


Review

# Lysine-Specific Demethylase 1 (LSD1/KDM1A) Inhibition as a Target for Disease Modification in Myelofibrosis

Harinder Gill 

Department of Medicine, LKS Faculty of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong SAR, China; gillhsh@hku.hk; Tel.: +852-22554542

**Abstract:** Myelofibrosis (MF) is the most symptomatic form of myeloproliferative neoplasm and carries the worst outcome. Allogeneic hematopoietic stem cell transplantation is the only therapy with potential for cure at present, but is limited by significant mortality and morbidity. JAK inhibition is the mainstay of treatment for intermediate- and high-risk MF. Ruxolitinib is the most widely used JAK1/2 inhibitor and provides durable effects in controlling symptom burden and spleen volumes. Nevertheless, ruxolitinib may not adequately address the underlying disease biology. Its effects on mutant allele burden, bone marrow fibrosis, and the prevention of leukemic transformation are minimal. Multiple small molecules are being tested in multiple phase 2 and 3 studies as either monotherapy or in combination with JAK2 inhibitors. In this review, the role of LSD1/KDM1A inhibition as a potential disease-modification strategy in patients with myelofibrosis is described and discussed.

**Keywords:** myelofibrosis; disease modification; LSD1; bomedemstat



**Citation:** Gill, H. Lysine-Specific Demethylase 1 (LSD1/KDM1A) Inhibition as a Target for Disease Modification in Myelofibrosis. *Cells* **2022**, *11*, 2107. <https://doi.org/10.3390/cells11132107>

Academic Editor: Jean Gabert

Received: 11 June 2022

Accepted: 2 July 2022

Published: 3 July 2022

Corrected: 19 December 2022

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



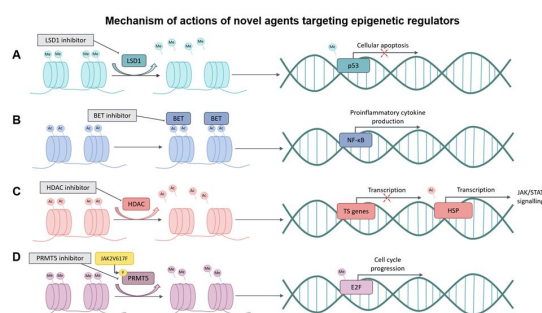
**Copyright:** © 2022 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Myeloproliferative neoplasms (MPNs) are unique hematopoietic stem cell disorders sharing mutations that constitutively activate the signal-transduction pathways involved in hematopoiesis [1]. They are characterized by stem cell-derived clonal myeloproliferation. The classical Philadelphia (Ph) chromosome-negative MPNs comprise polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), and are associated with the driver genes *JAK2*, *CALR*, and *MPL*. PMF is characterized by reticulin fibrosis, abnormal cytokine-mediated systemic symptoms, anemia, hepatosplenomegaly, and a propensity for progression to AML. Patients with PV and ET may progress to post-PV (PPV) and post-ET (PET)—myelofibrosis (MF), respectively. The incidence of PV, ET, and PMF is approximately 0.4 to 2.8, 0.38 to 1.7, and 0.1 to 1.0 per 100,000 persons per year, respectively [2]. MPNs generally affect the middle-aged, with the median age at presentation of PV, ET, and PMF being 65, 68, and 70 years, respectively [3]. Patients with MF carry the worst prognosis [4,5]. Median survival for PV, ET, and PMF is 14, 20, and 5.7 years respectively [6–8]. Allogeneic hematopoietic stem cell transplantation is the only therapy with potential for cure at present, but is limited by significant mortality and morbidity [9]. Thus, JAK inhibition is the cornerstone of treatment for intermediate- and high-risk MF. Ruxolitinib is the most widely used JAK1/2 inhibitor, provides durable effects in controlling patient symptoms and spleen volumes, and may prolong survival [10–16]. Nevertheless, the effect of ruxolitinib on mutant allele burden, bone marrow fibrosis, and the prevention of leukemic transformation has been little observed. Even the three other JAK2 inhibitors—fedratinib, pacritinib, and momelotinib—may not address all the unmet needs in patients with MF, especially in the second-line setting and the setting of disease modification [17–20]. Multiple “non-JAK inhibitor” molecules are being tested in phase 2 and 3 studies, either as monotherapy or in combination with JAK2 inhibitors [20,21]. In this review, the role of LSD1/KDM1A inhibition as a potential disease-modification strategy in patients with myelofibrosis is appraised.

## 2. Mutations in Epigenetic Regulators in Myelofibrosis

With the advent of next-generation sequencing and whole-genome analyses in myeloid malignancies, mutations in DNA methylation genes (*TET2*, *DNMT3A*, *IDH1/2*), histone modification genes (*EZH2*, *ASXL1*), RNA splicing factors (*SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*), and transcription factors (*TP53*, *CUX1*, *IKZF1*, *ETV6*, *RUNX1*) have been described in MPNs [22–24]. Nevertheless, these mutations are not restricted to MPNs, and are also seen in myelodysplastic syndrome (MDS), AML, and other myeloid malignancies. These mutations are involved in the phenotypic and disease evolution of MPNs. *TET2* (10–20% of MPNs) and *DNMT3A* (5–10% of MPNs) have been found to precede *JAK2*<sup>V617F</sup> mutations, and have a central role in self-renewal and disease initiation in MPN hematopoietic stem cells (HSCs) [25–32]. The role of *DNMT3A* and *TET2* in the progression to MF or secondary AML is yet to be elucidated. *EZH2* mutations are seen in 5% to 10% of PMF and portend a poor prognosis [33]. In murine MPN models, *Ezh2* loss modifies phenotype and is associated with disease progression [34–36]. Mutations in *ASXL* are seen in 25% of PMF and are associated with worse outcomes [37–39]. Loss-of-function mutations in *ASXL1* are associated with a higher risk of leukemic transformation. In murine models, *Asxl1* loss is associated with dysplasia, cytopenia, and defective HSC self-renewal [40,41]. *SRSF2* mutations are mostly restricted to ET and PMF and associated with poor outcomes [42]. They are especially enriched in patients with secondary AML from preceding MF. *TP53* mutations are uncommon in PMF or other MPNs in the chronic phase. However, they are found in up to 50% of patients with secondary AML and are often associated with *ASXL1*, *SRSF2*, *IDH1/2*, *CBL*, and *LNK* mutations [43,44]. They are especially common in secondary AML from preceding post-PV or post-ET MF and are associated with *DNMT3A* mutations. Other mutations associated with late events in the clonal progression of MPNs and secondary AML include *RUNX1*, *FLT3-ITD*, *NRAS*, *NF1*, *IKZF1* and *CUX1* [45,46]. Mutations in epigenetic regulators and transcription factors are often associated with advanced MF and increased risk of progression [27,28,47–49]. Manipulation of these genetic alterations may offer an additional therapeutic option in patients with an otherwise dismal outcome, and targeting epigenetic regulators with novel agents may potentially alter disease biology in MF (Figure 1).



**Figure 1.** Mechanism of actions of novel agents targeting epigenetic regulators. (A) Removal of methyl groups by LSD1, inhibiting p53 methylation and abrogating cellular apoptosis. LSD1 inhibitor antagonizes LSD1 to restore tumor-suppressive effects of p53. (B) Anchoring of BET proteins to acetylated lysine residues to activate NF-κB pathway. BET inhibitors block BET proteins and the proinflammatory pathway to reduce synthesis of proinflammatory cytokines. (C) Removal of acetyl groups by HDAC, decreasing tumor-suppressor gene transcription while deacetylating HSP to aggravate JAK/STAT signaling pathway. This effect can be overcome by HDAC inhibitors. (D) Aberrant phosphorylation of PRMT5 by JAK2V617F, leading to impaired methylation activity. Thus, E2F is methylation for cell cycle progression and myeloproliferation. The aberrant activation can be inhibited by an PRMT5 inhibitor. Me: methylation; Ac: acetylation; LSD1: lysine-specific demethylase-1; BET: bromodomain and extraterminal domain; NF-κB: nuclear factor kappa-light-chain enhancer of activated B cells; HDAC: histone deacetylase; TS genes: tumor suppressor genes; HSP: heat shock protein; JAK: Janus kinase; STAT: signal transducer and activator of transcription; PRMT5: protein arginine methyltransferase 5; E2F: E2F transcription factor 1.

### 3. The Functional Role of LSD1 in Hematopoiesis

*LSD1* is an essential gene, the loss of which leads to early embryonic lethality [50,51]. The protein also regulates the balance between self-renewal and proliferation [52]. Conditional in vivo *LSD1* knockdown using a doxycycline-inducible short hairpin *LSD1* (*shLSD1*) established *LSD1* as a central regulator of HSPCs [53]. An inducible *LSD1* knockdown resulted in profound but reversible thrombocytopenia, neutropenia, and anemia with concurrent monocytosis. *LSD1* knockdown for 27 days led to an increase in circulating multipotent progenitors and HSCs with a concomitant downregulation of chemokine (C-X-C motif) receptor 4 (CXCR4) without affecting the size of the quiescent long-term hematopoietic stem cell (HSC) pool [53].

*LSD1* is a key regulator of the progression from pluripotency to terminal differentiation and balancing self-renewal and proliferation [52,54]. *LSD1* is recruited to promoters and enhancers of genes essential for normal development by the transcription factors octamer-binding transcription factor 4 (OCT4), SRY (sex determining region Y)-box 2 (SOX2), Nanog, and the coactivator mediator. *LSD1* maintains the pluripotency program allowing embryonic stem cells (ESCs) to differentiate. *LSD1* is also essential for the complete shutdown of ESC gene expression, as cells undergo transition to more differentiated cell states [54]. *LSD1* plays a similar role during myelopoiesis, allowing commitment of progenitors to specific myeloid lineages [55]. Enhancers essential for terminal myeloid differentiation in lineage-specific progenitor cells are activated by the placement of H3K4me1 marks. As progenitors commit to differentiation, *LSD1* is significantly downregulated, allowing enhancers and promoters to be gradually activated with progressive addition of methyl or acetyl groups to H3K4 and H3K27, respectively [55].

### 4. LSD1 as an Epigenetic Regulator

Lysine methyltransferases and demethylases are able to catalyze N-methylation and N-demethylation of histone (H) lysines (K) [56,57]. *LSD1*, or KDM1A, is an enzyme that removes mono- and dimethyl groups from the histone H3 at the critical lysines K4 and K9 [58]. Methylation of histone H3K4 and H3K9 is a posttranslational modification that results in conformational change of chromatin [59,60]. Chromatin is a constellation of nuclear macromolecules and comprises DNA, protein scaffolding, and enzymes that drive RNA transcription and synthesis [61]. The DNA and its protein scaffold of histones form the nucleosome. Each nucleosome comprises two copies of each of the four histone proteins—H2A, H2B, H3, and H4—forming an octamer around which DNA is wrapped. The rates of gene transcription are heavily influenced by the accessibility of transcription factors and RNA polymerase complexes to template DNA at promoters and enhancers [59,60].

Histone and nucleic acid modifications provide binding sites for proteins and components of the transcriptional machinery that affect transcriptional gene silencing or activation. Histone modifications include acetylation (Ac), methylation (Me), phosphorylation (Ph), and ubiquitination (Ub). *LSD1* acts as an epigenetic regulator of gene expression by altering the local state of the chromatin. Inhibition of *LSD1* results in alteration of gene expression and inhibits the maturation of JAK-STAT activated megakaryocytes and myeloid cells from their progenitors. This also results in the inhibition of self-renewal potential of HSPCs harboring the pathogenic driver mutations [62–64].

*LSD1* also regulates nonhistone substrates [65]. *LSD1* is localized to specific sites in the genome through various transcription factors that bind DNA [54,66]. Transcription activators, such as V-Myb avian myeloblastosis viral oncogene homolog (MYB) and steroid hormone receptors, as well as repressors, such as growth factor independence 1 transcription repressor (GFI1) and RE-1 silencing transcription factor (REST), recruit *LSD1* to specific locations on the genome [67,68]. *LSD1* is part of a larger protein complex, containing Co-RE-1 silencing transcription factor (CoREST), nucleosome remodeling and histone deacetylase (NuRD), or other factors that determine cell- and site-specific chromatin remodeling [51,69]. These complexes may also include DNA methyltransferase 1 (DNMT1) and histone deacetylases 1, 2, and 3 (HDAC1, 2, and 3) activities, all of which contribute to

maintaining or modifying the epigenetic state at that genomic site [70,71]. Therefore, an important property of LSD1 is its function as a scaffold for other proteins and epigenetic enzymes that are corecruited to genomic sites. LSD1 bound to specific sites precludes the binding of other factors that may influence transcription.

### 5. The Biological Role of LSD1 and the Effect of LSD1 Inhibitors in Murine Models of MPNs

Overexpression of *LSD1* messenger RNA (mRNA) and excess LSD1 protein have been observed in various malignancies, including neuroblastoma, squamous-cell carcinoma, Ewing sarcoma, AML, neuroendocrine tumors, breast cancer, prostate cancer, bladder cancer, small-cell lung cancer, and colorectal cancer [63,64,67,72–74]. In MPNs, LSD1 is overexpressed, mainly in the megakaryocytes, erythroid precursors, and to a certain extent in the early myeloid series [75]. Treatment of various malignant cell types in vitro with LSD1 inhibitors suppresses tumor growth, reduces their invasiveness, reduces clonogenic potential, eliminates cancer stem cells, induces markers of differentiation appropriate to the cell lineage, and induces apoptosis [76–78]. In various models of mouse leukemia, treatment with LSD1 inhibitors induced monocytic markers of differentiation, reduced clonogenic potential of leukemia-initiating cells (LICs), and induced apoptosis [78]. LSD1 is expressed in a high proportion of leukemic myeloblasts [79,80]. LSD1 gene expression is among the highest in the malignant myeloid stem and progenitor cell population [77,78]. LSD1 plays a direct role in regulating pathogenic JAK-STAT signaling pathways. The key MPN driver genes *JAK2*<sup>V617F</sup>, *CALR*, and *MPL* activate JAK-STAT signaling via phosphorylation of STAT3, STAT5, and transcription factors, which activate specific genes with pleiotropic effects [81]. STAT3 activity is modulated by methylation on lysine (K140) and is one of the substrates for LSD1 [82]. Proof-of-concept studies have been performed on well-established, preclinical mouse models of MPNs (*JAK2*<sup>V617F</sup>, *Mpl*<sup>W515L</sup>). LSD1 inhibition in *Mpl*<sup>W515L</sup> mice markedly suppressed myeloproliferation, reducing leukocyte and platelet counts. Splens in animals treated with LSDi showed a dose-proportional decrease in weight. Histologically, a marked reduction in myeloid proliferation was demonstrated in the bone marrow and the spleen alongside a reversal of extramedullary hematopoiesis (EMH). Intriguingly, there was marked reduction in the degree of bone marrow reticulin fibrosis with LSD1 inhibition. LSD1 inhibition also significantly reduced serum inflammatory cytokine concentrations, in particular the plasma concentration of the chemokine (C-X-C motif) ligand 5 (Cxcl5 or IL-8 in humans), a key mediator of the inflammatory state seen in MPNs. In these mouse models, a reduction in mutant allele burden of driver mutations was also demonstrated. The observation of reduction in the degree of marrow fibrosis and the mutant allele burden of driver genes support the proposition that targeting LSD1 may induce disease modification in MPNs.

### 6. Clinical Data of LSD1 Inhibitors in Myelofibrosis

Given the important roles that LSD1 plays in carcinogenesis, various LSD1 inhibitors have been evaluated in clinical trials. Some of the reported LSD1 inhibitors include tranylcypromine (TCP or PCPA), ORY-1001 (iadademstat), GSK-2879552, IMG-7289 (bomedemstat), INCB059872, CC-90011, and ORY-2001 (vafidemstat). Bomedemstat (IMG-7289, Imago Biosciences, San Francisco, CA) is the most extensively evaluated LSD1 inhibitor in myeloproliferative neoplasms. In *JAK2*<sup>V617F</sup>-positive MPN mice, daily dosing improved blood counts, reduced spleen volumes, reduced marrow reticulin fibrosis, and reduced mutant allele frequencies [83].

Bomedemstat is the only LSD1 inhibitor clinically evaluated in patients with advanced myelofibrosis. In an ongoing phase 2 study in 89 patients with advanced MF, the efficacy and safety of bomedemstat was confirmed [84,85]. Eighty-three percent of the patients had a history of treatment failure with ruxolitinib, with 70% also receiving a second treatment with an unfavorable experience. Thirty-seven percent of patients had received at least one red cell transfusion prior to dosing. The most frequently reported adverse event was throm-

bocytopenia, an expected observation, given that dosing to grade 3 thrombocytopenia was allowed. The commonest nonhematological toxicity was dysgeusia, reported in 33%, with one discontinuation. Other serious adverse events (SAEs) were reported in 49% of the patients. The most common SAEs, regardless of causality, were cellulitis, diverticulitis, and pneumonia. There were no deaths related to the study drug. The efficacy endpoints were reduction in spleen volume and reduction in total symptom scores (TSS) using the MPN symptom assessment form (SAF). At 24 weeks, 64% of patients had a decrease in spleen volume, with 6% of patients having more than 35% reduction. In patients with a high symptom burden (TSS > 20), 65% had a decrease in TSS, and for 19% of patients, the decrease in TSS was greater than 50%. By week 12, 44% of patients had an increase in hemoglobin of 1 g/dL or more and 46% had stable hemoglobin. At the data cutoff point, of 21 patients, three had become transfusion-independent. The improvement in hemoglobin is an intriguing observation and is likely to address the issue of anemia associated with ruxolitinib. A possible explanation for this observation is that the modulation of transcription by LSD1 is lineage-specific or that expression of the  $\gamma$ -globin gene is altered with LSD1 inhibition [86,87]. Eighty-five percent of patients had stable or improved fibrosis score of at least one grade. Patients with an elevated inflammatory chemokine, such as chemokine ligand 5 (CCL5), had a measurable decrease into normal concentrations. The mutant allele frequencies (MAF) of driver and nondriver mutations among the 261 genes were serially sequenced. Fifty-two percent of patients had a decrease in MAF, with ASXL1 being the most sensitive to bomedemstat. No patient progressed to secondary AML in this study.

## 7. Conclusions and Future Perspectives

As we progress to the era of novel therapies that could alter disease biology, there is a need to utilize end points that inform us how these novel agents could alter the disease trajectory (Table 1). The current data available from clinical studies support the definition of disease modification that comprises clinically meaningful improvement in survival, reduction in the risk of leukemic transformation, restoration of normal hematopoiesis, significant reduction in bone marrow fibrosis, and reduction in the clonal burden of the disease. Achieving disease modification will ultimately lead to beneficial effects in traditional outcome measures, such as symptom improvement and control of splenomegaly. In spite of the limited disease-modifying effect of JAK inhibitors, the JAK-STAT pathway remains pivotal. This is supported by the modest effect of single-agent bomedemstat on spleen volume. Treatment strategies combining JAK inhibitors and novel agents, such as bomedemstat, will provide synergic effects in improving outcomes and altering disease biology. The selection of JAK inhibitors to be used with bomedemstat should take into account the disease characteristics and clinical needs, such as the presence of anemia (where fedratinib or momelotinib could be considered) or thrombocytopenia (where pacritinib could be considered). Based on the effect of LSD1 inhibition on erythropoiesis, it will also be intriguing to observe if bomedemstat can circumvent anemia caused by ruxolitinib. In addition, the impressive responses seen with bomedemstat in patients with essential thrombocythemia [88] suggest that LSD1 inhibitors could potentially be beneficial when used earlier in MF, such as in prefibrotic or early PMF, an area that is yet to be explored.

**Table 1.** Selected novel agents showing improvement in surrogate markers for disease modification in myelofibrosis, either as single agent or in combination with ruxolitinib.

Class	Drug	Study Population	Design	SVR35 at 24 Weeks	TSS50 at 24 Weeks	Anemia Response	VAF Reduction	BM Fibrosis Reduction
LSD1 inhibitor	Bomedemstat [84,85]	Ruxolitinib exposed: 83% (74/89) N = 89	Phase 2 (ongoing) Single-agent bomedemstat	6% (3/50)	19% (5/26)	In TD patients: 52% (11/21) had stable or reduced transfusion burden; 14% (3/21) became TI	VAF reduction 52% (36/69), most frequently in <i>JAK2</i> <sup>V617F</sup> and/or <i>ASXL1</i>	31% (16/52) improved by 1 grade 50% (26/52) stable

Table 1. Cont.

Class	Drug	Study Population	Design	SVR35 at 24 Weeks	TSS50 at 24 Weeks	Anemia Response	VAF Reduction	BM Fibrosis Reduction
BET inhibitor	Pelabresib (MANIFEST) [89,90]	Both JAKi exposed and JAKi naïve, N = 271	Phase 1/2 (ongoing) Arm 1: JAKi exposed (pelabresib) Arm 2: JAKi exposed (pelabresib + ruxolitinib) Arm 3: JAKi naïve (pelabresib + ruxolitinib)	Arm 1: 11% (7/64) Arm 2: 20% (16/81) Arm 3: 68% (57/84)	Arm 1: 28% (18/64) Arm 2: 37% (30/81) Arm 3: 56% (46/82)	Arm 1: In TD patients, 16% (4/25) became TI Arm 2: In TD patients, 36% (13/36) became TI Arm 3: In patients with Hb < 10 g/dL; Hb improved by 1 g/dL	Not reported	Arm 1: 23% (7/30) improved at 24 weeks Arm 2: 25% (9/36) improved at 24 weeks Arm 3: 31% (16/52) improved at 24 weeks
Telomerase inhibitor	Imetelstat (IMBark) [91]	JAKi exposed N = 59	Phase 2 (complete) Single-agent imetelstat	10.2% (6/59)	32.2% (19/59)	In TD patients, 25% (3/12) became transfusion-independent	42% had $\geq 25\%$ reduction in VAF	41% (15/37) had reduction in BM fibrosis
BH3 mimetic; Bcl-2/Bcl-X <sub>L</sub> inhibitor	Navitoclax (REFINE) [92]	Ruxolitinib exposed N = 174	Phase 2 (ongoing) Navitoclax +/- ruxolitinib	27% (9/34)	30% (9/34)	In TD patients or patients with Hb < 10 g/dL; TI or $\geq 2$ g/dL in 64% (7/11)	46% (12/26) had >10% reduction in VAF	21% (7/34) had BM fibrosis reduction at 24 weeks
MDM2 inhibitor	Navtemadlin (BOREAS) [93]	JAKi exposed N = 113	Phase 2 (ongoing) Single-agent navtemadlin	Not reported	Not reported	Not reported	34% had $\geq 20\%$ reduction in VAF	27% $\geq 1$ grade reduction in BM fibrosis
Hypomethylating agent	Azacitidine [94]	JAKi naïve N = 60	Phase 2 Ruxolitinib + azacitidine	NR	54% (25/46)	In TD patients, 20% (1/5) became TI	81% (13/16) had reduction in VAF at 24 weeks	57% (8/14) had reduction in BM fibrosis at 24 weeks

SVR35:  $\geq 35\%$  reduction in spleen volume from baseline to 24 weeks; TSS50:  $\geq 50\%$  reduction in total symptom score from baseline to 24 weeks; VAF: variant allele frequency; BM: bone marrow; LSD1: lysine-specific demethylase 1; BET: bromodomain and extraterminal; Bcl-2: B-cell lymphoma 2; MDM2: murine double minute 2; TD: transfusion-dependent; TI: transfusion-independent; JAKi: JAK inhibitor; Hb: hemoglobin; NR: not reported.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** The author would like to acknowledge Hugh Young Rienhoff and his team at Imago Biosciences for their work on the role of LSD1 and the development of IMG-7289 (Bomedemstat), which inspired this manuscript.

**Conflicts of Interest:** The author declares no relevant conflict of interest.

## References

- Spivak, J.L. Myeloproliferative Neoplasms. *N. Engl. J. Med.* **2017**, *376*, 2168–2181. [[CrossRef](#)] [[PubMed](#)]
- Moulard, O.; Mehta, J.; Fryzek, J.; Olivares, R.; Iqbal, U.; Mesa, R.A. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur. J. Haematol.* **2014**, *92*, 289–297. [[CrossRef](#)] [[PubMed](#)]
- Srouf, S.A.; Devesa, S.S.; Morton, L.M.; Check, D.P.; Curtis, R.E.; Linet, M.S.; Dores, G.M. Incidence and patient survival of myeloproliferative neoplasms and myelodysplastic/myeloproliferative neoplasms in the United States, 2001–12. *Br. J. Haematol.* **2016**, *174*, 382–396. [[CrossRef](#)] [[PubMed](#)]
- Hultcrantz, M.; Kristinsson, S.Y.; Andersson, T.M.-L.; Landgren, O.; Eloranta, S.; Derolf, A.R.; Dickman, P.W.; Björkholm, M. Patterns of Survival Among Patients With Myeloproliferative Neoplasms Diagnosed in Sweden From 1973 to 2008: A Population-Based Study. *J. Clin. Oncol.* **2012**, *30*, 2995–3001. [[CrossRef](#)]
- Tefferi, A.; Guglielmelli, P.; Larson, D.R.; Finke, C.; Wassie, E.A.; Pieri, L.; Gangat, N.; Fjerza, R.; Belachew, A.A.; Lasho, T.L.; et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. *Blood* **2014**, *124*, 2507–2513. [[CrossRef](#)]

6. Vannucchi, A.M.; Harrison, C.N. Emerging treatments for classical myeloproliferative neoplasms. *Blood* **2017**, *129*, 693–703. [[CrossRef](#)]
7. Tefferi, A. Primary myelofibrosis: 2019 update on diagnosis, risk-stratification and management. *Am. J. Hematol.* **2018**, *93*, 1551–1560. [[CrossRef](#)]
8. Tefferi, A.; Barbui, T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. *Am. J. Hematol.* **2019**, *94*, 133–143. [[CrossRef](#)]
9. England, J.; Gupta, V. Novel therapies vs hematopoietic cell transplantation in myelofibrosis: Who, when, how? *Hematol. Am. Soc. Hematol. Educ. Program* **2021**, *2021*, 453–462. [[CrossRef](#)]
10. Verstovsek, S.; Mesa, R.A.; Gotlib, J.; Levy, R.S.; Gupta, V.; DiPersio, J.F.; Catalano, J.V.; Deininger, M.; Miller, C.; Silver, R.T.; et al. A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis. *N. Engl. J. Med.* **2012**, *366*, 799–807. [[CrossRef](#)]
11. Harrison, C.; Kiladjan, J.-J.; Al-Ali, H.K.; Gisslinger, H.; Waltzman, R.; Stalbovska, V.; McQuitty, M.; Hunter, D.S.; Levy, R.; Knoops, L.; et al. JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis. *N. Engl. J. Med.* **2012**, *366*, 787–798. [[CrossRef](#)] [[PubMed](#)]
12. Mesa, R.A.; Gotlib, J.; Gupta, V.; Catalano, J.V.; Deininger, M.W.; Shields, A.L.; Miller, C.B.; Silver, R.T.; Talpaz, M.; Winton, E.F.; et al. Effect of Ruxolitinib Therapy on Myelofibrosis-Related Symptoms and Other Patient-Reported Outcomes in COMFORT-I: A Randomized, Double-Blind, Placebo-Controlled Trial. *J. Clin. Oncol.* **2013**, *31*, 1285–1292. [[CrossRef](#)] [[PubMed](#)]
13. Verstovsek, S.; Mesa, R.A.; Gotlib, J.; Levy, R.S.; Gupta, V.; DiPersio, J.F.; Catalano, J.V.; Deininger, M.; Miller, C.; Silver, R.T.; et al. The clinical benefit of ruxolitinib across patient subgroups: Analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. *Br. J. Haematol.* **2013**, *161*, 508–516. [[CrossRef](#)] [[PubMed](#)]
14. Verstovsek, S.; Gotlib, J.; Mesa, R.A.; Vannucchi, A.M.; Kiladjan, J.-J.; Cervantes, F.; Harrison, C.N.; Paquette, R.; Sun, W.; Naim, A.; et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J. Hematol. Oncol.* **2017**, *10*, 156. [[CrossRef](#)]
15. Guglielmelli, P.; Ghirardi, A.; Carobbio, A.; Masciulli, A.; Maccari, C.; Mora, B.; Rumi, E.; Triguero, A.; Finazzi, M.C.; Pettersson, H.; et al. Impact of ruxolitinib on survival of patients with myelofibrosis in the real world: Update of the ERNEST Study. *Blood Adv.* **2022**, *6*, 373–375. [[CrossRef](#)]
16. Harrison, C.N.; on behalf of the COMFORT-II Investigators; Vannucchi, A.M.; Kiladjan, J.-J.; Al-Ali, H.K.; Gisslinger, H.; Knoops, L.; Cervantes, F.; Jones, M.M.; Sun, K.; et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. *Leukemia* **2016**, *30*, 1701–1707. [[CrossRef](#)]
17. Harrison, C.N.; Schaap, N.; Vannucchi, A.M.; Kiladjan, J.-J.; Tiu, R.V.; Zachee, P.; Jourdan, E.; Winton, E.; Silver, R.T.; Schouten, H.C.; et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): A single-arm, open-label, non-randomised, phase 2, multicentre study. *Lancet Haematol.* **2017**, *4*, e317–e324. [[CrossRef](#)]
18. Mascarenhas, J.; Hoffman, R.; Talpaz, M.; Gerds, A.T.; Stein, B.; Gupta, V.; Szoke, A.; Drummond, M.; Pristupa, A.; Granston, T.; et al. Pacritinib vs Best Available Therapy, Including Ruxolitinib, in Patients With Myelofibrosis: A Randomized Clinical Trial. *JAMA Oncol.* **2018**, *4*, 652–659. [[CrossRef](#)]
19. Chifotides, H.T.; Bose, P.; Verstovsek, S. Momelotinib: An emerging treatment for myelofibrosis patients with anemia. *J. Hematol. Oncol.* **2022**, *15*, 1–17. [[CrossRef](#)]
20. Vachhani, P.; Verstovsek, S.; Bose, P. Disease Modification in Myelofibrosis: An Elusive Goal? *J. Clin. Oncol.* **2022**, *40*, 1147–1154. [[CrossRef](#)]
21. Tremblay, D.; Hoffman, R. Emerging drugs for the treatment of myelofibrosis: Phase II & III clinical trials. *Expert Opin. Emerg. Drugs* **2021**, *26*, 351–362. [[CrossRef](#)] [[PubMed](#)]
22. Vainchenker, W.; Kralovics, R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. *Blood* **2017**, *129*, 667–679. [[CrossRef](#)] [[PubMed](#)]
23. Gill, H.; Leung, A.Y.; Kwong, Y.-L. Molecular and Cellular Mechanisms of Myelodysplastic Syndrome: Implications on Targeted Therapy. *Int. J. Mol. Sci.* **2016**, *17*, 440. [[CrossRef](#)] [[PubMed](#)]
24. Gill, H.; Leung, A.Y.; Kwong, Y.-L. Molecularly targeted therapy in acute myeloid leukemia. *Futur. Oncol.* **2016**, *12*, 827–838. [[CrossRef](#)]
25. Delhommeau, F.; Dupont, S.; Della Valle, V.; James, C.; Trannoy, S.; Massé, A.; Kosmider, O.; Le Couedic, J.-P.; Robert, F.; Alberdi, A.; et al. Mutation in TET2 in Myeloid Cancers. *N. Engl. J. Med.* **2009**, *360*, 2289–2301. [[CrossRef](#)]
26. Tefferi, A.; Pardanani, A.; Lim, K.-H.; Abdel-Wahab, O.; Lasho, T.L.; Patel, J.; Gangat, N.; Finke, C.M.; Schwager, S.; Mullally, A.; et al. TET2 mutations and their clinical correlates in polycythemia vera, essential thrombocythemia and myelofibrosis. *Leukemia* **2009**, *23*, 905–911. [[CrossRef](#)]
27. Ortmann, C.A.; Kent, D.G.; Nangalia, J.; Silber, Y.; Wedge, D.C.; Grinfeld, J.; Baxter, E.J.; Massie, C.E.; Papaemmanuil, E.; Menon, S.; et al. Effect of Mutation Order on Myeloproliferative Neoplasms. *N. Engl. J. Med.* **2015**, *372*, 601–612. [[CrossRef](#)]
28. Kent, D.G.; Ortmann, C.A.; Green, A.R.; Delhommeau, F. Effect of Mutation Order on Myeloproliferative Neoplasms. *N. Engl. J. Med.* **2015**, *372*, 1865–1866. [[CrossRef](#)]
29. Stegelmann, F.; Bullinger, L.; Schlenk, R.F.; Paschka, P.; Griesshammer, M.; Blersch, C.; Kuhn, S.; Schauer, S.; Dohner, H.; Dohner, K. DNMT3A mutations in myeloproliferative neoplasms. *Leukemia* **2011**, *25*, 1217–1219. [[CrossRef](#)]

30. Challen, G.A.; Sun, D.; Jeong, M.; Luo, M.; Jelinek, J.; Berg, J.S.; Bock, C.; Vasanthakumar, A.; Gu, H.; Xi, Y.; et al. Dnmt3a is essential for hematopoietic stem cell differentiation. *Nat. Genet.* **2011**, *44*, 23–31. [[CrossRef](#)]
31. Jaiswal, S.; Fontanillas, P.; Flannick, J.; Manning, A.; Grauman, P.V.; Mar, B.G.; Lindsley, R.C.; Mermel, C.H.; Burt, N.; Chavez, A.; et al. Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes. *N. Engl. J. Med.* **2014**, *371*, 2488–2498. [[CrossRef](#)] [[PubMed](#)]
32. Xie, M.; Lu, C.; Wang, J.; McLellan, M.D.; Johnson, K.J.; Wendl, M.C.; McMichael, J.F.; Schmidt, H.K.; Yellapantula, V.; Miller, C.A.; et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat. Med.* **2014**, *20*, 1472–1478. [[CrossRef](#)] [[PubMed](#)]
33. Guglielmelli, P.; Biamonte, F.; Score, J.; Hidalgo-Curtis, C.; Cervantes, F.; Maffioli, M.; Fanelli, T.; Ernst, T.; Winkelmann, N.; Jones, A.V.; et al. EZH2 mutational status predicts poor survival in myelofibrosis. *Blood* **2011**, *118*, 5227–5234. [[CrossRef](#)]
34. Yang, Y.; Akada, H.; Nath, D.; Hutchison, R.E.; Mohi, G. Loss of Ezh2 cooperates with Jak2V617F in the development of myelofibrosis in a mouse model of myeloproliferative neoplasm. *Blood* **2016**, *127*, 3410–3423. [[CrossRef](#)] [[PubMed](#)]
35. Shimizu, T.; Kubovcakova, L.; Nienhold, R.; Zmajkovic, J.; Meyer, S.C.; Hao-Shen, H.; Geier, F.; Dirnhofer, S.; Guglielmelli, P.; Vannucchi, A.M.; et al. Loss of Ezh2 synergizes with JAK2-V617F in initiating myeloproliferative neoplasms and promoting myelofibrosis. *J. Exp. Med.* **2016**, *213*, 1479–1496. [[CrossRef](#)]
36. Sashida, G.; Wang, C.; Tomioka, T.; Oshima, M.; Aoyama, K.; Kanai, A.; Mochizuki-Kashio, M.; Harada, H.; Shimoda, K.; Iwama, A. The loss of Ezh2 drives the pathogenesis of myelofibrosis and sensitizes tumor-initiating cells to bromodomain inhibition. *J. Exp. Med.* **2016**, *213*, 1459–1477. [[CrossRef](#)]
37. Carbuccia, N.; Murati, A.; Trouplin, V.; Brequeville, M.; Adelaide, J.; Rey, J.; Vainchenker, W.; Bernard, O.A.; Chaffanet, M.; Vey, N.; et al. Mutations of ASXL1 gene in myeloproliferative neoplasms. *Leukemia* **2009**, *23*, 2183–2186. [[CrossRef](#)]
38. Vannucchi, A.M.; Lasho, T.L.; Guglielmelli, P.; Biamonte, F.; Pardanani, A.; Pereira, A.; Finke, C.; Score, J.; Gangat, N.; Mannarelli, C.; et al. Mutations and prognosis in primary myelofibrosis. *Leukemia* **2013**, *27*, 1861–1869. [[CrossRef](#)]
39. Gelsi-Boyer, V.; Trouplin, V.; Adélaïde, J.; Bonansea, J.; Cervera, N.; Carbuccia, N.; Lagarde, A.; Prebet, T.; Nezri, M.; Sainty, D.; et al. Mutations of polycomb-associated gene ASXL1 in myelodysplastic syndromes and chronic myelomonocytic leukaemia. *Br. J. Haematol.* **2009**, *145*, 788–800. [[CrossRef](#)]
40. Abdel-Wahab, O.; Gao, J.; Adli, M.; Dey, A.; Trimarchi, T.; Chung, Y.R.; Kucsu, C.; Hricik, T.; Ndiaye-Lobry, D.; LaFave, L.M.; et al. Deletion of Asxl1 results in myelodysplasia and severe developmental defects in vivo. *J. Exp. Med.* **2013**, *210*, 2641–2659. [[CrossRef](#)]
41. Inoue, D.; Kitaura, J.; Togami, K.; Nishimura, K.; Enomoto, Y.; Uchida, T.; Kagiyama, Y.; Kawabata, K.C.; Nakahara, F.; Izawa, K.; et al. Myelodysplastic syndromes are induced by histone methylation altering ASXL1 mutations. *J. Clin. Investig.* **2013**, *123*, 4627–4640. [[CrossRef](#)] [[PubMed](#)]
42. Zhang, S.-J.; Rampal, R.; Manshouri, T.; Patel, J.; Mensah, N.; Kayserian, A.; Hricik, T.; Heguy, A.; Hedvat, C.; Gönen, M.; et al. Genetic analysis of patients with leukemic transformation of myeloproliferative neoplasms shows recurrent SRSF2 mutations that are associated with adverse outcome. *Blood* **2012**, *119*, 4480–4485. [[CrossRef](#)] [[PubMed](#)]
43. Harutyunyan, A.; Klampfl, T.; Cazzola, M.; Kralovics, R. p53 Lesions in Leukemic Transformation. *N. Engl. J. Med.* **2011**, *364*, 488–490. [[CrossRef](#)]
44. Wong, T.N.; Ramsingh, G.; Young, A.L.; Miller, C.A.; Touma, W.; Welch, J.S.; Lamprecht, T.L.; Shen, D.; Hundal, J.; Fulton, R.S.; et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature* **2015**, *518*, 552–555. [[CrossRef](#)]
45. Courtier, F.; Carbuccia, N.; Garnier, S.; Guille, A.; Adélaïde, J.; Cervera, N.; Gelsi-Boyer, V.; Mozziconacci, M.-J.; Rey, J.; Vey, N.; et al. Genomic analysis of myeloproliferative neoplasms in chronic and acute phases. *Haematologica* **2016**, *102*, e11–e14. [[CrossRef](#)] [[PubMed](#)]
46. Milosevic, J.D.; Puda, A.; Malcovati, L.; Berg, T.; Hofbauer, M.; Stukalov, A.; Klampfl, T.; Harutyunyan, A.S.; Gisslinger, H.; Gisslinger, B.; et al. Clinical significance of genetic aberrations in secondary acute myeloid leukemia. *Am. J. Hematol.* **2012**, *87*, 1010–1016. [[CrossRef](#)] [[PubMed](#)]
47. Tefferi, A.; Guglielmelli, P.; Lasho, T.L.; Gangat, N.; Ketterling, R.P.; Pardanani, A.; Vannucchi, A.M. MIPSS70+ Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. *J. Clin. Oncol.* **2018**, *36*, 1769–1770. [[CrossRef](#)] [[PubMed](#)]
48. Tefferi, A.; Guglielmelli, P.; Nicolosi, M.; Mannelli, F.; Mudireddy, M.; Bartalucci, N.; Finke, C.M.; Lasho, T.L.; Hanson, C.A.; Ketterling, R.P.; et al. GIPSS: Genetically inspired prognostic scoring system for primary myelofibrosis. *Leukemia* **2018**, *32*, 1631–1642. [[CrossRef](#)]
49. Grinfeld, J.; Nangalia, J.; Baxter, E.J.; Wedge, D.C.; Angelopoulos, N.; Cantrill, R.; Godfrey, A.L.; Papaemmanuil, E.; Gundem, G.; MacLean, C.; et al. Classification and Personalized Prognosis in Myeloproliferative Neoplasms. *N. Engl. J. Med.* **2018**, *379*, 1416–1430. [[CrossRef](#)]
50. Wang, J.; Hevi, S.; Kurash, J.K.; Lei, H.; Gay, F.; Bajko, J.; Su, H.; Sun, W.; Chang, H.; Xu, G.; et al. The lysine demethylase LSD1 (KDM1) is required for maintenance of global DNA methylation. *Nat. Genet.* **2009**, *41*, 125–129. [[CrossRef](#)]
51. Foster, C.T.; Dovey, O.M.; Lezina, L.; Luo, J.L.; Gant, T.W.; Barlev, N.; Bradley, A.; Cowley, S.M. Lysine-Specific Demethylase 1 Regulates the Embryonic Transcriptome and CoREST Stability. *Mol. Cell. Biol.* **2010**, *30*, 4851–4863. [[CrossRef](#)] [[PubMed](#)]



