A Phase 1 Study of ARRY-382, an Oral Inhibitor of Colony-stimulating Factor-1 Receptor (CSF1R), in Patients with Advanced or Metastatic Cancers

Abstract #A252
AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics
October 19-23, 2013, Boston, MA
Available at www.arraybiopharma.com

J. Bendell[1], A.W. Tolcher[3], S. Jones[1], M. Beeram[3], J. Infante[1], P. Larsen[2], K. Rasor[2], J.E. Garrus[2], J. Li[2], P.L. Cable[2], C. Eberhardt[2], J. Schreiber[2], S. Rush[2], K.W. Wood[2], E. Barrett[2], A. Patnaik[3]
[1]Sarah Cannon Research Institute, Nashville, TN; [2]Array BioPharma Inc., Boulder, CO; [3]South Texas Accelerated Research Therapeutics, San Antonio, TX

We Thank the Patients and Their Families

Introduction

- ARRY-382 is a potent, highly selective oral small-molecule inhibitor of CSF1R (colony-stimulating factor-1 receptor) with an IC_{50} for CSF1R autophosphorylation inhibition of 9 nM.
- CSF1R is a receptor tyrosine kinase normally expressed on the surface of mononuclear phagocytes. Within the tumor microenvironment, CSF1R signaling is thought to play an important role in recruitment and differentiation of tumor-associated macrophages (TAMs) and osteoclasts, promoting disease progression through suppression of anti-tumor immune response, promotion of angiogenesis, tumor cell metastasis and tumor-induced osteolysis.
- In cell-based models, ARRY-382 has demonstrated potent inhibition of osteoclast differentiation (IC_{50} = 4 nM) and bone resorption (IC_{50} = 58 nM). In mice tumor models using HEK-293 cells, ARRY-382 inhibited CSF1R activity (ED_{50} = 3 mg/kg).
- In rats implanted with MRMT-1 mammary gland carcinoma cells, ARRY-382 showed evidence of allodynia relief and significantly decreased tumor-induced osteolytic bone damage (ED_{50} = 9 mg/kg) and tartrate-resistant acid phosphatase (TRAP) serum levels.
- Because of the encouraging nonclinical activity demonstrated by ARRY-382, a Phase 1 first-in-human dose-escalation study was conducted to determine the maximum tolerated dose (MTD) and to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of ARRY-382 in patients with advanced or metastatic cancers refractory to standard treatment.

Study Design

- An accelerated titration design was used in which the initial cohorts included only a single patient each, with transition to a modified 3+3 design upon emergence of toxicities meeting protocol-defined criteria or by mutual agreement of investigators and sponsor.

ARRY-382 Schedule / Doses	Assessments (Cycle 1)	Assessments (Subsequent Cycles)
28-day cycles: 25 mg QD* 50 mg QD* 100 mg QD* 200 mg QD* 400 mg QD† 500 mg QD† * accelerated titration (1 patient evaluated at each dose level) † modified 3+3	**Safety** DLTs, AEs, clinical laboratory tests, physical exams, vital signs, ECGs **Pharmacokinetics (Blood)** Days 1 and 15 pre-dose and up to 24 hours post-dose Days 8 and 22 pre-dose **Biomarkers (Blood)** *Circulating tumor cells*: Day 1 pre-dose *Cytokines*: Days 1, 8, 15, 22 pre-dose *Nonclassical Monocytes*: Days 1 and 15 pre-dose and up to 24 hours post-dose **Biomarkers (Urine)** *Urine NTX*: Days 1, 8, 22 pre-dose	**Safety** AEs, clinical laboratory tests, physical exams, vital signs, ECGs **Pharmacokinetics (Blood)** Day 1 pre-dose **Biomarkers (Blood)** *Circulating tumor cells*: Day 1 pre-dose *Cytokines*: Day 1 pre-dose **Biomarkers (Urine)** *Urine NTX*: Day 1 pre-dose **Efficacy** Tumor response via RECIST v1.1 (every 2 cycles)

Methods

- Plasma concentrations of ARRY-382 and 3 metabolites were quantitated using a validated LC-MS/MS method. PK parameters were estimated using Phoenix WinNonlin noncompartmental analysis. Food effect was assessed by C_{trough} ratios following administration with and without food.
- Circulating tumor cells were enumerated using the CellSearch Profile kit. CSF1 and other circulating cytokines produced by, or affecting, macrophages were measured in serum using a Meso Scale Discovery custom quantitative multiplex immunoassay. Nonclassical monocytes (NCM) were analyzed in blood using flow cytometry. Urinary NTX was measured using the Vitros NTX assay.

