Trends-in-Medicine

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By Lynne Peterson

SUMMARY

Doctors are excited about the expected approval of Genentech's Avastin, but they are less optimistic about the outlook for most other angiogenesis inhibitors. ♦ OPAL-1, a new test appears to be highly predictive of which pediatric ALL patients will respond to therapy and which won't. ♦ AstraZeneca's Exanta looks promising to prevent VTE after knee replacement surgery, and Bristol-Myers Squibb's razaxaban looks promising for DVTs, but liver enzyme elevations need to be watched with Exanta. ♦ Medicare reimbursement changes are a hot button with oncologists and hematologists, and many are worried that they will be forced to stop doing infusions or retire early. ♦ There was promising new data on BiogenIdec's Rituxan, Celgene's Revimid, Genta's Genasense, Johnson & Johnson's Zarnestra, and Millennium's Velcade.

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AMERICAN SOCIETY OF HEMATOLOGY (ASH)

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Concern over upcoming Medicare reimbursement changes have hematologists and oncologists very worried, but this concern was overshadowed by positive news at the American Society of Hematology meeting on the treatment front. Thus, key topics at this meeting ranged from anemia treatment to anticoagulation, from genetics to angiogenesis inhibitors, from monoclonal antibodies to proteasome inhibitors and farnesyl transferase inhibitors.

ANEMIA

More than two million older Americans have anemia. That's approximately 13% of the elderly, with about 20% of these ≥ age 80. A researcher looked at 3,607 elderly patients in her institution's database and found:

- 12.5% of patients age ≥71 had anemia.
- Patients with lower hemoglobin had higher hospitalization rates and higher mortality.

She concluded that anemia and aging should not be ignored and that doctors should pay more attention to hemoglobin levels. But she also warned that just correcting hemoglobin levels without knowing the cause for low hemoglobin can be dangerous.

CASE STUDIES IN MULTIPLE MYELOMA

An audience-participation program highlighted how clinical practices relating to the treatment of multiple myeloma are changing. Compared to last year:

- More thalidomide (Celgene's Thalomid) is being used in combination with dexamethasone.
- More zoledronic acid (Novartis's Zometa), a bisphosphenate is being used in lieu of Novartis's Aredia (pamidronate).
- Doctors were urged to start using either MAC (melphalon + IV arsenic trioxide + IV vitamin C) or Velcade (Millenniium, bortezomib) in multiple myeloma patients with renal failure.

Use of Velcade has started, and usage is expected to increase substantially over the next year, particularly in combination with other drugs, including Johnson & Johnson's Doxil (pegylated doxorubicin).

Case #1: A patient with newly diagnosed myeloma, who is a potential candidate for stem cell transplant. More than half the audience would use thalidomide + dexamethasone (thal/dex) as initial therapy, which is a substantial increase in thal/dex use from last year's ASH meeting. A speaker suggested the voting may change again next year, predicting that more doctors will start patients on Velcade front-line.

A Mayo Clinic doctor said his choice would be to use thal/dex but within a clinical trial, at least until the results of the EA-100 trial are known – "because we need the results of a clinical trial of this regimen. However, he also warned clinicians to be wary of DVTs in thal/dex patients (a risk of 14%-15% in combination compared to ~3% with thalidomide alone). He said Mayo Clinic doctors do not routinely prescribe prophylactic anticoagulants, but Memorial Sloan Kettering Cancer Center doctors use warfarin prophylactically, and Cleveland Clinic doctors use aspirin prophylactically.

Case #2: A myeloma patient on maintenance therapy and an IV bisphosphenate who developed renal failure. The top choice of the audience (38%) was to perform a UPEP, but 28% would add thalidomide to the patient's current drug regimen. In reality, the woman was taken off monthly IV pamidronate and given monthly zoledronate, and she did well for three years, at which point thalidomide was added. The moderator suggested this is a good patient for Velcade. A speaker suggested either MAC or Velcade would be good, but when pushed to choose between these two he said he would have chosen MAC.

Case #3: A patient with Stage IIIa multiple myeloma who developed back pain and mild fatigue, and showed diffuse osteoporosis on x-ray, but had no other symptoms. The audience preference was for an autologous transplantation followed by reduced intensity conditioning regimen allotransplantation (mini-allotransplantation). In reality, the patient got VAD for four courses, followed by a peripheral stem cell transplant, and went into partial remission. The audience then would have done another mini-allo. A speaker said the data now support double ASCT over single ASCT.

Case #4: A patient with myeloma refractory to VAD, SCT, and thal/dex, who had developed progressive bone pain and Grade 1/2 peripheral neuropathy. The audience voted over-whelmingly to give her Velcade. A speaker noted that the median time to best response with Velcade is 38 days. Patients who may not do well on Velcade are older or have high marrow involvement. He commented that 80% of patients in the SUMMIT trial of Velcade developed peripheral neuropathy, and if this worsens, the dose of Velcade must be reduced and supportive measures started. He also called the emerging field of Velcade combination "exciting," particu-larly Velcade + Doxil, which appears synergistic. In terms of quality of life, he said Velcade responders "felt better," had fewer transfusions, and had an improvement in renal function.

