UPDATE on CLL

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Welcome & Introductions

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CLL Update on Diagnosis and Treatment

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The James
Ohio State is a Comprehensive Cancer Center designated by the National Cancer Institute

NCI CCC

Chronic Lymphocytic Leukemia

- **Most prevalent type of adult leukemia**
- **Defined by select flow cytometry markers on leukemia cells (CD5, CD19, CD20, CD23, sIg).]**
- **Median age of diagnosis of CLL is 72 years, with only 10% of patients under age 50.**
- **More common in men than women (2:1 ratio)**
- **Environmental predisposition uncertain, although Vietnam Veterans with Agent Orange exposure warrant "service-connected status"**
- **Genetic predisposition present, with approximately 10% of patients having a first-generation relative with CLL however no common gene has been identified**

Critical Decision Times for CLL Patients

- Diagnosis*
  - Learning about disease and impact on life
  - Working through stress of having a blood cancer and likely not doing anything (watch and wait versus watch and worry)
- At time of first treatment*
  - Appropriate tests and choice of initial therapy
  - Consideration of clinical trials with non-chemotherapy based treatment
- Relapse disease*
  - Appropriate tests and choice of and consideration of clinical trials/transplant

*All junctures, in particular relapse are ideal times to see a CLL specialist who can work with your local doctor

Diagnosis and Evaluation of CLL

- Immunophenotype of blood to confirm diagnosis
- Physical exam and labs to confirm Rai stage
  - Rai 0 just lymphocytosis
  - Rai 1 lymph node enlargement
  - Rai 2 spleen enlargement
  - Rai 3 anemia (hemoglobin < 11 in absence of AIHA)
  - Rai 4 low platelets (<100 in absence of ITP)
- Bone marrow biopsy and CT scans not needed
- Prognostic factors
  - FISH—del(17p) and del(11q22.3) less favorable
  - IVGH mutational status—un-mutated less favorable
  - B_2M—higher less favorable
  - Lymphocyte doubling time < 1 year—higher less favorable
  - Other prognostic factors include CD38, ZAP-70 and others

Typical Discussion Following Testing

- Asymptomatic low risk disease (Stage 1-2)
  - No therapy or consideration of early intervention as part of clinical trial
  - Follow up Q3 months for 1 year and than Q6m
- Asymptomatic high risk disease (Stage 1-2)
  - No therapy outside of trial but consideration of early intervention with non-chemotherapy approach in clinical trial
  - Follow up Q3m indefintely
- Symptomatic low or high risk disease or Stage 3-4
  - Consider treatment based upon genetic findings
- Discussion of complications of disease

Autoimmune Cytopenias of CLL

- Autoimmune hemolytic anemia and thrombocytopenia common in CLL (10-25%) and often presents when disease is active
- Anemia or thrombocytopenia due to autoimmune complication does not impact survival and should not be used for staging
- Approach of AIHA and ITP requires assessment of secondary causes and relationship to disease or therapy
- AIHA and ITP treatment are quite similar with prednisone ± rituximab

Infections in CLL

- Most common cause of morbidity and mortality in CLL
- Preventative strategies include
  - Prevnar 13 at diagnosis and Q5 years
  - Influenza vaccine yearly and prophylaxis if exposed
  - No live vaccine (Including varicella zoster vaccine)
  - Viral and PCP prophylaxis with fludarabine or bendamustine
- IVIG use
  - Although expensive, it is effective prevent recurrent infections not cleared with multiple antibiotic courses
  - Consider giving for 1-2 months post influenza if IgG low

Other CLL Related Complications

- Secondary cancers
  - more common in CLL and related to immune suppression- regular screening should be considered for these
  - Bone marrow damage (MDS) more common after FCR
- Richter's Transformation
  - Pathology can be large cell lymphoma or Hodgkin's Disease
  - PET scans can be extremely useful in deciding nodal region to biopsy
  - Outcome of these patients poor and transplant should be considered
- Hypersensitivity to insects

When to Treat CLL Patients

- No advantage to treating CLL until symptoms develop irrespective of genomic features
- IWCLL 2008 criteria for treatment
  - Enlarging, symptomatic lymph nodes (> 10 cm)
  - Enlarging, symptomatic spleen (> 6 cm)
  - Cytopenias due to CLL (hemoglobin < 11, platelets < 100)
  - Constitutional symptoms due to disease (fatigue, B-symptoms)
  - Poorly controlled AIHA or ITP
  - Lymphocyte doubling time < 6 months or increase of 50% over a 2-month time period (weakest criteria)
- Lymphocyte count < 300 x 10^9/L not an indication for Rx

Hallek M, et al. Blood 15:5446-56, 2008

History of CLL Therapy: 1970-2013

- Chlorambucil: well tolerated oral agent but low response
- Fludarabine: higher response, longer remission but no major impact on survival; not beneficial to age >65 years
- Fludarabine/cyclophosphamide: higher response, longer remission, but no major impact on survival; MDS
- Antibody rituximab: well tolerated with low response
- Rituximab addition to fludarabine ± cyclophosphamide (FCR): higher response, longer remission and overall survival
  - FCR currently standard therapy for younger CLL patients
  - Bendamustine + Rituximab often substituted for FCR

Complications of FCR Therapy

- More common in patients > age 65
- Early
  - More neutropenia with rituximab; thrombocytopenia, and infection are similar
- Late
  - More Neutropenia with rituximab
  - Richter's Transformation risk lowered with rituximab
  - Myelodysplasia (3%)
  - Secondary cancer 8-9%

Alternative Regimens for CLL Therapy

- Bendamustine/rituximab (Fischer et al, JCO 2012)
  - 117 pt phase II study of untreated pts, 30 > age 70
  - 88% ORR, 23% CR
  - 34 month PFS
  - less effective in del(17p) pts (35% PR)
  - Toxicity includes cytopenias, infections and rash with overall 3.4% mortality; ? Less than FCR
  - Phase III study testing this versus FCR
- High Dose Methylprednisolone + Rituximab
- Chlorambucil + Rituximab
- Lenalidomide

Therapy Approach for Patients < age 65

- Repeat interphase cytogenetics, perform a bone marrow biopsy to rule out non-CLL problem
- Clinical trial offered with strong consideration of non-chemotherapy bridge therapy
- Off trial
  - « Del(17p13.1): rituximab + high dose solumedrol or FCR followed by non-myeloablative allogeneic stem cell transplant
  - « Del(11q22.3): FCR, BR
  - « Other genetic features: FR, BR
- Do not use PCR, rituximab, alemtuzumab, CLB or rituximab maintenance

Therapy Approach in Older Population (> 65 yrs)

- **Not** Fludarabine-based regimens irrespective of functional status; can consider
  - Bendamustine + Rituximab
  - Chlorambucil + Rituximab
- Infirmed patients: chlorambucil or rituximab
- New options: lenalidomide (approved by NCCN but insurance sometimes does not pay for)
  - Immune modulating agent
  - Reverses hypogammaglobulinemia seen in disease
  - Diminished infections as compared to other chemotherapy approaches
  - 64% progression free at 3-years

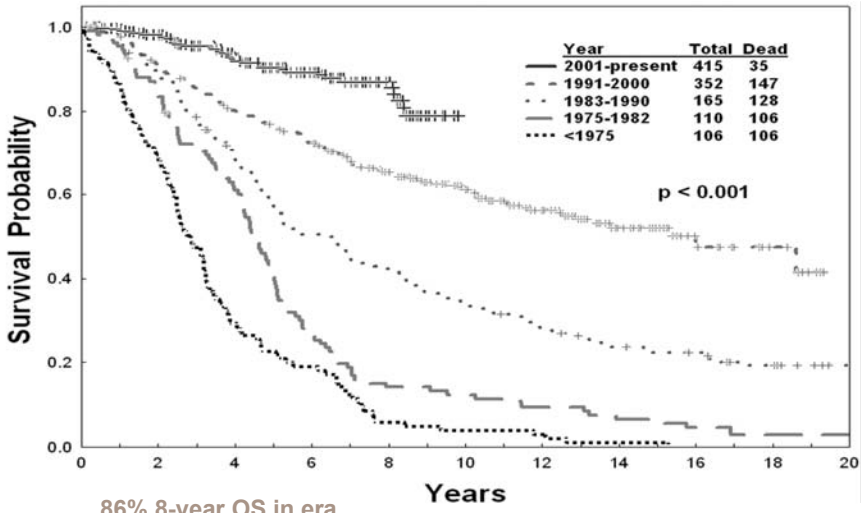
Considerations for Relapsed CLL

- **Outcome of pts at time of relapse depend upon**
  - **Interphase cytogenetics, β_2M, and stage**
  - **Prior therapy (i.e. monotherapy or chemoimmunotherapy)**
  - **Time of remission with last treatment**
- **Interphase cytogenetics should be repeated prior to initiating salvage therapy**
- **All pts with cytopenias should have repeat bone marrow biopsy to assess for MDS if prior FCR given**
- **Transplant evaluation should be considered early in this pt population if any unfavorable features present**

