AN EVENING WITH THE EXPERTS @ INDY HEMATOLOGY REVIEW 2019
State of the Art 2020: Emerging Therapies in Blood Cancers and Blood Disorders

Ruemu E. Birhiray, MD
Program Chair
CEO, Indy Hematology Education, Inc
Partner, Hematology Oncology of Indiana, American Oncology Network, PA, Indianapolis, IN
Clinical Professor of Medicine,
Marian University College of Medicine, Indianapolis, IN
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Treatment Strategies for Blood Cancers

- **Chemotherapy:** Chemicals designed to kill rapidly dividing and cancer cells.

- **Tyrosine Kinase Inhibitors/Signal Transduction Pathway Inhibitors:** Drugs designed to inhibit driver pathways that promote cancer cell growth.
Treatment Strategies for Blood Cancers

- **Monoclonal antibodies:** Antibody proteins targeting cancer cell surface proteins
- **Antibody Drug Conjugates:** Antibodies linked to chemotherapeutic agents targeting cell surface proteins to improve directed killing of cancer cells
- **BITE antibodies:** Antibodies designed to link immune T-cells to target cancer cells
- **CAR-T cells:** Individually designed T cells with antibody receptors targeting cancer cells
**Myeloma: Initial Therapy**

**ADDING DARATUMAB TO CHEMO:**

- **GRiffin Trial:** Daratumumab + VRd vs VRd Alone for Transplant-Eligible Myeloma: sCR by the end of treatment: 42.4% vs. 32.0%, no effect on stem cell collection.

- **MASTER Trial:** Daratumumab + KRd in Transplant-Eligible Myeloma: 21% African American, 51% High Risk.
  - 39% sCR post induction and 95% at MRD-based consolidation.
- **HOVON 143 Trial:** Non transplant, frail/unfit patients with Myeloma: Ixazomib/daratumumab/low-dose dexamethasone, ORR: 74%; mPFS: 23 mos.

**High-Risk Smoldering Myeloma GEM-CESAR:**

KRD, N=90, End of therapy response (Induction/ASCT/Consolidation): 76% ≥ CR, 63% MRD negative.
TARGETING MYELOMA CELL PROTEINS
RELAPSED/REFRACTORY MYELOMA

ANTI-CD38 ANTIBODY DARATUMUMAB

- CANDOR: Carfilzomib, Dexamethasone ± Daratumumab in relapsed Myeloma
- ORR 84.3% vs 74.7%, > VGPR 69.2% vs 48.7%, > CR 28.5% vs. 10.4%, MRD negative at 12 mos 17.6% vs. 3.9% (37% reduction in risk of progression/death, MRD-negative CR @12 mos ~10-fold > with KdD vs Kd)

BCMA: B-cell maturation antigen: Cell surface protein required for myeloma cell survival/signaling

CAR T THERAPY:

- CARTITUDE-1: JNJ-4528 CAR T-cells targeting domains for increased for improved binding:
  - ORR: 100% with ≥ 69% CR rate, 100% of evaluable patients MRD negative.
- LEGEND-2: LCAR-B38M CART-T-cells, ORR 88%, mPFS: 19.9 mos, mOS: 36.1 mos

BITE ANTIBODY: “Immune Matchmaker”

- CC93269: Humanized, IgG1 T-cell engager that binds BCMA and CD3ε on T-cells
  - ORR in 10-mg group: 88.9% (sCR/CR: 44.4% with 100% MRD), CRS: 76.7%, majority grade 1/2.
TARGETING MYELOMA CELL PROTEINS  
RELAPSED/REFRACTORY MYELOMA

ANTIBODY DRUG CONJUGATE (ADC): ANTIBODIES BEARING TOXINS

- **DREAMM-2**: Belantamab mafodotin, BCMA targeting ADC, Phase II, N=196, ORR 31-34%
- **DREAMM-6**: Belantamab mafodotin + Vd (ASCO2020): ORR of 78%, VGPR of 50%, and CBR of 83%

PROMOTING CANCER CELL DEATH

**XPO-1**: INHIBITING CANCER CELL SURVIVAL BY PROMOTING RETENTION OF CANCER KILLING PROTEINS IN CELLS

- **STOMP**: Phase I/II, Selinexor, Pomalidomide/Dexamethasone in R/RM, N=51, ORR 56%, CBR 78%

