Introduction to Clinical Trials

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Basic Principles in Oncology
ESO course, Ljubljana 2022

Disclosures

I have attended advisory boards and/or provided lectures for the following organizations:

- AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Roche, MSD, Pfizer, Takeda.

Clinical Cancer Research

Clinical research is aimed to:

- Discover new effective prevention, diagnostic and treatment strategies for cancer control
- Translate new discoveries into clinical practice and define state-of-the-art treatment
- Identify ineffective and/or redundant treatments

➢ Leading to best medical practice and optimal cancer control!

Clinical Cancer Research

Participation in clinical trials (CT) is associated with improved outcomes:

- Treatment in **centers participating in cooperative study groups** is associated with **higher survival rate** (*German experience in ovarian cancer; Du Bois A, et al. Int J Gynec Cancer 2005.*)
- **26 comparisons of outcome** of cancer **patients enrolled and not enrolled in clinical trials**, suggested that trial patients do better. **No studies** recorded **worse outcome** in trial-enrolled patients than in non-trial patients! (*Peppercorn JM, et al. Lancet 2004.*)

Participation in Clinical Trials
The Right of Patients

VOLUME 24 · NUMBER 21 · JULY 20 2006
JOURNAL OF CLINICAL ONCOLOGY
ASCO SPECIAL ARTICLE

ASCO-ESMO Consensus Statement on Quality Cancer Care (2006)

8. Innovative Cancer Care

Patients should be offered the opportunity to participate in relevant clinical trials and should have access to innovative therapies, which may improve their disease outcome.

Translational Research Clinical Trials

'From bench to bedside'

- Incorporating laboratory research into clinical studies

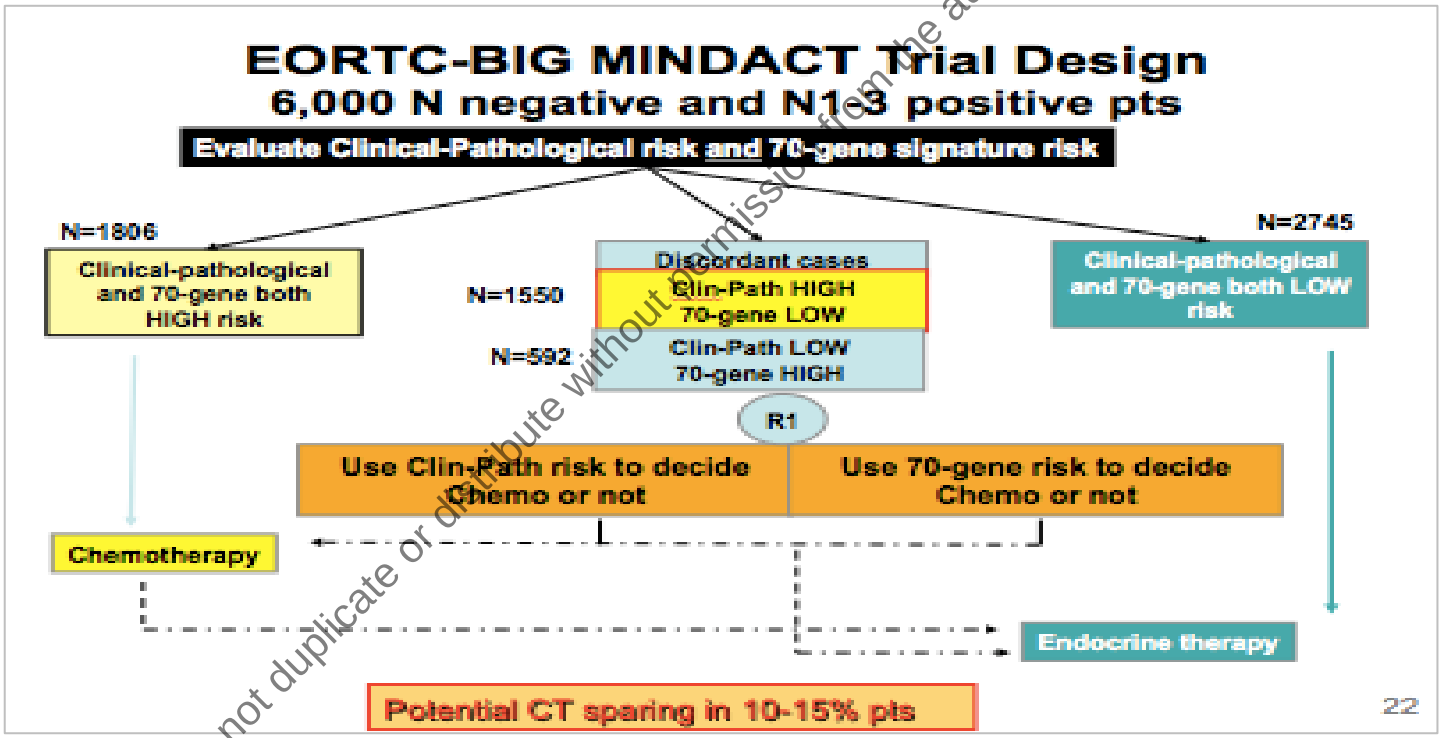
'From bedside to bench'

- Using clinical studies to influence laboratory research

- Close collaboration between basic and clinical scientists is a prerequisite for a high-quality translational research!

➢ Translation research should be a part of any modern clinical trial!

Excellent Example of Translational Research MINDACT trial



Cardoso F, et al. N Engl J Med 2016.

Types of Clinical Trials

	Phase I →	Phase II →	Phase III →	Phase IV
Aim	Pharmacokinetics, Dose finding-toxicity	Activity Safety	Efficacy compared to standard	Post-marketing safety/toxicity
Sample Size	1 – 25	9 – 50	200 - 1000 (Adv) 1000 - >5000 (Adjv)	
Population	refractory to all treatments	refractory to conventional treatments	1st/2nd line treat. (Adv) 1st line treatment (Adjv)	
Methods	Fibonacci, CRM…	Fleming, Simon, …	Randomized, stratification, double-blind, cross-over…	

CRM: Continual Reassessment Method

Courtesy of Patrick Therasse, EORTC

Phase I Study Principles

- Aims
  - Identify dose-limiting toxicities (DLTs)
  - Identify maximally tolerated dose (MTD)
  - ➢ **Determine optimal dose of drug/schedule for phase 2**
  - Evaluation of pharmacokinetics
  - Assessment of efficacy as secondary goal

- Design (most frequently used)
  - Dose escalation 3+3 design (modified Fibronacci)

- Inclusion criteria
  - Patients for whom there is no longer any “standard” treatment
  - Clinical trials in oncology involve only cancer patients, never volunteers!

Phase I Study Design: Classical 3+3

Cohort	Dose (mg/m^2)	Escalation (%)	DLT in patients	Comment
1	10	First dose	0/3	
2	20	100%	0/3	
3	33	67%	0/3	
4	50	50%	0/3	
5	70	40%	1/3	Add 3 more patients: 0/3 have DLT= 1/6
6	90	28%	2/3	This is > MTD
7	70		1/6	This is recommended phase 2 dose

Adopted from: Tannock, ASCO University, Research Design & Methodology.

Phase I Study Assumptions

The higher the dose, the greater the likelihood of efficacy

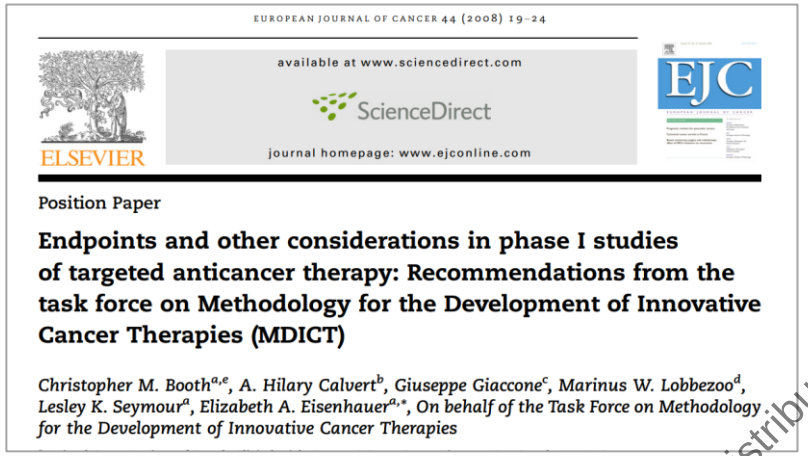
- The highest safe dose (MTD) is the dose most likely to be effective
- This assumption is not valid for many biological agents!

Non-cytotoxic drugs should have lowest biologically effective dose (BED) as goal of Phase I

- Dose-limiting toxicity (DLT) is not an optimal endpoint for biological agents, which might not cause DLTs even at doses higher than sufficient active doses
- **Biological effective dose (BED)** determined by evaluating target binding or inhibition and/or antitumor efficacy **as a primary endpoint** seems to be more appropriate

Adopted from: Ian Tannock, ASCO University, Research Design & Methodology.

Proposed Phase I Algorithm for Targeted Agents



EUROPEAN JOURNAL OF CANCER 44 (2008) 19–24

available at www.sciencedirect.com

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journal homepage: www.ejconline.com

ELSEVIER

EJC

Position Paper

Endpoints and other considerations in phase I studies of targeted anticancer therapy: Recommendations from the task force on Methodology for the Development of Innovative Cancer Therapies (MDICT)

Christopher M. Booth[a,e], A. Hilary Calvert[b], Giuseppe Giaccone[c], Marinus W. Lobbezoo[d], Lesley K. Seymour[a], Elizabeth A. Eisenhauer[a,], On behalf of the Task Force on Methodology for the Development of Innovative Cancer Therapies*

Dose Seeking Phase I
Standard Design
Dose "range" identified using Toxicity (or PK) Endpoint
Option: assess feasibility of molecular/imaging studies and obtain general "Proof of Principle" for target effect
Recommend highest tolerable dose

↓

If more detailed information on molecular effect, PK etc. required to refine recommendation

↓

"Phase Ib"or expanded level(s) in phase I
Selected doses (2-4) from range
More pts per level, uniform population
Molecular or imaging endpoint(s), PK

↓

Final dose identified based on multiple inputs
If lower dose than highest safe dose is to be recommended, further proof this does not reduce activity may be needed.

Fig. 2 – Proposed phase I algorithm for novel molecular compounds.

Booth CM, et al. EJC 2008.

