

Results of AJX-101, a Phase 1 Clinical Trial of the Type II JAK2 Inhibitor AJ1-11095, in Patients With Myelofibrosis Who Have Been Failed by a Type I JAK2 Inhibitor

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Disclosures: John Mascarenhas, MD

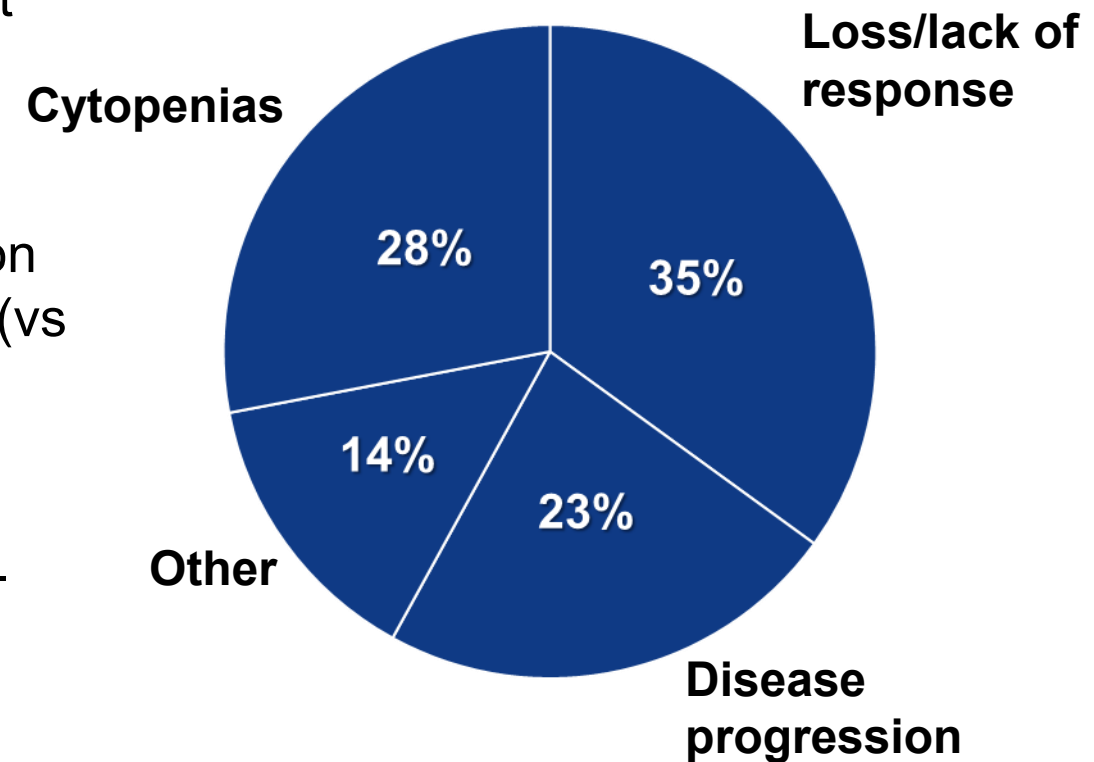
Consulting fee/honoraria: Incyte, Novartis, Geron, AbbVie, Sobi, Disc Medicine, Karyopharm, PharmaEssentia, Italfarmaco, Sumitomo, Merck, GSK, Takeda, Galecto, Blueprint Medicines, Cogent

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Unmet therapeutic need remains for patients with myelofibrosis

Primary reasons for ruxolitinib discontinuation

- Type I JAK inhibitors improve symptoms and spleen size, but do not meaningfully reduce clonal burden or prevent progression
- Absence of acquired resistance mutations at progression suggests incomplete pathway inhibition as likely cause (vs strong selective pressure)
- Post-JAK inhibitor response rates are limited: SVR35 0-32%, TSS50 6-39%¹

