What is New in Hematology Update 2021

Acute Leukemia and MDS

CPX-351 and HMA + Venetoclax as Frontline Therapy in AML: A Retrospective Comparative Analysis

Outcomes With CPX-351 or HMA + Ven: Background

- Liposomal daunorubicin/cytarabine (CPX-351) and venetoclax + an HMA are novel regimens that have both shown ***OS advantage*** as frontline therapies for ***older patients*** with acute myeloid leukemia[1,2]
- Current retrospective analysis compared clinical outcomes and patient characteristics in patients with AML receiving either CPX-351 or HMA + Ven in the frontline setting[3]

1. DiNardo. NEJM. 2020;383:617. 2. Kolitz. Leuk Lymphoma. 2020;61:631.
3. Grenet. ASH 2021. Abstr 32. 4. Sekeres. Blood Adv. 2020;4:3528.

Outcomes With CPX-351 or HMA + Ven: Investigators' Conclusions

- In this retrospective analysis of patients with newly diagnosed AML, there was no significant difference in response rate (CR/CRi) between CPX-351 and HMA + Ven in the overall population and in patients aged 60-75 yr
- CPX-351 treatment was associated with a longer OS compared with HMA + Ven in the overall population but not in the patient subgroup aged 60-75 yr
  - Subgroup analyses in patients aged 60-75 yr showed a higher OS with CPX-351 in patients with *TP53* mutations
- Among patients aged 60-75 years, there was no significant difference in OS between the 2 treatment groups despite more than double the rate of HSCT in the CPX-351 group compared to the HMA + Ven group

Grenet. ASH 2021. Abstr 32.

Venetoclax/Decitabine for Young Adults With Newly Diagnosed ELN Adverse-Risk AML: Phase II Trial Interim Analysis

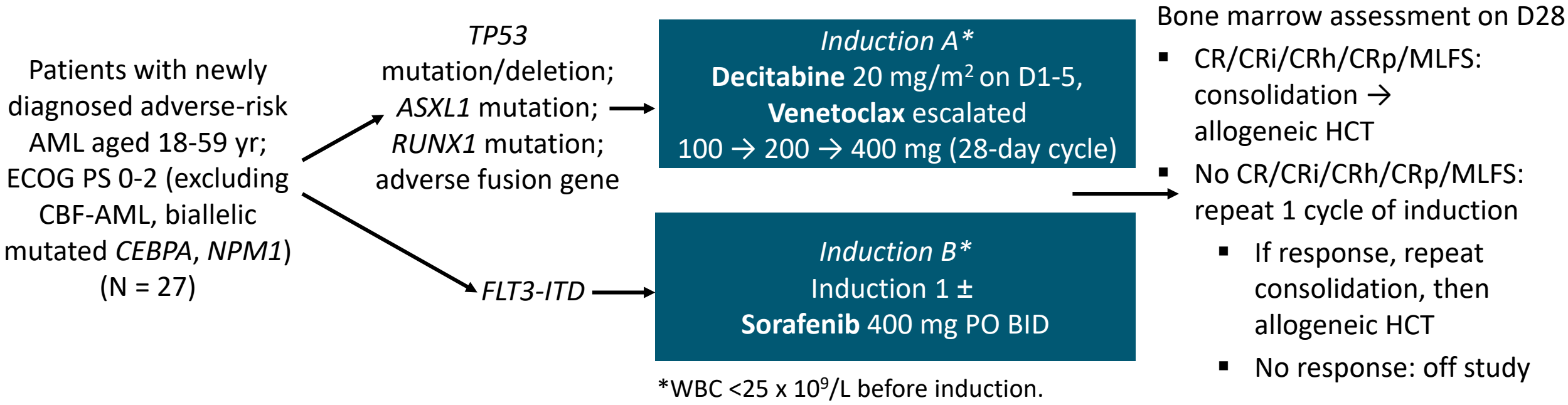
Venetoclax and Decitabine in AML: Background

- Standard cytarabine and anthracycline intensive induction therapy for fit patients with AML has changed little in decades
- High-dose anthracycline associated with higher CR rate and improved OS in patients <50 yr of age with low- or intermediate-risk cytogenetics[1]
- Among fit patients, ELN adverse risk is associated with lower CR rate following intensive induction[2]
- In the VIALE-A trial, venetoclax/azacitidine demonstrated a significant efficacy benefit vs azacitidine alone in previously untreated patients ineligible for intensive therapy[3]
- Current study evaluated ***venetoclax/decitabine as induction therapy in young adults with newly diagnosed ELN adverse-risk AML[4]***

1. Luskin. Blood. 2016;127:1551. 2. Herold. Leukemia. 2020;34:3161.
3. DiNardo. NEJM. 2020;383:617. 4. Chen. ASH 2021. Abstr 35.

Phase II Trial: Venetoclax/Decitabine Induction in Young Adults With Adverse-Risk AML

- Prospective, multicenter, single-arm trial



*WBC <25 x 10^9/L before induction.

- **Primary endpoint:** composite CR rate
- **Secondary endpoint:** MRD response (<10^{-3}), EFS, OS, AEs
- **Goal:** superiority vs historical controls with adverse-risk AML who received cytarabine plus idarubicin (12 mg/m²)

Chen. ASH 2021. Abstr 35.

Venetoclax/Decitabine in Young Adults With Adverse-Risk AML: Conclusions

- In young adult patients with ELN adverse-risk AML, venetoclax/decitabine associated with ***76% composite CR*** rate vs 38% for historical controls
  - MRD negativity rate after cycle 1: 64%
- Compared with historical controls, venetoclax/decitabine had:
  - Lower rates of infections (48% vs 67%)
  - Reduced RBC and platelet transfusions
- Median PFS and OS not reached for patients receiving venetoclax/decitabine
  - ***30-day and 60-day mortality rate: 0%***

Chen. ASH 2021. Abstr 35.

Pooled Analysis of Impact of *TP53* Mutations on Efficacy of Venetoclax + Azacitidine in Patients With AML and Poor-Risk Cytogenetics

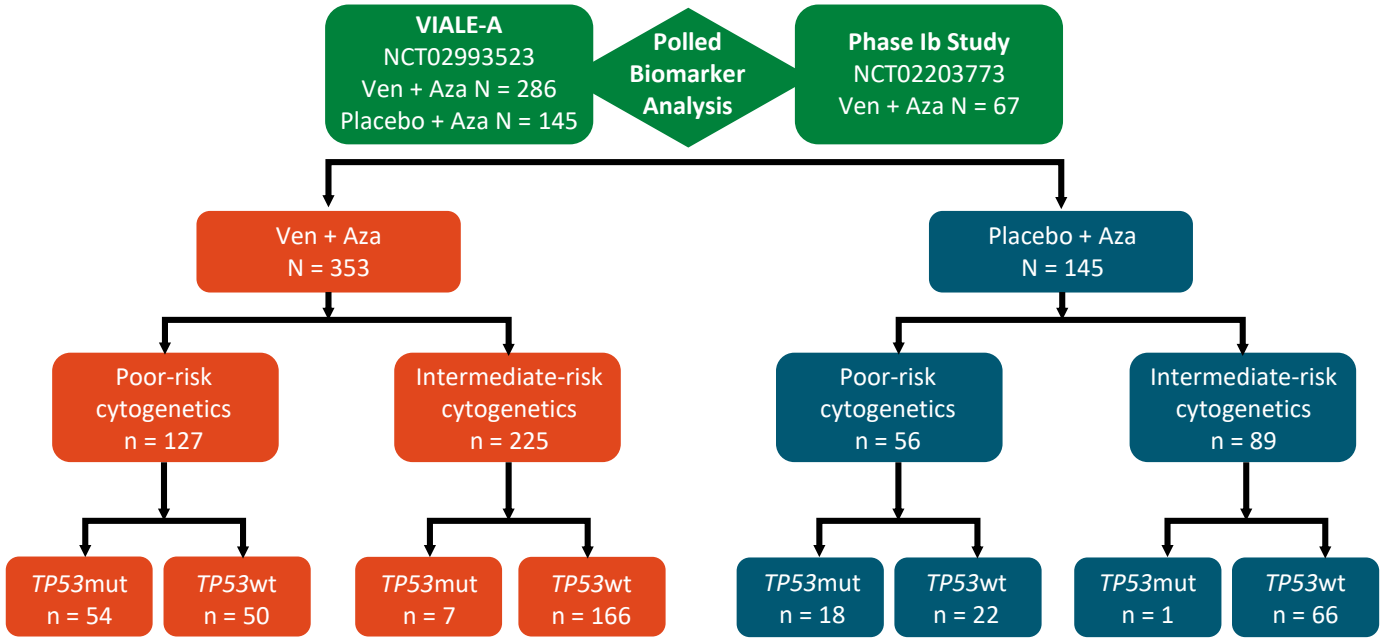
Ven + Aza in Poor-Risk AML: Background

- Outcomes of AML therapy inferior in patients with poor-risk cytogenetics
- Strong correlation between *TP53* mutations and poor-risk cytogenetics with poor outcomes
- Outcomes in treatment-naive patients with AML with poor-risk cytogenetics and no *TP53* mutations following Ven + Aza therapy not established
- Current study aimed to ***assess efficacy of Ven + Aza vs Aza alone in untreated AML patients with poor-risk cytogenetics ± TP53 mutations***

Pollyea. ASH 2021. Abstr 224.

Ven + Aza in Poor-Risk AML: Study Design

- Data pooled from phase III VIALE-A trial and phase Ib trial of Ven + Aza
- Eligibility: treatment-naive patients with AML, ineligible for CT due to age ≥75 yr and/or comorbidities
- Assessment: local analysis of cytogenetics, central analysis of mutations
- Endpoints: CR + CRi, DoR, OS



Pollyea. ASH 2021. Abstr 224.

