Mutant Isocitrate Dehydrogenase (mIDH) Inhibitors, Enasidenib or Ivosidenib, in Combination with Azacitidine (AZA): Preliminary Results of a Phase 1b/2 Study in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

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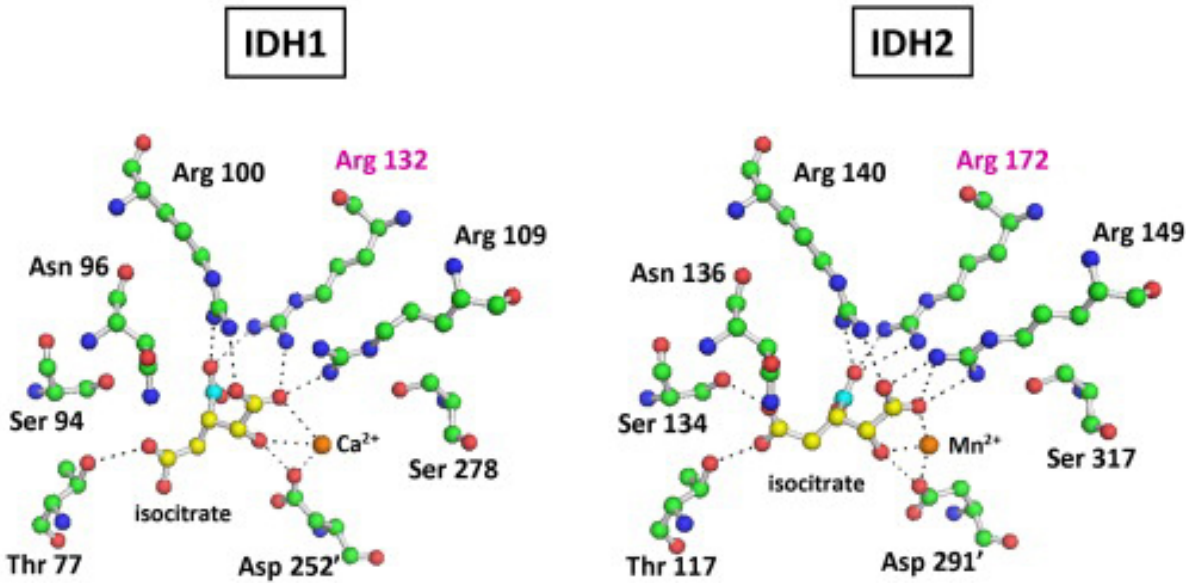
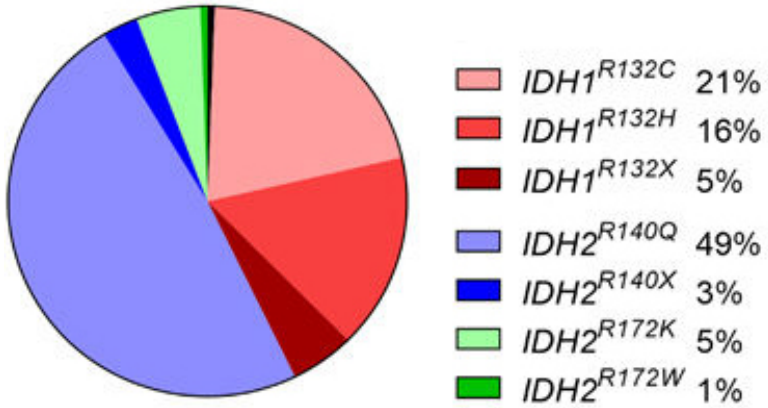
IDH1 AND *IDH2* MUTATIONS

- *IDH* mutations occur in ~20% of patients (pts) with AML
  - Higher prevalence with increased pt age
  - Enriched in certain molecularly and karyotypically defined populations (eg, normal karyotype, mutant-*NPM1* AML)
    - Most (~85%) occur in diploid or +8 *de novo* AML[1]
- "Hot-Spot" mutations in enzymatic active site
  - *IDH1*-R132, *IDH2*-R140 or *IDH2*-R172
- Often considered "founder mutations"
  - *IDH* mutations are ancestral in 20% of *IDH1* cases and 35% of *IDH2* cases[2]
- Can be acquired at time of progression[3]
  - 10-15% of AML from MDS
  - 20-25% of AML from MPN

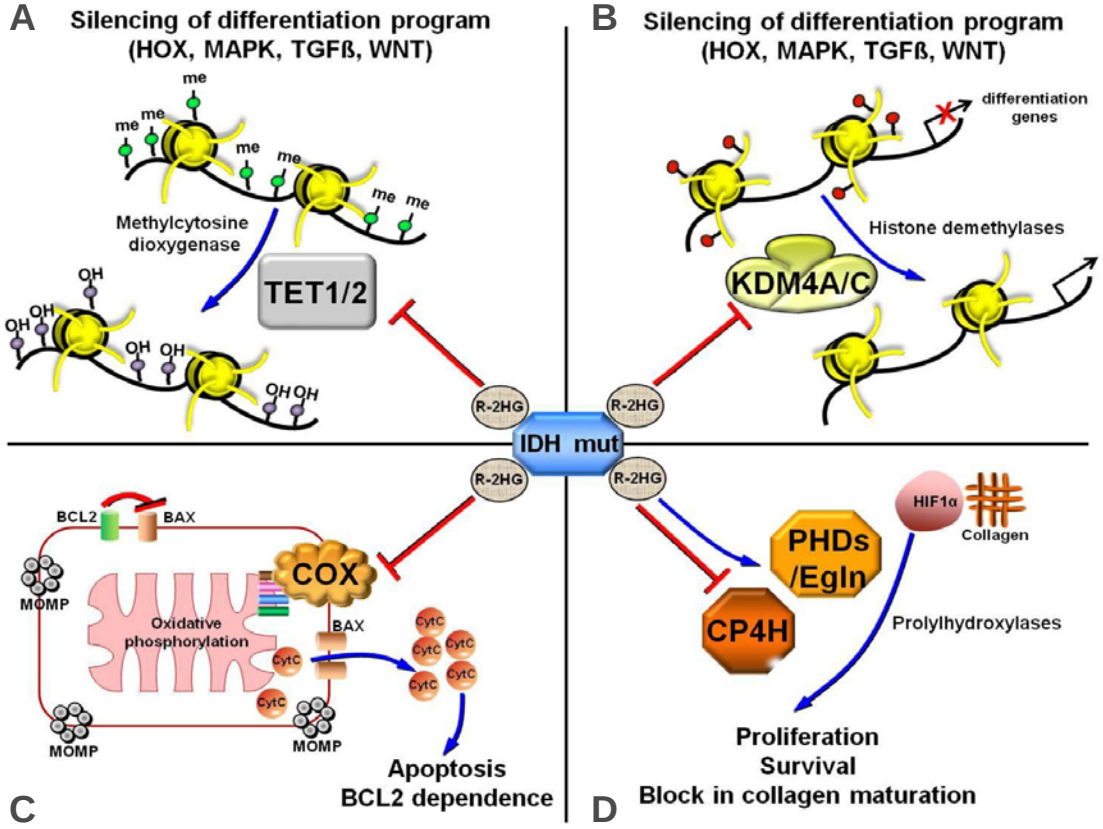




1. Chou et al, *Leukemia* 2011. 2. Molenaar et al, *Leukemia* 2015. 3. Dang et al, *Trends in Mol Med*, 2010.

2HG ACCUMULATION

- *IDH1/2* mutations lead to 2HG accumulation; the oncometabolite 2HG competitively inhibits enzymes that utilize αKG as a substrate
  - αKG is a substrate for >60 αKG-dependent dioxygenases
- 2HG-induced oncogenic activities are thought to include:



A and B: Differentiation block via inhibition of TET family enzymes and histone demethylases, yielding hypermethylated DNA and histones

C: BCL2 dependence via inhibition of Cyt C Oxidase in electron transport chain leading to lowered apoptotic threshold

D: Altered hypoxic response via dysregulated HIF-1α

Chan et al, *Nature Med* 2015. Heuser et al, *Exp Hematology* 2015.

BACKGROUND

Mutant-IDH (mIDH) inhibitors

- Enasidenib (IDHIFA®; CC-90007/AG-221) and ivosidenib (AG-120) are oral, small-molecule inhibitors of mIDH2 and mIDH1 proteins, respectively
- In pts with m*IDH2* R/R AML, enasidenib monotherapy associated with 40.3% overall response rate (ORR), complete remission (CR) rate of 19.3%, and median overall survival (OS) of 9.3 months[1]
- Updated outcomes with investigational ivosidenib monotherapy in pts with m*IDH1* AML to be presented at ASH (Abstract #725)
  - ORR for pts with m*IDH1* R/R AML was 41.6% and CR rate was 21.6%

Azacitidine (AZA)

- AZA reduces DNA methylation by inhibiting DNA methyltransferases
- AZA monotherapy prolonged OS vs conventional care regimens (CCR) in older pts with newly diagnosed (ND) AML (10.4 vs 6.5 months; *P*=0.101),[2] including in the subgroup of pts with AML-MRC (*P*=0.0264)[3]

mIDH inhibitors + AZA

- mIDH inhibitors + AZA showed synergistic effects on releasing differentiation block in m*IDH* leukemia models *in vitro*[4]
- We report initial results of the phase 1b portion of an ongoing phase 1b/2 study of mIDH inhibitors + AZA combinations in pts with m*IDH1* or m*IDH2* ND-AML (NCT02677922)

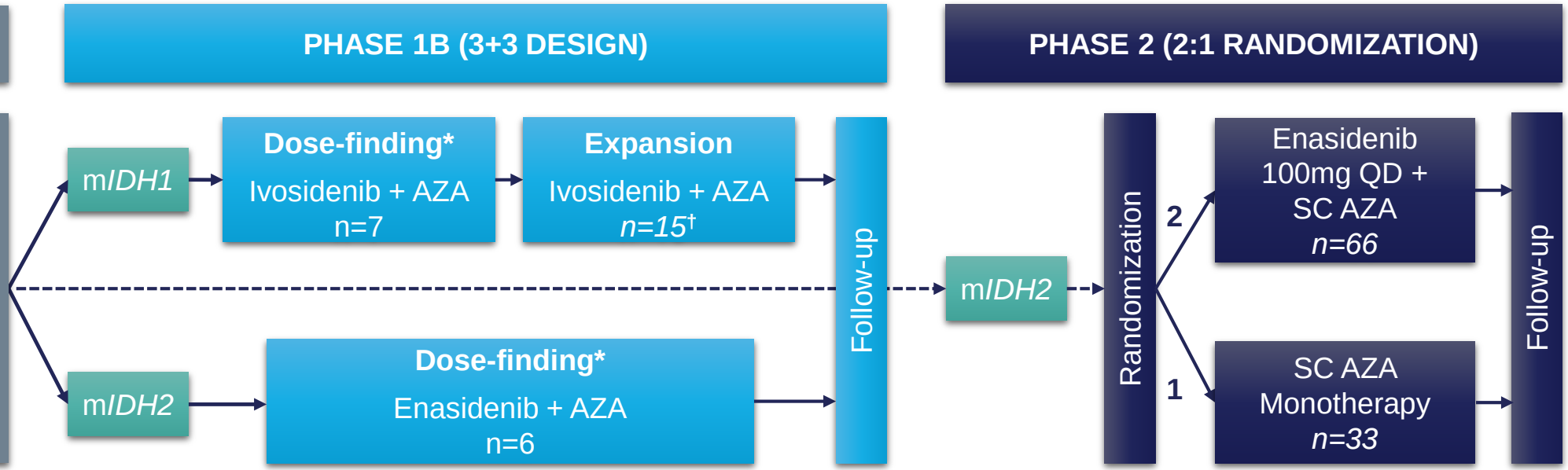
CCR, conventional care regimens; ND, newly diagnosed; R/R AML, relapsed/refractory acute myeloid leukemia

1. Stein et al, *Blood*, 2017. 2. Dombret et al, *Blood*, 2015. 3. Seymour et al, *BMJ Cancer*, 2017 (in press). 4. Chopra et al, *Cancer Res*, 2016.

PATIENTS, DOSING, AND ENDPOINTS

KEY ELIGIBILITY CRITERIA

- Newly diagnosed AML
- Age ≥18
- Ineligible for intensive chemotherapy
- Pts with antecedent hematologic disorders allowed but prior HMA excluded



SC AZA 75mg/m^2/day x 7 days/ 28-day cycle (all study phases)

PRIMARY ENDPOINTS:
Recommended combination dose (RCD); safety

KEY SECONDARY ENDPOINTS:
Overall response rate
PK/PD
QOL outcomes

PRIMARY ENDPOINT:
Overall response rate

KEY SECONDARY ENDPOINTS:
Safety
Event-free survival
Overall survival

*Dose finding for enasidenib or ivosidenib; AZA dose remained constant
†4 pts had enrolled in expansion as of data cutoff (1 Sep 2017); enrollment is now closed
ClinicalTrials.gov NCT02677922
AML, acute myeloid leukemia; AZA, azacitidine; IC, induction chemotherapy; ORR, overall response rate; QOL, quality of life; RCD, recommended combination dose

BASELINE DEMOGRAPHIC AND DISEASE CHARACTERISTICS

- 17 pts treated with enasidenib +AZA (n=6) or ivosidenib + AZA (n=11)
- At data cutoff (1-Sep-2017), 11 pts remained on-study (3 enasidenib, 8 ivosidenib)

	Enasidenib 100 mg + AZA (n=3)	Enasidenib 200 mg + AZA (n=3)	Combined Enasidenib + AZA (n=6)	Ivosidenib 500 mg + AZA (n=11)
Age (years), median (range)	76 (69–79)	65 (64–67)	**68 (64–79)**	**76 (72–88)**
Age <65, n (%)	0	1 (33)	**1 (17)**	**0**
Age ≥65, n (%)	3 (100)	2 (67)	**5 (83)**	**11 (100)**
Gender, n Male/Female	1/2	1/2	**2/4**	**5/6**
***IDH2* mutation type**, n (%)				
R140	2 (67)	2 (67)	**4 (67)**	**NA**
R172	1 (33)	1 (33)	**2 (33)**	**NA**
ECOG PS, n (%)				
0	0	1 (33)	**1 (17)**	**2 (18)**
1	3 (100)	2 (67)	**5 (83)**	**9 (82)**
Co-mutations, n (%)				
FLT3-ITD / *FLT3*-TKD	1 (33)	2 (67)	**3 (50)**	**0**
NPM1	0	1 (33)	**1 (17)**	**1 (9)**
Cytogenetic risk, n (%)				
Intermediate	3 (100)	3 (100)	**6 (100)**	**7 (64)**
Poor	0	0	**0**	**3 (27)**
Failure	0	0	**0**	**1 (9)**
Hemoglobin (g/dL), median (range)	9.8 (9.8–9.8)	9.7 (9.3–10.8)	**9.8 (9.3–10.8)**	**9.1 (7.8–14.1)**
Platelets (10^9/L), median (range)	141.5 (87–196)	42.0 (19–100)	**87.0 (19–196)**	**55.5 (11–200)**
WBC (10^9/L), median (range)	10.2 (0.8–19.6)	6.7 (1.3–19.2)	**6.7 (0.8–19.6)**	**1.7 (0.6–15.4)**

AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status score; NA, not applicable; WBC, white blood cell

ENASIDENIB: TREATMENT-EMERGENT ADVERSE EVENTS

- Median enasidenib Tx cycles: 9 (range 1-13)
- Most common TEAEs (any grade): nausea, hyperbilirubinemia (n=4 each)
- Enasidenib-related TEAEs (any grade) in >1 pt: nausea (n=3), vomiting (2), hyperbilirubinemia (2)
- IDH-differentiation syndrome (IDH-DS) occurred in 1 pt in the enasidenib 200-mg arm

Grade 3-4 treatment-emergent adverse events

	Enasidenib 100 mg + AZA (n=3)	Enasidenib 200 mg + AZA (n=3)	Enasidenib + AZA Total (N=6)
	n (%)		
Hematological			
Neutropenia	0	2* (67)	2* (33)
Thrombocytopenia	0	1* (33)	1* (17)
Febrile neutropenia	0	1* (33)	1* (17)
Anemia	0	1* (33)	1* (17)
Lymphocyte count decreased	0	1 (33)	1 (17)
WBC count decreased	0	1 (33)	1 (17)
Non-hematological			
Pneumonia	1 (33)	1 (33)	2 (33)
Hyperbilirubinemia	1 (33)	1* (33)	2* (33)
Colitis	1 (33)	0	1 (17)
Upper respiratory tract infection	1 (33)	0	1 (17)
Hypocalcemia	1 (33)	0	1 (17)
Hypokalemia	1 (33)	0	1 (17)
Hypophosphatemia	1 (33)	0	1 (17)
Hemorrhoidal hemorrhage	1 (33)	0	1 (17)
Hypoxia	0	1 (33)	1 (17)
Embolism	0	1* (33)	1* (17)

*One event considered to be treatment-related

IVOSIDENIB: TREATMENT-EMERGENT ADVERSE EVENTS

- Median ivosidenib Tx cycles: 3.0 (1-13)
- Most common TEAEs (any grade): nausea (n=8), constipation (6), fatigue (5), diarrhea (4)
- Tx-related TEAEs (any grade) in >1 pt: nausea (n=6), fatigue (4)
- IDH-DS reported for 1 pt
- 1 death on-study (pneumonia; not considered Tx-related)

Grade 3-4 treatment-emergent adverse events

	Ivosidenib 500 mg + AZA (N=11)
	n (%)
Hematological	
Anemia	2* (18)
Febrile neutropenia	2 (18)
Neutropenia	1* (9)
Thrombocytopenia	1* (9)
Non-hematological	
Pneumonia	2 (18)
Constipation	1* (9)
Dizziness	1 (9)
Atrial fibrillation	1 (9)
Blood creatinine increased	1* (9)
IDH differentiation syndrome	1* (9)
Parainfluenza virus infection	1 (9)
Sepsis	1 (9)
Cellulitis	1 (9)
INR increased	1 (9)
Gastrointestinal hemorrhage	1 (9)

*One event was considered to be treatment-related

OVERALL RESPONSE RATES

Overall response rate (ORR): CR + CRi/CRp + PR + MLFS (IWG 2003)

Enasidenib + AZA:

- ORR: 4 of 6
  - In the enasidenib 100 mg + AZA arm, 2 pts achieved CR
  - In the enasidenib 200 mg + AZA arm, 1 pt achieved PR and 1 had MLFS
    - 1 pt in the enasidenib 200 mg + AZA arm maintained SD on-study
    - 1 pt in the enasidenib 100 mg + AZA arm had PD

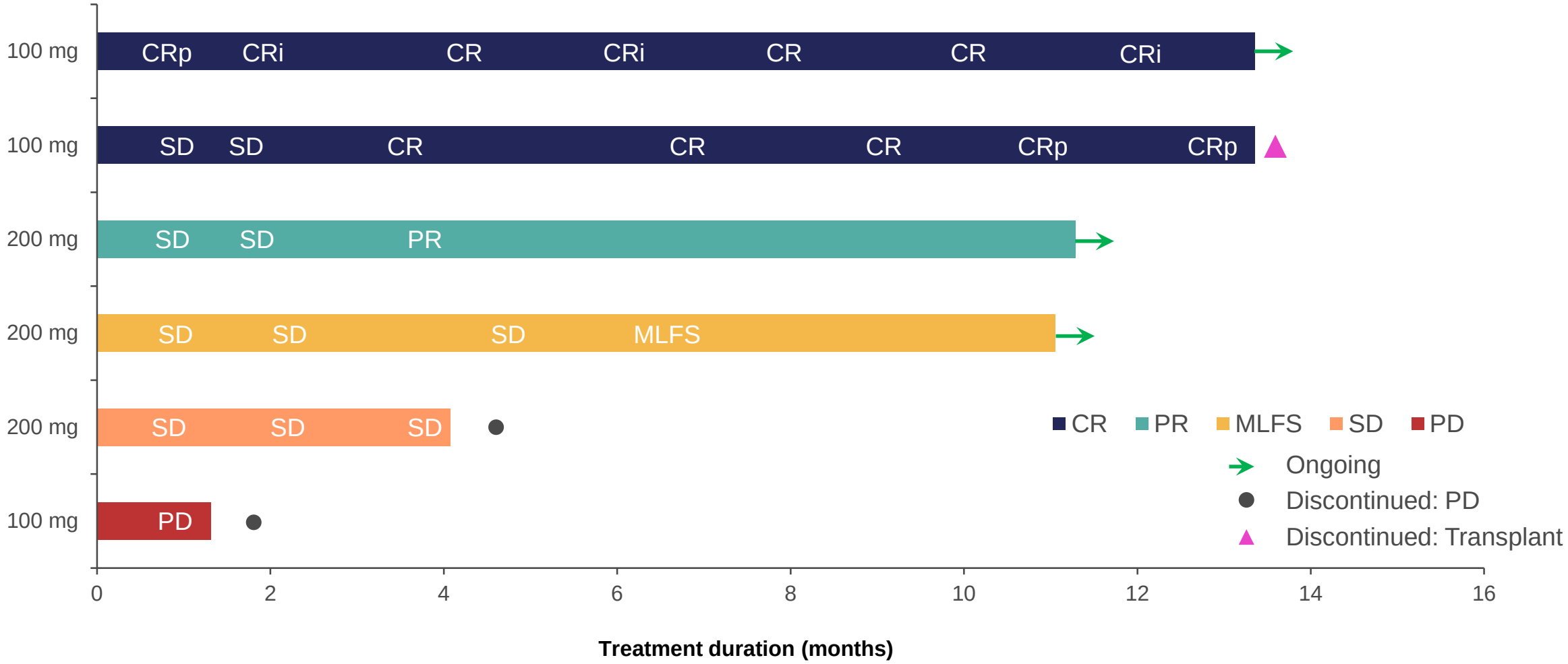
Ivosidenib 500 mg + AZA:

