7th Annual Symposium on Current Strategies in the Treatment of Hodgkins Lymphoma, B-cell Lymphoma, Multiple Myeloma and Leukemia

Saturday, June 23, 2018
7:00 AM - 4:00 PM

Program Director
Fredrick B. Hagemeister, MD
Professor of Medicine
Department of Lymphoma/ Myeloma
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, TX

Educational Grants
Amgen, Inc; Takeda Oncology; Bayer HealthCare Pharmaceuticals Inc.; Celgene Corporation; Novartis Pharmaceuticals Corporation

Display Support
Amgen, Inc; Takeda Oncology; Incyte, Corp

Jointly provided by

To view full slide handouts, visit www.cancernetus.com/2018hematology
Statement of Need/Program Overview
This symposium is intended to improve care of patients with Hodgkins lymphoma, B-cell lymphoma, multiple myeloma and leukemia by accelerating adoption of new guidelines and evidence-based practice change. The format will include didactic lectures from known opinion leaders, question and answer sessions, and ample opportunity for participant interaction with faculty.

Target Audience
This symposium is directed primarily to hematologists/oncologists, radiation oncologists, researchers, pharmacists, registered nurses, physician assistants, nurse practitioners and fellows in training interested in new development in hematological malignancies such as Hodgkins lymphoma, B-cell lymphoma, multiple myeloma and leukemia. No specific skill or knowledge other than a basic training in hematology/oncology is required for successful participation in this activity.

Learning Objectives
• Describe the biology and mechanism of action of CAR-T cells in hematological malignancies
• Evaluate the therapeutic efficacy and safety of axicabtagene ciloleucel, tisagenlecleucel and B-cell maturation antigen (BCMA) in patients with selected hematological malignancies
• Assess the efficacy and safety of PD-1 and PD-L1 blockade in combination with brentuximab vedotin and autologous stem cell and allogenic stem cell transplantation in patients with Hodgkin’s lymphoma
• Cite the newer treatment options for follicular lymphoma
• Identify the newer treatment options for mantle cell lymphoma
• Apply the novel treatment options for chronic lymphocytic lymphoma
• Identify benefit and risks of available immunomodulatory agents, proteasome inhibitors or both as systemic therapy for patients with newly diagnosed active multiple myeloma (MM)
• Evaluate available data on the selection, sequencing and/or combination of novel therapeutic agents in the treatment of patients with relapsed/refractory MM
• Evaluate the novel therapeutic options for adolescents and young adults (AYA) relapsed/refractory Philadelphia-positive and Philadelphia-negative patients with acute lymphoblastic leukemia
• Evaluate how compound genotypes are related to novel therapeutic option based outcomes in patients with acute myeloid leukemia
• Identify response assessment and management of tyrosine kinase inhibitor resistance in the treatment of chronic myeloid leukemia
## Agenda

**7th Annual Symposium on Current Strategies in the Treatment of Hodgkin’s Lymphoma, B-cell Lymphoma, Multiple Myeloma and Leukemia**

**SATURDAY – June 23, 2018**

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>7:00 AM</td>
<td>Pre-registration</td>
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<tr>
<td>8:25 AM</td>
<td>Welcome and Introductions</td>
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<tr>
<td>8:30 AM</td>
<td><strong>GENERAL TOPIC</strong></td>
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<tr>
<td>8:30 AM</td>
<td>Pretest – Case Report Vignettes.............................................</td>
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<tr>
<td></td>
<td>Satvaa S. Neelapu, MD / Fredrick Hagemeister, MD</td>
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<tr>
<td>8:40 AM</td>
<td>Overview of Biology and Mechanism of Action of CAR T-cells...............</td>
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<td></td>
<td>Satvaa S. Neelapu, MD and Potential Therapeutic Efficacy in Selected Hematological Malignancies</td>
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<tr>
<td>9:05 AM</td>
<td><strong>B-CELL LYMPHOMAS (HL, FL, MCL, CLL)</strong></td>
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<tr>
<td>9:05 AM</td>
<td>Overview of Immunotherapy and Combination Therapy.............</td>
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<td></td>
<td>Fredrick Hagemeister, MD Options for Hodgkin’s Lymphoma</td>
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<tr>
<td>9:30 AM</td>
<td>Posttest – Case Report Vignettes...........................................</td>
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<td>Satvaa S. Neelapu, MD / Fredrick Hagemeister, MD</td>
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<td>9:40 AM</td>
<td>Pretest – Case Report Vignettes.............................................</td>
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<td>Fredrick Hagemeister, MD / Nathan Fowler, MD</td>
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<tr>
<td>9:50 AM</td>
<td>Overview of Treatment Options for Diffuse..................................</td>
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<td></td>
<td>Fredrick Hagemeister, MD Options for Hodgkin’s Lymphoma Large Cell Lymphoma (DLCL)</td>
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<tr>
<td>10:15 AM</td>
<td>BREAK</td>
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<tr>
<td>10:30 AM</td>
<td>Overview of Treatment Options for Follicular Lymphoma (FL)..............</td>
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<td></td>
<td>Nathan Fowler, MD</td>
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<td>Fredrick Hagemeister, MD / Nathan Fowler, MD</td>
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<td>Pretest – Case Report Vignettes.............................................</td>
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<td>Jorge E Romaguera, MD / William Wierda, MD, PhD</td>
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<td>11:15 AM</td>
<td>Overview of Treatment Options for Mantle Cell Lymphoma..................</td>
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<td>Jorge E Romaguera, MD</td>
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<td>11:40 AM</td>
<td>Overview of Treatment Options for Chronic Lymphocytic....................</td>
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<td>William Wierda, MD, PhD</td>
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<td>Jorge E Romaguera, MD / William Wierda, MD, PhD</td>
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<td>1:00 PM</td>
<td><strong>MULTIPLE MYELOMA</strong></td>
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<td>Pretest – Case Report Vignettes.............................................</td>
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<td>Elisabet Manasanch, MD / Robert Orlowski, MD</td>
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<td>1:10 PM</td>
<td>An Overview on Systemic Therapy for Patients with.........................</td>
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<td>Elisabet Manasanch, MD</td>
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<td>1:35 PM</td>
<td>Outline the Selection, Sequencing and/or Combination.....................</td>
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<td>Robert Orlowski, MD</td>
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<td>2:00 PM</td>
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<td>Elisabet Manasanch, MD / Robert Orlowski, MD</td>
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<td>2:10 PM</td>
<td><strong>LEUKEMIA (ALL, AML AND CML)</strong></td>
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<td>2:10 PM</td>
<td>Pretest – Case Report Vignettes.............................................</td>
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<td>Nitin Jain, MD / Farhad Ravandi, MD / Jorge Cortes, MD</td>
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<tr>
<td>2:20 PM</td>
<td>Novel Therapies for adolescents and young adults (AYA),...................</td>
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<td>2:45 PM</td>
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<td>How Compound Genotypes are Related to Novel Therapy.........................</td>
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<td>Farhad Ravandi, MD</td>
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<td>Response Assessment and Management of Tyrosine Kinase.....................</td>
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<td>Jorge Cortes, MD</td>
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<td>Posttest – Case Report Vignettes.............................................</td>
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<td>Nitin Jain, MD / Farhad Ravandi, MD / Jorge Cortes, MD</td>
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<td>4:00 PM</td>
<td>Closing Remarks and Adjourn</td>
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<td>Fredrick Hagemeister, MD</td>
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Faculty

**Jorge Cortes, MD**
Professor and Chair, Department of Leukemia, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center Houston, TX

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<th>Name</th>
<th>Conflict of Interest Disclosures</th>
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<tr>
<td>Jorge Cortes, MD</td>
<td><strong>Consultant:</strong> BMS, Novartis, Pfizer, Takeda Oncology</td>
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<td><strong>Research Support:</strong> BMS, Novartis, Pfizer, Takeda Oncology</td>
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<tr>
<td>Nathan Fowler, MD</td>
<td><strong>Advisory Board:</strong> Celgene, Janssen, Roche</td>
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<tr>
<td>Fredrick B. Hagemeister, MD</td>
<td>No relevant financial relationships</td>
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<td>Sattva S. Neelapu, MD</td>
<td><strong>Research Support:</strong> BMS, Cellectis, Kite Pharma, Merck, Pharacyclics, Poseida</td>
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<tr>
<td>Robert Orlowski, MD, PhD</td>
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<td><strong>Research Support:</strong> Amgen, BioTheryX, Spectrum Pharma</td>
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<td>Farhad Ravandi, MD</td>
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<td>Jorge E. Romaguera, MD</td>
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<td>William G. Wierda, MD, PhD</td>
<td><strong>Consultant:</strong> Sanofi</td>
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<td><strong>Research Support:</strong> Abbvie, Acerta Pharma, Cyclacel, Genentech, Gilead Sciences, GSK/Novartis, Juno Therapeutics, Karyopharm, KITE Pharma, Miragen, Onceternal Therapeutics, Inc., Pharmacyclics LLC, Sunesis</td>
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<tr>
<td>Kamatham A. Naidu, PhD</td>
<td>No relevant financial relationships</td>
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REGISTRATION FORM
7th Annual Symposium on Current Strategies in the Treatment of Hodgkins Lymphoma, B-cell Lymphoma, Multiple Myeloma and Leukemia

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Participants may reserve guest rooms by calling (713) 796-0080

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7th Annual Symposium on Current Strategies in the Treatment of Hodgkins Lymphoma, B-cell Lymphoma, Multiple Myeloma and Leukemia

First Name ___________________________ Middle Initial _________ Last Name ___________________________
☐ Physician ☐ Pa-C ☐ NP ☐ PhD ☐ Pharmacist ☐ Industry ☐ Nurse ☐ Other

Mailing Address ____________________________________________________________

City __________________________ State ______ Zip Code __________

Phone __________________________ Fax __________________________

E-Mail __________________________

Speciality __________________________

Pharmacists only:
NABP e-profile # __________ Birth Date (MMDD): __________

Registration Fee
Registration fee partially covers breakfast buffet, lunch and syllabus book

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<tr>
<th>Registration Fee</th>
<th>Early Registration Fee (Up to 5/31/18)</th>
<th>Discounted Registration Fee (6/1/18 - 6/15/18)</th>
<th>Regular Registration Fee (6/16/18 - 6/23/18)</th>
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<tr>
<td>Physicians</td>
<td>$100.00</td>
<td>$130.00</td>
<td>$160.00</td>
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<td>Registered Nurses, Nurse Practitioners, Physician Assistants</td>
<td>$75.00</td>
<td>$95.00</td>
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<td>Pharmacists, Fellow</td>
<td>$75.00</td>
<td>$95.00</td>
<td>$115.00</td>
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<tr>
<td>Industry †</td>
<td>$350.00</td>
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† Person(s) employed by for-profit organizations such as pharmaceutical and biotech companies, and financial institutions

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Register online at www.cancernetus.com

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To reserve your place for the meeting, please complete the registration form and fax it to 443-267-0016. For questions, please call Brian Waggoner at 972-459-5222 or E-mail: brianw@cancernetus.com
Overview of Biology and Mechanism of Action of CAR T-cells and Potential Therapeutic Efficacy in Selected Hematological Malignancies

Sattva S. Neelapu, MD
Overview of CAR T-cell Therapy in Selected Hematological Malignancies

Satvaa S. Neelapu, M.D.
Professor and Deputy Chair ad interim
Department of Lymphoma and Myeloma
The University of Texas MD Anderson Cancer Center
Houston, TX
7th Annual Symposium on Current Strategies in the Treatment of Hodgkin’s Lymphoma, B-cell Lymphomas, Multiple Myeloma and Leukemia
June 23, 2018

Outline

- CAR T-cell therapy background
- Efficacy in diffuse large B-cell lymphoma and ALL
- Efficacy in other hematological malignancies and future directions

Chimeric Antigen Receptor (CAR) Modified T cells
Genetically engineered T cells altered to express an artificial receptor, CAR

CAR T development: From discovery to FDA approval

Discovery to FDA approval - 25 years
- Aug 25, 2011: First clinical data with CD19 CAR in NHL (Kochenderfer and Rosenberg)
- Jul 14, 2010: First clinical data with CD19 CAR in NHL (NCI) (Kochenderfer and Rosenberg)
- May 28, 2009: First CD19 CAR in NHL (Kochenderfer and Rosenberg)
- Aug 30, 2017: Kymriah/ALL
- Oct 18, 2017: Yescarta/DLBCL
- May 1, 2018: Kymriah/DLBCL

Conflict of Interest Disclosure

- Research support: Kite, Merck, BMS, Cellectis, Poseida, Karus, Acerta
- Advisory Board Member/Consultant: Kite, Merck, Celgene, Novartis, Unum Therapeutics
- I will discuss investigational use of CAR T-cell therapy in my presentation

CAR T development: From discovery to FDA approval

Development of CAR T cell therapy

- Killing ability ++ + +
- Ability to multiply ++ +
- Cytokine secretion ++ +
- Persistence ++ +
CD19 CAR T products in pivotal trials in NHL

<table>
<thead>
<tr>
<th>CD19 4a</th>
<th>NCI</th>
<th>U Penn</th>
<th>PHRC / SCH</th>
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<tbody>
<tr>
<td>Gene transfer</td>
<td>Retrovirus</td>
<td>Lentivirus</td>
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<td>Kite Pharma</td>
<td>Novartis</td>
<td>Juno Therapeutics</td>
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<td>KTE-C19</td>
<td>CTL-019</td>
<td>JCAR017 (CD4:CD8 = 1:1)</td>
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<tr>
<td>Axicabtagene ciloleucel</td>
<td>Tisagenlecleucel</td>
<td>Lisocabtane maraleucel</td>
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<td>Axi-cel</td>
<td>Liso-cel</td>
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Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015

Rationale for CD19 as a CAR T target

- CD19 is expressed on precursor and mature B cells
- Present on a wide range of B-cell malignancies
- Rarely lost during neoplastic transformation
- Not expressed on BM stem cells or other tissues

Adapted from Blanc et al. Clin Cancer Res 2011; 17:6448-6458

CAR T cell production

- Apheresis
- Product ready for bedside use
- Wash, Concentrate & Freeze
- Expand cells
- T cell separation
- Viral transduction
- Cell transfer to bag for growth
- The CAR is introduced into T cells using viruses and other means

Treatment schema for CAR T-cell therapy

- Day 0: Conditioning Chemotherapy
- Day -5: Leukapheresis
- Day 30: CAR T cell infusion
- Day 14: Toxicity monitoring
- 1st Tumor Assessment

CAR T cell response to antigen

- Proliferate
- Make cytokines
- Kill the target cells

CAR T-cell expansion and persistence after axi-cel infusion

- Peak expansion observed within 2 weeks
- CAR T cells detectable one year after infusion
- Each infused CAR T cell can proliferate to >10,000 cells in the body

Adapted from Locke, Neelapu et al, Mol Ther, 2017
Conditioning chemotherapy affects CAR T cell expansion, persistence, and clinical outcome

Subgroup N ORR CR
Cy or Cy/E 12 50% 8%
Cy/Flu 18 72% 50%
Total 32 63% 33%


Cytokine storm after axi-cel CAR T infusion

Peaking on days 3–4: Immune homeostatic cytokines, chemokines
Help T cells grow

Peaking on days 5–7: Inflammatory cytokines and markers
Make T cells more functional and help trafficking

Peaking on days 5–7: Immune effector molecules
Kill target cells

Cytokine pattern after CAR T infusion

Peaking on days 3–4: Immune homeostatic cytokines, chemokines
Help T cells grow

Peaking on days 5–7: Inflammatory cytokines and markers
Make T cells more functional and help trafficking

Peaking on days 5–7: Immune modulating cytokines, chemokines Make T cells more functional and help trafficking

Cytokine release syndrome (CRS)

• Systemic inflammatory response caused by cytokines released by CAR T cells and other immune cells and results in reversible organ dysfunction

Brudno and Kochenderfer, Blood 2016; 127:3321-3330

IL-6 levels correlate with severity of CRS

Tocilizumab (anti-IL-6R Ab) or siltuximab (anti-IL-6 Ab) are used for management of severe CRS


CAR T cells are serial killers!

Video: Provided by Dr. Lawrence Cooper
Outline

- CAR T-cell therapy background
- Efficacy in diffuse large B-cell lymphoma and ALL
- Efficacy in other hematological malignancies and future directions

### Multicenter CD19 CAR T-cell trials in aggressive NHL

<table>
<thead>
<tr>
<th>Study / Sponsor</th>
<th>Product</th>
<th>N</th>
<th>Best ORR</th>
<th>Best CR rate</th>
<th>F/U mo</th>
<th>N</th>
<th>Durable ORR</th>
<th>Durable CR rate</th>
<th>Ref</th>
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<tbody>
<tr>
<td>ZUMA1 / Kite</td>
<td>CD19/CD3</td>
<td>108</td>
<td>82%</td>
<td>56%</td>
<td>12</td>
<td>108</td>
<td>42%</td>
<td>40%</td>
<td>Neelapu et al. NEJM 2017</td>
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<tr>
<td>JULIET / Novartis</td>
<td>CD19/CD3/4-1BB</td>
<td>93</td>
<td>52%</td>
<td>40%</td>
<td>12</td>
<td>93</td>
<td>34%</td>
<td>29%</td>
<td>Borchmann et al. EHA 2018</td>
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<tr>
<td>TRANSCEND / Juno (Core)</td>
<td>CD19/CD3/4-1BB</td>
<td>73</td>
<td>80%</td>
<td>59%</td>
<td>6</td>
<td>73</td>
<td>47%</td>
<td>41%</td>
<td>Abramson et al. ASCO 2018</td>
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### CRS and NT in Multicenter CD19 CAR T Trials in Adult NHL

<table>
<thead>
<tr>
<th>Study / Sponsor</th>
<th>Product</th>
<th>N</th>
<th>CRS All Grades</th>
<th>CRS Grade ≥3</th>
<th>NT All Grades</th>
<th>NT Grade ≥3</th>
<th>Ref</th>
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<td>CD19/CD3/CD3 2B</td>
<td>101</td>
<td>93%</td>
<td>13%</td>
<td>64%</td>
<td>28%</td>
<td>Neelapu et al. NEJM 2017</td>
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<td>JULIET / Novartis</td>
<td>CD19/CD3/4-1BB</td>
<td>111</td>
<td>58%</td>
<td>22%</td>
<td>21%</td>
<td>12%</td>
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<td>1%</td>
<td>25%</td>
<td>15%</td>
<td>Abramson et al. ASCO 2018</td>
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</table>

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

### ZUMA1: CAR T-cell Expansion after axi-cell Infusion is Associated with Response

**ORR**

- Peak Fold $= 4.3$
- ASC Fold $= 6.4$

Neelapu et al. NeJm. 2017, Abstract 8

### Efficacy in multicenter CD19 CAR T trials in adult NHL

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<th>CR rate</th>
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<tr>
<td>JULIET / Novartis</td>
<td>CD19/CD3/4-1BB</td>
<td>93</td>
<td>52%</td>
<td>40%</td>
</tr>
<tr>
<td>TRANSCEND / Juno (Core)</td>
<td>CD19/CD3/4-1BB</td>
<td>73</td>
<td>80%</td>
<td>59%</td>
</tr>
</tbody>
</table>

### CRS and NT in Multicenter CD19 CAR T Trials in Adult NHL

<table>
<thead>
<tr>
<th>Study / Sponsor</th>
<th>Product</th>
<th>N</th>
<th>CRS All Grades</th>
<th>CRS Grade ≥3</th>
<th>NT All Grades</th>
<th>NT Grade ≥3</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZUMA1 / Kite</td>
<td>CD19/CD3/CD3 2B</td>
<td>101</td>
<td>93%</td>
<td>13%</td>
<td>64%</td>
<td>28%</td>
<td>Neelapu et al. NEJM 2017</td>
</tr>
<tr>
<td>JULIET / Novartis</td>
<td>CD19/CD3/4-1BB</td>
<td>111</td>
<td>58%</td>
<td>22%</td>
<td>21%</td>
<td>12%</td>
<td>Borchmann et al. EHA 2018</td>
</tr>
<tr>
<td>TRANSCEND / Juno</td>
<td>CD19/CD3/4-1BB</td>
<td>73</td>
<td>37%</td>
<td>1%</td>
<td>25%</td>
<td>15%</td>
<td>Abramson et al. ASCO 2018</td>
</tr>
</tbody>
</table>

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism

### ZUMA1: Representative CRs after axi-cell

- Lee criteria used for CRS grading on ZUMA1 and TRANSCEND
- U Penn criteria used for CRS grading on JULIET
- All trials used CTCAE criteria for neurotoxicity (NT) grading
- 3 deaths on ZUMA1 due to AEs – 2 CRS and 1 pulmonary embolism
ZUMA1 at median f/u of 15.4 months: 42% progression-free and 56% alive

Landmark PFS
- 6-month: 49%
- 12-month: 44%
- 18-month: 41%

Landmark OS
- 6-month: 78%
- 12-month: 59%
- 18-month: 52%

Progression-Free Survival
Overall Survival

Neelapu et al. N Eng J Med 2017

Overall survival: SCHOLAR-1
- N = 636
- ORR = 26%; CR rate = 7%
- Median OS = 6.3 months

Overall survival: ZUMA1
- N = 108
- ORR = 83%; CR rate = 56%
- Median OS = >18 months

Outcomes in Refractory DLBCL: Historical vs. ZUMA1

CD19 CAR T in NHL: Beginning of a Paradigm Shift

R-CHOP or similar
50-60% cured
2nd line chemo
HDT + ASCT (5% cured)
CD19 CAR T (15% cured)

CD19 CAR T in high-risk aggressive B-cell NHL
Randomized trials of CD19 CAR T vs. ASCT
CD19 CAR T in high-risk indolent B-cell NHL
CD19 CAR T in MCL

ELIANA: 1st Multicenter Trial of CTL019 in r/r Pediatric and Young Adult ALL

Day 0
Day -5
Day 28
1st response assessment

Cy – 500 mg/m2/d x 2
Flu – 30 mg/m2/d x 4
Leukapheresis

Median weight-adjusted dose of 3.1 x 10^6/kg

Eligibility
- r/r ALL with ≥5% lymphoblasts in BM
- Ages 3 yrs at screening to 21 yrs at initial diagnosis

Conditioning
Tisagenlecleucel

Endpoints
- Primary: ORR within 3 months, 4-week maintenance of remission
- Secondary: MRD status, DOR, OS, cellular kinetics, safety

CD19 CAR T in high-risk aggressive B-cell NHL

ELIANA: Efficacy (N = 75)

<table>
<thead>
<tr>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+CRI) within 3 months</td>
<td>61 (81)*</td>
</tr>
<tr>
<td>CR</td>
<td>45 (60)</td>
</tr>
<tr>
<td>CRI</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Day 28 response</td>
<td>58 (95)</td>
</tr>
<tr>
<td>CR or CRI with MRD negative bone marrow</td>
<td>61 (81)*</td>
</tr>
</tbody>
</table>

*P < 0.0001

• ORR = Complete remission
• CRI = Complete remission with incomplete blood count recovery
• MRD negative = Flow cytometry of ≤ 0.01%
Outcomes in r/r Pediatric ALL: Historical vs. ELIANA

Maude et al., N Eng J Med 2018

EFS and OS after CAR T

ELIANA: Safety (N = 75)

