

Development of Rational Drug Combinations with Investigational Targeted Agents



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Introduction and Background

Recent advances in basic research have led to a greater understanding of the molecular processes that underlie many complex diseases such as cancer, cardio-vascular disease, infectious diseases etc. We are now beginning to understand the complexity of disease biology, which usually involves multiple redundancies and crosstalk between molecular pathways. Thus, targeting a single step along a given pathway or even targeting a single pathway may not be effective to combat these diseases. Whole genome sequencing holds the promise of defining the entire catalog of somatic mutations present in each cancer under treatment, with the exciting prospect of the development of highly individualized combination therapies. In infectious diseases genomic and post-genomic approaches suggest that pathways in microbes and host cells can be targeted simultaneously to affect disease progression and elimination of pathogens. This offers the possibility of both reducing the risk of developing resistance and prolonging the effectiveness of antimicrobial therapies. These approaches require combinations of drugs and/or biologics to be developed simultaneously, rather than as individual entities. The lack of a clear regulatory structure to explore these prospects is clearly a barrier to progress.

The challenges facing development of safer and more effective therapies lie both with the specificity of new targeted agents and the known complexity of these diseases. Clinical evaluation of combinations of new agents (rather than the individual components) that inhibit multiple molecular targets is therefore the logical next step in targeted drug development. Frequently, to gain approval of two New Molecular Entities (2NMEs) in combination, a 4 arm trial (Drug A vs. Drug B vs. Drug A+B vs. SOC) is used to isolate and identify the effect of each drug in the combination. However, based on a better understanding of molecular biology and drug pharmacology, this may not be necessary in all cases particularly when the single drug arms have been shown to be inactive or modestly active pre-clinically, i.e. only the combination of the two NMEs holds the promise of improvements when compared to the standard of care. In this setting the use of a single agent arm in a clinical trial setting may even be considered unethical. These issues warrant a re-examination of our current developmental and regulatory model which is largely based on assessing the efficacy and toxicity of a single new investigational agent acting alone.

General Development Considerations

In order for 2 (or more) New Molecular Entities (NMEs) to be considered for combination drug development they should meet one or more of the following criteria:

- A strong biological rationale for using the NMEs in combination e.g. selective inhibition of two targets in the same pathway, inhibition of a primary and compensatory pathway, inhibition of the same target at different binding sites, targeting pathogens and the host, etc.

- Evidence of a greater than additive effect of the 2NME combination compared to the activity of either agent alone in *in vitro* cell lines and/or appropriate *in vivo* pre-clinical models.
- Pre-clinical characterization of the toxicity profile of each individual agent as well as the combination according to current ICH guidelines to determine any additive toxicities of the combination as well as characterize potential drug-drug interactions.
- Whenever possible, it is desirable to develop pharmacokinetic (PK) /pharmacodynamic (PD) markers for each of the drugs tested to demonstrate proof of mechanism of the individual agents, as well as the combination.
- Co-development of validated biomarkers to assess pathway inhibition or activity/effectiveness of the combination along with selection of the appropriate patient population is highly encouraged.
- Expansion cohort(s) in selected patient populations (i.e. with specific signaling alterations, mutations or in a particular subset of patients) may be considered and utilized to demonstrate evidence of activity of the 2NME combination. When the recommended dose for the combination is established early, the option to conduct the entire phase 1b trial in the same selected patient population is also highly encouraged.

Dosing Determination

Dosing determination for any new drug involves many complicated considerations. When 2 (or more) NME are in development for use in combination, dosing determination becomes increasingly complex. Strategies for determining optimal dosing of a 2NME combination will likely need to be developed on a case by case basis to consider factors such as pharmaceutical and pharmacological characteristics of the proposed 2NME combination, potential clinical indication(s), intended patient population, and method of administration (e.g., route, sequence, fed or fasting, etc.). However, general considerations include:

- Thorough characterization of the safety profile of each individual agent in Phase I studies (maximum tolerated dose (MTD), biologically active dose (BAD), dose limiting toxicity (DLT)). The decision to proceed with agent development would depend in part on whether the observed exposure-toxicity relationship of each drug as a single agent is adequate to consider its use in combination.
- The pharmacokinetic (PK), pharmacodynamic (PD) and metabolic characterization of each individual component in humans may also benefit from "Phase 0" micro dosing, the caveat being that micro dosing may be misleading as pharmacokinetic and drug interactions can change at therapeutic doses.
- Sequential testing in an individual healthy volunteer may be considered (i.e. test the subject with drug A, then drug B, then A+B) especially if toxicity and drug

resistance is not an issue. However, the use of healthy volunteers remains controversial, and would be unlikely to be used for the study of a regimen that includes a cytotoxic agent in oncology. Therefore, great caution must be used if healthy volunteers are to be exposed to potentially toxic agents.

- Determining the biologically effective dose or biologically active dose may require use of biomarkers to determine that each drug individually is able to inhibit its specific target and that the combination is also able to inhibit the targeted pathway(s). For studies in oncology, since paired tumor biopsies are difficult to obtain, validated surrogate tissues may, in very specific instances, need to be assayed to ensure that each of the drugs can inhibit their targets. However, for antibacterial or parasitic agents where the efficacy target does not reside within the host, inhibition of bacterial growth is the required endpoint and inhibition of pathways is not a relevant biomarker for drug effectiveness.
- A stepwise dose escalation scheme (increase drug A in a cohort, then increase drug B in the next cohort) could also be employed. The starting doses and magnitude of the dose steps would be informed by the single agent trials and by the preclinical combination studies. In addition, the dose escalation steps could also be informed by the clinical and biomarker observations in the trial.
- The use of biomarker and imaging biomarker defined endpoints (as in a single agent trial) for the combination is highly encouraged, if the assays have been qualified. However, biomarkers may not be necessary in all combination cases. For e.g. this concept may not be applicable to a broad range of antibacterial infections, because the treatment course is usually short, and sensitive and reliable biomarkers are usually not available.
- While, in general, determining optimal dosing is based on safety and toxicity profiles obtained during Phase Ia, there may be select situations that warrant basing dose determination at some other stage of the trial.
- Fixed dose, co-formulated combinations may be preferable for higher levels of patient compliance and discouraging inappropriate use of individual NMEs. However, this would depend on the method and mode of administration (i.e. in-patient or patient administered).

Examples and Decision-Making Criteria of 2NME Development

The following examples are meant to illustrate potential scenarios in which modifications to a four-arm factorial trial design for the development of 2NMEs would be appropriate. This is; however; not meant to exclude other possible situations where modifications to a traditional trial design would be appropriate.

1. Synthetic Lethality:

Each NME is individually inactive or modestly active except in genetically defined models (e.g., a specific background mutation). The specific genetic background where

each individual NME is active may not be broadly representative of the disease population. However, when the 2NMEs are used in combination, they exhibit highly potent activity and further, this activity would be detected in multiple representative model systems (various cell lines and/or animal models). In this example, the modest activity of each agent alone precludes a regulatory process for single agent approval and would support evaluation of an alternative developmental model for the 2NME combination.

Proposed development plan:

- 1) Thorough characterization of the safety profile of each individual agent in Phase Ia studies.
- 2) Evaluation of the safety and toxicology profile of the 2NME combination (Phase 1b) to determine maximum tolerated dose of the combination as well as dose limiting toxicities of the combination.
- 3) Demonstration of proof-of-concept for the 2NME combination in Phase II compared to SOC. The implication being that the individual NMEs are not being proposed as single agents with their use being limited to the proposed combination therapy only.
- 4) An alternative design to consider for components moderately active as single agents could be a potential 3-arm design, A or B versus A+B versus SOC, with patients on single agent (A or B) who progress crossing over to combination (A+B).
- 5) Standard two-arm Phase III trial design comparing 2NME combination to SOC.

2. Co-Enhancement:

Each NME is modestly active as an individual agent in model systems, but the combination demonstrates greater than additive activity in the exact same model systems. Therefore, a multiple arm Phase II trial may be sufficient to demonstrate the advantage of the combination, and allow for a 2 arm Phase III trial comparing the combination to the SOC.

Proposed development plan:

- 1) Thorough characterization of the safety profile of each individual agent in Phase Ia studies.
- 2) Evaluation of the safety profile of the 2 NME combination (Phase Ib). Thus, the proposed Phase Ia/Ib development plan would be identical to that for the synthetic lethality situation described above with the objective of providing adequate characterization of the safety profile of each individual agent and the 2NME combination as well as the appropriate dose selection for each agent in the 2NME combination.

- 3) Demonstration of proof-of-concept with a 4-arm comparison of the 2NME combination to each agent alone and to SOC during Phase II of development. An adaptive trial design might be employed: initially testing the 2NME combination versus SOC versus the single agent arms (A+B V SOC V A V B) which can be dropped early when or if evidence of greater than additive activity for the 2NME combination is obtained.
- 4) Proof-of concept for the combination, and the contribution of each agent to the combination, could be determined without exposing large numbers of patients typically required for Phase III trials to therapeutic agents with modest activity. This could potentially be done by using alternative endpoints to show that each agent independently contributes activity (distinct from benefit) to the 2 NME combination. For example, in Oncology, evidence of sufficient activity to proceed to Phase III could be provided by a Progression Free Survival (PFS) vs. Overall Survival (OS) comparison between A+B and SOC, whereas evidence of active contribution to the combination would be achieved by comparing A+B vs. A and A+B vs. B on the activity endpoint such as tumour size, PET. MRI etc. If there was still any doubt remaining on the contribution of each endpoint after Phase II, small arms could be added to Phase III and potentially dropped after an interim (an adaptive trial design).
- 5) Standard two-arm Phase III trial design comparing 2NME combination to SOC

3. Uni-Enhancement:

One of the NMEs is inactive or minimally active in model systems, the other NME is modestly active in the same model systems but the combination is highly potent in the model systems. An example of this situation would be where the minimally active NME's role is to prevent or slow development of drug resistance -- such as amoxicillin in combination with clavulanate. Amoxicillin, the anti-microbial is the more active NME, while clavulanate serves to prevent amoxicillin being broken down thus acting against the resistance factor, not against the microbe.

The more active NME will require greater scrutiny and should be studied as a single agent in Phase II. In contrast, the minimally active agent may not require study as a single agent beyond initial Phase I studies.

Proposed development plan:

- 1) Thorough characterization of the safety profile of each individual agent in Phase Ia studies.
- 2) Evaluation of the safety profile of the 2 NME combination (Phase Ib).
- 3) Demonstration of proof-of-concept with a 3-arm comparison of the active agent alone to SOC and to the 2NME combination during Phase II of development. However, under certain conditions add on therapy may be employed i.e. the active NME is started and at the time when there is a negative change to the slope of response, the 2nd NME is added to demonstrate its contribution to enhancement.

- 4) Standard two-arm Phase III trial design comparing 2NME combination to SOC.
- 5) Rather than the conventional Maximum Tolerated Dose, it may be more appropriate to consider the first agent in terms of the Minimal Effective Dose. While this would require additional testing, one may achieve all the enhancements at a low dose and there is no reason to stress the system with higher doses, even if they are tolerable.

In all three cases the Phase I studies will involve individual assessment of each NME to provide adequate characterization of the safety profile of each individual agent and the 2NME combination as well as the appropriate dose selection for each agent in the 2NME combination.

Other Considerations: Measurement of Drug Resistance

- Measurement of resistance would depend on the proposed indication for use (anti-viral, antibiotic, cancer etc). The level and rate of resistance acquisition may influence choice(s) of combinations.
- Reliable markers of resistance acquisition and rate of development (*in vitro/in vivo*) would be useful and development of these should be encouraged.
- Drug resistance could be indirectly tested by a study with at least two arms one being the active drug A vs. drug A + drug B with B being the resistance modulator. Superiority of the combination may indicate reversal or prevention of resistance. The latter situation could be partially assessed by allowing for crossover from the single agent arm to the combination arm upon disease progression and subsequently assessing secondary responses.
- A time-to-event design is probably the most useful, such as Time to Progression (TTP) or Progression Free Survival (PFS). More sophisticated approaches such as biopsies of residual tumor lesions would require prospective validation.

Appendix 1: Contributors

Jeff Allen, Ph.D, Friends of Cancer Research

Adam Clark, Ph.D, Lance Armstrong Foundation

Ronald DePinho, M.D, Dana Farber Cancer Institute

James Doroshow, M.D, National Cancer Institute

Matthew Ellis, M.B, B. Chair, Ph.D, Washington University, St.Louis

Charles Erlichman, M.D, Mayo Clinic

Carol Fabian, M.D, University of Kansas Cancer Center

Rasika Kalamegham, Ph.D, Friends of Cancer Research

Bruce Kimler, Ph.D, University of Kansas Cancer Center

Gary Nabel, M.D, Ph.D, National Institute of Allergies and Infectious Diseases

Richard Schilsky, M.D, University of Chicago

David Sidransky, M.D, Johns Hopkins University

Ellen Sigal, Ph.D, Friends of Cancer Research

Stephen Spielberg, M.D, Ph.D, Children's Mercy Hospitals

Maxine Stoltz, Ph.D, University of Kansas Cancer Center

Scott Weir, PharmD, Ph.D, University of Kansas Cancer Center

James Zwiebel, M.D, National Cancer Institute