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REVIEW ARTICLE

SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN: Path to the realization of biomarker-guided precision oncology in advanced solid tumors

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Abstract

Comprehensive genomic profiling enables the detection of genomic biomarkers in advanced solid tumors. However, efficient patient screening for the success of precision oncology remains challenging due to substantial barriers, such as genotyping costs and accessibility to matched therapies. To address these challenges, we launched GI-SCREEN, a nationwide gastrointestinal cancer genomic screening project within the SCRUM-Japan network in 2015 with the specific purpose of matching patients with a diverse portfolio of affiliated interventional targeted therapy trials. Subsequently, we initiated the molecular profiling projects GOZILA, MONSTAR-SCREEN-1, and MONSTAR-SCREEN-2, which incorporate tissue and plasma multiomics approaches to accurately identify patients with advanced solid tumors who would benefit from matched therapies. These projects have led to a significant increase in patient participation in targeted clinical trials and the approval of several therapeutics and companion diagnostics. Additionally, clinicogenomic analyses utilizing the SCRUM-Japan database have provided new insights into the molecular mechanisms of advanced solid tumors. In this review, we describe the path to the realization of cancer precision medicine for patients with advanced solid tumors based on the SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN platforms.

KEYWORDS

circulating tumor DNA, multiomics, next-generation sequencing, precision oncology, real-world data

1 | INTRODUCTION

Remarkable advances in precision oncology over the past two decades have highlighted the necessity of performing genotyping for patients with advanced cancers to ensure appropriate therapy selection. Practice guidelines outlined by the National Comprehensive Cancer Network (NCCN) and European and Japanese Societies of Medical Oncology (ESMO and JSMO) now comprise recommendations for genotyping to guide therapy selection in different cancer types.[1-3] Although an impressive progress has been achieved through the development of biomarker-targeted clinical trials, the pace of precision oncology innovations remains limited by the daunting

logistical realities of patient identification, and many actionable targets are present in only a small fraction of patients, which implies that hundreds or even thousands of patients should be screened for enrolment in a single study. Compounding this patient identification barrier is an additional substantial challenge associated with traditional trial designs, such as genotyping cost, lengthy screening periods, and limited access to screening populations, factors which collectively have led to increasingly low enrolment rates of otherwise eligible patients.

To address these challenges and to accelerate innovation in precision oncology, in 2015, we launched GI-SCREEN, a nationwide gastrointestinal (GI) cancer genomic screening project within the SCRUM-Japan network[4] that aims to match patients with advanced GI cancers with a diverse portfolio of affiliated interventional targeted therapy trials. In GI-SCREEN, patients with advanced GI cancers presenting to network institutions for clinical care were screened using a comprehensive tissue DNA sequencing panel before or during systemic therapy. After standard-of-care therapy, these patients were enrolled in a suitably matched clinical trial.

Recent tumor-agnostic regulatory approvals of targeted agents based on the presence of specific biomarkers rather than tumor sites, and the development of liquid biopsy technologies, have led to a paradigm shift in precision oncology.[5-7] To accelerate these innovations, based on the application of the GI-SCREEN network platform, the molecular profiling studies GOZILA, MONSTAR-SCREEN-1, and MONSTAR-SCREEN-2, which incorporate a tissue and plasma multiomics approach with artificial intelligence (AI), are being conducted to accurately identify patients with advanced solid tumors who will benefit from matched therapies. Additionally, to accelerate the development of precision medicine for rare cancer subtypes, we established the SCRUM-Japan Registry to collect registry-grade real-world data to be utilized as control data for regulatory submission.

In the present study, we have reviewed the timeline and application of SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN in the realization of biomarker-guided cancer precision medicine for patients with advanced solid tumors in Japan (Figure 1, Table 1).

