Mantle Cell Lymphoma
Update on Treatment

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Welcome and Introductions

Mantle Cell Lymphoma
Update on Treatment

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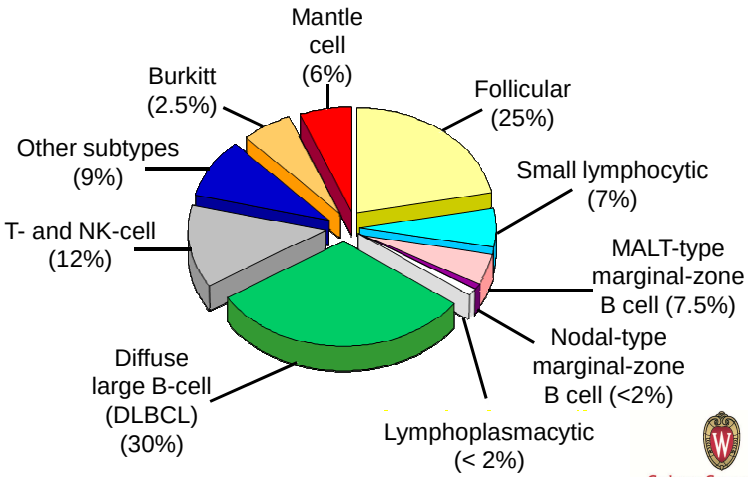
April 3, 2014

Disclosures

- **Consulting**
  - Genentech/Roche, Millennium, Celgene, Infinity, Gilead, Pharmacyclics
- Research Funding
  - Genentech/Roche, Millennium, Celgene, Infinity, Gilead, Pharmacyclics

3

Mantle Cell Lymphoma: 6% of NHL Cases



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Mantle Cell Lymphoma

- First recognized as unique entity ~ 1994
  - Often misdiagnosed initially
  - Relatively easy to identify currently
- No standard treatment
  - Variety of effective treatments
  - Several breakthroughs in last few years

Presentation

- Varies from patient to patient
  - B symptoms
    - Fever, night sweats, weight loss
  - Fatigue (anemia)
  - Pain from splenomegaly or nodal masses
  - Change in bowel habits
  - Enlarging lymph nodes
  - Detected in routine blood work

Clinical Features

- Median age ~ 64
- Male:female ratio 4:1
- Typically advanced stage at presentation
- Extranodal involvement common
  - Marrow, blood
  - Colon (lymphomatous polyposis)
- ? curable with conventional therapy
- Moderately aggressive

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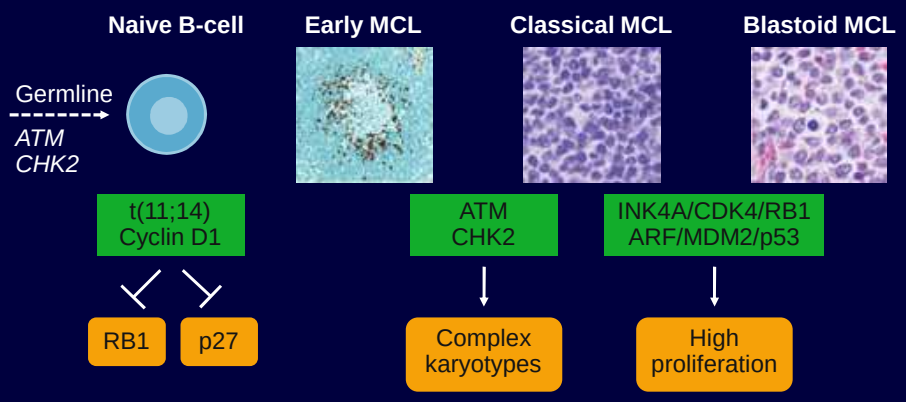
Overcoming Barriers to Optimal Treatment of Non-Hodgkin's Lymphoma
clinicaloptions.com/oncology

