Weill Cornell Medicine

Updates on MPNS

ASH 2021

- Ellen K. Ritchie MD
- Associate Professor of Clinical Medicine

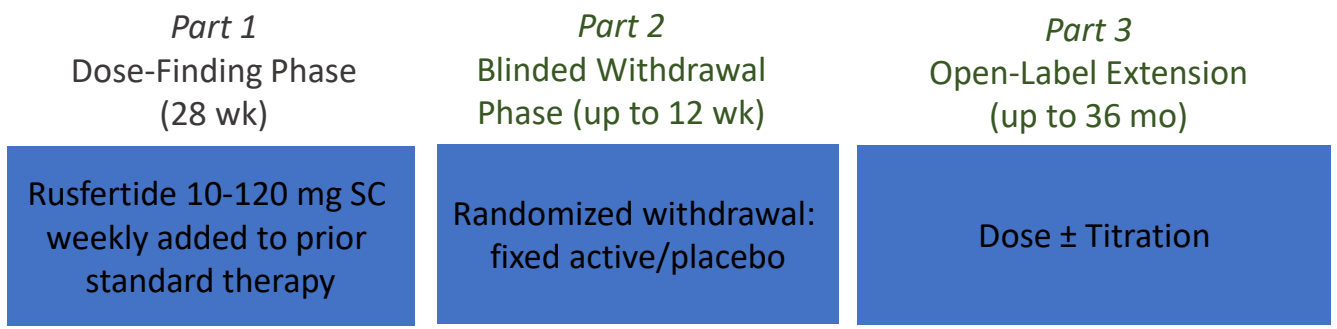
- ritchie@med.cornell.edu
- @DrEllenRitchie

Exciting information on new drugs to treat PV, ET, MF, and CML

- Rusfertide (PTG-300) in PV patients
- REVEAL data review on association between elevated blood counts and thrombotic events in PV
- Bomedemstat (LSD1 inhibitor) in ET patients
- Pelabresib (CPI-0610) BET inhibitor in MF patients
- Asciminib in CML
- Low dose vs Normal dose dasatinib in CML

Rusfertide in Phlebotomy-Dependent PV: Study Design

Patients with TP-dependent PV with ≥3 phlebotomies in 6 mo ± concurrent cytoreductive therapy; all patients were phlebotomized to a standardized HCT <45% (N = 63)



- Goal: maintain hematocrit <45%
  - Titration Q4W in dose-finding and extension phases

Hoffman. ASH 2021. Abstr 388.

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Rusfertide in Phlebotomy-Dependent PV: Baseline Characteristics

Characteristic	All Patients (n = 63)
Mean age, yr (range)	56.3 (27-76)
Male, n (%)	45 (71.4)
Risk, n (%)	
▪ Low	28 (44.4)
▪ High	35 (55.6*)
Time since PV diagnosis, n (%)	
▪ <1 yr	12 (19.0)
▪ 1 to <3 yr	23 (36.5)
▪ 3 to <5 yr	9 (14.3)
▪ ≥5 yr	19 (30.2)

Characteristic	All Patients (n = 63)
Therapies, n (%)	
▪ Phlebotomy only	31 (49.2)
▪ Phlebotomy + HU	18 (28.6)
▪ Phlebotomy + IFN	8 (12.7)
▪ Phlebotomy + RUX	3 (4.8)
▪ Phlebotomy + multiple agents	3 (4.8)
Phlebotomies in 28 wk prior, mean n (range)	4.71 (2-10)
Phlebotomies in 28 wk prior, n (%)	
▪ 2-3	15 (23.8)
▪ 4-5	33 (52.3)
▪ ≥6	15 (23.8)
Median time between phlebotomies, days	35

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Rusfertide (PTG-300) in Phlebotomy-Dependent PV

- 84% of patients required no phlebotomies during the 28-wk treatment period
  - 14% required 1 phlebotomy; 2% required 2 phlebotomies
  - HCT control maintained for 1.5 yr, usually <45%
- Significant reduction in RBC count observed as early as Wk 4 (*P* <.01)
- Iron stores normalized as early as Wk 4 as assessed by serum ferritin (*P* <.01) that increased over the treatment period
  - Associated with increases in MCV and TSAT %

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REVEAL ANALYSIS Methods: Study Design and Patients

- REVEAL is a multicenter, noninterventional, prospective observational study in patients with PV enrolled from US community practices and academic centers

Key inclusion criteria:	Key exclusion criteria:
• Age ≥18 years, • Clinical diagnosis of PV per physician judgment • Under physician supervision for management of PV	• Life expectancy <6 months • History of/planning to undergo allogeneic hematopoietic cell transplantation • Splenectomy

- Data collection timepoints included, at diagnosis, a 6-month period before, and during follow-up after enrollment (up to 3 years from last patient enrollment)
  - Data were collected between July of 2014 and August of 2019
- Patients included in this analysis were required to have ≥3 laboratory values (blood counts) in the post-enrollment period
- Patients were excluded if they had a post-enrollment TE but did not have a laboratory value <6 months before that TE

REVEAL: Elevated wbc, hb and plts significantly associated with thrombotic events

This analysis of REVEAL, representing the largest real-world cohort of PV patients to date, demonstrated significant associations individually between elevated HCT levels, elevated WBC, and elevated PLT counts and increased TE risk

Elevated WBC (>12×10^9/L) is significantly associated with increased risk of TE when HCT is controlled, indicating that TE risk may be reduced by controlling WBC as well as HCT

The data provide evidence to support incorporation of blood count values into risk stratification and treatment strategies for patients with PV in clinical practice, thus moving beyond the conventional risk model

Further studies to understand the causal relationship between elevated blood counts and TEs are warranted

- Additional analyses of REVEAL are ongoing to understand the relationship between TE risk and isolated WBC elevation, as well as time-dependent risk with elevated blood counts

Bomedemstat (LSD1 inhibitor) in Pts with ET: Study Design

IMG-7289-CTP-201 is an ***ongoing*** Phase 2 global study to assess the safety, efficacy and pharmacodynamics of IMG-7289 (bomedemstat) in Patients with ET.

Primary Endpoints

- Safety and tolerability
- Platelet count reduction (≤400 x 10^9/L) in the absence of thromboembolic events

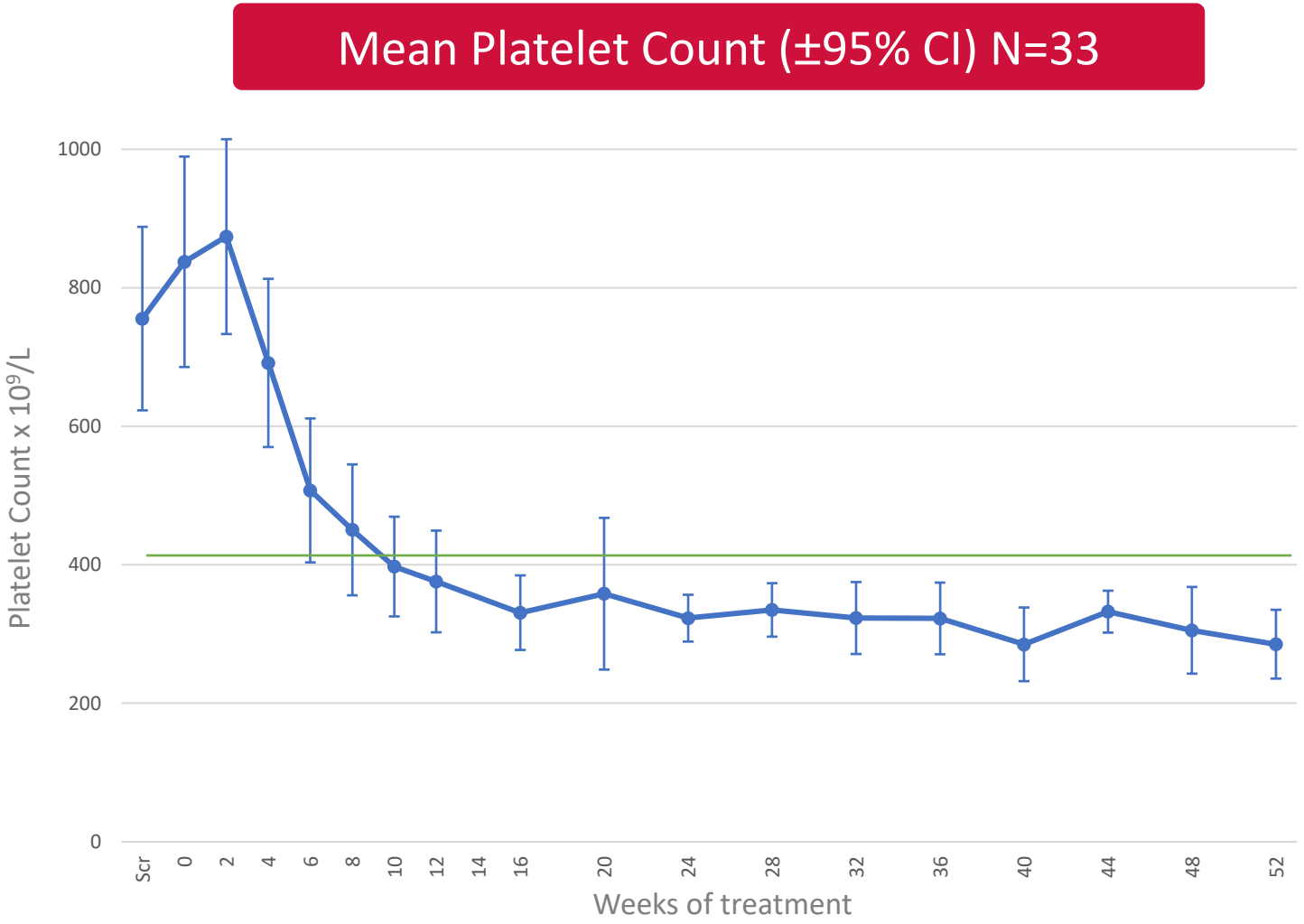
Secondary Endpoints

- Symptom reduction (MPN-SAF TSS)
- Durability of platelet and WBC count reduction
- Changes in mutant allele frequencies (MAF)

Key Eligibility Criteria

- Dx of ET
- Failed at least one standard therapy
- Platelet count >450 x 10^9/L
- Hemoglobin ≥10 g/dL
- Peripheral blasts <1%
- Fibrosis Score <2 per protocol criteria (modified from Arber et al., 2016)

Primary Objective: Reduction in Platelet Count



In the 29 patients treated for >6 weeks:

- 100% patients experienced a reduction in platelets
- 93% of patients achieved a platelet count of ≤400 x 10^9/L
- Response Rate*: 90% (26/29)

*Platelet count ≤400 x 10^9/L without thromboembolic events

Data cut-off date: 01 Nov 2021

Summary of Results of Bomemdemstat Trial

Bomedemstat (IMG-7289) is generally well tolerated in patients with ET

- Majority of AEs were low-grade

Bomedemstat as monotherapy demonstrates significant clinical activity:

- Majority of patients achieve the target platelet count with 0-2 dose titrations
- Normalization of platelet and WBC counts while maintaining hemoglobins
- Symptomatic improvement for some patients with significant MPN symptoms
- All genotypes respond to bomedemstat

Development Plans

- The ET study remains open for enrollment (NCT04254978*)*
- Planning for pivotal study in ET is underway
- Bomedemstat in PV is currently enrolling (NCT04262141)

MANIFEST (Arm 1): Study Design

- Arm 1 of an ongoing global, open-label phase II trial (data cutoff: September 10, 2021)

Pts with MF no longer on ruxolitinib;
DIPSS>int2;plts >75; TD cohort>2
Units prbc trans/mo x 12 wk;non-
TD cohort with BL spleen size>450cm3
(N=86)

→

TD Cohort 1A (n = 36)
Pelabresib starting dose 125 mg once daily
(14d on and 7d off)

Non-TD Cohort 1B (n = 50)
Pelabresib starting dose 125 mg once daily
(14d on and 7d off)

- Primary endpoints:
  - TD cohort 1A: TD to TI conversion
  - Non-TD cohort 1B: SVR35 at 24 wk
- Secondary endpoints:
  - TD cohort 1A: SVR35 and TSS50 at 24 wk
  - Non-TD cohort 1B: TSS50 at 24 wk

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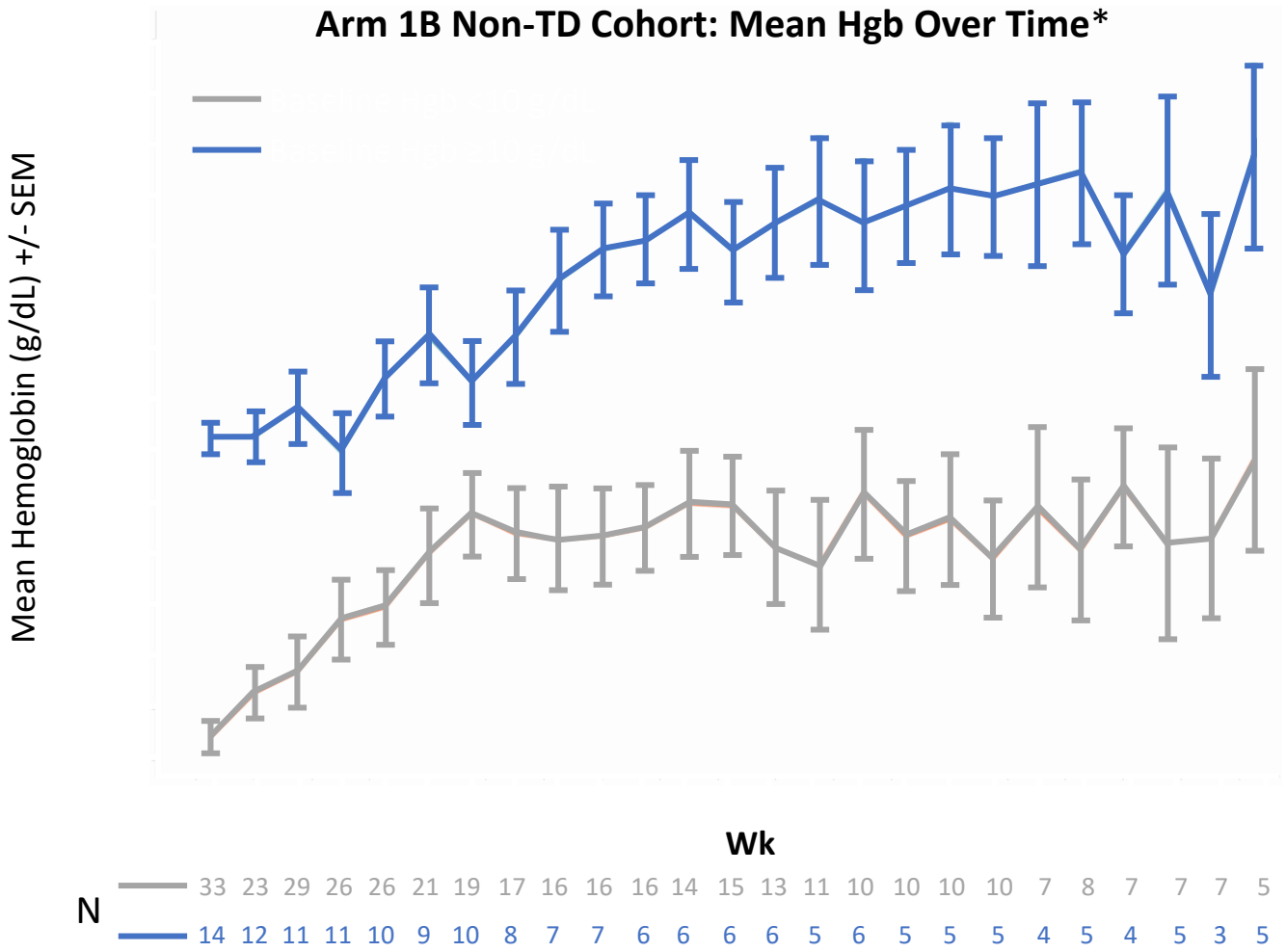
MANIFEST (Arm 1): Anemia Improvement



*Hgb values within 12 wk after transfusion are excluded; 3 patients NE due to missing baseline.

Outcome	Non-TD Cohort 1B
Hemoglobin response, % (n/N)	
▪ All patients	38 (18/47)
▪ JAKi refractory/resistant	34 (11/32)
▪ JAKi ineligible	66 (2/3)
▪ JAKi intolerant	41 (5/12)

Outcome	TD Cohort 1A (n = 25)
TD to TI conversion, n (%)	4 (16)
Median TI duration, wk (range)	41 (31-53)
Median time to TI conversion, wk	32

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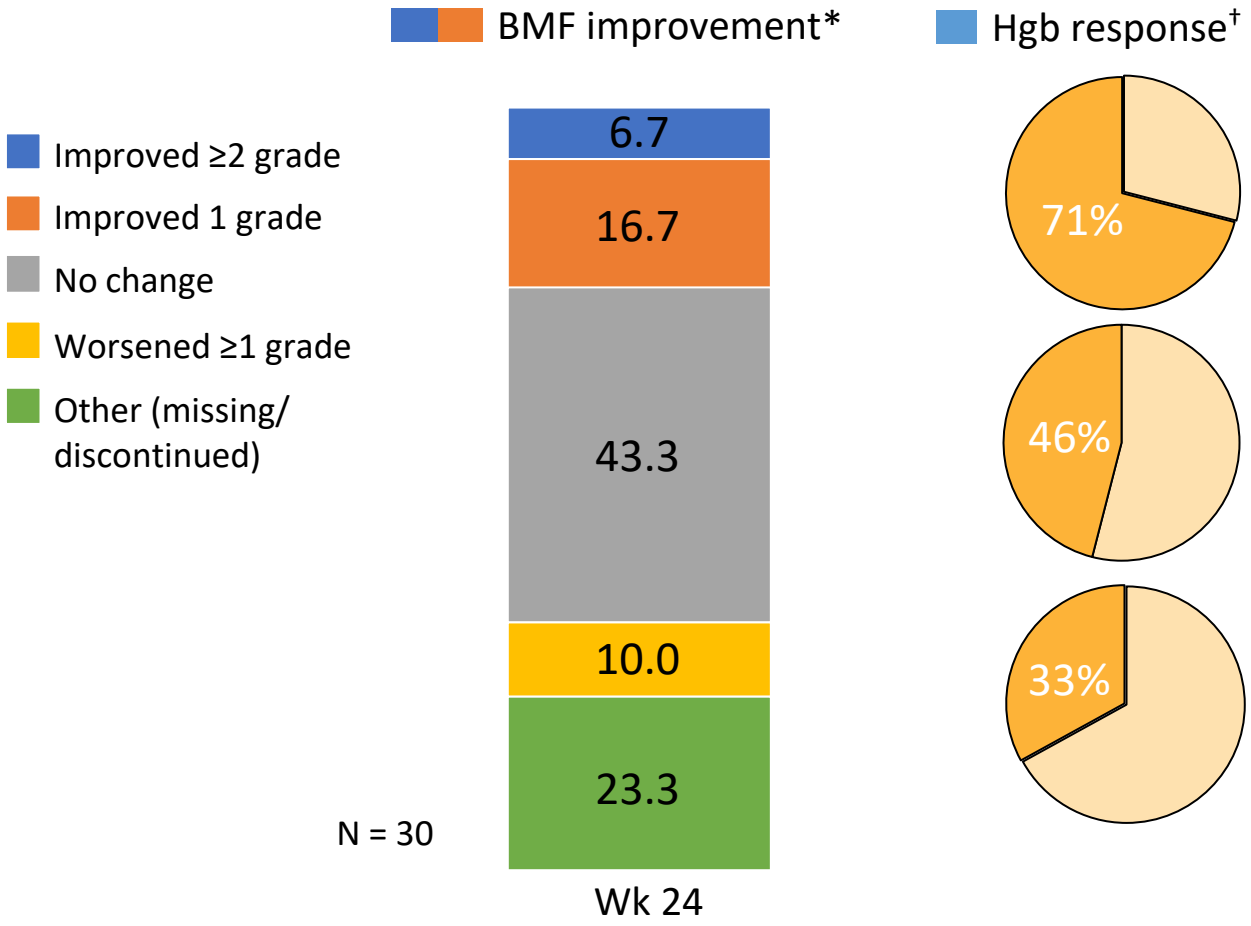
MANIFEST (Arm 1): Secondary Outcomes



- Bone marrow fibrosis improved by 1 grade in 16.7% of patients and by ≥2 grades in 6.7% of patients
- 71% of patients with bone marrow fibrosis improvement also had hemoglobin responses
- Multiple cytokines associated with MF and inflammation were downregulated following pelabresib therapy
  - Downregulations were observed as early as day 14 and sustained through 24 wk

*Exploratory endpoint: patients evaluable if nonmissing baseline bone marrow assessment.
†Secondary endpoint: postbaseline mean Hgb increase of ≥1.5 g/dL for any 12-wk RBC transfusion–free period.

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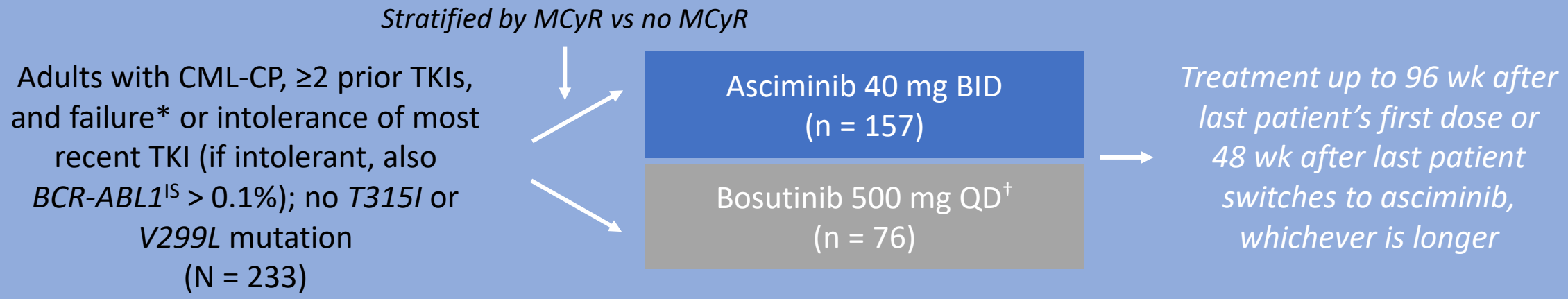
ASCEMBL 48-Week Update: Study Design

- 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.

