What's on the Horizon for Mantle Cell Lymphoma?

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Welcome & Introductions

Dr. Kumar's slides are available for download at www.LLS.org/programs, under the program listing.

1

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What's on the Horizon for Mantle Cell Lymphoma?

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2

What's on the Horizon for Mantle Cell Lymphoma?

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Disclosures

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

3

Outline

Diagnosing mantle cell lymphoma (MCL)

Emerging therapies for MCL

Side effects management

Communicating with your treatment team

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4

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 lymphatic system
- These cells can grow in lymph nodes (nodal sites) or outside the lymph nodes (extranodal sites)

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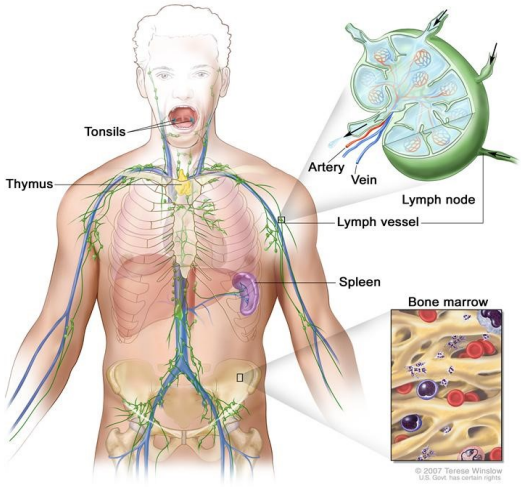
5

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

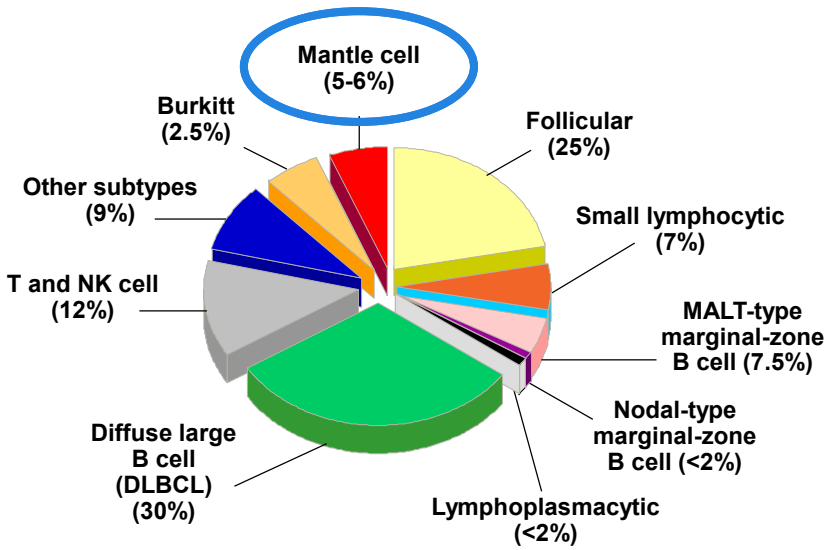
6

WHO Classification of Lymphoid Neoplasms

Precursor	Indolent B	Aggressive B	Mature T/NK	HL and PTLD
• B lymphoblastic leukaemia/lymphoma • B lymphoblastic leukaemia/lymphoma, NOS • B lymphoblastic leukaemia/lymphoma • with recurrent genetic abnormalities • B lymphoblastic leukaemia/lymphoma • with t(9;22)(q34;q11.2); *BCR-ABL1* • B lymphoblastic leukaemia/lymphoma • with t(v;11q23); *MLL* rearranged • B lymphoblastic leukaemia/lymphoma • with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)* • B lymphoblastic leukaemia/lymphoma • with hyperdiploidy • B lymphoblastic leukaemia/lymphoma • with hypodiploidy (hypodiploid ALL) • B lymphoblastic leukaemia/lymphoma • with t(5;14)(q31;q32); *IL3-IGH* • B lymphoblastic leukaemia/lymphoma with • t(1;19)(q23;p13.3); *E2A-PBX1; (TCF3-PBX1)* • T lymphoblastic leukaemia/lymphoma	• **Chronic lymphocytic leukaemia/ small lymphocytic lymphoma** • **B-cell prolymphocytic leukaemia** • **Splenic marginal zone lymphoma** • **Hairy cell leukaemia** • ***Splenic lymphoma/leukaemia, unclassifiable**** • ***Splenic diffuse red pulp small B-cell lymphoma*** • ***Hairy cell leukaemia-variant*** • **Lymphoplasmacytic lymphoma** • **Waldenström's macroglobulinemia** • **Heavy chain diseases** – **Alpha heavy chain disease** – **Gamma heavy chain disease** – **Mu heavy chain disease** • **Plasma cell myeloma** • **Solitary plasmacytoma of bone** • **Extraosseous plasmacytoma** • **Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)** • **Nodal marginal zone lymphoma** • ***Paediatric nodal marginal zone lymphoma*** • **Follicular lymphoma** • ***Paediatric follicular lymphoma*** • **Primary cutaneous follicle centre lymphoma**	• **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** • **Lymphomatoid granulomatosis** • **Primary mediastinal (thymic) large B-cell lymphoma** • **Intravascular large B-cell lymphoma** • **ALK positive large B-cell lymphoma** • **Plasmablastic lymphoma** • **Large B-cell lymphoma arising in HHV8-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***	• **T-cell prolymphocytic leukaemia** • **T-cell large granular lymphocytic leukaemia** • ***Chronic lymphoproliferative disorder of NK-cells*** • **Aggressive NK cell leukaemia** • **Systemic EBV positive T-cell lymphoproliferative disease of childhood** • **Hydroa vaccineforme-like lymphoma** • **Adult T-cell leukaemia/lymphoma** • **Extranodal NK/T cell lymphoma, nasal type** • **Enteropathy-associated T-cell lymphoma** • **Hepatosplenic T-cell lymphoma** • **Subcutaneous panniculitis-like T-cell lymphoma** • **Mycosis fungoides** • **Sézary syndrome** • **Primary cutaneous CD30 positive T-cell lymphoproliferative disorders** • **Lymphomatoid papulosis** • **Primary cutaneous anaplastic large cell lymphoma** • **Primary cutaneous gamma-delta T-cell lymphoma** • ***Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma*** • ***Primary cutaneous CD4 positive small/medium T-cell lymphoma*** • **Peripheral T-cell lymphoma, NOS** • **Angioimmunoblastic T-cell lymphoma** • **Anaplastic large cell lymphoma, *ALK* positive** • ***Anaplastic large cell lymphoma, ALK negative***	• **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 LYMPHOPROLIFERATIVE 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 #**

