HHS Public Access

Author manuscript

Expert Opin Investig Drugs. Author manuscript; available in PMC 2022 March 04.

Published in final edited form as:

Expert Opin Investig Drugs. 2020 August ; 29(8): 809–817. doi:10.1080/13543784.2020.1782886.

Novel agents for the treatment of polycythemia vera: an insight into preclinical research and early phase clinical trials

Leslie Padrnos[a], **Ruben Mesa**[b]

[a]Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix, Arizona, USA;

[b]Department of Hematology and Oncology, UT Health Science Center San Antonio MD Anderson Cancer Center, San Antonio, Texas, USA

Abstract

Introduction: Current treatment for polycythemia vera (PV) is limited and primarily targets thrombosis risk. Agents targeting distinct mechanisms of action within myeloproliferation are undergoing clinical evaluation to optimize efficacy, improve tolerance and augment long term disease complications.

Area covered: This article reviews the current data from completed early phase clinical trials in PV, either as monotherapy or in combination with the few currently approved agents.

Expert opinion: There remains an opportunity in PV management to improve efficacy and decrease risk of disease progression. Evolving data from use of long acting interferons are serving to clarifying the potential front line role of this therapy. JAK2 inhibition has made a significant impact on decreasing morbidity in patients with hydroxyurea resistant/refractory disease. New approaches may soon expand options including histone deactylase inhibitors (HDACi), either as monotherapy or combination therapy, which showed promising activity and symptomatic control of pruritus. Drugs targeting new molecular pathways (mammalian target of rapamycin, insulin receptor substrates 1/2, MDM2 protein) or the iron metabolism pathway are in early phase trial. Further translational studies assessing efficacy, long term complications, survival, and constitutional symptom control could pave a way for future success in PV drug development either as monotherapy or in combination.

Keywords

Polycythemia Vera; Myeloproliferative Neoplasm; Erythrocytosis; Hematologic Malignancy

1. Introduction

1.1. Background

Philadelphia-chromosome negative myeloproliferative neoplasms (MPN) are a group of neoplasms defined by hyperproliferative marrow resulting in thrombocytosis (Essential thrombocythemia [ET]), erythrocytosis (Polycythemia Vera [PV]), or marrow fibrosis and

✉**CONTACT** Leslie Padrnos Padrnos.leslie@mayo.edu Division of Hematology and Medical Oncology, Mayo Clinic, Phoenix Arizona 85054.

cytopenias (Myelofibrosis [MF]). In addition to these hematologic findings, patients with MPNs are at risk for systemic symptoms ([1]), arterial and venous thrombosis ([2]) and bone marrow progression to acute leukemia or secondary myelofibrosis. Myeloproliferative neoplasms are associated with mutually exclusive molecular mutations, with the most common mutation in the janus kinase 2 tyrosine kinase receptor, JAK2V617 F ([3]), and other mutations including MPL and CALR ([4]). While CALR and MPL mutations are present in a minority of ET and MF patients, the JAK2V617 F in exon 14 mutation is the most common mutation in MPNs and is present in 97% of patients with PV ([5]). The remaining PV patients having lesser known JAK2 mutations ([6]). The lesser common JAK2 exon 12 mutation in PV is associated with a distinct phenotype of younger age at diagnosis and laboratory findings of isolated erythrocytosis with less concurrent leukocytosis or thrombocytosis. The risk of thrombosis complication or bone marrow progression is similar regardless of JAK2 mutation type. ([7])([8]). Incidence of thrombosis in PV ranges from 23%([9])-39%([10]), with one study of 365 PV patients reporting a significant thrombosis history at enrollment, 17% reporting a history of arterial thrombosis and 12% with a history of venous thrombosis([11]). Reported thrombosis risk factors include age, thrombosis history, cardiovascular risk factors including hypertension, and elevated leukocyte count ([10])([12])([13]). The reported relevant elevated WBC count associated with increased risks of thrombosis ranges from $>11 \times 10^9$/L ([12]) to $>15 \times 10^9$/L ([14]). In addition to the physical complications of PV, patients are also high risk for constitutional symptoms with over 60% of patients endorsing symptoms of fatigue, weight loss, and night sweats ([15]) and over 30% having palpable splenomegaly at diagnosis ([16]).

Antiplatelet therapy is initiated in all patients with PV without a contraindication. In individuals without a prior history of thrombosis, antiplatelet therapy in the form of aspirin 81 mg PO daily has been shown to be effective in preventing arterial and venous thromboembolism in PV patients without resulting in a significantly increased risk of bleeding ([17]). The consistently identified thrombosis risk factors of prior history of thrombosis and age ≥60 years are incorporated into risk stratification regarding PV treatment ([13]). In the setting of active thrombosis, therapeutic anticoagulation should be utilized, similar to individuals with thrombosis without myeloproliferative neoplasms. In most cases, double antiplatelet therapy or combination antiplatelet plus anticoagulant therapy are not used concurrently due to the increased risk of bleeding with possible exceptions for PV patients with both arterial and venous thrombosis events or recurrent thrombotic events despite anticoagulation. ([18]).

1.2. Next generation sequencing

In addition to the commonly identified janus kinase mutations in PV, next generation sequencing (NGS) has also provided insight into gene sequence variants and mutations that can impact prognosis. A study investigating the utilization of NGS in PV patients revealed over half (52.6%) demonstrated gene sequence variants in addition to the JAK2 mutation, with 30% of patients having one gene sequence variant and 20% having two. The most common gene sequence variants were IDH2 and KIT. The variants associated with inferior survival included SRSF2, ASXL1 and IDH2, with SRSF2 and IDH2 associated with decreased leukemia free and MF-free survival. ([19]). Currently, the identification of one or

more of these gene sequence variants does not direct therapeutic agent selection, though this may change in the future.

1.3. Risk stratification for pv treatment

Treatment for the most common MPN, Polycythemia Vera, ([20]), is based on risk stratification to mitigate thrombosis risk through hematocrit control (Table 1). Treatment goals for PV include improvement in signs and symptoms of disease including reduction in splenomegaly and constitutional symptom improvement (based on the myeloproliferative neoplasm symptom assessment form total symptom score, MPN-SAF TSS [21]), normal white blood count and hematocrit <45% in the absence of phlebotomy, absence of thrombosis or hemorrhage and bone marrow response though this definition is not well defined ([22]). Patients who are low risk, based on thrombosis risk, defined as age <60 and no prior history of thrombosis, pursue a hematocrit goal <45% through repeat phlebotomy. This goal hematocrit level was identified in a randomized study investigating two hematocrit endpoints, with a more aggressive hematocrit goal <45% compared to >50% associated with decreased cardiovascular death and major thrombosis([11]).

Patients who are high risk, on the other hand, utilize cytoreductive therapy through hydroxyurea or interferon-alpha or peginterferon alpha ([23]). These agents have been shown to reduce thrombosis complications in PV patients ([24–26]). Hydroxyurea has the ease of oral administration but the concern for associated leukemic transformation([27]), though this concern has not born out consistently in the literature ([28]). There is also a concern of lack of response or lost response with hydroxyurea use. Recombinant Interferon-alfa has been a long utilized therapeutic agent in PV, but requires subcutaneous injection administration and is associated with not-insignificant nonhematologic side effects ([29]). The development of pegylated interferon, peginterferon-alfa (PegIFN-alfa) has been shown to increase the rate of molecular response in PV by decreasing JAK2 allele burden compared to hydroxyurea([30]). A recent phase 2 trial evaluated PegIFN-alfa in 50 PV patients and 65 ET patients who were resistant or intolerant to hydroxyurea([31]). While adverse events were not uncommon, there was an overall improvement in MPN related constitutional symptoms and a minority of patients discontinued drug due to adverse events. Interestingly, the JAK2 allele burden was significantly lower in individuals who achieved complete response, compared to those that did not achieve a response. This study demonstrated PegIFN-alfa's ability to provide effective salvage therapy following hydroxyurea resistance or intolerance, and the decreasing JAK2 allele burden suggested therapeutic benefit may be predicted based on a molecular response. Long-term follow up is necessary in this chronic malignancy, to determine if achievable molecular response is associated with decreased risk of bone marrow evolution to leukemia or fibrosis. A monopegylated interferon alfa, Ropeginterferon-alfa (RopegIFN), is a novel interferon formulation with a longer half-life requiring less frequent administration than the other interferon iterations, including weekly regimens or monthly maintenance. RopegIFN, investigated in 254 PV patients randomized against hydroxyurea, was shown to be non-inferior to hydroxyurea with regards to hematologic response but achieved a greater decrease in median JAK2 V617 F mutation allele burden([32]). A continuation of this trial was undertaken with 94 patients continuing on the interferon derivative and 76 patients in the control arm

continuing on hydroxyurea or best available therapy. After an additional 24 months of therapy the RopegIFN group demonstrated higher complete hematologic response (70.5% vs 49.3%) and partial molecular response (69.6% vs 28.6%) compared to the best available therapy([32]) with a comparable proportion of patients experiencing treatment related adverse events. These studies highlight a reinvigorated interest in the optimal front-line therapy for PV as well as a paradigm shift in clinical trial outcomes with a focus on the clinical implications of molecular response.

1.4. Hydroxyurea resistant pv

Intolerance to hydroxyurea is defined as ongoing need for phlebotomy after hydroxyurea dosing at 2grams/day, progressive proliferation of platelet or leukocyte populations, absence of splenomegaly reduction or splenic symptom improvement, neutropenia or thrombocytopenia or development of unacceptable toxicities including leg ulcerations (refer Table 2) ([33]). While treatment for PV is risk stratified by thrombosis risk, this complex condition burdens many aspects of patients' bodies and lives. Ruxolitinib, the JAK2-inhibitor, revolutionized therapy in patients with MF with subsequent interest in applying this therapeutic agent to PV. A phase 3 clinical trial in 222 PV patients with ongoing phlebotomy needs or splenomegaly were randomized to ruxolitinib or best available therapy determined by the treating physician. After 32 weeks, the proportion of patients who achieved hematocrit control and reduction in splenomegaly was significantly higher in the intervention arm (20.9% vs 0.9%). The ruxolitinib group also demonstrated a significantly higher improvement of symptoms as assessed by ≥50% reduction on the MPN-SAF TSS compared to the control arm (49% vs 5%). ([34]). Long term follow-up, reported on 72 patients who continued ruxolitinib therapy and 64 patients in the control group who crossed over to ruxolitinib, at week 80 showed ongoing benefit. This long term follow up demonstrated durable responses, including hematologic and splenomegaly responses, in ruxolitinib therapy. The benefit of JAK inhibition was also seen in patients who crossed over from best available therapy highlighting this agent's ability to be effective across multiple aspects of PV disease burden in those refractory or intolerant to hydroxyurea treatment. ([35]).

Beyond ruxolitinib and interferon based therapy in hydroxyurea resistant PV, busulfan is recommended as second line therapy particularly elderly patients ([23]) based on the ability to achieve hematologic response but with the concern for nonsignificant hematologic toxicity including leukemic transformation ([36]).

Even with the renewed interest in interferon therapy, and approval for Ruxolitinib, there remains a significant therapeutic necessity in patients with PV to avoid undesirable side effects, establish deep and durable response and to alter the course of the disease instead of merely mitigating complications. Development of novel therapies through varied mechanisms of action is underway in PV management providing insight into targets for this complex condition (refer to Table 3).