CLINICAL CARE OPTIONS ONCOLOGY

Proposed Model of MCL Pathogenesis



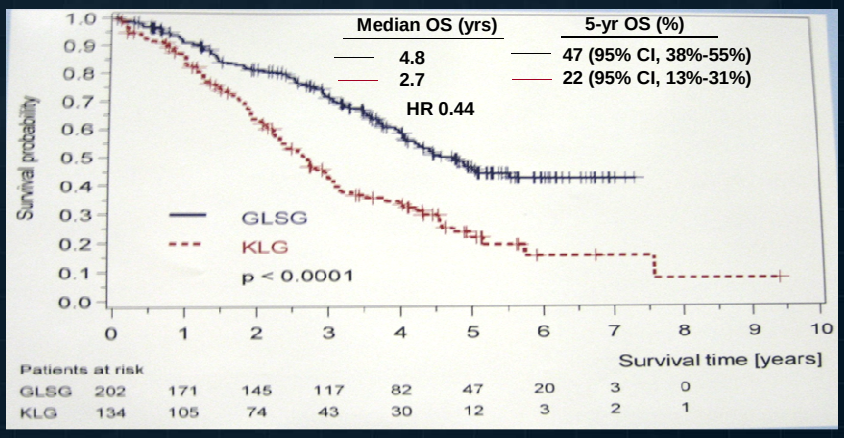
Jares P, et al. Nat Rev Cancer. 2007;7:750-762.

Diagnosis of Mantle Cell Lymphoma

Morphology	· Small-medium lymphoid cells with irregular to occasionally cleaved nuclei · Blastic variant
Cell of origin	· Mantle zone of the follicle
Immuno-phenotyping	· $CD5^+$, CD20 bright, $CD23^-$, cyclin D_1+, FMC7+ · t(11;14) detectable by FISH
Nodal Architecture	· Nodular · Diffuse · Mantle Zone growth

Skarin AT, Dorfman DM. *CA Cancer J Clin*. 1997;47:351-372. Harris NL et al. *Hematology.* 2001:194-220.

Improvement of OS in MCL During the Last Decade: GLSG Cohort (1996-2004) vs KLG Cohort (1975-1986)

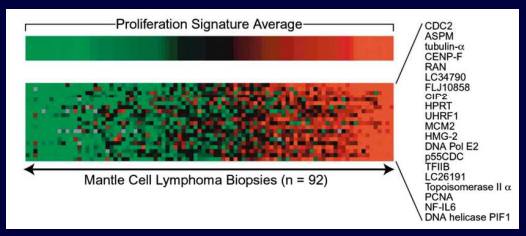


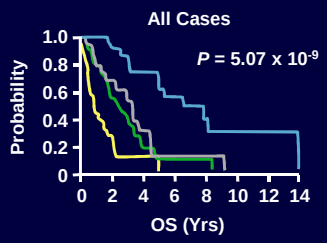
ASCO Annual '08 Meeting

Herrmann et al. ASH, 2006. Abstract and presentation 2446.

Prognostic Factors: Molecular Signature

The proliferation gene expression signature is a quantitative integrator of oncogenic events that predicts survival in MCL





Median OS varies from 0.7-8.0 yrs!

Reprinted from Rosenwald A, et al. Cancer Cell. 2003;3:185-197.
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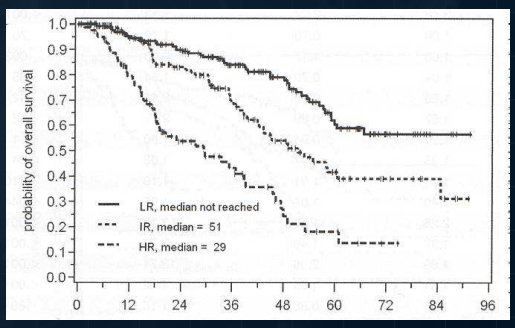
Clinical Prognostic Features: MIPI

- Four factors independently associated with OS
  - Age
  - PS
  - LDH
  - WBC
- Risk distribution
  - Low 44% (score < 5.7)
  - Int 35% (score 5.7-6.1)
  - High 21% (score > 6.1)



Formula for calculating MIPI:

[0.03535 x age (years)] + 0.6978 (if ECOG > 1) + [1.367 x log10(LDH/ULN)] + [log10(WBC count)]

Treatment

- No universally accepted first-line treatment
- I ask the following questions with a new diagnosis?
  - Is the patient a candidate for intensive treatment?
  - Should watch and wait be contemplated?

