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ORIGINAL RESEARCH

Nationwide precision oncology pilot study: KOrean Precision Medicine Networking Group Study of MOlecular profiling-guided therapy based on genomic alterations in advanced solid tumors (KOSMOS) KCSG AL-20-05

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Background: Next-generation sequencing (NGS) has become widely available but molecular profiling-guided therapy (MGT) had not been well established in the real world due to lack of available therapies and expertise to match treatment. Our study was designed to test the feasibility of a nationwide platform of NGS-guided MGT recommended by a central molecular tumor board (cMTB) for metastatic solid tumors.

Patients and methods: Patients with advanced or metastatic solid tumors with available NGS results and without standard treatment were enrolled. The cMTB interpreted the patients' NGS reports and recommended the following: (i) investigational medicinal products (IMPs) approved in other indications; (ii) alternative treatments; (iii) clinical trials. The primary variables were the proportion of patients with actionable genomic alterations and those receiving MGT as per cMTB recommendations. Others included treatment duration (TD), overall response rate (ORR), disease control rate (DCR), and safety.

Results: From February 2021 to February 2022, 193 cases [99 (51.3%) men; median age 58 years (range 24-88 years); median line of previous treatment 3 (range 0-9)] from 29 sites were enrolled for 60 cMTB sessions. The median time from case submission to cMTB discussion was 7 days (range 2-20 days), and to IMP treatment initiation was 28 days (range 14-90 days). Actionable genetic alterations were found in 145 patients (75.1%). A total of 89 (46.1%) patients received actual dosing of IMPs, and 10 (5.2%) were enrolled in cMTB-recommended clinical trials, achieving an MGT rate of 51.3%. ORR and DCR of IMPs were 10.1% and 72.5%, respectively. The median TD was 3.5 months [95% confidence interval (CI) 2.8-5.5 months], and the 4-month TD rate was 44.9%. The median overall survival of patients who received IMPs was 6.9 months (95% CI 5.2-10.0 months).

Conclusion: KOSMOS confirmed the feasibility of MGT recommended by the cMTB, achieving a high MGT match rate and promising effectiveness in heavily pretreated advanced cancer patients.

Key words: precision oncology, molecular profiling-guided therapy, molecular tumor board

INTRODUCTION

Precision oncology involves the integration of molecular tumor profiles into clinical decision making in cancer treatment.[1] The progress in next-generation sequencing (NGS) technology has enabled the identification of patient-specific genetic alterations, thereby facilitating the implementation of precision oncology tailored to each patient in real-world practice. Leveraging the advanced technology of

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NGS, several precision oncology trials, including IMPACT1, IMPACT2, SHIVA, NCI-MPACT, TAPUR, DRUP, and NCI-MATCH have been conducted.[2-9] These trials have played a crucial role in establishing NGS-based molecular profiling-guided therapy (MGT) and accumulating evidence for its efficacy. Furthermore, MGT has shown promising clinical outcomes compared to non-matched therapies across tumor types.[10]

MGT has also posed some challenges in its implementation in real-world practice. The interpretation of NGS results and identification of actionable genetic alterations from NGS results are essential for precision oncology. However, the complexity of NGS data makes it difficult for medical oncologists to review and interpret them precisely. This indicates that a multidisciplinary approach, involving molecular pathologists, bioinformaticians, and medical oncologists, is needed to ensure accurate analysis and decision making.[11-14] Drug accessibility, coupled with a low match rate of MGT to patients, is another limitation of precision oncology. Although NGS has been introduced in clinical practice, only 15%-67% of patients eventually receive genomic or molecular-matched treatment.[2-4,6,7,15-18] These unsatisfactory match rates could be attributed to the lack of reimbursement, restriction on the use of targeted therapy outside of its approved indication, and/or paucity of precision oncology trials.[1] Although MGT has shown promising clinical outcomes,[19] not all patients equally benefit from it[20] and its utility has not been fully confirmed, warranting further research and validation.

In South Korea, NGS testing has been reimbursed since 2017; however, it is not unified, and different types of NGS platforms have been approved and used. Additionally, the use of certain drugs outside their approved indications based on molecular profiling has been strictly regulated without reimbursement. Thus, patients may not be legally guaranteed the opportunity for proper treatment or may lose it because of considerable financial risk.

To overcome these limitations, it is necessary to build a precision oncology ecosystem comprising a multidisciplinary approach to NGS data analysis, recommendations for MGT, drug access, and a clinicogenomic database. To facilitate precision oncology in real-world practice, KOSMOS was developed as a pragmatic study to test the feasibility and clinical outcomes of MGT as recommended by a nationwide central molecular tumor board (cMTB).

PATIENTS AND METHODS

KOSMOS is a nationwide, multicenter prospective study in patients with advanced solid tumors who were no longer benefiting from standard anticancer treatment, to initiate MGT through the cMTB recommendation based on genomic alterations. The primary objective of this study was to characterize the clinical course of MGT based on genomic alterations. This involved the assessment of NGS results, cMTB feasibility, and drug accessibility. The secondary objectives were to assign patients to matched targeted therapy based on their actionable genetic alterations and cMTB recommendations and to evaluate the correlation between the molecular profile and clinical outcomes of patients treated with MGT.

Patients

Patients who met the following criteria were included: age $\geq$19 years; histologically proven locally advanced or metastatic solid tumors; no longer benefiting from standard treatment at the discretion of the site physician; available results of genomic tests (on blood or tumor tissue) carried out by a Korean Ministry of Food and Drug Safety (MFDS)-accredited laboratory.

Patients with Common Terminology Criteria for Adverse Events (CTCAE) grade $\geq$2 toxicity related to a previous antitumor treatment except for peripheral neuropathy; who were receiving any other anticancer treatment including chemotherapy, targeted therapy, or immunotherapy; or had a clinical condition that made the application of MGT impractical were not included in the study.

Study design

Site physicians enrolled patients with available local NGS results and submitted them to the cMTB. They were also required to upload their treatment of choice along with clinical, pathological, and genomic data of the patients for discussion. The cMTB comprised two or more medical oncologists, molecular pathologists, and bioinformaticians, as recommended by the Korean Society of Medical Oncology.

Site investigators who submitted their cases to the cMTB or their representatives were required to attend the meetings. The cMTB panels reviewed NGS reports, assessed the quality and credibility of the NGS test results, and identified actionable genetic alterations. They also evaluated the level of evidence of oncogenicity and actionability of the identified variants, matched potential therapies among the KOSMOS drugs, including investigational medicinal products (IMPs), approved by the MFDS for therapeutic use, and determined treatment-specific contraindications and eligibility criteria. Following discussion, the cMTB panels identified actionable genomic alterations and recommended molecular profile-based treatment options. KOSMOS had three different treatment options: tier 1, the therapeutic use of IMPs outside their approved indication as an expanded access program including: alectinib, atezolizumab, bevacizumab, bevacizumab and erlotinib, capecitabine, erlotinib, trastuzumab and/or pertuzumab, and trastuzumab emtansine; tier 2, alternative treatments including palliative care and on-label use or outside of approved indication by the Health Insurance Review & Assessment Service in Korea; tier 3, cMTB-recommended clinical trials.

