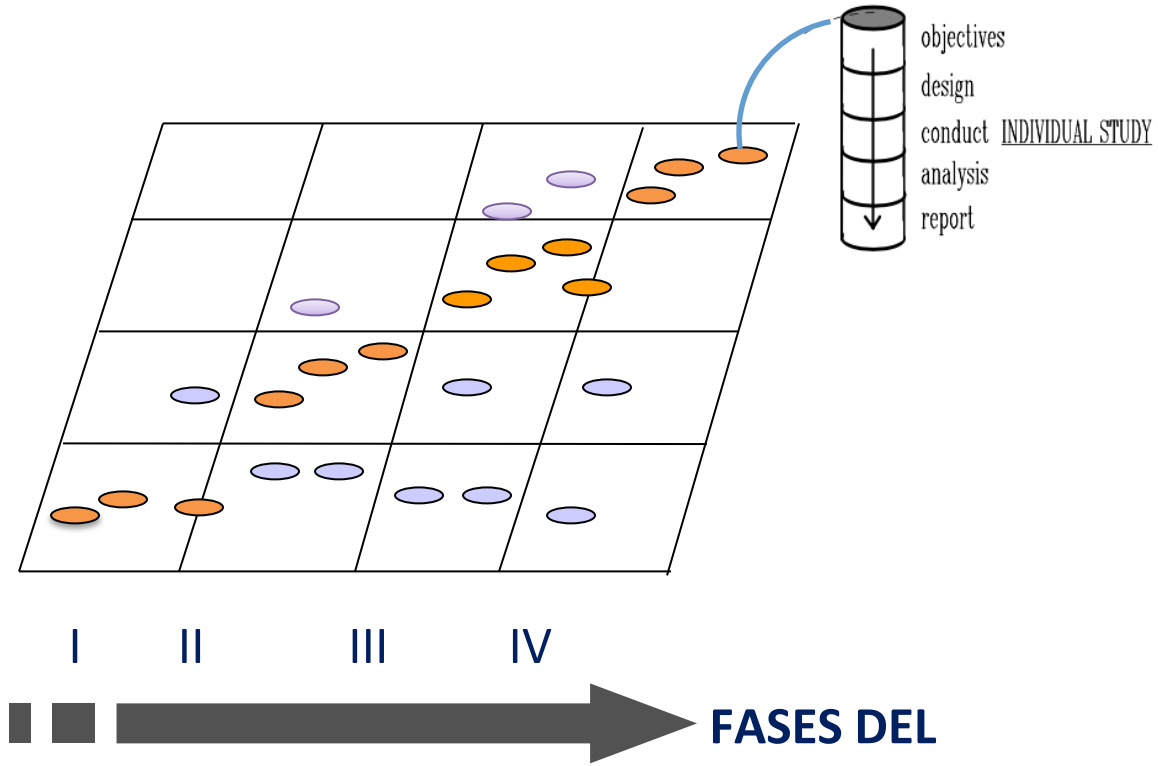
TIPO DE ESTUDIOS

Usos terapéuticos

Confirmación terapéutica

Exploración Terapéutica

Farmacología Humana

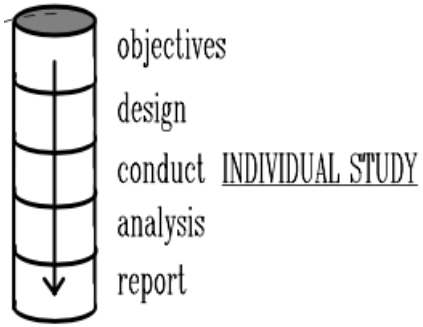


ICH Topic E 8
General Considerations for Clinical Trials

Diseño tradicional de los ensayos clínicos: RCT

Pre-defined:

- PROTOCOL
  - Hypothesis
  - Measurement methods
  - Bias minimization



Results according to protocol

- Double blind analysis at the end of the study
- Design able to answer a single principal analysis
- Accept or reject hypothesis

- **Robust, intuitive, clear**
- **Literally implements scientific method**
- **May be conclusive on causality**

Limitaciones de los EC tradicionales

Costly

- Fixed a priori sample size
- Depending on the variance and the expected difference between groups