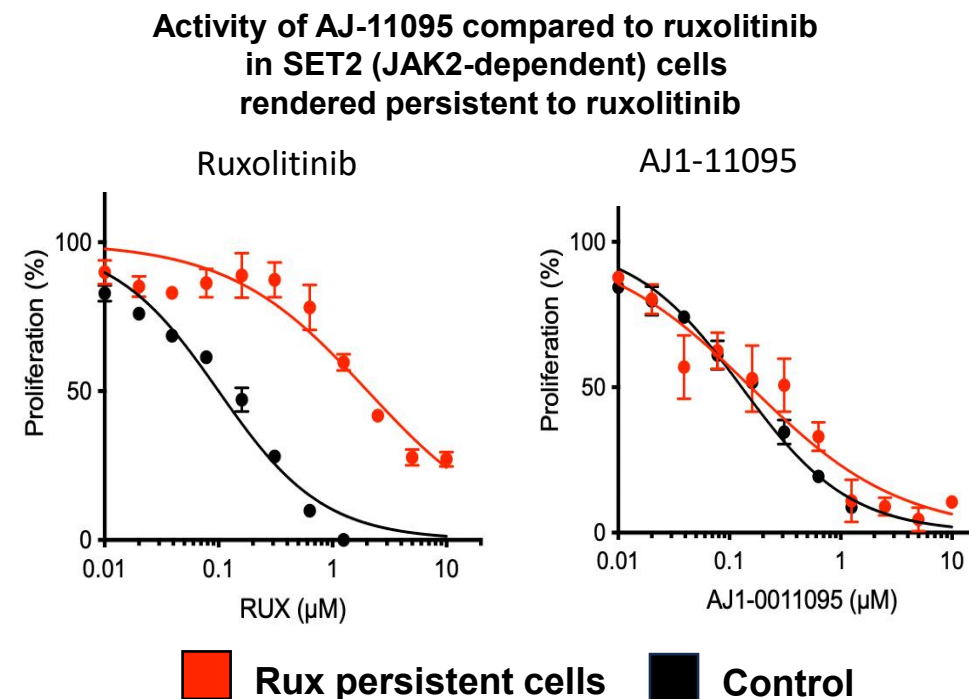
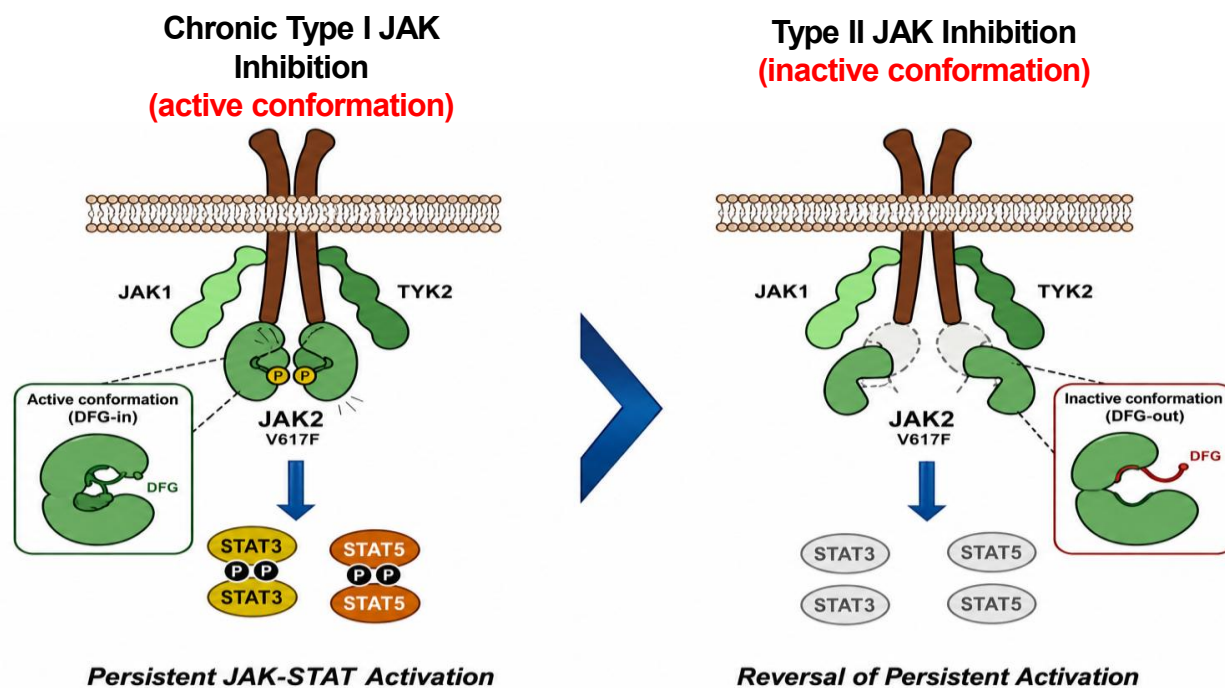


Based on 218 patients who discontinued among 524 ruxolitinib-treated patients in 20 European centers 2011-2019

Palandri F et al *Cancer* 2020; 126(6): 1243-1252

¹Harrison CN et al. *Lancet Haematol* 2018; Mascarenhas J et al. *JAMA Oncol* 2018; Harrison CN et al. *Blood* 2017. Abbreviations: JAK2 = Janus kinase 2, SVR35 = $\geq 35\%$ spleen volume reduction, TSS50 = $\geq 50\%$ reduction in total symptom score, BETi = bromodomain and extra-terminal domain, MDM = mouse double minute homolog, LDS1 = lysine-specific histone demethylase 1A, PI3K = phosphoinositide 3-kinase, BTK = Bruton tyrosine kinase, EGFR = epidermal growth factor receptor, ABL1 = Abelson proto-oncogene

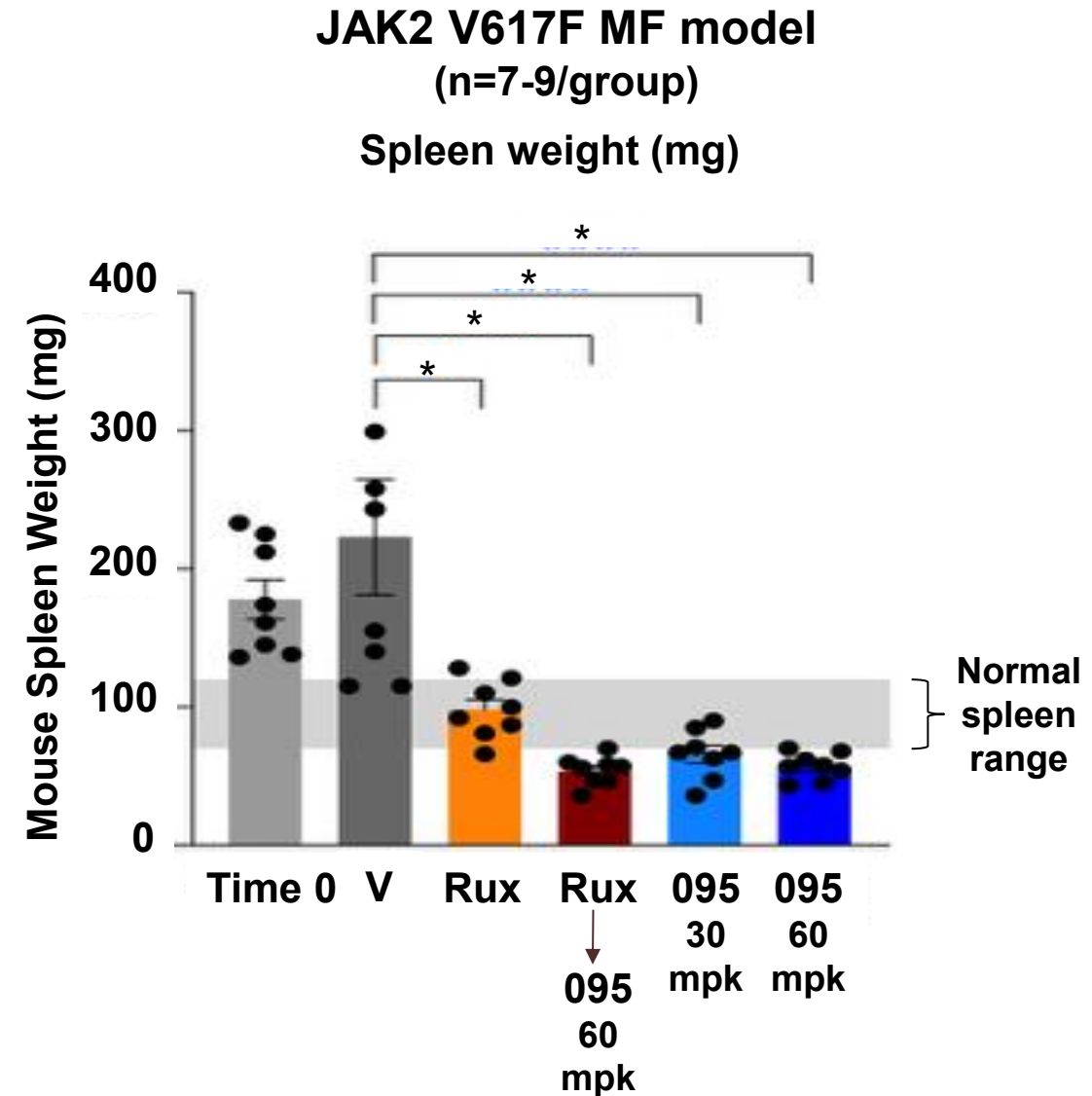
Underlying mechanism driving loss of response / lack of response to currently available Type I JAK2 Inhibitors