After the discussion, the cMTB suggested one to three treatment recommendations among tier 1, 2, and 3 based on the patients' molecular profiling results and clinical information. Treatment recommendations for each tier were allowed to be duplicated.

The panels offered preferred recommendations regardless of the availability of drugs (Rec1). They also offered actual recommendations considering the availability of drugs (Rec2), along with evidentiary support. Subsequently, the site physician made the final treatment decision within 7 business days after receiving the cMTB report (Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmoop.2024.103709).

Identification of actionable genomic alterations

In our study, a potentially actionable genomic variant was defined as the target of an approved drug for any cancer indication, a sensitivity predictor for such a drug, or present in the same molecular pathway but located upstream of the genomic target of the drug. Gene variant was a specific eligibility criterion for enrollment in a phase II-III clinical trial of an anticancer drug and an inactivating mutation in somatic or germline genes that results in unique susceptibility to a specific molecular intervention (e.g. *BRCA1* mutation and PARP inhibitors). Other gene variants that had appropriate justifications for selection based on published evidence of susceptibility to a specific targeted therapy or association with tumor response following treatment with a specific targeted therapy in a clinical study were considered of interest.

Statistical analyses

The primary variables assessed the adoptability of MGT based on the MTB recommendations. Adoptability was assessed by evaluating the following aspects: the proportion of patients with actionable genomic alterations, receiving MGT as MTB recommendations, and the overall time between MTB submission and treatment initiation. The secondary variables of interest were the treatment duration (TD), best overall response, and safety. TD was assessed only in patients who received IMPs and recorded from the date of initiation to the end date of treatment. Overall survival (OS) was evaluated in both, patients who received actual dosing of IMPs and the total study population and was defined as the duration from the date of consent to the date of death, regardless of the cause.

The MGT rate was defined as the number of patients who received IMPs plus the number of patients enrolled in cMTB-recommended clinical trials divided by the total number of study populations. Concordance was defined as the agreement between the pre-submitted physicians' choices and the cMTB recommendations or actual dosing of each IMP. For example, when physicians selected a certain IMP as a pre-submitted choice of treatment, and the cMTB recommended the same IMP, or when patients received the same IMP, these cases were considered to have a concordance.

The sample size determination was based on the total number of patients who provided informed consent and submitted for cMTB in the study and the percentage of patients receiving MGT as per MTB recommendations. The planned sample size of patients receiving MGT through 'treatment use of IMPs' was 100, and the total number of subjects was 300. For 300 patients, the 95% confidence interval (CI) would be ±9%, considering an expected 30% proportion of patients receiving IMPs in MGT.

Survival and duration were calculated using the Kaplan–Meier method, and survival was compared using a log-rank test. All statistical analyses and data visualizations were carried out using R software (version 4.2.2).

Tumor assessment and recording of serious adverse events

Response assessment was conducted only in patients who received the actual dosing of IMPs (tier 1). Response assessment of each IMP was carried out using RECIST (version 1.1). The overall response rate (ORR) was defined as the ratio of patients with complete remission (CR) and partial remission (PR) to the total number of patients available for response assessment. Similarly, the disease control rate (DCR) was defined as the ratio of CR, PR, and stable disease (SD) to the total number of patients available for response assessment. Adverse events (AEs) and serious adverse events (SAEs) were recorded and followed up until after the last administration of treatment. All AEs, including SAE, were assessed using CTCAE (version 4.1).

Ethics

Informed consent was obtained from all patients before the initiation of the study. The study protocol, informed consent forms, information to be provided to the patient, and relevant supporting information were submitted to the institutional review board (IRB) or ethics committee (EC) at all participating sites. All study materials, including the protocol, were reviewed and approved by the IRB/EC before the study was initiated.

RESULTS

Organization of the central molecular tumor board (cMTB)

In our study, four cMTB panels were organized, including medical oncologists, molecular pathologists, and bioinformaticians from 13 institutions in Korea. Between February 2021 and February 2022, 60 cMTB meetings were held. The median time from case submission to cMTB discussion was 7 days (range 2-20 days), and that from cMTB submission to treatment initiation with IMPs was 28 days (range 14-90 days).

Patient characteristics

For the 1-year study period, 198 cases were submitted to the cMTB from 29 sites. Five were withdrawn due to clinical deterioration or death before the cMTB discussion (Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmoop.2024.103709). A total of 193 cases were discussed by the cMTB and included in the final analysis set. The median age was 58 years (24-88 years), and 99 (51.0%) patients were men. The commonly observed types of cancer were colorectal (22.3%), lung (15.0%), and breast (11.9%) cancers (Table 1). The median number of lines of previous

Table 1. Baseline characteristics of the study population

		All patients	Patients who received MTB recommendation for tier 1 IMPs	Patients who received actual dosing of IMPs
Factors	*n*	193	125	89
Sex, *n* (%)	Female	94 (48.7)	63 (50.4)	45 (50.%)
	Male	99 (51.3)	62 (49.6)	44 (49.%)
Age, years	Age (range)	58 (24-88)	59 (29-88)	60 (32-87)
Previous treatments, *n* (range)	Previous treatments	3 (0-9)	3 (0-9)	3 (0-9)
Cancer type, *n* (%)	Colorectum	43 (22.3)	24 (19.2)	20 (22.5)
	Lung	29 (15.0)	18 (14.4)	13 (14.6)
	Breast	23 (11.9)	16 (12.8)	12 (13.5)
	Other	20 (10.4)	11 (8.8)	5 (5.6)
	Head and neck	15 (7.8)	10 (8.0)	10 (11.2)
	Stomach	11 (5.7)	7 (5.6)	2 (2.2)
	Biliary tract	9 (4.7)	6 (4.8)	4 (4.5)
	Brain	7 (3.6)	6 (4.8)	6 (6.7)
	MUO	7 (3.6)	6 (4.8)	4 (4.5)
	Pancreas	7 (3.6)	4 (3.2)	3 (3.4)
	Bladder	5 (2.6)	4 (3.2)	3 (3.4)
	Ovary	4 (2.1)	3 (2.4)	2 (2.2)
	Kidney	3 (1.6)	3 (2.4)	1 (1.1)
	Uterine	3 (1.6)	2 (1.6)	2 (2.2)
	Prostate	2 (1.0)	1 (0.8)	0 (0.0)
	Thyroid	2 (1.0)	1 (0.8)	1 (1.1)
	Adrenal gland	1 (0.5)	1 (0.8)	0 (0.0)
	Liver	1 (0.5)	1 (0.8)	1 (1.1)
	Skin	1 (0.5)	1 (0.8)	0 (0.0)
Pathology, *n* (%)	Adenocarcinoma	101 (52.3)	65 (52.0)	47 (52.8)
	Invasive ductal carcinoma	17 (8.8)	10 (8.0)	7 (7.9)
	Squamous cell carcinoma	12 (6.2)	8 (6.4)	4 (4.5)
	Glioblastoma	7 (3.6)	7 (5.6)	5 (5.6)
	Poorly differentiated carcinoma	5 (2.6)	4 (3.2)	1 (1.1)
	Invasive lobular carcinoma	4 (2.1)	2 (1.6)	4 (4.5)
	Sarcoma	4 (2.1)	2 (1.6)	1 (1.1)
	Renal cell carcinoma	3 (1.6)	1 (0.8)	1 (1.1)
	Small cell carcinoma	2 (1.0)	1 (0.8)	0 (0)
	Hepatocellular carcinoma	1 (0.5)	1 (0.8)	1 (1.1)
	Other	37 (19)	24 (19)	18 (20)

