



KORTUC

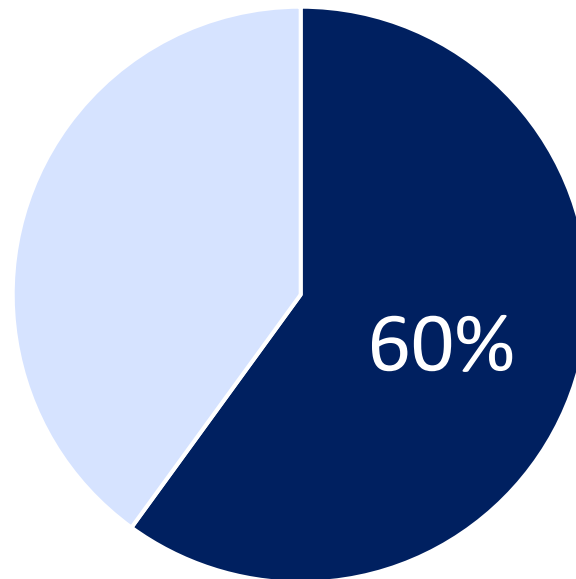
*Helping cancer patients live longer
by increasing the effectiveness of radiotherapy*

Kazuyuki Matsuda, CEO
in Tokyo Japan

The challenge of radiotherapy; limited efficacy

- Radiotherapy (RT) is established cancer treatment and 60% of cancer patients receive RT
- Although it is widely used, RT is positioned as adjuvant treatments for many indications because it does not work well for large tumors

% of patients receive RT



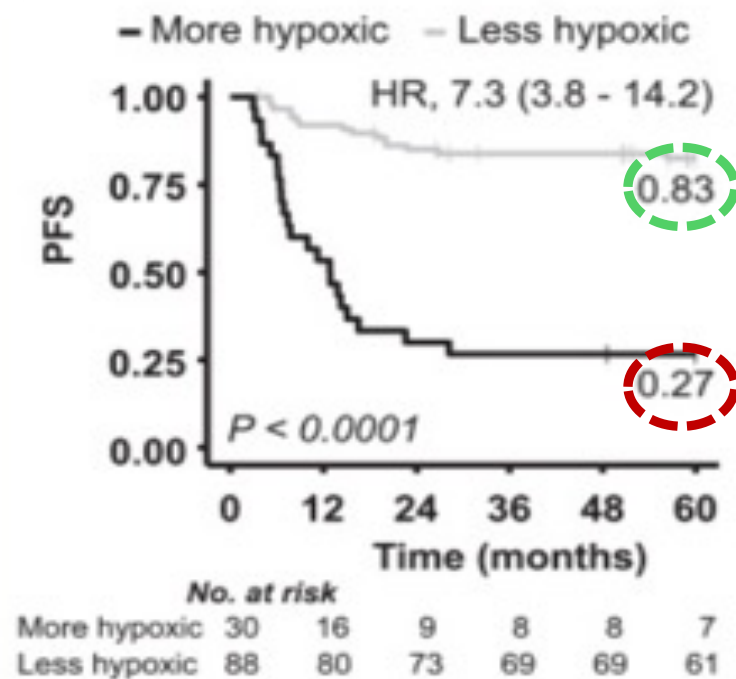
Total new cancer patients: 18 million

It has been known that Hypoxia is the fundamental issue

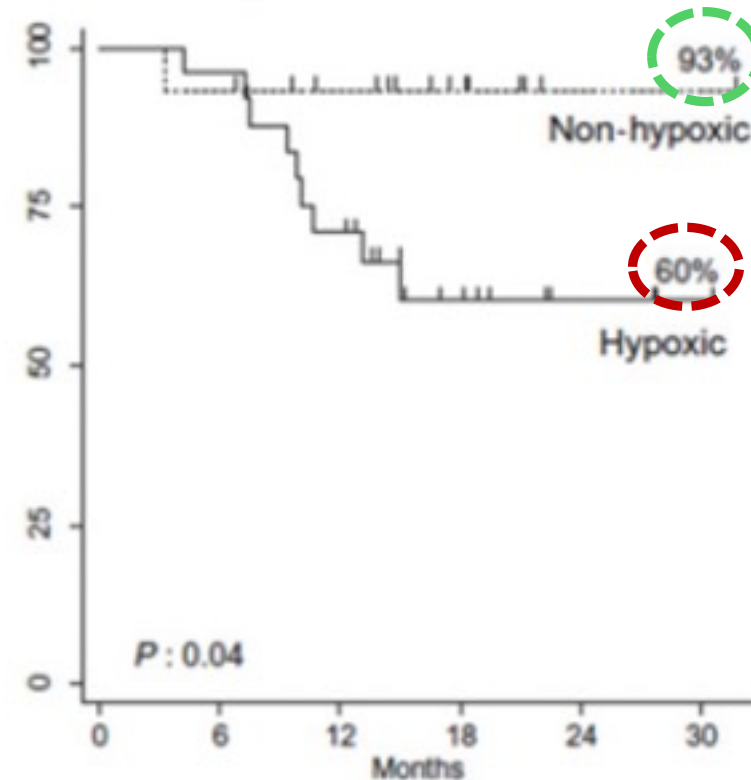
- Hypoxia (reduced oxygen level) in tumor cell creating resistance to RT
- Large difference among irradiated of Progression Free Survival depending on Hypoxia

Progression Free Survival

Cervical Cancer ¹



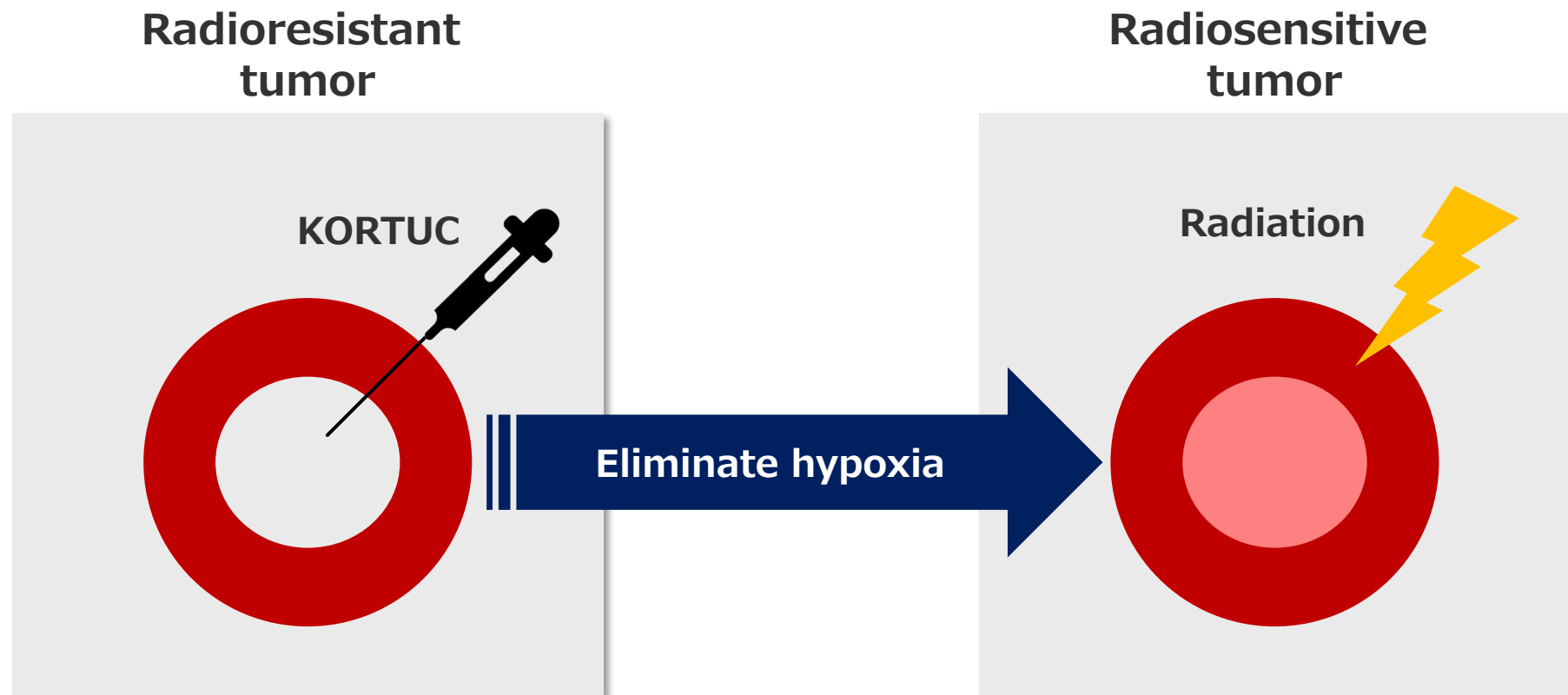
Head and Neck Cancer ²



KORTUC

KORTUC changes tumor radioresistant to radiosensitive

- KORTUC offers a fundamental solution to hypoxia
- KORTUC is comprised of Hydrogen peroxide solution and sodium hyaluronate directly injected into the tumor



Background story of KORTUC

Dr Ogawa, a professor at local small university in Japan with limited financial resources found the most basic and simple solution



**Dr. Yasuhiro Ogawa,
Inventor of KORTUC**



**Dr. John Yarnold,
Emeritus Professor
at The Institute of Cancer Research,
The Royal Marsden Hospital in the UK**

Proprietary patented prefilled injection device

- Offers user-friendly onsite operation, allowing to mix hydrogen peroxide and sodium hyaluronate with specific precise ratio
- Protected by usage patents and product patents

