THE LANCET
Haematology

ARTICLES | VOLUME 7, ISSUE 3, E226-E237, MARCH 01, 2020

Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study

Prof Jean-Jacques Kiladjian, MD • Pierre Zachee, MD • Masayuki Hino, MD • Fabrizio Pane, MD • Tamas Masszi, MD • Claire N Harrison, DM • et al. Show all authors

Published: January 23, 2020 • DOI: https://doi.org/10.1016/S2352-3026(19)30207-8 •

Summary

Background

Polycythaemia vera is a myeloproliferative neoplasm characterised by excessive proliferation of erythroid, myeloid, and megakaryocytic components in the bone marrow due to mutations in the *Janus kinase 2 (JAK2)* gene. Ruxolitinib, a JAK 1 and JAK 2 inhibitor, showed superiority over best available therapy in a phase 2 study in patients with polycythaemia vera who were resistant to or intolerant of hydroxyurea. We aimed to compare the long-term safety and efficacy of ruxolitinib with best available therapy in patients with polycythaemia vera who were resistant to or intolerant of hydroxyurea.

Methods

We report the 5-year results for a randomised, open-label, phase 3 study (RESPONSE) that enrolled patients at 109 sites across North America, South America, Europe, and the Asia-Pacific region. Patients (18 years or older) with polycythaemia vera who were resistant to or intolerant of hydroxyurea were randomly assigned 1:1 to receive either ruxolitinib or best available therapy. Patients randomly assigned to the

nib group received the drug orally at a starting dose of 10 mg twice a day. Single-ager

le therapy comprised hydroxyurea, interferon or pegylated interferon, pipobroman, a

lid

approved immunomodulators, or observation without pharmacological treatment. The primary endpoint, composite response (patients who achieved both haematocrit control without phlebotomy and 35% or more reduction from baseline in spleen volume) at 32 weeeks was previously reported. Patients receiving best available therapy could cross over to ruxolitinib after week 32. We assessed the durability of primary composite response, complete haematological remission, overall clinicohaematological response, overall survival, patient-reported outcomes, and safety after 5-years of follow-up. This study is registered with ClinicalTrials.gov, NCT01243944.

Findings

We enrolled patients between Oct 27, 2010, and Feb 13, 2013, and the study concluded on Feb 9, 2018. Of 342 individuals screened for eligibility, 222 patients were randomly assigned to receive ruxolitinib (n=110, 50%) or best available therapy (n=112, 50%). The median time since polycythaemia vera diagnosis was 8·2 years (IQR 3·9–12·3) in the ruxolitinib group and 9·3 years (4·9–13·8) in the best available therapy group. 98 (88%) of 112 patients initially randomly assigned to best available therapy crossed over to receive ruxolitinib and no patient remained on best available therapy after 80 weeks of study. Among 25 primary responders in the ruxolitinib group, six had progressed at the time of final analysis. At 5 years, the probability of maintaining primary composite response was 74% (95% CI 51–88). The probability of maintaining complete haematological remission was 55% (95% CI 32–73) and the probability of maintaining overall clinicohaematological responses was 67% (54–77). In the intention-to-treat analysis not accounting for crossover, the probability of survival at 5 years was 91·9% (84·4–95·9) with ruxolitinib therapy and 91·0% (82·8–95·4) with best available therapy. Anaemia was the most common adverse event in patients receiving ruxolitinib (rates per 100 patient-years of exposure were 8·9 for ruxolitinib and 8·8 for the crossover population), though most anaemia events were mild to moderate in severity (grade 1 or 2 anaemia rates per 100 patient-years of exposure were 8·0 for ruxolitinib and 8·2 for the crossover population). Non-haematological adverse events were generally lower with long-term ruxolitinib treatment than with best available therapy. Thromboembolic events were lower in the ruxolitinib group than the best available therapy group. There were two on-treatment deaths in the ruxolitinib group. One of these deaths was due to gastric adenocarcinoma, which was assessed by the investigator as related to ruxolitinib treatment.

Interpretation

We showed that ruxolitinib is a safe and effective long-term treatment option for patients with polycythaemia vera who are resistant to or intolerant of hydroxyurea. Taken together, ruxolitinib treatment offers the first widely approved therapeutic alternative for this post-hydroxyurea patient population.

Novartis Pharmaceuticals Corporation.

• View related content for this article

References

1. Spivak JL
Myeloproliferative neoplasms.
N Engl J Med. 2017; **376**: 2168-2181

View in Article
Scopus (119) • PubMed • Crossref • Google Scholar

2. Tefferi A • Rumi E • Finazzi G • et al.
Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study.
emia. 2013; **27**: 1874-1881

View in Article

Scopus (322) • PubMed • Crossref • Google Scholar

3. Geyer H • Scherber R • Kosiorek H • et al.

Symptomatic profiles of patients with polycythemia vera: implications of inadequately controlled disease.

