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PANEL 4

Development of Rational Drug Combinations with Investigational Targeted Agents

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Introduction and Background

Recent research advancements have identified molecular mechanisms underlying cancerous transformation and growth, leading to a new generation of therapies. Key signaling intermediates and genetic mutations associated with oncogenic cell-cycle regulation have been identified as specific targets for the development of new therapies that would be less toxic and more effective than currently available interventions. Progress has also been made in the understanding of how extracellular factors; such as hormones and growth factors; can influence the progression of tumor growth. For example, targeted agents against HER2 (trastuzumab) and Abl (imatinib) have altered the natural history of the diseases in populations for which they were initially developed. However, in the case of other cellular targets, such as Epidermal Growth Factor Receptor (EGFR) in colorectal cancer and mammalian target of rapamycin (mTOR) in renal cell cancer, clinical results have been more modest.

The challenge facing the development of safer and more effective therapies can lie both with the specificity of new targeted agents and the complexity of disease biology, which usually involves multiple redundancies and pathway crosstalk. By selectively and specifically inhibiting one aspect of tumor cell growth or survival, the therapeutic effect may be lessened by concomitant up-regulation of another aspect of the same pathway or by the development of acquired resistance through activation of a compensatory pathway. For example, clinical data suggest that Met pathway activation can compensate in lung tumors when EGFR signaling is inhibited¹, while inhibition of mTOR with rapamycin analogues results in an increase in AKT signaling² that may reduce the overall therapeutic effect. Given the limited number of approved targeted agents most rational combinations will require dosing of two or more (as yet) unapproved new molecular entities (NMEs). The strong scientific rationale for such combinations warrants a re-examination of our current developmental model and suggests that a new developmental model may; in select circumstances; facilitate evaluation of two investigational agents in combination.

The existing combination rule (21CFR300.50) provides one mechanism for approval of the combination of two investigational agents, typically by the demonstration in a Phase III trial of the contribution of each agent to the claimed effects of the combination, compared to standard of care therapy. However, there may be circumstances in which there is sufficient evidence to consider alternatives to the standard Phase III factorial trial design or to consider alternative criteria for the

regulatory burden of proof necessary for approval of the combination of two investigational targeted therapies. The objective of this panel is to explore specific examples and criteria in which an alternative regulatory process to the existing combination rule would be appropriate and feasible and thus could be adopted by developers.

Benefit to Patients

Any new model for the development of investigational agents must have as its ultimate goal an improvement in the therapeutic benefit to patients, both in terms of the efficacy and safety profile of the product as well as the efficiency of the drug development process itself. The putative benefits to patients include the potential for combination therapies to synergistically target tumors and therefore be more effective than a single agent alone. One of the theoretical benefits of combination targeted therapies is that by the inherent nature of their specificity, toxicities may be minimized relative to broader spectrum agents. Employing two targeted agents versus a single multi-targeted agent may allow for dose-reduction of either/both agents, thereby reducing toxicity while potentially maintaining or improving efficacy. There is also a possibility of achieving better safety profiles while using two agents with specific known targets rather than employing a single agent with multiple known and unknown targets. Thus, one criterion for the development of combination targeted therapies would be that toxicities of each individual agent would either be non-overlapping or merely additive in combination rather than synergistic, making it easier to monitor and manage in the clinic.

An estimated 20 percent of adult cancer patients are medically eligible for a cancer clinical trial, yet accrual rates remain at about 3 percent. These rates are even lower for ethnic and racial minorities as well as young adult cancer patients who have higher cancer mortality rates than the general population. The 2NME strategy has the potential to improve both the number and the quality of cancer clinical trials, enhance the access of new targeted therapeutics to cancer patients. In addition to matching likely responders to these treatments, potential 2NME approach would benefit patients where evidence suggests a therapeutic benefit for a highly refractory patient population or where no approved therapy exists but there exists a biological rationale for efficacy. The high unmet medical needs of these patients could support an alternative developmental model of two agents.

Finally, it should be acknowledged that the goal of all participants in the drug development process, including the research community, pharmaceutical industry, and regulatory agencies, is to expedite the availability of safe and effective therapies to the intended patient populations. The developmental models discussed below are an attempt to achieve this goal, without compromising existing regulatory standards that protect the safety of patients.

Examples and Decision-Making Criteria of 2NME development plan

In order to explore specific examples and decision-making criteria of conditions when approval of the combination of two new molecular entities (NMEs) would be appropriate and feasible, we have made certain general assumptions about the 2NMEs; which are listed below:

- Strong biological rationale for the 2NME combination, e.g, selective inhibition of two targets in the same pathway or inhibition of a primary and compensatory pathway.
- Biological indicators for likely responders in a patient population (i.e. paired markers to indicate the pathway is actually altered in a patient population.)
- Evidence of synergy of the 2NME combination in in vitro cell lines and enhancement of the 2NME combination compared to the activity of either agent alone in in vivo nonclinical models.
- Nonclinical characterization of the toxicity profile of each individual agent according to current ICH guidelines suggesting non-synergistic toxicity
- Thorough characterization of potential drug-drug interaction of the 2NME combination to minimize the potential for additive or synergistic toxicities.

Potential scenarios for the development of 2NMEs

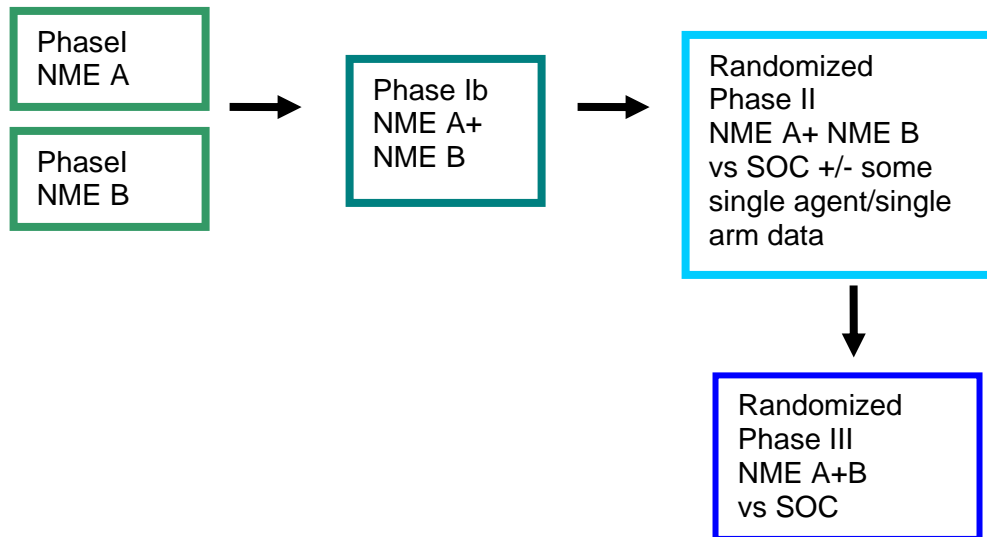
I. Synthetic Lethality

Synthetic lethality refers to situations in which each NME is individually inactive or minimally 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 would exhibit highly potent activity and further, this activity would be detected in multiple representative model systems (various cell lines and animal models). In this example, the minimal 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. In these cases, we propose limiting data collection about each individual agent to Phase 1 studies.

The rationale being that the individual NMEs are not being proposed as single agents with their use being limited to the proposed combination therapy only. Also, it is perhaps more informative to learn of the risks and benefits associated with the combination rather than each individual agent since the combination has different molecular targets than each agent individually.

Proposed development plan:

- 1) Thorough characterization of the safety profile and maximum tolerated dose of each individual agent in Phase I studies. The decision to proceed with the Phase 1b trial would be based on whether the observed exposure-toxicity relationship of each drug as a single agent is adequate to consider combination therapy feasible.
- 2) Evaluation of the safety profile of the 2NME combination and appropriate dose selection criteria for each agent in the combination (Phase 1b). Expansion cohort may be utilized to demonstrate evidence of activity for the combination such as tumor shrinkage.
- 3) Demonstration of proof-of-concept for the 2NME combination in Phase II compared to each agent alone and SOC. Surrogate efficacy endpoints (i.e. RR) may be utilized if appropriate for decision making in the face of compelling antitumor activity.
- 4) Standard Phase III design comparing 2NME combination with SOC.



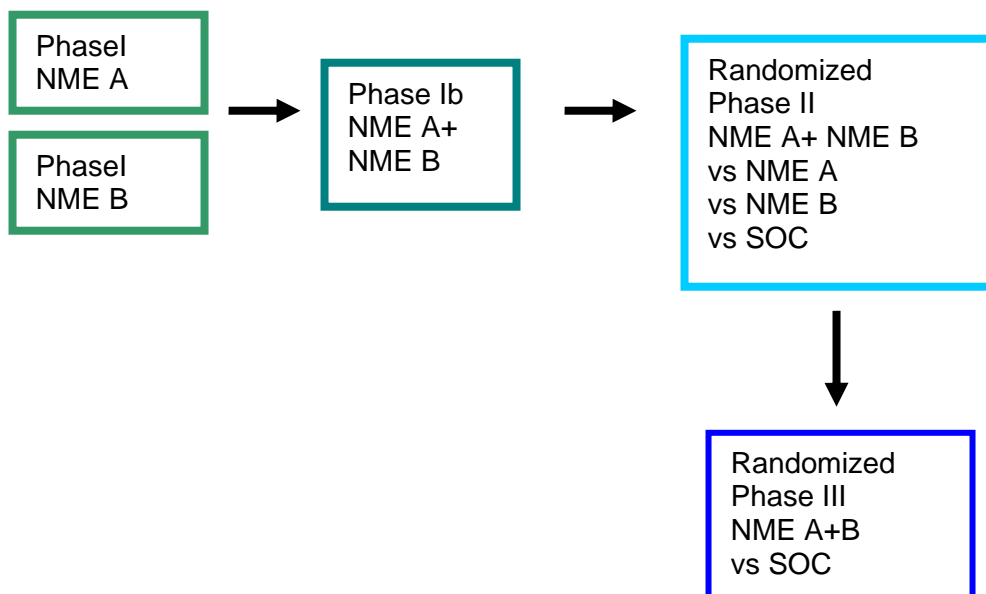
II. Co-Enhancement

Co-Enhancement refers to scenarios in which each NME is modestly active as an individual agent in model systems, but the combination is highly active 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) In this scenario, the proposed Phase I /Ib development plan would be identical to that 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.
- 2) 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 with addition of the single agent arms added once evidence of activity for the 2NME combination is obtained.
- 3) Proof-of concept for the combination, and the contribution of each agent to the combination, would be determined without exposing large numbers of patients typically required for Phase III trials to therapeutic agents with minimal activity.



III. Uni-Enhancement

This case of enhancement refers to scenarios where 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 resistance. In this situation, it is likely that 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. Therefore, the proposed modifications to the development plan would be similar to that of “co-enhancement.”

Conclusion

There is a clear need to modify the current regulatory approval process such that it is more in alignment with the reality of new therapies in development including the use of multiple therapies that target different molecular pathways. In addition to the specific scenarios sketched above, whenever feasible combining of clinical trials (ie. Phase Ib-II or Phase II-III) should also be considered to enhance clinical development timelines.

There are other facets of this issue that will require further discussion such as determining optimal dose of combinations, labeling and packaging to ensure safe and effective usage etc. Nevertheless, the issue of combinatorial therapies holds great promise for the future of cancer treatment. Enhanced understanding of complex signaling pathways that are mis-regulated in human cancer provide both an opportunity and present various challenges to advance cancer therapeutics. To take full advantage of this opportunity, drug development must evolve past the current norm of targeted agents either as individual agents effective in small patient groups or by empirically adding to the current standard of care, to develop targeted agents to be used in rational combinations.

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FDA response

The conventional approach to cancer drug development has concentrated on the evaluation of single agent therapies to determine efficacy and safety. Subsequently, the drug is evaluated in advanced stages of a malignancy or in combination regimens adding the new drug to approved drugs. Emerging knowledge of the molecular mechanisms of malignancies, however, may require increased use of multiple drugs combinations. Each component of a drug combination could target different parts of complex molecular pathways involved in tumor development. Interest in combining two unapproved drugs with a strong biological rationale may expedite the development of new treatment regimens for serious and life-threatening diseases.

The “combination rule” (21 CFR 300.5) refers to fixed drug combinations (i.e., drugs that are physically combined) and states that the contribution of each agent to the combination must be demonstrated. To demonstrate the contribution of specific drugs in these fixed combinations, randomized, factorial clinical trials are usually performed (e.g., drug A versus drug B versus the combination of drugs A and B).

Individual drugs are commonly combined in oncology treatment regimens (e.g., ABVD, MOPP, CHOP). Although factorial trial designs aimed at evaluating the individual contributions of separate drugs used in combination have been recommended, these drug regimens are not the subject of the combination rule.

Issues related to the co-development of two investigational drugs for cancer include:

1. The amount of toxicologic data for each individual drug and the drugs in combination needed prior to initiation of clinical studies.
2. The mechanistic rationale or animal model data needed to justify use of the investigational drugs in combination at various stages of development.
3. The rationale needed for omission of a factorial design in demonstration of effectiveness.

Although a factorial trial design is frequently used to evaluate fixed combinations, other data, including compelling mechanistic data (e.g., animal or *in vitro* data) may provide a sufficient rationale for regulatory approval of fixed combinations or of two investigational drugs used together. The acceptance of mechanistic data would be in the setting of a highly significant treatment benefit and a favorable benefit to risk assessment.

The use of multiple unapproved drugs in combination will also be investigated in therapeutic areas other than oncology. FDA recognizes that a clear regulatory pathway is required and that further public discussion and formal guidance in this area is required.

References

¹ Engelman J.A, The role of phosphoinositide-3-kinase pathway inhibitors in the treatment of lung cancers; [Clin Cancer Res.](#) 2007 Aug 1;13(15 Pt 2):s4637-40.

² [O'Reilly KE](#), [Rojo F](#), et al; mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt; [Cancer Res.](#) 2006 Feb 1;66(3):1500-8