PREVENTION OF INVASIVE FUNGAL INFECTIONS IN VULNERABLE HOSTS

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OUTLINE

- PROPHYLAXIS – FOUNDATION AND HISTORY
- REAL-LIFE EPIDEMIOLOGY
- TRIAL DESIGN
  - RESPECT: 1-DRUG PREVENTION WITH REZAFUNGIN
- FUTURE POTENTIALS: UNMET NEEDS IN HEMATOLOGIC MALIGNANCIES

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A CONTROLLED TRIAL OF FLUCONAZOLE TO PREVENT FUNGAL INFECTIONS IN PATIENTS UNDERGOING BONE MARROW TRANSPLANTATION

Jesse L. Goodman, M.D., Drew J. Winston, M.D., Ronald A. Greenfield, M.D., Pranatharthi H. Chandrasekar, M.D., Barry Fox, M.D., Herbert Kaizer, M.D., Richard K. Shadduck, M.D., Thomas C. Shea, M.D., Patrick Stiff, M.D., David J. Friedman, M.D., Ph.D., William G. Powderly, M.D., Jeffrey L. Silber, M.D., Harold Horowitz, M.D., Alan Lichtin, M.D., Steven N. Wolff, M.D., Kenneth F. Mangan, M.D., Samuel M. Silver, M.D., Ph.D., Daniel Weisdorf, M.D., Winston G. Ho, M.D., Gene Gilbert, Ph.D., and Donald Buell, M.D.

Efficacy and Safety of Fluconazole Prophylaxis for Fungal Infections after Marrow Transplantation—A Prospective, Randomized, Double-Blind Study

Monica A. Slavin, Barbara Osborne, Robyn Adams, Marcia J. Levenstein, H. Gary Schoch, Allen R. Feldman, Joel D. Meyers,* and Raleigh A. Bowden

Fred Hutchinson Cancer Research Center, Seattle; Pfizer Medica Division, New York, New York; Royal Melbourne Hospital Melbourne, Australi

705-713.

Intravenous and Oral Itraconazole versus Intravenous and Oral Fluconazole for Long-Term Antifungal Prophylaxis in Allogeneic Hematopoietic Stem-Cell Transplant Recipients

A Multicenter, Randomized Trial

Drew J. Winston, MD; Richard T. Maziarz, MD; Pranatharthi H. Chandrasekar, MD; Hillard M. Lazarus, MD; Mitchell Goldman, MD; Jeffrey L. Blumer, PhD, MD; Gerhard J. Leitz, MD, PhD; and Mary C. Territo, MD

blood

2004 103: 1527-1533
Prepublished online October 2, 2003;
doi:10.1182/blood-2003-08-2644

Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants

Kieren A. Marr, Fulvio Crippa, Wendy Leisenring, Maggie Hoyle, Michael Boeckh, S. Arunmozhi Balajee, W. Garrett Nichols, Benjamin Musher and Lawrence Corey

ORIGINAL ARTICLE

Posaconazole vs. Fluconazole or Itraconazole Prophylaxis in Patients with Neutropenia

Oliver A. Cornely, M.D., Johan Maertens, M.D., Drew J. Winston, M.D., John Perfect, M.D., Andrew J. Ullmann, M.D., Thomas J. Walsh, M.D., David Helfgott, M.D., Jerzy Holowiecki, M.D., Dick Stockelberg, M.D., Yeow-Tee Goh, M.D., Mario Petrini, M.D., Cathy Hardalo, M.D., Ramachandran Suresh, Ph.D., and David Angulo-Gonzalez, M.D.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 25, 2007 VOL. 356 NO. 4

Posaconazole or Fluconazole for Prophylaxis in Severe Graft-versus-Host Disease

Andrew J. Ullmann, M.D., Jeffrey H. Lipton, M.D., David H. Vesole, M.D., Ph.D., Pranatharthi Chandrasekar, M.D., Amelia Langston, M.D., Stefano R. Tarantolo, M.D., Hildegard Greinix, M.D., Wellington Morais de Azevedo, M.D., Ph.D., Vijay Reddy, M.D., Navdeep Boparai, M.S., Lisa Pedicone, Ph.D., Hernando Patino, M.D., and Simon Durrant, M.D.*

blood

Prepublished online Sep 8, 2010;
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Randomized double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection (IFI) after allo hematopoietic cell transplantation (HCT)

John R Wingard, Shelly L Carter, Thomas J Walsh, Joanne Kurtzberg, Trudy N Small, Lindsey R Baden, Iris D Gersten, Adam M Mendizabal, Helen L Leather, Dennis L Confer, Richard T Maziarz, Edward A Stadtmauer, Javier Bolaños-Meade, Janice Brown, John F DiPersio, Michael Boeckh and Kieren A Marr

AZOLE PROPHYLAXIS - BMT

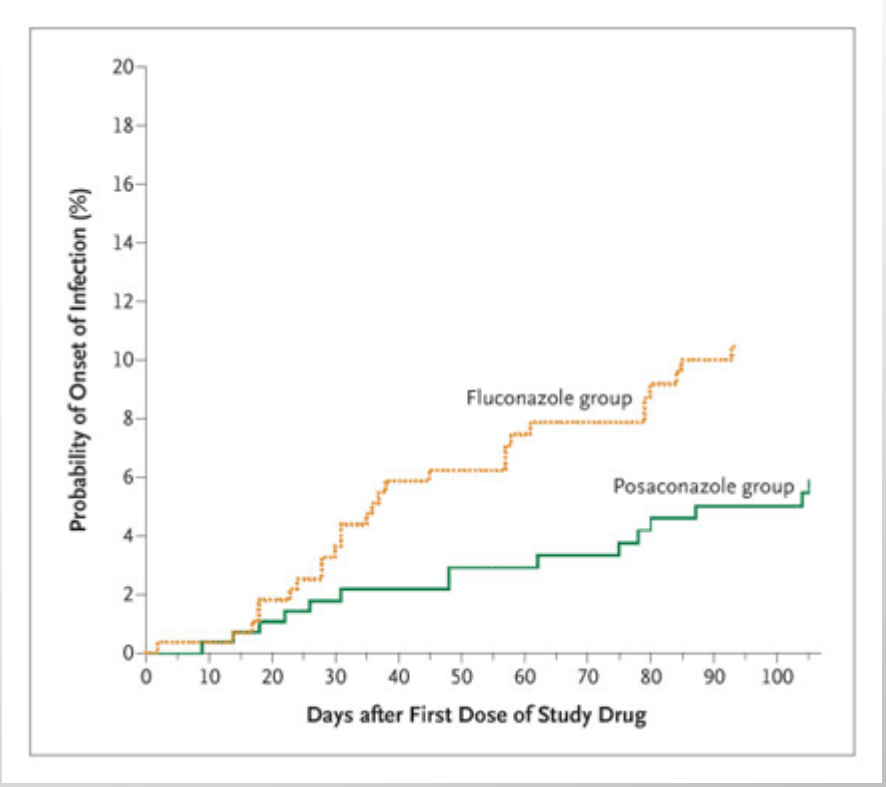
- FLUCONAZOLE PREVENTS CANDIDIASIS
  - NEW COMPARATOR FOR MOLD-ACTIVE AZOLES
- TWO RANDOMIZED TRIALS EVALUATING ITRACONAZOLE SOLUTION IN BMT PATIENTS
  - BOTH
    - DECREASED INVASIVE ASPERGILLOSIS IN ITRACONAZOLE ARM
    - TREND TO WORSE SURVIVAL IN ITRACONAZOLE ARM
    - TOXICITIES OF DRUG
      - GI TRACT TOXICITIES
      - DRUG INTERACTIONS

Is decreased IA "caused" by informative censoring ?

Winston et al. Ann Intern Med. 2003;138:705-713.
Marr et al, Blood 2004 103(4): 1527-33

POSACONAZOLE

- POSACONAZOLE VS. FLUCONAZOLE (N=600 PATIENTS)
  - DRUG WITH DIAGNOSIS OF GVHD
- APPROVED FOR PROPHYLAXIS IN BMT & AML/MDS



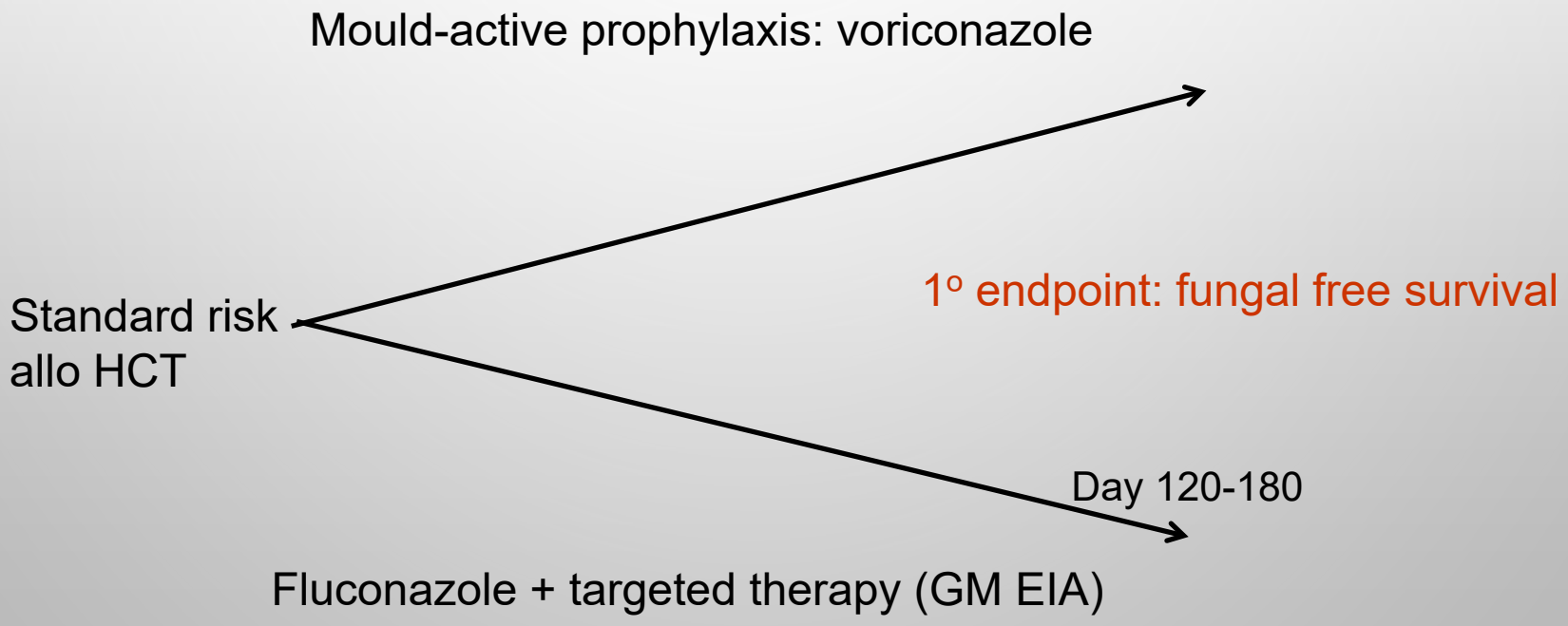
Ullmann et al. New Eng J Med 356;4 (2007)

Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation

John R. Wingard,[1] Shelly L. Carter,[2] Thomas J. Walsh,[3] Joanne Kurtzberg,[4] Trudy N. Small,[5] Lindsey R. Baden,[6] Iris D. Gersten,[2] Adam M. Mendizabal,[2] Helen L. Leather,[1] Dennis L. Confer,[7] Richard T. Maziarz,[8] Edward A. Stadtmauer,[9] Javier Bolaños-Meade,[10] Janice Brown,[11] John F. DiPersio,[12] Michael Boeckh,[13] and Kieren A. Marr,[10,13] for The Blood and Marrow Transplant Clinical Trials Network

Blood; 116(24):5111-5118 (2010)

600 PATIENTS ENROLLED IN NHLBI BMT CTN PROTOCOL 0101



ANTIFUNGAL PROPHYLAXIS TRIALS IN BMT PATIENTS

Ullmann trial **Characteristics**	**POS** **n (%)**	**FLU** **n (%)**	***P*** **Value**
Study Period (120 days)			
Total	**16 (5)**	**27 (9)**	**0.07**
***Aspergillus* spp.**	**7 (2)**	**21 (7)**	**0.006**

N=600 total patients (301 POS group, 299 FLU group).

BMT CTN trial **Characteristics**	**VORI** **n (%)**	**FLU** **n (%)**	***P*** **Value**
Study Period (180 days)			
Total	**14 (4.6)**	**24 (8.1)**	**0.11**
***Aspergillus* spp.**	**9 (3.0)**	**17 (5.8)**	**0.09**

N=600 total patients (305 VORI group, 295 FLU group).

Risk reduction 0.037 vs. 0.04

ISAVUCONAZOLE

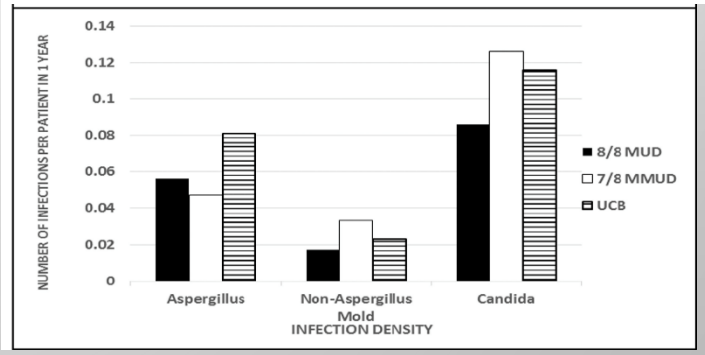
- APPROVED FOR THERAPY OF INVASIVE ASPERGILLOSIS
- OBSERVATIONS: USED FREQUENTLY, ESPECIALLY WITH LIVER TOXICITIES, PEOPLE WITH LONG QT
- REPORTS OF FREQUENT BREAKTHROUGH
- REASONS UNKNOWN
  - BIAS?
  - ANTIFUNGAL LEVELS? (TDM)
  - RESISTANCE? AT LEAST ONE CASE OF TR34-L98H RESISTANT *A. FUMIGATUS* BREAKTHROUGH REPORTED

Rauch et al. Clin Infect Dis 2018; Fontana et al. Clin Infect Dis 2019; Belanger et al. EID 2019

REAL-WORLD EPIDEMIOLOGY

- CIBMTR STUDY – ACUTE LEUKEMIA WITH ALTERNATIVE DONORS: MATCHED, UNRELATED DONORS (MUD), MISMATCHED, UNRELATED DONORS (MMUD) AND CORD BLOOD (UCB)
- INCIDENCE OF IFI REMAINS HIGH
- "PREVENTABLE IFI":
  - BOTH IA AND CANDIDIASIS

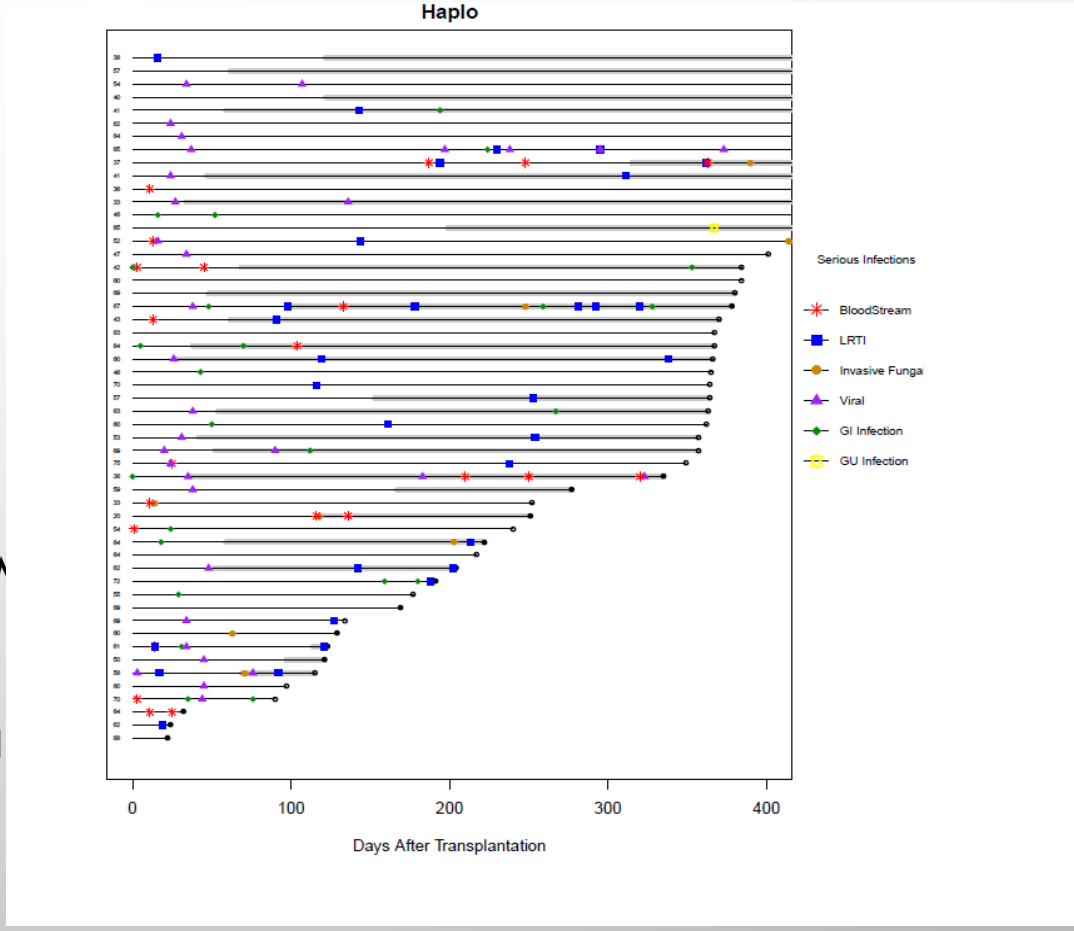
	MUD % (95% CI)	MMUD* % (95% CI)	UCB* % (95% CI)	p-value
Transplant Outcomes				
OS	69% (66 – 72%)	60% (54 – 66%)	51% (47 – 55%)	<0.0001
LFS	56% (56 – 72%)	49% (43 – 54%)	44% (40 – 48%)	<0.0001
Relapse	27% (24 – 30%)	25% (20 – 30%)	24% (21 – 28%)	0.43
NRM	14% (12–16%)	27% (22 – 32%)	33% (29 – 36%)	<0.0001
Infection Incidence				
Bacterial	59% (57 – 64%)	65% (59 – 70%)	72% (68 – 76%)	<0.0001
Viral	45% (42 – 48%)	53% (47 – 59%)	68% (64 – 72%)	<0.0001
Fungal	10% (8–12%)	16% (12–20%)	18% 15–21%)	0.0001



