Clinical utility of comprehensive genomic profiling tests for advanced or metastatic solid tumor in clinical practice

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Abstract

Previous clinical trials indicate that 10%–25% of patients received genomically matched therapy after comprehensive genomic profiling (CGP) tests. However, the clinical utility of CGP tests has not been assessed in clinical practice. We assessed the clinical utility of CGP tests for advanced or metastatic solid tumor and determined the proportion of patients receiving genomically matched therapy among those with common and non-common cancers. From August 2019 to July 2020, a total of 418 patients had undergone CGP tests, and the results were discussed through the molecular tumor board at our site. The median age of patients was 57 (range: 3–86) years. Colorectal cancer was the most common, with 47 (11%) patients. Actionable genomic alterations (median 3, range: 1–17) were identified in 368 (88.0%) of 418 patients. Druggable genomic alterations were determined in 196 (46.9%) of 418 patients through the molecular tumor board. Genomically matched therapy was administered...
as the subsequent line of therapy in 51 (12.2%) patients, which is comparable to the proportion we previously reported in a clinical trial (13.4%) \( (p = 0.6919) \). The proportion of patients receiving genomically matched therapy was significantly higher among those with common cancers (16.2%) than non-common cancers (9.4%) \( (p = 0.0365) \).

Genomically matched therapy after the CGP tests was administered to 12.2% of patients, which is similar to the proportion reported in the previous clinical trials. The clinical utility of CGP tests in patients with common cancers greatly exceeded that in patients with non-common cancers.

**KEYWORDS**
advanced solid tumor, common cancer, comprehensive genomic profiling, genomically matched therapy, investigational new drug

## 1 | INTRODUCTION

In Japan, comprehensive genomic profiling (CGP) tests were approved in December 2018, and the following two systems have been reimbursed by the national health insurance system since June 2019:\(^1\): The OncoGuide™ NCC Oncopanel System (Sysmex Corporation)\(^2\) and FoundationOne® CDx Cancer Genomic Profile (Chugai Pharmaceutical).\(^3\) The current indication for these CGP tests is for patients with any advanced or metastatic solid tumor who have already received standard therapies.

Several clinical trials of CGP tests in patients with advanced or metastatic solid tumors have reported a wide range of actionable genomic alterations per patient, ranging from 40% to 94%.\(^4\)–\(^6\) However, only 10%–25% of patients received genomically matched therapy. In the NCI-MATCH trial, 686 (12.3%) of 5540 patients received genomically matched therapy. In our previous study, 25 of 187 patients (13.4%) received genomically matched therapy after the CGP tests. However, these data were obtained from the clinical trials and may not be applicable to clinical practice. A major reason for this is that patients with advanced or metastatic solid tumors exhibit highly variable clinical behavior, and some patients may be unable to tolerate further therapy.

We investigated the clinical utility of CGP tests in clinical practice at the National Cancer Center Hospital (NCCH) and determined the proportion of patients receiving genomically matched therapy among those with common cancers and non-common cancers.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient population and study design

Patients with any advanced or metastatic solid tumor who had progressed on standard therapy or without prior therapy if no curative therapy existed were eligible for this research. There was no limitation on the number of prior systemic therapies. CGP tests were performed in clinical practice and covered by the national health insurance system. Indications for CGP tests were entrusted to the treating physician. Actionable and druggable genomic alterations were discussed through the molecular tumor board by a multidisciplinary team at the NCCH, which met weekly. The board included medical oncologists, pediatric oncologists, pathologists, genome researchers, bioinformaticians, and genetic counselors. Board members discussed genomically matched therapies and other issues, such as authorization of pathological diagnoses and interpretation of somatic/germline variants. A proposal for genomically matched therapy was provided to each patient by the treating physician. Medical record reviews were performed by medical oncologists (H.I., T.K., and T.M.) to observe the clinical course after the CGP tests. All medical records were reviewed to summarize the patients’ baseline clinical characteristics, specimen information, results of CGP tests, reports from the molecular tumor board, and outcomes (subsequent therapy and survival) after CGP. Baseline clinical characteristics included age, gender, Eastern Cooperative Oncology Groups (ECOG)-performance status (PS), distance from patient’s homes to the NCCH, and cancer type. Specimen information included the type of specimen and site of specimen collection.

