



# **Carbon Ion versus Conventional Photon Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer**

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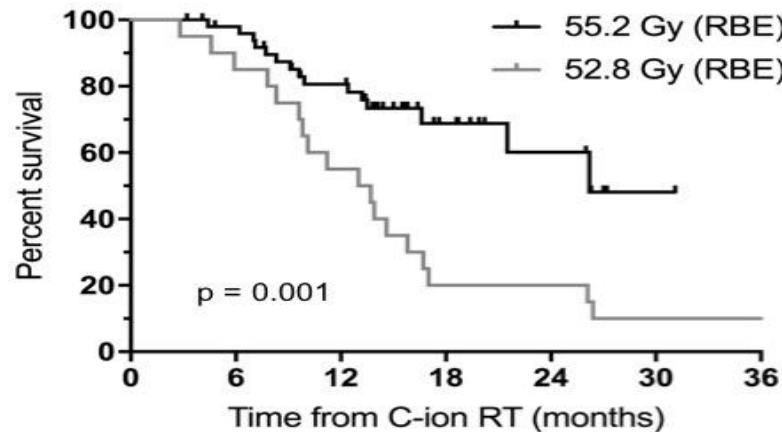
UT Southwestern Medical Center, Dallas, TEXAS, USA

Lecture for HITRIplus Course, MedAustron, Austria

# MOTIVATION

# Survival

- Our Japanese C12 colleagues showed in a **non-randomized fashion** that there is hope for pancreatic cancer patients
- 55.2 GyE with CIRT, 2-year OS ~60% (while conventional methods barely pass 2-year OS ~20%)

