15th Annual INDY HEMATOLOGY REVIEW 2018

State of the Art: Treatments, Targets, and Diagnosis

Ruemu E. Birhiray, MD

Program Chair

CEO, Indy Hematology Education, Inc

Partner, Hematology Oncology of Indiana, PC

Clinical Associate Professor of Medicine,

Marian University School of Medicine

HOI Hematology-Oncology Of Indiana, PC

Marian University Indianapolis College of Osteopathic Medicine

IHE

DISCLOSURES

SPEAKERS BUREAU

- JANSEN BIONCOLOGY, PFIZER, BMS, TAKEDA, AMGEN, TESSARO, PHARMACYCLICS, ASTRAZENECA, GENOMIC HEALTH, NORVATIS, INCYTE, SANOFI ONCOLOGY, CLOVIS ONCOLOGY, PUMA, EXCELIS, ELI-LILLY

CONSULTANT

- ALEXION
- JANSEN BIONCOLOGY

ADVISORY BOARD

- BAYER
- NORVATIS
- CELGENE
- HELSIN
- ABBVIE
- AMGEN

RESEARCH

- AMGEN
- PUMA
- TAKEDA

Lymphoma

HODGKIN'S LYMPHOMA

- **HL - ECHELON-1:** Brentuximab Vedotin Plus AVD Superior mPFS (23% improvement) versus ABVD in Previously Untreated Stage III or IV HL. (HR 0.77). GCSF needed
- **R/R cHL: BV + nivolumab** was associated with an ORR of 83% (CR: 62%)

MANTLE CELL LYMPHOMA

- **R^2 FIRSTLINE THERAPY in MCL:** lenalidomide + rituximab, @ median follow-up of 61 mos, ORR 87% (CR 61%)
- **R/R MCL:** Pooled data (3 clinical trials), ibrutinib ORR: 69.7% , median PFS of 13.0 mos
- **R/R MCL**: Acalabrutinib monotherapy, ORR: 81%, CR: 40%. 12-mo DoR: 72%

FOLLICULAR LYMPHOMA

- **FL maintenance therapy after BR (MAINTAIN)**: 4 yrs vs. 2 yrs; Non statistically significant DFS difference (HR: 0.63 (95% CI: 0.36-1.11), similar OS
- **R/R B-cell NHL**: Avadomide (novel iMiD) plus obinutuzumab, phase 1b: Preliminary activity: 68% ORR (84% in FL), Median PFS 11.3 mos (95% CI: 3.7-21.2)
- **R/R B-cell NHL**: CHRONOS-1 Trial Copanlisib; long term data, ORR of 58.5% and median DOR >1 year), low rate of severe toxicities and the lack of late-onset toxicities

WALDENSTROMS MACROGLOBULINEMIA

- Serum IgM levels and presence of CXCR4 mutations are associated with increased odds of acquired VWD.

Lymphoma

DIFFUSE LARGE B-CELL LYMPHOMA

- **R/R DLBCL (JULIET):** Phase II multicenter trial: Tisagenlecleucel (CTL019): anti-CD19 CAR T-cell therapy, ORR: 53% (CR: 40%)
- **R/R DLBCL (TRANSCEND):** Lisocabtagen Maraleucel ORR: 81%, CR 63%
- **R/R DLBCL**: Polatuzumab vedotin (humanized anti-CD79b mAb conjugated to MMAE) + BR superior to BR. CR: 40% vs 15% (P = .012).