Case #5: A patient with Stage 3 myeloma and progressive bone disease who had gotten a partial remission for 18 months with thal/dex and then showed no response to Velcade. More than three-quarters of the audience voted to put this patient in a clinical trial with a novel agent. The moderator suggested thalidomide, Revimid (CC-5013, an IMiD), Velcade + Doxil, but he noted that there are at least 18 new drugs in development for multiple myeloma, including: Novartis's PTK-787, SAHA/LAQ824, 2ME, and an LPAAT inhibitor. A speaker said the response rate with Revimid "will hold up" in data to be presented later at this meeting. In the pivotal Revimid trial, 70 patients have been enrolled in Europe and 79 of 302 patients in the U.S. She suggested prophylactic anticoagulation may be required with Revimid.

Case #6: A 45-year-old patient with plasma cell dyscrasia and neuropathy. More than three-quarters of the audience felt the correct diagnosis for this patient was the rare disease, POEMS syndrome (osteosclerotic myeloma). A speaker said Revimid might be a good novel agent to try, but he would not try Velcade in this patient.

ACUTE LYMPHOBLASTIC LYMPHOMA (ALL)

A new test – discovered through technologies from the human genome project – may be highly predictive of therapeutic outcomes of pediatric ALL, according to a study presented at ASH. Researchers reported that OPAL-1 (Outcome Predictor in Acute Leukemia 1), a novel, fully-cloned human gene, and additional newly identified genes, have a strong predictive power to identify children who may achieve remission or who may fail current therapeutic regimens for pediatric ALL, allowing physicians to tailor therapies more effectively to individual children with leukemia.

A study found that 87% of the patients with ALL and high OPAL-1 achieved long-term remission, compared to only 32% of all patients studied. OPAL-1 also was highly predictive of a favorable outcome in T-cell ALL, and a similar trend was observed in infant ALL.

Low OPAL-1 was associated with induction failure, while high OPAL-1 was associated with long-term event free survival, particularly in males. 86% of ALL cases with t(12;21) and high OPAL-1 achieved long-term remission vs. only 35% of t(12;21) cases with low OPAL-1, suggesting that OPAL-1 may be useful in prospectively identifying children who may benefit from further intensification.

ANTICOAGULATION

ASH President Dr. Ronald Hoffman of the University of Illinois Medical Center said he doesn't see any real blockbusters on the horizon, but anticoagulants are one area he identified as exciting. He emphasized that AstraZeneca's Exanta (ximelagatran) is not the only promising agent in this category, "There are a whole new generation of oral antithrombin agents that will dramatically change things – and it is not just Exanta."

The properties of an ideal anticoagulant are:

- Effective in both venous and arterial disease.
- Safe – in terms of both bleeding and other adverse events.
- Wide therapeutic window – so there is no worry about close titration.
- Oral administration.
- Simple dosing.
- No lab monitoring necessary.
- Easily reversible.
- Inexpensive.

Properties to consider in evaluating a new anticoagulant:

- Direct or indirect action.
- Biologic or synthetic.
- Single or multiple targets.
- Reversible or irreversible.
- Oral or parenteral.
- Antigenicity.
- Duration of action – There are currently agents with a short half-life (half hour), but others are in development with a half-life of up to a week.
- Can it be reversed?

Approved Direct Thrombin Inhibitors (DTIs)

Measurement	Berlex's Refludan (lepirudin)	Texas Biotechnology's Novastan (argatraban)	The Medicine Company's Angiomax (bivalirudin)
Approved for	HIT	HIT	PCI
Administration	IV	IV	IV
Half-life	80 min.	45 min.	25 min.
Clearance	Renal	Hepatic	Renal and proteolysis
Thrombin inhibition	Slowly reversible	Reversible	Reversible; cleaved by thrombin

Anticoagulants in Development

Drug	Company	Status	Activity
DX-9065	Sanofi	Phase I	Factor Xa
Nematode anti-coagulant peptide (NAPc2)	N/A	Phase II	TF: VIIa
Oral heparin	Emisphere Technologies	Phase II	Two forms
Razaxaban	Bristol-Myers Squibb	Phase II	Oral Factor Xa
Repinotan	Bayer	Phase II	Oral Factor Xa
TFPI	Gallus Immunotech	Phase II	VIIa: Factor Xa
Thrombomodulin	N/A	Phase II	IIa; APC
Vasoflux	Vascular Therapeutics	Phase II	Modified: HCII
BIBR-1048	Boehringer Ingelheim	Phase II or III	Oral Factor Xa
Idraparinux	Organon	Phase III	Factor Xa (not oral)
MLNM-1021 and MLNM-2201	Millennium	Discontinued	Factor Xa

ASTRAZENECA'S Exanta (ximelagatran)

Although ASH's Dr. Hoffman said this is a promising agent, he warned that the liver toxicity data will need to be examined carefully. Liver toxicity is a key issue because the drug will be widely used if it is approved, he explained.

➢ **THRIVE Study for venous thromboembolism (VTE).** VTE is a sometimes fatal disease that affects an estimated 250,000 to two million Americans each year. THRIVE was a six-month, international, double-blind, double-dummy non-inferiority study of 2,489 patients comparing Exanta 36 mg BID to Aventis's Lovenox (enoxaparin) 1 mg/kg BID for a minimum of five days followed by warfarin (target INR 2.0-3.0).

