



Phase 1 Dose-Escalation/Expansion Study of the p38/Tie2 Inhibitor ARRY-614 in Patients with IPSS Low/Int-1 Risk Myelodysplastic Syndromes

ASH 2011, Abstract 118

R. Komrokji¹, A. List¹, H. J. Khoury², J. Lancet¹, E. Jabbour³,
C. Foudray³, S. Winski⁴, S. Bell⁴, S. Rush⁴, L. Maloney⁴,
M. Ptaszynski⁴, H. Kantarjian³, G. Garcia-Manero³

¹H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

²Winship Cancer Institute of Emory University, Atlanta, GA

³University of Texas M.D. Anderson Cancer Center, Houston, TX

⁴Array BioPharma Inc., Boulder, CO

Disclosures

- No conflict of interest to disclose

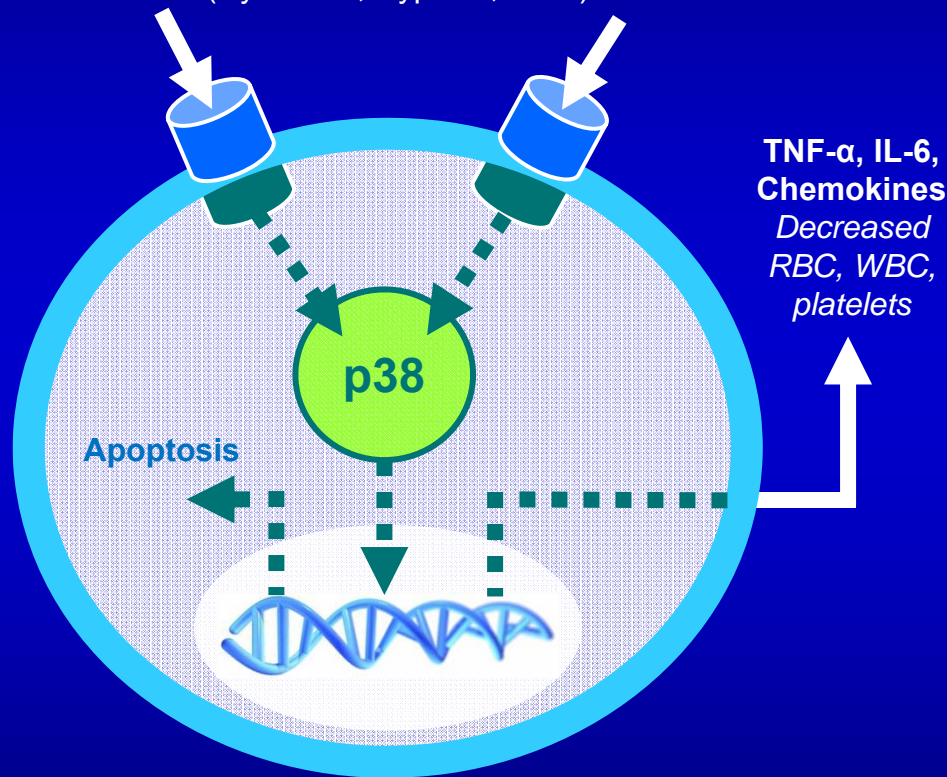
Background: Lower Risk MDS

- The majority of patients with myelodysplastic syndromes (MDS) present with lower risk disease
 - International Prognostic Scoring System (IPSS) score ≤ 1.0
- Treatment goal is hematologic improvement (HI) to alleviate symptomatic cytopenias and improve quality of life
 - Limited treatment options for anemia
 - Management of neutropenia and thrombocytopenia is a major unmet need
- No treatment options for patients for whom hypomethylating agents (HMAs) have failed

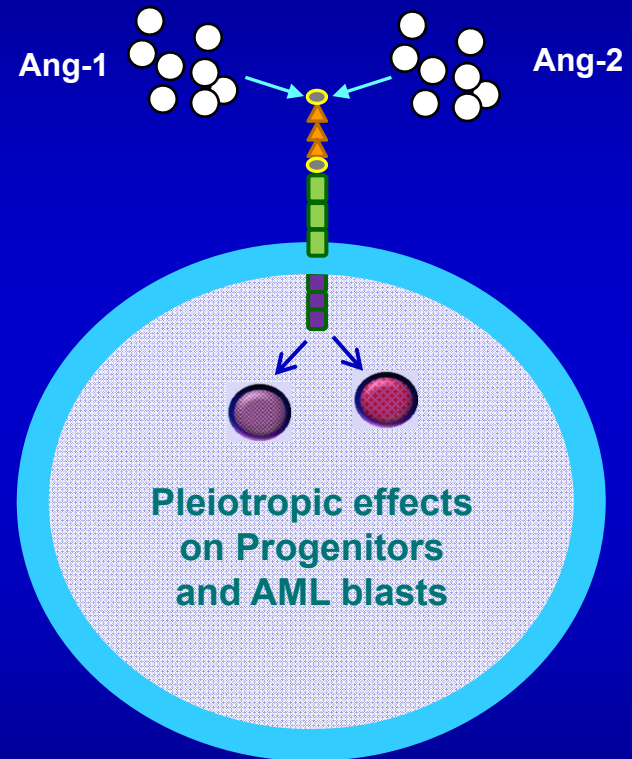
Dual Inhibition of p38 and Tie2 by ARRY-614 Blocks Myelosuppression in Bone Marrow

p38 MAPK in MDS

Stress/Inflammatory Stimuli
(Cytokines, Hypoxia, FasL)



