Phase I Trial of Bortezomib and Clofarabine in Refractory MDS, lymphomas, or solid tumors

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CTEP protocol 9762

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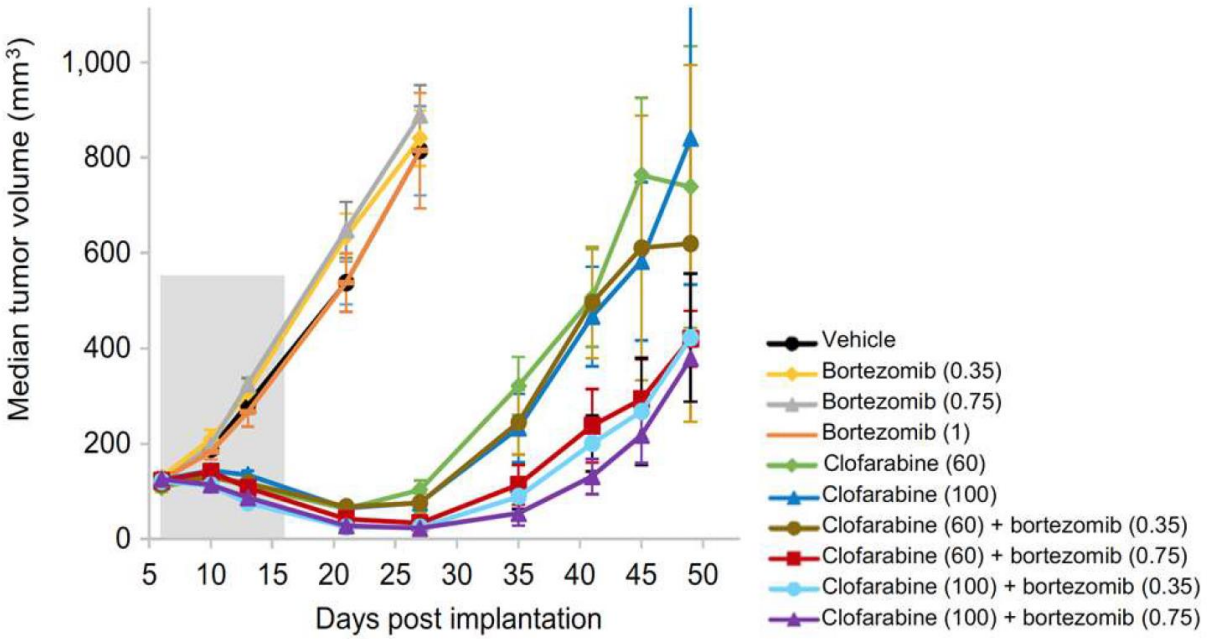
Introduction

- Use of known agents for new indications to save time and financial costs in drug development
- Bortezomib (proteasome inhibitor) is FDA approved in MM, mantle cell lymphoma [Drugs@FDA]
- Clofarabine (purine nucleoside analog) is FDA approved in pediatric relapsed/refractory ALL [Drugs@FDA]

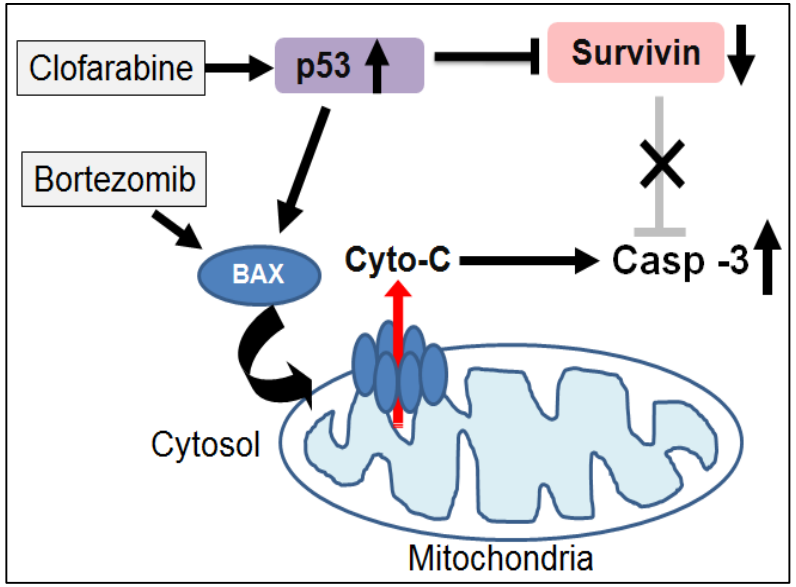
Rationale: pre-clinical model

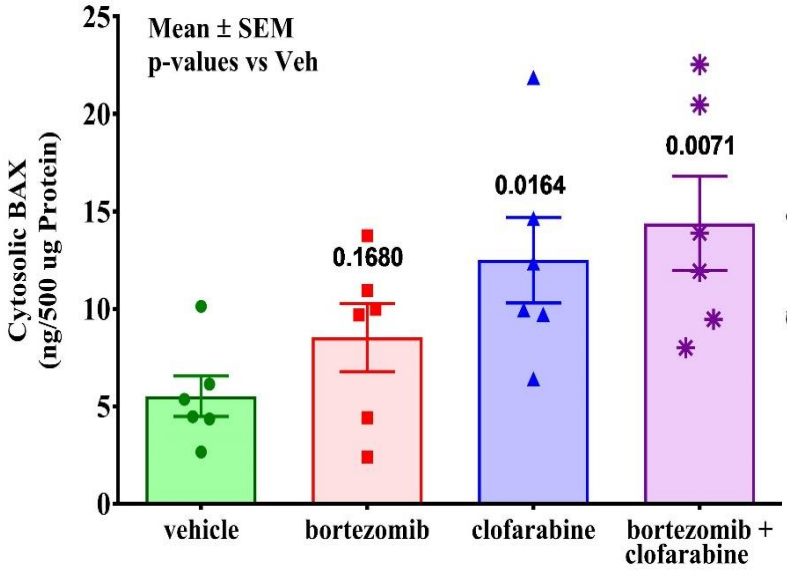
- NCI-ALMANAC (A Large Matrix of Anti-Neoplastic Agent Combination) study
- 5,000 pairs of FDA-approved cancer drugs; 2.8 million combinations tested
- NCI-60 human cancer cell lines & Patient Derived Xenograft (PDX) models
- 10 pairs of drugs identified with greater than additive activity

