Illuminating the Future with Our Innovation

Rakuten Medical

The 42nd Annual J.P. Morgan Healthcare Conference

January 10, 2024

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Rakuten Medical Presenter

Takashi “Tora” Toraishi, Ph.D.
Co-CEO and President

Abhijit Bhatia, MBA
Chief Operating Officer

Rakuten Medical: A global biotechnology company

Our mission:
To **conquer cancer.**

Rakuten Medical
ガン克服。生きる。
CONQUERING Cancer.

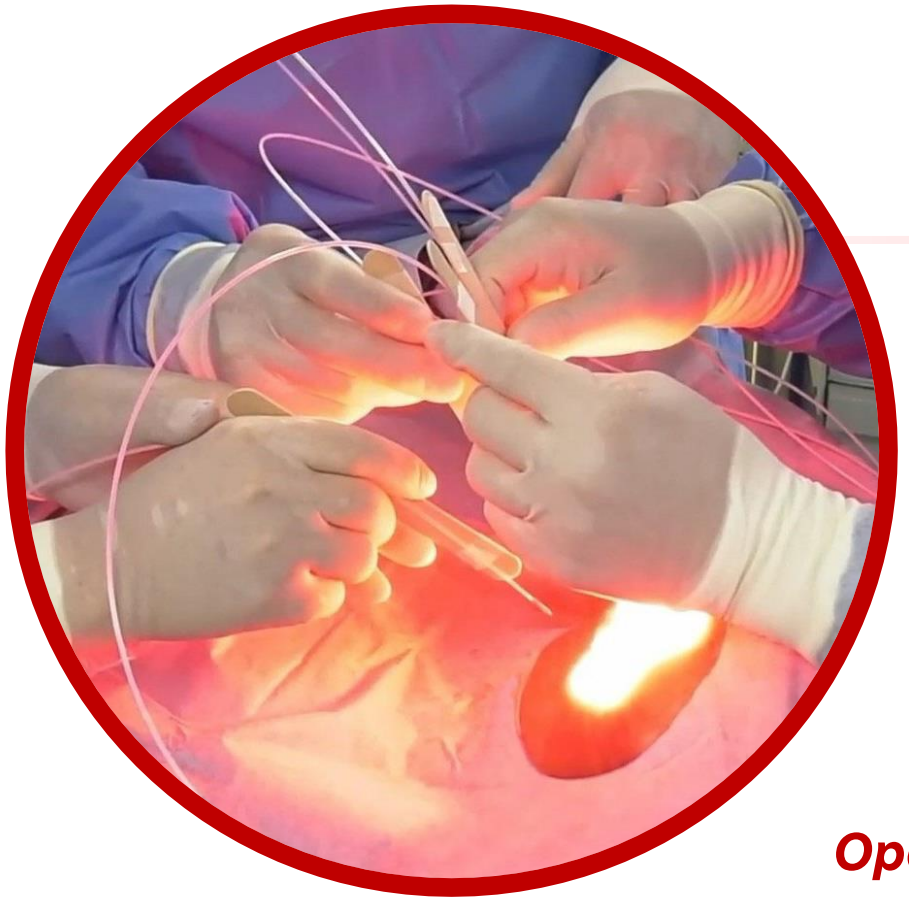
Our investigational technology:
Alluminox™ platform

Founded in	Employees Worldwide *	Operation in	Leading Assets
2010	**~160** As of Dec 2023	**5** Countries	**3** in Pipeline

* Number of permanent employees

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

Rakuten Medical's Alluminox™ Platform



Potential key advantages for our technology:

- ✓ **Rapid and selective** cell killing
- ✓ **Minimal effects** on surrounding tissues
- ✓ **Local and systemic immune activation**

Opening the door to a potential 5th pillar of cancer treatment

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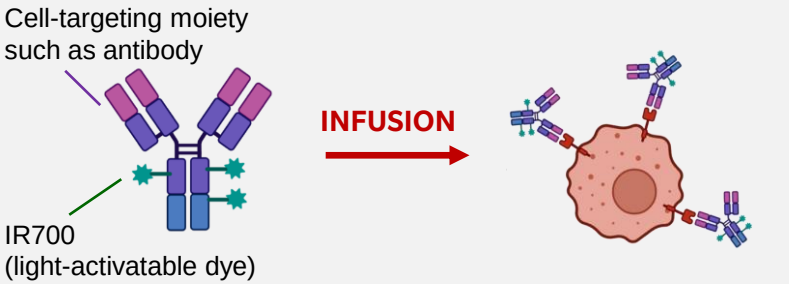
Overview of Therapies based on Alluminox™ Platform

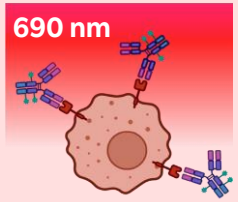
Intravenous Infusion (2hrs)



Conjugate with IR700

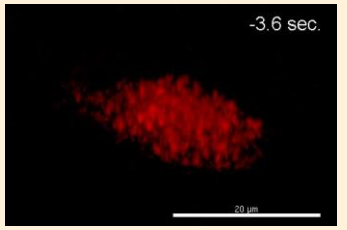
Conjugate binds to targeted cell

Illumination



Illumination with red light (690 nm) to activate conjugates bound to cells

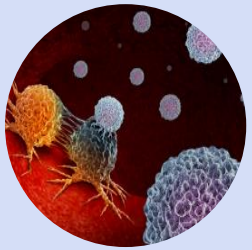
Necrosis



Rapid and acute cell death through disruption of cell membrane integrity

Ruptured cell releases cancer antigens

Immune Response

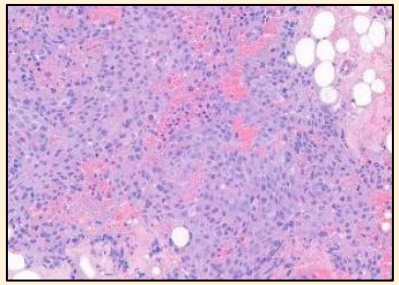


Anti-tumor innate and adaptive immunity generated

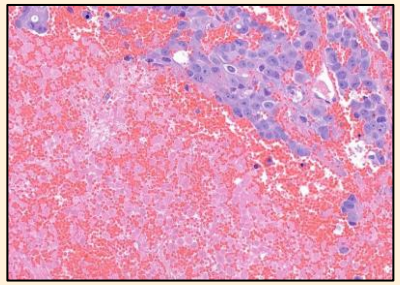
Pre-clinical data generated at Rakuten Medical

Dramatic cell necrosis observed 24hrs after treatment

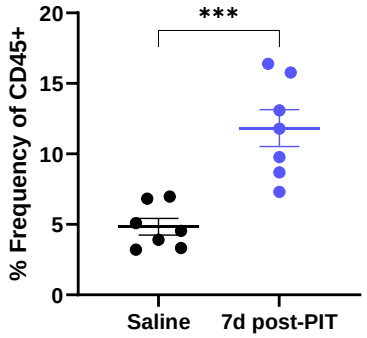
Tumor w/o PIT



Tumor post-PIT

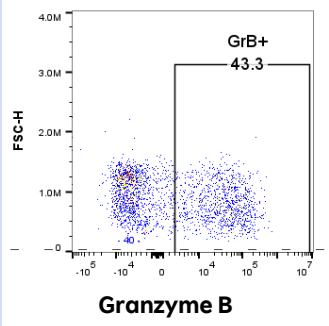


CD8+ T cell Frequency in Tumors 7 days post-PIT

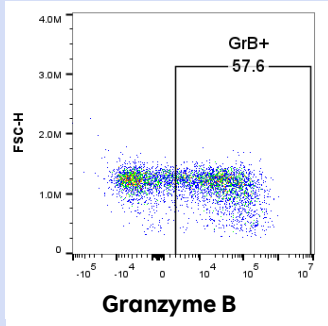


Increase in functionally active killer T cells (CD8+ GrB+) in TME at 7 days post-treatment

w/o PIT



post-PIT



PIT: Photoimmunotherapy TME: Tumor microenvironment w/o PIT: Saline + no illumination

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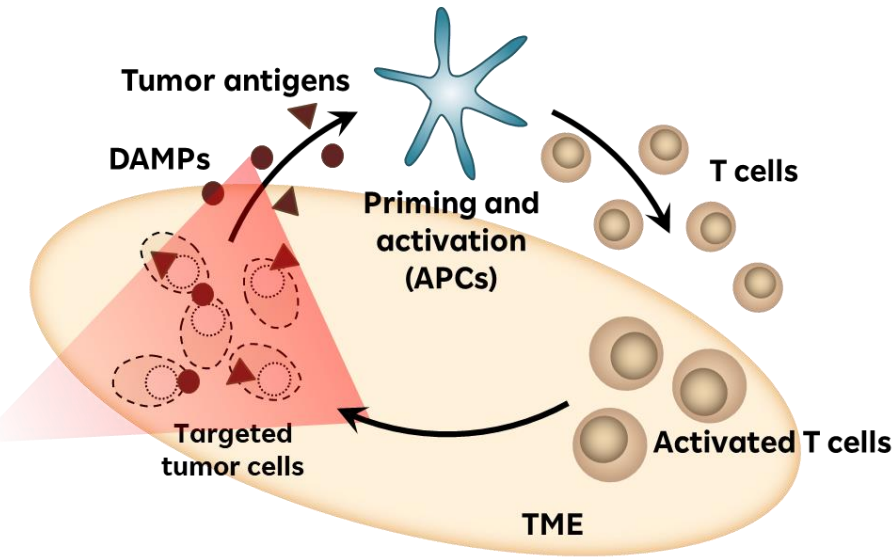
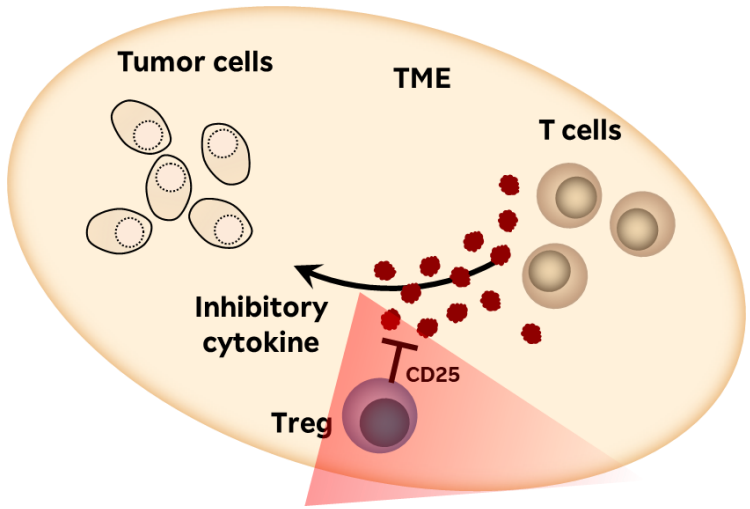
3 leading pipeline assets: ASP-1929, RM-1995, RM-0256

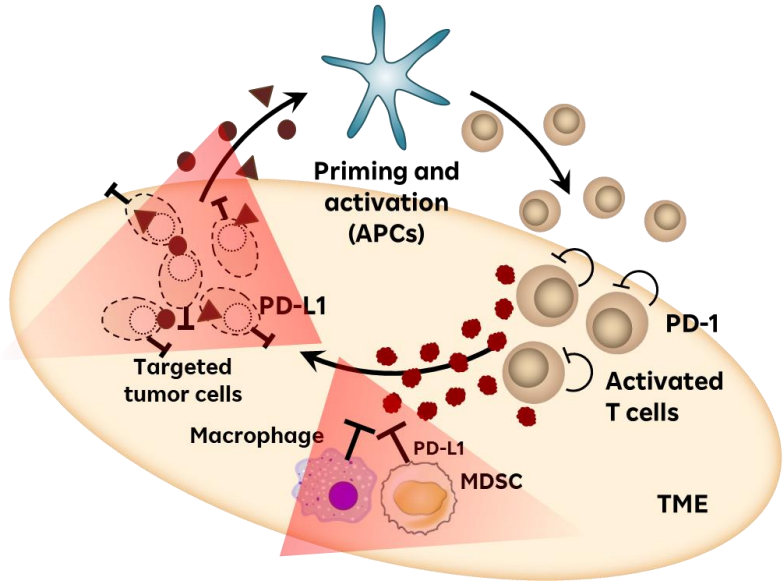
ASP-1929 Anti-**EGFR** antibody-IR700 conjugate

RM-1995 Anti-**CD25** antibody-IR700 conjugate

RM-0256 Anti-**PD-L1** antibody-IR700 conjugate







Targeting EGFR+ tumor cells

Targeting CD25+ immunosuppressive Tregs in TME

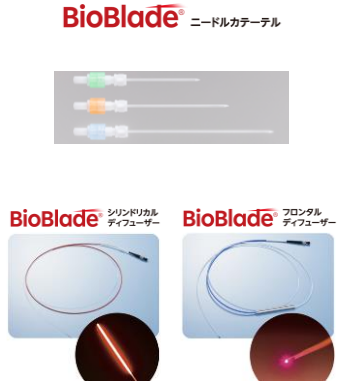
1. **Targeting PD-L1+ tumor cells**
2. **Targeting PD-L1+ immunosuppressive cells in TME**
3. **Immune checkpoint inhibition**

TME: Tumor microenvironment
DAMPs: Damage-associated molecular patterns
APC: Antigen-presenting cell
Treg: Regulatory T cell
EGFR: Epidermal growth factor receptor
MDSC: Myeloid-derived suppressor cell

ASP-1929: World-First & Early Approval in Japan

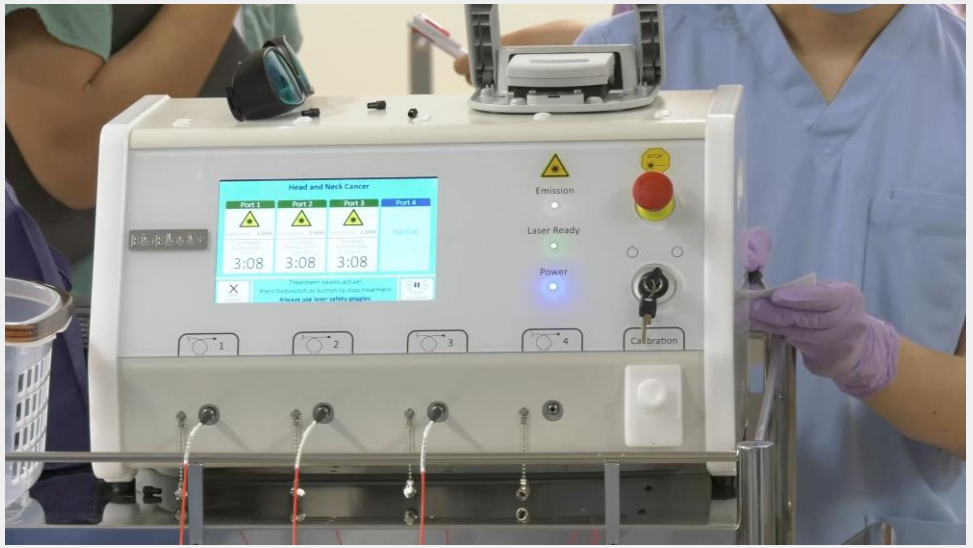
Akalux® IV infusion 250mg (ASP-1929) & BioBlade® Laser System

- Approved for **unresectable locally advanced or recurrent head and neck cancer** in Japan in Sep 2020 under the "**SAKIGAKE (fast track) designation**" and "**Conditional Early Approval System**".
- Early approval prior to the completion of Phase 3 enables us to provide our treatment for **6-7M yen (~$50K)** in Japan.
- Started with **head and neck surgeons** in Jan 2021, and expanded to **oral surgeons** in Dec 2023.



Cylindrical diffuser insertion

Illumination with cylindrical diffusers



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We received approval in Japan under the Conditional Early Approval System which is designed to accelerate patient access to drugs with particularly high medical needs that treat serious diseases with limited treatment options, and difficult to conduct confirmatory clinical trials due to the small number of patients or long trial period.

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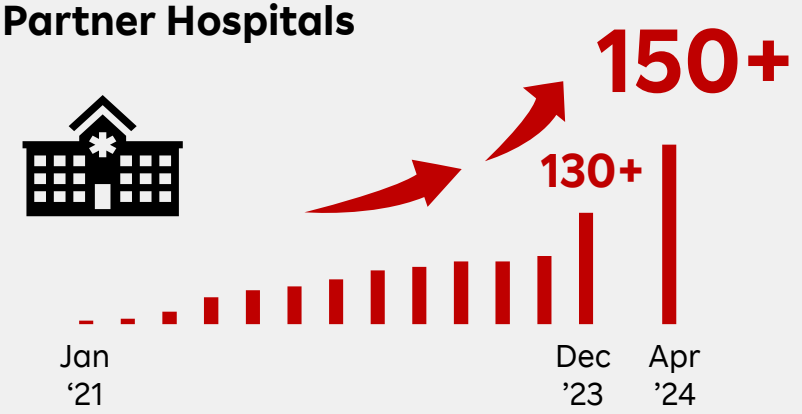
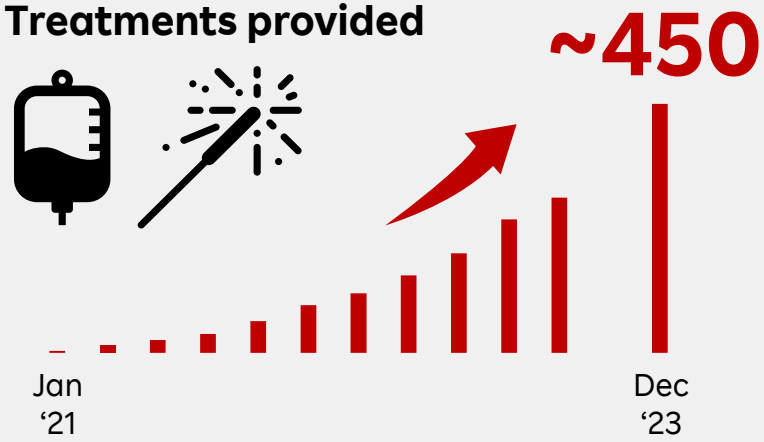
Strong Track Record in Japan Commercial Generated by Our Own Salesforce

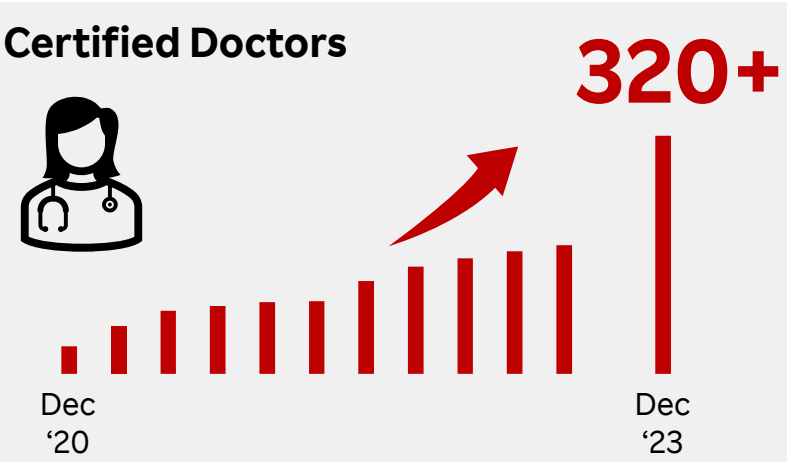
Partner Hospitals



Treatments provided



Certified Doctors



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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**					Approved in Japan*
Locoregional recurrent HNSCC	**Global**	**301**				
Window of Opportunity Study in HNSCC & CSCC	**US**	**103**				
Recurrent esophageal cancer	**Japan**	**IIT**				
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						
Metastatic liver cancer	**Japan**	**102**				
RM-0256						
Additional indications						

* We received approval in Japan under the Conditional Early Approval System which is designed to accelerate patient access to drugs with particularly high medical needs that treat serious diseases with limited treatment options, and difficult to conduct confirmatory clinical trials due to the small number of patients or long trial period.

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

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ASP-1929-301: Global Phase 3 Study Design

Phase 3, randomized, double-arm, open-label, controlled trial of ASP-1929 PIT vs physician's choice SoC

Eligible Adults:

- ✓ Have confirmed **locoregional recurrent HNSCC**, not amenable to curative treatment
- ✓ Have failed or progressed **on or after at least 2 lines** of therapy, incl. platinum-based chemotherapy
- ✓ Have completed prior curative radiation therapy
- ✓ Without distant metastatic disease outside of H&N area

2:1
n ~275

ASP-1929 PIT n ~183
up to a maximum of 8 cycles within a period of up to 12 months

SoC n~92
(methotrexate, cetuximab, paclitaxel, or docetaxel)

Follow-up until disease progression

Long-term follow-up for OS

First Primary endpoint
- **PFS***

Second Primary endpoint
- **OS**

Key Secondary endpoint
- ORR*

PIT: Photoimmunotherapy
SoC: Standard of Care
HNSCC: head and neck squamous cell carcinoma

PFS: progression-free survival
OS: overall survival
ORR: objective response rate

* per modified RECIST 1.1.

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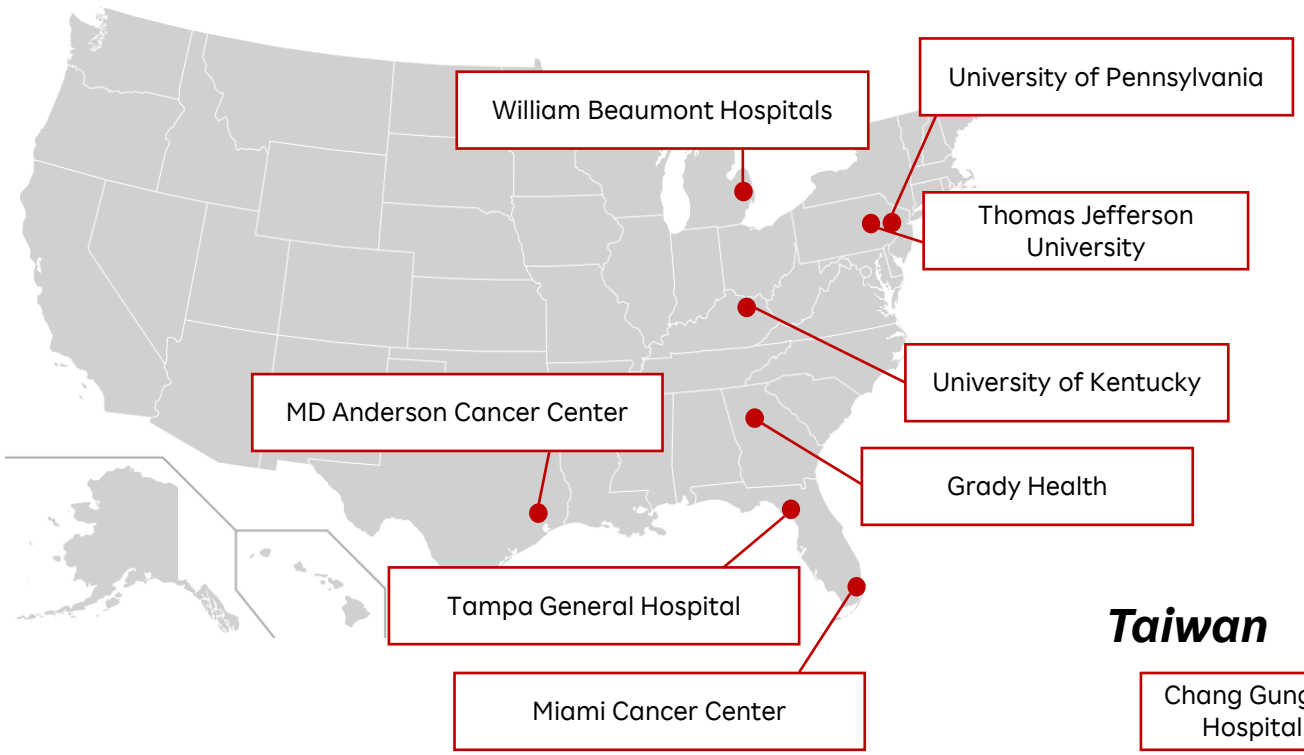
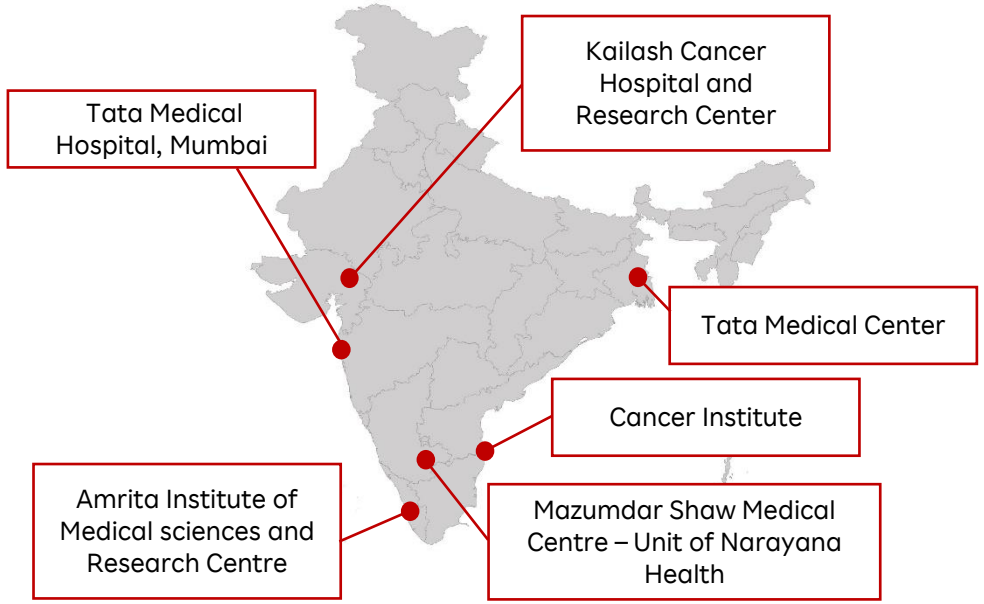
ASP-1929-301: Study Sites

As of Dec 2023

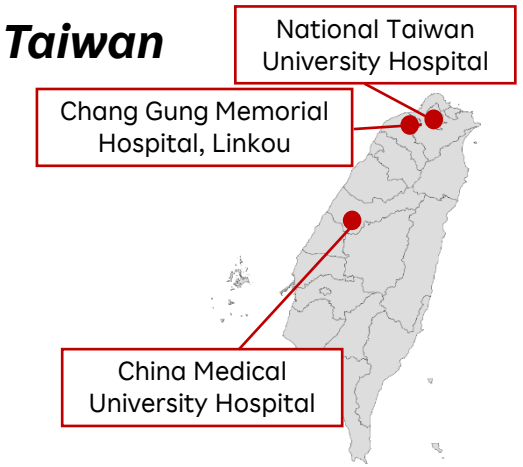
U.S.



India



Taiwan



MENA may join

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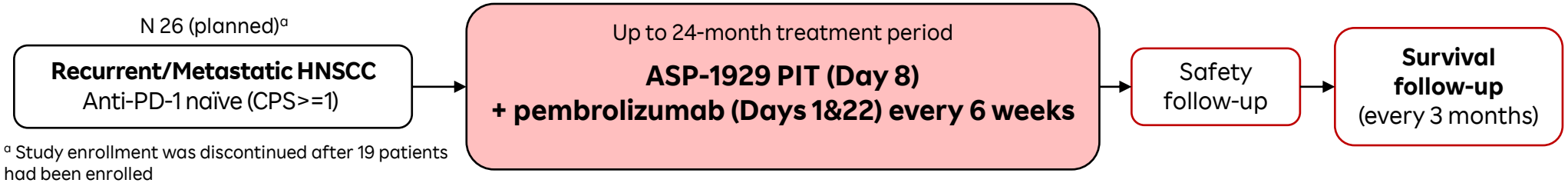
ASP-1929-181: Phase 1b/2 of ASP-1929 Alluminox Treatment + Anti-PD-1

An Open-label study using ASP-1929 PIT in combination with anti-PD-1 therapy in EGFR expressing advanced solid tumors



[a] Study enrollment was discontinued after 19 patients had been enrolled

Primary endpoint
- TEAE(Safety), ORR*

Secondary endpoint
- OS, PFS*, DOR*

* per modified RECIST 1.1.

Key findings

- **OS rate at 18 months: 53.5%** (95% CI 18.5–79.3) [1) 2)]
- ORR: 29.4% (5 patients, 95% CI 10.3–56.0), CR: 17.6% (3 patients), PR: 11.8% (2 patients) [2)]
- **Generally tolerated, manageable AEs with no fatal events** and 2 grade 4 events of laryngeal edema & tumor hemorrhage

1) Median OS has not been reached at data cutoff (Oct 4, 2022).
2) Of 19 enrolled patients, 17 were evaluable for efficacy.

These preliminary findings may change upon completion of follow up and final data analysis.

- ☐ **Plan to discuss with FDA on a new pivotal clinical trial based on this result in 2024H1**
- ☐ **Publication in 2024H1 will have updated data with recent data cut-off (Aug 31, 2023)**

PIT: Photoimmunotherapy
HNSCC: head and neck squamous cell carcinoma
TEAE: Treatment emergent adverse events
ORR: objective response rate
OS: overall survival
PFS: progression-free survival
DOR: Duration of response
CR: Complete response
CI: Confidence intervals
PR: Partial response

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ASP-1929-181: KOL Interview

The encouraging early safety and efficacy outcomes seen so far in this Phase 1b/2 study warrant additional clinical studies to substantiate and reinforce these preliminary findings. Furthermore, these preliminary findings may change upon completion of follow up and final data analysis.

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RM-1995-102: Encouraging RM-1995 Pre-Clinical Data

RM-1995
Targeting CD25+ Treg

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

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

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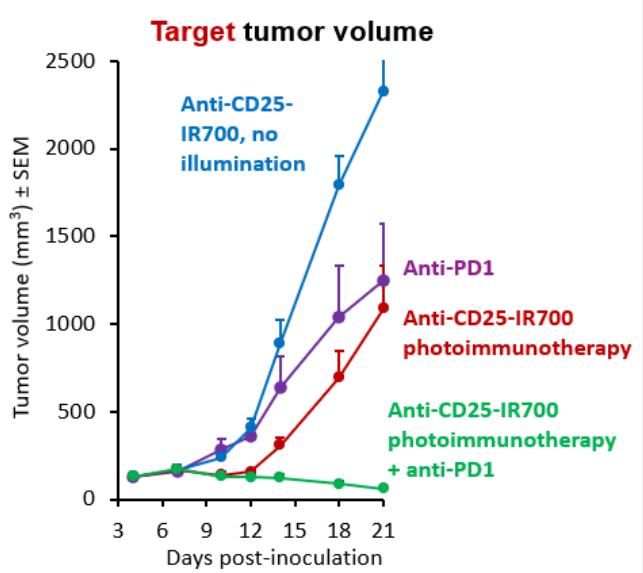
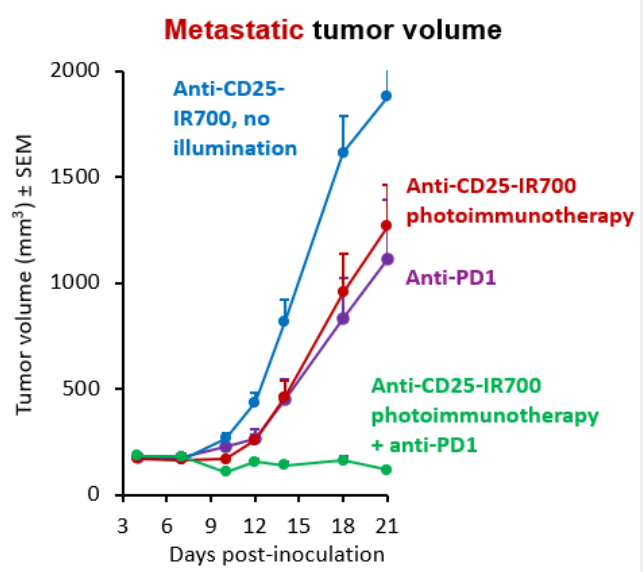
Pre-clinical* data generated at Rakuten Medical





* Mouse CD25 equivalent used in the study

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%)

RM-1995-102: Phase 1 Underway in Japan

A Phase 1, open-label, dose-escalation study of RM-1995 PIT alone or in combination with pembrolizumab in patients with advanced or recurrent solid tumor with liver metastasis

Eligible adults: N ~34

- Have advanced or recurrent solid tumor with **liver metastases**
- Eligible for pembrolizumab monotherapy (for Ph1c)

Primary endpoints

- DLT and AE (Safety)

Secondary endpoints

- PK, ORR*, Sum of diameters of target lesions*, DOR*, DCR*, PFS*, OS

* per modified RECIST 1.1.

Phase 1a:
Drug dose escalation
RM-1995 PIT
n ~18

Light dose: 100 J/cm

0.25 mg/kg (Cohort 1), n≥3 → **0.5 mg/kg** (Cohort 2), n≥3 → **0.75 mg/kg** (Cohort 3), n≥3 → **1.0 mg/kg** (Cohort 4), n≥3 → **1.5 mg/kg** (Cohort 5), n≥3 → **2.0 mg/kg** (Cohort 6), n≥3

Phase 1b:
Light dose escalation
RM-1995 PIT
n ~6

Optimal RM-1995 dose: TBD

200 J/cm (Cohort 7), n≥3 → **300 J/cm** (Cohort 8), n≥3

Phase 1c:
Fixed dose RM-1995 PIT + Anti-PD-1
n ~10

Optimal RM-1995 & light doses **+ pembro** (Cohort 9), n≥10

PIT: Photoimmunotherapy
DLT: Dose limiting toxicy
AE: Adverse event
ORR: Objective response rate

DOR: Duration of response
DCR: Dsease control rate
PFS: Progression-free survival
OS: Overall survival

MTD: Maximum tolerated dose
MAD: Maximum administered dose

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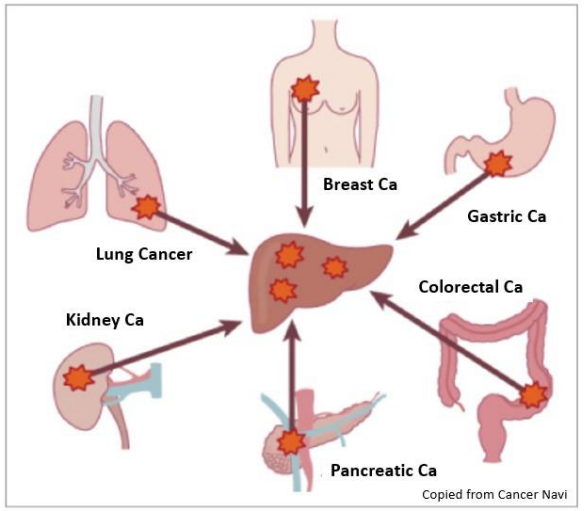
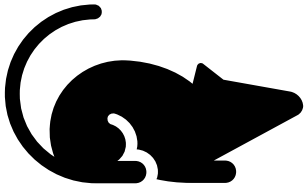
RM-1995-102: Targeting CD25 in Metastatic Liver Tumors



Potential significance of RM-1995-102 in the clinic

- Meeting **high unmet needs** **in patients with liver metastases**
- Potential induction of **antitumor immunity** **that may treat non-illuminated tumors including primary tumors (abscopal effect)**



Upcoming pre-clinical research to support the trial

- Study using transgenic mice that express human CD25 to confirm tumor control
- Developing a more clinically relevant rat model of hepatocellular carcinoma / liver metastasis

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Device Innovation to Accommodate Physicians' Feedback

Guide Tube

Launched in Sep 2023

A diffuser delivery device to support illumination at hypopharynx, larynx, root of tongue, buccal mucosa, etc.

Needle Catheter S1

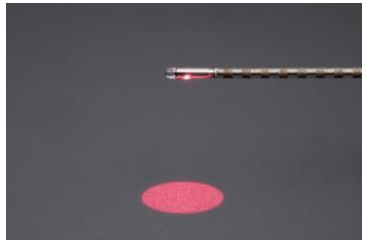
Launched in Sep 2023

New needle catheters with higher usability and improved functionality

Side-Firing Diffuser

To be launched in 2024 Q3

A diffuser illuminating from a side to perform treatment in a narrow, confined space such as hypopharynx, larynx, etc.



Low-Power BioBlade Laser

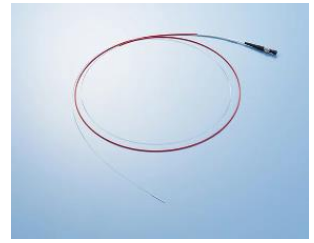
To be launched in 2024 Q3

A low-power laser compatible with a side-firing diffuser for shorter distance for illumination and a smaller spot diameter

10mm Cylindrical Diffuser

To be launched in 2024 Q3

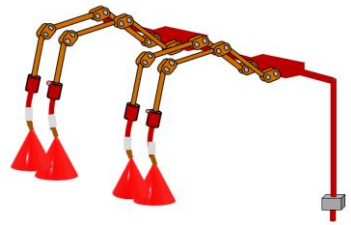
A cylindrical diffuser with a shorter effective length for more precise illumination



Diffuser Holder

To be launched in 2024 Q3

A support device to hold a frontal/side-firing diffuser or a guide tube for stable, hands-free illumination



Luer Adapter

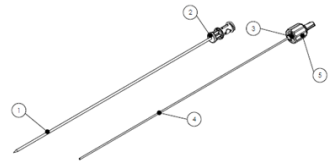
To be launched in 2024 Q2-3

A compact cylindrical diffuser fixture attached on a needle catheter

Needle Catheter S1 Long & Guide Wire

To be launched in 2025 Q1

A longer version of a needle catheter S1 to access larynx, hypopharynx, or liver and a flexible guiding wire for a needle catheter



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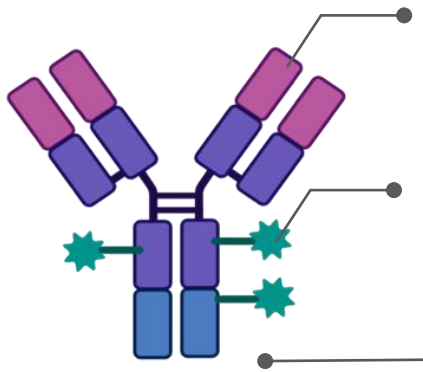
DISCLAIMER: *Rakuten Medical's therapies based on Alluminox™ platform are investigational outside of Japan. Not all devices in this slide have been approved/cleared for use.*

Rakuten Medical Owns and Controls Key Assets for the Treatments

DRUG

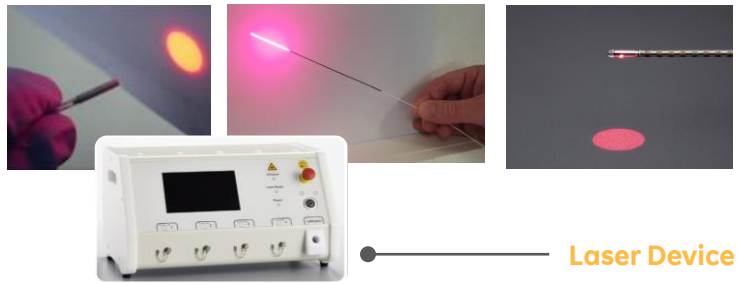


mAb (monoclonal Antibody)
- Cetuximab purchase agreement with Merck KGaA
- Rakuten Medical internal capability to establish and manufacture mAb

IR700 Dye
- Owned by Rakuten Medical (acquired from LI-COR)
- Composition patent
- Synthesis and manufacturing process trade secret

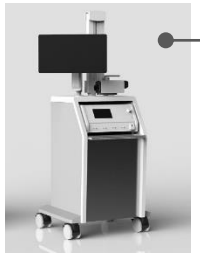
Conjugate
- Manufacturing process managed by Rakuten Medical
- IR700 conjugate compositions patent (Granted)
- Commercial formulation patent (Pending)
- Methods of manufacture patent (Granted)

DEVICE

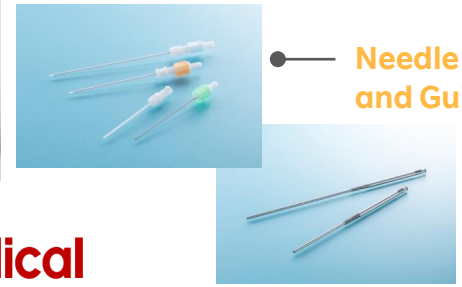


Diffusers
- Frontal and cylindrical diffusers acquired from Medlight
- Trade secret manufacturing processes
- Patent application filed and pending for the side-firing diffuser

Laser Device
- Joint development and potential joint IP for the new laser updates



Fluorescence Camera
- (Investigational product for clinical trial) Joint development and IP ownership



Needle Catheters and Guide Tube
- Design owned by Rakuten Medical
- Multiple patent applications filed and pending for the S1 needle catheters and the guide tube

TREATMENT

Methods of treatment – monotherapy patent (Granted)

Method of treatment in combination with PD-1 patent (Granted)

Rakuten Medical

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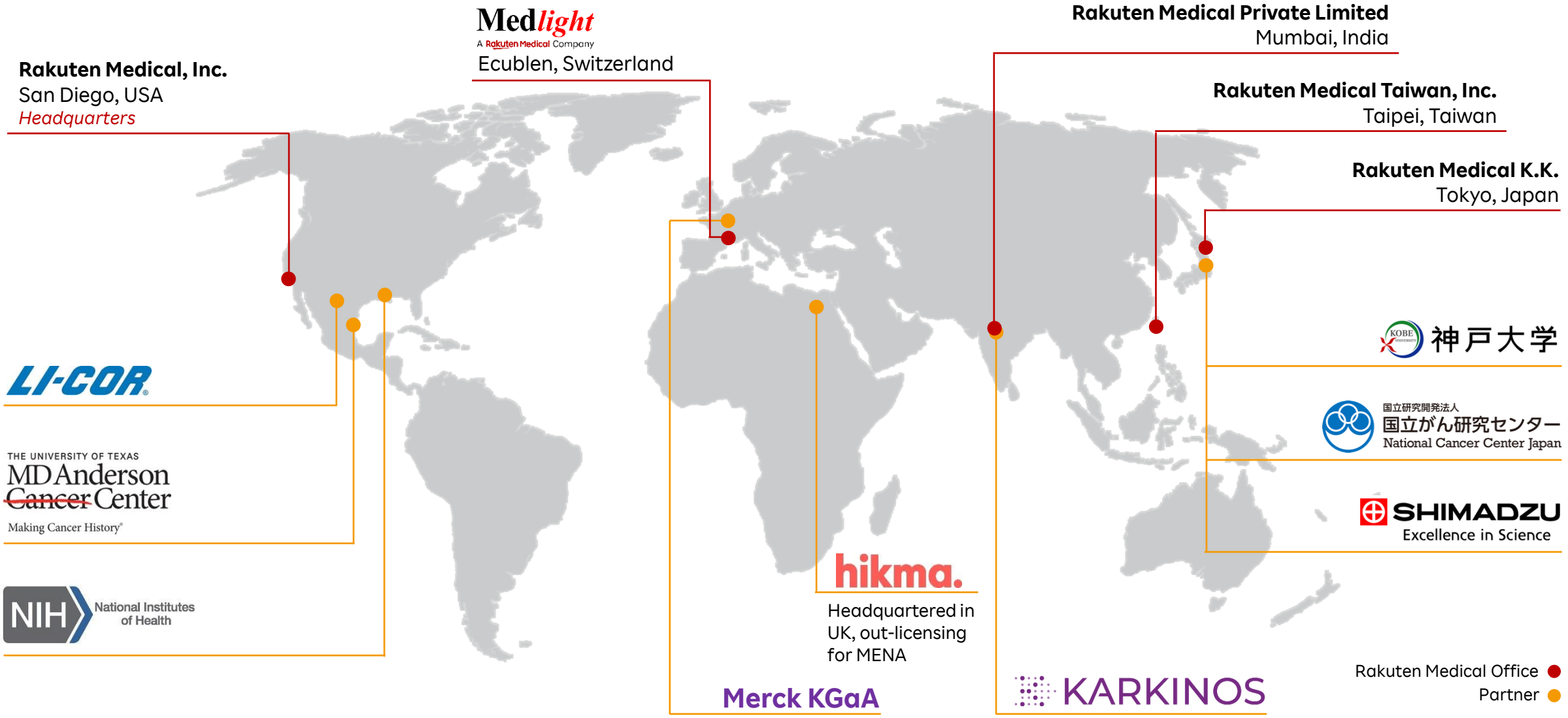
Co-Creating Innovation with Global Partners



Rakuten Medical

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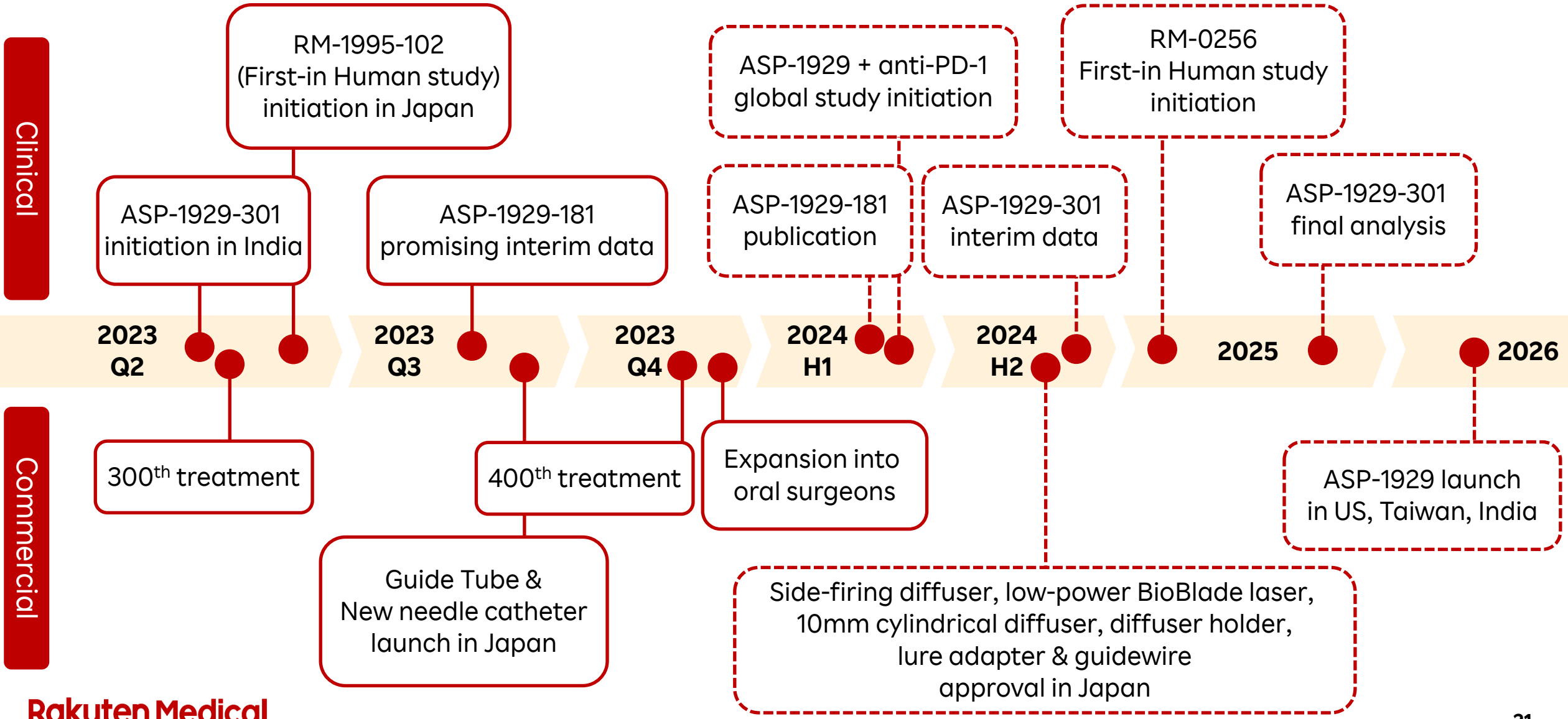
Many Achievements in 2023 and More to Come in 2024 and Beyond



Rakuten Medical

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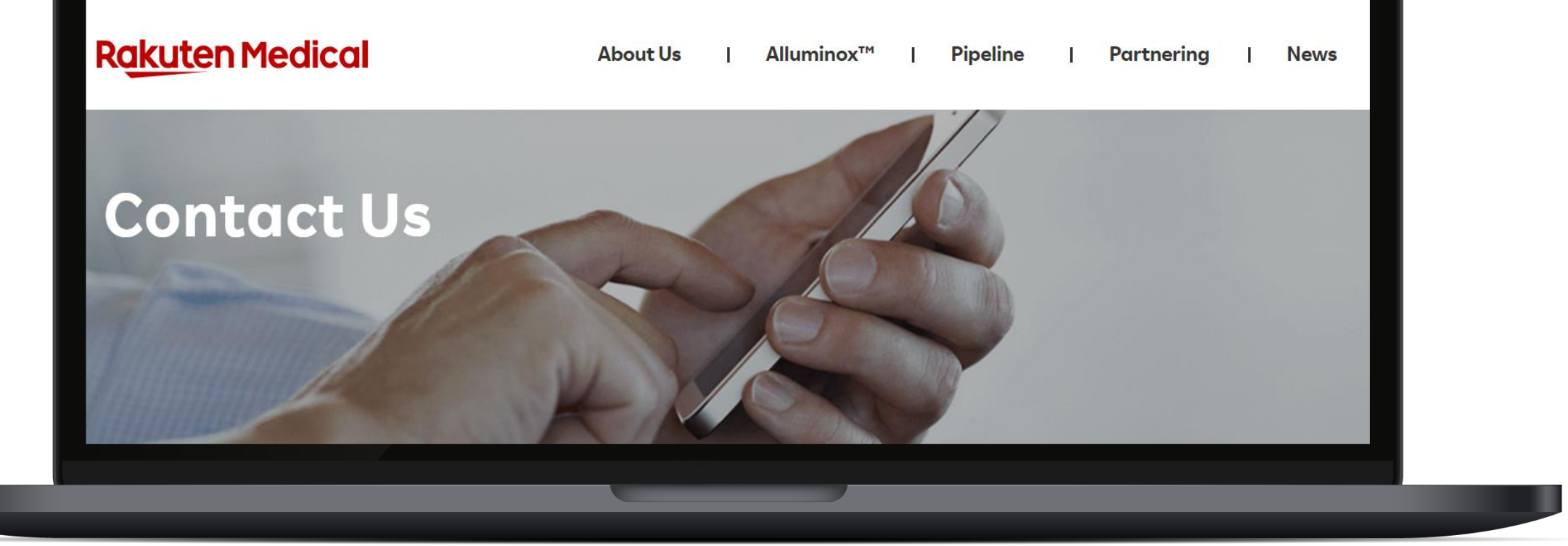

Partnership with Rakuten Medical

We are open to commercialization, co-development, and discovery partnership opportunities.

CONTACT US Partnerships@rakuten-med.com

Scan the QR code to visit our website: