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Long-term Effect of Ruxolitinib (RUX) in Inadequately Controlled Polycythemia Vera (PV) Without Splenomegaly: 5-Year Results From the Phase 3 RESPONSE-2 Study

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- M Griesshammer: honoraria and Speakers Bureau: AOP Orphan, Celgene, CTI, Novartis, Shire
- E Zor, G Gilotti, and Y Zhang are employees of Novartis

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Introduction

- RUX is potent and selective *JAK1/JAK2* inhibitor approved for patients with PV who have had an inadequate response to or are intolerant of HU
- In the RESPONSE study (NCT01243944) in patients with PV with splenomegaly who are HU-resistant or -intolerant, RUX showed a superior and durable response in controlling Hct and improving splenomegaly vs BAT[1,2]
- RESPONSE-2 was a phase 3 study assessing RUX vs BAT in patients with PV with no palpable splenomegaly who are HU-resistant or -intolerant (NCT02038036)[3,4]
  - In the Week 28 primary analysis, RUX was superior to BAT in controlling Hct, normalizing blood cell counts, and improving symptoms[3]
- Here we present the final RESPONSE-2 study results at Year 5 (end of treatment follow-up)

BAT, best available therapy; Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib.

1. Vannucchi AM, et al. *N Engl J Med*. 2015;372:426–435. 2. Kiladjian J-J, et al. *Blood*. 2017;130 [abstract 322]. 3. Passamonti F, et al. *Lancet Oncol*. 2017;18:88–99.
4. Passamonti F, et al. *Blood* 2018, 132: 1754-1754

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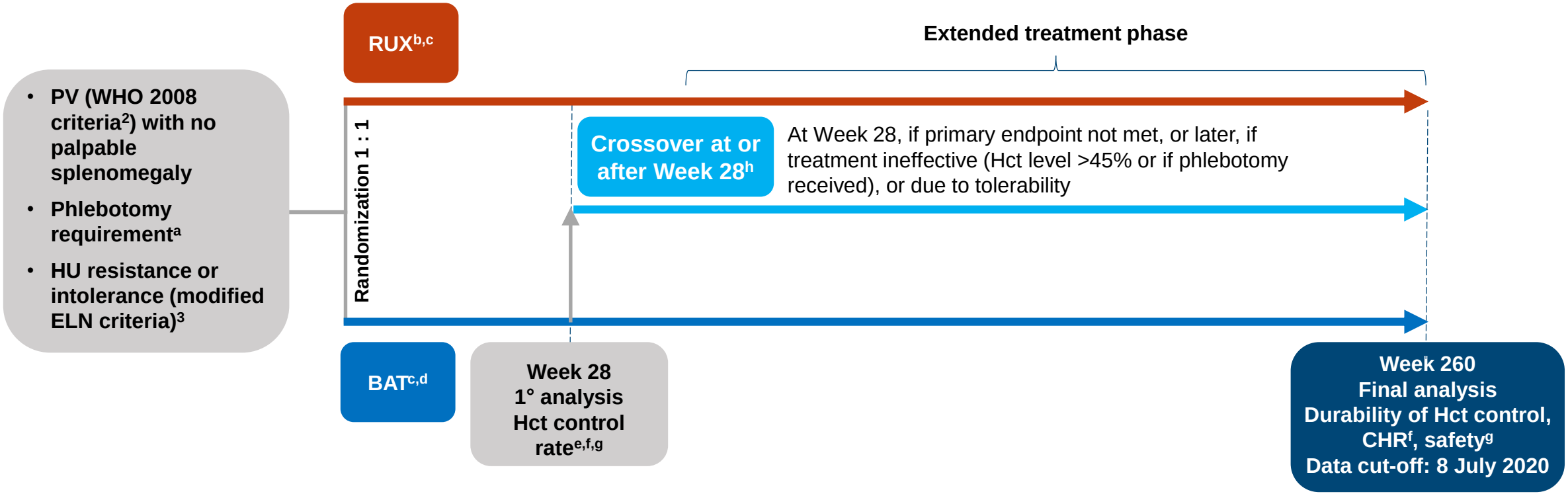
RESPONSE-2: Randomized, open-label, multicenter Phase 3 study[1]