IMPs, investigational medicinal products; MTB, molecular tumor board; MUO, metastasis of unknown origin.

treatments was 3 (0-9). Among 13 patients without prior treatment, 5 had a rare tumor without a standard of treatment, and 3 also had a rare tumor that recurred immediately after completing the adjuvant treatment. Three patients received the IMPs, and two were enrolled in a clinical trial as the first treatment based on decisions made by cMTB (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103709). As part of their previous targeted therapy, bevacizumab (46, 23.8%), trastuzumab (31, 16.1%), nivolumab (12, 6.2%), and pembrolizumab (12, 6.2%) were frequently administered (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103709). Before the NGS test, patients received targeted therapies such as bevacizumab (42, 21.8%), trastuzumab (27, 14.0%), pembrolizumab (11, 5.7%), cetuximab (10, 5.2%), lapatinib (7, 3.6%), and nivolumab (7, 3.6%) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103709).

NGS platform

More than 15 NGS platforms were used for each of the 29 sites. The most commonly used NGS platform was Cancer Scan, followed by Oncomine, TruSight, and First Cancer Panel (Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmoop.2024.103709). The most frequently used biopsy site for NGS was the colorectum (15.5%), followed by the lungs (11.9%), hepatobiliary sites (10.9%), and breasts (8.3%) (Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmoop.2024.103709). The biopsy samples for NGS included primary tumor (56.5%), metastatic lesion (30.1%), and blood (9.3%) (Supplementary Figure S2C, available at https://doi.org/10.1016/j.esmoop.2024.103709).

Actionable genetic alteration

In our study, 229 genes with significant alterations, including single-nucleotide variants, indels, frameshifts, amplifications, splicing, loss, and fusions, were identified in 193 patients. Among these, *ERBB2* was the most common, followed by *PIK3CA*, *TP53*, and *KRAS* (Supplementary Figure S3A, available at https://doi.org/10.1016/j.esmoop.2024.103709). A total of 48 actionable genetic alterations in addition to high tumor mutational burden (TMB) and microsatellite instability (MSI) were identified in 145 patients through a cMTB review (Figure 1A). OncoPrint, including MTB and MSI, cancer types, and IMPs, is

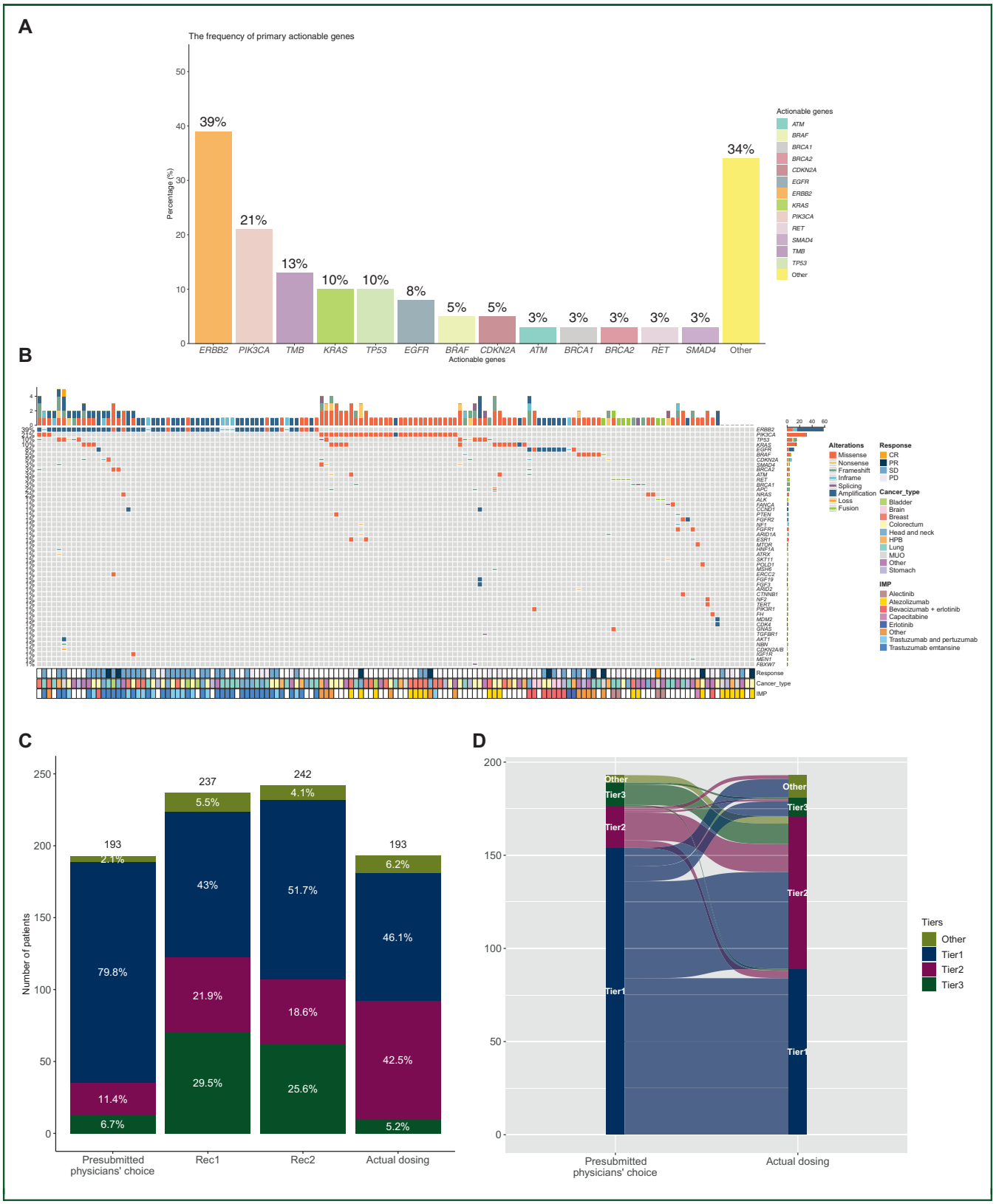

Figure 1. Actionable gene alterations and treatment choices. (A) Frequency of genes with actionable genetic alterations. A total of 48 genes, high tumor mutational burden (TMB), and high microsatellite instability (MSI) were observed in 145 patients. Percentage of each actionable gene was calculated by dividing the number of each actionable gene by 145. (B) OncoPrint illustration of the actionable genetic alterations in 145 patients with actionable genetic alterations. (C) Distribution of tiers according to pre-submitted physician choices, Rec1, Rec2, and actual dosing of IMPs. Numbers on the upper bar graphs represent the total number of patients or cases. Recommendations of each tier in Rec1 and Rec2 were permitted to be duplicated. (D) Decision flow between pre-submitted physicians' choices and actual dosing of IMPs. CR, complete remission; HPB, hepatopancreatobiliary; IMPs, investigational medicinal products; MUO, metastasis of unknown origin; PD, progressive disease; PR, partial remission; SD, stable disease.

