

Oncology Research Today

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PRA International

A Bold New Future for Oncology Research

By Dr. Ute Berger, Sr. Director, Therapeutic Expertise, and Dr. Robert Shepard, Vice President, Scientific Affairs

According to a recent Business Insights report on Innovative and Targeted Cancer Therapies, the companies that are innovative in their cancer research are those that will see sales growth over the next five to ten years. This requires a shift in how cancer drug developers approach their business.

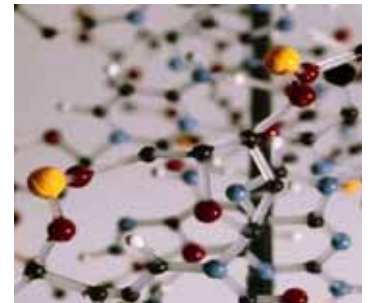
Limited progress has been made in the past 50 years in finding cures or fully effective palliatives for cancer. Drug developers were focused on two types of therapies—chemotherapy and radiation—and also tackling one

type of cancer at a time. Until recently they were not making much headway in the fight against cancer.

Chemotherapy and radiation alone as well as in combination or high dose chemotherapies result in longer disease-free survival. They can also improve overall survival in the metastatic setting of the most frequent tumor types like breast cancer, colorectal cancer as well as ovarian cancer, but have not been curative for most patients. Therefore, there is a need to develop new approaches towards curing cancer.

The New Focus

Cancer research today is focusing on detecting molecular de-



facts that lead to cancer with the goal of generating targeted therapies. One example is the detection of the Jak2 mutation in chronic myeloproliferative disorders a few years ago, resulting in the development of Jak2 inhibitors. Meanwhile several Jak2 inhibitors are in clinical development.

Several new approaches to killing tumor cells more selectively

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Capabilities Required to Unlock the "India Opportunity"

- *Thorough knowledge of local regulatory processes & operations*
- *Deep relationships with investigators & vendors*
- *Expertise in execution for FDA/ EMEA requirements*
- *Local application of global processes & systems*
- *Governance structures*

India—Opening Doors for Cancer Research

With its large population, a well trained, English-speaking physician pool and a progressive regulatory environment, India provides many opportunities for swift, meticulous and cost-effective clinical trials, especially for cancer. PRA is currently conducting 15 trials in India, including six in oncology.

There is a high incidence of cancer in India, with about 3 million diagnosed cases and 850,000 new cases diagnosed each year. Among this large patient population, every year 300,000 to half a million cancer victims die each year. By 2025, cancer incidence is expected to grow by 500 percent because of

aging and the prevalence of tobacco use in India. About half of the cancers are related to the lung, mouth and cervix, while other common cancers include the breast, head and neck, and pancreas.

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PRA and IntrinsiQ Align for Exclusive Data Access



Through an exclusive licensing agreement with IntrinsiQ Research, PRA International has access to the company's Intelidose™ electronic medical record software used to manage oncology patients in the United States. IntrinsiQ Research collects real-time, longitudinal data on more than 45,000 patient treatments for nearly every type of cancer monthly from more than 600 oncology physicians. The data can be used to precisely forecast patient recruitment and also to influence protocol design, thus improving the process and accelerating the pace of clinical trials.

