



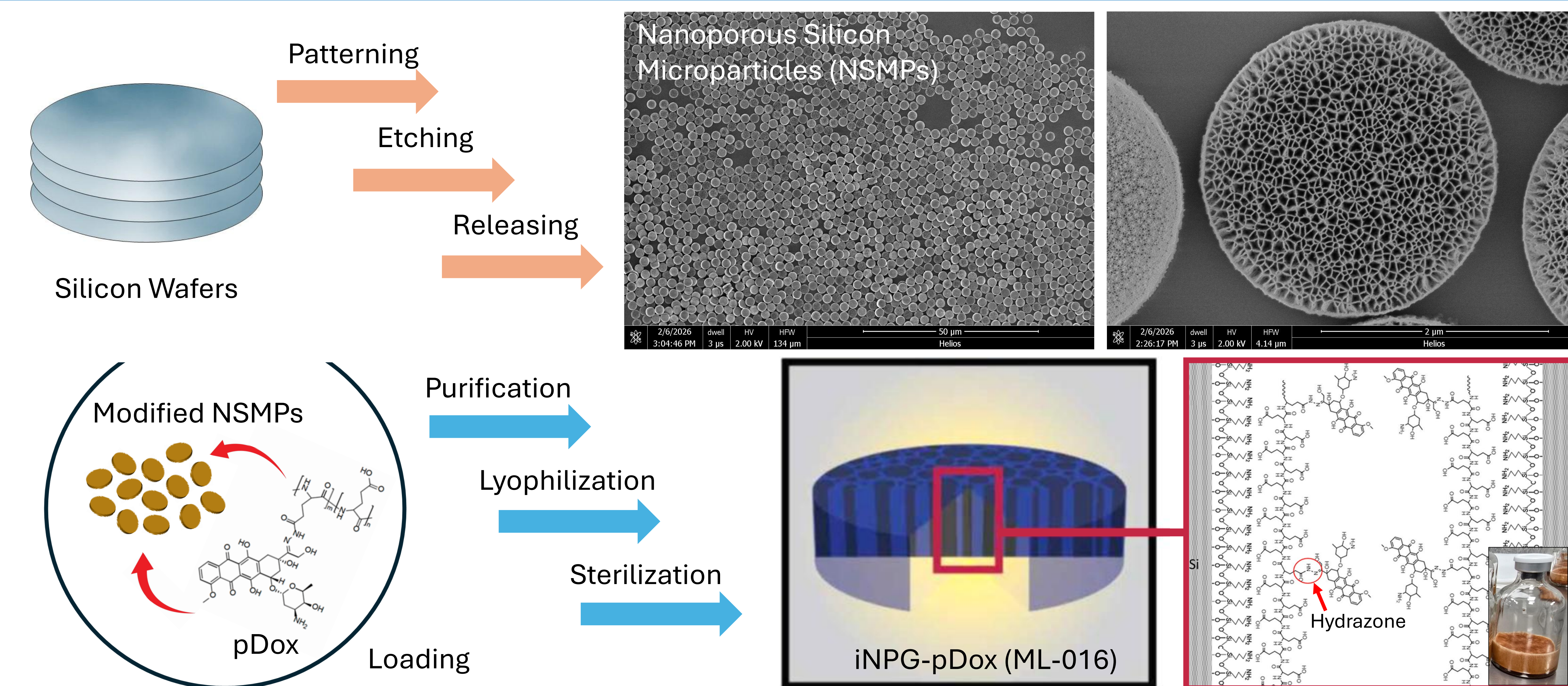
ML-016: A Silicon “Plateloid”–Based Phenotype Targeting Platform for Lung and Liver Malignancies

