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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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OVERVIEW OF ACTIVITY

More than 45 pharmaceutical agents with more than 55 distinct FDA-approved indications are currently available for the management of the numerous types of hematologic cancer. This extensive armamentarium of therapeutic options poses a challenge to clinicians who must maintain up-to-date knowledge of optimal treatment algorithms for diverse tumor types. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of state-of-the-art clinical management strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Apply the results of emerging research to effectively integrate novel agents and regimens into the management of follicular lymphoma.
- Recall early mortality in acute promyelocytic leukemia (APL), and formulate optimal management strategies for APL.
- Identify patients at high risk for tumor lysis syndrome (TLS), and incorporate recent research data into the prevention and management of TLS.
- Integrate innovative combination regimens into the management of multiple myeloma (MM), considering the benefits and risks of proteasome inhibitors and immunomodulatory agents.
- Evaluate maintenance therapy approaches for patients with MM.
- Optimize the management of myelodysplastic syndromes through rational integration of prospective and retrospective data.
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate.

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INTERVIEW

Mathias J Rummel, MD, PhD

Prof Rummel is Head of the Department of Hematology at the Hospital of the Justus-Liebig University in Gießen, Germany.

Tracks 1-17

Track 1 Phase III trial comparing bendamustine/rituximab (BR) to R-CHOP in the indolent lymphomas, including follicular lymphoma (FL), and in mantle-cell lymphoma (MCL)

Track 2 Toxicity comparison of BR to R-CHOP

Track 3 Tolerability and dosing of bendamustine for elderly patients and those with renal insufficiency

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Track 17 Ibritumomab consolidation after initial induction therapy in FL

Select Excerpts from the Interview

Tracks 1-2, 5

DR LOVE: Would you review your Phase III trial in indolent lymphoma evaluating bendamustine/rituximab (BR) versus R-CHOP?

PROF RUMMEL: The Study group indolent Lymphomas (StiL) designed a pivotal Phase III trial comparing BR to R-CHOP. Compared to R-CHOP, BR demonstrated much lower toxicity and better efficacy (Rummel 2009; [1.1]).

1.1

Efficacy and Safety of BR versus R-CHOP as Initial Therapy for FL, Indolent Lymphomas and MCL

	BR (n = 260)	R-CHOP (n = 253)	*p*-value
Overall response	92.7%	91.3%	—
Complete response	39.6%	30.0%	0.0262
Progression-free survival	54.9 months	34.8 months	0.00012
Grade III/IV neutropenia (% of cycles)	10.7%	46.5%	<0.0001
Infectious complications	36.9%	50.2%	0.0025
Peripheral neuropathy	6.9%	28.8%	<0.0001
Stomatitis	6.2%	18.6%	<0.0001
Allergic reaction (skin)	15.4%	5.9%	0.0003

Rummel MJ et al. Presentation. *Proc ASH* 2009;**Abstract 405**.

Tracks 3, 6, 12

DR LOVE: What about BR in elderly patients?

PROF RUMMEL: A Phase II study of BR for an elderly patient population (over age 75) (Rummel 2008; [1.2]) demonstrated good efficacy and acceptable toxicity. For patients with renal insufficiency, bendamustine is one of the best recommendations.

DR LOVE: Would you discuss the additional data you presented from the BR/R-CHOP study at the ASCO/ASH Joint Session?

PROF RUMMEL: A separate efficacy analysis for each of the subpopulations with FL, marginal zone lymphoma (MZL), Waldenström macroglobulinemia (WM) and MCL was presented. Among patients in each of the FL (Rummel 2010; [1.3]), WM and MCL subpopulations, progression-free survival is significantly improved with BR.

DR LOVE: Does BR have an impact on stem cell collection?

PROF RUMMEL: The ability to mobilize stem cells in patients receiving this regimen has been examined (Burchardt 2009), and we have evidence that it is indeed possible to mobilize stem cells after a patient has received BR.

1.2

Phase II Study of BR for Elderly Patients (Over Age 75) with Indolent Lymphomas or Mantle-Cell Lymphoma (n = 26)

Median age	Overall response	Complete response
79 years	88%	35%

Rummel MJ et al. *Proc ASCO* 2008;**Abstract 8572**.