Ven + Aza in Poor-Risk AML: Conclusions

- In patients with poor-risk cytogenetics AML, Ven + Aza associated with better outcomes with wild-type vs mutated *TP53*
  - Outcomes in patients with wild-type *TP53* similar regardless of poor- vs intermediate-risk cytogenetics
- Ven + Aza increased remission rates, extended DoR and OS vs Aza alone in patients with ***wild-type TP53***
- Ven + Aza increased remission rates vs Aza alone in patients with ***mutated TP53*** but had no impact on DoR and OS
- Ven + Aza ***well tolerated*** in this AML population, regardless of cytogenetics and *TP53* mutation status

Pollyea. ASH 2021. Abstr 224.

AGILE: Phase III Trial of Ivosidenib + Azacitidine vs Placebo + Azacitidine in Newly Diagnosed *IDH1*-Mutated Acute Myeloid Leukemia

AGILE: Background

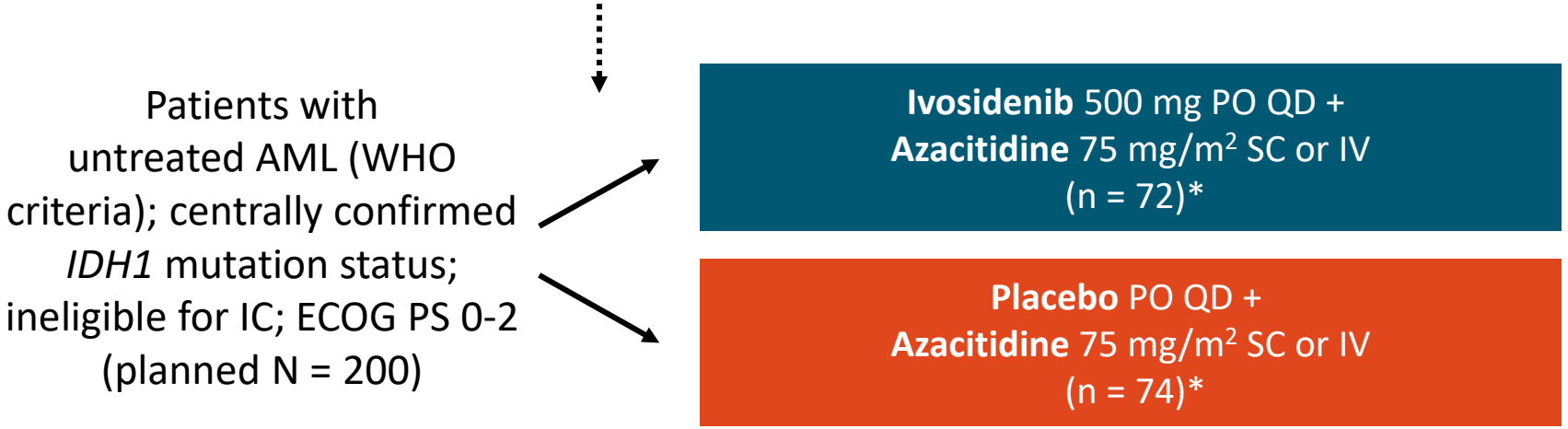
- *IDH1* mutations found in 6% to 10% of patients with AML[1-4]
  - Poor prognosis seen in this subset
- ***Ivosidenib***: first-in-class, oral IDH1 inhibitor approved as monotherapy for treatment of R/R AML and newly diagnosed AML in patients aged ≥75 yr or who have comorbidities that preclude use of intensive induction CT[5]
- Ivosidenib + azacitidine found active and tolerable in newly diagnosed *IDH1*-mutated AML in phase Ib study[6]
- Current phase III trial compared ***ivosidenib + azacitidine vs placebo + azacitidine*** in newly diagnosed *IDH1*-mutated AML[7]

1. Mardis. NEJM. 2009;361:1058. 2. Ward. Cancer Cell. 2010;17:225. 3. Patel. Am J Clin Pathol. 2011;135:3.
4. DiNardo. Am J Hematol. 2015;90:732. 5. Ivosidenib PI. 6. DiNardo. JCO. 2021;39:57-65. 7. Montesinos. ASH 2021. Abstr 697.

AGILE: Study Design

- Multicenter, double-blind, randomized phase III trial

Stratified by region (US/Canada vs Western Europe, Israel, and Australia vs Japan vs rest of world) and disease history (de novo vs secondary AML)



*Enrollment at time of data cutoff (May 18, 2021).

- Enrollment halted based on efficacy as of May 12, 2021 (N = 148)
- **Primary endpoint:** EFS with ~173 events (52 mo)
- **Secondary endpoints:** CRR, OS, CR + CRh rate, ORR

Montesinos. ASH 2021. Abstr 697.

AGILE: Investigators' Conclusions

- In patients with newly diagnosed *IDH1*-mutated AML ***ineligible for intensive CT***, ivosidenib + azacitidine significantly extended EFS vs placebo + azacitidine
  - HR: 0.33 (95% CI: 0.16-0.69; *P* = .0011)
  - OS and clinical response also were significantly improved
- Overall frequency of TEAEs similar between arms
  - Fewer infections with ivosidenib + azacitidine treatment arm
- Change in markers of health-related QoL favored ivosidenib + azacitidine over placebo + azacitidine
- Investigators concluded study findings demonstrated that ***ivosidenib + azacitidine provides clinical benefit in this patient population***

Montesinos. ASH 2021. Abstr 697.

LACEWING: Phase III Study of Gilteritinib + Azacitidine vs Azacitidine for Patients With Newly Diagnosed *FLT3*-Mutated AML Ineligible for Intensive Induction Chemotherapy

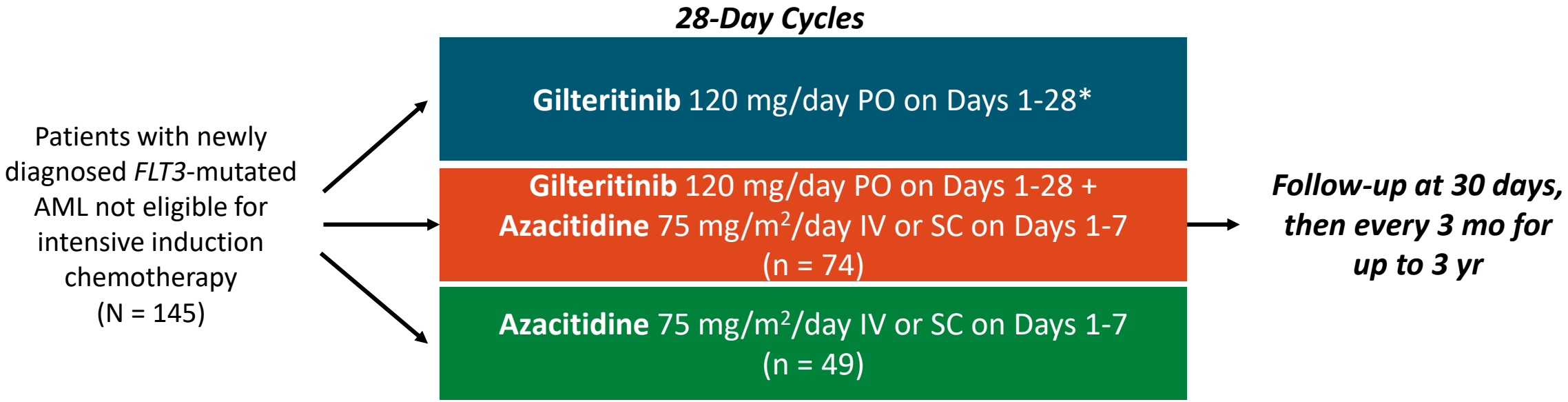
LACEWING: Background

- Gilteritinib is an FLT3 TKI approved by the FDA for the treatment of patients with R/R AML with an *FLT3* mutation as detected by an FDA-approved test[1]
- Limited therapeutic options for newly diagnosed patients with AML and *FLT3* mutations ineligible for intensive induction chemotherapy[2-4]
  - Survival rates low
- Current study investigated the ***efficacy and safety of gilteritinib + azacitidine vs azacitidine in adults with newly diagnosed FLT3-mutated AML ineligible for intensive induction chemotherapy***[6]

1.Gilteritinib PI. 2. Wei. Blood. 2020;135:2137. 3. Kantarjian. JCO. 2012;30:2670.
4. DiNardo. Blood. 2019;133:7. 5. Ueno. Oncotarget. 2019;10:2530. 6. Wang. ASH 2021. Abstr 700.

LACEWING: Study Design

- Randomized, open-label phase III study



*Gilteritinib arm was removed due to preferred therapy changes. Patients were then randomized 2:1 to gilteritinib + azacitidine or azacitidine alone.

- **Primary endpoint:** OS
- **Secondary endpoints:** EFS, response, safety/tolerability
- **Exploratory endpoint**: pharmacokinetics

Wang. ASH 2021. Abstr 700. NCT02752035.

LACEWING: Investigators' Conclusions

- In this phase III study, significantly ***higher CRc rates but similar OS with gilteritinib + azacitidine*** vs azacitidine alone in patients with newly diagnosed *FLT3*-mutated AML ineligible for intensive induction chemotherapy
  - Rate of CRc: 58.1% vs 26.5% (difference: 31.4%; 95% CI: 13.1-49.7; *P* <.001.)
  - Median OS: 9.82 vs 5.87 (HR: 9.16; 95% CI: 0.529-1.585; *P* = .753)
  - Patients with ECOG PS 0-1 or high *FLT3*-ITD allelic ratio had greater responses to gilteritinib + azacitidine
- Safety similar to that previously reported

Wang. ASH 2021. Abstr 700.

Evaluation of Quizartinib With Venetoclax and Decitabine Therapy in Patients With Newly Diagnosed or R/R *FLT3*-Mutated AML

Quizartinib/Venetoclax/Decitabine in *FLT3*-Mutated AML: Background

- Prognosis is poor for patients with newly diagnosed *FLT3*-mutated AML ineligible for intensive chemotherapy, as well as those with R/R disease
  - *FLT3* mutations detected in 20% to 30% of patients with AML
  - For older/unfit newly diagnosed patients, median OS is 8-11 mo with hypomethylating agents + venetoclax or with an FLT3 inhibitor[1,2]
- Quizartinib: potent ***second-generation FLT3 inhibitor***
  - Increased response rates and OS vs SoC in R/R *FLT3*-mutated AML[3]
  - Demonstrated synergy with venetoclax in AML cell lines and PDX models[4]
- Ongoing study is evaluating ***efficacy and safety of quizartinib combined with venetoclax and decitabine*** therapy in patients with R/R or newly diagnosed *FLT3*-mutated AML[5]

1. Ohanian. Am J Hematol. 2018;93:1136. 2. Konopleva. ASH 2020. Abstr 1904.
3. Cortes. Lancet Oncol. 2019;20:984. 4. Singh Mali. Haematologica. 2021;106:1034. 5. Yilmaz. ASH 2021. Abstr 370.

Quizartinib/Venetoclax/Decitabine in *FLT3*-Mutated AML: Study Design

- Ongoing, single-arm, open-label phase I/II trial

All: Patients with *FLT3*-mutated disease

- **R/R cohort**: R/R AML or high-risk MDS (≥10% blasts; n = 23)
- **ND cohort**: newly diagnosed with AML and ineligible for intensive chemo (n = 5)

Induction (1 Cycle)

Quizartinib 30-40 mg/day on Days 1-28
+
Venetoclax 400 mg/day on Days 1-21
(Days 1-14 for patients with BM blasts ≤5% or hypoplastic BM)
+
Decitabine 20 mg/m^2 on Days 1-10, all given in one 28-day cycle

Consolidation (Up to 12 Cycles)

Quizartinib 30-40 mg/day on Days 1-28*
+
Venetoclax 400 mg/day on Days 1-14†
+
Decitabine 20 mg/m^2 on Days 1-5, all given in 28-day cycles

*Quizartinib duration reduced to 14 days in patients with prolonged count recovery.
†Venetoclax duration reduced to 7-10 days for patients in CR based on count recovery durations.

- Primary endpoint: RP2D of quizartinib in combination with venetoclax + decitabine
- Key secondary endpoint: CR, CRi, MRD, OS

Yilmaz. ASH 2021. Abstr 370.

Quizartinib/Venetoclax/Decitabine in *FLT3*-Mutated AML: Investigators' Conclusions

- Quizartinib 30 mg/day established as RP2D in combination with venetoclax and decitabine
- ***Quizartinib + venetoclax + decitabine triplet therapy active in heavily pretreated and prior FLT3 inhibitor–exposed patients with R/R FLT3-mutated AML***
  - CRc rate of 78%
  - Median OS of 7.6 mo
- *RAS/MAPK* and *FLT3* F691L mutations found to be associated with resistance
- No major safety signals; no grade ≥2 QTcF prolongation
- Delayed ANC recovery can be mitigated with treatment interruption
- Recruitment of patients with R/R and ND *FLT3*-mutated AML ongoing

Yilmaz. ASH 2021. Abstr 370.

Retrospective Analysis of Venetoclax + Hypomethylating Agents for Patients With Higher-Risk Myelodysplastic Syndromes

Venetoclax and HMA in Higher-Risk MDS: Background

- HMAs remain standard of care for patients with higher-risk MDS
  - HMA treatment associated with <20% CR rate and median OS of 12-18 mo[1]
- Early suggestions of higher response rate with the addition of venetoclax to HMAs in higher-risk MDS[2,3]
- The current retrospective analysis compared clinical outcomes in patients with higher-risk MDS treated with ***first-line HMA, first-line HMA + venetoclax, or HMA with venetoclax given after HMA failure***[4]

1. Zeidan. Br J Haematol. 2016;175:829. 2. Garcia. ASH 2020. Abstr 656.
3. Zeidan. ASH 2020. Abstr 3109. 4. Komrokji. ASH 2021. Abstr 536.

Venetoclax and HMA in Higher-Risk MDS: Conclusions

- In this retrospective analysis, ***treatment with first-line HMA + venetoclax was associated with significantly higher CR rates*** vs HMA alone in patients with higher-risk MDS, including those with *ASXL-1*–mutant MDS
  - Investigators suggested promising clinical activity of first-line HMA + venetoclax in patients who proceed to AHSCT
  - Caveats: small population, short follow-up of combination therapy group
  - No adverse event or dose adjustment data available
- ***Adding venetoclax to HMA after relapse may prolong OS***
- Prospective, randomized trial needed to confirm findings

Komrokji. ASH 2021. Abstr 536.

Phase II Trial of Lenalidomide and Eltrombopag for Low-Risk/Intermediate-Risk MDS

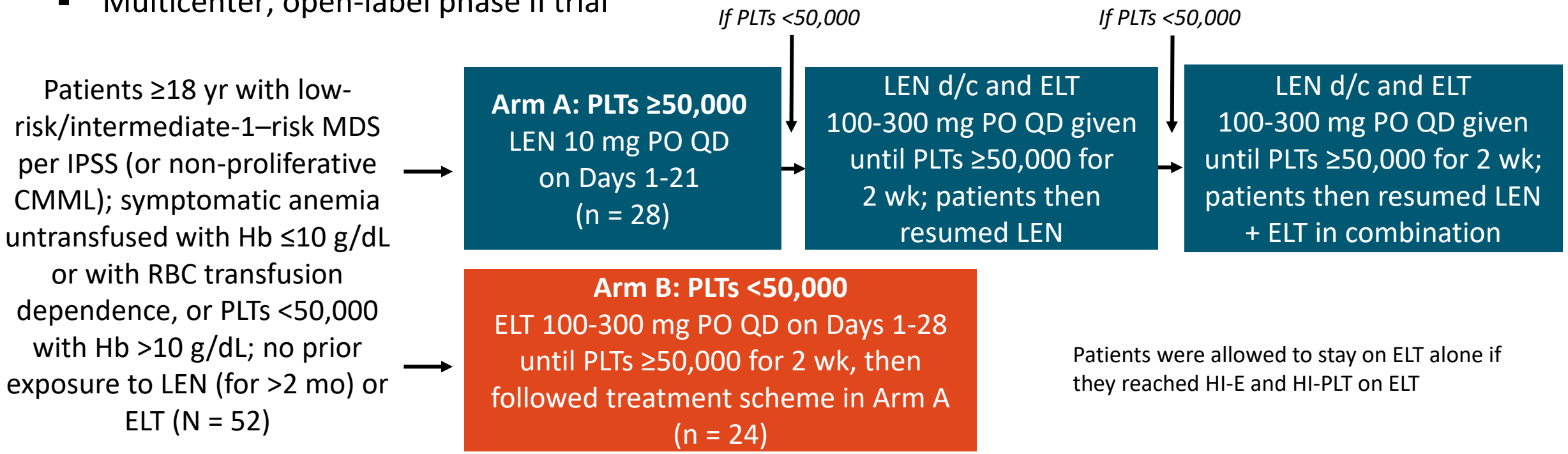
Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Background

- Treatment goals for low-risk/intermediate-risk MDS are to improve cytopenias so as to prevent complications and improve QoL
- LEN approved for MDS with del(5q) based on its ability to induce disease remission and confer transfusion independence in ~50% of patients[1]
- ***Although LEN reduces transfusion burden for ~25% of patients with MDS without del(5q), its use is limited by significant thrombocytopenia***[2]
- Eltrombopag: oral TPO-R agonist
  - Increases platelets in MDS[3]
  - Preclinical data suggest it can reverse LEN anti-megakaryopoietic effects[4]
- Current study determined ***safety and efficacy of LEN with ELT in patients with low-risk/ intermediate-risk MDS***[5]

1. Fenaux. Blood. 2011;118:3765. 2. Santini. J Clin Oncol. 2016;34:2988. 3. Oliva. Lancet Haematol. 2017;4:e127. 4. Tamari. Leuk Lymphoma. 2014;55:2901. 5. Gonzalez-Lugo. ASH 2021. Abstr 65.

Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Study Design

- Multicenter, open-label phase II trial



- Primary endpoints: HI (per 2006 IWG criteria), safety and tolerability
- Secondary endpoints: HI duration, time to HI, clinically significant bleeding events, BM response (CR + PR), cytogenetic response

Gonzalez-Lugo. ASH 2021. Abstr 65.

Lenalidomide and Eltrombopag for Low-Risk/ Intermediate-Risk MDS: Investigators' Conclusions

- Treatment with ELT and LEN showed good efficacy and safety in patients with low-risk/intermediate-risk MDS
  - ORR of 35% in ITT population
  - Median DoR: 1.5 yr
  - Acceptable safety profile
- ***ELT monotherapy yielded responses with a sizeable proportion of bilineage responses***
- 1 patient developed BM fibrosis and only 1 patient had transient increase in blasts, allaying these preexisting safety concerns

Gonzalez-Lugo. ASH 2021. Abstr 65.

CHRONIC LEUKEMIAS AND THE MYELOPROLIFERATIVE NEOPLASMS

Acalabrutinib versus ibrutinib in chronic lymphocytic leukemia

- The Bruton tyrosine kinase inhibitors ibrutinib and acalabrutinib are effective treatments for chronic lymphocytic leukemia (CLL).
- In a multicenter, randomized, open-label ***phase 3 trial (ELEVATE-RR)*** of >500 patients with relapsed CLL, acalabrutinib and ibrutinib resulted in similar progression-free survival, but different toxicity
- ***Acalabrutinib*** was associated ***with less cardiotoxicity and bleeding events***, and fewer discontinuations due to adverse events.
- For most patients, acalabrutinib is now suggested rather than ibrutinib given its better overall safety profile and similar efficacy

J Clin Oncol. 2021;39(31):3441. Epub 2021 Jul 26.

