YOUNG SCIENCE FORUM:
IL FUTURO NASCE IN LABORATORIO

Exportin-1: dalla biologia alla clinica

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Exportin-1: From Biology to the Clinic

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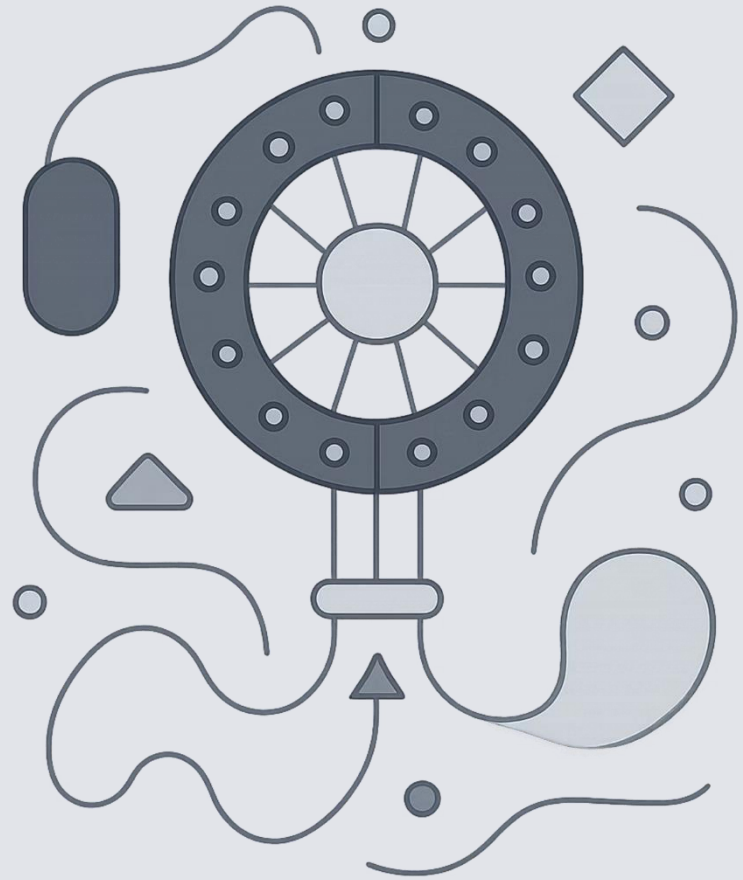
Young Science Forum — Regional SIES, Piedmont Delegation | "The future is born in the laboratory" | Torino, Accademia di Medicina | 5 June 2026



Disclosures

Consultancy

Novartis, MorphoSys, Menarini Stemline, GSK, Incyte, MSD, Sanofi, Sanofi, SOBI, Amgen, Protagonist Therapeutics, Grifols

Speakers Bureau

Novartis, Menarini Stemline, GSK, Recordati, Incyte, Sanofi, SOBI, SOBI, Amgen, Grifols, AOP

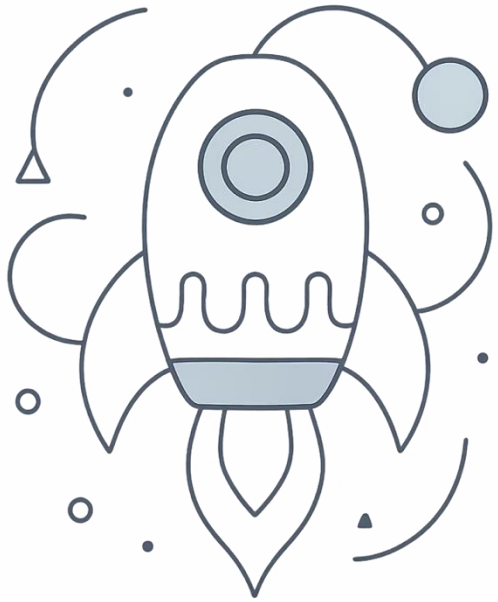
⚠ This lecture discusses selinexor in myelofibrosis, an **investigational** use. Selinexor is currently approved in in **multiple myeloma**. Its accelerated approval in DLBCL DLBCL was **withdrawn by the FDA in April 2026** following following failure to conduct the confirmatory phase 3 trial. phase 3 trial.

A question of address

Every protein in the cell carries a postcode. The nucleus is not a vault — it is a sorting office.

> What happens to a cancer cell when we seize control of the office that decides decides *what leaves the nucleus*?

The Logistics of the Nucleus



Nucleocytoplasmic traffic moves through the **nuclear pore complex**, directionally, against a gradient. **Exportin-1** (XPO1, also CRM1) is the principal export receptor — it binds leucine-rich nuclear export signals and ferries cargo out, powered by the **RAN-GTP/GDP gradient**.

Cargo: the cell's command structure

- **Tumour-suppressor proteins**: p53, p27, p21, RB, FOXO, IκBα, APC
- **Oncoprotein mRNAs** exported via eIF4E: MYC, cyclin D1, BCL2

One receptor, hundreds of cargoes, almost every cancer hallmark.

📚 Azizian NG & Li J, *J Hematol Oncol* 2020; Azmi AS, et al. *Nat Rev Clin Oncol* 2020; Sun Q, et al. *Signal Transduct Target Ther* 2016

XPO1 Is More Than a Doorway

Mitotic Regulation

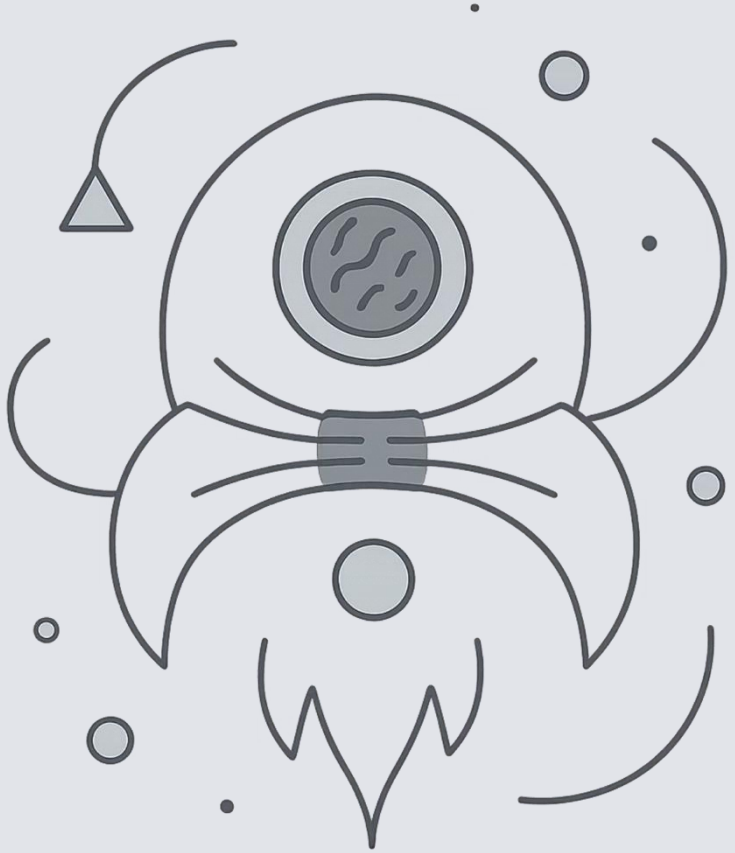
XPO1 regulates **mitotic spindle assembly** and chromosome segregation — functions well beyond bulk mRNA export.

