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Research article

Evidence blocks for effective presentation of genomic findings at molecular tumor boards: Single institution experience

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A B S T R A C T

Genomic profiling, or molecular profiling of the tumor, is becoming a key component of therapeutic decision making in clinical oncology, and is typically carried out via next generation sequencing. However, the interpretation of the results and evaluation of rationale for targeting the uncovered alterations is challenging and requires a deep understanding of cancer biology, genetics, genomics and oncology. Multidisciplinary molecular tumor boards represent a promising strategy in the facilitation of molecularly-informed therapeutic decisions, and usually consist of specialists with various fields of expertise. To effectively communicate the biological and clinical significance of genomic findings, as well as to make molecular tumor board discussions more productive, we developed and implemented evidence blocks into case discussions in our center. We found that this approach facilitated clinicians' understanding of the results of genomic profiling, and resulted in shorter yet more efficient case discussions within the molecular tumor board. Here, we discuss our experience with evidence blocks and how their implementation influenced the molecular tumor board practice.

1. Introduction

In the era of precision oncology, genomic profiling of the tumor is becoming increasingly relevant for therapy selection in various

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tumor types. Next generation sequencing (NGS) is capable of identifying thousands of mutations, including novel mutations. The European Society for Medical Oncology (ESMO) guidelines recommend that comprehensive genomic profiling via NGS should be performed for a range of tumor types, including metastatic non-small cell lung cancer, prostate, ovarian cancer and cholangiocarcinoma [**1**] as well as other tumor types. The interpretation of the genomic findings requires extensive expertise in cancer genomics, genetics, as well as understanding of oncology and mechanisms of action of various antineoplastic drugs. Existing databases [1–4] and level of evidence (LOE) systems [5,6] are widely used to rank genomic results. However, the utility of these approaches might be limited due to high heterogeneity of data [7]. Molecular tumor boards (MTB) represent a promising strategy in the facilitation of molecularly-informed therapeutic decisions, and usually consist of specialists with various fields of expertise, including geneticists and biologists. Discussion of genomic findings can be time-consuming and difficult for those without expertise in genomics. The National Comprehensive Cancer Network (NCCN) utilizes evidence blocks (EB), a graphical representation of the panel's recommendations in regard to the therapeutic intervention in question [8], which indicates the promise of this approach. Therefore, schematic solutions for efficient and comprehensive presentation of genomic findings are essential for productive discussions at MTB.

2. Materials and methods

This is a retrospective study evaluating the clinicians' experience with the use of evidence blocks at a local MTB.

The EB system was developed by a multidisciplinary group of biologists and oncologists with broad expertise in precision oncology. The proposed EB system was then established on the basis of expert consensus from the working group and consideration of the available evidence (including treatment guidelines, published literature, knowledge bases, etc.). The interpretation of genomic findings for EB is performed in accordance with community guidelines [9,10]. The methodology used for the shading of EB is described throughout the manuscript. Currently, EB are shaded following a preliminary discussion between biologists involved in our MTBs.

EB were used at MTBs held as part of routine clinical care from September 2022 to May 2023. MTBs were initiated upon request from the treating oncologist. The request was referred to an MTB secretary, who communicated with all MTB members. Biologists and the treating oncologist (presenting clinician) presented the patient's case and molecular findings, which was followed by a multidisciplinary discussion and a formulation of a treatment plan. Throughout the preparation for (including EB) and the course of MTB, de-identified patient information is used (age and sex, physician's name, diagnosis and date of diagnosis, treatment history, biopsy site and date, molecular test used, molecular profile results, and comments). To evaluate the impact of EB on MTBs, we conducted an online survey of oncologists who participated in the MTB discussions of at least 3 patients. Oncologists with all levels of expertise in cancer genomics were asked to complete the survey. Questions assessed perceived the oncologists' understanding of genomic profiling results and their implementation into clinical practice. For statistical analysis, we used a non-parametric Mann–Whitney *U* test.

An ethics statement is not applicable because this study uses only non-identifiable data and of negligible risk as far as results are based solely on survey of small group of physicians. This study was performed in accordance with the declaration of Helsinki. De-identified patient information was used for MTBs. MTB adhered to all HIPAA and local privacy laws. All patients referred to MTB provided informed consent. The respondents' answers were used anonymously.