7

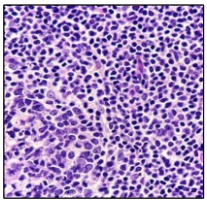
MCL is an uncommon type of Non-Hodgkin lymphoma



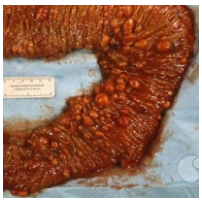
8

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



Small-medium sized lymphocytes



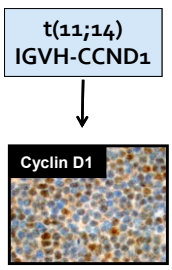
Lymphomatous Polyposis:
MCL of the Colon

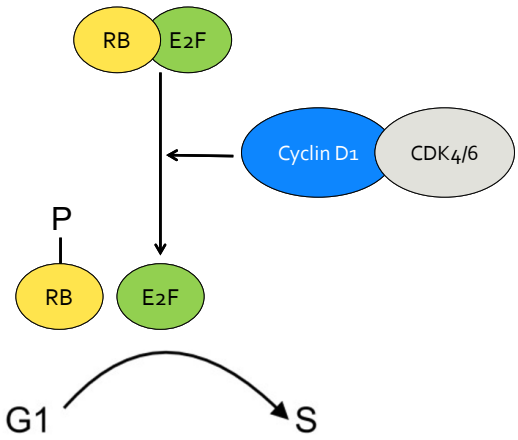
ASH Image Bank

Cause of MCL is unknown

9

Overexpression of Cyclin D1 is the genetic hallmark of MCL





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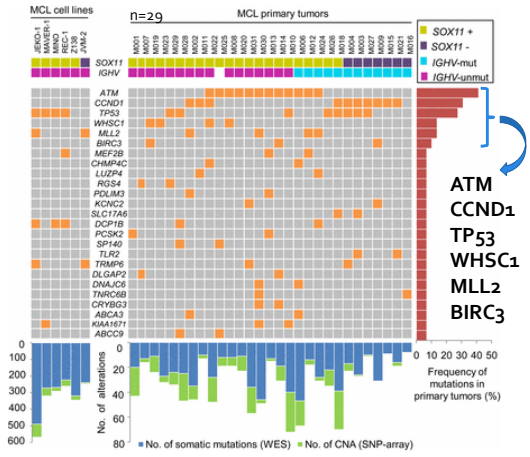
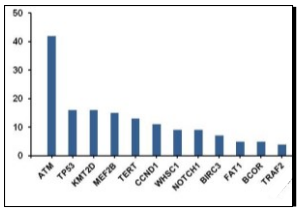
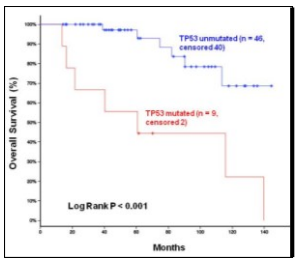
Dreyling, Cancer Res, 1997

10

The clinical significance of genetic alterations in MCL is subject of ongoing research







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Bea et al. PNAS, 2013
Kumar, ASH, 2016

