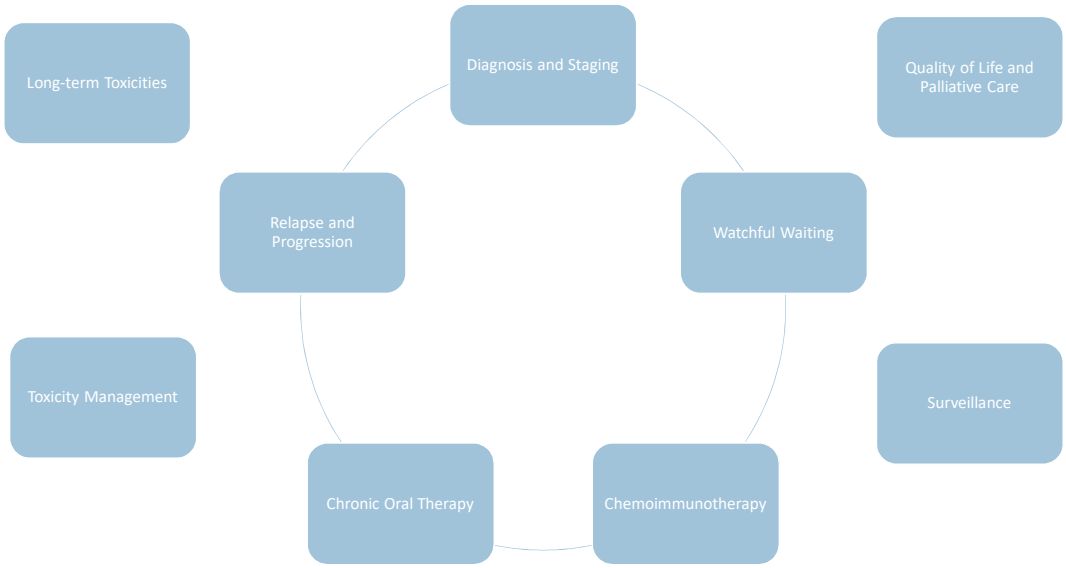
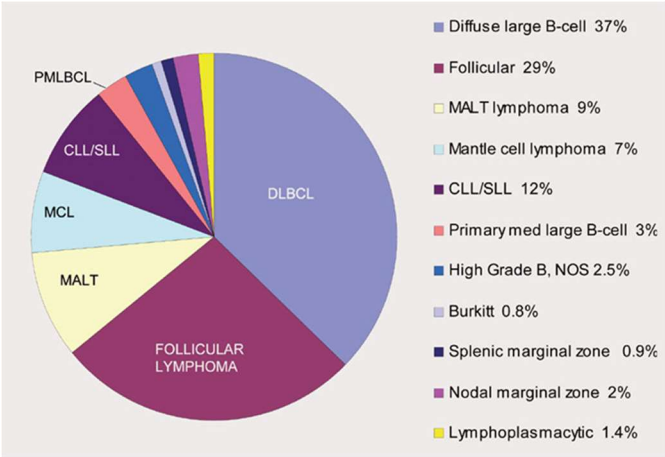
Disclosures

- Consulting/Advisory Services:
  - Abbvie, Celgene, Novartis, Pharmacyclics, Seattle Genetics
- Research Funding:
  - BMS, Janssen, Novartis, Takeda, BioInvent, Atara, Seattle Genetics, LAM
- I have received grant funding from ASH and LRF

Outline – Spectrum of indolent NHL lifespan



Indolent non-Hodgkin Lymphoma(s)



Jaffe, WHO 2008

Clinical Behavior of Indolent Lymphomas

There are many common features of indolent lymphomas

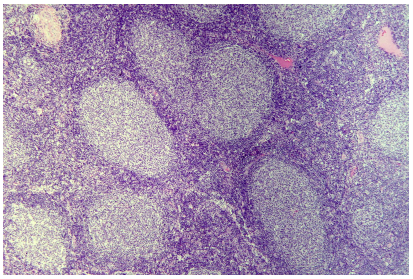
Positives	Challenges
Frequently non-aggressive	Considered "incurable"
Limited symptoms	Long course of treatments
Good prognosis	Challenging to explain to others
Many effective therapies (including oral)	Frequently require repeated treatments
May not require treatment upfront	

How is it Diagnosed?