Long-lasting

- No information until completed
- Acquired information is ignored until the end of the trial
- All included subjects must wait

Inflexible

- The design parameters are set in stone, and not rechecked until the end of the trial; often chosen with uncertainty
- All arms are completed to the end of the study, even if one is much better than other

Stand-alone

- Prior available information used only for sample size estimation applies
- Formally ignoring previous data
- Inference based only on current observation

Modelo de desarrollo tradicional: ⇧tiempo, N alta pacientes y costoso

Slide taken from Caridad Pontes

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Results

Our search strategy did not find any randomised controlled trials of the parachute.

Discussion

Evidence based pride and observational prejudice

It is a truth universally acknowledged that a medical intervention justified by observational data must be in want of verification through a randomised controlled

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Addressing limitations: alternative trials design

- **Sample size optimization**
  - Minimise intersubject variability
  - Maximize expected differences

Crossing over, enrichment designs

- **Shorten study duration**
  - Analyze data as it is acquired
  - Decision as soon as evidence supports; avoid unnecessary experimental exposures

Sequential methods

- **Adapt designs**
  - Correct deviation from reality in the study assumptions
  - Redefine the study using acquired information

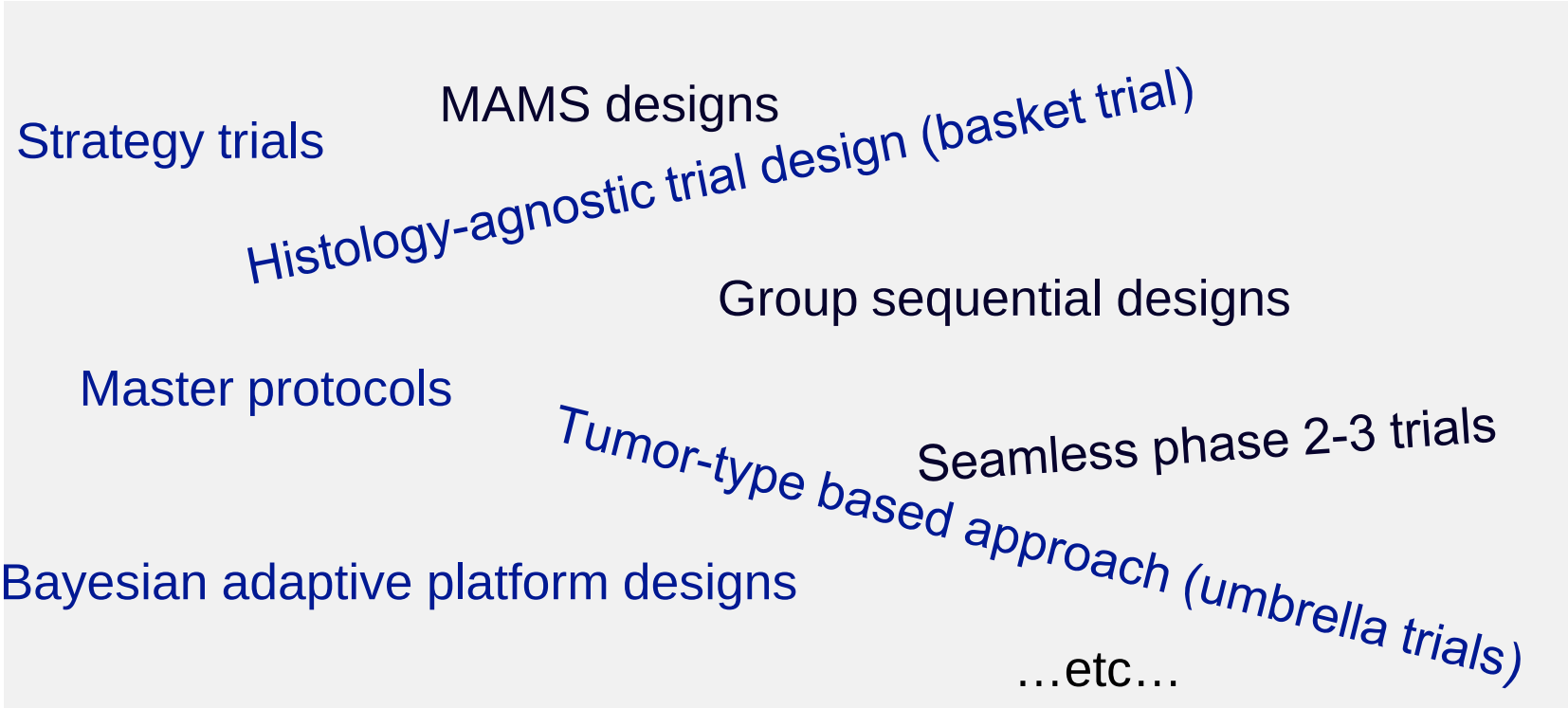
Adaptive designs

- **Integrate results**
  - Incorporate previous information
  - Infer taking profit of all the available knowledge

