

Mapping the Future in Oncology Drug Development

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Executive Summary

Against the backdrop of the ASCO 2010 theme “advancing quality through innovation”, Quintiles brought together an esteemed faculty of leading international experts in oncology drug development in a unique ancillary event, *Mapping the Future in Oncology Drug Development*.

Dr. Paul Bunn, Jr., M.D., Past-President of the American Society of Clinical Oncology (ASCO) 2002–2003, chaired the event, which included plenary presentations and stimulating discussions around key issues of the moment in oncology drug development.

In this paper, Harish Dave and Eric Groves review the insights from the ancillary event and discuss potential solutions to improve the productivity of oncology drug development and ultimately patient care; with thanks to our distinguished panel for the insights that they provided (for the full program see page 20). Owing to the wide scope of the subject, market-access strategies are not reviewed.

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Introduction

The 50% increase in the global incidence of cancer from 2000 to 2020 predicted by the World Health Organization is driving the need for more effective drugs.¹ There are currently more than 725 agents in active development,² and oncology drug development accounts for approximately 20–30% of the estimated \$336 billion research and development (R&D) budget. However, approximately 90–95% of agents tested in first-in-human studies never reach market.

Reasons for drug failure include:³

- > *Lack of understanding regarding drug mechanism of action (MOA)*
- > *Complexity of patient physiology*
- > *Inadequate characterization of patient tumors*
- > *Failure to use biomarkers to inform early clinical development*
- > *Inappropriate drug dose or schedule*
- > *Limitations of clinical trial methodology and endpoints*
- > *Regulatory challenges*

The average cost of developing one new drug from the laboratory to patients was reported at \$1.3 billion in 2007.² With the introduction of targeted therapies and the pursuit of personalized medicine, cancer, traditionally considered to be one disease, is now being subcategorized into multiple diseases, decreasing the size of target populations and making it more difficult to recoup R&D costs. Therefore, the current cost of oncology R&D is unsustainable. It is essential that oncology drug development becomes more cost-effective and productive.

“The current cost of oncology R&D is unsustainable.”
Dr. John Smyth,
University of Edinburgh

Key needs in oncology drug development

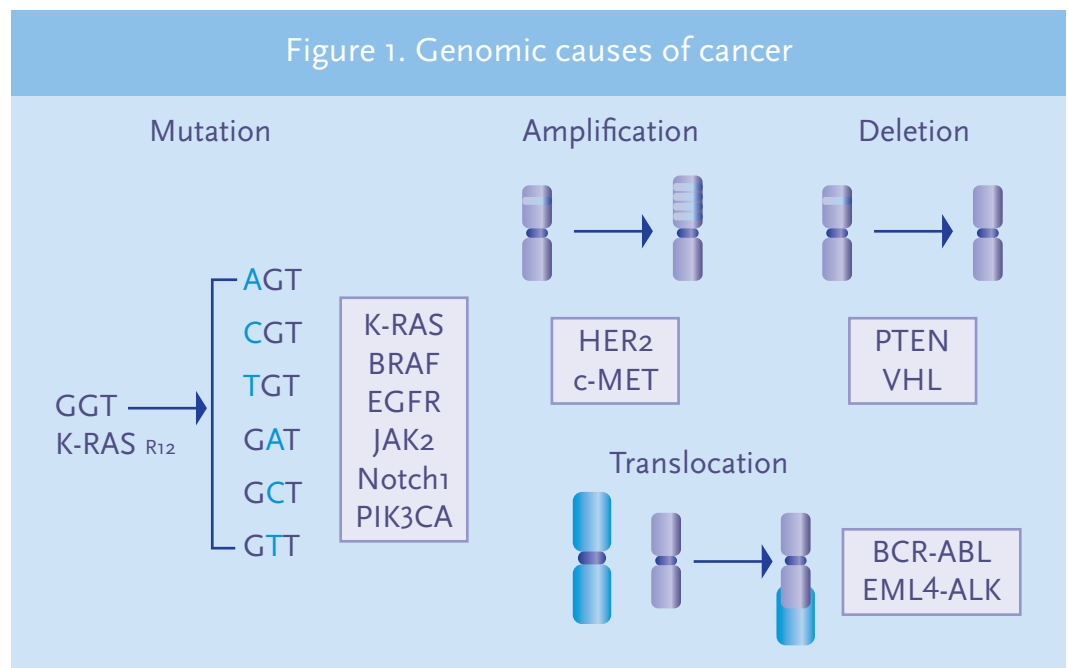
- > *The development of appropriate biomarkers*
- > *Improvements in clinical trial design*
- > *Strategies to navigate the regulatory environment or encourage its evolution*

Taken together, it is vital that strategies to improve the productivity of oncology drug development are identified and implemented to ensure that the most effective treatments are available for patients in the future.