Epigenomic & Stress Roles

Emerging roles at the **epigenome** and in stress-adaptive mRNA export, including export of DNA-damage-repair mRNAs (via eIF4E/THOC4) under genotoxic stress — conferring **tumour stress tolerance**.

Active Decision Node

XPO1 is not a passive conduit but an **active node of cellular decision-making**, integrating proliferative, inflammatory, and survival signals.



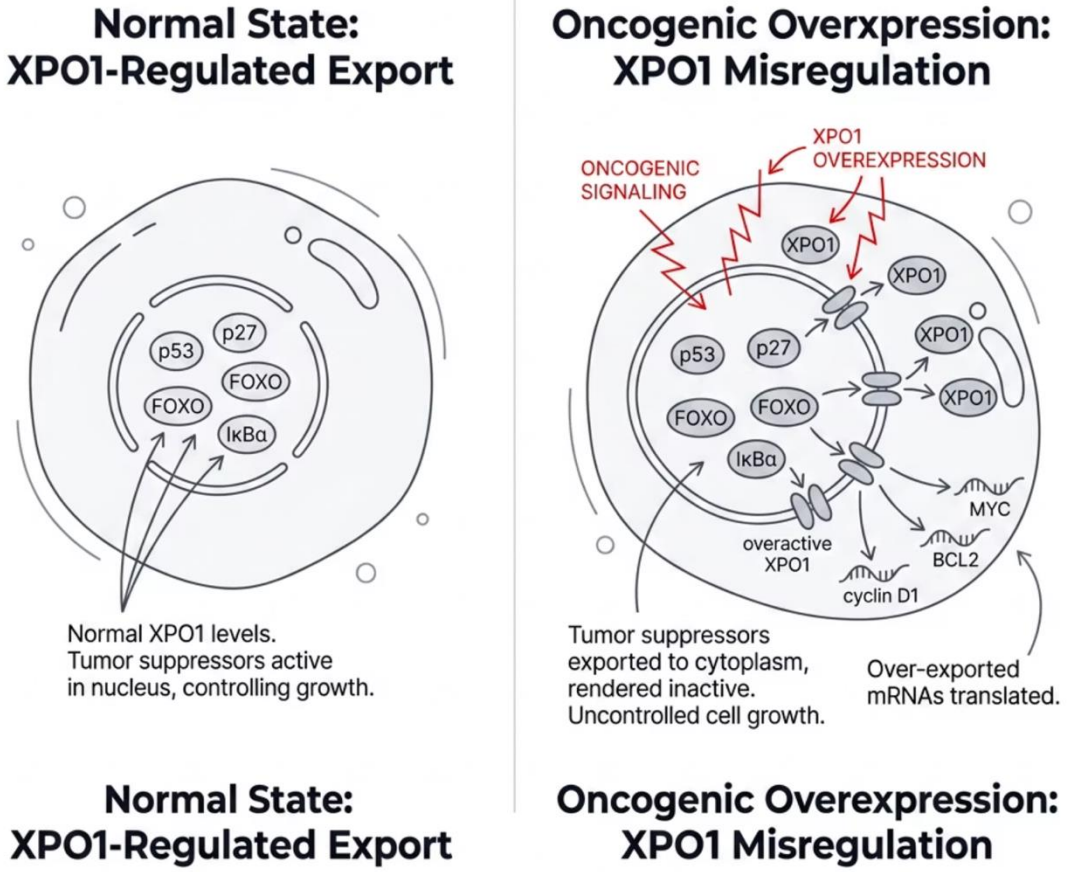
📚 Chen YF, et al. *Trends Pharmacol Sci* 2024; Marullo R, et al. *Cancer Res* 2023

When Export Becomes Oncogenic

The mechanism

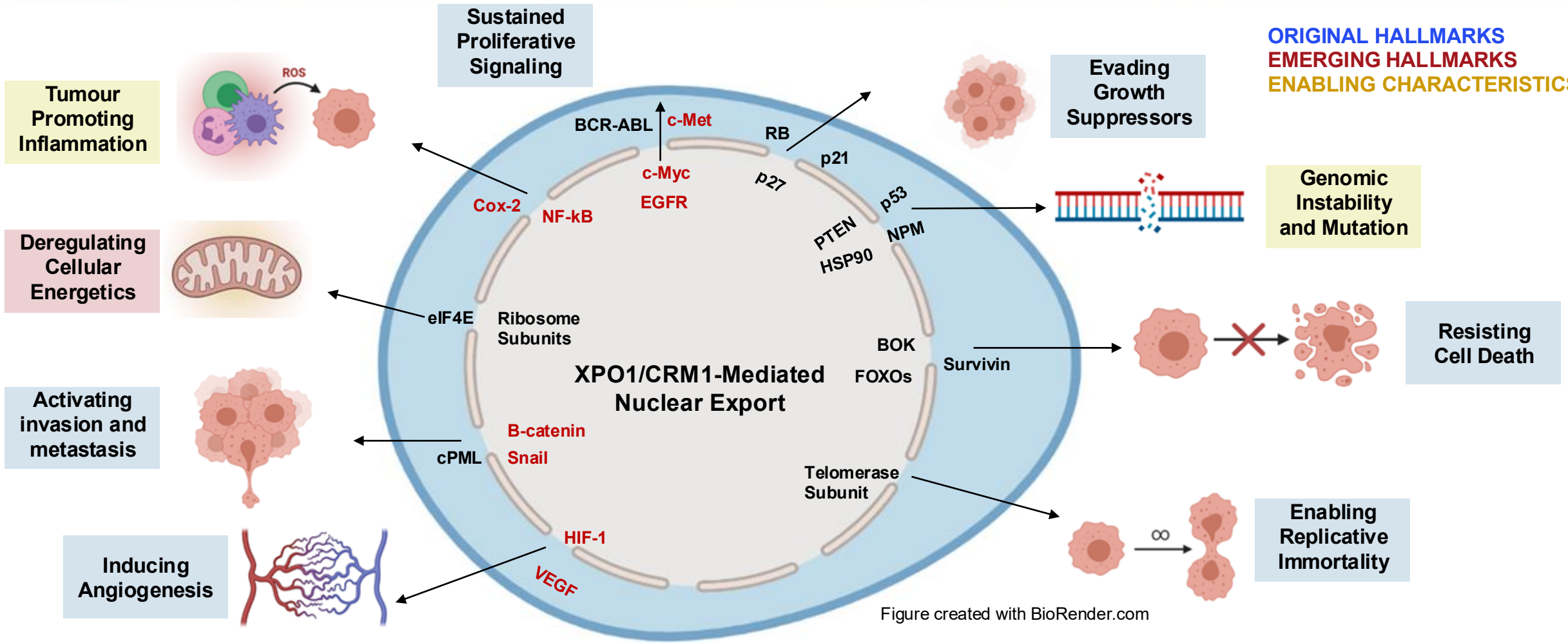
XPO1 is **overexpressed and/or mutated** across haematological and solid malignancies, functioning as an oncogenic driver. Chronic over-export **mislocalises tumour suppressors to the cytoplasm**, rendering them inert, whilst simultaneously sustaining oncoprotein translation.