11

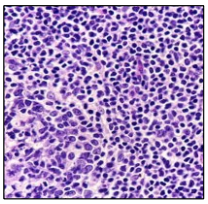
Pathologic Workup

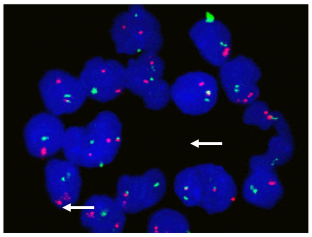
Method	Findings
Routine histologic study	Morphologic classification
Immunohistochemistry	Lineage, subtyping by protein expression
Flow cytometry	Lineage, evaluation principally of cell surface protein
Cytogenetics, FISH	Chromosomal abnormalities including translocations
Molecular tests	Clonality by immune receptor gene Immunoglobulin variable heavy chain status (mutated vs. unmutated) Genomic sequencing to identify presence of mutations (TP53, etc)

12

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



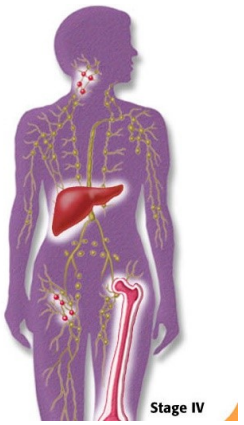


How do patients present with MCL?

- 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

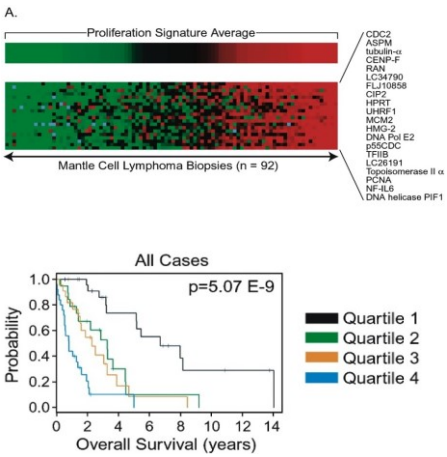
Staging: how much disease is present?

- 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)

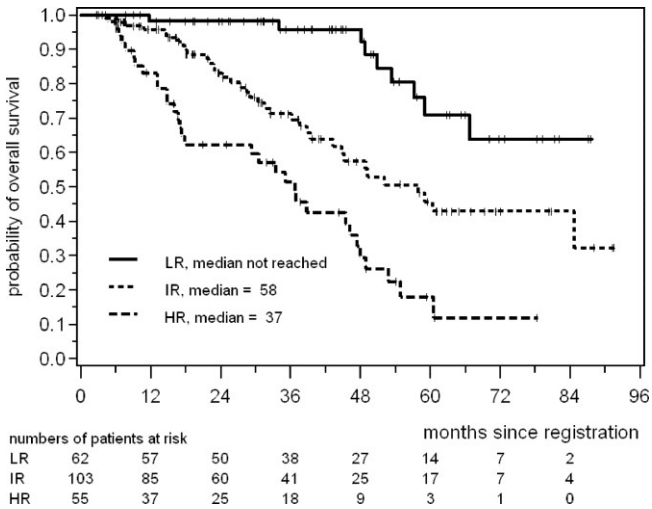
MCL proliferation signature predicts outcome



- 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

MIPI-Biologic Predicts Outcome in MCL



Factors:

Age
PS
LDH
WBC
Ki-67

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Hoster, Blood, 2008

17

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**

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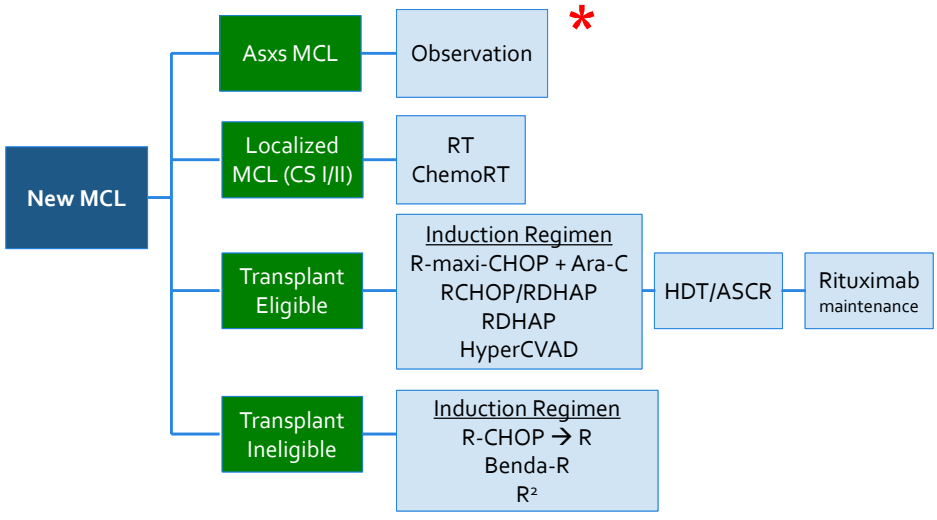
18

