# Trends-in-Medicine

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# Quick Pulse



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## FDA Advisory Committee Recommends Approval of New Leukemia Drug

The FDA took its Oncologic Drugs Advisory Committee (ODAC) on the road for the first time, holding a meeting in Atlanta in connection with the American Society of Clinical Oncology (ASCO) meeting to review Bristol-Myers Squibb's Sprycel (dasatinib) in chronic myelogenous leukemia (CML). The panel voted overwhelming that the drug is safe and effective for patients both resistant to and intolerant of Novartis's Gleevec (imatinib), the current standard of care for CML, and they agreed that it would be appropriate for accelerated approval.

It was an unusually short panel meeting, lacking in any real dispute or controversy. Dr. Richard Pazdur, Director of Oncology Drug Products for the FDA, said this is the first time an ODAC meeting has been held outside the greater Washington DC area, and he explained that this time and venue was chosen to provide more people with an opportunity to see how the FDA process works, "We hope ultimately this opportunity will provide the American public a more comprehensive understanding of the approval process."

Chronic myelogenous leukemia (CML) is caused by reciprocal translocation between chromosomes 9 and 22, leading to the synthesis of a constitutively activated tyrosine kinase, BCR-ABL. CML is a continuum of disease, and a patient's characteristics and prognosis are different at each phase. Gleevec is very effective in CML, but 10%-15% of patients either can't take it or develop molecular resistance to it.

Mechanisms of Gleevec-resistance are:

- Outgrowth of one or more clones harboring a Gleevec-resistant BCR-ABL kinase domain mutation (most common).
- Overproduction of BCR-ABL.
- BCR-ABL-independent mechanisms.

Intolerance to Gleevec was defined as:

- Toxicity leading to intolerance: Grade 3-4 non-hematologic toxicity or Grade 4 hematologic toxicity lasting >7 days.
- Patients who responded to Gleevec but developed intolerance while in response and were unable to resume therapy.
- Patients who never responded to Gleevec or were unable to tolerate Gleevec at a dose of at least 400 mg.

Sprycel is an oral, multi-targeted inhibitor of both BCR-ABL and SRC kinases. Bristol-Myers Squibb submitted one Phase I and five pivotal Phase II studies

(CA180005, CA180006, CA180013, CA180015, and CA180017) to the FDA in support of Sprycel. Patients in all of the studies had received prior Gleevec treatment and were either resistant or intolerant to Gleevec.

Bristol-Myers Squibb is seeking approval for the use of Sprycel for:

- Treatment of adults with chronic, accelerated, or blast phase CML with resistance or intolerance to prior therapy, including imatinib.
- Treatment of adults with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

However, experts questioned after the meeting strongly suggested that Sprycel will quickly move to front-line treatment, though off-label use will be limited by insurance reimbursement. One expert said, "Absolutely, it will move to front-line. There is a great deal of interest in individualizing therapy. Patients who are a good risk for Gleevec, would get that, but those who are a bad risk for Gleevec, would get dasatinib. Dasatinib is more powerful but a little more dangerous." Another doctor said, "Insurance companies will be the issue with front-line use (of dasatinib), but it will migrate to front-line…New data indicate that dasatinib is easier to give than imatinib." A third expert said, "Dasatinib will be commonly used front-line within a year or two. Initially, patients who fail Gleevec will get dasatinib. Dasatinib won't be used in newly diagnosed patients until there is a randomized clinical trial comparing the two drugs."

A front-line study is in the planning stages. Investigators said they are looking at doses now, and the study should start next year. At this point the plan appears to be Sprycel vs. 600 mg Gleevec.

Novartis also has a competing drug in development for CML, nilotinib (AMN-107), but it is about a year behind Sprycel. Experts predicted it would be submitted to the FDA in early 2007. One said, "It will be a challenge for Novartis. They will have to work hard to identify a niche, but they will probably succeed."

A Bristol-Myers Squibb official said, "We are encouraged by the committee's recommendation and we look forward to further discussions with the FDA." Another official said the company is prepared to launch Sprycel "within days" of final FDA approval. Officials declined to provide any information on pricing.