6-Month THRIVE Results

Measurement	Enoxaparin or warfarin n=1249	Exanta n=1240	p-value
Primary endpoint: Recurrent VTE	2.0%	2.1%	Nss
Major bleeding	2.2%	1.3%	---
Mortality	3.4%	2.3%	---
Pre-specified combination of VTE and bleeding by ITT	3.2%	3.7%	Nss
Pre-specified combination of VTE and bleeding by ITT	1.5%	2.0%	Nss
All-cause mortality by ITT	3.4%	2.3%	.094
All-cause mortality by on-treatment analysis	.9%	.7%	Nss
ALT ≥3xULN (by ITT)	2.0%	9.6%	---
ALT normalization whether drug continued or stopped	23 patients	104 patients	---
Median time to normalization	18 days	74 days	---
Hepatobiliary serious adverse event	1 patient	6 patients	---
Hepatobiliary deaths	2 patients	3 patients	---
Patients with ALT >3xULN	76 patients	43 patients	---
Patients in whom ALT normalized	68 patients	36 patients	---
Returned of ALT <2xULN at last report	5 patients	5 patients	---
Death	1 patient	0	---

There were both ALT and bilirubin increases with Exanta, and an investigator said they warrant monitoring, but he pointed out that they haven't shown any clinical sequelae – yet. An investigator said, "The frequency of 9.6% is somewhat high…I'm not sure monitoring will be helpful, but it will probably be required (by the FDA)."

Enoxaparin is known to cause transient ALT elevations acutely, but in THRIVE the ALT levels were not measured acutely (in the first week or two), so there is no way to compare that. The investigator said, "We didn't monitor patients in the first week, so we might not have picked that up…(Historically), there is an occurrence of 4%-5% of transient elevations with enoxaparin, and they go away…The pattern with Exanta is different; the elevations start after the first month."

- *Asked how transient the liver elevations were with Exanta,* this investigator said, "The mean occurrence was about 70 days...but they come back to normal whether the drug is continued or not…When we initiated this study, we had no inkling of this problem…When the signal appeared, we had to go back and try to find patients, which made it difficult to get all this information."

- *Asked about his level of concern with these liver elevations,* the investigator said, "It is of concern…As a clinician, I am not particularly concerned if a patient has transient AST elevation…but I am concerned about the clinical meaning – whether patients get sick or there is some important clinical outcome from that…since the vast majority go back (to normal levels), it is very difficult to know if any patients got sick…There were patients who got jaundice, but it seemed nearly all of them had other causes – gallstones, etc… It means there will need to be some routine liver monitoring …and patients with pre-existing liver disease shouldn't get Exanta, maybe."

Reportedly, AstraZeneca is conducting studies to see if there are any genetic markers to determine which patients are likely to get elevated ALT. The investigator said a new trial might be able to determine the significance of these ALT elevations, "If another large trial is done, we could design it prospectively to monitor follow-up better than was done in THRIVE or in SPORTIF-III or SPORTIF-V. It was hard to follow patients in those trials, especially in eastern Europe."

➢ **EXULT-B Study for Prevention of Venous Thromboembolism in Total Knee Replacement (TKR).** Without any preventive medication, harmful blood clots occur in two-thirds of all TKR surgery patients. The results showed that Exanta given 24 hours after TKR surgery appeared to have increased efficacy (vs. warfarin) and similar safety, without the need for coagulation monitoring or dose adjustment.

EXULT-B was a 2,303-patient, randomized, double-blind, double-dummy Phase III trial comparing a fixed dose of Exanta (36 mg BID) and warfarin (target INR 2.5; range 1.8-3.0), administered for 7-12 days. Researchers reported no significant ALT elevations in this short-term trial.

Measurement	Warfarin n=967	Exanta n=982	p-value
Primary eEndpoint: Recurrent VTE and/or all-cause mortality	31.9%	22.5%	Nss

BRISTOL-MYERS SQUIBB'S razaxaban (DPC-906)

This direct-acting Factor Xa inhibitor was tested in prevention of DVT in TKR. Researchers reported on a 656-patient, Phase II, randomized, double-blind, five-arm, parallel group, dose-response study of razaxaban 25 mg BID vs. Lovenox 30 mg BID. Treatment with razaxaban started eight hours after surgery, and standard therapy was started 12-24 hours after surgery. Treatment was continued for 10 days, and then venography of both legs was performed to see whether clots had developed in the veins.

The principal investigator said, "This new oral agent interacts directly with Factor Xa, eliminating the need for antithrombin III, a common target in the coagulation pathway for most antithrombotic drugs. Razaxaban shows future promise as an additive drug and may help to reduce thrombosis in patients undergoing major orthopedic surgery…The 25 mg dose is very interesting, and we are writing protocols for further development. We are designing pivotal trials now, trying to coordinate with the various regulatory agencies…We have shown the drug is effective in knees, and I haven't seen any drug that works here and doesn't work elsewhere."

Phase II Razaxaban Trial

Measurement	Razaxaban 25 mg BID	Razaxaban 50 mg BID	Razaxaban 75 mg BID	Razaxaban 100 mg BID	Lovenox 30 mg BID
Primary endpoint: VTE during treatment	8.6%	6.0%	3.6%	1.4%	15.9%
Major bleeding	0.7%	4.1%	3.5%	5.8%	0
Status	Ongoing	STOPPED	STOPPED	STOPPED	Ongoing
ALT elevation	<10%	N/A	N/A	N/A	~10%

SANOFI'S Arixtra (fondaparinux)

This synthetic pentasaccharide is administered once daily by subcutaneous injection. It has been shown to be highly effective and only has activity against Factor Xa (all other heparins have other activities besides Factor Xa). A speaker said, "The thrombotic potential is very high in patients undergoing major orthopedic surgery, so that is a good test of efficacy, but it is a very risky setting…so it is a stringent test

of safety…This is more effective than LMWH in preventing thrombosis in these orthopedic patients."

