Phase 1 Study of ARRY-520 and Carfilzomib in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)

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Disclosures

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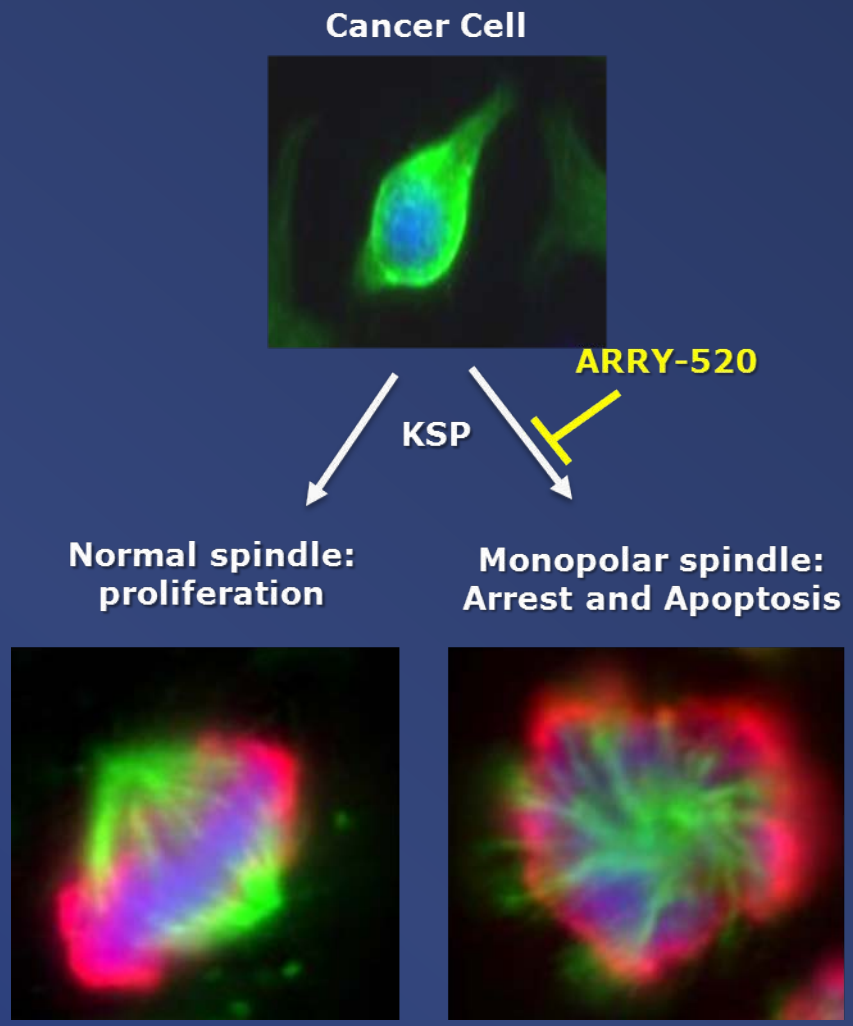
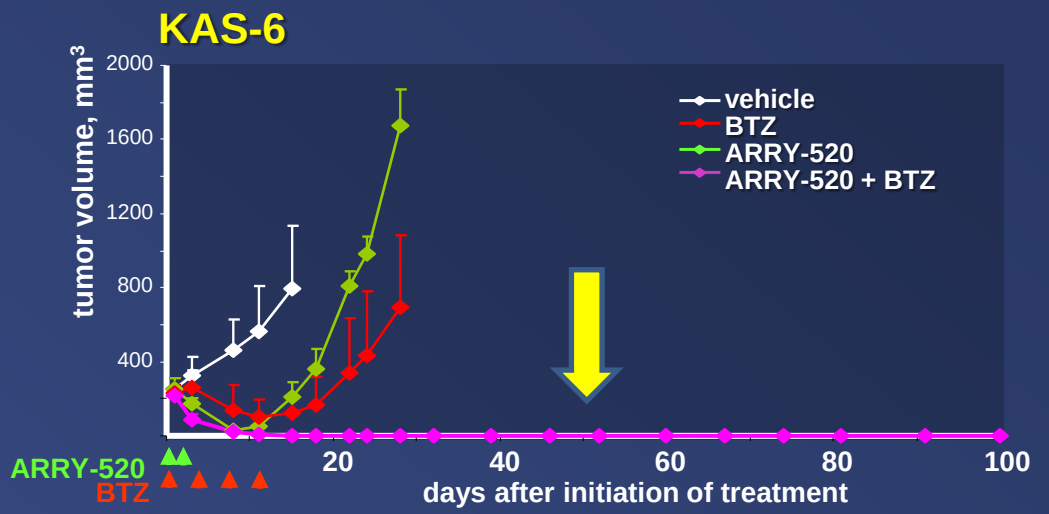
Background: Targeting Kinesin Spindle Protein Inhibition with ARRY-520

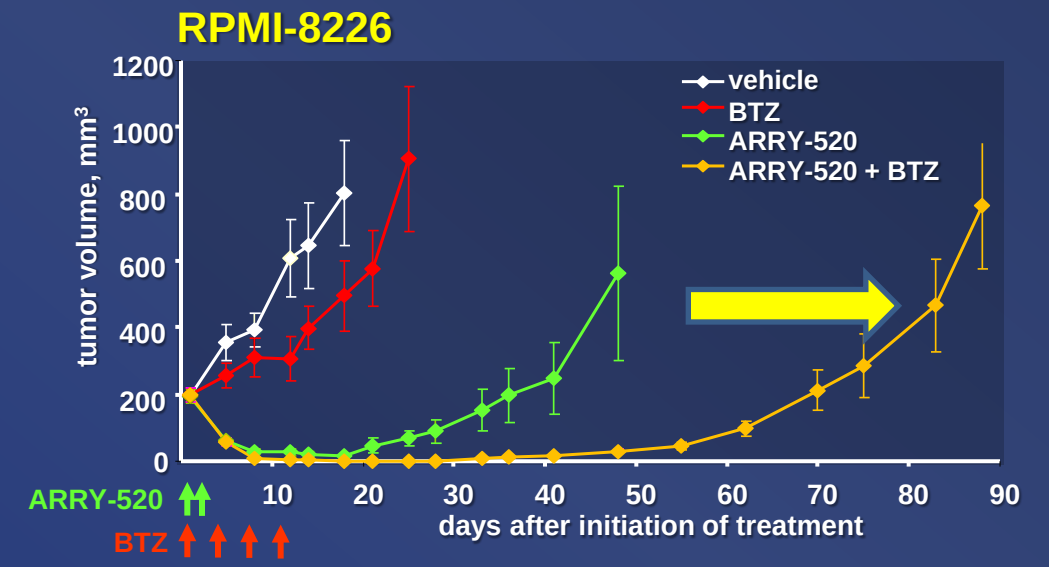
- Kinesin spindle protein (KSP) is a microtubule motor protein required for mitosis and spindle pole separation
  - KSP inhibition prevents formation of bipolar spindle, rapid apoptosis leading to cell death
- **ARRY-520** is a highly selective allosteric KSP inhibitor
  - Novel mechanism of action (MOA) for MM
  - Not expected to be cross-resistant with other drugs
  - Preferentially acts on MCL-1 dependent cells



Background: Preclinical Rationale ARRY-520 + Proteasome Inhibitor

- **ARRY-520** is highly active in vivo in preclinical MM models
- Additive/synergistic with bortezomib (BTZ)
- Supports the rationale for the combination of a proteasome inhibitor and ARRY-520





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Background: ARRY-520 and Carfilzomib

- **Carfilzomib** is a selective proteasome inhibitor with demonstrated single-agent activity in RRMM and recently received accelerated approval by the US FDA
- **Carfilzomib** is very well tolerated with a well described side effect and safety profile
  - Can be combined safely with multiple other agents

- **ARRY-520** also has single-agent activity with a clinical benefit rate (CBR) of 19%; in combination with dexamethasone in triple refractory MM CBR of 33%
- **ARRY-520** is well tolerated with a differentiated adverse event (AE) profile from proteasome inhibitors and immunomodulatory drugs (IMiDs)
  - **No treatment-emergent neuropathy**
  - **Minimal non-hematological toxicity**

Background: Rationale

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- Preclinical data demonstrating synergy support the rationale for the combination of carfilzomib + ARRY-520
- Clinically minimal overlapping non hematologic toxicity of carfilzomib and ARRY-520 supporting the feasibility of the combination
- We hypothesize that the combination will be well tolerated and will yield improved response rates
- The aim of this study was to determine the maximum tolerated dose (MTD) of the combination and evaluate preliminary activity

Objective

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Primary Objective

- To determine the safety and the maximum tolerated dose (MTD) of ARRY-520 when combined with carfilzomib

Secondary Objective

- To obtain preliminary estimates of the efficacy of ARRY-520 when combined with carfilzomib

Secondary Endpoints

- Overall response rate (ORR), complete response (CR), very good partial response (VGPR)
- Time to progression (TTP)
- Progression free survival (PFS)
- Time to best response
- Safety of the combination in patients with RRMM
- Time to next therapy

Study Design

- Part A, Phase I: Standard 3 + 3 design with fixed dose of carfilzomib, escalating doses of ARRY-520