**Efficacy of Sprycel in Chronic Phase CML**

| Measurement | Phase I Study 002 n=32 | Phase II Study 013 n=127 |
|---|---|---|
| **Efficacy in Gleevec-resistant patients** | | |
| Complete hematologic response (CHR) | 91% | 87% |
| Major cytogenetic response (MCyR) for all patients | 38% | 31% |
| MCyR for prior IFN patients | 34% | 31% |
| MCyR for patients on Gleevec >600 mg/day | 36% | 35% |
| MCyR in patients with BCR-ABL mutation | 43% | 42% |
| Complete cytogenetic response (CCyR) | 28% | 22% |
| Loss of CHR | 0 | 2 patients |
| Loss of MCyR | 0 | 0 |
| **Efficacy in Gleevec-intolerant patients** | | |
| CHR | 100% | 97% |
| MCyR for all patients | 75% | 73% |
| MCyR for prior IFN patients | 75% | 69% |
| CCyR | 63% | 56% |
| Loss of CHR | 0 | 0 |
| Loss of MCyR | 0 | 0 |

**Efficacy of Sprycel in Other Types of CML**

| Measurement | Phase I Study 002 n=11 | Phase II Study 005 n=107 | |
|---|---|---|---|
| **Accelerated Phase CML** | | | |
| Major hematologic response (MaHR) | 55% | 59% | |
| CHR | 45% | 33% | |
| No evidence of leukemia | 9% | 26% | |
| MCyR | 27% | 31% | |
| CCyR | 18% | 22% | |
| Loss of MaHR | 0 | 1 patient | |
| Loss of MCyR | 0 | 2 patients | |
| **Myeloid Blast Crisis** | | | |
| | **Phase I Study 002 n=23** | **Phase II Study 006 n=74** | |
| MaHR | 30% | 32% | |
| CHR | 13% | 24% | |
| No evidence of leukemia | 17% | 8% | |
| MCyR | 35% | 30% | |
| CCyR | 26% | 27% | |
| Loss of MaHR | 2 patients | 0 | |
| Loss of MCyR | 4 patients | 2 patients | |
| **Lymphoid Blast Crisis and Ph+ ALL** | | | |
| | **Phase I Study 002 n=23** | **Phase II Study 015 n=74** | |
| | | **L. Blast** | **Ph+ ALL** |
| MaHR | 50% | 31% | 42% |
| CHR | 30% | 26% | 31% |
| No evidence of leukemia | 20% | 5% | 11% |
| MCyR | 38% | 50% | 58% |
| CCyR | 30% | 43% | 58% |
| Loss of MaHR | 3 patients | 6 patients | 3 patients |
| Loss of MCyR | 6 patients | 10 patients | 8 patients |

## THE COMPANY PERSPECTIVE

Bristol-Myers Squibb submitted one Phase I trial (Study 002) and five Phase II trials (Studies 005, 006, 013, 015, and 017) to the FDA. The company presentation was thorough, unsurprising, and did not gloss over the safety issues. The company and the FDA disagreed slightly but not significantly on the interpretation of the efficacy data.

**Preliminary Data for Sprycel in Phase II Study 017**

| Response | Sprycel n=322 | Gleevec n=14 |
|---|---|---|
| **Efficacy in Gleevec-intolerant patients** | | |
| CHR | 95% | 93% |
| MCyR | 45% | 21% |
| CCyR | 32% | 7% |
| Crossover | 9% | 79% |

Dr. Hagop Kantarjian, chairman of the Leukemia Department at MD Anderson Cancer Center, spoke on behalf of Sprycel. Among the points he made were:

- "Patients in the dasatinib trial had a poor prognosis after imatinib failure: survival <2 years and <1 year in patients with a *P*-loop mutation."
- "There are limited treatment options for imatinib failures – stem cell transplant, escalated dose of imatinib, hydroxyurea, IFN-α, or an investigational agent."
- "The major benefit with dasatinib is a complete hematologic response (CHR) of 87%, a major cytogenetic response (MCyR) >30%, and a duration of response >1 year."
- *Accelerated and Blastic Phase CML:* "The survival of these patients is poor, with an estimated median survival <1 year. The treatment options in this phase are also very limited, and stem cell transplant may be the only alternative. The data presented here (on dasatinib) show high rates of durable hematologic and cytogenetic responses not achievable with anything else."
- "Imatinib-intolerant patients are the highest unmet medical need. They get no benefit from targeted therapy. This is uncommon, but often associated with resistance. The dasatinib program included 67 patients with intolerance, mostly non-hematologic, and they had hematologic and cytogenetic responses similar to those achieved with imatinib post-interferon, and the responses were durable."
- *Ph+ ALL:* "The situation is even worse, and the prognosis for these patients is quite bad…Dasatinib is one of the most active agents for Ph+ ALL. These patients already

**Sprycel Safety Data**

| Adverse events | Grade 1-4 | Grade 3-4 |
|---|---|---|
| Fluid retention | 44% | 8% |
| Pleural effusion | 21% | N/A |
| Diarrhea | 35% | 4% |
| Rash | 26% | 1% |
| Nausea | 20% | 1% |
| Headache | 24% | 1% |
| Fatigue | 21% | 2% |
| Dyspnea | 21% | 4% |
| Asthenia | 16% | 3% |
| Musculoskeletal pain | 15% | 1% |
| Vomiting | 13% | 1% |
| **Lab abnormalities** | | |
| AST elevation | 63% | 3% |
| ALT elevation | 58% | 5% |
| Bilirubin elevation | 26% | 3% |
| Creatinine increase | 34% | 1% |
| ↓ Ca++ | 62% | 10% |
| ↓ Mg++ | 34% | <1% |
| **Pleural effusion** | | |
| Medical intervention with diuretics | 77% | |
| Medical intervention with corticosteroids | 25% | |
| Dose interruption | 39% | |
| Dose reduction | 9% | |
| Discontinuations | 14% | |

**Additional Sprycel Safety Data**

| Measurement | Chronic Phase n=208 | Accelerated Phase n=118 | Myeloid Blast n=97 | L. Blast/ Ph+ ALL n=88 |
|---|---|---|---|---|
| **Myelosuppression** | | | | |
| WBC <2.0 x $10^9$/L | 24% | 60% | 68% | 68% |
| ANC <1.0 x $10^9$/L | 50% | 78% | 86% | 79% |
| Platelets <50 x $10^9$/L | 47% | 82% | 84% | 82% |
| **Time to severe thrombocytopenia** | | | | |
| <4 weeks | 26% | 47% | 86% | 87% |
| 4-8 weeks | 66% | 46% | 12% | 9% |
| >8 weeks | 8% | 7% | 1% | 4% |
| **Adverse reactions related to myelosuppression** | | | | |
| GI hemorrhage | 4% | 19% | 14% | 9% |
| CNS hemorrhage | <1% | 0 | 0 | 2% |
| Febrile neutropenia | 1% | 8% | 5% | 11% |
| Severe infections | 2% | 7% | 6% | 10% |
| **Management of myelosuppression** | | | | |
| Transient dose interruption | 51% | 47% | 27% | 13% |
| Median duration of dose interruption | 45% | 37% | 21% | 6% |
| Platelet transfusion | 22% | 60% | 74% | 61% |
| Red cell transfusion | 30% | 85% | 90% | 69% |
| Hematopoietic growth factors | 15% | 31% | 27% | 33% |
| Discontinuation | 1% | 1% | 1% | 1% |
| **Pleural effusion** | | | | |
| Drug-related | 18% | 22% | 30% | 17% |
| Grade 3-4 | 3% | 3% | 13% | 2% |
| Time to event | 7-319 days | 15-343 days | 1-296 days | 6-247 days |

received chemotherapy and imatinib, and many have undergone stem cell transplantation. Yet, the cytogenetic response rate (with dasatinib) was about 50%...PFS (progression-free survival) in this population was 30%, with some patients alive beyond one month, and this is unexpected with any therapy in this group of heavily pretreated Ph+ ALL patients."

- "The outstanding efficacy of dasatinib comes at the cost of some toxicity, most importantly myelosuppression and fluid retention. Myelosuppression is expected in these patients and is part of the day-to-day care of these patients…We also expect fluid retention. Dasatinib is somewhat different from imatinib, but we know the side effects are manageable with early intervention."

Dr. Neil Shah of the University of California, San Francisco, explained the rationale for the choice of the 70 mg BID dose of Sprycel. He said the 70 mg BID dose showed:

- Optimal drug exposure ($C_{max}$ 45 ng/mL), ~100% inhibition of pCRKL at doses ≥100 mg/day.
- The effective dose in the Phase I study was 70 mg BID.
- Acceptable safety was shown in the Phase I study.

## The FDA Perspective

On **efficacy**, FDA reviewers concluded:

- Dasatinib treatment results in major hematologic and cytogenetic responses in patients with all phases of CML and with Ph+ ALL who are Gleevec-resistant or intolerant, with 31%-59% of patients achieving a response.
- Responses occur within the first 3 months and appear to be durable. Median duration of response is 4-5 months in LB CML and Ph+ ALL. Median durations are longer in CP, AP, and MB CML, but the follow-up is too short for estimates.

**FDA View of Sprycel Efficacy in Phase II Patients**

| Disease phase | Number of patients | Median duration of response | MCyR | MaHR |
|---|---|---|---|---|
| Chronic | 186 | Not reached * | 45% | --- |
| Accelerated | 107 | Not reached * | 31% | 59% |
| Myeloid blast | 74 | Not reached * | 30% | 32% |
| Lymphoid blast | 42 | 3.7 months | 50% | 31% |
| Ph+ ALL | 36 | 4.8 months | 58% | 42% |

* with ~100% of responders in response at 6 months

**FDA Summary of Efficacy in Gleevec Intolerant/Resistant Patients in All Studies**

| Disease phase | Gleevec-intolerant (n=94) | | Gleevec-resistant (n=457) | |
|---|---|---|---|---|
| | MCyR | MaHR | MCyR | MaHR |
| Chronic | 73% | --- | 34% | --- |
| Accelerated | --- | 58% | --- | 58% |
| Myeloid blast | --- | 14% | --- | 33% |
| Lymphoid blast | --- | 33% | --- | 34% |
| Ph+ ALL | --- | 100% | --- | 36% |
| Total (all phases) | 65% | | 40% | |

- 70 mg BID is an effective dose, but lower dose also results in responses.
- In CP CML patients, Gleevec-intolerant patients have a higher response rate than Gleevec-resistant patients. Too few Gleevec-intolerant patients with other phases of CML and with ALL were enrolled to make a comparison.

On **safety**, FDA reviewers concluded:

- GI toxicity was common across all phases of disease.
- Fluid retention events, including edema (e.g., 26% peripheral edema) and effusions (e.g., 17% pleural effusion) were common.
- Grade 3-4 myelosuppression increased with Sprycel use.
- 4% of patients experienced cardiac failure. Of these, 60% had a prior cardiac history, primarily hypertension. One patient died of cardiac failure.
- 3% of patients had treatment-emergent QTc prolongation as an adverse event or on ECG.
- Approximately one-third of patients had bleeding events of any type; 5 of 6 fatal events were intracranial.
- Most patients required dose interruptions and/or reductions.

## The Panel Discussion

During the discussion, the panel appeared convinced that Sprycel works, but members were concerned about the toxicity – especially the GI, myelosuppression, intracranial bleeds, QTc prolongation, and pleural effusion. A panel member asked whether doctors need to be educated about how to use this drug. A company official said the only real answer to the side effects is dose interruption (and less commonly dose reduction), but he insisted that dose interruptions of <4 weeks do not appear to cause a drop in response. He also said it is not possible to identify which patients will develop these side effects.

Interestingly, one panel member suggested that the bleak prognosis for chronic phase CML patients who are either resistant to or intolerant of Gleevec is "unduly pessimistic." He said, "Once a patient is resistant to Gleevec, that does not always mean the disease will progress to the advanced phase."

*Several issues came up, but none were deemed significant.*

**Bleeding.** Dr. Kantarjian said, "GI bleeding…is related to thrombocytopenia in the large majority of patients… We tend to treat patients through myelosuppression because if you stop, the leukemia comes back…So, we give supportive care and try to keep them going. If they achieve complete remission, then we interrupt treatment

and let them recover…These are simple management approaches that we have developed over time."

**Dosing.** The FDA – and panel members – raised the issue of what the appropriate dose is, asking if 70 mg BID is optimal. It wasn't a matter of questioning the efficacy of that dose; safety concerns were behind the question. The company said it is conducting a trial to see if a lower dose will work, but those results won't be available for about nine months.

Meanwhile, Bristol-Myers Squibb is seeking approval for the 70 mg BID dose. A company official said, "We looked at dose reductions, and we have seen that with 70 mg BID, 50 mg BID, and to some extent 30 mg BID, the activity is maintained even if the patient has to reduce the dose. We have also seen that in patients not responding at 70 mg BID, when the dose was escalated to 90 mg or 100 mg, we were still able to rescue some of those patients and induce a response." Dr. Kantarjian said, "We've been using imatinib for six years, and we still don't know if the dose is 400 mg or 800 mg, and we argue about it. We've been using Ara-C (cytarabine) for 30 years, and yet the dose ranges from 1 g to 16 mg/m$^2$ per course…From the data we have on dasatinib, 70 mg BID is effective and safe, but we recognize there is a possibility that 50 mg BID may be as effective and associated with fewer side effects…It may be there is a better dose schedule…Then things can be adjusted. At this stage, there are so many patients who need this drug, the efficacy vs. risk ratio is very worthwhile, and 70 mg BID is effective and manageable." Another company expert added, "I feel 70 mg is a reasonable starting point."

**3-Month Results of Study 017: Sprycel vs. Gleevec**

| Measurement | Sprycel n=101 | Gleevec n=49 |
|---|---|---|
| Mean reduction of CML | 64% | 52% |
| **Results at 3 months** | | |
| MCyR | 35% | 2% |
| CCyR | 21% | 8% |
| **Results at any time prior to crossover** | | |
| MCyR | 92% | 82% |
| CHR | 42% | 33% |
| CCyR | 27% | 12% |
| **MCyR in patient subgroups** | | |
| Gleevec 600 mg/day | 35% | 21% |
| No prior cytogenetic response | 23% | 0 |
| **Discontinuations** | | |
| Any | 15% | 76% |
| Due to progression or lack of response | 8% | 55% |
| Due to intolerance | 7% | 18% |
| Due to non-compliance | 0 | 2% |
| **Adverse events** | | |
| Fluid retention | 25% | 43% |
| Pleural effusion | 11% | 0 |
| Diarrhea | 26% | 29% |
| Headache | 25% | 8% |
| GI hemorrhage | 2% | 0 |
| Fatigue | 28% | 20% |
| Rash | 16% | 16% |
| Myelosuppression | 54% | 14% |

Panel members asked the company for more details about the ongoing dosing study, but company officials appeared to misunderstand and presented new data instead from Study 017 (a head-to-head trial comparing Sprycel and Gleevec) in patients who had prior Gleevec treatment. This was a 3-month, crossover trial.

**GI toxicity.** Under panel questioning, company experts explained that proton pump inhibitors (PPIs) and H2 blockers do ***not*** work because they drastically decrease the efficacy of Sprycel. A Bristol-Myers Squibb expert said, "We did a pH study looking at Maalox, and it decreased exposure to dasatinib by 55%, but when the administration of Maalox and dasatinib were separated by two hours, it was okay…So our recommendation is to separate it by two hours."

**Hypophosphatemia.** Under panel questioning, the company provided figures on this.

**Hypophosphatemia with Sprycel**

| Grade | Patients n=511 |
|---|---|
| 0 | 55% |
| 1 | 7% |
| 2 | 20% |
| 3 | 16% |
| 4 | 1% |

**Patient follow-up.** A panel member asked, "Is there a learning curve in using this drug? Is there a way to anticipate (bleeding events from low platelet counts)? I am disturbed by the bleeding events and the clinically important fluid retention issues, which strike me as somewhat preventable."

**Patient selection.** Panel members discussed how patients were qualified for the trials. The company said that decisions on Gleevec-resistance and Gleevec-non-response were all made at the local level and the cytogenetics were not centrally reviewed. A panel member recommended that the company have a central reader in the future.

**Pleural effusion.** This is a side effect not commonly seen in CML, but Dr. Kantarjian said, "Pleural effusion is new in this setting…You can't predict the patients who will develop pleural effusion, but the patients always start by complaining of something – shortness of breath, etc. As soon as they have those, we interrupt the drug, bring the patient in, and do a chest x-ray…Then, there are two ways to treat patients. Most investigators have used diuretics. At our institution, we realize a short course of steroids is quite effective – 40 mg x 2 and then 20 mg x 2."

**QTc prolongation.** A company official said there was some prolongation but explained that it was "below the guidelines threshold" and there is "minimal risk of QTc prolongation."

### Public Witnesses

There were three public witnesses, but all used the time to address general or breast cancer issues, not anything specific to Sprycel or CML.

### FDA Questions and the Panel Votes

**1.** The FDA has accepted durable responses in hematologic malignancies for approval for both chronic leukemias and acute leukemias (regular approval). The FDA granted Gleevec (Novartis, imatinib) accelerated approval for chronic, accelerated, and blast crisis CML based on durable major cytogenetic responses and major hematologic responses. Based on the magnitude and duration of responses, **has the sponsor provided sufficient evidence of dasatinib's effectiveness** for:

- Chronic phase CML?
- Accelerated phase CML?
- Myeloid blast CML?
- Lymphoid blast CML?

**YES, unanimously for all.**

The panel agreed with this member's comment: "These are very refractory patients…I think the data for cytogenetic remission are valid across the board." He added that there is no subgroup in which he is not impressed with the action of Sprycel.

**2.** For approval in Gleevec-**resistant** populations (except Ph+ ALL): The major toxicities observed with dasatinib include the following: gastrointestinal and hematological toxicities, fluid retention, bleeding, and myelosuppression. Less frequent, but serious, adverse events include cardiac toxicity and intracranial bleeding. Based on the Phase II data, **does the risk:benefit profile support dasatinib's approval** for:

- Chronic phase CML?
- Accelerated phase CML?
- Myeloid blast CML?
- Lymphoid blast CML?

**YES, unanimously for all.**

Panel member comments included:

- "(Sprycel) is more complicated to give than imatinib, which was straightforward, with few dose reductions. This (dasatinib), with its potential for cardiac complications and pleural effusion, etc., will make it a little more complicated, but I think it is clear the risk:benefit is in favor of the benefit…There really is not a good alternative (for these patients), so I think this is a suitable and attractive alternative, and I would be in favor of seeing its approval for all of these (forms of CML)."
- "I agree…As clinicians we need to monitor these populations very carefully. Many times we forget when we prescribe an oral medication. We assume patients will call us (with adverse events), and the guidelines have to specify how to monitor these patients carefully."
- "It seems that as experience is gained, prophylaxis…will reduce the toxicity to individual patients…and in the individual setting, I think it is okay."
- "We aren't used to dealing with patient platelet counts, but that would not be particularly difficult…The (pleural) effusions are more difficult…If they can occur a year later, and the symptom is caught then, I think we will be dealing with a lot of upper respiratory infections with chest x-rays…So, there are a lot of practical issues here, but certainly nothing that would make me want to stop using the drug."

**3.** For approval in Gleevec-**intolerant** populations (except Ph+ ALL): Imatinib intolerance was defined as either (1) imatinib-related toxicity relating to imatinib discontinuation, or (2) inability to tolerate imatinib. The number of intolerant patients enrolled per study (except for the Chronic phase CML studies) was <10%.

**3A. Has the sponsor provided evidence of an effect on a surrogate endpoint (major cytogenetic response) for chronic phase CML patients *intolerant* to Gleevec?**

**YES 13, 1 Abstention.**

Panel member comments included:

- *Patient representative:* "I fear you will have a lot of patients saying this is newer and better, and so suddenly they will be 'intolerant' to Gleevec."
- "I wondered if you looked at intolerant patients and said, 'Are there other options?' And, clearly, the answer is no. Then, as a non-hematologist, the question is, 'Is there a risk if patients are truly not intolerant?' If they were called intolerant prior to truly being intolerant, the answer is no…So, I can't really see a downside to this."

**3B. Has the sponsor provided sufficient evidence to warrant accelerated approval in CML patients *intolerant* to Gleevec in either accelerated, myeloid blast, or lymphoid blast phases?**

**YES, unanimously for all.**

Panel member comments included:

- *Chair:* "It looks like this is the better of the two drugs (Sprycel and Gleevec). For me, that provided a certain comfort."
- "I think the response rate is such that I myself would vote for approval."

- "The issue is that an individual patient may have a really low threshold for deciding he or she is intolerant, knowing there is another agent…So, the threshold for defining intolerance is in the eyes of the patient...but in the clinic, the inclination would be to approve trying another drug."
- "When you look at the reason for intolerance, it is usually not subjective…It is usually obvious to both patient and physician…And I doubt it will be patients giving a more nebulous reason for stopping imatinib. I think it will be more obvious."

**4.** The FDA has approved drugs to treat acute leukemias based on complete responses. The sponsor has presented data (major hematological responses) for Ph+ ALL patients who have experienced disease progression on Gleevec and other therapies. **Has dasatinib demonstrated sufficient evidence to warrant regular approval in either the Gleevec-*resistant* or Gleevec-*intolerant* Ph+ ALL populations?**

**YES 12, 1 NO, 1 Abstention.**

The FDA's Dr. Pazdur said, "You could have accelerated approval for this indication and ask for other data from a single-arm trial. Accelerated approval means we want more follow-up…In other leukemias, we gave full approval based on similar data…You (also) could ask for a Phase IV commitment to update the data. The major distinction between accelerated and full approval is the strength we have to get the (post-approval) studies done…The commitment is mandatory (with accelerated approval)." A panel member responded, "I don't see the differential between accelerated and full approval (for Sprycel)…because there is nothing to randomize it against (in a post-market trial)…so we might as well give it full approval." Another panel member said, "It seems, given the rarity of this disease, that this is an approvable drug. To do another study would be very difficult…The data seem to support approval of this drug."

♦