Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2017-B-139 Ropeginterferon alfa-2b

Stand: August 2017

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Ropeginterferon alfa-2b [zur Behandlung der Polycythaemia vera]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	siehe Übersicht II: Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Allogene Stammzelltransplantation (für ausgewählte Patienten) - Phlebotomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie (AM-RL): - Ruxolitinib (neues Anwendungsgebiet) (Anlage XII – Nutzenbewertung nach §35a SGB V, Beschluss vom 15. Oktober 2015)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ropeginterferon alfa-2b *ATC-Code* BESREMi®	Geplantes Anwendungsgebiet laut Beratungsanforderung/Zulassungsantrag: Besremi ist indiziert bei erwachsenen Patienten zur Behandlung der Polycythaemia vera ohne symptomatische Milzvergrößerung.
Hydroxycarbamid L01XX05 z.B. Litalir®	Behandlung von Patienten mit essentieller Thrombozythämie oder Polycythämia vera mit hohem Risiko für thromboembolische Komplikationen. (FI Litalir®, Stand: Juli 2015)
Ruxolitinib L01XE18 Jakavi®	Jakavi ist angezeigt für die Behandlung von Erwachsenen mit Polycythaemia vera, die resistent oder intolerant gegenüber Hydroxycarbamid sind. (FI Ruxolitinib®, Stand: April 2017)

Quellen: AMIS-Datenbank, Fachinformationen

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation Polycythaemia vera durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.07.2017 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 92 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 5 Quellen, die in die synoptische Evidenzübersicht aufgenommen wurden.

Indikation:

- indiziert bei erwachsenen Patientinnen und Patienten zur Behandlung der Polycythaemia vera ohne symptomatische Milzvergrößerung

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
bid	zweimal täglich
BSC	best supportive care
CCO	Cancer Care Ontario
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
DVT	tiefe Venenthrombose
ECOG PS	Eastern Cooperative Oncology Group performance status (Index zur Lebensqualität)
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HCT	Hämatokrit
HRQoL	Gesundheitsbezogene Lebensqualität
HU	Hydroxyurea oder Hydroxycarbamid
ICTRP	International Clinical Trials Registry Platform
INF	Interferon
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NCI	***National Cancer Institute***
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
PV	Polycythaemia vera
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

Gemeinsamer Bundesausschuss (G-BA), 2015 [1]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Ruxolitinib. (neues Anwendungsgebiet) vom 15. Oktober 2015	**Zugelassenes Anwendungsgebiet (laut Zulassung vom 11. März 2015):** Jakavi® ist angezeigt für die Behandlung von Erwachsenen mit Polycythaemia vera, die resistent oder intolerant gegenüber Hydroxycarbamid sind. **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** *Zweckmäßige Vergleichstherapie:* Die zweckmäßige Vergleichstherapie für Patienten mit Polycythaemia vera, die resistent oder intolerant gegenüber einer Therapie mit Hydroxyurea sind, ist: - Eine patientenindividuelle Therapie nach Maßgabe des Arztes, grundsätzlich unter Berücksichtigung des Zulassungsstatus bei Arzneimitteltherapien; gegebenenfalls kommt auch eine Dosisreduktion von oder Retherapie mit Hydroxyurea in Frage. *Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:* Anhaltspunkt für einen beträchtlichen Zusatznutzen.

Cochrane Reviews

Zur Fragestellung konnten keine relevanten Cochrane Reviews identifiziert werden.