Patient Demographics and Baseline Characteristics

	N = 26
Gender (male / female), n	12 / 14
Median age (range), years	63 (45-78)
ECOG (0/1), n	14 / 12
Race (Black / White), n	2 / 24
Tumor type, n	
Colorectal	8
Breast, Pancreatic, Prostate, NSCLC	2 (each)
Other	10
Median prior systemic cancer treatments (range)	5 (2-16)
Chemotherapy, n	25
Targeted / Biologic, n	16
Hormonal, n	4

Safety

Dose-limiting Toxicities (DLTs) and Maximum Tolerated Dose

ARRY-382 Dose	DLT
25 mg QD (N=1)	none
50 mg QD (N=1)	none
100 mg QD (N=1)	none
200 mg QD (N=6)	none
MTD 400 mg QD (N=11)	1/11: CK increased (G3)†
Non-tolerated Dose 500 mg QD (N=6)	2/6: pyrexia (G3)‡ AST increased (G3)‡

The 200 mg QD cohort was expanded to enable further evaluation of ARRY-382 target coverage at that dose.
† Did not require dose modification. ‡ Required dose interruption and subsequent reduction to 400 mg QD.

All-cause Adverse Events (≥ 20% Patients)

	ARRY-382 Dose (QD)*											
	200 mg N = 6			400 mg N = 11			500 mg N = 6			Total (25 to 500 mg QD) N = 26		
Grade	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4
Fatigue	3	0	0	6	1	0	3	0	0	15 (58%)	1 (4%)	0
Nausea	1	0	0	1	1	0	3	0	0	7 (27%)	1 (4%)	0
Vomiting	1	0	0	2	1	0	1	1	0	6 (23%)	2 (8%)	0
Blood CK increased	0	0	0	0	4	0	1	2	0	1 (4%)	6 (23%)	0
Edema peripheral	1	0	0	4	0	0	2	0	0	7 (27%)	0	0
Decreased appetite	0	0	0	2	0	0	2	0	0	6 (23%)	0	0

* AEs reported at doses of 25 mg QD (n = 1), 50 mg QD (n = 1) and 100 mg QD (n = 1) are presented in the total column only.

Treatment-related Adverse Events (≥ 10% Patients)

	ARRY-382 Dose (QD)*											
	200 mg N = 6			400 mg N = 11			500 mg N = 6			Total (25 to 500 mg QD) N = 26		
Grade	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4
Fatigue	2	0	0	5	0	0	1	0	0	11 (42%)	0	0
Blood CK increased	0	0	0	0	4	0	1	2	0	1 (4%)	6 (23%)	0
Nausea	1	0	0	1	0	0	2	0	0	6 (23%)	0	0
Decreased appetite	0	0	0	1	0	0	1	0	0	4 (15%)	0	0
Vomiting	0	0	0	1	0	0	1	0	0	3 (12%)	0	0

* AEs reported at doses of 25 mg QD (n = 1), 50 mg QD (n = 1) and 100 mg QD (n = 1) are presented in the total column only.

Laboratory Abnormalities (Shift from Baseline)

	ARRY-382 Dose (QD)*											
	200 mg N = 6			400 mg N = 11			500 mg N = 6			Total (25 to 500 mg QD) N = 26		
Grade Shift	1/2	3	4	1/2	3	4	1/2	3	4	1/2	3	4
Creatine kinase	5	0	0	6	4	0	4	2	0	16 (62%)	6 (23%)	0
AST	6	0	0	10	0	1	6	0	0	23 (88%)	0	1 (4%)
ALT	2	0	0	2	0	1	1	0	0	5 (19%)	0	1 (4%)
Bilirubin	0	0	0	1	0	0	1	0	0	2 (8%)	0	0

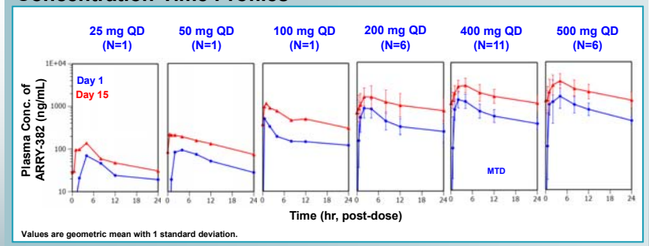
* Shifts reported at doses of 25 mg QD (n = 1), 50 mg QD (n = 1) and 100 mg QD (n = 1) are presented in the total column only .