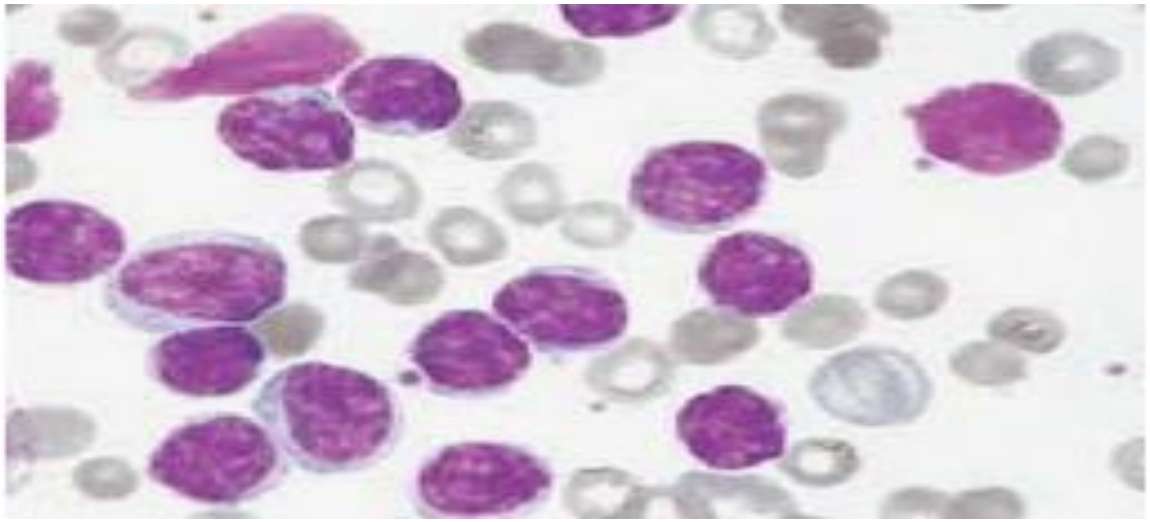
Durable remissions following venetoclax plus obinutuzumab in newly diagnosed chronic lymphocytic leukemia

- Fixed duration venetoclax plus obinutuzumab is one of preferred treatment options for previously untreated chronic lymphocytic leukemia (CLL)
- In the ***CLL14 trial***, four-year progression-free survival following ***venetoclax plus obinutuzumab*** was approximately ***75 percent***
- The durable remissions seen in this trial provide further support for the use of this combination who have comorbidities that make them ***poor candidates for a BTK inhibitor.***

Hemasphere. 2021

Ibrutinib plus venetoclax in newly diagnosed chronic lymphocytic leukemia

- For patients with chronic lymphocytic leukemia (CLL), several phase 2 trials suggest that the combination of ibrutinib plus venetoclax results in deep responses and may be administered for a fixed duration followed by a treatment free interval.
- An open-label, phase 3 triaal (GLOW) compared this combination versus chlorambucil plus obinutuzumab in >200 older or frail adults with previously untreated CLL ***without del(17p) or TP53 mutation***
- Ibrutinib plus venetoclax lead to a ***marked improvement in progression-free survival*** and time to subsequent therapy.



Hemosphere 2021

ASCEMBL: 48-Wk Update of Results From the Phase III Study of STAMP Inhibitor Asciminib vs Bosutinib for CML-CP Previously Treated With ≥2 TKIs

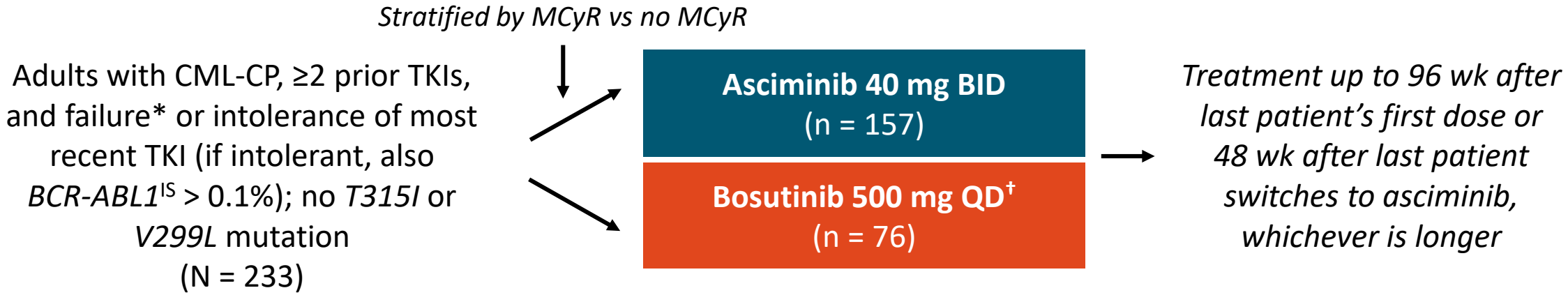
ASCEMBL 48-Week Update: Background

- ***Asciminib*** is a first-in-class STAMP inhibitor, which targets a myristoyl site of the BCR-ABL1 protein[1,2]
  - Asciminib recently received accelerated FDA approval for patients with ***Ph+ CML-CP previously treated with ≥2 TKIs and for adult patients with Ph+ CML-CP harboring the T3151 mutation***
- ***Superior efficacy and favorable safety of asciminib vs bosutinib*** were demonstrated in the phase III ASCEMBL study after a median follow-up of 14.9 mo among patients with CML-CP previously treated with ≥2 TKIs[2,3]
  - At 24 wk, the MMR rate was 25.5% vs 13.2% with asciminib vs bosutinib; difference in MMR rate after adjustments for MCyR at baseline was 12.2% (95% CI: 2.19-22.30; *P* = .029)
  - Lower rates of grade ≥3 AEs (50.6% vs 60.5%) and AEs leading to discontinuation of treatment (5.8% vs 21.1%) with asciminib vs bosutinib
- Current analysis reports updated safety and efficacy data in ASCEMBL for patients who have had ≥1 yr (48 wk) of treatment or who discontinued treatment earlier[4]

1. Hughes. NEJM. 2019;381.2315. 2. Réa. Blood. 2021;138:2031.
3. Hochhaus. ASH 2020. Abstr LBA-4. 4. Mauro. ASH 2021. Abstr 310.

ASCEMBL 48-Week Update: Study Design

- Multicenter, open-label, randomized phase III trial (data cutoff: January 6, 2021)



Median follow-up: 19.2 mo. *Per 2013 ELN recommendations. †Switch to asciminib 40 mg BID allowed for treatment failure.

- Primary endpoint: MMR rate at Wk 24 (meeting no tx failure criteria before Wk 24)
- Secondary endpoints: MMR rate at Wk 96 (meeting no tx failure criteria before Wk 96), safety and tolerability, CCyR/MMR rates, time to and duration of CCyR/MMR, time to treatment failure, PFS, OS, and pharmacology parameters

Mauro. ASH 2021. Abstr 310. NCT03106779.

ASCEMBL 48-Wk Update: Investigators' Conclusions

- Sustained superior efficacy of asciminib vs bosutinib among patients with CML-CP previously treated with ≥2 TKIs at Wk 48
  - Higher MMR rate of 29.3% vs 13.2%, respectively; treatment difference after adjustment for MCyR at baseline: 16.1% (95% CI: 5.7-26.6)
  - More patients achieved *BCR:ABL1*^{IS} *≤1%*: 50.8% vs 33.7%, respectively
  - More patients achieved deep molecular response
    - MR^4: 10.8% vs 3.9%, respectively; $MR^{4.5}$: 7.6% vs 1.3%, respectively
  - More patients remained on treatment: 56.7% vs 22.4%, respectively
- Safety results consistent with primary analysis
  - Accurate comparison between arms not possible since most pts receiving bosutinib discontinued early
- Study investigators conclude that the ASCEMBL data support the use of ***asciminib as a novel option for patients with CML, particularly for later-line CML***

Mauro. ASH 2021. Abstr 310.

Low-Dose Dasatinib vs Standard-Dose Dasatinib in Newly Diagnosed CP-CML: A Propensity Score Analysis

Low-Dose Dasatinib in CP-CML: Background

- Safety and efficacy of ***low-dose dasatinib*** demonstrated in patients with newly diagnosed CP-CML[1]
  - No randomized studies comparing vs standard-dose dasatinib
- Current study assessed responses and outcomes with frontline dasatinib
  50 mg/day vs standard-dose dasatinib 100 mg/day in patients with newly diagnosed CP-CML[2]

1. Naqvi. Cancer. 2020;126:67. 2. Sasaki. ASH 2021. Abstr 631.

Low-Dose Dasatinib in CP-CML: Investigators' Conclusions

- In patients with newly diagnosed CP-CML, propensity score analysis showed ***comparable efficacy with low-dose dasatinib*** vs standard-dose dasatinib
  - 4-yr OS >95% with both approaches
  - Investigators suggest caution in extending results to high-risk disease
- Less intolerance with low-dose dasatinib, potentially allowing combination therapy and thus higher CMR and TFR rates

Sasaki. ASH 2021. Abstr 631.