Oncology is at the Forefront of Personalized Medicine

Personalized medicine aims to ensure that patients receive the drugs and/or interventions from which they will derive most benefit. This concept has been spearheaded by the oncology community, driven by the appreciation that malignant tumors in two different people at the same site, with similar macroscopic and microscopic features, may exhibit completely different responses to a prescribed drug regimen. This stems from the fact that cancer biology is complex and typically involves multiple genetic factors and signaling pathways, which influence response to treatment (Figure 1).

An increased understanding of the molecular pathways involved in cancer biology has resulted in the development of agents targeted at changes in the pathway that promote or propagate tumor development/metastasis. For targeted agents, a thorough knowledge of the drug MOA and an understanding of how the heterogeneity of biology between patients affects drug response is important. Therefore, multiple layers of information at the level of individual genes, the genome, the proteome, and signaling pathways must be consolidated in order to correlate changes within the cancer biology with clinical phenotypes and outcomes following treatments. This has driven the development of biomarkers that provide information on pathogenic processes or expected pharmacologic response to a treatment.



Used with permission of Dr. Richard Gaynor.

Biomarkers

Definition

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.⁴

Types

- > *Pharmacologic – a factor that can be used to demonstrate drug activity/MOA*
- > *Predictive – a factor that can be used to predict response to a drug*
- > *Prognostic – a factor predictive of disease outcomes, irrespective of treatment*

Roles

Biomarkers can be used to support development:

- > *Drug identification (screen multiple agents for biological activity)*
- > *Establish drug MOA*
- > *Inform trial design*
- > *Assist in choosing dose and schedule*
- > *Increasingly used to make go/no-go decisions*
- > *Identify which patients may benefit from the drug*

To this end, biomarkers are becoming increasingly important throughout drug development.³ Pharmacologic biomarkers can be developed early to establish drug MOA and may also have utility in the screening and identification of candidate drugs for further development. Predictive biomarkers can be used later to identify a molecular profile that enables selection of patients in whom the drug is most likely to be effective. These may predict a positive response or negative response to a drug. For example, the presence of the BCR-ABL fusion protein in patients with chronic myeloid leukemia (CML) is predictive of a positive response to the small molecule kinase inhibitor, imatinib mesylate (Gleevec®) while, conversely, K-RAS mutations are predictive of a lack of response to the two EGFR inhibitors, cetuximab (Erbix®) and panitumumab (Vectibix®) when used in patients with colorectal cancer (CRC).⁵

The fact that biomarkers are not totally independent should not be overlooked. For example, a predictive biomarker may also be prognostic (e.g. cofilin [CFL1] in non-small cell carcinoma [NSCLC]⁶ and FK506-binding protein like [FKBP] in estrogen receptor-positive breast cancer⁷), potentially complicating the interpretation of data. Therefore, biomarkers should undergo comprehensive validation as early as possible during development so that decisions regarding the future development of an agent are founded on robust information. Furthermore, many biomarkers suffer from technical shortcomings, resulting from the lack of quantitative techniques to capture the impact of molecular alterations.⁸ Single markers, such as tumor protein p53 gene mutations, do not perform well in predicting outcome when applied to complex tumor types containing many synchronous alterations. Therefore, more comprehensive approaches to gene profiling are needed to determine prognostic and predictive signatures in tumors, leading to improved efficacy.

“[Predictive, prognostic, and pharmacologic] biomarkers are not totally independent. Sometimes, I think that this becomes important.”
Dr. Richard Gaynor,
Eli Lilly and Company

Understanding the Ras signaling pathway has paved the way for the development of effective targeted cancer therapies

- > *The Ras signaling pathway plays a central role in many cancers; Ras becomes cancer promoting when mutated and locked in a GTP-activated state.*
- > *Various approaches have been undertaken over the past 30 years by Dr. Frank McCormick's group and others to overcome the deleterious effects of oncogenic Ras.*
- > *Initial unsuccessful attempts to directly target Ras included attempts to:*
 - > *restore GTPase activity to switch off the activated protein*
 - > *preempt Ras activation through use of GTP analogs*
 - > *utilize drugs to bind and block Ras sites that interact with downstream effectors*
 - > *disrupt the processes that tether Ras to the intracellular membrane*
- > *When direct targeting of Ras proved unsuccessful, downstream effectors were targeted, requiring an in-depth knowledge of signaling pathways because blocking only one downstream effector may not be sufficient to abolish the effects of Ras as other signaling pathways compensated.*
- > *The McCormick group found that targeting the Raf/Mek/Erk pathway (MAP kinase pathway) yielded success, ultimately resulting in the development of sorafenib, which is now approved for the treatment of renal cell and liver carcinomas and is currently under evaluation in multiple cancer types.*
- > *New strategies for attacking the entire Ras network continue to be explored.*

For the development of a companion diagnostic as a predictive marker of drug response, it is important that the biomarker should first be validated in preclinical samples or in clinical samples to be assessed in translational research studies. The prevalence of the biomarker should then help to guide the developmental process and inform the trial design.