Safety Summary

- 26 patients were evaluated for safety at doses of 25 to 500 mg QD ARRY-382. Across all cohorts, patients received a median of 2 cycles (range 1 to 5 cycles).
- The 400 mg QD dose was declared the MTD.
- No reported serious adverse events (SAEs) or deaths were attributed to ARRY-382 treatment.
- QTcF changes were Grade 1 and did not appear to correlate with ARRY-382 plasma concentration.
- Elevations in AST and CK were frequently reported but rarely treatment limiting. Isoenzyme evaluations indicated that CK elevations were not attributed to cardiac muscle damage.

Pharmacokinetics

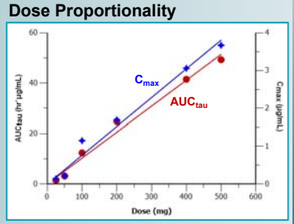
Concentration-Time Profiles



Values are geometric mean with 1 standard deviation.

- Consistent concentration-time profiles with increasing dose and repeat dosing.
- Low peak-to-trough suggesting QD is suitable.
- The exposure (AUC_{tau} and C_{max}) of ARRY-382 increased with increasing dose.
- Appears dose proportional for AUC_{tau} and C_{max} at steady-state.
- Good target coverage around the clock with ≥ 200 mg QD dosing. At the MTD (400 mg QD), ARRY-382 plasma concentrations were continuously > 200-fold above the cell-based IC_{50} for CSF1R inhibition.

Dose Proportionality



Pharmacokinetic Parameters

Visit (Cycle 1)	Parameter (units)	25 mg QD (N=1)	50 mg QD (N=1)	100 mg QD (N=1)	200 mg QD (N=6)	400 mg QD (N=11)	500 mg QD (N=6)	Total (N=26)
Day 1	AUC_{tau} (hr*µg/mL)	0.737 (NC)	1.25 (NC)	4.08 (NC)	9.47 (52.2)	15.4 (35.6)	19.5 (39.4)	NA
	C_{max} (µg/mL)	0.0706 (NC)	0.0943 (NC)	0.506 (NC)	0.923 (53.7)	1.38 (42.1)	1.77 (66.1)	NA
	T_{max} (hr)	4.00 (4.00 - 4.00)	3.85 (3.85 - 3.85)	0.517 (0.517 - 0.517)	3.00 (1.00 - 4.03)	2.05 (2.00 - 4.15)	3.06 (2.00 - 10.0)	2.15 (0.517 - 10.0)
Day 15	AUC_{tau} (hr*µg/mL)	1.43 (NC)	3.17 (NC)	12.4 (NC)	24.8 (68.7)	41.5 (39.4)	49.3 (41.6)	NA
	C_{max} (µg/mL)	0.140 (NC)	0.220 (NC)	1.15 (NC)	1.69 (64.0)	3.06 (37.7)	3.67 (34.2)	NA
	T_{max} (hr)	4.00 (4.00 - 4.00)	0.583 (0.583 - 0.583)	1.12 (1.12 - 1.12)	1.98 (0.550 - 4.08)	2.04 (1.00 - 4.15)	4.00 (2.00 - 4.15)	2.04 (0.550 - 4.15)
	Accumulation Ratio (R_{AUC})	1.94 (NC)	2.53 (NC)	3.05 (NC)	2.61 (37.4)	2.90 (27.8)	2.21 (31.4)	2.61 (30.6)

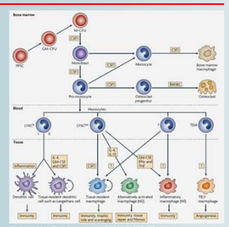
All values are geometric mean (%CV) except T_{max} which is median (min-max). NA = not applicable. NC = not calculated.

