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UPMC LIFE CHANGING MEDICINE

6° INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, May18-20, 2017

6th INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, 18-20 Maggio 2017

ATA Hotel

PROGRAMMA SCIENTIFICO PRELIMINARE

NEW HORIZONS IN THE THERAPY OF HCC

Ioannis Petridis MD, PhD

THE JOINT COMMISSION NATIONAL QUALITY APPROVAL

Epidemiology

- **Main cause** of death in cirrhosis and **3° cause of death** in cancer worldwide
- Incidence is globaly increasing
- Factors associated: HCV infection, metabolic syndrome, obesity
- 80% of all liver cancers are HCC
- USA: 8.4/100.000 new cases
- Screening program is the key but... more cases of advanced disease at the time of diagnosis

Diagnosis

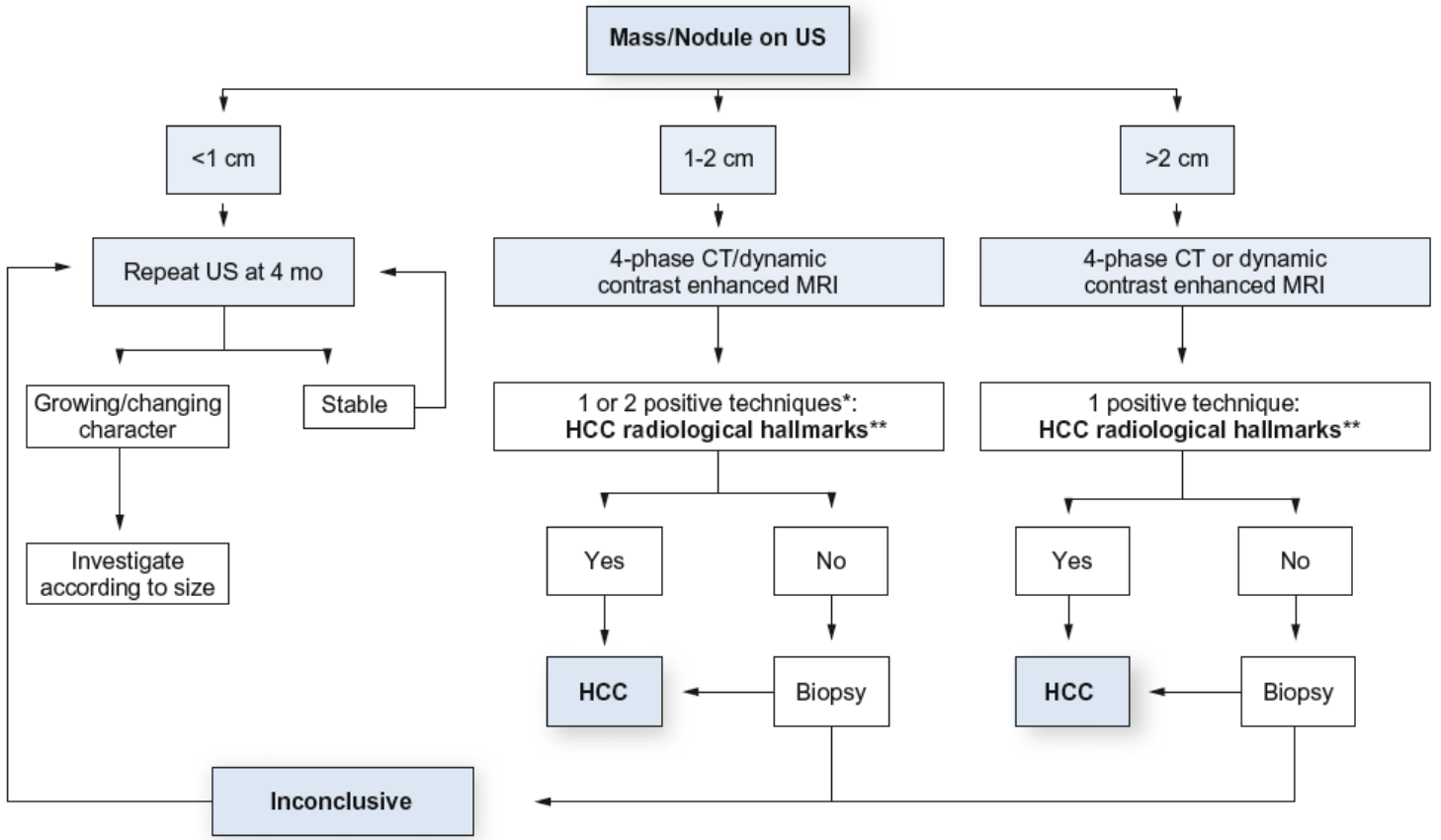

Fig. 2. Diagnostic algorithm and recall policy. *One imaging technique only recommended in centers of excellence with high-end radiological equipment. **HCC radiological hallmark: arterial hypervascularity and venous/late phase washout.

EASL–EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma Journal of Hepatology 2012 vol. 56 j 908–943
Available on: http://www.easl.eu/assets/application/files/d38c7689f123edf_file.pdf

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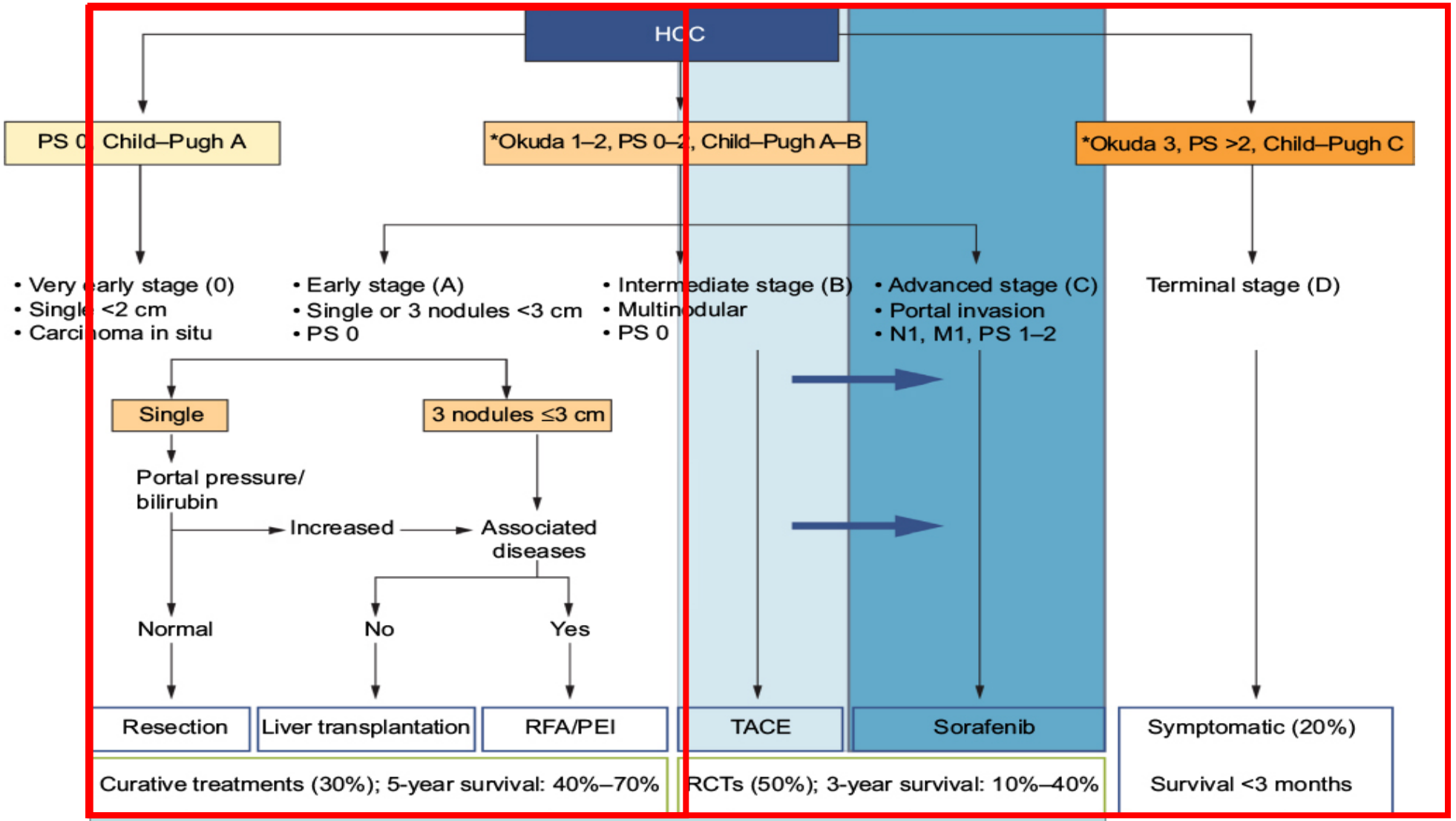
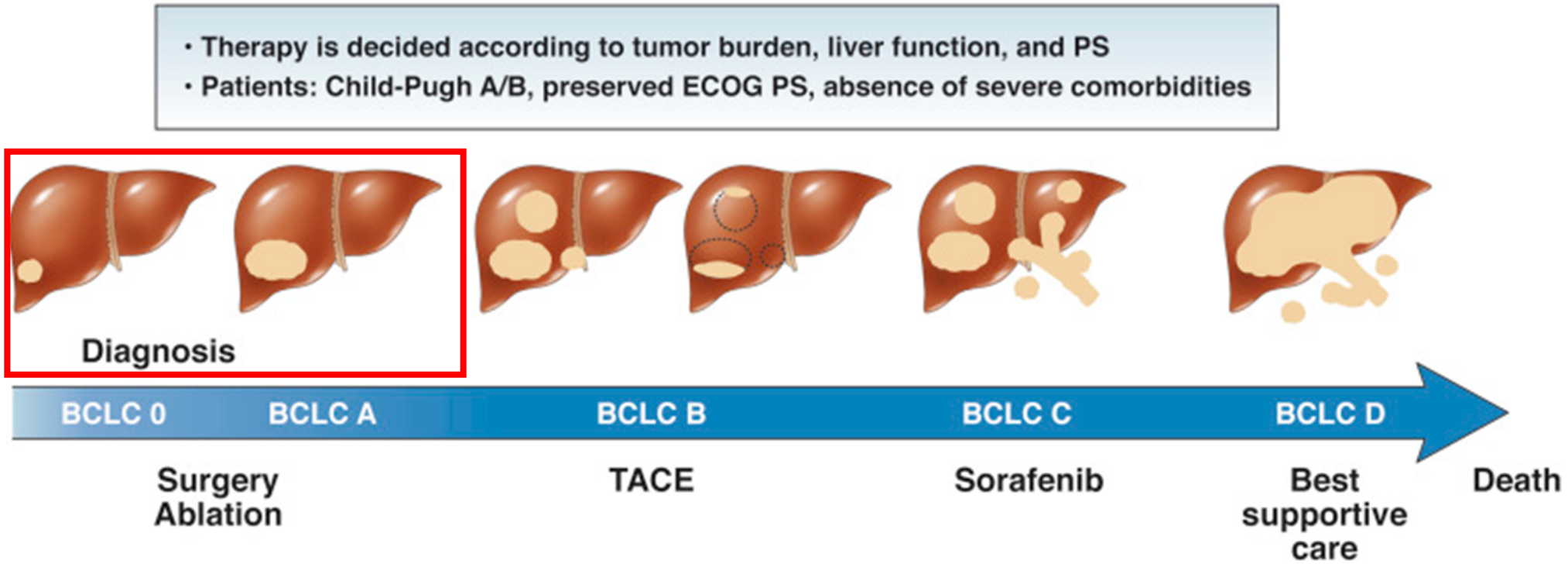
Barcelona Clinic Liver Cancer system



