# The Development of BrachySil® – From Bench to First-in-Man

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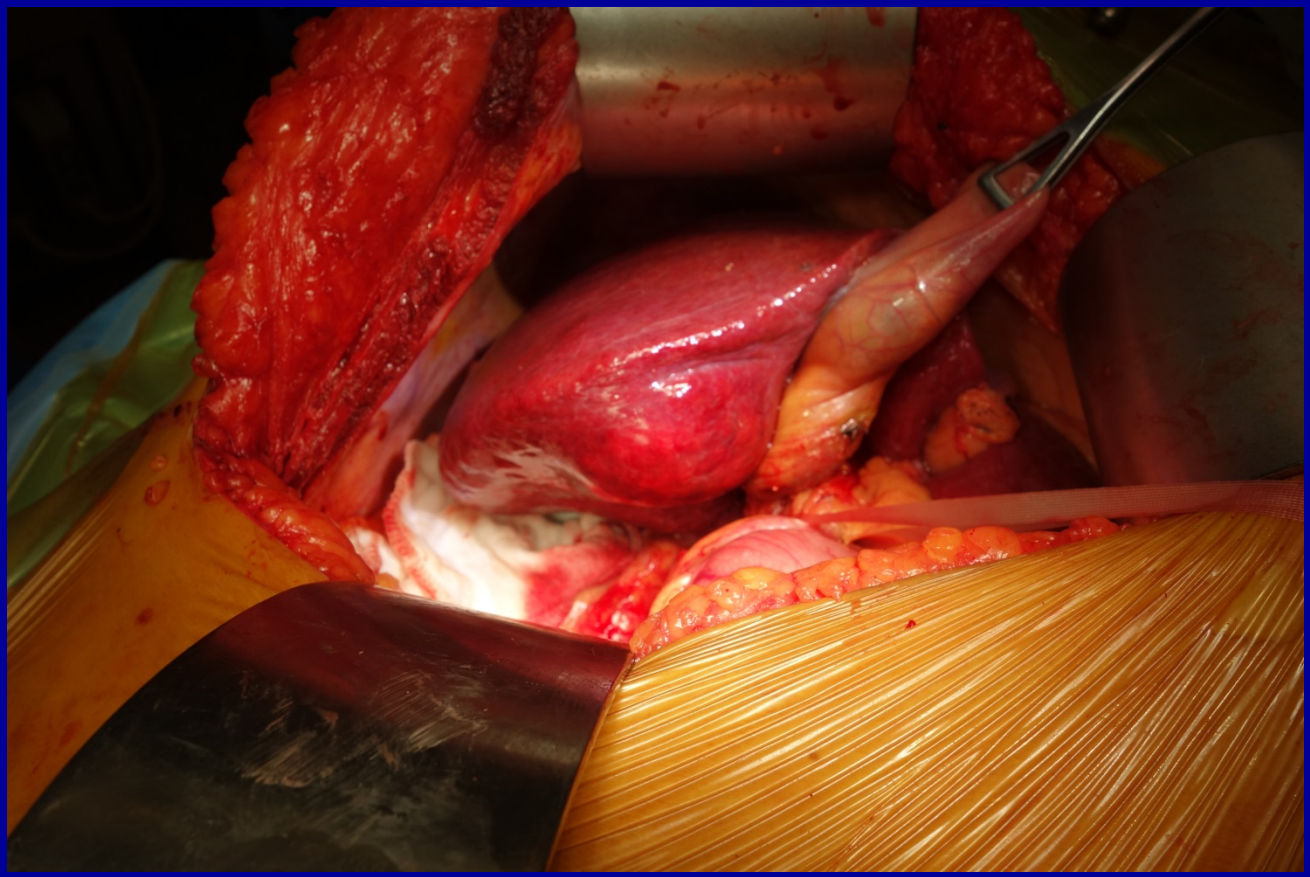
**2nd International Conference on Phase I and Early Phase Clinical Trials**

**Hyatt Regency, Tsim Sha Tsui, Hong Kong, 17th Nov 2015**

***SGH – Surgery***

# *Surgery*
# *is the standard of care of most solid cancers*



- No metastatic disease, favorable anatomy
- If underlying physiological function is adequate

# However many solid malignancies are inoperable at diagnosis

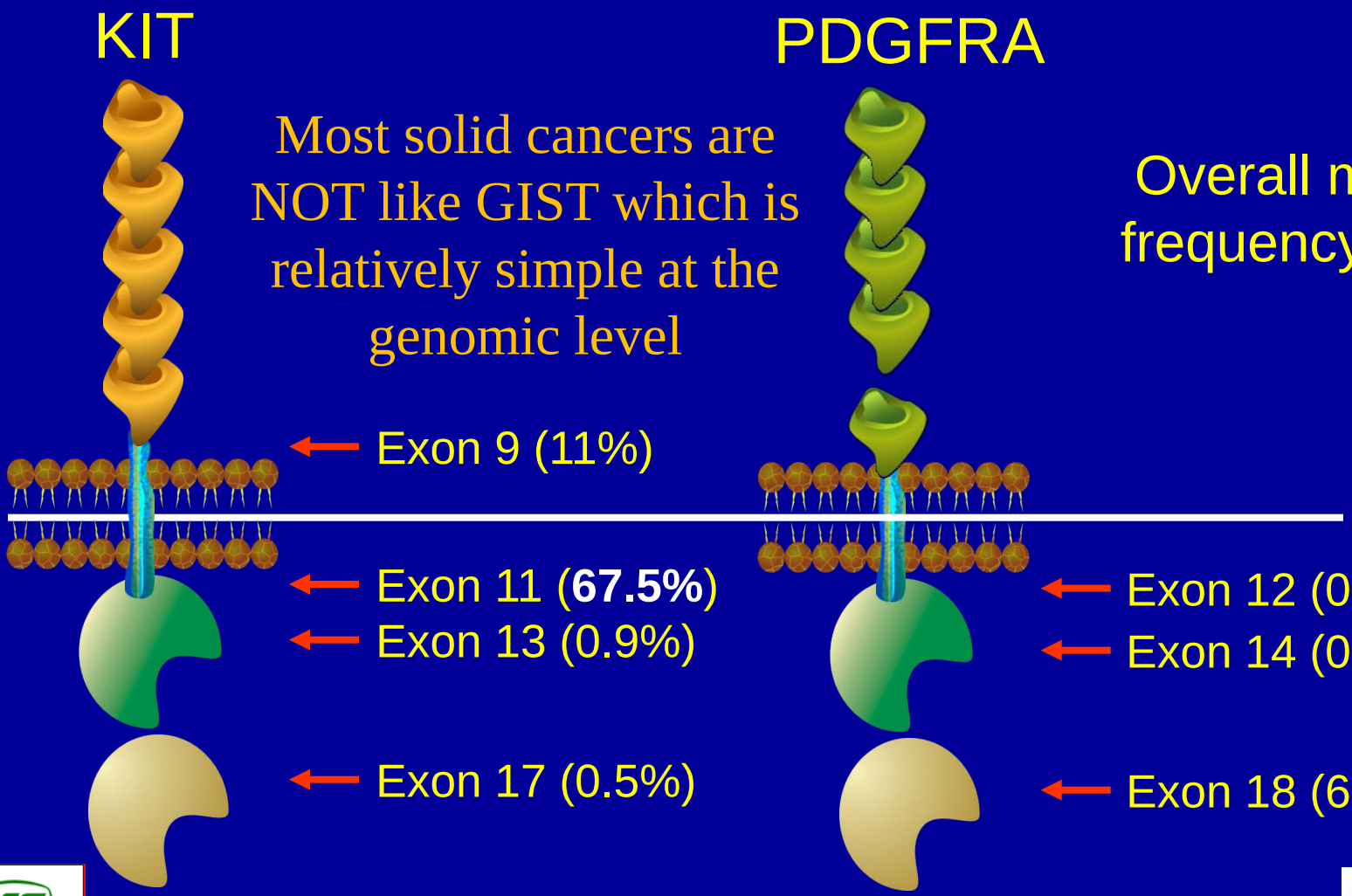
- Pancreatic Carcinoma:
  - 5 – 25% resectable at diagnosis
  - Median Survival of un-resectable pancreatic carcinoma (all stages): 9 months

- Hepatocellular Carcinoma:
  - 15 – 20% resectable at diagnosis
  - Median Survival of un-resectable HCC (all stages) : 8 months

# Current management of inoperable solid organ malignancies

- Palliative systemic therapy and radiation therapy are currently the standards of care in many inoperable solid organ malignancies
- *Drug toxicities* and *intra-tumoral heterogeneity* limit the effectiveness of systemic chemotherapy
- Similarly *collateral radiation injury* to surrounding structures limits the dosage and thus efficacy of external beam radiation

# Solid cancers highly responsive to systemic therapy are uncommon



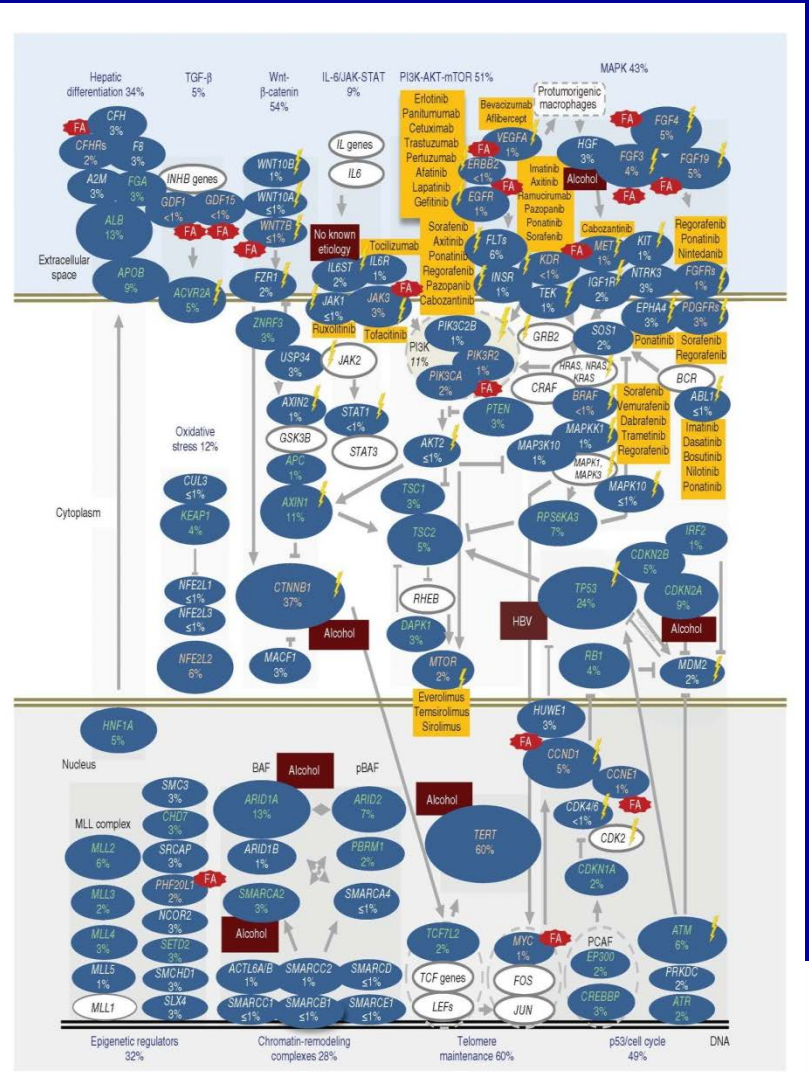



Heinrich et al. *Hum Pathol.* 2002;33:484.
Corless et al. *Proc Am Assoc Cancer Res.* 2003;44. Abstract R4447.

