Toxicological Aspects and Safety Profile of Paclitaxel

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Disclosures

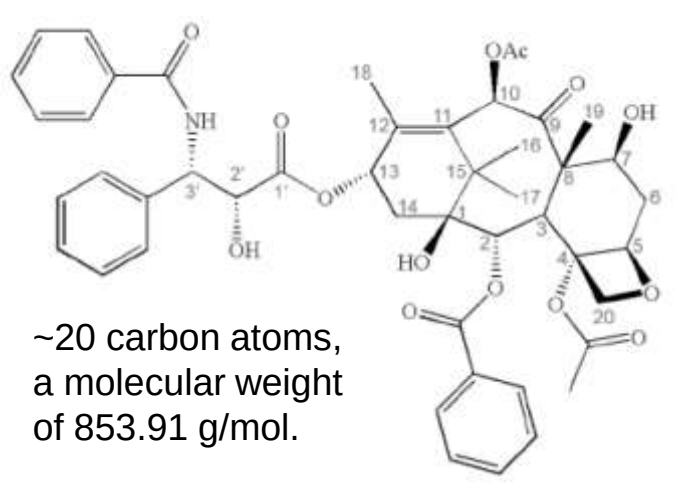
Speaker name: Juan Granada, MD

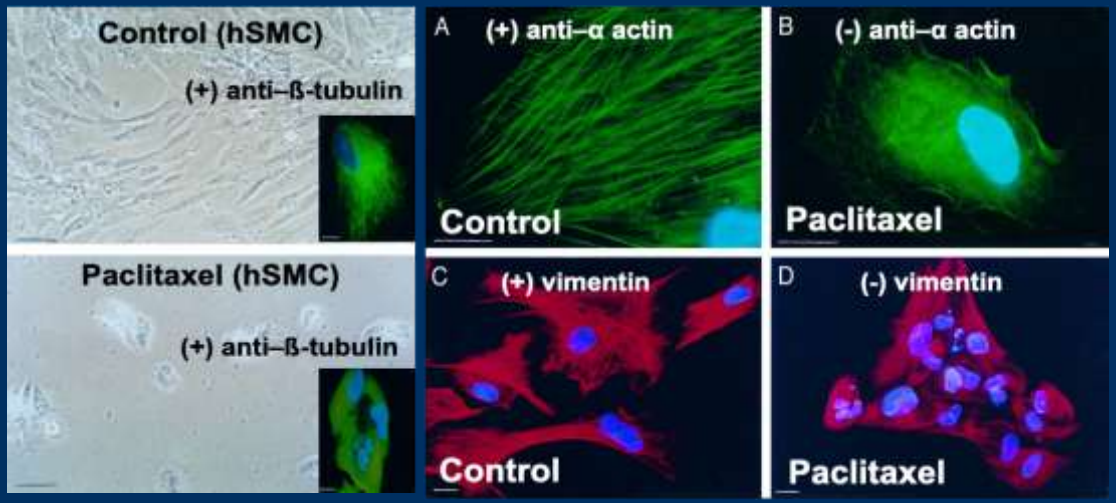
I have the following potential conflicts of interest to report:

- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s): Sponsored research, advisory role.

☐ I do not have any potential conflict of interest

The Chemistry and Pharmacological Properties of Paclitaxel Have Been Fully Characterized in Humans