Effective treatments with survival benefit

HCC and stage



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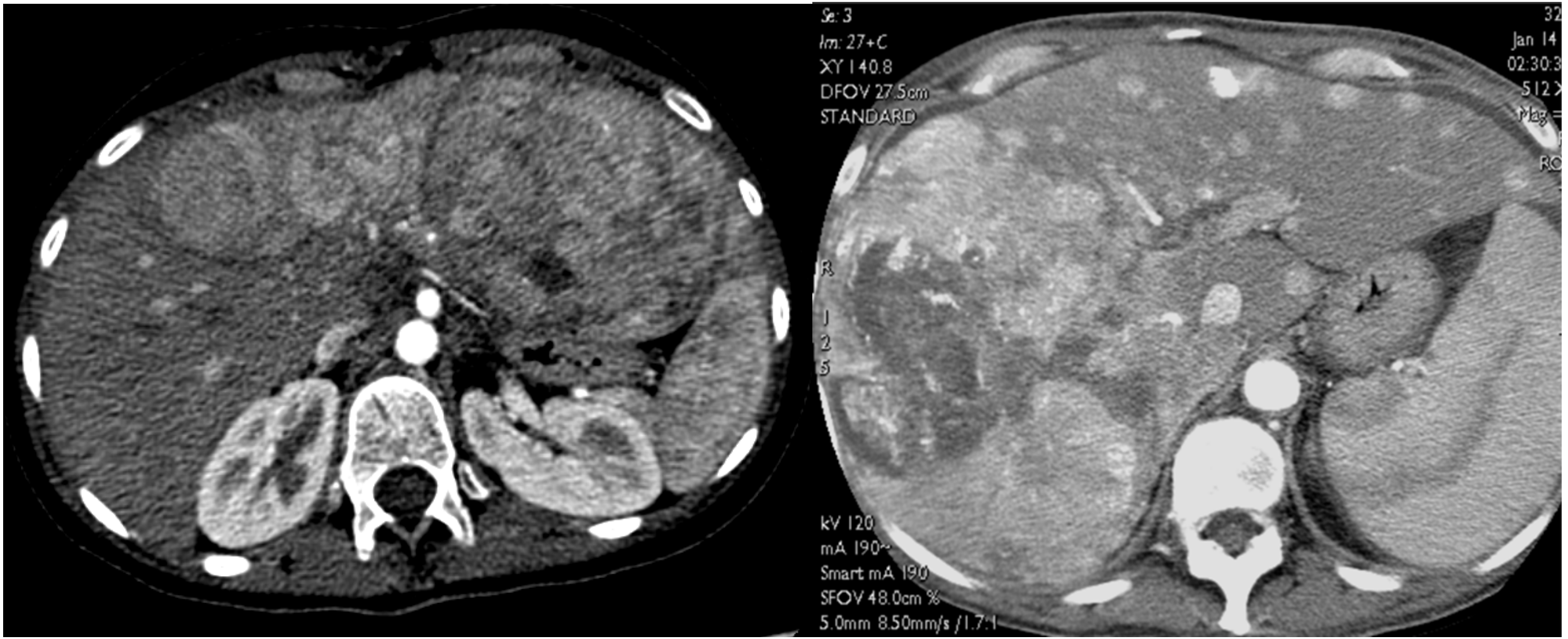

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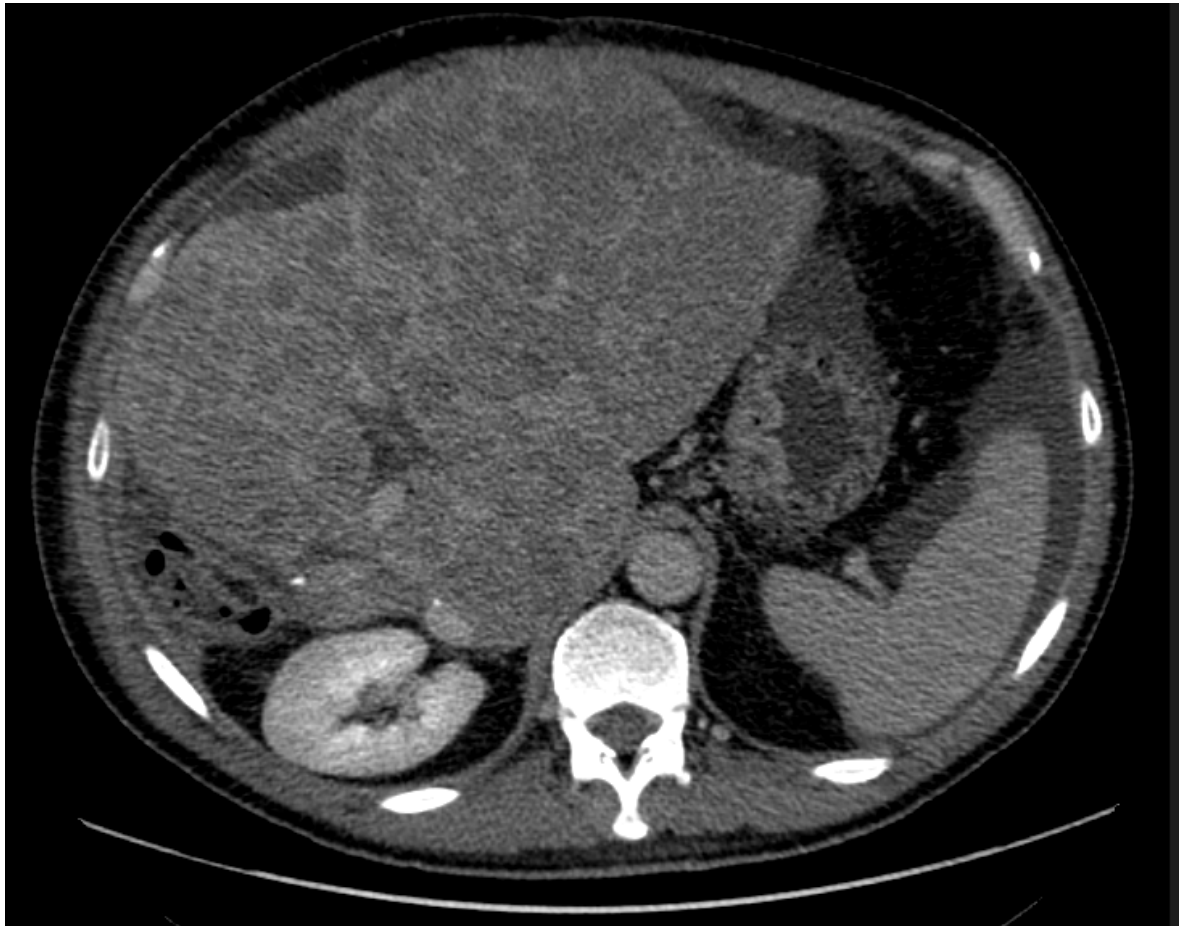
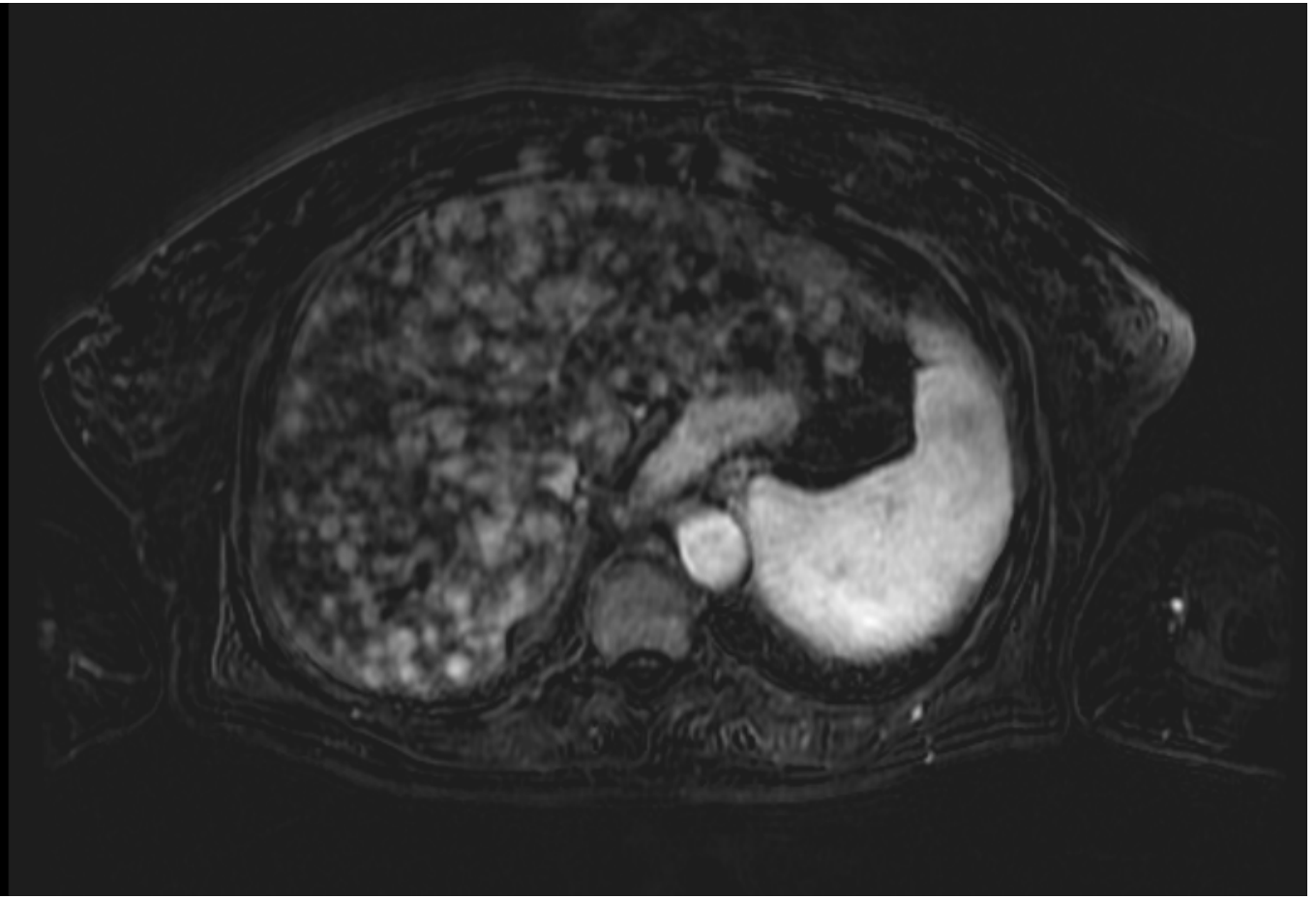
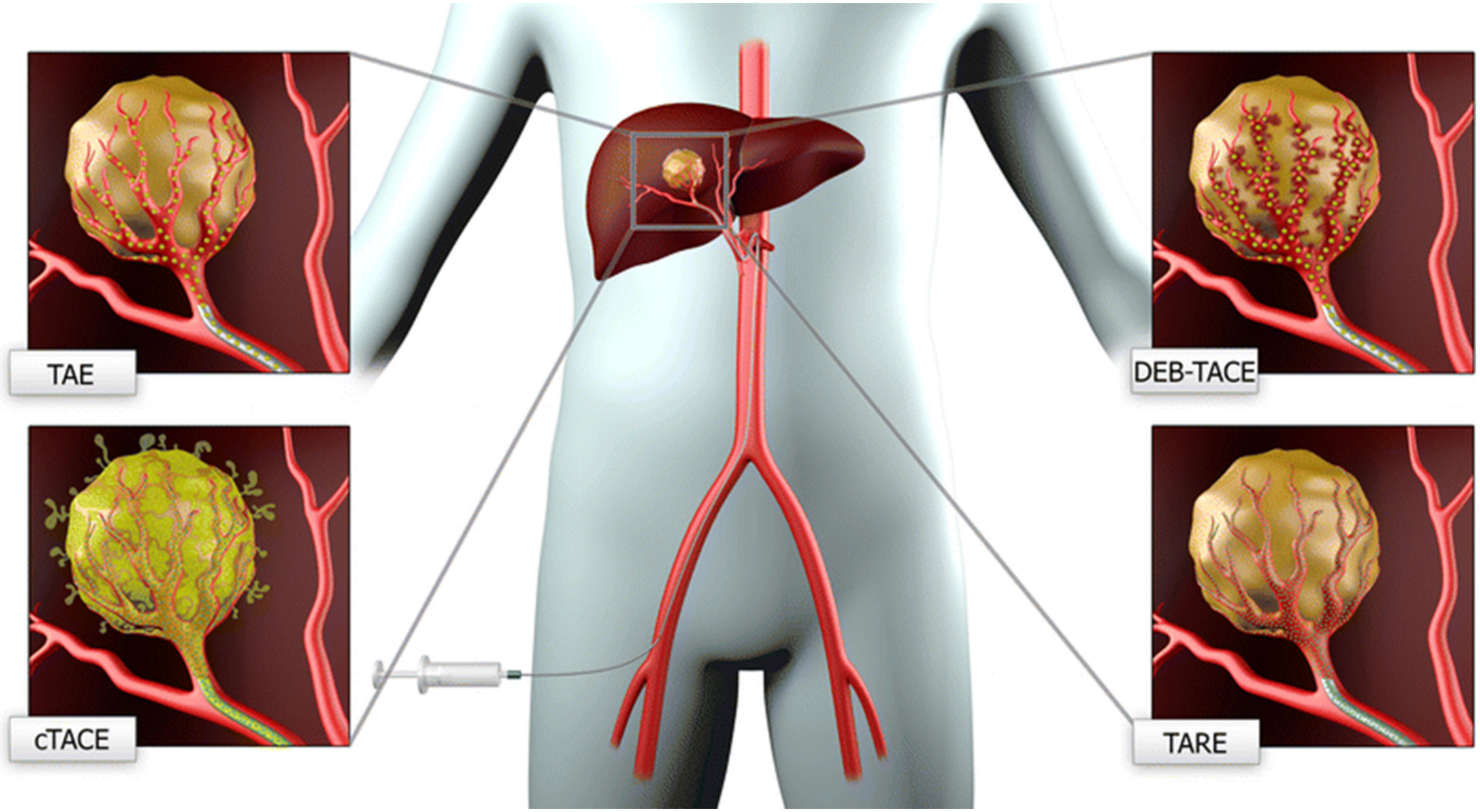