# Current efficacy of systemic therapy in cancer

- Incomplete understand of intra-tumoral heterogeneity
- Between 2002 and 2012, the *71 anti-cancer drugs* approved by FDA (including *52 molecular targeted drugs*) increased median OS by **2.1 months**

*Kantarjian 2013*

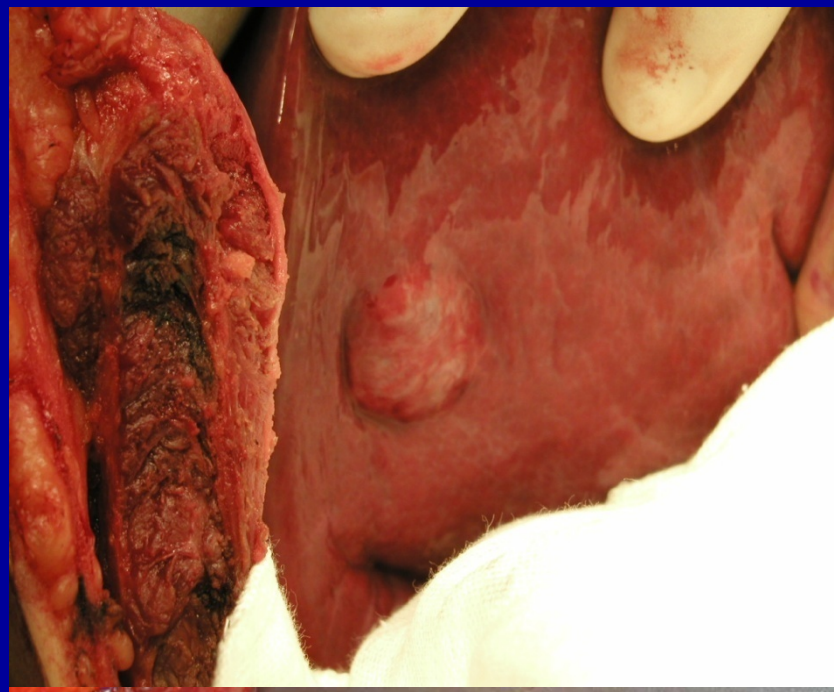


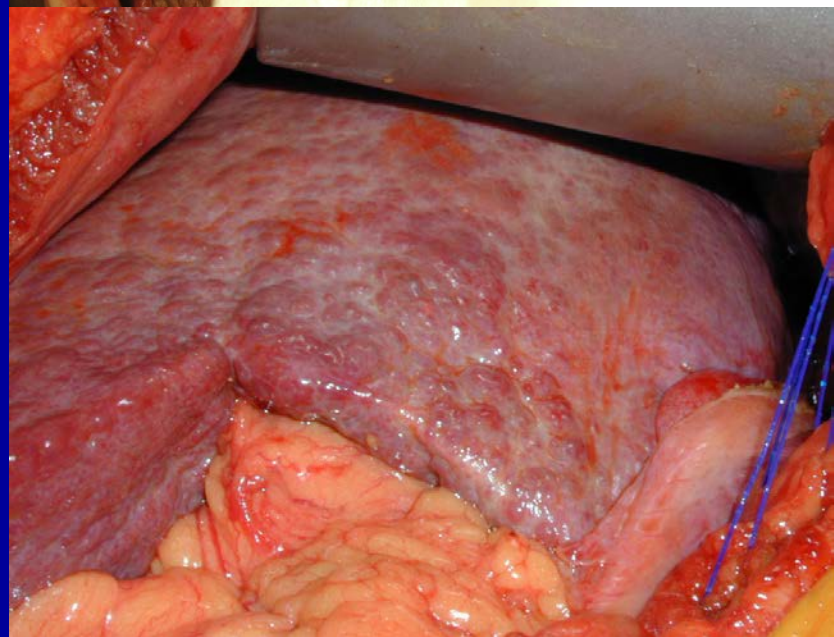

Schulze Nat Gen 2015

*Pierce Chow FRCSE PhD*

# Hepatocellular Carcinoma: especially challenging

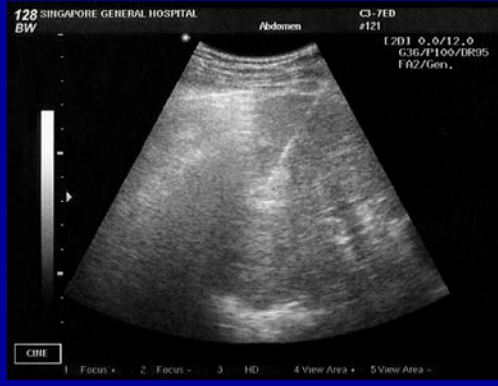
- HCC is highly heterogeneous
- Patients with HCC usually suffer from 2 diseases simultaneously
  - Liver cirrhosis
    - *Liver function can be poor*
  - Cancer
    - *Synergistic impact*





# Physical Ablation of solid cancers

- Physical Ablative therapy remain the most important way to eradicate HCC that is **not metastatic**
  - Surgical Resection
  - Heat Ablation: radiofrequency ablation
  - Radiation:
    - Interstitial Brachytherapy - **Phosporus-32**
    - Trans-arterial delivered Brachytherapy - **Ytrium-90**



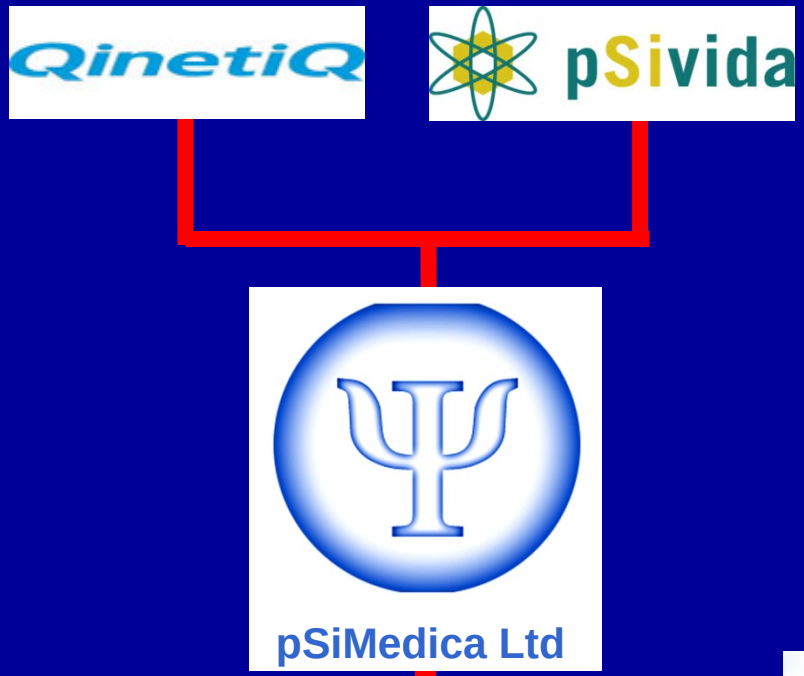

# Intra-tumoral/interstitial brachytherapy

- **Principle**
  - The therapeutic agent (radionuclide) is brought to bear directly on the tumour by implantation into the tumour

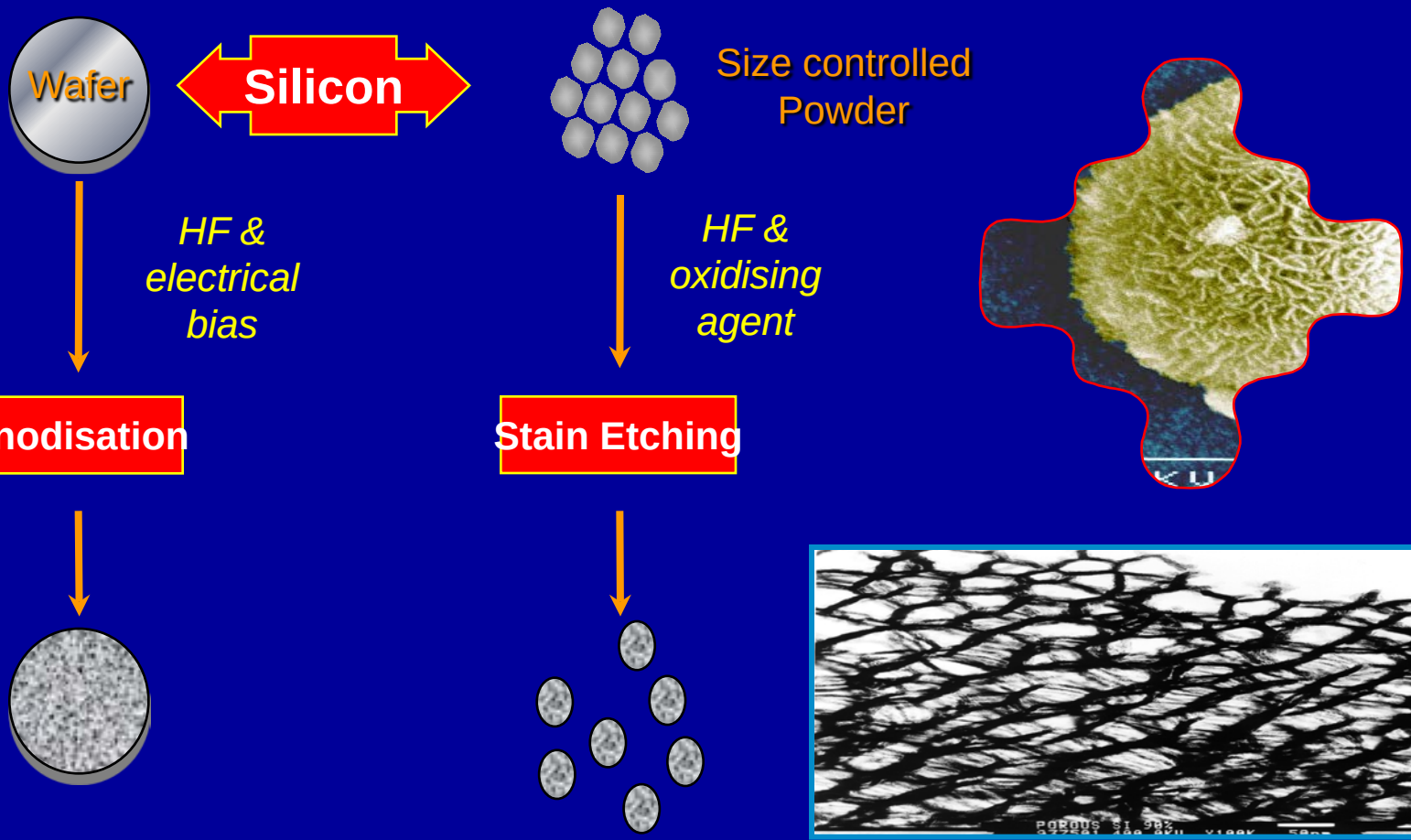
- **Theoretical advantages**
  - collateral radiation damage are minimised
  - much higher therapeutic doses are possible, and greater tumour response expected

