Acute and Chronic Leukemias and MDS

- **Acute Leukemias**
  - Acute Myeloid Leukemia (AML)
  - Acute Lymphoblastic Leukemia (ALL)

- **Chronic Leukemias**
  - Chronic Myeloid Leukemia (CML)
  - Chronic Lymphoid Leukemia (CLL)

- **Myelodysplastic Syndrome (MDS)**

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Disclosure Information

The following relationships exist related to this presentation:

• Dr. Richard Stone has served as a consultant for Abbvie, Amgen, Agios, Arog, Celgene, Cornerstone, Jazz, Karyopharm, Novartis, Orsenix, Pfizer,

Off-Label/Investigational Discussion

In accordance with CME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.
Leukemia: Definition

- Overabundance of white blood cells in peripheral blood
  - If immature (like stem cells) then acute leukemia
  - If mature (like normal cells) then chronic leukemia
Acute Leukemias arise from SC and committed SCs
Myeloid Malignancies

Acute Myeloid Leukemia

≥20% blasts

<20% blasts

Myelodysplastic Syndromes

Myelodysplastic/Myeloproliferative overlap

Myeloproliferative Neoplasms

Absence of cytosis

Dyserythropoiesis
Dysgranulopoiesis

Granulocytosis
Thrombocytosis
Eosinophilia
Mastocytosis

Monocytosis

Erythrocytosis

>1000/μL

≥20% blasts

<20% blasts
Chronic Myeloid Malignancies

CML - *BCR-ABL1* 100%
PV - *JAK2* 99%
ET - *JAK2/MPL* 60%
PMF - *JAK2/MPL* 70%
CNL - *CSF3R* 90%
          - *SETBP1* 33%
SM - *KITD816V* 90%
CEL
MPN-U

Myelodysplastic Syndromes
Myelodysplastic/Myeloproliferative overlap
Myeloproliferative Neoplasms

Absence of cytosis
Dyserythropoiesis
Dysgranulopoiesis
Granulocytosis
Thrombocytosis
Eosinophilia
Mastocytosis
Monocytosis
Erythrocytosis
Acute Leukemia: Clinical Presentation

• Bone marrow failure
  – neutropenia - infection/fever
  – anemia - fatigue/SOB
  – thrombocytopenia - bleeding

• Metabolic abnormalities
  – hypokalemia - renal tubular damage from myeloblasts
  – hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia - tumor lysis syndrome
Acute Leukemia: Selected Clinical Issues

- **Infection**
  - Do not delay antileukemic therapy while infection resolves
  - Early use of antifungals
  - Raw fruit and vegetables probably probably OK

- **Thrombocytopenia**
  - Platelet transfusion threshold of 10K/ul
  - Obligate use of single donor platelets is controversial

- **Tumor Lysis Syndrome**
  - Hydration, allopurinol, and judicious use of sodium bicarbonate is effective
  - Single dose of recombinant urate oxidase can be considered if pt cannot take po
Acute Leukemia:
Blasts on Wright stain

<table>
<thead>
<tr>
<th>feature</th>
<th>myeloid</th>
<th>lymphoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>cytoplasm</td>
<td>ample</td>
<td>scant</td>
</tr>
<tr>
<td>granules</td>
<td>a few</td>
<td>absent</td>
</tr>
<tr>
<td>chromatin</td>
<td>open</td>
<td>less so</td>
</tr>
<tr>
<td>nucleoli</td>
<td>many</td>
<td>few</td>
</tr>
<tr>
<td>Auer Rods</td>
<td>in 50%</td>
<td>no</td>
</tr>
</tbody>
</table>

Cytochem: perox-AML, NSE-AMo/ML; PAS-ALL
Acute Leukemia: Immunophenotypic Diagnosis

• AML: CD33 (in 90%), CD15, CD117 (c-kit); CD14, CD11c- monocytic

• ALL: 
  – pre-B cell: CD19, CD20, CD10 (CALLA) in most 
  – B-cell: CD19, surface immunoglobulin
  – T-cell: CD2, CD7, CD3
AML: FAB Classification

- M0: Cytochem neg; myeloid Ag on flow
- M1: Peroxidase pos.
- M2: Perox pos.; some differentiation
- M3: Acute Promyelocytic Leukemia
- M4: Acute Myelomonocytic Leukemia (perox and NSE pos.)
- M5: Acute Monocytic Leukemia (NSE pos)
- M6: Acute Erythroleukemia
- M7: Acute Megakaryocytic Leukemia
AML: What is it and how did it get there?