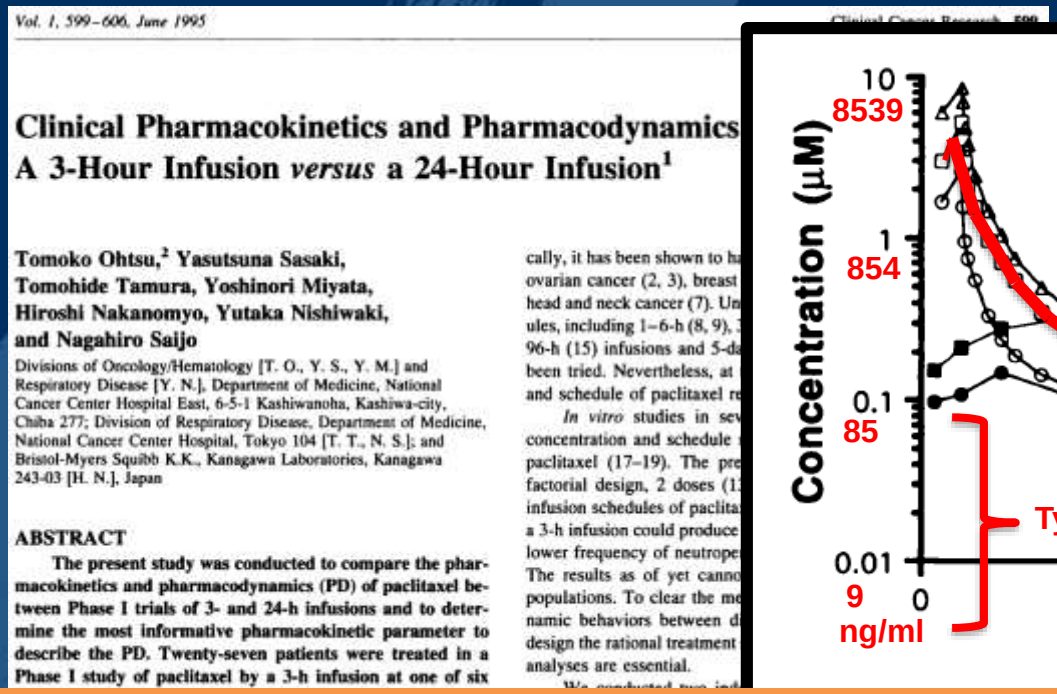


Axel DI. Circulation. 1997;96:636-645

- Mechanism of action: stabilization of microtubules during the final G2/M phase of cell division
- Highly lipophilic, and is freely soluble in common organic solvents[1]
- IV administration requires solubilization of drug with Cremophor®[2]
- Injected drug is immediately bioavailable in bolus or infusion
- Usually administered in multiple cycles

[1]IN.PACT Admiral IFU, [2]Taxol IFU, Bristol-Myers Squibb

Pharmacokinetics and Pharmacodynamics of Paclitaxel are Well Characterized



Vol. 1, 599–606, June 1995

Clinical Pharmacokinetics and Pharmacodynamics of Paclitaxel. A 3-Hour Infusion *versus* a 24-Hour Infusion[1]

Tomoko Ohtsu,[2] Yasutsuna Sasaki, Tomohide Tamura, Yoshinori Miyata, Hiroshi Nakanomyo, Yutaka Nishiwaki, and Nagahiro Saijo

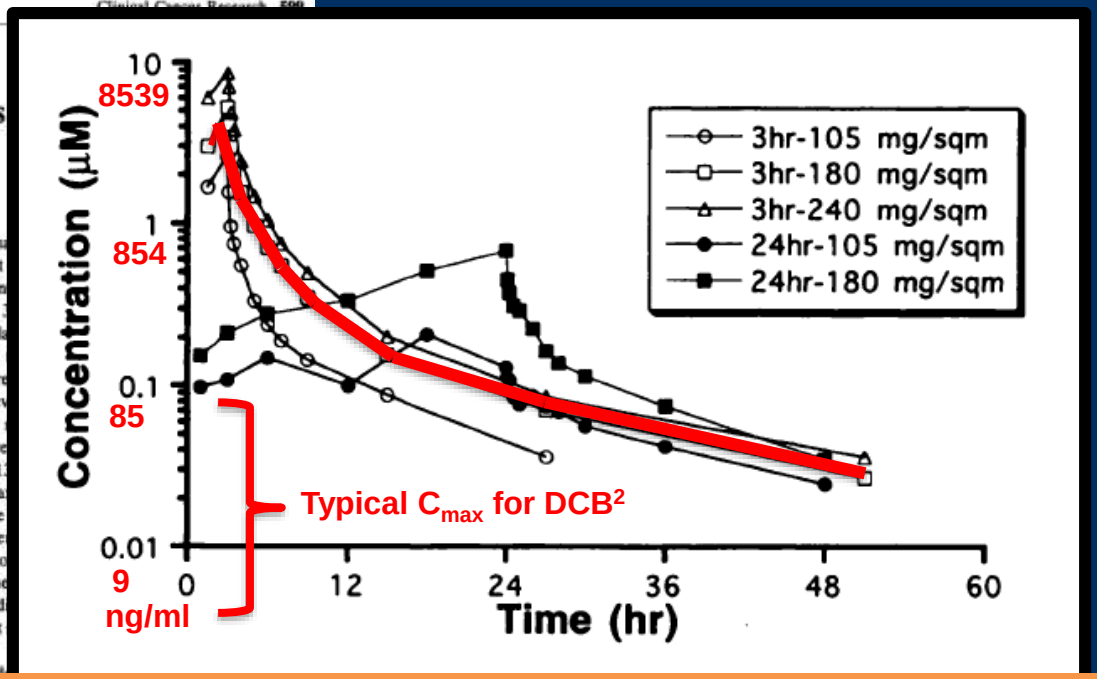
Divisions of Oncology/Hematology [T. O., Y. S., Y. M.] and Respiratory Disease [Y. N.], Department of Medicine, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa-city, Chiba 277; Division of Respiratory Disease, Department of Medicine, National Cancer Center Hospital, Tokyo 104 [T. T., N. S.]; and Bristol-Myers Squibb K.K., Kanagawa Laboratories, Kanagawa 243-03 [H. N.], Japan

