High-Throughput Testing of Novel–Novel Combination Therapies for Cancer: An Idea Whose Time Has Come

Uciane K. Scarlett¹, Dennis C. Chang¹, Thomas J. Murtagh¹, and Keith T. Flaherty²

Summary: Combination therapies are essential to address the genetic complexity, plasticity, and heterogeneity of tumors and to overcome resistance mechanisms that confound single-agent approaches, and are a paradigm that became well established in the era of conventional cytotoxic chemotherapies. Today, we are well equipped to address many of the scientific, clinical, and collaboration challenges that have existed historically; however, the pace of testing rational combinations is modest. Our analysis shows that the volume of clinical trials testing multiple investigational pipeline agents (“novel–novel” combinations) is dismayingly low, as of approximately 1.500 phase I to III investigational combination trials initiated in 2014–2015, only 80 were for novel–novel combinations, and only 9 of those involved more than one company. The Collaborative Novel–Novel Combination Therapies (CoNNECT) initiative aims to alleviate this bottleneck by developing a new, faster paradigm for early investigation of scientifically informed, novel–novel drug combinations. The initiative kicked off on March 7, 2016, when representatives from top academic centers, biopharma, nonprofits, the FDA, and other groups gathered to define an actionable path forward. Cancer Discov; 6(9): 956–62. ©2016 AACR.

COMBINATION THERAPIES ARE ESSENTIAL TO THE FUTURE OF CANCER CARE

Cancer is multifactorial at the genetic level, adaptable at the epigenetic level, may have a highly complex microenvironment, and consequently cannot be durably treated by targeting a single pathway. Consistently, drug combinations show superiority over single-agent therapy. This was first realized for cytotoxic chemotherapy with distinct mechanisms across DNA-targeted, antimetabolite, and microtubule-targeted drug classes. In the late 1950s and the early 1960s, chemotherapy combinations produced such dramatic responses in patients with leukemia and lymphoma that many people believed that a cure for cancer was imminent (1). Similar responses were observed in the 1970s and 1980s when combination chemotherapies achieved cures for metastatic reticular cancer (2). Following a plateau in the impact of conventional cytotoxic chemotherapy, a generation of agents has emerged targeting novel molecular mechanisms, but essentially all of these agents have been established as standalone therapies or in combination with conventional cytotoxics.

The opportunity to deploy agents with synergistic antitumor effects but nonoverlapping mechanisms of toxicity has only just begun. For example, the FDA-approved combination of palbociclib plus letrozole doubled the median progression-free survival versus single-agent letrozole (24.8 vs. 14.5 months) in ER-positive, HER2-negative breast cancer with manageable toxicities (3). Another example is the FDA-approved combination of ipilimumab and nivolumab, which demonstrated a 4.6-month increase in median progression-free survival over single-agent nivolumab and an extraordinary 4-fold increase over single-agent ipilimumab in metastatic melanoma (4), though at the expense of greater risk of autoimmune toxicity. The first wave of novel–novel combination investigations, for which new collaborations were forged across the pharmaceutical industry, was in pursuit of the promising strategy of cotargeting two RAS effector pathways: the MAPK and PI3K pathways. Unfortunately, after substantial investment of time and resources, these trials failed to define tolerable combination doses that could provide clinical benefit in RAS-driven malignancies. In retrospect, it is perhaps not surprising that normal tissue homeostasis might also depend on signaling through two pathways downstream of growth factor receptors. More importantly, this experience highlights the need for making the process of initiating such trials less onerous as well as the earlier abandonment of strategies that fail to meet preclinical expectations.

Advances in the molecular pathology, genomics, and immunobiology of many cancers have opened the floodgates for hypotheses for drug targeting and are reflected in the >800 agents being tested (2015) for cancer (5), in contrast to <200 FDA-approved cancer therapies. Al-Lazikani and colleagues summarized—in the context of identifying the best possible drug combinations—“the scale of the challenge is illustrated by the sheer number of mathematically possible drug combinations” (6). If we consider today’s pipeline, the number of theoretical double combinations would be approximately one million. Even if agents with redundant mechanisms were considered a single class, the number of two-drug combination remains in the thousands. The wealth of drugs and hypotheses forces the issue of how to efficiently and rigorously test novel–novel combinations to

