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 hypercoagulability reactions, have a broader therapeutic index and to enhance systemic exposure to docetaxel. The objective of this study was to establish 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 1/2 study enrolled 29 pts. The dosing (1 h infusion over 3 weeks) began at 15 mg/m² using an accelerated titration design, followed by a modified Fibonacci scheme to MTID. ATI-1123 doses ranged from 15 to 110 mg/m². Plasma samples were obtained at baseline, 0.25, 0.5, 1, 2, 4, 6, 10, 15, 20, 24, 48, 72 h, and day 8 and day 15 post-dose (day 28 and 56, respectively). PK parameters were determined for encapsulated, the non-encapsulated and total docetaxel in each subject by standard model independent methods (DAS2.1 and Ferrovi 2002) using WinNonlin Professional 3.2.2 (Pharsight Corp., Mountain View, CA). AUCs proportionality for the three analytes was assessed using a power-law model, linear-regression model and ARCH model.

Results: Total docetaxel, Encapsulated and Non-encapsulated Cₜₘₓ, Tₚₜₙ, Cs and Tₚₙ were estimated between 5000 and 16,200 (10,500 ± 4500 ng/ml), 6.75 ± 0.55 to 72.8 ± 0.54, 2.63 ± 0.74 to 3.41 ± 1.2, 10,500 and 13.3 ± 2.67 to 17.1 ± 0.4 U/I, respectively. Corresponding values for encapsulated docetaxel were 7500 to 10,500, 400 to 6800, 2200 to 5000, 10,000 to 3500, 4000 to 7000, 900 to 1500, 2.5 to 3.0, 13.3 ± 2.67 to 17.1 ± 0.4 U/I, respectively. Corresponding values for non-encapsulated docetaxel were 4800 to 5200, 4800 ± 200 to 5200 ± 200, 10,000 to 3500, 4000 to 7000, 900 to 1500, 2.5 to 3.0, 13.3 ± 2.67 to 17.1 ± 0.4 U/I, respectively. Docetaxel Cₜₘₓ and AUC were almost 4-fold higher while clearance was Cₜₘₓ lower than the corresponding values for non-encapsulated docetaxel (free portion). Tₚₙ values were 3-4-fold higher. The PK parameters for free docetaxel (with and without previously reported for standard docetaxel) (Rogers et al. 2000, Bono et al. 2003, Brown et al. 2003). 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 Cₜₘₓ or ln AUC vs ln dose was > 1 in both cases. AUC confidence intervals for the slopes included ± 0.2, which is within variability of the AUC regression models and AUC and Cₜₘₓ slopes and intercepts of Cₜₘₓ or AUC or non-encapsulated and Encapsulated AUC slope, supported dose proportionality.

Conclusions: ATI-1123 exhibited favorable PK in humans. The presence of the encapsulated docetaxel led to an 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 accordance 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 malignancies.

Materials and Methods

Study: A Phase 1/2, 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 weeks as a 1 h infusion at doses ranging from 15 to 110 mg/m². Blood samples were obtained at baseline, 0.25, 0.5, 1, 2, 4, 6, 10, 15, 20, 24, 48, 72 h and day 8 for cycle 1 and at pre-dose and 1 h for the following cycle.

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

PK Analysis: Plasma PK parameters (Cₜₘₓ, Tₚₙ, Tₚₙ, M₀, T½, M₀, T½, M₀, T½) of encapsulated, non-encapsulated and total docetaxel were determined using Model 202 in Pharsight WinNonlin Professional 3.2.2 (Pharsight Corp., Mountain View, CA)

Dose proportionality was examined using a simple linear regression model and a power-law model using GraphPad Prism 5.0 (GraphPad Inc, CA). The equations for linear regression is AUC = B + a X, where A represents the intercept and B is 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 AUC = log Cₜₘₓ + log X, where X is modeled as a function of subject, and log dose, with subject being considered as a random factor (Kopec et al., 1992; Gough et al., 1995). The equation for the power model is log AUC = log Cₜₘₓ + log X, where log dose = log (mg/kg) and B is the intercept and slope, respectively. On the back-transformed scale, this model is Cₜₘₓ = B X. A slope of 1.0 indicates perfect dose proportionality, a slope of less than or greater than 1.0 indicates less than or greater than dose proportionality, respectively.

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.

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

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.

Summary: Plasma exposure increases linearly in a dose proportional manner.

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.

Figure 2. Cₜₘₓ and AUC max of encapsulated Docetaxel versus ATI-1123 dose in human subjects following 1 h infusion of escalating doses of ATI-1123.