Protocol Development, Design and Analysis of Phase 1 Clinical Trials in Cancer Therapy

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Conflicts

I have no relevant conflicts to disclose

Types of Phase 1 Trials

- Dose finding, first-in-human
- Food effect study
- QTc prolongation study
- Bioequivalence study
- Approved or investigational agent with pharmacokinetic focus (adding of CYP inhibitor)
  - Typically considered drug-drug interaction study
- Investigational agent + investigational agent
- Investigational agent + approved agent(s)
- Approved agent + approved agent(s)
- Approved or investigational agent with pharmacodynamic focus (e.g. evaluation using functional imaging)
- Approved or investigational agent with radiotherapy

What Is Needed To Do A Phase I Study?

An Investigational New Drug Application (IND)

- Provides a means of advancing from pre-clinical to clinical testing (first-in-human)
- Required for products that have not received marketing approval
- May be required for already marketed products
- A formal application to study an intervention in patients
- Sponsor: usually a pharmaceutical company, but can be an academic institution
- Investigator

IND Application

Should include:

- Chemistry, manufacturing, and control information
- Animal pharmacology and toxicology
- Genotoxicity
- Toxicology
- Histopathology
- ***Non-clinical justification for proposed dose/schedule***
- Justification for duration of treatment
- Prior use in humans if applicable
- ***Clinical protocol and investigator information***

Protocol Development: What are the *Primary* Endpoints of a Phase I Trial?

- To characterize and quantify the toxicities of a new agent.
- To determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD).
- To characterize the pharmacology of the agent.
- To assess overall tolerability and feasibility.

Note that in oncology, cancer patients traditionally participate in Phase I testing, not normal volunteers (although some drugs are tested in both).

What are Some Examples of *Secondary* Endpoints in Phase I Trials?

- To assess the extent of preliminary anti-tumor activity.
- To determine if there are pharmacokinetic/ pharmacodynamic relationships (PK/PD).
- For targeted agents, to assess the feasibility and utility of a biological correlative assay.

Increasingly phase I trials have numerous secondary endpoints that sometimes are used as go/no-go decision points for moving forward with a drug

What are the *Key Protocol Elements* Required to Accomplish these Objectives?

- Justification of the starting dose and dose escalation plan.
- Appropriate patient eligibility/ exclusion criteria.
- Definition of DLT, MTD, and recommended phase II dose.
- Pharmacokinetic sampling schedule.
- A study calendar for safety assessments.
- Tumor assessment criteria and schedule.
- Reporting requirements for adverse events and serious adverse events.
- Consent form and other regulatory items.

Definitions of Key Concepts in Phase 1 Trials

Dose-limiting toxicity (DLT):

- Toxicity that is considered unacceptable (due to severity and/or irreversibility) and limits further dose escalation
  - Defined with standard criteria CTCAE 4.1 (criteria that standardize language and severity of adverse events)

- **DLT**
  - defined in advance prior to beginning the trial
  - is protocol-specific
  - Typically defined based on toxicity seen in the first cycle
  - Limits dose escalation (dose-limiting)

- With select agents that have a more delayed toxicity (eg $2^{nd}/3^{rd}$ cycle), time allowed for DLT definition being re-evaluated

Typical Definitions of DLT

Dose escalation proceeds, as planned until *DLT occurs*, as typically defined by:

- Grade 4 neutropenia for $\geq$ 5 days, or complicated by fever requiring antibiotics.
- Platelets < 25, 000/uL.
- Non-hematologic toxicity $\geq$ grade 3 (tailored for agent).
- Chronic $\geq$ grade 2 toxicity.

Once DLT occurs, more patients are treated to assess the frequency.

