Enasidenib (AG-221), a Potent Oral Inhibitor of Mutant Isocitrate Dehydrogenase 2 (IDH2) Enzyme, Induces Hematologic Responses in Patients with Myelodysplastic Syndromes (MDS)

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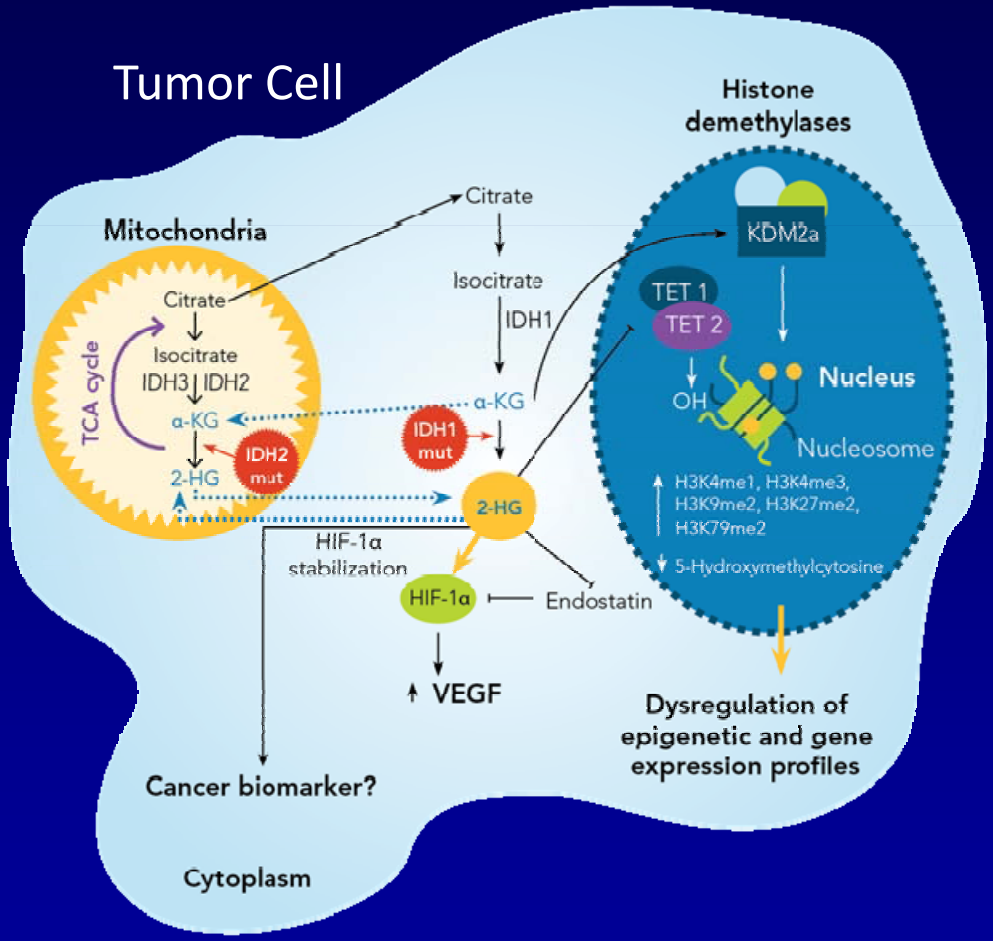
IDH Mutations as a Target in MDS

- IDH are critical enzymes of the citric acid cycle
- Mutant *IDH2* (m*IDH2*) produces 2-HG, which alters DNA methylation, blocks cellular differentiation
- m*IDH2* in ~5% of MDS[1]
- Enasidenib (AG-221/CC-90007) - selective, oral, potent inhibitor of mIDH2 enzyme
- Objective: safety and efficacy of enasidenib in m*IDH2* MDS