Emerging therapies for MCL

19

"Standard" frontline therapy

Newly Diagnosed MCL



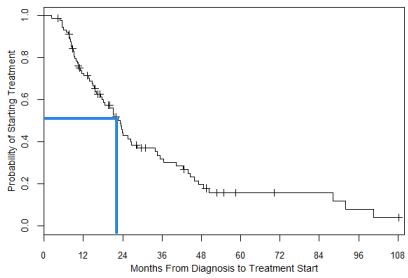
20

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 TP53 mutation
- **CLINICAL FEATURES**
  - Asymptomatic, do not meet criteria to initiate treatment
  - Leukemic phase, splenomegaly, absence of lymphadenopathy
  - GI tract only disease

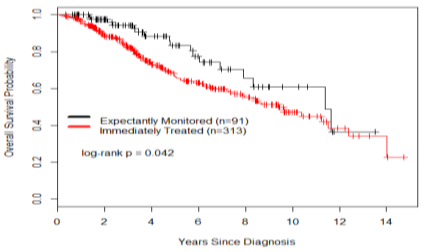
Observation in MCL: MSKCC Experience

The median time of observation is 18 months.



No decrease in overall survival (OS) with observation versus immediate treatment

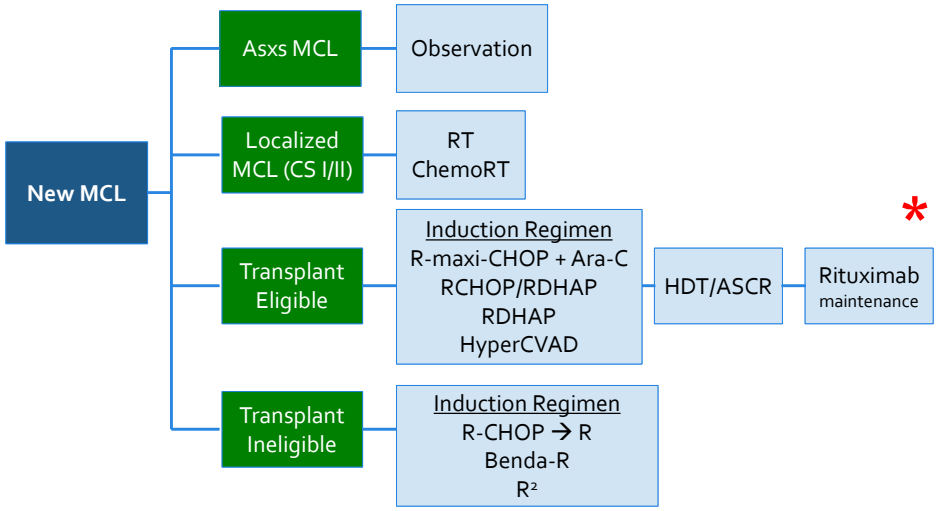
•Median overall survival of the immediate treatment group was 9.4 years and 11.4 years for the observation group.



Kumar, ASH, 2016

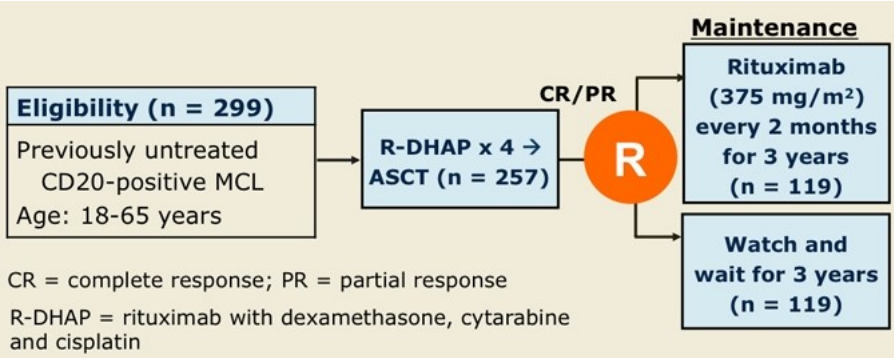
"Standard" frontline therapy

Newly Diagnosed MCL



23

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



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

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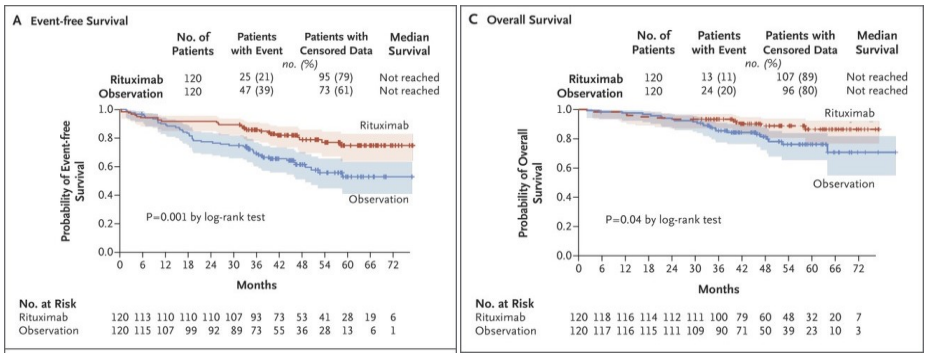
Le Gouill, NEJM, 2017