Phase II Study Principles

- Aim
  - To obtain preliminary evidence of anti-tumor effect
    - **Primary Endpoint: Objective Response Rate, measured by RECIST**
    - Alternatives: PFS, DFS , TTP, TTF
  - Further evaluation of safety and toxicity
  - ➢ **Demonstrate sufficient efficacy to warrant further testing in phase 3**
- Design
  - Single arm (one step, multi-steps design)
  - Randomized: Single control arm (↓selection bias, no statistical comparison between arms, can be extended to phase 3)
    - Multiple control arms to test multiple agents/schedules; 'winner selection'
- Inclusion criteria
  - Patients with a single type of cancer; limited "standard" treatment available

Clinical Trial Response Rate Evaluation

- RECIST (Response Evaluation Criteria In Solid Tumors)
  - Widely used and accepted
  - RECIST 1.0, JNCI, 2000
  - **RECIST 1.1, EJC 2009**

- Distinct RECIST criteria for lymphomas and for mesothelioma (Ann Oncol 2017, J Thor Oncol 2018)

- PERCIST (PET Response Criteria in Solid Tumors), J Nucl Med 2009

- Immuno-Oncology specific response criteria
  - RECIST 1.1 might underestimate the benefit of IO
  - iRECIST, Lancet Oncol 2017
  - imRECIST, J Clin Oncol 2018

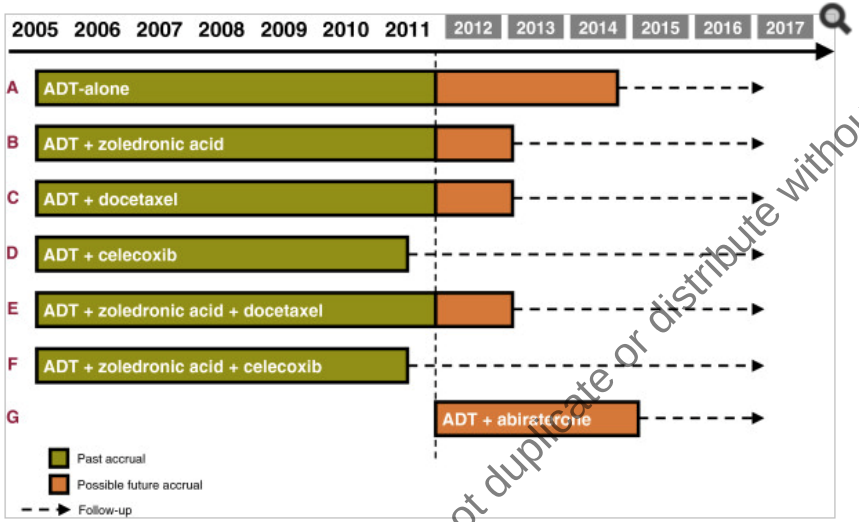
Clinical Trials - Adaptive Designs

- Definition:
  - Adaptive design **allows for prespecified adaptation in trial procedures** and/or statistical procedures after initiation of trial, without undermining the validity and integrity of the trial.
- Types:
  - Treatment effect-independent adaptive designs (sample size re-estimation based on lower event rate)
  - Treatment effect-dependent adaptive designs (patients inclusion criteria, pick the winner design, adaptive phase 2/3 seamless design)
  - Biomarker-driven adaptive design
- Adaptive designs hold a prominent place in the era of personalized medicine

Adopted from: Ian Tannock, ASCO University, Research Design & Methodology.

Adaptive Designs in Phase II Trials

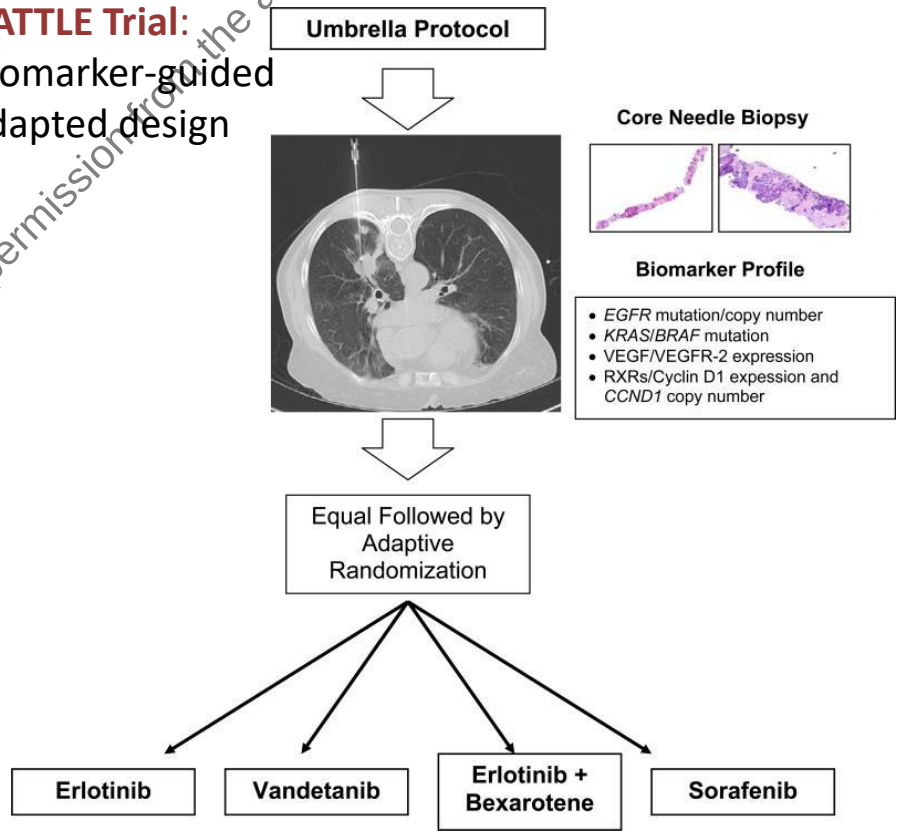
STAMPEDE Trial:
Treatment effect-dependent adapted design; pick up the winner



Trial arms open to allocat ion and fur ther t imelines as of Nov 2011.

