A Phase 1 Study of ARRY-520 (Filanesib) with Bortezomib in Relapsed or Refractory Multiple Myeloma

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Abstract #

Thank You to the Patients and Their Families

Introduction

ARRY-520 is a targeted Kinesin Spindle Protein (KSP) inhibitor
KSP is a microtubule motor protein critical to the function of proliferating cells

KSP inhibition induces aberrant mitotic arrest and rapid cell death[1]
Novel mechanism of action for multiple myeloma (MM)
Preferentially acts on MCL-1 dependent cells including MM
Not expected to be cross-resistant with other drugs

ARRY-520 shows synergistic activity with bortezomib (BTZ) in MM xenograft models[2]

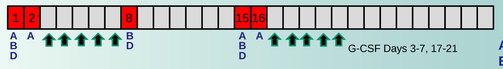
Study Design and Objectives

Primary Objective
- Determine the safety and maximum tolerated dose of ARRY-520 when combined with BTZ plus low-dose dexamethasone (Dex)

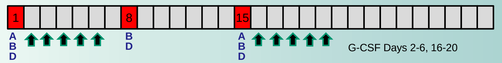
Secondary Objectives
- Assess preliminary estimates of the efficacy of this combination

Study Design
- Open-label, multicenter, dose-escalation study to assess the safety of ARRY-520 (IV) given with BTZ (IV or subcutaneous) and Dex
- 3 + 3 dose escalation
- Increasing doses of ARRY-520 and BTZ without or with Dex given in 28-day cycles in 2 dose schedules

Schedule 1



Schedule 2



A: ARRY-520
B: Bortezomib
D: ±Dex

	Schedule 1												Schedule 2	
Dose level	1	2	3	4	5	6	7	8	9	10	11	12	13	14
ARRY-520 (mg/m²/d)	1.0	0.5	0.5	0.75	1.0	1.25	0.75	1.0	1.25	1.5	1.25	1.5	2.25	3
BTZ (mg/m²/d)	1.3	1.0	1.0	1.0	1.0	1.0	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Dex (mg)	40	-	-	-	-	-	-	-	-	-	40	40	40	40
G-CSF	-	-	+	+	+	+	+	+	+	+	+	+	+	+
	Presented at International Myeloma Workshop 2013								Current presentation					

Eligibility – Key Inclusion Criteria

- Confirmed relapsed or refractory MM or plasma cell leukemia
  - ≥ 2 prior treatment regimens
  - Must have included at least one full cycle of a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and disease that progressed during or after last regimen
- Measurable disease
- ECOG Performance Status 0-1
- Age ≥ 18 years
- Adequate hematologic, hepatic and renal function
- No ≥Grade 2 neuropathy or any neuropathy with pain

Patient Baseline Characteristics

Patient Characteristics	Total Patients N=28
Gender	
Male, Female	17, 11
Age at Enrollment (yrs)	
Median (range)	64 (31 – 79)
ECOG	
0, 1	10, 18

Disease History	Total Patients N=28
Years since diagnosis	
Median (Range)	4.0 (1.6 – 12.0)
Monoclonal Protein Subtype	
IgG, IgA, IgM, None	17, 5, 1, 5
Light Chain Subtype	
Kappa, Lambda	17, 11
Cytogenetics	
High Risk*	9

* High risk = del 17p, t(14, 16), and/or gain 1q21

Prior Therapy	Schedule 1 ≥ 1.25 mg/m² ARRY-520 + 1.3 mg/m² BTZ	Schedule 2
N Patients	**19**	**9**
Prior Systemic Regimens		
Median	5	4
Range	3-11	1-8
Prior Proteasome Inhibitor	100%	100%
BTZ	89%	89%
Carfilzomib	26%	22%
Prior IMiD	100%	100%
Thalidomide	53%	22%
Lenalidomide	100%	100%
Pomalidomide	16%	33%
Refractory to BTZ	42%	0%
Refractory to Lenalidomide	68%	56%
Prior Alkylator	100%	78%
Prior Anthracycline	47%	11%
Prior Corticosteroid	100%	100%
Prior Stem Cell Transplant	89%	78%