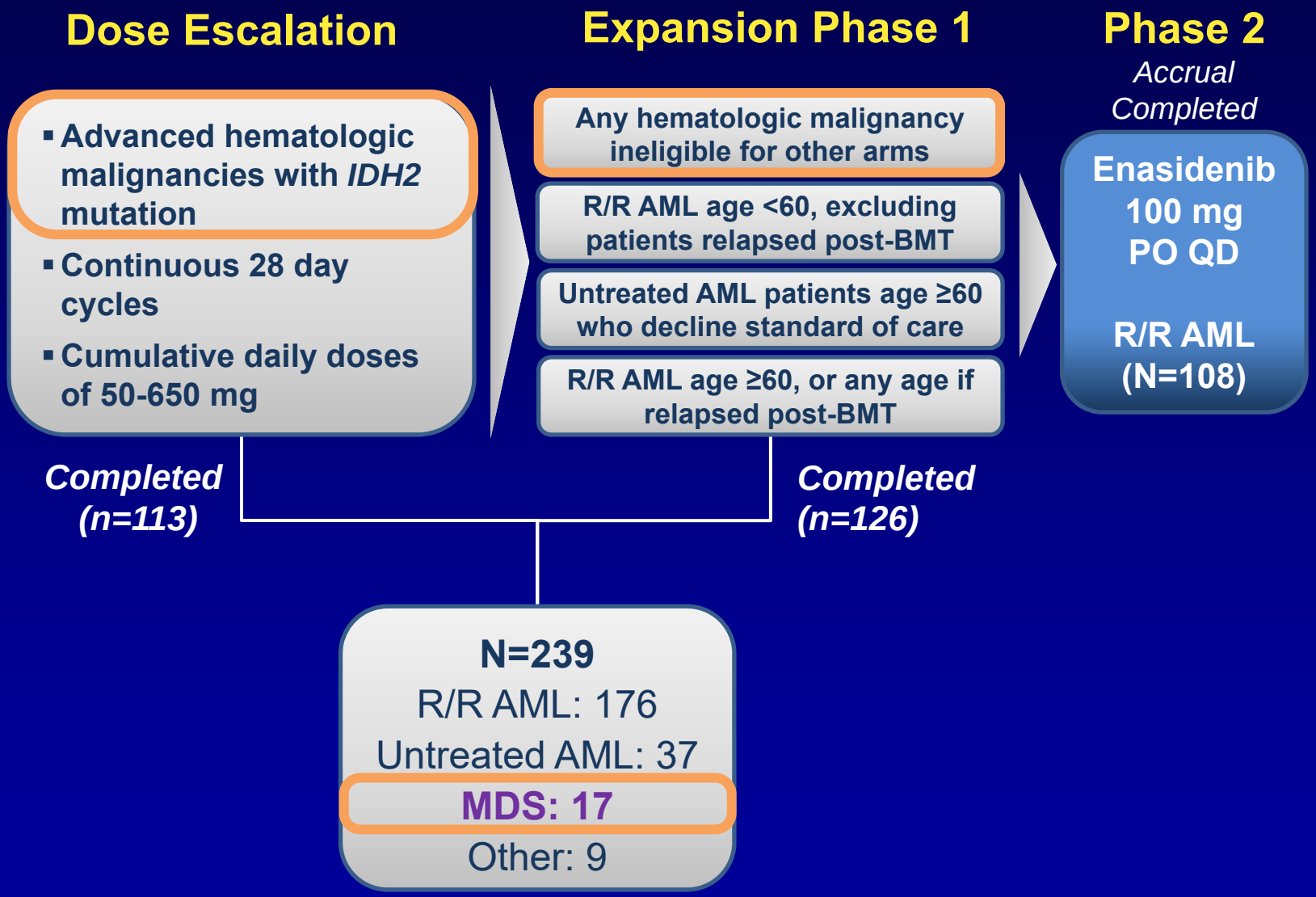
AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate; m*IDH2*, mutated IDH2