[a] Defined as Hct 40%-45% with ≥2 phlebotomies spaced ≥4 weeks apart within 24 weeks before screening ***or*** Hct >45% with ≥1 phlebotomy within 16 weeks before screening. [b] RUX-randomized patients had their doses individually titrated for efficacy and safety (max 25 mg bid). [c] All patients received low-dose aspirin unless medically contraindicated. [d] Investigator-selected BAT as monotherapy included HU (at a tolerated dose if patient likely to receive benefit), interferon/peg-interferon, anagrelide, pipobroman, immunomodulatory drugs, or no medication. [e] Hct control defined as absence of phlebotomy eligibility from Weeks 8 to 28, with only 1 post-randomization phlebotomy allowed prior to week 8; phlebotomy eligibility defined as confirmed Hct >45% and ≥3% higher than baseline, or >48%. [f] Key secondary endpoint was CHR, defined as the proportion of patients with Hct control, white blood cell count <10×10^9/L, and platelet count ≤400×10^9/L) at Week 28. [g] Additional endpoints included changes in patient-reported outcomes and *JAK2*^{V617F} allele burden over time.

BAT, best available therapy; bid, twice daily; CHR, complete hematologic remission; ELN, European LeukemiaNet; Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib; WHO, World Health Organisation.

1. Passamonti F, et al. *Lancet Oncol*. 2017;18:88–99. 2. Thiele J, Kvasnicka HM. *Curr Hematol Malig Rep* 2009;4:33–40. 3. Barosi G, et al. *Blood*. 2013;121:4778–4781.

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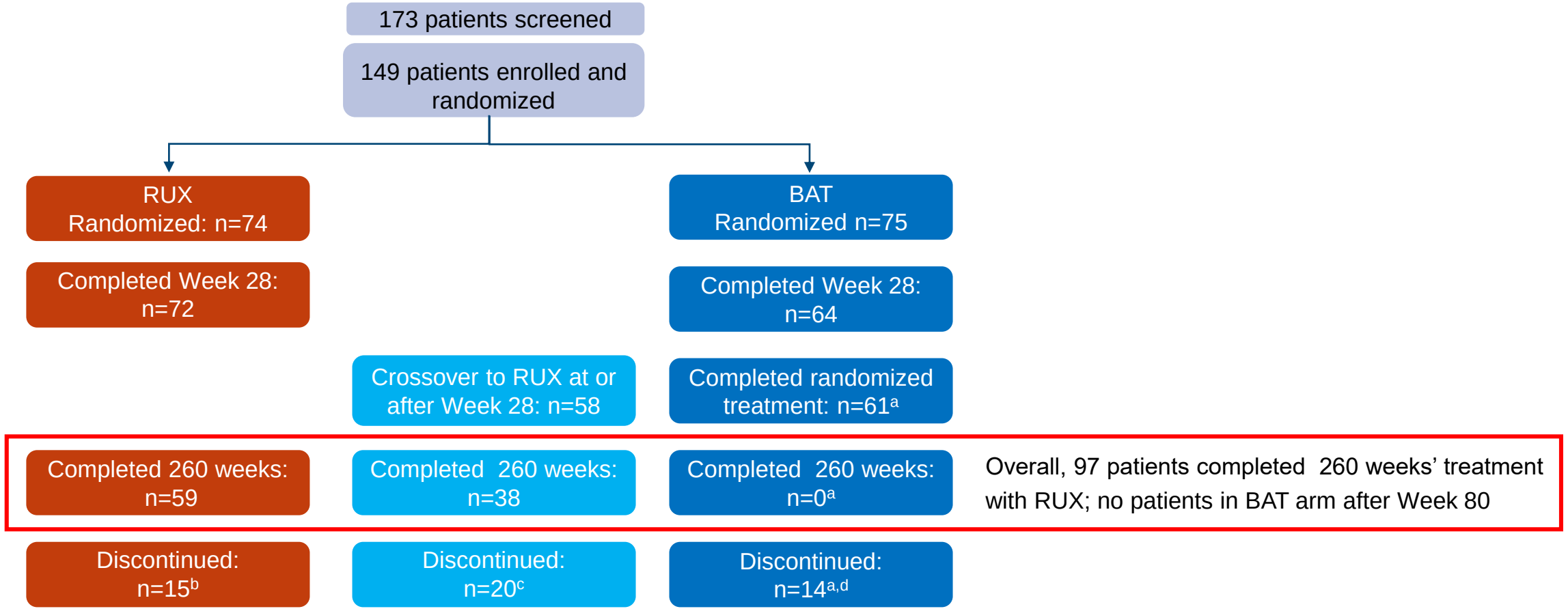
Patient disposition