- 2 deaths within 30 days of CTL019 (1 ALL, 1 cerebral hemorrhage)
- All patients who achieved CR/CRi developed B-cell aplasia and most received IVIG
- No deaths due to CRS
- No cases of cerebral edema

Maude et al., N Eng J Med 2018

CD19 CAR T in Pediatric ALL: Beginning of a Paradigm Shift

Outline

- CAR T-cell therapy background
- Efficacy in diffuse large B-cell lymphoma and ALL
- Efficacy in other hematological malignancies and future directions

Next Steps in CAR Cell Therapy

Improving efficacy
- Understand mechanisms of resistance
- Bimulti-specific CAR T cells to overcome antigen escape (CD19-CD22 or CD19-CD20)
- CAR T + immune modulators (e.g. PD-1/PD-L1 blockade; ibrutinib)

Improving safety
- Toxicity assessment and management guidelines
- Prophylactic interventions
- Safety switches to eliminate or regulate CAR T cells

Improving access
- CAR T therapy for other malignancies and earlier stages of disease
- Allogeneic off-the-shelf CAR cell therapy products
- Reducing cost of therapy

CD19/CD3ζ/CD28 CAR T Therapy in Adult ALL (MSKCC)

EFS of all patients

EFS according to disease burden

N = 53
CR rate = 85%
MRD negative = 67%
CD19 CAR T Therapy in r/r CLL

U Penn: CD19/CD3/4-1BB

FHLCRC: CD19/CD3/4-1BB (CD4:CD8 = 1:1)

- N = 14
- CR rate = 74%
- PR rate = 21%
- ORR = 74%

Porter et al. J Clin Oncol 2017

N = 14
CR rate = 21%
PR rate = 53%
ORR = 64%

Turtle et al. J Clin Oncol 2017

FHCRC: CD19/CD3

- N = 14
- CR rate = 28.5%
- PR rate = 28.5%
- ORR = 50%

Porter et al. Sci Trans Med 2015

CD19 CAR T Therapy in r/r Follicular Lymphoma

U Penn: CD19/CD3

- N = 14
- CR rate = 43%
- PR rate = 28.5%
- ORR = 79%

Schuster et al. N Eng J Med 2017

Improving Access: Off-the-shelf CAR T-cell Therapy

Molecular remission of infant B-ALL after infusion of universal TAL effector gene-edited CAR T cells

- PALL Study in pediatric ALL
  - 5 children treated
  - 5/5 CRs
  - 2 alive in CR
  - 1 death in CR

Qasim et al. ASH 2017, Abstract 1271

CALM study in adult ALL

- 6 adults treated
- 4/6 CRs
- 1 alive in CR
- 1 relapse
- 1 death in CR

Graham et al. ASH 2017, Abstract 887

Improving access: Off-the-shelf CAR-NK Cell Therapy

- No risk of GVHD with allogeneic NK cells
- > 100 doses of CAR-NK cells from one cord unit
- First-in-human phase I/II trial of CAR-NK cells at MDACC in NHL, CLL, and ALL
- Dose escalation: 1 x 10^5/kg; 1 x 10^6/kg; 1 x 10^7/kg
- CyFlu conditioning chemotherapy

Liu et al. Leukemia 2018

Alternatively Spliced Variants of CD19 After CAR T Therapy

- At relapse, 15/16 (94%) patients assessed had CD19 loss on ELIANA trial

Maude et al. N Eng J Med 2018

Loss of exon 2 or exons 5-6
Predominant protein products for CD19 isoforms

Improving Efficacy: Targeting Multiple Antigens

First-in-human trial of a multispecific CAR at Stanford
- Accrual: N = 9
- Clinical responses seen with 1x10^6/kg
- Expansion cohorts of 30 for DLBCL and ALL

53 yo M with chemo-refractory DLBCL

Baseline                        PR at 1 month
Persistent CAR-19-22 and B-cell aplasia
Other Lymphomas: CD30-specific CAR T (CD30/CD3ζ/CD28)

- CD30 has been successfully targeted by Ab-drug conjugate (brentuximab vedotin)
- A CD30-specific CAR has activity in pre-clinical models of Hodgkin lymphoma (Savoldo, Blood 2007)
- Two phase I trials in CD30+ lymphomas (No conditioning / Cy-Flu conditioning chemotherapy)
- Dose escalation on both trials: 2 x 10^7/m^2; 1 x 10^8/m^2; 2 x 10^8/m^2

Ramos et al. J Clin Invest 2017

Provided by Carlos Ramos, Baylor College of Medicine

- • CD30 has been successfully targeted by Ab-drug conjugate (brentuximab vedotin)
- • A CD30-specific CAR has activity in pre-clinical models of Hodgkin lymphoma (Savoldo, Blood 2007)
- • Two phase I trials in CD30+ lymphomas (No conditioning / Cy-Flu conditioning chemotherapy)
- • Dose escalation on both trials: 2 x 10^7/m^2; 1 x 10^8/m^2; 2 x 10^8/m^2

Provided by Carlos Ramos, Baylor College of Medicine

- First phase 1: Without conditioning
- # Age Sex Diagnosis DL CRS Response
  1 45 M NS HL 1 N CR
  2 25 F NS HL 1 N CR
  3 17 M HL NOS* 1 N PD
  4 30 F NS HL 2 Y CR
  5 27 M NS HL 2 N Too early

Second phase 1: With Cy-Flu conditioning

- Vector copies/μg PBMC DNA
- Days post CART infusion

- CAR expansion greater with Cy-Flu conditioning

Targeting Multiple Myeloma: BCMA-specific CAR T

- • BCMA is a member of TNF receptor superfamily
- • Receptor for BAFF and APRIL; promotes MM pathogenesis
- • Expressed nearly universally on MM cells
- • Expression largely restricted to plasma cells and some mature B cells

Improving Safety: CARTOX (CAR TOXicity) Guidelines

Summary 1: CD19 CAR T in Lymphoid Malignancies

- • Pivotal trials in r/r pediatric ALL and adult NHL met primary endpoints for ORR
- • Centralized manufacturing is feasible with turnaround time of ~2-3 weeks
- • ORR of >80% in both ALL and NHL trials
- • Durable remissions in ~50% of ALL patients and ~40% of NHL patients
- • CRS and neurotoxicity are the major toxicities but generally reversible
- • Responding patients return to near-normal quality of life
- • Early data suggests efficacy in FL, MCL, CLL, and adult ALL

Summary 2: Targets Beyond CD19 and Off-the-shelf CAR T

- • Bi-specific CAR T cell trials to overcome antigen escape have been initiated (CD19+CD22 or CD19+CD20)
- • Off-the-shelf allogeneic CAR-T and CAR-NK cell therapy is feasible and early data suggests high response rates
- • BCMA appears to be a safe and promising target for CAR T-cell therapy in multiple myeloma
- • CD30 appears to be a safe and promising target for CAR T-cell therapy for Hodgkin lymphoma and anaplastic large cell lymphoma
- • Standardized grading system for CRS and CRES is needed to be able to compare toxicities across different trials

Thank you!
Overview of Immunotherapy and Combination Therapy Options for Hodgkin’s Lymphoma

Fredrick Hagemeister, MD
Treatment of Patients with Hodgkin Lymphoma

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Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, TX
CancerNet Conference - 6/23/2018

Conflict of Interest Disclosure

No relevant financial relationships to disclose

PET vs CT for Stage I-IV HL: PFS Results by Radiographic Assessment after 2 CT Cycles

PET after 2 cycles

CT after 2 cycles

PET vs CT for Stage I-IV HL: PFS Results by Radiographic Assessment after 2 CT Cycles

PET ps 14 Pts, 11 prog 2 yr PFS 0%

PET neg 61 Pts, 3 prog 2 yr PFS 96%

The Deauville Scoring System for Classification of PET/CT Results

SCORE PET/CT Scan Result
1 No Uptake
2 Uptake ≤ Mediastinal Uptake
3 Uptake > Mediastinum But ≤ Liver Uptake
4 Uptake Moderately Higher Than Liver Uptake
5 Uptake Markedly Higher Than Liver Uptake and/or New Lesions
X New Areas of Uptake Unlikely to be Related to Lymphoma

Using the Deauville Score in Therapy of Hodgkin Lymphoma Trials

1. Stage I-II Favorable
   • “Negative” is DS 1-2
   • Goal of trials is to reduce chemotherapy intensity and radiotherapy for those with very low risk
2. Stage I-II Unfavorable
   • Should the cutoff for “high-risk” disease be “3” or “4”
   • May depend upon type of therapy given (BEACOPP, RT)
3. Stage III-IV
   • “Positive” is DS 4-5
   • Change in therapy is reserved for those with the highest risk of relapse because of increased intensity

Treatment of Patients with Hodgkin Lymphoma

Hodgkin Lymphoma
  • Untreated, Stage I-II
  • Untreated Stage III-IV
  • Relapsed Disease
Risk Factors for Early-Stage HL According to Cooperative Treatment Groups

<table>
<thead>
<tr>
<th>Risk factors (RF)</th>
<th>EORTC-GELA</th>
<th>GHS CANADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>A - Med mass</td>
<td>A - Med mass &gt; 1/3</td>
<td></td>
</tr>
<tr>
<td>B - Age ≥ 50yr</td>
<td>B - Extra nodal site E</td>
<td></td>
</tr>
<tr>
<td>C - ESR ≥ 50</td>
<td>C - ESR ≥ 50</td>
<td></td>
</tr>
<tr>
<td>D - ≥ 4 nod. areas</td>
<td>D - ≥ 3 nodal areas</td>
<td></td>
</tr>
<tr>
<td>E - B + ESR &gt; 50</td>
<td>E - B + ESR &gt; 50</td>
<td></td>
</tr>
</tbody>
</table>

Stage:
- Fav (F): I - II without RF
- unfav (UF): I - II with 1 or + RF
- advanced: III - IV

Unfavorable: ESR > 50, Age > 40, Nodes > 4, MC or LD

ABVD versus RT for Stage I-IIA, Non-Bulky Favorable or Unfavorable HL

<table>
<thead>
<tr>
<th>Years</th>
<th>Percent Alive</th>
<th>FFP</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>94.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>89.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>84.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>79.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hazard ratio, 0.50 (95% CI, 0.25-0.99) P = 0.04

Hazard ratio, 1.91 (95% CI, 0.99-3.69) P = 0.05

4 ABVD + RT for Stages I-IIA Hodgkin Lymphoma: FFS & OS Results by RT Extent

<table>
<thead>
<tr>
<th>Years</th>
<th>Freedom from Progression</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>0.90</td>
<td>0.85</td>
</tr>
<tr>
<td>10</td>
<td>0.80</td>
<td>0.75</td>
</tr>
<tr>
<td>15</td>
<td>0.70</td>
<td>0.65</td>
</tr>
<tr>
<td>20</td>
<td>0.60</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Therapy for Favorable Stage I-II HL: The H10 GHSG Trial Design

- 1375 patients enrolled.
- Arms balanced for age, gender, stage, pathology and PS.
- More toxicity with 4 ABVD, but adherence to therapy similar.
- 2 yr FFS - 96.6%, OS - 96.6%. Longest fu = 4.5 years
- No differences in second CAs. No % differences in arms.

IFRT vs None for PET Negative HL After 3 ABVD: The RAPID Trial

<table>
<thead>
<tr>
<th>Result</th>
<th>IF RT (n=210)</th>
<th>No RT (n=211)</th>
<th>4xABVD + IF RT (n=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET after 3 ABVD</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
</tr>
<tr>
<td>3 YR FFS</td>
<td>94.5%</td>
<td>98.5%</td>
<td>86%</td>
</tr>
<tr>
<td>3 YR OS</td>
<td>97.1%</td>
<td>99.5%</td>
<td>94%</td>
</tr>
</tbody>
</table>

PET Scan Results From the RAPID Trial

<table>
<thead>
<tr>
<th>Scores</th>
<th>Alive without PD (%), Alive with PD (%), Deaths Due to HL (%), Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET Score 1</td>
<td>280 (94)</td>
</tr>
<tr>
<td>2</td>
<td>111 (92)</td>
</tr>
<tr>
<td>3</td>
<td>86 (96)</td>
</tr>
<tr>
<td>4</td>
<td>30 (94)</td>
</tr>
<tr>
<td>5</td>
<td>15 (65)</td>
</tr>
</tbody>
</table>

EORTC Fav 284 (92) Unf 172 (92) GHSG Fav 299 (91) Unfav 144 (93)

There is a 2.4% improvement by giving RT to those with negative PET, considered “acceptable” for no RT.
Intergroup H10 Trial of PET Driven Therapy for Stage I/II HL: An Interim Analysis

Favorable: Supradiaphragmatic disease, CS1-2 with 1-3 nodal areas, MTR < .35, Age <50, ESR < 50 with B SX or < 30 with B Sx
Unfavorable: Any of the above features

Feature Therapy No. Pt Relapse 1 Yr PFS % P
Favorable 3 ABVD/RT 188 1 100
4 ABVD 193 9 94.9 0.017
Unfavorable 4 ABVD/RT 251 7 97.3
6 ABVD 268 16 94.7 0.026

Despite these good results, because of the inferior results with only chemotherapy, the chemotherapy-only arms were closed to patient entry.

Raemakers et al. JCO 32: 1-8, 2014

Therapy for Unfavorable Stage I-II HL: The GHSG HD 14 Trial Design

4 ABVD 30 Gy
2 escBEACOPP and 2 ABVD 30 Gy

5 Yr Results ABVD (n=765) BE/ABVD (n=763) P
TTF 87.7 94.8 <0.001
PFS 89.1 95.4 <0.001
OS 96.8 97.2 0.73

Causes of Death: HL – 3 with ABVD, 4 with B/A
Toxic death – 5 with ABVD, 4 with B/A
Toxicity from Salvage – 6 with ABVD, 1 with B/A


SGN-35 Mechanism of Action: Brentuximab Vedotin

• SGN-35 antibody-drug conjugate
  – CD30-targeted antibody (cAC10) conjugated to an auristatin (MMAE), an anti-tubulin agent
  – Selectively induces apoptosis in HL and ALCL cells:
    – Binds to CD30
    – Becomes internalized
    – Releases MMAE

• SGN-35 Antibody-toxin conjugate

Phase II BV Plus AVD for 34 Non-Bulky Stage I-II HL

• Treatment Schema
  Enroll
  BV x 2 1.2mg/kg q 2 wk
  PET CR, PR, SD
  PO off study
  BV-AVD X 2
  PET CR
  PET PR or SD
  BV-AVD X 4
  PO off study
  BV-AVD X 4

• Patients: Favorable in 68%, unfavorable in 32%.
• CR rates: After BV, 18 pt (53%). After 2 A-AVD, 33 pt (97%). At end of TX, CR=95%; 6/8 Pos PETs were false pos, (received no more therapy, and did not progress).
• Gr 3-4 AEs: FN in 29%, PN in 24%
• At med f/u of 14 mo, PFS=90% and OS= 97%.
• Randomized study needed to prove benefit of BV

Abramson et al. ASCO 2014, Abst 8005.

Phase 2 ABVD Followed by BV Consolidation for Non-Bulky Stage I-II HL

• 40 evaluable Pts, med age 29, Unfav Disease in 46%
• TX: ABVD 2-6 cycles, depending on risk factors.
  – 6 weeks following ABVD, 6 doses of BV given (1.8 mg/kg) q 3 wk
  – RT NOT given
• Results: 90% receive ≤ 4 cycles of ABVD
• 72% PET negative after ABVD, and 90% PET negative after BV
• One died with rare BV toxicity (hepatic failure)
• One year result: PFS = 90%, OS = 96%

Park et al. ASCO 2016 ( abst 7708).

Phase 2 ABVD Followed by BV Consolidation for Non-Bulky Stage I-II HL

• 40 evaluable Pts, med age 29, Unfav Disease in 46%
• TX: ABVD 2-6 cycles, depending on risk factors.
  – 6 weeks following ABVD, 6 doses of BV given (1.8 mg/kg) q 3 wk
  – RT NOT given
• Results: 90% receive ≤ 4 cycles of ABVD
• 72% PET negative after ABVD, and 90% PET negative after BV
• One died with rare BV toxicity (hepatic failure)
• One year result: PFS = 90%, OS = 96%

Park et al. ASCO 2016 ( abst 7708).

BV + AVD vs ABVD for Unfavorable Stage I-II HL: Study Design

• PET:response after 2 cycles, n(%)  
  BV-AVD 413
  ABVD 372
  Negative 93 (82.3) 43 (75.4)

Fonseca et al. ASH 2017 (ABST 736).
BV Plus AVD and RT for Unfavorable Stage I-II HL: Cohort 1 Schema and Result

- Results in 22 pt
- 1 yr PFS: 93%
- 2 had primary refractory disease on TX
- Both PD pts underwent SCT and no signs of progression at 30+ mo from SCT
- OS: 100% Med f/u 34 mo
- Cohort 2 Plan is the same as 1, but only 20 Gy ISRT Given

Kumar et al. ASH 2017 (ABST 734).

Involved Site RT
- Results in 22 pt
- 1 yr PFS: 93%
- 2 had primary refractory disease on TX
- Both PD pts underwent SCT and no signs of progression at 30+ mo from SCT
- OS: 100% Med f/u 34 mo
- Cohort 2 Plan is the same as 1, but only 20 Gy ISRT Given

Kumar et al. ASH 2017 (ABST 734).

Treatment of Patients with Hodgkin Lymphoma

Hodgkin Lymphoma
- Untreated; Stage I-II
- Untreated Stage III-IV
- Relapsed Disease

Prognostic Scoring System for Advanced HL: Unfavorable Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Rel Risk</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>&lt;10.5</td>
<td>1.35</td>
<td>0.006</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;4.0</td>
<td>1.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>1.35</td>
<td>0.001</td>
</tr>
<tr>
<td>Lymph Ct</td>
<td>&lt;600/8% WBC</td>
<td>1.38</td>
<td>0.002</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;45 Yr</td>
<td>1.39</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC</td>
<td>&gt;15,000</td>
<td>1.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Stage</td>
<td>IV</td>
<td>1.26</td>
<td>0.011</td>
</tr>
</tbody>
</table>


Treatment of Newly Diagnosed Advanced HL: FFP and OS by IPS Rank

ABVD Without RT for Advanced cHL (AcHL): Results for PET Negative Responses
- 43/316 ePET eval by SPS: Neg Score = 1-3
ePET result: 261 Neg, 49 Pos, 6 Indeterminate
- RT data: 259 (99%) Neg ePET not given RT
- 37 (75.5%) of Pos ePET given RT
- 12 (24.5%) Pos ePET not given RT
- 5 Yr FFTF 57% for Pos ePET pts receiving IFRT (30-35 GY)
- RT not needed for pts with Neg ePET, PFS bulky = 89%, non-bulky = 89%
- 5 Yr FFTF 57% for Pos ePET pts receiving IFRT (30-35 GY)

Savage et al. ASH 2015. ABST 578.
ABVD vs BEACOPP for Advanced HL When SCT is Planned for First Relapse

BEACOPP is better at preventing the first relapse, but SCT following first relapse after ABVD equalizes overall survival rates.


basBEACOPP for Patients Over 60 with Hodgkin Lymphoma

68 Patients, Age 66-75 years, Med f/u – 40 mo.
Therapy: COPP/ABVD (26) or Base BEACOPP (42) followed by RT to initial bulky or residual sites.

<table>
<thead>
<tr>
<th>Results</th>
<th>C-A (%</th>
<th>B-BEA (%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>77</td>
<td>76</td>
</tr>
<tr>
<td>TRM</td>
<td>7.6</td>
<td>21.3</td>
</tr>
<tr>
<td>TTF</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>FFP</td>
<td>55</td>
<td>74</td>
</tr>
<tr>
<td>OS</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>


Adcetris plus AVD versus ABVD for Advanced HL: Design


Adcetris plus AVD versus ABVD for Advanced HL: Primary Endpoint


Adcetris plus AVD versus ABVD for Advanced HL: GCSF Use and NF


Adcetris plus AVD versus ABVD for Advanced HL: Modified PFS Result

Therapy for Older Patients with HL:BV Alone as Initial Therapy

- Single agent brentuximab vedotin:
  - 1.8 mg/kg q 3 wks in 27 elderly HD pts
  - Median age 78 yrs, 63% stage III/IV
- ORR 92% (73% CR)
- 30% pts grade 3 neuropathy

Evens et al. ASH 2017 (ABST 733).

BV and Alternate Single Agents for Older Patients with HL

- 1.8 mg/kg BV + 50/70 mg/m² bendamustine
  - 65% SAE (including 2 toxic deaths)
- 1.8 mg/kg BV + 375 mg/m² DTIC (12 cycles)
  - 85% DTIC ORR 100% (62% CR)
- 27% pts grade 3 neuropathy

Evens et al. ASH 2017 (ABST 733).

BV Plus AVD for Older Patients with Hodgkin Lymphoma: Response

(N=60) BV x 2 AVD x 3 AVD x 3 BV x 4

ORR 87% CR 30% (PET)
ORR 96% CR 79%
ORR 95% CR 90%
ORR 95% CR 93%

ITT (n=48) after 6 AVD: ORR 85% and CR 81%

Evens et al. ASH 2017 (ABST 733).

BV Plus AVD for Older Patients with HL: PFS and OS Results

By Multivariate Analysis, only age (HR 1.19 for each year over 60) was important for PFS.

Evens et al. ASH 2017 (ABST 733).

Nivolumab and AVD as Initial Therapy for Advanced HL: Study Design

- Response were assessed using the IWG 2007 criteria
- Median duration of follow-up was 11.1 months (clinical cutoff 31 August 2017)
- lymphopenia was included due to potential overlapping pulmonary toxicity

Ramchandren et al. ASH 2017 (ABST 651).

Nivolumab and AVD as Initial Therapy for Advanced HL: Response

Ramchandren et al. ASH 2017 (ABST 651).
Nivolumab Alone and Nivolumab + AVD for Rel/Ref HL: Tumor Responses

Timmerman et al. ASH 2016, abstract 1110.
Ramchandren et al. ASH 2017 (ABST 651).

Nivolumab and AVD as Initial Therapy for Advanced HL: Modified PFS

Ramchandren et al. ASH 2017 (ABST 651).

Treatment of Patients with Hodgkin Lymphoma

Hodgkin Lymphoma
- Untreated, Stage I-II
- Untreated Stage III-IV
- Relapsed Disease

ICE and SCT for Rel/Ref HL: EFS and OS by PFS

MVA of PFS for EFS

<table>
<thead>
<tr>
<th>Feature</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>B SX Pre-ICE</td>
<td>1.68</td>
<td>0.012</td>
</tr>
<tr>
<td>Rel &gt; 1 year from DX</td>
<td>0.587</td>
<td>0.0237</td>
</tr>
<tr>
<td>ENDz</td>
<td>1.87</td>
<td>0.009</td>
</tr>
</tbody>
</table>

- 40 Pt with 0-1 Factor, 15 with 2, 10 with 3 Factors
- EFS rates (%): 83, 27, 10
- OS rates (%): 90, 57, 25


PET as a Predictor of Outcomes of AutoSCT (ASCT) for Rel/Ref HL

152 pts assessed for RFs at time of therapy
- B sx, EN disease, Rel within 1 year
- All get ICE: 1 RF = ICE; 2RFs = 1 ICE + 1 HD ICE, 3RFs = HD ICE
- All undergo GaScan or PET prior to ASCT
- Any PT with any response by CT goes to ASCT

Only predictor of OS or PFS by MVA was PET or GaScan

Integration of PET Into a Model for SCT: Therapy Plan

**Treatment stratified by RFs**

- **sICE=Standard Dose**
  - Arm A (0-1 RF): N=56
  - Arm B (2 RF): N=41
- **aICE=Ifos-10 gm/m² ci d1-2; C-800 mg q 12 h, day 1**
- RT to resid or original bulk
- SCT regimen depended on prior RT: TBI/CE or CBV
- Primary Endpoint: 45% 3 Yr EFS for PET POS Pts following GVD (compare 25% in prior study)

**PET and an ASCT Model: 3 Yr EFS by Scan and Therapy**

- No difference between Arm A and Arm B; did not include pt with 3 RFs
- Neg PET: 81% (14/17) after GVD; 80% (40/50) after ICE
- PET replaces Refractory vs Relapsed DZ and B SX prior to ICE
- Pos PET: 29% (6/21) after GVD; but 60% for all after GVD (met 1ry Endpoint)

**BV vs Placebo for Relapsed/Refractory HL: PFS and OS Results**

- **Risk Factors: Ref HL or PD in < 1 Yr; END or B SX at SCT ≥ 2 Salvage TX**
- Of 30 eval pts, 27 went to SCT, but 13 received additional chemo prior to SCT (48%)
- Follow-up and more data needed to determine value of Bretuximab alone prior to SCT

**BV Plus ESHAP for Rel/Ref Prior to ASCT: GELTAMO Trial**

- 66 Pts enrolled; 64 underwent SC Collection, none failed. 61% Primary Refractory Disease; 50% Gr3-4 ANC, PLT

**Nivo for Rel/Ref HL: Change in Tumor Burden After Progression for TBP Pts**

- Main reason for initial progression: Development of new lesions (47/70).
Nivo for Rel/Ref HL: Time from PD to Next Therapy and OS by Therapy Choice

Cohen et al. ASH 2017 (ABST 650).

Phase 1/2 BV Plus Nivolumab for Rel/Ref HL: Tumor Response

Herrera et al. ASH 2017 (ABST 649).

Treatment of Patients with Hodgkin Lymphoma

Hodgkin Lymphoma
- Untreated, Stage I-II
- Untreated Stage III-IV
- Relapsed Disease

Thank you

Fredrick B. Hagemeister, MD
Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, TX
Overview of Treatment Options for Diffuse Large Cell Lymphoma (DLCL)

Fredrick Hagemeister, MD
Treatment of Patients with Diffuse Large B-Cell Lymphoma (DLBCL)

Fredrick B. Hagemeister, MD
Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, TX
CancerNet Conference - 6/23/2018

Conflict of Interest Disclosure
No relevant financial relationships to disclose

Treatment of Patients with DLBCL
Diffuse Large Cell Lymphoma
Untreated Standard
Untreated Novel Therapy
Novel Relapse therapy

R-CHOP vs CHOP for Patients > 60 with DLBCL:
Follow-up of the GELA Trial

<table>
<thead>
<tr>
<th>Result</th>
<th>R-CHOP</th>
<th>CHOP</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med EFS</td>
<td>3.8 Yr</td>
<td>1.1 Yr</td>
<td>0.00002</td>
</tr>
<tr>
<td>5-Yr EFS</td>
<td>47%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Med PFS</td>
<td>NR</td>
<td>1 Yr</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>5-Yr PFS</td>
<td>54%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Med OS</td>
<td>NR</td>
<td>3.1 Yr</td>
<td>0.0073</td>
</tr>
<tr>
<td>5-Yr OS</td>
<td>58%</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

Coiffier et al. Blood 104: 2004 (abst 1383)

The International Prognostic Factors Index (IPI) for Diffuse Large B-Cell Lymphoma

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of Factors</th>
<th>5-year OS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years</td>
<td>3</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>PS ≥2</td>
<td>2</td>
<td>55</td>
<td>51</td>
</tr>
<tr>
<td>LDH &gt;Normal</td>
<td>2</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>Extralymphatic sites ≥2</td>
<td>1</td>
<td>40</td>
<td>33</td>
</tr>
<tr>
<td>Stage B IV</td>
<td></td>
<td></td>
<td></td>
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</table>

Age-Adjusted IPI

<table>
<thead>
<tr>
<th>Factor</th>
<th>Number of Factors</th>
<th>5-year OS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The International Non-Hodgkin's Lymphoma Prognostic Factors Project.

Multivariate Analysis of Prognostic Factors in the NCCN-IPI

<table>
<thead>
<tr>
<th>NCCN (n = 1650)</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;60 y</td>
<td>1.0</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>61-69 y</td>
<td>1.6</td>
<td>(1.4-1.9)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>70-75 y</td>
<td>2.2</td>
<td>(1.8-2.6)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>&gt;75 y</td>
<td>4.1</td>
<td>(3.0-5.7)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>LDH Rai 1.5</td>
<td>1.6</td>
<td>(1.3-2.0)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>LDH Rai 2-3</td>
<td>3.3</td>
<td>(2.4-4.3)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>LDH Rai &gt;3</td>
<td>4.5</td>
<td>(3.4-6.1)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>CD20 (PS) 2</td>
<td>1.3</td>
<td>(1.1-1.6)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>ANN HSB stage IV</td>
<td>1.6</td>
<td>(1.3-2.1)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Extramedullary</td>
<td>1.0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR = hazard ratio; LDH Rai, LDH ratio. *lymphoma status unknown.

Prognostic Subgroups in DLBCL

- DNA microarray can predict survival after chemo


High Level of expression

Germinal-center B-cell–like Type 1
Activated B-cell–like

Germinal-center B-cell–like Type 2
Activated B-cell–like

Overall survival (years)

Stage I-II
Stage III-IV

77%
49%

Markers Aiding in the Subclassification of DLBCL

CD10
MUM1
bcl6

GCB
non-GCB

GCB
non-GCB

5-Year OS
76%
34%

Other Criteria have been developed, but none are strikingly better than this one.


R-CHOP for DLBCL: PFS and OS Results by GCB Status

Newakowski et al JCO 2015

R-CHOP for DLBCL: PFS and OS Results by GCB Status

Primary Mediastinal Large B-Cell Lymphoma: The MDACC Experience

- 300 pt retrospectively analyzed, path reviewed by JM.

Feature

R-CHOP
EPOCH-R
HCVAD

# Pt
123
30
41

Stage III-IV, %
15
3
7

END, (%)
3
0
12

LDH, (%)
31
18
0

Pericard Eff, (%) 23/71 (32) 6/26 (23) 19/35 (54)

Pleur Eff, (%) 25/71 (35) 11/28 (39) 23/35 (61)

CR, %
76
83
93

4 Yr EFS, % 65
79
88

4 Yr OS, % 85
100
92

MVA for EFS: R-CHOP is inferior to more intensive therapy.
Effusions did not affect results.

Ahmed et al. JCO 32: 5s, 2014, abst 8564.

“Double Hit” DLBCL: A Poor-Risk GCB with BCL-2 and MYC Rearrangements

- MYC rearrangement induces rapid growth
  – IgH classic for BL, but also found in CLL/SLL, FL, and MCL, esp. in transformation
  – Found in 15-20% of de novo DLBCL, but in up to 60% in de novo DLBCL when Ki-67 >80%

- BCL-2 (14;18) associated with anti-apoptosis
  – Hallmark of FL, but found in DLBCL (20-30%) and CLL/SLL (rare)

- Pathology of “double hit”: DLBCL, BL, BLikeLCL

- Survival usually less than a year with any therapy


Double Hit DLBCL in 100 MDACC Patients: A Retrospective Analysis

- CR rates: All 59%, CHOP + R 49%, EPOCH + R 50%, HCVAD + R 60% (P=NS).

- 3 Year PFS (All pt) = 32%, OS = 41%. No diff by chemo regimen

PFS by Therapy Regimen

OS by Therapy Regimen

Similar results for DA-EPOCH-R from NCI.
R-CHOP for Advanced DLBCL: Impact of Double Expression vs HIT

Johnson et al. JCO 2012.

Positive Stains for MYC/BCL-2
Positive FISH for MYC/BCL-2

Combinations That Have Not Yet Been Proven to Be Better Than R-CHOP-21

<table>
<thead>
<tr>
<th>Combination</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-CHOP</td>
<td>Not, in company trial</td>
</tr>
<tr>
<td>R-CHOP-14</td>
<td>Not, in two large studies</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>Not, in favorable pts &lt; 60</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>Not, in advanced disease</td>
</tr>
<tr>
<td>R2-CHOP</td>
<td>Randomized trial ongoing</td>
</tr>
<tr>
<td>R-HCVAD</td>
<td>Better for some, not all</td>
</tr>
<tr>
<td>R-CHOMP</td>
<td>Randomized trial ongoing</td>
</tr>
<tr>
<td>BV + R-CHOP</td>
<td>Randomized trial ongoing</td>
</tr>
<tr>
<td>Brutinib + R-CHOP</td>
<td>Randomized trial ongoing</td>
</tr>
<tr>
<td>R-CHOP and SCT</td>
<td>Better for some groups, not all</td>
</tr>
<tr>
<td>R-CHOP and BV rituximab</td>
<td>Randomized trial ongoing</td>
</tr>
</tbody>
</table>

R-CHOP vs R-CHOP and SCT for IH/H IPI Risk Aggressive NHL: 2 Yr Results

- 370 pts started CHOP + R, 253 (68% PR/CR) were randomized (PD in 66, and 23 refused)
- P significant for H risk, not for IH risk (PFS and OS)
- Results not different for T vs B or R versus no R

Stiff et al. ASCO Meeting JCO 29, 2011 (abst 8001).

PFS and OS for Aggressive NHL by PET Results After 2 or 3 Cycles of non-R-CT


PET-Guided RT for Advanced Stage DLBCL: TTP by EOT-PET and RT

PET-NEG 83% (95% CI 79-87%)
PET-POS + XRT 78% (95% CI 68-85%)
PET-POS no XRT 34% (95% CI 24-43%)

PET-Guided RT for Advanced DLBCL: Impact of Bulk > 10 cm if PET Neg

Reasons for no RT for PET Positive Disease (N=97):
MD Choice in 25
Progression in 63 (12%)
PI Refused in 11
Surgery in 8

3-year TTP 84% 82%
MSKCC 01-142: Risk Adapted Therapy for Patients with DLBCL and AAII 1-3

4 Cycles of R-CHOP-14
- Pet Pos and Repeat Biopsy Pos
- Pet Pos and Repeat Biopsy Neg
- Pet Negative; No Biopsy Done

3 Cycles of ICE and HDT/SCT

Results by PET and Biopsy

Therapy of DLBCL: PFS by Interim PET and Biopsy Results

PET Neg               59      8
PET Pos, BxNeg  33      7
PET Pos, BxPos 5      2

Besides results, this is the most important finding!

ctDNA Levels Predict EFS Outcomes in Untreated Patients with DLBCL
- Pretreatment ctDNA measured in 181 patients
- ctDNA levels prognostic for Event-Free Survival

Changes in ctDNA Levels Post Cycle 1 Predict EFS for DLBCL Patients
- EFS by Early Molecular Response (EMR)
- 2-log (100 fold) drop in ctDNA following ONE cycle of therapy

The Continuous Individualized Risk Index (CIRI) in Therapy of DLBCL (2)

DA-EPOCH-R for DLBCL: PFS and OS Results by DHL and DEL Status
- DHL has excellent results with DA-EPOCH-R.
- DELs do as well as DHLs, but more study is needed.
- 84% of non DEL GCBs had Ki-67% > 80%; further comparison to R-CHOP needed.

Sathyamangalam et al. ASH 2016, abstract 106.
R-CHOP vs EPOCH-R for DLBCL: PFS and OS Results

Analysis by COO, DHL/DEL and other features pending.

Wilson et al. ASH 2016, abstract 469.

EPOCH-R for Burkitt Lymphoma: Risk Category Definitions in NCI 9177

CT and PET, BM, flow cytometry of blood and CSF

Roschewshi et al. ASH 2017 (ABST 188).

EPOCH-R for Burkitt Lymphoma: EFS for High and Low Risk Patients

EFS was not influenced by ePET results, HIV status or age of patient.

Roschewshi et al. ASH 2017 (ABST 188).

EPOCH-R for Burkitt Lymphoma: EFS by CNS, BM, or PB Status

Roschewshi et al. ASH 2017 (ABST 188).

Treatment of Patients with DLBCL

Diffuse Large Cell Lymphoma

Untreated Standard

Untreated Novel Therapy

Novel Relapse therapy

BV Plus R-CHP for Aggressive NHLs: Response

Svoboda et al. ASH 2017, ABST 191.
BV Plus R-CHP for PMBCL (N=22)

Svoboda et al. ASH 2017, ABST 191.

Lenalidomide: Targeting the Tumor Cell and Its Microenvironment


Maint Len for DLBCL in CR/PR after Relapse Therapy: PFS and OS Results

Met primary endpoint. Justifies a randomized trial.

Ferreri et al. ASH 2016, abstract 474.

Phase 3 REMARC : Outcomes


• OS (med f/u: 52 mo): No differences for len vs placebo (P = .2640)
• Similar rates of PR-to-CR conversion during maintenance period among patients with PR response to R-CHOP
• More gr 3/4 ANC (36% versus 22%) and discontinuation for toxicity (38% versus 18%) with lenalidomide vs placebo

Group Reported
Overall population 0.708
Patients ≥70 years 0.653
Patients with CR response to R-CHOP 0.722
Patients with positive PET at randomization 0.392

R-CHOP Compared with R2-CHOP for GCB and Non-GCB DLBCLs: PFS and OS Results


Len-Obin-CHOP for Untreated Diffuse Large B-Cell Lymphoma: Response

Westin et al. ASH 2017, ABST 189.
Len-Obin-CHOP for Untreated DLBCL: PFS and OS Results by COO

Westin et al. ASH 2017, ABST 188.

The Smart Start Trial for Untreated Non-GCB large Cell Lymphomas: Schema

Westin et al. ASH 2017, ABST 189.

Treatment of Patients with DLBCL

Diffuse Large Cell Lymphoma

Untreated Standard

Untreated Novel Therapy

Novel Relapse Therapy

ASCT for Relapsed DLBCL: Pre-Rituximab Era (PARMA study)

- 7 year EFS was 41% vs 13% for ASCT vs the chemo alone arm

Results are only for those in PR/CR after 2 DHAP
Only CRs to initial chemotherapy were enrolled

R-ICE/ASCT vs R-DHAP/ASCT for Rel/Ref DLBCL: EFS and OS by Induction


Polatuzumab (Anti-CD79b Antibody - Toxin) Plus BR vs BR: Patient Features

- Anti-CD79b linked to MMAE
- 78 pts SCT ineligible or post auto (no allo)
- Pola 1.8 mg/kg plus BR (90mg/m2)
- CR: PET and Marrow negative
- Med F/U: 10.9 vs 3.6 mo

Sohn et al. ASH 2017, ABST 3351.
Polatuzumab + BR vs BR for R/R DLBCL: Tolerability and Response

More AEs in Pola + BR group:
ANC: 54% vs 39%
PLT: 49% vs 23%
HGB: 43% vs 15%
PN: 39% vs 3%
FN: 10% vs 5%

Discontinued TX:
PD – 15% vs 54%;
Toxicity – 33% vs 10%

Sehn et al. ASH 2017, ABST 2821.

Polatuzumab + BR vs BR for R/R DLBCL: PFS and OS Results

MOR208 + Lenalidomide for R/R DLBCL: Response and PFS Data

Data from MORPHOSYS

Treatment of Patients with DLBCL
Diffuse Large Cell Lymphoma
 Untreated Standard
 Untreated Novel Therapy
 Novel Relapse therapy

Thank you
Fredrick B. Hagemeister, MD
Department of Lymphoma/Myeloma
M D Anderson Cancer Center
Houston, TX
CancerNet Conference
Houston, 6/23/2018
Overview of Treatment Options for Follicular Lymphoma (FL)

Nathan Fowler, MD
Follicular Lymphoma: Curing a Chronic Disease

Nathan Fowler MD
Associate Professor of Medicine
Director, Clinical and Translational Research
Lead, New Drug Development Program
Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure

Advisory Board: Celgene, Roche, Janssen

Indolent Lymphoma: MD Anderson Experience

Percent Survival

<table>
<thead>
<tr>
<th>Year</th>
<th>60 mos</th>
<th>120 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944-54</td>
<td>29.3</td>
<td>17.2</td>
</tr>
<tr>
<td>1955-64</td>
<td>41.5</td>
<td>20.3</td>
</tr>
<tr>
<td>1965-74</td>
<td>54.1</td>
<td>31.9</td>
</tr>
<tr>
<td>1975-84</td>
<td>63.5</td>
<td>41.0</td>
</tr>
<tr>
<td>1985-94</td>
<td>70.6</td>
<td>49.6</td>
</tr>
<tr>
<td>1995-04</td>
<td>82.7</td>
<td>72.3</td>
</tr>
</tbody>
</table>

Effect of Frontline Follicular Lymphoma Therapies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Rituximab</th>
<th>Lenalidomide+Rituximab</th>
<th>Bendamustine+Rituximab</th>
<th>CHOP+Rituximab†</th>
<th>CVP+Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III/IV</td>
<td>%</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>GELF Criteria for Response, %</td>
<td></td>
<td>0</td>
<td>49</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>Bulky Disease, %</td>
<td></td>
<td>0%</td>
<td>20</td>
<td>20</td>
<td>39</td>
</tr>
<tr>
<td>ORR, %</td>
<td></td>
<td>73</td>
<td>98</td>
<td>64*</td>
<td>86</td>
</tr>
<tr>
<td>CR, %</td>
<td></td>
<td>26</td>
<td>85</td>
<td>41*</td>
<td>20</td>
</tr>
<tr>
<td>PFS 1 year</td>
<td></td>
<td>80%</td>
<td>2 year</td>
<td>83%</td>
<td>2 year</td>
</tr>
<tr>
<td>*</td>
<td></td>
<td>Included indolent, MCL patients</td>
<td></td>
<td>±</td>
<td>Includes BLNI, ECOG Criteria</td>
</tr>
</tbody>
</table>

FLIPI Predicts Overall Survival

FLIPI Scores:
- Low Risk
- Intermediate Risk
- High Risk

FLIPI 10yr OS
- Good 71%
- Intermediate 51%
- Poor 36%

M7 FLIPI Clinicogenetic Risk Model

<table>
<thead>
<tr>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes</td>
</tr>
<tr>
<td>FLIPI</td>
</tr>
<tr>
<td>ECOG PS</td>
</tr>
</tbody>
</table>

Deep sequencing of 74 mutations in 151 samples from
remissions of pts. Who got CHOP as frontline.

Pastore, A. et al. Lancet Onc. 2015

Complex mutational landscape
PET as a Prognostic Tool

End of induction PET

Risk of death also increased in PET+ (HR 7.0 p=.0011)

OS of Patients With FL Who Relapsed Within 2 Years of R-CHOP (“Early POD”)

122 patients were classified as early progressors (n=110 POD and n=12 non-POD death within 2 years)

EFS12
Event Free Survival at 12 mo following Diagnosis

• Retrospective Analysis
  • Newly diagnosed FL pts (Gr I-IIa)
  • University of Iowa/Mayo Clinic (936 pts)
  • Lyon, Frances Hospital Registry (153 pts)

• EFS was defined as time from diagnosis to progression, relapse, re-treatment, or death due to any cause.

• EFS12: status of EFS 12 months following diagnosis.

• Survival compared to matched population cohort.

BR vs. R-CHOP  The StiL Study

Primary objectives
- To prove the noninferiority of BR vs. R-CHOP defined as a decrease of <10% in PFS after 3 years

Secondary objectives
- Response rates, time to next treatment, event-free survival, OS
- Acute and late toxicities, infectious complications
- Stem cell mobilization capacity in younger patients
**BR vs. R-CHOP**

**PFS 45 Months of Follow-Up**

**HR, 0.58 (95% CI 0.44 to 0.74)**

**P = 0.0000148 (stratified log rank)**

**Median (months)**

B‐R 69.5

CHOP‐R 31.2

OS at 5 years was 80% for BR and 78% for R‐CHOP

*Bright* Study

**Primary Objective:** Determine if BR is non-inferior (CR rate) to standard tx (R-CHOP or R-CVP)

### Indolent or Mantle Cell

- Stage II+
- Untreated

**BR vs R-CHOP/R-CVP: Bright Study**

**Efficacy**

<table>
<thead>
<tr>
<th>Overall Response Rate</th>
<th>BR</th>
<th>R-CHOP/R-CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>35%</td>
<td>25%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>65%</td>
<td>60%</td>
</tr>
</tbody>
</table>

**Toxicity**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>BR</th>
<th>R-CHOP/R-CVP</th>
</tr>
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<tbody>
<tr>
<td>Vomiting (%)</td>
<td>12-18</td>
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</tr>
<tr>
<td>Neutropenia (%)</td>
<td>4%</td>
<td>20%</td>
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<td>12-18</td>
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</tr>
</tbody>
</table>
| Neutropenia (Gr4+) | 1-2% | 12-16%
| Neutropenia (Gr5+) | 0-1% | 0-4%

**Obinutuzumab (GA101)**

- **GASH (obinutuzumab)** is a type II humanised and glycoengineered, anti-CD20 monoclonal antibody
  - Recognizing a different epitope on the CD20 molecule and therefore engaging different signals on the target cell (type II)
  - Optimised for direct cell death activity
  - Glycoengineering provides a higher affinity for FcγRIIIA receptors

- **GASH (obinutuzumab)** has demonstrated superior preclinical activity to type I antibodies *in vitro* and *in vivo*

**Obinutuzumab-chemo vs. rituximab-chemo in iNHL:**

**Gallium study**

**Results:** G-chemo vs. R-chemo has improved PFS but same Survival

**Antibody Dosing**

- Obinutuzumab 1080mg on D1, D8, D15 of C1 and D1 of subsequent cycles.
- Rituximab 375mg/m² on D1 of all cycles.

**Primary endpoint**

- Progression free survival

---

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**Primary endpoint**

- Progression free survival.
Safety in Follicular Lymphoma

<table>
<thead>
<tr>
<th>% (N)</th>
<th>Rituximab</th>
<th>Obinutuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>59.3% (367)</td>
<td>59.3% (352)</td>
</tr>
<tr>
<td>Grade 3-4 AEs</td>
<td>17.8% (267)</td>
<td>14.5% (244)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17.8% (267)</td>
<td>14.5% (244)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5.0% (76)</td>
<td>3.8% (61)</td>
</tr>
<tr>
<td>Platelet transfusions</td>
<td>4.9% (72)</td>
<td>4.9% (70)</td>
</tr>
<tr>
<td>Fever</td>
<td>3.7% (55)</td>
<td>4.7% (66)</td>
</tr>
</tbody>
</table>

Aim of the study: The safety of Idelalisib in combination with rituximab or obinutuzumab in patients with previously treated follicular lymphoma.