High XPO1 expression correlates with **proliferation, therapy resistance, and poor prognosis** — converting a housekeeping receptor into a **rational, broad-spectrum therapeutic target**.



Sun Q, et al. *Signal Transduct Target Ther* 2016; Azizian NG & Li J, *J Hematol Oncol* 2020; Balasubramanian S, et al. *Leukemia* 2022

XPO1-Mediated Nuclear Transport Contributes to 9 of the 10 Cancer Hallmark Processes



ORIGINAL HALLMARKS
EMERGING HALLMARKS
ENABLING CHARACTERISTICS

Figure created with BioRender.com

BCR-ABL, breakpoint cluster region Abelson; c-Met, MET proto-oncogene, receptor tyrosine kinase; c-Myc, MYC proto-oncogene; Cox-2, cytochrome c oxidase subunit II; cPML, cytoplasmic promyelocytic leukemia; CRM1, chromosomal region maintenance 1; EGFR, epidermal growth factor receptor; eIF4E, eukaryotic translation initiation factor 4E; FOXO, forkhead box, sub-group O; HIF-1, hypoxia-inducible factor 1; HSP90, heat shock protein 90; NF-kB, nuclear factor kappa B; NPM, nucleophosmin 1; PTEN, phosphatase and tensin homolog; RB, RB transcriptional corepressor 1; VEGF, vascular endothelial growth factor; XPO1, exportin 1.

Sun Q, et al. *Signal Transduct Target Ther*. 2016;1:16010.

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The Therapeutic Inversion

SINE Compounds

Selective Inhibitors of Nuclear Export Export (SINE) — selinexor (KPT-330), 330), eltanexor — covalently engage engage XPO1 at **Cys528**, blocking export and **restoring nuclear localisation** of p53, p27, FOXO, and and IκBα simultaneously, whilst curbing oncoprotein mRNA export. export.

Clinical Validation

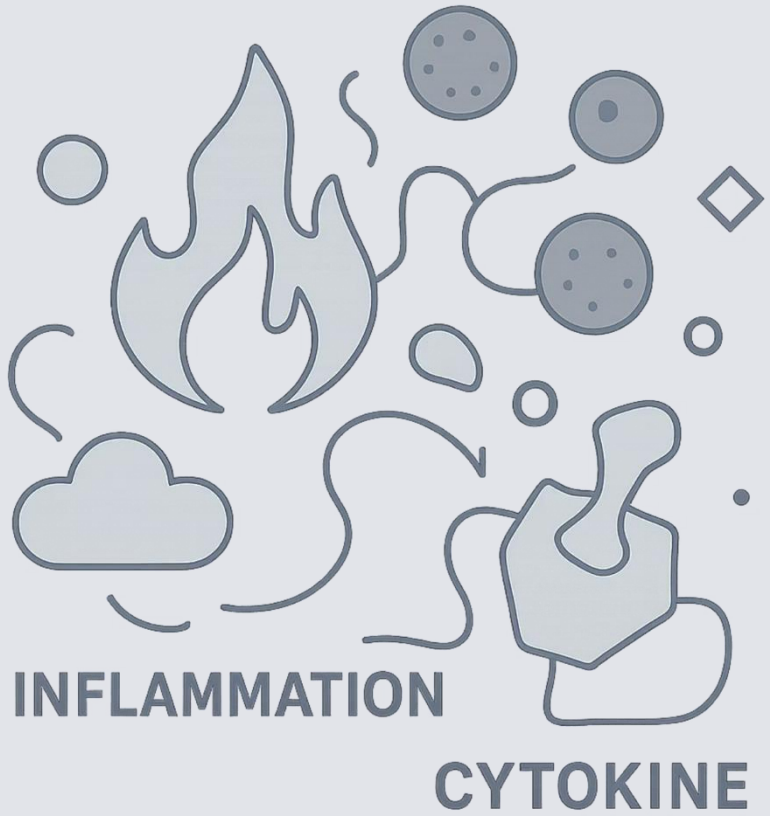
One pharmacological act re-engages engages *several* tumour-suppressive suppressive programmes at once. Selinexor is **approved in multiple myeloma**. Its accelerated approval in approval in R/R DLBCL was **withdrawn withdrawn (FDA, April 2026)** — a timely reminder of why the SENTRY SENTRY phase 3 matters.

📚 Azmi AS, et al. *Nat Rev Clin Oncol* 2020; Lai C, et al. *Clin Transl Med* 2024; FDA 2024; FDA Oncology Center of Excellence / ASCO, DLBCL accelerated-approval approval withdrawal, Apr–May 2026

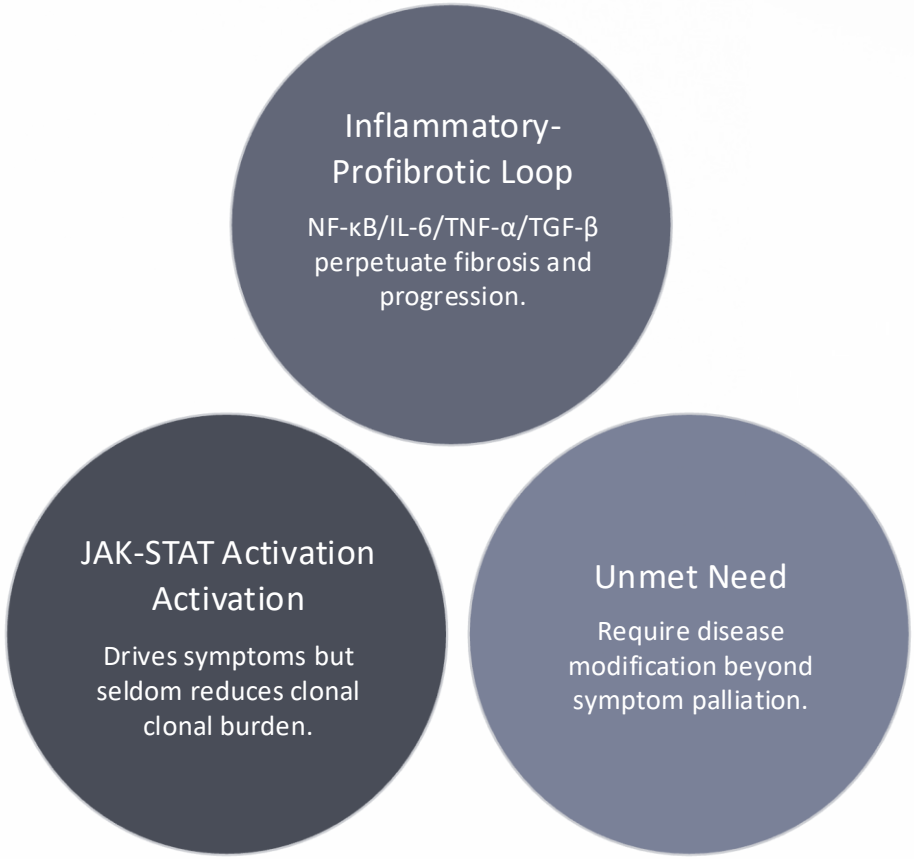
From a pan-cancer target to a disease made of inflammation inflammation