Systematische Reviews

pan-Canadian Oncology Drug Review (pCODR), 2016 [4]. pCODR Final Clinical Guidance Report - Ruxolitinib (Jakavi) for polycythemia vera	1. Fragestellung To evaluate the efficacy and safety of ruxolitinib (Jakavi) compared with standard therapy in adult patients with polycythemia vera (PV) who are resistant or intolerant to hydroxyurea (HU). • What type and degree of resistance and intolerance to HU would be considered in order to support a switch in treatment to ruxolitinib? Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group (PAG) were identified while developing the review protocol and are outlined in section 7.
	2. Methodik Population: Adult patients (≥ 18 years) with original diagnosis of PV and resistance or intolerance to HU (excludes patients who have transformed to myelofibrosis) Intervention: Ruxolitinib 10 mg bid (starting dose) to a maximum of 25 mg bid (minimum of 5 mg daily) Komparator: • Standard therapy can include the following: o Cytoreductive agents: ▪ HU (at a tolerated dose likely to provide benefit) ▪ Interferon ▪ Anagrelide ▪ Immunomodulators (e.g., lenalidomide, thalidomide), ▪ Busulfan ▪ Pipobroman ▪ Chlorambucil ▪ Phosphorus-32 o Aspirin o BSC (e.g., phlebotomy as needed, medications for symptom control) Endpunkt: Response rate, HCT control/frequency of phlebotomy, Spleen volume reduction, Hematologic response/remission, Proportion of patients achieving durable response, Control of symptoms (e.g., pruritus, systemic symptoms, sweats, weight-loss), Adverse events including thrombotic events and flare (of spleen size and blood counts upon drug withdrawal or interruption), HRQoL Suchzeitraum: August/September 2015 Anzahl eingeschlossene Studien/Patienten (Gesamt):

Qualitätsbewertung der Studien: SIGN-50 Checklists applied as a minimum standard

- Ergebnisdarstellung

Studieneigenschaften

- one ongoing, open-label randomized phase III study (RESPONSE) included
- examining the use of ruxolitinib (n=110) versus standard therapy (n=112) in patients with PV who had an inadequate response to or had unacceptable side effects from HU

Vannucchi AM, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-35.

- definitions of HU resistance and intolerance used in the RESPONSE trial:

Table 4: Definitions of hydroxyurea resistance and intolerance used in the RESPONSE trial.[19]

Criteria Used	Definition of Resistance	Definition of Intolerance
Modified ELN	An inadequate response to HU was defined as a dose ≥ 2g/day or a maximum tolerated dose < 2g/day resulting in at least 1 of the following: • Need for phlebotomy to maintain HCT < 45% • PLT count > 400 x 10^9/L • Failure to reduce splenomegaly extending > 10cm below the costal margin by > 50%, as measured by palpation	Unacceptable side effects from HU were defined as at least 1 of the following: • ANC < 1.0 x 10^9/l • PLT < 100 x 10^9/l or Hb < 100 g/L (i.e., 10 g/dl) at the lowest dose of HU required to achieve a response. • Presence of leg ulcers or other unacceptable HU-related non-hematologic toxicities (such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever an any dose of HU), defined as CTCAE grade 3-4 or > 1 week of CTCAE grade 2, permanent discontinuation of HU, interruption of HU until toxicity resolved, or hospitalization due to HU toxicity.

Abbreviations: ANC - absolute neutrophil count; CTCAE - Common Terminology Criteria for Adverse Events, version 3.0; ELN - European LeukemiaNet; Hb - hemoglobin; HCT - hematocrit; HU - hydroxyurea; PLT - platelet.

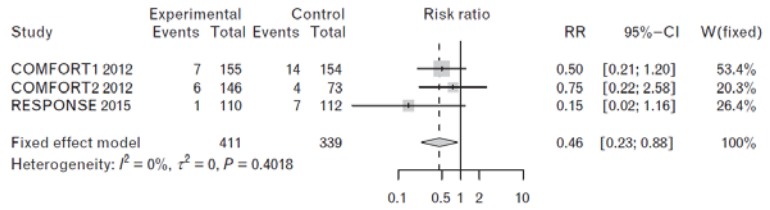
- choice of standard therapy was at the discretion of the investigator, could include any of the following single-agent regimens: HU (at a dose that did not cause unacceptable side effects), interferon alpha (INF-a) or pegylated INF-a, pipobroman, anagrelide, immunomodulators such as lenalidomide or thalidomide, or no medication
- all patients in both arms received low dose aspirin unless it contraindicated
- crossover to ruxolitinib at or after week 32 for patients randomized to standard therapy permitted
- primary outcome: composite response endpoint including the proportion of patients who achieved both HCT control and a reduction in spleen volume of ≥35%, as assessed by either MRI