1.3

Efficacy of BR versus R-CHOP in the FL Subpopulation (n = 279)

	BR	R-CHOP	Hazard ratio	*p*-value
Progression-free survival (months)	Not reached	46.7	0.63	0.0281

Rummel MJ et al. Presentation. *Proc ASH* 2009;**Abstract 405**.

Track 9

DR LOVE: Could you discuss the research your group is doing on bortezomib in indolent lymphomas?

PROF RUMMEL: A Phase II trial with single-agent bortezomib demonstrated that bortezomib has modest activity as a single agent and has the potential to be combined with other agents for low-grade lymphomas (Di Bella 2010; [1.4]).

A Phase II study with a combination of bortezomib, bendamustine and rituximab (VBR) has been presented (Fowler 2009; [1.5]) and has shown that the combination is feasible with promising results.

In view of this, StiL is planning to initiate a large, randomized Phase III study comparing BR to VBR in relapsed FL, MZL and WM. This study will evaluate the benefit of bortezomib added to BR. A similar Phase III Austrian study is being conducted in MCL.

1.4

Efficacy of Single-Agent Bortezomib in a Phase II Study in Relapsed or Refractory Indolent Lymphomas*

Overall response	Stable disease	Median time to response	Median duration of response	Median survival	Median progression-free survival
13.3%	64.2%	2.2 months	7.9 months	27.7 months	5.1 months

* n = 53 of 59 evaluable patients who completed more than two cycles

Di Bella N et al. *Blood* 2010;115(3):475–80.

1.5

Phase II VERTICAL Study: Efficacy and Safety of Bortezomib/Bendamustine/Rituximab in Relapsed or Refractory Follicular Lymphoma*

Overall response	Complete response	Partial response	≥Grade III peripheral neuropathy
86%	53%	34%	10%

* n = 59 of 63 patients with at least one postbaseline response assessment

Fowler N et al. *Proc ASH* 2009;**Abstract 933**.

Track 14

DR LOVE: What are your thoughts on rituximab maintenance in FL?

PROF RUMMEL: The Phase III PRIMA study evaluating maintenance rituximab after initial rituximab/chemotherapy induction in FL has now been presented (Salles 2010; [1.6]). More than 1,000 patients were randomly assigned to maintenance therapy with rituximab — one dose every two months for two years — or observation.

The magnitude of difference in progression-free survival was clinically relevant and much higher than I had anticipated, primarily because a good progression-free survival is achieved with rituximab/chemotherapy induction alone.

Slightly more side effects occurred with rituximab maintenance than on the observation arm (Salles 2010; [1.7]). The infection rate is slightly higher and a few more cytopenias occur. However, the progression-free survival clearly favors the rituximab maintenance arm, and the higher incidence of cytopenias and infections did not affect the progression-free survival benefit.

1.6

Phase III PRIMA Study: Efficacy Results with Rituximab Maintenance in Previously Untreated FL

	Observation (n = 513)	Rituximab maintenance (n = 505)	Hazard ratio	*p*-value
Two-year PFS	66%	82%	0.50	<0.0001

PFS = progression-free survival

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

1.7

Phase III PRIMA Study: Safety Events

	Observation (n = 508)	Rituximab maintenance (n = 501)
Grade III/IV infections	<1%	4%
Grade ≥II infections	22%	37%
Grade III/IV neutropenia	<1%	4%

Salles GA et al. *Proc ASCO* 2010;**Abstract 8004**.

Track 13

DR LOVE: What about duration of rituximab maintenance and maintenance after initial induction with BR?

PROF RUMMEL: We are addressing these questions in a StiL-sponsored study in Germany. Patients initially receive BR as up-front therapy and are then randomly assigned to either two or four years of rituximab maintenance (1.8). ■

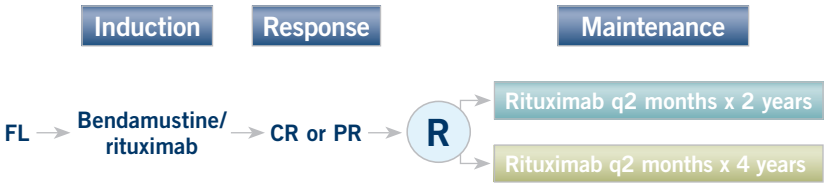
1.8

StiL MAINTAIN Phase III Study: Significance of Duration of Maintenance Therapy with Rituximab in Non-Hodgkin's Lymphoma

Protocol ID: StiL NHL 7-2008 **Target Accrual:** 874

Eligibility

- FL, immunocytoma, CLL without leukemic hemogram, marginal zone lymphoma or MCL
- No prior systemic therapy



FL = follicular lymphoma; CLL = chronic lymphocytic leukemia; MCL = mantle-cell lymphoma; CR = complete response; PR = partial response

www.clinicaltrials.gov. Accessed September 10, 2010.