Myelofibrosis is not only a proliferation. It is a *milieu* — a self-sustaining loop of loop of clonal drive, cytokines, and fibrosis.

> If XPO1 governs both proliferation **and** NF-κB-driven inflammation, myelofibrosis is its natural test case.



The Myelofibrosis Problem



Why JAKi alone is insufficient

Ruxolitinib relieves spleen and symptoms but **rarely rarely reduces clonal burden or reverses fibrosis**. **fibrosis**. Resistance and intolerance are common; common; cytopenias constrain dosing; outcomes outcomes after JAKi failure remain poor.

The driver is as much the **inflammatory-profibrotic loop** (NF-κB, IL-6, TNF-α, TGF-β) as the kinase itself. The unmet need is **disease modification**, not only palliation.

Metzger M, et al. *Blood Neoplasia* 2024; Wei CT, et al. *Hematol Oncol* 2025

Why XPO1 Inhibition Fits Myelofibrosis

Selinexor engages **both JAK/STAT and non-JAK/STAT** drivers of MF simultaneously:

Apoptosis

↑ nuclear p53 → restored apoptosis in clonal cells

Inflammation

↓ NF-κB activation → reduced inflammatory cytokine output

Signalling

↓ STAT3/STAT5 phosphorylation; ↓ AKT/mTOR

Selectivity

Apoptosis of JAK2-mutated MF CD34+ cells whilst **sparing healthy donor cells**; synergy with ruxolitinib irrespective of JAK2V617F or TP53 status

Maloof ME, et al. 15th Int Congress on MPNs 2023, Poster #123; Lu M, et al. *Blood* 2023;142(Suppl 1):1792; Metzger M, et al. *Blood Neoplasia* 2024

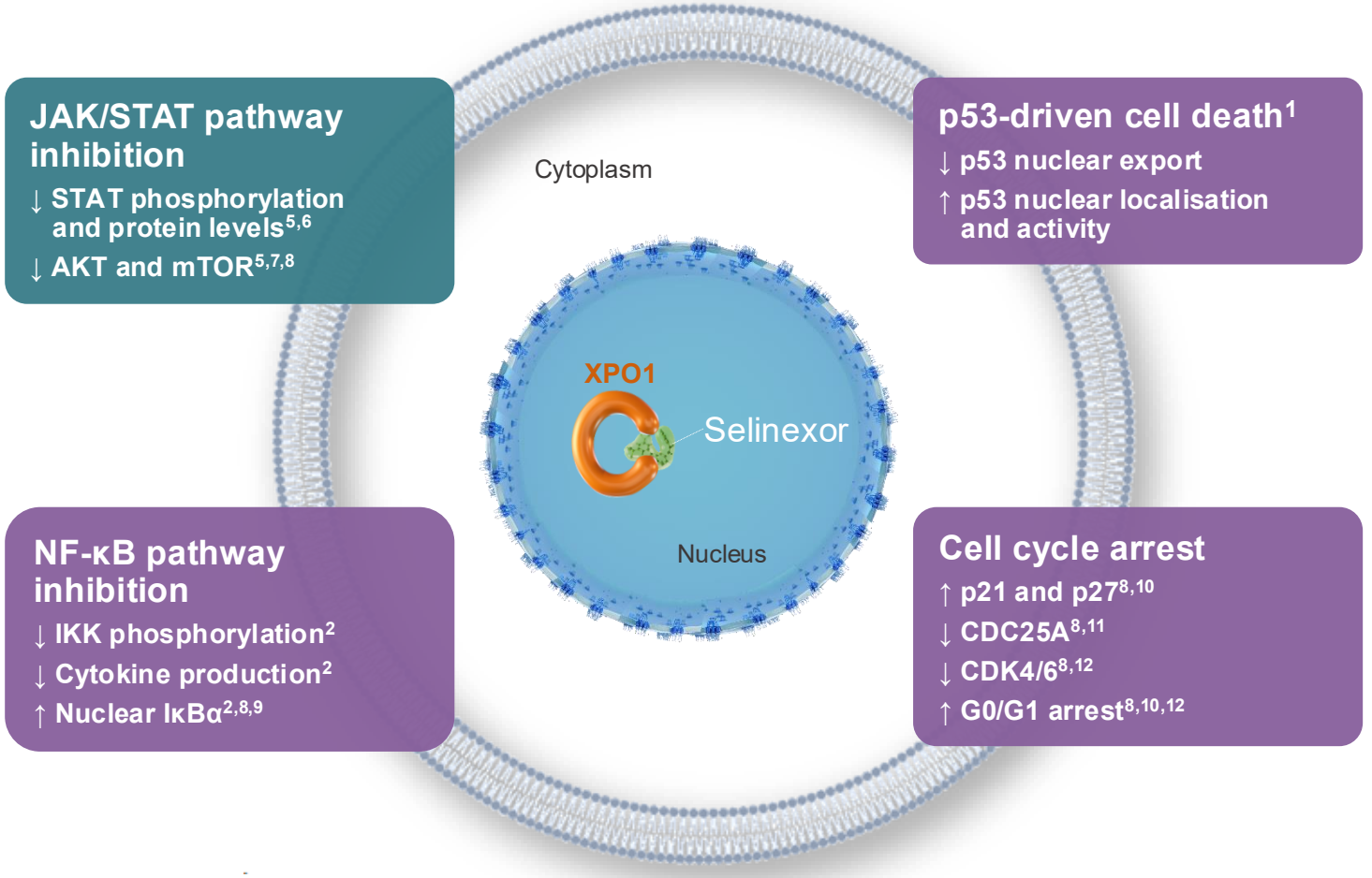
Selinexor is an investigational, targeted, oral XPO1 inhibitor

XPO1 inhibition is a fundamental mechanism of action that may target both JAK/STAT and non-JAK/STAT pathways in MF

Selinexor inhibits XPO1-mediated nuclear cargo protein export that may lead to:

- Increased malignant cell death[1]
- Reduced inflammation[2]
- Apoptosis of *JAK2*-mutated MF CD34+ cells but not healthy donor cells[3]
- Synergism with ruxolitinib and other therapeutic agents in cell lines with or without *JAK2*^{V617F} and *TP53* mutations[4]

Poster 1792
Lu M, et al. Use of Combination Therapies Including the XPO1 Inhibitor Selinexor Is a Potential Effective Therapeutic Strategy to Treat Myelofibrosis Patients Saturday, December 9, 2023: 6:00 PM–8:00 PM
Halls G–H (San Diego Convention Centre)



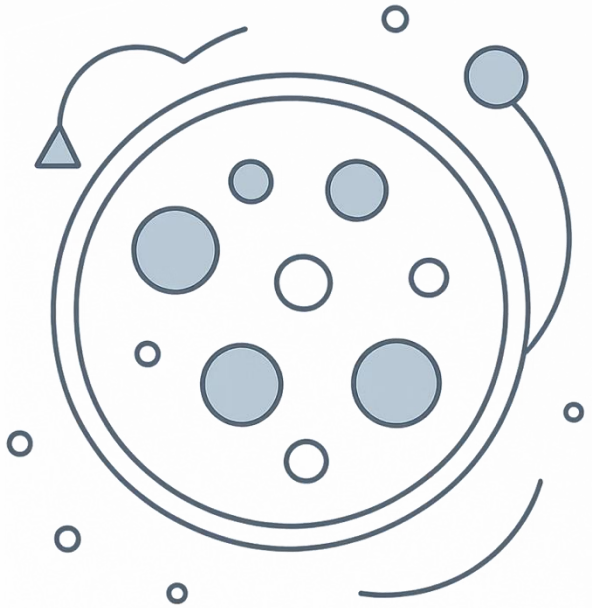
CD, cluster of differentiation; IκBα, inhibitor of nuclear factor kappa-B kinase subunit alpha; IKK, IκB kinase complex; *JAK2*, Janus kinase 2; JAK/STAT, Janus kinase/signal transducer and activator of transcription; MF, myelofibrosis; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; STAT, signal transducer and activator of transcription; XPO1, exportin 1.

1. Yan D, et al. *Clin Cancer Res*. 2019;25:2323–2335; 2. Kashyap T, et al. *Oncotarget*. 2016;7:78883–78895; 3. Lu M, et al. Presented at ASH 2023; Abstract #1792; 4. Maloof M, et al. Presented at 15th International Congress for MPNs 2023; Abstract #123; 5. Walker CJ, et al. *Blood*. 2013;122:3034–3044; 6. Cheng Y, et al. *Mol Cancer Ther*. 2014;13:675–686; 7. Argueta C, et al. *Oncotarget*. 2018;9;25529–25544; 8. Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:335–345; 9. Turner JG, et al. *Oncotarget*. 2016;7:78896–78909; 10. Gravina GL, et al. *BMC Cancer*. 2015;15:941; 11. Garg M, et al. *Oncotarget*. 2017;8:7521–7532; 12. Tan M, et al. *Am J Physiol Renal Physiol*. 2014;307:F1179–1186.

The Preclinical Case, in Brief

Single-agent activity

In vitro, selinexor reduced viability across MPN-derived lines and was **more potent (lower potent (lower IC50) than ruxolitinib, momelotinib, navitoclax, and pelabresib**, independent independent of JAK2/TP53 status. Activity is retained in **ruxolitinib-resistant clones** (IC50 **clones** (IC50 400 vs 320 nM).

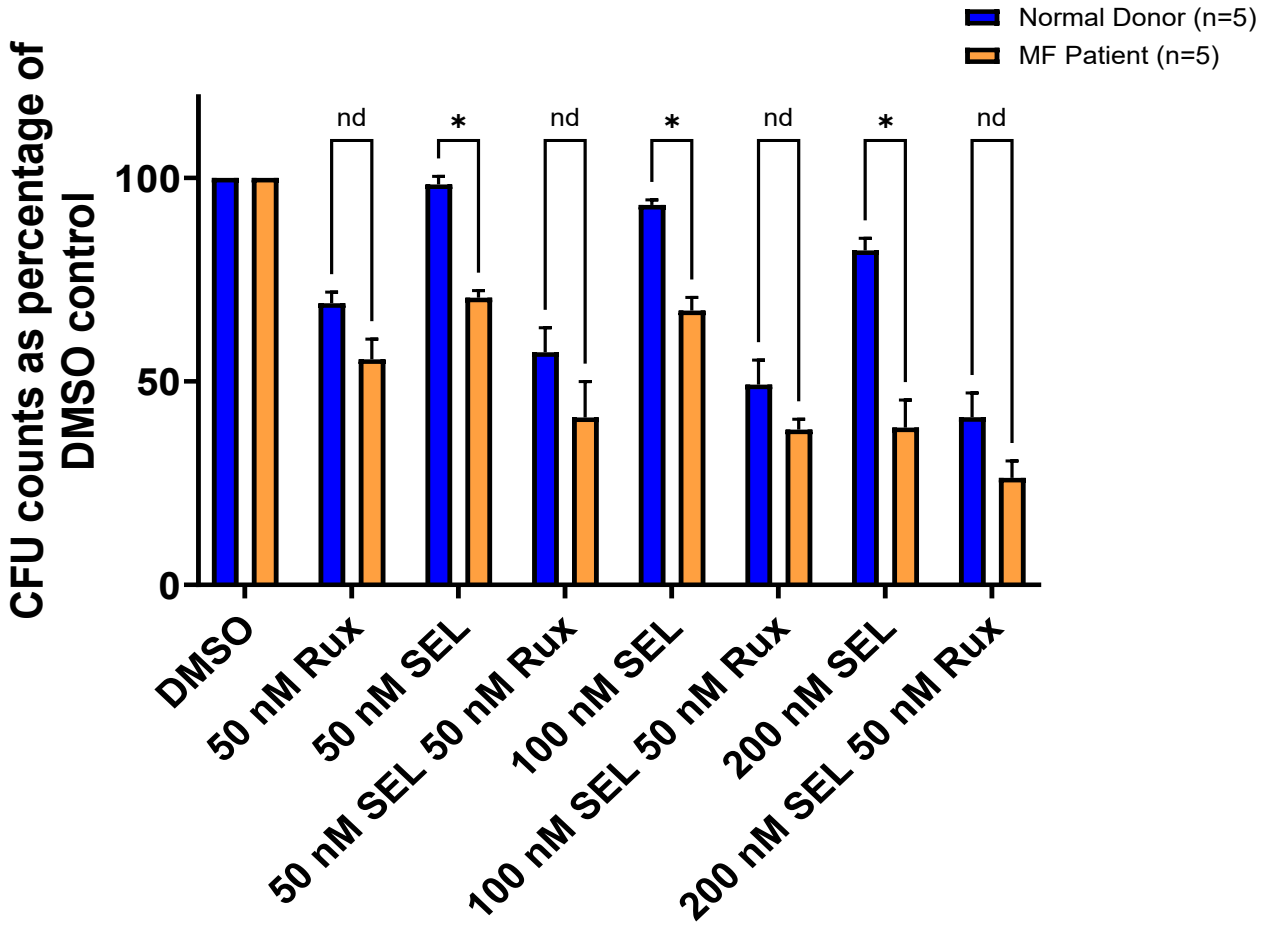


Combination and inflammation

Combination with MF agents yields predominantly **synergy or additivity** (Bliss). Selinexor Selinexor inhibits NF-κB transcriptional activity and **lowers secretion of key pro-inflammatory cytokines** — an axis where ruxolitinib has minimal effect.