52. Wang, J.; Scully, K.; Zhu, X.; Cai, L.; Zhang, J.; Prefontaine, G.G.; Kronen, A.; Ohgi, K.A.; Zhu, P.; Garcia-Bassets, I.; et al. Opposing LSD1 complexes function in developmental gene activation and repression programmes. *Nature* **2007**, *446*, 882–887. [[CrossRef](#)]
53. Sprüssel, A.; Schulte, J.H.; Weber, S.; Necke, M.; Händschke, K.; Thor, T.; Pajtlter, K.W.; Schramm, A.; König, K.; Diehl, L.; et al. Lysine-specific demethylase 1 restricts hematopoietic progenitor proliferation and is essential for terminal differentiation. *Leukemia* **2012**, *26*, 2039–2051. [[CrossRef](#)] [[PubMed](#)]
54. Whyte, W.A.; Bilodeau, S.; Orlando, D.A.; Hoke, H.A.; Frampton, G.M.; Foster, C.T.; Cowley, S.M.; Young, R.A. Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. *Nature* **2012**, *482*, 221–225. [[CrossRef](#)] [[PubMed](#)]
55. Lara-Astiaso, D.; Weiner, A.; Lorenzo-Vivas, E.; Zaretsky, I.; Jaitin, D.A.; David, E.; Keren-Shaul, H.; Mildner, A.; Winter, D.; Jung, S.; et al. Chromatin state dynamics during blood formation. *Science* **2014**, *345*, 943–949. [[CrossRef](#)]
56. Kaniskan, H.U.; Martini, M.L.; Jin, J. Inhibitors of Protein Methyltransferases and Demethylases. *Chem. Rev.* **2018**, *118*, 989–1068. [[CrossRef](#)]
57. Hoffmann, I.; Roatsch, M.; Schmitt, M.L.; Carlino, L.; Pippel, M.; Sippl, W.; Jung, M. The role of histone demethylases in cancer therapy. *Mol. Oncol.* **2012**, *6*, 683–703. [[CrossRef](#)]
58. Shi, Y.; Lan, F.; Matson, C.; Mulligan, P.; Whetstone, J.R.; Cole, P.A.; Casero, R.A.; Shi, Y. Histone Demethylation Mediated by the Nuclear Amine Oxidase Homolog LSD1. *Cell* **2004**, *119*, 941–953. [[CrossRef](#)]
59. Bannister, A.J.; Kouzarides, T. Regulation of chromatin by histone modifications. *Cell Res.* **2011**, *21*, 381–395. [[CrossRef](#)]
60. Beisel, C.; Paro, R. Silencing chromatin: Comparing modes and mechanisms. *Nat. Rev. Genet.* **2011**, *12*, 123–135. [[CrossRef](#)]
61. Kornberg, R.D. Chromatin Structure: A Repeating Unit of Histones and DNA. *Science* **1974**, *184*, 868–871. [[CrossRef](#)] [[PubMed](#)]
62. Karakaidos, P.; Verigos, J.; Magklara, A. LSD1/KDM1A, a Gate-Keeper of Cancer Stemness and a Promising Therapeutic Target. *Cancers* **2019**, *11*, 1821. [[CrossRef](#)] [[PubMed](#)]
63. Fang, Y.; Liao, G.; Yu, B. LSD1/KDM1A inhibitors in clinical trials: Advances and prospects. *J. Hematol. Oncol.* **2019**, *12*, 1–14. [[CrossRef](#)]
64. Fang, Y.; Liao, G.; Yu, B. Targeting Histone Lysine Demethylase LSD1/KDM1A as a New Avenue for Cancer Therapy. *Curr. Top. Med. Chem.* **2019**, *19*, 889–891. [[CrossRef](#)] [[PubMed](#)]
65. Zheng, Y.-C.; Ma, J.; Wang, Z.; Li, J.; Bailing, J.; Jiang, B.; Zhou, W.; Shi, X.; Wang, X.; Zhao, W.; et al. A Systematic Review of Histone Lysine-Specific Demethylase 1 and Its Inhibitors. *Med. Res. Rev.* **2015**, *35*, 1032–1071. [[CrossRef](#)] [[PubMed](#)]
66. Whyte, W.A.; Orlando, D.A.; Hnisz, D.; Abraham, B.J.; Lin, C.Y.; Kagey, M.H.; Rahl, P.B.; Lee, T.I.; Young, R.A. Master Transcription Factors and Mediator Establish Super-Enhancers at Key Cell Identity Genes. *Cell* **2013**, *153*, 307–319. [[CrossRef](#)] [[PubMed](#)]
67. Metzger, E.; Wissmann, M.; Yin, N.; Müller, J.M.; Schneider, R.; Peters, A.H.; Günther, T.; Buettner, R.; Schüle, R. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature* **2005**, *437*, 436–439. [[CrossRef](#)] [[PubMed](#)]
68. Saleque, S.; Kim, J.; Rooke, H.M.; Orkin, S.H. Epigenetic Regulation of Hematopoietic Differentiation by Gfi-1 and Gfi-1b Is Mediated by the Cofactors CoREST and LSD1. *Mol. Cell* **2007**, *27*, 562–572. [[CrossRef](#)]
69. Lee, M.G.; Wynder, C.; Cooch, N.; Shiekhattar, R. An essential role for CoREST in nucleosomal histone 3 lysine 4 demethylation. *Nature* **2005**, *437*, 432–435. [[CrossRef](#)]
70. Shi, Y.-J.; Matson, C.; Lan, F.; Iwase, S.; Baba, T.; Shi, Y. Regulation of LSD1 Histone Demethylase Activity by Its Associated Factors. *Mol. Cell* **2005**, *19*, 857–864. [[CrossRef](#)]
71. Orkin, S.H.; Hochedlinger, K. Chromatin Connections to Pluripotency and Cellular Reprogramming. *Cell* **2011**, *145*, 835–850. [[CrossRef](#)] [[PubMed](#)]
72. Kahl, P.; Gullotti, L.; Heukamp, L.C.; Wolf, S.; Friedrichs, N.; Vorreuther, R.; Solleder, G.; Bastian, P.J.; Ellinger, J.; Metzger, E.; et al. Androgen Receptor Coactivators Lysine-Specific Histone Demethylase 1 and Four and a Half LIM Domain Protein 2 Predict Risk of Prostate Cancer Recurrence. *Cancer Res.* **2006**, *66*, 11341–11347. [[CrossRef](#)] [[PubMed](#)]
73. Lim, S.; Janzer, A.; Becker, A.; Zimmer, A.; Schüle, R.; Buettner, R.; Kirfel, J. Lysine-specific demethylase 1 (LSD1) is highly expressed in ER-negative breast cancers and a biomarker predicting aggressive biology. *Carcinogenesis* **2010**, *31*, 512–520. [[CrossRef](#)] [[PubMed](#)]
74. Schulte, J.H.; Lim, S.; Schramm, A.; Friedrichs, N.; Koster, J.; Versteeg, R.; Ora, I.; Pajtlter, K.; Klein-Hitpass, L.; Kuhfittig-Kulle, S.; et al. Lysine-Specific Demethylase 1 Is Strongly Expressed in Poorly Differentiated Neuroblastoma: Implications for Therapy. *Cancer Res.* **2009**, *69*, 2065–2071. [[CrossRef](#)] [[PubMed](#)]
75. Niebel, D.; Kirfel, J.; Janzen, V.; Höller, T.; Majores, M.; Gütgemann, I. Lysine-specific demethylase 1 (LSD1) in hematopoietic and lymphoid neoplasms. *Blood* **2014**, *124*, 151–152. [[CrossRef](#)] [[PubMed](#)]
76. Somervaille, T.C.; Cleary, M.L. Identification and characterization of leukemia stem cells in murine MLL-AF9 acute myeloid leukemia. *Cancer Cell* **2006**, *10*, 257–268. [[CrossRef](#)]
77. Somervaille, T.C.; Matheny, C.J.; Spencer, G.J.; Iwasaki, M.; Rinn, J.L.; Witten, D.M.; Chang, H.Y.; Shurtleff, S.A.; Downing, J.R.; Cleary, M.L. Hierarchical Maintenance of MLL Myeloid Leukemia Stem Cells Employs a Transcriptional Program Shared with Embryonic Rather Than Adult Stem Cells. *Cell Stem Cell* **2009**, *4*, 129–140. [[CrossRef](#)]
78. Harris, W.J.; Huang, X.; Lynch, J.T.; Spencer, G.J.; Hitchin, J.R.; Li, Y.; Ciceri, F.; Blaser, J.G.; Greystoke, B.F.; Jordan, A.M.; et al. The Histone Demethylase KDM1A Sustains the Oncogenic Potential of MLL-AF9 Leukemia Stem Cells. *Cancer Cell* **2012**, *21*, 473–487. [[CrossRef](#)]
79. Lin, X.-M.; Zhong, W.-T.; Wang, C.-L.; Wang, S.-Q. Expression of histone demethylase lysine specific demethylase 1 in acute leukemia and its clinical significance. *Zhongguo Shi Yan Xue Ye Xue Za Zhi* **2011**, *19*, 1348–1352.