- Good reproducibility in exposure in this cancer population at the MTD of 400 mg QD (39% CV for steady-state AUC_{tau}).
- Accumulation with repeat dosing (2.61-fold) is consistent with longer $t_{1/2}$ (~18 hr) and not dose dependent.
- No food effect based on trough concentrations of ARRY-382.
- At steady-state (400 mg QD), the metabolite-to-parent ratios for AUC_{tau} ranged from 14% to 32%.

Biomarkers

- Inhibition of CSF1R may be expected to affect CSF1 (the ligand of CSF1R), decrease NCM counts and decrease urinary collagen type 1 cross-linked N-telopeptide (NTX).
- Although AST and CK increases are traditionally associated with organ damage, in the case of CSF1 inhibition they may also be mechanistic biomarkers of activity due to on-target effects on macrophages, Kupffer cells or other cell types.[1-3]
- Elevations in ALT, AST and CK were observed in ARRY-382 nonclinical studies, but the changes were reversible and there was no evidence of histological changes or organ damage.

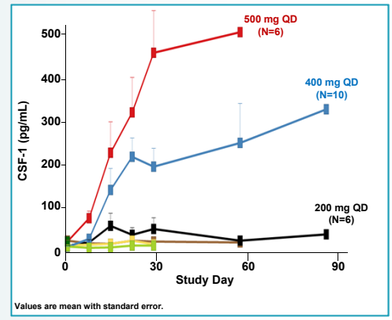
1. Smit et al. **JBC** (1987) 262:13020-6.
2. Nenseter et al. **J Lipid Res** (1992) 33:867-77.
3. Arany et al. **Growth Regul** (1996) 6:32-41.



Pollard **Nat Rev Immunol** (2008) 9:259-70.

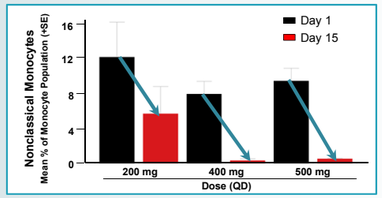
Increases in CSF1

- At doses < 200 mg QD, effects on CSF1 were not significant.
- Effects on CSF1 were observed at 200 mg QD (4-fold average maximum change from baseline).
- A 28-fold increase in CSF1 was observed for the 400 and 500 mg QD cohorts. Changes were related to trough drug concentrations.
- No significant changes were observed with other exploratory biomarkers (circulating tumor cells, IL-6, IL-8, IL-10, MCP-1, MIP1b, TRAP5b, or bALP).



Values are mean with standard error.

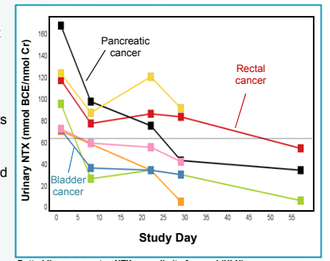
Decreases in CD14^{dim}/CD16^{+} Nonclassical Monocytes



- ARRY-382 had a significant effect on circulating NCM count.
- Following 15 days of dosing with 400 mg QD ARRY-382, NCM count was reduced to 4% of the pre-study count (N = 5 patients).

Decreases in Urinary NTX

- Urinary NTX (uNTX) decreased by 62% at 500 mg QD (average maximum change from baseline), with a ~40% reduction in the overall study population.
- uNTX time courses for 7 patients with elevated baseline NTX, including 3 patients with bone metastases, are displayed.
- uNTX concentrations decreased rapidly within 1 week of dosing (≥ 100 mg QD) and often continued to decrease to within normal limits while on study.
- Decreases were observed regardless of cancer type.



Dotted line represents uNTX upper limit of normal (ULN).

Tumor Response

- No responses to treatment were observed per RECIST criteria.
- Four patients (15%) with heavily pretreated cancer experienced a best response of stable disease, which lasted > 3 months for 2 patients.

Summary

- ARRY-382 is a highly selective, novel, oral CSF1R kinase inhibitor.
- First-in-human Phase I study completed in oncology patient population.
- MTD of 400 mg QD with biologic activity observed at doses ≥ 200 mg QD.
- Dose-proportional, predictable pharmacokinetics with good QD target coverage.
- Tolerability and evidence for activity support further development in a variety of potential indications including solid tumor therapy in combination with chemotherapy or metastatic bone disease.