

PANEL II

TREATMENT

18:36 – 19:06 · Cases 4–7 · 7–10 minutes per case

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CASE 4 Luspatercept vs ESA First-Line: Does COMMANDS Settle It?

PATIENT

- 69F · MDS low-risk (IPSS-R 2.5)
- Hb 8.0 g/dL · TD: 2 RBC/month ×8 months
- EPO 95 mU/mL · Malcovati ESA score Group 1 (favorable)
- ECOG 0 · No comorbidities

DIAGNOSTIC DATA

- SF3B1 VAF 38% · Ring sideroblasts 4% · TET2 VAF 22%
- Normal karyotype · No del(5q)
- Ferritin 720 ng/mL

PRIOR THERAPY

- ESA-naive · No prior MDS-directed therapy

CLINICAL DILEMMA

SF3B1-mutated, ESA-naive, low-risk MDS with favorable Malcovati Group 1 score:

Luspatercept first-line (COMMANDS data) or ESA given strong predictive score?

Does low ring sideroblast count (<5%) with SF3B1 mutation change the calculus?

DISCUSSION OPTIONS

- A** Luspatercept first-line — COMMANDS superiority holds; SF3B1 mutation is sufficient
- B** Darbepoetin first-line — Group 1 predicts >60% ESA response; luspatercept for failure
- C** Shared decision-making — both reasonable; access, cost, patient preference drive choice
- D** Luspatercept only if RS $\geq 15\%$; ESA first for low-RS SF3B1-mutated (extrapolation concern)

CASE 5 Post-Luspatercept Relapse: Imetelstat, Re-trial, or Escalation?

PATIENT

- 71M · MDS-RS low-risk (IPSS-R 2.0) · SF3B1-mutated
- TD: 3 RBC/month — relapsed after initial luspatercept response
- Luspatercept: TD-independence ×18 months → relapse
- EPO now 310 mU/mL · ECOG 0

DIAGNOSTIC DATA

- Sequential NGS: SF3B1 persistent · no new mutations
- IPSS-R stable · No del(5q) · No cytogenetic evolution
- Ferritin 1,950 ng/mL · Cardiac T2* 22 ms (borderline) · eGFR 68 mL/min

PRIOR THERAPY

- Darbepoetin ×5 months — inadequate response
- Luspatercept: responded ×18 months → relapsed
- ~28 RBC units total

CLINICAL DILEMMA

**Post-luspatercept relapse in SF3B1-mutated MDS after prior ESA failure:
Imetelstat (IMerge phase III data), ESA re-trial, or disease escalation check?
Iron overload with borderline cardiac T2* — chelation now or later?**

DISCUSSION OPTIONS

- A** Imetelstat — IMerge phase III: only agent with RCT data in ESA/luspatercept-refractory LR-MDS
- B** Re-trial darbepoetin — EPO 310 mU/mL; prior failure at lower EPO; residual benefit possible
- C** Reassess IPSS-R and cytogenetics first — exclude disease progression before next-line
- D** Clinical trial + initiate deferasirox given T2* 22 ms + ferritin 1,950 ng/mL

CASE 6 MF + Severe Thrombocytopenia: Which JAK Inhibitor?

PATIENT

- 58F · Primary MF · DIPSS Intermediate-2
- Hb 7.8 g/dL · TD: 3 RBC/month · PLT 38K
- Massive splenomegaly (26 cm) · JAK2 V617F+
- ECOG 1 · ASXL1 mutated · No HLA-matched donor

DIAGNOSTIC DATA

- BM: MF-3 fibrosis · CALR/MPL negative
- MIPSS70+: high molecular risk
- JAK inhibitor-naive · eGFR 72 mL/min

PRIOR THERAPY

- No prior JAK inhibitor · No prior MF-directed therapy

CLINICAL DILEMMA

JAK inhibitor-naive MF with PLT 38K, severe anemia, massive splenomegaly, high molecular risk. Pacritinib is NOT available in Brazil. Momelotinib vs ruxolitinib low-dose vs danazol bridge vs transplant-first — what is your approach?

DISCUSSION OPTIONS

- A** Momelotinib — ACVR1 inhibition addresses anemia; MOMENTUM data; PLT ≥25K in trial (borderline here)
- B** Ruxolitinib low-dose (5 mg BID) — start cautiously; dose-escalate with weekly PLT monitoring; risk of worsening thrombocytopenia
- C** Danazol bridge — modest evidence in MF-related anemia/thrombocytopenia; buys time while pursuing transplant
- D** Urgent haplo/MUD transplant evaluation first — MIPSS70+ high risk; JAK inhibitor as bridge only after PLT recovery
- E** Best supportive care + transfusion support while investigating transplant — no safe JAK inhibitor option at PLT 38K without pacritinib

CASE 7 Ruxolitinib Failure in Myelofibrosis: What Comes Next?

PATIENT

- 62M · Primary MF · DIPSS Intermediate-2
- On ruxolitinib 20 mg BID ×18 months — initial spleen response lost
- Progressive splenomegaly (return to 22 cm) · constitutional symptoms worsening
- Hb 8.2 g/dL · PLT 112K · ECOG 1 · ASXL1 + SRSF2 co-mutation

DIAGNOSTIC DATA

- BM: MF-2 fibrosis · JAK2 V617F VAF now 58% (was 34% at diagnosis)
- No cytogenetic evolution · No excess blasts
- MIPSS70+: high molecular risk · eGFR 74 mL/min
- No HLA-matched sibling · unrelated donor search initiated (8/10 match found)

PRIOR THERAPY

- Ruxolitinib 20 mg BID ×18 months: spleen response ×12 months → progressive loss
- No prior second-line therapy · Transfusion-independent (borderline)

CLINICAL DILEMMA

Ruxolitinib failure — spleen progression + constitutional symptoms + rising JAK2 VAF (34% → 58%).

**Momelotinib vs ruxolitinib + add-on (navitoclax/pelabresib)?
8/10 MUD available: transplant now or second-line therapy first?**

DISCUSSION OPTIONS

- A** Momelotinib — switch strategy; ACVR1 mechanism addresses anemia + symptoms; MOMENTUM data in ruxolitinib-exposed patients
- B** Ruxolitinib dose re-escalation + navitoclax add-on — combination strategy; REFINE/TRANSFORM data; thrombocytopenia risk
- C** Ruxolitinib + pelabresib (BET inhibitor) combination — MANIFEST-2 data; investigational in second-line context
- D** Proceed directly to allogeneic SCT with 8/10 MUD — MIPSS70+ high risk; second-line JAK inhibitor delays transplant
- E** Momelotinib bridge × 3–6 months → allogeneic SCT — stabilize anemia and symptoms before conditioning