2 | GI-SCREEN

To implement precision medicine for patients with advanced GI cancers, in February 2015, we launched GI-SCREEN, a nationwide tumor tissue cancer genomic profiling study involving 26 core cancer institutions in Japan (UMIN000016343, UMIN000016344). Patients with histopathologically confirmed unresectable or metastatic GI cancer who had received or were scheduled to receive systemic therapy were eligible. Genotyping of archival formalin-fixed paraffin-embedded (FFPE) tumor tissues derived from enrolled patients was performed using the Oncomine Comprehensive Assay (OCA; Thermo Fisher Scientific) v1 between February 2015 and March 2017 and OCA v3 between April 2017 and April 2019 at the Life Technologies Clinical Services Lab, a CLIA-certified, CAP-accredited laboratory, as per methods previously described.[8] These assays covered 143 (OCA v1) and 161 (OCA v3) cancer-related genes and detected the relevant single-nucleotide variants (SNVs), copy number variations, gene fusions, and indels in a streamlined

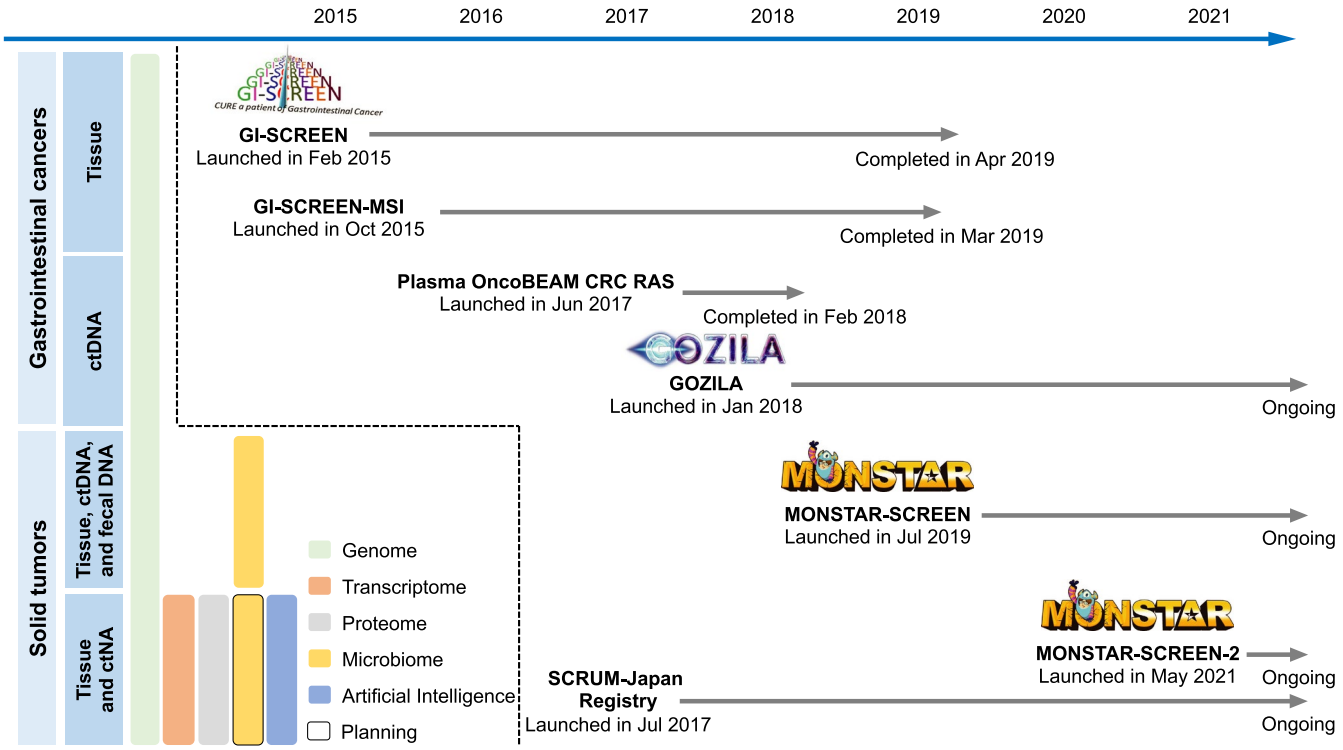

FIGURE 1 SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN studies. A timeline of the studies conducted based on the SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN study platforms

TABLE 1 Overview of SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN studies

	GI-SCREEN	GOZILA	MONSTAR-SCREEN	MONSTAR-SCREEN-2
Cancer	Gastrointestinal cancers	Gastrointestinal cancers	Solid tumors	Solid tumors
Sample size	5743	7000	2300	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	Active recruitment	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.

workflow. Our assessment of the DNA quality of FFPE samples for OCA analysis revealed that the sequencing success was significantly associated with a high DNA integrity, defined as the difference in threshold cycle (Ct) values of polymerase chain reaction (PCR) products, as well as surgical specimens and short sample storage periods.[9]

