Toward Efficient Trials in Colorectal Cancer: The ARCAD Clinical Trials Program

Aimery de Gramont, Hôpital Saint Antoine, Paris, France
Daniel G. Haller, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA
Daniel J. Sargent, Mayo Clinic, Cancer Center Statistics, Rochester, MN
Josep Tabernero, Vall d’Hebron University Hospital, Medical Oncology Service, Barcelona, Spain
Alastair Matheson, Foundation ARCAD, Paris, France
Richard L. Schilsky, University of Chicago, Biological Sciences Division, Chicago, IL

In 2002, Schilsky1 drew attention to growing concerns within the oncology community that established methods of clinical assessment had become poorly adapted to the needs of contemporary research: “As traditional end points prove more difficult to apply in evaluation of molecularly targeted therapies, a great need exists to define and validate surrogate markers of effect and of benefit. New clinical trial designs and end points are necessary to permit more efficient evaluation of putative cancer treatments.”

The targeted therapy era is now well established, but far from being resolved during the past 7 years, these concerns have become more pressing. Here, we first consider the difficulties confronting clinical cancer trials in greater detail, focusing in particular on colorectal cancer, then discuss how we are seeking to address them through a new model of independent academic collaboration that may have broad utility for clinical research.

**CLINICAL TRIALS: TOO SLOW, TOO EXPENSIVE, TOO LITTLE STANDARDIZATION**

The revolution in molecular biology continues to deepen our understanding of cancer and to generate new possibilities for treatment. Many targeted and immunomodulatory therapies are in development and there is a prospect of increasingly personalized management based on molecular diagnostics.2 However, our methods for evaluating new medicine remain laborious, imprecise, expensive, and incapable of efficiently processing the enormous number of agents currently in development.3,4 Large numbers of patients are required in registration trials to achieve statistical significance (Fig 1), a situation exacerbated by a preference for trials in which new agents are assessed as additions to standard care, rather than in head-to-head comparisons. Unless assessment methodologies are improved and greater standardization is achieved, the introduction of new therapeutics is likely to be slow and piecemeal, and many years will elapse before their full potential is realized.

The limitations and lack of standardization of traditional assessment procedures have already contributed to difficulties in recent regulatory approval decisions in oncology. Table 1 illustrates the continuing inconsistency between the primary efficacy assessments of registration trials, the overall survival results, and US Food and Drug Administration approval decisions in advanced colorectal cancer.3–12 For instance, the initial application for approval for oxaliplatin in advanced colorectal cancer, which was based on improvement in progression-free survival (PFS), was denied by the US Food and Drug Administration because no overall survival benefit was demonstrable.13 This agent was subsequently granted accelerated approval by the US Food and Drug Administration based on response rate13 and overall survival (OS) benefits for oxaliplatin.14 As a further example, erlotinib was recently approved in advanced pancreatic cancer,15 based on a statistically significant OS improvement that in the opinion of many is not clinically compelling. These difficulties are likely to multiply during the next decade.

**END POINTS AND BIOMARKERS**

Among the various challenges facing current clinical trials, two areas of particular interest to us are clinical end points and biomarkers. With respect to clinical end points, it is proving increasingly difficult in all forms of advanced cancer to achieve a significant difference in OS between two arms of a study investigating a single line of treatment. The growing number of therapeutically active options in second and
Table 1. Registration Trials for First-Line Therapy in Advanced Colorectal Cancer Therapy (oxaliplatin in combination was approved later, see text)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary Objective</th>
<th>PFS Benefit</th>
<th>OS Benefit</th>
<th>FDA Approval</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltitrexed</td>
<td>TTP</td>
<td>Inferior</td>
<td>No</td>
<td>No</td>
<td>Coconeï(^{13})</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>PFS</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>de Gramont(^{4})</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>RR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Douillard(^{5})</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>PFS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Saltz(^{6})</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>RR</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Hoff(^{7})</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>RR</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Van Cutsem(^{8})</td>
</tr>
<tr>
<td>UFT</td>
<td>TTP</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Carmichael(^{9})</td>
</tr>
<tr>
<td>UFT</td>
<td>OS(^{\dagger})</td>
<td>No</td>
<td>Yes(^{\dagger})</td>
<td>No</td>
<td>Douillard(^{10})</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>OS</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Hurwitz(^{11})</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; TTP, time to progression; RR, response rate; UFT, tegafur-uracil.