Salvage Regimens for CLL

- Fludarabine, Cyclophosphamide, and Rituximab
- Bendamustine + Rituximab-59% response and 14 m PFS with significant immune suppression
- High dose Solumedrol + Rituximab-30-50% response but very immunosuppressive
- Lenalidomide ± Rituximab-66% response and 24 m PFS
- Ofatumumab—50% response but short PFS and does not work in bulky del(17p13.1)
- Lymphoma salvage regimens (not effective except for Richters transformation

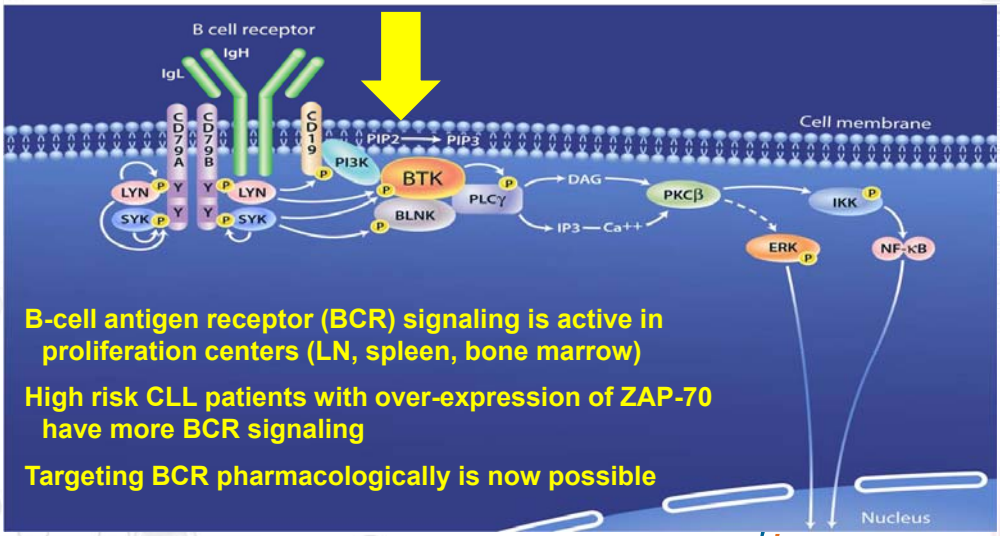
Our Goal in CLL Therapy: CML in 2012



86% 8-year OS in era of imatinib

Kantarjian H *et al*. Blood 2012;119:1981-1987

Targeting BCR Signaling in CLL



B-cell antigen receptor (BCR) signaling is active in proliferation centers (LN, spleen, bone marrow)

High risk CLL patients with over-expression of ZAP-70 have more BCR signaling

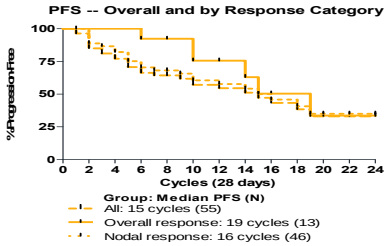
Targeting BCR pharmacologically is now possible

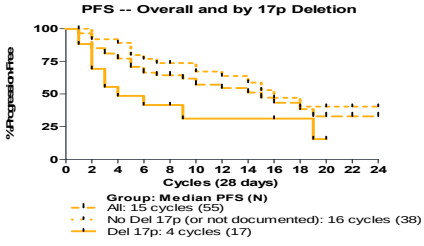
GS-1101 (CAL-101) in CLL

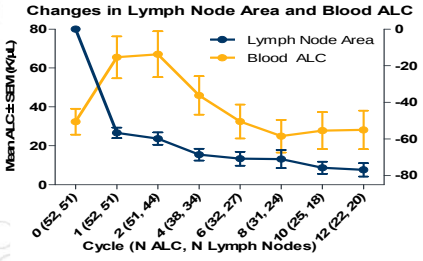
- GS-1101 is an oral agent that targets PI3K-delta
- Ph I study in relapsed CLL/NHL with 54 CLL pts
- Pts had a median 5 prior Rx, 82%; 31% del(17p13.1)
- Response to therapy remarkable
  - 91% with node/spleen response that was rapid concomitant with early increase in lymphocytosis
  - 24% response overall due to persistent lymphocytosis
  - Remissions durable except in del(17p13.) with median PFS of 18 m
- Toxicity modest (LFT abnormalities, pneumonia)