ABSTRACT

The present study was conducted to compare the pharmacokinetics and pharmacodynamics (PD) of paclitaxel between Phase I trials of 3- and 24-h infusions and to determine the most informative pharmacokinetic parameter to describe the PD. Twenty-seven patients were treated in a Phase I study of paclitaxel by a 3-h infusion at one of six

cally, it has been shown to h
ovarian cancer (2, 3), breast
head and neck cancer (7). Un
ules, including 1–6-h (8, 9),
96-h (15) infusions and 5-da
been tried. Nevertheless, at
and schedule of paclitaxel re

In vitro studies in sev
concentration and schedule
paclitaxel (17–19). The pre
factorial design, 2 doses (1
infusion schedules of paclita
a 3-h infusion could produce
lower frequency of neutrope
The results as of yet canno
populations. To clear the mo
namic behaviors between d
design the rational treatment
analyses are essential.

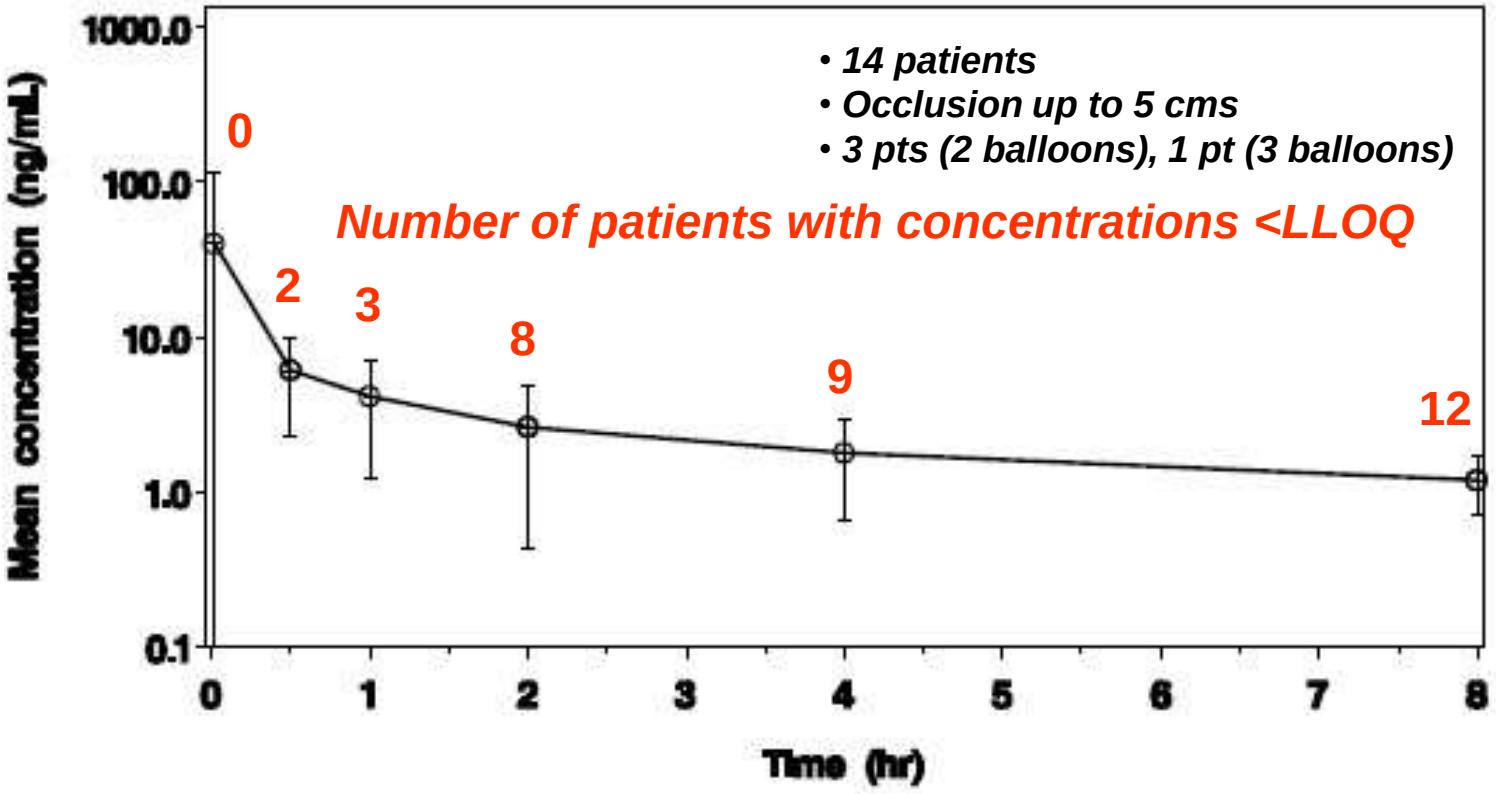


	C_{max} [ng/mL]	AUC [ng/mL*hr]
Paclitaxel IV 3h (180 mg/m^2)[1]	4468±1285	16463±3757
Stellarex[2]	54.4±116.9	37.2±59.2
IN.PACT Admiral[3]	7.9±7.7	29.4±22.1

[1]Clinical Cancer Research 1: 599-606, 1995, Ohstu T et al. [2]Circulation 136: 1102-1113, Krishnan P et al ; [3]IN.PACT Admiral IFU, Medtronic

Plasma Levels Following DCB Use in Human Femoro-Popliteal Arteries

Cotavance™ DCB FIH Study



Adapted from Thomas Zeller, LINC 2010.

