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The Role of the Molecular Tumor Board: Learnings from the ROME Trial

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Abstract

Precision Oncology transformed cancer therapy by personalizing treatment based on specific tumor molecular alterations. However, the increasing complexity of genomic and multi-omic data challenges clinical interpretation. Molecular Tumor Boards (MTBs) are critical for integrating expertise and translating genomic profiling into treatment recommendations.
The Phase II ROME trial compared personalized therapy, guided by genomic profiling and MTB review, with standard-of-care (SoC) in patients with advanced solid tumors. Between Nov 2020 and Aug 2023, 897 patients were discussed by the MTB, and 400 were randomized. Key drivers for randomization included high TMB, MSI, or actionable alterations, frequently affecting the PIK3CA/AKT/PTEN pathway. Exclusions were mainly due to a lack of actionable alterations or unavailable trial drugs.
The ROME trial demonstrates the substantial role of MTBs in interpreting complex molecular data and driving precision oncology, refining patient selection and optimizing therapy use. The standardization and implementation of MTBs are crucial for improving patient outcomes.
The trial is registered on ClinicalTrials.gov with identifier NCT04591431 and in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) with number 2018-002190-21. The competent authority, Agenzia Italiana del Farmaco (AIFA), authorized the trial on 8 July 2020 (AIFA/SC/P/76132).

INTRODUCTION

The increasing availability of clinical, genomic, environmental, and other relevant data, has enabled personalized therapies in oncology, improving efficacy and reducing unnecessary toxicities and avoidable costs [1]. Recently, the tumour-agnostic model has emerged, in which a single (investigational) agent or combination is used across different tumour types that share a common predictive biomarker.[2] In oncology, basket trials exemplify the agnostic approach[3], leading to histology-independent approvals of agents such as pembrolizumab and dostarlimab for mismatch repair-deficient (MMRd) or microsatellite instability-high (MSI-H) tumors, entrectinib, larotrectinib and repotrectinib for NTRK fusions, selpercatinib for RET rearrangements, the combination of dabrafenib and trametinib for BRAF mutations and trastuzumab deruxtecan for HER2-positive solid tumors, regardless of cancer histology [4–10].

Challenges for individual oncologists to interpret next-generation sequencing (NGS) results and molecular alteration profiles are rapidly increasing. Molecular Tumor Boards (MTBs) bridge this gap by integrating

expertise in clinical oncology, pathology, molecular biology, genetics, pharmacology, and bioinformatics, delivering personalized recommendations based on specific molecular alterations and offering guidance regarding the opportunity to receive innovative treatments or participate in clinical trials [11–13]. Recent consensus guidelines outline workflows and quality indicators for MTBs to ensure standardized, high-quality decision-making [14,15]. Moreover, decentralized prospective MTB platforms have proven feasible at the national level, achieving high genomic profiling success rates and identifying actionable findings in more than 80% of cases [16]. Advances in artificial intelligence, including large language model–driven agents, hold promise for automating literature reviews and enhancing self-learning capacities within MTBs [17,18]. Additionally, MTBs may offer a cost-effectiveness advantage by optimizing the costs associated with the personalization of treatment for patients who have undergone genomic profiling [19].

The ROME trial was a phase II, multicentric, multi-basket, randomized trial, focused on the personalization of oncological treatment based on data derived from extended genomic profiling and MTB evaluation versus non-personalized standard of care (SoC) [20]. Comprehensive details regarding the study characteristics are available in the supplementary materials.

In this paper, we aim to report the operational activities of the MTB within the framework of the ROME trial. Specifically, we delineate its pivotal role in evaluating and managing complex genomic landscapes derived from comprehensive NGS profiling, highlighting the transition from large-scale molecular data to actionable clinical recommendations for personalized patient management.

