



# Phase 1 Study of ATI-1123, a Novel Human Serum Albumin-Stabilized Nanoparticle Docetaxel Liposomal Formulation, in Patients with Advanced Solid Malignancies



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## Background and Aims

Liposomal nanoparticle docetaxel formulations may reduce hypersensitivity reactions, eliminate premedication requirements, have a broader therapeutic index, and enhance systemic exposure. ATI-1123 is a patented liposomal docetaxel formulation utilizing human serum albumin that facilitates tumor targeting. We studied safety, tolerability, pharmacokinetics and tumor response of ATI-1123 in patients with advanced solid tumors.

## Study Objectives

- The objectives of this study were to:
- Determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of ATI-1123 administered every 3 weeks in patients with advanced solid tumors
  - Establish the Phase II dose of ATI-1123
  - Establish the pharmacokinetics of intravenously administered ATI-1123
  - Observe patients for any evidence of anti-tumor activity

## Study Methods

- Eligible patients for this initial study with ATI-1123 had progressive disease following standard therapy, ECOG performance status of  $\leq 2$ , adequate organ function and anticipated survival  $\geq 3$  months.
- Dosing (1 hr infusion) began at 15 mg/m<sup>2</sup> using an accelerated titration design, followed by a modified Fibonacci schema to MTD. Dosing was continued until patients had progressive disease or unacceptable toxicities.
- Patients were not to be pre-medicated prior to Cycle 1

\*\*The ATI-1123101 data presented are preliminary, unaudited, and unlocked data

## Study Results

### Baseline Characteristics

- 29 patients enrolled
- Mean age 60 years; (range: 35 – 81)
- 48% male; 52% female
- Mean prior regimens = 3; (range: 1-11)
- Prior Taxotere™ (docetaxel) in 9 (31%) patients

### ATI-1123 Doses Studied

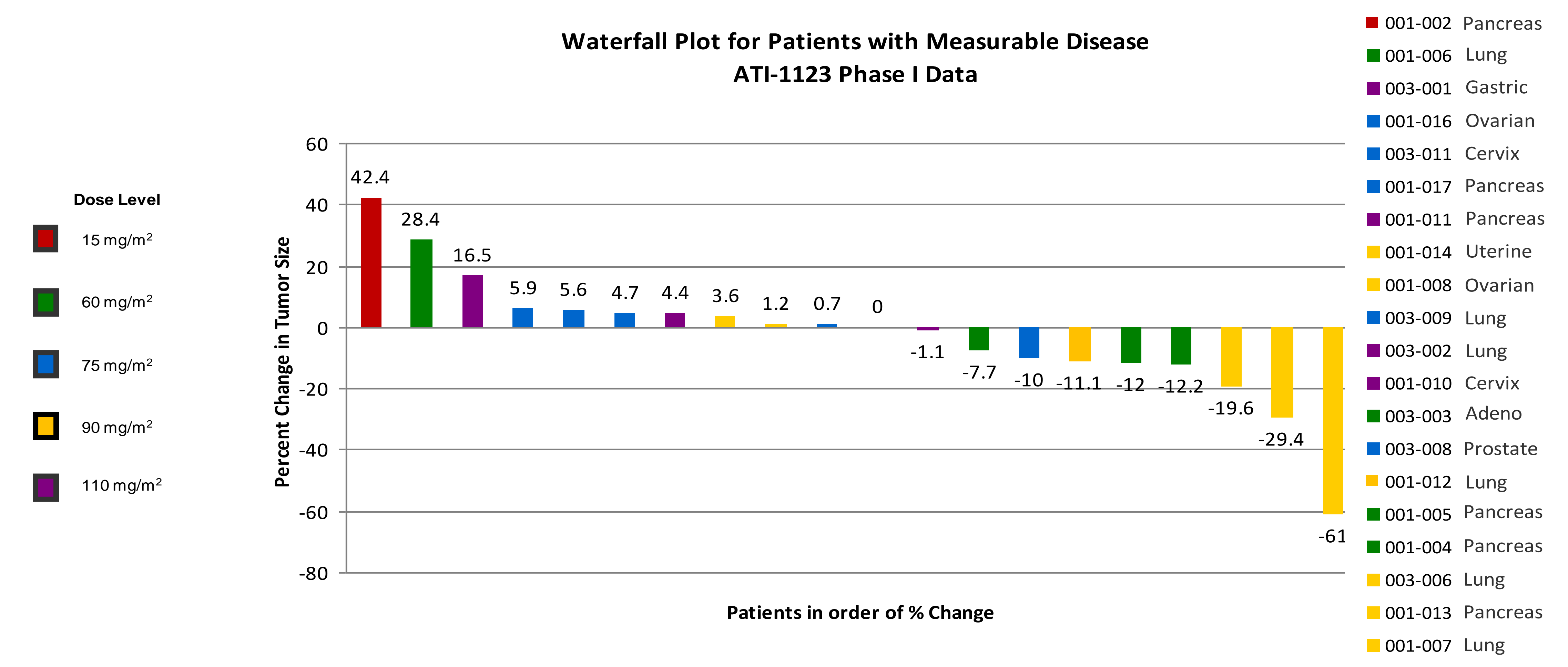
Dose (mg/m <sup>2</sup> )	15	30	60	90	110	90	75
No. of Patients	2	1	2	3	6	7	8