[a] For patients randomized to BAT, data collected after crossover are not included.
[b] Reasons: AE, n=7; death, n=1; disease progression, n=2; physician's decision, n=2; withdrawal of consent; n=3.
[c] Reasons: AE, n=9; death, n=2; disease progression, n=3; lost to follow-up, n=1; physician's decision, n=2; withdrawal of consent; n=3.
[d] Reasons: AE, n=7; death, n=1; disease progression, n=2; lost to follow-up, n=1; physician's decision, n=1; patient/guardian decision, n=1; withdrawal of consent; n=1.

AE, adverse event; BAT, best available therapy; RUX, ruxolitinib.

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Similar baseline characteristics between RUX and BAT groups

- Baseline characteristics of crossover patients were similar to those of patients originally randomized to BAT

	RUX (N=74)[1]	BAT (N=75)[1]
Median (IQR) age, years	63 (54–71)	67 (61–74)
Men, n (%)	39 (53)	47 (63)
Median (IQR) time since diagnosis, years	6.5 (2.9–10.7)	6.7 (3.2–10.6)
Previous lines of antineoplastic therapies, n (%)		
1	53 (72)	52 (69)
>1	21 (28)	23 (31)
Median (IQR) duration of previous HU therapy, months	33.95 (6.80–79.31)	42.61 (6.86–84.30)
Previous HU treatment status, n (%)		
Inadequate response	30 (41)	30 (40)
Unacceptable side-effects	44 (59)	45 (60)
Positive for *JAK2*^{V617F} mutation[a], n (%)	72 (97)	69 (92)
History of previous thromboembolic event, n (%)	21 (28)	18 (24)
Median (IQR) hematocrit level[b], %	43.0 (41.7–44.0)	42.7 (41.7–44.0)
Mean (SD) white blood cell count, × 10⁹ cells/L	12.0 (8.19)	13.0 (8.06)
Mean (SD) platelet count, × 10⁹ cells/L	469.5 (295.96)	471.5 (350.38)
≥2 phlebotomies within 24 weeks before screening, n (%)	58 (78)	57 (76)

[a] For five patients, the *JAK2*^{V617F} mutation was not confirmed by central laboratory assessment; these patients were not included as *JAK2*^{V617F} positive.
[b] Following hematocrit control period before randomization.
IQR, interquartile range; SD, standard deviation.
1. Passamonti F, et al. *Lancet Oncol*. 2017;18:88–99.

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Hematocrit control through Week 260

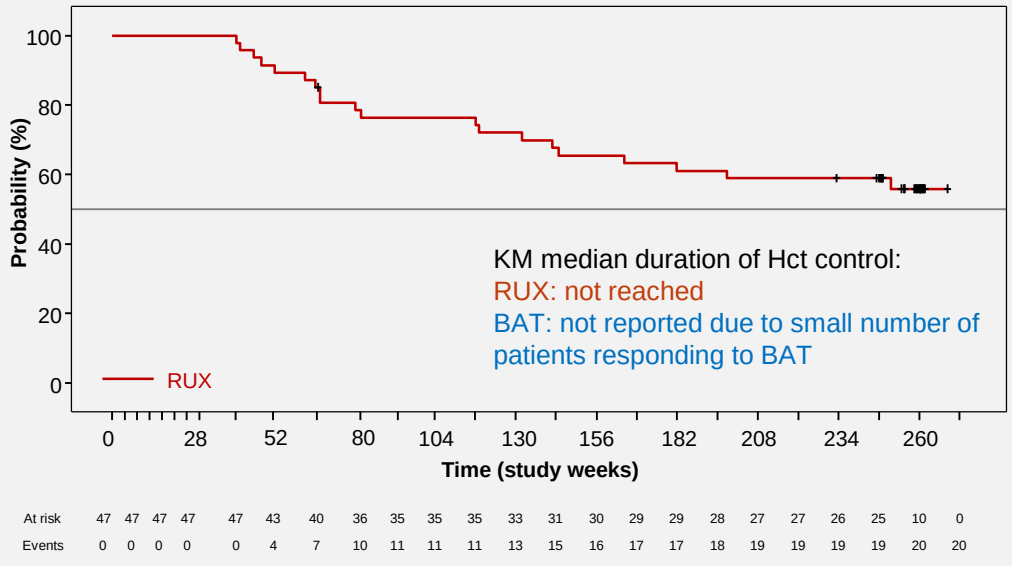
Durable Hct control in RUX patients

Primary response at Week 28[a]