1. DiNardo et al. Leukemia 2016;30(4):980-4

Eligibility and Methods

- MDS eligibility:
  - m*IDH2* relapsed/refractory RAEB-1 / RAEB-2,
  - IPSS-R High risk, or
  - Ineligible for other therapies
- Key Endpoints:
  - Safety
  - Tolerability
  - Overall response (IWG 2006 MDS criteria) per local investigator
- Co-molecular profiling performed with FoundationOne® Heme Panel, using next-generation sequencing (NGS)

Phase 1/2 Dose-escalation and Expansion



Baseline Characteristics

Characteristic	MDS Patients N=17
Age (yrs), median (min, max)	67 (45, 78)
Gender, %M / %F	71 / 29
***IDH2* mutation**, % R140, % R172	88 / 12
ECOG performance status, n (%)	
0-1	13 (76)
2	4 (24)
Number of prior anti-cancer regimens, n (%)	
0	4 (24)
1	7 (41)
≥2	6 (35)
Prior treatments, n (%)	
Hypomethylating agents	13 (76)
Lenalidomide	2 (12)
Others*	8 (47)
Untreated	4 (24)
Time since Dx (mos), mean [SD]	16.8 [14.5]

Data cutoff: April 15, 2016

*Sorafenib (n=2 pts), vosaroxin (1), procrit (1), pracinostat (1), cytarabine + clofarabine (1), ruxolitinib (1), rigosertib (1)
Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group

Baseline Characteristics

Characteristic	MDS Patients N=17
IPSS risk status, n (%)	
Intermediate-1	5 (29)
Intermediate-2 / High	8 (47)
Missing	4 (24)
MDS cytogenetic risk, n (%)	
Good	8 (47)
Intermediate	4 (24)
Poor	1 (6)
Missing	4 (24)
IPSS-R risk status, n (%)	
Low	3 (18)
Intermediate	2 (12)
High / Very High	8 (47)
Missing	4 (24)
Hematology, median (min, max)	
ANC (10^9/L)	0.7 (0.2, 32.1)
Platelets (10^9/L)	71 (19, 246)
WBC (10^9/L)	2.1 (0.5, 44.4)
Hgb (g/dL)	8.9 (7.3, 12.2)

Data cutoff: April 15, 2016

Grade 3-4 Treatment-emergent Adverse Events

- Grade 3-4 TEAEs (any cause), n=14 (82%)

Grade 3-4 TEAEs occurring in ≥2 patients	
Preferred Term	MDS Patients (n=17) n (%)
Hyperbilirubinemia*	5 (30)
Pneumonia	4 (24)
Thrombocytopenia	4 (24)
Anemia	3 (18)
Hypokalemia	3 (18)
Dyspnea	2 (12)
Tumor lysis syndrome	2 (12)

*Unconjugated. Includes hyperbilirubinemia and blood bilirubin increased

- Nine grade 3-4 drug-related TEAEs reported for 6 patients
- Enasidenib-related serious TEAEs, n=4 (tumor lysis syndrome [2], blood bilirubin increased, transaminitis)
- No treatment-related deaths