NEW HORIZONS

- TARE
- Medical therapy
- Gene therapy

Locoregional treatments-Embolotherapy



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TARE (Radioembolization)

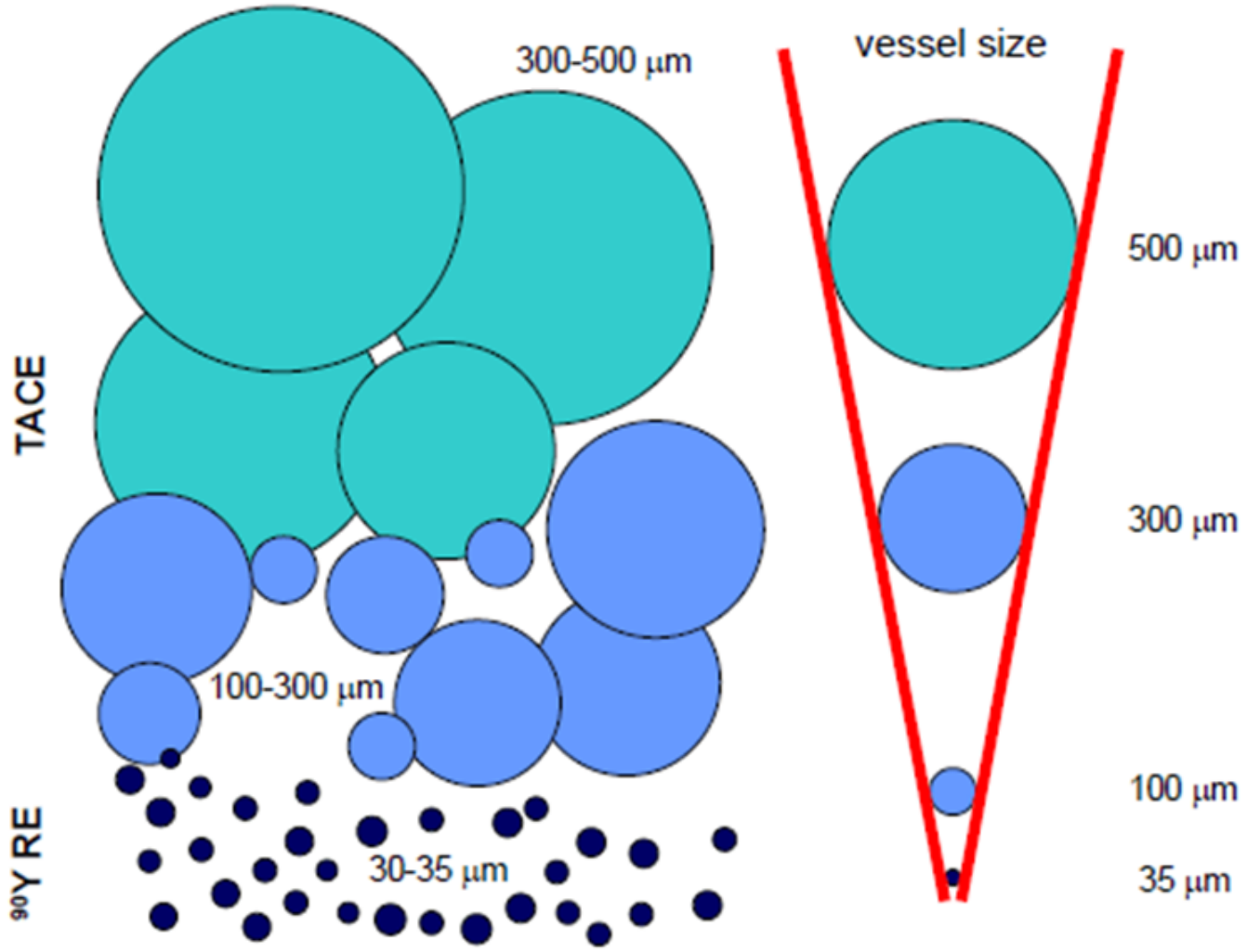
- Intra-arterial Injection of radioactive microspheres
- Mechanism of action: radioactive isotopes are deployed inside the tumor carried in microsheres
- Yttrium-90 (90Y) most common, short tissue penetration
- Resin microspheres (**SIR-Spheres®**) and glass spheres (**TheraSphere®**) (25-35 microns)
- Indications: Intermediate HCC poor candidates for TACE or not responsive to TACE, Large tumors (no ischemic effects) ± PVT, PS 1-2.

Sangro J Hepatol 2012

- Survival up to 16-18 months in Intermediate HCC

Sangro, Hepatology 2011, Salem Gastroenterology 2010, Mazzaferro Hepatology 2013

TARE



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TARE

- Complete necrosis in over 90% <3 cm 33% > 5 cm (more complete treatment of targeted lesions and tumor control)
- TARE vs TACE same OS, but lower toxicity/longer TTP, better QoL

  Salem, Gastroenterology 2016
- TARE vs Sorafenib, 2 retrospective studies, better OS in TARE

  De La Torre Liver Int 2016, Edeline Eur J Nucl Med Mol Imaging 2016
- Median survival in TARE 6-13 months compared to Sorafenib 6.5-10.7 months
- TARE failing TACE 15.4 compared to Sorafenib failing TACE 11.9-9.9
- For that reason in many centers TARE before Sorafenib

  Bolondi Semin Liver Dis 2012

TARE and potential implications

- Bridging therapy to OLTx, long TTP (up to 25.1 months) and low drop out rate.

- Downstaging therapy for OLTx or surgery (tumor shrinkage, controlateral lobe hypertrophy)

Kwan Liver Transplant 2012, Lewandowski Am J Transplant 2009

TARE

- 3 yrs survival 75% in TARE followed by RE or OLTx

  Iñarrairageui Eur J Surg Oncol 2012

- Retrospective review of 40 pts with HCC TARE as bridge before OLTx, OS 46 months, 23% HCC recurrence (15 months)

  Radunz Ann Transplant, 2017

- 4 cases of MC out and PVT, complete necrosis of the PVT and OLTx

  Levi Sandri HepatoBiliary Surg Nutr 2017

- Randomizzed prospective Clinical trial is ongoing

Sorafenib

- Multikinase inhibitor
- Inhibits tumor cell proliferation, has antiangiogenic effect, potential immunomodulatory effects
- Improves survival (10.7 vs 7.9 moths) prolonges TTP 5.5 vs 2.8 months

Llovet SHARP trial N Eng J Med 2008, Cheng Lancet Oncol 2009

- First line treatment for HCC BCLC stage C or stage A-B untreatable HCC

Sorafenib + locoregional treatments

- Sorafenib vs Sorafenib + cTACE same OSS

  Kudo Eur J Cancer 2011

- Sorafenib vs Sorafenib + DEB-TACE safe and well tollerated

  Pawlik J Clin Oncol 2011

- TARE+Sorafenib is safe with manageable toxicity

  Chow PLoS ONE, 2014, Ricke SORAMI, Liver Int 2015

- TARE vs Sorafenib (HCC with PVTT)

  RR 32.1 DCR 57.1% vs 3.2% and 41.9% OS TTP similar

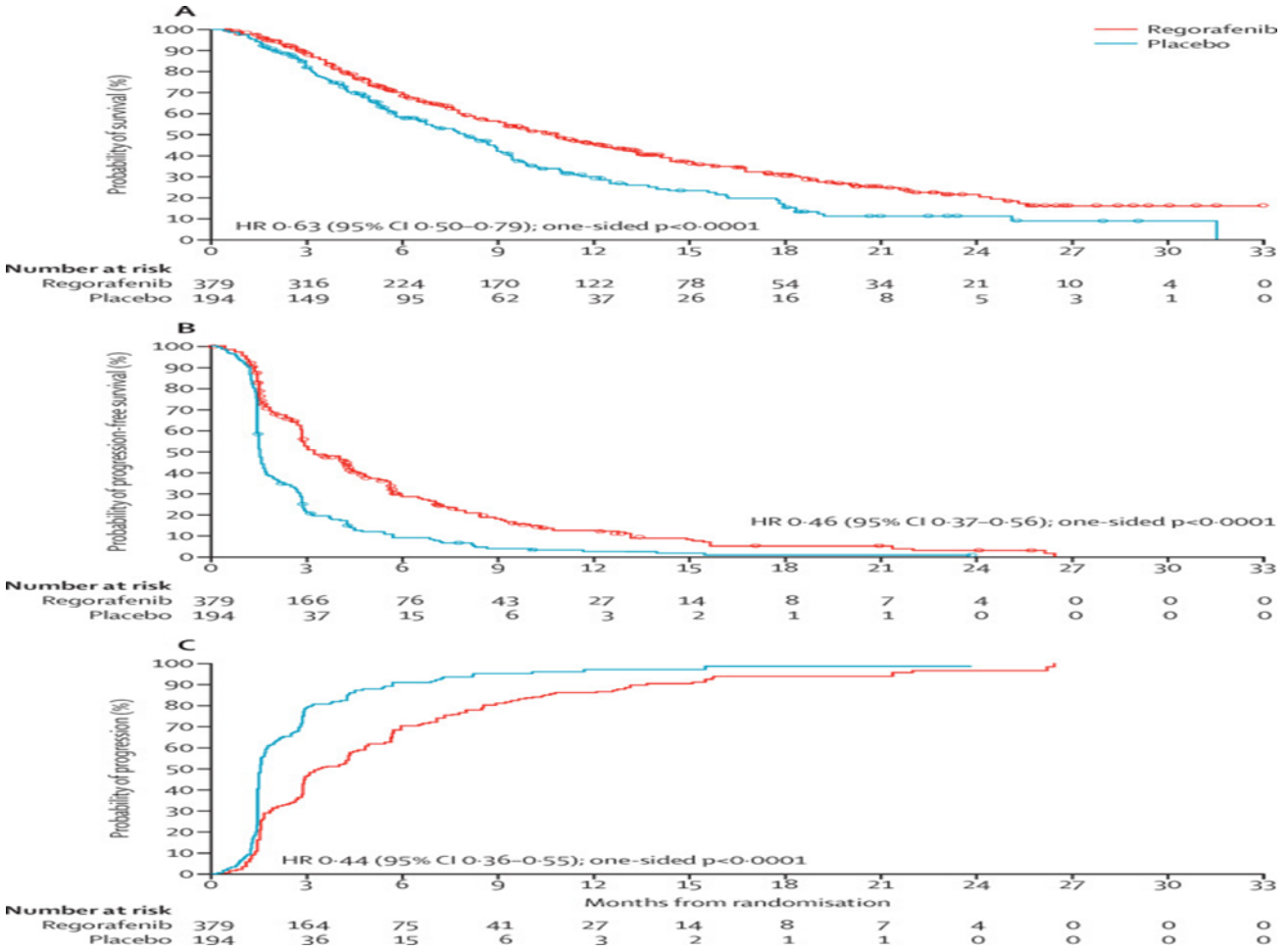
  Cho PLoS ONE, 2016.