KORTUC Kit



Mechanism of KORTUC

Please see Video

<https://vimeo.com/574688871>

To overcome this challenge, multiple approaches are taken by famous faces

- Physical improvements
 - maximizing dose/ escalating accuracy



- Biological improvements
 - combination with targeted agents (irradiating nearby the cancer cell)

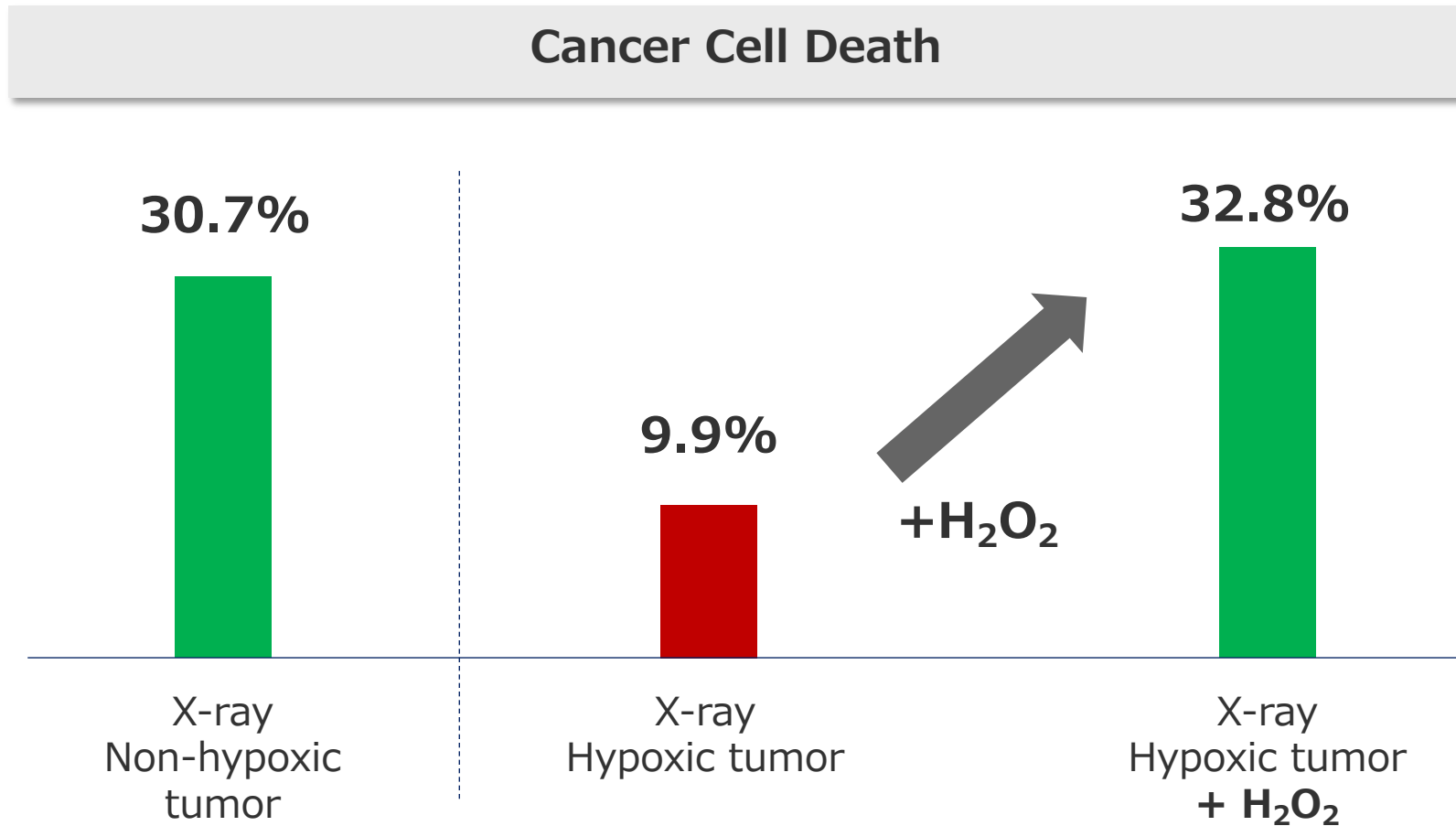


- yielding high energy/ managing typical RT adverse events and several start-up companies are backed by top tier VC investors



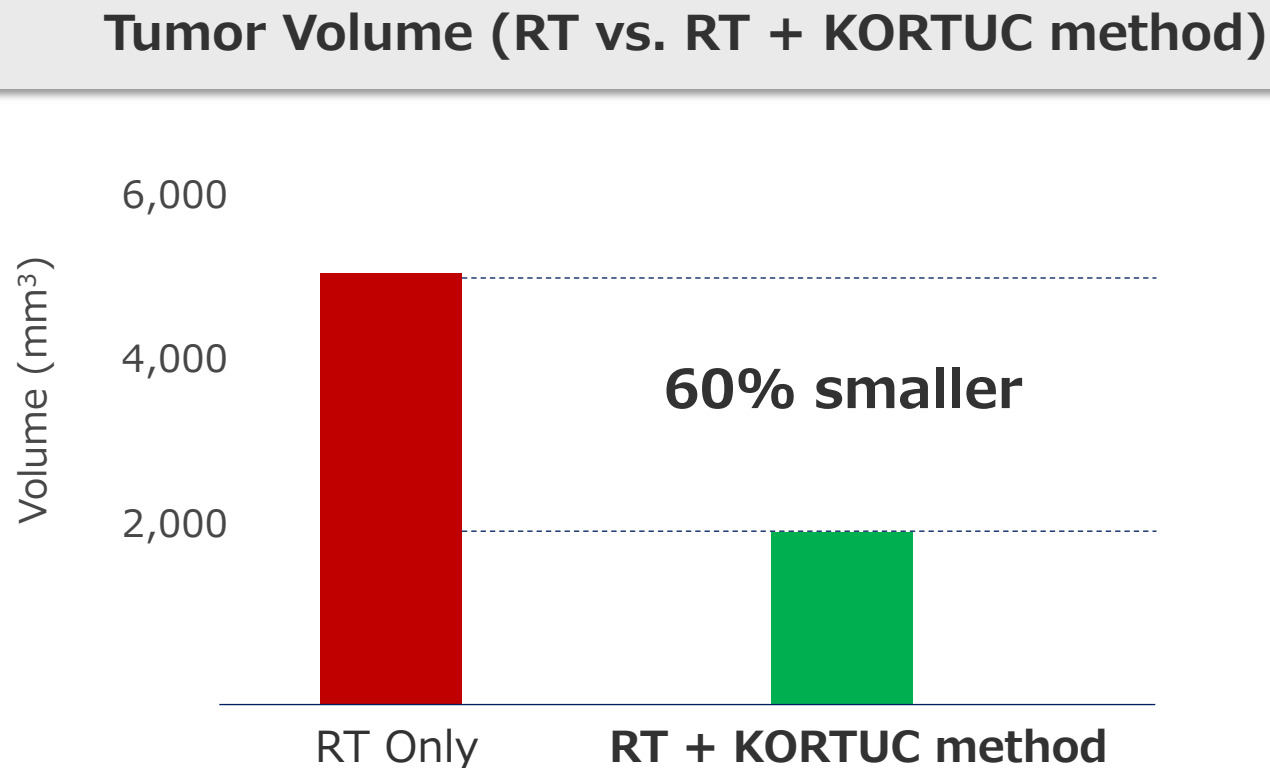
In vitro study: Significant increase in RT effect

H₂O₂ increased RT effect 3x, better than non-hypoxic tumor



In the animal model: Synergetic effect with RT

Tumor size of RT + KORTUC method was 60% smaller than the size of RT Only after 60 days from single RT shot



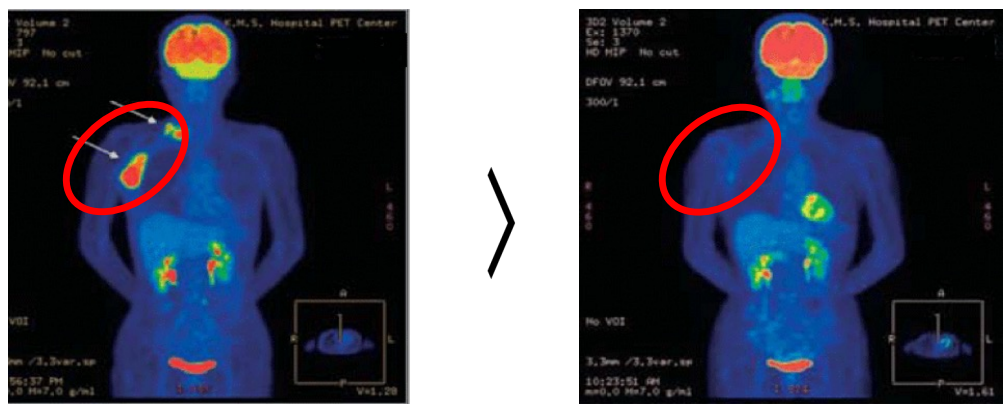
60 days after single treatment
(mouse with squamous epithelium cancer cell line)

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Records of many effective cases in clinical sites

- Over 1,000 patients were treated by RT + KORTUC method as Investigator initiated clinical research in Japan for various solid cancers
- No safety concerns have been reported and showed meaningful efficacy