- Durable Hct control at Week 260[b] was achieved by 21.6% (16/74) of patients randomized to RUX

KM plot for duration of Hct control

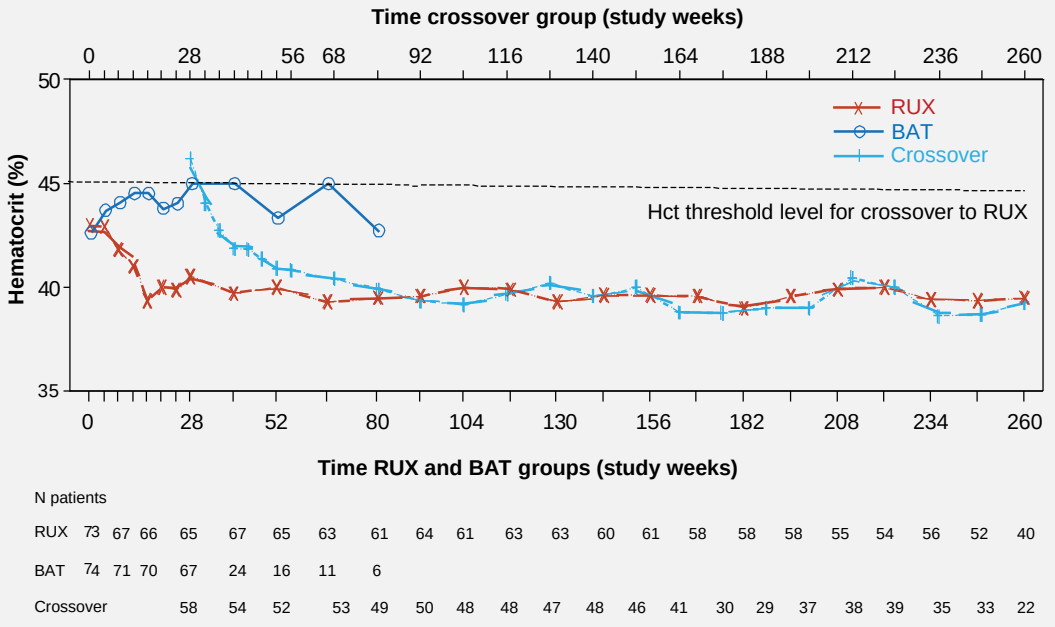
(Time from start of Hct control to phlebotomy eligibility, palpable spleen, transformation to MF or AML, or death)[b]



Hct control was achieved in both RUX and crossover patients

- After crossover from BAT to RUX, median Hct levels declined by – 7.1% (– 28.0, 8.1) at EOT

Median Hct levels (%) over time



[a] Defined as absence of phlebotomy eligibility from Weeks 8 to 28, with only 1 post-randomization phlebotomy allowed prior to Week 8. [b] Defined as no phlebotomy eligibility starting at Week 8 and continuing through Week 260, with ≤1 post-randomization phlebotomy eligibility prior to Week 8. Phlebotomy eligibility was defined as confirmed Hct >45% and ≥3% higher than baseline, or >48%.
[c] Defined as time from start of Hct control to earliest date of phlebotomy eligibility, palpable spleen (>0 cm), transformation to MF or AML, or death due to any cause.
RUX and BAT data based on full analysis set. Crossover data based on crossover set. AML, acute myeloid leukemia; EOT, end of treatment; Hct, hematocrit; KM, Kaplan-Meier; MF, myelofibrosis.

