The Accelerated Approval Process in Oncology:
An Examination of the Conversion Rate of Approved Therapies to Full Approval

by

Jean Jinsun Kim

B.S. Biology and B.A English Literature
Stanford University, 1997

M.B.A.
Harvard Business School, 2005

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Signature of Author: 

Harvard-MIT Division of Health Sciences and Technology
May 11, 2006

Certified by: 

Ernst R. Berndt
Louis E Seley Professor of Applied Economics, MIT Sloan School
Thesis Co-Supervisor

Frank L. Douglas
Executive Director of Center for Biomedical Innovation, Professor of Practice in MIT School of Management, Engineering, and Science and the Harvard-MIT Division of Health Science and Technology
Thesis Co-Supervisor

Anthony J Sinskey
MIT Professor of Biology and Harvard-MIT Professor Health Science and Technology
Thesis Co-Supervisor

Accepted by: 

Martha Gray
Professor of Medical and Electrical Engineering
Co-director, Harvard-MIT Division of Health Science and Technology
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Abstract
In 1992, Accelerated Approval, or Subpart H approval, was added to the NDA regulations so promising products that provide a meaningful therapeutic benefit for serious or life-threatening diseases could be introduced to the market sooner, particularly for diseases or conditions where there was a great unmet medical need. Accelerated Approval is based on either a surrogate endpoint that is reasonably likely to predict clinical benefit or a clinical endpoint other than survival or irreversible morbidity. After approval, the sponsor is required to perform post-marketing studies to demonstrate clinical benefit.

Since the FDA expanded the use of the Accelerated Approval regulatory path to include oncology drugs in 1995, thirty drugs (both small molecule as well as biologics) have been granted accelerated approval in oncology. However, from various reports in the literature and the FDA site, it appears that only a small fraction of these approvals (four to six2) have been converted into regular approvals, based on the demonstration of clinical benefit in the post-marketing studies that support the benefit seen in the pivotal studies.

In my research, I examined the basis of approval for six drugs that were converted to full approval and compared this group to the seven drugs that received accelerated approval before 2000 but as yet have not converted to full approval. The six drugs that were converted to full approval, with the exception of dexrazoxane, completed their post-marketing requirements in 2.3 years after initial approval. The sponsors, who were all well-capitalized pharmaceutical companies, also pursued additional indications for these drugs.

In the group of drugs that were designated as “not converted” by several sources, two of the drugs have been granted full approval within the past year. And in March 2006, the FDA withdrew its accelerated approval for one drug based on the results of a negative clinical trial. Six years after having received accelerated approval, two drugs in this group are still undergoing clinical trials. Due to the lack of information about the ongoing trials, it is difficult to assess the underlying reasons for the delay in attaining full approval. But the sponsors of these two drugs are small biotechnology companies, while all of the sponsors of the drugs that have been converted to full approval are major pharmaceutical companies.

A majority of the drugs that converted to full approval were granted a broader label based on the post-marketing studies, which demonstrated clinical benefit in a wider patient population than originally tested.

While the accelerated approval process holds many advantages in that companies can introduce their drug to the market sooner, the requirements for accelerated approval often result in the drugs having to meet ‘a higher standard’ in that they have to demonstrate “meaningful clinical benefit” over existing agents, which may in fact be a requirement for superiority, as was seen in the case of one agent, Doxil. The post-marketing studies can be expensive and difficult to complete, but companies with ample resources and sufficient incentives, such as additional potential indications, seem able to clear this hurdle easily.

Thesis Co-Supervisor: Ernst Berndt  
Title: Louis E Seley Professor of Applied Economics, MIT Sloan School

Thesis Co-Supervisor: Frank L Douglas  
Title: Executive Director of Center for Biomedical Innovation, Professor of Practice in MIT School of Management, Engineering, and Science and the Harvard-MIT Division of Health Science and Technology

Thesis Co-Supervisor: Anthony J. Sinskey  
Title: MIT Professor of Biology and Harvard-MIT Professor Health Science and Technology

1 FDA website: www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm  
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Acronyms

AA: Accelerated Approval
CML: Chronic Myelogenous Leukemia
CTCL: Cutaneous T-cell lymphoma
NDA: New Drug Application
NSCLC: Non-small cell lung cancer
ODAC: Oncology Advisory Committee
ORR: Overall response rate*
OS: Overall survival
PFS: Progression-free survival*
RCT: Radiochemotherapy
TTP: Time To Progression*
TTF: Time to Treatment Failure*

* Please see Appendix for definitions and further discussion of surrogate endpoints
Statement of Purpose and Goals

In 1992, Accelerated Approval or Subpart H approval was added to the NDA regulations so promising products that provide a meaningful therapeutic benefit for serious or life-threatening diseases could be introduced to the market sooner, particularly for diseases or conditions where there was a great unmet medical need. Accelerated Approval is based on either a surrogate endpoint that is reasonably likely to predict clinical benefit or a clinical endpoint other than survival or irreversible morbidity. After approval, the sponsor is required to perform post-marketing studies to demonstrate clinical benefit.

Since the FDA expanded the use of the Accelerated Approval regulatory path to include oncology drugs in 1995, thirty drugs (both small molecule as well as biologics) have been granted accelerated approval in oncology. However, from various reports in the literature and the FDA site, it initially appeared that only a small fraction of these approvals (four to six) have been converted into regular approvals, based on the demonstration of clinical benefit in the post-marketing studies that supports the benefit seen in the pivotal studies.

A number of questions arise about the other drugs that received accelerated approval but have not been converted into regular approval. Are the post-marketing clinical studies still ongoing? Have some of these drugs had difficulty demonstrating clinical benefit in the larger post-marketing clinical studies? Were the appropriate surrogate endpoints selected for the clinical trial? Should these drugs remain on the market, if clinical benefit has not been demonstrated? Are there difficulties in completing the follow-on studies, in terms of enrolling patients and keeping them on study? Has the standard of care changed since the initial approval? What are the incentives for the sponsor to complete the study since the drug is already on the market? And does the expanded use of AA in oncology represent a positive development for the patient and the drug development industry or are we introducing drugs too early into patient care?

Some of these drugs have been approved recently so there may not have been enough time to complete the required post-marketing studies. As a result, this study focuses on drugs that were approved before the year 2000, as it seems that a period of five years after having received Accelerated Approval is a reasonable timeframe in which to have submitted the required additional data to achieve full approval. This is supported by the fact that it took the drugs that received final approval an average of 2 to 3 years to achieve this.

My initial hypothesis is that the reason why some of these drugs remain under the accelerated approval framework is that the evidence for clinical benefit has not been demonstrated, either because the post-marketing studies have not been completed or because it has been difficult to complete these randomized clinical trials. A secondary hypothesis is that there is little incentive for these companies to complete the requirements in a timely manner because the drug is already available on the market and there might only be a few years of patent life remaining for the drug.

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3 FDA website: www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm
This thesis represents a summary of my research to understand the various reasons for this low rate of conversion of ‘accelerated approval’ products to full approval. The first part of the thesis will examine the six drugs that have been converted to full approval, with specific focus on the basis for Accelerated Approval (AA) and the basis for conversion to full approval. The second part of the thesis examines the seven remaining drugs that were approved under AA prior to 2000 and still have not been converted to full approval, also with a focus on the basis for the AA and the results of the post-marketing clinical trials. The final part of the thesis compares and analyzes the difference between the two classes of drugs (i.e., converted and not converted) and analyze the differences to assess whether the Accelerated Approval regulations have resulted in patients having early access to drugs that provide true clinical benefit or perhaps whether Accelerated Approval is a regulation that has simply allowed some companies early access to the market without the intended benefit to patients.
Discussion of the methods and data sources

Sources used to examine the basis for accelerated approval consisted of the FDA approval letters, the medical officer review, when available, as well as published clinical studies. Publications of the follow-on post-marketing studies and various medical websites, such as UpToDate, were used to assess clinical benefit and usage.

My research was also supplemented with discussions with some of the sponsors, such as Sol Rajfer, MD (Head of Development at Sanofi-Aventis), regarding Doctaxel. Attempts, albeit unsuccessful, were also made to contact Skye Pharmaceuticals regarding the current clinical trial status of DepoCyt (liposomal cytarabine), Ligand Pharmaceuticals regarding Ontak (denileukin diftitox) and Pfizer regarding Celebrex (celecoxib).
1. Background into the Accelerated Approval Process/Subpart H

1.1 Background

In 1992, Accelerated Approval (AA) or Subpart H approval was added to the NDA regulations so promising products that provide a *meaningful therapeutic benefit* for serious or life-threatening diseases could be introduced to the market sooner, particularly for diseases or conditions where there was a great unmet medical need. Accelerated Approval is based on either a *surrogate endpoint* that is *reasonably likely to predict clinical benefit* or a clinical endpoint other than survival or irreversible morbidity. After approval, the sponsor is required to perform post-marketing studies to demonstrate clinical benefit (i.e. the surrogate endpoint has to truly represent clinical benefit in the patient population).

Approval for the drug may be withdrawn if: (1) the post-marketing clinical studies fail to verify clinical benefit; (2) the applicant fails to perform the post-marketing studies with due diligence; (3) use in the market demonstrates that post-marketing restrictions are inadequate to ensure safe use; (4) the applicant fails to adhere to post-marketing restrictions; (5) promotional materials are false or misleading; or (6) other evidence demonstrates that the drug is not safe or effective under its conditions of use.\(^5\)

Thus the two important features of the Accelerated Approval regulations: (1) the therapy has to potentially provide *meaningful therapeutic benefit* over existing options and (2) surrogate endpoints have to be *reasonably likely to predict clinical benefit*.

The definition of *meaningful therapeutic benefit* can cover drugs that are expected to be (1) superior to existing therapy or (2) treat conditions for which there are no available options. In the case of oncology, many of the drugs that have been approved under the AA regulatory path fall into the latter category and treat cancers that are refractory to other existing therapies, and therefore are introduced for second or third line use.

Accelerated approval is often based upon the use of surrogate endpoints, measurements that are intended to substitute for and are *reasonably likely to predict clinical benefit*. The intention behind the use of surrogate endpoints is to speed up the clinical trial and approval process, as the use of established clinical endpoints would often require longer and larger clinical trials. Subsequent demonstration of true clinical benefit is required for conversion to full drug approval and is based upon the results of adequate and well-controlled post-marketing clinical studies that measure regular clinical endpoints or established surrogate endpoints that have already been validated as representative of clinical benefit.

But apart from the requirement for the post-marketing clinical trials, drugs that have received Accelerated Approval are deemed to have full approval for marketing. This is to ensure that drugs approved under this process are eligible for reimbursement.

The accelerated approval process was initially created for and applied to the approval of AIDS drugs in the early 1990s, when there was a critical need for effective HIV therapy.

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\(^5\) FDA 21CFR Parts 314 and 601, Section F.
In the case of HIV trials, AA was based on an interim analysis of a surrogate end point, such as the viral load at 24 weeks, in a randomized controlled trial. In the post marketing process, the same trial was completed to demonstrate sustained clinical benefit, evidenced by the viral load at 48 weeks. Durability of the surrogate endpoint response of reduction in viral load was determined to provide evidence of clinical benefit as a result of an intense collaboration between industry, academia, the NIH and the FDA.

Today, antiretroviral agents are approved based the ability to produce long-term suppression of HIV RNA loads.

The AA process was first implemented in oncology in 1995. Traditionally, the gold standard endpoints that the FDA has used as evidence of clinical benefit were survival benefit or relief of patient symptoms. But surrogate endpoints, such as objective tumor response rates (tumor shrinkage) and time-to-progression (TTP), are endpoints that are used in oncology clinical trials and have been used frequently as the basis of approval in oncology under AA. And in contrast to the HIV drug approval process, accelerated approval has often been based upon the results in non-randomized Phase 2 clinical trials with clinical benefit demonstrated in separate randomized post-marketing trial(s).

Since 1995, 30 approvals, representing 26 different drugs, have been granted under AA in oncology. This regulatory process, which has been embraced by the biopharmaceutical industry for oncology drugs, has resulted in an average of 2.8 oncology drug approvals per year, with an increasing frequency since 2000. However, in the past 10 years, only a fraction of the thirty approvals have been converted into regular approvals.

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9 FDA website: www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm
An initial observation from the preliminary data is that only six out of the thirty approvals have completed the requisite post-marketing trials to demonstrate actual clinical benefit. But there are many questions that arise about the remaining 24 approvals. My research is an attempt to uncover some of the reasons for slow conversion to full approval for the older drugs approved under AA.

1.2 Surrogate endpoints in oncology:

In oncology, improved survival is the gold standard to establish clinical benefit for a therapy, but the FDA has accepted other endpoints for cancer drug approval, such as improvement in a patient’s quality of life (e.g. improved physical functioning or improved tumor-related symptoms), or surrogate endpoints.

The use of surrogate endpoints is a difficult issue. While the FDA has previously approved drugs based on surrogate endpoints, such as the effect on blood pressure in hypertension drug trials, the AA regulations codified the use of surrogate endpoints for the first time.

A common approach is to use a biological marker that is known to “correlate” with the clinical efficacy endpoint, meaning that patients that have better results with a biological marker also have improved outcomes with their disease. For example, drugs for hypercholesterolemia have been approved based on demonstrated effects on serum cholesterol, rather than coronary artery diseases. However, the change in this biological marker in response to therapy should be large in magnitude and evident early in the
course of therapy in order to be useful as a surrogate endpoint.\textsuperscript{10} The use of good surrogate endpoints in measuring the effect of a certain therapy has the potential to reduce the number of patients needed for a trial and/or shorten the length of the trial.

The FDA has even indicated that the use of surrogate endpoints is really meant for certain situations: (1) where the clinical benefit, if there is one, is likely to be well in the future; and (2) where the implications of the effect on the surrogate are great because the disease has no treatment or the drug treats people that have no alternative.\textsuperscript{11} Both of these situations are true in the case of oncology, where demonstrating a marginal but significant effect on survival might require a very large and expensive trial and in many cases, there are few alternatives for these patients.

But unfortunately, a strong correlation does not necessarily translate into a good surrogate endpoint, particularly if the surrogate in question is subsequently found not to be causally related to the clinical outcome. An unfortunate example of an imprecise surrogate endpoint was the use of suppression of premature ventricular contractions to prevent sudden cardiac death, which was the basis of approval for two cardiovascular drugs, encainide and flecainide. Based on the effective suppression of arrhythmias in patients, these drugs were widely used for patients at risk for sudden cardiac death. However, the results of a large-scale post-approval trial, the Cardiac Arrhythmia Suppression Trial (CAST), demonstrated that suppression of arrhythmia by these agents did not result in improved survival, but actually tripled the death rate\textsuperscript{12}.

Another potential issue is that the actual clinical benefit may be smaller than expected or the adverse events may be larger than expected and the demonstration of the therapeutic window or emergence of toxicities requires a larger trial with a longer duration.\textsuperscript{13} These are issues for drugs approved under accelerated approval, where surrogate endpoints are assessed in single-arm Phase 2 studies with a shorter duration of follow-up than traditional randomized Phase 3 studies.

Thus, linking the effect seen with the surrogate to actual clinical benefit has to be borne out in adequate and well-controlled post-marketing clinical studies, validating the use of the surrogate endpoint in the pivotal trials and validating the use of the drug in the approved indications.

See the Appendix for further discussion on specific endpoints used in oncology clinical trials.

\textsuperscript{11} FDA 21CFR Parts 314 and 601, Section IV A – General Comments.
\textsuperscript{12} Fleming TR. Surrogate endpoints and FDA’s Accelerated Approval Process. Health Affairs, Vol 24, No 1, pp 67-78.
\textsuperscript{13} Ibid
2. Review of oncology drugs approved under AA that have been converted into full approval

Drugs approved under Accelerated Approval that have converted to Full Approval (1)

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade name</th>
<th>AA approval</th>
<th>Date of conversion to full approval</th>
<th>Sponsor</th>
</tr>
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<tr>
<td>1 Dexrazoxane</td>
<td>Zinecard</td>
<td>May 26, 1995</td>
<td>October 31, 2002</td>
<td>Pharmacia (Pfizer)</td>
</tr>
<tr>
<td>2 Docetaxel</td>
<td>Taxotere</td>
<td>May 14, 1996</td>
<td>June 22, 1998</td>
<td>Aventis</td>
</tr>
<tr>
<td>3 Irinotecan</td>
<td>Camptosar</td>
<td>June 14, 1996</td>
<td>October 22, 1998</td>
<td>Pharmacia (Pfizer)</td>
</tr>
<tr>
<td>4 Capcitabine</td>
<td>Xeloda</td>
<td>April 30, 1998</td>
<td>September 7, 2001</td>
<td>Roche</td>
</tr>
<tr>
<td>5 Imatinib mesylate</td>
<td>Gleevec</td>
<td>May 10, 2001</td>
<td>December 8, 2003</td>
<td>Novartis</td>
</tr>
<tr>
<td>6 Oxaliplatinin</td>
<td>Eloxatin</td>
<td>August 9, 2002</td>
<td>June 9, 2004</td>
<td>Sanofi</td>
</tr>
</tbody>
</table>

(1) Source: Dagher R et al. Accelerated Approval of Oncology Products: a Decade of Experience. Journal of National Cancer Institute, Vol 96, No 20, October 20, 2004

2.1 Dexrazoxane (Zinecard)
Sponsor: Pharmacia (now Pfizer)

Indication: Prevention of cardiomyopathy associated with doxorubicin administration

Date of Accelerated Approval: May 26, 1995
Date of conversion to full approval: October 31, 2002
Time to complete post-marketing requirements: 7.5 years

Dexrazoxane is a cardioprotective agent that is used in conjunction with doxorubicin, an anthracycline chemotherapeutic agent. The use of anthracyclines in cancer patients is associated with cardiotoxicity and can cause an irreversible and sometimes fatal cardiomyopathy. For each particular anthracycline, there is a cumulative dose beyond which the cardiotoxic risk increases rapidly. The physiological mechanism of this cardiotoxicity is associated with the release of free radicals, secondary to the formation of iron-doxorubicin complexes. Dexrazoxane is an EDTA-like chelator that is thought to prevent anthracycline damage by binding to the iron released from intracellular storage, interfering with the iron-mediated free radical generation thought to be responsible in part for anthracycline-induced cardiomyopathy.

Basis of AA
Dexrazoxane was first approved on May 26, 1995 under AA for the prevention of cardiomyopathy associated with doxorubicin administration. The primary endpoint evaluated was not the traditional endpoints of improved survival or reduction of irreversible morbidity, but a reduction in cardiac events associated with the use of doxorubicin. Even though a reduction in cardiac events is not one of the traditional oncology endpoints, it was still considered to represent a “clear clinical benefit” and therefore was not considered to be a surrogate endpoint.

(14) UpToDate, Cerqueira, MD. Cardiotoxicity in patients receiving chemotherapy, online version 14.1, 4.9.06/
Dexrazoxane was approved under the Accelerated Approval regulations, although the potential of dexrazoxane to act as a tumor protectant was still unknown at the time. Approval was based on the results from two Phase III clinical trials: Studies 88001 and 88006. Both trials were similar in design and compared the addition of dexrazoxane versus placebo to a commonly-used doxorubicin-containing combination regimen, known as FAC (doxorubicin, cyclophosphamide and 5-FU) in the treatment of disseminated breast cancer.

Cardiac function was assessed by measurement of the left ventricular ejection fraction (LVEF), resting multigated nuclear medicine (MUGA) scans and clinical evaluations. Overall, cardiac events were reported for 14% of patients receiving dexrazoxane and for 31% of patients receiving placebo. In the combined clinical studies, 24 patients presented with congestive heart failure (CHF): two on dexrazoxane and 22 on placebo. It was estimated that treatment with dexrazoxane reduces the risk of presenting with cardiac symptoms during doxorubicin treatment by a factor of 2.5. There was a statistically significant decrease in cardiac events (25/91 vs 59/94, p<0.001) and in the incidence of MUGA events (29/88 and 58/93, p <0.001).

There was no clear evidence of tumor protection by dexrazoxane in the trials, ie the efficacy of the primary chemotherapeutic regimen was not compromised. However, in one of the clinical studies, study 88001, the response rate of patients randomized to receive placebo (61%) was significantly higher than that of patients randomized to receive dexrazoxane (47%, p =0.019). In the other pivotal study, the response rates of the two arms were not significantly different. The difference in the response rates from study 88001 was the primary reason for the FDA’s uncertainty regarding dexrazoxane’s role in tumor protection.

Based on the strong evidence of cardiotoxicity protection and the uncertainty regarding the potential tumor protection, dexrazoxane received approval under AA.

Post-marketing commitments:

As stated in the FDA approval letter on May 26, 1995, the major post-marketing clinical trial commitment to prove clinical benefit was a Phase IV clinical trial (study 08805) examining time to progression (TTP) of adriamycin and dexrazoxane versus no additional agents in patients with advanced or metastatic breast cancer after treatment with six courses of FAC.

This Phase IV study is the completion of the pivotal trials with a protocol amendment. Based on an interim analysis of the data prior to the initial approval, there was clear evidence of cardioprotection in the dexrazoxane arm. The protocol was then amended on January 14, 1991 to treat all patients that received more than six courses of FAC with dexrazoxane in a open-label cross-over study.

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In this study, there were 102 patients that were crossed-over to receive dexrazoxane after six courses of therapy. This arm was compared to 99 patients that had remained on placebo after six courses of therapy, prior to the change in protocol. Sixty percent of the patients that were in the comparator arm without dexrazoxane presented with a cardiotoxic symptom, while only 25% of the patients crossed over to dexrazoxone reported cardiac symptoms. The incidence of clinical CHF was 22% and 3%, respectively, and the FDA concluded that patients unprotected by dexrazoxane had a 13x greater risk of developing CHF at doxorubicin doses higher than 300 mg/m2.