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ASCEMBL 48-Wk Update: Response Rates

Outcome, %	Asciminib (n = 157)	Bosutinib (n = 76)	Common Treatment Difference,* % (95% CI)
MMR at Wk 48	29.3	13.2	16.1 (5.7-26.6)
▪ If used third line	30.5 (n/N = 25/82)	26.7 (n/N = 8/30)	
▪ If used fourth line	31.8 (n/N = 14/44)	6.9 (n/N = 2/29)	
▪ If used ≥ fifth line	22.6 (n/N = 7/31)	0 (n/N = 0/17)	
Outcome,† %	**Asciminib (n = 142)**	**Bosutinib (n = 72)**	**Treatment Difference**
BCR:ABL1^{IS} ≤1%	42.3	19.4	22.9

*Adjusted for MCyR status at baseline. †Based on patients without this level of response at baseline.

Outcome	Asciminib (n = 157)	Bosutinib (n = 76)
Cumulative incidence of MMR at Wk 48, %	33.2	18.6
Probability of maintaining MMR for ≥48 wk, % (95% CI)	96.1 (85.4-99.0)	90.0 (47.3-98.5)
Maintained MMR at last assessment, n/N	60/62	17/18
Cumulative incidence of *BCR:ABL1^{IS} ≤1%* at Wk 48, %	50.8	33.7

Mauro. ASH 2021. Abstr 310.

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ASCEMBL 48-Wk Update: Additional Efficacy Results

Outcome	Asciminib (n = 157)	Bosutinib (n = 76)
MR^4, %	10.8	3.9
$MR^{4.5}$, %	7.6	1.3
Treatment failure, %*	48.4	80.3
K-M estimated proportion of patients without treatment failure by 12 mo, % (95% CI)	57.7 (49.5-65.0)	25.0 (15.9-35.1)
Median time to treatment failure, mo	NR	6

*Defined as lack of efficacy or discontinuation for any reason. HR: 0.4 (95% CI: 0.3-0.6; *P* <.0001).

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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.

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Low-Dose Dasatinib in CP-CML: Study Design

- Responses analyzed for patients with newly diagnosed CP-CML receiving low-dose dasatinib 50 mg/day (n = 83) or standard-dose dasatinib 100 mg/day (n = 150)
  - Patients receiving 50 mg dasatinib could receive 100 mg dasatinib if suboptimal response by ELN 2013 criteria
- Propensity score matching identified 77 patients in each cohort without significant baseline difference
  - Calculated with logistic regression from baseline characteristics including age, WBC, hemoglobin, spleen size (by examination), platelets, % blasts (BM and PB), % basophils (PB), clonal evolution, and Sokal risk classification
- Assessments: response, FFS, EFS, TFS, OS, safety

Sasaki. ASH 2021. Abstr 631.

Low-Dose Dasatinib in CP-CML: Outcomes

Outcome, % (95% CI)	Dasa 50 mg (n = 77)	Dasa 100 mg (n = 77)	*P* Value
4-yr FFS	89 (80.9-97.2)	77 (67.7-86.7)	.041
4-yr EFS	95 (88.7-100)	92 (86.4-98.4)	.556
4-yr TFS	100 (100-100)	100 (100-100)	1.000
4-yr OS	97 (93.4-100)	96 (91.9-100)	.781

Outcome, %	Dasa 50 mg (n = 77)	Dasa 100 mg (n = 77)	*P* Value
36-mo CCyR	96	88	.141
36-mo MMR	92	84	.234
36-mo MR.4	77	66	.038
36-mo MR4.5	77	62	.021

- Median follow-up dasa 50 mg and dasa 100 mg: 48 mo vs 131 mo

Sasaki. ASH 2021. Abstr 631.

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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.

Slide credit: clinicaloptions.com

Also worth mentioning:

Intriguing early data for Selinexor (SINE inhibitor) on MF with possible improvement in hb, TSS, spleen size and OS

More data on fedratinib safety and efficacy in MF patients who progress on ruxolitinib

Targeted anti-CD123 antibody treatment, Tagraxofusp, also may have impact on OS in MF.

Mutational analysis of EXPLORER trial of avapritinib in pts with adv systemic mastocytosis with reduced KIT D816V disease burden that is durable.