Turnaround time (TAT) was defined as the date of specimen shipment until the results of CGP tests were discussed through our molecular tumor board. Overall survival (OS) was measured from the date of specimen shipment. Patients still alive (for OS) on the date of data cutoff, or the date of last contact for patients lost to follow-up, were censored on that date. The probability of survival as a function of time was estimated using the Kaplan–Meier method. The median follow-up was calculated by the reverse Kaplan–Meier method. The data cutoff was on September 30, 2021.

All patients provided written informed consent for the CGP tests. This research was approved by the institutional review board of the NCCH (approval no. 2020-067).

### 2.2 | Comprehensive genomic profiling tests

The OncoGuide™ NCC Oncopanel System is a hybridization capture-based next-generation sequencing (NGS) assay designed to examine mutations, amplifications, and homozygous deletions of the entire coding region of 114 genes of clinical or preclinical relevance, along with rearrangements of 13 oncogenes, and to evaluate the tumor mutation burden (TMB).\(^2\) For the analysis, 10 5-μm sections
allow for discrimination of somatic and germline mutations.

The FoundationOne™ CDx Cancer Genomic Profile is a CGP platform that applies NGS to in vitro diagnostics using a hybrid capture shotgun library construction to identify the four classes of somatic genomic alterations, namely substitutions, insertions, and deletions (indels), copy number alterations, and select rearrangements. The typical median depth of coverage is >500x. FoundationOne CDx Cancer Genomic Profile detects alterations in a total of 324 genes, including all coding exons of 309 cancer-related genes, one promoter region, and one noncoding ribonucleic acid (RNA); the intronic regions of 34 commonly rearranged genes are selected, including 21 coding exons. The specimens are also simultaneously profiled for TMB and microsatellite instability (MSI) status. For the analysis, 10 5-μm sections (≥25 mm²) were prepared from FFPE tumor tissues.

2.3 | Definition of actionable and druggable genomic alterations and genomically matched therapy

“Actionable genomic alteration” for drug selection was defined in this research as those predicted to be involved in the susceptibility/resistance to either an approved targeted drug or an experimental targeted drug currently in clinical trials. Actionable genomic alteration included not only genomic alteration but also MSI-high and high TMB corresponding to ≥10 mutations per megabase. We defined “druggable genomic alteration” as genes that were determined through the molecular tumor board to be actionable genomic alteration and could be treated by administration of drugs, including approved drugs, investigational new drugs (INDs), and off-label drugs. “Genomically matched therapy” was defined as the actual therapy that patients received according to the results of their CGP tests.

2.4 | Common cancers and non-common cancers

We categorized patients into two subgroups: common and non-common cancers. Common cancers were defined as the top 10 most frequent cancer types in terms of mortality as reported by the World Health Organization: lung cancer, colorectal cancer, hepatocellular carcinoma, gastric cancer, breast cancer, esophageal cancer, pancreatic cancer, prostate cancer, cervical cancer, and endometrial cancer.

2.5 | Statistical analysis

We conducted a one-year retrospective study at a single site that is largely descriptive in nature. Sample size was not determined a priori but was based on the enrollment criteria (Subsection 2.1).

Univariate (χ² and Mann–Whitney tests) and multivariate (logistic regression model) analyses were performed to examine whether patients’ characteristics were related to the proportion receiving genomically matched therapy. All tests were two-sided, and a p-value <0.05 was considered statistically significant. All statistical analyses were performed using commercial software (JMP version 14.3; SAS).

