

# A Phase 1 Safety and Pharmacokinetic Study of ARRY-520 in Solid Tumors

P. Goncalves<sup>1</sup>, E. Sausville<sup>2</sup>, M. Edelman<sup>2</sup>, N. Pandya<sup>2</sup>, M. Houlehan<sup>1</sup>, B. Freeman<sup>3</sup>, H. Simmons<sup>3</sup>, J. Stallings<sup>3</sup>, M. Ptaszynski<sup>3</sup>, P. LoRusso<sup>1</sup>  
<sup>1</sup>Wayne State University, Karmanos Cancer Center, Detroit, MI; <sup>2</sup>University of Maryland, Greenebaum Cancer Center, Baltimore, MD; <sup>3</sup>Array BioPharma, Boulder, CO

Abstract # 2570

Thank You to the Patients and Their Families

## Introduction

- Kinesin Spindle Protein (KSP) is a novel antimitotic target
  - As KSP is not present in peripheral neurons, KSP inhibitors are not associated with neuropathy
- ARRY-520 is a novel, highly selective KSP inhibitor with activity in a variety of tumor xenograft models
- Preclinical data suggest that multi-day dosing may have better activity than a single dose per cycle
  - Supports clinical investigation of both a Day 1 and a Day 1 + Day 2 dosing schedule

## 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 in 2 different schedules:
    - Schedule 1: IV over 1 hour on Day 1 q 3 weeks
    - Schedule 2: IV over 1 hour on Day 1 + Day 2 q 2 weeks
      - As DLT of neutropenia was observed, dose escalation with prophylactic G-CSF was initiated at maximum tolerated dose (MTD) of Schedule 2 to determine whether significantly higher exposures could be achieved
  - Standard 3 + 3 dose escalation
- ### Primary Objectives
- Determine the safety and MTD of ARRY-520
    - Schedule 2: without and with G-CSF
- ### Secondary Objectives
- Evaluate the plasma PK profile of ARRY-520
  - Assess markers of PD activity
  - Assess preliminary anti-tumor activity of ARRY-520

## Key Eligibility Criteria

- Advanced solid tumors that have recurred or progressed following standard therapy
  - Patient is considered refractory to or ineligible for standard therapy
- ECOG Performance Status 0-2
- Age ≥ 18 years
- Adequate hematologic, hepatic and renal function
- No uncontrolled or symptomatic brain metastases

## Patient Characteristics

Patient Characteristics	Dose (mg/m <sup>2</sup> /day)				
	Schedule 1 (Day 1) 2.5 N=15	Schedule 1 (Day 1) 3.3 N=3	Schedule 2 (Day 1 + Day 2) 1.25 N=9	Schedule 2 (Day 1 + Day 2) 1.6 N=4	Schedule 2 (Day 1 + Day 2) 1.6 + G-CSF N=3
Median age (years) Range	60 47 – 70	59 54 – 73	62 49 – 70	68 40 – 79	58 55 – 67
Gender (male:female)	11:4	2:1	5:4	1:3	2:1
ECOG Performance Status					
0	2	0	1	0	0
1	12	3	6	4	3
2	1	0	2	0	0
Race					
Caucasian	13	2	9	3	2
Black or African American	0	1	0	1	1
Other	2	0	0	0	0

## Disease History

Disease History	Dose (mg/m <sup>2</sup> /day)				
	Schedule 1 (Day 1) 2.5 N=15	Schedule 1 (Day 1) 3.3 N=3	Schedule 2 (Day 1 + Day 2) 1.25 N=9	Schedule 2 (Day 1 + Day 2) 1.6 N=4	Schedule 2 (Day 1 + Day 2) 1.6 + G-CSF N=3
Type of cancer					
Head and neck	1	1	0	1	0
NSCLC	3	0	1	1	0
Melanoma	4	0	0	0	0
CRC	1	1	2	0	1
Pancreas	0	1	2	0	0
GEJ/esophagus	2	0	1	0	0
Other*	4	0	3	2	2
Median prior systemic tx Range	4 1 – 10	3 3 – 3	4 1 – 12	3 2 – 4	1 0 – 6

\*Cholangiocarcinoma, ovarian, ACUP, mesothelioma, thyroid, sarcoma, mixed NSCLC/SCLC, breast

## ARRY-520 Treatment

ARRY-520 Treatment	Dose (mg/m <sup>2</sup> /day)				
	Schedule 1 (Day 1) 2.5* N=15	Schedule 1 (Day 1) 3.3 N=3	Schedule 2 (Day 1 + Day 2) 1.25* N=9	Schedule 2 (Day 1 + Day 2) 1.6 N=4	Schedule 2 (Day 1 + Day 2) 1.6 + G-CSF N=3
Median cycles/patient Range	2 1 – 11	2 2 – 4	3 2 – 4	1.5 1 – 3	3 2 – 3
Dose modifications	8	2	3	2	0
Dose delay Event	6	0	2	1	0
	GI virus, sinusitis, infection, other (3)		anorexia, anemia	FN	
Dose reductions Event	2 N	2 FN	1 anorexia	1 FN	0
Patients with DLT Event	1 sepsis	2 T, FN	2 ↓Na, anorexia	2 FN, ↑AST	0