Tie2 in MDS – Emerging Target

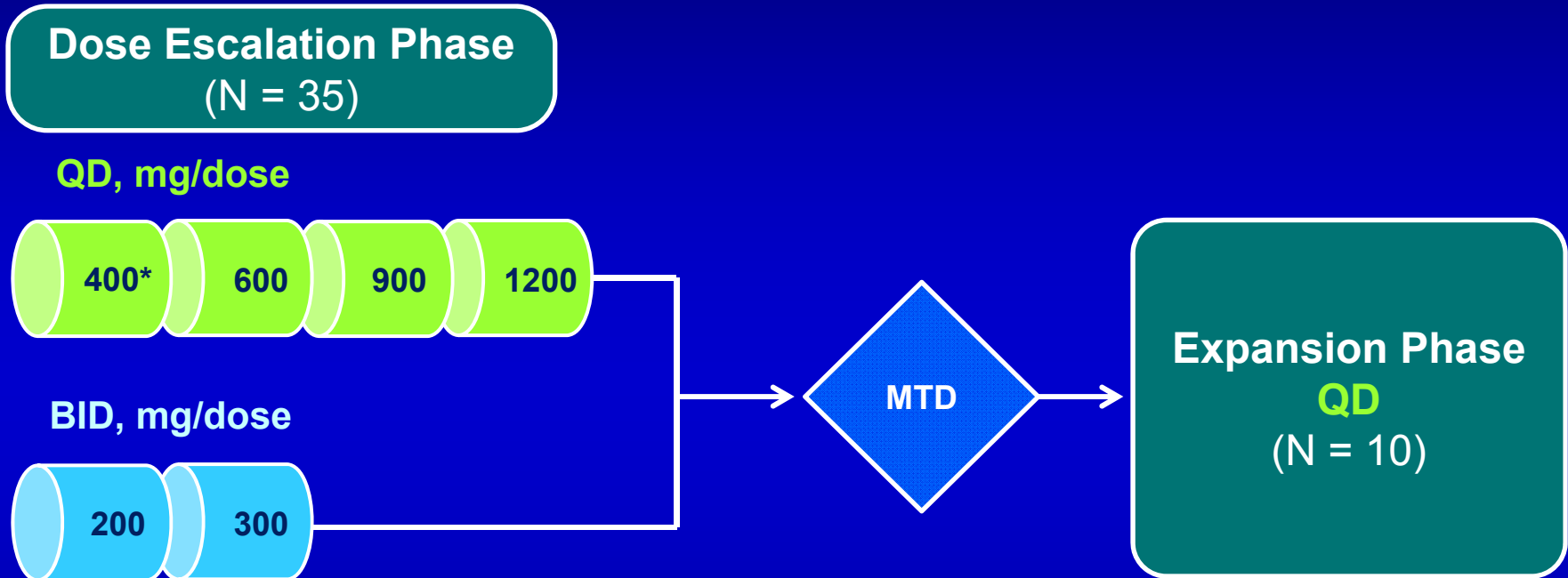


- Major regulator of the cellular pathways which sense stress (Cuadrado et al. Biochem. J. 2010. 429: 403.)
- Over-activated, leading to inappropriate production of myelosuppressive cytokines (Navas et al. Blood. 2006. 108: 4170.)

- Dysregulated, may be a survival factor for the AML blast (Keith et al. BJH. 2007. 137: 206.) (Wakabayashi et al. Hematol. J. 2004. 5: 353.)
- Increased signaling associated with poor prognosis (Cheng et al. BJC. 2011. 105: 975.)

ARRY-614 Phase 1 Study Design

Phase 1, open-label, dose-escalation study in MDS patients



*Both fasted and fed cohorts evaluated

- Standard 3+3 design
- 2 dosing schedules (fasted)
- A cycle is continuous oral dosing for 28 days

Study Objectives

- Primary
 - Determine safety, tolerability and MTD
 - Characterize PK
- Secondary
 - Evaluate response per IWG 2006
 - Explore PD profile

Key Eligibility Criteria

- Inclusion/Exclusion Criteria
 - IPSS Low/Int-1 Risk MDS at screening
 - No limit on number of prior therapies or cytopenias
 - ECOG PS 0-2
 - No concurrent MDS treatments allowed except supportive therapies (transfusions or growth factors)
- Additional Criteria During Expansion Phase
 - RBC transfusion dependent (IWG 2006)
 - Hematopoietic growth factors not allowed in Cycle 1

Baseline Characteristics (1)

Characteristic	N = 45
Median Age, years (range)	72 (47 – 84)
Median years since diagnosis (range)	3.3 (0.2 – 16.3)
Male / Female	39 / 6
	N = 45
	n (%)
IPSS Risk at screening	
Low	11 (24)
Intermediate-1	34 (76)
ECOG PS	
0	11 (24)
1	28 (62)
2	6 (13)

For all analyses, data up to 01 Aug 2011

Baseline Characteristics (2)

Characteristic	N = 45 n (%)
% Blasts¹	
≤ 5	40 (89)
> 5	4 (9)
Cytogenetics	
Normal	26 (58)
Abnormal	19 (42)
Transfusions	
Any RBC	36 (80)
Transfusion Dependent IWG 2006 ²	28 (62)
Platelets	7 (16)

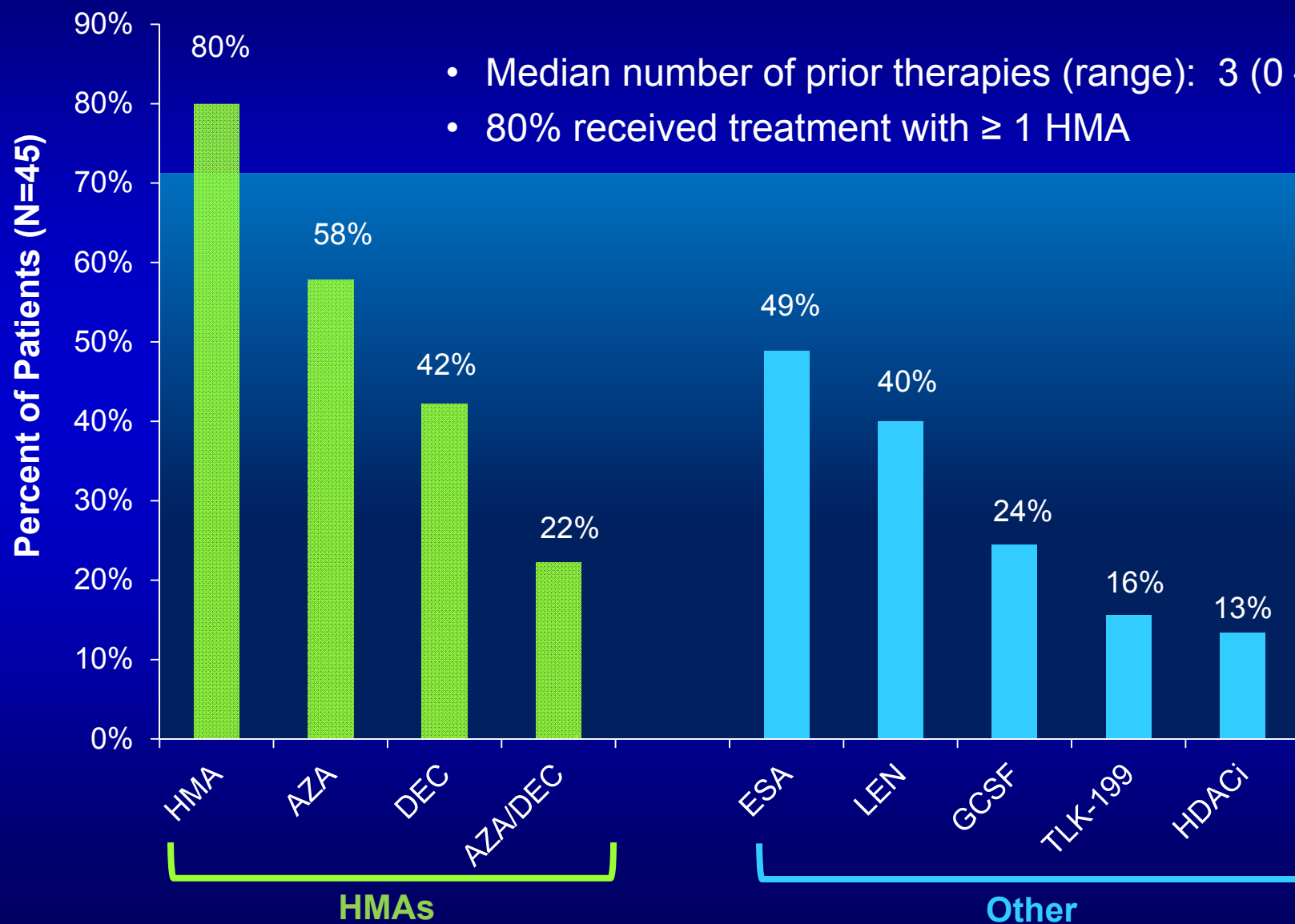
¹ One patient did not have results

² ≥ 4 RBC units within 8 weeks of first dose

Baseline Characteristics (3)

Lineage		N = 45
		n (%)
Erythroid (Hgb; g/dL)	< 11	41 (91)
Neutrophils ($\times 10^9/L$)	0.5 – 1.0	9 (20)
	≤ 0.5	7 (16)
Platelets ($\times 10^9/L$)	50 – 100	10 (22)
	20 – 50	9 (20)
	< 20	6 (13)
Number of Cytopenias	0 – 1	20 (45)
	2 – 3	25 (55)