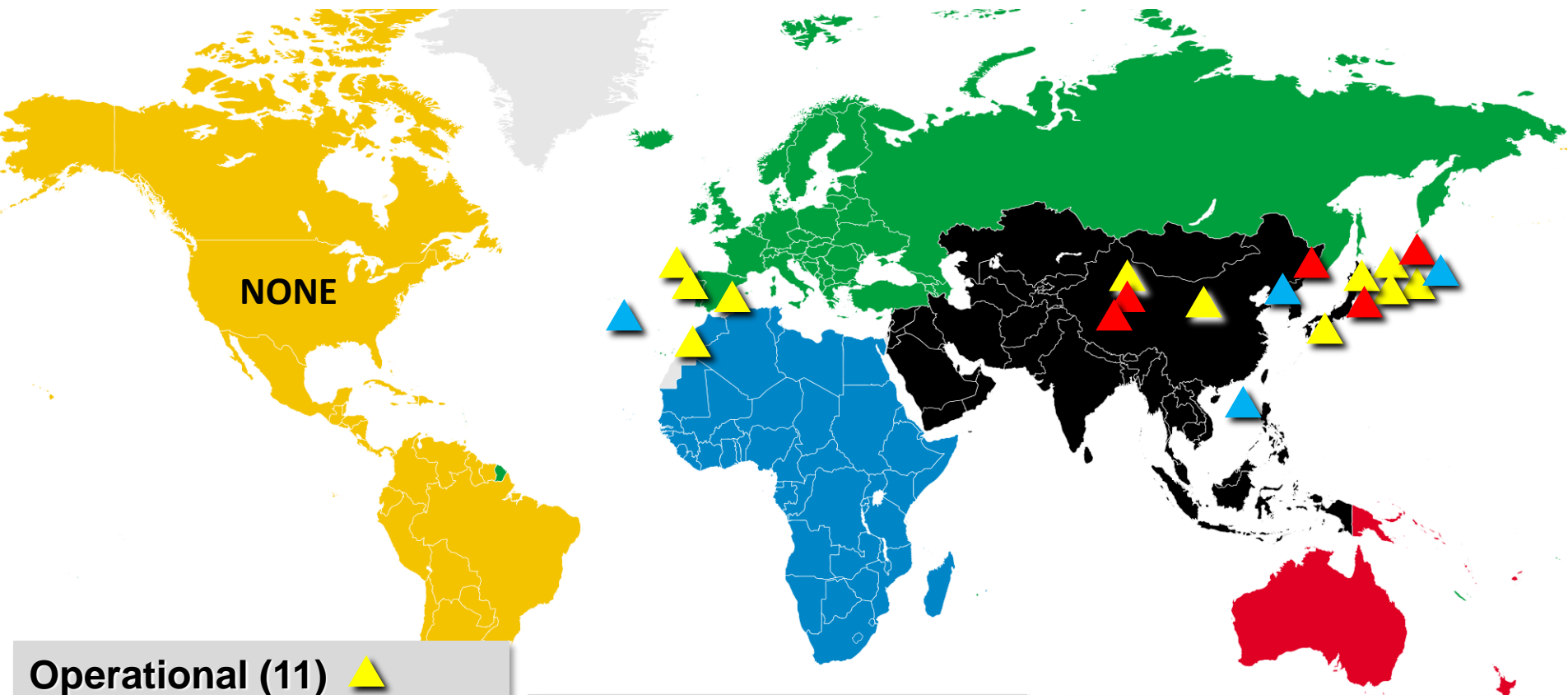


Number of patients at risk

55.2 Gy (RBE)	52	48	36	14	8	2	
52.8 Gy (RBE)	20	18	12	5	5	3	3

- Even the largest **skeptic** would accept **RANDOMIZED** results

# World Wide Heavy Ion Therapy Centers



## Operational (11) ▲

- Austria MedAustron, Wiener Neustadt
- China Fudan Univ CC, Shanghai
- China IMP-CAS, Lanzhou
- Germany HIT, Heidelberg
- Germany MIT, Marburg
- Italy CNAO, Pavia
- Japan HIMAC, Chiba
- Japan HIBMC, Hyogo
- Japan GHMC, Gunma
- Japan SAGA-HIMAT, Tosu
- Japan i-ROCK, Kanagawa

## Under Construction (5) ▲

- China HITFiL, Lanzhou
- China Another Center, Lanzhou
- Japan, Osaka
- Japan, Yamagata
- South Korea KHIMA, Busan

## Advanced Planning (5) ▲

- France ETOILE, Lyon
- Japan Okinawa
- Taiwan, CMU
- Taiwan: Taichung Univ.
- South Korea, Yonsei University

**Total : 21**

# Randomization

We always faced the “C12 is better, so WHY?” 😊

Arm1



Arm2 😊



# Lots Of Diplomacy



# But Ultimately this decided the faith of CIPHER



# And we had a handshake re CIPHER



**C12 system manufacturer supported Phase III randomized International Clinical trial comparing CIRT with IMRT was agreed upon to generate**