24

Excellent Outcomes with RDHAP(X) x4 → HDT/ASCR → Rituximab maintenance



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

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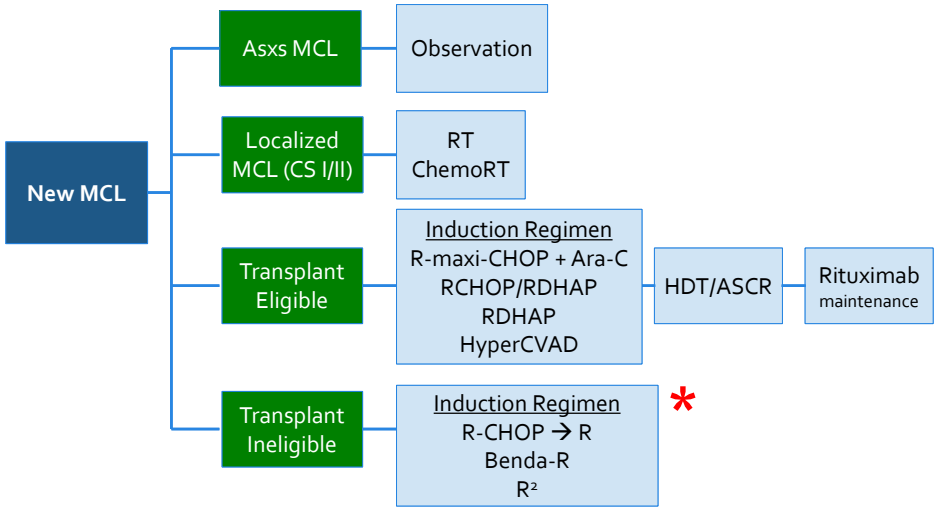
Le Gouill, NEJM, 2017

25

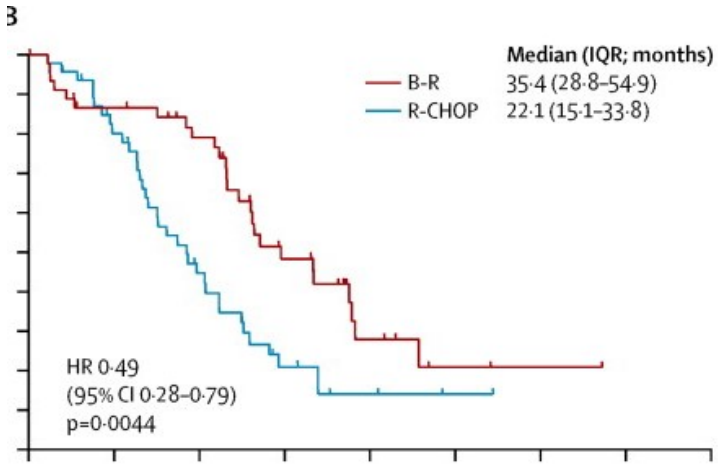
"Standard" frontline therapy

Newly Diagnosed MCL



26

Bendamustine-rituximab versus RCHOP for newly diagnosed MCL



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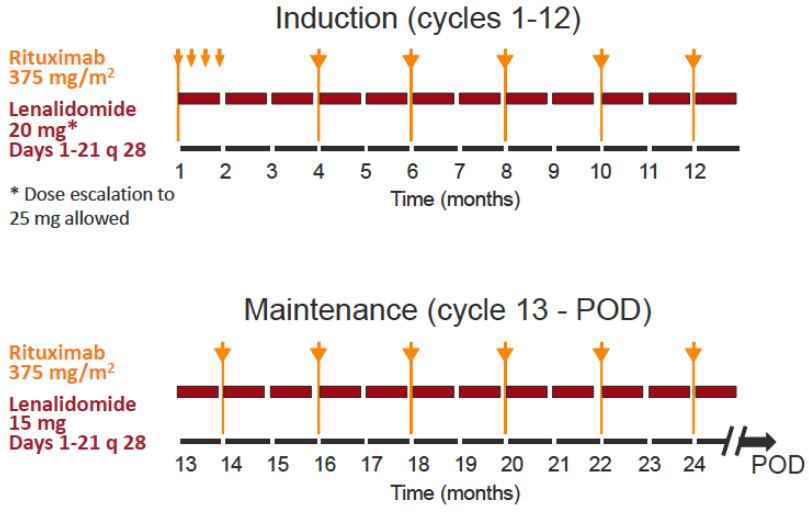
Mathias J Rummel , et al The Lancet, Volume 381, Issue 9873, 2013, 1203 - 1210