A Variety of Organ Systems Can Be Impacted Producing a Range of Systemic Toxicities[1]:

- Bone Marrow Supression
- Hypersensitivity
- Cardiovascular
- Abnormal ECG
- Peripheral Neuropathy
- Myalgia/Arthralgia
- Gastrointestinal
- Alopecia
- Hepatic
- Injection site reaction

SUMMARY[a] OF ADVERSE EVENTS IN PATIENTS WITH SOLID TUMORS RECEIVING SINGLE-AGENT TAXOL

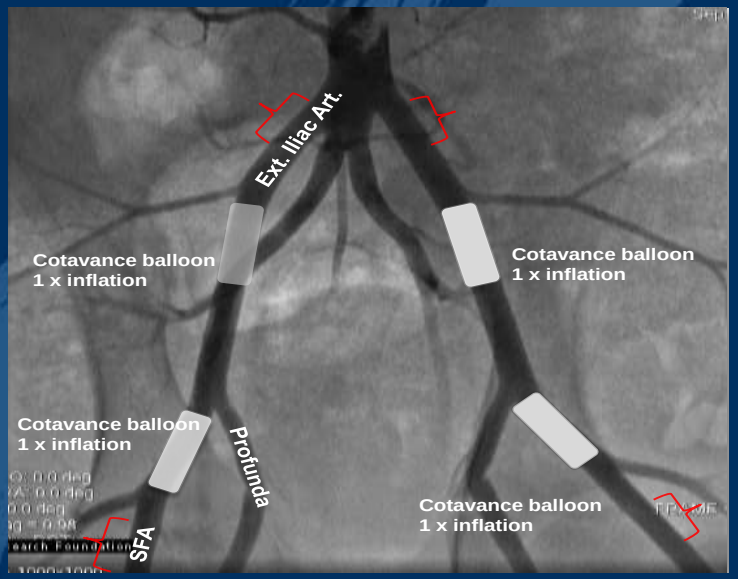
		Percent of Patients (n=812)
• ***Bone Marrow***		
—Neutropenia	<2000/mm^3	90
	<500/mm^3	52
—Leukopenia	<4000/mm^3	90
	<1000/mm^3	17
—Thrombocytopenia	<100,000/mm^3	20
	<50,000/mm^3	7
—Anemia	<11 g/dL	78
	<8 g/dL	16
—Infections		30
—Bleeding		14
—Red Cell Transfusions		25
—Platelet Transfusions		2
• ***Hypersensitivity Reaction***[b]		
—All		41
—Severe[†]		2
• ***Cardiovascular***		
—Vital Sign Changes[c]		
—Bradycardia (n=537)		3
—Hypotension (n=532)		12
—Significant Cardiovascular Events		1
• ***Abnormal ECG***		
—All Pts		23
—Pts with normal baseline (n=559)		14
• ***Peripheral Neuropathy***		
—Any symptoms		60
—Severe symptoms[†]		3
• ***Myalgia/Arthralgia***		
—Any symptoms		60
—Severe symptoms[†]		8
• ***Gastrointestinal***		
—Nausea and vomiting		52
—Diarrhea		38
—Mucositis		31
• ***Alopecia***		87
• ***Hepatic*** (Pts with normal baseline and on study data)		
—Bilirubin elevations (n=765)		7
—Alkaline phosphatase elevations (n=575)		22
—AST (SGOT) elevations (n=591)		19
• ***Injection Site Reaction***		13

