Phase 1 Pharmacokinetic (PK) Assessment of ATI-1123, a Novel Human Serum Albumin-Stabilized Nanoparticle Docetaxel Liposomal Formulation, in Patients with Advanced Solid Malignancies

D. Mahalingam[1], A. C. Mita[1], A. Kousba[2], S. Vemulapalli[1], N. S. Gallegos[3], G. Anderson[3], J. Charles[3], J. M. Rogers[4], J. Sarantopoulos[1], M. M. Mita[1], J. Hart[1], N. Senzer[1], J. J. Nemunaitis[5];
[1]Institute for Drug Development, Cancer Therapy and Research Center at University of Texas Health Science Center, San Antonio, TX, 78229. [2]BioAgilytix, San Diego, CA, 92121.
[3]Azaya Therapeutics, Inc., San Antonio, TX, 78249. [4]ResearchPoint, Austin, TX, 78746. [5]Mary Crowley Cancer Research Center, Dallas, TX, 75230.

ABSTRACT

Purpose:

ATI-1123, a novel nanoparticle docetaxel liposomal formulation, is being investigated in patients (pts) with advanced solid malignancies. ATI-1123 is expected to reduce hypersensitivity reactions, have a broader therapeutic index and to enhance systemic exposure to docetaxel. The objective of this study was to investigate the safety, tolerability, pharmacokinetics and tumor response of ATI-1123 in pts with advanced solid tumors following escalating doses of intravenously administered ATI-1123.

Methods:

This phase I study enrolled 29 pts. The dosing (1 hr infusion q 3 weeks) began at 15 mg/m2 using an accelerated titration design, followed by a modified Fibonacci schema to MTD. ATI-1123 doses ranged from 15 to 110 mg/m2. Plasma samples were obtained at baseline, 0.25, 0.5, 1, 2, 4, 8-10, 24, 48 hrs, day 8, and analyzed for encapsulated and non-encapsulated docetaxel using a validated HPLC MS/MS (BQL < 0.405 and 0.595 ng/mL, respectively). PK parameters were determined for encapsulated, the non-encapsulated and total docetaxel in each subject by standard model independent methods (Gibaldi and Perrier, 1982) using WinNonlin Professional 5.2.1 (Pharsight Corp., Mountain View, CA). Dose proportionality for the three analytes was assessed using a power-law model, linear-regression model and ANOVA model.

Results:

Total docetaxel Cmax, AUC(0-inf), T1/2 , CL, and Vss mean values ranged from 2060 ± 643 to 16200 ± 2310 ng/mL, 5710 ± 1550 to 40400 ± 6160 ng/mL/h, 6.57 ± 0.555 to 7.32 ± 0.958 h, 2.63 ± 0.741 to 3.43 ± 1.50 L/h/m2 and 13.3 ± 2.06 to 17.1 ± 10.4 L/m2, respectively. Corresponding values for encapsulated docetaxel were 1560 ± 460 to 9890 ± 2170 ng/mL, 4480 ± 1380 to 28500 ± 7040 ng/mL/h, 5.08 ± 1.08 to 6.23 ± 0.732 h, 3.51 ± 1.08 to 4.42 ± 1.09 L/h/m2 and 15.0 ± 3.11 to 21.3 ± 3.68 L/m2. Encapsulated docetaxel C_{max} and AUC were almost 4-fold higher while clearance was 4- fold lower than the corresponding values for non-encapsulated docetaxel (free portion). $T_{1/2}$ values were ~2-3-fold lower. The PK parameters for free docetaxel concurred with values previously reported for standard docetaxel (Stephen et al., 1999, Bruno et al., 1998, Bruno et al.,1997). The PK exposure of encapsulated, non-encapsulated and total docetaxel was dose proportional as determined by the power-law model where the slope of Ln C_{max} or Ln AUC vs. Ln dose has value of ~1 and 90% confidence intervals for the slope include 1. In addition, p values, determined by regression models and ANOVA for slope and intercepts of C_{max} or AUC (or normalized C_{max} and AUC) vs. dose, supported dose proportionality.

Conclusions:

ATI-1123 exhibited favorable PK in humans. The presence of the encapsulated docetaxel led to the enhanced exposure of docetaxel. The PK exposure of encapsulated, non-encapsulated and total docetaxel was dose proportional. The estimated PK parameters for non-encapsulated docetaxel (free portion) are in reasonable agreement with the corresponding values reported in the literature for standard docetaxel.