Sydes, et al. Trials 2012; Kim S, et al. Cancer Discovery 2011.

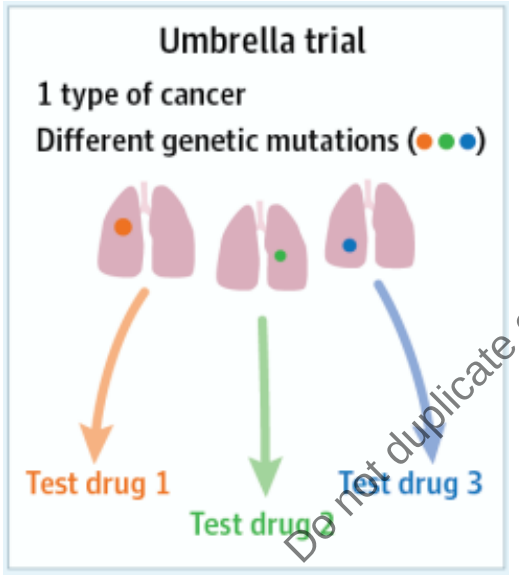
BATTLE Trial:
Biomarker-guided adapted design

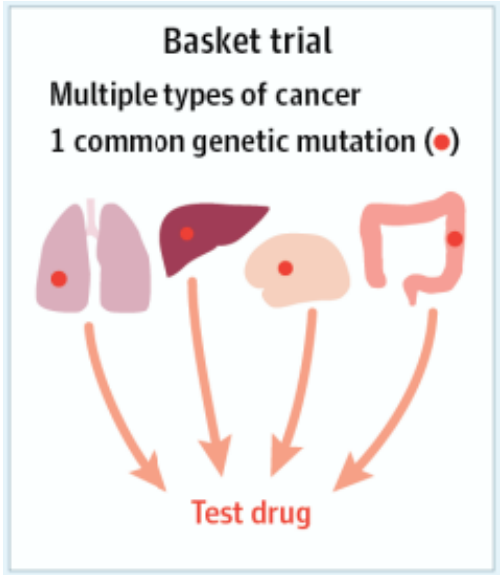


Modern Clinical Trials for Precision Oncology

Umbrella Trials: test **multiple drugs against a single cancer type.** People are assigned to a particular treatment arm based on the molecular characteristics of their cancer.

Basket Trials: test one drug against multiple cancer types with the same genetic characteristic. These design increases the number of eligible patients and decreases the time needed for the drug to be tested.





JAMA Oncology: doi: 10.101/jamaoncol.2016.5299.

Phase II Study Assumptions

- Phase 2 trials seek activity to warrant expense and resources for phase 3 study
- Results subject to uncertainty; primary endpoint NOT a measure of clinical benefit
- Many encouraging phase 2 trials are followed by negative phase 3 trials
- Randomized phase 2 trials are NOT small phase 3 studies
- Phase 2 study **can generate a hypothesis** about value of new treatment **that must be tested in a randomized phase 3 trial against standard management**
- ➢ Marketing approval is generally based on Phase 3 trial results; Accelerated/conditional **marketing approval based on phase 2** results is **possible, but** only for trials with well-defined surrogate marker for clinical benefit and **mandates re-assessment!**

Adopted from: Ian Tannock, ASCO University, Research Design & Methodology.

Targeted Therapy
Marketing Approval Characteristics, 2009-2019

Table 2 Regulatory Approval Characteristics of Targeted Multi-Indication Drugs Across the US (FDA), EU (EMA), Canada (HC), and Australia (TGA)

	US (FDA)		EU (EMA)		Canada (HC)		Australia (TGA)		*P-value*
	No	**(%)**	**No**	**(%)**	**No**	**(%)**	**No**	**(%)**	
Approval Type									*<.001*
Standard	52	(54.2%)	74	(80.4%)	41	(47.7%)	72	(86.8%)	
Conditional Approval	28	(29.2%)	12	(13.1%)	23	(26.7%)	3	(3.6%)	
Priority Review	16	(16.6%)	6	(6.5%)	22	(25.6%)	8	(9.6%)	
Orphan Designation									*<.001*
No	49	(51.0%)	70	(76.1%)	NA	NA	75	(90.4%)	
Yes	47	(49.0%)	22	(23.9%)	NA	NA	8	(9.6%)	
MA Supporting Trial †									*<.001*
No	57	(59.4%)	25	(27.2%)	48	(55.8%)	50	(60.2%)	
Phase 1	7	(7.3%)	14	(15.2%)	5	(5.8%)	2	(2.4%)	
Phase 2	15	(15.6%)	28	(30.4%)	13	(15.1%)	19	(22.9%)	
Phase 3	17	(17.7%)	25	(27.2%)	20	(23.3%)	12	(14.5%)	
Pivotal Trial Design ‡									*0.822*
Phase 1	4	(4.2%)	3	(3.2%)	5	(5.8%)	3	(3.6%)	
Phase 2	25	(26.0%)	18	(19.6%)	23	(26.8%)	19	(21.7%)	
Phase 3	67	(70.8%)	71	(77.2%)	58	(67.4%)	61	(74.7%)	
No. of Observations	**96**	**(100%)**	**92**	**(100%)**	**86**	**(100%)**	**83**	**(100%)**	

Based on Michaeli DT, et al. Invest New Drugs 2022.