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Complete hematologic remission (CHR) & *JAK2*^{V617F} allele burden

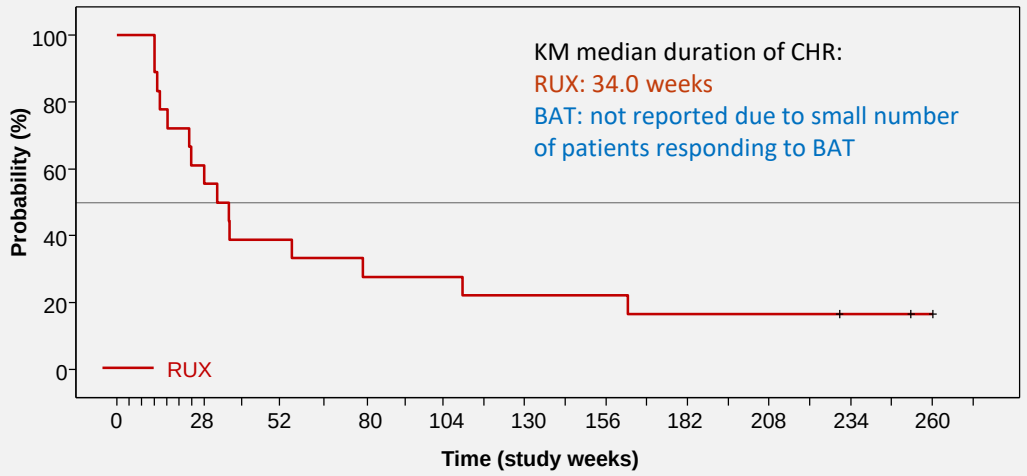
Duration of CHR in RUX patients

CHR = Hct control, WBC <10x10^9/L, and platelets ≤400x10^9/L; key secondary response at Week 28[a]

- Durable CHR at Week 260[b] was achieved by 12.2% (9/74) of patients randomized to RUX

KM plot for duration of CHR

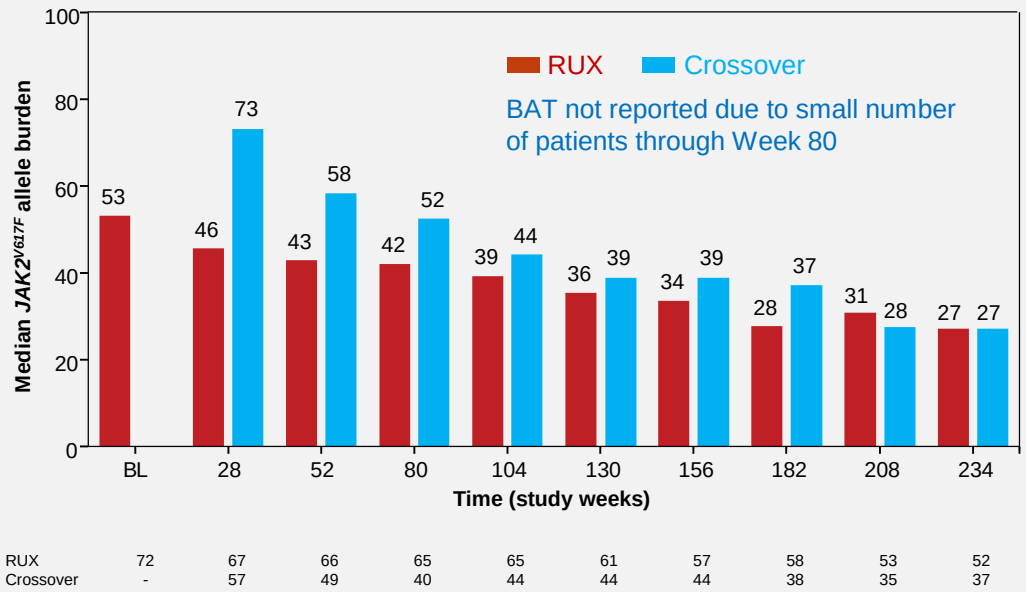
(Time from start of CHR to phlebotomy eligibility, palpable spleen, WBC ≥10x10^9/L, platelets >400x10^9/L, transformation to MF or AML, or death)[c]



RUX consistently reduced *JAK2*^{V617F} allele burden over time

- Median change at EOT in *JAK2*^{V617F} allele burden was –14.8% in RUX arm, and –13.5% in crossover arm

