第31回抗悪性腫瘍開発フォーラム
「プレシジョンメディシン時代の臨床開発とその体制」

SCRUM-Japan MONSTAR-SCREEN adaptive platform trials to accelerate precision oncology innovations – focusing on metastatic colorectal cancer clinical development –

国立がん研究センター東病院消化管内科・科長　吉野孝之

GI-SCREEN
CURE a patient of Gastrointestinal Cancer

MONSTAR

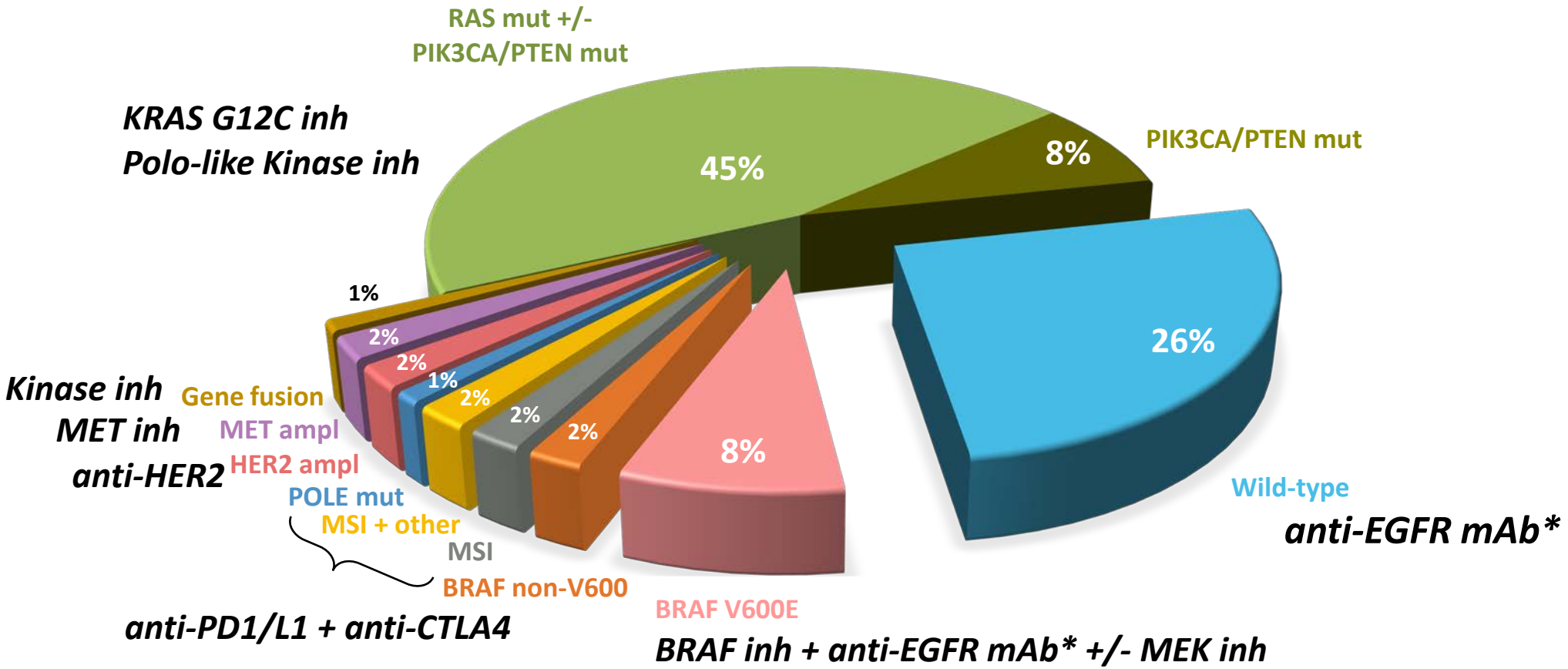
IRCULATE Japan

Feb 5th, 2022

Agenda in My Talk

- **SCRUM-Japan**
- CIRCULATE-Japan
- Beyond Genomics
- Toward global platformer

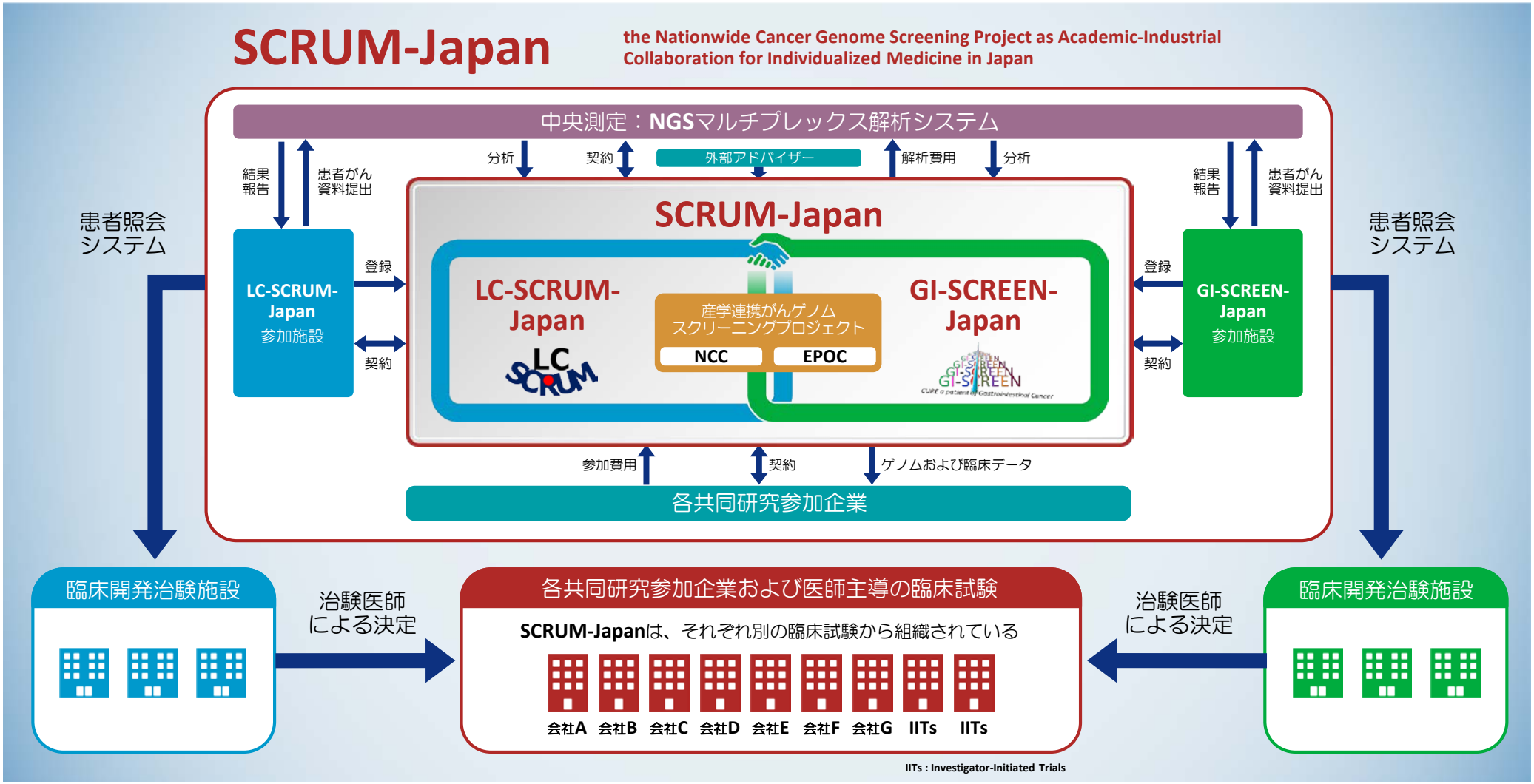
Genomic markers in mCRC with existing or potential matched therapies



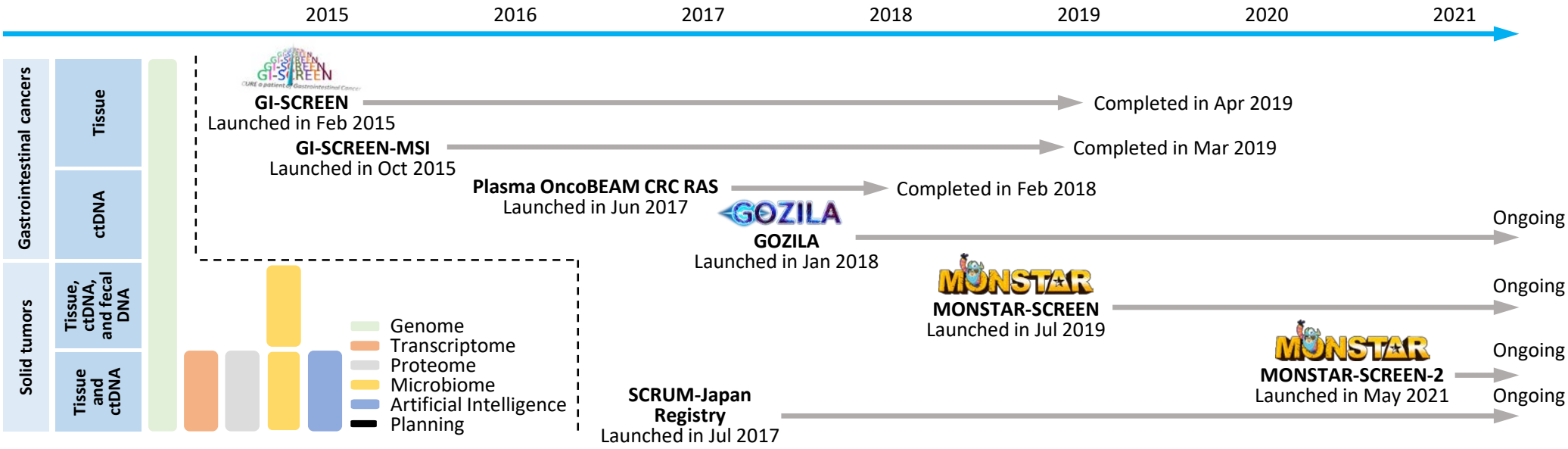
* mAb: monoclonal antibody

Modified citation from reference Dienstmann R, Tabernero J, et al. ASCO Edu. Book2018

SCRUM-Japanの体制



SCRUM-Japan GI-SCREEN, GOZILA and MONSTAR-SCREEN



	GI-SCREEN	GOZILA	MONSTAR-SCREEN	MONSTAR-SCREEN-2
Cancer	Gastrointestinal cancers	Gastrointestinal cancers	Solid tumors	Solid tumors
Sample size	5743	7000	2206	2750
Molecular profiling	Tissue DNA/RNA targeted sequencing (OCA)	Plasma DNA targeted sequencing (Guardant360)	Tissue and plasma DNA targeted sequencing (F1CDx and F1L CDx) Fecal microbiome (16S sequencing, shotgun metagenomic sequencing, single-cell metagenomics)	Tissue and plasma WES/WTS, and buffy coat WES (CARIS assay) Tissue IHC (HER2 and PD-L1) Multiplex IHC
Status	Completed	Active recruitment	Completed	Active recruitment

Abbreviations: F1CDx, FoundationOne CDx; F1L CDx, FoundationOne Liquid CDx; IHC, immunohistochemistry; OCA, Oncomine Comprehensive Assay; WES, whole exome sequencing; WTS, whole transcriptome sequencing.

Nakamura Y, Yoshino T, et al.: Cancer Science. 2021.

SCRUM-JapanのProject全体像

SCRUM-Japanの実績: がん個別化治療の挑戦

2015年2月からがん組織を用いたゲノム解析を始動

2020年7月10日時点

GI-SCREEN
CURE a patient of Gastrointestinal Cancer
Stage IV期消化器がん

MONSTAR
Stage IV期固形がん

LC SCRUM
Stage IV期肺がん

- **NGS*検査数 17,000+**
- **参加施設 270+**
- **企業 最大17社**
- **臨床試験参加人数 600+**
- **臨床試験数 50+**
- **薬事承認 9薬＆ 9CDXs****

備考；*本体研究のみ: **CDX=コンパニオン診断薬

大規模臨床・ゲノム統合DBをアカデミアおよび製薬企業と共有

米国NCI-MATCH と SCRUM-Japanとの比較

	NCI-MATCH（米）	SCRUM-Japan（日）
資金	公的資金	企業＋公的資金
プロジェクト開始年	2015	2015
遺伝子解析パネル	商用パネル（OCP）他	商用パネル（OCP）他
治験内容	医師主導治験	医師主導＋企業治験
スクリーニングから治験登録形態	Closed 型	Open platform型
試験数	40	56（医師主導20）
対象疾患	すべての固形がん	肺・消化器がん
症例登録数	6,000例	17,000+例
治験登録率	5%（改訂前）	3%
終了・報告試験数	11試験	30試験
薬事承認取得	2剤	11剤（13適応）で取得
臨床ゲノムデータ共有	無	アカデミア66施設＋企業17社
リキッドバイオプシー導入	未	7,000例収集済み
Microbiome解析導入	未	導入済み（2019）
規制対応レジストリ収集	未実施	収集中、薬事申請中

SCRUM-Japan ctDNA Screening Platform

As of Nov 2021

GI-SCREEN
CURE a patient of Gastrointestinal Cancer

GOZILA

N= 4776

Stage IV GI Cancers mainly
Since Jan 2018

MONSTAR

N= 2206

Stage IV solid tumors
Since July 2019

Ongoing Clinical Trials

GOZILA

Nationwide Genome Screening Project

SCRUM-Japan GI-SCREEN

CRC

Non-CRC GI

Non-GI Solid

N=5,000

Tumor-specific approach

ctDNA解析 (Guardant360)

- *HER2* amplification → Trastuzumab + Pertuzumab (TRIUMPH)
- *BRAF* V600E MT → Eribulin (BRAVERY)
- *BRAF* non-V600E MT → Encorafenib + Binimetinib + Cetuximab (BIG BANG)
- *MET* amplification → Cabozantinib ± Panitumumab (METBEIGE)
- *RAS* WT → Re-challenge with anti-EGFR mAb (PURSUIT)

Non-CRC GI

- *HER2* amplification → DS-8201a (HERB)

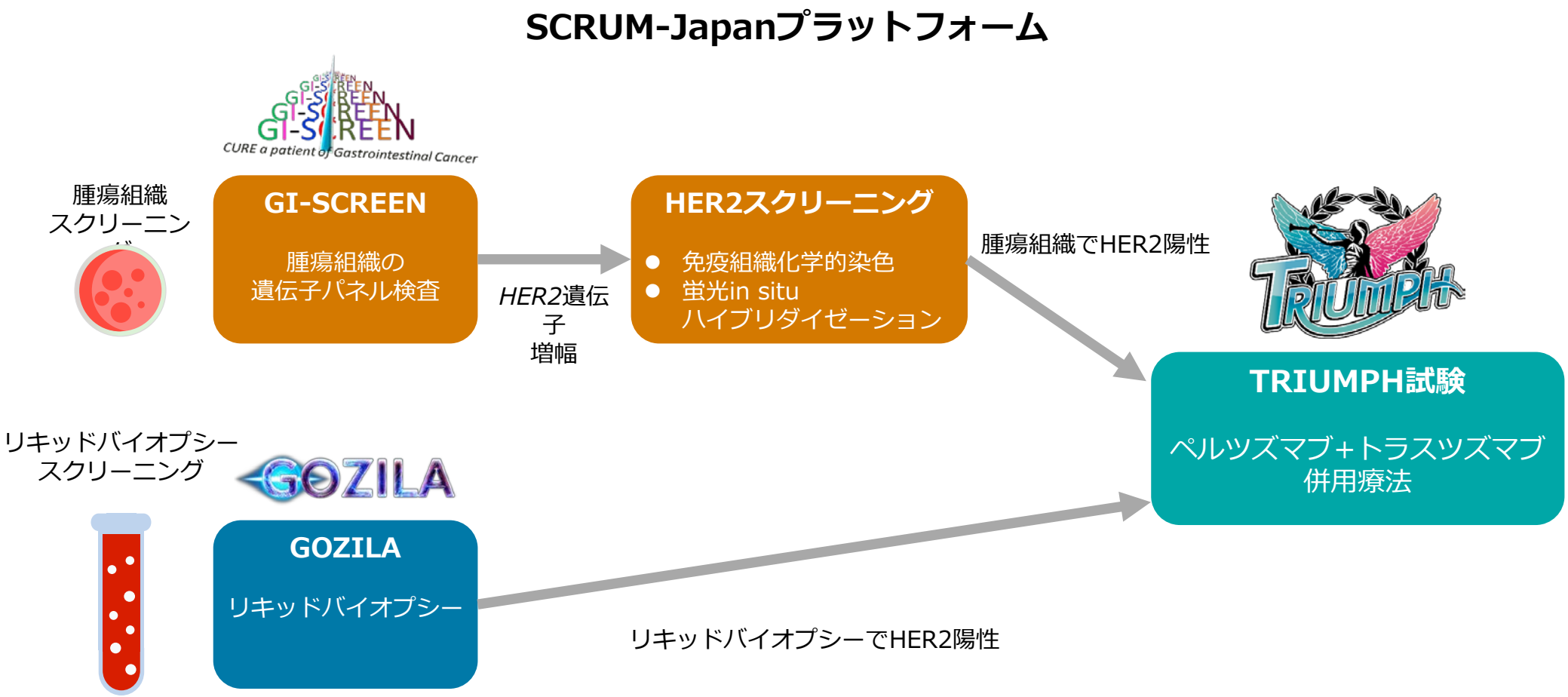
Tumor-agnostic approach

NEW

ctDNA解析 (Guardant360)

- bTMB-High → Nivolumab (bTMB-H basket)
- Any *FGFR* alteration → TAS-120 (TiFFFANY)
- *HER2* amplification → DS-8201a (HERALD)
- *ROS1* fusion → Brigatinib (Barossa)
- *BRCA* mutation → Niraparib (NIR-B)
- *NFE2L2* mutation → Sapanisertib (TRIGATE)

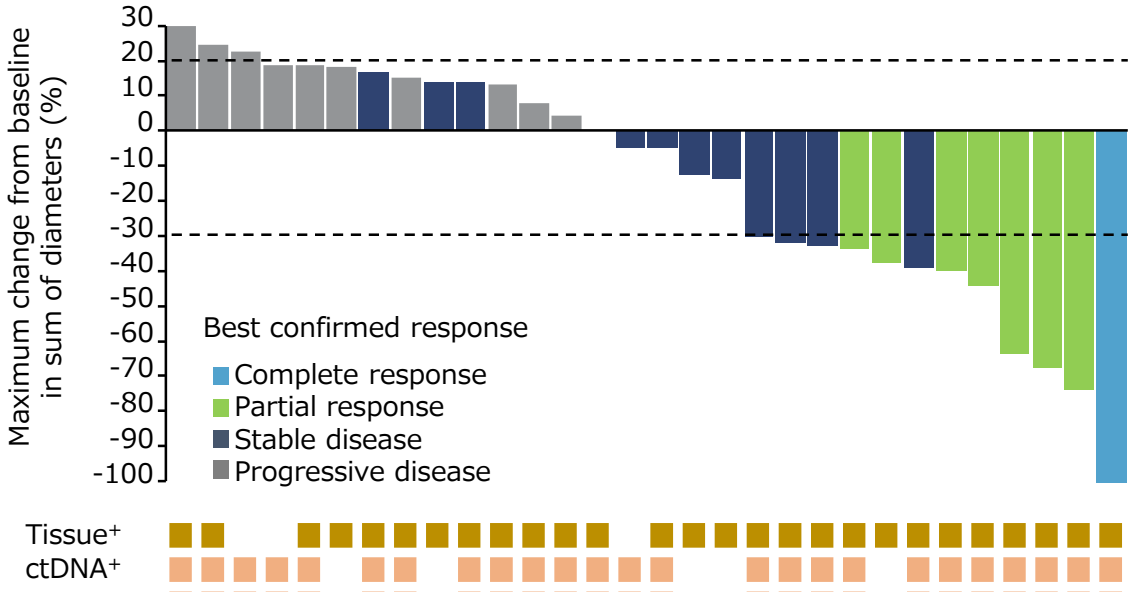
TRIUMPH試験の概要



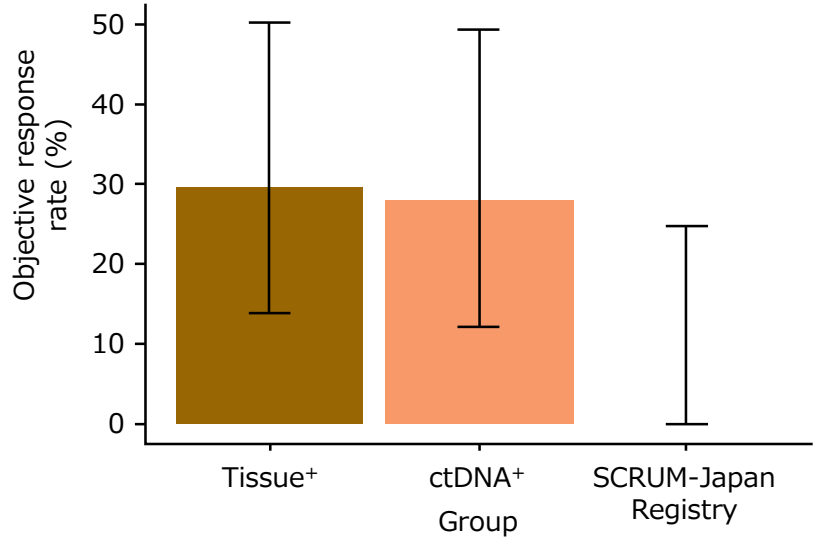
Nakamura Y, Yoshino T, et al.: Nat Med. 2021

腫瘍縮小率, 奏効率

Waterfall plot showing the change in the sum of the longest diameters of lesions from the baseline to the best post-baseline investigator assessment.



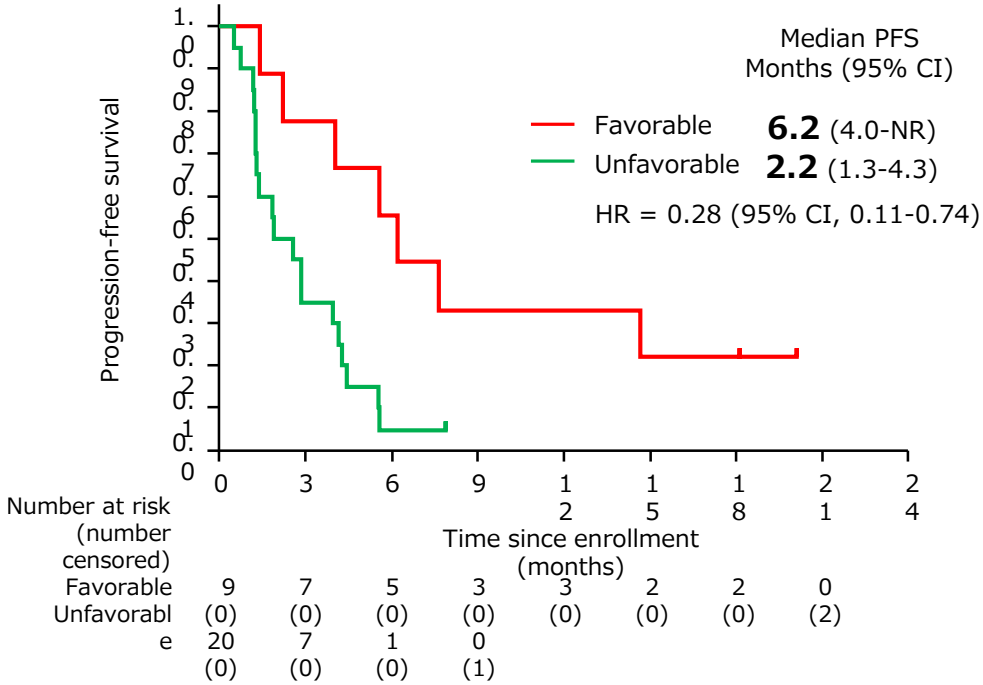
ORR in tissue+ (*n*= 27), ctDNA+ (*n*= 25) and SCRUM-Japan Registry (*n*= 13) patients.



Nakamura Y, Yoshino T, et al.: Nat Med. 2021

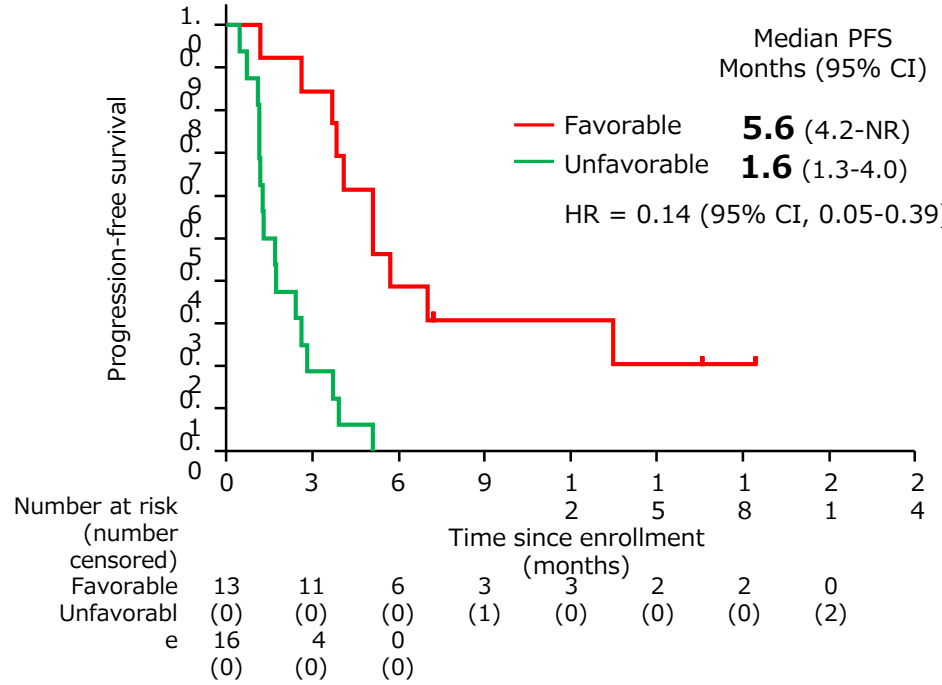
予後因子別のPFS

Tissue-based stratification (PFS)



tissue-based favorable factors
- tissue CN ≥ 68.7
- no concurrent *RTK/RAS/PI3K* alterations

ctDNA-based stratification (PFS)



ctDNA-based favorable factors
- ApCN ≥ 16.7
- no concurrent *RTK/RAS/PI3K* alterations

Nakamura Y, Yoshino T, et al.: Nat Med. 2021

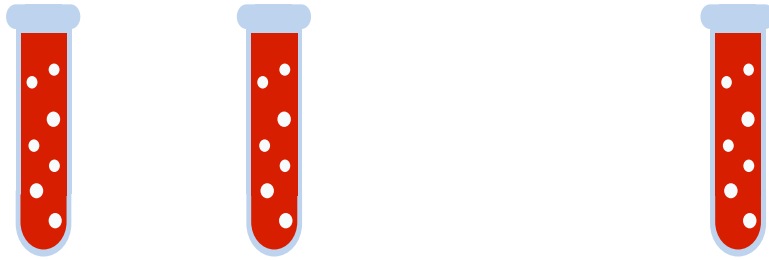
ctDNAと治療効果の関連性

TRIUMPH 試験で行われた経時的なリキッドバイオプシー

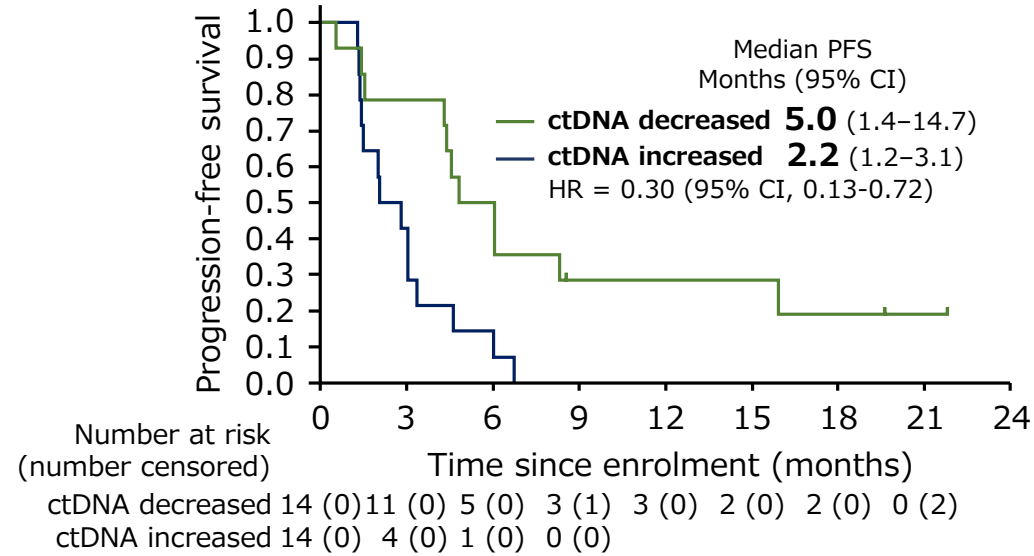
治療中に行われたリキッドバイオプシー

ペルツズマブ+トラスツズマブ療法

治療開始前　　治療開始3週間後　　病気が進行した後



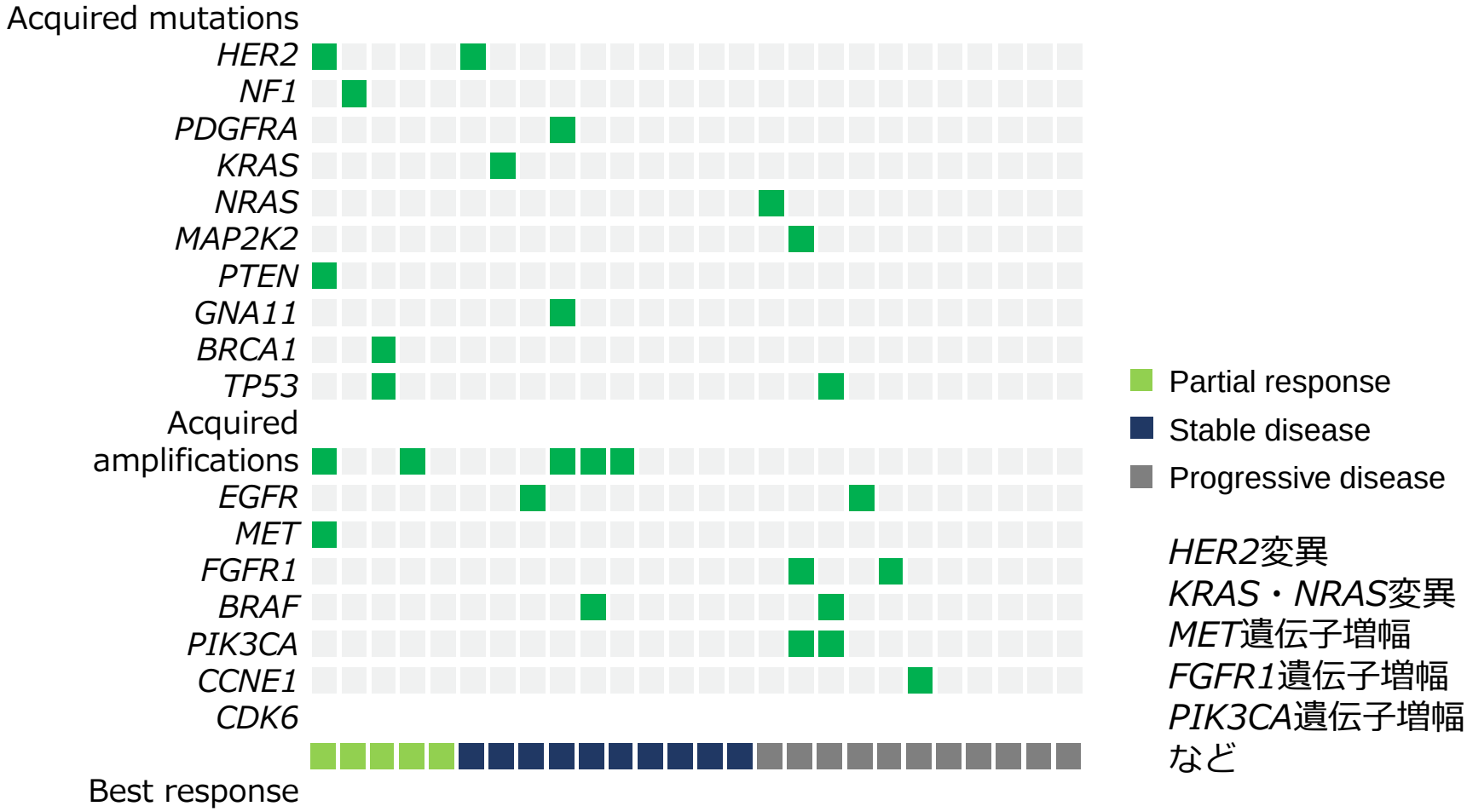
ctDNA fraction (PFS)



リキッドバイオプシーによる効果予測

Nakamura Y, Yoshino T, et al.: Nat Med. 2021

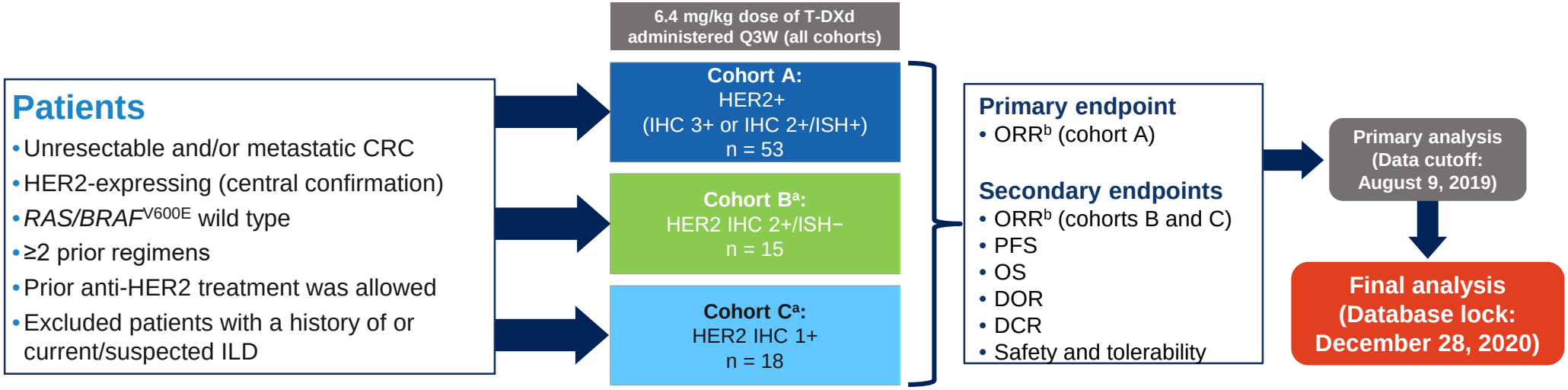
ペルツズマブとトラスツズマブの併用療法後に新たに出現したゲノム異常



Nakamura Y, Yoshino T, et al.: Nat Med. 2021

DESTINY-CRC01 Study Design

Final analysis of an open-label, multicenter, phase 2 study (NCT03384940)



Primary analysis of cohort A[1]

- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

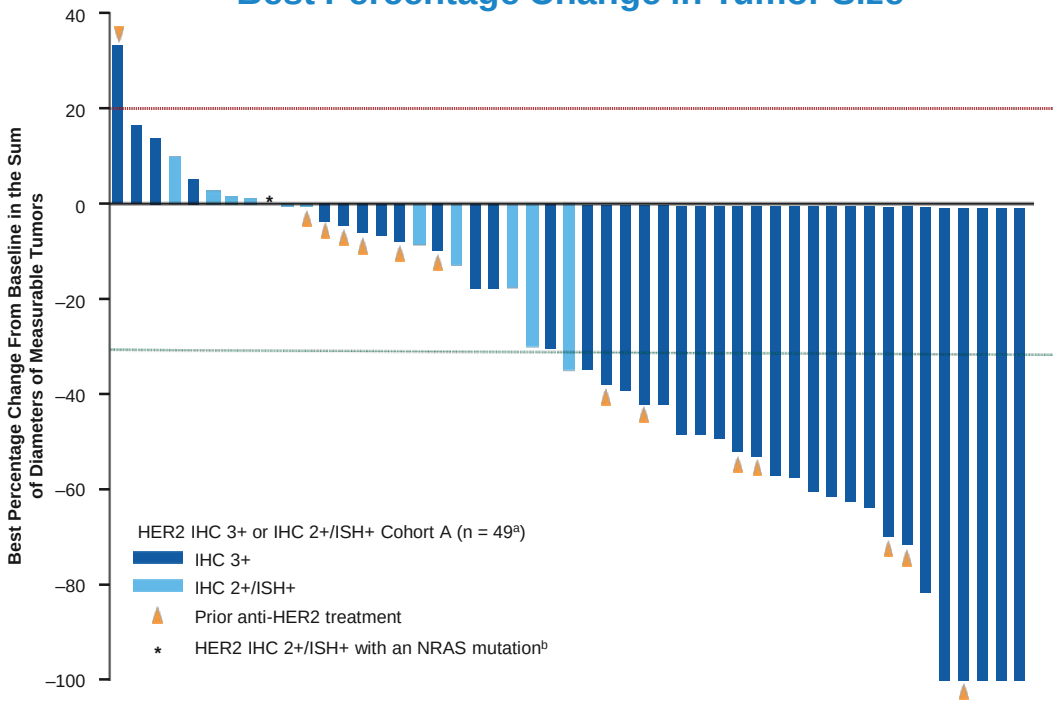
Patient disposition at final analysis[c]

- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

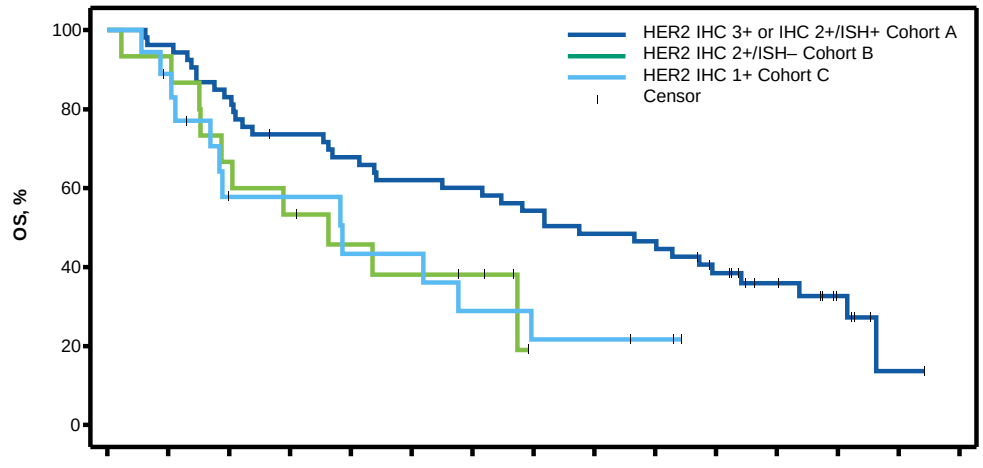
CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HER2+, HER2-positive; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; T-DXd, trastuzumab deruxtecan.
[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST v1.1 in all cohorts. [c]Data presented are from the full analysis set.
1. Siena S et al. *Lancet Oncol*. 2021;22(6):779-789.