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Introduction

- Lung and liver malignancies, among the leading causes of cancer-related mortality, remain difficult to treat with conventional chemotherapeutics due to limited tumor drug penetration, systemic toxicity, and multidrug-resistance mechanisms.
- ML-016 is a novel injectable Phase I/II drug candidate developed by BrYet based on a proprietary silicon “plateloid” (Si-Plateloid™*) technology designed to exploit tumor-specific vascular and microenvironmental phenotypes.
- The platelet-shaped silicon microstructures (~2.6 µm diameter, ~700 nm thickness) with nanopores (30-80 nm) are engineered to optimize hemodynamic margination, endothelial interaction, and tumor-targeted delivery.
- ML-016 employs a multi-node phenotype-targeting mechanism, including:
 - Enhanced vascular margination under tumor-associated shear stress;
 - Preferential transmigration via polyglutamic acid–doxorubicin (pDox) conjugates;
 - Formation of pDox “exosomoids” and efficient tumor cell internalization;
 - pH-triggered intracellular release of doxorubicin beyond the active range of multidrug-resistance pumps.
- Preclinical studies demonstrate strong antitumor efficacy and survival benefit, including 50-80% long-term tumor-free survival in lung metastasis models of triple-negative breast cancer and soft-tissue sarcoma, supporting first-in-human clinical evaluation in Australia following Phase I/II HREC approval.

Si-Plateloid™ Technology and ML-016 Manufacturing



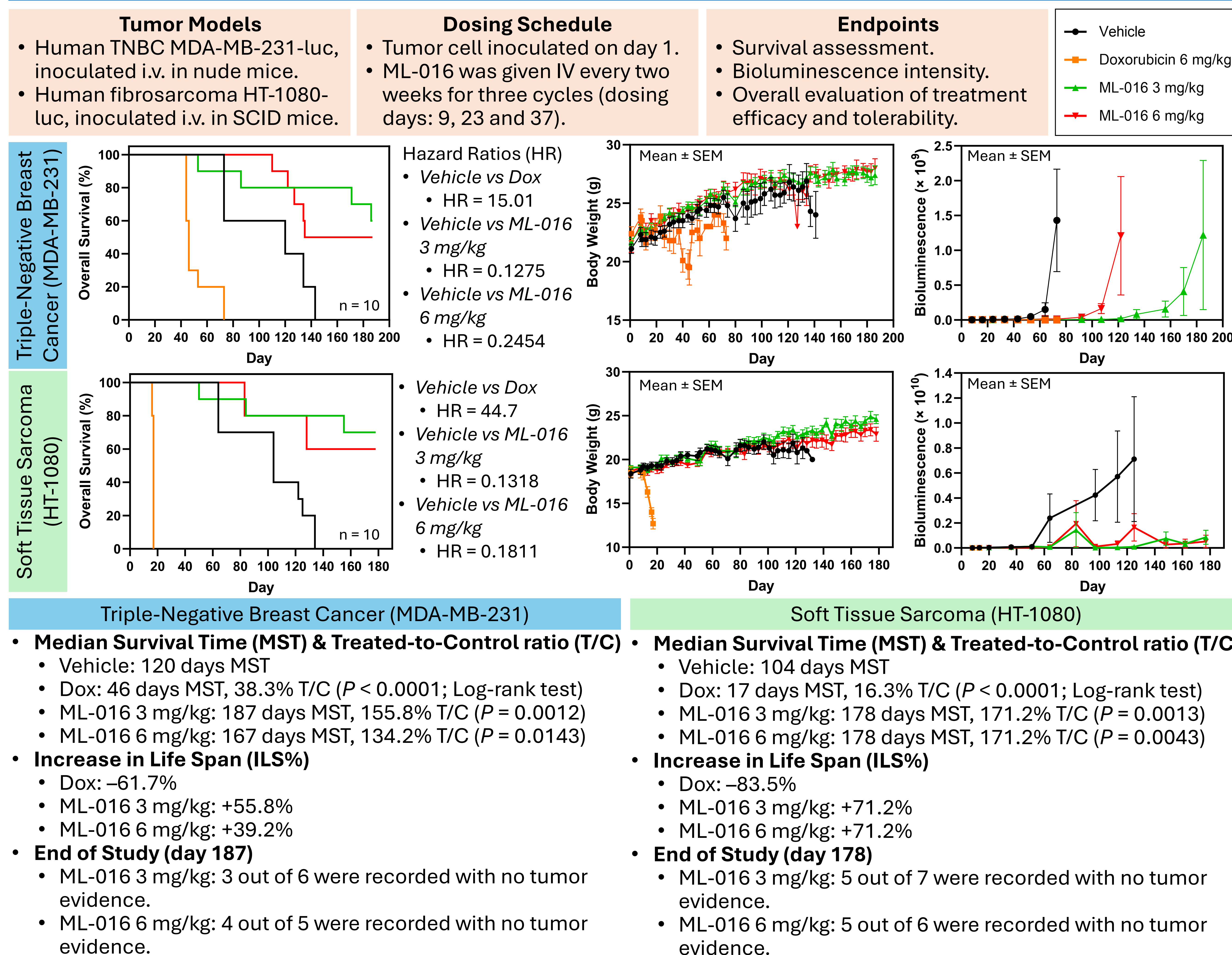
The chemical structures are for conceptual understanding and don't represent exact chemical configurations in the product.