- ATI-1123 dosing began at 15 mg/m<sup>2</sup> and was advanced to 110 mg/m<sup>2</sup>. At 110 mg/m<sup>2</sup> two DLTs were observed (Grade 3 febrile neutropenia and Grade 3 stomatitis).
- The ATI-1123 dose was decreased to 90 mg/m<sup>2</sup> and the dosing cohort was expanded. Three patients developed Grade 4 neutropenia at the 90 mg/m<sup>2</sup>, but recovered.
- An intermediate dose of 75 mg/m<sup>2</sup> was added for further study.

### Toxicities

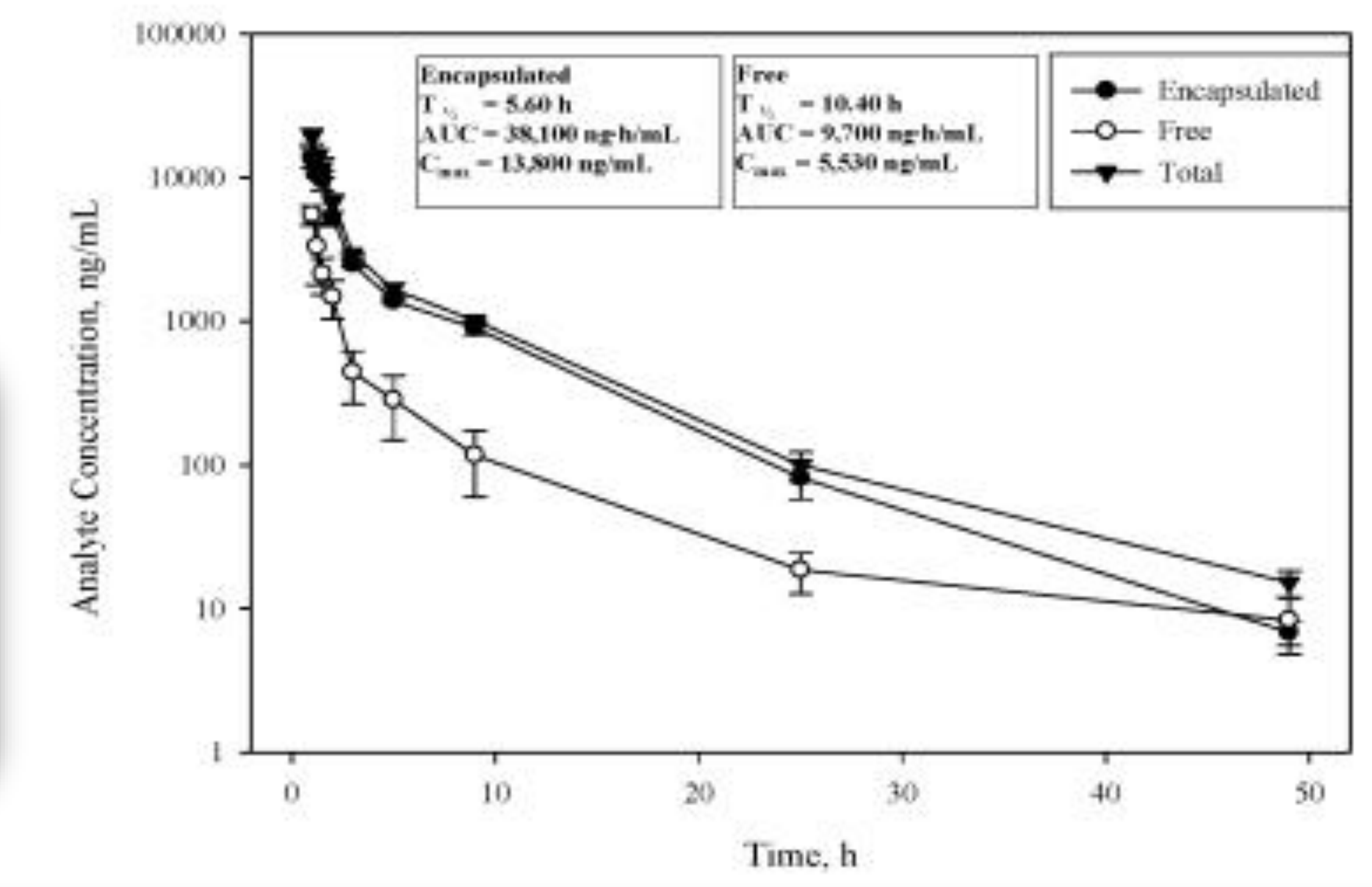
Treatment Related Adverse Events	Patients N (%)	Grade 1/2	Grade 3/4
ALOPECIA	9 (31.0%)	9 (31.0%)	0 (0.0%)
ANAEMIA	18 (62.1%)	10 (34.5%)	8 (27.6%)
ASTHENIA	9 (31.0%)	8 (27.6%)	1 (3.4%)
CHILLS	11 (38.0%)	11 (38.0%)	0 (0.0%)
DECREASED APPETITE	14 (48.3%)	14 (48.3%)	0 (0.0%)
DIARRHOEA	14 (48.3%)	14 (48.3%)	0 (0.0%)
DEHYDRATION	10 (34.5%)	8 (27.6%)	2 (6.9%)
FATIGUE	23 (79.3%)	19 (65.5%)	4 (13.8%)
FEBRILE NEUTROPENIA	3 (10.3%)	0 (0.0%)	3 (10.3%)
HYPERSENSITIVITY	11 (38.0%)	10 (34.5%)	1 (3.4%)
HYPONAETREMIA	7 (24.1%)	4 (13.8%)	3 (10.3%)
NAUSEA	19 (65.5%)	17 (58.6%)	2 (6.9%)
NEUROPATHY PERIPHERAL OR SENSORY	10 (34.5%)	10 (34.5%)	0 (0.0%)
NEUTROPENIA	19 (65.5%)	0 (0.0%)	19 (65.5%)
OEDEMA PERIPHERAL	11 (38.0%)	11 (38.0%)	0 (0.0%)
PYREXIA	10 (34.5%)	10 (34.5%)	0 (0.0%)
RASH	7 (24.1%)	7 (24.1%)	0 (0.0%)
STOMATITIS	6 (20.7%)	5 (17.2%)	1 (3.4%)
VOMITING	13 (44.8%)	11 (38.0%)	2 (6.9%)