SELECT PUBLICATIONS

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

Di Bella N et al. **Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma.** *Blood* 2010;115(3):475-80.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL study.** *Proc ASH* 2009;**Abstract 933**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL.** Presentation. ASCO/ASH Joint Session 2010. No abstract available

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Rummel MJ et al. **Efficacy and safety of bendamustine and rituximab in the treatment of indolent and mantle cell lymphomas in older patients.** *Proc ASCO* 2008;**Abstract 8572**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.

INTERVIEW

Antonio Palumbo, MD

Dr Palumbo is Chief of the Myeloma Unit in the Division of Hematology at the University of Torino in Torino, Italy.

Tracks 1-15

Track 1 Perspective on dosing of systemic agents for elderly patients with multiple myeloma (MM)

Track 2 Personalized induction therapy for elderly patients with MM

Track 3 Inclusion of lenalidomide in induction therapy for elderly patients with MM

Track 4 Maintenance lenalidomide after transplant in MM

Track 5 Incorporating bortezomib after transplant in MM with high-risk cytogenetics

Track 6 Maintenance lenalidomide after bortezomib-based induction therapy in MM

Track 7 Status of autologous transplantation for elderly patients (older than age 75) with MM

Track 8 Approach to the care of elderly patients (older than age 75) with MM using an up-front reduction in dose intensity

Track 9 Management of bortezomib-associated neuropathy with patient education, weekly dosing and dose-reduction protocols

Track 10 Maintenance lenalidomide for MM in the nontransplant setting

Track 11 Perspective on the choice of induction therapy prior to transplant in MM

Track 12 Long duration of remission with a four-drug induction regimen followed by bortezomib-based maintenance therapy for elderly patients with MM

Track 13 Effect of zoledronic acid on survival outcome in MM

Track 14 Efficacy and safety of VMPT induction therapy followed by maintenance bortezomib/thalidomide for elderly patients with MM

Track 15 New investigational agents in myeloma: pomalidomide, carfilzomib, vorinostat and panobinostat

Select Excerpts from the Interview

Track 4

DR LOVE: What are your thoughts regarding the new data presented at ASCO on maintenance lenalidomide for patients with MM after transplant?

DR PALUMBO: Unprecedented data were presented by two cooperative groups at ASCO 2010 (Attal 2010; [2.1]; McCarthy 2010; [2.2]) with lenalidomide maintenance therapy after autologous transplant in patients with MM.

Both studies showed that maintenance lenalidomide clearly provides clinical benefit by reducing the risk of progression by more than 50 percent. Additionally, the benefit occurs among all patients, not only those who achieve a partial response with transplant.

Maintenance therapy should be administered to all patients, independent of the response status after transplant.

2.1

Efficacy of Lenalidomide Maintenance After Transplant in Patients with Myeloma

	Placebo maintenance (n = 307)	Lenalidomide maintenance (n = 307)	Hazard ratio	*p*-value
Disease progression or death	143 (47%)	77 (25%)	—	—
Median progression-free survival (PFS)	24 months	Not reached	Not reported	$<10^{-7}$
Three-year postrandomization PFS	34%	68%	0.46	$<10^{-7}$

Attal M et al. *Proc ASCO* 2010;**Abstract 8018**.

2.2

CALGB-100104: Lenalidomide Maintenance versus Placebo After Transplant for Patients with Myeloma

	Placebo maintenance (n = 208)	Lenalidomide maintenance (n = 210)	Hazard ratio	*p*-value
Progression or death	58 (27.9%)	29 (13.8%)	0.42	<0.0001
Median time to progression	25.5 months	Not reached	Not reported	<0.0001

McCarthy P et al. *Proc ASCO* 2010;**Abstract 8017**.

Tracks 9-10

DR LOVE: What about lenalidomide maintenance for those patients with MM who are not eligible for transplant?