Breast cancer lymph node metastasis



Report	2017a	2016	2010	2011	2015-16	2010	2017b
Stage	4	Local-recurrent	2A-3C	1A-2A	1A-2A	1A	1A
RT dose (Gy)	57-71	57-67	57	71	71	71	66
cCR%*	71% (5/7)	79% (19/24)	100% (17/17)	100% (10/10)	99% (71/72)	100% (14/14)	100% (15/15)

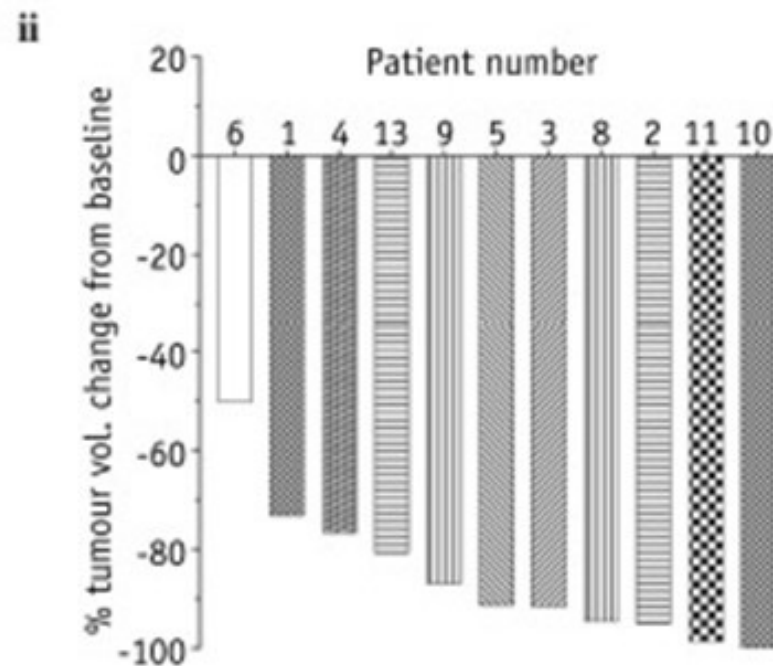
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Source: 8 publications for Breast Cancer (Ogawa 2015, Aoyama 2017 etc.) * cCR% clinical Complete Response rate

Completed Phase 1 study for breast cancer in UK

- **Demonstrated excellent safety** in locally advanced/recurrent Breast Cancer
- **Most patients showed > 80% volume reduction**
- Results were published on Red Journal* in 2020

% Tumor volume reduction in 12 months

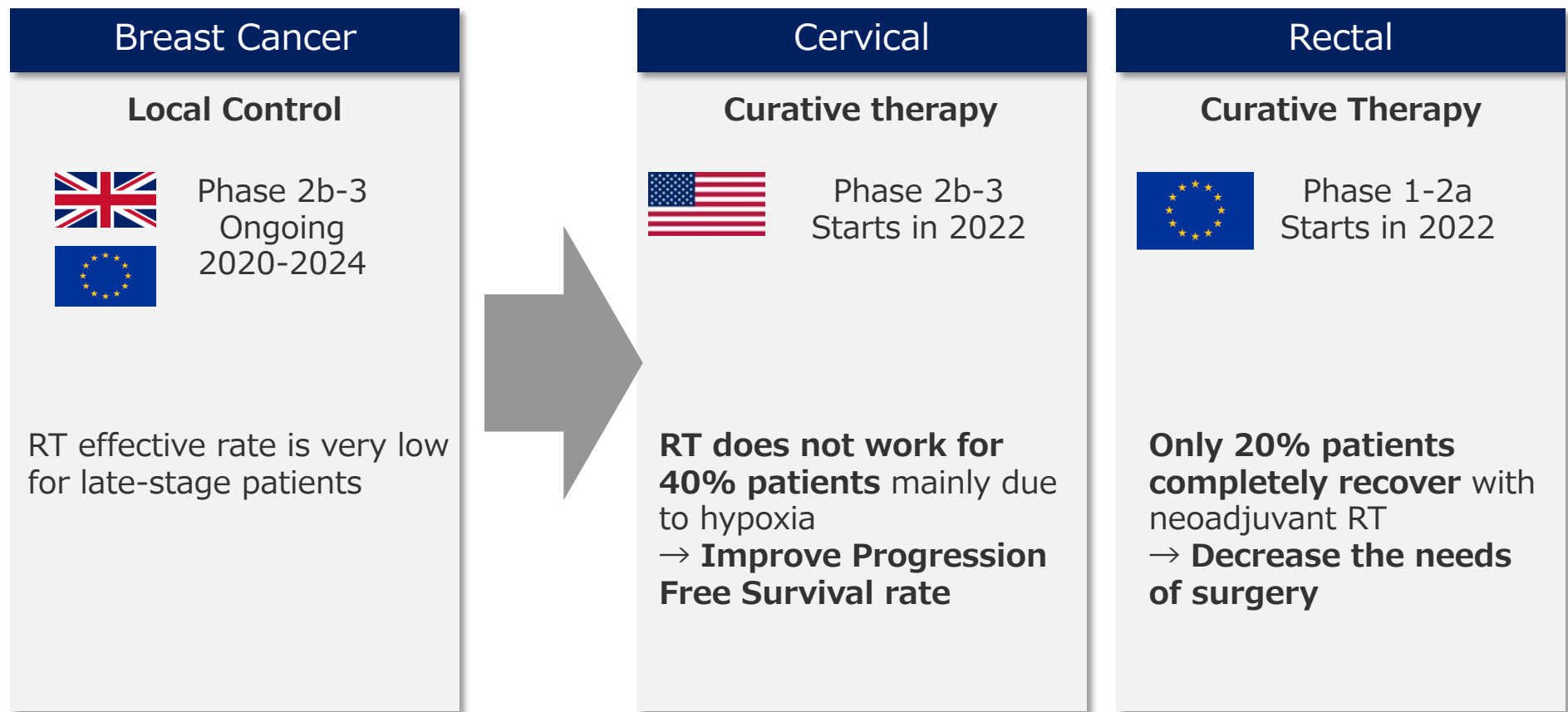


Open label study, n=12

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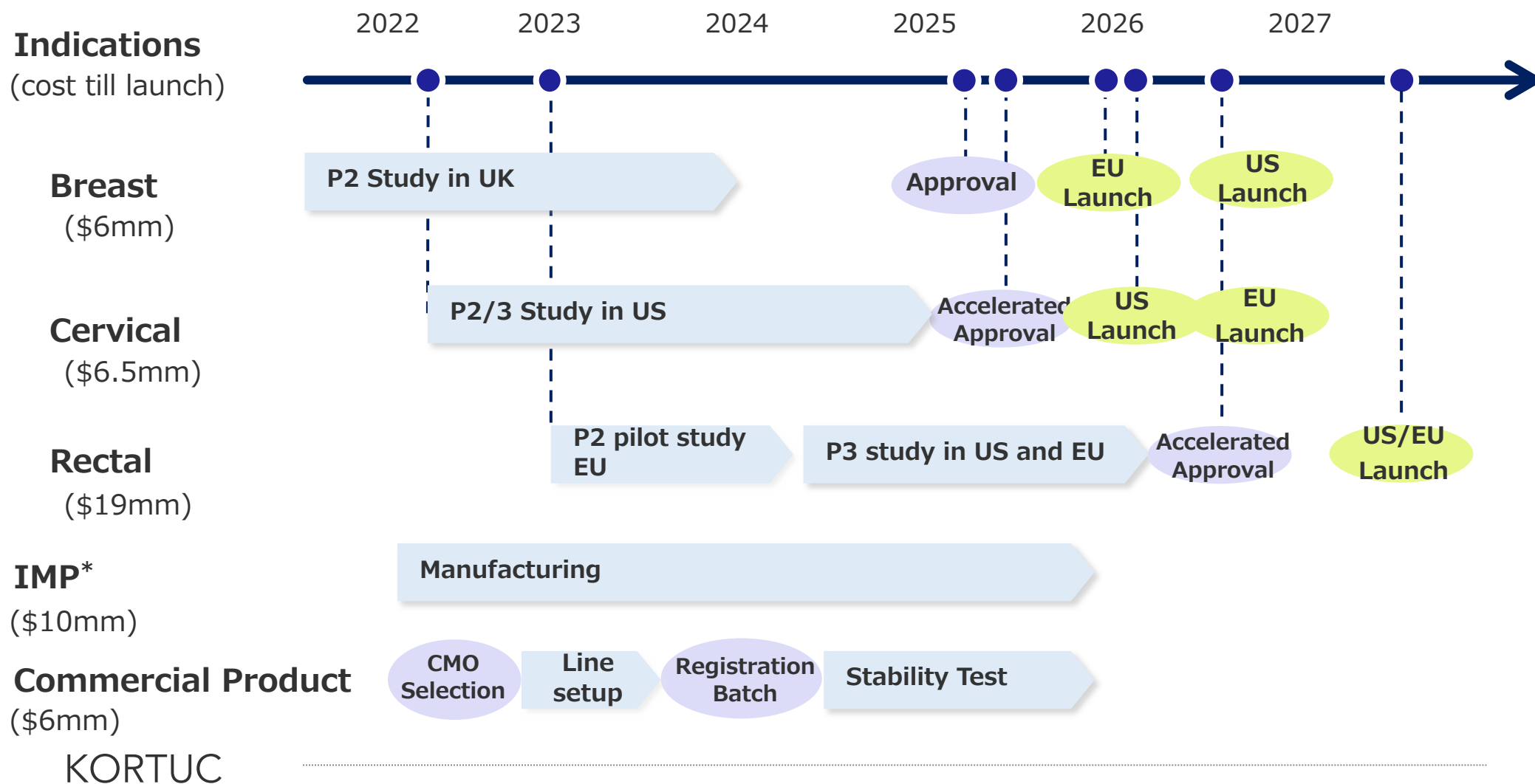
Clinical Development Strategy

