How is mantle cell lymphoma treated?

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Department of Malignant Hematology
Moffitt Cancer Center
Tampa, FL
How is Mantle Cell Lymphoma Treated?

- Celgene/Juno/BMS, Novartis, Spectrum/Acrotech, Adaptive, AstraZeneca, Precision BioSciences, Kite/Gilead, Pfizer, Amgen, BeiGene
  - Advisory Board, Honoraria

- Incyte, Jazz, Kite/Gilead
  - Research Funding

- Off-label content will be discussed
How Is Mantle Cell Lymphoma Treated?

Bijal Shah, MD, MS

Clinical Leader for Mantle Cell Lymphoma and Acute Lymphoblastic Leukemia
Director of Translational Research Initiatives in Lymphoma & Acute Lymphoblastic Leukemia
Associate Member
H. Lee Moffitt Cancer Center
Objectives

• Reconciling Heterogeneity in MCL: *The Inevitable Slope of Chemotherapy Resistance*

• Defining Treatment Objectives: *Is Intensity Still the Answer?*

• Relapsed & Refractory MCL: *Are We Getting Anywhere?*

• Roadmap for the Future: *Bringing Novel Approaches Forward*
Mr. RR

- 64yo WM in excellent health presented 5/2010 with WBC of 20 in the absence of B-symptoms. Differential confirmed a lymphocyte predominance, and flow cytometry ultimately disclosed an immunophenotype compatible with MCL.

- FISH studies performed 2/2011 revealed loss of 13q [71.5%], and loss of 17p [62.5%], in addition to the expected IgH-Bcl1 translocation

- Bone marrow biopsy 5/2011 demonstrated ~2/3 involvement with MCL, with a complex cytogenetic pattern:
  - 45,XY, +7p22, t(11;14)(q13;q32),-12, der(15)t(12;15)(q12;q26), ?del(16)(q22q23), +17p11.2, +22q11.2[cp13]
How Do I “Think” About Lymphoma

Low Grade Lymphomas
- Marginal Zone
- Follicular

Intermediate Grade Lymphomas
- Diffuse Large B-Cell
- Anaplastic large cell

High Grade Lymphomas
- Burkitt
- Lymphoblastic

Indolent
- 10-15%
- Classical
- 70-80%
- Blastoid / Pleomorphic
- 5-10%
Epidemiology

Summary of descriptive epidemiology of MCL in Europe and the US.

<table>
<thead>
<tr>
<th></th>
<th>Incidence rate of MCL in Europe 2000–2002 [8](^a) Per 100 000 person-years</th>
<th>Incidence rate of MCL in the US 1992–2001/2004 [7,9](^b) Per 100 000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.45</td>
<td>0.51/0.55</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.64</td>
<td>0.84</td>
</tr>
<tr>
<td>Female</td>
<td>0.27</td>
<td>0.34</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>50–59</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>60–69</td>
<td>NA</td>
<td>1.96</td>
</tr>
<tr>
<td>70–79</td>
<td></td>
<td>2.97</td>
</tr>
<tr>
<td>≥80</td>
<td></td>
<td>2.78</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td>0.84/0.61</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td>0.45/0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.32</td>
</tr>
</tbody>
</table>

NA, not available.

\(^a\) Rates were age-standardized for each included cancer register area in Europe.

\(^b\) Rates were age-standardized to the US population in the year 2000.
What Is MCL?

A

- CD20++
- CD5+
- CD23+/
- CD11c-

B

<table>
<thead>
<tr>
<th>Method</th>
<th>Approximate Sensitivity</th>
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<tbody>
<tr>
<td>Cyclin D1 (Paraffin)</td>
<td>90%</td>
</tr>
<tr>
<td>Cyclin D1 (Frozen)</td>
<td>25%</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>50-75%</td>
</tr>
<tr>
<td>FISH for t(11;14)</td>
<td>80-100%</td>
</tr>
<tr>
<td>PCR for t(11;14)</td>
<td>30-40%</td>
</tr>
</tbody>
</table>

What Is MCL?

