MYELODYSPLASTIC SYNDROMES (MDS) TRANSITIONING TO ACUTE MYELOID LEUKEMIA (AML)

JANUARY 23, 2020

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LEARNING OBJECTIVES

- Describe a management strategy for high-risk MDS/AML based on the clinical presentation, diagnostic workup and recent research findings
- Explain the role of genetic testing in risk assessment and stratification for this patient population
- Identify emerging treatment options for high-risk MDS and secondary AML
- Describe the roles of a multidisciplinary healthcare team in addressing treatment goals, including palliative care and other options, patient education, and financial issues
- Identify resources for support and education for patients

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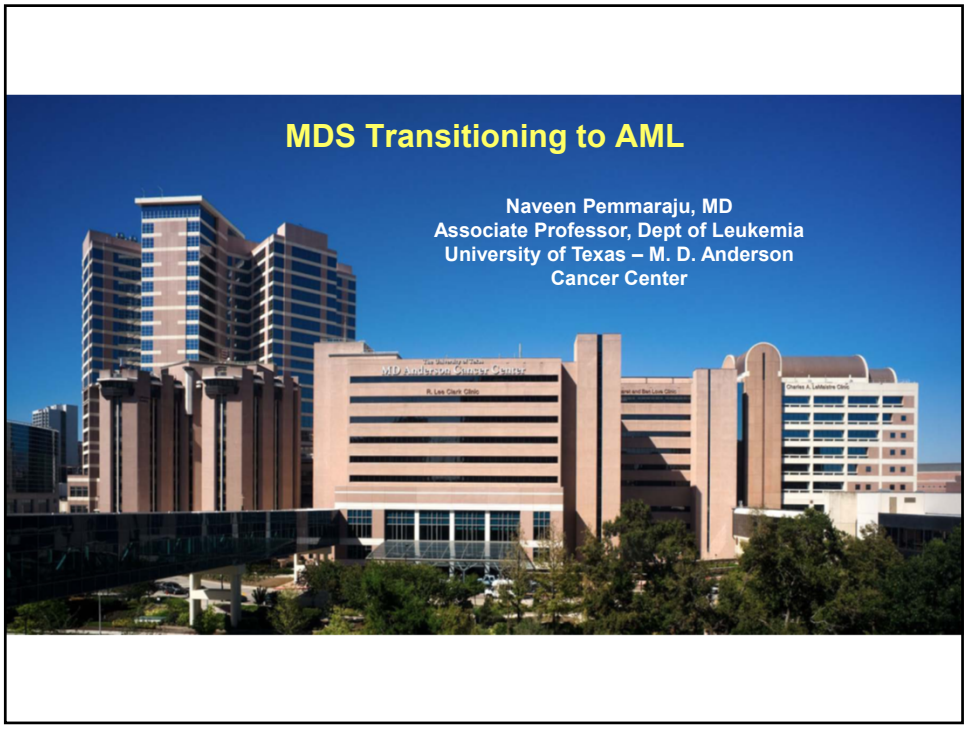

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COI/Disclosures

I am active clinical trialist. I have the following financial relationships to disclose:

- Research support, honorarium, consulting:
  - Incyte
  - Novartis
  - Stemline
  - Cellectis
  - LFB
  - Grant Funding: Affymetrix
  - Abbvie
  - Celgene
  - Daiichi-Sankyo
  - Plexxikon
  - Samus
  - SagerStrong Foundation
  - Mustang Bio

I WILL include discussion of investigational or off-label use of a product in my presentation.

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Overview & Objectives: MDS/CMML →AML

- MDS/CMML = Heterogenous grouping of myeloid diseases
- Peripheral blood: Cytopenias (anemia, thrombocytopenia, neutropenia, and the attendant risks from these)
- Increased risk→AML
- Older age
- Bone marrow bx: dysplasia; cytogenetics, molecular , flow cyto
- Prognostic scoring IPSS: % blasts, # cytopenias, cytogenetics
- Treatments: Based on risk category; Hypomethylators (Decitabine, AZA) , Lenalidomide, growth factors, AML-type therapy, allo-SCT, clinical trials/novel therapies

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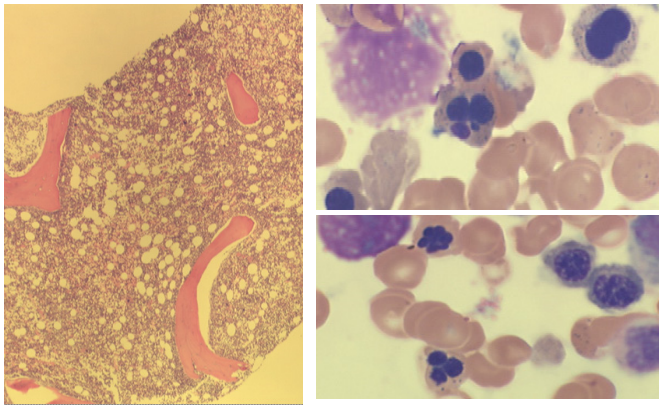
Diagnosis of MDS is based on morphology



