Rakuten Medical

New future of cancer treatment our technology may open up

J.P. Morgan Healthcare Conference 2023

Hiroshi “Mickey” Mikitani
Co-CEO, Rakuten Medical, Inc.

Image provided by Rush University Medical Center

Forward Looking Statements

This presentation contains forward-looking statements made pursuant to the safe harbor provisions of the (United States) Private Securities Litigation Reform Act of 1995 that involve risks, uncertainties, and assumptions that could cause Rakuten Medical's actual results and experience to differ materially from anticipated results and expectations expressed in these forward-looking statements. These forward-looking statements include information concerning Rakuten Medical's proprietary research platform known as Alluminox™ and the commercialization of services related to Rakuten Medical products such as ASP-1929 and other initiatives toward regulatory approval for products to be sold and marketed., including RM-1995. These products may not be granted regulatory approval to be sold or marketed or be commercially successful. Forward-looking statements suggest potential profitability, efficacy and safety, and the status of the application for approval. Rakuten Medical has in some cases identified forward-looking statements by using words such as "anticipates," "believes," "hopes," "estimates," "looks," "expects," "intends," "potential," "may," "suggest," "plans," "strategizes," "likely", "will", and similar expressions. Such forward-looking statements are based upon Rakuten Medical's current beliefs. Moreover, this presentation states an opinion related to clinical research data, hence the use of expressions such as "important," "notable" and "abnormal." Ongoing clinical studies involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including uncertainty of success in regulatory approval or commercialization of ASP-1929 which may be impacted by, among other things, problems with the manufacturing process for ASP-1929, the occurrence of adverse safety events, failure to demonstrate therapeutic benefit, and the other risks and uncertainties, both reasonable and unreasonable. Rakuten Medical undertakes no obligation to release publicly the results of any revisions to any such forward-looking statements that may be made to reflect new information obtained, events or circumstances after the date of this press release or to reflect the occurrence of unanticipated events, except as required by applicable law or regulation. In the event of one or more revisions to Rakuten Medical's forward-looking statement, it should not be inferred that such revisions or other forward-looking statements will be further revised.

What kind of FUTURE would open up

if we could kill only targeted cells?

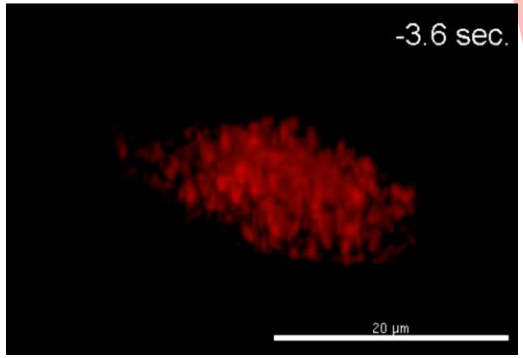
Alluminox technology video

Scan the QR code
to visit our YouTube
channel:

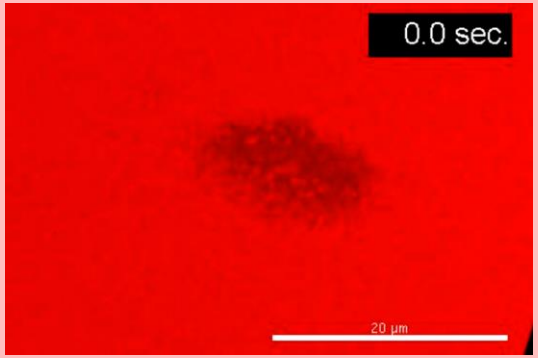
which develops conjugates combining substances such as antibodies,

Alluminox Treatment Induces Rapid Morphological Changes in Cancer Cells

Cancer Cell

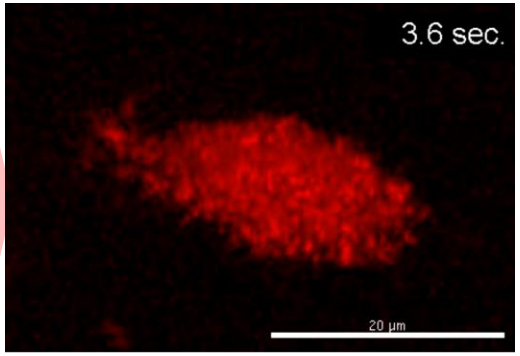


Illumination

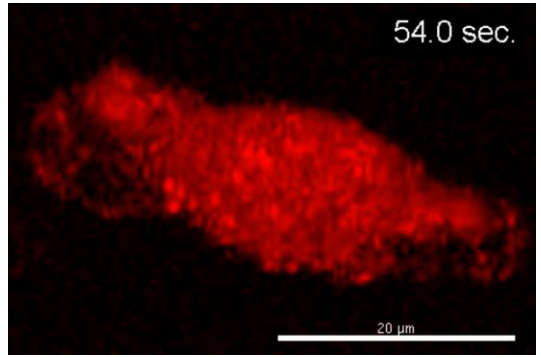


Non-thermal red light (690nm)

Swelling



Explosion



Cancer cell rapidly ruptures with cellular swelling and bleb formation after illumination.
Ruptured cell releases cancer antigens that trigger **local immune reaction**.[1.2.]

Rakuten Medical

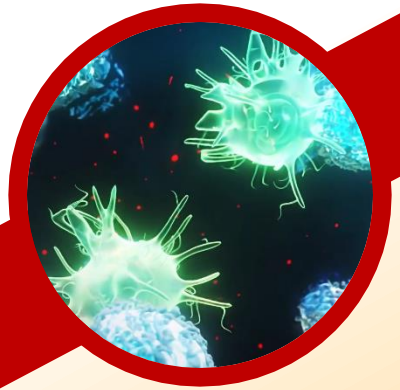
These pictures were taken during pre-clinical researches. The contents of this slide has not been evidenced in the clinical situation.

1. Mitsunaga M, et al. Nat Med. 2011 Nov 6;17(12):1685-91.
2. Kobayashi H, et al. Int Immunol. 2021 Jan 1;33(1):7-15.

Aspire to Transform Cancer Treatment

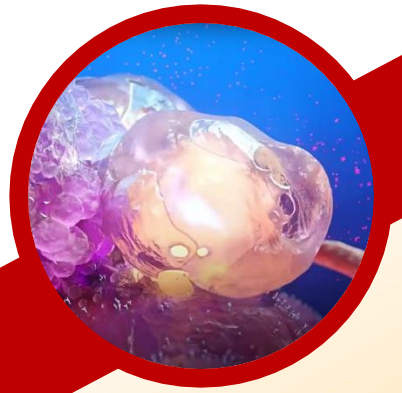
from "cut" to "illuminate"

Potential alternative to surgery



Opportunity for CANCER VACCINATION
stimulating the immune system against cancer cells

Potential option as SYSTEMIC THERAPY



To be a STANDARD OF CARE in locoregional therapy

Drug Development Program to Discover Antibody Conjugates Targeting Multiple Cancers

Alluminox Palette™

ONGOING CLINICAL & COMMERCIAL PROGRAM

ASP-1929	Anti-**EGFR** antibody-IR700 conjugate
RM-1995	Anti-**CD25** antibody-IR700 conjugate
RM-0256	Anti-**PD-L1** antibody-IR700 conjugate

FUTURE TARGETS

HER2 / MUC-1 / CEA / PSMA….