Side Effect	Arixtra	Lovenox	p-value
Thrombosis	12.5%	27.8%	<.001
Bleeding	2.1%	0.2%	.006

Arixtra for the Treatment of Pulmonary Embolism

Measurement	Arixtra n=1,103	Heparin n=1,110	p-value
Primary endpoint: **New or recurrent symptomatic VTE within 3 months**			
Initial treatment	1.3%	1.7%	Nss
Entire study	3.8%	5.0%	Nss
Major bleeding			
Initial treatment	1.3%	1.1%	Nss
Entire study	2.0%	2.4%	Nss
Death			
Initial treatment	0.8%	1.1%	Nss
Entire study	N/A	N/A	---

ANTI-ANGIOGENESIS

There was a good deal of excitement at ASH over the expected approval in 2004 of Genentech's Avastin (bevacizumab). There also are a number of other angiogenesis inhibitors in clinical trials, but a speaker predicted that few of these would make it to market, commenting, "I would argue that many of the drugs will fail due to poor pharmacology. It is hard to determine the most biologically effective dose… Novel dose escalation strategies in Phase I trials have not worked. They have been problematic since dose-limiting toxicity is not observed with many angiogenesis inhibitors. But the concept of enrolling fewer patients and using more rapid dose escalation steps at non-toxic levels has gained wide acceptance. Currently, most angiogenesis inhibitor Phase I trials continue to use MTD as an endpoint, but within the context of biological and pharmacological data."

Among the agents in development are:

- Agouron (prinomastat, AG-3340)
- AstraZeneca's
  - ZD-6126
  - ZD-6474
- EntreMed's
  - Endostatin
  - Angiostatin
- Ixsys's vitaxin
- Magainin Pharmaceuticals' squalamine
- Novartis's PTK-787
- Pfizer's
  - SU-5416
  - SU-11248
  - SU-6668
- Sirna Therapeutics' Angiozyme

MEDICARE

An ASH fall 2004 member survey found:

- The greatest challenge to the practice of hematology is inadequate insurance reimbursement.
- Support for more lobbying of Congress related to reimbursement and non-insured people.

Hematologists and oncologists are very concerned that the new Medicare drug reimbursement schedule (AWP reform) will unfairly impact them. Dr. Hoffman was very, very worried about the impact of this legislation on hematologists/oncologists. He said it will reduce the number of doctors providing chemotherapy or entering the field, but he did not think doctors will drop out of Medicare, "It will have a major impact on the ability of people to deliver comprehensive cancer care to patients with very bad disease…It will change accessibility of care…It will probably alter the attractiveness to work in this area…and I think, in that sense, it will be a negative impetus."

At a session to discuss Medicare and AWP reform, many doctors vented, predicting the new regulations will put them out of business – or inconvenience patients by forcing them to get their chemotherapy infusions at a hospital. One said, "I think a lot of doctors will stop providing chemotherapy services." Another doctor said, "We aren't buying any drugs now, and we are referring patients to the hospital for expert care…That may not be convenient for them, but it is proper care." An Illinois doctor said, "I've already taken a day job, so I can keep my practice…People are quietly going under one by one or retiring. I think we should stop doing it quietly."

However, the impact really won't be felt in 2004; it will hit in 2005, 2006, and beyond. A speaker said, "In 2004, on the practice expense side, it would be about a 2.4%-2.6% increase…The problem is 2005. We won't know until late in the second quarter of 2004 or early in the third quarter of 2004 about pricing for 2005. There is no way to predict with accuracy what 2005 will be. A lot of us believe ASP will have numbers where drugs are not attainable by many practices at those numbers, but we won't know until we see those numbers…(But) there is a lot of discretion for Medicare to fix problems as they arise down the road…There is no need to tell people (doctors) to close their offices or to scare patients."

ASH and ASCO intend to lobby Congress and CMS to obtain the best possible reimbursement for oncologists/hematologists. An ASH official said, "We (hematologists) are a small portion

of Medicare, and Congress obviously thought it was politically expendable…If we start dropping Medicare, the person who loses the most is the patient…We should have our patients as allies when we go to Capitol Hill or the AMA…There are all kinds of technical issues that the administration could change, such as self-injection issues that have not been prominent." Another expert said, "The decreases start in 2005 and beyond…Patients have made this into an access issue, but it got to the point where Congress felt strongly they had to do something, and strategically, they thought this was the easier way to do it…There is a lot of room for technical work… and we need to go back to the legislation for amendments."

AWP Reform

The legislation lays out a pricing strategy, but a lot of details have not yet been worked out.

➢ In 2004, drugs will be reimbursed at 85% of AWP, down about 10% from where they currently are. The exceptions are clotting factors, new drugs as of 4-1-2003, vaccines, and drugs billed via ESRD; those will be paid at 95% of AWP. Blood and blood products will be paid at the 2003 rates. The floor is 80% of AWP – which affects BiogenIdec's Rituxan (rituximab), Aventis's Taxotere (docetaxel), Bristol-Myers Squibb's Paraplatin (carboplatin), Pfizer's Camptosar (irinotecan), Lilly's Gemzar (gemcitabine), Aventis's Anzemet (dolasetron), Amgen's Neupogen (filgrastim), Roche's Kytril (granisetron), GlaxoSmithKline's Navelbine (vinorelbine), and GlaxoSmithKline's Hycamtin (topotecan).