Objective

The objective of the PK assessment was to investigate the systemic exposure of docetaxel following IV infusion of the liposomal docetaxel formulations, ATI-1123, in patients (pts) with advanced solid tumors.

Introduction

- ATI-1123, a novel nanoparticle docetaxel liposomal formulation, is being investigated in patients (pts) with advanced solid malignancies.
- ATI-1123 is expected to reduce hypersensitivity reactions, have a broader therapeutic index and to enhance systemic exposure docetaxel.
- This poster presents the PK of encapsulated docetaxel, non-encapsulated docetaxel and total docetaxel (the sum of encapsulated and nonencapsulated docetaxel) following IV infusion of ATI-1123.

Materials and Methods

Study

A Phase I, open-label, dose-escalation, safety, pharmacokinetic (PK), and pharmacodynamic study of intravenously administered ATI-1123, a liposomal docetaxel formulation, in patients with advanced solid tumors.

Dose

ATI-1123 was administered once every 3 week as a 1 h IV infusion at doses ranging from 15 to 110 mg/m^2. Blood samples were obtained at baseline, 0.25, 0.5, 1, 2, 4, 8-10, 24, 48 h and day 8 for cycle 1 and at pre-dose and 1 h for the following cycles.

Analytical Method

Plasma samples were analyzed for encapsulated and non-encapsulated docetaxel, using a validated HPLC-MS/MS assay.

PK Analysis

Plasma PK parameters (C_{max}, T_{max}, $T_{1/2}$ and $AUC_{(0-inf)}$) of encapsulated docetaxel, non-encapsulated docetaxel and total docetaxel were determined using Model 202 in Phoenix WinNonlin Professional 6.1 (Pharsight Corp., Mountain View, CA).

Dose proportionality was examined using a simple linear regression model and a power-law model using GraphPad Prism v 5.01 (GraphPad Inc., CA). The equation for linear regression is $AUC_{(0-inf)}$ or $C_{max} = \mu + \beta$ dose; where μ represents the intercept and β the slope of the regression model. If the slope was significantly greater than zero and the intercept not significantly greater than zero, then evidence of linearity was assumed. In the power model, log C_{max} and log $AUC_{(0-inf)}$ were modeled as a function of subject, and log dose, with subject being considered as a random factor (Klamerus, et al., 1992; Gough, et al., 1995). The equation for the power model is log C_{max} or log $AUC_{(0-inf)}$ = log (μ) + β log dose +ε; where log(μ) and β are the intercept and slope, respectively. On the back transformed scale, this model is $EAUC_{(0-inf)}$ or $C_{max} = \alpha$ doseβ. A slope of 1.00 indicates perfect dose proportionality, a slope of less than or greater than 1.00 indicates a less than or greater than dose proportionality, respectively.

Figure 1

Mean plasma concentration-time profiles of encapsulated, non-encapsulated and total Docetaxel in human subjects following 1 h infusion of escalating doses of ATI-1123

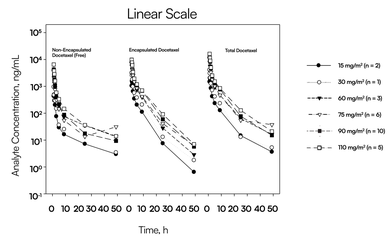


Table 1

Summary mean plasma PK parameters of encapsulated, non-encapsulated and total Docetaxel in human subjects following 1 h infusion of escalating doses of ATI-1123

PK Parameters	15 mg/m²							30 mg/m²						
	Encapsulated		Non-encapsulated		Total			Encapsulated		Non-encapsulated		Total		
	N	Mean	SD	Mean	SD¹	Mean	SD	N	Mean	SD	Mean	SD¹	Mean	SD
T_{max}, h²	2	1.25	1.25-1.25	1.14	1.03-1.25	1.14	1.03-1.25	1	1.03	NC	1.03	NC	1.03	NC
C_{max}, ng/mL	2	1,560	460	531	144	2,060	643	1	3,160	NC	951	NC	4,110	NC
$T_{1/2}$, h²	2	5.08	0.0405	18.0	7.30	7.16	0.600	1	5.57	NC	13.6	NC	6.10	NC
$AUC_{(0-\infty)}$, ng•h/mL	2	4,470	1,390	1,280	161	5,700	1,570	1	8,480	NC	2,070	NC	10,200	NC