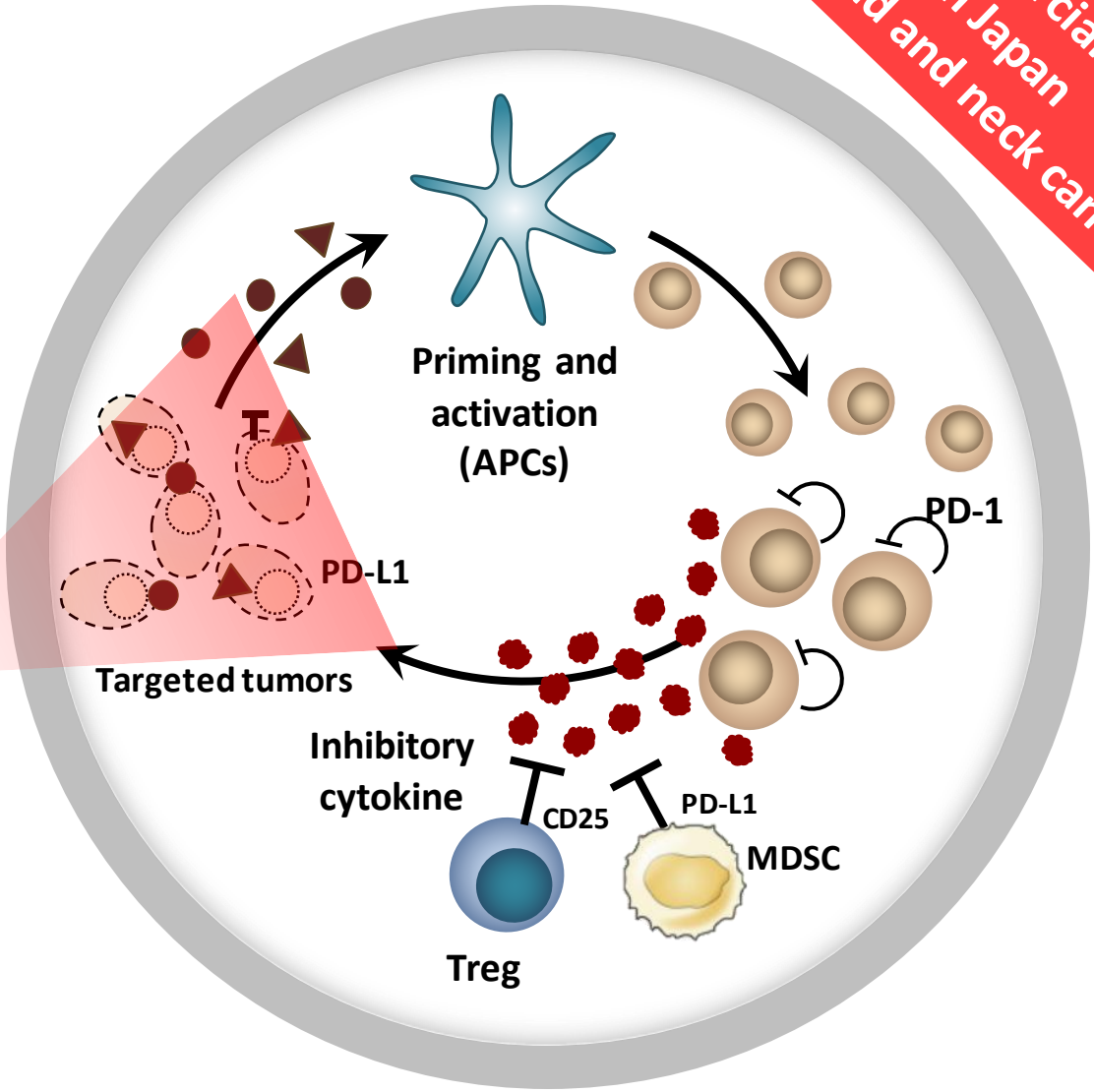
Rakuten Medical

Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

ASP-1929: Binding EGFR to Induce Selective Tumor Necrosis

Commercialized in Japan for head and neck cancer

Cancer cell-targeted Alluminox treatment
Local Targeted Therapy: EGFR-expressing tumor



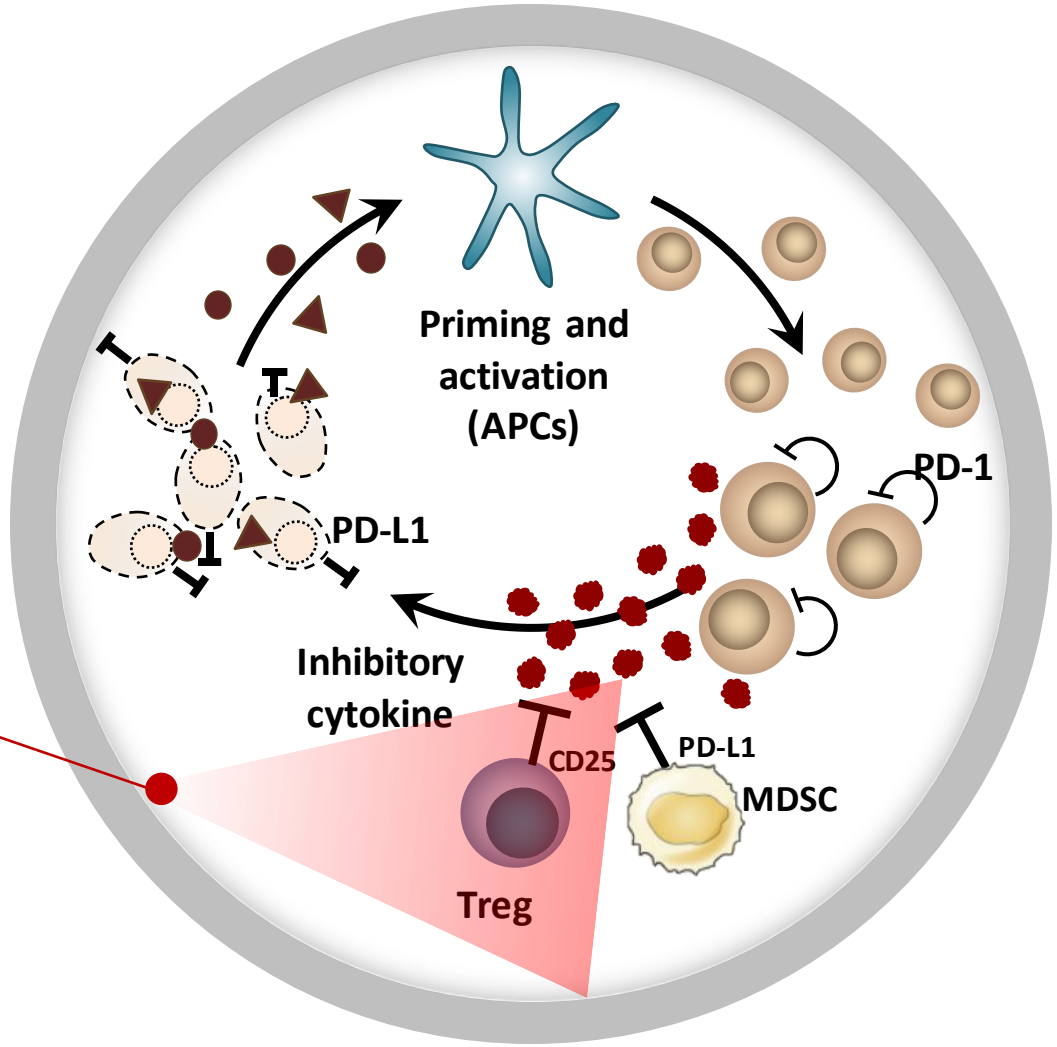
- **EGFR expressed in many solid tumors**: HNSCC, cSCC, esophageal, premalignant dysplasia, GBM, thyroid, lung SCC, prostate, penile, vulval, anal, renal, cBCC, cervical