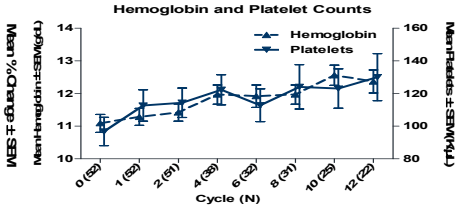
Coutre, et al: ASCO 2011

GS-1101 Response and Outcome Summary









Coutre S, et al: ASCO 2011

GS1101 Current Direction

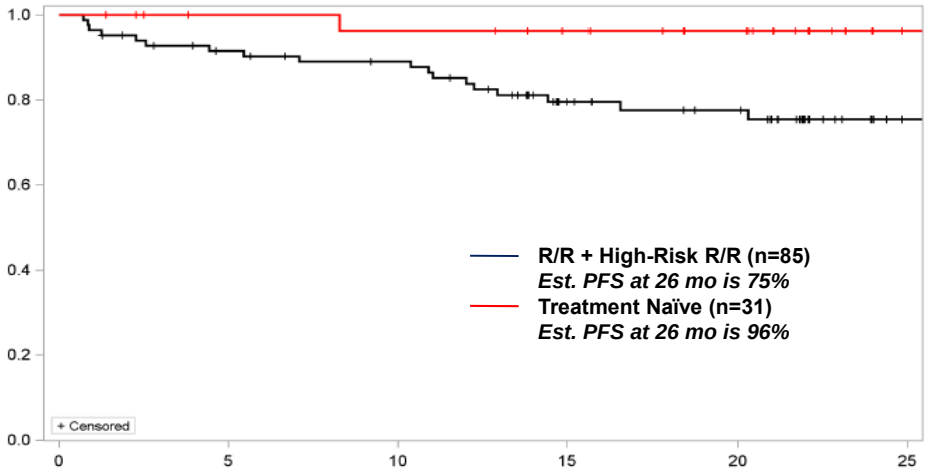
- **Ongoing studies in CLL**
  - **Phase III Bendamustine/Rituximab ± GS-1101 in relapsed CLL**
  - **Phase III Ofatumumab ± GS-1101 in relapsed CLL**
  - **Phase III Rituximab ± GS-1101 in elderly, refractory CLL**
  - **Phase II Rituximab + GS1101 in untreated CLL (done)—to be reported at ASCO**
  - **Phase II Ofatumumab + GS110 in untreated CLL**

Ibrutinib (PCI32765) in CLL

- Ibrutinib irreversibly inhibits of Bruton's tyrosine kinase
- Phase Ib/II study to assess efficacy
  - 85 relapsed CLL pts Rx with 420 mg (n=51) or 840 mg n=34) dose; median 4 prior Rx, 65% advanced Rai, 35% del(17p13.1)
  - 31 elderly (age ≥65) with no prior Rx; 48% advanced Rai
- Response similar between two doses in relapsed pts
  - 92% with node/spleen response
  - 71% ORR/2% CR in previously Rx and 67% ORR/10% CR due to transient lymphocytosis produced by this class of drugs
  - PFS at 26 months 75% in previously Rx and 96% in unRx
- Toxicity profile modest (loose stools, arthralgia, fatigue dyspepsia, rash) with minimal myelosuppression