**BCL-2**: INHIBITING CANCER CELL ANTI-DEATH PROTEINS

- **Phase I/II**: Venetoclax + Dexamethasone + Daratumumab± Bortezomib in t(11;14) R/R MM (ASH2019): 48% ≥ PR and 35% ≥ VGPR, 12-mo DoR of 61% for 11mos
- **BELLINI Phase III, Ven+Bort/Dex in RRMM (ASCO 2020)**: Improved PFS, ORR, MRD but worse OS except in t(11;14)
Chronic Leukemia

- **FIRST LINE THERAPY in CLL/SLL**
- **ELEVATE TN**
  - Acalabrutinib ± obinutuzumab significantly improved progression/death compared with obinutuzumab + chlorambucil in initial treatment of CLL, ORR: 93.9 vs 85.5 vs 78.5%, fewer deaths in either acalabrutinib treatment arms.

- **Extended Follow-Up of E1912**: Ibrutinib + Rituximab versus FCR in younger patients with CLL: PFS superior for IR over FCR (HR, 0.39; 95%; P <.0001), Improved PFS in IGHV-unmutated patients.

- **Venetoclax + ibrutinib**
  - First-line, fixed-duration treatment in high-risk CLL/SLL, ≥ 65 yrs of age, High risk CLL, MRD response of 75%.

- **CAPTIVATE**
  - First-line Ibrutinib Plus Venetoclax in CLL/SLL MRD: Blood: 75% and Bone marrow: 72%

- **Acalabrutinib, Venetoclax, and Obinutuzumab (AVO):**
  - Treatment-naive CLL, N=37, 48% undetectable MRD in BM after 8 cycles

- **RELAPSES/REFRACTORY CLL/SLL**

- **LOXO-305**: BRUIN, Next-generation, non-covalent BTK inhibitor: ORR 77%

- **SEQUOIA**: Zanabrutinib, Phase III, Arm C, TN-CLL: N=109, ORR 90%

- **CAR-T THERAPY: TRANSCEND CLL 004**: Lisocabtagene Maraleucel CART-T therapy; ORR: 81.5%, CR 45.5%

- **RELAPSES/REFRACTORY CML (FAILURE AFTER TKI THERAPY)**

- **Asciminib**: Allosteric inhibitor of BCR/abl: Phase I, N=141, MMR 48% (mT315I = 28%)
Lymphoma

- **Immune Engager BiTE:**
  - **GO2971: Mosunetuzumab:** Phase I/Ib Study in Relapsed NHL: Aggressive NHL responses: ORR: 37.1%, CR: 19.4%, Indolent NHL responses: ORR: 62.7%, CR: 43.3%

- **CART- Cells Immunotherapy:**
  - **TRANSCEND NHL 001:** Lisocabtagene Maraleucel in R/R LBCL, ORR: 73%, CR 53%, DoR @ 12: 54.7%, CAR+ T-cells at 1 yr in 53%
  - **ZUMA-2:** Trial of KTE-X19 CAR T-Cell Therapy in Relapsed/Refractory Mantle Cell Lymphoma. N=68, ORR of 93%, CR: 67%. 43% of initial cohort in remission with ≥ 2 years f/u.

- **TARGETED THERAPY FOR R/R INDOLENT LYMPHOMA**
  - **BRUIN:** LOXO-305, Non-Covalent BTK Inhibitor in MCL, N=6, ORR 50% (3/6), CR 17% (1/6)
  - **GO29834:** R/R FL of Polatuzumab vedotin, obinutuzumab and lenalidomide. ORR 83%, CR 61%, 83% PFS @ 12 mo.
  - **Tazemetostat:** EZH2 Inhibitor in R/R FL, N=99, ORR (MT): 45%, (WT) 83%
  - **FiLo:** Idelalisib plus obinutuzumab in R/R Waldenström macroglobulinemia: ORR 69%

- **TARGETED THERAPY FOR T-CELL LYMPHOMA**
  - Cerdulatinib with R/R PTCL and CTCL: Dual inhibition of SYK and JAK, ORR: 35%

