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First-Line Genomic Profiling in Previously Untreated Advanced Solid Tumors for Identification of Targeted Therapy Opportunities

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Abstract

IMPORTANCE Precision oncology using comprehensive genomic profiling (CGP) by next-generation sequencing is aimed at companion diagnosis and genomic profiling. The clinical utility of CGP before the standard of care (SOC) is still not resolved, and more evidence is needed.

OBJECTIVE To investigate the clinical utility of next-generation CGP (FoundationOne CDx [F1CDx]) in patients with previously untreated metastatic or recurrent solid tumors.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, prospective, observational cohort study enrolled patients with previously untreated advanced solid tumors between May 18, 2021, and February 16, 2022, with follow-up through August 16, 2022. The study was conducted at 6 hospitals in Japan. Eligible patients were aged 20 years or older and had Eastern Cooperative Oncology Group performance status of 0 to 1 with previously untreated metastatic or recurrent cancers in the gastrointestinal or biliary tract; pancreas, lung, breast, uterus, or ovary; and malignant melanoma.

EXPOSURE Comprehensive genomic profiling testing before SOC for advanced solid tumors.

MAIN OUTCOMES AND MEASURES Proportion of patients with actionable or druggable genomic alterations and molecular-based recommended therapy (MBRT).

RESULTS A total of 183 patients met the inclusion criteria and 180 patients (92 men [51.1%]) with a median age of 64 years (range, 23-88 years) subsequently underwent CGP (lung [n = 28], colon/small intestine [n = 27], pancreas [n = 27], breast [n = 25], biliary tract [n = 20], gastric [n = 19], uterus [n = 12], esophagus [n = 10], ovary [n = 6], and skin melanoma [n = 6]). Data from 172 patients were available for end point analyses. Actionable alterations were found in 172 patients (100.0%; 95% CI, 97.9%-100.0%) and druggable alternations were identified in 109 patients (63.4%; 95% CI, 55.7%-70.6%). The molecular tumor board identified MBRT for 105 patients (61.0%; 95% CI, 53.3%-68.4%). Genomic alterations included in the companion diagnostics list of the CGP test were found in 49 patients (28.5%; 95% CI, 21.9%-35.9%) in a tumor-agnostic setting. After a median follow-up of 7.9 months (range, 0.5-13.2 months), 34 patients (19.8%; 95% CI, 14.1%-26.5%) received MBRT.

CONCLUSIONS AND RELEVANCE The findings of this study suggest that CGP testing before SOC for patients with advanced solid tumors may be clinically beneficial to guide the subsequent anticancer therapies, including molecularly matched treatments.

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Key Points

Question Are comprehensive genomic profiling tests using next-generation sequencing clinically meaningful for patients with previously untreated metastatic or recurrent tumors of the gastrointestinal, pancreatic, biliary tract, lung, breast, gynecologic, and melanoma origin?

Findings In this cohort study including 180 patients, 100% of patients with previously untreated advanced cancer had actionable genomic alterations and 61% had options of molecular-based recommended therapy (MBRT) determined by the molecular tumor board. Of these, 20% of the patients received MBRT.

Meaning The findings of this study suggest that clinical benefits of comprehensive genomic profiling, which is currently limited to patients with cancer refractory to standard therapies in Japan, can be expanded to patients with previously untreated metastatic or recurrent solid tumors.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Precision oncology using comprehensive genomic profiling (CGP) testing by next-generation sequencing has been introduced into clinical practice to effectively select the treatment based on druggable genomic alterations.[1] Among several CGP tests, FoundationOne CDx software (Foundation Medicine) was approved by the Ministry of Health, Labour, and Welfare in Japan as a medical device for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and selected gene rearrangements. This software has the function of both a CGP test and a companion diagnostics (CDx) test. Therefore, it could be ideally used in the early stage of treatments, thereby enabling the CDx-positive cases to be selected for molecularly targeted treatments and patients with druggable gene alteration–positive cancers to be enrolled in clinical trials. Even if the CDx or druggable gene alteration is negative, standard treatments can be provided in the early setting.