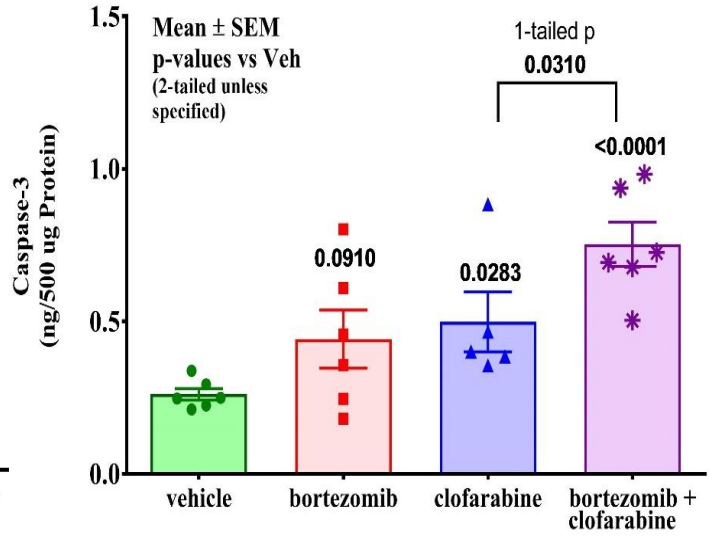


HCT-116 colon cancer xenograft model
Holbeck S et al, *Can Res* 2017

Hypothesized Mechanism of Action

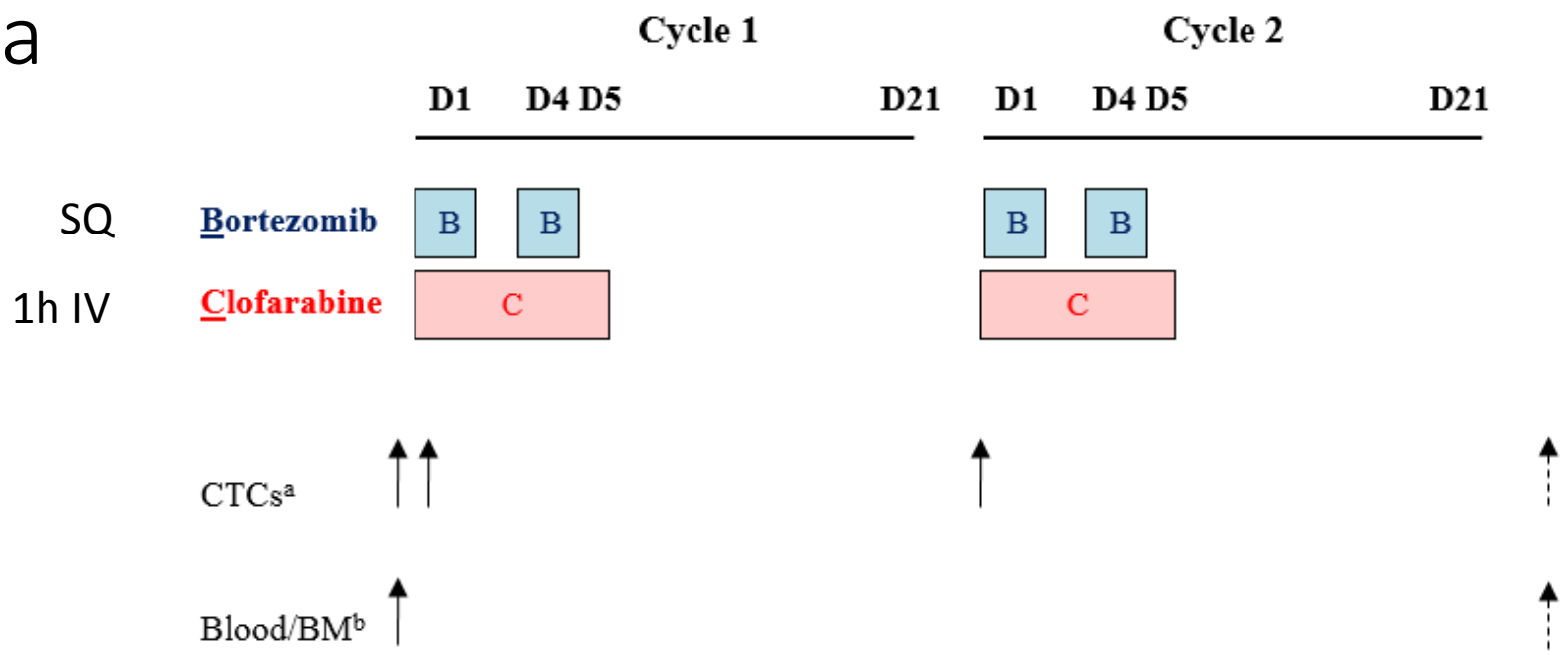






- Bortezomib can lead to mitochondrial apoptosis by increasing apoptosis promoter protein BAX, increasing downstream apoptosis coordination enzyme caspase-3 [Liu et al, Blood, 2008]
- Bortezomib resistance: inability to stabilize/accumulate BAX [Sayers et al, Blood, 2003]
- Clofarabine can upregulate p53, which can activate BAX [Rahmati et al, Adv Pharm Bulletin, 2015; Chuipuk et al, Science, 2004]
- Drug-pair led to higher BAX and a statistically significant increase in cleaved caspase 3

Trial Schema



- **Pre-med:** Hydrocortisone 100mg/m2 for cytokine release PPX, D1-3, with Ranitidine or PPI for PUD PPX
- **PPX:** Bactrim, Acyclovir
- **Clinic visit:** C1D1,8; then q 21 days
- **Labs:** C1D1,8,15; then q 21 days
- **Re-staging:** BM or CT every 2 cycles
- **Response criteria:** International Working Group (IWG) response criteria, RECIST 1.1, Lugano

Study Design

- Primary Objective: Safety, MTD, RP2D
- 3+3 dose-escalation design
- After two grade 2 hematologic toxicities observed in solid tumor, dose escalation split into two cohorts (MDS and solid tumors/lymphomas)

Dose Level	Bortezomib (SC) Days 1 and 4	Clofarabine (IV) administered over 1 hour Days 1-5
1	0.8 mg/m^2	1 mg/m^2
2	1 mg/m^2	1 mg/m^2
3	1 mg/m^2	1.5 mg/m^2
4	1.3 mg/m^2	1.5 mg/m^2
5	1.3 mg/m^2	2 mg/m^2

Key eligibility and exclusion criteria

Eligibility Criteria:

- ≥18 years old
- Progressed on standard therapy
- ECOG PS ≤2
- Washout period of 3 weeks

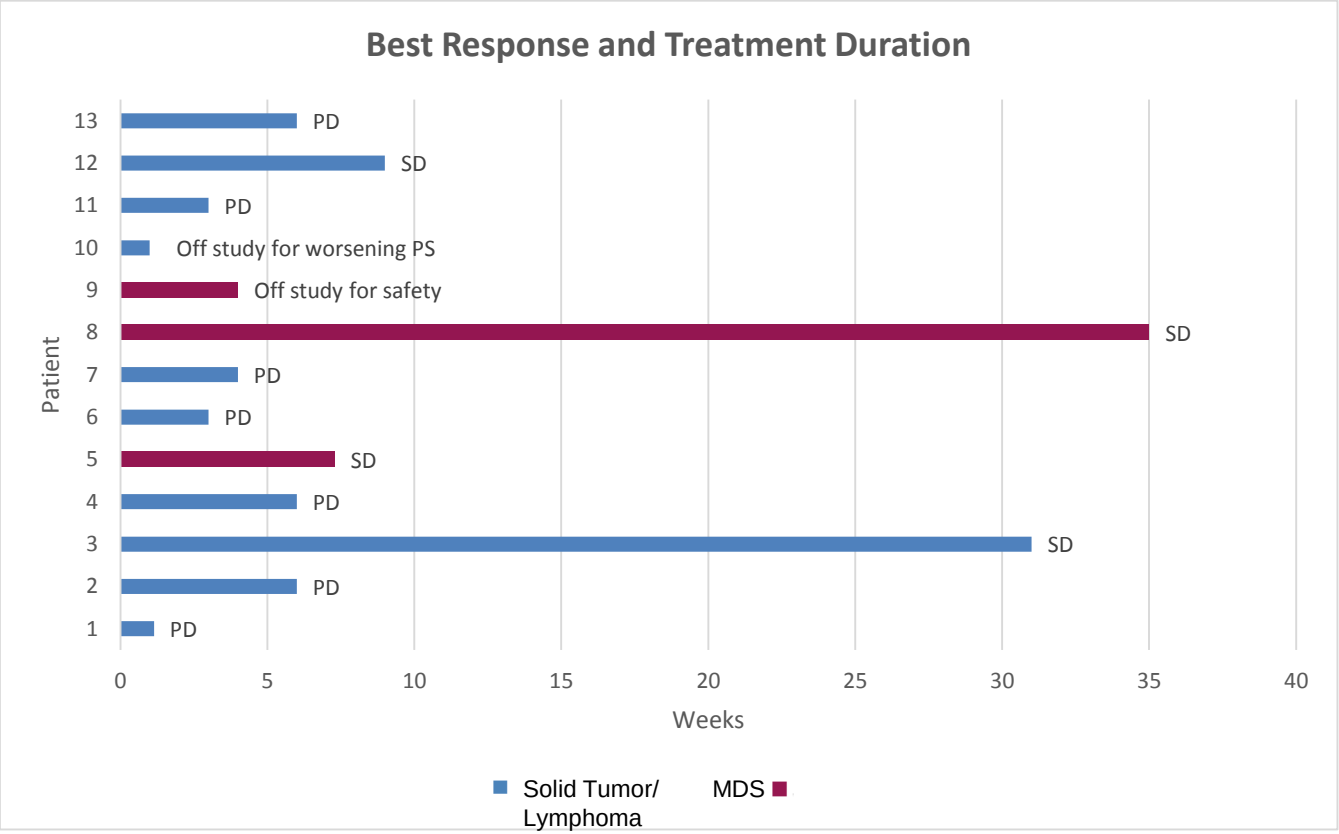
Exclusion Criteria:

- Previous clofarabine or bortezomib
- Uncontrolled intercurrent illness
- Neuropathy > Grade 2
- Active brain metastases, CNS disease
- Long QTc

Initial Results

Patient	Diagnosis	Dose Level
1	Colorectal adenocarcinoma	1
2	Leiomyosarcoma	1
3	Colorectal adenocarcinoma	1
4	Follicular lymphoma	2
5	MDS/paraganglioma	2
6	Colorectal adenocarcinoma	2
7	Colorectal adenocarcinoma	2
8	MDS	3
9	MDS	3
10	Pancreatic adenocarcinoma	3
11	Pancreatic adenocarcinoma	3
12	Renal Cell Carcinoma	3
13	Ampullary Carcinoma	3
14	*Cholangiocarcinoma*	*3*