Dose Level	ARRY-520 mg/m^2/day IV Days 1, 2, 15 and 16	Carfilzomib mg/m^2/day IV Days 1,2 8,9 and 15,16	Dexamethasone mg/day PO/IV Days 1, 2, 8, 9 and 15, 16
–1	0.5	20/27	4
1 Starting Dose	0.75	20/27	4
2	1.00	20/27	4
3	1.25	20/27	4
4	1.5	20/27	4

Dosing Schema

Induction Therapy Cycle 1–8: 28-day cycle

Carfilzomib + Dexamethasone 4 mg (IV/PO)

ARRY-520 (IV)

Neupogen Days 3–7 and 17–21

Maintenance Therapy: >8 cycles

- Carfilzomib: Days 1, 2, 15, 16 and ARRY-520

Patients treated until progressive disease

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Study Design: Eligibility Criteria

Inclusion Criteria:

- Patients with relapsed/refractory multiple myeloma

- **Prior treatment must have included at least one full cycle of a proteasome inhibitor and at least one full cycle of an IMiD**
- **Patients must be refractory or intolerant to bortezomib therapy**

- Adequate cardiac, pulmonary and renal function
- Adequate hematology laboratory values
  - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
  - Platelets $\geq 75 \times 10^9$/L
- Measureable disease

Exclusion Criteria:

- Patients who are eligible for autologous transplantation

Patient Demographics

	N=18
Age, median (range)	60 (47–80)
Male	13
Prior Lines of Therapy, median (range)	4 (2–10)
ISS Stage	
Stage I	6
Stage II	6
Stage III	2
Stage n/a	4
Cytogenetics	
Del 13	3
Del 17	2
t(14;16)	1

1 patient unevaluable, non-compliant.

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Prior Therapies

	N=18
Prior Regimens, median (range)	4 (2–10)
Prior ASCT, n (%)	16 (89)
Prior Bortezomib, n (%)	18 (100)
Bortezomib Refractory/Intolerant, n (%)	18 (100)
Prior Lenalidomide, n (%)	18 (100)
Refractory/intolerant, n (%)	15 (83)
Carfilzomib	1
ARRY-520	5

ASCT, autologous stem cell transplantation.

Phase I: Dose Escalation

- 18 patients enrolled (16 dose-limiting toxicity [DLT] evaluable): carfilzomib 20/27 mg/m^2 and escalating dose of ARRY-520

	Patients	DLT
Cohort 1: ARRY-520 0.75 mg/m^2/day	**3**	**0**
Cohort 2: ARRY-520 1.0 mg/m^2/day	**6**	**1**
Cohort 3: ARRY-520 1.25 mg/m^2/day	**3**	**0**
Cohort 4: ARRY-520 1.5 mg/m^2/day	**4 (ongoing)**	**1**

- DLT in cohort 2: 1 patient hospitalized with non-neutropenic fever admitted with parainfluenza 3 at end of Cycle 1
- DLT in cohort 4: 1 patient hospitalized with non-neutropenic low grade temperature (38.0) and pneumonia (who has a history of recurrent infections)
- Serious AE: febrile neutropenia/death (n=1); lethargy grade 2 (due to disease) (n=1); lung infection/PNA (n=4); community acquired MSSA bacteremia (n=1)

Hematologic Abnormalities
(N=18)

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	6	7	5	0
Thrombocytopenia	6	4	3	3
Neutropenia	3	4	3	5

- **One patient with febrile neutropenia**
- Toxicities were transient and reversible
- No cumulative toxicity

Non-Hematologic Adverse Events (N=18)

	Grade 1	Grade 2	Grade 3	Grade 4
ALT increased	6	0	1	0
AST increased	8	1	1	0
Alk phos increased	12	0	0	0
Blurred vision	4	2	0	0
Creatinine	6	0	0	1
Dyspnea	7	5	0	0
PN	6	3	0	0
Fatigue	6	8	2	0
Mucositis	5	2	0	0
Nausea	6	4	2	0
Constipation	6	0	0	0
Diarrhea	5	7	1	0

Alk phos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; PN, peripheral neuropathy