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identify the optimum regimens to treat different cancers. What is clear is that many such novel–novel combinations will ultimately be required to eradicate and hold cancer at bay, but that the current approach to drug development—the paradigm of single-agent drug development and development in combination with currently approved agents—will not suffice. There are simply too many combinations and too few patients for each, and the risks/rewards for such single-agent development are not aligned. And, with limited insights into the mechanisms of resistance to conventional cytotoxic agents, much of the opportunity to translate a molecular understanding of cancer into therapy lies in the realm of the growing portfolio of molecularly targeted agents, including those targeting the tumor microenvironment and immune-cell regulators.

**THE CHALLENGES TO COMBINATION THERAPY TESTING ARE NOW ADDRESSABLE**

The Institute of Medicine (IOM) organized a workshop in 2011 to articulate the key challenges that may impede development of combination therapies in oncology, especially novel–novel drug combinations, and to suggest possible solutions (7). These challenges fall into three main categories:

- **Scientific challenges**, regarding prioritizing which combinations to test
- **Clinical trial design challenges**
- **Challenges to collaboration**, whether logistical, legal, regulatory, and/or cultural

There is no doubt that the challenges articulated at the IOM meeting in 2011 remain significant. However, the continued proliferation of new investigational oncology agents in today’s pipeline has changed the risk-to-return ratio, and we now have a more compelling proposition to address these challenges. Fortunately, the field has also been actively generating advances in cancer biology and technology that can identify synthetic lethal interactions from among large numbers of treatment conditions, as well as innovative clinical study designs and collaboration models, and thus solutions to each of those diverse challenges have begun to emerge.

Furthermore, the FDA has started to address regulatory challenges through industry guidance (8). More specifically, the FDA guidance published in 2013 advises combination therapy sponsors on how to address regulatory issues and provides criteria for the consideration of novel–novel combination, including the seriousness of the disease, a strong biological rationale for the combination, and functional evidence of superiority of the combination over the individual agents.

**Addressing the Scientific Challenges**

Given the sheer number of possible combinations, investigators must leverage existing technologies and scientific/clinical advances to prioritize rationally designed drug combinations. Especially for therapies targeting oncogenic pathways, we have moved away from empirical clinical testing—based on very limited ad hoc preclinical evidence or pragmatic combinations of drugs with nonoverlapping toxicities—to hypothesis-driven approaches that utilize sophisticated techniques, such as network biology and knowledge-based algorithms (6, 9). Innovations in cancer biology and preclinical testing are providing increasing insight into which combination approaches should be tested in the clinic. For example, there are an increasing number of *in silico* models and predictive algorithms, such as Pathway Commons, and an increasing array of robust tools for preclinical experimentation, such as NCI60, which is a panel of 60 tumor cell lines that the NCI provides to researchers to evaluate two-drug combinations (9). Cell line repositories with in excess of 1,000 cancer models together with robotically maintained drug screening capabilities are becoming increasingly widespread and are uncovering novel combination strategies in molecularly defined subpopulations at an increasing rate (10). And, *ex vivo* testing of patients’ tumors using methodology previously confined to drug discovery with or without rapid expansion of tumor biopsy specimens has recently been suggested to provide a striking prediction of clinical response (11, 12). Lastly, multiple novel combination regimens can be explored in patient-derived xenografts to produce candidate therapeutic approaches within months while patients are receiving currently standard therapy. The rise of immunotherapies—for which biomarker strategies remain unclear and evidence supporting rational combinations is limited by the small number of immune competent models—has temporarily bucked the trend, pushing the field to more empirical testing of combination approaches, but one would predict that as the science advances, hypothesis-driven approaches will dominate immuno-oncology as well.

Of course, there remains a substantial gap in our understanding of how best to predict responses in patients using preclinical models, but the tools and materials for bridging that gap are continually improving.

