NEW AGENTS FOR HEMATOLOGIC MALIGNANCY TREATMENT: NEWLY APPROVED AGENTS AND EXPANDED INDICATIONS

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How the Experts Treat Hematologic Malignancies
Las Vegas, NV
March 16, 2017
Disclosures

• No disclosures
Objectives

• Recognize common components of generic drug names
• Identify resources for newly approved agents and for expanded indications
• Identify new agents approved to treat hematologic malignancies
What to Know

• Know the type of the drug
  – Monoclonal antibodies
  – Small molecules
  – Vaccines
  – Cytotoxic agents
• Know the generic name: Often challenging to pronounce but provides you information about the drug
• Know the target: What it does normally in the body, helps to indicate side effects
• Know if the drug is personalized: Based on genetic/genomic results/abnormalities
Resources for New Agents and Expanded Indications

• Food and Drug Administration (http://www.centerwatch.com/drug-information/fda-approved-drugs/)
• National Comprehensive Cancer Network guidelines (www.nccn.org)
• National Cancer Institute (www.cancer.gov)
Monoclonal Antibodies = mab

- Origin of monoclonal antibodies:
  - Mo = mouse (blinatumomab)
  - Xi = chimeric: cross of mouse and human (rituximab)
  - Zu = humanized (alemtuzumab)
  - U = fully human (daratumumab)

- Target helps guide knowledge of common side effects:
  - Tu = target is on the tumor cell: blinatumomab
  - Ci = target is circulatory or blood vessels: bevacizumab
  - Li or i = immunomodulator: pomalidomide
Small Molecules

• Many are oral agents
  – Adherence
  – Drug/drug interactions and drug/food interactions
  – Patient education
• Activity is intracellular
- Nibs

- Nibs and tinibs

- Tyrosine kinase inhibitors: block enzymes (BCR-ABL in CML) found on cancer cells

- Oral agents
  - Adherence
  - Drug/drug and drug/food interactions
  - Patient education

- Examples: Imatinib, dasatinib, nilotinib, bosutinib, ponatinib, ibrutinib
-Zomibs

- Small molecule proteasome inhibitor
- May be oral, subcutaneous or IV
- IV: Low chance of infusion reaction-not a monoclonal antibody
- PO: first on market last year
  - Adherence
  - Drug/drug
  - Drug/food interactions
  - Patient education
- Examples: Carfilzomib, bortezomib, ixazomib
- Inostat

- Small molecule: histone deacetylase (HDAC) inhibitors
- May be IV or oral
- IV: low risk of infusion reaction, not a monoclonal antibody
- PO:
  - Adherence
  - Drug/drug
  - Drug/food interactions
  - Patient education

Examples: Vorinostat, belinostat, panobinostat
- Toclax

- Small molecule: BCL-2 inhibitor
- Oral agent
- PO:
  - Adherence
  - Drug/drug
  - Drug/food interactions
  - Patient education
- Example: Ventoclax
Vaccines/Cytotoxic therapy

- Only currently approved vaccine for cancer treatment is **sipuleucel-T** to treat metastatic prostate cancer
- HPV vaccine: **Gardasil®**
- Hepatitis B vaccine
- CMV vaccine study
- Cytotoxic therapy
Agents approved in 2014
(Chronic Lymphocytic Leukemia)

- **Idelalisib** (Zydelig®) for the treatment of patients with relapsed chronic lymphocytic leukemia, in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

- **Ofatumumab**: (Arzerra®) in combination with chlorambucil, for the treatment of previously untreated patients with chronic lymphocytic leukemia, for whom fludarabine-based therapy is considered inappropriate

- **Ibrutinib** (Imbruvica®) for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy
Agents approved in 2014
(Acute lymphocytic leukemia/T-cell lymphoma/Polycythemia Vera)

- **Blinatumomab**: (Blincyto®) for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia

- **Belinostat** (Beleodaq®) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma

- **Ruxolitinib**: (Jakafi®) for the treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea
Agents approved in 2015
(Multiple Myeloma)

- **Elotuzumab**: (Empliciti®) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies.