FN = febrile neutropenia, N = neutropenia, T = thrombocytopenia

\*2.5 mg/m<sup>2</sup>/cycle was determined to be MTD for both schedules without G-CSF

## Safety

Adverse Event	Grade 3/4 Adverse Events, Regardless of Causality*					Total N=33
	Dose (mg/m <sup>2</sup> /day)					
	Schedule 1 (Day 1) 2.5 N=15	Schedule 1 (Day 1) 3.3 N=3	Schedule 2 (Day 1 + Day 2) 1.25 N=9	Schedule 2 (Day 1 + Day 2) 1.6 N=4	Schedule 2 (Day 1 + Day 2) 1.6 + G-CSF N=2	
Neutropenia	9 (60%)	3 (100%)	2 (22%)	2 (50%)	0	16 (48%)
Leukopenia	6 (40%)	1 (33%)	0	2 (50%)	0	9 (27%)
Hyponatremia	1 (7%)	1 (33%)	1 (11%)	1 (25%)	0	4 (12%)
Lymphopenia	3 (20%)	0	0	0	0	3 (9%)
Febrile neutropenia	0	2 (67%)	0	1 (25%)	0	3 (9%)

\*Grade 3/4 events, regardless of assessed causality, occurring in > 2 patients overall (interim data)

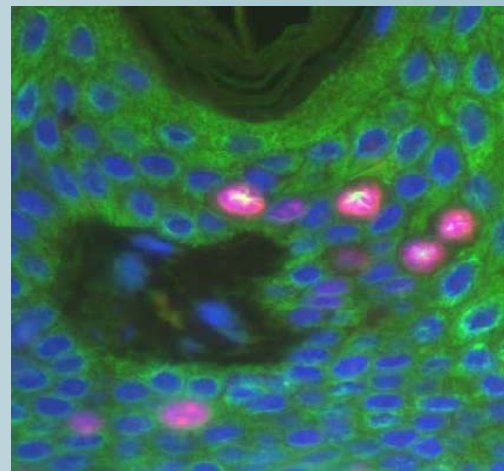
## Treatment-Related Adverse Events\*

Adverse Event	Dose (mg/m <sup>2</sup> /day)					Total N=33
	Dose (mg/m <sup>2</sup> /day)					
	Schedule 1 (Day 1) 2.5 N=15	Schedule 1 (Day 1) 3.3 N=3	Schedule 2 (Day 1 + Day 2) 1.25 N=9	Schedule 2 (Day 1 + Day 2) 1.6 N=4	Schedule 2 (Day 1 + Day 2) 1.6 + G-CSF N=2	
Neutropenia Grade 1/2 Grade 3/4	3 (20%) 9 (60%)	0 3 (100%)	0 1 (11%)	0 2 (50%)	0	3 (9%) 15 (45%)
Leukopenia Grade 1/2 Grade 3/4	4 (27%) 6 (40%)	1 (33%) 1 (33%)	0 0	1 (25%) 2 (50%)	0	6 (18%) 9 (27%)
Fatigue Grade 1/2 Grade 3/4	4 (27%) 0	0 0	2 (22%) 0	0 0	0	6 (18%) 0
Anorexia Grade 1/2 Grade 3/4	2 (13%) 0	0 0	1 (11%) 1 (11%)	1 (25%) 0	0	4 (12%) 1 (3%)
Lymphopenia Grade 1/2 Grade 3/4	1 (7%) 3 (20%)	0 0	0 0	1 (25%) 0	0	2 (6%) 3 (9%)

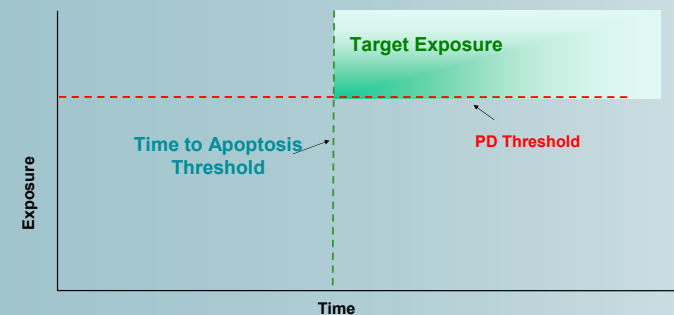
\*Events assessed as treatment related by the Investigator, occurring in ≥ 15% patients overall (interim data)