DR PALUMBO: Data on melphalan/prednisone with lenalidomide (MPR) followed by maintenance lenalidomide (MPR-R) have been presented (Palumbo 2009a; [2.3]), and this approach is clearly superior to melphalan/prednisone (MP) alone with a more than 50 percent reduced risk of disease progression.

In my view, maintenance therapy with lenalidomide is essential because it is providing more than 70 percent of this reduced risk of progression.

2.3

Response Rates and Progression-Free Survival (PFS) in a Phase III Study Evaluating MP versus MPR versus MPR-R for Elderly Patients with MM

Efficacy	MPR-R (n = 152)	MPR (n = 153)	MP (n = 154)	*p*-value (MPR-R vs MP)
Overall response rate[1]	77%	67%	49%	<0.001
CR rate[2]	18%	13%	5%	<0.001
≥VGPR rate[3]	32%	33%	11%	<0.001
PR rate	45%	34%	37%	—
Median PFS	Not reached	13.2 months	13.0 months	<0.001 (HR = 0.499)

[1] As measured using EBMT criteria (Blade 1998); [2] Immunofixation-negative with or without bone marrow confirmation; [3] VGPR: >90% reduction in M-protein. CR = complete response; VGPR = very good partial response; PR = partial response

Palumbo A et al. Presentation. ASH 2009a;**Abstract 613**; Blade J et al. *Br J Haematol* 1998;102(5):1115-23.

DR LOVE: Would you review your work on bortezomib-associated neuropathy, especially as it relates to the schedule of administration (Palumbo 2009b; [2.4])?

DR PALUMBO: Clearly no lack of efficacy was observed with a weekly bortezomib schedule versus a twice-weekly schedule in bortezomib/melphalan/prednisone (VMP) with or without thalidomide in terms of progression-free survival. Among elderly patients, the weekly schedule is now becoming the standard because higher-grade peripheral neuropathy is significantly reduced — from 14 to 18 percent with the twice-weekly schedule to two to four percent with the weekly schedule.

In addition to weekly scheduling, other issues to recognize are patients' education regarding the potential occurrence of neuropathy and bortezomib dose

2.4

Efficacy and Toxicity According to Bortezomib Infusion Schedule in a Phase III Study of VMPT versus VMP for Newly Diagnosed MM

	VMPT		VMP	
	Twice weekly (n = 71)	Weekly (n = 150)	Twice weekly (n = 64)	Weekly (n = 165)
Complete response	38%	32%	27%	20%
Grade III/IV peripheral neuropathy (PN)	18%	2%	14%	2%
Dose reduction due to PN	42%	11%	35%	13%
Discontinuation due to PN	10%	3%	15%	4%

Twenty-five patients receiving VMPT and 19 patients receiving VMP received both twice- and once-weekly bortezomib. V = bortezomib; M = melphalan; P = prednisone; T = thalidomide

Palumbo AP et al. *Proc ASCO* 2009b;**Abstract 8515**.

reduction, as needed. Bortezomib dose reduction to 50 percent should be considered when restarting after interruption for severe peripheral neuropathy.

Tracks 12, 14

DR LOVE: Would you discuss your trial of the four-drug regimen bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by maintenance bortezomib/thalidomide (VT) for elderly patients with myeloma?

DR PALUMBO: This is an important study and showed that the four-drug combination VMPT followed by VT maintenance therapy is superior to VMP for progression-free survival (Palumbo 2010; [2.5]). The current standard three-drug regimens, such as MPR, melphalan, prednisone and bortezomib (MPV) and melphalan, prednisone and thalidomide (MPT), result in progression-free survival of approximately two years. With this background, the progression-free survival with VMPT followed by VT is clearly unprecedented and is increasing the remission duration by around one year. ■

2.5

Phase III Trial Comparing VMPT → VT to VMP Followed by Observation for Elderly Patients with MM

	VMPT → VT	VMP	*p*-value
CR	38%	24%	0.0008
≥VGPR	59%	50%	0.03
≥PR	89%	81%	0.01
Three-year PFS	54%	40%	0.006

CR = complete response; VGPR = very good partial response; PR = partial response; PFS = progression-free survival

Palumbo AP et al. Presentation. ASCO 2010;**Abstract 8013**.

SELECT PUBLICATIONS

Attal M et al. **Lenalidomide maintenance after transplantation for myeloma.** *Proc ASCO* 2010;**Abstract 8018**.

Blade J et al. **Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant.** *Br J Haematol* 1998;102(5):1115-23.

McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104.** *Proc ASCO* 2010;**Abstract 8017**.

Palumbo A et al. **A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma.** Presentation. ASH 2009a;**Abstract 613**.

Palumbo AP et al. **A phase III study of VMPT versus VMP in newly diagnosed elderly myeloma patients.** *Proc ASCO* 2009b;**Abstract 8515**.

INTERVIEW

Mikkael A Sekeres, MD, MS

Dr Sekeres is Associate Professor of Medicine and Director of the Leukemia Program at Taussig Cancer Institute's Department of Hematologic Oncology and Blood Disorders in Cleveland, Ohio.

Tracks 1-15

Track 1 Management of lower-risk myelodysplastic syndromes (MDS) with isolated anemia

Track 2 Hypomethylating agents in lower-risk MDS

Track 3 Therapeutic options for elderly patients with acute myelogenous leukemia

Track 4 **Case discussion:** A 30-year-old woman is diagnosed with acute promyelocytic leukemia (APL) after experiencing refractory bleeding in the postpartum setting

Track 5 DIC-related mortality and urgent ATRA initiation with suspected APL diagnosis

Track 6 Incorporation of arsenic trioxide into the front-line management of APL

Track 7 Rasburicase for the prevention and treatment of tumor lysis syndrome

Track 8 Significance of classifying MDS as precancer versus cancer

Track 9 AVIDA: Prospective observational registry of patients with MDS receiving azacitidine

Track 10 Outcome with subcutaneous versus intravenous azacitidine administration in MDS

Track 11 Effect of schedule on the efficacy of azacitidine in MDS

Track 12 Duration of azacitidine therapy in MDS

Track 13 Investigating azacitidine with lenalidomide or HDAC inhibitors in the front-line treatment of MDS

Track 14 Efficacy of lenalidomide in del(5q) MDS

Track 15 Potential biomarkers for lenalidomide/azacitidine in MDS

Select Excerpts from the Interview

Tracks 9-11

DR LOVE: Would you describe your findings from the AVIDA registry evaluating the use of 5-azacitidine in MDS?

DR SEKERES: AVIDA is a prospective, longitudinal, multicenter registry that collects data from community-based hematology-oncology clinics in the United States on patients with MDS treated with 5-azacitidine. Currently it has enrolled nearly 500 patients, and we presented data at ASH 2009 on 331 patients.

Treating physicians made the decision to administer 5-azacitidine and also chose the route and the regimen. Approximately 17 percent of patients received the FDA-approved seven-day continuous regimen. Most patients either received 5-azacitidine on fewer than seven days in a cycle or on seven days with breaks in between (Sekeres 2009; [3.1]).

Examining the route of administration in the database, we found that about half of the patients received 5-azacitidine by the subcutaneous route and the other half received it intravenously. Rates of hematologic improvement are similar whether 5-azacitidine is administered by subcutaneous or by intravenous dosing (Sekeres 2009; [3.2]).

3.1

AVIDA: Use of Different 5-Azacitidine Regimens in the Community Setting

	FDA-approved seven-day continuous regimen	Seven days with breaks	Less than seven days	Greater than seven days
Overall population[1] n = 217	17.5%	29.0%	52.1%	1.4%
Lower risk[1] n = 150	14.0%	27.3%	58.0%	0.7%
Higher risk[1] n = 67	25.4%	32.8%	38.8%	3.0%

[1] 114 patients with missing IPSS or dosing information were excluded from this analysis.

Sekeres MA et al. *Proc ASH* 2009;**Abstract 3797**.

3.2

AVIDA: Hematologic Improvement (HI) by Route of 5-Azacitidine Administration

	All patients receiving 5-azacitidine (n = 319)[1]	Intravenous 5-azacitidine (n = 181)[1]	Subcutaneous 5-azacitidine (n = 138)[1]
Any HI	24.4%	24.1%	24.8%
HI-E[2]	10.4%	10.3%	10.3%
HI-P[2]	25.6%	23.0%	29.2%
HI-N[2]	19.8%	19.0%	21.2%

[1] Patients on the study fewer than 56 days were excluded from HI measurements.
[2] Individual cell-line denominators E, P and N include only patients eligible for the improvement in that line.

Sekeres MA et al. *Proc ASH* 2009;**Abstract 3797**.