- Many patients have no symptoms
  - Progressive swelling
  - Incidental finding (looking for something else)
  - Routine physical
- Others can have symptoms
  - Unexplained fevers
  - Drenching sweats
  - Weight loss
  - Fatigue?
  - Others depending on site of disease

Making the Correct Diagnosis

- Excisional biopsy (surgically removing the lymph node) is preferred whenever possible.
  - Some forms of indolent NHL can't be biopsied this way (CLL, MALT, others)
- Hematopathology review is important



Lymph node architecture is critical to making diagnosis

Making the Correct Diagnosis

- Each subtype has a specific signature and/or genetic characteristic
- These help make the diagnosis and can be prognostic

	Follicular lymphoma	Marginal zone lymphoma	CLL/SLL
Immunophenotype			
CD20	+	+	+
CD5	-	-	+
CD10	+	-	-
Genetic Rearrangement	t(14;18)	t(11;18) - sometimes	Varied

Evaluation of a Newly Diagnosed Patient

- Critical to make the right diagnosis
- CT scan (sometimes PET/CT)
- Appropriate prognostic evaluation
- HIV and Hepatitis Assessment
- Bone marrow biopsy (sometimes)
- Other assessments as indicated

- **Next steps: Discussion with your team about the diagnosis, stage, prognosis, and appropriate treatment**

Things to discuss with your oncologist

- Lymphoma subtype and stage
- General prognosis
- Your symptoms
- Why you may/may not need treatment right away
- Other medical conditions
- Life events
- Quality of life priorities
- Is there a clinical trial option?

You may *not* need immediate therapy

Decision to start treatment requires a discussion with your physician

GELF Criteria for Follicular Lymphoma
Largest mass < 7cm
≤ 3 sites with diameter > 3cm
Limited lymphoma cells in blood
Normal blood counts
No fluid collections
No organ damage or risked organ damage
No major spleen enlargement

Solal-Celigny, NEJM, 1993

iwCLL Criteria for CLL/SLL
Anemia or low platelets
Enlarged spleen
Massive lymph nodes
Rapid doubling time of WBC count
Disease-related symptoms

Hallek, *Blood,* 2008

****There is NO absolute WBC cutoff that requires Treatment in CLL****

Treating Follicular Lymphoma

- There are many options for your first treatment of follicular lymphoma
  - Is chemotherapy required?
  - Which chemotherapy?
  - Which antibody?
  - Is radiation appropriate and/or necessary?
  - What about maintenance?
- Essential to consider your goals, expected prognosis, other medical conditions, lifestyle, and overall disease-related expectations when choosing treatment.

Targeting CD20: The GALLIUM Study

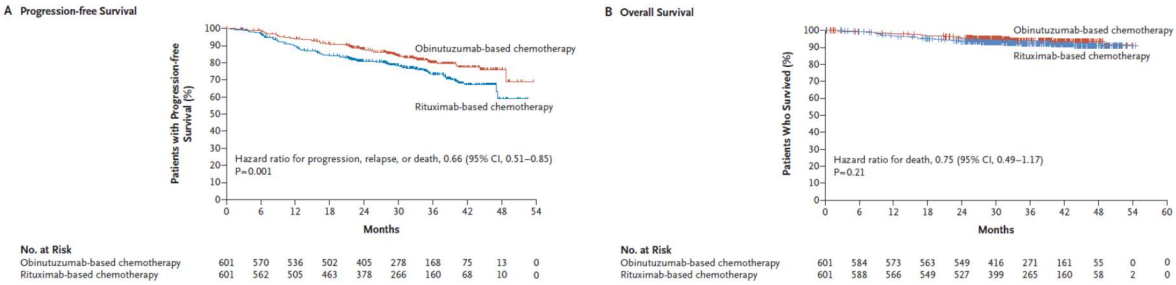
Untreated iNHL
- Stage III or IV disease, or stage II bulky disease requiring treatment
- ECOG PS 0, 1, or 2
- Exclude grade 3b follicular lymphoma, small lymphocytic lymphoma, or Waldenström macroglobulinemia

