Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Bristol-Myers Squibb's BMS-354825 and **Pfizer's** SU-11248 continue to look promising to treat Gleevec failures in CML, and they may eventually replace Gleevec front-line, but BMS-354825 increases QTc slightly, which is being monitored in the Phase II trial. However, there is a new player on the block: **Novartis's** AMN-107, which may give the other two a run-for-the money. ♦ **Biocryst's** forodesine (BCX-1777) looks very promising in CTCL, but the outlook in T-cell ALL – which is the more important market and the indication in which it will be filed – is less certain. ♦ The data on **Celgene's** Revlimid was hard to get but looked good, and sources believe it is approvable, but the trial deaths bear watching, and the MDS market may be somewhat more limited than expected. ♦ Interest in **Pharmion's** Vidaza is growing, and **SuperGen's** Dacogen has several hurdles to overcome. ♦ Development appears to be continuing for **Merck's** SAHA, an HDAC. ♦ Hematologists/oncologists are not happy with new CMS reimbursements for chemotherapy, but the sky does not appear to be falling in – yet.

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AMERICAN SOCIETY OF HEMATOLOGY

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The American Society of Hematology (ASH) is the world's largest professional society concerned with the causes and treatment of blood disorders. The annual meeting produced a wealth of information on new agents in development, particularly those for AML, CML, CTCL, leukemia, multiple myeloma, and MDS. Following is a discussion of key data on these agents.

ACUTE MYELOID LEUKEMIA (AML)

TYROSINE KINASE INHIBITORS

Several oral tyrosine kinase inhibitors are in Phase I/II development to treat AML, including:

➢ **CEPHALON'S CEP-701.** A poster reported on a Phase II study as first-line therapy at a dose of 60 mg BID (increased to 80 mg BID from Day 28) in 24 older patients. Of the 16 evaluable patients, 3 of 4 with FLT3 mutations had peripheral blood blast responses. There were no CR, but 46% Grade 1-2 GI toxicity. Researchers concluded, "CEP-701 has hematological activity in both mutant and wild-type patients. In view of the modest response of wild-type cases, it is proposed to amend the trial to assess sequential low-dose cytarabine and CEP-701 as a combined approach."

➢ **MILLENNIUM'S MLN-518.** A Phase II study was presented on MLN-518 (525 mg BID) in 20 patients with relapsed or refractory AML and in untreated patients ineligible for standard therapies. Toxicities have included: weakness, fatigue, QTc prolongation, nausea, and vomiting. No CR or PR was observed, but six patients had an 85%-100% reduction in peripheral blast count.

➢ **NOVARTIS'S PKC-412.** Phase Ib data were presented on PKC-412 (100 mg BID) in combination with daunorubicin and cytarabine (DA) in 15 newly diagnosed AML patients. Significant but transient and reversible Grade 3 toxicity (46% nausea, 32% vomiting, 18% transaminitis, and 18% hyperbilirubinemia) lead to a change in the treatment regimen to a "discontinuous schedule" – PKC-412 given with each cycle of DA on either Days 1-7 and 15-21 or on Days 8-21. Six of 13 evaluable patients had a CR. Researchers concluded: "100 mg BID is not feasible to be combined with daunorubicin. Discontinuous administration is feasible, but there is still too much nausea and vomiting. 50 mg BID will be tested in the future to see if that is feasible." Another expert said, "It is too early to say if this is a home run."

Grade 3-4 Non-Hematologic Adverse Events with Novartis's PKC-412

Measurement	Original Protocol	Amended Protocol
Vomiting	29%	9%
Nausea	14%	17%
Diarrhea	20%	25%
Bilirubin	21%	25%
CR	50%-57%	N/A

➢ **PFIZER'S SU-5614 and SU-11248.** A speaker who has worked with several of these agents said, "I won't say one drug is better or worse than another." However, he did offer some generalizations on them:

- Generally well-tolerated with modest toxicity.
- Inhibit the pharmacologic target (FLT3).
- Active in treating relapsed AML with FLT3 mutations. The most impressive clinical responses have been in reduction of peripheral blood blast percent.
- Some patients that over express wild-type FLT3 also respond – and this is a large group.
- Resistance develops rapidly in responding patients – and not much is known about the mechanism of resistance.
- Being moved to up-front therapy.

Questions that have been raised about FLT3s in AML:

1. *Why are peripheral blood responses consistently more impressive than bone marrow responses?* The speculation is that it could be microenvironmental resistance. It could be growth factors/stromal cells in bone marrow rescue leukemic cells from FLT3 inhibition.

2. *Why don't these drugs work as well as Novartis's Gleevec (imatinib) does for CML blast crisis?* In AML, FLT3 mutation may be acquired late, and late acquisition could confer relative resistance to FLT3 inhibitors.

3. *What is the basis for rapid development of resistance?* A potential explanation is drug clearance, but the reason also could be acquisition of resistance mutations in the context of FLT3. Two mutations have been identified with PKC-412 and SU-5614 that may explain their – and perhaps other FLT3 inhibitor – resistance: N676D and G697R.

The next steps for FLT3s are:

➢ Combination therapy.
➢ PKC-412 + induction therapy.
➢ CEP-701 + induction therapy.
➢ Higher affinity inhibitors are under development.
➢ Develop inhibitors that can overcome resistance.
➢ FLT3 inhibitor + another signal transferase inhibitor.

HISTONE DEACETYLASE INHIBITORS (HDACS)

Among the HDACs discussed were:

➢ **ABBOTT'S valproic acid.** An investigator-initiated trial of ATRA+valproic acid found several patients with some decrease in blast counts. Two other trials (Abstracts #1805 and 1808) also showed activity.

➢ **MERCK'S SAHA.** Several sources insisted that SAHA is moving forward, though there are backup compounds as well.

➢ **SCHERING AG'S MS-275.** Updated results from a Phase I trial in solid tumors were presented. The drug was well-tolerated when administered biweekly at doses up to 6 mg/m^2. Two DLTs were reported at 5 mg/m^2, so additional patients are being enrolled at 4 mg/m^2. Hypophosphatemia was more common with twice weekly dosing vs. biweekly dosing, but it was manageable with oral replacement therapy. Additional PK and PD studies are ongoing. One partial response was seen in a melanoma patient who has remained on MS-275 for >22 months.

CHRONIC MYELOID LEUKEMIA (CML)

When Novartis's Gleevec was approved in 2001, it represented a breakthrough in the treatment of CML – a disorder marked by an overproduction of white blood cells – and it quickly became the standard of care. At a symposium sponsored by the Leukemia & Lymphoma Society, Dr. Brian Drucker of Oregon Health & Science University said Gleevec continues to have an outstanding response rate, but there are patients who develop resistance, and the disease is not completely eradicated even in complete responders. Among the points he made were:

➢ In the pivotal Gleevec trial that was stopped early due to the positive effects of the drug, 97% of patients had a CR at 18 months (vs. 69% with IFN+Ara-C). New data on Gleevec showed similar levels of response.

Gleevec Response

Measurement	Response
Results at 18 months	
Normal blood counts	97%
Become Philadelphia chromosome negative	80%
3-log decrease in qPCR	55%
PCR undetectable	5%
Results at 42 months	
Overall response	~ 4%/year (16% of patients)
Complete hematologic response	48% (10% of patients)
Complete cytogenic response	10% (27% of patients)
3-log decrease in PCR	2% (55% of patients)

- Even patients who respond well to Gleevec have some degree of persistence. Higher dose Gleevec or more potent inhibitors may improve this.

- Patients on Gleevec relapse due to mutations that are resistant to Gleevec, and several drugs are in development to treat patients who are Gleevec-resistant, including Bristol-Myers Squibb's BMS-354825 and Novartis's AMN-107. However, neither of these agents works in patients with the T315I mutation, so there is still a need for additional agents to target that mutation.

Where will these new agents be useful? Dr. Drucker predicted, "They will be useful immediately in imatinib-resistant patients. In the future it will be likely they will be moved upfront…And more potent inhibitors may yield a high response rate as single agents. They may be used sequentially or in combination therapy to prolong remission or prevent relapse…Neither inhibits T315I, and that may become the default pathway on which patients relapse, so we need one more agent." T315I inhibitors in preclinical development include **STRUCTURAL GENOMICS' SGX-67686A.**

Phase I Results of BMS-354825 in Chronic Phase CML
(in Gleevec-Resistant or Gleevec-Intolerant Patients)

Measurement	BMS-354825 n=36
Half-life	~ 3-5 hours
T_{max}	~ 1 hour
C_{max}	~ 2 hours
Patients studied >4 weeks	
Complete hematologic response	86% (31 of 36 patients)
Major hematologic response	8% (3 of 36 patients)
Progressive disease	2 patients (both originally blast patients who became chronic after Gleevec and then developed resistance)
Patients treated >3 months	
Overall cytogenic response	45% (13 of 29 patients), including one complete cytogenic response
Safety	
Grade 4 thrombocytopenia	3 of 26 patients evaluable (requiring treatment modification)
GI bleeding	2 patients possibly related

BRISTOL-MYERS SQUIBB'S BMS-354825 – Excellent early efficacy but a QT prolongation question

BMS-354825, which is progressing to Phase II trials, is a dual SRC/Abl inhibitor administered BID. It is >100-fold more potent than Gleevec. Gleevec only inhibits Abl, not SRC, and BS-354825 inhibits Abl in a "different" way. Data presented at ASH indicated that BMS-354825 inhibits all but one mutation associated with Gleevec resistance. A speaker said, "BMS-354825 very, very potentially inhibits the mutations that occur in Gleevec resistance."

Initially, BMS-354825 is likely to be used in CML for Gleevec failures, but it may eventually move front-line and replace Gleevec or be combined with it. An investigator, Dr. Charles Sawyers of UCLA, said, "This is an example of how precise molecule targeting can rapidly lead to a new drug. Five years ago, we had the first presentation of Gleevec, and here we are with another drug."

Researchers from UCLA School of Medicine and M.D. Anderson Cancer Center reported on a Phase I study of 36 patients in the chronic phase of Ph+ CML who had experienced hematologic progression or intolerance on Gleevec. They were given oral doses (15 mg/day to 180 mg/day) of BMS-354825 for 5-7 days/week for ≤9 months. The researchers reported BMS-354825 appears effective and as safe as Gleevec.

UCLA and M.D. Anderson researchers also reported on 29 additional – blast or accelerated phase CML – patients treated with BMS-354825. Of these, 19 were evaluable. Two were inevaluable because they lost the response quickly (in 2-3 months). He described the responses as "surprisingly high" since Gleevec produced only 3% ≤8% CR in blast patients).

Phase I Results of BMS-354825 in Accelerated and Blast Phase CML

Measurement	BMS-354825
Blast Phase (n=21)	
Hematologic response	79% OR (32% CR, 47% PR)
Cytogenic response	40% (of ~14 evaluable patients)
Accelerated Phase (n=8)	
Hematologic response	6 OR (5 CR, 1 PR, all ongoing) 75% OR (62.5% CR, 12.5% PR)
Cytogenic response	None

Dr. Sawyers, Dr. Moshe Talpaz of M.D. Anderson Cancer Center (another BMS-354825 investigator), and a Bristol-Myers Squibb official made several points about BMS-354-825, including:

- **On side effects:** There was a small signal of mild QTc prolongation in Phase I, so the company plans to continue to follow QTc in Phase II with EKGs. The Bristol-Myers Squibb official said, "It is probably a class thing… Currently, there are no major safety issues." Dr. Sawyers said, "So, far it has been extremely well tolerated. There have been some problems with low blood counts that resolve with lowering the dose. It is very similar to Gleevec in terms of how well-tolerated it is."

- **On mutations:** BMS-354825 appears effective against all but the T315I mutation. However, Dr. Talpaz reported five patients who developed resistance to BMS-354825:
  - 3 primary – 1 with mutation of T315I, one with no mutation, and resistance unexplained in the other patient.
  - 2 acquired – both developed T315I mutation on treatment.
- **On any potential downside:** Dr. Talpaz said, "This is less specific, so maybe there is collateral damage that we haven't seen…The risk is collateral damage to other systems."
- **On molecular responses:** Dr. Sawyers said, "Using quantitative PCR to follow patients is early, but we are seeing a significant reduction of tumor burden as well… but that is early."
- **On a comparison of AMN-107 and BMS-354825:** Dr. Sawyers said, "I haven't worked directly with AMN-107 …but I understand its chemical structure is related to Gleevec, and it binds similarly…BMS-354825 has a completely different structure and binds to Abl in a different way…I don't know if that will make a difference. The other agent (AN-107), to my knowledge, does not inhibit SRC."
- **On what percent of patients become resistant to Gleevec:** "In the early days when Gleevec was used in patients with all stages of CML, we learned resistance was extremely common if you had gotten to the accelerated or blast stage (75%-100% relapse rate in those patients)…The earlier you start it, the longer the response time…Among patients who started on Gleevec when first diagnosed, at 40 months the relapse rate is 16%, which most of us think is about 5% per year."
- **On other uses for BMS-354825:** Dr. Talpaz suggested, "It may have other benefits through SRC. We are testing it extensively in the test tube, and there appears to be a lot of activity against a large number of solid tumors, so it has a theoretical potential in other diseases."
- **On how to use BMS-354825:** Dr. Sawyers said, "With time we will want to know if there is a benefit compared to Gleevec…Preclinical work from us might argue for using it in combination with Gleevec…I would use it with Gleevec." The Bristol-Myers Squibb official said, "We are still studying the biology. We need to understand why we see the emergence of resistance (with Gleevec). We don't know if patients had mutations all along, or if those mutations developed during (Gleevec) treatment… Combination therapy is one approach, but so is using the most potent first, and then using Gleevec sequentially, or alternating therapy…Patients intolerant to Gleevec (for instance, because of skin toxicity) – and there are a handful of those – have tolerated BMS-354825 very well. They actually responded and tolerated it well without a recurrence of intolerance." Dr. Talpaz said, "I don't know the rationale for combination use, for using two drugs with the same target."

Bristol-Myers Squibb plans to submit BMS-354825 to the FDA for three indications simultaneously:

- Chronic CML.
- Accelerated CML.
- Blast Phase CML.

The submission will be based on the results of five Phase II trials that will start in the next month, with the first expected to start enrollment this month. The company currently is enrolling investigators in the U.S., Europe, South America, Canada, and Asia. The plans are for at least 60 patients per study with a total of ~500 patients. A Bristol-Myers Squibb official said, "We are currently in discussions with regulatory authorities on the follow-up required in the trials…We hope to have most investigators on board by February 2005, and the usual follow-up is three to six months." It is possible there will be data at ASH 2005.

- Chronic CML – two trials.
- Accelerated CML – one trial, to start enrollment in France in December 2004.
- Blast CML – one trial.
- Ph+ ALL – one trial.

NOVARTIS'S AMN-107 – Looks very promising and could be come-from-behind kid

AMN-107 is 10-20-fold more potent than Gleevec against Abl. It is progressing to Phase II trials.

A researcher reported on the interim results on 55 patients in an ongoing Phase I/II trial of daily oral AMN-107 in adult patients with Gleevec-resistant advanced-phase chronic CML or relapsed/refractory Ph+ ALL. He said, "AMN-107 is many times more potent than Gleevec. It selectively induces apoptosis and inhibits BCR-Abl more than Gleevec…It inhibits more mutations, increases survival in murine models, and has a better absorption pattern in cells."

There had been some thinking that this agent would not affect as many Gleevec mutations as BMS-354825, but an AMN-107 researcher offered new information on AMN-107:

- "Mutations account for about 50% of the response (to AMN-107)…In 36 patients with accelerated phase, 15 had mutations, and 12 responded. In 17 patients with no mutation, there were 8 responders. T315I remains the only major significant mutation to this agent."
- No DLT has been defined. The drug is well-tolerated up to 1200 mg daily, with rare liver, skin, and marrow adverse events.
- The current plan is to move to BID dosing.

Interim AMN-107 Phase I Results in CML

Measurement	AMN-107
Doses	50-100-200-400-600-800-1200/day
Primary Gleevec resistance	26%
Acquired Gleevec resistance	74%
Half-life	16 hours
Median time to peak concentration	3 hours post-dose
Overall Hematologic Response by Disease Category	
AP	63%
CML-bp-myeloid	58%
CML-bp-lymphoid	50%
ALL Ph+	14%
Cytogenic Response by Disease Category	
AP	0 (2 CR, 2 PR)
CML-bp-myeloid	8% (no CR or PR)
CML-bp-lymphoid	17% (1 CR)
ALL Ph+	N/A

AMN-107 Phase I Safety Results in CML

Measurement	AMN-107
Hematologic adverse events	5% at doses ≥200 mg
Liver toxicity	None at doses <800 mg
Elevated bilirubin	3 patients at 800 mg, 1 patient at 1200 mg
Grade 3 elevation in sGOT and sGPT	1 at 800 mg, 1 at 1200 mg
Skin rash	3 patients (within 28 days of treatment at ≥600 mg)
QTc prolongation >500 ms	None
QTc >60 ms change from baseline	2 patients at 400 mg 2 patients at 800 mg

Comparison of Gleevec, AMN-107, and BMS-354825

Kinase	Gleevec	AMN-107	BMS-354825
Abl	300 nM	13 nM	1 nM
PDGFR	100 nM	61 nM	28 nM
KIT	100 nM	160 nM	22 nM
SRC >1000	>100 nM	ND	<1 nM
Issues			
Mutation inhibition	Several mutations resistant	Inhibits all mutations except T315I	Inhibits all mutations except T315I
Potential pitfalls	Resistance and persistence	Bind inactive form of Abl	Less specific inhibitor with the possibility of immunosuppression
		Higher concentrations required to inhibit some common mutations	More potential for long-term toxicity, including immunosuppression
		More potential for resistance	

CUTANEOUS T-CELL LYMPHOMA

BIOCRYST'S forodesine (BCX-1777) – Very promising in CTCL but the outlook in the more important T-ALL is less certain

Currently, this PNP-inhibitor is administered in a 30-minute infusion, but an oral formulation also is being explored. A Phase II trial in CTCL is underway of the IV formulation, and a Phase I trial of the oral formulation in CTCL has started. In other malignancies, the IV formulation will be used. The half-life is 5.8-18.4 hours. An opinion leader offered a lukewarm review, "Forodesine has a chance. It can't compete with nelarabine (GlaxoSmithKline, 506U78), which is more advanced than forodesine. They can't do T-ALL; the data are not good enough. Only 2 of 7 patients had responses."

There were two posters on forodesine at ASH:

1. **CTCL.**
2. **An ongoing Phase I/II study in T-cell ALL (T-ALL).** A researcher said, "I'm remarkably excited about forodesine. Tolerability and efficacy are great." The most common adverse events that were believed related to the drug were headache, nausea, diarrhea, and leukopenia.

Phase I/II Results of Forodesine in B-Cell ALL

Measurement	Forodesine 40 mg/m^2
Number of B-ALL patients	7 patients
Withdrawn for disease progression	2 patients
Completed study	3 patients
Ongoing treatment	2 patients
Dose escalation to 90 mg/m^2 required	2 patients
Hematologic improvement	4 patients (1 CR)

In B-cell ALL (B-ALL), a Phase II trial is just starting. In T-ALL, forodesine was tested in Phase I in refractory patients and in Phase II in relapsers. There are 2,000-3,000 T-ALL patients diagnosed in the U.S. each year. A researcher said, "I see this going to front-line treatment as monotherapy or possibly in combination with steroids. We give five-drug regimens now front line, but we lose some to death in induction. Forodesine is amazing. There is no toxicity, and it works. The Phase II trial is ongoing. So far, seven patients have been enrolled, and the goal is 20 patients." There may be six-week data at ASCO 2005.

A Biocryst official said T-cell leukemia is the lead program for forodesine. There are 1,000-2,000 T-cell leukemia patients in the U.S. B-ALL and T-ALL together are another ~5,000 patients. If CTCL lymphoma is included that adds another 35,000-40,000 patients. The official said, "In 1Q05 we will meet with the FDA – after the Phase IIa trial is finished to discuss the protocol for Phase IIb, and we will start that in 1H05. We hope the FDA will allow that trial to be less than a year. We want to get a Special Protocol

Assessment. We have orphan drug designation…We consider forodesine similar to Gleevec but in different malignancies."

An official said a DSMB will be used for Phase IIa and Phase IIb trials. The principal investigator for the Phase IIb in T-cell leukemia will be Dr. Richard Furman of Weill Cornell Medical Center.

LEUKEMIA

Leukemia, a malignant disorder usually of white blood cells, originates in the bone marrow but quickly spreads to the blood and many organs. Because of the complexity and varying courses of the disease in each patient, the development of new and effective treatments has been challenging, but new "molecular targeting" agents appear promising.

Farnesyl Transferase Inhibitors (FTIs)

It used to be thought that FTIs worked on the Ras pathway, but that has pretty much been disproven. A speaker said, "We don't have any idea how these drugs are active. We started out thinking they would target Ras…but we found that is not true…We have had a not very complete but substantial impact on the clinical outcome in elderly patients with AML, myelodysplasia, refractory multiple myeloma, etc." Another expert said, "For patients who are not Gleevec-sensitive, the class with the most development so far is the FTIs…Can they change the natural history of the disease? That remains to be seen…But perhaps we can control the disease with this strategy."

➢ **JOHNSON & JOHNSON'S Zarnestra (tipifarnib, R-115777).** A speaker said the response rate in various trials has been about 30% in relapsed and refractory acute leukemias – all independent of Ras mutation. The drug appears to be concentrated in bone marrow at a level two- to three-fold higher than serum levels. The MTD (due to CNS side effects and myelosuppression) appears to be 600 mg BID. Phase II data for Zarnestra 600 mg BID (for 21/28 days) in previously untreated, poor-risk AML and DS patients showed an overall response of 34%, 18% CR, median duration of response 6.4 months, median DFS 18.5 months, median OS 12.5 months, and overall survival in CR patients of 14.4 months. Grade ≥3 toxicity was 43%: 18% infection, 17% GI, 11% neurological, and 3% renal. Hospitalization was required in 36% of patients, for a median duration of 14 days. Two new toxicities were reported: rash and pancreatitis.

Zarnestra also is being studied in multiple myeloma, Gleevec-resistant CML, and in MDS. A speaker said researchers are reporting ~30% response rate in MDS, with 5% CR, no relationship between Ras mutational status and response, and a possible early decrease in TNF-α that may correlate with CR. The duration of response has been good (14+ months in one trial).

➢ **SCHERING-PLOUGH'S Sarasar (lonafarnib, SCH-6636).** The company reportedly is going on to a Phase III trial in thrombocytopenia rather than MDS.

PR1 vaccine. This vaccine, a nine amino acid HLA-A2 restricted peptide derived from proteinase 3, is made from peptides found on the surface of leukemia cells. It may make the body generate an immune response and kill cancer cells. Researchers from M.D. Anderson Cancer Center reported on a 35-patient study which found the vaccine (given every three weeks for a total of three injections) resulted in a complete molecular remission and significantly improved PFS in some myeloid leukemia patients. Median treatment was 26 months, and follow-up was 1-4 years.

Results of Study of PR1 Vaccine

Measurement	0.25 mg	0.50 mg	1.0 mg
Immune response	60% of evaluable patients (20 of 33)		
Overall survival at 4 years in patients with an immune response	33%		
Clinical response (CR, PR) in relapsed or refractory AML patients (n=16)	25% (3 CR, 1 PR)		
Clinical response (CR, PR) in CML patients (n=10)	10% CR (cytogenic), 33% SD		
Clinical response in MDS patients (n=5)	1 PR		
Progression-free survival			
Patients with an immune response	6.4 months (p=.003)		
Patients without an immune response	2.4 months		

Proteasome Inhibitors

➢ **MILLENNIUM'S Velcade (bortezomib).** Researchers are exploring this agent with different schedules in a variety of solid tumors. A speaker said, "We studied Velcade twice weeklyx4 followed by 2 weeks off. The MTD was 1.02 mg/m^2. The DLT was thrombocytopenia, electrolyte abnormalities, fatigue, and malaise. We saw responses in 9 of 9 evaluable patients, with plasma cell dyscrasias having some response, and 2 patients with NHL responding."

- There is some data emerging that there may be activity with Velcade as upfront therapy alone, with dexamethasone.
- One complete remission in NHL.
- The most utility is likely to be in: NHL (dosed 1.5 mg/m^2 twice weekly for two weeks), myeloma, follicular lymphoma (58% OR), and mantle cell lymphoma (48%-54% response).

Updated Results of Single-Arm Phase II Trial in Multiple Myeloma

Measurement	Results
Evaluable patients	193
CR or near CR	10%
PR	18%
Minimal response	7%
Any response	35%
SD	24%
Median response duration	7 months (vs. 3 months on prior therapy)
Median survival	17.2 months

- Velcade also may have utility in metastatic breast cancer. A speaker showed pictures of a woman with metastatic breast cancer who had almost a complete response after two cycles of Velcade.
- A Phase I trial of Velcade with pegylated liposomal doxorubicin with 22 of 24 patients evaluable found: 36% CR, 73% OR. In 13 patients who had not benefited from prior anthracycline, 4 had a CR and 3 a PR, suggesting some chemosensitization.

MULTIPLE MYELOMA

Myeloma is caused by an abnormality in plasma cells, which synthesize and secrete antibodies that are crucial in fighting infections. Thus, disorders of plasma cells reduce the body's protection against infection. Multiple myeloma is the second most common blood cancer in the U.S., affecting an estimated 50,000 people annually. About 14,600 new cases are diagnosed each year, and almost 11,000 Americans are expected to die of multiple myeloma in 2004.

Unanswered multiple myeloma questions:

- Genes involved in deletions.
- Mechanism of transformation by fusion proteins.
- Expressions/protein profile of genetic subtypes.
- Biological basis for good vs. poor outcome within and between cytogenic subsets, and genetic changes associated with progression and drug resistance.
- Patterns of mutations.
- Biologic basis for phenotypes.

ASTRAZENECA'S ZD-6474 – Probably no future in hematologic malignancies

This oral VEGFR inhibitor hasn't worked in multiple myeloma (at 100 mg). The adverse events were nausea, vomiting, and one case of Grade 3 anemia. There was no QTc prolongation at this dose, but QTc prolongation was seen at "much higher" doses. ZD-6474 is continuing in Phase II development for NSCLC.

CELGENE'S Thalomid (thalidomide) – Thal/dex becoming standard of care

A Phase III ECOG E1A00 trial was presented comparing Thalomid+dexamethasone (Thal/dex) to dexamethasone alone in patients newly diagnosed, naïve, symptomatic multiple myeloma. The results suggested that adding Thalomid to the standard treatment regimen of dexamethasone is significantly more beneficial to patients. The principal investigator, Dr. S. Vincent Rajkumar of the Mayo Clinic, said, "While we feel that this therapy should be carefully considered on an individual basis due to the higher toxicity level, we are confident that the combination does demonstrate a superior response in newly diagnosed multiple myeloma patients. The regimen offers a better option than standard treatment with intravenous VAD (vincristine, adriamycin, and dexamethasone) and negates its use in patients suffering from this disease."

In this randomized, 207-patient trial, Thalomid was given at a dose of 200 mg/day and dexamethasone at a dose of 40 mg (on Days 1-4, 9-12, and 17-20). The study was designed with stopping rules for response and toxicity. The DSMB determined at the interim analysis on 109 patients that the trial met both stop rules. At ASH, data on 199 of 200 eligible patients were presented.

4-Month Results of Phase III E1A00 Trial of Thalomid in Newly Diagnosed Multiple Myeloma

Measurement	Thalomid+ dexamethasone n=103	Dexamethasone n=104	p-value
Evaluable for ITT analysis	99 patients	101 patients	---
Primary endpoint: Best response (OR) within 4 months by ITT	63%	41%	.002
OR in patients with serum M-protein but unmeasurable urine M-protein	73%	50%	N/A
Median time to response	1.1 months	1.1 months	Nss
Confirmed disease progression	2%	4%	---
Grade ≥3 non-hematologic toxicity	68%	43%	---
Grade ≥3 cardiac ischemia	3 patients	2 patients	---

A second interim analysis was presented of the European IFM-99-06 trial, comparing melphalan+prednisone+Thalomid (MP-T) to melphalan+prednisone (MP). Researchers found that patients on this regimen should get prophylaxis treatment for DVT. The DSMB reported the observed adverse events were as expected in each arm and that there was no excess

Second Interim Analysis of IFM-99-06 Trial

Measurement	MP (Melphalan + Prednisone)	MP-T (Melphalan+Prednisone +Thalomid)
Safety		
Neutropenia	32%	41%
Thromboembolism	14%	9%
Anemia	18%	14%
Infection	11%	17%
Infection-related death	2%	2%
Peripheral neuropathy	N/A	36%
DVT	5%	12%
Toxic deaths related to DVT	0	0
Efficacy		
CR	3%	14%
≥90%	8%	51%
≥50%	34%	84%

Interim Analysis of Italian Trial

Measurement	MP (Melphalan + Prednisone)	MP-T (Melphalan+Prednisone + Thalomid)
Discontinuations	N/A	42%`
Early deaths	5	5 (Nss)
DVTs	4%	19% (p=.003)
Neurotoxicity	11%	41% (p<.001)
Infections	13%	24%
Grade 1-2 adverse events		
Hematologic	29%	35%
Constipation	N/A	28%
Neurologic	11%	32%
Cardiac	3%	17%
Cutaneous	3%	15%
Infection	12%	14%
Thromboembolism	4%	19%
Grade 3-4 adverse events		
Hematologic	25%	18%
Neurologic	N/A	9%
Cardiac	4%	3%
Cutaneous	N/A	2%
Infection	1%	10%
Efficacy		
CR + nearCR	5.4%	27.7% (p<.001)
PR	13.3%	33.8%
Any response	46.7%	77.1%
Median progression-free survival	13.7 months	25.2 months (p<.001)
Overall survival	68.2%	78.7% (Nss)

number of toxic deaths in any arm. A third interim analysis will be done in April 2005.

Italian researchers also reported on the interim results of a trial of 117 newly-diagnosed multiple myeloma patients. A speaker said, "If you look at the >age 73 patients and the under age 73 patients, the patients over age 73 have almost double the incidence of side effects…We should address the dose we use of Thalomid."

CELGENE'S Revlimid (lenalidomide)

New data were presented from a 25-patient Phase II trial in advanced relapsed and refractory multiple myeloma with the combination of Revlimid, Doxil, vincristine, and reduced-frequency dexamethasone. The trial was intended to find the MTD of Revlimid in this combination and was amended to determine efficacy and safety. Revlimid was started at 5 mg/day for 21 days, followed by 7 days off, then dose escalation.

The dose-limiting toxicity was sepsis/septic shock that occurred at Dose Level 3 (Revlimid 15 mg), with 2 patients developing non-neutropenic sepsis. There was one Grade 4 hyper-coagulation event (a pulmonary embolism) in a refractory patient with renal failure, but the patient recovered.

Results of Phase II Trial of Revlimid in Advanced Relapsed and Refractory Multiple Myeloma

Measurement	Revlimid+Doxil+ Vincristine+Dexamethasone
Evaluable patients	21
CR	3 patients (12.5%) *
Near CR (decrease of M–protein by >90%)	4 patients (16.1%) *
Unconfirmed CR	2 patients (8.1%)
CR+nCR	36%
PR	8 patients (33%)
SD >25% ≤50%	5 patients (20%)
DLT	Sepsis/septic shock
Overall survival	78% alive at 1 year
Grade 3 neutropenia	2 patients (9%) **
Grade 3 neuropathy	1 patient **
Decrease in M-Protein	
SD patients	5 of 6 achieved ≥25% decrease
>25% reduction in M-protein after one cycle of therapy	17 of 21 patients
>25% reduction in M-protein after two cycles of therapy	3 of 4 patients

* All had been refractory MM patients.
** Required dose reduction of Revlimid and Doxil.

Data were presented from a Phase II trial of Revlimid (25 mg QD on Days 1-21, then off for 7 days) plus dexamethasone (40 mg on Days 1-4, 9-12, 17-20 of each cycle) and low-dose (81 mg) aspirin in 34 patients with newly diagnosed multiple myeloma. Researchers reported on the first 30 consecutive patients: Ten patients had Grade 3 adverse events – one episode each: CD4- <200 mm^3, anemia, neutropenia, increased liver enzymes, muscle weakness, agitation, hyperglycemia, cardiac arrhythmia, pneumonitis, erlichiosis, and colonic perforation. There was no DVT and no Grade ≥4 adverse events. Response was defined as M-protein serum decrease ≥50% and M-protein urine decrease ≥90% or to a level <200 mg/24 hours; and the findings had to be confirmed with two readings at least 4 weeks apart.

Results of Phase II Trial of Revlimid in Newly Diagnosed Multiple Myeloma

Measurement	Results
Evaluable patients	30
OR	25 patients (83%)
Grade 3 non-hematologic adverse events	33%

ECOG has started a large, randomized study of Revlimid+ dexamethasone in newly diagnosed multiple myeloma.

MYELODYSPLASTIC SYNDROMES (MDS)

By current estimates, 15,000-30,000 people in the United States and 87,000 worldwide are diagnosed with MDS each year, and many specialists agree that the overall incidence is increasing. MDS is a collection of disorders in which the bone marrow does not function normally and not enough normal blood cells are made. There is no test for MDS; it is diagnosed based on abnormal bone marrow morphology.

MDS may develop following treatment with drugs or radiation therapy for other diseases, or it may develop without any known cause. Some forms of MDS can progress to acute myeloid leukemia (AML), a type of cancer in which too many white blood cells are made. MDS typically affects adults over age 60. Bleeding and infection are the causes of death for a majority of these patients, and the survival time, depending on the severity of the disorder, is typically only about six months to six years, but transplant is curative.

Therapy-related MDS occurs after treatment of APL, breast cancer, testicular cancer, ALL, AML, etc. Corixa's Bexxar (tositumomab) has been associated with a risk of MDS. A new study of >1,000 Bexxar patients found only 22 confirmed cases of secondary MDS/AML, for an incidence of 1.0%/year. The median time from Bexxar treatment was 3.1 years, and 100% had chromosomal abnormalities. The clinical outcome of therapy-induced MDS is not very good. Two-year survival is 8%.

Two issues in MDS have been:

1. **Lack of physician awareness.** Dr. Steven Gore of Johns Hopkins University School of Medicine, said, "Patients with MDS have been an underserved community. The disorder is under-diagnosed, under-researched, and under-treated, and is definitely an area which is in need of more attention."
2. **Lack of research funding.** ASH has worked to improve this, and the National Heart, Lung, and Blood Institute committed ~$3 million for MDS research in 2005.

Dr. Alan List of H. Lee Moffitt Cancer Center in Tampa FL pointed to three promising therapeutic areas in low/ intermediate risk MDS:

1. **AMGEN'S Aranesp (darbepoetin).** New data from French researchers to be presented here on 55 evaluable patients found Aranesp produced an erythroid response in 60% of patients (47% major), and 3 of 6 EPO failure patients responded, suggesting Aranesp could be used for patients who fail EPO in addition to allowing for better/more convenient scheduling.

2. **Angiogenesis inhibitors.**

➢ **CELGENE'S Thalomid (thalidomide).** A Phase II trial found 18% of patients had an erythroid response (13% major). Dr. List said, "There certainly is a dose response to the toxicity, but I'm not sure there is a dose response to clinical benefit…For this to be used, it has to be given over an extended period of time at the lowest possible dose."

➢ **CELGENE'S Revlimid (lenalidomide, CC-5013).** Celgene plans to submit Revlimid to the FDA in 1Q05 for the treatment of MDS in patients with 5q deletion chromosomal abnormalities. Dr. List noted that Revlimid:

- Is devoid of neurotoxic effects of thalidomide.
- Lacks, in a rabbit model, the teratogenicity seen with thalidomide.
- Has the same ability as thalidomide to modulate a ligand-induced response.
- Has the ability to potentiate EPO receptor signaling.
- When combined with EPO is ***at least*** additive in clonogenic response.

3. Immunosuppressive therapy. Dr. List said, "There may be an autoimmune pathogenesis in a subset of patients to treatment with antithymocyte globulin (ATG). This type of therapy – for patients who do respond – is very effective and durable."

Other Agents in Development to Treat MDS

Class	Agent	Mechanism
MDS Clone	Roche's Cera	EPO agonist
	Novartis's RAD-001	mTOR
	Telik's Telintra (TLK-199)	Gst-p-1-1
Microenvironment	Scios's SCIO-469	p38
	PTK-787	VEGFR
Supportive	Apotex's Ferriprox (deferiprone)	Iron chelation
	Novartis's Exjade (deferrasirox, ICL-670A)	Iron chelation

Proposed MDS Treatment Algorithm

Low/intermediate risk MDS	With anemia	EPO±C-GSF
	Normal EPO	ATG, Revlimid/Thalomid, Vidaza, or ATO
	5q(del)	Revlimid
SCT candidates	Allogeneic donor	SCT
	No donor	Vidaza. Then for Vidaza failures: Zarnestra or another investigational drug.

Other agents Dr. List described as exciting included:

- **Scios's SCIO-469**, an oral agent. A Phase I/II trial will begin in 1Q05.
- **Iron chelators.** Treatment for iron deficiency anemia includes iron replacement (oral, intramuscular, or intravenous), but too much iron can be just as problematic as too little, requiring chelation therapy to remove it. The most commonly used drug is Novartis's Desferal (deferoxamine), which requires slow infusion by pump over 8-12 hours for five days a week.

Two new oral chelators – Novartis's once-daily Exjade and Apotex's Ferriprox – are seeking FDA approval as orphan drugs. Sources indicated the new products are likely to replace the IV products ***and*** expand the market. Exjade appears to have the edge.

12-Month Phase III Trial Results of Exjade

Measurement	Exjade (oral QD 5-30 mg/kg/day) n=296	Desferal (QD subcutaneous 20-60 mg/kg/day x 5) n=290
Primary endpoint: Mean decrease in liver iron content by magnetic susceptometry	-5.3 mg Fe/g (p<.001)	-4.3 mg Fe/g
Discontinuations due to adverse events	8 patients	2 patients

Researchers reported the results of a 586-patient, multicenter, randomized, open-label, Phase III trial of Exjade in beta-thalassemia and transfusional hemosiderosis. Non-inferiority was not shown, despite statistically significant better results with Exjade, because Desferal was dosed higher than usual. Adverse events were similar in the two groups, and Exjade was well tolerated. New treatment algorithms are being explored.

CELGENE'S Revlimid (lenalidomide) – Data looks good, sources believe its approvable, but deaths bear watching

After two days of controversy over what data Celgene and its investigators did or would release from the Revlimid MDS trials, the company decided to clear the air and provide more preliminary data for the two ongoing trials, MDS-002 and MDS-003. The bottom line is: Revlimid appears quite effective in 5q(del) patients, but this is a very niche population – about 800 Americans a year are newly diagnosed with this condition, which has a life expectancy of about 3.8 years, so the pool of eligible patients is <4,000.

There have been questions about deaths in the trials, but, based on investigator-determinations, only 1% of the deaths have been drug-related. However, five additional deaths in MDS-002 and two additional deaths in MDS-003 – none considered drug related – were announced. Principal

Other Results of Revlimid MDS-001 Trial

Measurement	Revlimid
Prior EPO failures	78%
Prior Thalomid failures	28%
Dose reduction due to myelosuppression	~90% at 25 mg po QD 62% at 10 mg po QD 45% at 10 mg x21 days
Primary endpoint: Erythroid response (≥50% reduction in transfusions or increase in Hgb of 2 g/dL)	67%
No transfusions required among erythroid responders	88%
≥50% reduction in transfusions among erythroid responders	12%
Complete transfusion independence in 5q deletion patients	10 of 11 patients
Erythroid response in early-stage MDS patients with refractory anemias	82%
Erythroid response in patients with low- and intermediate-1 risk MDS	75%
Median duration of response after 109 weeks of follow-up	76 weeks +
Most common adverse event	Myelosuppression ≥Grade 3
Grade-2 adverse events	Transient scalp pruritus, diarrhea, urticaria, hypothyroidism
Deaths	2 (not related to drug)
Evaluable patients	36

Trials of Revlimid in MDS

Trial	MDS-001	MDS-002	MDS-003
Trial design	5q and non-5q deletion	Non-5q deletion	5q deletion
Number of patients	43	215	148
Evaluable patients	36	N/A	N/A
Patients still on study	0	109	105
First patient enrolled	N/A	Summer 2003	July 2003
Median age	---	72	71
Median time from diagnosis	---	2.7 years	3.4 years
Median time to response	N/A	> 8 weeks	< 8 weeks
Status of trial	Completed trial, final results	Ongoing, first patient enrolled summer 2003, June 2004 cut point	Ongoing, first patient enrolled July 2003, September 2004 cut point
Deaths to date	N/A	148 patients	215 patients
Analysis	Final	Preliminary ITT results	Preliminary by ITT results
Results			
Primary endpoint: Transfusion independence	N/A	~ 26% (56 patients)	~ 64% (93 patients)
Erythroid response	67%	44% (95 patients)	N/A
Cytogenic response in transfusion-independent patients	N/A	Remissions were observed	76%
Normalization of bone marrow histology	N/A	Analyses pending	~30% of responders
Median duration of response	76 weeks +	Not yet reached	Not yet reached
Median Hgb increase	N/A	~2.3 g/dL	~3.9 g/dL
Safety			
Neutropenia	N/A	N/A	52.7%
Thrombocytopenia	N/A	N/A	52
Serious adverse events			
Pneumonia	N/A	3.7%	8.1%
Neutropenia	N/A	---	5.4%
Febrile neutropenia	N/A	---	4.1%
Thrombocytopenia	N/A	---	4.1%
Fatigue	N/A	29.3%	---
Anemia	N/A	3.7%	---
Atrial fibrillation	N/A	2.3%	---
Mortality as of the cut point			
Total deaths	2 patients (8%)	12 patients (8%)	12 patients (6%)
Disease-related deaths	0	10 patients (7%)	10 patients (5%)
Drug-related deaths	0	2 (1%)	2 (1%)
Mortality as of 12-1-2004			
Total deaths	2 patients (8%)	17 patients (8%)	14 patients (9%)
Drug-related deaths	0	2 (1%)	2 (1%)

investigator Dr. List said, "You would expect a death rate of 10%, but we see less than that, so for me there is nothing out of the ordinary here." Another expert said, "I think the ODAC (Oncology Drugs Advisory Committee) panel will be comfortable with the deaths in these trials."

Although a Celgene official insisted the company is committed to the 600-patient, Phase III trial for approval of Revlimid in multiple myeloma under the Special Protocol Assessment, the company plans to "move as fast as appropriate" to submit Revlimid to the FDA for MDS in 1Q05, based on the MDS-001, -002, and -003 trials. Additional data from these trials are expected to be presented at one or more major medical meeting in 2Q05 (perhaps ASCO and/or AACR).

A Phase III trial in 5q(del) will be initiated in 2005 for potential European filing.

The outlook for Revlimid, at least initially, appears to be primarily for 5q(del) patients plus off-label use in some non-5q(del), for a total of perhaps 15% of MDS patients within a year.

Physician comments about Revlimid included:

- "About 800 5q(del) patients are diagnosed each year. The prevalence is several thousand because patients live several years."
- "About 10% of MDS patients have true 5q(del), and about 20% have any 5q(del)…The duration of treatment is generally 24 weeks with Revlimid."
- "I've had 5q(del) patients who refused Thalomid."
- "Revlimid is exciting and promising. A lot of MDS patients in the community don't get fully worked up, so the diagnosis may not be accurate. Most patients start with EPO (if the Hg is 9-9.5). If they don't respond or have 5q(del), they could still start EPO because it is non-toxic. 5q(del) patients who fail EPO might get Revlimid. But I think this is a fairly small pool of patients. 5q(del) is a niche population – about 15% of MDS patients. I wouldn't switch patients from Thalomid to Revlimid off-label in other hematologic malignancies, but I would use it off-label in MDS for non-5q(del) patients. In a year 10%-15% of MDS patients will be on Revlimid."

PHARMION'S Vidaza (5-azacitidine) – Use increasing as it catches on

This was the first drug to be approved specifically to treat MDS. A speaker said, "Many people have been confused by the label. The FDA did not allow the 60% (hematologic) response rate on the label, just the 23% CR+PR (7% CR, 16% PR)…but those of us who use it have seen very significant clinical benefit." This expert was critical of measuring transformation, saying he preferred to call it a PFS change rather than a transformation change." He also commented that it is critical that Vidaza and other sequential methyltransferase inhibitors must be given first, not in combination with or after histone deacetylase inhibitors.

A PK study of Vidaza found peak plasma concentration 4.1 μM and trough 0.2 μM.

Is methylation important? A expert said, "DNA methyltransferase inhibitors are the most active single agents for MDS. So, the answer is probably yes…Clearly these drugs have a class effect on the natural history of MDS. We need to think carefully about why that is."

Do we know the molecular targets now? No, and the mechanism of action of Vidaza is unclear, but best responses are associated with methylation reversal.

Doctors offered these comments about Vidaza:

- "It's not a home run, but it is an advance. It works a 'little.'"
- "I haven't used Vidaza yet. With growth factors, I don't see that many transfusion-dependent patients. Subcutaneous is always easier than IV, from a time basis."

New Data on Vidaza in MDS

Dose	Number	DLT	Response
75 mg x 5	6	1	2
50 mg x 5	6	0	0
50 mg x 10	8	0	4 (4 CR/PR)
50 mg x 14	3	2	2
25 mg x 14	6	0	3 (1 CR)

SUPERGEN'S Dacogen (decitabine) – Approval possible but IV a disadvantage and market may be smaller than expected

In November 2004, SuperGen filed Dacogen, which is to be co-marketed by MGI Pharma, with the FDA for the treatment of MDS, and in early January 2005, the FDA accepted the filing. The PDUFA date for an FDA decision is September 1, 2005. Dacogen was filed in Europe in October 2004. The company also plans to initiate a Phase III trial in AML in early 2005.

In a Phase II trial, Dacogen showed clear evidence this drug worked, a speaker said. He reported on some preliminary findings from the Phase III trial, concluding, "It now seems that decitabine will have a role in these two disorders – MDS and AML." Another speaker said the Dacogen trial was similar to the Vidaza trial, but he appeared put off by the way the data were released, saying, "The preliminary data were released in a webcast – which is new for me – looking at time to AML or death."

An expert from M.D. Anderson Cancer Center said that Dacogen has shown encouraging activity in AML, RAEBT, and CML as well as MDS. However, he warned doctors to be patient because it can take time for patients to get a response, "Patients can go into CR as late as 6-8 weeks into therapy without additional treatments." He also thinks Dacogen may work better in combination with valproic acid or idarubicin.

Pharmion's approval of Vidaza in MDS was based on very few patients, and he thinks low dose Dacogen will have a similar response rate. He thought Dacogen would have had a better than 33% OR and perhaps a statistically significant impact on TTP if the dose had been pushed for multiple cycles or given indefinitely. He also argued that you can't compare the Phase III trials of these two drugs because the trials were too different and that Dacogen patients were sicker, "My feeling has always been that decitabine is a unique, active agent in MDS and CML, so at M.D. Anderson we optimize the schedule of decitabine further…and we are trying to develop easier schedules (including subcutaneous administration)."

A study of different Dacogen dosing regimens is underway in really high risk patients, and in the first 53 evaluable patients, there has been no renal or liver toxicity, myelosuppression has been "tolerable," the OR was >70%, and the CR 40%-43%. An expert said, "In my opinion, this is the highest degree of activity of a single agent at a not-intensive chemotherapy dose …And we are looking at patients who got intensive chemotherapy vs. decitabine…and so far it appears decitabine is matching or improving survival compared to intensive chemotherapy, and that is very reassuring."

Dacogen also is being studied in:

- CML patients who fail Gleevec, and the data so far look "very favorable."
- MDS patients who fail Vidaza.
- As combination therapy with an HDAC, such as Johnson & Johnson's Zarnestra (R-115777) or Celgene's Revlimid.
- In solid tumors.
- Sickle cell disease.

Dr. Hussain Saba of H. Lee Moffitt Cancer Center (as well as the University of South Florida and the VA Hospital, Tampa), a Dacogen researcher, is very optimistic about the outlook for this agent, but he does expect Dacogen to go to an FDA Advisory Panel. Among the points he made were:

- **On approval.** "I feel very comfortable that the FDA will approve it because our endpoint is very much in line with what the FDA wanted us to do. They wanted two co-primary endpoints, which we did."
- **On comparison to Vidaza.** "The response criteria for this is completely different from Vidaza; at that time (of the Vidaza trial), IPSS criteria was not out…My patients were sicker and higher risk than the Vidaza patients, and my patients had more disease duration – and they still showed a response."
- **On mode of administration.** Dr. Saba said a new mode of administration is being developed that will make Dacogen easier to administer, "All the Vidaza is subcutaneous, and so far Dacogen has been IV. But some companies are working on a home infusion pump for Dacogen. That will make a huge difference…Vidaza seems to show more activity with subcutaneous administration, and an M.D. Anderson Cancer Center study shows subcutaneous Dacogen is more effective (than IV Dacogen). Subcutaneous Dacogen may not be given every day – maybe it will be given for 3-5 days."
- **On efficacy in Vidaza failures.** Dr. Saba said researchers don't know yet if Dacogen will work in Vidaza failures, "There is some thinking that it could work in Vidaza failures…That trial is ongoing."
- **On how to choose between Vidaza and Dacogen.** "I'd use Dacogen, not Vidaza. If a patient failed Dacogen, then I'd see what other options there are. They are sister drugs, and the data look more concrete for Dacogen."
- **On the role for Revlimid in MDS.** "My thinking is that we have two different MDS patients – low risk and high risk…Revlimid has been shown to have good efficacy in low risk patients. Whether there is any activity in high risk patients we don't know. It might be a good drug for low risk patients. I would be interested in a trial of Dacogen+Revlimid."
- **On other interesting potential combinations with Dacogen.** He is interested in Dacogen in combination with arsenic and amifostine.

Asked how they will choose between Vidaza and Dacogen, doctors offered these comments:

- "Dacogen is about the same as Vidaza. It is probably an active treatment, and it may be more convenient."
- "Vidaza is easier to administer. The Phase III toxicity with Dacogen will be important; treatment-related mortality with Vidaza is about 1%."
- "I'm not interested in Dacogen. I'm used to Vidaza, and I like its subcutaneous administration. I put even low risk patients on Vidaza."
- "Dacogen made its primary endpoint of response, but missed on time to AML…I think Dacogen is much better (than Vidaza). I'll do a study in Vidaza failures, and a head-to-head vs. Vidaza after Dacogen gets approved."

TELIK'S Telintra (TLK-199)

Telik is exploring new dosing schedules for the IV version of Telintra. Currently, dosing is QDx3, and they will try QDx5, but there won't be any data on this before ASH 2005; reportedly another ~20 patients need to be enrolled.

The company also will file an IND for an oral version in 1H05. The oral version is currently in preclinical toxicology studies.

NON-HODGKIN'S LYMPHOMA (NHL)

MILLENNIUM'S Velcade (bortezomib)

An ongoing, Phase II, multicenter study in NHL found that single-agent Velcade, like other agents, produces different responses in different subtypes of the disease. An average of four cycles of treatment was administered at a dose of 1.5 mg/m^2 to 51 patients: 19 with follicular lymphoma, 23 with mantle cell lymphoma, five with small lymphocytic lymphoma, and four with marginal zone lymphoma.