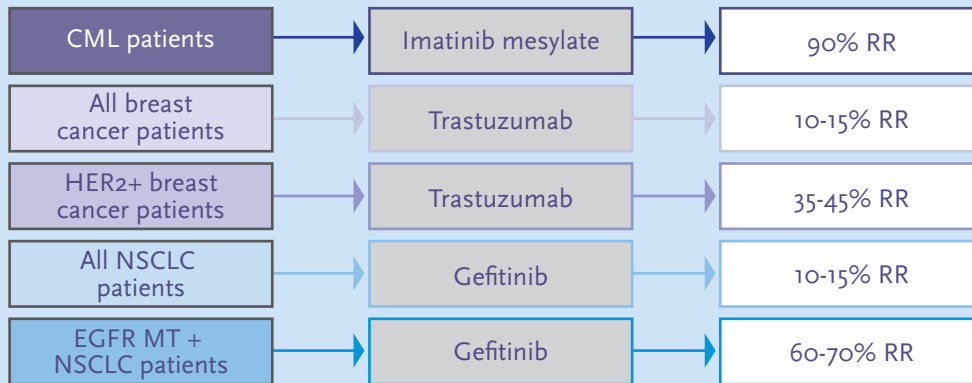
“Biomarkers are especially important in diseases with low response rates in the overall population.”

*Dr. Richard Gaynor,
Eli Lilly and Company*

When the prevalence of the biomarker is low and a targeted agent consequently has a low response rate in the patient population, appropriate patient stratification and enrichment of the treatment populations based on well-validated biomarkers will help to improve trial outcomes and reduce exposure to drugs in patients who are unlikely to respond.³ Enrichment designs can substantially reduce the trial population size required to demonstrate efficacy, particularly in populations where the positive-predictive biomarker is present in less than 50% of the treatment population and the efficacy of the agent in negative patients is minimal.⁹ For example, in patients with breast cancer, enrichment of the treatment population for patients with HER2+ tumors increased the response rate to trastuzumab (Herceptin®) compared with that in the general breast cancer population. Similarly, the EML4-ALK fusion oncogene, which is present in approximately 4% of patients with NSCLC, is currently facilitating the development of the ALK inhibitor crizotinib. When a biomarker has moderate prevalence, patients may be stratified by marker positivity. However, if the prevalence of the marker is very high (>80%) and patients would be expected to have a high response rate to targeted therapy in the patient population, a prospective (ideal) or retrospective analysis on an unselected population becomes feasible. For example, in CML, in which translocations in BCR-ABL occur in >95% of patients, the response rate to imatinib mesylate is high, indicating that the biomarker, although helpful, would not be essential for drug development (Figure 2).

Figure 2. When is a biomarker truly necessary?

Biomarkers are especially important in diseases with low response rates (RR) in the overall population



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Taken together, experience has demonstrated that biomarkers play a critical role throughout the oncology drug development process. They should be identified and validated as early as possible during oncology drug development and should be used thereafter to maximize the likelihood of success. Correct use of biomarkers for patient selection can enrich the clinical trial population by identifying those most likely to benefit from the treatment. This reduces the risk to the non-responder population and, by allowing earlier assessment of therapeutic efficacy, substantially shrinks the costs of development – enabling smaller trial sizes to demonstrate efficacy.

The EML4-ALK fusion oncogene is guiding the development of the ALK inhibitor crizotinib

- > **Echinoderm Microtubule-associated protein-Like 4 (EML4)-Anaplastic Lymphoma Kinase (ALK) fusion oncogene** was discovered to be present in tumors from 5/75 (6.7%) of patients with NSCLC examined.¹⁰
- > The transforming fusion kinase (EML4-ALK) was proposed as a candidate therapeutic target and diagnostic marker in NSCLC.¹⁰
- > In the first large study of patients with lung cancer, the EML4-ALK fusion mRNA was shown to be present in 5/149 (3.4%) adenocarcinomas tested, but in 0/72 carcinomas of other types (squamous cell carcinoma [n=48], large-cell neuroendocrine carcinomas [n=3], and small-cell carcinomas [n=21]).¹¹
- > Identification and characterization of two novel EML4-ALK isoforms in NSCLC further supported investigation of the oncogene.¹²
- > A phase I trial was initiated with the ALK inhibitor crizotinib in patients with NSCLC harboring the EML4-ALK fusion gene and who had previously received chemotherapy,^{13,14} very promising data were presented at ASCO 2010:^{15,16}
 - > Objective response rate: 57%
 - > Disease control rate (complete response, partial response, or stable disease at 8 weeks): 87%

Generating and Validating a Preclinical Hypothesis

“A lot of the time, the science doesn’t catch up with the drug development.