Definitions of Key Concepts in Phase 1 Trials

- **Examples of chronic DLTs – can be associated with daily dosing:**
  - Threshold for DLTs is lower
  - Some Grade 2 toxicities may be unacceptable and intolerable due to their persistence and lack of time period for recovery
  - **Examples:**
    - Grade 2 intolerable or worse non-hematologic toxicity despite supportive measures: Nausea, vomiting
    - Grade 3 or worse hematologic toxicity
    - Inability to complete a pre-specified percentage of treatment during the cycle due to toxicity (e.g. missing 10-15% of doses)

Definitions of Key Concepts in Phase 1 Trials

- **Maximum Administered Dose (MAD), Maximum Tolerated Dose (MTD): confusing**
  - Usage of these 2 phrases varies with country
  - Typically, *MTD is used* and generally defined as the highest dose where less than 30% of patients have DLT in first cycle
  - Should treat enough patients at MTD to provide confidence that it is tolerable
- **Recommended Phase 2 Dose (RPTD or RD):**
  - Dose associated with DLT in a pre-specified proportion of patients (e.g. $\leq$ 33%) – dose that will be used in subsequent phase 2 trials

Why the **MTD** is ***Not Always Equivalent*** to the **RP2D!!!**

- **DLT** and **MTD** are used for the purposes of making decisions about *dose escalation*.
- The occurrence of DLT in the *first* course of therapy is what limits dose escalation.
- The phase II dose should incorporate *multiple-cycle toxicity* (including DLT), tolerability, dose reductions, and dose delays.
- This distinction should be clarified in the protocol.

Definitions of Key Concepts in Phase 1 Trials

Optimal biological dose (OBD):

- Dose associated with a pre-specified desired effect on a biomarker
- Examples:
  - Dose at which $\geq$ X% of patients have ***inhibition of a key target*** in tumor/surrogate tissues
  - Dose at which $\geq$ X% of patients ***achieve a pre-specified immunologic parameter***
  - Dose at which $\geq$ X% of patients achieve a ***specific drug exposure*** that correlates with preclinical activity
- Challenge with defining OBD is that the "desired effect on a biomarker" may not be known or validated before initiation of the phase 1 trial

Definitions of Key Concepts in Phase 1 Trials

Expanded Cohort: Enrollment of patients at the end of a Phase I trial of a particular tumor type and/or genetic subtype.

- Increasingly utilized in Phase I trials and results have been submitted to the FDA for NDAs (crizotinib).
- At times can be as large as “mini-Phase II” and these designs are criticized for not having statistical parameters
- Often used to justify launch of Phase III following Phase II or for accelerated approval

Phase 1 Trials: Fundamental Questions

- ***At what dose do you start?***
- What type of patients?
- How many patients per cohort?
- How quickly do you escalate?

Preclinical Toxicology

- Typically a rodent (mouse or rat) and non-rodent (dog or non-human primate) species

- Reality of animal organ specific toxicities – very few predict for human toxicity
  - Myelosuppression and GI toxicity more predictable
  - Hepatic and renal toxicities – large false positive

- Toxicologic parameters:
  - LD_{10} – lethal dose in 10% of animals
  - TDL (toxic dose low) – lowest dose that causes any toxicity in animals
  - NOAEL – no observed adverse effect level

Justification of the Starting Dose

- 1/10th of the dose that leads to deaths in 10% (LD_{10}) of rodents is used in man.
- 1/6-1/3rd of the lowest toxic dose (TDL) is used in larger animals
- This dose is usually in mg/kg, so it must be converted to mg/m^2 for man- and there are conversion tables for this.
- If toxicology is performed in several species, then the starting dose is used from the *most sensitive* species.

This is very rudimentary and traditional, a lot of work is going into refining these rules, particularly with targeted agents

Phase 1 Trials: Fundamental Questions

- At what dose do you start?
- ***What type of patients?***
- How many patients per cohort?
- How quickly do you escalate?
- What are the endpoints?

Patient Eligibility Criteria: Inclusion

The purpose of ***inclusion*** criteria are to define the minimum requirements of the phase I population under study:

- Regulatory: Signed consent, age $\geq$ 18.
- Disease: Failed standard therapy (or no standard therapy exists), histologically confirmed.
- Constitutional: Performance status 0-1/2 (out of bed > 50%)
- Organ function: ANC $\geq$ 1500/uL; plts $\geq$ 100 K/uL; hgb $\geq$ 9 g/dL; creatinine $\leq$ 1.5 g/dL, SGPT/SGOT 2-5 X ULN, total bilirubin $\leq$ ULN.
- Mental: Able to comprehend and comply with study requirements.