Pivotal studies of Breast Cancer is ongoing and Cervical and Rectal cancers will start in 2022



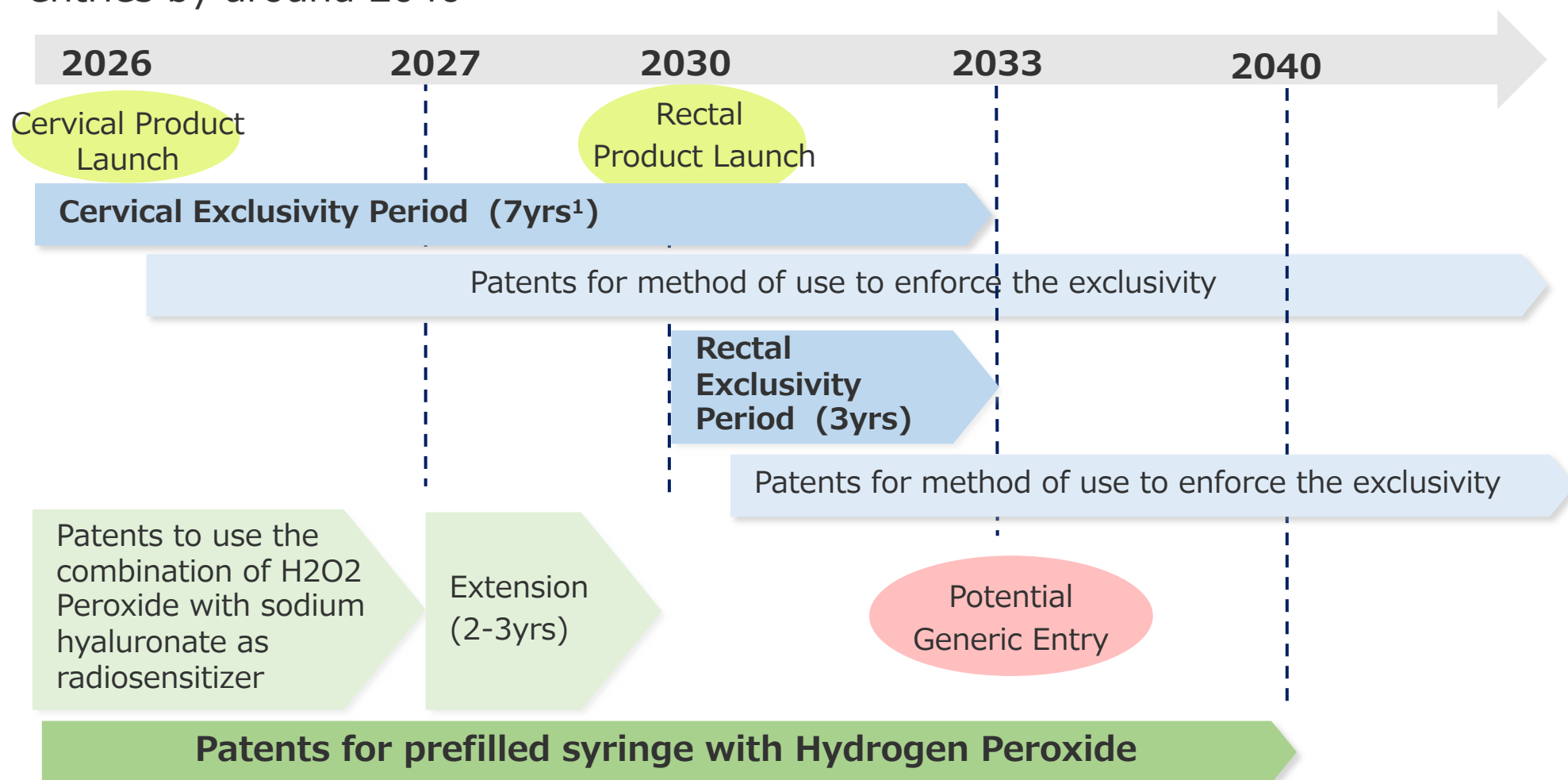
Future Milestone

Plan to launch in 2026 for Cervical cancer in the US then in EU and Breast Cancer in the US and the EU



Product Exclusivity (US Case)

- Exclusivity will be protected by FDA exclusive period by 2033
- Even after that, product patents for easy administration can be a hurdle for generic entries by around 2040



KORTUC

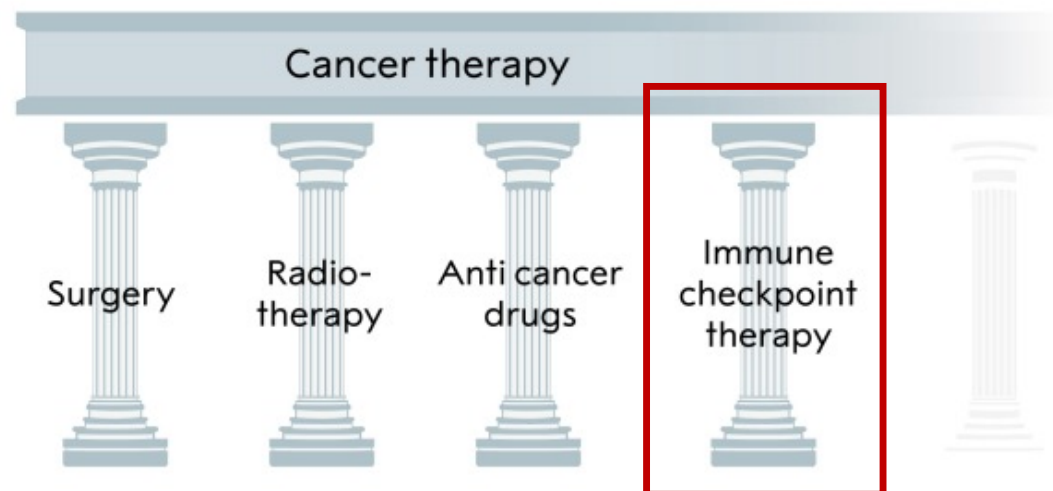
*1 Indication for cervical cancer is expected to be an orphan drug

Further Potential with Immunotherapy/RT

- As the fourth pillar of Cancer treatment, immunotherapy is projected to expand to about USD 130 billion globally by 2026

HOWEVER,

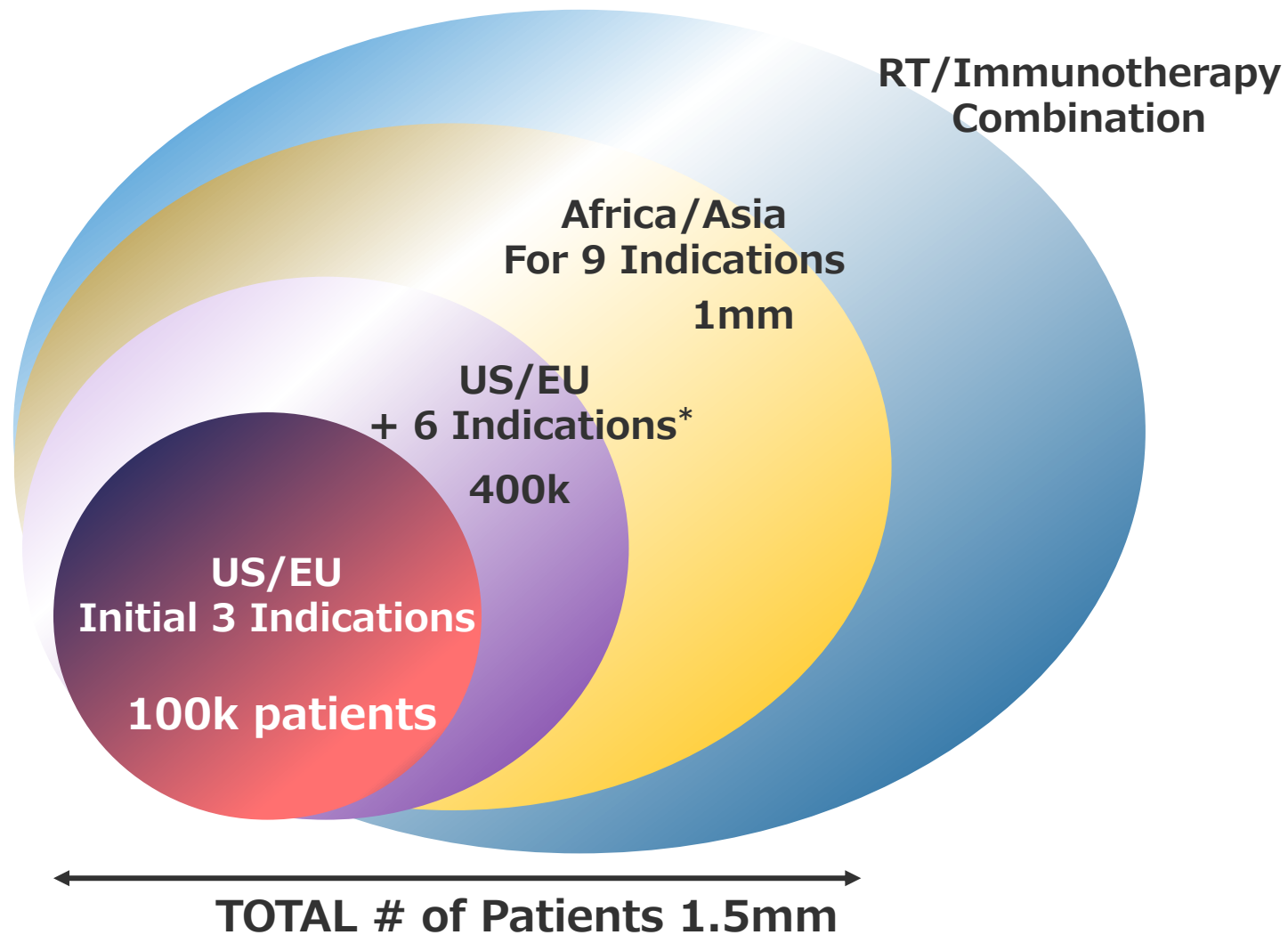
- **Only 20-40% of patients respond to immunotherapy**
- RT is expected to improve efficacy of cancer immunotherapy
- KORTUC could **further enhance efficacy of immunotherapy with RT**
- The company has initiated a pre-clinical animal study and expected to announce the result in 2022