\(^{\dagger}\)Equivalency.

subsequent lines, as well as frequently used and often ethically mandated salvage therapies, may blunt or confound the initial treatment effect, ultimately prohibiting the demonstration of a statistically significant OS benefit.\(^{16,17}\) Prolonged patient survival and the resultant increasingly modest OS hazard ratio differences between treatment groups will necessitate increasingly large patient populations in clinical trials and longer trial durations to obtain statistically significant and clinically relevant effects on OS. PFS, defined as the time elapsed between treatment initiation and disease progression or death from any cause, was recently shown to be a valid surrogate for survival in the context of fluoropyrimidine-based chemotherapy for colorectal cancer, but not for combination therapy with newer targeted agents.\(^{16}\)

Similar findings were observed in advanced breast cancer, where several therapeutic options are available.\(^{16,18}\) Nonetheless, PFS is now acceptable in principle by the US Food and Drug Administration as a basis for approval of new drugs in advanced cancer.\(^{19}\) While this is a welcome step, greater clarification and standardization of multiple aspects of the PFS end point is required, for instance, with respect to tumor measurement, censoring rules, and the timing of assessments. Indeed, it is possible that PFS will need to be replaced by a related but simpler end point for disease control, such as progression rate at a fixed time point.\(^{20}\)

A further concern in end point selection is the growing importance of trials comparing clinical strategies (ie, treatment programs involving a structured series of interventions and/or breaks in therapy). Whereas industry trials are conducted to assess the clinical activity of individual agents, multiple-line and combinatorial strategies are necessary in trials and in practice to secure the maximum benefits for patients. As a specific example, several recent trials have evaluated therapeutic reduction strategies in the form of holidays\(^{21-23}\); such trials are of clear patient benefit but of more limited interest to industry. OS remains highly relevant as an end point for strategy trials, but traditional single-line end points such as response rate and PFS are less appropriate, and greater clarification is required for end points and trials design in this setting.

With respect to biomarkers, the difficulties are even greater than those relating to end points.\(^{24}\) The complexity of cancer biology, and its response to targeted therapies, allied with the relatively modest clinical benefit deriving from individual therapeutics and the large scale outcome studies required for biomarker validation, make the identification of robust predictive biomarkers for novel therapeutics challenging.\(^{25}\) Confirmed predictive biomarkers therefore remain few in number in most areas of oncology, and many candidates do not survive independent validation. Studies on hormone receptor status in breast cancer have been the most successful conducted on a common malignancy to date.\(^{26}\) In colorectal cancer, progress has been more modest, notwithstanding the identification of the KRAS mutation as a negative predictive factor for epidermal growth factor receptor–directed therapies, and the discovery of additional markers of resistance mediated through adjacent pathways.\(^{27-30}\)

These advances have given rise to new problems, including those of assessing continuous variables and identifying a robust and nonoverlapping set of markers from the multitude of markers under study. No reliable predictive biomarkers have yet been found for