Byrd JC, et al: ASH 2012

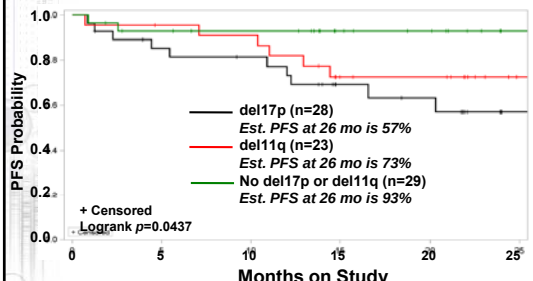
Ibrutinib Remissions Are Durable



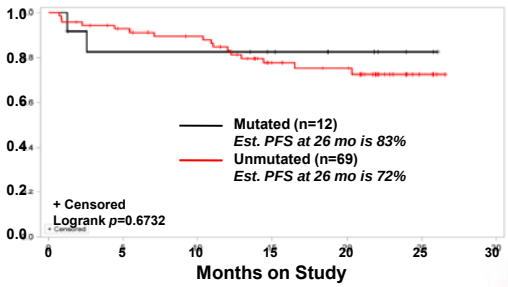
Progression Free Survival by Genomic Feature

Relapsed/Refractory including High-Risk R/R

del(17p13.1)/del(11q22.3) Status



IgV_H Status



Combination Studies with Ibrutinib

- PCYC 1109: Ibrutinib + Ofatumumab in relapsed CLL/SLL (completed, OSU)
- PCYC 1108: Ibrutinib + BR or FCR in relapsed CLL/SLL (completed, multicenter)
- IIT: Ibrutinib + Rituximab in high-risk CLL (completed, MDA)
- CTEP: Ibrutinib + Lenalidomide (U Col and OSU)

Summation of Results: Higher response rate and no obvious added toxicity

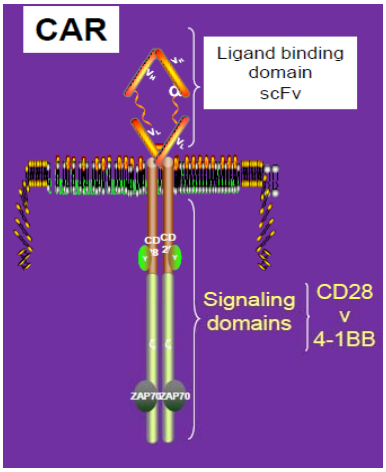
- **Planned Intergroup Phase III studies**
  - FCR vs Ibrutinib + Rituximab (< 70 yrs)
  - BR vs Ibrutinib + Rituximab vs Ibrutinib (> 65 yrs)

Where are BTK Inhibitors Going?

- Ibrutinib in relapsed phase III studies in CLL
  - Ibrutinib versus Ofatumumab (relapsed)
  - Ibrutinib + BR versus BR (relapsed)
  - Ibrutinib in relapsed del(17p) CLL
- Ibrutinib in untreated CLL - minimal development
  - Phase III study of Ibrutinib versus CLB in elderly CLL
  - Phase II of Ibrutinib in elderly CLL (MDA)
- Alternative agents
  - AVL292 (Does not appear as active as ibrutinib to date)
  - ONO-WG-307
  - HM71224
  - Others with improved features

Chimeric Antigen Receptor (CAR) T-Cells in CLL

- CAR contains and extracellular domain targeting CD19 and internal CD3 zeta chain, and costimulatory domain containing 4-1BB or CD28
- N=10 pts; Median age 66
- Chemotherapy 4-7 days pre-infusion
- 3 CR, 4 PR, 2 NR, 1 NE due to being too early



Porter D, et al: ASH 2012

Other New Drugs (Before BCR antagonists)

- IPI-145—second generation PI3-kinase delta inhibitor
- Dinaciclib and Flavopiridol—active in CLL including del(17p)*
- ABT263 and ABT199—active in CLL including del(17p13.1)*
- Xm5574—CD19 engineered antibody active in CLL*
- GA101—CD20 engineered antibody active in CLL
- Tru-016—CD37 SMIP active in CLL*
- KPT330—XPO1 inhibitor—early activity in B-cell malignancies*

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Important Conclusions

- Select genomic studies can assist in risk stratification of newly diagnosed patients.
- Rituximab chemoimmunotherapy offers a survival advantage for symptomatic CLL.
- Patients with del(17p13.1) who require therapy have very poor outcomes with traditional therapies
- BTK inhibitor ibrutinib is very active in symptomatic untreated and treated CLL including those with del(17p) and yields very durable remissions
- CAR-T cells are promising alternative to allo SCT

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Question and Answer Session

Dr. Byrd's slides are available for download at
www.LLS.org/programs


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• WEBSITE: www.LLS.org/copay
• TOLL-FREE PHONE: (877) LLS-COPAY
For more information about CLL and other LLS programs, please contact an LLS Information Specialist.
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