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Pathogenesis and management of high molecular risk myeloproliferative neoplasms

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Abstract
Classical myeloproliferative neoplasms (MPNs) are clonal stem cell disorders characterised by driver mutations that affect the constitutive activation of JAK-signalling. Additional
mutations to an MPN-driver occur in a large number of patients and have been shown be
associated with disease presentation and progr by driver mutations that affect the constitutive activation of JAK-signalling. Additional
mutations to an MPN-driver occur in a large number of patients and have been shown be
associated with disease presentation and progr associated with disease presentation and progression. In this review, we will outline the
current hypotheses regarding how clonal evolution in MPN is thought to occur and the
functional mechanisms as to how concomitant som associated with discussion in MPN is thought to occur and the functional mechanisms as to how concomitant somatic mutations (i.e. mutations in generation and the 'driver' genes) contribute to disease progression. We will d functional mechanisms as to how concomitant somatic mutations (i.e. mutations in gen
other than the 'driver' genes) contribute to disease progression. We will discuss the
definitions of high molecular risk MPN, provide an other than the 'driver' genes) contribute to disease progression. We will discuss the
definitions of high molecular risk MPN, provide an overview as to how concomitant
mutations influence the clinical management of MPN and definitions of high molecular risk MPN, provide an overview as to how concomitant
mutations influence the clinical management of MPN and suggest how this rapidly
developing genetic risk stratification can be utilised to im

Main Text

mutations influence the clinical management of MPN and suggest how this rapidly
developing genetic risk stratification can be utilised to improve clinical outcomes.
Main Text
The classical *BCR*::*ABL*-negative myeloprol developing genetic risk stratification can be utilised to improve clinical outcomes.
 Main Text

The classical *BCR*::*ABL*-negative myeloproliferative neoplasms (MPNs), polycythemia vera

(PV), essential thrombocythemia Main Text
The classical *BCR*::*ABL*-negative myeloproliferative neoplasms (MPNs), polycythen
(PV), essential thrombocythemia (ET) and myelofibrosis (MF), are characterized by
mutations that affect the constitutive activat The classical BCR ::ABL-negative myeloproliferative neoplasms (MPNs), polycythemia vera The classical BCR::ABL-negative myeloprolinerative neoplasms (WH), polycythemia vera
(PV), essential thrombocythemia (ET) and myelofibrosis (MF), are characterized by driver
mutations that affect the constitutive activatio (P), essential thrombochial thrombochial thrombochial thrombochia (S). Such as mutations in Jan
Kinase 2 (JAK2), Calreticulin (CALR) and the thrombopoietin receptor (MPL). While the MF
phenotype is often dominated by exce Kinase 2 (JAK2), Calreticulin (CALR) and the thrombopoietin receptor (MPL). While the MPN
phenotype is often dominated by excessive production of mature myeloid cells, these driver
mutations are initiated and maintained in Kinase 2 (JAK2), calleticulin (CALN) and the thrombopoicentreceptor (MPL). While the MPN
phenotype is often dominated by excessive production of mature myeloid cells, these driver
mutations are initiated and maintained in

phenotype is entitled and maintained in hematopoietic stem cells (HSCs); thus MPNs are
considered clonal stem cell disorders.
Most patients present in a 'chronic-phase' (CP) of the disease (i.e. PV, ET, pre-fibrotic MF),
w maintend are initiated and maintains arrivance preservations (MSL), and maintains are
considered clonal stem cell disorders.
Most patients present in a 'chronic-phase' (CP) of the disease (i.e. PV, ET, pre-fibrotic MF),
wi considered clonal stem cell disorders.

Most patients present in a 'chronic-phase' (CP) of the disease (i.e. PV, ET, pre-fibrotic MF),

with elevated peripheral blood (PB) parameters and accompanying systemic inflammation. 「\「(こ)に with elevated peripheral blood (PB) parameters and accompanying systemic inflammation
Relevant clinical challenges include (i) symptom control, (ii) prevention of thromboembolic
(TE) complications and (iii) prevention of d Relevant clinical challenges include (i) symptom control, (ii) prevention of thromboembolic
(TE) complications and (iii) prevention of disease progression. Symptom control can be
achieved by supportive measures, cytoreduct (TE) complications and (iii) prevention of disease progression. Symptom control can be achieved by supportive measures, cytoreduction or symptom-oriented therapy (e.g. JAK-
inhibitors) and prevention of TE events achieved achieved by supportive measures, cytoreduction or symptom-oriented therapy (e.g. JAK-
inhibitors) and prevention of TE events achieved using acetylsalicylic acid or anticoagulan
and cytoreductive measures, such as phleboto disease progression during their lifetimes, either from CP to fibrotic MF, or CP/MF to an
accelerated phase (AP) (10-20% blasts) or overt acute myeloid leukemia (AML) (≥20% blasts), and cytoreductive measures, such as phlebotomy or pharmacologic agents (e.g.
Hydroxyurea, interferon or JAK-inhibitors). Patients can also present with more advanced
phases of the disease resulting from excessive fibrotic Hydroxyurea, interferon or JAK-inhibitors). Patients can also present with more a
phases of the disease resulting from excessive fibrotic deposition in the bone ma
fibrotic phase of MF) and exhibit aggravated symptoms, spl phases of the disease resulting from excessive fibrotic deposition in the bone marrow (i.e.
fibrotic phase of MF) and exhibit aggravated symptoms, splenomegaly and cytopenias tha
require pharmacologic and supportive interv fibrotic phase of MF) and exhibit aggravated symptoms, splenomegaly and cytopenias that
require pharmacologic and supportive interventions. Up to 40% of MPN patients experience
disease progression during their lifetimes, five pharmacologic and supportive interventions. Up to 40% of MPN patients experience disease progression during their lifetimes, either from CP to fibrotic MF, or CP/MF to an accelerated phase (AP) (10-20% blasts) or over require procures of uring their lifetimes, either from CP to fibrotic MF, or CP/MF to an accelerated phase (AP) (10-20% blasts) or overt acute myeloid leukemia (AML) (≥20% blasts), also referred to as blast-phase (BP) MPN. accelerated phase (AP) (10-20% blasts) or overt acute myeloid leukemia (AML) (≥20% blasts also referred to as blast-phase (BP) MPN. Progression is frequently associated with clinic deterioration and shortened overall survi also referred to as blast-phase (BP) MPN. Progression is frequently associated with clinical
deterioration and shortened overall survival. Allogeneic hematopoietic stem cell
transplantation (alloHSCT) is the only potential deterioration and shortened overall survival. Allogeneic hematopoietic stem cell
transplantation (alloHSCT) is the only potentially curative therapy currently available for
MPN, however due to high morbidity and mortality deterioration and shortened overally curative therapy currently avails
determing the only potentially curative therapy currently avails
MPN, however due to high morbidity and mortality rates, is only indicated for yo
patie

MPN, however due to high morbidity and mortality rates, is only indicated for younger/f
patients at higher risk for disease progression.
Next generation sequencing (NGS) technology has facilitated increased resolution of Matter to thigher risk for disease progression.
Next generation sequencing (NGS) technology has facilitated increased resolution of the
mutational landscape that underpins the process of malignant transformation in humans patient of the Branch

Patt generation sequencing (NGS) technology

mutational landscape that underpins the proce

This is exemplified by AML, where particular pa

prognostically relevant sub-classes ¹. Somatic c

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| | Next, general landscape that underpins the process of malignant transformation in humans
This is exemplified by AML, where particular patterns of mutational co-occurrence define
prognostically relevant sub-classes ¹. Som This is exemplified by AML, where particular patterns of mutational co-occurrence define
prognostically relevant sub-classes 1 . Somatic co-mutations of relevance in myeloid cancer
in addition to MPN-drivers are present prognostically relevant sub-classes $\frac{1}{1}$. Somatic co-mutations of relevance in myeloid cance
in addition to MPN-drivers are present in approximately 50% of patients with CP MPN²⁻⁵.
note, these studies highlight gen prognostically relevant sub-classes ⁺
in addition to MPN-drivers are prese
note, these studies highlight genetic
clinical phenotypes. The number of
inical phenotypes. The number of in addition to MPN-drivers are present in approximately 50% of patients with CP MPN²⁻⁵. Of
note, these studies highlight genetic subgroups associated with outcomes, independent of
clinical phenotypes. The number of mutat in addition to MPN-drivers are present in approximately 50% of patients with CP MPN²⁹. Of
note, these studies highlight genetic subgroups associated with outcomes, independent of
clinical phenotypes. The number of muta note, these studies inginging generating, they are critical with christmas, independent of contained phenotypes. The number of mutations increases with disease progression and

correlates with progression to MF and AP/BP MPN^{2,7}. The concept and definition of high
molecular risk (HMR) mutations has facilitated their predictive use in addition to clinical
disease parameters for patient outcomes a molecular risk (HMR) mutations and informed treatment decisions.
In this review, we will outline the current hypotheses regarding how clonal evolution in M
is thought to occur and the functional mechanisms as to how concom In this review, we will outline the current hypotheses regarding how clonal evis thought to occur and the functional mechanisms as to how concomitant so mutations (i.e. mutations in genes other than the 'driver' genes, JAK | i r c こく In this thought to occur and the functional mechanisms as to how concomitant somatic
mutations (i.e. mutations in genes other than the 'driver' genes, JAK2, CALR and MPL)
contribute to disease progression. We will discuss is thought to occur and the functional mechanisms as to how concomitant somatic mutations (i.e. mutations in genes other than the 'driver' genes, JAK2, CALR and MPL) contribute to disease progression. We will discuss the d an overview as to how concomitant mutations influence the clinical management of MPN
and suggest how this rapidly developing genetic risk stratification can be utilized to improv
clinical outcomes.
Mechanisms of mutational contribute to discusse the discussion. The discussion overview as to how concomitant mutations influence the clinical management of MPN and suggest how this rapidly developing genetic risk stratification can be utilized to

Mechanisms of mutational acquisition

and suggest how this rapidly developing genetic risk stratification can be utilized to improv
clinical outcomes.
Mechanisms of mutational acquisition
CP MPN are a neoplastic state consequent to a single oncogenic driver, phenotypic diversity in the pathogenesis of MPNs cannot always be explained by progressive
consequences of a single genetic driver event and thus may be related to the presence of
concomitant somatic mutations. Clonal dyna | (r
| c
| c CP MPN are a neoplastic state consequent to a single oncogenic driver, like JAK2 V617F, CP MPN are a neoplastic state consequent to a single oncogent driver, the JAM2 V617T,
necessary but insufficient for secondary transformation. However, the complexity and
phenotypic diversity in the pathogenesis of MPNs ca phenotypic diversity in the pathogenesis of MPNs cannot always be explained by progromsequences of a single genetic driver event and thus may be related to the presence concomitant somatic mutations. Clonal dynamics of MPN consequences of a single genetic driver event and thus may be related to the presence of concomitant somatic mutations. Clonal dynamics of MPN are further complicated by the understanding that the MPN-driver mutation is n concomitant somatic mutations. Clonal dynamics of MPN are further complicated by the understanding that the MPN-driver mutation is not always the initiating mutational event Therefore, the acquisition of additional somatic understanding that the MPN-driver mutation is not always the initiating mutational event
Therefore, the acquisition of additional somatic mutations in MPN must be considered as
function of both an MPN-driver and pre-existi understanding that the MPN-driver mutation is not always the initiating mutational event⁸
Therefore, the acquisition of additional somatic mutations in MPN must be considered as a
function of both an MPN-driver and pre-e .
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MPN-driver mediated

Therefore, the acquisition of both an MPN-driver and pre-existing somatic mutations (e.g. as in clonal
hematopoiesis (CH)).
MPN-driver mediated
In HSCs, the JAK2 V617F mutation accelerates cell division and is associated function of both and the matopoiesis (CH)).
Function of both and pre-existion of both and is associated with increases of the JAK2 V617F mutation accelerates cell division and is associated with increased DNA damage can be MPN-driver mediated
In HSCs, the JAK2 V61
DNA damage^{7,8}. Incre
instability inherent to
transformation. In CP
the loss of key regulat In HSCs, the JAK2 V617F mutation accelerates cell division and is associated with increased INTISES, the JAK2 V617T indication accelerates cen division and is associated with increased DNA damage^{7,8}. Increased DNA damage can be considered a precursor to the genetic instability inherent to most cancer genomes a instability inherent to most cancer genomes and has been established as causal in malignant
transformation. In CP MPN, this state of DNA damage may provide a selective pressure for
the loss of key regulators of DNA-damage transformation. In CP MPN, this state of DNA damage may provide a selective pressure for
the loss of key regulators of DNA-damage checkpoints, like p53. Alternatively, it could
facilitate an increased rate of mutagenesis, the loss of key regulators of DNA-damage checkpoints, like p53. Alternatively, it could
facilitate an increased rate of mutagenesis, leading to the emergence of mutations that
confer a further selective advantage. Current facilitate an increased rate of mutagenesis, leading to the emergence of mutations that confer a further selective advantage. Current evidence suggests that this is mediated intrinsic manner through the ability of JAK2 ac confer a further selective advantage. Current evidence suggests that this is mediated in
intrinsic manner through the ability of JAK2 activation to directly drive downstream PI3H
AKT signaling ⁷. However, Jak2 mutant ce intrinsic manner through the ability of JAK2 activation to directly drive downstream PI3K-AKT signaling ⁷. However, *Jak2* mutant cells may also generate an inflammatory microenvironment⁹, that enhances mutagenesis¹⁰

Consistently, individuals exclusively harbouring JAK2 mutations may experience long-term
stability of the mutated clone or even clonal regression. Lineage tracing approaches to AKT signaling '. However, Jak2 mutant cells may also generate an inflammatory
microenvironment⁹, that enhances mutagenesis¹⁰, and specifically provides a se
advantage for the loss of p53¹¹.
In contrast, longitudinal microenvironment⁹, that enhances mutagenesis², and specifically provides a selective
advantage for the loss of p53¹¹.
In contrast, longitudinal studies in serial human samples found a low mutation rate of 1
mutation advantage for the loss of p53²¹.
In contrast, longitudinal studies
mutation per 66 patient years¹²,
Consistently, individuals exclusiv
stability of the mutated clone or
assess the time course of clonal
be acquired deca | r C vic - k
| r mutation per 66 patient years¹², arguing against a strong hypermutable state in MPN.
Consistently, individuals exclusively harbouring JAK2 mutations may experience long-ter
stability of the mutated clone or even clonal mutation per 66 patient years⁴⁴, arguing against a strong hypermutable state in MPN.
Consistently, individuals exclusively harbouring JAK2 mutations may experience long-t
stability of the mutated clone or even clonal reg Consistently, individuals exclusively harbouring JAR2 mutations may experience long-term
stability of the mutated clone or even clonal regression. Lineage tracing approaches to
assess the time course of clonal expansion pr stable) the time course of clonal expansion provided first evidence that driver mutation
be acquired decades before clinical manifestation of MPN^{13,14}, as in some cases, *JAK2*
mutations could already be detected in cor be acquired decades before clinical manifestation of MPN^{13,14}, as in some cases, JAK2
mutations could already be detected in cord blood. However, data investigating the
behaviour of mutated cells from 385 older individu be acquired decades before clinical manifestation of MPN²⁰¹,²⁴, as in some cases, JAK2
mutations could already be detected in cord blood. However, data investigating the
behaviour of mutated cells from 385 older indivi mutations could already be detected in cord blood. However, data investigating the
behaviour of mutated cells from 385 older individuals found growth trajectories of JA
mutated clones to be particularly erratic, with only behaviour of mutated cells from 385 older individuals found growth trajectories of JAK2growth trajectories of JAR2-
playing stable growth¹⁵. The mutated clones to be particularly erratic, with only 58% displaying stable growth**. The reason for this behavior remains unclear.
reason for this behavior remains unclear.

Age-related clonal hematopoiesis (ARCH)-mediated
Somatic mutations acquired prior to the driver (e.g. a JAK2 mutation) may provide a 'fertile Somatic mutations acquired prior to the driver (e.g. a JAR2 mutation) may provide a fertile
ground' for malignant transformation^{8,12}. CH is where the maturing cell progeny derived
from a single HSC ancestor, or "clone", ground' for malignant transformation".". CH is where the maturing cell progeny derived
from a single HSC ancestor, or "clone", dominates the hematopoietic compartment of an
individual. CH occurs as a consequence declining individual. CH occurs as a consequence declining clonal diversity during aging and may no
be associated with a neoplastic state, leading to the terminology of ARCH or CH of
indeterminate potential (CHIP). Mutations with r be associated with a neoplastic state, leading to the terminology of ARCH or CH of
indeterminate potential (CHIP). Mutations with relevance in myeloid malignancies include
DNMT3A, TET2 and *ASXL1 (DTA* mutations) accoun indeterminate potential (CHIP). Mutations with relevance in myeloid malignancies
DNMT3A, TET2 and ASXL1 (DTA mutations) account for over 90% of cases of ARCH.
association with increased risk of future development of myelo DNMT3A, TET2 and ASXL1 (DTA mutations) account for over 90% of cases of ARCH. Due to
association with increased risk of future development of myeloid malignancies, including
MPNs, ARCH can thus represent a pre-neoplastic DNMT3A, TET2 and ASXET (DTA mutations) account for over 30% of cases of ARCH. Due to its
association with increased risk of future development of myeloid malignancies, including
MPNs, ARCH can thus represent a pre-neoplast MPNs, ARCH can thus represent a pre-neoplastic state¹⁶. Consistently, *DTA* mutations are found in both MPN-driver positive and negative cells in post-MPN AML ^{3,4}. Although they influence the balance towards self-rene found in both MPN-driver positive and negative cells in post-MPN AML ^{5,4}. Although they
influence the balance towards self-renewal over lineage commitment, there is no definitiv
evidence that *DTA* mutations lead to enha evidence that *DTA* mutations lead to enhanced mutational acquisition. *Dnmt3a*-null murine
HSCs show progressive loss in clonal diversity leading to increased variant allele frequency
(VAF) of existing somatic variants th evidence that DTA mutations lead to emitticed mutational acquisition. Different HSCs show progressive loss in clonal diversity leading to increased variant allele frequency (VAF) of existing somatic variants that have been (VAF) of existing somatic variants that have been maintained in expanded clones¹⁷. DTA
mutations may therefore rather facilitate continued clonal expansion in the presence of a
mutagenic stimulus, such as inflammation¹

(VAF) of existing somatic variants that have been maintained in expanded clones²⁷. DTA
mutations may therefore rather facilitate continued clonal expansion in the presence of
mutagenic stimulus, such as inflammation¹⁸. mutagenic stimulus, such as inflammation¹⁸.
 Pathways of clonal evolution in MPN

Although the chronic, accelerated and blast phases of MPN can be appreciated as a linear

trajectory, this pathway of disease progressio mutagenic stimulus, such as inflammation²⁰.
Pathways of clonal evolution in MPN
Although the chronic, accelerated and blast _k
trajectory, this pathway of disease progressic
without a prior diagnosis of PV or ET, or A 「ノ t ヽ ド r Pathways of clonal evolution in MPN Altrajectory, this pathway of disease progression is not uniform. Patients can present with M
without a prior diagnosis of PV or ET, or AP/BP without a prior diagnosis of MF. Furthermo
disease progression to MF or AP/BP is without a prior diagnosis of PV or ET, or AP/BP without a prior diagnosis of MF. Furthermore
disease progression to MF or AP/BP is not an inevitable outcome in PV or ET with chronic
phases lasting sometimes for many decade disease progression to MF or AP/BP is not an inevitable outcome in PV or ET with chronic
phases lasting sometimes for many decades. The linear directionality to the evolution of
MPN is further challenged and complicated by phases lasting sometimes for many decades. The linear directionality to the evolution of
MPN is further challenged and complicated by the fact that an MPN driver mutation may
always represent the foundational event in MPN phases in the formulation of the fact that an MPN driver mutation may
always represent the foundational event in MPN and can either be present or absent in p
MPN AML blasts^{3,4}. MPN may therefore emerge and progress along always represent the foundational event in MPN and can either be present or absent in post-
MPN AML blasts^{3,4}. MPN may therefore emerge and progress along separable evolutionary
paths dictated by the order of mutational MPN AML blasts^{3,4}. MPN may therefore emerge and progress along separable evolutionary
paths dictated by the order of mutational events, being either linear, branching or parallel
(Figure 1).
The validity of these potenti

(i) Is it possible that an MPN driver mutation is lost from a cell as it undergoes leukemic
transformation? paths differed as the order of these potential paths distance determined by the answers to two key
questions:
(i) Is it possible that an MPN driver mutation is lost from a cell as it undergoes leukem
transformation?
JAK2 V

The validity

questions:

(i) Is it
 LAK2 V617

therapy res |
| c
|
| t The valid paths can be detected in patients with MPN and gene dosage in the valid paths of the and MPN driver mutation is lost from a cell as it undergoes transformation?

JAK2 V617F homozygosity can be detected in patient (i) Is it
(i) Is it
*IAK2 V*617I
Iherapy res
consequen
homozygou
However, s (interary or an intertation)

IS IS IS it ansformation?

IS IS IS IS IS it posted in patients with MPN and gene dosage influences

therapy response and the clinical phenotype. Homozygosity is presumed to occur as a

conseq therapy response and the clinical phenotype. Homozygosity is presumed to occur as a
consequence of mitotic recombination, which would result in the generation of both JAK2
homozygous mutant and wildtype progeny from a JAK2 JAK2 V617F homozygosity can be detected in patients with MP is and gene dosage influences
therapy response and the clinical phenotype. Homozygosity is presumed to occur as a
consequence of mitotic recombination, which woul consequence of mitotic recombination, which would result in the generation of both *J*,
homozygous mutant and wildtype progeny from a *JAK2* V617F heterozygous founder.
However, single nucleotide polymorphisms (SNPs) withi consequence of mitotic recombination, which would result in the generation of both JAK2
homozygous mutant and wildtype progeny from a JAK2 V617F heterozygous founder.
However, single nucleotide polymorphisms (SNPs) within Homozygous mutant and whatype progeny from a JAR2 V6171 heterozygous founder.
However, single nucleotide polymorphisms (SNPs) within and telomeric to a mutant *J*,
locus can only be identified in *JAK2* V617F homozygous c Hocus can only be identified in JAK2 V617F homozygous clones, both supporting the
occurrence of mitotic recombination and indicating that JAK2 wildtype loss of heterozygo.
(LOH) progeny do not expand appreciably in MPN pat locus can only be identified in JAK2 V617F homozygous clones, both supporting the
occurrence of mitotic recombination and indicating that JAK2 wildtype loss of hetero
(LOH) progeny do not expand appreciably in MPN patients occurrence of mitotic recombination and indicating that JAN2 whatype loss of heterozygosity
(LOH) progeny do not expand appreciably in MPN patients¹⁹. Furthermore, in JAK2-wildtype
post-MPN AML, LOH, determined by SNP ge

(LOH) progeny do not expand appreciably in MPN patients²⁵. Furthermore, in JAK2-wildtype
post-MPN AML, LOH, determined by SNP genotyping, was not detected in leukemic
blasts^{19,20}, providing evidence against loss of JA poster (a) the system and the context of the SNP during blast transformation.

(ii) Can AML evolve in the context of MPN, from an independent clonal precursor

Combined analysis of JAK2 V617F granulocytes and JAK2 wildtype (ii) Combined analysis of *JAK2* V617F granulocytes and *JAK2* wildtype leukemic blasts from same patient have demonstrated the inactivation of the same parental X-chromosome² Ecombined analysis of JAK2 V617F granulocytes and JAK2 which be reakennic blasts from the
same patient have demonstrated the inactivation of the same parental X-chromosome²⁰. same patient have demonstrated the inactivation of the same parental X-chromosome²⁰.
20.
20.
20.

Also, shared somatic mutations in JAM2 V617T cells and JAM2-wildtype leukemic blasts (like
DTA), support the hypothesis that MPN and post-MPN AML share a common clonal ancesto
(Figure 1, branching evolution). However, the DTA), support the hypothesis that MPN and post-MPN MAML share a common clonal ancestor
(Figure 1, branching evolution). However, the possibility that MPN and AML may arise in the
same individual independently (Figure 1, pa

(Figure 2) and the pendently (Figure 1, parallel evolution) cannot be excluded, especially
considering the inflammatory microenvironment that occurs in MPN.
Together, these findings suggest that transformation to MPN-drive same individual independently (Figure 1, parameter creating, considering the inflammatory microenvironment that occurs in MPN.
Together, these findings suggest that transformation to MPN-driver expressing AML is most
likel Together, these findings suggest that transformation to MPN-driver exilely a consequence of linear evolution whereas MPN-driver negative consequence of branching or parallel evolution (Figure 1). Pathways o parallel evolut ヿーヽドミド The likely a consequence of linear evolution whereas MPN-driver negative AML rather a
consequence of branching or parallel evolution (Figure 1). Pathways of branching and
parallel evolution in MPN, however, appear to be le mary security a consequence of branching or parallel evolution (Figure 1). Pathways of branching an parallel evolution in MPN, however, appear to be less efficient, given that retrospect analysis across multiple independen parallel evolution in MPN, however, appear to be less efficient, given that retrospectiv
analysis across multiple independent cohorts of post-MPN AML suggest that MPN -dri
positive leukemia accounts for approximately 80% o

paralysis across multiple independent cohorts of post-MPN AML suggest that MPN -drive
positive leukemia accounts for approximately 80% of this disease subset^{4,5,21}.
Functional consequences of mutational heterogeneity
Som positive leukemia accounts for approximately 80% of this disease subset^{4,5,21}.
Functional consequences of mutational heterogeneity
Somatic mutations that occur in MPN include epigenetic regulators, splicing factors and
r positive leukemia accounts for approximately 80% of this disease subset^{-1,3,21}.
Functional consequences of mutational heterogeneity
Somatic mutations that occur in MPN include epigenetic regulators, splicing fa
regulat Functional consequences of mutational heterogeneity
Somatic mutations that occur in MPN include epigenetic regulators, splicing factors and regulators of transcription². The majority of functional studies on concomitant mutation
MPN have employed genetically modified mouse models, with engineered alleles either
constitutively expressed or conditionally activ regulators of transcription". The majority of functional studies on concomitant mutations in
MPN have employed genetically modified mouse models, with engineered alleles either
constitutively expressed or conditionally act Constitutively expressed or conditionally activated and restricted to the hematopoietic
system either through tissue specific Cre-recombinases or generation of bone marrow
chimeras.
Epigenetic Regulators
Epigenetic regula

system either through tissue specific Cre-recombinases or generation of bone marrow
chimeras.
Epigenetic Regulators
Epigenetic regulators, including DTA, are frequently mutated in MPN ^{2–5,21}. As in ARCH,
mutations are i system eras.
 Epigenetic Regulators

Epigenetic regulators, including DTA, are frequently mutated in MPN ^{2–5,21}. As in ARCH,

mutations are implicated in self-renewal of MPN HSCs ^{22–25}, counteracting the reduced

qu *Epigenetic
Epigenetic*
Epigenetic
mutations
According
stemness-ノード パーパード Epigenetic Regulators Epigenetic regulators, including DTA, are frequently mutated in MPN ^{2–3,24}. As in ARCH, DTA mutations are implicated in self-renewal of MPN HSCs ^{22–25}, counteracting the reduced HSC quiescence²⁶ and limited long-ter mutations are implicated in self-renewal of MPN HSCs^{22–25}, counteracting the reduced HSC
quiescence²⁶ and limited long-term replicative potential mediated by Jak2 V617F expression
Accordingly, both Tet2 and Dnmt3a-los quiescence²⁰ and limited long-term replicative potential mediated by Jak2 V617F expression.
Accordingly, both *Tet2* and *Dnmt3a*-loss are associated with the increased expression of
stemness-related genes^{22,23}. Howev stemness-related genes^{22,23}. However, additional *DTA* mutations occur more frequently is patients diagnosed with MF, compared to PV or ET², suggesting co-existing *DTA* mutation also modify the MPN phenotype, rather stemness-related genes^{22,25}. However, additional DTA mutations occur more frequently in
patients diagnosed with MF, compared to PV or ET², suggesting co-existing DTA mutations
also modify the MPN phenotype, rather tha patients diagnosed with MF, compared to PV or ET², suggesting co-existing DTA mutations
also modify the MPN phenotype, rather than just maintain it. These observations can be
reconciled by considering myelofibrosis as a reconciled by considering myelofibrosis as a function of time, which can be accelerated b
co-occurring DTA mutations. Consistent with this, MF is diagnosed at a higher mean age t
ET and PV, and transgenic expression of JA co-occurring *DTA* mutations. Consistent with this, MF is diagnosed at a higher mean age th
ET and PV, and transgenic expression of *JAK2* V617F is sufficient to drive MF in mice, albeit
with incomplete penetrance, in age ET and PV, and transgenic expression of JAK2 V617F is sufficient to drive MF in mice, albeit
ET and PV, and transgenic expression of JAK2 V617F is sufficient to drive MF in mice, albeit
with incomplete penetrance, in aged ET and PV, and transgenic expression of JAR2 V617F is sufficient to drive MF in mice, albeit
with incomplete penetrance, in aged cohorts^{27,28}. However, the acceleration of MF onset
with *Dnmt3a*-loss in combination with with incomplete penetrance, in aged cohorts^{27,28}. However, the acceleration of MF onset
with *Dnmt3a*-loss in combination with a conditional *Jak2V617F* allele is also associated w
increased expression of genes involved with Dimit5a-loss in combination with a conditional Juk2V617F allele is also associated with increased expression of genes involved in TNFα signaling²², suggesting Dnmt3a-loss may directly promote fibrosis. These trans apparent *in vitro²²,* suggesting an important interplay with the BM microenvironment
Similarly, heterozygous Asxl1-loss accelerates MF latency in the context of a JAK2 V61
transgenic allele^{25,28}. Notably, *Tet2*-loss apparent *in vitro*²², suggesting an important interplay with the BM microenvironment.
Similarly, heterozygous *Asxl1*-loss accelerates MF latency in the context of a JAK2 V617
transgenic allele^{25,28}. Notably, *Tet2*-Similarly, heterozygous Asxl1-loss accelerates MF latency in the context of a JAK2 V617F
transgenic allele^{25,28}. Notably, *Tet2*-loss does not drive MF in mice. It is unclear whether t
reflects discrete functional conse

reflects discrete functional consequences of the individual DTA mutations, or rather nuances
in the respective experimental models of MPN.
Mutations in other epigenetic regulator genes are also relevant in MPN. *Ezh2*-los in the respective experimental models of MPN.
Mutations in other epigenetic regulator genes are also relevant in MPN. *Ezh2*-loss and
expression of gain-of-function mutations in *IDH1* and *Idh2* increase the repopulation In the respective experimental models of Mutations in other epigenetic regulator genes a
expression of gain-of-function mutations in *IDH.*
potential of *Jak2* V617F HSCs. *Ezh2*-loss exacerb
both *JAK2* V617F transgenic a |
|}
|
| expression of gain-of-function mutations in *IDH1* and *Idh2* increase the repopulation
potential of *Jak2* V617F HSCs. *Ezh2*-loss exacerbates the fully penetrant MF phenotype
both *JAK2* V617F transgenic and knock-in str expression of gain-or-function mutations in *IDH1* and *funz* increase the repopulation
potential of *Jak2* V617F HSCs. *Ezh2*-loss exacerbates the fully penetrant MF phenotyp
both *JAK2* V617F transgenic and knock-in stra potential of Jak2 V617F H3Cs. Ezh2-loss exacerbates the fully penetrant MF phenotype in
both JAK2 V617F transgenic and knock-in strains. This is associated with a bias towards
megakaryocyte differentiation at the expense both JAK2 V617F transgenic and Khock-in strains. This is associated with a bias towards
megakaryocyte differentiation at the expense of erythropoiesis^{29,30}. The increased fibro
megakaryocyte differentiation at the expens megakaryocyte differentiation at the expense of erythropoiesis^{29,30}. The increased fibrosis is
3
-
-

recapitulated with megakaryocyte-restricted loss of *Ezh2* using *Pf4*-Cre²⁷. The terminal
disease phenotype in both *IDH1* and *Idh2* co-mutated strains, however, appears to be
comparable to *Jak2* V617F alone³¹. Int disease phenotype in both IDH1 and Idh2 co-mutated strains, however, appears to be
comparable to Jak2 V617F alone³¹. Interestingly, co-existing IDH mutations also reduce
erythroid bias without a compensatory increase in erythroid bias without a compensatory increase in megakaryocytes. In contrast, Asx/1-loss in
combination with Jak2 V617F promotes megakaryocyte differentiation but not at the
expense of erythropoiesis²⁵, whereas Tet2-lo erythroid bias without a compensatory increase in megakaryocytes. In contrast, Asxi1-10ss in
combination with *Jak2* V617F promotes megakaryocyte differentiation but not at the
expense of erythropoiesis²⁵, whereas *Tet2*expense of erythropoiesis²⁵, whereas *Tet2-loss* does not alter lineage commitment²³.
Together, these findings suggest that MF may be driven by dysregulation of epigenetic
modifiers, with lineage-specific consequences,

expense of erythropoiesis²⁵, whereas *Tet2-loss* does not alter lineage commitment²⁵.
Together, these findings suggest that MF may be driven by dysregulation of epigenetic
modifiers, with lineage-specific consequences, modifiers, with lineage-specific consequences, primarily within the megakaryocyte lineage.
The order of mutation acquisition is also important in MPN pathogenesis. To date, this has
not been tested in mice directly. Using modules, minimizing a parameterical princes, primarily minimizing integrating at the order of mutation acquisition is also important in MPN pathogenesis. To date, this has not been tested in mice directly. Using primary pa ך
| r ⊦
| r r not been tested in mice directly. Using primary patient samples in colony assays, studies
have demonstrated that TET2 mutations acquired prior to an MPN-driver reduce mature ce
expansion, associated with a less severe dise have demonstrated that *TET2* mutations acquired prior to an MPN-driver reduce mature
expansion, associated with a less severe disease presentation. This is consistent with *TET*
mutations shifting the balance towards sel mate demonstrated that TET2 mutations acquired prior to an MPN driver reduce mature cell
expansion, associated with a less severe disease presentation. This is consistent with TET2
mutations shifting the balance towards s expansion, associated with a less severe disease presentation. This is consistent with TET2
mutations shifting the balance towards self-renewal over differentiation. When TET2
mutations are acquired subsequent to an MPN-dr mutations similing the balance towards sen-renewal over differentiation. When TET2
mutations are acquired subsequent to an MPN-driver however, they facilitate HSC exp
while mature cell expansion is largely mediated by the while mature cell expansion is largely mediated by the MPN-driver only clone⁶. This
contrasts with the functional studies in mice demonstrating the exacerbation of the disease
phenotype with co-existing *Tet2*-loss comp phenotype with co-existing Tet2-loss compared to Jak2V167F alone²³. Order of DNMT3a
mutational acquisition in relation to an MPN-driver is also associated with distinct cellular
and clinical phenotypes³².
Splicing fac

phenotype with co-existing *Tet2-loss compared to Jak2V167F* alone²⁹. Order of *DNMT3a*
mutational acquisition in relation to an MPN-driver is also associated with distinct cellula
and clinical phenotypes³².
Splicing f and clinical phenotypes³².
Splicing factors
Mutations in genes encoding components of the spliceosome have been identified in MPN
notably in *SRSF2, U2AF1, SF3B1* and *ZRSR2,* some of which confer inferior clinical progn י
| תוד תוד
| תוד תוד Splicing factors
Mutations in genes encoding components of the spliceosome have been identified in MPN, notably in *SRSF2, U2AF1, SF3B1* and *ZRSR2,* some of which confer inferior clinical prognosis.
Thus surprisingly, co-expression of *Srsf2* P95H reduces MPN severity in *Jak2* V617F knock-in
mice, evident from reduced sple notably in SRSF2, U2AF1, SF3B1 and ZRSR2, some of which confer inferior clinical progrosss.
Thus surprisingly, co-expression of *Srsf2* P95H reduces MPN severity in Jak2 V617F knock-in
mice, evident from reduced splenomega Thus surprisingly, co-expression of Srsf2 P311 equates MP N severity in Juk2 V617P knock-in
mice, evident from reduced splenomegaly and blood cell counts³³. Furthermore, *Srsf2* P95H
co-expression can attenuate MF and r co-expression can attenuate MF and reduce the expansion and repopulation capacity of HSCs³³. However, serial transplantation studies demonstrate the capacity of *Srsf2* P95H c expression to prevent *Jak2* V617F stem cel HSCs³³. However, serial transplantation studies demonstrate the capacity of *Srsf2* P95H co-expression to prevent *Jak2* V617F stem cell exhaustion by extending their long-term replicative capacity³⁴. These functional HSCs³³. However, serial transplantation studies demonstrate the capacity of *Srsf2* P95H co-
expression to prevent *Jak2* V617F stem cell exhaustion by extending their long-term
replicative capacity³⁴. These functiona

expression to prevent Jak2 V617T stem cen exhaustion by extending then long-term
replicative capacity³⁴. These functional studies may suggest additional cooperating fa
are necessary for spliceosome mutations to alter MPN replicative capacity³⁴. These functional studies may suggest additional cooperating factors
are necessary for spliceosome mutations to alter MPN disease pathology.
Recently, global analysis of the Jak2 V617F-mediated pho Recently, global analysis of the *Jak2* V617F-mediated phosphoproteomic landscape has
identified mRNA splicing and processing related molecules as relevant targets of *Jak2*-
dependent post-translational modification. Ina FicerFr Recently, global analysis of the JAK2 V6171-inediated phosphopoteomic landscape has
identified mRNA splicing and processing related molecules as relevant targets of *Jak2*-
dependent post-translational modification. Inacti identified mRNA spitcing and processing related molecules as relevant targets of JuX2-
dependent post-translational modification. Inactivation of non-mutated splicing factor
sensitized Jak-inhibitor persistent cells to apo dependent post-translational models and resulted in RNA mis-splicing, interaction and eventually disruption of relevant oncogenic signaling pathways. Genetic a pharmacologic inactivation of these molecules and pathways ind retention and eventually disruption of relevant oncogenic signaling pathways. Genetic and
pharmacologic inactivation of these molecules and pathways induced regression of the
malignant clone and molecular remission³⁵. Th pharmacologic inactivation of these molecules and pathways induced regression of the
malignant clone and molecular remission³⁵. Therefore, post-translational modification of
(unmutated) splicing factors may contribute to

Transcriptional requlators

phalignant clone and molecular remission³⁵. Therefore, post-translational modification of
(unmutated) splicing factors may contribute to clonal persistence and progression of MI
Transcriptional regulators
Mutations in tr (unmutated) splicing factors may contribute to clonal persistence and progression of MPN.
Transcriptional regulators
Mutations in transcription factors $RUNX1$ and $TP53$ have been associated with post-MPN
AML^{3,4,36}. Strik Transcriptional regulators

Mutations in transcription factors $RUNX1$ and $TP53$ have been associated with post-MPN

AML^{3,4,36}. Strikingly, none of the individual aforementioned concomitant mutations

investigated in muri *Hansemphond regulators*
Mutations in transcription
AML^{3,4,36}. Strikingly, none a
investigated in murine fun
mutations for leukemic tra
in combination with a *JAK*2 Mutations in transcription factors NOWLT and TP53 have been associated with post-MITV
AML^{3,4,36}. Strikingly, none of the individual aforementioned concomitant mutations
investigated in murine functional studies appear s AML^{9,4,39}. Strikingly, none of the individual aforementioned concomitant mutations
investigated in murine functional studies appear sufficient in combination with *Jak2*
mutations for leukemic transformation, with the e investigated in murine functional studies appear sufficient in combination with Juk2-
mutations for leukemic transformation, with the exception of *Trp53*. Loss of *Trp53* fu
in combination with a *JAK2*-driver mutation d in combination with a JAK2-driver mutation drives a fully penetrant $AML^{3,37,38}$ following a
in combination with a JAK2-driver mutation drives a fully penetrant $AML^{3,37,38}$ following a in combination with a *JAK2-*driver mutation drives a fully penetrant AML^{3,37,38} following a
a
combination with a *JAK2-*driver mutation drives a fully penetrant AML^{3,37,38} following a
discrepance of the state of the s

preceding MPN disease phase³⁷. Here, megakaryocytic-erythroid progenitors (MEPs) are the
leukemia initiating cell (LIC) population able to generate AML directly in secondary
recipients. In contrast, transplant of more pr recipients. In contrast, transplant of more primitive LSK (lineage negative, Sca1⁺, kit⁺) cells
only generate leukemia after an MPN disease phase³⁷. This finding suggests that *Trp53*-los:
alone may not be sufficien , kit
t *Trp*
onsi:
mage
how
cop
ated
olate only generate leukemia after an MPN disease phase". This finding suggests that *Trp53-loss*
alone may not be sufficient to drive leukemia on a JAK2-mutated background. Consistent
with this, p53 inhibition in chronic-phase alone may not be sumclem to drive leakerma on a JAK2-mutated background. Consistent
with this, p53 inhibition in chronic-phase JAK2-mutated MPN increases DNA damage in
erythroblasts without affecting their survival or prol with this, p53 inhibition in chronic-phase JAK2-mutated WHV increases DNA damage in
erythroblasts without affecting their survival or proliferation⁷. It has also been shown th
BM from Jak2 V617F/Trp53-null leukemic mice erythroblasts without affecting their survival or proliferation'. It has also been shown that
BM from Jak2 V617F/Trp53-null leukemic mice harbors recurrent chromosomal copy
number variations, that are absent in the MPN pha BM from Jak2 V61717 *HP53*-null leukemic mice harbors recurrent chromosomal copy
number variations, that are absent in the MPN phase³⁷. Furthermore, MEPs isolated f
Jak2 V617F/*Trp53*-null leukemic mice are transcripti number variations, that are absent in the MPN phase". Furthermore, MEPs isolated from
Jak2 V617F/Trp53-null leukemic mice are transcriptionally distinct from MEPs isolated from
chronic-phase Jak2 V617F/Trp53-null MPN mice, Jakz V6171771253 Hall leake the contributionally distinct from MET 3 ISO atted from
chronic-phase Jak2 V617F/Trp53-null MPN mice, suggesting that the altered expression of
genes contained in these regions of recurrent chro

emome phase Jak2 V6171771233-null MPN mice, suggesting that the altered expression of
genes contained in these regions of recurrent chromosomal losses and/or gains may be
responsible for leukemic transformation.
Continued genesiable for leukemic transformation.
The separation continued functional studies of two-way genetic interactions will continue to delineate to
nature of cooperation between MPN driver and concomitant mutation/s that det Continued functional studies of two-way
nature of cooperation between MPN driv
progression to myelofibrosis and AML in J
TP53, mutational burden represents the k
and BP MPN. Therefore, the functional co
with all MPN driver (「ド・ミール nature of cooperation between MPN driver and concomitant mutation/s that determine
progression to myelofibrosis and AML in JAK2, CALR and MPL-mutated contexts. Beyond
TP53, mutational burden represents the best genetic pre progression to myelofibrosis and AML in JAK2, CALR and MPL-mutated contexts. Beyond
TP53, mutational burden represents the best genetic predictor of inferior outcomes in CF
and BP MPN. Therefore, the functional consequence progression to myelomolosis and AML in JAK2, CALR and MPL-indiated contexts. Beyond
TP53, mutational burden represents the best genetic predictor of inferior outcomes in CF
and BP MPN. Therefore, the functional consequence TP53, mutational burden represents the best genetic predictor of inferior outcomes in Cr, AP
and BP MPN. Therefore, the functional consequences of 3- and 4-way genetic interactions
with all MPN drivers on MPN disease progr

Influence of mutational heterogeneity on current clinical management of MPN
We now discuss how molecular risk is defined clinically and how it influences clinical

with all MPN drivers on MPN disease progression will be valuable to expanding
understanding of the pathogenesis of HMR MPN.
Influence of mutational heterogeneity on current clinical management of MPN
We now discuss how mol with all MPN drivers on MPN drivers progressions with a transmitter engaging
understanding of the pathogenesis of HMR MPN.
Influence of mutational heterogeneity on current clinical management of MPN
We now discuss how mole Influence of mutational heterogeneity on current
We now discuss how molecular risk is defined clin
management of MPN. Current clinical guidelines a
algorithms for the management of patients with N
phenotypes of PV, ET and ーパ にっぽん しょうしょう algorithms for the management of patients with MPNs, separated into the clinical
phenotypes of PV, ET and MF. The canonical driver mutation (*JAK2*, *MPL* and *CALR*) occurs as
a sole genetic abnormality in 45% of MPNs, b management of MPN. Current clinical guidelines and consensus documents^{39–44} provide
algorithms for the management of patients with MPNs, separated into the clinical
phenotypes of PV, ET and MF. The canonical driver muta phenotypes of PV, ET and MF. The canonical driver mutation (*JAK2*, *MPL* and *CALR*) a sole genetic abnormality in 45% of MPNs, but more frequently co-occurs with co (passenger) mutations, especially in myelofibrosis². phenotypes of PV, ET and WH. The canonical driver induction (JAK2, *MP* Eald CAER) occurs as
a sole genetic abnormality in 45% of MPNs, but more frequently co-occurs with concomitant
(passenger) mutations, especially in my (passenger) mutations, especially in myelofibrosis². Approximately 5-10% of patients with ET
or MF lack a canonical driver and are termed 'triple-negative'^{2,42}. Triple negative MF
patients may harbor non-driver mutati modifying genes and have inferior survival compared to MF with a canonical driver $42,43$.
These 'additional' mutations (regardless of driver status) have prognostic influence and
implications for response to therapy and s moditying genes and have interior survival compared to MF with a canonical driver^{42,43}.
These 'additional' mutations (regardless of driver status) have prognostic influence and
implications for response to therapy and su implications for response to therapy and survival. The clinical definition of high-risk
mutations or 'HMR' differs for PV, ET and MF. It derives from NGS-profiling studies of pa
cohorts, that have identified genetic mutati mutations or 'HMR' differs for PV, ET and MF. It derives from NGS-profiling studies o
cohorts, that have identified genetic mutations associated with inferior overall survi
leukemia-free survival (LFS) and (for PV and ET) cohorts, that have identified genetic mutations associated with inferior overall survival (OS),
leukemia-free survival (LFS) and (for PV and ET) myelofibrosis free survival (MFFS). A large
study incorporating 2035 patients leukemia-free survival (LFS) and (for PV and ET) myelofibrosis free survival (MFFS). A large
study incorporating 2035 patients (including 1321 ET, 356 PV and 309 MF and 49 other MPN)
demonstrated that mutations in chromati study incorporating 2035 patients (including 1321 ET, 356 PV and 309 MF and 49 other MP
demonstrated that mutations in chromatin modifier genes (e.g. *ASXL1, EZH2*) and
spliceosome genes (e.g. *ZRSR2, SRSF2*), defined a ge demonstrated that mutations in chromatin modifier genes (e.g. ASXL1, EZH2) and
spliceosome genes (e.g. ZRSR2, SRSF2), defined a genomic subgroup with inferior prognosis².
In this cohort, sixty-three clinical and genomic demonstrated that mutations in chromatin modifier genes (e.g. ASXL1, L2/12) and
spliceosome genes (e.g. ZRSR2, SRSF2), defined a genomic subgroup with inferior |
In this cohort, sixty-three clinical and genomic variables w spliceosome genes (e.g. *ZRSR2*, *SRSF2*), defined a genomic subgroup with inferior prognosis²
In this cohort, sixty-three clinical and genomic variables were identified as significant to
prognosis and integrated to desi prognosis and integrated to design a prognostic model. This model is directly accessible
an online calculator (https://cancer.sanger.ac.uk/mpn-multistage/), facilitating 'personal
predictions of prognosis for individuals a program and calculator (https://cancer.sanger.ac.uk/mpn-multistage/), facilitating 'personalized
predictions of prognosis for individuals and has been approved as a medical device within
the United Kingdom (https://blood.p predictions of prognosis for individuals and has been approved as a medical device within
the United Kingdom (https://blood.predict.nhs.uk/). Studies such as this highlight the
heterogeneous landscape of concomitant mutati predictions of programs of the United Kingdom (https://blood.predict.nhs.uk/). Studies such as this highlight the heterogeneous landscape of concomitant mutations and complexity of integration into prognostication and sele the United Kingdom (https://blood.predict.nhs.uk/). Studies such as this highlight the
heterogeneous landscape of concomitant mutations and complexity of integration into
prognostication and selection of therapeutic approa heterogeneous landscape of concernment mutations and completely of integrations and selection of the
rapeutic approaches in clinical practice.

Box 1. PV management in a snapshot: $m + v$, hyperpromeration of erythropoiesis is
predominant resulting in high hematocrit (Hct) levels, and the therapeutic focus is o
reduction. This is achieved by anti-platelet therapy (reducing the risk of venous and arterial thromboembolic complications and symptom
reduction. This is achieved by anti-platelet therapy (100 mg of aspirin daily) in all PV
patients⁴⁴ and cytoreduction using venesection a reduction. This is achieved by anti-platelet therapy (100 mg of aspirin daily) in all PV
patients⁴⁴ and cytoreduction using venesection and/or cytoreductive therapies targeti
Hct of <0.45⁴⁵. Indication for medical cyt patients⁴⁴ and cytoreduction using venesection and/or cytoreductive therapies targeting a
Hct of <0.45⁴⁵. Indication for medical cytoreductive therapies is predominantly based on
stratification of thrombosis risk, int Hct of <0.45⁻⁵. Indication for medical cytoreductive therapies is predominantly based on
stratification of thrombosis risk, integrating risk factors such as age ≥60 years, prior TE
event, cardiovascular risk factors and event, cardiovascular risk factors and leucocytosis⁴⁶, although other factors including
platelet >1000 x 10⁹/L, symptomatic splenomegaly, microcirculatory disturbances and
persistent high phlebotomy frequency (>2x/mon platelet >1000 x 10°/L, symptomatic splenomegaly, microcirculatory disturbances and
persistent high phlebotomy frequency (>2x/month) also represent indications. Hydrox
(HU) remains the most frequently used drug worldwide f (HU) remains the most frequently used drug worldwide for primary PV therapy. Limitations
including skin and mucosal toxicity, poor symptom control, and potential leukemogenic risk,
have prompted investigation of other the including skin and mucosal toxicity, poor symptom control, and potential leukemogenic risk
have prompted investigation of other therapies. Ropeginterferon alfa-2b has shown
superiority in clinical trials⁴⁷ and was recen

have prompted investigation of other therapies. Ropeginterferon alfa-2b has shown
superiority in clinical trials⁴⁷ and was recently approved for PV treatment in several
countries. For second-line treatment after HU refra superiority in clinical trials⁴⁷ and was recently approved for PV treatment in several
countries. For second-line treatment after HU refractoriness or intolerance, Ruxolitin
effective for cytoreduction and symptom contr effective for cytoreduction and symptom control compared with best available
therapies^{48,49}. Progression to secondary myelofibrosis occurs in 10-15% of cases and to
secondary leukemia in up to 15% of PV and 25% of post

therapies^{48,49}. Progression to secondary myelofibrosis occurs in 10-15% of cases and to secondary leukemia in up to 15% of PV and 25% of post PV-MF patients⁴³ and thus represent significant causes of morbidity and mort secondary leukemia in up to 15% of PV and 25% of post PV-MF patients⁻³ and thus
represent significant causes of morbidity and mortality in PV.
HMR influence on Prognostication of PV
Concomitant mutations in PV can predic Figure 1.1 The MR influence on Prognostication of PV
Concomitant mutations in PV can predict higher risk of reduce
progression, as well as thrombosis. Mutations in ASXL1, SRSF2
reduced OS and LFS⁵⁰, with SRSF2 integrated HMR influence on Prognostication of PV
Concomitant mutations in PV can predict higher risk of reduced survival and disease progression, as well as thrombosis. Mutations in *ASXL1, SRSF2* and *IDH2* were associant reduced OS and LFS⁵⁰, with *SRSF2* integrated into the weighted prognostic score, MIF that stratifies patients into low, intermed progression, as wen as thrombosis. Mutations in ASXL1, SPI72 and IDH2 were associated
reduced OS and LFS⁵⁰, with *SRSF2* integrated into the weighted prognostic score, MIPSS-P
that stratifies patients into low, intermedi that stratifies patients into low, intermediate and high risk for survival⁵¹. The MFPS (Multiple Factor-Based Prognostic Score) is an assessment tool used to predict the risk of thrombosis in PV patients. This scoring s Factor-Based Prognostic Score) is an assessment tool used to predict the risk of thrombosis risk (0–1 points), intermediate-risk (2–3 points), and high-risk (≥ 4 points) groups. This system risk factors, history of thrombosis and presence of specific high-risk mutations (e.g.
DNMT3A, ASXL1, BCOR, BCORL1), assigned a weighted score. Patients are classified into love
risk (0–1 points), intermediate-risk (2–3 p *DNMT3A, ASXL1, BCOR, BCORL1*), assigned a weighted score. Patients are classified
risk (0–1 points), intermediate-risk (2–3 points), and high-risk (≥4 points) groups. Th
has shown better predictive power compared to prev

HMR influence on response to therapy

responses to specific therapies in PV and/or other MPN types. The effect of frequent
concomitant mutations (TET2, ASXL1, DNMT3A, EZH2, IDH1 and IDH2, sequenced by Sanger Fig. 1.1 points), intermediate points (2–3 points), intermediately. This shown better predictive power compared to previous models⁵².

HMR influence on response to therapy

Further groups investigated the impact of conc Further groups investigated the impact
Further groups investigated the impact
responses to specific therapies in PV areoncomitant mutations (TET2, ASXL1, L
sequencing) on response to interferon
patients achieved a complete responses to specific therapies in PV and/or other MPN types. The effect of frequent
concomitant mutations (*TET2, ASXL1, DNMT3A, EZH2, IDH1* and *IDH2*, sequenced by Sang
sequencing) on response to interferon in PV and ET concomitant mutations (*TET2, ASXL1, DNMT3A, EZH2, IDH1* and *IDH2,* sequenced by
sequencing) on response to interferon in PV and ET was investigated ⁵³. In this study,
patients achieved a complete molecular response (CM concomitant mutations (TET2, ASXL1, DIWITISA, L2TI2, IDIT and IDI2, sequenced by Sanger
sequencing) on response to interferon in PV and ET was investigated ⁵³. In this study, 17% of
patients achieved a complete molecular sequencing) on response to interferon in PV and ET was investigated ³⁵. In this study, 17% of
patients achieved a complete molecular response (CMR) (defined as undetectable JAK2
V617F based on an assay with sensitivity o patients achieved a complete molecular response (CMR) (defined as andetectable JAR2
V617F based on an assay with sensitivity of 5%) over a median of 42 months follow-up.
those failing to achieve CMR, there was a trend towa Those failing to achieve CMR, there was a trend towards higher frequency of concomitant
mutations at baseline and more frequent acquisition of new mutations (64% vs 0% in thos
who achieved CMR). In patients with CMR, conco mutations at baseline and more frequent acquisition of new mutations (64% vs 0% in those who achieved CMR). In patients with CMR, concomitant mutations were also cleared.
Genomic predictors of response were investigated i who achieved CMR). In patients with CMR, concomitant mutations were also cleared.
Genomic predictors of response were investigated in the DALIAH trial (low dose interferon
alpha (IFNa) vs hydroxyurea (HU)) including 202 p Genomic predictors of response were investigated in the DALIAH trial (low dose interferent) alpha (IFNa) vs hydroxyurea (HU)) including 202 patients with PV, ET and MF⁵⁴. Patient
alpha (IFNa) vs hydroxyurea (HU)) includ alpha (IFNa) vs hydroxyurea (HU)) including 202 patients with PV, ET and MF⁵⁴. Patients had
do set of response in the DALIAH of the DALIAH transies in the AT
down does not do set of the DALIAH transies in the AT transie alpha (IFNa) vs hydroxyurea (HU)) including 202 patients with PV, ET and MF⁵⁴. Patients had
;
;

in 32 patients (24%) at 24 months. In IFNa treated patients, these were most commonly *DTA*
mutations. Interestingly, *TP53* and *PPM1D* were commonly acquired mutations in HU
treated patients, paralleling findings of *TP5* in 32 patients (24%) at 24 months. In IFNa treated patients, these were most commonly DTA
mutations. Interestingly, TP53 and PPM1D were commonly acquired mutations in HU
treated patients, paralleling findings of TP53 and P mutations. Interestingly, *TF53* and *TFM1D* were commonly acquired mutations in HO
treated patients, paralleling findings of *TP53* and *PPM1D* clonal hematopoiesis emerg
post cytotoxic therapy in solid cancer patients⁵⁵ treated patients, paralleling midings of *TP* 53 and *TPM1D* clonal hematopoiesis emerging
post cytotoxic therapy in solid cancer patients^{55,56}. The emergence of *DNMT3A* mutations
was the only factor described in the st was the only factor described in the study to be associated with failure to achieve complete
hematologic response to IFNa. The authors speculate that *DNMT3A* mutated clones were
likely pre-existing at baseline and were se effect of Dnmt3a co-mutation⁵⁷. In a randomized Phase 3 study comparing the effects of hematologic response to ITNa. The authors speculate that DNMT3A mutated clones were
likely pre-existing at baseline and were selected for with IFNa therapy, perhaps due to
aberrant self-renewal described as a consequence o aberrant self-renewal described as a consequence of cooperation between JAK2 V617I
DNMT3A mutation²². Recent pre-clinical studies in JAK2 V617F and *Dnmt3a* mutant mu
hematopoiesis provided first evidence that combined aberrant sen-renewal described as a consequence or cooperation between JAK2 V617T and
DNMT3A mutation²². Recent pre-clinical studies in JAK2 V617F and Dnmt3a mutant murine
hematopoiesis provided first evidence that combi DNMT3A mutation²². Recent pre-clinical studies in JAK2 V617F and Dnmt3a mutant murine
hematopoiesis provided first evidence that combined treatment with IFNa and
hypomethylating agents (HMA, 5-Aza) enhances clonal regres hypomethylating agents (HMA, 5-Aza) enhances clonal regression overcoming t
effect of *Dnmt3a* co-mutation⁵⁷. In a randomized Phase 3 study comparing the ₁
Ropeg-Interferon alpha 2b against Best Available Therapy (BAT) effect of *Dnmt3a* co-mutation⁵⁷. In a randomized Phase 3 study comparing the effects of
Ropeg-Interferon alpha 2b against Best Available Therapy (BAT), PV patients harboring ASX;
mutations showed relevant responses whe mutations showed relevant responses when treated with IFNa⁵⁸. In the MAJIC-PV study,
Ruxolitinib showed a higher rate of molecular response (defined as a 50% reduction in *JAK2*
V617F allele frequency) which was associa mutations showed relevant responses when treated with IFNa³⁰. In the MAJIC-PV study,
Ruxolitinib showed a higher rate of molecular response (defined as a 50% reduction in JA
V617F allele frequency) which was associated w V617F allele frequency) which was associated with improved progression-free survival (PFS), event-free survival (EFS), and OS. Here, the presence of *ASXL1* mutations was associated with worse EFS (adjusted hazard ratio (event-free survival (EFS), and OS. Here, the presence of *ASXL1* mutations was associated with worse EFS (adjusted hazard ratio (HR) of 3.02 compared to those without these mutations)⁴⁹. An additional study supported th with worse EFS (adjusted hazard ratio (HR) of 3.02 compared to those without these
mutations)⁴⁹. An additional study supported the negative impact of additional baseline
mutations on PFS event rate during ruxolitinib tr mutations)⁴⁹. An additional study supported the negative impact of additional baseline
mutations on PFS event rate during ruxolitinib treatment, and further highlighted the
association between acquisition of new variant mutations)³⁵. An additional study supported the negative impact of additional baseline
mutations on PFS event rate during ruxolitinib treatment, and further highlighted the
association between acquisition of new variants

association between acquisition of new variants, especially in ASXL1, during treatmen
reduced molecular responses and increased progression to MF⁵⁹.
Implications of HMR on management of PV
Currently, the presence of HMR association between acquisition of new variants, especially in ASXL1, during treatment and
reduced molecular responses and increased progression to MF⁵⁹.
Implications of HMR on management of PV
Currently, the presence of reduced molecular responses and increased progression to MF³³.
Implications of HMR on management of PV
Currently, the presence of HMR mutations does not alter manage
target thresholds for cytoreductive therapies. Whilst ノハ しょうしょう Currently, the presence of HMR mutations does not alter management recommendations or target thresholds for cytoreductive therapies. Whilst there is increasing information about
predictors of response to therapies like interferon, there is no clear recommendation to
select therapies based on concomitant mut predictors of response to therapies like interferon, there is no clear recommendation to
select therapies based on concomitant mutational profile. Given that concomitant mutatio
can be cleared with the driver mutation in s predict therapies based on concomitant mutational profile. Given that concomitant mutation can be cleared with the driver mutation in some cases, it could be speculated that select of therapies that have increased chance o can be cleared with the driver mutation in some cases, it could be speculated that selection
of therapies that have increased chance of inducing molecular remissions might be
preferable. AlloHSCT is currently not recommen of therapies that have increased chance of inducing molecular remissions might be
preferable. AlloHSCT is currently not recommended for treatment of PV that has not
clinically progressed to secondary MF or AML, even in the preferable. AlloHSCT is currently not recommended for treatment of PV that has no
clinically progressed to secondary MF or AML, even in the presence of HMR mutatic
Nevertheless, genomic features are highly predictive of pr preferable. All allocates the presence of HMR mutation Nevertheless, genomic features are highly predictive of progression from CP to AP or and MIPSS-PV high risk patients have a predicted median OS of 4.6 years⁶⁰. Thus, Nevertheless, genomic features are highly predictive of progression from CP to AP or BP²
and MIPSS-PV high risk patients have a predicted median OS of 4.6 years⁶⁰. Thus, close
monitoring for clinical symptoms and signs monitoring for clinical symptoms and signs of clonal progression, especially in the setting of
HMR is warranted to facilitate early referral of eligible patients for alloHSCT.
ET
Box 2. ET management in a snapshot: ET ph

ET

MMR is warranted to facilitate early referral of eligible patients for alloHSCT.

ET

Box 2. ET management in a snapshot: ET phenotypically affects the megakaryocytic cell line

characterized by peripheral thrombocytosis a ET
Box 2. ET management in a snapshot: ET phenotypically affects the megaka
characterized by peripheral thrombocytosis and hyperproliferation of large,
megakaryocytes in the bone marrow. ET should be distinguished from pre |
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| || C || C
| F |
| N Box 2. ET management in a shapshot: ET phenotypically affects the megakaryocytic cell line,
characterized by peripheral thrombocytosis and hyperproliferation of large, hyperlobulated
megakaryocytes in the bone marrow. ET s megakaryocytes in the bone marrow. ET should be distinguished from pre-fibrotic MF or PV
Reactive thrombocytosis represents a further differential diagnosis and should be strongly
considered in 'triple-negative ET'. The pr Reactive thrombocytosis represents a further differential diagnosis and should be strongly
considered in 'triple-negative ET'. The primary therapeutic goal in the treatment of ET is to
prevent TE and bleeding events (due t considered in 'triple-negative ET'. The primary therapeutic goal in the treatment of ET is to
prevent TE and bleeding events (due to extreme thrombocytosis-related secondary von
Willebrand syndrome), as well as to reduce prevent TE and bleeding events (due to extreme thrombocytosis-related secondary von
Willebrand syndrome), as well as to reduce disease-associated symptoms⁶¹. The indication
Willebrand syndrome), as well as to reduce dise previllebrand syndrome), as well as to reduce disease-associated symptoms⁶¹. The indicational syndrome thromation
Willebrand syndrome), as well as to reduce disease-associated symptoms⁶¹. The indicational syndrome
Mill Willebrand syndrome), as well as to reduce disease-associated symptoms^{or}. The indication
indication
control is the indication of the indication

for treatment is based on the thrombosis risk profile guided by established and guidelineanchored risk stratification systems, dividing patients into low, intermediate and high-risk for thrombosis⁴⁶. Numerous studies have shown that the presence of a *JAK2* mutation is associated with a significantly higher thrombosis⁺⁺. Numerous studies have shown that the presence of a JAK2 mutation is
associated with a significantly higher thrombosis risk compared to the presence of *CA*
mutations. JAK2 mutation is incorporated as a risk associated with a significantly higher diffeomosis risk compared to the presence of CALR
mutations. JAK2 mutation is incorporated as a risk factor into scores such as the IPSET-
thrombosis score⁶². Treatment strategies mutations. JAR2 mutation is incorporated as a risk factor into scores such as the IPSET-
thrombosis score⁶². Treatment strategies include low-dose aspirin for intermediate- an
high-risk patients with microcirculatory di thrombosis score⁶². Treatment strategies include low-dose aspirin for intermediate- and
high-risk patients with microcirculatory disturbances, in those without contraindications
to bleeding risk, although prospective stu to bleeding risk, although prospective studies for this recommendation are lacking. Data
suggest that low-risk patients with *CALR* mutation do not benefit from anti-platelet
therapy⁶³. Cytoreductive medication is speci to bleeding risk, although prospective studies for this recommendation are lacking. Data
suggest that low-risk patients with CALR mutation do not benefit from anti-platelet suggest that low-risk patients with *CALR* mutation do not benefit from anti-platelet
therapy⁶³. Cytoreductive medication is specifically indicated for high-risk patients and
options include HU, anagrelide and peg-IFN (suggest that low-risk patients with CALR mutation do not benefit from anti-platelet
therapy⁶³. Cytoreductive medication is specifically indicated for high-risk patients ar
options include HU, anagrelide and peg-IFN (wher options include HU, anagrelide and peg-IFN (where approved)⁶⁴. Ropeg-Interferon is being
evaluated in an international multicenter trial for ET^{65} . Data on Ruxolitinib from two studies
in relatively small patient popu options include HU, anagrelide and peg-IFN (where approved)⁹⁴. Ropeg-Interferon is being
evaluated in an international multicenter trial for ET⁶⁵. Data on Ruxolitinib from two studies
in relatively small patient popul evaluated in an international multicenter trial for ET^{os}. Data on Ruxolitinib from two studies
in relatively small patient populations with HU-refractory or -intolerant ET showed a
reduction in platelets and leukocytes a reduction in platelets and leukocytes and an improvement in ET-associated symptom
no significant improvement in the hematological complete remission rate or the rate
thrombosis, hemorrhages, or leukemic transformation^{66,6}

HMR influence on Prognostication of ET

reduction improvement in the hematological complete remission rate or the rate of
thrombosis, hemorrhages, or leukemic transformation^{66,67}.
HMR influence on Prognostication of ET
In ET, mutations in SH2B3, SF3B1, U2AF1, thrombosis, hemorrhages, or leukemic transformation^{66,67}.

HMR influence on Prognostication of ET

In ET, mutations in SH2B3, SF3B1, U2AF1, TP53, IDH2, and EZH2 were associated with

inferior OS⁵⁰. In a further analysi thrombosis, hemorrhages, or leukemic transformation^{86,67}.
HMR influence on Prognostication of ET
In ET, mutations in SH2B3, SF3B1, U2AF1, TP53, IDH2, and E
inferior OS⁵⁰. In a further analysis, SF3B1 and SRSF2 predict
 HMR influence on Prognostication of ET In ET, mutations in SH2B3, SF3B1, O2AF1, H133, IBH2, and E2H2 were associated with
inferior OS⁵⁰. In a further analysis, SF3B1 and SRSF2 predicted reduced OS, while muta
in SF3B1 and U2AF1 predicted reduced MFFS and tho in *SF3B1* and *U2AF1* predicted reduced MFFS and those in *TP53* predicted inferior LFS. These
genes have been integrated into the MIPSS-ET score that significantly stratifies patients into
low, intermediate and high ris

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in SF3B1 and U2AF1 predicted reduced MFFS and those in TF33 predicted inferior LFS. These
genes have been integrated into the MIPSS-ET score that significantly stratifies patients into
low, intermediate and high risk for s general external extending have been integrated into the MIPSS-ET score patterns into the MIPSS-
Implications of high molecular risk on management of ET
Overall, the risk of progression in ET is considerably low. Most dat low, intermediate and high risk for survival"¹.
Implications of high molecular risk on manage
Overall, the risk of progression in ET is conside
obtained from patient cohorts diagnosed befor
separated ET from the pre-fibr Overall, the risk of progression in ET is considerably low. Most data on risk factors were Optained from patient cohorts diagnosed before the WHO 2016 classification of MPN
separated ET from the pre-fibrotic phase of myelofibrosis. For ET, prevention of
thromboembolic complications is therefore the major clinica obtained from the pre-fibrotic phase of myelofibrosis. For ET, prevention of
thromboembolic complications is therefore the major clinical challenge. Monitoring of
molecular risk mutations may be indicated.
Myelofibrosis
 separated ET from the pre-fibrotic phase of major clinical challenge. Monito
thromboembolic complications is therefore the major clinical challenge. Monito
molecular risk mutations may be indicated.
Box 3. PMF management

Myelofibrosis

molecular risk mutations may be indicated.
 Myelofibrosis
 Box 3. PMF management in a snapshot: The early phase of PMF is associated with an

increase in megakaryocytic and granulocytic proliferation. Later, bone marro Myelofibrosis

Box 3. PMF management in a snapshot: The

increase in megakaryocytic and granulocytic

accompanied by progressive splenomegaly

phenotype. According to the current WHO 2 | [] (阝 (阝 Box 3. Finn manigement in a shapshot: The early phase of PMF is associated with an
increase in megakaryocytic and granulocytic proliferation. Later, bone marrow fibrosis
accompanied by progressive splenomegaly and pancytop accompanied by progressive splenomegaly and pancytopenia may be the predominant
phenotype. According to the current WHO 2022 classification, the pre-fibrotic phase is
distinguished from overt (fibrotic) myelofibrosis. Ther accompanies by pregnant temperature processive splenomegally and phenotype. According to the current WHO 2022 classification, the pre-fibrotic phase is distinguished from overt (fibrotic) myelofibrosis. Therapeutic strateg phenotype. Therapeutic strategies are based on risprogression and symptom burden. In addition to dynamic risk scores with emphasis on clinical and hematologic parameters, molecular and cytogenetically driven predictors and are progression and symptom burden. In addition to dynamic risk scores with emphasis on clinical and hematologic parameters, molecular and cytogenetically driven predictors are currently gaining relevance to allow reliable provided and hematologic parameters, molecular and cytogenetically driven predictors are currently gaining relevance to allow reliable risk stratification especially for younger pat
(Table 1). Especially for younger patien currently gaining relevance to allow reliable risk stratification especially for younger patie
(Table 1). Especially for younger patients with PMF and those without relevant
comorbidities, the curative option of alloHSCT i (Table 1). Especially for younger patients with PMF and those without relevant
comorbidities, the curative option of alloHSCT is recommended for intermediate-2 or high-
risk patients. Here, pretreatment with JAK inhibitors (Table 1). Especially for younger patients with PMF and those without relevant
comorbidities, the curative option of alloHSCT is recommended for intermediate-2 or high-
risk patients. Here, pretreatment with JAK inhibitors ratients. With splenomegaly and symptom burden. Symptom-oriented treatment with
experimental therapies in clinical trials are available, if alloHSCT is not indicated or po
experimental therapies in clinical trials are avai experimental therapies in clinical trials are available, if alloHSCT is not indicated or possible.
experimental therapies in clinical trials are available, if alloHSCT is not indicated or possible.
10 experimental therapies in clinical trials are available, if allohSCT is not indicated or possible.
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Higher the Trughosteation of PMF
Risk stratification tools for myelofibrosis (T
determine treatment approaches for patie
mutation-enhanced international prognos
and the genetically inspired prognostic sco
other genetic dat determine treatment approaches for patients. Newer risk classifications such as the mutation-enhanced international prognostic scoring system (MIPSS70)⁶⁸ and its iterat
and the genetically inspired prognostic scoring sy mutation-enhanced international prognostic scoring system (MIPSS70)⁶⁸ and its itera
and the genetically inspired prognostic scoring system (GIPSS) incorporate molecular
other genetic data in risk stratification scores t mutation-enhanced international prognostic scoring system (MIPSS70)^{ov} and its iterations^{ov}
and the genetically inspired prognostic scoring system (GIPSS) incorporate molecular and
other genetic data in risk stratificat and the generation, inspired programmed by the generation of the generation scores that help to identify patients at high risk of disease progression that were previously not identified by clinical markers. These represe disease progression that were previously not identified by clinical markers. These represe
evolution from more traditional prognostic scores which solely assess clinical and
hematological factors, such as the Internationa evolution from more traditional prognostic scores which solely assess clinical and
hematological factors, such as the International prognostic scoring system (IPSS)⁷⁰ and
dynamic IPSS (DIPSS)⁷¹ and with the additional

hematological factors, such as the International prognostic scoring system (IPSS)⁷⁰ and
dynamic IPSS (DIPSS)⁷¹ and with the additional prognostic influence of karyotype, DIPS:
plus⁷².
In early studies, the prognostic dynamic IPSS (DIPSS)'¹ and with the additional prognostic influence of karyotype, DIPSS-
plus⁷².
In early studies, the prognostic influence of molecular mutations in MF using Sanger
sequencing analysis of a limited pa plus⁷².
In early studies, the prognostic influence of molecular mutations in MF using Sanger
sequencing analysis of a limited panel of genes including *EZH2*, *TET2, DNMT3A, CBL, ASXL1*,
IDH1/2, SRSF2 and *MPL* was hi | si / ci / w
| ci / w sequencing analysis of a limited panel of genes including *EZH2*, *TET2, DNMT3A, CBL,*
IDH1/2, *SRSF2* and *MPL* was highlighted ⁷³. *ASXL1, EZH2, SRSF2, IDH1* and *IDH2* were
associated with high risk for death or leuk sequencing analysis of a limited panel of genes including EZH2, TET2, DIWITSA, CDE, ASXL1, IDH1/2, SRSF2 and MPL was highlighted ⁷³. ASXL1, EZH2, SRSF2, IDH1 and IDH2 were associated with high risk for death or leukemic IDH1/2, SRSF2 and MPL was highlighted ¹⁵. ASXL1, EZH2, SRSF2, IDH1 and IDH2 were
associated with high risk for death or leukemic transformation. The number of mutat
was also predictive, with ≥2 associated with inferior was also predictive, with ≥2 associated with inferior LFS⁷⁴. The mutation status of these 5 genes (coined 'high molecular risk' (HMR) mutations) as well as absence of *CALR* type 1/lil mutations, were then combined with genes (coined 'high molecular risk' (HMR) mutations) as well as absence of CALR type 1/like
mutations, were then combined with clinical variables in the MIPSS70 model, stratifying
patients into low, intermediate and high-r patients into low, intermediate and high-risk patients. Further iterations incorporated
karyotypic information (MIPSS70-plus)⁶⁸ and adding *U2AF1* Q157 hotspot variant as an
additional HMR variant (MIPSS70-plus Version 2 partivulary information (MIPSS70-plus)⁶⁸ and adding *U2AF1* Q157 hotspot variant as andditional HMR variant (MIPSS70-plus Version 2.0)⁷⁵, which is now widely used aided online calculator (http://www.mipss70score.it/). additional HMR variant (MIPSS70-plus Version 2.0)⁷⁵, which is now widely used aided by an online calculator (http://www.mipss70score.it/). GIPSS is solely based on genetic mutations and karyotype abnormalities, without additional HMR variant (MIPSS70-plus Version 2.0)", which is now widely used aided by an
online calculator (http://www.mipss70score.it/). GIPSS is solely based on genetic mutations
and karyotype abnormalities, without the

and karyotype abnormalities, without the inclusion of clinical variables such as symptoms,
blood counts, or the degree of fibrosis⁷⁶.
Additional high-risk mutations have been identified with expanded molecular
character blood counts, or the degree of fibrosis⁷⁶.
Additional high-risk mutations have been identified with expanded molecular
characterization. A study using a 77-gene NGS panel to molecularly profile patients with
myelofibros blood counts, or the degree of fibrosis'^o.
Additional high-risk mutations have been
characterization. A study using a 77-gene
myelofibrosis (n=479, incorporating 305 F
patients) was performed by the French In
Within this ノ C r F Z i r characterization. A study using a 77-gene NGS panel to molecularly profile pat
myelofibrosis (n=479, incorporating 305 PMF and 174 SMF (70 post-PV and 1C
patients) was performed by the French Intergroup of Myeloproliferat myelofibrosis (n=479, incorporating 305 PMF and 174 SMF (70 post-PV and 104 post-ET)
patients) was performed by the French Intergroup of Myeloproliferative Neoplasms (FIM
Within this cohort, 4 prognostic groups with signif patients) was performed by the French Intergroup of Myeloproliferative Neoplasms (FIM)⁷⁷.
Within this cohort, 4 prognostic groups with significantly different rates of OS and LFS were
identified including 1) *TP53*-muta identified including 1) *TP53*-mutated (median OS 20 months), 2) presence of \geq 1 high-risk mutation (*EZH2, CBL, U2AF1, SRSF2, IDH1, IDH2, NRAS* or *KRAS* (median OS 49 months), 3) *ASXL1* without *TP53* or other highidentified including 1) Tr 55-mutated (including 05 20 months), 2) presence of 21 ingn-risk
mutation (*EZH2, CBL, U2AF1, SRSF2, IDH1, IDH2, NRAS* or *KRAS* (median OS 49 months), 3
ASXL1 without *TP53* or other high-risk mutation (EZH2, CBL, OZAF1, SRSF2, IDH1, IDH2, IWAD OF KNAS (medialities 49 months), 3)
ASXL1 without TP53 or other high-risk mutation as per group 2) (ASXL1^{mut}-only) (median O.
90 months) and 4) other mutational profil ASXL1 without TP53 or other high-risk mutation as per group 2) (ASXL1""-only) (median OS
90 months) and 4) other mutational profiles (median OS 116 months). When assessed in
multivariate analyses with clinical and hematolo multivariate analyses with clinical and hematological factors, the *TP53*-mutated and high-
mutation group independently maintained higher risk of death and progression to leuken
The study thus provided evidence of additi multivariate analyses with clinical and hematological factors, the TF53-multated and high-risk
multation group independently maintained higher risk of death and progression to leukemia.
The study thus provided evidence of The study thus provided evidence of additional mutations that could be considered 'HMR', including *TP53, CBL, NRAS, KRAS* and all *U2AF1* variants and highlighted a context-specific qualifier for *ASXL1* mutations, which including *TP53*, *CBL, NRAS, KRAS* and all *U2AF1* variants and highlighted a context-specific
qualifier for *ASXL1* mutations, which were not independently adversely prognostic when
occurring without high-risk mutations. including TP53, CBL, WAAS, KAAS and all U2AP1 variants and ingimigined a context-specific
qualifier for ASXL1 mutations, which were not independently adversely prognostic when
occurring without high-risk mutations. Notably

qualitier for ASXL1 mutations, which were not intelpendently adversely prognosite when
occurring without high-risk mutations. Notably, RAS mutations have been independently
associated with inferior overall survival in mult occurring without high-risk mutations. Notably, *RAS* mutations have been independently
associated with inferior overall survival in multiple independent MF patient cohorts^{78,79}.
HMR influence on response to therapy
Vari associated with inferior overall survival in multiple independent MF patient cohorts^{78,79}.
HMR influence on response to therapy
Various groups have examined molecular predictors of response to ruxolitinib. Predictive
fac ノリトル しょうしょう しょうしゅう しゅうしゃ しゅうしゅう しゅうしゅう しゅうしゅう しゅうしゅう しゅうしゃ しゅうしゃ しゅうしゃ しゅうしゃ しゅうしゃ しゅうしゃ しゅうしゃ HMR influence on response to therapy Factors differ amongst groups but overall suggest high-risk mutations do not preclude
responses to ruxolitinib, but may shorten the durability of response. The efficacy of
responses to ruxolitinib, but may shorten the dura factors differ amongst groups but overall suggest high-risk mutations do not preclude
responses to ruxolitinib, but may shorten the durability of response. The efficacy of