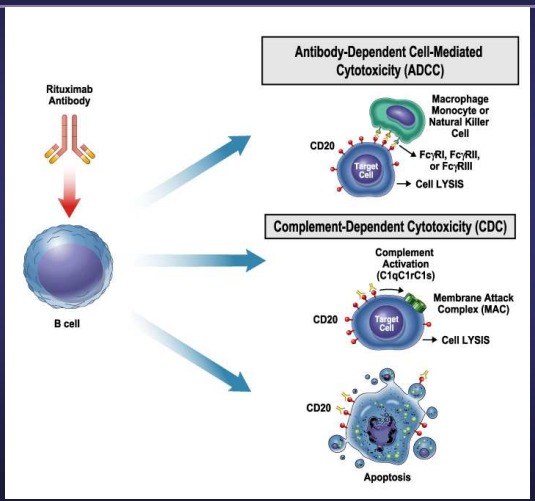
Intensive Treatments

- Generally reserved for patients 65 and under
  - R-CHOP with alternating R-DHAP for 6 cycles followed by autologous stem cell transplantation
  - R-HyperCVAD with alternating R-MTX/AraC for 6-8 cycles
  - Nordic regimen
- Average remission length ~ 5 years

Non-intensive Treatments

- Generally considered for older patients or younger patients with comorbidities
  - R-CHOP for 6-8 cycles
  - R-bendamustine for 6 cycles
- Followed by maintenance rituximab

Rituximab: Anti-CD20 moAb



Anderson et al. *Biochem Soc Trans* 1997; 25:705-8; Golay et al. *Blood* 2000; 95:3900-8; Reff et al. *Blood* 1994; 83:435-45; Clynes et al. *Nat Med* 2000; 6:443-6; Shan et al. *Cancer Immunol Immunother* 2000; 48:673-83.

Watch and Wait

- Why even consider this?
- Data from Cornell

Novel Treatments for Mantle Cell Lymphoma

Targeting Intracellular Pathways

Potential Targets	Agent
• Proteasome →	Bortezomib
• mTOR →	Temsirolimus
• ??? →	Lenalidomide
• PI3 kinase →	Idelalisib
• BTK →	Ibrutinib
• BCL-2 →	ABT-199

Bortezomib

- FDA approved for R/R MCL
  - 1.3 mg/m2 IV days 1, 4, 8, 11 q 21 days
  - SQ dosing now an option
- Pinnacle Trial (n = 155)
  - ORR 33%
  - mDOR 9.2 months, mTTP 6.2 months
  - Peripheral neuropathy main toxicity
    - 55% any grade, 13% > grade 3

Fisher et al, JCO 2006

Temsirolimus

- EU approval for R/R MCL
  - 175 mg IV weekly x 3, then 75 mg IV/week
- Tem vs. investigator choice (n = 54 vs. 53)
  - ORR 22% vs. 2%
  - mPFS 4.8 months vs. 1.9 months
  - Major toxicities
    - Thrombocytopenia 59% grade 3-4
    - Asthenia 63% any grade

Hess et al, JCO 2009

Lenalidomide

- FDA approved for R/R MCL after 2 prior therapies, one including bortezomib
  - 25 mg po days 1-21 q 28 days
- Emerge Study (n = 134)
  - ORR 28%
  - mDOR 16.6 months; mPFS 4.0 months
  - Major toxicities
    - Neutropenia (19%) and low plts (17%) - grade 3-4
    - Fatigue (34%), diarrhea (31%), nausea (30%) - any grade

Goy et al, JCO, 2013

Lenalidomide and Rituximab (R^2)

- Not FDA approved in combination but both agents commercially available
- Phase I/II Study in R/R MCL (n = 52)
  - Phase II dose
    - Lenalidomide 20 mg po days 1-21 every 28 days
    - Rituximab 375 mg/m^2 weekly x 4 on cycle 1
  - ORR 57%
  - mDOR 18.9 months; mPFS 11.1 months
  - Major toxicities
    - Neutropenia (66%) & low plts (23%) – grade 3-4
    - Fatigue (89%), diarrhea (50%), rash (48%) – any grade

Wang et al, Lancet Oncology, 2012

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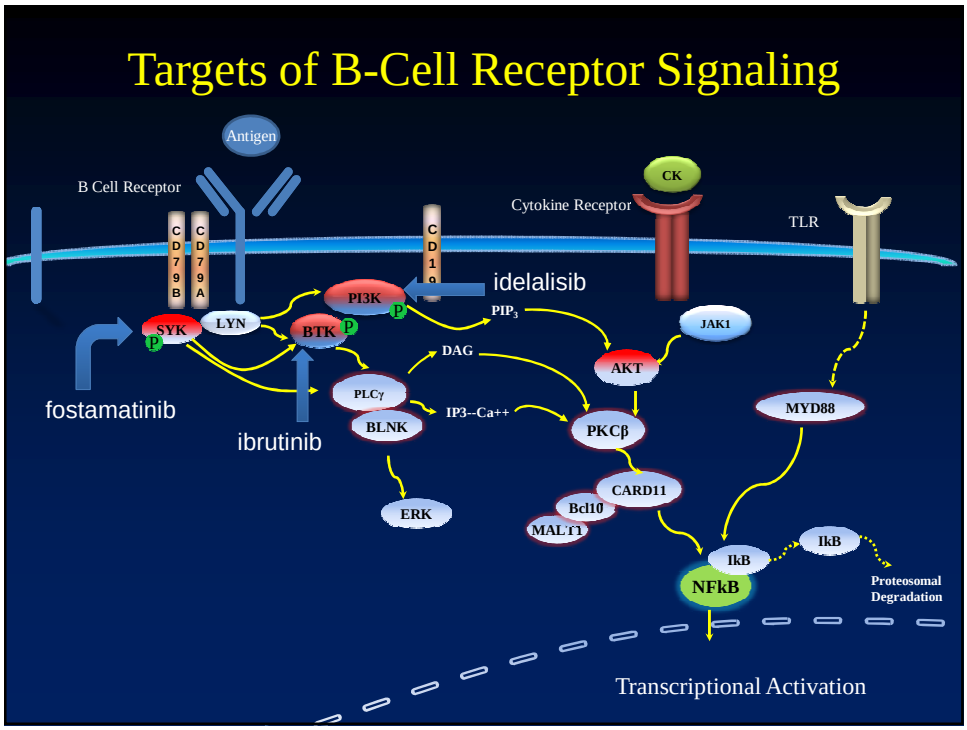


Idelalisib

- Not FDA approved for MCL
  - Selective PI3k delta inhibitor
- Phase I experience in R/R MCL (n = 40)
  - Phase II dose of 150 mg po BID
  - ORR 40%; ORR at/above 150 mg BID 69%
  - mDOR 2.7 months; mPFS 3.7 months
  - Major toxicities
    - Transaminitis 60% any grade, 20% grade 3-4
    - Diarrhea 40% any grade, 18% grade 3-4

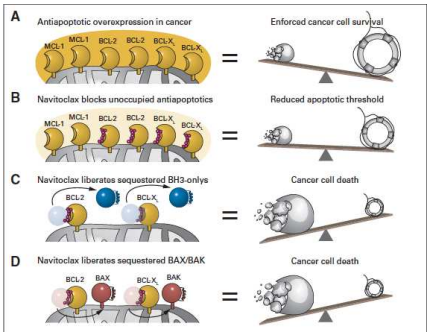
Kahl et al, Blood, 2014.