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Staged approach for the large addressable markets

KORTUC can potentially treat as many as 1.5m+ cancer patients globally



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Potential competitor

KORTUC directly and safely resolves the fundamental problems of RT

	KORTUC	Nanobiotix
Product	KORTUC Kit (Hydrogen peroxide & Hyaluronic acid)	Hensify (nanoparticles, hafnium oxide)
Mode of Action	Resolves underlying issues, hypoxia and excessive antioxidantase through hydroxy radical	Physically activates RT (yields high energy of ionizing radiation)
Safety	P1 exempt (> 1,000 use cases)	P1 required (300 use cases)
Main Indications	Cervical Cancer, Rectal Cancer, Breast Cancer	Head and Neck Cancer, Soft Tissue Sarcoma

Efficient marketing due to the market characteristics

Small Doctor's Community



- Treatment decision maker is Radiation Oncologists (RO)
- The number of RO is approximately only 4,000 in the US and 5,000 in EU

High Patients Concentration



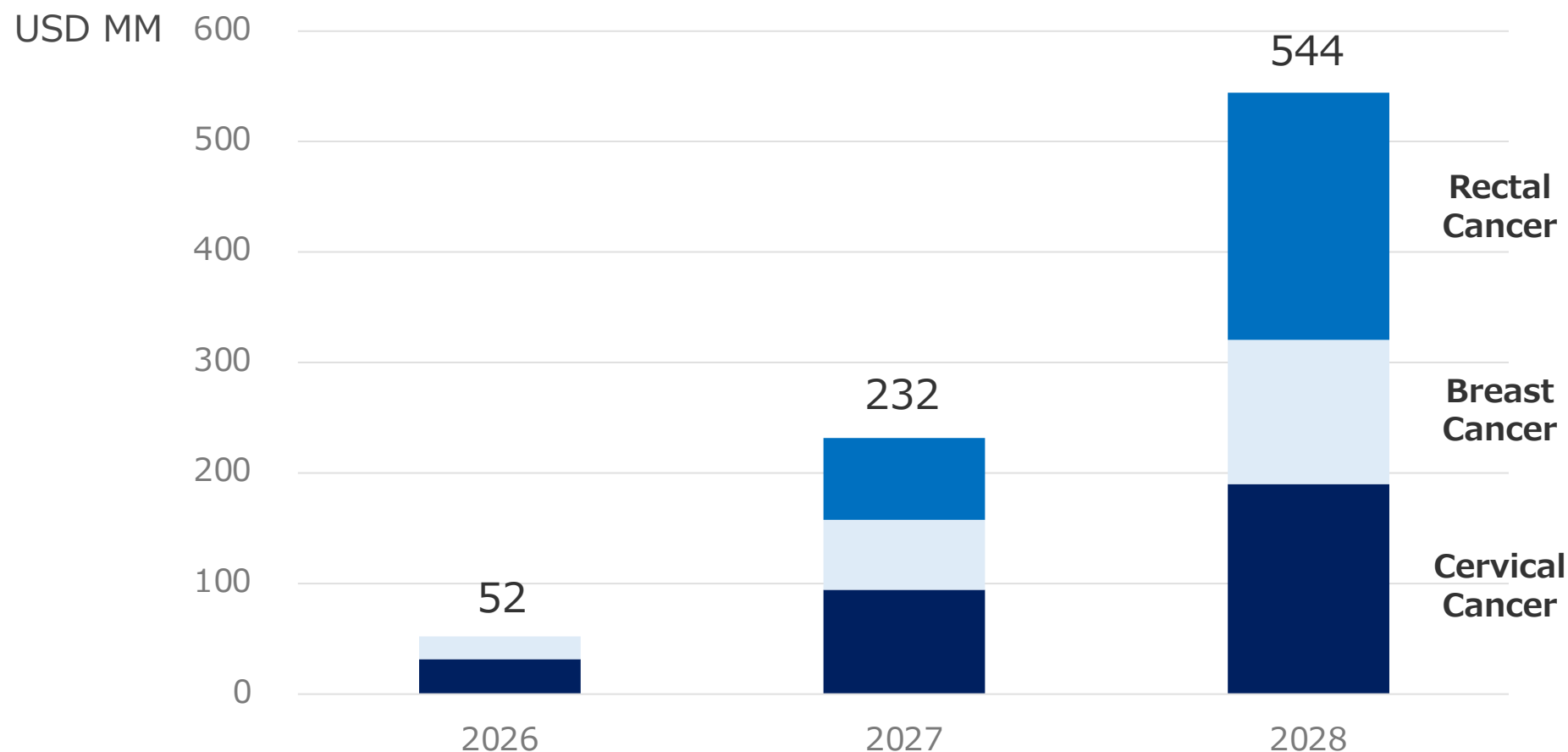
- All targeted cancer patients concentrates on large hospitals
- For example, **covering 10% of ROs enables to reach about 50%** of all Breast Cancer patients

Less Competitive Market

- Only few pharmaceutical players focus on ROs as their target customer
- No direct substitutes of KORTUC

Sale Projection: 3 Initial indications in the US/EU

In 3 years after the launch, sales is projected to reach over \$500mm based on a competitive price of \$30k per patient



Experienced Team

Management



Kazu Matsuda
Founder, CEO



Clinical Development



Minako Koga
R&D Head



Hiroyuki Suda



Finance



Yukiko Sawa
CFO



Masaya Ishibashi



Shogo Yamashita



Business Development



Kazuhiko Tawara



KORTUC

Scientific Experts

Inventor/Advisor of KORTUC



Dr Yasuhiro Ogawa

Emeritus Professor
Kochi University

Clinical Experts



Bob Kneller MD

Emeritus Professor
University of Tokyo



Michihiko Wada, MD

Professor at Keio University

UK Clinical Trial Leads



Dr John Yarnold

Emeritus Professor at The
Institute of Cancer
Research



Dr Navita Somaiah

Team Leader, Translational Breast Radiobiology
at The Institute of Cancer Research, London
Clinical oncologist at The Royal Marsden
Hospital

Funding Ask

Our ask

- \$60mm Series C (runway to Oct 2024)
 - \$18.5mm raised from AXA Insurance and SBI Investment
- 36 months of runway to proceed with
 - clinical studies for breast and cervical cancers
 - clinical studies of P2 for rectal
 - commercial product development

We have raised

- \$8mm from 2017-2019
 - Nissay Capital
 - Fenox Venture (Pegasus Tech Ventures)
 - Sparx Group
 - JST (Japan Science and Technology Agency) etc.

Thank you!

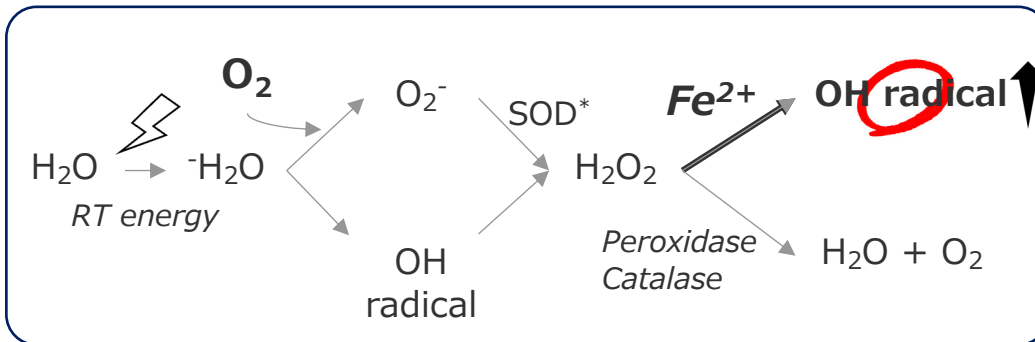
Kazuyuki Matsuda, CEO
kazu.matsuda@kortuc.com