<table>
<thead>
<tr>
<th>Table 2. ARCAD Principles and Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ARCAD Clinical Trials Program</strong></td>
</tr>
<tr>
<td>Ongoing program of original research and consensus discussions, focused on endpoints, biomarkers, and clinical trials design</td>
</tr>
<tr>
<td>Free academic collaboration—members receive no remuneration for attending meetings/participating in consensus discussions</td>
</tr>
<tr>
<td>Sponsorship will be sought to meet general running costs and costs of specific research initiatives</td>
</tr>
<tr>
<td><strong>ARCAD Database Project</strong></td>
</tr>
<tr>
<td>Initial goal will be clarifying/standardizing PFS and related end points</td>
</tr>
<tr>
<td><strong>Activities and outputs</strong></td>
</tr>
<tr>
<td>2009-2011 occasional discussion articles published</td>
</tr>
<tr>
<td>2011-2012 ARCAD Database Project results</td>
</tr>
<tr>
<td>2011-2013 position articles in advanced colorectal cancer</td>
</tr>
</tbody>
</table>

vascular endothelial growth factor–directed therapies, despite the
clear utility of such agents in colorectal cancer.\textsuperscript{31}

**CLINICAL TRIALS: TIME FOR AN UPGRADE**

The varied constituencies which together make up the clinical research
community all have a role to play in developing a more efficient
clinical assessment paradigm. Industry has a responsibility to conduct
clinical trials of therapies whose efficacy may be predicted by a biomarker
to be limited to specific patient subtypes, to target clinically meaning-
ful improvements in outcome, and to make publicly available data
that may accelerate the introduction of novel biomarkers and end
points. Public-private initiatives, such as the Foundation for the Na-
tional Institutes of Health Biomarkers Consortium,\textsuperscript{32} may help to
mobilize industry’s resources and pool them with those of academia.
Regulatory authorities must review their approval criteria as new
evidence emerges; the US Food and Drug Administration has taken a
lead in sponsoring initiatives on end points and clinical trials design
that will in time improve its own procedures, as well as supporting
translational research through its Critical Path Initiative.\textsuperscript{33,34}

In our opinion, the role of the independent academic commu-
nity remains the third critical element of this partnership. On one
level, original research is the key driver of progress, both through
individual projects and collaborations such as the Adjuvant Colon
Cancer End Points and St Gallen initiatives, which have contributed to
the adjuvant treatment of colorectal and breast cancer, respective-
ly.\textsuperscript{35,36} Government research organizations, such as the National Can-
cer Institute in the United States, play an integral role in sponsoring
such independent research as well as conducting their own initiatives,
and are important contributors to innovation in clinical trials assess-
ment.\textsuperscript{37,38} Equally importantly, independent academics should use
their collective voice to highlight important advances and influence
clinical practice, future trials, and regulatory policy. The major profes-
sional societies and leading journals have a key role at this level,
notably through the publication of guidelines. But there remains a
need for experts in individual areas of oncology to explore how to
optimize clinical development within their own fields and to make
consensus recommendations.

**THE ANALYSIS AND RESEARCH IN CANCERS OF THE
DIGESTIVE SYSTEM CLINICAL TRIALS PROGRAM: A MODEL
FOR INDEPENDENT ACADEMIC COLLABORATION?**

Recognizing these needs, a new model of independent academic col-
laboration has recently been initiated in gastrointestinal oncology. The
Analysis and Research in Cancers of the Digestive System (ARCAD)
Clinical Trials Program is a collaboration of oncologists, trialists, and
statisticians, formed specifically with the goal of accelerating the develop-
ment of new drugs and treatment strategies in gastrointestinal oncology
by helping to establish guidelines for smaller, faster, and less expensive
clinical trials (Table 2). The group’s initial focus is on advanced colorectal
cancer, a field that has evolved rapidly over the past decade.

The membership and organization of the ARCAD Clinical Trials
Program merits brief discussion, since it could readily be replicated or
adapted for use in other research settings. There is no formal mem-
bership, but rather a free collaboration that has grown from an initial
group of colleagues in Europe and the United States. The specialists
who have participated in the program to date are listed in Appendix
Table A1 (online only). The first meeting of the program took place in
June 2007 and subsequent meetings have been held during major
congresses in the United States and Europe, with plans that future
meetings will take place at least once yearly.