RANDOMIZE

- Obinutuzumab + chemotherapy of choice*
- Rituximab + chemotherapy of choice*

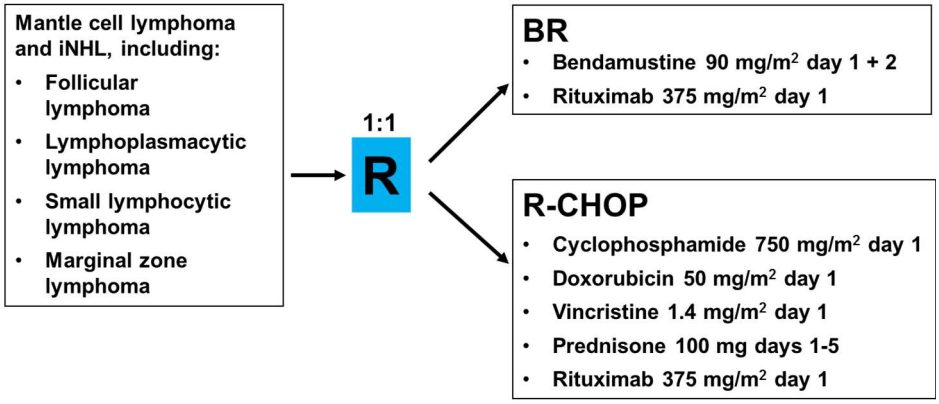
*CHOP, CVP, or Bendamustine

Targeting CD20: The GALLIUM Study

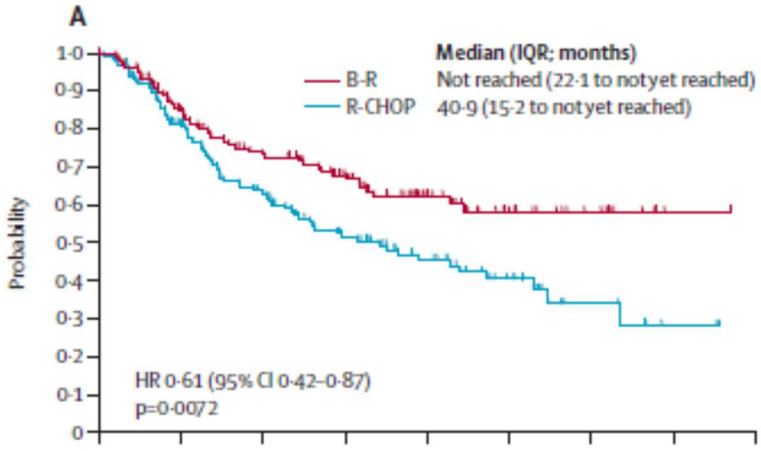


Marcus et al, *NEJM* 2017

Which chemotherapy is best? The StiL Study



The StiL Study



Rummel, *Lancet*, 2013

Side Effects

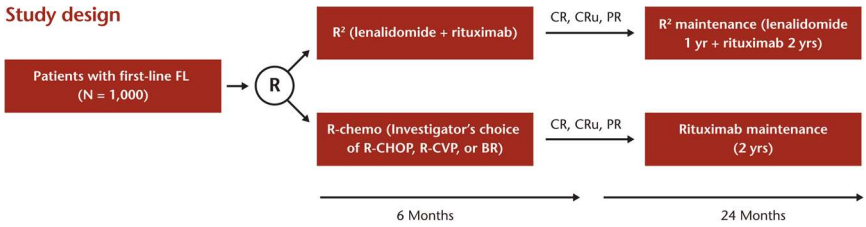
CD20 Antibodies (Rituximab/Obinutuzumab)
Infusion Reaction
Low antibody levels / recurrent infection
Rare neurologic complications
Low blood counts (worse with obinutuzumab)

Side effects are different for every patient and not always predictable.

CHOP	Bendamustine
Hair Loss	Low blood counts (can be persistent)
Low blood counts	Nausea/vomiting
Peripheral Neuropathy	Rash
Rare – heart failure	Others
Prednisone side effects	
Nausea/vomiting	
Others	

What about non-chemotherapy treatment?