- **IMMUNOTHERAPY FOR HODGKINS LYMPHOMA**
  - Brentuximab Vedotin Plus Nivolumab in Hodgkin Lymphoma
    - **First line Therapy:** Older patients, N=18, ORR 100%, CR 77%, mDoR NR
    - **Relapsed/Refractory HD:** N=91, ORR 85%, CR 67%.
Acute Leukemia

**ACUTE MYELOGENOUS LEUKEMIA**

- **MAINTENANCE THERAPY**
  - **QUAZAR AML-001:** Phase III, N=472, CC-486 maintenance vs. placebo, after First CR in ND AML
  - Significant improvement in OS and RFS mOS extended 9.9 mos, and mRFS extended 5.3 mos.
  - **ECOG-ACRIN E2906:** Phase II, 1 yr maintenance Decitabine (3 days/cycle) after CR/Cri after 7+3 (or Clofarabine) induction Older AML Patients. N=120, 87.5% FLT3-ITDneg Superior OS (P = .06), trend to improved DFS (P = .12) compared to observation alone

- **TARGETED THERAPY**
  - **Enasidenib + Azacitidine vs Azacitidine** in ND AML with IDH2 mutations, Phase II, N=
  - Significantly improved ORR (71% vs 42%; P = .0064) and CR (53% vs 12%; P = .0001).
  - **FLAG-IDA Plus Venetoclax:** ND AML or in R/R AML, Phase Ib/II Study, N=30,
  - CR/Cri in R/R AML 70-75%, ND AML 85%, 3 deaths in CR reported. Dose modified study ongoing.

**ACUTE LYMPHOBLASTIC LEUKEMIA**

- **COG AALL1331:** Phase III, Anti-CD19 BITE: Blinatumomab vs Chemotherapy maintenance for children and AYA with R/R B-ALL, N=208.
  - Superior DFS and OS, higher rates of MRD and bridging to HSCT, lower AEs and toxicity
  - **GIMEMA LAL 2116 D-ALBA:** Frontline Dasatinib + Blinatumomab in ND Ph+ ALL, Phase II,
    - N=63, 60.4% CMR/PNQ status after 2 cycles, OS and DFS: 95.2% and 89.7%, @ mF/u  14mos.
  - **M16-106:** Venetoclax Plus Navitoclax in R/R ALL and Lymphoblastic Lymphoma, Phase I, N=45
  - CR/CRi/CRp: 49%, MRD negative CR: 29%, mDoR: 9.1 mos
Myelodysplastic Syndromes and Myeloproliferative Neoplasms

**MPN**

- **Luspatercept (Inflammation protein trap) in Myelofibrosis**: Phase II, N=76, Hg response in all patients independent of RBC transfusion dependence.
  - Effects more profound in patients who also received ruxolitinib.
- **MANIFEST, CPI-0610**, N=54, Phase II
  - Bromodomain and Extraterminal Domain Inhibitor (BETi), onotherapy or “Add-on” to Ruxolitinib, in Refractory or Intolerant Advanced Myelofibrosis.
  - N=54, 24.9% reduction in SV @ 24 weeks and a 58.8% improvement in TSS for TD myelofibrosis.
  - 43% converted from TD to TI following treatment with the combination

**MDS**

- **GFM**: APR-246 Plus Azacitidine in TP53-mutated MDS and AML, Phase II, N=53
  - CR in 49% (MDS: 66%, AML: 44%), MRD (Negative TP53 by NGS): 39%, 100% in CR
- **Venetoclax ± Azacitidine** in MDS: Phase Ib, N=64,
  - ORR: 40% ORR vs 8% with venetoclax only, 12-mo OS with venetoclax + azacitidine was 65%
- **MEDALIST** Long-term analysis: N=229, RBC-TI ≥ 8 Wks
  - Luspatercept-treated patients attained RBC-TI compared with placebo (47.7% vs 15.8%)
Malignant/Non Malignant Hematology

- **Updated Phase III Study of Avatrombopag**: N=49
  - Median cumulative duration of PLT ≥ 50,000/µL (primary endpoint): 12.4 wks with avatrombopag vs 0 wks with placebo (P < .0001)
- **Novel BTKi PRN1008**: R/R Primary or Secondary ITP, Phase I, N=31
  - ORR: 39%, Response rate increased to 54% with PRN1008 BID dosing for ≥ 12 wks
- **Phase III Northstar-3 (HGB-212) Gene Therapy: Betibeglogene Autotemcel** in Severe Transfusion-Dependent β-Thalassemia, Interim results: N=17, 9/11 patients with ≥ 6 mos of follow-up off transfusions for ≥ 3 mos
  - 70.8% Transfusion Independence from wks 5-26, markedly increased Hb, controlled hemolysis.
- **BCL11A Targeted Gene Therapy in Sickle Cell Disease**: N=15, Pilot Study, HSC transduction efficiency ≥ 93%, Effective HbF induction, significantly decreased clinical sickling signs/symptoms
- **Adjuvant Oral Arginine in Pediatric SCD**, in Severe vaso-occlusive pain episodes (VOE) versus placebo, N=68, Statistically significant decrease in mean total opioid dose use, a shorter time-to-crisis resolution, and shorter length of hospital stay, without serious AEs.
- **CARDINAL**: Sutimlimab, first-in-class inhibitor of classical CP, Phase III, in transfusion dependent Cold Agglutinin Disease, N=24
- **Bevacizumab Highly Effective for Chronic Bleeding in Hereditary Hemorrhagic Telangiectasia**
  - N= 140, RBC transfusions and iron infusions decreased by 86% and 66%, with bevacizumab therapy.
- **SOAR**: Fostamatinib, SYK Inhibitor, for Warm Antibody Autoimmune Hemolytic Anemia (wAIHA)
  - N=25, ORR 48% (Hg >10 without transfusion)
Hematopoietic Stem Cell Transplantation and Cellular Therapy

- “Breaking the Glass Ceiling of Age in Transplant in Multiple Myeloma.”
- **Autologous Hematopoietic Cell Transplantation in Older patients with Multiple myeloma.**
  - N=16,000, CIBMTR database. ASCT is safe and effective in patients >70 years, with improved outcomes with 200 mg/m2, compared to 140 mg/M2.
  - Reduced dose Melphalan results in significantly worse outcomes and survival: NRM at 100 days (1% vs 0%; P = .003), PFS at 2 years (64% vs 69%; P = .003) and OS at 2 years (85% vs 89%, P = .01).
- African Americans are twice as likely to have myeloma than Caucasians, but have significantly lower autologous hematopoietic cell transplantation.
- **STaMINA Long-term Follow-up (ASCO2020):** PFS benefit for ASCT/ASCT cohort (in high risk group), No OS difference

- **CAR-Transduced Natural Killer Cells in CD19-Positive R/R Lymphoid Malignancies**
  - Phase I/II, N=17
  - HLA-mismatched anti-CD19 CAR-NK cells derived from cord blood (Potential “OFF THE SHELF” THERAPY).
  - ORR 73%, 7/17 CR (3 CLL, 4 NHL)
  - No CRS, neurotoxicity, or GVHD, or increased inflammatory cytokines, including interleukin-6
Update from ASCO 2020 and Beyond

- **Epcoritamab CD3 x CD20 Bispecific Antibody:** Phase I/II in R/R B-Cell NHL, q1, then q 4 wks s.c, ORR in evaluable patients: DLBCL @ ≥ 12 mg, 50.0%; FL @ ≥ 0.76 mg, 85.7%. Neurotoxicity, 6.9% and CRS, 56.9% (all grade 1/2).
- **ASPEN:** Phase III, in Waldenström’s Macroglobulinemia: Zanubrutinib vs. Ibrutinib, CR + VGPR: IRC, 28.4% vs 19.2% (P = .0921, Primary Endpoint) NS statistically; PFS at 12 mos: 89.7% vs 87.2%; OS at 12 mos: 97.0% vs 93.9%.
  - Lower rates of AF/flutter, bleeding, diarrhea, and HTN, higher rate of neutropenia with zanubrutinib.
- **KEYNOTE-204:** Phase III, in R/R cHL, Pembrolizumab significantly improves PFS vs. Brentuximab vedotin, mPFS: 13.2 vs 8.3 mos (HR: 0.65; 95%; P = .00271). ORR: 65.6% vs 54.2% (P = .0225); mDoR: 20.7 vs 13.8 mos.
- **BOSTON:** Phase III, in RRMM, Selinexor, Bortezomib, and Dexamethasone vs Bortezomib and Dexamethasone: 30% improved PFS, HR 0.70, P = .0075.
- **L-MIND:** Tafasitamab (anti-CD19) + lenalidomide, Phase II, in RR DLBCL, ORR: 60%, CR: 43% and PR;18%.
- **ENDURANCE:** Phase III: Carfilzomib (20/36mg/M2 TW)/Len/Dex vs Bortezomib/Len/Dex without early ASCT, non high risk NDMM similar PFS.
- **KarMMa:** Idecabtagene Vicleucel, R/R Multiple Myeloma, Phase II, N = 158, ORR: 73%; CR: 33%, mDoR: 10.7mos; mPFS: 8.8mos, mOS 19.4mos (CR/SCR: mPFS: 20.2 mos)
What does it all mean? My thoughts

- **PRACTICE changing:**
  - Upfront Daratumumab in transplant eligible MM with RVD, and KRD
  - Belantamab Mafodotin in R/R Myeloma
  - Upfront Acalabrutinib in CLL, and Ibrutinib + Rituximab in younger patients with CLL
  - Venetoclax in t(11:14) RRMM (or NDMM)
  - Blinatumomab maintenance in RR B-ALL
  - Tafasitamab and Lenalidomide in R/R DLBCL
  - Tazemetostat: In EZH2 mutated FL

- **Potentially Practice changing:**
  - Sutimlimab in Cold Agglutininn Disease
  - Maintenance therapy after induction therapy for AML: Decitabine/CC-486
  - Enasidenib in IDH2 mutant NDAML,
  - Upfront Blinatumomab and Dasatinib in ND Ph+ B-ALL
  - Frontline Brentuximab vedotin plus Nivolumab in HL, Pembrolizumab in RR cNHL
  - CAR-T Therapy in Myeloma and KTE-X19 CAR-T in RR MCL
  - Bevacizumab in Hereditary Hemorrhagic Telangiectasia
  - Upfront therapy for High Risk Asymtomatic Multiple Myeloma with Curative Intent?

- **Stay tuned**
  - Mosunetuzumab in RR lymphoma and Cerdulatinib in RR PTCL/CTCL
  - Gene Therapy in SCD and Thalassemia and NK Cell – CAR-T Cell
Co-Chair Indy Hematology Review

Michael C. Wiemann, MD, FACP
President, Clinical
St. John Providence Physician Network
Detroit, Michigan
Multiple Myeloma

Kenneth Anderson, MD
PAST PRESIDENT AMERICAN SOCIETY OF HEMATOLOGY 2017
Kraft Family Professor,
Harvard Medical School, Myeloma
Program Director and Chief, Division of Hematologic Neoplasia,
Dana Faber Cancer Institute, Boston, MA
Waldenström's Macroglobulinemia

Steven P. Treon, MD, PhD
Director, Bing Center for Waldenström's Macroglobulinemia
Professor of Medicine,
Harvard Medical School
Boston, MA
Lymphoma

Sonali M. Smith, MD
Elwood V. Jensen Professor of Medicine,
Interim Section Chief of Hematology/Oncology,
and Director of the Lymphoma Program at the
University of Chicago’s Department of Medicine Chicago, IL
Myeloproliferative Neoplasms

Rami S. Komrokji, MD
Professor of Oncologic Sciences, USF, Tampa, FL
Senior Member, Leukemia and MDS Section
Head Vice Chair, Department of Hematologic Malignancies, Moffitt Cancer Center Tampa, FL
Hematopoietic Stem Cell Transplantation

Richard Childs, MD, RADM
Clinical Director, National Heart, Lung, and Blood Institute (NHLBI),
Section Chief and Senior Investigator,
Laboratory of Transplantation Immunotherapy,
Rear Admiral, United States Public Health Service,
National Institutes of Health, Bethesda, MD
TREATMENTS AND CURRENT RESEARCH IN LEUKEMIA

Charles Schaffer MD,
Professor of Medicine and Oncology and
The Joseph Dresner Chair for Hematologic Malignancies at Wayne State University School of Medicine and the Karmanos Cancer Institute
Detroit, MI
Surviving Cancer With Art Therapy

Meaghan E. Wiggins, MA
Art Therapist
Clinical Hospital Coordinator,
Cancer Support Community,
Indianapolis, IN
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