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

A. Chari1, M. Htut2, J.A. Zonder3, J. Fay4, B. Hilder5, M. Ptaszynski5, D. Walker5, J.L. Kaufman6

1Mount Sinai School of Medicine, New York, NY; 2City of Hope, Duarte, CA; 3Karmanos Cancer Institute, Detroit, MI; 4Baylor Research Institute, Dallas, TX; 5Array BioPharma, Boulder, CO; 6Emory University, Atlanta, GA

Abstract

INTRODUCTION
ARRY-520 is a targeted Kinesin spindle fiber (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. Novel mechanism of action for multiple myeloma (MM) Previously active 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.

Study Design and Objectives

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

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

Schedule 1
- 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

Schedule 2
- 2.0 mg/m2 ARRY-520 (D1,15) + 1.3 mg/m2 BTZ (D1,8,15) + low-dose Dex (D1,15) with prophylactic G-CSF

Maximum Planned Dose (MPD) reached in both schedules

Safety

Maximum Dose (MPD) reached in both schedules

Eligibility – Key Inclusion Criteria
- Confirmed relapsed or refractory MM or plasma cell leukemia
- 2 or more 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 the last regimen
- Measurable disease
- ECOG Performance Status 0-1
- Age ≥ 18 years
- Adequate hematologic, hepatic and renal function

No >= 2 neuropathy or any neuropathy with pain

No creatinine > 1.5 x upper limit of normal

No uncorrected coagulation defects

No prior therapy within 28 days of study entry

No uncorrected grade 3 or 4 neutropenia

Blood tests

Hematologic Abnormalities** (Regardless of Causality)

(≥15% Reported Dose Levels, Regardless of Causality)

SCHEDULE 1

SCHEDULE 2

Prior Therapy

Schedule 1: ARRY-520 + BTZ/Dex shows promising signs of activity in this dose-escalation study

- ARRY-520 + BTZ demonstrated an acceptable safety profile

- Hematological toxicity was the most commonly observed adverse effect

- No DLTs were reported at the higher dose levels summarized

- Rapidly reversible, non-cumulative neutropenia was the most significant toxicity

- Low incidence of non-hematologic AEs

- Predominantly Grade 1/2

- PI-refractory patients: responses and prolonged stable disease occurred only in patients with low AAG levels

- 0/26 responses (≥PR) were observed in patients administered ARRY-520 at doses ≤ 1.25 mg/m

- 1 unconfirmed PR (uPR), 2 MR to date

- In 10 patients with PI-refractory (BTZ and/or carfilzomib) disease: 3 PR (30% ORR)

- 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)

- 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 of 2 mg/m2 for dose 2 for ARRY-520 + BTZ/Dex has been established for two different dosing schedules of ARRY-520

- 1.15 mg/m2 ARRY-520 (D1,15) + 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

- 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 myelosuppression

- ARRY-520 + BTZ/Dex shows promising signs of activity in this dose-escalation study

- ORR: 42% (2/5 patients with dose ≥ 1.25 mg/m reached ARRY-520 Schedule 1

- 30% ORR in PI-refractory patients

- 63% ORR (CRR) in PI-sensitive patients

- Expansion cohorts in both schedules are enrolling patients with RRMM, 1-3 prior therapies and BTZ-sensitive disease

References


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Thank You to the Patients and Their Families