📚 Maloof ME, et al. 15th Int Congress on MPNs 2023; Tantravahi SK, et al. *Clin Lymphoma Myeloma Leuk* 2024; Ali H, et al. *Blood* 2024;144(Suppl 1):6676

Selinexor reduced colony formation by MF patient-derived CD34+ cells, while having minimal effect on clonogenicity of normal donor CD34+ cells



Haematopoietic colony-forming unit (CFU) of CD34+ cells from patients with MF and normal donors (ND) were evaluated in the presence of selinexor, ruxolitinib or the combination. *P<0.05.
CFU, colony-forming unit; DMSO, dimethyl sulphoxide; MF, myelofibrosis; nd, no difference; Rux, ruxolitinib; SEL, selinexor.
Lu M, et al. *Blood*. 2023;142(Supplement 1):1792.

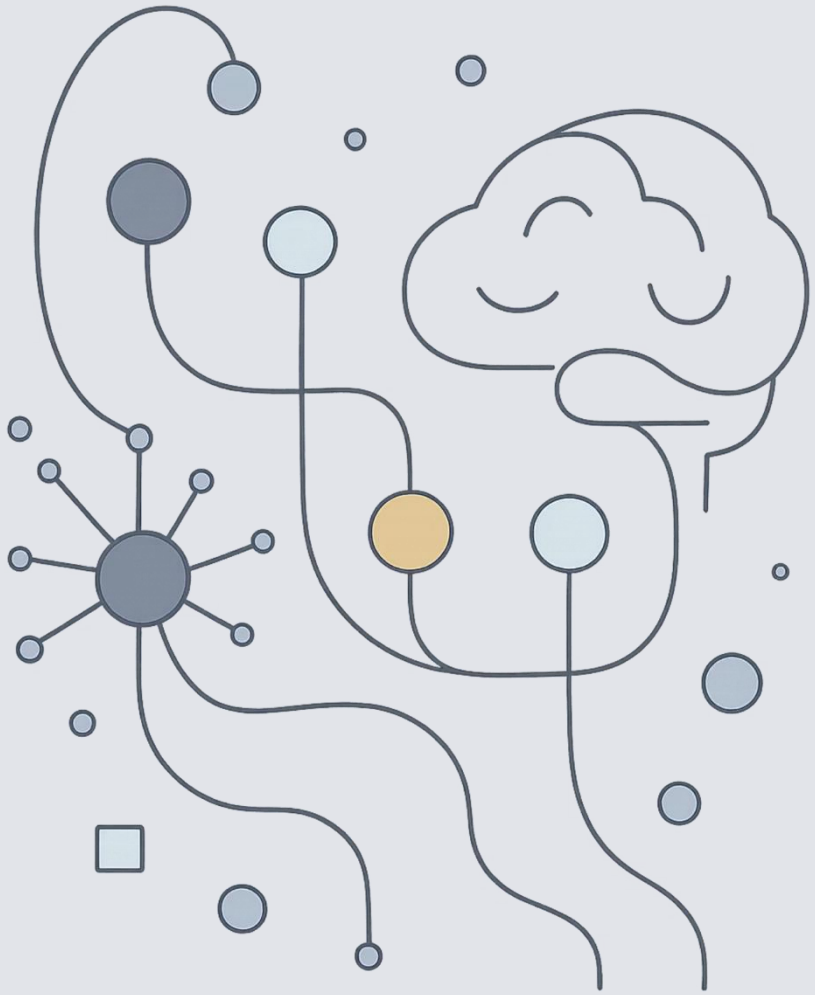
Results: Single-agent cell viability and synergy

- Selinexor as a single agent reduced cell viability in all cell lines tested, independent of *JAK2* and *TP53* mutation status, and was more potent than ruxolitinib, momelotinib, navitoclax, and pelabresib

IC_{50} cell viability of single agents

Line	SEL IC_{50}	RUX IC_{50}	MMB IC_{50}	PAC IC_{50}	NAV IC_{50}	PEL IC_{50}
HEL *JAK2*$^{MUT/MUT}$	0.32 µM	1 µM	2.7 µM	0.82 µM	0.43 µM	2.2 µM
UKE-1 *JAK2*$^{MUT/MUT}$	0.32 µM	2.3 µM	1.3 µM	0.32 µM	0.054 µM	1.7 µM
MUTZ-8 *JAK2*$^{MUT/MUT}$	0.012 µM	3 µM	3.8 µM	0.52 µM	0.028 µM	4.5 µM
ELF-153 *JAK2*$^{WT/WT}$	1.8 µM	64.6 µM	6.2 µM	0.82 µM	3.99 µM	1.6 µM

IC_{50}, 50% inhibitory concentration; *JAK2*, Janus kinase 2; MMB, momelotinib; NAV, navitoclax; PAC, pacritinib; PEL, pelabresib; RUX, ruxolitinib; SEL, selinexor; WT, wild type.
Maloof ME, et al. Presented at 15th International Congress for MPNs 2023; Poster #123.



The thesis

> Myelofibrosis is not, at its root, a **kinase disease**. The clone is *selected by by inflammation* — it thrives because it inflames, and inflames because it because it thrives.

The aim is not to raze an aberrant population, but to *quieten the circuit that selects that selects it*. Nuclear traffic is the grammar of that circuit — the language in which language in which proliferation and inflammation are spoken together.

Blocking nuclear export **restores tumour-suppressor restraint and dampens NF-κB-driven inflammation at once**. The endpoint that follows is not only the spleen, but the **inflammatory and clonal architecture** of the disease — and, for the first time, an early survival signal suggests we may be touching it.

Does the mechanism mechanism translate? translate?

Biology earns its place only at the bedside.

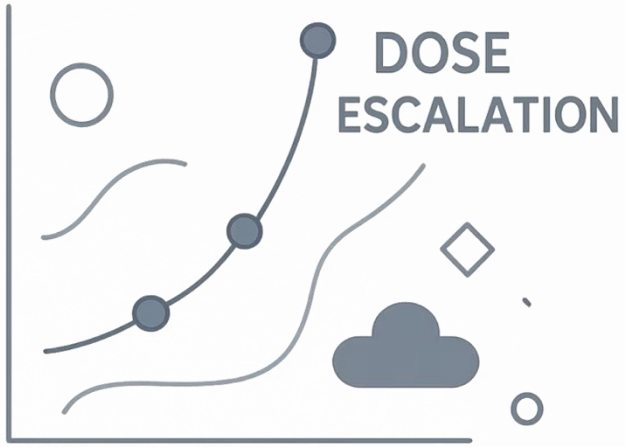
> The SENTRY programme is where the hypothesis met the endpoint.

XPORT-MF-034 — Phase 1

SELINEXOR + RUXOLITINIB | JAKI-NAÏVE

Selinexor (40 or 60 mg once weekly) + ruxolitinib in JAKi-naïve MF (n = 24). (n = 24). **No dose-limiting toxicities** observed.

60 mg selected as the recommended phase 3 dose. Nausea transient, mainly grade 1, antiemetic-managed.



Ali H, et al. *Blood Adv* 2026;10(10):3383–3397 (XPORT-MF-034, phase 1 portion)

60 mg — Week 24

SVR35 79%
TSS50 58%

40 mg — Week 24

SVR35 38%
TSS50 25%

Suboptimal Rux (≤5 mg BID)

SVR35 100% (6/6)

Selinexor Monotherapy — Phase 2 (XPORT-MF-035)

GLOBAL | RANDOMISED | JAKI PRE-TREATED | NCT04562870 | N = 24

Open-label phase 2: **single-agent selinexor vs physician's choice (PC)** in MF previously treated with a JAKi; 1:1, crossover allowed on progression. on progression.

SVR35 (any time)

29% (2/7) selinexor vs 13% (1/8) PC; **40% 40% (2/5) after crossover** to selinexor. selinexor. Symptom improvement seen seen with selinexor, not PC.

Mechanistic Signal

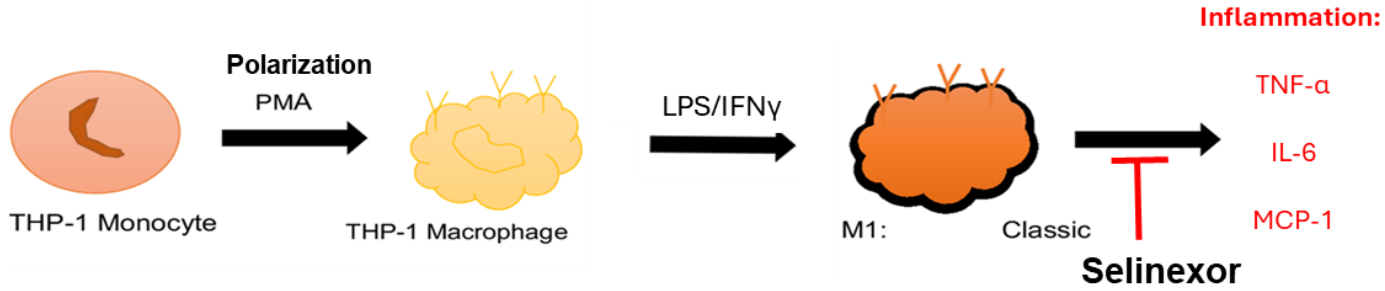
Fewer grade ≥3 anaemia events, lower lower transfusion burden, and reductions in multiple pro-inflammatory inflammatory cytokines — the circuit circuit being quietened, not only the spleen.

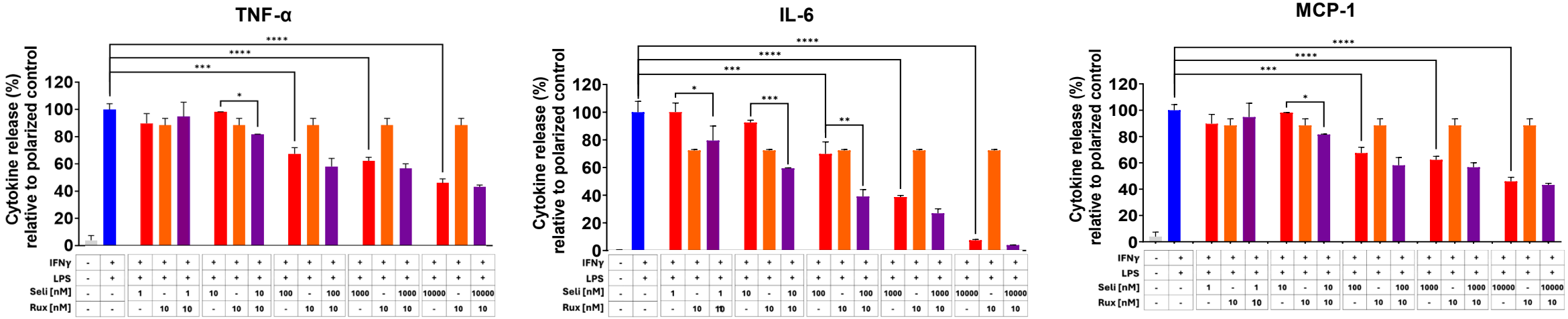
Significance

A small, descriptive study — but a **coherent biological signal** that established the rationale for the combination programme.

Grosicki S, et al. (senior author A. Lucchesi). *eJHaem* 2026;7:e70301. doi:10.1002/jha2.70301 (XPORT-MF-035; NCT04562870)

Selinexor reduces extracellular secretion of key pro-inflammatory cytokines





Selinexor single agent and in combination with ruxolitinib induces a dose-dependent effect on the release of pro-inflammatory cytokines

IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; PMA, phorbol-12-myristate-13-acetate; rux, ruxolitinib; sel, selinexor; TNF-α, tumour necrosis factor-alpha.

Ali H, et al. *Blood*. 2024;144(Supplement 1):6676.

SENTRY — Phase 3 (XPORT-MF-034)

☆ LATE-BREAKING | EHA 2026 & ASCO 2026

Double-blind, 2:1, selinexor + ruxolitinib vs placebo + ruxolitinib in JAKi-naïve MF; **n = 353**.

49.8%

SVR35 at Week 24

vs 28.0% placebo arm (OR 2.58; *P* < 0.0001); separation by week 12, sustained to week 36

HR 0.43

Overall Survival Signal

95% CI 0.19–1.00; nominal *P* = 0.022 — an an early but notable signal

70.1%

Grade ≥3 AEs

vs 50.0% in control: anaemia, thrombocytopenia, neutropenia; nausea mostly low-grade and early

⚠ Symptom co-primary (AbsTSS, fatigue excluded) **NOT met**: −9.9 vs −10.9, no significant difference.

