

# The Evolution of Oncologic Drug Development



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Oncology

Despite a doubling in the number of candidates in the cancer drug pipeline from 1990 through 2006, the overall US approval rate for cancer drugs remains low (8%).<sup>1</sup>

As the cures for cancers remain elusive, cancer treatment approaches—especially for hematologic, prostate and breast cancers—have evolved into chronic therapies with long-term disease management. To support this evolving paradigm, drug developers are focusing on orally bioavailable therapies (alone or in combination with other therapies) with easier-to-use dosing regimens.

Two overall patterns have emerged in oncologic drug development within the US and the EU over the last 10 years:

- The first pattern involves targeting refinement. Historically, cytotoxics and cytostatics sought to block malignant cell replication at the DNA/nucleus/mitosis level in an indiscriminate way. Newer entities seek to target specifically altered pathways (e.g., mammalian target of rapamycin (mTOR) inhibitors downstream of several possibly altered pathways or imatinib focusing on a unique altered receptor) either by small molecules or monoclonal antibodies (mAbs). While beyond the scope of this article, the search of computerized drug designs aimed at increasing specificity is another novel oncologic approach worth mentioning.
- The second pattern involves the reformulation and chemical modification of existing oncology products. The goals behind these efforts include:
  - prolonged lifecycle management (for economic benefits)
  - improved safety
  - better quality of life while on treatment

- potential survival benefit through better compliance and full dose delivery
- ease of administration (oral route vs. venous catheterization sometimes requiring implantable devices or even an infusion pump)
- an improved health economic benefit (cost difference between taking oral tablets at home vs. IV administration in a community office or outpatient infusion center)

Efficacy is the key issue; however, better-tolerated and less-complicated dosing schedules remain important issues in oncology so patients can be compliant and obtain maximum benefit, hospital costs can be trimmed, and patients continue to enroll in clinical trials.

This article discusses selected approaches to reformulations, key US reimbursement issues, recently identified molecular targets, preclinical considerations, newer dosing schedules and combined therapy regimens, and selected US regulatory strategies to increase speed to market.

## Reformulations

Most cytotoxics are reaching patent expiry, with the last cytotoxic genericization expected in 2011 (e.g., Xeloda; Roche). To combat patent expirations, companies are developing branded analogs that differ from the original product in formulation or method of delivery. Consider the following approaches:

- Oral formulations of 5-FU:
  - Xeloda—an oral prodrug—was among the first designed to be more convenient, especially when compared to the complexity and cost of infusion pumps (a continuous intravenous drug delivery system involving an external reservoir pump)

- connected to a catheter at one end implanted in a patient's vein).
- S-1, a fourth-generation oral fluoropyrimidine containing 5-FU, is approved in Asia and currently under evaluation in the EU and US.
  - Multiple new formulations of paclitaxel have been developed since Taxol (BristolMyersSquibb) patent expiry in 2001. Generic versions, including Cell Therapeutics' Xyotax/Opaxio (polyglutamate paclitaxel—currently in development) and Abraxis Oncology's Abraxane (nanoparticle albumin-bound paclitaxel—currently approved), have been developed to offer advantages over Taxol in terms of reduced adverse effects and drug delivery.<sup>2</sup>
    - Xyotax, a biodegradable polyglumex polymer bound to paclitaxel—tested in lung cancer—did not prove superior to Taxol,<sup>3</sup> but further evaluation is underway in subgroups of female patients because it is thought that estrogens may play an activating role, releasing the active agent at the tumor site.
    - Abraxane, an albumin-bound paclitaxel, allowed higher dosing with equivalent limiting toxicity and proved to be more efficacious in breast cancer.<sup>4</sup> It is currently approved for metastatic breast cancer.
    - Tocosol-paclitaxel (Sonus), a new formulation of Taxol using vitamin E as a vector, proved to be more toxic and less efficacious in a recent Phase 3 breast cancer trial.<sup>5</sup>
  - For reformulations of cisplatin, several vectors are undergoing testing. While oral taxanes have not proved successful thus far, satraplatin (GPC Biotech), an oral prodrug of cisplatin, is currently in development to provide an easier route of administration, less neurotoxicity and no hyperhydration.
  - Nanoparticle technology is under development to increase drug tolerance and improve delivery at the tumor site. Various vectors—including polymeric nanoparticles, nanocrystals, polymeric micelles, and dendrimer and carbon nanotubes—have been evaluated for their suitability for simultaneous in vivo imaging (when co-encapsulated