Patient enrollment was completed in April 2019. In total, 5743 patients with advanced GI cancers, including colorectal (n = 2791), gastric (n = 1141), esophageal (n = 369), pancreatic (n = 652), biliary tract (n = 416), liver (n = 67), small intestine (n = 93), appendiceal (n = 47), anal canal cancers (n = 13), GI stromal tumors (n = 79), and neuroendocrine tumors (n = 75), were enrolled. The landscape of genomic alterations was comparable to that reported in other profiling studies in Western countries, and revealed a high prevalence of mutations in trunk genes such as *TP53*, and a considerable number of alterations were detected at a low prevalence showing a "long-tail" distribution.[10-14] RNA sequencing performed using the OCA assay aided the successful identification of rare fusions involving *ERBB2*, *FGFR2* or *3*, *RET*, *ROS1*, *NTRK*, and others.

The GI-SCREEN has been utilized not only to accelerate clinical trials but also for novel research related to cancer biology. Clinical outcomes have been updated with a median follow-up time of more than 3 years, and comprehensive clinicogenomic analyses have been performed. An international collaborative study reported by GI-SCREEN, the Memorial Sloan Kettering Cancer Center, and the Massachusetts General Hospital Cancer Center showed that patients with class 2 non-V600E *BRAF*-mutant metastatic colorectal cancer (mCRC) were less likely to exhibit responses to anti-EGFR therapy than those with class 3 diseases.[15] An analysis involving 2329 patients with mCRC showed that *FLT3* amplification was identified in 85 patients (3.6%) patients.[16] Additionally, *FLT3*-amplified CRC presented with fewer coalterations of driver genes and was significantly associated with short overall survival, suggesting its oncogenic role in mCRC. An international collaboration among GI-SCREEN, NCTN-SWOG, and Korea established an international harmonization of diagnostic criteria that integrated data based on immunohistochemistry (IHC), fluorescence in situ hybridization, and NGS for HER2-positive mCRC.[17]

In parallel with GI-SCREEN, the SCRUM-Japan GI-SCREEN-MSI study was conducted to assess the tissue microsatellite instability (MSI) status of patients with metastatic GI cancers. Tissue MSI status was ascertained using the MSI test kit (FALCO Biosystems), which is used to assess the unstable alleles of five mononucleotide markers outside the quasi-monomorphic variation range generated via DNA amplification. Such DNA samples are extracted from tumor tissue samples that are in perfect agreement with the gold standard for MSI testing using tumor and normal samples.[18] Patients with MSI-high CRC confirmed by considering GI-SCREEN-MSI, who did not receive immune checkpoint inhibitor (ICI) treatment, demonstrated a shorter overall survival than those with MSI-high CRC with ICI treatment or those with microsatellite-stable CRC.[19] Based on the results of GI-SCREEN-MSI, the MSI test kit (FALCO) was approved as a companion diagnostic for pembrolizumab in advanced solid tumors and for nivolumab with or without ipilimumab for metastatic CRC as well as an in vitro diagnostic for the screening of Lynch syndrome in Japan.

3 | GOZILA

Despite the marked success of the design of GI-SCREEN, the requirement for tissue samples hampers patient recruitment, resulting in lengthy screening durations. Recently, the analysis of circulating tumor DNA (ctDNA) has been demonstrated in the detection of genomic alterations with high accuracy compared with tumor tissue analysis.[5,6] To rapidly perform screening of patients for trial eligibility, in January 2018, we initiated the GOZILA study, a nationwide plasma genomic profiling study involving 31 core institutions in Japan based on the GI-SCREEN using Guardant360 (Guardant Health), a 74-gene comprehensive ctDNA sequencing assay (UMIN000029315).[20] Patients with advanced GI cancers or solid tumors with specific alterations in tissue were deemed eligible, and it was necessary to monitor disease progression in patients during systemic chemotherapy and in those who had not commenced subsequent therapy at the time of blood sampling to avoid the suppression of ctDNA shedding

due to chemotherapy. As of June 2021, the sample size was 7000, and 4296 patients were enrolled.

Of the 1573 patients with advanced GI cancers enrolled in the GOZILA study, ctDNA was successfully detected in 91.4% of the patients, with the highest ctDNA detection rates in CRC and esophageal squamous cell carcinoma.[21] The landscape of ctDNA genomic alterations showed frequent gene amplification events in receptor tyrosine kinase and cell cycle–related genes; oncogenic activating mutations in the RAS/RAF, PI3K, and WNT pathways; and inactivating mutations in DNA damage response and tumor suppressor pathways, consistent with reports of previously treated advanced GI malignancies.

To assess the clinical utility of ctDNA genotyping vs. tissue analysis for the identification of patients as candidates for targeted clinical trials, we compared data derived from 1687 patients with advanced GI cancers in GOZILA with data derived from 5621 patients in GI-SCREEN.[21] Despite the similar composition of the screening population, the tumor testing characteristics were significantly improved in GOZILA compared with those in GI-SCREEN. Specifically, for GOZILA vs. GI-SCREEN, the sample unavailability rate was 0.3% vs. 1.5%, the failure rate was 0.1% vs. 10.6%, the median sample acquisition duration was 4 vs. 14 days, and the median test duration was 7 vs. 19 days. Accordingly, the median time from testing to trial enrolment was only 1 month for cfDNA testing vs. 5.9 months for tumor testing (a decrease of 83%). Overall, ctDNA genotyping led to a statistically significant increase in enrolment in genotype-matched clinical trials relative to enrolment conducted via tumor-based screening (9.5% vs. 4.1% of patients; $P < .0001$) without compromising treatment efficacy (response rate of 20.0% vs. 16.7%; median progression-free survival, 2.4 vs. 2.8 months).

The clinical utility of such a rapid screening method based on ctDNA genotyping is leveraged in umbrella/basket-type clinical trials utilizing the GOZILA platform. The TRIUMPH study is a GI-SCREEN/GOZILA-related phase 2 clinical trial evaluating the efficacy of pertuzumab plus trastuzumab in patients with mCRC with *HER2* amplification confirmed via tumor tissue or ctDNA analysis. The study met its primary endpoint with a confirmed ORR of 30% in 27 tissue-positive and 28% in 25 ctDNA-positive patients.[22] These results support our report comparing GOZILA and GI-SCREEN, indicating that ctDNA genotyping can be used to accurately identify patients who may benefit from targeted therapy as well as conventional tissue-based genotyping.

4 | MONSTAR-SCREEN

In addition to facilitating trial enrolment through rapid screening, ctDNA genotyping demonstrates the advantage of being able to assess chronological tumor evolution and intratumoral genomic heterogeneity for accurate treatment selection. MONSTAR-SCREEN profiles and monitors genomic alterations using FoundationOne Liquid CDx (Foundation Medicine),[23] which targets alterations of 324 genes as well as complex biomarkers, such as MSI, the blood tumor mutational burden (bTMB), and tumor fraction, to assess the landscape of genomic evolution throughout systemic therapy (UMIN000036749). Moreover, MONSTAR-SCREEN is used to identify candidates for targeted trials. Patients harboring solid tumors were eligible for the study, and plasma samples were collected before and after systemic therapy to identify acquired resistance alterations. The study involved the same 31 hospitals as considered in GOZILA, with a sample size of 2300; as of June 2021, 1932 patients with solid tumors were enrolled.

MONSTAR-SCREEN comprehensively characterized the DNA genomic profile across solid tumors.[24,25] GI cancers presented with higher ctDNA levels than other cancers, while head and neck, gynecological, and renal cell, and malignant melanoma cancers presented with lower ctDNA levels. Moreover, the ctDNA genomic profile revealed the following cancer type-specific enrichment of oncogenic signaling pathway alterations: the RAS/RAF/MEK-related pathway in GI and hepatobiliary pancreatic cancers, the DNA damage response pathway in genitourinary and gynecologic cancers, and the PI3K pathway in breast cancer.

Tissue genotyping using FoudationOne CDx, a tissue NGS panel for similar alterations as FoundationOne Liquid CDx, was also performed in previously untreated patients in the MONSTAR-SCREEN. A comparison of the genomic profile between tissues and ctDNA genotyping for untreated patients enrolled in MONSTAR-SCREEN revealed that 21%-44% of the genomic alterations detected in ctDNA were not identified via tissue analysis. These results suggest that ctDNA genotyping may be more effective for candidates who may derive benefit from targeted therapy via identification of patients harboring alterations missed by tissue analysis.

FoundationOne Liquid CDx can be used to calculate bTMB by aiding the enumeration of the number of somatic mutations (single nucleotide and indels, including synonymous variants, excluding germline and driver mutations) with a variant allele frequency of ≥0.5% in ctDNA. In a retrospective biomarker analysis reported by clinical trials conducted for non–small cell lung cancer, higher bTMB was significantly associated with longer progression-free survival when treatment with atezolizumab was performed.[26] MONSTAR-SCREEN conducted the assessment of tissue TMB for 167 332 tissue biopsies and bTMB for 9312 liquid biopsies in patients with advanced solid tumors in collaboration with the Foundation Medicine.[27] The frequency of tissue TMB-H (≥10) tumors was higher than that of bTMB-H (≥10) tumors (19% vs. 13%), although the prevalence of bTMB-H by cancer type was correlated with the prevalence of elevated tissue TMB. The detection of bTMB-H and MSI-H in liquid biopsies was associated with elevated ctDNA levels, potentially indicating a more aggressive pathobiology in samples positive for these biomarkers. An association between bTMB-H and somatic mutations in homologous recombination repair–related genes was also shown in the MONSTAR-SCREEN cohort.

In parallel with tissue and ctDNA genomic analysis, we analyzed the fecal microbiome before and after subjection to systemic therapy by 16S ribosomal RNA (rRNA) gene sequencing of the V3-V4 region. A preliminary analysis showed that antibiotic use was

associated with the composition of the microbiome. Additionally, patients with biliary tract cancer were suggested to possess lower alpha diversity. We plan to further investigate the relevance of the microbiome to cancer characteristics and the efficacy of treatment in advanced solid tumors using a single-cell genomics approach.

5 | MONSTAR-SCREEN-2

As cancer cells demonstrate various abnormalities that cannot be highlighted by considering DNA changes alone, molecular profiling via multiomics analysis including RNA and protein is necessary in addition to DNA analysis. It has been shown that the incorporation of RNA sequencing approaches into DNA sequencing improves the detection of alterations, such as fusion genes and gene expression abnormalities,[28] and clinical trial enrollment.[29] In May 2021, we launched MONSTAR-SCREEN-2, a nationwide multilayered molecular profiling study based on the SCRUM-Japan platform (UMIN000043899). In this study, 2750 patients with solid tumors were enrolled, and whole-exome and whole-transcriptome sequencing of tumor tissue and plasma samples were performed for comprehensive molecular multiomics profiling using assays developed by Caris Life Sciences. Tumor tissue samples were also used for multiplex IHC analysis to assess the tumor microenvironment, as well as IHC testing for HER2 and PD-L1. These multilayered integrative data will be analyzed using an AI-based approach to unravel the mechanisms of cancer biology and to identify targeted populations to facilitate clinical trial enrolment.

6 | SCRUM-JAPAN–BASED PLATFORM TRIALS AND THE SCRUM-JAPAN REGISTRY

Presently, umbrella/basket-type investigator-initiated clinical trials are being actively conducted for patients with advanced solid malignancies utilizing the SCRUM-Japan platform to perform screening of candidates for targeted therapies (Figure 2). Patients with specific cancer types with genomic alterations are enrolled in organ-specific trials. Tumor-agnostic basket-type trials are also being conducted for rare alterations identified in different types of cancers, such as bTMB-H, *FGFR* alterations, and *HER2* amplification. Targeted alterations have been identified in GOZILA, MONSTAR-SCREEN, and MONSTAR-SCREEN-2 studies.

Most studies are single-arm phase 2 trials without a control arm because of the rarity of the targeted alterations. To accelerate drug development based on such single-arm phase 2 trials, we established the SCRUM-Japan Registry, a longitudinal prospective observational study generating regulatory-grade real-world data on patients with

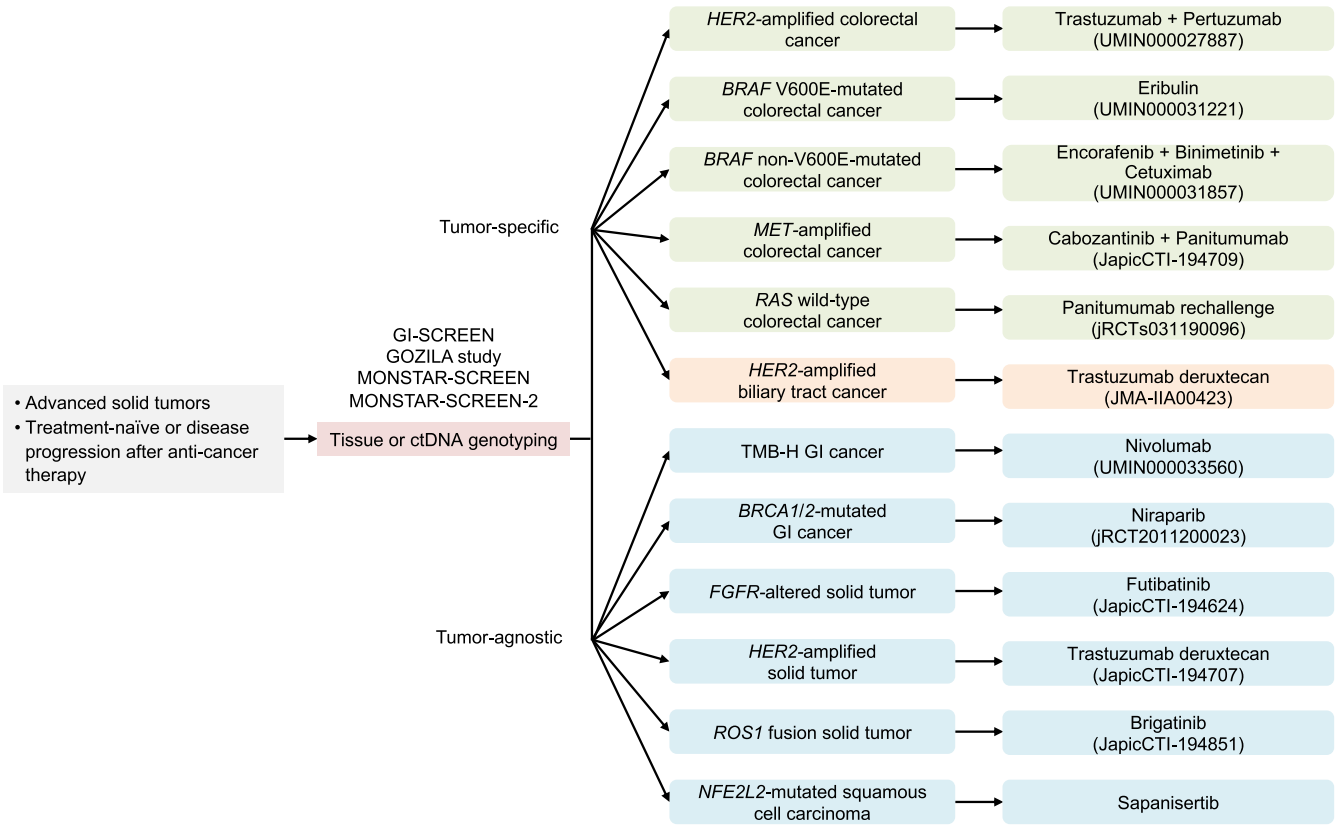

FIGURE 2 Investigator-initiated umbrella/basket-type clinical trials related to SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN. Patients with target alterations identified in the SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN studies were enrolled in the investigator-initiated umbrella/basket-type clinical trials

advanced solid tumors harboring rare alterations identified in the SCRUM-Japan project (UMIN000028058). The primary purpose of this registry is to use real-world data derived from patients with rare alterations as an external control for prospective trials targeting the same genomic alteration in the case of novel drug evaluation for regulatory approval. To ensure that endpoints such as objective response rate and progression-free survival were assessed in a manner comparable to prospective clinical trials, prospective radiographic imaging was performed every 6-10 weeks according to the study protocol, and the response was assessed using RECIST v1.1 by local site investigators. This study involved 71 core cancer institutions in SCRUM-Japan and was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects, as well as the Basic Principles on Utilization of Registry for Applications notified by the Pharmaceuticals and Medical Devices Agency (PMDA). The adequacy of the quality assurance procedures was confirmed in consultation with the PMDA for registry utilization. The aforementioned TRIUMPH study, a phase 2 trial for *HER2*-amplified CRC, compared treatment with pertuzumab plus trastuzumab in the trial and non–HER2-targeted standard-of-care therapies in the SCRUM-Japan Registry, and demonstrated superior efficacy of the dual-HER2 blockade.[22] The results will be utilized for regulatory submissions.

Several therapeutics and in vitro diagnostics have been developed based on the SCRUM-Japan platform. The OncoBEAM RAS CRC kit, which is based on the use of BEAMing digital PCR technology, is an in vitro diagnostic tool used for detecting *RAS* mutations in ctDNA derived from mCRC. *RAS*-mutant clones have been identified as drivers of acquired resistance to anti-EGFR therapy in *RAS* wild-type mCRC in clinical and preclinical studies.[30,31] Interestingly, the temporal withdrawal of anti-EGFR antibodies resulted in a decline in *RAS*-mutant alleles, suggesting that sensitivity to anti-EGFR antibodies was restored. Liquid biopsy *RAS* testing, such as that involving the use of the OncoBEAM RAS CRC kit, can potentially be considered to monitor the dynamics of acquired *RAS* mutations and to provide patients with an opportunity to rechallenge with anti-EGFR antibodies. To evaluate the performance of the OncoBEAM RAS CRC kit, we conducted a prospective multicenter study in patients with mCRC to investigate the concordance of *RAS* mutational status determined via plasma- and tissue-based BEAMing.[32] The study included 280 patients and compared the plasma- and tissue-based *RAS* mutational statuses determined via BEAMing in patients with mCRC who had not previously received anti-EGFR antibodies or regorafenib. The overall agreement between plasma- and tissue-based analyses was 86.4%, with a positive percent agreement of 82.1% and a negative percent agreement of 90.4%. In the logistic regression analysis, lung metastasis alone was the most significant factor associated with discordance. The agreement between plasma- and tissue-based analyses was 64.5% in patients with lung metastasis, indicating the presence of a low amount of ctDNA. Conversely, when only patients with lung metastasis were excluded, the overall concordance rate was 89.2%. Based on these results, the OncoBEAM RAS CRC kit was approved in Japan for ascertaining the use of molecularly targeted anti-EGFR antibodies in the course of treatment for patients with mCRC.[32,33]

7 | CONCLUSION

The SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN projects are among the largest molecular screening studies in the world. The implementation of these projects has provided important insights into the field of precision oncology. Several therapeutic agents and companion

TABLE 2 Therapeutic drugs and companion diagnostics approved based on studies involving patients with genomic alterations identified in the SCRUM-Japan GI-SCREEN and MONSTAR-SCREEN projects

Therapeutic drug	Indication
Pembrolizumab	MSI-H advanced solid tumor
Nivolumab ± ipilimumab	MSI-H metastatic colorectal cancer
Encorafenib + cetuximab ± binimetinib	*BRAF* V600E colorectal cancer
Companion diagnostic	**Indication**
MSI test kit (FALCO)	Companion diagnostic for pembrolizumab in advanced solid tumors and for nivolumab with or without ipilimumab for metastatic colorectal cancer as well as an in vitro diagnostic for screening of Lynch syndrome and selection of adjuvant chemotherapy
RASKET-B	Companion diagnostic for cetuximab and panitumumab for *RAS* wild-type metastatic colorectal cancer and encorafenib plus cetuximab with or without binimetinib for *BRAF* V600E metastatic colorectal cancer
OncoBEAM CRC RAS Kit	Companion diagnostic for cetuximab and panitumumab for *RAS* wild-type metastatic colorectal cancer
FoundationOne Liquid CDx	Companion diagnostic for several targeted therapies and mutation profiling

Abbreviation: MSI-H, microsatellite instability high.

diagnostics have been approved via enrolment of patients with targeted alterations identified by utilizing these platforms in international clinical trials (Table 2). Additionally, the molecular mechanisms underlying solid tumors have been elucidated through integrated clinicogenomic analyses utilizing the SCRUM-Japan database. The findings and experiences have been considered for the establishment of guidelines and clinical practice, which promote cancer precision medicine conducted under the health insurance plan in Japan as of 2019.[34,35]

To expand the potential of our projects to promote precision oncology, we initiated a collaboration with the International Cancer Genome Consortium–Accelerating Research in the Genomic Oncology project (ICGC ARGO), a consortium aimed at translating genomic knowledge to improve outcomes for people affected by cancer.[36] Furthermore, by incorporating AI technology into our projects, we are continuously investing efforts into rendering increased efficiency to cancer precision medicine. Through the consideration of such new initiatives, we aim to revolutionize cancer treatment by improving the prognosis of patients with cancer.

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