➢ In 2005, Medicare will move to 106% of ASP, which is defined as the price the manufacturer reports for total sales divided by total units sold non-government. Medicare can pay a lower amount if ASP is >5% greater than WAMP (widely available market price), the price a prudent physician would pay (that involves discounts in payments).

➢ In 2006, doctors have a choice of :

(a) 106% of ASP and stay in Medicare, or

(b) Use a competitive bidding program where drugs are obtained by a Medicare contractor. There will be at least two contractors competitively bidding in each area. The contractor purchases the drugs, collects the co-pays, and handles all billing of patients. The physician orders a drug with a prescription – for the entire course of therapy or a shorter period.

Medicare Physician Fee Schedule for 2004

A 4.5% reduction in all physician fees was scheduled, but Congress interceded, and there will now be a 1.5% increase in payments.

- Bone marrow aspiration – down 10.33%
- Bone marrow biopsy – down 8.98%
- Photophoresis – up 283.1%

Medicare Hospital Outpatient Prospective Payment System for 2004

Changes due to go into effect in 2004:

- Transfusion – down 4.7%
- Bone marrow biopsy – up 97.48%
- Blood product exchange – down 8.01%
- Chemotherapy administered by a technique other than infusion – up 7.91%
- Paclitaxel injection – down 7.15%
- Leuprolide suspension – down 8.83%
- Irinotecan injection – up 10.56%
- Gemcitabine – up 16.44%
- Herceptin (trastuzumab) – up 23.51%
- RBC leukocytes – down 10%

Medicare Payment for Drug Administration

In 2004:

- Practice expense RVUs will be increased, using data submitted by ASCO.
- Physician work value will be set for drug administration codes.
- A 32% transitional adjustment factor will be used. In 2005, there will be a 3% transitional fee, and this fee will disappear in 2006. Several studies have been mandated to see if this is an adequate payment over time.
- The current policy of one push administration per day will be reviewed to see if Medicare will allow more than one push per day.

SPECIFIC DRUGS

BIOGENIDEC'S Rituxan (rituximab)

ECOG-4494

As previously disclosed, this 632-patient study found that adding Rituxan to standard chemotherapy (CHOP – cyclophosphamide, doxorubicin, vincristine, and prednisone) does not significantly improve survival in older patients with diffuse large B-cell lymphoma, which accounts for about a third of lymphomas in patients age 60 or older. Median follow-up was 2.7 years.

Results of ECOG-4494

Measurement	R-CHOP n=318	CHOP alone n=314	p-value
Overall response	78%	77%	Nss
Progressive disease during treatment	6.5%	10.5%	N/A
TTF at 6 months	15%	17%	Nss

R-CHOP was administered as cyclophosphamide 750 mg/m2 IV Day 1; doxorubicin 50 mg/m^2 IV Day 1; vincristine 1.4 mg/m^2 (maximum dose=2) Day 1; prednisone 100 mg/m^2 Days 1-5; Rituxan 375 mg/m^2 Day 7, 3, and two days before cycles three, five, and seven. CHOP was given two cycles beyond complete remission, for a total of six to eight cycles. Researchers further randomized patients who achieved either complete or partial response to maintenance Rituxan at 375 mg/m^2 weekly for four weeks repeated every six months times four vs. observation.

Other Rituxan Trial Results

Disease	Trial	Therapy	Results	Notes
Front-line follicular lymphoma	ECOG-1496	CVP +/- Rituxan	Stopped early by DSMB for positive benefit with Rituxan	Data at ASCO 2004
LG NHL	---	CVP +/- Rituxan	TTF: 81% R-CVP vs. 57% CVP ORR: 40% R-CVP vs. 10% CVP	Researchers called this a "major clinical advance."
Naïve follicular NHL	---	CHOP +/- Rituxan	ORR: 97% R-CHOP vs. 93% CHOP CR: 21% R-CHOP vs. 18% CHOP TTF; not reached vs. 2.6 years	---
Front-line indolent NHL	---	R-CHOP	All patients responded. CR 58%, PR 42% At 9 years: median time to progression reached: 82.3 months	Remission on-going in half of patients
Relapsed LG NHL	---	Rituxan maintenance vs. scheduled re-treatment	ORR: 52% maintenance vs. 35% re-treatment at relapse CR: 27% maintenance vs. 4% PFS: 31% maintenance vs. 8%	The duration of response to Rituxan can be prolonged with either strategy.
CLL	CALGB-9712	Concurrent vs. sequential Rituxan +Fludarabine vs. historic control of Fludarabine alone (CALGB-9011)	PFS: 67% with Fludarabine+Rituxan vs. 45% with Fludarabine alone OS: 93% vs. 81%	F+R merits more investigation and has advantages over Rituxan alone.

In an unplanned, post-hoc analysis, researchers found that use of Rituxan as either induction or maintenance therapy had a TTF benefit. An investigator commented, "This implies the addition of Rituxan to CHOP benefits patients in that there is a significantly lesser chance they will progress, die, or go on to new, other treatments…There also was an improvement in overall survival in patients who received Rituxan – but that was unplanned analysis…At this time in the planned analysis, there is no difference in overall survival, but in the unplanned, weighted analysis there is a difference, with a p-value of .033." A BiogenIdec official said, "R-CHOP did not influence ORR over early TTF, but it did prolong TTF overall …Maintenance Rituxan significantly prolonged TTF in responders, with the advantage seen primarily after CHOP induction."

How does this compare to the French GELA study presented two years ago? An investigator said, "It (ECOG-4494) supports the observations of GELA and of the Vancouver experience. There were differences in the study design, but the relative risks of failure appear similar. But at six and 12 months the curves in this study did not separate as they did in the GELA study, which found an overall survival benefit of 47% with CHOP vs. 59% with R-CHOP.

Asked what this data means to American clinicians, an investigator said it is unlikely to change the way doctors here use Rituxan. He said the study mostly confirms what U.S. doctors already are doing – giving R-CHOP. He commented, "We feel Rituxan should be incorporated into CHOP therapy…At this time, the results don't show an advantage to induction or maintenance therapy; they both seem to be efficacious…Rituxan should be incorporated into therapy, and the study results don't show a distinct advantage as to how you give it – initially or in maintenance. The data suggest that patients should get Rituxan, and it doesn't matter when they get it, but it is likely that Rituxan will be adopted with CHOP in this country."

Thus, doctors in Europe, using the GELA model, will give 8 doses of Rituxan. If ECOG-4494 had confirmed a benefit to R-CHOP+maintenance Rituxan, doctors might have moved to 16 doses of Rituxan. With induction use only (R-CHOP), the investigator predicted that the average patient would get 4-5 doses of Rituxan.

CELGENE'S REVIMID (CC-5013)

Among the interesting news on this thalidomide analog (IMiD) was:

- Myelosuppression is dose and time dependent. At a 25 mg dose, everyone gets myelosuppression, at 10 mg 70%, and 20 mg for only 21 days <50%.
- Celgene is aiming for Revimid approval in late 2005 or 1Q06.

Phase I Revimid Trial Results

Revimid dose	Dana-Farber Cancer Institute		Arkansas Cancer Research Center	
	Number of patients responding	Number of responders	Number of patients responding	Number of responders
5 mg	3	1	3	0
25 mg	5	1	3	0
50 mg	5	3	3	1

- The Phase II trial of Revimid is enrolling faster than expected, according to a Celgene official. A change was made in dosing, allowing doctors to drop the dose from 10 mg to 5 mg. The official said, "I think the FDA will be okay with the range of dosing."
- A Phase II study found 30 mg QD dosing was less toxic and equally effective as 15 mg BID dosing.
- The Phase III trial, for which the FDA has granted a special protocol assessment (SPA), is enrolling slower, this official said.
- Studies are ongoing in patients who fail arsenic and then get either Thalomid (thalidomide) or Revimid. Reportedly, all patients have responded so far. Results should be available at ASH 2004.
- DVd-R –Doxil, vincristine, and dexamethasone plus Revimid – was described as a "grand slam" in relapsed or refractory multiple myeloma (MM).
- There is an indication of synergy with biologicals.
- Alternate day dosing appears to reduce toxicity.

Measurement	Daily dosing	Alternate day dosing
Grade 4 neutropenia	25%	15%
Grade 3 neutropenia	33%	30%
Grade 3 DVT	16%	0
MTD	2 mg	5 mg
Median duration of therapy	7 days	3 days
CR	17%	10%
Very good PR	29%	15%
PR	54%	35%
MR	66%	55%
Stable disease	96%	85%
Progressive disease	4%	10%

GENTA'S Genasense (oblimersen sodium)

A Genta-sponsored symposium reviewed the various potential uses for Genasense. A doctor in the audience who has not worked with Genasense had an interesting perspective on the drug. He said, "The science looks promising, but the question for the clinician now is that there are so many choices that it is difficult to know what to use. For example to treat multiple myeloma should we give dexamethasone, Velcade, or Genasense? It's confusing."

Some general comments that came from the question-and-answer session at the end of the symposium were interesting:

- Rash may indicate a clinical response to AstraZeneca's Iressa (gefitinib), but there is no correlation between the thrombocytopenia/neutropenia seen with Genasense and clinical activity.
- It is very important to pre-treat hematologic cancer patients with Genasense, not administer it concurrently with – or after – other chemotherapy agents. A speaker said, "We know by in vitro and in vivo experiments that Genasense is clearly sequence dependent...If you change the sequence and give them all together, we know that there is a marked difference in response vs. pre-treating (by one to two days) tumor cells with Genasense…If you reverse the sequence (and give Genasense last), the benefit of Genasense is clearly lost…So, there is a time dependent response, at least in the lab."
- The cause of the thrombocytopenia side effect in hematologic cancer patients is not known yet.

Melanoma

Genta started submitting Genasense to the FDA for melanoma in fall 2003, and a company official said the submission should be complete before the end of 2003. The pivotal, 771-patient, Phase III trial missed its primary endpoint, which was overall survival on an intent-to-treat (ITT) basis once 508 events (deaths) had been reached. A speaker tried to present the findings in a positive light emphasizing:

- Median survival was two months longer (10.1 months vs. 7.9 months) with Genasense in patients who were followed longer than one year.
- Genasense had a statistically significant benefit in terms of all three secondary endpoints: progression-free survival, time-to-progression, and tumor response.
- There was a bolus of patients (~200) who were enrolled late (from November 2002 - February 2003), so the complete picture of median survival at one year is not yet available. A researcher commented that it "is relatively likely" that the ITT overall survival will eventually be statistically significant once the data on these late-enrolling patients mature. He indicated the additional survival data should be available before the FDA makes a final decision on the approvability of Genasense for melanoma, and he believes the FDA will consider this