- Relevance Study



- No clear improvement over chemotherapy but may be similar in outcome

Fowler et al, *ASCO* 2018

Initial Therapy Summary

- Important to use a monoclonal antibody targeting CD20
- Combination partner can vary
- Important to consider side effects of treatment
- Most patients respond well to treatment and remain in remission

Maintenance Therapy

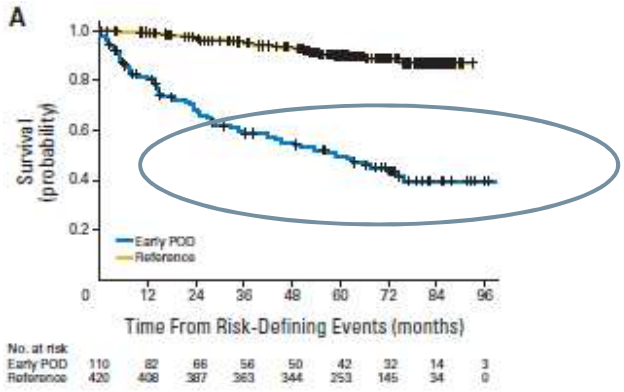
- Different ways to give maintenance
- Best data are for after R-CHOP
  - Role of maintenance after bendamustine is less clear
- Caution on side effects of prolonged treatment

- There is NO long-term survival benefit with maintenance therapy
- Goal is to prolong time before more treatment is needed

- Should be a *discussion* with your doctor and not a foregone conclusion

Follow-up after treatment for FL

- Time to first relapse is an important predictor of long term outcome



Patients with early relapse may have transformed disease and are more at risk of dying from the lymphoma.

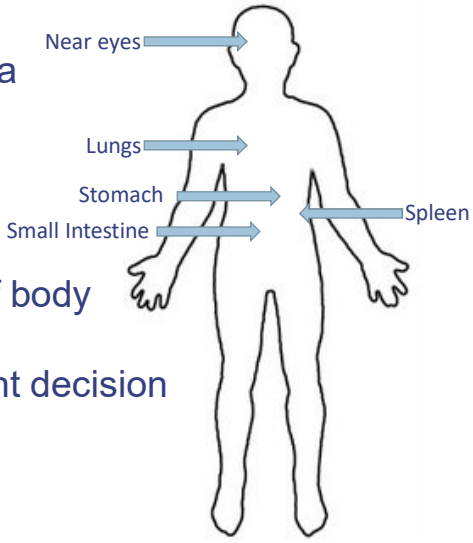
Casulo et al, *J Clin Oncology* 2015

Considerations for relapsed FL

- Many of same considerations as at initial diagnosis
  - Patient fitness and other medical conditions
  - Overall goals of treatment and patient lifestyle
  - Disease burden (big vs small nodes)
  - Symptoms
- Time to relapse often influences treatment decisions
- Most patients will relapse several times over the course of the disease
- Consider clinical trial

Marginal Zone Lymphoma

- Several types of marginal zone lymphoma
  - Splenic MZL
  - MALT lymphoma (extranodal)
  - Nodal MZL
- MALT can be diagnosed in many parts of body
- Specific disease type influences treatment decision

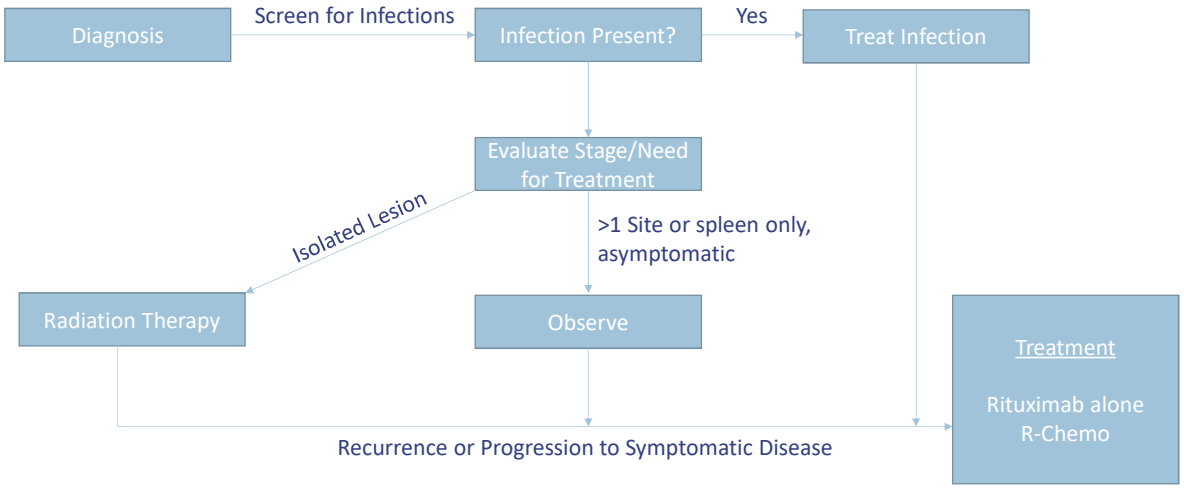


MZL associated with infections

- Hepatitis C
- H. Pylori (stomach ulcers)
- C. Psittaci (ocular)
- Others – less common

- Patients with an infectious cause of MZL should receive treatment for the infection first….this can be curative.