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illustrated in Figure 1B. The proportion of patients with actionable genomic alterations was 75.1% (145/193). Among the 48 actionable genetic alterations, *ERBB2* amplifications, or mutations, were the most frequently observed, affecting 39% of patients, followed by *PIK3CA* (21%), high TMB (13%), *TP53* (10%), *KRAS* (10%), and *EGFR* genetic alterations (8%). The OncoPrint for IMP, response, TD, and OS in 89 patients who received IMPs was presented in Supplementary Figure S3B, available at https://doi.org/10.1016/j.esmoop.2024.103709. Similarly to 145 patients with actionable genetic alterations, *ERBB2* amplification or mutations were the most common, followed by high TMB, *EGFR*, and *PIK3CA* genetic alterations. When evaluating the relationship between actionable genetic alterations and cancer types, *ERBB2* alterations were frequently observed in colorectal, head and neck, and lung cancers. *PIK3CA* mutations were frequently observed in breast cancers, whereas *EGFR* amplifications or mutations were commonly found in colorectal cancers and brain tumors (Supplementary Figure S3C, available at https://doi.org/10.1016/j.esmoop.2024.103709).

cMTB recommendations and matching rate

Among the 193 pre-submitted physician choices, tier 1 was predominantly chosen by site physicians (154 cases, accounting for 79.8% of choices) (Figure 1C and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2024.103709). A total of 237 Rec1 and 242 Rec2 recommendations were provided to 193 patients through the cMTB review. Choice of tier 1 in Rec1 and Rec2 was 102 (43.0%) and 125 (51.7%), respectively. The cMTB recommended 70 and 62 clinical trials to patients as Rec1 and Rec2, respectively, based on their own genomic alterations. Among 193 patients, 89 (46.1%) patients finally received genomic alteration-matched IMPs, and 10 (5.2%) participated in cMTB-recommended clinical trials. The match rate of patients who received MGT based on the cMTB recommendations was 51.3% (89 IMPs + 10 clinical trials out of a total of 193), exceeding the expected match rate of our study (30%). The treatment flow from the pre-submitted physician choices to the actual dosing of IMPs is presented in Figure 1D.

Investigational medicinal products

Among 89 patients who received IMPs, the most frequently administered IMP was trastuzumab emtansine (30 patients, 33.7%), followed by atezolizumab (20, 22.5%), trastuzumab plus pertuzumab (14, 15.7%), and bevacizumab plus erlotinib (12, 13.5%) (Figure 2A). Trastuzumab emtansine was predominantly administered to patients with lung and head and neck cancers (Figure 2B and Supplementary Table S5A, available at https://doi.org/10.1016/j.esmoop.2024.103709). Trastuzumab plus pertuzumab or atezolizumab were mainly administered to patients with colorectal cancer and breast cancer. In contrast, bevacizumab plus erlotinib was mainly administered to patients with brain tumors and colorectal cancer. Trastuzumab emtansine and trastuzumab plus pertuzumab were administered to patients harboring *ERBB2* amplification or mutations, whereas atezolizumab was predominantly administered to patients with high TMB or MSI (Figure 2B and Supplementary Table S5B, available at https://doi.org/10.1016/j.esmoop.2024.103709). Bevacizumab ± erlotinib was mainly given to patients with *EGFR* mutations or amplification. Those without specific actionable genetic alterations received either capecitabine or bevacizumab.

The concordance rate between pre-submitted physician choices and the actual dosing of IMPs was 57.5% [111/193; Figure 2C (left panel), and Supplementary Table S6A, available at https://doi.org/10.1016/j.esmoop.2024.103709]. Additionally, there was a 68.5% concordance rate between pre-submitted physician choices and MTB recommendations, as shown in Figure 2C (right panel) and Supplementary Table S6B, available at https://doi.org/10.1016/j.esmoop.2024.103709.

Among the 75 patients with no pre-submitted physician choices or other choices except for IMPs, 14 (18.7%) received IMPs based on cMTB recommendations. The agreement between the site investigator's opinion and cMTB recommendations for each IMP and actual dosing was well balanced (Figure 2D). However, the discrepancy between the pre-submitted physician choices and cMTB recommendations or actual dosing of IMPs was mostly observed for atezolizumab.

Clinical outcomes

Among the 89 patients who received at least one IMP, 69 (77.5%) were available for tumor response assessment. The data cut-off date was 15 May 2023. ORR and DCR were 10.1% and 72.5% (1 CR, 6 PR, and 43 SD), respectively (Table 2 and Figure 3A). Notably, CR was observed in one patient with metastasis of unknown origin harboring *ALK* fusion who was treated with alectinib. The response rates to trastuzumab emtansine, atezolizumab, and bevacizumab plus erlotinib were 8.3%, 21.4%, and 9.1%, respectively (Figure 3B).

The median follow-up duration of 193 patients was 14.8 months (95% CI 10.5-17.6 months). The median TD of patients who received IMPs was 3.5 months (95% CI 2.8-5.5 months), with a 4-month TD rate of 44.9% (Figure 3C). Trastuzumab emtansine, trastuzumab plus pertuzumab, atezolizumab, and bevacizumab plus erlotinib showed a median TD of 4.2 months (95% CI 3.0-7.5 months), 4.6 months (95% CI 3.5-6.3 months), 1.9 months (95% CI 0.7-6.5 months), and 3.4 months (95% CI 2.8 months-NA), respectively (Table 2). Among 89 patients with IMPs, 9 (10.1%) patients showed long TD (over 12 months) (Figure 3D). The median OS of patients who received IMPs was 6.9 months (95% CI 5.2-10.0 months) (Figure 3E). The median OS of the 193 patients was 6.5 months (95% CI 5.2-8.8 months).

The pathway from actionable genetic alterations, IMPs, and finally to tumor response is depicted in Figure 3F. The figure shows that the IMPs were appropriately matched to patients based on their specific molecular targets. Similar to Figure 3B, Figure 3F also shows a favorable response to the *ERBB2*—trastuzumab emtansine flow, as well as a high TMB—atezolizumab flow.