## Pharmacodynamics

- ### Schedule 1
- PD evaluations included core needle biopsies of tumor lesions, analyzed for monopolar spindles
  - ARRY-520 showed evidence of PD activity
  - Monopolar spindles were observed at 24 and 48 hours postdose in all biopsies at 2.5 mg/m<sup>2</sup>/day q 3 weeks



Blue DNA  
Green Tubulin  
Red Ki-67 (proliferation)



Data suggest that antitumor activity requires prolonged exposure above a concentration that can arrest cells in mitosis for sufficient time to allow apoptosis to occur

- The goal of the Day 1 + Day 2 dosing schedule (Schedule 2) was to prolong exposure to ARRY-520 and potentially improve antitumor activity

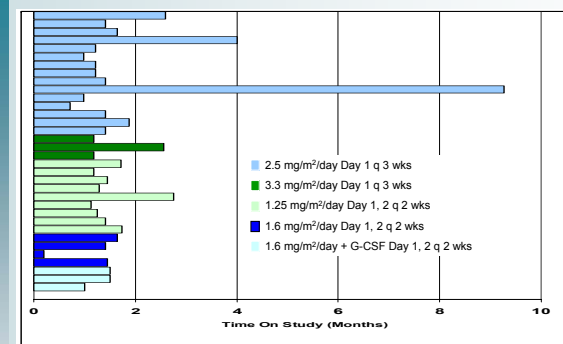
## Pharmacokinetics

- Plasma samples were collected during Cycle 1 and 2 for up to 2 weeks after the last ARRY-520 infusion
- Preliminary population and individual (post-hoc) plasma PK parameters were estimated
- To assess urinary excretion of ARRY-520, selected patients underwent 24-hour urine collections on Day 1 of Cycles 1 and 2
- ARRY-520 PK was best described by a two-compartment linear model
- Population PK estimates showed moderate-to-high inter-individual variability (IIV) as %CV
  - CL (L/hr/m<sup>2</sup>) – 1.69 (45.8%)
  - V<sub>1</sub> (L/m<sup>2</sup>) – 14.5 (71.2%)
- 2-8% of the ARRY-520 dose was excreted unchanged in the urine over a 24-hour period following infusion
  - N=6 from Schedule 1

Parameter	Schedule 1 (Day 1)		Schedule 2 (Day 1 + Day 2)	
	2.5 mg/m <sup>2</sup> N=15	3.3 mg/m <sup>2</sup> N=3	1.25 mg/m <sup>2</sup> /day N=9	1.6 mg/m <sup>2</sup> /day N=7
CL (L/hr/m <sup>2</sup> )	1.61 (31.3%)	2.29 (77.5%)	1.57 (53.8%)	1.92 (51.9%)
V <sub>1</sub> (L/m <sup>2</sup> )	11.7 (24.5%)	13.1 (37.2%)	16.2 (96.6%)	28.1 (94.7%)
AUC <sub>inf</sub> (hr-ng/mL)	1560 (39.6%)	1440 (46.3%)	1590 (37.7%)	1670 (37.1%)
C <sub>max,obs</sub> (ng/mL)	56.4 (38.8%)	46.6 (15.8%)	43.2 (48.9%)	55.7 (54.6%)
T <sub>1/2α</sub> (hr)	0.220 (0.146 – 0.275)	0.192 (0.164 – 0.257)	0.237 (0.126 – 0.880)	0.415 (0.200 – 1.34)
T <sub>1/2β</sub> (hr)	69.5 (27.4 – 93.7)	63.9 (43.8 – 96.2)	62.3 (24.4 – 196)	79.1 (54.8 – 138)

CL, V<sub>1</sub>, AUC<sub>inf</sub> and C<sub>max,obs</sub> values reported as geometric mean (CV), t<sub>1/2</sub> values reported as median (range)

## Preliminary Anti-Tumor Activity



- A total of 30 patients were evaluable for tumor response using modified RECIST criteria
- Two patients experienced prolonged SD at 2.5 mg/m<sup>2</sup> q 3 weeks
  - Patient with malignant melanoma: SD for 9.3 months, 5 prior systemic therapies
  - Patient with ovarian cancer: SD for 4.0 months, 10 prior systemic therapies

## Summary

- ARRY-520, a novel, first in class agent administered as a single IV dose demonstrated an acceptable safety profile at dose levels up to 1.6 mg/m<sup>2</sup>/day + G-CSF
- The MTD was 2.5 mg/m<sup>2</sup>/day in both schedules without G-CSF
  - Neutropenia was the most commonly reported AE
- Patients displayed linear PK, a low CL and a moderate V<sub>1</sub>, with a modest IIV in PK parameters
- Urinary excretion of unchanged ARRY-520 appears to be minor (2%-8% of dose over 24 hours) and is consistent with preclinical ADME studies
- Although ARRY-520 showed on-target pharmacodynamic activity, there was little evidence of antitumor activity
  - This contrasts with observed clinical benefit seen in patients with relapsed/refractory multiple myeloma (ASCO abstract # 8132)