HAIRY CELL LYMPHOMA

- **R/R HCL:** Vemurafenib + rituximab CR: 100% CR

T-CELL LYMPHOMA

- **R/R CTCL (MAVORIC):** Mogamulizumab, novel anti-CCR4 antibody significantly improved PFS, ORR vs vorinostat. Median PFS: 7.7 vs 3.1 mos; (HR: 0.53 (95% CI: 0.41-0.69; P < .0001)). ORR: 28.0% vs 4.8% (P < .0001)
- **ALCANZA**: Extended follow-up (median: 33.9 mos) continued superiority of brentuximab vedotin vs physician's choice of methotrexate or bexarotene in pts with previously treated CD30+ MF and pcALCL. ORR4: 60.9% vs 7.8%; CR: 18.8% vs 0%; ORR: 68.8% vs 21.9%

MARGINAL ZONE LYMPHOMA

- Subset Analysis CHRONOS-1 Trial: ORR: 70%, CR: 13% (n = 23) median DOR: NR

Chronic Leukemia

CLL

- **MURANO**: Venetoclax + Rituximab in R/R CLL (Interim Analysis): Phase III: VEN + R significantly increased PFS vs BR in pts with R/R CLL across subgroups and independent of del(17p) status. PFS: NR vs 17 mos (HR: 0.17; P < .0001), ORR: 93.3% vs 67.7%. PB MRD negativity at Mo 18: 60% vs 5%
- **CLARITY**: R/R CLL, combination therapy with ibrutinib + venetoclax (n=54), 1 case of TLS, ORR:100% @6 mo, 47% CR/Cri, 32% MRD negative BM
- **Venetoclax + ibrutinib** high response rate in R/R (n=29, 9 CR/CRi, 5 PR) or previously untreated high-risk CLL (n =32, 9 CR/CRi, 7 PR), with high BM MRD-negativity
- **Idelalisib Real World Data**: UK study, n = 68, median duration of treatment 12 mos (range 3-49), 24% (16/68) completed ≥24 months of treatment. Three patients (4%) NR.

CML

- **PETALs:** (Phase III) Interim Analysis: Nilotinib ± PegIFN alfa-2a Initial therapy CP CML: At Mo 12, MR4.5 rate with nilotinib + pegIFN vs nilotinib alone: 24.21% vs 15.38% (P = .048)
- **EUROSKI:** Primary endpoint: molecular recurrence (BCR-ABL > 0.1%, ie, loss of MMR): TKI duration: 5.8 yrs, MR4 duration: 3.1 yrs, Probability of treatment-free remission increased per each additional yr of first-line imatinib and duration of MR4.

Acute Leukemia

AML THERAPY

- **RATIFY:** Midostaurin maintenance; No effect DFS or OS significantly. Role of midostaurin maintenance in FLT3-mutated AML remains unclear
- **Gilteritinib**: novel oral FLT3/AXL inhibitor active in *FLT3*-ITD and *FLT3*-TKD mutations: 100% pts with FLT3-mutated AML achieved composite CR
- **Ivosidenib** in Mutant IDH1 AML: Oral, IDH1 inhibitor, in R/R AML, CR + CRh: 30.4%; duration: 8.2 mos, ORR: 41.6%; duration: 6.5 mos
- **Ivosidenib or Enasidenib + Standard Induction Chemotherapy in Newly Diagnosed AML With IDH1/IDH2 Mutations**: Active/safe: CR + CRi/CRp rates 67% (enasidenib) to 91% (ivosidenib) in de novo AML and 44% (ivosidenib) to 57% (enasidenib) in secondary AML
- **Frontline Cytarabine, Idarubicin, Nivolumab for AML**: EFS: 8.3 mos; median RFS: 17.3 mos; median OS: 15.8 mos
- **Venetoclax + LDAC in Elderly AML**: CR + CRi rate: 62%. OS after ≥ 1-yr follow-up: 11.4 mos (95% CI: 5.7-15.7). 1-yr OS: 45.9%
- **Selinexor + Ara-C in R/R AML**: Exportin 1 (XPO1) antagonist: CR 45%, CRi 21%

Acute Leukemia

AML PROGNOSIS:

- **MRD Detection by NGS**: Persistence of *DNMT3A, TET2,* and *ASXL1* (DTA) mutations in CR not associated with relapse
  - Mutations associated with clonal hematopoiesis in CR (DTA mutations) do not influence relapse
  - Identification of residual leukemia by targeted NGS of non-DTA mutations present in CR an independent predictor for AML relapse and survival
- **Prognostic Analysis of NPM1/FLT3-ITD Genotypes in RATIFY**: ELN favorable-risk genotype (NPM1mut/FLT3-ITDlow) have good long-term outcomes with midostaurin, but not from allogeneic HCT. ELN adverse-risk genotype benefit from midostaurin + allogeneic HCT

Acute Lymphoblastic Leukemia

- GIMEMA LAL1811: Frontline Ponatinib + Steroids in elderly or unfit pts with Ph+ ALL: CHR 90.5% at Wk 24, CMR at Wk 24: 60.6%. OS rate at 6 mos: 97.6%; 1 yr: 87.5%
- Inotuzumab Ozogamicin + Bosutinib in R/R Ph+ ALL or CML in Lymphoid Blast Phase: ORR: 81%, with majority of responders achieving CCyR and flow negativity. OS in R/R Ph+ ALL: 10.7 mos

Myeloproliferative Neoplasms and Myelodysplatic Syndromes

MPNs

- **RUXOLITINIB (REPONSE TRIAL in PV):** 4 year follow up (208 weeks) 37% ongoing response vs none, 5 year survival 90.6%
- **Myelofibrosis:** Sotatercept (activin receptor IIA ligand trap); Monotherapy response 7/18, Combo with Ruxolitinib response, 3/10.
- **IDASANUTLIN:** Nutlin antagonist, 75% response rate in PV as monotherapy or in combo with Peg-interferon

Advanced Systemic Mastocytosis

- **KIT D816V Inhibitor Avapritinib** (BLU-285): ORR 72% in pts evaluable by IWG-MRT-ECNM criteria
- **MEK Inhibition in Histiocytic Disorders**: **Cobimetanib**: CBR 100%, 64%, CR, DoR 6.6 mo

Myelodysplastic Syndrome

- **HOVON97**: Older pts with AML/RA in CR, azacitidine maintenance significantly improves DFS vs placebo through 30 mos (P = .03), but not OS

Multiple Myeloma

INITIAL THERAPY

- **ALCYONE:** Daratumumab Plus VMP vs VMP Alone in Newly Diagnosed, Transplantation-Ineligible Myeloma: Dara-VMP reduced risk of progression or death by 50% vs VMP alone, with significantly deeper response, including a > 3-fold higher rate of MRD negativity
- **CENTAURUS**: Daratumumab monotherapy in intermediate- and high-risk SMM: ORR: 54% to 56% in longer-dose arms. 12-Month PFS: 88% to 95% in longer-dose arms vs 81% in short dose
- **Elotuzumab/Lenalidomide/Dexamethasone Maintenance After ASCT**: 36% treat with maintenance eRD following ASCT improved quality of response. 20% converted to sCR/CR
- **Ixazomib Maintenance** in ASCT-Ineligible Patients With Newly Diagnosed MM: ixazomib induction and maintenance tx, ORR: 94% (CR: 35%). Responses deepened after maintenance in 23% of pts (CR from 22% to 35%
- **IFM Study Ixazomib/Rd**: all-oral triplet combo as induction prior to and as consolidation following ASCT; safe, convenient, and effective, CR 48%,after maintenance, 2-year PFS 83% and 2-year OS 95%.

