DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

# Effect of YQ23 as Radiation Sensitizer in a Hepatoma Model


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Singapore General Hospital
SingHealth

**4th International Conference on Phase 1 and Early Phase Clinical Trials**

**2nd March 2018, Hyatt Regency Hong Kong, Tsim Sha Tsui**

National Cancer Centre Singapore
SingHealth

# Disclosures

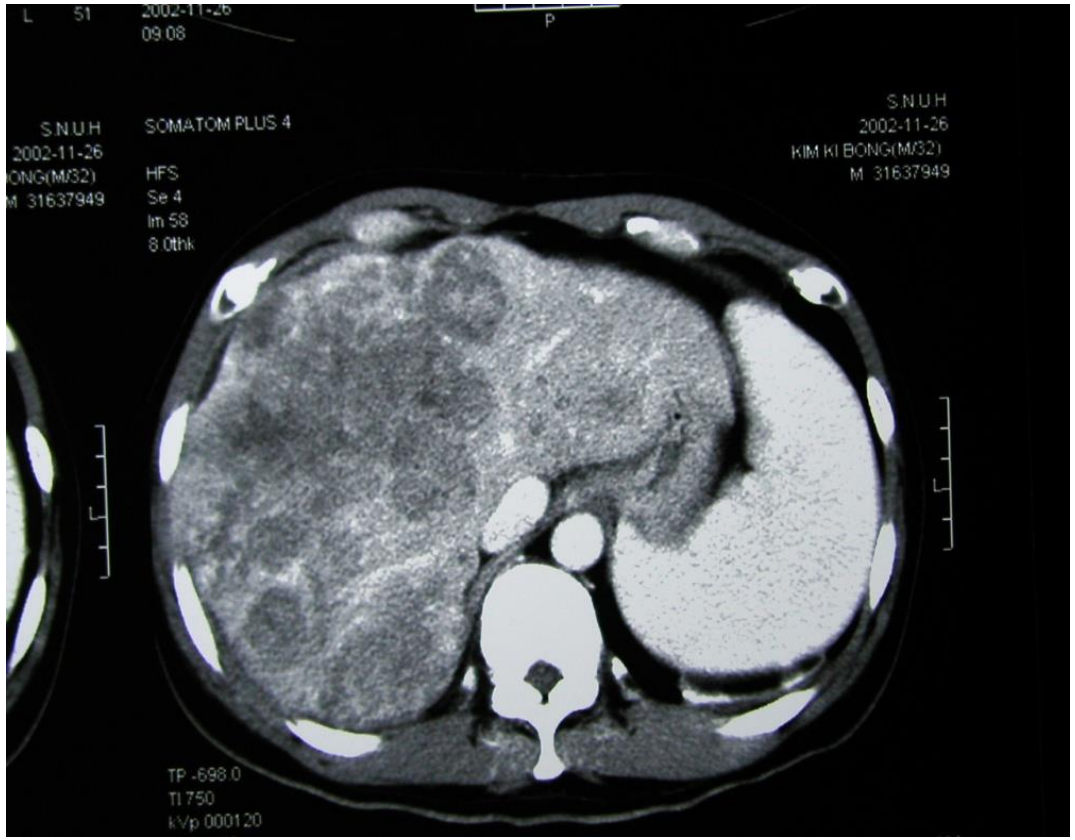
- Research grants last 5 years
  - *Bayer AG*
  - *Sirtex Medical Ltd*
  - *Merck Sharp & Dohme (MSD)*
  - *New B Innovative Pte Ltd*
  - *NMRC Singapore, BMRC Singapore*
  - *IQVIA (previously Quintiles and IMS Health)*
- Advisory Board, honorariums, travel grants last 5 years
  - *Ipsen Pharma Singapore Pte Ltd*
  - *OncoSil Medical Ltd*
  - *Sirtex Medical Ltd*
  - *Bristol-Myers Squibb*
  - *F. Hoffmann-La Roche Ltd*
  - *New B Innovative Pte Ltd*

# Significant Gaps in Hepatocellular Carcinoma

- More than **1 million new cases** a year, 80% in the Asia-Pacific, but **few efficacious therapies**
  - **20%** of patients are diagnosed at an early stage and benefit from potentially curative therapies – *resection, transplantation, radiofrequency ablation* - recurrences common and limit long term survival
  - No adjuvant therapy
- **Challenges**
  - Currently few efficacious systemic therapies: *4 TKIs, 1st line (2) 2nd line (2)*
  - Hypoxia is associated with resistance to chemo- or radio-therapy and results in poor disease prognosis.
- Targeting tumor hypoxia could be a strategy for cancer therapy and drug-resistance

# Hypoxia and Hepatocellular Carcinoma

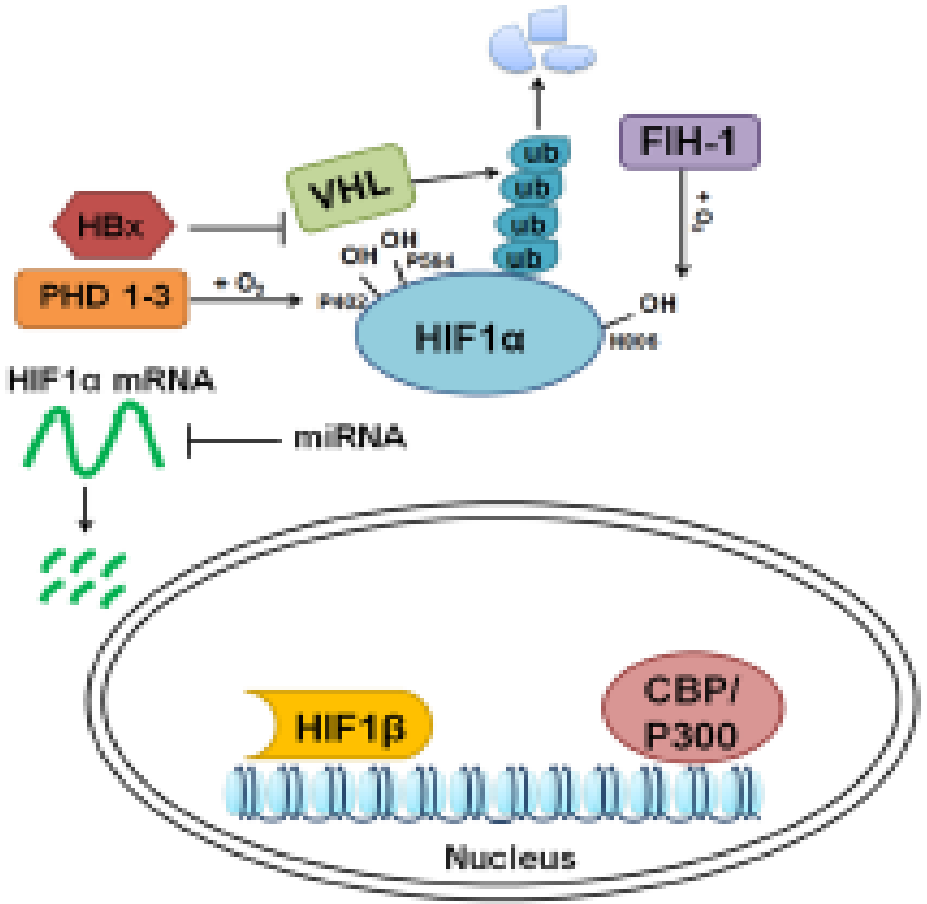
- HCC is one of the most hypoxic tumors with median oxygen level as low as 0.8%.
  - McKeown  Br J Radiol. 2014
- Inadequate intra-tumoral oxygen level is known to trigger a vast array of molecular and cellular responses mediated through HIFs which influence:
  - tumor aggressiveness
  - therapeutic response



# Hypoxia inducible factors (HIFs) in Cancer

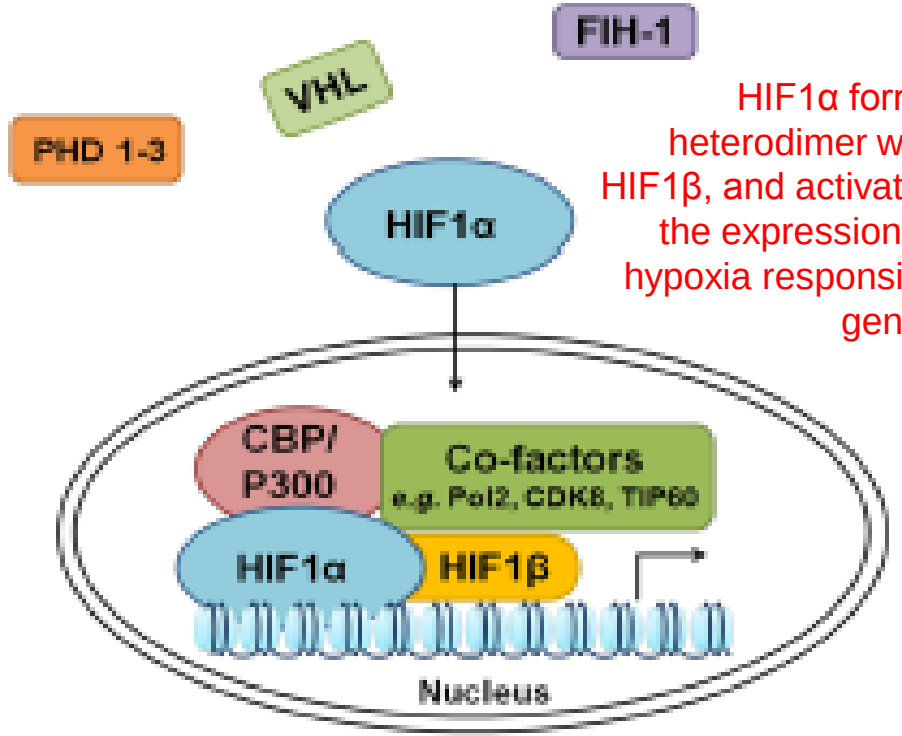
## Normoxia

HIF1α protein is hydroxylated and degraded by pVHL and FIH-1




## Hypoxia

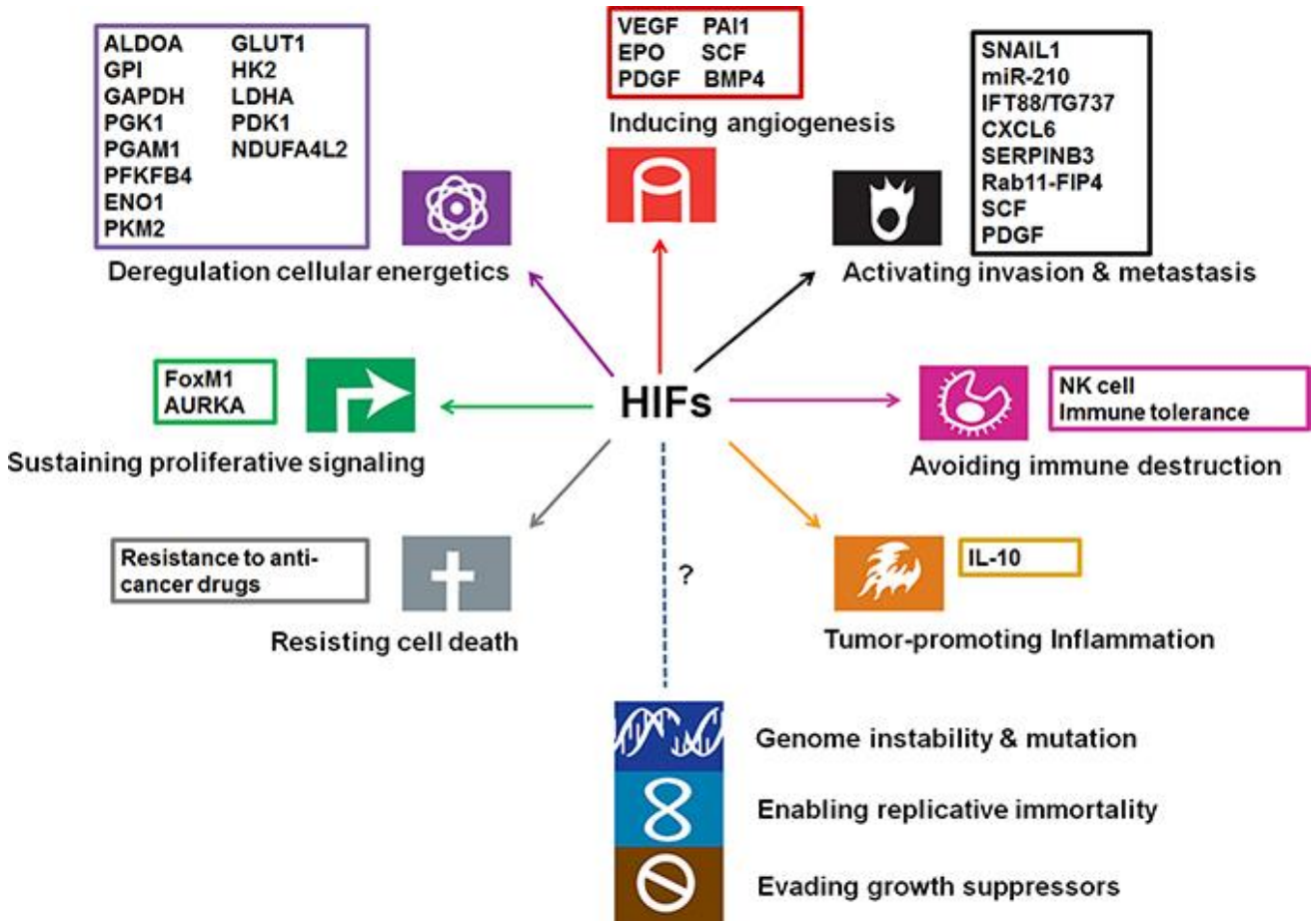
Hypoxia blocks degradation of HIF1α, leads to stabilization and nuclear translocation.