# Existing predicate therapies in 2002

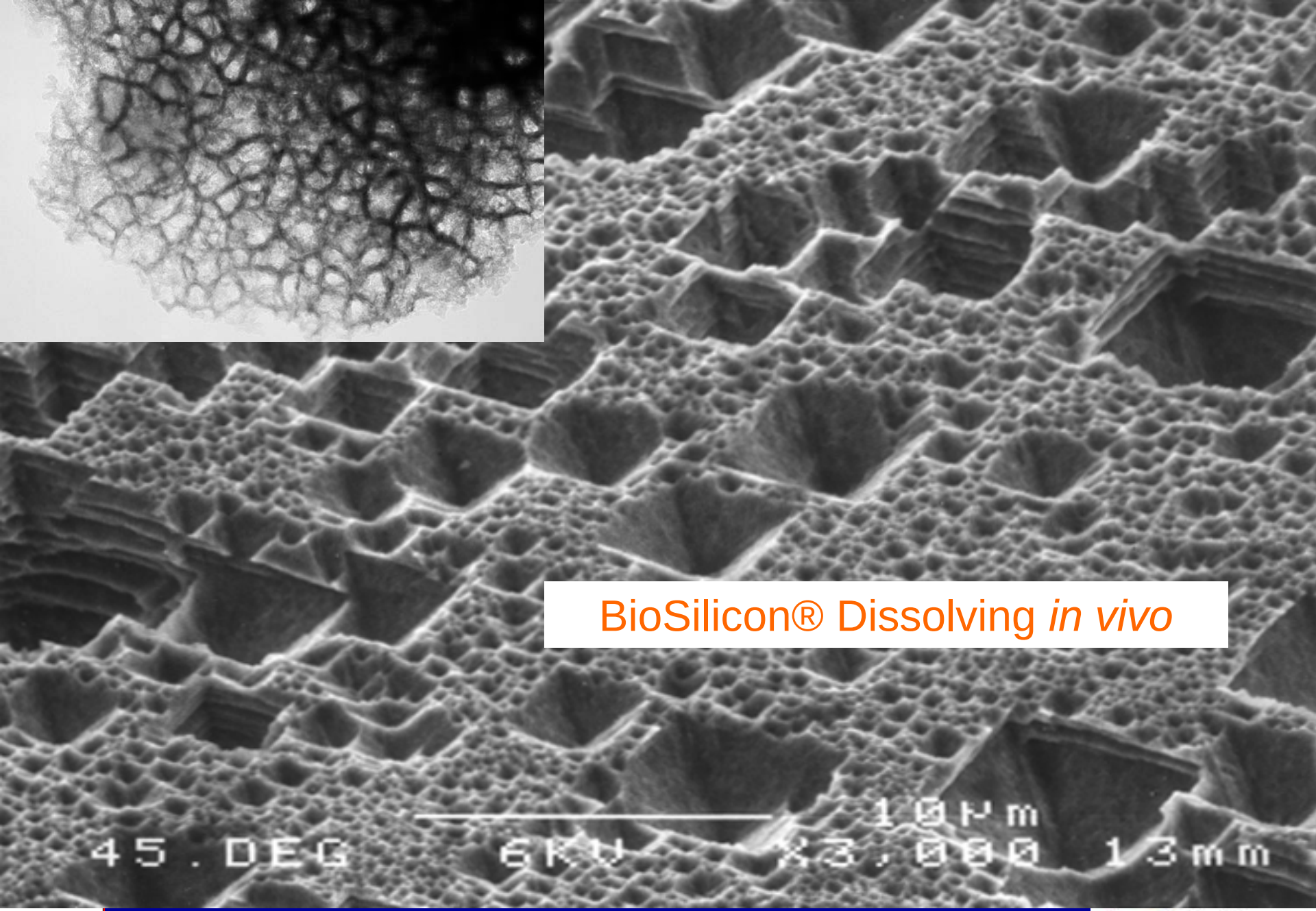
- *Radio-gold $^{198}$Au brachytherapy*
  - *Permanent implant*
- *Phosphocol brachytherapy*
  - *chromic phosphate colloid (P32)*
  - *Unable to "lock" source of radiation to site of implant*
  - *Significant bio-distribution*
- Technical hurdles to overcome to enable:
  - Local therapy with no systemic *"leak" (bio-distribution)*
  - "Fire and forget" implant - *biodegradable*


QinetiQ
pSivida
pSiMedica Ltd
SingHealth
Singapore General Hospital
National Cancer Centre
SingHealth
BRV
Discussion

# Silicon-Biomaterial: BioSilicon®




IP - Exquisite control over nano-structuring to make silicon porous




BioSilicon® Dissolving *in vivo*

# BioSilicon®: Potential Applications in Oncology

**Our assessment** (under Non-Disclosure Agreement)

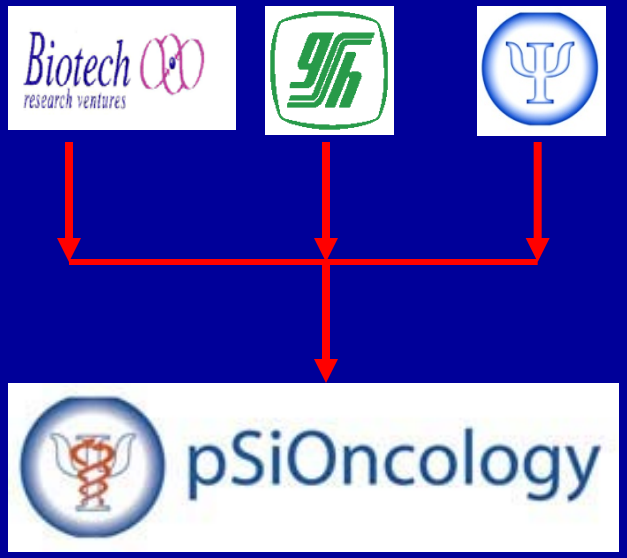
- Porosity can be controlled
- Rate of bio-degradation can be tightly controlled
- Rate of *release* tightly controlled
- "Radio-hard" and can be made *radioactive* by nuclear bombardment
- Radio-opaque

**Our Recommendation**

- Ideal vehicle for delivery of intra-tumoral radiation

# Bench-to-Bedside
# Research Plan for $^{32}P$ Brachytherapy

***Bio-degradable silicon carrier***




Pre-clinical study on
HCC/pancreatic cancer
(Brachy)therapy
BrachySil®

PHASE IIA TRIAL
SGH/NCC

*SGH – Surgery*

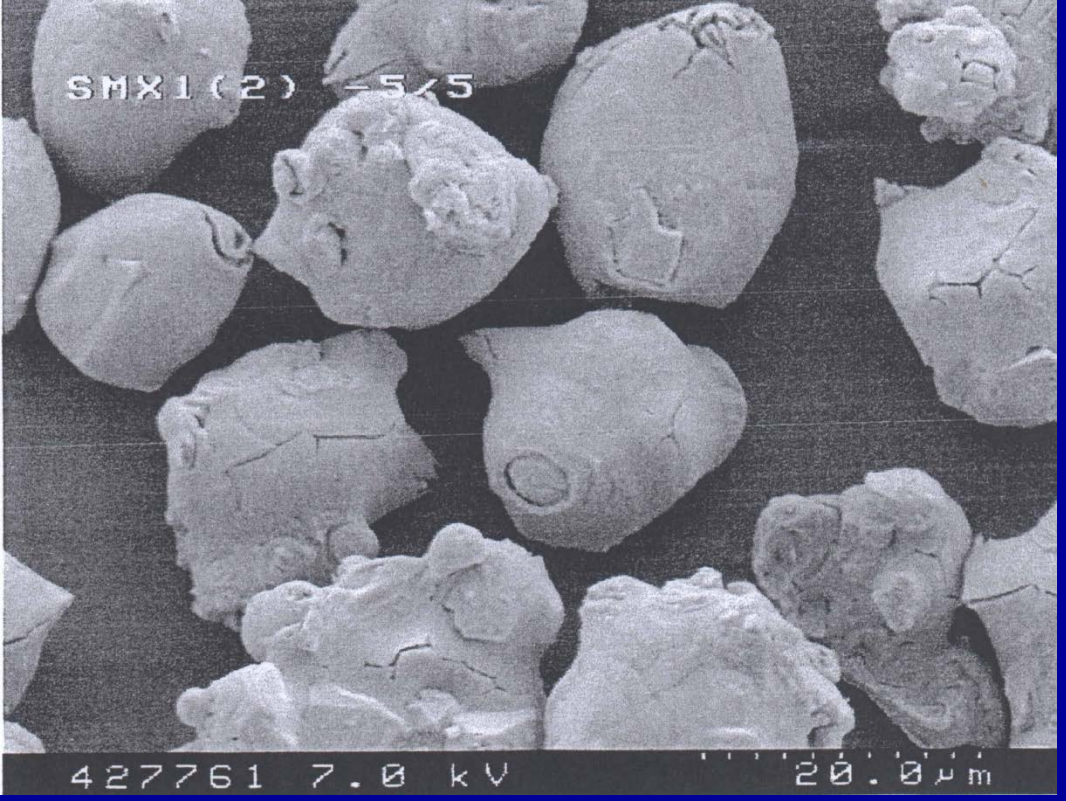
National Cancer Centre Singapore
SingHealth

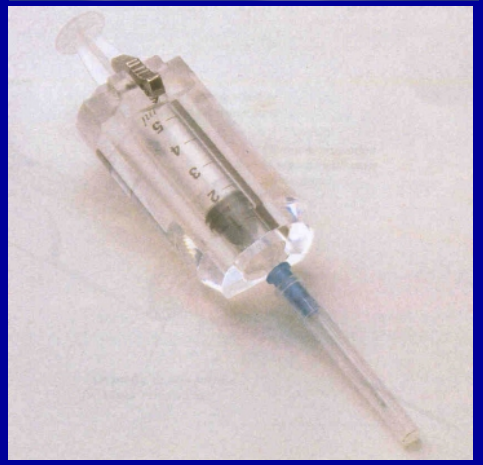
# Symbiotic collaboration

- **PsiMedica**
- Material Science company
- Facilities: physical science and drug formulation laboratories and staff
- Expertise in nano-particle technology
- Expertise in drug formulation
- Expertise in nuclear physics

- **Surgery, SingHealth**
- Academic Medical Center
- Facilities: full spectrum of animal based research facilities and expertise
- Expertise in Experimental Oncology
- Expertise in Radiation Oncology
- Expertise in Nuclear Medicine

