The 25th Anti-Cancer Drug Development Forum

Forefront practical application of cancer genome

Venue; The Cancer Research Institute Hospital of Japanese Foundation for cancer Research in Tokyo

Tumor-agnostic clinical development - ideal and reality

Academia Task for Tumor-Agnostic Clinical Development and the Post-Launch

Takayuki YOSHINO, MD, PhD
Director, Department of Gastroenterology and Gastrointestinal Oncology,
National Cancer Center Hospital East, Japan

NCC NATIONAL CANCER CENTER JAPAN
EPOC
Exploratory Oncology Research & Clinical Trial Center

June 30th, 2018

News Release

平成 30 年 3 月 30 日

各 位

会 社 名　株式会社ファルコホールディングス
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（コード番号：４６７１　東証第一部）
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（TEL. ０７５－２５７－８５８５）

- ✓ **In May 2017, the U.S. FDA granted accelerated approval for pembrolizumab, an anti-PD-1 monoclonal antibody for treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors. The FDA approval represents the first disease agnostic anti- cancer therapy based on tumor biomarker.**
- ✓ **MSD Merck Japan & FALCO has submitted the application for approval for adult patients with unresectable or metastatic, MSI-H solid tumors at March 2018.**
- ✓ **Japanese PMDA is also anticipated to grant the same regulatory for pembrolizumab, to which the PMDA has applied ‘Conditional Early Approval System for Pharmaceuticals (one of Priority Review System)’ at June, 2018.**

今後の見通し
平成 31 年 3 月期連結会計年度の業績に与える影響は軽微であります。

本件に関するお問い合わせ先:
株式会社ファルコバイオシステムズ　バイオメディカル部　電話 075-257-8583

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局所進行性又は転移性の高頻度マイクロサテライト不安定性(MSI-High)癌に対する承認を申請

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類以上のがんについて検討が行われています。
MSDは、重点分野と位置付けるがん領域で患者さんと医療従事者のニーズに応えていけるよう、革新的な医薬品の開発を進め、承認取得に向けて取り組んでいきます。

Agenda

- **TODAY:**

  Accomplishment of SCRUM-Japan for MSI-High tumors before the launch

- **TOMORROW:**

  Guideline in place

- **THE DAY AFTER TOMORROW:**

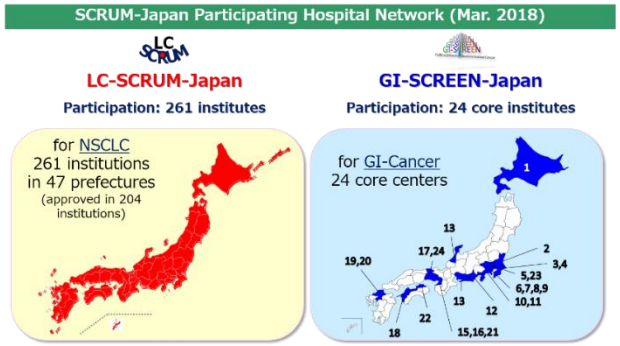
  TMB-high

  RWD

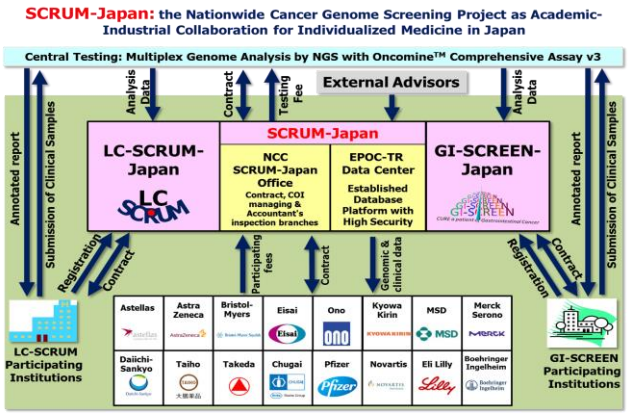
  International Collaboration

The Nationwide Cancer Genome Screening Consortium in Lung and GI Cancers: SCRUM-Japan (n= 9,590 : Feb/2015 - May/2018)

More than 260 participating institutions

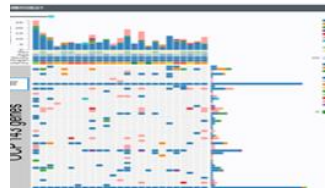


Collaboration with 17 pharma

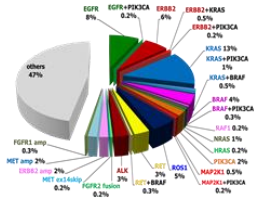


Pan-cancer panel (OCP/OCAv3) analysis

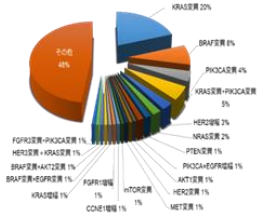
Clinico-Genomic Database



Non-Sq NSCLC



CRC



No. of enrollment

	No. of enrollment
Lung Cancer	**4,309**
Non-sq NSCLC	3,673
Sq NSCLC	636
GI Cancer	**5,281**
Esophageal	370
Gastric	1,142
Small intestine	93
CRC	2,329
HCC	66
Biliary	417
Pancreas	652
NET	73
GIST	79
Others	60
Total	**9,590**

Molecular-profile based IND regist trials

Umbrella type 26 studies

Organ	Target	agent	Phase	sponsor
NSCLC	RET	vandetanib	I /II	IIT (NCCE)
NSCLC	RET	alectinib	I /II	IIT (Kanazawa U)
NSCLC	RET	lenvatinib	II	Eisai
NSCLC	ROS1	entrectinib	II	Ignyta
NSCLC	ROS1	Crizotinib	II	Pfizer
NSCLC	ROS1	DS6051b	II	Daiichi
NSCLC	ROS1/ALK	PF06463922	II	Pfizer
NSCLC	MET	capmatinib	II	Novartis
NSCLC	MET	tepotinib	II	Merck Serono
NSCLC	MET	AZD6049	II	AZD
NSCLC	MET	Crizotinib	II	IIT (Kyusyu CC)
NSCLC	ALK	capmatinib	II	Novartis
NSCLC	ALK	LDK378	II	IIT (NCCE)
NSCLC	ALK	entrectinib	II	Ignyta
NSCLC	ALK	Alectinib	III	Chugai
NSCLC	ALK	brigatinib	II	Takeda
NSCLC	HER2	T-DM1	II	IIT (Okayama U)
NSCLC	HER2	Trastuzumab	II	IIT (Hokkaido U)
NSCLC	KRAS	abemaciclib	III	Lilly
NSCLC	BRAF	Dabra+trame	II	Novartis
SCLC	PI3K/AKT/mTOR	gedatolisib	II	IIT(NCCE)
CRC	MSI-H	pemprolizumab	III	MSD
CRC	HER2	Tmab+Pertuzumab	II	IIT (NCCE)
CRC	BRAF V600E	Eriblin	II	IIT(Aichi CC)
CRC	BRAF nonV600E	Cmab+Bim+Enc	II	IIT(NCCE)
BTC	HER2	DS8201a	II	IIT(NCCH)

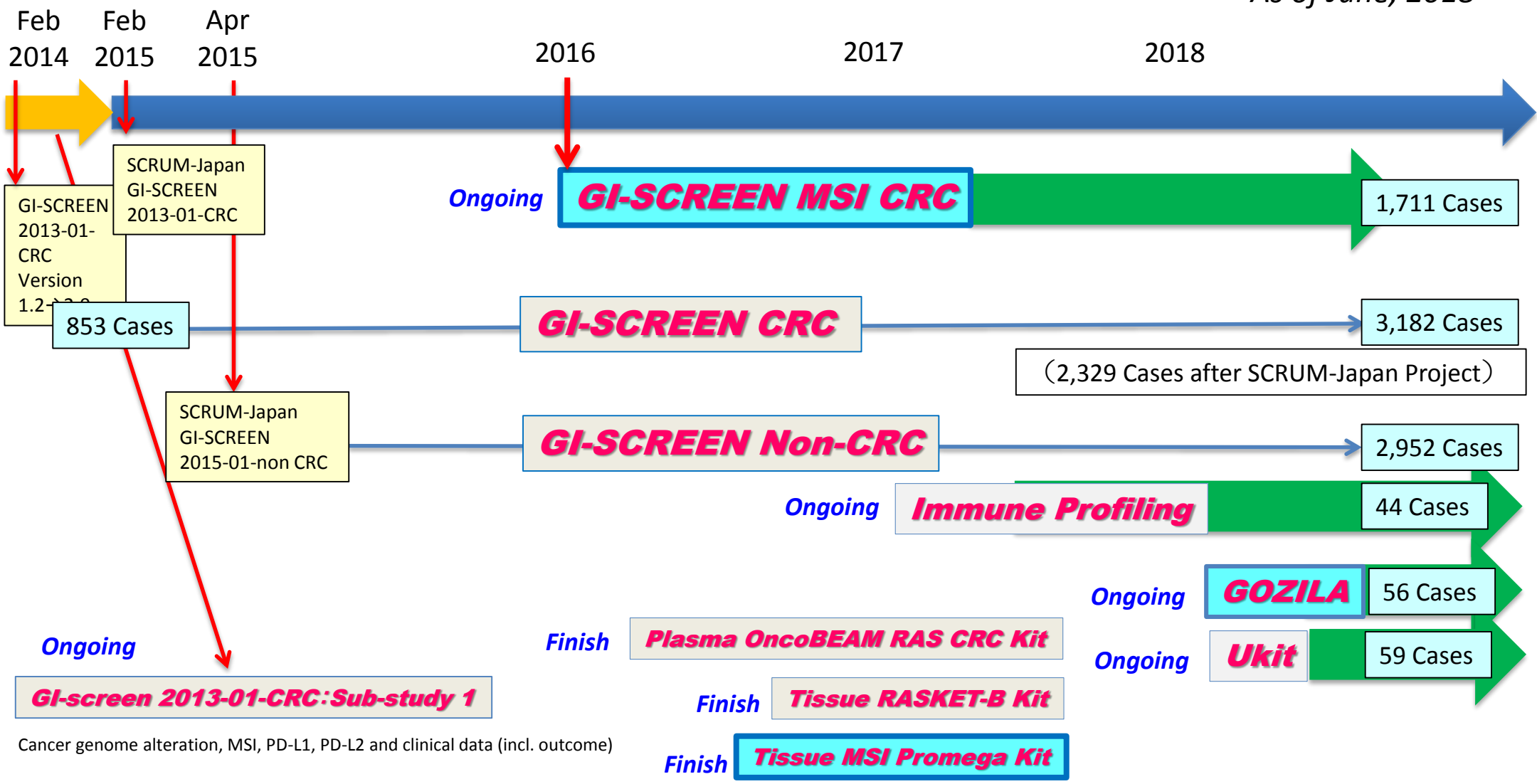
Phase I / basket type 16 studies

Organ	Target	agent	Phase	sponsor
Solid tumor	MET	Merestuinib	I	Lilly
Solid tumor	FGFR	DS1123	I	Daiichi
Solid tumor	FGFR	TAS120	I	Taiho
Solid tumor	EGFR/HER2	varlitinib	I	Aslan
Solid tumor	HER2	DS8201a	I	Daiichi
Solid tumor	NTRK1/2/3	LOXO-101	I	Loxo onc
Solid tumor	NTRK1/2/3	entrectinib	I	Ignyta
Solid tumor	NTRK1/2/3	DS6051	I	Daiichi
Solid tumor	ROS1/ALK	entrectinib	I	Ignyta
Solid tumor	PI3K/AKT/mTOR	TAS117	I	Taiho
Solid tumor	PI3K/AKT/mTOR	AZD5363	I	AZD
Solid tumor	PI3K/AKT/mTOR	BYL719	I	Bayer
Solid tumor	FGFR	TAS120	I	Taiho
Solid tumor	FGFR	BGJ398	I	Novartis
Solid tumor	FGFR	ASP5878	I	Astellas
Solid tumor	FGFR	INCB054828	I	Incyte
Solid tumor	FGFR	E7090	I	Eisai
Solid tumor (GI)	TMB-H	Nivolumab	II	IIT (NCCE)

Accomplishment on GI-SCREEN

CURE a patient of Gastrointestinal Cancer

As of June, 2018



Prevalence of microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) CRC: Cross-trial comparison

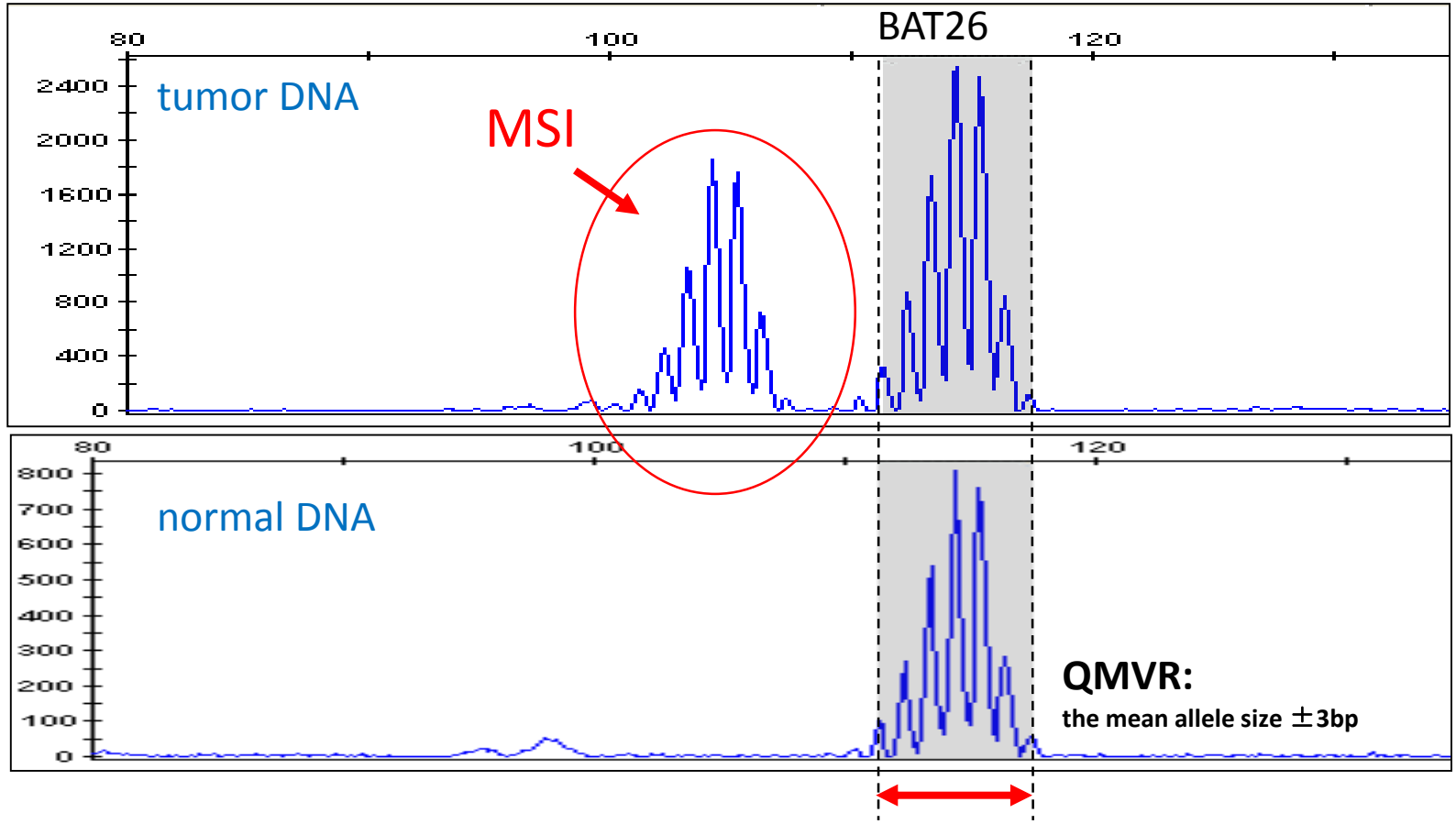
Trial Name	N	Prevalence of MSI-H/dMMR	Overlapping *BRAF* V600E mutation
Pooled dataset [1]	3,063	5.0%	34.6%
AIO Colorectal Study Group [2]	104	4 %	Not reported
Australia and United States [3]	NA	Not reported	30%
Review Article [4]	NA	3 - 5%	Not reported
GI-SCREEN-JAPAN [5]	**853**	**1.9%**	**40%**
NCCE [6]	**277**	**1.9%**	**40%**
GI-SCREEN CRC - MSI * *unpublished*			
Universal Screening in Stage II and III [+] *unpublished*			

Note: GI-SCREEN-JAPAN is the Nationwide Cancer Genome Screening Project for Gastrointestinal Cancer in Japan: NA, not applicable: *Ongoing Prospective Observational Study as of 31st Mar, 2018: [+]Our institutional Data as of 31st Mar, 2018

1 Venderbosch S, et al. *Clin Cancer Res* 2014, 2 Muller CI, et al. *Int J Colorectal Dis* 2008, 3 Goldstein J, et al. *Ann Oncol.* 2014, 4 Cohen R, et al. *Curr Ocol Rep* 2016, 5 Kajiwara T, Yoshino T. *ASCO* 2016, 6 Kawazoe A, Yoshino T. *ASCO-GI* 2016

Quasi-monomorphic variation range: QMVR

Okamoto W, …., Yoshino T. ESMO 2017



- The mean allele size of mononucleotide markers was generated from the normal DNA.
- QMVR was defined as the mean allele size ±3bp.
- Because of few variant alleles observed in Caucasians as well as in Asians, QMVR might be applicable as references.

Tissue MSI Promega Kit

Background

Tissue MSI Promega Kit

Okamoto W, …., Yoshino T. ESMO 2017

- According to the pilot study performed by FALCO Biosystems, the QMVR in 149 healthy Japanese individuals were almost the same as those of the Caucasian group. (1)

	NR21	BAT26	BAT25	NR24	MONO27
Pilot study (1)	**98.4-104.4**	**111.4-117.4**	**121.0-127.0**	**129.5-135.5**	**149.9-155.9**
Patil DT, et al. (2)	98-104	112-118	121-127	129-135	149-155

- Three large Japanese cohorts suggested that the frequencies of variant alleles for 5 mononucleotide markers were rare.(1)

	NR21	BAT26	BAT25	NR24	MONO27
MSI analysis of GI-SCREEN 2013-01-CRC	**4/602 (0.66%)**	**0/602 (0%)**	**3/602 (0.50%)**	**0/602 (0%)**	**0/602 (0%)**
Saitama Cancer Center	**3/774 (0.39%)**	**2/3320 (0.06%)**	**12/3320 (0.36%)**	**2/774 (0.26%)**	**Not evaluated**
FALCO Biosystems	**2/252 (0.79%)**	**0/252 (0%)**	**1/252 (0.40%)**	**0/252 (0%)**	**0/252 (0%)**

(1) Bando H, et al. ASCO GI. 2017
(2) Patil DT, et al. Diagn Mol Pathol. 2012

Schema of the clinical evaluation study

Standard method
(GI-SCREEN CRC-MSI study)

Tumor tissue

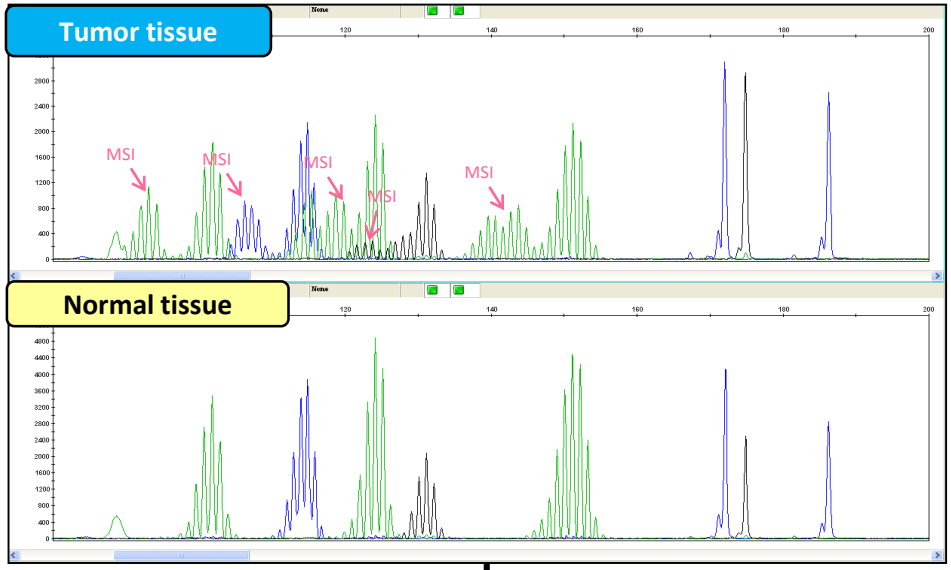
Normal tissue

DNA extraction

PCR
(NR-21, BAT-26, BAT-25, NR-24, MONO-27)

The Promega MSI testing was performed using genomic DNA extracted from both tumor and paired normal tissue.

Capillary electrophoresis



Decision

The presence of MSI was determined by the appearance of new alleles in the tumor sample that were not present in the normal sample

Testing method
(This study)

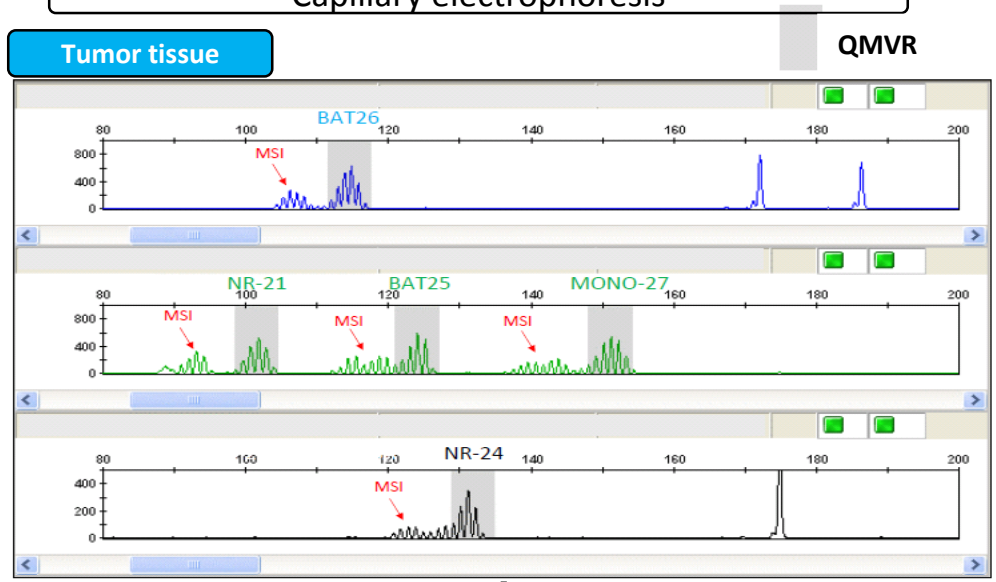
Tumor tissue

DNA extraction

PCR (The New MSI kit)
(NR-21, BAT-26, BAT-25, NR-24, MONO-27)

The new MSI kits were manufactured under the Quality Management System (QMS) for in vitro diagnostics (IVDs).

Capillary electrophoresis



Decision

The presence of MSI was determined by appearance of the tumor allele peak outside the Quasi-Monomorphic Variation Range (QMVR)

Results: Primary and Secondary endpoints

Okamoto W, …., Yoshino T. ESMO 2017

		Standard method	
		Negative (MSS/MSI-L)	Positive (MSI-H)
Testing method	Negative (MSS/MSI-L)	424	0
	Positive (MSI-H)	0	11

N = 435

Primary endpoint

- **Sensitivity : 11 / (0+11) =100%**
- **Specificity : 424 / (424+0) =100%**

Secondary endpoints

- Concordance rate : (424+11) / (424+0+0+11) =100%
- Positive predictive value : 11 / (0+11) =100%
- Negative predictive value : 424 / (424+0) =100%

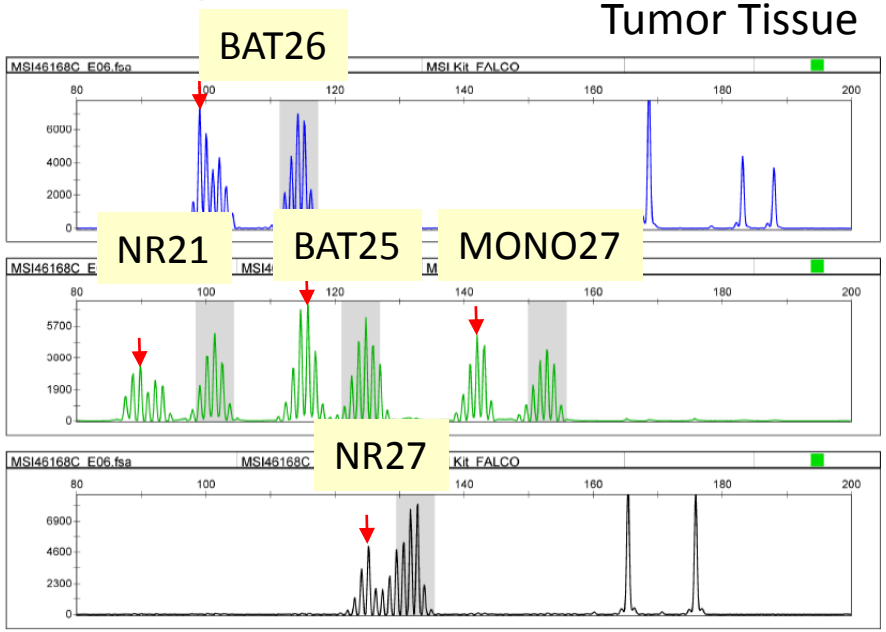
Tissue MSI Promega Kit

Can we adapt the findings from the CRC study to Non-CRC?

-Our Experience-

MSI-High CRC

Tumor Tissue



We will soon start the confirmatory study to investigate the concordance between MMR-IHC and MSI-PCR in Non-CRC, utilizing the SCRUM-Japan Platform before the launch of pembrolizumab.

The Journal of Molecular Diagnostics, Vol. 19, No. 1, January 2017

ELSEVIER

the Journal of Molecular Diagnostics

jmd.amjpathol.org

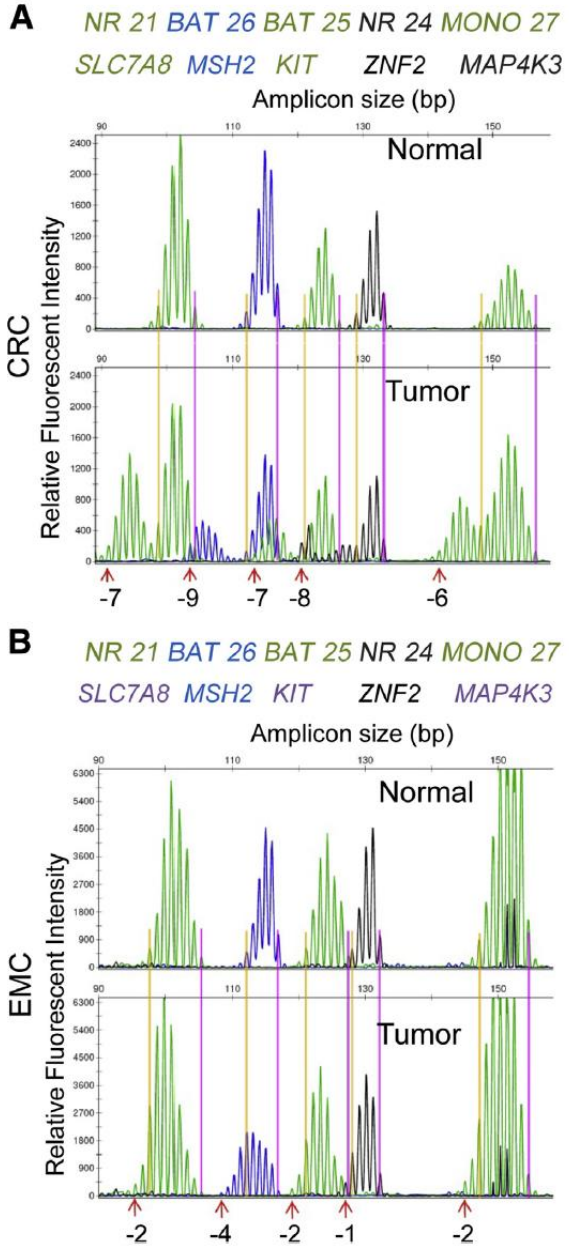
Differences in Microsatellite Instability Profiles between Endometrioid and Colorectal Cancers

A Potential Cause for False-Negative Results?

Yang Wang, Chanjuan Shi, Rosana Eisenberg, and Cindy L. Vnencak-Jones

From the Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee

Colorectal (CRCs) and endometrioid (EMCs) cancers in patients with Lynch syndrome exhibit microsatellite instability (MSI) detected by PCR or immunohistochemistry (IHC). While both assays are equally sensitive for CRCs, some suggest that PCR has a higher false-negative rate than IHC in EMCs. We assessed the MSI profiles of 91 EMC and 311 CRC specimens using five mononucleotide repeat markers: BAT25, BAT26, NR21, NR24, and MONO27. EMCs with high MSI (MSI-H) showed a mean left shift of 3 nucleotides (nt), which was significantly different from 6 nt in CRCs. A shift of 1 nt was observed in multiple markers in 76% of MSI-H EMCs, whereas only 12% of MSI-H CRCs displayed a 1-nt shift in one of five markers. IHC against four mismatch repair proteins was performed in 78 EMCs. Loss of staining in one or more proteins was detected in 18 of 19 tumors that were MSI-H by PCR. When EMC tumor cell burden was diluted to <30%, MSI-H was no longer observed in two of three EMCs with a mean nucleotide shift of 1 nt. These results indicate that EMC and CRC MSI profiles are different and that caution should be exercised when interpreting the results, as subtle, 1-nt changes may be missed. These findings provide a potential cause of previously reported discordant MSI and IHC results in EMCs. *(J Mol Diagn 2017, 19: 57–64; http://dx.doi.org/10.1016/j.jmoldx.2016.07.008)*



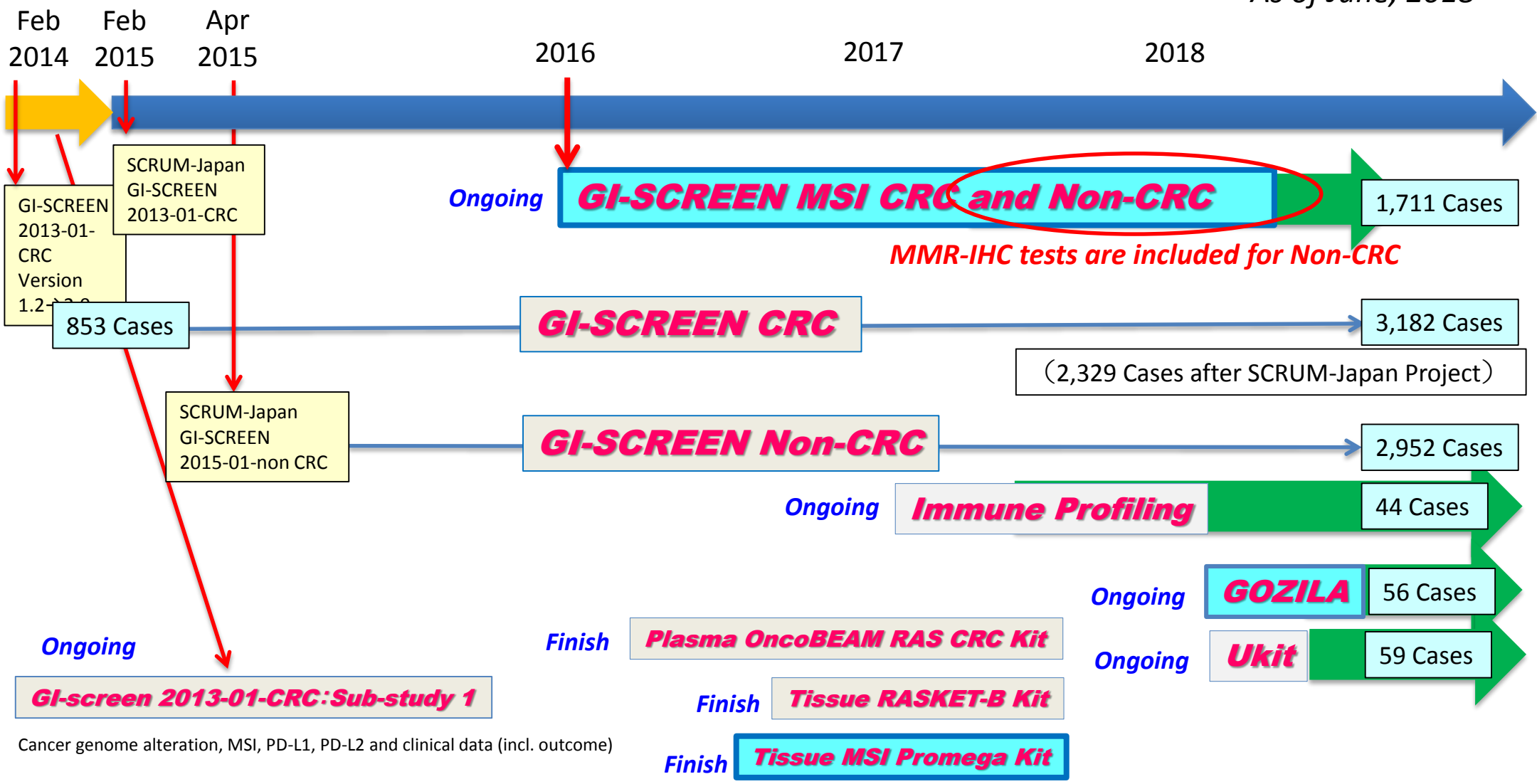
Can we adapt the findings from the CRC study to Non-CRC?

-Our Experience- *We also identified this difference in Ovarian and Breast Cancers.*

Accomplishment on GI-SCREEN

CURE a patient of Gastrointestinal Cancer

As of June, 2018



Clinical Questions

- Should all cancer patients be tested for MSI / MMR?
- When is the optimal timing for tests?
- Which tests are recommended?
- What is the appropriate biospecimen for tests?
- Which treatment is best for MSI-H / MMR-D patients, particularly for metastatic solid tumors?
- Which line of therapy should immunotherapy be used in MSI-H / MMR-D solid tumors ?

etc.

Annals of Oncology 29: 44–70, 2018
doi:10.1093/annonc/mdx738
Published online 16 November 2017

SPECIAL ARTICLE

25,487 Total Views (17,167 Page views and 8,320 PDF Downloads)
Since November 2017 as of 29th June 2018

Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO–ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS

T. Yoshino[1*], D. Arnold[2], H. Taniguchi[3], G. Pentheroudakis[4], K. Yamazaki[5], R.-H. Xu[6], T. W. Kim[7], F. Ismail[8], I. B. Tan[9], K.-H. Yeh[10], A. Grothey[11], S. Zhang[12], J. B. Ahn[13], M. Y. Mastura[14], D. Chong[15], L.-T. Chen[16], S. Kopetz[17], T. Eguchi-Nakajima[18], H. Ebi[19], A. Ohtsu[20], A. Cervantes[21], K. Muro[22], J. Tabernero[23], H. Minami[24], F. Ciardiello[25] & J.-Y. Douillard[26]

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Summary of Asian Recommendations including consideration of left-versus right-sided primary tumour location

Yoshino T, et al. ***Annals of Oncology*** 2018

Molecular pathology and biomarkers
Recommendation 6 with revision: Tumour mismatch repair（MMR）testing 6a. **Immunohistochemistry（IHC）tests for MMR proteins or PCR tests for microsatellite instability（MSI）** in the metastatic disease setting can assist clinicians in genetic counselling［Ⅱ, B］. 6b. **Tumour MMR** testing has strong predictive value for the use of immune check-point inhibitors in the treatment of patients with mCRC［Ⅱ, B］.

The frequency of DNA MMR deficiency in stage IV CRC is about 4–8% in Western countries [9], and about 1.9–3.7% in Japan [61, 62]. Since Asian experts view IHC and PCR as complementary techniques for evaluating tumour MMR deficiency, all the Asian experts agreed [A=100%] with the recommendations for tumour MMR testing accompanied by the modifications to *recommendations 6a and b* indicated in bold text above. They also all agreed that tumour MMR testing has strong predictive value for the use of immune check-point inhibitors in the treatment of mCRC patients [63, 64].

Next Step: GL for MSI-High Solid Tumor

9. Van Cutsem E, Yoshino T, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386-1422.
61. Fujiyoshi K, Yamamoto G, Takenoya T et al. Anticancer Res 2017; 37: 239-247.
62. Kajiwara T, Shitara K, Denda T, …. Yoshino T. The Nationwide Cancer Genome Screening Project for Gastrointestinal Cancer in Japan (GI-SCREEN): MSI-Status and cancer-related genome alterations in advanced colorecta cancer (CRC)- GI-SCREEN 2013-01-CRC substudy. J Clin Oncol 2016; 34 (15 suppl): abstr 3573.
63. Le DT, et al. N Engl J Med 2015; 372: 2509-2520. 64. Overman MJ, et al. Lancet Oncol 2017; 18: 1182-1191.

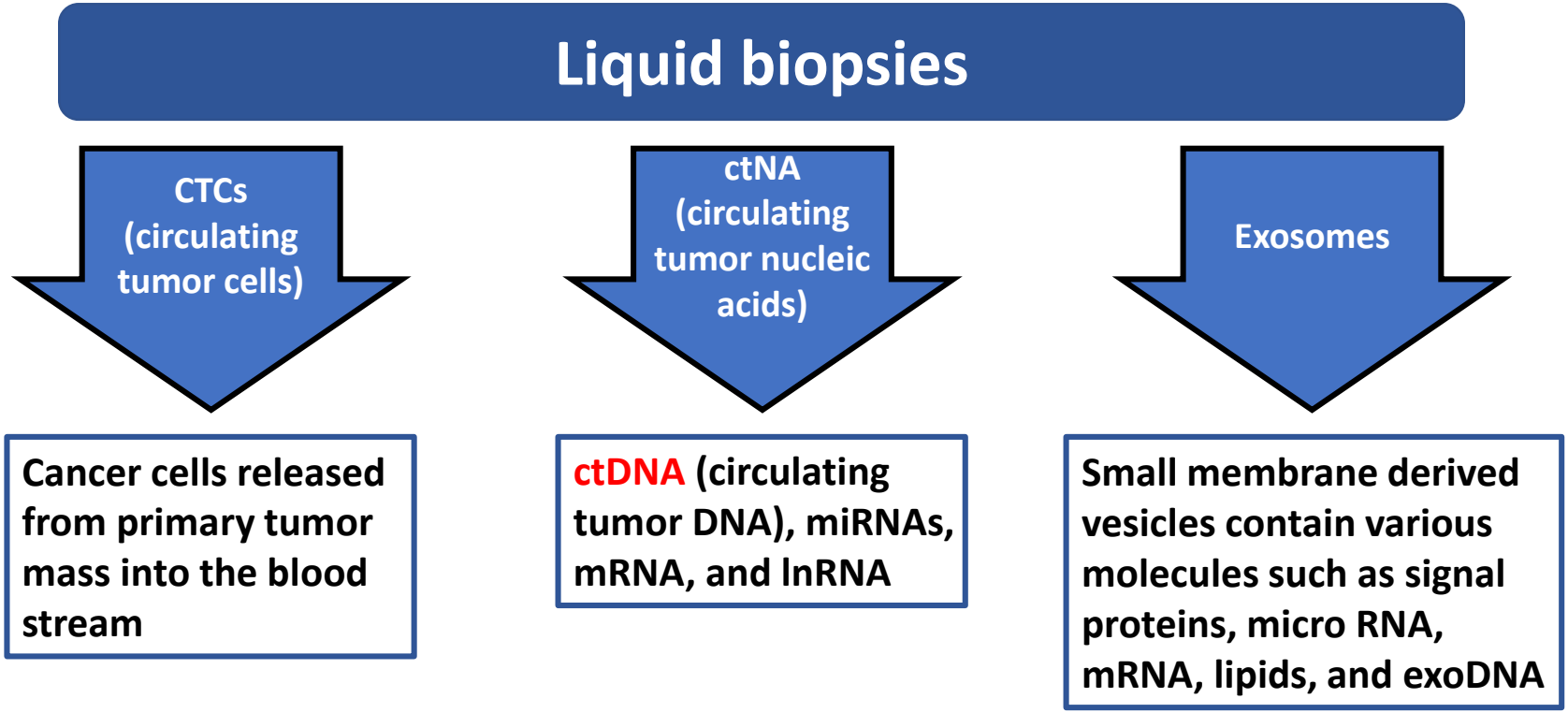
What we learned from the US FDA Approval

Goal is to identify patients most likely to benefit from treatment

Challenges in drug development for a tumor-agnostic indication

- Study design for providing evidence of clinical efficacy (*vs traditional randomized controlled studies*)
- Identification of study population

Liquid Biopsy



Samples: blood, serum/plasma, urine, CSF, saliva

Diaz LA, et al. J Clin Oncol. 2014.

Advantages of ctDNA Analysis

- Minimal Invasiveness
- Rapid turnaround time
- Low cost of sampling procedure
- Capturing intratumoral heterogeneity

Nakamura Y and Yoshino T. Oncologist 2018.

GI-SCREEN GOZILA Project

A Comprehensiv

Point Mutations and Splice Site–Disrupti

AKT1	*ALK*	*APC*	*AR*
CCND1	*CCND2*	*CCNE1*	*CDH1*
ERBB2	*ESR1*	*EZH2*	*FBXW7*
GNAS	*HNF1A*	*HRAS*	*IDH1*
MAP2K2	*MAPK1*	*MAPK3*	*MET*
NOTCH1	*NPM1*	*NRAS*	*NTRK1*
RB1	*RET*	*RHEB*	*RHOA*
TP53	*TSC1*	*VHL*	

Indels – 23 Genes

ATM	*APC*	*ARID1A*	*BRCA1*
KIT	*MET*	*MLH1*	*MTOR*
TP53	*TSC1*	*VHL*	

Amplifications – 18 Genes

AR	*BRAF*	*CCND1*	*CCND2*
FGFR2	*KIT*	*KRAS*	*MET*

Fusions – 6 Genes

ALK	*FGFR2*	*FGFR3*	*RET*

The Guardant360® Assay Receives Expedited Access Pathway Designation for Breakthrough Devices from FDA

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Feb 15, 2018, 12:18 ET

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REDWOOD CITY, Calif., Feb. 15, 2018 /PRNewswire/ -- The Guardant360® assay, the leading comprehensive liquid biopsy, received an Expedited Access Pathway (EAP) designation from the United States Food and Drug Administration, Guardant Health announced. If approved, the Guardant360 assay could be the first FDA-approved comprehensive liquid biopsy.

"This marks a critical milestone for our work with the FDA, and an important moment in the development of comprehensive liquid biopsies," said Guardant Health Co-Founder and President AmirAli Talasaz. "This designation allows us to work hand in hand with the FDA as we prepare our submission to the FDA later this year. Accomplishing this goal will be critical as we deepen our capabilities for our partners in the biopharma industry."

Guardant360 is a comprehensive liquid biopsy that helps oncologists select the optimal treatment for advanced cancer patients without the need for an invasive tissue biopsy. Guardant360 has been extensively validated and is supported by more than 20 clinical outcome studies. It is available in more than 30 countries.

The Expedited Access Pathway is intended to speed review of breakthrough technologies and medical devices that serve unmet medical needs. Through the program, the FDA will work with Guardant Health to finalize its data development plan, providing access to senior FDA officials and facilitating a collaborative, cross-disciplinary review. The FDA is expected to replace the EAP soon with its new Breakthrough Devices Program. Premarket Approval Applications from EAP-designated devices typically receive priority review at the FDA, and all submissions designated as Breakthrough Devices are set to receive priority review.

"Our FDA submission for Guardant360 is Guardant Health's top priority for 2018," said Guardant Health Co-Founder and CEO Helmy Eltoukhy. "The ability to tap into the FDA's expertise and support will be invaluable as we work toward our goal of seeking the first FDA approval for a comprehensive liquid biopsy."

Simultaneous Press Release from Japan and USA

National Cancer Center Japan

To the press

SCRUM-Japan GI-SCREEN Aims for Realizing of Cancer Precision Medicine Utilizing Liquid Biopsy by Analyzing Comprehensive Cancer Genome Alterations in Blood

March 13, 2018

National Cancer Center, Japan

In February 2018, National Cancer Center（President, Dr. Hitoshi Nakagama, Tokyo, Japan）and National Cancer Center Hospital East（Director, Dr. Atsushi Ohtsu, Kashiwa, Japan）launched a new project "Research on Liquid Biopsy in Patients with Advanced Gastrointestinal Cancers". This study is conducted using a highly sensitive genetic analysis technology "Guardant360® assay" as part of a Nationwide cancer genome screening project for various gastrointestinal cancer, "SCRUM-Japan GI-SCREEN". The Guardant360® assay, developed by Guardant Health in the U.S. is a new diagnostic technique capable of analyzing fragments of tumor DNA circulating in the blood by next-generation sequencer technology, and providing cancer genetic information accurately and quickly. As conventional tumor tissue biopsies are highly invasive, biopsies of multiple regions and repeated biopsies can cause significant risk to the patients and delays in reaching a treatment decision. However, liquid biopsy is minimally invasive and enables the analysis of fragments of tumor DNA circulating in the blood. For these reasons, it can overcome the problems faced by tumor tissue biopsy.

Guardant Health and National Cancer Center East Japan Announce Liquid Biopsy Arm of GI Cancer Trial

NEWS PROVIDED BY
Guardant Health →
Mar 12, 2018, 22:00 ET

SHARE THIS ARTICLE

REDWOOD CITY, Calif., March 12, 2018 /PRNewswire/ -- The Guardant360® assay, the leading comprehensive liquid biopsy, will be used to launch a new arm of a nationwide trial run by SCRUM-Japan GI-SCREEN, organized by the National Cancer Center Hospital East (NCCE), Kashiwa, Japan. The study will match patients with advanced gastrointestinal (GI) cancer, including gastric and colorectal cancer (CRC), to novel therapies in clinical trials that target specific gene alterations.

GOZILA (Guardant Originates in ZIpangu Liquid biopsy Arrival) trial will initially use Guardant360 to test 200 advanced CRC patients in Japan whose cancer has progessed after standard treatment with anti-EGFR therapy. Those who test positive for amplification in the *ERBB2* gene will be enrolled in a clinical trial exploring the effectiveness of changing to an anti-ERBB2 combination targeted therapy with trastuzumab + pertuzumab (Clinical trial information: UMIN000030505). The study will expand to include 2,000 patients with a variety of GI cancers and treatment arms.

"We are more than happy to collaborate with Guardant Health to investigate new therapeutic options for patients with GI cancers. Other treatment arms will open in the upcoming year," said GI-SCREEN Principal Investigator Dr. Takayuki Yoshino.

The study is part of a larger effort in Japan, called SCRUM-Japan GI-SCREEN, to assess the genomic profile of patients with advanced cancer in their GI tracts and match them to associated targeted therapies.

"We are excited to be working with NCCE Japan to help study new therapeutic options for patients in Japan with GI cancers," said Guardant Health CEO Helmy Eltoukhy. "Tumors that metastasize from the GI tract can be especially difficult to access, making tissue specimen collection challenging. Through a simple blood draw, we can help match these patients to the experimental treatments being studied by NCCE Japan."

GI-SCREEN GOZILA Project

Umbrella & Basket Clinical Trials (IIS Only to be listed) based on NGS-Based Liquid Screening

Nakamura Y, Yoshino T. ***Oncologist.*** 2018

- Each arm to have a junior/senior investigator leadership team
- Flexible design: arms open and close with best available science

GOZILA Project

Guardant **O**riginates in **Z**ipangu **L**iquid biopsy **A**rrival

Nationwide Genome Screening Project

SCRUM-Japan GI-SCREEN
24 sites

CRC cohort, N = 1,000
- Before anti-EGFR, N = 500
- Refractory to anti-EGFR, N = 500

CRC Only

ctDNA analysis

- **HER2 Positive** → **Trastuzumab + Pertuzumab (TRIUMPH)**
- ***BRAF* V600E MT** → **Eribulin (BRAVERY)**
- ***BRAF* Non-V600E MT** → **Binimetinib+ Encorafenib + Cetuximab (BIG BANG)**
- ***MET* Amplification** → **Drug A + Drug B** FPI, 1Q 2019

Non-CRC cohort, N = 1,000
- Gastric cancer, N = 300
- Esophageal cancer, N = 150
- Hepatocellular carcinoma, N = 100
- Biliary tract cancer, N = 150
- Pancreatic cancer, N = 100
- Neuroendocrine tumor/carcinoma, N = 50
- GIST, N = 100
- Others, N = 50

Non-GI Cancer cohort, N = 100

Pan Cancer

ctDNA analysis

FPI, 3Q, 2018

- **bTMB-High Cancer** → **Nivolumab (TMB-H basket)**
- **Any X alteration** → **X-targeted Tx** FPI, 1Q, 2019
- **Any Y alteration** → **Y-targeted Tx** FPI, 4Q, 2019

Global Collaboration for ctDNA Analysis to elucidate the Clinical Utility

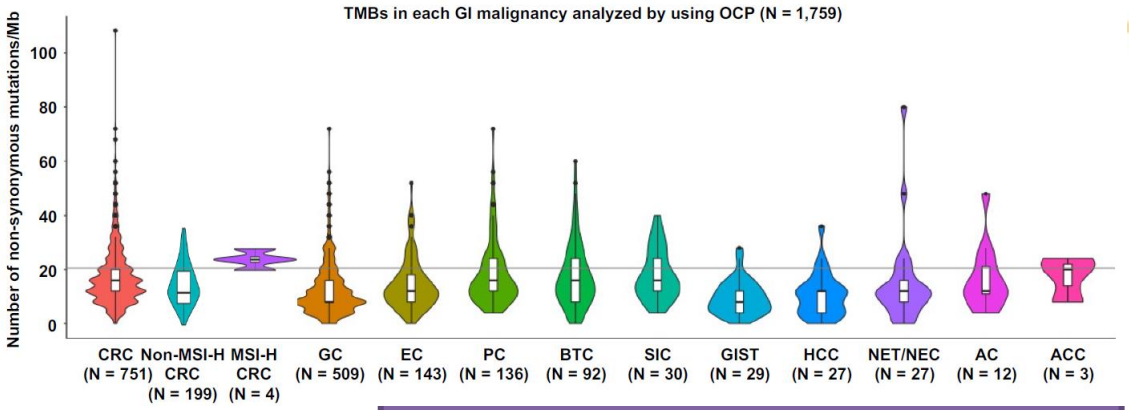
Opportunities for collaboration

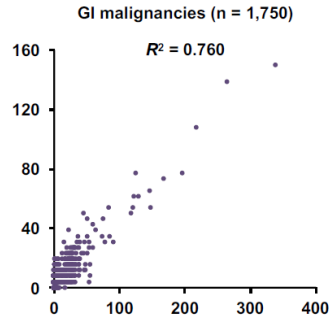
- Pooling and comparing cfDNA profiling results
- Pooling efficacy results (of similar trials)
- Develop novel concepts utilizing blood-based biomarkers
- International multi-site trials for extremely rare targets (FGFR, RET, NTRK1/2/3)
- Pool data for establishing cutoffs (copy number corrected, etc)

Next steps

- Follow up at GI ASCO, potentially ESMO – update progress on treatment arms, collaborative data sharing
- Proposal: COLOMATE-GOZILA investigator summit at Mayo CME conference (San Diego, CA) in March 2019
  - Will include pharma collaborators

TMBs Across Various Advanced GI Malignancies in GI-SCREEN & Collaboration with Certain Companies





X-Axis =
Number of non-synonymous mt/Mb (OCP)

Y-Axis =
Number of non-synonymous mt/Mb (WES)

	N	Median TMB, mt/Mb (Range)	Frequency of TMB > 20 mt/Mb, %
CRC	751	15.3 (0.0 - 103.6)	23.6
Non-MSI-H	199	15.3 (0.0 - 34.5)	17.1
MSI-H	4	23.0 (19.2 - 26.8)	75.0
GC	509	7.7 (0.0 - 69.0)	13.3
EC	143	11.5 (0.0 - 49.9)	17.5
PC	136	15.3 (3.8 - 69.0)	27.9
BTC	92	15.3 (0.0 - 57.5)	26.1
SIC	30	15.3 (3.8 - 38.4)	30.0
GIST	29	7.7 (0.0 - 26.8)	6.9
HCC	27	11.5 (0.0 - 34.5)	7.4
NET/NEC	27	11.5 (0.0 - 76.7)	14.8
AC	12	11.5 (3.8 - 46.0)	25.0
ACC	3	19.2 (7.7 - 23.0)	33.3

Nakamura Y, Yoshino T. ASCO 2018

- The OCP panel can assess TMB with a high correlation with WES.
- TMB varied widely across various advanced GI malignancies.
- TMB analysis may be used as an agnostic histologic indicator to identify patients with GI malignancies who can benefit from immunotherapy

Nakamura Y, Yoshino T. ASCO 2018

TMB-H Basket| Nivolumab for TMB-H GI Cancers

From September, 2018

- ☐ **Advanced GI cancers refractory or intolerant to standard chemotherapy**
  - ■ **Colorectal cancer**
  - ■ **Gastric cancer**
  - ■ **Esophageal cancer**
  - ■ **Others (Biliary tract cancer, Pancreatic cancer, Hepatocellular carcinoma, Small intestine cancer, Appendiceal cancer, Anal canal cancer, Neuroendocrine tumor/carcinoma, GIST**
- ☐ **Tumor mutation burden-high identified by Guardant360**

→ **Nivolumab**
3 mg/kg DIV, Q2W
until PD

Sample size: **70 (40 at 1st sate, 30 at 2nd stage)**
Study design: **Bayesian two-stage adaptive design**
Primary endpoint: **Objective response rate (ORR) by RECIST v1.1**
Secondary endpoints: **Progression-free survival (PFS) by RECIST v1.1 and irRECIST, Duration of response (DoR) by RECIST v1.1 and irRECIST, Disease control rate (DCR) by RECIST v1.1 and irRECIST, Overall survival (OS), Incidences of adverse events**

UMIN000033182

Prospective registry study for control data at CTD evaluation :
SCRUM-Japan Registry (since 07/2017)

◆ **Data collection for efficacy**

①Following data collection in each line Tx

- **➢ORR：Objective Response Rate**
- **➢DoR：Duration of Response**
- **➢DCR：Disease Control Rate**
- **➢PFS：Progression Free Survival**
- **➢TTF：Time to Treatment Failure**

② OS：Overall Survival

Subjects for SCRUM registry

Lung cancer

LC-SCRUM	target	Freq.(%)*	Estimated sample size
Non-sq NSCLC	RET fusion	3.0	60
	MET ex14skip	4.8	97
	MET amp	1.0	20
	ERBB2 mut	6.2	124
	ERBB2 amp	2.0	40
Sq NSCLC	FGFR1 amp	10.0	30
	FGFR2 amp	0.6	2
	FGFR3 fusion	0.6	2
	PIK3CA amp	14.4	43
	PIK3CA mut	6.8	20
total			438

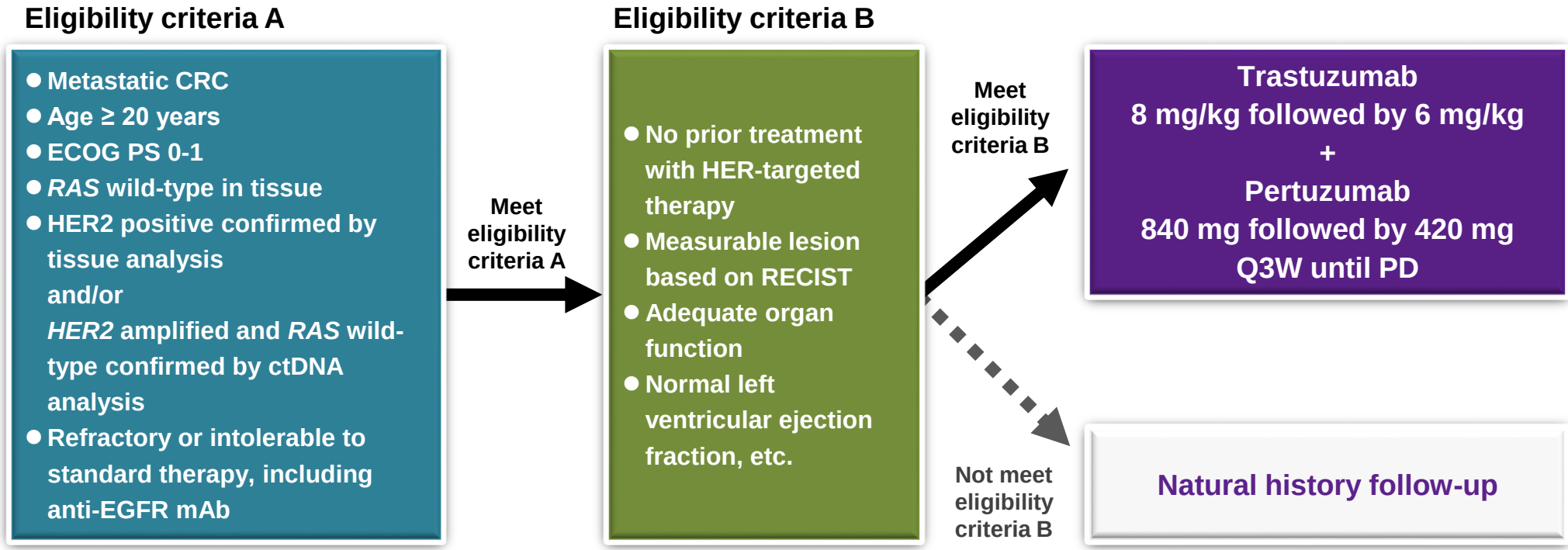
*: frequency in the SCRUM-Japan previous cohort

GI cancers

GI-SCREEN	target	Freq (%)*	Estimated sample size
CRC	BRAF mut	9.9	99
	ERBB2 amp	3.1	31
	MET amp	0.4	4
	NTRK fus	0	0
	RSPO2 fus	-	-
	RSPO3 fus	-	-
	RNF43 mut	-	-
	BRAF mut	9.9	99
GC	FGFR2 amp	3.0	15
	MET amp	2.3	11
EC	ERBB2 amp	2.8	4
	PIK3CA mut	7.3	11
	PIK3CA amp	1.8	3
Biliary tract cancer	FGFR2 fusion	0	0
	ERBB2 amp	1.6	3
	IDH1 mut	4.8	8
Pancreatic ca	BRCA2 mut	1.0	2
	ATM mut	1.9	4
	PALB2 mut	-	-
total			195

TRIUMPH Study Design

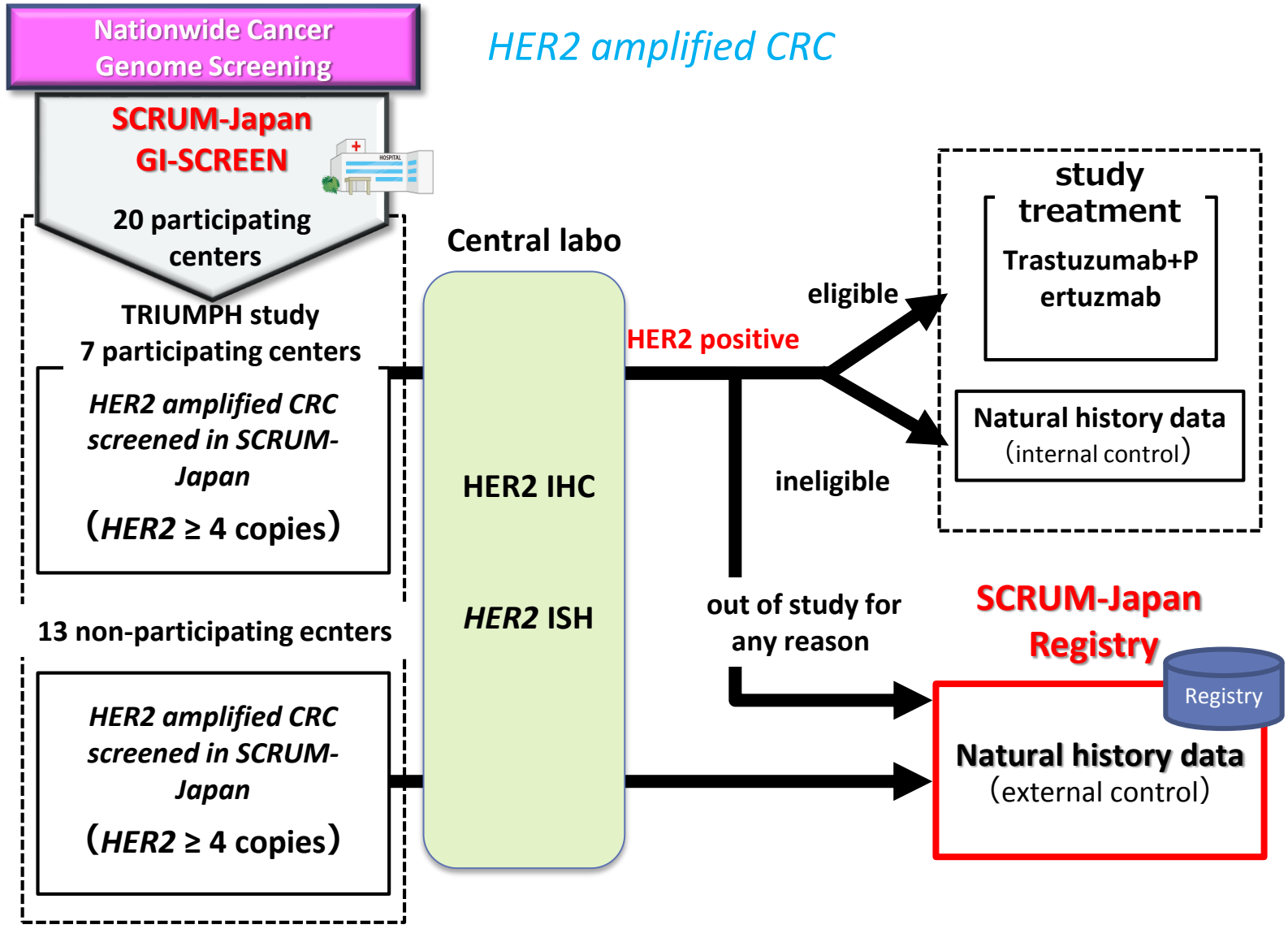
Nakamura Y, Yoshino T. ***Oncologist.*** 2018



- Design: Unblinded, single-arm, multi-center phase II study
- Primary endpoint*: Objective response rate (ORR) by investigator's assessment
- Secondary endpoints*: PFS, DoR, TTF, DCR, OS, Incidence of adverse events, Efficacy of the previous anti-EGFR treatment
- Sample size: 18 patients (25 patients, if enrolled at good rate)

* Endpoints will be evaluated in each analysis set with HER2 positive in tissue or ctDNA

Ongoing investigator-initiated IND registration study for orphan-fractionated cancer associated with registry data collection: TRIUMPH study / SCRUM-Japan Registry



International Harmonization of Diagnostic Criteria for *HER2*-Amplified Metastatic Colorectal Cancer, collaborated with SWOG-USA, HERACLES-Italy, and Korea

Prospective collaboration for HER-2 +ve for mCRC

TRIUMPH Study

- HER2-positive mCRC
- Age ≥ 20 years
- ECOG PS 0-1
- *RAS* wild-type
- Refractory or intolerable to standard therapy, including anti-EGFR mab

Meet eligibility

Trastuzumab
8 mg/kg followed by 6 mg/kg
+
Pertuzumab
840 mg followed by 420 mg
Q3W until PD

Not meet eligibility

Natural history follow-up

Prospective combination for regulatory approval

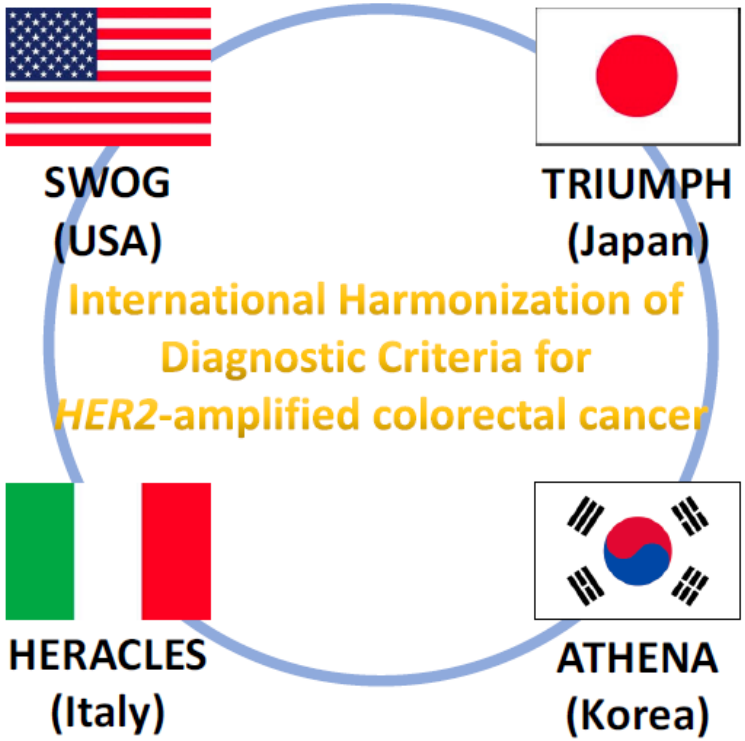
KOREAN Study

- HER2-positive mCRC
- Age ≥ 20 years
- ECOG PS 0-1
- *RAS* wild-type
- Refractory or intolerable to standard therapy, including anti-EGFR mab

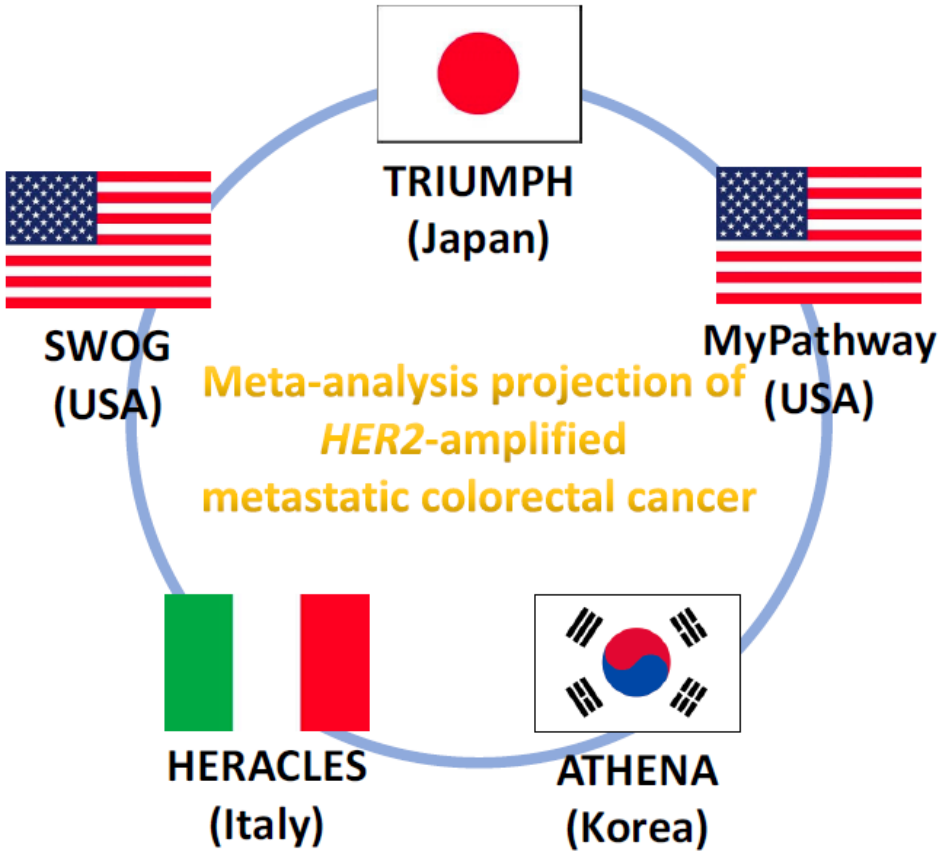
Natural history follow-up

Trastuzumab
+
Pertuzumab
+
Atezolizumab

Global Collaboration for HER2 Positive mCRC



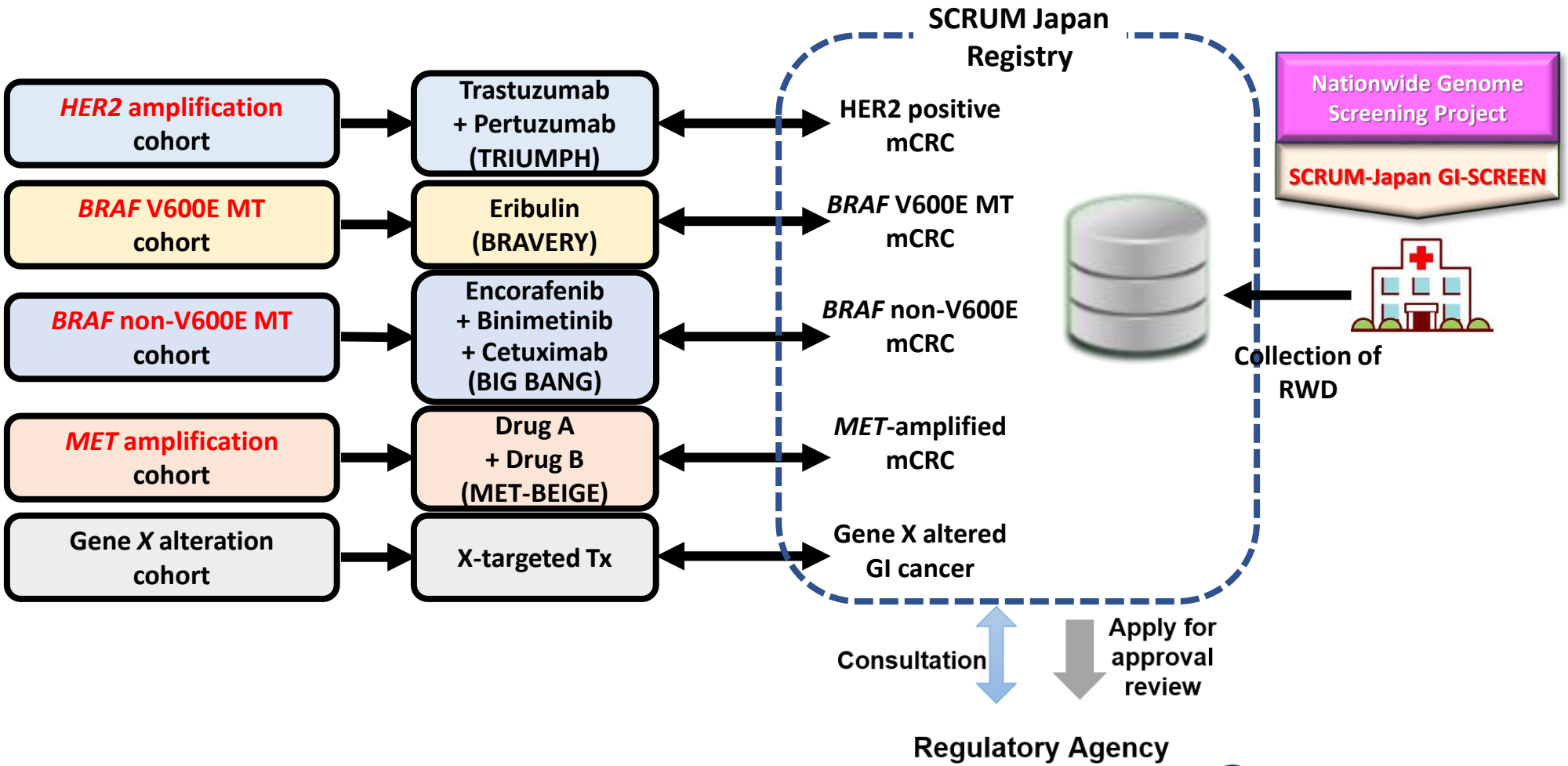
Fujii S, Yoshino T, et al, ASCO 2018



Ongoing project

Ongoing project

Utilization of Real World Data| Comparison of Endpoints in Each Sub-study with Data in SCRUM Japan Registry



Conclusion

- **TODAY:**

  Elucidate the prevalence & characteristics of MSI-High Pan-Cancer before the launch

- **TOMORROW:**

  New Guideline Projection with US Investigators (Dr. Axel Grothey as one of co-chairs)

- **THE DAY AFTER TOMORROW:**

  Further identification of study population for a tumor-agnostic indication

  Utilization of RWD for approval

  International Collaboration to get approval from regulators, incl. FDA, EMA and PMDA

Our mission is to provide an engaging smile on patients' face, prioritized for cancer patients.

Achievement of SCRUM-Japan: The Nationwide Cancer Genome Screening Project

https://ncc-kashiwa.smktg.jp/public/seminar/view/53

Contact email address;
scrum-seika2018@east.ncc.go.jp


SCRUM-Japan 成果報告会 2018

日時 2018年7月26日(木) 10:00～16:00 定員 350名
(受付開始: 9:30 休憩: 12:55～13:40)

会場 JPタワー ホール&カンファレンス ホール1+2(JR東京駅 徒歩1分)
東京都千代田区丸の内二丁目7番2号 Tel: 03-5222-1800

主催 国立研究開発法人 国立がん研究センター東病院
後援 国立研究開発法人 日本医療研究開発機構 (AMED)

開会挨拶 10:00-10:10
国立がん研究センター 理事長 中釜 斉

第1部 SCRUM-Japanの成果 10:10-12:55
司会: 国立がん研究センター東病院長 大津 敦

1. SCRUM-Japanの概要
国立がん研究センター東病院長 大津 敦
2. LC-SCRUM-Japanの成果と新規プロジェクトおよび展望
国立がん研究センター東病院 呼吸器内科長 後藤 功一
3. GI-SCREEN-Japanの成果と新規プロジェクトおよび展望
国立がん研究センター東病院 消化管内科長 吉野 孝之
4. 臨床ゲノム統合データのシェアリングがもたらす成果
国立がん研究センター 先端医療開発センター
トランスレーショナルインフォマティクス分野長 土原 一哉
5. 製薬企業の研究開発におけるSCRUM-Japanの活用 ～ゲノムデータ、臨床情報、サンプル、診断プラットフォーム～
第一三共株式会社 バイオマーカー推進部 中丸 健治
6. 本邦における遺伝子検査パネル等の承認に向けた薬事規制の動き
医薬品医療機器総合機構 体外診断薬審査室長 矢花 直幸
7. SCRUM-Japanレジストリの概要と進捗
国立がん研究センター東病院 臨床研究支援部門
トランスレーショナルリサーチ推進部
バイオバンク・トランスレーショナルリサーチ支援室長 岡本 渉
8. クリニカル・イノベーション・ネットワーク(CIN)構想におけるこれまでの取組みと今後の方針
厚生労働省 医政局研究開発振興課
臨床研究推進指導官 金津 佳子
9. 質疑応答

第2部 希少フラクション治療開発のための国際協調の現状と展望 13:40-15:30
Current Status and Future Perspective of International Collaboration for Clinical Development on Orphan-Fractionated Cancer Subtypes
Chairperson: Katsuya Tsuchihara
Chief, Division of Translational Informatics, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center
Director of Datacenter, SCRUM-Japan

1. Mission of AMED : Data sharing empowers clinical genetics
Makoto Suematsu
President, Japan Agency for Medical Research and Development (AMED)
2. New agent development for orphan-fractionated cancers in NCTN incl. SWOG
Scott Kopetz
Associate Professor, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
3. International collaboration between Taiwan and Japan on the genomic screening to establish the cancer precision medicine in east-Asia
Tzu-Chen Yen
Professor, Chang Gung Memorial Hospital, Taipei, Taiwan
4. East-Asian international collaborations of the genomic screening to develop precision medicine in lung cancer
Koichi Goto
Chief, Department of Thoracic Oncology, National Cancer Center Hospital East
Co-principal investigator, LC-SCRUM-Japan
5. International collaborations standardizing orphan-fractionated GI cancer
Takayuki Yoshino
Chief, Department of Gastrointestinal Oncology, National Cancer Center Hospital East
Co-principal investigator, GI-SCREEN-Japan

総合討論 15:30-16:00
Discussion
Chairperson: Atsushi Ohtsu
National Cancer Center Hospital East Director, SCRUM-Japan

■問合せ先: SCRUM-Japan成果報告会2018運営事務局 scrum-seika2018@east.ncc.go.jp
■SCRUM-Japan HP http://www.scrum-japan.ncc.go.jp/index.html

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Thank you for your kind attention!!

tyoshino@east.ncc.go.jp

Let's go where no one has gone before!