	or CT imaging, at week 32 • Key secondary endpoints included: duration of primary response at week 48, complete hematological response (CHR) at week 32, symptom reduction, and quality of life (QOL) measured using the EORTC Quality of Life Questionnaire-Core 30 where a 10-point change in score from baseline to week 32 was considered the minimally important difference (MID) *Potential limitations and sources of bias* • open-label design (investigators and patients not blinded to treatment assignment) • risk of performance bias is of particular concern as 59% of patients in the standard therapy arm received HU, a treatment they knew they were intolerant or resistant to • high percentage (87.5%) of patients discontinued treatment due to lack of efficacy (expected outcome) • longer term efficacy and safety of ruxolitinib is limited to an abstract with outcomes reported up to 80 weeks • high-level of crossover (also limits the assessment of longer-term outcomes) • three amendments were made to the protocol, first resulted in significant changes to the inclusion criteria • standard therapy arm included several different treatment regimens, which may not be considered standard of care in some Canadian jurisdictions **Stichprobenbeschreibung** • median age was 60 years (range, 33 to 90 years) • majority had an ECOG PS of 0 (69%) • 54.1% and 45.9% of all patients had unacceptable side effects from or inadequate response to HU • median duration of previous HU therapy: 3.1 and 2.8 years in the ruxolitinib and standard therapy groups • most common initial therapy: HU (59%), no medication (15%), and INF (12%) • median duration of standard therapy: 34 weeks • 96 (86%) patients assigned to standard therapy crossed over to the ruxolitinib arm (mainly at week 32, or shortly after) **Efficacy** • trial is ongoing, median duration of ruxolitinib 34 weeks at week 32, 81 weeks at week 48 and 111 weeks at week 80 • composite response rate at week 32 was 20.9% versus 0.9% in the ruxolitinib and standard therapy arms, respectively (OR=28.6, 95%CI: 4.5-1206, p<0.001) • duration of primary response at week 48: 19.1% versus 0.9% in the ruxolitinib and standard therapy arms (OR=26.11, 95%CI: 3.98-1080, p<0.0001)

	• Complete hematological response (CHR): 24% versus 9% in the ruxolitinib and standard therapy arms (OR=3.35, 95%CI: 1.43-8.35, p=0.003) • EORTC MID achieved in 46% and 10% of patients in the ruxolitinib and standard therapy arms • 50% reduction in the total symptom score was observed in 49% and 5% in the ruxolitinib and standard therapy arms • similar results reported in the Patient Global Impression of Change instrument • Pruritus: improvement from baseline with ruxolitinib (mean change ranged from -1.5 to -2.2) and standard therapy (mean change ranged from -0.1 to 0.3) **Harms** • rates of grade 3 or 4 adverse events similar in both study arms (33% in ruxolitinib arm and 29% in standard therapy arm) • at week 48, 16% and 96% of patients in the ruxolitinib and standard therapy arms discontinued randomized treatment • discontinuations in standard treatment arm primarily attributed to lack of efficacy • follow-up analysis at week 80: 83% of patients had ongoing treatment with ruxolitinib (randomized and crossover) • herpes zoster infection continued to be higher in the ruxolitinib arm • thromboembolic events higher in the standard therapy arm
	3. Anmerkungen/Fazit der Autoren The Clinical Guidance Panel concluded that there is a net overall clinical benefit with the use of ruxolitinib in patients with PV who have specifically demonstrated intolerance or resistance to HU based on one ongoing phase III RCT (RESPONSE). There is a statistically significant and clinically meaningful benefit demonstrated with ruxolitinib in this patient population in controlling the HCT and reducing spleen size. Compared to standard therapy, symptom scores related to PV were also significantly reduced. Grade 3/4 adverse events were uncommon, manageable and the rates were similar across treatment arms. The Clinical Guidance Panel also considered that from a clinical perspective: • The clinical benefit demonstrated in the RESPONSE trial aligned with what was reported in the patient advocacy input. • It is noted that the evidence for use of ruxolitinib is only in a specific population of patients with PV in the second-line setting. There is no current data for its use in the first-line setting. • Ruxolitinib may be used with a 32-week observation period where an absence of response within this time period should be a marker for discontinuation and movement to other forms of therapy such as experimental therapy. • The duration of ruxolitinib therapy is indefinite at this time.