Idelalisib: Selective PI3K Inhibitor Phase II in Refractory iNHL

- Tumor assessments:
  - Weeks 0, 8, 16, 24, 36, 48
  - Every 12 weeks thereafter
  - Evaluated by Independent Review Committee
  - 2 radiologists with adjudication if needed
  - Clinical review

- Primary endpoint: Overall Response Rate (ORR)
- Secondary endpoints:
  - Duration of Response (DOR)
  - Progression Free Survival (PFS)
  - Safety
  - Quality of life

Ritux + Alkylator Refractory Indolent NHL

Historical Control:
- Bendamustine: DOR 10mo

Six Idelalisib Studies Closed Due to Safety Concerns

1. GS-US-312-0123: a phase 3 study evaluating idelalisib in combination with bendamustine and rituximab for previously untreated CLL
2. GS-US-313-0124: a phase 3 study of idelalisib in combination with rituximab for previously treated iNHL
3. GS-US-313-0125: a phase 3 study of idelalisib in combination with bendamustine and rituximab for previously treated iNHL
4. GS-US-313-1414: Idelalisib with rituximab for previously untreated follicular lymphoma and small lymphocytic lymphoma
5. GS-US-312-0118: Idelalisib in combination with obinutuzumab compared to chlorambucil in combination with obinutuzumab for previously untreated chronic lymphocytic leukemia
Selected Pi3K inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Company</th>
<th>Route</th>
<th>Efficacy Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copanlisib</td>
<td>Global</td>
<td>Oral</td>
<td>Ph 2 Double Refractory iNHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR: 57% CR: 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS: 11 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Double Refractory population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Transamanitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diarrhea/colitis</td>
</tr>
<tr>
<td>Duvelisib</td>
<td>Verastem</td>
<td>Delta</td>
<td>Ph 2 Double Refractory iNHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gamma</td>
<td>ORR: 46% CR: 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS: 8.4 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Highly refractory population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 ANC 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 diarrhea 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 deaths (n=129) due to toxicity</td>
</tr>
<tr>
<td>Umbralisib</td>
<td>TG Therapeutics</td>
<td>Delta</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph 1/2 relapsed CLL/NHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR (iNHL): 49% CR: 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ORR (aNHL): 24% CR: 8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PFS (NHL/CLL): 27 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 Neutropenia 16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 Diarrhea 3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AST/ALT ↑6% (3% Gr 3/4)</td>
</tr>
<tr>
<td>Copanlisib</td>
<td>Bayer</td>
<td>Alpha</td>
<td>Ph 2 Relapsed iNHL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delta</td>
<td>ORR: 59%, CR: 12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>PFS: 11.2 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph 2 Relapsed DLBCL ORR: 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 Hypertension: 22%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 Hyperglycemia: &gt;33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(AG) Diarrhea/Colitis: 18%/1%</td>
</tr>
<tr>
<td>INCB050465</td>
<td>Incyte</td>
<td>Delta</td>
<td>Oral</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ph 1/2 Relapsed NHL FL: ORR (7/9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DLBCL: ORR (5/14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MCL: ORR 3/4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 Diarrhea/colitis 31%/6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gr 3 ANC 21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No grade 2+ transamanitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Exploring weekly dosing beyond week 9</td>
</tr>
</tbody>
</table>

Dreyling M. AACR 2017, Ann Oncol 2017

PI3Ki: Copanalisib (BAY 80-6946)

- Inhibitor of PI3K- alpha and beta isoforms.
- Phase II study:
  - 142 pts, relapsed or refractory to ≥ 2 lines of therapy.
  - IV on days 1, 8, and 15.
  - Primary endpoint: ORR

Results:

- ORR 61%, CR 15% (n=104 fl pts)
- Median PFS: 11.2 months

Lenalidomide: Mechanism of Action in Lymphoma

- T-Cell Effects
- Neutrophil effects
- Immune suppression

Lenalidomide 20mg Days 1-21 Cycles 1-6*
Rituximab 375mg/m² Day 1 of Cycles 1-6

- Months
- SLL patients: Dose escalation of lenalidomide starting with cycle 1: (10mg, 15mg, 20mg)

Response Rates

<table>
<thead>
<tr>
<th></th>
<th>SLL (N=30)</th>
<th>Marginal (N=27)*</th>
<th>Follicular (N=46)*</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Eval (N=33)</td>
<td>ITT (N=101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>24 (80)</td>
<td>24 (80)</td>
<td>45 (98)</td>
<td>93 (90)</td>
</tr>
<tr>
<td></td>
<td>93 (85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR, n (%)</td>
<td>8 (27)</td>
<td>18 (67)</td>
<td>40 (87)</td>
<td>66 (64)</td>
</tr>
<tr>
<td></td>
<td>66 (60)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD/PD, n (%)</td>
<td>16 (53)</td>
<td>6 (22)</td>
<td>5 (11)</td>
<td>27 (26)</td>
</tr>
<tr>
<td></td>
<td>27 (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>4 (13)</td>
<td>3 (11)</td>
<td>12 (2)</td>
<td>8 (8)</td>
</tr>
<tr>
<td></td>
<td>8 (7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/PR, n (%)</td>
<td>2 (7)</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td></td>
<td>2 (2)</td>
<td></td>
<td></td>
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</table>

*ITT not evaluable for response:
- 7 pts due to adverse event in cycle 1
- 1 due to non-compliance
- 1 due to withdrawal of consent

Fonseca N. et al ASH 2012.
**Progression Free Survival**

- Follicular Lymphoma

**Alliance Phase II Study of Rituximab + Len in Follicular Lymphoma: Responses**

<table>
<thead>
<tr>
<th>Response, n (%)</th>
<th>Overall (N = 57)</th>
<th>FLIPI 0-1 (n = 17)</th>
<th>FLIPI 2 (n = 38)</th>
<th>FLIPI 3 (n = 2)</th>
</tr>
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<tbody>
<tr>
<td>ORR 53 (83)</td>
<td>16 (94)</td>
<td>33 (92)</td>
<td>2 (100)</td>
<td></td>
</tr>
<tr>
<td>CR 41 (72)</td>
<td>13 (77)</td>
<td>25 (76)</td>
<td>2 (100)</td>
<td></td>
</tr>
<tr>
<td>PR 12 (21)</td>
<td>3 (18)</td>
<td>8 (22)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>SD 2 (4)</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Unevaluate 2 (4)</td>
<td>1 (6)</td>
<td>1 (3)</td>
<td>--</td>
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- 4 additional patients in PET-CR but not confirmed by bone marrow biopsy
- There was no significant association between CR rate and FLIPI score, presence of bulky disease, or age

**Phase III: RELEVANCE**

- Rituximab and Lenalidomide vs. Any Chemotherapy
- Co-primary endpoints (superiority)¹
  - CR/CRu at 120 weeks
  - PFS

- R² Maintenance
- R² Maintenance
- R + Chemo
- Rituximab Maintenance

- R + chemo: Investigator’s choice of R-CHOP, R-CVP, BBR
- Lenalidomide 20 mg for 6 cycles, then 10 mg if CR

**Interim PFS By Investigator Review**

- 3-year DOR was 77% for R² vs 74% R-chemo (IRC)
- Investigator results were consistent with IRC

**Adverse Events**

- TEAEs for R² (n = 507), %
- TEAEs for R-chemo (n = 503), %

**CALGB 50401:**

- Randomized Study of Lenalidomide plus Rituximab vs Rituximab

Leonard J. et al. JCO. 2015
Pembrolizumab in FL

Responses in Follicular Lymphoma

Wei, D et al. ASH 2017  #4055

Pembrolizumab with Rituximab in Relapsed Follicular Lymphoma

- Phase II, single arm study
- Subjects received rituximab (375 mg/m² IV) on days 1, 8, 15, and 22 of cycle 1 and pembrolizumab (200 mg IV) every 3 weeks for up to 16 infusions starting on day 2 of cycle 1.

Primary Endpoint
- Overall Response Rate (ORR)

Nastoupil L. et al. ASH 2017

Pembrolizumab with Rituximab in Relapsed Follicular Lymphoma

CAR-T Overview

From: Jacobson C and Ritz J. Blood 2011. 4761:118-212

CAR-T Vector Co-Stim

- Abramson J et al. JCAR 017 Lentivirus 4-1BB
- Schuster S et al. CTL019 Lentivirus 4-1BB
- Neelapu S et al. KTE-019 Retrovirus CD28

Conclusions

- Large minority of patients with follicular lymphoma are likely cured with standard chemo-immunotherapy.
- No validated model exists to predict who these patients are on an individual basis.
- Indolent B-cell malignancies have unique dependence on microenvironmental factors for survival and persistence.
- Immunotherapy and novel small molecule inhibitors represent a paradigm shift in the approach to treatment of NHL.
- Identifying the optimal combination of (potentially curative) agents will require investment in correlative and mechanistic studies.

Schuster S et al. NEJM 2017

CAR-T cells for FL

• CR Rate: 10 of 14 patients with follicular lymphoma (71%; 95% CI, 42 to 92)

Schuster S et al. ASH 2017

• No validated model exists to predict who these patients are on an individual basis.
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Thank you

Nathan Fowler MD
Associate Professor of Medicine
Director, Clinical and Translational Research
Lead, New Drug Development Program
Department of Lymphoma/Myeloma
MD Anderson Cancer Center
Houston, TX
Overview of Treatment Options for Mantle Cell Lymphoma (MCL)

Jorge E. Romaguera, MD
Update in Management of Mantle Cell Lymphoma

Jorge E. Romaguera, MD, FACP
Professor of Medicine
Department of Lymphoma/Myeloma
University of Texas M. D. Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure
No relevant financial relationships to disclose

Mantle Cell Lymphoma

6% of NHL
90% diffuse histology
Most common cytology is classic
IHC- CD5+, CD23-, CD200 – (vs. CLL), CyclinD1 + (if negative, SOX-11 + can help diagnosis
Cytogenetics- t(11;14); FISH- 95% sensitive
Improved outcome but still incurable

Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>MDACC</th>
<th>EMCLN</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F ratio</td>
<td>3:1</td>
<td>3:2:1</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>60(41-80)</td>
<td>64(27-86)</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>PS (ECOG) 0-1</td>
<td>98%</td>
<td>84%</td>
</tr>
<tr>
<td>AA Stage IV</td>
<td>99%</td>
<td>92%(III-IV)</td>
</tr>
<tr>
<td>Bone marrow involved</td>
<td>91%</td>
<td>72%</td>
</tr>
<tr>
<td>GI tract involved</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Peripheral blood involved</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>25%</td>
<td>29%</td>
</tr>
<tr>
<td>IPI score 0-1</td>
<td>12%</td>
<td>17%</td>
</tr>
<tr>
<td>Histology</td>
<td>89%</td>
<td>81%</td>
</tr>
<tr>
<td>Diffuse</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Nodular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blastoid cytology</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Frontline Treatment of Mantle cell lymphoma

Frontline Treatment

Young Fit Patients
( biological age ≤ 65 years )
R-CHOP → IFN vs. R-CHOP → CyTBI/ASCT

At median follow up of 5 years:

Median overall survival better for ASCT group
(7.5 years vs. 4.5 years, \( p = 0.034 \))


NO TBI/SCT: R-HCVAD/R-MA 15 yr Update NO Pre-emptive or Maintenance Rituximab

NO TBI/SCT: R-CHOP/R-DHAP + TBI-HDAC/SCT vs R-CHOP + CY-TBI/SCT in untreated MCL: TTF (A) and OS (B)

Hermine O et al. Lancet 2016

Intense therapy and high Dose cytarabine Doesn’t improve survival for Young Fit patients

HD cytarabine and SCT currently recommended.

Why survival data not different?
Better salvage therapies? possible Comparing apples and oranges? data was balanced for MIPI, blastoid, Ki-67 maybe other variables prognostic?

Simplified MIPI Prognostic index

<table>
<thead>
<tr>
<th>Points</th>
<th>Age, y</th>
<th>ECOG</th>
<th>LDHULN</th>
<th>WBC, 10^9/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;50</td>
<td>0-1</td>
<td>&lt;0.67</td>
<td>&lt; 6,700</td>
</tr>
<tr>
<td>1</td>
<td>50-59</td>
<td>—</td>
<td>0.67-0.99</td>
<td>6,700-9,999</td>
</tr>
<tr>
<td>2</td>
<td>60-69</td>
<td>2-4</td>
<td>1.000-1.49</td>
<td>1,000-14,999</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>—</td>
<td>1.5000</td>
<td>15,000</td>
</tr>
</tbody>
</table>

For each prognostic factor, 0 to 3 points were given to each patient and points were summed up to a maximum of 11. Patients with 0 to 3 points in summary were classified as low risk, patients with 4 to 5 points as intermediate risk, and patients with 6 to 11 points as high risk. ECOG performance status was weighted with 2 points if patients were unable to work or bedridden (ECOG 2-4). LDH was weighted according to the ratio to the ULN. Thus, for an ULN of 240 U/L, the cutpoints were 180 U/L, 240 U/L, and 360 U/L, for example.
Overall Survival According to MIPI – GLSG

Alternative Combination of Ki-67 Index and MIPI: MIPI-c: Combined Mantle Cell Lymphoma International Prognostic Index

OS Risk Model of Ki-67 Combined with MIPI (MIPIc)

Overall Survival

Role of Rituximab Maintenance After Auto-SCT
Did Maintenance Rituximab Improve OS in High Risk Groups?

Difficult to say

- MIPI used here, MIPI-C used in prior study
- RDHAP + RCHOP here vs RCHOP alternating with RDHAP X 3 followed by HDAC X 1 in prior study

Did Maintenance rituximab improve OS regardless of Minimal disease status?

Not analyzed

Median duration of response (DOR) of single-agent lenalidomide for responders with relapsed/refractory MCL (central review). 57 pts; ORR 35 % (CR 12%)
**Response Rate with Ibrutinib in r/r MCL**

- **BTZ-naïve** (n=63): 71% (Grade 1), 65% (Grade 2), 66% (Grade 3)
- **BTZ-exposed** (n=48): 49 (Grade 1), 44 (Grade 2), 47 (Grade 3)


**Grade 3/4 Hematologic Toxicity** (regardless of relationship to PCI-32765)

<table>
<thead>
<tr>
<th>Grade 3 Hematologic toxicity</th>
<th>Total (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3%</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>0%</td>
</tr>
</tbody>
</table>


**Common Non-Hematologic AEs**

- Grade 3: 2%
- Grade 4: 3%

Wang et al. NEJM 2013

**Schematic Representation of the “Triangle” Trial by the European MCL Network.**

Martin Dreyling and Simone Ferrero. Haematologica 2016;101:104-114

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**Ibrutinib/Rituximab in Relapsed MCL: Study Schema**

- Relapsed MCL (N = 90)
  - No limit of prior therapies
  - Good PS and adequate organ function

  - Ibrutinib 560 mg/day until PO or intolerability
  - Rituximab: 375 mg/m² weekly × 4, then every 3 cycles 3-8, then every other cycle x 2y

  - After 2y maint ibrutinib until PO or intolerance

  - 6 AFIB still on RX / 2 off / POO / 2 stopped / AFIB

OS: Median Follow Up 11 Months (4-6 months)

Total Over Survival

Over Survival by Ki67

- Median follow up 11 months (4-6 months)
- P-value = 0.0005

Treatment-Emergent AEs: Incidence > 15%

- Hematological AE
- Thrombocytopenia

Non-Hematological AE
- Regurgitation
- Constipation
- Fever
- Nausea
- Nystagmus
- Migraine

- No Grade 5

MDACC “Window” Trial for Patients 65 yrs or Younger with Untreated MCL

- Ibrutinib 560 mg PO daily
- Rituximab 375 mg/M2 weekly X 4 X 1 month, then monthly from months 3 on, until best response
- If in CR: Consolidation with 4 cycles of intense therapy [RHCVAD (one cycle)]
  Alternating with R-Mtx Cytarabine (1 cycle)
- If less than CR: Consolidation with RHCVAD/RMA until CR plus 2 cycles

Wang M et al. ASH 2016

Proposed model of molecular pathogenesis in the development and progression of major subtypes of MCL. Precursor B cells usually with but sometimes without a CCND1 rearrangement mature to abnormal naïve B cells which may initially colonize, often the inner p...


Best Practice & Research Clinical Haematology 2018 31, 90-98 DOI: (10.1016/j.beha.2017.10.008)

MDACC “Window” Trial for Patients 65 yrs or Younger with Untreated MCL (50 Patients)

- Part I – 100% Overall Response Rate (90% complete response)
- Part II - 100% complete response
- Median follow up 15.9 months and median duration of response, progression free survival and overall survival have not been reached

Wang M et al. ASH 2016

Treatment Algorithm for Newly Diagnosed Young Fit
Neurologic Spread in MCL

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>No. Pts</th>
<th>CNS sx</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheah 2012 EMCLN</td>
<td>57</td>
<td>4% (1% at Dx)</td>
<td>No limit</td>
</tr>
<tr>
<td>Valdez 2004</td>
<td>108</td>
<td>23%</td>
<td>1-5 yrs</td>
</tr>
<tr>
<td>Oinonen 1999</td>
<td>16</td>
<td>4%</td>
<td>1-5 yrs</td>
</tr>
<tr>
<td>Montserrat 1996</td>
<td>22</td>
<td>23%</td>
<td>1-5 yrs</td>
</tr>
</tbody>
</table>

Chemotherapy + XRT for Stage I-IIA Untreated MCL: 26 pts

Frontline Treatment of Mantle cell lymphoma

Patients with Biological Age > 65 years or Unfit

Bendamustine-R vs. R-CHOP for MCL

MCL: Role of Maintenance Therapy

HOWEVER:
Maintenance rituximab 375 mg/m2 q 2 months X 2 yrs did not improve PFS or OS in patients who responded to Bendamustine and Rituximab
Study Design

**Population:** newly diagnosed MCL subjects who are 65 years or older

**Stratification factor:** sMIPI score: low vs. intermediate vs. high

**A cycle is defined as 28 days.**

**US Intergroup Randomized Phase II Study in Untreated MCL (ECOG 1411)**

- **age > 60 yrs**
- **4 groups:**
  - A: BR X 6, then R q 2 mo. X 2 yrs
  - B: BVR X 6, then R q 2 months X 2 yrs
  - C: BR X 6, then Len-R X 2 yrs
  - D: BVR X 6, then Len-R X 2 yrs
- **Stratified for MIPI low vs int vs high**
- **V given subcutaneously**
- **Len given days 1-21 every 4 weeks; R given day 1**

**Bendamustine, Cytarabine, Rituximab for MCL**

- **Non-candidates for stem cell transplant**
- **R 375 mg/m² day 1; B 70 mg/M2 days 2,3; C 800 mg/m² days 2-4 Q 28 days**
- **40 patients; > 65 yrs old; treated and untreated; 49% high MIPI**
- **100 % ORR/95% CR in untreated; 80% ORR/70% CR in treated. 2-yr PFS 85% untreated/70% treated**

**Visco et al; J Clin Oncol 2013**

**Visco et al; J Clin Oncol 2013**
In (A, B) previously untreated and (C, D) relapsed or refractory (R/R) patients with mantle-cell lymphoma, Kaplan-Meier survival curves for (A, C) overall survival and (B, D) progression-free survival.

Bendamustine, Cytarabine, Rituximab for MCL (cont.)

85% patients completed treatment

Major toxicity hematologic:
- 87% transient grade 3-4 thrombocytopenia
- 12% febrile neutropenia

Bendamustine, Cytarabine, Rituximab for MCL (cont.)

85% patients completed treatment

Major toxicity hematologic:
- 87% transient grade 3-4 thrombocytopenia
- 12% febrile neutropenia

Bortezomib + R-CVAD in MCL

- Bortezomib-Rituximab-CVAD in MCL, n=75
- Bortezomib dose was initially 1.5 mg/m² on days 1 & 4 only => Went down to 1.3 mg/m²
- Likewise, Vincristine dose went down to a total of 1mg
- CR/CRu 68%, ORR 97%. 22 pts elected consolidation SCT. Others received maintenance R.
- PFS in the MR group is 75% at 3 yrs.

Key Cellular Pathways in Mantle Cell Lymphoma Targeted by Novel Mechanism-based Treatments

Lenalidomide

Chan Yoon Cheah et al. JCO 2016;34:1256-1269

©2016 by American Society of Clinical Oncology

R2 in Untreated MCL

Induction phase (N=38)
- 12 x 28-day cycles
- Len: 20 mg/days 1-21
- Rituximab: 375 mg/m²/weekly x4, Then 2x cycle x9

Maint phase (n=27)
- Len 21/28 days w/ rituximab every other cycle until PD
- 23 pts remained on maintenance

R2 in Untreated MCL

Response

ITT (n=38) Evaluateable (n=26)

CR 53% 57%
PR 20% 30%
SD 6% 7%
PO 6% 7%

Not better (MIP) score nor R2-63 index correlated with response
**Bendamustine-rituximab-lenalidomide in Untreated Elderly MCL (MCL4 trial)**

- Bendamustine 90 mg/m² IV D1,2
- Rituximab 375 mg/m² IV D1
- Lenalidomide 10 mg daily D1-14 starting cycle 2
- Repeat q 28 days X 6
- Then Lenalidomide 25 mg PO daily D1-21 q 28 D q 6
- Prophylaxis: Aspirin 75 mg/d; LMWH if history of DVT or Known hypercoagulable state; Co-trimazole

Albertsson-Lindblad A et al, Blood 2016

---

**Frontline treatment options for frail patients**

- Single agent rituximab (ORR 27%; CR 3%)
- Rituximab/Chlorambucil (ORR 95%; CR 90%)

---

**Opportunities in Mantle Cell Research**

**Global therapies**
- Immunomodulators
- HDAC inhibitors, Hypomethylating agents
- miRNA
- Vaccines
- Checkpoint inhibitors
- CAR T cell therapy

**Targeted therapies**
- Second generation proteosome inhibitors
- mTOR inhibitors
- PKC inhibitors
- CDK inhibitors
- Bcl-2 inhibitors
- BCR pathway inhibitors
- PI3 Kinase inhibitors

---

**Treatment of relapsed/refractory MCL**

**Principles:**
- Clinical trial
- Non-cross resistant regimen. Any of already mentioned plus R-GemOx.
- Address goal with patient. If fit, allo SCT after response with goal of cure. If not, then control of disease with quality of life.