The use of CGP tests was reimbursed by the National Health Insurance in 2019 in Japan[2] as well as in the US and Europe.[3-5] However, the indication in Japan is limited to patients with advanced solid tumors who had completed standard treatment or rare cancers that have no standard treatment, and CGP cannot be used before the initiation of systemic therapy, even though there are no timing restrictions on this indication in other countries. Thus, the full potential of CGP is not used. Moreover, recent advances in tumor-agnostic CDx and the corresponding effective treatments have supported the use of CGP before rather than after the standard of care (SOC) for advanced solid tumors.[6-8] Given the indication in Japan, many patients may miss an opportunity to receive molecularly matched therapies early in their treatment. Furthermore, some patients who had completed the standard treatment could not enroll in the clinical trial of new drugs matched by CGP because of their deteriorated physical condition and restriction of the acceptable treatment line.[9-12] In addition, CGP for patients who had completed the SOC did not achieve an improved prognosis.[13,14] The National Comprehensive Cancer Network and the European Society for Medical Oncology recommend the use of CGP for selected cancers in daily practice,[5,7] as well as for research purposes in academic centers. To our knowledge, the outcomes shown with CGP before first-line cancer treatments have not been reported and more evidence is needed.[15,16]

We previously reported that CGP for patients with chemotherapy-naive gastrointestinal cancer or cancer of unknown primary site had the potential to provide molecularly matched therapies in 23% of the patients,[17] including targeted therapies for cancers in which the corresponding CDx test was not covered by the National Health Insurance. Thus, upfront comprehensive molecular profiling might be clinically important to provide an opportunity for such patients to receive potentially effective molecularly matched therapy. However, the usefulness of CGP before SOC has not been established.[18] In the present study, we prospectively investigated the clinical utility of a CGP test in patients with previously untreated metastatic or recurrent tumors of the gastrointestinal, pancreatic, biliary tract, lung, breast, gynecologic, and melanoma origin (the FIRST-Dx study).

Methods

Study Design and Patient Selection

This study was an investigator-initiated, multi-institutional, prospective cohort clinical study performed as part of Advanced Medical Care B, which is a program that is approved by the Ministry of Health, Labour, and Welfare in Japan, and conducted at the following 6 hospitals: Kyoto University Hospital, The University of Tokyo Hospital, Tokyo Medical and Dental University Hospital, Aichi Cancer Center, Toyama University Hospital, and Wakayama Medical University Hospital. Eligible patients were aged 20 years or older with previously untreated, histologically confirmed metastatic and/or recurrent carcinomas in the gastrointestinal or biliary tract; pancreas, lung, breast, uterus, or ovary; and malignant melanoma. Other inclusion criteria were an Eastern Cooperative Oncology

Group performance status of 0 or 1 and the availability of an archival formalin-fixed, paraffin-embedded tissue sample for the CGP test. Patients who had received previous adjuvant or neoadjuvant chemotherapy, radiotherapy, or hormone therapy for the carcinoma concerned were eligible. Patients with other concurrent cancers were excluded. The study protocol and all amendments were approved by the institutional review boards of Kyoto University Hospital (Kyoto, Japan) and all participating hospitals. The study was conducted in accordance with the 2013 Declaration of Helsinki.[19] All patients provided written informed consent before enrollment in the study; no financial compensation was provided. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

The primary end point was the proportion of patients with actionable cancer genomic alterations detected using the next-generation CGP (FoundationOne CDx) test. Secondary end points were the proportion of patients with options of molecular-based recommended therapy (MBRT) determined by the molecular tumor board,[16] the proportion of patients with druggable genomic alterations, the proportion of patients with genomic alterations covered by CDx, the success rate of the CGP test, the proportion of patients who received MBRT, matching score of MBRT calculated using a matching score system,[20] and overall survival. While the proportion of patients who received MBRT was considered the most important secondary end point, we also considered the proportion of patients with options of MBRT as one of the most important secondary end points because of the lack of off-label use due to regulations and other factors, such as clinical trial and geographic availabilities.

Definition of Outcomes

Actionable cancer genomic alterations and druggable cancer genomic alterations were defined based on the CGP test report for each patient from Foundation Medicine. We defined alterations described in the sections of biomarker findings, genomic findings, and genomic findings with no reportable therapeutic or clinical trial options in the CGP test report as actionable cancer genomic alterations. If the alteration had a therapeutic drug option in the report, it was defined as a druggable cancer genomic alteration. Alterations reported as having only therapeutic resistance were not included in druggable alterations, for example, *RAS* mutations in colorectal cancer with resistance to antiepidermal growth factor receptor antibodies.

Turnaround time was defined as the interval between the shipping date and the date on which we received the report from Foundation Medicine. The evidence level classification was decided according to the second edition of the clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment.[21] Overall survival was defined as the time from the date of registration to the date of death due to any cause.

Molecular Tumor Board

The molecular tumor board of this trial was mandatory and consisted of specialized physicians in the following 5 fields: medical oncology, clinical genetics, pathology, molecular genetics, and bioinformatics according to the requirements of Japanese medical insurance reimbursement. Attendance of at least 1 specialist from each field was required for the board conference. All patients started first-line treatment before the findings of the molecular tumor board were received to avoid the delay in the treatment timing (eFigure 1 in Supplement 1).

Matching Score

A matching score system was used for each patient as described previously.[20] The matching score was calculated by dividing the total number of molecular alterations matched to the MBRT (numerator) by the total number of actionable cancer genomic alterations (denominator). We stratified patients based on matching scores (>50% designated as high or ≤50% designated as low).

Statistical Analysis

The sample size of the FIRST-Dx study was calculated to have the width of the 95% CI of the primary end point as 15% (±7.5%). The expected actionable alteration ratio of 70%, which was based on a previous report,[17] required a total of 141 patients in this study. Because we assumed the success rate of CGP to be 80%, we planned to enroll 180 patients.

The success rate of the CGP tests was calculated in the full analysis set of patients. All other end points were calculated in the per-protocol set of patients (**Figure 1**). Regarding the proportion of patients who received MBRT and overall survival, the interim analysis was prespecified at 6 months after the final patient enrollment. The Kaplan-Meier method was used to estimate the median for overall survival. All comparisons used a 2-sided, 5% type I error, and *P* value based on the Mann-Whitney test. Statistical analyses were performed using R, version 3.5.3 (R Foundation for Statistical Computing).

Results

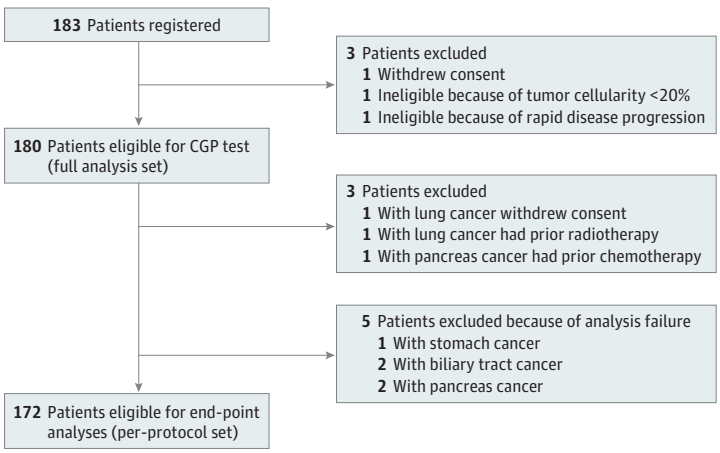
Patient Characteristics

From May 18, 2021, to February 6, 2022, a total of 183 patients were registered in the study (Figure 1). Three patients were excluded because of consent withdrawal (n = 1), ineligibility due to low tumor cellularity (<20%) of the specimen (n = 1), and rapid disease progression (n = 1), resulting in 180 patients who underwent CGP (full analysis set) (92 men [51.1%]; 88 women [48.9%]; mean age, 64 [range, 23-88] years). Among them, 1 patient withdrew consent later and 2 patients were ineligible for the study due to their receipt of prior radiotherapy or chemotherapy. The CGP test was unsuccessful in 5 patients (stomach: 1, biliary tract: 2, pancreas: 2). Finally, 172 patients were eligible for end point analyses (per-protocol set; Figure 1). Patient characteristics are summarized in eTable 1 in Supplement 2. The 3 organs with the most primary tumors in the study were the lung (n = 28), colon/small intestine (n = 27), and pancreas (n = 27). The other sites affected were breast (n = 25), biliary tract (n = 20), gastric (n = 19), uterus (n = 12), esophagus (n = 10), ovary (n = 6), and skin melanoma (n = 6) (**Figure 2**A). Ninety-nine patients developed relapsed disease after surgery; follow-up was conducted through August 16, 2022.

Comprehensive Genomic Profiling

The success rate of CGP was 97.2% (175 of 180; 95% CI, 93.6%-99.1%) (eTable 2 in Supplement 2). The median turnaround time was 13 days (range, 8-26 days).