PK Parameters	60 mg/m²							75 mg/m2						
	Encapsulated		Non-encapsulated		Total			Encapsulated		Non-encapsulated		Total		
	N	Mean	SD	Mean	SD¹	Mean	SD	N	Mean	SD	Mean	SD¹	Mean	SD
T_{max}, h²	3	1.05	1-1.13	1.05	1-1.13	1.05	1-1.13	6	1.05	1-1.13	1.05	1-1.13	1.05	1-1.13
C_{max}, ng/mL	3	6,950	1,310	3,480	1,340	10,500	1,960	6	7,290	2,290	3,770	2,370	11,100	1,130
$T_{1/2}$, h²	3	5.15	0.534	15.7	2.53	7.75	1.55	6	6.24	0.655	11.3	3.86	6.57	1.57
$AUC_{(0-\infty)}$, ng•h/mL	3	18,200	5,840	7,220	2,590	25,200	4,760	6	19,500	3,180	6,270	2,900	25,800	644

PK Parameters	90 mg/m²							110 mg/m2						
	Encapsulated		Non-encapsulated		Total			Encapsulated		Non-encapsulated		Total		
	N	Mean	SD	Mean	SD¹	Mean	SD	N	Mean	SD	Mean	SD¹	Mean	SD
T_{max}, h²	10	1.06	1-1.23	1.06	1-1.23	1.06	1-1.23	5	1.17	1.03-3.93	1.08	1.03-3.93	1.08	1.03-3.93
C_{max}, ng/mL	10	9,890	3,220	4,280	1,550	14,200	4,060	5	9,890	2,170	6,510	1,590	16,200	2,310
$T_{1/2}$, h²	9	5.56	0.246	9.75	2.56	6.40	0.466	5	5.66	0.190	10.7	1.55	6.69	0.216
$AUC_{(0-\infty)}$, ng•h/mL	9	28,000	8,980	7,940	2,980	35,900	10,300	5	30,700	11,200	13,300	4,080	43,900	13,900

Summary:

1) Plasma PK of the two analytes and their summation was dose proportional and linear.
2) Exposure of encapsulated analyte is 3-4 fold that of the non-encapsulated analyte.

Table 2.

Summary statistics for the assessment of dose proportionality of encapsulated, non-encapsulated and total Docetaxel in human subjects following 1 h infusion of escalating doses of ATI-1123. A. Linear regression model and B. Power model.

A

Analyte	Parameter	Mean (SE)	Slope 95% CI	P-value (Slope = 0)	Mean (SE)	Intercept 95% CI	P-value (Intercept = 0)
Encapsulated	C_{max}	92.11 (18.78)	53.42 to 130.8	< 0.0001	817.3 (1565)	-2406 to 4041	0.6061
	$AUC_{(0-inf)}$	290.5 (56.27)	174.4 to 406.6	< 0.0001	-2916 (4672)	-9673 to 9615	0.9951
Non-encapsulated	C_{max}	58.91 (12.39)	33.39 to 84.43	< 0.0001	-579.0 (1032)	-2705 to 1547	0.5798
	$AUC_{(0-inf)}$	115.9 (23.73)	-5446 to 2689	< 0.0001	-1378 (1971)	-5446 to 2689	0.4910
Total	C_{max}	149.8 (20.87)	106.9 to 192.8	< 0.0001	314.3 (1739)	-3267 to 3896	0.8580
	$AUC_{(0-inf)}$	407.5 (64.60)	274.2 to 540.9	< 0.0001	-1559 (5365)	-12630 to 9514	0.7738

B

Analyte	Parameter	Mean (SE)	Slope 95% CI	P-value (Intercept = 0)
Encapsulated	Log C_{max}	0.9524 (0.1105)	0.7637 to 1.141	0.6700
	Log $AUC_{(0-inf)}$	0.9766 (0.1085)	0.7910 to 1.162	0.8511
Non-encapsulated	Log C_{max}	1.211 (0.1446)	0.9637 to 1.458	0.1576
	Log $AUC_{(0-inf)}$	1.088 (0.1421)	0.8450 to 1.331	0.5410
Total	Log C_{max}	1.047 (0.07867)	0.9128 to 1.182	0.5538
	Log $AUC_{(0-inf)}$	1.019 (0.08842)	0.8672 to 1.170	0.8357