Track 14

DR LOVE: What do we know about lenalidomide in MDS with chromosome 5q deletion?

DR SEKERES: The pivotal Phase II study (List 2006; [3.3]) produced high rates of transfusion independence and complete cytogenetic response. The median duration of transfusion independence has been reported to be as high as 2.2 years.

3.3

Lenalidomide in MDS with the Chromosome 5q Deletion

Transfusion independence	Complete cytogenetic response	Partial cytogenetic response
67%	45%	38%

List A et al. *N Engl J Med* 2006;355(14):1456–65.

Track 6

DR LOVE: How do you approach the initial management of APL?

DR SEKERES: Our approach at Cleveland Clinic is to follow the Intergroup C9710 protocol evaluating arsenic trioxide consolidation, as results from that study showed a survival benefit with arsenic trioxide as initial postremission therapy for patients with newly diagnosed APL (Powell 2010; [3.4]).

I think arsenic trioxide is an active agent in APL, and for an older person who cannot tolerate chemotherapy/ATRA/arsenic combinations, I would consider administering ATRA or arsenic trioxide alone in the up-front setting. ■

3.4

Consolidation with Arsenic Trioxide (As_2O_3) in Newly Diagnosed APL Following Standard Induction with Tretinoin, Cytarabine and Daunorubicin

	As_2O_3 consolidation x 2 cycles	No As_2O_3 consolidation	*p*-value
Three-year EFS	80%	63%	<0.0001
Three-year DFS	90%	70%	<0.0001
Three-year OS	86%	81%	0.059

EFS = event-free survival; DFS = disease-free survival; OS = overall survival

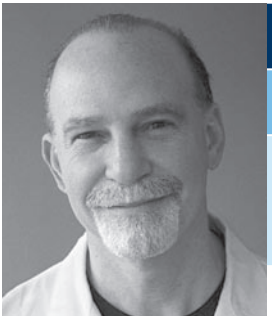
Powell BL et al. *Blood* 2010;[Epub ahead of print].

SELECT PUBLICATIONS

List A et al. **Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion.** *N Engl J Med* 2006;355(14):1456–65.

Powell BL et al. **Arsenic trioxide improves event-free and over-all survival for adults with acute promyelocytic leukemia: North American Leukemia Intergroup Study C9710.** *Blood* 2010;[Epub ahead of print].

Sekeres MA et al. **A study comparing dosing regimens and efficacy of subcutaneous to intravenous azacitidine for the treatment of myelodysplastic syndromes (MDS).** *Proc ASH* 2009;**Abstract 3797**.



INTERVIEW

Steven T Rosen, MD

Dr Rosen is Genevieve Teuton Professor of Medicine and Director of the Robert H Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois.

Tracks 1-10

Track 1	Classification and spectrum of T-cell lymphomas
Track 2	Pralatrexate: A novel antifolate agent with activity in T-cell lymphomas
Track 3	HDAC inhibitors depsipeptide and vorinostat in T-cell lymphomas
Track 4	Role of denileukin diftitox in T-cell lymphomas
Track 5	Efficacy and safety of bexarotene in cutaneous T-cell lymphomas
Track 6	Common side effects of pralatrexate, depsipeptide and denileukin diftitox
Track 7	Treatment algorithm in the management of T-cell lymphomas
Track 8	**Case discussion:** A 60-year-old man with Sézary syndrome remains in complete response for four years with matched sibling miniallogeneic transplant after a relapsing-remitting course over 10 years
Track 9	**Case discussion:** A 65-year-old man with systemic cytotoxic T-cell lymphoma is in complete response for two years after receiving combination chemotherapy
Track 10	**Case discussion:** A 75-year-old man with mycosis fungoides achieves a partial response with single-agent pralatrexate after a relapsing-remitting course over nine years with multiple therapeutic regimens

Select Excerpts from the Interview

Tracks 2, 6

DR LOVE: Would you discuss what we know about the efficacy and safety of pralatrexate in T-cell lymphomas (Savage 2009; [4.1]; Shustov 2010; [4.2])?

DR ROSEN: Within the past few months, two new agents have been approved for the treatment of T-cell lymphomas. Although these agents do not have a novel mechanism of action, they do have a novel level of activity. Pralatrexate is an antifolate agent and has a higher affinity for the folate carrier compared to methotrexate. It also appears to be more potent than methotrexate in vitro.