Appendix

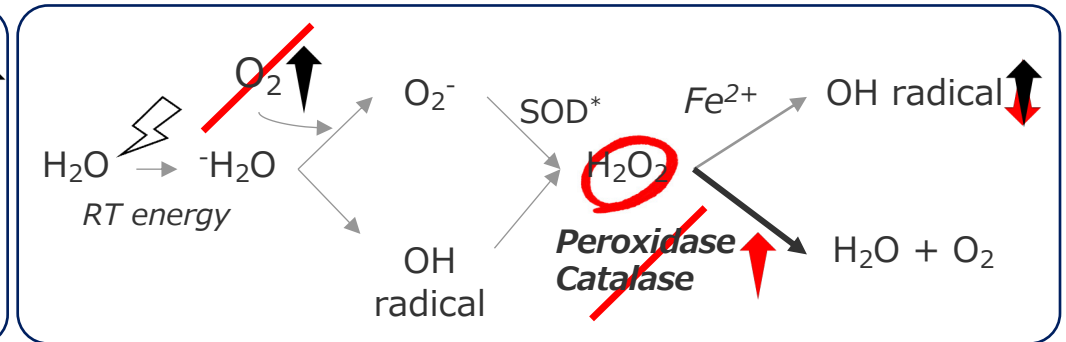
Reasonable approach to produce OH radical

- RT efficacy is mainly driven by OH radical
- To produce OH radical, oxygen and iron ions play the key roles
- In tumor tissues, the lack of oxygen and excessive antioxidant avoids OH radical production
- By KORTUC Kit, hydrogen peroxide is directly provided, and antioxidants are consumed to produce oxygen which leads effective production of OH radical

Normal tissue



Tumor tissue



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Multiple approaches are taken around the heart of the problem

- Through the reaction, multiple approaches are attempting at the intermediate points
- KORTUC tackles the most fundamental, bottleneck point in the flow

To increase radiation

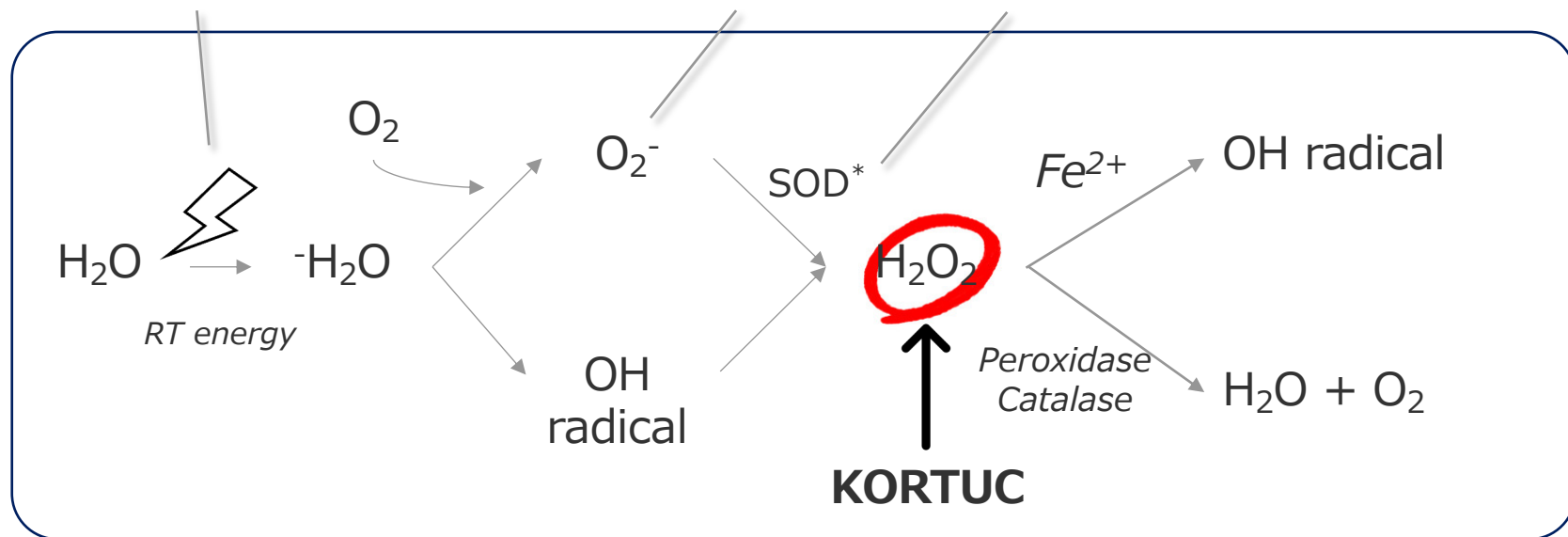
- ✓ New radiation technique
- ✓ New radiosensitizer (Hensify, AguIX)

To increase oxygen

- ✓ Nimorazole (oxygen mimetic)
- ✓ Hyperbaric oxygen
- ✓ Hb transfusion
- ✓ NVX-108

To increase SOD

- ✓ GC4711, SOD mimetics to produce H₂O₂



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*SOD: Super Oxide Dismutase

LIMITED DISTRIBUTION

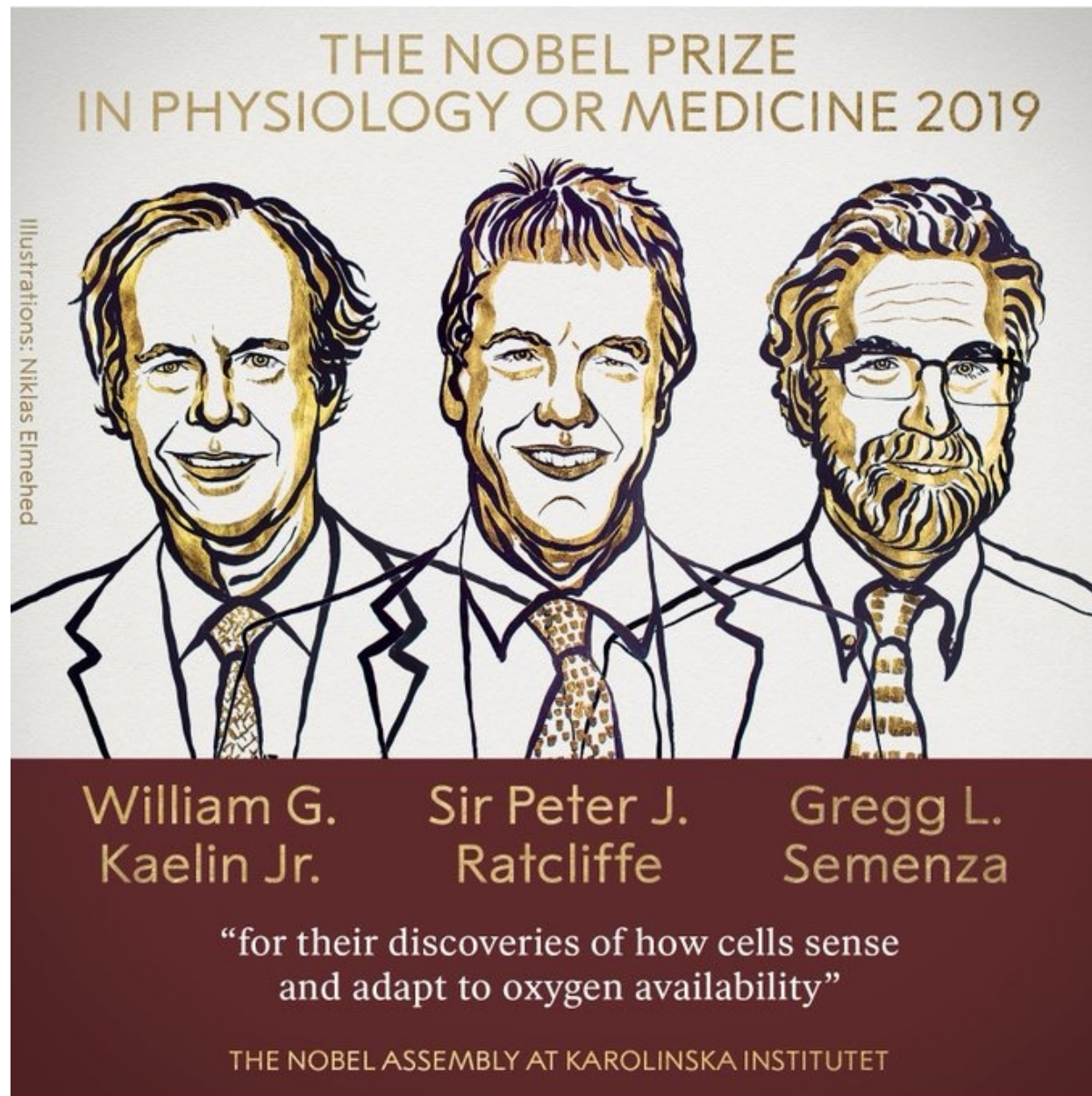
Executive Summary

– a beautiful solution to improve cancer radiotherapy efficacy –

1. KORTUC is the only solution in the world which resolves tumor hypoxia to overcome radio-resistance.
2. KORTUC first targets 100k radiotherapy patients for 3 indications in the US/EU markets, with additional upsides in combination with radiotherapy and **immunotherapy**, additional indications and Asian/African markets.
3. Late Stage Program
 - In the UK, currently a **phase 2/3 registrational study** is ongoing in locally advanced/recurrent breast cancer. (NDA in 2025, Launch in 2026)
 - In the US, meetings with FDA were held in 2020-2021. The IND filing is planned for advanced cervical cancer in 2022.
 - In EU, a phase 2 pilot study in rectal cancer is planned in 2022.
 - In Japan, KORTUC has been **used over 1,000 patients** with various types of solid tumor in clinical researches.
4. **Seasoned management team** with successful track record of building/exiting biotech startups with highly experienced medical collaborators recognized in global oncology arena with leading academic publication track record.

