A phase II study of the oral JAK1/JAK2 inhibitor ruxolitinib in advanced relapsed/refractory Hodgkin lymphoma

Eric Van Den Neste,[1] Marc André,[2] Thomas Gastinne,[3] Aspasia Stamatoullas,[4] Corinne Haioun,[5] Amine Belhabri,[6] Oumedaly Reman, [7]Olivier Casasnovas,[8] Hervé Ghesquieres,[9] Gregor Verhoef,[10] Marie-José Claessen,[11] Hélène A. Poirel,[12] Marie-Christine Copin,[13] Romain Dubois,[13] Peter Vandenberghe,[14] Ioanna-Andrea Stoian,[15] Anne S. Cottereau,[16] Sarah Bailly,[1] Laurent Knoops[17] and Franck Morschhauser[18]

[1]Department of Hematology, Cliniques Universitaires Saint-Luc, UCL Brussels, Belgium; [2]Hematology Department, CHU UCL Namur, Yvoir, Belgium; [3]Hematology, CHU Nantes, France; [4]Clinical Hematology, Centre Henri Becquerel, Rouen, France; [5]Lymphoid Malignancies Unit, AP-HP, Groupe Hospitalier Mondor, Créteil, France; [6]Onco-hematology, Centre Leon Berard, University Claude Bernard Lyon 1, France; [7]Hematology, Centre Hospitalier Universitaire, Caen, France; [8]Hematology Department, Hopital Le Bocage, CHU Dijon, France; [9]Hospices Civils de Lyon, Université Claude Bernard, Centre Hospitalier Lyon-Sud, Pierre Bénite, France; [10]Department of Hematology, University Hospitals Leuven, Belgium; [11]Erasmus MC, Rotterdam, the Netherlands; [12]Center for Human Genetics, Cliniques universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [13]CHRU de Lille, France; [14]Center for Human Genetics, Katholieke Universiteit - Leuven, Belgium; [15]Nuclear Medicine, Cliniques Universitaires Saint-Luc, UCL Brussels, Belgium; [16]Nuclear Medicine, Hôpital Tenon, Paris, France; [17]Cliniques Universitaires Saint-Luc and de Duve Institute, Université Catholique de Louvain, Brussels, Belgium and [18]CHU Lille, Hematology Department, and Université de Lille, GRITA, France

 doi:10.3324/haematol.2017.180554

Received: September 12, 2017.

Accepted: January 10, 2018.

Pre-published: January 19, 2018.

Correspondence: franck.morschhauser@chru-lille.fr

Hijak study by E. Van Den Neste *et al*

Supplementary data:

Mandatory dose decreases or interruptions for hematological toxicity:

There are mandatory dose decreases or interruptions for declining platelet count or ANC level while on ruxolitinib therapy. Dosing must be held if platelet count decline below 25 x 109 /L, or if ANC falls below 0.5 x 109 /L. Patients with platelets below 50 x 109 /L and/or ANC below 0.5 x 109 /L should be followed biweekly.
The dose reduction strategy for platelet count is depicted in Table 1 This table takes into account doses that might be present after a prior dose reduction. Ruxolitinib dose will not be adapted to lymphocytes count.

Table 1 : dose reduction strategy for low platelet count

Platelet count at time of decline	Dosing at the time of platelet decline			
	20 mg BID	15 mg BID	10 mg BID	5 mg BID
	Dose that MUST be instituted			
≥ 75 x 10^9/L	No dose reduction required			
50 to < 75 x 10^9/L	10 mg BID	10 mg BID	10 mg BID	5 mg BID
25 to < 50 x 10^9/L	5 mg BID	5 mg BID	5 mg BID	5 mg BID
< 25 x 10^9/L	MUST stop dosing			

Restarting or re-instituting previous dose

Dosing may be restarted following recovery of platelet count and/or ANC to acceptable levels. ANC level recovery to above 500/µL but less than 750/µL will allow dosing to be restarted at 5 mg BID. ANC level between 750 and 1000/µL may restart at 10 mg BID. Increase of ANC above 1000/µL will allow a further dose increase to the initial dosing (15 mg BID or 20 mg BID).

Table 2: Restarting or increasing ruxolitinib dose after safety interruptions or dose reductions for low ANC count

Current ANC level	Recommendation
< 0.5 x 10^9/L	Continue hold
0.5 to < 0.75 x10^9/L	5 mg BID for at least one week; if stable, may increase to 10 mg BID
0.75 to < 1 x 10^9/L	10 mg BID for at least one week; if stable, may increase to 15 mg BID
≥ 1 x 10^9/L	15 mg BID. If stable for at least one week, increase to 20 mg BID for patients who were initially at 20 mg BID

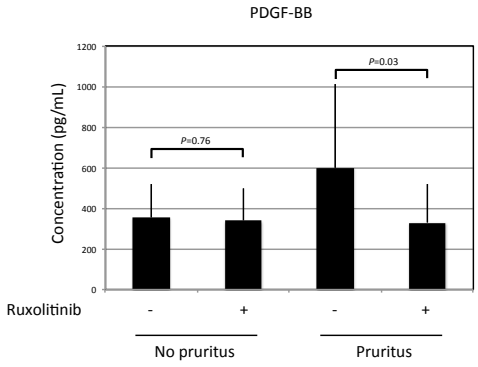
Table 3: Restarting or increasing ruxolitinib dose after safety interruptions or dose reductions for low platelet count

Current platelet level	Recommendation
< 25 x 10^9/L	Continue hold
25 to < 50 x 10^9/L	5 mg BID for at least one week; if stable, may increase to 10 mg BID
50 to < 75 x 10^9/L	10 mg BID for at least one week; if stable, may increase to 15 mg BID
≥ 75 x 10^9/L	15 mg BID. If stable for at least one week, increase to 20 mg BID for patients who were initially at 20 mg BID

Rules for permanent discontinuation

If the study drug is interrupted for any reason for more than 4 weeks, dosing may not be restarted. Study drug must be permanently discontinued if the lowest allowed dose (5 mg BID, or 5 mg QD with concomitant CYP3A4 inhibitor) is not tolerated due to the following: platelet count cannot be maintained > 25 x 109 /L, ANC cannot be maintained > 0.5 x 109 /L. Study drug must also be permanently discontinued due to the following: > grade 3 clinical event after re-challenge with the drug. Exceptions NOT requiring study withdrawal are fatigue, insomnia, obesity, constitutional symptoms (disabling but not life-threatening), salivary gland changes, arthritis, and joint effusion.

Cytokines



PDGF-BB concentration in patients with (n=8) or without (n=17) pruritus before treatment (-) and after one cycle of ruxolitinib (+).