---

**Multiple Early-stage Inhibitors Emerging in the BTK Landscape**

- **ONO-4059**
  - Expected to reach clinic in 2015 and target ibrutinib failures
  - Further development of ONO-4059 is in progress

- **Other BTK inhibitors**

- **Irreversible Binding**
  - CC-292
  - CNX-774
  - ONO-4059 (irreversible covalent)

- **Reversible Binding**
  - GDC0853/RG7845
  - Binding Unknown

- **Discovery/Preclinical**
  - ACP-196
  - PLX-4032
  - TP-4207
  - GL2-761
  - DUAL BTKi/Jak3i
  - GI/1746
  - PLS-123

- **Launched**
  - MSI-1879
  - MSI-423
  - MSI-121
  - MKC4659
**Acalabrutinib (ACP-196)**

- Does not inhibit NK cell cytolytic activity or Interferon gamma CD8+ cells
- No inhibition of platelet function
- No inhibition of Epidermal Growth Factor

**Zanubrutinib (BGB-3111) for DLBCL and MCL: Best Responses**

- **Response rates based on CT for majority of trials**
- **Median efficacy follow-up time (range):**
  - DLBCL: 4.2 (0.1-24)
  - MCL: 9.5 (0.8-31.9)
  - Aggressive Total: 5.6 (0.1-31.9)
- **Best response, n (%)**
  - **ORR:**
    - CR: 0 (1)
    - PR: 4 (15)
    - SD: 13 (50)
    - PD: 4 (15)
    - NE**: 1 (4)
  - **CRi:** 0 (1)
  - **PRi:** 0 (1)
  - **SD:** 0 (1)
  - **PD:** 2 (6)
  - **NE**: 3 (5)

**PI3Ki Development Pipeline**

**Bcl-2 inhibitor Venetoclax (V) Phase I**

- 28 MCL patients with RR MCL
- 75% ORR (21% CR)
- Median PFS 14 months
- Low grade toxicity- diarrhea (44%), fatigue (41%), Nausea (48%)
- TLS – 2 patients

**Ibrutinib (IB)-Venetoclax (V)**

- 4 week induction IB 560 mg po,d
- Add Venetoclax ramp up to 400 mg/d
- Continue both drugs
- 24 MCL patients (23 treated); 0-6 prior Tx
- median F/U 15.9 months
- 71% ORR (42% CR)
- 78% PFS at 15 months
- Low grade toxicity- diarrhea (83%) fatigue (75%), NV (71%)
- TLS – 2 patients
MCL: Allogeneic Transplantation

*Reduced intensity ++*

Issues: age, cGVH > 50% pts

Clinical Success of CAR T-cells

Screening/Enrollment

Conditioning Chemotherapy

Patient Leukapheresis

KTE-C19 Infusion

Day 0

Day -5

Day 30

Day 7

1st Tumor Assessment

Manufacturing 6 – 8 days

Investigational Product Hospitalization Period

Follow-up Period (Post-treatment assessment and long term follow up)

Registration Trial - Breakthrough designation for DLBCL

ASCT model for Relapsed/refractory MCL:

Favorable:

- MIPI ≤ 2, No Bsx, RQ > 6
- MIPI ≤ 2, Bsx, RQ ≥ 13
- MIPI 3, No Bsx, RQ ≥ 13

5 yr PFS 58%, OS 76%

5 yr PFS 15%, OS 32%

For other

Median FU = 5 yrs

Cassady RD et al. Biol Blood Marrow Transpl 2013

Summary

- MCL response rates and survivals have improved with current treatment strategies
- MCL responds to immunotherapy and XRT
- Knowledge of pathways and development of targeted therapies has impacted treatment and will serve as basis for personalized therapy

Thank you

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Overview of Treatment Options for Chronic Lymphocytic Leukemia (CLL)

William Wierda, MD, PhD
Overview of Treatment Options for Chronic Lymphocytic Leukemia (CLL)

William G. Wierda, MD, PhD
Professor of Medicine, Department of Leukemia
Division of Medicine, UT MD Anderson Cancer Center
Houston, TX
23 JUNE 2018

Treatment Goals for CLL

- Potentially curative treatments: FCR for m-IGHV and SCT
- Majority requiring treatment are older (>70yo) with comorbidities and more treatment-associated toxicities
- Goals for first-line –
  - Best opportunity for most effective treatment, most eventually relapse and need retreatment:
    - Deeper remission with CIT and treatment-free interval
    - Maintain disease control on continuous (IBR) treatment
- Goal for relapsed and refractory:
  - Durable disease control, keep options open

Characteristics Enabling Personalized Management Approach

- Current:
  - FISH: del(17p)
  - TP53 mutations
  - Age / comorbidities
  - IGHV mutation status (stimulated)
  - Metaphase karyotype
  - Prior treatment(s)
  - Refractory CLL
- Future ?:
  - MRD status
  - BTK / PLCG2 mutations
  - β2M
  - Gene mutation profile
- Others ?:
  - ZAP70

Standard First-line Treatments for CLL by Patient Characteristics and Goals

- Del(17p) / m-TP53 – 5% - Durable disease control
  - BTK-inhibitor - Ibrutinib
- Older, Unfit – 75% - Durable control vs. deeper remission, retreatment
  - BTK-inhibitor - Ibrutinib
  - CIT – Chlorambucil + obinutuzumab; BR
  - CD20 mAb
- Young, Fit – 20% - Durable control vs. deep remission, retreatment
  - BTK-inhibitor - Ibrutinib
  - CIT – FCR; BR (FCR for m-IGHV)
- Consider treatments for relapsed CLL

Conflict of Interest Disclosure

Advisory Board: Sanofi

Research Support: GSK/Novartis, AbbVie, Genentech, Karyopharm, Pharmacyclics, Acerta, Gilead, JUNO Therapeutics, KITE Pharma, Miragen, Sunesis

RESONATE-2 (PCYC-1115/1116) Study Design

- Patients [N=269]
  - Treatment-naive CLL/SLL with active disease
  - Age >65 years
  - For patients 65-69 years, comorbidity that may preclude FCR
  - del17p excluded

  Ibrutinib 420 mg once daily until progression
  Chlorambucil 0.5 mg/kg (to maximum 0.8 mg/kg)
  days 1 and 15 of 28-day cycle up to 12 cycles

  FCR progression or 1115 study closure

  PCYC-1116 Extension Study*
  In FCR arm
  PFS improved over to obinutuzumab following PD

Stratification factors
  - ECOG status (0-1 vs. 2)
  - Rai stage (III-IV vs. ≤II)

*Efficacy (PFS, OS, ORR) determined by investigator-assessment.

Barr et al. ASH 2016, Abstract 234
RESONATE-2: First-line, Age >65yrs Ibrutinib Prolonged PFS Over Chlorambucil

- 88% reduction in the risk of progression or death for patients randomized to ibrutinib
- Subgroup analysis of PFS revealed benefit was observed across all sub-groups

RESONATE-2: Ibrutinib Significantly Improved PFS in Patients with Del11q

- In del11q subgroup, ibrutinib led to 99% reduction in risk of progression or death and 82% reduction in those without del11q, compared to chemotherapy

RESONATE-2: Ibrutinib Significantly Improved PFS in Patients Regardless of IGHV Status

- Ibrutinib led to 83% and 92% reduction in the risk of progression or death in patients with mutated and unmutated IGHV, respectively, compared to chemotherapy

RESONATE-2: ORR in the Ibrutinib* Arm

- Ibrutinib CR rates continue to improve over time: increasing from 7% at 12 months to 15% at 24 months to 18% with median follow-up of 29 months.

5-Year Experience With Ibrutinib Monotherapy

Survival Outcomes: Overall Population

- Median PFS: TN (n=31) NR 92% R/R (n=101) 52 mo 43%

- Median OS: TN (n=31) NR 92% R/R (n=101) NR 57%

O'Brien et al. ASH 2016, Abstract 233
CLL11 PFS: G-Clb vs R-Clb

- Patients with events, n(%): G-Clb = 244 (73.3), R-Clb = 252 (76.5)
- 5-year PFS, % (95% CI): G-Clb = 23 (19–28), R-Clb = 9 (6–12)
- Median PFS, months: G-Clb = 28.9, R-Clb = 15.7
- HR (95% CI), p-value: G-Clb vs R-Clb = 0.49 (0.41–0.58), p<0.0001

Median observation time: 59.4 months

CLL11 OS: G-Clb vs R-Clb

- Patients with events, n(%): G-Clb = 121 (36.3), R-Clb = 147 (44.5)
- 5-year OS, % (95% CI): G-Clb = 66 (61‒72), R-Clb = 57 (51–62)
- Median OS, months: G-Clb = NR, R-Clb = 73.1
- HR (95% CI), p-value: G-Clb vs R-Clb = 0.76 (0.60–0.97), p=0.0245

CLL10 Study: FCR vs BR in Front-Line

- Progression-free survival by age group
  - Patients ≤ 65 years: P < 0.001 (FCR 53.6 months, BR 38.5 months)
  - Patients > 65 years: P = 0.170 (FCR not reached, BR 48.5 months)

- Infections CTC 3-4 in detail
  - Adverse event: FCR, BR
  - p value
    - All Infections: 39.1, 26.8, <0.001
    - Infections during therapy only: 22.6, 17.3, 0.1
    - Infections during first 5 months after therapy: 11.8, 3.6, <0.001
    - All infections in patients ≤ 65 years: 35.2, 27.5, 0.1
    - All infections in patients > 65 years: 47.7, 20.6, <0.001

CLL10 Study: FCR vs BR in Front-line Progression-free survival by age group

- Patients ≤ 65 years: P = 0.001 (FCR 43.1 months, BR not reached)
- Patients > 65 years: P = 0.170 (FCR 48.5 months, BR 46.5 months)

FCR300: PFS by IGHV Mutation Status

First-line Phase III Clinical Trials in CLL

<table>
<thead>
<tr>
<th>Treatment Arms</th>
<th>Subgroup</th>
<th>N</th>
<th>MRD Status</th>
<th>Sponsor</th>
<th>NCI Number</th>
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</thead>
<tbody>
<tr>
<td>ibr-&gt;ibr</td>
<td>BR</td>
<td>523</td>
<td>2</td>
<td>Enrolled</td>
<td>NCT0186573</td>
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<tr>
<td>ibr-&gt;FCR</td>
<td>Fit</td>
<td>519</td>
<td>No</td>
<td>Enrolled</td>
<td>NCT0204813</td>
</tr>
<tr>
<td>Acal-&gt;Acal</td>
<td>Unfit</td>
<td>535</td>
<td>No</td>
<td>Enrolled</td>
<td>NCT0247588</td>
</tr>
<tr>
<td>Ven-&gt;Ob</td>
<td>Unfit</td>
<td>445</td>
<td>2</td>
<td>Enrolled</td>
<td>NCT0224241</td>
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<tr>
<td>Ven-&gt;Ven-&gt;ibr</td>
<td>Fit</td>
<td>520</td>
<td>1</td>
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<td>NCT0295005</td>
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<tr>
<td>Toll-&gt;Ob</td>
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<td>450</td>
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<td>NCT2812331</td>
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<td>Zanub-&gt;BR</td>
<td>All</td>
<td>467</td>
<td>No</td>
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<td>NCT3383333</td>
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<tr>
<td>ibr-&gt;Ven-&gt;ibr</td>
<td>Fit</td>
<td>720</td>
<td>2</td>
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<td>ECOG</td>
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<tr>
<td>ibr-&gt;Ven-&gt;ibr</td>
<td>&gt;65y</td>
<td>510</td>
<td>2</td>
<td>Planned</td>
<td>Alliance</td>
</tr>
</tbody>
</table>

Standard Treatments for Rel / Ref CLL by Disease Characteristics

- Relapsed / Refractory CLL - Durable disease control
  - Del(17p) / m-TP53
  - Prior CIT
  - Prior BTK-inhibitor ± CIT
  - Fludarabine-refractory (CIT)
  - Ibrutinib-refractory
  - Idelalisib-refractory

<table>
<thead>
<tr>
<th>Treatment Options:</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK-inhibitor</td>
</tr>
<tr>
<td>Bcl-2-inhibitor ± rituximab</td>
</tr>
<tr>
<td>PI3K-inhibitor + rituximab</td>
</tr>
<tr>
<td>Lenalidomide ± CD20 mAb</td>
</tr>
<tr>
<td>CIT</td>
</tr>
<tr>
<td>Allo-SCT</td>
</tr>
</tbody>
</table>

5-Year Experience With Ibrutinib Monotherapy

Survival Outcomes: Overall Population

- Progression-Free Survival
- Overall Survival

O'Brien et al. ASH 2016, Abstract 233
5-Year Experience with Ibrutinib Monotherapy
Survival by Complex Karyotype

- The majority (90%) of patients with complex karyotype had R/R disease (median 4 prior therapies).

### Progression-Free Survival

- **Complex karyotype (n=41)**: Median PFS 33 months, 5-year PFS 36%
- **No complex karyotype (n=71)**: NR, 69%

### Overall Survival

- **Complex karyotype (n=41)**: Median OS 57 months, 5-year OS 46%
- **No complex karyotype (n=71)**: NR, 84%

O'Brien et al. ASH 2016, Abstract 233

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5-Year Experience With Ibrutinib Monotherapy
Survival by IGHV-MS in R/R Patients*

- *Only 2 patients in the TN group showed disease progression. Subgroup analyses, therefore, focused on the R/R population.

### Progression-Free Survival

- **Mutated IGHV (n=16)**: Median PFS 63 months, 5-year PFS 53%
- **Unmutated IGHV (n=79)**: 43 months, 5-year PFS 38%

### Overall Survival

- **Mutated IGHV (n=16)**: Median OS 69 months, 5-year OS 66%
- **Unmutated IGHV (n=79)**: NR, 55%

O'Brien et al. ASH 2016, Abstract 233

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PFS by Prior Lines of Therapy:
RESONATE and RESONATE-2

### Time-to-Ibrutinib Discontinuation


### Multivariable Models for Ibrutinib Discontinuation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transformation</th>
<th>Progressive CLL**</th>
<th>Other Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex karyotype (yes vs no)</td>
<td>5.00 (1.51–16.52)</td>
<td>0.08</td>
<td>—</td>
</tr>
<tr>
<td>MYC abnormality (yes vs no)</td>
<td>2.15 (1.00–4.65)</td>
<td>—</td>
<td>0.051</td>
</tr>
<tr>
<td>Del(17)(p13.1) present on FISH (yes vs no)</td>
<td>2.14 (1.15–3.96)</td>
<td>—</td>
<td>0.016</td>
</tr>
<tr>
<td>Age (≥ vs &lt;65 years)</td>
<td>0.49 (0.27–0.91)</td>
<td>—</td>
<td>0.023</td>
</tr>
<tr>
<td>Prior therapies &gt;3 (yes vs no)</td>
<td>1.99 (1.23–3.23)</td>
<td>—</td>
<td>0.005</td>
</tr>
</tbody>
</table>

All models were adjusted for treatment with ibrutinib monotherapy versus combination therapy with ibrutinib and ofatumumab.

Wierda JA et al. J Clin Oncol. 35:1437, 2017

### Venetoclax (ABT-199) for Rel/Ref del(17p) CLL

#### Patient Characteristics and Current Disposition

- All Patients, N=158
  - Age, median (range), years: 67 (29 – 85)
  - Number of prior therapies, median (range): 2 (0 – 10)
  - Fludarabine-containing regimen, n (%): 60 (38)
  - Prior B-cell pathway receptor inhibitor, n (%): 18 (11)
  - Unmutated IGHV, n/N (%): 45/58 (78)
  - TP53 mutation, n/N (%): 55/77 (71)
  - Chromosome 11q deletion, n/N (%): 38/157 (24)
  - Serum β-2 microglobulin, median (range), μg/mL: 3.6 (1.3 – 31)

#### Current Disposition

- Active on study as of April 2017, n (%): 79 (50)
- On venetoclax, n: 72
- In post-treatment follow-up, n: 72
- Drug interruption, n: 1
- Discontinued, n (%): 35 (22)
- CLL disease progression: Richter’s transformation, n: 21 (14)
- Stem cell transplant*: 10 (10)
- Other reasons: 2 (1)
- Deaths, n (%): 3 (2)

*Three additional patients discontinued venetoclax and went on to stem cell transplant and remain in post-treatment follow up.

Wierda, WG et al. SOHO, 2017
** Venetoclax (ABT-199) for Rel/Ref del(17p) CLL

** Investigator-Assessed Response to Venetoclax **

- Median time to first response: 1 month (range: 0.5 – 4.4)
- Median time to CR/CRi: 9.8 months (range: 2.7 – 31.1)

<table>
<thead>
<tr>
<th>ORR (%)</th>
<th>CR/CRI (%)</th>
<th>nPR/PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
<th>NE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients, N=158</td>
<td>77</td>
<td>20</td>
<td>57</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Prior BCRi, n=18</td>
<td>61</td>
<td>11</td>
<td>50</td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-naive, n=5</td>
<td>80</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>High TLS risk, n=62</td>
<td>76</td>
<td>8</td>
<td>66</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>TP53 mutation, n=35</td>
<td>68</td>
<td>18</td>
<td>51</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Fludarabine refractory, n=45</td>
<td>78</td>
<td>24</td>
<td>53</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>

*One patient discontinued after the first venetoclax dose, one patient died after 3 weeks of treatment due to liver dysfunction not related to venetoclax, and one patient had pseudo-obstruction of the small bowel mesentery and retroperitoneum during dose ramp up and discontinued the study.

** Venetoclax (ABT-199) for Rel/Ref del(17p) CLL

** Outcome on Venetoclax Monotherapy **

- Median time to first dose: 1 month (range: 0.5 – 4.4)
- Median time to CR/CRi: 9.8 months (range: 2.7 – 31.1)

** Venetoclax (ABT-199) for Rel/Ref del(17p) CLL

** Best MRD Status by Flow Cytometry and/or NGS **

<table>
<thead>
<tr>
<th>Flow Cytometry and/or NGS*</th>
<th>Peripheral blood</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>101</td>
<td>74</td>
</tr>
<tr>
<td>MRD negative</td>
<td>40</td>
<td>18</td>
</tr>
<tr>
<td>MRD positive</td>
<td>61</td>
<td>56</td>
</tr>
</tbody>
</table>

*Specimens assayed by flow cytometry and/or NGS. Discordant results at the same visit were called MRD positive.

- 30% (48/158) patients demonstrated blood MRD negativity by flow cytometry and confirmed by NGS in 21/29 who had an evaluable matched time point specimens

** Venetoclax (ABT-199) for Rel/Ref del(17p) CLL

** Duration of Response by MRD in Peripheral Blood **

** Time-to-Progression with Venetoclax in Rel/Ref CLL **

** MURANO Study Design **
Ventoclax in Ibrutinib- or Idelalisib-Ref / Intolerant CLL M14-032: Efficacy

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>Assessed by IRC</th>
<th>Assessed by Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>30 (70)</td>
<td>29 (67)</td>
</tr>
<tr>
<td>CR/CRi</td>
<td>2 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>nPR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>9 (21)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Non-responder*</td>
<td>13 (30)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>SD</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PR</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>D/C‡</td>
<td>14 (23)</td>
<td>9 (21)</td>
</tr>
</tbody>
</table>

*Non-responder category for IRC includes both SD or PD, which were not identified as separate categories per IRC.
†CCL progression and discontinued due to progression.
‡D/C, patient discontinued the study prior to assessment.

Jones et al. ASH 2016, Abstract 637

Idelalisib - Potent and Selective Inhibitor of PI3Kδ

- FDA approved for relapsed CLL appropriate for rituximab monotherapy
- Twice daily dosing, continuous + rituximab
- Toxicities: elevated LFTs, GI / diarrhea; less common colitis and pulmonary
- Most responses are partial, residual disease
- Median PFS was 19.4 months
- Efficacy in relapsed CLL with del(17p) & del(11q)
- Improved OS vs. rituximab + placebo
- Infection concerns in first-line

Ventoclax in Ibrutinib- or Idelalisib-Ref / Intolerant CLL M14-032: Efficacy Per Independent Review

- Median DoR, PFS, and OS had not been reached after 11.8 months of follow up
- Estimated 12 month PFS for all patients: 80% (95% CI: 67%, 89%)

Jones et al. ASH 2016, Abstract 637

Response to Subsequent Therapy Following Initial Kinase Inhibitor Therapy

<table>
<thead>
<tr>
<th>Initial Kinase Inhibitor</th>
<th>Ibrutinib (N=683)</th>
<th>Idelalisib (N=683)</th>
<th>Venetoclax (N=683)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (%)</td>
<td>46</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>CR (%)</td>
<td>0</td>
<td>5</td>
<td>32</td>
</tr>
<tr>
<td>PR/PR with lymphocytosis (%)</td>
<td>46</td>
<td>70</td>
<td>42</td>
</tr>
<tr>
<td>Stable disease (%)</td>
<td>39</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Progressive disease (%)</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Mato, AR, et. al, Ann Oncol. 28:1050, 2017

PFS Following First Kinase Inhibitor (N=683)

Mato, AR, et. al, Ann Oncol. 28:1050, 2017
Conclusions
• Same indications for treatment
• First-line is best opportunity to achieve best response
• Consider patient characters when developing treatment plan:
  – Del(17p)/mutated TP53
  – Age / comorbidities
  – IGHV mutation status
  – Prior treatment and refractory disease
• Del(17p)/mutated TP53 still high-risk feature, but now have several active agents
• Sequence important with effective treatments in relapsed / refractory CLL

THANK YOU!
wwierda@mdanderson.org
An Overview on Systemic Therapy for Patients with Newly Diagnosed Active Multiple Myeloma (MM)

*Elisabet Manasanch, MD*
An Overview on Systemic Therapy for Patients with Newly Diagnosed Multiple Myeloma

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Division of Cancer Medicine, MD Anderson Cancer Center, Houston, TX

06/23/2018

Conflict of Interest Disclosure

Consultant: Seattle Genetics, Novartis, Amgen, Takeda
Research Support: Quest, Merck, Sanofi, JW pharma

Multiple Myeloma

Plasma cell malignancy — molecular heterogeneity
Natural history progression from MGUS/SMM
Evidence of end-organ damage or biomarkers of malignancy (CRAB+)

<table>
<thead>
<tr>
<th>Myeloma biomarkers of malignancy</th>
<th>MYND</th>
<th>Natural progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical BM cell percentage: ≥50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased uninvolved SFLC ratio ≥100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 focal lesions on MRI studies of at least 5 mm in size</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Immune markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>PD-L1</td>
</tr>
<tr>
<td>NRAS</td>
<td>PD‐L1</td>
</tr>
<tr>
<td>BRAF</td>
<td>CTLA‐4</td>
</tr>
</tbody>
</table>

Proteasome Inhibitors as Initial Treatment

Absence of comorbidities, even if advanced age. Most patients are treated with ASCT
Several Phase III trials with bortezomib as initial treatment have shown the superiority of adding this agent in the frontline treatment of myeloma

VRD (lenalidomide, bortezomib, dexamethasone)
CyBoRd (cyclophosphamide, bortezomib, dexamethasone)

Bortezomib as Initial Treatment
Randomized phase II study EVOLUTION (140 patients)
8 x 3 week cycles initial therapy followed by 6-week cycles of bortezomib-maintenance

<table>
<thead>
<tr>
<th>Best response arms of cycles</th>
<th>ORR</th>
<th>PFS at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>lenalidomide </td>
<td>R 25 mg, Dex 20 mg, Panobinostat</td>
<td>84% nCR/CR, 77% VGPR, 95% PR after 4 cycles</td>
</tr>
</tbody>
</table>

Small numbers of patients
PFS at one year: 86% vs 93 vs 100 (PS)
OS at one year: 94% vs 100% in all other arms

VRD + Panobinostat in NDMM

<table>
<thead>
<tr>
<th>Phase II, n = 33 enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
</tr>
<tr>
<td>R 1.3 mg/m², R 25 mg, Dex 20 mg, Panobinostat 10 mg</td>
</tr>
<tr>
<td>Extended dosing</td>
</tr>
<tr>
<td>R 25 mg, Dex 20 mg, Panobinostat 10 mg</td>
</tr>
<tr>
<td>Transplant</td>
</tr>
<tr>
<td>HDM optional, all patients adequate stem cell collection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase I/II, n = 33 enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
</tr>
<tr>
<td>50% nCR/CR, 77% VGPR, 95% PR after 4 cycles</td>
</tr>
<tr>
<td>PFS</td>
</tr>
<tr>
<td>92% (at 24 months)</td>
</tr>
</tbody>
</table>
Carfilzomib Combinations as Initial Treatment

<table>
<thead>
<tr>
<th>Jakubowiak et al (Phase I/II, n=53)</th>
<th>Korde et al (Phase II, n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td></td>
</tr>
<tr>
<td>CRd (Phase II, C10/20mg/m²)</td>
<td>CRd (Phase II, C10/20mg/m²)</td>
</tr>
<tr>
<td>8 cycles</td>
<td>8 cycles</td>
</tr>
<tr>
<td>Extended dosing</td>
<td></td>
</tr>
<tr>
<td>CRd (C10 every other week) 16 cycles, offtreatment up to last tolerated dose for 21 cycles after 16 cycles</td>
<td>CRd 10mg C10, 21 cycles</td>
</tr>
<tr>
<td>Transplant</td>
<td></td>
</tr>
<tr>
<td>Stem cell collection, HDC optional</td>
<td>Stem cell collection</td>
</tr>
<tr>
<td>ORR 62% CR/CN, 82% VGPR, 98% PR at 12 cycles</td>
<td>ORR 56% CR/nCR (100% FLOW MRD NEGATIVE – 67% NEGATIVE by NGS), 62% CR, 89% VGPR, 98% PR (without ASCT) after 8 cycles</td>
</tr>
<tr>
<td>PFS 92% (at 24 months)</td>
<td>92% (at 18 months)</td>
</tr>
</tbody>
</table>

Carfilzomib Daratumumab as Initial Treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>KCDv</th>
<th>IDel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented Response Rate at 24 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRd + IDel</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>CRd + KCDv</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>CRd + KCDv</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>CRd + IDel</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>CRd + KCDv</td>
<td>16%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Carfilzomib Combinations as Initial Treatment

**FORTE: Study Design**
- Multicenter, randomized, open-label phase II study
- Endpoints: induction phase safety, PBSC mobilization, preliminary efficacy
- Treatments: CRd, IDel, CRd + KCDv, CRd + IDel, CRd + KCDv, CRd + IDel + KCDv
- PBSC harvest: 80% at 21 days, 90% at 28 days
- Poor PBSC mobilization (harvest < 4 x 10^9/kg and/or requiring pemfimer) more likely with KCDv vs KCD
  - OR: 8.05 (95% CI: 2.88-14.91, P < 0.001)

Carfilzomib Combinations as Initial Treatment

**FORTE: Preliminary Efficacy**

- ORR 74%
- CR 35%
- VGPR 26%
- PR 7%
- SD 10%

Carfilzomib Daratumumab as Initial Treatment

**Study Design**
- Open-label, multicenter Phase II study (n ≥ 30)
- Eligibility: 18 - 75 years old
- Diagnosed with NDMM
- PBSC mobiliation required
- Daratumumab: 260 mg/m² every 2 weeks
- CRd: C10/20 mg/m², administered IDel at 4 mg/kg on days 1, 8, 15, and 22
- PBSC harvest: 80% at 21 days, 90% at 28 days
- Poor PBSC mobilization: harvest < 4 x 10^9/kg and/or requiring pemfimer more likely with KCDv vs KCD
- OR: 8.05 (95% CI: 2.88-14.91, P < 0.001)
Carfilzomib Daratumumab as Initial Treatment

**Patient Disposition**
- Median follow-up: 10.8 months (range: 4.6–12.5 months)
- Median number of treatment cycles: 11.5 (range: 5.0–15.9)
- Except for 3 patients, all escalated to carfilzomib 70 mg/m² by cycle 20
- 1 discontinued treatment before cycle 20
- 1 dose reduction to 35 mg/m² at cycle 20
- 1 escalated to 100 mg/m² at cycle 20

**Response Rate**
- Median number of treatment cycles: 11.5 (range: 7.0–15.3)
- Depth of response improved with duration of treatment

**Upfront/delayed Autologous Transplant**
- **EMN02/HO95: Phase III Study Design**
  - Pts with ND MM who received VCD induction 3–4 cycles + PBSC collection
  - ** pts induction + PBSC collection (N = 1192)**
  - ** pts VMP* for 4 cycles (n = 497)**
  - ** pts HDM* + single/double ASCT (n = 695)**
  - ** pts VRD x 2 Consolidation**
  - ** pts No Consolidation**

**First randomization**
- **pts VMP** (n = 294)
- **Single ASCT** (n = 280)
- **VMP** (n = 203)
- **Single ASCT** (n = 208)
- **Double ASCT** (n = 207)

**CavoM et al. ASH 2017. Abstract 401**

**EMN02/HO95: Single vs Double ASCT**
- **Pts with high cytogenetic abnormality**
  - **Pts > 3 high-risk abnormalities**
  - **Pts ≥ VGPR**

**EMN02/HO95: Phase III Study Design**
- Key secondary endpoints for this analysis: PFS from first randomization for ASCT-1 vs ASCT-2

**Cavo M et al. ASH 2017. Abstract 401**
New Agents in NDMM

RANDOMIZED PHASE 3 STUDIES
1. Bortezomib, lenalidomide, dexamethasone vs Carfilzomib, lenalidomide, dexamethasone in newly diagnosed myeloma
2. Bortezomib, lenalidomide, dexamethasone +/- elotuzumab for high-risk NDMM patients
3. Lenalidomide, dexamethasone +/- daratumumab in transplant ineligible NDMM patients
4. ALCYONE: Daratumumab Plus VMP vs VMP Alone in Newly Diagnosed, Transplantation-Ineligible Myeloma

EARLY PHASE TRIALS
1. Phase II randomized, Daratumumab-RVD versus RVD in NDMM
2. CyBorD with daratumumab in NDMM
3. Carfilzomib, lenalidomide, dexamethasone with elotuzumab in transplant eligible NDMM
4. Isaxomib, lenalidomide, dexamethasone with Daratumumab in NDMM
5. Durvalumab, lenalidomide +/- dexamethasone in NDMM
6. Carfilzomib, bendamustine, dexamethasone
7. Isaxomib, lenalidomide, dexamethasone

Goals of Treatment – Frail Patients

- FRAIL ELDERLY PATIENTS:
  - Controlling symptoms
  - Maintenance of status independence
  - Preservation of cognitive function
  - Quality of Life
  - Stable disease without symptoms related to myeloma is an acceptable goal
  - Avoid excessive toxicities
  - If toxicities, use dose reductions
  - Keep balance between disease control and toxicity

Treatment Options

- Proteasome inhibitor based
- Lenalidomide based
- Oral only regimens (isaxomib, lenalidomide, dex)

Treatment Options – First Trial

- Benboubker et al. NEJM (2014);371(10):906-17.

Treatment Options – SWOG 50777

- Durie et al. VRd vs Rd in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplantation: results of a randomized phase III trial SWOG 50777. ASH. 2015.
### Treatment Options – SWOG S0777

#### Confirmed Response*: VRd vs Rd

<table>
<thead>
<tr>
<th></th>
<th>VRd</th>
<th>Rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>15.3%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Very good partial response (VGPR)</td>
<td>27.8%</td>
<td>23.4%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>33.5%</td>
<td>38.7%</td>
</tr>
<tr>
<td>ORR (PR or better)</td>
<td>81.5%</td>
<td>71.5%</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>13.7%</td>
<td>24.3%</td>
</tr>
<tr>
<td>SD or better</td>
<td>97.2%</td>
<td>89.4%</td>
</tr>
<tr>
<td>PD or death</td>
<td>2.0%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

*Assessable patients

Durie et al. VRD vs Rd in patients with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant: results of a randomized phase III trial SWOG S0777. ASH. 2015.

---

#### Incorporation of Daratumumab

**ALCYONE: Daratumumab Plus VMP vs VMP Alone in Newly Diagnosed, Transplantation-Ineligible Myeloma**

Randomized phase III study

- 706 patients, 1:1 randomization
- **Daratumumab ± Bortezomib, melphalan and prednisone**

Primary objective was Progression Free Survival (Relapse or Death)

Safety and efficacy when 231 events of disease progression or death

Final OS analysis will be presented after 330 deaths have occurred


---

#### ALCYONE: Daratumumab Plus VMP vs VMP Alone in Newly Diagnosed, Transplantation-Ineligible Myeloma

- Grade 3/4 infections
  - VMP: 14.7%
  - Dara-VMP: 23.5%

- Discontinued treatment due to infection
  - VMP: 1.4%
  - Dara-VMP: 0.9%

- IRRs in Dara-VMP arm
  - All grade: 9 (28%)
  - Grade 3: 15 (4%)%
  - Grade 4: 2 (1%)


---

#### BEST RESPONSES

- Overall response
  - Dara-VMP: 87.9%
  - VMP: 87.0%

**Incorporation of Carfilzomib**

- Elderly subgroup treated with CRd
- Median age 72 (65-81) – other CRd studies have treated patients up to 89 years of age
- Median 24 CRd cycles received (range 1–24), 2 at a carfilzomib dose level of 20 mg/m², 4 at 27 mg/m², and 17 at 36 mg/m²
- 38% of patients proceeded to maintenance, 33% went to receive autologous stem cell transplant

**Incorporation of Carfilzomib**

Phase I (15 patients)/II (50 patients) of IRd in NDMM

- Elderly subgroup treated with IRd (55% of patients above 65 years of age and 20% older than 75 years of age)
- 12 cycles of IRd followed by ixazomib single agent maintenance
- All patients (100%) achieved at least a partial response (PR), 91% at least a very good PR (VGPR), 87% at least an nCR, 79% at least a CR, and 65% a stringent CR (sCR)
Acknowledgements

Lymphoma/Myeloma
- Dr. Erina Patel
- Dr. Hans Lee
- Dr. Sheeba Thomas
- Dr. Donna Becker
- Dr. Swarn Iyer
- Dr. Robert Zhivotovsky
- Dr. Sativa Kandpal
- Dr. Eric Davis
- Dr. Rohit Mathur
- Dr. John Ma

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- Dr. Linghua Wang
- Dr. Guanghui Han

Neoantigen vaccine
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- Dr. Anjali Salakder
- Dr. Chantal Bernatchez

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- Dr. Pei Lin
- Dr. Watsuka

Biostatistics/Bioinformatics
- Dr. Veera Baladandayuthapani
- Dr. Lei Feng
- Dr. Ronald Barry
- Dr. Yun Qing

Patients and Families
Outline the Selection, Sequencing and/or Combination of Novel Therapies for Patients with Relapsed/refractory MM

Robert Orlowski, MD
Selection, Sequencing, and/or Combination Therapies for Relapsed/Refractory Multiple Myeloma

Robert Z. Orlowski, PhD, MD.
Florence Maude Thomas Cancer Research Professor
Chair, Department of Lymphoma/Myeloma
Principal Investigator, MD Anderson SPORE in Multiple Myeloma & MD Anderson Moon Shot in High Risk Multiple Myeloma
Chair, SWOG Myeloma Committee

Options for Relapsed/Refractory Disease

APEX: Bortezomib vs. Dex
78% improvement in median time to progression

Bortezomib/PLD vs. Bortezomib
9.3 months
Bortezomib
6.5 months
Statistical analysis:
HR (95% CI) 1.82 (1.41-2.35)
p = 0.000004

Len/Dex vs. Dex

PANORAMA: PFS
• Clinically relevant increase in PFS of 3.9 months.

Carfilzomib

- Results from PX-171-003-A1 study of carfilzomib in patients with relapsed and refractory myeloma
- ORR of 23.7%

ASPIRE Study: Response Rates


Pomalidomide: Response Rates


ENDEAVOR Study: PFS by ITT


TOURMALINE1: Key Efficacy Data


Antibodies: Mechanisms of Action

**SIRIUS : Response Data**


**Daratumumab + Bortez/Dex**


**Daratumumab + Len/Dex**


**ELOQUENT2 : PFS Curves**


**Daratumumab/Pomalidomide/Dexamethasone**

- ORR was 58% in double refractory patients


**ARROW Trial**

Mateos, MV et al. 2018 ASCO Abstract # 8000.
**PFS Data**

Mateos, MV et al. 2018 ASCO Abstract # 8000.

**Selected AEs**

Mateos, MV et al. 2018 ASCO Abstract # 8000.

**OPTIMISM trial**

Richardson, P et al. 2018 ASCO Abstract # 8001.

**PFS Data**

Richardson, P et al. 2018 ASCO Abstract # 8001.

**Selected AEs**

Richardson, P et al. 2018 ASCO Abstract # 8001.

**SINE**

Richardson, P et al. 2018 ASCO Abstract # 8001.
Phase I Data
- In WM & MM
- ORR 4% as a single agent
- Addition of dex provided 50% ORR

Selinexor + Dexamethasone
- ORR 21%, including quad-/penta-refractory
- Toxicities: Cytopenias, hyponatremia, fatigue

Waterfall Plot

STOMP Study Design

Efficacy Data

Durability

**BCL2 Family Proteins**

**Venetoclax ± Dexamethasone**


**Outcomes by Molecular Subtypes**


**Outcomes by BCL2 Expression**


**Venetoclax + Bortezomib/Dex**


**BCL2 Expression**

GSK2857916 : BCMA ADC


Response Data

Overall ORR = 60%, 95%CI (42%, 76%), n=35

Response Durability

Adverse Events

Most frequent adverse events:
- Corneal events: 63%
- Thrombocytopenia: 49%

Corneal events - mostly low grade (9% Grade 3)
- Manageable with steroid eye drops
- Dose reductions

Hematologic AEs (including thrombocytopenia)
- Frequent in MM population due to disease

Infusion Related Reactions (IRR): 23%
- Occur at first dose without premedication
- Manageable
- Do not recur with subsequent doses

CAR T Cells


CAR Constructs
BCMA CAR


- CAR-BCMA expression determined by flow cytometry

Toxicities

- Patient 10
  - After CAR-BCMA T-cell infusion, the pt experienced cytokine release syndrome (including fever, hypotension, tachycardia, high creatinine kinase, liver enzymes) which resolved in 2 wks.
  - ANC < 500/μL at time of infusion and for 45 days after.
  - Pt was platelet transfusion dependent for 9 wks after infusion.

- Patient 11
  - Toxicities included fever, delirium, dyspnea, hypotension, tachycardia, acute kidney injury, prolonged thrombocytopenia

PET Response


Overall Responses


Adverse Events

Cohen, AD et al. 2017 ASH Abstract # 505.

Penn BCMA CAR T Data

Cohen, AD et al. 2017 ASH Abstract # 505.
Outcomes

- ORR
  - 8 PR: 11/24 (46%)
  - 3 MR: 16/24 (67%)
- ORR with 10^6 BCMA-CART
  - 8 PR: 10/19 (53%)
- Median DoR: 4 mos

Safety

- Response Data

Response Durability

Nanjing Legend BCMA CAR Data
**Conclusions**

- Early use of novel agents is increasing, making relapsed and especially refractory disease more challenging
- Dara-based combinations appear to be the best 2nd line therapies currently, and venetoclax and selinexor appear promising
- Immunotherapies are showing activity in the relapsed and refractory setting, including CAR T-cells, and other agents (BiTEs) are coming
Novel Therapies for adolescents and young adults (AYA), Philadelphia-positive and Philadelphia-negative Relapsed/Refractory Patients with Acute Lymphoblastic Leukemia

*Nitin Jain, MD*
Novel Therapies for AYA, Ph+, and Ph-negative Relapsed/Refractory Acute Lymphoblastic Leukemia

Nitin Jain, MD
Department of Leukemia
MD Anderson Cancer Center
Houston, TX
June 23, 2018

Conflicts of Interest Disclosure

Research Funding: Pharmacyclics, Abbvie, Genentech, Infinity, BMS, Pfizer, ADC Therapeutics, Seattle Genetics, Incyte, Celgene, AstraZeneca, Servier, Verastem, Cellectis, Adaptive Biotechnologies

Advisory Board: Pharmacyclics, Novartis, ADC Therapeutics, Pfizer, Servier, Novimmune, Abbvie, Verastem, Adaptive Biotechnologies, Janssen

Survival of Children with ALL Treated on Sequential CCG/COG Clinical Trials

Hunger et al. NEJM. 2015;373(16):1541-1552


40-45% at 5 years

Poor Outcomes with Adult ALL

ALL: Diagnostic Pre requisites

- Morphology + stains: L1, L2, L3
- Immunophenotype
  - Pre B ALL ± CALLA positive
  - TALL: early, thymic, mature → ETP vs others
  - Burkitt
- Cytogenetics-molecular
  - Ph +
  - Burkitt: t (8;14), t (8;2), t (8;22)
  - t (4;11)
  - t (12;21) / TEL-AML1
  - Ph-like: CRLF2, JAK2, Abl translocations

PH-LIKE ALL
**Ph-like ALL: Definition**

- Gene expression profile = Similar to Ph+ ALL
- No Ph chromosome or BCR-ABL1


**Ph-like ALL Occurs in 25-30% of Young Adults with B-cell ALL**


**2016 WHO Classification**


**Ph-like ALL Molecular Lesions**

- Ph-like ALL
- 50% CRLF2 Overexpression
- 50% Non-CRLF2 cases
- JAK2 (JAK2R683) JAK1 Mutations
- Fusions – ABL1, ABL2, JAK2, EPOR, PDGFRB
- Mutations – IL7R, FLT3, RAS


**Ph-like ALL Incidence (N=148)**

Ph-like ALL: Inferior Overall Survival


CRLF2 Subgroup of Ph-like ALL Worst Outcomes


Ph-like ALL: More Common in Patients of Hispanic Ethnicity

<table>
<thead>
<tr>
<th>B-ALL Categories (N=155)</th>
<th>Ph-Like</th>
<th>Ph+</th>
<th>B-other</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>60</td>
<td>13</td>
<td>20 (33)</td>
<td>27 (45)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>70</td>
<td>38</td>
<td>16 (23)</td>
<td>16 (23)</td>
</tr>
<tr>
<td>African-American</td>
<td>16</td>
<td>2</td>
<td>8 (50)</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>3</td>
<td>2 (28)</td>
<td>2 (28)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>


Ruxolitinib or Dasatinib with Chemotherapy in Patients with Ph-Like ALL: A Phase I-II Trial

Ruxolitinib Plus Chemotherapy

Dasatinib Plus Chemotherapy

Ph-like ALL testing

ABL1, ABL2, PDGFRB fusions

SH2B3 deletion

JAK mutations/fusions

CRLF2 overexpression


NCT02420717

PI: N. Jain

Early T-cell Precursor (ETP) Flow-cytometry

Definition

- CD1a negative (<5%)
- CD8 negative (<5%)
- Absent or weak CD5 (<75%)
- Presence of 1 or more of myeloid/stem cell marker (>25%)
  - CD117, CD34, HLA-DR, CD13, CD33, CD11b, CD65

Coustan-Smith et al. Lancet Oncology 2009
Overall Survival in T-ALL by Subtype

CD1a(-), CD8(-), CD5(-/dim), and positivity for one or more stem cell or myeloid antigens


Hyper-CVAD + Nelarabine in T-ALL Design

Induction-Consolidation

Maintenance


Hyper-CVAD + Dasatinib in Ph+ ALL

Hyper-CVAD + Ponatinib. Design

**Hyper-CVAD + Ponatinib in Ph-Positive ALL: Survival**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR*</td>
<td>65/65 (100)</td>
</tr>
<tr>
<td>CCyR**</td>
<td>55/55 (100)</td>
</tr>
<tr>
<td>MMR***</td>
<td>73/75 (97)</td>
</tr>
<tr>
<td>CMR***</td>
<td>63/75 (84)</td>
</tr>
<tr>
<td>Flow negativity***</td>
<td>74/75 (99)</td>
</tr>
<tr>
<td>Early death</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

- *11 pts in CR at start
- **21 pts diploid by CG at start
- ***1 pts no sample

**Hyper-CVAD + Ponatinib in Ph-Positive ALL: Overall Results**

- 44 pts ≥ 60 yrs (9 pts < 60 yrs); median age 68 (21-85)
- Ponatinib 45mg/D x 6 weeks x 8 = 1 yr of Rx; steroids during induction; TIT Q mo
- CHR 42/42=100% post induction
- 6-mos CHR 90%, CGCR 90%, CMR 13/32=40%
- Estimated 2-yr 62%
- 13 SAEs and 2 deaths from ponatinib

**Blinatumomab-ponatinib in Ph-Positive ALL**

- MVA for OS
- CMR at 3 months (HR 0.42 [95% CI 0.21-0.82], P=0.01)

**CMR in Ph-Positive ALL: OS for CMR vs. others**

- *MVA for OS
- CMR at 3 months (HR 0.42 [95% CI 0.21-0.82], P=0.01)
What's New In Treatment of Ph- B-ALL

**Newer Targeted Therapies in ALL**

- Inotuzumab
- Blinatumomab
- Chimeric Antigen Receptor (CAR) T cell
- Ruxolitinib for Ph-like ALL
- Venetoclax

**Inotuzumab**

- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell
  - Calicheamicin is more potent than other cytotoxic chemotherapeutic agents
  - Calicheamicin binds to DNA, inducing double-stranded DNA breaks
  - Development of DNA breaks is followed by apoptosis of the tumor cell

**Inotuzumab vs ChemoRx in R-R ALL: Design**

- Open-label, phase 3 study; 326 pts randomized at 117 sites in 19 countries

**Inotuzumab vs ChemoRx in R-R ALL: Responses**

<table>
<thead>
<tr>
<th>Response</th>
<th>n (% [95% CI])</th>
<th>InO (n=109)</th>
<th>SOC (n=109)</th>
<th>1-sided P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRi</td>
<td>88 (80.7) [72–92]</td>
<td>32 (29.4) [21–39]</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>MRD neg b</td>
<td>69/88 (78.4) [68–87]</td>
<td>32/92 (28.1) [14–47]</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* Among the first 218 pts randomized, over 4X more achieved CR/CRi and proceeded directly to SCT after CR/CRi with InO vs SOC (n=41/109 vs n=10/109; P<0.0001)
**MiniHCVD-INO in R/R ALL. Survival**

- 2-yr PFS and OS rates 54% and 39%, respectively

**MiniHCVD-INO vs INO in R/R ALL. Survival**

- **Blinatumomab**
  - Pre-B-Lymphoblast
  - CD19
  - CD3
  - Lysis

**Blinatumomab in ALL MRD-positive**

- 116 pts (median age 45 yr; range 18-76) with ALL in CR but MRD ≥ 0.1% post ≥ 3 intensive courses: 35% in ≥ CRD2
- 88 pts (78%) MRD-negative post Cycle 1
- 90 (78%) received allo-SCT
- Median follow-up 29 mos, Median OS 36 mos

<table>
<thead>
<tr>
<th>Median (mos)</th>
<th>Overall</th>
<th>MRD negative</th>
<th>MRD positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>36</td>
<td>39</td>
<td>12</td>
<td>0.001</td>
</tr>
<tr>
<td>RFS</td>
<td>19</td>
<td>35</td>
<td>7</td>
<td>0.002</td>
</tr>
<tr>
<td>DOR</td>
<td>NR</td>
<td>NR</td>
<td>15</td>
<td>0.015</td>
</tr>
</tbody>
</table>

- No difference in OS (HR=1.39; p=0.37) and RFS (HR=0.89; p=0.73) between allo-SCT vs no allo-SCT

Kantarjian, Blood. 130: abst 1099; 2017

Phase 3 TOWER Study: Randomization and Dosing

- Randomization 2:1 (blinatumomab:SOC)
  - Stratified by age, prior salvage, and prior allo-HSCT