Safety

Schedule	1 (D1,2,15,16)								2 (D1,15)					
ARRY-520 (mg/m²)	1.25			1.5			1.25		1.5		2.25		3	
Dex (40 mg)	No						Yes				Yes			
N Patients	3			7			3		6		3		6*	
Grade	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4	1-2	3	4
Hematologic Abnormalities (Regardless of Causality)**																		
Neutrophils	1	1		2	2	2				2			2		1	2	1	
WBC	2			4	3					4	2		2	1		2	1	
Platelets	2		1	5	2		3			2	1	1	1			2	1	
Hemoglobin	3			4	2		3			5	1		3			2	2	
Non-Hematologic AEs (≥15% Reported Dose Levels, Regardless of Causality)																		
Diarrhea	1			6			2	1		3			2			1		
Nausea	2			3	1		1						1					
Cough	1			3			1			1			1					
Fatigue	1			2			1			1			1			1		
Constipation				3	1					1			1					
Dizziness	1	1		2			1			1								
Vomiting	1			1	1		1						2					
Decreased appetite	1			2						1			1					
Headache	1			2									2					
Pyrexia	2			3														
URTI	1			2			1						1					
Treatment Experience																		
# Cycles Median Range	6 2 - 13			14 3 - 14+			4 2 - 9+			Not reached 1 - 5+			Not reached 4 - 8+			Not reached 1+ - 3+		

NOTE: All pts at the presented dose levels received BTZ at 1.3 mg/m² D1,8,15 &prophylactic G-CSF
*** Safety data in this cohort includes patients who had not completed a full cycle at data cutoff.**
**** Hematologic abnormalities based on laboratory values. + Patient ongoing.**

Maximum Planned Dose (MPD) reached in both schedules

- Schedule 1 = 1.5 mg/m² ARRY-520 (D1,2,15,16) + 1.3 mg/m² BTZ (D1,8,15) + low-dose Dex (D1,8,15) with prophylactic G-CSF
- Schedule 2 = 3.0 mg/m² ARRY-520 (D1,15) + 1.3 mg/m² BTZ (D1,8,15) + low-dose Dex (D1,8,15) with prophylactic G-CSF (determined after the data cutoff)
- These are the respective maximum single-agent doses of ARRY-520 and BTZ

ARRY-520 + BTZ demonstrated an acceptable safety profile

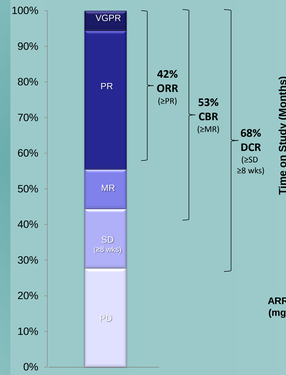
- Hematological toxicity was the most commonly observed adverse effect
  - G-CSF adequately manages neutropenia (3/48 patients at all dose levels with Grade 4 neutropenia when given prophylactic G-CSF)
  - Neutropenia and thrombocytopenia have been reversible and not cumulative
- Low incidence of Grade 3/4 non-hematologic toxicity
- 1/28 (4%) patients experienced neuropathy (Grade 1), with full dose BTZ
- 1/28 (4%) patients required a dose reduction in ARRY-520 due to an adverse event, regardless of causality
- 3/28 (11%) patients discontinued treatment with ARRY-520 due to an adverse event, regardless of causality
- 4/28 (14%) patients experienced any SAE, regardless of causality or grade
  - 2 related SAEs (Grade 3 febrile neutropenia, Grade 2 subdural hematoma)
- No DLTs were reported at the higher dose levels summarized
  - 3 DLTs were reported previously at lower doses of ARRY-520

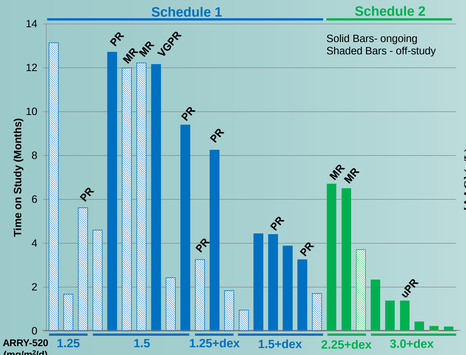
References

1. Tunquist et al (2009) Mol Cancer Ther. 9: 2046-56.
2. Woessner *et al. Blood* (ASH Annual Meeting Abstracts) 2009 114: Abstract 2858.