- Sorafenib + DEB-TACE: better Disease Control rate, no difference in TTP in Intermediate HCC

  Lencioni, The SPACE trial, J Hepatol 2016, Sansonno D, Oncologist 2012

RESORCE STUDY

- Randomized, double-blind placebo controlled, phase 3 trial
- Regorafenib vs Placebo in HCC patients under progression on Sorafenib treatment.
- OS 10.6 vs 7.8, TTP 3.2 vs 1.5 months, DCR 65.2% vs 36.1%
- Safety and efficient profile with a Survival benefit



Bruix J, RESORCE study Lancet 2017

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Regorafenib

- Multikinase inhibitor
- Indications: GIST tumors, Metastatic colorectal cancer.
- Phase 2 trial: TTP 4.3, DCR 79%, OS 13.8 m

  Bruix Eur J Cancer 2013
- Phase 3 trial: Regorafenib vs Placebo in HCC patients in progression on sorafenib treatment, OS 10.6 vs 7.8, TTP 3.2 vs 1.5 months, DCR 65.2% vs 36.1%
- Safety profile and efficient with a Survival benefit

  Bruix J, RESORCE study Lancet 2017

Novel drugs

- **Everolimus** + Sorafenib (phase 1-2)
- **Erlotinib** (phase 2)
- **Erlotinib**+Sorafenib vs Sorafenib (phase 3)
- **Sunitinib** vs Sorafenib (phase 3)
- **Brivanib** vs Sorafenib (phase 3)
- **Linifanib** vs Sorafenib (phase 3)

Toxicity and lack of survival benefit

- **Brivanib** + BSC vs Sorafenib + BSC (phase 3)
- **Everolimus** vs Placebo + BSC (phase 3)
- **Ramucirumab** vs Placebo (phase 3)

Failed to improve OS

- **Conventional chemiotherapy ineffective**

- **Enzyme deprivation therapy** (ADI-PEG) (phase 1,2, 3)

Immunotherapy

- Role of inflammation and cancer
- Imbalance between inflammation and immune control
- Reconstitution of immune surveillance and stromal cell remodeling plays role in HCC

Prieto, Nat Rev Gastroenterol Hepatol 2015 Sprinzl, Semin Liver Dis, 2014 agents

- Immunotherapeutic agents such as Monoclonal Antibodies seems to be effective

- Tremelimumab failed to improve efficacy provided the first evidence that i works.
- Ipilimumab (phase 2 trial ongoing)
- Nivolumab Approved for melanoma and small cell lung cancer, Ongoing phase 3 trial (vs Sorafenib)
- Pembrolizumab Approved for advanced melanoma, Phase 3 trial ongoing

Molecular targeted therapies

Tivantinib

- MET (mesenchymal-epithelial transition factor) inhibitor
- Randomizzed controlled trials phase 2 showed better OS, TTP and OR
- 2 Phase 3 trials ongoing

Cabozantinib

- MET inhibitor, Metastatic medullary thyroid cancer
- Phase 3 trial ongoing

Refametinib

- MEK inhibitor,
- Phase 2 study Asian study showed that Refametinib+Sorafenib was effective specially in patients with mutant *KRAS* tumors
- Ongoing Phase 2 Trial of Refametinib in Combination With Sorafenib as First Line Treatment in Patients With RAS Mutant Hepatocellular Carcinoma (HCC)

Molecular targeted therapies

Apatinib

- VEGFR2 inhibitor, phase 3 trial ongoing

Lenvatinib

- Tyrosine kinase inhibitor of VEGFR1-3, FGFR1-4, PDGFRβ, RET, KIT
- Apporved for Thyroid cancer
- phase 3 trial ongoing

Ramucirumab

Human IgG1 monoclonal antibody binds with extracellular domain of VEGFR2

- Apporved for metastatic colorectal cancer, phase 3 trial ongoing

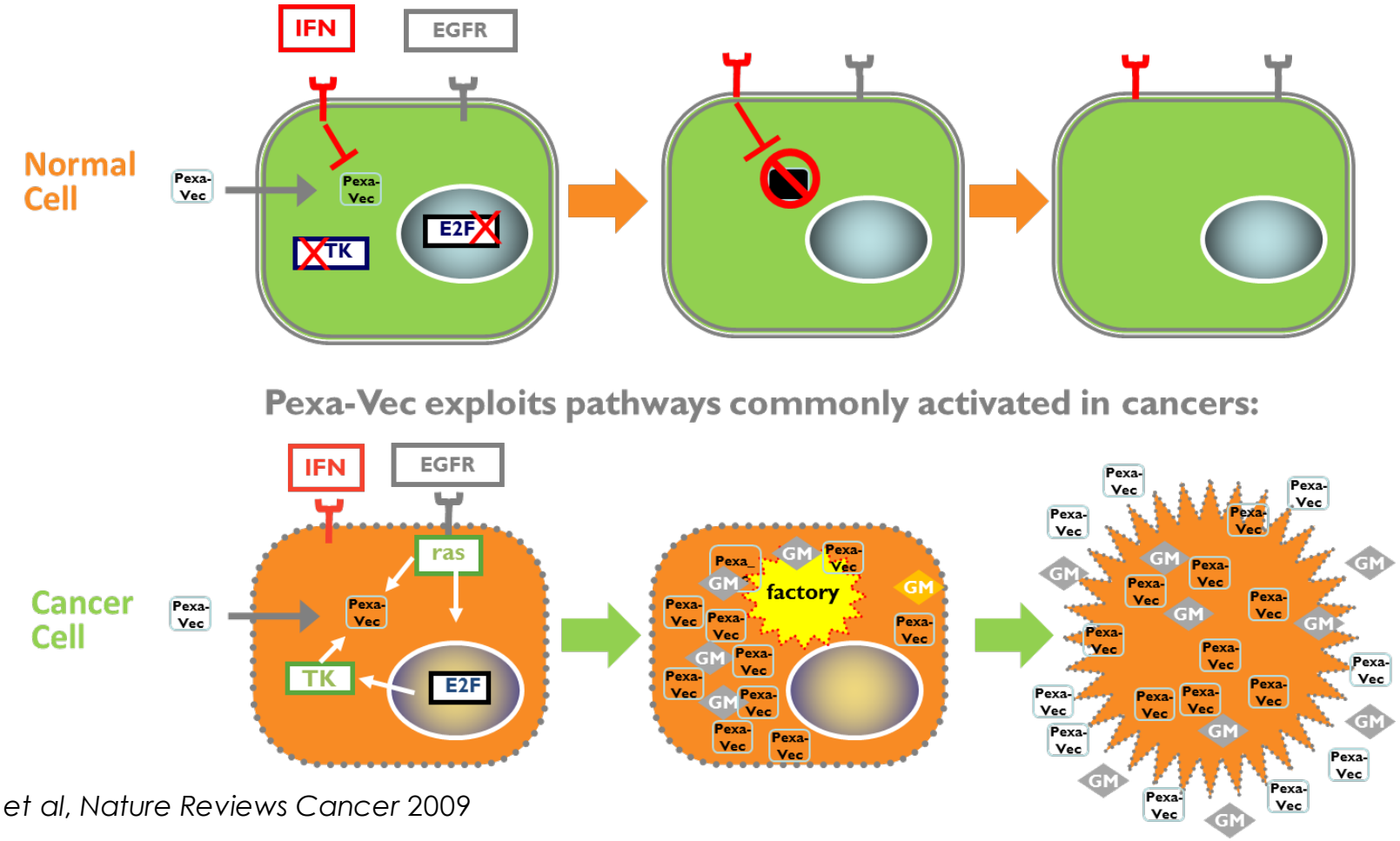
What is next ?

Gene therapy

Use of vectors of viral origin in order to transfer genetic material (trangenes) into cells to modify gene-expression

Cancer's Achilles' Heel

Tumor cells defenseless against virus infection



Kirn *et al, Nature Reviews Cancer* 2009

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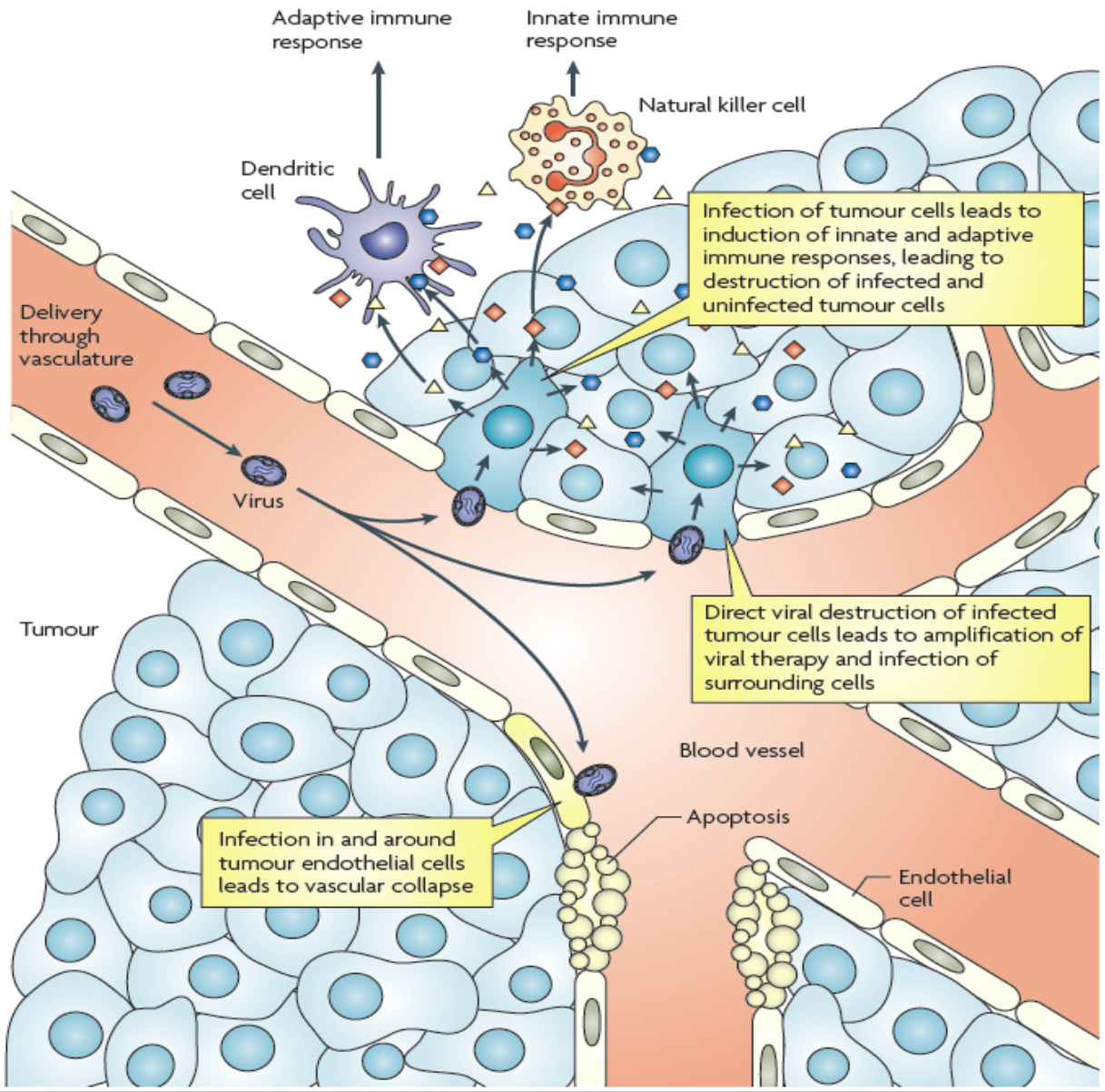
Virus Attack Tumors by Multiple Mechanisms