Ballen et al. BBMT 2016 22(9)

REAL – WORLD RECURRENT INFECTIONS

- INFECTIOUS MORBIDITY BETTER APPRECIATED AS CUMULATIVE, RECURRENT EVENTS
- SWIMMER-LANE PLOTS: PROVIDE CONTROL FOR INFORMATIVE CENSORING AND DEMONSTRATES 'REAL-LIFE' FAILURE
- A LOT OF MORBIDITY DESPITE EFFECTIVE PREVENTION ALGORITHM
- HETEROGENEITY
- IFI OCCUR LARGELY BEFORE DEATH



SUCCESS = BALANCE

<u>Benefits</u>

Prevent IFI
- morbidity
- mortality

Secondary

<u>Risks</u>

Toxicities
Drug interactions
Drug resistance
Costs

Each drug has different benefits and risks when utilized in different settings

PNEUMOCYSTIS INFECTION FRENCH BMT OBSERVATION

- ONLY 45% OF 139 CONSECUTIVE PATIENTS RECEIVED FULL COURSE OF TMP/SMX
  - 60 PATIENTS SWITCHED DUE TO SIDE EFFECT
  - 18 CONFIRMED PCP CASES (12.9% INCIDENCE)
- FREQUENT FAILURE DUE TO POOR TOLERABILITY IN REAL-WORLD

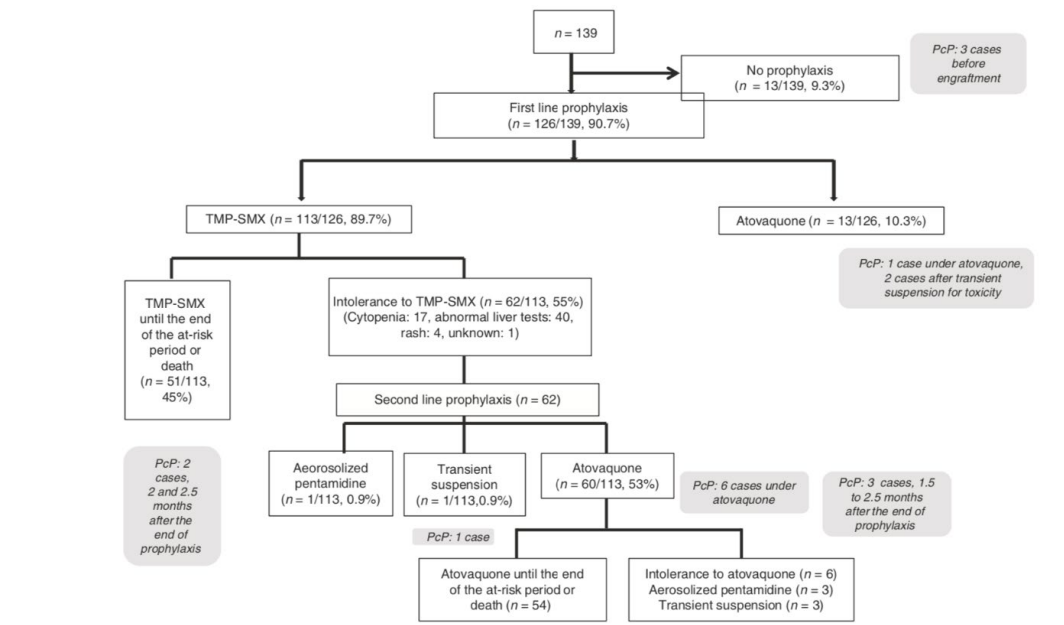


Fig. 1 Flow chart of pneumocystis prophylaxis in 139 consecutive allogeneic HCT recipients