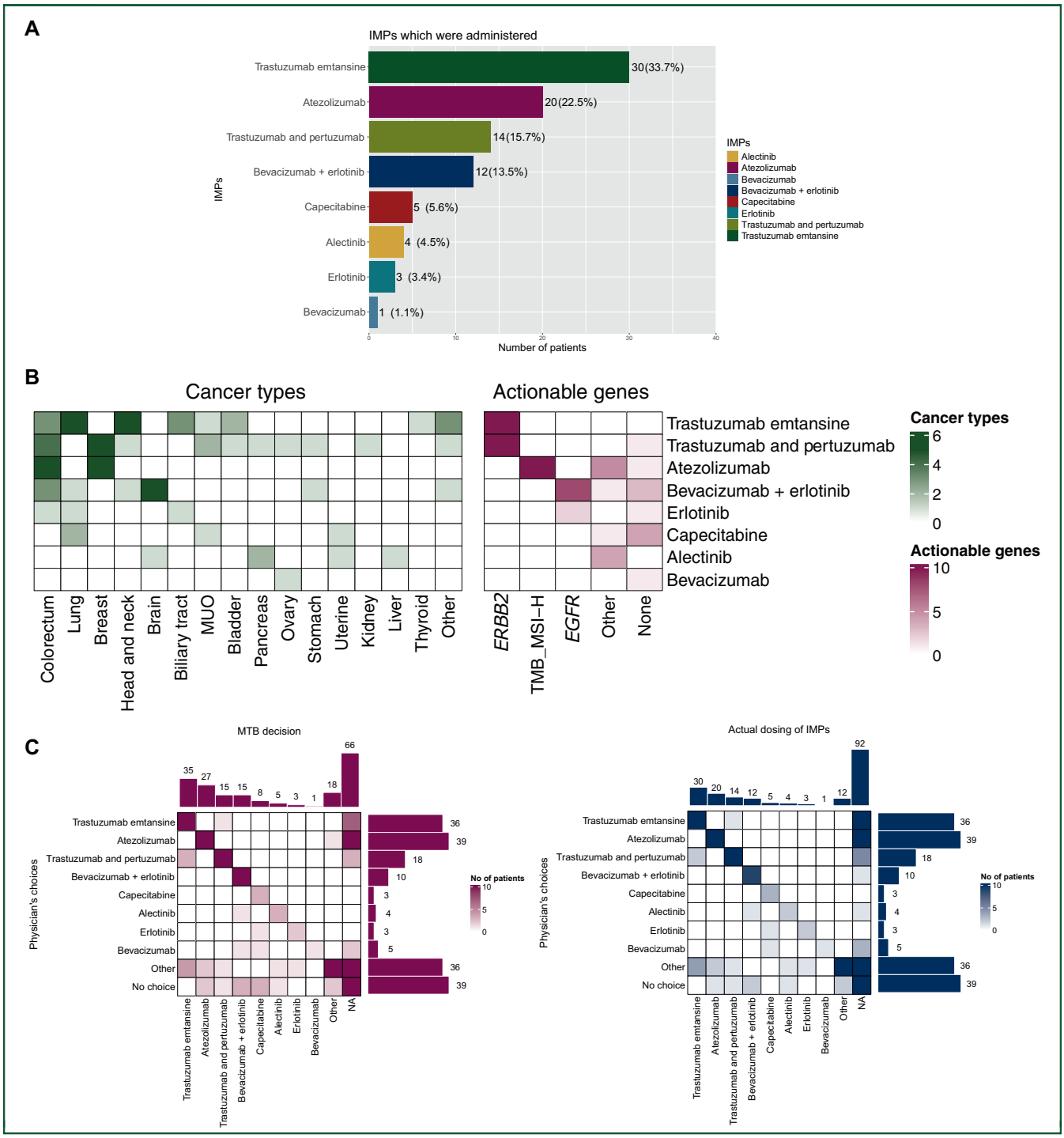

Figure 2. Assessment of IMP administration. (A) Bar graph representing the number and percentage of each IMP in 89 patients. (B) Relationship between IMPs and cancer types (left), and between IMPs and actionable genes (right). (C) Concordance of MGT between pre-submitted physicians' choices and actual dosing of IMPs (left panel) and between pre-submitted physician choices and the cMTB recommendation (right panel). (D) Discrepancy of each IMP between pre-submitted physicians' choice, Rec2, and actual dosing of IMPs.

cMTB, central molecular tumor board; IMPs, investigational medicinal products; MGT, molecular profiling-guided therapy; MSI-H, high microsatellite instability; MUO, metastasis of unknown origin; NA, not available; TMB, tumor mutational burden.

Adverse events

As shown in Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2024.103709, asthenia (4.5%), increased bilirubin (3.4%), and pneumonia (3.4%) were the most commonly reported SAEs. Among AEs, diarrhea (13.5%), nausea (9.0%), decreased appetite (7.9%), and vomiting (7.9%) were commonly observed. Hematologic toxicities, such as thrombocytopenia and anemia, were observed in 6.7% and 4.5% of patients, respectively.

DISCUSSION

KOSMOS successfully organized a cMTB by bringing together experts from multiple disciplines and institutions from across the country. Over a 1-year study period, 60

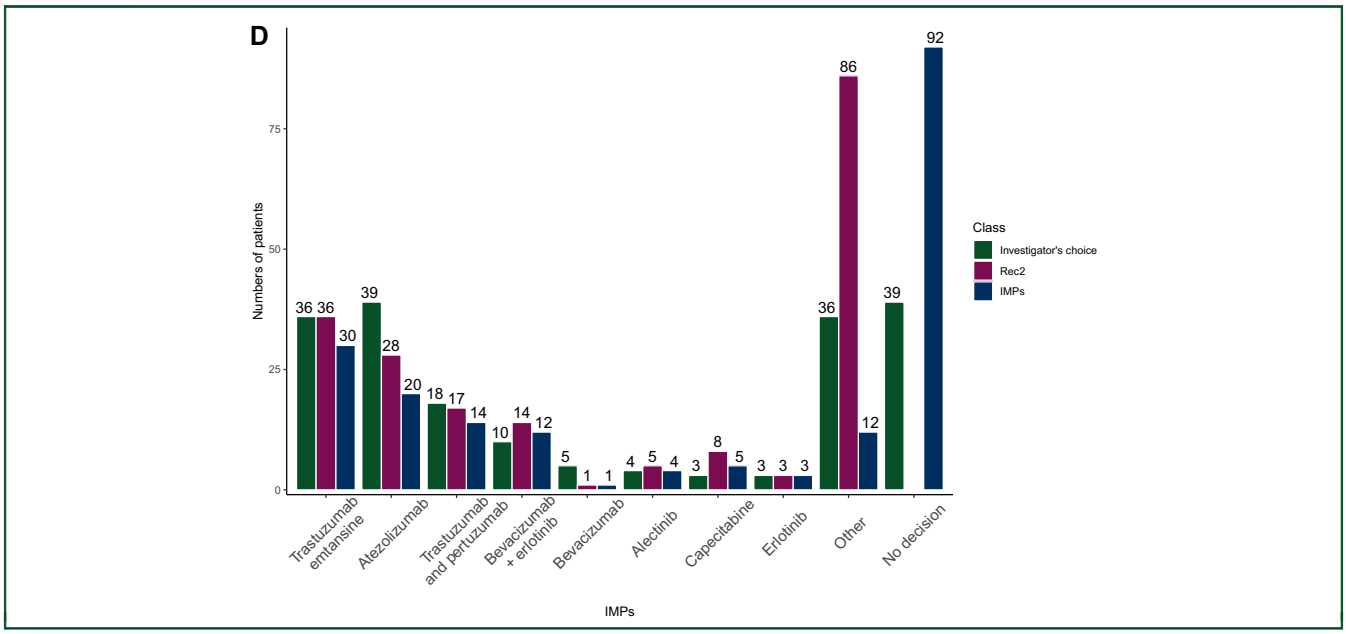

Figure 2. **Continued.**

cMTB meetings were conducted to discuss the cases of 193 patients from 29 institutions. The 7 days' median time between the submission of cases to cMTB and subsequent discussions suggests that the approach was feasible.