3 | RESULTS

3.1 | Patient characteristics

From August 2019 to July 2020, a total of 418 patients underwent the CGP tests, and the results were discussed through the molecular tumor board at the NCCH. Colorectal cancer was the most common, with 47 patients (11%), followed by lung cancer, with 38 patients (9%), and soft tissue sarcoma, with 38 patients (9%) (Figure 1A). A total of 173 patients (41.4%) had a common cancer. The median age was 57 (range: 3–86) years, and there was no difference in the number of male versus female patients (Table 1). A total of 407 (97.4%) patients had an ECOG-PS of 0 or 1. While 146 (34.9%) of 418 patients had received ≥3 prior systemic therapies, 6 (1.4%) of 418 patients had received no prior systemic therapy. Among the 418 patients, 44.8% had a smoking history. Surgical specimens and biopsy specimens were used for the CGP tests in almost equal proportions (56.5% and 43.5%, respectively), and the specimens were most commonly collected from the primary site (60.0%). Of 418 patients, 267 (63.9%) underwent the CGP tests with the OncoGuide™ NCC Oncopanel System, and 151 (36.1%) did so with FoundationOne™ CDx Cancer Genomic Profile. The median distance traveled from patients’ homes to the NCCH was 31.5 (range: 1.5–2640) km. The median TAT was 27 (range: 14–49) days, and the median time between the molecular tumor board and the administration of the genomically matched therapy was 58 (range: 1–239) days. The median observation period was 9.6 (range: 0.5–27.1) months.

3.2 | Actionable and druggable genomic alterations and genomically matched therapy

Actionable genomic alterations (median 3, range: 1–17) were identified in 368 (88.0%) of 418 patients (Figure 1B). Druggable genomic alterations were determined through the molecular tumor board to be present in 196 (46.9%) of 418 patients. Genomically matched therapy was administered as the subsequent line of therapy to 51 (12.2%) patients, most of whom had lung cancer (N = 10), followed by colorectal cancer (N = 6), and soft tissue sarcoma (N = 5) (Figure 2A).

Genomically matched therapy comprised INDs (targeted small-molecule inhibitors [N = 27], immune checkpoint inhibitors/immune-oncology drugs [N = 8], antibody-drug conjugates [ADCs] [N = 1]), approved drugs (targeted small-molecule inhibitors [N = 3], immune checkpoint inhibitors/immune-oncology drugs [N = 5] and ADCs [N = 1]) and off-label drugs (targeted small-molecule inhibitors...
Cancer types and CONSORT diagram. (A) Distribution of cancer types \((N = 418)\). This study was conducted on the 418 patients whose comprehensive genomic profiling results were discussed through the molecular tumor board at the National Cancer Center Hospital (NCCH) from August 1, 2019, to July 31, 2020. Cancer type, number of patients. ACC, adenoid cystic carcinoma; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumor; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; SCLC, small cell lung cancer. (B) CONSORT diagram of patients. “Actionable genomic alterations” for drug selection were defined as genes predicted to be involved in the susceptibility/resistance to either an approved targeted drug or an experimental targeted drug currently in clinical trials. Actionable genomic alterations included not only genomic alterations but also microsatellite instability and high tumor mutation burden corresponding to ≥10 mutations per megabase. We defined “druggable genomic alterations” as genes that were considered by the molecular tumor board to be actionable genomic alterations and could be treated by administration of drugs to patients, including investigational new drugs, approved drugs and off-label drugs. “Genomically matched therapy” was defined as the actual therapy that patients received according to the results of their comprehensive genomic profiling tests. Actionable genomic alterations were identified in 368 (88.0%) of 418 patients; druggable genomic alterations were determined in 196 (46.9%) of 418 patients; and genomically matched therapy was administered to 51 (12.2%) of 418 patients.
TABLE 1 Patient characteristics

| Characteristic                          | Number of patients (%) |
|----------------------------------------|------------------------|
| Age                                    |                        |
| Median (range)                         |                        |
| ≤64/≥65                                | 282 (67.4)/136 (32.5)  |
| Gender                                 |                        |
| Male/Female                            | 216 (51.7)/202 (48.3)  |
| ECOG-PS                                |                        |
| 0/1/2/3                                | 217 (51.9)/190 (45.5)/9 |
| Prior systemic therapy                 |                        |
| ≤2/x3                                  | 272 (65.1)/146 (34.9)  |
| Cancer type                            |                        |
| Common cancer/Non-common cancer        | 173 (41.4)/245 (58.6)  |
| Smoking history                        |                        |
| Yes/No/Unknown                         | 187 (44.8)/229 (54.8)/2 |
| Type of specimen                       |                        |
| Surgical/Biopsy/Other                  | 236 (56.5)/179 (42.8)/3 |
| Sites of specimen collection           |                        |
| Primary site/Metastatic site           | 251 (60.0)/167 (40.0)  |
| Comprehensive genomic profiling test   |                        |
| NCC Oncopanel/FoundationOne CDx        | 267 (63.9)/151 (36.1)  |
| Distance from patients’ homes to the NCCH|                  |
| Median (range), km                     | 31.5 (1.5–2640)       |
| ≤50km/>50km                            | 305 (73.0)/113 (27.0)  |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FoundationOne® CDx Cancer Genomic Profile; NCC Oncopanel, OncoGuide™ NCC Oncopanel System; NCCH, National Cancer Center Hospital; PS, performance status.

Most patients (35 of 51 patients, 68.6%) receiving genomically matched therapy were treated with targeted small-molecule inhibitors, including poly-adenosine diphosphate ribose polymerase (PARP) inhibitors in 5 patients, epidermal growth factor receptor tyrosine (EGFR) kinase inhibitors in 3 patients, mitogen-activated protein kinase (MEK) inhibitors in 3 patients, Wnt/CREB-binding protein (CBP) inhibitors in 3 patients, mouse-double minute 2 (MDM2) inhibitors in 2 patients, and isocitrater dehydrogenase 1 (IDH1) inhibitors in 2 patients (Tables 2 and 3). Additional commonly genomically matched therapies included immune checkpoint inhibitors/immune-oncology drugs for MSI-high and high TMB in 13 patients (25.5%), and ADCs targeting Erb-B2 receptor tyrosine kinase 2 (ERBB2) in 3 patients (5.9%). Genomic alterations that led to administration of genomically matched therapy in 49 patients were detected in both the OncoGuide™ NCC Oncopanel System and FoundationOne® CDx Cancer Genomic Profile, respectively (Figure S1). However, neuregulin 1 (NRG1) fusion (1 patient) was only included in the OncoGuide™ NCC Oncopanel System, and Raf-1 proto-oncogene, serine/threonine kinase (RAF1) rearrangement (1 patient) was only detected by the FoundationOne® CDx Cancer Genomic Profile.

A total of 196 (46.9%) of 418 patients were identified as having druggable genomic alterations. However, 145 (34.7%) of 418 patients could not receive genomically matched therapy, despite the druggable genomic alterations being determined through the molecular tumor board. Sixty (14.4%) of 418 patients continued previous systemic therapy, and 46 (11.0%) of 418 patients could not receive further systemic therapy because their physical condition deteriorated as their cancer progressed. Of 418 patients, 20 (4.8%) could not participate in the IND trial because enrollment was suspended. Of 418 patients, 13 (3.1%) refused to participate in the IND trial. Five (1.2%) of 418 patients died of disease progression before the CGP tests results were returned.

Five pathogenic germline variants (3 in BRCA1 and 2 in BRCA2) were identified in 5 (9.9%) of 267 patients using the OncoGuide™ NCC Oncopanel System, while eight presumed germline pathogenic variants (2 in BRCA1, 2 in BRCA2, 2 in ATM, 1 in NF1, and 1 in TP53) were detected in 8 (5.3%) of 151 patients using the FoundationOne® CDx Cancer Genomic Profile. Genetic counseling was conducted for 9 (69.2%) of the 13 patients with pathogenic or presumed germline pathogenic variants, during which their clinical management was discussed. Of note, two of the 13 patients did not exhibit clear clinical or family histories of disease associated with the variants.

The median survival time (MST) of patients who received genomically matched therapy (N = 51) was not reached (95% confidence interval [CI], 12.9–not estimated), while that of patients with druggable genomic alterations who did not receive genomically matched therapy (N = 145) and patients without druggable genomic alterations (N = 222) was 15.3 months (95% CI, 11.0–18.0) and 16.1 months (95% CI, 12.9–18.3), respectively (Figure 2B). The overall survival time of patients who received genomically matched therapy was longer than that of patients who did not (P = 0.0320).

### 3.3 Common and non-common cancers

The proportion of actionable genomic alterations and druggable genomic alterations was significantly higher in patients with common cancers (94.8% and 59.5%, respectively) than that in non-common cancers (83.3% and 38.0%, respectively; Figure 2C). The proportion of patients receiving genomically matched therapy was significantly higher among those with common cancers (16.2%) than non-common cancers (9.4%) (p = 0.0365). Thus, the clinical utility of CGP tests in patients with common cancers greatly exceeded that in patients with non-common cancers. The subgroup of common cancers was independently and significantly predictive of receiving genomically matched therapy (p = 0.0365 [univariate analysis], p = 0.0306 in [logistic regression]; Table 4). The other patient characteristics (age, gender, ECOG-PS, number of prior systemic therapies, and distance from patient’s homes to the NCCH) were not associated with receiving genomically matched therapy.
This research demonstrated that 12.2% of patients received genomically matched therapy among 418 after the CGP tests conducted in clinical practice. In clinical trials, CGP tests are performed on a relatively homogeneous population because patients need to meet eligibility criteria for participation in the clinical trials. However, in clinical practice, the CGP tests can be applied to a wide variety of patients (e.g., elderly or those with impaired organ function) (Table S1). Further, indication for and timing of CGP tests are entrusted to the treating physician in clinical practice. Our rate of 12.2% is not significantly different from the proportion...
who received genomically matched therapy in our previous clinical trial (13.4%) \( (p = 0.6919) \).\(^4\) In Japan, the treating physician can choose from either the OncoGuide™ NCC Oncopanel System or FoundationOne® CDx Cancer Genomic Profile for conducting CGP tests in clinical practice. Genomic alterations that led to administration of genomically matched therapy in 49 patients were included in both OncoGuide™ NCC Oncopanel System and FoundationOne® CDx Cancer Genomic Profile (Figure S1). NRG1 fusion found in 1 patient was only detected by the OncoGuide™ NCC Oncopanel System, and RAF1 rearrangement found in 1 patient was only detected by the FoundationOne® CDx Cancer Genomic Profile. Kikuchi et al. (2021) and Inagaki et al. (2021) reported that 11.1% (21 of 189 patients) and 3.6% (6 of 221 patients) of patients received genomically matched therapy after CGP tests, respectively.\(^{10, 11}\) Our rate of 12.2% seems to be higher than those previously reported at the other sites in Japan. A major reason for this is that the largest number of IND trials (mainly industry sponsored trials) are conducted at our site in Japan. In our research, 11.0% (46 of 418) patients could not receive genomically matched therapy after the CGP tests because their physical condition deteriorated as their cancer progressed. We made a similar observation in our previous report (24 of 187 patients, 12.8%).\(^4\) Performing CGP tests earlier in the course of the disease could minimize the attrition of patients qualifying for IND trials.

| Cancer type (number of patients) | Genomic alteration | Drug (number of patients) |
|----------------------------------|--------------------|--------------------------|
| Lung cancer (10)                 | NRG1 fusion        | Afatinib (1)              |
|                                  | ERBB2 A775_G776insYVMA | ERBB2 (HER2)-ADC (1) |
|                                  | EGFR E746_A750delELREA | EGFR-TKI (1)          |
|                                  | EGFR H773_V774insNPH | EGFR-TKI (1)          |
|                                  | EZR-RoS1 fusion     | Entrectinib (1)         |
|                                  | ROS1-CD74 fusion     | Entrectinib (1)         |
|                                  | KIF5B-RET fusion     | RET inhibitor (1)       |
|                                  | High TMB*            | Nivolumab (2)           |
|                                  |                     | Pembrolizumab (1)       |
| CRC (6)                          | ATM R2993*           | ATR inhibitor (1)       |
|                                  | RET-NCOA4 fusion     | RET inhibitor (1)       |
|                                  | KRAS G13D            | SHP-2 inhibitor (1)     |
|                                  | APC L1488fs*19       | WNT/β-Catenin inhibitor (1) |
|                                  | APC R876* S1411fs*4  | WNT/β-Catenin inhibitor (1) |
|                                  | APC R1114*, APC K1182* | WNT/β-Catenin inhibitor (1) |
| Pancreatic cancer (4)            | High TMB*            | Immune-oncology drug (1) |
|                                  | RET-TRIM24-RET fusion | RET inhibitor (1)     |
|                                  | ERBB2 A775_G776insYVMA | T-DM1 (1)               |
|                                  | NF1 I1518fs*56       | MEK inhibitor (1)       |
| Breast cancer (3)                | High TMB*            | Immune-oncology drug (1) |
|                                  | ERBB2 amplification  | Trastuzumab deruxtecan (1) |
|                                  | FGFR1 amplification  | FGFR inhibitor (1)      |
| Cervical cancer (3)              | KRAS G12C            | KRAS G12C inhibitor (1) |
|                                  | High TMB*            | Immune-oncology drug (2) |
| Endometrial cancer (2)           | FGFR2 S252W          | FGFR inhibitor (1)      |
|                                  | MSI-high             | Pembrolizumab (1)       |

**Table 2** Genomic alteration and corresponding drugs in 28 patients with common cancers

**Abbreviations:** ADC, antibody-drug conjugate; CRC, colorectal cancer; IND, investigational new drug; MSI, microsatellite instability; TKI, tyrosine kinase inhibitor; TMB, tumor mutation burden.

*High tumor mutation burden corresponding to ≥10 mutations per megabase.
evaluate the feasibility and utility of CGP tests prior to the initial systemic therapy in patients with advanced or metastatic solid tumors, we are conducting a multicenter, prospective study (UPFRONT-trial) under Advanced Medical Care B (study cohort; NCCH1908). The objective of this study is to evaluate the feasibility and utility of CGP tests before the initial systemic therapy in patients with advanced or metastatic forms of cancers: non-small cell lung cancer, breast cancer, gastric cancer, colorectal cancer, pancreatic cancer, and biliary cancer. Simultaneously, we are also conducting another prospective observational study (control cohort) in patients with advanced or metastatic solid tumors who do not undergo CGP tests prior to the initial systemic therapy to evaluate whether the timing of CGP tests (before systemic therapy vs after the completion of standard systemic therapy) affects the proportion of patients who receive

### TABLE 3 Genomic alteration and corresponding drugs in 23 patients with non-common cancers

| Cancer type (number of patients) | Genomic alteration | Drug (number of patients) |
|---------------------------------|-------------------|--------------------------|
| Soft tissue sarcoma (5)         | High TMB<sup>a</sup> | Immune-oncology drug (1) |
|                                 | NTRK1 rearrangement intron 10 | Entrectinib (1) |
|                                 | MDM2 amplification | MDM2 inhibitor (2) |
|                                 | BRCA2 loss exons 2-4 | PARP inhibitor (1) |
| Biliary cancer (4)              | BRAF V600E        | BRAF inhibitor + MEK inhibitor (1) |
|                                 | High TMB<sup>a</sup> | Immune-oncology drug (2) |
|                                 | IDH1 R132C        | IDH1 inhibitor (1) |
| Melanoma (4)                    | BRCA2 G1892fs<sup>*17</sup> | PARP inhibitor (1) |
|                                 | KIT L576P         | KIT-TKI (1) |
|                                 | NF1 R416<sup>*</sup> | Trametinib (1) |
|                                 | RAF1 rearrangement intron 9 | MEK inhibitor (1) |
| Ovarian cancer (3)              | BRCA1 Q1182<sup>*</sup> | Olaparib (1) |
|                                 | BRCA1 L63<sup>*</sup> | Olaparib (1) |
|                                 | BRCA2 R2842C      | PARP inhibitor (1) |
| Ampullary carcinoma (1)         | BRAF V600E        | BRAF inhibitor + MEK inhibitor (1) |
| Glioma (1)                      | IDH1 R132H        | IDH1 inhibitor (1) |
| Histiocytosis juvenile (1)      | KIF5B-ALK fusion | ALK inhibitor (1) |
| NEC (1)                         | High TMB<sup>a</sup> | Immune-oncology drug (1) |
| Small intestine cancer (1)      | SP100-ALK fusion | ALK inhibitor (1) |
| Thymic carcinoma (1)            | KIT V560del       | Sunitinib (1) |
| Urothelial cancer (1)           | High TMB<sup>a</sup> | Pembrolizumab (1) |

 Abbreviations: IND, investigational new drug; NEC, neuroendocrine carcinoma; TMB, tumor mutation burden.

<sup>a</sup>High tumor mutation burden corresponding to ≥10 mutations per megabase.
TABLE 4 Univariate and multivariate analyses of patient characteristics associated with the proportion of genomically matched therapies

|                         | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | Odds ratio (95% CI) | p-value               | Odds ratio (95% CI) | p-value               |
| Age (64/65)             | 1.658 (0.8307-3.179) | 0.1545               | 1.743 (0.6199-2.124) | 0.1798               |
| Gender (male/female)    | 0.6143 (0.3417-1.103) | 0.1055               | 0.6649 (0.3595-1.211) | 0.1856               |
| ECOG-PS                 | -                   | 0.3607               | 0.7426 (0.4147-1.285) | 0.3008               |
| Prior systemic therapy (≥2/3) | 0.8104 (0.4471-1.493) | 0.5318               | 1.016 (0.5215-1.949) | 0.9618               |
| Distance from homes to the NCCH (≤50km/50km) | 0.9763 (0.5034-1.860) | 0.9429               | - | - |
| Cancer type (common/non-common) | 1.864 (1.035-3.279) | 0.0365               | 2.059 (1.072-3.991) | 0.0306               |

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NCCH, National Cancer Center Hospital; PS, performance status.

genomically matched therapy based on their genomic alterations, cost-effectiveness, and prognosis.

Most administered genomically matched therapies were INDs (36 of 51 drugs, 70.6%). Not all patients identified with a druggable genomic alteration could participate in the IND trials. To reduce the reliance on INDs as a genomically matched therapy, 12 designated core hospitals in Japan have launched a phase II basket trial of multiple targeted agents based on genomic alterations using the results of CGP tests (BELIEVE study, NCCH1901) conducted under Patient-Proposed Healthcare Services.13,14 In principle, the molecular tumor board at the NCCH does not recommend off-label drugs as genomically matched therapies.

Our research showed that patients who received genomically matched therapy (N = 51) had a longer survival time than those who did not (N = 367) (p = 0.0320). No other reports have shown that genomically matched therapies prolong the survival of patients with advanced cancer. The only randomized clinical trial to have examined prolonged progression-free survival following the administration of genomically matched therapies failed to show any clinical utility.15 Our result is inconclusive as we did not randomly compare the survival time between two patient groups (treated with genomically matched therapies vs not treated with genomically matched therapies). However, it is challenging to conduct a randomized controlled trial to confirm the associated increase in survival because genomically matched therapies are implemented in clinical practice.

This is the first report to show that the proportion of patients receiving genomically matched therapy was significantly higher among those with common cancers (16.2%) than non-common cancers (9.4%) (p = 0.0365), which confirmed our hypothesis that the clinical utility of CGP tests might differ between patients with common and non-common cancers. Current CGP tests are primarily based on DNA sequencing that cannot detect all gene fusions, which could have significant clinical implications for diagnosis and treatment-related decisions in patients with non-common cancers, such as sarcoma and pediatric cancer.16,17 Additionally, patients with non-common cancers have less opportunity to participate in IND trials than those with common cancers (Figure S2A–C). Thus, the next step is to develop new methods to detect cancer drivers in patients with non-common cancers. Combined DNA and RNA sequencing may be a powerful approach for (i) detecting gene rearrangements, (ii) verifying intratumoral expression of single nucleotide variants and indels, and (iii) evaluating the transcriptional effects of gene amplifications and deletions.18

In conclusion, we demonstrated the clinical utility of CGP tests in patients with advanced or metastatic solid tumors in clinical practice. Genomically matched therapy after the CGP tests was administered to 12.2% of patients, a similar rate to that reported in the previous clinical trials. Further, the proportion of patients receiving genomically matched therapy was significantly higher among those with common cancers than non-common cancers.

AUTHOR CONTRIBUTIONS

Drs Ida, Koyama, Mizuno, and Yamamoto had full access to all of the data and take responsibility for the integrity of the data and accuracy of the data analysis. Concept and design: Ida, Koyama and Yamamoto. Acquisition, analysis, or interpretation of data: Ida, Koyama, Mizuno, Sunami, Kubo and Yamamoto. Drafting of the manuscript: Ida, Koyama and Yamamoto. Critical revision of the manuscript for important intellectual content: Ida, Koyama, Mizuno, Sunami, Kubo, Sudo, Tao, Hirata, Yonemori, Kato, Okusaka, Ohe, Matsui, Yamazaki, Ogawa, Kawai, Narita, Esaki and Yamamoto. Statistical analysis: Koyama and Yamamoto. Supervision: Koyama and Yamamoto.

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DISCLOSURE

Dr Koyama reported receiving personal fees from Chugai and Sysmex and grants from PACT Pharma outside the submitted work. Dr Sunami reported receiving personal fees from Chugai Pharma and Sysmex outside the submitted work. Dr Sudo reported receiving grants from Daiichi Sankyo, NanoCarrier, AstraZeneca, Merck Sharp & Dohme, Takeda, Gilead Sciences, and Chugai Pharmaceutical; and personal fees from Pfizer, Eisai, and AstraZeneca outside the submitted work. Dr Yonemori reported receiving research funding from Ono Pharmaceutical; personal fees from Eisai,
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**ETHICAL APPROVAL**

Approval of the research protocol by an Institutional Reviewer Board: All experimental procedures were approved by the NCCH Institutional Review Board (approval No. 2020-067).

- Informed Consent: N/A.
- Registry and the Registration No. of the study/trial: N/A.
- Animal Studies: N/A.

**REFERENCES**

1. Ebi H, Bando H. Precision oncology and the universal health coverage system in Japan. JCO Precis Oncol. 2019;3:PO.19.00291.

2. https://products.sysmex.co.jp/products/genetic/AK401170/index.html

3. https://www.foundationmedicine.com/test/foundationone-cdx

4. Sunami K, Ichikawa H, Kubo T, et al. Feasibility and utility of a panel testing for 114 cancer-associated genes in a clinical setting: a hospital-based study. Cancer Sci. 2019;110(4):1480-1490.

5. Zehir A, Benayed R, Shah RH, et al. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nat Med. 2017;23(6):703-713.

6. Stadler ZK, Maio A, Kemel Y, et al. Targeted therapy based on germline analysis of tumor-normal sequencing (MSK-IMPACT) in a pan-cancer population. Am Soc Clin Oncol. 2020;38:1500.

7. Kondo T, Matsubara J, Quy PN, et al. Comprehensive genomic profiling for patients with chemotherapy-naive advanced cancer. Cancer Sci. 2021;112(1):296-304.

8. Cobain EF, Wu YM, Vats P, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol. 2021;7(4):525-533.

9. https://gco.iarc.fr/today/home

10. Kikuchi J, Ohhara Y, Takada K, et al. Clinical significance of comprehensive genomic profiling tests covered by public insurance in patients with advanced solid cancers in Hokkaido, Japan. Jpn J Clin Oncol. 2021;51(5):753-761.

11. Inagaki C, Maeda D, Hatake K, et al. Clinical utility of next-generation sequencing-based panel testing under the universal health-care system in Japan: a retrospective analysis at a single university hospital. Cancer. 2021;13(5):1121.

12. Mizuno T, Yoshida T, Sunami K, et al. Study protocol for NCCH1908 (UPFRONT-trial): a prospective clinical trial to evaluate the feasibility and utility of comprehensive genomic profiling prior to the initial systemic treatment in advanced solid tumour patients. Jpn J Clin Oncol. 2021;51(12):1757-1760.

13. https://jrc.niph.go.jp/latest-detail/JRCTs031190104

14. Shimoi T. The prospective trial of patient-proposed healthcare services with multiple molecular targeted therapy based on the result of comprehensive genomic profiling. Gan To Kagaku Ryoho. 2021;48(1):12-16.

15. Le Tourneau C, Delord JP, Gonçalves A, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol. 2015;16(13):1324-1334.

16. Hay MA, Severson EA, Miller VA, et al. Identifying opportunities and challenges for patients with sarcoma as a result of comprehensive genomic profiling of sarcoma specimens. JCO Precis Oncol. 2020;4:PO.19.00227.
17. Hiemenz MC, Ostrow DG, Busse TM, et al. OncoKids: a comprehensive next-generation sequencing panel for pediatric malignancies. *J Mol Diagn*. 2018;20(6):765-776.

18. Horak P, Heining C, Kreutzfeldt S, et al. Comprehensive genomic and transcriptomic analysis for guiding therapeutic decisions in patients with rare cancers. *Cancer Discov*. 2021;11(11):2780-2795.

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.