The Best of American Society of Hematology

Top Research Studies Reviewed

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Rocky Mountain Cancer Centers
Leukemia and Lymphoma Society Conference
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Outline

• Chronic lymphocytic leukemia
  – Background and impact of 17p- and TP53 mutations
  – RESONATE-17: ibrutinib in R/R CLL with 17p-
    • O’Brien SM et al., ASH 2014; abstract 327.
  – Idelalisib-rituximab in genetic subgroups
    • Sharman JP et al., ASH 2014; abstract 330.

• Checkpoint blockade in cancer therapy
  – Phase 1 study of nivolumab in Hodgkin lymphoma
Epidemiology

• About 15,000 new cases per year in U.S.

• Median age at diagnosis is about 70 years

• Only 10% occur in patients under age 50 years

• M:F = 2:1
Prognostic Factors in CLL

- Rai (United States) and Binet (Europe) staging systems
- Serology: $\beta_2$-microglobulin, thymidine kinase
- IgV_H sequence mutation
- ZAP-70
- FISH cytogenetics: 17p-, 11q-, +12, 13q-
- CD38 on CLL cells

Survival According to Chromosomal Abnormalities in CLL

The TP53 gene is located on the short arm of chromosome 17 (17p).
Genes with Significant Mutation Frequencies in 91 Patients with Chronic Lymphocytic Leukemia.

In an integrated model using cytogenetic analysis and mutational analysis, TP53 mutations (and BIRC3 mutations) confer the worst prognosis.

Cytogenetic Risk among Patients with Chronic Lymphocytic Leukemia.

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Cytogenetic Abnormality</th>
<th>10-Yr Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>TP53 abnormalities, BIRC3 abnormalities, or both</td>
<td>29</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NOTCH1 mutations, SF3B1 mutations, or both, with or without 11q22.3 deletion</td>
<td>37</td>
</tr>
<tr>
<td>Low</td>
<td>Trisomy 12 or normal cytogenetic profile</td>
<td>57</td>
</tr>
<tr>
<td>Very low</td>
<td>13q14 deletion only</td>
<td>69</td>
</tr>
</tbody>
</table>

* Data are from Rossi et al. 8

In the CLL8 trial, patients with TP53 mutations did poorly regardless of whether they received FCR or FC.

Stephan Stilgenbauer et al. Blood 2014;123:3247-3254
Almost all patients with 17p- in the CLL8 trial progressed in less than 2 years.

Stephan Stilgenbauer et al. Blood 2014;123:3247-3254
Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.
Ibrutinib causes immediate movement of CLL cells from nodes to peripheral blood, followed by reduction in peripheral blood lymphocytosis.

Ibrutinib causes almost universal reduction in lymphadenopathy in CLL.
Single-agent ibrutinib results in a high rate of response over time in patients with CLL.

Ibrutinib seems to overcome some of the adverse genetic prognostic factors in CLL.

**RESONATE-17: Phase II Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL**

- **CLL/SLL**
  - Relapsed/refractory disease after 1-4 prior therapies
  - del(17p)13.1 in peripheral blood*
  - ECOG PS 0-1
  - Measurable nodal disease

*Confirmed by FISH.


**Ibrutinib**

420 mg/day PO (N = 144)

- **Primary endpoint:** ORR
- **Secondary endpoints**
  - DoR
  - Safety
  - Tolerability
- **Exploratory endpoints**
  - PFS
  - OS

Until unacceptable toxicity or disease progression
Primary analysis 12 mos after last enrolled pt
Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL: Main Findings

- Best response (ORR + PR-L) by IRC (no 2nd confirmatory CT scan) was 74% (95% CI: 66% to 80%)
- Median DOR was not reached at median follow-up of 11.5 mos; 12-mo DOR was 88.3%

Ibrutinib in del(17p) Relapsed/Refractory CLL/SLL: Conclusions

- Ibrutinib showed efficacy with favorable risk–benefit profile in pts with del(17p) CLL/SLL
- 12-mo PFS: 79%, consistent with previous study of 26-mo PFS (75%)
- PFS outcomes in this relapsed/refractory setting favorable compared with previous results for frontline FCR regimen or alemtuzumab in del(17p) CLL (median PFS: 11 mos)
- Safety profile consistent with known profile for ibrutinib

