Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Hi, my name is John Mascarenhas. I'm from the Icahn School of Medicine at Mount Sinai. Today, we'll be talking about novel agents and treatment strategies for relapsed/refractory myelofibrosis. The reason why this is an interesting, important, and relevant topic to those people in the field, whether they are physicians, NPs, PAs, or other mid-level providers to patients with myelofibrosis, this is a dynamic area of clinical translational research. In the last decade, we've enjoyed benefit of JAK inhibitors, but one will appreciate from this presentation that there are many other therapies now that are in clinical development, either in combination or in lieu of JAK inhibitors. The field is really poised to change in significant ways in which the practitioner will need to be aware of and the impact on patients will be notable. I hope from this presentation that we'll come across and the viewers will come away with a better appreciation of where we've been and where we're going.

Disclosures

- Dr. John Mascarenhas has received honoraria related to formal advisory activities and as a consultant from AbbVie Inc., Bristol-Myers Squibb Company, Celgene Corporation – A Bristol-Myers Squibb Company, Constellation Pharmaceuticals, F. Hoffmann-La Roche Ltd, Geron, Incyte Corporation, and PharmaEssentia Corporation. He has received grant support related to research activities from AROG Pharmaceuticals, Inc., CTI BioPharma Corp., F. Hoffmann-La Roche, Forbius, Incyte, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Merus, Novartis AG, and PharmaEssentia.

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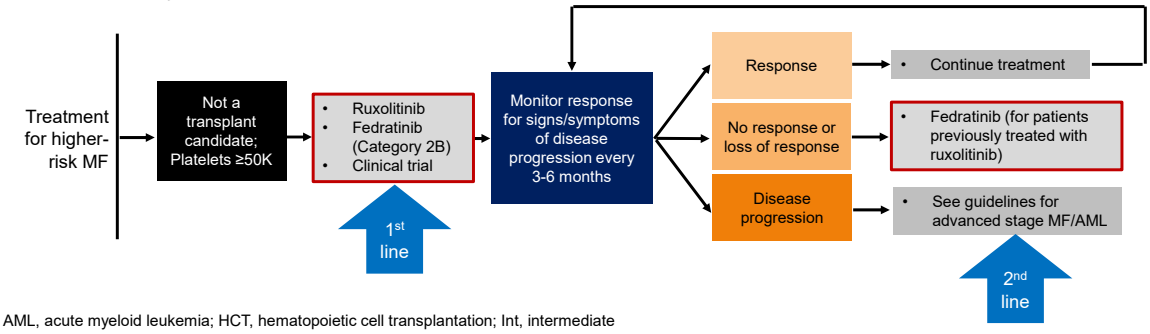
The NCCN Guidelines for Treatment of Myelofibrosis in the First- and Second-line Setting

- Guidelines from the US NCCN recommend fedratinib as:
  - Category 2B for initial treatment of higher-risk patients with MF who are not transplant candidates and have platelet counts ≥50×10^9/L
  - Category 2A for post-rux therapy if no response or loss of response is observed in patients previously treated with ruxolitinib



AML, acute myeloid leukemia; HCT, hematopoietic cell transplantation; Int, intermediate
NCCN Clinical Practice Guidelines: Myeloproliferative Neoplasms. Version 1.2021. Published April 13, 2021. Accessed June 28, 2021.

I've started off the talk with the NCCN guidelines for the treatment of MF, and I sat in both the first- and second-line option. Of course, the first-line option for patients with intermediate- or high-risk disease by any of the risk scoring systems would be a JAK inhibitor therapy, really geared to addressing spleen and symptom burden. Ruxolitinib approved since 2011, is usually the first-line choice for patients with myelofibrosis in need of treatment, but it is important to realize that fedratinib, now approved in August of 2019 in the US, and now recently in the UK, is a second-line option, but can also be used frontline with a category 2B recommendation. For those patients who received JAK inhibitors, it's important to remember that they can induce some degree of on-target myelosuppression, reduction in hemoglobin and platelet count, and that should be explained upfront, and monitored in an appropriate fashion. But the majority of patients who are treated with these agents do enjoy symptom and spleen benefit and have to be observed for that response and/or lack of response or loss of response. Patients who ultimately lose response or who never have an optimal response in spleen and symptom benefit, really need to be evaluated in a dynamic fashion for second-line therapies, such as fedratinib, listed here, which is a commercially available JAK2/FLT3 inhibitor that can be used second-line, and is mostly used second-line currently in the US to salvage responses, particularly spleen responses in patients who've had a previous ruxolitinib treatment.

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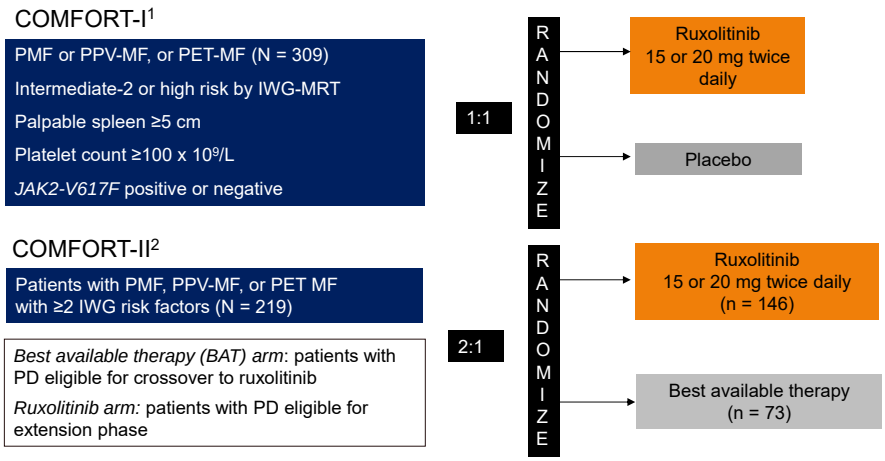
Phase 3 COMFORT-I and -II: Ruxolitinib in MF



IWG-MRT: International Working Group consensus criteria for Myelofibrosis Research and Treatment; PD: progressive disease; PET-MF: post-essential thrombocythemia MF; PPV-MF: post-polycythemia vera MF.
1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. 2. Harrison C, et al. *N Engl J Med*. 2012;366:787-798.

Just to remind the audience, the COMFORT studies were the pivotal studies, the Phase 3 studies that led to the approval of ruxolitinib, COMFORT-I in the US and Canada, COMFORT-II below in nine European countries. COMFORT-I was ruxolitinib versus placebo and COMFORT-II was ruxolitinib versus best available therapy.

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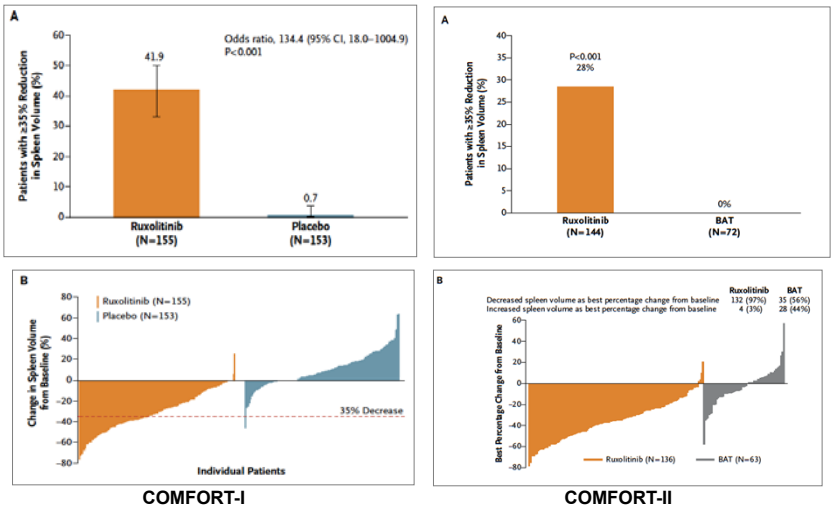
Ruxolitinib Phase 3 Trials (COMFORT-I and –II: Spleen Response)



COMFORT-I COMFORT-II

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.; Harrison C, et al. *N Engl J Med*. 2012;366:787-798.

It was quite obvious from these trials that ruxolitinib was superior in terms of spleen volume reduction, 35% is considered the regulatory benchmark for positive response, which was hitting 42% of patients who received ruxolitinib versus less than 1% placebo in COMFORT-I, and similarly in COMFORT-II significant reduction in spleen. If you look at the waterfall plots below, which I think are even more meaningful, there's a spectrum of responses that even occur in most patients, even 10% or greater is thought to be clinically relevant. Whereas, if you look at the patients who got placebo or best available therapy, most of those patients had worsening of their spleen volume, which is an indication of the natural history of the disease.

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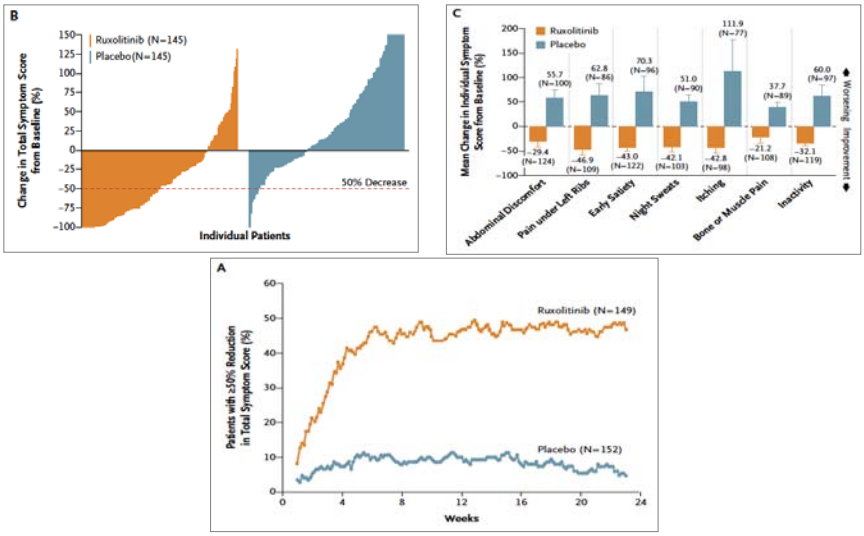
Ruxolitinib Phase 3 Trials (COMFORT-I: Symptom Response)



Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.

Symptoms were also greatly improved shown here, and I show you the waterfall plots. Patients enjoyed, usually rapid improvement in their symptoms, and no matter what type of symptom burden you looked at, orange indicates those patients in COMFORT-I who got ruxolitinib, going below the line indicates a reduction and improvement in symptom burden. This was seen across each symptom type with ruxolitinib treatment and not seen with placebo, and that symptom burden was both rapid and durable as shown in the graph below.

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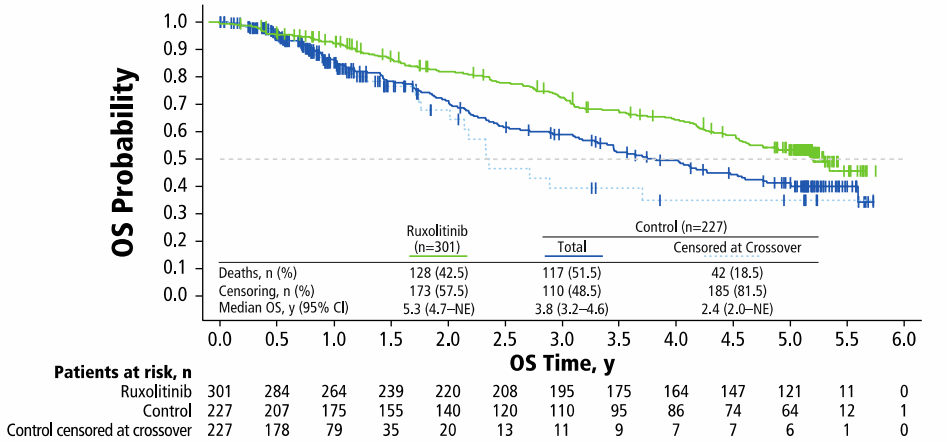
Pooled OS Analysis of Five-year Data from COMFORT-I and -II Trials of Rux for Tx of MF



Verstovsek S, et al. *Blood.* 2016;128(22):3110-3110.

Now, what was very interesting and unexpected, we did not see bone marrow histopathologic responses or complete molecular responses with ruxolitinib, but we did see, and this is a five-year data of pooled analysis of COMFORT study survival benefits. If you look at the green line, those are patients who received ruxolitinib upfront. The median survival is approximately five years in those patients. Where the patients who are in the blue line, who received either BAT or placebo and crossed over, the median survival is approximately 3.8/4 years. The dotted line is an interesting line. It's a model, a statistical model, that would suggest those patients who received the control arms, and if they were to exist and continue on those control arms and were modeled based on their initial response and survival, that is a rank preserving structural failure test model that shows what those patients would look like if they were existed in terms of survival, and that's about 2.4 years. It's compelling evidence that despite the absence of molecular and pathologic remission, there is a survival benefit of early use of ruxolitinib, which we believe is mediated by improvements in symptom burden, and reversal of cachexia and performance status rather than anti-clonal deletion.

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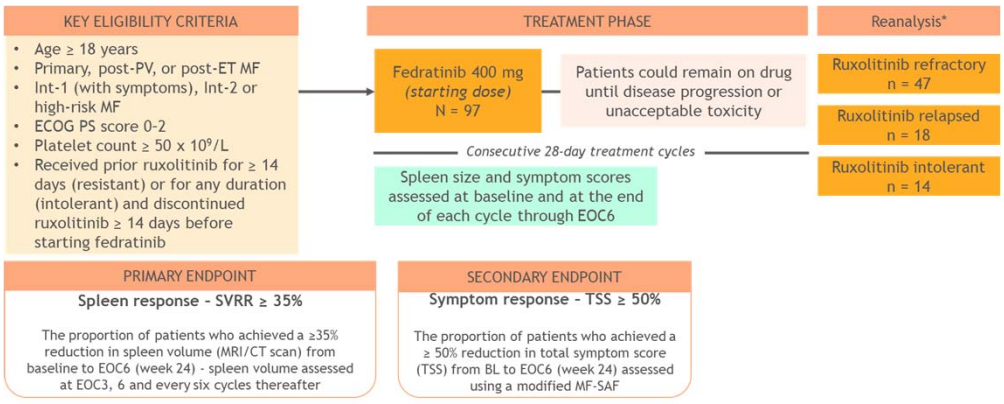
Fedratinib: JAKARTA2 Study Design



*Patients were recategorised for prior ruxolitinib failure based on revised stringent criteria.
BL, baseline; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EOC, end of cycle; ET, essential thrombocythaemia; Int, intermediate; IWG-MRT, International Working Group-Myeloproliferative Neoplasms Research and Treatment; LCM, left costal margin; MF, myelofibrosis; MF-SAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PV, polycythaemia vera; SVRR, spleen volume response rate; TSS, total symptom score.
a. Primary endpoint was defined by Passamonti F, et al. *HemaSphere*. 2020;4:EP1109, as "spleen response was defined as a ≥50% reduction in spleen size by palpation for patients with spleens measuring ≥10 cm from the LCM at BL, or a reduction to a non-palpable spleen for patients with BL spleen sizes >5–10 cm from LCM (IWG-MRT criteria). Spleen size by palpation was measured at BL and at the end of each treatment cycle."
Harrison CN, et al. *Am J Hematol*. 2020;95:594-603.;Talpaz M, Kiladjian J-J. *Leukaemia*. 2020;35:1-17.; Passamonti F, et al. *HemaSphere*. 2020;4:EP1109.

Fedratinib is the second JAK inhibitor approved. It's actually been in clinical development for quite some time, it took some time to get it approved. I show you here the JARKATA-2 study because that may be the most pivotal study, the JAKARTA study. The original study was randomized Phase 2/3 comparing to ruxolitinib in patients who are JAK inhibitor naive. This is patients who've seen at least 14 days of ruxolitinib previously and received fedratinib in a single-arm Phase 2 open-label study at 400 milligrams daily.

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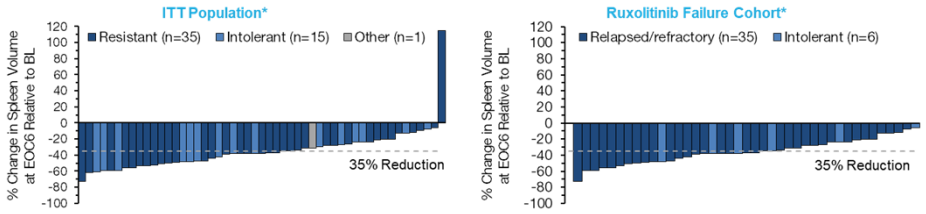
Spleen and Symptom Response Rates

- Clinically relevant prognostic BL disease characteristics indicate a population of difficult-to-treat patients with advanced MF disease and high-disease burden
- Spleen volume and symptom response rates were consistent among the three patient cohorts
- Median duration of spleen response was not reached (95% CI: 7.2 months, NR) in the ITT population, ruxolitinib failure cohort, or sensitivity cohort

	ITT population (N = 97)		Ruxolitinib failure cohort (n = 79)		Sensitivity cohort (n = 66)	
	N	% of patients (95% CI)	N	% of patients (95% CI)	N	% of patients (95% CI)
Spleen volume response rate	97	31% (22–41%)	79	30% (21–42%)	66	36% (25–49%)
Symptom response rate*	90	27% (18–37%)	74	27% (17–39%)	62	32% (21–45%)

*Includes patients with an evaluable baseline and ≥1 post-baseline MFSAF assessment.

Individual Changes in Spleen Volume from Baseline to End of Cycle 6



BL, baseline; CI, confidence interval; EOC, end of cycle; ITT, intention to treat; NR, not reached.
Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.

What this study showed very nicely in this patient population that was both refractory and resistant or intolerant to ruxolitinib is a 30% improvement in spleen volume and a 30% improvement in symptom response. Despite "failure of first-line JAK inhibitor therapy," fedratinib afforded a third of the patients that benchmark response. Again, if you look at the waterfall plots below, one can appreciate in an intention-to-treat rigorous analysis that the majority of patients treated with fedratinib enjoyed some degree of spleen volume response. This is a meaningful second-line agent clearly for patients with ruxolitinib failure that's commercially available.

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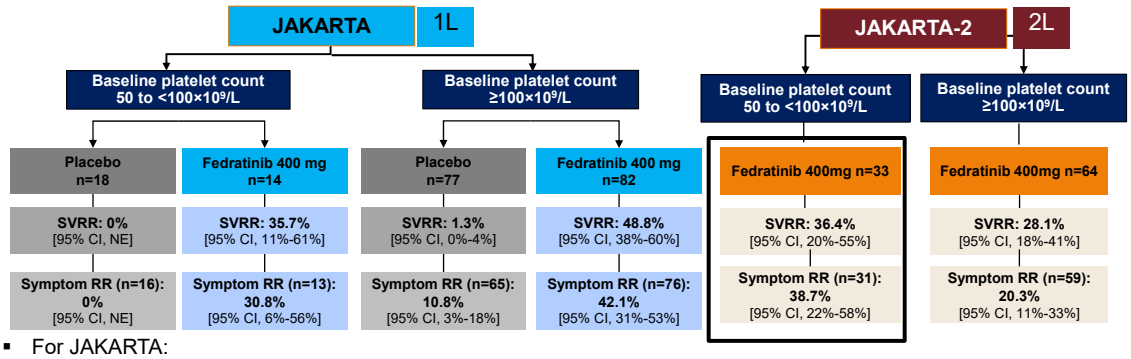
Fedratinib Induced Similar Levels of Spleen and Symptom Responses in Patients with Platelet Counts 50×10^9/L to <100×10^9/L



- For JAKARTA:
  - Within the fedratinib 400-mg treatment arm, there was no statistically significant difference in spleen volume response rate (SVRR) or symptom response rate (RR) between baseline platelet count subgroups
  - Median duration of exposure for this analysis was 24 weeks in both treatment arms and across baseline platelet count subgroups
- For JAKARTA-2:
  - There was no statistically significant difference in SVRR or symptom RR between baseline platelet count subgroups
  - Median exposure to fedratinib on-study was similar for patients with baseline platelet counts of 50 to <100×10^9/L or ≥100×10^9/L

Symptom RR is the proportion of patients who achieved a ≥50% reduction from baseline to end of Cycle 6 (EOC6) in TSS on the modified Myelofibrosis Symptom Assessment Form (MFSAF). NE, not estimable.
Harrison CN, et al. *Am J Hematol.* 2020;95:594-603.

Fedratinib has also been explored. I think this slide is important because platelets matter. Low platelets factor into risk scoring, they also limit the ability to effectively give JAK inhibitors, the label for ruxolitinib label is greater than 50,000. Similarly, for fedratinib, the label is greater than 50,000. What the analysis here shows that you can effectively give fedratinib at 400 milligrams daily to patients with platelet counts of 50,000 to 100,000 without dose reduction, which would, in theory, reduce the efficacy of the drug or attenuate the efficacy, and you still get spleen volume responses that exceed 30% as well as spleen symptom responses, so highly effective at similar doses in patients with platelet counts of 50,000 to 100,000 without the need for dose reduction.

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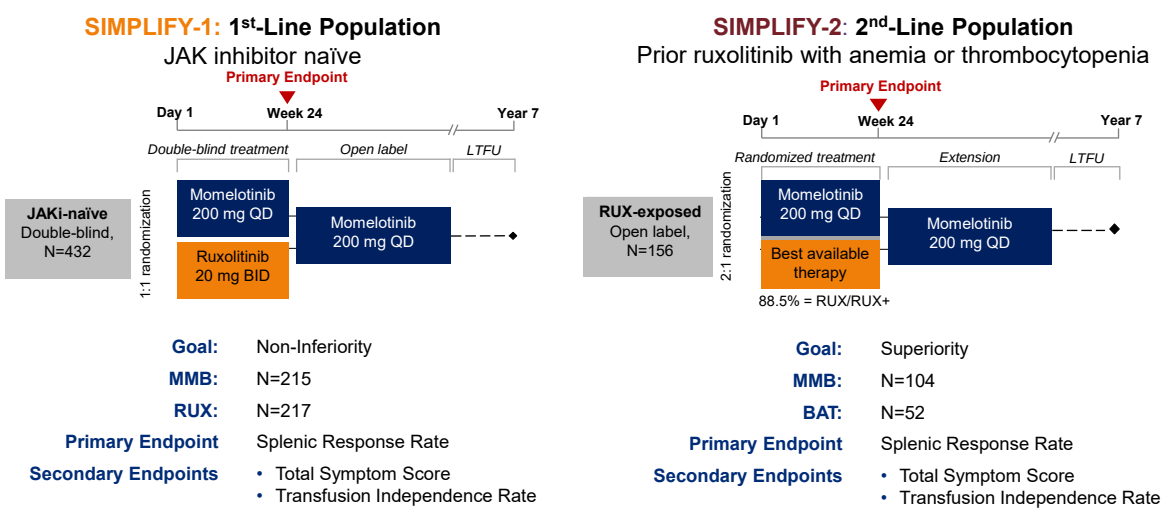
Momelotinib – Background: Completed Phase 3 Studies SIMPLIFY-1 and -2



Mesa R, et al. *J Clin Oncol.* 2017;35(34):3844-3850.; Harrison C, et al. *Lancet Haematol*. 2018;5(2):e73-e81.

Now, it's important to note the other JAK inhibitors that are very far advanced in clinical development, like momelotinib. This is a JAK1/2 ACVR1 inhibitor. Here I'm showing you the two pivotal studies, SIMPLIFY-1 and SIMPLIFY-2. SIMPLIFY-1 was momelotinib versus ruxolitinib in those that are JAK inhibitor naïve, and SIMPLIFY-2 were those patients who had Rux exposure and then got randomized to momelotinib or best available therapy in which ruxolitinib could be used as well.

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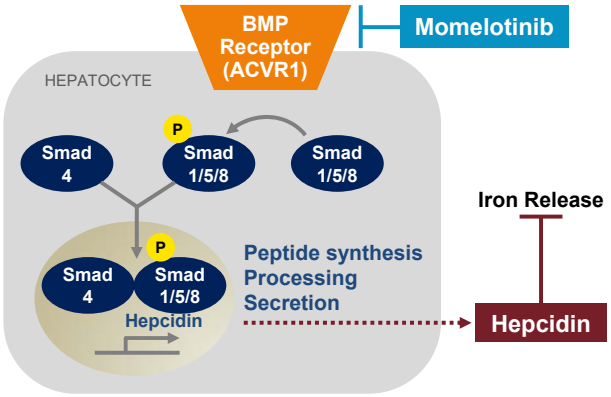
Off-Target Effect of Momelotinib May Explain Potential Anemia Benefit

- MMB also inhibits activin A receptor, Type 1 (ACVR1)
- ACVR1 activation leads to increased hepcidin gene expression[1]
- Hepcidin decreases plasma iron and hepcidin is elevated in MF[2]
- MMB ameliorates anemia in a rodent ACD model[1]



Adapted from Peterson P, et al. AACR 2015. Abstract 3647.

ACVR1, Activin A Receptor Type 1; BMP, bone morphogenic protein.
1. Asshoff M, et al. *Blood.* 2017;129:1823-1830. 2. Pardanani A, et al. *Am J Hematol.* 2013;88:312-316.

What I want to skip to is the fact that momelotinib has potentially a distinction amongst the other JAK inhibitors as it inhibits activin A receptor Type 1 which mediates SMAD signaling and then eventually hepcidin expression which may affect iron metabolism and distribution and can affect erythropoiesis in a meaningful way. This may underlie the reason why in the early phase studies, there was a clear improvement in anemia and reduction transfusion dependence that was durable. That is quite distinct from ruxolitinib and fedratinib in which there's on-target and essentially expected anemia and thrombocytopenia.

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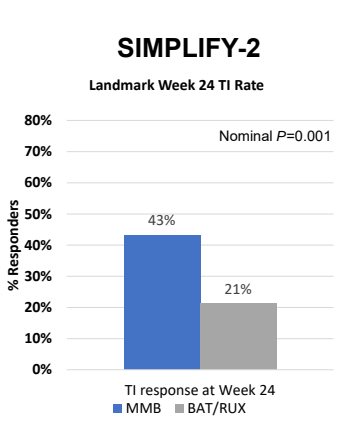
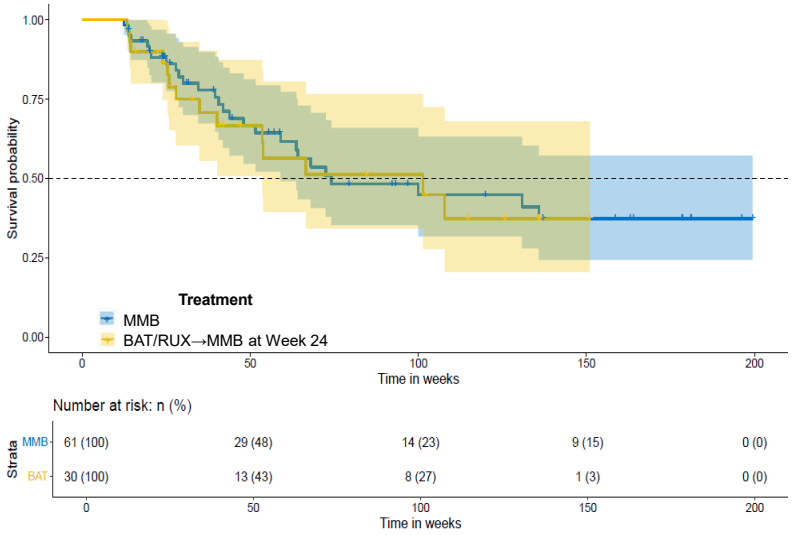
SIMPLIFY-2: Transfusion Independence and Duration of TI





Verstovsek S, et al. ASH 2020.

Most recently at ASH Srdan Verstovsek and colleagues looked at the SIMPLIFY-2 studies, this was after ruxolitinib exposure. If you look at the patients who received momelotinib in blue, the transfusion independence rate, those that were converted from dependent to independent was 43% compared to 21% in those patients who received the best available therapy. That translated to a durable transfusion independence-free survival, as shown on the graph on the right and a distinction of this JAK inhibitor amongst the other JAK inhibitors.

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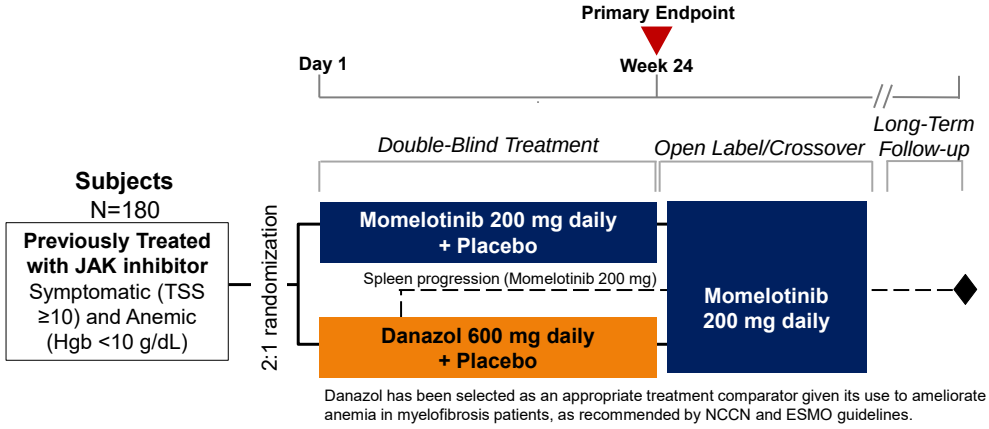
MOMENTUM P3 Trial: Phase 3 Registration Trial Schema

A Randomized, Double-Blind, Phase 3 Study to Evaluate the Activity of Momelotinib (MMB) versus Danazol (DAN) in Symptomatic, Anemic Subjects with Primary Myelofibrosis (PMF), Post-Polycythemia Vera (PV) Myelofibrosis, or Post Essential Thrombocythemia (ET) Myelofibrosis who were Previously Treated with JAK Inhibitor Therapy



Danazol has been selected as an appropriate treatment comparator given its use to ameliorate anemia in myelofibrosis patients, as recommended by NCCN and ESMO guidelines.

ClinicalTrials.gov NCT04173494. Available at: https://clinicaltrials.gov/ct2/show/NCT04173494.

For this reason, the MOMENTUM study is an important study to keep in mind and refer patients to if appropriate. These are patients who have previously been treated with ruxolitinib and have symptom and spleen burden and anemia, then randomized to momelotinib versus danazol which has anemia response rate of about 30% in most studies. The primary endpoint of this study is a total symptom score improvement, but the key secondary endpoints are spleen volume response and transfusion independence anemia response. We look forward to this study because this could add a drug that could provide JAK inhibition benefits, but also with effects on anemia.

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Pacritinib: PERSIST-1/-2: Platelet Count <50,000/μL

Spleen volume response in patients with severe thrombocytopenia

	Pooled PAC all doses N=104	Pooled PAC 400 mg QD N=73	PAC 200 mg BID N=31	Pooled BAT N=48
N (%) with ≥35% SVR	23%	21%	29%	2%
***P*-value vs BAT**	**0.0007**	**0.0025**	**0.0059***	-

* *P*-value compared to BAT from PERSIST-2

Total Symptom Score reduction in patients with severe thrombocytopenia

	Pooled PAC all doses N=80	Pooled PAC 400 mg QD N=49	PAC 200 mg BID N=31	Pooled BAT N=37
N (%) with ≥35% SVR	20%	18%	23%	11%
***P*-value vs BAT**	0.29	0.38	0.34*	-

* *P*-value compared to BAT from PERSIST-2

Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

Which leads us to pacritinib which has been evaluated in the PERSIST studies. I'm showing you here a composite of PERSIST-1 and PERSIST-2. These were randomized Phase 3 studies comparing pacritinib, which is a selective JAK2, FLT3, IRAK1 inhibitor particularly in patients with low platelets. It was learned early on in the development of this drug, this drug seemed to be less myelosuppressive than the other inhibitors and could be delivered effectively in patients with an unmet need. Those are patients with less than 50,000, which the current JAK inhibitors exclude, and you can see here from this analysis, the SVR rate was approximately 30%. This is an outstanding finding that allows patients with low platelets that would normally be discriminated against due to their platelet count and the on-target thrombocytopenia of other JAK inhibitors to enjoy a spleen benefit on top and even symptom benefit below.

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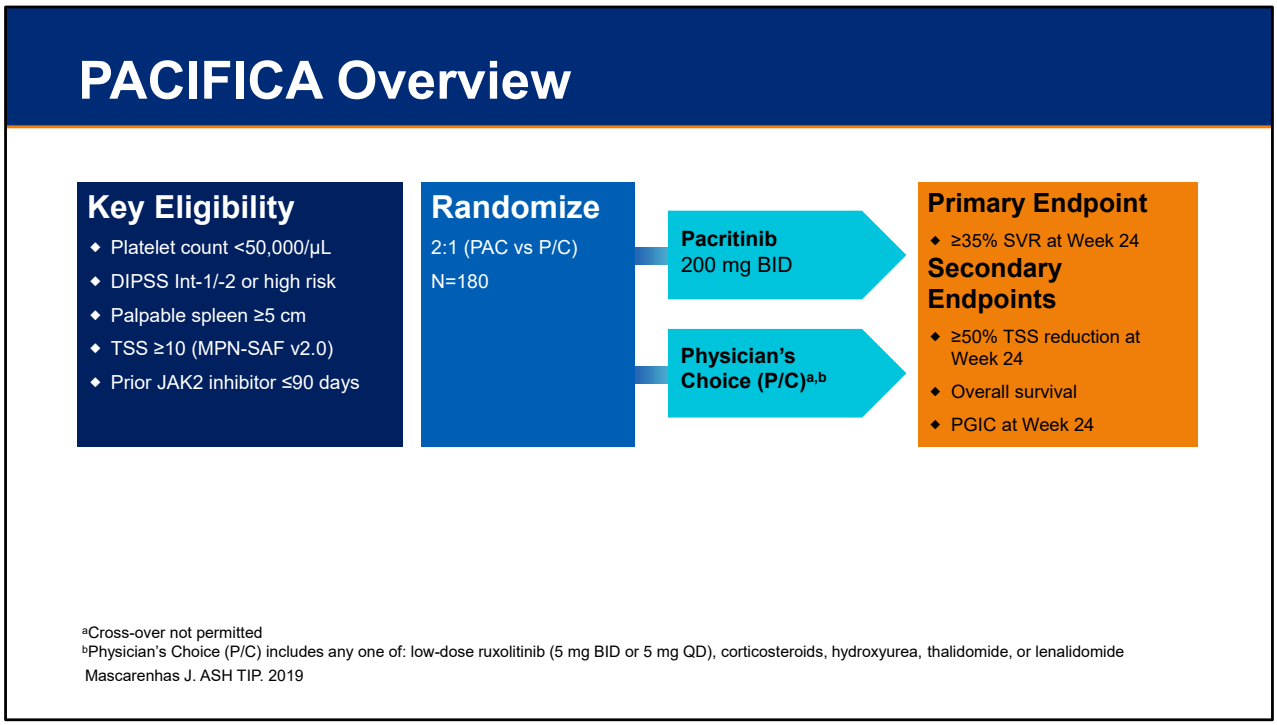

This ultimately led to the PACIFICA study, which is an ongoing randomized Phase 3 study in low platelets, exclusively patients with less than 50,000 who have spleen and symptom burden who have less than 90 days of prior JAK inhibitor, they're randomized two to one to pacritinib. Then best available or physician's choice with a primary endpoint of SVR and a key secondary endpoint of symptom improvement.

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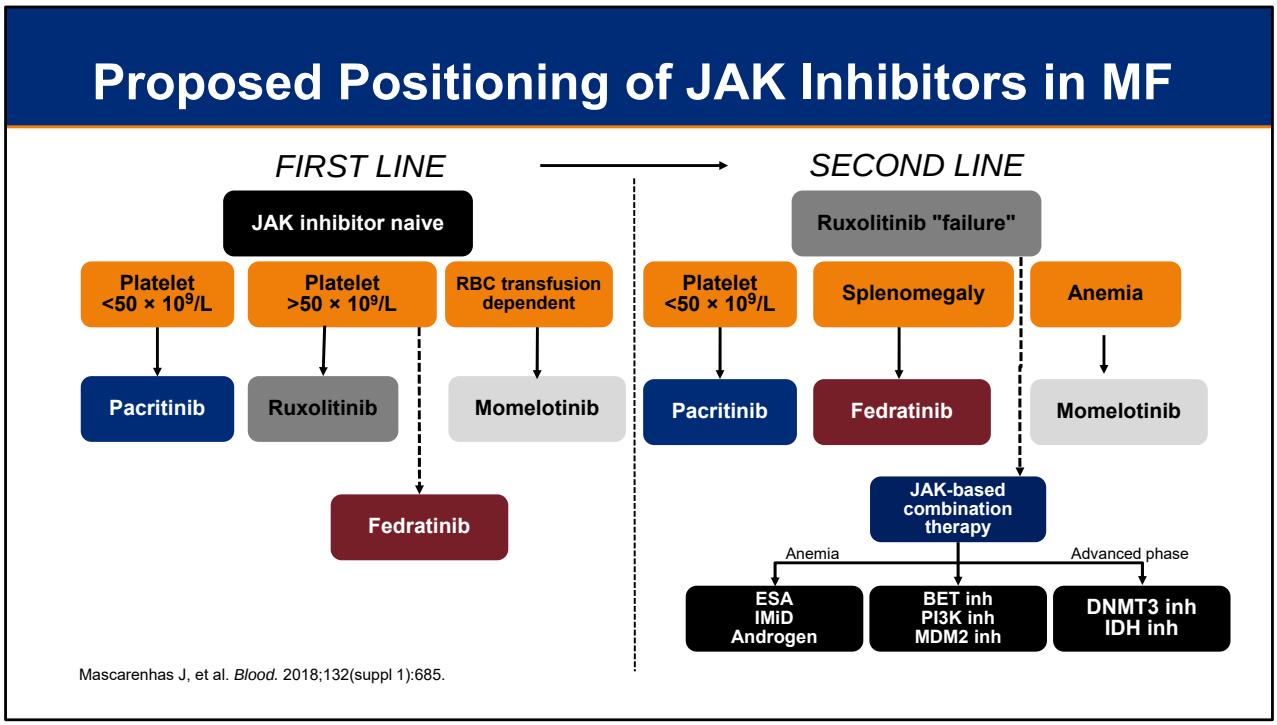

Here's my slide I've shown multiple times at talks. I have envisioned in a perfect world where there were multiple agents involved, one could see in the second-line on the right, if you fail ruxolitinib and low platelets pacritinib could meet that need. For those that have profound progressive splenomegaly, fedratinib is likely a great option. Then for those patients that have significant anemia, transfusion independence, that's driving the disease burden, momelotinib would be a great option. Now there are many drugs, and this is where the remaining part of this talk that are in clinical investigation, either as add-on strategies to JAK inhibitors to improve upon them in suboptimal or failure situations and/or drugs that could be used with different mechanism of action after JAK inhibitor failure.

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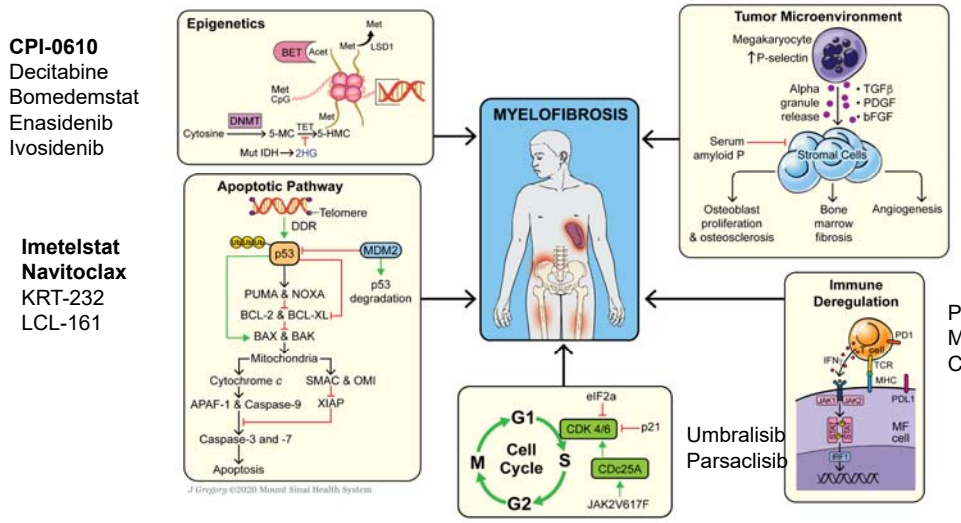
Novel Non-JAK Inhibitor Therapies in MF



Venugopal S, Mascarenhas J. *Hematol Oncol Clin North Am.* 2021;35(2):353-373., J Gregory © 2020 Mount Sinai Health System.

Here's a summary slide looking at the novel non-JAK inhibitor therapies that are in development in MF. What I try to do is break it down into groups, epigenetics on the left. I've highlighted the ones that we will quickly mentioned in today's talk CPI-0610 is an oral pan-BET inhibitor. Very interesting drug that has relevance and preclinical data in this setting. As well as down below those that affect the apoptotic pathway mechanisms like imetelstat the telomerase inhibitor, navitoclax the BCL-2/BCL-XL inhibitor. Then on the right, we are very aware that the tumor micro-environment supports the malignant stem cell population and drugs that can target, for example, TGF-beta or P-selectin can be very effective here. These are still in early clinical development. Immune deregulation is a hallmark of myelofibrosis, but actually immune targeting agents are still in its infancy. We have data on pembrolizumab that we are on the verge of publishing that would suggest that it's an inactive drug alone but that the correlative data would suggest that there are clear changes in the immune repertoire of patients treated with pembrolizumab that would suggest that it may be a great combinatorial partner. Of course recently, a calreticulin vaccine trial was published, although negative results suggest that this is an avenue that should be pursued more intensely. Then lastly, signaling pathway inhibitors that could compement the JAK inhibition such as the PI3 kinase inhibition.

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CPI-0610, a Bromodomain and Extraterminal Domain Protein (BET) Inhibitor, As Monotherapy in Advanced Myelofibrosis Patients Refractory/Intolerant to JAK Inhibitor: Update from Phase 2 MANIFEST Study

Moshe Talpaz[1], Raajit K. Rampal[2], Srdan Verstovsek[3], Claire Harrison[4], Mark W Drummond[5], Jean-Jacques Kiladjian[6], Alessandro M. Vannucchi[7], Marina Kremyanskaya[8], Gary J. Schiller[9], Andrea Patriarca[10], Gwendolyn Van Gorkom[11], Prithviraj Bose[3], Ronald Hoffman[12], Katarina Luptakova[12], Jessica Christo[12], Jing Wang[12], Jennifer A Mertz[12], Gözde Colak[12], James Shao[12], Suresh Bobba[12], Patrick Trojer[12], Adrian Senderowicz[12], John Mascarenhas[8]

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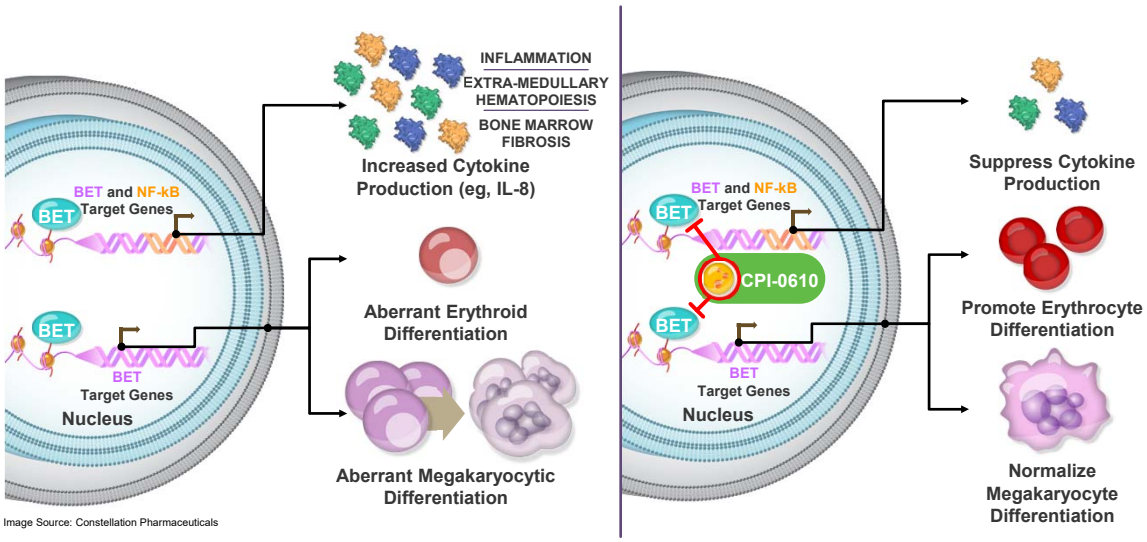
Abstract #2163

CPI-0610, these are one of the few that I'll highlight because I think they're important and they have the potential for paradigm shifts in this field is a pan-BET inhibitor. This is the MANIFEST-2 study.

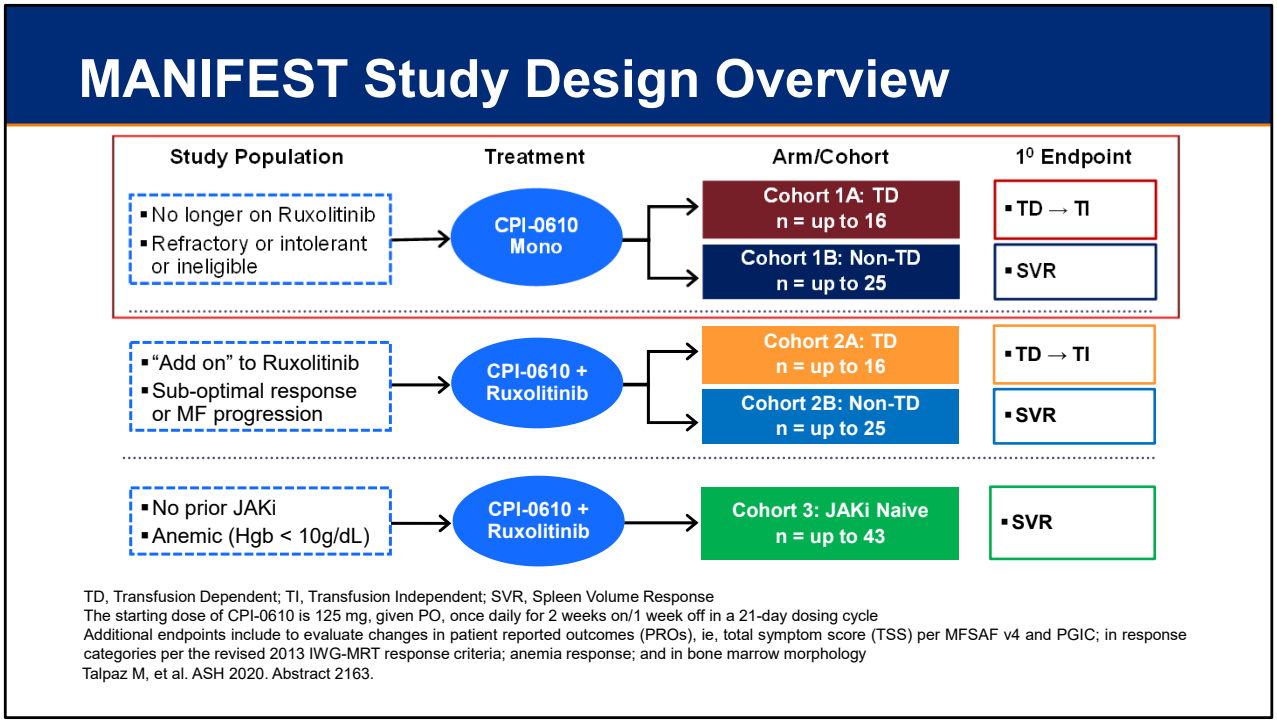
Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

BET Inhibitor CPI-0610 in Myelofibrosis



BET proteins are important epigenetic proteins. They are considered reader proteins and they facilitate gene transcription in the context of the epigenome. It is known that BET proteins, particularly BRD4 as there are a number of these BET proteins, regulate transcription of NF-κB target genes that are important for inflammation, extramedular hematopoiesis, and regulate factors that mediate bone marrow fibrosis and may also play an important role in aberrant, erythroid, and megakaryocyte differentiation, and this has been shown in preclinical modeling. Therefore, drugs that could block this, like CPI-0610, could have ameliorating effects on all these aspects that are meaningful to myelofibrosis.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis



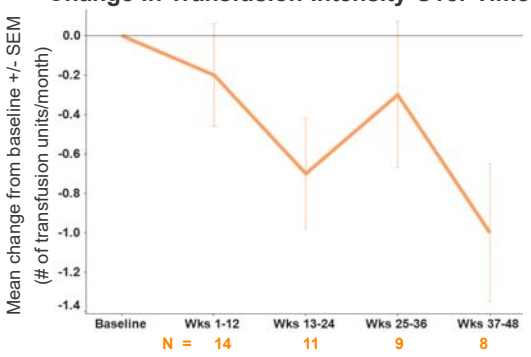
For that reason, we took this drug into the Phase 2 setting, the MANIFEST study. Today, I'm just going to concentrate on, there are three cohorts, I'm going to concentrate on the cohort up on top which is the monotherapy cohort. This is patients who have failed ruxolitinib and got CPIs monotherapy at 125 mg two week on/one week off and were stratified by those patients who are transfusion dependent. The endpoint would be conversion to transfusion independence and those patients who had big spleens and SVR would be the endpoint. The other cohorts that were included in the study were those that were add-on strategies to patients who were having a suboptimal response to ruxolitinib. Then for those patients, ultimately, who had never seen a JAK inhibitor, we're using this drug CPI-0610, now known as pelabresib, in combination with ruxolitinib upfront. Very paradigm-shifting as ruxolitinib has really been the mainstay as monotherapy for over a decade.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

CPI-0610 Monotherapy–Transfusion Dependent Cohort Primary Endpoint: 21% of Patients Converted to Transfusion Independence

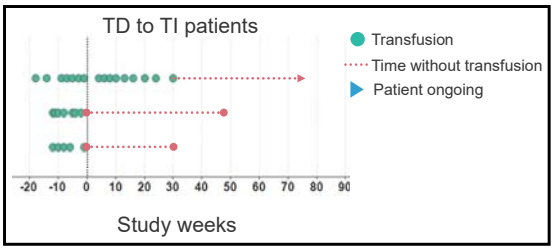
- 57% (8/14) of patients had ≥30% reduction in transfusion intensity

Change in Transfusion Intensity Over Time



TD Cohort Primary Endpoint	
TD to TI conversion	21% (3/14)
Median duration of TI*	32 wk (range 20, 38)

*Transfusion-free duration after 12 weeks conversion time



29 Sep 2020 data cut

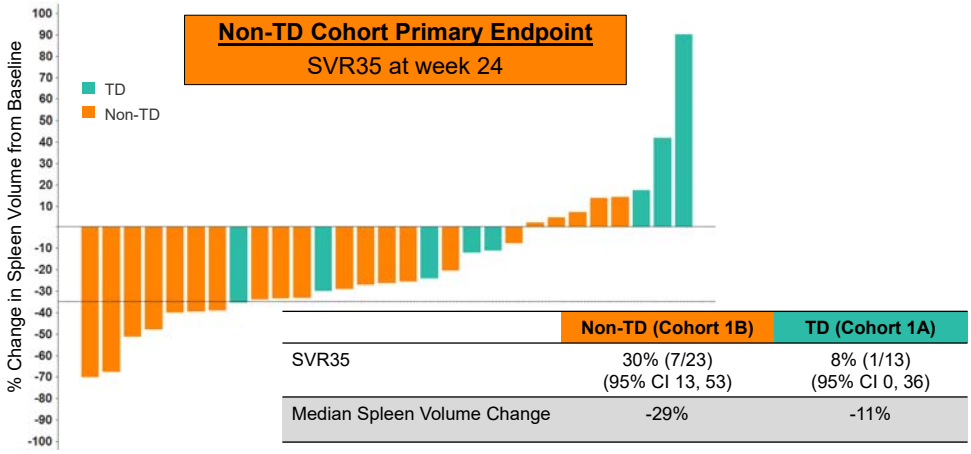
Baseline transfusion intensity=Average # of transfusion units per month (4 weeks) during 16 weeks prior to study entry
Post-baseline transfusion intensity=Average # of transfusion units per month (4 weeks) during 12-week period
Timepoints where N>4

Talpaz M, et al. ASH 2020. Abstract 2163.

What do we see with CPI-0610 as monotherapy? First of all, 21% of patients that were transfusion-dependent converted to transfusion independence, 57% of those patients had at least a 30% reduction in transfusion intensity, and the mean duration of transfusion independence was approximately 32 weeks. There was a clear signal of anemia response with this single agent after ruxolitinib failure.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

CPI-0610 Monotherapy–Non-transfusion Dependent Cohort Primary Endpoint: 30% of Patients had SVR35 Response at Week 24



	Non-TD (Cohort 1B)	TD (Cohort 1A)
SVR35	30% (7/23) (95% CI 13, 53)	8% (1/13) (95% CI 0, 36)
Median Spleen Volume Change	-29%	-11%

29 Sep 2020 data cut

SVR, spleen volume reduction. SVR35: ≥35% reduction in spleen volume from baseline

Patients are evaluable for SVR35 at wk 24 if they have had wk 24 assessment by the data cutoff date or discontinued after having had a wk 12 assessment.

Talpaz M, et al. ASH 2020. Abstract 2163.

In those patients where spleen was the major treating factor, I'm showing you here color-coded by whether they were transfusion-dependent in green or non-transfusion dependent where spleen was the major issue. There was significant reduction in spleen volume with 30%, SVR 35%. You will remember if you look back at the slides, that's comparable to what fedratinib showed in second-line in the JAKARTA-2 study. Effective in these patients for spleen volume reduction, effective in the transfusion-dependent patients in anemia improvement.

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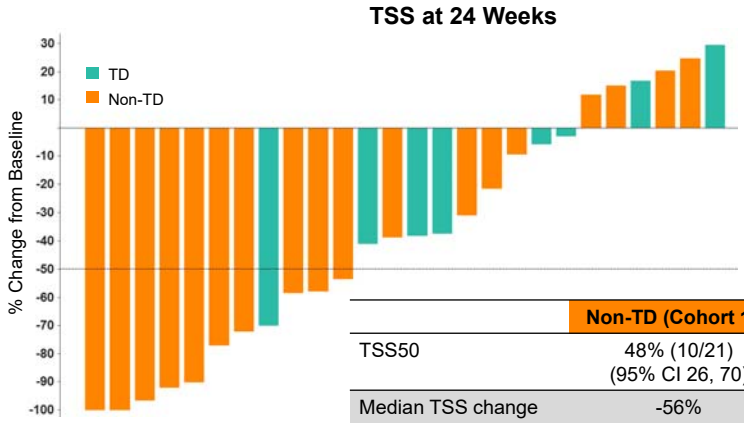
CPI-0610 Monotherapy – Key Secondary Endpoint: Majority of Patients had a Reduction of TSS



	Non-TD (Cohort 1B)	TD (Cohort 1A)
TSS50	48% (10/21) (95% CI 26, 70)	8% (1/13) (95% CI 0, 36)
Median TSS change	-56%	-22%

TSS, total symptom score; TSS50: ≥50% reduction in total symptom score from baseline
Patients are evaluable for TSS50 at wk 24 if they have had wk 24 assessment by the data cutoff date or discontinued after having had a wk 12 assessment.
Talpaz M, et al. ASH 2020. Abstract 2163.

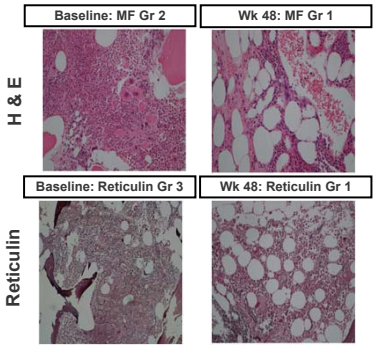
It also improved symptoms, this was dramatic. I treated many of these patients with single-agent, the symptom improvement was rapid within the first week and was durable in approximately 50% of patients who had non-transfusion dependence. Really spleen and symptom hyperproliferative disease really benefited from this drug in terms of symptom benefit after Rux failure.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

CPI-0610 Monotherapy: Bone Marrow Fibrosis Grade Improvement

- 21% (6/29) of patients had at least one grade improvement in bone marrow fibrosis
- Two patients had worsening in bone marrow fibrosis

Representative Example of Bone Marrow Biopsy



29 Sep 2020 data cut
Assessments of bone marrow grade or reticulin grade per local pathology read.
Gr, grade; H&E, hematoxylin and eosin.
Talpaz M, et al. ASH 2020. Abstract 2163.

Interestingly importantly, there was evidence of disease modification with pelabresib in which 21% of patients with monotherapy had at least one grade reduction in bone marrow fibrosis. This happened in a relatively short period of time, you typically don't see this with single-agent ruxolitinib.

Summary of Adverse Events

Treatment-Emergent Adverse Events[1]	All Grade N=46[2] n (%)	Grade 3 N=46[2] n (%)	Grade 4 N=46[2] n (%)
Hematological Events			
Thrombocytopenia[3]	14 (30)	7 (15)	0
Anemia	7 (15)	6 (13)	0
Non-hematological Events			
Gastrointestinal Events			
Nausea	18 (39)	0	0
Diarrhea	17 (37)	2 (4)	0
Constipation	10 (22)	1 (2)	0
Other Non-hematological Events			
Dysgeusia	14 (30)	0	0
Asthenic conditions[4]	14 (30)	0	0
Respiratory tract infection[5]	13 (28)	1 (2)	0
Cough	12 (26)	0	0
Weight decreased	10 (22)	1 (2)	0

- CPI-0610 as monotherapy in TD and non-TD cohort patients was generally well tolerated
- 45 patients (98%) reported at least one TEAE; 29 patients (63%) reported at least one ≥ Gr 3 TEAE
- The most common (≥20%) hematologic TEAE was thrombocytopenia
- The most common (≥20%) non-hematologic TEAEs were – nausea, diarrhea, taste changes, asthenic conditions, respiratory tract infections, cough, constipation and weight decreased
- 9 patients (20%) reported TEAEs that lead to CPI-0610 discontinuation
- Other G3/4 TEAEs (≥5%) include hyperuricemia (9%), hyperkalemia (7%) and dyspnea (7%)

29 Sep 2020 data cut

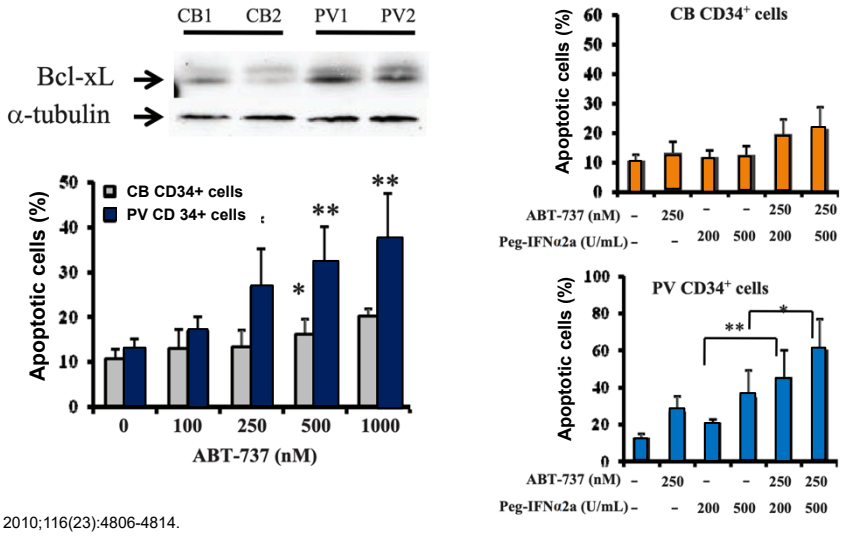
[1]TEAEs of all grade that occurred in ≥20% of patients and TEAEs of special interest [2]Safety evaluable population: Received at least one dose of study drug as of the data cut [3]Includes TEAE platelet count decrease [4]Include TEAEs of fatigue and malaise [5]Includes TEAEs of upper respiratory tract infection, lower respiratory tract infection, viral upper respiratory tract infection, influenza, laryngitis, bronchitis, sinusitis, nasopharyngitis, pneumonia

Talpaz M, et al. ASH 2020. Abstract 2163.

Most importantly, well-tolerated drug. You can see there were no grade 4 events and the grade 3 events, particularly the thrombocytopenia and anemia, were relatively infrequent, 15% and 13%. This is favorable compared to most drugs that we use including JAK inhibitors like ruxolitinib in this setting. There is on-target GI toxicity which is very manageable in the first cycle, it was very rarely a reason for discontinuation.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Bcl-2 and Bcl-xL Inhibition



Liu F, et al. *Blood*. 2010;116(23):4806-4814.

Now, moving on to BCL-2/BCL-XL inhibition, Johns Hopkins lab over a decade ago show that the BCL-2/BCL-XL is upregulated in PV but also MF samples and that blocking this with a BCL-2/BCL-XL inhibitor that was originally in development ABT-737, significantly led to selective reduction in MPN CD34 cells. This was actually even more impressive in combination with drugs like interferon, and the rationale is that JAK-STAT signaling released up-regulation of these pro-survival proteins and then inhibiting this would lead to apoptosis.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Results From a Phase 2 Study of Navitoclax in Combination With Ruxolitinib in Patients With Primary or Secondary Myelofibrosis

Claire Harrison[1], Jacqueline S. Garcia[2], Ruben Mesa[3], Tim Somervaille[4,5], Ellen K. Ritchie[6], Rami S. Komrokji[7], Naveen Pemmaraju[8], Catriona Jamieson[9], Nikolaos Papadantonakis[10], James M. Foran[11], Casey L. O'Connell[12], Leanne Holes[13], Jia Jia[13], Jason Harb[13], Jessica E. Hutti[13], Josef T. Prchal[14]

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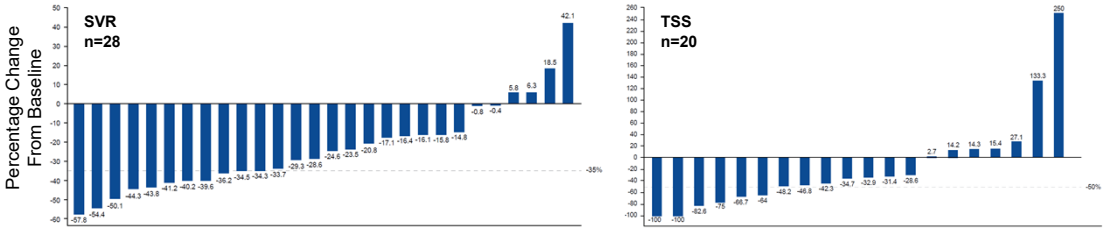
This led to the Phase 2 study of navitoclax in combination with ruxolitinib in patients with primary/secondary myelofibrosis. This study is an add-on strategy to patients who were on Rux who have residual spleen and symptom benefit.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Overall Efficacy and Safety

- A total of 9/34 (27%) patients achieved SVR ≥35% at week 24
- TSS reduction ≥50% at week 24 was attained in 6/20 (30%) evaluable patients
- 12/26 (46%) patients had driver gene (JAK2 or CALR) VAF reductions >10%
- Bone marrow fibrosis improvements of at least one grade at any time were observed in 10/34 (29%) patients



- All patients experienced treatment-emergent adverse events (TEAEs)
  - The most common TEAEs were thrombocytopenia (88%), diarrhea (68%), and fatigue (62%)
- Grade ≥3 TEAEs occurred in 85% of patients
  - Most common were thrombocytopenia (53%), anemia (32%), and pneumonia (12%)
  - Thrombocytopenia is manageable with dose modifications

Pemmaraju N, et al. ASH 2020.; Harrison CN, et al. *HemaSphere*. 2020;4:EP1081.

What you can see is 30% of patients achieved an SVR of 35% with the add-on in navitoclax and approximately 30% also had a symptom improvement. Improving upon ruxolitinib by combining it to ruxolitinib in this select patient population and there was a sense that there was disease modification with 50% of patients having at least a 10% reduction in JAK-2 or CALR VAF levels and about a third of the patients again having reduction in bone marrow fibrosis. This drug does induce on-target thrombocytopenia by inhibiting BCL-XL. That causes some degree of need for dose modification and more attention, but seem to be mostly manageable in this clinical trial.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

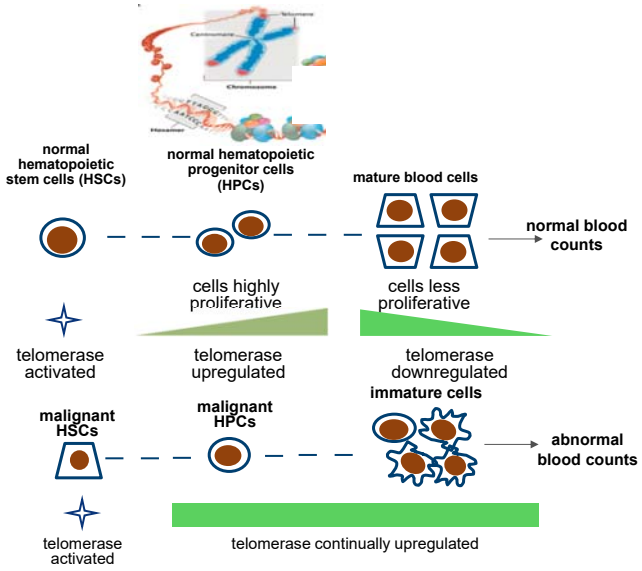
Phase 3 Trials

- Pelabresib phase 3 trial:
  - MANIFEST-2 trial (NCT04603495)
    - Pelabresib + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor-naïve MF patients
- Navitoclax phase 3 trials:
  - TRANSFORM-1 (NCT04472598)
    - Navitoclax + ruxolitinib vs placebo + ruxolitinib in JAK inhibitor-naïve MF patients
  - TRANSFORM-2 (NCT04468984)
    - Navitoclax + ruxolitinib vs best available therapy in RRMF

I should mention that both the pelabresib and the navitoclax studies have moved on now to the Phase 3 setting, both upfront in the case of pelabresib with ruxolitinib and JAK inhibitor-naive patients, that's the MANIFEST-2 study, and then the studies with navitoclax are in both upfront and in second-line. Those patients with a suboptimal response.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Telomerase as a Novel Target



Telomerase enzyme:

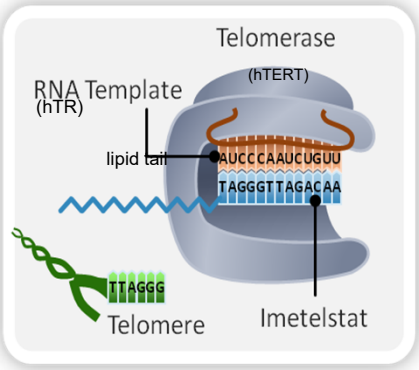
- Reverse transcriptase comprised of an RNA component (hTR) and a reverse transcriptase catalytic protein subunit (hTERT)
- Binds to the 3' strand of DNA and adds TTAGGG nucleotide repeats to offset the loss of telomeric DNA occurring with each replication cycle
- Not active in somatic cells; transiently upregulated in normal hematopoietic progenitor cells to support controlled proliferation
- Highly upregulated in malignant progenitor cells, enabling continued and uncontrolled proliferation

Lastly, I'll talk about telomerase. This is an enzyme that's constituently actively expressed in MPN hematopoietic stem cells and only transiently in normal stem cells. It's important for adding repeats, what are called telomere repeats at the ends of chromosomes, which are lost upon cell division. Cells get to a certain critical point where they undergo senescence and ultimately apoptosis. This drug inhibits that enzyme and therefore removes that advantage that malignant stem cells have for immortality by adding these important telomere repeats.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Imetelstat: First-in-Class Telomerase Inhibitor

Imetelstat binds to RNA template preventing maintenance of telomeres



- **Proprietary:** 13-mer thio-phosphoramidate oligonucleotide complementary to hTR, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Long half-life** in bone marrow, spleen, liver (estimated human t½ = 41 hr with doses 7.5 – 11.7 mg/kg)
- **Potent competitive inhibitor of telomerase:** IC_{50} = 0.5-10 nM (cell-free)
- **Target:** malignant progenitor cell proliferation

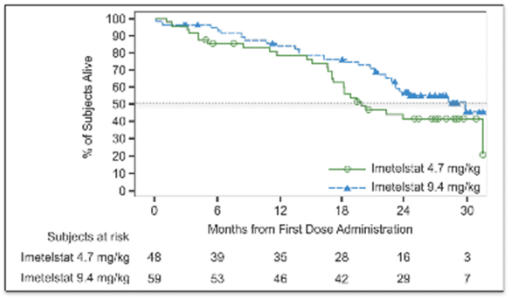
Dikmen ZG, et al. *Cancer Res*. 2003;65(17):7866-7873.; Hochrieter AE, et al. *Cl Cancer Res*. 2006;12(10):3184-3192.; Joseph I, et al. *Cancer Res*. 2010;70(22):9494-9504.

It binds to the RNA template and is a very potent competitive inhibitor that's given as an intravenous infusion and was taken into the clinic in a large multicenter Phase 2 study.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

SVR Per IRC at Week 24: Symptom Response Based on TSS at Week 24

- 6 (10%) patients in the 9.4 mg/kg arm and ≥35% SVR at Week 24
- 23 (37%) patients in the 9.4 mg/kg arm had ≥10% SVR at Week 24
- 19 (32%) patients in the 9.4 mg/kg arm had ≥50% symptom response at Week 24



- Median follow-up: 27.4 months
- Median survival:
  - 19.9 months (95% CI, 17.1, NE) in the 4.7 mg/kg
  - 29.9 months (95% CI, 22.8, NE) in the 9.4 mg/kg

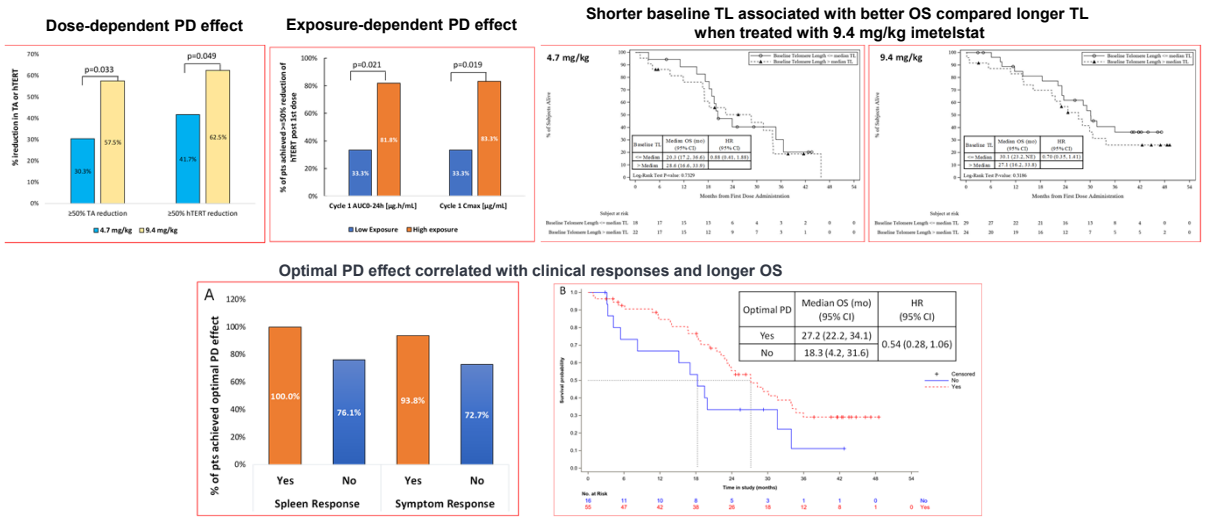
Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAK inhibitor or stem cell transplant and excluding patients who were dose escalated or randomized after closure of 4.7 mg/kg arm, all generating similar results

Mascarenhas J, et al. *Blood.* 2018;132(suppl 1):685.

I should mention that original pilot study was done by Ayalew Tefferi published in *New England Journal of Medicine* that showed that there was a signal of activity, a rapid signal of activity of not only spleen and symptom, but of pathologic responses and molecular responses in patients with this disease. We tested this at two doses, 9.4 milligrams per kilogram every three weeks, and a lower dose of 4.7 milligrams per kilogram every two weeks. It was the 9.4 milligrams that was the active dose; 10% of patients had SVR of 35%; 30% had a 50% response rate from a symptom score, these were patients who had previously failed ruxolitinib, but what was most impressive, and I've circled in red is the median survival of approximately 30 months. What I did not mention previously, patients who failed ruxolitinib and the median time to discontinuation is approximately 3 years, patients who fail ruxolitinib have a median survival shown in multiple studies approximately 1 to 1.5 years, so increasing this to 30 months would be significant.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Telomerase Activity, Telomere Length and hTERT Expression Correlate with Clinical Outcomes in Higher-Risk MF R/R to JAK Inhibitor Treated with Imetelstat



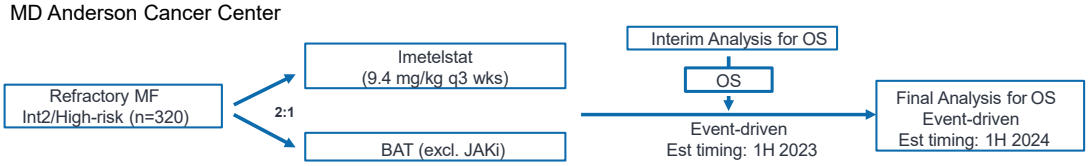
Mascarenhas J, et al. ASH 2020. Abstract 347.

We showed that this improvement in disease aspects was not by chance. Here we show on the left that there was a dose-dependent pharmacodynamic effect in reducing telomerase activity in the hTERT RNA expression levels a readout of telomerase inhibition. This was true with exposure. Irrespective of the dose, the higher the exposure, the more likely you were to get the intended optimal pharmacodynamic effect. If you look at the graph on the right on the top at 9.4 milligrams per kilogram IV, the effective dose, there was a sense that those patients with a shorter telomere were more likely to benefit from a survival benefit which lends itself to the telomere biology understanding. At the bottom, I show that the optimal pharmacodynamic effect hTERT RNA expression level of telomerase activity reduction was enriched in those patients who had spleen and symptom benefit and on the right survival benefit. Linking dose exposure, telomere length at baseline and pharmacodynamic effect with meaningful clinical outputs of spleen symptom, and most importantly, survival.

Novel Agents and Treatment Strategies for Relapsed/Refractory Myelofibrosis

Phase 3 Trial Design in Int-2/HR MF with OS as Primary Endpoint

- **Plan to open for enrollment 1Q 2021**
- **Principal Investigators:** John Mascarenhas, MD, Icahn School of Medicine, Mt. Sinai, Srdan Verstovsek, MD, MD Anderson Cancer Center



- **Population: Int-2/High-risk MF refractory to a JAKi**
  - Inadequate spleen or symptom response after treatment with JAKi for ≥6 months, including an optimal dose of JAKi for at least 2 months
  - Inadequate spleen or symptom response after treatment with maximal doses of JAKi for ≥3 months
- **Primary endpoint: Overall Survival (OS; HR=0.6)**
  - Secondary endpoints include: symptom response, spleen response, progression free survival, complete response, partial response, clinical improvement, duration of responses, safety, pharmacokinetics, patient reported outcomes
- **Imetelstat treatment arm: 9.4 mg/kg every 3 weeks**
- **Comparator arm: Best Available Therapy (BAT), excluding JAKi**

That's led to the pivotal IMPACT study, IMPACT MF study, shown here patients who have refractory MF to ruxolitinib and they are randomized to imetelstat in a two to one fashion to best available therapy with an overall survival endpoint, which is really quite different. Most of the endpoints to date have been spleen and more recently symptom, but here we're looking at trying to actually improve survival in patients where we know the survival is quite limited and the options are limited.

Conclusions

- Second-line options after ruxolitinib failure include fedratinib and JAK inhibitor-based combination salvage therapy approaches (experimental)
- Novel non-JAK inhibitor therapeutics may offer additional clinical benefit for those patients who have discontinued ruxolitinib
  - Epigenetic directed therapies such as CPI-0610 and bomedemstat
  - Apoptosis pathway inducing agents such as navitoclax
  - MPN stem cell directed therapy exploiting telomerase such as imetelstat
- These rational agents appear to provide early signal of clinical benefit but will need to be evaluated in P3 trials to quantify actual extent of benefit and prove extension of life

In conclusion, second-line options after ruxolitinib failure include fedratinib and JAK inhibitor-based combination salvage therapy approaches, but those are all experimental at this point. Novel non-JAK inhibitor therapeutics may offer additional clinical benefit for those patients who have discontinued Rux. I showed you examples of CPI-0610, but I didn't show you bomedemstat which is another epigenetic therapy, which is a lysine-specific demethylase 1 inhibitor (LSD1), which is earlier on in development, but there are many similar drugs in this epigenetic class that one must keep an eye on. Then drugs like the navitoclax that induced apoptosis pathway, again, that have preclinical rationale really have an opportunity to improve upon, for example, suboptimal responses to ruxolitinib. Then ultimately, drugs that can try to delete and target the MPN hematopoietic stem cell, such as imetelstat, which is a telomeres inhibitor, are very exciting with the prospect of improving survival in these patients and potentially even as a bridge to transplant. These rational agents really appear to provide early signals of clinical benefit, I hope I've provided that data to convince you of that, but they ultimately needed to be proved in a Phase 3 study, which is what is ongoing in many cases. I would encourage any of the listeners who are seeing patients with myelofibrosis as a rare disease, if they have the opportunity to enroll these patients in trials or refer them to tertiary centers where these trials exist, it is very important to get this information to try to move the field forward.

With that, I want to thank the audience for listening to this topic and I hope I've convinced you that we've come a long way in the treatment of myelofibrosis and we're making strides. I think the next three to five years we'll see significant changes and dare I say, even the additions of agents to the commercial space to help our patients with myelofibrosis. Thanks for listening.