Figure 1. Study Flowchart



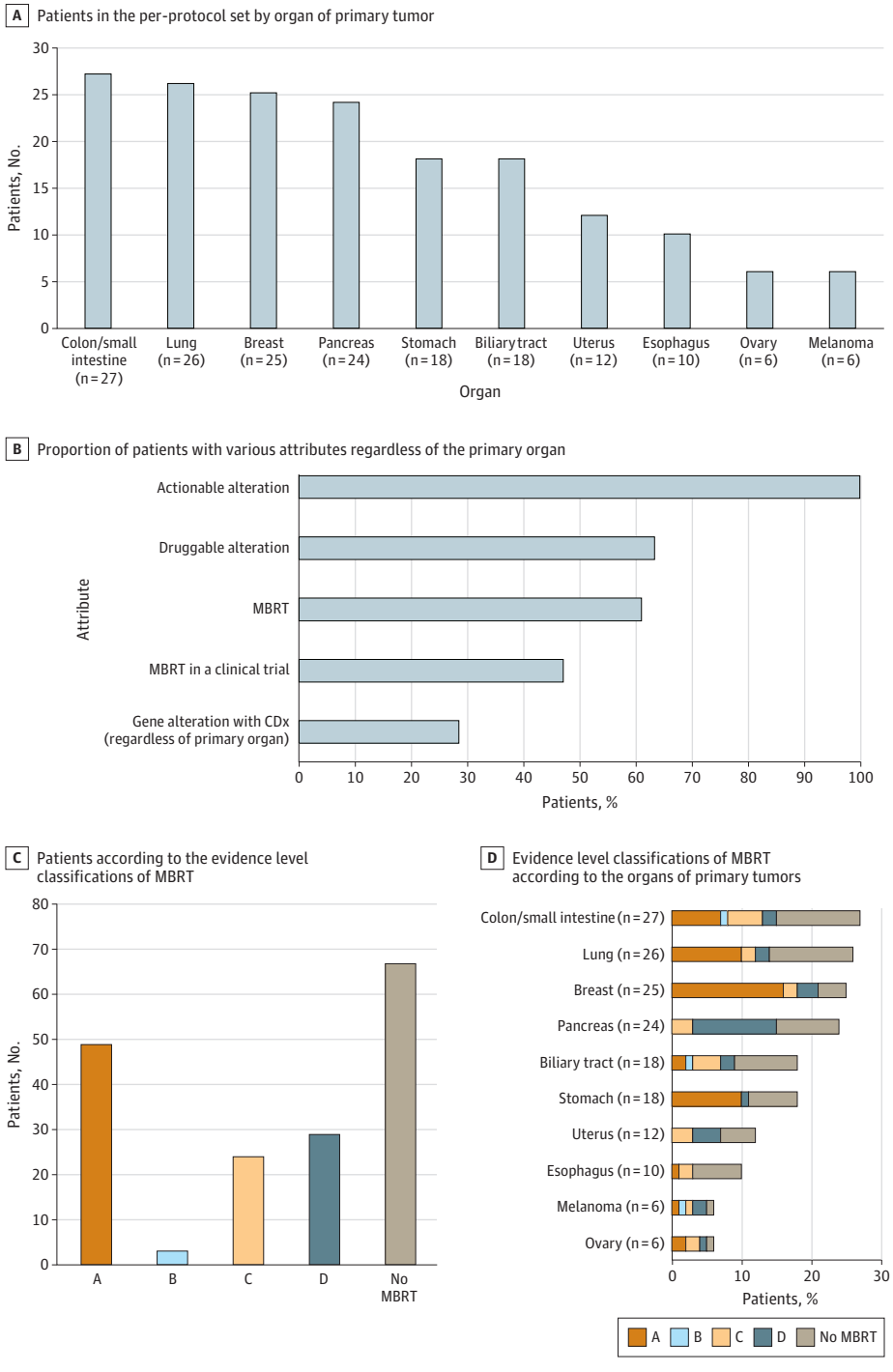
CGP indicates comprehensive genomic profiling.

Cancer Genomic Alterations and MBRT

Actionable cancer genomic alterations were found in all patients of the per-protocol set (n = 172; 95% CI, 97.9%-100.0%) (Figure 2B). The gene list of actionable alterations and the frequency are shown in eFigure 2 in Supplement 1.

Druggable cancer genomic alterations were found in 109 patients (63.4%; 95% CI, 55.7%-70.6%) (Figure 2B). The gene list of druggable alterations and the frequency according to primary tumors are shown in **Figure 3**. The top 3 most frequently altered genes were *BRAF* in skin

Figure 2. Genomic Alterations and Molecular-Based Recommended Therapies for Per-Protocol Set of Patients

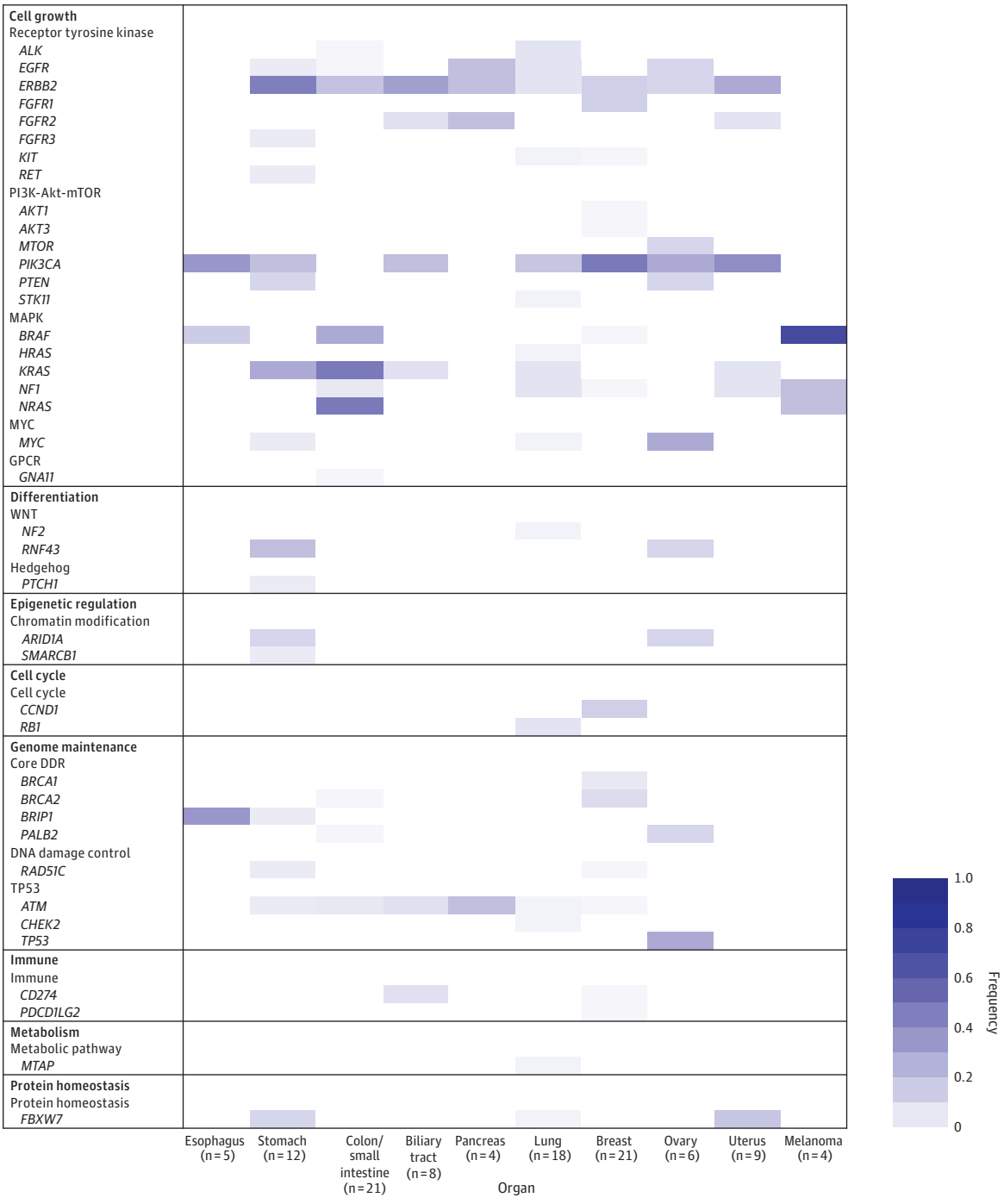


A, Number of patients by the organ of the primary tumor in the per-protocol set of patients. B, The proportion of patients with actionable cancer genomic alterations, druggable cancer genomic alterations, molecular-based recommended therapy (MBRT) determined by the molecular tumor board, MBRT available in clinical trials, and genomic alterations related to the companion diagnostics (CDx) regardless of the primary organ. C, Number of patients according to the evidence level classifications of MBRT. The highest evidence level per patient was counted. D, Evidence level classifications of MBRT according to the organs of primary tumors. Primary organs are listed in descending order of the number of patients.

melanoma, *PIK3CA* in breast cancer, and *ERBB2* in gastric cancer, after excluding the *KRAS/NRAS* alterations in colon cancer that reportedly had only therapeutic resistance.

The molecular tumor board discussed and determined the MBRT for each patient based on the CGP test report. A summary flowchart of patients after receipt of the CGP test report is shown in **Figure 4**A. Molecular-based recommended therapy was determined for 105 patients (61.0%; 95%

Figure 3. Frequency of Druggable Cancer Genomic Alterations



The vertical axis shows the list of druggable cancer genomic alterations categorized by pathway analysis. The heatmap value represents the frequency of the "number of druggable cancer genomic alterations" divided by the "number of patients" in each cancer type.

CI, 53.3%-68.4%) (Figure 2B and Figure 4A). The highest proportion of patients with options of MBRT was those having breast cancer (21 of 25 [84.0%]), and the lowest proportion was those with esophageal cancer (3 of 10 [30.0%]) (eFigure 3A in Supplement 1). Among 109 patients with druggable genomic alterations, 86 patients had options of MBRT and 23 patients did not. However, among 63 patients without druggable genomic alteration, 19 patients had options of the following MBRT (Figure 4A; eFigure 3B in Supplement 1): palbociclib plus trametinib for patients with concomitant *CDKN2A* and/or *CDKN2B* alterations (upregulate CDK4/6) along with *KRAS* or *BRAF* alterations (activate the MEK pathway) (n = 12),[22] anti-HER2 agents for *HER2* amplification

Figure 4. Summary of Patient Flow After Receipt of Comprehensive Genomic Profiling (CGP) Test Reports and Biological Targets of Molecular-Based Recommended Therapy (MBRT) in Tumor-Agnostic Setting

A, Summary of the patient flow after the receipt of the CGP test reports, including those who received MBRT. Druggable alteration was defined as the alteration with a therapeutic drug option in the CGP test report. MBRT was decided by the molecular tumor board. MBRT in the CDx list was in a tumor-agnostic setting. B, Number of patient assignments to tumor-agnostic MBRT. Horizontal labels indicate each MBRT with its biological target in parentheses. CDx indicates companion diagnostics; HRR, homologous recombination repair; ICI, immune checkpoint inhibitor; MBRT, molecular-based recommended therapy; MSI, microsatellite instability; and TMB, tumor mutational burden.

[a] CDx list is available in eTable 5 in Supplement 2.

[b] Patients who received MBRT were identified at the time of interim analysis for prognosis.

(n = 1),[23,24] alpelisib for *PIK3CA* alteration (n = 1),[25] selective FGFR 1-3 inhibitors for *FGF* amplifications (n = 1),[26,27] trametinib for *NRAS* mutation (n = 1),[28] immune checkpoint inhibitors for *SMARCA4* alteration (n = 1),[29] tazemetostat for *SMARCB1* alteration (n = 1),[30] and an MDM2 inhibitor for *MDM2* amplification (n = 1)[31] (eTable 3 in Supplement 2). Forty-nine patients (28.5%; 95% CI, 21.9%-35.9%) had 1 option of MBRT per patient and 56 patients (32.6%; 95% CI, 25.6%-40.1%]) had 2 or more options of MBRT per patient (eTable 4 in Supplement 2). Eighty-one patients with options of MBRT (47.1%; 95% CI, 39.5%-54.8%) could become candidates for clinical trials to access the recommended agents (Figure 2B).

Evidence Levels of MBRT

The evidence level of each MBRT was decided by the molecular tumor board based on the published criteria.[21] Evidence level A MBRT was suggested to 49 patients (28.5%; 95% CI, 21.9%-35.9%) (Figure 2C). Evidence level B MBRT was suggested to 3 patients (1.7%; 95% CI, 0.4%-5.0%), evidence level C to 24 patients (14.0%; 95% CI, 9.2%-20.1%), and evidence level D to 29 patients (16.9%; 95% CI, 11.6%-23.3%). The proportion of MBRT evidence levels according to organs of the primary tumor is shown in Figure 2D.

The proportion of patients with genomic alterations included in the CDx list of the FoundationOne CDx test was 28.5% (95% CI, 21.9%-35.9%; n = 49) when gene alterations in the tumor-agnostic setting were considered (Figure 2B). However, the proportion decreased to 15.1% (95% CI, 10.1%-21.4%; n = 26) when the primary cancer type was limited to the CDx indication of FoundationOne CDx in Japan (eTable 5 in Supplement 2).

MBRT Corresponding Biological Target in Tumor-Agnostic Setting

The number of patients assigned to each tumor-agnostic MBRT is shown in Figure 4B. The most recommended therapy was platinum agent therapy followed by poly(adenosine diphosphate-ribose) polymerase inhibitor (n = 25) therapy for patients with deleterious alterations in at least 1 of the 15 prespecified genes involved in homologous recombination repair, as reported previously.[32] The second most tumor-agnostic MBRT was anti-HER2 agents for HER2-activating alterations (n = 20) and the third most tumor-agnostic MBRT was immune checkpoint inhibitor for tumor mutational burden (TMB)-high (n = 17). The results of discussions of the molecular tumor board are summarized in eTable 3 in Supplement 2.

The number of patients with microsatellite instability (MSI)-high or TMB-high tumors according to primary cancer type is shown in eFigure 4A in Supplement 1. The most MSI-high and TMB-high tumors were gastric (n = 5) and lung (n = 6). The TMB scores in patients with MSI-high or microsatellite stable tumors are summarized in eFigure 4B in Supplement 1. All MSI-high tumors were categorized as TMB-high tumors.

The molecular tumor board discussed the matching scores of MBRT for each patient (n = 105), using the published principle of scoring.[20] The MBRT with matching scores greater than 50, which would provide higher efficacy than those with scores less than or equal to 50, were recommended to 27 patients (25.7%; 95% CI, 17.7%-35.2%) (eTable 6 in Supplement 2). The top 2 cancer types with MBRT matching scores greater than 50 were gastric (n = 5) and breast (n = 5) cancers. The background genomic alterations between the 2 groups of matching scores were similar (eFigure 5 in Supplement 1).

At the time of prespecified interim analysis with a median follow-up of 7.9 months (range, 0.5-13.2 months), 34 patients (19.8%; 95% CI, 14.1%-26.5%) received MBRT (**Table**; Figure 4A; eFigure 6A, B in Supplement 1). Among 49 patients with options of MBRT included in the CDx list of FoundationOne CDx in a tumor-agnostic setting, 30 patients (61.2%) received the corresponding MBRT. Among 56 patients with options of MBRT not in the CDx list, 4 patients received the corresponding MBRT (Figure 4A). Twenty-six patients received evidence level A MBRT, 2 received evidence level B MBRT, and 6 received evidence level C MBRT (Table; eFigure 6A in Supplement 1). Eleven patients could receive the corresponding MBRT in clinical trials. Patients who had not

received MBRT at the time of interim analysis had potentially effective treatment regimens (eFigure 6C, D in Supplement 1). In particular, 23 patients had an option of evidence level A MBRT, including immune checkpoint inhibitors for MSI-high or TMB-high tumors. At the time of interim analysis for prognosis, 28 patients had died (the median overall survival had not been reached) and

Table. Summary of Patients Who Received MBRT

Patient	Cancer type	Histologic details	Biomarker		MBRT	Evidence level	Genomic alterations[a]	Access
			Type	Annotation				
012	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial
017	Uterus	Adenocarcinoma	ERBB2	Amplification	Trastuzumab	C	Yes	Clinical trial
025	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
026	Lung	Small cell carcinoma	TMB-high (21 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
028	Breast	Adenocarcinoma	BRCA1	Others	PARP inhibitor	A	Yes	Clinical trial
030	Stomach	Adenocarcinoma	ERBB2	Amplification	Trastuzumab, T-DXd	A	Yes	Approved
031	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
032	Ovary	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
038	Lung	Adenocarcinoma	ALK fusion	Fusion	ALK inhibitor	A	Yes	Approved
045	Lung	Adenocarcinoma	EGFR L858R	Missense mutation	EGFR-TKI	A	Yes	Approved
047	Pancreas	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
059	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
062	Ovary	Adenocarcinoma	LOH score-high	Others	PARP inhibitor	A	No	Approved
067	Colon	Others	RANBP2-ALK fusion	Fusion	ALK inhibitor	B	Yes	Clinical trial
074	Skin melanoma	Others	BRAF V600E	Missense mutation	Dabrafenib + trametinib, encorafenib + binimetinib	A	Yes	Approved
075	Colon	Others	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
087	Lung	Adenocarcinoma	TMB-high (35 mutations/Mb)	Adenocarcinoma	Immune checkpoint inhibitor	A	Yes	Approved
093	Breast	Adenocarcinoma	BRCA1	Truncation	PARP inhibitor	A	Yes	Approved
096	Biliary tract	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	C	Yes	Clinical trial
108	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
112	Stomach	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
118	Colon	Adenocarcinoma	BRAF V600E	Missense mutation	Cetuximab + encorafenib ± binimetinib	A	Yes	Approved
			CDK12 E659*	Truncation	Platinum, PARP inhibitor	C	No	Approved
122	Colon	Small cell carcinoma	ERBB2 S310Y	Missense mutation	pan-HER TKI, T-DXd	C	No	Clinical trial
125	Ovary	Adenocarcinoma	LOH Score-high	Others	PARP inhibitor	C	No	Approved
134	Lung	Adenocarcinoma	EML4-ALK fusion	Fusion	ALK inhibitor	A	Yes	Approved
135	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial
145	Biliary tract	Adenocarcinoma	TMB-high (20 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
155	Skin melanoma	Others	BRAF V600R	Missense mutation	Dabrafenib + trametinib, encorafenib + binimetinib	B	No	Clinical trial
165	Biliary tract	Adenocarcinoma	FGFR2-KIAA1598 fusion	Fusion	FGFR inhibitor	A	Yes	Approved
166	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Approved
167	Breast	Adenocarcinoma	ERBB2	Amplification	Anti-HER2 agents	A	Yes	Approved
179	Lung	Adenocarcinoma	TMB-high (10 mutations/Mb)	Others	Immune checkpoint inhibitor	A	Yes	Approved
181	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Approved
183	Stomach	Adenocarcinoma	MSI-high	Others	Immune checkpoint inhibitor	A	Yes	Clinical trial

Abbreviations: MBRT, molecular-based recommended therapy; MSI, microsatellite instability; PARP, poly(adenosine diphosphate-ribose) polymerase; TMB, tumor mutational burden.

[a] Alterations included in the companion diagnostics list in the tumor-agnostic setting.

the 1-year survival rate was 79.7% (95% CI, 71.3%-86.0%) (eFigure 7 in Supplement 1) in the per-protocol set of patients (n = 172).

Discussion

To our knowledge, this study is the first comprehensive analysis to prospectively evaluate the clinical utility of the next-generation CGP (FoundationOne CDx [F1CDx]) test in patients with chemotherapy-naive cancer. Actionable cancer genomic alterations were found in 100.0% of the patients, druggable cancer genomic alterations in 63.4%, and MBRT in 61.0%. These findings are clinically important because more than 50% of patients with advanced solid tumors had druggable cancer genomic alterations and potentially had the opportunity to access molecularly matched treatments based on CGP before starting the SOC.

In the present study, 34 patients (19.8%) received MBRT at the time of interim analysis. Among them, 26 patients received evidence-level A MBRT. Moreover, because as many as 23 patients had options of evidence-level A MBRT among 71 patients who had not received MBRT, we expected that more patients would benefit from CGP before the SOC. The proportions of MBRT evidence levels observed in this study were similar to those in previous reports,[12,17,33] except a few more patients with evidence-level A MBRT were present in our study than the others. Therefore, the present findings suggest that CGP before the SOC could provide an opportunity for receiving potentially effective treatments. We need continuous efforts to standardize and update the molecular tumor board discussion as reported previously.[34]

Molecular-based recommended therapy targeting genes included in the CDx list in a tumor-agnostic setting were recommended to 49 patients, and 30 (61.2%) of them received the MBRT early in their treatment journey. Molecularly targeted drugs accompanied by CDx generally exhibit high efficacy in the tumor-agnostic setting, including tropomyosin receptor kinase (TRK) inhibitors for *TRK* fusion-positive cancers[35,36] and pembrolizumab for MSI-high or TMB-high tumors.[37,38] Thus, CGP before the SOC might present patients with an opportunity to receive effective treatments in the subsequent lines of chemotherapy.

Limitations

This study has limitations. Because the median follow-up period was short (7.9 months), overall survival could not be determined accurately. To investigate the survival benefit of CGP before the SOC, we are currently performing a prospective observational study to follow up the patients in the FIRST-Dx study. Second, access to drugs was limited because off-label use was not accepted in Japan. That means, even if a patient has a recommended evidence level C or D treatment with rare driver gene alterations or treatment with more than a 50% matching score, the patient cannot be treated with off-label use drugs. To introduce precision oncology effectively in clinical practice, an extended option for patients with cancer to gain access to an investigational drug outside of clinical trials, such as a compassionate use program, might improve the accessibility of anticancer drugs in Japan.

Conclusions

The findings of this prospective observational cohort study suggest that CGP testing for patients with previously untreated metastatic or recurrent tumors of gastrointestinal, pancreatic, biliary tract, lung, breast, gynecologic, and melanoma origin might have a notable clinical benefit for individual patients by providing them an opportunity to receive highly effective MBRT early in the disease course. These findings may support the modification of the insurance coverage in Japan of CGP from the last line to prior-to-initiation of the primary treatment in patients with metastatic or recurrent solid tumors. The genomics-guided oncology using CGP testing before SOC for patients with advanced solid tumors may be the first step for future advances in precision oncology.

ARTICLE INFORMATION

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SUPPLEMENT 1.

eFigure 1. Events in FIRST-Dx Study According to the Timeline
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SUPPLEMENT 2.

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SUPPLEMENT 3.
Data Sharing Statement