Management Approach to MZL



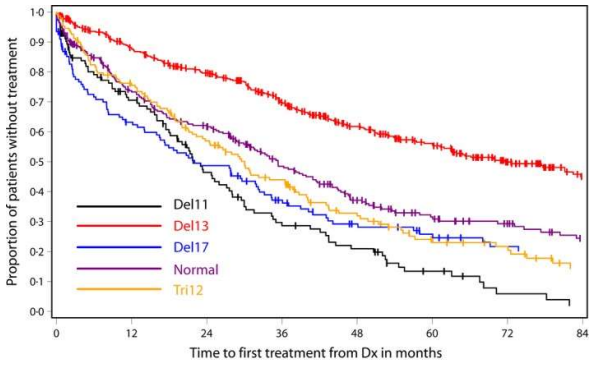
Treatment Considerations

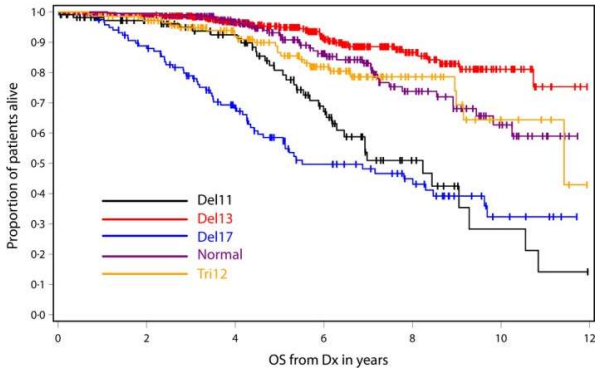
- Similar treatments to follicular lymphoma
- Patients with isolated lesions can receive radiation therapy
- Most others who require treatment will benefit from a CD20 antibody +/- chemotherapy (frequently bendamustine)
- My approach: Frequently rituximab alone followed by bendamustine-rituximab if not a great response
- Maintenance less well established in marginal zone lymphoma

Chronic Lymphocytic Leukemia & Small Lymphocytic Lymphoma

- These are basically the *same disease*
  - Cells identical under the microscope
  - Prognosis is similar
  - Treatment is similar
  - Some patients have a WBC count that we follow, others have lymph nodes, some have both
- Prognosis is variable – important to complete appropriate work-up

CLL/SLL Prognostic Work-up (FISH)