Multiple Myeloma

RELAPSED REFRACTORY MYELOMA

- **Extended follow-up of POLLUX** trial improved PFS with addition of daratumumab to Rd in R/R MM. DRd reduced risk of progression or death by 56% vs Rd
- **PAVO**: Daratumumab coformulated with rHuPH20 enables SC dosing in 3-5 mins
- **IFM 2013-01**: PomCycloDex demonstrated activity in pts with myeloma in first relapse following RVD (with or without ASCT. ≥ PR in 85% of pts
- **BCMA bb2121** confers deep, durable responses at active doses (150-800 x 106 CAR T cells) in heavily pretreated pts with R/R MM. ORR: 94%, ≥ VGPR: 89%, CR: 56%
- **Human scFv-derived BCMA CAR T-cells (MCARH171):** CAR T-cells with EGFRt/hBCMA scFv/41BBz/CD3ζ retrovirus vector): MCARH171 has favorable safety profile. No dose-limiting toxicity observed
- **BCMA-Targeted CAR T-Cells ± Cyclophosphamide**: Active in heavily pretreated MM: ORR (≥ PR): 46%
- **Combined CD19- and BCMA-specific CAR T-cells in R/R MM**: 100% ORR, 90% ≥ PR, 30% ≥ VGPR. Safety profile of combined infusion consistent with single-target CAR T-cell therapy
- **Venectoclax** active in RRMM, predominantly in patients with t(11;14) abnormality and a favorable BCL2 family profile: CR 21%, ≥VGPR 15%
- **Selinexor/Bortezomib/Dex in RRMM**: ORR 84% in relapsed/PI naïve, 43% in refractory

Hematopoeitic Transplantation

- **EMN02/HO95:**
- Double Vs Single ASCT in Newly Diagnosed Multiple Myeloma: Phase III Trial: Double ASCT significantly improved PFS and OS following VCD induction vs single ASCT: high-risk cytogenetics most likely to benefit from double ASCT
- 3-yr PFS for ASCT-2 vs ASCT-1: 69.2% vs 44.2% (HR: 0.42; P = .014)
- 3-yr PFS similar for pts with standard-risk vs high-risk MM following ASCT-2, suggesting that ASCT-2 may overcome adverse prognosis of high risk cytogenetics
- Depth of response improved in 24% of pts after second planned ASCT
- > 50% of these pts achieved ≥ CR

- **Phase II GEM-CESAR**:
- KRd + ASCT in High-Risk Smoldering Myeloma: depth of response improved over course of treatment with KRd induction, ASCT, KRd consolidation, and Rd maintenance
- 90% of pts who received maintenance therapy achieved CR, with 60% MRD-negative rate

Benign and Not So Benign Hematology

- **Hokusai VTE-Cancer Study**: Edoxaban vs Dalteparin for VTE in Adult Cancer Patients: noninferior to dalteparin for composite primary endpoint of recurrent VTE and major bleeding
- **SELECT-D**: Dalteparin vs Rivaroxaban Anticoagulation Therapy for Patients With Cancer at Risk of VTE Recurrence: low rates of recurrent VTE, bleeding in pts with cancer receiving dalteparin or rivaroxaban anticoagulation therapy
- **Rozanolixizumab**: humanized, high-affinity, monoclonal antibody against FcRn in ITP: Platelet responses observed in ≥ 30% of pts
- **Avatrombopag** in relapsed chronic ITP, superior to placebo, 12.0 vs 0.1 wks, respectively ($P < .0001$)
- **Eltrombopag** in Persistent/Chronic ITP: Sustained platelet increases with 2 yrs of eltrombopag evident across ITP subgroups
- **HERCULES**: **Caplacizumab**, humanized monoclonal antibody to vWF in aTTP, improves platelet normalization rates by 55% vs placebo ($p< 0.01$) , aTTP-related death/recurrence/major thrombotic events: 12.7% vs 49.3% ($p< 0.0001$)
- **CRISPR/Cas9 gene edited iPSCs** improves transfusion safety and reduces delays in SCD.

Benign and Not So Benign Hematology

- **HAVEN 2**: **Emicizumab**, bispecific monoclonal antibody, in children with Hemophilia A and Factor VIII Inhibitors: Reduces bleeds; 54/57 (94.7%) with zero bleeds.
- **Gene Therapy for Hemophilia:**
- **Valactocogene roxaparvovevec (Valrox);** safe and effective, 11/13 adults with Severe Hemophilia A, eliminated bleeds, factor infusions with durable effects up to 72 weeks.
- **SPK-9001**: One infusion of single stranded recombinant adeno-associated viral vector, prevents bleeding and eliminates factor infusion in Hemophilia B
- **SUSTAIN:** Crizanlizumab vs Placebo in SCD, subgroup analysis: Time to first SCD–related pain crisis and delay in time to first SCPC event with high-dose crizanlizumab in all examined subgroups (SCPC history, sickle cell disease genotype, hydroxyurea use).
- **Voxelotor:** Hemoglobin polymerization inhibitor in SCD: improved hg, hemolysis and patient related scores (94% reduction in TSS @ 16 wks)
- **Severe AA**: Retrospective chart review of response to immunosuppression, 98% pts received RBC or PLT transfusions, 75% received ≥ 1 HSCT

What does it all mean ? *My thoughts*

- **PRACTICE changing:**
  - Daratumumab + Chemo as first line therapy in Myeloma
  - Brentuximab Vedotin + AVD as first line therapy in Hodgkin's lymphoma
  - NOACs in cancer associated VTEs
- **Potentially Practice changing:**
  - Venectoclax and Rituximab in refractory CLL
  - TKI discontinuation in CML
  - Tandem transplants in High risk Myeloma
  - Mogamulizumab in R/R CTCLs
- **PRACTICE confirming:**
  - Midostuarin + 7+3 in Kit Mutated AML,
  - Copansilib in Follicular NHL, Acalabrutinib and Ibrutinib in MCL
  - Antibody therapy in in Relapsed Myeloma
  - Single ASCT/maintenance in Myeloma
  - Ruxolinib in hydoxyuria refractory/intolerant PV
  - CAR-T therapy in relapsed DLBCL NHL
- **Stay tuned**
  - CAR-T therapy in Myeloma
  - All oral (iRD) triple: induction and then consolidation iR therapy after ASCT in Myeloma
  - Venectoclax and Ibrutinib in CLL
  - Avapritinib in Systemic Mastocytosis
  - Elderly AML: Venectoclax + LDAC
  - Gene therapy in Hemophilia A and B

Co-Chair Indy Hematology Review Challenging Cases

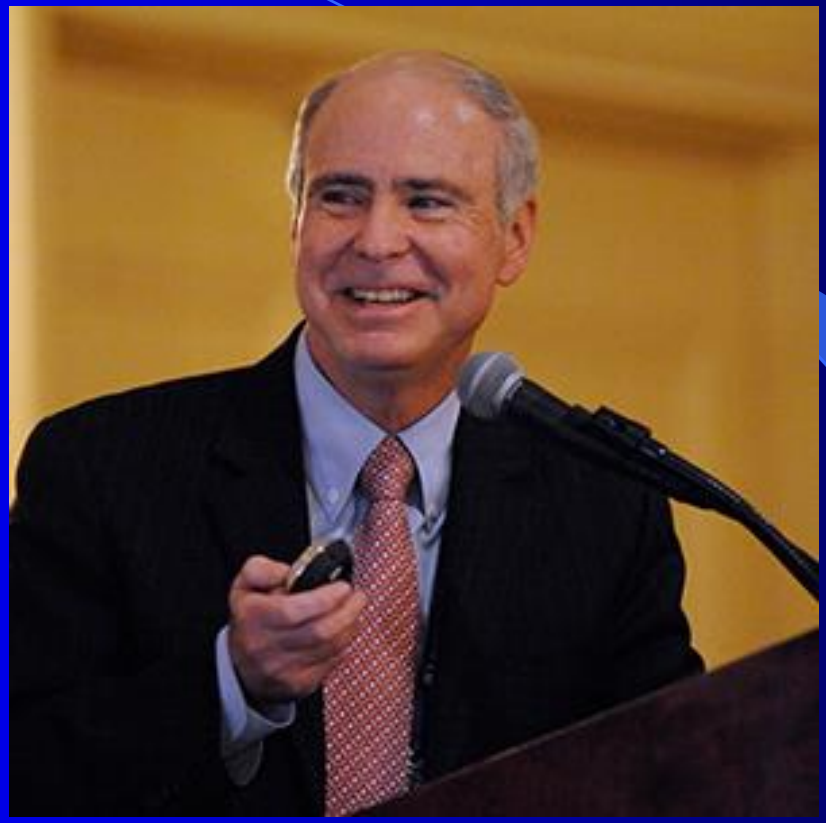
Michael C. Wiemann, MD

President, Clinical

St. John Providence Physician Network

Detroit, Michigan

Multiple Myeloma: Emerging therapies



Kenneth Anderson, MD

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

Multiple Myeloma: What I recommend and how you should treat

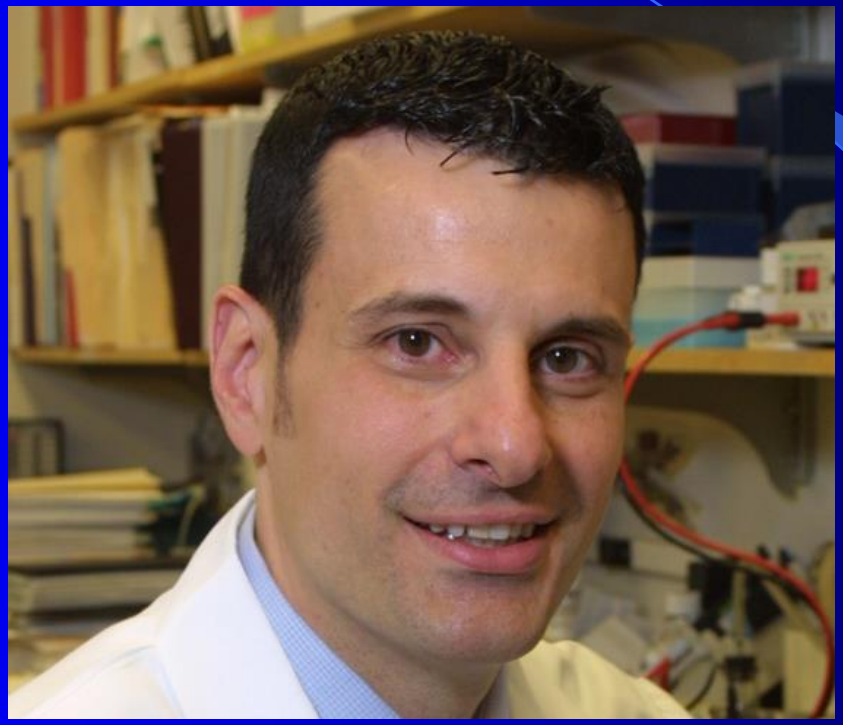
Paul G. Richardson, MD

Clinical Program Leader and Director of Clinical Research,

Jerome Lipper Multiple Myeloma Center
Professor of Medicine, Harvard Medical School,

Dana Faber Cancer Institute, Boston, MA

Waldenström's Macroglobulinemia: How I treat; Emerging and current therapies



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

Benign Hematology: Changing Paradigms

Craig M Kessler, MD
Professor of Medicine and Pathology
Director of Division of Coagulation, Department of Laboratory Medicine and Director of Therapeutic and Cellular Apheresis Unit
Director of the Comprehensive Hemophilia and Thrombophilia Treatment Center,
Georgetown University, Washington, DC

NOT SO BENIGN HEMATOLOGY

Robert Brodsky, MD

Director, Division of Hematology
Professor of Medicine and Oncology
The Johns Hopkins Family Professor,