Median *JAK2*^{V617F} allele burden over time



[a] Defined as HcT control, WBC <10x10^9 /L, and platelets ≤400x10^9/L, at Week 28. [b] Defined as Hct control at Week 260 (absence of phlebotomy eligibility starting at Week 8 through Week 260, with ≤1 post-randomization phlebotomy eligibility prior to Week 8, WBC <10 x10^9/L at Week 260, and Platelets ≤400 x 10^9/L at Week 260. [c] Defined as time from start of CHR to earliest date of phlebotomy eligibility, palpable spleen (>0 cm), WBC ≥10x10^9 /L, platelets >400x10^9/L, transformation to MF or AML, or death due to any cause. RUX and BAT data based on full analysis set. Crossover data based on crossover set. AML, acute myeloid leukemia; CHR, complete hematologic remission; KM, Kaplan-Meier; MF, myelofibrosis; WBC, white blood cell count.

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Phlebotomies

Fewer phlebotomies with early vs delayed RUX initiation

- ~2x lower rate of phlebotomies (per patient per week) with early RUX vs delayed RUX initiation

	RUX (N=74)	BAT (N=75)	Crossover (N=58)
Total number of phlebotomies, n			
	60 (within 260 weeks)	106 (within 80 weeks)	99 (within 232 weeks)
Phlebotomy frequency category, n (%) of patients			
>0 – ≤2	12 (16.2)	29 (38.7)	23 (39.7)
>2 – ≤4	7 (9.5)	16 (21.3)	16 (27.6)
>4 – ≤6	4 (5.4)	2 (2.7)	2 (3.4)
>6 – ≤8	0 (0)	1 (1.3)	1 (1.7)

Phlebotomy eligibility was defined as confirmed Hct level >45% and ≥3 percentage points higher than baseline, or confirmed Hct level >48%.
RUX and BAT data based on full analysis set. Crossover data based on crossover set.

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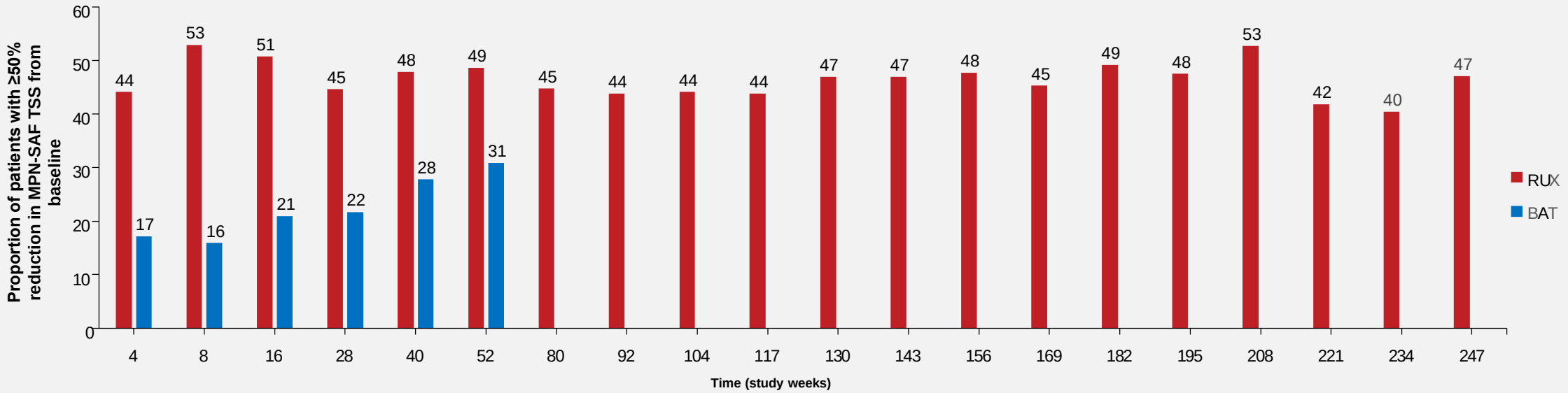
PV-associated symptoms (MPN-SAF TSS)

Significant improvement in PV symptoms (MPN-SAF TSS) with RUX vs BAT



	4	8	16	28	40	52	80	92	104	117	130	143	156	169	182	195	208	221	234	247
RUX	30/68	36/68	34/67	29/65	32/67	34/70	30/67	28/64	30/68	28/64	30/64	30/64	31/65	29/64	31/63	29/61	29/55	23/55	23/57	24/51
BAT	12/70	11/69	14/67	5/23	5/18	4/13	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- At EOT, 45.2% (28/62) patients randomized to RUX achieved ≥50% reduction in MPN-SAF TSS from baseline vs 15.9% (10/63) of patients randomized to BAT
  - Difference RUX vs BAT[a]: 29.3% (95% CI 14.0, 44.6)
- Odds ratio ≥50% reduction MPN-SAF TSS (RUX/BAT):
  - 4.36 (95% CI 1.88, 10.12)

[a] Crossover patients not included. RUX and BAT data based on full analysis set.
CI, confidence interval; EOT, end of treatment; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score.