RESULTS

Between November 2020 to August 2023, a total of 1,794 patients were screened for inclusion in the ROME trial. Of these, 897 patients were discussed during 127 MTB meetings. Following evaluation, 425 patients were proposed for enrolment, and 400 were randomized into the trial across 26 distinct drug or drug combination regimens. Baseline characteristics of randomized patients are outlined in Suppl. Table 1. Enrolment was based on the presence of high-tumor mutational burden (hTMB), MSI, or alterations in specific genes and pathways (Suppl. Fig. 1). Ultimately, 472 patients were excluded from randomization. Consort is provided in Suppl. Fig 2. Additionally, a total of 153 patients received indication for germline testing.

Reasons for Screening Failures

Of the 472 patients not enrolled, 408 (86.4%) were excluded due to a single reason, 54 (11.4%) for two reasons, 9 (1.9%) for three, and 1 (0.2%) for four reasons, respectively. The most frequent reason for exclusion (88 cases – 16.1%) was the detection of rare molecular alterations without supporting scientific evidence for targeted therapy efficacy or identified in tumor types lacking literature-based actionability (Fig. 1 A). Exclusions were based on established literature evidence in 81 cases (14.8%), indicating lack of efficacy of the target drug for the specific tumor–histology–alteration combination (Fig. 1 B). In 80 cases (14.6%), no targetable alterations were detected in either liquid or solid biopsy (Fig. 1 C). Sixty cases (11%) were excluded due to alterations with low variant allele frequency (VAF) (Fig. 1 D). In 54 cases (9.9%), potentially actionable alterations were identified, but the relevant therapy was not available within the trial for logistical/regulatory constraints (E Fig. 1); in five of these, no alternative trials or expanded access programs were accessible nationally. Resistance mechanisms were also a key reason for exclusion: in 44 patients (8%), potentially actionable alterations coincided with established resistance to the corresponding therapy (F Fig. 1). In 43 cases (7.9%), exclusion resulted from access to the investigational

drug being available outside the trial through standard, compassionate, or off-label use (Fig. 1 G). This approach facilitated treatment outside the structured confines of the clinical trial protocol, ensuring direct access for patients to the tailored drug. Twenty-eight patients (5.1%) had previously received targeted therapy for the alteration detected at screening and experienced disease progression (Fig. 1 H). Twenty patients (3.7%) were withdrawn due to worsened clinical conditions requiring urgent intervention (Fig. 1 I). These were patients who reached the MTB discussion phase but became ineligible prior to randomization. Fourteen participants (2.6%) were excluded where standard treatment option had high level of evidence and expected benefit was available (including cases with established biomarker-guided therapies already available in routine practice) (Fig. 1 J). Fourteen further cases (2.6%) were ineligible due to unmet study criteria (Fig. 1 K), nine patients (1.6%) due to discordance between solid and liquid biopsy (Fig. 1 L), seven participants (1.3%) for borderline TMB (Fig. 1 M), and five patients (0.9%) due to medical contraindications (e.g., insufficient data for decision-making) (Fig. 1 N). (Fig. 1 and Suppl. Table 2).

MTB guided inclusion

Among the 400 patients randomized, 198 (49.5%) were selected based on a single targetable alteration, while 202 (50.5%) had multiple potentially targetable alterations. For the latter subgroup, the MTB identified the most likely driver alteration to guide therapy (Fig. 2).

For patients with multiple alterations, in 24 cases (12%) the choice of the target was made for multiple reasons, and 178 (88%) on single reason. Among the patients with multiple alterations, the most prevalent reason (50 cases) for the selection of a specific alteration was that a specific target was prioritized based on the strength of the supporting evidence in the scientific literature, which validated its clinical relevance and therapeutic potential within the given tumor histology. In 30 cases, the identified alterations either affected the same critical molecular pathway, suggesting functional redundancy or pointed to a shared therapeutic vulnerability, thereby guiding the selection of an identical treatment approach. For 22 patients, a specific molecular alteration was deemed non-actionable considering published data that consistently reported treatment failure or demonstrated its role as a biomarker of resistance to the proposed therapy. In 21 cases, the therapeutic option was ruled out because the patient had been previously treated with a therapy targeting that specific alteration and had subsequently experienced disease progression. This clinical history strongly suggested the development of acquired resistance, rendering a repeated therapeutic challenge with a similar agent unlikely to be effective . An alteration was not considered actionable because the VAF was deemed too low for therapeutic targeting or if the TMB fell within a borderline range, failing to meet the established cutoff for predicting immunotherapy response, in 17 cases. For 14 patients, despite the molecular alteration being deemed “actionable”, the corresponding targeted agent was unavailable, both within the scope of the study and via any alternative

access programs. Consequently, despite its potential biological relevance, this finding could not be therapeutically exploited for the patient. In 13 cases, the assessment of an alteration's driver potential involved a comprehensive review of both the overall genomically driven profile, to identify co-existing drivers, and the clinical history, to evaluate responses to earlier lines of therapy. For 11 patients, the alteration was not deemed a viable therapeutic target due to a scarcity of supporting evidence in the scientific literature. This lack of robust, published data precluded a confident assessment of its role as a true oncogenic driver and its potential sensitivity to targeted therapy. In 10 instances, the determination of one alteration over the other was influenced by the concomitant presence of resistance-conferring alterations with the potential to adversely affect the treatment outcome. In 10 cases, given the simultaneous presence of multiple alterations, they were managed collectively by implementing a multi-drug regimen. The rationale was to target distinct oncogenic pathways concurrently, thereby aiming to achieve a synergistic anti-tumor effect and minimize the risk of treatment escape. An alteration was selected specifically as the initial therapeutic target for enabling a sequential therapeutic plan, thereby preserving the option for a subsequent treatment upon disease progression in 10 cases. For 9 patients, an alteration's driver status was ascertained by cross validating its presence between matched solid tissue and liquid biopsy samples. Concordance supported its classification as a primary target, while discordance led to its deprioritization in favour of more robustly detected variants. For 8 patients, the selection of the primary therapeutic target was guided by the class of the molecular alteration itself (for example, presence of amplification rather than mutation or rare mutation with a poorly characterized or unknown predictive value). The significance of an alteration remained uncharacterized due to the absence of supporting data in 3 patients. In 2 cases, an alteration was deprioritized due to patient-specific clinical factors (history of a prior intolerance to the therapy in one case and comorbidities that would not permit treatment in the second case) (Fig 3).

Additional clinical impact of MTB discussion

MTB recommendations had additional impact on patient management beyond trial inclusion: 95 (20% of total excluded patients) were referred for germline genetic testing, 16 (4%) underwent modification of standard therapy based on molecular findings, and 73 (15%) patients gained direct drug access or optimal planning for future treatments. In 54 of these latter cases, actionable molecular alterations were identified, though the corresponding drug was unavailable within the study context. (Fig. 4)

DISCUSSION

Despite the transformative impact of the tumour agnostic treatment paradigm, which has revolutionized the landscape of oncology in recent years, several critical issues remain unresolved. Presence of rare entities or uncommon biomarkers makes randomization impossible, cutting these pathologies out of the possibility of receiving personalized treatment. Moreover, access to treatments is often constrained by the availability of drug approvals from regulatory authorities and by ethical and economic concerns [21].

Beyond the agnostic framework, the molecular model for treatment decision-making enables identification of potential responses to targeted therapies, often guided by pathway-based reasoning in the absence of high-level clinical trial evidence. This model integrates the molecular alterations identified by NGS with the patient's clinical context to support individualized treatment decisions [22].

This comprehensive molecular approach introduces new complexities in data interpretation, particularly when integrating the vast information generated by extended NGS profiling with clinical and histopathological context. In this scenario, MTBs represent a pivotal tool to support clinicians in selecting the most appropriate personalized therapy. Increasingly, MTB deliberations incorporate not only genomic and histological features, but also a range of emerging biomarkers and patient-specific factors (such as gut microbiota, circulating immune profiles, TMB, epigenetic changes, metabolic and nutritional status, lifestyle, comorbidities, and demographic characteristics). These dimensions are recognized as potential modulators of treatment response, and their structured inclusion in MTB workflows can further individualize care. Recent evidence supports the role of expert multidisciplinary review in maximizing the yield of actionable molecular alterations and translating this complexity into clinically meaningful recommendations [16].

The composition of the MTB is pivotal in enhancing the collective knowledge and expertise of the decision-making team. The introduction of tumor boards has generally improved patient outcomes, particularly when the patient's treatment pathway involves genomic analysis, necessitating the involvement of various specialists within the MTB as reported in ESMO Precision Oncology Working Group recommendations [15]. Recent experiences with molecular tumor boards have demonstrated higher rates of matched therapy uptake and improvements in patient outcomes, including prolonged progression-free and overall survival, among patients managed with MTB input. MTB involvement can accelerate decision-making, particularly when virtual or multicenter boards are employed.

In this study, we conducted an in-depth analysis of the Molecular Tumor Board within the ROME trial, examining the decision-making process for each patient discussed. The MTB meticulously reviewed each patient's comprehensive molecular profiling data, alongside their clinical features such as performance status, comorbidities, and previous treatment history, ensuring that therapeutic decisions were tailored to the individual patient's unique genetic and clinical profile. We analysed patients excluded from randomization to better understand the complexity of MTB's decisional process. Deterioration events and specific clinical metrics within the broader screened cohort were not systematically recorded prior to MTB presentation. The unavailability of granular data for the pre-MTB population represents a limitation, as it precludes a full assessment of the cohort's clinical evolution before expert review.

Several patients were theoretically eligible for targeted therapy by algorithmic criteria but were excluded from randomization for multiple reasons, reflecting the complexity of integrating genomic, clinical, and literature data. The MTB process nonetheless proved valuable beyond trial eligibility, frequently guiding germline testing or optimizing standard therapy for excluded patients. In randomized cases, we analysed the criteria used by the MTB to prioritize among multiple actionable alterations.

Our study revealed the pivotal role of the MTB in interpreting molecular data. The involvement of the MTB led to a more refined selection of patients, effectively excluding those with minimal or no likelihood of benefiting from targeted treatments. It is therefore necessary to redefine the setting in which the MTB can be most beneficial, specifically at an earlier stage rather than after the clinical evaluation by an individual oncologist. Early discussion within MTB can assist the clinician not only in interpreting molecular profiling results but also in deciding whether re-biopsy of a lesion is necessary and, if so, at which site. This decision should be based on the individual case, considering the locations of metastases, neoplastic histology, and disease burden. The MTB is also crucial for evaluating whether molecular profiling should be performed on solid tissue, liquid biopsy, or both and if alternative approaches such as

immunohistochemistry and fluorescence in situ hybridization (FISH) complement data obtained from NGS tests. In our trial, the integration of data from both solid and liquid biopsies proved beneficial in patients' selection.

Patient enrolment was based on a single alteration in 54% of the randomized cohort and on multiple alterations in 46%. For patients with multiple alterations, the MTB decision was chiefly guided by the strength of evidence in the literature. The second most common factor influencing target selection was the strategic choice of an alteration within a shared pathway, or one with the potential to indirectly inhibit co-occurring alterations. Previous treatments often affected the selection of a targetable alteration, highlighting the significance of the clinical context for optimal therapeutic choices. This complex decision-making process emphasizes the necessity of an MTB for robust genomic interpretation.