So the better you can correlate the marker and the drug development, the better chance you have of being successful.”

Dr. Richard Gaynor,
Eli Lilly and Company

“If you assume that you know the MOA before we really do, you may miss the activity of the drug. You have to look no further than [the idea of developing sorafenib in melanoma]. [Sorafenib] has no activity in melanoma, but it does in RCC because it is also a VEGF receptor inhibitor.”

Dr. Mace Rothenberg, Pfizer

“The expense of biomarkers is only warranted when time, money, and collaborations occur prior to phase I.”

Dr. Gail Eckhardt,
University of Colorado
Cancer Center

Traditionally, all oncology compounds demonstrating a favorable profile in preclinical tests entered phase I trials in small groups of patients. This approach evolved to include additional screening at the preclinical stage to garner a greater understanding of MOA. However, this still resulted in high numbers of compounds entering clinical trials with limited preclinical development and subsequently a low chance of successful patient outcomes. As the molecular understanding of cancer biology has evolved, this has prompted a return to generating and validating a solid preclinical hypothesis prior to clinical testing.

In today’s environment, a validated preclinical hypothesis based on a thorough understanding of cancer biology and drug MOA should be generated prior to progressing into phase I clinical development. This ensures that the MOA of a compound is verified, pharmacodynamic activity evaluated, and potential safety issues are identified. In addition, it enables the identification and validation of biomarkers, which can then be used to screen and prioritize agents for phase I development. In a drug with multiple MOAs, some of which may be relevant in the treatment of one disease but not another, careful validation of the MOA, together with a sound knowledge of the cancer biology, will help to identify the agents most likely to be effective in a specific disease. This reduces the risk of inappropriate development of an agent or indeed of missing the opportunity for development of a potentially active agent.

Biomarker and drug co-development

- > Confirms reproducibility and validity of assays
- > Optimizes time to assay results
- > Determines timing of sampling during the course of disease.

This will be facilitated by greater access to banked tissue/blood.

Investment at the preclinical stage can improve the productivity of clinical stages of drug development by more effective identification of valid targets and agents.

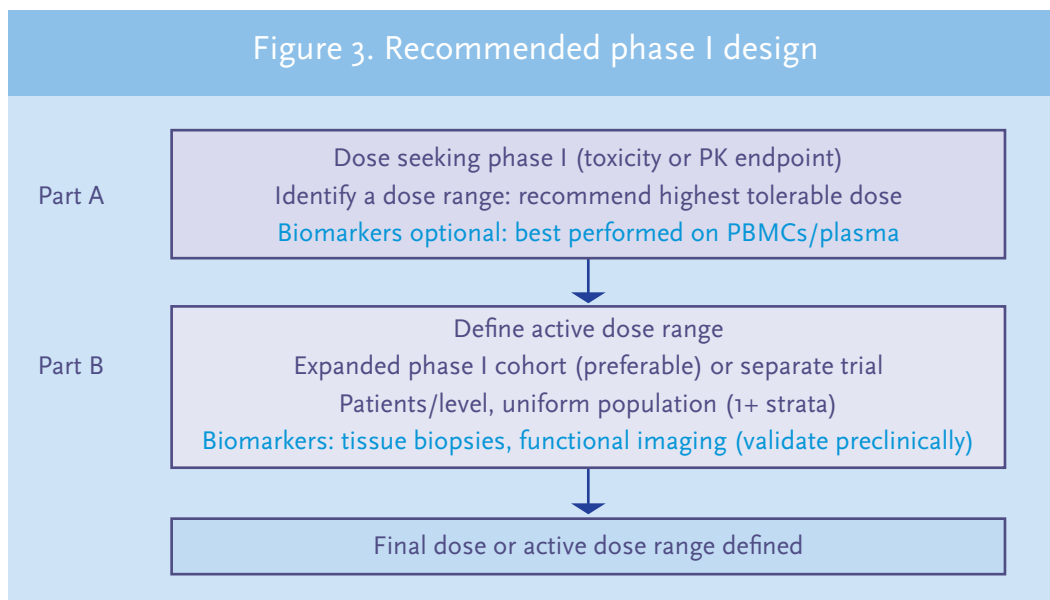
Translating Preclinical Results into Early Phase Trials to Maximize Phase III Success

An analysis of drugs that entered clinical pipelines between 1993 and 2002 revealed that approximately 75% of oncology drugs entering the pipeline never attained marketing approval and just over half (57%) of oncology drugs that entered phase III clinical testing never made it to US regulatory approval.¹⁷ Given the high cost associated with phase II and III clinical trials, with average out-of-pocket clinical costs alone estimated at \$24 million and \$86 million, respectively, phase 0 and I studies that provide accurate information to facilitate an early go/no-go decision are imperative.¹⁷ Furthermore, it is important that insights obtained during the preclinical phase are integrated into early phase clinical trial design.