with a contrast agent) and treatment of cancer. Ultimately, nanoparticles—combined with antibodies targeting a tumor-specific antigen—may be capable of detecting malignant cells with the hope of selectively increasing cancer cell killing. Such reformulations proved successful for doxorubicin using pegylated liposomal technology (Caelyx; Schering Plough), demonstrating better cardiac tolerance and a slightly different spectrum of activity.<sup>6</sup> Other liposomal formulations are in development for agents that would otherwise be rapidly degraded in the circulation (e.g., anti-sense oligonucleotides).

### Reimbursement: A US Perspective

Primarily driven by changes in Medicare payment policy for physician-administered drugs over the past five years, oncology treatments have evolved significantly from a reimbursement perspective. In particular, the movement from Average Wholesale Price (95% of AWP) to Average Sales Price (ASP +6%) has led to a reduction in the payment an oncologist receives for the purchase of oncology medications, while at the same time fees associated with administration of injections have increased.<sup>7</sup> The rationale behind these changes has been compensating the physician for work associated with injections and processing costs associated with buying and billing drugs or biologics, as opposed to placing economic incentives on the agent administered.

Medicare ASP is based on the purchase price reported to Medicare in the previous quarter. Because generics are grouped under the same payment code as their branded counterparts, the ASP for a particular product falls rapidly in the two to four quarters following generic introduction. How Medicare will interpret line-extension improvements of generically available products is the key question for many companies investing in development of injectables. Although new chemical entities typically will be provided a separate payment code, there are situations where Medicare has put measures into place to limit payment amounts—often when the difference in price between similar compounds is significant. Examples of these include:

- prostate cancer therapies leuprolide and goserelin paid at the same level despite the fact they are different chemical entities with different modes of administration and different data on quality of

life associated with administration (e.g., goserelin is more painful)<sup>8,9</sup>

- Epo agents paid at dose equivalent prices (e.g., Epogen, Procrit, Aranesp)
- all hyaluronan (sodium hyaluronate) drugs or derivatives grouped into the same billing code

As a result, the primary question for companies making minor improvements to marketed drugs is: Will the benefit be substantial enough to justify premium reimbursement from Medicare? As the examples above illustrate, small improvements may not be rewarded. In the end, Medicare (US) or NICE (UK) will determine whether the incremental benefit of the line extension outweighs the cost. At the present time, there are no clear guidelines on how payers will make the cost/benefit decision. Therefore, oncology-focused companies making minor improvements to marketed drugs should produce as much data as possible to justify this cost/benefit decision (e.g., side effects and consequences for quality of life, treatment satisfaction and resource utilization).

## Oncology Targets

### Overview

Besides the search for new non-cross-resistant analogues of known cytotoxic agents (e.g., epithilones) with a broad range of activity, considerable effort is underway to develop targeted agents. When a specific abnormal molecule or pathway is identified as responsible for the malignant phenotype, the targeted agent is supposed to block that particular pathway without disturbing the normal cellular physiology. However, these agents sometimes yield more adverse events than anticipated because the mechanism of action for unprecedented targets is not fully ascertained.

The targeted approach can be further divided into three categories:

- validated target for which new drugs (small molecule and mAb) and new combinations of drugs are developed
- validated pathways with plausible targets
- new hypothetical targets that are still at the conceptual stage of knowledge

Targeted cytostatic agents primarily fall into two classes: small molecules that block receptors for a few hours and, therefore, must be given repeatedly (thus orally) to sustain their activity; and monoclonal antibodies (mAbs), usually displaying a much longer half-life and, therefore, amenable to intermittent IV administration, i.e., every two to three weeks.



