Phase I Study of the Novel Kinesin Spindle Protein Inhibitor Filanesib (ARRY-520) + Carfilzomib (Car) in Patients with Relapsed and/or Refractory Multiple Myeloma

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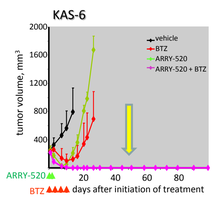
Introduction

ARRY-520 – A New Drug Target in MM

- Targeted inhibitor of KSP
  - Novel mechanism of action in MM
  - Not expected to be cross-resistant with other drugs
- ARRY-520 shows synergistic activity with bortezomib (BTZ) and IMiDs in MM xenograft models



Background: ARRY-520 and Carfilzomib

Carfilzomib
- A selective proteasome inhibitor(PI) with single-agent activity in RRMM
- Well tolerated with a well described side effect and safety profile
- Can be combined safely with multiple other agents

ARRY-520
- Single agent activity in heavily pretreated MM patients
- Clinical activity in combination with PIs and dexamethasone
- Hematologic toxicity has been transient and non-cumulative
  - **Minimal non-hematological toxicity**
  - **No treatment-emergent neuropathy**

Objective

Primary Objective
- To determine the safety profile 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

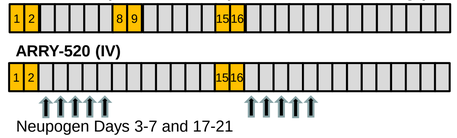
Standard 3 + 3 design with fixed dose of carfilzomib, escalating doses of ARRY-520

Dose Level	ARRY-520 mg/m²/day IV	Carfilzomib mg/m²/day IV	Dexamethasone mg/day PO/IV
−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

Study Therapy / Schema

Dosing Schema

Induction Therapy Cycle 1-8: 28 day cycle



Maintenance Therapy: >8 cycles
- Carfilzomib: Days 1,2,15,16 and ARRY-520 Days 1,2,15,16

- Patients treated until progressive disease

Inclusion/Exclusion 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) ≥1.5 × 10^9/L
  - Platelets ≥75 × 10^9/L
- Measureable disease

Exclusion Criteria:
- Patients who are eligible for autologous stem cell transplantation

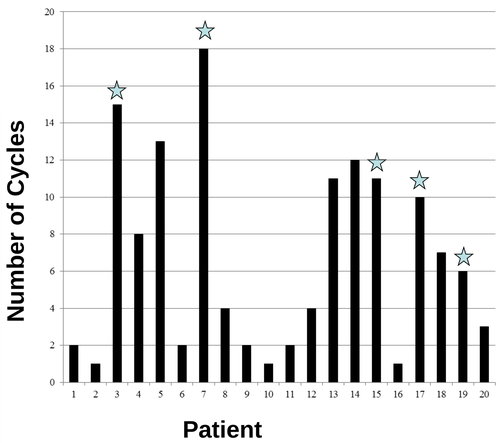
Patient Demographics

	N=20
Age, median (range)	61 (43–80)
Male	15
Prior Lines of Therapy, median (range)	4 (2−10)
ISS Stage	
Stage I	10
Stage II	3
Stage III	7

Prior Therapies

	N=20
Prior Regimens, median (range)	4 (2−10)
Prior ASCT, n (%)	18 (90)
Prior Bortezomib, n (%)	20 (100)
Bortezomib Refractory/Intolerant, n (%)	20 (100)
Prior Lenalidomide, n (%)	20 (100)
Refractory/intolerant, n (%)	16 (80)
Carfilzomib	1
ARRY-520	5

Patients on Trial: Number of Cycles



Phase I DLT

	Patients	DLT
Cohort 1: ARRY-520 0.75 mg/m²/day	3	0
Cohort 2: ARRY-520 1.0 mg/m²/day	6	1
Cohort 3: ARRY-520 1.25 mg/m²/day	3	0
Cohort 4: ARRY-520 1.5 mg/m²/day	6	1

20 patients enrolled (18 DLT evaluable):
- 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 (patient had history of recurrent infections)

Hematologic Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	8	6	6	0
Thrombocytopenia	8	3	4	2
Neutropenia	3	5	3	6

Non-Hematologic Adverse Events

	Grade 1	Grade 2	Grade 3	Grade 4
ALT increased	8	0	1	0
AST increased	8	2	1	0
Blurred vision	5	2	0	0
Bone pain	5	2	0	0
Creatinine	6	0	0	1
Dizziness	9	1	0	0
Dyspnea	9	6	0	0
Fatigue	7	10	3	0
URTI	0	7	0	0
Mucositis	5	2	0	0
Neuropathy	7	3	1	0
Nausea	7	5	2	0
Constipation	7	1	0	0
Diarrhea	6	7	1	0

Efficacy

	n=19
Near-Complete Response/Complete Response	1
Partial Response	6
Minimal Response (MR)	5
Stable Disease	4
Progressive Disease	3

1 pt removed during cycle one due to non-compliance

Overall response rate (ORR) ≥ PR of 37%
Clinical Benefit Rate(CBR) ≥ MR of 63 %

- In Cohort 1 and 2, growth factors were not needed beyond cycle 1 and 2
- No cumulative cytopenias or bone marrow toxicity

Conclusions

- **Carfilzomib (27 mg/m²/d) can be combined with full dose ARRY-520 (1.5 mg/m²/d)**
  - **This is the recommended dose for phase II and phase III trials**
  - **Further dose-escalation of carfilzomib with full-dose ARRY-520 is ongoing in Part B of this study**
- **The combination is well tolerated with minimal non hematologic toxicity**
  - **Hematologic toxicity is easily managed, transient and non cumulative**
- **The combination is active and durable**
  - **CBR of 63% in patients who were refractory/ intolerant to bortezomib**
- **Part B Dose escalation is ongoing**
  - **2 patients enrolled: Carfilzomib 36 mg/m² and ARRY-520 1.5 mg/m² and tolerated well with no DLT**
- **Enrollment at dose expansion is ongoing**