According to data from the original trials, pralatrexate was effective in patients who were unresponsive to methotrexate and in those with only brief responses to methotrexate.

Regarding the adverse events, thrombocytopenia and mucositis have been reported with the administration of pralatrexate. The use of folic acid and vitamin B_{12} appear to reduce this complication.

4.1

Treatment Response to Pralatrexate in Patients with Peripheral T-Cell Lymphomas and No Evidence of Response to Most Recent Prior Therapy (n = 69)

Overall response	Median response duration	Median number of therapies
25%	99 days	3

Savage K et al. *Proc ASH* 2009;**Abstract 1678**.

4.2

Relationship between Response and Survival in Patients with Peripheral T-Cell Lymphoma Treated with Pralatrexate (n = 109)

Overall response*	Reduction in risk of death for responding patients	Hazard ratio	*p*-value
29%	44%	0.56	0.07

* By independent central review using International Workshop Criteria

Shustov AR et al. *Proc ASCO* 2010;**Abstract 8054**.

Tracks 3, 6

DR LOVE: What about the other new agent, romidepsin? Would you discuss the novel histone deacetylase (HDAC) inhibitors in T-cell lymphomas and the data recently presented at ASCO (Kim 2010; [4.3])?

DR ROSEN: Romidepsin — formerly called depsipeptide — is another new drug and is classified as an HDAC inhibitor. Vorinostat, an orally administered agent, is another HDAC inhibitor that was approved earlier for mycosis fungoides and Sézary syndrome. Romidepsin is administered intravenously, and associated adverse effects include fatigue, malaise, nausea and transient

4.3

Romidepsin Activity in All Three Disease Compartments (Skin, Blood and Lymph Nodes) in Patients with Cutaneous T-Cell Lymphoma

Overall response by composite endpoint[1]	≥50% skin response	≥50% reduction in Sézary cells	≥30% reduction by RECIST
33/96 (34%)	38/96 (40%)	10/13 (77%)	13/37 (35%)

[1] Composite endpoint defines complete response as total resolution of skin disease, no abnormal lymph nodes and no circulating Sézary cells. A partial response is 50 percent or greater improvement in the sum of the three assessments with at least a 30 percent reduction in skin disease.

Kim E et al. *Proc ASCO* 2010;**Abstract 8047**.

cytopenias. Some concern surrounds potential cardiac toxicity due to QT prolongation, but this has not been a major problem during the clinical trials for patients with lymphoma.

Tracks 4, 6

DR LOVE: Which other agents have been used for the treatment of T-cell lymphomas, and how do they compare to some of the newer ones?

DR ROSEN: Another agent is denileukin diftitox, a recombinant protein comprising interleukin-2 and diphtheria toxin. It affects protein synthesis using the diphtheria toxin, and approximately one third of the patients who receive this agent seem to respond.

Of note, the response rates do not differ dramatically according to the expression of CD25, which is one of the three peptides that make up the interleukin-2 receptor. Patients who express the other two peptides still experience favorable benefits from this treatment.

The major problem associated with denileukin diftitox is peripheral edema because of a vascular leak syndrome that can occur. Other problems can include transient liver enzyme abnormalities, fatigue and malaise. When steroids are administered concurrently, these symptoms are ameliorated.

Track 5

DR LOVE: What is the role of bexarotene for the treatment of T-cell lymphomas?

DR ROSEN: Bexarotene, an oral agent, is effective. It is associated with higher response rates than other agents we've discussed, although a direct comparison has not been made. Bexarotene is extremely well tolerated, but two issues must be addressed during treatment. One issue is fairly simple: Patients develop central hypothyroidism, which requires the use of levothyroxine. The second issue, hyperlipidemia, can consist of elevations in both triglyceride and cholesterol levels, and it can be significant. ■

SELECT PUBLICATIONS

Horwitz SM et al. **Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial.** *Proc ASH* 2009;**Abstract 919**.

Kim E et al. **Romidepsin activity in all three disease compartments (skin, blood, lymph nodes) in patients with cutaneous T-cell lymphoma (CTCL).** *Proc ASCO* 2010;**Abstract 8047**.

Piekarz R et al. **Final results of a phase 2 NCI multicenter study of romidepsin in patients with relapsed peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2009;**Abstract 1657**.