ruxolitinib compared to best available therapy (BAT) in IPSS intermediate-2 or high-risk
myelofibrosis was established in the Phase III COMFORT-I and II trials^{80,81}. Molecular
profiling of 14 myeloid genes was performed profiling of 14 myeloid genes was performed and analyzed in a representative subset of the COMFORT-II patients to determine molecular predictors of response⁸². High-risk mutations
in this study (*ASXL1, EZH2, SRSF2* and *IDH1/2*) conferred inferior survival compared to
patients without these mutations within in this study (ASXL1, L2T/2, SRSF2 and *IDH1/2*) comeried merior survival compared to
patients with high-risk mutations still demonstrated equivalent benefits of ruxolitinib v
no statistical differences between spleen res patients with high-risk mutations still demonstrated equivalent benefits of ruxolitinib with
no statistical differences between spleen response, constitutional symptoms or survival. Ir
contrast, recent studies on 95 ruxoli patitical differences between spleen response, constitutional symptoms or survival. In contrast, recent studies on 95 ruxolitinib treated patients using a 28-gene NGS panel (notably not including *SRSF2*)⁸³, revealed mu contrast, recent studies on 95 ruxolitinib treated patients using a 28-gene NGS panel
(notably not including SRSF2)⁸³, revealed mutations in *ASXL1, EZH2* or *IDH1/2*, as well as
those with \geq 3 mutations were associa (notably not including *SRSF2*)⁸³, revealed mutations in *ASXL1*, *EZH2* or *IDH1/2*, as wel
those with \geq 3 mutations were associated with lower rates of spleen response, time to
treatment discontinuation and shorter (notably not including *SRSF2*)⁹⁹, revealed mutations in *ASXL1*, *EZH2* or *IDH1/2*, as well as those with \geq 3 mutations were associated with lower rates of spleen response, time to treatment discontinuation and sho treatment discontinuation and shorter OS (in contrast to the COMFORT-II analyses⁸²). ASXL1
or *EZH2* mutations along with other clinical factors of pre-JAKi transfusion dependence and
high DIPSS score were also identifie or EZH2 mutations along with other emited ractors of pre-JAKi transfusion dependence and
high DIPSS score were also identified as predictive factors for treatment failure of JAKi,
ruxolitinib or momelotinib⁸⁴. Lower freq

mg. Function of the second of the second as predictions, including those in NRAS, KRAS and CBL were shown to associate with reduced symptom and spleen response to ruxolitinib⁸⁵.
Clonal evolution during therapy has also CBL were shown to associate with reduced symptom and spleen response to ruxolitinib⁸⁵.
Clonal evolution during therapy has also been associated with poor outcomes to ruxolitinil
therapy. In 46 ruxolitinib and 25 HU treat (t c c - 1
| 1 therapy. In 46 ruxolitinib and 25 HU treated patients with MF, sequential samples
demonstrated acquisition of new mutations in 8 of ruxolitinib treated patients (17.4%)
compared to 6 HU-treated patients (24%) ⁸⁶. The pre demonstrated acquisition of new mutations in 8 of ruxolitinib treated patients (17
compared to 6 HU-treated patients (24%) ⁸⁶. The presence of HMR mutation (ASXI
SRSF2, IDH1, IDH2) at baseline did not alter spleen and sy compared to 6 HU-treated patients (24%) 86 . The presence of HMR mutation (ASXL1, E2
SRSF2, IDH1, IDH2) at baseline did not alter spleen and symptomatic responses, howev
HMR, as well as acquisition of new clones was as compared to 6 HU-treated patients (24%) ⁸⁶. The presence of HMR mutation (ASXL1, *EZH2,* SRSF2, IDH1, IDH2) at baseline did not alter spleen and symptomatic responses, however HMR, as well as acquisition of new clones wa SRSF2, IDH1, IDH2) at baseline did not alter spleen and symptomatic responses, nowever
HMR, as well as acquisition of new clones was associated with loss of spleen responses at
years. Notably, similar patterns and rates of years. Notably, similar patterns and rates of clonal evolution was seen in both ruxolitinib and
HU-treated patients suggesting clonal evolution was associated with disease rather than
treatment received. Outcomes from 107 years. Notably, similar patterns and rates of clonal evolution was seen in both ruxolitinib and
HU-treated patients suggesting clonal evolution was associated with disease rather than
treatment received. Outcomes from 107 Hureatment received. Outcomes from 107 patients with MF who discontinued ruxolitinib walso reported ⁸⁷. At time of discontinuation, 14 (33%) patients had acquired at least 1 additional mutation during treatment, with th

also reported ⁸⁷. At time of discontinuation, 14 (33%) patients had acquired at least 1
additional mutation during treatment, with the majority (64%) being variants in ASXL1,
which was associated with shorter OS after ru also reported ^o'. At time of discontinuation, 14 (33%) patients had acquired at least 1
additional mutation during treatment, with the majority (64%) being variants in ASXL:
which was associated with shorter OS after rux additional mutation during treatment, with the majority (64%) being variants in ASXL1,
which was associated with shorter OS after ruxolitinib discontinuation.
The benefit of IFNa in myelofibrosis can be pronounced in early The benefit of IFNa in myelofibrosis can be pronounced in early and pre
However, recent reports indicate adverse prognostic influence of specif
mutations in patients treated with IFNa^{89,90}. Further analyses should co
imp ך
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-The benefit of IFNa in myelofibrosis can be pronounced in early and pre-fibrotic phases^{42,68}.
However, recent reports indicate adverse prognostic influence of specific concomitant
mutations in patients treated with IFNa

mutations in patients treated with IFNa^{89,90}. Further analyses should continue to identi
impact of the clonal landscape on IFNa response to enhance patient selection for this
therapy.
Several studies have identified mol impact of the clonal landscape on IFNa response to enhance patient selection for this
therapy.
Several studies have identified molecular associations with inferior outcome alloHSCT.
Number of mutations (\geq 3 additional therapy.
Several studies have identified molecular associations with inferior outcome alloHSCT.
Number of mutations (≥3 additional to driver mutations)⁹¹ as well as specific mutatior
ASXL1, CBL, DNMT3A, IDH2 and U2AF1⁹ *nverapy.*
Several s
Number
ASXL1, C.
transplar
supporte c, II d, C
i Number of mutations (≥3 additional to driver mutations)⁹¹ as well as specific mutations in ASXL1, CBL, DNMT3A, IDH2 and U2AF1^{92–95} have been associated with inferior OS followin_; transplant, although the prognostic ASXL1, CBL, DNMT3A, IDH2 and U2AF1²²³⁵ have been associated with inferior OS following
transplant, although the prognostic influence of the individual genes have not been
supported in all studies. The myelofibrosis tr manepoted in all studies. The myelofibrosis transplant scoring system (MTSS) aimed t
determine prognosis (from relapse and non-relapse related mortality) after transpla
in both PMF and SMF⁹³. Here, molecular features of supportion prognosis (from relapse and non-relapse related mortality) after transplant
in both PMF and SMF⁹³. Here, molecular features of *ASXL1* mutation and non-*CALR/M*
driver mutation genotype were independent predic in both PMF and SMF⁹³. Here, molecular features of ASXL1 mutation and non-*CALR/MPL*
driver mutation genotype were independent predictors of outcome. Other genetic factors
considered, but not found to be significant in in both PMF and SMF³³. Here, molecular features of *ASXL1* mutation and non-*CALR/MPL*
driver mutation genotype were independent predictors of outcome. Other genetic factor
considered, but not found to be significant in driver mutation genotype were independent predictors of outcome. Other genetic factors
considered, but not found to be significant in multivariate analyses included mutations in
U2AF1, DNMT3A and TP53, >3 concomitant mutat considered, but not found to be significant in multipleted multipleted multipleted multipleted.
U2AF1, DNMT3A and TP53, >3 concomitant mutations and cytogenetic risk category, U_2 AF1, DNMT3A and TP33, >3 concomitant mutations and cytogenetic risk category,

support and the surface did note of portons of high molecular risk on management of PMF
Taken together, the clinical and molecular heterogeneity of MPNs support a molecularly-
informed risk stratification system, but shoul alloHCT.
Implications of high molecular risk on management of PMF
Taken together, the clinical and molecular heterogeneity of MPNs support a molecularly-
informed risk stratification system, but should be ideally matched w ノコ I F S Taken together, the clinical and molecular heterogeneity of MPNs support a molecularlyprinciples based on DIPSS still hold and remain valid in the ruxolitinib era. In clinical practice,
along with molecular insights described above, clinical predictors remain relevant in management approaches. Prior to ruxolitinib era, patients with intermediate-2 or hig
DIPSS scores were shown to have improved survival after transplantation, with intern
1 showing no difference between a transplant and non management approaches in prior of survival after transplantation, with intermediat 1 showing no difference between a transplant and non-transplant approach and low risk benefitting from a non-transplant approach⁹⁶, form score' (RR6) is a prognostic model incorporating ruxolitinib dose, spleen response and red
blood cell transfusions and used to predict survival in patients with MF treated with benefitting from a non-transplant approach⁹⁶, forming the basis of transplant referral
guidelines for MF⁹⁷. The addition of molecular data refines risk stratification, however the
principles based on DIPSS still hold a guidelines for MF⁹⁷. The addition of molecular data refines risk stratification, however the principles based on DIPSS still hold and remain valid in the ruxolitinib era. In clinical practic along with molecular insights treatments or allo-SCT⁹⁸. Other high-risk molecular features not captured within standard provided a bove, clinical predictors remain relevant in
predicting long-term response to ruxolitinib. The 'Response to Ruxolitinib after 6 months
score' (RR6) is a prognostic model incorporating ruxolitinib dose, spleen re predicting long-term response to ruxolitinib. The 'Response to Ruxolitinib after 6 mo
score' (RR6) is a prognostic model incorporating ruxolitinib dose, spleen response an
blood cell transfusions and used to predict surviv predicting a proposition model incorporating ruxolitinib dose, spleen response and red
blood cell transfusions and used to predict survival in patients with MF treated with
ruxolitinib. This model helps identify patients blood cell transfusions and used to predict survival in patients with MF treated with
ruxolitinib. This model helps identify patients who may need a shift to second-line
treatments or allo-SCT⁹⁸. Other high-risk molecula ruxolitinib. This model helps identify patients who may need a shift to second-line
treatments or allo-SCT⁹⁸. Other high-risk molecular features not captured within star
prognostic scores include mutations in *TP53*, *C* treatments or allo-SCT⁹⁸. Other high-risk molecular features not captured within standard prognostic scores include mutations in *TP53*, *CBL*, *NRAS*, *KRAS* and all *U2AF1* mutations⁸¹. Clonal evolution, especially

Future considerations

prognostic scores include mutations in *TP53, CBL, NRAS, KRAS* and all *U2AF1* mutations⁸⁴.
Clonal evolution, especially within a *TP53*-mutated context, also predict poor response to
medical therapies and is associated Clonal evolution, especially within a TP53-mutated context, also predict poor response to medical therapies and is associated with leukemic transformation¹¹.
 Future considerations

While the field has made significant medical therapies and is associated with leukemic transformation**.
Future considerations
While the field has made significant advances in the understanding c
MPN and its clinical relevance, several questions remain in the While the field has made significant advances in the understanding of molecular high-risk While the field is clinical relevance, several questions remain in the clinical management of the
patients:
1) Should patients be monitored for development or clonal evolution of molecularly-
high-risk lesions prior to cli

-
- Material relevant and interesting process in the clinical relationships of molecularly-

MPN be treated differently to those without

high-risk aberrations in chronic phase?

MPN be treated differently to those without

hi 1) Sh
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of 1) Should patients with high-molecular risk MPN be treated differently to those with

1) Should patients with high-molecular risk MPN be treated differently to those with

1) What are relevant endpoints for clinical trials mond patients with high-molecular risk MPN
high-risk aberrations in chronic phase?
What are relevant endpoints for clinical trials
of cytopenias? Progression-, Event-Free and C
Which therapies are considered disease modi
l
	-
	-

2) Show high-risk aberrations in chronic phase?

2) What are relevant endpoints for clinical trials? Hematologic responses? Improvement

2) Which therapies are considered disease modifying?

2) Which therapies are consider mg.