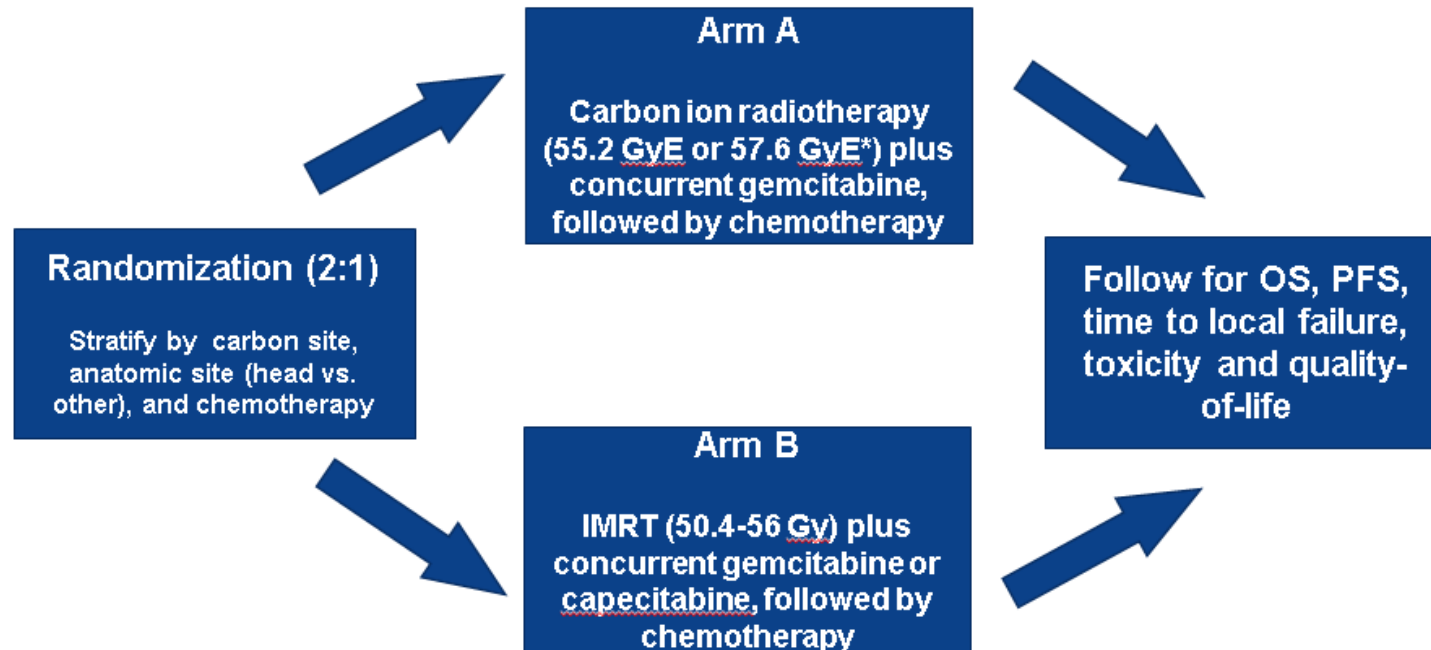
# CIPHER – what is it?

- **Phase III randomized trial comparing carbon ion RT (55.2 GyE in 12 fractions) with IMRT (50.4-56 Gy in 28 fractions), both with concurrent chemotherapy, with 4 cycles of systemic chemotherapy**
- **Patients receive 4 cycles of gemcitabine/nab-paclitaxel or FOLFIRINOX, either 2 cycles before and 2 cycles after CRT, or 4 cycles after CRT**
- **Carbon ion RT is delivered with concurrent gemcitabine, IMRT with gemcitabine or capecitabine**