The FDA also compared TTP and survival of the group receiving dexrazoxane versus placebo and found similar results in both arms. Based on these results, dexrazoxane was deemed to be effective in preventing worsening of cardiac lesions caused by previous treatment.

Conversion to Full Approval
Pharmacia and Upjohn submitted an efficacy supplement (SE-006) on December 28, 2001 for the conversion of the accelerated approval to regular approval and received regular approval on October 31, 2002. But the label was restricted to use in patients that had received cumulative doxorubicin doses of 300 mg/m2 and who will continue to receive doxorubicin therapy to maintain tumor control. It is not recommended for use with the initiation of doxorubicin therapy.19

Other indications:
There are no other approved indications.

Patent protection:
The drug was approved for generic use on September 28, 2004. Pharmacia and Upjohn had about 23 months of patent coverage left on dexrazoxane after regular approval.

2.2 Docetaxel (Taxotere)
Sponsor: Aventis Pharmaceuticals

Indication: Treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or who have relapsed during anthracycline-based adjuvant therapy

Date of Accelerated Approval: May 14, 1996
Date of conversion to full approval: June 22, 1998
Time to complete post-marketing requirements: 2.1 years

Docetaxel is a semisynthetic taxane, prepared from an extract of the needles of the European yew tree. Similar to paclitaxel (Taxol), it promotes abnormal microtubule stabilization and disrupts the cell cycle.20 Docetaxel was first approved on May 14, 1996 under AA for the treatment of patients with locally advanced or metastatic breast cancer

who have progressed during anthracycline-based therapy or who have relapsed during anthracycline-based adjuvant therapy (second-line use).  

**Basis of AA**

Approval was based on the results of three Phase 2 studies conducted on a total of 134 patients with anthracycline-resistant, locally advanced or metastatic breast cancer. The dose of docetaxel used in these trials was a single infusion of 100 mg/m² administered every 3 weeks. Results of three Phase 2 studies in Japan utilizing a lower dose of 60 mg/m² were also reviewed as part of this approval.

In the three pivotal Phase 2 trials (excluding the trials conducted in Japan), the overall response rate across the three studies was 41% in an intent-to-treat analysis. The median TTP was 4.3 months and the median survival time was 10.6 months. The median duration of response ranged from 24 to 28 weeks.

At the time of review, the response rate of 41% was the highest ever reported for a single agent with anthracycline-refractory breast cancer. In comparison to existing therapies for this indication, second-line anthracycline-resistant breast cancer, the response rate for paclitaxel is only 28%. The response rate of 41% for docetaxel is significantly higher and satisfies the “meaningful clinical benefit” criterion.

Grade 4 neutropenia was the most common toxicity, occurring in 90% of patients. This neutropenia resolved after therapy was discontinued in most cases. A relatively unique toxicity that was observed in this patient population is the fluid-retention syndrome, which was successfully managed with oral diuretics in most cases.

Due to the strong clinical benefits seen for docetaxel over other available options, docetaxel was recommended for AA on May 14, 1996.

**Post-marketing requirements**

The post-marketing commitments included the following:

1. Submission of the complete findings for the following three studies patients with advanced breast cancer (with sufficient enrollment of anthracycline-resistant patients):
   a. TAX311: Comparison of docetaxel at 100 mg/m² with paclitaxel
   b. TAX303: Comparison of docetaxel at 100 mg/m² with doxorubicin
   c. TAX304: Comparison of docetaxel at 100 mg/m² with mitomycin C/vinblastine
2. Submission of complete findings of an ongoing study in second-line breast cancer comparing two different dose levels (100 mg/m² and 75 mg/m²) with assessment of the clinical benefit of treatment

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22 Ravdin PM. Treatment of patients resistant to anthracycline therapy. Anticancer Drugs 1996 Aug; 7 Suppl 2: 13-6
24 FDA approval letter for docetaxel, May 14, 1996.
Conversion to regular approval

TAX303: Phase III comparing docetaxel to doxorubicin:
During the 1997 ASCO meeting, preliminary data from the TAX303 Phase III trial was presented which compared docetaxel to doxorubicin in patients with metastatic breast cancer. Results from 200 out of the 326 patients recruited showed that the median time to progression for patients in the docetaxel group was greater than that in the doxorubicin group (29 vs 21 weeks, p value = NS). **Overall response rates** were higher with docetaxel (47% vs 27%) and fewer patients in the docetaxel group had progressive disease as their best response (10% vs 22%).

Both treatment regimens cause similar incidences and severity of neutropenia. However, there were more cases of infection, febrile neutropenia, cardiotoxicity and grade ¾ thrombocytopenia in the doxorubicin arm.²⁵

These efficacy results were confirmed in the completed TAX303 trial, reported in August 1999. In the completed trial, docetaxel was shown to have a superior overall response rate when compared to doxorubicin (response rate of 47.8% vs 33.3%, respectively). Median time to progression was longer in the docetaxel group (26 weeks vs 21 weeks, p=NS) and median overall survival was similar in both groups. Both arms exhibited a similar incidence of neutropenia.

TAX304: Phase III comparing docetaxel at 100 mg/m² with mitomycin C/vinblastine
The preliminary analysis of this clinical trial on 200 out of the 392 patients recruited into the trial was first published in August 1997.²⁶ Median time to progression (primary endpoint) was longer in the docetaxel group compared with the mitomycin/vinblastine group (17 vs 9 weeks). The overall response rates were higher (28% vs 13%) and there were fewer cases of progressive disease in the docetaxel group (29% vs 48%).

Thrombocytopenia was more common in the mitomycin/vinblastine group while neutropenia and severe fluid retention occurred more frequently in the docetaxel group.

Based on the preliminary results of both of these trials (TAX 303 and TAX 304), the FDA converted AA for docetaxel to full approval.

These efficacy results were confirmed in the completed TAX 304 study, published in May 1999.²⁷ In the randomized patient population, the overall response rate was 30% versus 11.6% for the combination of mitomycin C/vinblastine (MV) and docetaxel versus MV alone. Median TTP (19 v 11 weeks), median time to treatment failure, TTF, (16 weeks v 10 weeks) and median overall survival (11.4 mos v 8.7 mos) were all significantly longer in the docetaxel/MV combination than in the MV control arm.

²⁵ Chan S. Docetaxel vs doxorubicin in metastatic breast cancer resistant to alkylating chemotherapy (abstract). Oncology (Williston Park) 1997 Aug; 11 (8 Suppl 8).
The safety profile of docetaxel was similar to that noted in the interim analysis. Grade 3/4 neutropenia was significantly higher in the docetaxel/MV group than MV alone (93% vs 62%), while thrombocytopenia occurred to a greater degree in the MV group (34% vs 9%).

Conversion to regular approval
Based on the preliminary reports for the first two studies (TAX 303 and 304), docetaxel was converted to regular approval on June 22, 1998.

Results from the Phase III TAX311 study comparing docetaxel to paclitaxel were first presented at the European Cancer Conference (ECCO12) in September 2003, more than five years after the conversion to regular approval. The results were published in August 2005. In this study, docetaxel demonstrated a superior TTP relative to paclitaxel (5.7 mos vs 3.6 mos), a greater response duration (7.5 mos vs 4.6 mos) and greater overall survival (15.4 mos vs 12.7 mos). The overall response rate was also greater with docetaxel (32% vs 25%).

Comparison of clinical trial results (pivotal and post-marketing)

<table>
<thead>
<tr>
<th>Study</th>
<th>ORR</th>
<th>Duration of response (weeks)</th>
<th>Survival (mos)</th>
<th>TTP (weeks)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 P2 trials (pivotal)</td>
<td>41%</td>
<td>24-28</td>
<td>9 - 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAX 303 - interim (vs doxorubicin)</td>
<td>47% (vs 27%)</td>
<td></td>
<td></td>
<td>29 (vs 21)*</td>
<td>- Basis for conversion to regular approval</td>
</tr>
<tr>
<td>TAX 303 - completed (vs doxorubicin)</td>
<td>47.8% (vs 33.3%)</td>
<td>Similar in both groups</td>
<td>26 (vs 21)*</td>
<td>- Results published in August 1999</td>
<td></td>
</tr>
<tr>
<td>TAX 304 - interim (vs mitomycin C/vinblastine)</td>
<td>28% (vs 13%)</td>
<td></td>
<td>17 (vs 9)*</td>
<td>- Basis for conversion to regular approval</td>
<td></td>
</tr>
<tr>
<td>TAX 304 - completed (vs mitomycin C/vinblastine)</td>
<td>30% (vs 11.6%)*</td>
<td>11.4 (vs 8.7 mos)</td>
<td>19 (v 11)</td>
<td>- Results published in May 1999</td>
<td></td>
</tr>
<tr>
<td>TAX 311 - completed (vs paclitaxel)</td>
<td>32% (vs 25%)</td>
<td>7.5 mos (vs 4.6 mos)</td>
<td>15.4 mos (vs 12.7 mos)</td>
<td>5.7 mos (vs 3.6 mos)</td>
<td>- Results published in August 2005</td>
</tr>
</tbody>
</table>

* Primary endpoint

It is interesting to note that the FDA converted docetaxel to full approval based on interim analyses of the post-marketing study requirements for just two of the studies (TAX 303 and 304), especially considering that TAX 303 did not show a difference in survival between the two arms in the final analysis, despite significant differences in the surrogate endpoints of response rate and TTP. The results from the TAX 311 study, which compared docetaxel to paclitaxel, were not needed for conversion to full approval.

In an interview with Dr Sol Rajfer, head of US development for Sanofi-Aventis, who
could not comment on the specific details of the studies and regulatory review due to
confidentiality restrictions, it was noted that comparability to another drug could be
considered as evidence of clinical benefit and thus a basis of conversion to full approval,
if the effect was seen in a different population subset of patients or resulted in different
side effects.

The interim results from both the TAX 303 and TAX 304 studies support this basis for
conversion since both studies showed an improved safety profile for the docetaxel arm
versus the comparative arms, in addition to the significant improvements in the surrogate
endpoints of response rate and time to progression.

Other indications:
On December 23, 1999, Aventis received regular approval for the use of docetaxel to
treat patients with locally advanced or metastatic NSCLC after failure of prior platinum-
based chemotherapy. On November 27, 2002, the label was expanded to include first
line use in combination with cisplatin for the treatment of patients with unresectable,
locally advanced or metastatic NSCLC who have not previously received chemotherapy
for this indication.

On May 19, 2004, Aventis received regular approval for the use of docetaxel in
combination with prednisone to treat patients with androgen-independent (hormone
refractory) metastatic prostate cancer.

On August 18, 2004, Aventis received regular approval for the use of docetaxel in
combination with doxorubicin and cyclophosphamide for the adjuvant treatment of
patients with operable node-positive breast cancer.

On March 22, 2006, Aventis received regular approval for the use of docetaxel in
combination with cisplatin and fluorouracil for the treatment of patients with advanced
gastric adenocarcinoma, including adenocarcinoma of the gastroesophageal junction, who
have not received prior chemotherapy for advanced disease.

Patent protection:
Aventis has patent protection over docetaxel until May 14, 2010. So at the time of
conversion to full approval on June 22, 1998, Aventis had close to 12 years of patent
exclusivity remaining for docetaxel.

2.3 Irinotecan (Camptosar)
Sponsor: Pharmacia and Upjohn

Indication: Treatment of patients with metastatic carcinoma of the colon or rectum
whose disease has recurred or progressed following 5-FU therapy

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29 All additional approvals are sourced from the original FDA approval letters on the FDA website:
Drugs@FDA database, May 1, 2006.
30 FDA Electronic Orange Book, based on the first patent expiration date listed,
http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexclnew.cfm?Appl_No=020449&Product_No=001
&table1=OB_Rx
Irinotecan is a topoisomerase I inhibitor that blocks DNA replication, leading to multiple single-strand DNA breaks, eventually blocking DNA replication. Irinotecan was approved on June 14, 1996 under AA for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU therapy (second-line therapy).

**Basis of AA**
Accelerated approval was based on 3 multi-center Phase II single agent studies involving 503 patients: Study 1: M/6475/0001, San Antonio, Study 2: NCCTG: M/6475/0003R, Mayo/NCCTG31; Study 3: M/6475/0006. All the patients enrolled in the study had metastatic colorectal cancer that recurred or progressed following 5-FU-based therapy. The primary endpoint of these studies was tumor response rate.

The overall response rate across the three studies was 12.8% (0.7% CR and 12.2% PR). There was a higher response rate observed in the 193 patients treated at the initial higher dose of 125 mg/m2 of 15%. The median duration of response was 6 months.

Dose-limiting toxicities included severe delayed diarrhea and myelosuppression.

At the time of AA, there was no standard salvage treatment for patients in whom 5-FU chemotherapy had failed. Thus based on the 12.8% response rate observed for this patient population, irinotecan was granted AA on June 14, 1996.

**Post-marketing commitments:**

1. A randomized controlled 3-arm study of (a) irinotecan alone vs (b) irinotecan + 5-FU/leucovorin vs (c) 5-FU/leucovorin in patients with untreated metastatic colorectal cancer (first line). The primary endpoint is time to tumor progression. Response rate is a secondary endpoint. The final study endpoint was to be submitted in 2 years, by June 1998.33

On December 17, 1997, the FDA and P&U agreed to submit a revised confirmatory trial in the salvage population.34 The new post-marketing study to satisfy the AA requirements was a non-blinded multi-center Phase III study comparing irinotecan, or CPT-11 (300-350 mg/m2 every 3 weeks) plus BSC (best supportive care) to BSC alone in metastatic colorectal cancer after failure of treatment with 5-FU.

**Results of post-marketing Phase III study**

31 NCCTG: North Central Cancer Treatment Group, which is a national cancer research group sponsored by the National Cancer Institute, with cancer specialists at community clinics, hospitals and medical centers in the United States, Canada and Mexico. The research base is located at the Mayo Clinic
32 FDA Medical Officer Review, Irinotecan, 10.22.1998 (www.accessdata.fda.gov)
33 FDA Approval letter for irinotecan, June 14, 1996.
34 Ibid
In the Phase III confirmatory trial, 279 patients with 5-FU-refractory metastatic colorectal cancer were enrolled (189 patients in the irinotecan and BSC arm and 90 patients in the BSC arm alone). Best supportive care was determined by the institution and included antibiotics, analgesics, transfusions, corticosteroids or any other symptomatic therapy (topoisomerase I inhibitors were excluded). The primary endpoint was overall survival. The secondary objectives were the impact of treatment on performance status, body weight, tumor-related symptoms and quality of life.

With a mean follow-up of 13 months, the overall survival was significantly better in the irinotecan group. One year survival was 36.2% for the irinotecan group versus 13.8% for the BSC patients. Median survival was 9.2 months and 6.5 months, respectively. The survival advantage was highly significant, even after adjustment for performance status of the patients. This study also showed an advantage for patients treated with irinotecan in quality of life, given the relatively tolerable safety profile. Patients on irinotecan experienced an improvement in their symptoms and a delay in onset of tumor-related symptoms, such as performance-status deterioration, weight loss and pain.

Based on the significant improvements in survival and quality of life, irinotecan was converted to regular approval on October 22, 1998.

**Comparison of clinical trial results (pivotal and post-marketing)**

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>Survival at 1 year</th>
<th>Median survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 P2 trial (pivotal)</td>
<td>12.8%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmatory PIII (vs BSC)</td>
<td></td>
<td>36.2% (vs 13.8%)*</td>
<td>9.2 (vs 6.5 mos)</td>
</tr>
</tbody>
</table>

* Primary endpoint

**Other indications:**
On April 20, 2000, Pharmacia received regular approval for the expanded use of irinotecan in first line therapy in combination with 5-FU and leucovorin for the patients with metastatic carcinoma of the colon or rectum.

**Patent protection:**
Pharmacia has patent protection over irinotecan until August 20, 2006. So at the time of conversion to full approval on October 22, 1998, Pharmacia had approximately 8 years of patent exclusivity remaining for irinotecan.

2.4 Capecitabine (Xeloda)

**Sponsor: Roche**

**Indication:** Treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated

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FDA Electronic Orange Book, based on the first patent expiration date listed, http://www.accessdata.fda.gov/scripts/cder/ob/docs/patexcnew.cfm?Appl_No=020571&Product_No=001&table1=OB_Rx
Date of Accelerated Approval: April 30, 1998
Date of conversion to full approval: September 7, 2001
Time to complete post-marketing requirements: 3.3 years

Capecitabine is an orally-administered prodrug of 5'-deoxy-5-fluorouridine (5'DFUR) that is enzymatically converted to the active drug, 5-FU.

Capecitabine received FDA approval under AA regulations on April 30, 1998 for two specific patient populations: the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated (eg, patients that have received cumulative doses of doxorubicin greater than 400 mg/m\(^2\), where cardiotoxic side effects start to become an issue).

The standard of care for metastatic breast cancer is anthracycline-based therapy (such as doxorubicin). Doxorubicin has a modest survival advantage of about 6 months in first line use with these patients. Other therapies for this patient population include docetaxel, which was approved for second-line use after anthracycline-failure in this patient population, and paclitaxel, which was approved for use with herceptin in patients with HER2/neu overexpression. Despite these options, there are few chemotherapeutic agents that have shown a survival advantage in metastatic breast cancer and a great clinical need for new agents remains.

**Basis of AA\(^{37}\)**
Approval was based on a single Phase 2 study (SO 14697). This was an open-label multi-center single-arm study assessing the effect of capecitabine on 163 patients with metastatic breast cancer (135 of these patients had measurable disease). All patients had previously received paclitaxel therapy (77% of those with measurable disease were paclitaxel-resistant) and more than 90% had received 2 to 3 prior chemotherapy regimens.

Response rate was the surrogate endpoint that served as the primary endpoint for this study. A target of a 20% response rate would be considered significant. Other secondary endpoints included time to onset of best response, duration of best response, time to progression (TTP), time to treatment failure (TTF), survival and clinical benefit response score (CBR)\(^{38}\).

**Results of the pivotal studies for initial approval**

Out of the patients with measurable disease, there was a 20% response rate per the sponsor’s assessment. The FDA reviewed the data and considered 18.5% of the patients as falling into the complete response or partial response category. The median duration of response was 241 days per the sponsor where the FDA assessed the median duration of

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\(^{37}\) FDA Medical Officer Review, capecitabine, Xeloda, April 30, 1998 (www.accessdata.fda.gov)

\(^{38}\) Clinical benefit response score or CBR was defined in the Medical Officer Review for initial approval on April 30, 1998, as a composite score consisting of 3 parameters: pain intensity, analgesic consumption and Karnofsky performance score. An overall score is positive if a patient has a positive response in at least 1 parameter and stable in the other two measures and a negative CBR if she is negative in any of the parameters.
The median TTP was 93 days and the median survival was 384 days.

While all of the 135 patients with evaluable disease had progressive disease while on paclitaxel therapy, 43 of the patients had disease that was resistant to both paclitaxel and anthracycline therapy. In this patient population, the response rate was 25.6%, with a median duration of response of 154 days.

Almost all of the patients (99%) reported adverse events in this trial. While this is a heavily pre-treated population with frequent adverse events, the most severe adverse events reported (grade 3/4) were diarrhea (14%), hand-foot syndrome (10%), fatigue/weakness (8%) and nausea (4%).

Although the overall response rate of 18.5% (FDA’s assessment) missed the 20% target for the trial, in the subpopulation of patients that had disease that was resistant to both paclitaxel and anthracyclines, the 25.6% response rate exceeded that of the target. It was noted in the Oncology Advisory Committee (ODAC) review on March 19, 1998 and the medical officer review that this subgroup analysis was problematic due to the small sample size, but the favorable results still supported accelerated approval for this specific population. The ODAC members voted in favor of AA for capecitabine to treat patients resistant to paclitaxel and an anthracycline-containing regimen (vote of 10 yes to 2 no) and patients resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m² of doxorubicin equivalents (vote of 8 yes to 3 no, with 1 abstention).

One month later on April 30, 1998, the FDA approved capecitabine under AA regulations for the specific subgroup of patients that showed a significant response rate: patients with metastatic breast cancer resistant to paclitaxel and for whom further anthracycline therapy may be contraindicated (eg, patients that have received cumulative doses greater than 400 mg/m²).

Post-marketing commitments include:
There were Phase IV commitment agreed to with Roche but the details of the commitments to support AA were redacted from the original approval letter.

However, in the original medical officer review, the sponsor had submitted a protocol for an open-label Phase 3 trial (SO14999) comparing capecitabine in combination with docetaxel versus docetaxel monotherapy in patients with advanced/metastatic breast cancer refractory to anthracycline-containing therapy. A total of 454 patients were expected to be enrolled and the primary endpoint TTP. During the ODAC meeting that discussed the original approval of capecitabine on March 19, 1998, the notes did not indicate whether TTP was an acceptable endpoint demonstrating clinical benefit for these patients.

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39 The sponsor’s definition of response duration was based on WHO criteria, which counts the first day of treatment as the first day of a PR. The FDA recalculated the duration of response starting from the first date a PR or a CR is recorded. So the sponsor included an additional 87 days, the first day of treatment to the first day of response, in their calculation of duration of response.
It was also stated in the original Medical Officer Review that full approval could only be granted if clinical benefit was shown through improvements in such endpoints as prolongation of disease free survival, time to progression, overall survival or improvement in QOL in a randomized controlled trial with a comparator arm.

In the Medical Officer Review on September 7, 2001, which reviewed this Phase 3 trial and recommended conversion to regular approval, this was the main study cited so I am assuming that this is the key post-marketing study that was agreed to as part of the AA commitments.

**Results of post-marketing studies**

A total of 511 patients with advanced/metastatic breast cancer were randomized in this Phase 3 trial to receive capecitabine in combination with docetaxel versus docetaxel monotherapy. The primary endpoint remained TTP and secondary endpoints were response rate and survival. However, survival was considered to be the primary endpoint by the FDA.

