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ORIGINAL RESEARCH

Clinical benefits of precision medicine in treating solid cancers: European Society of Medical Oncology-Magnitude of Clinical Benefit Scale score-based analysis

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Background: Precision and matched cancer medicine has the potential to complement the existing biomarker approaches in cancer treatment. However, despite their promising potential, certain negative results have highlighted their limitations in molecular biology-driven treatment strategies. This study aimed to evaluate the clinical benefits of precision therapies.

Materials and methods: Three reviewers independently identified and assessed precision and matched cancer treatment studies published between January 2015 and December 2020. Clinical benefits of the treatments included in our cohort were assessed using two established frameworks; the European Society of Medical Oncology-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS) and the American Society of Clinical Oncology Value Framework.

Results: Of the 290 eligible studies, 130 were for lung cancer, 51 for solid tumors, 24 for melanoma, and 24 for breast cancer. The common targets were: epidermal growth factor receptor ($N = 66$), serine/threonine-protein kinase B-Raf ($N = 40$), anaplastic lymphoma kinase (ALK) ($N = 34$), breast cancer protein ($N = 26$), phosphatidylinositol-3 kinase/protein kinase B/phosphatase and tensin homolog (PI3K/AKT/PTEN) pathway ($N = 19$), receptor tyrosine-protein kinase erbB-2 (HER2) ($N = 19$), mitogen-activated protein kinase (RAS/RAF/MAPK) pathway ($N = 18$), programmed death-ligand 1 ($N = 12$), fibroblast growth factor receptor ($N = 8$), and others ($N = 43$). The ESMO-MCBS scales ranged from 0 to 4. Based on the clinical benefit values, tumor mutational burden/mismatch repair-deficient/microsatellite instability-high for immunotherapy, anaplastic lymphoma kinase, and neurotrophic receptor tyrosine kinase therapeutic targets were considered high, whereas RAS/RAF/MAPK and PI3K/AKT/PTEN were considered low. Additionally, we found a significant difference between each average score ($P < 0.001$).

Conclusions: This study showed that precision and matched cancer therapies require further improvement. This is consistent with the views of the tumor board and of clinicians that precision strategies need to be revised to improve their therapeutic effects.

Key words: precision medicine, clinical benefit, European Society of Medical Oncology-Magnitude of Clinical Benefit Scale, American Society of Clinical Oncology Value Framework

INTRODUCTION

Cancer treatment has been completely revolutionized in the past few decades, as several molecular alterations have been identified as drivers of cancer development and progression.[1] Increasing advancements in genomics have given rise to a growing interest in precision medicine, which aims to improve treatment strategies by identifying therapies that can affect specific targets based on their molecular make-up. Furthermore, personalized strategies have led to a higher proportion of responding patients, longer progression-free survival (PFS), and improved overall survival (OS) compared with trials with unselected patients.[2,3] To this end, several basket trials enrolled participants based on the type of mutation, regardless of the histology or affected organs,[4] while umbrella trials enrolled participants with the same type of cancer histology or organ involvement and assigned them to different cohorts based on specific mutations.[5]

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Therapies that offer true 'clinical benefit' should significantly improve the quantity and/or quality of survival. The concept of 'value' is being increasingly recognized in both the interpretation of clinical trials and the delivery of cancer care. Small incremental gains in therapeutic endpoints, especially those that are unproven surrogates for survival or its quality, provide minimal value.[6] The European Society of Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) and the American Society of Clinical Oncology Value Framework (ASCO-VF) have proposed frameworks to assess the clinical benefits of new cancer therapies.[7,8]

Precision and matched cancer medicine has the potential to complement current genomic approaches. The minor role of molecular profiling in predicting the response to targeted therapies and the limitations of preclinical models currently used for drug selection have hindered the proper validation of precision medicine strategies. Additionally, certain negative results have highlighted the limitations of precision medicine in molecular biology-driven treatment strategies, despite its promising biological potential. Thus, in this study, we evaluated the clinical benefits of cancer precision and matched therapies for each target, using the ASCO-VF and ESMO-MCBS frameworks.