Of the 48 actionable genes identified in our study, *ERBB2, PIK3CA*, and *KRAS* were identified as genes with frequent genetic alterations, similar to other landscape studies on cancer genetics.[21-23] However, *ERBB2* amplifications and mutations were observed more frequently in our study than in other studies. The MGT match rate was 57.5%, indicating that our study met the pre-planned hypothesis with 30% match rate. Large-scale molecular-guided profiling trials reported 15%-57% MGT match rates.[2-4,6,7,15-18] The match rate of our study was also relatively higher than that of previous studies. The relatively high frequency of ERBB2 alterations and the high match rate could be attributed to the fact that the site investigators enrolled more patients with specific genetic alterations known to be associated with the IMPs used in this study. An intriguing finding was observed in 75 patients with no specific pre-submission choices or choices other than IMPs made by physicians. Among these patients, 14 were administered at least one IMP through the cMTB recommendations, even though the investigators had no specific or non-IMP choices. These findings suggest that cMTB plays an important role in selecting appropriate patients and providing molecular-matched treatments for precision oncology. Among the eight IMPs, *ERBB2*-targeted agents and atezolizumab were the most frequently used in tier 1 treatments (Figure 2A). Most IMPs showed good concordance between the site physicians' choice and the actual dosing, except for atezolizumab (Figure 2B-D). This discrepancy could be attributed to the differences in the way the site investigators and cMTB members weighed the significance of TMB.

In several clinical trials, MGT has shown promising clinical outcomes with an ORR of 2%-45% and a PFS of 2.3-6.5 months.[2,3,5,7,15,16,18,19,24-26] NCI-MATCH reported response rates of 0%-50% and a 6-month PFS rate of 3.3%-68.4% across targeted agents and genetic alterations.[27] DRUP showed that the CR, PR, or SD beyond 16 weeks was 34% and the overall median duration of clinical benefit was 9 months[9] (Supplementary Table S8, available at

Table 2. **Clinical outcomes of 89 patients with each IMP**

IMPs	CR	PR	SD	PD	Total	Evaluable	ORR	DCR	4M TD	TD	CI of TD	OS	CI of OS
Alectinib	1 (33.3%)	0 (0.0%)	0 (0.0%)	2 (66.7%)	4	3	33.3%	33.3%	50.0%	3.4	0.6-NA	1.7	NA-NA
Atezolizumab	0 (0.0%)	3 (21.4%)	5 (35.7%)	6 (42.9%)	20	14	21.4%	57.1%	30.0%	1.9	0.7-6.5	6.3	3.7-NA
Bevacizumab	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	1	1	0.0%	100.0%	100.0%	8.3	NA-NA	NA	NA
Bevacizumab and erlotinib	0 (0.0%)	1 (9.1%)	5 (45.5%)	5 (45.5%)	12	11	9.1%	54.5%	33.3%	3.4	2.8-NA	4.9	3.07-NA
Capecitabine	0 (0.0%)	0 (0.0%)	3 (100.0%)	0 (0.0%)	5	3	0.0%	100.0%	0.0%	1.6	0.5-NA	7.1	1.9-NA
Erlotinib	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	3	1	0.0%	100.0%	66.7%	6.5	1.4-NA	*NA*	*NA*
Trastuzumab and pertuzumab	0 (0.0%)	0 (0.0%)	12 (100.0%)	0 (0.0%)	14	12	0.0%	100.0%	57.1%	4.6	3.5-6.3	12.5	8.5-NA
Trastuzumab emtansine	0 (0.0%)	2 (8.3%)	16 (66.7%)	6 (25.0%)	30	24	8.3%	75.0%	56.7%	4.2	3.0-7.5	7.3	5.2-19.53
All	1 (1.4%)	6 (8.7%)	43 (62.3%)	19 (27.5%)	89	69	10.1%	72.5%	44.9%	3.5	2.8-5.5	6.9	5.2-10.0

4M TD, 4-month treatment duration; CI, confidence interval; CR, complete remission; DCR, disease control rate; IMPs, investigational medicinal products; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial remission; SD, stable disease; TD, treatment duration.

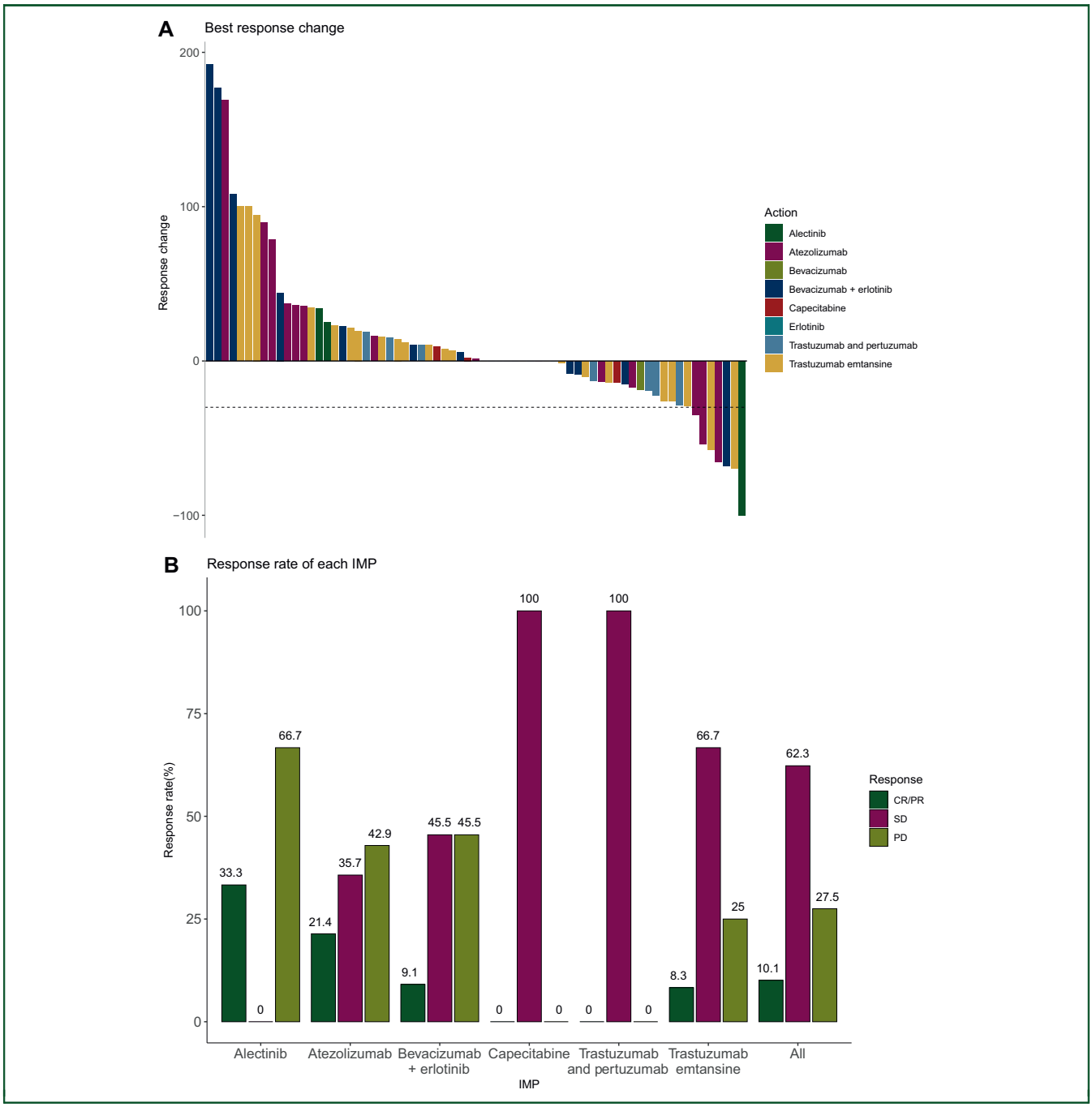

Figure 3. Clinical outcomes of IMP treatment. (A) Waterfall for the best response change of each IMP. Different colors in bars represent each IMP. (B) Bar graph representing complete remission/partial remission (CR/PR), stable disease (SD), and progressive disease (PD) of each IMP. (C) TD for the 89 patients who received the actual dosing of IMPs. (D) Swimmer's plot of 89 patients who received the actual dosing of IMPs. Among them, nine patients, long-term survivors, received IMPs for >12 months. (E) OS of the 89 patients who received the actual dosing of IMPs. (F) The flow of the molecular profiling, matched IMPs, and response.
IMPs, investigational medicinal products; OS, overall survival; TD, treatment duration.

https://doi.org/10.1016/j.esmoop.2024.103709). Although clinical outcomes varied depending on the targeted agent and tumor types, the TAPUR study also reported an ORR of 0%-58%, a DCR of 21%-69%, and a PFS of 7.2-38.4 weeks with several targeted agents, including cetuximab, olaparib, palbociclib, pembrolizumab, and pertuzumab and trastuzumab, in different tumor types harboring various genetic alterations[28-41] (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2024.103709). In our study, the median TD and the ORR of IMPs were 3.5 months (95% CI 2.8-5.5 months) and 10.1%, respectively, and were comparable to the results of previous studies. Interestingly, nine patients (10.1%) received IMPs for a long duration (>12 months) (Figure 3D). This finding suggests that the MGT can provide clinical benefit to some patients who did not have further standard treatment.

Although 70 and 62 clinical trials were suggested to site physicians by the cMTB in Rec1 and Rec2, respectively, only

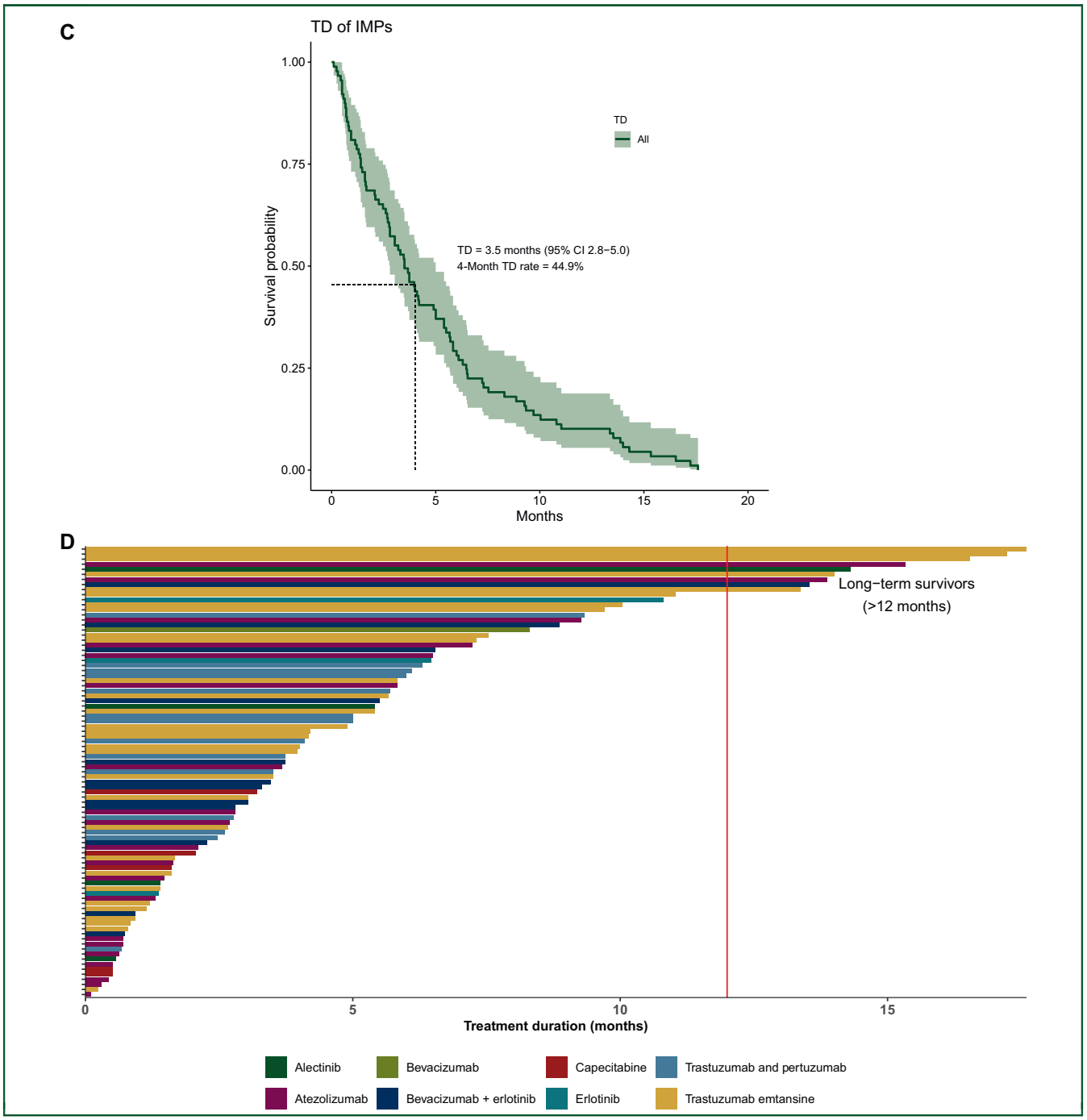

Figure 3. Continued.

10 patients were enrolled in the cMTB-recommended trials. The low enrollment can be attributed to several factors, such as the limited accessibility of clinical trials, poor general condition of patients, and non-fulfillment of the inclusion criteria, such as the absence of brain metastasis. These findings suggest that, although patients have actionable genetic alterations, there are numerous obstacles to their enrollment in clinical trials. Therefore, it is worth considering the use of targeted agents outside their approved indications for these patients and the development of more inclusive clinical trials.