What are relevant endpoints for clinical

of cytopenias? Progression-, Event-Free

Which therapies are considered disease

lar profiling in clinical practice is not rou

ng more widely available, and several st

n NGS 3) Which therapies are considered disease modifying?
3) Which therapies are considered disease modifying?
3) Which therapies are considered disease modifying?
3) Hecular profiling in clinical practice is not routinely perf Which therapies are considered disease modifying?
lar profiling in clinical practice is not routinely performed⁹⁹. Re
ng more widely available, and several studies have shown larg
n NGS testing for mutations in periphera Figure 1.1 The

4) Mecular profiling in clinical practice is not routinely perfor

1) Oming more widely available, and several studies have s

1) Which therapical utility of this knowledge requires sufficient

1) The set o Molecular profiling in clinical practice is not routinely performed⁹⁹. Recently, NGS is
becoming more widely available, and several studies have shown largely concordant
between NGS testing for mutations in peripheral b between NGS testing for mutations in peripheral blood compared to bone marrow ^{100,101}.
Providing clinical utility of this knowledge requires sufficient evidence that changes in
genetic profiles constitute actionable info Providing clinical utility of this knowledge requires sufficient evidence that changes in genetic profiles constitute actionable information. Studies of serial sampling demonstrate the majority of patients will not have a the majority of patients will not have additional mutations detected over time^{54,102}. An general profiles and interactional mutations detected over time^{54,102}. An exception may be in the context of *TP53* mutations, which are an important driver of leukemia transformation⁵. Likewise, clonal diversification exception may be in the context of TF53 mutations, which are an important driver of
leukemia transformation⁵. Likewise, clonal diversification and evolution with loss of the
respective driver mutations may indicate accel leukemia transformation". Likewise, clonal diversification and evolution with loss of the
respective driver mutations may indicate acceleration and progression to MPN-BP. Speci
work delineating clonal evolution of *TP53* m work delineating clonal evolution of *TP53* mutations demonstrate that some low VAF
mutations can remain stable for long periods of time prior to expansion, causing late AML
transformations^{5,102} following loss of the re work delineating clonal evolution of TP53 mutations demonstrate that some low VAF
mutations can remain stable for long periods of time prior to expansion, causing late *i*
transformations^{5,102} following loss of the rema transformations 5,102 following loss of the remaining wild-type allele^{37,102,103}. The optimal ro
transformations 5,102 following loss of the remaining wild-type allele^{37,102,103}. The optimal ro transformations^{5,102} following loss of the remaining wild-type allele^{57,102,103}. The optimal role
13
13

or serial monitoring for *TF53* VAF and acquisition of new genetic lesions, including structural
variants or copy number variations is unknown. Methods to stratify a serial monitoring
approach in MPNs is required to define variants or copy number variations is unknown. Methods to stratify a serial monitoring
approach in MPNs is required to define and detect high-risk clonal evolution. In high-risk
patients, prospective evaluation during cyto

patients, prospective evaluation during cytoreductive therapies (e.g. clonal evolution) or
failure to achieve molecular responses could help to identify patients who require escalat
of treatment or evaluation of alloHSCT.
 patients, prospective molecular responses could help to identify patients who require escalat
of treatment or evaluation of alloHSCT.
The design of clinical trials can potentially assist in exploring knowledge gaps. In 201 of treatment or evaluation of alloHSCT.
The design of clinical trials can potentially assist in exploring knowledge gaps. In 2015, the
European LeukemiaNET (ELN) and International Working Group-MPN Research and
Treatment (The design of clinical trials can potentia
European LeukemiaNET (ELN) and Inter
Treatment (IWG-MRT) groups provided
drug treatment trials in BCR::ABL negati
relevant time-to-event endpoints (eg. O
endpoints. While time-to-The design of clinical trials (ELN) and International Working Group-MPN Research and
Treatment (IWG-MRT) groups provided guidelines as to acceptable clinical endpoints for
drug treatment trials in BCR::ABL negative MPNs¹⁰ Treatment (IWG-MRT) groups provided guidelines as to acceptable clinical endpoint
drug treatment trials in BCR::ABL negative MPNs¹⁰⁴. The group distinguished clinical
relevant time-to-event endpoints (eg. OS or progressi drug treatment trials in BCR::ABL negative MPNs¹⁰⁴. The group distinguished clinically
relevant time-to-event endpoints (eg. OS or progression free survival) vs surrogate
endpoints. While time-to-event endpoints like OS drug treatment trials in BCR::ABL negative MPNs³⁰⁴. The group distinguished clinically
relevant time-to-event endpoints (eg. OS or progression free survival) vs surrogate
endpoints. While time-to-event endpoints like OS endpoints. While time-to-event endpoints like OS or LFS are arguably the gold stane
Phase III clinical trials, they require large sample sizes and long-term follow up, whi
be unachievable in PV or ET where events accrue sl Phase III clinical trials, they require large sample sizes and long-term follow up, which may
be unachievable in PV or ET where events accrue slowly over decades. Surrogate endpoint
such as molecular response, overall resp be unachievable in PV or ET where events accrue slowly over decades. Surrogate endpoints
such as molecular response, overall response and reductions in spleen size occur earlier, ar
only appropriate as surrogates for OS or such as molecular response, overall response and reductions in spleen size occur earlier, are
only appropriate as surrogates for OS or LFS if they reliably predict these endpoints.
Regarding molecular responses, the workin only appropriate as surrogates for OS or LFS if they reliably predict these endpoints.
Regarding molecular responses, the working group concluded there was insufficient data to
validate these as reliable surrogates for sur Regarding molecular responses, the working group concluded there was insufficient
validate these as reliable surrogates for survival endpoints. Other endpoints of clinics
ignificance are those that indicate 'disease modifi walidate these as reliable surrogates for survival endpoints. Other endpoints of clinical
significance are those that indicate 'disease modification' and are being increasingly
incorporated into trials of newer agents (es significance are those that indicate 'disease modification' and are being increasingly
incorporated into trials of newer agents (especially trials investigating non-JAKi)¹⁰⁵. In
where clinical trial endpoints historicall incorporated into trials of newer agents (especially trials investigating non-JAKi)¹⁰⁵. I
where clinical trial endpoints historically focused on symptom and spleen responses,
by the striking improvements seen with JAKi, incorporated into trials of newer agents (especially trials investigating non-JAKi)²⁰⁰. In MF,
where clinical trial endpoints historically focused on symptom and spleen responses, driver
by the striking improvements seen

by the striking improvements seen with JAKi, PFS, OS and improvement of cytopenias
represent relevant readouts for future trials^{105–107}.
Finally, focus on the very high molecular risk groups should be prioritized for res by the striking improvements seen the trials^{105–107}.
Finally, focus on the very high molecular risk groups should be prioritized for research.
molecular heterogeneity of MPNs creates multiple subgroups with differential represent relevant readouts for future trials^{205–107}.
Finally, focus on the very high molecular risk group
molecular heterogeneity of MPNs creates multiple
therapy, leaving increasingly smaller subgroups of p
single muta molecular heterogeneity of MPNs creates multiple subgroups with differential responses to
therapy, leaving increasingly smaller subgroups of patients for study when focusing on a
single mutation or combination of mutations molecular heterogy, leaving increasingly smaller subgroups of patients for study when focusing on a
single mutation or combination of mutations and masking treatment trends within these
subgroups. In a disease type where t therapy, thereing, thereing, thereing, the therapy in patient therapy interesting these subgroups. In a disease type where the majority of patients will have good clinical outcol with standard of care, clinical trials ded subgroups. In a disease type where the majority of patients will have good clinical outcon
with standard of care, clinical trials dedicated to high-risk groups, like high-molecular risk
MPNs should be undertaken, enriching with standard of care, clinical trials dedicated to high-risk groups, like high-molecular risk
MPNs should be undertaken, enriching for events and increasing the likelihood of a
statistically significant outcome and thus MPNs should be undertaken, enriching for events and increasing the likelihood of a
statistically significant outcome and thus ability to progress treatments from trials to rout
clinical practice. No relevant prognostic dif statistically significant outcome and thus ability to progress treatments from trials to
clinical practice. No relevant prognostic differences were seen between the clinical
phenotype of ET vs PV in equivalent molecular s statistical practice. No relevant prognostic differences were seen between the clinical
phenotype of ET vs PV in equivalent molecular subtypes², which suggests a molecular
classification in chronic-phase MPNs could be ap phenotype of ET vs PV in equivalent molecular subtypes², which suggests a molecular classification in chronic-phase MPNs could be applicable, rather than traditional morphologic and clinical diagnostic criteria for clin morphologic and clinical diagnostic criteria for clinical trial inclusion criteria. The
of better treatments for HMR MPNs needs to be overcome via international effo
catalogue patient genetics and treatment outcomes to fac of better treatments for HMR MPNs needs to be overcome via international effort to
catalogue patient genetics and treatment outcomes to facilitate large-scale meta-analyses
assisted by Al/machine-learning approaches¹⁰⁸ a catalogue patient genetics and treatment outcomes to facilitate large-scale meta-ana
assisted by Al/machine-learning approaches¹⁰⁸ and supported by evidence from robu
clinical models. assisted by Al/machine-learning approaches¹⁰⁸ and supported by evidence from robust preclinical models.
clinical models. assisted by Al/machine-learning approaches²⁰⁰ and supported by evidence from robust pre-
clinical models.
^{clinical} models.

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Table 1. Prognostic stratification scores in myelofibrosis.

Prognos	For use			Patient	Peripheral	Karyoty	Molecular
tic score	Diag nosis	After diagn osis	Seco ndar y MF	characterist ics	blood / BM parameters	pe	
IPSS	Yes			Age >65 years Constitution a _l symptoms	Hb < 10 Leuk >25 Circulating blasts ≥1%	$\bar{}$	$\ddot{ }$
DIPSS	$\overline{}$	Yes	÷.	As for IPSS	As for IPSS (weighting on Hb < 10	\overline{a}	$\ddot{ }$
DIPSS- Plus		Yes		As for IPSS	As for DIPSS Plus, need for RBC transfusion Platelets <100	$Yes^{\overline{1}}$	\overline{a}
MIPSS70	Yes	$\ddot{}$	\equiv	(validated in age ≤ 70) Constitution a _l symptoms	Hb < 10 Leuk >25 Platelets <100 Circulating blasts ≥2% BM fibrosis \geq MF-2	No	Absence of CALR Type 1 mutation Presence of \geq 2 HMR mutations ²
MIPSS70 -Plus	Yes	$\ddot{}$		(validated in age ≤ 70) Constitution a _l symptoms	Hb < 10 Circulating blasts ≥2%	Yes - high risk	Absence of CALR Type 1 mutation Presence of \geq 2 HMR mutations ²
MIPSS70 -Plus v2.0	Yes				As for MIPSS70- Plus with adjusted Hb thresholds	Yes - high and very high risk	As for MIPSS70- Plus Included U2AF1 Q157 as an HMR mutation
GIPSS	Yes	\blacksquare	\sim	\blacksquare		$Yes -$ very high risk and unfavo	Absence of CALR Type 1/like mutation Presence of
							2

syl
ab
ear
cy <u>Platelets <1</u>
hat include:
RBC, red blo t,

-ASXL1,
^

³ASXL1, SRSF2, or U2AF1 Q157

symptoms
abnormalit
earrangeme
cytes, x10⁹ Plate include tris
Plate
Referred blood
Referred blood 1 (2 3 H complex karyotype or two about that include trisomy, space, $\frac{1}{2}$, $\frac{1}{2}$ A
ASXL1, EZH2, SRSF2, and IDH1/2
 A SXL1, SRSF2, or U2AF1 Q157
Hb, haemoglobin, g/dL; leuk, leukocytes, x10⁹/L,
myelofibrosis; HMR, high molecular risk. ASXL1, SRSF2, or U2AF1 Q157
Ib, haemoglobin, g/dL; leuk, leuk
nyelofibrosis; HMR, high molecul
nyelofibrosis; HMR, high molecul Hb, haemoglobin, g/dL; leuk, le
nyelofibrosis; HMR, high moled
1 myelofibrosis; HMR, high molecular risk. /L, RBC, red blood cell; BM, bone marrow; MF, myelofibrosis; HMR, high molecular risk.

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| || || || Figure 1: Potential paths of clonal evolution in MPN. The combinations of mutations that
occur in chronic-phase MPN and disease progression to accelerated or blast-phase MPN
(AML) can be explained by the theories of linear occur in chronic-phase MPN and disease progression to accelerated or blast-phase MPN
(AML) can be explained by the theories of linear, branching and parallel evolution. Linear
evolution pertains to the sequential acquisiti (AML) can be release to the sequential acquisition of multiple mutations within the same cloud in this scenario, the founder mutation may represent the MPN-driver or a somatic mutation. Reflowing to the theories of MPN and evolution may represent the MPN-driver or a somatic mutation
known to drive clonal hematopoiesis. Branching evolution pertains to the emergence of
MPN and AML in separate clones with a common clonal ancestor harboring a dr known to drive clonal hematopoiesis. Branching evolution pertains to the emergence of
MPN and AML in separate clones with a common clonal ancestor harboring a driver of clona
hematopoiesis. Parallel evolution pertains to t MPN and AML in separate clones with a common clonal ancestor harboring a driver of cl
hematopoiesis. Parallel evolution pertains to the emergence of MPN and AML in separat
clones with no common ancestor. The acquisition of Mematopoiesis. Parallel evolution pertains to the emergence of MPN and AML in separate
clones with no common ancestor. The acquisition of an MPN or AML driver may be preceded
by a driver of clonal hematopoiesis. It is note clones with no common ancestor. The acquisition of an MPN or AML driver may be preced
by a driver of clonal hematopoiesis. It is noted that prior presentation of PV or ET is not
required for the emergence of MF, and prior by a driver of clonal hematopoiesis. It is noted that prior presentation of PV or ET is not
required for the emergence of MF, and prior presentation of MF is not required for the
emergence of AML. by a driver of the emergence of MF, and prior presentation of MF is not required for the
emergence of AML.
The prior of AML. required for the emergence of AML, and presentation of MML, and presentation of MF is not required for the presentation of $\frac{1}{2}$ emergence of AML.