📚 Bose P, et al. *J Clin Oncol* 2026; doi:10.1200/JCO-26-01080 (SENTRY phase 3); presented EHA 2026 & ASCO 2026 (late-breaking)

Reading the Result Honestly

The Gains

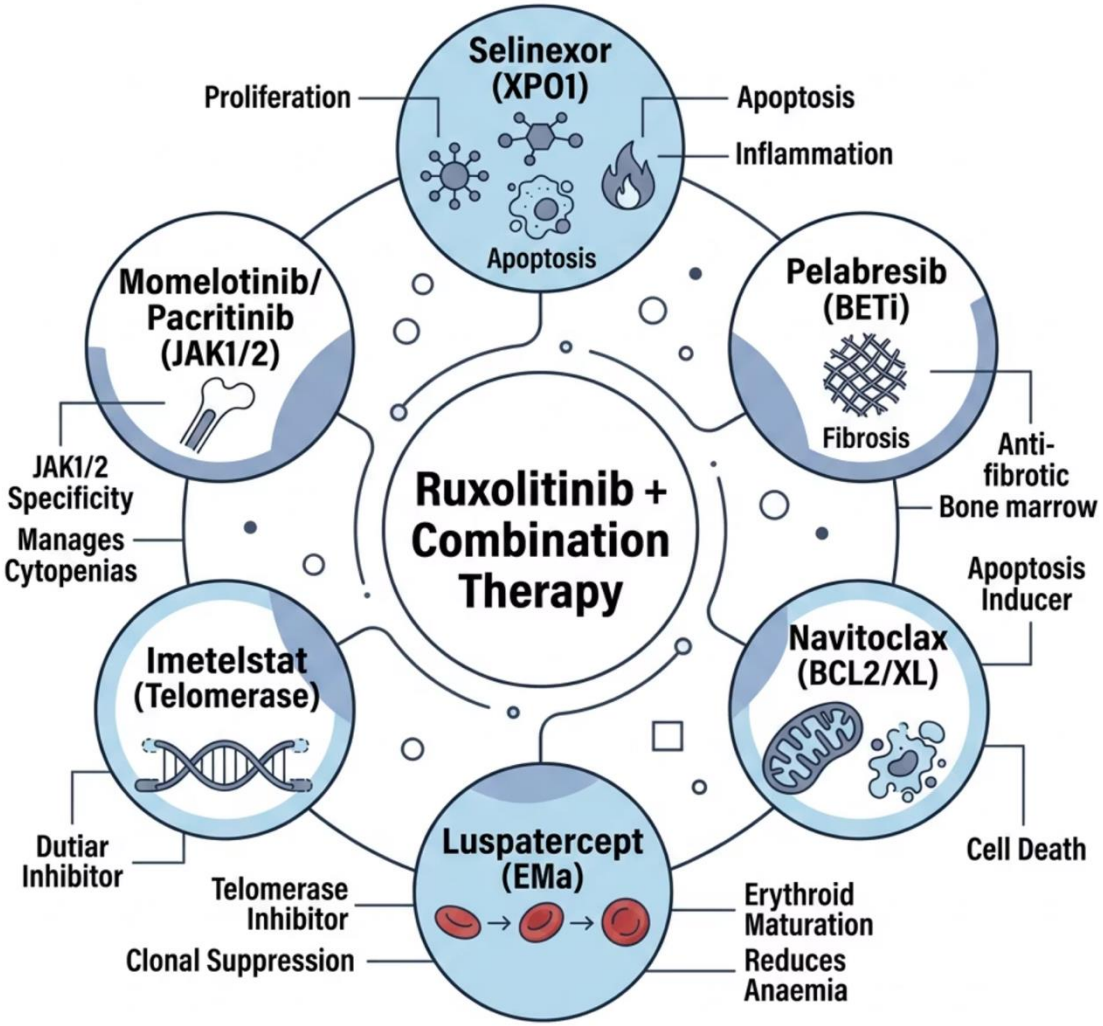
A **near-doubling of spleen response** with a mechanistically coherent, disease-modifying rationale. An **early overall survival signal** suggests we may be touching the clonal and inflammatory architecture of the disease — not merely the spleen volume.

The Caveats

- Symptom co-primary **not met**; endpoint definition shifted from shifted from phase 1 (TSS50) to phase 3 (absolute TSS, fatigue fatigue excluded) — endpoint choice shapes the verdict
- Added **myelosuppression and nausea**: net benefit will depend on patient selection and supportive care
- Open questions: **biomarkers of response**, and whether gains reflect true **clonal or fibrosis modification**

Bose P, et al. *J Clin Oncol* 2026; Ali H, et al. *Blood Adv* 2026; Chen YF, et al. *Trends Pharmacol Sci* 2024

Where It Sits in the Landscape



A crowded field, a distinct mechanism

In a network meta-analysis of ruxolitinib-based combinations, **ruxolitinib + selinexor ranked among the among the most active** (SVR35 ~92%, TSS50 ~78% in the in the pooled JAKi-naïve estimate).

Each competitor addresses a different axis — fibrosis, anaemia, cytopenias. The differentiator of XPO1 inhibition is its **breadth**: proliferation, apoptosis, and inflammation addressed simultaneously.

Tan S, et al. *Ann Med* 2026 (systematic review/meta-analysis); Wei CT, et al. *Hematol Oncol* 2025; Bose P, et al. *Curr Hematol Malig Rep* 2025

The Biology Has Already Reached the Clinic — A Multiple Myeloma Footnote

XPO1 is overexpressed in myeloma plasma cells; selinexor restores tumour-suppressor function and disrupts oncoprotein export. Two landmark trials validate the target clinically:

BOSTON Trial

Selinexor + bortezomib + dexamethasone in R/R myeloma (≥1 prior line). **Approved combination**.

Grosicki S, et al. *Lancet* 2020

STORM Trial

Selinexor + dexamethasone in penta-exposed/refractory disease. Proof of single-agent agent nuclear-export inhibition efficacy.

Chari A, et al. *N Engl J Med* 2019; Tai YT, et al. *Leukemia* 2014

Proof that nuclear-export inhibition is a *bona fide* therapeutic principle — not a preclinical curiosity.

Take-Home

1 XPO1 — a hub, not a conduit

A single receptor governing nuclear traffic of tumour suppressors and oncoprotein mRNAs, touching almost every cancer hallmark.

2 SINE compounds invert the logic

Covalent blockade at Cys528 re-engages **multiple tumour-suppressive programmes** simultaneously — a one-act pharmacological inversion.

3 Myelofibrosis: a mechanistically coherent fit

Selinexor + ruxolitinib targets JAK/STAT *and* the NF-κB-driven inflammatory loop — both pillars of the disease.

4 SENTRY phase 3 — a meaningful step, with caveats

Near-doubling of spleen response and an early survival signal — tempered by an unmet symptom co-primary and added myelosuppression. Patient selection and Patient selection and biomarker development will be decisive.

5 The destination is still being mapped

From biology to the clinic, the journey is real. **Disease modification** — clonal and fibrotic — remains the horizon towards which the evidence is pointing. pointing.

📚 Azmi AS, et al. *Nat Rev Clin Oncol* 2020; Ali H, et al. *Blood Adv* 2026; Bose P, et al. *J Clin Oncol* 2026

The question I leave you with

If we can decide what stays in the nucleus, are we silencing a symptom of myelofibrosis — or teaching its circuit, at last, to sleep?

Thank you. alessandro.lucchesi@irst.emr.it

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