### Tumor Genetics

“Targeted” refers to the concept that the agent will be selectively efficacious at controlling the proliferation of cancer cells through a specific molecular pathway. These pathways may have been abnormally up- or down-regulated due to a chromosome translocation, mutation or combination of mutations responsible for the malignant phenotype. The search to identify such abnormalities producing dysregulation of gene expression, or autoactivation of the pathway, aims at selecting patients with a higher chance of responsiveness to the targeted agent.

For example, epidermal growth factor (EGFR) inhibitors demonstrate efficacy with excessive activation of the receptor, provided no downstream activating mutation—such as

K-Ras—has occurred. Identifying the receptor activation and downstream mutation in an individual patient's tumor tissue is required to avoid treating patients who would otherwise be exposed to the toxic effect without deriving any benefit of the treatment (e.g., panitumumab restricted to patients with EGFR overexpression and no K-Ras mutation in the EU).<sup>10</sup>

Agents such as those used in breast cancer are restricted to patients harboring the target at the required expression level in breast cancer tissue (estrogen receptors (ERs) for Nolvadex or aromatase inhibitors, or the human epidermal growth factor (HER) receptor highly positive for Genentech/Roche's Herceptin). Regulatory authorities have not yet issued guidelines or imposed label restrictions that define all of the clinical limitations for every targeted agent; therefore, clinicians may alter treatment. For example, Novartis' Gleevec—active in Philadelphia chromosome-positive chronic myelogenous leukemia (CML)—is not active in T315I mutated cells, and these patients require different (e.g., nonlabeled) treatment.<sup>11,12</sup>

Identification of specific tumor genetic abnormalities is useful for preselecting patients for targeted therapies, but not always mandatory or feasible. Targeted agents blocking multiple receptors (e.g., Sorafenib and Sunitinib) attempt to control multiple pathways, including rescue pathways. However, the multiplicity of the potential targets—along with the lack of validated assays to monitor target modulation—make it difficult to determine the exact mechanism of action and thus to preselect patients with a higher likelihood to benefit from the treatment. On the other hand, in some hematologic malignancies, a given clinical phenotype is sufficient to guide the choice of the targeted agent (e.g., membrane receptor in some lymphomas for Biogen-Idec/Roche's MabThera (Rituxan)), thus making individualized genetic abnormality identification unnecessary.<sup>13</sup>

In some instances, the drug target is present in different tissues and, therefore, can be used for different types of cancers. For example, some broadly targeted agents, such as vascular endothelial growth factor (VEGF) inhibitors (Genentech's Avastin), are not strictly dependent upon a tumor type or mutation of a particular gene product to be efficient.<sup>14</sup> In essence, the target is the gene/protein, not the disease.

### *Targeting Perspectives*

Most approved agents target the angiogenic

process or pathways related to the HER family receptors and their known downstream effector molecules, such as those related to cell cycle activation (e.g., cyclin D kinase inhibitors). Heat shock protein (Hsp 90) inhibitors and blockers are also related to cell cycle activation, although none is yet approved. All approved anti-angiogenic agents are blocking agents (small molecules) or antibodies blocking a receptor or a circulating molecule. Other approaches under investigation use antibodies stimulating receptors to trigger the apoptosis pathway (Apo-TRAIL by Genentech/Amgen), which may prove useful. But, attempts at modulating the extracellular matrix with MMP inhibitors have failed. Other modulating agents are under investigation.