RM-1995: Targeting CD25 to Deplete Intertumoral Tregs

Immunosuppressive cell-targeted Alluminox treatment

Systemic Therapy: CD25+ Tregs

- Potential applications for **many solid tumors**, based on suitability of light application



Targeted immunosuppressive cells

Rakuten Medical

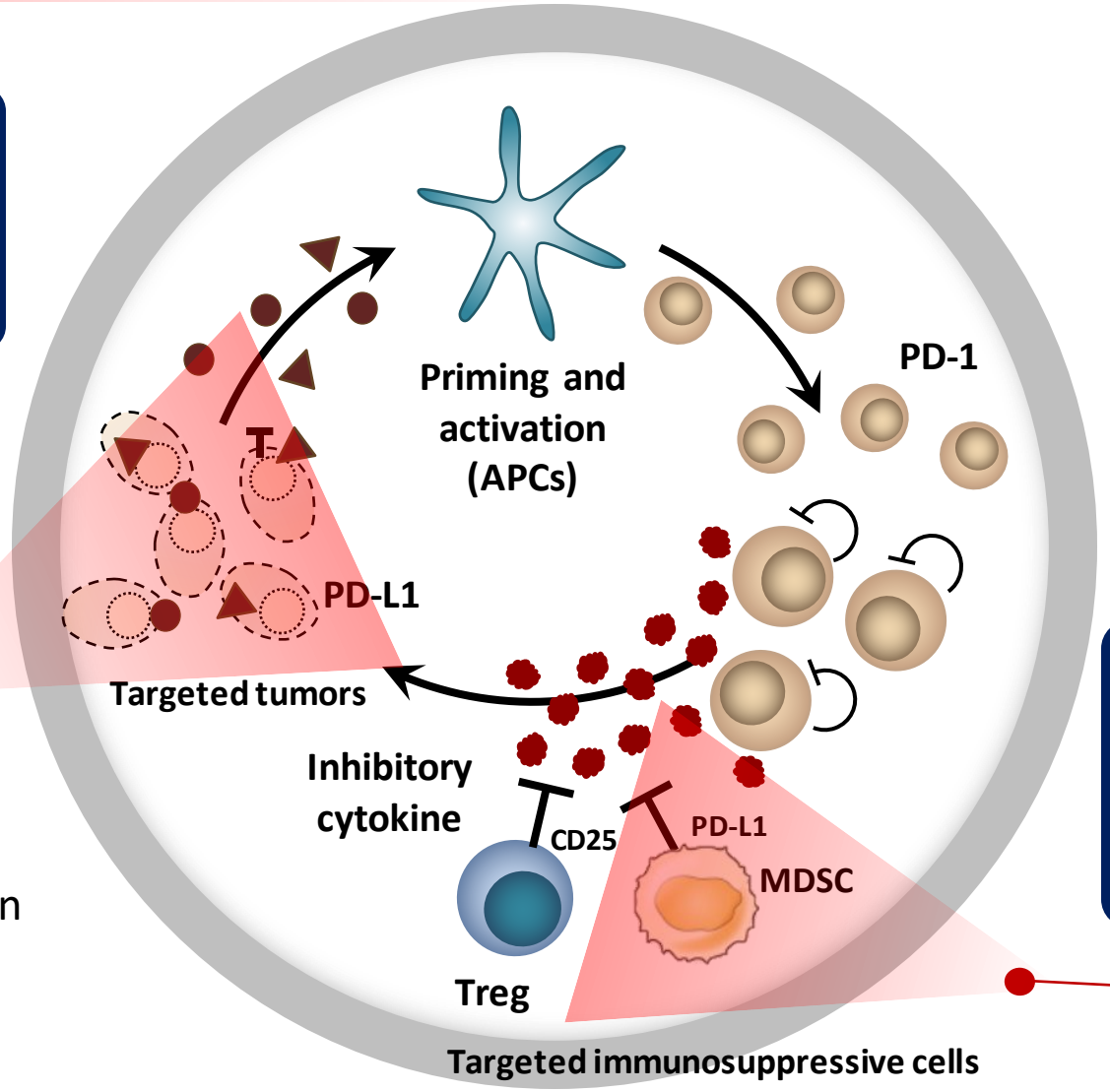
Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.
The contents of this slide has not been evidenced in the clinical situation.

Hsu, et al. Cancer Immunol. Immunoth. 2022

RM-0256: Aiming Both PD-L1+ Tumor & Immunosuppressive Cells Depletions

1 Cancer cell-targeted Alluminox treatment
(Local Targeted Therapy)

3 Immune checkpoint inhibition



2 Immunosuppressive cell-targeted Alluminox treatment
(Systemic Therapy)

- Broader expression of PD-L1 in **both solid and hematological cancer**

World-First Approval of ASP-1929 in Japan

Akalux IV infusion 250mg & BioBlade Laser System:

Received **our first approval** in Japan in Sep 2020, just 6 months after application under the "SAKIGAKE (fast track) designation" and "Conditional Early Approval System".

Early approval enables us to provide our treatment for **~ $53K** in Japan.