- Unbridled proliferation of hematopoietic stem cells (myeloid lineage) resulting in marrow failure and patient death unless successfully treated
- Risk factors: AGE, prior chemo for other cancers, ionizing radiation, industrial solvents (last 3 probably <10% of incidence=15K new US cases annually)
• AML genomes have fewer mutations than most other adult cancers (n=13, 5 of which are among the 23 recurrently mutated genes)

• 9 Key categories:
  – transcription-factor fusions (18%)
  – nucleophosmin (NPM1) (27%)
  – tumor-suppressor genes (16%)
  – DNA-methylation–related genes (44%)
  – signaling genes (59%)
  – chromatin-modifying genes (30%)
  – myeloid transcription-factor genes (22%)
  – cohesin-complex genes (13%)
  – spliceosome-complex genes (14%).

The Cancer Genome Atlas Research Network
# Current Risk Assessment in AML

## Key Prognostic Data in AML in 2014

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Cytogenetics / karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary versus secondary disease</td>
</tr>
<tr>
<td></td>
<td>(secondary = post-antecedent hematologic disorder, or therapy-related)</td>
</tr>
</tbody>
</table>

## Molecular studies:

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLT3 ITD (internal tandem duplication) mutation</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>NPM1 mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>CEBPA biallelic mutation</td>
<td>Favorable</td>
</tr>
<tr>
<td>KIT mutation [in ~25% of t(8;21) or inv(16) AML]</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

Of Future Importance: mutation status of *IDH1/2, DNMT3A, TET2*, etc.
Acute Leukemia: General treatment principles

• **Goal 1**: Induction rx to reduce gross leukemia to undetectable levels (2-3 log cell kill)

• **Goal 2**: Reduce $10^9 - 10^{10}$ cells, undetectable by standard means, present at CR, to a level low enough to achieve prolonged disease-free survival (‘cure’)
Older Patients With AML Continue to Have Inferior Outcomes

<table>
<thead>
<tr>
<th>Age group</th>
<th>Complete remission rate (with “3&amp;7”-like regimens)</th>
<th>Early mortality</th>
<th>Disease-free survival</th>
<th>Long-term overall survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 years</td>
<td>70%</td>
<td>10%</td>
<td>45%</td>
<td>30%</td>
<td>24 months</td>
</tr>
<tr>
<td>≥60 years</td>
<td>45%</td>
<td>&gt;25%</td>
<td>&lt;20%</td>
<td>10%</td>
<td>10 months</td>
</tr>
</tbody>
</table>

*Data are based on CALGB & MRC trials for which adults of all ages were eligible*
AML in > 60 yo: Lack of Effect of induction chemo choice on DFS- HOVON AML-9
Selected Lower-Intensity Approaches in Older, Poor Prognosis Patients With AML

- **Clofarabine 30 mg/m²/d x 5d (n = 112) (nucleoside analogue)**
  - Median age 71 years, 36% with prior MDS
  - 38% CR, 8% CRp (seen even with several risk factors)
  - Early death rate = 10%

- **Decitabine 20 mg/m²/d x 5d (n = 55) (DNAMTi)**
  - Median age 74 years, 42% had secondary AML
  - 24% CR, 2% CRp
  - Early death rate = 4%
  - Ph III v lowdac: 18% v 8% CR, 7.7v 5.0 mo med OS (missed primary EP; n=485; Kantarjian et al, JCO, 2012)

- **Decitabine 20 mg/m²/d x 10d (n = 53)**
  - Median age 74 years, 36% had secondary AML
  - 47% CR, 64% CR + CRi
  - Early death rate (8 weeks) = 15%
  - Higher levels of miR-29b associated with increased likelihood of response

AML: Treatment of those under age 60 (non-APL)

- Induction
  - anthracycline (3d) plus cytarabine (7d, IVCI)

- Post-remission Therapy
  - intensive chemo
  - auto BMT
  - alloBMT
Consolidation: DFS Benefit Only in Patients < 60 Years Receiving High-Dose Ara-C

Patients in Remission (%)

Age < 60

Age > 60

Patients with CBF cytogenetics or RAS mutations benefitted most from HiDAC

# Treatment of Acute Promyelocytic Leukemia

## Key Principles of APL Management

### Suspect the disease!

- Risk of death is greatest in the first two weeks after diagnosis, especially if ATRA initiation is delayed…

- So, if the clinical setting suggests the possibility of APL (e.g., clefted blasts, strong CD33+, DIC) **do not wait** for molecular confirmation to start ATRA

### Document disease

- Use cytogenetics or FISH for t(15;17), or RT-PCR for *PML-RARA* fusion

- Variant translocations are rare, but important to know about, since several do not respond to ATRA

### Assess risk

- If WBC >10 x 10^9/L: **high risk**

- If WBC ≤10 x 10^9/L: **standard risk** (lowest risk if platelets also >40 x 10^9/L)

Is the patient an anthracycline candidate?
Acute Promyelocytic Leukemia
Low/intermediate risk patients
(WBC ≤10 x 10⁹/L, AGE 16-70)

ATO

ATRA

Chemotherapy

LoCoco et al (NEJM 2013)
Overall survival probability

98.7% 91.1%
p = 0.02

ATRA+ATO  ATRA+Chemo

Overall Survival

LoCoco et al (Abs #6), ASH 2012
ALL: Therapy

• Childood ALL-85% cured: The great success story based on anthracycline, vincristine, steroid, L-asp induction; CNS prophylaxis; intensification; and POMP maintenance

• Adult ALL-35% cured: More difficult biology (increased inc PH+), but perhaps therapy could be improved even with available agents
  – Ongoing trial lead by DFCI adult leukemia team: almost exact pediatric rx to adults
### ALL: Therapy in Children

- Successive steady improvements in recent past such that even high risk children are doing well; DFCI studies
  
<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Details</th>
<th>EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-5</td>
<td>hd MTX, no L-asp ind’n</td>
<td>74%</td>
</tr>
<tr>
<td>1985-7</td>
<td>ld MTX, L-asp ind’n</td>
<td>78%</td>
</tr>
<tr>
<td>1987-91</td>
<td>no CNS XRT, SR</td>
<td>78%</td>
</tr>
<tr>
<td>1991-5</td>
<td>hd MTX, L-asp ind’n, 30 wk intens dexamethsone</td>
<td>83%</td>
</tr>
</tbody>
</table>
Childhood ALL: Late Complications of Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>brain Tumor</td>
<td>Cranial XRT</td>
</tr>
<tr>
<td>AML</td>
<td>topo II drugs (teniposide, anthracylines)</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td>anthracyclines</td>
</tr>
<tr>
<td>encephalopathy</td>
<td>Cr XRT, steroids, MTX</td>
</tr>
<tr>
<td>AVN of bone</td>
<td>steroids</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>steroids, Cr XRT, ametab</td>
</tr>
<tr>
<td>short stature</td>
<td>Cr XRT, steroids, h.d chemo</td>
</tr>
<tr>
<td>obesity</td>
<td>Cr XRT</td>
</tr>
<tr>
<td>hypothyroidism</td>
<td>Cr XRT, h.d. chemo</td>
</tr>
</tbody>
</table>
## Outcome Comparison of Adolescent/Young Adults with ALL on Pediatric vs. Adult Clinical Trials

<table>
<thead>
<tr>
<th>Cooperative Group</th>
<th>Study Period/ No. Pts.</th>
<th>Age (yrs)</th>
<th>CR (%)</th>
<th>EFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North America (Stock)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCG (peds)</td>
<td>1988-1998 196 pts</td>
<td>16-21</td>
<td>96%</td>
<td>64%</td>
</tr>
<tr>
<td>CALGB (adults)</td>
<td>1988-1998 103 pts</td>
<td>16-21</td>
<td>93%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>French (Boissel)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRALLE (peds)</td>
<td>1993-1994 77 pts</td>
<td>15-20</td>
<td>94%</td>
<td>67%</td>
</tr>
<tr>
<td>LALA (adults)</td>
<td>1993-1994 100 pts</td>
<td>15-20</td>
<td>83%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Dutch (deBois)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SKION (peds)</td>
<td>1985-1999 47 pts</td>
<td>15-21</td>
<td>98%</td>
<td>69%</td>
</tr>
<tr>
<td>HOVON (adults)</td>
<td>1985-1999 73 pts</td>
<td>15-21</td>
<td>91%</td>
<td>31% / 46%</td>
</tr>
<tr>
<td><strong>Italian (Testi)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIEOP (peds)</td>
<td>1996-2000 153</td>
<td>14-18</td>
<td>94%</td>
<td>83%</td>
</tr>
<tr>
<td>GIMEMA (adults)</td>
<td>1996-2000 95</td>
<td>14-18</td>
<td>95%</td>
<td>55%</td>
</tr>
</tbody>
</table>
DFCI Pediatric-Inspired ALL for adults age 18-40