New perspectives are considered when developing agents targeting other pathways abnormally activated or depressed in the malignant process, such as those related to inflammation (TGFb, IL1) or immune response (IL2, CTLA4, vaccines). The broad range of interactions with other metabolic pathways implicated in these processes makes it very difficult to target key proteins without causing major deleterious side effects (e.g., GSK3 involved in lowering blood glucose levels). Some molecules, such as TGFb and IL, may have opposite effects (tumor promoting effect and/or inhibiting effect) according to the stage of the malignant process development and, thus, require very cautious clinical development. Individualized therapies are underway such as Oncophage (Antigenics) for kidney cancer and melanoma, but, to date, no vaccine has been approved. Additional elucidation of the immune system is required, especially regarding the role of the subset of Treg lymphocytes and myeloid-derived suppressor cells stimulated by the tumor cells to protect them from the action of the other cytotoxic lymphocytes, to know how and when to use them as well as how to combine them with other treatment modalities.

The concept of targeting cancer stem cells to eradicate the source of relapse and offer a cure at least in the early stage of the disease appears remote. To date, stem cells have not been fully identified, localized or characterized relative to the more mature malignant cells and, therefore, cannot be studied adequately to develop new therapeutics. Only indirect evidence is obtained. For example, the complete pathologic response rate—and, it is hoped, the cure rate—increases dramatically with the

Table 1. Selected Oncology Acronyms

Acronym	Definition	Interpretation/Use
RR	response rate	Documents drug activity in terms of reduction in tumor size by >30% in the measurable patient population; can be considered an established surrogate of potential benefit in survival (e.g., topotecan for refractory small cell lung cancer (SCLC); “reasonably likely surrogate” for other cancers).
PFS	progression free survival	Interpreted as “when the disease does not get worse;” usually correlated with absence of progression in measurable lesions or in markers of disease progression such as prostate specific antigen (PSA); it includes death due to any cause related or not to cancer, to toxicity or without documentation of disease progression.
Median OS	median overall survival	Mathematical way to report and compare survival between experimental drug/active Standard of Care (SoC) and placebo/active SoC comparator drug treatments at time when 50% of the events have occurred; usually reported in number of months.
HR	hazard ratio	Mathematical report on the cumulated difference between the two arms over time during the whole observation period.
P-value	percentage of probability	Complements any mathematical value to provide the percentage of chance to erroneously conclude that the observed difference is not due to chance; usually set at <5% or $p < 0.05$ .

administration of chemotherapy with lapatinib and herceptin as pre-operative treatments for localized breast cancer.

### Pharmacogenomics

In oncologic drug development, pharmacogenomics (PGx) is applied to find new targets, monitor efficacy and safety, and select patient subpopulations. Within the realm of PGx and proteomics, it is important to note that “targeted” also refers to genomically linked therapeutics. Genomic signatures are emerging as a new tool for better predicting the benefit of a given treatment than prognostic factors alone (e.g., TNM and histologic features). For example, the OncotypeDX (Genomic Health—21 gene signature) and MammaPrint (Agendia—70 gene signature) prognostic tools can be used to guide decision making in prescribing or avoiding adjuvant treatment of early stage breast cancer.

### Preclinical Considerations

Work remains to be done to identify better predictive preclinical models of new drug activity. While lack of activity in preclinical experiments is reasonably predictive of lack of clinical activity, and might still improve with the identification of better predictive models based upon genomics, the reverse is not true.

There are innumerable examples of positive preclinical results that have not translated into clinical efficacy.

Preclinical experiments will continue with limited efficacy extrapolation power in humans, mainly because of inherent limitations. For example, there are no existing models to reconstitute the interplay between the tumor and its surrounding stroma, matrix proteins, immune cells, endothelia and lymphatics. Moreover, xenograft models employing human tumor cells—isolated from metastatic deposits—may have been passaged in vitro hundreds of times before injection into an orthotopic site of an immunodeficient mouse host. Also of importance, although some of the original molecular and cellular pathways of the tumor cells are preserved in cell lines, the macro- and microenvironments surrounding such tumors are artificial, and the true heterogeneity within the tumor is likely compromised. The use of genetically manipulated mouse model systems may bring some progress; however, their inability to replicate advanced cancer states and metastases will remain a major limitation.