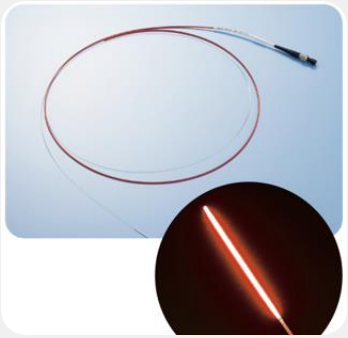
アキャルックス® 点滴静注 250mg

$35K / 4 vials

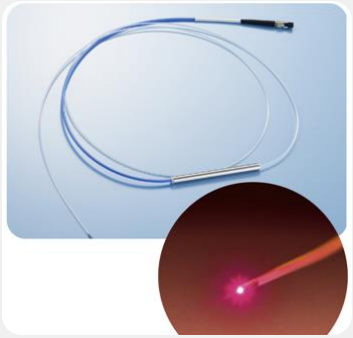
BioBlade® レーザシステム

$0.3K for rent
$35K for sale

BioBlade® シリンドリカル ディフューザー



BioBlade® フロンタル ディフューザー



$2K/diffuser
(# of diffusers required depends on patient)

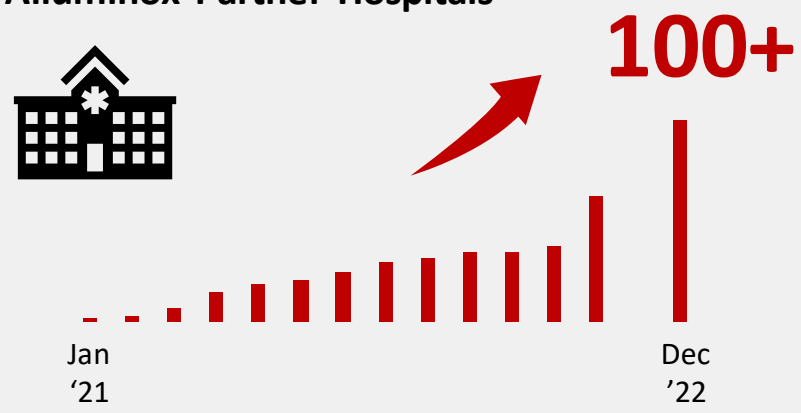
BioBlade® ニードルカテーテル

$17/needle
(# of needles required depends on patient)

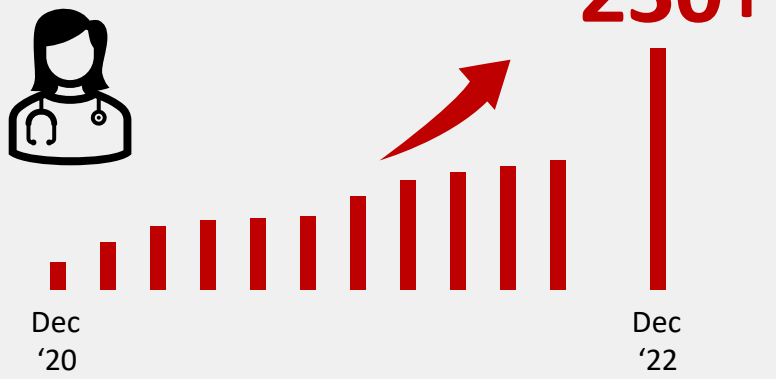
Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

Strong Track Record Demonstrates Proof of Concept of ASP-1929

Alluminox Partner Hospitals



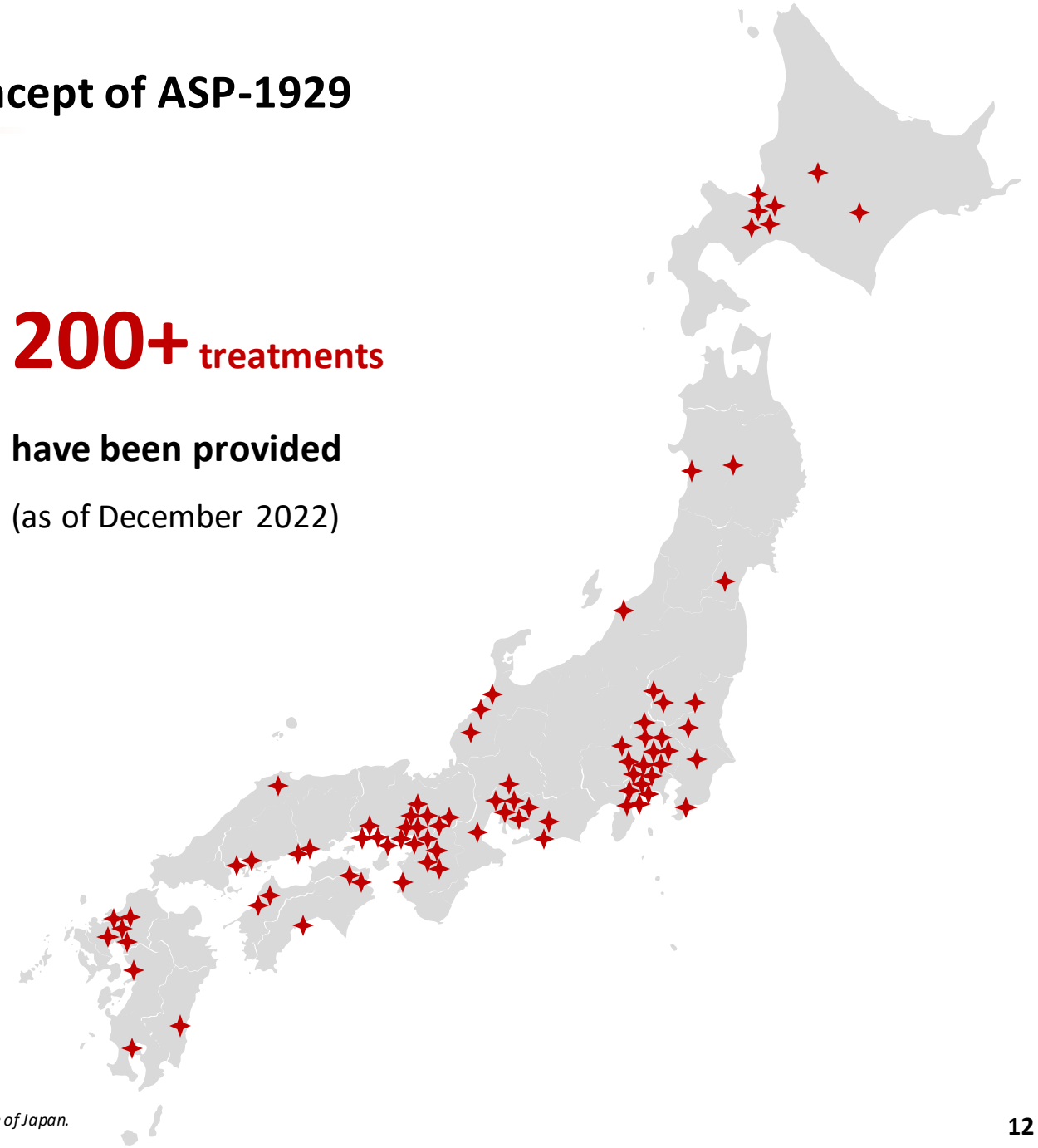
Certified Doctors



200+ treatments

have been provided

(as of December 2022)



Rakuten Medical

Rakuten Medical’s therapies based on Alluminox™ platform are investigational outside of Japan.