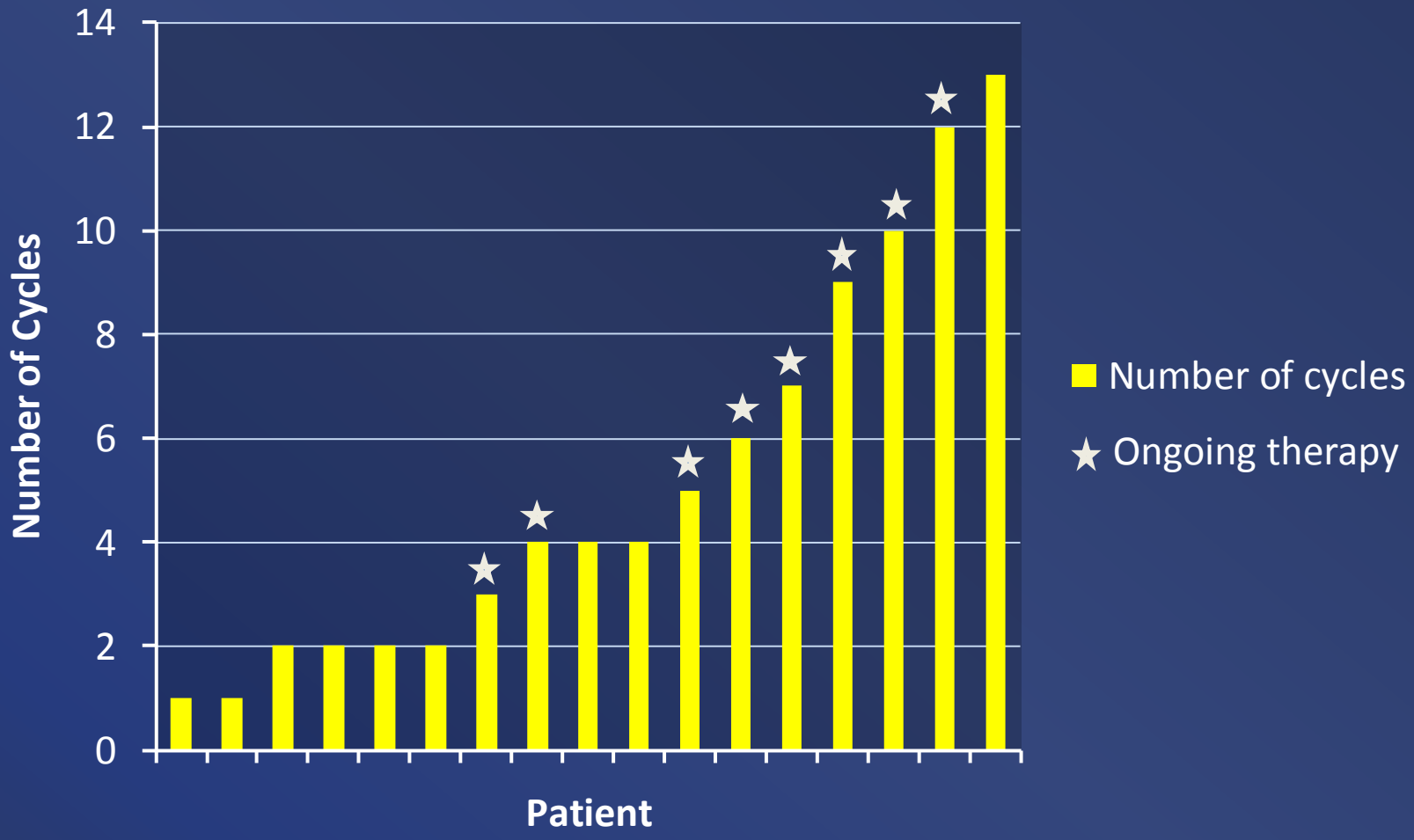
Preliminary Efficacy Results

	n=17
Near-Complete Response/Complete Response	1
Partial Response	4
Minimal Response (MR)	4
Stable Disease	5
Progressive Disease	3

Clinical Benefit Rate (≥MR): 53%

1 patient was not evaluable for efficacy as they were noncompliant and were removed during cycle 1

Patients on Trial: Number of Cycles



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Conclusions

- Enrollment is ongoing in cohort 4 with full dose ARRY-520 established from single agent Phase 1 (1.5 mg/m^2/day) and 20/27 mg/m^2 carfilzomib; MTD has not been established

- ARRY-520 can be **safely combined** with carfilzomib, and the combination thus far is **well tolerated** with a manageable side effect profile and no unexpected toxicity
  - Limited grade 3/4 non-hematologic toxicity
- Preliminary **clinical benefit rate of 53%** that appears durable; many patients still on study

- Subsequent Phase 1b dose expansion is planned at the MTD or maximum planned dose (MPD) of part A
  - Part B with Phase 1 dose escalation of carfilzomib planned after MTD or MPD of ARRY-520 established in Part A

Acknowledgments

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- **Array BioPharma and Onyx**
  - Trial was conceived, supported and started before carfilzomib was approved, **combining 2 unapproved agents**

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- Patients/Caregivers