Modelling, Bayesian approaches

Slide taken from Caridad Pontes

Addressing limitations: alternative trials design



In summary…
- Enrichment
- Adaptions

Justified <u>early</u> and/or late in clinical development

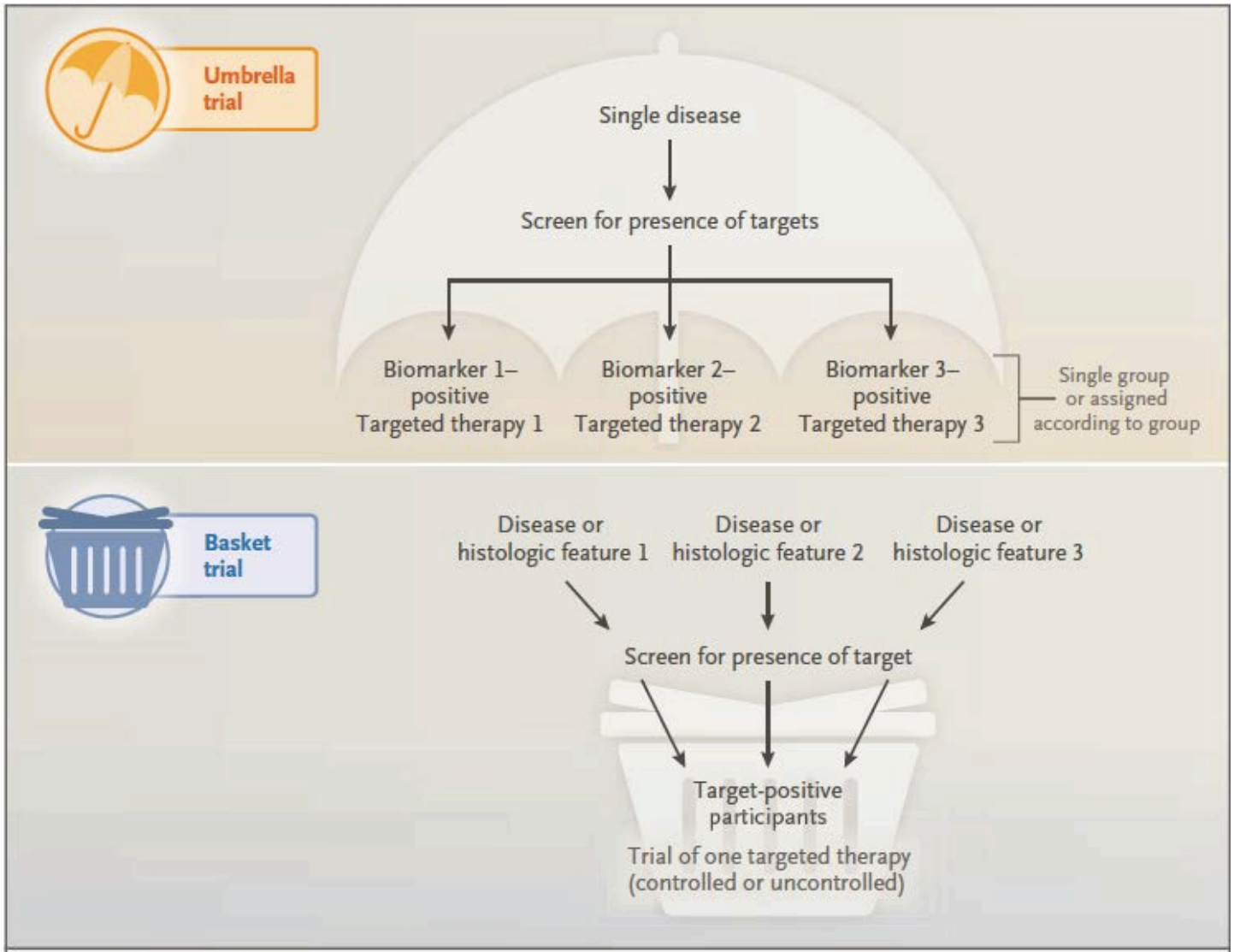


Figure 1. Umbrella Trial and Basket Trial.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