# CIPHER

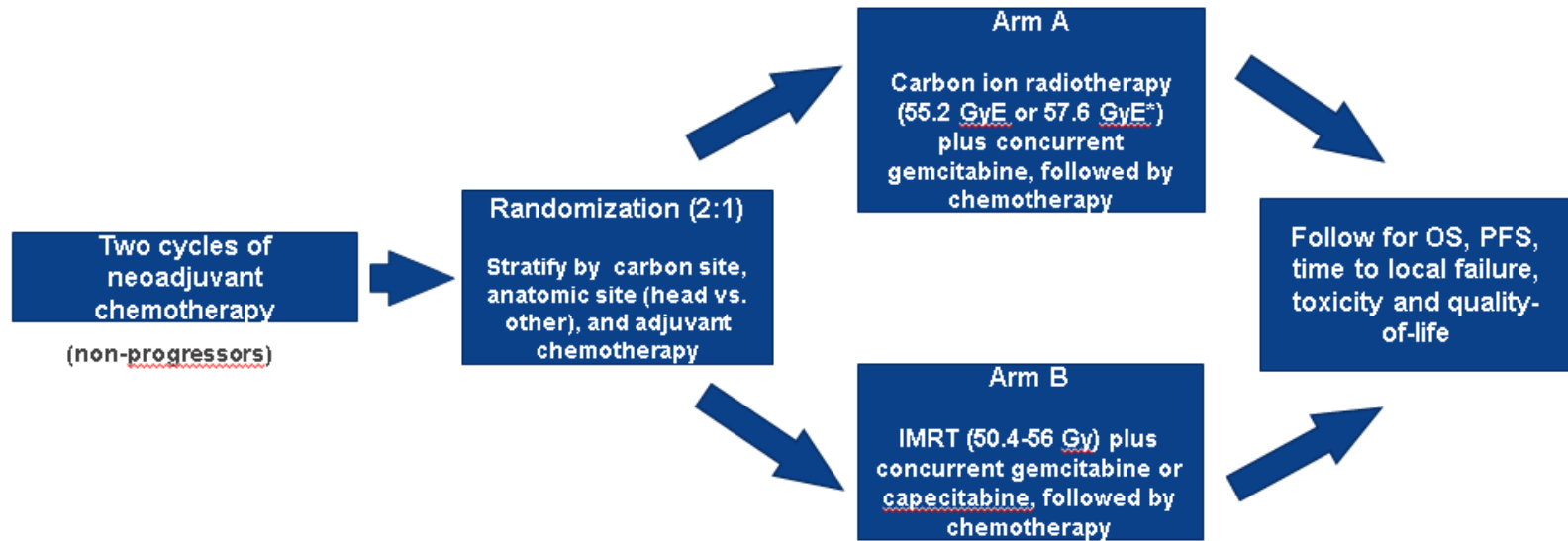
- **Eligibility**
  - **Locally advanced, unresectable pancreatic cancer**
  - **Distance between tumor and viscera  $\geq 3$  mm**
  - **$\leq 100$  kg**
  - **No metal stents**
  - **Ability to travel to foreign country within 2 weeks**
  - **At most 2 cycles of chemotherapy may be delivered at an outside institution**
  - **If neoadjuvant chemotherapy delivered, non-progression after cycle 2**

# Schema (Option A)



- Adjuvant chemotherapy: 4 cycles of gemcitabine/nab-paclitaxel or FOLFIRINOX
  - Gemcitabine alone if these regimens are unavailable
- \* = 57.6 GyE in Europe

# Schema (Option B)



- **Chemotherapy: Total of 4 cycles of gemcitabine/nab-paclitaxel or FOLFIRINOX**
  - Gemcitabine alone if these regimens are unavailable
- \* = 57.6 GyE in Europe

# Participating Patients and Centers

- **Patient recruitment will occur at NIRS/QST Japan, Gunma Japan, CNAO Italy and IEO Italy, plus UTSW USAQ, with more in discussion**
- **International traveling patients will receive CIRT at NIRS/QST**
  - **Patients randomized to CIRT will be flown to Japan for treatment, with adjuvant treatment and follow-up at home**
- **Patients randomized to IMRT will receive entire treatment at home**
- **Japanese patients will receive CIRT at NIRS or Gunma**
- **Italian patients will receive CIRT at CNAO**

# Endpoints

- **Overall survival (OS)**
  - With a total of 93 patients to complete (62 CIRT, 31 IMRT), there will be 80% power to detect a difference in 2 year OS between 22% to 48% at a 0.05 significance level
  - (need to enroll 110 subjects to account for early dropouts)
- **Progress Free Survival**
- **Cumulative incidences of Local/Regional Recurrence and Distant Failure**
- **Quality-of-life (FACT-Hep, EQ-5D)**
- **Rate of grade 3-4 non-hematologic toxicity**

# Quality Assurance

- **All contours will be reviewed by NIRS physicians prior to planning (CIRT or IMRT), with NIRS contours reviewed by CNAO physicians**
- **All CIRT plans will be reviewed by NIRS physicians prior to treatment, with NIRS plans reviewed by CNAO physicians**
- **All IMRT plans will be reviewed by UTSW physicians prior to treatment**

# Credentialing

- **All sites undergo rigorous credentialing procedure before enrollment is enabled**
- **Photon sites**
  - **UTSW partnered with IROC Houston Quality Assurance Center**
  - **All sites get IGRT, IMRT credentialed by IROC**
  - **All sites will participate in annual dosimetric output audits performed by IROC**
  - **All sites demonstrate CIPHER specific electronic data transfer capabilities**
- **Carbon sites – RTOG style credentialing**
  - **All sites get IGRT credentialed by UTSW**
  - **All sites demonstrate planning, delivery and patient QA capabilities to meet CIPHER constraints on “CIPHER QA test image set”**
  - **UTSW performs annual dosimetric output check at all sites with US NIST traceable equipment**
  - **All sites demonstrated protocol knowledge assessment**
  - **All sites demonstrate CIPHER specific electronic data transfer capabilities**
  - **Performed biological dose cross calibrations between sites**



# Easy to say, hard to do! **List of challenges:**

- Funding
- Credentialing of sites
- IRB
- C12 Biological Modeling in 3 continents
- Randomization
- Eligibility review
- Travel to C12 center
- Lodging
- Insurance
- Information Transfer and Storage
- Contours review
- Dose review
- Biology samples for science
- Annual dose output constancy check of C12 & Xray machines





**We opened the trial! We activated sites and we were recruiting subjects!!!!**

# Incredible International Team

- **UTSW (USA):**
  - Hak Choy MD, David Sher MD, Robert Timmerman MD, Steve Jiang PhD, Mike Story PhD, Kajal Desai, Arnold Pompos PhD
- **NIRS/QST (Japan):**
  - Dr. Hirano MD, Hirohiko Tsujii MD PhD, Dr. Kamada MD PhD, Dr. Shigeru Yamada MD PhD, Dr. Matsufuji PhD, Naoya Saotome PhD, Mizuno PhD, Dr. Noda PhD, Takuji Furukawa PhD
- **Gunma (Japan):**
  - Dr. Tatsuya Ohno MD PhD
- **CNAO (Italy):**
  - Sandro Rossi, Piero Fossati MD PhD, Mario Ciocca PhD, Silvia Molinelli PhD, Roberto Orecchia MD PhD
- **IEO (Italy):**
  - Veronica Del'Aqua MD, Roberto Orecchia MD PhD

# We overcome all challenges!!

- ✓ **Funding:** Toshiba fully sponsored all expenditures!
- ✓ **Credentialing of sites:** Finished and Credentialing letters issued.
- ✓ **IRB:** Approved on 3 continents
- ✓ **C12 Biological Modeling in 3 continents:** MKM vs LEM biological dose factor established. Raysearch TPS commissioned for recalcs.
- ✓ **Randomization:** all sites agreed UTSW will randomize. No headache for C12 sites.
- ✓ **Eligibility review:** fast communication between Japan, Italy, USA developed and thresholds agreed upon
- ✓ **Travel to C12 center:** Medical travel agency contracted. Pickup patient at Tokyo Airport and accompany till drop off at Tokyo airport
- ✓ **Lodging:** Trial funded ALL expenditures of patient and one accompanying person. Apartment rented in the vicinity of NIRS/QST for 4 weeks.
- ✓ **Insurance:** Travel agent for travel. Trial resources inc C12 site for unexpected complications and hospitalization in Chiba.
- ✓ **Information Transfer and Storage:** Health Protection Information Act compliant transfer and RedCapt storage developed
- ✓ **Contours review:** Intercontinental timelines set and agreed upon
- ✓ **Dose review:** Intercontinental timelines set and agreed upon
- ✓ **Biology samples for science:** Trial covers blood collection, storage and shipment
- ✓ **Annual Irradiation output constancy check:** Performed with same electrometer, same ion chamber calibrated with USA's National Institute of Standards and Technology calibration factors

**We Activated Participating sites and we opened the trial for recruitment and were recruiting subjects**





# Coronavirus travel bans



**Killed (perhaps hibernated only?) CIPHER**



# SUMMARY

- **World's first Phase 3, Randomized, International Clinical trial comparing CIRT with IMRT was generated and was opened for recruitment**
- **COVID-19 killed the trial**
- **Times have changed, perhaps it was only hibernated and can be resurrected 😊**