Courtesy of Dr. Carlos Bueso-Ramos

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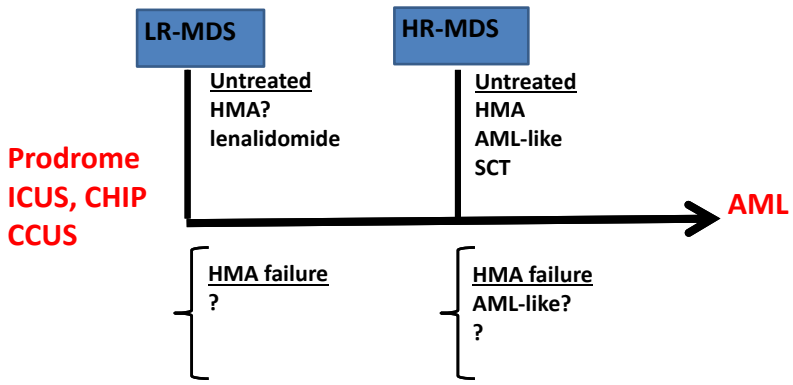
Natural history of MDS after incorporation of Hypomethylating Agents (HMAs)



HMA lower risk failure survival: 14-17 months
HMA higher risk failure survival: 4-6 months

Jabbour. Cancer 2015; Jabbour. Cancer 2010; Steensma Blood 2015.

Garcia-Manero G, MDACC

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What are the major needs in MDS?

(problems that limit significant cure rate)

- **Identification of poor prognosis "lower risk" patients**
  - **By default sparing patients with no need of therapy**
  - **Concept of early intervention**
- **Development of new targeted therapies for patients with lower risk MDS**
- **Development of new therapies for patients with higher risk MDS**
- **Understanding mechanisms of resistance to epigenetic modulators in MDS (critical)**
- **Understanding mechanisms of transformation to AML**
- **Incorporation of alloSCT in MDS**
- **Minimizing risk of relapse post alloSCT in MDS**

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International Prognostic Scoring System: IPSS

- Greenberg et al 1997 Blood

- % BM blasts
- Cytogenetics
- Cytopenias

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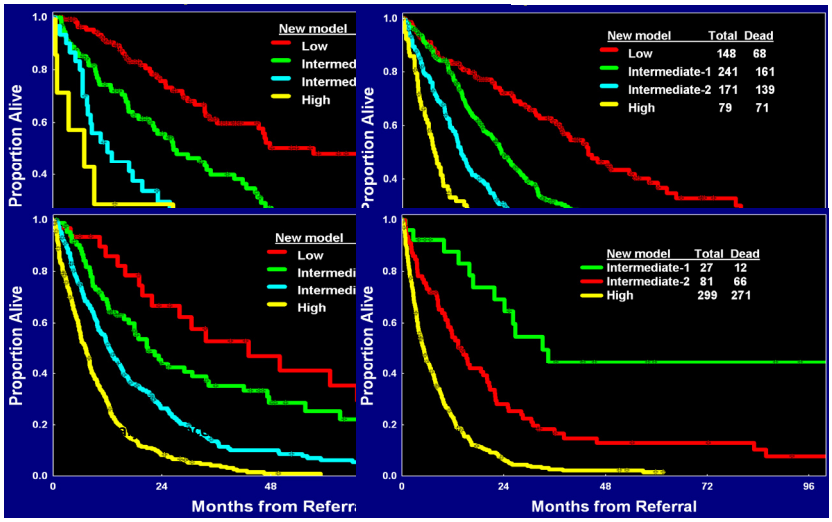
Survival by MDS model within IPSS Risk



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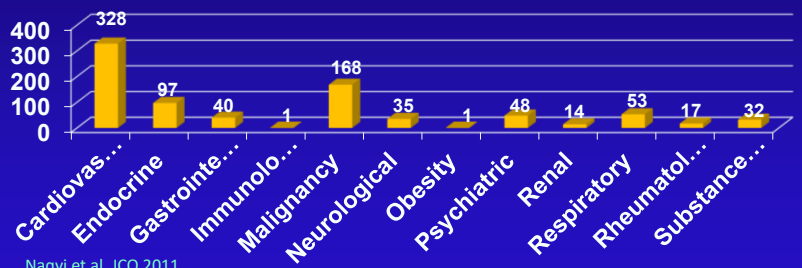
Comorbidities in MDS. Results

Comorbidities by ACE-27	N/(%)
None (0)	137 (23)
Mild (1)	254 (42)
Moderate (2)	127 (21)
Severe (3)	82 (14)