Results of Velcade in NHL

Measurement	Follicular lymphoma n=19	Mantle cell lymphoma n=23	Small lymphocytic lymphoma n=5	Marginal zone lymphoma n=4
Overall OR	55%			
OR by subgroup	60% (1 CR, 1 Cru)	56%	20% PR	100% PR
Most common Grade 3 toxicity	Lymphopenia and sensory neuropathy			
Duration of remission	Not yet reached	6-19 months	10-18+ months	N/A

Miscellaneous Information on Specific Companies

Celgene

Other than the MDS trials mentioned above, Celgene has several other trials ongoing, including:

Revlimid

- Multiple myeloma – pivotal trial fully accrued.
- MD-014 – a Phase II, 225-patient trial. The full data are expected at ASH 2005. So far, 222 patients have been enrolled, and TTP is 6.2 months, but no data are available on responses. Adverse events have been "consistent with other Revlimid studies." Grade 3-4 adverse events are primarily myelosuppression, and prior Velcade treatment does not appear to affect response.
- Phase III Revlimid+dexamethasone.
- Revlimid+Velcade.
- Studies beginning in:
  - NHL, pancreatic, and ovarian cancer.
  - Prostate and renal cancer.
  - Others.

CC-11006 – non-oncology IMiD in Phase I.

CC-401 – a JNK inhibitor in Phase II for AML.

CC-10004 – PDE4 inhibitor in Phase II for:

- Reactive airway disease.
- Psoriasis.

CC-8490 – Phase II for GMB/AA.

Thalomid.

- Phase III trial for newly diagnosed multiple myeloma ongoing.
- Phase IV program continuing.
- Celgene plans to submit an amendment to the multiple myeloma NDA based on the ECOG trial.

Novartis

At the Novartis booth, the company outlined the oncology drugs in its pipeline.

Novartis Oncology Drugs in Development

Drug	Type
Preclinical	
---	RAF Kinase
---	IGF-1R
Phase I	
LBH-589	HDAC
AEE-788	TKI
ABJ-879	Microtubule stabilizer
AMN-107	TKI
Phase II	
RAD-001	mTOR
Patupilone	Microtubule stabilizer
PKC-412	FLT3 inhibitor
SOM-230	Somatostatin analog
G-matecan	Topo-I inhibitor
Phase III	
PTK-787	Multi-VEGF inhibitor
ICL-670 (Exjade)	Oral iron chelator

Regulatory News

Toxicity of off-label drugs. A speaker criticized what he described as legislation and FDA policies that prohibit pharmaceutical companies from disseminating information on potential toxicities that occur with off-label use of oncology agents. A BiogenIdec official said, "I applaud the purpose of this presentation. I do believe that…the availability of safety data of all products is hard to get at, difficult for people to find…And the quality of information that comes from physician reports of adverse events is sorely lacking. We have a very aggressive pharmacovigilance group at BiogenIdec, and I can't tell you how hard it is to chase people down to get data so we can have accurate databases on adverse events. (I'm a physician and) In 20 years of practice, I never filed an AER (adverse event report to the FDA)."

However, FDA officials in the audience disagreed. An FDA medical officer said, "I'm surprised you said there is legislation that prohibits pharmaceutical companies from discussing off-label toxicity. I think you could find labels with mentions of off-label comments – where safety has not been established in a specific indication. That might be a stop-gap measure…There was a court case where the FDA proposed regulations on how companies could disseminate off-label data before that off-label use was approved. The court struck that down and said it interferes with freedom of speech, so my understanding is companies have more latitude now than they did a few years ago. A lot of us in the FDA feel there is value in having added indications, so we want to be

circumspect." Another FDA official said, "It is incorrect to say pharmaceutical companies are prohibited from talking about safety – if it is in the label. And they can disseminate information at medical meetings."

Accelerated approvals. Another speaker questioned whether accelerated approvals are appropriate for hematology drugs. On the one hand, she said, accelerated approvals improve access to new drugs, but, on the other hand, they delay the confirmatory evaluation of the efficacy and/or safety of those drugs, allowing extended periods of use for drugs that may not be worthwhile.

FDA officials also disagreed with this. An FDA medical reviewer said, "The accelerated approval process is a challenge in weighing information...We are trying as quickly as possible to get adverse events incorporated into labels, but it is a challenge to get products on the market as soon as possible, so patients can benefit vs. the safety issues arising from that. And it is a challenge to interpret the safety data… Another issue that is somewhat embarrassing is that we have never taken a drug off the market for not finishing a confirmatory study. It is very difficult to get drugs off the market for that, but there is a pendulum that seems to swing. Five years ago we approved too slowly, and now we are approving them too quickly. Perhaps sometime we can strike a balance." The chair of the 2003 ODAC panel said, "I agree with the concerns on due diligence and getting the final results out or confirmatory studies done…but one unanimous panel thinking is that ODAC would be happy to recommend pulling a drug if due diligence is not followed…I am very comfortable with the decisions the FDA makes on giving accelerated approval to get drugs like Gleevec and Bexxar out to the public as soon as possible."

Effect of CMS reimbursement changes on physicians. Oncologists and hematologists are not happy with the new drug and physicians payments in 2005 and beyond, but the effects may not be as dire as some have predicted. A few doctors may decide to quit practicing, and some others will stop providing in-office chemotherapy, sending patients to the hospital for it instead. However, most doctors questioned do not plan to do either of these things – and, perhaps surprisingly, none predicted that the changes would spur increased use of oral agents. Several doctors said they will close satellite offices, which will make some patients have to travel farther to get chemotherapy, but they do not plan to stop offering it altogether.

Among the comments doctors had on this subject were:

- "Our hospital is not equipped to provide chemotherapy on an outpatient basis."
- "I expect more referrals for clinical trials, which is a good thing."
- "I have both an academic and a private office, and I will continue providing chemotherapy in the office to my private patients because the hospital is already at capacity. I won't like it, but I'll do it. There is nothing we can do in private practice."
- "I will send all my Medicare patients to the hospital. I have to, or I will lose money on every patient. Our hospital is not prepared to do outpatient chemotherapy, so they will admit them."
- "The issue is utilization of resources. We are looking at increasing our hours (opening nights and weekends)."
- "It is too early to say how it will affect us. It will be business as usual until we see what develops." Asked if he will use more oral agents like Roche's Xeloda (capecitabine), he said, "Xeloda is not tox-free, so that is still an issue."

DATA TO WATCH

April 2005: Third interim analysis to be done of European IFM-99-06 trial comparing melphalan+prednisone+Thalomid (MP-T) to melphalan+prednisone (MP).

April 10-15, 2005: International Myeloma Workshop in Sydney, Australia (**www.myeloma2005.org**).

April 16-20, 2005: American Association for Cancer Research (AACR), Anaheim.

- Possibly additional data from MDS-001, -002, and -003 trials of Celgene's Revlimid (lenalidomide).

May 12-15, 2005: MDS International Symposium in Nagasaki, Japan.

May 13-17, 2005: American Society of Clinical Oncology (ASCO), New Orleans.

- Additional data from MDS-001, -002, and -003 trials of Celgene's Revlimid (lenalidomide) if not at AACR.
- Possibly six-week data on Biocryst's forodesine (BCX-1777) in T-ALL.

September 1, 2005: PDUFA date for SuperGen's Dacogen.

December 3-6, 2005: ASH, Orlando.

- Possibly Phase II data BMS-354825.
- Final results expected for the MD-014 trial of Revlimid in multiple myeloma**.**

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