**Addressing the Clinical Trial Design Challenges**

Innovations in clinical trial designs are making it feasible to test cancer therapies with greater throughput than ever before. Numerous trials, such as NCI’s MATCH trial, the Lung-MAP trial, I-SPY 2, BATTLE, BATTLE-2, FOCUS4, and others, test many different regimens within a single protocol, in umbrella or basket trial designs (13). The capabilities and expertise required to manage these complex protocols have been developed across many sites. Furthermore, these initiatives share the feature of being coordinated by the NCI and nonprofit foundations and institutions who serve as neutral intermediaries in deliberating on the therapeutic and biomarker strategies that offer the strongest level of evidence.

Adaptive trial designs further enhance the potential throughput of clinical trials. In essence, the results for patients enrolling earlier in a trial are used to inform how subsequent patients are treated, thus improving the efficiency of the study; this means that fewer patients are required to achieve the same answers regarding safe dosing and/or efficacy. The BATTLE and BATTLE-2 trials exemplify this approach—the investigators randomized patients to treatment arms in a Bayesian...
adaptive manner, such that treatment arms with greater observed efficacy would accrue faster (14). Adaptive designs require greater statistical expertise and often specialized software, but such capabilities now exist and are becoming more widespread. And, these approaches provide the much-needed ability to terminate investigation of a therapeutic approach or biomarker assignment strategy once prespecified boundaries for inadequate efficacy have been crossed.

The field also continues to see growth in the utilization of genome/exome sequencing and other forms of multiplex molecular testing, and improvement in the infrastructure to process and manage the data generated, allowing for maximal information to be gleaned even from small cohorts in whom the maximum molecular information is gathered. At major academic centers and other organizations (e.g., Foundation Medicine is helping to broaden access to genomic testing), the personalization of oncogene-targeted therapies can be done more readily than ever before.

Addressing the Challenges to Collaboration

Trials like Lung-MAP, MATCH, I-SPY 2, and others have demonstrated unprecedented levels of cooperation and collaboration across multiple biopharmaceutical companies, nonprofit entities, government bodies, and academic centers. Although these trials are not focused on novel–novel combinations—in fact, they primarily test monotherapies with some combinations of approved agents—they present models for collaborative funding, logistics, governance, data sharing, and the allocation of intellectual property. Furthermore, collaborative trial initiatives are not restricted to those led or co-led by government institutions: For example, the Melanoma Research Foundation’s Breakthrough Consortium is a coalition of academic sites united by a dedicated nonprofit entity to conduct trials with various companies; the BATTLE trial was run by academic centers (albeit with a grant from the Department of Defense); and the recently announced National Immunotherapy Coalition is an initiative of industry partners.

The dialog has shifted: Whereas in 2011, the IOM workshop reported cultural barriers as an important issue, stakeholders are increasingly receptive to novel–novel combination therapies. The FDA signaled their receptiveness as early as 2010 by publishing a draft guidance (full guidance released in 2013) on the codevelopment of such therapies. As mentioned above, biopharma companies are increasingly engaging in collaborative studies, both in studies driven by academic/nonprofit/government entities (MATCH, Lung-MAP, etc.) and in studies driven by industry partnerships. Finally, the federal government announced a Precision Medicine initiative in 2015 and a cancer “moonshot” initiative in 2016, both aiming to reinvigorate innovation and cooperation in cancer drug development.

It is clear that early investigation of combinations in oncology provides a strong value proposition not only for patients and investigators, but also for drug manufacturers, by allowing individual agents to reach the maximum potential population for which that agent can play a role in a treatment regimen. Furthermore, the probability of success would be higher than that for single-agent development strategies by anticipating and addressing resistance mechanisms that may mute monotherapy impact and therefore outweigh the perceived risks associated with this approach.

In short, there are now capabilities and models to draw upon to greatly accelerate the pace of development of combination therapies. However, to date this potential has remained largely untapped.

**THE NEED: PROGRESS IN CLINICAL TESTING OF NOVEL–NOVEL COMBINATIONS IS MODEST**

Despite all the advances, the pace of testing combinations in the clinical setting has been modest to date. A Stanford group recently assessed the oncology clinical trial landscape from 2008 to 2013 (phase 0–IV interventional and noninterventional trials) and reported that of the approximately 14,650 trials found on clinicaltrials.gov, only 25% involved combinations (15). We found a comparable rate in a similar analysis performed for 2014 and 2015 (see methodology in ref. 15); of the approximately 5,650 oncology trials initiated in those two years, only approximately 30% involved combinations. This is surprising given the increasing level of innovation within the oncology pipeline and the evidence for rational combinations.