- ORR: 8 of 11
  - 4 pts achieved CR, 1 achieved CRi, 1 achieved PR, and 2 pts had MLFS
    - 3 pts maintained SD

Data cutoff: Sep 1, 2017

CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; PR = partial remission; MLFS = morphologic leukemia-free state; SD = stable disease; PD = progressive disease; MR = morphologic relapse after CR/CRi/CRp

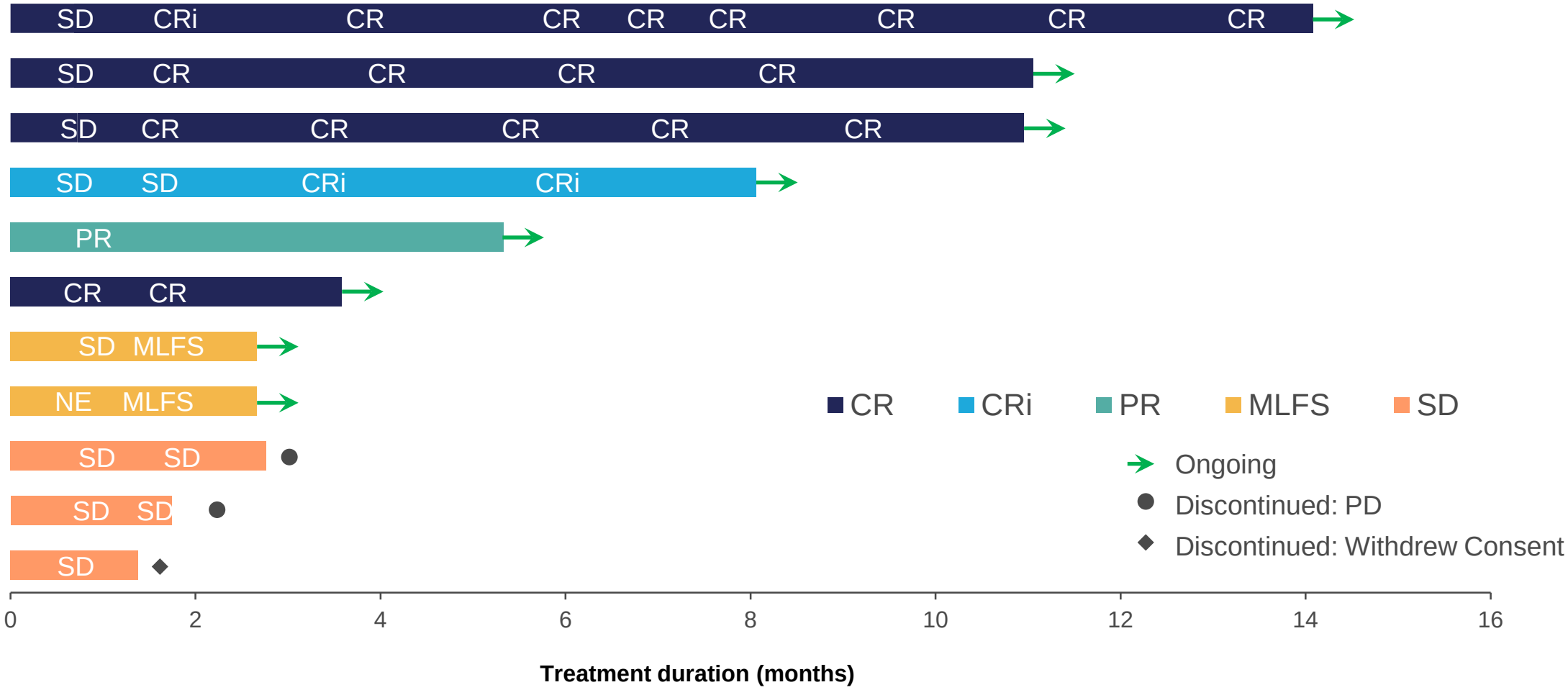
ENASIDENIB + AZA: TREATMENT DURATIONS, RESPONSE AND DISPOSITION



Data cutoff: Sep 1, 2017

CR, complete remission; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial remission; SD, stable disease