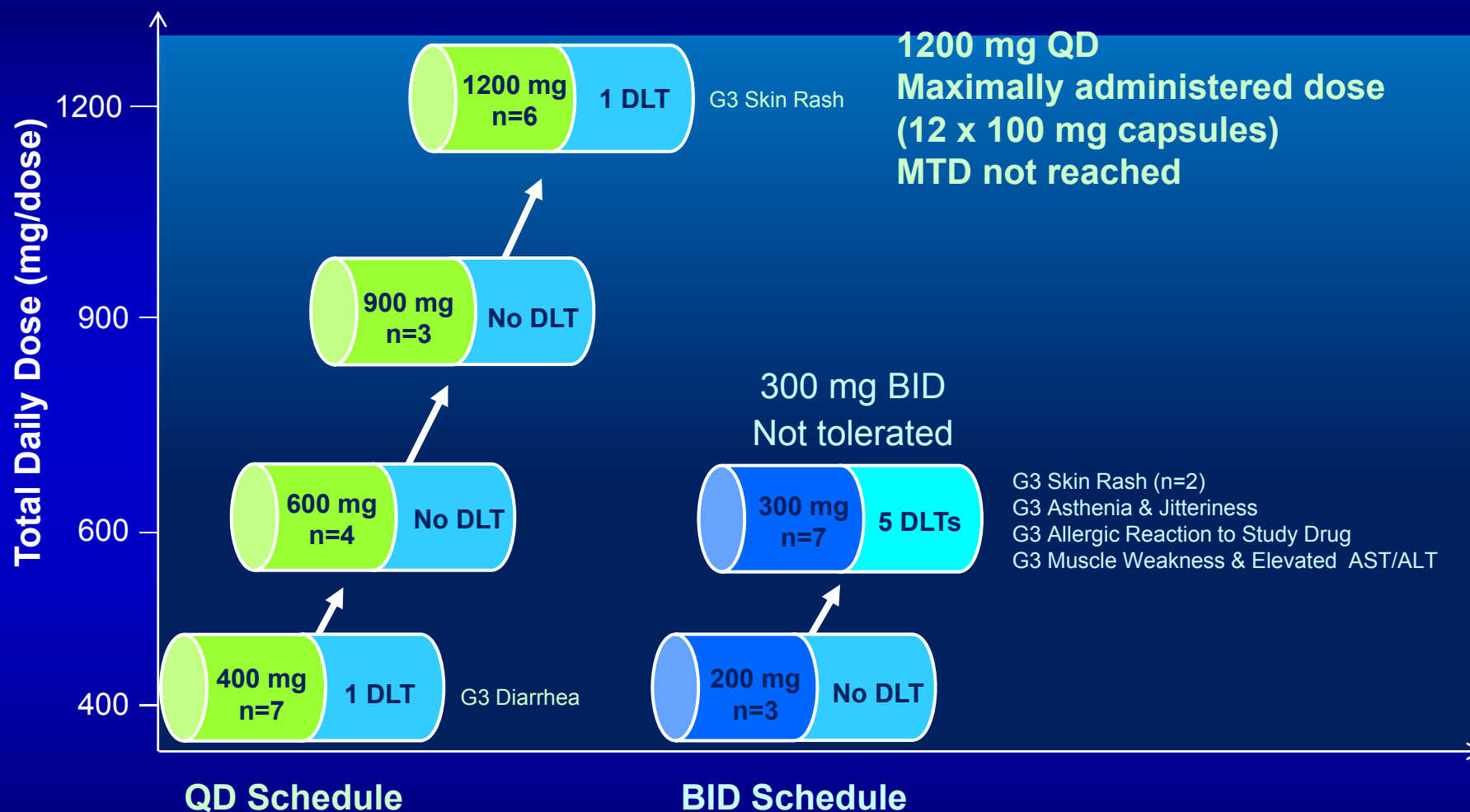
Prior Therapies



Treatment Summary

- Enrollment complete, 7 patients ongoing
- Median duration of treatment (range): 20 weeks (1 – 80)

Dose-Limiting Toxicities



DLT Criteria (First Cycle):

- Grade 3/4 nausea, vomiting, or diarrhea despite maximum supportive care
- Any other Gr 3/4 non-hematologic AE
- Neutrophils: Gr 4 (if Gr 0/1 at baseline [BL]) OR $< 0.1 \times 10^9/L$ and decrease of $> 75%$ from BL (if Gr ≥ 2 at BL) for > 7 days
- Platelets: Gr 4 (if Gr 0/1 at BL) OR $< 10 \times 10^9/L$ for > 7 days and decrease of $> 75%$ from BL (if Gr ≥ 2 at BL)
- Interruption of dosing or delay of starting C2 beyond Day 56

Treatment-Related AEs ($\geq 5\%$)

Adverse Event	Cohort (mg/dose)										
	200 – 300 BID (n=10)		400 – 600 ¹ QD (n=16)		900 QD (n=3)		1200 QD (n=16)		Total (N=45)		All (%)
CTC Grade	1/2	3	1/2	3	1/2	3	1/2	3	1/2	3	
Rash ²	2	2	3	-	-	1	4	2	9	5	14 (31)
Diarrhea	2	-	2	1	-	-	2	2	6	3	9 (20)
Dry skin	-	-	3	-	1	-	2	-	6	-	6 (13)
Anorexia	2	-	2	-	1	-	-	-	5	-	5 (11)
Fatigue	-	1	-	-	-	-	4	-	4	1	5 (11)
Pruritus	1	-	1	-	1	-	1	-	4	-	4 (9)
ALT increased	1	-	-	-	-	-	2	-	3	-	3 (7)