Current Controversies and Emerging Treatment Options for CLL

Phase III Idelalisib and Rituximab for Previously Treated Patients With CLL: Study Design

*Stratified by del(17p)/TP53 mutation, IGHV mutation status

- Patients with heavily pretreated, relapsed CLL

- Disease progression, *death, or discontinuation due to AE

- Primary Study 116
  - Idelalisib 150 mg BID
  - n = 110
  - Rituximab† (6 mos)

- Extension Study 117
  - Idelalisib 300 mg BID
  - Clinical Endpoints
    - Primary: PFS as assessed by IRC
    - Events: Disease progression or death
    - Secondary: ORR, LNR, OS

- Placebo BID
  - n = 110
  - Rituximab† (6 mos)

- Planned interim analyses at 50% and 75% of events

*Patients with disease progression continued on idelalisib Extension Study 117.

†Rituximab schedule: 375 mg/m², then 500 mg/m² every 2 wks x 4, then 500 mg/m² every 4 wks x 3.

Idelalisib and Rituximab for Previously Treated Patients With CLL: PFS


Idelalisib + rituximab
- Median PFS: not reached
- HR: 0.15 (95% CI: 0.08-0.28; P < .0001)

Placebo + rituximab
- Median PFS: 5.5 mos

Pts at Risk, n
- Idelalisib + rituximab: 110 69 44 34 30 14 6 2 0
- Placebo + rituximab: 110 62 30 18 13 6 1 1 0
Idelalisib and Rituximab for Previously Treated Patients With CLL: OS

Phase III 2nd Interim Analysis: Idelalisib + Rituximab in Relapsed CLL

**Primary Study 116**
- Double blind
- Idelalisib 150 mg BID
- Rituximab* (n = 110)
- Placebo BID
- Rituximab* (n = 110)

**Extension Study 117**
- Blinded dose
- Idelalisib 300 mg BID
- Idelalisib 150 mg BID

- Relapsed CLL; ≥ 1 prior anti-CD20 or ≥ 2 prior cytotoxic therapies

- Primary endpoint: PFS, OS by subgroup analysis

*Rituximab given in 8 doses; first dose 375 mg/m², then 500 mg/m² every 2 wks x 4, then every 4 wks x 3

Idelalisib + Rituximab in Relapsed CLL: PFS Subgroup Analysis* (n = 110)

<table>
<thead>
<tr>
<th>IGHV: Unmutated vs Mutated</th>
<th>del(17p)/TP53mut: Present vs Not Present</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGHV</strong></td>
<td><strong>del(17p)/TP53mut</strong></td>
</tr>
<tr>
<td>Unmutated (n = 91)</td>
<td>Unmutated (n = 91)</td>
</tr>
<tr>
<td>Median PFS, Mos (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Mut</td>
<td>NR (10.7-NR)</td>
</tr>
<tr>
<td>Unmut</td>
<td>19.4 (16.6-NR)</td>
</tr>
<tr>
<td>No del</td>
<td>20.3 (19.4-NR)</td>
</tr>
<tr>
<td>Del</td>
<td>16.6 (13.9-NR)</td>
</tr>
</tbody>
</table>

*Including extension study.
Idelalisib + Rituximab in Relapsed CLL: PFS Subgroup Analysis* (n = 110)

- PFS: Idelalisib + rituximab favored in all subgroups vs placebo + rituximab (median follow-up: idelalisib, 13 mos; placebo, 11 mos)

<table>
<thead>
<tr>
<th>Median PFS, Mos</th>
<th>Idelalisib + Rituximab (n = 110)</th>
<th>Placebo + Rituximab (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pts</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rai stage III/IV</td>
<td>NR</td>
<td>13</td>
</tr>
<tr>
<td>• del(17p)/TP53 mutation</td>
<td>NR</td>
<td>4.0</td>
</tr>
<tr>
<td>• del(11q)</td>
<td>10.7</td>
<td>6.9</td>
</tr>
<tr>
<td>• Unmutated IGHV</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>• Zap70+</td>
<td>NR</td>
<td>5.5</td>
</tr>
<tr>
<td>• CD38+</td>
<td>NR</td>
<td>6.9</td>
</tr>
<tr>
<td>• B2-microglobulin &gt; 4 mg/L</td>
<td>NR</td>
<td>5.0</td>
</tr>
</tbody>
</table>