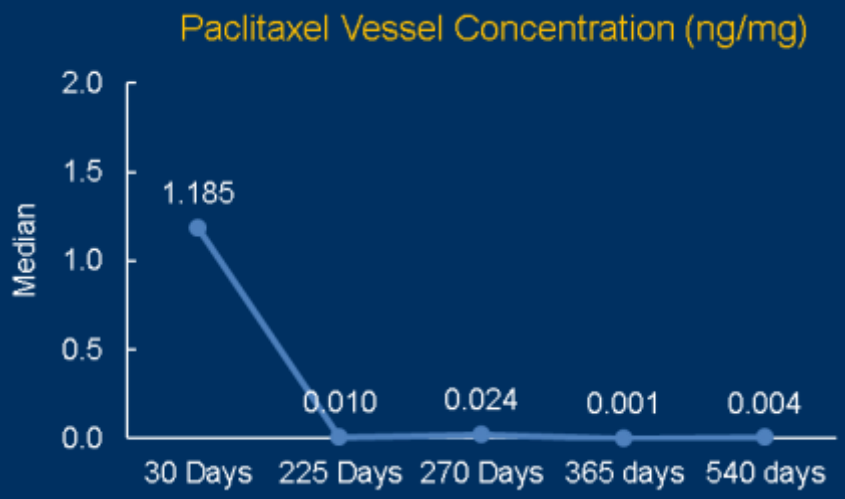
[a] Based on worst course analysis.
[b] All patients received premedication.
[c] During the first 3 hours of infusion.
[†] Severe events are defined as at least Grade III toxicity.

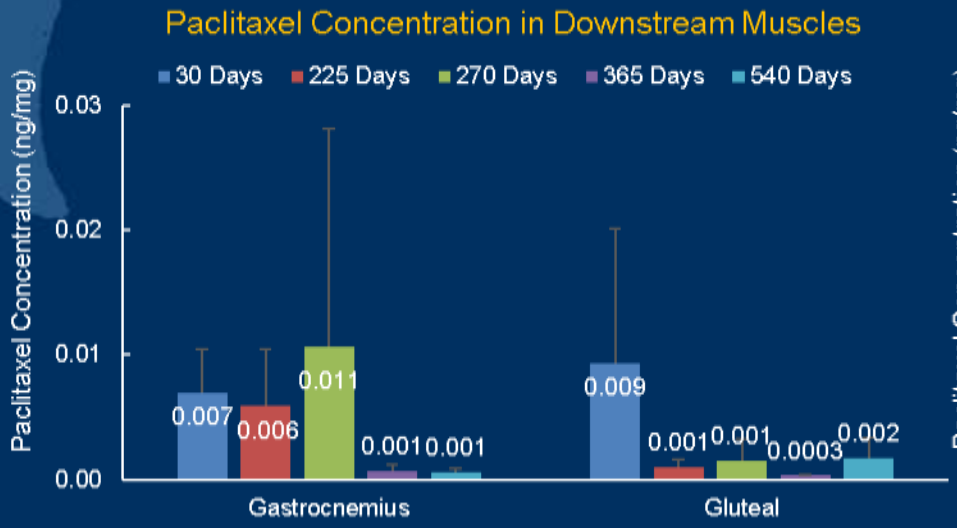
Bone marrow suppression (primary neutropenia) is dose dependent and is the dose-limiting toxicity