Deange lo et al Leukemia 2014
CML Stable Phase
Presentation and Clinical Course
Chronic Phase

• 85-90% present in chronic phase
• 50% asymptomatic at presentation
• symptoms are often non-specific
  – fatigue 80%
  – weight loss 60%
  – abdominal discomfort 40%
  – easy bruising 35%
  – leukostasis, priapism, thrombosis are unusual
CML Prevalence

- US Prevalence is currently 40-50,000 patients with ~4600 new cases per year.

- Anticipated increase of >10% per year.
Survival in Early Chronic Phase CML

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965-1974</td>
<td>123</td>
<td>122</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>127</td>
</tr>
<tr>
<td>1982-1989</td>
<td>365</td>
<td>265</td>
</tr>
<tr>
<td>1990-2000</td>
<td>960</td>
<td>334</td>
</tr>
<tr>
<td>Imatinib</td>
<td>230</td>
<td>7</td>
</tr>
</tbody>
</table>

Proportion surviving

Years from referral

95%
CML: Current Status in 2015

Imatinib
Nilotinib
Dasatinib

Nilotinib
Dasatinib
Bosutinib
Ponatinib
Omacetaxine*

Re refractory response
Suboptimal response
Relapse
Intolerance

*SCT

* 2 or more TKIs
Goals of Therapy and Assessing Response

- Landmarks of response in CML:

  - **CHR**
  - **CCR**
  - **MMR**
  - **CMR**

Putative Leukemic cell burden:

- $10^{13}$
- $10^{12}$
- $10^{11}$
- $10^{10}$
- $10^{9}$

**“Complete Molecular Response”; qPCR (-); Undetectable BCR-ABL transcripts**

Established Landmarks; Unambiguously Defined

Dependent on Assay Sensitivity; Ambiguous
Myelodysplastic Syndromes: Definition

• Heterogeneous Marrow Stem Cell Disorder
  Characterized by
  Hypercellular Marrow and
  Peripheral Cytopenias
# Current “Standard” Therapy for MDS

Supportive care for all (transfusions and antimicrobials PRN, ?iron chelation)

<table>
<thead>
<tr>
<th>Cytopenia(s)</th>
<th>Disease feature</th>
<th>First-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia only</strong></td>
<td>Del (5q)</td>
<td><strong>Lenalidomide</strong></td>
</tr>
<tr>
<td>No del(5q), sEPO &lt;500</td>
<td></td>
<td><strong>ESA ± G-CSF</strong></td>
</tr>
<tr>
<td>No del(5q), sEPO &gt;500</td>
<td></td>
<td>?Immunotherapy</td>
</tr>
<tr>
<td><strong>Neutropenia or</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>thrombocytopenia or both</strong></td>
<td></td>
<td>None established;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>observation, growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>factors, aza/decit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reasonable</td>
</tr>
</tbody>
</table>

**Lower-risk MDS (assessed using IPSS, etc.)**

**Higher-risk MDS**

<table>
<thead>
<tr>
<th>Allogeneic SCT candidate?</th>
<th>Therapeutic approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Proceed to transplant ASAP; a hypomethylating agent (HMA) or cytotoxic chemotherapy</td>
</tr>
<tr>
<td></td>
<td>may be used as a “bridge”</td>
</tr>
<tr>
<td>No</td>
<td><strong>Azacitidine; decitabine</strong> as alternate</td>
</tr>
</tbody>
</table>

Partly based on 2014 NCCN guidelines; see www.nccn.org
Allogeneic Stem Cell Transplant: The only known curative modality, but practical only in a small subset (<10%) of patients.

Non-Curative Goals: Decreased transfusion needs, decreased infection, delay of disease progression, prolonged survival, increased quality of life
Azacitidine Survival Study

AZA-001 Survival Study Design

Higher-risk MDS (FAB)
1:1 Randomization

Azacitidine SC 75 mg/m² × 7 days,
Repeated every 28 days

N=358

Standard of Care Options:
1. Best supportive care
2. Low-dose cytarabine
3. 3&7 chemotherapy

Overall Survival: Azacitidine vs CCR
ITT Population

Log-Rank  p=0.0001
HR = 0.58 [95% CI: 0.43, 0.77]
Deaths: AZA = 82, CCR = 113

Difference: 9.4 months

Survival benefit seen even in non-CR pts.