Challenges in current phase I trials

- > Determination of optimal dosing schedule
- > Identification of dose for phase II trials
- > Challenges in making go/no-go decisions for targeted agents if limited efficacy as monotherapy
- > Design of phase II trials

New approaches are required to address the ongoing challenges associated with phase I trials. To help address these challenges, Dr. Gail Eckhardt (University of Colorado Cancer Center) has proposed an optimal phase I trial design (Figure 3), which should include a dose escalation phase and an expansion phase.



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The dose escalation phase enables the identification of the maximum tolerated dose (MTD) or biologically active dose and provides a range of tolerability thresholds, which may be helpful when proceeding into combination studies. At this stage, it is important to recruit sufficient patients at each dose level to ensure adequacy of pharmacokinetic (PK)/pharmacodynamic (PD) sampling. The expansion phase, including an expanded cohort of patients, then provides the opportunity, not only to obtain initial evidence for a favorable efficacy/safety profile of an agent, but to confirm that the agent is inducing the expected biological effects. Therefore, taken together, the overall aims of phase I studies are to prioritize agents for phase II development, inform go/no-go decisions, and guide the design of phase II trials and the choice of dosing regimens to be tested. Importantly, the recommended phase II dose is not equivalent to the MTD identified in phase I studies. Instead, it should be derived from multiple factors, including chronic toxicity, biomarkers, and PK/PD profiles.

The promising profile of an agent observed during phase I development needs to be thoroughly tested and assessed throughout phase II development to ensure that the phase III studies are most appropriately designed. Too often agents with a promising phase I profile fail during phase III trials,

“What is important is that the MTD does not equal the recommended phase II dose.”
Dr. Gail Eckhardt,
University of Colorado
Cancer Center

“I don’t like the classical terminology of phase I, phase II, phase III, but I don’t have a better proposal. We need to redefine how we move from early to late stage development.”

Dr. Denis Lacombe,
EORTC

highlighting the crucial role of phase II studies in drug development. For example, a dose response to vatalanib was observed by DCE-MRI in elegant phase I studies in patients with advanced CRC and liver metastases, but did not translate into positive clinical outcomes when vatalanib was administered as first- or second-line therapy in patients with advanced CRC in the phase III CONFIRM trials.^{18,19} These late-stage failures highlight the need to redefine how an agent should progress from early- to late-stage development.

Phase II clinical trials provide an opportunity to:

- > estimate clinical activity
- > further characterize safety profile
- > identify factors that predict activity or toxicity
- > further understand the drug MOA and disease biology
- > inform decisions for phase III development

“We have to consider that phase II patient selection may be biased and that this may support the role of randomized phase II studies of these agents.”

Dr. Denis Lacombe,
EORTC

However, often the current designs of phase II trials are limited by methodology and the choice of endpoints. Randomized phase II trials and trials with adaptive design are two potential trial designs that may improve phase II methodology.

The concept of randomized phase II trials in targeted agents can be supported by observations from the gemcitabine (Gemzar®)/bevacizumab (Avastin®) development program for advanced pancreatic cancer. While the results from the phase II trial of gemcitabine and bevacizumab indicated efficacy of the combination treatment in patients with advanced pancreatic cancer, the phase III trial did not.^{20,21} Comparisons between the populations enrolled in the nonrandomized phase II trial and the phase III trial indicate several differences, which may suggest a bias in the selection of patients enrolled into the phase II study. Therefore, phase II patient selection in nonrandomized studies may bias trial interpretation, leading to inadequate decision making and increasing the potential for failure at phase III.

Adaptive designs, in which multiple agents or several doses/schedules of the same agent are evaluated, provide another innovative phase II approach in which the most promising agents (or doses) are selected for further development, while the less effective agents are dropped. One exciting new study pursuing this approach is the I-SPY 2 TRIAL, which is described on page 11.²²

Taken together, there is a need for continuous revision of existing clinical development scenarios, particularly in phase I and II, to identify the optimal development pathway. New bioinformatics platforms based on the integration of multifactorial parameters can then be used to support go/no-go decisions. Most importantly, a robust hypothesis and well-validated biomarkers should be in place before progression into phase III development.

Investment in early clinical trials will ensure well designed phase III clinical trials are implemented for agents that have a higher chance of meeting the efficacy and safety standards that will enhance patient outcomes.

“If you don’t have a hypothesis and a biomarker, then don’t do a phase III trial.”