Comorbidities by System



Naqvi et al. JCO 2011

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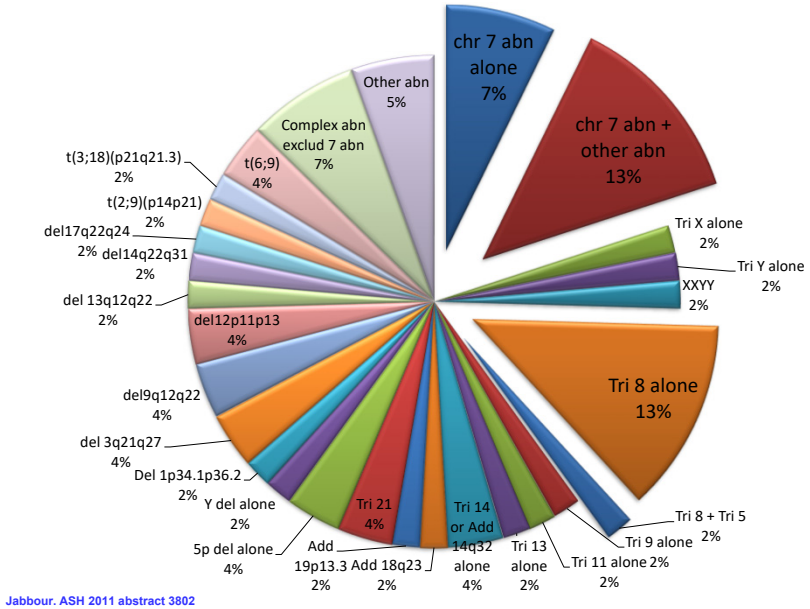
Cytogenetic acquisition in MDS



Jabbour. ASH 2011 abstract 3802

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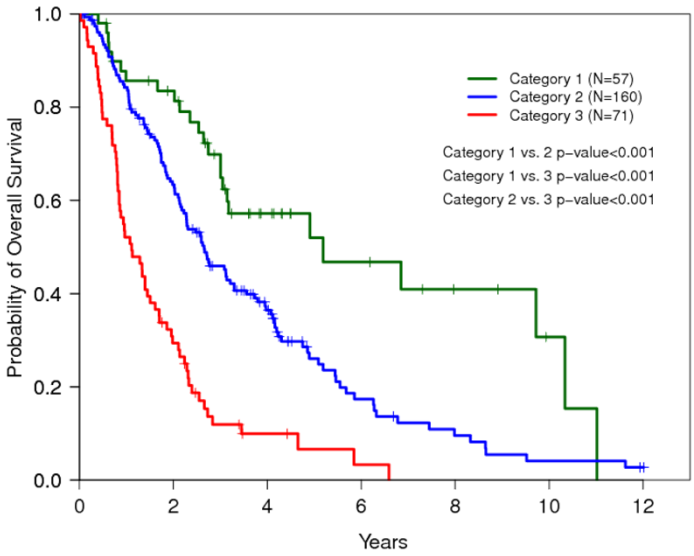
Identification of poor prognosis "lower risk" patients with MDS



Garcia-Manero et al. Leukemia 2008 and Neuberg, Bejar, Ebert, JCO in press

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Decitabine

- Incorporated into DNA and blocks DNA methyltransferase →hypomethylation→cell death in S-phase of cell cycle
- Phase III trial randomized DAC vs supp care (n=170) w/primary and secondary MDS w/IPSS INT-1 , INT-2, and High risk
- ORR (CR/PR) 17%, additional 13% with HI
- Median duration response: 10 months
- Kantarjian et al Cancer 2006

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Azacytidine

- Phase III randomized: AZA vs supp care (n=191 MDS pts), all IPSS risk groups
- 23% CR/PR; 37% HI compared to 5% HI and no responses in supp care group
- Median time to AML progression or death was signif increased in AML group compared to supp group (21 vs 13 mo, p=0.007)
- Fenaux, AZA 001 phase III study/Lancet Oncol 2009

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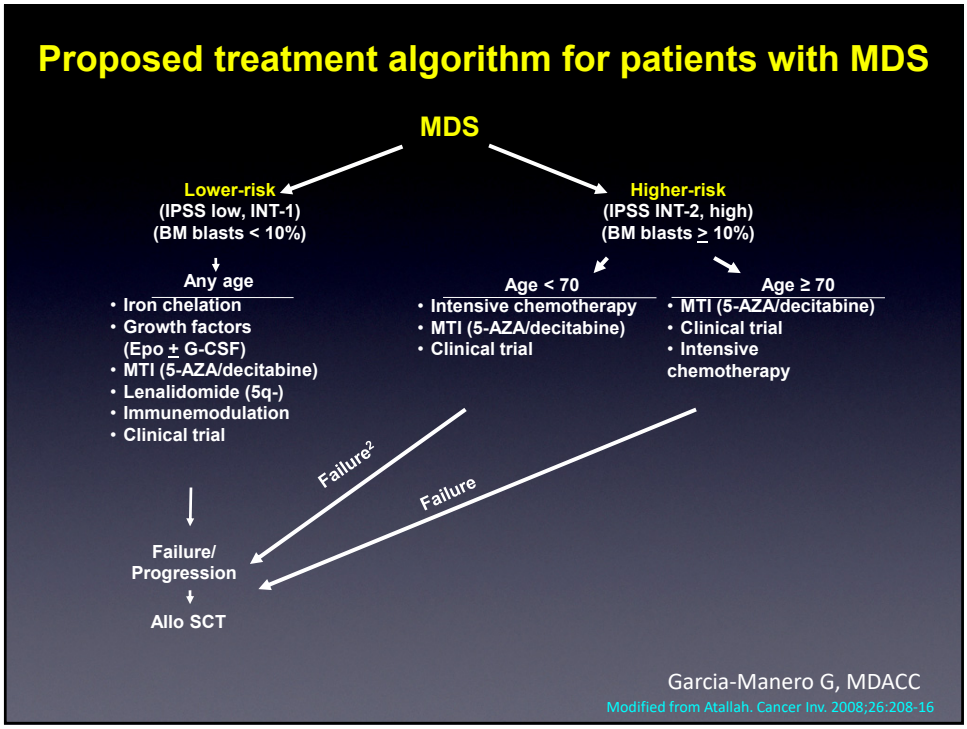
Proposed treatment algorithm for patients with MDS
MDS
Lower-risk
(IPSS low, INT-1)
(BM blasts < 10%)
Higher-risk
(IPSS INT-2, high)
(BM blasts ≥ 10%)
Any age
• Iron chelation
• Growth factors (Epo ± G-CSF)
• MTI (5-AZA/decitabine)
• Lenalidomide (5q-)
• Immunemodulation
• Clinical trial
Age < 70
• Intensive chemotherapy
• MTI (5-AZA/decitabine)
• Clinical trial
Age ≥ 70
• MTI (5-AZA/decitabine)
• Clinical trial
• Intensive chemotherapy
Failure²
Failure
Failure/ Progression
Allo SCT
Garcia-Manero G, MDACC
Modified from Atallah. Cancer Inv. 2008;26:208-16

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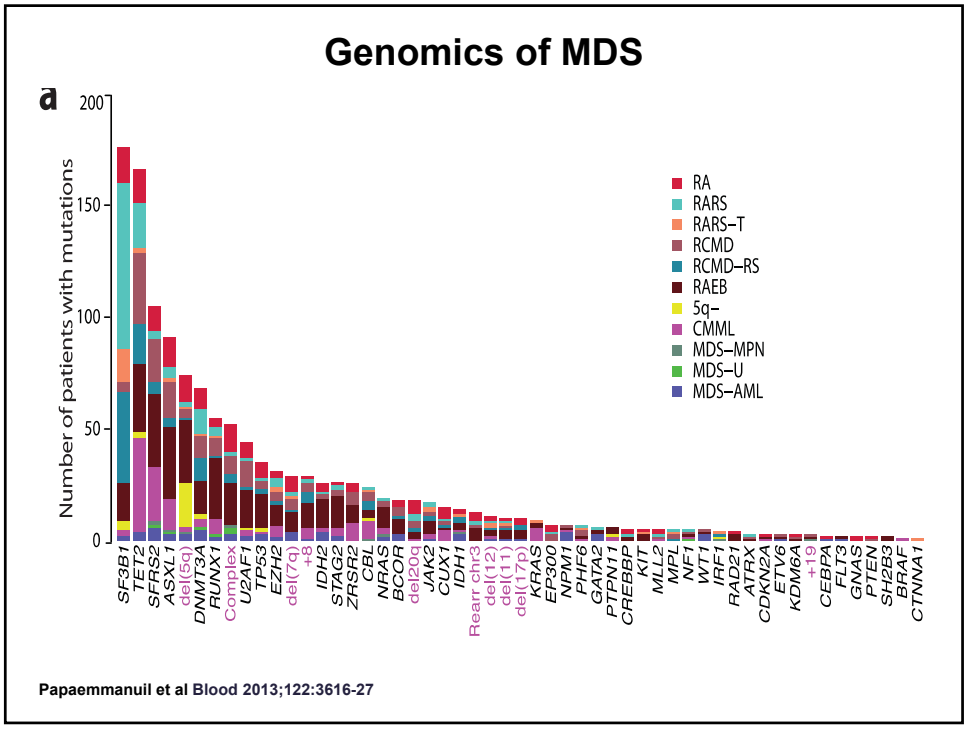
Genomics of MDS
a
Number of patients with mutations
200
150
100
50
0
RA
RARS
RARS–T
RCMD
RCMD–RS
RAEB
5q–
CMML
MDS–MPN
MDS–U
MDS–AML
SF3B1
TET2
SFRS2
ASXL1
del(5q)
DNMT3A
RUNX1
Complex
U2AF1
TP53
EZH2
del(7q)
+8
IDH2
STAG2
ZRSR2
CBL
NRAS
BCOR
del20q
JAK2
CUX1
IDH1
Rearr chr3
del(12)
del(11)
del(17p)
KRAS
EP300
NPM1
PHF6
GATA2
PTPN11
CREBBP
KIT
MLL2
MPL
NF1
WT1
IRF1
RAD21
ATRX
CDKN2A
ETV6
KDM6A
+19
CEBPA
FLT3
GNAS
PTEN
SH2B3
BRAF
CTNNA1
Papaemmanuil et al Blood 2013;122:3616-27

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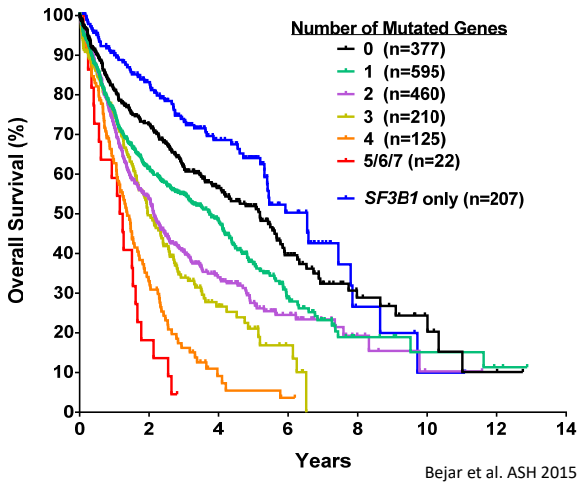
Overall Survival by Mutation Number

17 genes sequenced in 1996 patients with OS data

ASXL1
CBL
DNMT3A
ETV6
EZH2
IDH1
IDH2
JAK2
KRAS
NPM1
NRAS
RUNX1
SRSF2
TET2
TP53
U2AF1

SF3B1



Bejar et al. ASH 2015

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MDS 2020: Novel Therapies

- **Immediate :**
  - **Luspatercept**
  - **ASTX727 (oral decitabine)**
- **Coming :**
  - **Venetoclax**
  - **APR-246**
  - **IDH2/ IDH1 ihibitors**
  - **Magrolimab (CD47 Ab)**
- **Other agents: TIM-3, rigosertib, CB393, H3BIO**

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AML

- *De novo* AML
  - No prior MDS, MPN, Antecedant hematologic disorder (AHD)
- MDS→ AML
  - Represents a special subset of AML with often challenging prognosis and treatment options
- BPDCN : a special subset of AML now its own myeloid malignancy that commonly occurs with /arises out of MDS/CMML

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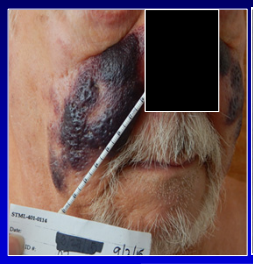
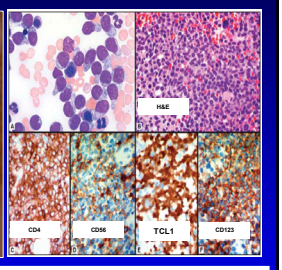
BPDCN: Aggressive Hematologic Malignancy

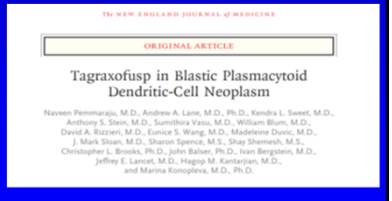
- Primary sites: Skin, Bone marrow
- Secondary sites: LN, CNS, Visceral
- Hallmark: Overexpression → CD123 (IL3Rα)
- Classic Triad: CD123+, CD4+, CD56+
- TCL-1, CD303, TCF-4
- *TET2, ASXL1, RAS, TP53*
- Historical OS ~8-14 mo/ high rates transformation to AML
- Tagraxofusp (SL-401) → first-in-class anti-CD123 Tx for patients with BPDCN
- ~20 % cases of BPDCN → prior/concomitant myeloid malignancies (MDS/CMML)

BPDCN skin lesions



BPDCN bone marrow





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tagraxofusp in Blastic Plasmacytoid Dendritic-Cell Neoplasm

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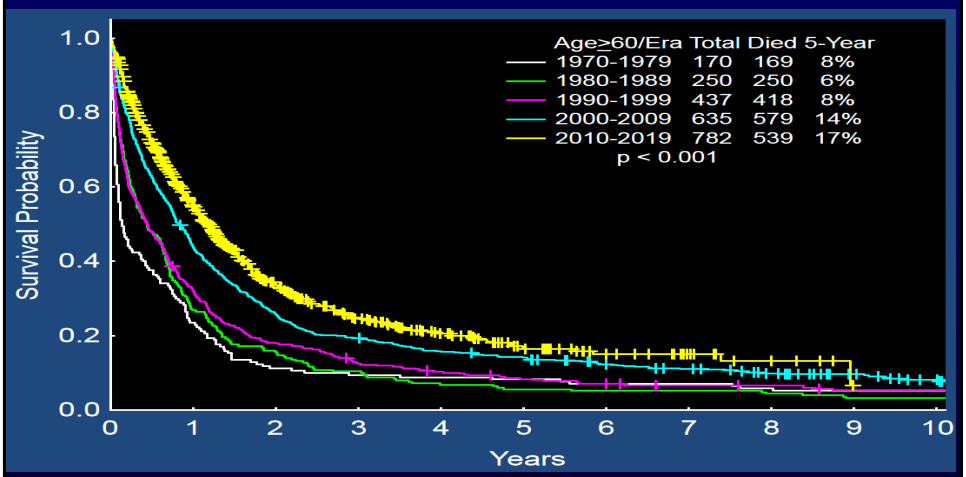
AML Survival at MD Anderson Cancer Center by Decade– Age>60 Yrs



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AML in 2017-2020, FDA Approvals and Beyond

- Midostaurin (RYDAPT) for de novo younger AML (< or = 60 yrs), FLT3 mutation—April 2017 (FLT3 inhibitor)
- Gilterinib (FLT3 inhibitor) for FLT-3 + R-R AML
- Enasidenib (AG-221; IDHIFA) for R-R AML and IDH2 mutation—August 2017
- Ivosidenib (AG-221) for R-R AML and IDH1 mutation —August 2018
- CPX 351 (Vyxeos) for newly Dx Rx-related AML and post MDS AML—August 2017
- Gemtuzumab ozogamycin revival for frontline AML Rx— August 2017
- Venetoclax for newly Dx older/unfit for intensive chemo, with AZA/DAC, ara-C
- Glasdegib for newly Dx older/unfit, with ara-C
- Tagraxofusp (SL-401) for BPDCN ages 2 and up, Dec 2018
- Data + with FLT3 inhibitor quizartinib
- Data with oral azacitidine maintenance positive

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CPX-351

- CPX 351 (Vyxeos) for newly Dx Rx-related AML and post MDS AML—approved August 2017
- Fixed 5:1 liposomal formulation of 7+3
- OS benefit (statistically significant) in randomized clinical trial in t-AML/s-AML (arising out of MDS) vs 7+3

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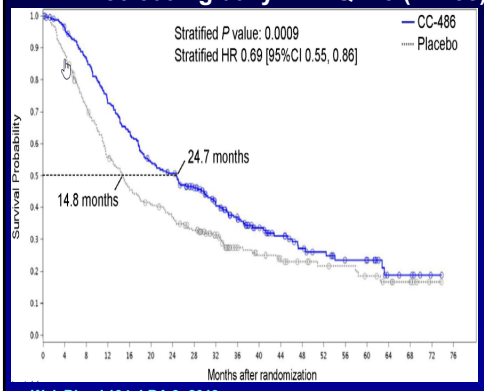
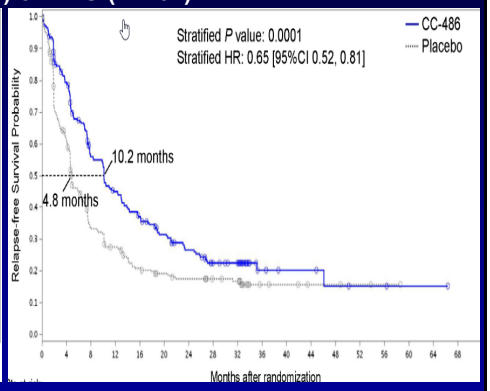
Phase 3 Study of Oral Azacitidine vs Placebo as Maintenance in AML (QUAZAR-AML-001)

- **472 pts 55+ yrs (median age 68 yrs) with AML in CR-CRi<4 mos randomized to CC-486 300mg/daily x 14 Q mo (n=238) or PBO (n=234)**





Wei. Blood 134: LBA 3; 2019

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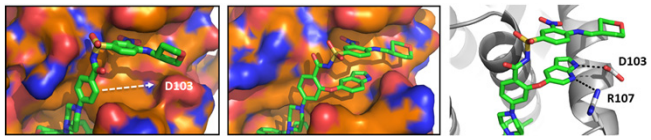
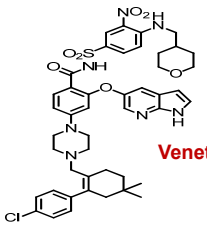
Structure-Based Drug Design of BCL-2-Selective Inhibitor



Insights from X-ray crystal structures drove the design of first-in-class BCL-2-selective inhibitor, venetoclax

- Selective, high affinity for BCL-2
- Kills tumor cells but spares platelets
- Orally bioavailable



Venetoclax

Souers et al. (2013) Nature Medicine

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Venetoclax in AML -- Preclinical

- BCL-2 is highly expressed in AML blasts and stem/progenitor cells
- ABT-199 effectively kills AML cells, with IC_{50}<10nM in the majority of primary AML samples tested
- Sensitivity of primary AML cells to ABT-199 positively correlates with BCL-2 protein levels
- Bcl-2 inhibition by ABT-199 effectively kills AML cells *in vivo* (AML cell line and primary AML PDX)
- BH3 profiling: A predictive biomarker for Bcl-2 inhibition

Konopleva M; Pan .Cancer Discovery 2014; 4:362-75

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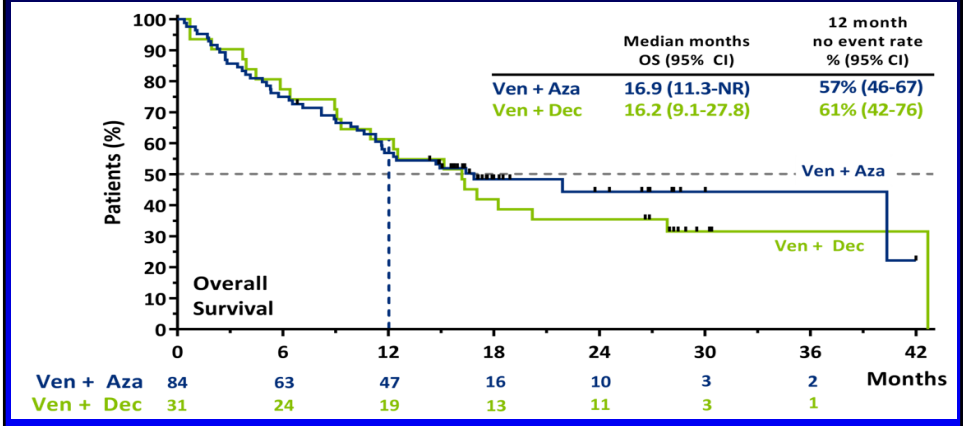
Venetoclax + HMAs in Older AML: Overall Survival