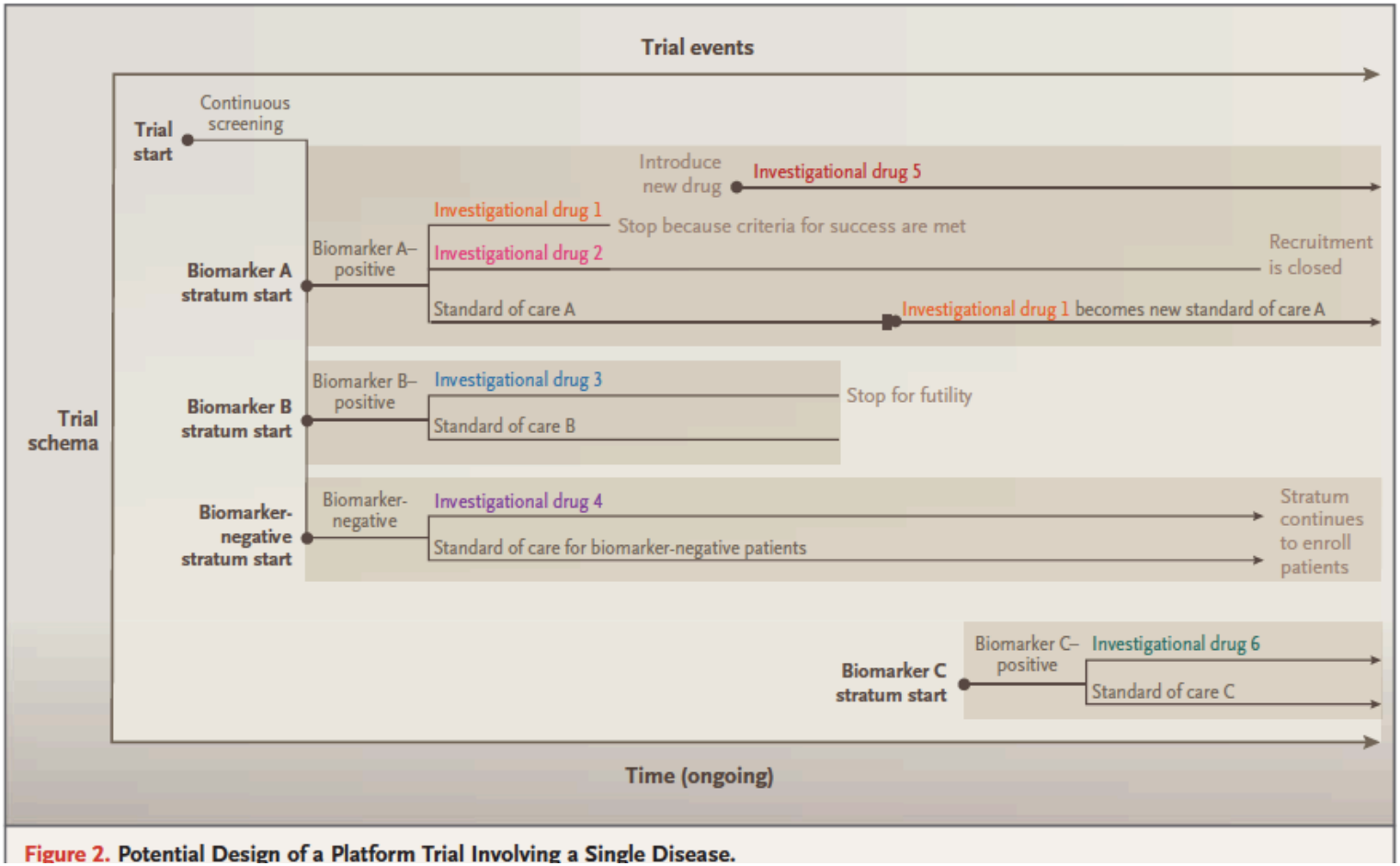


Figure 2. Potential Design of a Platform Trial Involving a Single Disease.

The figure depicts the trial schema over time, not the flow of individual patients. The platform trial is ongoing over time, with no fixed stopping date, and is governed by a master protocol that envisions adding and dropping strata. At trial start, entering patients undergo screening for biomarkers A and B and are assigned to one of three strata on the basis of the results. Biomarker A–positive patients are randomly assigned to one of three groups, testing two investigational drugs against a common standard of care. When investigational drug 1 meets the criteria for success, that group of the stratum is stopped, and after further testing, drug 1 ultimately replaces the previous standard of care as the control. Randomization to an investigational drug 5 group is initiated in the biomarker A stratum when that drug becomes available, sharing the common control group for patients with similar biomarker profiles. The investigational drug 2 group completes planned enrollment and stops. Entry of patients into the biomarker B stratum is stopped when investigational drug 3 appears unlikely to provide benefit. At that point, new biomarker B–positive patients are assigned to the biomarker-negative stratum. A biomarker C stratum is opened when both a biomarker assay and an investigational targeted drug become available to the trial. At this time in the trial, patients are screened for biomarkers A and C and then assigned to the appropriate stratum. Only one possible platform-trial schema is depicted in this figure. The statistical methods shown here involve randomized treatment assignment, sharing of common control patients, and sequential analyses with the possibility of stopping early for success or failure. Other types of adaptive designs are possible, including adaptive randomization, as are the use of other criteria for early stopping. For example, if a biomarker stratum includes only a single treatment group without randomized assignment, then stopping early after exceeding a specified threshold for the response rate might be used.