¹ Includes 5 patients who were treated in the 400 mg QD fed cohort

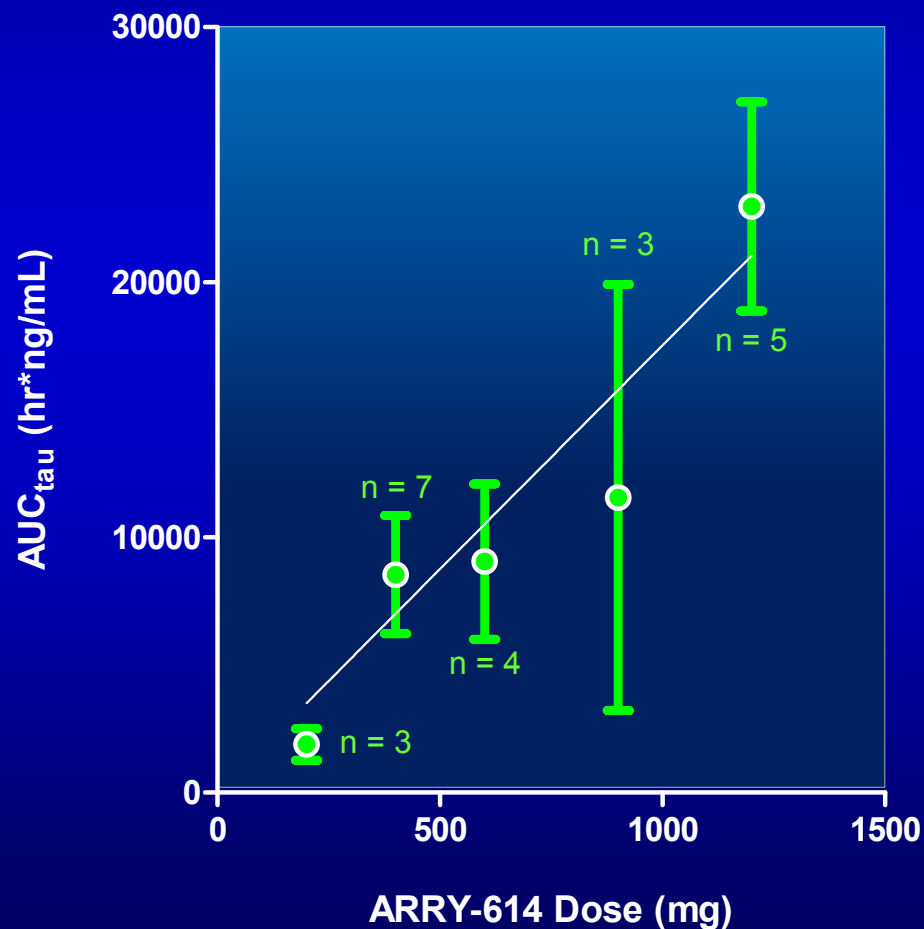
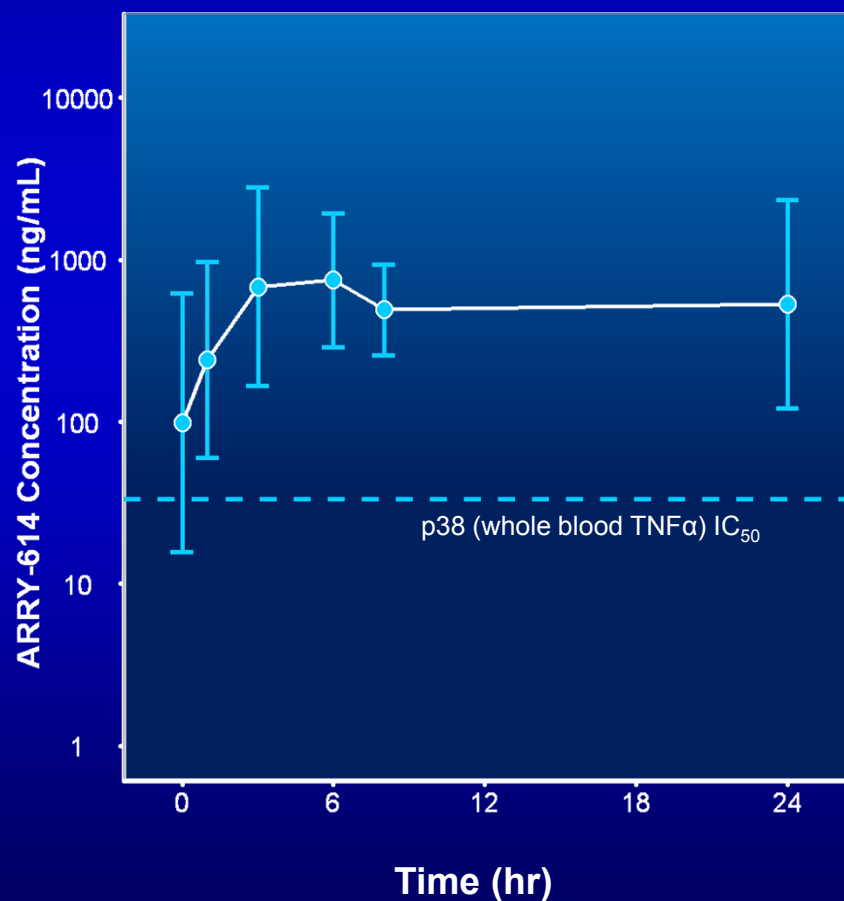
² Includes preferred terms of acne, dermatitis acneiform, maculopapular rash, pruritic rash, rash, skin irritation, and skin exfoliation

- 8/45 (18%) patients had dose reductions due to treatment-related AEs
- 8/45 (18%) patients came off study due to treatment-related AEs