Dr. Paul Bunn, University
of Colorado Cancer Center

Introducing a trial with adaptive design: I-SPY 2 TRIAL

(Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2)

Sponsorship

- > *Highly collaborative trial led by the Foundation for the National Institutes of Health*

Objectives

- > *To compare the efficacy of novel drugs in combination with standard chemotherapy with the efficacy of standard therapy alone as neoadjuvant treatment for patients with newly diagnosed advanced breast cancer*
- > *To reduce the cost of drug development and the speed of screening drugs with the goal of bringing safe and effective new drugs to market more efficiently*
- > *To identify improved treatment regimens for subsets of patients on the basis of the molecular characteristics (biomarker signatures) of disease*
- > *To correlate MRI results with molecular markers to identify the right surrogate marker for early response*

Trial design

- > *Phase II clinical trial with an adaptive design*
- > *Over the course of the trial up to 12 drugs will be tested, the first five of which are figitumumab, neratinib, ABT-888, AMG 386, and conatumumab*
- > *Data from patients treated early within the trial guide decisions regarding:*
 - > *Regimens with a high Bayesian predictive probability of greater effectiveness than standard of care will graduate from the trial with their corresponding biomarker*
 - > *Regimens with a low probability of improved efficacy versus standard of care will be dropped from the trial*
 - > *New drugs will enter the trial, as the previous drugs are graduated or dropped*

A New Model of Drug Development – Regulatory Opportunities

Regulators desire well-written applications based on well-designed clinical trials, with a clear hypothesis, statistically robust methodology, randomized comparisons, and a strong efficacy and safety profile. In addition, regulators value good communication with companies as early as possible during the development plan of a potential drug. However, all too often, regulators receive applications based on a single pivotal trial, with low efficacy (in the range of 10–15%), significant toxicity (including new toxicities) occurring in >80% of patients, and a short follow-up time, all of which considerably reduce the licensing potential of the agent.

Regulators desire well-written applications based on well-designed clinical trials, with a clear hypothesis, statistically robust methodology, randomized comparisons, and a strong efficacy and safety profile.

Regulatory strategies used in the registration of oncology indications with the US Food and Drug Administration (FDA) have varied widely, and discordance between prospectively selected primary efficacy endpoints in clinical trials and criteria used for approval has been documented.²³ Thus, selection of appropriate clinical endpoints remains one of the key challenges in clinical trial development.

Endpoints currently used in clinical trials for oncology drugs submitted to the FDA

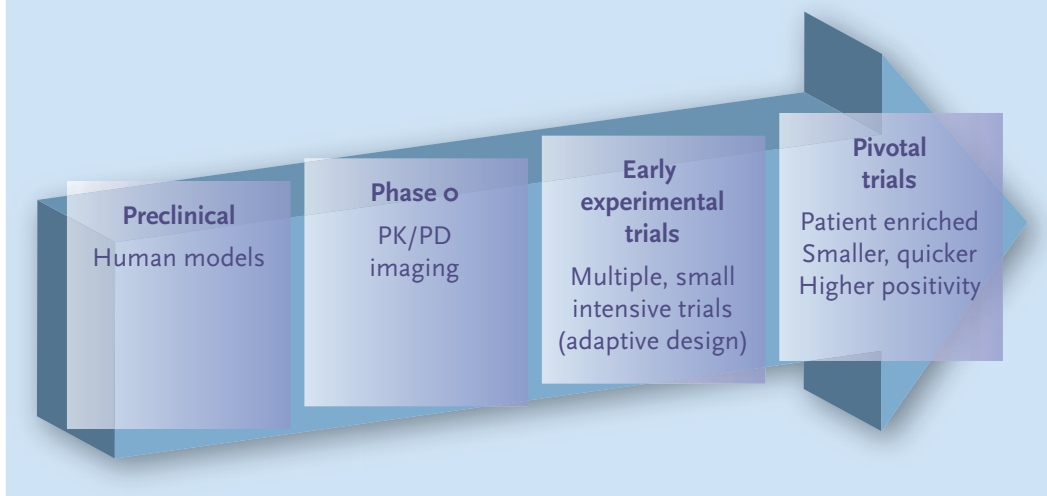
- > *Objective response*
- > *Time to disease progression*
- > *Palliation of disease-related symptoms*
- > *Overall survival*
- > *Progression-free survival*

Of importance, it is increasingly difficult to achieve a difference in overall survival (OS) between two study arms in advanced cancer, and this may be further prohibited by a potential blunting or confounding of initial treatment effect with the increasing number of therapeutically active options in second- and subsequent-line therapy and with the use of salvage therapies.²⁴ Furthermore, prolonged patient survival, which results in more modest OS hazard ratio differences between treatments, necessitates larger patient populations and longer trial durations to obtain clinically significant differences in OS. Progression-free survival (PFS) has recently been shown to be a valid surrogate for survival for chemotherapy regimens but not in combination with newer targeted agents in CRC and advanced breast cancer,^{25,26} and in principle is now acceptable to the US FDA as the basis for new drug approvals. Nonetheless, standardization with respect to tumor measurement, censoring rules, and timing of assessments in PFS is still required.²⁴ In addition, greater clarification is required for endpoints and trial design when comparing clinical strategies, such as treatment programs involving a structured series of interventions and/or breaks in therapy.