IVOSIDENIB + AZA: TREATMENT DURATIONS, RESPONSE AND DISPOSITION



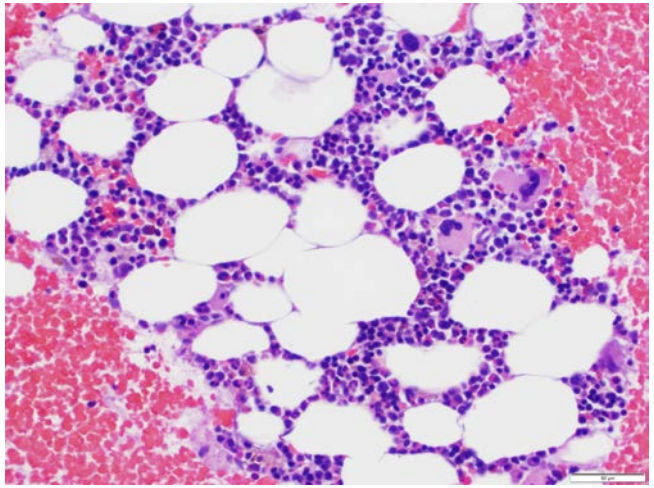
One additional patient was enrolled but did not have response data available at data cutoff
Data cutoff: Sep 1, 2017
CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; PR = partial remission; MLFS = morphologic leukemia-free state; SD = stable disease; PD = progressive disease; MR = morphologic relapse after CR/CRi/CRp; NE = not evaluable

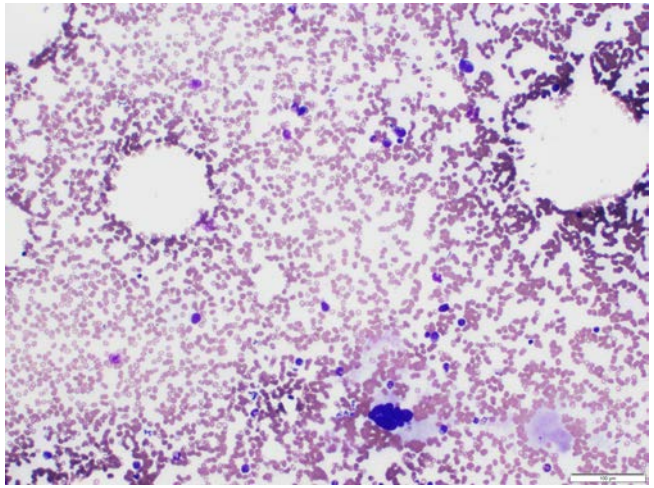
AG-221-AML-005 STUDY: CASE PRESENTATION

- 77-year-old female with atrial fibrillation / atrial flutter and pulmonary emboli at diagnosis
  - WBC 16K, Hgb 8.4 g/dl, platelets 186K, 14% peripheral blasts
- July 2016 BM Biopsy:
  - Hypercellular with MDS-related changes and 27% blasts
  - Cytogenetics with t(7;11)(p15;p15); *IDH2*-R140Q, *NRAS* G12D, *DNMT3A* N797I, and *FLT3*-ITD 0.016
- Enasidenib 100 mg/ day - Cycle 1 - Day 28 marrow:
  - Hypercellular marrow with 2% blasts
  - Persistent cytogenetics; *IDH2*, *NRAS*, *DNMT3A* and *FLT3*-ITD abnormalities detected
- Cycle 2 - Day 28 marrow:
  - Normocellular, diploid, only *DNMT3A* and *IDH2* remain. Flow with 2% blasts
- Cycle 4 - Day 28 marrow:
  - *IDH2* no longer detected. MRD negative by flow cytometry
- After Cycle 8:
  - AZA dose reduced by 50% for progressive cytopenias
- **Cycle 11:**
  - **Ongoing CR; MRD-negative by cytogenetics, molecular analysis, and flow cytometry**