N Engl J Med 2017;377:62-70.
DOI: 10.1056/NEJMra1510062

Increased interest, why now?

"The perfect storm"

- **Personalized medicine (led by anticancer MP)**
  - Targeted therapies
  - Biomarkers
  - Switching from highly prevalent to rare conditions
  - Accrual limitations
  - Objectives of phase I-II CT for targeted therapies: no proper dose-finding studies

- **Need to be efficient:**
  - patient´s protection: only the strictly required sample is exposed and minimize numbers o failed studies due to design errors
  - research sustainability(recourse optimization)

- **Real time access to information: e-CRF**

- **Less methodological concerns about novel methods: numerous examples**
  - if applied rigorously, useful and robust but should be understood and interpreted

- **High interest:** statistician, methodologist, patients, researchers and regulators

Seventh Framework Programme (FP7) small-population research methods projects and regulatory application workshop

REFLECTION PAPER ON METHODOLOGICAL ISSUES IN CONFIRMATORY CLINICAL TRIALS PLANNED WITH AN ADAPTIVE DESIGN

Successful examples

Use of Canakinumab in the Cryopyrin-Associated Periodic Syndrome

Helen J. Lachmann, M.D., Isabelle Kone-Paut, M.D., Jasmin B. Kuemmerle-Deschner, M.D., Kieron S. Leslie, M.B., B.S., Eric Hachulla, M.D., Ph.D., Pierre Quartier, M.D., Xavier Gitton, Ph.D., Albert Widmer, M.Sc., Neha Patel, M.S., and Philip N. Hawkins, Ph.D., F.Med.Sci., for the Canakinumab in CAPS Study Group*

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

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The Safety and Efficacy of Subcutaneous Enoxaparin Versus Intravenous Unfractionated Heparin and Tirofiban Versus Placebo in the Treatment of Acute ST-Segment Elevation Myocardial Infarction Patients Ineligible for Reperfusion (TETAMI)