Real World Data Indicating Good Local Control without Decreasing QOL

"As for the efficacy, the ORR was 89%, and the DCR (Disease Control Rate) was 100%."
"HN-PIT did not decrease QOL and had a good local control rate. The safety was also acceptable"

cancers MDPI

Article

Quality-of-Life Evaluation of Patients with Unresectable Locally Advanced or Locally Recurrent Head and Neck Carcinoma Treated with Head and Neck Photoimmunotherapy

Isaku Okamoto *, Takuro Okada, Kunihiko Tokashiki and Kiyoaki Tsukahara

Department of Otorhinolaryngology, Head and Neck Surgery, Tokyo Medical University, 6-7-1 Nishishinjuku, Shinjuku-ku, Tokyo 160-0023, Japan
* Correspondence: isaku@tokyo-med.ac.jp; Tel.: +81-333-426-111; Fax: +81-333-469-275

Simple Summary: Head and neck photoimmunotherapy (HN-PIT) is a new treatment developed for local control of head and neck carcinoma. This study assessed the quality of life (QOL) of nine patients with unresectable locally advanced or locally recurrent head and neck carcinoma (LA/LR-HNC) treated with HN-PIT. QOL was compared before and 4 weeks after HN-PIT. There were no significant changes in all the QOL assessment parameters after treatment with HN-PIT. For patients with unresectable LA/LR-HNC, HN-PIT provided good local control without decreasing the QOL.

Abstract: Head and neck photoimmunotherapy (HN-PIT), a new treatment developed for local control of head and neck carcinoma, uses cetuximab sarotalocan sodium with a laser system to specifically destroy only tumor cells. No studies have examined the impact of HN-PIT on the quality of life (QOL) of patients with head and neck cancer. This study assessed the QOL of patients with unresectable locally advanced or locally recurrent head and neck carcinoma (LA/LR-HNC) treated with HN-PIT. Nine eligible patients with unresectable LA/LR-HNC who underwent HN-PIT at our institution between 20 January 2021 and 30 April 2022 were included in the study. They completed a QOL evaluation form. The primary endpoint was QOL assessment. The secondary endpoints were overall response rate, overall survival (OS), progression-free survival, and adverse events. QOL was compared before and 4 weeks after HN-PIT. There were no significant changes in all QOL assessment parameters after treatment with HN-PIT. The overall response rate was 89%, and safety was acceptable. For patients with unresectable LA/LR-HNC, HN-PIT provided good local control without decreasing the QOL. The addition of HN-PIT to conventional head and neck carcinoma treatment may lead to the prolongation of OS in head and neck carcinoma.

Keywords: head and neck photoimmunotherapy; cetuximab sarotalocan sodium; unresectable locally advanced or locally recurrent head and neck carcinoma; quality of life

check for updates

Citation: Okamoto, I.; Okada, T.; Tokashiki, K.; Tsukahara, K. Quality-of-Life Evaluation of Patients with Unresectable Locally Advanced or Locally Recurrent Head and Neck Carcinoma Treated with Head and Neck Photoimmunotherapy. *Cancers* **2022**, *14*, 4413. https://doi.org/10.3390/cancers14184413

Academic Editor: Burkhard Brandt

Received: 17 August 2022
Accepted: 9 September 2022
Published: 11 September 2022

The QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) Core 30 Module (QLQ-C30), a basic QOL questionnaire used for patients with malignancies, and the EORTC QLQ Head and Neck Cancer Module (QLQ-H&N35), a disease-specific questionnaire.

"NIR-PIT is considered to have particularly promising applications in head and neck cancers and these tumors are typically more easily accessed for illumination."

"Two patients with oropharyngeal lesions treated with NIR-PIT at our institution had good response with no serious adverse events and no functional disorders"

cancers MDPI

Review

Near-Infrared Photoimmunotherapy for Oropharyngeal Cancer

Daisuke Nishikawa *, Hidenori Suzuki, Shintaro Beppu, Hoshino Terada, Michi Sawabe and Nobuhiro Hanai

Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya 464-8681, Japan
* Correspondence: dsknishi@aichi-cc.jp; Tel.: +81-52-762-6111; Fax: +81-52-764-2944

Simple Summary: Near-infrared photoimmunotherapy (NIR-PIT) represents a potential novel treatment modality for a range of cancer types, including head and neck cancers. NIR-PIT is based on the conjugation of photoactivating chemicals to cancer cell-specific antibodies. Antibody-photoabsorber-conjugate causes killing of cancer cells when activated by near-infrared light. NIR-PIT is considered to have particularly promising applications in head and neck cancers and these tumors are typically more easily accessed for illumination. Two patients with oropharyngeal lesions treated with NIR-PIT at our institution had good response with no serious adverse events and no functional disorders.

Abstract: Human papillomavirus (HPV)-associated oropharyngeal cancer has a better prognosis than other head and neck cancers. However, rates of recurrence and metastasis are similar and the prognosis of recurrent or metastatic HPV-associated oropharyngeal cancer is poor. Near-infrared photoimmunotherapy (NIR-PIT) is a treatment involving administration of a photosensitizer (IRDye®700DX) conjugated to a monoclonal antibody followed by activation with near-infrared light illumination. It is a highly tumor-specific therapy with minimal toxicity in normal tissues. Moreover, NIR-PIT is expected to have not only direct effects on a treated lesion but also immune responses on untreated distant lesions. NIR-PIT with cetuximab-IR700 (AlluminoxTM) has been in routine clinical use since January 2021 for unresectable locally advanced or locally recurrent head and neck cancer in patients that have previously undergone radiotherapy in Japan. NIR-PIT for head and neck cancer (HN-PIT) is expected to provide a curative treatment option for the locoregional recurrent or metastatic disease after radiotherapy and surgery. This article reviews the mechanism underlying the effect of NIR-PIT and recent clinical trials of NIR-PIT for head and neck cancers, treatment-specific adverse events, combination treatment with immune checkpoint inhibitors, illumination approach and posttreatment quality of life, and provides a case of series of two patients who receive NIR-PIT for oropharyngeal cancer at our institution.

