INVINCIBLE-3 STUDY

A MULTICENTER, RANDOMIZED, PHASE 3 STUDY OF INTRATUMORAL INT230-6 COMPARED TO STANDARD OF CARE THERAPY IN SELECTED METASTATIC SOFT TISSUE SARCOMAS

Christian Meyer, MD, PhD

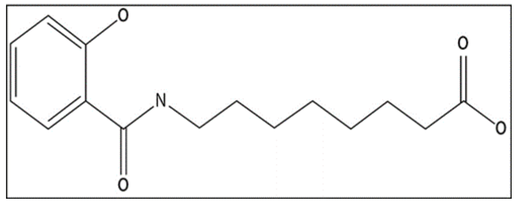
2024
ANNUAL MEETING

INT230-6 is a Novel Intratumoral Agent Consisting of Cisplatin, Vinblastine and SHAO Designed for Dense, Stromal, Fatty Tumors

Cisplatin & Vinblastine are co-formulated in a fixed ratio with SHAO, a tissue dispersion and cell penetration amphiphilic agent

SHAO (10mg/mL)

sodium 8-((2-hydroxybenzoyl)amino)octanoate



Cisplatin 0.5mg/mL

Direct killing: Binds to DNA to cause apoptotic cell death

Immune effects: Attracts and binds T-Cells via TL9 receptors

Clin Cancer Res; 20(11) June 1, 2014

Vinblastine 0.1mg/mL

Direct killing: Destroys tubulin to stop replication

Immune effects: induces dendritic cell maturation

Cancer Res; 2009 Sept 1: 69(17): 6987-6994

Intratumoral INT230-6 is Absorbed by Tumors and Causes Immunological Cell Death

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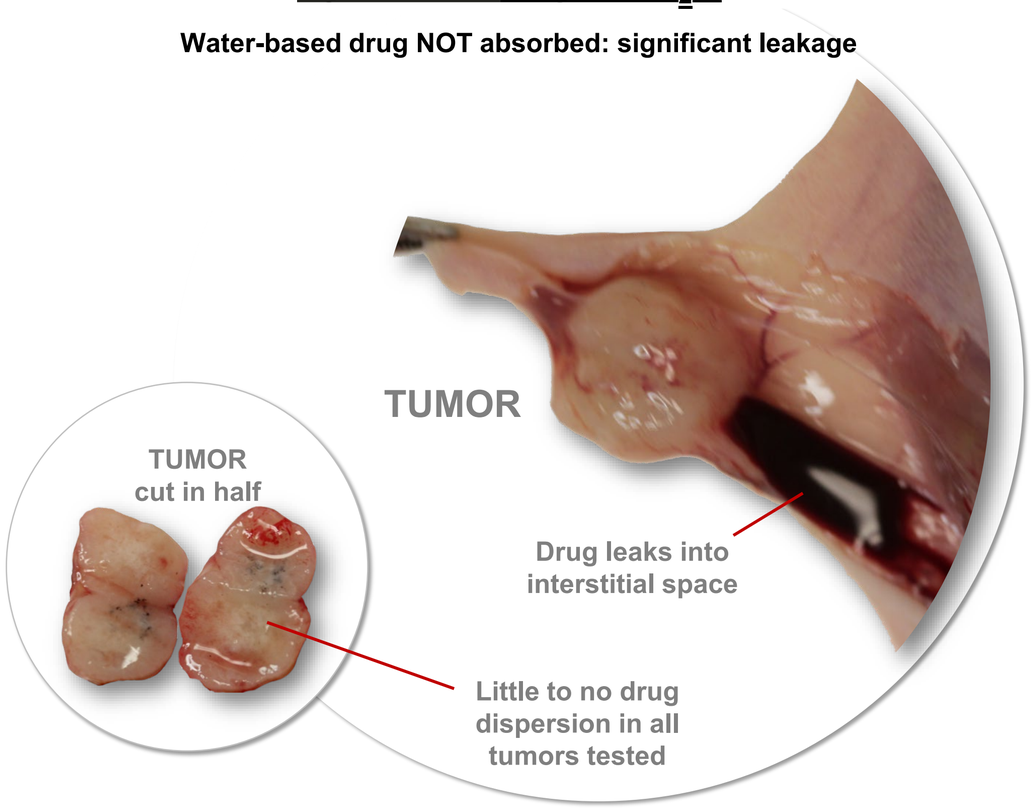
Intratumoral INT230-6 is Diffused and Absorbed Into Tumors

Human pancreatic cancer in mouse model
Tumor dose is set by the longest diameter or volume from 3 dimensions
Injections made to center of tumor over 90 seconds

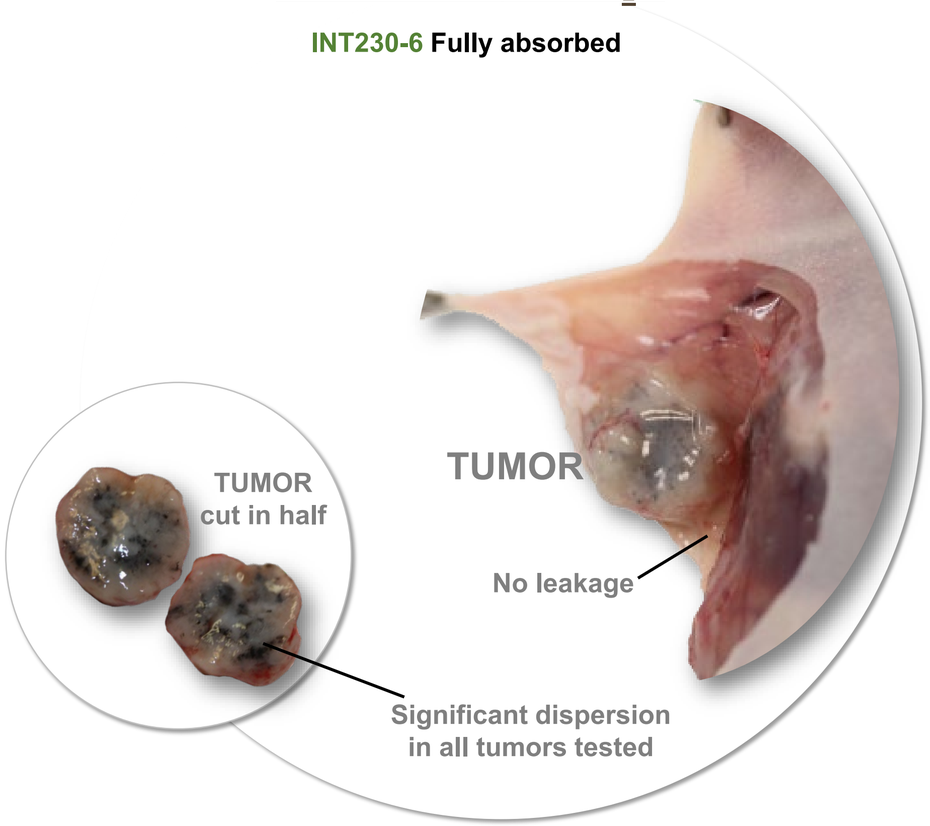
Cytotoxics + dye in H_2O

Water-based drug NOT absorbed: significant leakage



INT230-6 + *dye in* H_2O

INT230-6 Fully absorbed



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INT230-6 Achieves Significant Tumor Killing with One or Two Doses in Multiple Types of Cancers

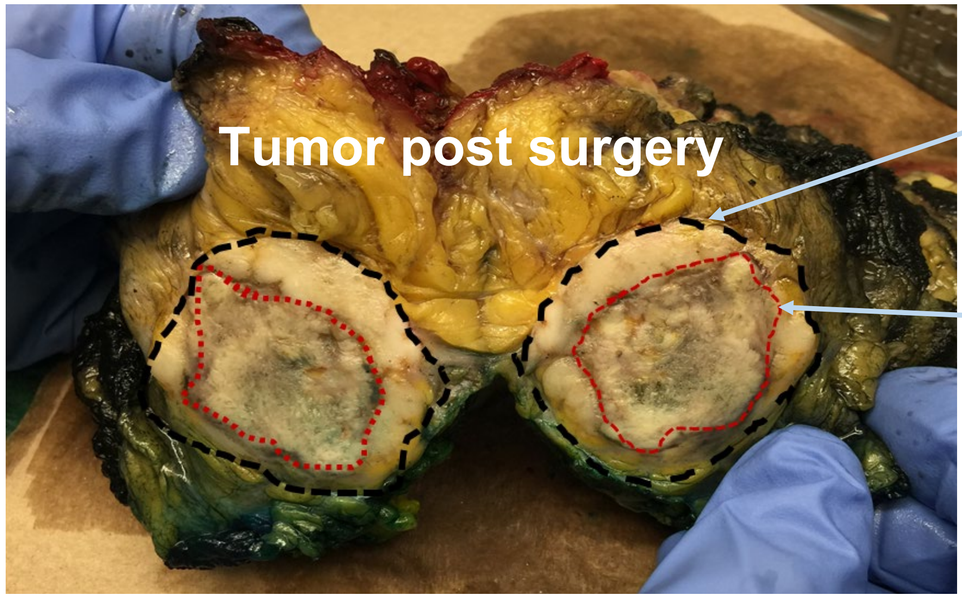
Breast cancer tumors fully resected

3.9 cm invasive ductal cancer: Grade 3 given 2 injections

May 6 — Injection #1: Dose 7.4 cc

May 13 — Injection #2: Dose 14.8 cc

May 20 — Surgery



Final Pathology (significant necrosis ~85%)

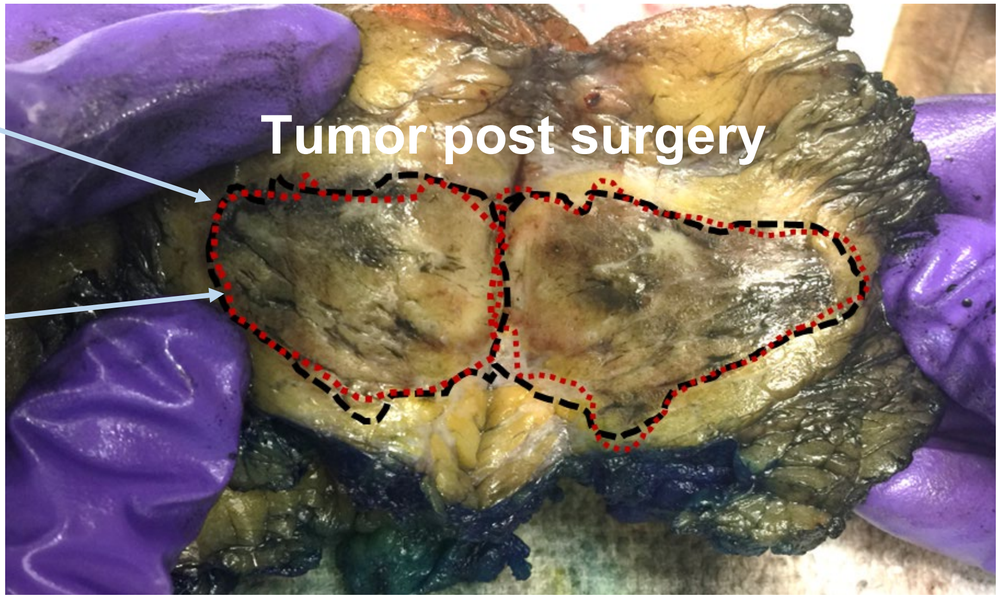
Tumor Extent

Extent of Necrosis within Tumor

4.4 cm invasive lobular cancer: Grade 2 single injection

May 27 — Injection #1 (only) Dose 21.3 cc

June 16 — Surgery



Final Pathology (significant necrosis ~95%)

Percent tumor death is dependent on total dose given per size of tumor

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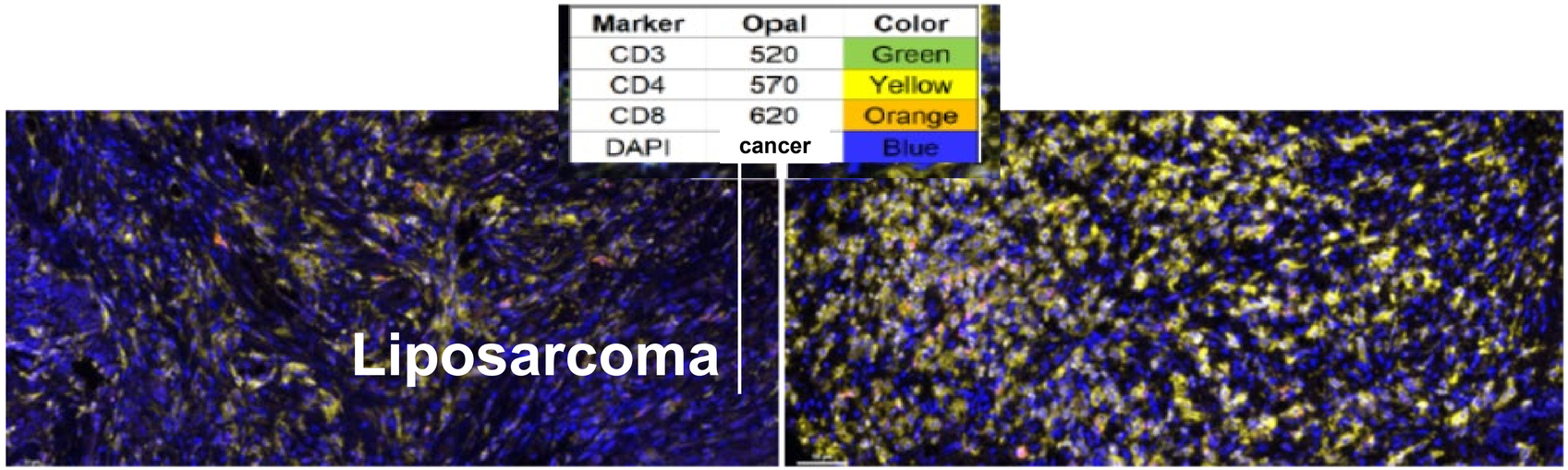
Multiplex IHC Staining From Matched Pair Biopsies Using Monotherapy INT230-6 Produces Immune Infiltration in Non-immunogenic Cancers such as sarcoma

Day 0
Pre-Dose

Day 28
Post 2 Doses



At 28 days, post two doses, there is an increased presence of CD3, CD4 and CD8 T-cells (green, yellow and orange stains)

Blue is cancer via DAPI

In metastatic disease injected tumors shrink in volume over time

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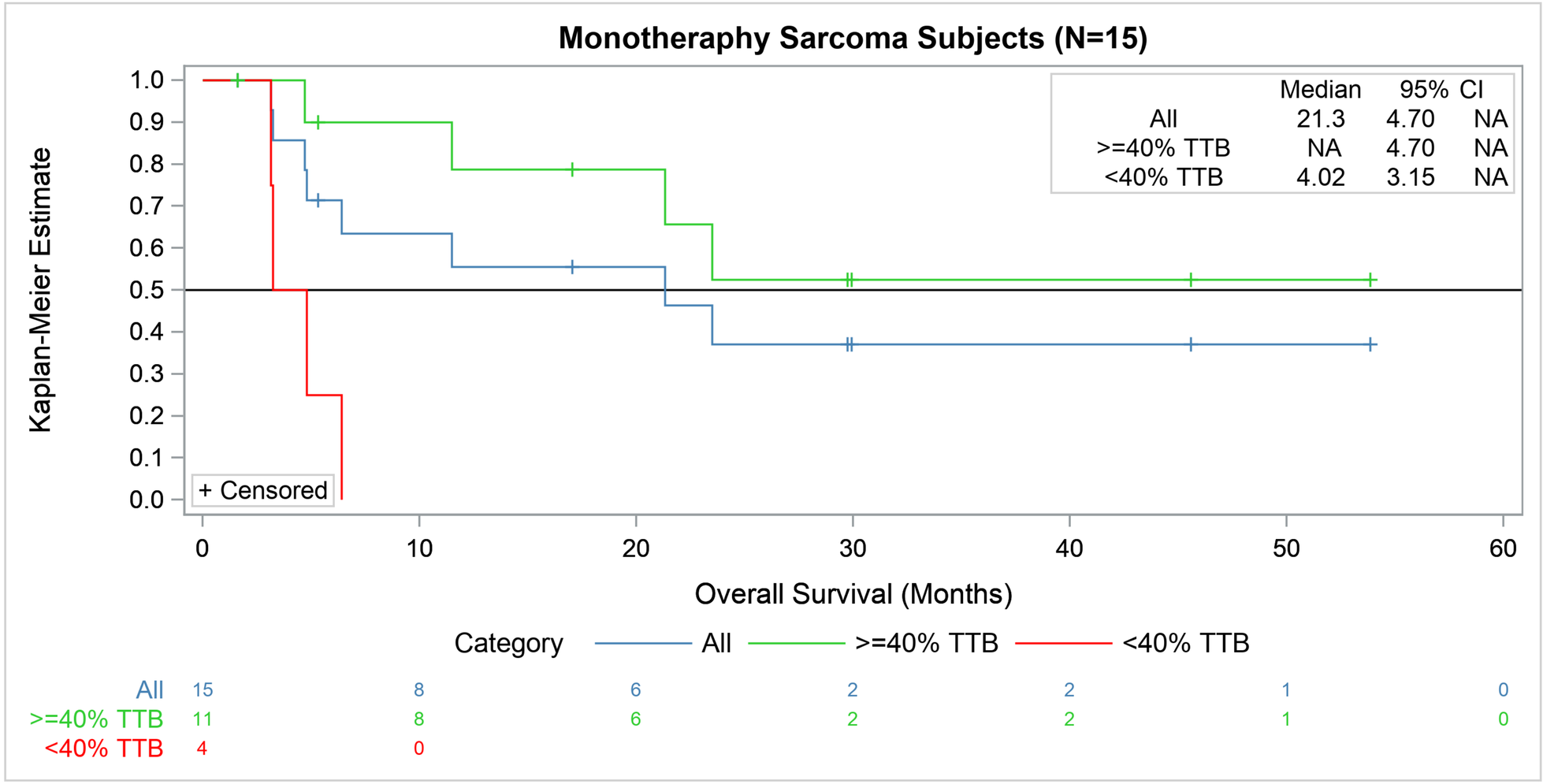
Phase 1/2 Refractory or Metastatic Cancer Study *(IT-01)*

Overall survival increases with higher INT230-6 doses as monotherapy relative to the sarcoma patient's presenting total tumor burden (TTB)

Exploratory analysis indicates that treating a higher percentage of the patient's total tumor burden correlates with increased survival

Sarcoma Types

- Leiomyosarcoma
- Liposarcoma
- Pleomorphic (UPS)
- Chondrosarcoma
- Kaposi's
- Sacral sarcoma
- Myofibroblastic
- Osteosarcoma



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Sarcoma Results

The sarcoma diagnoses of the Phase 2 patients included liposarcoma, pleomorphic sarcoma, leiomyosarcoma, chondrosarcoma, osteosarcoma (chondroid syringoma), myofibroblastic, osteosarcoma, Kaposi sarcoma and chordoma

Efficacy:

- INT230-6 extended mOS in refractory sarcoma subjects by 14.6 months as monotherapy compared to a synthetic control group (21.3 versus 6.7* months)

- Disease control rate (DCR): 93.3% (95% CI: 68.1, 99.8) for the sarcoma population

- Duration of response (DOR): 4.0 months (95% CI: 1.7, NA) full population
- DOR: 11.3 months (95% CI: 2.8, NA) for subjects who received a dose of ≥ 40% of the total incoming total tumor burden

- 27% of patients had uninjected tumors shrink (abscopal effects)#

* Calculated based on the Royal Marsden Hospital scoring method

Tumors less than 1 cm were uninjected, untracked, and unreported by investigators, the true abscopal percentage is unknown; further radiomics work is ongoing

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Phase 3 Trial Design For INT230-6 in Soft Tissue Sarcoma (STS) Schema for 2nd or 3rd line

n = 333

Randomized, open-label, multicenter, Phase 3

Enrollment Criteria

- Subtypes: unresectable or metastatic
  - Liposarcoma
  - Undifferentiated pleomorphic sarcoma
  - Leiomyosarcoma
- ≥ 18 years
- ECOG PS ≤ 2
- 2L/3L
- Measurable disease by RECIST 1.1
- At least one target tumor for injection > 2 cm in longest diameter

2:1

222 patients

INT230-6 Monotherapy

- INT230-6 every 14 days, 5 sessions
- Maintenance every 12 weeks, for 22 months (treat all tumors possible)

Dose: 1 mL of INT230-6 per every 2cc of an injected tumor (max 175 mL per session)

111 patients

Standard of Care

- Pazopanib: 800 mg PO QD

or

- Trabectedin: 1.5 mg/M^2 BSA as a 24-hour IV infusion Q21 days

or

- Eribulin: 1.4 mg/M^2 BSA IV on Days 1 and 8 q21 days EU 1.23 mg//M^2

Radiographic disease progression is determined using WHO criteria

Primary Endpoint
•Overall Survival (OS)

Secondary Endpoints
•OS for leiomyosarcoma
•OS for liposarcoma

Exploratory
Quality of Life (QoL)

Interims Looks
At 20%, 40% and 60% of events (deaths)

*Final **D**ata **R**eadout*
At 80% of events (deaths)

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Dosing Information:
A Session's Dose is Set by the Number of Tumors Being Injected

- Dosing must be performed with ultrasonography or CT guidance
- INT230-6 will be injected with the largest tumors possible first, through to the smallest
- The oncologist and interventional radiologist determine which tumors are to be injected per session
- Dose as many tumors as possible during the treatment phase.
- Drug dose for a given tumor is set as follows:
    - For longest diameters > 1 cm and ≤ 1.6 cm, a dose of 2.5 mL is used
    - For longest diameters > 1.6 cm and < 9 cm, dose is calculated using a table (from prior studies)
    - For tumors ≥ 9 cm, use the modified ellipsoid model from 3 dimensions

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Phase 3 Trial Information:

Countries that have authorized the study:

US, Canada, Australia, Europe (France, Germany, Italy, Poland, Spain): Total sites expected: up to 69

Key Inclusion Criteria:

- who had disease progression prior to study enrollment following standard therapies, which must have included an anthracycline-based regimen, unless contraindicated,
- may also have received a maximum of 1 additional regimen,
- must have measurable disease per RECIST 1.1 criteria.
- must have at least 1 target tumor > 2 cm suitable for injection using routine image guidance measurable by CT or MRI.
- must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
- must have adequate organ function as defined by screening laboratory values

Key Exclusion Criteria:

- who lack the capacity to consent
- with prior primary or metastatic brain or meningeal tumors unless clinically and radiographically stable
- other prior malignancy, except for adequately treated basal or squamous cell skin cancer or superficial bladder cancer
- who require uninterrupted anticoagulants
- Participants with a QTc of > 450 ms for men and > 470 ms for women

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