Phase III Study Principles

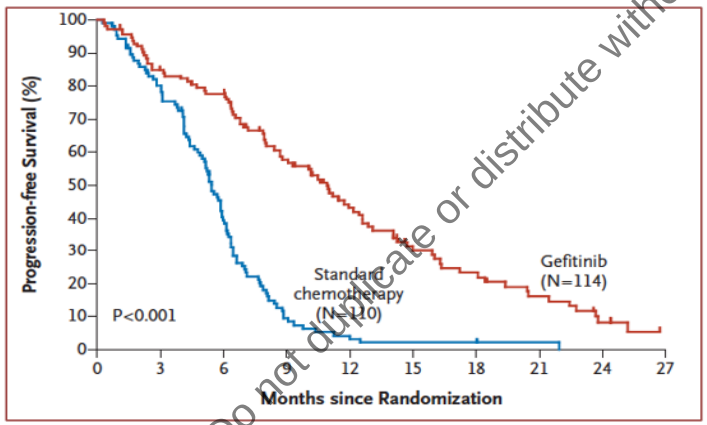
- Aim
  - **Determine whether a new treatment** provides **sufficient benefit to** patients that it should **replace (or add to) current standard treatments**
  - Primary endpoint should be measure of patient benefit, i.e. overall survival (OS) or Quality of Life (QL)
  - Other endpoints: PFS, DFS, pCR, if they are shown to be validate surrogates for OS or QoL (they rarely are)
- Design
  - **Randomization is fundamental**; stratification is possible
  - Double-blind design preferred; intention to treat analysis
- Inclusion criteria
  - Usually single type of cancer
  - Entry criteria should be broad to represent general population
  - Requires collaboration between multiple sites and usually organized either by cooperative groups or companies

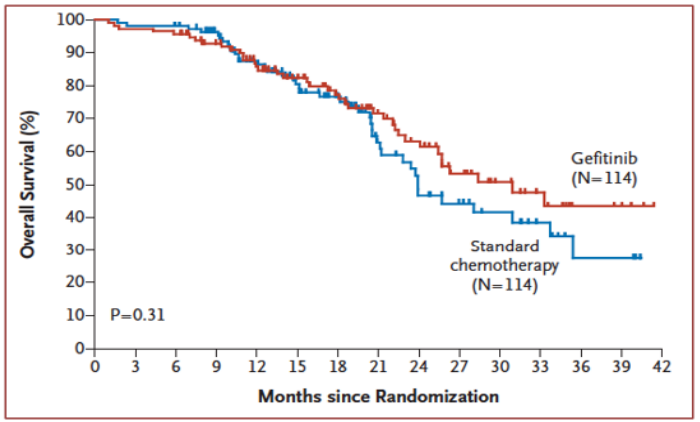
Phase III Study
Challenges to Study Endpoints

Overall Survival might be **confounded by cross-over rate** and/or post-trial treatment!

Gefitinib vs. Cht for EGFR Mutated NSCL

Cross-over rate in ChT arm 68%



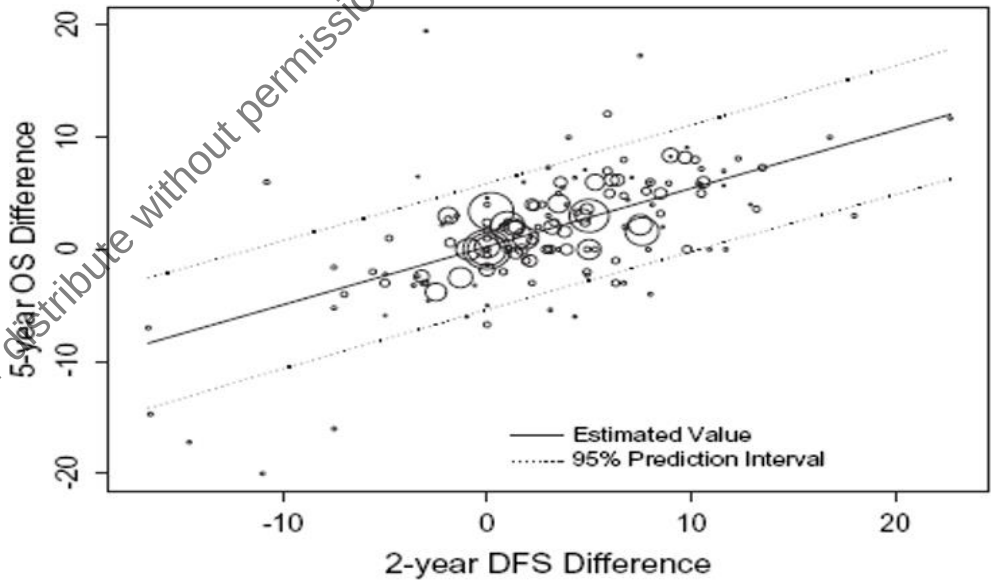


Maemondo M, et al. N Engl J Med 2010.