Patient Eligibility Criteria: ***Exclusion***

The purpose of ***exclusion*** criteria are to ***minimize the risks*** of drug-related toxicity, thus some are agent-specific:

- Constitutional: Almost all phase I studies exclude pregnancy due to the lack of information on fetal effects, as well as other serious underlying medical diseases.
- Prior therapy: For myelosuppressive compounds, patients with extensive prior therapy are excluded.
- Cardiac: Patients may be excluded with known underlying diseases, or may require a MUGA, EKG, etc.
- Gastrointestinal: Studies of oral drugs exclude patients with refractory N/V or extensive bowel surgery.

Phase 1 Trials: Fundamental Questions

- At what dose do you start?
- What type of patients?
- ***How many patients per cohort?***
- ***How quickly do you escalate?***
- What are the endpoints?

Phase 1 Trial Basic Principles

- Begin with a safe starting dose
- Minimize the number of pts treated at sub-toxic (and thus maybe sub-therapeutic) doses
- Escalate dose rapidly in the absence of toxicity
- Escalate dose slowly in the presence of toxicity

Phase 1 Trial *Assumptions*

The higher the dose, the greater the likelihood of efficacy

- Dose-related acute toxicity regarded as a surrogate for efficacy
- Highest safe dose is dose most likely to be efficacious
- This dose-effect assumption is primarily for cytotoxic agents and may not apply to molecularly targeted agents

Mechanism-Based Toxicity

- With drugs that interact with a target on normal tissues, mechanism-based toxicity is a type of biomarker:
    - skin rash, diarrhea- EGFR agents
    - hypertension, proteinuria- VEGF agents
- Overall, not unlike the myelosuppression and GI effects (mucositis, diarrhea) observed with traditional cytotoxic agents
- If a tissue-based biomarker is difficult to obtain, mechanism based toxicity may establish biological activity- and you don't need to biopsy the patient!
- *This is why reaching an MTD with a biological agent may in fact still be relevant*

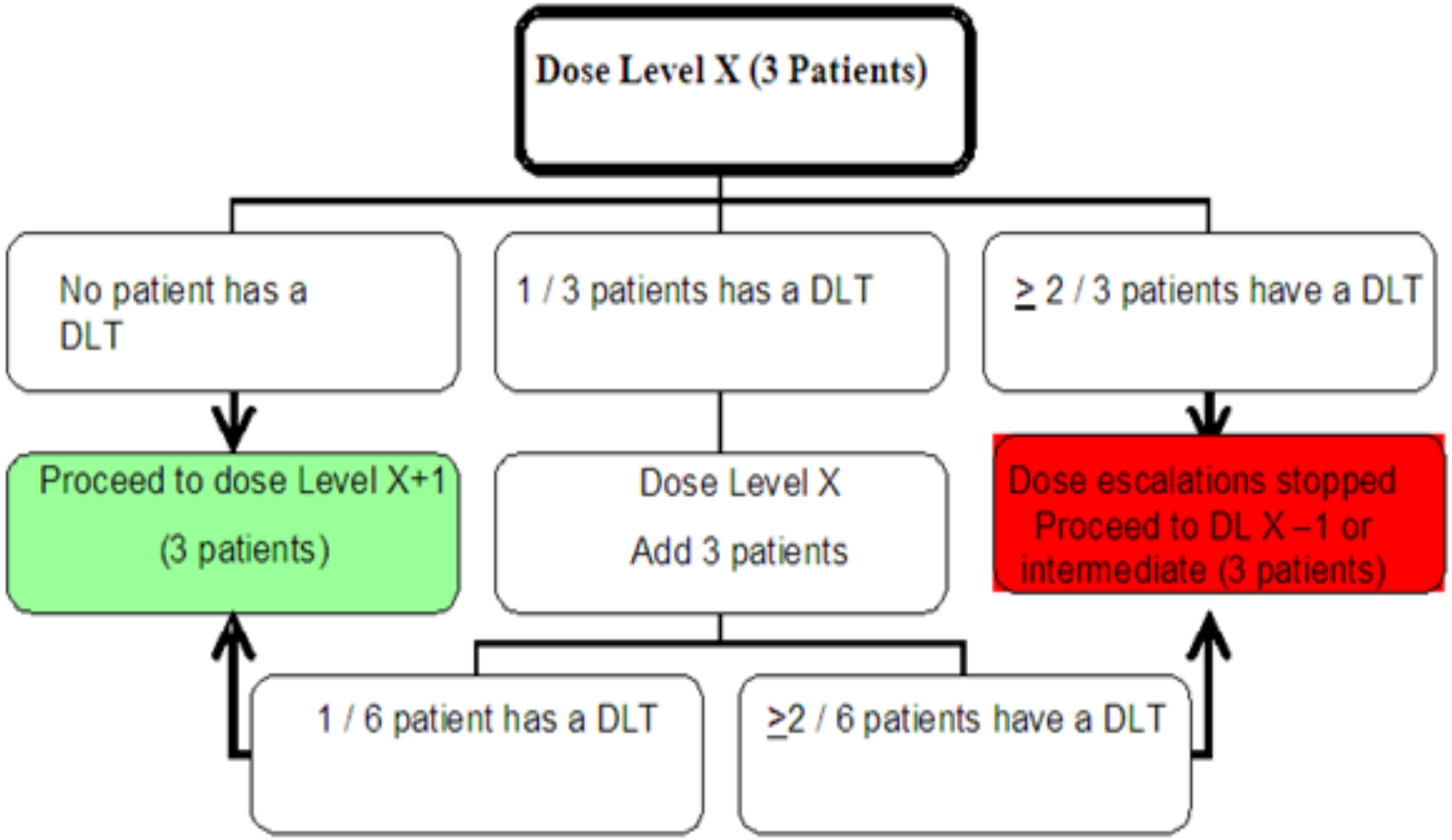
Dose Escalation Scheme and Schedule
Factors to be considered