1. **Infection of cancer cells**
   - *Cell lysis*
   - *Virus amplification & spread within tumor*
2. **Shutdown of tumor blood flow**
   - *Uninfected tumor cell death*
3. **Stimulation of immune response**
   - *Rejection of tumor by host immune cells*

NATURE REVIEWS | CANCER
VOLUME 9 | JANUARY 2009 | 65
David H. Kirn and Steve H. Thorne

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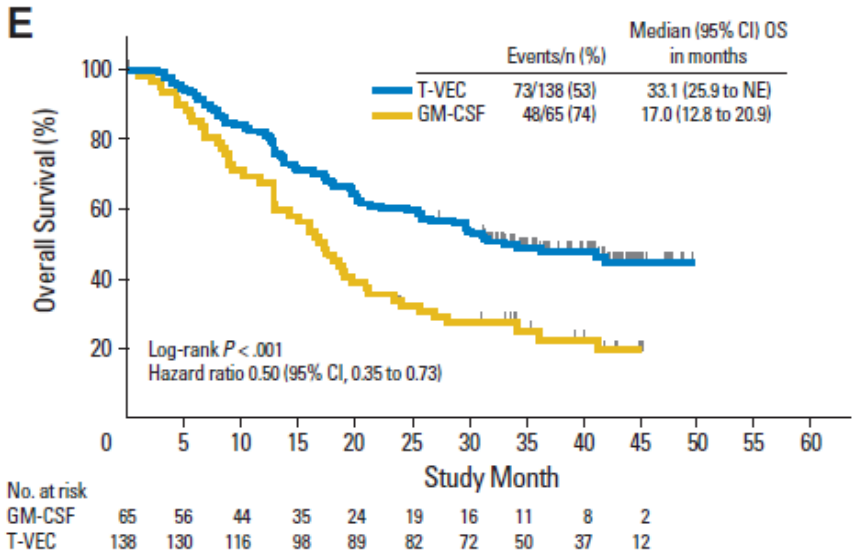
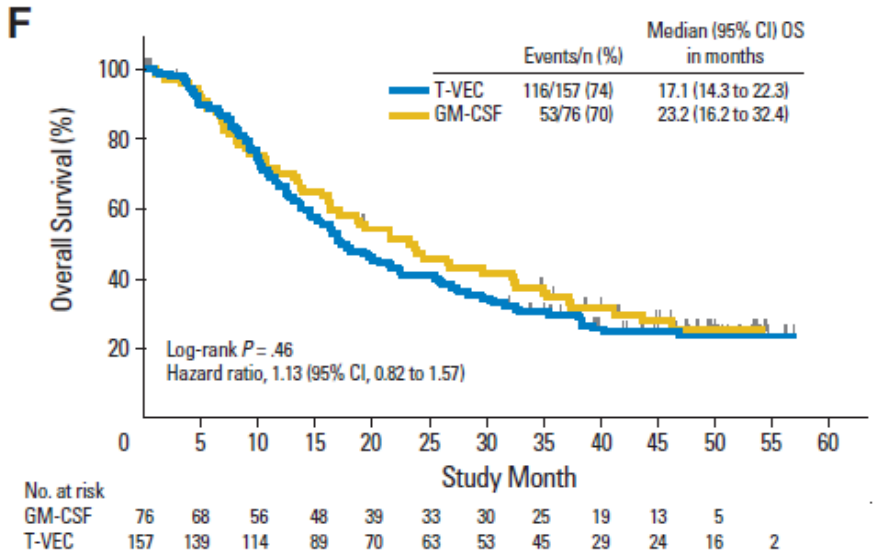
T-Vec: Oncolytic Immunotherapy for Melanoma

Oncolytic immunotherapy T-VEC has completed Phase 3 testing in melanoma and showed OS improvement in 1st-line and no improvement in ≥2nd line

First-Line Therapy



≥ Second-Line Therapy



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Pexa-Vec story

- Pexa-Vec is an **oncolytic immunotherapy** that utilizes the **vaccinia poxvirus** strain as its backbone. This strain has been used safely in millions of people as part of a worldwide vaccination program.

- This strain naturally targets cancer cells due to common genetic defects in cancer cells;

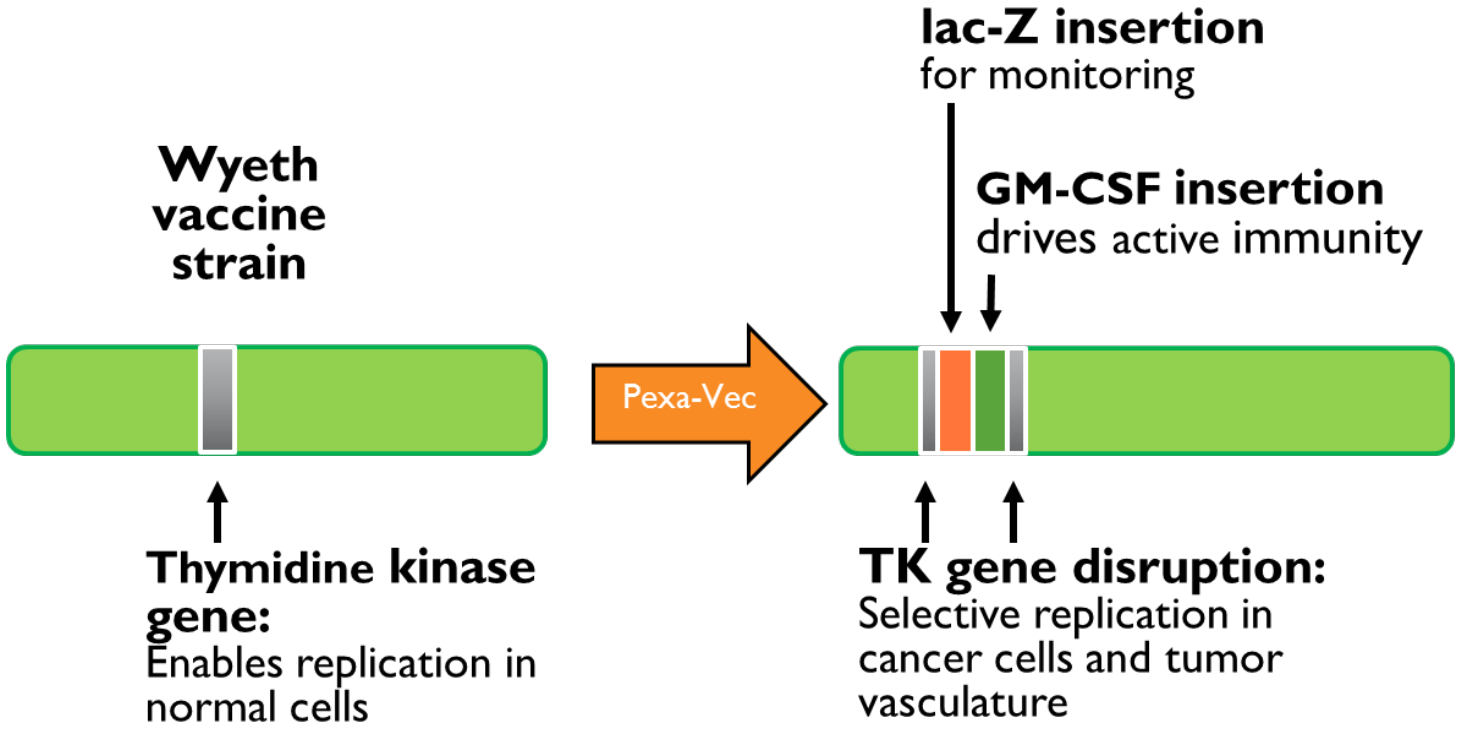
- Pexa-Vec was engineered to enhance this by **deleting its thymidine kinase (TK) gene**, thus making it dependent on the cellular TK expressed at persistently high levels in cancer cells.

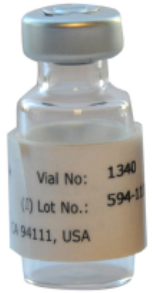
- Pexa-Vec is also engineered to express the immunogenic **GM-CSF protein**.

Pexa-Vec

- A vaccinia virus engineered for tumor selectivity and enhanced potency

- A frozen viral suspension
- Administered IV and/or IT





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Pexa-Vec Pre-Clinical Development Overview

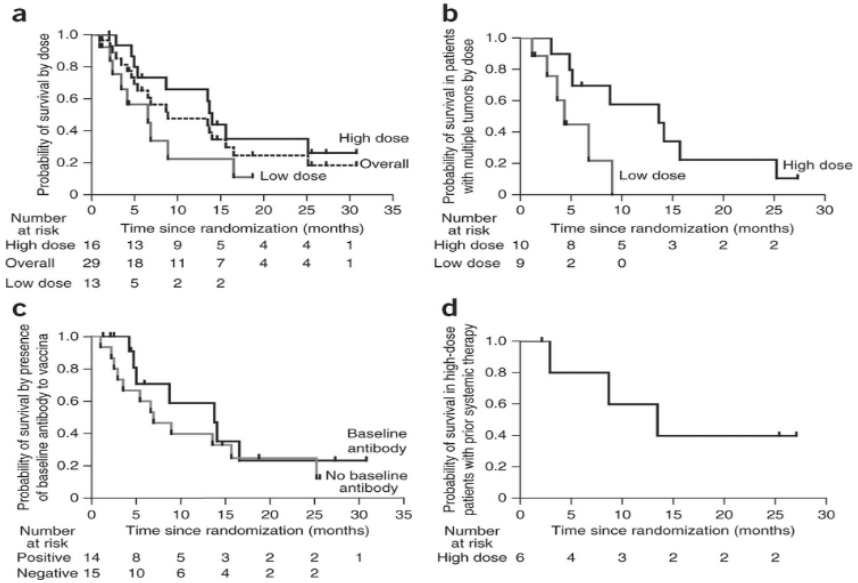
- Pexa-Vec used in 2 liver cancer models: in rabbits and in rats

- Cancers cell lines in vitro (including human HCC cell lines)

Clinical experience

- Traverse study (Phase 2 second line treatment, 129 pt, advance unresectable HCC, failure or intolerance to sorafenib), Pexa-Vec 109 IV: no benefit in overall survival (probably because very advanced disease)

Confirmed an **acceptable safety profile**



- HEP007 (Phase2 Frontline dose-finding trial in HCC), 30 pt, high dose vs low dose of Pexa-Vec

Overall **survival increase with High dose** Pexa-Vec

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Phase 2 Frontline Dose-Finding Trial in HCC (HEP007)

N= 30
N. America & Korea

Eligibility Criteria
- Advanced, unresectable HCC
- Tumor progression during or following at least one prior HCC regimen
- 1-5 hepatic tumors ≥ 1 cm
Child-Pugh A or B

Stratification:
- +/- viral etiology

Randomized 1:1

Arm A:
High Dose
Pexa-Vec 1×10^9 pfu[1t]

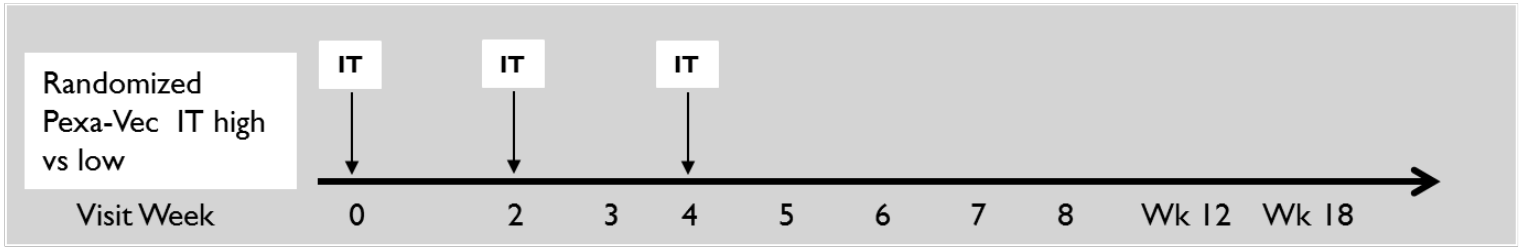
Arm B:
Low Dose
Pexa-Vec 1×10^8 pfu[2]

Endpoints:

Clinical: tumor response, overall survival, safety

MOA: Necrosis, vascular disruption, active immunotherapy

1 - Phase 1 MTD
2 - 10% of high dose; activity observed in Phase 1 trials



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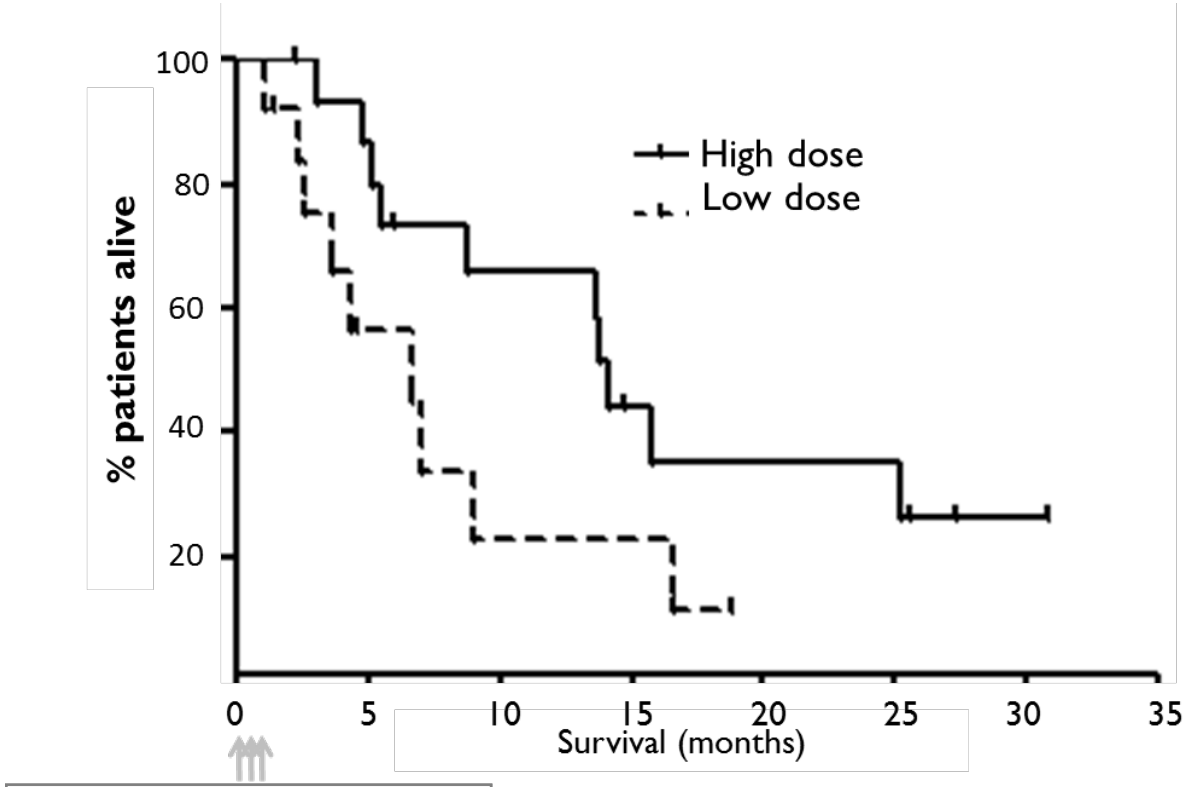
Overall Survival Increase with High Dose Pexa-Vec



Overall Survival:
14.1 vs. 6.7 mos.,
HR = 0.39, n = 29
p = 0.020

Historical reference (sorafenib vs. placebo)
SHARP: 10.7 vs 7.9 mos.
HR = 0.69, n = 602

Asia/Pac: 6.5 vs 4.2 mos.
HR = 0.68, n = 226

- High-dose Pexa-Vec resulted in greater systemic exposure
- Tumor responses observed in both treatment arms

Heo et al, Nature Medicine 2013

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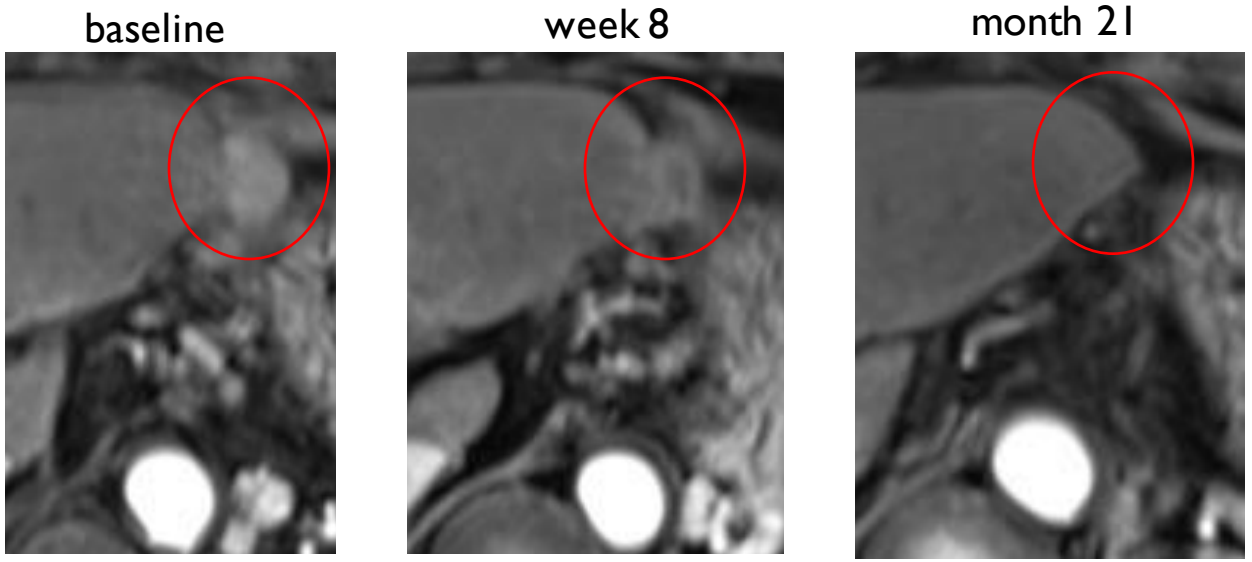
RECIST Complete Response in HCC Patient



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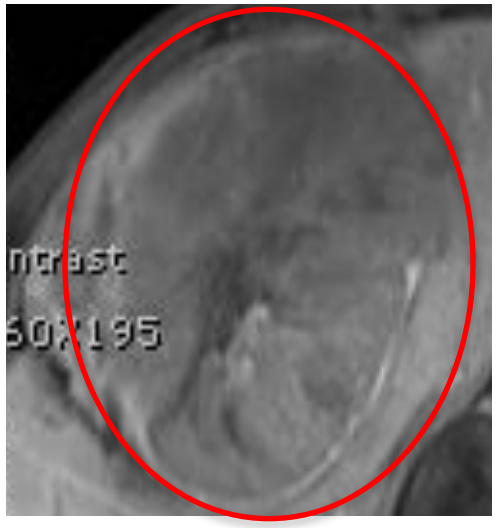
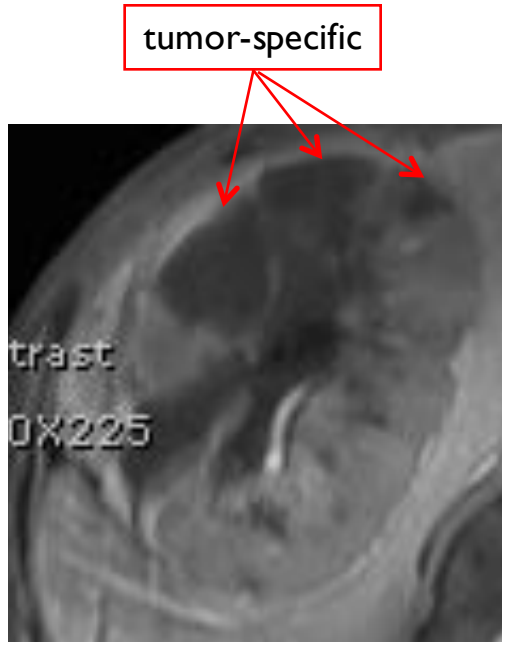
Acute Reduction in Tumor Blood Flow



10 cm
Large, highly
vascular tumor

5 Days



Acute response
diffuse vascular disruption
tumor-specific

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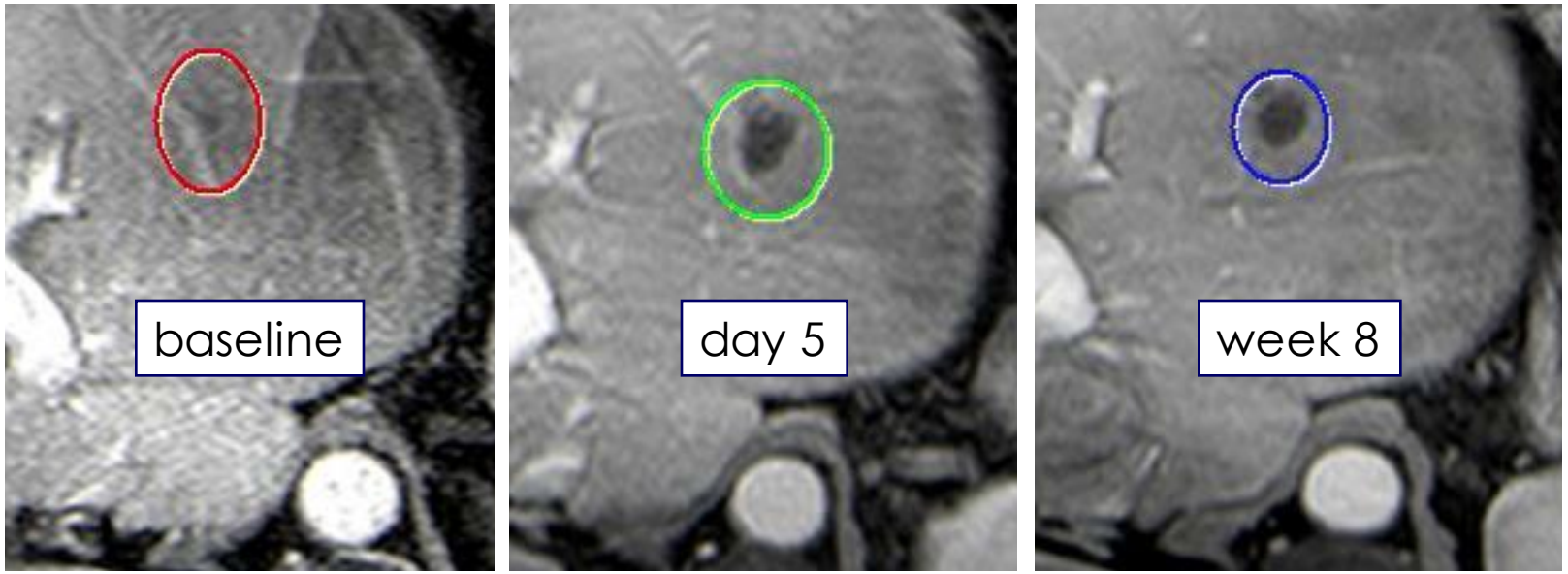
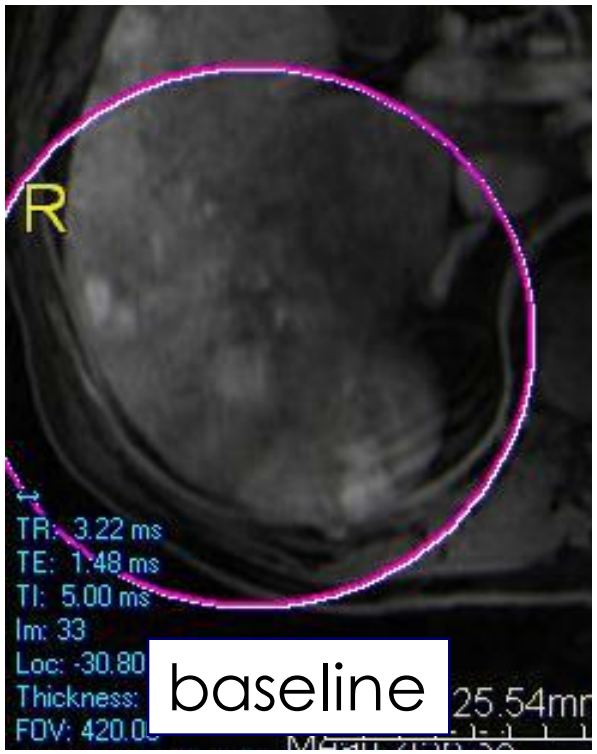
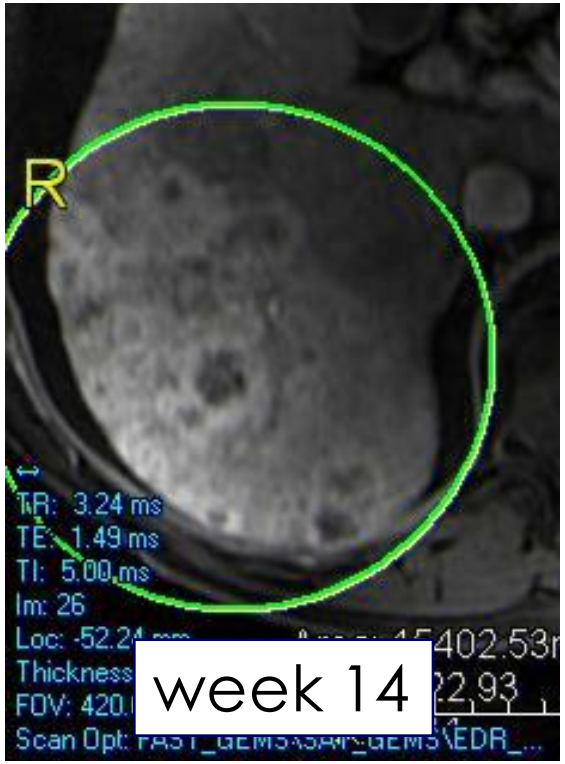
Non-injected tumor response: acute



Non-injected tumor response: chronic

indicative of chronic peritumoral inflammation with central necrosis





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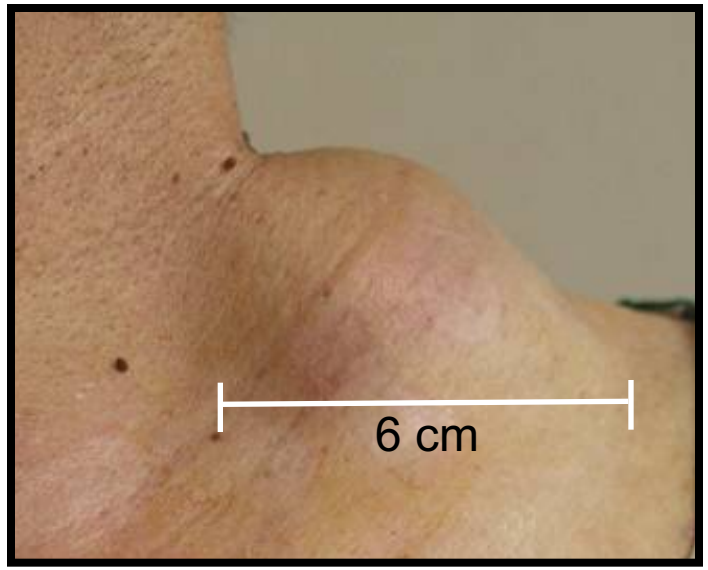
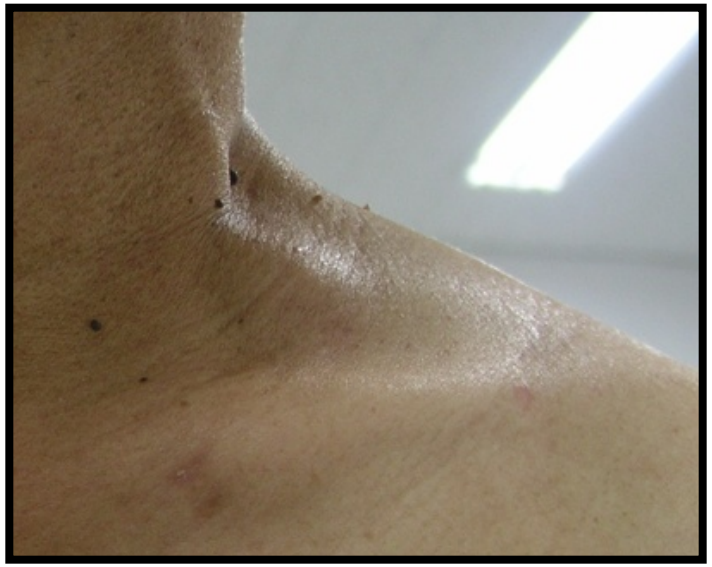
Tumor Response Following Pexa-Vec Therapy

Liver cancer metastasis response



12 wks



- Terminal, failed 5 prior therapies
- IT in liver – partial response
- Rapidly growing neck tumor (6 month later)
- Severe neck pain, lack of neck mobility, severe weight loss
- Pexa-Vec IT x 4 in neck metastasis (every 3 weeks)

- Neck pain and mobility issues resolved
- 10 kg weight gain

Park *et al, Lancet Oncol* 2008

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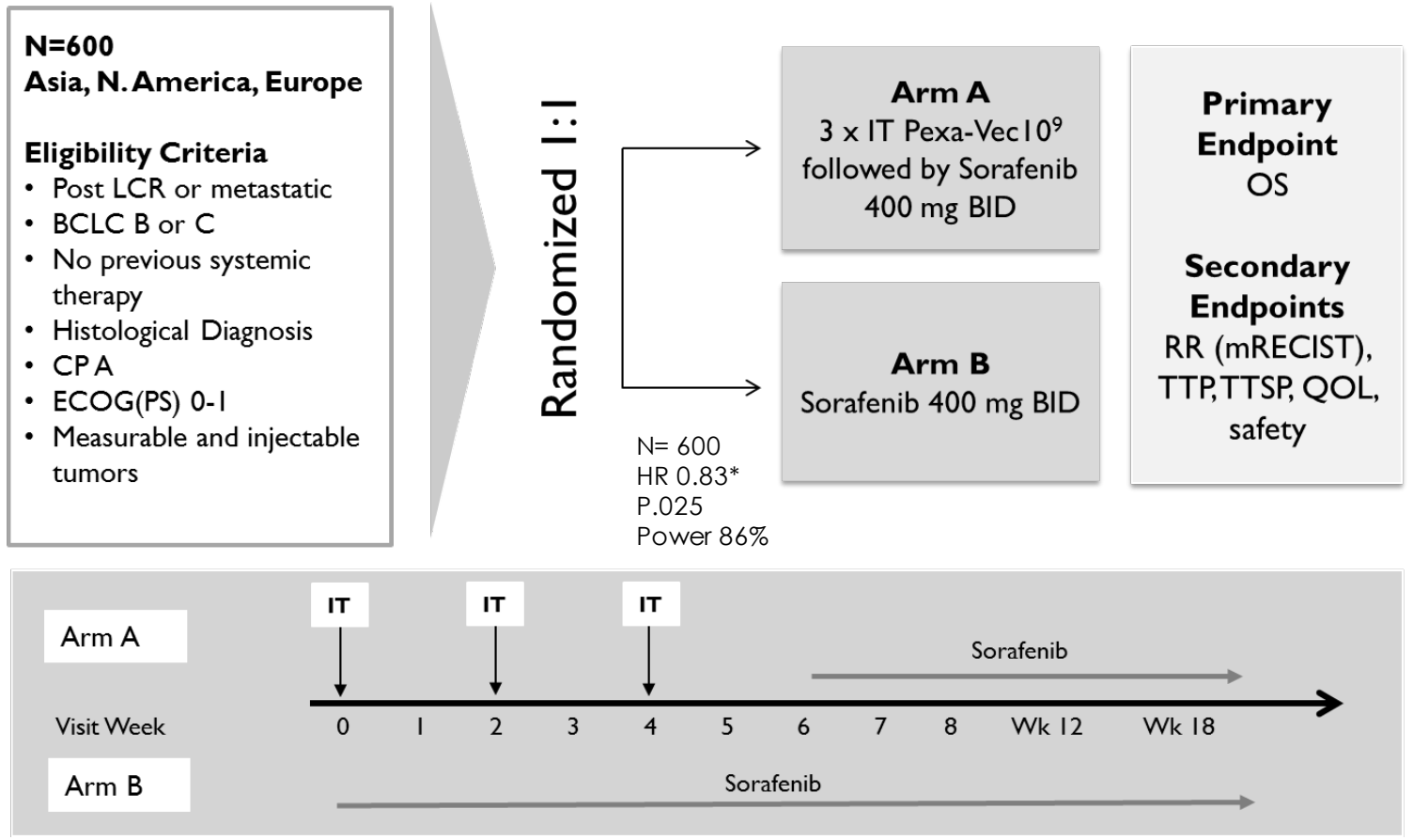
Phase 3 First-Line HCC Trial (PHOCUS)



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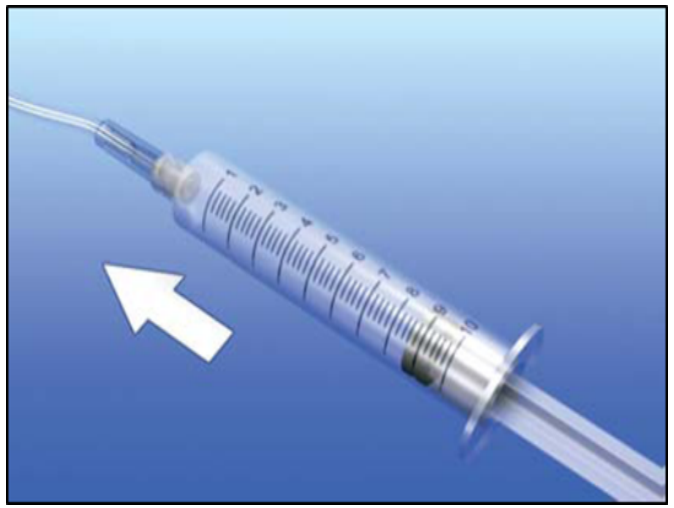
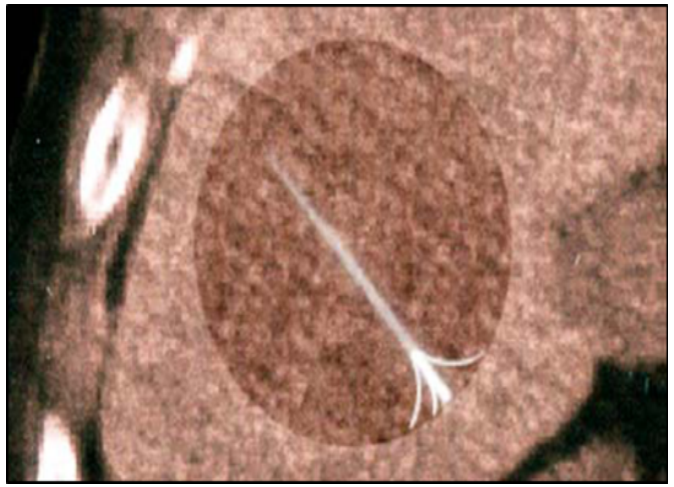
IT Injection





Attach syringe containing Pexa-Vec to the QF or QF ST needle luer connector

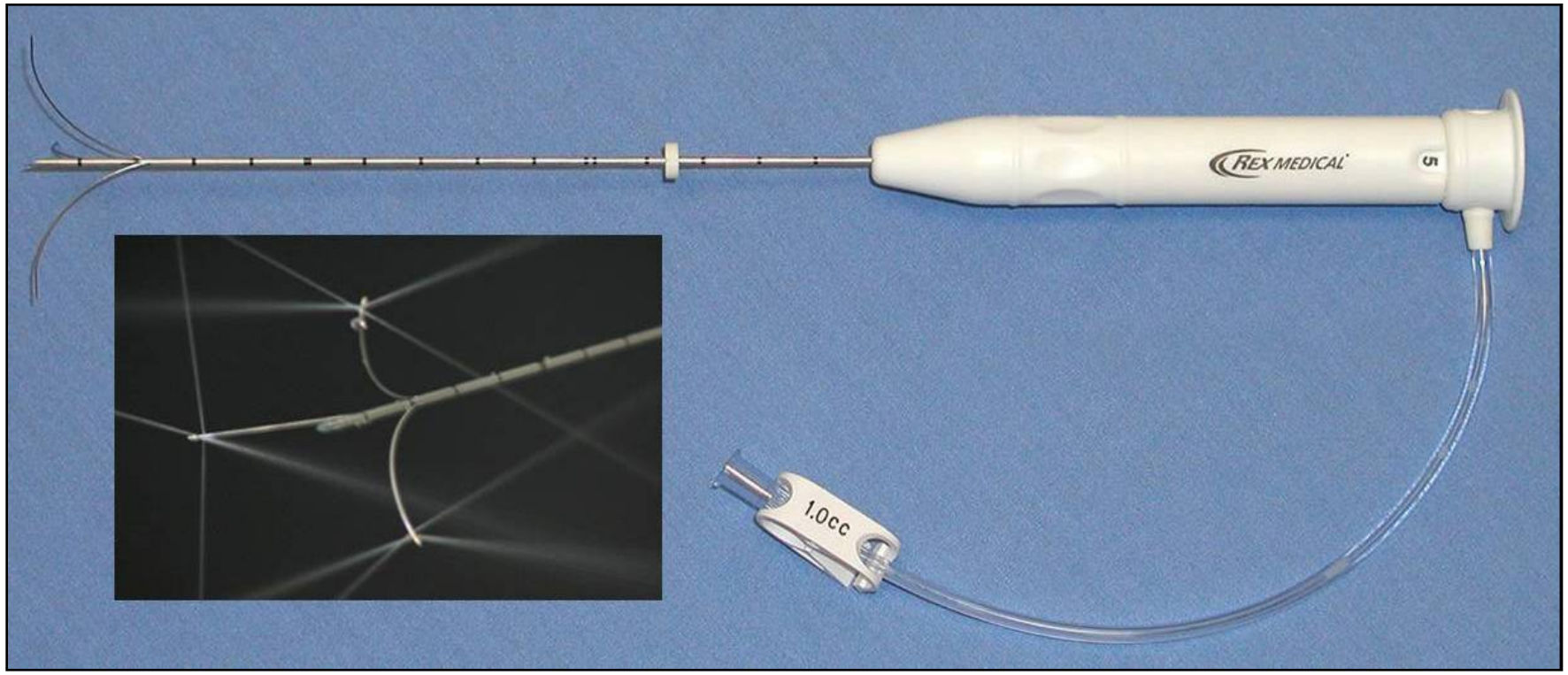
- Acceptable to transfer to sterile syringe and/or use 3-way stop cock

Deploy the tines to the edge of the tumor by advancing the plunger to maximal deployment for that particular tumor size (see IVT)

NOTE: Once QF needle tines are deployed **keep procedure moving** or tines may clog (if tines clog, use new QF needle)

Quadra-Fuse Multipronged Injection Needle

Quadra-Fuse (QF) / Quadra-Fuse ST (REX Medical)



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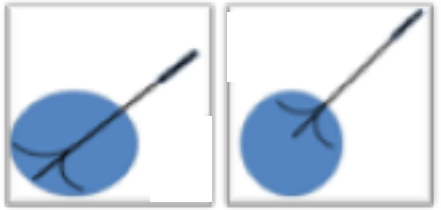
Number of Injection Sites Within Tumor

Dependent on tumor size

Tumor Size	QF Needle Stopping Points
Small Tumors *(1.0 – 2.9cm LD)*	 Middle
Intermediate Tumors *(3.0-5.9cm LD)*	 Distal Proximal
Large Tumors *(6.0cm and larger LD)*	 Distal Middle Proximal

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Precautions

- **Infectivologist** should be involved for eventual management of toxicity or rashes related to latent virus reactivation (including Varicella, herpes zoster and Herpes Simplex)
- **Dedicated room for preparation and storage** Pexa-Vec is a Biologic Agent (**Biosafety level classification- 2 / BSL-2**)
  - Place Biohazard sign in designated area
  - Limit access to designated area (e.g. prep hood) during preparation
- **Equipment**
  - Wear personal protective equipment (PPE): **gloves, goggles, mask, gown**
  - Prepare in a Class IIA Biological Safety Cabinet (e.g. a standard **chemotherapy prep hood** with properly maintained **HEPA filter**)
- **Hood Cleaning & Decontamination**
  - Prior to Pexa-Vec prep: Follow institutional SOP after chemotherapy preparation
  - After Pexa-Vec prep: Wipe down inside of hood with **≥ 60% alcohol**, OR bleach solution followed by ≥ 60% alcohol, OR institution recommended agent

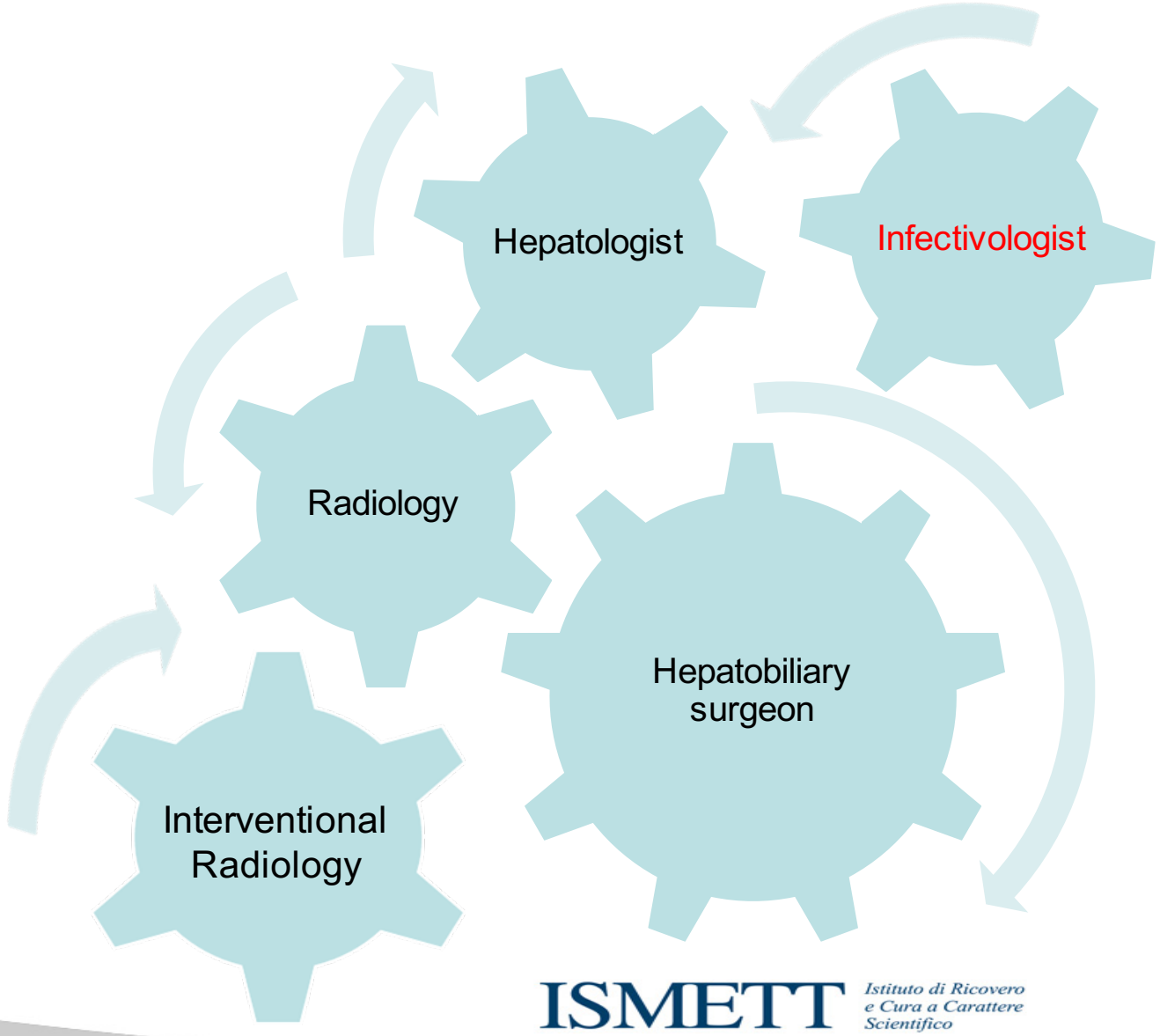
CONCLUSIONS

- Despite encouraging preclinical results, only Sorafenib and Regorafenib provide acceptable survival benefit in advanced HCC

- New approaches with TARE seems to be promising

- Studying gene expression and caracterizing the molecular profile of the HCC are the keys for a targeted and «tailored» therapy based on the use of novel tareted molecular drugs

Management of Hepatocellular Carcinoma requires a multidisciplinary approach



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THANK YOU

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