HIF1α forms heterodimer with HIF1β, and activates the expression of hypoxia responsive genes

# Hypoxia in Hepatocellular Carcinoma

- Hypoxia inducible factors (HIFs) is overexpressed in human HCC samples and associated with poor disease prognosis.
- Currently, indirect genetic evidences have reported the identification and function of HIF target genes in HCC




Chu Chen and Tao Lou Oncotarget, 2017, Vol. 8, (No.28), pp: 46691-46703

# Therapeutic Targeting of Hypoxia in HCC

- Inhibitors targeting hypoxia in clinical trials:

| | | | | |
|---|---|---|---|---|
| RO7070179 | HIF1α mRNA Antagonist | Hepatocellular Carcinoma | Phase 1 | NCT02564614 |
| EZN-2968 | HIF1α antisense oligonucleotide inhibitor | Advanced Solid Tumors/ Lymphoma/Advanced Solid Tumors With Liver Metastases | Phase 1 completed | NCT02564614 |
| OXY111A | Anti-hypoxic molecule | Hepato-Pancreato-Biliary Neoplasm | Phase 1 and 2 | NCT02528526 |
| TH-302 | Hypoxia-Activated Prodrug | Advanced Kidney Cancer or Liver Cancer | Phase 1 and 2 suspend | NCT01497444 |
| | | Hepatocellular Carcinoma | Phase 1 | NCT01721941 |
| Tirapazamine | Hypoxia-Activated Prodrug | Hepatocellular Carcinoma Combined with Transarterial embolization | Phase 1 | NCT02174549 |

**Chu Chen and Tao Lou Oncotarget, 2017, Vol. 8, (No.28), pp: 46691-46703**

# Hemoglobin-Based Oxygen Carrier – Novel Strategy for Cancer Therapy?

- **YQ23** (crossed-linked hemoglobin) – by New B Innovation Limited, Hong Kong, was developed as a oxygen carrier for transfusion.

- Features:
  - A stabilized bovine-derived non-polymeric cross-linked tetrameric hemoglobin (65 kDa). PCT/US12/46130
  - Undetectable/ low level of dimeric hemoglobin (32 kDa)
  - Low phospholipid, DNA and protein impurities

- Specifications:
  - pH 7.4 – 8.4
  - Osmolality > 250 mOsm/kg

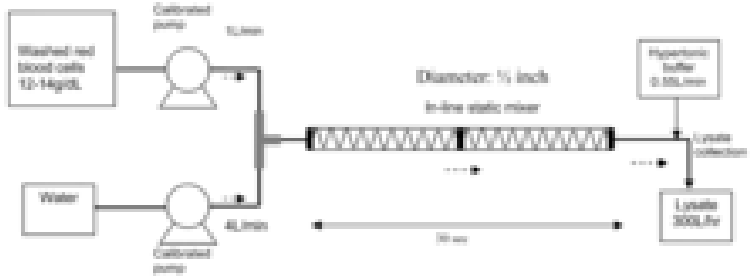
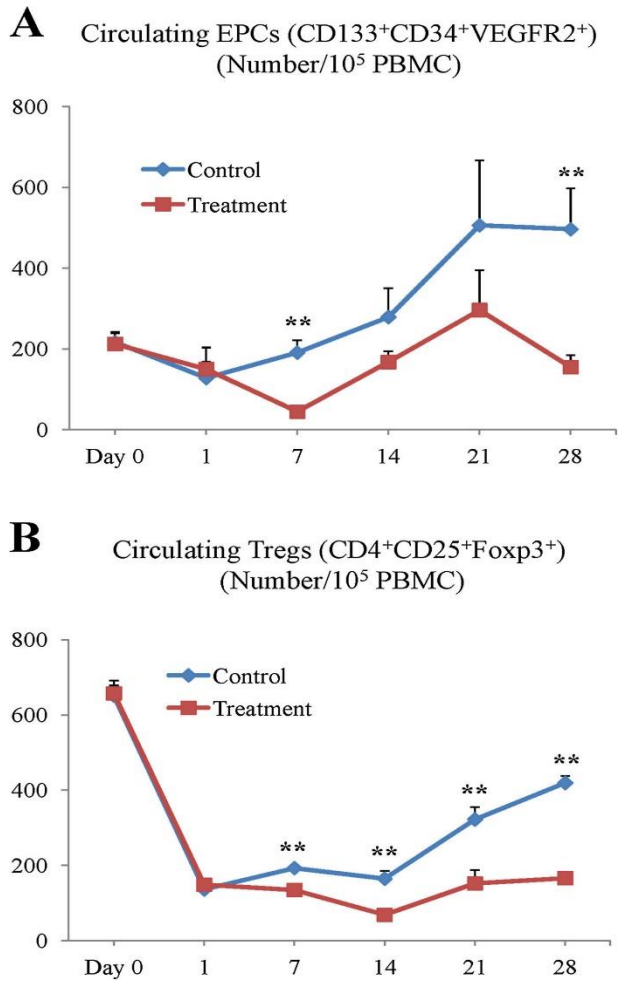



FIG. 3

# YQ23 suppresses HCC metastases and decreases circulatory EPC and Tregs

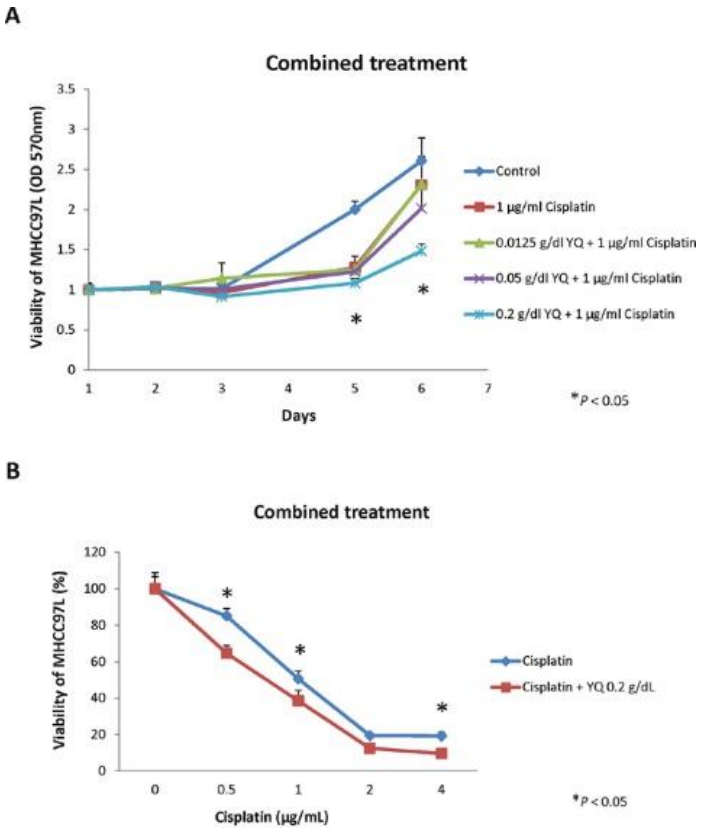
- inhibited intrahepatic and lung metastases in hepatocellular carcinoma after hepatectomy and ischemic reperfusion injury in an ***orthotopic rat model***
- Possibly due to reduced circulating endothelial progenitor cells (EPC) and Treg
- Down-regulated CXCR3, TNF-alpha and IL6 after iscahemic\reperfusion injury
- increased liver pO2 levels




***Li BMC Cancer 2014***

# YQ23 sensitizes Cisplatin-based chemotherapy in HCC cells and xenografts

- Significantly ***suppressed proliferation*** of HCC cells under Cisplatin treatment
- Significantly sensitizes Cisplatin treatment in ***orthotopic xenograft*** model
- It increased ROS generation, caused irreversible DNA damage/intrinsic apoptosis.
- ***inhibit angiogenesis*** through the Hypoxic Inducible Factor 1 alpha signaling pathway
- Confocal microscopy shows YQ23 is accumulated in HCC cells ***1 – 3 days***, and also accumulated around tumor tissues




Qi Oncotarget 2017

# Radiation Therapy in Oncology

- Radiotherapy is a major therapeutic modality in Oncology together with Surgery and Systemic Therapy (chemotherapy, immunotherapy)

- It works by damaging DNA directly or by creating charged particles (free radicals) within the cells that can in turn damage the DNA.

Direct Route

↓

DNA damage

↓

Cell death

Indirect Route

↓

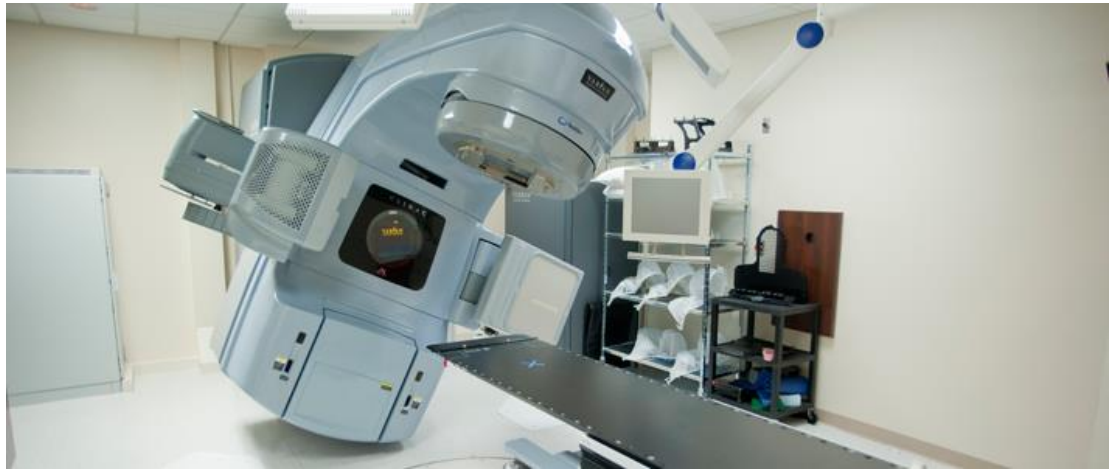
Free radicals

↓

DNA damage

↓

Cell death



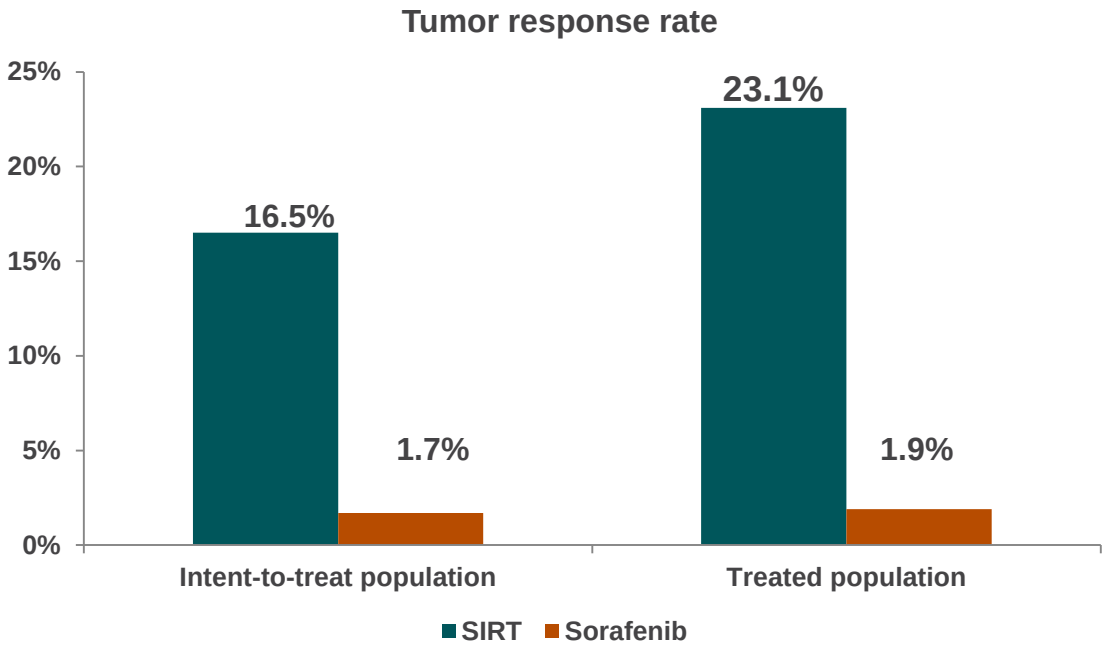
**Generation of free radicals is oxygen dependent**

# Radiation Therapy in HCC: Yttrium-90

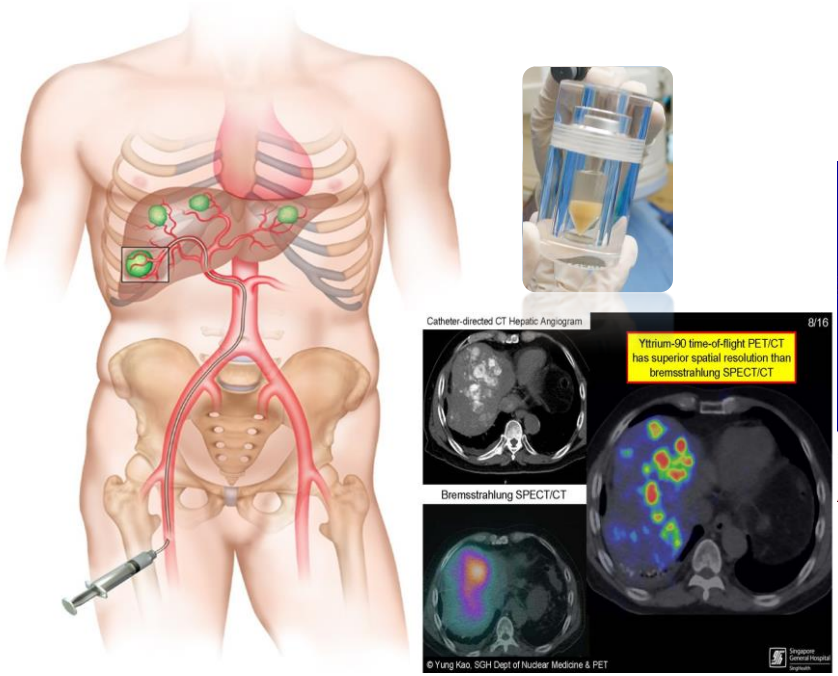
**AHCC06 SIRveNIB** Phase III
Randomized Controlled Trial

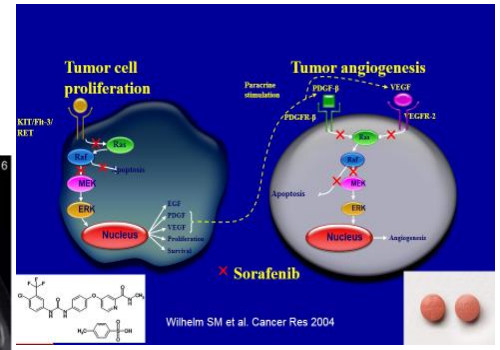
| | Intent-to-treat population | | | Treated population | | |
|---|---|---|---|---|---|---|
| | SIRT ( N = 182 ) | Sorafenib ( N = 178 ) | P-value | SIRT ( N = 130 ) | Sorafenib ( N = 162 ) | P-value |
| Tumor response rate (CR + PR), n (%) | **30 ( 16.5)** | **3 ( 1.7)** | **<.001** | **30 ( 23.1)** | **3 ( 1.9)** | **<.001** |
| Disease control rate (CR + PR + SD), n (%) | 76 ( 41.8) | 76 ( 42.7) | 0.915 | 76 ( 58.5) | 76 ( 46.9) | 0.059 |