ARRY-614 Pharmacokinetics

1200 mg QD provides
24 hour target coverage $>IC_{50}$

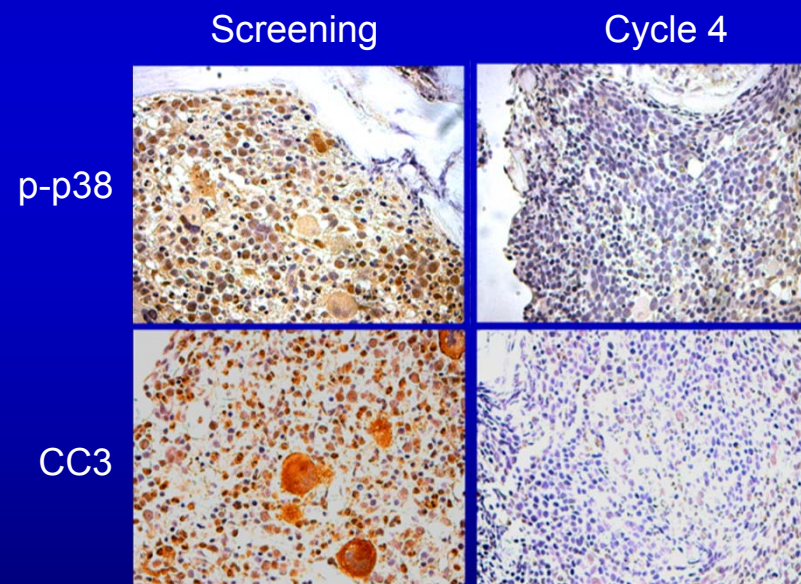
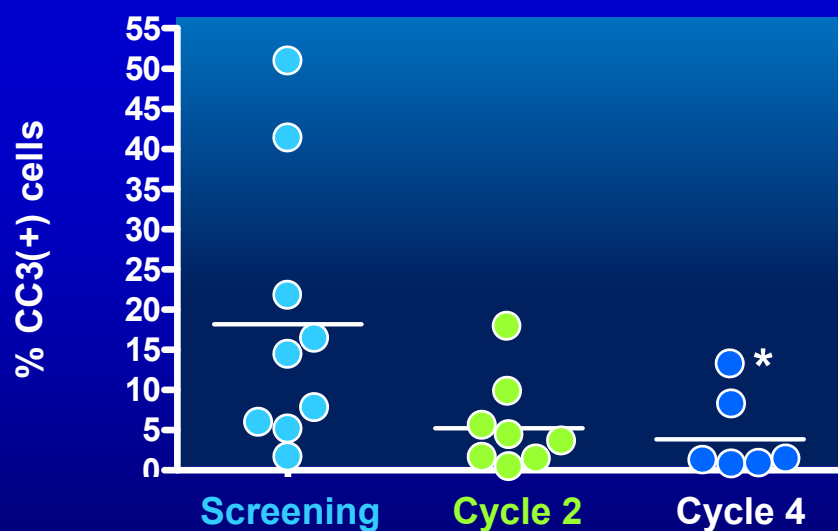
Exposure increases
with increasing dose



Reduced Apoptosis in Bone Marrow

- phospho-p38 observed at baseline and decreased following treatment
- Increased apoptosis at baseline which decreases by >75% over 4 months

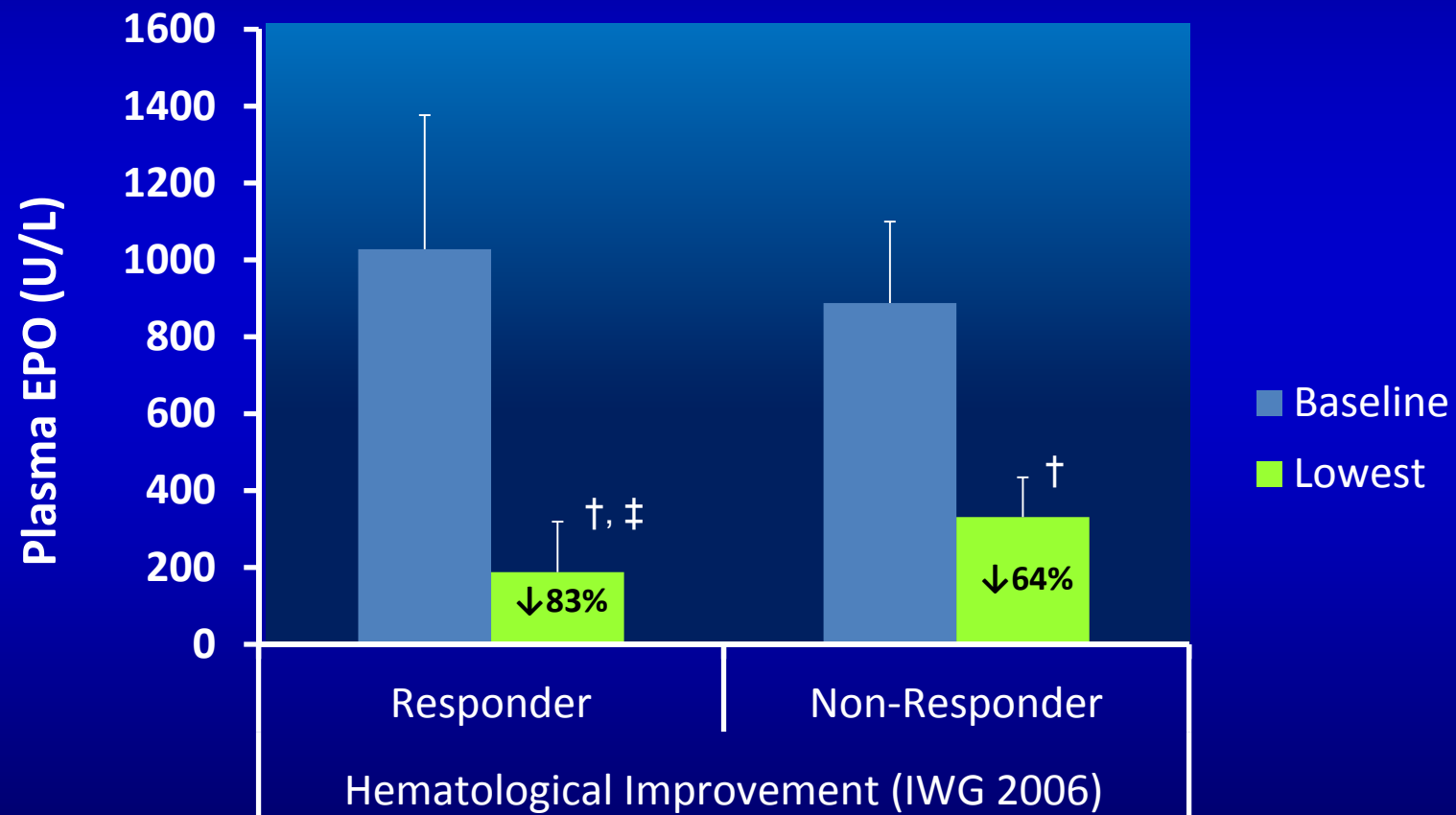
Presence of cleaved caspase 3 (CC3) is indicative of apoptosis