Phase III Genasense Melanoma Trial Results

Measurement	Genasense+ DTIC	DTIC	p-value
Primary endpoint: Median survival by ITT (n=771)	9.1 months	7.9 months	0.184
Secondary endpoint #1: Progression-free survival by ITT	78%	49%	0.0003
Time-to-progression by ITT	78%	49%	0.0003
Secondary endpoint #2: Overall anti-tumor response	11.7%	6.8%	0.0185
Durable anti-tumor response	3.4%	1.3%	N/A
Ongoing responses	6.0%	3.6%	N/A
Patients Followed >1 Year			
Median survival by ITT (n=520)	10.1 months	7.9 months	0.067
Median survival per protocol	10.1 months	8.1 months	0.035

data. He suggested that the approval of Iressa may make approval of Genasense easier.

Multiple Myeloma

A speaker discussed Genasense in multiple myeloma, noting that it has shown preclinical synergy with dexamethasone, doxorubicin, and Velcade (bortezomib). He noted that pre-treatment with Genasense increases a tumor cell's susceptibility to these other agents. However, he said there was "a trend" to a benefit with Genasense pre-treatment before Velcade, suggesting there was no statistically significant benefit. The completed Phase I/II and II Genasense trials in multiple myeloma were reviewed, but he did not give any data from the completed but not yet reported Phase III trial.

Non-Hodgkin's Lymphoma (NHL)

In NHL, a speaker concluded Genasense:

- Has ***modest*** single-agent activity.
- Can be safely combined with chemotherapy and with Rituxan.
- Has more side effects in NHL than in solid tumors "because NHL patients are more sensitive than solid tumor patients to Genasense."
- Has a lower MTD – 3 mg/kg/day vs. 7 mg/kg/day for solid tumors. In fact, in all hematologic malignancies – multiple myeloma, CLL, NHL, etc. – Genasense is much more toxic (more hypotension and fever) than in solid tumors.
- Is being tested in planned/ongoing combination studies, with RICE, R-CHOP, and Rituxan.

Chronic Lymphocytic Leukemia (CLL)

In CLL, Genasense was reported to:

- Have statistically significant synergy with Berlex's Campath (alemtuzumab), Velcade, and Rituxan.
- **Limited** single-agent activity.
- More side effects than with solid tumors (more hypotension and fever).
- Need to be dosed no higher than 3 mg/kg/day. This was the Phase III trial dose.
- Accrual is complete (241 patients) in the pivotal Phase III trial of fludarabine + cyclosphosphamide ± Genasense, but a company official said the trial has not reached its pre-specified "event point" yet, and would not comment on when it will be made public. A speaker said, "The data have been promised to us next year."

Competing Apoptosis-Based Therapies

Several other agents got a very brief review. A speaker commented, "We are still at a very early stage in most of these agents." These included:

- **TRAIL**
  - Genentech and Amgen's TRAIL(Apo2-Ligand). This tumor sensitizer is a member of the TNF family, and has been shown to be safe (no remarkable toxicity) in primates.
  - Human Genome Science's DR4 (death receptor 4) monoclonal antibody.
  - Sankyo's DR5 monoclonal antibody.
- **RXR-selective agonists (rexinoids).**
- **4-Hydroxy-Retinamide** (Johnson & Johnson's Fenretinide), a form of vitamin A.
- **Inserm's AHPN (CD437)** and AHPN analogs.
- **Glossypol**, a Chinese herbal medicine that induces bcl-2 apoptosis of tumor cell lines in vitro and has been tested in Phase I clinical trials. The mechanism of action is unknown.
- **Synthetic triterpenoids.**
- **IAP antagonists**. These sensitize tumor cells to chemotherapy and biologics (TRAIL), are well-tolerated in rodents, and have single-agent activity.
- **Gallium nitrate**. This NCI-investigational drug (NSC-15200) is ***not*** a heavy metal. It binds to transferring (Tf) and interferes with cellular iron utilization. So far, it has shown significant activity in lymphoma and bladder cancer and minor activity in small cell lung cancer. Doctors in the audience appeared very interested in this agent. A Phase IIb trial in NHL, started in 2002, is still ongoing. Side effects of gallium include reductions in :
  - Calcium that may require parenteral replacement.
  - Phosphate but rarely requiring replacement.
  - Magnesium, and replacement may be needed.
  - Carbon dioxide. Asymptomatic, transient, reportedly alkalosis may occur.
  - Hemoglobin. Anemia is generally mild-to-moderate.