2. Novel experimental therapies (see table 3)

2.1. Mechanism: targeting genetic transcription

One mechanism of action under investigation is histone deacetylase inhibitors (HDACi), which works to limit transcription of cellular DNA. There are multiple mechanisms of JAK2 directed hyperproliferation in the bone marrow that may be impeded by HDACi. These include JAK2 translocation to the nucleus and phosphorylation of histone H3 ([37]) and JAK2 impairment of arginine methyltransferase PRMT5 thus regulating chromatin modification ([38]). There is evidence for increased HDAC expression in MPNs ([39]) suggesting a potential therapeutic target through inhibition. In vitro investigation of combination therapy of an oral HDACi, givinostat, plus hydroxyurea, in a JAK2 V617F mutated PV cell line revealed synergistic apoptosis ([40]). Another HDACi, vorinostat, proved to inhibit proliferation of JAK2 V617F expressing cells in murine and human PV hematopoietic progenitor cells. This HDACi monotherapy improved blood count and splenomegaly in the PV mouse model ([41])).

In a pilot study, 29 JAK2V617 mutated MPN patients, including 12 patients with PV diagnosis, were treated with HDACi, givinostat. Treatment at 50 mg twice a day was planned for 24 weeks, and 18 patients completed the 24 week treatment regimen. Among the 13 patients with PV or ET, 7 (54%) demonstrated a clinical response based on blood counts or spleen size. In patients with PV, a decrease in the mean JAK2 V617F mutant allele burden was noted at 12 and 24 weeks. No grade 4 toxicities were noted. ([42])

A phase II study investigated combination therapy of givinostat (either 50 mg or 100 mg daily) with hydroxyurea in 44 JAK2 V617F mutated PV patients deemed unresponsive to hydroxyurea monotherapy for at least 3 months. Clinical response by the ELN 2009 criteria was noted in 50–55% at either drug dosage. A symptom specifically monitored was pruritus control, which was achieved in nearly two thirds of patients at either drug dosage. No grade 4 toxicities were noted. Common toxicities included thrombocytopenia, diarrhea, nausea and anemia. ([43])

Another phase II clinical trial evaluated monotherapy HDACi, Vorinostat, in patients with ET or PV. There was a high discontinuation rate from the study due to nonhematologic adverse effects including fatigue, renal impairment, gastrointestinal symptoms and hair loss. Of the 48% of patients who completed the planned 24 weeks of therapy, an intention-to-treat analysis revealed 35% response and resolution of pruritus in the 19% of patients who endorsed this at baseline. ([44]).

Studies of this mechanism suggest that efficacy and safety vary with agent selection. Givinostat studies suggest at least 50% hematologic response and pruritus symptom improvement. There is a concern for toxicity particularly with the high therapy discontinuation rate seen vorinostat monotherapy. Future studies should investigate clinical characteristics or biomarkers that predict rate of response and risk of toxicity of these agents to inform medical decision making with these agents.

2.2. Mechanism: targeting apoptosis

Avoiding apoptosis is one mechanism for malignant cell populations to persist and proliferate. One of the main surveillance proteins facilitating appropriate cellular apoptosis in humans is the TP53 protein. Laboratory data has shown interferon-alfa upregulates TP53 activity in vitro in JAK2V617 F mutant polycythemia vera cell lines ([45]). The protein MDM2 interacts with and degrades TP53 protein, reducing TP53's ability to facilitate apoptosis. Prior studies revealed MDM2 levels are elevated in PV progenitor stem cells, leading to decreased TP53 and decreased cell cycle surveillance and apoptosis ([45]). Through inhibition of MDM2, TP53 persists and its apoptotic effects can lead to clinical benefits in PV. Inhibition of MDM2 can increase apoptosis in patients with PV, through combination therapy with interferon-alfa ([45]) and monotherapy ([46]). A phase 1 clinical trial of an oral MDM2 inhibitor, idasanutlin, in 13 high risk JAK2 V617F mutated PV or ET patients determined to be intolerant or refractory to prior therapy (hydroxyurea, interferon alfa, or anagrelide) were treated with either 100 mg or 150 mg daily, and if no response noted by cycle 6 interferon-alfa was added to idasanutlin for subsequent cycles. No dose-limiting toxicities were noted, with gastrointestinal adverse events particularly during the first few days of each cycle being the most common. Overall response after 6 cycles of therapy was 58% (7/12) in the monotherapy group and 50% (2/4) in the combination therapy. Improvements were noted in blood counts, splenomegaly and systemic symptoms. ([47]). A phase 2 study of patients with phlebotomy dependent PV randomized to MDM2 inhibitor, KRT-232 monotherapy or ruxolitinib is ongoing (https://clinicaltrials.gov/ct2/show/NCT03669965). While encouraging to note response in the intolerant and refractory PV population, the sample size of 13 greatly limits projecting the clinical benefit this agent can provide PV patients. As next generation sequencing has revealed the common finding of gene sequence variants on the bone marrow complications in PV, identifying biomarkers that predict MDM2 efficacy could enrich patient population selection for this emerging therapy.

2.3. Mechanism: targeting iron metabolism pathway

Hepcidin, the main iron metabolism regulator in the body, inhibits the ferroportin receptor. In settings of iron deficiency, hepcidin is suppressed, allowing for increased iron absorption to facilitate red blood cell production (15). Modulating iron metabolism could provide needed benefit to the intricate relationship between chronic hematologic processes and iron stores. In a murine model of beta-thalassemia, a nonmalignant hematologic condition defined by ineffective erythropoeisis and iron overload, increased hepcidin levels proved to improve anemia, red blood cell maturation and splenomegaly([48]). This iron nutrient regulator may prove beneficial in PV. The mechanism of phlebotomy to facilitate hematocrit control is two-fold. First phlebotomy actively decreases a patient's red blood cell mass at the time of intervention but with hyperproliferation this effect is transient. The second effect is through facilitating iron deficiency and limiting further erythropoiesis. A JAK2 V617F mutated murine model was exposed to a minihepcidin-small molecule to facilitate phlebotomy-independent iron restriction and hematocrit control. The subcutaneous biweekly injection of the minihepcidin demonstrated hematocrit control, improved splenomegaly and reduction of erythroid progenitor cell after 3 weeks of therapy. Prolonged exposure resulted in iron deficiency ([49]). A Phase 2 study in patients with PV requiring routine phlebotomy is currently enrolling (https://clinicaltrials.gov/ct2/show/NCT04057040). This agent is in the

early stages of investigation, but future studies will be needed to define and quantify the effect of iron deficiency symptoms and side effects in PV patients. Keeping in mind that while phlebotomy impacts hematocrit and platelet count, it does not control white blood count, thus the impact of thrombosis must be carefully assessed and eventually compared to cytoreductive agents.

2.4. Mechanism: targeting erythroid lineage differentiation

In addition to the JAK/STAT, other cellular signaling pathways are involved in myeloproliferative neoplasms including Phosphoinositide 3-kinase (PI3 K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway ([50]). The PI3 K signaling is involved in erythropoietin-independent differentiation erythroid progenitors in PV ([51]). In vitro studies of JAK2 V617F mutated cell lines, both human and murine, treated with mTOR inhibition demonstrated inhibition of proliferation ([52]). The mTOR monotherapy inhibited proliferation through slowed cell cycling while combination therapy of mTOR and JAK inhibition increased apoptosis. Future clinical trials in humans will be necessary to assess efficacy and safety.

2.5. Mechanism: targeting cytokine

The JAK2-V617 F driver mutation, present in the great majority of PV patients, can increase sensitivity or independence of cytokines in PV cells leading to proliferation ([53]). Two receptors that interact with JAK2 mutated cells in the myeloproliferative phenotype are the insulin receptor substrates (IRS) 1 and 2 ([54]). In vitro investigation of a small molecule inhibitor, NT157, has been shown to inhibit expression of IRS1/2 receptors and inhibit phosphorylation JAK2 and STAT3/5. Additionally, NT157 has been shown to inhibit erythropoietin-independent colony formation in PV and specifically inhibit IRS1/2 and STAT3/5 in JAK2 mutated cells with decreased proliferation and cell survivability. In combination with ruxolitinib, NT157 demonstrated no increase in apoptosis compared to monotherapy of ruxolitinib. ([55]). Future clinical trials in humans will be necessary to assess efficacy and safety.

3. Post-polycythemia vera

3.1. Antifibrotic agents

Complications of PV include transformation to distinct bone marrow malignancies including acute leukemia or myelofibrosis. Transformation to acute leukemia can occur in 4–5.4% of PV patients within 10 years. ([56])([19]). Myelofibrotic transformation is a rare but significant complication of polycythemia vera, termed post-polycythemia myelofibrosis (post-PV MF) associated with progressive splenomegaly, variable cytopenias, and decreased survival ([57]). The pathogenesis of this progressive marrow fibrosis is not entirely understood and is likely multifactorial including circulating proinflammatory cytokines and cellular interactions within the bone marrow environment including the osteoblastic cell lineage leading to hematopoietic stem cell dysregulation ([57]). The 15 year risk of developing this marrow event is 6% ([58]). While discussion of current and all emerging therapies in MF ([59])([60]) is beyond the scope of this article, the emerging data regarding antifibrotic agents will be discussed here. It is important to note that while these may

be relevant to PV patients these have only been studied in patients with MF. One agent that has been shown to decrease bone marrow fibrosis severity in patients with MF is PRM-151, a recombinant human pentraxin-2 protein that induces macrophage differentiation to either prevent of reverse fibrosis ([61]). In the phase 2 clinical trial of 27 MF patients, intravenous PRM-151 therapy alone or in combination with ruxolitinib was well tolerated with 6 individuals found to have decreased marrow fibrosis severity on repeat biopsy. It has also been shown to be beneficial in other fibrosing conditions including idiopathic pulmonary fibrosis ([62]).

4. Conclusion

Hydroxyurea or pegylated interferon in combination with low dose antiplatelet remains the cornerstone of front-line therapy for patients with PV. These agents pose a risk of resistance in nearly 25% patients or significant adverse events. Thus, there remains an unmet clinical need in patients with PV for safer and more effective agents that not only improve hematologic laboratory results and reduce the risk of thrombosis, but also mitigate the other complications of PV including bone marrow progression to fibrosis or leukemia and constitutional symptom mitigation. Research has identified a number of active targets ranging from transcription inhibition to iron metabolism, reflecting the complexity and variety of disease complications facing PV patients. Additional, larger studies are needed to better define efficacy and side effects and ideal patient characteristics for agent selection as the therapeutic armamentarium for PV expands.

5. Expert opinion

Treatment for polycythemia vera, the most common myeloproliferative neoplasm, has been predominantly focused on thrombosis risk reduction with few randomized controlled trials informing medical decision making. In fact, the ideal front-line cytoreductive therapy is currently undergoing investigation between oral hydroxyurea therapy vs interferon-alfa. As PV is a chronic, incurable malignancy in most patients, long-term follow up to assess the therapeutic impact on morbidity, mortality and bone marrow complications based on molecular response will take time. This is an important paradigm shift in PV, suggesting that science is poised to better answer the short- and long-term consequences of this disease by expanding response criteria and outcomes assessed in clinical trials. Since the identification of the JAK2 V617 F mutation associated with myeloproliferative neoplasms [3]), particularly the high prevalence in PV patients, investigation on the impact of JAK inhibitors and alternative mechanisms of action in this disease are being sought both in the laboratory and at the bedside. JAK inhibitors are continuing to be developed and assessed in myeloproliferative neoplasms, particularly in myelofibrosis and future generations may prove increasingly beneficial to PV patients in the post-hydroxyurea setting. As two of the most active therapeutic agents in this space, combination therapy of PegINF-alfa and ruxolitinib studies are also underway, with the goal of combining the benefits of both. One phase 2 study, assessing ruxolitinib in combination with pegIFN-alfa, enrolled 32 PV and 18 MF patients, reported preliminary results at 12 months([63]). In the PV patient population, no patient achieved a complete response, 9% achieved a partial response and 44% a complete hematologic response. The JAK2 allele burden did decrease from a median

of 47% to 23% at 12 months. Six patients (18%) discontinued therapy due to treatment related adverse events with hematologic toxicity being the most common. The authors surmised that synergistic effect between the two agents may have increased treatment related toxicity and may also increase the durability of molecular response. Future combination studies – likely at lower drug doses – should be pursued. The field is innovating within established therapeutics to organize and optimize PV management. In addition to continuing to aggressively investigate approved agents, the field is also evaluating new mechanisms and targets to augment treatment outcomes and provide options for patients.

Most of the novel interventions described above currently under development in early stages can be categorized by 3 cell cycle mechanisms:

1. Modulation of genetic transcription
2. Modulation of erythroid cell lineage proliferation
3. Modulation of apoptosis

The major limitation at this time is the significantly early stage of most of these studies, with iron metabolism, cytokine regulation and erythroid cell lineage regulation occurring in murine models alone. Further studies are necessary to define and describe the efficacy, toxicity and tolerance of these agents in PV patients. Following further, larger studies quantifying these clinical outcomes, additional questions of timing, combination and long-term consequences will need to be answered to inform medical decision making between patients and treating physicians.

In our view, modulation of apoptosis through MDM2 is one of the most promising therapies undergoing investigation in PV. This mechanism of action, unleashing cell regulated apoptosis through the MDM2 interaction with TP53, typically downregulated in malignancy, is being investigated in other cancers. ([64])([65])([66]. The early phase success of this target in PV with multiple endpoints ranging from hematologic to constitutional symptom response suggests the ability to meaningfully impact this complex disease. Due to the complicated physiological burdens of PV, a therapy with a single dimension of benefit, would likely either be inadequate, or require combination therapy to address the multiple aspects of the condition. Additionally, for a disease that imparts a high constitutional burden at baseline, a reportedly well tolerated agent is an important consideration. Due to the non-insignificant occurrence of next generation sequencing gene variants in PV, there is a possibility that biomarkers may identify patients with the highest likelihood for MDM2 benefit. As JAK2 allele burden is being utilized more often as a reported clinical outcome in PV studies, the association of NGS variants on outcomes should be increasingly included and reported.

The other promising therapy, particularly in low risk patients, is through augmentation of the iron metabolism pathway through the pharmacologically derived iron deficiency restrictive erythropoiesis through a mini-hepcidin. This could provide ideal hematocrit control without the need for phlebotomy particularly for those patients fearful of the procedure, or for whom the repeat procedural necessity demands a significant time commitment. Lack of human clinical trials limits the ability to discuss key findings at this time. Major issues this agent

must answer in future studies include the duration of treatment necessary to effectively reduce and control hematocrit compared to traditional phlebotomy. Additionally, long term thrombosis risk will need to be assessed and compared to traditional phlebotomy, as the thrombogenesis in myeloproliferative neoplasms is not attributable to hematocrit alone.

As described above, future research and medical decision making in PV, will need to include predictive biomarkers for the various disease complications including thrombosis, constitutional symptoms and bone marrow evolution. This article highlights emerging novel therapeutics, and soon, PV patients and treating physicians will have more options for therapy selection requiring enhanced and nuanced medical decision making. Future treatment algorithms should be reflective of active disease burden. This may mean that those with venous thrombosis are best treated with one pharmacological therapy compared to those with arterial events. Certain systemic symptoms may be mitigated more effectively by one therapeutic agent compared to another, and understanding this agent specific efficacy would facilitate true individualization of therapy.

In addition to these pharmacological investigations, further understanding regarding improved risk stratification not just for thrombosis but for bone marrow progression is needed to better inform health care decision making and treatment selection. Additionally, further risk stratification or biomarkers to individualize therapeutic choices, improve response rates and minimizing adverse events are necessary as many of these patients receive treatment over several years posing a risk of treatment related adverse events in addition to the physiologic complications of this chronic malignancy. Future therapies in PV should be expected to alleviate the complex symptoms, physiologic risks and bone marrow progression to improve quality and length of life.

Funding

This paper was not funded.

Declaration of interest

R Mesa is a Consultant for Novartis, Sierra Onc, La Jolla Pharma and has received research Support from Celgene, Incyte, Abbvie, Samus, Genetech, Promedior/CTI. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

One referee received Consultancy fees from Incyte Corporation, Daiichi Sankyo, Trovagene, Ariad, Amgen, Pfizer, Cardinal Health, BMS/Celgene, Merck, Astellas, Premier, and Agios. He/she also receives research funding from Incyte Corporation, Amgen, Forma Therapeutics, Janssen, Genentech, and Novartis. Peer reviewers on this manuscript have no other relevant financial or other relationships to disclose

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients.

Cancer. 2007 Jan 1;109(1):68–76. [PubMed: 17123268] • Highlights the burden of the common constitutional symptom of fatigue in patients with myeloproliferative neoplasms.

2. Barbui T, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. Blood. 2013 Sep 26;122(13):2176–2184. [PubMed: 23823316]
3. Baxter EJ, Scott LM, Campbell PJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet. 2005 Mar 19–25;365(9464):1054–1061. [PubMed: 15781101]
4. Pietra D, Li S, Brisci A, et al. Somatic mutations of JAK2 exon 12 in patients with JAK2 (V617F)-negative myeloproliferative disorders. Blood. 2008 Feb 1;111(3):1686–1689. [PubMed: 17984312]
5. Tefferi A. Somatic JAK2 mutations and their tumor phenotypes. Blood. 2016 Aug 11;128(6):748–749. [PubMed: 27516428]
6. Alghasham N, Alnouri Y, Abalkhail H, et al. Detection of mutations in JAK2 exons 12–15 by Sanger sequencing. Int J Lab Hematol. 2016 Feb;38(1):34–41. [PubMed: 26361084]
7. Passamonti F, Elena C, Schnittger S, et al. Molecular and clinical features of the myeloproliferative neoplasm associated with JAK2 exon 12 mutations. Blood. 2011 Mar 10;117(10):2813–2816. [PubMed: 21224469]
8. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med. 2007 Feb 1;356(5):459–468. [PubMed: 17267906]
9. Barbui T, Carobbio A, Rumi E, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood. 2014 Nov 6;124(19):3021–3023. [PubMed: 25377561] •• Describes expectations of thrombosis experience and risk factors in the modern era.
10. Finazzi G. low-dose aspirin in p. A prospective analysis of thrombotic events in the European collaboration study on low-dose aspirin in polycythemia (ECLAP). Pathol Biol. 2004 Jun;52 (5):285–288. [PubMed: 15217715]
11. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013 Jan 3;368(1):22–33. [PubMed: 23216616]
12. Barbui T, Masciulli A, Marfisi MR, et al. White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study. Blood. 2015 Jul 23;126(4):560–561. [PubMed: 26206947]
13. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol. 2005 Apr 1;23(10):2224–2232. [PubMed: 15710945]
14. Landolfi R, Di Gennaro L, Barbui T, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood. 2007 Mar 15;109(6):2446–2452. [PubMed: 17105814] • Illustrates the efficacy and safety of aspirin antiplatelet therapy being utilized in PV patients.
15. Mesa R, Boccia RV, Grunwald MR, et al. Patient-reported outcomes data from reveal at the time of enrollment (baseline): a prospective observational study of patients with polycythemia vera in the United States. Clin Lymphoma Myeloma Leuk. 2018 Sep;18 (9):590–596. [PubMed: 30122202]
16. Tefferi A, Rumi E, Finazzi G, et al. Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study. Leukemia. 2013 Sep;27(9):1874–1881. [PubMed: 23739289]
17. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004 Jan 8;350 (2):114–124. [PubMed: 14711910]
18. Arachchillage DR, Laffan M. Pathogenesis and management of thrombotic disease in myeloproliferative neoplasms. Semin Thromb Hemost. 2019 Sep;45(6):604–611. [PubMed: 31382304] • Detailed discussion on pathogenesis and management of myeloproliferative neoplasm thrombosis
19. Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv. 2016 Nov 29;1(1):21–30. [PubMed: 29296692]
20. Mehta J, Wang H, Iqbal SU, et al. Epidemiology of myeloproliferative neoplasms in the United States. Leuk Lymphoma. 2014 Mar;55 (3):595–600. [PubMed: 23768070]
21. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol. 2012 Nov

20;30(33):4098–4103. [PubMed: 23071245] •• Characterizes and quantifies the constitutional symptom burden that can be utilized to assess response to therapy or progression.

22. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood. 2013 Jun 6;121(23):4778–4781. [PubMed: 23591792]
23. Network NCC. Myeloproliferative Neoplasms (Version 1.2020–5.2020) 2020 [cited 2020 Apr 27]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf
24. Kaplan ME, Mack K, Goldberg JD, et al. Long-term management of polycythemia vera with hydroxyurea: a progress report. Semin Hematol. 1986 Jul;23(3):167–171.
25. Radin AI, Kim HT, Grant BW, et al. Phase II study of alpha2 interferon in the treatment of the chronic myeloproliferative disorders (E5487): a trial of the eastern cooperative oncology group. Cancer. 2003 Jul 1;98(1):100–109. [PubMed: 12833462]
26. Samuelsson J, Hasselbalch H, Bruserud O, et al. A phase II trial of pegylated interferon alpha-2b therapy for polycythemia vera and essential thrombocythemia: feasibility, clinical and biologic effects, and impact on quality of life. Cancer. 2006 Jun 1;106 (11):2397–2405. [PubMed: 16639737]
27. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: a polycythemia vera study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol. 1997 Jan;34(1):17–23. [PubMed: 9025158]
28. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. Blood. 2005 Apr 1;105(7):2664–2670. 10.1182/blood-2004-09-3426. [PubMed: 15585653]
29. Silver RT. Interferon-alpha 2b: a new treatment for polycythemia vera. Ann Intern Med. 1993 Dec 1;119(11):1091–1092. [PubMed: 8239228]
30. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood. 2008 Oct 15;112(8):3065–3072. [PubMed: 18650451] •• Highlights the molecular response of decreasing JAK2 allele burden possible through interferon-based therapy.
31. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019 Oct 31;134 (18):1498–1509. [PubMed: 31515250]
32. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020 Mar;7(3):e196–e208. [PubMed: 32014125]
33. Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011 Feb 20;29(6):761–770. [PubMed: 21205761]
34. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015 Jan 29;372(5):426–435. [PubMed: 25629741]
35. Kiladjian JJ, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study. Lancet Haematol. 2020 Mar;7(3):e226–e237. [PubMed: 31982039]
36. Alvarez-Larran A, Martinez-Aviles L, Hernandez-Boluda JC, et al. Busulfan in patients with polycythemia vera or essential thrombocythemia refractory or intolerant to hydroxyurea. Ann Hematol. 2014 Dec;93(12):2037–2043. [PubMed: 24981691]
37. Dawson MA, Bannister AJ, Gottgens B, et al. JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin. Nature. 2009 Oct 8;461(7265):819–822. [PubMed: 19783980]
38. Liu F, Zhao X, Perna F, et al. JAK2V617F-mediated phosphorylation of PRMT5 downregulates its methyltransferase activity and promotes myeloproliferation. Cancer Cell. 2011 Feb 15;19(2):283–294. [PubMed: 21316606]
39. Wang JC, Chen C, Dumlao T, et al. Enhanced histone deacetylase enzyme activity in primary myelofibrosis. Leuk Lymphoma. 2008 Dec;49(12):2321–2327. [PubMed: 19052980]

40. Amaru Calzada A, Pedrini O, Finazzi G, et al. Givinostat and hydroxyurea synergize in vitro to induce apoptosis of cells from JAK2 (V617F) myeloproliferative neoplasm patients. Exp Hematol. 2013 Mar;41(3):253–60 e2. [PubMed: 23111067]
41. Akada H, Akada S, Gajra A, et al. Efficacy of vorinostat in a murine model of polycythemia vera. Blood. 2012 Apr 19;119 (16):3779–3789. [PubMed: 22408262]
42. Rambaldi A, Dellacasa CM, Finazzi G, et al. A pilot study of the Histone-Deacetylase inhibitor Givinostat in patients with JAK2V617F positive chronic myeloproliferative neoplasms. Br J Haematol. 2010 Aug;150(4):446–455. [PubMed: 20560970]
43. Finazzi G, Vannucchi AM, Martinelli V, et al. A phase II study of Givinostat in combination with hydroxycarbamide in patients with polycythaemia vera unresponsive to hydroxycarbamide monotherapy. Br J Haematol. 2013 Jun;161(5):688–694. [PubMed: 23573950]
44. Andersen CL, McMullin MF, Ejerblad E, et al. A phase II study of vorinostat (MK-0683) in patients with polycythaemia vera and essential thrombocythaemia. Br J Haematol. 2013 Aug;162 (4):498–508. [PubMed: 23758082]
45. Lu M, Wang X, Li Y, et al. Combination treatment in vitro with Nutlin, a small-molecule antagonist of MDM2, and pegylated interferon-alpha 2a specifically targets JAK2V617F-positive polycythemia vera cells. Blood. 2012 Oct 11;120(15):3098–3105. [PubMed: 22872685]
46. Lu M, Xia L, Li Y, et al. The orally bioavailable MDM2 antagonist RG7112 and pegylated interferon alpha 2a target JAK2V617F-positive progenitor and stem cells. Blood. 2014 Jul 31;124(5):771–779. [PubMed: 24869939]
47. Mascarenhas J, Lu M, Kosiorek H, et al. Oral idasanutlin in patients with polycythemia vera. Blood. 2019 Aug 8;134(6):525–533. [PubMed: 31167802]
48. Guo S, Casu C, Gardenghi S, et al. Reducing TMPRSS6 ameliorates hemochromatosis and beta-thalassemia in mice. J Clin Invest. 2013 Apr;123(4):1531–1541. [PubMed: 23524968]
49. Casu C, Oikonomidou PR, Chen H, et al. Minihepcidin peptides as disease modifiers in mice affected by beta-thalassemia and polycythemia vera. Blood. 2016 Jul 14;128(2):265–276. [PubMed: 27154187]
50. Bartalucci N, Guglielmelli P, Vannucchi AM. Rationale for targeting the PI3K/Akt/mTOR pathway in myeloproliferative neoplasms. Clin Lymphoma Myeloma Leuk. 2013 Sep;13(Suppl 2):S307–9. [PubMed: 24290217]
51. Ugo V, Marzac C, Teyssandier I, et al. Multiple signaling pathways are involved in erythropoietin-independent differentiation of erythroid progenitors in polycythemia vera. Exp Hematol. 2004 Feb;32 (2):179–187. [PubMed: 15102479]
52. Bogani C, Bartalucci N, Martinelli S, et al. mTOR inhibitors alone and in combination with JAK2 inhibitors effectively inhibit cells of myeloproliferative neoplasms. PLoS One. 2013;8(1):e54826. [PubMed: 23382981]
53. Delhommeau F, Pisani DF, James C, et al. Oncogenic mechanisms in myeloproliferative disorders. Cell Mol Life Sci. 2006 Dec;63 (24):2939–2953. [PubMed: 17131059]
54. de Melo Campos P, Machado-Neto JA, Eide CA, et al. IRS2 silencing increases apoptosis and potentiates the effects of ruxolitinib in JAK2V617F-positive myeloproliferative neoplasms. Oncotarget. 2016 Feb 9;7(6):6948–6959. [PubMed: 26755644]
55. Fenerich BA, Fernandes JC, Rodrigues Alves APN, et al. NT157 has antineoplastic effects and inhibits IRS1/2 and STAT3/5 in JAK2 (V617F)-positive myeloproliferative neoplasm cells. Signal Transduct Target Ther. 2020;5(1):5. [PubMed: 32296029]
56. Cervantes F, Tassies D, Salgado C, et al. Acute transformation in nonleukemic chronic myeloproliferative disorders: actuarial probability and main characteristics in a series of 218 patients. Acta Haematol. 1991;85(3):124–127. [PubMed: 2042444]
57. Zahr AA, Salama ME, Carreau N, et al. Bone marrow fibrosis in myelofibrosis: pathogenesis, prognosis and targeted strategies. Haematologica. 2016 Jun;101(6):660–671. [PubMed: 27252511]
58. Passamonti F, Rumi E, Pungolino E, et al. Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med. 2004 Nov 15;117 (10):755–761. [PubMed: 15541325]
59. Bose P, Verstovsek S. Developmental therapeutics in myeloproliferative neoplasms. Clin Lymphoma Myeloma Leuk. 2017 Jul;17S: S43–S52. [PubMed: 28760302]

60. Patel AB, Vellore NA, Deininger MW. New strategies in myeloproliferative neoplasms: the evolving genetic and therapeutic landscape. Clin Cancer Res. 2016 Mar 1;22(5):1037–1047. [PubMed: 26933174]

61. Srdan Verstovsek RM, Lynda F, Gupta V, et al. Phase 2 Trial of PRM-151, an antifibrotic agent, in patients with myelofibrosis: stage 1 results. Abstract 634. Blood. 2014;124(21):713.

62. Raghu G, van den Blink B, Hamblin MJ, et al. Long-term treatment with recombinant human pentraxin 2 protein in patients with idiopathic pulmonary fibrosis: an open-label extension study. Lancet Respir Med. 2019 Aug;7(8):657–664. [PubMed: 31122893]

63. Mikkelsen SU, Kjaer L, Bjorn ME, et al. Safety and efficacy of combination therapy of interferon-alpha2 and ruxolitinib in polycythemia vera and myelofibrosis. Cancer Med. 2018 Aug;7 (8):3571–3581. [PubMed: 29932310]

64. Qi SM, Cheng G, XD C, et al. Targeting USP7-mediated deubiquitination of MDM2/MDMX-p53 pathway for cancer therapy: are we there yet? Front Cell Dev Biol. 2020;8:233. [PubMed: 32300595]

65. Das S. MDM2 inhibition in a subset of sarcoma cell lines increases susceptibility to radiation therapy by inducing senescence in the polyploid cells. Adv Radiat Oncol. 2020 Mar-Apr;5(2):250–259. [PubMed: 32280825]

66. Sha MX, Huang XW, Yin Q. MiR-548b-3p inhibits proliferation and migration of breast cancer cells by targeting MDM2. Eur Rev Med Pharmacol Sci. 2020 Mar;24(6):3105–3112. [PubMed: 32271428]

Article highlights

- Current management of polycythemia vera (PV) is primarily focused on thrombosis risk reduction.
- Other considerations of PV therapy must consider constitutional symptom and bone marrow progression mitigation to acute leukemia or myelofibrosis.
- Active investigation into ideal front line therapy of interferon-based agents and their impact of decreasing janus kinase 2 allele burden will inform initial therapeutic decision making for patients and physicians.
- Combination therapy of current accessible and investigational agents may prove synergistic to improve and expand clinical outcomes.
- Early phase PV trials provide opportunities through new mechanisms of action to increase therapeutic options for second and third line.

This box summarizes key points contained in the article.

Table 1.

Current standard of polycythemia vera management.

Risk Category	Patient Characteristics	Treatment	Monitor
Low Risk	Age <60 years old And No prior thrombosis	• Aspirin 81 mg daily • Phlebotomy to maintain hematocrit <45% • Manage cardiovascular risk factors	• Thrombosis or hemorrhage • Constitutional symptoms • Disease progression
High Risk	Age ≥60 years old And/Or Prior thrombosis	• Aspirin 81 mg daily • Cytoreductive therapy with hydroxyurea or interferon • Manage cardiovascular risk factors	• Thrombosis or hemorrhage • Constitutional symptoms • Adverse events from therapy • Disease progression
High Risk with progressive symptoms on initial cytoreductive therapy	Intolerance to prior cytoreductive therapy due to adverse effects New thrombosis or hemorrhage Frequent need for phlebotomy in addition to cytoreductive therapy Unresponsive or progressive splenomegaly Leukocytosis Systemic symptoms	• Ruxolitinib • Hydroxyurea if not previously utilized • Interferon (interferon alpha, peginterferon alfa, ropeginterferon alfa • Clinical trial	• Thrombosis or hemorrhage • Constitutional symptoms • Adverse events from therapy • Disease progression

Expert Opin Investig Drugs. Author manuscript; available in PMC 2022 March 04.

Table 2.

Hydroxyurea resistance or intolerance in polycythemia vera.

Definition of Resistance/Intolerance to Hydroxyurea Requires only 1 of the following:	
Ongoing phlebotomy	Need for ongoing phlebotomy to maintain HCT<45% after 3 months of at least 2 grams/day of hydroxyurea
Myeloproliferation	Uncontrolled myeloproliferation defined as both platelet count >400 × 10^9/L and white blood count >10 × 10^9/L) after 3 months of at least 2 grams/day of hydroxyurea
Splenomegaly	Failure to reduce significant splenomegaly by >50% via physical exam or failure to completely resolve splenomegaly symptoms after 3 months of at least 2 grams/day of hydroxyurea
Cytopenias	Absolute neutrophil count <1.0 × 10^9/L; or Platelet count <100 × 10^9/L; or Hemoglobin <10 g/dL Occurring at the lowest dose of hydroxyurea necessary to achieve a clinicohematologic response
Nonhematologic Adverse Events	Including leg ulcerations, mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever Occuring at any dose of hydroxyurea

Table 3.

Novel polycythemia vera therapies under investigation.

Level of Study	Author	Target	Mechanism of Action	Active Clinical Trials for each mechanism (ClinicalTrials.gov)
Phase 2 Ongoing		Iron Metabolism Pathway	Hepcidin mimetic	NCT04057040 Recruiting
		Apoptosis	MDM2 inhibitor	NCT03669965 Recruiting
Phase 1 Ongoing		Erythroid Lineage Differentiation	Phosphoinositide 3-kinase (PI3 K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway	NCT02493530 Active, Not Recruiting
Phase 2	Finazzi, G. et al. [43] Anderson, C. et al. [44]	Genetic transcription Genetic transcription	Histone deacetylase inhibitor, 3in combination with hydroxyurea Monotherapy Histone deacetylase inhibitor,	
Phase 1	Rambaldi, A. et al. [42] Mascarenhas, J. et al. [47]	Genetic transcription Apoptosis	Monotherapy Histone deacetylase inhibitor, MDM2 inhibitor	
Animal Study	Casu, C. et al [49].	Iron Metabolism Pathway	Minihepcidin-small molecule	
In-vitro	Amaru Calzada, A. et al [40]. Akada, H. et al. [41] Bogani, C. et al. [52] Fenerich, B. et al [55].	Genetic transcription Genetic transcription Erythroid Lineage Differentiation Erythroid lineage proliferation through cytokines	Histone deacetylase inhibitor,, in combination with hydroxyurea Monotherapy Histone deacetylase inhibitor, Phosphoinositide 3-kinase (PI3 K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway Insulin receptor substrate 1/2 small molecule inhibitor	

Expert Opin Investig Drugs. Author manuscript; available in PMC 2022 March 04.