### Newer Dosing Schedules

Cytotoxic agents were usually administered intravenously on a basis ranging from weekly to

every four to five weeks because of the delayed onset of adverse effects (such as myelosuppression), which require one to two weeks for recovery, and their prolonged effect on the cell cycle. With antibodies, the antagonist effect is prolonged over weeks and their chemical nature does not allow oral formulation. Therefore, they can be administered in a parallel time frame to that of chemotherapeutic agents. In contrast, small molecules developed against specific targets (such as EGFR, mTOR, Vascular endothelial growth factor receptor (VEGFR), Bcr-Abl protein or c-Kit receptor) have a short duration of action and require continuous drug exposure to blockade their target and, ultimately, shut down cancer cell growth. Their simple chemical structures are amenable to oral formulation. The most fully developed small molecule class is tyrosine kinase inhibitors (e.g., Gleevec and Sprycel) given on a continuous schedule for the control of CML.<sup>11,15</sup> The long-term control of the leukemic cell clone is sometimes obtained with a continuous blockade of the abnormal kinase Bcr-Abl, and there is hope for cure in some patients.

In endocrine-sensitive tumors, a prolonged disease-free interval has been achieved with extended hormone therapy in endocrine-responsive breast cancer. Treatments initially administered over one year were replaced by treatments over two, then five years, after demonstrated survival benefit. Ongoing trials are testing the benefit of a 10-year therapy. In the case of prostate cancer, where a vast majority of tumors are androgen-dependent at diagnosis, hormonal treatment is now given on an intermittent basis in an attempt to prolong the period of hormone sensitivity, increase quality of life and possibly translate into a survival benefit.

It is plausible that, in solid tumors, targeted agents could be used (after maximum response has been obtained; with other treatment modalities; in selected patients) for maintenance purposes due to ease of administration, but this has not yet been demonstrated.

Finally, metronomic administration (e.g., repeated dosing of a low amount of cytotoxics) might become more popular as different efficacy profiles are demonstrated. The benefit of combining this mode of administration with targeted agents—such as anti-angiogenic agents—deserves further exploration.

## Evolution of Selected US Regulatory Strategies

Due to the lead author's US-centric regulatory experience, US regulatory guidelines are summarized to illustrate the evolution of oncologic regulatory guidance. Selected acronyms that might prove useful while studying FDA documents and oncology package inserts are provided in **Table 1**.

Oncology-focused companies are seeking ways to ensure that new molecules successfully enter the clinical arena and receive market approval quickly and efficiently. To accomplish these goals, development strategy has included biological markers (biomarkers) and surrogate markers.<sup>16</sup> Following is a review of key regulatory strategies.

- 1991—Surrogate markers were first utilized as a viable pathway to regulatory approval during the AIDS epidemic when CD4 counts were used as a surrogate marker, leading to the approval of didanosine for the treatment of HIV. Six years later, in 1997, HIV RNA, was used as a surrogate to support accelerated and traditional approvals of HIV therapies because it was believed HIV RNA levels were highly predictive of meaningful clinical benefit.
- 1992—FDA adopted the accelerated approval rule that allowed the agency to grant marketing approval for a new drug or biological based upon a surrogate endpoint, possibly resulting in accelerated approval, if certain criteria—such as a serious or life-threatening condition—were met.
- 1996—FDA's report, "Reinventing the Regulation of Cancer Drugs," expanded the use of the accelerated approval process for cancer treatments, based upon verified and recognized demonstration of objective tumor shrinkage (Subpart H of the NDA regulations and Subpart E of the Biologic License Application (BLA) regulations). This was one of the first reports to specify surrogate markers that would be acceptable for accelerated approval of oncology drugs.
- 1997—The *Food and Drug Administration Modernization Act (FDAMA)* permitted FDA to approve a marketing application under section 505(c) of the *Food, Drug and Cosmetic Act* or section 351 of the *Public Health Service Act*, "upon determination that

the product has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit.” FDA’s 1992 Accelerated Approval Rule was codified in *FDAMA*.