- Are there significant inter-species differences in tolerance? (may want faster escalation)
- Is the drug a typical cytotoxic agent or more targeted agent?
- What is the PK half-life? (short vs. long)
- Does the therapeutic index appear narrow? (slower dose escalation)
- Is cumulative toxicity an issue? (may need to assess longer than 30 days for dose limiting toxicity)
- Is there schedule-dependent toxicity or efficacy? (continuous vs. intermittent)
- What is the formulation? (can't give daily IV)

Frequently Used Dose Escalation Schemes

- Modified Fibonacci: sequentially smaller increments of dose escalation- 100%, 67%, 50%, 40%, 33%, etc.
- Doubling method: doubling of the dose until any grade 2 drug-related toxicity, then reversion to modified Fibonacci or fixed (25-40%) dose escalation.
- Pharmacologically guided: use of real-time PK data to guide escalation with intent to achieve target AUC.
- Continual Reassessment Method (CRM): statistically-guided dose escalation that uses real-time toxicity data to predict the dose closest to the MTD.
- Accelerated Titration Design: a constellation of designs that utilize single-patient toxicity-guided escalations (intra-patient dose escalation allowed).

Phase I "Standard" 3 + 3 Design



Bottom line is that there are many ways to design a dose escalation scheme and a lot of flexibility as long as it is safe for patients!

Dose Escalation: Lessons Learned

- Adaptive dose escalation methods have demonstrated that cohort size can be toxicity-based and not fixed at 3 or 6.
- With biological agents, its important to enroll sufficient numbers of patients to assess dose-response relationships of PK and PD.
- Currently, the trend is towards standard cohort sizes during dose escalation with cohort expansion around the MTD to 10-12 patients
- There are also novel adaptive designs in development that can incorporate PK/PD data and enhance enrollment around biologically-active dose levels

Clinical Development of Novel Agents Challenges

1. **Difficulty in determining the optimal dose/schedule in phase I**
   - *MTD versus biologically efficacious dose?*
2. **Absent or low-level tumor regression as single agents in unselected patients**
   - *Predictive biomarker may be needed early to enhance efficacy*
   - *Problematic for making decisions regarding phase II trials*
3. **Need for large randomized trials to definitively assess clinical benefit**
   - *This can result in underpowered randomized phase II trials or high risk phase III trials*

Approaches That Have Been Utilized in Early Clinical Trials of Novel Agents

- Novel/rapid dose escalation
- Use of biological correlative studies to assess biological effects
- Alternative endpoints to the Maximum Tolerable Dose (MTD)- Optimal Biological Dose (OBD)
- Functional imaging studies (PET, DCE-MRI) to determine tumor-derived biological effects non-invasively.
- Revision of response criteria to include disease stability as a “clinical benefit”
- Early phase I combination studies with chemotherapy (“Octopus” trials).