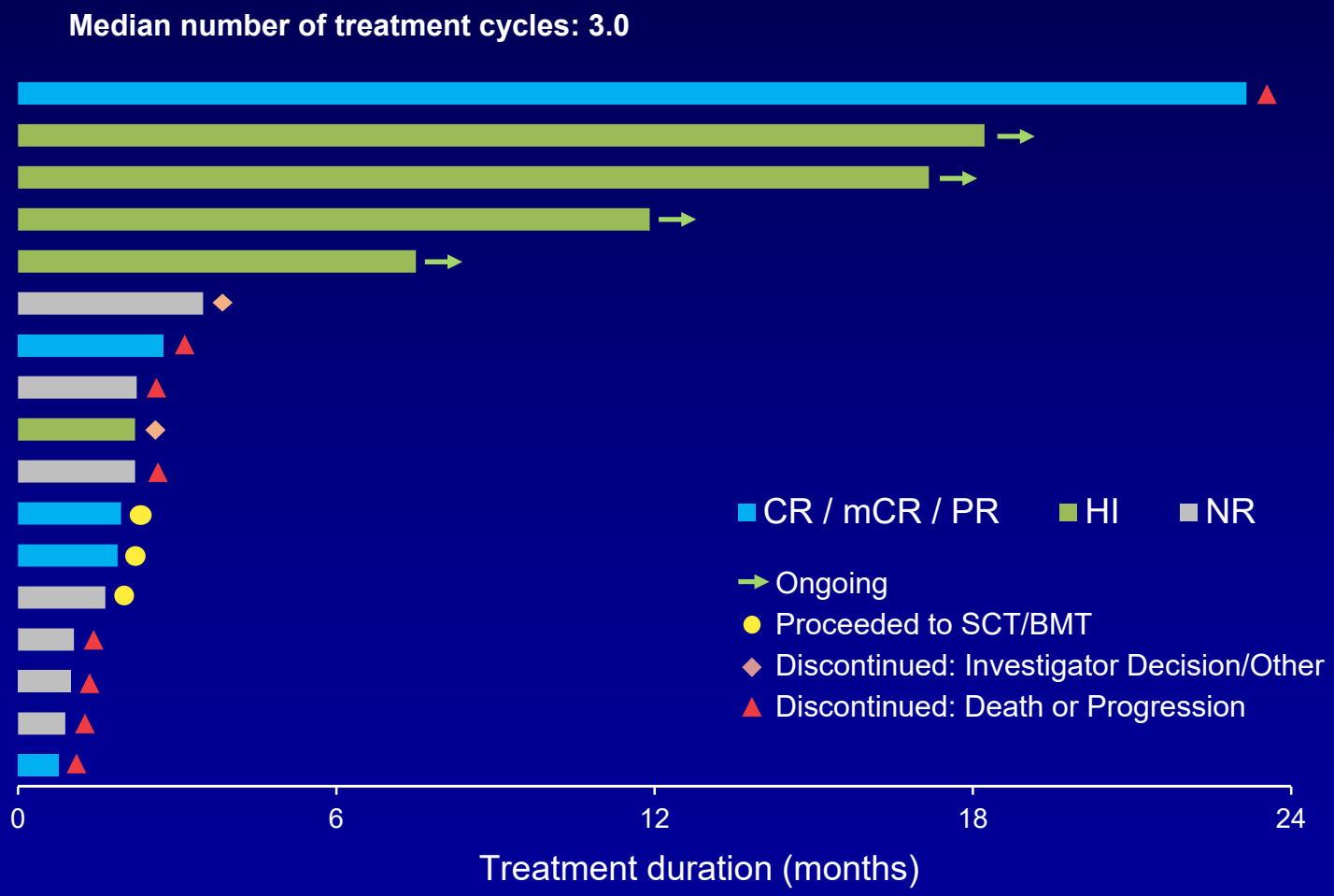
Response

	MDS Patients (N=17) n (%)
Overall response rate (CR + PR + mCR + HI)	**10/17 (59)**
Best Response	
Complete remission*	1/11 (9)
Partial remission*	1/11 (9)
Marrow CR*	3/11 (27)
Any hematologic improvement (HI)†	5/17 (29)
HI-E	3/15 (20)
HI-P	4/12 (33)
HI-N	4/10 (40)

*Investigator-assessed; evaluable pts had ≥5% bone marrow blasts at baseline
†HI was programmatically adjudicated per IWG 2006 criteria for MDS; denominators reflect eligibility
CR, complete remission; PR, partial remission; mCR, marrow CR; HI, hematologic improvement

- Of 13 patients who had received prior HMA therapy, 7 (54%) had a response with enasidenib
- Of patients who attained HI, 2 had trilineage and 2 had bilineage improvement
- Median time to response was 21 days (range 10-87)