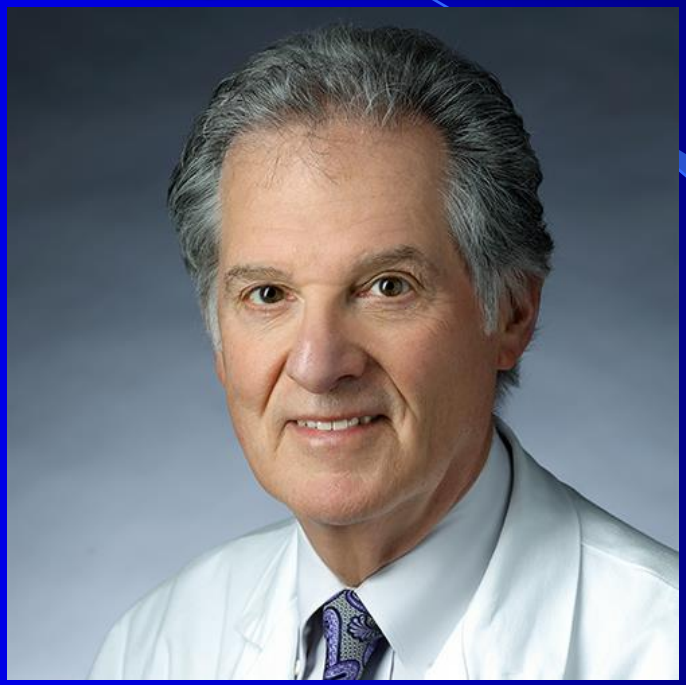
Johns Hopkins University,

Baltimore, MD

Aggressive B and T Cell Lymphomas: Treatment Paradigms in 2018

John P. Leonard, M.D.
Richard T. Silver Distinguished Professor of
Hematology and Medical Oncology
Weill Cornell Medical College
Professor of Medicine
Weill Cornell Medical College
New York, New York

Indolent Lymphomas and Hodgkins Lymphoma



Bruce D. Cheson, MD

Professor of Medicine,
Head of Hematology and Director of Hematology Research, Deputy Chief, Division of Hematology/Oncology, Lombardi Comprehensive Cancer Center.
Georgetown University, Washington DC

Chronic Myeloid Leukemia

Professor of Medicine,
Section of Hematology/Oncology
Director, Hematologic Malignancies Clinical Research Program
The University of Chicago Comprehensive Cancer Center
Chicago, IL

Myeloproliferative Neoplasms: What about JAK? PV, ET, MF

John Mascarenhas, MD
Associate Professor of Medicine
Myeloproliferative Disorders Program Tisch Cancer Institute,
Division of Hematology/Oncology
Mount Sinai School of Medicine

Beyond JAK 2: Mastocytosis, CMML, Eosinophilic and Neutrophilic leukemia

Ayalew Tefferi, MD

Professor of Medicine
Mayo Clinic,

Rochester, MN

Acute Lymphoblastic Leukemia and Myelodysplastic Syndrome: CARS, CARTS, Mechanics, and beyond

Associate Professor,

Section Chief, Acute Lymphocytic Leukemia,

Department of Leukemia,

Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX,

Acute Promylelocytic and other Acute Myeloid Leukemias: Slaying of the Old Dragon

Martin S. Tallman
Chief, Leukemia Service
Memorial Sloan Kettering Cancer Center, New York
Chair of the Leukemia Committee of the Eastern Cooperative Oncology Group (ECOG)

Hematopoietic Stem Cell Transplantation: When to offer and when to treat?