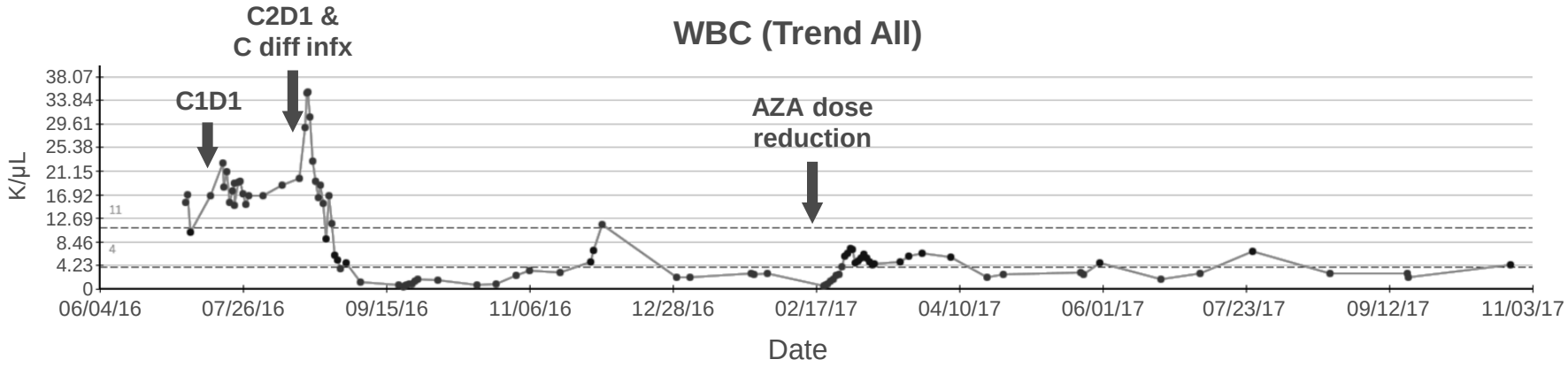
AG-221-AML-005 STUDY: CASE PRESENTATION

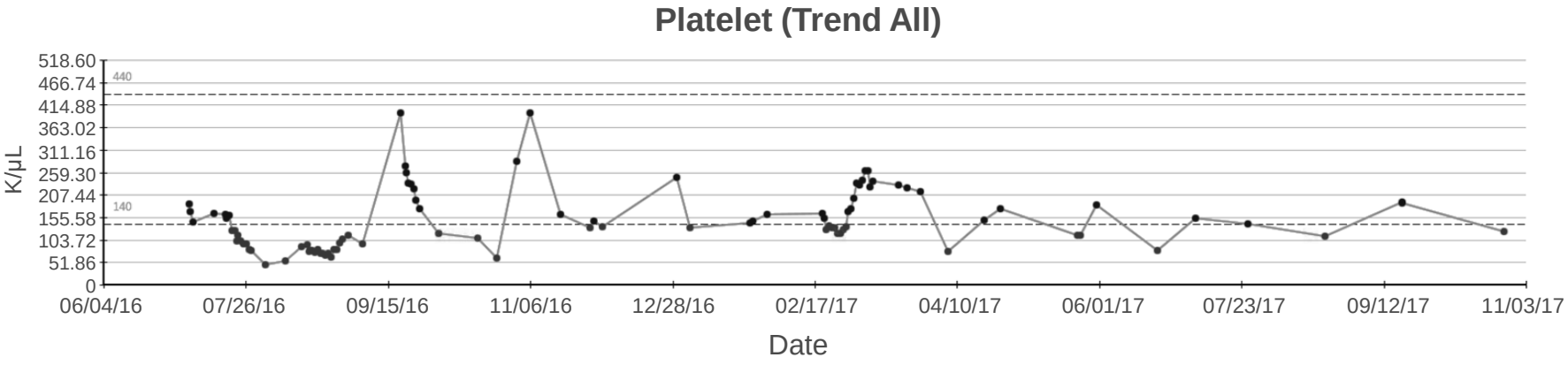
Clot and Smear at Cycle 9





Counts over time





DISCUSSION

- Enasidenib or ivosidenib + AZA combinations were well tolerated in pts with ND-AML
  - 11 pts remained on-study at data cutoff
  - 3 of 6 pts in the enasidenib + AZA arms and 8 of 11 pts in the ivosidenib + AZA arm remained on-study at time of data cutoff
- Most common TEAEs with all regimens: grade 1-2 GI events
  - Indirect bilirubinemia in enasidenib-treated pts likely due to off-target inhibition of UGT1A1 enzyme
- Preliminary efficacy is encouraging:
  - 4 of 6 enasidenib-treated pts had a response (2 CR, 1 PR, 1 MLFS)
  - 8 of 11 ivosidenib-treated pts had a response (4 CR, 1 CRi, 1 PR, 2 MLFS)
- Phase 1b confirms 100 mg enasidenib + AZA and 500 mg ivosidenib + AZA for further study
- Ongoing studies of mIDH inhibitors + AZA:
  - Randomized phase 2 portion of the current study of enasidenib + AZA (enrollment complete in the ivosidenib + AZA arm)
  - Phase 3 placebo-controlled AGILE study of ivosidenib + AZA (NCT03173248) in ND-AML not suitable for intensive therapy