Phase III SEQUOIA Trial of Zanubrutinib vs Bendamustine and Rituximab in Previously Untreated CLL/SLL

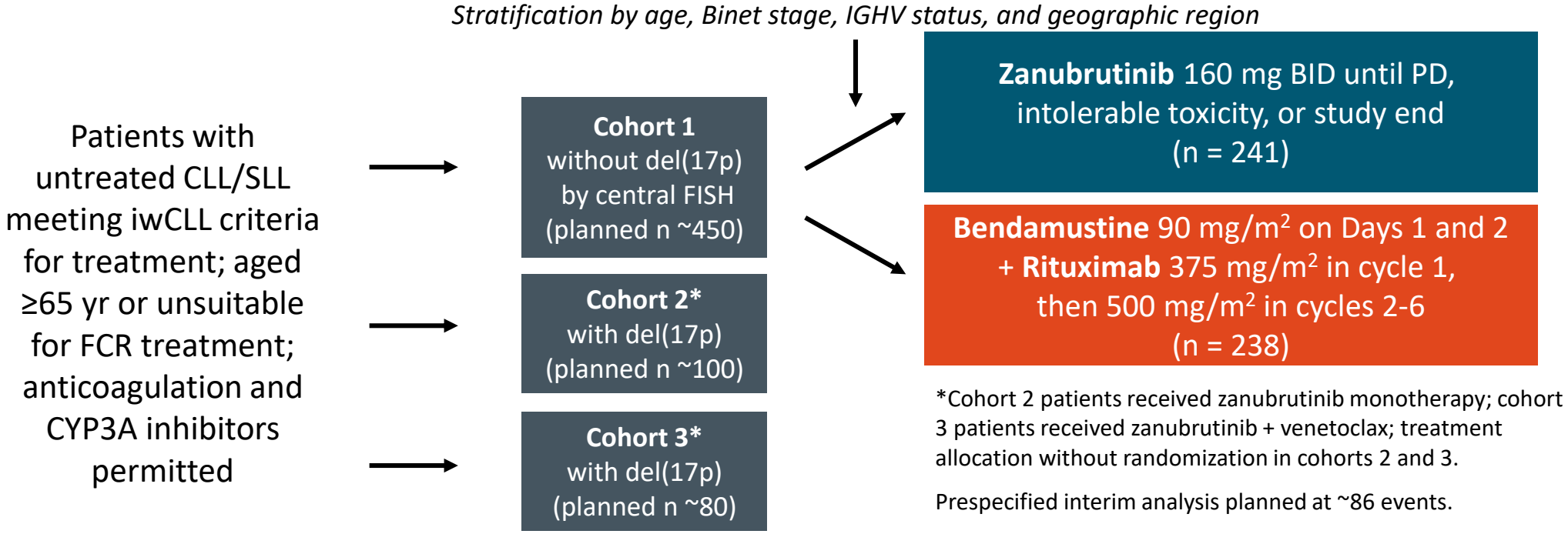
SEQUOIA: Background

- BTK inhibitors ibrutinib and acalabrutinib are preferred first-line treatments for CLL/SLL[1]
- ***Zanubrutinib*** is a selective ***second-generation BTK inhibitor***[2]
- In the phase III ALPINE trial, zanubrutinib demonstrated improved PFS and a lower rate of atrial fibrillation compared with ibrutinib in R/R CLL/SLL[3]
- Phase III SEQUOIA trial is investigating ***zanubrutinib alone or in combination with venetoclax*** in multiple cohorts of patients with previously untreated CLL/SLL[4]
  - In the cohort of patients with del(17p), zanubrutinib monotherapy was active[5]
  - Current interim analysis reports the efficacy and safety of zanubrutinib vs BR[4]

1. NCCN. Clinical practice guidelines in oncology: CLL/SLL. v.1.2022. nccn.org. 2. Guo. J Med Chem. 2019;62:7923.
3. Hillmen. EHA 2021. Abstr LB1900. 4. Tam. ASH 2021. Abstr 396. 5. Tam. Haematologica. 2020;106:2354.

SEQUOIA: Study Design

- Multicenter, multicohort, open-label, part-randomized phase III trial



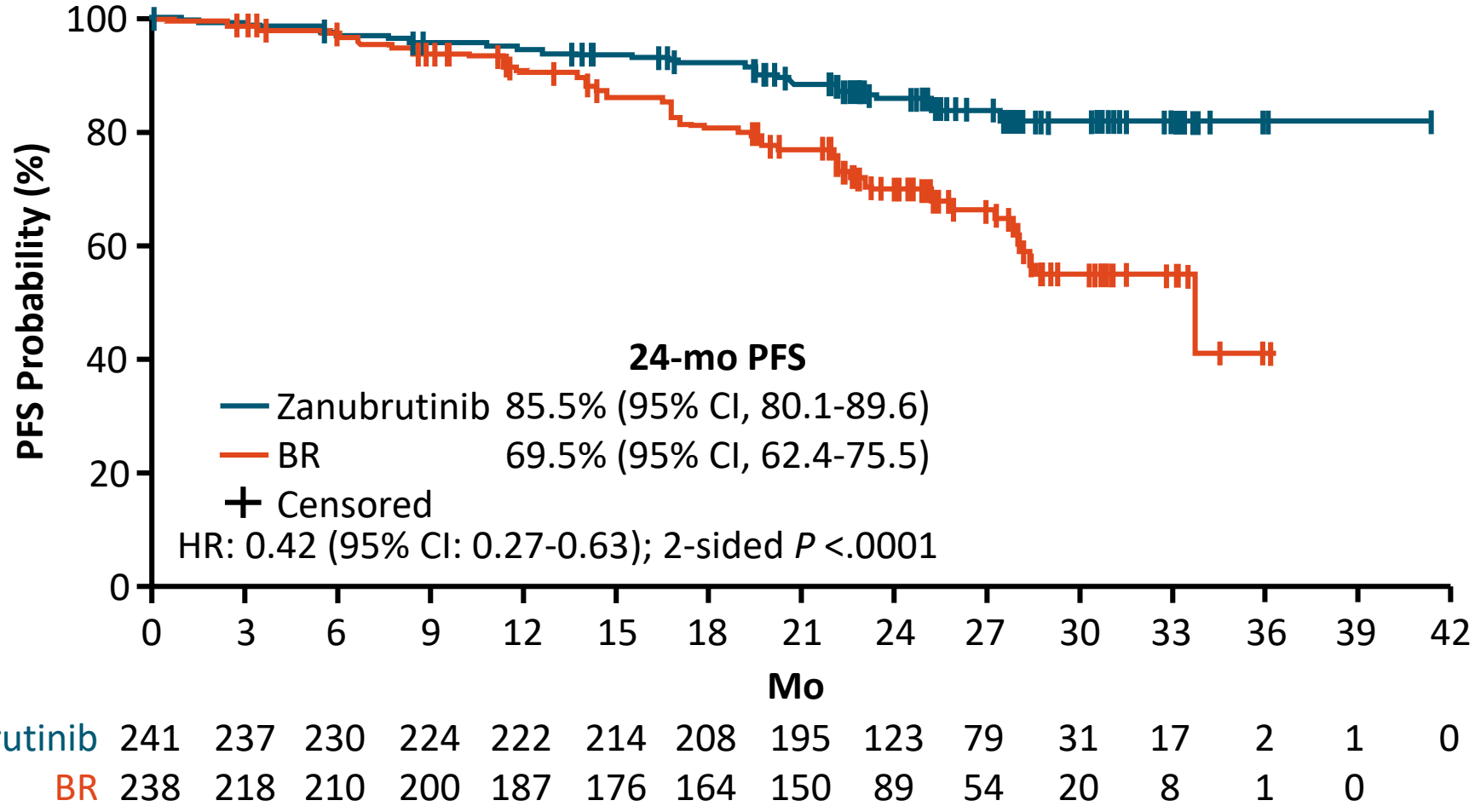
*Cohort 2 patients received zanubrutinib monotherapy; cohort 3 patients received zanubrutinib + venetoclax; treatment allocation without randomization in cohorts 2 and 3.

Prespecified interim analysis planned at ~86 events.

- Primary endpoint (cohort 1): IRC-assessed PFS
- Secondary endpoints (cohort 1): investigator-assessed PFS, ORR, OS, safety

Tam. ASH 2021. Abstr 396.

SEQUOIA (Cohort 1): IRC-Assessed PFS (Primary Endpoint)



Tam. ASH 2021. Abstr 396. Reproduced with permission.

SEQUOIA: Investigators' Conclusions

- In patients with untreated CLL/SLL, IRC-assessed PFS was significantly improved with zanubrutinib compared with bendamustine + rituximab
  - 24-mo PFS: 85.5% (95% CI: 80.1-89.6) vs 69.5% (95% CI: 62.4-75.5); HR: 0.42 (95% CI: 0.27-0.63; *P* <.0001)
- ***PFS*** also was ***superior*** with zanubrutinib across high-risk subgroups, including patients with unmutated *IGHV* and del(11q)
- Zanubrutinib was ***well tolerated***, and no new safety signals were observed; atrial fibrillation was infrequent
- Investigators concluded that ***zanubrutinib is a safe and effective treatment for patients with previously untreated CLL/SLL***

Tam. ASH 2021. Abstr 396.

Plasma cell dyscrasia

GRIFFIN 2-Yr Maintenance Phase Update: Dara + VRd With Dara-R Maintenance vs VRd With R Maintenance for ASCT-Eligible Patients With Newly Diagnosed MM

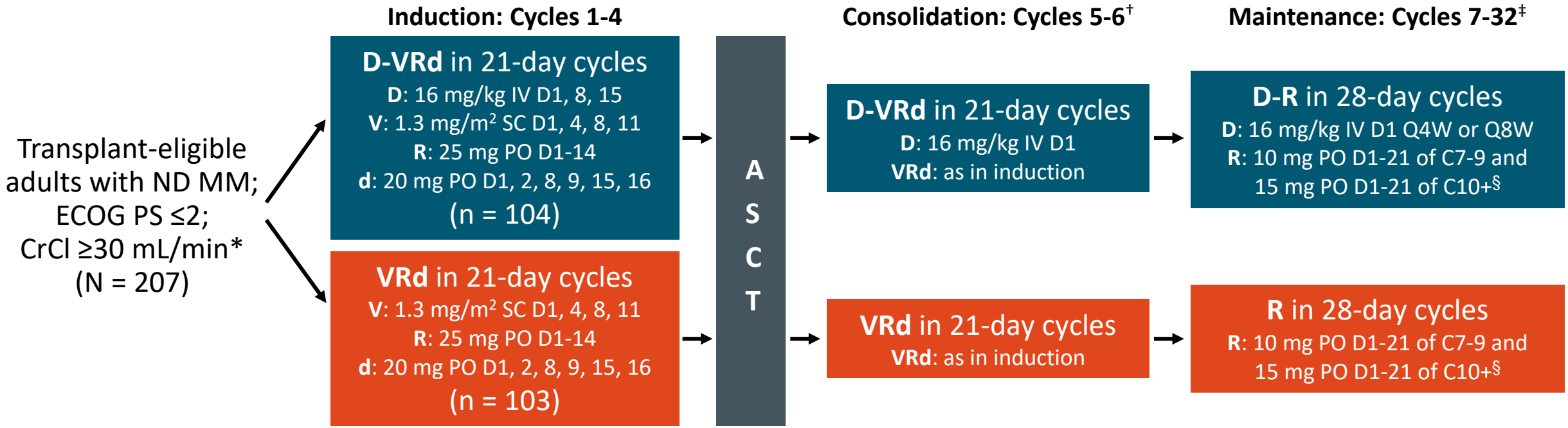
GRIFFIN 2-Yr Maintenance Phase Update: Background

- Standard-of-care management strategies in transplant-eligible ND MM include VRd induction followed by ASCT, consolidation,[1,2] and R maintenance therapy[3,4]
- Phase II GRIFFIN study designed to ***compare D-VRd followed by D-R maintenance with VRd followed by R maintenance*** in ASCT-eligible patients with ND MM5
  - Primary analysis (median follow-up: 13.5 mo): addition of D to VRd increased sCR by the end of consolidation (42.4% vs 32.0%; 1-sided *P* = .068), rate of MRD negativity (51.0% vs 20.4%), and estimated 24-mo PFS (95.8% vs 89.8%)[5]
  - After 12 mo of maintenance, sCR rate was 63.6% in D arm vs 47.4% (*P* = .0253), and more patients receiving D-VRd had achieved ≥CR (*P* = .0014)[6]
- Current report: updated data from GRIFFIN after 24 mo of maintenance therapy[7]

1. Engelhardt. Haematologica. 2014;99:232. 2. Moreau. Ann Oncol. 2017;28(suppl_4):iv52. 3. Attal. NEJM. 2012;366:1782. 4. Holstein. Lancet Haematol. 2017;4:e431. 5. Voorhees. Blood. 2020;136:936. 6. Kaufman. ASH 2020. Abstr 549. 7. Laubach. ASH 2021. Abstr 79.

GRIFFIN 2-Yr Maintenance Phase Update: Study Design

- Multicenter, open-label, randomized phase II trial



*Lenalidomide dose was adjusted in patients with CrCl ≤50 mL/min. †Consolidation began 60-100 days after transplant. ‡Patients completing maintenance phase were permitted to continue single-agent lenalidomide. §15 mg administered only if tolerable.

- Primary endpoint: sCR by end of consolidation with 1-sided $\alpha = 0.1$
- Key secondary endpoints: rates of MRD negativity, ORR, ≥VGPR, CR, PFS, OS

Laubach. ASH 2021. Abstr 79.

GRIFFIN 2-Yr Maintenance Phase Update: Conclusions

- After 24 mo of maintenance therapy in the phase II GRIFFIN trial of ASCT-eligible patients with ND MM, D-VRd followed by D-R maintenance continued to show ***significant improvement in sCR and depth of response*** vs VRd followed by R maintenance[1]
  - Patients with sCR after 24-mo maintenance: 66.0% vs 47.4% (*P* = .0096)
  - Patients with MRD negativity after 24-mo maintenance at 10^{-5} threshold: 64.4% vs 30.1% (*P* <.0001); at 10^{-6} threshold: 35.6% vs 14.6% (*P* = .0007)
- Safety at 24 mo of maintenance cutoff was consistent with earlier analyses with no new safety concerns identified[2,3]
- Investigators conclude results support use of ***D-VRd induction and consolidation with D-R maintenance in transplant-eligible patients with ND MM***
  - Phase III PERSEUS trial ongoing (NCT03710603)

1. Laubach. ASH 2021. Abstr 79. 2. Voorhees. Blood. 2020;136:936. 3. Kaufman. ASH 2020. Abstr 549.

NON Hodgkin lymphoma

Phase III BELINDA Trial of Tisagenlecleucel vs Standard of Care as Second-line Treatment for R/R Aggressive B-Cell Non-Hodgkin Lymphoma

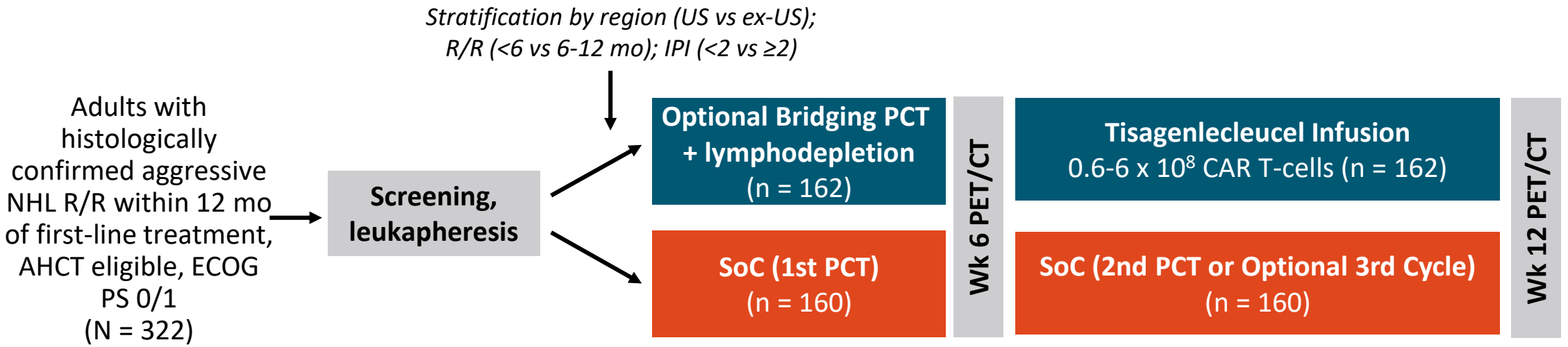
BELINDA: Background

- Patients with aggressive B-cell lymphoma who experience disease progression ≤12 mo of initial treatment have a poor prognosis[1]
- Second-line SoC options include PCT followed by high-dose chemotherapy and AHCT in responsive patients; however, a large proportion of patients will be ineligible for AHCT due to inadequate response[2]
- ***Tisagenlecleucel is an autologous CD19-directed CAR T-cell therapy*** approved for use in patients with R/R DLBCL after ≥2 lines of therapy[3]
- Current study compared the ***efficacy and safety of tisagenlecleucel vs SoC as second-line therapy for R/R aggressive B-cell NHL***

1. Costa. Am J Hematol. 2017;92:161. 2. van Imhoff. J Clin Oncol. 2017;35:544. 3. Tisagenlecleucel PI. 4. Bishop. ASH 2021. Abstr LBA-6.

BELINDA: Study Design

- Multicenter, randomized, open label, phase III trial



SoC arm received first PCT + AHCT for responders or second PCT for nonresponders, based on Wk 6 assessment. Crossover to tisagenlecleucel permitted for SoC at Wk 12 for nonresponders. Patients assessed at Wk 6 and 12, then 3-monthly to Mo 12, 6-monthly to Mo 24, and yearly to Mo 60.

- Primary endpoint: EFS
  - EFS event defined as SD/PD per BIRC at/after Wk 12 ± 1 Wk or death
- Secondary endpoints: ORR, safety, cellular kinetics

Bishop. ASH 2021. Abstr LBA-6.

BELINDA: Investigators' Conclusions

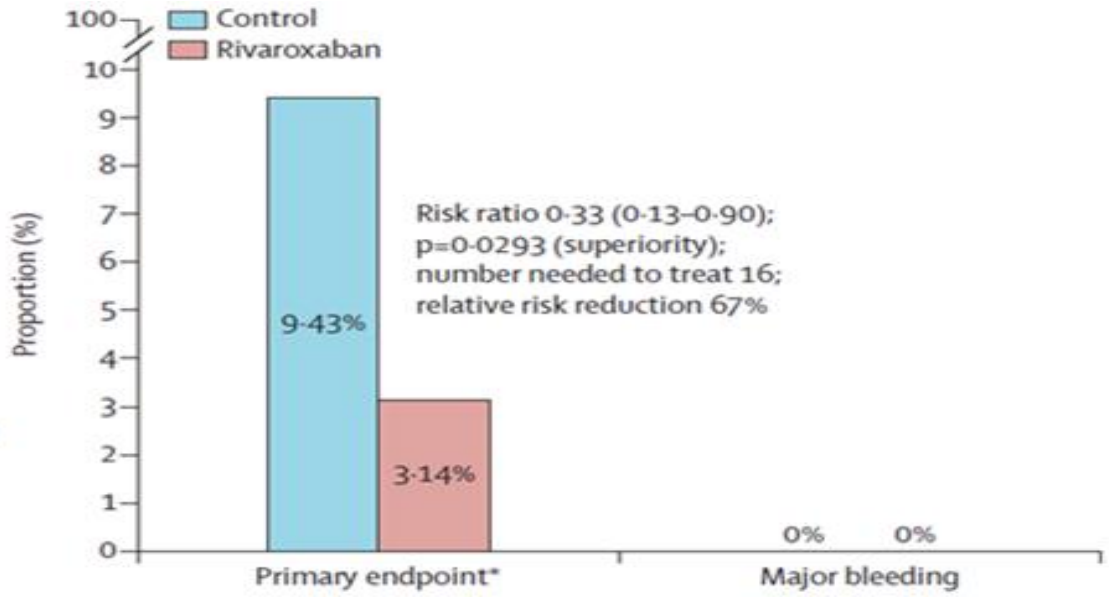
- In patients with early R/R aggressive B-cell NHL, the use of tisagenlecleucel as second-line therapy had ***no significant impact on EFS vs SoC***
- PD at Wk 6 (prior to CAR T-cell infusion) was more frequent in patients in the tisagenlecleucel arm vs SoC
  - This finding highlights the need for ***effective bridging prior to CAR T-cell infusion*** in patients with R/R aggressive B-cell NHL

Bishop. ASH 2021. Abstr LBA-6.