check for updates

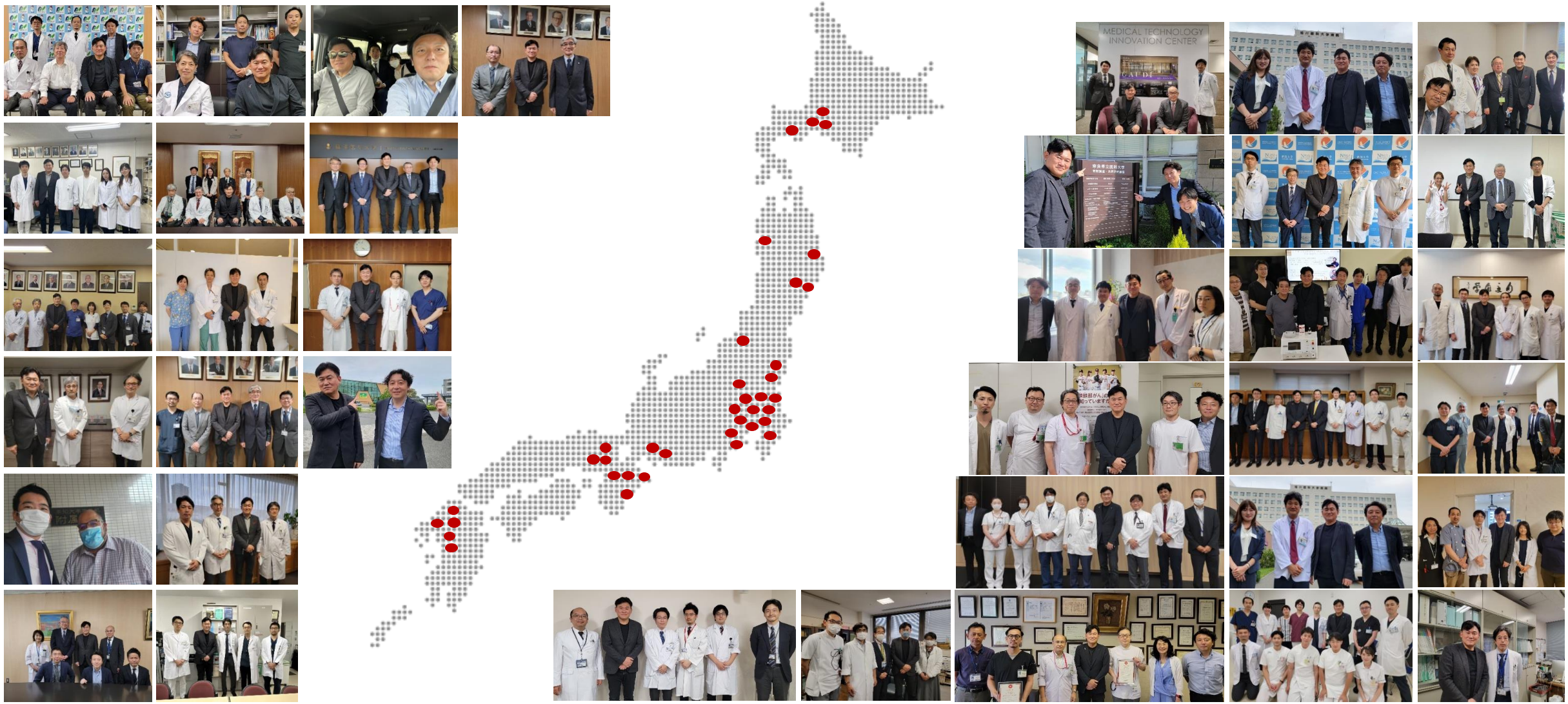
Citation: Nishikawa, D.; Suzuki, H.; Beppu, S.; Terada, H.; Sawabe, M.; Hanai, N. Near-Infrared Photoimmunotherapy for Oropharyngeal Cancer. *Cancers* **2022**, *14*, 5662. https://doi.org/10.3390/cancers14225662

Academic Editors: Norihiko Narita

Case	Gender	Age	ECOG PS	Histology	Primary site	Location of Target Lesion	Diffuser	Cycle	Complication	BOR
1	M	84	1	SCC	Floor of mouth	Cervical skin	Cylindrical, frontal	3	Pain G2 Bleeding G2 Edema G1	PR
2	M	84	1	SCC	Upper gingiva	Oropharynx	Cylindrical	2	Pain G1	PR
3	M	54	0	SCC	Upper gingiva	Subcutaneous tissue of face	Cylindrical	2	Pain G2 Edema G1 Fistula G1	CR
4	M	77	0	SCC	Oropharynx	Oropharynx	Cylindrical	1	Pain G2 Edema G1	PR
5	M	68	0	SCC	Larynx	Glottis	Cylindrical, frontal	3	Edema G1	PR
6	M	79	1	SCC	Oropharynx	Cervical skin	Cylindrical, frontal	2	Pain G2	PR
7	M	42	0	SCC	Buccal mucosa	Tongue	Cylindrical	1	Pain G2 Edema G2	CR
8	M	88	1	SCC	Lower gingiva	Lower gingiva	Cylindrical, frontal	1	Edema G4	CR
9	F	74	1	SCC	Maxilla	Nasal cavity	Cylindrical	3	Pain G1	PR
10	M	80	1	SCC	Oral cavity	Subcutaneous tissue of face	Cylindrical	1	Fistula G2	PR

ECOG-PS, Eastern Cooperative Oncology Group Performance Status; BOR, best overall response; SCC, squamous cell carcinoma; PR, partial response; CR, complete response.

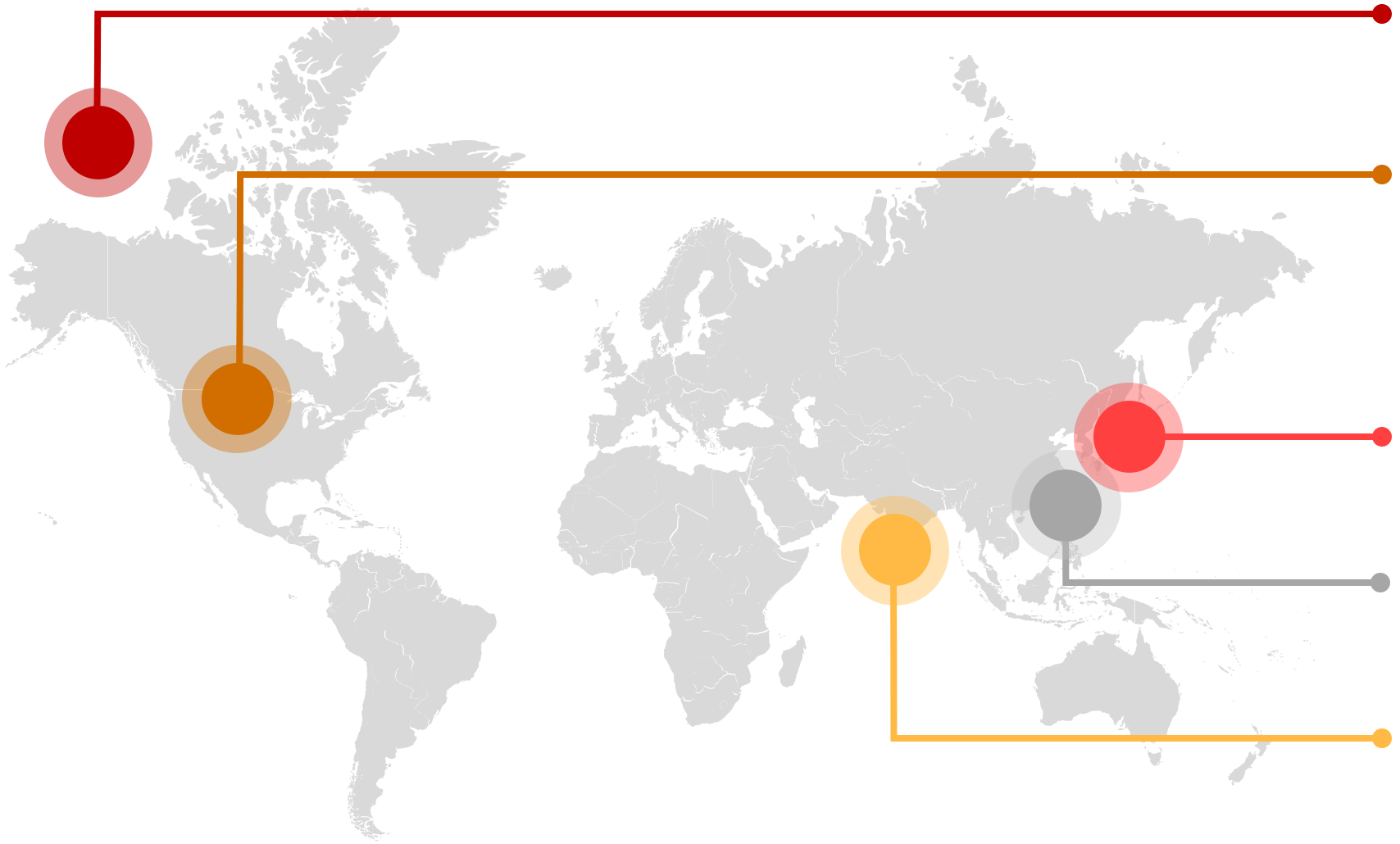
Alluminox Caravan – 50+ Visits by Co-CEOs