27

Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide



Response assessment: Cheson 2007; DVT prophylaxis: ASA

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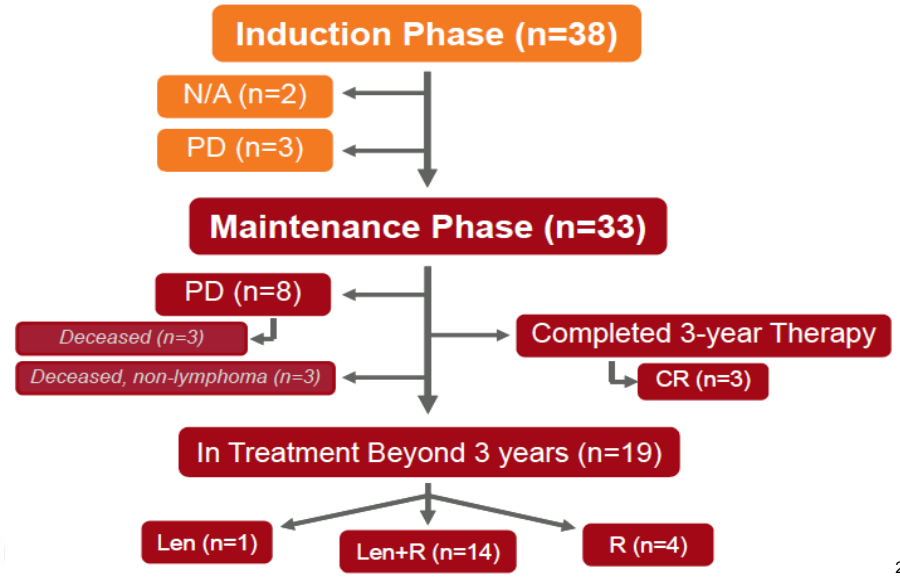
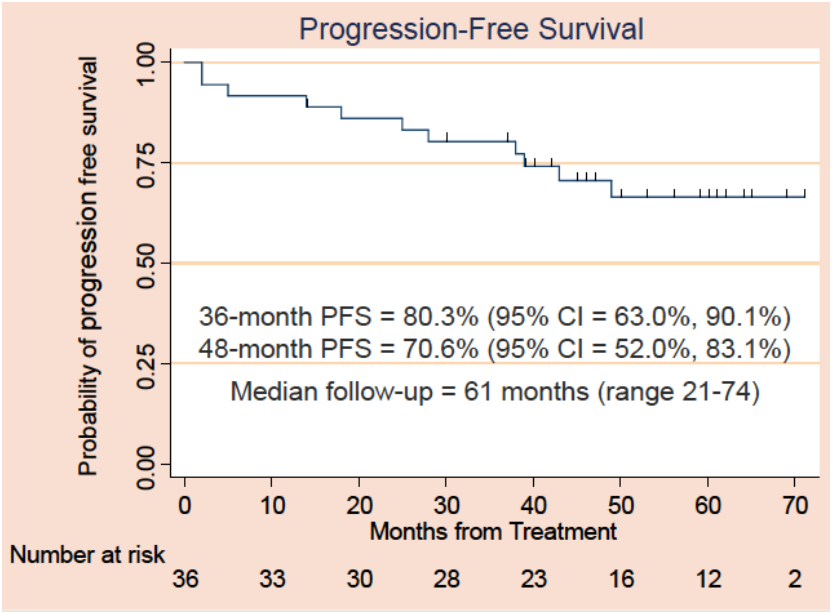
28

Chemotherapy–free initial treatment for MCL: Rituximab and Lenalidomide



29

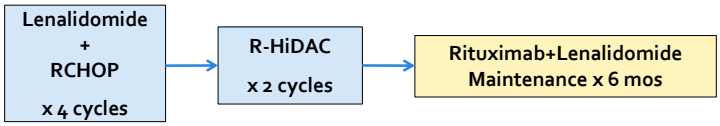
R2: Outcomes



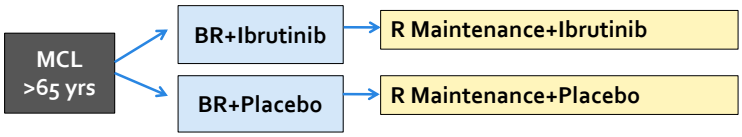
30

Adding targeted therapies to frontline treatment may improve outcomes

- MSKCC 15-196 Phase II Clinical Trial:



- SHINE: Randomized Phase III Study in Elderly MCL



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

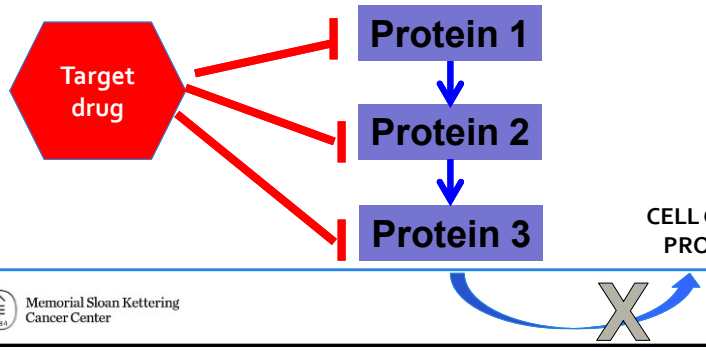
BR+Ibrutinib+Venetoclax

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



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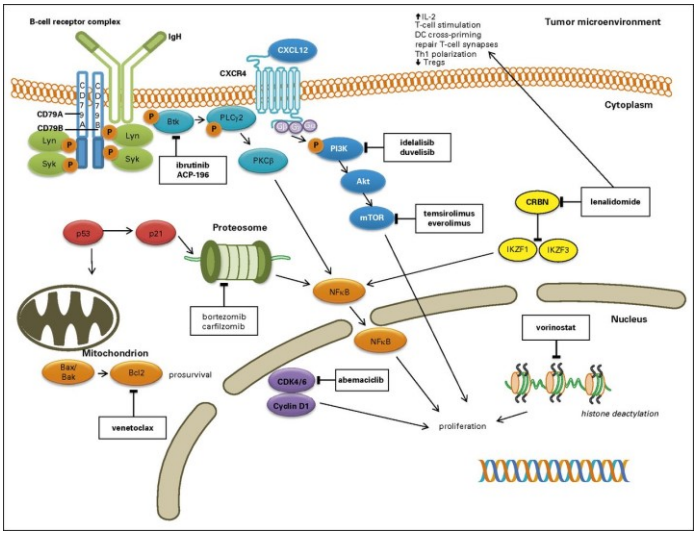
33

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



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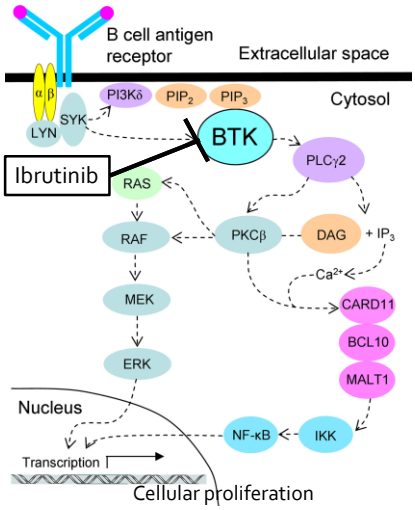
Cheah, JCO, 2015

34

Ibrutinib in relapsed / refractory MCL



Outcome	All Patients (N=111)
Overall Response Rate	75 (68%)
Complete Response Rate	23 (21%)
Partial Response Rate	52 (47%)
Median Duration of Response	17.5 months
Progression free survival	13.9 months

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Wang, NEJM, 2013

35

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	All Patients (N=134)
Overall Response Rate	37 (28%)
Complete Response Rate	10 (7.5%)
Partial Response Rate	27 (20%)
Median Duration of Response	16.6 months
Progression free survival	4 months

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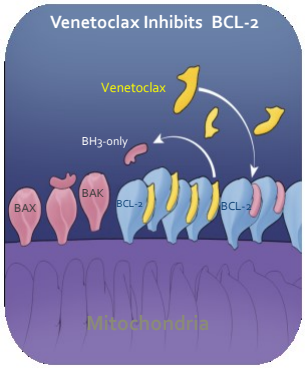
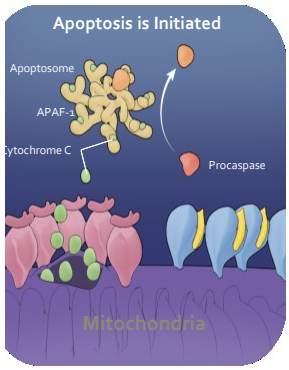
Kotla, J Hem & Oncol, 2009
Goy, JCO, 2013

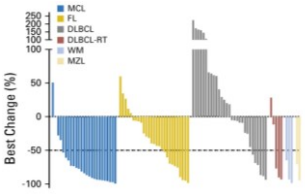
36

Venetoclax in relapsed / refractory MCL





Outcome	All Patients (N=28)
ORR	21 (75%)
CRR	6 (21%)
PRR	15 (54%)



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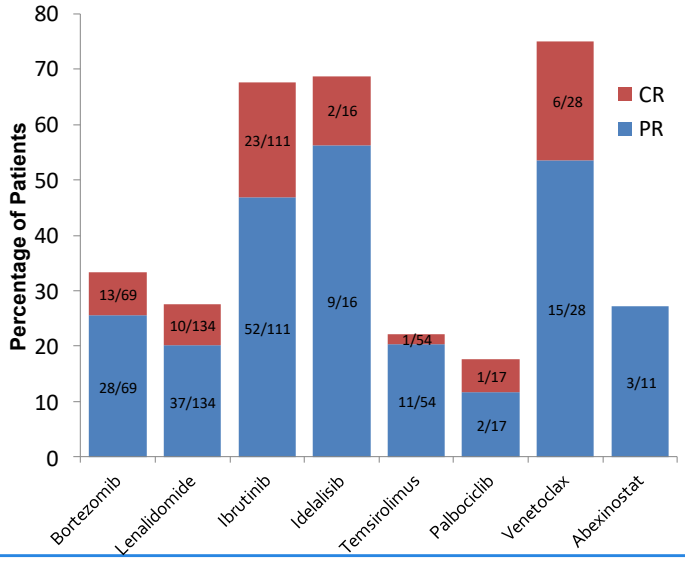
Davids MA, JCO, 2016

37

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



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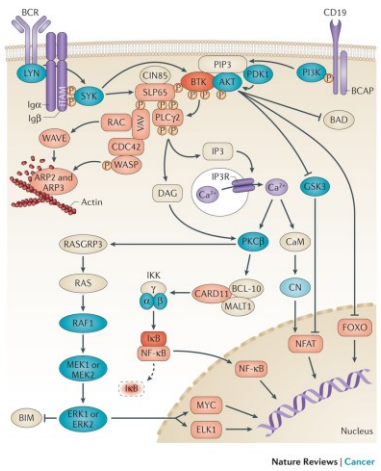
Fisher JCO 2006; Goy JCO 2013; Wang, NEJM, 2013; Kahl, Blood, 2014; Hess JCO 2013; Leonard Blood 2012; Gerecitano ASH 2015; Evens CCR 2016

38

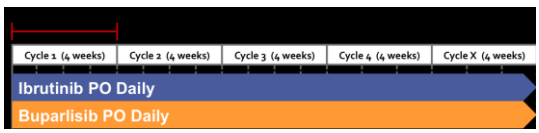
Many new treatment categories for MCL in development…to name a few:

- PI3-kinase inhibitors
- Cyclin-dependent kinase inhibitors
- PRMT5 inhibitors and other epigentic modifiers (HDAC inhibitors like abexinostat)
- Immune therapy
  - CAR T-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



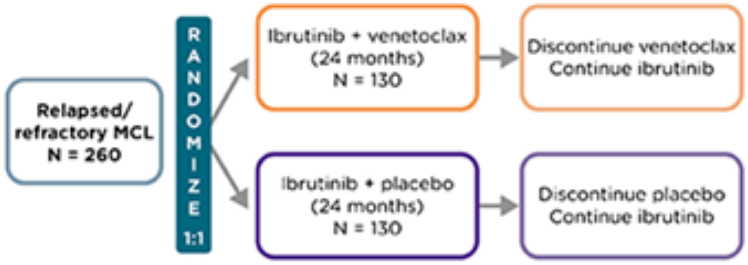
Dose Escalation		
Dose Level	Buparlisib (mg/day)	Ibrutinib (mg/day)
-1a	50	420
0	80	420
1	80	560
2	100	560

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

Hendricks, Nature Reviews Cancer, 2014
MSKCC IRB 16-009; Dr. Connie Batlevi, ICML 2017

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



Tam, ICML, 2017

41

Side effects management

42

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

	All grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5*
Most common events†						
Headache	47 (38%)	30 (24%)	15 (12%)	2 (2%)	0	0
Diarrhoea	38 (31%)	21 (17%)	13 (10%)	4 (3%)	0	0
Fatigue	34 (27%)‡	24 (19%)	8 (6%)	1 (1%)	0	0
Myalgia	26 (21%)	19 (15%)	6 (5%)	1 (1%)	0	0
Cough	24 (19%)	21 (17%)	3 (2%)	0	0	0
Nausea	22 (18%)	12 (10%)	9 (7%)	1 (1%)	0	0
Pyrexia	19 (15%)	14 (11%)	5 (4%)	0	0	0
Most common grade 3 or worse events§						
Anaemia	15 (12%)	1 (1%)	3 (2%)	10 (8%)	1 (1%)	0
Neutropenia	13 (10%)	0	0	6 (5%)	7 (6%)	0
Pneumonia	7 (6%)	0	1 (1%)	6 (5%)	0	0

- 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

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Wang, Lancet, 2017

45

Communicating with your treatment team

46

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?

LEUKEMIA & LYMPHOMA SOCIETY®

Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

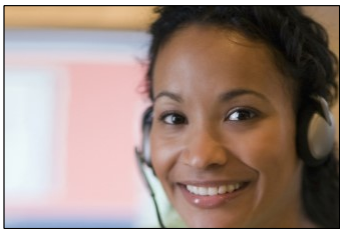
- Click "Ask a question"
- Type your question
- Click "Submit"

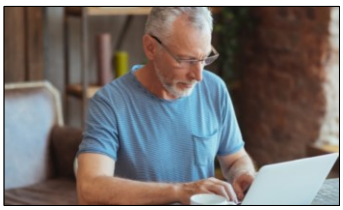
Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

49

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

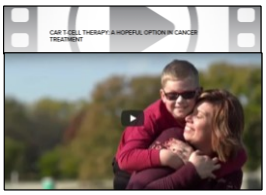




50

The Leukemia & Lymphoma Society Offers:

- **Support Resources:** LLS Community, discussion boards, blogs, support groups, financial assistance and more: 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**
- **Education Video:** Free education videos about survivorship, treatment, disease updates and other topics: 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
- **Free Nutrition Consults:** Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition
- **What to ask:** Questions to ask your treatment team: www.LLS.org/whattoask



51

THANK YOU FOR PARTICIPATING!

We have one goal:
A world without blood cancers

LEUKEMIA & LYMPHOMA SOCIETY®

52