Hemostasis and Thrombosis

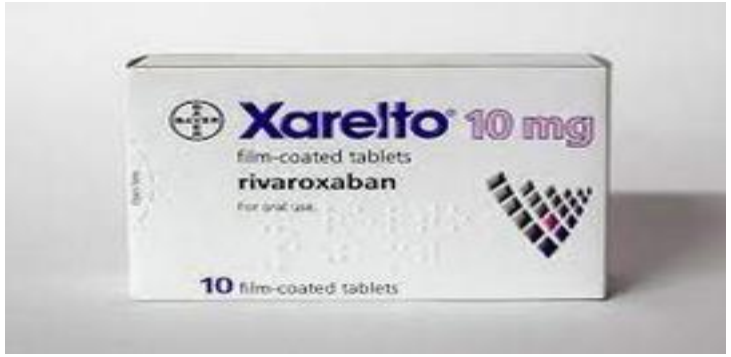
Prophylactic anticoagulation after discharge from COVID-19 hospitalization (December 2021)

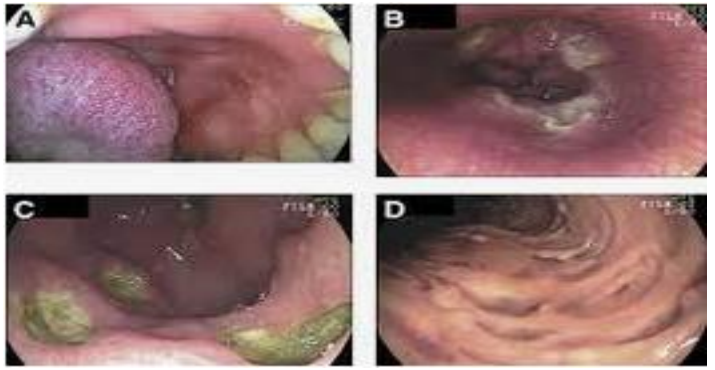
- ***Prophylactic anticoagulation*** has become the standard of care during hospitalization for COVID-19, but the role of post-discharge anticoagulation is unclear.
- In the MICHELLE trial, 320 individuals hospitalized with COVID-19 and deemed at high risk for venous thromboembolism (VTE) were randomly assigned to ***receive post-discharge*** rivaroxaban 10 mg daily for 35 days or no anticoagulant after
- The composite endpoint of VTE, symptomatic arterial embolism, and fatal cardiovascular events, occurred in ***3 percent of the rivaroxaban-treated patients and 9 percent of the controls***.
- Despite this result, most clinicians are unlikely to provide post-discharge thromboprophylaxis until more data become available



Risk of GI bleeding with DOACs (October 2021)

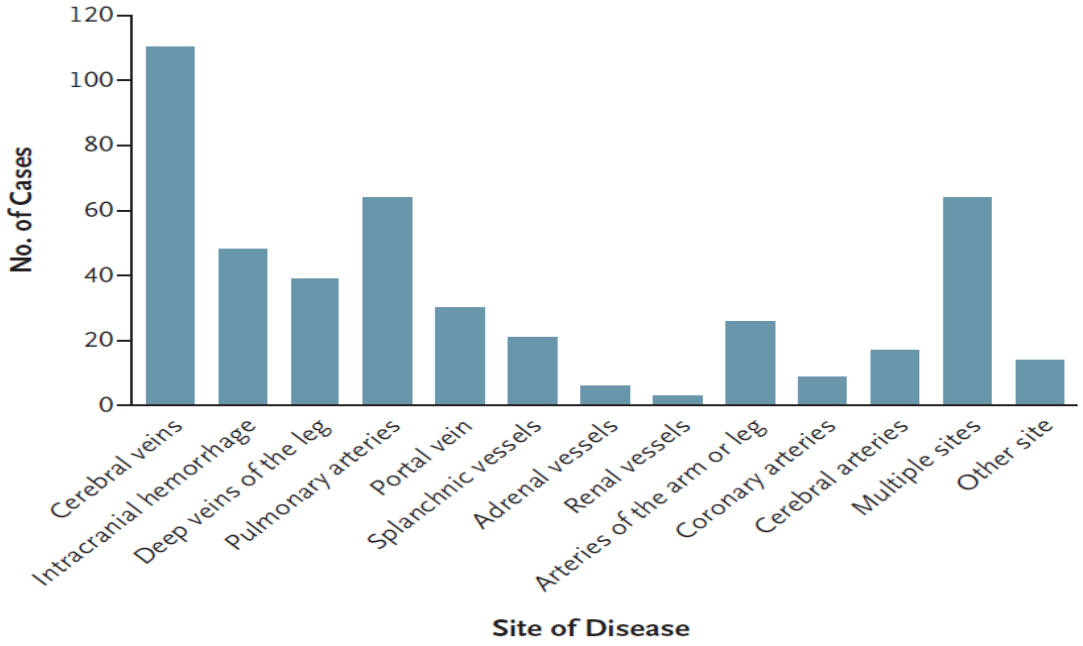
- Direct oral anticoagulants (DOACs) are generally preferred over warfarin in individuals with non-valvular atrial fibrillation or venous thromboembolism.
- A new study evaluated the risk of gastrointestinal (GI) bleeding in over 5000 individuals taking apixaban, rivaroxaban, or dabigatran
- ***Higher rates of GI bleeding*** were seen in individuals taking ***rivaroxaban*** than with the other agents





Clinical features of VITT associated with COVID-19 vaccination

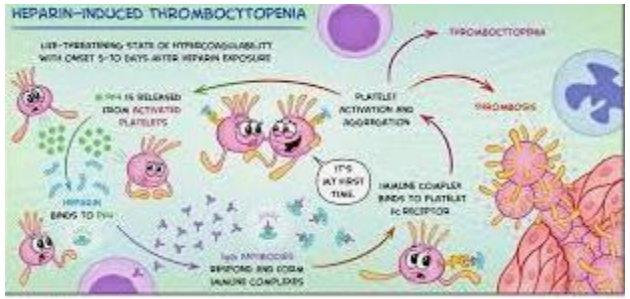
- A new case series has documented the clinical features of ***vaccine-induced immune thrombotic thrombocytopenia (VITT)*** among 220 individuals
- Most presentations were with ***thrombosis***.
- The most common sites were the ***cerebral veins*** (including intracranial hemorrhage), deep veins of the leg, pulmonary arteries, and splanchnic vessels.

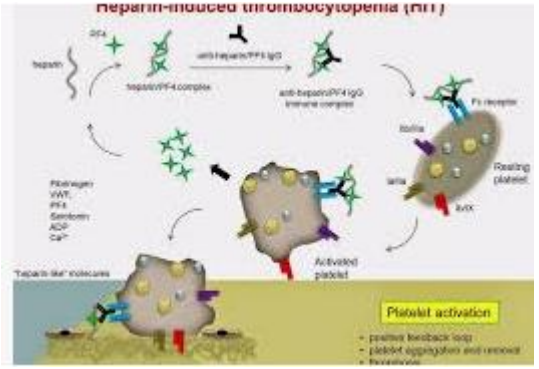


N Engl J Med. 2021;385(18):1680. Epub 2021 Aug 1

Choice of non-heparin anticoagulant in HIT (June 2021)

- Individuals with heparin-induced thrombocytopenia are at high risk for thrombosis and require full-dose anticoagulation with a non-heparin agent.
- A new meta-analysis has evaluated data from 92 studies involving nearly 5000 patients with HIT and found similar efficacy in reducing thrombosis among parenteral agents (argatroban, danaparoid, bivalirudin, fondaparinux) and ***direct oral anticoagulants (DOACs)***





ATLAS-INH: Phase III Trial of Fitusiran Prophylaxis in Patients With Hemophilia A or B With Inhibitors

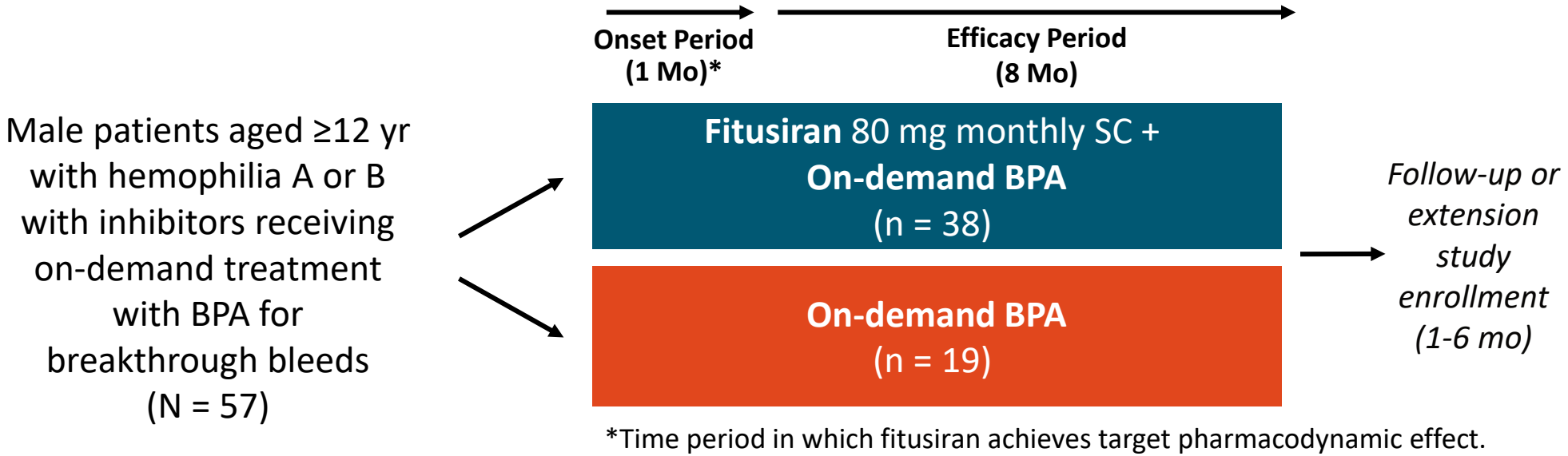
ATLAS-INH: Background

- Hemophilia A and B are bleeding disorders characterized by missing or dysfunctional blood clotting factors, for which the SoC treatment relies on replacing the missing factor[1]
- The development of neutralizing antifactor inhibitors occurs in ~30% of patients with hemophilia A and ~5% of patients with hemophilia B; this is associated with a worse prognosis, including a higher rate of mortality[2-5]
- ***Fitusiran*** is a subcutaneously administered antithrombin-directed siRNA therapeutic with the aim of ***restoring thrombin production and rebalancing hemostasis in hemophilia A or B with or without inhibitors***[6]
- Current analysis reports the efficacy and safety of monthly fitusiran prophylaxis in patients with hemophilia A or B with inhibitors[7]

