Sindromi Mieloproliferative

Chronic Myeloid Leukemia

- Teatment of CML in Pegnancy
- Management of CML resistant to 2/more TKIs
- Transplantation in CML in the TKI era: who, when and how?

Treatment of CML in pregnancy

- Teratogenicity render TKIs
  controindicate during pregnancy

- A paucity of good evidence available to guide treatment (mainly in pregnancies unplanned !)

- IFN-a can used in any trimester

- TKIs in the later stages of pregnancy

Management of CML resistant to 2/more TKIs

- Ponatinib: high doses → more response
  lower doses → maintain response

- Asciminib: novel allosteris ABL1 inhibitor

- T315I Mutation: higher doses are critical for success

Management of CML resistant to 2/more TKIs

- Asciminib + Ponatinib: excellent results

- Asciminib or Ponatinib: followed by HSCT ?

- New drugs: Vodobatinib (no cardiovascular toxicity)
  Olverambatinib
  (T315 mutated: 73% MMR)
  ELVN-001

Transplantation in CML in the TKI era:

Timing is essential: early stages of disease has the best outcome

Candidates for HSCT:

- Not responding to 2G-TKI
- AP/BP
- High-risk additional cytogenetic abnornalities/molecular signs of Leukemia progression (gene mutations)
- Do not tolerate/severe adverse events +/- vascular events to multiple TKIs

Policitemia Vera

e

Trombocitemia Essenziale

Low Risk PV

Ropeginterferon alfa 2-b is safe,
well tolerated and more effective
vs phlebotomy in keeping
the HCT at target level

PV/ET

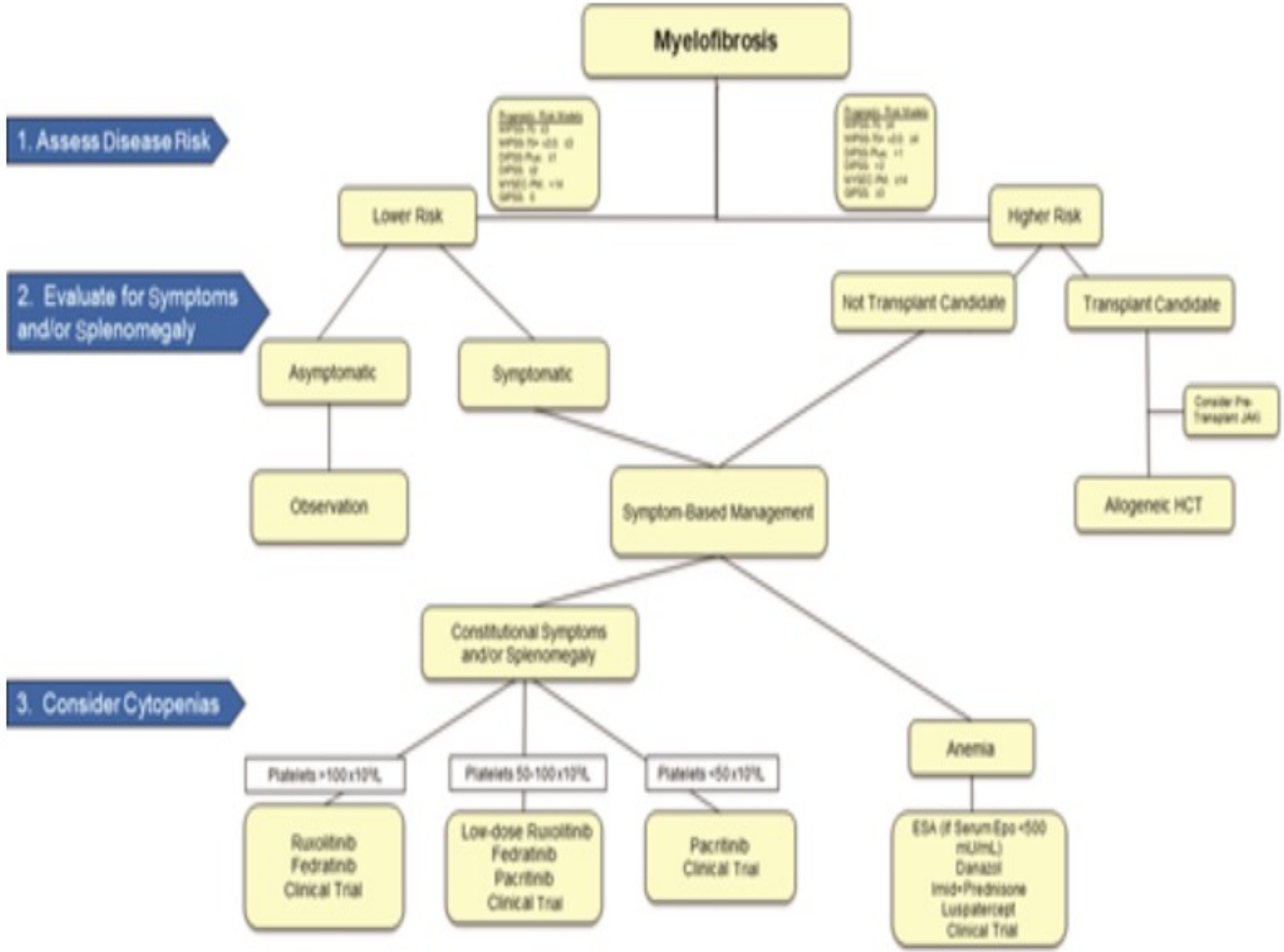
JAK2 V617F Molecular Response to Ruxolitinib in patients with PV and ET is associateted with lower risk of progression to secondary Myelofibrosis

PV

Rusfertide (PTG-300) mimichs the effect of natural hormone hepcidin and controls HCT levels (effective also in hereditary hemochromatosis)

JAK/STAT inhibition and beyond in Ph negative MPNs

- Hitting the brakes on AP/BP myeloproliferative neoplasms: current and emerging concepts
- Molecular prognostication MPNs in 2022
- New approches to tackle cytopenic myelofibrosis


Myelofibrosis
1. Assess Disease Risk
Lower Risk
Higher Risk
2. Evaluate for Symptoms and/or Splenomegaly
Asymptomatic
Symptomatic
Not Transplant Candidate
Transplant Candidate
Observation
Symptom-Based Management
Allogeneic HCT
3. Consider Cytopenias
Constitutional Symptoms and/or Splenomegaly
Platelets >100 x10⁹/L
Platelets 50-100 x10⁹/L
Platelets <50 x10⁹/L
Anemia
Ruxolitinib
Fedratinib
Clinical Trial
Low-dose Ruxolitinib
Fedratinib
Pacritinib
Clinical Trial
Pacritinib
Clinical Trial
ESA (if Serum Epo <500 mU/mL)
Danazol
Imid+Prednisone
Luspatercept
Clinical Trial

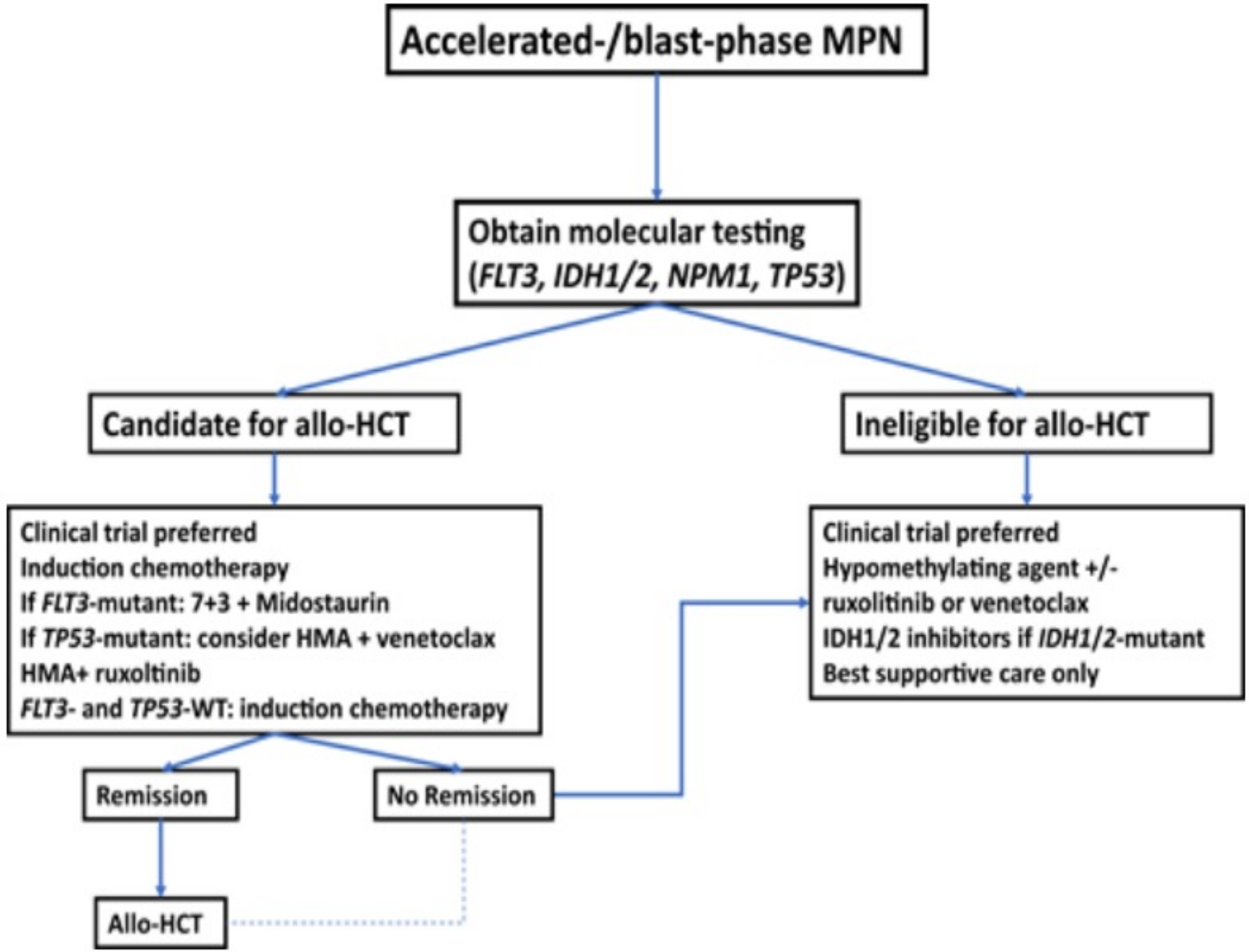
BCR-ABL neg MPNs: variable risk of progression to MPN/AP (10-19%) /MPN-BP (≥20% blasts)

- Molecular processes underlying the progression to AP/BP
- Additional mutations (ASXL1, EZH2, TET2)
- TP53
- Ras pathway
- Splicing factors (SRSF2, U2AFT)

THERAPY of BP-MPN

- Allografting: only a minority of patients are eligible

- Palliative treatment:
  Hypomethylating agents as monotherapy or in combination with Venetoclax or Ruxolitinib


Accelerated-/blast-phase MPN
Obtain molecular testing (*FLT3, IDH1/2, NPM1, TP53*)
Candidate for allo-HCT
Ineligible for allo-HCT
Clinical trial preferred
Induction chemotherapy
If *FLT3*-mutant: 7+3 + Midostaurin
If *TP53*-mutant: consider HMA + venetoclax
HMA+ ruxoltinib
FLT3- and *TP53*-WT: induction chemotherapy
Clinical trial preferred
Hypomethylating agent +/- ruxolitinib or venetoclax
IDH1/2 inhibitors if *IDH1/2*-mutant
Best supportive care only
Remission
No Remission
Allo-HCT

Overview of selected ongoing clinical trials in MPN-BP

Agent	NCT	Phase	Patient population
Decitabine + ruxolitinib or fedratinib	NCT04282187	2	MPN-AP and MPN-BP as bridge to allo-HCT
Ruxolitinib + enasidenib	NCT04281498	2	*IDH2*-mutant MPN-AP, MPN-BP, chronic-phase myelofibrosis
Fedratinib + ivosidenib or enasidenib	NCT04955938	1	*IDH1*- or *IDH2*-mutant MPN with ≥5% blasts
Azacitidine + venetoclax	NCT05074355	2	MPN-AP and MPN-BP
KRT-232 (MDM2 inhibitor)	NCT04113616	1/2	post-MPN AML
ZN-d5 (BCL2 inhibitor) + ZN-c3 (WEE1 inhibitor)	NA	1/2	AML including post-MPN AML

33 yrs,F, CP-CML, HR EUTOS

Dasatinib (NO MR)

Nilotinib (NO MR)

NO KD mutation/NO cardiovascular events

OPTIONS

Bosutinib: very low response

Ponatinib: 45mg (OPTIC dosing: 50%MR)

Asciminib: (in cases with the risk of vascular events was high)

BEST OPTION: Ponatinib 45mg ➡ 15mg, HSCT

Ponatinib: 30mg (low risk of AOEs and lower MR

Asciminib: 40mg x 2/d: 40% rate of
MMR by 6mo.

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