- **Ixazomib**: (Ninlaro®) in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. Ixazomib is the first approved oral proteasome inhibitor.

- **Daratumumab**: (Daralex®) administered as a single agent for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent, or who are double-refractory to a PI and an immunomodulatory agent.
Agents approved in 2015
(Multiple Myeloma continued)

• **Panobinostat**: (Farydak®) in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

• **Carfilzomib**: (Kyprolis®) in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma who have received one to three prior lines of therapy.
Agents approved in 2015  
(Hodgkin Lymphoma/Waldenstrom’s macroglobulinemia/biosimilar)

• **Brentuximab vedotin**: (Adcetris®) for the post-autologous hematopoietic stem cell transplantation (auto-HSCT) consolidation treatment of patients with classical Hodgkin lymphoma (HL) at high risk of relapse or progression.

• **Ibrutinib**: (Imbruvica®) for the treatment of patients with Waldenstrom’s macroglobulinemia.

• **Filgastrim-sndz**: (Zarxio® Injection) as a biosimilar to US-licensed Neupogen for the five indications for which US-licensed Neupogen is approved. The formulation of ZARXIO differs from that of US-licensed Neupogen in one inactive component.
Agents approved in 2015 (antifungal)

- Isavuconazonium sulfate (Cresemba®): is indicated for the treatment of invasive aspergillosis and invasive mucormycosis in adults.
Agents approved in 2016
(Chronic lymphocytic leukemia and supportive care)

- **Ventoclax**: (Venclexta®) for the treatment of patients with chronic lymphocytic leukemia with 17p deletion who have received at least one prior therapy

- **Ofatumumab**: (Arzerra ® Injection) for extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive chronic lymphocytic leukemia

- **Defibrotide sodium**: (Defitelio®) for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstructive syndrome, with renal or pulmonary dysfunction following hematopoietic stem cell transplantation
Agents approved in 2016
(Multiple Myeloma/Lymphoma)

- **Daratumumab**: (Daralex®) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received minimum of one prior therapy.

- **Nivolumab**: (Opdivo®) for the treatment of patients with classical Hodgkin lymphoma relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplant brentuximab vedotin.

- **Obinutuzumab**: (Gazyva®) for use in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen.
Agents approved in 2017
(Hodgkin Lymphoma)

• Pembrolizumab (Keytruda®) received accelerated approval for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or those who have relapsed after three or more prior lines of therapy.
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Breakthrough Therapy Designation by the FDA in 2016

- **Ruxolitinib**: (Jakafi®): for the treatment of patients with acute graft-versus-host disease (GVHD)
Future Directions

• Further expanded use of current agents
• Immunotherapy
  – CAR T-cell therapy
• Clinical trials
References

- Food and Drug Administration (http://www.centerwatch.com/drug-information/fda-approved-drugs/)
- National Comprehensive Cancer Network guidelines (www.nccn.org)
- National Cancer Institute (www.cancer.gov)
How the Experts Treat Hematologic Malignancies
Las Vegas, NV
March 16, 2017
Objectives

• Define clinical trials
• Identify some available City of Hope hematology clinical trials to review clinical trial / patient eligibility considerations
• Describe patient awareness and involvement in clinical trials
What is a Clinical Trial?

- A prospective research study of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments or devices)

- Used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective

- Also known as interventional or experimental research
Number of Registered Studies Over Time and Some Significant Events (as of March 12, 2017)

Source: https://ClinicalTrials.gov

Key:

ICMJE: Indicates when the International Committee of Medical Journal Editors began requiring trial registration as a condition of publication (September 2005)

FDAAA: Indicates when the expanded registration requirements of FDAAA began and were implemented on ClinicalTrials.gov (December 2007)
Roles in Clinical Trials

• Principal Investigator - Individual overseeing study
• Sponsor – Hospital or other organization, pharmaceutical companies, universities, National Institutes of Health (e.g. National Cancer Institute), other
  – Targeted number of patients to enroll
  – Patient inclusion and exclusion criteria
  – Start and stop dates
  – Stopping criteria
• Clinical Research Nurse (CRN)
Phases (ClinicalTrials.gov)

- **Phase I**
  - Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

- **Phase II**
  - The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.