Best Percentage Change in Tumor Size in Cohort A and OS in All Cohorts

Best Percentage Change in Tumor Size



Overall Survival



No. at Risk

Cohort A	53	51	44	38	35	32	31	28	25	24	18	12	6	1	0
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0

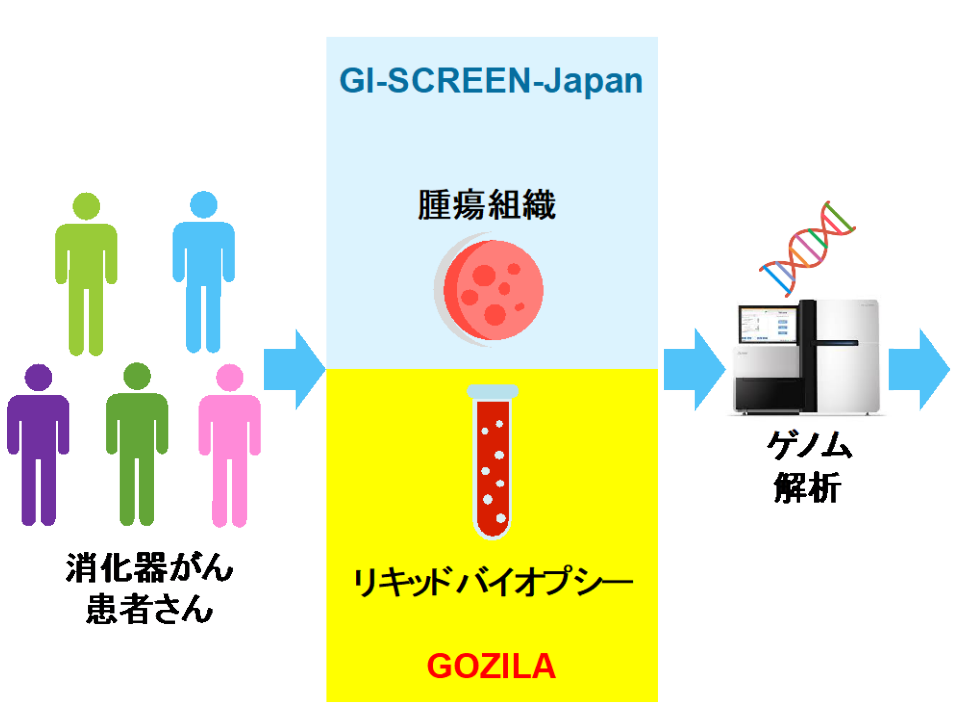
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OS, overall survival.
The line at 20% indicates progressive disease. The line at –30% indicates partial response. [a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment. Reprinted from *The Lancet Oncology*, Vol 22, Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. Pp 779-789, 2021, with permission from Elsevier.

ctDNA解析のゲノム医療に対する有用性

Metastatic Disease

2015年2月に開始した腫瘍組織パネル検査のスクリーニングプロジェクト

5000名以上の患者さんが参加



GI-SCREEN-Japanと

GOZILAで以下の項目を比較

- 登録から結果到着までの期間
- 治験に登録された患者さんの割合
- 治験治療の効果

対象（~2019年8月）

GI-SCREEN：5743名

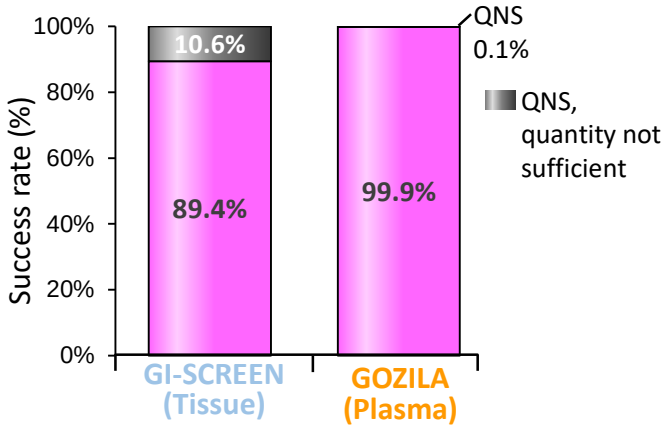
GOZILA：1787名

2018年1月に開始したctDNAパネル検査のスクリーニングプロジェクト

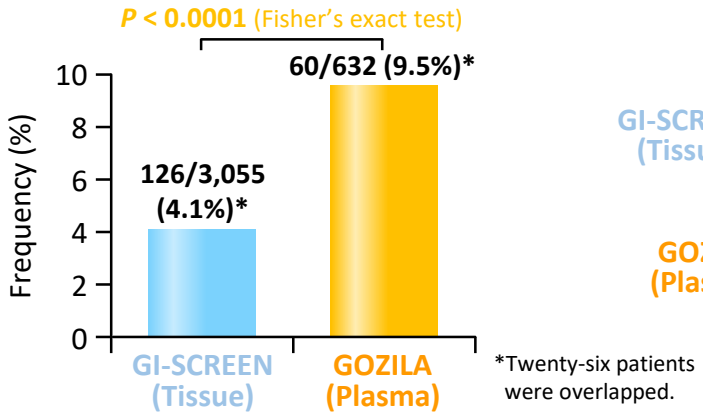
3000名以上の患者さんが参加

SCRUM-Japan GI-SCREEN & GOZILA Studies
Achievements of GOZILA Project

Sequencing success rates for tissue and ctDNA genotyping

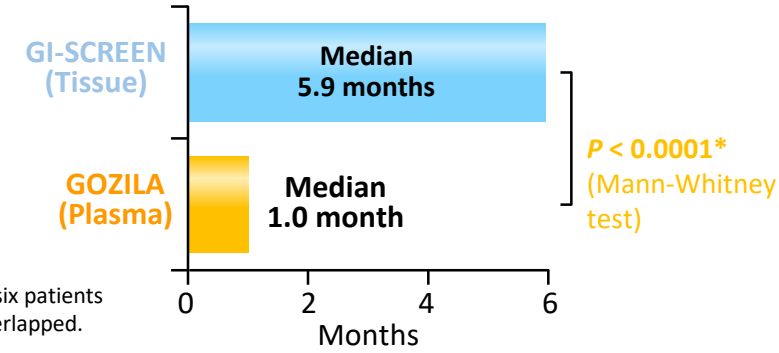


Trial enrollment rate in patients with actionable alterations

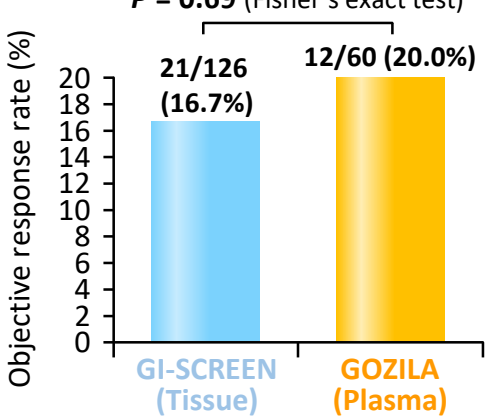


*Twenty-six patients were overlapped.

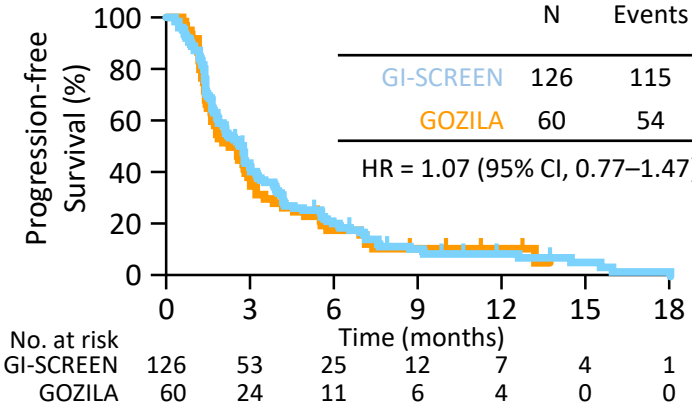
Interval between enrollment to genotyping studies and matched clinical trials



Objective response rate



Progression-free survival

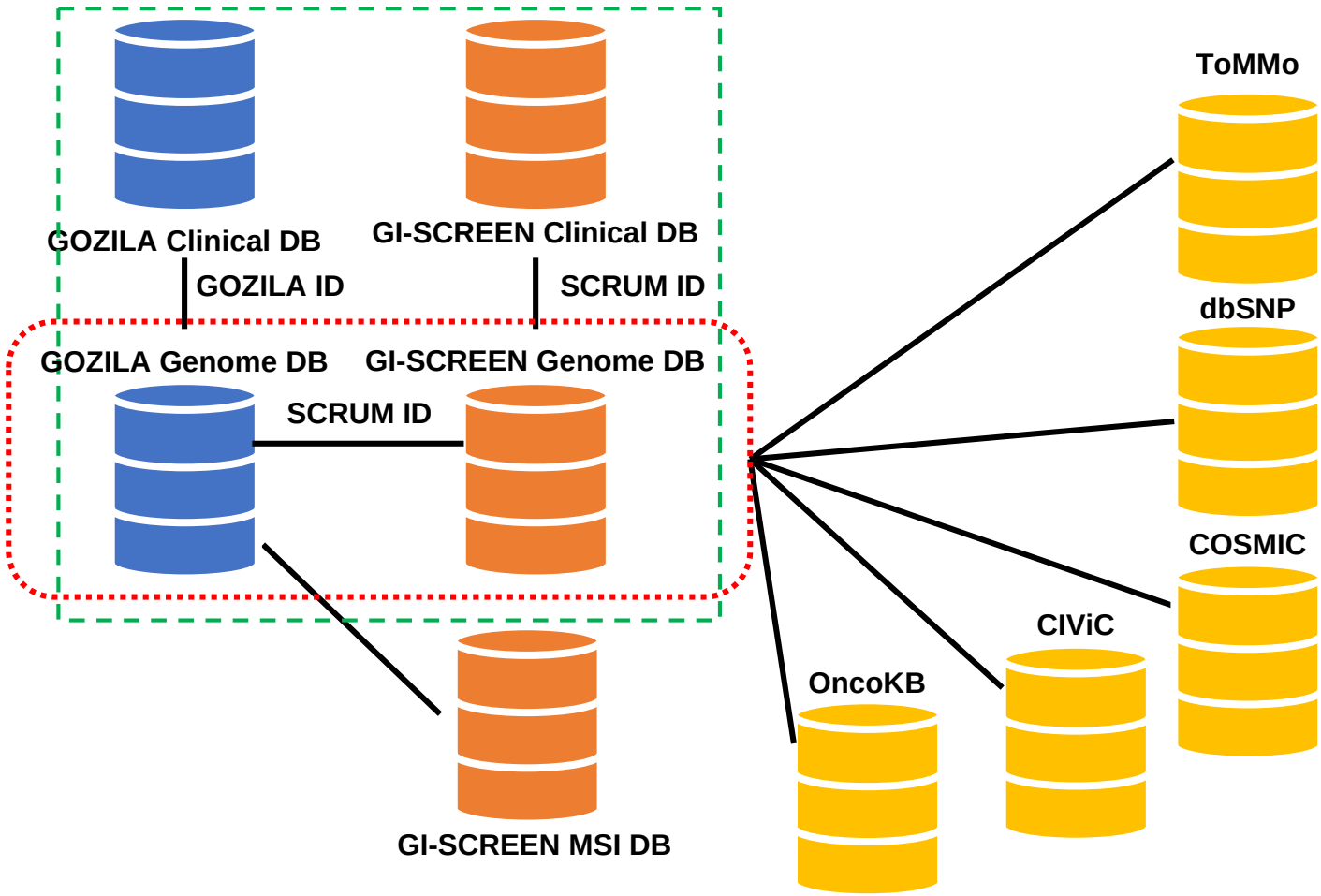


	N	Events	Median (months)	95% CI
GI-SCREEN	126	115	2.8	(2.2–3.3)
GOZILA	60	54	2.4	(1.3–3.3)

HR = 1.07 (95% CI, 0.77–1.47), Log-rank test $P = 0.70$

Nakamura Y, Yoshino T.: Nat Med 2020.

Huge DBs in GI-SCREEN, GOZILA, etc.



Enables cross-search among DBs

Global Collaboration to Promote Each Platform

ORIGINAL RESEARCH

GASTROINTESTINAL CANCER

Comparing GOZILA and COLOMATE: Ongoing Umbrella/Basket Trials Examining Genetic Testing in Gastrointestinal Malignancies

Hideaki Bando, MD*; Yoshiaki Nakamura, MD*; Daisuke Kotani, MD; and Takayuki Yoshino, MD

REVIEW ARTICLE

COLORECTAL CANCER

The Current Molecular Treatment Landscape of Advanced Colorectal Cancer and Need for the COLOMATE Platform

Kristen K. Ciombor, MD, MSCI[1]; Jeremy C. Jones, MD[2]; John Strickler, MD[3]; Tanios S. Bekaii-Saab, MD[4]; Christina Wu, MD[5]

PERSPECTIVE BY

Takayuki Yoshino, MD, PhD

The COLOMATE Platform: An Indispensable Initiative Promoting True Precision Oncology Prioritized for Patients With Cancer—From "MAYBE" to "MUST BE"

Yoshino T. ***Oncology (Williston Park)***. 2021.

Global Collaboration led by ours (representative example)

Unification of International Diagnostic Criteria

International Harmonization of Provisional Diagnostic Criteria for *ERBB2*-Amplified Metastatic Colorectal Cancer Allowing for Screening by Next-Generation Sequencing Panel

Satoshi Fujii, MD, PhD[1]; Anthony M. Magliocco, MD, FRCPC, FCAP[2]; Jihun Kim, MD, PhD[3]; Wataru Okamoto, MD, PhD[4]; Jeong Eun Kim, MD, PhD[5]; Kentaro Sawada, MD, PhD[6]; Yoshiaki Nakamura, MD, PhD[6]; Scott Kopetz, MD, PhD[7]; Woong-Yang Park, MD, PhD[8]; Katsuya Tsuchihara, MD, PhD[9]; Tae Won Kim, MD, PhD[10]; Kanwal Raghav, MD, MBBS[7]; and Takayuki Yoshino, MD, PhD[6]

Fujii S, Yoshino T. ***JCO Precision Oncology***, 2020

World's First Guideline for Tumor-agnostic Precision Oncology in Advanced Solid Cancer

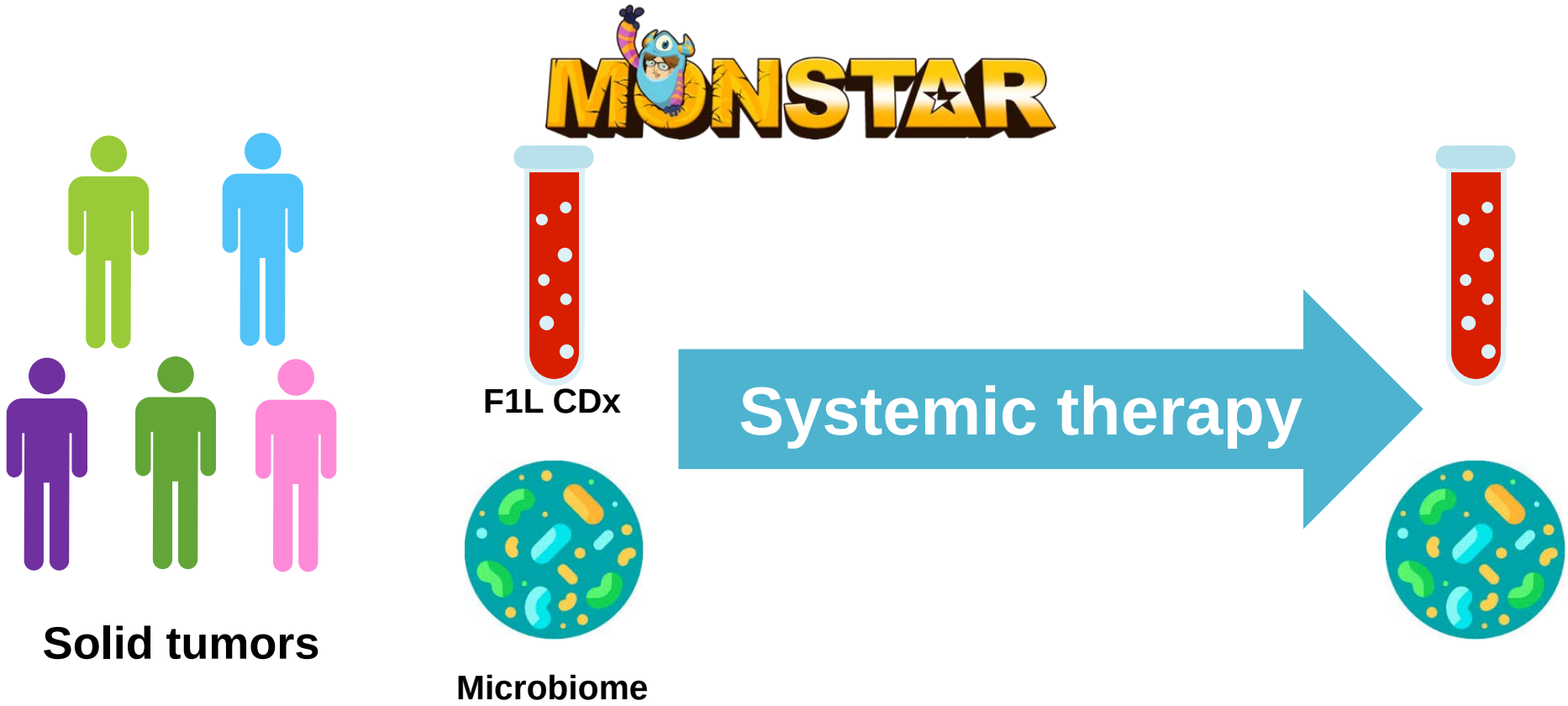
JSCO—ESMO—ASCO—JSMO—TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions

T. Yoshino[1*], G. Pentheroudakis[2], S. Mishima[1], M. J. Overman[3], K.-H. Yeh[4], E. Baba[5], Y. Naito[6], F. Calvo[7], A. Saxena[8], L.-T. Chen[9], M. Takeda[10], A. Cervantes[11], H. Taniguchi[1], K. Yoshida[12], Y. Kodera[13], Y. Kitagawa[14], J. Tabernero[15], H. Burris[16] & J.-Y. Douillard[17]

Yoshino T, ***Ann Oncol.*** 2020

MONSTAR-SCREEN

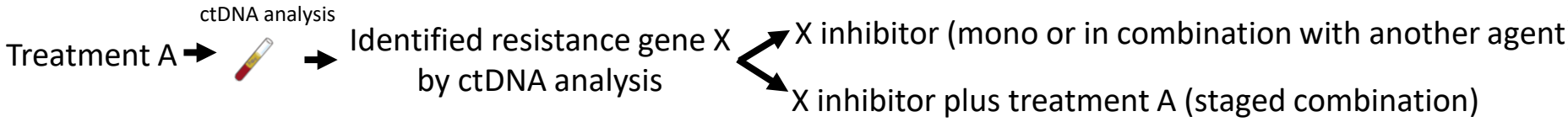
Metastatic Disease



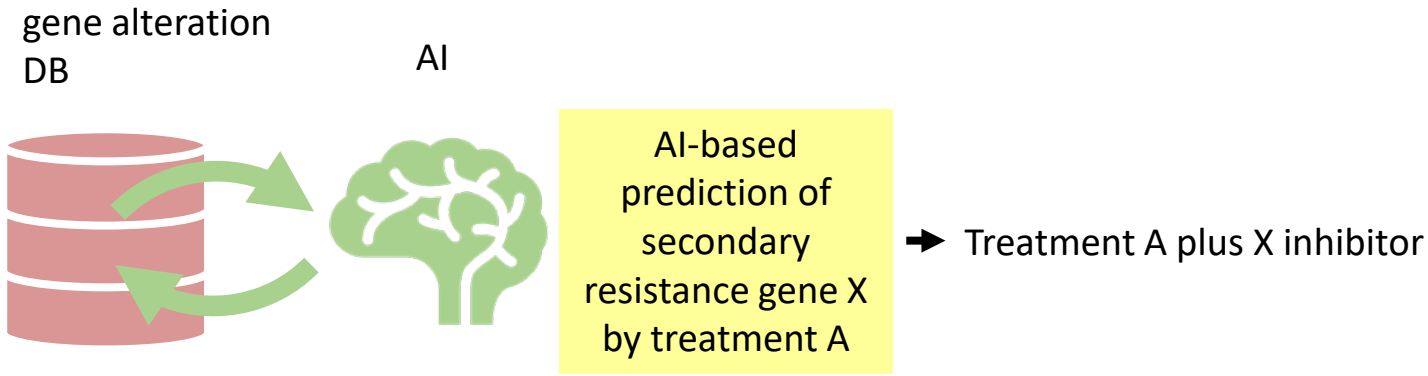
Assess temporal changes in cancer biomarkers thorough systemic therapy

Present & next generation clinical trial designs

a. Present clinical trial design; reactive treatment for secondary resistance



b. Next generation clinical trial design; preemptive treatment for secondary resistance

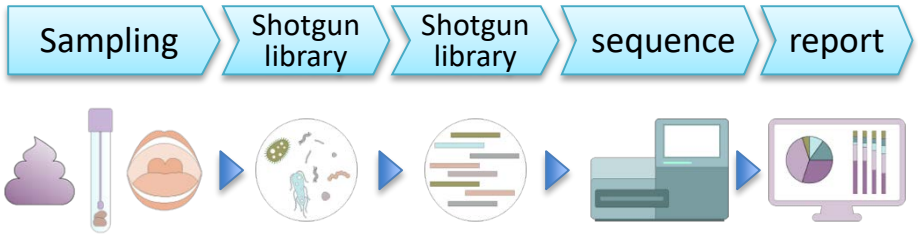


Yoshino T. COLOMATE challenge to overcome resistance in metastatic colorectal cancer. ***Oncology*** (Williston Park). 2021 Oct 21;35(10):656. doi: 10.46883/ONC.2021.3510.0656. PMID: 34677923.

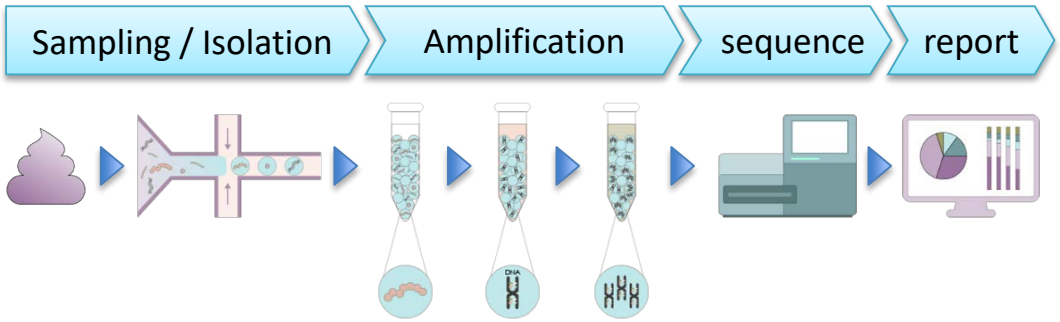
便検体を使用して行う細菌叢解析

	MONSTAR本研究で施行	BIG BEN studyで施行	
	16Sリボソーム	ショットガン解析	シングルセル解析
用途	菌叢組成解析	菌叢・遺伝子組成解析	個々の細胞の機能解析
対象領域	16S rRNA遺伝子	ゲノムの集合	個別の全ゲノム
読み取り長	400塩基	数十～数百億塩基	数百万～億塩基×細胞数(100個程度)
微生物組成	○	○	○
機能遺伝子組成	×	○	○
菌種-機能の結び付け	×	△	○
菌株の区別	×	×	○

<ショットガン解析>



<シングルセル解析>



腸内細菌叢とICI治療効果の関連

MONSTAR　臨床情報　F1L　Microbiome

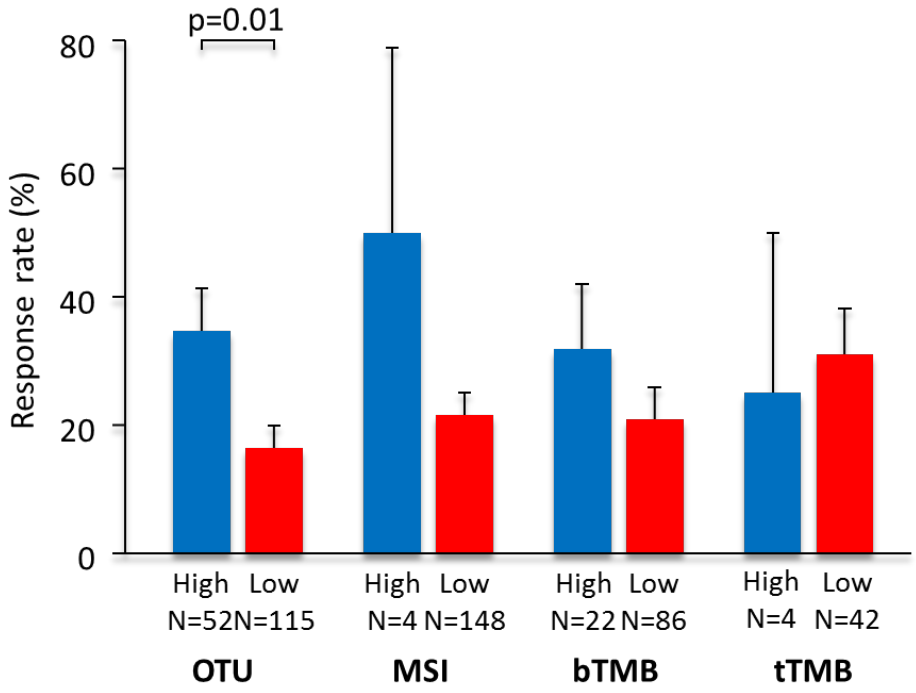
ESMO congress 2021
JSCO 2021, Plenary session

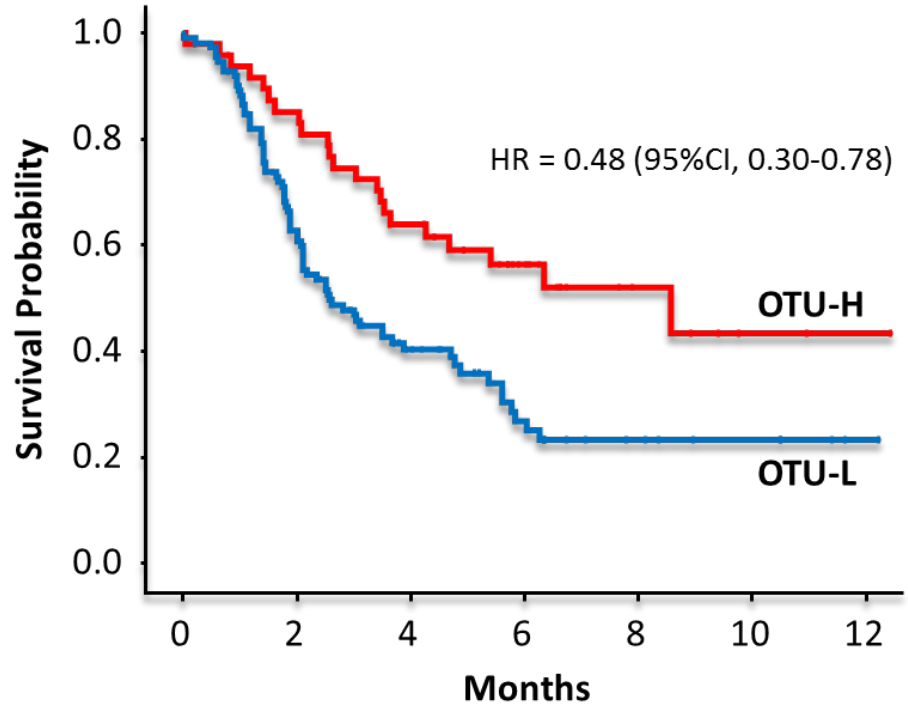
コホートA：薬物療法未治療の患者　N = 800

コホートB：特定の遺伝子異常が同定された患者　N = 200

コホートC：免疫療法を含む治療を受ける患者　N = 500

コホートD：分子標的薬治療に伴う Clonal Evolutionの可能性がある患者　N = 500





腸内細菌叢のα多様性が高い症例（OTU-High）の症例はICIの治療効果が高い

大腸癌におけるシングルセル解析

MONSTAR　臨床情報　F1L　Microbiome

日本分子生物学会年会 2021

コホートA：薬物療法未治療の患者　N = 800

コホートB：特定の遺伝子異常が同定された患者　N = 200

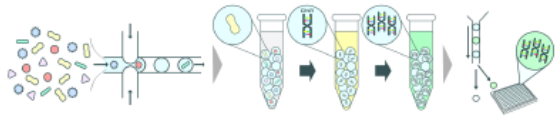
コホートC：免疫療法を含む治療を受ける患者　N = 500

コホートD：分子標的薬治療に伴う Clonal Evolutionの可能性がある患者　N = 500

菌体液調製

糞便保存液 200 μL

シングルセルゲノム調製　Chijiiwa et al., 2020



細菌の単離	溶菌・ゲノム増幅	カプセル回収
細菌1細胞を1つのゲルカプセルに封じ込み	1チューブで多数のゲルカプセルを一度に処理	ゲノム増幅したゲルカプセルのみ回収

ライブラリー調製

QIAseq FX DNA Library kit(QIAGEN)

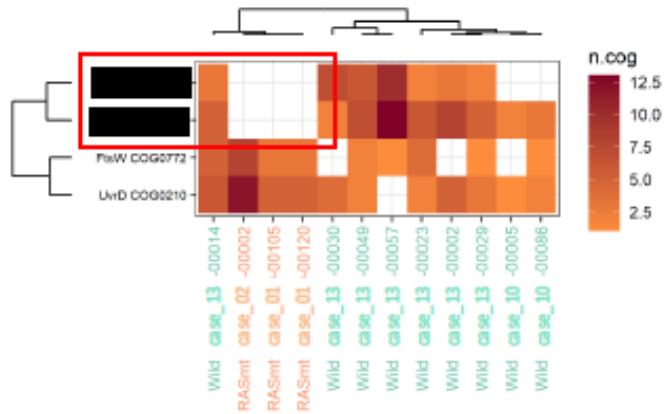
シーケンス

NextSeq2000
150 bp x 2

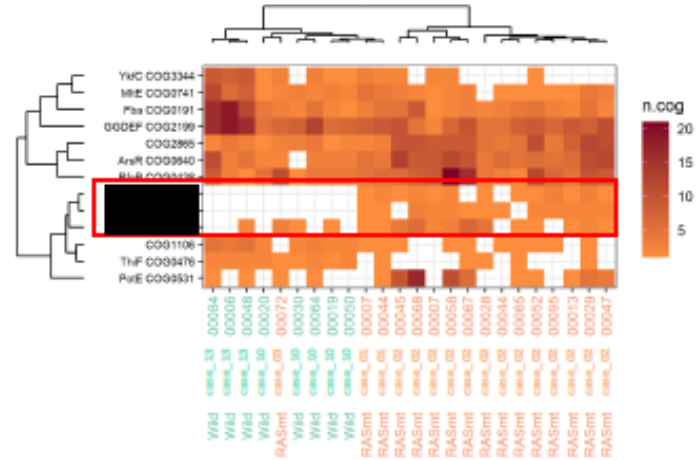
データ解析

de novo assembly 等

Lachnospira eligens_B

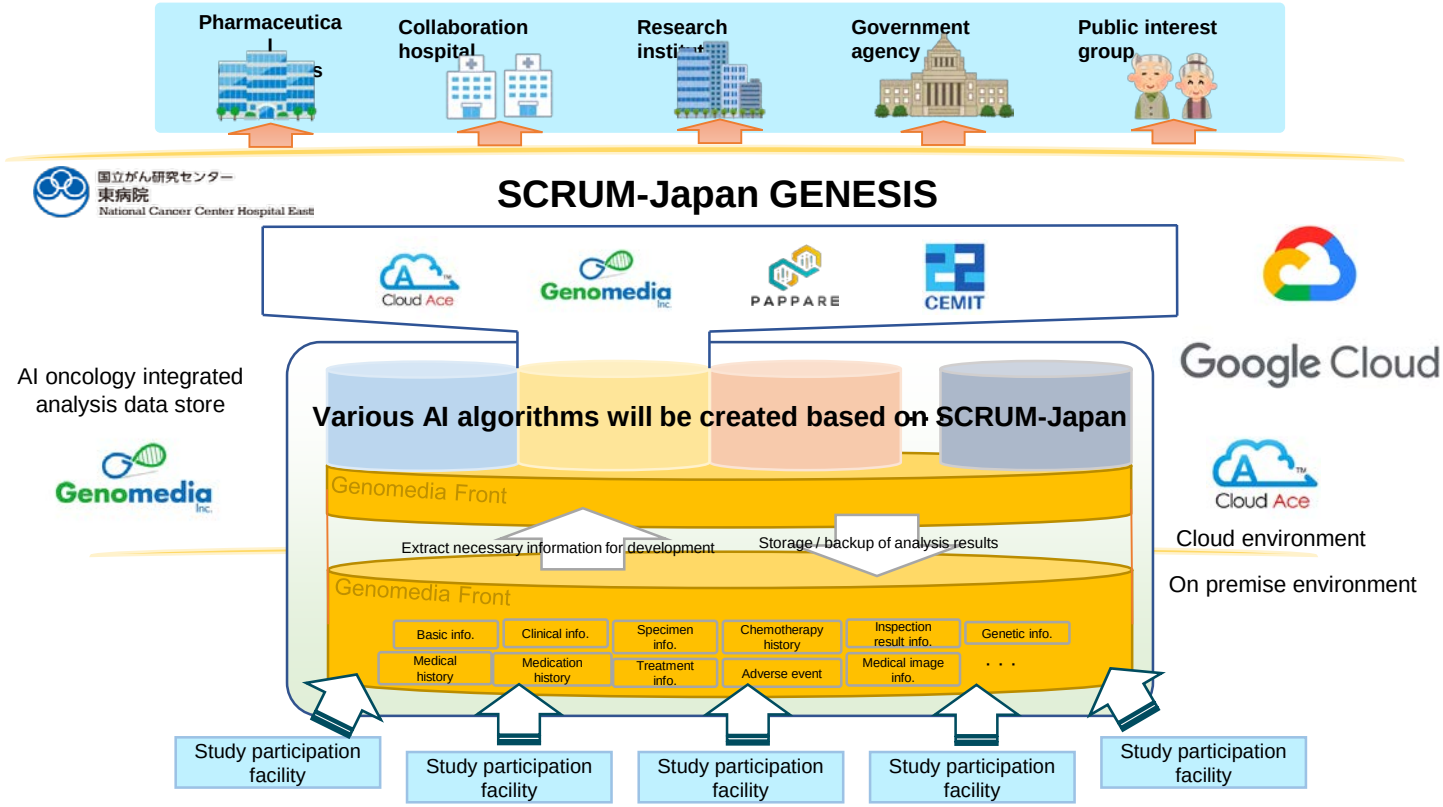


Blautia_A obeum



RAS変異型大腸癌では、野生型と比較し特徴的に欠損もしくは存在している遺伝子が存在する
⇒シングルセルゲノム解析で初めて判明

SCRUM-Japan GENESIS Project



Yoshino T, et all. Oral presentation at Google Cloud Next '19
https://www.youtube.com/watch?v=iO4x1aJw_Jc

AI/ML

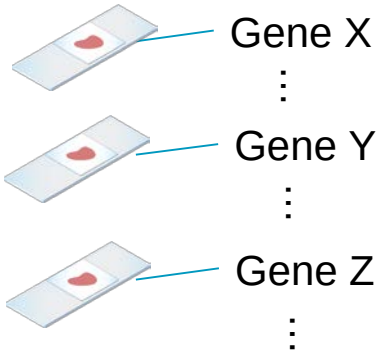
SCRUM-Japan GENESIS Virtual Sequencing Project

Virtual Sequencing VSQ

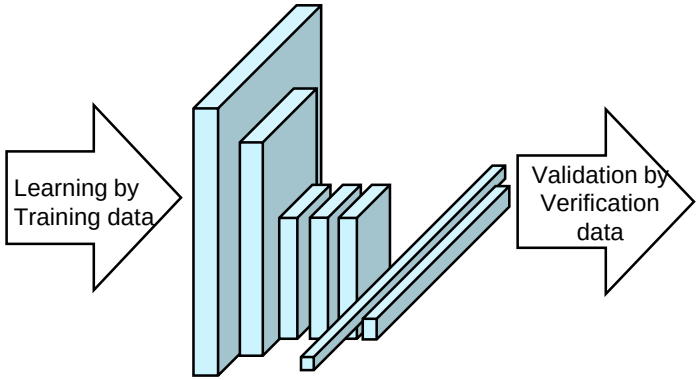
HE staining → dissection → NGS sequencing → Genetic alteration identification

Virtual Sequencing

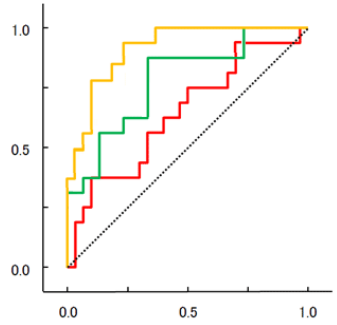
Development of prompt & accurate genome alteration estimation method using AI image processing



FFPE section image and genome analysis results, collected by SCRUM-Japan



Virtual Sequencing algorithm



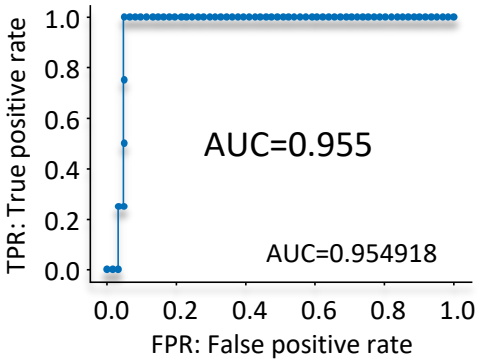
Verify the accuracy of the algorithm using verification data

Yoshino T, et all. Oral presentation at Google Cloud Next '19
https://www.youtube.com/watch?v=iO4x1aJw_Jc

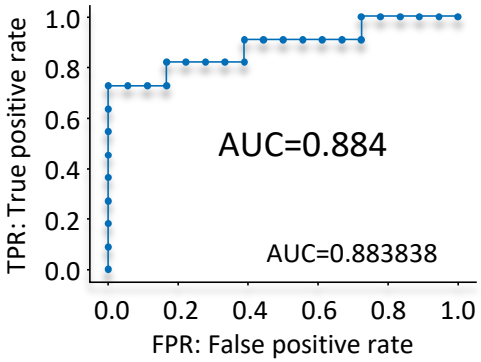
Overview of predictive model creation for each pathological morphological features.

Validation Set 1 (247 pts)

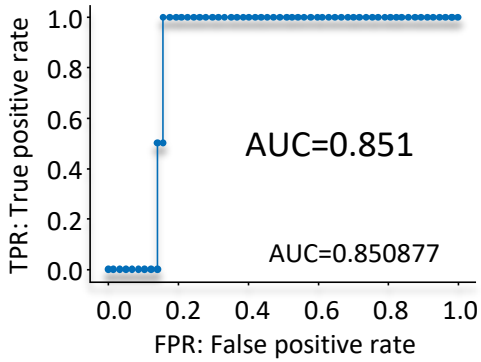
BRAF



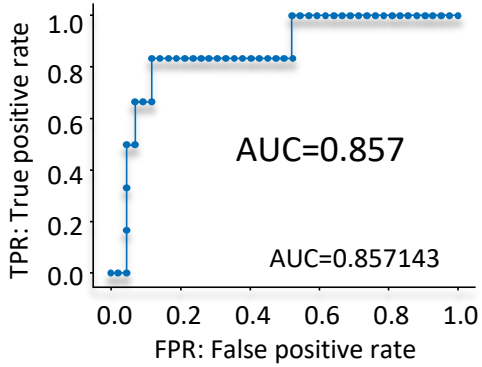
KRAS



ERBB2 amp

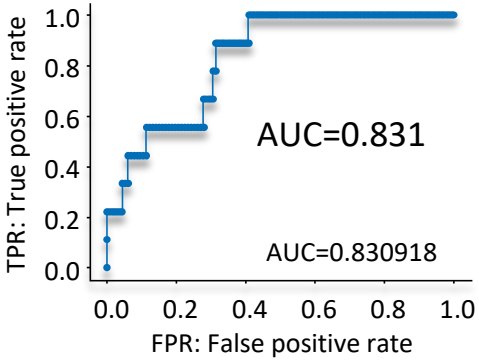


MSI-H

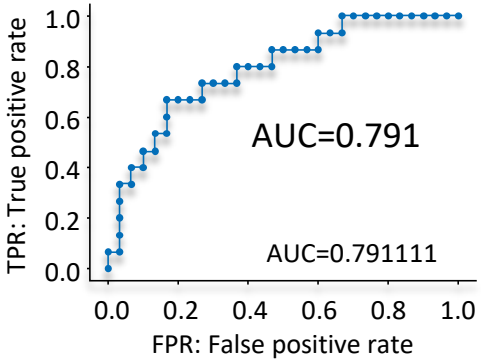


Validation Set 2 (247 pts)

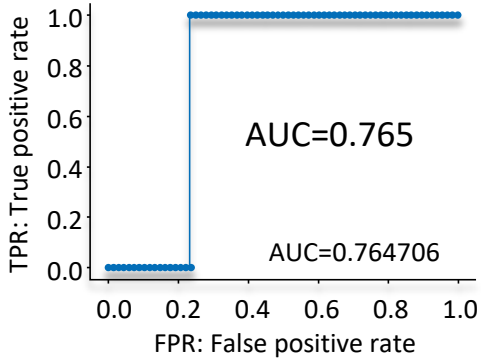
BRAF



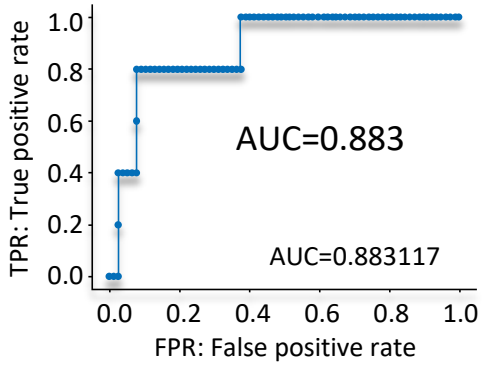
KRAS



ERBB2 amp



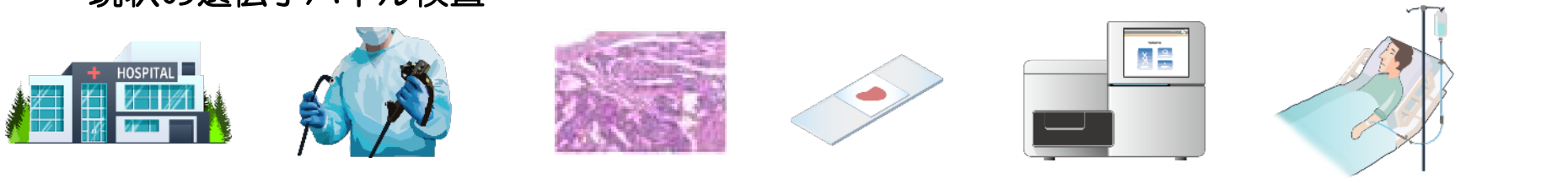
MSI-H



Fujii S, et al.: ASCO-GI2021 #112.

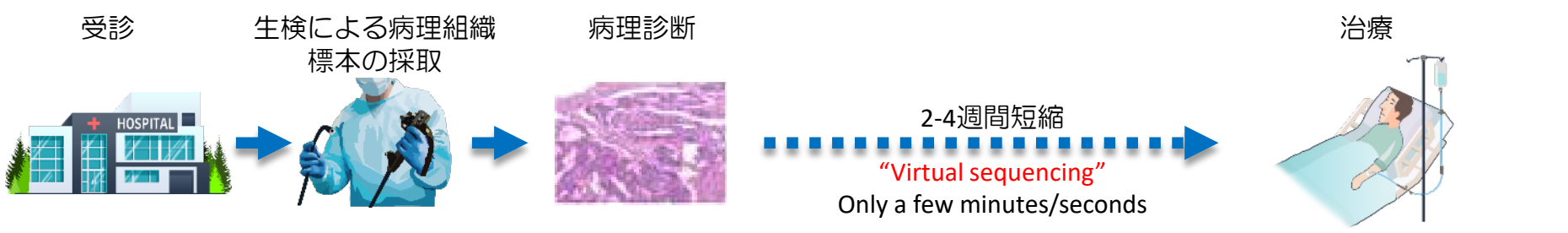
AIを使った新しい病理診断学の概念図

現状の遺伝子パネル検査



＊次世代シークエンサー

新規検査　“Virtual sequencing”



（藤井誠志氏提供）

大腸癌の遺伝子変異を病理画像から高精度で予測：日経メディカル

Agenda in My Talk

- SCRUM-Japan
- **CIRCULATE-Japan**
- Beyond Genomics
- Toward global platformer

–Stage IV期（見えるがん）から 術後微小残存病変*（見えないがん）の臨床開発への挑戦

*Precision Oncology*から*Precision Onco-surgery*へ

SCRUM-Japan

GOZILA

N= 4776

Stage IV期消化器がん
2018年2月から

MONSTAR

N= 2206

Stage IV期固形がん
（肺がんを除く）
2019年7月から

2021年11月時点

CIRCULATE Japan

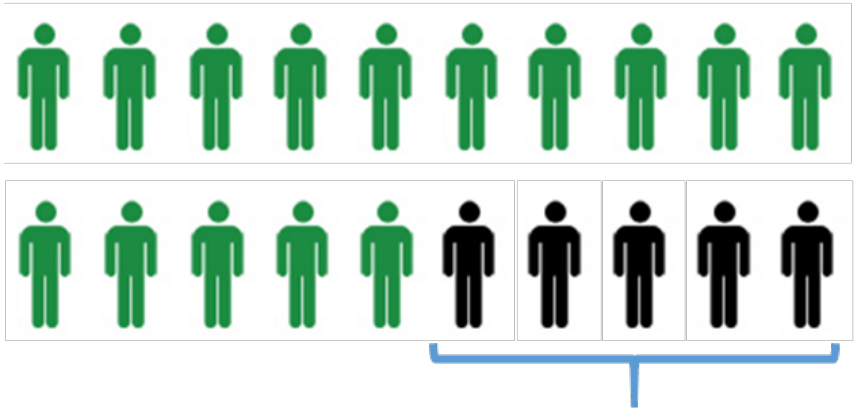
術後微小残存病変
(MRD; minimal residual disease)
臨床開発への挑戦

*患者さんの体内にまだ残っているだろうと想定されるがん病変（細胞）のこと。現在の診断技術では無再発と判断される。

今行われている”見えないがん”への治療の実際

例

手術のあと抗がん剤治療を
実施しなかった20人



再発率25%

手術のあと抗がん剤治療を
実施した20人

再発率20%

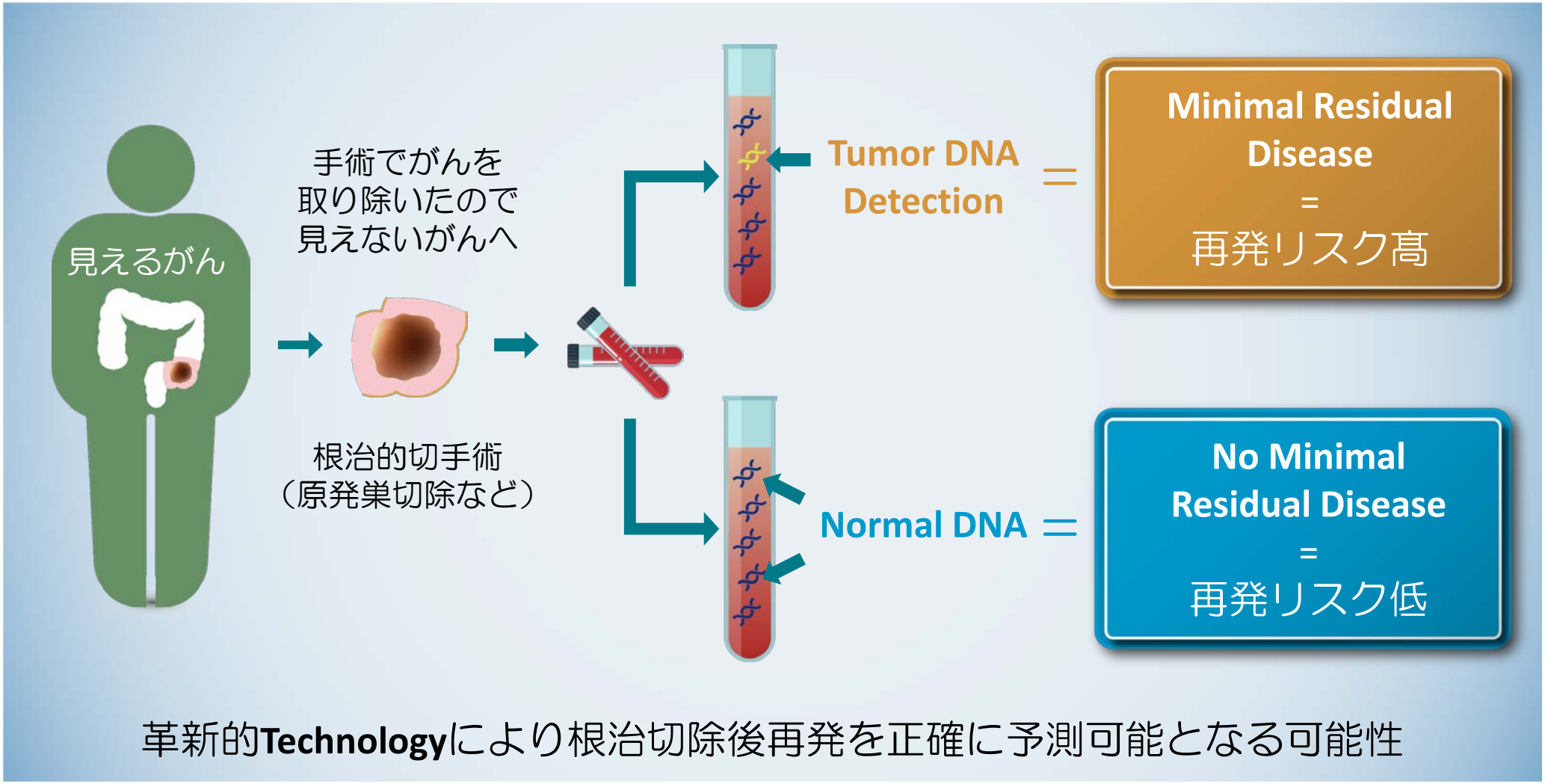
抗がん剤治療により
恩恵を受けた患者さん

残りの19人は恩恵を受けていない

術後抗がん剤治療（術後補助化学療法）：全体として再発抑制効果が示されているものの、実際には無益な治療を受けている患者さんが多いのが課題である

術後MRDによる再発リスクの層別化

MRD= Minimal Residual Disease　微小残存病変.



革新的**Technology**により根治切除後再発を正確に予測可能となる可能性

Yoshino T. ESMO 2019

術後MRD評価のAssay SIGNATERA

Personalized and Tumor-Informed Methodology Means Each Patient Gets Custom-Built Assay

❶ Analyze sequencing of tumor tissue and matched normal blood at initial timepoint

❷ Select individual-specific, clonal, somatic variants and design custom primers for each patient

❸ Obtain whole blood samples at longitudinal timepoints (eg, every 3 months)

❹ Cell-free DNA extraction and patient-specific multiplex PCR followed by NGS

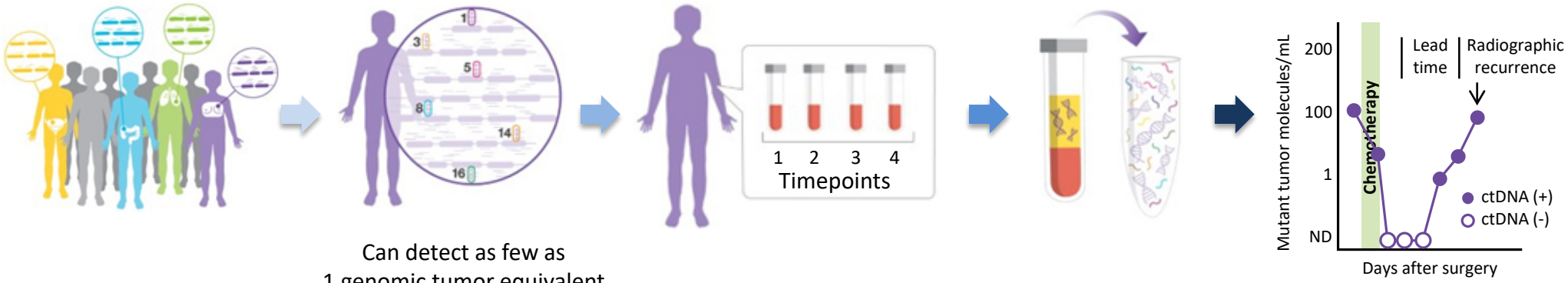
❺ Analyze ultra-deep NGS data in plasma to detect presence of ctDNA

全エクソーム解析
（正常部および癌部）

患者毎にカスタム
パネルを作製

カスタムパネルに
よるモニタリング

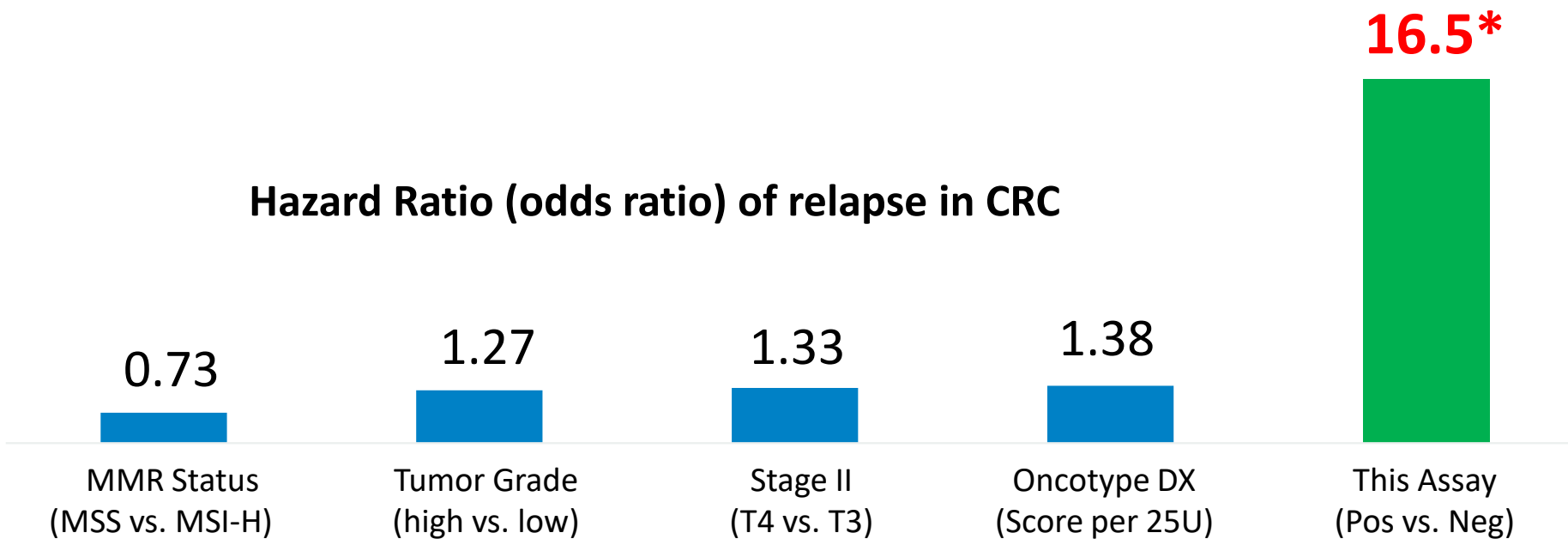
**ctDNA陽転化による
再発の早期同定**



Can detect as few as
1 genomic tumor equivalent
in 10 ml of blood
(VAF = 0.01%)

Reinert T, et al.: JAMA Oncol 5:1124-1131, 2019.

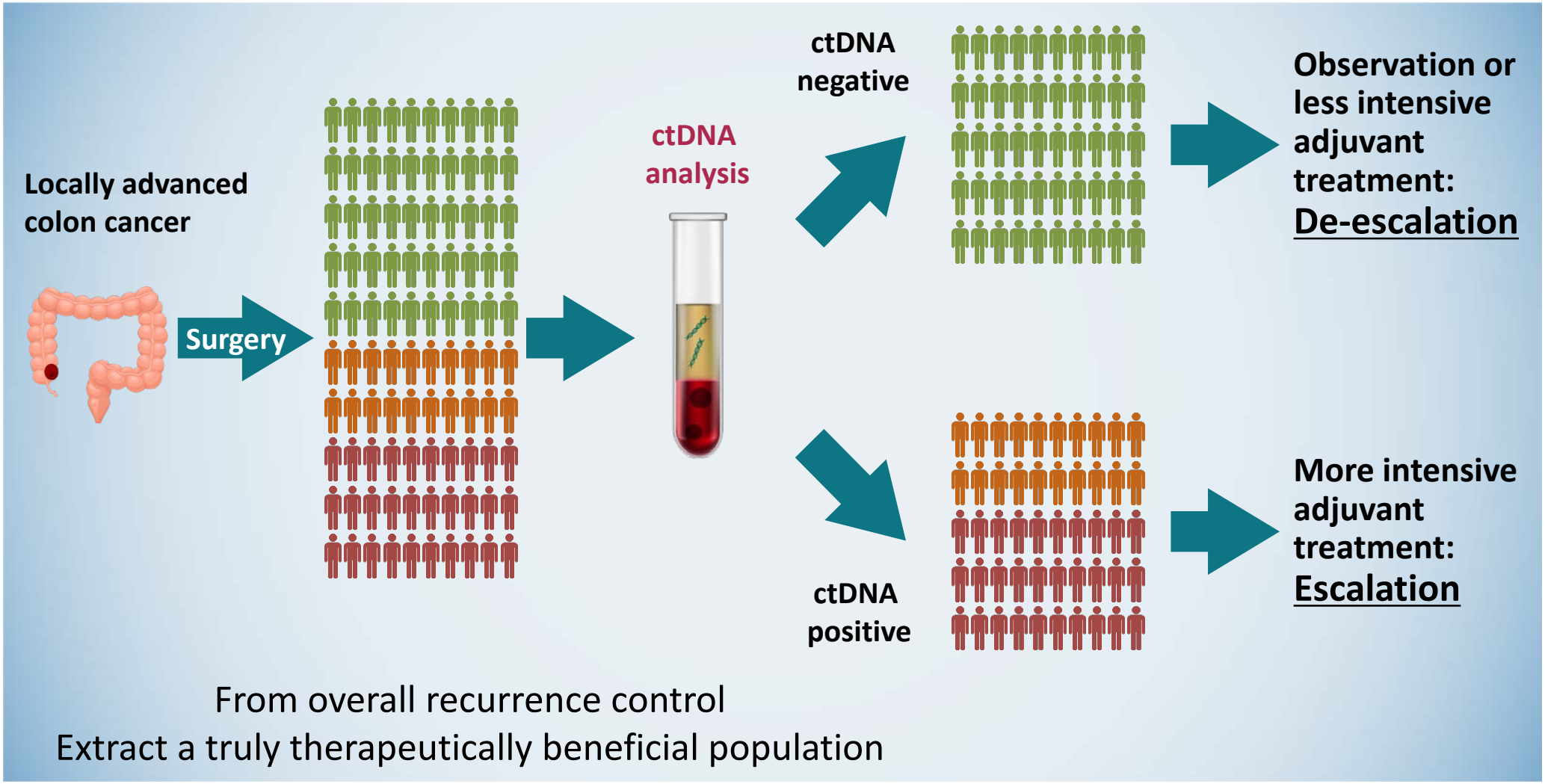
Cross-comparison of Predictivity



*Tarazona N, et al. Abst #4009 ASCO 2020

Ideal Precision for Localized CC

～From Precision Oncology to Precision Onco-Surgery

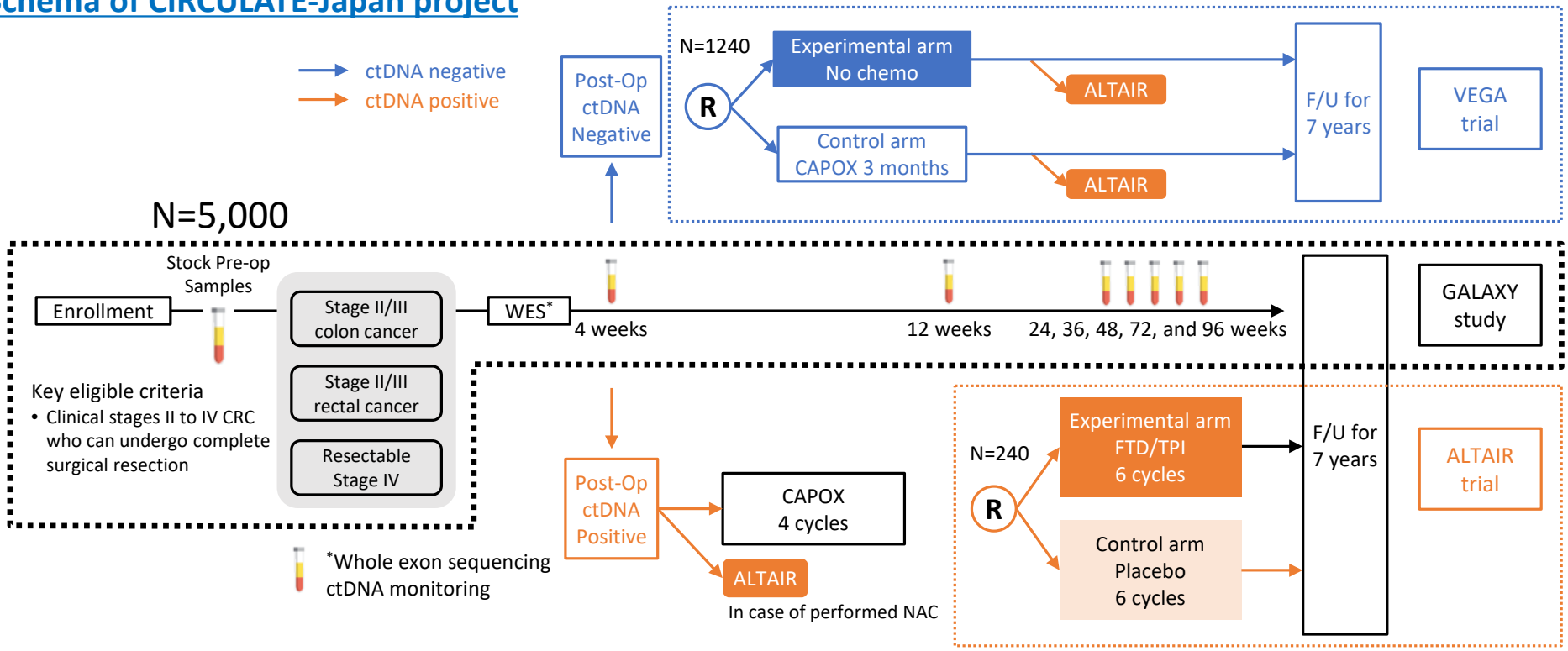


From overall recurrence control
Extract a truly therapeutically beneficial population

Overall Architecture of CIRCULATE-JAPAN

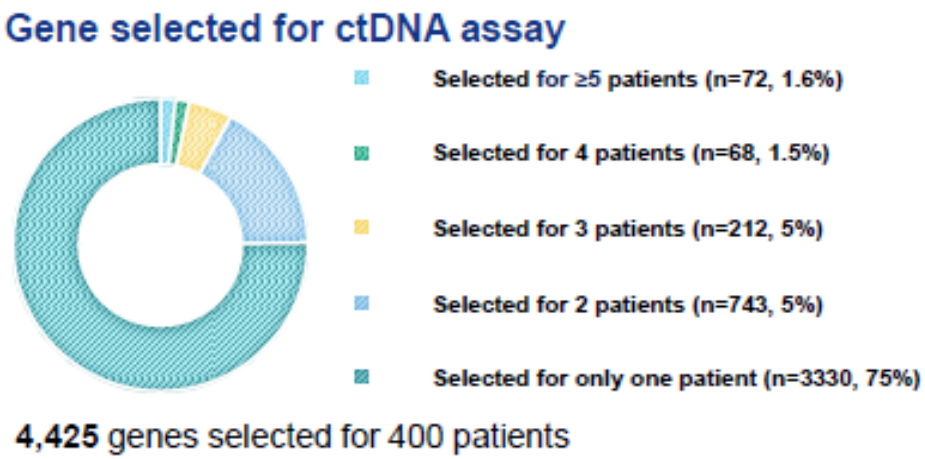
- CIRCULATE-Japan project is large platform enrolling resectable CRC (clinical stage II to IV) to evaluate the clinical utility of ctDNA analysis. The study comprises of one observational (GALAXY study) and two randomized phase III trials (VEGA and ALTAIR trial)[1].

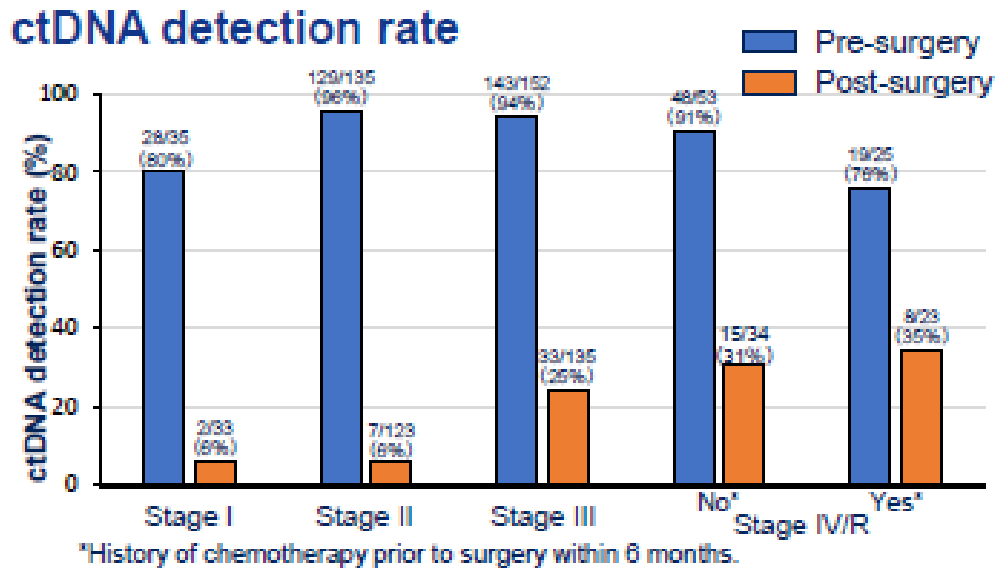
Schema of CIRCULATE-Japan project



1. Taniguchi H, et al. Cancer Sci 2021.

Signatera Performance in CIRCULATE-JAPAN





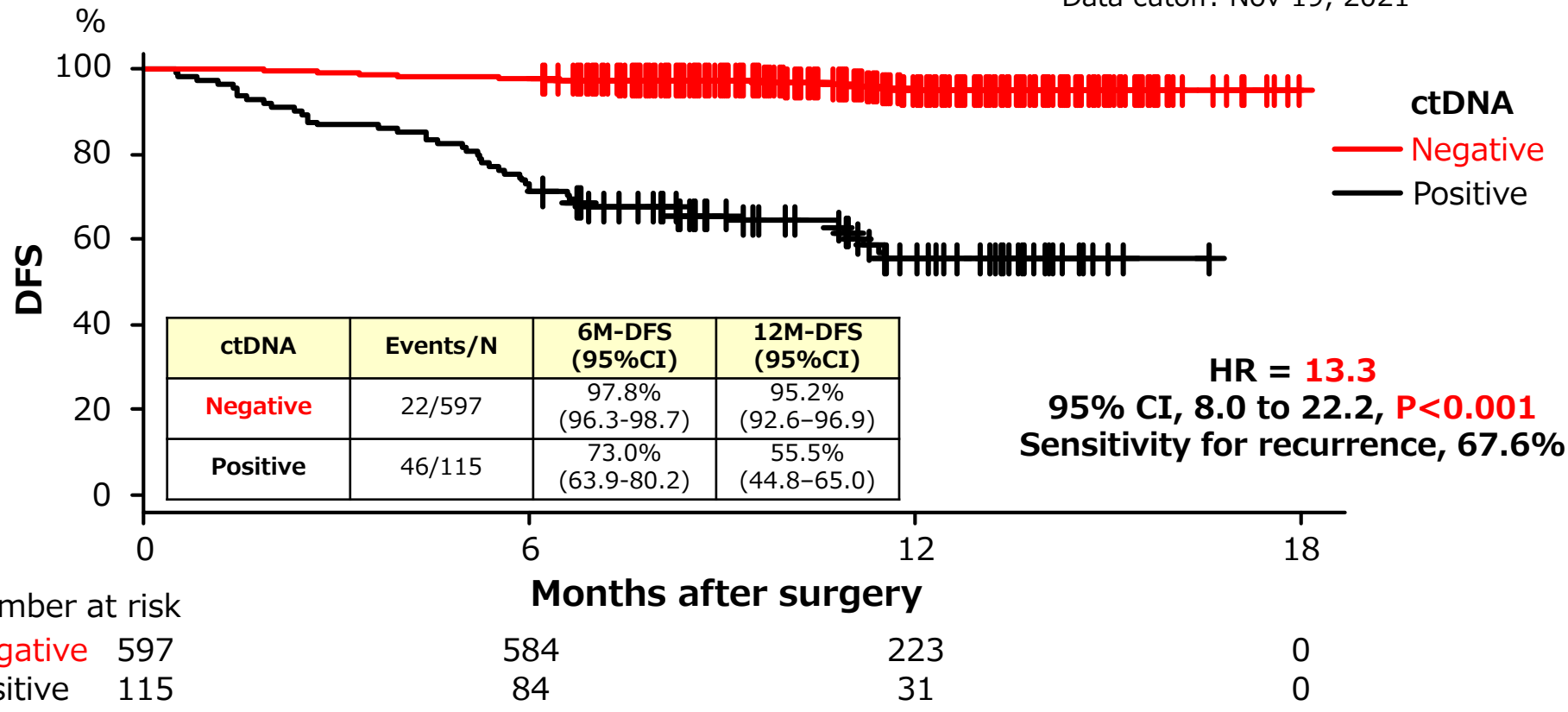
- ✓ Pre-surgical ctDNA detection rates of 95% in stage II-III disease and greater than 90% overall.
- ✓ Longitudinal relapse sensitivity of 92%, which has improved to >93% in the most recent analysis. Updated results will be presented at future conferences in mid-2021.
- ✓ Exceptionally low tissue failure rate of 2.1% and plasma failure rate of 0.4%.
- ✓ Of the 4,425 genes selected for analysis across these 400 patients, only 3% were common to four or more patients, reinforcing the value of an MRD test that is personalized to each patient's unique genetic signature.

Yukami H, Yoshino T, et al. ASCO 2021, Abstract #3608

https://www.natera.com/company/news/natera-to-present-clinical-data-from-largest-prospective-mrd-guided-trial-in-colorectal-cancer-at-the-2021-asco-annual-meeting/

DFS by post-op-4w ctDNA status in overall population (pStage II-III)

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

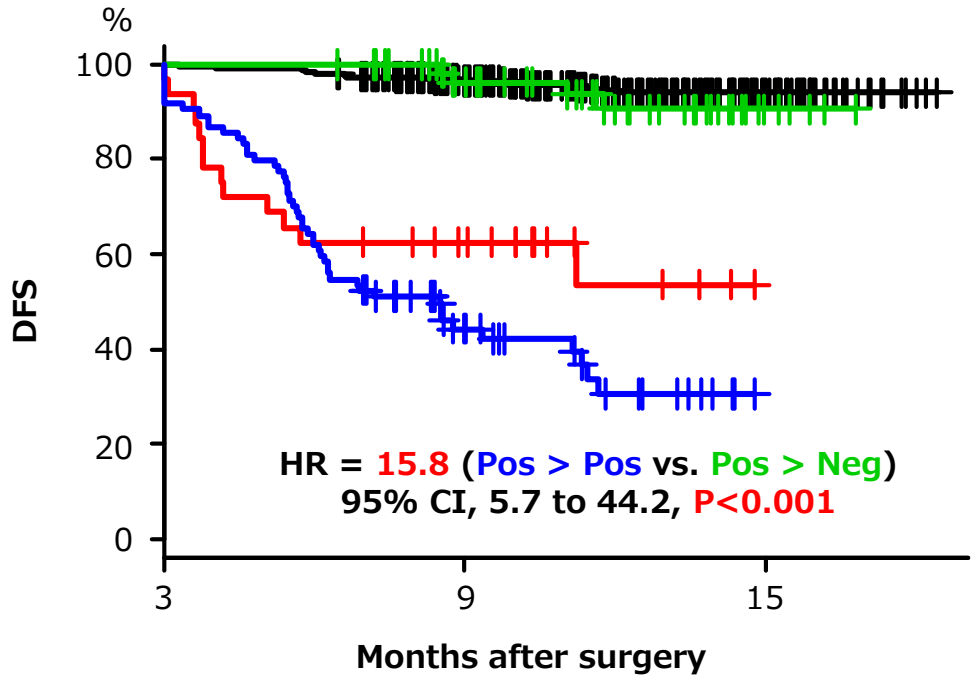


ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
Negative	22/597	97.8% (96.3-98.7)	95.2% (92.6–96.9)
Positive	46/115	73.0% (63.9-80.2)	55.5% (44.8–65.0)

DFS, disease-free survival; HR, hazard ratio; CI, confidential interval DFS curve was estimated by the Kaplan-Meier method.
HR and 95%CI were calculated by the Cox proportional hazard model.

Kotaka M, et al.: ASCO-GI2022 #9.

DFS by ctDNA dynamics from post-op-4w to 12w



Number at risk

Neg > Neg	660	490	60
Neg > Pos	32	15	0
Pos > Neg	62	46	5
Pos > Pos	84	23	0

ctDNA dynamics: Neg > Neg, Neg > Pos, Pos > Neg, Pos > Pos

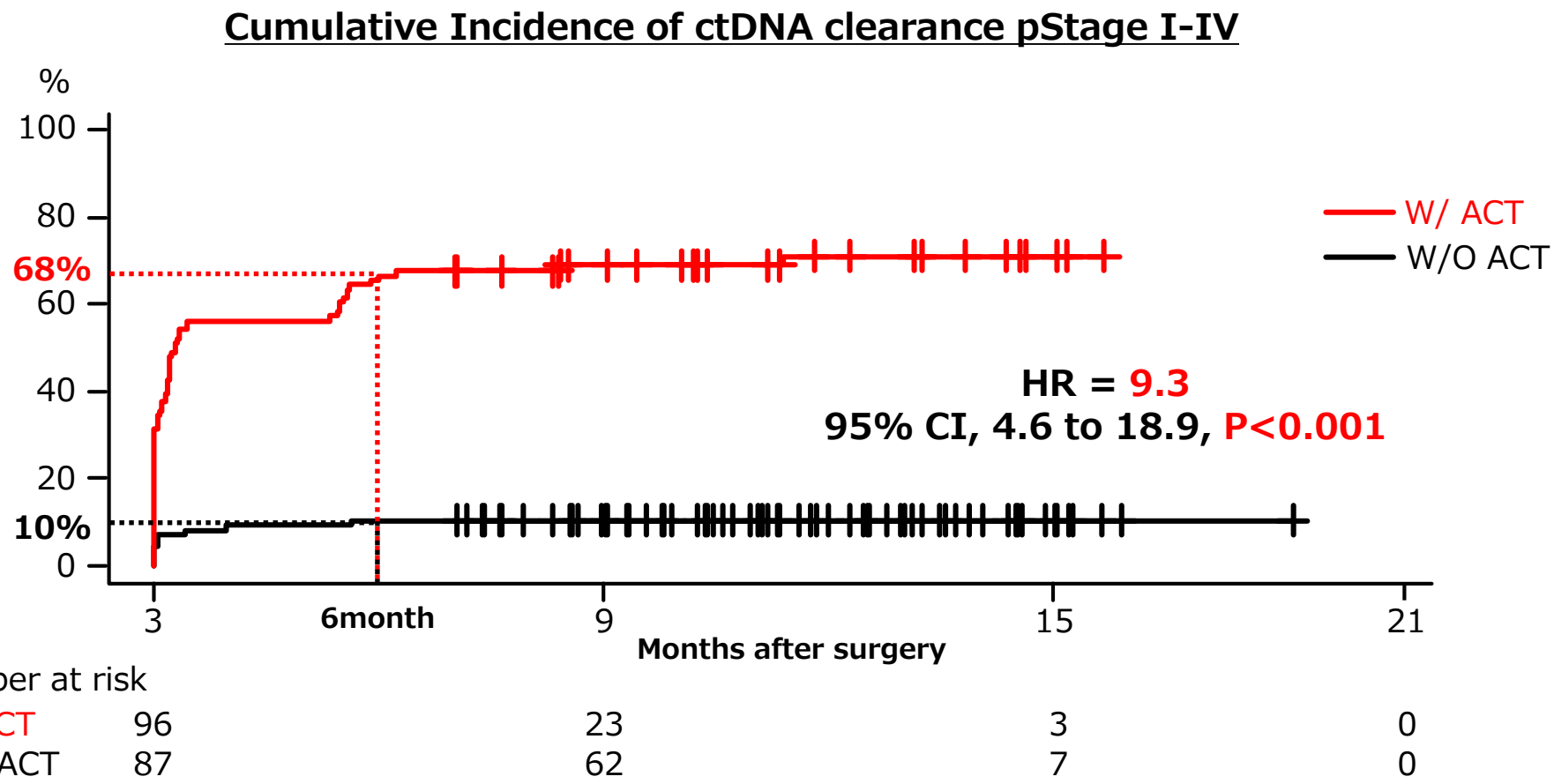
dynamics	Neg > Neg	Neg > Pos	Pos > Neg	Pos > Pos
Events/N	31/660	13/32	4/62	50/84
6M-DFS	98.0%	62.5%	100%	58.3%
HR	0.8	9.2	Reference	15.8
95%CI	0.27-2.15	3.0-28.4	-	5.7-44.2
P	0.60	**<0.001**	-	**<0.001**

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021

Landmark analysis at the post-op-12w was performed.
DFS, disease-free survival; HR, hazard ratio; CI, confidential interval
DFS curve was estimated by the Kaplan-Meier method.
HR and 95%CI were calculated by the Cox proportional hazard model.

Kotaka M, et al.: ASCO-GI2022 #9.

ctDNA clearance rate

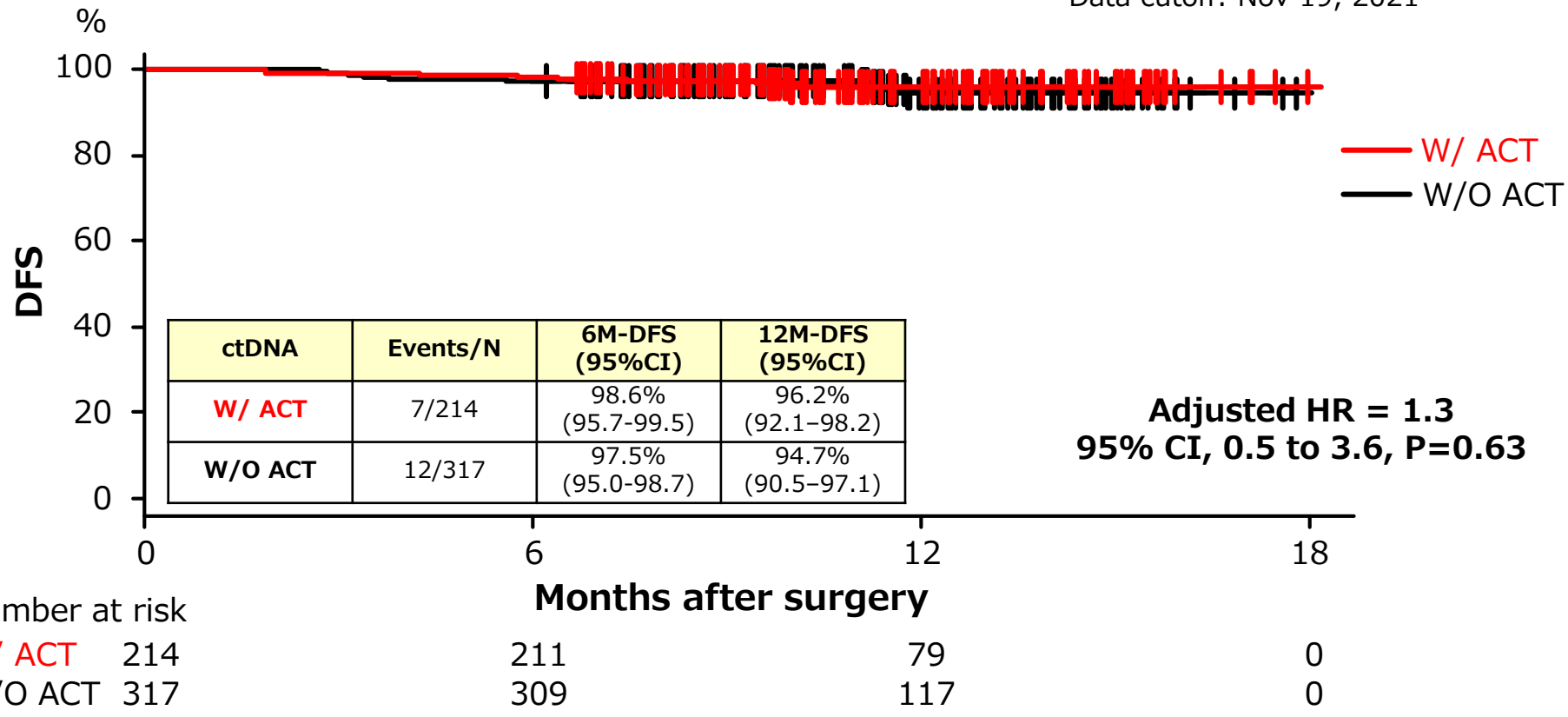


Landmark analysis at the post-op-12w was performed. HR was adjusted by sex, performance status, and pStage.
ACT, adjuvant chemotherapy; HR, hazard ratio, cumulative curve was estimated by the gray`s test. HR and 95%CI were calculated by Fine-Gray sub-distribution hazard model.

Kotaka M, et al.: ASCO-GI2022 #9.

DFS by ACT in post-op-4w ctDNA negative population (High-risk pStage II-III)

Median follow-up time: 11.4 months
Data cutoff: Nov 19, 2021



ctDNA	Events/N	6M-DFS (95%CI)	12M-DFS (95%CI)
W/ ACT	7/214	98.6% (95.7-99.5)	96.2% (92.1–98.2)
W/O ACT	12/317	97.5% (95.0-98.7)	94.7% (90.5–97.1)

Adjusted HR = 1.3
95% CI, 0.5 to 3.6, P=0.63

Number at risk

W/ ACT	214	211	79	0
W/O ACT	317	309	117	0

HR was adjusted by age, performance status, pStage, and MSI status that are imbalanced between two groups.
ACT, adjuvant chemotherapy; DFS, disease-free survival; HR, hazard ratio; CI, confidential interval.
DFS curve was estimated by the Kaplan-Meier method. HR and 95%CI were calculated by the Cox proportional hazard model.

Kotaka M, et al.: ASCO-GI2022 #9.

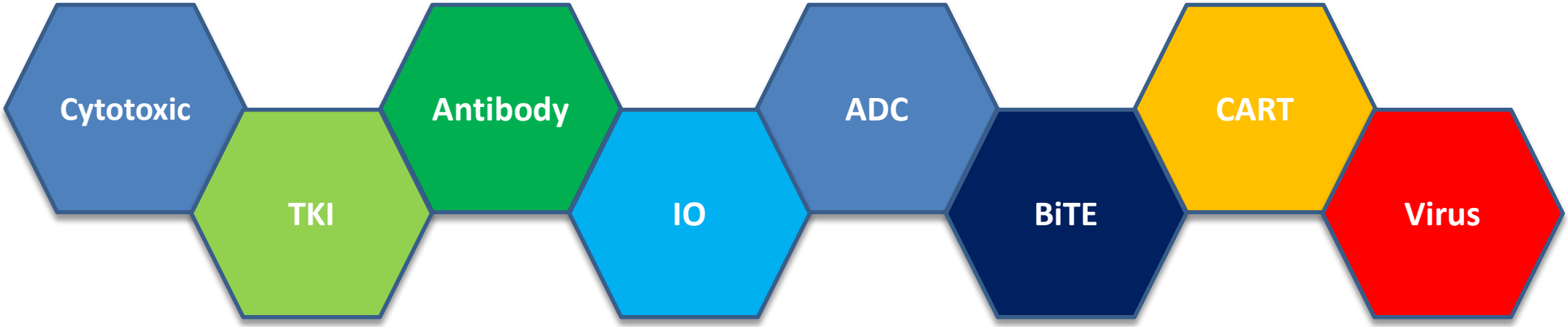
Agenda in My Talk

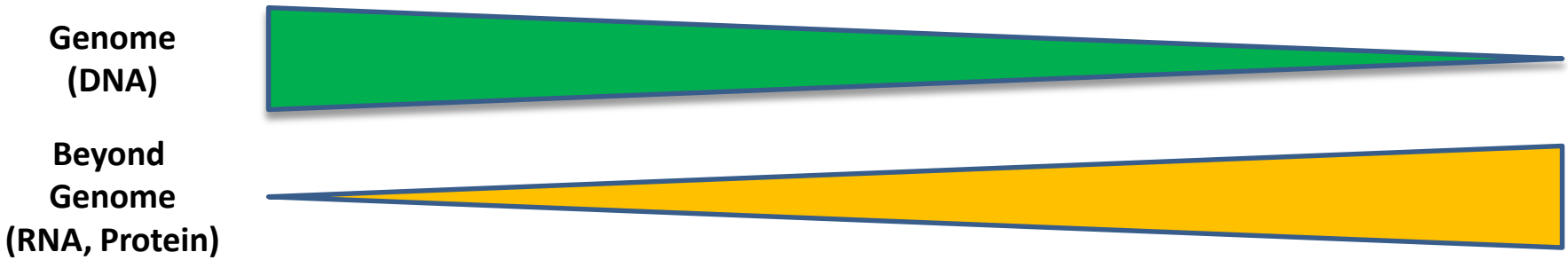
- SCRUM-Japan
- CIRCULATE-Japan
- **Beyond Genomics**
- Toward global platformer

Development of Anti-cancer Drugs

1st Gen:
DNA-alteration Driven
Precision Oncology

2nd Gen:
Expression Driven & TME-Targeted
Precision Oncology





Hypothesis

- ✓ AI-driven multi-omics analysis reveals what is actually happening in tissues & cells as well as tumor micro-environment.

Clarify More Molecular Blueprint

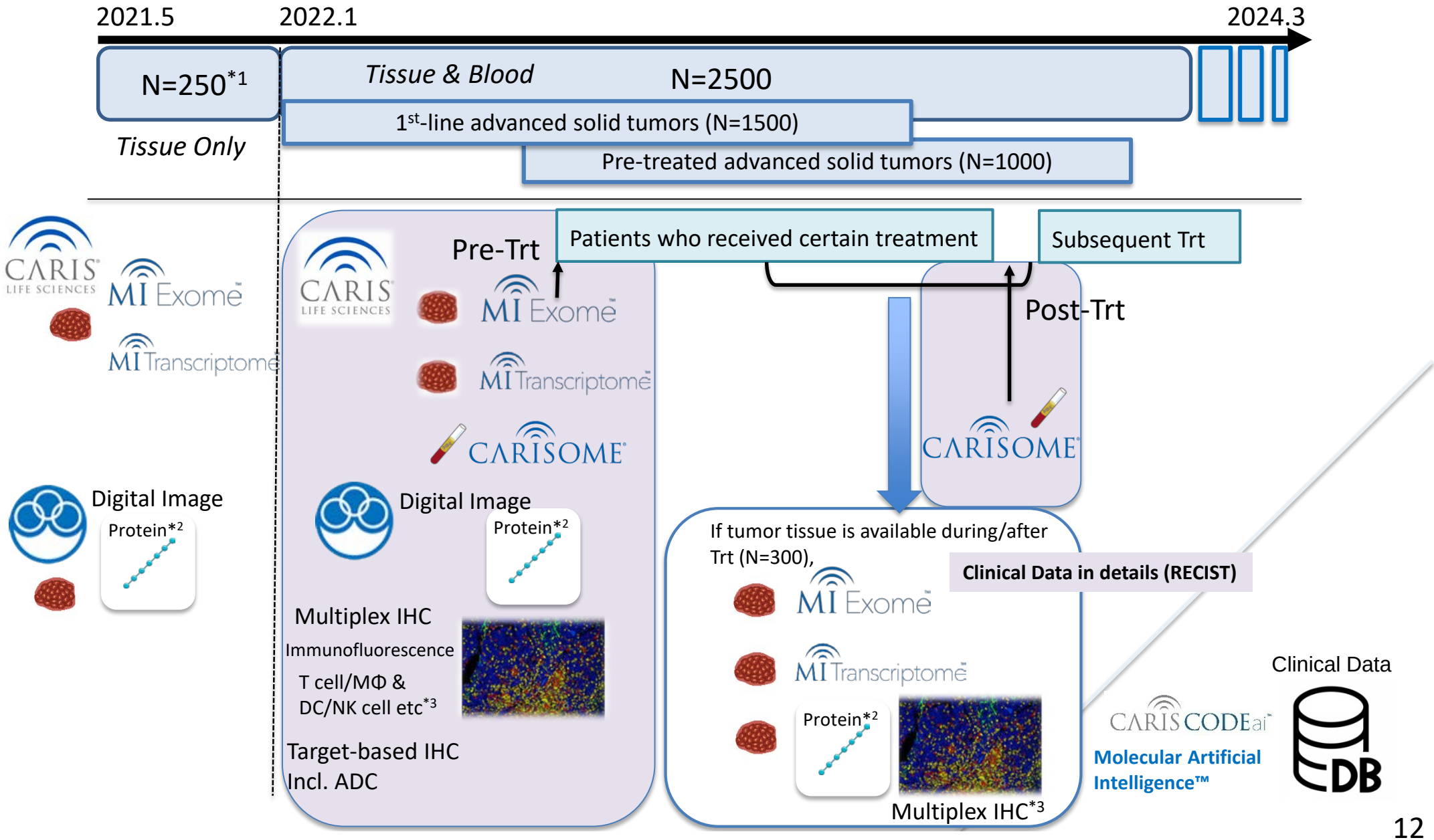
- ✓ AI-driven multi-omics analysis identify candidate multidimensional biomarkers.

Beyond Single Biomarkers

From Genomics to Multi-Omics with AI

MONSTAR-SCREEN-2 Architecture

Beyond Genomics



Note: Trt, treatment: ADC, Antibody Drug Conjugate: *1; 1st-line CRC, BP, and Prostate: *2; HER2, PD-L1, and HE: *3 Under construction of MDSC Panel

Protein

MONSTAR-SCREEN-2: IHC study

Omics Analysis

CARIS LIFE SCIENCES

MI Exome™

MI Transcriptome™

CARISOME®

+

Localization Analysis

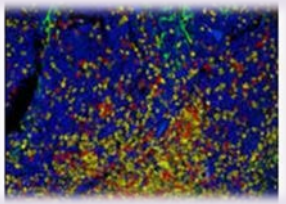
Digital Image

Protein*2

Multiplex IHC

Immunofluorescence

T cell/MΦ & DC/NK cell etc



Target-based IHC
Incl. ADC

MONSTAR-SCREEN-2 Data Base (DB) (DB Size; 1 PB = 1000 TB)

Beyond Genomics

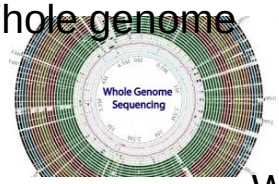
Free Access Right for Research & Commercial Use incl. IF images

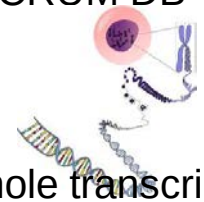
Funding Companies

Can also obtain the IF images with annotation

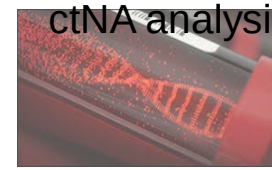
SCRUM DB

Whole genome





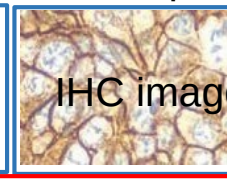
ctNA analysis

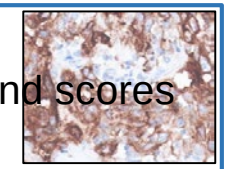


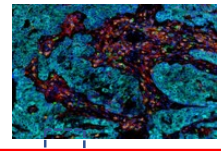
Whole transcriptome

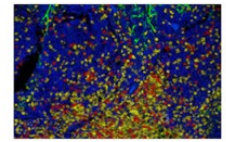
HE images and Pathological Dx

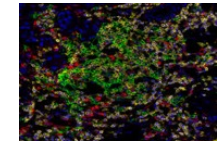
IHC images and scores







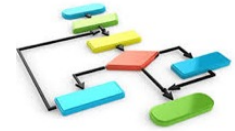




AI-based integrated study

All of the images will definitely be essential for the subsequent studies as training data

Academia

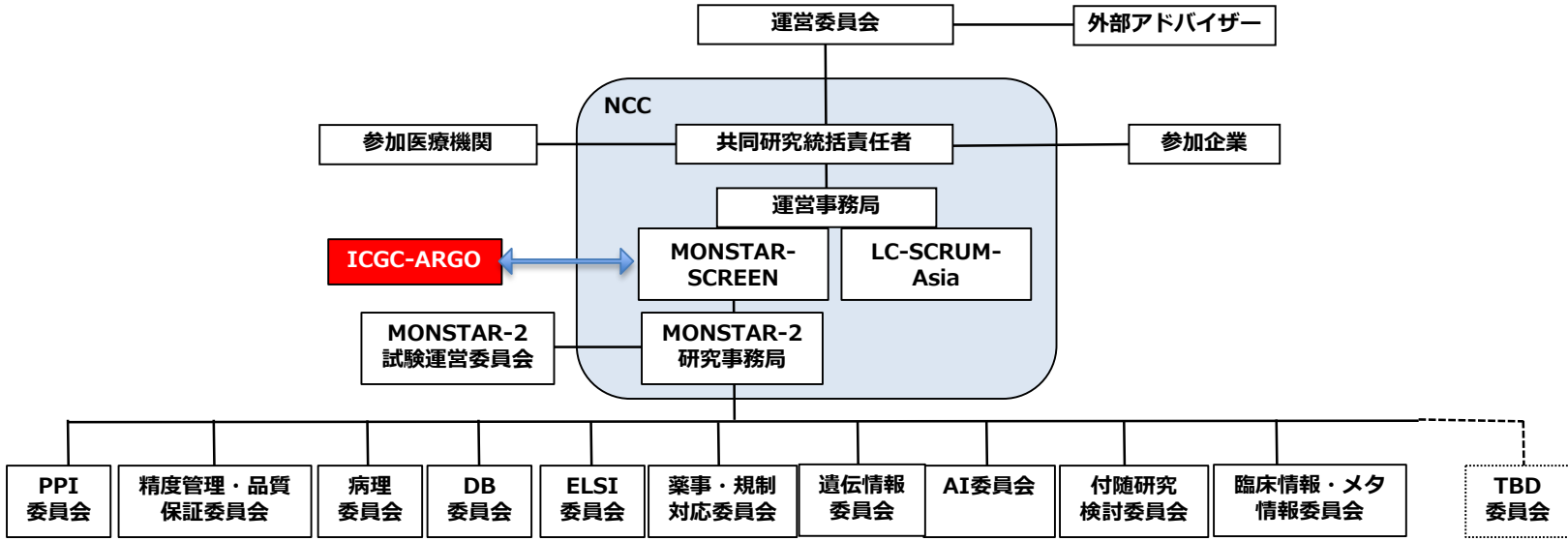


Permission of Assess for Registered Investigators for Research Use Only

Must upload the annotation for the IF image

Note; IF, Immunofluorescence

Structure of SCRUM-Japan & MONSTAR-SCREEN



注釈；
- ✓ 共同研究統括責任者はNCC東病院長（大津敦）。
- ✓ 運営委員会は、本共同研究統括責任者を委員長とし、NCCの代表者、参加医療機関の代表者、参加企業の代表者、その他運営委員として選任された者から成る。なお運営委員会の構成比は、NCC及び参加医療機関から選出される運営委員の数と参加企業から選出される運営委員の数を各半数程度とする。
- ✓ 運営事務局はNCC内に設置する。本共同研究の研究事務局機能、データセンター機能、運営委員会の開催、参加団体との契約にかかる業務等を担う。
- ✓ MONSTAR-2試験運営委員会は、MONSTAR-2研究代表者（吉野孝之）、研究事務局、その他研究代表者が指名するもので構成される。
- ✓ 各委員会は委員長および委員から構成される。

MONSTAR-SCREENは ARGOのメンバーになりました

ICGC-ARGO（International Cancer Genome Consortium- Accelerating Research in Genomic Oncology）（https://www.icgc-argo.org）ICGC における次期プロジェクト。ICGC や PCAWG プロジェクトの後継として、100,000症例のがんに ついて全ゲノムデータを集積し、同時に豊富な臨床病理情報を付加することによって、革新的な治療・予 防法の開発や、治療抵抗性の分子機構の解明などを目指すプロジェクト。現在日本を始め、米国・カナ ダ・英国・ドイツ・フランス・イタリア・スイス・韓国・中国・香港・サウジアラビア等の 13カ国が参加を表明している。

ARGO Accelerating Research in Genomic Oncology
International Cancer Genome Consortium

24th February 2021

Takayuki Yoshino, MD
National Cancer Center Hospital East, Japan
tyoshino@east.ncc.go.jp

Dear Takayuki,

We welcome your expression of interest and proposal to become a member of the ICGC ARGO project, as part of the International Cancer Genome Consortium. Your proposal has been reviewed by the Management Committee and fits well within the objectives and scientific remit set out by the ARGO project, and we're pleased to accept your project for inclusion. This Letter of Intent document confirms your proposal details and contains an Enrolment Pack of necessary administrative documents to get your project formally enrolled in ICGC ARGO.

経緯

2020年12月15日 ARGOから打診
2021年1月8日 ARGO DirectorとのWEB会議
2021年2月1日 ARGO運営委員会でプレゼン
2021年2月24日 ARGOから正式参加の承認
2021年4月2日 ARGOへすべてのdocumentsを提出

https://www.amed.go.jp/pr/2016_seikasyu_01-04.html
https://www.ncc.go.jp/jp/information/pr_release/2020/0206/20200206.pdf

Structure of ARGO

ICGC-ARGO
Executive Board

ICGC-ARGO
Independent Advisory Committee

Data Access Compliance Office
(DACO)

ICGC-ARGO
Management Committee

ICGC-ARGO
Scientific Forum

ICGC-ARGO
Working Groups

- Technologic Advancements
- Tissue & Clinical Annotation
- Public & Patient Engagement
- Ethics, Policy & Governance
- Phenomics
- Data Coordination & Management
- Pathology
- Education & Training

WG where I am a chair (renewal to the Clinical and Metadata working Group)

WGs that wish to participate from MONSTAR

https://www.icgc-argo.org/page/105/icgc-working-groups

Regularly & Longitudinal Report in the Snapshot in The Lancet Oncology

- Form a joint team to judge
- Fair & Competitive Way
- Monthly Contest
- Authorship Policy （3+3+ARGO WG)
- 1st report focus on the diagnosis with multi-omics
- 2nd report focus on treatment outcome

Dear ICGC ARGO Program leads,

On behalf of the Clinical and Metadata Working Group I write to you with an exciting opportunity. ICGC ARGO has secured a regular feature in **Lancet Oncology** (IF = 41) to highlight the work of the ICGC ARGO community. Lancet Oncology has a perspective section which includes "Snapshots"- snapshots describe challenging, precision medicine-informed cases discussed by clinical teams in tumour boards or multidisciplinary team meetings. Attached is an example. Snapshot articles are around 750 words and one figure or table to fit on one page. They will be updated in future issues of the journal (every 3-4 months) to provide a continuous case history over time (standalone case reports will not be considered).

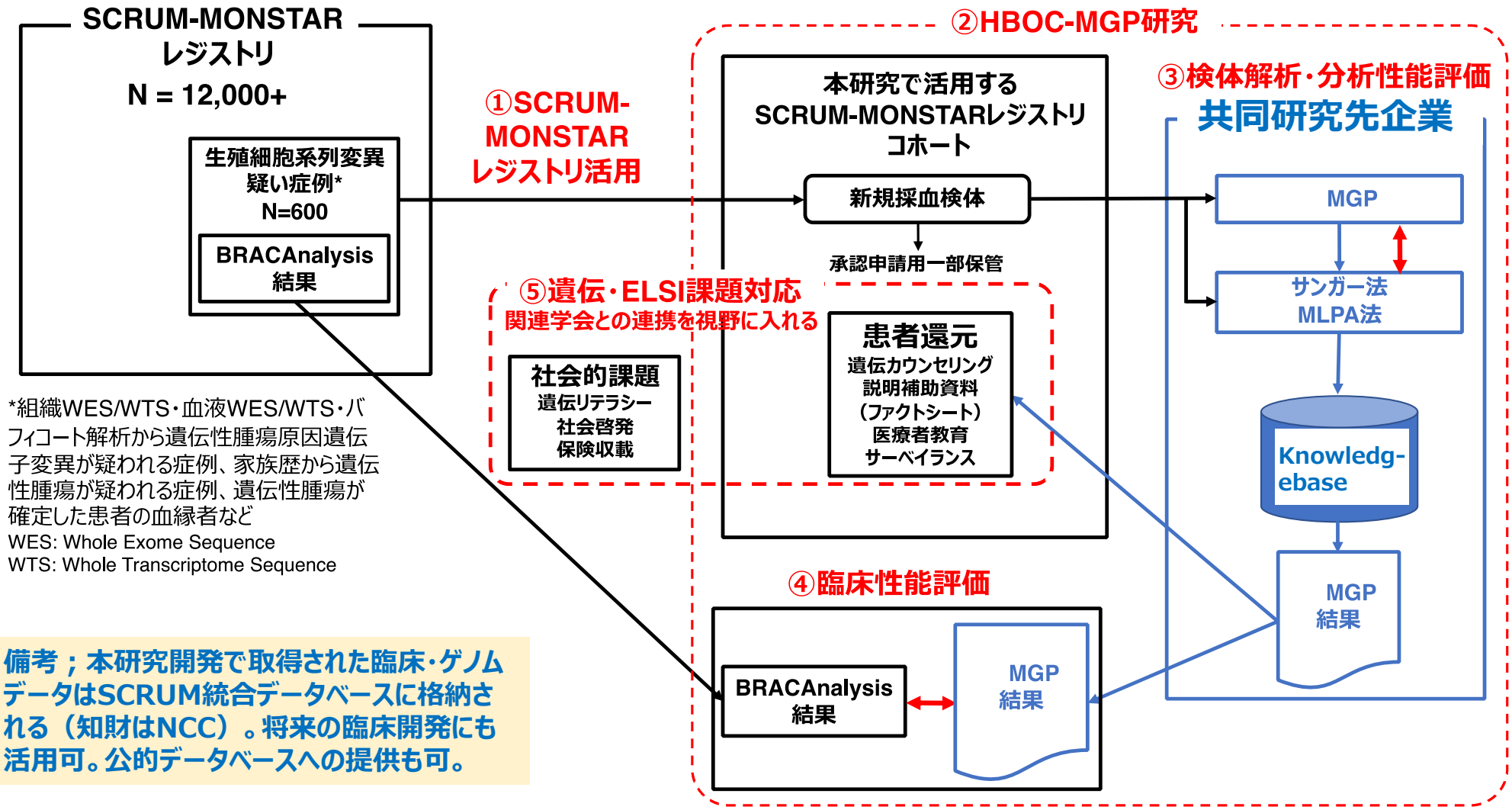
We invite all our programs to submit an Expression of Interest via this short form if you have a proposal or case study you would like considered for publication in the snapshot series. The EOI's will be reviewed by an internal team and selected for publication. We encourage you to submit your EOI as soon as possible to be considered as the editor is keen to progress immediately. Any questions please get in touch.

Snapshot

ICGC-ARGO precision medicine: familial matters in pancreatic cancer

Milella M, Luchini C, Lawlor RT, Johns AL, Casolino R, **Yoshino T**, Biankin AV; ICGC-ARGO. ***Lancet Oncol.*** 2022 Jan

生殖細胞系列バリアント確定プロジェクトと患者還元



*組織WES/WTS・血液WES/WTS・バフィコート解析から遺伝性腫瘍原因遺伝子変異が疑われる症例、家族歴から遺伝性腫瘍が疑われる症例、遺伝性腫瘍が確定した患者の血縁者など

WES: Whole Exome Sequence
WTS: Whole Transcriptome Sequence

備考；本研究開発で取得された臨床・ゲノムデータはSCRUM統合データベースに格納される（知財はNCC）。将来の臨床開発にも活用可。公的データベースへの提供も可。

SCRUM-Japan研究変遷とわが国でのゲノム医療との時差

年度	SCRUM-Japan研究	日本での実診療
2015	組織遺伝子パネルによる全国的スクリーニングの開始	
2016	産学での臨床ゲノムデータのオンライン共有開始	
2017	規制対応レジストリの構築開始 リキッドバイオプシーによるスクリーニング開始	
2018		
2019	台湾、中国からの登録開始 リキッド＋腸内細菌叢解析をすべての固形がんに拡大	遺伝子パネルの薬事承認、ゲノム医療中核拠点＋連携施設での組織遺伝子スクリーニング開始 C-CATへの登録開始
2020	全エキソーム＋リキッドバイオプシーによる術後補助薬物療法個別化試験開始 全トランスクリプトーム解析による新規標的探索研究開始 経時的遺伝子モニタリングによる耐性因子検出研究	患者申出療養制度での先進医療試験
2021	全エキソーム・トランスクリプトーム含むマルチオミックス解析開始	リキッドバイオプシーの薬事承認 C-CATでのデータ共有開始？

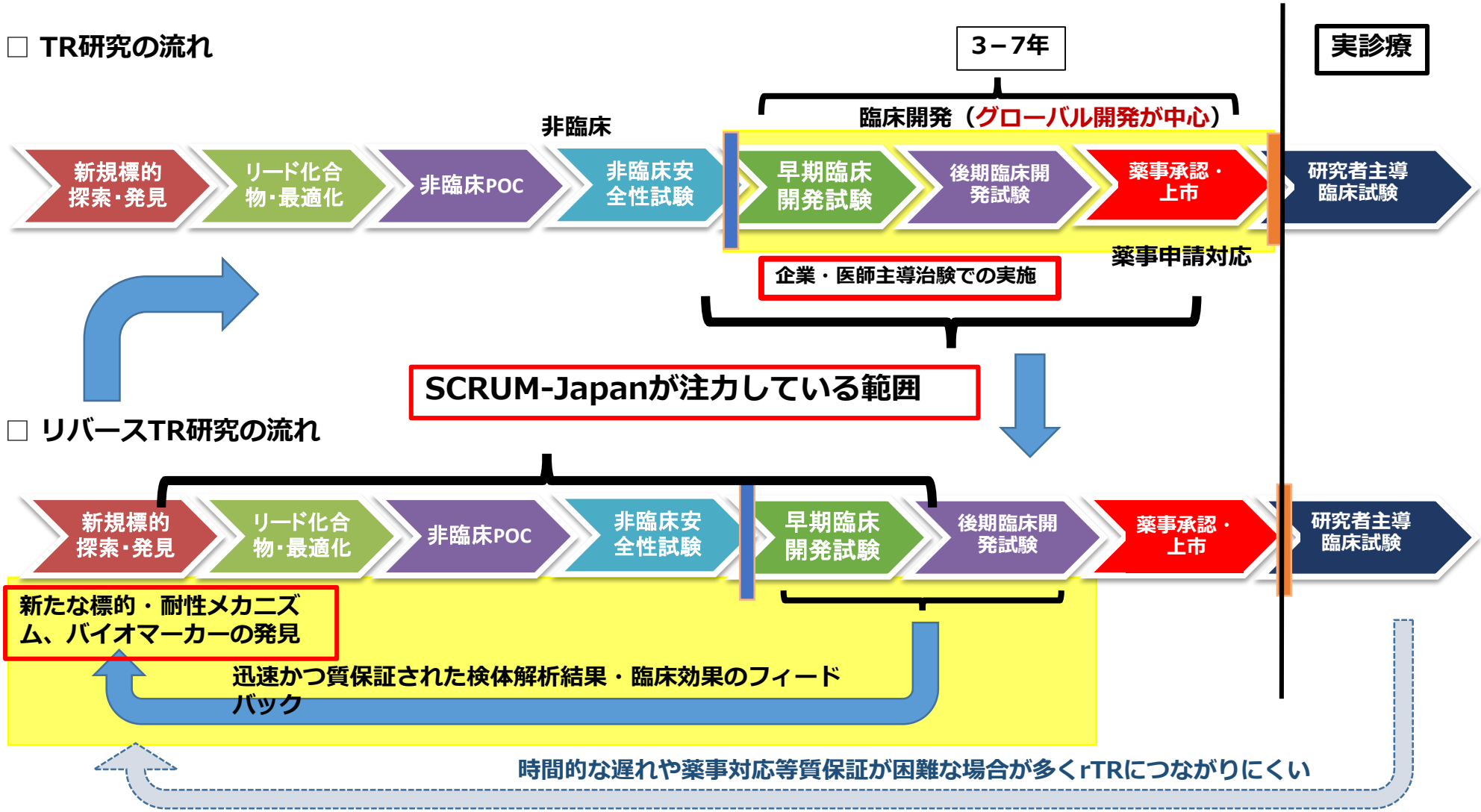
SCRUM-Japanは実診療に導入される3－5年前での開発研究

---> 薬事承認取得し海外に遅れなく（世界に先駆けて）患者さんへ届けている

＋実臨床での活用法の世界的エビデンス創出及び課題の抽出を行っている

＋産学連携による新しい標的発見や次の創薬に結び付けている

医薬品開発におけるSCRUM-Japanの主な研究範囲：黄色塗り範囲



Agenda in My Talk

- SCRUM-Japan
- CIRCULATE-Japan
- Beyond Genomics
- **Toward global platformer**

日本がリードした国際研究データプラットフォーム構築

NCCHEが構築している国際データベース

SCRUM-Asia	CIRCULATE-Japan	ARCAD-Asia
アジア諸国と連携した進行がんゲノムスクリーニング研究	リキッドバイオプシーによる術後大腸がんの個別化治療プロジェクト（日台）	がんのアジア地域国際臨床試験データベース構築プロジェクト

NCCHE研究者がコアメンバーとなっているグローバルデータベース

ICGC-ARGO	TITANIA
世界最大の国際がんゲノムコンソーシアム	世界最大の国際共同マルチオミックス研究

国内・欧米の法規制・ガイドラインに対応したデータ収集・保管・共有・質保証のためのシステム構築・SOP整備
（個人情報保護法、3省2ガイドライン、EU臨床試験法、監査証跡対応等）

データマネージャー、データスペシャリスト、バイオインフォマティシャン、倫理専門家等の整備・人材育成

マルチオミックスデータストレージ・解析に対応可能なスパコン設置（NCC内）

臨床マルチオミックスデータの統合AI解析プラットフォームの構築

セキュリティを担保したアカデミア・企業とのデータ共有システムの構築

期待される成果

- 国内の産学データ共有システムによる世界最先端データへのアクセスによる新たな創薬・イノベーション創出
- わが国全体の医薬品開発研究の活性化および製薬/診断薬開発企業からの大規模投資
- 新興感染症や他の生活習慣病における日本主導型の創薬にむけた先駆的モデルの確立

次世代に明るい未来を届けるために

Toward global platformer

- ✓ 国内研究基盤整備
  消化器がんから固形がんへ拡大
- ✓ 国際連携の強化
  日本から世界へ発信
- ✓ 開発スペースの発掘
  Tumor biologyの解明や新規テクノロジーの導入
- ✓ 医師主導治験促進
  大規模なスクリーニング・プラットフォームの確立

MONSTAR

志を共にする皆様と一緒に！

Let's go where no one has gone before!

tyoshino@east.ncc.go.jp