Biological Correlative Studies: *Why are They Important?*

In early clinical trials of targeted agents:

- Normal tissue may not be used as a surrogate for effects, as is the case with standard cytotoxic agents
- The relative lack of toxicity to normal tissue often means that deriving the MTD, or optimal biological dose may be difficult.
- Therefore, biological correlative studies may be used to derive the best dose and schedule of an agent, *and*
- To determine whether the drug is inducing a biological effect in the patient before advancing to phase II.

Pitfalls of Phase 1 Trials

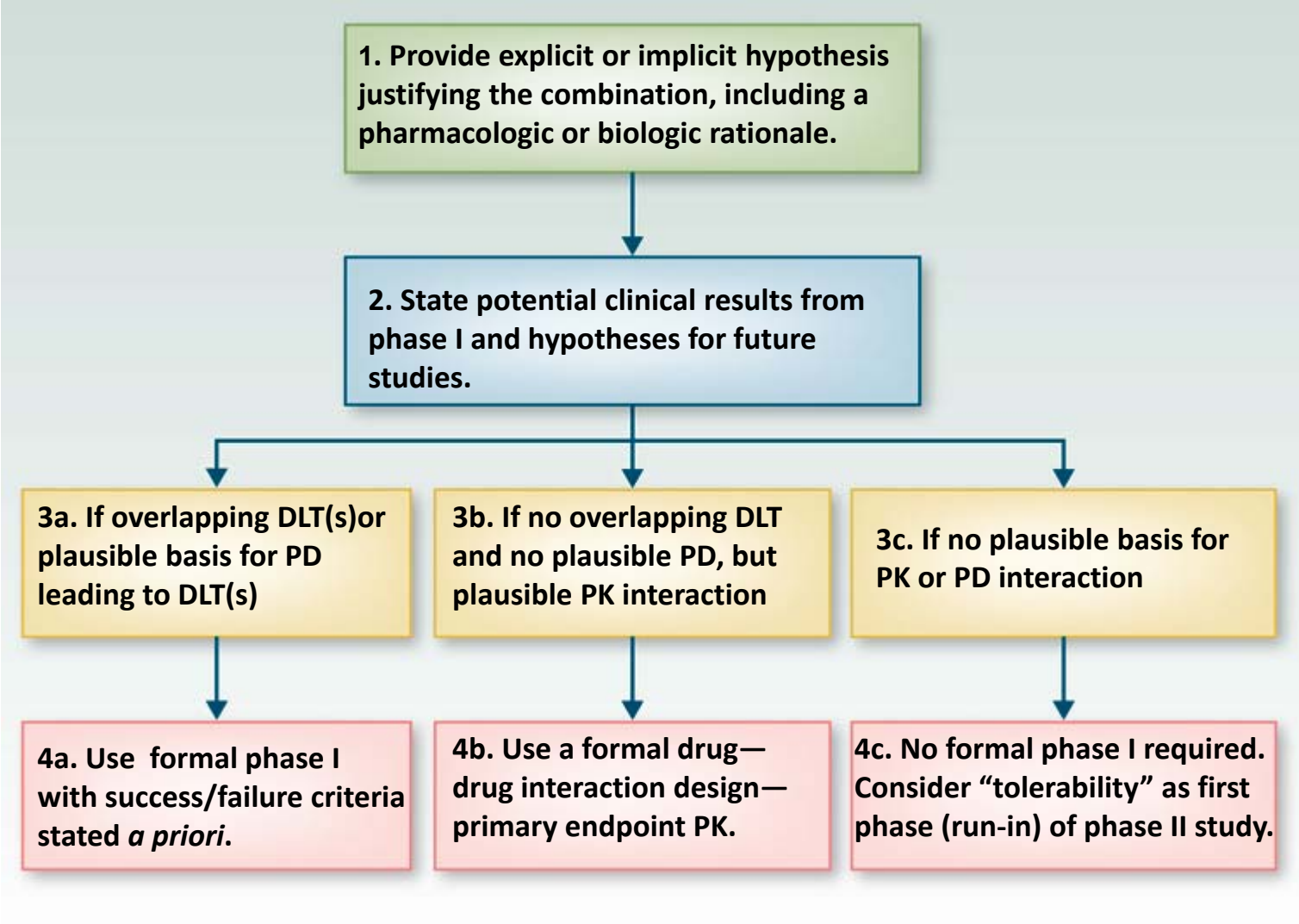
- ***Chronic and cumulative toxicities usually cannot be assessed & may be missed***
  - Most patients do not stay on trial beyond 2 cycles
- ***Uncommon toxicities will be missed***
  - Too few patient numbers in a phase 1 trial
  - Reason for toxicity evaluation & reporting through phase IV drug testing
- ***Exactly what tumor or tumor cell subset are you treating***
  - Heterogeneity
  - Resistance