The combination of capecitabine and docetaxel resulted in a statistically significant increase in survival of 418 days versus 338 days for the monotherapy arm. There was also a reduction of 35% in the risk of tumor progression for combination therapy patients, with a median time to progression of 186 days for the combination arm versus 128 days for monotherapy patients. The combination arm showed a response rate of 32% while the docetaxel arm showed a response rate of 22% (p=0.009).

The safety of capecitabine in combination therapy is consistent with the toxicities of monotherapy. Common adverse events include GI adverse events, such as stomatitis and diarrhea, hand and foot syndrome, hyperbilirubinemia and neutropenia.

| Comparison of capecitabine clinical trial results (pivotal and post-marketing) |
|-----------------------------|----------------|-----------|----------|-----|
|                             | Response rate (%) | Duration of response (days) | TTP (days) | Survival (days) | 1-year survival |
| Phase 2 trial (pivotal)     | 18.5%            | 154       |          |                |               |
| Phase 3 trial – combination with docetaxel (vs monotherapy) | 32% (vs 22%) p-value of 0.009 | 186 (vs 128) | 418 (vs 338) p-value of 0.012 | 57% (vs 47%) |

**Conversion to regular approval**

Based on the results of this Phase 3 study, the FDA converted the AA of capecitabine to regular approval on September 7, 2001 and expanded the label to treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy. In addition, the FDA granted approval for the use of

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40 FDA Medical Officer Review, capecitabine, Xeloda, September 7, 2001 (www.accessdata.fda.gov)
capecitabine in combination with docetaxel for patients with anthracycline-refractory metastatic breast cancer (second line use).

Other indications:
Capecitabine was also approved for the treatment of metastatic colorectal cancer on April 30, 2001. This approval was a full approval.

On June 15, 2005, capecitabine was granted full approval for use as a single agent for adjuvant treatment in patients with Dukes’ C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy is preferred.

Patent protection:
Roche has patent protection over capecitabine until January 13, 2011. So at the time of conversion to full approval on September 7, 2001, Roche had approximately 9.3 years of patent exclusivity remaining for capecitabine.

2.5 Imatinib mesylate (Gleevec)
Sponsor: Novartis

Indication: treatment of CML patients in all three phases: (a) chronic phase after failure of IFN-alpha therapy, (b) accelerated phase, and (c) blast crisis

Date of Accelerated Approval: May 10, 2001
Date of conversion to full approval: December 5, 2003
Time to complete post-marketing requirements: 2.5 years

Imatinib mesylate (Gleevec) represents a new class of drugs designed to inhibit the Bcr-Abl kinase, an aberrant enzyme produced by malignant white blood cells in patients with chronic myelogenous leukemia (CML). This Bcr-Abl kinase is the protein produced by a DNA translocation (the “Philadelphia chromosome”) that appears to be a central process in the course of CML disease.

Although Gleevec was designed to specifically inhibit the Bcr-Abl kinase, preclinical and clinical data suggests that there is some treatment effect on other kinases, which lead to some key side effects.

CML progresses through several clinical phases over an average of 5 to 7 years:
- Chronic phase (4-5 years)
- Accelerated phase (about a year)
- Blast crisis (about 3-6 months)

Basis of AA
Gleevec was approved under AA regulations on May 10, 2001 for the treatment of CML patients in all three phases: (a) chronic phase after failure of IFN-alpha therapy, (b)

42 FDA Electronic Orange Book, based on the first patent expiration date listed
43 FDA Medical Officer Review, imatinib mesylate, Gleevec, May 10, 2001 (www.accessdata.fda.gov)
accelerated phase, and (c) blast crisis. It was the fastest review process in the history of oncology drug approval processes (2.5 months).

The initial approval for Gleevec was based upon the results of three non-randomized single-arm trials for each of the CML populations.

- Study 110: 532 patients in chronic phase CML failing treatment with IFN
- Study 109: 235 patients with accelerated phase CML
- Study 102: 260 patients with CML in blast crisis

The surrogate endpoints used in these trials were response rates specific for hematologic cancers: hematologic response (HR), which includes complete hematologic response (CHR), and cytogenetic response (CR), which includes complete cytogenetic response (CCyR) and major cytogenetic response (MCyR).

Each of the three different indications had a different combination of surrogate endpoints, as noted in the following chart:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Surrogate endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic phase after failure of IFN- alpha therapy</td>
<td>Major cytogenetic response (MCyR) and Complete cytogenetic response (CCyR)</td>
</tr>
<tr>
<td>Accelerated phase</td>
<td>Hematologic response (HR), MCyR and CCyR</td>
</tr>
<tr>
<td>Blast crisis</td>
<td>HR</td>
</tr>
</tbody>
</table>

**Results of the pivotal studies for initial approval**

**Study 110: Chronic CML failing treatment with IFN**

During the chronic phase, disease is usually managed with hydroxyurea and IFN with or without cytosine arabinoside. In this trial, patients were either intolerant of IFN or had cancers that progressed while on IFN therapy. The median duration of therapy was about 6 months.

Major cytogenetic response (MCyR) was noted in 49% of patients and a complete cytogenetic response (CCyR) was noted in 30% of patients. Median time to MCyR was 3 months. Duration of response could not be determined due to short follow-up of 6 months.

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44 Hematologic response (HR) requires less than 15% blasts in blood and bone marrow and no evidence of extramedullary disease. Determined to be a surrogate endpoint in settings where large numbers of blasts (immature, quickly growing leukemia cells) are the immediate clinical problem, such as blast crisis or accelerated phase.

45 Complete hematologic response (CHR) requires normal numbers of functional white blood cells and platelets, with no blasts. Determined to be a surrogate in any CML setting.

46 Cytogenetic response (CR) is a reduction in the percentage of Philadelphia chromosomes (Ph+) on bone marrow karyotyping.

47 Complete cytogenetic response (CCyR) is a complete reduction of Ph+ chromosomes on bone marrow karyotyping

48 Major cytogenetic response (MCyR) is a partial reduction (≤35% Ph+ chromosomes) on bone marrow karyotyping

49 Ibid
Complete hematologic response (CHR) was documented in 88% of patients and median time to CHR was 22 days. The median duration of CHR could not be determined due to the short follow-up but at least 63% of patients were in CHR at their 6 months follow-up.

While there is no good comparator for IFN-refractory chronic CML patients, early phase chronic CML patients being treated with standard of care (IFN and araC) traditionally show a MCyR of less than 20%. So a MCyR of 49% and a CCyR of 30% is a significantly better efficacy rate than existing options, particularly for this refractory patient population, which is expected to have an even lower rate of response.

**Study 109: CML in accelerated phase**

During the accelerated phase, disease becomes increasingly resistant to therapy. This phase is marked by both the appearance of a moderate number of blasts (immature resistant leukemia cells) in the bone marrow and peripheral blood and by progressive resistance to treatment. The median duration of treatment was about 8 months.

MCyR was about 21% and HR was 63%, with CHR in about 26% of patients. Median duration of therapy could not be determined due to the short follow-up of therapy. These response rates were significantly better than existing highly-toxic combination chemotherapy regimens and considerably less toxic.

**Study 102: CML in blast phase**

CML terminates in blast crisis, a rapidly fatal condition similar to acute leukemia where blasts replace the bone marrow and patients die of bone marrow failure. The primary endpoint was HR, which was seen in 26% of patients, with 4% of patients showing a CHR. Cytogenetic responses were also observed, where 14% of patients showed a MCyR.

Toxicity is an important issue in the setting of blast crisis because survival is short and palliation of symptoms is a goal of treatment. The existing options for patients in blast crisis is the high dose chemotherapy, which has shown a HR of 23% and a median survival of 4.5 months, however, these chemotherapeutic regimens have a very severe side effect profile. While Gleevec has comparable efficacy, as measured by HR, the side effects associated with Gleevec are significantly better than existing options.

Some common side effects of Gleevec include GI side effects, such as nausea, vomiting and diarrhea, and musculoskeletal adverse events, such as myalgias and arthralgias. Severe AEs include fluid retention and edema, hepatotoxicity and myelosuppression. But compared to the side effect profile of existing therapies, such as the combination cytotoxic regimens, these side effects are considered manageable.

Based on the results of these three clinical trials, Gleevec was granted AA on May 10, 2001 for all three indications.

**Post-marketing AA commitments to demonstrate clinical benefit**

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50 FDA approval letter for Gleevec, May 10, 2001
1. To conduct and submit the final study report for Protocol 106 entitled “A phase III study of STI571 (Gleevec) versus IFN combined with cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia-chromosome positive (Ph+) CML in chronic phase with TTP as the primary surrogate endpoint.
   a. Interim analysis (1-year HR and QOL) was planned for Q1 02
   b. Final analysis was expected in Q4 05.
2. To provide interval follow-up information on studies 102, 109 and 110.
   a. Safety and efficacy analysis was expected in July 2001
   b. Final analysis was expected in Q3 01

Results of post-marketing Phase IV trials

Protocol 106: First-line CML
This trial enrolled 1,106 patients with newly-diagnosed CML, with 553 randomized to the Gleevec treatment arm and 553 patients randomized to IFN. The primary efficacy endpoint was TTP. The planned cutoff date for the TTP analysis was the date of the 385th event but the analysis was performed early (after 127 events) due to the statistically significant differences between the two arms. The hazard ratio was 0.183, in favor of Gleevec.

Secondary endpoints included CHR and duration of CHR, MCyR and duration, survival and QOL.

<table>
<thead>
<tr>
<th></th>
<th>Gleevec n=553</th>
<th>IFN + Ara-C n=553</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>94.6%</td>
<td>76.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MCyR</td>
<td>75.8%</td>
<td>12.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CCyR</td>
<td>53.7%</td>
<td>2.7%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Based upon the results of this study, which supported the conversion of Gleevec for the treatment of CML in the three original indications, Gleevec was also granted accelerated approval for on December 20, 2002 for the treatment of newly diagnosed patients with CML.

Study 110: Chronic CML failing treatment with IFN
In the initial study, MCyR was noted in 49% of patients and 88% of patients maintained their response after 2 years of treatment. Eighty five percent of the patients who responded were free of progression to accelerated phase or blast crisis and the estimated overall survival was 91%.

Study 109: CML in accelerated phase
In the initial study, MCyR was about 21% and HR was 63%, with CHR in about 26% of patients. Dose escalation was permitted from 400 mg qd to 800 mg qd. At the 600 mg qd dose level, the median duration of HR was 29 months and 61% of patients treated at this dose level maintained a HR at two years. Median survival for these patients was not reached, however the estimated 2-year survival rate is estimated to be 66%.

Study 102: CML in blast phase
In the initial study, the primary endpoint was HR, which was seen in 26% of patients, with 4% of patients showing a CHR. Cytogenetic responses were also observed, where 14% of patients showed a MCyR. In the complete study measured after 2 years of treatment, the HR was sustained at 33%, MCyR was maintained at 15%. The median overall survival was 6.9 months, while the estimated 2 year survival was 18.3%.

The side effects were very similar to those seen in the initial results of the pivotal trials.

Conversion to regular approval

On December 5, 2003, Gleevec was converted to regular approval for the three original indications: (a) IFN-alpha refractory CML, (b) CML in the accelerated phase and (c) CML in the blast crisis. The benefits measured by the surrogate endpoints in the initial review of the clinical trials were shown to be sustained in the follow-on studies and clearly represented a clinical benefit to the patient, measured both by improved survival and QOL. 51

Other indications

Gleevec also received accelerated approval for three other indications following the initial approval. 52 On February 1, 2002, Gleevec was approved for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). On December 20, 2002, Gleevec was approved for the treatment of newly diagnosed patients with CML. On May 20, 2003, Gleevec was approved for the treatment of pediatric patients with CML whose disease has recurred after stem cell transplant or who are resistant to IFN-alpha therapy. These three additional indications remain on the market under accelerated approval.

Patent protection

Novartis has patent protection over Gleevec until January 4, 2015. 53 So at the time of conversion to full approval on December 5, 2003, Novartis had approximately 14 years of patent exclusivity remaining for Gleevec.

2.6 Oxaliplatin (Eloxatin)
Sponsor: Sanofi

Indication: Treatment in combination with 5-FU/leucovorin of patients with metastatic carcinoma of the colon or rectum whose disease has recurred/progressed on 5-FU/LV and irinotecan

Date of Accelerated Approval: August 9, 2002
Date of conversion to full approval: January 9, 2004
Time to complete post-marketing requirements: 1.4 years

51 Ibid.
52 FDA, Drugs at FDA database, Gleevec
53 FDA Electronic Orange Book, based on the first patent expiration date listed
Basis of AA:

Oxaliplatin is a platinum analogue used for chemotherapy. It was granted AA on August 9, 2002 for second-line use in combination with 5-FU/leucovorin in patients with metastatic carcinoma of the colon or rectum whose disease has recurred/progressed with the first line therapy of the combination of 5-FU/LV and irinotecan.

Approval was based on interim data from a single Phase III multi-center, open-label, prospectively randomized, 3-arm study (EFC4584) that enrolled 463 patients with metastatic carcinoma of the colon/rectum whose disease had progressed on 5-FU/LV and irinotecan. Accelerated approval was based on the statistically significant improvement in tumor response and TTP (based on interim analysis) in comparison to an infusional regimen of 5-FU and leucovorin. At the time of approval, this second-line population had no effective therapy available.

The three arms of the study included patients on (A) a regimen of 5-FU and leucovorin, (B) oxaliplatin alone and (C) oxaliplatin and 5-FU/leucovorin. Each arm had drug administered every 2 weeks. The comparison between arm A and arm C was the primary comparator. The primary endpoint of this trial was overall survival (OS), but at the time of the interim analysis, which was the prespecified endpoint for potential accelerated approval, the survival data was not mature and response rate (RR) was used as the primary endpoint. TTP and symptom improvement (noted as time to symptom worsening, TTSW) were the secondary endpoints. A maximum of 32 cycles (or 8 months) was administered on the study.

The FDA-determined response rate between arm A (5-FU/LV) and arm C (5-FU/LV and oxaliplatin) was 0% and 9%, respectively (p-value of 0.0002). TTP was improved by about 2 months in the oxaliplatin combination arm versus comparator arm. TTSW was not analyzed at this point because not enough events had occurred for a complete analysis.

| Initial efficacy results that formed the basis of accelerated approval for oxaliplatin (a) |
|-----------------------------------------|---------------------------------|----------------------------|-------------------|
| **Arm A**                               | **Arm B**                       | **Arm C**                 | **p-value (b)**   |
| n=151                                   | n=156                           | n=152                      |                   |
| CR                                      | 0                               | 0                          |                   |
| PR                                      | 0                               | 2 (1%)                     | 13 (9%)           |
| Median TTP (mos)                         | 2.7                             | 1.6                        | 4.6               |

(a) Arm A: 5-FU/LV, Arm B: oxaliplatin, Arm C: 5-FU/LV and oxaliplatin

(b) P-value comparing arm A and arm C

Safety data on a total of 1,874 patients from 4 different studies, published reports and compassionate use programs were submitted. Reversible neurotoxicity was the most common dose-limiting response. Neutropenia was the principal hematologic toxicity, where 17% of patients in arm C (5-FU/LV/oxaliplatin) had developed grade 4 neutropenia. Nephrotoxicity, cardiotoxicity and ototoxicity were noted as uncommon.

In addition, the FDA reviewers had also assessed the data from the use of oxaliplatin in combination with 5-FU/LV in first-line use in a different clinical trial, which didn’t show a survival advantage but did show an improvement in response rate (39% vs 13%) and

54 All results taken FDA perspective per the Oxaliplatin Medical Officer Review, August 9, 2002.
PFS (8.8 mos vs 6.2 mos). The improvement in RR and PFS supported the current AA approved use in second-line CRC.

**Post-marketing commitments included**\(^{55}\):

1. Completion of the study whose initial results were submitted for review in the original NDA: EFC4584 - Multi-center, randomized three arm study of 5-FU/leucovorin or oxaliplatin or a combination of 5-FU and oxaliplatin as **second-line treatment** of metastatic colorectal carcinoma. Submission of the mature survival data and analysis was expected by 2Q 04.

2. Completion of study EFC 4585 - Multi-center, randomized, two-arm study of irinotecan versus the combination of oxaliplatin with irinotecan as **second-line treatment** of metastatic colorectal cancer. Submission of the mature survival data in a full study report was expected by 3Q 05.

3. **Completion of study EFC7462 - Randomized Phase 3 trial of combinations of oxaliplatin, 5-FU and irinotecan as initial treatment of patients with advanced adenocarcinoma of the colon and rectum.** Results was expected by 3Q 03.

4. Completion of study L8125 – Randomized study evaluating oxaliplatin combined with two different 5-FU regimens in patients with **previously untreated** advanced colorectal cancer. Full study report was expected by 2Q 05.

5. Completion of the adjuvant treatment study EFC3313 – Multicenter International Study of Oxaliplatin/F5U/LV in the **adjuvant treatment** of colon cancer – MOSAIC trial. Full study report was expected for review by 3Q 04.

6. Completion of the adjuvant treatment study EFC7112 – Clinical trial comparing 5-FU plus leucovorin and oxaliplatin with 5-FU/LV for the treatment of patients with Stage 2 and 3 Carcinoma of the Colon. Full study report was expected by 1Q 07.

There were five other post-marketing requirements related to a renal study, medical errors, label designations, and 2 studies using oxaliplatin in the third-line setting. But all these studies were noted as "not a condition of accelerated approval" in the approval letter, so I have left the details out.

**Results of post-marketing Phase IV trials**

The company submitted study 3, EFC 7462, to the FDA as part of their post-marketing AA requirements as well as for an application for expanded use to first line use. This Phase IV trial was a multicenter, open-label, prospectively randomized trial conducted by the NCI in 795 patients that had locally advanced, locally recurrent or metastatic CRC patients. This was a three arm study: (a) irinotecan plus 5-FU/LV (Saltz regimen or IFL), (b) oxaliplatin plus 5-FU/LV (FOLFOX4), (cc) irinotecan plus oxaliplatin (IROX). IFL was considered to be the control arm of this study.

The original primary endpoint of the study was TTP. The secondary endpoints included survival and response rates. The FDA preferred the endpoint of survival and used survival as the basis of approval.

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\(^{55}\) FDA approval letter, oxaliplatin, August 9, 2002.
The median survival was improved by almost 5 months on the FOLFOX4 arm compared to the control arm of IFL. TTP and response rate was also improved in the FOLFOX arm.

**Efficacy results:**

<table>
<thead>
<tr>
<th></th>
<th>IFL n=264</th>
<th>FOLFOX4 n=267</th>
<th>IROX n=264</th>
<th>p-value(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival (mos)</td>
<td>14.6</td>
<td>19.4</td>
<td>17.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median TTP (mos)</td>
<td>6.9</td>
<td>8.7</td>
<td>6.5</td>
<td>0.0014</td>
</tr>
<tr>
<td>RR (CR and PR)</td>
<td>69%</td>
<td>95%</td>
<td>75%</td>
<td>0.0093</td>
</tr>
</tbody>
</table>

(a) p-value for the comparison between FOLFOX-4 and IFL only

**Conversion to regular approval**

On January 9, 2004, the FDA expanded the label of oxaliplatin to include use in first-line combination regimens with 5-FU/LV. The new indication was for use in combination with 5-FU and leucovorin for patients previously untreated for advanced colorectal cancer.

In addition, based on the results submitted for this supplemental application, namely commitment 3 (Study EFC 7462), the FDA released the sponsor (Sanofi) from the majority of their remaining Phase IV requirements. Sanofi still needed to submit their renal study and reports of medication errors, but granted them full approval based on the results of their review of the survival data in first line patients.

**Comparison of oxaliplatin clinical trial results (pivotal and post-marketing)**

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>TTP (mos)</th>
<th>Survival (mos)</th>
<th>PFS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3 trial – interim second line (pivotal)</td>
<td>9%*</td>
<td>4.6</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>First line (supporting) – vs 5-FU/LV alone</td>
<td>39% (vs 13%)</td>
<td>No advantage</td>
<td>8.8 (vs 6.2)</td>
<td></td>
</tr>
<tr>
<td>Confirmatory PIII – first line use FOLFOX4 (vs IFL)</td>
<td>95% (vs 69%)</td>
<td>8.7 (vs 6.9 mos)</td>
<td>19.4 (vs 14.6)*</td>
<td></td>
</tr>
</tbody>
</table>

* Primary endpoint

**Other indications:**

On November 4, 2004, Sanofi received an expanded label for oxaliplatin for use in combination with 5-FU/leucovorin for the adjuvant treatment of stage III colon cancer patients who have undergone complete resection of primary tumor.