Phase III Study
Challenges to Study Endpoints

Early **difference in a surrogate marker** may **not predict for** the same scale of **benefit in OS**!

Correlation between 2-year DFS and 5-year OS in adjuvant breast cancer trials

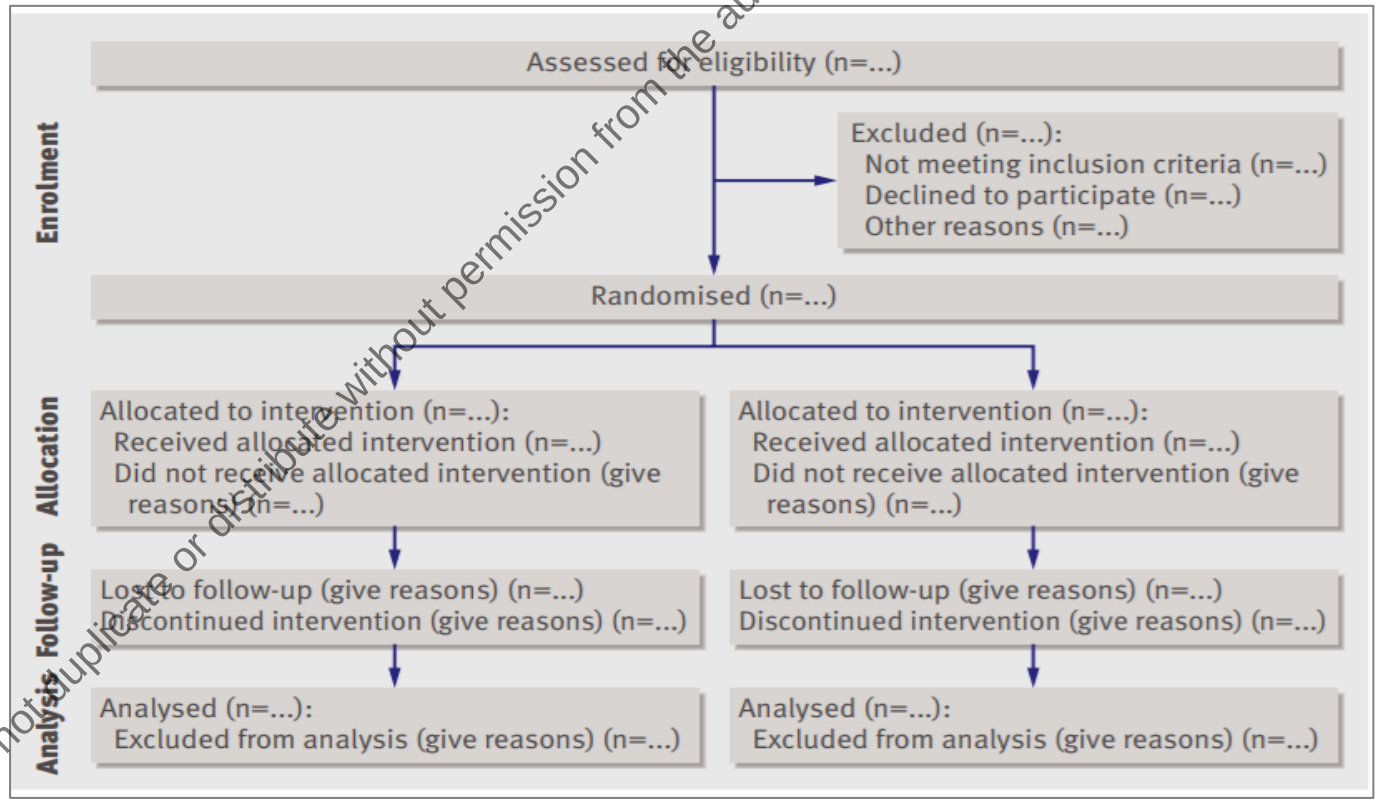


Ng R et al, Ann Oncol 2008.

Phase III Study

CONSORT (Consolidated Standards of Reporting Trials) Statement

- Aimed to improve quality of reporting of randomized clinical trials
- Each study is required to account for **the flow of patients i**n the early stages of recruitment, **treatment assignment, follow-up and analysis.**
- To avoid any attrition bias **ITT (intent to treat) analysis is highly recommended**



Moher D, et al. Lancet 2001; Moher D, et al. BMJ 2010.

Phase III Study Challenges

- Control arm is not an accepted standard treatment
- Sample size too small to detect or rule out a reasonable difference in outcome (failing to find a difference is not the same as proving no difference)
- Sample size so large that difference in clinical outcome is statistically significant but not clinically meaningful
- Making conclusions on the basis of secondary endpoints
- Failure to provide detailed report of toxicity
- Participation of selected patients (inclusion criteria) does not allow for the transfer of results to the general population of patients with the type of cancer under investigation

Adopted from: Ian Tannock, ASCO University, Research Design & Methodology.

Phase III Study Enrichment Design

- Many targeted agents designed to act only against target "biomarker"
- Only patients with biomarker are included
- Appropriate to first test predictive value of any candidate biomarker in phase 2 trial
- ➢ Successful examples: trastuzumab (HER2+ breast cancer), vemurafenib (BRAF-expressing melanoma), crizotinib (ALK rearranged NSCLC), etc.

Chemotherapy +/- Trastuzumab in HER2+ ABC

	Actual Targeted Trial	Hypothetical Non-targeted Trial
N=469	HER-2+	All patients
Response rate	50% vs 32% P<0.001	37% vs 32% P=0.27
One-year Overall survival	22% vs 33% P=0.008 *Slamon, et al. NEJM 2001*	30% vs 33% P=0.45

Piccart M, et al. ASCO 2005.

Drug killed!

Phase IV Post-Marketing Studies

- ...evaluate a **wider population of patients** treated with a new **therapy after therapy is provisionally approved by regulatory agency**
- They can help **to better define** its tolerance and side effects in a wider population
- Usually the same inclusion criteria as for the phase 3 trial are used; therefore **phase 4** data **does not represent real-world data**!
- Often the unstated purpose of such studies is to encourage oncologists to become familiar with the new treatment (sometimes with financial reward) so that they will continue to use it when it is marketed

Adopted from: Ian Tannock, ASCO University, Research Design & Methodology.

Real-world data: Population – Based Studies

- **Efficacy** is the effect on outcome in an **ideal population** selected to take part in a **randomized clinical trials**
- **Effectiveness** is the effect on outcome in the real world **everyday clinical practice** , evaluated by population-based studies

Examples of Efficacy-Effectiveness Gap for Treatments of People With Cancer - Median Survival (months)

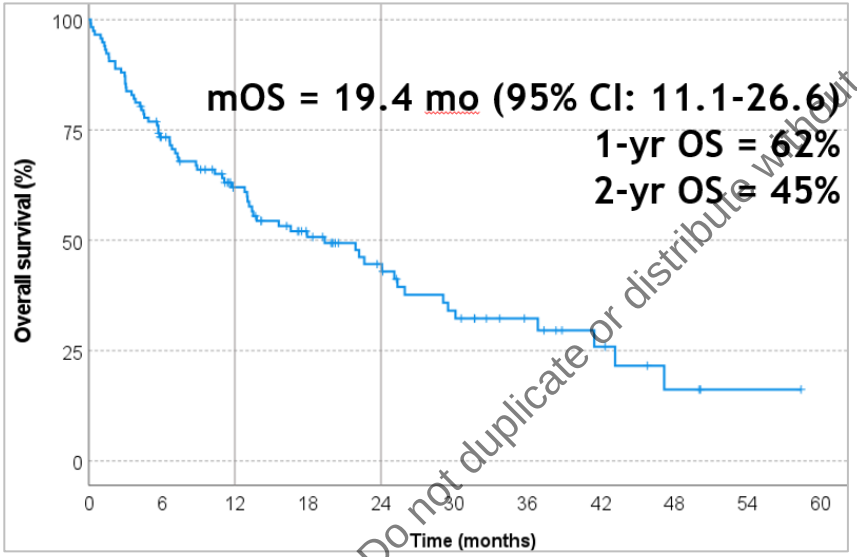
Reference (first author)	Indication	In Trials	Trial Eligible	Daily Practice or Not Trial Eligible	Hazard Ratio, p
Mol et al[3]	Cht for metastatic colorectal cancer	17.0 (ref)	15.7	9.3	1.70, <0.01 1.03, 0.70
Templeton et al[4]	Docetaxel for metastatic CRPC	20.4 (ref)		13.6	1.35, 0.089
Heng et al[5]	TKI for metastatic RCC		28.4	12.5	1.6, <0.001
Westgeets et al[6]	Treatment of metastatic CRPC	35		24	NS
Karim et al[7]	Cht for metastatic pancreatic cancer	11.1		8.2	NS
Aspinall et al[8]	Targeted therapies for advancer RCC	24-30		~ 12	NS

Templeton AJ, et al. J Clin Oncol 2020.

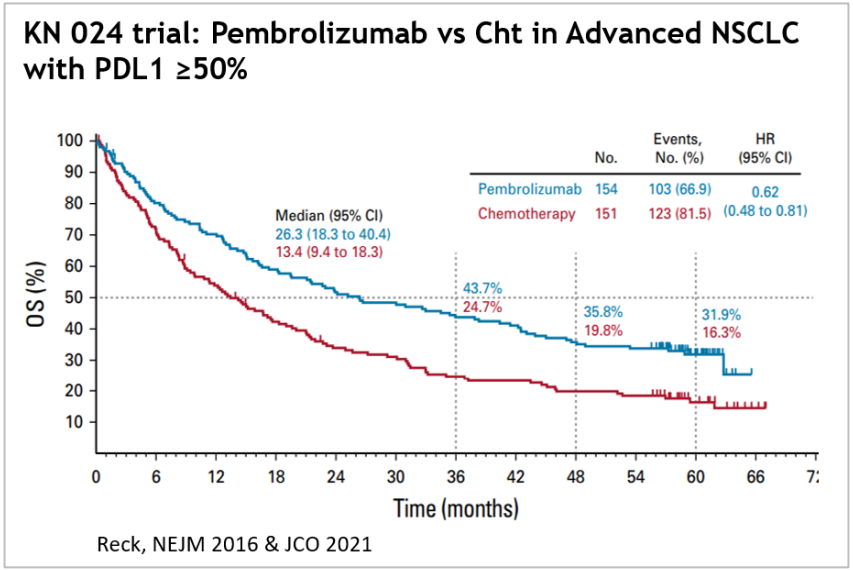
Real-world data: Population – Based Studies

- Population-based cohort studies using prospectively collected data (registry databases) are ideal tools for real-world cancer research!

