


**ASH Updates**

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T-Cell and B-Cell Non-Hodgkin Lymphoma: Recent  
Advances and Controversies in Treatment  
01/10/09

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**Disclosure Information**

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I have no financial relationships to disclose relevant to the  
content of this presentation.

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**Overview of ASH Abstracts – Lymphoma/CLL**


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Total number of abstracts presented at the 50<sup>th</sup> annual  
meeting of the American Society of Hematology on NHL  
were 1275

135 Oral Sessions  
297 Poster Presentations

1 Plenary session- NHL/CLL

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### ASH Review

- Pathobiology and Molecular Profiling
- Minimal Residual Disease in NHL
- Combination Chemotherapies and Novel Agents



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### Pathobiology and Molecular Profiling



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### WHO 2008 Classification

- Leukemic or Disseminated
  - T-cell prolymphocytic leukemia-
  - T-cell granular lymphocytic leukemia
  - Chronic lymphoproliferative disorders of NK cells\*
  - Aggressive NK cell leukemia
  - Adult T-cell leukemia/lymphoma (HTLV1+)
- Extranodal
  - Extranodal nasal and nasal-type NK/T cell lymphoma.
  - Enteropathy-associated T cell lymphoma
  - Hepatosplenic T-cell lymphoma
- Extranodal Cutaneous
  - Mycosis fungoides
  - Sezary syndrome
  - Primary cutaneous CD30+ lymphoproliferative disorders
    - Primary cutaneous anaplastic large cell type
    - Lymphomatoid papulosis
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Primary cutaneous  $\gamma\delta$  T-cell lymphoma \*
  - Primary cutaneous small/medium CD4+ T-Cell Lymphoma \*
- Nodal
  - Angioimmunoblastic T-cell lymphoma
  - Peripheral T-cell lymphoma unspecified
  - Anaplastic large cell lymphoma (ALCL) ALK-positive
  - Anaplastic large cell lymphoma ALK-negative \*



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### Anaplastic Large Cell Lymphoma (CD30 Positive)

**Anaplastic Large Cell Lymphoma**

Primary Systemic      Primary Cutaneous

ALK-positive      ALK-negative

|           | ALK+VE ALCL | ALK-VE ALCL | Cutaneous ALCL |
|-----------|-------------|-------------|----------------|
| T(2;5)    | +ve         | -ve         | -ve            |
| EMA       | +ve         | +ve/-ve     | -ve            |
| Prognosis | favorable   | Poor        | favorable      |

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### Overall Survival of Peripheral T-Cell Lymphoma Subtypes

CGH studies demonstrate that ALK-pos and ALK-neg tumors have unique gene expression signatures and are distinct entities at a molecular and genetic level

*J Clin Oncol: 26:4124-4130 2008*

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### Clinical Prognostic Factors in ALCLs

Patients with ALK-pos ALCL and a high or high-intermediate IPI risk score have a poor prognosis

*Savage et al., Blood 2008 111:5496*

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### Subcutaneous Panniculitis-like T-cell Lymphoma (SCPTCL)

- Rare tumors <0.9% of cases
- Tumors of  $\gamma\delta$  T-cell phenotype have inferior prognosis than the  $\alpha\beta$  T-cell phenotype

| Features                | $\gamma\delta$            | $\alpha\beta$           |
|-------------------------|---------------------------|-------------------------|
| IHC                     | CD4-, CD8-, CD56+/-, BF1- | CD4+, CD8+, CD56-, BF1+ |
| Hemophagocytic syndrome | +                         | -                       |
| 5-yr survival           | 11%                       | 82%                     |

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### Molecular Profiling in CLL

| Prognosis    | Favorable                   | Unfavorable      |
|--------------|-----------------------------|------------------|
| Cytogenetics | Del 13p, normal, trisomy 12 | Del 17p, del 11q |
| IgVH         | Mutated                     | Unmutated        |
| ZAP70        | negative                    | Positive         |
| CD38         | Negative                    | Positive         |

**ZAP-70 has a high relative prognostic value for patients with early, asymptomatic disease.**

**ZAP 70 positive patients have a median time to initial therapy of 3 years**

*Rassenti et al., Blood 2008;112:1923*

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### CLL- Molecular Profiling and Clinical Practice

- Decision making in clinical practice should be made on the basis of clinical features of the disease
- Molecular profiles in the management of CLL is limited to a clinical trial question
- EXCEPTION: Symptomatic patients with 17p- need aggressive approaches and consideration for an allogeneic stem cell transplant early