Median age 62 (48-80)



PD (Progression of disease)
SD (Stable disease)
PS (performance status)

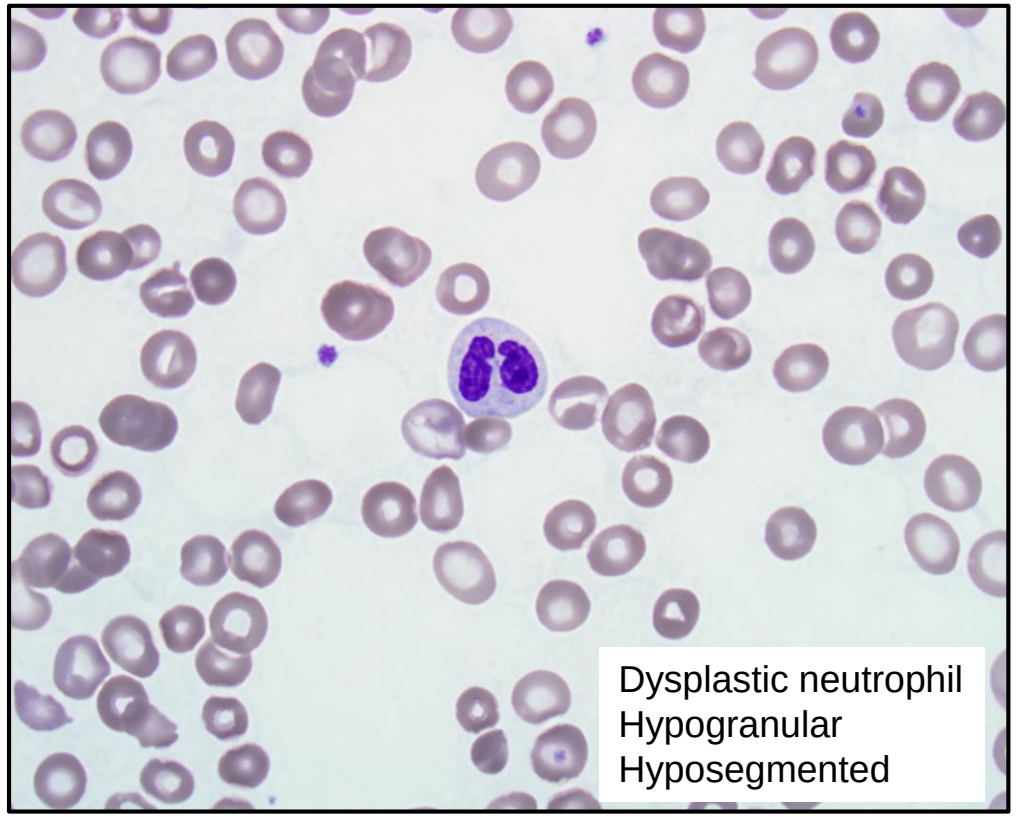
MDS patient on trial

- Hx MTX x 5 years, for vasculitis
- At age 77, new cytopenias
- BM 19% myeloblasts, dysgranulopoiesis, dysplastic megakaryocytes
- Cytogenetics/FISH normal
- MDS-excess blasts II
- R-IPSS 5.5 (Poor Risk)