CR: Complete response; PR: Partial response; SD: Stable disease




Chow P et al ASCO 2017



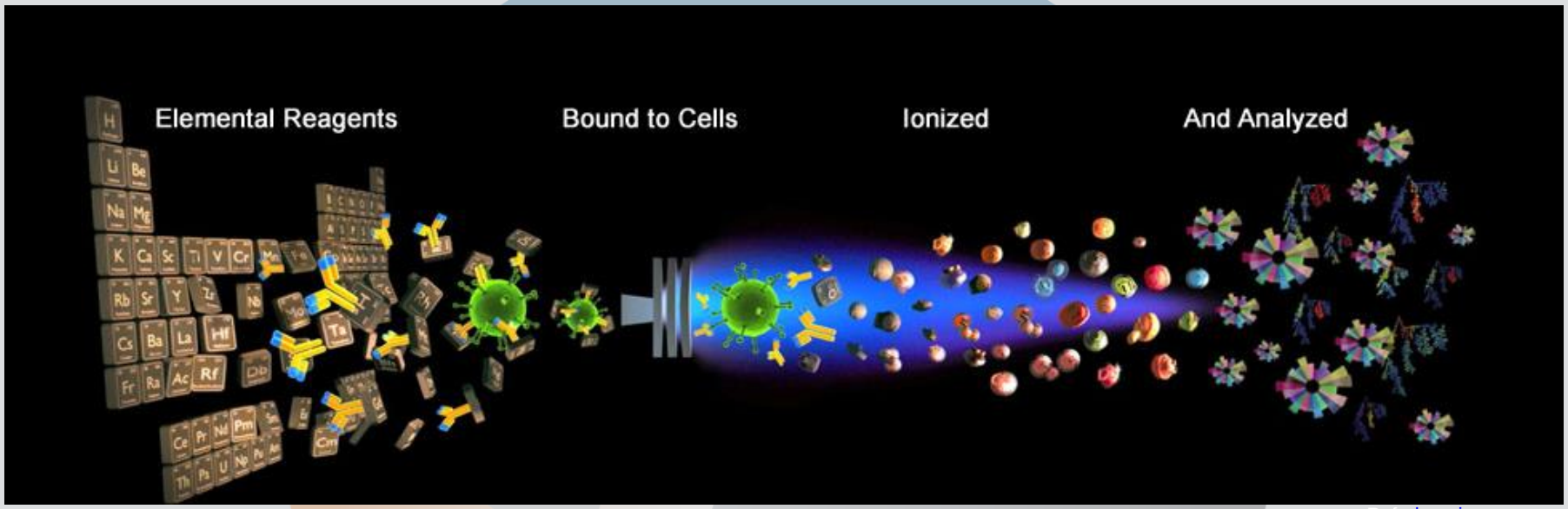




**Sorafenib**

Selective Internal Radiation Therapy with Yttrium-90 **SIRSphere®**

National Cancer Centre Singapore
SingHealth

# Assessment of Immuno-modulation by Time of Flight Mass Cytometry (CyTOF)




Ref: dvssciences.com

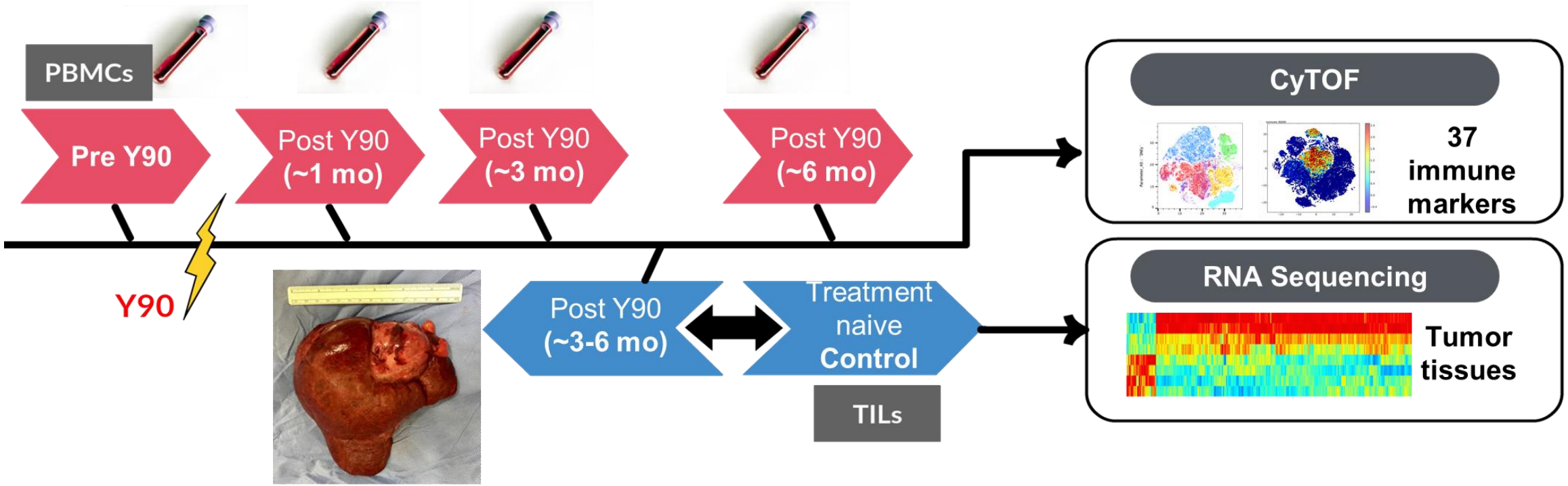
Panel Design: up to 41 parameters

Process optimisation: Lower cell requirement

Barcoding

In-house analysis pipeline

# SIRT-Y90 RE in HCC: study design and biomarker plan




- 41 patients
  - 36 patients treated with Y90
  - 7 subsequently resected after downstaging
  - 7 matched resected HCC without prior Y90

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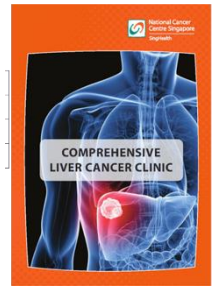
Singapore General Hospital
SingHealth

SingHealth DUKE-NUS
TRANSLATIONAL IMMUNOLOGY AND INFLAMMATION CENTRE

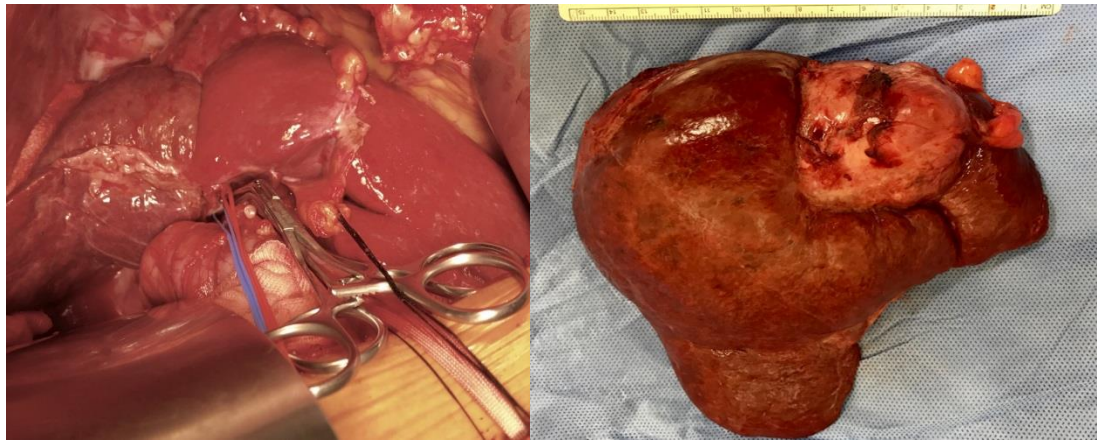



Chew et al. Gut 2018
Courtesy Dr Valerie Chew,TII-SingHealth-DukeNUS

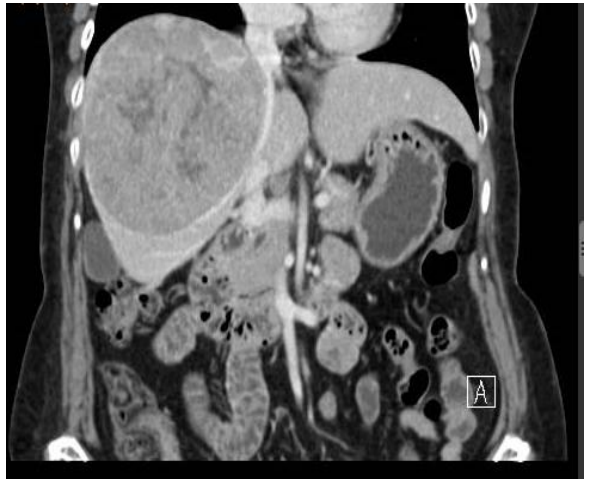
# SIRT-Y90 RE in HCC: resection after downstaging with SIRT-Y90

**Example**

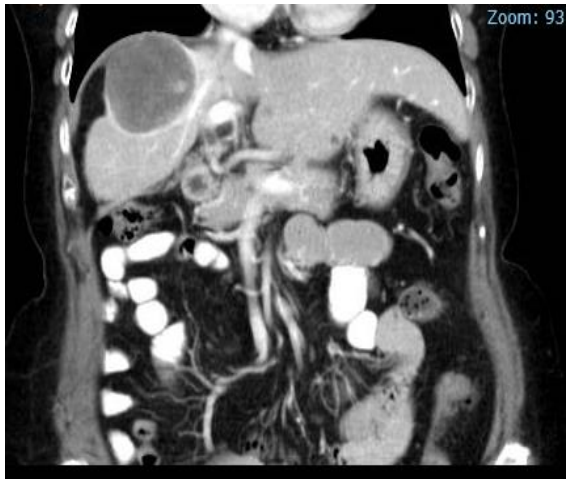
- Single delivery of Y90
- HCC regressed from **11.1cm** to **5.5cm**
- Increased future liver remnant: hypertrophied from **27%** to **43%**

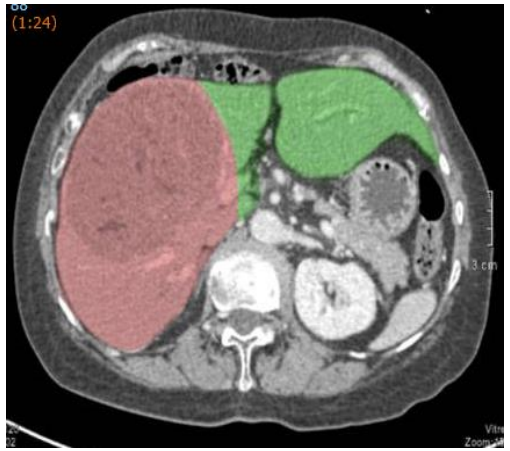


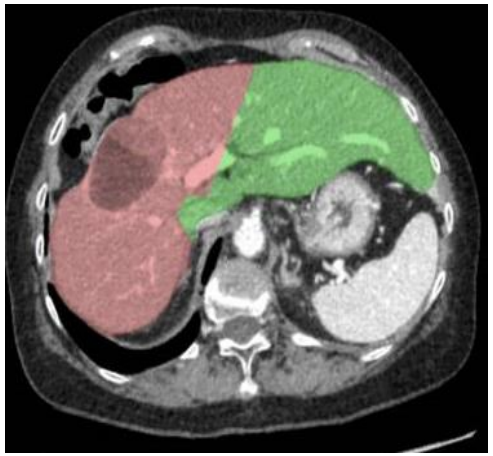
**Pre-treatment**



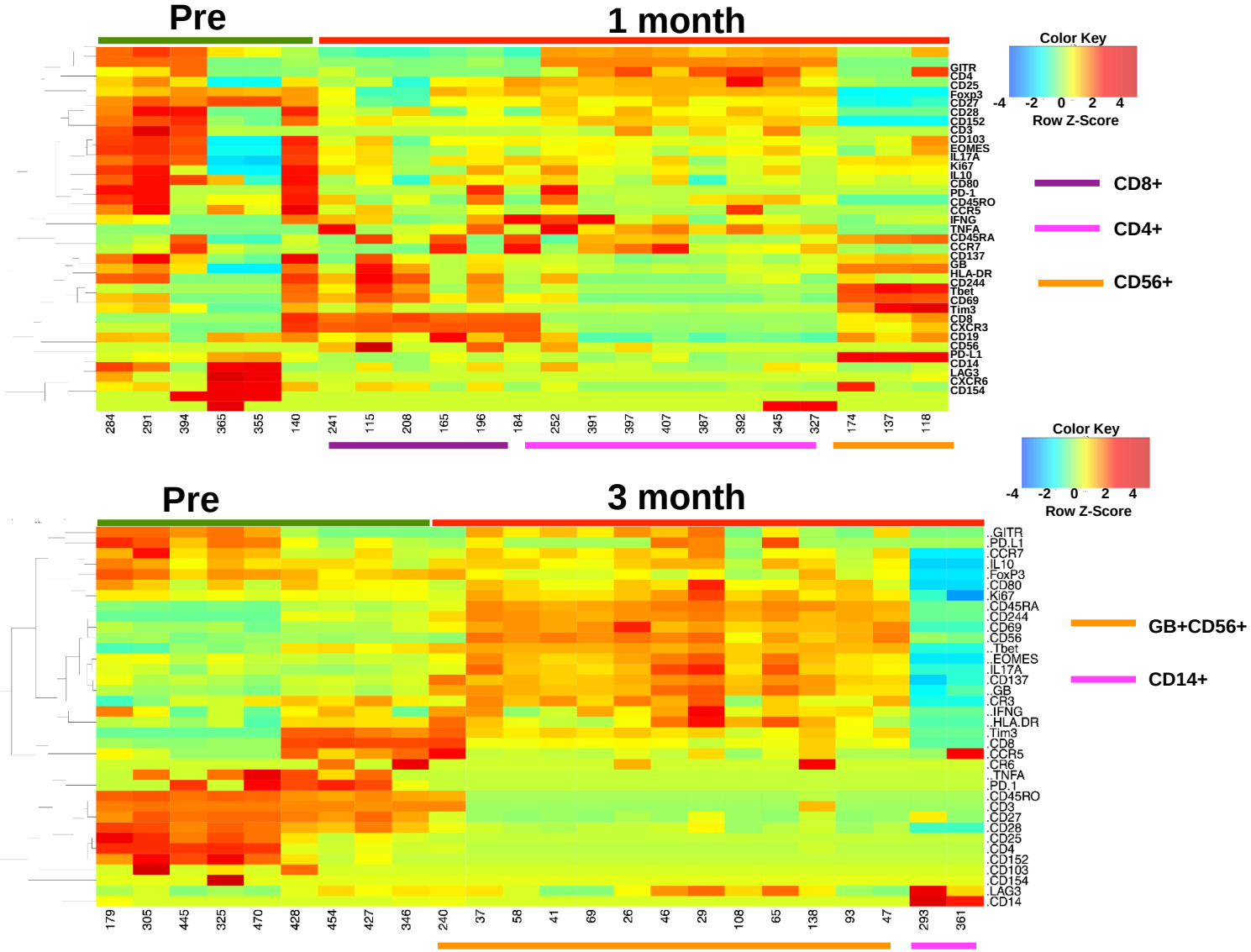
**Post-treatment**



# SIRT-Y90 RE in HCC: systemic immune upregulation of pre- vs post-Y90 peripheral PBMC




At **one month**:

- Increased TNFalpha expression in
  - CD8+Tims3
  - CD4+ T cells

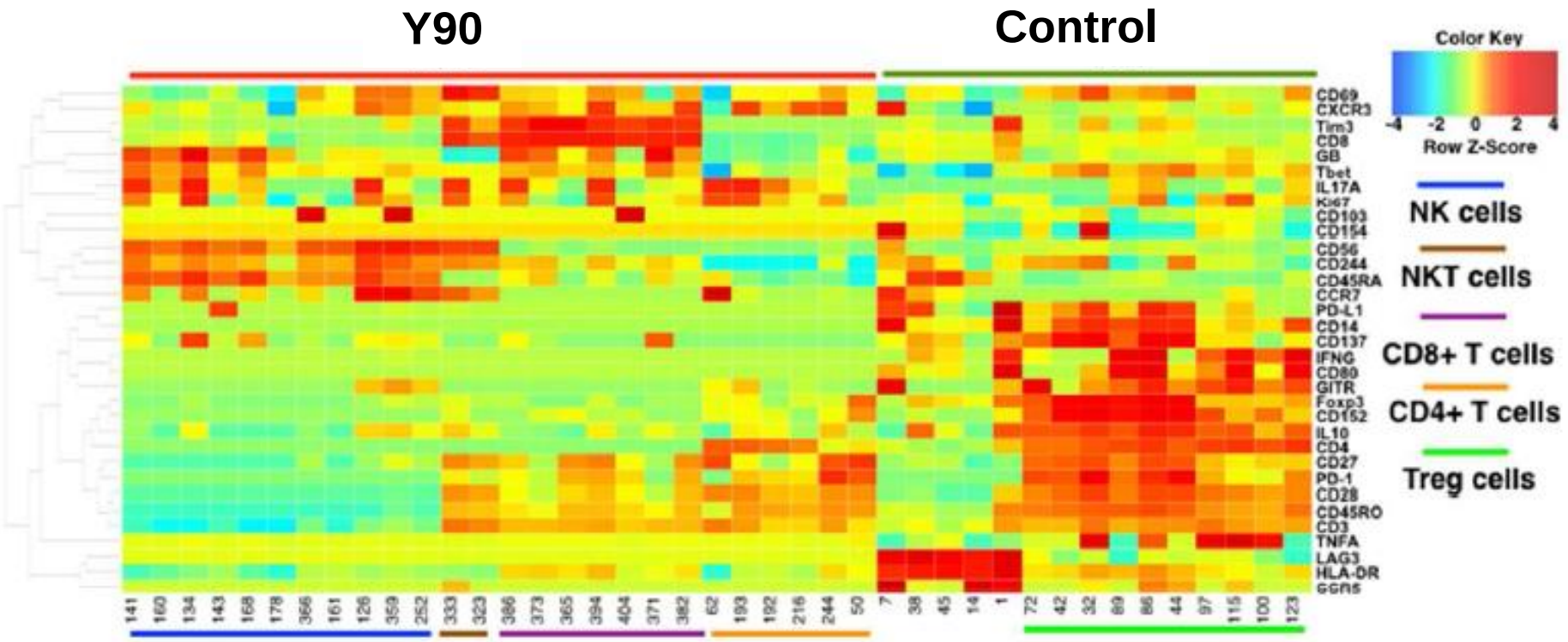
At **three months:**

- Increased proportion of CD14+HLADR+ APC

**Chew et al. Gut 2008**

# SIRT-Y90 RE in HCC: immune upregulation in resected HCC comparing matched post-Y90 vs treatment naïve control tumors

**Immune profiles of tumor infiltrating leukocytes (TILs) isolated from Y90-RE-treated and treatment-naïve tumors: 2D heat map showing the differential expression of immune markers by nodes enriched in TILs isolated from post Y90-RE (red bar) or treatment naïve (control; green bar) HCC tumors, n=7**




- Enriched immune subsets in TILs from **post Y90-RE** were CD56+ natural killer (NK) cells, CD8+CD56+ NKT cells, CD8+Tim3+ T and CD4+CD45RO+ T cells while regulatory $T_{reg}$ cells were enriched in TILs from control HCC

**Chew et al. Gut 2008**

# Rhenium- 188 (Re-188)

- Important therapeutic radioisotope in cancer, metastatic bone pain palliation, peptide radionuclide therapy, radioimmunotherapy, radiosynovectomy and for intravascular radionuclide therapy.

- Emission of high energy of beta- particle (maximal 2.12 MeV) and gamma photon (155 KeV, 15%).
- Half-life 16.9 hrs
  - Short half-life of Re-188 makes it safer for patients, staff and environment.
- β- emission provides optimal therapeutic dose for affecting tumors.
- γ-component enables the monitoring in patient's body using SPECT.

# Objectives

- To investigate the effect of YQ23 as Radiation Sensitizer in HepG2 xenografts treated by Re-188.

- **Hypothesis**
  - **YQ23 a novel oxygen carrier** can decrease hypoxia in the tumor and thus sensitize radiation treatment with **Re-188** in HepG2 xenografts in nude mice giving rise to better tumor response.

  - **YQ23** monotherapy has intrinsic anti-tumor effects on HepG2 xenografts in nude mice.

# Study Outline

- **Xenograft model:**
  - Species: balb/c nude mice (ARC)
  - Age: 6 - 8 w.o.
  - Cell Line: HepG2
  - Cell inoculation: 5 x $10^6$ cells in 0.1 ml (50% matrigel in serum free media), *s.c.*

- Tumor volume was measured by caliper and estimated by equation

$$\frac{L \; x \; W^2}{2}$$ *where* $L$ *is length (the longest dimension) and* $W$ *is width*

# Treatment Plan

- Treatment of Re-188 (3mCi) suspended in normal saline, injection volume 0.1-0.2 ml. Obtained from Nuclear Medicine, SGH.

- YQ23 (400mg/kg) started when tumor volume reached ≥ 300mm$^3$
  1. Control (normal saline, *i.v.*)
  2. **YQ23** once a week (*i.v.*)
  3. **Re-188** single dose (*i.t*)
  4. **Re-188** single dose (*i.t.*) + **YQ23** single dose (*i.v.*)
  5. **Re-188** single dose (*i.t.*) + **YQ23** once a week (*i.v.*)
  6. **YQ23** twice a week (*i.v.)*
  7. **Re-188** single dose (*i.t.)*+ **YQ23** twice a week (*i.v.*)

- No of animal per group = 6

**Creation of Mouse Ectopic Hepatoma Model**

- 42 male nude mice
- Subcutaneously injected with human HCC Hep G2 into the right flank

Baseline 18F-FMISO microPET Scan on day 14 and 18F-FDG microPET scan on day 16

**Animals are divided into 7 groups and treated as follows on day 19:**

| Group | Treatment |
|---|---|
| 1 | Control with IP normal saline on day 19 |
| 2 | YQ23 IV (0.4 g/kg in 0.5mL) once a week (on days 19, 26, 33, and 40) |
| 3 | One single dose intratumoral injection of 20 mCi of Re-188 in 0.05mL on day 19 |
| 4 | One single dose intratumoral injection of 20 mCi of Re-188 in 0.05mL<br>**plus** One dose YQ23 IV (0.4 g/kg in 0.5mL) on day 19* |
| 5 | One dose of Re-188 intratumoral injection at 20 mCi in 0.05mL<br>**plus** One dose of YQ23 at 0.4 g/Kg in 0.5mL IV on day 19*<br>followed by one dose of YQ23 per week at 0.4 g/Kg in 0.5mL IP in week 2, week3, and week 4 ( days 16, 33, and 40) |
| 6 | 2 doses of YQ23 at 0.4 g/Kg in 0.5mL IV per week for 4 weeks (day 19, day 22, day 26, day 29, day 33, day 36, day 40, day 43) |
| 7 | One dose of Re-188 intratumoral injection at 20 mCi in 0.05mL<br>**Plus** One dose of YQ23 at 0.4 g/Kg in 0.5mL IV on day 19*,<br>followed by another dose of YQ23 at 0.4 g/Kg in 0.5mL IV on day 22, and then 2 doses of YQ 23 at 0.4 g/kg in 0.5mL in week 2, week 3, and week 4 (day 26, day 29, day 33, day 36, day 40, day 43) |

*For groups 4, 5 and 7, Re-188 will be administered 4hrs after YQ23 IV injection. After Re-188 injection, the animal will be placed inside the SEMC Rodent Imaging Holding room for up to 10 X half life time of the radioisotope to ensure safe limit of remaining radioactivity before returning the animal to the animal holding room (i.e. 7 days).

**Treatment response is monitored by measuring:**

- Tumour size by caliphers every other day
- SUV by 18F-FMISO microPET scan: (Days 21, 28, 35, 42)
- SUV by 18F-FDG microPET scan (Days 23, 30, 37, 44)

**All animal will be sacrificed on week 5 after baseline scans**

Tumours will be removed for histological and immune-histo studies

# SingHealth Experimental Medicine Center

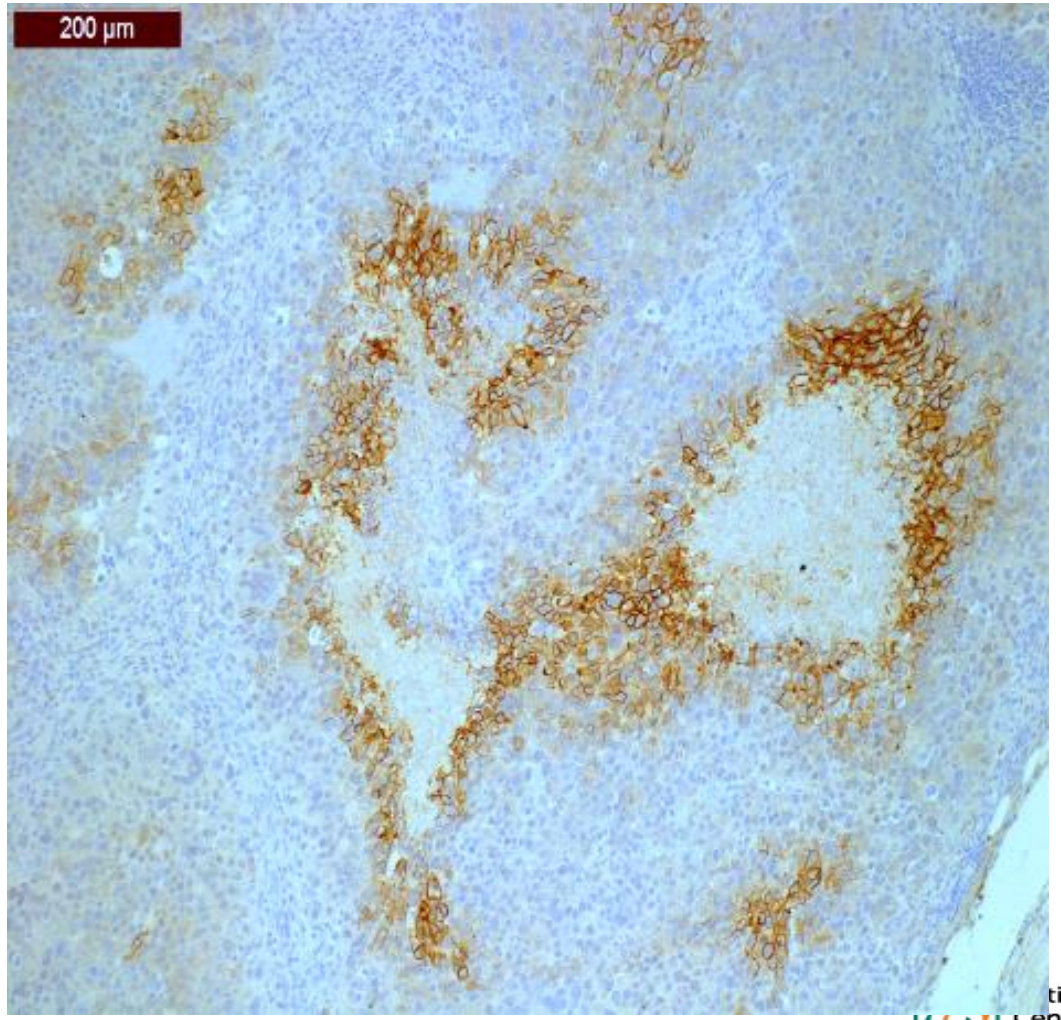
Research was carried out at a **AAALAC** accredited academic core facility at the SingHealth Academic Medical Center, Singapore

Research was approved by SingHealth **IACUC**

PI: Prof Pierce Chow
National Cancer Center Singapore
Duke-NUS Medical School

# Assessment of HIF1-a activity

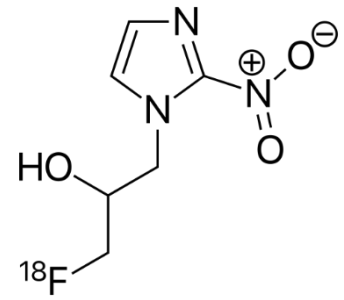
- Carbonic anhydrase 9 (CA9) is a hypoxic marker directly regulated by HIF1-a.
- Immuno-histochemistry of CA9 expression in YQ23 treated group compared to control.
- IHC carried out by **New B Innovative, Hong Kong**



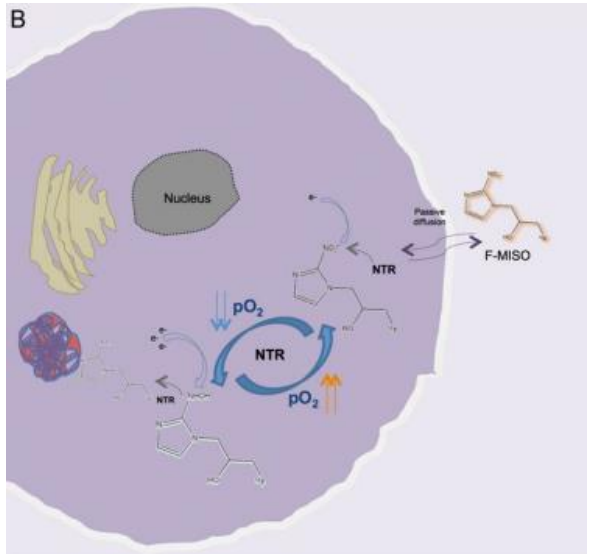
# Imaging of Hypoxia and Metabolism

The hypoxic level and blood flow in tumor was assessed by FMISO and FDG PET imaging respectively

- FMISO (18F- Fluoromisonidazole)
  - Rapid and high uptake in tumor-to-normal tissue ratios.
  - Selective uptake in tumor hypoxia.




