MDS Overlap Disorders and Diagnostic Boundaries

Tiffany N. Tanaka MD, Rafael Bejar MD, PhD
Division of Hematology and Oncology, University of California, San Diego, Moores Cancer
Center, La Jolla, CA, USA $\frac{1}{2}$ Division of Hematology and Oncology, University of California, San Diego, Moore Cancer
Center, La Jolla, CA, USA Center, La Jolla, CA, USA

 $\frac{1}{2}$ $\frac{1}{1}$ Dr. Rafael Bejar
UC San Diego Mo
3855 Health Scien
La Jolla CA 92093 Dr. Ammerica
DC San Diego M
3855 Health Scie
La Jolla, CA 920 3855 Health Sciences Drive MC 0820
La Jolla, CA 92093-0820
USA
Phone: 858-534-5204 La Jolla, CA 92093-0820 La John, 2008
USA
Phone: 858-534-5204
E-mail: <u>rabejar@ucsd.ed</u> Phor
Phor
E-ma E-mail: <u>rabejar@ucsd.</u>
 E-mail: rabejar@ucsd.edu

Abstract

Myelodysplastic syndromes (MDS) are clonal diseases defining the parameter groups and genetic features often shared by related myeloid disorders. The diagnostic boundaries between these diseases can be arbitrary and not ne general consideration in the analysis of the disorders. The angles of the disease biology or
outcomes. In practice, measures that distinguish MDS from related disorders may be difficult to
quantify and can vary as disease outcomes. In practice, measures that distinguish MDS from related disorders may be difficult
quantify and can vary as disease progression occurs. Patients may harbor findings that are not
consistent with a single diagnosti out the process of the state and statement with the state and the proposition of quantify and can vary as disease progression occurs. Patients may harbor findings that are not consistent with a single diagnostic category. consistent with a single diagnostic category. Several overlap disorders have been formally
described such as the myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). These
disorders are characterized by hematopoietic d described such as the myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). These
disorders are characterized by hematopoietic dysplasia with increased proliferation of
monocytes, neutrophils, or platelets. They may hav disorders are characterized by hematopoietic dysplasia with increased proliferation of
monocytes, neutrophils, or platelets. They may have mutational profiles that distinguish the
from the disorders they resemble and refle disorders are characterized by hematopoietic dysplasia with increased proliferation of
monocytes, neutrophils, or platelets. They may have mutational profiles that distinguish then
from the disorders they resemble and refl monocytes, new process in pathophysiology. MDS
also shares diagnostic borders with other diseases. For example, aplastic anemia and
hypoplastic MDS can be difficult to distinguish in patients with pancytopenia and bone mar from the discrete they resemble and reflect important differences in pathophysiology. Meso
also shares diagnostic borders with other diseases. For example, aplastic anemia and
hypocellularity. Genetic features may help in hypoplastic MDS can be difficult to distinguish in patients with pancytopenia and bon
hypocellularity. Genetic features may help in this regard as they can identify difference
prognosis and risk of progression. The boundar hypocellularity. Genetic features may help in this regard as they can identify differences in
prognosis and risk of progression. The boundary between MDS and secondary acute myelo
leukemia (SAML) is arbitrary defined and h prognosis and risk of progression. The boundary between MDS and secondary acute myeloid
leukemia (sAML) is arbitrary defined and has been redefined over the years. Genetic studies
have demonstrated that sAML clones can pre leukemia (sAML) is arbitrary defined and has been redefined over the years. Genetic studies dysplastic bone marrow failure syndrome and an oligoblastic leukemia. This review will describe months, suggesting that MDS with excess blasts could be viewed as an overlap between a
dysplastic bone marrow failure syndrome and an oligoblastic leukemia. This review will des
the diagnostic boundaries between MDS, MDS/M months, suggesting that MDS with excess black countries as an increasing process be
dysplastic bone marrow failure syndrome and an oligoblastic leukemia. This review will de
the diagnostic boundaries between MDS, MDS/MPNs, diagnostic boundaries between MDS, MDS/MPNs, sAML, CHIP, CCUS and aplastic anemia.
and how genetic approaches may help better define them.
. and how genetic approaches may help better define them. and how genetic approaches may help better define them.

Introduction

Myelodysplastic syndromes (MDS) are clonal hematopoietic disorders that typically present
with features indicative of bone marrow failure including inefficient hematopoiesis,
morphologic dysplasia, and cytopenias of the pe specific and can be a consequence of a variety of benign or malignant conditions. Both MDS diagnostic boundaries between MDS and related conditions can, in practice, be much more appropriate diagnosis. This is exacerbated by the fact that the apparently well-defined vague and difficult to characterize. This can occur at initial presentation, where a patient with diagnostic boundaries between MDS and related conditions can, in practice, be much r
vague and difficult to characterize. This can occur at initial presentation, where a patier
MDS-like features might also have evidence of diagnostic boundaries between MDS and relative conditions and difficult to characterize. This can occur at initial presentation, where a patient wit
MDS-like features might also have evidence of hypoplasia or a myeloprolif V
MDS-like features might also have evidence of hypoplasia or a myeloproliferative neoplasm
(MPN), and over time, as patients with MDS can evolve into another diagnosis such as a
secondary acute myeloid leukemia (SAML). Re (MPN), and over time, as patients with MDS can evolve into another diagnosis such as a
secondary acute myeloid leukemia (sAML). Recent advances in our understanding about the
genetics of MDS and its diagnostic neighbors ma (MPN), and over the sumpling pattents with MDS can evolve into another angles in the secondary acute myeloid leukemia (SAML). Recent advances in our understanding about genetics of MDS and its diagnostic neighbors may help genetics of MDS and its diagnostic neighbors may help sharpen their boundaries or ultimately,
redefine them altogether.

genetine them altogether.
The Mosterics of MDS and its diagnosing patients with MDS overlap syndromes can have important clinical
implications. Often, the prognosis associated with an overlap syndrome is distinct from the reasing instructing
Correctly diagnosing patier.
Implications. Often, the prindividual disorders they re implications. Often, the prognosis associated with an overlap syndrome is distinct from the
individual disorders they resemble. This is driven in part by differences in their genetic profiles
and pathobiology. Consequently individual disorders they resemble. This is driven in part by differences in their genetic profiles
and pathobiology. Consequently, overlap disorders may be amenable to different therapeutic
options and can harbor unique m options and can harbor unique molecular vulnerabilities. While genetics can aid in the diagnosis apprions and can harbor unique molecular vulnerabilities. While genetics can aid in the diagnos
of overlap disorders, somatic mutations rarely define them independent of the clinical context
in which they are found. Other of overlap disorders, somatic mutations rarely define them independent of the clinical context
in which they are found. Other factors, including patient characteristics, epigenetic alterations,
and microenvironmental inter of overlap measures, somalism manufacture, as including particular formatics, epigenetic alterations,
and microenvironmental interactions, such as inflammation and adaptive immune responses,
help shape the disease phenotyp and microenvironmental interactions, such as inflammation and adaptive immune responses,
help shape the disease phenotype. Together, these characteristics can help establish an
accurate diagnosis in cases with overlapping and microenvironmental interactions, such as inhuming iteractions, and planetic responses,
help shape the disease phenotype. Together, these characteristics can help establish an
accurate diagnosis in cases with overlappin

help shape the disease phenotype. Together, these characteristics can help establish and
accurate diagnosis in cases with overlapping features.
This review will focus on those diagnostic categories that have features of MD accurate angulations in cases with observe panglements of
This review will focus on those diagnostic categories th
elements of other disorders in the context of our great
molecular genetics. This includes the individual MD elements of other disorders in the context of our greater understanding about their underlying
molecular genetics. This includes the individual MDS/MPN overlap disorders recognized the
World Health Organization (WHO) class elemble cular genetics. This includes the individual MDS/MPN overlap disorders recognized the
World Health Organization (WHO) classification of myeloid neoplasms. We will also examine
the diagnostic boundaries between apla world Health Organization (WHO) classification of myeloid neoplasms. We will also examine
the diagnostic boundaries between aplastic anemia (AA) and MDS as well as with MDS and
sAML, disorders that can lead to or arise fro The diagnostic boundaries between aplastic anemia (AA) and MDS as well as with MDS and
SAML, disorders that can lead to or arise from MDS, respectively. Finally we explore the
diagnostic boundary between lower risk MDS, cl the angulary process that can lead to or arise from MDS, respectively. Finally we explore the
diagnostic boundary between lower risk MDS, clonal hematopoiesis of indeterminate poter
(CHIP), and idiopathic cytopenias of und diagnostic boundary between lower risk MDS, clonal hematopoiesis of indeterminate po
(CHIP), and idiopathic cytopenias of undetermined significance (ICUS), a substantial fract
which harbor somatic mutations typical of MDS. (CHIP), and idiopathic cytopenias of undetermined significance (ICUS), a substantial fraction of which harbor somatic mutations typical of MDS. which harbor somatic mutations typical of MDS.
 $\frac{1}{2}$

which harbor somatic mutations typical of MDS.
The MDS/MPN Overlap Disorders

Classification scheme. They include diagnoses with very different clinical manifestations,
underlying genetics, and overall prognosis. Their shared features can include cellular dysplasia
or cytopenias in addition to an el anderlying genetics, and overall prognosis. Their shared features can include cellular dysport cytopenias in addition to an elevation in one or more blood cell counts. At the molecular dysport client clinical manifestation underlying generics, and overall progresses their shared features can include cellular as persons or cytopenias in addition to an elevation in one or more blood cell counts. At the molecular level, MDS/MPN disorders are mo devel, MDS/MPN disorders are more likely to carry gene mutations associated with the
activation of growth factor signaling pathways in conjunction with mutations in epigenetic
regulators or splicing factors associated with level, the eyemic measure are more many to carry gene mutations are exacted and an
activation of growth factor signaling pathways in conjunction with mutations in epigene
regulators or splicing factors associated with morp

regulators or splicing factors associated with morphologic dysplasia.
 Chronic myelomonocytic leukemia (CMML) is the most common of the MDS/MPN overlap

diseases even though its prevalence is estimated to be only about 1 regulators or splitting factors associated with morphologic applements.
Chronic myelomonocytic leukemia (CMML) is the most common of f
diseases even though its prevalence is estimated to be only about 1C
is defined by the diseases even though its prevalence is estimated to be only about 10% of that for MDS. CM
is defined by the presence of monocytosis in addition to at least one cytopenia (typically
anemia) and bone marrow findings that typ anemia) and bone marrow findings that typically meet MDS diagnostic criteria. The
monocytosis in CMML has to be both relative ($\geq 10\%$ of white blood cells) and absolute ($\geq 1 \times$ anemia) and bone marrow findings that typically meet MDS diagnostic criteria. The
monocytosis in CMML has to be both relative ($\geq 10\%$ of white blood cells) and absolute ($\geq 10^9$ /L) and must persist for at least 3 maring that the manner mannings that typically meet magnetic criteria. The
monocytosis in CMML has to be both relative ($\geq 10\%$ of white blood cells) and absol
10⁹/L) and must persist for at least 3 months. (1, 2) Cr monocytosis in CMML had a dicated with the both reports in the both relative of the present of the myeloid ineqularms and alternative causes of monocytosis should be absent. Historically, the French-
American-British class 10 TV) and must persist for at least 3 months. (1, 2) Criteria indicative of other myeloid
neoplasms and alternative causes of monocytosis should be absent. Historically, the Fre
American-British classification scheme cons blood cell (WBC) count ≥ 13 x 10° /L and a "dysplastic type" with a WBC count below this
threshold to reflect clinical and genetic distinctions between these two subtypes. (3, 4) In th
most recent WHO classification, CMML Subsequent WHO classification divided CMML into a "proliferative type" with a total w
blood cell (WBC) count ≥ 13 x 10⁹ /L and a "dysplastic type" with a WBC count below the
threshold to reflect clinical and genetic dist subsequent WHO count 2 13 x 10⁹/L and a "dysplastic type" with a WBC count below this
threshold to reflect clinical and genetic distinctions between these two subtypes. (3, 4) In the
most recent WHO classification, CMML threshold to reflect chines and general and membershold to reflect the energy pertupy of the most recent WHO classification, CMML is considered a separate entity from MDS and is classified into subtypes based on blood and classified into subtypes based on blood and bone marrow blast proportions and not on t
WBC count (Table 1).
Despite what seems like an arbitrary numerical distinction between MDS and CMML, the

classified into subtypes based on blood and bone marrow blast proportions and not on total
WBC count (Table 1).
Pespite what seems like an arbitrary numerical distinction between MDS and CMML, there is
evidence that the un WBC count (Table 1).
Despite what seems li
evidence that the und
level, patients with CN evidence that the underlying pathobiology in these disorders is quite different. At the cellular
level, patients with CMML have a high percentage of classical monocytes that are CD14⁺ and
CD16⁻. (5, 6) These cells show evel, patients with CMML have a high percentage of classical monocytes that are CD14⁺ and
CD16. (5, 6) These cells show a hypersensitivity to growth factor stimulation with granulocyte
macrophage colony-stimulating facto level, patients with CMML have a high percentage or classical monocytes that are CD14 and
CD16 . (5, 6) These cells show a hypersensitivity to growth factor stimulation with granulocyte
macrophage colony-stimulating factor CD16
macro
patier
includ
natier . (5) The set of $\frac{1}{2}$ is the set of $\frac{1}{2}$ of $\frac{1}{2}$ in the triad of $\frac{1}{2}$ patients also have distinct mutational profiles (Figure 2). Somatic mutations in several genes,
including TET2, ASXL1, SRSF2, EZH2, NRAS, KRAS and CBL are all significantly more common in
patients with CMML and are therefo patients also have distinct mutational profiles (Figure 2). Somatic mutations in several genes,
including TET2, ASXL1, SRSF2, EZH2, NRAS, KRAS and CBL are all significantly more common in
patients with CMML and are therefo including TET2, ASXL1, SRSF2, EZH2, NRAS, KRAS and CBL are an significantly more common in
patients with CMML and are therefore, more likely to co-occur. (7-9) In fact, the triad of TET2,
ASXL1, and SRSF2 mutations is high patients with CMML and are therefore, more likely to co-occur. (7-5) in fact, the triad of TET2,
ASXL1, and SRSF2 mutations is highly specific for CMML. (10-12) In contrast, mutations of SF3B
and TP53 are observed less oft

ASXL1, and SASI 2 mutations is highly specific for CNML. (10-12) In contrast, mutations of SISB1
and TP53 are observed less often than in MDS.
Clinically, patients with proliferative type CMML are enriched for RAS signalin and 77.55 are observed less often than in MDS.
Clinically, patients with proliferative type CMM
mutations and appear to have slightly greater d
similar blast proportions. (10, 13) The original a mutations and appear to have slightly greater disease related risk than MDS patients wit
similar blast proportions. (10, 13) The original and revised International Prognostic Scoria
Systems (IPSS and IPSS-R, respectively) similar blast proportions. (10, 13) The original and revised International Prognostic Scoring
Systems (IPSS and IPSS-R, respectively) only included a small fraction of patients with dysp
CMML (WBC < 13 x 10⁹ /L) while p Systems (IPSS and IPSS-R, respectively) only included a small fraction of patients with dyspla
CMML (WBC < 13 x 10⁹ /L) while proliferative CMML was excluded. (14, 15) This has led to the SMML (WBC < 13 x 10⁹ /L) whil $S₂$ CMML (WBC < 13 x 10⁹/L) while proliferative CMML was excluded. (14, 15) This has led to the $CMWL (WBC < 13 \times 10^{9})$ /L) while proliferative CMML was excluded. (14, 15) This has led to the

development of several CMML specific prognostic tools. (10, 16-19) Where these models
consider molecular abnormalities, mutations of ASXL1 are universally identified as
independent, adverse prognostic markers.
Therapeutic

consider molecular abnormalities, mutations of ASXL1 are universally identified as
independent, adverse prognostic markers.
Therapeutic approaches for CMML aim to improve symptoms related to peripheral
or blood count proli independent, adverse progressis manuscrictus
Therapeutic approaches for CMML aim to i
or blood count proliferation. Similar to pati
considered for patients with CMML if poor Therapeutic approaches for CMML and to patients with MDS, hypomethylating agents may be
considered for patients with CMML if poor prognostic factors or excess blasts are present.
Response rates and benefit from treatment w or blood count promotes with CMML if poor prognostic factors or excess blasts are present.
Response rates and benefit from treatment with hypomethylating agents appear comparab
between patients with CMML and MDS. (20, 21) Response rates and benefit from treatment with hypomethylating agents appear comparal
between patients with CMML and MDS. (20, 21) Surprisingly, responding CMML patients car
revert to a normal monocyte profile with improve Response patients with CMML and MDS. (20, 21) Surprisingly, responding CMML patients can
revert to a normal monocyte profile with improved blood counts, without demonstrating
changes in clonal burden. (22) And unlike in MD between patients with chinese matrices (20, 22) compressions, without demonstrating
revert to a normal monocyte profile with improved blood counts, without demonstrating
changes in clonal burden. (22) And unlike in MDS, DN changes in clonal burden. (22) And unlike in MDS, DNA methylation profiles predictive of I
response have been identified in CMML. (23) Allogeneic hematopoietic stem cell
transplantation (HSCT) remains the only curative tre response have been identified in CMML. (23) Allogeneic hematopoietic stem cell
transplantation (HSCT) remains the only curative treatment for CMML and should be
considered in younger patients with higher-risk CMML, althoug response have been identified in CMML. (23) Allogeneic hematopoietic stem cell
transplantation (HSCT) remains the only curative treatment for CMML and should be
considered in younger patients with higher-risk CMML, althoug considered in younger patients with higher-risk CMML, although the increased use of
intensity conditioning and alternative donor sources have allowed increased impleme
HSCT in older patients. Expert opinion, including a re intensity conditioning and alternative donor sources have allowed increased implementation of
HSCT in older patients. Expert opinion, including a recent international panel, suggests
treatment before HSCT particularly when intensity commissions and alternative alternative must have allowed interesting implementation of
HSCT in older patients. Expert opinion, including a recent international panel, suggests
treatment before HSCT particularly Holder in order patients. Expert opinion, including a recent international panel, suggests
treatment before HSCT particularly when marrow blasts are >10% or other higher-risk f
are present. (24, 25)
The next most common MD

treatment before HSCT particularly when marrow blasts are solven blasts in the basic features
are present. (24, 25)
thrombocytosis (MDS/MPN-RS-T). This entity has very little resemblance to CMML despite are present. (24, 25)
The next most comm
<mark>thrombocytosis (MD</mark>
being in the same dia The next most common MDS/MPN overlap disorder is MDS/MPTN with ring sideroblasts and
thrombocytosis (MDS/MPN-RS-T). This entity has very little resemblance to CMML despite
being in the same diagnostic category. Patients w thrombocytosis (MD3) MH N-N3-1). This entity has very little resemblance to CMML despite
being in the same diagnostic category. Patients with MDS/MPN-RS-T meet criteria for MDS
ring sideroblasts 215% and also must have a p being in the same angular category. Patients with MDS yin to the structure with MDS-Window
ring sideroblasts 215% and also must have a persistently elevated platelet count (2.450 x 10⁹
/L). Classical hotspot mutations of ring sideroblasts ≥15% and also must have a persistently elevated platelet count (≥ 450 x 10
/L). Classical hotspot mutations of *SF3B1* are found in over 80% of cases resembling the rate
SF3B1 mutation observed in MDS- $\frac{1}{2}$ *SF3B1* mutation observed in MDS-RS patients with single lineage dysplasia (MDS-RS-SLD), and
are often the likely founder mutation based on variant frequency and occurrence as the sole
abnormality in some patients. (26) MD in JAK2 (50-70%), CALR (10-20%), and MPL (2-5%) comparable to the mutational spectrum abnormality in some patients. (26) MDS/MPN-RS-T patients also have a high rate of mutation
in JAK2 (50-70%), CALR (10-20%), and MPL (2-5%) comparable to the mutational spectrum
observed in essential thrombocythemia (ET). (in JAK2 (50-70%), CALR (10-20%), and MPL (2-5%) comparable to the mutational spectrum
observed in essential thrombocythemia (ET). (27, 28) Mutations in several other genes may be
present, including TET2, DNMT3A, ASXL1, and in JAK2 (50-70%), CALR (10-20%), and MPL (2-5%) comparable to the mutational spectrum
observed in essential thrombocythemia (ET). (27, 28) Mutations in several other genes may
present, including TET2, DNMT3A, ASXL1, and S observed in equal to the latter two being considered
prognostically adverse. (29) The prognosis of patients with MDS/MPN-RS-T lies between that of
patients with MDS-RS-SLD and ET and the leukemic transformation rate per 10 present, including TET2, DWWT3A, ASXL1, and SETBT1 with the latter two being considered
prognostically adverse. (29) The prognosis of patients with MDS/MPN-RS-T lies between that
patients with MDS-RS-SLD and ET and the leu patients with MDS-RS-SLD and ET and the leukemic transformation rate per 100 years is similar
in MDS/MPN-RS-T (1.8) and MDS-RS-SLD (2.4), and higher in MDS/MPN-RS-T when compared
to ET (0.7). (30) Rates of thrombosis are s pation MDS/MPN-RS-T (1.8) and MDS-RS-SLD (2.4), and higher in MDS/MPN-RS-T when compared
to ET (0.7). (30) Rates of thrombosis are similar in MDS/MPN-RS-T to that of ET, but higher than
in MDS-RS. (30, 31) In patients with in MDS-RS. (30) Rates of thrombosis are similar in MDS/MPN-RS-T to that of ET, but higher that
in MDS-RS. (30, 31) In patients with anemia, treatment is usually supportive with ESA and
transfusions following guidelines for to Et (1.7). (2.9) these of thrombosis are similar in MDS-7, thromatic to the thrombosis in MDS-RS. (30, 31) In patients with anemia, treatment is usually supportive with ESA and
transfusions following guidelines for lower transfusions following guidelines for lower risk MDS. Low-dose aspirin may be prescribed to
patients with JAK2 mutations, older age, or cardiovascular risk factors. While del(5q) is not
common in MDS/MPN-RS-T, case reports transfusions following guidelines for the term and the settom in particular processes patients with JAK2 mutations, older age, or cardiovascular risk factors. While del(5q) is not common in MDS/MPN-RS-T, case reports have patients with JAK2 mutations, older age, or cardiovascular risk factors. While del(5q) is not
common in MDS/MPN-RS-T, case reports have described activity of lenalidomide, a drug th
typically causes thrombocytopenia. (32) common in MDS/MPN-RS-T, case reports have described activity of reports in M_D mass
typically causes thrombocytopenia. (32) Cytoreductive therapy is generally avoided as it can
experience thrombocytopenia. $t_{\rm F}$ causes there is generally is generally is generally avoided as it can as it can be defined as it can be def

thrombosis, vasomotor symptoms, or acquired von Willebrand syndrome.
Atypical chronic myeloid leukemia (aCML) is another WHO-recognized MDS/MPN overla
syndrome characterized by leukocytosis. (33) As its name suggests, it i thrombosis, vasomotor symptoms, or acquired von Willebrand syndrome. syndrome characterized by leukocytosis. (33) As its name suggests, it is distinct from classical
chronic myeloid leukemia (CML) driven by the *BCR-ABL1* fusion gene. Specifically, aCML
requires some degree of dysgranulopoi syndrome characterized by leading (25) and the main suggests, it is name to the increased
chronic myeloid leukemia (CML) driven by the *BCR-ABL1* fusion gene. Specifically, aCML
requires some degree of dysgranulopoiesis in chronic myeloid leukemia (CML) driven by the BCA-ABL1 fusion gene. Specifically, aCML
requires some degree of dysgranulopoiesis in the blood and bone marrow, minimal or no
absolute basophilia (common in CML), minimal or no absolute basophilia (common in CML), minimal or no absolute monocytosis (common in
CMML), and no gene rearrangements associated with other neoplasms (e.g., *BCR-ABL1*,
PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2). Mutations typica CMML), and no gene rearrangements associated with other neoplasms (e.g., *BCR-ABL1,
PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2*). Mutations typical of *BCR-ABL1* MPN, like thos
JAK2, CALR, and MPL, make a diagnosis of aCML less l CMML), and no gene rearrangements associated with other neoplasms (e.g., BCA-ABL1,
PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2). Mutations typical of BCR-ABL1⁻ MPN, like thos
JAK2, CALR, and MPL, make a diagnosis of aCML less li PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2). Mutations typical of BCR-ABL1-MPN, like those in
JAK2, CALR, and MPL, make a diagnosis of aCML less likely. The same is true for mutations of
CSF3R that is found in <10% of patients wi SANZ, CALA, and MPL, make a diagnosis of activitiess likely. The same is true for mutations of
CSF3R that is found in <10% of patients with aCML, compared to 80-90% of patients with
chronic neutrophilic leukemia (CNL), a c CSF3R that is found in <10% of patients with aCML, compared to 80-90% of patients with
chronic neutrophilic leukemia (CNL), a clinically similar disorder that also presents with
leukocytosis but no dysgranulopoiesis. (34-3 eukocytosis but no dysgranulopoiesis. (34-36) No single molecular abnormality specific
aCML has been described, although SETBP1 mutations occur more frequently in aCML (
compared to CMML (6-15%) and JMML (3%). (37) Recurre aCML has been described, although *SETBP1* mutations occur more frequently in aCML (25%)
compared to CMML (6-15%) and JMML (3%). (37) Recurrent mutations in several other CMM
like genes have also been detected in patients compared to CMML (6-15%) and JMML (3%). (37) Recurrent mutations in several other CMML-
like genes have also been detected in patients with aCML (**Figure 2**). (38) In general, aCML
patients tend to have a more aggressive d ϵ compared to CMM and the CMML (39) ϵ CMM (39) and ϵ commonly a separate mutations in several other CMMLpatients tend to have a more aggressive disease course compared to patients with MDS/MPN, unclassifiable (MDS/MPN-U). (33) While there is no consensus on the role of HSCT, long-term remissions have been reported with this patients tend to have a more aggressive allevate courspace of patients with MDS/MPN-1,
include in the been reported with this strategy. (39) Other commonly employed treatments
include hypomethylating agent therapy and cyto manutation (MDS/MPN-U). Carry there is no consensute on the role of Jong Carne
include hypomethylating agent therapy and cytoreduction with hydroxyurea. The
investigational use of JAK inhibitors has also been implemented i include hypomethylating agent therapy and cytoreduction with hydroxyurea. The
investigational use of JAK inhibitors has also been implemented in aCML and CNL based on the
knowledge that some CSF3R mutations, most commonly investigational use of JAK inhibitors has also been implemented in aCML and CNL knowledge that some *CSF3R* mutations, most commonly *CSF3R*^{T618}, may activate to pathway. (40) knowledge that some *CSF3R* mutations, most commonly *CSF3R^{T618|},* may activate the JAK/STAT
pathway. (40)
Juvenile myelomonocytic leukemia (JMML) is an uncommon MDS/MPN overlap syndrome tha

knowledge that some CS*F3R* mutations, most commonly CS*F3RTT ,* may activate the JAK/STAT
pathway. (40)
J<mark>uvenile myelomonocytic leukemia (JMML)</mark> is an uncommon MDS/MPN overlap syndrome tha[.]
occurs in early childhood wi pathway. (40)
Juvenile myek
occurs in early
minority of pat Survenile myelomonocytic leukemia (JMML) is an uncommon MDS/MPN overlap syndrome that
occurs in early childhood with median age of 2 years. Clinical outcomes vary in JMML, with a
minority of patients experiencing spontaneo occurs in early children than the main age of 2 years. Children children the childhood minority of patients experiencing spontaneous remission, particularly those with germline diseases such as Noonan or CBL syndrome, and minority of patients experiencing spontance is continuity, parameter, and spontaneously diseases such as Noonan or CBL syndrome, and some patients relapsing despite SCT. While
there are shared clinical features with CMML, there are shared clinical features with CMML, such as monocytosis and marked
hepatosplenomegaly, the genetic landscape in JMML is distinct from adult myeloid neoplas
by the near absence of mutations in epigenetic and splic hepatosplenomegaly, the genetic landscape in JMML is distinct from adult myel
by the near absence of mutations in epigenetic and splicing modifiers. Up to 95?
with JMML will possess either a somatic or germline mutation in hepatosplenomegaly, the general antisoty is a number and myeloid neutron yelds to perform by the near absence of mutations in epigenetic and splicing modifiers. Up to 95% of children with JMML will possess either a somatic by the JMML will possess either a somatic or germline mutation in a Ras pathway gene (PTPN1

NF1, NRAS, KRAS, CBL). (41-43) Despite some patients having identical genetic mutation

profiles, differing clinical outcomes are *NF1, NRAS, KRAS, CBL*). (41-43) Despite some patients having identical genetic mutation
profiles, differing clinical outcomes are observed. Recently, DNA methylation patterns were
shown to improve the prediction of outcom NF1, NNAS, KNAS, CBL). (41-43) Despite some patients having identical genetic mutation
profiles, differing clinical outcomes are observed. Recently, DNA methylation patterns w
shown to improve the prediction of outcomes, d profiles, the word of the prediction of outcomes, distinguishing JMML patients who experience
spontaneous remission from those who experienced an aggressive disease course. (44)
Other Myeloid Neoplasms with Overlapping Dys shown to improve the prediction of anothers, altemgenting them pattents the superioristic
spontaneous remission from those who experienced an aggressive disease course. (44)
Other Myeloid Neoplasms with Overlapping Dysplas

Spontaneous remission from the componenced an aggressive means remissive.
Other Myeloid Neoplasms with Overlapping Dysplastic and Proliferative Features. Other Myeloid Neoplasms with Overlapping Dysplastic and Proliferative Features