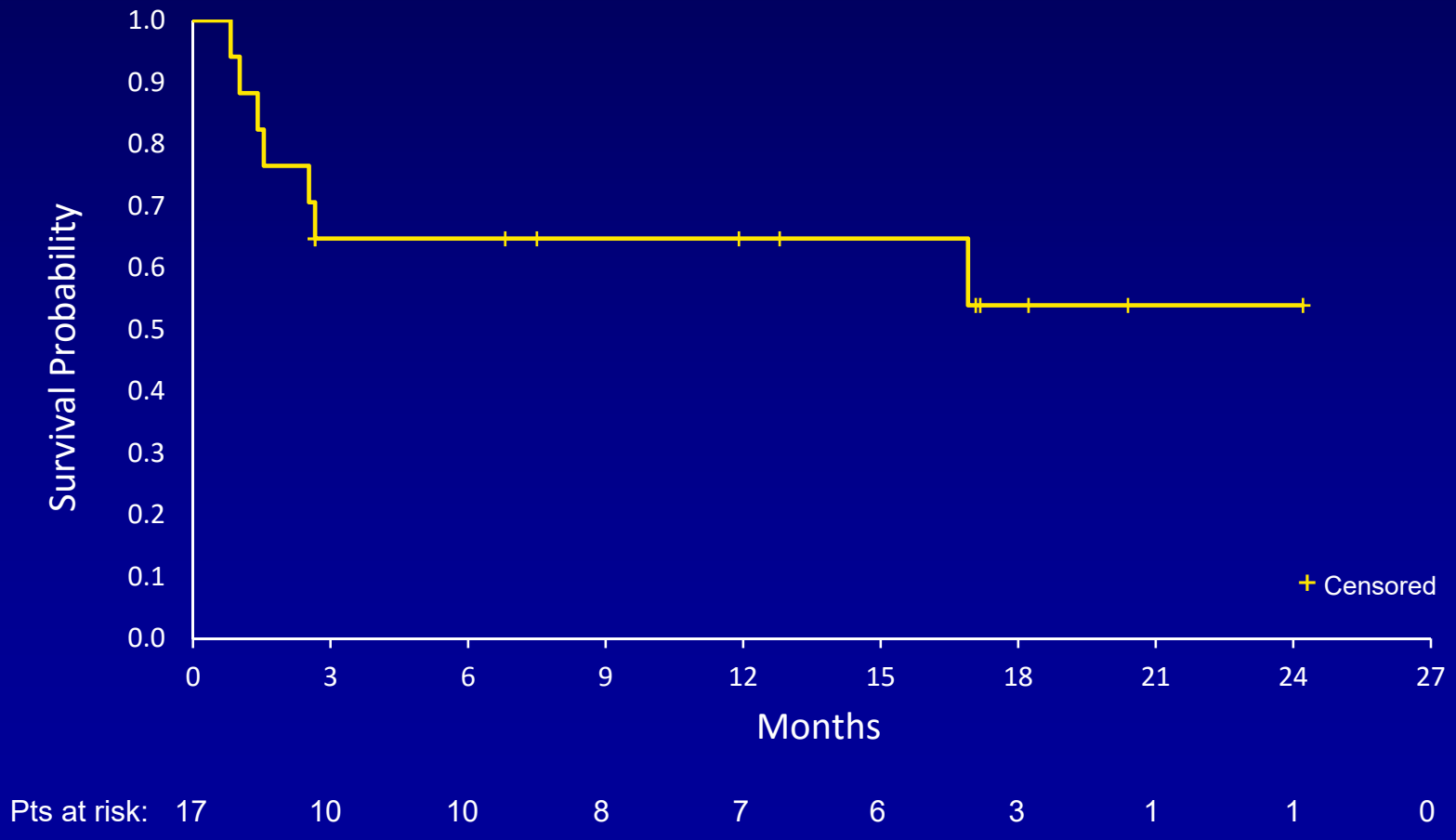
Treatment Durations and Study Outcomes



CR, complete remission; HI, hematologic improvement; mCR, marrow CR; NR, no response; PR, partial remission; SCT/BMT, stem cell transplant / bone marrow transplant