Several precision oncology studies have been conducted, including the DRUP, TAPUR, and NCI-MATCH trial.[6,8,9,27] Notably, DRUP and NCI-MATCH have carried out NGS sequencing in their central laboratories. In contrast, our study and TAPUR used the results of local NGS tests carried out in a Korean MFDS-accredited laboratory or a laboratory with certification under the Clinical Laboratory Improvement Amendments, and accreditation by the College of American Pathologists.[8] KOSMOS shared similarities with TAPUR or DRUP in terms of utilizing Food and Drug Administration-approved targeted agents outside of their

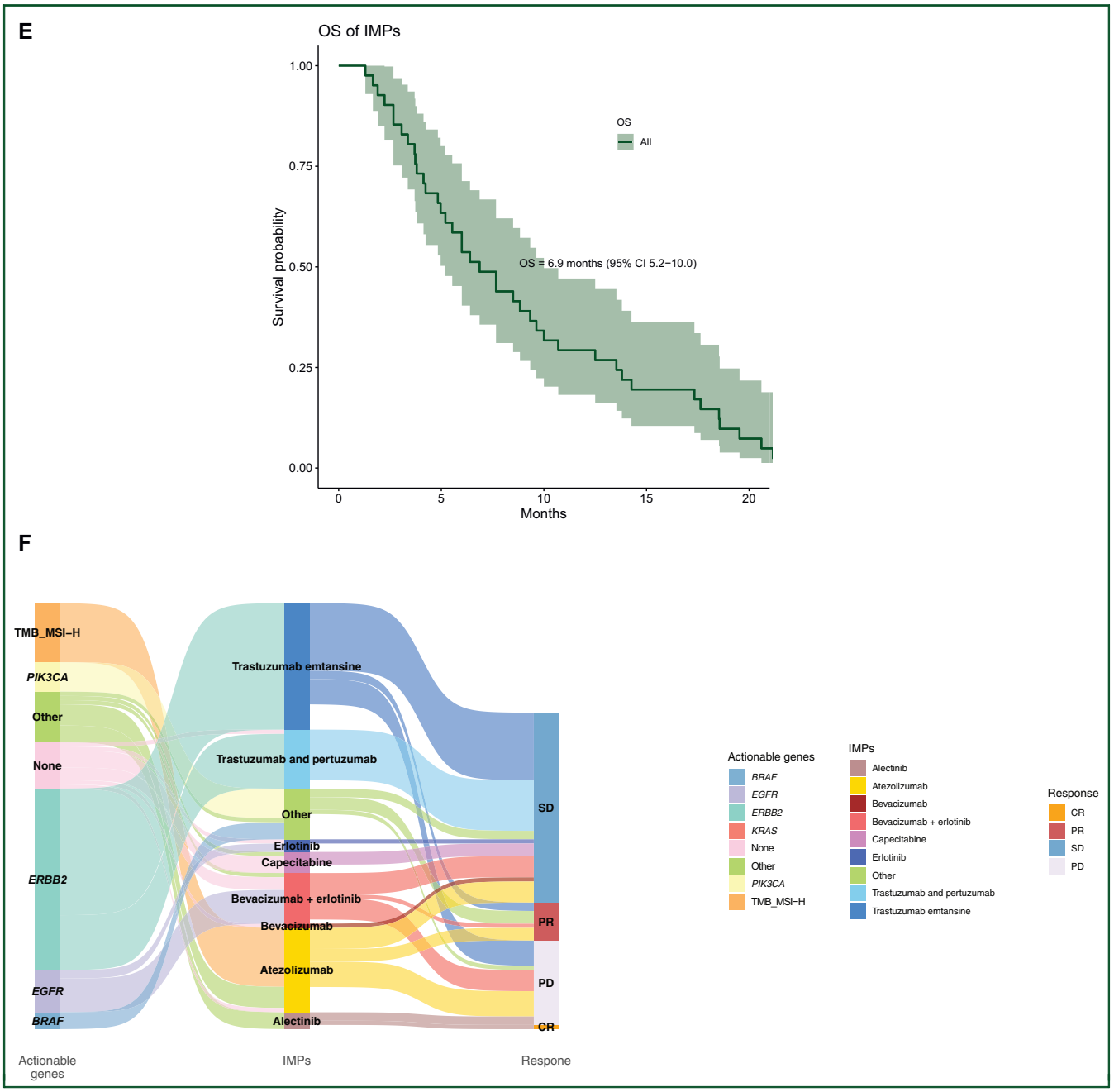

Figure 3. Continued.

indications. While KOSMOS is a prospective, observational study and not a strictly defined clinical trial, TAPUR, DRUP, and NCI-MATCH were structured as prospective, multicohort clinical trials akin to phase II trials. As a result, KOSMOS was deemed optimal in terms of streamlined patient recruitment and the provision of IMPs.

To the best of our knowledge, KOSMOS is the first precision oncology study conducted outside the United States, Europe, and Japan. Our study has potential implications for precision oncology in other Asian countries that have recently adopted NGS testing and strictly regulated the use of targeted agents outside their approved indications. Several studies on precision oncology have attempted to implement MTB in all or some specific cases, especially those with multiple genetic alterations or without matched treatment.[7-9,15,18] Compared with these, the strength of our study lies in the comprehensive cMTB meetings and discussions for all 193 cases.

However, our study also had a few limitations. In our study, all NGS tests from each institution were allowed if they were conducted in an MFDS-accredited laboratory. Thus, the NGS platforms were highly diverse. Given that the identification of actionable genes relies primarily on NGS platforms, the lack of a unified platform could potentially influence the accurate detection of specific actionable genetic alterations, particularly TMB. Moreover, the site physicians may have enrolled their own patients considering the IMPs provided by KOSMOS, implying a potential

selection bias in our study. For example, patients harboring *ERBB2* amplification or mutations might have been over-represented compared with other precision oncology studies. Additionally, KOSMOS facilitated four cMTB panels, which could be a cause for disagreements over cases. Furthermore, our study was an observational study and not a phase II basket trial; therefore, OS was not a major variable. We collected clinical data, including OS, TD, and ORR, specifically for patients who received the actual dosing of IMPs (tier 1). Sufficient data on those who received tier 2 or tier 3 treatments were not collected. As a result, our study may not sufficiently explain the clinical significance of MGT compared with unmatched treatment. Therefore, we are currently conducting a large-scale study, KOSMOS-II (NCT05525858). The primary aim of KOSMOS-II is to investigate the clinical significance of MGT. With this study, we hope to further validate the effectiveness of MGT in a larger scale.

Conclusions

KOSMOS established a nationwide cMTB and demonstrated its effective operation in the treatment of advanced or metastatic solid tumors. Our study achieved the presumed target numbers for the actual dosing of IMPs with a high MGT match rate. It also showed promising clinical results for MGT with manageable toxicity, indicating the potential of implementing NGS-based MGT in real-world practice.

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DISCLOSURE

The authors have declared no conflicts of interest.

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