*SGH – Surgery*



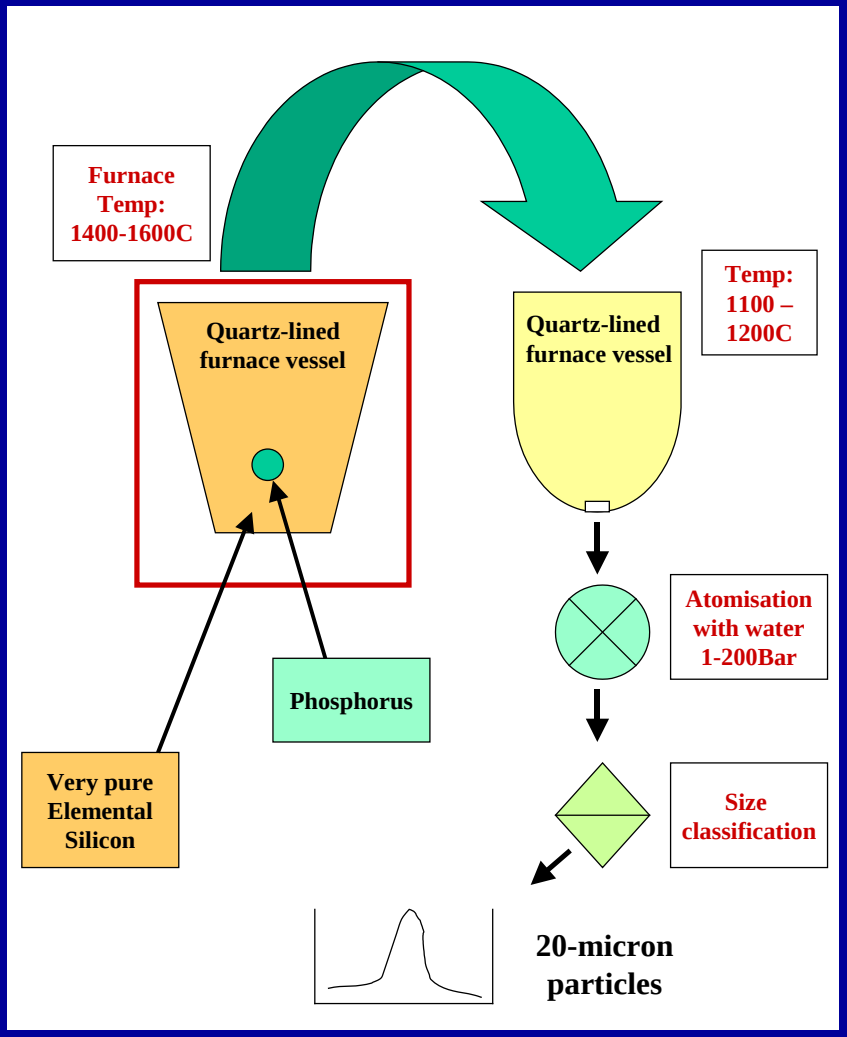



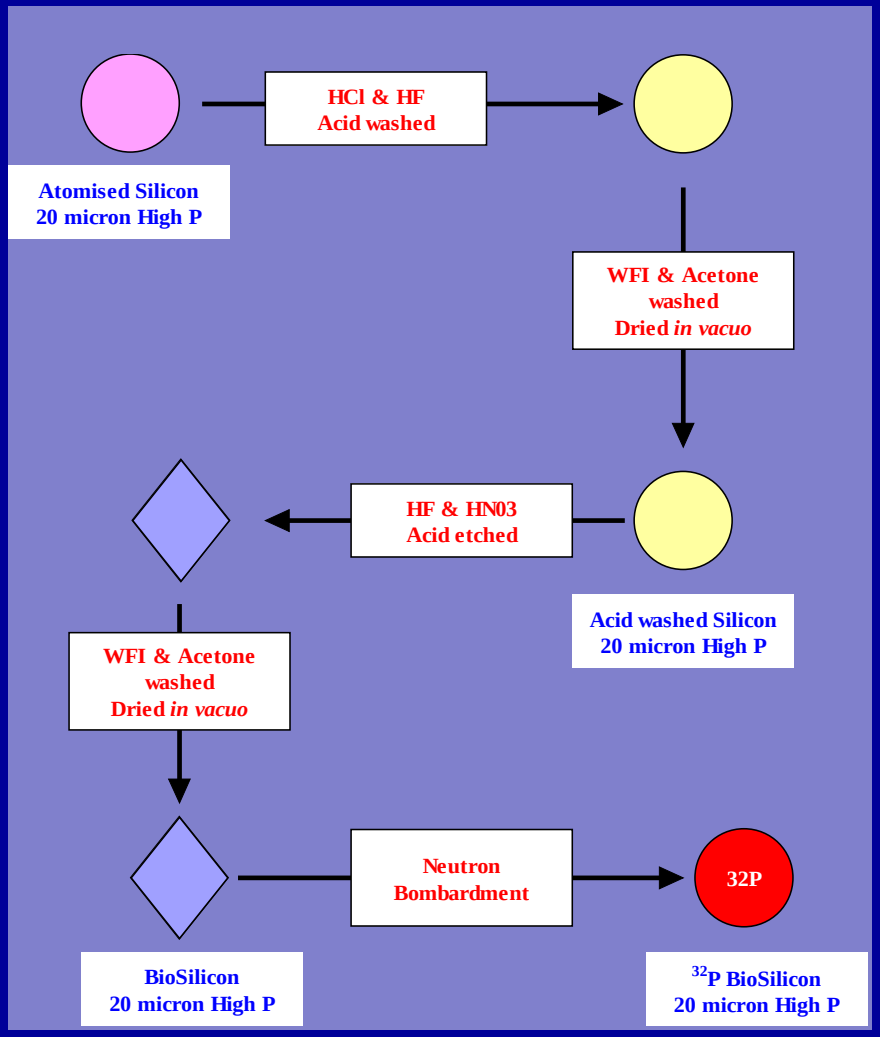
# BioSilicon ->BrachySil

Highly pure silicon encapsulating $^{32}$Phosphorus for Brachytherapy

- 20-micron etched Silicon particles containing the **radionuclide $^{32}$P**
- For direct intra-tumoural administration
- Using a conventional shielded syringe and narrow bore needle

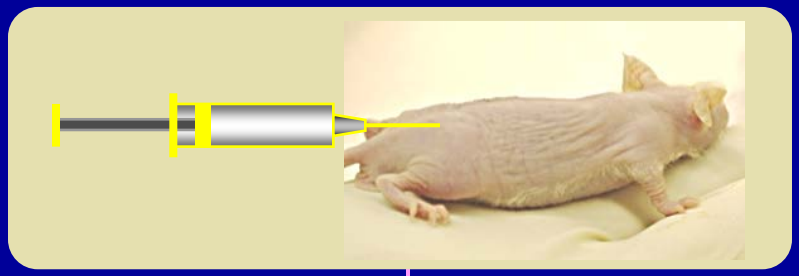
# How BrachySil® is made



# Proof-of-principle in mice

**In vitro culture of human tumour cells**
( HepG2/pancreatic adenoCa )



**Implantation of cultured tumour cells to nude mice** (5 x $10^5$ cells/mouse)

14 days

**5 – 8 mm Ø tumours**

**Intra-tumoural injection of $^{32}$P BioSilicon**

Controls,
0.5, 1.0 and 2.0 MBq

**$^{32}$P activity in blood, liver, & tumour**

**Histological studies**

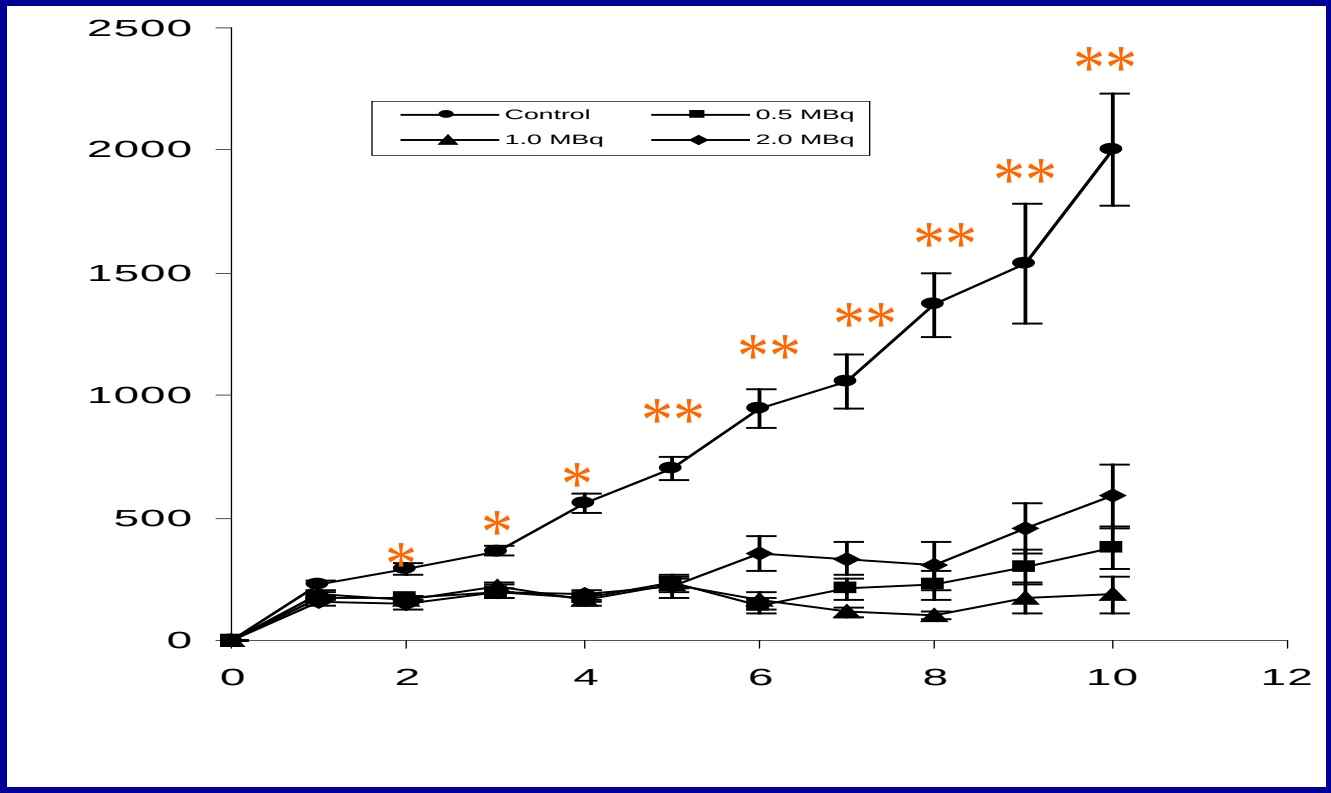
**Tumour volumetrics**

**BrachySil®**
**2.0 MBq**

**Control**

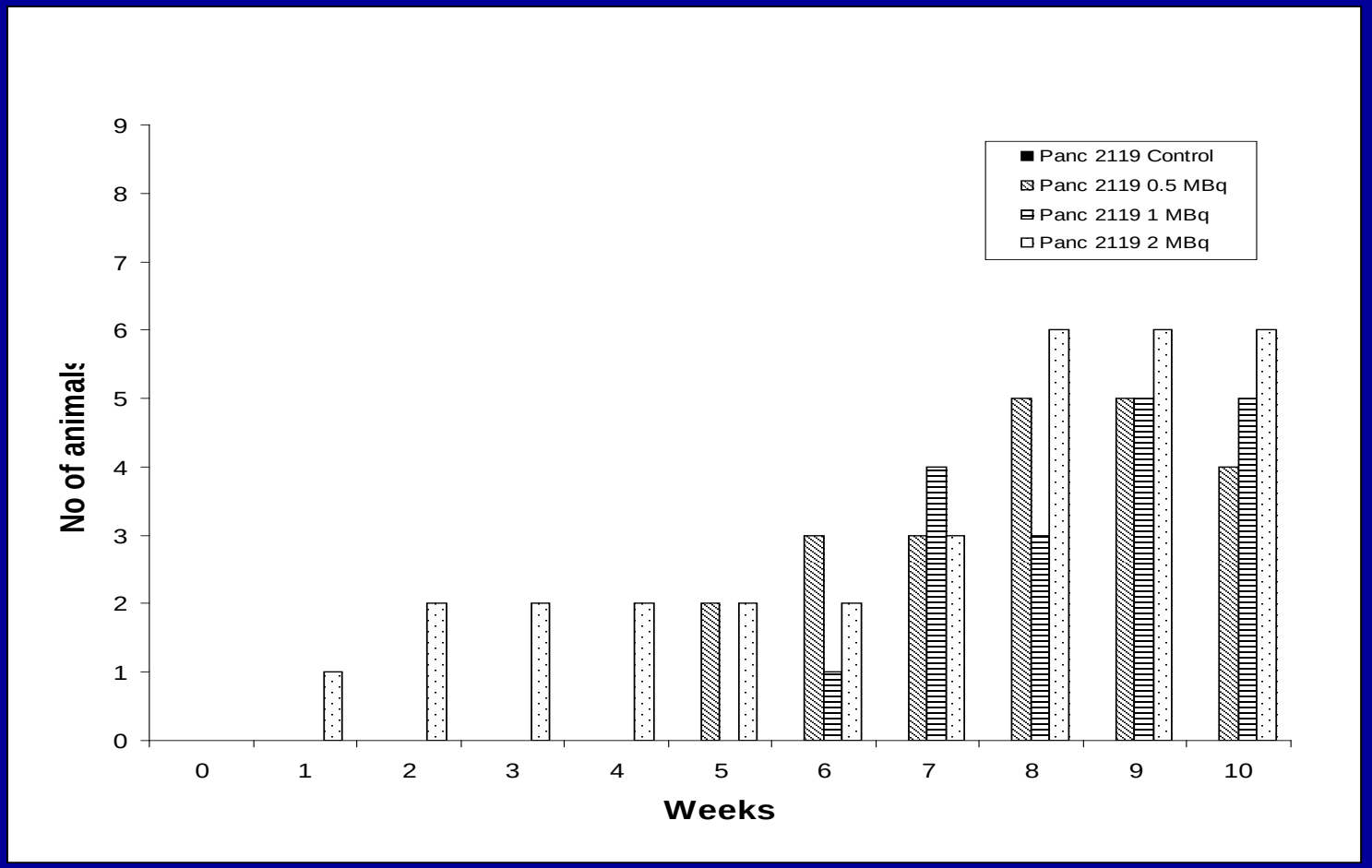
Beginning of study

After 12 weeks

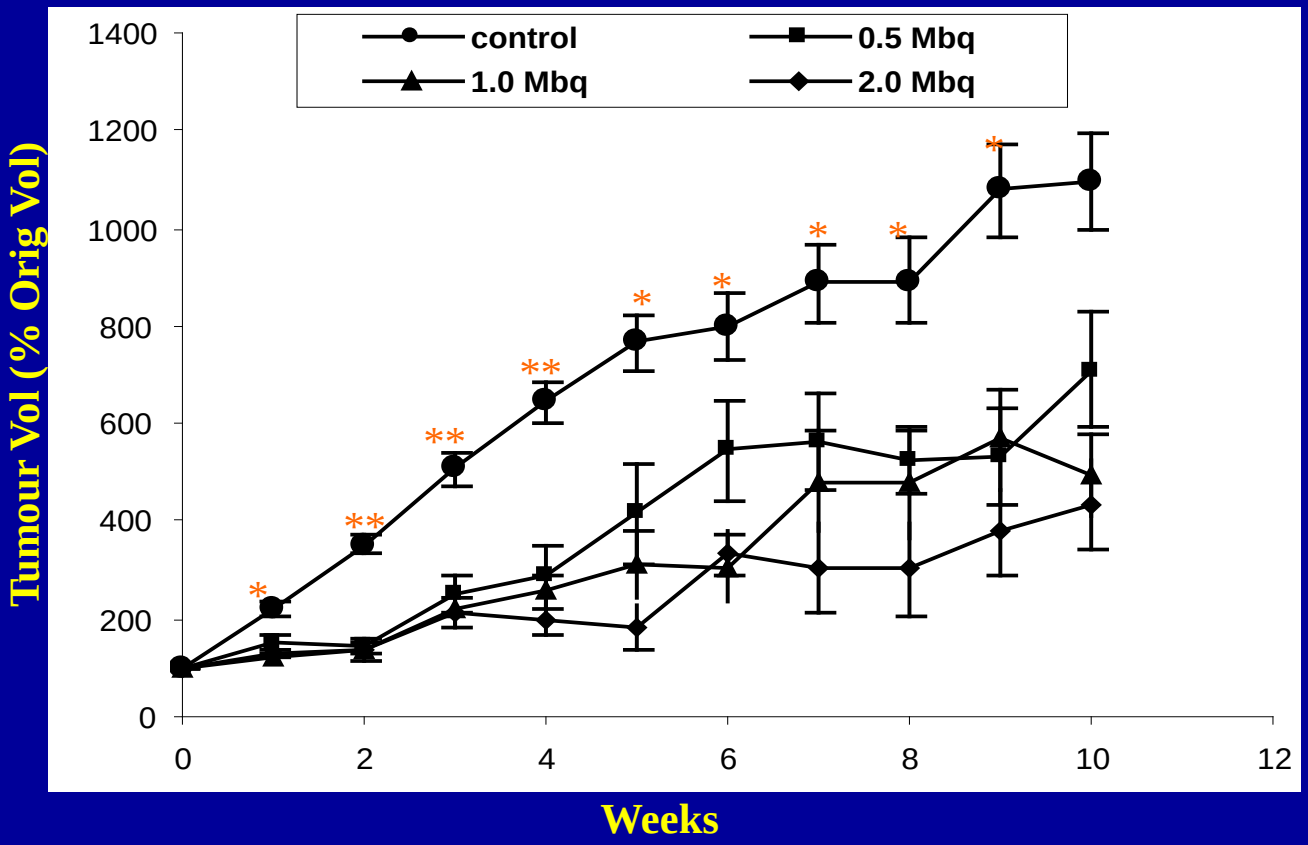



# Effect of BrachySil on growth of human pancreatic cancer cell xenografts in nude mice

Points are means ± SEM/2, * Compared with 32p-biosilicon treated groups, P< 0.05; ** compared with 32p-biosilicon groups, P< 0.005.



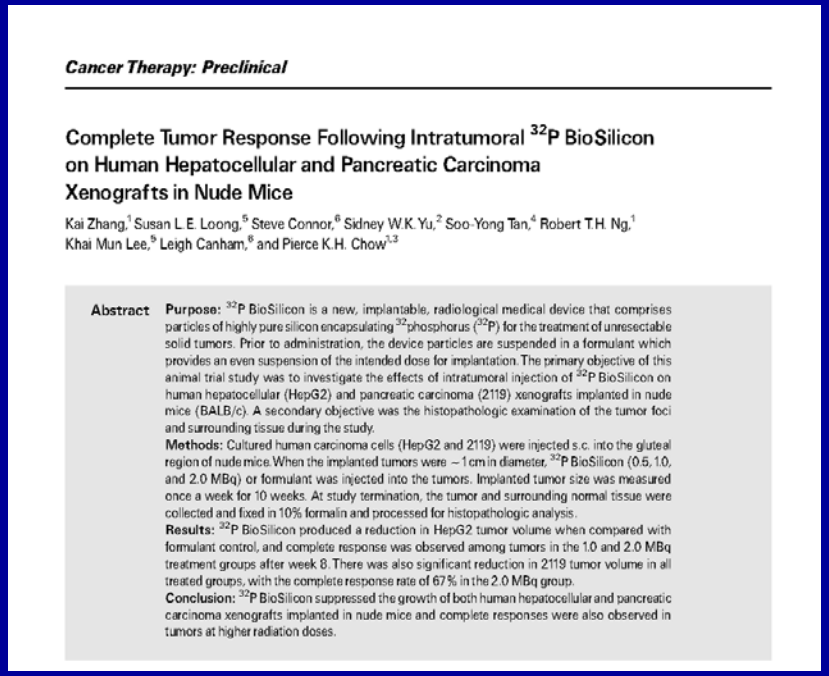

Tumor complete responses (CR) in pancreatic 2119 xenografts. The number of animals with complete tumor responses for each dose are shown.




# Effect of BrachySil on growth of human liver cancer cell xenografts in nude mice.

Points are mean±SEM/2, * Compared to 32p-biosilicon treated groups p< 0.05,
** compared to 32p-biosilicon treated groups P< 0.01.

# Feasibility study and development of a delivery system with BrachySil® in a large animal model



*Cancer Therapy: Preclinical*

**Complete Tumor Response Following Intratumoral $^{32}$P BioSilicon on Human Hepatocellular and Pancreatic Carcinoma Xenografts in Nude Mice**

Kai Zhang,[1] Susan L.E. Loong,[5] Steve Connor,[6] Sidney W.K. Yu,[2] Soo-Yong Tan,[4] Robert T.H. Ng,[1] Khai Mun Lee,[5] Leigh Canham,[6] and Pierce K.H. Chow[1,3]

**Abstract** **Purpose:** $^{32}$P BioSilicon is a new, implantable, radiological medical device that comprises particles of highly pure silicon encapsulating $^{32}$phosphorus ($^{32}$P) for the treatment of unresectable solid tumors. Prior to administration, the device particles are suspended in a formulant which provides an even suspension of the intended dose for implantation. The primary objective of this animal trial study was to investigate the effects of intratumoral injection of $^{32}$P BioSilicon on human hepatocellular (HepG2) and pancreatic carcinoma (2119) xenografts implanted in nude mice (BALB/c). A secondary objective was the histopathologic examination of the tumor foci and surrounding tissue during the study.

**Methods:** Cultured human carcinoma cells (HepG2 and 2119) were injected s.c. into the gluteal region of nude mice. When the implanted tumors were ~1 cm in diameter, $^{32}$P BioSilicon (0.5, 1.0, and 2.0 MBq) or formulant was injected into the tumors. Implanted tumor size was measured once a week for 10 weeks. At study termination, the tumor and surrounding normal tissue were collected and fixed in 10% formalin and processed for histopathologic analysis.

**Results:** $^{32}$P BioSilicon produced a reduction in HepG2 tumor volume when compared with formulant control, and complete response was observed among tumors in the 1.0 and 2.0 MBq treatment groups after week 8. There was also significant reduction in 2119 tumor volume in all treated groups, with the complete response rate of 67% in the 2.0 MBq group.

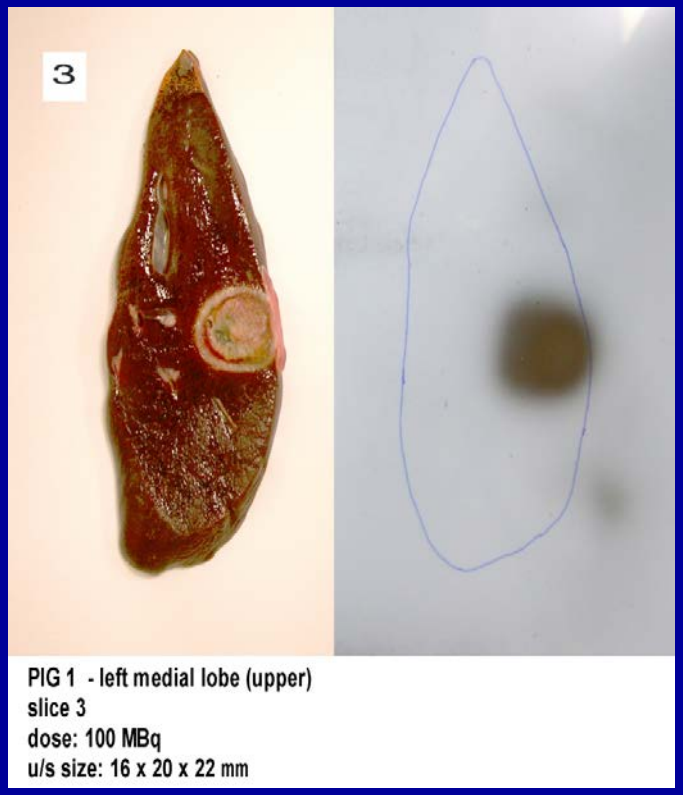
**Conclusion:** $^{32}$P BioSilicon suppressed the growth of both human hepatocellular and pancreatic carcinoma xenografts implanted in nude mice and complete responses were also observed in tumors at higher radiation doses.

- Prelude to early phase clinical trial
- Opportunity to trouble-shoot in a hands-on manner
- Bio-safety study
- Ascertain kill-zone
- Dry run for the *clinical team*