List et al, JCO 2010.
Transfusion therapy results in iron overload

<table>
<thead>
<tr>
<th>Moderate transfusion requirement:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2 units / month</td>
<td></td>
</tr>
<tr>
<td>• 24 units / year</td>
<td></td>
</tr>
<tr>
<td>• ~ 100 units / 4 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High transfusion requirement:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 4 units / month</td>
<td></td>
</tr>
<tr>
<td>• 48 units / year</td>
<td></td>
</tr>
<tr>
<td>• ~ 100 units / 2 years</td>
<td></td>
</tr>
</tbody>
</table>

100 units: ≥ 20 g iron
Normal body iron: 3-4 g
Chronic Lymphocytic Leukemia

- A lymphoproliferative disease of CD5 + mature B-cells.
- More a lymphoma (LN counterpart: small lymphocytic lymphoma) than a leukemia.
Chronic Lymphocytic Leukemia: Clinical Features

• May Present asymptomatically (typically high absolute lymphocyte count in older adults)
• Other features in some pts: lymphadenopathy, splenomegally, anemia, thrombocytopenia, systemic symptoms (fevers, et loss)
• Anemia or thrombocytopenia may be on the basis of auto-antibodies. Such pts respond to steroids.
• Hypogammaglobulinemia with associated infections with encapsulated bacteria (S. Pneumo, H. flu)
Chronic Lymphocytic Leukemia: Diagnosis

- Classically - send PB for flow cytometry, find CD5+, CC20+, CD23 + (MCL usually CD23-)
- Prognosis based on clinical staging
- Add in cytogenetics/FISH
  - 13q- is good
  - 11q- or 17p- bad
- Molecular studies: IgH rearranged- good, ZAP 70 bad
<table>
<thead>
<tr>
<th>System</th>
<th>Stage</th>
<th>Definition</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rai staging system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Lymphocytosis only</td>
<td>11.5 years</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>Lymphocytosis and lymphadenopathy</td>
<td>11.0 years</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Lymphocytosis in blood and marrow with splenomegaly and/or hepatomegaly (with or without lymphadenopathy)</td>
<td>7.8 years</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Lymphocytosis and anemia (hemoglobin &lt;11 g/dL or hematocrit &lt;33%)</td>
<td>5.3 years</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Lymphocytosis and thrombocytopenia (platelet count &lt;100,000/mm³)</td>
<td>7.0 years</td>
</tr>
<tr>
<td><strong>Binet staging</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Enlargement of &lt;3 lymphoid areas (cervical, axillary, inguinal, spleen, liver); no anemia or thrombocytopenia</td>
<td>11.5 years</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Enlargement of ≥3 lymphoid areas</td>
<td>8.6 years</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Anemia (hemoglobin &lt;10 g/dL or thrombocytopenia (platelet count &lt;100,000/mm³), or both</td>
<td>7.0 years</td>
</tr>
</tbody>
</table>
Chronic Lymphocytic Leukemia: Therapy

- Disease is incurable, but many pts live for >8 ys
- Therapy indicated for a) clinical symptoms a) diffuse LAN, wt loss, profound fatigue b) cytopenias not due to autoimmunity c) rapid doubling of lymphocyte count
- Special situations
  - Steroids for auto-immune mediated cytopenias
  - IVIG for recurrent pyogenic infections
Chronic Lymphocytic Leukemia: Therapy

- Acceptable initial regimens
  - FCR (fludarabine, cyclophosphamide, rituximab (anti CD20))
  - FR (fludarabine, rituximab)
  - BR (bendamustine, rituximab)
Chronic Lymphocytic Leukemia: Therapy

- Incredible new drugs for relapse (moving upfront)
  - Ibrutinib (sm mol inhibitor of Bruton’s tyrosine kinase)
  - Idelalisib (sm mol inhibitor of PI 3 kinase)
  - Obinotuzumab (novel anti CD20 antibody)
  - Ofatumumab (novel anti CD20 antibody)
  - Obatoclax (ABT-199, sm mol inhib of bcl-2) (not yet approved)
Ibrutinib is very active in previously treated CLL

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