	Regular monitoring for the duration of therapy, spleen size, blood counts, and evidence of transformation is essential. Phlebotomy needs may change with treatment with ruxolitinib. • Discontinuation of therapy should be through a tapering routine if possible and will require careful monitoring because of the potential for significant rebound symptoms. 4. *Kommentar zum Review* • *Ruxolitinib nur bei Resistenz oder Intoleranz gegenüber Hydroxycarbamid zugelassen*
Samuelson BT et al., 2016 [5]. The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis	1. Fragestellung The aim of this study was to evaluate the impact of ruxolitinib on the risk of thrombosis among patients with polycythemia vera or myelofibrosis.
	2. Methodik Population: patients with polycythemia vera and myelofibrosis Intervention: ruxolitinib Komparator: placebo (COMFORT-1) or best available therapy (COMFORT-2 and RESPONSE) Endpunkte: all thrombosis as defined by the authors of the studies and/or as reported by investigators, including venous events, arterial events/ischemia and 'other' events such as thrombotic microangiopathy (primary outcome); arterial thrombosis and venous thrombosis (secondary outcomes) Suchzeitraum: k.A. Anzahl eingeschlossene Studien/Patienten (Gesamt): 3/750 (nur RESPONSE mit 222 Patient*innen für polycythemia vera) Qualitätsbewertung der Studien: Cochrane RoB-tool
	3. Ergebnisdarstellung (zur Studie RESPONSE) • best available therapy: hydroxyurea, interferon, pipobroman, anagrelide, immunomodulators or no medication • overall high risk of bias due to crossover, all documented events occurred prior to crossover (at week 32) • **alle Studien:** significant reduction of thrombotic events in the ruxolitinib group with low, nonsignificant heterogeneity (risk ratio = 0.46; 95% CI 0.23–0.88; I2 = 0%; Fig. 1).

Fig. 1



Forest plot for relative risk of all thrombotic events comparing ruxolitinib to control. CI, confidence interval; RR, risk ratio.

- arterial thrombosis risk and venous thrombosis risk were also lower among patients treated with ruxolitinib, but the risk ratios did not achieve statistical significance

4. Anmerkungen/Fazit der Autoren

In conclusion, our analysis suggests that JAK2 inhibition with ruxolitinib decreases the risk of arterial and/or venous thrombosis in patients with polycythemia vera or myelofibrosis. These findings will require confirmation in a prospective study.

5. *Kommentar zum Review*
   - *Conflicts of interest: There are no conflicts of interest.*
   - *Ruxolitinib nur bei Resistenz oder Intoleranz gegenüber Hydroxycarbamid zugelassen*

Leitlinien

Zur Fragestellung konnten keine relevanten Leitlinien identifiziert werden.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Anmerkung: Aus der Handsuche der Literaturlisten unsystematischer Übersichtsarbeiten und „point of care“ Informationsdiensten wurden zwei relevante Artikel identifiziert. Eine britische Leitlinie von 2005 mit Hinweisen auf einen systematischen Erstellungsprozess und eine randomisierte kontrollierte Studie von 2014.

Marchioli R et al., 2014 [2]. Cardiovascular Events and Intensity of Treatment in Polycythemia Vera	• **Background** • Current treatment recommendations for patients with polycythemia vera call for maintaining a hematocrit of less than 45%, but this therapeutic strategy has not been tested in a randomized clinical trial. • **Methods** • We randomly assigned 365 adults with JAK2-positive polycythemia vera who were being treated with phlebotomy, hydroxyurea, or both to receive either more intensive treatment (target hematocrit, <45%) (low-hematocrit group) or less intensive treatment (target hematocrit, 45 to 50%) (high-hematocrit group). The primary composite end point was the time until death from cardiovascular causes or major thrombotic events. The secondary end points were cardiovascular events, cardiovascular hospitalizations, incidence of cancer, progression to myelofibrosis, myelodysplasia or leukemic transformation, and hemorrhage. An intention-to-treat analysis was performed. • **Results** • After a median follow-up of 31 months, the primary end point was recorded in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high haematocrit group (9.8%) (hazard ratio in the high-hematocrit group, 3.91; 95% confidence interval [CI], 1.45 to 10.53; P = 0.007). The primary end point plus superficial-vein thrombosis occurred in 4.4% of patients in the low-hematocrit group, as compared with 10.9% in the high-hematocrit group (hazard ratio, 2.69; 95% CI, 1.19 to 6.12; P = 0.02). Progression to myelofibrosis, myelodysplasia or leukemic transformation, and bleeding were observed in 6, 2, and 2 patients, respectively, in the low-hematocrit group, as compared with 2, 1, and 5 patients, respectively, in the high-hematocrit group. There was no significant between-group difference in the rate of adverse events. • **Conclusions** • In patients with polycythemia vera, those with a hematocrit target of less than 45% had a significantly lower rate of cardiovascular death