Thus, a new and sustainable model of oncology drug development is needed, leading to greater success of the pivotal trials, facilitating drug approval, and ultimately increasing the effective treatment options available for patients. The new model of drug development proposed by Dr. John Smyth (University of Edinburgh, UK) moves away from the traditional linear pathway of phase I, phase II, and phase III development and towards a more integrated and considered approach where data is generated in multiple studies at each phase of development and fully assessed and refined before proceeding to the next phase (Figure 4).

A new and sustainable model of oncology drug development is needed.

Figure 4. The new model



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Preclinical testing can increasingly be performed in human models, improving the validity of results. The first-in-human phase 0 trials, although extremely labor-intensive, have the potential to provide an enormous amount of information, particularly with respect to the PK and PD of a drug, which is invaluable for the future development of the agent. In particular, advances in imaging technologies provide an excellent means of confirming drug MOA. Instead of conducting phase I and phase II trials, multiple intensive small clinical exploratory trials could be performed concurrently to address numerous questions; trials with an adaptive design can be particularly useful at this stage. Data from these early experimental trials needs to be thoroughly assessed before the pivotal trials are designed. The use of small patient-enriched pivotal trials designed based on the results of these early phase trials should improve the likelihood of achieving phase III success and subsequent regulatory approval.

Small clinical exploratory trials can replace phase I and II trials and explore:

- > *Dosing*
- > *Dosing schedules*
- > *PK/PD parameters*
- > *Safety*
- > *Initial evaluation of efficacy*

As the clinical trial process evolves, it is therefore important to continually re-evaluate existing data to inform the next phase of development. A rigid process where the design of phase III trials occurs before the completion and analysis of phase II trials should be avoided. Instead, flexible developmental algorithms, in which strategies are adapted according to the data received, should be implemented.

Exploring Novel Approaches

Various collaborative initiatives have been established in recent years in response to the many challenges associated with oncology drug development. Two such initiatives, ARCAD and NEWDIGs, are pursuing innovative approaches in an attempt to address some of these challenges.

Aide et Recherché en CAncerologie Digestive (ARCAD)

ARCAD, an independent academic collaborative group of leading international oncologists, statisticians, and trialists was established with the intent of “accelerating the development of new drugs and treatment strategies in gastrointestinal oncology by establishing guidelines for smaller, faster, and less expensive clinical trials” (www.foundationarcad.org).²⁴ In particular, ARCAD drives an ongoing program of original research and consensus discussions focused on the optimal use of endpoints, biomarkers, and clinical trial design.²⁴

ARCAD is the secretariat of the Colorectal Cancer Specialists’ Collaboration (CCSC). The primary objective of the CCSC is to foster, enhance, and facilitate clinical trials in CRC, and by doing so to move the most effective new treatments through clinical development as rapidly and economically as possible. The main research initiative of the CCSC is not to perform clinical trials per se, but to generate a database of large clinical trials in advanced CRC. The ARCAD database, ACCENT, currently contains more than 20,000 patients. It is hoped that the data within the database will be used to standardize PFS and related endpoints to facilitate the economical development of effective drugs.

ARCAD also works closely with the seven task forces of the National Cancer Institute Gastrointestinal Intergroup. The colon task force discusses and prioritizes phase III concepts put forward by the cooperative groups in the US and Canada and provides feedback to the investigators and steering committees; once a phase III trial is underway, the task force monitors its progress. In addition, the task force discusses and comments on phase II trial design, particularly the design of large randomized phase II studies.

Ultimately, ARCAD aims to develop consensus guidelines that formulate specific evidence-based recommendations, engage advocacy with industry, regulators, and clinical oncologists, and lobby for new laws, which will lead to a more dynamic clinical development process, translating into the launch of new clinical trials requiring fewer patients, and less time and money.

New Drug Development Paradigms (NEWDIGs)*

The Massachusetts Institute of Technology (MIT) New Drug Development Paradigms (NEWDIGs) initiative was formed to address concerns that the current approach to pharmaceutical research and development is not extracting the full potential of innovation for either industry or the patient, and to validate new approaches that help realize that full potential. The initiative operates on the premise that innovation and product development never work in isolation, but require an entire system of support to take place and evolve – research strategies, product regulation, government policies, insurer policies, medical practices, and patient needs.

*This section is authored by the MIT Center for Biomedical Innovation.