MATERIALS AND METHODS

Data sources and extraction

On 11 April 2020, the PubMed, Medline, and EMBASE databases were searched for studies published between 1 January 2015 and 11 April 2020, using the keywords, '(Cancer OR neoplasm) AND (matched OR precision) AND Clinical Trial [Publication type]'. Three reviewers (YH, SK, and YI) independently searched and identified eligible trials related to 'prospective trials of matched therapies and precision medicines for cancer patients,' which were then included in this study. Neoadjuvant or adjuvant therapies were excluded (Figure 1).

Scoring of clinical benefit

The reviewers individually analyzed the data from all the eligible studies (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100187). To evaluate the clinical benefits of the cancer treatments included in our cohort, we applied two established value frameworks: the ESMO-MCBS version 1.1 and the ASCO-VF version 2. The ESMO-MCBS grades and ASCO-VF scores were assigned to the entire cohort by each reviewer at two time points, roughly 1 month apart; the values assigned at the second time point were used in the analysis. The 'Evaluation form 3' was used to derive the ESMO-MCBS grades for evaluation of the clinical benefits of phase I/II studies. As for the ASCO-VF scores, we used point estimated OS or PFS for phase III trials and response rate for phase I/II trials. Only grade 3 or 4 toxicities presented in the studies were scored. Quality-of-life (QoL) data were scored when reported. We evaluated clinical benefits without determining the treatment costs because the data used in this study included unapproved drugs and treatments.

Statistical analyses

The Student's *t*-test was carried out to compare the data, and Spearman correlation was used to assess the association between ESMO-MCBS and ASCO-VF grades. All the analyses were carried out using the SPSS version 23.0 (IBM SPSS, Armonk, NY).

RESULTS

Study subjects

A total of 290 precision and matched cancer treatment trials published between January 2015 and December 2020 were validated by three reviewers. Of the 290 eligible trials, 130 (45%) were for lung cancer [non-small-cell lung cancer (NSCLC)] treatments, 51 (18%) for solid tumors, 24 (8%) for melanoma, and 24 (8%) for breast cancer (Figure 2A). The common targets and pathways were: epidermal growth factor receptor (EGFR) ($N = 66$, 23%), serine/threonine-protein kinase B-Raf (BRAF) ($N = 40$, 14%), anaplastic lymphoma kinase (ALK) ($N = 34$, 12%), breast cancer protein (BRCA) ($N = 26$, 9%), phosphatidylinositol-3 kinase/protein kinase B/phosphatase and tensin homolog (PI3K/AKT/PTEN) pathway ($N = 19$, 7%), receptor tyrosine-protein kinase erbB-2 (HER2) ($N = 19$, 7%), mitogen-activated protein kinase (RAS/RAF/MAPK) pathway ($N = 18$, 6%), programmed death-ligand 1 (PD-L1) ($N = 12$, 4%), fibroblast growth factor receptor (FGFR) ($N = 8$, 3%), hepatocyte growth factor receptor (MET) ($N = 5$, 2%), tumor mutational burden/mismatch repair-deficient/microsatellite instability-high (TMB/MMR/MSI-H) ($N = 6$, 2%), neurotrophic receptor tyrosine kinase (NTRK) ($N = 4$, 2%), proto-oncogene c-KIT (KIT) ($N = 4$, 1%), RET proto-oncogene (RET) ($N = 4$, 1%), and others ($N = 43$, 8%) (Figure 2B). Receptor tyrosine kinases were the most common therapeutic targets in this study.

Clinical benefit scoring based on each target and pathway

In this study, the ESMO-MCBS scales ranged from 0 to 4. Based on the grade of each target (Figure 3A), TMB/MMR/MSI-H, ALK, and NTRK were of high clinical benefit on the scale (mean more than grade 3). ROS-1, PD-L1, RET, BRAF, BRCA, and EGFR were of low clinical benefit for the target during the research period. Moreover, RAS/RAF/MAPK (excluding BRAF) and PI3K/AKT/PTEN pathways were of very poor clinical benefit for therapeutic targets and were statistically lower than other targets ($P < 0.001$). With respect to the cancer type (Figure 3B), solid tumors showed poor clinical benefit, and these findings demonstrate the difficulty of the basket study using matched and precision therapies. Similarly, urothelial, breast, and colorectal cancers (CRCs) were of lower grade, and the difficulty of the umbrella studies for these diseases was identified.