*SGH – Surgery*

*Pierce Chow FRCSE, PhD*

# Delivery systems for BrachySil® developed in a porcine model

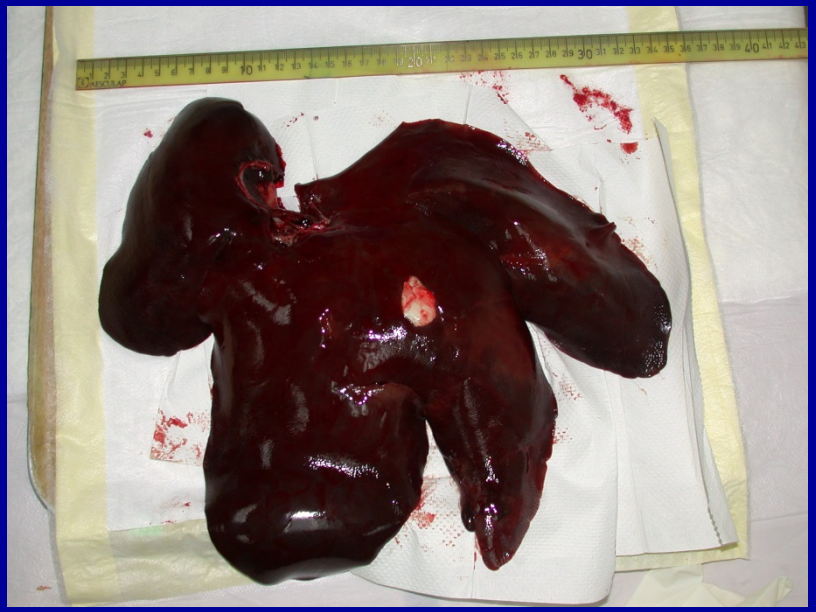


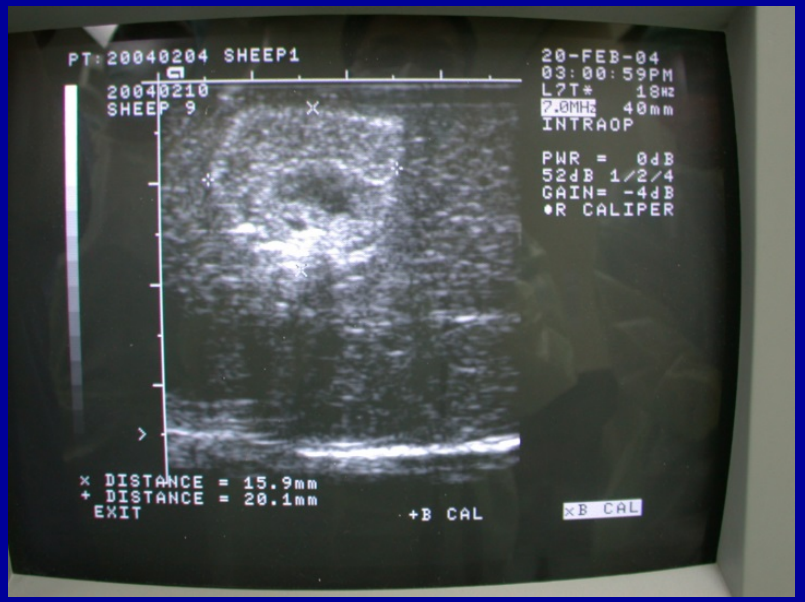

**Multi-disciplinary clinical team**

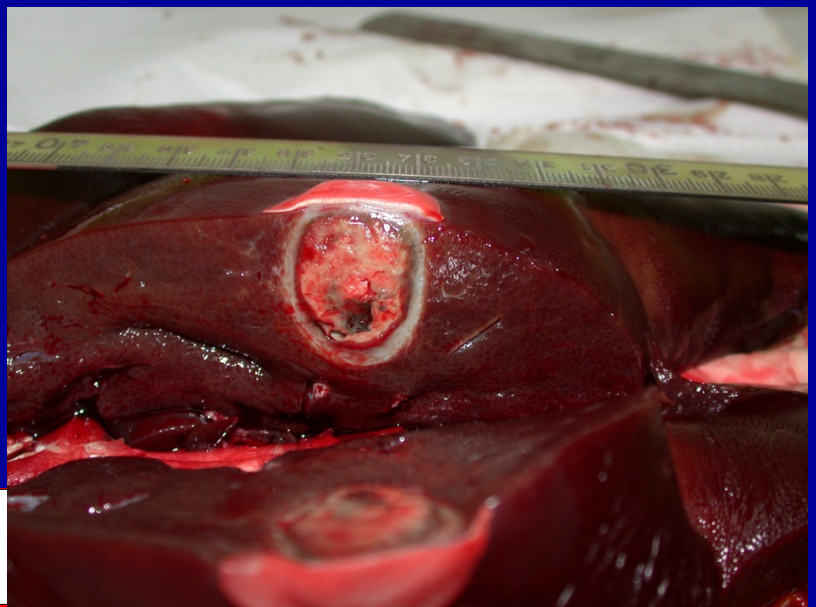
*SGH – Surgery*

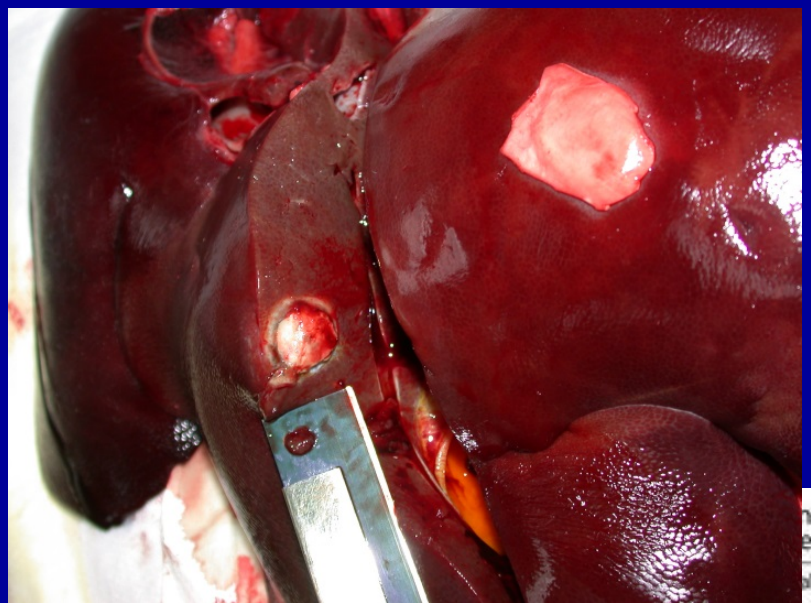
National Cancer Centre Singapore
SingHealth

# Liver harvested 60 days later

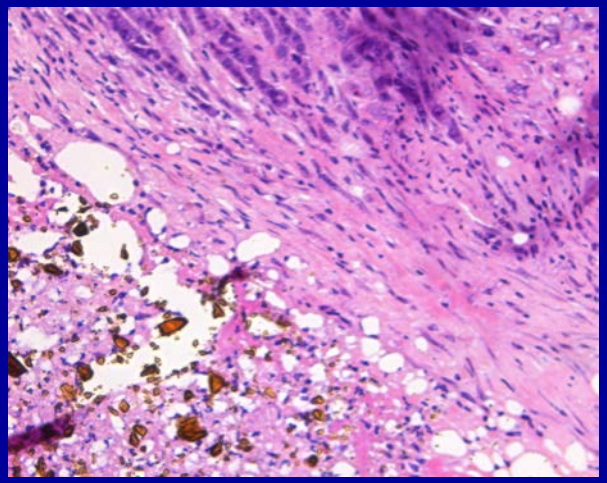




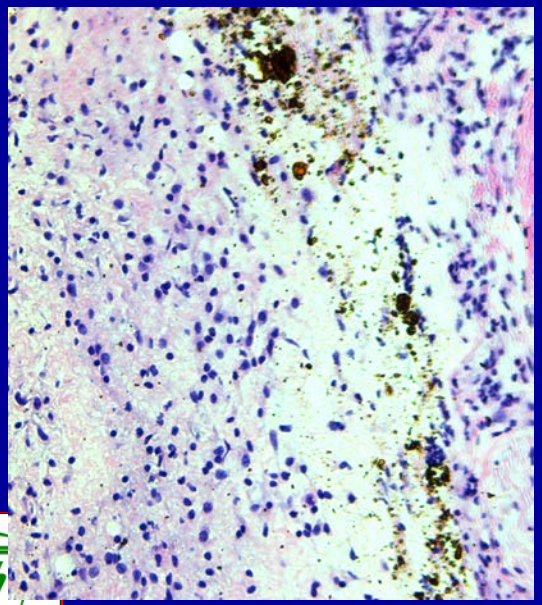





# Histology



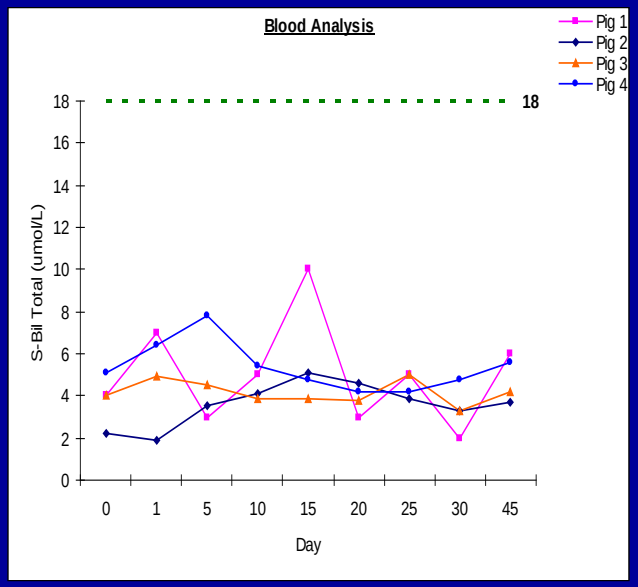
Low Power



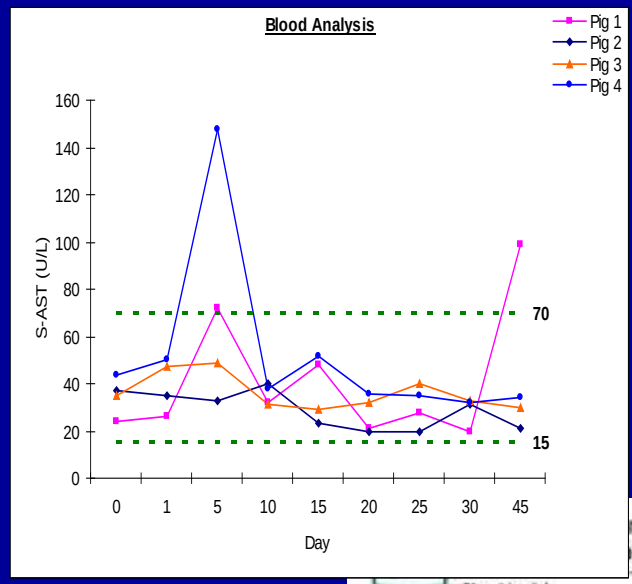
High power

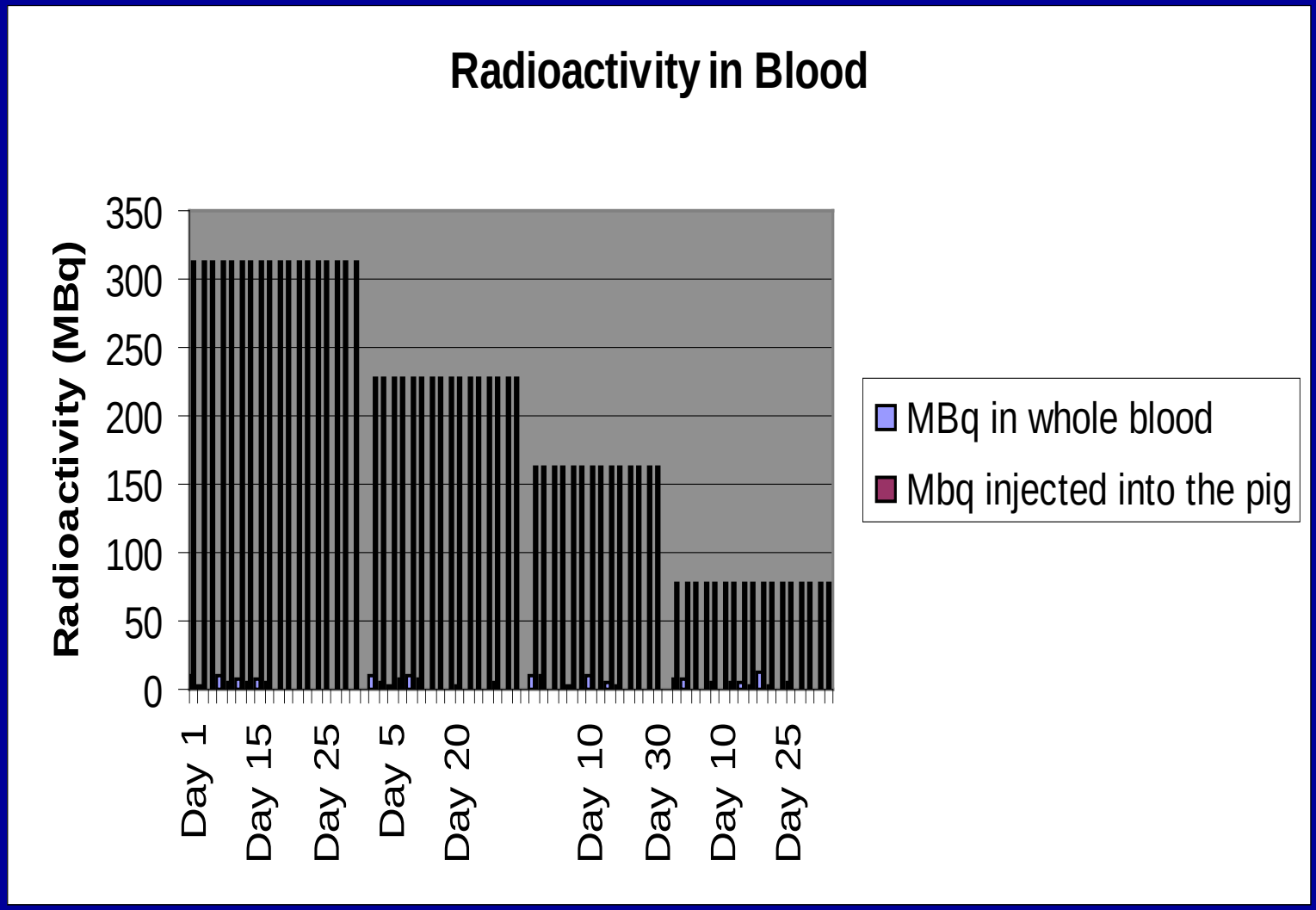
# Extent of global liver damage

Serum bilirubin




Aspartate transaminase




Radioactivity in Blood
Radioactivity (MBq)
350
300
250
200
150
100
50
0
Day 1
Day 15
Day 25
Day 5
Day 20
Day 10
Day 30
Day 10
Day 25
MBq in whole blood
Mbq injected into the pig

# Conclusions from the large animal study

Blood sampling and autoradiography showed that the ***radioactivity remained localized*** at the site of implantation.

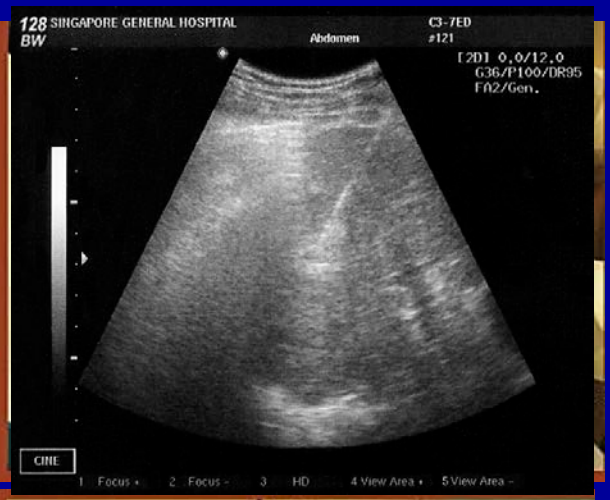
There was ***no significant systemic toxicity***.

Gross examination and histopathology of the liver showed ***highly localized tissue damage***.

*Pierce Chow FRCSE PhD*

# Translated into Therapy for Man








# Overview of Clinical Studies [1]

The four studies were:

| STUDY | DESIGN | No of Patients |
|---|---|---|
| DB2-201(pancreatic cancer) | Open Label, Phase IIa, Safety Study OncoSil™ | 17 patients (6 completed study, 6 withdrawn due to disease progression, 3 died) |
| DB2-202(pancreatic cancer) | Open Label, Phase IIB, Dose Escalating Safety Study of OncoSil | 6 patients (3 completed study, 3 withdrawn due to disease progression) |
| BIOSP-201(liver cancer) | Single-dose, open-label, single centre study | 8 patients (with 5 completing the study)<br>• All patients were of Asian race |
| BIOSP-202(liver cancer) | Open-label, three cohort dose ranging study | 11 patients (1 withdrawn)<br>• Terminated early due to poor recruitment<br>• All patients were of Asian race |

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

*Pierce Chow FRCSE PhD*

# $^{32}$P BioSilicon ( BrachySil ® ) brachytherapy in hepatocellular carcinoma

BIOSP201 Phase IIA trial

***Single center early-phase trial***

*SGH – Surgery*

# Study objectives

*1st in man trial, a phase IIA trial*

**PRIMARY** - evaluate safety

Determine the ***toxicity profile*** of $^{32}$P BioSilicon (BrachySil ®) in patients with unresectable HCC.

**SECONDARY** - evaluate response

Determine the ***anti-cancer activity*** of $^{32}$P BioSilicon.

# Targets and Dosage

***4 MBq/ml*** of tumour

Maximum of ***3 lesions*** will be injected

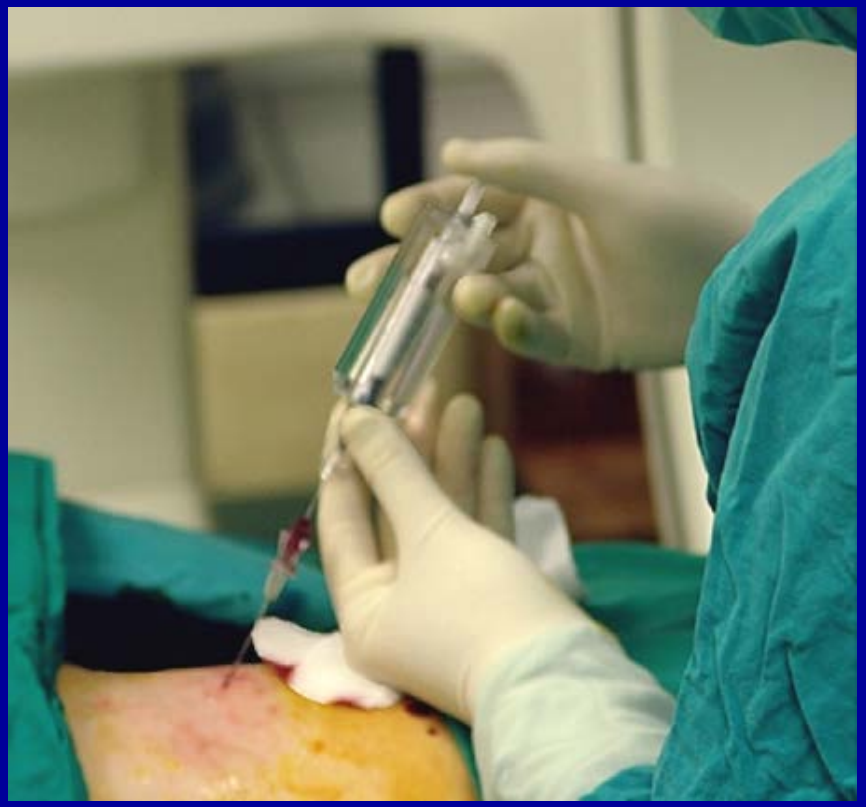
Longest dimension ***≤3 cm***, volume ≤15 ml

Max dose per lesion is ***60 MBq***

Max dose per patient is ***180 MBq***

*Pierce Chow FRCSE PhD*

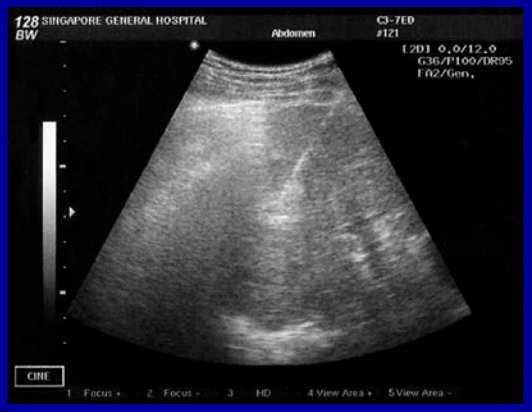
# BrachySil ® implantation procedure



Under real-time u/s, a **19G 15 cm** introducer needle is placed in the liver at the pre-determined location. The stylet of the introducer needle is removed and the **22G Chiba needle** (connected to syringe containing 32P BioSilicon) is inserted co-axially into the introducer needle.

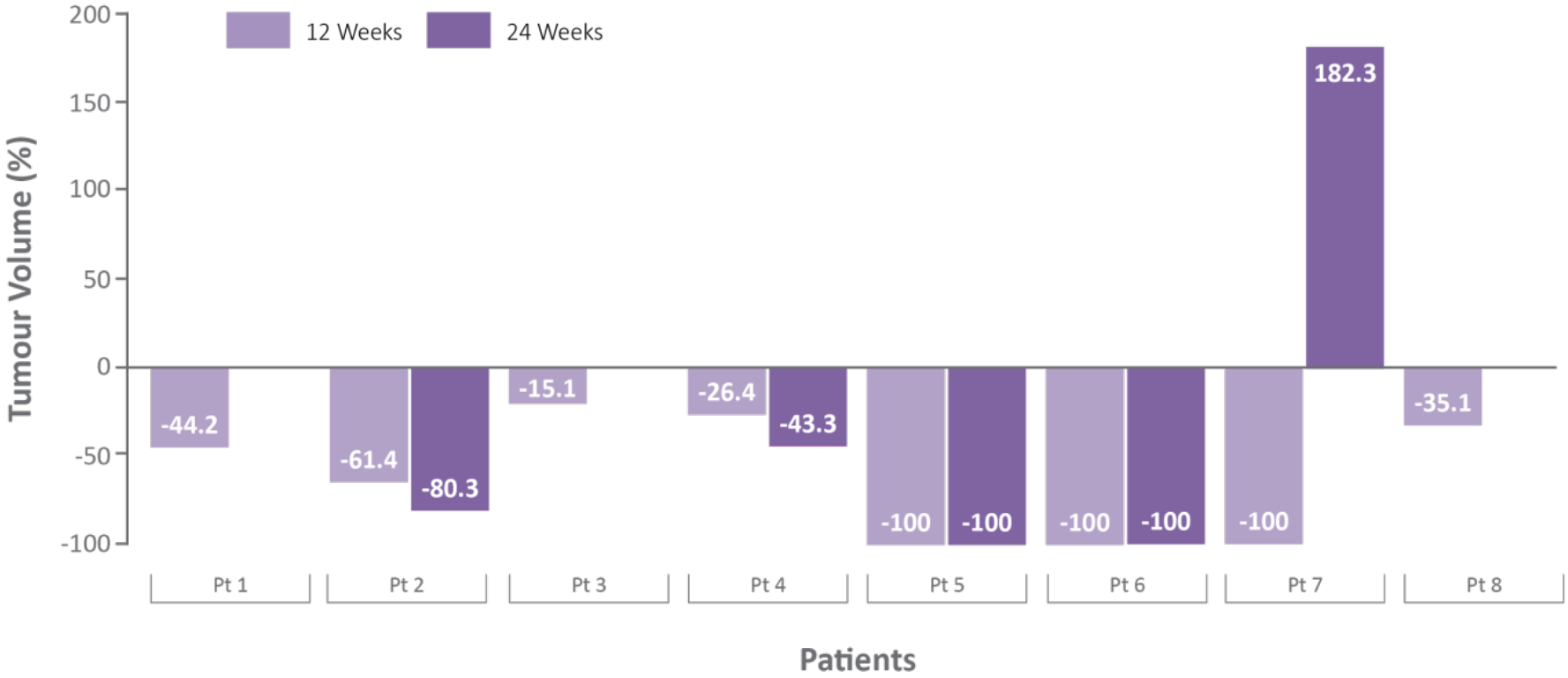
*Pierce Chow FRCSE PhD*

# BrachySil ® Ultrasound guidance



# Results: Study BIOSP-201 [1]

## Tumour Volume Response (Wk 12 and Wk 24)




Adapted from Goh MD 2007. Results from tumour volume regression at week 12 and week 24 by CT scan post implantation. Patient 1,3 and 8 withdrew before the scan at week 24 not due to an adverse events

**1.** Goh AS, 2007, Int J Radiat Oncol Biol Phys; 67(3):786-92. Epub 2006 Dec 4

# Results: Study BIOSP-201 [1]

## Tumour RECIST

| Target tumour response on longest diameter (RECIST) | | | |
|---|---|---|---|
| Patient No. | **RECIST Wk 12** | Patient No. | **RECIST Wk 24** |
| 1 | SD | 1 | N/A |
| 2 | PR | 2 | PR |
| 3 | SD | 3 | N/A |
| 4 | SD | 4 | PR |
| 5 | PR | 5 | CR |
| 6 | CR | 6 | CR |
| 7 | CR | 7 | PD |
| 8 | SD | 8 | N/A |

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; N/A – not available

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

# First-in-Man Study

Safety of 32P BioSilicon in Patients With Hepatocellular Carcinoma - Full Text View ... Page 1 of 4

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary Search

Full Text View | Tabular View | No Study Results Posted | Related Studies

**Safety of 32P BioSilicon in Patients With Hepatocellular Carcinoma**

This study is ongoing, but not recruiting participants.

First Received: October 31, 2005 Last Updated: March 13, 2007 History of Changes

| | |
|---|---|
| Sponsor: | pSiVida Limited |
| Collaborator: | pSiOncology Private Limited |
| Information provided by: | pSiVida Limited |
| ClinicalTrials.gov Identifier: | NCT00247260 |

**Purpose**

Brachytherapy is a recent technique used in the treatment of tumours and involves the use of radioactive sources brought into close contact with the target tissues. One of the principal benefits of brachytherapy is that high radiation doses can be localised within the tumour with the consequence of minimal side effects. 32P is a radionuclide ideal for brachytherapy as it has high energy beta emitting properties, typically a maximum tissue range of about 8 mm and a half life of 14.3 days. 32P BioSiliconTM is an active implantable medical device encapsulating 32P within the internal microcrystalline structure of highly pure inert silicon and acts as a sealed source for the provision of 32 phosphorous.

Tumours targeted with 32P BioSiliconTM are hypothesized to show a reduction in volume with a low incidence of side effects associated with the treatment. Prolongation of survival and improved quality of life would be favourable outcomes of the investigational product.

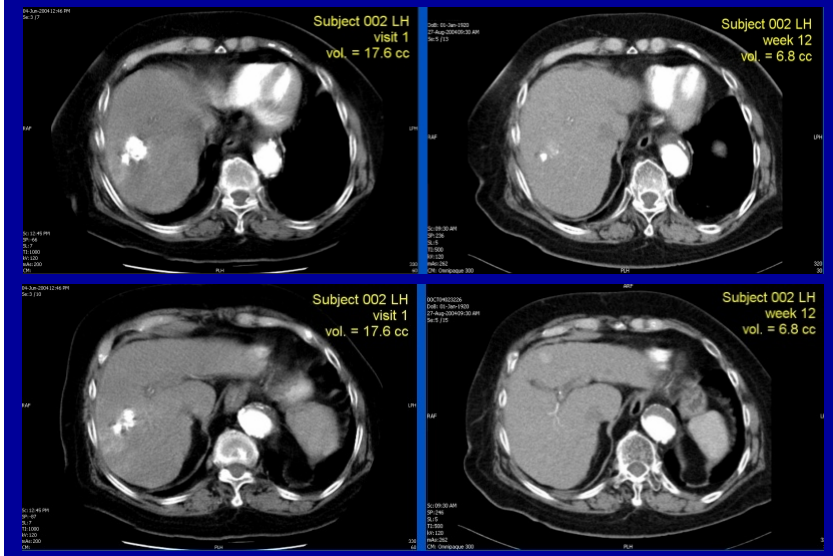
| Condition | Intervention | Phase |
|---|---|---|
| Liver Cancer | Device: 32P BioSilicon | Phase II |

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Control: Uncontrolled
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label

All target lesions shrank by **16-100%**. Complete response was seen in 3 of 8 patients

By the end of study:

**2 CR, 2 PR, 3 SD, 1 PD**




**4 Jun 2004** **27 Aug 2004**

*SGH – Surgery* Goh AS et al **Int J Radiat Oncol Biol Phys 2007**;67:786-9

# Multi-disciplinary Team

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*SGH – Surgery*

# Pancreatic cancer studies:

## Efficacy Results

# Study DB2-201 and DB2-202 [1]

| STUDY | Primary Objective | Secondary Objective | Sites | Radiation Dose | Chemotherapy |
|---|---|---|---|---|---|
| DB2-201 | To determine the safety of OncoSil™ | • Tumour response<br>• Acceptability of procedure<br>• Systemic radioactivity<br>• Survival | UK/SG | 100 Gy<br><br>6.6 MBq/ml | • Gemcitabine (at approved dose) |
| DB2-202 | To determine the safety of OncoSil administered at absorbed doses of 200Gy and 400Gy | • Tumour response<br>• Acceptability of procedure<br>• Systemic radioactivity<br>• Survival | UK | 200 or 400 Gy<br><br>26.4 MBq/ml | • Gemcitabine (at approved dose) |

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

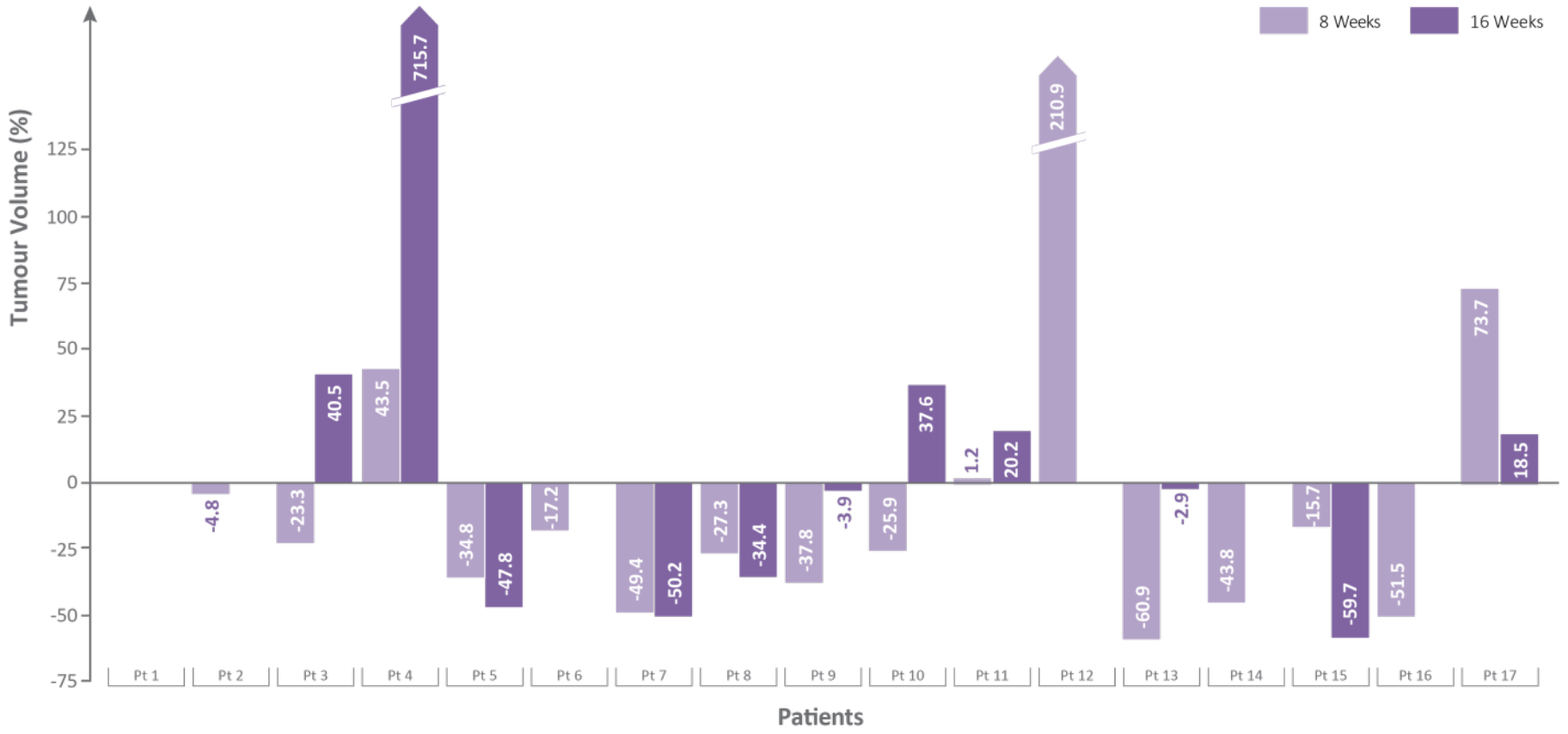
# Study DB2-201 and DB2-202 [1]

| STUDY | Target Tumour Size | Intra-tumoural Implantation method | Target Tumour Assessments by CT |
|---|---|---|---|
| DB2-201 | 3-6cm longest diameter | **Endoscopic Ultrasound** | 8, 16 & 24 wks |
| DB2-202 | 2-6cm longest diameter | **Endoscopic Ultrasound** | 8, 16 & 24 wks |

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

# Results: Study DB2- 201 [1]

## Tumour Volume Response (Wk 8 and Wk 16)

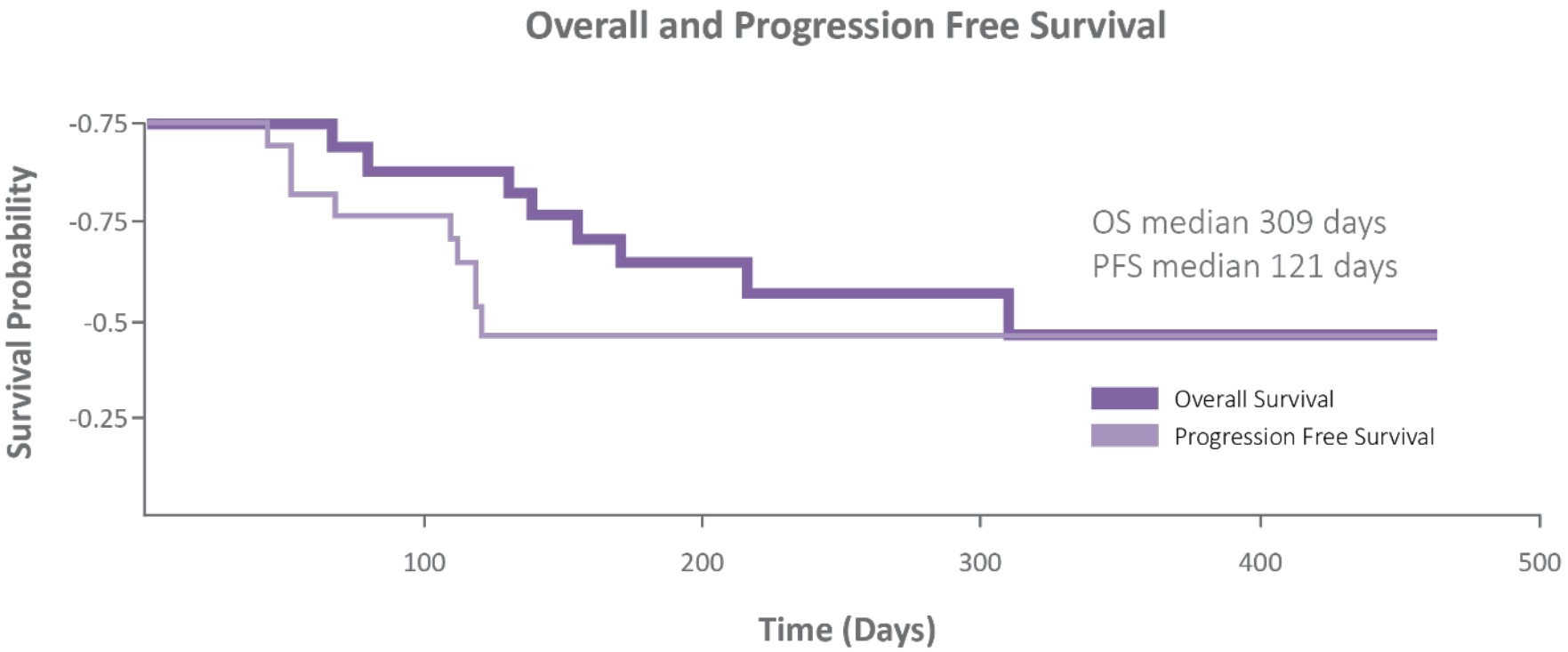



Results of tumour volume response at week 8 and 16. response was determined by CT scan.

**1.** Clinical Dataset Summary Report, OncoSil™ ONCSP-32, Version 2, 2015

# Results: Study DB2-201 [1]

## Overall and Progression Free Survival




Adapted from Ross PJ et al. Patient survival in terms of progression free survival and overall survival

**1.** Ross PJ et al, 2008,"Novel delivery via endoscopic ultrasound of a $^{32}P$ brachytherapy device in addition to gemcitabine (G) in advanced pancreatic cancer", ASCO, Chicago,Illinois.

# Results: Study DB2-201 [1]

## Tumour RECIST

| Tumour Response based on longest diameter (RECIST) Wk 8 | |
|---|---|
| Response | No. of Patients |
| CR | 0 |
| PR | 2 |
| SD | 12 |
| PD | 2 |
| N/A | 1 |

| Tumour Response based on longest diameter (RECIST) Wk 16 | |
|---|---|
| Response | No. of Patients |
| CR | 0 |
| PR | 1 |
| SD | 9 |
| PD | 2 |
| N/A | 5 |

CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; N/A – not available

**1.** Ross PJ, 2008,"Novel delivery via endoscopic ultrasound of a $^{32}P$ brachytherapy device in addition to gemcitabine (G) in advanced pancreatic cancer", ASCO, Chicago, Illinois

OncoSil MEDICAL Ltd

# OncoSil™: Advancing Pancreatic and Liver Cancer Treatment

# The Development of OncoSil™ [1]

- **2004** - OncoSil was originally developed as Brachysil, a Biosilicon product that delivers a therapeutic dose of $^{32}P$ directly into a tumour. **pSivida** had an exclusive worldwide royalty-bearing license agreement with **Enigma Therapeutics** for the development of BrachySil
- **February 2013** - **Enigma Therapeutics** was acquired by **NeuroDiscovery Ltd**
- **June 2013** - **NeuroDiscovery Ltd** changed its name to **OncoSil Medical Limited** and focussed on developing OncoSil

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

# Therapeutic Device:OncoSil™?[1]

- It is an **active implantable (radiological) device** intended for use in brachytherapy
- OncoSil comprises of 30 micron **biocompatible radioactive microparticles** and a unique diluent
- The microparticles have been specially designed to deliver localised beta radiation within the target tumour and remain permanently after implantation

**1.** Clinical Evaluation Report, OncoSil™ ONCSP-32, Document No: RA-CER01, 20 August 2015 Version B

# OncoSil®:
# Future?

# *Thank You*