- JAK2 exists in two conformations: Type I (active, DFG-in) and Type II (inactive, DFG-out)
- All approved JAK2 inhibitors (including ruxolitinib) bind the active Type I conformation
 - Type I inhibitors allow JAK2 heterodimerization with JAK1/TYK2, enabling clonal persistence and resistance
- Type II inhibition stabilizes JAK2 in its inactive state, prevents heterodimerization, and achieves disease modification in preclinical models

AJ1-11095, a next-generation, selective, Type II inhibitor

- First-in-class Type II JAK2 inhibitor designed using computational chemistry and structure-based design
- More selective, potent, and better tolerated than first-generation Type II inhibitors (e.g., CHZ868)
- Demonstrated superior efficacy and disease modification vs ruxolitinib in head-to-head preclinical studies across validated MF/MPN models



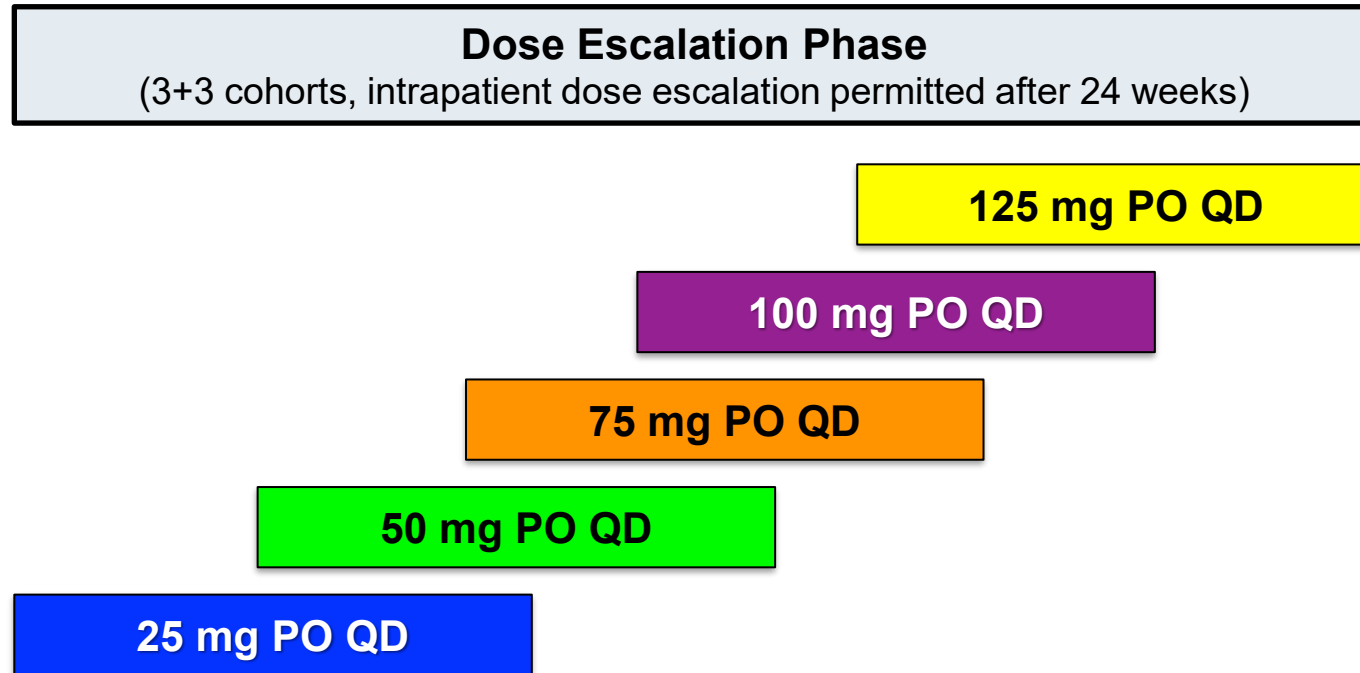
AJ1-11095 monotherapy demonstrated superior spleen reduction vs ruxolitinib in V617F preclinical model

*p = <0.05

AJX-101 trial design: A phase 1 first-in-human trial of AJ1-11095

Dose escalation phase

(ClinicalTrials.gov: NCT06343805)



Key Eligibility

- Adults with PMF, post-PV MF, or post-ET MF
- DIPSS Int-2 or High risk with $\leq 10\%$ blasts
- Spleen volume $\geq 450\text{cm}^3$
- MFSAF v.4.0 TSS ≥ 10 , or at least 2/7 symptoms ≥ 3
- ECOG PS 0-3
- Prior therapy with at least 1 type I JAK2 inhibitor
- Platelet count $\geq 75 \times 10^9/\text{L}$
- eGFR $\geq 45 \text{ mL/min/1.73m}^2$
- Adequate liver function