J Clin Oncol. 2016; **34**: 151-159

View in Article

Scopus (35) • PubMed • Crossref • Google Scholar

4. 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; **23**: 2224-2232

View in Article

Scopus (447) • PubMed • Crossref • Google Scholar

5. 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; **117**: 755-761

View in Article

Scopus (334) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

6. 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; **29**: 761-770

View in Article

Scopus (570) • PubMed • Crossref • Google Scholar

Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet.

Leukemia. 2018; **32**: 1057-1069

View in Article

Scopus (172) • PubMed • Crossref • Google Scholar

8. Alvarez-Larrán A • Kerguelen A • Hernández-Boluda JC • et al.

Frequency and prognostic value of resistance/intolerance to hydroxycarbamide in 890 patients with polycythaemia vera.

Br J Haematol. 2016; **172**: 786-793

View in Article

Scopus (36) • PubMed • Crossref • Google Scholar

9. Alvarez-Larrán A • Pereira A • Cervantes F • et al.

Assessment and prognostic value of the European LeukemiaNet criteria for clinicohematologic response, resistance, and intolerance to hydroxyurea in polycythemia vera.

Blood. 2012; **119**: 1363-1369

View in Article

Scopus (133) • PubMed • Crossref • Google Scholar

10. Reiter A • Harrison C

How we identify and manage patients with inadequately controlled polycythemia vera.

Curr Hematol Malig Rep. 2016; **11**: 356-367

View in Article

Scopus (10) • PubMed • Crossref • Google Scholar

11. Scherber RM • Geyer HL • Dueck AC • et al.

The potential role of hematocrit control on symptom burden among polycythemia vera patients: insights from the CYTO-PV and MPN-SAF patient cohorts.

Leuk Lymphoma. 2017; **58**: 1481-1487

Scopus (10) • PubMed • Crossref • Google Scholar

12. Vannucchi AM • Kiladjian JJ • Griesshammer M • et al.

Ruxolitinib versus standard therapy for the treatment of polycythemia vera.

N Engl J Med. 2015; **372**: 1670-1671

View in Article

Scopus (93) • PubMed • Crossref • Google Scholar

13. Incyte

Jakafi (ruxolitinib): package insert.

https://www.jakafi.com/pdf/prescribing-information.pdf

Date: 2019

Date accessed: January 9, 2020

View in Article

Google Scholar

14. Novartis

Jakavi (ruxolitinib): SmPC.

https://www.ema.europa.eu/en/documents/product-information/jakavi-epar-product-information_en.pdf

Date: 2017

Date accessed: January 9, 2020

View in Article

Google Scholar

15. Kiladjian JJ • Verstovsek S • Griesshammer M • et al.

Results from the 208-week (4-year) follow-up of RESPONSE trial, a phase 3 study comparing ruxolitinib (rux) with best available therapy (BAT) for the treatment of polycythemia vera (PV).

Blood. 2017; **130** (abstr).: 322

View in Article

le Scholar

16. Verstovsek S • Vannucchi AM • Griesshammer M • et al.
Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial.
Haematologica. 2016; **101**: 821-829

View in Article
Scopus (92) • PubMed • Crossref • Google Scholar

17. Griesshammer M • Saydam G • Palandri F • et al.
Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial.
Ann Hematol. 2018; **97**: 1591-1600

View in Article
Scopus (23) • PubMed • Crossref • Google Scholar

18. Passamonti F • Griesshammer M • Palandri F • et al.
Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study.
Lancet Oncol. 2017; **18**: 88-99

View in Article
Scopus (110) • PubMed • Summary • Full Text • Full Text PDF • Google Scholar

19. Mesa R • Jamieson C • Bhatia R • et al.
Myeloproliferative Neoplasms, Version 2. 2018 Featured updates to the NCCN guidelines.
J Natl Compr Canc Netw. 2017; **15**: 1193-1207

View in Article
Scopus (48) • PubMed • Crossref • Google Scholar

20. Kiladjian JJ • Guglielmelli P • Griesshammer M • et al.
Efficacy and safety of ruxolitinib after and vs interferon use in the RESPONSE studies.
Ann Hematol. 2018; **97**: 617-627

Scopus (12) • PubMed • Crossref • Google Scholar

21. Verstovsek S • Mesa R • Jones MM • et al.

Ruxolitinib efficacy by hematocrit control in patients with polycythemia vera: an analysis of the RESPONSE trial.

Blood. 2014; **124** (abstr).3201

View in Article

PubMed • Crossref • Google Scholar

22. Antonioli E • Guglielmelli P • Pieri L • et al.

Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN.

Am J Hematol. 2012; **87**: 552-554

View in Article

Scopus (75) • PubMed • Crossref • Google Scholar

Article Info

Publication History

Published: January 23, 2020

Identification

DOI: https://doi.org/10.1016/S2352-3026(19)30207-8

ScienceDirect

Access this article on ScienceDirect