Newer Drugs for Myelofibrosis

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New Drugs in Hematology
Bologna, 9-11 May 2016

Specific targeted therapies for MF

Category	Drugs	Rationale
1. Epigenetic therapies	• histonedeacetylase inhibitors *(panobinostat, givinostat, pracinostat, vorinostat)* • hypomethylating agents *(5-azacytidine, decitabine)*	Presence of epigenetic deregulating mutations in MF (ASXL1, EZH2..)
2. PI3K-AKT-mTOR inhibitors	• *Everolimus* • *BEZ235*	PI3K/AKT/ m-TOR pathway highly activated in MF
3. Anti-fibrotics	• *pentraxine II (PRM-1)*	Plasma pentraxine II decreases with increasing of bone marrow fibrosis
4. Heat shock protein (HSP)90 inhibitors	• *PU-H71* • *AUY922*	Targets the stability of JAK2 (antagonizes aberrant JAK signaling)
5. Aurora kinase A inhibitors	• *dimethylfasudil* • *MLN8237-Alesertib*	Targeting megakaryocyte atypia

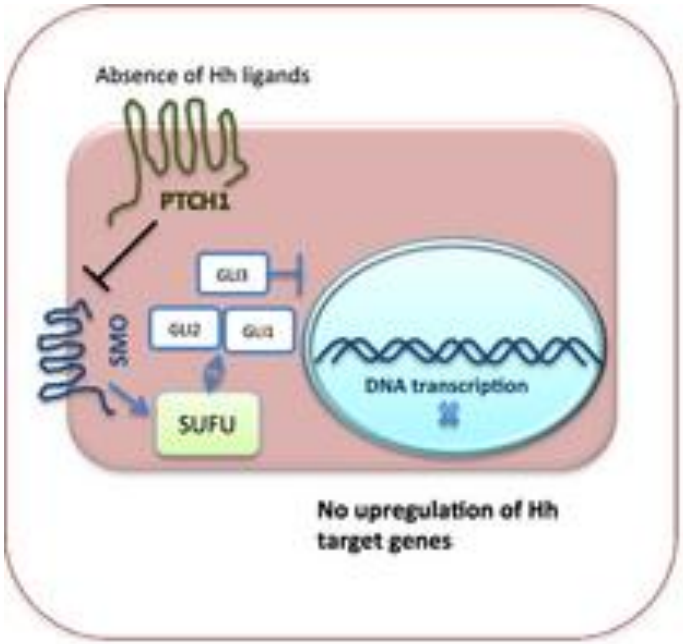
Non specific targeted therapies for MF

Category	Drugs	Rationale
1. **Hedhgehog inhibitors**		Activation of hedgehog signaling patway ciontributes to cancer progression
2. **Antitelomerase**	• *Imetelstat*	Upregulation of telomerase produces unlimited relpication potential of malignant cells
3. **PIM kinase inhibitor**	• *INCB53914*	PIM stimulates the proto oncogene MYC and inhibits its native apoptotic signal
4. **NEDD8-acitvating enzyme inhibitor**	• *Pevonedistat MLN4924*	NEDD8-activating enzyme is implicated in ubuiquitin-proteasome protein degradation
5. **Anti PD-1**	• *Nivolumab*	Tumor cells express PD ligand1 which interacts with PD1 on T cells to decrease T-cell activity

Newer drugs for myelofibrosis

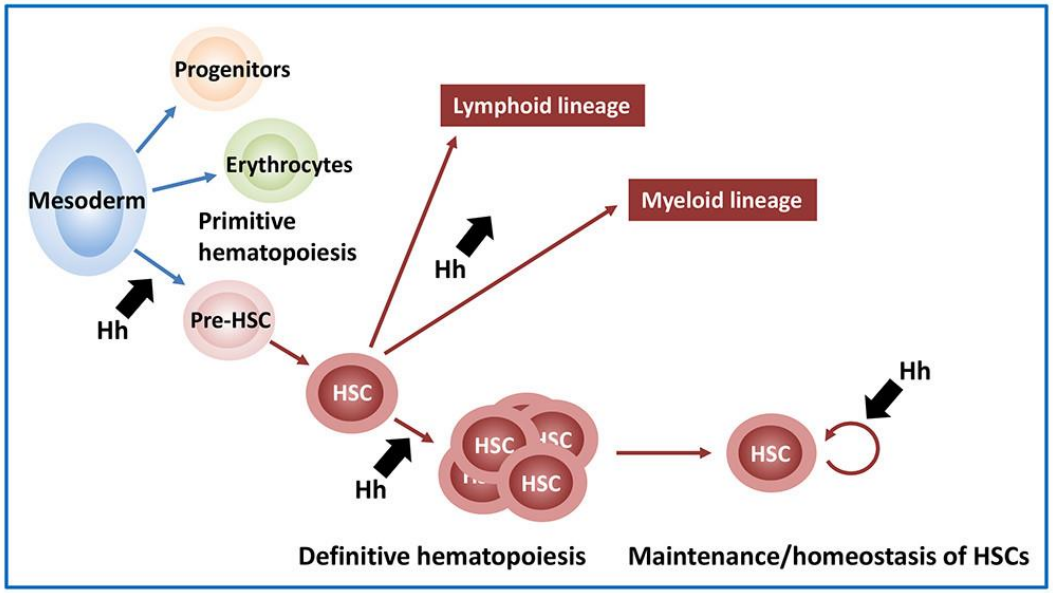
Category	Drugs	Status
1. **Epigenetic therapies**	• histonedeacetylase inhibitors • hypomethylating agents	*Phase I and phase II trials. Now is tested in combination with anti-JAK2 drugs*
2. **Hedhgehog inhibitors**		*Phase II*
3. **PI3K-AKT-mTOR inhibitors**	• everolimus	*Phase II*
4. **Antifibrotics**	• pentraxine II (PRM-1)	*Phase II*
5. **Antitelomerase**	• Imetelstat	*Phase II*
6. **Heat shock protein 90 inhibitors**	• PU-H71 • AUY922	*Preclinical*
7. **PIM kinase inhibitor**	• INCB53914	*Preclinical*
8. **Aurora kinase A inhibitors**	• dimethylfasudil • MLN8237-Alesertib	*Preclinical*
9. **NEDD8-acitvating enzyme inhibitor**	• Pevonedistat-MLN4924	*Preclinical*
10. **Anti PD-1**	• Nivolumab	*Preclinical*

The Hedgehog pathway



'Off mechanism '

1. In the absence of Hh, PTCH1 maintains inhibitory effect on SMO
2. Downstream signaling is not activated.
3. GLI3 represses Hh target genes from being transcribed.



Hedgehog signaling is required during development and adult hematopoiesis

Hedgehog inhibitors – clinical studies

Agent	Trials	Patients	Results
Saridegib-IPI-926 (SMO antagonist)[1]	Phase II	MF (14 patients)	*All patients discontinued the treatment by 7.5 months due to lack of response or progression*
PF-04449913 (SMO antagonist)[2]	Phase I	AML, MDS, CML, CMML, MF (7)	*Phase 2 dose = 200mg /day* *5 of 6 MF achieved stable disease* *Limited side effects*
Sonidegib-LDE225 (SMO antagonist)[3]	Phase I-II in combination with ruxolitinib	MF (23 patients)	*Over 65% of patients had >50% reduction in splenomegaly*

1. Sasaki et al. Leuk&Lymph 2015;56:2092-2097
2. Martinelli et al. Lancet Haematol 2015; 2:2339-346
3. Gupta et al. Blood 2014; 124 s634

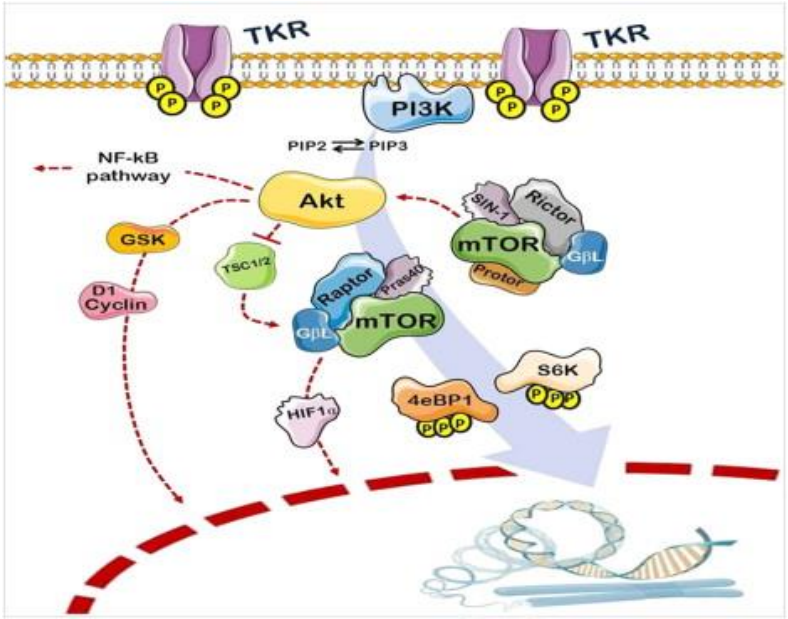
Hedgehog inhibitors – clinical studies

Agent	Trials	Patients
Sonidegib-LDE225 (SMO antagonist)[3]	Phase I-II in combination with ruxolitinib	MF (23 patients)

- Combination of ruxolitinib and sonidegib generally well tolerated with no observable PK interactions
- Early efficacy results similar to ruxolitinib monotherapy (majority of pts achieved resolution of palpable splenomegaly, ≥ 35% reduction in spleen volume)
- *JAK2* V617F allele burden and bone marrow fibrosis improved in some patients.
- Wk 24 efficacy failed to attain predetermined benchmark for additional patient enrollment
- Study will pursue longer-term follow-up of current patients

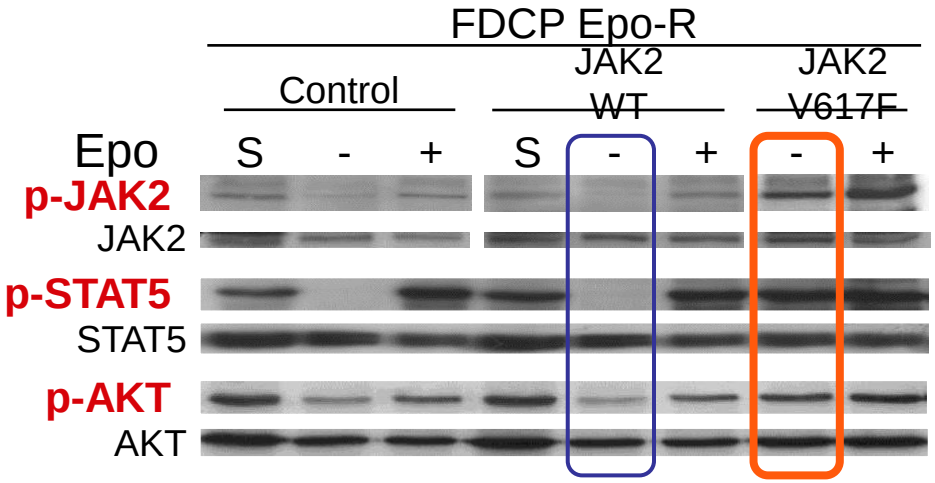
3. Gupta et al. Blood 2014; 124 s634

PI3K/AKT/mTOR pathway



PI3K = fosfatidilinostolo-3 kinase
AKT = protein kinase B
mTOR = mammalian target of rapamycin

Cytokine-independent activation of the PI3K/Akt pathway has been described in cells harboring the *JAK2*V617F mutation



James C, Nature 2005; 434:1144-8

Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis

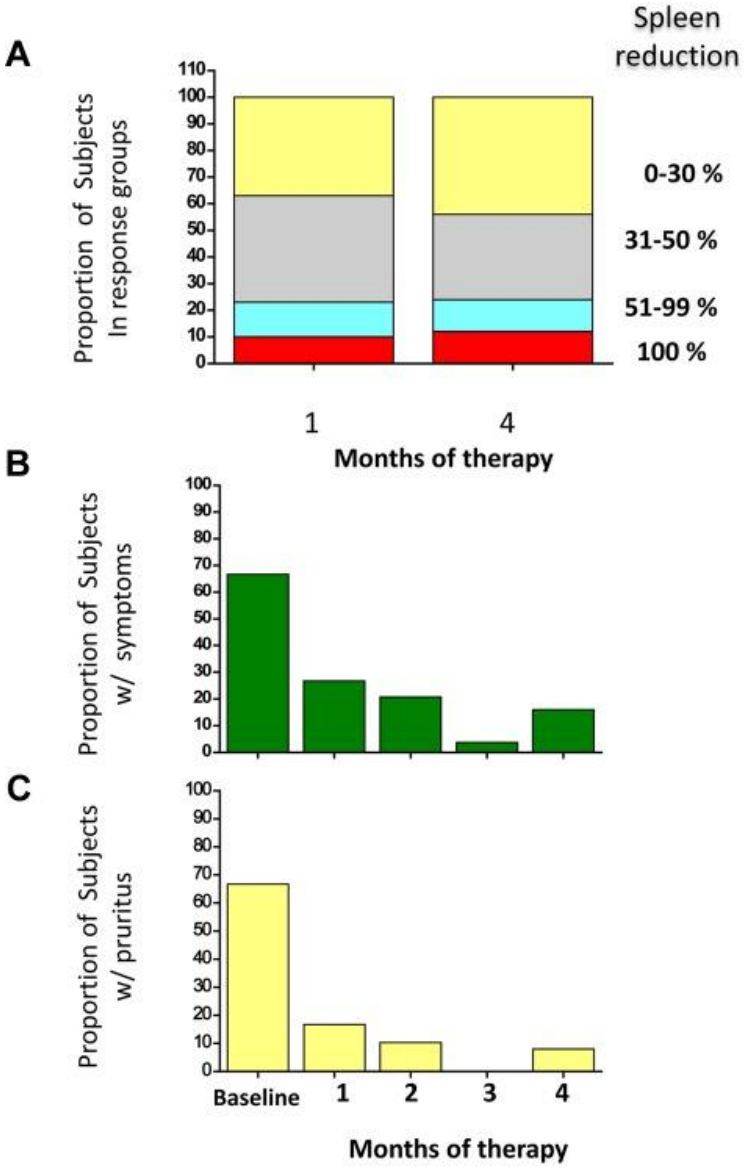
Paola Guglielmelli,[1] Giovanni Barosi,[2] Alessandro Rambaldi,[3] Roberto Marchioli,[4] Arianna Masciulli,[4] Lorenzo Tozzi,[1] Flavia Biamonte,[1] Niccolò Bartalucci,[1] Elisabetta Gattoni,[2] Maria Letizia Lupo,[2] Guido Finazzi,[3] Alessandro Pancrazzi,[1] Elisabetta Antonioli,[1] Maria Chiara Susini,[1] Lisa Pieri,[1] Elisa Malevolti,[1] Emilio Usala,[5] Ubaldo Occhini,[6] Alberto Grossi,[7] Silvia Caglio,[8] Simona Paratore,[8] Alberto Bosi,[1] Tiziano Barbui,[3] and Alessandro M. Vannucchi,[1] on behalf of the AIRC-Gruppo Italiano Malattie Mieloproliferative (AGIMM) investigators

[1]Department of Medical and Surgical Care, Section of Hematology, University of Florence and Istituto Toscano Tumori, Florence, Italy; [2]Unit of Clinical Epidemiology and Center for the Study of Myelofibrosis, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy; [3]Hematology Department, Ospedali Riuniti di Bergamo, Bergamo, Italy; [4]Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy; [5]Hematology and Bone Marrow Transplant Unit, Ospedale A. Businco, Cagliari, Italy; [6]UOC di Ematologia, Ospedale San Donato, Arezzo, Italy; [7]Oncology Unit, Ospedale di Prato, Prato, Italy; and [8]Novartis Farma SpA, Origgio, Varese, Italy

Blood
Volume 118(8):2069-2076
August 25, 2011

- A non-sponsored, investigator-initiated trial
- Non-randomized, open-label phase I/II study
- Phase II two-stage design according to Simon's
- Supported by Agenzia Italiana per il Farmaco (AIFA)
- Drug provided at no cost from Novartis

Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis



- Enrollment criteria: patients refractory to previous therapy
- Evaluable patients (Intention to treat): 25
- Response on anemia: 25% (partial)
- Response on splenomegaly: 43% (complete and partial)
- Response on constitutional symptoms: 69%
- Response on pruritus: 80%
- EUMNET responders: 60% (27% major responses)
- No difference between JAK2 V617F mutated and non mutated patients

OPEN ACCESS Freely available online

PLOS ONE

mTOR Inhibitors Alone and in Combination with JAK2 Inhibitors Effectively Inhibit Cells of Myeloproliferative Neoplasms

Costanza Bogani, Niccolò Bartalucci, Serena Martinelli, Lorenzo Tozzi, Paola Guglielmelli, Alberto Bosi, Alessandro M. Vannucchi*, on behalf of the Associazione Italiana per la Ricerca sul Cancro AGIMM Gruppo Italiano Malattie Mieloproliferative

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Published OnlineFirst February 27, 2013; DOI: 10.1158/1535-7163.MCT-12-0862

Molecular Cancer Therapeutics

Chemical Therapeutics

Dual PI3K/AKT/mTOR Inhibitor BEZ235 Synergistically Enhances the Activity of JAK2 Inhibitor against Cultured and Primary Human Myeloproliferative Neoplasm Cells

Warren Fiskus[1], Srdan Verstovsek[2], Taghi Manshouri[2], Jacqueline E. Smith[1], Karissa Peth[1], Sunil Abhyankar[1], Joseph McGuirk[1], and Kapil N. Bhalla[1]