	and major thrombosis than did those with a hematocrit target of 45 to 50%. (Funded by the Italian Medicines Agency and others; ClinicalTrials.gov number, NCT01645124, and EudraCT number, 2007–006694-91.)
McMullin MF et al., 2005 [3]. British Committee for Standards in Haematology Guidelines for the diagnosis, investigation and management of polycythaemia/ erythrocytosis	Fragestellung/Zielsetzung The purpose of this guideline is to provide a rational approach to the diagnosis, investigation and management of patients with an erythrocytosis. This will include recommendations on the management of PV, …
	Methodik Grundlage der Leitlinie: repräsentatives Gremium, Interessenkonflikterklärung Voraussetzung für Teilnahme, systematische Suche und Auswahl der Literatur, Evidenzbewertung anhand des Studiendesigns (siehe LoE), informale Konsensusprozesse, Review durch externe Fachleute, Aktualisierungsrecherchen alle drei Jahre (siehe unten) Suchzeitraum: 1966 to June 2004 LoE: Classification of evidence levels Ia: Evidence obtained from meta-analysis of randomised controlled trials Ib: Evidence obtained from at least one randomised controlled trial IIa: Evidence obtained from at least one well-designed controlled study without randomisation IIb: Evidence obtained from at least one other type of well-designed quasi-experimental study* III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies IV: Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities GoR: Classification of grades of recommendations A: Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation (evidence levels Ia, Ib) B: Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (evidence levels IIa, IIb, III) C: Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV) Sonstige methodische Hinweise: Patientenvertretung unklar, Interessenkonflikterklärungen liegen nicht vor, nur konsentierte Empfehlungen in der Leitlinie abgebildet • „Every three years all BSH Guidelines must have the literature search re-run as a check for new evidence. If new evidence requires changes the options are: Archive Guidance, Update the guideline page on the BSH guideline website.", unklar ob Aktualisierungsrecherchen tatsächlich durchgeführt wurden • Zur Zytoreduktion ist von den unten empfohlenen nur Hydroxycarbamid zugelassen. • In 2007 erfolgte ein Addendum zur Leitlinie zur Diagnostik der JAK2-Mutationen.
	Freitext/Empfehlungen/Hinweise

Management of polycythaemia vera

Recommendations: Management of polycythaemia vera.

- Venesection to maintain the HCT to <0,45.
- Aspirin 75 mg/d unless contraindicated.
- Cytoreduction should be considered if:
    - poor tolerance of venesection;
    - symptomatic or progressive splenomegaly;
    - other evidence of disease progression, e.g. weight loss, night sweats;
    - thrombocytosis.
- Choice of cytoreductive therapy, if indicated:
    - <40 years old: first line interferon, second line hydroxycarbamide or anagrelide;
    - 40–75 years old: first line hydroxycarbamide, second line interferon or anagrelide;
    - >75 years old: first line hydroxycarbamide, second line 32P or intermittent low dose busulphan.

Grade C recommendation: Evidence level IV

Randomised clinical trials (siehe auch Abbildung 1 im Anhang)

The PVSG-01 study established venesection as the first line therapy for PV. In comparison with 32P and chlorambucil, overall survival was significantly longer in the venesection arm, and associated with much lower risks of leukaemia and non haematological malignancy. An increased risk of thrombosis was seen in the venesection arm, but this was predominantly observed during the first 3 years when the target Hct was 0,52 (Berk et al, 1995). In later years, it was reduced to 0,45. There was a large degree of cross-over between arms, with 91% of patients randomised to venesection having changed to alternative treatments by 10 years in the French subgroup of patients in the trial (Najean et al, 1994). Thus the role of purely using venesection as treatment for PV is unclear. … Chlorambucil is not now recommended in the treatment of PV.