3. Results

3.1. The overview of evidence blocks for MTB

To effectively communicate the biological and clinical significance of genomic findings and assist clinicians with further decision-making, we developed and implemented EB into MTB practice in our center.

The blocks are divided into three major parts representing the biological and clinical rationale for targeting the observed alteration, as well as the availability of relevant therapy (Fig. 1).

Each column reflects different measures of the evidence supporting biomarker-drug association. Column **O** reflects the level of

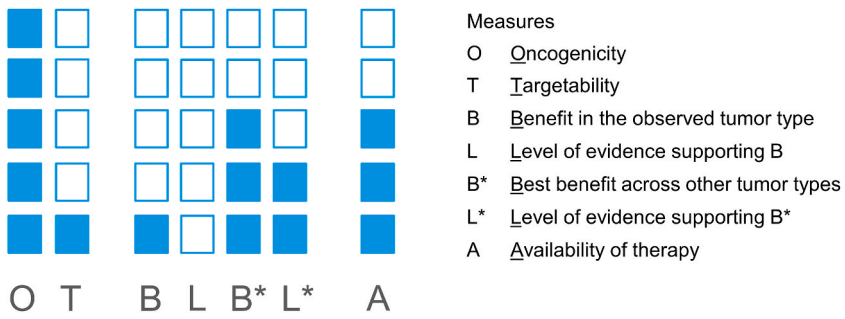

Fig. 1. Example of evidence blocks for a biomarker-drug class pair, and the corresponding measures that are reflected in the blocks. More shading reflects more confidence in the evidence supporting the effect of alteration and the feasibility of targeting the biomarker. In this example, the evidence blocks reflect the evidence supporting the rationale for targeting a deletion of RAD54D by PARP inhibitors in a patient with colon adenocarcinoma.

confidence of activating/deleterious (for oncogenes/tumor suppressor genes, respectively) effect of the alteration, **T** - Feasibility of targeting the observed biomarker (by relevant molecularly matched therapy for the specific patient) as well as the necessity of targeting of the observed biomarker to suppress carcinogenesis. Columns **B-L*** reflect the rationale (with the consideration of available evidence and potential benefit of molecularly-matched therapy) for targeting the observed biomarker based on published data (including results of clinical studies, retrospective studies, case reports, preclinical and biological evidence). Specifically, the columns are as follows: **B** - Expected magnitude of clinical benefit of the drug in question in the context of the observed biomarker in the observed tumor type; **L** - LOE supporting biomarker-drug pair in the observed tumor type; **B*** – Best magnitude of benefit for the biomarker–drug pair anticipated across other tumor types; **L*** – Best LOE supporting the biomarker-drug pair across other tumor types. Finally, column **A** represents the availability of the drug, considering the in-label and off-label indications for use, as well as available clinical trials.

3.2. How different measures are impacted by data

The scoring system used to fill in the blocks is similar to the one used by NCCN [8], with shading of more blocks indicating the better score of each measure considered. EB are prepared following the literature search prior to the MTB, as well as the interpretation of all genomic findings reported following comprehensive genomic profiling.

Shading of blocks in the **O** column reflects the anticipated functional effect of the observed alteration, which is based on the analysis of relevant literature and estimation of oncogenicity as per community guidelines [9,11]. Noteworthy, this column only provides information regarding the observed variant and its impact on the tumorigenesis, and does not consider the patient's tumor type or the effect of molecularly-matched therapy. For tumor suppressors, the deleterious effect of the alteration is considered, whereas for protooncogenes the activating effect (i.e., the increase of the protein or signaling cascade activity, or known oncogenicity of the variant) is measured. The shading of all five blocks corresponds to the very high probability of the oncogenic effect of the observed alteration (e.g. BRAF p. V600E, BRCA1 p. Q1777fs), whereas the shading of zero blocks reflects the lack of the oncogenic effect (e.g. synonymous genetic variations). Shading of three blocks corresponds to variants of unknown significance (VUS), two blocks indicate a likely non-oncogenic alteration, and shading of four blocks indicates a likely oncogenic alteration.

Shading of the **B** and **B*** reflects the expected benefit of the therapy in question, considering the patient's tumor type and the efficacy of previous therapy, where applicable (for instance, platinum sensitivity might influence the recommendation of PARP inhibitors). The shading of blocks in this column is based on the expected magnitude of benefit of the molecularly-matched therapy in comparison with standard of care (SoC) and/or historical control (HC). One block is shaded when the expected magnitude of benefit of molecularly-matched therapy is comparable to SoC/HC; two shaded blocks reflect the expected improvement in disease stabilization; three blocks reflect the expected improvement of objective response rate; shading of 4 and 5 blocks corresponds to the anticipated improvement in progression-free survival (PFS) and overall survival (OS), respectively, of molecularly-matched therapy as compared to SoC/HC. In cases when level of evidence is low (L and L* columns, see below) or contradicting results of clinical/pre-clinical studies, this column might be shaded based on a subjective opinion of an expert biologist regarding this alteration-drug pair, considering the results of therapy in question in other tumor types or for functionally similar alterations in this or other members of the signaling cascade.

Consistently, shading of the columns **L** and **L***, reflecting the LOE for the biomarker-drug pair in question, for the observed tumor type and across other tumor types, is as follows - shading of zero blocks corresponds to LOE X, of one block - ESCAT IV, two blocks - ESCAT IIIB, three, four and five blocks - IIIA, II and I, respectively, according to the ESCAT [5].

Shading of the column **T** is dependent on the measures reflected in the **O**, **B**, **L**, **B*** and **L***, as well as on tumor context considering the possibility that the observed alteration is the driving event and not passenger. This column reflects the subjective opinion of an expert biologist on whether the observed biomarker should be targeted by relevant therapies, and is based on the shading of O, B, L, B*, L* columns.

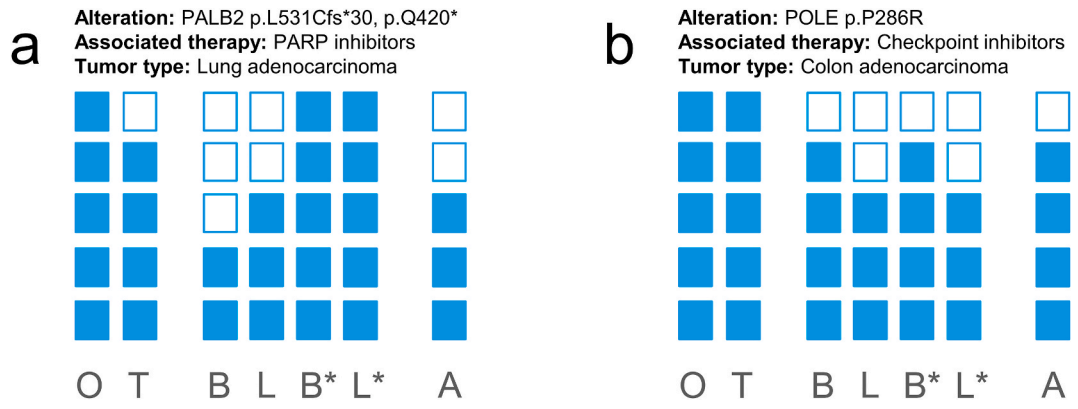

Fig. 2. Examples highlighting the use of evidence blocks at molecular tumor board: a - a case of lung adenocarcinoma with two coexisting deleterious mutations of the PALB2 gene; b - a case of POLE-mutant colon adenocarcinoma.

Finally, shading of zero blocks in column **A** reflects that the drug is undergoing evaluation in clinical trials, and is not currently available for off-label use. Shading of five blocks corresponds to the observed biomarker-drug pair being the standard of care in the observed tumor type.

3.3. Evidence blocks at our MTB

To illustrate how EB facilitate MTB discussion and consecutive decision-making, we will discuss two examples of EB (Fig. 2).

The first example is a case of PALB2-mutant lung adenocarcinoma (Fig. 2a). The presence of two distinct deleterious mutations, one of which is a known founder mutation [12], suggested the biallelic inactivation of PALB2. These events were considered oncogenic, resulting in the shading of all 5 blocks in the O column. PARP inhibitor therapy is considered standard of care for patients with PALB2-mutant prostate cancer, however data on the effect of PARP inhibitor therapy for PALB2-mutant lung adenocarcinoma is limited. Results of several trials demonstrate moderate efficacy of PARP inhibitors in the treatment of homologous recombination deficiency (HRD)-positive non-small cell lung cancer [13–15]. Therefore, two and three blocks were shaded in the B and L columns, respectively, and all 5 blocks were shaded in both B* and L* columns. Altogether, the functional effect of alterations, promising results of PARP inhibitor activity against PALB2-mutated tumors, as well as evidence for antitumor activity of PARP inhibitors in NSCLC, resulted in the shading of four blocks in the column T. Lastly, since PARP inhibitors are not routinely used for the treatment of NSCLC, three blocks were shaded in column A.

On Fig. 2b, the EB for POLE mutation found in a colon adenocarcinoma sample and its association with checkpoint inhibitors are presented. This mutation is a hotspot loss-of-function mutation affecting exonuclease activity and causing high tumor mutational burden [16,17]. Therefore, this alteration was considered oncogenic, as reflected in the O column. Retrospective studies show that patients with POLE-mutant solid tumors, including colorectal cancer, are sensitive to checkpoint inhibitors [18], however, this is not a standard of care approach. Based on the functional consequences of the alteration and expected high magnitude of benefit of checkpoint inhibitors, all blocks in the T column are shaded. Lastly, since checkpoint inhibitors are approved for the use in patients with colorectal cancer based on other molecular profiles, four blocks are shaded in column A.

3.4. Clinicians' feedback on how evidence blocks influence the decision making

To understand specific aspects of EB that clinicians find the most useful, we surveyed 7 oncologists, resident experts at our MTB. We asked experts to rank their perceptions of several key aspects of EB in the form of a questionnaire (Supplementary file). Overall, all oncologists agreed that the use of EB clarifies the understanding of the genomic profiling results (Fig. 3a). Similarly, the majority (85.6

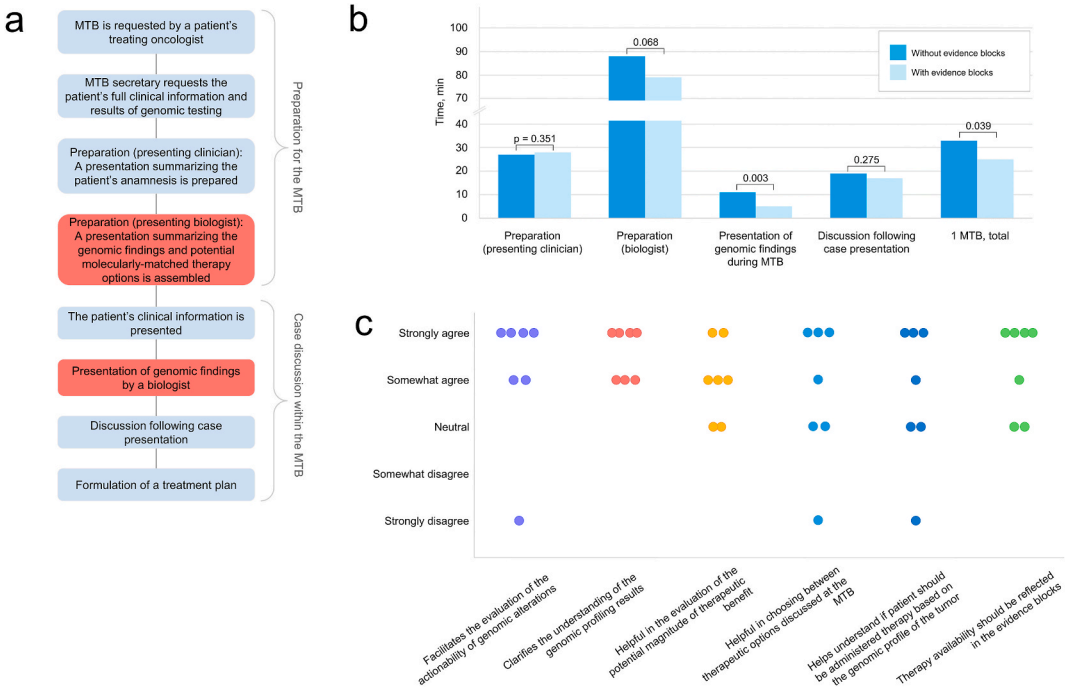

Fig. 3. Our experience with the implementation of evidence blocks (EB) at molecular tumor board (MTB) discussions: a - an overview of an MTB workflow (steps where EB are utilized are highlighted in red); b - the implementation of EB resulted in a more time-efficient MTB discussion while not significantly affecting the preparation time; c - clinicians' perception of the EB (color coding is used to indicate answers to different questions in the survey). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

%) of the respondents agreed that the use of EB facilitates the evaluation of the actionability of genomic alterations during discussion within MTB (Fig. 3c). Most oncologists (71.5 %) agreed that the use of EB is helpful in the evaluation of the potential magnitude of therapeutic benefit. When evaluating whether EB influence the understanding of whether the patient should be administered therapy based on the genomic profiling results, 57.1 % of the respondents found EB useful, while 26.3 % of respondents remained neutral and 14.3 % strongly disagreed. The majority of the experts (57.1 %) agreed that the use of EB helps them choose between therapeutic options discussed at the MTB. Finally, 5 (71.5 %) respondents agreed with the need for the reflection of therapy availability.

3.5. *The use of evidence blocks results in a quick and efficient case discussion*

The use of EB significantly reduced time required to present the genomic findings, as well as improved the clinicians' understanding of their effects (Fig. 3b). 15 and 27 cases were discussed at the MTB, prior to and following the implementation of EB, respectively. Consistent with the practice of other cancer centers, our MTB includes oncologists, molecular biologists, clinical geneticists and bioinformaticians [19,20]. At our cancer center, prior to the MTB, the oncologist and biologist prepare a presentation describing the patient's case and genomic findings. During MTB, first presenting oncologist and biologist share their presentations, which is followed by a multidisciplinary discussion, where further treatment strategies and management plans are formulated for each patient. Typically, prior to the implementation of EB, each case required an average of 31 min (range 14–52) worth of clinicians' time. With the use of EB, biologists were able to present genomic information more effectively, limiting their presentation to a maximum of 4 min, as compared to an average of 14 min prior to the implementation of EB. The time required for multidisciplinary discussion following the presentation of clinical and biological information was reduced by an average of 5 min, and was more comprehensible based on respondents' answers (Fig. 3a). The implementation of EB also influenced the overall time required for a single MTB. The preparatory work required for the presentation of clinical information was not influenced by the implementation of the EB. Time spent assembling the presentation on genomic findings by a biologist did not differ significantly depending on the use of EB, though there was a trend towards reduction of labor time possibly due to workflow structuring (average 88 vs 79 min per case, p-value 0.068). Additionally, the use of EB simplified the perception of genomic information when provided to clinicians beforehand (Fig. 3a). Altogether, implementation of EB resulted in a reduced amount of man hours required for each MTB (average 165 vs 125 h per case). Thus, we believe that EB is an effective and useful tool for MTB.

4. Discussion

With the advances of precision oncology, tumor genomic testing has become a key component for the selection of systemic therapy for various tumor types. For instance, ESMO recommends the use of multigene NGS in non-small cell lung cancer, cholangiocarcinoma, prostate and ovarian cancers [21]. Information derived from tumor genomic profiling can be overwhelming and different to interpret, thus complicating the implementation of test results into clinical practice. MTBs accommodate the translation of the genomic information into clinical practice with the help of multidisciplinary experts, including biologists and geneticists. In this work, we describe our experience with EB used to facilitate the understanding of genomic profiling results at our MTB.

EB provide a visual representation of the evidence behind the biomarker-drug pair, as well as the variant effect and overall expediency for targeting the observed alteration with specific molecularly-matched therapy. Schematic representation of evidence and recommendations has been long used by the NCCN to assist clinicians with decision-making, suggesting that graphic tools might be useful in clinical practice [8]. Levels of evidence (such as OncoKB, ESCAT, etc.) are widely used for ranking of the genomic findings based on the evidence supporting its targetability by relevant therapeutic options [5,6]. However, although informative, this approach is designed to provide only the final conclusion, and not the information regarding the effect of the observed alteration. Typically, a functional effect of a genomic alteration is established following thorough analysis of published literature, assessment of biological considerations (including protein position, domain, *in silico* predictors), genomic context (including the level of mutational load, presence of other driver mutations, etc.), and publicly available knowledge bases (JAX, OncoKB, etc.). Considering these limitations, EB were designed to provide graphical representation of all of the relevant information needed to make an informed decision (such as biological consequences of the observed alteration, the evidence base supporting the biomarker-drug association, levels of evidence, as well as the availability of therapy in question).

Since the EB for every observed potentially targetable alteration are prepared by biologists, we aimed to evaluate clinicians' feedback on the EB. Overall, the majority of clinicians agreed that EB facilitated a general understanding of the genomic findings, clarified the potential for the targetability of the alterations discussed, facilitates decision making regarding indication whether molecularly-matched therapy should be used, and in cases where more than a single targetable biomarker was observed, choose between the suggested options. Noteworthy, this effect did not compromise biologists' preparation time. Therefore, although the time required for case discussions was only moderately reduced, the discussions were more productive due to the significant improvement in clinicians' understanding. Additionally, the implementation of EB at our MTBs did not alter the existing workflow (Fig. 3a), and only influenced the biologists' preparation process, making their preliminary search and, consequently, presentations for MTB, more structured. Additionally, in cases when several potentially targetable alterations are identified, EB may facilitate the decisions regarding combination therapies targeting several. Therefore, we speculate that EB represent a useful tool for efficient MTB discussions.

The proposed EB have several limitations. First, by their nature, EB may only serve as illustrative material, and accompany and enhance the biologist's point of view. Therefore, an oral discussion of all the existing data cannot be eliminated. Next, only a limited number of cases was included in the time-efficiency analysis. Furthermore, although the majority of clinicians agreed that EB are

practical for MTBs, their responses suggest that there is still room for improvement. Additionally, only clinicians who are resident at our MTB were polled, and therefore polling other clinicians from other cancer centers and/or with different levels of expertise in cancer genomics may further diversify the results. Finally, we recognize that even when operating with the same evidence, shading of EB may slightly differ when shaded by different experts or expert groups.

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Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Alexandra Lebedeva: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Olesya Kuznetsova:** Writing – review & editing, Formal analysis. **Maxim Ivanov:** Writing – review & editing, Formal analysis, Conceptualization. **Alexandra Kavun:** Writing – review & editing, Formal analysis. **Egor Veselovsky:** Writing – review & editing, Formal analysis. **Ekaterina Belova:** Writing – review & editing, Formal analysis. **Vladislav Mileyko:** Writing – review & editing, Formal analysis. **Valentina Yakushina:** Writing – review & editing, Formal analysis. **Polina Shilo:** Writing – review & editing, Formal analysis. **Alexey Tryakin:** Writing – review & editing, Formal analysis. **Alexey Rumyantsev:** Writing – review & editing, Formal analysis. **Fedor Moiseenko:** Writing – review & editing, Formal analysis. **Mikhail Fedyanin:** Writing – review & editing, Formal analysis. **Dmitry Nosov:** Writing – review & editing, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Alexandra Lebedeva reports a relationship with OncoAtlas LLC that includes: employment. Olesya Kuznetsova reports a relationship with OncoAtlas LLC that includes: employment. Maxim Ivanov reports a relationship with OncoAtlas LLC that includes: employment. Alexandra Kavun reports a relationship with OncoAtlas LLC that includes: employment. Egor Veselovsky reports a relationship with OncoAtlas LLC that includes: employment. Ekaterina Belova reports a relationship with OncoAtlas LLC that includes: employment. Vladislav Mileyko reports a relationship with OncoAtlas LLC that includes: employment and equity or stocks. Valentina Yakushina reports a relationship with OncoAtlas LLC that includes: employment.

Abbreviations

MTB	Molecular tumor board
NGS	Next generation sequencing
EB	evidence blocks
ESMO	European Society for Medical Oncology
LOE	level of evidence
NCCN	National Comprehensive Cancer Network
VUS	variant of unknown significance
SoC	standard of care
HC	historical control
PFS	progression-free survival
OS	overall survival
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets
HRD	Homologous recombination deficiency

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30303.

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