We further evaluated the oncology trials for 2014 and 2015 and focused on drugs or biologic combination interventions undergoing phase I–III clinical testing, which accounted for approximately 1,494 of the approximately 5,650 trials. Our analysis showed that academia (and “other” organizations which include government entities and nonprofit foundations) has a greater track record in sponsoring combination trials versus industry, as only approximately 40% of combination trials were industry-sponsored compared with approximately 60% sponsored by academia/others (Fig. 1). This supports the view that companies remain largely focused on developing their agents as monotherapies at least initially, and is of course realized in the core focus of drug registrations for single agents.

There are, of course, exceptions. For example, AstraZeneca/MedImmune with several institute partners recently launched the DREAM challenge, which seeks to explore and reveal key traits of effective combination therapy and drug synergy through genomic data (16). Additionally, our analysis showed that the total number of industry-sponsored combination trials increased modestly from 2014 (273 trials) to 2015 (322 trials).

Nevertheless, most industry-sponsored combination studies are focused on combining their investigational agents with already-approved, standard-of-care agents, e.g., Five Prime Therapeutics’ FPA008 with nivolumab, or Genentech/Roche’s GDC-0032 with trastuzumab. It is surprising, with the current level of innovation, that only approximately 5% of all combination trials involve novel–novel combinations: 2.5% of academia-sponsored, 2% of NIH-sponsored, and 10% of industry-sponsored trials (Fig. 1). Furthermore, when novel–novel combination trials are conducted, they are usually with agents residing in a single company’s pipeline, as only 15% of the 58 novel–novel industry-sponsored combinations involve two collaborating companies (Fig. 1), e.g., AstraZeneca/MedImmune’s durvalumab with Incyte’s INCB024360.
The low rate of novel–novel combination testing is based on the existing clinical trial model, whose roots lie in a framework developed decades ago for testing highly toxic chemotherapeutics and which therefore focuses on the establishment of safety and efficacy for individual agents before attempts are made for combinations. We are now in the era of targeted therapies and immunotherapies, and their properties are distinct enough to warrant a significant shift in how we test and develop combinations of these agents. Furthermore, with this current model, we are prolonging the process for bringing more effective treatment options to the market. For example, although it was established that MEK-dependent MAPK pathway reactivation was a resistance mechanism for the activity of the already-approved BRAF inhibitor vemurafenib (approved in 2011), GSK initially developed its BRAF inhibitor dabrafenib and its MEK inhibitor trametinib as monotherapies (both approved in 2013) before receiving approval for the combination in 2014 for melanoma. And that was for a combination where both agents were developed by the same company. In multiple myeloma, the combination of Celgene’s lenalidomide plus Takeda’s bortezomib plus dexamethasone (also known as Revlimid–Velcade–dexamethasone, or RVD) is a standard first-line regimen because it produces a response rate of 100%. However, this dramatic efficacy was not discovered until 2010, several years after the approval of lenalidomide (2005) and bortezomib (2003). If the combination had been tested earlier, thousands of additional patients with myeloma would have benefited, and the field could have moved on more quickly to even higher-order combination regimens and/or induction and maintenance therapy strategies. Furthermore, there are constraints on and imperfections within today’s clinical research model that disincentivize participation and inhibit faster, less expensive, and more efficient trials from being conducted; for example:

- Limited patient pool: <5% of adult patients with cancer participate in clinical trials (17)
- Limited bandwidth of clinical trial experts to conduct or participate in trials (17)
- The cost of conducting a phase I trial ranges from approximately $40K to $60K per patient, whereas a phase III trial ranges from $70K to $125K per patient (5, 18)
- Trial sponsors have limited financial resources for all possible trials
- In the context of novel–novel combination trials, there are cumbersome processes for formal agreements between companies to test combinations involving drugs of different owners when such a combination may be explored in only a few dozen patients and abandoned

Still, we are faced today with an unparalleled opportunity to reinvent our approach to testing novel–novel combinations. The time is right to challenge our present thinking on novel–novel combinations and implement a paradigm to (i) shift perspectives on the perceived risks, (ii) leverage existing innovations, and (iii) align with organizational philosophy on control.
THE CONNCT INITIATIVE: WHAT IS IT, AND WHAT IS REQUIRED FOR ITS SUCCESS?

