Welcome & Introductions

Dr. Kumar’s slides are available for download at [www.LLS.org/programs](http://www.LLS.org/programs), under the program listing.

What’s on the Horizon for Mantle Cell Lymphoma?

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What’s on the Horizon for Mantle Cell Lymphoma?

Disclosures

Anita Kumar, MD, has affiliations with AbbVie Pharmaceuticals, Adaptive Biotechnologies, Celgene, Pharmacyclics, and Seattle Genetics (Research Funding); and Celgene (Advisory Board).

Outline

Diagnosing mantle cell lymphoma (MCL)

Emerging therapies for MCL

Side effects management

Communicating with your treatment team
What is lymphoma?

Lymphoma is a family of blood cancers derived from white blood cells called lymphocytes.

- **B-cells**
- **T-cells**
- **NK-cells**

- Lymphocytes normally fight viruses, bacteria, fungi, and foreign organisms
- Lymphocytes travel in the lymphatic system
- These cells can grow in lymph nodes (nodal sites) or outside the lymph nodes (extranodal sites)

Lymphatic system: where the cells of the immune system work and travel

- Lymphatic system:
  - bone marrow
  - spleen
  - lymph nodes
  - lymph vessels
  - thymus
  - tonsils
  - blood

**Lymphoma grows in lymphoid tissues**

- "nodal" = growing in a lymph node
- "extranodal" = growing outside of a lymph node
WHO Classification of Lymphoid Neoplasms

Precursor
- B lymphoblastic leukaemia
- B lymphoblastic leukaemia, NOS
- B lymphoblastic leukaemia
- with recurrent genetic abnormalities
- B lymphoblastic leukaemia
- with t(12;21)(p13;q22); PBX1
- B lymphoblastic leukaemia
- with t(8;14)(q24;q32); BCR-ABL1
- B lymphoblastic leukaemia
- with t(6;12)(p13;q22); TEML1
- B lymphoblastic leukaemia
- with t(1;14)(p11;q32), ALK
- B lymphoblastic leukaemia
- with mythoerythron (myeloid ALL)
- B lymphoblastic leukaemia
- with t(11;14)(q13;q32), IGH
- B lymphoblastic leukaemia
- with t(1;19)(q23;p13.3), E2A-PBX1
- T lymphoblastic leukaemia

Indolent B
- Chronic lymphocytic leukaemia
- Small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Heavy chain lymphoma
- MALT lymphoma
- Waldenström’s macroglobulinaemia
- Heavy chain disease
- Alpha heavy chain disease
- Gamma heavy chain disease
- Myeloma
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Extramedullary marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodular marginal zone lymphoma
- Paediatric nodal marginal zone lymphoma
- Follicular lymphoma
- Paediatric follicular lymphoma
- Primary cutaneous follicle centre lymphoma

Aggressive B
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphohistiocytosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intervascular large B-cell lymphoma
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HDV-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Mature T/NK
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocyte leukaemia
- Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroxycytolymphoid-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extramedullary T-cell lymphoma
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Primary cutaneous gamma/delta T-cell lymphoma
- Primary cutaneous peripheral T-cell lymphoma
- Mycosis fungoides/NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative

HL and PTLD
- HODGKIN LYMPHOMA
- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
- Nodular sclerosis classical Hodgkin lymphoma
- Lymphocyte-rich classical Hodgkin lymphoma
- Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte depleted classical Hodgkin lymphoma
- POST-TRANSPLANT LYMOPHOPROLIFERATIVE DISORDERS (PTLD)
- Early lesions
- Plasmacytic hyperplasia
- Infectious mononucleosis-like PTLD
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)
- Classical Hodgkin lymphoma type PTLD

MCL is an uncommon type of Non-Hodgkin lymphoma

Mantle cell (5-6%)
Burkitt (2.5%)
Other subtypes (9%)
T and NK cell (12%)
Diffuse large B cell (DLBCL) (30%)
Follicular (25%)
Small lymphocytic (7%)
MALT-type marginal-zone B cell (7.5%)
Nodal-type marginal-zone B cell (<2%)
Lymphoplasmacytic (<2%)

12/20/2017
MCL is uncommon & usually aggressive

- Uncommon
  - ~6% of Non-Hodgkin Lymphomas
  - 5,000 new cases in USA per year
- Median age 68
- Male predominance (3:1 to 4:1)
- Advanced stage disease
  - Bone marrow and GI tract
- Usually aggressive
- Incurable

**Cause of MCL is unknown**

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Overexpression of Cyclin D1 is the genetic hallmark of MCL

![Diagram showing the genetic hallmark of MCL](Dreyling, Cancer Res, 1997)
The clinical significance of genetic alterations in MCL is subject of ongoing research

Pathologic Workup

<table>
<thead>
<tr>
<th>Method</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine histologic study</td>
<td>Morphologic classification</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td>Lineage, subtyping by protein expression</td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>Lineage, evaluation principally of cell surface protein</td>
</tr>
<tr>
<td>Cytogenetics, FISH</td>
<td>Chromosomal abnormalities including translocations</td>
</tr>
<tr>
<td>Molecular tests</td>
<td>Clonality by immune receptor gene</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulin variable heavy chain status (mutated vs. unmutated)</td>
</tr>
<tr>
<td></td>
<td>Genomic sequencing to identify presence of mutations (TP53, etc)</td>
</tr>
</tbody>
</table>
Complete pathologic work up of MCL

- Excisional lymph node biopsy
- Morphology: small-medium sized abnormal lymphocytes
- Immunohistochemical stains and flow cytometry tests
  - CD20+, CD19+, CD5+, CD23-
  - Cyclin D1+ cells
  - MIB-1 (Ki-67) proliferation index
- Chromosomal evaluation
  - FISH positive for t(11;14)(q13;q32)
- IGHV status: unmutated
- Targeted genomic sequencing: TP53 mutation

How do patients present with MCL?

- Lymph node enlargement
- Low blood counts
  - If hemoglobin is low, patients can have fatigue
- “B” symptoms (fevers, night sweats, weight loss)
- Enlarged spleen
  - Left upper quadrant pain, decreased appetite, feeling full early, weight loss
- Gastrointestinal symptoms
  - Change in bowel movements, bright red blood per rectum, tarry black stools
- No symptoms
  - Might be found during a colonoscopy
  - Incidentally noted abnormal blood test
Staging: how much disease is present?

- Standard tests:
  - PET scan
  - CT scans of neck, chest, abdomen, pelvis
  - Bone marrow biopsy
  - Blood tests for complete blood count, chemistries, LDH

- Other tests that may be useful:
  - Spinal tap (lumbar puncture)
  - Colonoscopy and EGD

Most patients have stage IV disease (BM, blood, GI tract)

MCL proliferation signature predicts outcome

- Gene expression profiling (GEP) of MCL identified a signature associated with proliferation that predicted outcome
- Determination of proliferation by Ki-67 expression by immunohistochemistry can substitute for the GEP
- Ki67 (MIB-1) is a marker of proliferation
- MCL with high Ki67 is generally more aggressive

Rosenwald, Cancer Cell, 2003
MCL is biologically heterogeneous and risk stratification incorporates multiple biologic factors

**LOW RISK**
- Low Ki-67 (≤10%)
- SOX-11 negative
- IGHV hypermutated
- Stable karyotype

**HIGH RISK**
- Blastic / blastoid / pleomorphic
- High Ki-67 (>30%)
- Complex karyotype
- TP53 alterations

**Indolent MCL**

**Classic MCL**

**Blastic MCL**
Emerging therapies for MCL

“Standard” frontline therapy

**Newly Diagnosed MCL**

- Asxs MCL
- Observation

- Localized MCL (CS I/II)
- RT
- ChemoRT

- Transplant Eligible
  - Induction Regimen
  - R-maxi-CHOP + Ara-C
  - RCHOP/RDHAP
  - RDHAP
  - HyperCVAD

- Transplant Ineligible
  - Induction Regimen
  - R-CHOP → R
  - Benda-R
  - R²

- HDT/ASCR
- Rituximab maintenance
No clear criteria to select pts for OBS in MCL

– BIOLOGIC FEATURES
  • Lack of Sox-11 expression
  • IGHV hypermutated
  • Low Ki-67 <10%
  • Lack of blastic, blastoid, pleomorphic histology
  • Lack of TP53 mutation

– CLINICAL FEATURES
  • Asymptomatic, do not meet criteria to initiate treatment
  • Leukemic phase, splenomegaly, absence of lymphadenopathy
  • GI tract only disease

Observation in MCL: MSKCC Experience

The median time of observation is 18 months.

No decrease in overall survival (OS) with observation versus immediate treatment
  • Median overall survival of the immediate treatment group was 9.4 years and 11.4 years for the observation group.

Kumar, ASH, 2016
"Standard" frontline therapy

Newly Diagnosed MCL

- Asxs MCL
  - Observation
- Localized MCL (CS I/II)
  - RT
  - ChemoRT
- Transplant Eligible
  - Induction Regimen
    - R-maxi-CHOP + Ara-C
    - RCHOP/RDHAP
    - HyperCVAD
  - HDT/ASCR
  - Rituximab maintenance
- Transplant Ineligible
  - Induction Regimen
    - R-CHOP → R
    - Benda-R
    - R²

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

Eligibility (n = 299)
- Previously untreated CD20-positive MCL
- Age: 18-65 years

CR/PR

R-DHAP × 4 → ASCT (n = 257)

R

Maintenance
- Rituximab (375 mg/m²) every 2 months for 3 years (n = 119)
- Watch and wait for 3 years (n = 119)

CR = complete response; PR = partial response
R-DHAP = rituximab with dexamethasone, cytarabine and cisplatin

- Patients who did not achieve ≥PR after DHAP could receive 4 additional courses of R-CHOP
- **Primary endpoint:** Event-free survival (EFS) at 4 years after randomization

Le Gouill, NEJM, 2017
Excellent Outcomes with RDHAP(X) x4 → HDT/ASCR → Rituximab maintenance

4-year event free survival 79% vs. 61% for R maintenance vs. Observation

“Standard” frontline therapy

Newly Diagnosed MCL

Asxs MCL ↔ Observation

Localized MCL (CS I/II) ↔ RT ChemoRT

Transplant Eligible ↔ Transplant Ineligible

New MCL

Induction Regimen
- R-maxi-CHOP + Ara-C
- RCHOP/RDHAP
- RDHAP
- HyperCVAD

HDT/ASCR → Rituximab maintenance

*
Bendamustine-rituximab versus RCHOP for newly diagnosed MCL

Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide

Induction (cycles 1-12)

Maintenance (cycle 13 - POD)

Response assessment: Cheson 2007; DVT prophylaxis: ASA
Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide

**Induction Phase (n=38)**
- N/A (n=2)
- PD (n=3)

**Maintenance Phase (n=33)**
- PD (n=8)
- Deceased (n=3)
- Deceased, non-lymphoma (n=3)
- Completed 3-year Therapy (CR (n=3))

**In Treatment Beyond 3 years (n=19)**
- Len (n=1)
- Len+R (n=14)
- R (n=4)

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**R2: Outcomes**

**Progression-Free Survival**

- 36-month PFS = 80.3% (95% CI = 63.0%, 90.1%)
- 48-month PFS = 70.6% (95% CI = 52.0%, 83.1%)

Median follow-up = 61 months (range 21-74)
Adding targeted therapies to frontline treatment may improve outcomes

• MSKCC 15-196 Phase II Clinical Trial:
  - Lenalidomide + RCHOP x 4 cycles
  - R-HiDAC x 2 cycles
  - Rituximab+Lenalidomide Maintenance x 6 mos

• SHINE: Randomized Phase III Study in Elderly MCL
  - MCL >65 yrs
  - BR+Ibrutinib → R Maintenance+Ibrutinib
  - BR+Placebo → R Maintenance+Placebo

• MSKCC 17-216 Phase I/II Clinical Trial: BR+IBR+VEN
  - BR+Ibrutinib+Venetoclax

WHEN MCL COMES BACK
(also called recurrent or relapsed disease)
What are signaling pathways?

- Cascade of events inside a cell
- Usually cause cancer cells to grow and stay alive
- Can be targeted
- Some cancer cells are “addicted” to certain pathways

![Diagram of signaling pathways]

Improved understanding of aberrant cellular pathways in MCL has led to development of mechanism-based treatments

Cheah, JCO, 2015
Ibrutinib in relapsed / refractory MCL

**Outcome**

<table>
<thead>
<tr>
<th>All Patients (N=111)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>75 (68%)</td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>Partial Response Rate</td>
<td>52 (47%)</td>
</tr>
<tr>
<td>Median Duration of Response</td>
<td>17.5 months</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>13.9 months</td>
</tr>
</tbody>
</table>

Ibrutinib

Lenalidomide in relapsed / refractory MCL

**Immunomodulatory Agent with Various Antitumor Effects:**

- Increased Th1 Cytokines
  - IL-2 and IFN-γ
- Increased Activity of Cytotoxic T-cells
- Augments NK cell function and number
- Inhibition of angiogenesis
- Down-regulation of cyclin D1

**Outcome**

<table>
<thead>
<tr>
<th>All Patients (N=134)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>37 (28%)</td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>10 (7.5%)</td>
</tr>
<tr>
<td>Partial Response Rate</td>
<td>27 (20%)</td>
</tr>
<tr>
<td>Median Duration of Response</td>
<td>16.6 months</td>
</tr>
<tr>
<td>Progression free survival</td>
<td>4 months</td>
</tr>
</tbody>
</table>

Kotla, J Hem & Oncol, 2009

Goy, JCO, 2013
**Venetoclax in relapsed / refractory MCL**

**Outcome**

<table>
<thead>
<tr>
<th>All Patients (N=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR 21 (75%)</td>
</tr>
<tr>
<td>CRR 6 (21%)</td>
</tr>
<tr>
<td>PRR 15 (54%)</td>
</tr>
</tbody>
</table>

Venetoclax Inhibits BCL\(_2\)

Apoptosis is Initiated

Mitochondria

Davids MA, JCO, 2016

**Low complete response rates with single-agent biologically-targeted agents in rel/ref MCL**

<table>
<thead>
<tr>
<th>Agent</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>13/69</td>
<td>28/69</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>10/134</td>
<td>37/134</td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>52/111</td>
<td>52/111</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>9/16</td>
<td>9/16</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>1/54</td>
<td>1/54</td>
</tr>
<tr>
<td>Paltocidab</td>
<td>1/17</td>
<td>1/17</td>
</tr>
<tr>
<td>Venetoclaks</td>
<td>15/28</td>
<td>15/28</td>
</tr>
<tr>
<td>Abovacostat</td>
<td>6/28</td>
<td>6/28</td>
</tr>
</tbody>
</table>

Percentage of Patients

CR

PR

Many new treatment categories for MCL in development...to name a few:

- PI3-kinase inhibitors
- Cyclin-dependent kinase inhibitors
- PRMT5 inhibitors and other epigenetic modifiers (HDAC inhibitors like abexinostat)
- Immune therapy
  - CART-cell (genetically engineered immune effector T-cells)
  - Checkpoint inhibitors
  - Bispecific antibodies
- New anti-CD20 inhibitors
  - Obinutuzumab
  - Ofatumumab
- Antibody drug conjugates

Synergistic combinations of biologically-targeted agents may enhance efficacy in rel/ref MCL

Phase I-IB clinical trial of buparlisib and ibrutinib in mantle cell, follicular, and diffuse large B-cell lymphoma

Among 11 patients with MCL, ORR was 100%, including eight CR and three PR.
### Ibrutinib and Venetoclax

- Phase II study
- N=24 patients
- Overall response rate 71%.
- Improved CR rate of 63% (of these 77% were MRD negative in the bone marrow)
- Toxicities
  - Fatigue, diarrhea, nausea, upper respiratory infection, GERD, neutropenia, cough, bruising, and tumor lysis syndrome

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### Side effects management

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### Side effect profile of a treatment

- The side effects of any treatment can be generally estimated, but hard to predict what side effects will occur in any individual patient
  - Likely (>20%)
  - Less Likely (<20%)
  - Rare but serious (<2-3%)
- In addition to incidence (how common or rare), how severe?
  - Manageable with supportive care?
  - Require inpatient hospitalization?
  - Reversible?
  - Potentially life-threatening?

### Selection of treatment

- **Consider goals of treatment**
  - Optimize initial remission duration
  - Optimize short-term quality-of-life
- **Consider age, health status, and other medical problems**
  - Age and functional status
  - Cardiac disease
    - Atrial fibrillation
  - Peripheral neuropathy
  - History of bleeding
  - Other medications
Acalabrutinib

Acalabrutinib is a more selective, potent BTK inhibitor developed to minimize off-target activity.

- FDA-approved Oct 2017
- Ibrutinib associated with atrial fibrillation (6–9% of patients), infection (14–29%), and bleeding (up to 6%)
- Acalabrutinib is possibly associated with a more favorable safety profile
  - No cases of atrial fibrillation
  - One case of severe bleeding event

Wang, Lancet, 2017

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>47 (38%)</td>
<td>30 (24%)</td>
<td>15 (12%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>38 (31%)</td>
<td>21 (17%)</td>
<td>13 (10%)</td>
<td>4 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34 (27%)</td>
<td>24 (19%)</td>
<td>8 (6%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>26 (21%)</td>
<td>19 (15%)</td>
<td>6 (5%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>24 (19%)</td>
<td>21 (17%)</td>
<td>3 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>22 (18%)</td>
<td>12 (10%)</td>
<td>9 (7%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>19 (15%)</td>
<td>14 (11%)</td>
<td>5 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Wang, Lancet, 2017

Communicating with your treatment team
Communication

• Your oncologist and health care team are your advocates
  – Be sure to tell them what are your wishes, needs, goals, questions, and concerns
• Bring another "set of ears" to your appointments
• Ask about clinical trial options
  – Many new therapies
  – Best access to new drugs and novel combinations is in the context of a clinical trial
  – Take home a copy of the informed consent document. Read it and bring back questions. Your team can help explain the rationale, the experience on the study thus far, the anticipated side effects, etc..

CONCLUSION

• Great sense of optimism in the field of MCL
• Many new treatments with exciting activity
• A real hope that novel treatment strategies will translate into significant improvements in survival and quality of life for MCL patients

THANK YOU!
What’s on the Horizon for Mantle Cell Lymphoma?

Q&A Session

Ask a question by phone:
• Press star (*) then the number 1 on your keypad.

Ask a question by web:
• Click “Ask a question”
• Type your question
• Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

The Leukemia & Lymphoma Society Offers:

• Information Resource Center: Information Specialists, who are master’s level oncology professionals, are 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

• Free Education Booklets:
  ➢ www.LLS.org/booklets

• Free Telephone/Web Programs:
  ➢ www.LLS.org/programs

• Live, weekly Online Chats:
  ➢ www.LLS.org/chat
The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance and more: [www.LLS.org/support](http://www.LLS.org/support)
  - **NEW 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 Video:** 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)

- **Free Nutrition Consults:** 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)

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**THANK YOU FOR PARTICIPATING!**

We have one goal: A world without blood cancers