A Randomized Trial

Marc Cohen, MD, FACC,* Gian Franco Gensini, MD,† Frans Maritz, MD,‡

Original Investigation

Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation

Randomized Clinical Trial

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

lice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

Phase II, Open-Label Study Evaluating the Activity of Imatinib in Treating Life-Threatening Malignancies Known to Be Associated with Imatinib-Sensitive Tyrosine Kinases

Michael C. Heinrich,[1] Heikki Joensuu,[2] George D. Demetri,[3] Christopher L. Corless,[1] Jane Apperley,[5] Jonathan A. Fletcher,[4] Denis Soulières,[6] Stephan Dirnhofer,[7] Amy Harlow,[1] AjiaTown,[1] Arin McKinley,[1] Shane G. Supple,[10] John Seymour,[11] Lilla Di Scala,[8] Allan van Oosterom,[12] Richard Hermann,[9] Zariana Nikolova,[8] and Grant McArthur[11] for the ImatinibTarget Exploration Consortium Study B2225

Abstract **Purpose:** To evaluate the activity of imatinib in treating advanced, life-threatening malignancies expressing one or more imatinib-sensitive tyrosine kinases.
Experimental Design: This was a phase II, open-label, single arm study. Patients ≥15 years old with malignancies showing histologic or molecular evidence of expression/activation of imatinib-sensitive tyrosine kinases were enrolled. Patients were treated with 400 or 800 mg/d imatinib for hematologic malignancy and solid tumors, respectively. Treatment was continued until disease progression or unacceptable toxicity. The primary objective was to identify evidence of imatinib activity with tumor response as the primary end point.
Results: One hundred eighty-six patients with 40 different malignancies were enrolled (78.5% solid tumors, 21.5% hematologic malignancies). Confirmed response occurred in 8.9% of solid tumor patients (4 complete, 9 partial) and 27.5% of hematologic malignancy patients (8 complete, 3 partial). Notable activity of imatinib was observed in only five tumor types (aggressive fibromatosis, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, myeloproliferative disorders, and systemic mastocytosis). A total of 106 tumors were screened for activating mutations: five *KIT* mutations and no platelet-derived growth factor receptor mutations were found. One patient with systemic mastocytosis and a partial response to therapy had a novel imatinib-sensitive *KIT* mutation (D816T). There was no clear relationship between expression or activation of wild-type imatinib-sensitive tyrosine kinases and clinical response.
Conclusion: Clinical benefit was largely confined to diseases with known genomic mechanisms of activation of imatinib target kinases. Our results indicate an important role for molecular characterization of tumors to identify patients likely to benefit from imatinib treatment.

Enzalutamide in Metastatic Prostate Cancer before Chemotherapy

T.M. Beer, A.J. Armstrong, D.E. Rathkopf, Y. Loriot, C.N. Sternberg, C.S. Higano, P. Iversen, S. Bhattacharya, J. Carles, S. Chowdhury, I.D. Davis, J.S. de Bono,

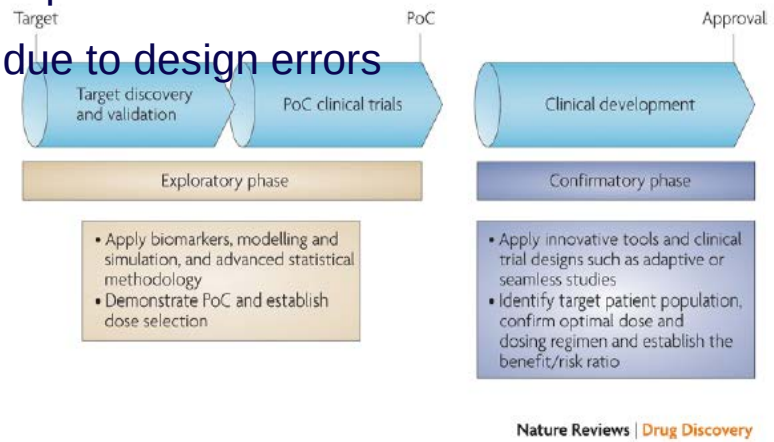
An Adaptive, Dose-Finding, Seamless Phase 2/3 Study of a Long-Acting Glucagon-Like Peptide-1 Analog (Dulaglutide): Trial Design and Baseline Characteristics