Overall Survival

- At median follow-up of 7.5 months, median OS was not reached



Co-occurring Mutations

	CR	mCR			PR	HI			NR					Total
IPSS risk	NA	NA	Int-2	Int-2	Int-2	Int-1	Int-1	Int-1	Int-2	Int-2	Int-2	Int-1	NA	
SRSF2	■	■	■		■	■	■		■					7
ASXL1		■	■		■	■	■		■		■			6
KRAS	■								■	■				3
TP53									■	■				2
SETBP1										■		■		2
MPL	■					■								2
U2AF1										■	■			1
DNMT3A				■										1
CSF3R					■									1
FAT3						■								1
CBL						■								1
TCF3									■					1
STAG2									■					1
NRAS												■		1
JAK2												■		1
BRAF												■		1

■ Responders

■ Non-responders

Molecular profiling performed with FoundationOne® Heme Panel, using next-generation sequencing (NGS)
Mutational data available for 13 of 17 MDS patients
CR, complete remission; HI, hematologic improvement; mCR, marrow CR; NR, no response; PR, partial remission

- This small patient cohort prevents definitive conclusions regarding potential correlations between response and co-mutations

Conclusions

- Daily Tx with oral enasidenib monotherapy was well tolerated and induced responses in the majority of these MDS patients with m*IDH2*, most of whom had higher-risk disease, and three-fourths of whom had failed prior HMA Tx
- Notably, more than one-half of MDS patients (7/13) who had failed prior HMA Tx had a response with enasidenib monotherapy
- Only 2 patients experienced disease progression during Tx
- Mutational testing is rapidly becoming essential to diagnosis and prognostication in MDS, and assessment of *IDH2* mutations can identify MDS patients who may benefit from targeted Tx with enasidenib