Rakuten Medical

Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

Leveraging Commercial Success in Japan for Geographic and Clinical Expansion



Global

ASP-1929-301, global Phase 3 study acceleration

US

ASP-1929-103, Window of Opportunity study acceleration

ASP-1929-181, combination with anti-PD1 study data publication

Japan

RM-1995-102, Phase 1 study of second asset IND and FPI

Taiwan

ASP-1929-218, combination with anti-PD1 study acceleration

India

New entity set-up and top hospitals recruited for **ASP-1929-301**, global Phase 3 study

Rakuten Medical

Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

Robust Pipeline from Alluminox™ Platform

Indication	Region	RM Trial #	Pre-clinical	Phase 1	Phase 2	Phase 3
ASP-1929						
Unresectable locally advanced or recurrent head and neck	**Japan**	**101/102**				Approved in Japan
Locoregional recurrent HNSCC	**Global**	**301**				
Window of Opportunity Study in HNSCC & CSCC	**US**	**103**				
Recurrent esophageal cancer	**Japan**	**IIT**				
Additional indications						
ASP-1929 + anti- PD-1 Combination Therapy						
Recurrent or metastatic HNSCC & advanced CSCC	**US**	**181**				
Recurrent HNSCC ± metastases	**Taiwan**	**218**				
Unresectable advanced or recurrent esophageal cancer or gastric cancer	**Japan**	**IIT**				
RM-1995						
Recurrent head and neck cancer	**US**	**101**				
Metastatic liver cancer	**Japan**	**102**				
Additional indications						
RM-0256						
Additional indications						

Rakuten Medical

HNSCC: Head and Neck Squamous Cell Carcinoma
CSCC: Cutaneous Squamous Cell Carcinoma
IIT: investigator-initiated study

Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

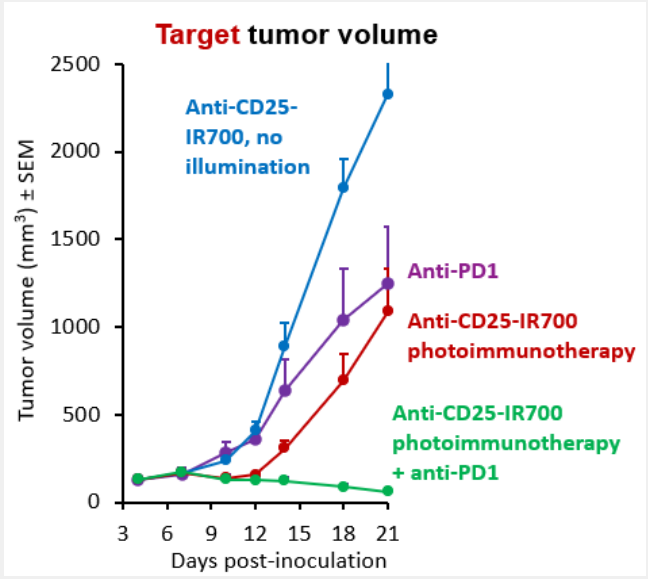
Encouraging RM-1995 Pre-Clinical Data

RM-1995

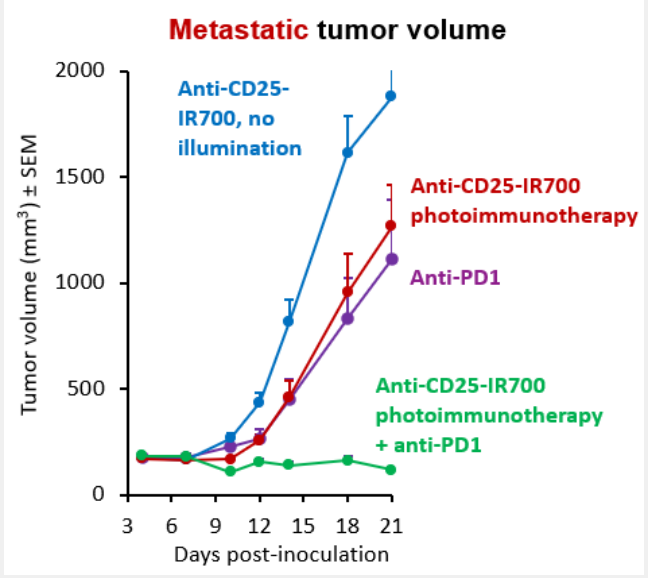
Anti-CD25 Alluminox treatment

Monotherapy (in mice):
Research indicated target and abscopal anticancer activity

Combination with anti-PD-1 (in mice):
Research indicated significant synergy in target and abscopal lesions



Treatment (in Mice)	# of CRs
Anti-CD25-IR700, no illumination	0/12 (0%)
Anti-CD25-IR700 photoimmunotherapy	7/20 (35%)
Anti-PD-1	1/12 (8%)
Anti-CD25-IR700 photoimmunotherapy + anti-PD-1	17/23 (74%)



Treatment (in Mice)	# of CRs on both sides
Anti-CD25-IR700, no illumination	0/15 (0%)
Anti-CD25-IR700 photoimmunotherapy	1/15 (6.7%)
Anti-PD-1	2/15 (12.5%)
Anti-CD25-IR700 photoimmunotherapy+ anti-PD-1	12/15 (80%)

Source: Company Materials.

DISCLAIMER: RM-1995 has not been approved by any regulatory authority.