Primary endpoints: safety, tolerability (AE profile), observe MTD and/or inform RP2D selection

Secondary endpoints: PK of AJ1-11095, spleen volume reduction, MFSAF v4.0 TSS (ePRO)

Exploratory endpoints: biomarkers (eg JAK2 V617F VAF, cytokine levels, marrow fibrosis), PGIC PRO, IWG-MRT/ELN

Note: Patients are those enrolled to dose escalation by May 28

Abbreviations: PK = pharmacokinetics, MTD = maximally tolerated dose, RP2D = recommended phase 2 dose, MFSAF TSS = Myelofibrosis Symptom Assessment Form Total Symptom Score, PV = polycythemia vera, ET = essential thrombocythemia, MF = myelofibrosis, eGFR = estimated glomerular filtration rate, PMF = primary myelofibrosis, ECOG PS = Eastern Cooperative Oncology Group Performance Score, DIPSS = Dynamic International Prognostic Scoring System, PGIC = Patient Global Impression of Change, PRO = patient reported outcome, IWG = International Working Group for Myeloproliferative Neoplasms Research and Treatment, ELN = European Leukemia Network

AJX-101 dose escalation cohorts: demographics, prior therapies, and disease characteristics

Characteristics	AJX-101 (n=23)
Median age (range), years	69 (47-87)
Female, n (%)	7 (30%)
Median time from initial diagnosis (range), years	6.1 (0.6-20.7)
DIPSS risk status during screening, n (%)	
Int-1 risk (previously Int-2 or DIPSS+ Int-2)	3 (13%)
Int-2 risk	17 (74%)
High risk	3 (13%)
Driver mutation	
JAK2 V617F	16
MPL W515	1
CALR Type 1	5
CALR Type 2	1
Prior therapies**, range (median)	1-6 (2)
Myelofibrosis subtype, n (%)	
Primary MF	10 (43%)
Post-ET	8 (35%)
Post-PV	5 (22%)

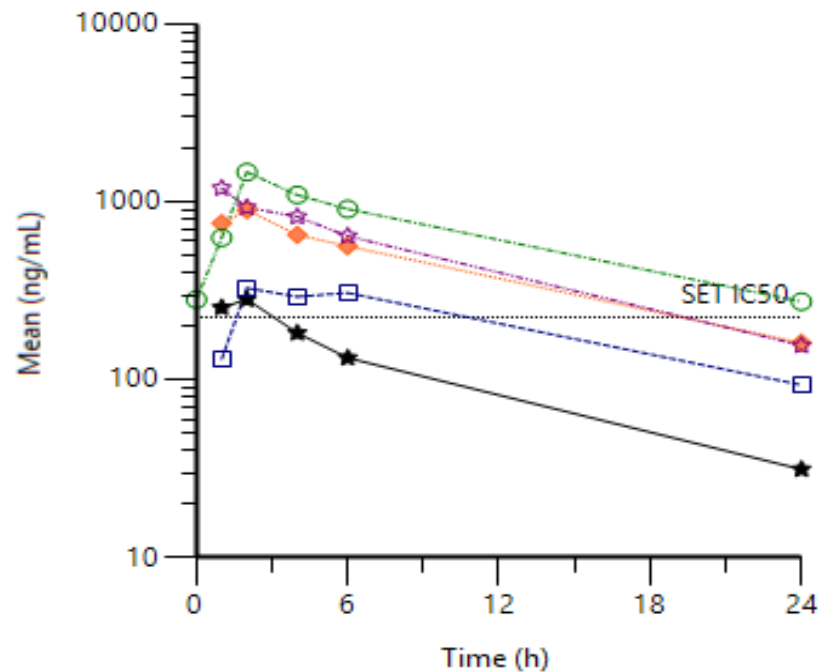
Characteristics	AJX-101 (n=23)
AJ1-11095 dose level	
25 mg	3
50 mg	3
75 mg	6
100 mg	6
125 mg	5
Mean MPN-SAF TSS (0-70pts) (range)	22 (6-55)
Mean spleen volume (range), cm ³	2389 (610-4511)
Mean hemoglobin* (range), g/dL	10.2 (7.2-13.8)
RBC transfusion dependent (%)	6 (26%)
Mean platelet count (range), x10 ⁹ /L	175 (74-444)
Mean absolute neutrophil count (range), x10 ⁹ /L	9.0 (1.5-40.5)
Mean monocyte count (range), x10 ⁹ /L	0.9 (0.0-3.2)