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Array CGH can identify regions associated with different clinical outcome in DLBCL treated with R-CHOP

- Scandurra et al., Abstract # 478
- Genomic differences were observed among responders and non-responders

| RESPONDERS                                       | NON-RESPONDERS                        |
|--|---------------------------------------|
| Loss of 2p11.2, 8p23, 10p12, 15q11<br>Gain of 1q | Gain of 3p (FOXP1 locus), 3q29, 11q24 |

CONCLUSION: Gain of 3p14.1 (FOXP1 locus) is associated with lack of response to R-CHOP

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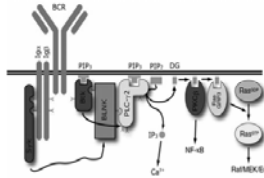
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Spleen Tyrosine Kinase (SYK) is Over-expressed and Represents a Potential Therapeutic Target in CLL



BCR signaling contributes to apoptosis resistance

High SYK expression in Unmutated CLL cells

SYK protein expression may predict response to therapy

*Buchner et al., Blood 2008 Abstract #543*

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Expression of Hypoxia-Inducible Factor (HIF) is an Independent Favorable Prognostic Factor in Diffuse Large B-Cell Lymphoma

- Elevated HIF protein correlates with poor prognosis lung, breast, bladder, pancreatic and renal tumors
- TMA of 78 patients treated with R-CHOP were compared to 75 patients treated with CHOP
- In patients treated with CHOP there was no difference in the HIF positive and negative groups

*Evens et al., Blood 2008 Abstract # 479*

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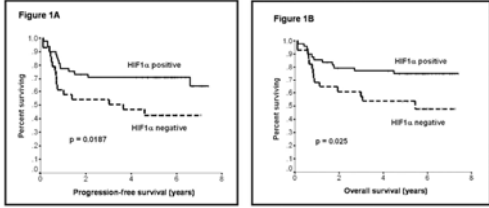
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### Survival According to HIF-1a Status in Patients Treated with R-CHOP



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### Molecular Remission after Combined Immunochemotherapy is of Prognostic Relevance in Patients with MCL

- 182 patients with mantle cell lymphoma and peripheral blood involvement demonstrated by IGH-PCR were evaluated
- MRD was evaluated in the PB and BM samples
- MIPI score: 20%- Adverse, 37%- Intermediate and 43%- Good prognosis
- BM was sensitive for detection of MRD than PB
- Patients achieving an MR in the BM after induction correlated with increased remission duration
- MRD+ve 24 months- 66% were in remission compared to those with MRD -ve 100% were in remission at 24 months

*Pott et al., blood 2008 Abstract # 582*

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Quantitative MRD Assessments Predict Pprogression Free Survival in CLL Patients Treated with Fludarabine and Cyclophosphamide

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- Treatment with FCR improves response rates and PFS when compared to FC chemotherapy alone: Abstract #325
- Minimal Residual disease- Flow cytometry
- Peripheral blood MRD levels at completion of therapy with  $<10^{-4}$  or Bone marrow MRD level of  $<10^{-2}$  Corresponds to a longer PFS (irrespective of the treatment received)

Therapeutic applications: MRD may be used a surrogate marker.  
Future studies need to be directed towards consolidation+/-maintenance phase

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*Boettcher et al., Blood 2008 Abstract # 326*

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Autologous Stem Cell Transplant as First Line Therapy in PTCL


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- Multicenter Phase II Study
- N=83; PTCL NOS- 32, AITL- 27 (Excluded ALK+ve)
- 4-6 x CHOP (CR/PR) → Myeloablative Chemo-Radiotherapy followed by Auto Transplant
- 3 Year OS- 48%

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*Reimer et al., JCO 2009 vol 27;106*

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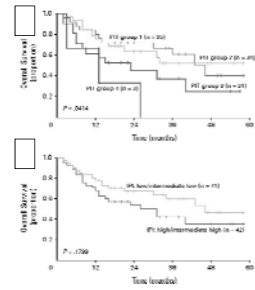
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### Overall Survival by PIT and IPI



Patients with low risk IPI appear to benefit from Auto transplant in first CR/PR

Reimer et al., JCO 2009 vol 27:106



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### PROPEL: Phase 2 Study of Pralatrexate in Patients with Relapsed Refractory PTCL

- Multicenter phase II study single arm study
- N=115 patients
- Pralatrexate- 30mg/m<sup>2</sup> IV weekly for 6-7 doses (B12 and Folic acid)
- Median number of regimens- 3
- Mixed histology



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### Efficacy Results According to Central Review

- 109 evaluable patients
- 29 patients responded to treatment- 11 patients attained a CR

O'Connor et al., Blood 2008 Abstract # 261



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Results of Phase II Study of Bortezomib in Patients with Relapsed Refractory Indolent Lymphoma

- Bortezomib monotherapy in patients with rituximab refractory indolent lymphoma
- N=60 (Bortezomib 1.3mg/m<sup>2</sup> days 1,4,8 and 11- eight cycles)
- If CR- additional 4 cycles, If <CR- maintenance phase every 42 days
- Grade 3/4 toxicities- Thrombocytopenia(22%), fatigue(10%) and neuropathy (6%)

RESULTS: ORR- 31% - 1 CR,2 CRu, 3 PR and 34 SD

Di Bella et al., Blood 2008; Abstract # 1572



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Role of Radiotherapy to Bulky Disease in the Rituximab Era: DLBCL

- RICOVER 60 6xR-CHOP 14 was superior in elderly patients with DLBCL (included XRT to bulky disease)
- 166 patients were prospectively recruited to receive 6xR-CHOP 14 and no XRT to bulky adenopathy.
- RESULTS: No difference in EFS, PFS or OS among patients who attained a CR after chemoimmunotherapy

CONCLUSION: In the rituximab era additional radiation to bulky disease has no role for elderly patients in CR/Cru after completion of 6xR-CHOP 14



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Confirmation of the Efficacy and Safety of Lenalidomide Monotherapy in Patients with Relapsed/Refractory DLBCL

- Phase II study
- 73 patients were enrolled and evaluable for response (heavily pretreated)
- Lenalidomide -25mg daily on days 1-21 q 28 days
- ORR- 29%, 4% CR and 25% PR , 15%- Stable disease
- Grade 3/4 events- Myelosuppression and asthenia

Czuczman et al., Blood 2008; Abstract # 268



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Fostamatinib Disodium (FosD), an Oral Syk Inhibitor has Significant Clinical Activity in Diffuse Large B Cell Lymphoma and CLL

- Malignant B-Cells rely on B-Cell receptor mediated signaling leads to activation of Spleen Tyrosine Kinase (SYK)
- FosD is an oral inhibitor of SYK
- Phase I= 13 patients; Phase II- 68 patients
- MTD- 200mg bid (dose limiting toxicity- Neutropenia)
- Phase II-Relapsed, refractory (all histologies)



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Friedberg et al., Blood 2008 Abstract # 3 (Plenary Session)

| Histology    | Response   | Stable disease |
|--------------|------------|----------------|
| DLBCL(23)    | 1 CR, 4 PR | 4              |
| CLL/SLL (24) | 6 PR       | 2              |
| MCL (9)      | 1 PR       | 4              |
| FL (21)      | 2 PR       | 12             |
| MALT (4)     | -          | 1              |

CONCLUSIONS: FosD is well tolerated, safe with significant responses in DLBCL and CLL and prolonged stable disease observed in patients with FL.  
 Future development as a single agent and in rational combinations are under investigation



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Phase III Study of FCR vs. PCR in B-Cell CLL  
Reynolds et al., Abstract # 327

Primary end point: Infectious complications  
 Secondary end point: safety and efficacy  
 N= 184 (92 patients in each arm)

RESULTS

|                      | FCR     | PCR    | P-value |
|----------------------|---------|--------|---------|
| Infection rate       | 30.7%   | 33.7%  | NS      |
| ORR/CR               | 57%/17% | 45%/6% | 0.04    |
| Discontinued therapy | 28%     | 27%    |         |

Both regimens possess significant toxicity. Response rates were lower than previously reported Phase II studies .

This trial did not demonstrate a lower infection rate for PCR



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n=25 patients  
 Starting dose- 2.5mg- target dose of 10mg. With allopurinol for tumor lysis prophylaxis and increase frequency of tumor lysis lab monitoring.  
 Dose modifications: 25 % patients required dose modifications to 5mg

| Grade %           | n(%)     |
|-------------------|----------|
| <b>TOXICITIES</b> |          |
| neutropenia       | 10 (43%) |
| Thrombocytopenia  | 3 (13%)  |
| Fatigue           | 74%      |
| Tumor Flare       | 48%      |

*Chen et al., Blood 2008 Abstract #44*

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**Chen et al., Blood 2008 Abstract #44**

- Responses: 17 patients evaluable for response  
 11- PR  
 6- stable disease  
 No CR  
 No Progressive disease

Responses were reached after a median of 4 cycles

Conclusions: Lenalidomide has significant clinical activity in previously untreated patients with CLL.

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**Lenalidomide as Initial Treatment for Elderly Patients with CLL**

- 53% of patients are older than age 70 at the time of diagnosis
- Phase I/II study- patients > 65 yrs, No prior therapies
- Dose: start at 5 mg and titrate up to 25mg daily in 5mg increments (continuous dosing)

*Ferrajoli et al., Blood 2008 Abstract #45*

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Ferrajoli et al., Blood 2008 Abstract #45

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35 patients evaluable for response

19 patients- PR

14 patients- stable disease


2 patients experienced disease progression after 4 months

| Patient characteristics                | n         |
|--|-----------|
| Median age                             | 72 years  |
| Rai stage III/IV                       | 42%       |
| Unfavorable cytogenetics ( 17p-, 11q-) | 30%       |
| ZAP 70 +ve                             | 44%       |
| Median B2-microglobulin                | 4.5 mg/dl |

CONCLUSIONS: Lenalidomide given as a continuous therapy at a start dose of 5mg followed by slow dose escalation is safe and well tolerated as initial therapy in elderly patients with CLL

Lenalidomide in CLL- Start low, go slow with safe monitoring

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Flavopiridol Induces Durable Responses in Relapsed CLL Patients with High Risk Cytogenetic Abnormalities

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- Flavopiridol induces p53 independent apoptosis of CLL cells in vitro
- 117 patients with relapsed CLL
- Median # of prior therapies- 4
- Flavopiridol was given as an IV infusion days 1-4 every 6 weeks X 6 cycles

| Response Rates | # of patients |
|----------------|---------------|
| ORR            | 48%           |
| PR             | 52 patients   |
| CR             | 1 patient     |
| Median PFS     | 10 months     |

*7 patients went on to receive Reduced Intensity Allogeneic Stem Cell Transplant*

*Lin et al., Blood 2008 Abstract #46*

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Rituximab and High Dose Methylprednisolone for the Initial Treatment of CLL is Associated with Promising Clinical Activity and Minimal Hematologic Toxicity

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- 28 patients : >65 yrs
- Chemotherapy naïve patients (46% high risk, 39% unfavorable Cytogenetics)
- Rituximab 375mg/mt2 weekly X 12 doses + Solumedrol- one gram IV X3 days q 4 weeks.
- Responses: ORR- 96%, CR- 32%, 22% no detectable MRD by Flow
- Follow up time- 36.3 months- Median PFS not reached.
- No Grade ¾ toxicities were observed

*Abstract #47*

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Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL Refractory to both Fludarabine and Alemtuzumab or bulky fludarabine –refractory disease.

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- Results of interim analysis- 138 patients
- 8 weekly infusions followed by 4 monthly infusions
- Dose 1, 300mg; doses 2-12, 2000mg

*Osterborg et al., Blood 2008 Abstract # 328*

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**Abstract #328 (Results of Ofatumumab)**

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| Characteristics          | DR (n=59) | BFR (n=79) |
|--------------------------|-----------|------------|
| Age                      | 64        | 62         |
| # of prior treatments    | 5         | 4          |
| Rai stage III/IV         | 54        | 70         |
| CR                       | 0         | 1          |
| Partial Response         | 51        | 43         |
| Stable disease           | 39        | 43         |
| Time to next CLL therapy | 9 months  | 7.9 months |

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**Bendamustine in Combination with Rituximab for Patients with Relapsed CLL: A Multicenter Phase II Trial of the German CLL Study Group**

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- 81 patients enrolled between March 2006- June 2007
- 70mg/mt<sup>2</sup> of bendamustine on days 1 and 2+rituximab 375-500mg/mt<sup>2</sup> q 28 days x6 cycles


| RR    | CR    | PR    |
|-------|-------|-------|
| 77.4% | 14.5% | 62.9% |

No Patients attained MRD negative status in the bone marrow

| Molecular profile          | ORR             |
|----------------------------|-----------------|
| 11q-                       | 11/13- PR; 1-CR |
| 17p-                       | 4/9- PR         |
| Unmutated IgV <sub>H</sub> | 29/39- PR       |

*Fischer et al., Blood 2008 Abstract #330*

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For further information regarding ongoing clinical trials in  
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