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

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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 10^9 /L, or if ANC falls below 0.5 x 10^9 /L. Patients with platelets below 50 x 10^9 /L and/or ANC below 0.5 x 10^9 /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 |
|-----------------------------------|---------------------------------------|
| > 75 x 10^9 /L                    | Dose that MUST be instituted           |
| ≥ 50 to < 75 x 10^9 /L            | 10 mg BID                             |
| > 25 to < 50 x 10^9 /L            | 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 x 10^9 /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
### 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 (pg/mL) | PDGF-BB concentration in patients with (n=8) or without (n=17) pruritus before treatment (-) and after one cycle of ruxolitinib (+). |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Ruxolitinib                | PDGF-BB                                                                                                                        |
| -                           | No pruritus                                                                                                                     |
| +                           | Pruritus                                                                                                                        |

\[P_{0.05}\]