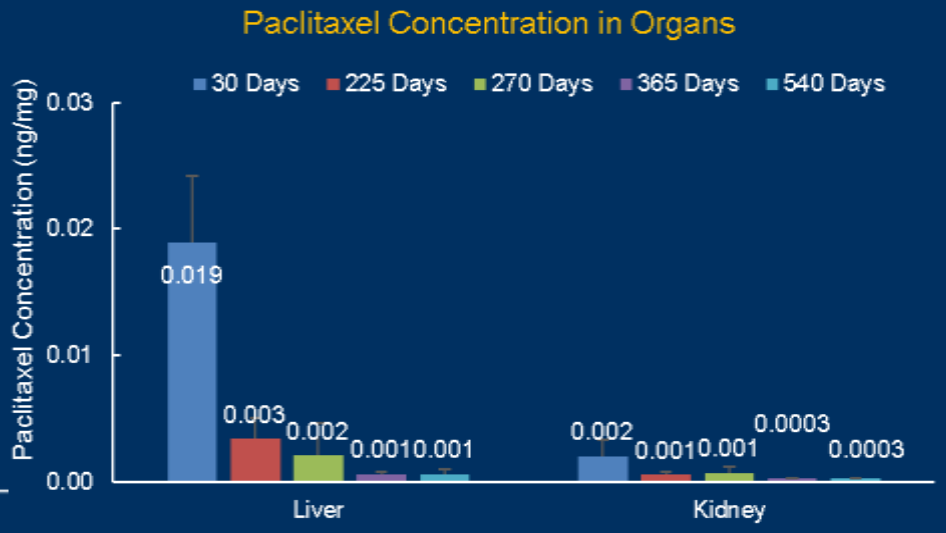
[1]Taxol IFU, Bristol-Myers Squibb

Non-Target Tissue Drug Concentrations (Cotavance DCB, 3.0-ug/mm^2) at 18-Months



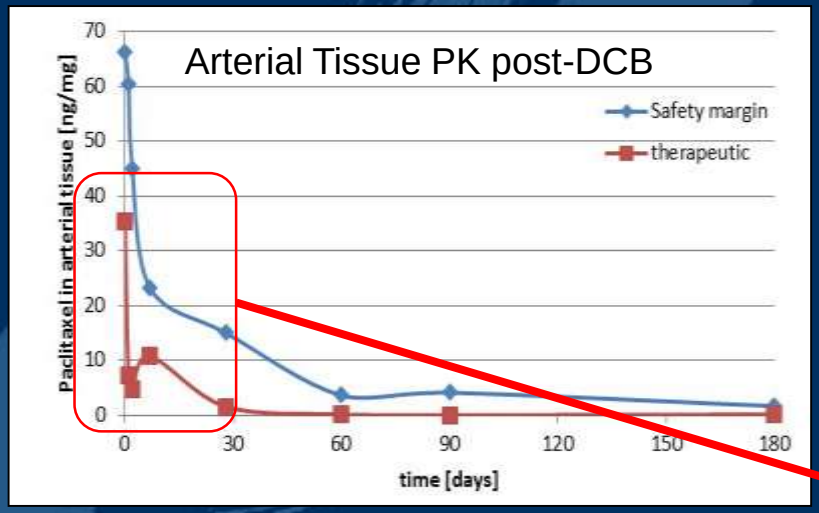




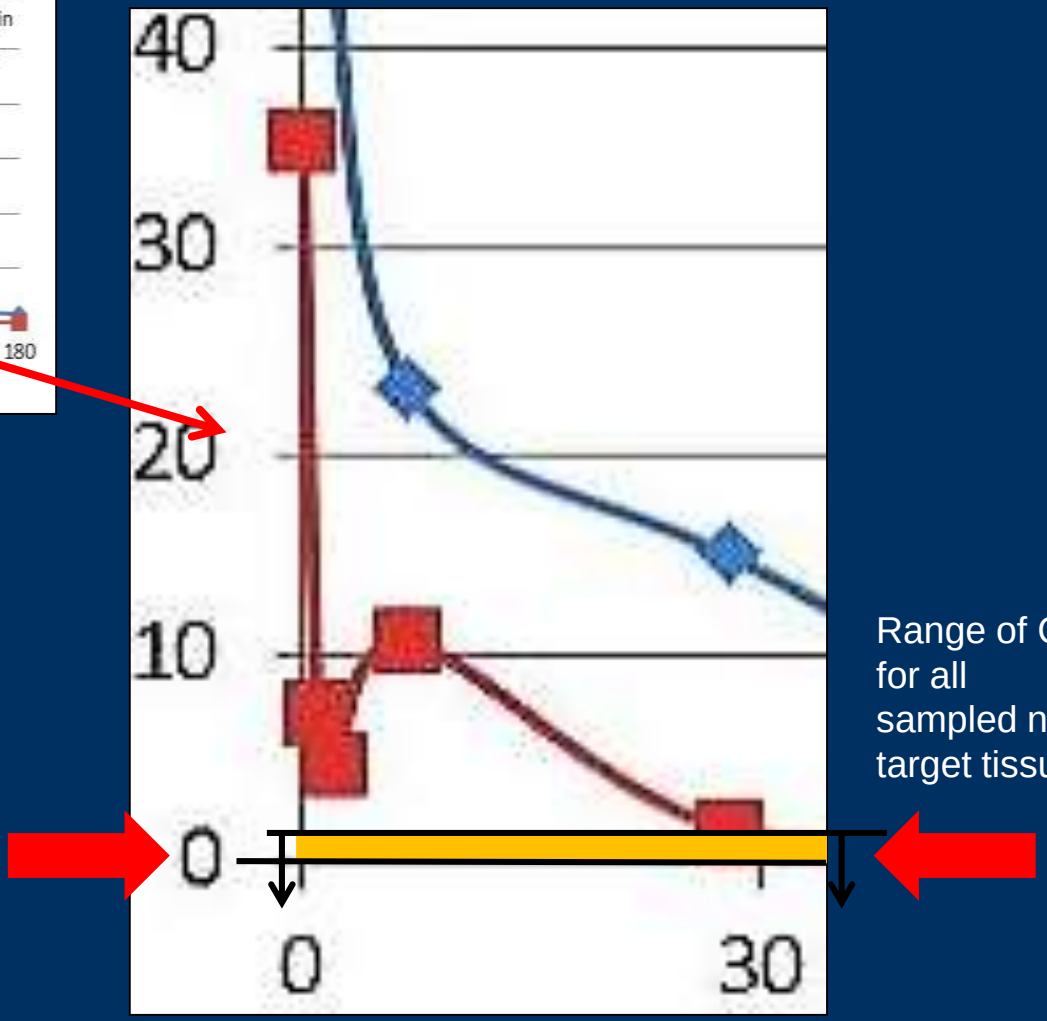


Data on File. CRF-Skirball Center for Innovation

Non-Target Tissue Drug Concentrations are Consistently Lower than in Arteries