### Patient Response Summary



### Pharmacokinetic Results

Encapsulated docetaxel concentrations, C<sub>max</sub> and AUC were up to 4-fold higher, while CL values were up to 4-fold lower than corresponding values for free docetaxel. The estimated T<sub>1/2</sub>, CL, C<sub>max</sub> AUC, V<sub>ss</sub> for free docetaxel are in reasonable agreement with corresponding values reported in literature for Taxotere (docetaxel). (<sup>1</sup>Clarke *et al.*, 1999, <sup>2</sup>Bruno *et al.*, 1998, <sup>3</sup>Bruno *et al.*, 1997)



### Summary and Conclusions

- ATI-1123 had an acceptable safety profile in this heavily pretreated population of patients.
- MTD at 90 mg/m<sup>2</sup>.
- One (3.4%) partial response (PR) in NSCLC and 22 (75.9%) stable disease (SD) were observed.
- DLTs observed were expected based on the known profile of Taxotere (docetaxel).
- PK exposure appeared to be linear through most doses (data not shown). ATI-1123 appears to enhance the exposure of docetaxel as compared to standard docetaxel.
- ATI-1123 may represent an alternative therapy for patients with advanced solid tumors. Additional clinical trials are required to assess tumor response in a broad cancer population.

<sup>1</sup>Clarke S, Rivory L. Clinical Pharmacokinetics of Docetaxel. Clin Pharmacokinet. 1999 Feb; 36(2): 99-114  
<sup>2</sup>Bruno R, et al. Population Pharmacokinetics/Pharmacodynamics of Docetaxel in Phase II Studies in Patients with Cancer. J of Clinical Oncology. 1998 Jan 16; 1: 187-196  
<sup>3</sup>Bruno R, Riva A, Hille D, Lebecq A, Thomas L. Pharmacokinetic and pharmacodynamic properties of docetaxel: results of phase I and phase II trials. Am J Health Syst Pharm. 1997 Dec 15; 54(24 Suppl 2):S16-9