- **Phase III**
  - The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

- **Phase IV**
  - Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.
**DISCOVERY SCIENCE**

- **Studies in the lab**
- **Studies in animal models**

**CLINICAL TRIALS**

**PHASE 0:** first study in a patient to see how the body metabolizes the drug

**PHASE I:** study of a small number of patients to evaluate safety and dosing

**PHASE II:** study of more patients to assess drug’s effectiveness and further evaluate safety

**PHASE III:** study with the largest number of patients to confirm drug is effective and safe; assess side-effects and compare this drug to the current treatments

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Leukemia

- 49 trials available at City of Hope
- Targeted therapies
- Disease-based trials (AML, ALL, CML)
- Drugs for induction, consolidation, maintenance therapies. Usually in combination with known therapies
- Trials for relapse, refractory disease, survivorship, long-term follow-up
# Leukemia Trial 15367

<table>
<thead>
<tr>
<th>Title: Pilot Study of Crenolanib Combined with Standard Salvage Chemotherapy in Subjects with Relapsed/Refractory Acute Myeloid Leukemia</th>
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| Purpose of This Research Study: Patients eligible to participate in this study will be asked to consider a research consent form which includes the following information: 

*This study is being done to find out if it helps to add the investigational drug called crenolanib to standard treatment with high-dose cytarabine and mitoxantrone, (HAM) in patients with leukemia that has progressed despite previous treatments.* This document describes the procedures and risks for treatment with the investigational drug crenolanib. In addition to crenolanib, you are to have treatment with mitoxantrone and high-dose cytarabine. These two chemotherapy drugs are considered standard treatment for acute myeloid leukemia (AML). |
| Background: Crenolanib has been tested in more than 52 patients who have acute myeloid leukemia. Promising results have been seen among these patients. However, crenolanib needs to be tested in more patients to confirm these results. Researchers do not know whether it will work to improve your leukemia. Although the standard chemotherapy regimen has been approved by FDA, adding crenolanib to your regular chemotherapy has not been tested before. |
| Contact: Please call 1-877-482-HOPE(4673) or click [here](#) to contact City of Hope to receive information on new patient services and referral to one of our physicians. |
### GENERAL INFORMATION

- **Protocol Owner (Primary Sponsor):** AROG PHARMACEUTICALS, INC
- **Protocol Sponsor Group:** Industrial
- **Study ID Assigned by Primary Sponsor:** ARO-011
- **PI Department:** Hematology & Hematopoietic Cell Transplantation
- **WIRB 20152580 Current Version:** 06/07/2016
- **WIRB 20152580 Current Version Date:** 6/7/2016
- **GCRC Sponsored?** No
- **Summary 4 Category:** Agent / Device
- **Cancer Center Program:** Hematologic Malignancies
- **CTO Disease Cluster:**
- **Disease Program:** Leukemia/MDS

### PROTOCOL ELIGIBILITY

- **Min Age - Max Age:** 18 - 100
- **Min Stage - Max Stage:**
- **KPS (Minimum):** 50
- **Eligible Diagnoses:** Myeloid Leukemia, Acute Myeloid Leukemia (AML)

### PROTOCOL DESIGN

- **Study Type:** Non-Adjuvant Rx
- **Study Design:** Pilot
- **Dose Escalating?** No
- **Treatment Involved?** Yes
- **Modalities Involved:** Chemotherapy, Drug
- **Cancer Related?** Yes
- **Transplant Related Study?** No
- **Precautioned/Prohibited Medications?** Yes
- **COH Estimated Annual Accrual:** 5
- **COH Target Accrual:** 10
- **Total Study Accrual:** 72
- **Estimated Months of Accrual:** 24
Lymphoma