80. Rhodes, D.R.; Kalyana-Sundaram, S.; Mahavisno, V.; Varambally, R.; Yu, J.; Briggs, B.B.; Barrette, T.R.; Anstet, M.J.; Kincaid-Beal, C.; Kulkarni, P.; et al. OncoPrint 3.0: Genes, Pathways, and Networks in a Collection of 18,000 Cancer Gene Expression Profiles. *Neoplasia* **2007**, *9*, 166–180. [[CrossRef](#)]
81. Chen, E.; Mullally, A. How does JAK2V617F contribute to the pathogenesis of myeloproliferative neoplasms? *Hematol. Am. Soc. Hematol. Educ. Program* **2014**, *2014*, 268–276. [[CrossRef](#)] [[PubMed](#)]
82. Yang, J.; Huang, J.; Dasgupta, M.; Sears, N.; Miyagi, M.; Wang, B.; Chance, M.R.; Chen, X.; Du, Y.; Wang, Y.; et al. Reversible methylation of promoter-bound STAT3 by histone-modifying enzymes. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 21499–21504. [[CrossRef](#)] [[PubMed](#)]
83. Jutzi, J.S.; Kleppe, M.; Dias, J.; Staehle, H.F.; Shank, K.; Teruya-Feldstein, J.; Gambheer, S.M.M.; Dierks, C.; Rienhoff, H.Y., Jr.; Levine, R.L.; et al. LSD1 Inhibition Prolongs Survival in Mouse Models of MPN by Selectively Targeting the Disease Clone. *HemaSphere* **2018**, *2*, e54. [[CrossRef](#)] [[PubMed](#)]
84. Gill, H.; Yacoub, A.; Pettit, K.M.; Bradley, T.; Gerds, A.T.; Tatarczuch, M.; Shortt, J.; Curtin, N.J.; Rossetti, J.M.; Burbury, K.; et al. A Phase 2 Study of the LSD1 Inhibitor Img-7289 (bomedemstat) for the Treatment of Advanced Myelofibrosis. *Blood* **2021**, *138*, 139. [[CrossRef](#)]
85. Gill, H.; Yacoub, A.; Pettit, K.; Bradley, T.; Gerds, A.; Tatarczuch, M.; Shortt, J.; Curtin, N.; Rossetti, J.; Burbury, K.; et al. A phase 2 study of IMG-7289 (bomedemstat) in patients with advanced myelofibrosis. *HemaSphere* **2022**, *6*, 1809. [[CrossRef](#)]
86. Kohrogi, K.; Hino, S.; Sakamoto, A.; Anan, K.; Takase, R.; Araki, H.; Hino, Y.; Araki, K.; Sato, T.; Nakamura, K.; et al. LSD1 defines erythroleukemia metabolism by controlling the lineage-specific transcription factors GATA1 and C/EBP $\alpha$ . *Blood Adv.* **2021**, *5*, 2305–2318. [[CrossRef](#)]
87. Rivers, A.; Vaitkus, K.; Ibanez, V.; Ruiz, M.A.; Jagadeeswaran, R.; Sauntharajah, Y.; Cui, S.; Engel, J.D.; DeSimone, J.; Lavelle, D. The LSD1 inhibitor RN-1 recapitulates the fetal pattern of hemoglobin synthesis in baboons (*P. anubis*). *Haematologica* **2016**, *101*, 688–697. [[CrossRef](#)]
88. Palandri, F.; Vianelli, N.; Ross, D.M.; Cochrane, T.; Lane, S.W.; Larsen, S.R.; Gerds, A.T.; Halpern, A.B.; Shortt, J.; Rossetti, J.M.; et al. A Phase 2 Study of the LSD1 Inhibitor Img-7289 (bomedemstat) for the Treatment of Essential Thrombocythemia (ET). *Blood* **2021**, *138*, 386. [[CrossRef](#)]
89. Kremyanskaya, M.; Mascarenhas, J.; Palandri, F.; Vannucchi, A.; Verstovsek, S.; Harrison, C.N.; Bose, P.; Schiller, G.J.; Rampal, R.; Drummond, M.W.; et al. Pelabresib (CPI-0610) Monotherapy in Patients with Myelofibrosis—Update of Clinical and Translational Data from the Ongoing Manifest Trial. *Blood* **2021**, *138*, 141. [[CrossRef](#)]
90. Verstovsek, S.; Salama, M.E.; Mascarenhas, J.; Talpaz, M.; Mesa, R.A.; Vannucchi, A.; Rampal, R.; Oh, S.T.; Olteanu, H.; Chiu, A.; et al. Disease-Modifying Potential of BET Inhibitor Pelabresib (CPI-0610) As Demonstrated By Improvements in Bone Marrow Function and Clinical Activity in Patients with Myelofibrosis—Preliminary Data. *Blood* **2021**, *138*, 2568. [[CrossRef](#)]
91. Mascarenhas, J.; Komrokji, R.S.; Palandri, F.; Martino, B.; Niederwieser, D.; Reiter, A.; Scott, B.L.; Baer, M.R.; Hoffman, R.; Odenike, O.; et al. Randomized, Single-Blind, Multicenter Phase II Study of Two Doses of Imetelstat in Relapsed or Refractory Myelofibrosis. *J. Clin. Oncol.* **2021**, *39*, 2881–2892. [[CrossRef](#)]
92. Pemmaraju, N.; Garcia, J.S.; Potluri, J.; Holes, B.L.; Harb, J.; Jung, P.; Hutti, J.E.; Prchal, J.T.; Verstovsek, S.; Harrison, D.C. The Addition of Navitoclax to Ruxolitinib Demonstrates Efficacy within Different High-Risk Populations in Patients with Relapsed/Refractory Myelofibrosis. *Blood* **2020**, *136*, 49–50. [[CrossRef](#)]
93. Vachani, P.; Lange, A.; Delgado, R.G.; Al-Ali, H.K.; Hernández-Rivas, J.M.; Kiladjian, J.-J.; Vannucchi, A.; Perkins, A.C.; Valmeekam, V.; Krejsa, C.M.; et al. Potential Disease-Modifying Activity of Navtemadlin (KRT-232), a First-in-Class MDM2 Inhibitor, Correlates with Clinical Benefits in Relapsed/Refractory Myelofibrosis (MF). *Blood* **2021**, *138*, 3581. [[CrossRef](#)]
94. Masarova, L.; Verstovsek, S.; Hidalgo-Lopez, J.E.; Pemmaraju, N.; Bose, P.; Estrov, Z.; Jabbour, E.J.; Ravandi-Kashani, F.; Takahashi, K.; Cortes, J.; et al. A phase 2 study of ruxolitinib in combination with azacitidine in patients with myelofibrosis. *Blood* **2018**, *132*, 1664–1674. [[CrossRef](#)] [[PubMed](#)]