1-9 mo
No Lymphoma

10-11 mo
FC-μMCL1 (4/6)

12-14 mo
FC-μMCL1 (13/15)

No B-NHL

Eμ-CyclinD1

No B-NHL

+bcl2

+pmtane

B & T-cell NHL

+myc

Bodrug SE, et al. EMBO J. 1994 May;13(9):2124
“Indolent” Phase?

Low Grade Lymphomas
- Marginal Zone
- Follicular

Intermediate Grade Lymphomas
- Diffuse Large B-Cell
- Anaplastic large cell

High Grade Lymphomas
- Burkitt
- Lymphoblastic

MCL

Indolent
Classical
Blastoid / Pleomorphic

10-15%  70-80%  5-10%
Reconciling of Indolent MCL

Indolent MCL: Moffitt Experience

Time to Treatment in Mantle Cell Lymphoma

- Time <12mo (n=136)
- Time >12mo (n=25)

But How Do We Know Which Patients Have Indolent MCL?
Indolent MCL

Median time to first treatment among those observed was 23 months

Baseline PET

- **MCL-BV**
  - median SUV 16.88
  - range 14.33–18.84

- **MCL**
  - median 6.79
  - range 2.3–12.26

*B*P = 0.000062

Brepoels L, et al. Leukemia & Lymphoma. 2008 Sep;49(9):1693
SOX11 -- Controversial

High Risk Genetic Mutations May Come with Shorter Time to Treatment

Observation time among 85 patients with **TP53** mutation in MCL

Median Time to First Treatment: **2mo**

4 patients remain under watchful waiting with a median 7mo of follow-up (4-56 months)

Shah N, et al. ASH 2019, Abstract 3991
• We decide to watch him without therapy given a lack of symptoms.

• He does well for approximately 2 years.

• In 4/2012, he was noted to have a rapidly rising WBC, with imaging showing limited lymph node enlargement (largest 2.2x1.3cm), and an enlarging spleen (16.6cm).
“Aggressive” Phase?

Low Grade Lymphomas
- Marginal Zone
- Follicular

Intermediate Grade Lymphomas
- Diffuse Large B-Cell
- Anaplastic large cell

High Grade Lymphomas
- Burkitt
- Lymphoblastic

10-15% 70-80% 5-10%
Indolent Classical Blastoid / Pleomorphic
Predicting & Understanding Survival in MCL
The Mantle Cell Prognostic Index (MIPI)

• Evaluated 455 patients with MCL across three large German studies

• Identified four major prognostic variables
  – AGE
  – PERFORMANCE STATUS
  – LDH
  – WHITE BLOOD CELL COUNT

• A Complicated Formula
  – $0.03535 \times \text{age (years)} + 0.6978 \ (\text{if ECOG performance status} > 1) + 1.367 \times \log_{10} (\text{LDH/ULN}) + 0.9393 \times \log_{10} (\text{white blood cells k/uL})$

• The Simplified MIPI:

<table>
<thead>
<tr>
<th>Points</th>
<th>Age, y</th>
<th>ECOG</th>
<th>LDHULN</th>
<th>WBC, 10^9/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;0.67</td>
<td>&lt; 6.700</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td></td>
<td>0.67-0.99</td>
<td>6.700-9.999</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1.000-1.49</td>
<td>1.000-14.999</td>
</tr>
<tr>
<td>3</td>
<td>≥70</td>
<td></td>
<td>≥1.5000</td>
<td>≥15000</td>
</tr>
</tbody>
</table>

The Mantle Cell International Prognostic Index (MIPI)

MIPI: Moffitt Experience

**Survival Functions**

- MIPI Low: 145 mo, n=70
- MIPI Intermediate: 79.4 mo, n=71
- MIPI High: 41 mo, n=69
What About Length of Remission?
“Progression-Free Survival” (PFS) According to the MIPI

MIPI Low: 30.95 mo, n=63
MIPI Intermediate: 33.3 mo, n=60
MIPI High: 14 mo, n=63
PET Signature

N=36
Median f/u: 21 mo

Survival rate

Time (years)

p=.07

SUVmax < 6
SUVmax ≥ 6

Ki-67 (or MIB-1 index) is a marker of cells that are committed to growing to make copies of themselves.