Building on a history of leadership in industry transformation at MIT, NEWDIGS efforts at biomedical industry transformation rely on a rigorous analysis of current stakeholder interests, policies and incentives, and the desired future state of drug development. Key areas of need are addressed in a series of demonstration projects on real drug candidates, which may focus (for example) on a new approach to regulatory approval, improved clinical trial design, or new technologies to enable active monitoring of drug safety and effectiveness in real-world settings. An innovation “microenvironment” is set up around the projects by bringing together key stakeholders who provide the support system for drug development – companies, regulatory agencies, policy makers, and patients – and who are committed to implementing change and adapting when testing and evaluating new ideas.

With its home base in the neutral academic environment of MIT’s Center for Biomedical Innovation, the NEWDIGS initiative serves as catalyst, convener, and change agent as it assembles all the stakeholders and resources needed to test, evaluate and validate new models for the entire life cycle of pharmaceutical innovation.

The first demonstration project will examine a new approach to regulatory approval known as “progressive authorization.” In this approach, early studies are focused on establishing proof of efficacy, enabling an earlier no-go decision on compounds unlikely to succeed. Later stage studies examine safety, uncoupled from the evaluation of efficacy, and with evidence gathered from use of the drug in real-world settings in a limited patient population. Progressively larger populations are granted access to the drug as continuous monitoring and evaluation establish key safety benchmarks. The idea of continuous regulatory evaluation and engagement to reduce risk in approved drugs differs dramatically from the current “binary” approval/non-approval paradigm of today, and may lead to more timely access for patients to important new therapies, and more accurate assessment of safety and efficacy in actual clinical settings.

“Drug development is a process of managing risk and gradually decreasing uncertainty so that we can label compounds and give them to the patients who benefit.”

Dr. King Jolly, Quintiles

Conclusions

Oncology drug development needs to become more productive to ensure that the most effective treatments are available for patients in the future. The conventional rigid, linear process of drug development is outdated and is being replaced by flexible developmental algorithms that are responsive to advances in the understanding of a disease, emerging data of the investigational drug, and the evolving regulatory environment.

New bioinformatics platforms based on the integration of multifactorial parameters can be used to support decisions at each stage of the developmental pathway. Indeed, careful validation of a drug and its MOA in the context of a specific cancer, together with the identification of appropriate biomarkers early during development, will help to ensure that the agents with the most promising risk-to-benefit ratio are identified, while minimizing the risk of costly failures.

In recognition of the challenges currently facing oncology drug development, various highly collaborative initiatives have been established, bringing together multidisciplinary stakeholders from across academia, industry, regulatory agencies, and policy makers, among others. These initiatives will shape future developmental processes to maximize the success of oncology drug development and ensure that patients receive optimal treatment.

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Dr. Dave is Vice President and Global Therapeutic Head of Hematology-Oncology and Transplantation in Medical and Scientific Services at Quintiles where he oversees a number of hematology and oncology studies at all phases of drug development, as well as providing drug development strategy and guidance. Dr Dave has 15 years of academic hematology-oncology experience, during which he served as a Principal Investigator on multiple studies. He also served as Chairman of a NIH Study Section and chaired the Research and Development Committee at a major academic medical institution. In the latter capacity, Dr. Dave oversaw all research and Institutional Review Board-related activity, reviewing and managing more than 170 protocols annually. Dr. Dave is board certified in internal medicine, medical oncology, and hematology and was previously Associate Professor of Medicine at George Washington University and Assistant Chief of Hematology and Chief of Laboratory of Molecular Hematology at the Veterans Affairs Medical Center in Washington, DC.

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Board certified in oncology and internal medicine, Dr. Groves has more than 20 years' experience in drug development as corporate officer/senior manager, clinician, and researcher. Prior to joining Quintiles in August of 2007, Dr. Groves was at Ligand Pharmaceuticals Inc., starting in August 1999 as Vice President, Project Management, and corporate officer. From 1994 until joining Ligand, Dr. Groves held a number of positions at Sanofi Pharmaceuticals, most recently as Vice President, Project Direction, where he was responsible for the worldwide strategy of and project direction for late-stage Sanofi oncology projects. From May 1991 through October 1994, Dr. Groves served as Senior Project Director for the research division of Sterling Winthrop Corporation, and served as acting Vice President, Discovery and Clinical Research, Immunoconjugate Division. He was Director of Clinical Research and Development at CETUS Corporation from 1989 through 1991.

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Appendix I: Program of the Quintiles Ancillary Event at ASCO

Mapping the Future in Oncology Drug Development

Welcome and Introductory Remarks

*Paul Bunn
University of Colorado Cancer Center
(Chair)*

Biomarkers as an Approach to Improving Productivity

*Richard Gaynor
Eli Lilly and Company*

Improvements in Trial Design

*Gail Eckhardt
University of Colorado Cancer Center
Denis Lacombe
European Organization for Research
and Treatment of Cancer*

Regulatory Opportunities

*John Smyth
University of Edinburgh*

New Pilot Examples Exploring Novel Approaches

*Daniel Haller
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Audience Questions and Closing Remarks

Paul Bunn

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