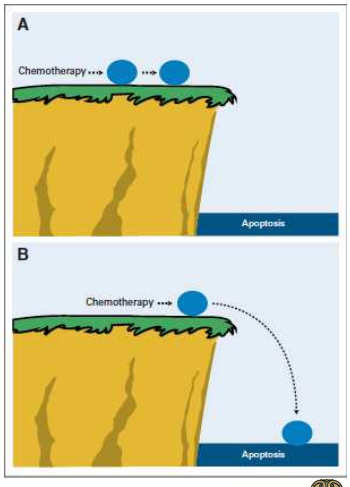
Ibrutinib

- FDA approved for R/R MCL - Nov 2013
  - 560 mg po daily
- Phase II Trial (n = 111)
  - ORR 68%
  - mDOR 17.5 months; mPFS 13.9 months
  - Major toxicities
    - Neutropenia 16%, low plts 11% – grade 3-4
    - Diarrhea 50%, fatigue 41%, edema 28% - any grade

Wang et al, NEJM 2013

BCL-2 Inhibitors





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ABT-199

- Not FDA approved
  - Oral daily dosing
  - 400 mg po QD in CLL/SLL; ? In NHL
- Ongoing phase I update
  - MCL: ORR 82% (9/11); mDOR tbd
  - CLL: ORR 84%; (47/56); appears durable
  - Toxicities
    - Diarrhea 43%, nausea 40% - any grade
    - Tumor lysis syndrome in CLL/SLL

ASH abstracts: #872 (oral – Tue, Dec 10), #1789 (poster Sat, Dec 7)

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How to sequence in R/R MCL

- Assume no clinical trial and using commercially available agents
  1. Ibrutinib
     - Most active and well tolerated
  2. Rituximab-Lenalidomide (R^2)
     - Likely synergistic; tolerable
  3. Bortezomib
     - Useful agent for some; neuropathy

The Future

- Rational combinations of targeted agents
  - In vitro data most supportive for a BCR pathway agent plus an agent outside pathway
- Ibrutinib plus….
  - ABT-199
  - Bortezomib or other proteasome inhibitor
  - Lenalidomide
  - Standard front-line therapy

Conclusions

- **Prognosis appears to be improving for MCL patients**
- **May be due to new therapies and/or stem cell transplant strategies**
- **Clinical trials are essential**
- **We are gaining knowledge about MCL and are optimistic we can take advantage**
- **Several recent exciting breakthroughs**

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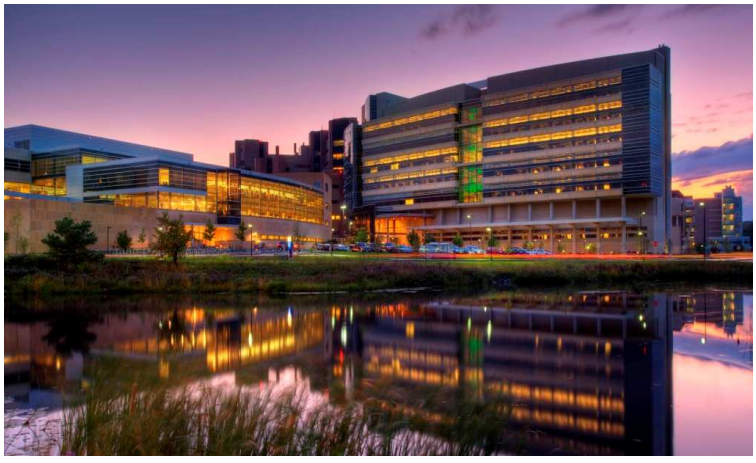

Questions?

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Question & Answer Session

The speaker's slides are available for download at www.LLS.org/programs

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The Leukemia & Lymphoma Society (LLS) offers:

• Live, weekly Online Chats that provide a friendly forum to share experiences and chat with others about anything from the initial phase of diagnosis to treatment and survivorship. Each chat is moderated by an oncology social worker and is password protected.

- **WEBSITE: www.LLS.org/chat**

• Co-Pay Assistance Program offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

• For more information about blood cancers and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**