- 1998—FDA’s *Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review; Availability; Collection of Information* expedited the development of drugs, such as oncology drugs, that treated serious or life-threatening conditions and had the potential to address an unmet medical need. FDA’s accelerated approval language was codified into this statute.
- 1998—FDA’s *Guidance for Industry: FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products* addressed the number and type of studies recommended to support accelerated approval of new oncology products. This guidance specified that objective response rates would be considered a surrogate endpoint in the refractory cancer setting if they were reasonably likely to predict a clinical benefit. Follow-up evidence to confirm that the surrogate correlated with a clinical benefit could be obtained after approval.
- 2002—FDA’s *Guidance for Industry: Special Protocol Assessment*, issued in May, is not specific to cancer treatments, but has been used in the oncology space. Agreement on the trial design generally cannot be altered without written agreement between the sponsor and FDA or if the FDA review division decides that a “substantial scientific issue essential to determining the safety or effectiveness of the drug” was identified after the testing began (section 505(b)(4)(C) of the Act). For example, when it was discovered that paclitaxel poliglumex treatment was associated with longer survival in younger women, it led the FDA to approve an SPA—a modification and agreement to the trial design that addresses a scientific issue that became apparent after the trial began.<sup>5</sup>
- 2007/2008—No formal FDA guidance has been issued regarding adaptive trial design and there have been no drugs approved in the US or EU using an adaptive trial design (ATD) approach.

Although no statistical algorithms are provided, EMEA’s CHMP recently adopted legislation (1Q 2008).<sup>17</sup>

Advantages of ATD include:

- potential to cut costs if interim analyses fail to detect a positive signal regarding the primary efficacy endpoint
- avoid restarting from zero when a subgroup appears to derive a better benefit (e.g., if a predictive marker could be identified, it allows eligibility to be restricted to that subgroup)
- ability to switch from progression free survival (PFS) to overall survival (OS); for example, the trial might be powered differently and proceed with a higher number of patients based upon more robust data
- FDA Deputy Commissioner for Medical and Scientific Affairs Scott Gottlieb, MD, in a speech before the 2006 Conference on Adaptive Trial Design<sup>18</sup> stated: “What does this mean for a patient with cancer? The benefits could be that fewer patients are exposed to the less effective therapy. Presumably more safety information can be collected from the more effective therapy. It may also require that fewer patients be studied overall before determining the statistical and clinical significance of a therapy.”

Disadvantages include:

- lack of familiarity within regulatory agencies regarding ATD; e.g., no drug in the US or EU has been approved using ATD
- need to collect data in almost “real time”—Are data collected quickly at one interim analysis enough to conclude that a significant benefit has been established? Can the study be closed, results analyzed and the next study be started so quickly?

In the lead author’s opinion, the burden of oncologic data collection and corrections, statistical analysis and results evaluation is a time-consuming process and may not be completely amenable to the ATD process.

For additional details regarding FDA's thinking, the reader is referred to the agency's website, specifically Oncology Advisory Committee (ODAC) meetings.<sup>19,20</sup>

## Summary

- Despite a greater number of candidates in the global oncology pipeline, only a small number are actually being approved in the US.
- Expiration of patents for branded cytotoxic agents is a major economic driver of drug development in oncology companies.
- While targeted therapies and reformulations are the two most common oncologic drug development pathways, better preclinical models are needed to support new oncology therapies.
- Pharmacogenomic and proteomic approaches have had a positive impact on new cancer drugs. Regulatory agencies are adopting newer pathways that are less burdensome to sponsors and may bring oncology therapies more quickly to market.