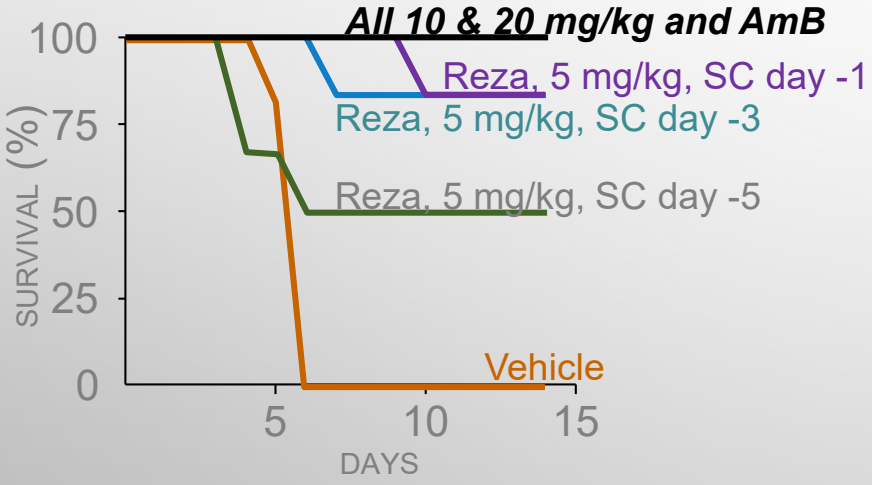
Redjoul et al. BMT 2019 54: 1082-88

REZAFUNGIN ANTIFUNGAL PROPHYLAXIS: RATIONALE

- ONCE – WEEKLY INFUSION
- NO CYTOCHROME P450 INTERACTIONS
- PRECLINICAL, CLINICAL ACTIVITY AGAINST *CANDIDA* SPP.
- PRECLINICAL ACTIVITY AGAINST *ASPERGILLUS* & PCP

Rezafungin
Aspergillosis & PCP models

Aspergillosis in neutropenic mice:
Equivalent survival in humanized doses relative to AmB

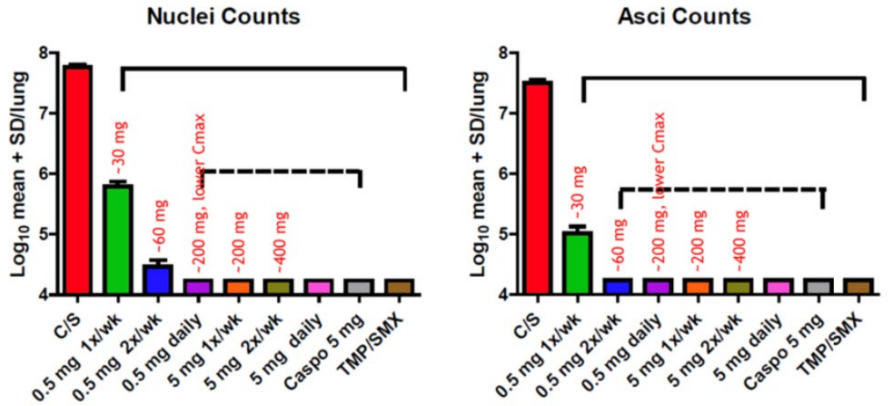


10 mg/kg ≈ human dose of 200mg
20 mg/kg ≈ human dose of 400mg

ECCMID and EHA 2017

PCP in neutropenic and steroid-suppressed mice:
Equivalent reduction in cysts and trophic forms relative to TMP/SMX

Log_{10} mean nuclei and asci counts after 42 days of study drug administration.



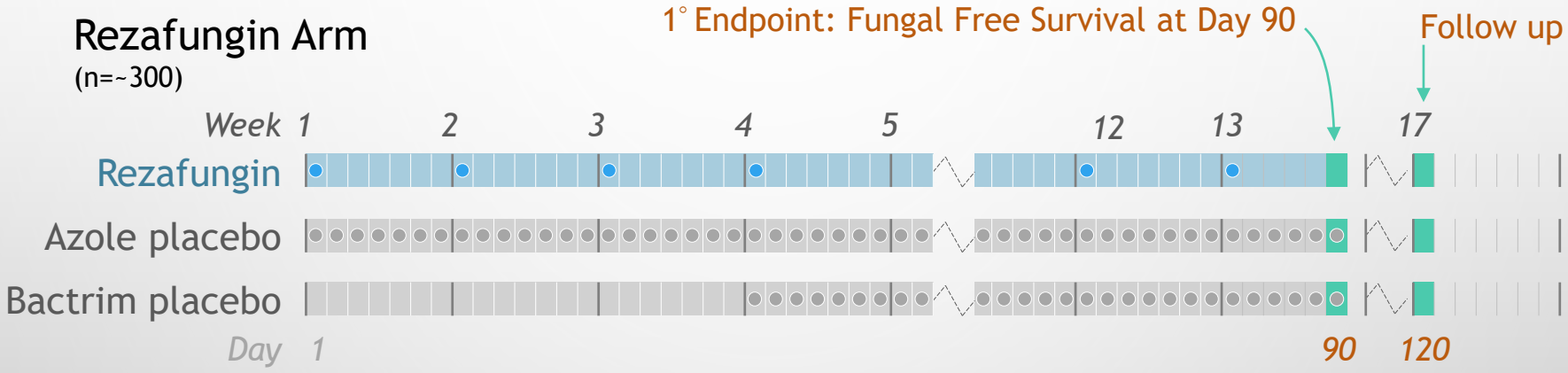
Cushion et al. TCT, Feb 2019

RESPECT TRIAL ANTIFUNGAL PROPHYLAXIS IN BMT

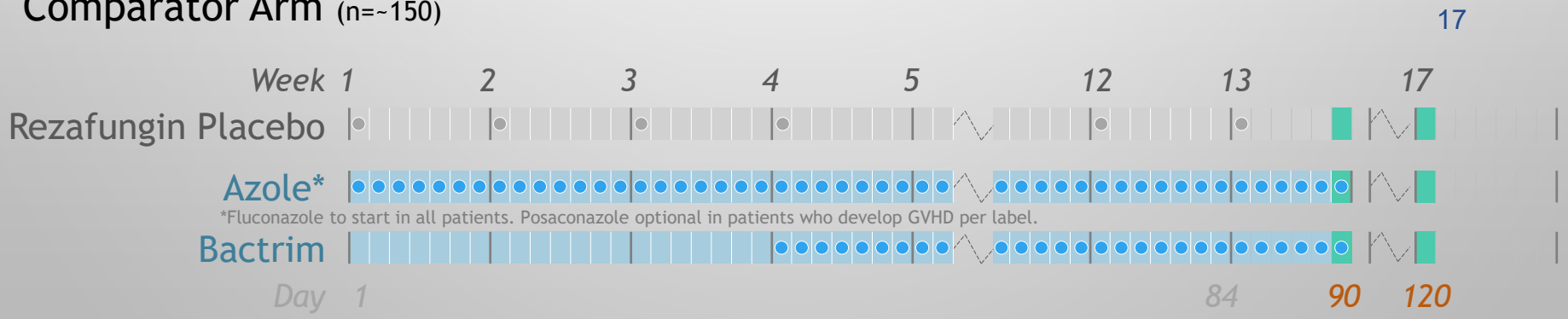
- TO START Q12020 IN EUROPE
- RANDOMIZED, DOUBLE-BLIND COMPARISON OF ONCE WEEKLY REZAFUNGIN VS. STANDARD ANTIFUNGAL PROPHYLAXIS (AZOLE + TMP-SMX) AFTER ALLOBMT
- DESIGN (462, 2:1 RANDOMIZATION)
  - STANDARD-RISK ALLOGENEIC BMT (NO CBT, AML NOT IN MORPHOLOGIC REMISSION, RECENT IFI)
  - 90 DAYS REZA VS. CURRENT STANDARD (FLUCONAZOLE WITH POSA FOR GVHD & TMP/SMX)
  - POWERED TO MEASURE NON-INFERIORITY OF FUNGAL – FREE SURVIVAL & SUPERIORITY OF PROPHYLAXIS SUCCESS

RESPECT PHASE 3 TRIAL

Rezafungin Arm
(n=~300)



Comparator Arm (n=~150)



FUTURE APPLICATIONS? UNMET NEEDS IN HEMATOLOGY

- INFECTIOUS RISKS POORLY DESCRIBED IN CLINICAL DEVELOPMENT
- EXPERIENCE UNDERLINING COMPLEX SECONDARY RISKS FOR IFI IN SEVERAL DRUGS
- MANY CONTRAINDICATIONS TO AZOLES DUE TO CYTOCHROME P450 INTERACTIONS

New chemotherapic agents already in use or coming in Hematology

AML

1. FLT3-inhibitors (Quizartinib, Midostaurin, Sorafenib)
2. Monoclonal antibodies anti-CD33 (Gentuzumab)
3. Arsenic Trioxide
4. IDH1-2 inhibitors
5. Combined liposomal cytarabine and daublastine (CTX1)

Lymphomas (low and high grade)

1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Rituximab, Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)

Hodgkin's Lymphoma

1. Monoclonal antibodies anti-CD30 (Brentuximab)
2. IgG4 anti-PD-1 (Nivolumab)

ALL

1. Monoclonal antibodies
   a. anti-CD19 (Blinatuzumab)
   b. anti -CD22 (Inotuzumab)
2. TK inhibitors (Imatinib, Nilotinib, Dasatinib, Ponatinib)

Multiple Myeloma

1. IMIDS (Talidomide, Lenalidomide Pomalidomide)
2. Proteosome inhibitors (Bortezomib, Carfizomib)
3. Monoclonal antibodies
   a. anti-CD38 (Daratumumab)
   b. anti-CD319 (Elotuzumab)

CLL

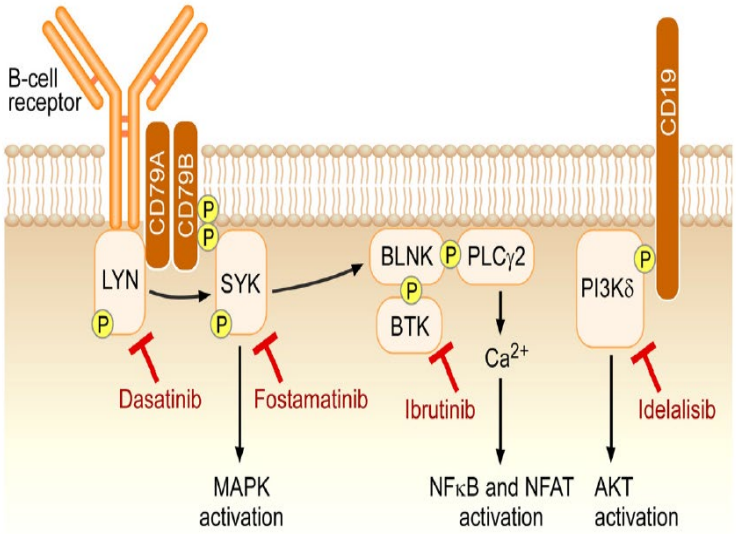
1. BTK-inhibitors (Ibrutinib)
2. Monoclonal antibodies anti-CD20 (Ofatumumab)
3. PI3Kδ signaling- inhibitor (Idelalisib)
4. Anti apoptotic BCL-2 (Venetoclax)

Slide: L. Pagano

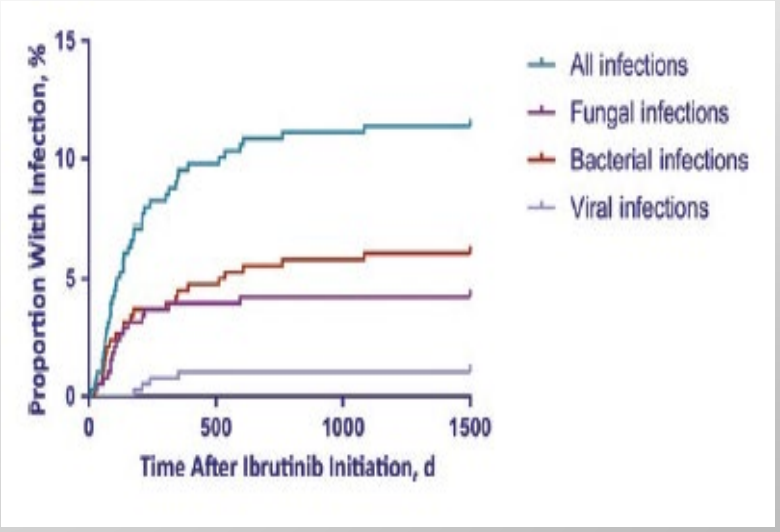
IFI RISKS ARE COMPLEX AND SOMETIMES UNEXPECTED

- RISKS REPRESENT
  - CUMULATIVE FUNCTION OF HOST RISKS (EX. AGE, LUNG DISEASE), UNDERLYING DISEASE, PRIOR THERAPIES
  - MANY DRUGS (EX. CHECKPOINT INHIBITORS) CAUSE INFLAMMATORY SYNDROMES THAT REQUIRE SECONDARY IMMUNOSUPPRESSION
    - EXAMPLE: IFI AFTER STEROIDS GIVEN FOR PNEUMONITIS, COLITIS
  - NON-SPECIFIC EFFECTS OF 'TARGETED' DRUGS

TYROSINE KINASE INHIBITORS



- DRUGS TARGET B CELL RECEPTOR, INHIBIT ACTIVATION AT DIFFERENT SIGNALING TARGETS. USED FOR CLL, LYMPHOMAS
- IFI RISKS COMPLICATED. EXAMPLE IBRUTINIB (BRUTON'S TK INHIBITOR)
  - SINGLE-CENTER REVIEW: 11% INCIDENCE INFECTION
  - RELATIVELY HIGH INCIDENCE IFI (ESPECIALLY PCP & IA)
  - CNS ASPERGILLOSIS
  - MECHANISTIC STUDIES REVEAL INHIBITION OF MACROPHAGE AND PMN KILLING
- LIMITED OPTIONS FOR PROPHYLAXIS DRIVING EXPLORATION OF ALTERNATIVES



Varughese et al. Clin Infect Dis 2018; 67(5): 687-92; Bercusson A. Blood 2018 132(18): 1985-88; Blez et al. Haematologica 2019 (in press); Lee et al. Am J. Hematol 2017; 92

CONCLUSIONS

- LONG HISTORY OF STUDIES IN BMT DEMONSTRATE UTILITY OF ANTI-FUNGAL PROPHYLAXIS IN TRIALS
  - ANTI-CANDIDA, ASPERGILLUS AND PJP
- REAL-LIFE OUTCOMES COMPLICATED BY INABILITY TO TAKE PREVENTATIVE DRUGS FOR A LONG PERIOD OF TIME (DRUG INTERACTIONS, TOXICITIES)
- NEW STUDY TO START NEXT YEAR:
  - REZAFUNGIN 1-DRUG PROPHYLAXIS VS. STANDARD APPROACH
  - DESIGN CONSIDERS LESSONS LEARNED
- EVOLVING COMPLEX FIELD WITH UNMET NEEDS IN OTHER VULNERABLE HOSTS, ESPECIALLY WITH TARGETED BIOLOGICS

THANK YOU