Berk, P.D., et al (1995) Treatment of polycythaemia vera, a summary of clinical trends conducted by the polycythaemia vera sub-group. In: Treatment of Polycythaemia Vera, a Summary of Clinical Trends Conducted by the Polycythaemia Vera Study Group (ed. by L.P. Wasserman & P.D. Berk), pp. 166–194. W.B. Saunders, Philadelphia, PA.

PVSG-05 was a two-arm study that compared 32P with venesection plus high doses of anti-platelet agents, aspirin (300 mg t.i.d.) and dipyridamole (75 mg t.i.d.) (Tartaglia et al, 1986). The rationale for this trial was to use anti-platelet agents to reduce the increased risk of thrombosis that was observed initially in the phlebotomy arm of PVSG-01. The haemorrhage and death rate was significantly increased in the venesection and antiplatelet arm and the trial was therefore stopped. In the majority of cases a high platelet count was found at the time of haemorrhage but the platelet count was controlled by 32P in the other arm.

Tartaglia, A.P., et al (1986) Adverse effects of antiaggregating platelet therapy in the treatment of polycythemia vera. Seminars in Hematology, 23, 172–176.

The European Organisation for Research on Treatment of Cancer (EORTC) conducted a trial comparing 32P to busulphan (EORTC, 1981). Venesection was added in each arm to maintain the Hct

	between 0,42 and 0,47. Overall survival was significantly better in the busulphan group, with the major reason for the difference being an increase in vascular complications. There were no differences between the arms for other complications, such as leukaemia, myelofibrosis or non-haematological malignancy. European Organisation for Research on Treatment of Cancer (1981) Treatment of polycythaemia vera by radiophosphorus or busulphan: a randomised trial. ''Leukemia and Hematosarcoma'' Cooperative Group, European Organisation for Research on Treatment of Cancer (EORTC). British Journal of Cancer, 44, 75–80. The French Polycythaemia Study Group (FPSG) published two randomised trials in 1997. The first was a two-arm comparison of 32P alone against 32P with maintenance hydroxycarbamide (formerly known as hydroxyurea) in patients over the age of 65 years (Najean & Rain, 1997a). Significant numbers of patients crossed between the two treatment arms. Median survival was not significantly different. No differences were observed for vascular end-points or progression to myelofibrosis. The actuarial risk of leukaemia was significantly greater for the 32P and hydroxycarbamide group, with the difference becoming apparent after 5 years, and the gap continuing to widen up to the 15th year. In addition, the acturial risk of non-haematological malignancy was also much greater for the 32P and hydroxycarbamide arm, with a similar 5–15 year latency observed. Najean, Y. & Rain, J.D. (1997a) Treatment of polycythemia vera: use of 32P alone or in combination with maintenance therapy using hydroxyurea in 461 patients greater than 65 years of age. The French Polycythemia Study Group. Blood, 89, 2319–2327. The second trial from the FPSG was a comparison of hydroxycarbamide therapy with pipobroman in patients under the age of 65 years (Najean & Rain, 1997b). Overall actuarial survival was 70% in the two arms at 14 years, compared with an estimated 84% for the age- and sex-matched population. There were no differences between the two groups in vascular end-points or rates of leukaemia or non-haematological malignancy. Myelofibrosis risk was significantly increased in the hydroxycarbamide arm, and tended to occur earlier. Najean, Y. & Rain, J.D. (1997b) Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. Blood, 90, 3370–3377. The European Collaboration on Low-dose Aspirin in Polycythemia vera (ECLAP) study established the therapeutic benefit of aspirin in PV (Landolfi et al, 2004), and followed an earlier pilot study (Gruppo Italiano Studio Policitemia, 1997). Patients were randomised between aspirin 100 mg/d and placebo. Aspirin significantly reduced the risk of the combined end-point of non-fatal thromboembolic events, or death from cardiovascular causes. The risk of major or minor thrombosis was also significantly decreased. There was no significant increase in haemorrhage. The results of this large, well designed multicentre trial eliminated the concerns about the efficacy and safety of aspirin that were raised by the earlier, smaller PVSG-05 trial (Tartaglia et al, 1986) and provided evidence for the use of aspirin in the management of PV. Landolfi, R., & European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators (2004) Efficacy and safety of low-dose aspirin in polycythemia vera. The New England Journal of Medicine, 350, 114–124.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 25.07.2017