Progression-Free Survival by Ki-67

MIPI-C: MIPI+Ki67 (30%)
Ki-67: Inter-Observer Agreement
MCL35 Nanostring Signature

Treatment Decision Making in MCL
What Have We Learned?

What Have We Learned?

But Dr. Shah, You Gave Me R-CHOP??!

This Medicare Analysis of “Real World” patients suggests that things are not so simple!

Defining Treatment Objectives: *How Intensively Should We Treat?*
R-Hyper-CVAD

Retrospective Evaluation of Treatment Intensification

Overall Survival with/out CyA with 1st Chemox

Cytarabine (n=42)
No Cytarabine (n=126)

P(two-sided) = 0.9433

But is this because we are only giving intensive therapy to those with more aggressive MCL?
Treatment Intensity in Low & Intermediate Risk MCL

TP53 Mutation Status and Outcome with Intensive Therapy

<table>
<thead>
<tr>
<th>Variables</th>
<th>OS</th>
<th>PFS</th>
<th>CIR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>P</td>
<td>HR</td>
</tr>
<tr>
<td>mut TP53</td>
<td>6.2</td>
<td>&lt;.0001</td>
<td>6.8</td>
</tr>
<tr>
<td>mut NOTCH1</td>
<td>2.7</td>
<td>.09</td>
<td>2.3</td>
</tr>
<tr>
<td>del TP53</td>
<td>1.4</td>
<td>.37</td>
<td>1.5</td>
</tr>
<tr>
<td>del CDKN2A</td>
<td>1.3</td>
<td>.55</td>
<td>1.3</td>
</tr>
<tr>
<td>Blastoid</td>
<td>1.3</td>
<td>.53</td>
<td>0.8</td>
</tr>
<tr>
<td>MIPI-c high-risk</td>
<td>1.8</td>
<td>.11</td>
<td>2.2</td>
</tr>
<tr>
<td>mut WHSC1</td>
<td>0.8</td>
<td>.58</td>
<td>—</td>
</tr>
</tbody>
</table>

The Challenge...

The Growth Rate of MCL is Tightly Coupled to Mutations That Impact DNA Damage Recognition and Response

Defining Treatment Objectives: *How Intensively Should We “Consolidate”?*
Consolidation in MCL

Consolidation in Younger Patients with MCL

5-Year Outcomes with Low Intensity Therapy Followed by Autologous Transplant

A trend for improvement with transplant was only apparent in those getting lower intensity therapy (R-Bendamustine)

Consolidation in MCL: The VCR-CVAD Experience

Consolidation in Low & Intermediate Risk MCL

Duration of Rituximab Maintenance

Can We Have Our Cake & Eat It Too?

R+DHAP x4 -> AutoSCT -> mR x3y

Perhaps... But Should We?

ECOG-ACRIN EA4151
Mr. RR: The Challenge

• The presence of rapidly growing disease and complex cytogenetics, including loss of TP53, suggests poor sensitivity to chemotherapy, and a bad outcome...
Mr. RR: The Outcome

Frontline Induction: Lenalidomide + Rituximab

ORR: 87%
CR: 61%

Looking Specifically Among TP53m MCL

Shah N, et al. ASH 2019, Abstract 3991
How “I Treat MCL”

• Balance aggressiveness of disease with intensity of therapy, age/patient tolerance, and unique disease features
  – Young + Rapidly Growing = High Intensity
    • Induction: R+Hyper-CVAD, RCHOP-RDHAP, VCR-CVAD/VR-CAP, RBAC
    • Consolidation: Autologous Transplant+R, Allogeneic Transplant (p53)
  – Old + Rapidly Growing = Moderate Intensity
    • Induction: RCHOP, R+Lenalidomide
    • Consolidation: Maintenance Rituximab, Autologous Transplant+R
  – Young/Old + Slow Growing = Low Intensity
    • Induction: Watchful Waiting, R monotherapy, R+Bendamustine, R+Lenalidomide
    • Consolidation: Maintenance Rituximab
Mr. RR: 7 Years Later...

• Unfortunately, approximately 7 years later he develops a rapidly growing relapse (ki67 90%)...
“Highly Aggressive” Phase?

Low Grade Lymphomas
- Marginal Zone
- Follicular

Intermediate Grade Lymphomas
- Diffuse Large B-Cell
- Anaplastic large cell

High Grade Lymphomas
- Burkitt
- Lymphoblastic

10-15% 70-80% 5-10%
Indolent Classical Blastoid / Pleomorphic
Relapsed & Refractory MCL: Can We Arrest the Descent?

Median survival (95% CI): 27.7 (26.38,33.75)  
N=106
BTK Inhibitors: PFS

Ibrutinib

Acalabrutinib

Zanubrutinib

Median PFS: 13mo

BTK Inhibitors: OS

Median OS: 22.5mo

Ibrutinib

Median OS: NR (95% CI, 32.2, NR)
24-Month OS rate: 72.4% (95% CI, 63.5, 79.5)

Be Careful Comparing Across Trials!

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib (n=111)</th>
<th>Acalabrutinib (n=124)</th>
<th>Zanubrutinib (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age</strong></td>
<td>68</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td><strong>Age &gt; 65y</strong></td>
<td>63%</td>
<td>65%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>ECOG &gt; 2</strong></td>
<td>11%</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>MIPI High</strong></td>
<td>49%</td>
<td>17%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Median Prior Tx</strong></td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>&gt;3 Prior Tx.</strong></td>
<td>55%</td>
<td>23%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Prior Hyper-CVAD</strong></td>
<td>30%</td>
<td>21%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Prior AutoSCT</strong></td>
<td>11%</td>
<td>18%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Prior Lenalidomide</strong></td>
<td>24%</td>
<td>7%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Refractory</strong></td>
<td>45%</td>
<td>24%</td>
<td>52%</td>
</tr>
<tr>
<td><strong>Median Followup</strong></td>
<td>26.7 mo</td>
<td>15.2 mo</td>
<td>~16mo</td>
</tr>
</tbody>
</table>

## BTKi Non-Hematologic Toxicities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>G1-2</td>
<td>G3-4</td>
<td>G1-2</td>
</tr>
<tr>
<td>Headache</td>
<td>13%</td>
<td>0%</td>
<td>36%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>37%</td>
<td>1%</td>
<td>19%</td>
</tr>
<tr>
<td>Nausea</td>
<td>31%</td>
<td>0%</td>
<td>18%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46%</td>
<td>5%</td>
<td>33%</td>
</tr>
<tr>
<td>Cough</td>
<td>19%</td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td>Rash</td>
<td>22%</td>
<td>3%</td>
<td>12%</td>
</tr>
<tr>
<td>A Fib</td>
<td>1%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>HTN</td>
<td>7%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Infection</td>
<td>54%</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>PNA</td>
<td>6%</td>
<td>8%</td>
<td>1%</td>
</tr>
<tr>
<td>UTI</td>
<td>11%</td>
<td>3%</td>
<td>2%</td>
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</tbody>
</table>

## BTKi Hematologic Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib</th>
<th>Acalabrutinib</th>
<th>Zanubrutinib</th>
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</thead>
<tbody>
<tr>
<td><strong>Heme</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>32%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
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<tr>
<td>On Anticoag</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>55%</td>
<td>46%</td>
<td>NR</td>
</tr>
<tr>
<td>Bruising</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>GI Bleed</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>CNS Bleed</td>
<td>G1-2</td>
<td>G3-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Mr. RR

- He is treated with a BTK inhibitor for 3 mo without response, confirming resistance...

BTKi Resistance: An Emerging Problem
The Problem of BTKi Resistance

Overall Survival Post-Ibrutinib

Novel Approaches?
Ibrutinib + Rituximab

Ki67<50%

Med PFS 8mo

Ibrutinib + Venetoclax

18mo Estimated OS: 74%

18mo Estimated PFS: 57%

But We Are Still Fighting the Same Battles...

Can We Do Better?
CAR T-Cell (KTE-X19) Therapy in MCL

Characteristics | Frequency
---|---
Age ≥65y | 53%
Ki67>50% | 69%
TP53m | 17%
≥3 prior lines | 81%
BTKi R/R | 96%

![Graph showing ORR, SD, and PD with 93% ORR, 67% CR (n = 40), 27% PR (n = 16), 3% SD (n = 2), and 3% PD (n = 2).]

KTE-X19: Clinical Outcomes

KTE-X19: Outcomes in High-Risk MCL

How “I Treat Relapsed & Refractory MCL”

• Balance aggressiveness of disease with intensity of therapy, age/patient tolerance, and unique disease features
  – Aggressive
    • Induction: BTKi + Rituximab +/- Venetoclax, VCR-CVAD/VRCAP, RBAC, CAR T, Clinical Trial
    • Consolidation: Allogeneic Transplant
  – Non-Aggressive
    • Induction: BTKi +/- Rituximab, Lenalidomide+Rituximab, Bendamustine+Rituximab, Clinical Trial
    • Consolidation: Maintenance Rituximab
Where Are We Going Next In MCL

• General Themes
  – Improve Tolerance
    • Low Intensity Chemotx + Novel Agent(s)
    • Replace Chemotx with Novel Agent(s)

  – Optimize the duration and intensity of maintenance
    • Rituxan vs Rituxan + Novel Agent(s)
    • CAR T-cell Therapy
Conclusions

• Mantle Cell Lymphoma is incurable with tendency to “evolve” to a more resistant state over time

• Intensive chemotherapy-based approaches are slowly giving way to novel therapies

• CAR T-cell therapy may finally allow us to overcome the challenge of rapidly growing and resistant MCL
Acknowledgments

Moffitt
• Jianguo Tao
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• Ken Shain
• Ariosto Silva

Weill Cornell
• John Leonard
• Jia Ruan
• Peter Martin

GWU
• Eduardo Sotomayor
• Edward Seto
Thank You!!
Question & Answer Session
RESOURCES

• Information Specialists

Master’s level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

  – Email: infocenter@LLS.org

  – Toll-Free Phone: 1-800-955-4572

• Clinical Trial Support Center

Work one-on-one with an LLS Clinical Trial Nurse Navigator who will personally assist you throughout the entire clinical-trial process. Clinical Trial Nurse Navigators are registered nurses with expertise in blood cancers.

  – Email: www.LLS.org/CTSC

• Additional Information about lymphoma:
  – www.LLS.org/Lymphoma
FREE LLS EDUCATION & SUPPORT RESOURCES

• Education Booklets about MCL:
  – www.LLS.org/Booklets

• Telephone/Web Programs:
  – www.LLS.org/Programs

• Weekly Non-Hodgkin Lymphoma Chat:
  – www.LLS.org/Chat

• Additional LLS Information about Coronavirus:
  – www.LLS.org/Coronavirus
FREE LLS EDUCATION & SUPPORT RESOURCES

• LLS Podcast, *The Bloodline with LLS*
  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: [www.thebloodline.org](http://www.thebloodline.org)

• Education Videos
  Free education videos about survivorship, treatment, disease updates and other topics: [www.LLS.org/EducationVideos](http://www.LLS.org/EducationVideos)

• Patti Robinson Kaufmann First Connection Program
  Peer-to-peer program that matches newly diagnosed patients and their families: [www.LLS.org/FirstConnection](http://www.LLS.org/FirstConnection)

• Nutrition Consultations
  Telephone and email consultations with a Registered Dietitian: [www.LLS.org/Nutrition](http://www.LLS.org/Nutrition)

• What to Ask
  Questions to ask your treatment team: [www.LLS.org/WhatToAsk](http://www.LLS.org/WhatToAsk)

• Other Support Resources
  LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/PatientSupport](http://www.LLS.org/PatientSupport)
We have one goal: A world without blood cancers

THANK YOU