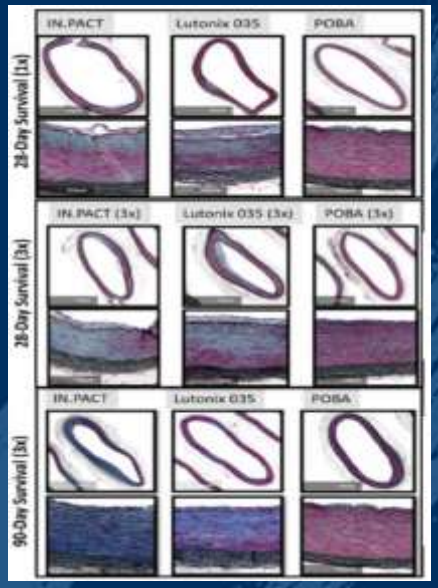
All non-target tissue C_{max} values (distal muscle, lungs, liver, spleen, kidney) are less than 2 ng/mg for the 3X dose and 1.2 ng/mg for the nominal therapeutic dose (single 5.0 or 6.0 x 80mm IN.PACT Admiral)[1]

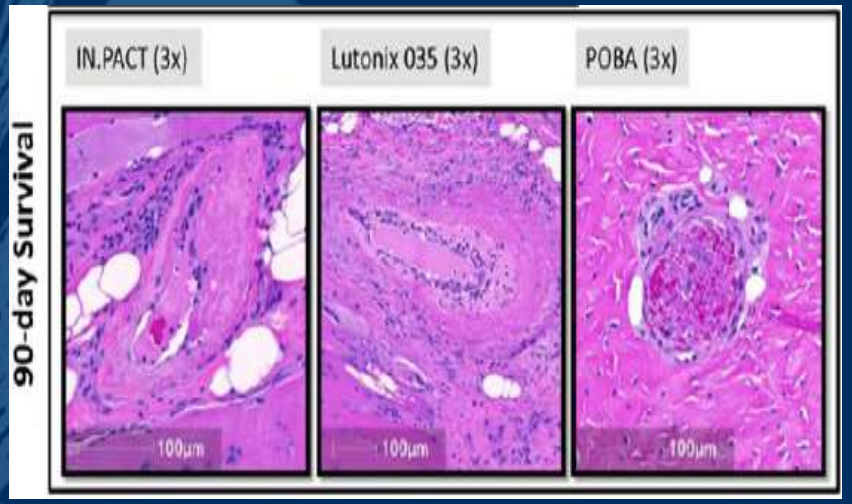


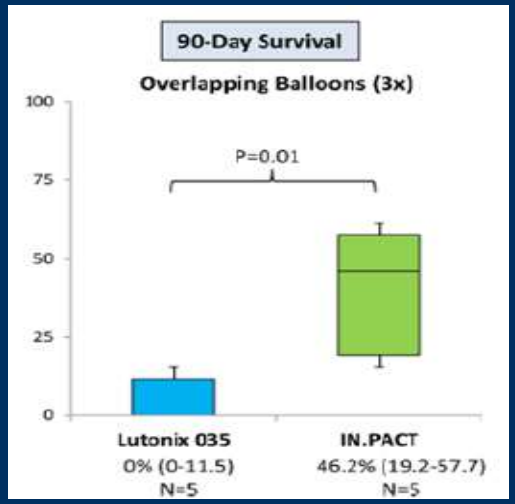
Range of C_{max} for all sampled non-target tissue

