

Introduction

- Kinesin Spindle Protein (KSP) is a novel anti-neoplastic target
 - As KSP is not present in peripheral neurons, KSP inhibitors are not associated with neurotoxicity
- ARRY-520 is a potent and highly selective inhibitor of KSP
- Preliminary multiple myeloma is one of the most responsive tumor types to ARRY-520¹
 - Regression in multiple myeloma models, including bortezomib- and lenalidomide-resistant models²
 - Synergistic activity in vivo when combined with bortezomib, including in bortezomib-refractory models³
 - Superadditive activity in vivo when combined with lenalidomide³
 - Apoptosis in myeloma cells treated with ARRY-520 requires loss of the short-lived survival protein Mcl-1, providing a mechanistic explanation for ARRY-520 activity
- These data support the initiation of studies with ARRY-520 in multiple myeloma patients who have progressed after treatment with bortezomib and an IMiD
 - This is the first report of investigation of KSP inhibitors in multiple myeloma

Study Design and Objectives

Study Design

- Open label, multicenter, dose-escalation study to assess safety, PK and PD of ARRY-520 given IV over 1 hour on Days 1 and 2 q 2 weeks
 - Without and with G-CSF
 - Since neutropenia was the more prominent AE in the initial dose escalation, further escalation with prophylactic G-CSF was initiated
- Standard 3 + 3 dose escalation

Primary Objectives

- Determine the safety and maximum tolerated dose (MTD) of ARRY-520 without and with G-CSF support

Secondary Objectives

- Evaluate the plasma PK profile of ARRY-520
- Assess preliminary anti-myeloma activity of ARRY-520

Key Eligibility Criteria

- Confirmed relapsed or refractory multiple myeloma or plasma cell leukemia
 - At least 2 prior treatment regimens which must include both bortezomib and an IMiD, unless patients were not eligible or refused these treatments
- Measurable disease (Ig in blood, light chain in urine, FLC in serum or ≥ 30% plasma cells in bone marrow)
- ECOG Performance Status 0-1
- Age ≥ 18 years
- Adequate hematologic, hepatic and renal function
- No primary amyloidosis
- No bone marrow or stem cell transplant within 3 months of first dose

MM Patient Characteristics

Patient Characteristics	Dose (mg/m ² /day)				
	1 N=3	1.25 N=7	1.5 + G-CSF N=7	2 + G-CSF N=3	Total N=20
Median age (years)	54	57	64	61	59
Range	49 – 78	46 – 63	44 – 77	58 – 79	44 – 79
Gender (male:female)	2:1	3:4	3:4	2:1	10:10
ECOG Performance Status					
0	0	2	0	1	3
1	3	5	7	2	17
Race					
Caucasian	1	6	5	1	13
Black/African American	2	1	2	2	7

Disease History

Disease History	Dose (mg/m ² /day)				
	1 N=3	1.25 N=7	1.5 + G-CSF N=7	2 + G-CSF N=3	Total N=20
Median years since initial dx	4.5	1.8	2.1	2.7	2.5
Range	1.6 – 5.8	1.4 – 9	0.6 – 6.6	2.3 – 6.1	0.6 – 9
Ig subtype					
IgG	1	5	3	1	10
IgA	1	0	2	2	5
IgD	0	0	1	0	1
Light Chain only	1	2	1	0	4
Light Chain subtype (κ:λ)	3:0	5:2	4:3	3:0	15:5
Median prior systemic treatments	4	4	5	3	4
Range	8-9	5-13	2-16	2-5	2-16
Prior proteasome inhibitor					
Bortezomib	3	7	7	2	19
Carfilzomib	0	1	1	1	3
Prior IMiD					
Thalidomide	3	6	4	3	16
Lenalidomide	2	7	6	2	17
Pomalidomide	0	1	0	0	1
Other prior treatments					
Alkylator	3	7	5	3	18
Anthracycline	2	3	4	1	10
Corticosteroids	3	7	7	3	20
Stem cell transplantation	2	6	5	2	15

ARRY-520 Treatment

Treatment Experience	Dose (mg/m ² /day)				
	1 N=3	1.25 [†] N=7	1.5 + G-CSF N=7	2 + G-CSF N=3	Total N=20
Median cycles/pt	5	4	4	4	4
Range	3-24+	4-15+	1-10+	3-6+	1-24+
Dose reduction	0	0	1 (10)	0	1
Event			T (1)		
Dose delay					
Event	N (2)	6	2	0	10
	N+PTDec (1)	N (3), T (2), N+T (1)	N+T (2)		
Dose escalation					
Event	0	2	0	0	2
Patients with DLT					
Event	0	1	FN (1)	0	2

FN = febrile neutropenia, N = neutropenia, PDec = patient decision, T = thrombocytopenia
 No patient came off study due to AE [†]MTD without G-CSF

Safety

Adverse Event	Grade 3 – 4 Adverse Events, Regardless of Causality*				
	Dose (mg/m ² /day)				
	1 N=3	1.25 N=7	1.5 + G-CSF N=7	2 + G-CSF N=3	Total N=20
Neutropenia	1 (33%)	4 (57%)	3 (43%)	1 (33%)	9 (45%)
Thrombocytopenia	0	3 (43%)	3 (43%)	0	6 (30%)
Anemia	0	2 (29%)	1 (14%)	1 (33%)	4 (20%)
Fatigue	1 (33%)	0	1 (14%)	0	2 (10%)
Febrile neutropenia	0	0	1 (14%)	1 (33%)	2 (10%)
Leukopenia	0	1 (14%)	1 (14%)	0	2 (10%)

*Grade 3 – 4 events, regardless of assessed causality, occurring in > 1 patient overall (interim data)
 Data Cut-Off: 03 May 2010

Adverse Event	Treatment-Related Adverse Events*				
	Dose (mg/m ² /day)				
	1 N=3	1.25 N=7	1.5 + G-CSF N=7	2 + G-CSF N=3	Total N=20
Neutropenia					
Grade 1/2	0	0	2 (29%)	0	2 (10%)
Grade 3/4	1 (33%)	4 (57%)	3 (43%)	0	8 (40%)
Thrombocytopenia					
Grade 1/2	0	0	2 (29%)	2 (67%)	4 (20%)
Grade 3/4	0	3 (43%)	3 (43%)	0	6 (30%)
Fatigue					
Grade 1/2	0	3 (43%)	1 (14%)	1 (33%)	5 (25%)
Grade 3/4	1 (33%)	0	1 (14%)	0	2 (10%)
Anemia					
Grade 1/2	1 (33%)	0	1 (14%)	0	2 (10%)
Grade 3/4	0	2 (29%)	1 (14%)	1 (33%)	4 (20%)
Leukopenia					
Grade 1/2	1 (33%)	1 (14%)	0	1 (33%)	3 (15%)
Grade 3/4	0	1 (14%)	1 (14%)	0	2 (10%)
Nausea					
Grade 1/2	0	2 (29%)	1 (14%)	0	3 (15%)
Grade 3/4	0	0	1 (14%)	0	1 (5%)

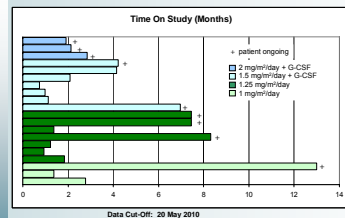
*Events assessed as treatment-related by the Investigator, occurring in ≥ 20% of patients overall (interim data)
 Data Cut-Off: 03 May 2010

Pharmacokinetics

PK Parameter	Dose (mg/m ² /day)			
	1 N=3	1.25 N=6	1.5 + G-CSF N=7	2 + G-CSF N=2
CL (L/hr/m ²)	2.32 (63.2%)	2.22 (31.1%)	2.34 (53.7%)	4.62 (41.0%)
V _d (L/m ²)	12.6 (98.4%)	13.6 (120%)	34.6 (54.0%)	52.8 (21.4%)
AUC ₀₋₂₄ (hr·ng/mL)	862 (99.2%)	1120 (36.2%)	1280 (76.6%)	870 (41.0%)
C _{max,0.5h} (ng/mL)	39.0 (150%)	59.1 (94.9%)	25.9 (71.7%)	36.3 (16.1%)
t _{1/2α} (hr)	0.428 (0.096 – 0.893)	0.500 (0.230 – 1.63)	0.499 (0.218 – 0.933)	0.804 (0.800 – 0.807)
t _{1/2β} (hr)	53.0 (31.9 – 71.2)	59.0 (36.2 – 93.2)	74.4 (55.3 – 91.5)	59.7 (52.8 – 66.6)