Overall survival of Advanced NSCLC with PDL1 ≥ treated with Pembrolizumab in everyday practice



Registrational trial



Pelicon V, et al. CEOC 2022

Ethical Principles in Clinical Research

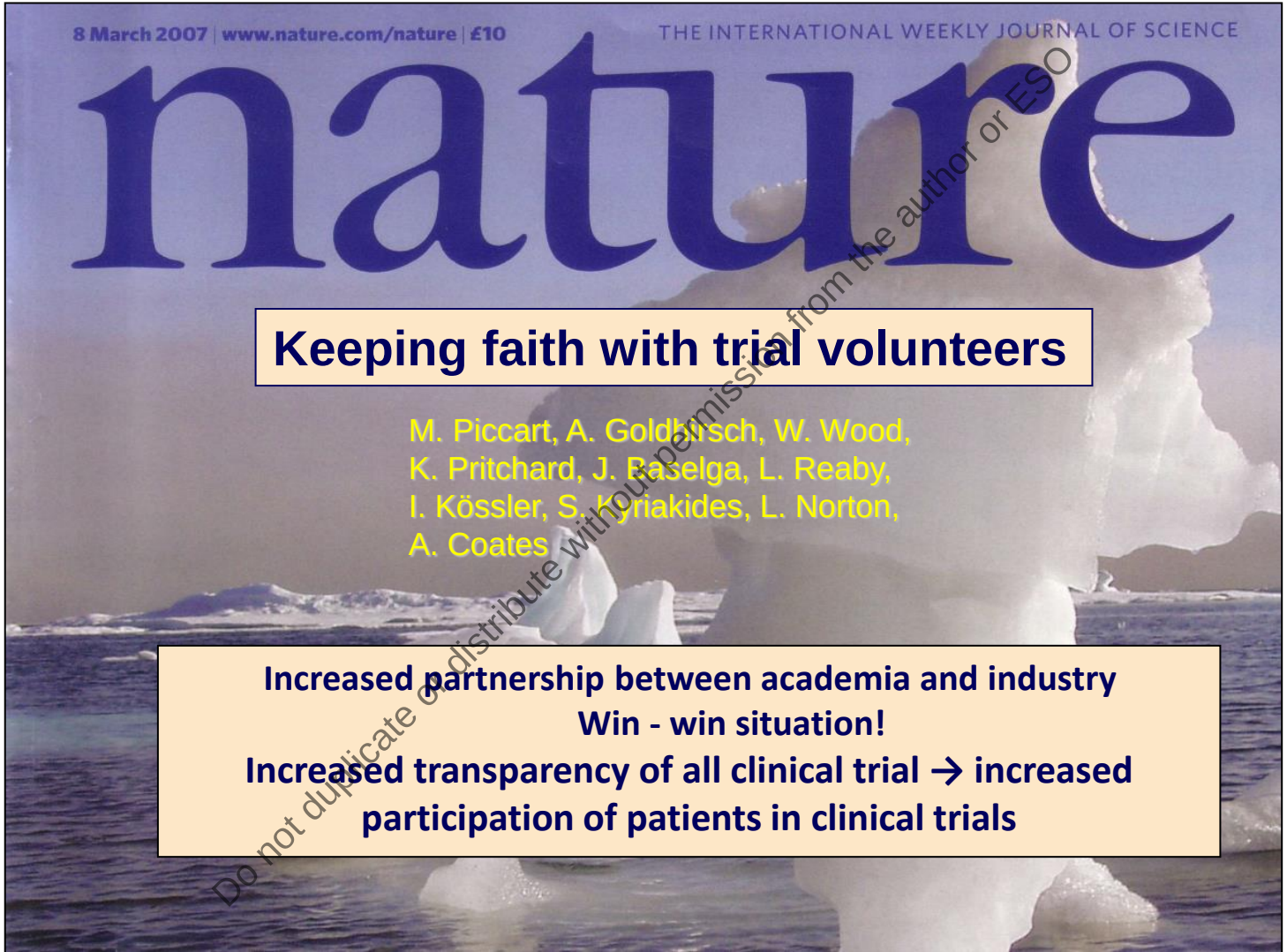
- Clinical trial must **be scientifically sound**, need clear, **detailed protocol**
- Must be conducted according to the protocol approved by **a Research Ethics Board (REB)**
- Each member of **research team** must **be qualified** by education, training, and experience to perform his or her respective task
- Freely given **informed consent** should be obtained from every subject
- Data and **reported results** should be **credible and accurate**
- Must satisfy **ethical principles** in **Declaration of Helsinki**, and meet **IHC/GCP requirements** (https://ichgcp.net/)

➢ Rights, safety, and well-being of trial subjects should prevail over interests of science and society!

Transparency of Clinical Research

- **High level of transparency** is needed **to increase trust** in medical science and to increase **participation in clinical trials**
- Despite many ongoing clinical trials **only about 5% of adult cancer patients** are **included into clinical trials worldwide**

- ICMJE (International Committee of Medical Journal Editors) 2005 – Mandatory registration of clinical trials, only registered trials can be published
- Publication of all (positive and negative) results is required
- Publicly available CTs platforms:
  - WHO, ICTRP: https://trialsearch.who.int/
  - NCI: https://clinicaltrials.gov
  - EudraCT register: https://eudract.ema.europa.eu/



Increased partnership between academia and industry

Win - win situation!

Increased transparency of all clinical trial → increased participation of patients in clinical trials