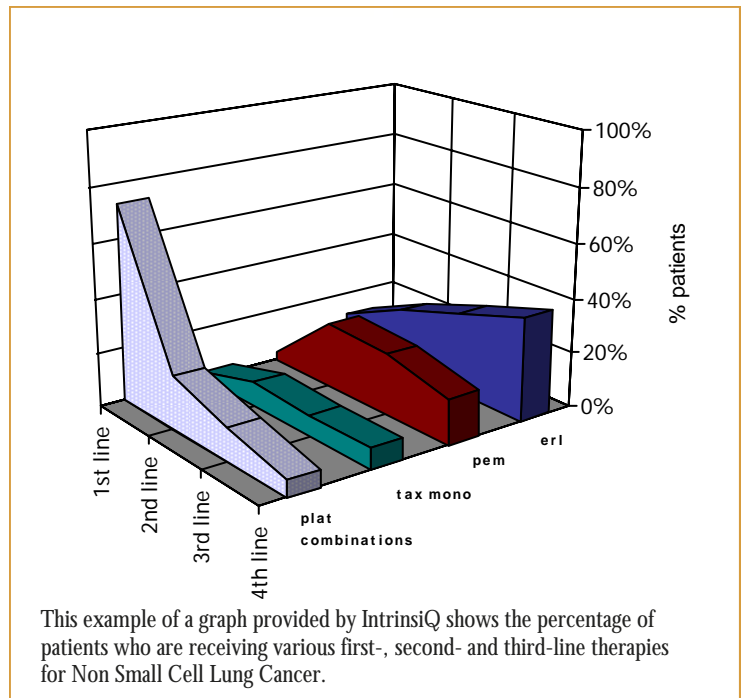
IntrinsiQ's proprietary warehouse of oncology data holds information covering more than 107,489 cancer patients and more than 6.7 million administrations of drug therapy.

The data gathered via Intelidose is entered by medical oncologists and hematologist/oncologists who use the application in their practice. These

users are representative of the overall population of oncologists who practice in the US with respect to specialty, size of practice, type of practice and geographic location.

Kent Thaelke, PRA's Senior Vice President, Therapeutic Expertise, said, "The most critical issue today in oncology drug development is the ability to

determine the available patient population for any specific tumor type. PRA is using the data from IntrinsiQ Research to accurately predict patient enrollment for clinical trials in oncology and we have already demonstrated the benefits to several sponsors by exceeding their expectations for patient recruitment timelines and budgets."



US Oncology Alliance Streamlines Clinical Research

PRA International and US Oncology Research, one of the largest cancer research networks in the United States, are working together to accelerate the clinical development of new cancer treatments.

Kent Thaelke, Senior Vice President and Head of Therapeutic Expertise at PRA said that the "expanded access to

patients and investigators translates into faster study start-up, patient accrual and a more productive development process."

US Oncology's working relationships with research sites lead to a more detailed feasibility assessment to accurately forecast the eligible population and timeframes required for a trial. Also, by eliminating the duplication of

efforts, regulatory review can occur more quickly.

US Oncology Research has 536 physicians enrolling patients for Phase I-IV cancer trials, 88 research sites and 72 open research trials. Its national network of top cancer researchers has contributed to the development of 23 of 29 of the latest approved cancer-fighting drugs.

Meet John Constant, PhD — Oncology Design Expert

John Constant, PhD, Vice President, Scientific Affairs with a specialization in oncology, has more than 15 years in pharmaceutical research and more than 20 years of experience in applied statistics. He has served on Data Monitoring, Steering and Advisory Committees and as statistical advisor in oncology to various biotechnology and pharmaceutical companies.

With degrees in statistics from the University of Waterloo and academic appointments at several universities including a Visiting Professorship in Statistics at University of California at Berkeley, he is one of our resident experts in statistical design.

Dr. Constant makes frequent trips to the FDA on behalf of

PRA's clients, working in that capacity with key FDA figures. He has also provided statistical consulting services to clients for oncology submissions in response to ODAC feedback. Additionally, he has participated in (voted on, organized and written charters for) many DSMBs for oncology studies.

In oncology, his experience includes design, analysis, reporting and regulatory agency representation on national and global trials. Dr. Constant has to his credit many regulatory submissions in ovarian cancer, prostate cancer, myeloma, lymphoma, melanoma, renal cancer, head and neck cancer, lung cancer, pancreatic cancer, colon cancer and breast cancer.

On oncology clinical development at PRA Dr. Constant says, "It's very exciting to be work-

ing at the leading edge of oncology clinical development. Since coming to PRA I've worked with both medical and biostatistical thought leaders across multiple indications with dozens of FDA and EMEA interactions, as well as on blockbuster therapies such as Nexavar, Avastin and Velcade."

"In NSCLC alone," he adds, "in the last year I've been involved in design and regulatory interactions with four major programs including about 5,000 patients in first through fourth lines and an orphan sub-indication for different sponsors. The broad experience on major oncology trials across functional areas at PRA provides a very supportive environment for this sort of high level development."



John Constant, PhD
Vice President,
Scientific Affairs

India—continued from page 1

Patient recruitment in India for oncology trials can be up to seven times faster than in the U.S. In 2006, PRA formally launched clinical operations in Mumbai and a data management center in Pune. Both units are enjoying buoyant growth. PRA continues to invest in developing relationships with the oncology investigator community at India's first- and second-tier oncology centers, in order to ensure site capacity that will meet sponsors' demands.

Mumbai's Tata Memorial Hos-

pital is a leading site for PRA's oncology studies. With 440 inpatient beds, it conducts 10,000 major operations and 5,000 radiation and chemotherapy treatments per year.

"PRA India is able to offer international sponsors the combination of local knowledge & relationships along with global expertise & processes required for timely study initiation and subject enrollment in India," said Nermeen Varawalla, Vice President, Investigator Relations.

India has more than 500,000 medical doctors, with 17,000 more emerging from India's 171 medical colleges each year. Many leading specialists obtain post-graduate training in the U.S. or U.K. A large and growing number of physicians trained in Good Clinical Practices are ready for global trials, and they are able and willing to meticulously adhere to study protocols. Additionally, because of strong patient-doctor relationships, patient retention is high.



Command Center Keeps Large Oncology Program on Track for Pivotal Colorectal Trials



“We achieved a near zero outstanding query status for tumor data and we certainly couldn’t have done it without you!” —

Client’s Representative

The use of PRA’s Command Center model led to on-time completion of the interim milestones for ten Phase II and III trials for a major biotechnology sponsor and its important new cancer drug. The large program, which studied four indications, including colon cancer, involved more than 1,200 sites and nearly 7,500 patients.

Because of the program’s size, PRA organized a team of dedicated staff into a Command Center—trained across all studies—to recruit and qualify investigational sites and manage

their activities, process regulatory documents, and provide support for patient recruitment activities and ongoing site needs. The Command Center kept weekly contact with the sites to support patient recruitment and monitor enrollment, ensure supply of clinical materials, schedule in-services and collect information necessary to project CRF in-flow from the sites. The Center also assisted with query resolution during the analysis. By locating the staff centrally, PRA facilitated consistent communication across the program.

The Command Center included 15 lead CRAs, in-house CRAs and clinical operations specialists.

The Command Center responded to up to 900 queries per month from the sites, especially when traveling monitoring CRAs were unavailable. The sponsor’s satisfaction survey yielded high ratings for the Command Center from the 80 responding sites. Moreover, the Center helped build strong rapport and created a positive study experience for investigators.

Prioritized Data Collection Leads to On-time Database Lock

One of PRA’s many successes in locking a database on schedule and per sponsor quality standards, involved a large Phase II and III colorectal cancer program that included more than 250 sites, 1,125 patients, 150,000 Case Report Forms, 39,000 queries, and in excess of five million data points.

Because the trials had nearly overlapping pivotal interim analyses, PRA’s clinical and data management teams proactively prioritized data collection to handle the large volume and avoid unexpected boluses. This prioritization involved an initial focus on data collection and cleaning for completed and discontinued patients, then for sites with issues and sites with the highest enrollment, and then all others. This planning and imple-

mentation was a critical first step to ensure that all data was collected in the most effective manner to lead toward a successful database lock.

After arrival at PRA, patient data was divided into subsets for entry, review, query resolution and quality control processing. Resourcing assignments were also aligned with these tasks, resulting in highly specialized teams focused on specific areas. Additionally, because of the importance of tumor assessment for the efficacy analysis, PRA selected a team of data managers to review and query tumor assessment data for each patient. These tumor assessment specialists provided a high level of consistency to the review of tumor data and developed close working relationships with the spon-

sor’s clinical staff.

The above-mentioned plans and strategies were closely governed under the umbrella of PRA’s functional and project management staff. Ongoing weekly functional and project team meetings through the final analyses successfully ensured that work was progressing according to timelines and that resourcing modifications were completed as needed. Also, they provided an opportunity to address study-specific issues or questions.

PRA’s prioritization of data collection and organization of the workload enabled the databases for the Phase II and III studies to be locked on schedule and to sponsor quality standards, ultimately leading to a successful BLA filing and FDA approval.

Why Choose Electronic Data Capture Over Paper?

With PRA's EDC system, ClinPhone, clients soon learn its many advantages:

- Faster data collection
- Better initial data quality
- Eliminated management of paper (tracking and process-

- ing) and associated overhead costs (shipping)
- Fewer and less duplication of queries
- Speedier query resolution process
- Continuous and parallel processing of data

- "Real-time" access to data
- Improved resource utilization
- Reduced time from last patient last visit to database lock

User friendly, PRA's ClinPhone also provides robust automatic edit checks for high quality data.



PRA's Global Reach Expands Breast Cancer Enrollment

A long-standing client approached PRA to conduct a Phase III breast cancer trial in the United States. The trial was projected to require 12 months to enroll more than 900 patients at 130 sites. After the drug was approved shortly after initiation of the trial, enrollment was slow due to placebo control. PRA and the client immediately recognized that the trial would take much more time to meet the enrollment goal.

Capitalizing on its experience conducting trials outside of the US, PRA recommended to the client to expand the trial to central and eastern Europe (CEE) and Mexico. With the client's permission, PRA conducted feasibility and confirmed significant interest and patient availability at a large number of investigational sites and also that the standard treatment practice in each country met the protocol's requirements.

With the client's approval, initial sites were activated in Poland, Russia and Mexico in 2-3 months. Approximately 40 sites enrolled over 800 patients within 9 months in these countries. On average, each site enrolled 20 patients; in the U.S. PRA had enrolled 2-3 patients for just over 90 activated sites. Enrollment was completed two months ahead of the revised timeline, without affecting trial management or data quality.

PRA's Presence Spans Six Continents



PRA Around the Globe

- ***Trials conducted in more than 60 countries***
- ***Clinical Staff across the globe***
- ***Regulatory knowledge and experience in every region of the world***
- ***Data Management hubs in 4 world regions providing 24/7 coverage***

Clean Data Facilitates Renal Cancer Drug Approval



A new oncology drug approved by the U.S. Food & Drug Administration (FDA) and the European Commission to treat patients with advanced renal cell carcinoma (RCC) was the first such drug developed and approved in more than a decade. The landmark drug proved, in trials conducted by PRA, to double progression-free survival rates in patients with advanced RCC—with minimal but “manageable” side effects.

overall original timeline by one year, accelerating the process so the client could submit for approval and make the life-extending drug available sooner.

This success is largely due to the efforts of PRA’s highly committed project, clinical and data management teams, as well as to a strong, open client relationship. Also, the study team built close relationships with the study nurses and doctors, since

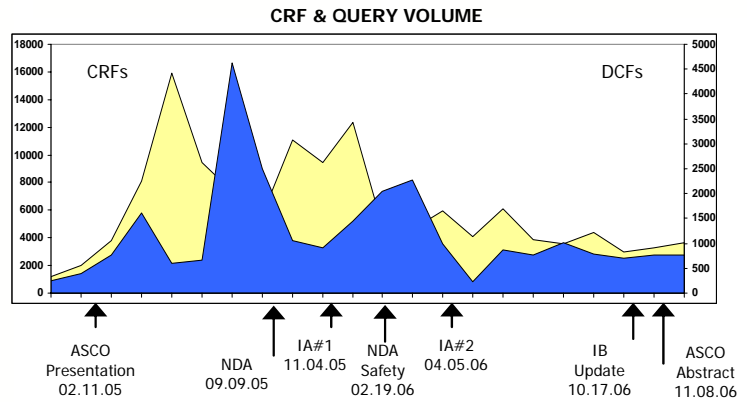
much was required from them over an extended time.

For the fifth time in three years, a major cancer drug, a tyrosine kinase inhibitor for which PRA conducted the pivotal trials, was approved by the FDA. It also marked the first simultaneous FDA approval of an oncology drug for two indications—advanced kidney cancer (RCC) and gastrointestinal stromal tumors (GIST).

“The team members on this study were some of the best and most skillful people I have ever worked with.”

—Client Executive

Over three and a half years, PRA conducted the Phase III clinical trials. With 900 patients enrolled on schedule in nearly 20 countries at almost 125 sites, PRA exceeded the enrollment minimum by 20 patients, with the FDA-required 100 U.S. patients enrolled two months early. The database lock for the interim analysis was done in five weeks, significant in a trial in which the timing depends on the unpredictable progression of the disease. PRA shortened the



With close collaboration, clinical and data management teams collected, processed and cleaned a large volume of data to meet two formal interim analyses, NDA safety data sweeps and various other commitments. At the peak, 16,000 CRF pages and over 4,000 DCFs (per month) were processed. Meeting the commitments was only possible through careful management and oversight by the entire project team. Key success factors were early identification of potential issues and proactive issue management.

Ovarian Cancer in the Future—What’s Expected?

Forecast epidemiology of ovarian cancer across the seven major markets, 2006-12

	2006	2007(f)	2008(f)	2009(f)	2010(f)	2011(f)	2012(f)
EU 5 (France, Germany, Italy, Spain & UK)							
Incidence	28,647	28,898	28,943	28,987	29,030	29,072	29,114
Prevalence	74,009	74,123	74,236	74,345	74,452	74,557	74,659
Japan							
Incidence	6,581	6,743	6,747	6,750	6,753	6,757	6,760
Prevalence	22,008	22,019	22,030	22,042	22,053	22,064	22,075
US							
Incidence	23,710	24,508	24,733	24,961	25,190	25,419	25,644
Prevalence	71,024	71,677	72,337	73,002	73,674	74,342	75,000
Total							
Incidence	58,938	60,149	60,423	60,698	60,974	61,248	61,517
Prevalence	167,041	167,820	168,603	169,389	170,179	170,962	171,734

SOURCE: Business Insights: IARC/Globocan 2002



Clinical Trials Needed for Ovarian Cancer—An Overview

By Robert C. Shepard, MD, FACI, Vice President, Scientific Affairs, Hematology/Oncology

“The frustration experienced by clinicians who treat ovarian cancer was evident” at a recent meeting of the American Society of Clinical Oncology, according to a leading expert on ovarian cancer. There are more than 800 trials ongoing in the U.S., with over 300 actively accruing therapeutic trials for advanced disease. However, the cure rate for Stage IV remains at zero, and survival has been only minimally improved over the last four decades.

In 2007, there were 22,430 new cases and 15,280 deaths in the U.S. Epithelial carcinoma accounts for over nine out of ten cases and less than 5 percent are familial. These familial cases are predominantly a genetic linkage to the BRCA1 locus, and patients with this have a better prognosis

Ovarian cancer has been called a silent killer as there are no symptoms or signs with early

disease and the vague symptoms of abdominal pain, early satiety, bloating, etc. are from advanced disease, leading to most patients having widespread disease at presentation. The only curative treatment is surgery which is successful only in early disease.

The European Organization for Research and Treatment of Cancer and National Cancer Institute of Canada have an ongoing trial with neoadjuvant chemotherapy followed by debulking surgery for Stages III and IV to determine if this will improve the survival rate. Standard therapy is either intraperitoneal or intravenous platinum-based chemotherapy after surgery which consists of paclitaxel with either cisplatin or carboplatin. The Gynecologic Oncology Group and others have done many studies over the years looking at more aggressive chemotherapy, but the results have been negative. These include ones with high dose chemotherapy and autologous bone marrow transplant; sequential doublets with carboplatin/

topotecan followed by carboplatin/gemcitabine; and triplets, including adding gemcitabine, pegylated liposomal doxorubicin, or alkylating agents such as cyclophosphamide to platinum/paclitaxel.

Maintenance or consolidation chemotherapy as well as using chemosensitivity assays have also not improved survival. Recent studies show that secondary cytoreduction with a second surgery or “second look laparotomy” has also not increased survival, although it was the norm for decades until a clinical trial was conducted. One recent study suggested that the mainstay of therapy with optimal debulking has better results just from selection bias, with the patients able to be optimally debulked even when they have less extensive and aggressive disease at presentation.

Treatment for recurrence and Stage IV disease is divided into two categories:

- Potentially platinum sensitive patients who recur after

“Patients with any stage of ovarian cancer are appropriate candidates for clinical trials.”

—National Cancer Institute

more than six months

- Platinum refractory which recurs less than six months after chemotherapy.

The main FDA-approved therapies used for platinum refractory disease are topotecan, pegylated liposomal doxorubicin and gemcitabine. Many other agents have been tried, but none has been a cure or improved overall survival or even time to progression. That is why clinical trials with new investigational therapies are so important for patients with ovarian cancer.

Bold New Future—continued from page one

are currently under development in this pioneering phase of oncology research:

- Angiogenesis, which controls the blood supply to cancer cells
- Pro-apoptotic, in which cancer cells lose their selective advantage over normal cells in avoiding a programmed cell death
- Targeting cell pathways of

growth, which are different in cancer cells than in regular cells

Business Insights reports that of the top ten leading cancer innovatives in 2006, four were monoclonal antibodies, three were novel chemotherapeutics, two were targeted therapies and one was a novel hormonal. That year six innovative cancer therapies to reach the market generated sales of more than \$1

billion. The prediction is that targeted therapies and kinase inhibitors will dominate the field among future cancer therapy developments.

Applicability to extended indications for therapies proven effective for an initial type of cancer is also going to be a growth driver for the industry. Last year, when Sutent™ became the first cancer agent ever to be approved for two

indications simultaneously—gastrointestinal stromal tumors (GIST), a rare stomach cancer, and advanced kidney cancer—it set the stage for looking at a broad range of cancers with each new molecule being developed as well as those already explored, tested and approved for a single cancer type.

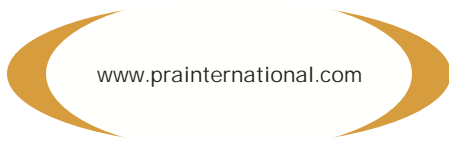


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About PRA International

PRA International is a global, full-service clinical research organization with expertise in all therapeutic areas but especially in oncology, central nervous system, respiratory and cardiovascular indications, also providing safety, regulatory and data management services. With more than 3,500 employees based in North America, Europe (including Central and Eastern Europe), Asia, South America, Australia and South Africa., PRA conducts trials on all six continents.

PRA International offers a broad array of services encompassing the entire spectrum of clinical development programs, from filing of Investigational New Drug (IND) and similar applications to product registration and post-marketing surveillance. PRA's global clinical development services include:

- Phase I - IV study management
- Feasibility and protocol design
- Clinical development strategies
- Data Monitoring Committee management and support
- Traditional and electronic data capture (EDC)
- Prospective and retrospective database integration
- Regulatory approval strategies and electronic submissions

PRA's Oncology Experience Since 2003

Indication	# Studies by Phase				Consulting	Total # Studies	Total # Sites	Total # Subjects	Total # Current Studies
	I & I/II	II/ IIb	III/ IIIb	IV					
Colorectal	2	11	8	3	2	26	2,002	9,091	16
Breast	5	11	4	0	1	21	676	5,599	6
Renal	2	2	5	0	1	10	554	2,640	5
Ovarian	2	2	1	0	1	6	219	1,141	4
Multiple Solid Tumors	15	3	0	1	10	29	225	14,364	18
Multiple Myeloma	0	2	7	1	3	13	517	2,597	6
All Oncology (Current and Completed)	56	92	57	17	56	278	10,738	108,276	137