[1]LINC 2013, Medtronic, R. Melder

Paclitaxel Particulate Downstream Effect

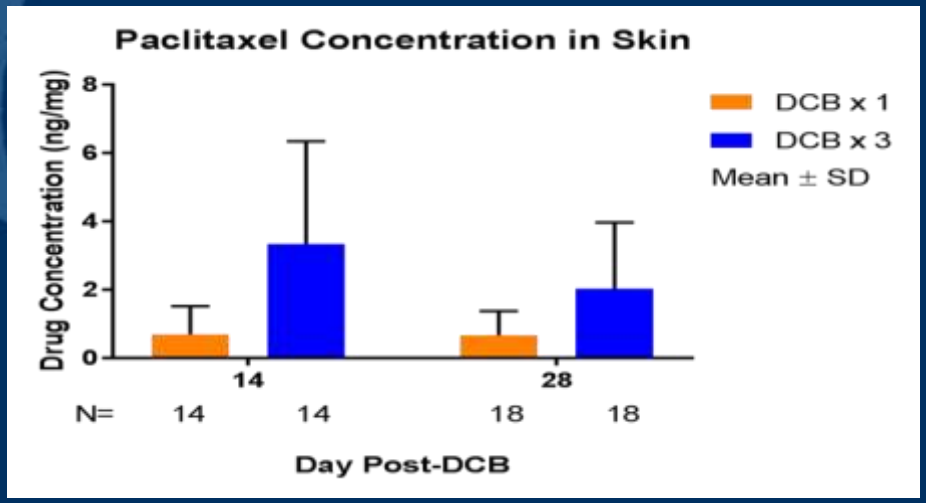


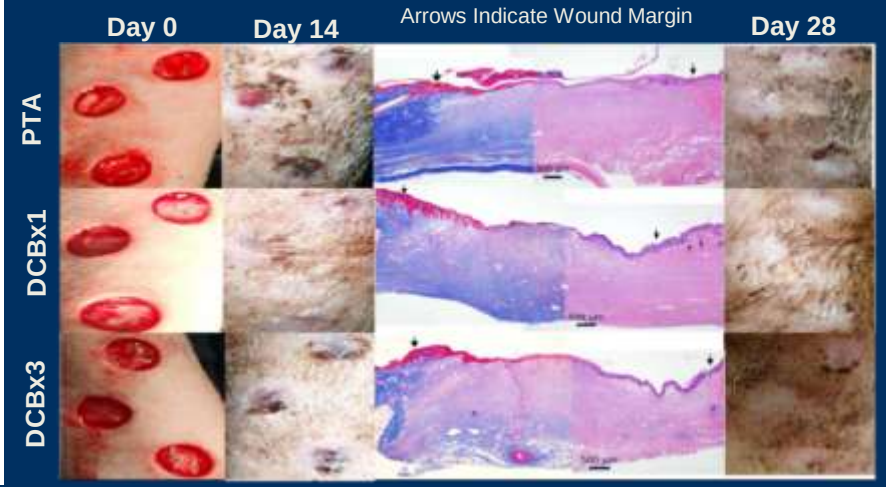




Kolodgie FD, J Vasc Interv Radiol 2016;27:1676-85

Paclitaxel Particle and Wound Healing





Granada JF, TCT2018

Consideration of Factors Relevant to DCBs

- Paclitaxel use may induce a constellation of toxicities which are usually dose and schedule dependent:
  - A single DCB use results in a small fraction of bioavailable drug at any time[1] compared to the IV infusion of Paclitaxel for cancer therapy which involves multiple cycles[2, 3]
- Systemic Paclitaxel exposure post DCB use is several orders of magnitude lower than that of a single cycle of drug infusion[2, 3]
- Multi-organ distribution and concentration of Paclitaxel resulting from DCB use is lower and more transient than at the target site[4], limiting exposure of systemic tissues
- Understanding the role of drug-induced toxicity in mediating treatment-associated mortality requires a careful and rational examination of dosing and exposure in the context of the known pharmacology of Paclitaxel

[1]Journal Drug Delivery Volume 2019, Article ID 9560592 Granada, J et al. [2]Taxol IFU, Bristol-Myers Squibb, .
[3]IN.PACT Admiral IFU; Circulation 136: 1102-1113, Krishnan P et al. [4]LINC 2013 Review, Melder R

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