- 116 trials at City of Hope
- Disease specific
  - Diffuse large B cell lymphoma
  - Mantle cell lymphoma
  - Hodgkin lymphoma
  - Non Hodgkin lymphoma
  - Follicular lymphoma
  - Cutaneous T Cell Lymphoma
  - Burkitts lymphoma
  - Chronic lymphocytic leukemia
  - Hairy cell leukemia
  - Waldenstrom’s Macroglobulinemia
- Trials for untreated disease, previously treated disease, salvage, consolidation
## Lymphoma Trial 16006

| Purpose | This open-label, **Phase I study will evaluate the safety, tolerability, and pharmacokinetics of increasing doses of DCDS0780A** in patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. In the combination portion of the study, the safety and tolerability of DCDS0780A in combination with rituximab will be assessed. |
| Study Type: | Interventional |
| Study Design: | Allocation: Non-Randomized  
Intervention Model: Single Group Assignment  
Masking: Open Label  
Primary Purpose: Basic Science |
| Official Title: | An Open-label, Multicenter, Phase 1/1B Dose Escalation Study Evaluating the Pharmacokinetics, Safety, Tolerability, and Preliminary Efficacy of DCDS0780A, Alone or in Combination With Rituximab, in Patients With Relapsed/Refractory B-cell Non-Hodgkin's Lymphoma |
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### PROTOCOL ELIGIBILITY

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### PROTOCOL DESIGN

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Multiple Myeloma / AL Systemic Amyloidosis

- 29 trials at City of Hope
- Trials
  - New diagnosis
  - Smoldering myeloma
  - Relapse and refractory disease
  - AL Systemic Amyloidosis
**Myeloma Trial 13336**

<table>
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<th>Title: A Randomized Phase III Study Comparing Conventional Dose Treatment Using a Combination of Lenalidomide, Bortezomib and Dexamethasone (RVD) to High-Dose Treatment with Peripheral Stem Cell Transplant in the Initial Management of Myeloma in Patients up to 65 Years of Age.</th>
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**Purpose of This Research Study:**
Patients eligible to participate in this study will be asked to consider a research consent form which includes the following information:

You have been asked to participate in this research study because you have been newly diagnosed with multiple myeloma. The purpose of this research study is to evaluate the side effects and effectiveness of a combination of three drugs called lenalidomide, bortezomib and dexamethasone (RVD) with or without autologous stem cell transplantation, followed by lenalidomide therapy as a possible treatment for newly diagnosed multiple myeloma. Another purpose is to determine the quality of life of research participants receiving the treatments given on this study. Your treatment on this study is expected to last until your multiple myeloma worsens and you will continue to be followed for up to 3 years.

**Background:**
This research study is a Phase III clinical trial. Phase III clinical trials compare different study treatments to see if one is better for treating the type of cancer you have.

For fifteen years, high-dose therapy (HDT) has been the standard treatment for multiple myeloma in younger patients. In the 1990s, several randomized studies demonstrated the superiority of high-dose treatments versus conventional chemotherapies in terms of response, event-free survival and overall survival. HDT is better than standard therapy because patients treated with HDT are more likely to respond to treatment.

In this research study, we are looking to explore the drug combination, lenalidomide, bortezomib and dexamethasone alone or when combined with autologous stem cell transplantation to see what side effects it may have and how well it works for treatment of newly diagnosed multiple myeloma. It is expected that about 660 people will take part in this research study.

**Contact:** Please call 1-877-482-HOPE(4673) or click [here](#) to contact City of Hope to receive information on new patient services and referral to one of our physicians.
### GENERAL INFORMATION

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### PROTOCOL ELIGIBILITY

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Transplant Trials

- 38 trials at City of Hope
- Trials
  - Overall transplant
  - Disease specific
  - Transplant type
    • Conditioning
    • Stem cell source
  - aGVHD
  - cGHVD
  - Infectious disease
  - Supportive care regimens
**Title:** Multi-Center, Open-Label Randomized Study of Single or Double Myeloablative Cord Blood Transplantation with or without Infusion of Off-the-Shelf Ex Vivo Expanded Cryopreserved Cord Blood Progenitor Cells in Patients with Hematologic Malignancies (FH2603)