1. Ellsworth. Hematology Am Soc Hematol Educ Program. 2021;1:219. 2. Konkle. Blood. 2017;130:1689.
3. Male. Haematologica. 2021;106:123. 4. Meeks. Hematology Am Soc Hematol Educ Program. 2016;2016:657.
5. Walsh. Am J Hematol. 2015;90:400. 6. Pasi. NEJM. 2017;377:819. 7. Young. ASH 2021. Abstr 4.

ATLAS-INH: Study Design

- Randomized, open-label phase III trial



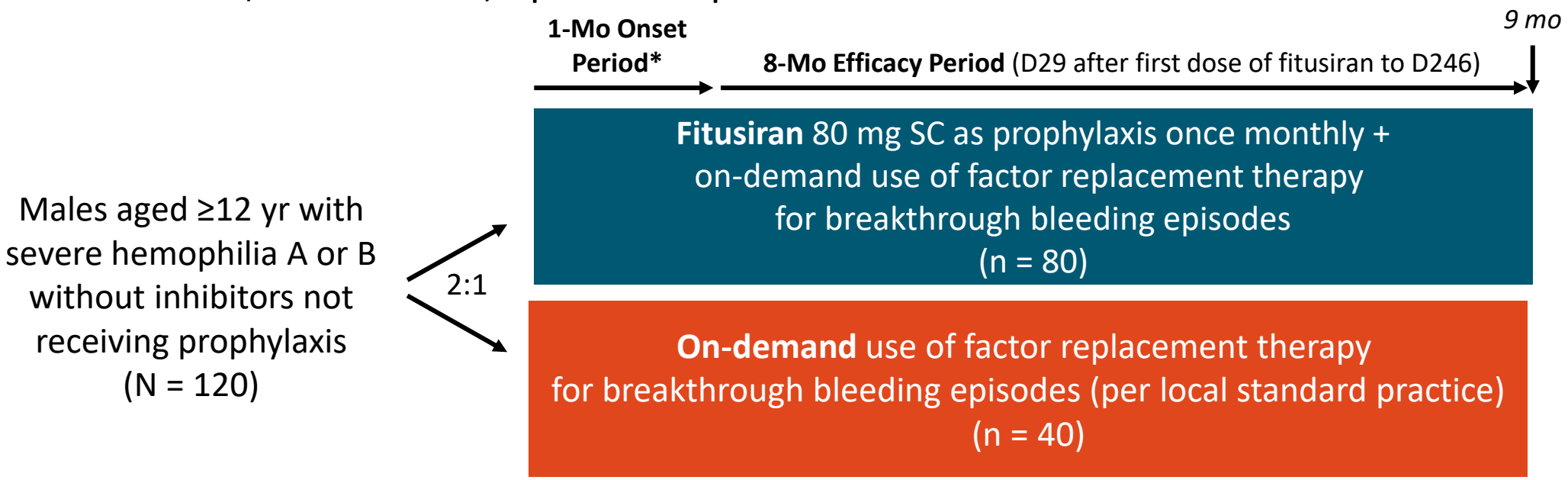
*Time period in which fitusiran achieves target pharmacodynamic effect.

- Primary endpoint: ABR in the efficacy period
- Secondary endpoints: spontaneous ABR, joint ABR, QoL (by Haem-A-QoL), frequency of bleeding episodes during onset period, safety and tolerability

Young. ASH 2021. Abstr 4.

ATLAS-A/B: Study Design

- Multicenter, randomized, open-label phase III trial



*Time required for fitusiran to reach target PD effect of antithrombin lowering (first 28 days).

- **Primary endpoint:** annualized bleeding rate
- **Secondary endpoints:** annualized joint bleeding rate, HRQoL (per Haem-A-QoL), safety and tolerability

Srivastava. ASH 2021. Abstr LBA3.

ATLAS-INH: Investigators' Conclusions

- ***Monthly fitusiran prophylaxis*** at a dose of 80 mg significantly reduced the rate of bleeding events among individuals with hemophilia A or B ***with and without inhibitors***
- Fitusiran prophylaxis improved health-related quality of life

Young. ASH 2021. Abstr 4.

HEMATOPOIETIC CELL TRANSPLANTATION

- Immunocompromised individuals who are recipients (HCT) or (CAR)-T-cell therapies are at risk for a ***suboptimal immune response*** to COVID-19 vaccination.
- Updated guidance from (CDC) now recommends revaccination with a ***full primary series*** for patients who were vaccinated prior to receiving HCT or CAR-T-cell therapy and who are at least ***three months*** post-HCT or CAR-T-cell therapy.

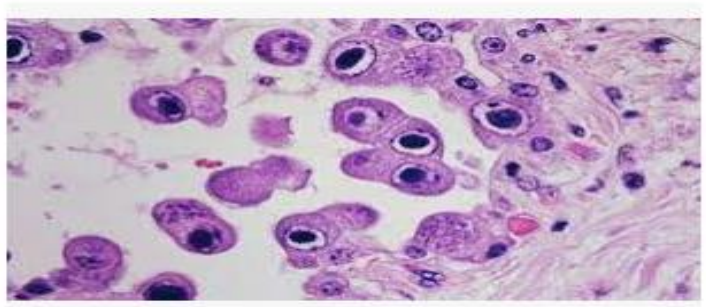
Ruxolitinib for treatment of steroid-refractory (SR)-chronic graft-versus-host disease (cGVHD)

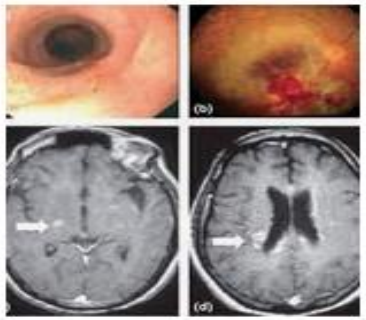
- A recent randomized trial reported that adding ruxolitinib (JAK kinase inhibitor) to prednisone was superior to adding the best available treatment
- Ruxolitinib achieved ***superior overall responses, improved symptoms***, and longer failure-free survival, with comparable rates of serious adverse events.
- For patients with SR-cGVHD, adding ruxolitinib to prednisone is suggested.

N Engl J Med. 2021;385(3):228.

Risk of CMV infection with post-transplant cyclophosphamide use in allogeneic hematopoietic cell transplant recipients

- Post-transplant cyclophosphamide (PTCy) is increasingly used as prophylaxis against graft-versus-host disease (GVHD) in allogeneic hematopoietic cell transplantation (HCT), but there are concerns that PTCy may be associated with ***increased risk for cytomegalovirus (CMV) infection***.
- A registry-based study of >2700 allogeneic HCT recipients reported that among CMV-seropositive transplant recipients, ***PTCy doubled the risk of CMV infection***, compared with calcineurin-based GVHD prophylaxis
- This effect was most notable in recipients of haploidentical grafts
- For ***seropositive recipients of haploidentical HCT grafts***, we consider broader or earlier use of antiviral prophylaxis (eg, letermovir), particularly when PTCy is given for GVHD prophylaxis



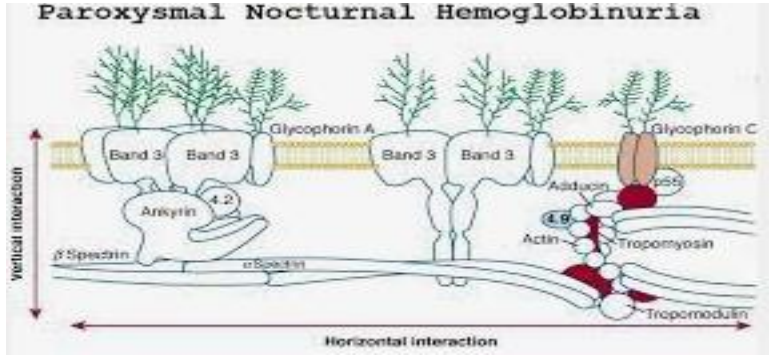


Blood. 2021;137(23):3291.

OTHER HEMATOLOGY

Oral C3 inhibitor in patients with paroxysmal nocturnal hemoglobinuria (PNH)

- For most patients with paroxysmal nocturnal hemoglobinuria (PNH), treatment with a C5 inhibitor (C5i; ravulizumab or eculizumab) effectively reduces intravascular hemolysis, transfusions, and thromboses and improves quality of life (QoL).
- Some patients treated with a C5i require ongoing transfusions due to extravascular hemolysis caused by opsonization of red blood cells by C3.
- ***Danicopan*** is an investigational oral agent that inhibits C3 production.
- Danicopan is under review by the US Food and Drug Administration for control of extravascular hemolysis in PNH



Blood. 2021;138(20):1928.