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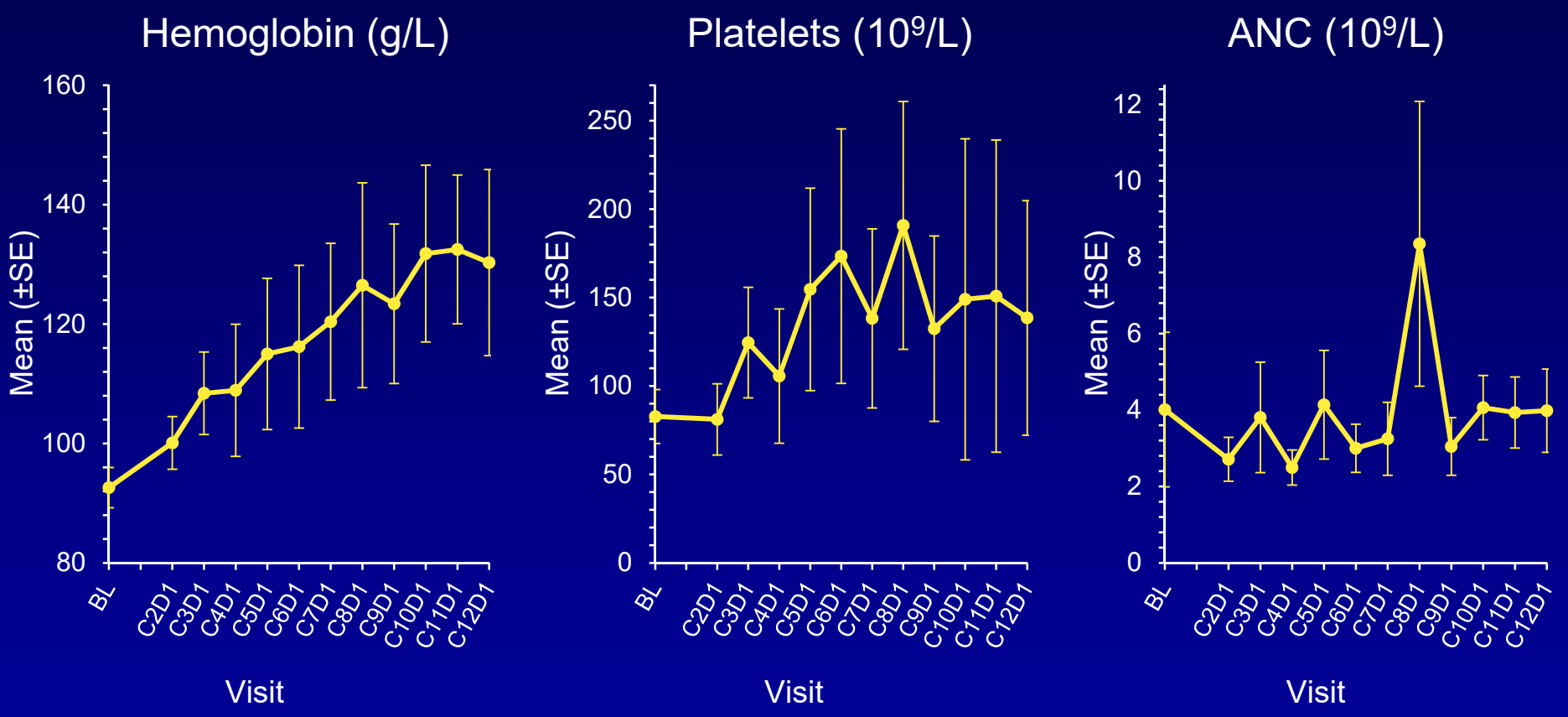
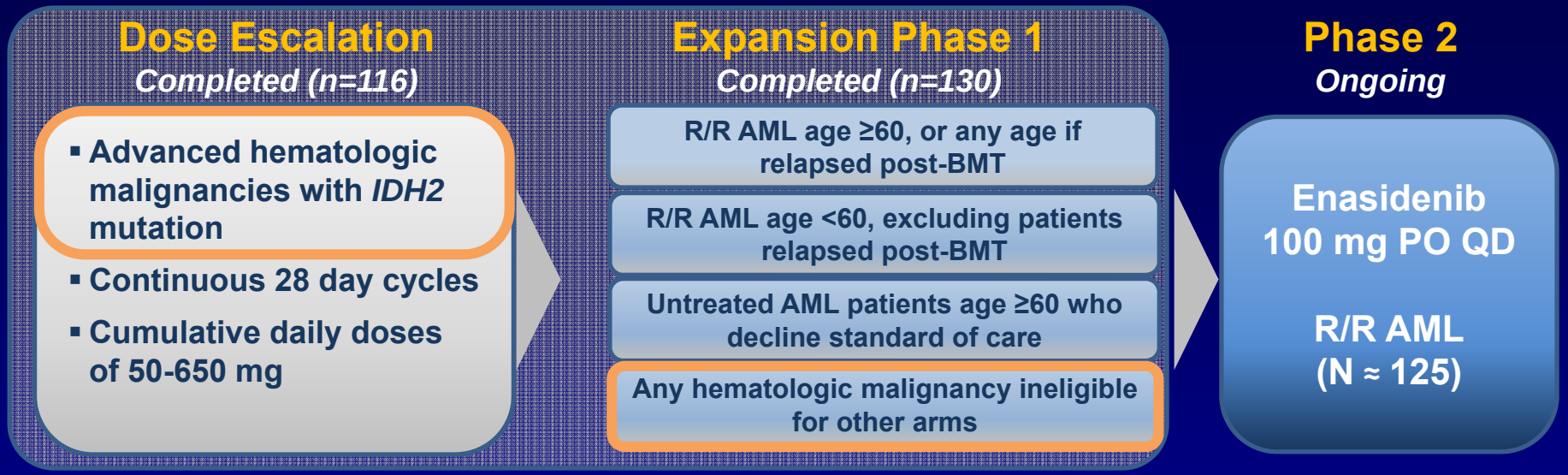
Backup slides

Hematologic Changes



Phase 1/2 Study Design



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