**Purpose of This Research Study:**
You have been asked to participate in this research study because you have leukemia, or myelodysplastic syndrome and are eligible for an umbilical cord blood transplant. **The purpose of this research study is to see how long it takes for research participants who receive expanded cells (Delta1-cultured Cryopreserved Umbilical Cord Blood Cells or DCC-UCB), along with one or two unexpanded cord blood units, recover their blood counts as compared with research participants who receive one or two unexpanded cord blood units without expanded cells.** Expanded cells are cells from a cord blood unit that are cultured (grown) in the lab in order to greatly increase the number of cells available for the transplant. We will also study which of the two or three cord blood units makes up the subject's new blood system, how long subjects stay in the hospital after transplant, how the immune system is rebuilt, and how many infections they get. Your treatment and follow-up on this study will be at least two years after your transplant.

**Background:**
Transplantation with cord blood is a standard therapy in many transplant hospitals around the world. Previous experience with cord blood stem cell transplantation has led to extended disease-free survival or cure for some patients.

In a laboratory at Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, researchers have developed a way of growing or “expanding” the number of cord blood cells in the lab so that there are more cells available for transplant. In the expansion process, cells from a cord blood unit are cultured (grown) in the lab in a controlled environment for 14-16 days, during which their number increases to several hundred times the original amount. At the end of the culture period, the cells are frozen and stored for later use. They have already done two small studies using cord blood cells grown in the lab. The first study used partially HLA-matched expanded cells that were grown in the lab while the patient waited for transplant. In the second study the expanded cells had already been made and then frozen for use. In that trial the expanded cells were given without matching the patient and expanded cells for “HLA type” (also known as tissue typing). In 29 patients who have received the expanded cells as part of their transplants in these two studies so far, there have been no unexpected side effects.

**Contact:**
Please call 1-877-482-HOPE(4673) or click [here](#) to contact City of Hope to receive information on new patient services and referral to one of our physicians.
### General Information

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<tr>
<td>Protocol Owner</td>
<td>FRED HUTCHINSON CA AND RES CTR</td>
</tr>
<tr>
<td>(Primary Sponsor)</td>
<td></td>
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<tr>
<td>Protocol Sponsor</td>
<td>NCI Approved External Peer Review</td>
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<td>Study ID Assigned by</td>
<td>FHCRC 2603</td>
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<td>PI Department:</td>
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### Protocol Eligibility

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<tbody>
<tr>
<td>Min Age - Max Age:</td>
<td>0 - 45</td>
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<td>Min Stage - Max Stage:</td>
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<td>KPS (Minimum):</td>
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<td>Eligible Diagnoses:</td>
<td>Lymphoid Leukemia, NOS Myeloid Leukemia, NOS Other Hematopoietic, Myelodysplastic Syndrome (including JMML)</td>
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### Protocol Design

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<td>Treatment Involved?:</td>
<td>Yes</td>
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<td>Modalities Involved:</td>
<td>Hematopoietic Cell Transplantation, Other - Umbilical cord transplantation, Drug, Radiation, Other - Cord Blood Transplant</td>
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<td>Yes</td>
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<td>Transplant Related Study?:</td>
<td>Yes</td>
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<td>Precautioned/Prohibited Medications?:</td>
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<td>36</td>
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How do Patients Find a Clinical Trial?

- Many patients become aware of trials through online searches or general media sources (nih.gov)
- Physicians and providers have knowledge of available trials
- Research RNs review trials with patients and assist with informed consent
- Physicians and providers have standing meetings (usually weekly) to discuss patients who may be eligible for trials
- 32% indicate they are willing to participate in a clinical trial if asked (nih.gov)
Responsibility of RNs When Treating Patients on Clinical Trials

- Reviews the details of the clinical trial with patient and family
- Promotes ethical care, informed consent
- Delivers therapies safely
- Monitors for and manages side effects and adverse events
- RN needs to know
  - Prohibited medications
  - Concomitant medications
  - Precautioned medications
  - Schema / treatment plan
  - Specific labs, pharmacokinetic studies
References

- Hepner, E. [Personal interview by E. Boettcher, December 20, 2016]