Mary Jane Geiger, M.D., Ph.D.,[1] Zachary Skrivanek, Ph.D.,[1] Brenda Gaydos, Ph.D.,[2] Jenny Chien, Ph.D.,[1] Scott Berry, Ph.D.,[3] Donald Berry, Ph.D.,[3,4] and James H. Anderson, Jr., M.D.[5]

Novel study designs in early development

Potential benefits

- ***Greater efficiency in drug development***
  - Faster detection of innovative agents
  - More accurate selection of patients
  - Can address multiple objectives within a single protocol
  - Hypothesis generating for confirmatory trial
  - Exposure of less patients to potentially inactive agents
  - Only the strictly required sample is exposed
  - Minimize numbers of failed studies due to design errors
  - Less resource consumption



Sources: Orloff, J., et al. (2009). "The future of drug development: advancing clinical trial design." Nat Rev Drug Discov 8(12): 949-957.

Novel study designs in early development

Potential challenges:

- ***For regulators:***
  - Interpretation of results and regulatory decisions
    - Single arm studies
    - Biomarkers poorly qualified (diagnostic and/or predictive and/or prognostic)
    - Exploratory endpoints (e.g. ORR)
    - Proper selection of the target population?
    - Proper (feasible) adjustment for multiplicity?
    - Feasibility of confirmatory trials: clinical equipose
  - *Often linked to an early access regulatory tools: AA, CMA*

BENEFIT-RISK ASSESSMENT

REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004

laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

The B/R is key concept
It does not differ for drugs based on biomarkers/novel designs
Robustness of the whole lot of data: biological plausibility, validity

Novel study designs in early development

Potential challenges:

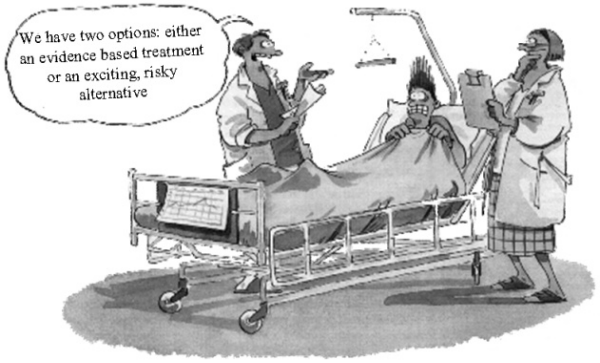
- ***For sponsors: Retention of integrity of trial designs***
    - Susceptibility for bias
    - Logistically complex:
        - New trial networks (collaborative groups) and informatics infrastructures needed to enable dynamic nature of the trial design=centralized shared governance,
        - Biomarker screening platforms
        - Increased planning efforts and coordination. Intensive pretrial discussions among sponsors-parties involved to agree on data use, publication rights, timing of regulatory submissions, etc
    - Complexity of safety monitoring
    - Long-running master protocols: changes in SOC !

Novel study designs in early development

Potential challenges:

- ***For Competent Authorities and RECs***
  - Huge divergence among CA: unclear how central CT approval will handle this
  - RECs: Need to guarantee patient´s rights (informed consent) and well-being of participants…¿?

Conclusions



– Alternative designs ARE tools to manage complex situations

– Refined trial designs and analysis methods should be used to maximize the information obtained

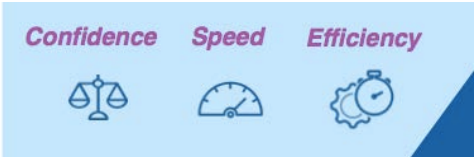
– Alternative designs ARE NOT means to reduce or relax methodological requirements or apriorism

- **NEED TO ADAPT**

– A balance should be reached between statistical efficiency and results that can be clinically interpreted

– Alignment with regulatory agency interest in supporting achievement of better quality and efficiency

– Subjects rights and well-being need to be guaranteed



Hypothesis...experiment...conclusion.
Wow. This is *so* last century.

GRACIAS