*Screening values

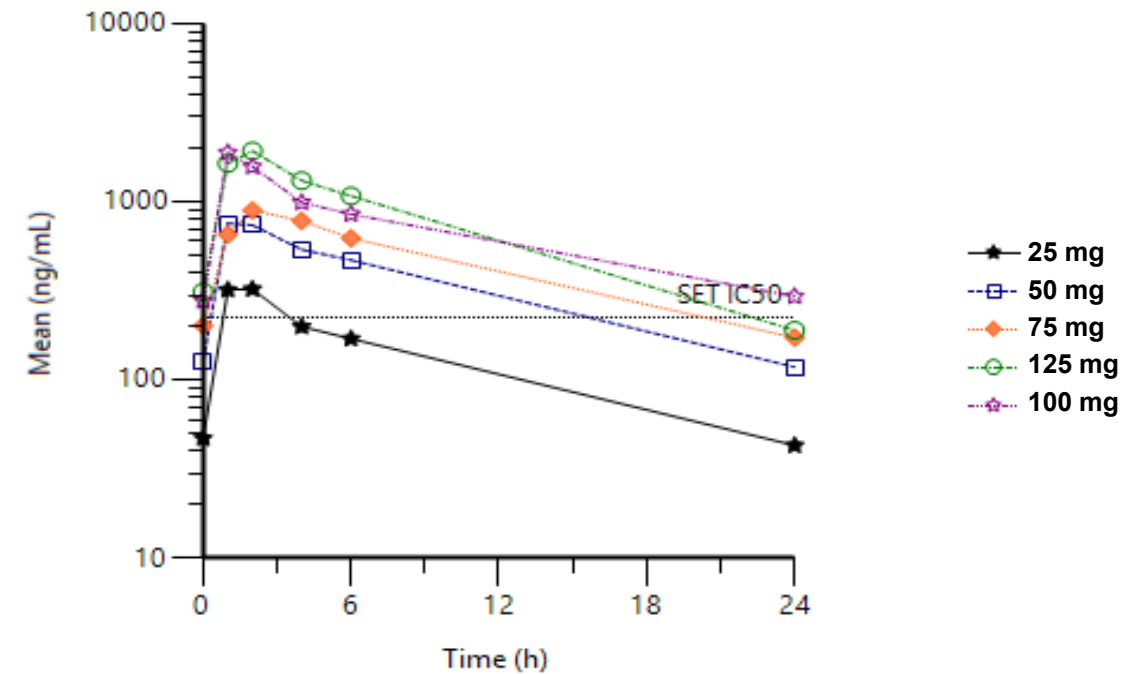
**Counted as prior therapies: JAK2 inhibitors, interferons, hydroxyurea, experimental therapies (navitoclax, pelabresib, INCB160058, PRT543, pascalisib, navtemadlin, nuvisertib, selinexor, NS-018), allogeneic transplant (counted as a single therapy). A drug used at different doses or different times in the disease course was counted as a single prior therapy. Not counted: aspirin, red cell stimulating agents (epoetin/darbepoetin, danazol, luspatercept), supportive care medications. All 23 patients had received prior ruxolitinib; 6 had received momelotinib, 2 each received pacritinib and fedratinib.

Mean time-concentration for AJ1-11095 (Dose levels 25 to 125 mg): C_{max} and AUC increased dose-proportionally

AJ1-11095 mean plasma exposure on C1D1



AJ1-11095 mean plasma exposure on C2D1



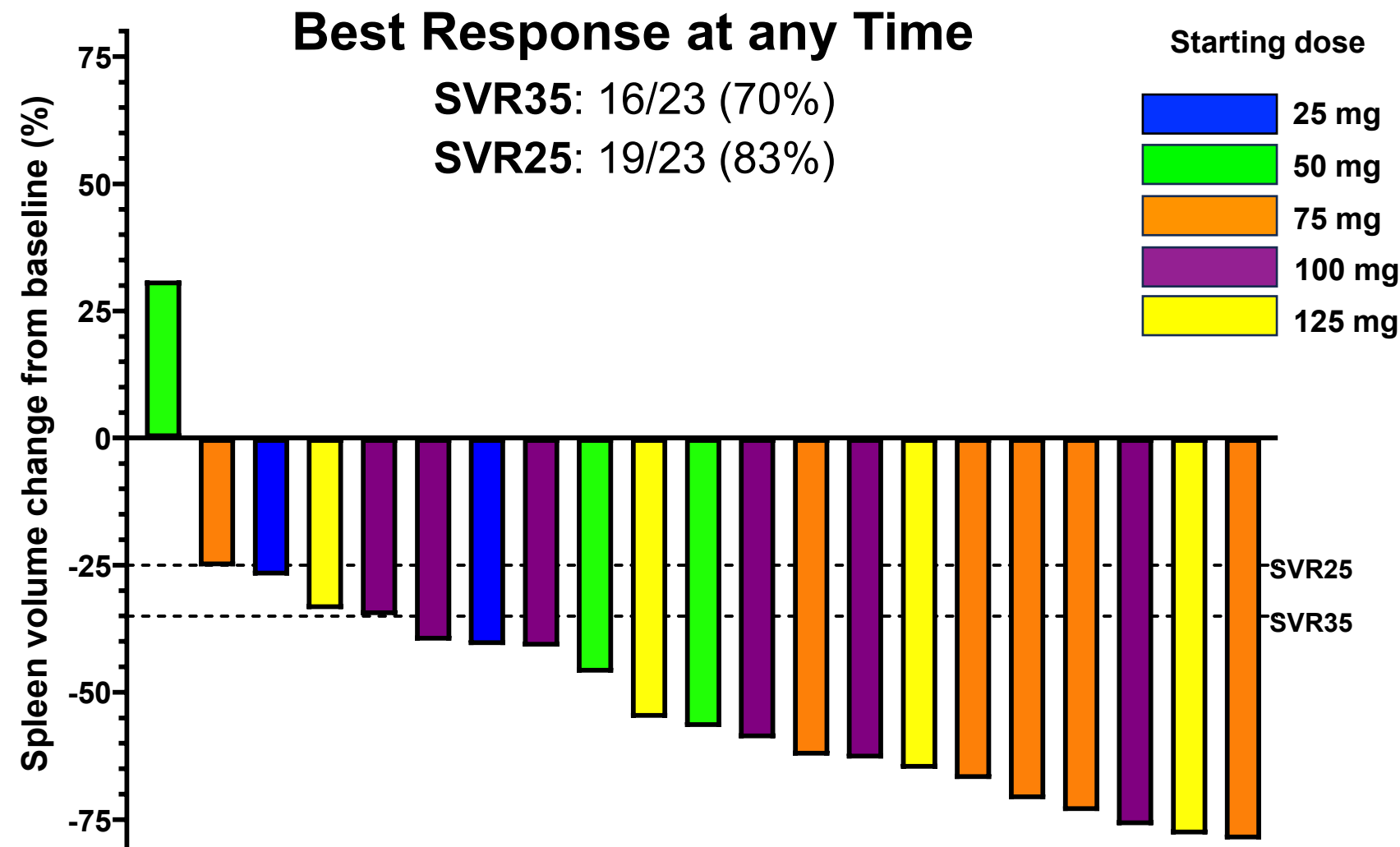
- Longer coverage above SET2 IC₅₀ with increasing dose
- AJ1-11095 time to maximum concentration (T_{max}) was 1 to 4 hours across subjects/cohorts
- The mean terminal half-life is estimated at ~ 8 to 11 h across all cohorts