Richard Childs, MD

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

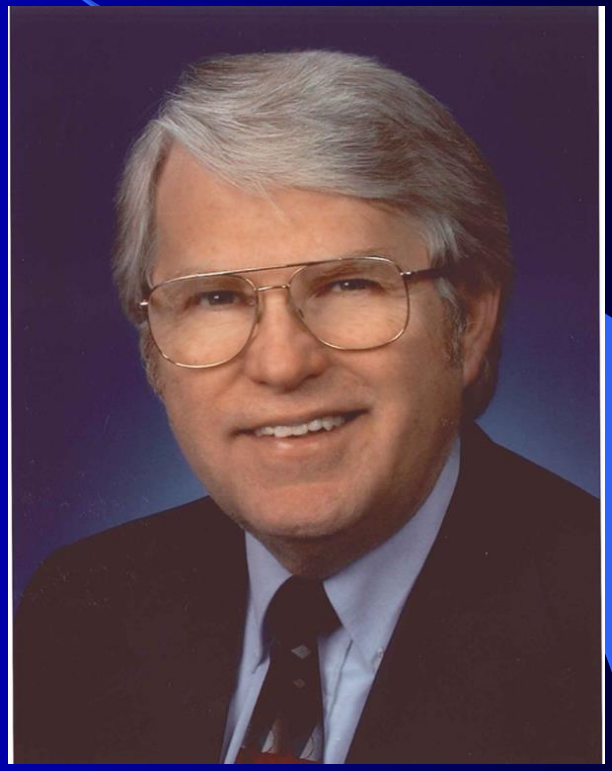
Nursing Symposium: Recognition and Management of Toxicities of Oral Therapeutics in Hematologic Malignancies

Michelle Wright-Mast, NP-C
Hematology Oncology of Indiana PC.
St Vincent Hospital Indianapolis, Indiana

T. Howard Lee Keynote Lecture

CHRONIC LYMPHOCYTIC LEUKEMIA: Targets, treatments, and resistance

Thomas J. Kipps, M.D., Ph.D.
Deputy Director of Research,
Moores UCSD Cancer Center;
Professor of Medicine
UC San Diego, School of Medicine, CA

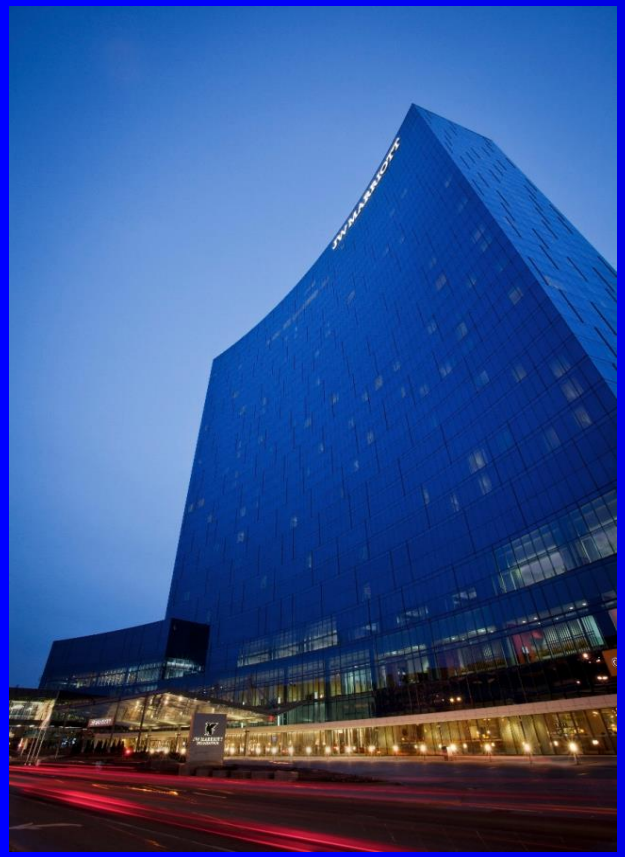


T. HOWARD LEE, MD
Founder and
President Emeritus,
Hematology Oncology of Indiana, PC
Indianapolis, IN

SAVE THIS DATE !

16th Annual Indy Hematology Review 2019

(http://www.indyhematologyreview.com)



March 9th, 2019

JW Marriott,

Indianapolis,

Indiana, 46225

Announcements and Acknowledgments

And

ASH 2017