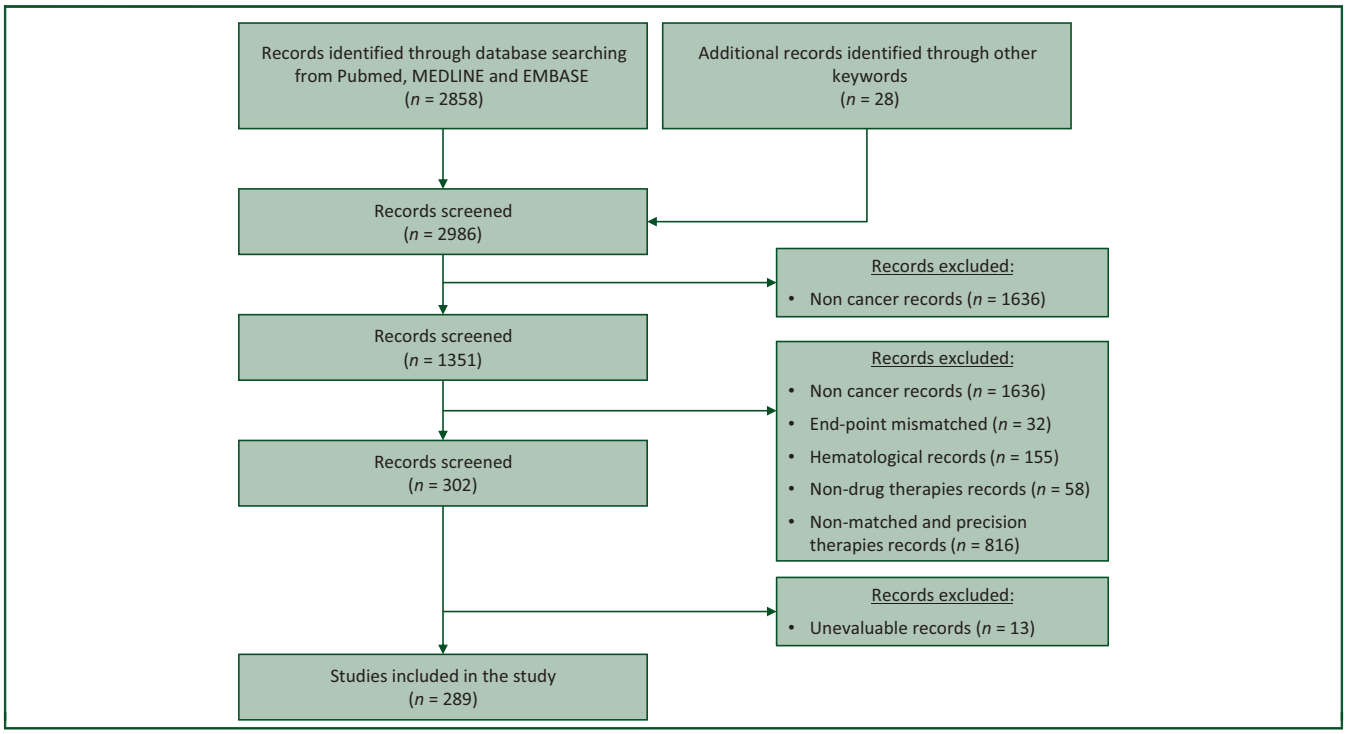

Figure 1. Flow diagram for literature search.

The analysis based on target of maultiple cancers was in Figure 4 (TMB/MMR/MSI-H, ALK, NTRAK, and ROS). However, FGFR alteration for bile tract cancer showed higher clinical benefit than other cancer types ($P < 0.001$). Moreover, several clinical trials that were considered low clinical benefit grade targets showed high clinical benefit. For example, matched therapy alpelisib for tumor tissue phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation-positive breast cancer showed prolonged PFS in phase III clinical trials.[9] Furthermore, a study showed that the RAF/MEK pathway group had a longer median PFS than the control group.[10] In NSCLC with high TMB, nivolumab plus ipilimumab showed better survival than chemotherapy, although their relevance is under discussion and further studies are needed.[11]

In this study, we analyzed the clinical benefit using the evaluation form 3 ($N = 206$, 71%), form 2B ($N = 60$, 21%), and form 2A ($N = 22$, 8%) (Figure 5A). There were no statistical differences in the clinical benefit scale between the three forms (Figure 5B, $P > 0.05$). Moreover, ESMO-MCBS score differences based on Food and Drug Administration (FDA) approval status showed higher clinical benefit in groups of FDA approval matched therapies (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100187).

Association between ESMO-MCBS and ASCO-VF grades

Examination of the relationship between ESMO-MCBS and ASCO-VF grades using Spearman's rank correlation coefficient analysis yielded a value of $r = 0.78$ ($P < 0.001$) (Figure 6).

DISCUSSION

Given the challenges presented by precision and matched therapies, efforts to accelerate genomic analyses for personalized medicine must continue to be embedded within the context of clinical trials and integrated with scientific and clinical collaborative structures to deliver measurable benefits to patients. However, we need to discuss whether these approaches are useful for cancer patients. Here, we described the clinical benefit parameters of matched and precision therapies for cancer patients by analyzing matched and precision therapy studies published between January 2015 and December 2020. We found several targeted and matched therapies that were of low clinical benefit grade, especially RAS/RAF/MAPK (excluding BRAF) and PI3K/AKT/PTEN. Moreover, we found that basket studies for several cancers have faced a harsh reality. However, limited disease organ and several precision and matched therapy targets may increase therapeutic effects.

Before 2015, the detection of HER2 amplification as a driver mutation had contributed immensely towards identifying another important subgroup of patients who benefited from anti-HER2 inhibition in all clinical settings.[12] A fundamental shift was also observed in patients diagnosed with NSCLC. The identification of EGFR mutations[13,14] and echinoderm microtubule-associated protein-like 4/ALK (EML4-ALK) translocation[15] has affected outcomes of advanced NSCLC. Moreover, identification of the BRAF-V600E mutation and its subsequent treatment with BRAF and MEK inhibitors[16] is being studied in phase III clinical trials. After the declaration of Cancer Moonshot, now named Cancer Breakthroughs, several basket and umbrella studies were conducted in an attempt to advance precision

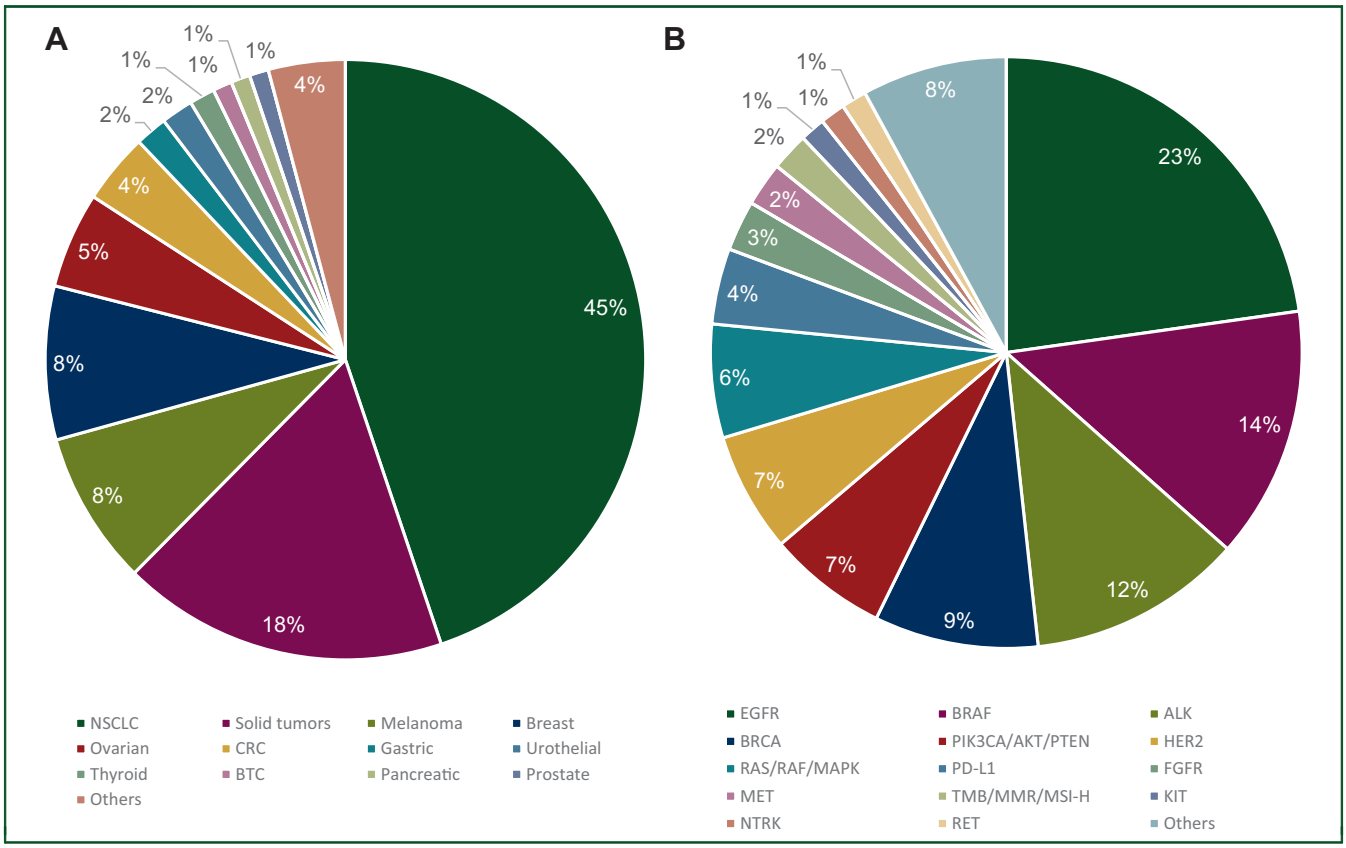

Figure 2. Study characteristics of the cohort. A pie chart of (A) the proportion of cancer types, (B) the proportion of the common molecular targets and pathways. ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-protein kinase B-Raf; BRCA, breast cancer protein; BTC, bile tract cancer; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HER2, receptor tyrosine-protein kinase erbB-2; KIT, proto-oncogene c-KIT; MET, MET receptor tyrosine kinase; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PD-L1, programmed death-ligand 1; PI3K/AKT/PTEN, phosphatidylinositol-3 kinase/protein kinase B/phosphatase and tensin homolog; RAS/RAF/MAPK, RAS proto-oncogene/RAF proto-oncogene serine/threonine-protein kinase/mitogen-activated protein kinases; RET, RET proto-oncogene; TMB/MMR/MSI-H, tumor mutational burden/mismatch repair-deficient/microsatellite instability-high; TP53, protein p53.

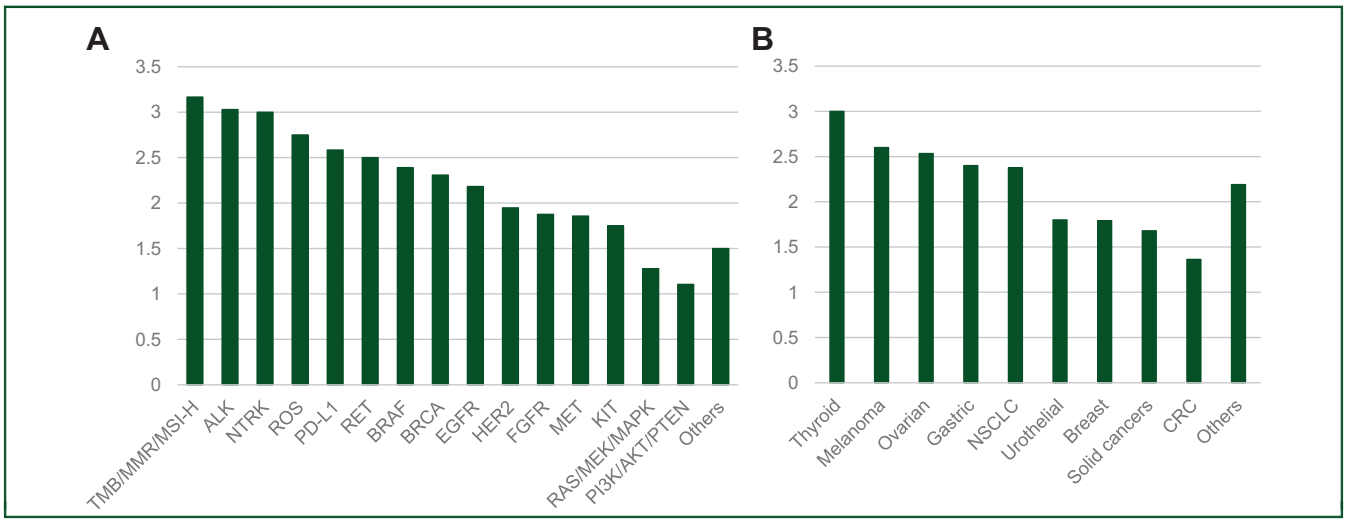

Figure 3. Clinical benefit values based on ESMO-MCBS scale in each target (A) and pathway and each cancer type (B). ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-protein kinase B-Raf; BRCA, breast cancer protein; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit; FGFR, fibroblast growth factor receptor; HER2, receptor tyrosine-protein kinase erbB-2; KIT, proto-oncogene c-KIT; MET, MET receptor tyrosine kinase; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PD-L1, programmed death-ligand 1; PI3K/AKT/PTEN, phosphatidylinositol-3 kinase/protein kinase B/phosphatase and tensin homolog; RAS/MEK/MAPK, RAS proto-oncogene/RAF proto-oncogene serine/threonine-protein kinase/mitogen-activated protein kinases; RET, RET proto-oncogene; ROS, c-ros oncogene; TMB/MMR/MSI-H, tumor mutational burden/mismatch repair-deficient/microsatellite instability-high; TP53, protein p53.

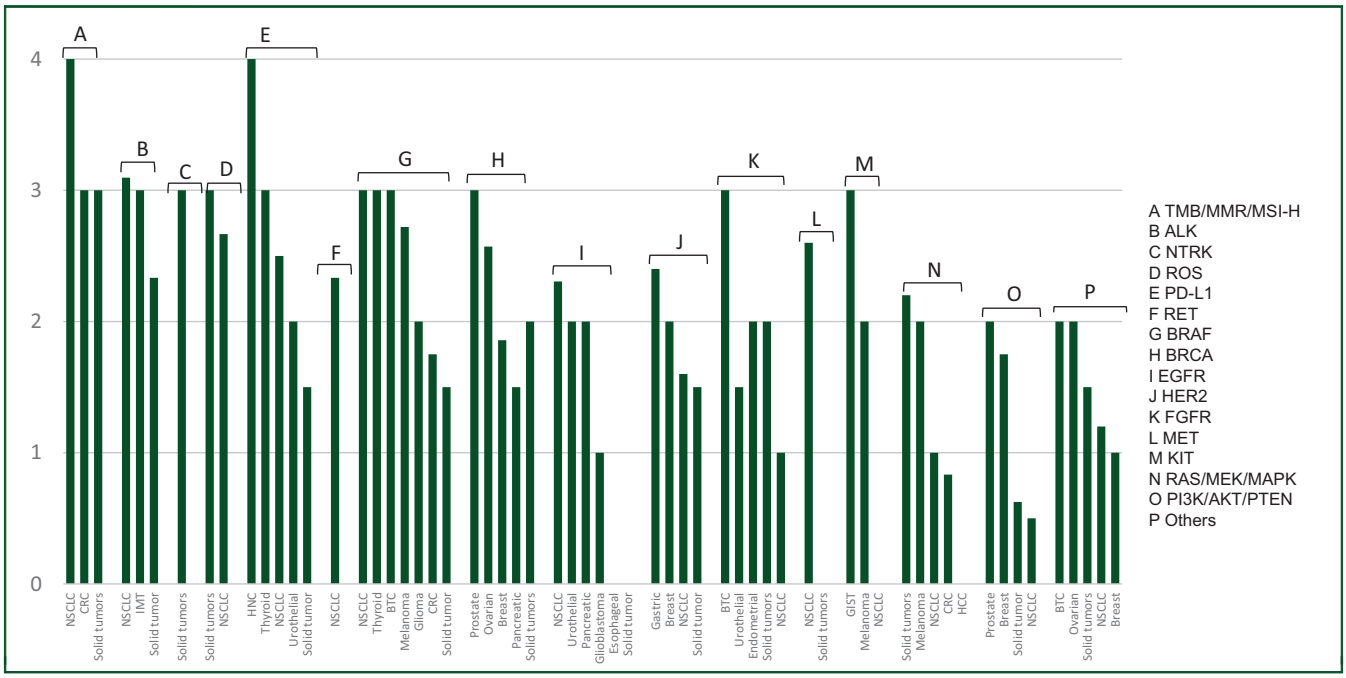

Figure 4. Clinical benefit value in each cancer type and target.
ALK, anaplastic lymphoma kinase; BRAF, serine/threonine-protein kinase B-Raf; BRCA, breast cancer protein; BTC, bile tract cancer; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HER2, receptor tyrosine-protein kinase erbB-2; HNC, head and neck cancer; IMT, inflammatory myofibroblastic tumor; KIT, proto-oncogene c-KIT; MET, MET receptor tyrosine kinase; NSCLC, non-small-cell lung cancer; NTRK, neurotrophic receptor tyrosine kinase; PD-L1, programmed death-ligand 1; PI3K/AKT/PTEN, phosphatidylinositol-3 kinase/protein kinase B/phosphatase and tensin homolog; RAS/MEK/MAPK, RAS proto-oncogene/RAF proto-oncogene serine/threonine-protein kinase/mitogen-activated protein kinases; RET, RET proto-oncogene; ROS, c-ros oncogene; TMB/MMR/MSI-H, tumor mutational burden/mismatch repair-deficient/microsatellite instability-high; TP53, protein p53.

medicine cancer treatment using targeted next-generation sequencing analysis, such as the molecular analysis for most suitable therapy (NCI-MATCH) (NCT0246506), molecular profiling-based assignment of cancer therapy (NCI-MPACT) (NCT01827384), and the LungMap study for NSCLC (NCT03851445). In 2014, the SAFIR01/UNICANCER study showed that 13% of the patients received matched therapy based on genomic analyses and concluded that the personalization of medicine was feasible for rare genomic alterations.[17] However, the response rate was limited to 10%, and the therapy was of low clinical benefit (ASCO-VF score: 8, ESMO-MCBS: score 2). Additionally, the SHIVA study showed that molecularly targeted agent-based molecular profiling and matched therapy did not improve survival benefit.[10]

In the present study, we classified the promising therapeutic targets based on their respective clinical benefit values. Already established gene alterations and targets, namely EGFR, ALK, BRAF, and HER2, maintained their clinical benefit; however, the RAS/RAF/MAPK (excluding BRAF mutation) and PI3K/AKT/PTEN pathways, which are well known important factors in regulating the signaling of cancer treatment targets,[18] did not have high clinical

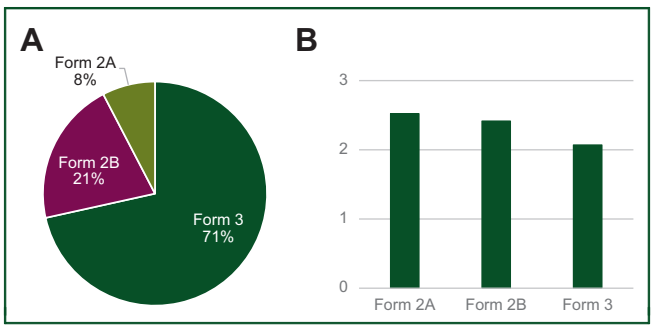

Figure 5. A pie chart of (A) form usage ratio, (B) clinical benefit value with respect to each European Society of Medical Oncology-Magnitude of Clinical Benefit (ESMO-MCBS) form.

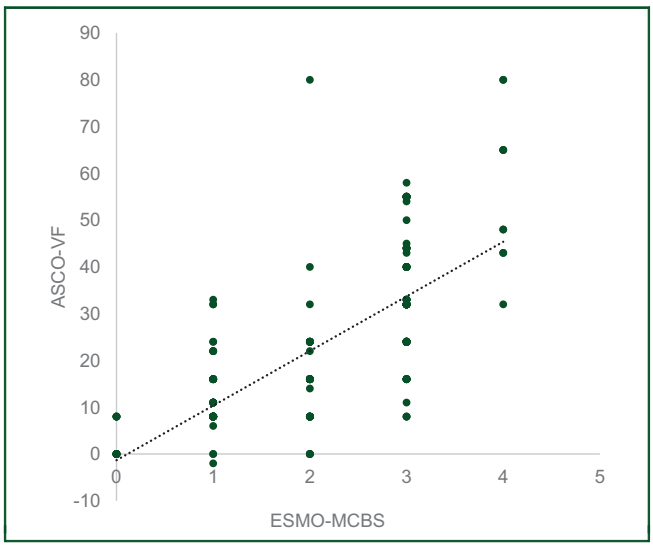

Figure 6. Association between ESMO-MCBS scale and ASCO-VF score.
ESMO-MCBS, European Society of Medical Oncology-Magnitude of Clinical Benefit; ASCO-VF, American Society of Clinical Oncology Value Framework.

benefits for matched and precision medicine in our study. In contrast, alpelisib for PIK3CA-mutated breast cancer had clinical benefits based on the endpoint of PFS in the phase III clinical trial.[9] Moreover, tepotinib and capmatinib for MET exon 14 skipping mutation-positive NSCLC showed some response rate (41%-50%) in phase II.[19,20] In KRAS G12C mutation solid cancers (almost purely NSCLC and CRC), sotorasib showed a response, but its survival benefit has not been verified in clinical trials.[21]

There are a few limitations in this study. First, we analyzed data that were published after 2015. EGFR mutations for NSCLC, ALK-positive for NSCLC, and HER2-positive for breast and gastric cancers have already been established as therapeutic targets and are well known to have high clinical benefit. However, our study showed that their clinical benefit score was low because old clinical trials were excluded. Second, ESMO-MCBS forms 2A- and 2B-based clinical benefit scoring is for phase III clinical trials and has bonus points with QoL improvement. In contrast, precision and matched clinical trials included high unmet target requirements; therefore, the usefulness of precision and matched treatments was validated by the response in phase I/II clinical trials using the ESMO-MCBS form 3. ESMO-MCBS form 3 has limited points for ESMO-MCBS grade 3 without QoL evaluation. In contrast, ASCO-VF scores, including phase I/II and phase III clinical trials, highly correlated with the ESMO-MCBS scores in our study. We believe that our study findings are meaningful evaluations and hold high clinical relevance.

In previous reports, precision and matched cancer therapies based on molecular profiling of cancer patients were assumed to have established the clinical paradigm.[22] Nevertheless, their therapeutic effect is not always of high clinical benefit within current treatment strategies.

In this study, we showed that precision and matched cancer therapies are still underdeveloped with respect to clinical benefit values. The tumor board and clinicians annotated these precision strategies and determined that they need to be revised and their therapeutic targets need to be narrowed down to improve efficacy in the clinical setting.

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DISCLOSURE

The authors have declared no conflicts of interest.

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