WHO-defined MDS/MPNs are considered distinct diagnoses, separate from the overlapping
syndromes they resemble. Yet myeloid malignancies can co-occur or have such nebulous
boundaries that there exists an area of apparent di s
boundaries that there exists an area of apparent diagnostic overlap. This can be challengin
clinically as treatment recommendations may differ across what may be rather arbitrary
diagnostic borders. Consideration of clin boundaries that there enter the there exists an argument diagnosing that the existing diagnostic borders. Consideration of clinical and molecular features may help determine whis condition should take precedence. cliagnostic borders. Consideration of clinical and molecular features may help determine
condition should take precedence.
Due to its unique clinical and pathologic features, **systemic mastocytosis (SM)** is now

condition should take precedence.
Due to its unique clinical and pathologic features, systemic mastocytosis (SM) is now
recognized as its own disease category by the WHO. SM is divided into indolent SM (ISM), Due to its unique clinical and pathologic features, systemic mastocytosis (SM) is now
recognized as its own disease category by the WHO. SM is divided into indolent SM (ISM),
smoldering SM (SSM), SM with an associated clon Bue to its unique clinical and pathologic reatures, systemic mastocytosis (SM) is now
recognized as its own disease category by the WHO. SM is divided into indolent SM (IS
smoldering SM (SSM), SM with an associated clonal recognized as its own district energies, by the WHO with district materials in (CM,)
smoldering SM (SSM), SM with an associated clonal hematologic non-MC-lineage disease t
was renamed to systemic mastocytosis with associat smolder in the associated hematologic neoplasm (SM-AHN) in th
WHO 2016 update, aggressive SM (ASM) and mast cell leukemia (MCL). (1) In addition to
activating mutations in KIT, mutations in TET2, SRSF2, ASXL1, CBL, RUNX1 a WHO 2016 update, aggressive SM (ASM) and mast cell leukemia (MCL). (1) In addition to
activating mutations in KIT, mutations in TET2, SRSF2, ASXL1, CBL, RUNX1 and RAS have been
identified in patients with SM-AHN, ASM and activating mutations in *KIT*, mutations in *TET2, SRSF2, ASXL1, CBL, RUNX1* and *RAS* have b
identified in patients with SM-AHN, ASM and MCL. (45) Additionally, mutations in *ETNK1*
frequently seen in patients with SM wit activating mutations in KIT, mutations in TET2, SRSF2, ASXL1, CBL, NOWAT and AAS have been
identified in patients with SM-AHN, ASM and MCL. (45) Additionally, mutations in ETNK1 are
frequently seen in patients with SM with frequently seen in patients with SM with eosinophilia. (46) Among patients with SM-AHN, these
mutations may be co-expressed with KIT D816V in the same cells, or expressed by other nonmutations may be co-expressed with KIT D816V in the same cells, or expressed by other non-
MC myeloid cells. (47, 48) Colony assay studies found that KIT D816V mutations are often late
events, frequently preceded by mutati MC myeloid cells. (47, 48) Colony assay studies found that *KIT* D816V mutations are often late events, frequently preceded by mutations of *TET2, SRSF2*, and *ASXL1*, indicating that SM-AHN a multi-mutated malignancy with MC myeloid cells. (47, 48) Colony assay studies found that KIT D816V mutations are often late
events, frequently preceded by mutations of TET2, SRSF2, and ASXL1, indicating that SM-AHN i
a multi-mutated malignancy with div a multi-mutated malignancy with diverging molecular evolution in subclones that have distinct

CMML (29%), SM-MDS (23%). (49) The largest study to date comparing patients with SM-CMML Myeloid neoplasms account for 90% of all SM-AHN patients, including SM-MPN (45%), SM-
CMML (29%), SM-MDS (23%). (49) The largest study to date comparing patients with SM-CM
(n=50) versus CMML alone (n=501) evaluated differ for V/T and CRL mutations in the SM-CMMIL cohert, suggesting that late V/T mutations may (n=50) versus CMML alone (n=501) evaluated differences in clinical, cytogenetic and genetic
features and clinical outcomes. (50) Both groups had similar mutation profiles, with exception
for KIT and CBL mutations in the S (n=50) versus Community (n=50) seminarity interested in clinical, cytogenetic and generic
features and clinical outcomes. (50) Both groups had similar mutation profiles, with exceptio
for KIT and CBL mutations in the SM-CM for *KIT* and *CBL* mutations in the SM-CMML cohort, suggesting that late *KIT* mutations may alte
an initial CMML phenotype into one consistent with SM-CMML.
Of note, *KIT* D816V may be viewed as a differentiation-inducer

for KIT and CBL mutations in the SM-CMML cohort, suggesting that fate KIT mutations may alter
an initial CMML phenotype into one consistent with SM-CMML.
Of note, *KIT* D816V may be viewed as a differentiation-inducer in n an initial CMML phenotype into one consistent with CMML.
Of note, *KIT* D816V may be viewed as a differentiation-inducer ir
dominant driver of oncogenesis, as patients with ISM express *KI*:
have limited survival. (51, 52) Of note, KIT D816V may be viewed as a differentiation inducer in neoplastic cells rather than a
dominant driver of oncogenesis, as patients with ISM express KIT D816V and do not typically
have limited survival. (51, 52) Ad have limited survival. (51, 52) Additional pathways mediated by oncogenic lesions preceding KIT mutations are likely responsible for a more aggressive disease phenotype, treatment resistance and shortened survival. To this mutations are likely responsible for a more aggressive disease phenotype, treatment resistance higher-risk CMML and resultant peripheral cytopenias may be treated with a hypomethylating component requires more immediate intervention. For example, a patient with an assoc
higher-risk CMML and resultant peripheral cytopenias may be treated with a hypomethy
agent, whereas mast cell directed therapy may be app component requires more immediate intervention. The manging part in the area bigher-risk CMML and resultant peripheral cytopenias may be treated with a hypomethylating
agent, whereas mast cell directed therapy may be appro higher-risk CMML and resultant peripheral cytopenias may be a constant with a lower-risk
non-MC malignancy and symptoms or organ dysfunction ("C findings") related to the MC
component of the disease. (53) Midostaurin is an non-MC malignancy and symptoms or organ dysfunction ("C findings") related to the MC
component of the disease. (53) Midostaurin is an approved tyrosine kinase inhibitor with non-malignancy and symptoms or organ ay entired to chinange y center to the MC
component of the disease. (53) Midostaurin is an approved tyrosine kinase inhibitor with
activity against KIT D816V that demonstrated an overal activity against KIT D816V that demonstrated an overall response rate of 60% among pation and the disease in the
activity against KIT D816V that demonstrated an overall response rate of 60% among pation. activity against KIT D816V that demonstrated an overall response rate of 60% among patients

selective KIT inhibitors. Future treatment strategies that extend beyond KIT are under
investigation and include targeting pathways involving RAS, PI3K, mTOR, STAT5 and members
of the BCL2 family. (55, 56) investigation and include targeting pathways involving RAS, PI3K, mTOR, STAT5 and m
of the BCL2 family. (55, 56)
 investigation and include targeting pathways involving RAS, MTOR, mTOR, STAT5 and members
of the BCL2 family. (55, 56)
STATISTICS

of the BCL₂
Aplastic Anemia and Hypoplastic MDS

 $\frac{1}{2}$ Another area of diagnostic overlap occurs between aplastic anemia (AA) and hypoplastic MDS
(hMDS). While the etiology of AA is typically considered distinct from that of MDS, with AA
driven by immune-mediated destruction o driven by immune-mediated destruction of hematopoietic stem/progenitor cells (HSPCs) and MDS driven by a selective growth advantage of somatically mutated clonal HSPCs, in practice,
these mechanisms may co-occur (Figure 1). First, among a subset of patients with lower-risk
MDS, immune activation and inflammati These mechanisms may co-occur (Figure 1). First, among a subset of patients with lower-risk
MDS, immune activation and inflammation drive the selection of somatically mutated clones,
potentiating response to immunosuppress MDS, immune activation and inflammation drive the selection of somatically mutated clones
potentiating response to immunosuppressive therapies (ISTs). (57, 58) Second, up to 15% of
patients with severe AA (SAA) will evolve potentiating response to immunosuppressive therapies (ISTs). (57, 58) Second, up to 15% of
patients with severe AA (SAA) will evolve into MDS and/or acute myeloid leukemia (AML). (59
60) Distinguishing AA from hMDS may be patients with severe AA (SAA) will evolve into MDS and/or acute myeloid leukemia (AML). (5
60) Distinguishing AA from hMDS may be challenging as patients with these diseases share
many clinical features such as bone marrow patients with these diseases share

patients with these diseases share

patients with these diseases share

marphologic dysplasia, clonal cytogenetic and/or genetic abnormalities, and clinically

meaningful responses to IS many clinical features such as bone marrow hypocellularity that hinders accurate evaluation
morphologic dysplasia, clonal cytogenetic and/or genetic abnormalities, and clinically
meaningful responses to ISTs. Additionally, many clinical features such as bone matrix in type centrality and minister accurate evaluation of
meaningful responses to ISTs. Additionally, a subset of patients with AA harbor somatically
mutated clones defined by mutati morphologic dysplasia, (62) Excluding *PIGA* mutations 29 of 150 (19%) patients with AM
study evaluated somatic mutations in bone marrow samples from 150 patients with A
morphologic dysplasia, (62) Excluding *PIGA* mutatio mutated clones defined by mutations recurrently found in patients with MDS. (61) A recent
study evaluated somatic mutations in bone marrow samples from 150 patients with AA and
morphologic dysplasia. (62) Excluding *PIGA* study evaluated somatic mutations in bone marrow samples from 150 patients with AA and no morphologic dysplasia. (62) Excluding PIGA mutations, 29 of 150 (19%) patients harbored morphologic dysplasia. (62) Excluding PIGA mutations, 29 of 150 (19%) patients harbored
mutations, predominantly in ASXL1, DNMT3A, and BCOR (Figure 2). 17 (11%) patients
experienced progression to MDS, with 11 of these pat experienced progression to MDS, with 11 of these patients belonging to the group of 29
patients who possessed mutations. Somatic mutations were significantly associated with longer
disease duration, shorter telomere length experienced progression to the system of these patients a stragging to the group of the group of patients who
disease duration, shorter telomere lengths and greater likelihood of progressing to MDS
compared to patients wit patients who possessed uration, shorter telomere lengths and greater likelihood of progressing to MDS or AML
compared to patients without mutations. A similar study of 439 patients with AA found clonal
hematopoiesis in 47% discompared to patients without mutations. A similar study of 439 patients with AA found clonal
hematopoiesis in 47% of patients, with inferior survival outcomes seen among patients with
DNMT3A and ASXL1 mutations, and hig compate poiss in 47% of patients, with inferior survival outcomes seen among patients with
COMMT3A and ASXL1 mutations, and higher IST response rates seen among patients with BCOR
and PIGA mutations. (63) SAA patients with behavior of patients in the matrices.

hematom and PIGA mutations. (63) SAA patients with MDS-like mutations were more likely to have the

clones expand over time, particularly after IST. Other patients can harbor somatic DIWITSA and ASXL1 mutations, and inglier is Fresponse rates seen among patients with DCON
and PIGA mutations. (63) SAA patients with MDS-like mutations were more likely to have these
clones expand over time, particularly a clones expand over time, particularly after IST. Other patients can harbor somatic copy number-
neutral loss of heterozygosity at the HLA locus on chromosome arm 6p (6p CN-LOH) (64) or
mutations in human leukocyte antigens controlled over the process expanding over the community attending and process of more often in younger patients, and are associated with lower rates of neoplastic progression.
(67, 68) neutral loss of heterosygosity at the HLA locus on chromosome arm op (op ON-LOH) (64) or
mutations in human leukocyte antigens (HLA) and related pathways. (65-66) These
abnormalities appear to provide escape from HLA-restr mutations in human leukocyte antigens (HLA) and related pathways. (CC-CO) increases
abnormalities appear to provide escape from HLA-restricted T cell immunity driving
more often in younger patients, and are associated with more often in younger patients, and are associated with lower rates of neoplastic progression.
(67, 68) $(6, 6)$

Approximately 15-20% of MDS bone marrows are hypocellular for age. These patients have
differences in genetic profiles that include both a lower rate of mutations and lower frequency
of splicing factor gene mutations compa of splicing factor gene mutations compared to hyperplastic patients. (69) This pattern is more
similar to that observed in SAA. Since bone marrow cellularity is limited, morphologic dysplasia
is difficult to evaluate when of spiring factor gene mutations compared to hyperplastic patterns (e.g.) the pattern is more
similar to that observed in SAA. Since bone marrow cellularity is limited, morphologic dysplasia
is difficult to evaluate when c is difficult to evaluate when considering hMDS vs. SAA or non-severe AA. Other morphologic
features outside of dysplasia that support a diagnosis of hMDS, or a MDS/MPN overlap
syndrome, over AA include excess bone marrow b features outside of dysplasia that support a diagnosis of hMDS, or a MDS/MPN overlap
syndrome, over AA include excess bone marrow blasts (≥2%), ring sideroblasts, extensive
fibrosis, and circulating pseudo-Pelger-Huet cell features secures on appearance or process and computers of that spideroblasts, extensive
fibrosis, and circulating pseudo-Pelger-Huet cells. Certain cytogenetic abnormalities suc
del(5q), monosomy 7, or inversion 3 are con syndrome, our Christman and Christman Christman (≥2%), ring sideromancy, sideroles is
del(5q), monosomy 7, or inversion 3 are considered presumptive evidence of MDS. (70, 7)
paucity of splicing factor and cohesin mutations fibrosis, and christming predicting transitional certain cytogenetic above and del(5q), monosomy 7, or inversion 3 are considered presumptive evidence of MDS. (70, 71)
paucity of splicing factor and cohesin mutations in AA paucity of splicing factor and cohesin mutations in AA suggests that these lesions may also help
define the distinction between these disorders in the future. A lack of common MDS mutations
or the presence of abnormalities define the distinction between these disorders in the future. A lack of common MDS mutations
or the presence of abnormalities of *BCOR, PIGA,* or the HLA loci correlate with more favorable
outcomes in SAA and may be surrog or the presence of abnormalities of *BCOR, PIGA,* or the HLA loci correlate with more favorable
outcomes in SAA and may be surrogate molecular markers of this disorder absent MDS defining
features. In the meantime, a pract or the presence of abnormances of BCOR, PTOA, or the HLA loci correlate with more favorable
outcomes in SAA and may be surrogate molecular markers of this disorder absent MDS definin
features. In the meantime, a practical features. In the meantime, a practical approach would be to minimize the distinction between
hMDS and AA and simply consider patients at this boundary to be potentially responsive to
immune suppression, reserving molecular hMDS and AA and simply consider patients at this boundary to be potentially responsive to
immune suppression, reserving molecular studies to identify patients at risk for evolution to
higher risk disease. immune suppression, reserving molecular studies to identify patients at risk for evolution to
higher risk disease.
One important caveat to this approach involves patients with inherited bone marrow failure

implies the suppression of the suppression included the higher risk disease.
The important caveat to this approach involves patients with inherited bone marrow failure
Syndromes, many of which can evolve into MDS or AML. F mg. There we have
One important cave
syndromes, many o
mutations of *GATA2* syndromes, many of which can evolve into MDS or AML. For example, individuals with germline
mutations of *GATA2*, *DDX41*, Fanconi anemia genes, or telomerase complex genes can have
hypoplastic marrow findings well before step of the Manuscript Can evolve in the mutations of GATA2, DDX41, Fanconi anemia genes, or telomerase complex genes can have
thypoplastic marrow findings well before the development of a clonal myeloid disorder which in
 mutations of GATA2, DDA41, Fancom anemia genes, or telomerase complex genes can have
hypoplastic marrow findings well before the development of a clonal myeloid disorder which
some cases, might never occur. Identifying the does not respond to immune suppression. There are also important implications involving the
health of family members, related stem cell donor candidates, and increased toxicity of IST or cytotoxic therapy. To make matters worse, some germline predisposition mutations, such as does not response to immune suppression. There are an any completence in the and the suppression of the proper
cytotoxic therapy. To make matters worse, some germline predisposition mutations, such as
those in *RUNX1* and extotoxic therapy. To make matters worse, some germline predisposition mutations, such as
those in RUNX1 and ANKRD26, may cause thrombocytopenia and megakaryocyte dysplasia that
could be mistaken as MDS-defining criteria. chose in *RUNX1* and *ANKRD26*, may cause thrombocytopenia and megakaryocyte dysplasia the
could be mistaken as MDS-defining criteria. (72, 73) This diagnosis should not be made in the
absence of other diagnostic elements. could be mistaken as MDS-defining criteria. (72, 73) This diagnosis should not be made in the absence of other diagnostic elements. (74) In this context, however, the presence of somatic mutations may indicate a greater ri absence of other diagnostic elements. (74) In this context, however, the presence of somatic mutations may indicate a greater risk of neoplastic progression. (75, 76) Mutation testing of
presumed *de novo* MDS patients may also detect germline variants, as many of the genes
tested are included in these panels. (77 mutations may mutations government may provide progression (23, 76) mutation testing of
presumed de novo MDS patients may also detect germline variants, as many of the genes
tested are included in these panels. (77) These presumed de novo WDS patients may also detect germine variants, as many or the genes
tested are included in these panels. (77) These variants can occur even in patients without
family history, young age of onset, or associ the mily history, young age of onset, or associated physical findings typical of germline
predisposition syndromes. (78) Dedicated testing of non-hematopoietic tissue is recommend
in cases where such a germline variant is family matricy, young age of ontoes, or account to priy from manings typical or germine
predisposition syndromes. (78) Dedicated testing of non-hematopoietic tissue is reco
in cases where such a germline variant is suspect in cases where such a germline variant is suspected. (79, 80)