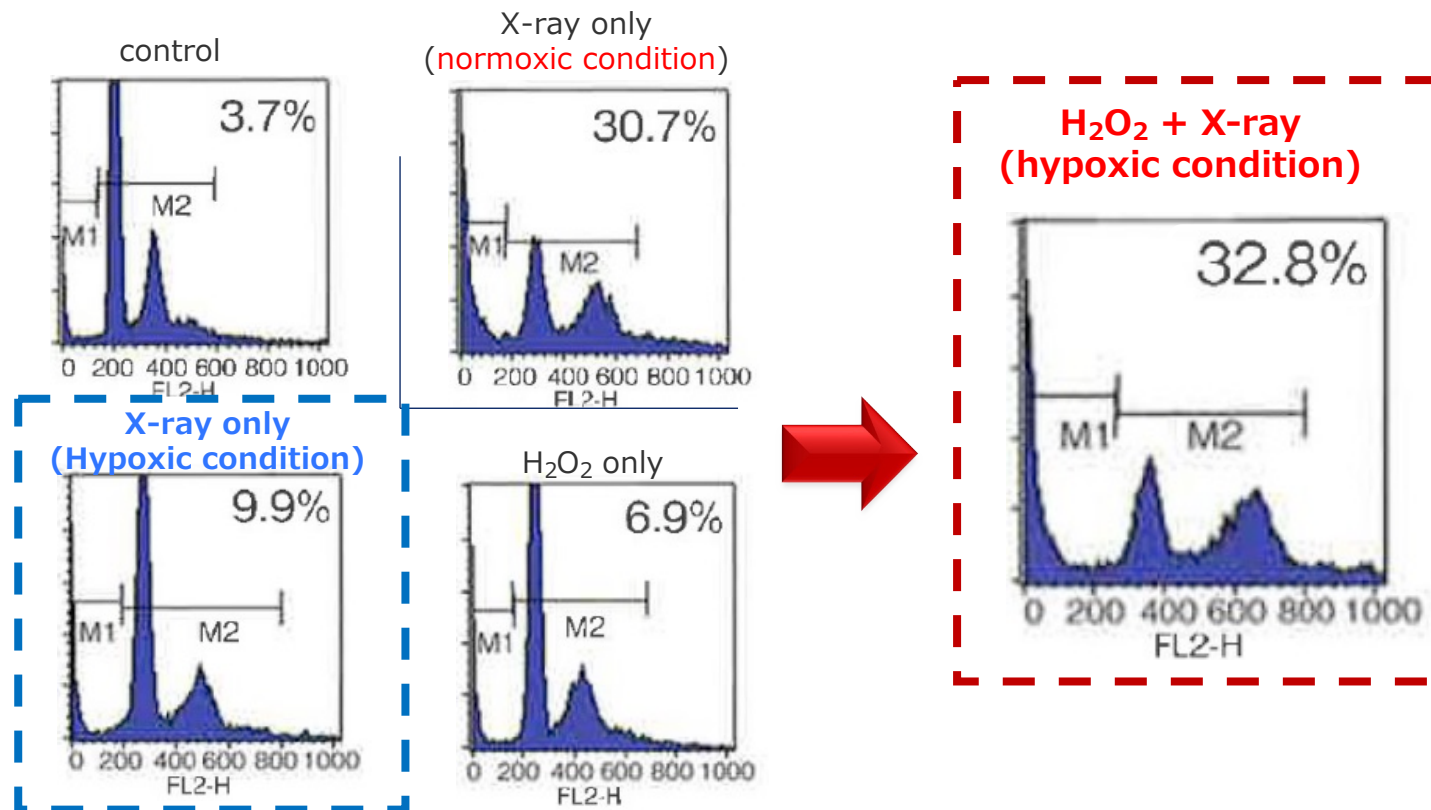
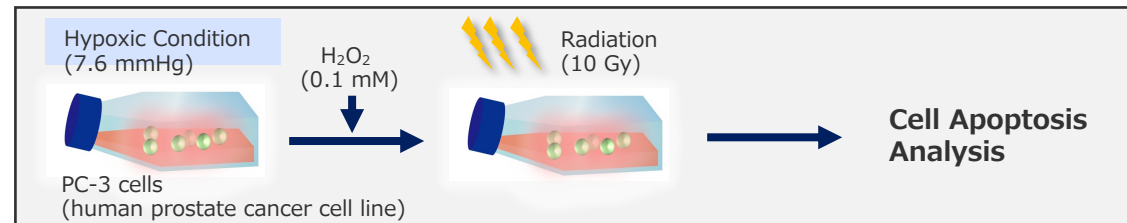
Hypoxia (How cells sense and adapt to oxygen availability)

won the Nobel Prize in 2019



In vitro study, KORTUC showed significant increase in RT effect

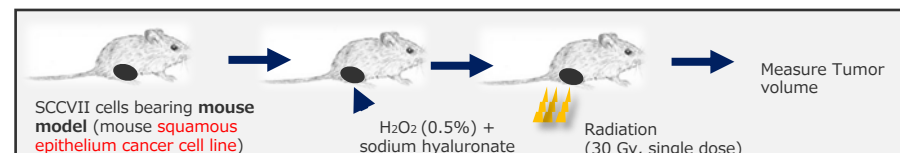
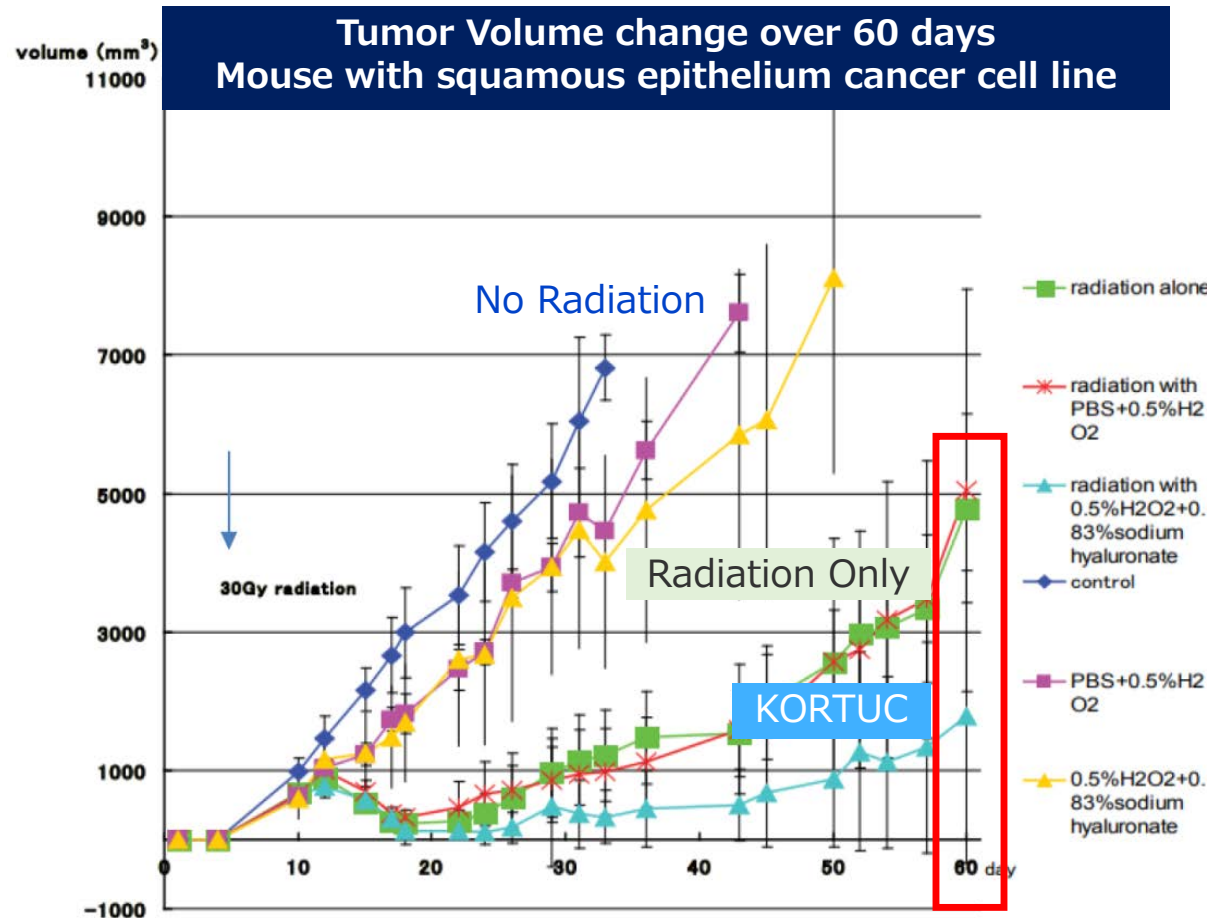
H_2O_2 increases RT effect 3x (9.9% to 32.8%) in hypoxic condition which is same level as RT effect in normoxic condition.