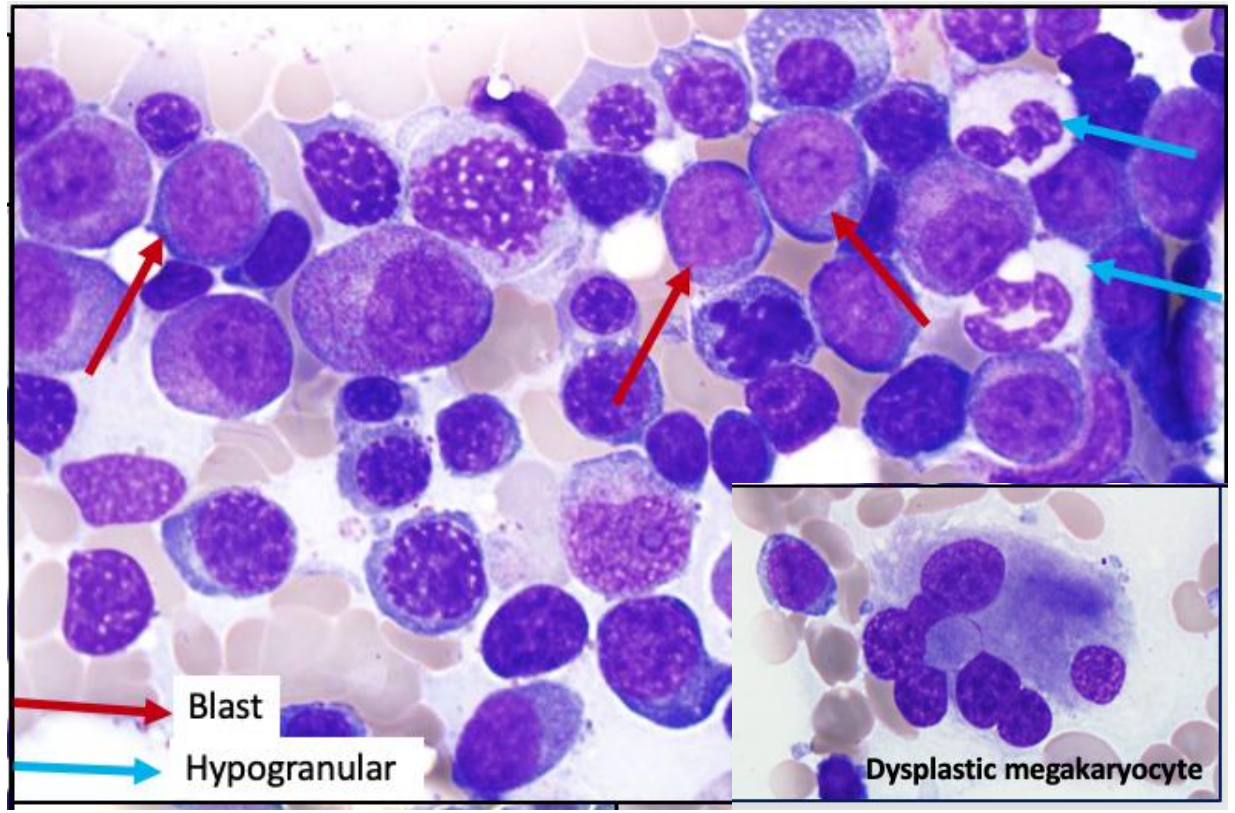
- Azacitidine x 7 cycles, but ANC near <200, Plt 15k, & needed pRBC transfusions
- Given co-morbidities, not candidate of allo-HSCT

Trial baseline peripheral smear & marrow

- Pancytopenia with rare blasts and dysplastic myeloid cells



- Cellular aspirate with dysplastic megakaryocytes, dysplastic myelopoiesis, increased blasts (~10%)



Slide adapted from DLM, NIH

Trial course

- Bortezomib/clofarabine x 8 months
- Continued pRBC every 2 months
- BM 25% myeloblasts
- NIH trial of Decitabine/Pembrolizumab x 3 months, with initial response
- Death at age 81, ~2 years after Azacitidine failure, and 4 years after initial diagnosis of poor risk, treatment related, MDS-EBII)

Adverse Events

AE possibly attributed to drug	Number of patients			
	Grade 1	Grade 2	Grade 3	Grade 4
HEMATOLOGIC:				
Anemia	2	2	2	
Lymphopenia	2		4	1
Neutropenia	1		1 (MDS)	
Thrombocytopenia	3	1		
INFECTION: Thrush	1			
CONSTITUTIONAL: Fatigue	2			
GASTROINTESTINAL:				
Nausea	4	2		
Constipation/Flatulence	2			
Hypoalbuminemia		1		
ELECTROLYTES	6	1		

*Grade 1 AE reported if over 1 patient had toxicity, or notable

Correlatives and future studies

- Evaluate mechanism of drug pair with:
  - Apoptosis multiplex assay to detect BAX, survivin, caspase 3
  - NGS for P53 status
  - Immunofluorescence assay to detect DNA double-stranded break marker γH2AX
  - Correlate drug-induced changes with clinical response

- Bone marrow at baseline and throughout study for MRD analysis, and molecular studies comparing de novo MDS to GATA2 deficiency-associated MDS

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Our Patients

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