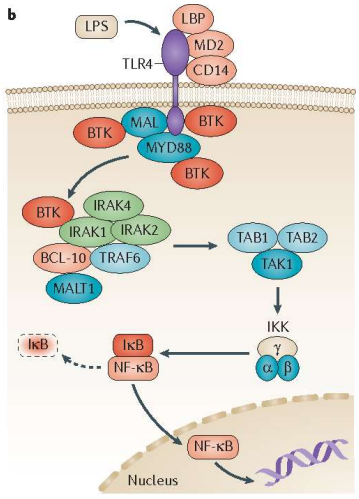


Van Dyke et al, BJH 2016

Treatment of CLL/SLL is evolving

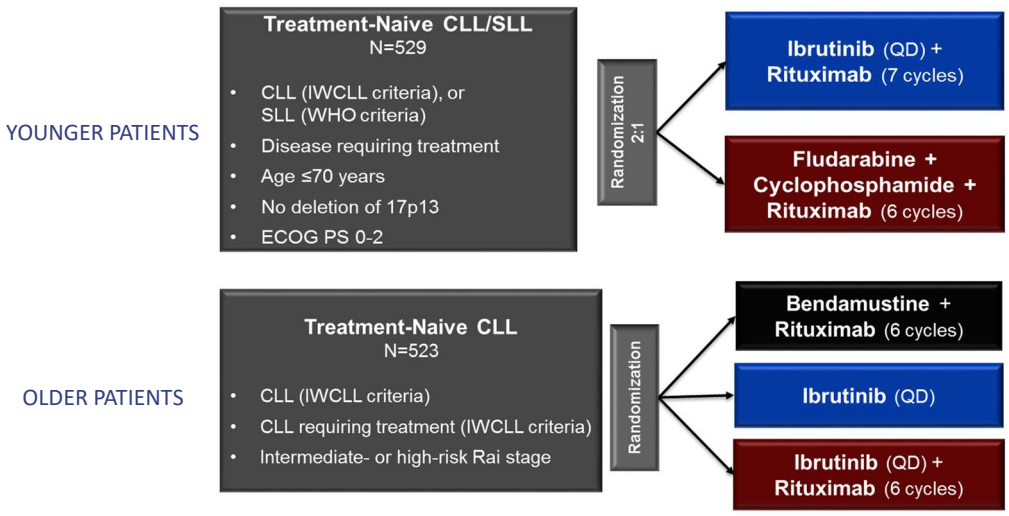
- Recent history:
  - Chemoimmunotherapy (FCR or BR)
  - Limited duration treatment
  - Long-term bone marrow toxicities
  - *Some* patients receiving FCR can have very long remissions
  - FCR likely better than BR in young patients – no difference in those > 65
- Two new studies compared chemo-immunotherapy to ibrutinib

Ibrutinib – Bruton's tyrosine kinase inhibitor

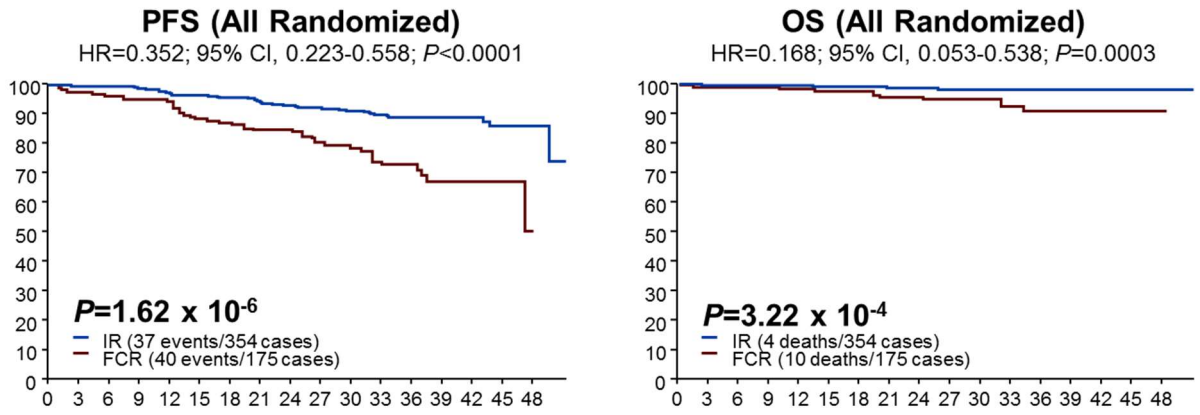


- Oral, daily therapy
- Administered indefinitely
- Meant to disrupt important pathway in CLL/SLL

Chemo-immunotherapy vs ibrutinib

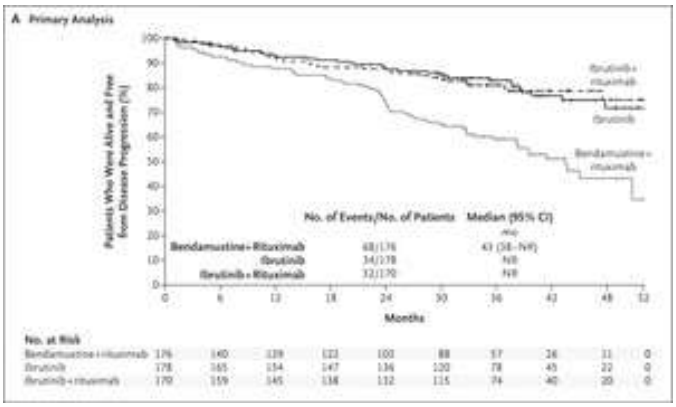


E1912 – FCR vs R-Ibrutinib in Young Pts



Shanafelt et al, ASH 2018

Alliance Study – Older Patients



Woyach et al, NEJM 2018

Considerations Front-line treatment CLL

- Chronic vs defined duration of treatment
- Finances
- Long-term mild toxicity vs short-term more significant toxicity
- What is long-term goal? Is time off of therapy meaningful?