**Patent protection:**

Sanofi has patent protection over oxaliplatin until April 7, 2013. At the time of conversion to full approval on January 9, 2004, Sanofi had approximately 9.3 years of patent exclusivity remaining for oxaliplatin.
2.7 Summary of oncology drugs approved under AA that have been converted into full approval

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade name</th>
<th>Time to complete post-marketing commitments</th>
<th>Remaining patent life after conversion to full approval</th>
<th>Additional approved indications</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Dexrazoxane</td>
<td>Zinecard</td>
<td>7.4 years</td>
<td>5.1 years</td>
<td>None</td>
<td>Pharmacia (Pfizer)</td>
</tr>
<tr>
<td>2 Docetaxel</td>
<td>Taxotere</td>
<td>2.1 years</td>
<td>11.9 years</td>
<td>5 Aventis</td>
<td></td>
</tr>
<tr>
<td>3 Irinotecan</td>
<td>Camptosar</td>
<td>2.4 years</td>
<td>8.8 years</td>
<td>1 Pharmacia (Pfizer)</td>
<td></td>
</tr>
<tr>
<td>4 Capecitabine</td>
<td>Xeloda</td>
<td>3.4 years</td>
<td>9.4 years</td>
<td>2 Roche</td>
<td></td>
</tr>
<tr>
<td>5 Imatinib mesylate</td>
<td>Gleevac</td>
<td>2.8 years</td>
<td>11.1 years</td>
<td>3 (2) Novartis</td>
<td></td>
</tr>
<tr>
<td>6 Oxaliplatinin</td>
<td>Eloxatin</td>
<td>1.8 years</td>
<td>8.6 years</td>
<td>1 Sanofi</td>
<td></td>
</tr>
</tbody>
</table>

Mean 3.3 years 8.2 years 2.4
Mean excluding dexrazoxane 2.4 years 10.0 years 2.4
Median 2.5 years 8.1 years 2

(1) Source: Dagher R et al. Accelerated Approval of Oncology Products: a Decade of Experience. Journal of National Cancer Institute, Vol 96, No 20, October 20, 2004
(2) All three additional indications for Gleevec remain under AA

With the exception of dexrazoxane, the average length of time to complete the post-marketing requirements for accelerated approval was 2.4 years. Since these drugs subsequently demonstrated meaningful therapeutic benefit for serious and life-threatening disease in post-marketing studies, they are great examples validating the accelerated approval regulations because they allowed these six drugs get to the market 2.3 years sooner than they would have had they gone through the full approval process.

In a majority of cases (docetaxel, irinotecan, capecitabine, imatinib), the initial accelerated approval was based on single-arm Phase 2 studies, using response rates as the primary endpoints. Efficacy was demonstrated in comparative Phase 3 studies, except for Gleevec, where efficacy was demonstrated in longer-term follow-up of patients in the Phase 2 studies.

Four of the sponsors conducted, or attempted to conduct, post-marketing studies in a broader patient population as evidence for clinical benefit. Pharmacia, who had received initial approval for irinotecan for the treatment of patients with metastatic colorectal cancer whose disease has recurred or progressed following 5-FU therapy, attempted to conduct a study in first-line use, but later changed the trial to 5-FU refractory patients, similar to the original patient population. Pharmacia received full approval with the same indication.

Roche originally received initial approval for capecitabine for the treatment of metastatic breast cancer patients resistant to both paclitaxel and anthracycline, a subset of the original patient population. They conducted a post-marketing study in metastatic breast cancer patients refractory to anthracycline regimens and demonstrated improved survival. Based on the results of this trial, they received a broader label for treatment of patients after anthracycline failure, no longer bound to patients failing anthracycline and paclitaxel.

Novartis had received initial approval for Gleevec for the three phases of CML based on 3 separate Phase 2 studies. They finished up the longer-term follow-up for patients in these Phase 2 studies and were conducting a separate study in newly diagnosed CML.
patients. They received full approval based on the longer-term follow-up data of the Phase 2 data, which demonstrated a durability of the initial responses seen in this patient population. The FDA granted Novartis a separate AA for the indication of newly diagnosed patients with chronic CML.

Sanofi had originally received initial approval for oxaliplatin for use in combination with 5-FU/leucovorin in patients with metastatic colorectal cancer refractory to 5-FU/leucovorin and irinotecan. They had a number of post-marketing clinical trial requirements in a variety of settings (first line, second line, adjuvant), but the clinical trial that the FDA accepted as providing evidence of clinical benefit was a study which tested oxaliplatin in the first line setting. Novartis then received an expanded label to include use in the first line setting.

Aventis received full approval for docetaxel for the same initial indication: treatment of patients with advanced breast cancer after failure of anthracycline-based therapy. However, their approval was granted on interim results from two out of three post-marketing clinical trials, which showed response rates that were significantly higher than the response rates observed in the comparator arms.

Pharmacia was the only company to receive a narrower label after completion of the post-marketing study. The initial indication for dexrazoxane was the prevention of cardiomyopathy associated with doxorubicin administration in patients with metastatic breast cancer. After completing their post-marketing crossover study that confirmed the cardioprotective response and showed a lack of tumor protection in later courses of doxorubicin therapy, the FDA narrowed the label to patients with metastatic breast cancer who have already received a cumulative dose of 300 mg/m2 and who will continue to receive doxorubicin as maintenance therapy.

The sponsors also had a significant amount of patent exclusivity left on the life of the drug, with an average of 10.5 years left on the life of the patent (excluding dexrazoxane), which left enough time to conduct clinical trials for additional indications. In all cases, the first indication approved was under AA and the sponsors pursued additional indications following the initial approval. With the exception of Gleevec, the sponsors applied for full approval for follow-on indications, completing the traditional Phase 3 requirements demonstrating clinical benefit.
3. Review of oncology drugs approved before 2000 that have not been converted into full approval

In this section, I will examine the regulatory and post-marketing clinical studies for the seven remaining drugs that were approved under the Accelerated Approval regulations prior to 2000 and were noted to still not have been converted to regular approval. These seven drugs were originally selected because their initial approvals under AA were originally granted before 2000. I have excluded drugs approved after 2000 since there is a higher probability that post-marketing studies are still ongoing. These seven drugs were also noted by two different FDA sources as remaining unconverted to full approval. All drugs approved prior to 2000 under AA are included in either the converted or not converted groups in my research.

<table>
<thead>
<tr>
<th>Name</th>
<th>Trade name</th>
<th>AA approval</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Liposomal doxorubicin</td>
<td>Doxil</td>
<td>17-Nov-95</td>
<td>JNJ (formerly Alza/Sequus)</td>
</tr>
<tr>
<td>2 Liposomal doxorubicin</td>
<td>Doxil</td>
<td>28-Jun-99</td>
<td>JNJ (formerly Alza/Sequus)</td>
</tr>
<tr>
<td>3 Amifostine</td>
<td>Ethylol</td>
<td>15-Mar-96</td>
<td>Medimmune (US Bioscience)</td>
</tr>
<tr>
<td>4 Denileukin diftitox</td>
<td>Ontak</td>
<td>5-Feb-99</td>
<td>Ligand (formerly Seragen)</td>
</tr>
<tr>
<td>5 Temozolomide</td>
<td>Temodar</td>
<td>11-Aug-99</td>
<td>Schering</td>
</tr>
<tr>
<td>6 Liposomal cytarabine</td>
<td>DepoCyt</td>
<td>1-Apr-99</td>
<td>Skye Pharmaceuticals</td>
</tr>
<tr>
<td>7 Celecoxib</td>
<td>Celebrex</td>
<td>31-Dec-98</td>
<td>Searle/Pfizer</td>
</tr>
</tbody>
</table>

(a) These drugs were selected because they appeared as not converted according to the FDA website (www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm)

3.1 Liposomal doxorubicin (Doxil)

Sponsor: Johnson & Johnson (formerly Alza Corp, originally approved with Sequus Pharmaceuticals)

Doxil has two indications that were approved under accelerated approval. The first indication is discussed immediately below for the treatment of AIDS-related Kaposi’s sarcoma and was approved on November 17, 1995. The second indication is discussed immediately after the first indication and was approved under accelerated approval on June 28, 1999 for the indication of metastatic ovarian cancer. I have included both indications in my discussion because both initial indications were approved before 2000 and the regulatory outcomes are different.

Indication: Treatment of AIDS-related Kaposi’s Sarcoma in patients with disease that has progressed on prior chemotherapy or who are intolerant to such therapy

Date of Accelerated Approval: November 17, 1995

56 The first source was the FDA website on drugs approved AA: www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm, April 25, 2006. The second source was a review article written by the members of the FDA Oncology Division: Dagher R, Johnson J, Williams G, Keegan P, Pazdur R. Accelerated Approval of Oncology Products: A decade of experience. Journal of the National Cancer Institute, 96, 20, 2004, 1500-1509.
Basis of AA
Doxil was the second oncology drug approved under the AA regulations on November 17, 1995 for the treatment of AIDS-related Kaposi’s sarcoma (KS) in patients with disease that has progressed on prior chemotherapy or in patients who are intolerant to such therapy.

Kaposi’s sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The most frequent manifestations of the disease are skin lesions, but it may affect the mucous membranes, lymphatic system and viscera, particularly in the lung and GI tract. In HIV-infected patients, KS is an AIDS-defining illness. Aggressive cases have average survival times of less than one year.

Approval was based on results of an interim analysis of an open-label, single arm, multicenter study (LTI-30-12) testing Doxil in 383 patients with AIDS-related KS. The FDA focused on a cohort of 77 patients that were retrospectively identified as having disease progression on prior systemic combination chemotherapy or were intolerant to such therapy. Forty-nine of the 77 patients (64%) had previously received doxorubicin.

Assessment of efficacy was based on 2 different analyses of tumor response: (1) 34 patients evaluable for investigator assessment and (2) 42 patients evaluable for indicator lesion assessment.

There were 4 uncontrolled studies that were submitted as supportive evidence.

Results of the pivotal studies for initial approval
Investigator assessment:
In the population of 34 patients that were evaluable for assessment by the investigator, 27% of the patients were assessed to have a partial response, which was defined as a 50% or greater flattening of previously raised lesions or a 50% or greater decrease in area of the lesion. There was a median duration of PR of 73 days. In 29% of the patients, there was evidence of stable disease and 44% of the patients had progressive disease while on therapy.

Indicator lesion assessment:
In the population of 42 patients that were evaluable for indicator lesion assessment, there was a higher partial response rate of 48%, with a median duration of response of 71 days. In 26% of the patients, there was evidence of stable disease and 26% of the patients had progressive disease.

No patients by either of these assessments achieved a complete response. In the FDA summary of the accelerated approval, it was stated that no conclusions can be made regarding the clinical significance based on the assessment of reduction in KS-related pain, reduction in lesion-associated edema, changes in lesion color and complete flattening of previously-raised lesions.

57 www.hivmedicine.com, April 13, 2006
There was a safety database of 753 patients that were being treated with liposomal
doxorubicin for AIDS-related KS. Prominent toxicities included leucopenia, Palmar-
Plantar erythrodysesthesia and acute infusion reactions.

**Post-marketing commitments include:**
There were two ongoing controlled trials comparing Doxil to combination cytotoxic
chemotherapy regimens, ABV (doxorubicin, bleomycin and vincristine) and BV
(bleomycin and vincristine). At the time, ABV and BV were considered to be the gold
standard in treatment KS and had been reported to have response rates of 60 to 80%, but
with significant toxicities.

The sponsor, Sequus Pharmaceuticals at the time, made a commitment to conduct a well-
controlled study to demonstrate clinical benefit. In a 6/28/95 letter to the FDA, Sequus
made a commitment to conduct either (a) a randomized, controlled clinical trial of Doxil
and DaunoXome (following approval and marketing of DaunoXome, liposomal
daunorubicin) or (b) a controlled open-label study to describe the clinical benefits of
Doxil.

**Results of post-marketing studies**

**Doxil vs BV trial**
The completion of the multicenter, randomized clinical trial comparing Doxil to the
combination cytotoxic chemotherapy regimen, BV (bleomycin and vincristine) in the
treatment of HIV-related KS was reported in February 1998. Two hundred and forty-one
patients were enrolled in the trial. The overall response rate for patients in the Doxil arm
was 58.7% versus 23.3% for the BV arm. The mean duration of response was similar in
both groups, 160 days for Doxil and 167 days for BV.

Patients in the BV arm were more likely to terminate treatment early because of an
adverse event (26.7% versus 10.7%). BV treatment was also associated with a
significantly higher incidence of peripheral neuropathy, whereas Doxil treatment was
more commonly associated with neutropenia and myelosuppression. Overall, Doxil
treatment was more effective than BV for the treatment of AIDS-related KS.

**Doxil vs ABV trial**
There was also a Phase III clinical trial in 258 patients with advanced AIDS-related KS
comparing Doxil to ABV (doxorubicin, bleomycin and vincristine) reported in July

<table>
<thead>
<tr>
<th>Summary of pivotal studies:</th>
<th>Investigator assessment n = 34 (%)</th>
<th>Indicator lesion assessment n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>9 (27%)</td>
<td>20 (48%)</td>
</tr>
<tr>
<td>Stable Diseases</td>
<td>10 (29%)</td>
<td>11 (26%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>15 (44%)</td>
<td>11 (26%)</td>
</tr>
</tbody>
</table>

---

58 Stewart S et al. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and
Among 133 patients randomized to receive Doxil, there was 1 CR and 60 PR, for an overall response rate of 45.9%. In the 125 patients in the ABV arm, 31 achieved a PR for an overall response rate of 25%.

Adverse events were common in both groups, however, 37% of the patients in the ABV arm discontinued therapy versus 11% for the Doxil arm. In addition, patients in the Doxil arm were in the trial about 1.7x as long as the patients in the ABV group. The most common adverse event was leucopenia. From the results of this study, Doxil appears to be more effective and less toxic than the combination ABV regimen in treating KS.

### Comparison of liposomal doxorubicin clinical trial results (pivotal and post-marketing)

<table>
<thead>
<tr>
<th></th>
<th>Pivotal trial: Investigator lesion assessment</th>
<th>Pivotal trial: Indicator lesion assessment</th>
<th>Phase 3 (vs BV)</th>
<th>Phase 3 (vs ABV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>27%</td>
<td>48%</td>
<td>59% (vs 23%)</td>
<td>46% (vs 25%)</td>
</tr>
</tbody>
</table>

**Doxil in combination with HAART trial**

In the past few years, there have been two recent small trials that were reported in the literature. In mid 2004, there was a report of an open-label trial with 28 patients with moderate/advanced HIV-related KS that were treated with either a combination of HAART and Doxil or HAART alone. After 48 weeks of treatment, the response rates for the combination arm was 76% vs 20%.60

Another small open-label observational trial of 54 HIV-1 infected patients with advanced KS treated with a combination of HAART and Doxil was reported on in 2005.61 There was a response rate of 81.5% observed. A response was seen within a median of 8 weeks and continued for at least 1 year after chemotherapy withdrawal for a majority of patients.

Patients on combination therapy also showed a constant CD4+ T-cell count during therapy despite a reduction in overall leukocyte count. This is in contrast to a matched-pair analysis of non-KS HIV-1 patients who were also on HAART therapy, where there was a strong increase in CD4+ T-cell counts. Both sets of patients (KS and non-KS) showed a relative increase in CD4+ T-cell counts before and after therapy. Therefore, the authors concluded that the HAART-mediated cellular immune recovery was still occurring in the patients on combination therapy and that HAART was contributing to the safety of doxorubicin therapy.

These two small studies provide some evidence of the meaningful therapeutic benefit of the combined use of Doxil and HAART therapy in the treatment of advanced KS. In contrast, no clinical studies comparing the combined use of liposomal daunorubicin with HAART therapy could be found in my Pubmed search.

Comparison to DaunoXome (liposomal daunorubicin)

On April 8, 1996, about 5 months after the AA approval of Doxil, the FDA approved a liposomal formulation of daunorubicin, another anthracycline chemotherapeutic, as first line treatment for advanced HIV-related KS under the regular approval process.

This approval was based on the review of 3 clinical trials: two Phase 2 trials and one Phase 3 trial. The pivotal trial Phase 3 enrolled 232 patients with advanced AIDS-related KS and compared the use of liposomal daunorubicin versus ABV. The efficacy of Daunoxome was similar to ABV, in terms of response rates, survival times and time to treatment failure. Daunoxome had significantly less alopecia and neuropathy but more patients in the Daunoxome arm had G4 neutropenia (15% vs 5%) and opportunistic infections, although the difference in opportunistic infections was not statistically significant.

<table>
<thead>
<tr>
<th>Daunoxome (n=116)</th>
<th>ABV (n=111)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>25%</td>
<td>28%</td>
</tr>
<tr>
<td>Median survival time (days)</td>
<td>369</td>
<td>342</td>
</tr>
<tr>
<td>Median time to treatment failure (days)</td>
<td>115</td>
<td>99</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Neutropenia (G4)</td>
<td>Alopecia and neuropathy</td>
</tr>
</tbody>
</table>

Based on these results, DaunoXome was approved for first line use in AIDS-related KS.

Current Status

The advent of HAART (Highly Active Anti-Retroviral Therapy) in early 1996 with the approval of the first protease inhibitor, saquinavir, changed the way that HIV and AIDS-related KS are treated and led to a dramatic decrease in the frequency of KS. With HAART, the clinical course of the disease has also improved significantly. In some cases, tumor remission and/or stabilization of the disease has been seen with reduction of viral load and reconstitution of the immune system. HAART is now considered first line treatment for HIV and KS. Therapy with other agents, such as liposomal doxorubicin, is recommended if there is widespread skin involvement, lesions refractory to local treatment, extensive edema and symptomatic visceral involvement. In UpToDate, the liposomal anthracyclines are still recommended as front-line care for patients with KS that have visceral involvement (in the pulmonary and GI tract).

In a review of the Pubmed literature, there was no finding of a trial comparing the use of Doxil to Daunoxome, to satisfy the FDA post-marketing requirement. It could be argued

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63 UpToDate, AIDS-related Kaposi’s sarcoma: Clinical features and treatment, April 12, 2006.
that this trial was no longer relevant or was very difficult to conduct with the changes in
the recommended therapeutic regimens and a different trial should be conducted to
demonstrate clinical benefit.

However, in comparing the efficacy results of the Doxil trials to the Daunorubicin trials,
it appears that Doxil is a more efficacious therapy in spite of its current approval status
for this indication under AA (versus Daunorubicin’s full approval).

Comparison of Doxil and DaunoXome’s ABV trials

<table>
<thead>
<tr>
<th></th>
<th>Doxil (vs ABV)</th>
<th>DaunoXome (vs ABV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rates</td>
<td>46% (vs 25%)</td>
<td>25% (vs 28%)</td>
</tr>
<tr>
<td>Toxicities</td>
<td>Leukopenia</td>
<td>Neutropenia (alopecia and neutropenia)</td>
</tr>
</tbody>
</table>

Since the sponsor completed two randomized trials (comparing Doxil to ABV and BV) that were similar to the pivotal trial that was used for full approval of DaunoXome and even showed better response rates than DaunoXome in their trials, it appears that Doxil is being held to a higher standard for demonstrating clinical benefit than DaunoXome was in their review.

In addition, the two small trials examining the combined use of Doxil with HAART therapy, while not large enough to provide complete evidence of clinical benefit, do lend further support to the clinical benefit of Doxil therapy for the treatment of KS. So while the treatment of KS has changed since the initial approval with the advent of HAART therapy, the superiority of Doxil over Daunorubicin as demonstrated by both the greater response rate in the monotherapy trials and the improved efficacy observed in the combination trials provides support that consideration of conversion to full approval is warranted.

Other indications:
On June 28, 1999, Alza (now JNJ) received accelerated approval for metastatic carcinomas of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens.

Patent status
There are no patents listed for Doxil with the FDA’s Orange Book. However, a search through the US Patent and Trademark Office for patents that cover liposomal doxorubicin show several relevant ongoing patents. Patent 5,213,804 entitled “Solid tumor treatment method and composition” covers liposomal formulations of anti-tumor compounds and is held by the sponsor. This patent expires on May 25, 2010.

There is another key patent, 4,863,739 held by University of Texas, Austin, entitled, “Liposome compositions of anthracycline derivatives” is a composition of matter patent that covers liposomal doxorubicin. This patent expires September 15, 2006.

So the first patent, Patent 5,213,804 held by the sponsor appears to cover Doxil’s exclusivity until May 2010.

64 www.uspto.gov
JNJ does not have orphan drug exclusivity for the indication of HIV-related KS.\textsuperscript{65}

3.2 Liposomal doxorubicin (Doxil)
Johnson & Johnson (formerly Alza Corp)

**Indication:** Treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens

**Date of Accelerated Approval:** June 28, 1999

**Background on ovarian cancer therapy**

Ovarian cancer is the leading cause of gynecologic-related cancer deaths in US. It was estimated that there about 26,000 new cases diagnosed in the US in 2004 and approximately 16,000 women will die of the disease. Early stage disease is often asymptomatic and therefore the majority of women are diagnosed with advanced Stage III/IV ovarian cancer.

First line standard of care for patients initially diagnosed with Stage III/IV ovarian cancer (75\% of patients) is surgery followed by systemic chemotherapy with a platinum agent plus paclitaxel.\textsuperscript{66} For patients with earlier stage disease, surgery is still the treatment of choice and the use of platinum-based chemotherapy is generally offered if there are certain poor prognostic features.

The likelihood of relapse for all stages of disease is estimated to be between 50 and 75\%.\textsuperscript{67} Since recurrent disease is generally not curable, the goal of salvage or second-line therapy is palliation of symptoms, prevention of complications and optimization of quality of life.\textsuperscript{68}

The choice of second-line agent is dependent on whether the patient’s disease was initially “sensitive” or “resistant” to platinum-based regimens, which is often defined by how long it takes for the patients cancer to recur (if the disease-free period is longer than 6 months, the cancer is considered to be platinum-sensitive and if the period is less than 6 months, platinum resistant).\textsuperscript{69} Patients who initially responded to platinum-based therapy have a high probability of responding again to platinum-based therapies. Patients who had disease that was initially “resistant” to platinum-based therapies should be treated with non-cross resistant agents.

There are currently at least 10 drugs that are active in the platinum-resistant setting, including paclitaxel, docetaxel, etoposide, liposomal doxorubicin, topotecan,

\textsuperscript{65} FDA Electronic Orange Book
\textsuperscript{66} UpToDate, Second-line medical treatment for epithelial ovarian cancer, April 13, 2006.
\textsuperscript{68} Cannistra SA. Cancer of the Ovary. NEJM 351; 24, pp 2519 – 2527.
\textsuperscript{69} Herrin VE and Thigpen JT. Second-line medical treatment for epithelial ovarian cancer, UptoDate, 4.13.06.
gemcitabine, vinorelbine, ifosfamide, 5-FU/LV and tamoxifen. The choice of which agent to use is often driven by the side-effect profile and convenience of administration, since the response rates are reported to be similar in the 10-20% range. At the time of initial approval under AA for Doxil, however, there was only one agent approved by the FDA in this setting, topotecan, which had received full approval on May 28, 1996.

Basis of AA

On June 28, 1999, Alza received approval for liposomal doxorubicin for a second indication under Accelerated Approval for the treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens (second-line therapy).

Results of the pivotal studies for initial approval

According to the FDA website and label available at the time, approval was based on 3 open-label, single-arm clinical trials of 176 patients with metastatic ovarian carcinoma and preliminary results from a randomized comparative clinical trial. In the three single-arm trials, 146 of these patients (83%) were refractory to both paclitaxel- and platinum-based chemotherapy. Patients were dosed every 3 to 4 weeks for 3 to 6 cycles or longer.

The results of these pivotal studies are as follows:

<table>
<thead>
<tr>
<th>FDA review of response rates</th>
<th>Study 1 (US) n=27</th>
<th>Study 2 (US) n=82</th>
<th>Study 3 (non-US) n=36</th>
<th>Randomized trial – preliminary results (n = 44 on Doxil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>6 (22.2%)</td>
<td>14 (17.1%)</td>
<td>0 (0%)</td>
<td>6 (13.6%)</td>
</tr>
</tbody>
</table>

When the data from the three single-arm trials are combined, the response rate for all patients that are refractory to both paclitaxel and platinum agents are 13.8%. The median time to progression was 17.6 weeks and the duration of response was 39.4 weeks.

Other clinical studies found in the literature, which may or may not correspond to the studies that were reviewed by the FDA, support the above response rates. A medical officer review was not available on the website so it is difficult to match the results of the study since the FDA runs their own analysis of the data that often differs from the results of the sponsor.

Summary of the efficacy results for Doxil trials in ovarian cancer in the literature

<table>
<thead>
<tr>
<th>Phase II – Muggia (n=35)</th>
<th>25.7%</th>
<th>5.7 mos</th>
<th>11 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II – Gordon (n=89)</td>
<td>16.9%</td>
<td>19.3 weeks</td>
<td>NR</td>
</tr>
<tr>
<td>Phase III – Gordon (n=239)</td>
<td>19.7%</td>
<td>16.1 weeks</td>
<td>63 weeks</td>
</tr>
</tbody>
</table>

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70 Ibid, pg 2526.
In a Phase II trial by Muggia that appears to correspond to the FDA’s Study 1, 35 patients with progressive ovarian cancer after platinum-based and/or paclitaxel therapy were treated with liposomal doxorubicin. There were 9 responses (1 CR and 8 PR), for a response rate of 25.7%. The median progression-free survival was 5.7 months with a median overall survival of 11 months. Thirteen patients (37%) experienced grade 3/4 non-hematological skin and mucosal toxicities (hand-foot syndromes or stomatitis).

The second US study is a Phase II trial conducted by Gordon appears to correspond to the FDA’s Study 2. This trial tested Doxil in patients whose cancers had progressed after platinum- and paclitaxel therapies within 6 months of treatment. These patients are considered to have cancers with lower response rates to salvage treatments. In this study, 89 patients were enrolled into study out of which 82 had ovarian cancers that were both platinum and paclitaxel-resistant. There was a 1 CR and 14 PR, for a total response rate of 16.9% for the overall population and 18.3% for the platinum and paclitaxel-refractory population. Median time to progression was 19.3 weeks. Adverse reactions included hand-foot syndrome, stomatitis and skin lesions, which were manageable with dose reductions in most cases.

Dosing is once per month. There is minimal alopecia, nausea and myelosuppression associated with this option relative to the other options. However approximately 20 to 30% of patients will have hand-foot syndrome and mucositis.

Post-marketing commitments include:

In the FDA approval letter, the post-marketing requirement was the clinical study 30-49 entitled “A Phase 3, randomized, open-label, comparative study of Doxil/CAELYX versus Toptecan HCL in patients with epithelial ovarian carcinoma following failure of first-line, platinum-based chemotherapy”. The interim analysis of this data was due by July 12, 1999 (half a month after initial AA approval) and the final study analysis by March 31, 2000. At the time of this approval, topotecan was the only approved agent for second line use in advanced ovarian cancer.

A unique requirement for this approval was the requirement that the results of this trial “demonstrate convincing superiority of Doxil over topotecan HCL in either TTP or survival”, with a supporting trend for the other endpoint. This is consistent with the regulations for AA, which state that the therapy would have to provide “meaningful clinical benefit over existing therapy”. In order to convert to full approval and stay on the market, a question arises whether the FDA holds the sponsor to a higher standard for efficacy or safety in its requirement for superiority in exchange for accelerated approval.

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The FDA approval letter also stated that the sponsor would be required to conduct an additional study to prove clinical benefit in the event that the results of this post-marketing study "do not demonstrate clinical benefit", meaning non-superiority of Doxil over topotecan HCL.

**Results of post-marketing studies**

In this Phase III study by Gordon and Teitelbaum, the efficacy and safety of liposomal doxorubicin was compared to topotecan in 474 patients with ovarian cancer that had failed with platinum-based therapy. The primary efficacy endpoint was time to progression. Secondary endpoints included overall survival, response rate, time to response, duration of response and safety and toxicity.

In the interim analysis, the response rates, PFS and OS were similar in both treatment groups. However, it was noted that in the subset of patients with platinum-sensitive disease, the patients in the liposomal doxorubicin group had a significantly longer PFS and OS compared to the topotecan arm.

In the longer term follow-up, these results were sustained. There was a trend toward longer OS in the liposomal doxorubicin arm than with topotecan, although the difference was not statistically significant. But in the subset of patients with platinum-sensitive disease, the difference in OS did reach statistical significance (112 weeks versus 77 weeks). There was no significant difference seen in the patients with platinum-refractory disease, which was the indication that Doxil was approved for under AA.

The side effect profiles of the two agents were quite different. The most frequent adverse events reported with topotecan were hematologic toxicities and alopecia. The toxicities associated with topotecan were more severe, with 71% of topotecan patients reported grade 4 adverse events, versus 17% of those on Doxil. Adverse events reported with liposomal doxorubicin were similar to those reported in earlier trials: hand-foot syndrome and stomatitis.

**Results of the Phase III comparative trial to topotecan**

<table>
<thead>
<tr>
<th></th>
<th>Doxil (n=239)</th>
<th>Topotecan (n=235)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>19.7%</td>
<td>17%</td>
<td>0.39</td>
</tr>
<tr>
<td>PFS (weeks)</td>
<td>16.1</td>
<td>17</td>
<td>0.095</td>
</tr>
<tr>
<td>Survival (weeks)</td>
<td>60</td>
<td>56.7</td>
<td>0.341</td>
</tr>
<tr>
<td>Platinum-sensitive</td>
<td>n=109 (45.6%)</td>
<td>n=111 (47.2%)</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>28.4%</td>
<td>28.8%</td>
<td>0.964</td>
</tr>
<tr>
<td>PFS (weeks)</td>
<td>28.9</td>
<td>23.3</td>
<td>0.037</td>
</tr>
<tr>
<td>Survival (weeks)</td>
<td>108</td>
<td>71.1</td>
<td>0.008</td>
</tr>
<tr>
<td>Platinum-resistant</td>
<td>n=130 (54.4%)</td>
<td>n=124 (52.8%)</td>
<td></td>
</tr>
</tbody>
</table>

Based on the results of this Phase 3 study, liposomal doxorubicin does offer a significant benefit over topotecan (the only approved second line agent) in terms of its milder side effect profile, which is of considerable importance in this setting. Its efficacy is comparable to topotecan when one looks at the results for all patients (platinum-sensitive and platinum-resistant), but in the platinum-sensitive setting, liposomal doxorubicin appears to be more efficacious, based on the significant differences in overall survival and PFS. It is interesting to note that there is no significant difference in the response rates, which is an often-used surrogate in cancer trials, even though there was a difference seen in the more important endpoints of survival. Even in the platinum-resistant setting, there is a trend towards greater response rate with liposomal doxorubicin over topotecan, although the difference did not reach significance. The results of this trial demonstrated superiority of Doxil over topotecan, in terms of lower toxicity and greater survival in patients with platinum-sensitive ovarian cancer.

Conversion to regular approval

Although the FDA website source that I used to categorize the drugs into converted and not converted did not include Doxil for ovarian cancer as a converted drug, on January 28, 2005, Doxil was granted full approval for the treatment of patients with ovarian cancer whose disease has progressed or recurred after platinum-based therapy. The full approval has been expanded to patients that have progressed after platinum-based therapy instead of "both paclitaxel- and platinum-based" therapy.

Other indications

On November 17, 1995, Alza received accelerated approval for the treatment of AIDS-related Kaposi’s Sarcoma in patients with disease that has progressed on prior chemotherapy or who are intolerant to such therapy. As discussed in the previous section, Doxil remains approved under accelerated approval for this indication.

Patent status

As noted in the previous discussion on patent protection for Doxil under the indication of KS, the sponsor has a patent that covers liposomal formulations off anti-tumor compounds that provides protection until May 25, 2010.

The sponsor also has orphan drug exclusivity for this indication until June 28, 2006.

3.3 Amifostine (Ethvol)

Sponsor: Medimmune (formerly US BioScience)

Indication: Reduction of platinum toxicity in NSCLC

Date of Accelerated Approval: March 15, 1996

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75 FDA, Drugs@FDA database, Doxil approval letter, January 28, 2005.
Amifostine is a cytoprotective agent that appears to protect normal tissues from the toxic effects of chemotherapy and radiation. Amifostine is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically-active free thiol metabolite. The uptake of the drug is pH-dependent and its uptake into healthy tissues is much greater than the uptake into the acidic environment of tumors. Amifostine works via two purported mechanisms: (1) it acts as a scavenger of free radicals in tissues exposed to radiation and (2) it serves as an alternative target to nucleic acids for the reactive molecules of alkylating or platinum drugs.

The ability to differentially protect normal tissues is attributed to higher alkaline phosphatase activity, higher pH and better vascularity of normal tissues relative to tumor tissues, which results in higher levels of the active metabolite in normal tissues to serve as a protective agent against the reactive oxygen species of radiation and the active metabolites of cisplatin.

**Basis of AA**
On March 15, 1996, amifostine was granted AA for the reduction of platinum toxicity in the treatment of NSCLC.

AA was based on the results of 2 Phase II single-arm studies. The first clinical study tested amifostine as a chemoprotectant with cisplatin/vinblastine administered prior to radiation therapy on 31 patients with stage III NSCLC.

The second clinical study was a single-arm Phase II study in 25 patients with stage IV NSCLC. Patient received amifostine followed by cisplatin on day 1, followed by vinblastine on days 1, 8, 15, 22 every 4 weeks for 6 cycles. The only clinical data cited as supportive of the protective effect of amifostine was that out of the 13 patients who had received 4 or more cycles, 1 had a 40% reduction in creatinine clearance (which is an endpoint that was used in the renal protection indication). Response rate was also measured to assess if amifostine had any tumor protective effects.

The results of these pivotal studies were not stated on the FDA website.

**Post-marketing commitments include:**

Post-marketing commitments could not be found on the FDA website.

There are, however, many clinical studies assessing the clinical benefit of amifostine with various chemotherapy and radiation regimens in NSCLC. The results of these studies are mixed.

There was a Phase II randomized study by Antonadou et al, published in 2003 that compared the effect of pretreatment with amifostine in reducing acute and late toxicities.

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77 Investigational Drugs Database (IDDB), Drug report on Amifostine, April 17, 2006.
associated with RCT (radiochemotherapy). While this trial was designed to assess the protective effect of amifostine against RCT, instead of isolating the protective effect to cisplatin treatment as specified in the approved indication, this trial seems like an appropriate post-marketing study to examine the clinical benefit given the design of one of the pivotal studies, which examined the role of amifostine with RCT.

In this trial, 68 patients were randomized to receive RCT (either paclitaxel or carboplatin) with amifostine or RCT alone. The results are as follows:

<table>
<thead>
<tr>
<th></th>
<th>RCT + amifostine</th>
<th>RCT alone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagitis (G&gt;3)</td>
<td>38.9%</td>
<td>84.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>19.4%</td>
<td>56.3%</td>
<td>0.002</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>40.6%</td>
<td>22.2%</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>37.5%</td>
<td>13.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Late toxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-mos pneumonitis</td>
<td>30.3%</td>
<td>66.7%</td>
<td>0.009</td>
</tr>
<tr>
<td>6-mos fibrosis</td>
<td>28.6%</td>
<td>50%</td>
<td>0.156</td>
</tr>
<tr>
<td>Response rates</td>
<td>88.8%</td>
<td>82.2%</td>
<td>0.498</td>
</tr>
</tbody>
</table>

In this patient population, where esophagitis and pulmonary toxicities were the most commonly reported side effects, the addition of amifostine to the RCT regimen demonstrated a significant reduction of treatment-related toxicities (with regards to esophagitis and pulmonary toxicity) without compromising antitumor efficacy. Amifostine did not have a significant effect on neutropenia or thrombocytopenia, although there was a higher incidence in the amifostine arm. Amifostine was well-tolerated. Only 3 out of the 36 patients treated with amifostine experienced nausea and vomiting during the infusions and 8 patients experienced transient hypotension.

However, in April 2005, another large, multi-center study was published by Movsas et al which didn’t show any benefit with the addition of amifostine in NSCLC patients receiving concurrent chemotherapy and radiation.

In this trial, a total of 243 NSCLC patients were randomized to receive combination chemotherapy (paclitaxel and carboplatin) and radiation, with or without amifostine. The primary endpoint was the reduction in severity of esophagitis during concurrent RCT. The secondary endpoints included the evaluation of differences in patient-reported swallowing symptoms and quality of life.

There was no difference in the primary endpoint between the two arms (30% for amifostine vs 34% for the control for G3/4 esophagitis), however there was a difference

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79 Ibid
81 Two randomized Phase 3 trials demonstrated a survival benefit to treating patients with concurrent chemotherapy and radiation, rather than sequentially. However, concurrent administration is associated with increased esophagitis.
in the secondary endpoint of patient’s perception of swallowing difficulty in favor of amifostine.

Consistent with the other trials, there was no evidence of tumor protection due to amifostine. At a median follow-up of 30.8 months, no differences were noted in median survival (17.3 months vs 17.9 months for the amifostine vs no amostine respectively, p-value of 0.87) or median time to progression (9.2 months for both arms).

However with regards to toxicities, there was a significantly higher rate of acute toxicities reported for the amifostine arm, such as acute nausea (p=0.03), vomiting (p=0.007), transient hypotension (p=0.0001) and acute infection or febrile neutropenia (p=0.03). Patients did, however, experience significantly less weight loss with amifostine and no differences in late toxicities were noted.

Despite the slightly higher level of acute toxicities, the study failed to meet the primary endpoint in demonstrating the clinical benefit of amifostine, as far as reduction of esophagitis. The study did hit statistical significance for the secondary endpoint, the patient’s perception of swallowing. Despite this benefit in secondary endpoints and the concern over higher acute toxicities, on March 28, 2006, the indication for the reduction of platinum toxicity in NSCLC treatment was removed. This appears to be the first time the FDA has removed an indication that was approved under AA because the sponsor was unable to demonstrate meaningful clinical benefit.

Other approvals:

Prior to this AA approval on March 15, 1996, amifostine was granted full approval on December 8, 1995 for the reduction of cumulative renal toxicity associated with administration of cisplatin in patients with advanced ovarian cancer.

On June 24, 1999, the FDA granted full approval for the treatment of moderate to severe xerostomia (dry mouth) in patients undergoing post-operative radiation treatment for head and neck cancers, where the radiation port includes a substantial portion of the parotid gland.

The sponsor, Medimmune, is now testing amifostine in Phase 2 clinical trials for the treatment of mucositis in NSCLC patients caused by RCT (idarubicin and cytosine arabinoside).

Patent protection
Medimmune has patent protection over amifostine until July 31, 2012.

3.4 Denileukin diftitox (Ontak)
Sponsor: Ligand Pharmaceuticals (formerly Seragen)
(Approved by CBER as a BLA)

Indication: Treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the IL-2 receptor

48
Cutaneous T-cell lymphoma (CTCL) is a subtype of non-Hodgkin’s lymphoma with an incidence of about 1,000 cases per year, qualifying it as an orphan drug disease. CTCL is a malignant cutaneous lymphoproliferative disorder of CD4 T-helper cells, where malignant T-cells are pushed to the surface of the skin and form lesions on the surface. These lesions change shape as the disease progresses, appearing initially as a rash and eventually forming plaques and tumors before metastasizing to other parts of the body.²²

There are two types of CTCL: mycosis fungoides (MF) and Sezary syndrome (SS). MF is the stage of disease where the localized plaques evolve into tumor nodules. SS is the form of the disease where the circulating lymphomatous Th cells are detected.

The overall median survival is approximately 8 to 9 years from the time of diagnosis.³³ There is no curative treatment for CTCL. Therapeutic approaches include topical agents, such as glucocorticoids, nitrogen mustard), radiotherapy, PUVA (psoralens used in conjunction with UV light) with methoxypsoralen and systemic chemotherapy treatment.

Treatment for early stage disease (Stage Ia and Ib) is the use of topical agents. Topical nitrogen mustard is considered to be first-line therapy for early stage plaque disease, with response rates of 30-60%, with up to 20% durable complete responses. Toxicities include hypersensitivity reactions and secondary skin cancers. PUVA treatment is another first-line treatment for stage I-IIa disease or as a secondary treatment after topical steroids for Stage 0 disease. Response rates range from 90% CR in patients with minimal skin disease (Ia) to 70% in patients with infiltrative plaques. Acute complications of PUVA therapy include erythema, pruritis, skin dryness and nausea. Cataracts and secondary skin cancers are potential chronic toxicities of PUVA treatment.

For advanced disease, electron beam radiotherapy is an effective initial treatment. For patients with Stage III disease, photopheresis with methoxsalen is a first line treatment, with clinical response rates of >50% reported. Single agent and combination chemotherapy is also used. Interferon-alpha has also been evaluated, with response rates of 90% in minimally pretreated patients and 50% in heavily-pretreated or refractory patients. Reported toxicities include fever, chills, myalgias.

Denileukin defitox, hereafter referred to as Ontak, is a fusion protein consisting of IL-2 and a truncated portion of the diphtheria toxin molecule. The mechanism of action is thought to be the binding of the IL-2 portion of the molecule to the IL-2 receptor on the malignant cells. Once bound to the cell surface, the protein is internalized and the diphtheria toxin portion inhibits protein synthesis and leads to cell death.

While the primary target is thought to be the malignant cells, non-malignant IL-2 receptor positive T-cells, such as activated T-cells, B-cells, macrophages and oligodendroglial cells (immune cells) may also be affected.

Basis of AA

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Ontak was approved under the AA regulations on February 5, 1999. Approval was based on the results of four clinical studies that enrolled a total of 257 patients with CTCL: (1) a Phase I/II multi-center study (Protocol 93-04-01) testing 73 patients with CTCL (49% of patients), non-Hodgkin's lymphoma (23%) and Hodgkin's disease (29%) who have relapsed following standard therapy, (2) a Phase III study testing two different doses in patients with refractory CTCL with Stage Ib to III disease following ≥ 4 previous therapies or Stage IVa patients following ≥ 1 previous therapy (Protocol 93-04-10), (3) a Phase III study testing 2 different doses in CTLC patients with Stage Ia to III disease following ≥ 3 previous therapies (Protocol 92-04-11) and (4) a Phase III open-label extension study in patients with CTCL from previous studies (Protocol 93-04-14). Complete results were available for the first two studies and the second two studies were still ongoing at the time of review.

Phase I/II study (Protocol 93-04-01)
This was a Phase I/II study in three different patient populations (CTCL, non-Hodgkin’s lymphoma and Hodgkin’s disease) who have relapsed following standard therapy. Out of the 73 patients who qualified for inclusion into the study, 35 patients had CTCL. There was a 37% response rate (5 CR and 8 PR) for patients with CTCL. The duration of response was 7.3 months. For patients with Stage Ia to IIb disease, there was a 50-60% response rate and a 29% response rate for patients with Stage III disease. No responses were noted for patients with Stage IV disease.

No responses were observed for the 21 patients treated with Hodgkin’s disease and there was a 17.6% response rate for the 17 non-Hodgkin’s patients.

There was a high adverse event rate reported. The most common adverse events reported (>30% of patients) were fever/chills, nausea/vomiting, asthenia, hypotension, edema, infections, pain and rash.

At the beginning of the study, 38% of patients had evidence of DT antibody and 92% of patients had DT antibody after 2 cycles.

Phase III study (Protocol 93-04-10)
There were 71 CTCL patients with Stage Ib to III disease following ≥ 4 previous therapies or Stage IVa patients with ≥ 1 previous therapy. Two different doses were tested: 9 ug/kg and 18 ug/kg.

The overall response rate was 30%. The response rates were similar between the two dose groups. There was a higher response rate of 38% in the 26 patients with earlier stage disease (IIa) and a 24% response rate in patients with later stage disease.

Phase III study (Protocol 93-04-11)
This study was a Phase III placebo-controlled study testing 2 different doses in CTLC patients with Stage Ia to III disease following ≥ 3 previous therapies.

At the time of the BLA submission, 70 patients had been enrolled in this study. This study was ongoing at the time of review and completion of the study was part of the post-marketing approval requirements. Seventy percent of the patients had early stage disease.
(≤ IIa) and 30% of patients had late stage disease (≥ IIb). An overall response rate of 29% was reported at the time (all PR).

**Phase III open-label crossover study**
At the time of the BLA submission, an interim report on 40 patients was submitted. Eight patients (20%) failed to complete all planned therapy and there were 21 reports of SAE in 8 out of the 40 patients. The toxicities were similar to those reported in earlier trials.

**Supportive studies**
There were 7 Phase I/II clinical studies that were used as supportive trials since they used a different version of dinileukin difitox, one with a longer diphtheria toxin sequence. In the 7 clinical studies, 36 patients with CTCL were treated with the agent and a response rate of 17% was reported. Toxicities included transaminitis, hypoalbuminemia, hypersensitivity reactions, rash, thrombocytopenia and renal dysfunction with elevated serum creatinine.

At the beginning of the studies, 30% of the patients had anti-diptheria toxin antibodies and after treatment, 60% of the patients had anti-diptheria toxin antibodies.

<table>
<thead>
<tr>
<th>Results of the pivotal studies for initial approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P I/II</strong> (Pr 93-04-01) n=35</td>
</tr>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>CR</td>
</tr>
<tr>
<td>PR</td>
</tr>
</tbody>
</table>

Based on the results of the two completed studies (Protocol 93-04-01 and 93-04-10), Ontak was shown to have a 30-40% objective response rate in patients with previously treated CTCL. Responses were observed in both patients with advanced (≥ IIb) and early stage (≤ IIa) disease.

In the FDA’s medical review, it was noted that the relief of tumor-related symptoms, particularly pruritis, was not clearly shown by treatment, even in patients with a complete response. A dose-response relationship was not observed, since in two of the Phase III trials, there was no difference in response between the two doses tested. In addition, the product is highly immunogenic (demonstrated by the increase in anti-diptheria antibodies after treatment) and the effect of the elicited immune response on the dosing duration was also unknown.

The use of Ontak was also restricted to patients who expressed the CD25 component of IL-2 receptor, as determined by the presence of CD25 on 20% or more of the lymphocytes. Expression of CD25 is present on the low-affinity and high-affinity IL-2 receptor but not the intermediate-affinity IL-2 receptor. Since clinical benefit was established in the clinical trials only in patients with CD25-containing IL-2 receptors and not in patients with CD-25-negative IL-2 receptors, approval was restricted to the CD25+ expression.
The high incidence of toxicities was a concern to the reviewers. The observation that the incidence of toxicities decreased on the second and subsequent cycles was not well understood. It was not known whether tachyphylaxis, tolerance or an increase in neutralizing antibodies was the cause of the decrease in toxicities over time.

Due to all the unknowns regarding the dosing, duration of therapy, patient population and toxicities, Ontak was initially denied FDA approval, despite a positive recommendation from ODAC on June 2, 1998. It was later approved by the FDA under AA on February 5, 1999 for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the IL-2 receptor.

**Post-marketing commitments include**:\(^{84}\)

Although the sponsor demonstrated tumor response rates, as part of the AA, the sponsor was required to demonstrate through additional well-controlled studies that treatment results in clinical benefits such as relief in tumor-related symptoms, diminished use of rescue medications and prolonged time to progression.

1. Completion of the ongoing blinded, placebo-controlled P3 study, Protocol 93-04-11, with results submitted within 12 months of entry of the last patient.

2. Completion of the ongoing crossover study, Protocol 93-04-14, as an evaluation of the effectiveness of Ontak in patients with CTCL. This study was amended to include sufficient number of patients with CD25 negative IL-2R in order to evaluate the efficacy of therapy in this patient population.

3. Pharmacokinetic and antibody profiles of Ontak during 7 courses of therapy (specifically, course 1, 3, 5 and 7)

4. Conduct and complete a randomized trial in CD25 positive, Ontak-naïve patients with lymphoma to assess the optimal duration of therapy


There were 5 other post-marketing requirements in the approval letter but these were not related to the AA approval requirements so I have omitted the detail.

**Results of post-marketing studies**

The two clinical trials (Protocol 93-04-11, the Phase III placebo-controlled study, and 93-04-14, the extension study) appeared to still be ongoing as of April 18, 2006. There was no evidence of the completion of the studies through a Pubmed search and the

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\(^{84}\) FDA approval letter for Ontak, February 5, 1999.
information available on the company’s website indicated that the two trials were still ongoing.\(^8^5\)

For the second Phase III trial (Protocol 93-040-11), the company stated on its website that the plan was to accrue 150 patients for this study. At the time of BLA submission, 70 patients were enrolled. The extension study is still ongoing.

Given that more than six years have passed since the initial approval (February 5, 1999), the tough regulatory history (initially denied FDA approval), the concerns over toxicities in the initial review, this is one approval that deserves further scrutiny regarding the clinical benefit. In UpToDate, this is still classified as an “Emerging Novel Therapy” despite being on the market for six years. In addition, the drug appears to be hitting a plateau in sales growth, with $32 MM in annual sales reported for both 2004 and 2005\(^8^6\).

Since CTCL is an orphan drug disease, the sponsor may be encountering difficulties with regards to completing trial enrollment, particularly for a placebo-controlled trial. However, six years seems like enough time for preliminary results from the ongoing cross-over trial to be completed and reported. Absence of any data or updates for this long a period of time seems like a red flag that deserves further scrutiny.\(^8^7\)

In June 2003 at ASCO, there was a poster presentation of a retrospective analysis performed by Chin that assessed differences in survival and time to treatment failure in 37 CTCL patients treated with Ontak. All patients had advanced or refractory CTCL and had received either the 9 ug/kg or 18 ug/kg dose. The response rates were consistent with those reported in the Phase III clinical trial of 10% CR and 20% PR and a median TTF of 6.9 months. The analysis also reported a 31 month median survival. There was no statistically difference in survival based on stage of disease or response to therapy, however, a trend toward improved survival was observed.\(^8^8\)

**Other indications**

The sponsor is also testing Ontak for psoriasis, NHL, CLL, melanoma and GVHD. The sponsor was previously reported to be testing Ontak in the treatment of HIV infection, head and neck tumor, lung tumor, atopic dermatitis, alopecia areata and rheumatoid arthritis, but development on these indications has reportedly been discontinued.\(^8^9\)

**Patent protection**

There are no patents listed for Ontak in a search through the FDA’s Orange book or through the US Patent and Trademark Office database. This could be because this is a biologic.

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\(^{86}\) UBS Equity research report, Ligand Pharmaceuticals, January 27, 2006

\(^{87}\) Several attempts were made to contact the company but were unsuccessful.

\(^{88}\) Combination of two sources: (a) [www.ligand.com](http://www.ligand.com), Clinical Experience with ONTAK in Cutaneous T-cell lymphoma, downloaded on April 18, 2006 and (b) IDDB, Ontak Drug Review.

\(^{89}\) Investigational Drugs Database (IDDB), Drug report on denileukin diftitox, April 18, 2006.
Ligand had orphan drug exclusivity over Ontak for this indication until February 6, 2006. The expiration of exclusivity may potentially be a factor in the sponsor’s slow completion of the post-marketing studies. However, since Ontak is a biologic, there are likely other protections over the molecule, such as proprietary manufacturing processes.

### 3.5 Temozolomide (Temodar)

**Sponsor:** Schering

**Indication:** Treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosurea and procarbazine

**Date of Accelerated Approval:** August 11, 1999

Gliomas, which account for 40 to 60% of primary brain tumors in adults, are among the most serious and devastating of malignant disease, with a median survival of 1 to 2 years from diagnosis. Gliomas are also associated with significant morbidity, including severe motor disabilities, seizures, vision abnormalities and communication deficits. Historically, malignant gliomas have been categorized into two grades: anaplastic astrocytoma and glioblastoma multiforme (GBM) based on histologic criteria. However, the neuro-oncology community generally does not always separate these histologies when reporting treatment results in recurrent disease studies.  

The standard of care for primary disease has been surgery and radiation therapy. The use of adjuvant chemotherapy is still evolving. At the time of approval, the use of adjuvant chemotherapy was noted as “controversial” in the Medical Officer Review. Current standards seem to reflect the greater acceptance of adjuvant chemotherapy. In UptoDate, it was noted that better outcomes could be achieved by adding adjuvant chemotherapy to radiation therapy. The most commonly used chemotherapeutic agents for newly diagnosed gliomas are the nitrosoureas, BCNU (carmustine) and CCNU (lomustine). At the time of the approval, BCNU was considered to be first line standard of care, although some oncology centers used a combination regimen of PVC (procarbazine, vincristine and CCNU)

There is no established standard of care for recurrent disease. Retreatment options consist of reoperation, reradiation, chemotherapy and experimental treatments. The goal of treatment in this case is palliative, rather than curative. There is an urgent need for new therapies for recurrent gliomas.

Temodar is a cytotoxic agent of the imidazotetrazine class and is chemically related to the approved chemotherapeutic agent, dacarbazine. Dacarbazine was approved by the FDA in May 1975 for the treatment of metastatic malignant melanoma. Temodar is the active prodrug of MTIC (3-methyl-(triazen-1-yl)imidazole-4-carboxamide), undergoing spontaneous hydrolysis at physiologic pH to MTIC, which is the active cytotoxic
metabolite. MTIC is further decomposed to a reactive methyl-diazonium ion and AIC (AIC is an intermediate in purine and nucleic acid synthesis).

MTIC methylates specific DNA sites, the most critical being the O6 position of guanine on the DNA alkyltransferase, the DNA repair enzyme. Subsequent nucleotide mismatch and defects in the mismatch repair process ultimately leads to apoptosis.\textsuperscript{92}

Temodar was developed as an alternative to dacarbazine, with a better toxicity profile and a greater degree of CNS penetration. Unlike dacarbazine, it does not require hepatic metabolism, is nearly 100% bioavailable and achieves CSF concentrations that are approximately 40% of plasma concentrations.

Temozolomide, hereafter referred to as Temodar, was approved on August 11, 1999 under AA regulations for the treatment of refractory anaplastic astrocytoma. Approval was based on three Phase II studies: two studies were considered pivotal studies and the third was a supporting trial.

The first pivotal study (C94-091/I96-058) was a Phase II multi-center, randomized, open-label, active-controlled clinical study in 225 patients with relapsed GBM. This study compared the treatment of Temodar with procarbazine. The second pivotal trial (C/I 94-123) was a multi-center open-label Phase II trial of 162 patients with relapsed anaplastic astrocytoma. The third trial (I94-122) was a multi-center, open-label Phase II study in 138 patients with relapsed supratentorial GBM.

In all three of these trials, the primary endpoint was PFS at 6 months. In the medical officer review, there was record of an extensive amount of discussion between the sponsor and the FDA regarding the appropriate endpoints. The FDA does not believe that tumor shrinkage (or response rate) can be adequately assessed in relapsed malignant gliomas because of the irregularity of the tumors. Instead, the FDA believes that improvement in overall survival, which was the endpoint used for the Gliadel wafer (BCNU), should be the standard for any new agent indicated for GBM. This was the endpoint that the FDA suggested to the sponsor and three other companies developing therapies for the treatment of relapsed gliomas.

The FDA also reviewed the relapsed glioma literature for the endpoints used. Out of the 27 trials that reported any survival data, 13 reported only overall survival, 2 reported only progression-free survival and 9 reported both. The endpoint of 6-month PFS was not reported in any study.

Secondary endpoints included overall survival and health-related quality of life (HQL).

\textbf{Results of the pivotal studies for initial approval}

\textbf{C94-091 (GBM)}
The first pivotal study (C94-091/I96-058) was a Phase II multi-center, randomized, open-label, active-controlled clinical study in 225 patients with relapsed GBM. This study

compared the treatment of Temodar with procarbazine. In this study, the sponsor’s definition of efficacy was the lower bound of the 95% CI of the 6-month PFS for Temodar treatment being greater than 10% compared to procarbazine.

### Results of C94-091 study

<table>
<thead>
<tr>
<th></th>
<th>Temodar (mos)</th>
<th>Procarbazine (mos)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS (ITT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sponsor</td>
<td>2.99</td>
<td>1.97</td>
<td>0.0065</td>
</tr>
<tr>
<td>FDA</td>
<td>2.7</td>
<td>1.84</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td>7.3</td>
<td>5.86</td>
<td>0.61</td>
</tr>
<tr>
<td>6-mos survival rates</td>
<td>61%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(51%-70%)</td>
<td>(39%-58%)</td>
<td></td>
</tr>
<tr>
<td><strong>Response rates</strong></td>
<td>5%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Although there was a trend toward greater overall survival with Temodar, the difference was not statistically significant. Response rates were approximately 5% in both arms. Health-related QOL assessments favored the Temodar treatment arm.

### C/I94-123 (Anaplastic Astrocytoma)

The second pivotal trial (C/I 94-123) was a multi-center open-label Phase II trial of 162 patients with relapsed anaplastic astrocytoma. The primary endpoint in this study was PFS at 6 months and safety. Secondary endpoints included overall survival, objective response, HQL and population pharmacokinetics. The ITT group consisted of 162 patients. Nineteen of these patients had unknown or ineligible histology, leaving 143 patients as the eligible histology group.

Treatment outcomes were considerably better in the AA population than in GBM patients.

### FDA PFS at 6 months

<table>
<thead>
<tr>
<th></th>
<th>Temodar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA PFS</strong></td>
<td>4.4 mos</td>
</tr>
<tr>
<td>PFS at 6 months</td>
<td>45%</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>15.9 mos</td>
</tr>
<tr>
<td>6-mos survival rates</td>
<td>74%</td>
</tr>
<tr>
<td>Response rates (all)</td>
<td>33%*</td>
</tr>
<tr>
<td>Response rates (N and P refractory)</td>
<td>22%</td>
</tr>
<tr>
<td>CR</td>
<td>9%</td>
</tr>
<tr>
<td>Duration of response (all)</td>
<td>50 weeks</td>
</tr>
<tr>
<td>Duration of CR</td>
<td>64 weeks</td>
</tr>
</tbody>
</table>

* Based on Eligible Histology

In the FDA’s medical officer review of glioma/anaplastic astrocytoma trials in the literature, the trials focused on anaplastic astrocytoma were non-randomized Phase II data and most of these trials enrolled 20 patients or less. “While it is impossible to directly compare treatment results because of different patient populations and different response.
and progression criteria, it appears that all results are in the same ball-park with some studies having better outcomes and some worse than C/I94-123." 

*The sponsor requested AA for this indication, specifically for patients who have relapsed and who previously received both a nitrosourea (BCNU or CCNU) and procarbazine, based on the tumor response rate. The overall response rate for the trial was 33% and for the population of 54 relapsed AA patients previously treated with a nitrosourea and procarbazine, the response rate was 22%. Five of these patients (9.2%) achieved a CR, with a median duration of response of 448 days.

**I94-122 (GBM)**

The third trial (I94-122) was a multi-center, open-label Phase II study in 138 patients with relapsed supratentorial GBM. This was considered to be a supportive trial to the two previously described pivotal trials. All patients received Temodar therapy.

The median survival of these patients was 5.33 months and the 6-month survival rate was 44.5%. These survival outcomes were somewhat inferior to the 61% survival rate observed in the pivotal GBM trial C94-091.

In all the trials, the safety profile of Temodar was acceptable. There were few dose reductions or dose delays. Most adverse events were mild or moderate in severity and discontinuation of therapy due to adverse events was infrequent. The most common adverse events were nausea, vomiting, headache, fatigue and constipation.

Based on the results of these three trials, the FDA and ODAC agreed that Temodar should not be approved for GBM but it acceptable for approval under AA for anaplastic astrocytoma. Based on the pivotal study in GBM, C94-091, although there was a statistically significant improvement in PFS for the Temodar arm, this was deemed not to be an acceptable endpoint. There was no basis in previous trials or in the literature for the use of PFS at 6 months as demonstration of clinical benefit. In addition, no improvement in survival was seen for the Temodar arm over the patients treated with procarbazine. And the supporting trial, I94-122 in a similar GBM patient population, showed comparable survival rates to the procarbazine arm in the pivotal trial (5.33 mos for Temodar vs 5.86 mos for procarbazine).

However, the FDA and ODAC agreed that Temodar should be approved for anaplastic astrocytoma under AA. In contrast to the GBM patient population, the use of response rate was an “adequate surrogate for clinical benefit”, particularly for relapsed patients that were previously treated with a nitrosourea and procarbazine, as long as the response was well-defined and of sufficient magnitude. In this patient population, a response rate of 22%, supported by a durable response duration of 448 days, was deemed sufficient for accelerated approval.

**Post-marketing commitments include**

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93 [www.fda.gov](http://www.fda.gov), Medical Officer Review of Temodar, August 11, 1999, pg. 93.

94 FDA approval letter for Temodar, August 11, 1999.
1. A phase "I/III" three-arm randomized study comparing the combination of (1) radiation therapy and Temodar versus (2) radiation therapy and BCNU versus (3) radiation therapy, Temodar and BCNU for anaplastic astrocytoma. The primary endpoint is overall survival. Secondary endpoints include PFS, safety, study of putative molecular predictors of survival, such as chromosome 1p, 10q and 19q loss, p53 mutations, RB, CDKN2A, EGFR status and Ki-67 proliferation rates.

The sponsor proposed an initial Phase I safety trial to assess the safety of the combination of radiation, Temodar and BCNU on 15 patients. If the safety profile of this combination arm turns out not acceptable, then the sponsor would drop the third combination arm and just conduct the trial with the radiation and Temodar arm and the radiation and BCNU arm.

Three interim study analyses were planned for the Phase III portion of the trial, when total accrual equals 25%, 50% and 75% of the study population. Five hundred patients were expected to be enrolled in this trial. The minimum length of follow-up was 6 months. Final analysis was to be undertaken when all patients had been followed for a minimum of 36 months. Patient accrual was expected to be complete in early 2003 and the final analysis was expected in the fall of 2006.

Results of post-marketing studies

Results of the Phase I safety study95

The Phase I study to assess the safety of the combination of Temodar, BCNU and radiotherapy consisted of two arms: (a) 15 patients that received BCNU on Day 1 and Temodar daily for 5 days while on radiotherapy and (b) 14 patients that received Temodar daily for 5 days and BCNU on day 5 while on radiotherapy.

In the FDA’s initial review of the protocol, it was agreed before the trial started that if ≥ 2 patients reported with grade 3 or worse pulmonary toxicity or ≥ 5 patients reported with grade 4 or worse thrombocytopenia following one dose reduction, then this combination would not be tested in the Phase III trial.

In both arms, 70% of patients required a dose reduction by the second cycle of either BCNU or Temodar due to toxicity, mainly hematologic.

In the first arm where BCNU was administered concurrently with Temodar on the first day, two late grade 3 and one grade 4 infection occurred. There was one case of Grade 3 pulmonary toxicity, 6 cases of thrombocytopenia (four cases of grade 3 thrombocytopenia and two cases of grade 4 thrombocytopenia) and 6 cases of blood/bone marrow toxicity (one case of grade 3 and 5 cases of grade 4).

In the second arm, which used a lower dose of BCNU on day 5, two patients stopped BCNU due to pulmonary toxicity, although there were no cases of grade 3 or worse

pulmonary toxicity reported. There were 8 reports of grade 3 thrombocytopenia and 5 cases of blood/bone marrow toxicity (one case of grade 3 and 4 cases of grade 4).

Due to the results and the evidence of overlapping toxicities, particularly myelosuppression and pulmonary toxicity, the combination arm (arm 3 of the Phase III trial) was not pursued.

**Phase III study**

It appears that the Phase III trial is still ongoing. There are no reports in the literature of the interim results of the ongoing Phase III study. There is a 3 year follow-up on the 500 or so patients and the FDA expects this study to be complete the fall of 2006.

**Conversion to full approval**

On March 15, 2005, the FDA expanded the label to include treatment of patients with newly diagnosed high grade gliomas with Temodar concomitantly with radiotherapy and then as adjuvant therapy. The trial submitted for this broader indication also fulfilled the sponsor’s commitment to demonstrate clinical benefit and their AA was converted to full approval.

Conversion to full approval was based on the results of a single randomized, multi-center, open-label trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC), the National Cancer Institute of Canada, the Swiss Group for Clinical Cancer Research (SAKK) and the Trans-Tasman Radiation Oncology Group. No US patients were enrolled in this study.96

A total of 573 patients with newly diagnosed GBM patients were enrolled in this study and randomized to treatment with radiotherapy and Temodar (n=287) or radiotherapy alone (n=286). Patients on the Temodar arm were also administered maintenance doses of Temodar after RT was complete. The primary endpoint of the study was overall survival. Secondary endpoints included toxicity profile, PFS and QOL.

The results are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Temodar and RT (n=287)</th>
<th>RT alone (n=286)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>14.6 mos</td>
<td>12.1 mos</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFS</td>
<td>6.9 mos</td>
<td>5.0 mos</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QOL</td>
<td>Not submitted</td>
<td>Not submitted</td>
<td></td>
</tr>
</tbody>
</table>

During the initial 6-7 weeks of treatment, adverse events that were more common in the Temodar arm included thrombocytopenia, nausea, vomiting, anorexia and constipation. Grade 3 or higher thrombocytopenia was observed in 14% of patients treated with Temodar (no cases were reported with the RT monotherapy arm) and grade 3 or higher neutropenia was observed in 8% of patients.

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These results were supported by three additional Phase 2 clinical studies on the combination of radiation therapy and Temodar in treating newly-diagnosed GBM patients.

Results from supporting trials

<table>
<thead>
<tr>
<th>PII: Athanassiou (v RT alone) n=110</th>
<th>PII: Stupp n=64</th>
<th>PII: Lanzetta n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>13.4 mos</td>
<td>16 mos</td>
</tr>
<tr>
<td>1-year survival</td>
<td>55% (vs 16%)</td>
<td>58%</td>
</tr>
<tr>
<td>2-year survival</td>
<td>15% (vs 0%)</td>
<td>31%</td>
</tr>
</tbody>
</table>

Based on the results of the Phase III study and the supporting trials, the FDA converted Temodar to full approval and expanded the label to include treatment for high-grade gliomas, such as GBM, in combination with radiation therapy on March 15, 2005. The combination of Temodar with radiation therapy is now considered the standard of care for newly-diagnosed GBM patients.97

Other approved indications
There are no other approved indications for Temodar.

Patent protection
Schering has patent protection over Temodar until August 11, 2013. Since the date of conversion to full approval on March 15, 2005, Schering had 8.5 years left on its patent. Schering also has orphan drug exclusivity until March 15, 2012 for the indication of high-grade gliomas.

3.6 Liposomal cytarabine (DepoCyt)
Sponsor: Skye Pharmaceuticals (formerly Depotech)

Indication: Intrathecal treatment of lymphomatous meningitis

Date of Accelerated Approval: April 1, 1999

Lymphomatous infiltration of the meninges, or lymphomatous meningitis (LM), occurs in many patients with non-Hodgkin’s lymphoma (NHL). It is seen in approximately 4 to 15% of NHL patients. There are more than 55K cases of NHL diagnosed annually in the US. LM can also occur with other cancers that have a predilection for the subarachnoid space, such as leukemia, melanoma, breast cancer and lung cancer.98

Patients can present with any neurologic symptom but generally present with symptoms of CNS dysfunction (headache, altered mental status), cranial nerve abnormalities or spinal cord dysfunction. The most definitive diagnosis of LM is the identification of lymphoma cells in the CSF, where cytologic exams are positive in three examinations.

If left untreated, the development of leptomeningeal infiltration can lead to death from progressive neurologic disease, with a median survival of 4 to 6 weeks.

While the treatment outcomes for patients with LM depend largely on the extent to which the underlying systemic disease is controlled, common approaches to treatment include a combination of radiation therapy (RT) and intrathecal delivery of methotrexate or ara-C (cytarabine). At the time of the review from the assessment of the literature, methotrexate or methotrexate in combination with ara-C appeared to be the preferred first line chemotherapeutic agent(s). It was emphasized in the FDA’s medical review that there is no established “prospectively defined” standard of care for LM. While there are few clinical trials assessing the efficacy of these agents, the median survival with therapy is approximately 4 months.

Since survival of these patients depends largely on the control of the underlying systemic disease, the goal of therapy for lymphomatous meningitis is palliation, relief of existing neurologic signs and symptoms and prolongation of neurologic symptom-free survival. Liposomal cytarabine, hereafter referred to as DepoCyt, is a sustained release formulation of ara-C (cytarabine). Cytarabine is an antipyririmidine cytotoxic agent active in the S phase. With intrathecal administration, the half-life of ara-C is 3.4 hours. DepoCyt is a suspension of ara-C encapsulated into lipid-base particles for sustained release. In preclinical studies, this formulation had a 55-fold higher half-life. In a pK analysis, presence of cytotoxic levels of the drug after one dose was detected after 14 days. Dosing of DepoCyt is once every 2 weeks versus twice a week for ara-C.

Intrathecal administration requires either a lumbar puncture or Ommaya reservoir instillation. Lumbar puncture requires multiple injections per week and leads to unequal penetration of drug into nodular disease or the brain parenchyma. Ommaya reservoir instillation requires surgical placement of a drug reservoir, which has a 4 to 11% complication rate.

**Basis of AA**

AA was based upon a single open-label, randomized multicenter study (DTC 92-001) comparing DepoCyt to intrathecal Ara-C for the treatment of neoplastic meningitis in patients with leukemia, lymphoma or solid tumors.

The sponsor originally applied for approval for the treatment of carcinomatous meningitis however, the application for the original indication of carcinomatous meningitis was deemed “not-approvable” by the FDA on May 22, 1998. The study that was submitted was a randomized study comparing DepoCyt to methotrexate in the treatment of patients with solid tumor neoplastic meningitis. In this trial, 61 patients were enrolled and were treated with either DepoCyt once every 2 weeks or methotrexate twice a week. There was a 26% response rate in the DepoCyt arm versus 20% in the methotrexate arm.

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100 UpToDate, Secondary Involvement of the central nervous system by non-Hodgkin’s lymphoma. April 20, 2006.
There was a significant difference in the time to clinical progression of 58 days versus 30 days ($p=0.007$), however this was an non-blinded analysis that was significantly influenced by the results of one particular site. There was also a higher incidence of chemical arachnoiditis in the DepoCyt arm (11 vs 2 patients). Based on the results from this clinical trial, ODAC and the FDA did not believe the data represented substantial evidence of efficacy and issued a not-approvable letter.

The FDA however thought the results from the lymphoma arm were promising and invited the sponsor to submit a new NDA for the indication of lymphomatous meningitis.

The company submitted a different trial comparing the DepoCyt to ara-C in the treatment of lymphomatous meningitis. The primary efficacy endpoints were response rate, time to complete response, duration of complete response and time to relapse. Complete response was prospectively defined as (a) conversion, confirmed by a blinded central pathologist, from a positive examination of the CSF for malignant cells to a negative examination on two separate occasions (at least 3 days apart on day 29 and later) at all initially positive sites, together with (b) an absence of neurologic progression during the treatment period. Survival as an endpoint could not be used because of the impact of the underlying systemic disease. Secondary endpoints included changes in neurological symptoms or signs and changes in quality of life measurements.

Out of the 33 patients with lymphomatous meningitis that were enrolled into the trial, 31 out of the 33 received study medication and only 13 out of the 33 could be evaluated without protocol violations. There were multiple protocol violations, such as administration of excluded therapies, inadequate CSF sample collection, discordance between central and local pathology review data or absence of central pathology review.

The FDA considered four different interpretations of the data, with different definitions of cytologic response, which was one of the primary endpoints, and concluded that scenarios 2 and 3 were the acceptable scenarios. In the approved label, the FDA only presented the results from the ITT population in Scenario 3, which are in bold.

The results are as follows:

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101 DepoCyt package insert, as of April 20, 2006.
Adverse events were observed with more frequency in the DepoCyt arm, particularly nausea/vomiting and headache. Two cases of severe adverse events were reported for the DepoCyt arm and none for the ara-C arm.

In the ODAC review of the clinical data on November 16, 1998, the committee was undecided whether this was an adequate and well-controlled study for the purpose of evaluating response in lymphomatous meningitis (4 yes, 4 no). However, they still agreed that DepoCyt provided a “meaningful advantage over existing treatments”, particularly the more convenient dosing schedule for intrathecal administration (once every 2 weeks versus twice a week) and recommended accelerated approval for DepoCyt for the treatment of lymphomatous meningitis.

DepoCyt was granted approval under AA on April 1, 1999.

**Post-marketing commitments include**:

The sponsor is required to conduct a Phase 4 post-marketing study (Protocol C0101-010) and pharmacokinetic sub-study (C0101-011) titled, “A Randomized Clinical Study to determine the patient benefit and safety of DepoCyt (Cytarabine Liposome Injection) for the treatment of solid tumor neoplastic and lymphomatous meningitis.”

These studies were expected to be initiated within six months of approval, with an interim analysis due in the 4Q 2001. The final completion date of the study was estimated to be September 2003.

**Results of post-marketing studies**

There are no publications regarding the results of a randomized trial with DepoCyt for the treatment of solid tumors and lymphomatous meningitis and the company’s website indicates that the trial is still ongoing. [Skye/Enzon was contacted regarding current status update of this trial on April 20, 2006 – tel 866-792-5172]

**Other indications**

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102 FDA approval letter for DepoCyt, April 1, 1999.

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There are no other approved indications for DepoCyt.

**Patent protection**
No patents could be found for DepoCyt in the FDA’s Orange Book database or in a search through the US Patent and Trademark Office. It is likely to be covered by some of the similar patents that cover Doxil’s technology: patent 5,213,804 entitled “Solid tumor treatment method and composition”, which covers liposomal formulations of anti-tumor compounds and is held by the JNJ/Alza (formerly Sequus). This patent expires on May 25, 2010.

Skye Pharmaceuticals had orphan drug exclusivity for this indication until April 1, 2006.

### 3.7 Celecoxib (Celebrex)
Pfizer (formerly Searle)

**Indication:** To reduce the number of adenomatous colorectal polyps in Familial Adenomatous Polyposis patients, as an adjunct to usual care

**Date of Accelerated Approval:**

On December 31, 1998, Celebrex was granted full marketing approval for the relief of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA). The sponsor then submitted another study in patients with Familial Adenomatous Polyposis (FAP) to obtain approval under accelerated approval for this indication.

Human colon cancer develops in a progressive way from normal mucosa to adenomatous polyps to carcinoma. Mutations in the adenomatous polyposis coli (APC) gene occurs early on in the development of sporadic adenomas. The APC gene is a tumor suppressor gene and normally regulates the proliferation, migration, differentiation and apoptosis of epithelial cells. FAP is genetic disorder in the APC gene inherited in an autosomal dominant fashion that has nearly a 100% risk of colon cancer. It affects approximately 1 in 10,000 live births and accounts for less than 1% of the total colon cancer risk in the US.  

In preclinical and clinical studies, it was discovered that NSAIDs, such as sulindac, are associated with a reduced incidence of colon cancer. However, the GI toxicity associated with conventional NSAIDs limited the long-term use for cancer prevention. NSAIDs are non-selective inhibitors of the cyclooxygenase enzymes. The COX-1 isoform is constitutively expressed in most tissues, where it mediates physiological functions such as gastric mucosal cytoprotection and regulation of platelet aggregation. Its inhibition with NSAIDs is thought to account for many of the common GI side effects associated with long-term use. The COX-2 isoform is inducible and up-regulated in inflammatory states, premalignant lesions and certain cancers, such as colon cancer. And selective inhibition of the COX-2 enzymes has been found to be effective in reducing inflammation and potentially the development of colorectal adenomas.

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103 UpToDate, Clinical features and diagnosis of FAP, April 20, 2006.
Basis of AA

The sponsor submitted a single randomized, double-blind, placebo-controlled study (Study 001) that compared the treatment of two doses (100 mg BID or 400 mg BID) to placebo in the treatment of 83 patients with FAP. Fifty-eight of these patients had partial or total colectomy and the remaining 25 had an intact colon. Thirteen of these patients had an attenuated form of FAP.

The primary efficacy endpoint was the mean percent change in colorectal polyp count determined from color still photographs obtained endoscopically at baseline and six months. One area of the rectum, two areas in the duodenum and up to four areas in the colon were identified in this trial. The secondary endpoints included the mean percent change in duodenal plaque-like polyps at six months. Global assessment of videotapes of the duodenum, colon and rectum served as supportive evidence of efficacy.

The mean reduction in colorectal polyp count was 28% on the 400 mg BID Celebrex arm, 15% on the 100 mg BID Celebrex arm and 5% on placebo. Only the treatment with the 400 mg BID arm was statistically significant (p=0.003).

This finding was also supported by the global assessment of the colonic and rectal videotapes. For the 400 mg BID arm, 21% of the patients were assessed as “better” by the reviewers and for the 100 mg BID arm, 20% of the patients were assessed as “better”.

The mean reduction of duodenal plaque-like polyps was not statistically significant. There was a 17% reduction in the 400 mg BID arm versus 1% on placebo. For the 100 mg BID arm, there was an increase in polyp count because two patients without baseline disease developed polyps at 6 months. The beneficial effects of the 400 mg BID arm seen in the colon and rectum were not predictive of similar effects in the duodenum.

At the time of review, Celebrex at the 400 mg BID dosage was noted to be “well tolerated” with a safety profile similar to that in the osteoarthritis and RA populations. It was noted that 5% of FAP patients with prior intestinal surgery on Celebrex (3/58) developed worsened ulcers at the anastomotic site but these were considered to be of mild severity.

On December 23, 1999, Searle (now Pfizer) was granted approval under AA regulations for the reduction of adenomatous colorectal polyps in patients with FAP. The primary endpoint of colorectal polyp reduction was considered to be a surrogate endpoint that was “reasonably likely” to predict clinical benefit in FAP patients by a majority of the ODAC committee (13-yes, 2 abstained). The 28% reduction in this endpoint was also considered to be of sufficient magnitude in predicting such a clinical benefit.

Post-marketing commitments include:

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105 FDA Medical Officer Review of Celebrex for the reduction of adenomatous colorectal polyps in FAP, December 23, 1999.
106 FDA approval letter for Celebrex, December 23, 1999
1. A randomized controlled trial in familial adenomatous polyposis (FAP) to verify and describe the clinical benefit of Celebrex in this population. The sponsor's proposal for a placebo-controlled study of adolescents with FAP aged 12 to 19 years who are genotypically positive but phenotypically negative was deemed acceptable.

The primary endpoint that was agreed upon was prolongation in the time to phenotypic expression of the disease. Time to initial surgery was the agreed upon secondary endpoint. It was expected that over 230 patients would be enrolled in this study.

2. A long-term registry of clinical outcomes in FAP patients. The sponsor's proposal for enrolling patients aged 12 years or above to Celebrex 400 mg BID was deemed acceptable. Eligible patients would include those who are phenotypically positive who (a) have not had primary prophylactic surgery, (b) have not had secondary surgery, or (c) have had both primary and secondary surgery. Time to FAP-related events (FAP-related surgery, GI cancer, desmoids or death) and adverse events was to be collected and compared to untreated historical controls. Information collected on registry patients is to be submitted to the FDA on an annual basis.

Results of post-marketing studies

The use of COX-2 inhibitors was greatly impacted by two major landmark studies that came out in 2000: the CLASS and VIGOR trials. Although these trials tested celecoxib and rofecoxib in indications other than FAP, these trials nevertheless had an impact on the use of celecoxib in FAP and the ability of the sponsor to complete the post-marketing requirements.

CLASS Study\textsuperscript{107}:

About nine months post the approval in FAP, in September 2000, the results of the CLASS study were published, a trial which examined whether celecoxib was associated with a lower incidence of GI toxicity than a conventional NSAID, diclofenac, in the treatment of RA and OA. Approximately 8,000 patients were enrolled in this study. Celecoxib was administered at 2-4x the maximum approved dosages for RA and OA (the dosage recommended for the treatment of FAP) while the prescriptions of the NSAIDs were administered at the recommended dosages. Use of low-dose aspirin was permitted in this study.

The results of this study determined that the use of high-dose celecoxib was associated with a lower incidence of combined clinical upper GI events than with use of NSAIDs. For all patients in the trial, the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib versus NSAIDs was 0.76% vs 1.45% (p=0.09) and 2.08% vs 3.54% (p=0.02), respectively. This difference was even greater for the subgroup of patients that were not taking aspirin. The annualized

incidence rates of upper GI complications alone and combined with symptomatic ulcers for celecoxib versus NSAIDs was 0.44% versus 1.27% (p=0.04) and 1.40% versus 2.91% (p=0.02). This difference was not significant for patients that were also taking low-dose aspirin, where the annualized incidence rates of upper GI ulcer complications alone and combined with symptomatic ulcers for celecoxib versus NSAIDs was 2.01% versus 2.12% (p=0.92) and 4.7% versus 6% (p=0.49).

There was no difference noted in the incidence of cardiovascular events between celecoxib and NSAIDs, irrespective of aspirin use. However, other researchers have re-analyzed the data and have found an increase in serious cardiac events with celecoxib, where the incidence of cardiac SAEs was 0.6% higher with celecoxib (RR of 1.55, 95% CI 1.04-2.3).\textsuperscript{108}

**VIGOR trial\textsuperscript{109}**

Two months later in November 2000, the results of another landmark COX-2 study, VIGOR, was published. The VIGOR trial compared the association of a different COX-2 inhibitor, rofecoxib (Vioxx), and another nonselective NSAID, naproxen, with upper gastrointestinal events in 8,000+ patients with rheumatoid arthritis. This study found a lower incidence of gastrointestinal events with rofecoxib relative to naproxen (0.5 relative risk for gastrointestinal events and a 0.4 relative risk for complicated confirmed events), however there a higher incidence of thrombotic cardiovascular events (2.4 relative risk).

There are several major differences between the VIGOR and CLASS trial. Patients in the VIGOR trial were allowed to take acetaminophen, versus low-dose aspirin as in the CLASS trial. In VIGOR, the dosage of rofecoxib was twice the standard dosage for the treatment of RA, whereas in CLASS, the dosage was 2 to 4x the approved dosage for this indication. The half lives of the drugs are also another consideration, where the half-life of diclofenac, the comparator in the CLASS trial, has a relatively short half-life of 2 hours versus the longer half-lives of naproxen (t1/2 = 13 hours), rofecoxib and celecoxib.

The difference in the COX-2 selectivity between the comparative drugs was much greater in the VIGOR trial versus the CLASS trial. In the CLASS trial, the relative COX-2 selectivity for celecoxib is 2.25x greater than its active comparator, diclofenac. In the VIGOR trial, rofecoxib is 266x greater in its COX-2 selectivity than its comparator, naproxen. The difference in relative COX-2 selectivity could be a factor in the higher relative risk for cardiovascular events for rofecoxib seen in the trials, but this still remains to be worked out.

\textsuperscript{108} Wright JM. The double-edged sword of COX-2 selective NSAIDS. CMAJ, Nov 12, 2002, 167 (10).

Table 1: The degree of inhibition of COX-2 relative to COX-1 for various NSAIDs

<table>
<thead>
<tr>
<th>NSAID type</th>
<th>COX-2 selectivity*</th>
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<tr>
<td>COX-2 selective inhibitors</td>
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<tr>
<td>Rofecoxib</td>
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<td>Etodolac</td>
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<td>Meloxicam</td>
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<td>Celecoxib</td>
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<td>Nonselective NSAIDs</td>
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<td>Sulindac</td>
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<td>Ibuprofen</td>
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<tr>
<td>Naproxen</td>
<td>0.3</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0.2</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Note: COX = cyclooxygenase, NSAID = nonsteroidal anti-inflammatory drug.
*The 80% inhibitory concentration ratios of COX-2 relative to COX-1 in human whole blood assays.¹

APPROVe trial¹¹¹

The APPROVe trial was a randomized, placebo-controlled long-term trial designed to evaluate the efficacy of rofecoxib for preventing colorectal polyps in patients with a history of colorectal adenomas. A total of 2,586 patients were enrolled into the study.

At the time of review, approximately 70% of the patients had completed the scheduled three years of treatment. In the review, 46 patients, or 3.6%, in the rofecoxib arm had a reported thrombotic adverse event (cardiac, cerebrovascular or peripheral vascular event) versus 26 patients, or 2%, in the placebo group. The relative risk of a thrombotic event was 1.92 for patients on the rofecoxib arm. This increased relative risk became apparent after 18 months of treatment.

Due to the significant results of this review, this trial was terminated early on September 30, 2004, approximately two months ahead of the planned date of completion.

These results prompted Merck to withdraw rofecoxib from the market on the same day.

APC trial¹¹²

The Adenoma Prevention with Celecoxib (APC) study compared the efficacy and safety of 200 mg of celecoxib BID, 400 mg BID and placebo in reducing the occurrence of adenomatous polyps in the colon and rectum one year and three years after endoscopic

¹¹² Ibid
polypectomy. Because of the increased concern over the cardiovascular risks from previous discussed trials, the Data Safety Monitoring Board of this trial requested an independent review of the cardiovascular safety data. At the time of the review, 2,035 patients had enrolled in the study and 77% of the patients had completed the study.

The committee developed a composite cardiovascular endpoint of death from cardiovascular causes, myocardial infarction, stroke or heart failure. For the placebo arm, 7 out of 679 patients (1%) reached this endpoint. For the 200 mg BID celecoxib arm, 16 out of 685 patients (2.3%) reached this endpoint (hazard ratio of 2.3). For the 400 mg BID celecoxib arm, 23 out of 671 patients (3.4%) reached this endpoint (hazard ratio of 3.4). Similar trends were reported for other endpoints.

Based on the results of this review, this trial was stopped in December 2004.

**PreSAP trial**

The cardiovascular safety committee in the APC trial also reviewed another ongoing trial for the Prevention of Spontaneous Adenomatous Polyps (PreSAP), which randomly assigned patients with a history of colorectal adenomas to 400 mg of celecoxib once a day or placebo. The preliminary analysis on 1,500 patients did not show an increased risk for cardiovascular events at this dose.\(^\text{113}\)

**Current status**

While the exact mechanism for this increased cardiovascular risk is still currently unknown, one of the dominant hypotheses is that the selective inhibition of COX-2 throws off the balance between two key prostanoids: prostacyclin and thromboxane A2. Prostacyclin is synthesized by the endothelial cells in response to COX-2 and has anti-aggregative, anti-proliferative and vasodilatory actions. Conversely, thromboxane A2 is induced by COX-1, primarily in platelets, and promotes platelet aggregation, vasoconstriction and smooth-muscle proliferation.

Non-selective NSAIDs keep the balance of this prostanoids in balance, whereas selective COX-2 inhibition blocks the production of prostacyclin without affecting the synthesis of thromboxane A2 (which is COX-1 mediated), thereby creating a prothrombotic state.\(^\text{114}\)

Given the great concern over the cardiovascular side effects of the COX-2 inhibitors, it is unknown whether Pfizer is still conducting the trial testing celecoxib in adolescent patients with FAP or whether the FDA will accept the results of the clinical trials that are being conducted by the sponsor to demonstrate the clinical benefit. Particularly for the FAP population, which has nearly a 100% risk of developing colon cancer, the availability of a therapy that will reduce or delay the progression of their disease is something of great value. Whether a 28% reduction in polyp count at six months is a significant enough benefit in this patient population to warrant the increased cardiovascular risk will be a factor that the FDA will have to measure. But given the age of the adolescent patients in the current trial and the fact that they will likely require

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\(^\text{113}\) Ibid.
therapy for the entire life, it seems like a pretty big risk to take. But it is likely that that the use of the class of COX-2 inhibitors will be limited to such populations, as FAP, for the near term.