Rakuten Medical

Rakuten Medical Milestones and Anticipated Timeline

2021

- ✓ **ASP-1929 Japan Launch**
- ✓ RM-1995 US FDA IND

2022

- ✓ ASP-1929-103 (US Ph2 HNSCC) 1st Patient
- ✓ ASP-1929-181 (US Ph2 HNSCC) interim safety analysis
- ✓ ASP-1929-218 (Taiwan PD-1 combo Ph2 HNSCC) 1st Patient
- ✓ Japan: 200+ treatments

2023

- ✓ ASP-1929-181 (US PD-1 combo Ph2 HNSCC) interim efficacy analysis
- ✓ ASP-1929-301 (Global Ph3 HNSCC) interim analysis
- ✓ ASP-1929-218 (Taiwan PD-1 combo Ph2 HNSCC) complete stage 1 enrollment

2024

- ✓ ASP-1929-181 (US PD-1 combo Ph2 cSCC) Last Patient
- ✓ RM-0256 1st patient
- ✓ ASP-1929-218 (Taiwan PD-1 combo Ph2 HNSCC) full data read-out
- ✓ Additional new study initiation (details currently being finalized)

2025

- ✓ **US / EU / Taiwan Global Launch**
- ✓ **India approval**
- ✓ ASP-1929-103 (US Ph2 HNSCC neoadjuvant) Last Patient

Rakuten Medical

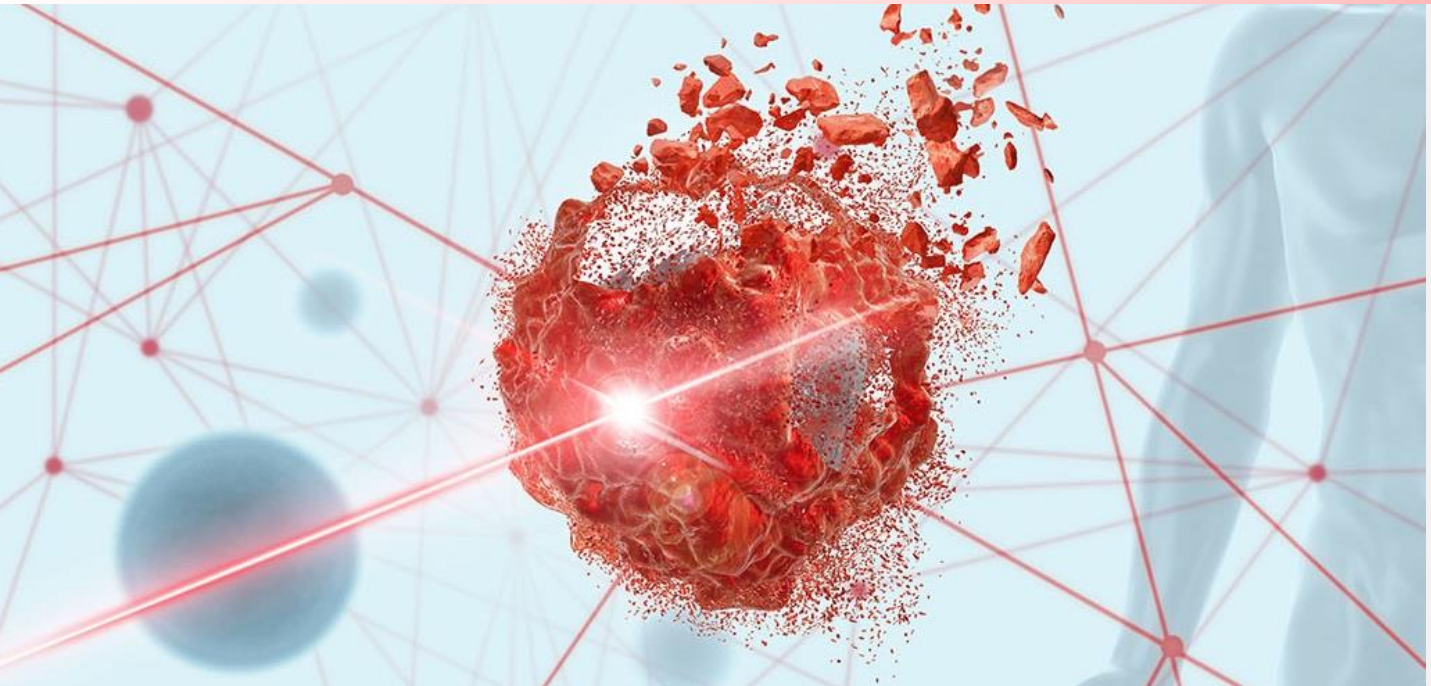
Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan.

How could I cure my father's cancer?

How could I help as many people as possible by providing innovative treatment?

Rakuten Medical

Rakuten Medical's Mission:
To Conquer Cancer.

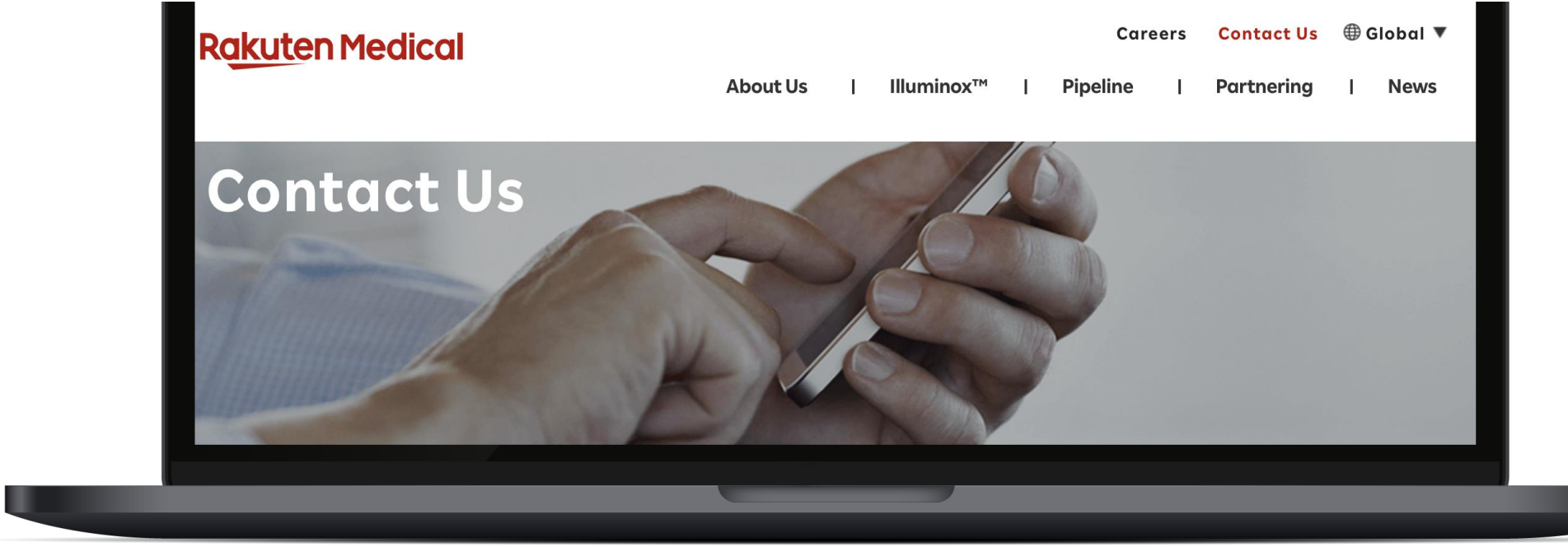


Harnessing the power of light to deliver a knockout blow to cancer cells

Hiroshi Mikitani
Vice Chairman & Co-CEO

Takashi Toraishi
Co-CEO and President

Abhijit Bhatia
Chief Operating Officer



CONTACT US Partnerships@rakuten-med.com

Scan the QR code to visit our website: