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Beyond traditional therapies: clinical significance of complex molecular profiling in patients with advanced solid tumours—results from a Turkish multi-centre study

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Abstract

Objective: The objective of this multi-centre, real-world study was to examine the potential influence of comprehensive molecular profiling on the development of treatment decisions or adjustments for patients with advanced solid malignancies. We then evaluated the impact of these informed choices on patient treatment outcomes.

Methods: The study encompassed 234 adult patients (mean age: 52.7 ± 14.3 years, 54.7% women) who were diagnosed with solid tumours at 21 different medical centres in Turkey. Remarkably, 67.9% of the patients exhibited metastasis at the time of diagnosis. We utilized an OncoDNA (Gosselies, Belgium) platform (OncoDEEP) integrating next-generation sequencing with additional tests to harvest complex molecular profiling data. The results were analyzed in relation with two specific outcomes: (i) the impact on therapeutic decisions, including formulation or modifications, and (ii) associated treatment response.

Results: Out of the 228 patients with final molecular profiling results, 118 (50.4%) had their treatment modified, whilst the remaining 110 (47.0%) did not. The response rates were comparable, with 3.9 versus 3.4% for complete response, 13.6 versus 29.3% for partial response, 66.9 versus 51.7% for

progressive disease and 15.5 versus 15.5% for stable disease for treatments informed and not informed by complex molecular profiling, respectively ($P = 0.16$).
Conclusion: Our real-world findings highlight the significant impact of complex molecular profiling on the treatment decisions made by oncologists for a substantial portion of patients with advanced solid tumours. Regrettably, no significant advantage was detected in terms of treatment response or disease control rates.

Key words: advanced solid tumours, next-generation sequencing, complex molecular profiling, therapeutic planning, treatment response

Introduction

In recent years, the emergence of next-generation sequencing (NGS) technologies has revolutionized our understanding of the molecular underpinnings of a variety of solid tumours, providing unique perspectives on molecular-guided therapy (1–3). This technological innovation has paved the way for a more individualized approach to oncology, given its potential to impact therapeutic decision-making and patient care (4,5). Notably, the European Society for Medical Oncology recommends the routine use of NGS on tumour samples, especially in cases of metastatic cholangiocarcinoma, advanced non-squamous non-small-cell lung cancer (NSCLC), prostate cancer and ovarian cancer (6). Moreover, in the field of colon cancer, there is an increasing interest in using NGS as a potential alternative to polymerase chain reaction (PCR)-based tests (6). However, despite the potential advantages of conducting thorough genetic profiling on tumour tissue to detect actionable mutations and targeted therapies, there is an ongoing discussion about the practicality and clinical value of incorporating NGS into everyday clinical practices (7,8). Numerous obstacles remain, including the absence of extensive cohort studies focusing on specific solid tumour types, the complexity of interpreting results, the substantial expenses involved and the necessity for a multidisciplinary oncology tumour board to effectively evaluate these tests for decision-making purposes (9,10). Whilst NGS holds the potential to mitigate these challenges by circumventing misguided therapies and their corresponding expenses, it remains crucial to evaluate its practical clinical application via comprehensive multi-centre research studies (11,12).

Another caveat to consider is that utilizing NGS alone may not consistently produce actionable data in a significant percentage of cases (13). This was exemplified in a previous study that analyzed the molecular profiles of 1057 advanced cancer samples, revealing that a mere 6.6% of treatment decisions were based solely on NGS (3). However, when data from additional tests, such as immunohistochemistry (IHC) and other molecular analyses, were either assessed individually or integrated with NGS, the percentage of treatments informed by molecular data dramatically climbed to 93.4% (3). This approach of combining NGS with other molecular tests is known as complex molecular profiling (3). In accordance with the findings of Laes et al.'s research (3), preliminary data from a real-world precision medicine platform, MONDTI, revealed that complex molecular profiling informed targeted therapy recommendations for 55.6% of the 295 patients involved in the study (14). However, only a meagre 16 of these recommendations were solely based on the NGS panel (14).

In an effort to elucidate the clinical relevance of NGS, either standalone or in combination with complex molecular profiling, we conducted a comprehensive, multi-centre, real-world study. This research utilized aggregated data from the Turkey Molecular Profiling in Advanced Cancers Trial (TUMPACT), which combines molecular profiling results with clinical outcomes in patients with advanced solid tumours. Our primary focus was to delve into the potential influence of complex molecular profiling on the formulation of therapeutic decisions or modifications. Subsequently, we assessed how these informed choices influenced patient responses to treatment.

Patients and methods

Study population

TUMPACT is a comprehensive multi-centre study conducted in Turkey, designed to evaluate the effectiveness and influence of complex molecular profiling in the routine clinical management of patients with advanced solid tumours. This research involved the participation of 234 adult patients (mean age: 52.7 ± 14.3 years, 54.7% women) diagnosed with solid tumours at 21 diverse Turkish facilities. The study utilized an OncoDNA (Gosselies, Belgium) platform (OncoDEEP) integrating NGS with additional tests to harvest complex molecular profiling data (3). Initiated in October 2018, the study concluded in March 2020. Eligibility criteria included patients who had readily available formalin-fixed paraffin-embedded (FFPE) archival tumour tissue (from the primary tumour site or a metastatic lesion) and had provided consent for genetic profiling during their routine clinical visits. The patients' performance status (PS) was determined using the Eastern Cooperative Oncology Group (ECOG) scale (15). Only patients with ECOG scores of 0 (completely active, unrestricted pre-disease performance) or 1 (limited in rigorous physical activity but ambulatory and capable of performing light or sedentary work, such as light housekeeping or office tasks) (15) were deemed eligible. The study protocol followed the principles set forth in the Declaration of Helsinki, and approval was granted by the institutional ethics committee at each participating centre. Moreover, we secured written consent from patients for the use of their data for publication purposes.

Data collection

The study collected patient data from clinical records. In addition, detailed tumour characteristics such as cancer type and metastasis status were recorded. We also took note of concurrent diseases, complex molecular profiling details (including the type of test and its findings) and treatment characteristics. This included information about past and present anticancer treatments, the line of therapy and any modifications made by oncologists based on complex molecular profiling reports. Treatment responses were documented for each patient. For the purpose of analysis, upper gastrointestinal cancers included oesophageal, stomach, pancreatic, duodenal, gall bladder, bile duct, liver and small bowel cancers. Conversely, lower gastrointestinal cancers included colon, rectal and anal cancers.

Complex molecular profiling

DNA extractions were performed on FFPE tissue and blood samples, using the Qiagen DNA FFPE Tissue Kit and Qiagen DNA Blood Mini Kit, respectively (Qiagen, Valencia, CA, USA). The quantity of DNA extracted was then measured via the Qubit 2.0 Fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). To detect somatic mutations in tumour samples, we employed a custom AmpliSeq panel designed to amplify via NGS. This platform covered 313 genes, which included hot spot variants and whole exons, based on the updated version of the Ion AmpliSeq Cancer Hotspot Panel version 6 (Supplementary Table 1), known as OncoDEEP (3). The targeted sequencing libraries were generated in compliance with the manufacturer's instructions, using the Ion AmpliSeq Library kit 2.0 (Thermo Fisher Scientific). Our starting material comprised 10 ng DNA from the FFPE samples. The amplification primers were partially digested using the *Pfu* enzyme. This digested product was then ligated with matching barcoded adapters and purified with Ampure Beads (Agilent Technologies, Santa Clara, CA, USA). Following a further five amplification cycles, the product was once again purified using Ampure Beads. The libraries underwent quality evaluation using the Qubit dsDNA HS Assay kit (Thermo Fisher Scientific). To initiate the emulsion PCR, we introduced 10 pM of each library into the IonChef system (Thermo Fisher Scientific) and subsequently transferred it onto the chip. Our primary goal was to attain an average coverage of ×1000 to enable the identification of variants as low as 5 and 1% from the hot spot list. The sequencing process was carried out using the 5XL device (Thermo Fisher Scientific), with the device selection based on the required throughput. In addition to NGS, OncoDEEP integrates additional tests like IHC and molecular analyses such as O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation. This approach, known as PACKAGE PLUS (3), ensures a comprehensive and tailored analysis for each tumour type—potentially enabling more accurate and personalized treatment recommendations.

Outcome measures

Complex molecular profiling results were analyzed in relation with two specific outcomes: (i) the impact on therapeutic decisions, including formulation or modifications, and (ii) the associated treatment response. A questionnaire concerning therapy guided or altered by molecular profiling was electronically sent to oncologists 3 months after they received the laboratory results (3). Treatment response was evaluated using the established guidelines from the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (16). Responses were categorized into four distinct groups: complete remission (CR), partial remission (PR), progressive disease (PD) and stable disease (SD) (16).

Statistical analysis

Data are expressed using descriptive statistics (means, standard deviations, medians, ranges, counts and percentages). The distribution of categorical variables was examined with the chi-squared test or the Fisher's exact test when the expected cell count was lower than five. Analyses were performed using SPSS for Windows, version 24.0 (IBM, Armonk, NY, USA), with all tests two-sided at a 5% level of significance.

Results

Patient characteristics

Table 1 depicts the general characteristics of the 234 study patients. In the study cohort, the most frequently observed types of solid organ malignancies, with a prevalence rate exceeding 10%, comprised upper gastrointestinal cancer at 29.5%, breast cancer at 17.5%, lung cancer at 16.2% and lower gastrointestinal cancer at 11.5%. A significant 67.9% of patients displayed metastasis at the time of diagnosis, with the liver, at 35%, being the most frequently observed metastatic site. In addition, comorbidities were present in 28.2% of the study patients. Out of the study participants, 36.4% succumbed to their illness after an average follow-up period of 18 months.

Table 1. General characteristics of the study participants ($n = 234$)

Variable	Count (%)
Mean age at diagnosis (SD), years	52.7 (14.3)
Median age at diagnosis (min–max), years	54.0 (18–90)
Sex	
Female	128 (54.7)
Male	106 (45.3)
Hospital type	
Private	206 (88.0)
Other	28 (12.0)
Comorbidities ($n = 234$)[a]	66 (28.2)
Type of co-morbid diseases ($n = 98$)[a]	
Hypertension	26 (26.5)
Diabetes mellitus	25 (25.5)
Other diseases	47 (48.0)
Cancer type	
Upper gastrointestinal cancer	69 (29.5)
Breast cancer	41 (17.5)
Lung cancer	38 (16.2)
Lower gastrointestinal cancer	27 (11.5)
Sarcoma	12 (5.1)
Endometrial cancer	9 (3.8)
Ovarian cancer	9 (3.8)
Head and neck cancer	5 (2.1)
Primary unknown origin	4 (1.7)
Glioblastoma	3 (1.3)
Renal cell carcinoma	3 (1.3)
Bladder cancer	2 (0.9)
Brain cancer	2 (0.9)
Cervix cancer	2 (0.9)
Neuroendocrine cancer	2 (0.9)
Prostate cancer	2 (0.9)
Adenoid cystic cancer	1 (0.4)
Gastrointestinal stromal tumour	1 (0.4)
Sinonasal tumour	1 (0.4)
Testicular cancer	1 (0.4)
Metastasis at diagnosis	159 (67.9)
Metastatic sites ($n = 217$)[a]	
Liver	76 (35.0)
Lung	42 (19.4)
Bone	31 (14.3)
Lymph nodes	23 (10.6)
Other sites	45 (20.7)
Biomarker investigation before complex molecular profiling	81 (34.6)

Data are presented as counts and percentages in parentheses, unless stated otherwise.

[a]The alphabet represents the number of patients for whom the specific variable was available. Abbreviations: SD, standard deviation; min, minimum; max, maximum.

Table 2. Treatment-related characteristics of the study participants ($n = 234$) before complex molecular profiling

Variable	Number (n)	Percentage (%)
Previous therapy ($n = 232$)[a]		
Metastatic	144	62.1
Adjuvant	15	6.5
Neoadjuvant	6	2.6
Current anticancer therapy ($n = 226$)[a]		
Metastatic	165	72.9
Lines of therapy before complex molecular profiling ($n = 232$)[a]		
None	38	16.4
1	51	22.0
2	82	35.3
3	34	14.7
4	17	7.3
5	10	4.3

[a]The alphabet represents the number of patients for whom the specific variable was available.

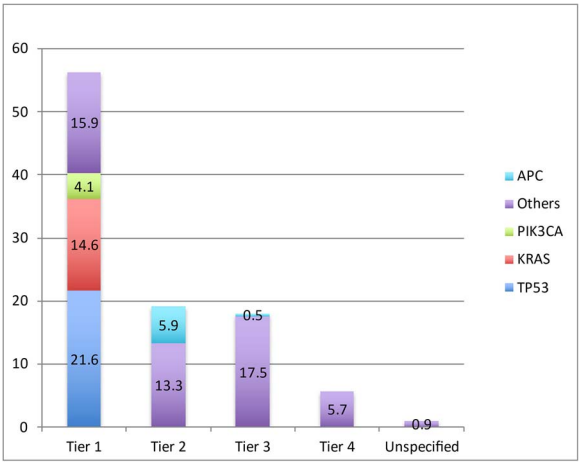

Figure 1. Distribution of molecular alterations according to their pathogenicity. The pathogenicity of molecular alterations was categorized into four tiers: tier I (variants with strong clinical significance), tier II (variants with potential clinical significance), tier III (variants of unknown clinical significance) and tier IV (variants deemed benign or likely benign). The *TP53, KRAS, APC* and *PIK3CA* genes exhibited the highest number of mutations.

Baseline treatment characteristics

Table 2 summarizes the treatment characteristics of patients prior to receiving complex molecular profiling. A significant majority, 82.9%, had received treatment prior to testing, and of these, 70.5% were undergoing therapy at the time of testing. At the time of complex molecular profiling, 87.3% of the study patients were receiving therapy for metastatic disease, whilst 9.1 and 3.6% were undergoing adjuvant and neoadjuvant therapy, respectively. A small percentage of patients (16.1%) had not received any treatment before profiling. The remaining patients had undergone a median of two therapeutic lines.

NGS and complex molecular profiling results

The mean time required for obtaining the complex molecular profiling report was 15.3 ± 8.6 days (median: 14 days; range: 5–71 days) from the date of sample dispatch. Out of the total 234 tests conducted, 138 (59.0%) were carried using PACKAGE PLUS (i.e. complex molecular profiling), whilst the remaining 96 (41.0%) were performed using NGS alone. Final molecular profiling data were available for 228 patients (97.4%).

Spectrum of molecular alterations

Amongst the 228 patients with available molecular profiling results, a significant majority ($n = 172$; 75.4%) exhibited at least one detectable molecular aberration. A total of 400 molecular alterations were identified, with 30 being copy number variations (amplifications or losses) and the majority ($n = 370$) consisting of single nucleotide variants (SNVs) and multi-nucleotide variants (MNVs). The pathogenicity of these alterations was categorized into four tiers: tier I (variants with strong clinical significance), tier II (variants with potential clinical significance), tier III (variants of unknown clinical significance) and tier IV (variants deemed benign or likely benign) (17). Out of the 370 SNVs/MNVs, their distribution amongst the tiers was as follows: tier I ($n = 208$; 56.2%), tier II ($n = 71$; 19.2%), tier III ($n = 67$; 18%) and tier IV ($n = 21$; 5.7%). The pathogenicity of the remaining three variants (0.9%) was unspecified. The *TP53*, *KRAS*, *APC* and *PIK3CA* genes exhibited the highest number of mutations (Fig. 1). All variants in *TP53* ($n = 80$), *KRAS* ($n = 54$) and *PIK3CA* ($n = 15$) genes were classified as tier I, indicating their pathogenic significance. Conversely, the *APC* gene exhibited a different distribution with 22 tier II and 2 tier III variants.

Complex molecular profiling results in relation to treatment decision or modification

Out of the 228 patients with final molecular profiling results, 118 (50.4%) had their treatment modified, whilst the remaining 110 (47.0%) did not. Amongst the 138 patients who underwent PACKAGE PLUS (i.e. comprehensive molecular profiling), 29 (24.6%) had their treatment decisions or modifications influenced by the results. Similarly, amongst the 96 patients who only had NGS performed, 89 (75.4%) experienced treatment decisions or modifications based on the results obtained. NGS either with or without PACKAGE PLUS resulted in a substantially higher likelihood of treatment decision-making or modification in patients with breast cancer as compared with all other solid cancer types (65.9 versus 46.1%, respectively; $P = 0.032$). However, we found no statistically significant difference in the implementation of genetic-informed treatments based on the line of therapy. The likelihood was 48.8% for zero to two lines of therapy as opposed to 59.7% for more than two lines of therapy ($P = 0.094$).

Complex molecular profiling results in relation to treatment response

The response rates were comparable, with 3.9 versus 3.4% for CR, 13.6 versus 29.3% for PR, 66.9 versus 51.7% for PD, and 15.5 versus 15.5% for SD for treatments informed and not informed by complex molecular profiling, respectively ($P = 0.16$).

Discussion

The results of the TUMPACT study revealed that the implementation of complex molecular profiling through the OncoDEEP

platform influenced or altered the treatment decisions made by oncologists for 50.4% of the examined patients with advanced solid tumours. This was particularly noticeable in those diagnosed with breast cancer. Unfortunately, there was no substantial advantage observed in relation to treatment response or disease control rates.

The role and effectiveness of NGS panels in guiding therapy for advanced cancer patients remains a subject of ongoing debate. Notably, the central issue still revolves around the extent to which they can influence the clinical course of treatment in everyday clinical settings (8–11). Recently, Colomer et al. (18) conducted an analysis of real-world outcomes following NGS testing and presented compelling evidence that genomic profiling may not provide significant value in cases involving poor PS, rapidly progressing cancer, short life expectancy or absence of standard therapeutic options. The results we have acquired from our current cohort, where nearly 67.9% of patients exhibited metastasis at diagnosis and 36.4% sadly succumbed to their illness within an average follow-up period of 18 months, align substantially with the findings of this study (18). In addition, the European Society for Medical Oncology (ESMO) Precision Medicine Working Group recommends the use of NGS panels for selected cases with metastatic malignancies, specifically in NSCLC, cholangiocarcinoma, prostate and ovarian cancers (6). Our study cohort consisted mainly of upper gastrointestinal cancer (29.5%), breast cancer (17.5%), lung cancer (16.2%) and lower gastrointestinal cancer (11.5%). Therefore, it is not surprising that we observed a minor impact of complex molecular profiling on treatment response. In addition, a substantial 82.9% of patients in the TUMPACT study had undergone treatment before testing, typically after a median of two therapeutic lines. Due to the implementation of molecularly informed therapy as a later-line treatment option, the influence of NGS results on therapeutic outcomes was likely not immediately observable for a considerable number of patients. Collectively, in our multi-centre investigation, which included a diverse group of patients with advanced solid tumours, we have found evidence to support an individualized, rather than generalized, approach to complex molecular profiling in clinical settings. Nevertheless, it is incumbent upon academic research centres to catalyse innovative treatment approaches by integrating NGS into their research objectives (6).

In the course of this study, out of the 96 patients who underwent only NGS, a significant majority (75.4%) had their treatment strategies adjusted based on the results procured. This illustrates the substantial influence NGS has on treatment decisions when used in isolation. However, a noteworthy finding is that the integration of PACKAGE PLUS resulted in therapeutic modifications for an additional 29 patients, whose treatment plans would have remained unchanged with solely NGS results. This implies that PACKAGE PLUS was successful in identifying certain molecular attributes that NGS could not effectively capture, thus affecting the treatment decisions for these individuals. Essentially, PACKAGE PLUS could potentially broaden the scope of targeted treatment beyond what NGS alone can offer (3). Despite these intriguing results, the study did not shed light on immediate clinical implications in terms of treatment responses. As such, more extensive analysis is necessary to comprehend the clinical outcomes and cost-effectiveness of incorporating PACKAGE PLUS into the treatment decision-making process. Future research in this direction will be instrumental in ascertaining whether the advantages of integrating PACKAGE PLUS surpass the expenses and if its utilization should be expanded in clinical practice.

The concept of 'actionability' has surfaced as a pivotal factor in discussions concerning the clinical usefulness of NGS (19–21). As per the findings of our study, the genes most commonly mutated in advanced solid tumours were identified as *TP53*, *KRAS*, *APC* and *PIK3CA*. Of special note is that all variations found in the *TP53*, *KRAS* and *PIK3CA* genes were categorized under tier I (17), underscoring their substantial pathogenic significance. The *TP53* gene, commonly considered as 'undruggable', is known to lose its standard functions frequently, triggering a chain reaction of signalling pathways that promote tumour growth and compensate for the loss of its original functions (22). Nevertheless, considerable research efforts are currently underway to target *TP53* by reinstating the functions of the wild type p53 protein and eliminating the mutant p53 (22). *KRAS* mutations were, for an extended period, deemed as non-targetable alterations (23). However, recent early clinical trial results, preceded by preclinical studies, have shown that the pharmacological inhibition of the *KRAS* G12C mutated protein is plausible, paving the way for new targeted treatments (24). Pathogenic *PIK3CA* mutations can be theoretically addressed through the kinase inhibitor alpelisib (25). Alpelisib specifically targets PI3Kα, and its application across various solid cancer malignancies is currently under scrutiny (26). The observation that most of the cancer driver mutations identified in the current investigation were not easily actionable provides an additional explanation for the limited impact of complex molecular profiling on patient outcomes.

Our study has several limitations that should be considered when interpreting the findings. Although we utilized molecular profiling as a unifying feature, a diverse array of tumours, disease stages and therapies were included. We are aware that this approach may lead to methodological criticisms from proponents of molecular profiling. However, we believe that our research provides a valuable counter-narrative reflecting the real-world scenario of Turkish hospitals. Conversely, our results shed light on the potential for molecular profiling to potentially make significant strides in more controlled clinical environments, encompassing more uniform patient groups and specific clinical situations where molecularly actionable targets may be anticipated. In addition, this investigation was not designed as a cohort study, and as such, we were unable to conduct a cost-effectiveness analysis or an evaluation for decision-making. Our results should be simply viewed as descriptive of a multi-centre Turkish experience aimed at clarifying whether molecular profiling may provide clinically significant improvements in an everyday scenario in the oncology clinic. Notably, subgroup analyses performed on breast cancer, cholangiocellular carcinoma and lung cancer still yielded negative results (data not shown). However, we acknowledge that this could be due to an insufficient number of patients in each tumour subgroup. In this study, we opted to utilize the PACKAGE PLUS approach—which combines NGS with IHC and other tests—based on the hypothesis that employing different techniques could offer more comprehensive information to assist oncologists in making clinical management decisions in routine practice. However, we recognize that the use of different commercial packages can significantly impact the implications of molecular profiling in clinical practice. Although a comprehensive central pathology review was conducted to ensure precise diagnosis and confirmation for all cases included in our investigation, the real-world nature of the study setting introduced variability in the origin of analyzed samples. This aspect, which includes some samples taken from metastatic sites, could potentially impact the generalizability and reliability of our findings. Furthermore, the assessment of molecular profiling's impact on treatment was based solely on the presence or absence of related

treatment decisions or adjustments. However, it did not include information on the specific molecular-based treatments that were recommended and actually implemented. Secondly, a majority of the patients in our study had already undergone at least two lines of systemic therapy and were diagnosed with metastatic disease. This could potentially affect their eligibility for further therapy when the results of molecular testing were reported. Lastly, all the patients were from a single country with limited ethnic diversity. These factors might restrict the applicability of our findings to other populations.

In conclusion, our real-world findings highlight the significant impact of complex molecular profiling on the treatment decisions made by oncologists for a substantial portion (50.4%) of patients with advanced solid tumours. Regrettably, no significant advantage was detected in terms of treatment response or disease control rates. It could be posited that patients battling advanced malignancies, even those with an optimal PS, should be selectively subjected to complex molecular profiling, adhering to the guidelines set by the ESMO. Whilst the utility of profiling in enhancing the clinical trajectory of unselected patients remains questionable, these findings warrant validation through more extensive prospective studies.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Ethical statement

The study protocol followed the principles set forth in the Declaration of Helsinki, and approval was granted by the institutional ethics committee at each participating centre. Moreover, we secured written consent from patients for the use of their data for publication purposes.

Conflict of interest statement

None declared.

Collaborators

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