- Induction (2 cycles)
  - Blinatumomab
  - SOC chemotherapy
  - Continuous infusion 4 wk on, 2 wk off; 8 mcg/d for 7 d, then 28 mcg/d wk 2-4

- Consolidation (3 cycles)
  - Blinatumomab
  - Investigator's choice: FLAG ± anthracycline, HiDAC-based, high-dose MTX-based, or clofarabine-based
  - Continuous infusion 4 wk on, 8 wk off; 28 mcg/d

- Maintenance (up to 12 mo)
  - Blinatumomab
  - Continuous infusion 4 wk on, 2 wk off; 9 mcg/d for 7 d, then 28 mcg/d wk 2-4

- Follow-up

Patients with relapsed/refractory ALL
N = 405

Phase 3 TOWER Study: Hematologic Response

- Patients with relapsed/refractory ALL
  - N = 405
  - 83% P < .001
  - Hazard ratio for EFS 0.55 (0.43, 0.71); P < .001

- Median OS (95% CI):
  - Blinatumomab, 7.7 months (5.6, 9.6)
  - SOC, 4.0 months (2.9, 5.3)
  - Stratified log-rank p = 0.012
  - Hazard ratio: 0.71 (0.55, 0.93)

CHIMERIC ANTIGEN RECEPTOR (CAR) T CELL THERAPY

Rationale for CD19 as a CAR T Target

- CD19 is expressed on precursor and mature B cells
- Not expressed on BM stem cells or other tissues
- Rarely lost during neoplastic transformation
- Present on a wide range of B-cell malignancies

CD19 CAR T products in pivotal trials in ALL and NHL

- Adapted from Blanc et al. Clin Cancer Res 2011; 17:6448-6458

- Adapted from van der Steegen et al. Nat Rev Drug Discov, 2015
Published CD19 CAR T Trials in B-ALL

<table>
<thead>
<tr>
<th>Disease</th>
<th>Construct</th>
<th>No of pts</th>
<th>Pediatric or adult</th>
<th>CR %</th>
<th>MRD neg %</th>
<th>CRS</th>
<th>CRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maude 2014 (U Penn)</td>
<td>CD19</td>
<td>24</td>
<td>Pediatric (21)</td>
<td>40</td>
<td>78</td>
<td>27</td>
<td>severe</td>
</tr>
<tr>
<td>Davila 2014 (MSKCC)</td>
<td>CD19</td>
<td>24</td>
<td>Adult (5)</td>
<td>90</td>
<td>78</td>
<td>27 (severe)</td>
<td>43</td>
</tr>
<tr>
<td>Lee 2015 (NIH)</td>
<td>CD28</td>
<td>24</td>
<td>Pediatric and young adults</td>
<td>67</td>
<td>57</td>
<td>28 (severe)</td>
<td>29</td>
</tr>
<tr>
<td>Turtle 2016 (FHCRC)</td>
<td>4-1BB</td>
<td>24</td>
<td>Adults</td>
<td>97</td>
<td>93</td>
<td>23</td>
<td>severe</td>
</tr>
<tr>
<td>Gardner 2017 (FHCRC)</td>
<td>4-1BB</td>
<td>24</td>
<td>Pediatric and young adults</td>
<td>93</td>
<td>93</td>
<td>23</td>
<td>severe</td>
</tr>
<tr>
<td>Maude 2018 (ELIANA trial)</td>
<td>4-1BB</td>
<td>24</td>
<td>Pediatric and young adults</td>
<td>81</td>
<td>81</td>
<td>46 (severe)</td>
<td>40</td>
</tr>
<tr>
<td>Park 2018 (MSKCC)</td>
<td>CD28</td>
<td>24</td>
<td>Adults</td>
<td>83</td>
<td>60</td>
<td>26 (severe)</td>
<td>44</td>
</tr>
</tbody>
</table>

ELIANA: 1st Multicenter Trial of CTL019 in Relapsed/refractory Pediatric and Young Adult ALL

**Conditioning**
- Low dose Cy (500 mg/m2/day x 2 days)
- Flu (30 mg/m2/day x 4 days)
- Leukapheresis
  - 0.2-5.0 x 10^6/kg for patients ≤50 kg
  - 0.1-2.5 x 10^8 for patients >50 kg

**Endpoints**
- Primary: ORR within 3 months, 4-week maintenance of remission
- Secondary: MRD status, DOR, OS, cellular kinetics, safety

**Patient Disposition**
- Median time from enrollment to CTL019 infusion was 45 days

**Patient Characteristics**
- Age (years), median (range): 11 (3-23)
- Male, %: 57
- Prior therapies, median (range): 3 (1-8)
- Prior stem cell transplant, %: 61
- Blast count in BM, %, median (range): 74 (5-99)

**Efficacy (N=75)**
- ORR (CR+CRi) within 3 months: 61 (81)
- CR: 45 (60)
- CRi: 16 (21)
- MRD negative bone marrow: 61 (81)

**EFS and OS**
- CD19 at relapse
  - 1 CD19+ and 3 CD19- and CD19- and 12 CD19- and 6 unknown CD19
Tisagenlecleucel (CTL019 / Kymriah) indicated for pediatric and young adult (up to 25 years) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Overall goal is to maximize the benefit from the CAR T-cell therapy while minimizing the risk for life-threatening complications of toxicities.

<table>
<thead>
<tr>
<th>ELIANA: Safety (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Events</strong></td>
</tr>
<tr>
<td><strong>All grades (%)</strong></td>
</tr>
<tr>
<td><strong>Grade 3 (%)</strong></td>
</tr>
<tr>
<td><strong>Grade 4 (%)</strong></td>
</tr>
<tr>
<td>Cytokine release syndrome (CRS)</td>
</tr>
<tr>
<td>Neurological events</td>
</tr>
</tbody>
</table>

- 2 deaths within 30 days of CTL019 (1 ALL, 1 cerebral hemorrhage)
- No deaths due to CRS
- No cases of cerebral edema
- No replication-competent lentivirus or insertional oncogenesis

<table>
<thead>
<tr>
<th>ELIANA: CRS Onset, Duration, and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients with CRS (N=58) Median (range)</strong></td>
</tr>
<tr>
<td>Time of onset (days)</td>
</tr>
<tr>
<td>Duration of CRS (days)</td>
</tr>
<tr>
<td>Admitted to ICU*</td>
</tr>
<tr>
<td>ICU stay (days)</td>
</tr>
<tr>
<td>Anti-cytokine therapy</td>
</tr>
<tr>
<td>High-dose vaspressors</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
</tr>
<tr>
<td>Dialysis</td>
</tr>
</tbody>
</table>

* ICU admission for all patients: 47% (35/75)

CD19-CD28z CAR (MSKCC) Responses (N=53)
- Median age 44 (23-74)
- Median no. prior Rx = 3
- CR 83%, MRD- CR 60%

UCART19 (CD19CAR/RQR8+_TCRαβ_ T-cells)
Allogeneic, universal, adoptive T-cell therapy targeting CD19+ malignancies

CD19-CD28z CAR (MSKCC) Responses (N=53)
- Median age 44 (23-74)
- Median no. prior Rx = 3
- CR 83%, MRD- CR 60%

UCART19 (CD19CAR/RQR8+_TCRαβ_ T-cells)
Allogeneic, universal, adoptive T-cell therapy targeting CD19+ malignancies
UCART Concept

- But they are a different concept. UCARTs are
  - Made from healthy donor T-cells, do not depend upon patient’s lymphocytes
  - Not a bespoke production, manufactured ahead of time that could be deployed in a broad range of points of care and thus be made available to broad patient populations

- In addition, through TALEN®-mediated gene editing, specific features are enabled such as
  - Loss of allo-reactivity to limit the risk of GvHD when using allogeneic T-cells
  - Resistance to specific chemotherapies or antibody therapies or lymphodepleting agents resistance to checkpoint inhibitors
  - Capacity to target T-cell born targets without UCART-fratricide cell killing


UCART19 CD19 CAR T-cell in R/R B-ALL

- Lymphodepletion with CTX-FLU + alemtuzumab followed by UCAR19
- 12 pts received UCART19
  - Median age 29.5 (18-62)
  - Median prior therapies 3.5 (1-5)
  - 58% had prior allo-SCT
- CR 67%, MRD neg CR 58%
- Grade 3-4 CRS 17%, Grade 3-4 CRES 0%

Jain N et al. EHA 2018

The Future of CART in B-ALL

- Tisagenlecleucel approved for R/R B-ALL
- Approval for adult patients soon?
- Dual targeting CARs (CD19 and CD22)
- Off the shelf CART
- Introduction of CART in earlier lines of Rx

Venetoclax in ALL

- ETP cells are preferentially sensitive to venetoclax

Chonghaile et al. Cancer Discovery 2014

Venetoclax in ALL

- MLL ALL sensitive to venetoclax


ALL. Progress and Future Directions

- Incorporation of inotuzumab, blinatumomab in frontline therapy
- CAR-T cells Rx (early phases for high-risk patients: MLL, complex CG, etc..)
- Explore venetoclax and MoAbs targeting CD19, CD22, and CD123
- MRD studies critical: assessment by NGS
Thank you!

njain@mdanderson.org
How Compound Genotypes are Related to Novel Therapy Based Outcomes in Patients with Acute Myeloid Leukemia?

Farhad Ravandi, MD
Genotypes and Novel Therapies in Acute Myeloid Leukemia

Farhad Ravandi, MD
Professor of Medicine
Chief, Section of Developmental Therapeutics
Department of Leukemia
MD Anderson Cancer Center
Houston, TX

Impact of cytogenetic entities recognized in 2008 WHO classification on survival


Timeline of Genetic Landscape in AML


The genomic landscape of AML

Clinical Relevance of Molecular Landscape

- **Prognostication**
- **Therapeutic choice:**
  - identify targetable lesions
  - prioritize targets based on VAF
  - identify/verify genotype-sensitivity associations
- **Markers for MRD**
- Inform preemptive therapy - such as AlloSCT
- Inform mechanisms of chemoresistance and relapse
- Inform treatment decisions at relapse

Prognostication in AML: ELN 2017

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Mutated NPM1 and FLT3-ITDlow</td>
</tr>
<tr>
<td></td>
<td>Wild type NPM1 without FLT3-ITD or with FLT3-ITDlow</td>
</tr>
<tr>
<td></td>
<td>Wild type KIT or FLT3-ITDlow</td>
</tr>
<tr>
<td>Adverse</td>
<td>Wild type NPM1 and FLT3-ITD</td>
</tr>
<tr>
<td></td>
<td>Wild type RUNX1</td>
</tr>
<tr>
<td></td>
<td>Wild type ASXL1</td>
</tr>
<tr>
<td></td>
<td>Wild type TP53</td>
</tr>
</tbody>
</table>

2017 European LeukemiaNet (ELN) Recommendations for AML

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Genetic Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>favorable</td>
<td>t(8;21)(q22;q22); RUNX1-RUNX1T1</td>
</tr>
<tr>
<td></td>
<td>t(15;17)(q22;q12); AML1-ETO</td>
</tr>
<tr>
<td></td>
<td>inv(16)(p13.1q22); CBFB-MYH11</td>
</tr>
<tr>
<td></td>
<td>Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow</td>
</tr>
<tr>
<td>intermediate</td>
<td>Mutated NPM1 and FLT3-ITDlow</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>Wild type ASXL1</td>
</tr>
<tr>
<td></td>
<td>Wild type TP53</td>
</tr>
</tbody>
</table>
|               | Low, low allelic ratio (<0.5); high, high allelic ratio (≥0.5)
Poor Outcomes With Secondary and Treatment-Related AML

De novo sAML tAML

Survival Probability


AML Ontogeny Can Be Mutationally Defined


De Novo AML, Age ≥60 Years

Genetic Subtype

Secondary-Type Mutations Are Associated With Adverse Outcomes

Secondary-type mutations are associated with adverse outcomes.


TP53 Mutations and Prognosis


• 1:5 molar ratio of daunorubicin to cytarabine
• Synergistic activity in both in vitro and animal models
• 100-nm bilamellar liposomes
• 1 unit = 0.44 mg daunorubicin plus 1 mg cytarabine (1:5 molar ratio) complexed with copper
• Targets bone marrow and preferentially targets leukemic compared with normal marrow progenitors

Liposomal Daunorubicin and Cytarabine (CPX-351)

CPX-351 Versus 7+3 in Older Patients With Newly Diagnosed High-Risk AML


Key eligibility
• Previously untreated
• Aged 60-75 years
• Able to tolerate intensive therapy
• PS 0-2

Primary endpoint: OS

Induction
- CPX-351 44 mg/100 mg per m2 IV days 1, 3, 5
- Cytarabine 100 mg/m2/day x 7 plus daunorubicin 60 mg/m2/day x 3

Reinduction
- CPX-351 days 1 and 3
OR
5+2

Consolidation
- CPX-351 29 mg/65 mg per m2 IV days 1, 3
- Cytarabine 100 mg/m2/day x 5 plus daunorubicin 60 mg/m2/day x 2

CPX-351 Versus 7+3 in High-Risk AML: Response Rate

<table>
<thead>
<tr>
<th>Group</th>
<th>CR Rate</th>
<th>CR + CRi Rate</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPX-351</td>
<td>37.3%</td>
<td>47.7%</td>
<td>1.68 (1.03, 2.78)</td>
<td>0.040</td>
</tr>
<tr>
<td>7+3 + CRi</td>
<td>25.6%</td>
<td>33.3%</td>
<td>1.77 (1.11, 2.81)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

CPX-351 Improves Survival Among Older, Fit, High-Risk AML Patients

Clinical Relevance of Molecular Landscape

- Prognostication
- Therapeutic choice:
  - identify targetable lesions
  - prioritize targets based on VAF
  - identify/verify genotype-sensitivity associations
- Markers for MRD
- Identify preemptive therapy - such as AlloSCT
- Inform mechanisms of chemoresistance and relapse
- Inform treatment decisions at relapse

APL Randomized Trial - Regimens

Survival Outcomes for the Whole Population

Median F/U 47.6 months, Range 27 – 159.7 months
ATRA + ATO: Long-Term Follow-up

FLT3 Mutations in AML

- ~25% of AMLs will have FLT3-ITD
  - Associated with poor prognosis and increased relapse risk
- ~5%-10% of AMLs will have FLT3-TKD
  - Unclear effect on prognosis
- Downstream effects
  - FLT3-WT is a critical signaling molecule in myeloid development
  - Associated with increased downstream signaling to promote survival and proliferation

FLT3 Kinase Inhibitors

- Lestaurtinib
- Midostaurin
- MLN-518
- Sunitinib
- Sorafenib
- AC220

SORAML Design

- Favorable risk (FR): t(8;21), inv(16);
- High risk (HR): ≥3 aberrations, monosomy 7 or 5, t(6;9), t(6;11), t(11;19) or insufficient response on day 16 after DA I
- Intermediate risk (IR): all cytogenetics not FR or HR

SORAML Results

(A) EFS, (B) RFS, and (C) OS

Phase 3 RATIFY Study: Chemotherapy ± Midostaurin in Newly Diagnosed AML

- CALGB 10602
- FLT3-ITD or FLT3-TKD
- Age ≥60 years

- Favorable risk (FR): Cytarabine (200 mg/m²/d, d 1-7) + Daunorubicin (50 mg/m²/d, d 1-3) + Midostaurin (50 mg twice daily, d 1-28)
- High risk (HR): Cytarabine (200 mg/m²/d, d 1-7) + Daunorubicin (50 mg/m²/d, d 1-3) + Cytarabine (200 mg/m²/d, d 15-21)
- Intermediate risk (IR): Placebo (twice daily, d 1-28)
OS improved with addition of midostaurin
- 74.7 vs 25.6 months ($P = .009$)

Transplantation during first CR
- 28.1% in the midostaurin group vs 22.7% in the placebo group

Overall HCT
- 58% in the midostaurin group vs 54% in the placebo group

4-y OS among HCT patients
- 63.7% in the midostaurin group vs 55.7% in the placebo group ($P = .08$ by log-rank test)

**RATIFY: Survival Outcomes and Transplantation Rate**

**Median Overall Survival according to ELN Subgroups and Midostaurin versus Placebo**

**Overall Survival according to ELN Subgroups and Midostaurin versus Placebo**

**Phase 2 Study of Quizartinib in First Salvage AML: Response**

- 70% of FLT3-ITD+ and 55% of FLT3-ITD- patients refractory to last prior therapy achieved at least a PR

- Median CRc duration: 10.4 wk for FLT3-ITD+ and 9.3 wk for FLT3-ITD-

**CHRYSALIS: Response by Dose and TKI Status**

- ORR: 42%
- CRc: 31%

- ORR: 56%
- CRc: 44%

(n = 45) (n = 124)
IDH Mutations as a Target

- IDH: critical enzymes of the citric acid cycle
- mIDH2 produces 2-HG, which alters DNA methylation and blocks cellular differentiation
- mIDH2 occurs in ~15% of AML/MDS
- Enasidenib (AG-221/CC-90007): a selective, oral, potent inhibitor of mIDH2 enzyme
-ivosidenib, IDH-305, FT2102, and Bay-6032 are potent inhibitors of IDH1

Enasidenib in Patients With IDH2 Mutations: Phase 1/2 Study Design

Key endpoints
- Safety, tolerability, MTD, DLTs
- Response rates in R/R AML patients, assessed by local investigator per IWG criteria
- Assessment of clinical activity

Enasidenib in Patients With IDH2 Mutations: Responses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relapsed or Refractory AML</th>
<th>Enasidenib 100 mg/d (n = 109) [95% CI]</th>
<th>All Doses (n = 176) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % [n/N]</td>
<td>CR, n (%) [95% CI]</td>
<td>38.5% [40/109] [29.4-48.8]</td>
<td>40.3% [71/176] [33.0-48.0]</td>
</tr>
<tr>
<td>Best response</td>
<td>CR, n (%) [95% CI]</td>
<td>22 [20.2] [13.1-30.9]</td>
<td>26 [19.3] [13.0-29.3]</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>CRi or CRp, n (%)</td>
<td>7 [5.4] [3.0-11.8]</td>
<td>12 [8.8] [5.8-18.3]</td>
</tr>
<tr>
<td>MLD, n (%)</td>
<td>MDR, n (%) [95% CI]</td>
<td>10 [8.2] [5.4-14.4]</td>
<td>14 [9.0] [5.9-18.1]</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>PD, n (%) [95% CI]</td>
<td>58 [53.2] [46.8-66.3]</td>
<td>85 [48.3] [41.0-63.2]</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>Time to first response (mo) [range]</td>
<td>2 [1.6] [1.0-3.0]</td>
<td>3 [1.7] [1.0-3.0]</td>
</tr>
<tr>
<td>Duration of response (mo) [95% CI]</td>
<td>5.6 [5.3, 5.9]</td>
<td>5.8 [5.0-6.6]</td>
<td>5.8 [5.0-6.6]</td>
</tr>
<tr>
<td>Duration of CR (mo), median [95% CI]</td>
<td>8.8 [5.3, NR]</td>
<td>8.8 [5.4, NR]</td>
<td>8.8 [5.4, NR]</td>
</tr>
</tbody>
</table>

Enasidenib in Patients With IDH2 Mutations: OS by Best Response

| Parameter                           | Relapsed or Refractory AML | Enasidenib 100 mg/d (n = 109) [95% CI] | All Doses (n = 176) [95% CI] |
|-------------------------------------| CR, n (%) [95% CI]         | 38.5% [40/109] [29.4-48.8]             | 40.3% [71/176] [33.0-48.0] |
| Best response                       | CR, n (%) [95% CI]         | 22 [20.2] [13.1-30.9]                  | 26 [19.3] [13.0-29.3]      |
| PR, n (%)                           | CRi or CRp, n (%)          | 7 [5.4] [3.0-11.8]                     | 12 [8.8] [5.8-18.3]       |
| MLD, n (%)                          | MDR, n (%) [95% CI]        | 10 [8.2] [5.4-14.4]                    | 14 [9.0] [5.9-18.1]       |
| SD, n (%)                           | PD, n (%) [95% CI]         | 58 [53.2] [46.8-66.3]                  | 85 [48.3] [41.0-63.2]     |
| NE, n (%)                           | Time to first response (mo) [range] | 2 [1.6] [1.0-3.0]                      | 3 [1.7] [1.0-3.0]        |
| Duration of response (mo) [95% CI]  | 5.6 [5.3, 5.9]             | 5.8 [5.0-6.6]                          | 5.8 [5.0-6.6]             |
| Duration of CR (mo), median [95% CI]| 8.8 [5.3, NR]              | 8.8 [5.4, NR]                          | 8.8 [5.4, NR]            |

Speed of Response With IDH2 Inhibition

| Parameter                           | Relapsed or Refractory AML | Enasidenib 100 mg/d (n = 109) [95% CI] | All Doses (n = 176) [95% CI] |
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| Duration of CR (mo), median [95% CI]| 8.8 [5.3, NR]              | 8.8 [5.4, NR]                          | 8.8 [5.4, NR]            |

Enasidenib in Patients With IDH2 Mutations: OS by Best Response

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| Duration of CR (mo), median [95% CI]| 8.8 [5.3, NR]              | 8.8 [5.4, NR]                          | 8.8 [5.4, NR]            |
Ivosidenib: Clinical Activity

Patient achieved CR by end of cycle 1

<table>
<thead>
<tr>
<th>Response</th>
<th>Dose Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R/R AML (n = 62)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>DR/CRp, n (%)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>mCR/MLFS, n (%)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>SD, n (%)</td>
<td>27 (43)</td>
</tr>
<tr>
<td>PD, n (%)</td>
<td>8 (13)</td>
</tr>
<tr>
<td>NE, n (%)</td>
<td>7 (11)</td>
</tr>
<tr>
<td>DRR, n (%)</td>
<td>(95% CI) 21 (32, 46)</td>
</tr>
</tbody>
</table>

Response to Dose Escalation

R/R AML (n = 63)

Overall (N = 78)

CR, n (%) 10 (16) 14 (18)
DR/CRp, n (%) 8 (13) 8 (10)
PR, n (%) 1 (2) 2 (3)
mCR, n (%) 2 (3) 6 (8)
SD, n (%) 27 (43) 30 (38)
PD, n (%) 8 (13) 8 (10)
NE, n (%) 7 (11) 10 (13)


Clinical Relevance of Molecular Landscape

• Prognostication
• Therapeutic choice:
  - identify targetable lesions
  - prioritize targets based on VAF
  - identify/verify genotype-sensitivity associations
• Markers for MRD
• Inform preemptive therapy - such as AlloSCT
• Inform mechanisms of chemoresistance and relapse
• Inform treatment decisions at relapse