- PFS improvement with idelalisib + rituximab vs placebo + rituximab significant after crossover in extension study

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Median PFS, Mos (95% CI)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idelalisib + rituximab (n = 110)</td>
<td>19.4 (16.6 to NR)</td>
<td>0.25 (0.16-0.39)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Placebo + rituximab (n = 110)</td>
<td>7.3 (5.5-8.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Including extension study.
Idelalisib + Rituximab in Relapsed CLL: OS

Idelalisib + Rituximab in Relapsed CLL: Conclusions

- Overall, median PFS has not been reached in idelalisib + rituximab arm vs 5.5 mos for rituximab monotherapy
- Idelalisib + rituximab had comparable efficacy in pts with relapsed CLL regardless of high-risk genomic features, including del(11q), del(17p)/TP53 mutation, and unmutated IGHV
- OS significantly improved for pts receiving idelalisib + rituximab vs rituximab monotherapy despite crossover in extension trial design
- Combination has manageable toxicity profile in pts with relapsed/refractory CLL

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• Checkpoint blockade in cancer therapy
  – Phase 1 study of nivolumab in Hodgkin lymphoma
A Roadmap of Immunotherapy Agents in the Cancer: Immune System Interaction

Release of cancer cell antigens: chemotherapy, radiation, targeted therapy

Killing of cancer cells: anti–PD-1, anti–PD-L1

Cancer antigen presentation: vaccines

Priming and activation: anti–CTLA-4
CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for Cancer Treatment

Nivolumab

• Anti-PD1 antibody

• FDA approvals
  – Melanoma no longer responding to other drugs, 12/22/2014
  – Squamous cell lung cancer progressing after prior platinum-based therapy, 3/4/2015

• Administered IV every 2 weeks
Study Design

- Phase 1 study with dose escalation and expansion cohorts

- Included patients with relapsed/refractory hematologic cancers (only HL reported in this paper)

- Starting dose 1 mg/kg, then escalated to 3 mg/kg

- Administered week 1, then week 4, then every 2 weeks until progression, complete remission, or a maximum of 2 years

- No maximum tolerated dose (MTD) was reached

Characteristics of the 23 Patients at Baseline in the Phase 1 Study.

Table 1. Characteristics of the 23 Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
</tr>
<tr>
<td>Range</td>
<td>20–54</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>12 (52)</td>
</tr>
<tr>
<td>Race — no. (%)*</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Black</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (4)</td>
</tr>
<tr>
<td>ECOG performance-status score — no. (%)†</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (26)</td>
</tr>
<tr>
<td>1</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Histologic findings — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis</td>
<td>22 (96)</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>1 (4)</td>
</tr>
<tr>
<td>No. of previous systemic therapies — no. (%)</td>
<td></td>
</tr>
<tr>
<td>2 or 3</td>
<td>8 (35)</td>
</tr>
<tr>
<td>4 or 5</td>
<td>7 (30)</td>
</tr>
<tr>
<td>≥6</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Previous treatment — no. (%)</td>
<td></td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Autologous stem-cell transplantation</td>
<td>18 (78)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>19 (83)</td>
</tr>
<tr>
<td>Extranodal involvement — no. (%)‡</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

Drug-Related Adverse Events in the 23 Patients.

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>18 (78)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>Drug-related adverse events reported in ≥5% of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (22)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased platelet count</td>
<td>4 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased lymphocyte count</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>2 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Increased lipase level</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2 (9)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Drug-related serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Lymph-node pain</td>
<td>1 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Nivolumab therapy results in a high response rate in patients with relapsed-refractory Hodgkin lymphoma.

Reed-Sternberg cells demonstrate gain of copy numbers and amplification of PDL1 and PDL2.

6 green-red (yellow) fusion signals > 3 centromeric signals (aqua) indicates copy number gain in PDL1 and PDL2.

More yellow signals than aqua indicates amplification of PDL1 and PDL2.

The malignant Reed-Sternberg cells (arrows) show high expression of PD-L1 (top row) and PD-L2 (bottom row).

Conclusions

• In patients with CLL with 17p- or TP53 mutations, both ibrutinib and idelalisib-rituximab appear more promising than conventional chemoimmunotherapy.

• Anti-PD-1 antibodies offer great promise in patients with relapsed Hodgkin lymphoma. Additional research needs to be done to determine how best to incorporate these agents into treatment algorithms.