#	Suchfrage
1	MeSH descriptor: [Polycythemia Vera] explode all trees
2	((polycythemia*):ti,ab,kw) and ((vera or veras or primary):ti,ab,kw) (Word variations have been searched)
3	#1 or #2
4	#3 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 25.07.2017

#	Suchfrage
1	polycythemia vera[MeSH Terms]
2	(((Erythremia*[Title/Abstract]) OR polycythemia*[Title/Abstract]) OR polycythaemia*[Title/Abstract]) OR erythraemia*[Title/Abstract]
3	#1 OR #2
4	(#3) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))))
5	(#4 AND ("2012/07/01"[PDAT] : "2017/07/25"[PDAT]))

Leitlinien in Medline (PubMed) am 25.07.2017

#	Suchfrage
1	polycythemia vera[MeSH]
2	(((Erythremia*[Title/Abstract]) OR polycythemia*[Title/Abstract]) OR polycythaemia*[Title/Abstract]) OR erythraemia*[Title/Abstract]
3	#1 OR #2
4	(#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
5	(#4 AND ("2012/07/01"[PDAT] : "2017/07/25"[PDAT]))

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5. **Samuelson BT, Vesely SK, Chai-Adisaksopha C, Scott BL, Crowther M, Garcia D.** The impact of ruxolitinib on thrombosis in patients with polycythemia vera and myelofibrosis: a meta-analysis. Blood Coagul Fibrinolysis 2016;27(6):648-652.

Anhang:

Table V. Randomised trials in polycythaemia vera with rates of important end-points for each of the treatment arms.

Trial	Therapy	*n*	Follow-up (years)	Median survival	Thrombosis	Acute leukaemia	Cancer	MF
PVSG-01§	Phleb	134	Minimum 12; maximum 18	12·6 years*	40%*,† (5 years)	1·5%*,‡ (10 years)	No ↑*	9% (12 years)
	^{32}P	156		10·9 years*	23%*,† (5 years)	9·6%* (10 years)	2·5x↑*	9% (12 years)
	Cbl	141		9·1 years*	17%*,† (5 years)	13·5%* (10 years)	3·5x↑*	9% (12 years)
PVSG-05¶	Phleb + Anti-plt	83	1·2		7 pts			
	^{32}P	83			2 pts			
EORTC**	Bu	147	8	70%* (10 years)	5% deaths*	2%	3%	5%
	^{32}P	146		55%* (10 years)	17% deaths*	1%	5%	4%
FPSG >65 years††	^{32}P	242	0·3–16	11·2 years	22%† (10 years)	12%*,† (10 years)	15%*,† (10 years)	8%† (10 years)
	^{32}P + HU	219		9·1 years	36%† (10 years)	20%*,† (10 years)	20%*,† (10 years)	15%† (10 years)
FPSG <65 years‡‡	HU	150	0·3–16	70% (14 years)	16%† (10 years)	3%† (10 years)	4%† (10 years)	17%*,† (10 years)
	Pipob	142		70% (14 years)	15%† (10 years)	5%† (10 years)	8%† (10 years)	2%*,† (10 years)
ECLAP§§	Aspirin	253	3		6·7%*			
	Placebo	265			15·5%*			

*Variables which are significantly different between arms in the trial.
†Estimates which have been derived from actuarial survival curves for the purposes of this table.
‡selected patients, not intention to treat.
§Berk *et al* (1995).
¶Tartaglia *et al* (1986).
**European Organisation for Research on Treatment of Cancer (1981).
††Najean & Rain (1997a).
‡‡Najean & Rain (1997b).
§§Landolfi *et al* (2004).

Abbildung 1: aus McMullin MF et al., 2005 [3].