Adapted from Grimwade D, et al., Blood, 127, 29-41, 2016

AML Minimal Residual Disease Assessment: Available Assays

<table>
<thead>
<tr>
<th>Method</th>
<th>Target</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Chromosomal Aberrations</td>
<td>1 in 20 (5%)</td>
<td>Widely available</td>
<td>Insensitive</td>
<td></td>
</tr>
<tr>
<td>FISH</td>
<td>Chromosomal Aberrations</td>
<td>1 in 500 (0.2%)</td>
<td>Widely available</td>
<td>Detection of numeric cytogenetic abnormalities</td>
<td></td>
</tr>
<tr>
<td>Flow Cytometry</td>
<td>Leukemia Associated Aberrant Immunophenotype</td>
<td>1 in 10,000 to 1 in 100,000 (0.01% to 0.001%)</td>
<td>Wide applicability (&gt;90%); Relatively quick (results ≤1 day); Leukemia- stem cell phenotype</td>
<td>Challenging; experienced pathologist; Dependent on antibody panel; Limited standardization; Phenotype not always stable</td>
<td></td>
</tr>
<tr>
<td>RT-qPCR</td>
<td>Fusion Transcripts, Gene Mutations, Over-expressed genes</td>
<td>1 in 100,000 to 1 in 1,000,000 (0.001% to 0.0001%)</td>
<td>Wide applicability, high sensitivity, well standardized</td>
<td>Multiple days; Expensive; Applicable to only ~50% of AML cases</td>
<td></td>
</tr>
<tr>
<td>NGS</td>
<td>Gene Mutations</td>
<td>1 in 100,000 to 1 in 1,000,000 (0.001% to 0.0001%)</td>
<td>Relatively easy to perform; Sensitive</td>
<td>Limited standardization; CHIP mutated genes; Persistent mutants in CR</td>
<td></td>
</tr>
</tbody>
</table>


MRD Detection by RT-qPCR for Leukemia-specific MRD Targets According to Age

Grimwade D, and Freeman S. Blood 2014;124:3345-3355

MRD in NPM1 Mutated AML

**NGS: Mutation Clearance After Induction Therapy and Outcomes**

- **Age-related Clonal Hematopoiesis**
  - WES of PBMC from 17,182 patients, screened for mutations in 160 hematologic neoplasm-related genes
  - Mutations found at increasing frequency with age, most single
  - The majority of variants in 3 genes: DNMT3A, TET2, ASXL1

**A) Mutations at Diagnosis and at CR**

**B) Allele Frequency at CR**

**Non-DTA Mutations in CR Independently Predicted for Relapse and Survival**

**Agents to Eradicate MRD**
- Monoclonal antibodies
  - SGN-CD33A, AMG-330, SL-140
- Demethylating agents
  - Oral azacytidine
- Check-point inhibitors
  - Nivolumab
- Small molecule inhibitors
  - FLT3 Kinase inhibitors, IDH inhibitors, ABT-199
- Vaccines
- CAR-T cells
- Allogeneic Stem Cell Transplant
Conclusions

- Reaching the limit of cytotoxic chemotherapy in AML
- Characterization of specific subsets based on molecular events and pathogenic pathways
- Addition of target specific drugs
  - to chemotherapy regimens in younger patients
  - To hypomethylating agents in older/less fit patients
- Better detection of MRD
- Better tools for eradicating MRD

Thank you

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Chief, Section of Developmental Therapeutics
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MD Anderson Cancer Center
Houston, TX
Response Assessment and Management of Tyrosine Kinase Inhibitors Resistance in the Management of Patients with Chronic Myeloid Leukemia

Jorge Cortes, MD
Response Assessment and Management of Tyrosine Kinase Inhibitors Resistance in the Management of Patients with Chronic Myeloid Leukemia

Jorge Cortes, MD
Chief CML & AML Sections
Department of Leukemia
The University of Texas, MD Anderson Cancer Center
Houston, TX

Conflict of Interest Disclosure
Consultant: BMS, Novartis, Pfizer, Takeda
Research Support: BMS, Novartis, Pfizer, Takeda

Survival in Early Chronic Phase CML


Relative Survival with TKI by Response to Therapy

- 483 pts with CML treated with imatinib 400mg (n=71), imatinib 800 mg (n=201), dasatinib (n=152) or nilotinib (n=101)
- 5-yr relative survival 94.8% [92.1 - 97.4]

Sasaki et al. Lancet Hematology 2015

The Evolution of CML

The Treatment
Hydroxyurea IFN TKIs

The Monitoring
CMR Cephalosporin FISH PCR

The Endpoints
CHR MCR CCyR MMR MR4.5

The Goals
Symptom control Survival Transformation-free EFS TFR

When Do We Change Therapy?

Resistance Suboptimal Response/Warning
1st Line Rx CHR CCyR MMR CMR
Intolerance Low-grade Toxicity

The Goals
Symptom control Survival Transformation-free EFS TFR
Rates of Discontinuation by TKI – Long-Term

Survival Post Imatinib Failure by CML Phase

Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

Dasatinib in CML CP After Imatinib Failure

TKI Change Approaches

Long-Term Outcome After Multiple TKI

Dasatinib in CML CP After Imatinib Failure

- 670 pts randomized to 4 dasatinib schedules
- 6-year follow-up

Outcome (100 mg/d) Percent

MCR / CCyR (within 2 yr) 63 / 50
MMR 46
IM Resistant 43
IM Intolerant 55
7-yr OS 65
7-yr PFS 42
Discontinued treatment 78

* Reason for discontinuation: AE 30% (related 24%, unrelated 6%), progression 21%, other 47%.
* Pleural effusion 28%, pulmonary hypertension 2%.
Nilotinib in CML CP Post Imatinib Failure

- 321 pts: imatinib resistant (71%) or intolerant (29%)
- Minimum 48 mo follow-up
- Nilotinib 400 mg PO BID

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCyR / CCyR</td>
<td>59 / 45</td>
</tr>
<tr>
<td>Resistant*</td>
<td>56 / 41</td>
</tr>
<tr>
<td>Intolerant*</td>
<td>66 / 51</td>
</tr>
<tr>
<td>48-month OS</td>
<td>78</td>
</tr>
<tr>
<td>48-month PFS</td>
<td>57</td>
</tr>
<tr>
<td>Discontinued treatment</td>
<td>70</td>
</tr>
</tbody>
</table>

* Reason for discontinuation: progression 30%, AEs 21% (related 17%, unrelated 4%)
* AEs: Rash 31%, pruritus 26%, nausea 25%

2nd-line Bosutinib in CP CML: 8-Year Update

- Phase 1/2 bosutinib 500 mg/d
- 284 pts: imatinib resistant 195, intolerant 89
- Median age 53 y (18-91 y), prior IFN 35%, SCT 3%

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Imatinib-resistant</th>
<th>Imatinib-intolerant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCyR</td>
<td>110 (60)</td>
<td>48 (60)</td>
<td>158 (60)</td>
</tr>
<tr>
<td>CCyR</td>
<td>80 (40)</td>
<td>41 (51)</td>
<td>130 (50)</td>
</tr>
</tbody>
</table>

Survival outcomes
- Cumulative incidence of progression or death: 67 (24%)
- Deaths: 51 (18%)

New toxicities year 5-8: renal (14%), diarrhea 1 (0.8%), psychiatric 1 (0.6%)
- Vascular events (per 100 pt/year): cardiovascular 0.008, cerebrovascular 0.005, peripheral vascular 0.001

2nd Generation TKI in CML CP Post-Imatinib Resistance

<table>
<thead>
<tr>
<th>Response</th>
<th>Dasatinib†</th>
<th>Nilotinib‡</th>
<th>Bosutinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU (mo)</td>
<td>&gt;24</td>
<td>&gt;24</td>
<td>&gt;24</td>
</tr>
<tr>
<td>CHR</td>
<td>89</td>
<td>77</td>
<td>86</td>
</tr>
<tr>
<td>MCyR</td>
<td>59</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>CCyR</td>
<td>44</td>
<td>41</td>
<td>41</td>
</tr>
<tr>
<td>24 mo PFS*</td>
<td>80%</td>
<td>64%</td>
<td>81%</td>
</tr>
<tr>
<td>24 mo OS*</td>
<td>91%</td>
<td>87%</td>
<td>91%</td>
</tr>
</tbody>
</table>

† For MMR 45%, PFS 42%, OS 65%; discontinued 78%
‡ For PFS 71%, OS 75%, discontinued 75%

Phase II Studies of Dasatinib After Imatinib Failure – Advanced Phase

<table>
<thead>
<tr>
<th>Response</th>
<th>Percent by Disease Stage</th>
<th>AP</th>
<th>MyBP</th>
<th>LyBP</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=174</td>
<td>n=109</td>
<td>n=48</td>
<td>n=46</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHR</td>
<td>64</td>
<td>50</td>
<td>39</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>NEL</td>
<td>19</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cytogenetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>39</td>
<td>47</td>
<td>58</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>32</td>
<td>26</td>
<td>46</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Progression-Free Survival in CML After Dasatinib

2nd Generation TKI in CML CP Post-Imatinib Intolerance

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>100</td>
</tr>
<tr>
<td>MCyR</td>
<td>77</td>
</tr>
<tr>
<td>CCyR</td>
<td>67</td>
</tr>
</tbody>
</table>

† 7-yr MMR 43%, PFS 42%, OS 65%; discontinued 78%
‡ 4-yr PFS 57%, OS 78%; discontinued 70%
Cross-Intolerance of TKI

Discontinued due to same toxicity
Occurrence of same grade 3-4 toxicity

<table>
<thead>
<tr>
<th>TKI</th>
<th>Discontinued</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=43)</td>
<td>(n=31)</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>9 (21%)</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>(8 the same, 1 different; not specified which one)</td>
<td>(+2 persistent grade 2, 61%)</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>10 (15%)</td>
<td>28 (45%)</td>
</tr>
</tbody>
</table>

* Arterio-thrombotic event cross-intolerance not explored


Outcome of Patients Failing Frontline 2G-TKI

- 23 pts (nilotinib 13, dasatinib 10)
- Malignity: BP 2, 5 patients response 2, other 9
- Subsequent therapy: imatinib (8), nilotinib (2), dasatinib (1), bafetinib (1), HCVAD + TKI (2), SCT (2), LFU (4)

TKI Selection Based on Selected Co-Morbidities and Risks

<table>
<thead>
<tr>
<th>History with prior TKI or co-morbidity</th>
<th>Preferred</th>
<th>Less preferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Dasatinib, Bosutinib</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Pulmonary disease/PAH</td>
<td>Bosutinib, Nilotinib</td>
<td>Dasatinib</td>
</tr>
<tr>
<td>GI Issues</td>
<td>Nilotinib, Dasatinib</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>Cardio-vascular</td>
<td>Bosutinib</td>
<td>Nilotinib, Dasatinib</td>
</tr>
<tr>
<td>Peripheral arterial</td>
<td>Bosutinib (Dasatinib?)</td>
<td>Nilotinib</td>
</tr>
<tr>
<td>Liver</td>
<td>Dasatinib (Nilotinib?)</td>
<td>Bosutinib</td>
</tr>
<tr>
<td>Renal</td>
<td>Nilotinib (Dasatinib?)</td>
<td>Bosutinib</td>
</tr>
</tbody>
</table>

CCyR by Mutations in CML Treated with 2nd Generation TKI after IM Failure

- 86/169 (51%) pts treated had mutation
- CP 30/59 (51%), AP 41/71 (58%), BP 15/39 (38%)
- IC50 for dasatinib, nilotinib predictive for response in CP and AP

Switch to Nilotinib 400 BID after Imatinib or Nilotinib 300 BID – ENESTnd Extension

- ENESTnd extension: option to change therapy for suboptimal response or treatment failure (ELN 2009)
- Median follow-up 19 months

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>TKI</th>
<th>Eligible, n</th>
<th>Enrolled, n (%)</th>
<th>Discontinued, n (%)</th>
<th>CCyR&lt; %</th>
<th>MMR&lt; %</th>
<th>MMR (CCyR baseline)&lt; %</th>
<th>Grade 3-4 AE&lt; %</th>
<th>Discontinue b/o AE&lt; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Imatinib</td>
<td>57</td>
<td>35 (61)</td>
<td>13 (37)</td>
<td>58</td>
<td>32</td>
<td>25</td>
<td>54</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Nilotinib 300</td>
<td>28</td>
<td>19 (68)</td>
<td>5 (26)</td>
<td>33</td>
<td>39</td>
<td>42</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

Criteria for Failure and Suboptimal Response to Imatinib – ELN 2013

- ENESTnd extension: option to change therapy for suboptimal response or treatment failure (ELN 2009)
- Median follow-up 19 months

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Failure</th>
<th>Response</th>
<th>Optimised</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>No CHR, And/or Ph+&gt;50, And/or Ph=35-95, And/or Ph&lt;10</td>
<td>BCR-ABL &lt;10%, And/or Ph=35-95, And/or Ph&lt;10, And/or Ph=35-95</td>
<td>BCR-ABL ≤10%, And/or Ph&lt;35</td>
</tr>
<tr>
<td>6</td>
<td>BCR-ABL &gt;10% And/or Ph&gt;35, And/or Ph=1-15</td>
<td>BCR-ABL &lt;10%, And/or Ph=1-15, And/or Ph&lt;10, And/or Ph=35-95</td>
<td>BCR-ABL &lt;1%, And/or Ph&lt;35</td>
</tr>
<tr>
<td>12</td>
<td>BCR-ABL &gt;1% And/or Ph&gt;10</td>
<td>BCR-ABL &lt;0.1-1%, And/or Ph&lt;0.5</td>
<td>BCR-ABL &lt;0.1%</td>
</tr>
<tr>
<td>Any</td>
<td>Loss of CHR And/or CCyR And/or MMR (MMR And/or CCyR baseline)</td>
<td>CCyR&lt; (7, or 7q-), And/or MMR (MMR And/or CCyR baseline)</td>
<td>BCR-ABL &lt;0.1%</td>
</tr>
</tbody>
</table>

Hughes et al. Haematologica 2014; 99: 1204-11
Baccarani et al. Blood 2013; 122: 872-84
Switch to Nilotinib vs HD-Imatinib in CP-CML with Suboptimal Response - LASOR

Response, %

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib (n = 96)</th>
<th>Imatinib (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-mo CCyR</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>Before crossover</td>
<td>50</td>
<td>36</td>
</tr>
<tr>
<td>24-mo CCyR</td>
<td>51</td>
<td>61</td>
</tr>
<tr>
<td>Before crossover</td>
<td>51</td>
<td>25</td>
</tr>
<tr>
<td>12-mo MMR</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>Before crossover</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>24-mo MMR</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Before crossover</td>
<td>36</td>
<td>21</td>
</tr>
</tbody>
</table>

AE leading to discontinuation* 8 + 9 1 + 0


Selective Dose Escalation and Early Switch for CML Therapy

* 210 pts: cohort 1 (n=105) IM 600 ⇒ IM 800 ⇒ Nil; cohort 2 (n=105) IM 600 ⇒ Nil
* Median follow-up: cohort 1 = 33 mo, cohort 2 = 14 mo
* Still on Rx: Cohort 1 84% (55% IM, 29% Nil); cohort 2 89% (55% IM, 33% Nil)

Sequential Frontline Treatment for CML - TIDEL II

* 210 pts enrolled (105 Cohort 1, 105 Cohort 2)
* Median age 40 yrs (24-65 yrs)
* Median follow-up 40 months
* Outcome:
  - 24-month MMR 73%, MR4.5 25%
  - 3 year OS 96%, TFS 95%
  - Treatment @ 24-months: imatinib 55%, nilotinib 30%, discontinuation 15%

Deep Molecular Response Prediction in CML Molecular Response: sustained MR4.5

* The equation for “best fit average” PCR:
  \[ \log_{10}(PCR) = -0.2154 \times (\text{Months}) - 0.1161 \]

* The equation for “minimum acceptable” PCR:
  \[ \log_{10}(PCR) = -0.2248 \times (\text{Months}) + 1.5052 \]

<table>
<thead>
<tr>
<th>Time point</th>
<th>Best fit average</th>
<th>Minimum acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>0.173</td>
<td>6.775</td>
</tr>
<tr>
<td>6 months</td>
<td>0.039</td>
<td>1.434</td>
</tr>
<tr>
<td>9 months</td>
<td>0.009</td>
<td>0.304</td>
</tr>
<tr>
<td>12 months</td>
<td>0.002</td>
<td>0.064</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time point</th>
<th>Best fit average</th>
<th>Minimum acceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>0.173</td>
<td>6.775</td>
</tr>
<tr>
<td>6 months</td>
<td>0.039</td>
<td>1.434</td>
</tr>
<tr>
<td>9 months</td>
<td>0.009</td>
<td>0.304</td>
</tr>
<tr>
<td>12 months</td>
<td>0.002</td>
<td>0.064</td>
</tr>
</tbody>
</table>

ENESTd - Probability of Sustained MR4.5

* Cumulative incidence MR4.5: Nil 600 56%, Nil 800 55%, Imatinib 33%
ENESTcmr: Results

* 207 pts with CML CP treated with imatinib ≥2 years, in CCyR with persistent disease by PCR
* Randomized to continue imatinib vs change to nilotinib.

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Nilotinib (n = 104)</th>
<th>Imatinib (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed CMR 12 mo&lt;sup&gt;*&lt;/sup&gt;</td>
<td>12.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Confirmed CMR 24 mo</td>
<td>22.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Cumulative 24-mo MR&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>42.9</td>
<td>20.8</td>
</tr>
<tr>
<td>Confirmed MR&lt;sup&gt;4.5&lt;/sup&gt;</td>
<td>25.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Undetectable</td>
<td>31.7</td>
<td>17</td>
</tr>
<tr>
<td>Adverse event(s)</td>
<td>11.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Cardiovascular events by 36-mo&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>


Rate of Sustained MR<sup>4</sup> After ≥ 2 Years of 2<sup>nd</sup> Line Nilotinib - ENESTcmr

- Pts with ≥2 yrs of 2<sup>nd</sup> line nilotinib who achieved MR<sup>4</sup>, n (%)<sup>a</sup>
  - At any time 41 (39)
  - By 3 years 39 (38)

- Pts with ≥2 yrs of 2<sup>nd</sup> line nilotinib with MR<sup>4</sup> maintained for ≥ 1 year<sup>b</sup> n = 26

- Rate ITT population<sup>a</sup> 25%

- Rate among pts who achieved MR<sup>4</sup> by 3 yrs (n = 39) 67%

ENESTnd - Probability of Sustained MR4.5

- Cumulative incidence MR4.5: Nil 600 56%, Nil 800 55%, Imatinib 33%

ENESTcmr Cardiovascular Events

<table>
<thead>
<tr>
<th>Patients With a Cardiovascular Event, n (%)</th>
<th>Nilotinib (n = 101)</th>
<th>Imatinib Up to Crossover (n = 103)</th>
<th>After Crossover (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13 (13)</td>
<td>2 (2)</td>
<td>3 (7)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Ischemic cerebrovascular event</td>
<td>4 (4)</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>7 (7)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients with multiple occurrences of any AE were counted only once in the total. Hughes et al. ASH 2015

Change (and Its Consequences)
Switch to Nilotinib for Low-Grade AEs with Imatinib

The ENRICH Trial

- 52 pts on imatinib with G1/2 non-hematologic AE persisting >2 mo or recurred >3x despite best supportive care
- Switch to nilotinib 300 mg BID
- 132/210 (63%) AEs resolved, 6% improved, 3% worsened
- 85% of patients improved by 12 cycles
- 30 pts (58%) improved all symptoms (6% none)
- 50% improved QoL (14% worsened)

However:
- 85% had nilotinib-related AEs; 31% grade 3
- 44% dose reduction/interruption; 15% discontinued

Cortes et al. CLML 2016; 16: 286-96

ATP Binding Site Mutations

- T315I
- E255K
- F359V
- Y253H
- G250H

Myristoyl Binding Site Mutations

- A337V
- P465S
- V468F

Proliferation IC50 Profiles in Ba/F3 BCR-ABL1–Mutant Lines

- 0.0001
- 0.001
- 0.01
- 0.1
- 1
- 10

WT

- Nilotinib
- ABL001

ABL001 and Classical TKIs Exhibit Different Mutation Profiles

Phase 1 ANL001 - Responses With Single-Agent BID in Patients With ≥3 Months Exposure on Study

- 47/77 (61%) patients treated with single-agent ABL001 BID were resistant to last TKI
- MMR: 13% and 38% by 6 and 12 months
- 8/10 (80%) with >35% Ph+ achieved CCyR by 6 months
- 4/10 patients with T315I and >35% Ph+ achieved CCyR by 6 mo

Hughes et al. ASH 2016; abstract #625

Combination of ABL001 and Nilotinib Prevents the Emergence of Resistance

- KCL-22 CML Xenograft
- Nilotinib (75mg/kg) BID
- ABL001 (30mg/kg) BID
- Nilotinib (75mg/kg) BID + ABL001 (30mg/kg) BID
- Dosing stopped on day 77, all mice remain disease free >176 days

Wylie A et al, Blood 2014: Abstract #398

PF-114 –3rd Generation Inhibitor of Bcr-Abl

- 3rd generation Abl inhibitor, structural analog of ponatinib
- Rationally designed to avoid inhibition of off-target kinases

Turkina et al. ASH 2017; abstract #895

Phase 1 of PF-114 in CML

- 3rd generation Abl inhibitor, structural analog of ponatinib
- Rationally designed to avoid inhibition of off-target kinases

- 24 pts with CML any phase with failure to ≥2 TKI or with T315I

<table>
<thead>
<tr>
<th>CML Phases</th>
<th>Mutation</th>
<th>N</th>
<th>CHR</th>
<th>MCyR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic</td>
<td>T315I</td>
<td>9</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Chronical</td>
<td>All</td>
<td>21</td>
<td>36</td>
<td>4/11</td>
</tr>
<tr>
<td>Accelerated</td>
<td>T315I</td>
<td>1</td>
<td>0</td>
<td>0/1</td>
</tr>
<tr>
<td>Blast</td>
<td>T315I</td>
<td>1</td>
<td>0</td>
<td>0/1</td>
</tr>
</tbody>
</table>

- No DLT at doses up to 500 mg
- Main AE rash: 13 grade 2, 4 grade 3 (1 DLT)
- No cardiac events (54% high- to fatal-risk per European SCORE)
**Good Outcome: Just in Clinical Trials?**

- 65 pts treated off protocol & 71 on protocols
- Imatinib 400 mg; Median f/u 51 mo

<table>
<thead>
<tr>
<th>Metric</th>
<th>On protocol</th>
<th>Off protocol</th>
<th>US Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 [15-79]</td>
<td>49 [15-84]</td>
<td></td>
</tr>
<tr>
<td>High-risk Sokal</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3-mo MCyR</td>
<td>71</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>12-mo CCyR</td>
<td>84</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>12-mo MMR</td>
<td>30</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>5-yr EFS</td>
<td>86</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>5-yr TFS</td>
<td>96</td>
<td>94</td>
<td></td>
</tr>
<tr>
<td>5-yr OS</td>
<td>90</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Median income, $</td>
<td>45,735</td>
<td>44,606</td>
<td>42,148</td>
</tr>
<tr>
<td>Education HS or less</td>
<td>42</td>
<td>43</td>
<td>48</td>
</tr>
<tr>
<td>Uninsured</td>
<td>10</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

*Yilmaz M, et al. CLML 2013; 13: 693-9*

**OS and PFS of CML-CP Patients Treated with First-line TKI**

- 418 patients treated in community setting in US
- As any recommended monitoring time during the first 13 months, 57-69% of patients did not have a PCR

**Sequential TKI in CML Conclusions**

- Sequential TKI Therapy is standard
- Multiple strategies available
- Define goals, assess pros and cons
- Short-term changes vs long-term outcomes
- Single endpoint vs all-inclusive evaluation

*Only the wisest and stupidest of men never change*

Confucius
Questions?

jcortes@mdanderson.org

713-794-5783