* Cycle 4 statistically different from screening (ANOVA, Dunn's multiple comparison test post hoc); n = 6 – 9

Disease-Associated EPO Decreased

- Plasma EPO decreases in patients regardless of reaching HI



† Lowest statistically different from baseline (Wilcoxon Signed Rank test)

‡ Change in responder statistically different from non-responder (Mann Whitney U test)

HI Responses

- Overall, durable HI observed in 13 of 44 evaluable patients (30%)
 - 5 bi-lineage responses

N patients	HI-E	HI-P	HI-N	Total HI
	n = 41	n = 25	n = 16	N = 44
Total (%)	8 (20)	5 (20)	5 (31)	13 (30)
Median duration, weeks (range)	32 (9-80)	16 (8-67)	21 (14-26)	
5 of 7 platelet transfusion-dependent patients became transfusion independent (TI) for a median duration of 20 weeks (range 15 – 31)				
3 of 28 RBC transfusion-dependent patients became TI for a median duration of 21 weeks (range 11 – 72)				

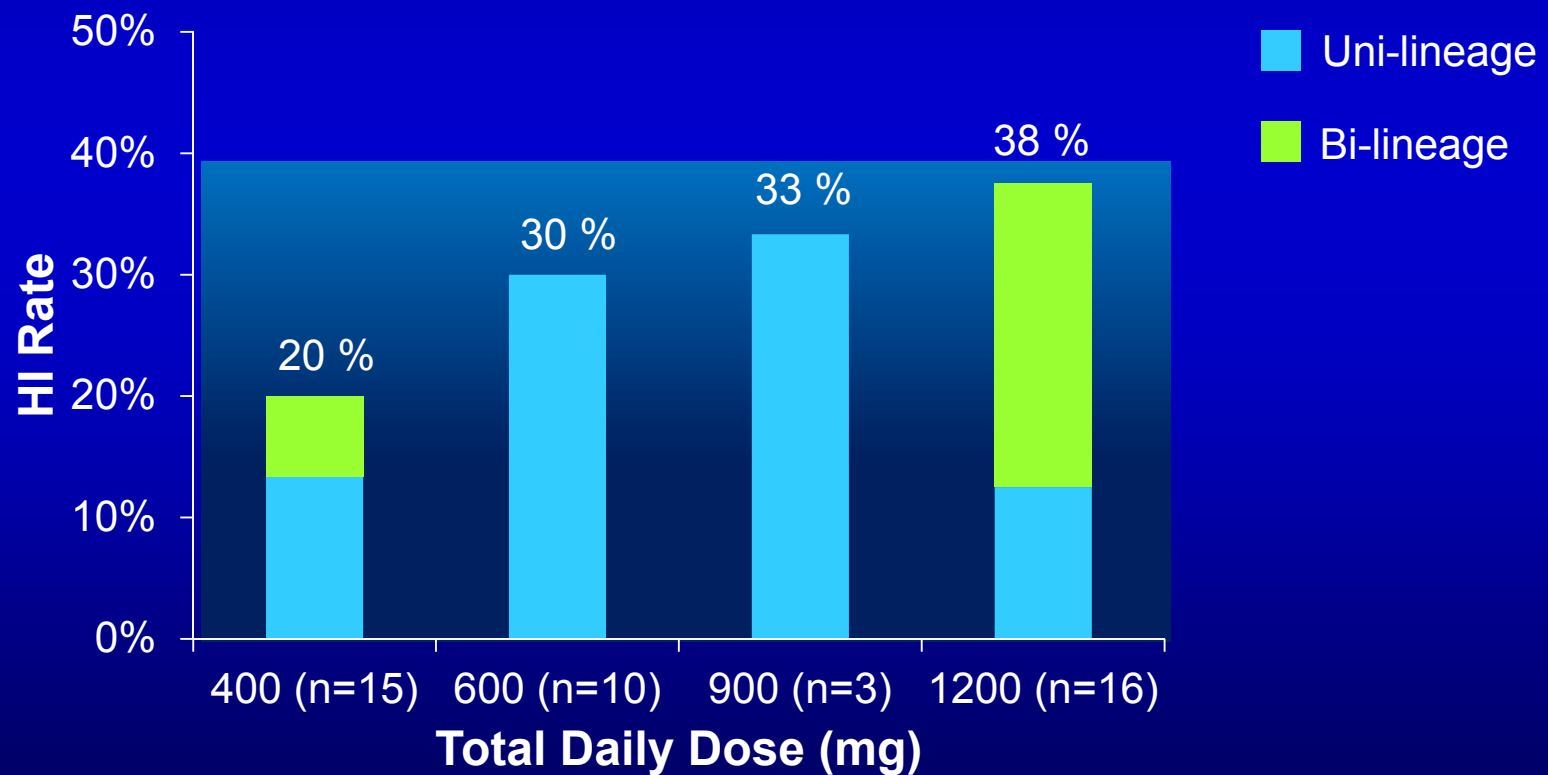
- Responder (n = 13) baseline characteristics
 - **All ≥ 1 prior HMA**
 - 12 IPSS Int-1
 - 11 2-3 cytopenias
 - 6 abnormal cytogenetics¹