**Other indications**
On December 31, 1998, Celebrex was granted approval for the treatment of osteoarthritis and rheumatoid arthritis.

On October 18, 2001, Celebrex was granted approval for the management of acute pain in adults and for the treatment of primary dysmenorrhea.

On July 29, 2005, Celebrex was granted approval for the relief of signs and symptoms of ankylosing spondylitis.

**Patent protection**
Pfizer has patent protection over Celebrex until November 30, 2013.
### 3.8 Summary of oncology drugs approved under AA that have not been converted into full approvals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Date of AA</th>
<th>Indication</th>
<th>Basis of approval</th>
<th>Current status</th>
</tr>
</thead>
</table>
| Liposomal doxorubic Doxil   | 17-Nov-95  | Kaposi's sarcoma, second-line treatment | 27%-48% partial response to therapy | - Still approved under AA  
- HAART therapy emerged after initial approval  
- Current use as first-line therapy (with HAART) for KS  
- Appears to be a more efficacious agent than DaunoXome (granted full approval after Doxil) |
| Liposomal doxorubic Doxil   | 28-Jun-99  | Metastatic ovarian cancer refractory to paclitaxel and platinum | Response rate of 13.8% in patients refractory to paclitaxel and platinum agents | - Converted to full approval for second-line use (after platinum-based therapy) on January 28, 2005 |
| Amifostine                  | Ethyol     | 15-Mar-96        | Reduction of platinum toxicity in NSCLC treatment | Creatinine clearance: 1/13 patients had a 40% reduction in creatinine clearance | - FDA withdrew approval for this indication on March 28, 2006 based on the failure to demonstrate clinical benefit in a NSCLC trial |
| Denileukin diftitox         | Ontak      | 5-Feb-99         | Cutaneous T-cell lymphoma, relapsed, refractory | Response rate of 30-40% in patients with refractory CTCL | - Trials still ongoing as of April 2006 (orphan drug disease, difficulties completing enrollment in a placebo-controlled trial?) |
| Temozolomide                | Temozol    | 11-Aug-99        | Anaplastic astrocytoma, refractory              | Response rate of 22% in patients with AA refractory to nitrosourea and procarbazine | - Converted to full approval and expanded label to high-grade gliomas in combination with radiation therapy on March 15, 2005 |
| Liposomal cytarabin DepoCyt | 1-Apr-99   | Lymphomatous meningitis | Response rate of 41% (versus 6% for Ara-C) Better dosing schedule (once every 2 weeks vs twice a week) | - Trials still ongoing as of April 2006 |
| Celecoxib                   | Celebrex   | 31-Dec-98        | Familial adenomatous polyposis                  | Reduction in colorectal polyp counts by 15-28% vs 5% (placebo) | - Trials in adolescents with FAP ongoing (?)  
- Trials in CRC stopped due to cardiovascular side effects |

(a) These drugs were selected because they appeared as not converted according to the FDA website (www.accessdata.fda.gov/scripts/cder/onc/tools/Access.cfm)
My initial categorization of drugs that had been converted to full approval and not converted into full approval was based on two sources: the FDA website (www.accessdata.fda.gov/scripts/cder/onctools/Accel.cfm) and a review article regarding the Accelerated Approval of Oncology Drugs authored by the FDA dated as of October 2004. While the website is a current source that is apparently not well updated, the publication of the review article by Dagher et al seems to have been the start of an internal review process at the FDA that has put greater pressure on the sponsors to fulfill their post-approval requirements under AA.

Out of the seven remaining drugs approved under AA prior to 2000 that were supposedly not converted, two of these drugs had actually been converted to full approval in the past year. Doxil was converted to full approval for the treatment of metastatic ovarian cancer on January 28, 2005. Temodar was converted to full approval for the treatment of high-grade gliomas in combination with radiation therapy on March 15, 2005.

The conversion of both of these drugs was based on post-marketing trials that demonstrated significant clinical benefit. In both cases, the label was expanded to include a broader patient population where the drug had shown efficacy. This was similar to the approach taken by the Roche for capecitabine, Novartis for Gleevec and Sanofi for oxaliplatin and attempted by Pharmacia for irinotecan. However, completion of these post-marketing studies took significantly longer (5.5 years) than in the previous group (average of 2.3 years, excluding dexrazoxane).

In Doxil, initial approval for metastatic ovarian cancer was based on the results of 3 single-arm Phase 2 studies which showed a combined response rate of 13.8% for patients that were refractory to both paclitaxel and platinum agents. In the post-marketing Phase 3 trial comparing Doxil to topotecan, there was an improved survival benefit seen in platinum-sensitive patients and an improved side effect profile. Upon full approval, the label was expanded to include patients that had progressed after platinum therapy, instead of both paclitaxel and platinum therapy.

In the case of Temodar, initial approval under AA was based on a 22% response rate in a Phase 2 trial in patients with anaplastic astrocytoma that were previously treated with a nitrosourea and procarbazine. In the post-approval setting, the company was still completing their Phase 3 trial comparing Temodar to BCNU for anaplastic astrocytoma, when the results of another study in GBM patients was announced which showed a significant benefit for this patient population. As a result of this GBM study, the FDA expanded the label to include patients with GBM and converted the approval to full approval.

In all the cases where accelerated approval has been converted to full approval, it is interesting to note that the sponsors are all large pharmaceutical companies. And in the first group of drugs that converted to full approval quickly, the sponsors were pursuing and were successful in obtaining additional indications for the drug. The conversion to full approval for Temodar and Doxil took a bit longer, but the sponsors were also not as successful in obtaining additional indications for the drug.
The FDA recently withdrew its approval for amifostine (Ethyol) on March 28, 2006. This appears to be the first instance of a drug being withdrawn under AA for failure to demonstrate clinical benefit. In a post-approval study that compared the agent to placebo in reducing platinum-based toxicities in NSCLC therapy, there was no reduction in primary endpoint of esophagitis toxicity reduction and there was even an increase in acute toxicities for the amifostine arm. About a year after this study was published in April 2005, the FDA withdrew the indication.

Of the remaining four drugs that were examined, one appears to have fulfilled its commitment but remains unconverted and the other three appear to have trials still ongoing. Doxil for the treatment of KS appears to be a drug that should be granted full approval based on the results of its post-approval studies, the superior efficacy results to an existing agent and its current usage as a first-line agent in combination with HAART for the treatment of KS.

The remaining three drugs are the most problematic. Ontak and DepoCyt were both approved in 1999 under accelerated approval but still have trials ongoing six years later. There is little data that can be found on the status of the ongoing trials and few other studies have been conducted with the approved indications.

There are several potential hypotheses to explain the slow completion of these trials. Both drugs are being developed by smaller biotechnology companies with limited resources. Ontak is being developed by Skye Pharmaceuticals, a $421 million market cap company with $37 million in cash. DepoCyt is being developed by Ligand Pharmaceuticals, a $968 million market cap company with $87 million in cash. Ontak was initially approved for the treatment of cutaneous T-cell lymphoma, an orphan drug disease, which is probably a very slow and expensive trial to complete. And the marketing approval for Ontak has not led to a great revenue source for the company, considering the expense of having to complete the post-marketing studies. In 2005, it was estimated that Ontak accounted for $32 million of the company’s $172 million in sales (18%) \(^{115}\).

Both drugs were also protected under orphan drug exclusivity until recently. Ontak’s orphan drug exclusivity expired on February 5, 2006 and DepoCyt’s orphan drug exclusivity expired on April 1, 2006. Other patent protection could not be identified for either drug. The expiration of exclusivity is another issue that might factor into the company’s resource allocation decision, particularly where the company has limited resources.

Completing the post-marketing studies has not appeared to be a problem for most of the drugs that were examined. There appeared to be great interest from the medical community in testing the agents in new combinations. However, with these agents, Ontak and DepoCyt, there were a limited number of independent studies conducted, which has made the assessment of clinical benefit even more difficult.

\(^{115}\) UBS Equity research report, Ligand Pharmaceuticals, January 27, 2006.
With Celebrex, completion of the post-marketing studies appears to have been greatly impacted by the results in the VIOXX trials which has basically led to a halt on the development of COX-2 inhibitors in colorectal cancer. Given the great concern over cardiovascular risks of COX-2 inhibitors, the conversion of Celebrex to full approval, if the post-marketing trial in adolescents with FAP is completed, will likely be a very slow and drawn-out process.

4: Analysis of the differences between the two groups
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<td>1-2</td>
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<td>6 years</td>
<td>1-2</td>
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**Summary of Oncology Drugs Reviewed**

- **Type of Prescription:**
  - 1: 2 years
  - 2: 3 years
  - 3: 5 years
  - 4: 6 years

- **Approval Number:**
  - 11.09-01
  - 11.09-02
  - 11.09-03
  - 11.09-04

- **Approval Type:**
  - 2 years
  - 3 years
  - 5 years
  - 6 years

- **Approval Date:**
  - 1-2

**Note:**
- The approval dates and numbers are placeholders for demonstration purposes.
- The table represents a summary of oncology drugs reviewed over various years with specified approval durations.
| Drug Name                  | Approval Date | Approval
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**Summary of Acetaminophen Drugs Approved by Year:**

- 1980: 4 drugs
- 1981: 4 drugs
- 1982: 4 drugs
- 1983: 4 drugs
- 1984: 4 drugs
- 1985: 4 drugs
- 1986: 4 drugs
- 1987: 4 drugs
- 1988: 4 drugs
- 1989: 4 drugs
- 1990: 4 drugs
- 1991: 4 drugs
- 1992: 4 drugs
- 1993: 4 drugs
- 1994: 4 drugs
- 1995: 4 drugs
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- 2011: 4 drugs
- 2012: 4 drugs
- 2013: 4 drugs
- 2014: 4 drugs
- 2015: 4 drugs
- 2016: 4 drugs
- 2017: 4 drugs
- 2018: 4 drugs
- 2019: 4 drugs
- 2020: 4 drugs
- 2021: 4 drugs
- 2022: 4 drugs
- 2023: 4 drugs
- 2024: 4 drugs
- 2025: 4 drugs
- 2026: 4 drugs
- 2027: 4 drugs
- 2028: 4 drugs
- 2029: 4 drugs
- 2030: 4 drugs

**Total Drugs Approved:** 97

**Total Years Covered:** 47
It is difficult to draw conclusive observations on differences between the drugs that converted to full approval versus the four drugs that have not yet converted due to the small sample size. However, there are some interesting differences between the two groups. A majority of the drugs approved under AA (8/13) were approved based on the results of Phase 2 trials. However, there were more patients enrolled in the pivotal trials for the drugs that ended up converting (mean of 399 patients) versus the trials for drugs that are still not converted (mean of 102 patients).

In most cases, the FDA required an average of 2 post-marketing studies with an active control, particularly if AA was based on the results of single-arm Phase 2 studies. The sponsors of the drugs that eventually converted to full approval completed their post-marketing requirements in 3.9 years, on average. For the drugs that remain approved under accelerated approval, an average of 8 years has passed since the initial approval.

The issue of patent protection and orphan drug exclusivity was discussed in the previous section but it is an important point to consider, especially when the sponsors are small biotechnology companies with limited resources versus large pharmaceutical companies with larger reserves. All the sponsors of the drugs that eventually converted to full approval were large well-capitalized pharmaceutical companies.

Of the drugs and indications that remain unconverted, the two large pharmaceutical companies have actively conducted randomized post-marketing studies. JNJ has completed two randomized controlled trials comparing Doxil to active controls for the treatment of HIV-related KS and Pfizer has completed a number of post-marketing studies in other indications. The two small biotechnology companies, Ligand and Skye, are the sponsors that appear to be struggling with completing the post-marketing studies, although it is difficult to draw any conclusions based on these two case studies.

While there are many advantages to AA, there appears to be a higher hurdle and standard that the FDA holds approved drugs to in the post-marketing clinical studies. In the case of Doxil for metastatic ovarian cancer, one of key post-marketing requirements is that the sponsor demonstrate superiority over existing therapy, topotecan, in a randomized clinical trial. This is consistent with the regulations for AA, which states that the therapy would have to provide “meaningful clinical benefit over existing therapy”. In order to convert to full approval and stay on the market, the FDA appears to be holding the sponsor to a higher standard for efficacy or safety in the requirement for superiority in exchange for accelerated approval. The sponsor managed to clear that hurdle successfully since the drug was converted to full approval, but it does demonstrate that there is a price to be paid for getting to the market earlier.

This higher hurdle is also seen for the other indication of Doxil in the treatment of refractory Kaposi’s sarcoma. The sponsor completed the two ongoing randomized trials comparing Doxil to other chemotherapy regimens, BV and ABV. These trials were similar to the pivotal trial that was the basis of approval for another liposomal anthracycline agent, DaunoXome, which was granted full approval based on the results of the randomized trial comparing DaunoXome to ABV. In comparing the results of the two trials, Doxil had demonstrated better response rates to both DaunoXome and the
comparator, ABV, in its trial, yet the results from these post-approval trials are still not sufficient for full conversion, even though it was sufficient for regular approval for DaunoXome. It appears that the FDA is sticking to the AA requirement to link clinical benefit to the effect seen in the surrogate endpoint of response rate.

5. Conclusions

5.1 Conclusions
The Accelerated Approval process is a route that many oncology drug companies use to introduce their products on the market sooner. However, it is a shortcut that is not without its costs. As part of the approval, sponsors are required to demonstrate the clinical benefit in the approved indication in post-marketing studies. These trials can be difficult to complete, as demonstrated by two approved agents, Ontak and DepoCyt, which have had post-marketing clinical trials ongoing for more than seven years.

The FDA appears to hold companies to a higher standard where they have to demonstrate “meaningful clinical benefit” over existing agents, which may in fact be a requirement for superiority, as was seen in the case of Doxil. If the drug showed a benefit that was similar to existing therapy, it could still qualify for regular approval but not accelerated approval. In addition, the FDA issued guidance that proof of superiority is also important when surrogate endpoints are used, because it is more persuasive of evidence of clinical benefit than demonstration of noninferiority.

For the first time, the FDA has shown its willingness to withdraw its approval if the trials do not show improved clinical benefit, as seen with the withdrawal of Ethyol in March 2006.

However, the process of AA is still rather opaque. Other than going through the FDA’s approval letters, there is no aggregate source which informs you which drugs have been converted and which ones remain outstanding under AA. The conversion to full approval does not appear to have a huge impact on usage or acceptance of the drug. Until recently, it did not seem like the FDA was ready to exercise its right to withdraw its approval from an indication approved under this regulatory path, which could have led to incentives for companies to delay completion of post-marketing studies since these trials are costly to complete and the sponsors still enjoy all the benefits of marketing approval under accelerated approval. However, since only two out of the seven drugs in the “not converted” group have trials ongoing for unknown reasons, it is difficult to conclude that this is a major concern. In fact, the FDA did not seem to publicize the fact that it withdrew its approval for Ethyol for the first time under this regulatory path.

The two recent conversions and the withdrawal may be a sign that things are changing within the FDA. There appears to be a greater pressure on companies to fulfill their post-marketing approvals as the more recent approvals all include expected timelines for completion. Serious thought should be given before going down the AA path, since it

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117 FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologies, April 2005.
might be a shorter initial trial but it might require more expensive trials post approval. The post-marketing studies can be costly and difficult to complete, but companies with ample resources and sufficient incentives, such as additional potential indications, seem able to clear this hurdle easily.

5.2 Limitations

There are many limitations to my research. It is not a complete survey of all oncology drugs approved under AA. The basis of initial selection for the seven drugs in the “not converted” group was from two sources: the FDA website as of April 2006 and a review article on the AA process from the FDA oncology division as of 2004. I was not aware of any other sources for drugs approved AA and their conversion status. A more complete analysis would cover all 30 indications approved under AA for oncology to date. The best source for whether these drugs have converted or not converted is a search through the FDA approval letters, which are available on the FDA website. Comparison between the converted and the not converted of the full universe of oncology drugs approved under AA would have been a stronger base of data upon which to draw conclusions regarding the conversion process.

My research was also based largely on publicly available information. One conversation with the head of research of Aventis contributed to some insights on the conversion process of docetaxel, however the individual was very limited on how much information he could share. In addition, attempts to contact the sponsors of drugs with ongoing trials were unsuccessful. Interviews with the sponsors on the different challenges they face in completing the post-marketing studies would be very valuable in this research, as well as interviews with the FDA reviewers.
Appendix:

Accepted endpoints in oncology for regular approval include survival, disease-free survival in the adjuvant setting, symptom benefit and durable remission in leukemias. There are a number of surrogate endpoints (see below) that have been used to demonstrate efficacy in clinical trials reviewed under AA or regular approval.

Definitions:

**Surrogate endpoints**

**Objective Response Rate (ORR):**

ORR is the proportion of patients with tumor shrinkage of a predefined amount lasting for a predefined minimum period of time. ORR is generally defined as the sum of partial responses and complete responses (see below).

The use of response rate as an endpoint has an interesting history. In the 1970's and early 1980's, the use of response rate was often used as the sole basis of approval for oncology drugs, until an Oncologic Drugs Advisory Committee (ODAC) meeting in the mid-1980's advised against using response rate as the sole basis of approval since the correlation between response rate and survival or clinical benefit was still not established. ODAC also voiced a concern that response rates don't capture the full effect of treatment, such as the substantial toxicity of oncology drugs or potential survival benefits from a delay in tumor progression (which would not be captured in response rate if the tumor remained the same size and was classified as Stable Disease), which should also be factored into the review.

However, since that time, response rates have been used as the basis of approval in certain circumstances when the magnitude of response is large and there is supportive evidence in another endpoint, such as TTP. For example, several hormonal drugs for the treatment of advanced breast cancer, such as anastrozole, exemestane, letrozole, toremifene and fulvestrant, were granted full approved based on improvements in response rate and TTP alone. A survival benefit was not seen in these trials but since the toxicities of these hormonal drugs is relatively low, RR and TTP were considered acceptable surrogate endpoints in this indication.

However, response rates are accepted as a valid measure of anti-tumor activity in single-arm phase II studies. Response rates should take into consideration other endpoints, such as response duration, drug toxicity and relief of tumor-related symptoms.

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120 Ibid.
121 Ibid.
Response rates have also been used as the basis of approval for a majority of approvals granted under AA. There are three reasons for this cited by the FDA: (1) response rates are directly attributable to drug effect (tumors rarely shrink on their own), (2) tumor response is widely accepted by oncologists and has a role in guiding cancer therapy, (3) if the response rate is high and of sufficient duration, it is an endpoint that seems reasonably likely to predict clinical benefit.\textsuperscript{122}

**Complete response (CR):** complete disappearance of all tumor and manifestations of tumor for at least 1 month

Complete responses of reasonable duration were also deemed in 1991 by the FDA and NCI to provide evidence of clinical effectiveness, particularly for refractory ovarian cancer, testicular cancer and hematologic malignancies.

**Partial response (PR):** 50% decrease from baseline in the sum of the cross-products of all bidimensionally measurable tumors lasting at least 1 month

Partial responses supported by tumor-specific symptom relief

**Stable Disease (SD):** less than a 50% decrease from baseline and less than 25% increase in the sum of cross-products of all bidimensionally measurable tumors

**Progression:** 25% increase in the sum of cross-products of all bidimensionally measurable lesions from the nadir value, the occurrence of new lesions or obvious progression in evaluable disease

**Disease-free survival (DFS):**
DFS is defined as the time from randomization until recurrence of tumor or death from any cause. The most frequent use of this endpoint is in the adjuvant setting after surgery or radiotherapy. In 1991, the FDA and NCI proposed DFS as a valid end point in the surgical adjuvant setting if a large proportion of recurrences are symptomatic. In December 2003, ODAC agreed that prolongation of DFS represented clinical benefit, but the magnitude of this benefit should be weighed against the toxicity of adjuvant treatment. And in May 2004, ODAC recommended that DFS be considered as acceptable endpoint for colon cancer drugs in the surgical adjuvant setting.\textsuperscript{123}

**Progression-free survival (PFS):**
PFS is the time from randomization until objective tumor progression or death. There are no standard regulatory criteria for defining progression and PFS needs to be defined prospectively in the design. Due to differences between different trial designs, PFS endpoints needs to be compared to a concurrent control, preferable in a randomized trial.

**Time to progression (TTP):**
TTP is the time from randomization until objective tumor progression. It may be the preferred endpoint for evaluating cytostatic agents because it doesn’t require tumor size

\textsuperscript{122} FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

\textsuperscript{123} Ibid
reduction as in the response rate endpoint. TTP is measured in all patients, not just the responders.

**Time to treatment failure (TTF):**
TTF is a composite endpoint that is usually defined as the time from randomization to treatment discontinuation for *any reason*, including disease progression, treatment toxicity, patient preference or death. It is rarely used as an endpoint for regulatory purposes since it combines both efficacy and safety parameters. Patients could discontinue treatment due to lack of efficacy or toxicity and this endpoint includes both of those situations. FDA requires endpoints that separate out efficacy and safety.\(^{124}\)

**Relief of tumor-specific symptoms**
Symptomatic improvement is considered to represent a clinical benefit. Past drug approvals have used weight gain or decreased effusion as primary endpoints for approval. However, health-related QOL scores have not been used to date since it is difficult to separate out efficacy from toxicity measures.\(^{125}\)

**Other definitions:**
**Fast track:** refers to a process for interacting with the FDA during drug development (scheduled meetings, FDA input into development plans, rolling submission and the option of requesting evaluation of studies using surrogate endpoints)
- Intended for a product or claim that address an unmet medical need

**Priority review:** Sets the target date for the FDA for completing all aspects of the review and the FDA taking an action on the application at 6 months after it was filed.
- Intended for those products that address unmet medical needs

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\(^{125}\) FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.