## References

1. *Impact Report (Analysis and Insight into Critical Drug Development Issues)*, Tufts Center for the Study of Drug Development, Tufts University; Volume 9, Number 5. September/October 2007.
2. "Emerging oncology treatments: A focus on targeted therapeutics, supergeneric reformulations and supportive care." Bioportfolio. [www.bioportfolio.com/news/DailyUpdates\\_74.htm](http://www.bioportfolio.com/news/DailyUpdates_74.htm) accessed 9 May 2008.
3. Hede K. "Lung Cancer May be Different for Men and Women, But Researchers Ponder What to Do?" *JNCI*, Vol. 99, Issue 24; 19 December 2007; pp1830-1832.
4. Gradishar WJ et al. "Phase III Trial of Nanoparticle Albumin-Bound Paclitaxel Compared with Polyethylated Castor Oil Based Paclitaxel in Women with Breast Cancer." *Journal of Clinical Oncology*. Vol. 23, No. 31 (1 November), 2005: pp7794-7803.
5. Sonus Pharmaceuticals, Phase 3 Pivotal Trial of Tocosol Paclitaxel Does Not Meet Primary Endpoint, press release dated September 24, 2007.
6. Batist G. "Cardiac Safety of Liposomal Anthracyclines." *Cardiovasc Toxicol*. 2007; 7(2):72-4.
7. Department of Health and Human Services (June 2005) at [www.oig.hhs.gov/oei/reports/oei-03-05-00200.pdf](http://www.oig.hhs.gov/oei/reports/oei-03-05-00200.pdf) accessed 16 May 2008.
8. Leuprolide package insert at [http://pitap.abbott.com/lupron3month22\\_5mg.pdf](http://pitap.abbott.com/lupron3month22_5mg.pdf) accessed 7 August 2008.
9. Goserelin package insert at [http://patient.cancerconsultants.com/druginsets/Goserelin3\\_6.pdf](http://patient.cancerconsultants.com/druginsets/Goserelin3_6.pdf) accessed 7 August 2008.
10. Baselga J, Rosen N. "Determinants of RASistance to Anti-Epidermal Growth Factor Receptor Agents." *Journal of Clinical Oncology*. Vol. 26, No. 10 (1 April), 2008: pp1582-1584.
11. Gleevec package insert at [www.pharma.us.novartis.com/product/pi/pdf/gleevec\\_tabs.pdf](http://www.pharma.us.novartis.com/product/pi/pdf/gleevec_tabs.pdf) accessed 7 August 2008.

12. Benichou A, et al. "Multicenter open label study of subcutaneous (SC) omacetaxine (OMA) in imatinib (IM)-resistant chronic myeloid leukemia (CML) patients (Pts) with the T3151 mutation." *Journal of Clinical Oncology*. Vol. 26:2008 (May 20 suppl; abstr 7021).
13. MabThera/Rituxan package insert at [www.rituxan.com/lymphoma/images/AboutNHLGuide.pdf](http://www.rituxan.com/lymphoma/images/AboutNHLGuide.pdf) accessed 7 August 2008.
14. Avastin package insert at [www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf](http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf) accessed 7 August 2008.
15. Sprycel package insert at [www.fda.gov/cder/foi/label/2006/0219861bl.pdf](http://www.fda.gov/cder/foi/label/2006/0219861bl.pdf) accessed 7 August 2008.
16. Huml et al. "Surrogate Markers vs. Biological Markers: Different Roles in Drug Approval." *Regulatory Affairs Focus*. June 2004, pp47-49.
17. *Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design* (approved 18 October 2007). European Medicines Agency at [www.emea.europa.eu/pdfs/human/ewp/245902enadopted.pdf](http://www.emea.europa.eu/pdfs/human/ewp/245902enadopted.pdf); accessed 15 May 2008.
18. Gottlieb S. FDA Deputy Commissioner for Medical and Scientific Affairs. Speech before 2006 Conference on Adaptive Trial Design. [www.fda.gov/oc/speeches/2006/trialdesign0710.html](http://www.fda.gov/oc/speeches/2006/trialdesign0710.html), accessed 15 May 2008.
19. FDA website at: [www.fda.gov/](http://www.fda.gov/) accessed 16 May 2008.
20. FDA's ODAC meetings listed at [www.fda.gov/cder/cancer/ODACframe.htm](http://www.fda.gov/cder/cancer/ODACframe.htm) - accessed 16 May 2008.

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