- Plasma samples were collected at the following time points
 - Cycle 1: 1, 8 and 24 hours after the start of the Day 1 ARRY-520 infusion and 1, 8, 24, 48 and 144 hours after the start of the Day 2 infusion
 - Cycle 2: 24 hours after the start of the Day 1 ARRY-520 infusion and 1 hour after the start of the Day 2 infusion
- Preliminary population and individual (post-hoc) PK parameters were estimated
- Similar to other studies with ARRY-520 (see poster – ASCO abstract # 2570)
 - ARRY-520 PK was best described by a two-compartment linear model
 - Population PK estimates showed moderate-to-high inter-individual variability (IV) as %CV
 - CL (L/hr/m²) = 2.36 (60.4%)
 - V_d (L/m²) = 15.5 (181%)
- Urinary excretion of unchanged ARRY-520 is minimal: 2-8% of the dose over 24 hours (see ASCO abstract # 2570); the main metabolism occurs in the liver

Preliminary Anti-Myeloma Activity



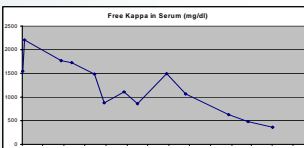
- Responses per IMWG and EBMT criteria (20 evaluable patients)
- 13 Stable Disease
 - 2 PR (unconfirmed, 2 mg/m²/day)
 - 5 ≥ SD for > 6 months
 - 9 patients remain on study
 - 6 Progressive Disease

- Other signs of ARRY-520 activity
- Spontaneous increase in Hgb levels in some patients
 - Regression of plasmacytomas

Clinical activity has not correlated with any baseline characteristics or disease parameters to date

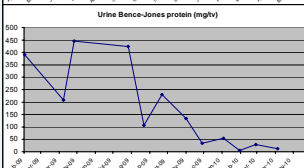
Partial Response

- 50-year-old black male diagnosed in 2003
- First dose 21 April 2009
- Currently ongoing in Cycle 24 at 1 mg/m²/day on Days 1, 2
- % Plasma cells in BM from 30% at baseline to 5% at Cycle 12 (~ 6 months)
- No SAEs
- Main treatment-related AE: neutropenia



Prior MM Therapy (Best response)

- 2003 VAD (PR)
 - 2004 Tandem BMT (PR)
 - 2007
 1. Thal-Dex (UNK)
 2. Rev-Dex (UNK)
 - 2008
 1. Velcade-Doxil-Dex (UNK)
 2. Investigational (SD)
 3. Cytoxin IV (PD)
 4. VDT-PACE w/ CDDP (SD)
- Relapsed March 2009



Summary

- ARRY-520, a novel, first-in-class agent was well tolerated as monotherapy at doses levels up to 2 mg/m²/day IV on Days 1 and 2 + G-CSF
- MTD was 1.25 mg/m²/day without G-CSF
 - Neutropenia was the most commonly reported AE
 - Dose escalation is continuing with prophylactic G-CSF
- Patients displayed linear PK, a low CL and a moderate V_d, with moderate-to-high IV in PK parameters
- ARRY-520 has shown promising preliminary clinical activity as a single agent in a heavily pretreated patient population
 - 1 PR and 2 unconfirmed MRs seen to date
 - 41% of patients in Cohorts 1-3 achieved a PR or SD > 12 weeks
 - 5 patients have been treated for > 6 months to date
- Further studies, including a single agent Phase 2 study and combination trials in multiple myeloma, are planned
 - Synergistic activity in vivo when combined with bortezomib, including in bortezomib-refractory models³
 - Superadditive activity in vivo when combined with lenalidomide³