Ibrutinib	Chemo-immunotherapy
Chronic, indefinite treatment	6 months of treatment
Expensive	Low blood counts
Diarrhea	Bone marrow toxicity
Bleeding/bruising	Nausea/vomiting
Atrial fibrillation	
Infection risk	
Arthralgias	

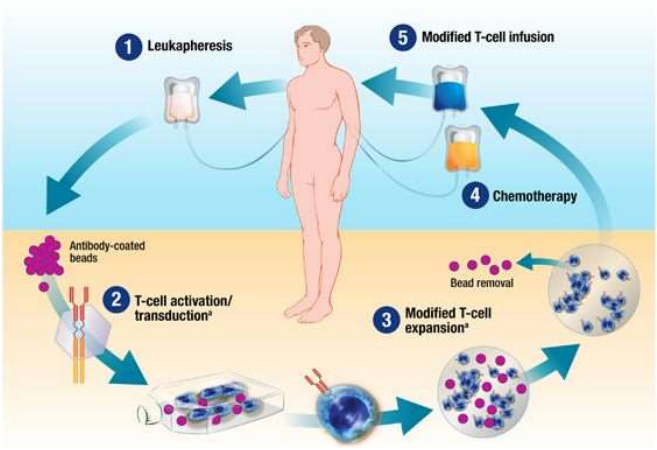
New/Emerging Treatments

- Oral targeted therapies
  - Pi3 Kinase inhibitors
  - BTK Inhibitors
  - Venetoclax
  - Others (syk, Pikfyve, mTOR) inhibitors
- Immunotherapies
  - Vaccine
  - CAR-T
  - Monoclonal antibodies
  - Bispecific antibodies
- Combination approaches

Incorporation of Novel Therapies in iNHL

- FDA approvals:
  - Idelalisib, Duvelisib, Copanlisib
  - Ibrutinib
  - Venetoclax
- Most approvals are for monotherapies – combinations may be better
- Caution – some combinations are toxic
- Ongoing clinical trials are critical. Patients with relapsed indolent NHL are often ideal candidates due to slow progression of disease.

Chimeric Antigen Receptor (CAR-T)



CAR-T currently approved for aggressive NHL

- Used for patients with *aggressive* or *transformed* NHL
- Cellular therapies ARE available for other lymphoma types on study
- These therapies typically not considered for untreated patients
- Ask your physician about any potential trials for relapsed patients

General Considerations

- Many patients with indolent NHL can live “normal” lives
  - Full time work
  - Families
  - Travel
  - Hobbies
- But…..living with cancer is often a source of stress and anxiety
- Patients need ongoing support

How to Help Loved Ones with Lymphoma

- Provide support at level desired by patient
- Patient experience fluctuates over the course of the disease
  - Level of day-to-day support may wax and wane depending on disease status, symptoms, side effects, etc.
- Be an advocate for the patient but not their doctor
- Respect their wishes and decisions
- Take notes, ask questions, be another pair of eyes/ears
- If you use the internet, use reputable sources for information:
  - www.LLS.org
  - www.Lymphoma.org

Summary

- Indolent NHL is a variety of diseases with different treatments
- Many patients are observed (for years) before first therapy initiated
- Patients will be treated on several occasions over their disease course
- Newer therapies are approved/in development, including combinations
- Clinical trial enrollment critical to success of future treatments
- Ask questions and be informed!

Thank You!

Q&A SESSION

Treatment Advances for Slow-Growing Non-Hodgkin Lymphomas

- **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.

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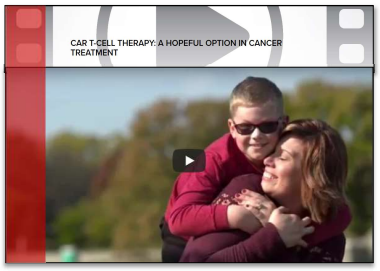

- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: **www.thebloodline.org**

- **Education Videos**

  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**

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: **www.LLS.org/support**

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THANK YOU
We have one goal: A world without blood cancers
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