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In the animal model, KORTUC showed synergetic effect with RT

In animal model, with KORTUC, the tumor volume size growth was about 1/3 compared to radiation alone



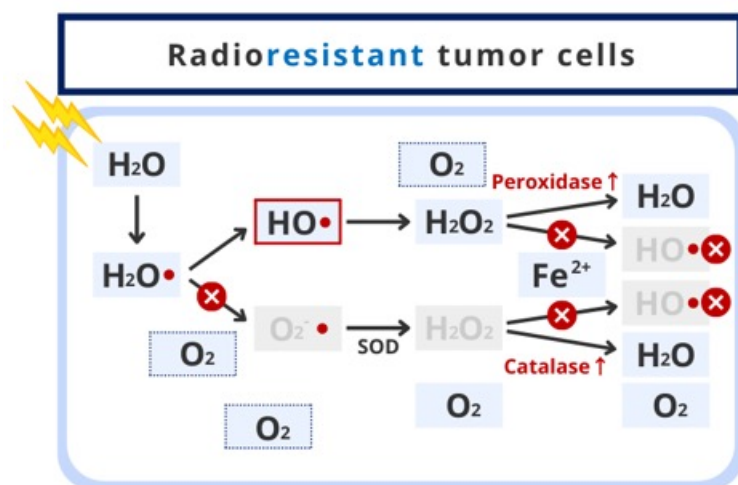
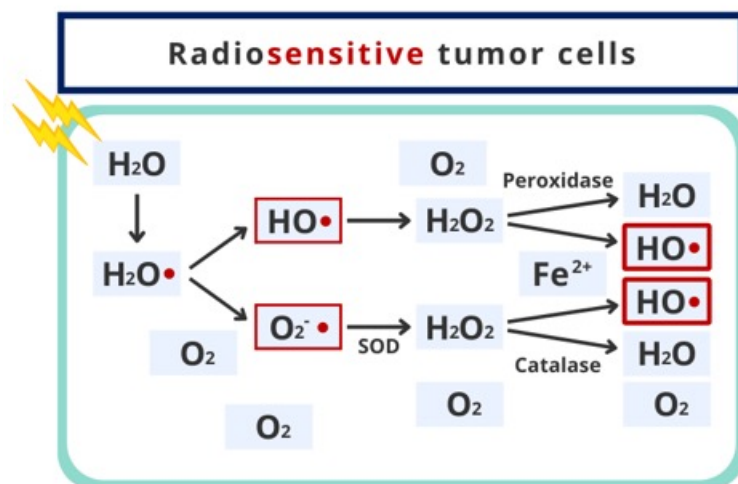
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KORTUC makes radioresistant tumor to radiosensitive tumor

Mechanism of KORTUC

Please see Video

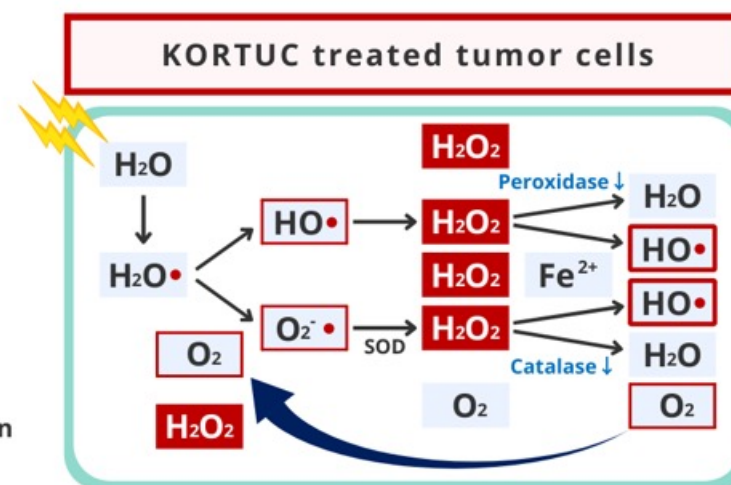
<https://vimeo.com/574688871>



KORTUC converts
Radio~~resistant~~ to
Radio~~sensitive~~



1. Increase H_2O_2
2. Oxygen Production
3. Peroxidase Inactivation



KORTUC

The world first patented prefilled injection device

- Unique pre-filled device for intra-tumoral injection
 - The injection can be performed by a radiologist under ultrasound guidance with no specific training
 - The kit allows to mix hydrogen peroxide and sodium hyaluronate with specific precise ratio
- Usage and product patents granted/being filed
 - 2 use patents for radiation sensitizer: granted in US, UK, Germany, Japan and others
 - 4 product patents for device: granted in Japan and being filed in other countries



KORTUC kit includes:

- One pre-filled syringe of hydrogen peroxide
- One pre-filled syringe of sodium hyaluronate
- Other parts of injection device
- (syringe socket to insert two pre-filled syringes and rod connector)

Any needles can be attached with universal luer lock of syringe socket.

Patent Portfolio

Patent	Title	Priority date	Expiration	Other granted countries
Granted in US/Europe				
Use patent	Radiation sensitizer or anti-cancer chemotherapy sensitizer* ¹	9/21/2007	2027	Japan, China, Canada, Australia
Granted in Europe (under examination in US)				
Use patent	Radiation/chemotherapy sensitizer to be used for intratumoral local injection and for controlled release of hydrogen peroxide with hydrogel as carrier	2/14/2014	2034	Japan
Product (KORTUC kit)	Hydrogen peroxide solution-prefilled syringe with excellent hydrogen Peroxide preservation due to silicone oil included in oil composition * ²	4/16/2019	2039	Japan, Bangladesh
Under examination in US/Europe				
Product (KORTUC kit)	Syringe suitable for hydrogen peroxide solution and kit thereof * ²	6/21/2019	2039	Japan, Bangladesh
	Syringe suitable for hydrogen peroxide solution and kit thereof * ³	11/16/2018	2038	Japan
	Holder for administering radiation or anti-cancer chemotherapy sensitizer * ³	5/31/2019	2039	Japan
	Oil composition to store hydrogen peroxide stably * ³	3/29/2019	2039	Japan

Other use and product patents have been filed and to be published

*1: Exclusive license from Kochi University

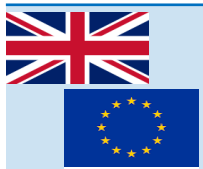


*2: Applications filed in 60 countries worldwide

*3: Applications filed in 13 countries, in the major countries of each region

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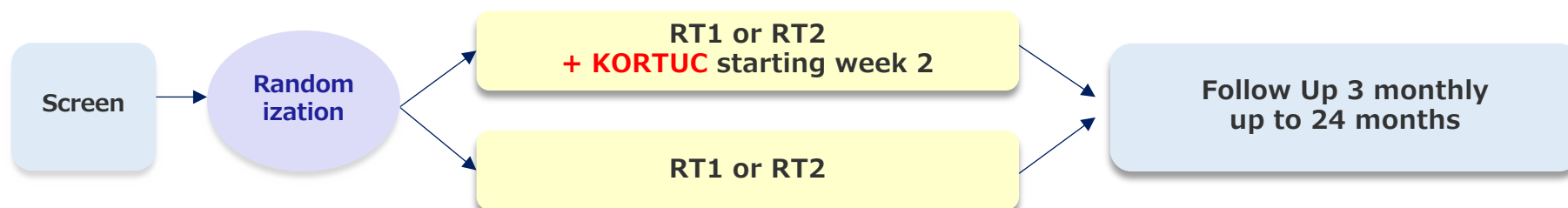
LIMITED DISTRIBUTION

KORTUC is in a late clinical stage

Area	Indication	Regimen	Early stage (Ph1-2a)	Late stage (P2b-3)	Sponsor
	Breast Cancer	With RT	Completed	Ongoing	The Institute of Cancer Research, UK
	Cervical Cancer	With RT		Preparing	KORTUC
	Rectal Cancer	With RT	Preparing		Universitair Ziekenhuis Brussel, Belgium

Details of ongoing registrational Phase 2/3 study (Breast Cancer)

Title	Randomized phase II trial testing the efficacy of intratumoral KORTUC as a radiosensitizer in patients with locally advanced/recurrent breast cancer
Design	Multi-center, non-blinded randomized open-label trial with two groups comparing radiotherapy with/without KORTUC
Subject	Patients with poorly controlled symptoms of primary or recurrent locally advanced breast cancer requiring high dose radiotherapy for lifetime control of moderate or severe morbidities
Pts No.	184 subjects (92 in each randomized group). This provides 80% power to detect a 20% difference in complete response at 12 months, assuming a 65% rate in the control group, 2-sided $\alpha=0.05$, and allowing for 10% unevaluable at 12 months.
Study Treatment	RT1: 49.5 Gy in 18 daily fractions of 2.75 Gy with/without sequential boost in 3-5 daily fractions of 2.75 Gy RT2: 36.0 Gy in 6 twice-weekly fractions of 6.0 Gy
Endpoint	Primary Endpoint Complete tumor response 12 months post-radiotherapy assessed by MRI



MHRA agreed to file MAA with one registrational study.

KORTUC

Records of efficacy in breast cancer at clinical investigation

Breast Cancer: Comparison of Response Rate with/without KORTUC

RT only		RT + KORTUC						
Report	Mukai 2013	Miyatake 2010	Hitomi 2010	Tsuzuki 2011	Ogawa 2015/ Aoyama 2016	Aoyama 2016	Aoyama 2017a	Aoyama 2017b
n	108	17	14	10	72	20 (24 lesions)	7	15
Stage	Stage 1A-3A	Stage 2A-3C	Stage 1A	Stage 1A-2A	Stage 1A-2A	Local- recurrent	Stage 4	Stage 1A
RT dose (Gy)	55	57	71	71	71	57-67	57-71	66
Outcome: cCR rate	43% (46/108)	100% (17/17)	100% (14/14)	100% (10/10)	99% (71/72)	79% (19/24)	71% (5/7)	100% (15/15)

RT only: RT was used as neo-adjuvant setting and CR was estimated at 12 weeks after RT (before surgery)
 Stage: UICC 8th edition

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