Structure of FMISO




After passive diffusion through the membrane, FMISO is retained according to the oxygen tension (pO2) present in the intracellular environment: in the presence of reduced pO2, F-MISO undergoes progressive reduction by the nitroreductase enzyme (NTR); Both processes are reversible in the presence of sufficient O2, and the molecules of F-MISO are free to leave the cell. In contrast, the reduced F-MISO is covalently bound to the intracellular proteins.

Lopsi et al, Am J Nucl Med Mol Imaging 2014;4(4):365-384

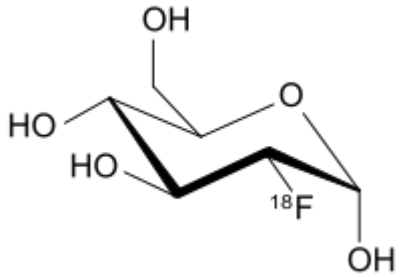
# FDG (18F- Flourodeoxyglucose)

- FDG (18F- Flourodeoxyglucose)
  - Like glucose, is actively transported into the cells by glucose transporter. Tumors are known to have increased consumption of glucose, which provides energy for cell growth and also provides precursors for nucleotide and lipid synthesis. Indicator of vascularization.

PET radiopharmaceuticals for imaging of tumor hypoxia

**Table 2.** Principal radiopharmaceuticals applied in PET imaging of tumor hypoxia

| Uptake mechanism | Tracer | Tumors imaged | Benefits | Limitations |
|---|---|---|---|---|
| Pasteur effect (anaerobic glycolysis) [25] | $^{18}$F-FDG ($^{18}$F-fluorodeoxyglucose) | NSCLC [23, 27, 32, 37]<br>Head and neck tumors [31]<br>Oral squamous cell carcinoma [40, 41]<br>Gastric cancer [39] | Good correlation with tumor aggressiveness and prognosis<br>Easily reproducible and broad availability | Overlap between uptake in normoxic (Warburg effect) [26] and hypoxia tumor tissue |
| Nitroimidazole-like uptake: reduction into RNO2 radicals and RNHOH compounds in hypoxic conditions. Then covalent binding to macromolecules [21, 59] | $^{18}$F-MISO ($^{18}$F-fluoromisonidazole) | Head and neck tumors [35, 42-45]<br>Locally advanced HNSCC [35, 46]<br>Glioblastoma multiforme (GBM) [37, 47, 48]<br>Breast cancer [49]<br>NSCLC [32, 33, 50]<br>Renal cell carcinoma [51] | Broadest evidence of value as a hypoxia tracer.<br>Good correlation with immunohistochemistry and prognosis in most cases.<br>Good availability | Lack of correlation in all tumors<br>Low tumor-to-background ratio<br>Variable reproducibility |




Structure of FDG by Anypodetos

Lopsi et al, Am J Nucl Med Mol Imaging 2014;4(4):365-384

- FMISO PET- was used to visualize tumor hypoxia.

- FDG PET - was used to visualize where tumor was metabolically active.

- **Procedure:**
  - Fasting hrs = 4
  - F-18 FDG or F-18 FMISO activity ~20MBq in <0.2ml were injected, *i.v.*
  - Incubation time 60 mins
  - Anesthesia: 1.5 – 2 % isoflurane.
  - Scan time: 20 mins static PET scan; 12 mins **MRI (material map)**

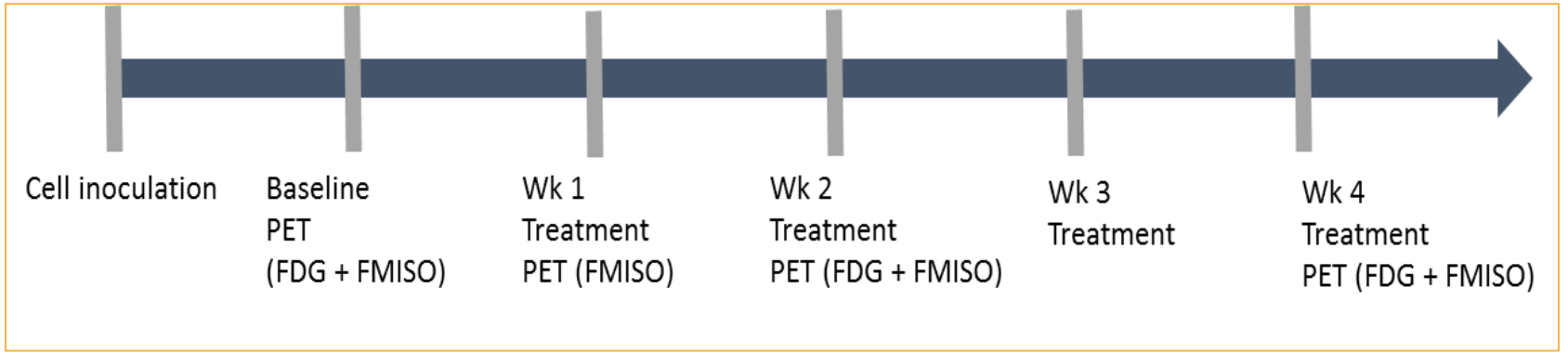
- **Image Reconstruction: Nucline software**
  - The region of interest (ROI) was traced manually around the tumor's boundary by visual inspection using Interview Fusion v3.01 software.

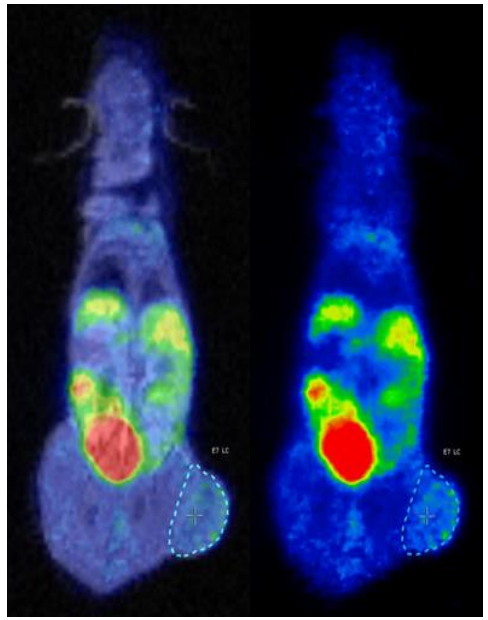
- The percentage of injected dose (% ID) was calculated as follows:

***% ID = ROI activity (MBq/ml) / Injected Dose (MBq) x 100***

# Study Workflow

- FMISO PET at baseline, wk 1, wk 2 and wk 4.
- FDG PET at baseline, wk2  and wk 4.
- Tumor tissues collected were stained for **IHC** targeting hypoxia



# Results – Tumor volume

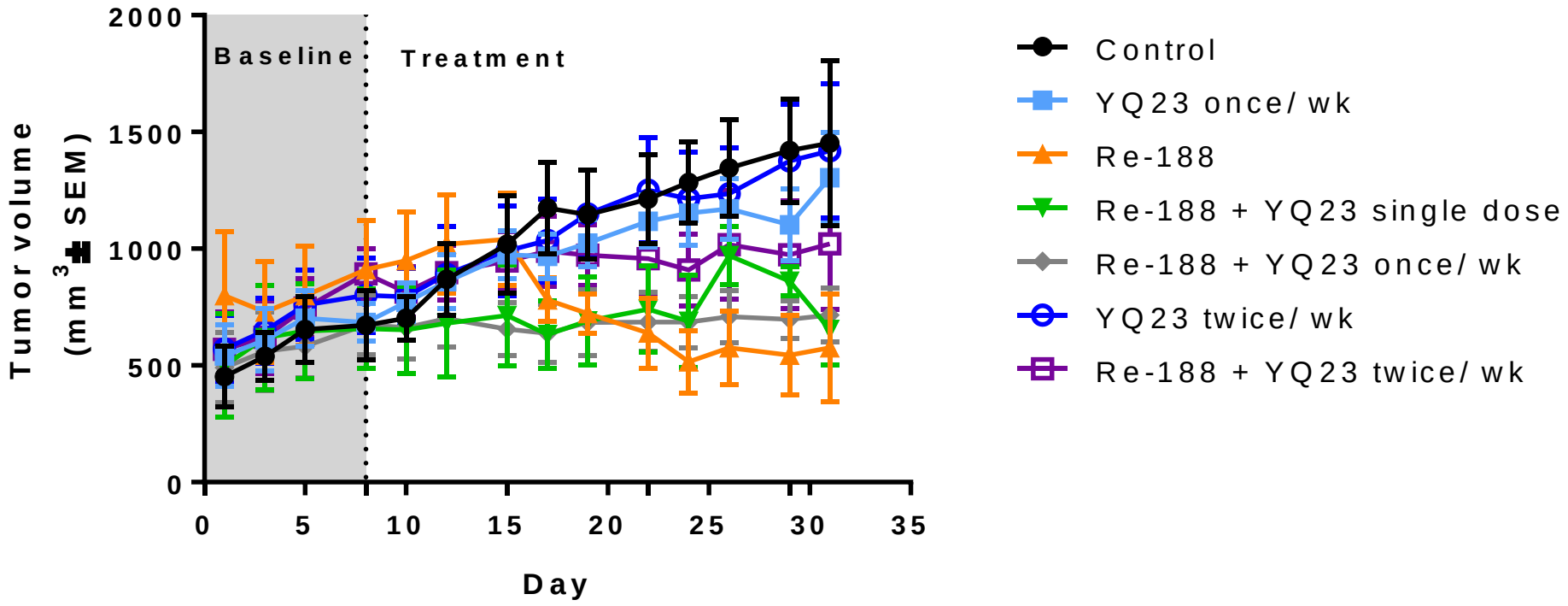



Figure 1: In vivo efficacy study in HepG2 xenograft model. Points, mean tumor volume; bars, SEM

# Mean Tumor volume

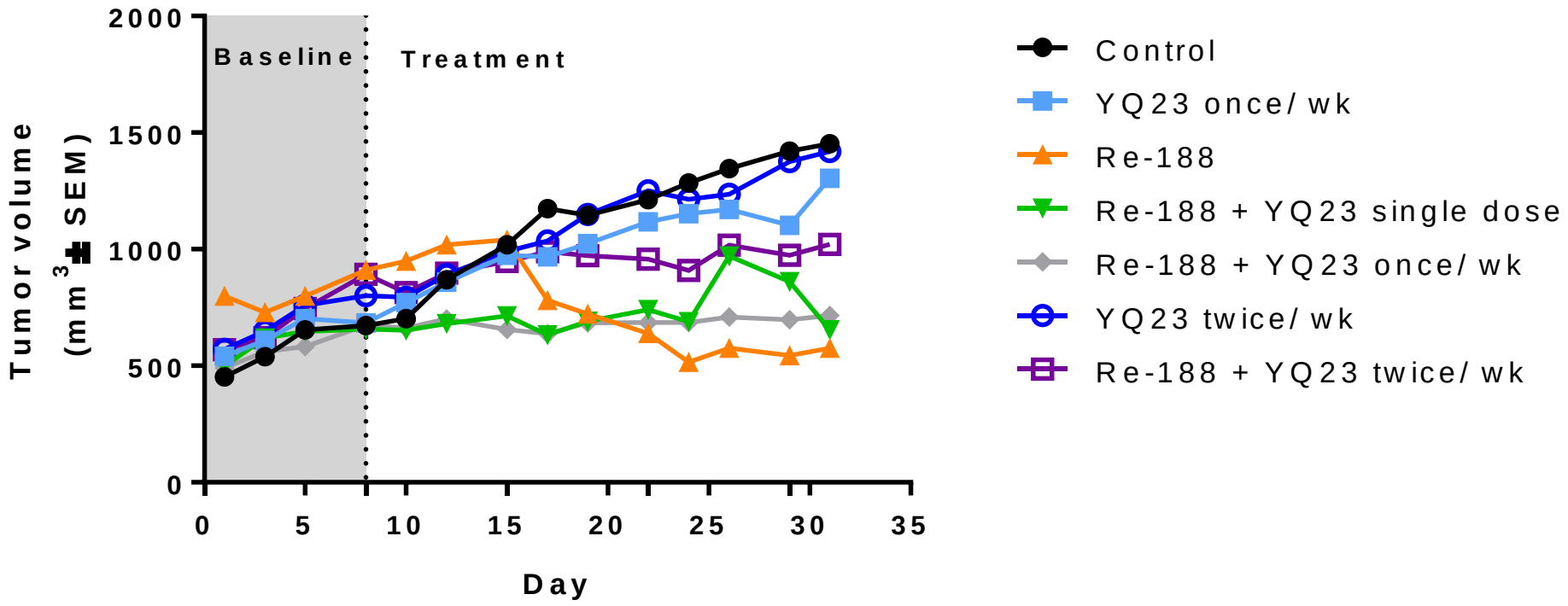
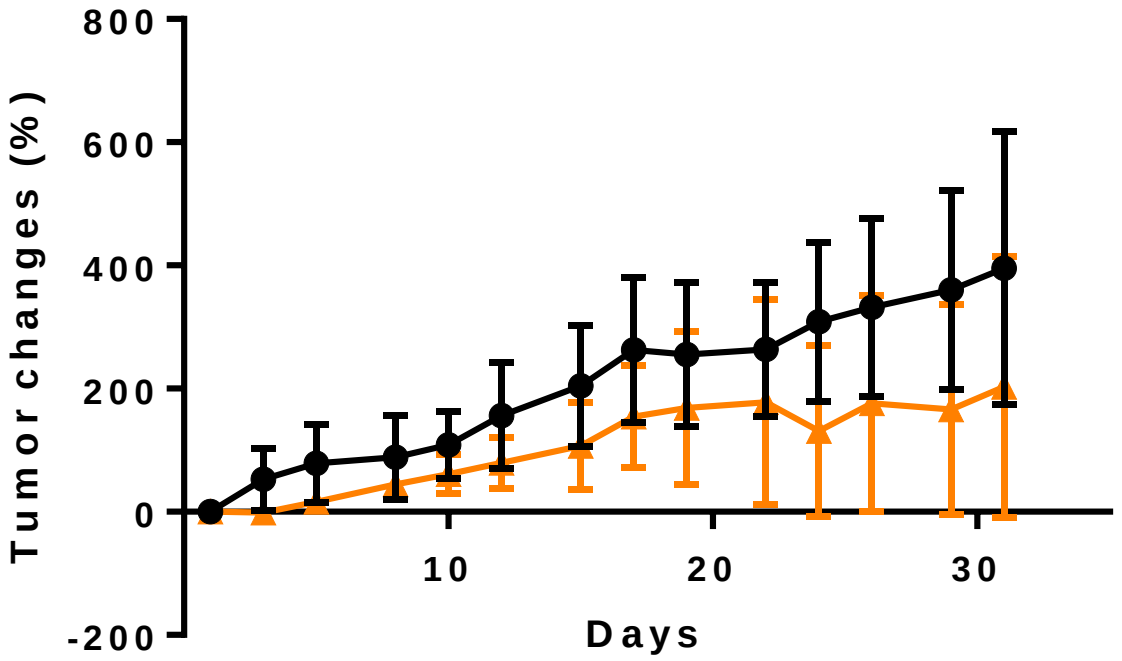



Figure 1: In vivo efficacy study in HepG2 xenograft model. Points, mean tumor volume; bars, SEM

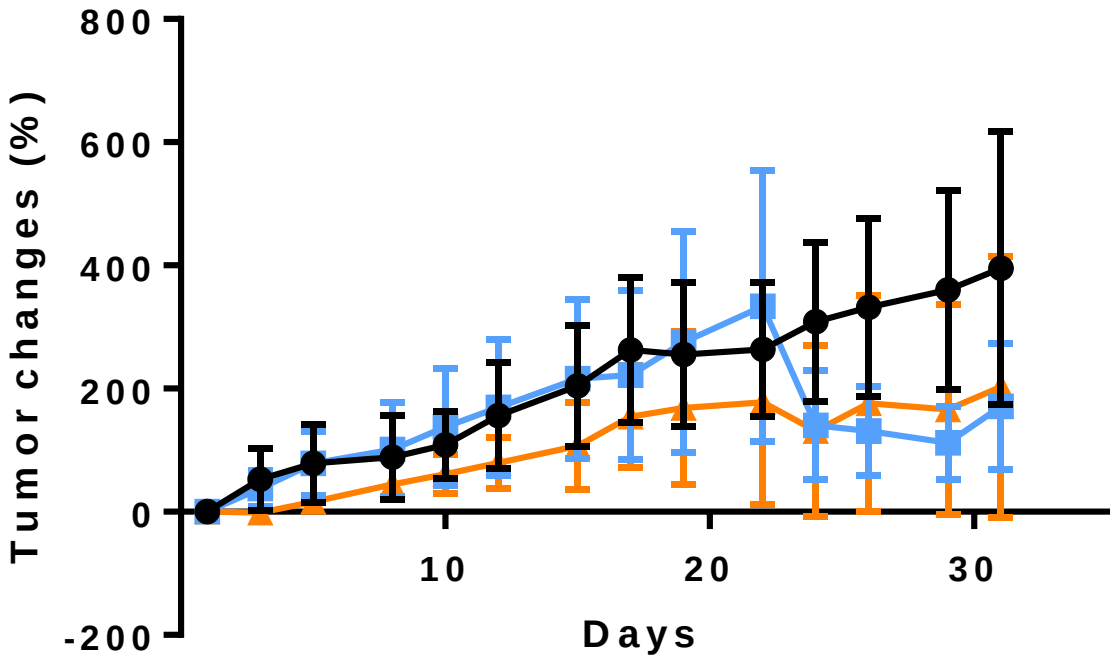
# Results – Re-188 therapy




| | P value |
|---|---|
| Control vs. Re-188 | **0.0252 *** |

Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

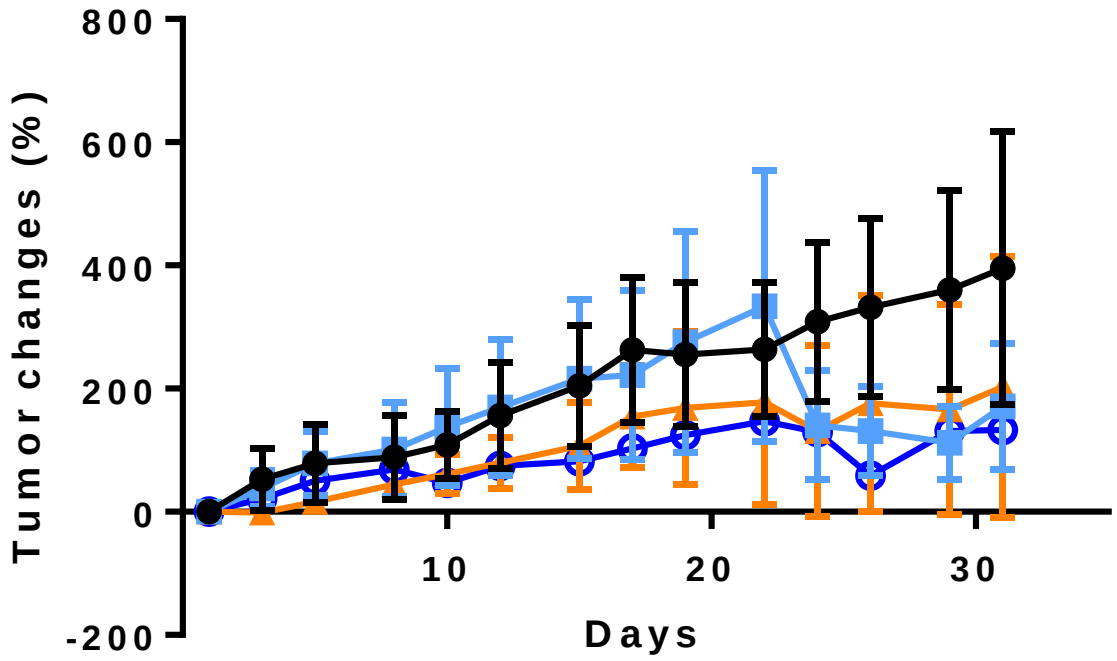
# Results – YQ23 once a week




| | P value |
|---|---|
| Control vs. Re-188 | 0.0252 * |
| Control vs. YQ23 once/ wk | > 0.9999 |

Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

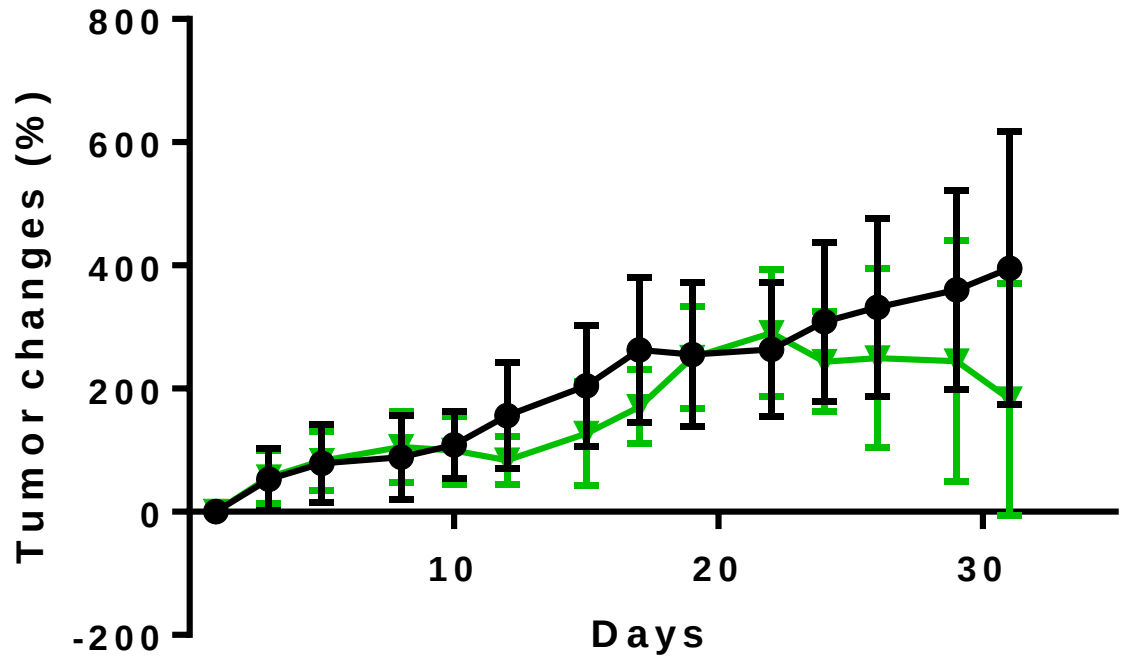
# Results – YQ23 twice/ wk




| | P value |
|---|---|
| Control vs. Re-188 | 0.0252 * |
| Control vs. YQ23 once/ wk | > 0.9999 |
| YQ23 once/ wk vs. Re-188 | > 0.9999 |
| Control vs. YQ23 twice/ wk | **0.0019**** |

Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

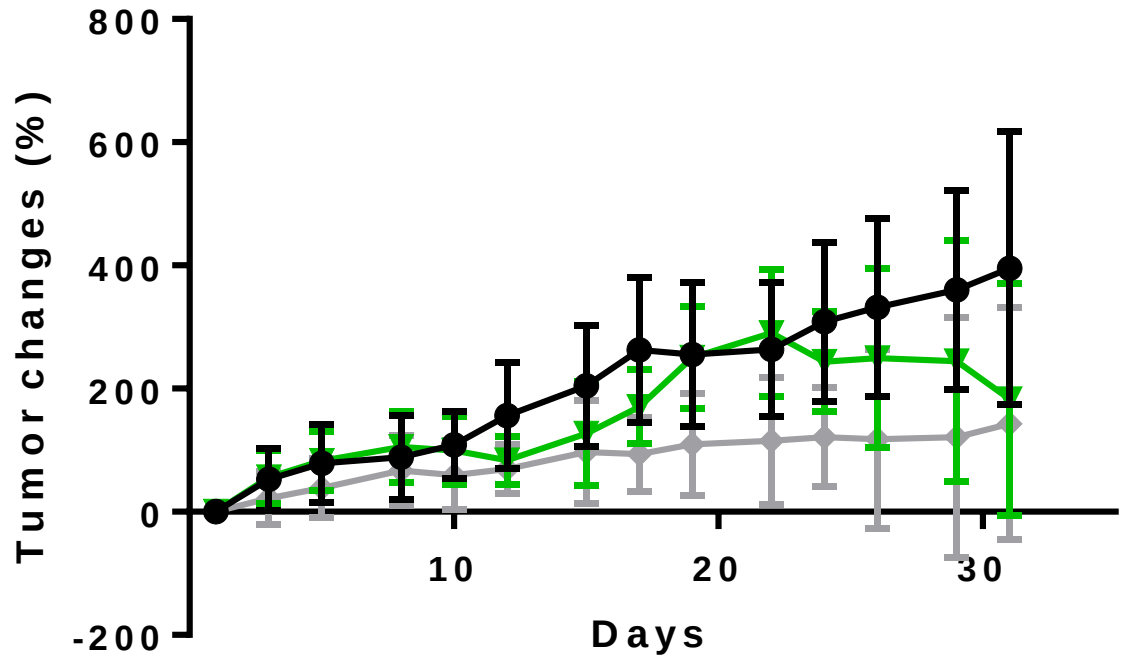
# Results – Re-188 + YQ23

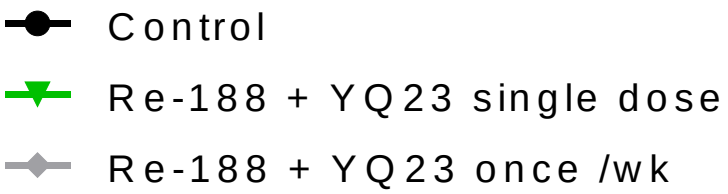



| | P value |
|---|---|
| Control vs. Re-188 + YQ23 single dose | > 0.9999 |

Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

# Results – Re-188 + YQ23 once/ wk




| | P value |
|---|---|
| Control vs. Re-188 + YQ23 single dose | > 0.9999 |
| Control vs. Re-188 + YQ23 once /wk | **0.0019**** |

Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

# Results – Re-188 + YQ23 twice/ wk

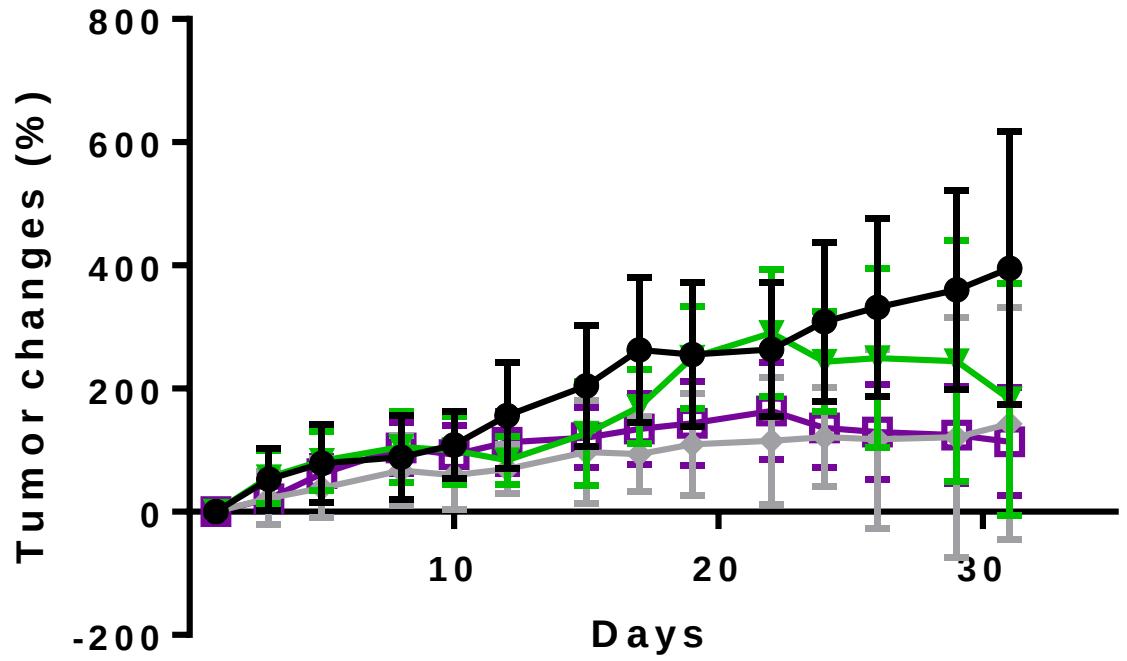



Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

Control
Re-188 + YQ23 single dose
Re-188 + YQ23 once/ wk
Re-188 + YQ23 twice/ wk

| | P value |
|---|---|
| Control vs. Re-188 + YQ23 single dose | > 0.9999 |
| Control vs. Re-188 + YQ23 once /wk | 0.0019** |
| Re-188 + YQ23 single dose vs. Re-188 + YQ23 once /wk | 0.3477 |
| Control vs. Re-188 + YQ23 twice/ wk | **0.0207*** |

# Results

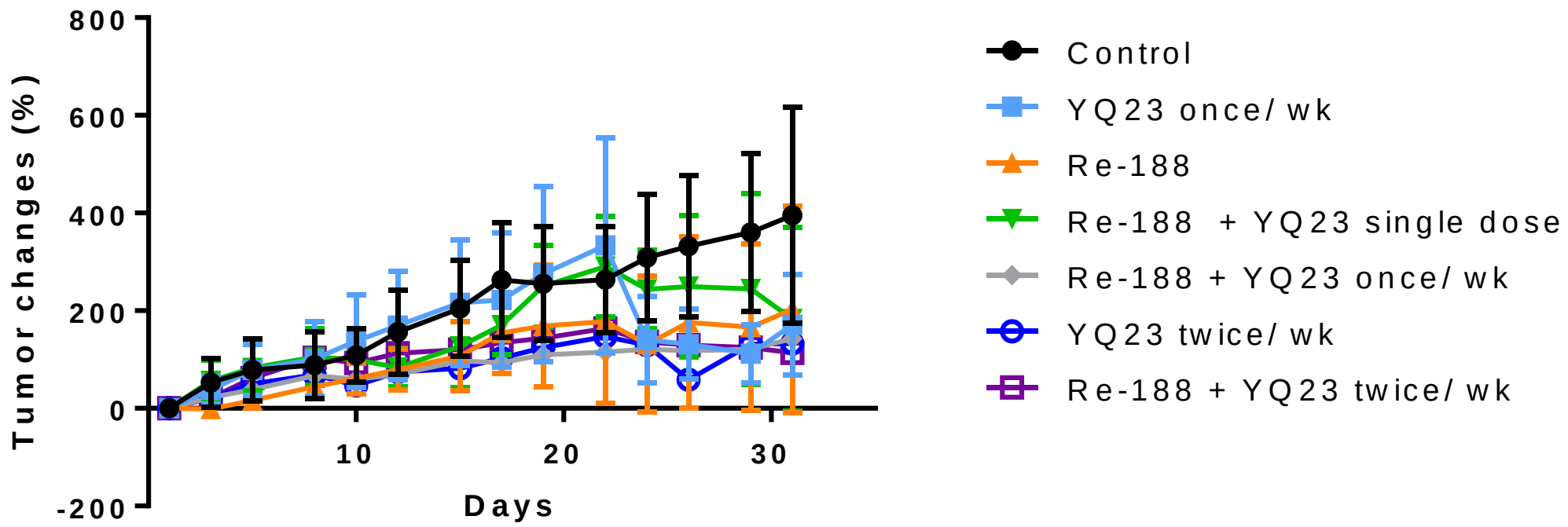
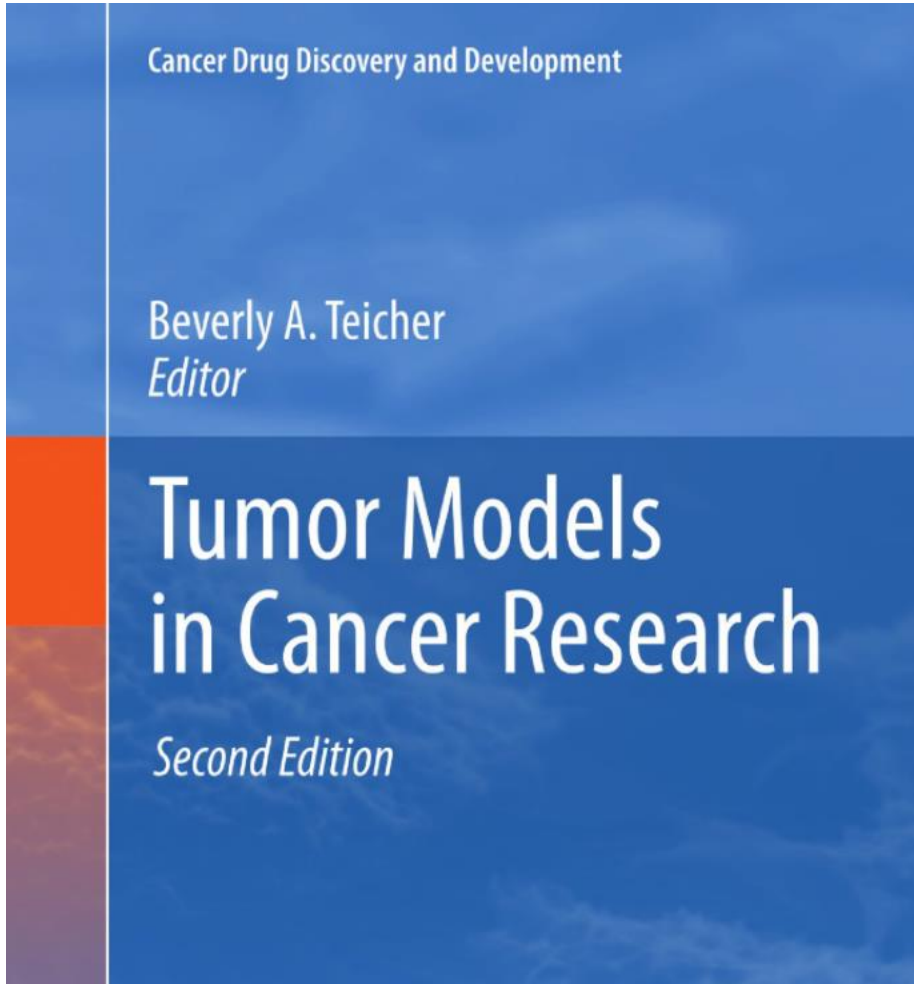



Figure 2: Tumor volume changes in % after treatment the treatment started. One-way ANOVA Bonferroni's Multiple Comaprison Test (GraphPad Prism)

# Results – Treatment/ control ratio (T/C %)






- qd × 4 (once daily for consecutive 4 days)
- qd × 5 (once daily for consecutive 5 days)
- q4d × 3 (once every 4 days for three times)
- q7d × 3 (once every 7 days for three times)

At each dose or schedule level, each drug was ranked by five efficacy levels:

- 0 = inactive, % *T/C* (change in tumor weight, each treated [*T*] or control [*C*] group of mice) > 40
- 1 = tumor inhibition, % *T/C* range 1–40
- 2 = tumor stasis, % *T/C* range 0 to −49
- 3 = tumor regression, % *T/C* range −50 to −100
- 4 = % *T/C* range −50 to −100 with > 30% tumor-free mice

To screen and prioritize compounds for testing in the xenograft models, so-called hollow fiber assays were used, in which tumor cells are cultured in sealed hollow fibers and implanted either subcutaneously or intraperitoneally in the nude mouse. After drug treatment for 6–8 days, cell survival is quantified by MTT dye conversion measurements [82]. The in vivo drug sensitivity profiles of these human tumor xenografts have served as worldwide benchmarks for the testing of new agents.

More recently, xenograft tumor models have been used to evaluate molecularly targeted therapies. Efforts devoted to such "target-oriented" drug discovery have produced fruitful results [83–86, 87]. Table 5.3 lists examples of therapeutics and xenograft models representing such achievements. One successful example of this effort has focused on the epidermal growth factor receptor tyrosine kinase

# Results – Treatment/ control ratio (T/C %)

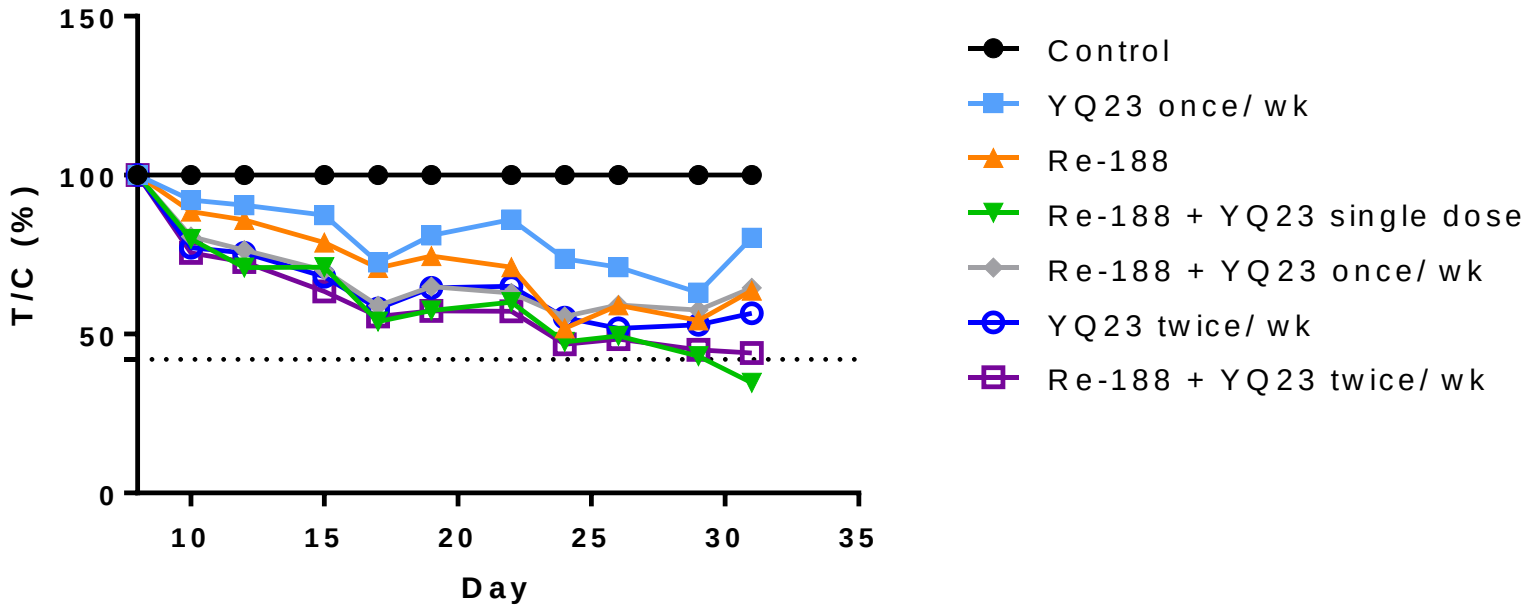
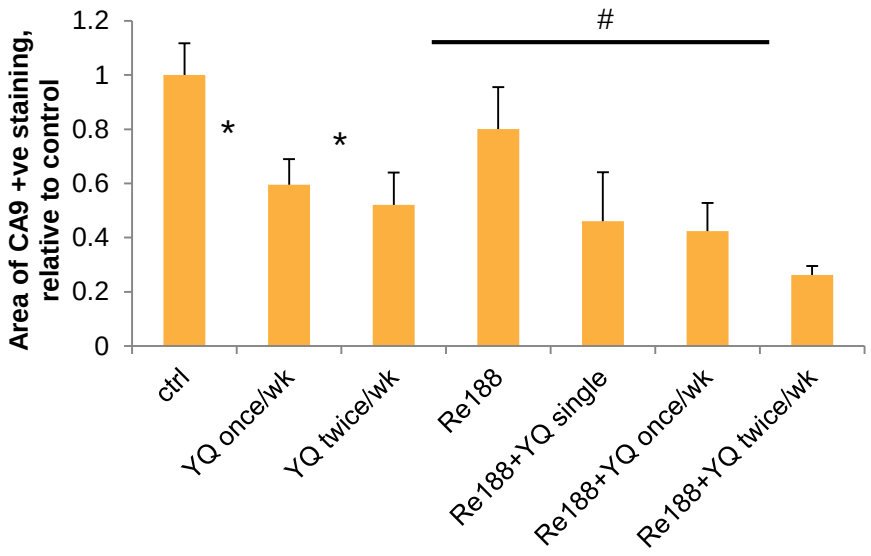



Fig 2: Re-188 + YQ23 single dose shows significant tumor inhibition effect (< 40%) on D31. The T/C% are 80.3% (YQ23), 63.7% (Re-188), 34.7% (Re-188 +YQ23), 64.6% (Re-188 + YQ23 once/wk), 56.6% (YQ23 twice/wk) and 44% (Re-188 + YQ23 twice/wk) respectively.

# Histology – CA9 IHC staining

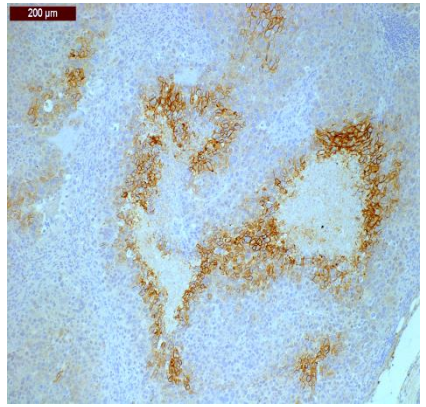
- **Carbonic anhydrase 9 (CA9)** is a hypoxic marker directly regulated by HIF1-a.
- Results showed a significant decrease in CA9 expression on **YQ23 treated group** compared to control.
- For **Re-188 treated group**, only Re188+ YQ twice/week showed significant decrease in CA9 compared to Re-188 alone.



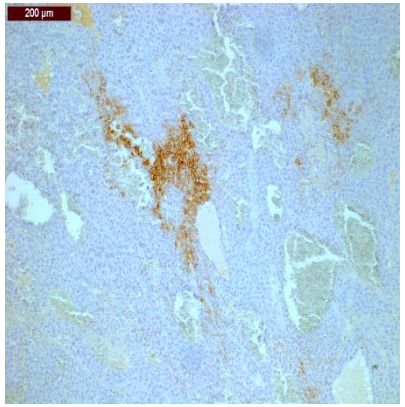

- p<0.05 vs control; # p<0.05 vs Re188

Image courtesy from Mr. Eddie Ho (New B Innovative)

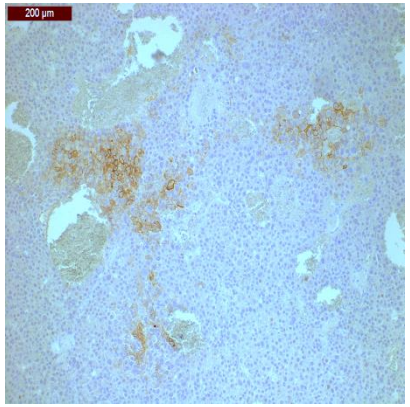
# CA9 IHC staining



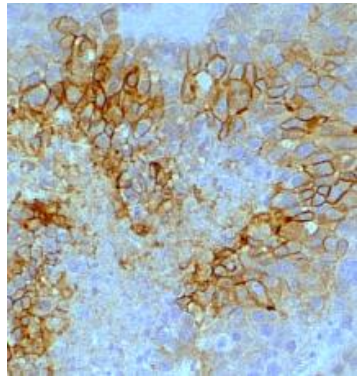

control



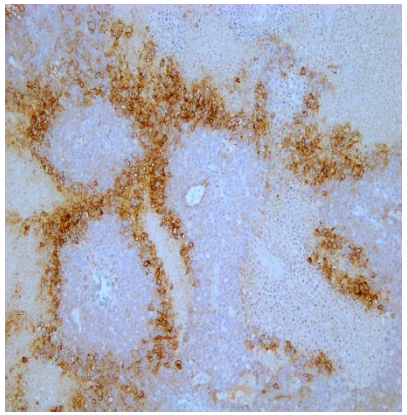

YQ23 once/week



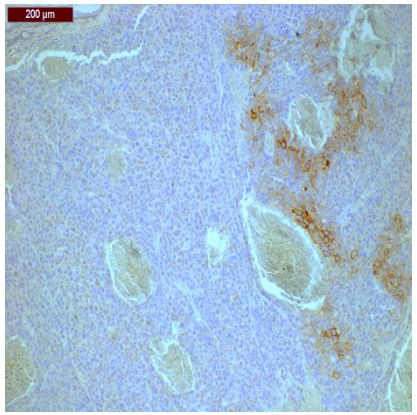

YQ23 twice/week



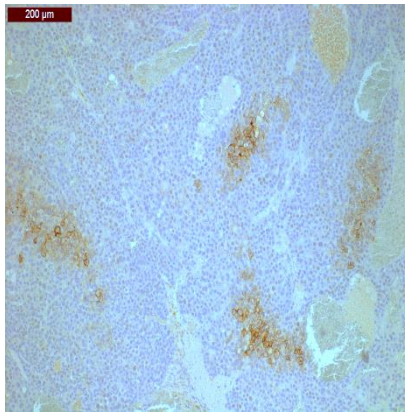
Larger image



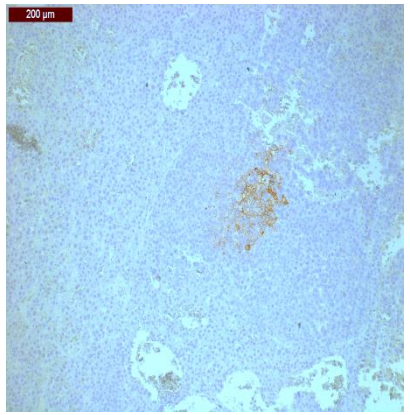
Re-188




Re-188
+ YQ23 single dose




Re-188
+ YQ23 once/wk




Re-188
+ YQ23 twice/wk

Image courtesy from Mr. Eddie Ho (New B Innovative)

# FMISO PET Imaging

**FMISO**

Baseline

Wk 1

Wk 2

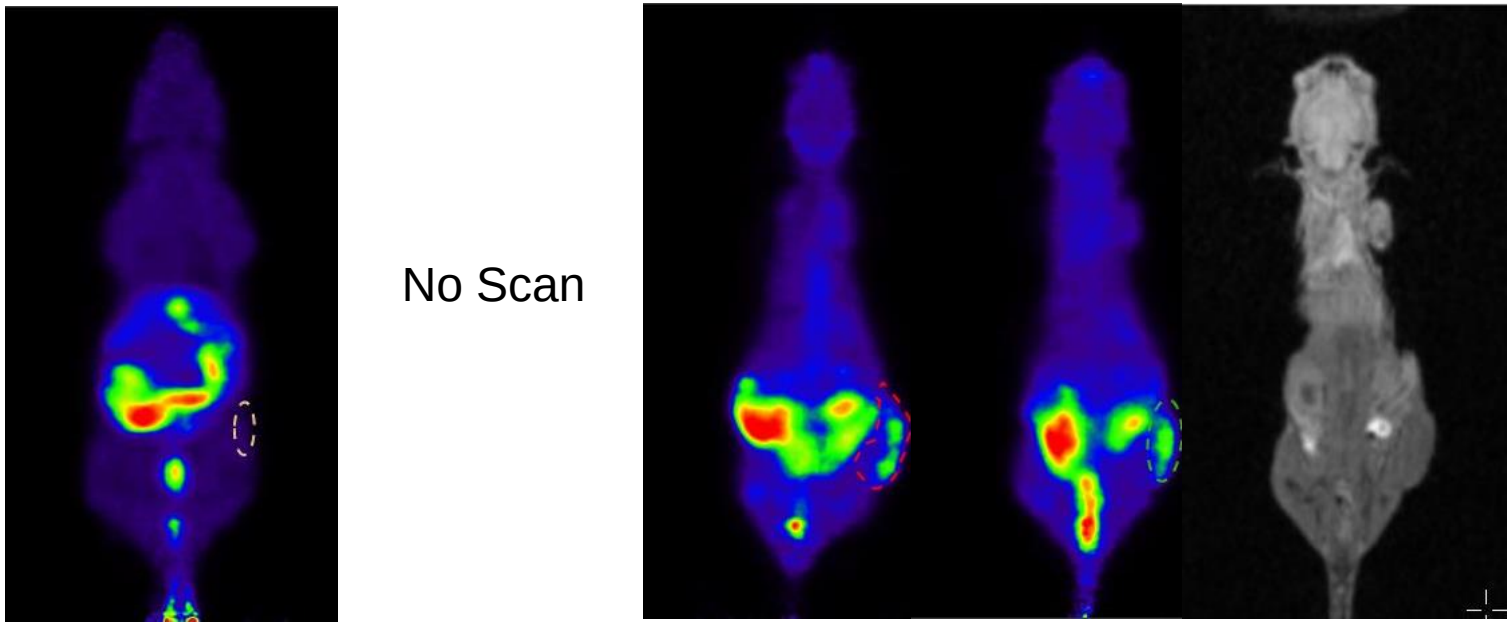
Wk 4

Material map

*% ID = ROI activity (MBq/ml) / Injected Dose (MBq) x 100*

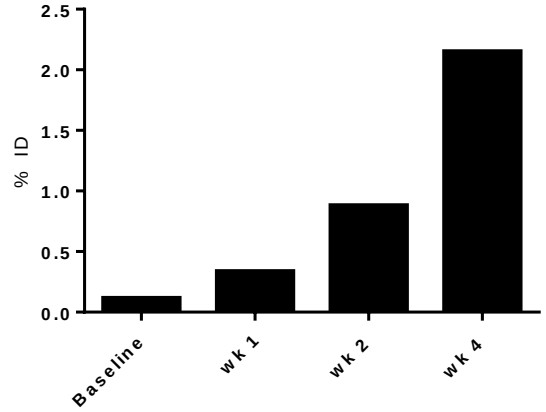
**Control**

No Scan

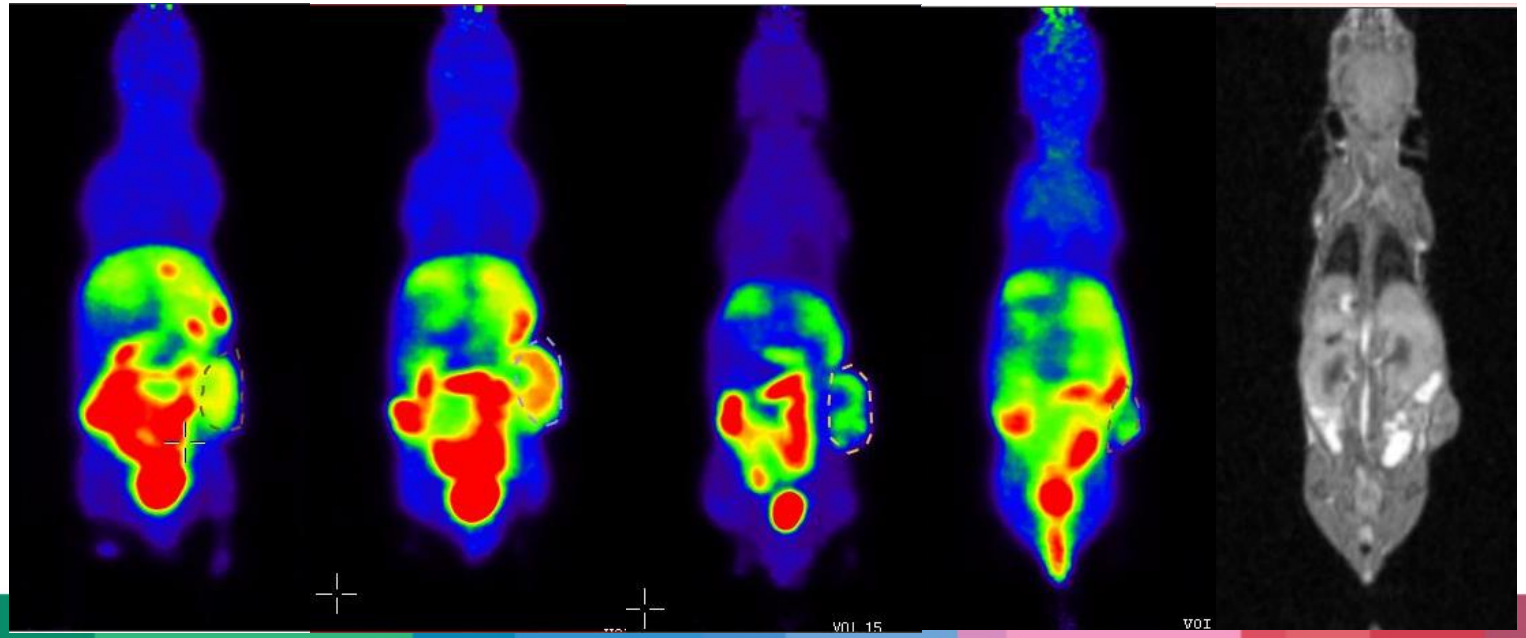


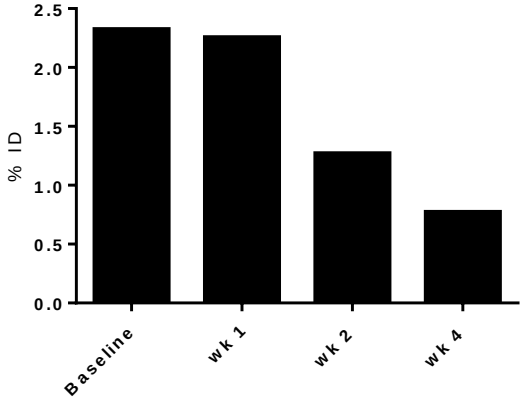
1000 (kBq/ml)

0




**Re-188 + YQ23 twice/wk**

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# Conclusion

- **Re-188** has significant tumoricidal effect on HepG2 xenografts
- **YQ23** has significant tumoricidal effect on HepG2 xeografts
- The addition of **YQ23** to **Re-188** has a synergistic effect in HepG2 xenograft model in nude mice giving rise to better tumor response
- **YQ23 a novel oxygen carrier** can decrease hypoxia in HepG2 xenografts
- **The data supports a potential role for combining YQ23 with radiation therapy in HCC**

# Acknowledgement


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- Dr Connelia Man
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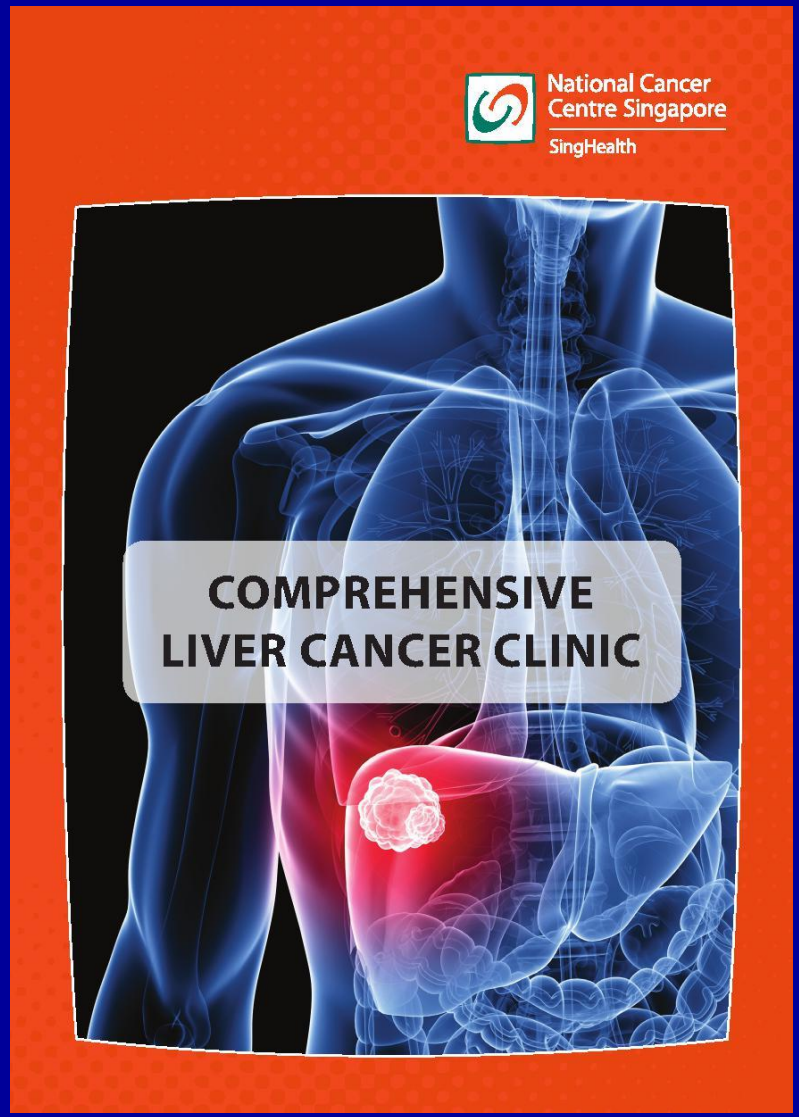


*Thank You!*

**National Cancer Center Singapore Guidelines on Liver Cancer**

*http://www.nccs.com.sg/PatientCare/ComprehensiveLiverCancerClinic/Documents/CLCC guideline Final Ver to upload PDF 26092014.pdf*