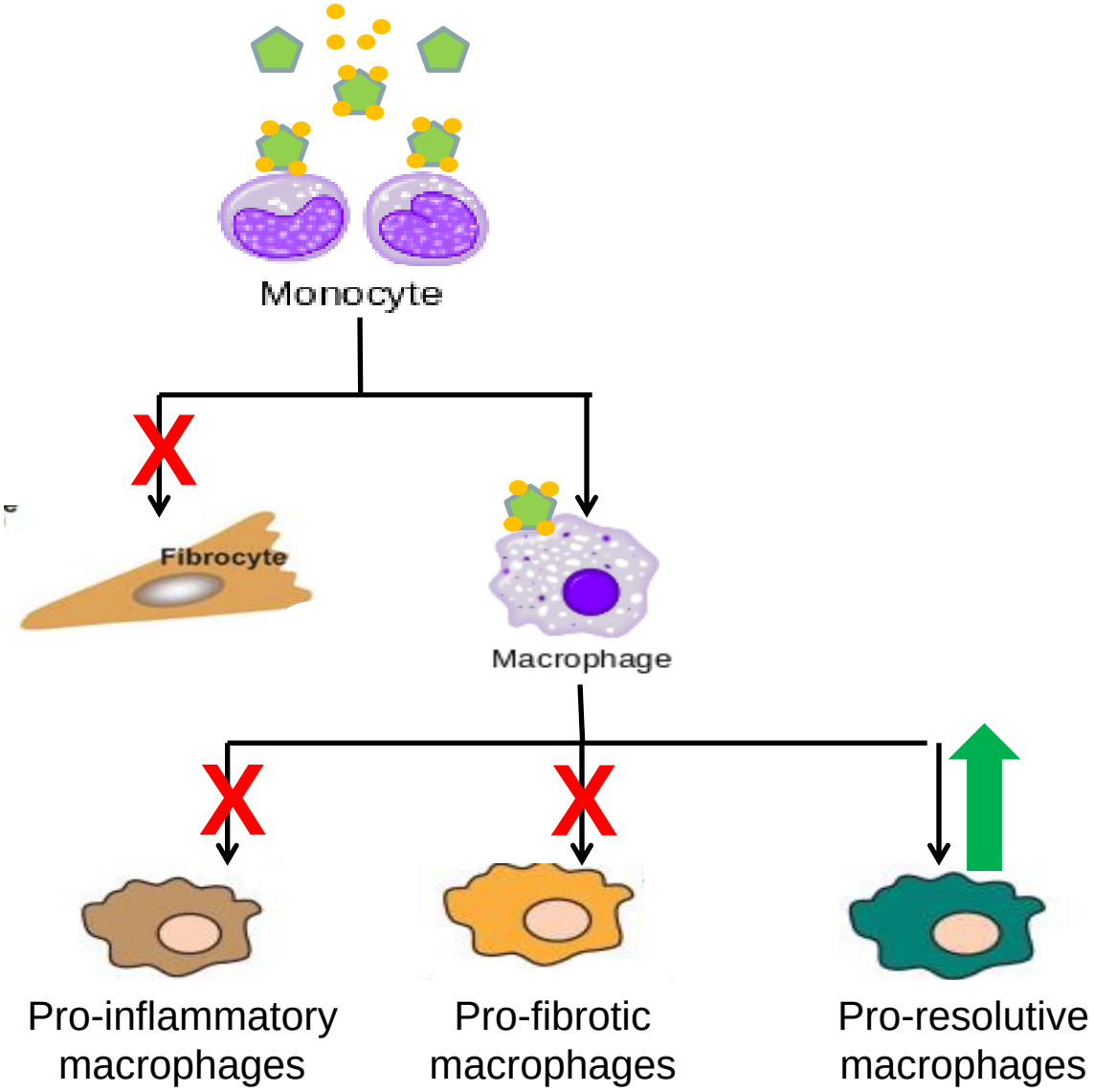
PI3K/Akt/mTOR pathway inhibitors

- Preclinical evidence and results of phase I/II trial indicate that the PI3K/Akt/mTOR might represent a novel target for treatment in MF

- The synergisim demonstrated in vitro with JAK2 inhibitors open additional therapeutic possibilities

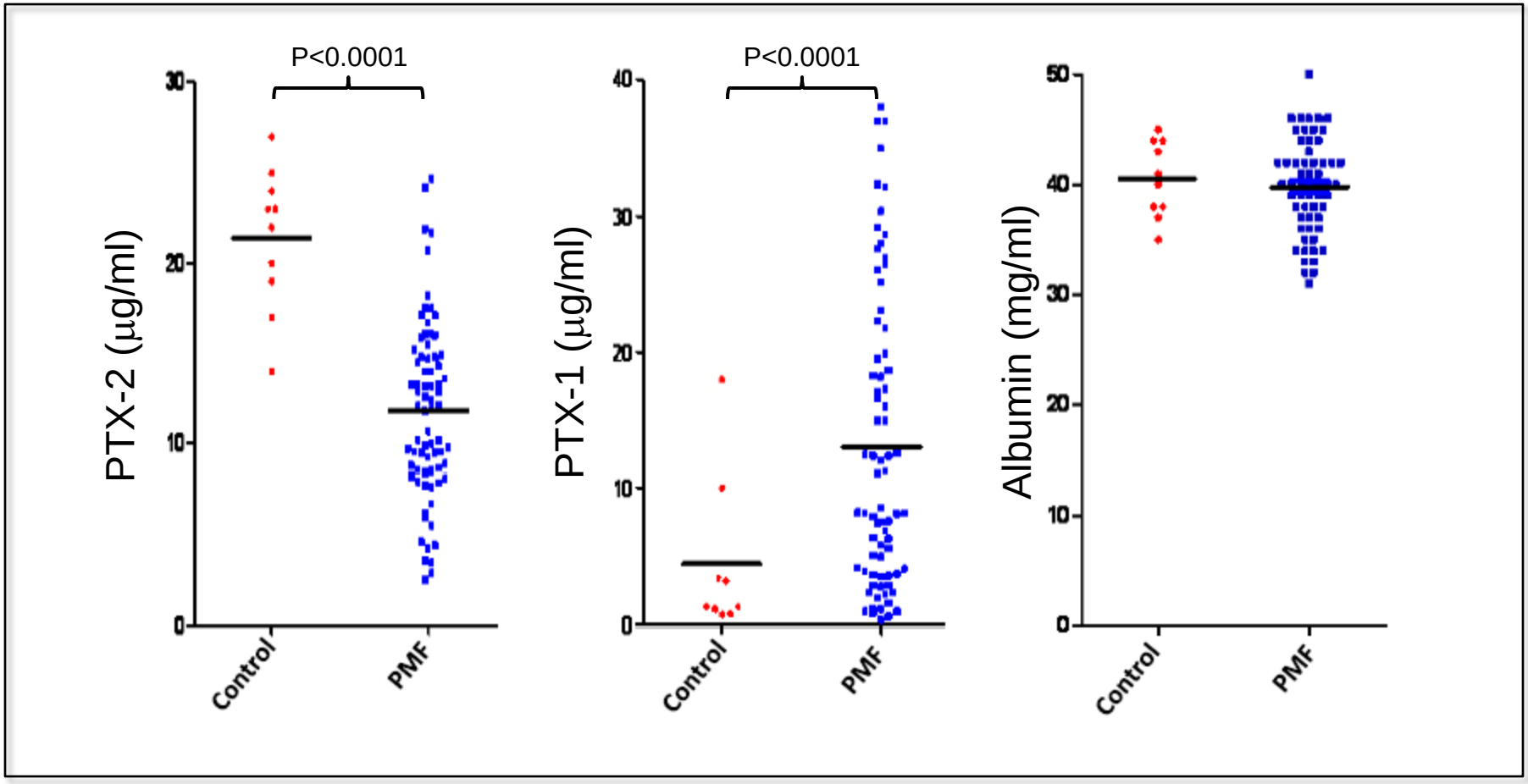
PRM-151 (Pentraxin-II)

- PTX-2 (Serum Amyloid P [SAP]), a member of the pentraxin family of proteins, is a 125 kD circulating plasma protein
  - Synthesized by the liver
  - Homopentamer: 5 x 25 kD monomers
- Acts as a pattern recognition receptor for the innate immune system.
- Inhibits the differentiation of monocytes into fibrocytes
- Shown to stop/reverse fibrosis in multiple organ systems
- Recombinant human PTX-2 produced in CHO cells = PRM-151



Low Serum PTX-2 Levels in MF Patients

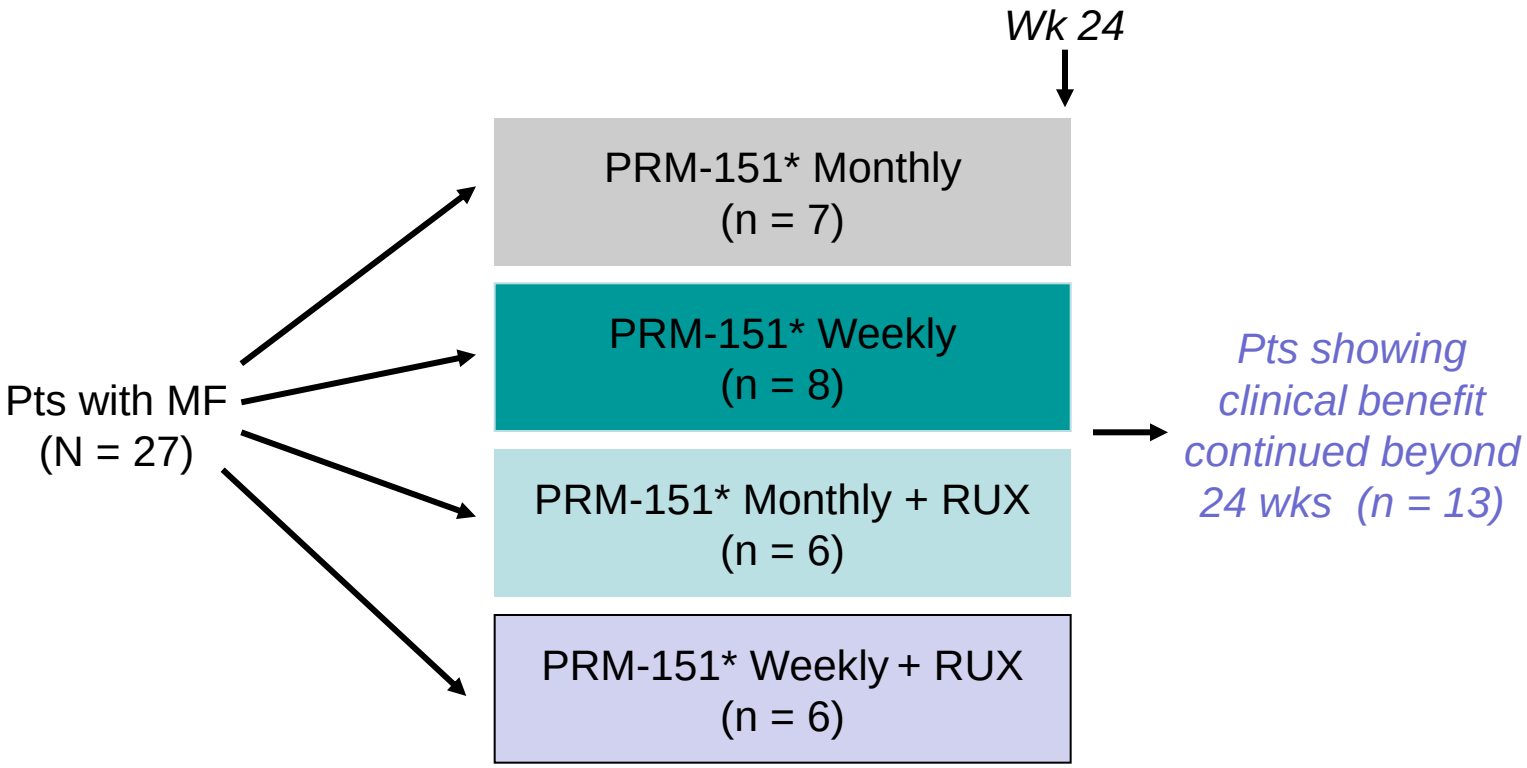
Low PTX-2, High PTX-1 and Normal Albumin Suggest PTX-2 Consumption versus Decreased Production



Verstovsek S. et al., MD Anderson Cancer Center, manuscript in preparation

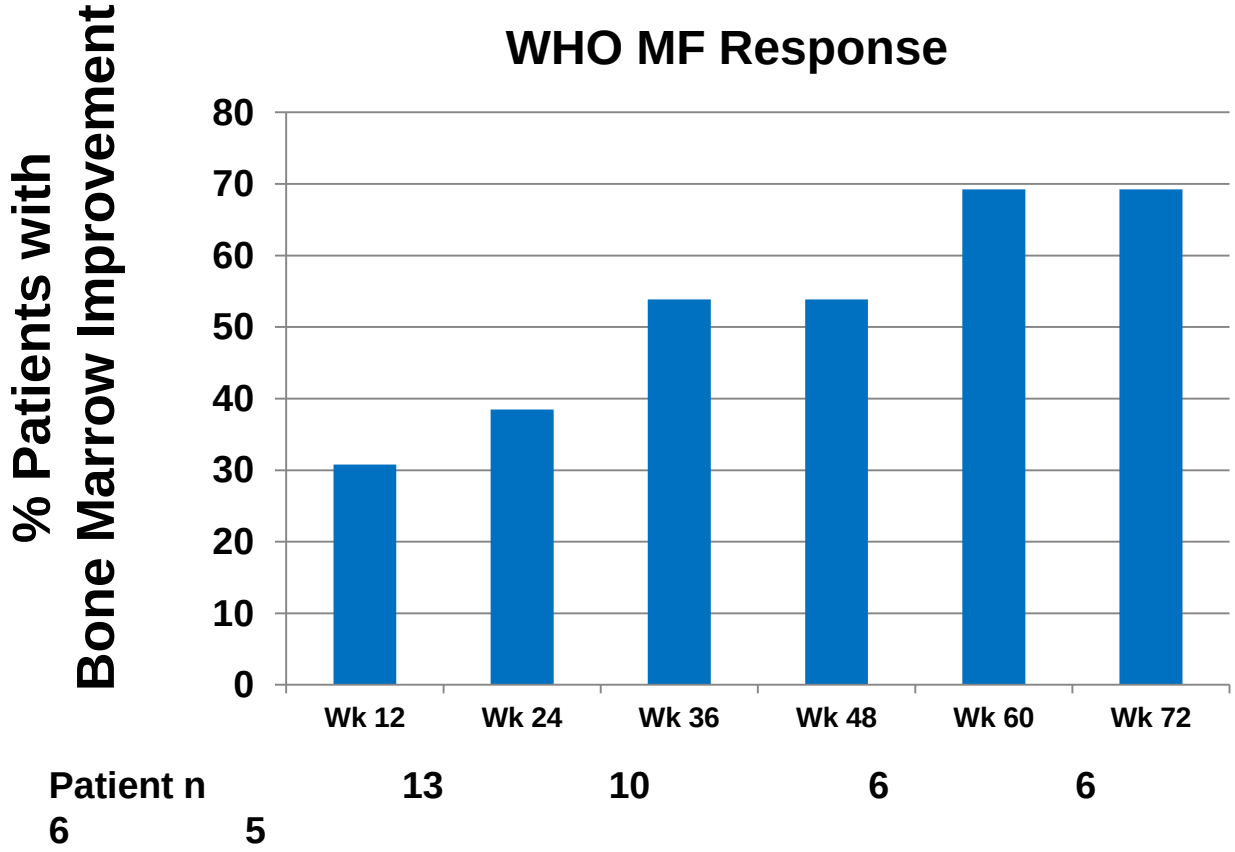
PRM-151 in MF: Study Design

Open-label, randomized phase II trial



Verstovsek S, et al. ASH 2015. Abstract 56. ClinicalTrials.gov. NCT01981850.

Bone Marrow Fibrosis Improvement as Measured by WHO Criteria

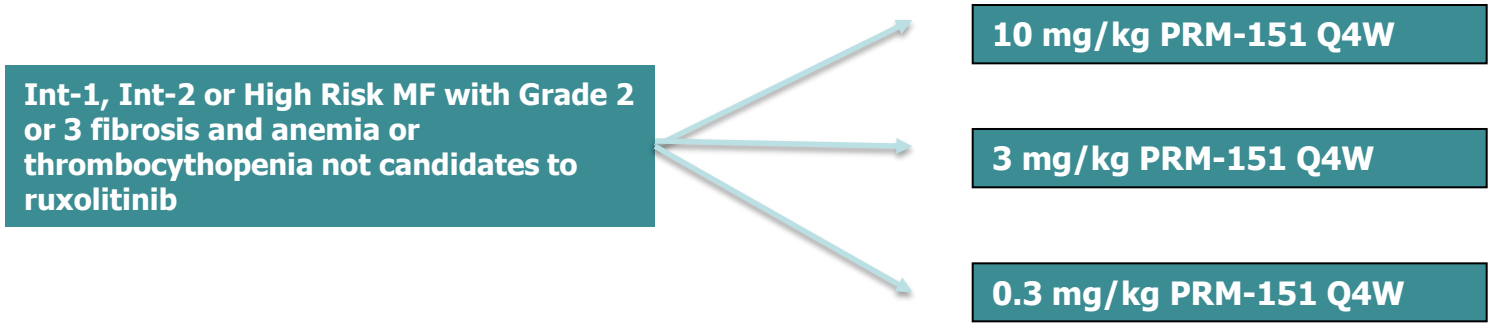


- Response assessment by central hematopathologists blinded to patient, treatment and time point
- WHO MF Response = % of patients with 1 grade reduction in MF score at any time point

Conclusions from 72 weeks of treatment in MF

- 13 patients have completed 72 weeks of PRM-151 treatment
- Reductions in bone marrow fibrosis have been accompanied by
  - Median increase in Hgb in patients with baseline Hgb < 100 g/L
  - Decreased RBC transfusions
  - Median increase in PLT in patients with baseline PLT < 100 x 10^9/L
  - Decreased PLT transfusions
  - > 50% reduction in symptoms in 62% of patients
  - > 50% reduction in splenomegaly in 2 patients on PRM-151 alone
- PRM-151 was well-tolerated
  - 13 related adverse events, 11 Grade 1
  - 6 SAEs, none related

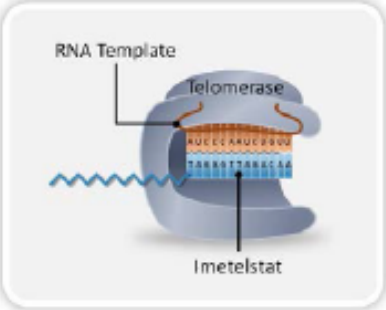
A Phase 2, Prospective Study of PRM-151 in Subjects with Primary Myelofibrosis (PMF), Post-Polycythemia vera MF (post-PV MF), or Post-Essential Throbocythemia MF (post-ET MF)



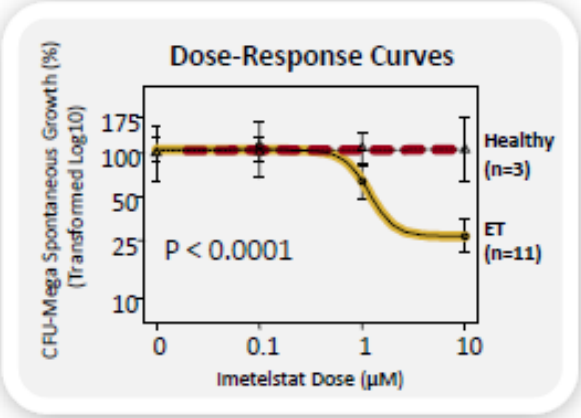
- This study is primarily intended as a Phase 3 renabling study
- If the Phase 2 data are very positive, the Company (Promedior) will propose uasing it for registration

Imetelstat: First-in-class Telomerase Inhibitor

- First telomerase inhibitor in clinical development
- 13-mer oligonucleotide with palmitoyl lipid tail
- Competitively binds to RNA template of telomerase
- Potent inhibitor of telomerase enzyme activity



Imetelstat Reduces Neoplastic Progenitor Proliferation *in vitro*:



- Imetelstat inhibits neoplastic megakaryocyte growth from patients with ET but not from healthy individuals

Imetelstat, a telomerase inhibitor, therapy for myelofibrosis: a pilot study

(Tefferi et al, Mayo Clinic – Drug and research funding provided by Gerion Corporation)

Background:	Short telomeres and up-regulated telomerase activity in myeloproliferative neoplasms (Ruella et al, Exp Hematol 2013;41:627; Spanoudakis et al, Leuk Res 2011;35:459)
Patients:	DIPSS plus high or intermediate 2 risk MF
Primary endpoints:	Safety ad efficacy

Tefferi et al, N Engl J Med. 2015;373: 908

Imetelstat, a telomerase inhibitor, therapy for myelofibrosis: a pilot study

(Tefferi et al, Mayo Clinic – Drug and research funding provided by Gerion Corporation)

Results:

- 33 pts were accrued

- 66% patients discontinued because of suboptimal response or disease progression

- 3 patients had died

- grade 4 neutropenia in 18%
- grade 4 thrombocytopenia in 21%
- grade 3 anemia in 27%.
- grade 1 or 2 liver function test abnormalities in 46%.

Tefferi et al, N Engl J Med. 2015;373: 908

Imetelstat Activity in Myelofibrosis

	Total (N = 33)
Best Response by IWG-MRT	N (%)
Overall Response (CR+PR+CI)	12 (36.4%)
Complete Remission (CR)	4 (12.1%)
Partial Remission (PR)	3 (9.1%)
Clinical Improvement (CI) by Anemia	1 (3.0%)
Clinical Improvement (CI) by Spleen	4 (12.1%)
Stable Disease (SD)	21 (63.6%)

CR/PR: 21.2%

- All 4 CR patients achieved reversal of BM fibrosis and 3 achieved complete molecular response
- 3 CR/PR patients who were transfusion dependent at baseline became transfusion independent
- 4 CR/PR patients with splenomegaly at baseline achieved splenic response

Tefferi A et al. *N Engl J Med* 2015;373(10):908-19

Association Between Response and Molecular Markers in Myelofibrosis Patients Treated with Imetelstat

CR/PR by Mutation Status

Mutation Type	Mutant	WT	P-value‡
Spliceosome	4/11 (36.4%)	3/22 (13.6%)	0.186
SF3B1/U2AF1	3/8 (37.5%)	4/25 (16.0%)	0.32
JAK2V617F	7/26 (26.9%)	0/7 (0%)	0.299
ASXL1	0/11 (0%)	7/22 (31.8%)	0.067
CALR	0/6 (0%)	7/27 (25.9%)	0.301

CR by Mutation Status

Mutation Type	Mutant	WT	P-value‡
Spliceosome	3/11 (27.3%)	1/22 (4.5%)	0.097
SF3B1/U2AF1	3/8 (37.5%)	1/25 (4.0%)	0.036
U2AF1	2/5 (40.0%)	2/28 (7.1%)	0.099
JAK2V617F	4/26 (15.4%)	0/7 (0%)	0.555
ASXL1	0/11 (0%)	4/22 (18.2%)	0.276

Tefferi A et al. *N Engl J Med* 2015;373(10):908-19

Imetelstat - conclusions

- Selective anticlonal activity
- Significant association between a complete response and spliceosome pathway
- Results of telomere lenght were inconclusive in terms of either prognostic relevance or mechanism of action