SWOG Phase I Response Rates with Gallium

Type of NHL	% responding in Phase I SWOG Study	% responding in Phase I/II MSKCC Study
Diffuse histocytic	20%	40%
Diffuse poorly differentiated	33%	50%
Diffuse mixed	33%	---
Hodgkin's disease	14%	18%
Diffuse well-differentiated	0	---
Diffuse undifferentiated	0	---
Nodular poorly differentiated	0	40%
Nodular histocytic	0	---

Single Agent Gallium Nitrate Activity in Relapsed NHL

Drug	Responses (CR+PR)
Fludarabine	50%-60%
Rituxan	48%
Ifosamide	46%
Gallium nitrate	43%
2'CDA	43%
Methotrexate	41%
Doxorubicin	37%-65%
Ara-C (high dose)	28%
Cisplatin	26%

JOHNSON & JOHNSON'S ZARNESTRA (tipifarnib, RW-115777)

About 30% of AML patients are cured at five years with existing treatment, but some subgroups do particularly poorly, including the elderly. So, there is a lot of interest in compounds with fewer side effects and less toxicity. That's the hope with Zarnestra, an oral farnesyl transferase inhibitor (FTI). A Phase II Zarnestra trial has enrolled 103 patients to date, with a mean age of 74, and researchers plan to re-open the trial to accrue an additional 50-60 patients over age 75 with a previous diagnosis of MDS. The DLT in Phase I was neurotoxicity. A researcher said, "We want to increase the experience with this agent in worse of the worst…Initially, we achieved a CR of 21% which is in the range we would expect with standard chemotherapy, so we feel this response rate is significant and demonstrates the drug is active."

MILLENNIUM'S Velcade (bortezomib, PS-341)

Multiple Myeloma

When used in multiple myeloma, speakers at a Millennium-sponsored symposium indicated that Velcade is associated clinically with:

- 12% hypotension, and caution should be used when treating patients with a history of syncope.
- 43% overall incidence of thrombocytopenia, with 27% Grade 3 and 3% Grade 4. The discontinuation rate due to this side effect is 4%. Thrombocytopenia usually occurs during cycles 1-2 and is generally dose related. Levels tend to return to baseline during the rest period (days 12-21). Platelet transfusions usually are not required but are at the physician's discretion.
- 32% anemia.
- Rare (1.4%) tumor lysis syndrome (TLS). Generally, this has occurred soon after initiation of therapy. A speaker warned, "Patients with high tumor burden and rapidly progressing disease should be monitored carefully at the start of Velcade, with supportive care instituted promptly if metabolic abnormalities develop."
- 37% overall peripheral neuropathy, with 14% Grade 3 and 0% Grade 4. The discontinuation rate due to this side effect is 6%. However, >80% of multiple myeloma patients have signs of peripheral neuropathy at baseline. Symptoms may improve or return to baseline in some patients upon discontinuation of Velcade.

Velcade Side Effects

Grade	Action
Peripheral Neuropathy	
Grade 1	No action
Grade 1 with pain or Grade 2	Reduce Velcade dose from 1.3 mg/m^2 to 1.0 mg/m^2
Grade 2 with pain	Withhold drug until toxicity resolves, and then resume with lower dose (0.7 mg/m^2)
Thrombocytopenia	
Overall	43%

Preliminary data show that Velcade can be safely combined with standard chemotherapy agents with encouraging results and no increase in toxicity.

- **Doxorubicin** – The synergy is slightly greater if doxorubicin is present first.
- **Melphalan** – Responses were seen in patients who had relapsed from prior melphalan, even at the lowest melphalan dosing level.
- **Celgene's Thalomid** (thalidomide) – There has been no aggravation of pre-existing thalidomide-related neuropathy, and there is no apparent response difference with respect to thalidomide dose; patients with doses of thalidomide as low as 50 mg showed a response.
- **Johnson & Johnson's Doxil** (pegylated doxorubicin) – The same toxicities as seen with other agents (thrombocytopenia, neutropenia, weight loss, syncope, peripheral neuropathy, etc. The response rate is good and suggests that chemosensitization is occurring.

A speaker cautioned: "We've had several patients on and off study whose monoclonal protein has increased during first cycle but after six weeks of therapy had a response so I wouldn't recommend stopping Velcade after one cycle based on monoclonal protein levels."

What's the future for Velcade? More trials in combinations and in earlier disease. A speaker said a large, multicenter, Phase II trial should be done to see if the impressive activity seen to date can be reproduced. He also suggested that a Phase III trial may be necessary to determine which combinations are superior for patients with relapsed and/or refractory multiple myeloma. He added, "Some regimens may merit testing in the up-front setting where patients will have

less drug-resistant disease…A Phase II CALGB-10301 study will be starting soon, looking at the combination of Velcade and Doxil in patients with previously untreated multiple myeloma."

There also is likely to be a focus on finding which patients respond best to Velcade. A speaker said, "There is a great need for identification of prognostic factors that would predict response to certain regimens…One could already make the argument that, in patients with chromosome 13 abnormalities, either Velcade or Velcade-based combinations should be started early or even be standard of care."

Lymphoma

Velcade appears to work in several forms of lymphoma, but not all forms (not SLL or CLL). Data from a 28-patient Phase II trial of Velcade in lymphoma was recently reported, and it showed efficacy but substantial toxicity (similar to that seen in other hematologic malignancies) – thrombocytopenia (68% Grade 1, 48% Grade 2, 18% Grade 3), 4% motor neuropathy, 8% Grade 3 sensory neuropathy – plus a new side effect, 7% small vessel necrotizing vasculitis. In this trial, 35% of patients missed at least one dose.

Phase II Velcade Lymphoma Results

Type of lymphoma (evaluable patients)	Response
Follicular (8/12)	8 patients
Mantle cell (9/11)	9 patients had PR, with one lasting 19 months
SLL/CLL (3/3)	No response
Marginal zone (2/2)	1 patient

Chronic Lymphocytic Leukemia (CLL)

Are doctors using Velcade for CLL? ASH's Dr. Hoffman said, "Yes, and in B-cell lymphomas. Some doctors are using it for maintenance therapy, but we aren't doing that because we don't treat a large number of CLL patients."

♦