



# **Investigator Sponsored Trials in Oncology**

## **Strategy Position Paper**

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## Introduction

### *What is an IST Program in Oncology?*

Investigator-Sponsored Trials (ISTs) are a key component of product development in oncology. ISTs are studies in which a qualified investigator assumes the responsibilities of drug product Sponsor-Investigator in accordance with Food and Drug Administration (FDA) regulations and guidelines.

This position paper is intended to present a personal perspective of strategic issues regarding IST studies in oncology; tactical issues will be addressed in another position paper. It will focus on clinical trials that are intended to produce publishable data based on planned investigational interventions and observations, and will not address the related issues of expanded access, compassionate use and registry investigations. Although “post-registrational” studies are often restricted to approved products in other therapeutic areas, oncology IST trials are often initiated and even published prior to approval in the first indication. Similarly, there are excellent reasons why IST studies in oncology often involve indications and regimens that are not subsumed within the label, and may incorporate dose-finding, combination and combined modality trials.

IST trials may include studies done with an Investigational Agent, which is defined as an agent or formulation that has not been approved for marketing by the appropriate Regulatory Agency. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use, may be considered investigational.

Like other industrial activities, ISTs should be carried out based on Standard Operating Procedures that define the rules and processes. Elements that should be considered in SOP development will be discussed in the tactical position paper. Activities must be balanced between the efficient, close cooperation possible with field-based company personnel at the site, and the standardization that results from centrally-conducted processes.

These studies ideally involve clinical investigation outside of planned registrational efforts, and must be coordinated with those plans. In addition, the commercial arm of the company has a clear interest in the IST program, and IST activities must be included as a part of the overall product life cycle plan. Biostatistical components of the study design must be evaluated carefully to understand the likelihood of a valid and robust result. The IST program sometimes involves correlative studies to investigate scientific questions, and the expertise of preclinical scientists and clinical pharmacologists is often helpful in

evaluation of these concepts. Regulatory and legal aspects of IST trials often require input from the respective company departments. Medical publication specialists and medical information providers can make important contributions.

An integrated team approach is therefore essential. The Operating Committee (OC) provides a forum in which these stakeholders can form a consensus regarding each concept, early in the process of developing the trial.

Design of an effective IST program in oncology requires attention to basic principles:

1. Establish a clear-cut process and communicate it to all who are involved
2. Collect adequate information early
3. Anticipate time-consuming processes and eliminate them (or start them early)
4. Eliminate unnecessary steps (multiple reviews and sign-offs, etc)
5. Track progress regularly
6. Have a contract that covers all required elements (indemnification, budget, review of final product, drug supply, regulatory responsibilities, patent rights, etc.)
7. Most important: manage expectations of all involved

### ***Why are IST Studies Done in Oncology?***

The mission of an IST program is to generate reliable publications that will be helpful to customers and facilitate evidence-based use of the product. The priorities will usually be dictated by the potential impact of an IST study on clinical practice, by considerations of quality and speed, and by the potential value of the investigator as a clinical scientist and advocate for the product.

A few key concepts underlie post-registrational development in oncology.

First, oncologists adopt chemotherapy based on results of published clinical trials. Due to the high level of medical need, off-label use dominates the practice of oncology for most approved agents. Generation of published data in all potential indications is key to product success.

Second, combination chemotherapy is standard, preferred practice in oncology. Regimens combining a product with other active agents expand usage of both products. A marketed agent will be used in combinations and in other indications, either through random research activities or through a focused program.

Third, companies have an ethical obligation to facilitate generation of good research data for their products. Data-based Medical Information

prevents product misuse and hence promotes use that satisfies customer needs. Patient benefits must be maximized and risks minimized, particularly in a burdened population.

Fourth, corporate image (and sales) is enhanced by clinical research activities. There is little or no direct sales impact of study drug use for protocol subjects. There is some “halo” effect on non-protocol sales through increasing individual physician/center comfort and awareness, but the major impact is through publication.

In 2005, GCP-level research in oncology costs a company \$10,000 to >\$30,000 per patient, with no off-setting revenue. In contrast, ISTs usually involve per-patient costs of \$3,500 to \$10,000. Due to this cost advantage, and due to the relatively small size of each study, it is normal for an IST program in oncology to conduct many more trials than would be possible for a GCP-level program, and to explore indications and regimens that would not justify a registrational program.

Trials should be conducted if (and only if) there is a reasonable expectation of benefit for the patient. Inevitably, some IST trials will generate data that do not support the hypothesis that benefit has occurred, or generate data that reveal unexpected toxicities, toxicities that are unexpectedly severe, or toxicities that occur with higher frequency than expected. In oncology, these results seldom if ever decrease the market value of the product in its approved indication, and often allow the oncologist to avoid misuse of the product. Publication of these data and inclusion of such information in responses to unsolicited inquiries by health care providers is important. Company stakeholders must be educated regarding the positive value of such investigations, and should not fear to approve a valid study concept because of possible negative results.

Among the dozens of diseases treated by oncologists, hematologists, radiation therapists and other disciplines, a new product will usually reach the market with a label for one indication, which is often a subset of a single tumor type. Although the labeled indication is the only valid basis for promotion by the company, oncologists will want to use the product in other indications, particularly if the product is related to an older agent that is used in multiple indications and combination regimens. For older agents, more than 50% of clinical use is off-label, based on publications. To guide this process based on valid evidence, companies typically support studies prior to launch. Tables 1 and 2 list estimated program costs (for ISTs and market conditioning) and publication activities for several major oncology products in the pre-launch and first post-launch year. Note that IST trials often take at least 2.5 years from initiation to publication; launch-year publications result from studies started at least 2.5 years before product launch.

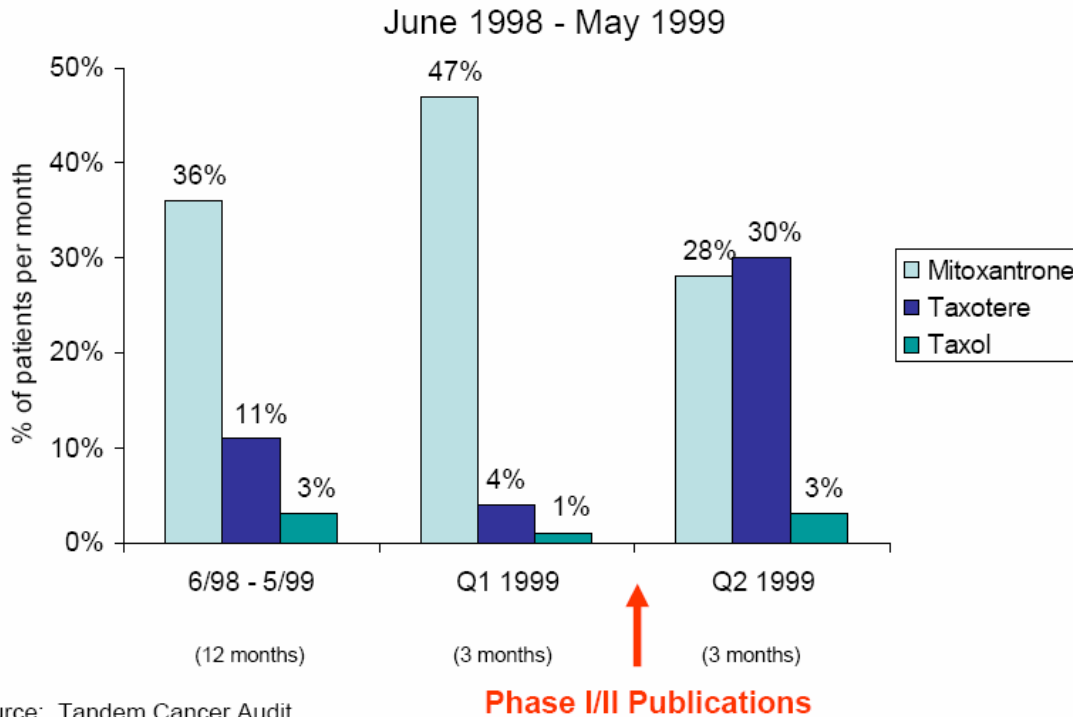
Table 1: Pre-launch Support in Oncology				
Product	Launched	2002 Sales	Pre-Launch Publications	Pre-Launch Spend (estimated)
Taxol (BMS)	1992	\$857 M	20 (11 clinical trials and 9 review articles)	NA
Taxotere (RPR)	1996	\$1261 M	53 (32 clinical trial articles and 21 review articles)	NA
Eloxatin (Sanofi)	2002	\$389 M	89 (71 clinical trial articles and 18 review articles)	\$10-15M
Rituxan (Genentech)	1997	\$1B	3 (2 clinical trial articles and 1 review article)	\$8-10M
Gemzar (Lilly)	1996	\$875M	38 (18 clinical trial articles and 20 review articles)	NA

Table 2: Launch Support in Oncology				
Product	Launched	2002 Sales	Launch Year Publications	Launch Year Spend (estimated)
Taxol (BMS)	1992	\$857 M	49 <i>(18 Clinical Trial Articles and 31 Review Articles)</i>	NA
Taxotere (RPR)	1996	\$1261 M	22 <i>(16 Clinical Trial Articles and 6 Review Articles)</i>	NA
Eloxatin (Sanofi)	2002	\$389 M	57 <i>(49 Clinical Trial Articles and 8 Review Articles)</i>	\$15-20M
Rituxan (Genentech)	1997	\$1B	3 <i>(2 Clinical Trial Articles and 1 Review Article)</i>	\$15-20M
Gemzar (Lilly)	1996	\$875M	28 <i>(14 Clinical Trial Articles and 14 Review Articles)</i>	NA

As an example of the best case impact of an IST program on the profile of a marketed agent, Figure 1 presents Tandem Survey data regarding treatment of hormone-refractory prostate cancer between June 1998 and May 1999. In this time period, docetaxel (Taxotere®, Sanofi-Aventis) was indicated for treatment of anthracycline-resistant metastatic breast cancer. Phase II trials had shown that Taxotere was active in lung, ovarian, head and neck, gastric, pancreatic, bladder and prostate carcinoma. Under the Medical Affairs IST program, a combination regimen incorporating Taxotere plus estramustine for hormone-refractory prostate cancer was studied in 1996-98. These Phase I/II studies resulted in two publications in March 1999 (Kreis et al, *Annals of Oncology* 10:33-38, 1999 and Petrylak et al, *J Clin Oncol* 17:958-67, 1999). In summary, the combination produced overall response rates based on PSA improvement in 63% of patients with hormone-refractory prostate cancer; 19% had normalization of their elevated PSA. More importantly, other studies had reported median survival of 10 months for mitoxantrone (the approved standard agent in this indication) and median survival from 11-17 months for other estramustine combinations. The Taxotere plus estramustine combination produced an unprecedented median survival of 23 months in this study. The immediate effects of these two publications on

Taxotere use in 2Q1999 can be appreciated from Figure 1. In that quarter, Taxotere use in prostate cancer surpassed that of mitoxantrone, the approved product; prostate cancer accounted for 20% of overall Taxotere sales in that period.

Figure 1: Taxotere Market Share Among Chemotherapeutics in Prostate Cancer



The long-term impact of these studies was actually more important. Based on these data, an Intergroup Phase III study was conducted (SWOG 9916, A Multicenter, Randomized Phase III Study of Docetaxel + Estramustine versus Mitoxantrone + Prednisone in Patients with Hormone-Refractory Prostate Cancer). When combined with a registrational Phase III study conducted by the company, an sNDA was filed, and in spring 2004, Taxotere received FDA approval for use in prostate cancer.

The relationship between an IST program and the commercial organization can be close, but must be managed by keeping all stakeholders aware of the needs of both groups. Fundamental points that the commercial organization needs to understand about IST studies:

- A clinical trial may not be the best solution to a marketing problem, and should not be the first (or only) option which is considered.
- Clinical trials are *never* to be used as rewards for prescribing habits



- Clinical trials are **never** to be used as inducement to change prescribing habits
- All clinical studies are to be funded and administered through the Investigator-Sponsored Trial (IST) process, or as company-sponsored and -monitored trials.
- Sales budgets will not be used for this purpose.
- All Adverse Medical Events are to be investigated and reported through Safety/Pharmacovigilance.

## IST Studies and Registrational Trials

The IST studies should complement registrational trials. Indeed, an IST program can permit Clinical Development personnel to focus their efforts exclusively on registrational efforts, and shape those trials to address their primary audience, the FDA.

The nature of the study will often be decided at the request of various extramural investigators who see potential applications for the product beyond its labeled indication. The program should have a mixture of larger studies that would be expected to have more impact on clinical practice, and smaller pilot studies that would generate a steady flow of publishable data and would be predicates to more expanded efforts if successful. Exploration of combinations with other marketed or experimental agents that have activity in the indication should be included if clinically relevant. Table 3 compares registrational and IST trials with regard to several key differences.

Table 3: IST and Registrational Trials: Key Differences	
• Registrational Trials	• IST Trials
– Company-Sponsored	– Investigator-Sponsored
• Company design	• Investigator design
• Company QA	• Investigator QA
– Focus on the drug	– Focus on practice
• Efficacy	• Convenience
• Safety	• Economy
– Investigational Drug	– Commercial Drug
– GCP Monitoring	– No GCP monitoring
– Audience = FDA	– Audience = Health Care Providers
– Product = NDA	– Product = publication

Appropriate Projects for IST support:

1. Studies of a company product in a labeled indication, employing a labeled regimen
2. Studies of a company product or investigational agent in a non-labeled indication. Such studies should be carefully designed to complement

- registrational development, rather than to compete or interfere with registrational projects.
3. Studies of a company product or investigational agent in combination with one or more marketed products or investigational agents, either from the company or from a collaborating partner.
  4. Studies of a company product or investigational agent administered by a schedule, route and/or dose that differs from that used in registrational studies.
  5. Studies of the pharmacokinetics and/or pharmacodynamics of a company product or investigational agent, or of concomitantly-administered agents, if such information is not required in the registrational plan.
  6. Studies of pharmaceutical compatibility of a company product or investigational agent with diluents, excipients or other drugs, outside of the labeled information.
  7. Studies involving translational research and/or methods development relevant to company products or investigational agents.
  8. Studies designed to investigate activities or toxicities of a company product or investigational agent that are not included in the clinical development plan for the agent in question.

The accelerated approval process provides early commercial availability of a product in situations of medical need, and is often used in oncology. Accelerated approval is usually associated with a post-marketing trial commitment to confirm clinical benefit and safety in an adequately-sized study. Such trials are not appropriate as ISTs, because GCP-level processes are needed for proper evaluation by regulatory authorities. Similarly, it is risky to promise regulatory agencies that data from ongoing ISTs will be provided in response to questions that are unresolved at the time of approval; the company does not have adequate control over the conduct of the trial or the quality of the data.

In terms of priorities for resource allocation, it is often useful to divide the IST program into three categories:

- I High-priority study (will have significant scientific or clinical impact)
- II Medium-priority study (will answer a useful scientific question, but may not have significant clinical impact)
- III Low-priority study (exploratory, limited applicability, or potential unproven)

Based on available information, the expected progress of active and planned IST studies should be tracked to provide information that can be integrated into the budget, publication and marketing plans. However, all stakeholders should be educated in the nature of IST studies; because the Sponsor-Investigator controls the project, estimates of trial milestone dates change as the trial progresses (usually later than originally planned, although exceptions often occur). It is very useful to track abstract publication in terms of the date of the meeting at which

the abstract is expected to be published, so it is important to be cognizant of abstract submission dates for all important meetings. Estimation of the date of (final) publication should be the date when the publication will be available, and the timeline should include a 6-month period for manuscript review and approval by the journal.

### ***Role of Good Clinical Practices in an Oncology IST Program:***

Good Clinical Practices (GCPs) are a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. The heart of company-sponsored GCP research is documentation of all processes involved in the generation, collection and analysis of clinical data, in a form that is amenable to review by regulatory authorities. In the GCP forest, if the fall of a tree is not documented, the tree did not fall.

Everyone involved in an IST should be made aware of the differences between GCP-monitored registrational studies and non-GCP ISTs. In particular, multicenter studies may require the assistance of a Contract Research Organization to collect and possibly to analyze data. Such companies frequently attempt to apply their standard GCP-based processes to IST studies, and if this is permitted, the cost and inconvenience of the study will be greatly increased with minimal improvement in overall quality of the eventual publication. Web-based data collection systems are available, and provide an inexpensive solution to the problem.

The absence of GCP monitoring by the company does not absolve the company from ascertaining that accepted standards of clinical research are being employed in the trial, and the contract and protocol must contain language that establishes the responsibilities of the Sponsor-Investigator. In particular, CIOMS VI recommends that "If company provides any support for an independent trial (e.g., supplies, research grant, etc.), it should obtain at a minimum all reports of serious suspected adverse reactions from the investigational site(s)". Note that this recommendation should be applied to both IND and IND-exempt studies, although the latter may not have reporting responsibilities to the regulatory agency. In general, however, the strict documentation processes (paper trail) that are an essential part of GCP research are not done in ISTs.

### ***Appropriate IST Investigators:***

Clinical and preclinical data available for the product may suggest that use of the product in combination with other active agents should result in regimens that are true advances in the care of patients with malignant disorders. Certain combinations present limited potential risk and wide potential applicability in

community practice; trials to address these possibilities would be appropriate to conduct in large community-based consortia.

Some investigators are well prepared to contribute patients to large, company-sponsored registrational studies, but are not experienced in the role of Sponsor-Investigator. Others are not interested in company-directed research, but prefer to investigate hypotheses that they have generated independently. Investigators who are active members or subcommittee chairs within Cooperative Oncology Groups are particularly important, because they can provide an entry point to larger Cooperative Group studies.

Other trials require application of specialized translational research methodology to investigate the pharmacodynamics of the treatment or effects on the disease. These trials should be conducted by experienced academic centers that have the required laboratory capabilities. Trials of regimens with higher theoretical potential for unexpected toxicity, or involving patient populations with higher risk of disease-related adverse events, should be targeted to centers that are experienced in the close monitoring required by such investigations. In particular, investigators often think that pharmacokinetic information should be collected because it is possible, rather than because it is needed to answer the scientific question. Collection of pharmacokinetic data involves considerable expense and inconvenience to both patients and support staff. If such information serves a scientific purpose, the study should be done at a site that has appropriate experience in the collection, processing and analysis of such samples. Similarly, collection of quality-of-life data is often included in study designs without adequate consideration of the limited value of such data in small study populations.

Finally, the best protocol cannot be successful without an adequate patient population for the efficient execution of the trial, and full commitment of the institution, the investigator and other parties to the trial as a high-priority activity. Enthusiasm is the single most valuable characteristic of an IST investigator.

Note that the selection of a study design and protocol details usually is based on the area of specialty of the investigator, which may not extend to all areas of cancer treatment. For example, a study of combined modality treatment (chemotherapy given concurrently with radiation therapy) should be conducted only with close, planned collaboration between a radiation oncologist and a medical oncologist.

Investigator and protocol selection has implications beyond Medical Affairs. If the labeled indication and commercial focus of the product is in a subspecialty such as ovarian cancer, but an IST study develops an important publication in prostate cancer, the company needs to understand the differences between the practice of gynecologic oncology and urologic oncology. Sales representatives must be trained to understand the restrictions on off-label promotion, and why

these mean that they cannot shift their activities from the labeled indication. In particular, a strict compartmentalization between IST trials and sales representatives is prudent. Confusion may arise at sites where sales representatives inquire about the progress of an IST; reps should never initiate such conversations, and if investigators or their staff initiate the discussion, they should be politely referred to the appropriate MSL.

The company should be able to provide trial support beyond quality review and financial grants. Listing IST trials with patient advocacy groups and other compilations of clinical trial resources can enhance accrual. The investigator should be able to disseminate information about the trial through local referral networks (tumor boards, etc.) and regional advisory boards conducted by the company. Sometimes, accrual can be facilitated by publication of an interview between the investigator and local print or broadcast media. There are service providers that can facilitate such events. The company Medical Information resource should be able to refer unsolicited patient or Health Care Provider inquiries to appropriate clinical trials, and summary sheets can be provided if requested. However, Sales Representatives should take care to avoid active solicitation of such referrals.

## Conclusions

1. Investigator-Sponsored Trials (ISTs) are a key component of product development in oncology.
2. The mission of an IST program is to generate reliable publications that will be helpful to customers and facilitate evidence-based use of the product.
3. Companies have an ethical obligation to facilitate generation of good research data for their products.
4. It is normal for an IST program in oncology to conduct many more trials than would be possible for a GCP-level program, and to explore indications and regimens that would not justify a registrational program
5. The IST studies should complement registrational trials and be coordinated with them.
6. Post-marketing trial commitments resulting from accelerated approval are not appropriate as ISTs.
7. Oncology IST studies are often initiated and even published prior to approval in the first indication.
8. IST studies in oncology often involve indications and regimens that are not subsumed within the label, and may incorporate dose-finding, combination and combined modality trials
9. In terms of priorities for resource allocation, it is often useful to divide the IST program into high-priority studies, medium-priority studies, and low-priority studies.
10. ISTs must be carried out based on Standard Operating Procedures that define the rules and processes.

11. IST trials often take at least 2.5 years from initiation to publication; launch-year publications result from studies started at least 2.5 years before product launch.
12. The relationship between an IST program and the commercial organization can be close, but must be managed by keeping all stakeholders aware of the needs of both groups.

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