Phase I Trial Combination Trials

Combination phase I trials:

- New drug A + Standard drug B
- Need to provide rationale: why add A to B?
- Need to think about overlapping toxicity in your definition of DLT
- Ideally keep standard drug dose fixed and escalate the new drug (e.g. 1/2, 2/3, full dose)

Process for determination of the Phase I combination trial design: pharmacodynamic (PD); pharmacodinetic (PK)



Paller, Bradbury, et al. Clin Cancer Res; 20(16); 1-8, 2014

IDSC Consensus Recommendations for Evaluation of Combination Therapies

Recommendations	
1	All phase I combination trials should state an explicit or implicit hypothesis justifying the combination, including a pharmacological or biological rationale that includes at least one of the following: *in vitro* data, *in vivo* data, or clinical data. The rationale may extrapolate from results with similar drugs and may be based on *in silico* analyses. The hypothesis supporting the combination should be clearly stated in the protocol.
2	The potential results and next steps of the development plan of the combination should be clearly described. The description should include two parts: the rationale for why the biologic or pharmacologic interactions should translate into clinical effects, and one or more examples of phase II studies to test the hypothesis. The phase II example(s) should follow the guidelines of the Phase II Consensus Recommendations of the NCI's IDSC CTD Task Force.
3	The design of combination phase I studies should address the following three factors: overlapping dose limiting toxicities (DLTs); a plausible mechanistic basis for a pharmacodynamic interaction leading to DLTs; and a plausible mechanistic basis for a pharmacokinetic interaction.
4	Selection of the clinical trial design should be based on the scientific rationale, underlying data and hypothesis for the combination, and the intended development plan for the combination
A	Combination therapies with overlapping DLTs or a plausible basis for a pharmacodynamic interaction leading to DLTs require formal phase I evaluation. The selected doses to be studied should be justified based on the specific phase II plans.
B	Combinations without overlapping DLTs and without a plausible basis for pharmacodynamic interaction, but with a plausible pharmacokinetic interaction, should be studied using a formal drug-drug interaction design. The primary endpoint is pharmacokinetics. Crossover design is often optimal.
C	Combinations without overlapping toxicities, without a plausible basis for a pharmacodynamic interaction leading to a DLT, and without a plausible basis for a pharmacokinetic interaction do not require a formal phase I study.

Design of Phase I Combination Trials: Recommendations of the Clinical Trial Design Task Force of the NCI Investigational Drug Steering Committee: Clin Cancer Res 2014;20:4210-17.

Opportunities/Pitfalls: Combination Therapies

Opportunities	Pitfalls
Validate novel biological hypotheses	Unreliable pre-clinical models
Synergize anti-tumor effect without synergizing toxicity	Optimal selection of drugs and targets to study in combination
Increase therapeutic index/window	Optimal sequence and dose of combination therapy
Synthetic lethality: optimize combination use of single agents with limited single agent activity	Risk overlapping toxicity
Counteract primary and secondary resistance	Lack of standard design for phase 1 / 2 for combination therapies
Develop novel indications for existing and approved drugs	Competing interests of researchers, corporations and / or institutions to combine treatments

Yap, Omlin & de Bono, JCO 2013

The Successful Phase 1 TEAM

- The Patient
- Investigators
- Scientists
- Fellows
- Data Coordinators
- Pharmacists
- Lab Personnel: pharmacology, reference, PK, PD
- Bio-statisticians
- Radiologists, pathologists, IR
- Finance
- And many others…….

Thank You!