AJX-101: Adverse events (AEs)

Treatment-emergent AEs in ≥20% of patients, n (%)	AJ1-11095 (n=23)	
	Any Grade	Grade ≥3
Anemia*	15 (65)	12 (52)
Dysgeusia	11 (48)	0
Platelet count decreased*	9 (39)	7 (30)
ALT increased	8 (35)	1 (4)
Amylase increased	7 (30)	0
Constipation	7 (30)	0
Diarrhea	7 (30)	0
Dizziness	7 (30)	0
AST increased	6 (26)	0
Headache	6 (26)	0
Hyperkalemia	6 (26)	1 (4)
Cough	5 (22)	0
Muscle spasms	5 (22)	0

- No DLTs were observed
- No treatment-related discontinuations due to AEs
- Dose reductions due to AEs occurred in 13 (57%) patients
- At doses ≤100mg, only grade 3/4 AEs observed were cytopenias
- Amylase and transaminase elevations were transient, occurred primarily at 125mg and resolved on treatment
- Five discontinuations: transplant (n=1), logistics (n=1), non-response (n=2), unrelated AE (n=1); none due to drug-related toxicity

High rates of SVR25 and SVR35 observed with AJ1-11095 therapy

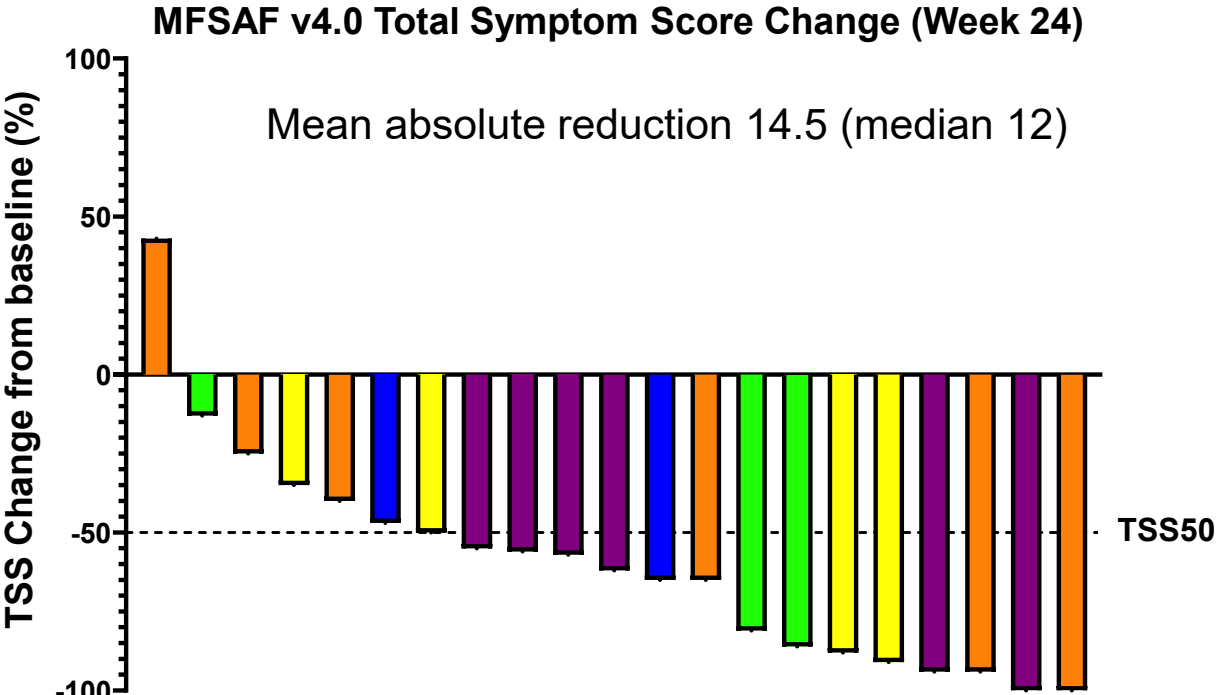
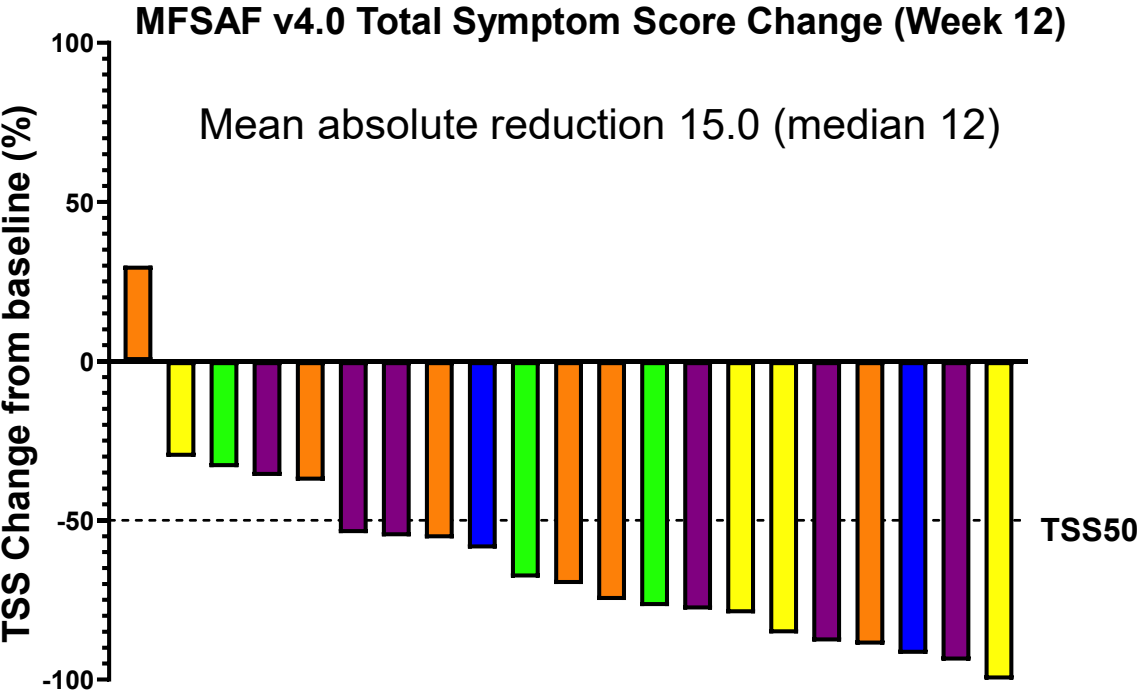


■ At a median follow up of 8.1 months, 78% (18/23) of patients remain on study therapy, with the longest followed patients treated for more than 18 months.

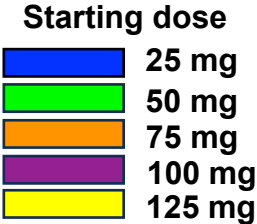
Data Cut: 28 May 2026. Two patients did not have formal on-study C4 (week 12) imaging due to early discontinuation due to logistics and a non-related AE . For one patient, an intercurrent scan performed during Cycle 2 showed 40% SVR; this is not included in the total.

High rates of TSS50 observed with AJ1-11095 therapy

Week 4 TSS50	Week 12 TSS50	Week 24 TSS50	TSS50 at any time
10/23 (43%)	16/23 (70%)	15/23 (65%)	22/23 (96%)

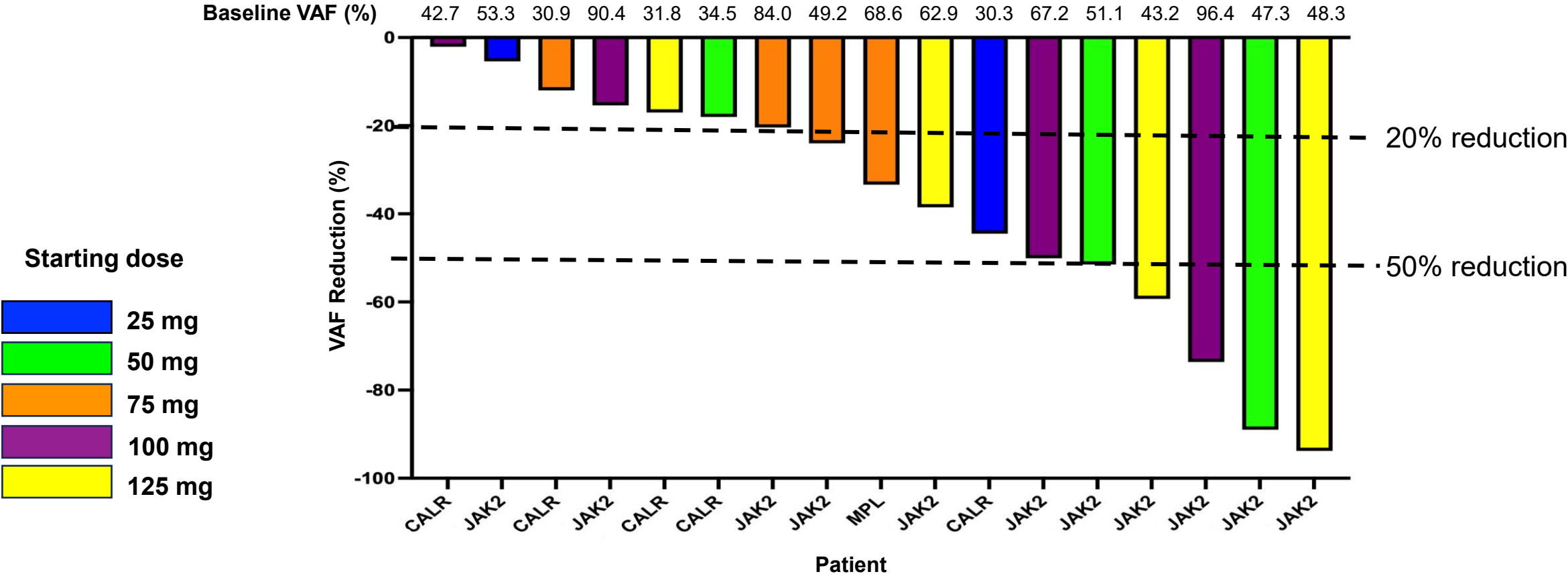


- Improvement was observed in all 7 domains of MFSAF v.4.0, including fatigue
- Improvement was observed regardless of duration since discontinuing prior therapy



Driver mutation variant allele frequency (VAF) changes during AJ1-11095 therapy

Best relative VAF reduction to date for patients for whom Cycle 7 (week 24) data are available

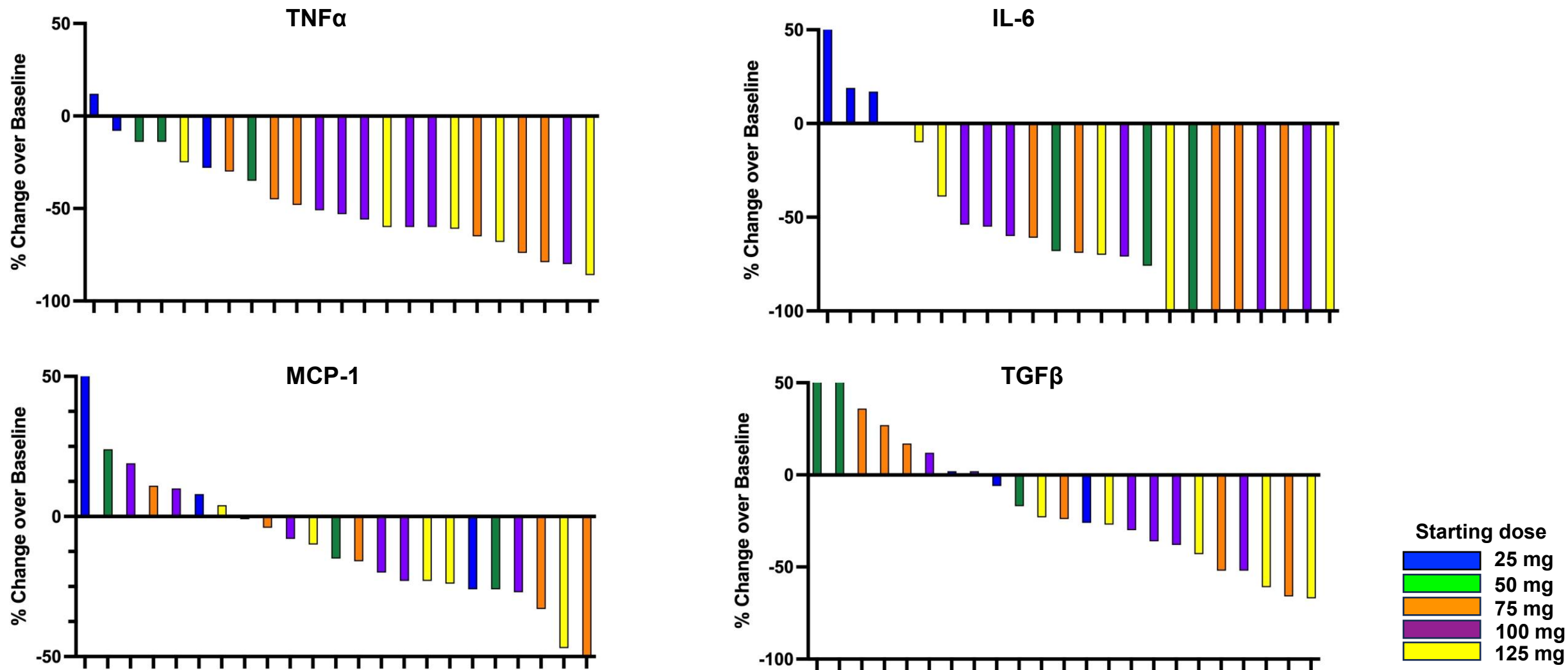


- 21/23 patients had a post-baseline VAF reduction
- 10/17 (59%) who have reached C7 (week 24) have had $\geq 20\%$ relative reduction so far
- 6/17 (35%) who have reached C7 (week 24) have had $\geq 50\%$ relative reduction so far

Note: n=17 denominator does not include 3 patients who are ongoing but yet to reach C7, and 2 patients who discontinued prior to C7

AJ1-11095 reduces pro-inflammatory cytokine levels

Representative cytokines depicted: TNF α , MCP-1(CCL2), TGF β , and IL-6
Best reduction from baseline (C2, C4, or C7) is depicted



Method: Meso Scale Discovery Proinflammatory V-PLEX assay

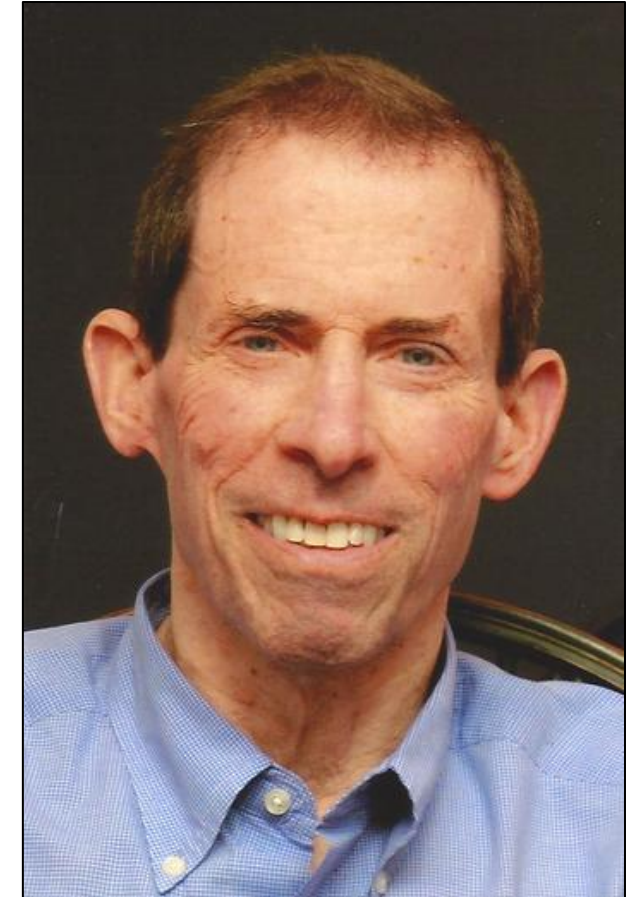
Conclusions

- AJ1-11095 is the first Type II selective JAK2 inhibitor to enter the clinic
 - Reduces spleen volume and improves symptoms
 - Reduces the variant allele frequency (VAF) of driver mutations in JAK2 pre-treated patients with MF
- Responses to AJ1-11095 are durable, and most patients enrolled in the dose escalation phase remain on study
- VAF reduction is observed in patients with JAK2, MPL, and CALR Type 1 and Type 2 mutations
- Most common AE is on-target anemia, which has been manageable with dose adjustment
- AJ1-11095 is currently being studied in an expansion phase in patients with MF previously treated with a JAK2 inhibitor, with plans to enroll patients with high-risk PV and patients with MF who have not yet received a JAK2 inhibitor

Acknowledgements

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- Ajax Therapeutics: Martin Vogelbaum (CEO), Maria Kleppe (Discovery Biology), Craig Masse (Chemistry), Karen Andreas (Program Manager and Integration Lead), David Waller (CMC), Shyamala Navada (Medical Director)
- Keri Urwin, Elevate Consulting (Clinical Operations)
- Nathalie Rioux, Certara (PK modeling)
- Tonya Marmon, Marmon Biostatistics Consulting
- Ross Levine and lab
- Eli Lilly and Company recently added this program to its pipeline following the completion of the acquisition of Ajax Therapeutics, Inc.



*Arthur H. Kern, 1946-2022,
inspiration for the foundation of
“Attack Jak”, which became
Ajax Therapeutics*