Early (30 day) mortality 2% (Aza/Ven) and 7% (DEC/Ven)

DiNardo. Blood:133: 7; 2019

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MDS/CMML transitioning to AML

- Intermediate/higher risk MDS/CMML → high rates of transformation to AML
- Prognostic scoring based on:
  - Traditional clinical factors (IPSS; clinical such as blasts/cytogenetics/cytopenias)
  - Newer techniques including high risk molecular mutations and # of mutations (ASXL1, TP53, etc)
- Can also commonly be present with/transform to BPDCN
- Represents a challenging clinical situation with several emerging therapeutic options now, but still urgent need for more clinical trial/novel approaches

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- Describe the roles of a multidisciplinary healthcare team in addressing treatment goals, including palliative care and other options, patient education, and financial issues

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MULTIDISCIPLINARY APPROACH

- Multidisciplinary care teams: "integrated team approach to health care in which medical and allied health care professionals consider all relevant treatment options and develop an individual treatment plan for each patient collaboratively"
  - Improve communication & patient coordination
  - Routine meetings to discuss patient treatment plans
    - Increased adherence to evidence-based practice
    - Patient treatment plan revisions
- As advanced practice providers (APPs), including Physician Assistants and Nurse Practitioners, we work in conjunction with our physician colleagues
  - Our parallel approach creates a dynamic relationship with patients

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MULTIDISCIPLINARY APPROACH

- Rationale: Team Approach
  - Management of cancer varies
    - Type (solid, liquid)
    - Stage/prognosis
    - Treatment center (academic institute)
  - Treatment plans are individualized
  - Necessitates an involvement of a variety of providers & individuals to help facilitate and carry out plans
  - Evidence suggests that a team-based approach helps organize and optimize tasks; improve patient outcomes

- **Healthcare team**
  - Primary clinic team
  - Inpatient team
  - Research team
  - Behind the scenes
- **Patient education**
  - New patient acute leukemia education program
  - Tools/resources
  - Learning center
- **Referrals**
  - Stem cell
  - Palliative care
  - Supportive care/pain management
- **Financial issues**
  - Financial counselors
  - Resources
- **Socioeconomic issues**
  - Social workers
  - Case managers
  - Patient advocates

REFERENCES

- Abdulrahman, Ganiy Opeyemi Jnr. The effect of multidisciplinary team care on cancer management. *The Pan African Medical J*: 2011; 9:20.
- Silbermann M, Pitsillides B, Al-Alfi N, et al. Multidisciplinary care team for cancer patients and its implementation in several Middle Eastern countries. *Ann Oncol*. 2013;24 Suppl 7(Suppl 7):vii41–vii47. doi:10.1093/annonc/mdt265
- Stephen H. Taplin H., Stephen, Weaver, Sallie, et al. Reviewing Cancer Care Team Effectiveness. *Journal of Oncology Practice*: 2015. Volume 11: 239-246. https://ascopubs.org/doi/abs/10.1200/JOP.2014.003350

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SO WHAT'S THE PLAN?

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SO WHAT'S THE PLAN?

- It takes everyone working together, communicating, and understanding the whole situation for a plan to work.
- In order to plan:
  - *What do you need to consider before proposing treatment options?*
  - *What do you need to discuss?*
  - *How do you do it?*
    - *Patients and caregivers cannot be compliant without this, for numerous reasons.*

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WHAT TO CONSIDER: PSYCHOSOCIAL ISSUES

- **For the patient:**
  - May be unable to care for self, or others they previously cared for (children, parents)
  - May be struggling with physical and cognitive side effects of treatment
  - Anxiety and Depression- Diagnosis and treatment can cause, especially in people who are already predisposed to one or both
  - May worry about lack of income and being able to provide for family, especially if they were the only ones working and are not now
  - May worry about their cancer's affect on spouse, children or other family members

WHAT TO CONSIDER: PSYCHOSOCIAL ISSUES

- **For the caregiver:**
  - Balancing family responsibilities and caring for the patient
  - Potentially trying to care for other family as well- children, elderly parents or relatives
  - Traveling or needing to stay close to the hospital for an extended period of time
  - Changes in access to support when traveling for treatment
  - Self-care for the caregiver
  - Ensuring patient safety upon discharge
  - Reliance on the caregiver to communicate changes in patient status

WHAT TO DISCUSS WITH THE PATIENT AND CAREGIVER BEFORE AND THROUGHOUT TREATMENT

- **What Are Their Treatment Options and Why?**
- **Potential Side Effects**
  - Recognize adverse effects of treatment and **stress importance of communicating with the healthcare team.**
    - *What are "normal" side effects and what needs immediate attention*
  - What to do for fever and emergency management
  - 24-hour access to providers- who to contact and best method of communication.
  - Explain importance of palliative care and how it is different from hospice.

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WHAT TO DISCUSS WITH THE PATIENT AND CAREGIVER BEFORE AND THROUGHOUT TREATMENT

- **Financial concerns**
  - Duration of stay and travel to and from the treating hospital
  - Insurance concerns
  - Paying for child or pet care
  - Missing work and dealing with employers- loss of income of both patient and caregiver
  - Cost of the actual treatment, even after insurance

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HOW TO DO IT:

- Provide clear (written) directions for the patient and caregiver about what to expect, and what is expected of them, throughout treatment. ***Emphasize importance of them communicating with the healthcare team overall***
- Discuss any concerns they have overall.
- Discuss clinical trials as a treatment option, if appropriate.
- Discuss advance directives due to disease or potential treatment side effects.
- Discuss potential impact on fertility or ability to have a family, and if there are options for sperm or egg preservation before treatment, if applicable.

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HOW TO DO IT:

- Recognize the financial impact on the patient and caregiver, their ability to complete treatment because of cost, and refer to appropriate resources.
- Assess for emotional impact of treatment on patients and caregivers - anxiety, depression, anger-and be prepared to provide support.
- Discuss what is available and connect families with full array of services offered at the institution (social work, nutrition, integrative medicine, child life, palliative care etc.) and in the community, or organizations like LLS.

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MYELODYSPLASTIC SYNDROMES TRANSITIONING TO ACUTE MYELOID LEUKEMIA

Resources for Patients

- ❑ Telephone and Web Education Programs: www.LLS.org/Programs and www.LLS.org/Educationvideos
- ❑ Support Resources: www.LLS.org/Support
  - ❑ Financial Assistance
    - Co-pay
    - Travel assistance
    - Referral to medication access programs
  - ❑ LLS Chapters
  - ❑ Caregiver support
  - ❑ LLS Podcast (patients)
  - ❑ LLS Community (social media platform)
  - ❑ Online chats
  - ❑ Patti Robinson Kaufmann First Connection Program (peer-to-peer)
  - ❑ One-On-One Nutrition Consultations (PearlPoint)

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MYELODYSPLASTIC SYNDROMES TRANSITIONING TO ACUTE MYELOID LEUKEMIA

Resources for Patients

- ❑ **Information Resource Specialists and Clinical Trial Specialists:** **www.LLS.org/IRC**. Assist through treatment, financial & social challenges, and give treatment and support information

  Patients and caregivers can work **one-on-one with a Clinical Trial Nurse Navigator** who will provide personalized clinical trial searches, help overcome barriers to trial enrollment and personally assist patients through the entire clinical trial journey.

  M - F, 9 am to 9 pm ET:

  - Phone: (800) 955-4572
  - Live chat: www.LLS.org/InformationSpecialists
  - Email: infocenter@LLS.org

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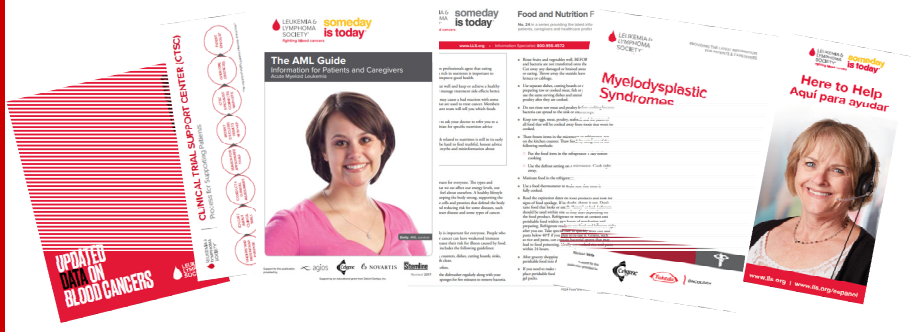
FREE GUIDES, BOOKLETS, AND FACT SHEETS

Supporting Patients, Caregivers and Professionals

www.LLS.org/Booklets



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MYELODYSPLASTIC SYNDROMES TRANSITIONING TO ACUTE MYELOID LEUKEMIA

Resources for HCPs

- ❑ Online & In-person free CME & CE courses: www.LLS.org/CE
- ❑ **New!** Podcast series for healthcare professionals: www.LLS.org/HCPpodcast. Tune in as experts discuss the latest developments in treating blood cancers, side-effects management, survivorship, and more.

Clinical Trials and Research

- ❑ Clinical Trials: Learn more about clinical trials: www.LLS.org/ClinicalTrials
- ❑ Research: Focused on finding cures and driving research: www.LLS.org/Research

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AAMDSIF Resources for Health Professionals

- **MDS/AML Rounds** CME program for community hospitals
- Regional CME Bone Marrow Failure Disease Symposia
- CME webinars
- **Treating MDS Toolkit**
- Patient education materials in print and digital formats
- Patient information specialist
- Patient education webinars
- Peer support network
- Community Connection support groups

www.aamds.org

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Q & A

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THANK YOU
We have one goal:
A world without blood cancers
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