¹Includes one each: Pseudodiploid Clone, T(1:8)(Q21;Q22), Del (7), Pseudo Hyperdiploid Clone del (20q), del 5q, and Trisomy 8

Trend for Increased HI by Dose

IWG 2006 HI by Total Daily Dose

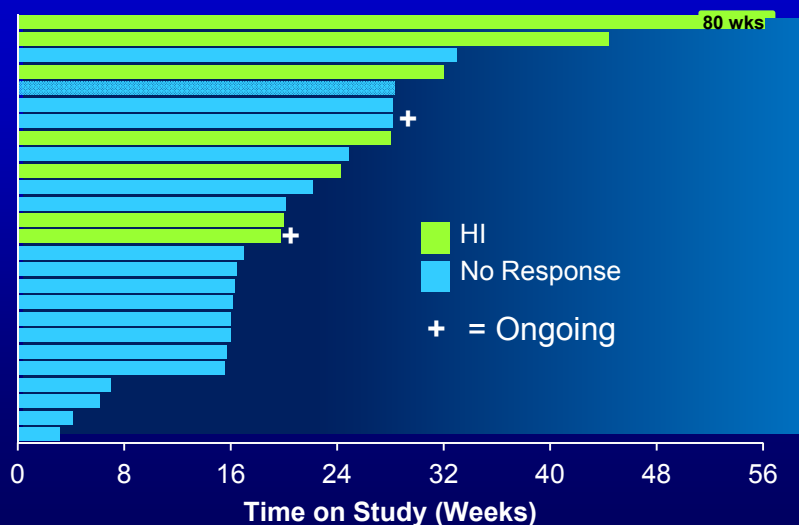
- 38% HI at highest dose (1200 mg daily)
 - 67% bi-lineage responses



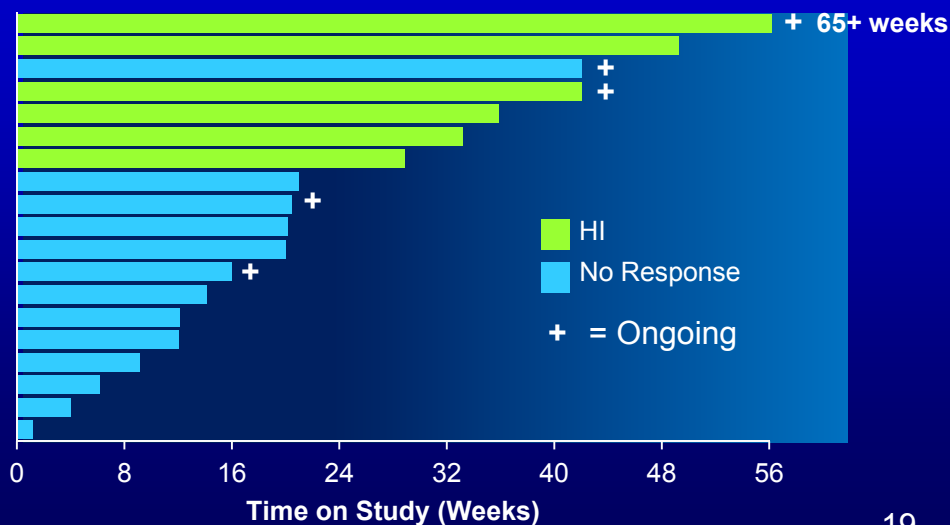
Activity Across MDACC Risk Groups

- MDACC Risk Scoring System (Kantarjian HM, et al. Cancer 2008)
 - Refines the prognostic values of IPSS
 - Dynamic model for evaluating patients throughout the course of their disease
- Baseline characteristics used to retrospectively calculate MDACC score
 - 19 lower risk patients per IPSS would have been at higher risk per MDACC score at study entry; 6/19 achieved HI
- HI and time on study was similar between MDACC higher and lower risk

MDACC Lower Risk (Low/Int-1) n = 26



MDACC Higher Risk (Int-2/High) n = 19



ARRY-614 MDS Summary

- QD dosing schedule well tolerated at doses up to 1200 mg
 - MTD not reached
 - Optimized formulation in clinical trials
- Decreases in phospho-p38 and apoptosis consistent with on target effect
- Multi-lineage HI observed in patients for whom HMAs had failed
 - 30% HI overall
 - 38% HI at 1200 mg QD; 67% multi-lineage
- Encouraging results in this heavily pre-treated population warrants additional investigation

Acknowledgments

Patients and their families

- Moffitt Cancer Center
 - Alan List
 - Jeffrey Lancet
 - Heather Orr
 - Debra VanDonkelaar
- Emory
 - H. Jean Khoury
 - Andrena Lawrence
 - Mersiha Torlak
- MDACC
 - Guillermo Garcia-Manero
 - Hagop Kantarjian
 - Maria Cielo Foudray
 - Elias Jabbour
 - Jin Jin
 - Little Pullock
- Array BioPharma Inc.

All staff and personnel who helped on the study