ML-016 Targets Key Nodes in Tumor Transport Phenotypes

Size scale	Phenotype Node	Main Mode of Targeting Selectivity	Principal Targeting Drug Component	Discriminant of Selectivity
Centimeter	Capillary network structure	Hemorheology (flow velocity, shear stress at wall, capillary length)	Mesoporous silicon “Plateloid”	Increased margination velocity by size, shape, charge
Millimeter	Microvascular endothelia	Fenestrated or leaky tumor vasculature (EPR effect); transcytosis	Linear polymeric amino acid chain of pDox	Preferential transmigration of polyglutamic acid
Micrometer	Tumor microenvironment (TME)	Fibrotic network permeability	Linear polymeric amino acid chain of pDox	Hydro-/Lipo-philic Interaction
	TR cells – membrane	Internalization	pDox as “Exosomoid”	Exosomoid size & charge
Nanometer	TR cells – intracellular traffic	Increased perinuclear concentration	pDox as “Endosomoid”	Active transport to perinuclear late endosomes/lysosomes
	TR cells – MDR pumps	MDR primary localization on cell membrane	Free Dox (after pH-induced pDox cleavage)	Trafficked beyond active range of MDR pumps
	TR cell – nuclear membrane	Migration to Dox activity sites	Free Dox (after pH-induced pDox cleavage)	Small molecule diffusion

iNPG: injectable nanoparticle generator; pDox: polyglutamic acid–doxorubicin conjugate; TR: Therapy resistant; MDR: Multi-drug resistance

ML-016 Preclinical Efficacy in TNBC and STS



Summary of ML-016 GLP Toxicology

- Study design: ML-016 was evaluated in a GLP repeated-dose toxicity study in Han Wistar rats (M/F), administered intravenously every other week for 6 weeks at doses up to 3 mg/kg (Dox equivalent).
- General safety: No adverse systemic clinical signs were observed at doses up to 3 mg/kg. Injection-site changes occurred in all particle-treated groups but were not dose-dependent.
- Expected particle-related findings: Histological changes in the injection site, liver, and spleen at 0.75–3 mg/kg were consistent with expected responses to intravascular foreign-body particles (iNPG carrier) and were not considered adverse.
- Toxicity threshold: The severely toxic dose in 10% of rats (STD10) was established at 3 mg/kg.

Phase I/II First-in-Human Clinical Study Plan

- Evaluation of multiple doses of intravenously administered ML-016 in participants with advanced solid malignancies in lungs and/or liver (i.e., locally advanced or metastatic).
- Phase 1: dose escalation. To characterize the safety and tolerability and determine the maximum tolerated dose (MTD), or the maximum tested dose of ML-016 in participants with advanced solid tumors, and to determine the dose recommended for expansion. The starting dose in patients is 1.8 mg/m² which is 0.3 mg/kg Dox equivalent in rats (1/10 of STD10).
- Phase 2: dose expansion. To determine anti-tumor activity of ML-016 at the dose recommended for expansion.

References

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Si-Plateloid™*: trademark pending

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