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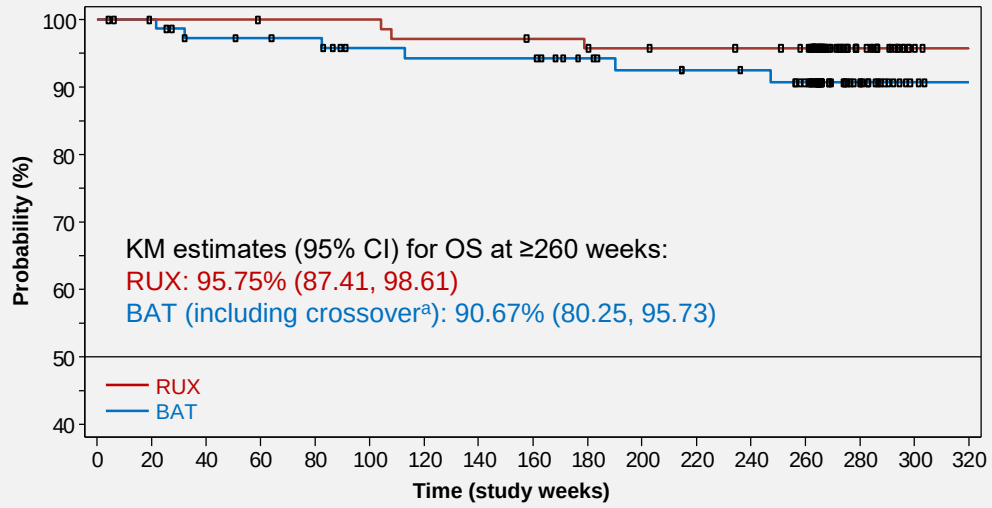
Overall survival and event-free survival

Overall survival

- Median OS not reached in RUX and BAT/crossover arms
- Overall few deaths, which is not unexpected given the long life expectancy in this population

KM plot for overall survival

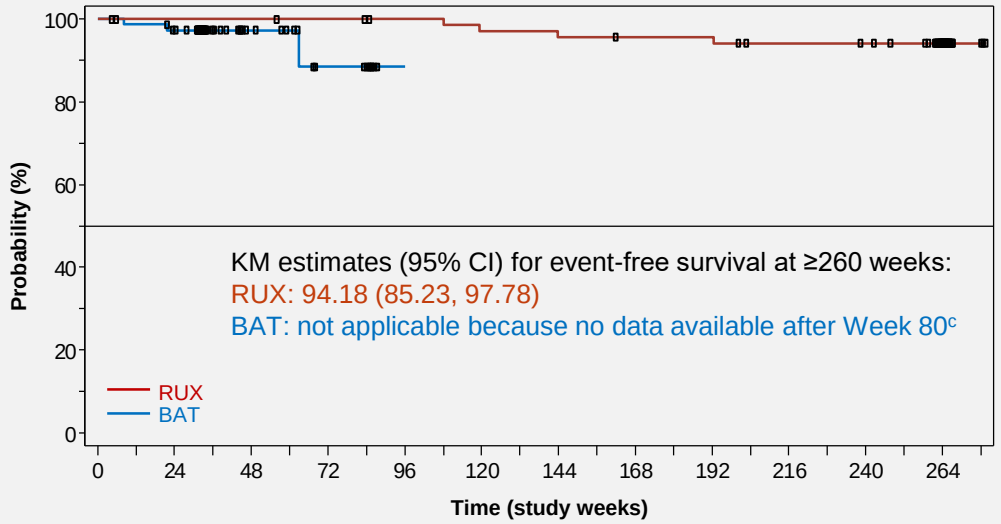


At risk RUX	74	72	72	71	71	71	69	69	68	67	66	65	64	62	18	2	0
At risk BAT	75	74	69	68	67	62	61	61	61	56	53	51	50	45	16	2	0
Events RUX	0	0	0	0	0	0	2	2	2	3	3	3	3	3	3	3	3
Events BAT	0	0	2	2	2	3	4	4	4	4	5	5	5	6	6	6	6

