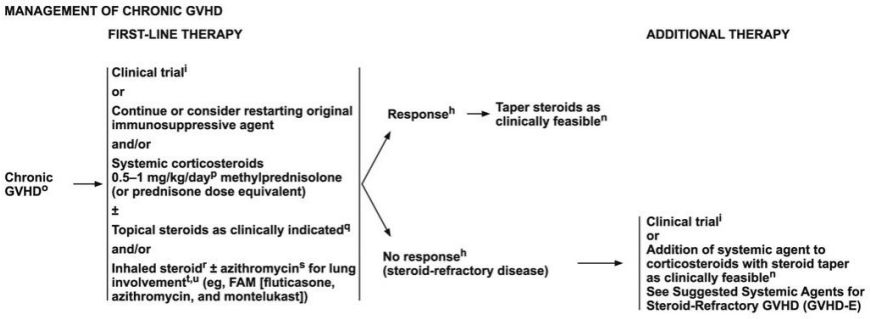
The Ohio State University
College of Pharmacy
Journal Club

Background and Overview	
Title	• Zeiser R, Polverelli N, Ram R, et al. Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. *N Engl J Med.* 2020; 382:1800-1810. DOI: 10.1056 • The Impact Factor for the New England Journal of Medicine is 91.245 and this research is appropriate for this journal as it publishes a wide range of clinical research for new therapies and practices
Funding Source	• This research was sponsored by Novartis and Incyte • A majority of the authors for this paper received speaking fees from Novartis and Incyte

Introduction/Background	• Graft-versus-host disease (GVHD) is a major complication in patients who have undergone allogenic stem-cell transplantation, occurring in 30-70% of patients
	  ○ In GVHD, the donor cells recognize the recipient's body as foreign and mounts an immune response resulting in damage to multiple organ systems
	  ○ Therapeutics (pharmacological)
	  ▪ The National Comprehensive Cancer Network (NCCN) guideline on hematopoietic stem cell transplant
	 

Objective(s)	
Methods	

Study Design	• Type of study:
	  ○ Retrospective, multi-center, phase 3 open-label, randomized trial evaluating the efficacy and safety of ruxolitinib at a dose of 10 mg twice daily, as compared with established 2nd line therapies outlined by the European Society for Blood and Marrow Transplantation
	  ○ The list of 10 options includes extracorporeal photopheresis, low-dose methotrexate, mycophenolate mofetil, everolimus or sirolimus, infliximab, rituximab, pentostatin, imatinib, or ibrutinib
	  ○ The trial was adequately powered to show superiority versus the control treatments
	  ○ Study protocol was approved at each participating study center by institutional review boards
	• Outcomes:
	  ○ Primary endpoint was overall response (including complete and partial) at 24 weeks
	  ○ Two key secondary endpoints were failure free survival (defined as time to recurrence of underlying disease, start of new systemic treatment for chronic GVHD, or death) and response on the modified Lee Symptom Scale (defined as a ≥7-point reduction from baseline in total symptom score on the scale, which measures the symptoms of chronic GVHD on a scale of 0 to 100, with higher scores indicating worse symptoms) at week 24
	• Efficacy & Safety
	  ○ Standard supportive care such as growth factors, antibiotics, transfusions, and other miscellaneous measures were allowed in both treatment groups
	  ○ Continued use of calcineurin inhibitors (tacrolimus, cyclosporine) and glucocorticoids was allowed
	  ○ Weekly patient visits occurred from day 1 to day 56 with follow up visits every 4 weeks afterwards through week 24
	  ○ A follow-up for safety was conducted 30 days after completion of the trial treatment and 6, 9, 12, 18, and 24 months to gather data on long term survival, progression, and safety outcomes
	• Interventions:
	  ○ Patients who received JAK inhibitors for acute GVHD were included if they had discontinued JAK inhibitor treatment at least 8 weeks before receiving the first dose of ruxolitinib or control treatment
	  ○ Monitoring of adherence was not explicitly addressed

	• Length of study was 24 weeks • Intention to treat analysis
Study Population	• 323 subjects recruited for the study (165 in the ruxolitinib group and 158 in the control group) • Patients were randomly assigned in a 1:1 ratio to receive either ruxolitinib or one of the control treatments • Inclusion Criteria: Patients were at least 12 years of age, had undergone allogeneic stem-cell transplantation, and had moderate to severe glucocorticoid-refractory or –dependent cGVHD based on the NIH consensus criteria • Exclusion Criteria: Patients treated previously with 2 or more systemic therapies for cGVHD in addition to glucocorticoids with or without calcineurin inhibitors. Patients who had a relapse of the primary cancer or had graft loss within 6 months before treatment initiation or if they had an active, uncontrolled infection.
Statistical Analysis	• The study population was large enough to provide a power of approximately 90% to test the primary and secondary endpoints • The Cochran–Mantel–Haenszel chi-square test, stratified according to the randomization stratification factor was used to compare endpoints between the treatment groups • The analyses were designed to test the hypothesis that ruxolitinib is superior to the current standards of care • P values were not reported for secondary outcomes, definitive treatment effects cannot be inferred from comparisons of the secondary outcomes • Cochran–Mantel–Haenszel chi-square test was used appropriately to determine associations between ruxolitinib and overall response rates to treatment versus control treatments across the stratified groups
Results	
Results of Study	• The median age of the patients was 52.5 in the treatment group versus 54 in the control group • 60:40 male to female, median BMI of 23 • Overall response (OR) at day 28 was 62% for the ruxolitinib group vs 39% for the control, odds ratio 2.64; 95% confidence interval [CI], 1.65 to 4.22; P<0.001 • Complete response at day 28 was 34% vs 19% • When comparing patients with grade II, III, and IV acute GVHD at baseline, grades II and III saw the highest rates of overall response with 75% vs 51% for grade II and 56% vs 38% for grade III • Ruxolitinib versus control had longer overall response even at day 56 versus control • Median failure free survival was 5 months vs 1 month, significantly longer for ruxolitinib (hazard ratio 0.46; 95% CI, 0.35 to 0.60)

	• Median overall survival was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15) • Adverse events of any grade occurred in 97.6% of the patients who received ruxolitinib as compared with 91.8% of the patients who received control therapy • Occurrence of adverse events of grade 3 or higher was similar in the two groups (in 57.0% of the patients who received ruxolitinib and in 57.6% of the patients who received control therapy) • Treatment discontinuation occurred in 111 of 154 patients (72%) in the ruxolitinib group and in 132 of 155 (85%) in the control group; the most common reason was lack of efficacy (in 32 [21%] and 68 [44%])
Authors' Conclusion	• Ruxolitinib was superior to current standards of care for patients with moderate to severe cGVHD with inadequate response to glucocorticoids in terms of overall response to treatment, longer failure-free survival, and greater symptom reduction • Patients receiving ruxolitinib had a higher incidence of grade 3 or worse thrombocytopenia and anemia than the control group • Previous trials have been conducted to study the efficacy of the control treatments which often encountered poor sustained response to treatments and high rates of infectious complications
Student's Discussion and Conclusion	
Strengths/Limitations	• Forms of bias in study include patient selection and patients unblinded to treatments received • Study medications and dosages received were in line with current NCCN guidelines on hematopoietic stem cell transplant • The study met power for the primary and secondary endpoints • Internal & external validity ○ Patient recruitment- 309 patients were recruited from 105 treatment centers in 22 countries • Limitations include severity of illness and high rate of adverse events in both control and treatment groups that led to high rate of discontinuation of therapy • High rate of mortality due to GVHD and underlying disease limited follow up • Compared to the results of similar studies on the control treatments, there is slight variations seen in terms of frequency of adverse events and efficacy • This may be due to small sample size leading to underpowered studies

Conclusion/ Recommendations for practice site	• Ruxolitinib offers a more robust initial response to treating GVHD compared to current standards of care when glucocorticoids are ineffective
	• Clinically significant in terms of its duration of response with a greater median failure-free survival and median overall survival
	  o The number needed to treat (NNT) to see a complete response in 28 days is 6.7
	• Adverse events were high in both treatment groups with thrombocytopenia, anemia, and cytomegalovirus infection being the most common
	• Clinical versus statistical significance
	  o Clinical trials are a recommended 1st line treatment for patients with glucocorticoid refractory GVHD per NCCN guidelines, this medication is already being used in practice to treat this condition
	• Further studies will most likely lead to FDA approval for its use in cGVHD, the REACH 2 trial led to its approval for use in aGVHD
	• This a specialty medication

Glossary	**Modified Lee Symptom Scale:** 28-item scale measuring the symptoms of cGVHD considering the patient's quality of life, functional status, and survival using a 7-day recall period **Cochran–Mantel–Haenszel chi-square test**: a modification of the traditional chi-square test that is used to test the associations between different interventions and a binary outcome while still taking into account stratification of groups
References	C Teh, L Onstad, SJ. Lee. Reliability and validity of the modified 7-day Lee chronic graft-versus-host disease Symptom Scale. Biol Blood Marrow Transplant. 2020; 26:562-567. DOI: 10.1016. Malard F., Huang XJ., and Sim J.P.Y. Treatment and unmet needs in steroid-refractory acute graft-versus-host disease. Leukemia. 2020; 34**:**1229–1240. DOI: 10.1038.