ی
Clonal Hematopoiesis, Unexplained Cytopenias, and Lower Risk MDS
این که در این کلیه ا $\overline{}$

Another diagnostic boundary with MDS involves patients with unexplained cytopenias often
described as **idiopathic cytopenias of undetermined significance (ICUS)**. These patients lack
MDS-defining bone marrow criteria that described as idiopatine cytopermas of undetermined significance (ICOS). These patients lack
MDS-defining bone marrow criteria that include an increased blast proportion, specific
cytogenetic abnormalities, or morphologic d experience and the matrix is that in the matrix of marrier and the proportion, specific cytogenetic abnormalities, or morphologic dysplasia in at least 10% of cells of a given lin
(Figure 3). (81) Sequencing studies have i hematopoiesis in nearly 40% of ICUS patients and closer to 70% in those who have some degree
of dysplasia. (82, 83) These individuals are described as having a clonal cytopenia of (Figure 3). (81) Sequencing studies have identified somatic abnormances indicative of clonar
hematopoiesis in nearly 40% of ICUS patients and closer to 70% in those who have some deg
of dysplasia. (82, 83) These individual of dysplasia. (82, 83) These individuals are described as having a clonal cytopenia of
undetermined significance (CCUS). Patients with CCUS can have many of the same mutated
genes observed in lower risk MDS and have compar of dysplasia. (82, 83) These individuals are described as having a clonal cycopenia or
undetermined significance (CCUS). Patients with CCUS can have many of the same m
genes observed in lower risk MDS and have comparable v genes observed in lower risk MDS and have comparable variant allele frequencies although
mutations of *SF3B1* appear to be more specific for MDS. Patients with CCUS have a high rate
progression to MDS or other myeloid mali mutations of *SF3B1* appear to be more specific for MDS. Patients with CCUS have a high rate
progression to MDS or other myeloid malignancies, particularly if they carry higher risk feati
such as somatic mutations in *JAK2* progression to MDS or other myeloid malignancies, particularly if they carry higher risk features
such as somatic mutations in JAK2, RUNX1, one of the commonly mutated splicing factors progression to MDS or other myeloi manguments, particularly if they can progression to MDS or such as somatic mutations in JAK2, RUNX1, one of the commonly mutated splicing factors
(SF3B1, SRSF2, U2AF1, ZRSR2), or two or m (*SF3B1, SRSF2, U2AF1, ZRSR2*), or two or more mutations. (84) This risk may be as high as 90%
at 5-years. For single mutations of *DNMT3A, TET2,* or *ASXL1,* the risk of progression is lower at
~50% at 5-years. An absence (SF3B1, SRSF2, U2AF1, ZRSR2), or two or more mutations. (84) This risk may be as high as 30%
at 5-years. For single mutations of *DNMT3A, TET2, or ASXL1*, the risk of progression is lower at
~50% at 5-years. An absence of at 5-years. For single mutations of DNMT3A, TET2, or ASXL1, the risk or progression is lower at

~50% at 5-years. An absence of mutations on a broad panel of the 40 most frequently mutated

MDS genes has a very low rate of MDS genes has a very low rate of progression approaching 1% per year of follow up. Since MDS
defining bone marrow dysplasia can be hard to quantify, future revisions to MDS diagnostic
criteria may include more clearly def MDS genes has a very low rate of progression approaching 1% per year of follow up. Since MDScriteria may include more clearly defined higher risk CCUS patients just as *SF3B1* mutations are
currently accepted as evidence of MDS-RS in patients with as few as 5% ring sideroblasts. (1)
An important caveat to remembe

criteria may include more clearly defined higher risk CCO5 patients just as SF3B1 mutations are
currently accepted as evidence of MDS-RS in patients with as few as 5% ring sideroblasts. (1)
An important caveat to remember current of the line of the tend as the tend as the tend as An important caveat to remember is that somatic mutations typical of MDS can also occur in
the blood cells of *hematologically normal persons,* with a prevalence t The blood cells of *hematologically normal persons*, with a prevalence that increases markedly
with age. (85, 86) These individuals are said to have clonal hematopoiesis of indeterminate
potential (CHIP) and in the absence the blood cells of *hematologically hormal persons*, with a prevalence that increases markedly
with age. (85, 86) These individuals are said to have clonal hematopoiesis of indeterminate
potential (CHIP) and in the absence potential (CHIP) and in the absence of cytopenias (or another concerning clinical context sud
as a germline predisposition) are believed to have a very low risk of neoplastic progression (
per year). CHIP mutations are mos potential (CHIP) and in the absence of cytoperias (or another concerning clinical context such
as a germline predisposition) are believed to have a very low risk of neoplastic progression (~1)
per year). CHIP mutations are per year). CHIP mutations are most often found in DNMT3A, TET2, or ASXL1 (Figure 2) as
isolated lesions with a low VAF (<10%) and should not be considered diagnostic of MDS or any
myeloid neoplasm. CHIP should also not be per year). CHIP mutations are most often found in DNMT3A, TET2, or ASXL1 (Figure 2) as
isolated lesions with a low VAF (<10%) and should not be considered diagnostic of MDS o
myeloid neoplasm. CHIP should also not be equat myeloid neoplasm. CHIP should also not be equated with CCUS where mutations are more
frequent, of greater abundance, and associated with a much higher probability of malignar
progression. (82-84, 87, 88) frequent, of greater abundance, and associated with a much higher probability of malignant frequent, of greater abundance, and associated with a much higher probability of malignant
progression. (82-84, 87, 88)

progression. (82-84, 87, 88)
MDS Progression to Secondary AML

At the other end of the prognostic spectrum for MDS lies the boundary with secondary acute

myeloid leukemia (sAML). The border between these disorders has shifted over time with the

WHO classification for sAML currently myeloid leukemia (sAML). The border between these disorders has sinted over time with the
WHO classification for sAML currently defined as \geq 20% bone marrow and/or peripheral blood
blasts. Under the earlier French-Ameri WHO CONDITENTS IS NOT 2000 AND THE VEHING ASSEMBLE TO THE WATER AND, THE PREPIDENTIC LETTING BOTH blasts were
Were considered to have refractory anemia with excess blasts in transformation. The poor
Were considered to have were considered to have refractory anemia with excess blasts in transformation. The poor were considered to have refractory anemia with excess blasts in transformation. The poor

outcome of this latter group prompted the lower blast threshold set by the WHO, but in
retrospect, it is not clear that MDS patients with 10-19% bone marrow blasts have meaningfully
different outcomes. In practice, these t different outcomes. In practice, these two groups straddling the divide between MDS and AML MDS with excess blasts and low blast count sAML, unifying them under the term oligoblastic when appropriate. For these reasons, there have been calls to do away with the concepts of
MDS with excess blasts and low blast count sAML, unifying them under the term oligoblasti
leukemia. (89) However, arbitrarily redef WHEN appropriate. For these reasons, were noted to an allege and y there is a way with the conseptents.
MDS with excess blasts and low blast count sAML, unifying them under the term oligoblastic
leukemia. (89) However, arb MDS WITH EXCESSIONS INTERTMENT COUNTRILING, AND JUSTIM SINCE AND CONDITED THE TERM ORGETS BE
Leukemia. (89) However, arbitrarily redefining the boundary between MDS and AML may not
enough. The challenge will be to identify enough. The challenge will be to identify those MDS patients who are headed toward leukemic
progression and those that may have excess blasts but largely fail to progress.

enough the challenge whose to identify these the eponement are headed to identify any
progression and those that may have excess blasts but largely fail to progress.
The existence of the latter group can be inferred from t The existence of the latter group can be inferred from the population of prognostically higher The exist patients who live longer than the median for their IPSS-R risk group. (90) These individuals
have a time-dependent risk that more closely resembles that of MDS patients with lower risk
disease. Since this determi have a time-dependent risk that more closely resembles that of MDS patients with lower risk disease. Since this determination is not made at diagnosis, several studies have attempted to
risk stratify MDS patients based on their leukemic potential earlier in the course of their
disease. For example, Makishima et a risk stratify MDS patients based on their leukemic potential earlier in the course of their
disease. For example, Makishima et al. examined tumor samples from over 2000 patient
mutated genes enriched in higher risk MDS and disease. For example, Makishima et al. examined tumor samples from over 2000 patients for mutated genes enriched in higher risk MDS and sAML. (91) Mutations of *NPM1, IDH1, IDH2,*
WT1, NRAS, PTPN11, and *FLT3* were found significantly more often in the sAML cohort.
Mutations of these genes were typically subc mutated genes enriched in higher risk MDS and SAML. (91) Mutations of *NPM1, IDH1, IDH2,*
WT1, NRAS, PTPN11, and *FLT3* were found significantly more often in the sAML cohort.
Mutations of these genes were typically subc WT1, WAS, PTPN11, and FLT3 were found significantly more often in the sAML cohort.
Mutations of these genes were typically subclonal to a more abundant mutation (sugge
they were acquired later) and were associated with sig Mutations of these genes were typically subclonal to a mutation mutation (suggesting
they were acquired later) and were associated with significantly shorter progression free
survival. In MDS, acquisition of these gene mut they were acquisition of these gene mutations may define leukemic clones that mill

survival. In MDS, acquisition of sAML for many months. Such patients could be said to h

an overlap disorder between MDS and sAML. One imp survival. In MDS, and interest and the mutations may be all the said to harbor these generalistics of the said to harbor overlap disorder between MDS and sAML. One implication of this hypothesis is that therapies targeted an overlap disorder between MDS and sAML. One implication of this hypothesis is that
therapies targeted at these subclones (such as IDH or FLT3 inhibitors, for example) may not lead
to traditionally defined hematologic res therapies targeted at these subclones (such as IDH or FLT3 inhibitors, for example) may
to traditionally defined hematologic responses, but may nonetheless delay leukemic
transformation. This prediction will have to be tes to traditionally defined hematologic responses, but may nonetheless delay leukemic
transformation. This prediction will have to be tested in prospective clinical trials.
Patterns of gene expression have also been used to i

transformation. This prediction will have to be tested in prospective clinical trials.
Patterns of gene expression have also been used to identify MDS patients at greatest
leukemic progression. Shiozawa et al. examined the tratterns of gene expression have also been used to identify MDS patients at great
leukemic progression. Shiozawa et al. examined the transcriptomes of CD34⁺ bone
from patients with MDS. (92) Unsupervised clustering ide Patterns of gene expression. Shiozawa et al. examined the transcriptomes of CD34⁺ bone marrow c
from patients with MDS. (92) Unsupervised clustering identified two major subgroups, one
enriched for the expression of gene from patients with MDS. (92) Unsupervised clustering identified two major subgroups, one
enriched for the expression of genes associated with erythroid and megakaryocytic ubgroups, one
vocytic
nature progenitors
pSE3B1 mutations From patients with the expression of genes associated with erythroid and megakaryocytic
differentiation (EMK) and another defined by transcripts associated with immature progeni
(IMP). The EMK subgroup had longer overall s enriched for the expression of genes associated with error ingenes associated with immature
(IMP). The EMK subgroup had longer overall survival and was associated with SF3B1
ring sideroblasts and a strong erythroid signatu (IMP). The EMK subgroup had longer overall survival and was associated with *SF3B1* mutations, ring sideroblasts and a strong erythroid signature. In contrast, the IMP subgroup had lower platelet counts, increased marrow b The EMK subgroup had longer overall survival and was associated with SF3B1 mutations,
ring sideroblasts and a strong erythroid signature. In contrast, the IMP subgroup had lower
platelet counts, increased marrow blasts, an ring succession takes a strong erythroid signature in contrast, the line can greep make terms
platelet counts, increased marrow blasts, and higher-risk mutations. Strikingly, only patients
the IMP subgroup transformed into plate IMP subgroup transformed into sAML suggesting that even in the absence of "leukemic"
mutations, some forms of MDS have greater leukemic potential that can be recognized well
before progression takes place. the IMP subgroup transformed into stand suggesting that even in the absence of "leadering
mutations, some forms of MDS have greater leukemic potential that can be recognized well
before progression takes place. mutations, some forms of MDS have greater leaking potential that can be recognized well
before progression takes place. before progression takes place.

The second area of overlap between MDS and AML involves patients who may not have had a
recognized antecedent MDS but are diagnosed with AML with myelodysplasia-related changes
(AML-MRC) suggesting a pathogenic link with M recognized and anti-oughly with MDS. (93, 94) Molecular profiling may help
segregate those with MDS and AML-MRC from *de novo* AML, providing prognostic information
for the patient and clinician. These patients will freque ence they angle pathogenic link with ML-MRC from the new AML, providing prognostic inform
for the patient and clinician. These patients will frequently harbor MDS-associated cytoge
abnormalities and are often classified as segregate those with MDS and AML-MNC from de *novo* AML, providing prognostic information
for the patient and clinician. These patients will frequently harbor MDS-associated cytogenetic
abnormalities and are often classifi for the patient and are often classified as having higher risk disease. Not surprisingly, patients
with AML-MRC are more likely to harbor mutated genes typical of MDS and sAML including
splicing factors (SRSF2, SF3B1, and abilities and are of the state classified as having the state of MDS and SAML including
splicing factors (SRSF2, SF3B1, and U2AF1), chromatin modifiers (EZH2 and ASXL1), as well as
STAG2 and BCOR (Figure 2). (95, 96) Older splicing factors (SRSF2, SF3B1, and U2AF1), chromatin modifiers (EZH2 and ASXL1), as well a
STAG2 and BCOR (Figure 2). (95, 96) Older individuals with AML are more likely to carry som
mutations in these genes even if they splicing factors (SRSF2, SF3B1, and U2AF1), chromatin modifiers (E2FI2 and ASXL1), as well as
STAG2 and BCOR (Figure 2). (95, 96) Older individuals with AML are more likely to carry soma
mutations in these genes even if th STAG2 and BCOR (Figure 2). (55, 56) Older individuals with AML are more likely to carry somatic
mutations in these genes even if they are not described as having AML-MRC. Importantly, older
de novo AML patients without the de novo AML patients without these mutations have a more favorable response to therapy and
duration of remission making it important to identify them at diagnosis.

duration of remission making it important to identify them at diagnosis.
From another perspective, one could consider MDS with excess blasts to be an overlap
syndrome between lower risk MDS defined by clonal cytopenias wit From another perspective, one could consider MDS with excess blasts to be an overlap
syndrome between lower risk MDS defined by clonal cytopenias with bone marrow failure ano
oligoblastic myeloid leukemia (Figure 3). (97, From anotasyondrome between lower risk MDS defined by clonal cytopenias with bone marrow fails

oligoblastic myeloid leukemia (Figure 3). (97, 98) In practice, patients with higher risk M

low blast count AML have a simila syndrome between lower risk MDS and (Figure 3). (97, 98) In practice, patients with higher risk MDS or
low blast count AML have a similar prognosis and are often treated with hypomethylating
agents or, if appropriate, cons oligobiastic myeloid leukemia (Figure 3). (97, 98) in practice, patients with higher risk MDS or
low blast count AML have a similar prognosis and are often treated with hypomethylating
agents or, if appropriate, considered low blast count AML have a similar progress and are often treated with hypomethylating
agents or, if appropriate, considered for stem cell transplantation. (99) Altering our diagno
boundaries between MDS and AML based on u boundaries between MDS and AML based on underlying mutations and clinical phenotypes may
more accurately classify patients with these conditions. between MDS and AML based on underlying mutations and clinical phenotypes may
more accurately classify patients with these conditions. more accurately classificate conditions.
The conditions with the conditions with the conditions.
. The conditions with the conditions.

Conclusion

 $\frac{1}{2}$ MDS overlap syndromes are genetically and clinically heterogeneous disorders that can
represent distinct biological entities or areas of diagnostic ambiguity. While WHO-defined
disease classifications rely largely on morph increasingly able to identify differences in clinical phenotypes when considered in the increasingly able to identify differences in clinical phenotypes when considered in the
appropriate clinical context. There are no specific mutations that stringently diagnose MDS
overlap syndromes or unequivocally define increasingly able to include, increasing phenotypes interesting in the appropriate clinical context. There are no specific mutations that stringently diagnose
overlap syndromes or unequivocally define diagnostic boundaries appropriate clinical content. There are no specific mutations that stringently imagines in a
overlap syndromes or unequivocally define diagnostic boundaries with MDS, however, futu
classification schemes are sure to incorp classification schemes are sure to incorporate our growing understanding of the molecular basis of these disorders. classification schemes are sure to incorporate our growing understanding of the molecular
basis of these disorders.

Authorship

Drs. Tiffany Tanaka and Rafael Bejar co-wrote this review and edited the submitted draft. Conflict of Interest Statement

 \overline{a} TT has no conflicts to report. RB has served as a consultant to Celgene and Genoptix, has
received research funding from Celgene and Takeda, and has served on a data safety monitoring board for Celgene sponsored clinical trials. RB has received honoraria for speaking at education conferences sponsored by Celgene and Xian Janssen. at education conferences sponsored by Celgene and Xian January Celegene and Xian January Celegene and Xian Jan
September 2003 - Andre Stevensored by Celgene and Xian January Celegene and Xian January Celegene and Xian Jan

References

- $\begin{array}{c} \n\cdot & \cdot \\ \n\cdot & \cdot \n\end{array}$ Health Organization classification of myeloid neoplasms and acute leukemia. Blood.
2016;127(20):2391-405.
2. Solary E, Itzykson R. How I treat chronic myelomonocytic leukemia. Blood. 2017;130(2):126-
- Health Organization classification of mystem in presents and acute leukemia.
1998; Solary E, Itzykson R. How I treat chronic myelomonocytic leukemia. Blood. 2017;130
1999: C. Forma E. Corti S. Moltoni M. Farissiotti A. et 2020;220122012012
Solary E, Itzykson R. How
36.
Ricci C, Fermo E, Corti S,
- 36.
Ricci C, Fermo E, Corti S, Molteni M, Faricciotti A, et al. RAS mutations contribute to
evolution of chronic myelomonocytic leukemia to the proliferative variant. Clinical Cancer
Research. 2010;16(8):2246-56. 3. Ricci C, Fermo E, Corti S, Molteni M, Faricciotti A, et al. RAS mutations contribute to 3. Process, Fermo E, Fermo Corticiano, Fermo C, Fermon E, Antarations Clinical C
Research. 2010;16(8):2246-56.
4. Cervera N, Itzykson R, Coppin E, Prebet T, Murati A, et al. Gene mutations differently
the prognosis of the
- evolution of chronic myelomology of characterized in premium control chronic respectively.
Cervera N, Itzykson R, Coppin E, Prebet T, Murati A, et al. Gene mutations differently impathe prognosis of the myelodysplastic and Research. 2021, 2012.
2010 Represent Research. 2010
The prognosis of the myelodysp
2011 Represent D. Badaoui B. Ba the prognosis of the myelodysplastic and myeloproliferative classes of chronic
myelomonocytic leukemia. American Journal of Hematology. 2014;89(6):604-9.
5. Selimoglu-Buet D, Badaoui B, Benayoun E, Toma A, Fenaux P, et al.
- myelomonocytic leukemia. American Journal of Hematology. 2014;89(6):604-9
Selimoglu-Buet D, Badaoui B, Benayoun E, Toma A, Fenaux P, et al. Accumulation
monocytes defines a subgroup of MDS that frequently evolves into CMML myelomonocyte leukemia. American Journal of Hematology. 2021, 2014; 1916.
Selimoglu-Buet D, Badaoui B, Benayoun E, Toma A, Fenaux P, et al. Accumulation
2017;130(6):832-5.
Talati C. Zhang L. Shaheen G. Kuykendall A. Ball M monocytes defines a subgroup of MDS that frequently evolves into CMML. Blood.
2017;130(6):832-5.
6. Talati C, Zhang L, Shaheen G, Kuykendall A, Ball M, et al. Monocyte subset analysis
- monocytes defines a subset of MDS 2017;130(6):832-5.
Talati C, Zhang L, Shaheen G, Kuykendall A, Ball M, et al. Monocyte subset analysis
accurately distinguishes CMML from MDS and is associated with a favorable MDS p
Blood 2020, 2020, 2020
Talati C, Zhang L, Sh
accurately distinguis
Blood. 2017;129(13 $\overline{6.7}$
accurately distinguishes CMML from MDS and is associated with a favorable MDS p
Blood. 2017;129(13):1881-3.
7. Meggendorfer M, Roller A, Haferlach T, Eder C, Dicker F, et al. SRSF2 mutations in 2
1. With chroni
- alood. 2017;129(13):1881-3.
Meggendorfer M, Roller A, Haferlach T, Eder C, Dicker F, et al. SRSF2 mutations in 275 cases
with chronic myelomonocytic leukemia (CMML). Blood. 2012;120(15):3080-8.
Patnaik MML ltzykson B, Jash Meggendorfer M, Roller A, Ha
Weggendorfer M, Roller A, Ha
Patnaik MM, Itzykson R, Lash
- with chronic myelomonocytic leukemia (CMML). Blood. 2012;120(15):3080-8.
8. Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. ASXL1 and SETBP1
mutations and their prognostic contribution in chronic myelomonocy Patnaik MM, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. ASXL1 and SETI
mutations and their prognostic contribution in chronic myelomonocytic leuker
center study of 466 patients. Leukemia. 2014;28(11):2206-12. mutations and their prognostic contribution in chronic myelomonocytic leukemia: a two-
center study of 466 patients. Leukemia. 2014;28(11):2206-12. center study of 466 patients. Leukemia. 2014;
Leukemia. 2014;
28(11):2206-12.0206-12.0206-12.0206-12.0206-12.0206-12.0206-12.0206
- 9. Papaemmanuil E, Gerstung M, Malcovati L, Tauro S, Gundem G, et al. Clinical and biological
implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616-
27.
10. Itzykson R, Kosmider O, Rennevi
- implications of the conservations of the conservations of the conservations of the conservations of the corre
inplications of the system of the system of the syndromes. Blood is sent to determine the correlations of Clinic 27.
Itzy
Ond
Pad 10. Italya 11. Padron E, Garcia-Manero G, Patnaik MM, Itzykson R, Lasho T, et al. An international dat
11. Padro
- Score including gene mutations in chronic myelomology. 2013;31(19):2428-36.
Padron E, Garcia-Manero G, Patnaik MM, Itzykson R, Lasho T, et al. An international data
for CMML validates prognostic scoring systems and demonst Padron E, Garcia-Manero G, Patn
for CMML validates prognostic sc
prognostication strategies. Blood
Mughal TL Cross NC, Padron E, Ti 11. Padron E, Franch Prognostic scoring systems and demonstrates a need for novel
prognostication strategies. Blood Cancer Journal. 2015;5:e333.
12. Mughal TI, Cross NC, Padron E, Tiu RV, Savona M, et al. An International
- For Communication strategies. Blood Cancer Journal. 2015;5:e333.
Mughal TI, Cross NC, Padron E, Tiu RV, Savona M, et al. An International MDS/MPN
Group's perspective and recommendations on molecular pathogenesis, diagnosis progressment changed a series control communication
Mughal TI, Cross NC, Padron E, Tiu RV, Savona M, et al. An Inter
Group's perspective and recommendations on molecular patho
clinical characterization of myelodysplastic/m 12. Group's perspective and recommendations on molecular pathogenesis, diagnosis and
clinical characterization of myelodysplastic/myeloproliferative neoplasms. Haematologica.
2015;100(9):1117-30.
13. Kantarijan H. O'Brien Group's perspective and recommendations on molecular pathogenesis, diagnosis and
clinical characterization of myelodysplastic/myeloproliferative neoplasms. Haematolo_{
2015;100(9):1117-30.
Kantarjian H, O'Brien S, Ravandi
- 2015;100(9):1117-30.
Kantarjian H, O'Brien S, Ravandi F, Cortes J, Shan J, et al. Proposal for a new risk model in
myelodysplastic syndrome that accounts for events not considered in the original
International Prognostic S Xantarjian H, O'Brien S
myelodysplastic syndr
International Prognost
Greenherg P, Cox C, Le 13. Kantarjian H, O'Brien S, Ravandi F, Cortes J, Shan J, et al. Proposal for a new risk model in
myelodysplastic syndrome that accounts for events not considered in the original
International Prognostic Scoring System. Ca
- mernational Prognostic Scoring System. Cancer. 2008;113(6):1351-61.
Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, et al. International scoring sy
evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):207 Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, et al. International
evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2
Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero Get al. Revis
prognost
- evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079-88.
15. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero Get al. Revised international
prognostic scoring system for myelodysplastic syndro eranning program in myelodysplastic syndromes. Blood. 2012;120(12):2079-88.
Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero Get al. Revised interr
prognostic scoring system for myelodysplastic syndromes. Blood. 2
- prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454-65.
16. Nazha A, Patnaik MM. Making Sense of Prognostic Models in Chronic Myelomonocytic
Leukemia. Current Hematologic Malignancy Reports. 2 16. Nazha A, Patnaik MM. Making Sense of Prognostic Models in Chronic Myelomonocytic
Leukemia. Current Hematologic Malignancy Reports. 2018;13(5):341-7.
17. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. Mol
- 16. Nazha A, Patham Mahing Sense of Progress (2018; 13(5): 341-7.
17. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. Molecular and prognostic
17. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. Wassie EA, Itzykson R, Lasho TL, Kosmider O, Finke CM, et al. Molecular
correlates of cytogenetic abnormalities in chronic myelomonocytic leuk
French Consortium Study. American Journal of Hematology. 2014;89(12
Beran M. We 17. Wassie En, Italian, Lashin, Lashin R, Italian Programmer Correlates of cytogenetic abnormalities in chronic myelomonocytic leukemia: a Mayo Cl
French Consortium Study. American Journal of Hematology. 2014;89(12):1111-5
- Scoring System. Leukemia & Lymphoma. 2007;48(6):1150-60. French Consortium Study. American Journal of Hematology. 2014;89(12):1111-5.
18. Beran M, Wen S, Shen Y, Onida F, Jelinek J, et al. Prognostic factors and risk assessment in
chronic myelomonocytic leukemia: validation stud
- 19. Elena C, Galli A, Such E, Meggendorfer M, Germing U, et al. Integrating clinical features and Scoring System. Leukemia & Lymphoma. 2007;48(6):1150-60.
Elena C, Galli A, Such E, Meggendorfer M, Germing U, et al. Integrating clinical feature
genetic lesions in the risk assessment of patients with chronic myelomonocyt Elena C, Galli A, Such E, Meggendorfer M, Germing U, et al. Int
genetic lesions in the risk assessment of patients with chronic
Blood. 2016;128(10):1408-17.
Drummond MW, Pocock C, Boissingt M, Mills L, Brown L et al. 19. Elena C, Gallin C, Meggendorfer M, Germing C, Calching clinical features and
19. Blood. 2016;128(10):1408-17.
20. Drummond MW, Pocock C, Boissinot M, Mills J, Brown J, et al. A multi-centre phase 2 study
19. Statistic
- geneur certic in the risk assessment of patients with chronic myelomones, as examined as a set of azacitidine in chronic myelomonocytic leukaemia. Leukemia. 2014;28(7):1570-2.
Tantravabi SK, Szankasi P, Khorashad IS, Dao K Drummond MW, Pocock C, Bo
of azacitidine in chronic myelo
Tantravahi SK, Szankasi P, Khor
officacy, safoty, and dotermina
- 20. Drummond MW, Pocock C, Boissinot M, Miller, Brown, Poland MMM Penalt Drug phase 2 study
21. Tantravahi SK, Szankasi P, Khorashad JS, Dao KH, Kovacsovics T, et al. A phase II study of the
21. Tantravahi SK, Szankasi P, of azacition in chronic myelomonocytic leukaritic azachtidine in chronic mysteric leukaemia.
Tantravahi SK, Szankasi P, Khorashad JS, Dao KH, Kovacsovics T, et al. A phase II stude
efficacy, safety, and determinants of res efficacy, safety, and determinants of response to 5-azacitidine (Vidaza(R)) in patients with chronic myelomonocytic leukemia. Leukemia & Lymphoma. 2016;57(10):2441-4. chronic myelomonocytic leukemia. Leukemia & Lymphoma. 2016;57(10):2441-4.
Chronic leukemia & Lymphoma. 2016;57(10):2441-4.
Chronic leukemia & Lymphoma. 2016;57(10):2441-4.
- 22. Merlevede J, Droin N, Qin T, Meldi K, Yoshida K, et al. Mutation allele burden remains
unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents.
Nature Communications. 2016;7:10767.
23. Meldi
- Nature Communications. 2016;7:10767.
Meldi K, Qin T, Buchi F, Droin N, Sotzen J, et al. Specific molecular signatures predict
decitabine response in chronic myelomonocytic leukemia. The Journal of Clinical
Investigation. 2 Meldi K, Qin T, Buchi F, Droin N, Sotzen J
decitabine response in chronic myelomo
Investigation. 2015;125(5):1857-72.
de Witte T. Bowen D. Bobin M. Malcovat decitabine response in chronic myelomonocytic leukemia. The Journal of Clinical
Investigation. 2015;125(5):1857-72.
24. de Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, et al. Allogeneic hemato
- decitability response in chronic myelomology are concerned the Common Prominsiple
de Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, et al. Allogeneic hem
stem cell transplantation for MDS and CMML: recommendations Investigation. 2021, 2021, 2022, 2023
In de Witte T, Bowen D, Robin M, Malc
Stem cell transplantation for MDS an
Expert panel. Blood. 2017;129(13):1 stem cell transplantation for MDS and CMML: recommendations from an international
expert panel. Blood. 2017;129(13):1753-62.
Robin M, Fenaux P. Hypomethylating Agents as Bridging Therapy before Allogeneic
Hematopoietic Ste
- stem cell transplantation for MDS 20002.
Step channel. Blood. 2017;129(13):1753-62.
Robin M, Fenaux P. Hypomethylating Agents as Bridging Therapy before Allogeneic
Hematopoietic Stem Cell Transplantation in Patients with C expert panel. 2018. 2021, 2021, 2017. 2018.
Robin M, Fenaux P. Hypomethylating Agents
Hematopoietic Stem Cell Transplantation in
Leukemia. Biology of Blood and Marrow Trai 25. Robin M, Fematopoietic Stem Cell Transplantation in Patients with Chronic Myelomonocytic
Leukemia. Biology of Blood and Marrow Transplantation. 2016;22(1):1-2.
26. Jeromin S, Haferlach T, Weissmann S, Meggendorfer M, E
- Hematopoietic Stem Cell Transplantation in Patients With Chronic Myelomonic Step
Leromin S, Haferlach T, Weissmann S, Meggendorfer M, Eder C, et al. Refractory and
with ring sideroblasts and marked thrombocytosis cases har Jeromin S, Haferlach T, Weissmann S, Meggendorfer M, Eder C, et al. Refr
with ring sideroblasts and marked thrombocytosis cases harbor mutations
spliceosome genes accompanied by JAK2V617F and ASXL1 mutations. Hae
2015:100(with ring sideroblasts and marked thrombocytosis cases harbor mutations in SF3B1 or other
spliceosome genes accompanied by JAK2V617F and ASXL1 mutations. Haematologica.
2015;100(4):e125-7.
- 27. Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with splices:100(4):e125-7.
Patnaik MM, Tefferi A. Refractory anemia with ring sideroblasts (RARS) and RARS with
thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and manageme
American Journal of Hematolog ANTA, Tefferi
2015;100(1):
2015;100(1):
2015;100(1):100(1):100
2016;100(1):100(1):100 27. Patham MM, Tefferi Methanic P, anemia with ring sideroblast (Patha) and manageme

American Journal of Hematology. 2017;92(3):297-310.

28. Meggendorfer M, Jeromin S, Haferlach C, Kern W, Haferlach T. The mutational lan
- thrombocytosis (RARS-T): 2021-2017;92(3):297-310.
American Journal of Hematology. 2017;92(3):297-310.
18 investigated genes clearly separates four subtypes of myelodysplastic/myeloproliferation.
18 investigated genes clear Meggendorfer M, Jeromin S, Haferlach C, Kern W, Hafe
18 investigated genes clearly separates four subtypes of
neoplasms. Haematologica. 2018;103(5):e192-e5.
Patnaik MM, Lashe TL, Einke CM, Hanson CA, King PL, 6 18 investigated genes clearly separates four subtypes of myelodysplastic/myeloproliferative
neoplasms. Haematologica. 2018;103(5):e192-e5.
29. Patnaik MM, Lasho TL, Finke CM, Hanson CA, King RL, et al. Predictors of surviv
- 18 investigated genes clearly separates four subtypes of myeloppy propendicities in the model of membership is

Patnaik MM, Lasho TL, Finke CM, Hanson CA, King RL, et al. Predictors of survival in

refractory anemia with r Patnaik MM, Lasho TL, Finke CM, Hanson CA, King
refractory anemia with ring sideroblasts and thron
generation sequencing. American Journal of Hema
Broseus J. Florensa J. Zinnerer E. Schnittger S. Mak 2022. Pathwarman, 2022. Pathwarman, 2022. Pathwarman, 1989. Pathwarman, 1989. Pathwarman, 1989. Perspectively
29. Broseus J, Florensa L, Zipperer E, Schnittger S, Malcovati L, et al. Clinical features and
20. Broseus J, Fl
- Haematologica. 2012;97(7):1036-41. generation sequencing. American Journal of Hematology. 2016;91(5):492-8.
30. Broseus J, Florensa L, Zipperer E, Schnittger S, Malcovati L, et al. Clinical features and course
30. of refractory anemia with ring sideroblasts
- 31. Patnaik MM, Lasho TL, Finke CM, Hanson CA, King RL, et al. Vascular events and risk factors Haematologica. 2012;97(7):1036-41.
Patnaik MM, Lasho TL, Finke CM, Hanson CA, King RL, et al. Vascular events and risk
for thrombosis in refractory anemia with ring sideroblasts and thrombocytosis. Leuk
2016:30(11):2273.5 Patnaik MM, Lasho TL, Finke CM, Har
for thrombosis in refractory anemia v
2016;30(11):2273-5.
Huls G. Mulder AB, Posati S, van de Le 32. Huls G, Mulder AB, Rosati S, van de Loosdrecht AA, Vellenga E, et al. Efficacy of single-agent
2016;30(11):2273-5.
32. Huls G, Mulder AB, Rosati S, van de Loosdrecht AA, Vellenga E, et al. Efficacy of single-agent
20 M
- for thrombosis 10.6;30(11):2273-5.
for the Loosdrecht AA, Vellenga E, et al. Efficacy of single-agent 12. Huls G, Mulder AB, Rosati S, van de Loosdrecht AA, Vellenga E, et al. Efficacy of single-agent
lenalidomide in patie sideroblasts and thrombocytosis. Blood. 2010;116(2):180-2.
- 33. Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, et al. Atypical chronic myeloid sideroblasts and thrombocytosis. Blood. 2010;116(2):180-2.
Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, et al. Atypical chronic myeld
leukemia is clinically distinct from unclassifiable myelodysplastic/myeloprolife Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, et al. At
leukemia is clinically distinct from unclassifiable myelodyspla
neoplasms. Blood. 2014;123(17):2645-51. 33. Wang SA, Masser, March, Fox Ps, Rogers H, Server, Server, Premeric, Premeric myeloir
leukemia is clinically distinct from unclassifiable myelodysplastic/myeloproliferative
neoplasms. Blood. 2014;123(17):2645-51. $\frac{1}{2}$ leukemia is chinemia, distinct from unclassifiable myelogy-plastiny in yeloproliferative meoplasms. Blood. 2014;123(17):2645-51. neoplasms. Blood. 2014;
Blood. 2014;123(17):2645-51.
2014; 123(17):2645-51.
- mutations in chronic neutrophilic leukemia and atypical CML. The New England Jou
Medicine. 2013;368(19):1781-90.
35. Pardanani A, Lasho TL, Laborde RR, Elliott M, Hanson CA, et al. CSF3R T618l is a high
prevalent and speci
- Medicine. 2013;368(19):1781-90.
Pardanani A, Lasho TL, Laborde RR, Elliott M, Hanson CA, et al. CSF3R T618I is a highly
prevalent and specific mutation in chronic neutrophilic leukemia. Leukemia.
2013:27/9):1870-3 Medicine. 2013;368(19):1781-90.
Pardanani A, Lasho TL, Laborde RR, Elliott M, Hanson CA, et al. CSF3R T618I i
prevalent and specific mutation in chronic neutrophilic leukemia. Leukemia.
2013;27(9):1870-3. 35. prevalent and specific mutation in chronic neutrophilic leukemia. Leukemia.
2013;27(9):1870-3.
36. Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, et al. Atypical chronic myeloid
- present and specific mutation in chronic mutation is anti-mutation in 2013;27(9):1870-3.
Wang SA, Hasserjian RP, Fox PS, Rogers HJ, Geyer JT, et al. Atypical chronic m
leukemia. is clinically distinct from unclassifiable m 2020;27(9):2013;27
Wang SA, Hasserjiar
leukemia is clinically
neoplasms. Blood. 2 36. Wang SA, Masser, Marser, Force, Progressing Server, Server, Promotypical chronic myeloir

1998. Makisma Blood. 2014;123(17):2645-51.

37. Makishima H, Yoshida K, Nguyen N, Przychodzen B, Sanada M, et al. Somatic SETBP:
- leukemia is clinically distinct from unclearning myeloppedially in proportions in
the matishima H, Yoshida K, Nguyen N, Przychodzen B, Sanada M, et al. Somatic SETBP1
mutations in myeloid malignancies. Nature Genetics. 201 neophamic entertainment (et) entertainment.
Makishima H, Yoshida K, Nguyen N, Przych
mutations in myeloid malignancies. Nature
Gotlib J, Maxson JE, George TI, Tyner JW. T
- 38. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics 2013;45(8):942-6.
38. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic let
39. Langabeer SE, McCarron SL, Haslam K, O'Donovan mutations in myeloid manipulations in the consideration of chronic nearborship.
Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic near
Langabeer SE, McCarron SL, Haslam K, O'Donovan MT, Conneally E. The
- and atypical CML: implications for diagnosis and treatment. Blood. 2013;122(10):1707-11.
39. Langabeer SE, McCarron SL, Haslam K, O'Donovan MT, Conneally E. The CSF3R T618I
mutation as a disease-specific marker of atypical mutation as a disease-specific marker of atypical CML post allo-SCT. Bone Marrow 39. Langabeer SE, McCarron SL, Haslam K, O'Donovan MT, Conneally E. The CSF3R T618I
mutation as a disease-specific marker of atypical CML post allo-SCT. Bone Marrow
Transplantation. 2014;49(6):843-4.
40. Dao KH, Solti MB,
- Transplantation. 2014;49(6):843-4.
Dao KH, Solti MB, Maxson JE, Winton EF, Press RD, et al. Significant clinical respons
JAK1/2 inhibition in a patient with CSF3R-T618I-positive atypical chronic myeloid le
Loukomia Pesearc Transplantation.
Dao KH, Solti MB, Maxson JE, Winto
JAK1/2 inhibition in a patient with C
Leukemia Research Reports. 2014;3
Stieglitz E. Taylor-Weiner AN. Chang 14. David Max 1/2 inhibition in a patient with CSF3R-T6181-positive atypical chronic myeloid leuker
Leukemia Research Reports. 2014;3(2):67-9.
41. Stieglitz E, Taylor-Weiner AN, Chang TY, Gelston LC, Wang YD, et al. The ge
- JAK 19 inhibition in a patient with CSF3R-T618I-position in a patient chronic landscape.
JAK 1999 Stieglitz E, Taylor-Weiner AN, Chang TY, Gelston LC, Wang YD, et al. The genomic landscape
of juvenile myelomonocytic leuk Stieglitz E, Taylor-Weiner AN, Chang TY, Gelst
of juvenile myelomonocytic leukemia. Nature
Sakaguchi H, Okuno Y, Muramatsu H, Yoshida
identifies secondary mutations of SETBB1 and
- 11. Stieglitz E, Taylor, Theorems, Tamigora, Schemarz, Tamigora, Taminia genomic landscape
of juvenile myelomonocytic leukemia. Nature Genetics. 2015;47(11):1326-33.
42. Sakaguchi H, Okuno Y, Muramatsu H, Yoshida K, Shirai of juvenile myelomonocytic leukemia. Nature Genetics 2021, N. (22) 2222 2023.
Sakaguchi H, Okuno Y, Muramatsu H, Yoshida K, Shiraishi Y, et al. Exome seque
identifies secondary mutations of SETBP1 and JAK3 in juvenile myel 142. Sakanguchi H, Okuno Y, Sakaratian Sakaratian Sidentifies secondary mutations of SETBP1 and JAK3 in juvenile myelomonocytic leuke
Nature Genetics. 2013;45(8):937-41.
43. Caye A, Strullu M, Guidez F, Cassinat B, Gazal S
- identifies secondary mutations of SETBP and JAM and JAP and JAP promins processes.
Caye A, Strullu M, Guidez F, Cassinat B, Gazal S, et al. Juvenile myelomonocytic leukemia.
displays mutations in components of the RAS path Caye A, Strullu M, Guidez F, Cassinat
displays mutations in components of
Genetics. 2015;47(11):1334-40.
Stieglitz E. Mazor T. Olshen AB. Geng. displays mutations in components of the RAS pathway and the PRC2 network. Nature
Genetics. 2015;47(11):1334-40.
44. Stieglitz E, Mazor T, Olshen AB, Geng H, Gelston LC, et al. Genome-wide DNA methylation
predictive of outc
- displays of the Rassettions of the Rassettions of the Rassettions of the Rassettions of the Stieglitz E, Mazor T, Olshen AB, Geng H, Gelston LC, et al. Genome-wide DNA methylat
predictive of outcome in juvenile myelomonocy Stieglitz E, Mazor T, Olshen AB, O
predictive of outcome in juvenik
2017;8(1):2127.
Schwaab L Schnittger S. Sotlar K predictive of outcome in juvenile myelomonocytic leukemia. Nature Communications.
2017;8(1):2127.
45. Schwaab J, Schnittger S, Sotlar K, Walz C, Fabarius A, et al. Comprehensive mutational
profiling in advanced systemic m
- predictive of outcome in juvenile myelomonocytic lemanika ruski communications.
Schwaab J, Schnittger S, Sotlar K, Walz C, Fabarius A, et al. Comprehensive mutational
profiling in advanced systemic mastocytosis. Blood. 201 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 2020, 20
Lasho TL, Finke C
Athanolamine kit
- profiling in advanced systemic mastocytosis. Blood. 2013;122(14):2460-6.
46. Lasho TL, Finke CM, Zblewski D, Patnaik M, Ketterling RP, et al. Novel recurrent mutational ethanolamine kinase 1 (ETNK1) gene in systemic masto proming in advanced systemic master system and all spaces (and the basic casho TL, Finke CM, Zblewski D, Patnaik M, Ketterling RP, et al. Novel recurred thanolamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosin ethanolamine kinase 1 (ETNK1) gene in systemic mastocytosis with eosinophilia and chronic
myelomonocytic leukemia. Blood Cancer Journal. 2015;5:e275.
47. Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, et a
- myelomonocytic leukemia. Blood Cancer Journal. 2015;5:e275.
Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann M, et al. Additional
mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients wi myer menser, actomonocytic leukemia. Blood Cancer Journal.
Jawhar M, Schwaab J, Schnittger S, Meggendorfer M, Pfirrmann
mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk gro
D816V(+) advanced systemic mastocytosi mutations in SRSF2, ASXL1 and/or RUNX1 identify a high-risk group of patients with KIT $D816V(+)$ advanced systemic mastocytosis. Leukemia. $2016;30(1):136-43$. D816V(+) advanced systemic mastocytosis. Leukemia. 2016;30(1):136-43.
- 48. Jawhar M, Schwaab J, Schnittger S, Sotlar K, Horny HP, et al. Molecular profiling of myeloid
progenitor cells in multi-mutated advanced systemic mastocytosis identifies KIT D816V as a
distinct and late event. Leukemia.
- progentian
distinct and late event. Leukemia. 2015;29(5):1115-22.
Pardanani A, Lim KH, Lasho TL, Finke C, McClure RF, et al. Prognostically relevant breakdowr
of 123 patients with systemic mastocytosis associated with othe distinct and late event and late the event of the Cardianani A, Lim KH, Lasho TL, Finke C, McClure RF, et a
of 123 patients with systemic mastocytosis associated v
Blood. 2009;114(18):3769-72. of 123 patients with systemic mastocytosis associated with other myeloid malignancies.
Blood. 2009;114(18):3769-72.
50. Patnaik MM, Rangit V, Lasho TL, Hoversten KP, Finke CM, et al. A comparison of clinical and
molecular
- of 123 patients with systems with system account with the city seta manghameter.
Blood. 2009;114(18):3769-72.
Patnaik MM, Rangit V, Lasho TL, Hoversten KP, Finke CM, et al. A comparison of clinical a
molecular characterist Patnaik MM, Rangit V, Lasho T
Patnaik MM, Rangit V, Lasho T
molecular characteristics of pa
myelomonocytic leukemia to C molecular characteristics of patients with systemic mastocytosis with chronic
myelomonocytic leukemia to CMML alone. Leukemia. 2018;32(8):1850-6.
51. Mayerhofer M, Gleixner KV, Hoelbl A, Florian S, Hoermann G, et al. Uniqu
- molecular characteristics of patients with systemic masters, the with site in
myelomonocytic leukemia to CMML alone. Leukemia. 2018;32(8):1850-6.
Mayerhofer M, Gleixner KV, Hoelbl A, Florian S, Hoermann G, et al. Unique ef myer mensely are menseles comme are not commenced to compare the Mayerhofer M, Gleixner KV, Hoelbl A, Florian S, Hoermann G, et al. Unique.
D816V in BaF3 cells: induction of cluster formation, histamine synthesis, a
differ D816V in BaF3 cells: induction of cluster formation, histamine synthesis, and early mast cell
differentiation antigens. Journal of immunology. 2008;180(8):5466-76.
52. Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, et al
- DEFT IN ENTERTMINISHED IN BAFBAFINDING, INTERTION (8):5466-76.
Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, et al. Systemic mastocytosis in 342
consecutive adults: survival studies and prognostic factors. Blood. 2009;1 Lim KH, Tefferi A, Lasho TL, Finke C, Patnaik M, et al. Systemic mastocyt
consecutive adults: survival studies and prognostic factors. Blood. 2009
Scherber RM, Borate U. How we diagnose and treat systemic mastocyto
- consecutive adults: survival studies and prognostic factors. Blood. 2009;113(23):57
53. Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adult
54. Gotlib L Kluin-Nelemans HC George TL Akin C Sotla Scherber RM, Borate U. How we diagnose and treat systemic mastocytosis in adults. Britis
Journal of Haematology. 2018;180(1):11-23.
Gotlib J, Kluin-Nelemans HC, George, Tl, Akin C, Sotlar K, et al. Efficacy and safety of
m
- 54. Gotlib J, Kluin-Nelemans HC, George, Tl, Akin C, Sotlar K, et al. Efficacy and safety of
54. Gotlib J, Kluin-Nelemans HC, George, Tl, Akin C, Sotlar K, et al. Efficacy and safety of
5718.74.2530.2541 Gotlib J, Kluin-Nelemans HC, George, Tl, Akin
midostaurin in advanced systemic mastocyto
2018;74:2530-2541.
Gleivner KV, Mayerbofer M, Cerny-Beiterer S midostaurin in advanced systemic mastocytosis. The New England Journal of Medici
2018;74:2530-2541.
55. Gleixner KV, Mayerhofer M, Cerny-Reiterer S, Hormann G, Rix U, et al. KIT-D816V-
- midostamin in advanced systemic mastery court first the New England Lemmarch 2018;74:2530-2541.
Gleixner KV, Mayerhofer M, Cerny-Reiterer S, Hormann G, Rix U, et al. KIT-D816V-
independent oncogenic signaling in neoplastic *C*
Gleixner KV, Mayerh
independent oncoge
Btk activation and di: independent oncogenic signaling in neoplastic cells in systemic mastocytosis: role
Btk activation and disruption by dasatinib and bosutinib. Blood. 2011;118(7):1885-
56. Peter B, Cerny-Reiterer S, Hadzijusufovic E, Schuch
- Bik activation and disruption by dasatinib and bosutinib. Blood. 2011;118(7):1885-98.
Peter B, Cerny-Reiterer S, Hadzijusufovic E, Schuch K, Stefanzl G, et al. The pan-Bcl-2 blocker
obatoclax promotes the expression of Pum Peter B, Cerny-Reiterer S, Hadzijusufovic E, Schuch K, Stefanzl G, et al. The pan-Bcl-2 blood. 2011
obatoclax promotes the expression of Puma, Noxa, and Bim mRNA and induces apopto
neoplastic mast cells. Journal of Leukocy obatoclax promotes the expression of Puma, Noxa, and Bim mRNA and induces apoptosis in
neoplastic mast cells. Journal of Leukocyte Biology. 2014;95(1):95-104.
57. Stahl M, DeVeaux M, de Witte T, Neukirchen J, Sekeres MA, e
- obatoclari promotes the expression of Linna, 1998, 2014;95(1):95-104.
Stahl M, DeVeaux M, de Witte T, Neukirchen J, Sekeres MA, et al. The use of
immunosuppressive therapy in MDS: clinical outcomes and their predictors in Stahl M, DeVeaux M, de Witte T, Neukirchen J, Sekeres MA, et al. The u
immunosuppressive therapy in MDS: clinical outcomes and their predic
international patient cohort. Blood Advances. 2018;2(14):1765-72.
Passweg JR, Giag immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large
international patient cohort. Blood Advances. 2018;2(14):1765-72.
58. Passweg JR, Giagounidis AA, Simcock M, Aul C, Dobbelstein C, et al.
- international patient cohort. Blood Advances. 2018;2(14):1765-72.
Passweg JR, Giagounidis AA, Simcock M, Aul C, Dobbelstein C, et al. Immunosuppressi
therapy for patients with myelodysplastic syndrome: a prospective random Passweg JR, Giagounidis AA, Simcock M, Aul C, Dobbelstein C, et al.
therapy for patients with myelodysplastic syndrome: a prospective
phase III trial comparing antithymocyte globulin plus cyclosporine v
care-SAKK 33/99. Jo therapy for patients with myelodysplastic syndrome: a prospective randomized multicen
phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive
care--SAKK 33/99. Journal of Clinical Oncology. phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive
care--SAKK 33/99. Journal of Clinical Oncology. 2011;29(3):303-9.
59. Socie G, Henry-Amar M, Bacigalupo A, Hows J, Tichelli A, et al M
- phase III trial comparts of the United States-SAKK 33/99. Journal of Clinical Oncology. 2011;29(3):303-9.
Socie G, Henry-Amar M, Bacigalupo A, Hows J, Tichelli A, et al Malignant tumors occurring the States of the St
after Socie G, Henry-Amar M, Bacigalupo A, Hows J, Tichelli A, et al Mal
after treatment of aplastic anemia. European Bone Marrow Trans
Anaemia Working Party. The New England Journal of Medicine. 19 France Controller Community States (States Controller Community Community Community)

after treatment of aplastic anemia. European Bone Marrow Transplantation-Severe Aplast

Anaemia Working Party. The New England Journal o
- Anaemia Working Party. The New England Journal of Medicine. 1993;329(16):1152-7.
Socie G, Rosenfeld S, Frickhofen N, Gluckman E, Tichelli A. Late clonal diseases of treated
aplastic anemia. Seminars in Hematology. 2000;37(Anaemia Wormig Party. The New England Pentrum Protection 2009;3200 (20):200 P.
Socie G, Rosenfeld S, Frickhofen N, Gluckman E, Tichelli A. Late clonal diseases of treat
aplastic anemia. Seminars in Hematology. 2000;37(1):9 aplastic anemia. Seminars in Hematology. 2000;37(1):91-101. aplastic anemia. Seminars in Hematology. 2000;
37. (1):91-101.
101-101.
-
- in aplastic anaemia. British Journal of Haematology. 2017;177(4):509-25.
62. Kulasekararaj AG, Jiang J, Smith AE, Mohamedali AM, Mian S, et al. Somatic mutations
identify a subgroup of aplastic anemia patients who progress in alternation and the Rudasekararaj AG, Jiang J, Smith AE, Mohamedali AM, Mian S, et al. Somatology.
identify a subgroup of aplastic anemia patients who progress to myelodys.
Blood. 2014;124(17):2698-704.
Yoshizato T. Dum For Marketin Angrey Manger, Jaman Ag, Mohammedali Angre Symmetry Managerial

Blood. 2014;124(17):2698-704.

63. Yoshizato T, Dumitriu B, Hosokawa K, Makishima H, Yoshida K, et al. Somatic Mutations

Clonal Homatonoiosis in
- Blood. 2014;124(17):2698-704.
63. Yoshizato T, Dumitriu B, Hosokawa K, Makishima H, Yoshida K, et al. Somatic Mutations and
Clonal Hematopoiesis in Aplastic Anemia. The New England Journal of Medicine.
2015:373(1):35-47. Clonal Hematopoiesis in Aplastic Anemia. The New England Journal of Medicine. 64. Katagiri T, Sato-Otsubo A, Kashiwase K, Morishima S, Sato Y, et al. Frequent loss of HLA
2015;373(1):35-47.
alleles associated with convinumber-peutral fol OH in acquired anlastic anomia. Blood
- Clonal Hematopoiesis in Aplastic Mematoma The New England Lematoma Dimermia.
2015;373(1):35-47.
alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia.
2011:118(25):6601.9 2020;3737,273-47.
Katagiri T, Sato-Otsu
alleles associated w
2011;118(25):6601alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. Blood.
2011;118(25):6601-9.
Maciejewski JP, Follmann D, Nakamura R, Saunthararajah Y, Rivera CE, et al. Increased
frequency of HLA-DR2 in patie
- 2011;118(25):6601-9.
Maciejewski JP, Follmann D, Nakamura R, Saunthararajah Y, Rivera CE, et al. Increased
frequency of HLA-DR2 in patients with paroxysmal nocturnal hemoglobinuria and the
PNH/anlastic anemia.syndrome. Blo 2020, 2020, 2020, 2020
Maciejewski JP, Follma
frequency of HLA-DR2
PNH/aplastic anemia s 65. PNH/aplastic anemia syndrome. Blood. 2001;98(13):3513-9.
66. Saunthararajah Y, Nakamura R, Nam JM, Robyn J, Loberiza F, et al. HLA-DR15 (DR2) is
- overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002;100(5):1570-4. overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a resp
to immunosuppression in myelodysplastic syndrome. Blood. 2002;100(5):1570-4.
67. Fuhrer M, Durner J, Brunnler G, Gotte H, Deppner C, et al
- to immunosuppression in myelodysplastic syndrome. Blood. 2002;100(5):1570-4.
Fuhrer M, Durner J, Brunnler G, Gotte H, Deppner C, et al. HLA association is different in
children and adults with severe acquired aplastic anem to immunosuppression in myelodysplastic yndicante chemical yn greg yndicantellin mythem.
Fuhrer M, Durner J, Brunnler G, Gotte H, Deppner C, et al. HLA association is differ
children and adults with severe acquired aplasti children and adults with severe acquired aplastic anemia. Pediatric Blood & Cancer.
2007;48(2):186-91.
68. Babushok DV, Duke JL, Xie HM, Stanley N, Atienza J, et al. Somatic HLA Mutations Expose
- 2007;48(2):186-91.
Babushok DV, Duke JL, Xie HM, Stanley N, Atienza J, et al. Somatic HLA Mutations Ex
the Role of Class I-Mediated Autoimmunity in Aplastic Anemia and its Clonal Complio
Blood Advances. 2017:1/22):1900-10 2007;44;47:2007
Babushok DV, Duke
the Role of Class I-N
Blood Advances. 20 the Role of Class I-Mediated Autoimmunity in Aplastic Anemia and its Clonal Complication
Blood Advances. 2017;1(22):1900-10.
69. Nazha A, Seastone D, Radivoyevitch T, Przychodzen B, Carraway HE, et al. Genomic patter
assoc
- Blood Advances. 2017;1(22):1900-10.
69. Nazha A, Seastone D, Radivoyevitch T, Przychodzen B, Carraway HE, et al. Genomic patterns
associated with hypoplastic compared to hyperplastic myelodysplastic syndromes.
Haematologic associated with hypoplastic compared to hyperplastic myelodysplastic syndromes.
- 70. Afable MG, 2nd, Wlodarski M, Makishima H, Shaik M, Sekeres MA, et al. SNP array-based Haematologica. 2015;100(11):e434-7.
Afable MG, 2nd, Wlodarski M, Makishima H, Shaik M, Sekeres MA, et al. SNP array-
karyotyping: differences and similarities between aplastic anemia and hypocellular
myelodysplastic syndro Afable MG, 2nd, Wlodarski M, Makishi
karyotyping: differences and similaritie
myelodysplastic syndromes. Blood. 20
Mikhailova N. Sessarego M. Eugazza G. 10. Afable 12. Afable Maryotyping: differences and similarities between aplastic anemia and hypocellular
11. Mikhailova N, Sessarego M, Fugazza G, Caimo A, De Filippi S, et al. Cytogenetic
1996:81/51:418.22 and array-based
- karyotyping: differences and similar myelodysplastic syndromes. Blood. 2011;117(25):6876-84.
Mikhailova N, Sessarego M, Fugazza G, Caimo A, De Filippi S, et al. Cytogenetic
abnormalities in patients with severe aplastic an myelodysplastic syndromes. Blood. 2011;117(25):6876-84.
- abnormalities in patients with severe aplastic anemia. Haematologica. 1996;81
72. Stanley N, Olson TS, Babushok DV. Recent advances in understanding clonal ha
in aplastic anaemia. British Journal of Haematology. 2017;177(4 abilies IV and the Stanley N, Olson TS, Babushok DV. Recent advances in understanding clonal haematopoies
in aplastic anaemia. British Journal of Haematology. 2017;177(4):509-25.
Noris P, Favier R, Alessi MC, Geddis AE, Ku
- in aplastic anaemia. British Journal of Haematology. 2017;177(4):509-25.
73. Noris P, Favier R, Alessi MC, Geddis AE, Kunishima S, et al. ANKRD26-related
thrombocytopenia and myeloid malignancies. Blood. 2013;122(11):1987-In approach and strategies and the Hammer Community of Lachystan (1,1000 Lachystan)

Noris P, Favier R, Alessi MC, Geddis AE, Kunishima S, et al. ANKRD26-relat

thrombocytopenia and myeloid malignancies. Blood. 2013;122(11
- Thrombocytopenia and myeloid malignancies. Blood. 2013;122(11):1987-9.
74. Niemeyer CM, Mecucci C. Practical considerations for diagnosis and manage
patients and carriers. Seminars in Hematology. 2017;54(2):69-74. thrombor, repondentality commingenticity and the state of the state of the
Niemeyer CM, Mecucci C. Practical considerations for diagnosis and manage
patients and carriers. Seminars in Hematology. 2017;54(2):69-74. patients and carriers. Seminars in Hematology. 2017;54(2):69-74. patients and carriers. Seminars in Hematology. 2017;
Seminars in Hematology. 2017;
54(2):69-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.09-74.0
- Inherited Myelodysplastic Syndrome/Acute Myeloid Leukemia Predisposition Syndrom
Hematology/Oncology Clinics of North America. 2018;32(4):643-55.
76. Churpek JE, Pyrtel K, Kanchi K-L, Shao J, Koboldt D, et al. Genomic anal
- Hematology/Oncology Clinics of North America. 2018;32(4):643-55.
Churpek JE, Pyrtel K, Kanchi K-L, Shao J, Koboldt D, et al. Genomic analysis of germ line and
somatic variants in familial myelodysplasia/acute myeloid leuke Hematology Chines of North America. 2015; 1914 1914
Somatic variants in familial myelodysplasia/acute myeloid leukemia.
2015;126(22):2484-90.
Drazer MW, Kadri S. Sukbanova M. Patil SA. West AH, et al. Prognest For the constants in familial myelodysplasia/acute myeloid leukemia. Blood.
2015;126(22):2484-90.
77. Drazer MW, Kadri S, Sukhanova M, Patil SA, West AH, et al. Prognostic tumor sequencing
2020 frequently identify germ lin
- somatic variants in familial myelodysplasts, acute myelodic leukemia. Blood
Drazer MW, Kadri S, Sukhanova M, Patil SA, West AH, et al. Prognostic tume
panels frequently identify germ line variants associated with hereditar 2020;22020;2016;2016
Drazer MW, Kadri S, Sul
panels frequently ident
malignancies. Blood Ad Frazer MW, Manuely and M, Patil M, Pressum, Pressum, Pressum Manuel D, equivalenting
panels frequently identify germ line variants associated with hereditary hematopoietic
malignancies. Blood Advances. 2018;2(2):146-50.
78
- panels frequently identify germ line variable association that the ends of protons in alignancies. Blood Advances. 2018;2(2):146-50.
Brown AL, Churpek JE, Malcovati L, Dohner H, Godley LA. Recognition of familial myeloi
ne mangummen en en manumen er en partier en en en
Brown AL, Churpek JE, Malcovati L, Dohner H, God
neoplasia in adults. Seminars in Hematology. 2017
National Comprehensive Cancer Network. Myeloo
- neoplasia in adults. Seminars in Hematology. 2017;54(2):60-8.
National Comprehensive Cancer Network. Myelodysplastic Syndromes (Version
2.2019). <u>https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf</u>. Accessed
Nove 79. National Comprehensive Cancer Network. Myelodysplastic Syndromes (Version 2.2019). https://www.nccn.org/professionals/physician gls/pdf/mds.pdf. Acces
November 26, 2018.
80. Guidugli L, Johnson AK, Alkorta-Aranburu G, Nelakuditi V, Arndt K, et al. Clinical u
- November 26, 2018.
2018). Guidugli L, Johnson AK, Alkorta-Aranburu G, Nelakuditi V, Arndt K, et al. Clinical utilit
2017:31/5):1226-9
2017:31/5):1226-9 gene panel-based testing for hereditary myelodysplastic syndrome/acute leukemia
predisposition syndromes. Leukemia. 2017;31(5):1226-9. 80. Superior of the setting for hereditary myelodysplastic syndrome/acute leukemia
81. Valent P, Orazi A, Steensma DP, Ebert BL, Haase D, et al. Proposed minimal diagnostic
81. Valent P, Orazi A, Steensma DP, Ebert BL, Haa
- gene predisposition syndromes. Leukemia. 2017;31(5):1226-9.
Valent P, Orazi A, Steensma DP, Ebert BL, Haase D, et al. Proposed minimal diagnost
criteria for myelodysplastic syndromes (MDS) and potential pre-MDS conditions. predisposition syndromes. Leukemia. 2017;21(2):2227-21
Valent P, Orazi A, Steensma DP, Ebert BL, Haase D, et al. P
criteria for myelodysplastic syndromes (MDS) and potenti
Oncotarget. 2017;8(43):73483-500. entitution, Channy Correlation, 2012, Supercent P, Oranic D, 2014. Correlation minimal angles incorrections.

Stephen Depths Conditions.

Stephen Haal J. M., Witte JS, Xu Y, Reddy P, et al. MDS-associated somatic mutations
- Oncotarget. 2017;8(43):73483-500.
Kwok B, Hall JM, Witte JS, Xu Y, Reddy P, et al. MDS-associated somatic mutation:
clonal hematopoiesis are common in idiopathic cytopenias of undetermined signi
Rlood, 2015:126(21):2255-61 Encouragemental, everywhere even
Kwok B, Hall JM, Witte JS, Xu Y, Rede
clonal hematopoiesis are common in
Blood. 2015;126(21):2355-61. 82. Kwok B, Hall J, Hall J, Hall J, Hall J, J, B and the successive transfer and the conditional hematopoiesis are common in idiopathic cytopenias of undetermined significant Blood.
83. Cargo CA, Rowbotham N, Evans PA, Bar
- Blood. 2015;126(21):2355-61.
Cargo CA, Rowbotham N, Evans PA, Barrans SL, Bowen DT, et al. Targeted sequencing
identifies patients with preclinical MDS at high risk of disease progression. Blood.
2015:126(21):2362-5 Cargo CA, Rowbotham N, Evan
identifies patients with preclin
2015;126(21):2362-5.
Malcovati L. Galli A. Travaglino identifies patients with preclinical MDS at high risk of disease progression. Blood.
2015;126(21):2362-5.
84. Malcovati L, Galli A, Travaglino E, Ambaglio I, Rizzo E, et al. Clinical significance of some
mutation in unexpl
- identifies patients with 2015;126(21):2362-5.

Malcovati L, Galli A, Travaglino E, Ambaglio I, Rizzo E, et al. Clinical significance of at

mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371-8.

laiswal S. F 2015;126(21):2362-5.
84. Malcovati L, Galli A, Travaglino E, Ambaglio I, Rizzo E, et al. Clinical significance of sor
2017;129(25):3371-8.
85. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, et al. Age-related
- mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371-8.
85. Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, et al. Age-related clonal
hematopoiesis associated with adverse outcomes. The New Englan Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, et al. Age-re
hematopoiesis associated with adverse outcomes. The New England Journal 2014;371(26):2488-98.
Genovese G, Kabler AK, Handsaker BE, Lindberg J, Bose 86. Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, et al. Clonal hematopoies
2014;371(26):2488-98.
86. Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, et al. Clonal hematopoies
- hematopoiesis associated with adverse outcomes the New England Lemmato Medicine.
Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, et al. Clonal hematopoiesis and
blood-cancer risk inferred from blood DNA sequence. Cenovese G, Kahler AK,
2014;371(26):2477-87.
2014;371(26):2477-87.
Bojar B, CHIB, ICUS, CCL blood-cancer risk inferred from blood DNA sequence. The New England Journal of Medicine.
2014;371(26):2477-87.
87. Bejar R. CHIP, ICUS, CCUS and other four-letter words. Leukemia. 2017;31(9):1869-71.
-
- blood-cancer risk inferred from blood-capcing from the New England China sections.
Bejar R. CHIP, ICUS, CCUS and other four-letter words. Leukemia. 2017;31(9):1869-71.
Valent P. ICUS, IDUS, CHIP and CCUS: Diagnostic Criter *A*
2014 R. CHIP, ICUS, CCU
2014 Valent P. ICUS, IDUS, CH
2018:1-9 88. Valent P. ICUS, IDUS, CHIP and CCUS: Diagnostic Criteria, Separation from MDS and Clim
Implications. Pathobiology: Journal of Immunopathology, Molecular and Cellular Biolog
2018:1-9. Implications. Pathobiology: Journal of Immunopathology, Molecular and Cellular Biology.
2018:1-9. $\frac{1}{2018:1-9}$. Pathology: Journal of Immunopathology, Molecular and Cellular Biology.
- $\frac{1}{c}$ and does <5% marrow myeloblasts represent a remission? The history and ambiguity of
arbitrary diagnostic boundaries in the understanding of myelodysplasia. The Oncologist.
2013;18(9):973-80.
90. Pfeilstocker M. Tuechler H and does the marrow my securities represent a remission the inset, and amogate, ex-
arbitrary diagnostic boundaries in the understanding of myelodysplasia. The Oncologist.
2013;18(9):973-80.
Pfeilstocker M, Tuechler H, San
- arbitrary diagnostic boundaries in the 2013;18(9):973-80.
Pfeilstocker M, Tuechler H, Sanz G, Schanz J, Garcia-Manero G, et al Time-dependent
Changes in mortality and transformation risk in MDS. Blood. 2016;128(7):902-10.
 2020;2013-90.
Pfeilstocker M, Tued
changes in mortality
Makishima H, Yoshi:
- 90. Pfeilstocker M, Tuechler H, Sanz G, Schanz J, Garcia-Manero G, et al Time-dependent
changes in mortality and transformation risk in MDS. Blood. 2016;128(7):902-10.
91. Makishima H, Yoshizato T, Yoshida K, Sekeres MA, R changes in mortality and transformation risk in more of the single politicial single single in Makishima H, Yoshizato T, Yoshida K, Sekeres MA, Radivoyevitch T, et al. Dynamic
evolution in myelodysplastic syndromes. Nature
- evolution in myelodysplastic syndromes. Nature Genetics. 2017;49(2):204-12.
92. Shiozawa Y, Malcovati L, Galli A, Pellagatti A, Karimi M, et al. Gene expression and risk of
leukemic transformation in myelodysplasia. Blood. evolution in myelody-plastic syndromes. Natural excrementation is chocal Shiozawa Y, Malcovati L, Galli A, Pellagatti A, Karimi M, et al. Gene expression and leukemic transformation in myelodysplasia. Blood. 2017;130(24):2
- eukemic transformation in myelodysplasia. Blood. 2017;130(24):2642-53.
93. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal
haematopoiesis to secondary leukaemia. Nature Reviews Cance leaning a and compute many competition in the control of the sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome
haematopoiesis to secondary leukaemia. Nature Reviews Cancer. 2017;17(
Corces-Zimmerma
- Mature Reviews Cancer. 2017;17(1):5-19.
94. Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukemic
94. Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukemic
7. mutations in hu Corces-Zimmerman MR, Hong WJ, Weissman IL, Medeiros BC, Majeti R. Preleukem
mutations in human acute myeloid leukemia affect epigenetic regulators and persis
remission. Proceedings of the National Academy of Sciences of th mutations in human acute myeloid leukemia affect epigenetic regulators and persist in
remission. Proceedings of the National Academy of Sciences of the United States of
America. 2014;111(7):2548-53. remission. Proceedings of the National Academy of Sciences of the United States of
America. 2014;111(7):2548-53.
Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, et al. Acute myeloid leukemia
ontogony is defined by d
- America. 2014;111(7):2548-53.
Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, et al. Acute myeloid leuken
ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-76.
Yokovama K. Shimizu E. Yokovam AMERICA. 2027, 2027.
Lindsley RC, Mar BG, Mazzola E,
ontogeny is defined by distinct :
Yokoyama K, Shimizu E, Yokoyar
- 999. Lindsley RC, Mar BB, Mazzola B, Scientific M, Statistic M, Scincentry, Premission, 2015; 125(9):1367-76.
96. Yokoyama K, Shimizu E, Yokoyama N, Nakamura S, Kasajima R, et al. Cell-lineage level-
targeted sequencing to ontogeny is definive in the Yokoyama N, Nakamura S, Kasajima R, et al. Cell-lineage
The distinct somation is defined a state in the some than the some distinct the distinct of the distinct of th
Tichtman MA, Doos a diagnos targeted sequencing to identify acute myeloid leukemia with myelodysplasia-related
changes. Blood Advances. 2018;2(19):2513-21.
97. Lichtman MA. Does a diagnosis of myelogenous leukemia require 20% marrow myeloblasts,
- targeted sequencing to identify acute myeloid lemanum that myeloysplasia tensor
changes. Blood Advances. 2018;2(19):2513-21.
and does <5% marrow myeloblasts represent a remission? The history and ambiguity
arbitrary diagno Coman MA. Does a diagnosis of myelogenous
and does <5% marrow myeloblasts represent a
arbitrary diagnostic boundaries in the understal
2013-18/9):973-80 and does <5% marrow myeloblasts represent a remission? The history and ambiguity of
arbitrary diagnostic boundaries in the understanding of myelodysplasia. The Oncologist.
2013;18(9):973-80. arbitrary diagnostic boundaries in the understanding of myelodysplasia. The Oncologist.
2013;18(9):973-80.
- 98. Bejar R. What biologic factors predict for transformation to AML? Best practice & research
Clinical Haematology. 2018;31(4):341-5.
99. DiNardo CD, Garcia-Manero G, Pierce S, Nazha A, Bueso-Ramos C, et al. Interactions Clinical Haematology. 2018;31(4):341-5.
- 99. Dinical Haematology. 2018;31(4):341-5.
99. DiNardo CD, Garcia-Manero G, Pierce S, Nazha A, Bueso-Ramos C, et al. Interactions and
199. DiNardo CD, Garcia-Manero G, Pierce S, Nazha A, Bueso-Ramos C, et al. Interactions DiNardo CD, Garcia-Manero G, Pierce S, I
relevance of blast percentage and treatm
with acute myeloid leukemia (AML) and i relevance of blast percentage and treatment strategy among younger and older patients
with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). American Jour
of Hematology. 2016;91(2):227-32. with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). American Journal
of Hematology. 2016;91(2):227-32. of Hematology. 2016;91(2):227-32.
 $\begin{array}{ccc}\n\bullet & \bullet & \bullet \\
\bullet & \bullet & \bullet\n\end{array}$ \overline{c}

Table 1: Clinical features associated with different MDS/MPN overlap conditions and disorders at the diagnostic boundary with MDS.

Figure Legends

Figure 1: Diagram depicting myeloid disorders with clinical and genetic features shared with MDS and the degree to which they are driven by proliferative and immunologic mechanisms.

Figure 2: Differences in gene mutation frequency across different MDS/MPN overlap conditions and disorders at the diagnostic boundary with MDS.

Figure 3: Comparison of features between cytopenic and clonal hematopoietic states that border MDS. Abbreviations include VAF – variant allele frequency; ICUS – idiopathic cytopenia of undetermined significance; CCUS – clonal cytopenia of undetermined significance; MDS – myelodysplastic syndromes; sAML – secondary acute myeloid leukemia; AML-MRC – AML with myelodysplasia-related changes; Obs – observation; BSC – best supportive care; GF – growth factors; IMiD – immunomodulatory imide drugs; IST – Immunosuppressive therapy; HMA – hypomethylating agent; HST – hematopoietic stem cell transplant; IC – induction chemotherapy.

Figure 2

+

+

20+%

ry High A/IC/HST

Clonal Cytopenias Oligoblastic Leukemia

$AML/$ L-MRC

 $0 - 50%$

Figure 3

doi:10.1182/blood-2018-10-844670 Prepublished online January 22, 2019;

MDS overlap disorders and diagnostic boundaries

Tiffany N. Tanaka and Rafael Bejar

http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests Information about reproducing this article in parts or in its entirety may be found online at:

<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints> Information about ordering reprints may be found online at:

<http://www.bloodjournal.org/site/subscriptions/index.xhtml> Information about subscriptions and ASH membership may be found online at:

digital object identifier (DOIs) and date of initial publication. indexed by PubMed from initial publication. Citations to Advance online articles must include final publication). Advance online articles are citable and establish publication priority; they are appeared in the paper journal (edited, typeset versions may be posted when available prior to Advance online articles have been peer reviewed and accepted for publication but have not yet

[Copyright 2011 by The American Society of Hematology; all rights reserved.](http://www.bloodjournal.org/site/subscriptions/ToS.xhtml) Hematology, 2021 L St, NW, Suite 900, Washington DC 20036. Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of