Event-free survival

- Median event-free survival not reached in RUX or BAT arms

KM plot for event-free survival (MF, AML, or death)[b]



At risk RUX	74	72	72	72	72	71	71	70	69	69	67	67	66	66	65	65	65	62	62	62	61	59	43	3
At risk BAT	75	74	71	24	16	13	8	7	0															
Events RUX	0	0	0	0	0	0	0	0	0	1	2	2	3	3	3	3	3	4	4	4	4	4	4	4
Events BAT	0	1	2	2	2	2	3	3	3															

[a] BAT patients not censored at the time of crossover; survival time was censored at the date of last contact irrespective of whether patients randomized to BAT crossed over to RUX.
[b] Defined as time from date of randomization to date of earliest development of myelofibrosis, acute myeloid leukemia, or death. [c] Data for crossover patients not included.
Full analysis set. AML, acute myeloid leukemia; KM, Kaplan-Meier; MF, myelofibrosis; OS, overall survival.

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Adverse events (exposure-adjusted rates)

	RUX (N=74)		BAT (N=75)		Crossover (N=58)	
Median (range) exposure	260.0 (0.1– 273.1) weeks		28.4 (6.7– 83.0) weeks		224.7 (2.7– 236.1) weeks	
Patient-year (PY) exposure[a]	334.27 days		53.35 days		205.96 days	
	Any Grades, n (rate/100 PY)	Grade 3/4, n (rate/100 PY)	Any Grades, n (rate/100 PY)	Grade 3/4, n (rate/100 PY)	Any Grades, n (rate/100 PY)	Grade 3/4, n (rate/100 PY)
Any AE	74 (22.1)	50 (15.0)	64 (120.0)	22 (41.2)	57 (27.7)	33 (16.0)
AEs of special interest						
Thromboembolic events (TEE)	5 (1.5)	4 (1.2)	2 (3.7)	0	6 (2.9)	3 (1.5)
Herpes zoster	13 (3.9)	3 (0.9)	0	0	8 (3.9)	0
Malignant tumors	15 (4.5)	7 (2.1)	4 (7.5)	3 (5.6)	9 (4.4)	5 (2.4)
Non-melanoma skin cancer (NMSC)	9 (2.7)	4 (1.2)	1 (1.9)	0	6 (2.9)	2 (1.0)
Myelofibrosis	2 (0.6)	0	1 (1.9)	1 (1.9)	1 (0.5)	0
Deaths	1 (1.4)		1 (1.3)		3 (5.2)	

- Safety profile was consistent with previous reports of RUX
- The most common AEs (>5%, exposure adjusted rate) associated with RUX were anemia, arthralgia, and increased weight in the RUX arm, and anemia and hypertension in patients after crossover
- Exposure-adjusted TEE rate (any Grade) was ~2.5x lower with RUX vs BAT, and ~2x lower with early RUX vs delayed RUX initiation
- Exposure-adjusted rates for NMSC were similar between crossover and RUX patients

[a] Defined as sum of each patient's exposure in days, divided by 365.25.
Safety set. AE, adverse event; PY, patient-years; NMSC, Non-melanoma skin cancer; TEE, thromboembolic events.

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Conclusions

- The RESPONSE-2 study establishes the long-term safety and efficacy of RUX in patients with HU-resistant or HU-intolerant PV without splenomegaly

- 5-Year efficacy results for RUX show:
  - Durable Hct control
  - Lower rate of phlebotomies with early RUX vs delayed RUX
  - Significantly improved PV symptoms vs BAT

- Safety profile was consistent with previous reports with no new safety signals
  - Lower rate of thromboembolic events with RUX vs BAT, and with early vs delayed RUX initiation

- 5-Year results from RESPONSE-2:
  - Build on the positive results from RESPONSE in PV patients with splenomegaly
  - Support RUX as 2nd-line therapy of choice in inadequately controlled PV without splenomegaly

BAT, best available therapy; Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib.

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