The ARCAD Clinical Trials Program was formally established by
Fondation ARCAD, a French research and patient-support nonprofit
charity, in which the ARCAD acronym stands for Aide et Recherche
en Cancérologie Digestive. A secretariat has been established provid-
ing logistical and scientific support, with coordination from Paris and
managerial assistance from scientific associates in the United States
and United Kingdom. The program has received, and will continue to
seek, funding from industry for logistical, secretarial, editorial, and
research support, and funding will also be sought from philanthropic
organizations. However, industry is not consulted or represented at
ARCAD meetings and has no scientific or editorial influence on the
activities or outputs of the program. The collaborating specialists have
received no remuneration or reimbursement for their participation,
although sponsorship will be sought to meet costs relating to infra-
structure, staffing, and academic research time in respect of specific
research initiatives established by the program.

The ARCAD Clinical Trials Program is active on two levels:
conducting original research and developing consensus positions.
With regard to original research, the first substantive contribution will
be the ARCAD Database Project. In this project, individual patient
data from a series of recently completed large trials in advanced colo-
rectal cancer will be incorporated within a single database. Once es-
ablished, the database will be analyzed by statisticians and trialists,
with the initial objective of clarifying and helping to standardize the
role of PFS and related end points in advanced colorectal cancer trials.
The database will be developed and used with appropriate consider-
ation for patient and commercial confidentiality, and will be modeled
on the successful and highly productive Adjuvant Colon Cancer End
Points database for adjuvant therapy.\textsuperscript{39}

The ARCAD Program’s consensus positions will be based in part
on its own research, but will also draw on the findings of wider
biologic, medical, and statistical research. In developing consensus
positions, the focus of the group will be on formulating specific,
evidence-based recommendations rather than statements of general
values. The principal output of the program will be one or more
position papers authored collectively by the collaborating specialists.
A position article on PFS and related end points based on results from
the database project is projected to be available in 2011 to 2012.

The specialists collaborating on the ARCAD project are appro-
priately qualified to form an authoritative consensus. All the group’s
members are directly involved in ongoing research, and the collabo-
raton includes leading experts in gastrointestinal oncology, advisors
to industry and regulatory authorities, editors of oncology journals,
members of key advisory committees, and officers of professional
groups and societies. Importantly, the function of the group is not
only to publish position articles but to engage in advocacy. It is antici-
patated that the findings on PFS will be of assistance to regulatory
authorities in evaluating new drug applications, and the group will
seek to engage with industry, regulators, and colleagues in clinical
oncology when its recommendations are finalized. In this regard,
ARCAD functions as a matrix organization, bringing together experts
from a variety of backgrounds and communicating its findings to a
number of distinct groups and organizations. Preliminary discussions
have taken place between ARCAD and representatives of the US Food and Drug Administration, who have encouraged the initiative. The group hopes to undertake further discussions with the US Food and Drug Administration and other regulatory authorities once the program’s research activities yield substantive results.

The ARCAD Clinical Trials Program is notable in that it has not been instigated by industry or any interest group, but is a free collaboration of experts with an interest in clinical development and treatment optimization. Collaborations led by academia are particularly desirable in the current clinical research environment in which the role of independent science risks becoming diminished; by working collectively, academics retain the capability not only to conduct original research but to form an authoritative consensus and influential voice. In this respect, the program may represent a model for international collaboration that is applicable in other fields of oncology and clinical medicine.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS
Conception and design: Aimey de Gramont, Daniel G. Haller, Daniel J. Sargent, Josep Tabernero, Alastair Matheson, Richard L. Schilsky


Final approval of manuscript: Aimey de Gramont, Daniel G. Haller, Daniel J. Sargent, Josep Tabernero, Alastair Matheson, Richard L. Schilsky

REFERENCES
DOI: 10.1200/JCO.2009.25.2544; published online ahead of print at www.jco.org on October 19, 2009