
Workshop
Developing a cancer drug

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Designing a clinical trial in oncology

Clinical endpoints and predictability of outcome

Comparability of different trials

Regulatory and ethical requirements

Q&A

Developing a clinical plan for a new drug in oncology



Prerequisites

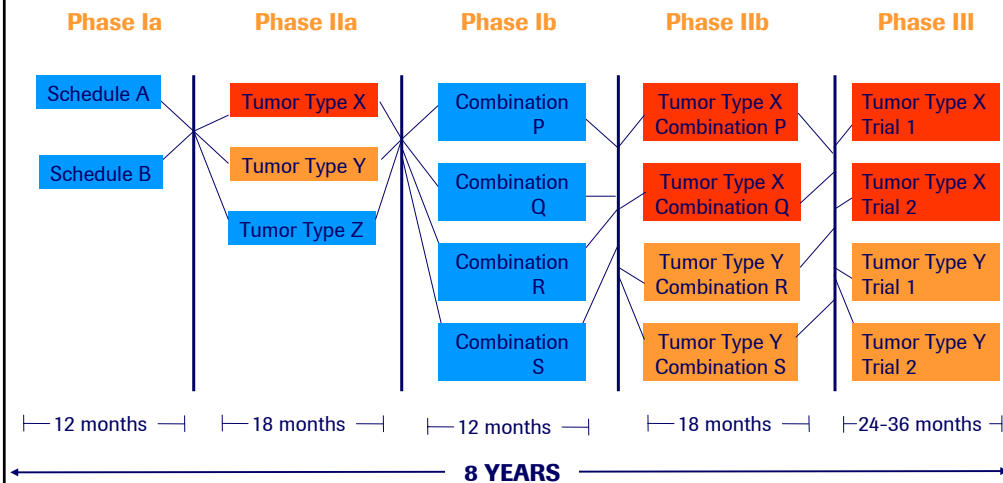
Disease	Target	Drug
Epidemiology - incidence, mortality, natural history Current standards of care Unmet medical need - efficacy, toxicity, convenience Ease of drug development - endpoints, trial design	Prevalence - expression - structural alterations; e.g. mutations, amplification Biological correlates - proliferation - invasion/ metastases Clinical consequences - impact on natural history - drug resistance	Formulation, solubility, stability Preclinical efficacy - dose - schedule - biomarkers Preclinical toxicology - target organs - mechanism related - target-related - 'collateral' damage - idiosyncratic ADME - drug-drug interaction

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Conventional drug development in oncology



A complex undertaking



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How to design a clinical trial in oncology

Traditional drug development paradigm in oncology

Metastatic/ Advanced setting					Adjuvant
Phase Ia	Phase IIa	Phase Ib (combination)	Phase IIb (combination)	Phase III (randomized)	Phase III
Refractory	Failed therapy with proven survival benefit	Refractory	Failed 1 or more prior treatments	Failed 0-1 prior treatments	Post curative surgery
n= 30-40 pts./ study	n= 40-50 pts./ study	n= 30-40 pts./ study	n= 40-50 pts./ study	n= 400-800 pts./ study	n= 2000-8000 pts./study
EPs: - Toxicity - PK	EPs: - RR - Toxicity	EPs: - Toxicity - PK	EPs: - RR - TTP	EPs: - PFS - OS	EPs: - DFS - OS

EP=end point, PK=pharmacokinetics, RR=response rate, TTP=time to progression, PFS=progression-free survival, OS=overall survival, DFS=disease-free survival

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Special drug development challenges in oncology

- Poor understanding of molecular pathogenesis of most cancers
- Poor predictivity of pre-clinical models
- Heterogeneity of tumors
 - Inter-individual
 - Intra-tumoral
 - Clonal evolution over time
- Sicker patient population
- Increasing diversity of available treatments
- Differences in international standards of care
- Lack of dramatic tumor shrinkage with novel targeted therapies
- Long duration of trials
 - Survival determination in trials in metastatic cancer
 - Adjuvant trials

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Typical clinical trial endpoints in oncology

Assessment of different endpoints

Response rate	Time to progression & progression-free survival	Overall survival
<p>Pros</p> <ul style="list-style-type: none"> Most common endpoint used in routine practice Tumor shrinkage clearly attributable to drug Objectively measurable Usually associated with symptom palliation 	<p>Pros</p> <ul style="list-style-type: none"> Increasingly becoming preferred primary endpoint in PIII trials Smaller sample size Shorter follow-up Not impacted by crossover therapy Objectively measurable in most cases 	<p>Pros</p> <ul style="list-style-type: none"> 'Hard' endpoint Reflects the eventual goal of all cancer therapies
<p>Cons</p> <ul style="list-style-type: none"> May not necessarily indicate clinical benefit May not be durable May not correlate with survival benefit 	<p>Cons</p> <ul style="list-style-type: none"> Potential for bias in unblinded trials Rigorous schedule and quality of assessment of disease status essential 	<p>Cons</p> <ul style="list-style-type: none"> May be impacted by subsequent lines of therapy May take a long time to measure Some drugs may provide clinical benefit without increasing OS



Why do adjuvant trials take so long?

- Significant efficacy data in advanced/ metastatic disease generally required before initiation of adjuvant trials
- High hurdles set by standard adjuvant therapy
 - Large sample size to show difference
- Cancer may recur after many years
 - Long time to primary endpoint
- Essential to evaluate the long term safety of the drug
 - Lesser tolerance for side effects

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Comparability of different trials

Why you cannot compare results across trials...

- Differences in disease characteristics
- Differences in prior therapy
- Differences in clinical practice in individual countries, across sites
 - e.g. use of hematopoietic growth factors, supportive care
- Differences in stringency of endpoint measurement
- Differences in patient characteristics
 - Overall health
 - Diet
 - Lifestyle

Results are increasingly difficult/impossible to compare across trials

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Regulatory requirements

FDA vs. EMEA - similarities

- Similar guidance from health authorities regarding requirements for approval
- Primary endpoints in pivotal trials are
 - Progression-free survival
 - Overall survival
- Conditional (EU) / Accelerated (US) approval regulation in place
- Review timelines specified for
 - Standard approval
 - EU 210 days
 - US 10 months
 - Accelerated (EU) / Priority (US)
 - EU 150 days
 - US 6 months

Trials becoming increasingly global in scope and acceptability

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Regulatory requirements

FDA vs. EMEA - differences

FDA

- US oncology NMEs usually accelerated approvals
 - Iressa experience (2002, 2004)
- Advisory Committee (public) process in the US

EMEA

- 1st EU conditional approval
 - Sutent (2006)
- No similar public forum in EU
 - Impact on patient advocacy in EU
- Local interpretation of guidelines for early phase clinical trials in EU
 - National approval of clinical trial applications by health authorities and ethical committees
- EU label perceived as more restrictive and potentially influenced by cost/benefit analysis although cost not official part of approval

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Acceptability of non-EU/US clinical trials

Clear guidelines

Trials conducted in China, India and other developing countries are only acceptable if...

- Study design conforms with EU/US/ICH guidelines
 - Treatment regimen
 - Choice of comparator
 - Dose selection, etc.
- Quality of data is adequate (GCP, GLP)
 - Possibility for auditing of foreign clinical sites by EU/US authorities
- Comparability of study population (age, gender, ethnicity, etc.) to EU/US patient population is shown

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Risk/ benefit ratio – how “clean” must/ can a cancer drug be?

- Metastatic setting
 - Improvement of PFS and/or OS generally necessary
 - Significant toxicity acceptable, e.g.
 - 2 %+ treatment related mortality
 - 20 %+ grade 3/4 toxicities, including some irreversible toxicities
- Adjuvant setting
 - Limited tolerance for serious toxicity
 - Short-term treatment mortality ~ 1 %
 - Grade III toxicity acceptable if reversible
 - Significant tolerance for non-life threatening toxicity

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Appendix

How to choose a comparator and endpoints?

TTP and PFS

- Increasingly becoming the preferred primary endpoint in phase III trials
- Smaller sample size
- Shorter follow-up
- Not impacted by crossover therapy
- Objectively measurable in most cases
- Limitations:
 - potential for bias in unblinded trials
 - rigorous schedule and quality of assessment of disease status essential

Response rate

- Pros**
- Most common endpoint used by clinical oncologists in routine practice
 - Tumor shrinkage clearly attributable to drug
 - Objectively measurable
 - Usually associated with symptom palliation
- Cons**
- May not necessarily indicate clinical benefit
 - may be associated with prohibitive toxicity – e.g. high-dose chemotherapy for breast cancer
 - response may not be durable
 - may not correlate with survival

Tumor markers

- Secreted proteins that can be easily measured in the blood
- Objectively measurable
- Frequently elevated in most common cancers, e.g., colon cancer, ovarian cancer, breast cancer
- Commonly used in clinical practice by oncologists to make treatment decisions
- Not accepted by regulatory authorities as objective evidence of antitumor activity due to less than perfect correlation with radiologically measured disease

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FDA requirements framework

FDA – standard framework

- Federal Food, Drug, and Cosmetic Act Amendment (1962)
 - Demonstration of effectiveness by providing “substantial evidence”
 - “Substantial evidence” defined as “evidence consisting of adequate and well controlled investigations”
 - Generally at least two adequate and well controlled studies, each convincing on its own, required to establish effectiveness
- FDAMA (1997)
 - Single trial may be sufficient if other supportive data exists
 - e.g. evidence from other trials using different dose, populations, regimens, etc
 - single trial must be well-conducted, internally consistent and demonstrate a compelling result

FDA – accelerated framework, subpart H

- Approval based on surrogate endpoints that are reasonable likely to predict clinical benefit
- Generally granted for treatments that provide significant medical benefit over currently available therapy for serious-life threatening diseases
- Most commonly used for oncology and HIV
- Common Oncology Endpoints:
 - Response rate
 - Time to Progression (TTP)
 - Disease free survival (DFS)
- Phase IV trials mandatory

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Key statistics for clinical trials in oncology



Abbreviation	Term	Definition	Example
HR	Hazard ratio	Risk of event occurring; drug arm vs. placebo	HR=0.8
-	Risk reduction	Reduction in risk of event occurring	$1 - HR = 1 - 0.8 = 20\%$
-	Survival	Survival benefit	$(1/HR) - 1 = 1/0.8 - 1 = 25\%$
-	Median time to event	Time when event has occurred in 50 % of the population	X-axis reading on a survival curve at Y value of 50 %
p	p value	Statistical robustness/significance	$p = 0.01 \sim p < 0.05$ is normally regarded as statistically significant