At the 2015 Roundtable event held by Massachusetts General Hospital’s Termeer Center for Targeted Therapies, a vision for a faster, more streamlined approach for testing novel–novel combinations to treat cancer was articulated. Out of that vision, the CoNNCT initiative (Fig. 2) was born, aiming to form a consortium for fast, early signal-finding (nonregistrational) studies of novel–novel combinations. The envisioned value proposition for CoNNCT is multidimensional and addresses the need of a variety of stakeholder groups; for example:

- Safe and efficacious combinations more rapidly made available to patients
- Access to a broad set of novel combination partners for biopharma
- Lower hurdle and more streamlined process for collaborative studies
- Neutral entity to protect intellectual property during cross-company collaborations
- Easier/faster access to world-class investigators and institutions
- Improved process efficiencies (e.g., centralized institutional review board) for cross-company collaborations
- Improved cost efficiency (e.g., shared trial cost) for biopharma

We recognize that developing novel therapeutics for cancer is hard, developing novel combination therapeutics is even harder, and developing novel combinations among multiple companies adds still another layer of complexity. Thus, the effort required for the success of the CoNNCT paradigm is no small undertaking, as it requires finding the right balance across multiple priorities in order to realize the vision and address distinct yet critical issues:

- Incentive for participation
- Ensuring delivery on a value proposition for each stakeholder
• Ensuring speed, breadth of exploration, and cost efficiency
• External constraints and requirements
  • Regulatory requirements and guidance
  • Legal liability and risk mitigation strategies
• Internal processes and structural requirements
  • To facilitate scientific and clinical decisions, e.g., scope of study, regimen prioritization, and protocol design/review processes
  • For contract negotiation process and structure
  • To ensure sufficient bandwidth requirements are met for trial execution
  • To develop a consensus funding model and structure
  • To ensure open collaboration across participating companies

As an initial step toward developing this paradigm, we gathered a diverse group of stakeholders—senior executives from over a dozen biopharmaceutical companies, world-class academic clinicians from four leading cancer centers, representatives from oncology nonprofits, the FDA, a leading strategic consulting firm, and other key stakeholder organizations—to participate in an Action-Planning Workshop, held on March 7, 2016.

The goal for this group was simply yet audacious: to breathe life into a conceptual paradigm by exploring its potential and framing solutions to the numerous and obvious challenges to making this vision a reality. The participants tackled the issues listed above and aligned on a set of strategic recommendations in terms of the clinical study, organizational structure, and decision-making processes. Workshop participants agreed that the first generation of studies should be strongly hypothesis-driven, incorporate the most innovative participants agreed that the first generation of studies should be strongly hypothesis-driven, incorporate the most innovative and expertise from biopharma, the group believed that each and expertise from biopharma, the group believed that each and modifiable changes of biomarker selection strategy; national nomination, study design, and integration of institutional knowledge. And, for trials in which a company’s agent and expertise from biopharma, the group believed that each and expertise from biopharma, the group believed that each company should elect a small number of representatives to participate in critical discussions, including topics on combination nomination, study design, and integration of institutional knowledge. And, for trials in which a company’s agent is involved, a representative would join the protocol steering committee to weigh in on dose escalation, interpretation of toxicity, and modifications of biomarker selection strategy; the CoNNCT organizational structure should be as lean as possible to maintain the focus on speed. Although the Action-Planning Workshop was viewed by many as a success, we must still execute a set of critical next steps, e.g., identify and put in place a nonprofit organization that will play the central role, and engage a broader team to define more specifically the scope and goals of the first set of pilot studies. We have begun the process and expect to see progress toward these objectives within the coming months, though we recognize the challenge of motivating biopharmaceutical companies sufficiently to nominate champions to support and build momentum around CoNNCT.

The creative and bold thinking behind CoNNCT is not new to the decades-old war on cancer, but rather further evidence of our community’s commitment to eradicating the disease. Together, this group has not only better framed the value proposition for CoNNCT but has begun to outline the first steps in making CoNNCT a reality.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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