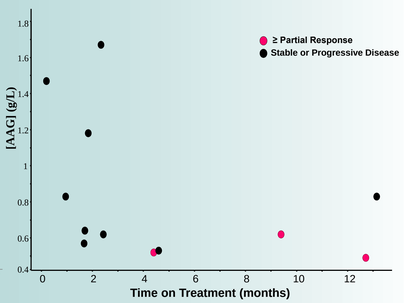
Activity

68% Disease Control Rate (DCR) to Date in Schedule 1 (N=19)





AAG Levels Correlate with Response in Patients with PI-refractory Disease
(Patients in Schedules 1 and 2)



- **In Schedule 1: 19 patients received ARRY-520 at doses of ≥ 1.25 mg/m² with 1.3 mg/m² weekly BTZ**
  - 8 patients are still ongoing at time of data cutoff
  - 1 VGPR, 7 PR, 2 MR: 42% overall response rate (ORR ≥ PR), 53% clinical benefit rate (CBR ≥ MR)
    - In 10 patients treated with weekly BTZ without Dex: 1 VGPR, 3 PR and 2 MR (40% ORR, 60% CBR)
    - In 8 patients who were previously PI sensitive: 1 VGPR, 4 PR and 2 MR (63% ORR, 88% CBR)
    - In 10 patients with PI-refractory (BTZ and/or carfilzomib) disease: 3 PR (30% ORR)
    - In 9 patients with high risk cytogenetics: 1 VGPR and 2 PR (33% ORR)
  - 0/26 responses (≥PR) were observed in patients administered ARRY-520 at doses ≤1mg/m²
- **In Schedule 2: 9 patients received ARRY-520 at doses of ≥ 2.25 mg/m² with 1.3 mg/m² weekly BTZ**
  - 8 patients are ongoing (4 patients have received < 2 cycles of therapy) at data cutoff
    - 1 unconfirmed PR (uPR), 2 MR to date
- **AAG is a potential marker of ARRY-520 response**
  - In PI-refractory patients, responses and prolonged stable disease occurred only in patients with low AAG levels

Summary

- An MPD/recommended Phase 2 dose for ARRY-520 + BTZ/Dex has been established for 2 different dosing schedules of ARRY-520
  - Schedule 1: 1.5 mg/m² ARRY-520 (D1,2,15,16) + 1.3 mg/m² BTZ/Dex (D1,8,15) with prophylactic G-CSF
  - Schedule 2: 3.0 mg/m² ARRY-520 (D1,15) + 1.3 mg/m² BTZ/Dex (D1,8,15) with prophylactic G-CSF (determined after the data cutoff)
  - These are the respective maximum single-agent doses of ARRY-520 and BTZ.
- The combination of ARRY-520 and BTZ is well-tolerated with prophylactic G-CSF
  - Rapidly reversible, non-cumulative neutropenia was the most significant toxicity
    - G-CSF adequately manages neutropenia
  - Low incidence of non-hematologic AEs
    - Predominantly Grade 1/2
    - Low incidence of neuropathy
- ARRY-520 + BTZ/Dex shows promising signs of activity in this dose-escalation study
  - 42% ORR observed in patients dosed at ≥ 1.25 mg/m² ARRY-520 in Schedule 1
    - 30% ORR in PI-refractory patients
    - 63% ORR (88% CBR) in PI-sensitive patients
- Expansion cohorts in both schedules are enrolling patients with RRMM, 1-3 prior therapies and BTZ-sensitive disease