Savage K et al. **Pralatrexate induces responses in patients with highly refractory peripheral T-cell lymphoma (PTCL).** *Proc ASH* 2009;**Abstract 1678**.

Shustov AR et al. **Pralatrexate in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL): Relationship between response and survival.** *Proc ASCO* 2010;**Abstract 8054**.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In the Phase III trial comparing BR to R-CHOP in the up-front treatment of FL, indolent lymphomas and MCL, which of the following was improved with BR?**
   a. Progression-free survival
   b. Complete response rate
   c. Both a and b

2. **Which of the following has been shown in the PRIMA trial with maintenance rituximab in FL?**
   a. Improvement in progression-free survival
   b. Improvement in overall survival
   c. Both a and b
   d. None of the above

3. **The reported hazard ratio with maintenance rituximab in the PRIMA trial is 0.5.**
   a. True
   b. False

4. **What is the overall response rate reported by Rummel and colleagues at ASCO 2008 with BR in elderly patients with indolent lymphomas?**
   a. 28 percent
   b. 48 percent
   c. 68 percent
   d. 88 percent

5. **Which of the following improvements has been shown in MM with lenalidomide maintenance in the post-transplant setting?**
   a. Improvement in progression-free survival
   b. Improvement in overall survival
   c. Both a and b
   d. None of the above

6. **An assessment of a small number of patients indicated that mobilizing stem cells after a patient has received BR is _____.**
   a. Possible, with results similar to post-R-CHOP mobilization
   b. Not possible

7. **Incorporating arsenic trioxide as initial consolidation therapy in the Intergroup C9710 protocol resulted in a statistically significant improvement in _____.**
   a. Disease-free survival
   b. Event-free survival
   c. Both a and b

8. **Which of the following correctly defines the scope of the AVIDA registry?**
   a. Registry of patients with MDS treated with either 5-azacitidine or decitabine in the community practice setting
   b. Registry of patients with MDS treated with decitabine in the community practice setting
   c. Registry of patients with MDS treated with 5-azacitidine in the community practice setting

9. **In the AVIDA registry, 17.5 percent of patients with MDS were found to have received the FDA-approved continuous seven-day 5-azacitidine regimen.**
   a. True
   b. False

10. **The use of bexarotene has been associated with the development of _____.**
    a. Hypothyroidism
    b. Hyperlipidemia
    c. Both a and b
    d. None of the above

Post-test answer key: 1a, 2a, 3a, 4d, 5a, 6a, 7c, 8c, 9a, 10c

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Phase III trial of BR versus R-CHOP in low-grade lymphomas	4 3 2 1	4 3 2 1
PRIMA trial: Rituximab maintenance after up-front rituximab/ chemotherapy induction in FL	4 3 2 1	4 3 2 1
Phase III trials of lenalidomide maintenance after autologous transplant in MM	4 3 2 1	4 3 2 1
Studies of arsenic trioxide in initial APL	4 3 2 1	4 3 2 1
Rasburicase in the management of tumor lysis syndrome	4 3 2 1	4 3 2 1
Recognition of common side effects of pralatrexate	4 3 2 1	4 3 2 1
AVIDA: Prospective observation registry of patients with MDS receiving 5-azacitidine	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Apply the results of emerging research to effectively integrate novel agents and regimens into the management of follicular lymphoma..... 4 3 2 1 N/M N/A
- Recall early mortality in acute promyelocytic leukemia (APL), and formulate optimal management strategies for APL..... 4 3 2 1 N/M N/A
- Identify patients at high risk for tumor lysis syndrome (TLS), and incorporate recent research data into the prevention and management of TLS..... 4 3 2 1 N/M N/A
- Integrate innovative combination regimens into the management of multiple myeloma (MM), considering the benefits and risks of proteasome inhibitors and immunomodulatory agents..... 4 3 2 1 N/M N/A
- Evaluate maintenance therapy approaches for patients with MM..... 4 3 2 1 N/M N/A
- Optimize the management of myelodysplastic syndromes through rational integration of prospective and retrospective data..... 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials in which they may be eligible to participate..... 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Mathias J Rummel, MD, PhD	4 3 2 1	4 3 2 1
Antonio Palumbo, MD	4 3 2 1	4 3 2 1
Mikkael A Sekeres, MD, MS	4 3 2 1	4 3 2 1
Steven T Rosen, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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