Summary:

Plasma exposure increases linearly in a dose proportional manner

Figure 2

C_{max} and $AUC_{(0-inf)}$ of encapsulated Docetaxel versus ATI-1123 dose in human subjects following 1 h infusion of escalating doses of ATI-1123

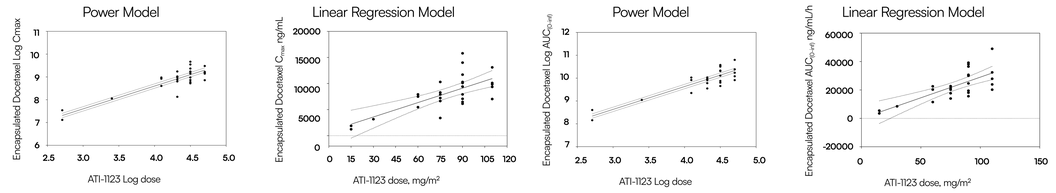


Figure 3

C_{max} and $AUC_{(0-inf)}$ of non-encapsulated Docetaxel versus ATI-1123 dose in human subjects following 1 h infusion of escalating doses of ATI-1123

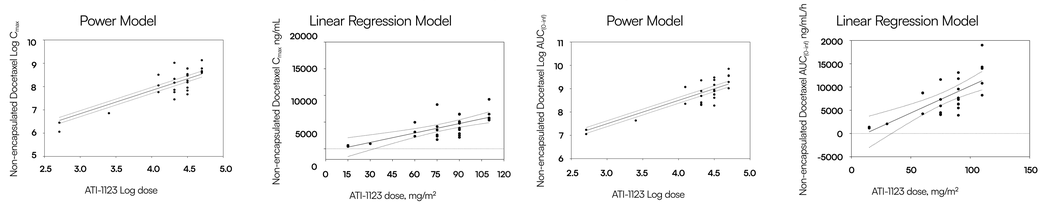
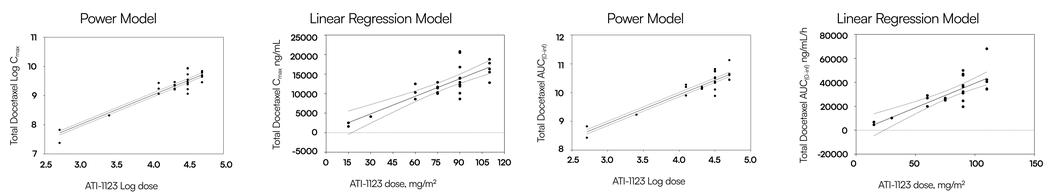


Figure 4

C_{max} and $AUC_{(0-inf)}$ of total Docetaxel versus ATI-1123 dose in human subjects following 1 h Infusion of escalating doses of ATI-1123



Conclusions

ATI-1123 exhibited favorable PK in humans. The presence of the encapsulated docetaxel led to enhanced exposure of docetaxel. The PK exposure of encapsulated, non-encapsulated and total docetaxel was dose proportional. Estimated PK parameters for non-encapsulated docetaxel (free portion) concurred with the corresponding values previously reported for standard docetaxel.

AZAYA THERAPEUTICS™

CANCER THERAPY & RESEARCH CENTER
UT HEALTH SCIENCE CENTER™
INSTITUTE FOR DRUG DEVELOPMENT

References

Gough, K., Hutchison, M., Keene, O., Byrom, B., Ellis, S., Lacey, L. and McKellar. J. Assessment of dose proportionality: Report from the statisticians in the pharmaceutical industry/pharmacokinetics UK joint working party. Drug Info. J. 29:1039—1048.

K. J., Maloney, K., Rudolph, R. L., Sisenwine, S. F., Jusko, W. J. and Chiang, S. T. Introduction of a Composite Parameter to the Pharmacokinetics of Venalfaxine and its Active O-desmethyl Metabolite. J. Clin. Pharmacol. 32:716—724.