A critical methodological consideration is that the ROME trial did not prespecify a formal endpoint assessing MTB activity per se. The design provides only indirect evidence supporting the clinical utility of the MTB, as it uses clinical outcomes as surrogate endpoints for the effectiveness of the entire MTB-guided strategy rather than for the quality of individual board recommendations. This creates what epidemiologists describe as an "inference gap": the observed superiority of MTB-guided treatment over standard of care provides prospective, randomized evidence of clinical utility, yet only indirectly validates the MTB as a process. A direct evaluation of concordance between local and MTB treatment proposals would have required each participating center to generate parallel strategies for both arms, an approach considered methodologically ambiguous and ethically questionable. The trial aligns with ESCAT (ESMO Scale of Clinical Actionability for Molecular Targets) principles of actionability by linking therapeutic choices to well-characterized molecular alterations but does not constitute a head-to-head evaluation of MTB performance metrics. Consequently, the ROME trial provides stronger evidence than retrospective analyses but represents indirect validation of MTB clinical value, and future studies should explore standardized frameworks for direct evaluation of MTB decision-making.

The most prevalent reason for exclusion from randomization in the ROME trial was the uncertain clinical significance of certain genetic alterations. This finding highlights the necessity of a multidisciplinary approach, the sharing of large datasets, and the avoidance of simplistic alteration-drug algorithms. This observation underscores the critical importance of exercising caution when interpreting novel or unvalidated biomarkers. The temptation to overinterpret such signals carries significant risks and can misdirect therapy selection. Our MTB deliberately adopted a conservative stance, requiring robust clinical or biological evidence before recommending a targeted therapy. This approach reflects a broader principle that precision oncology must remain firmly grounded in validated data, with emerging biomarkers introduced into clinical care only in research contexts or under careful multidisciplinary deliberation.

Resistance mechanisms were frequently encountered as a reason for screening failure. These mechanisms often remain undetected without comprehensive NGS, which is crucial for identifying resistance alterations, emphasizing the need to move beyond basic alteration-drug algorithms. ESMO Precision Oncology Working Group notes that MTB recommendations should use "recognized scales of clinical actionability" [15], but it is necessary to develop a broader scale encompassing not only actionable alterations, but also resistance alterations.

Furthermore, we observed a self-learning capacity of the MTB throughout meetings over time. Artificial intelligence (AI) agents could help identify patterns and optimize workflows. The implementation of informatic tools and AI could assist clinicians and the MTB in verifying literature data with automatic

literature search and variant interpretation platforms, thereby enhancing decision-making processes [18]. Such innovations are increasingly important for managing the expanding volume and complexity of data that MTBs must evaluate.

The ROME Trial MTB records serve as a complete video collection of actual MTB discussions, which researchers can use to train future precision oncologists while standardizing MTB procedures between healthcare facilities. In Italy, this model is currently being finalized within the Alliance Against Cancer (AAC), underscoring both its feasibility and the institutional commitment necessary for nationwide implementation.

Moreover, a prospective nationwide MTB platform should facilitate discussions, systematic data collection, and access to clinical trials available within the country [16]. Establishing such a federated or virtual network would standardize data management and trial access while mitigating disparities in the availability of MTB expertise. Patients treated in resource-limited or remote centers may otherwise lack the benefit of comprehensive molecular deliberation; a nationwide framework could ensure equitable access to expert recommendations across institutions. Possible limitations of the study are discussed in Suppl. Table 3. The strengths and challenges along with recommendations for other centers, are detailed in Suppl. Table 4.

METHODS

The ROME trial was a phase II, randomized, prospective, and multicenter clinical trial that included patients aged at least 18 years with advanced or metastatic solid tumors, independent of histology. Eligible patients had at least received one line of treatment and underwent NGS profiling of tumor tissue (Foundation One CDx) and/or blood samples (Foundation One Liquid CDx). All patients were required to have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) or immune-related response criteria (irRC). Magnetic resonance imaging and positron emission tomography scans were performed as clinically indicated. Sufficient renal, hepatic, and bone marrow function was required at baseline. Exclusion criteria included patients with only bone and/or brain metastases, uncontrolled or symptomatic brain disease, or unmonitored brain metastases for over two months, as well as those with severe or uncontrolled comorbidities that might compromise study participation.

In this study, the genomic information obtained from either tumor tissue or liquid biopsy was evaluated by an MTB panel of multidisciplinary experts who provided guidance on tailored therapy when actionable alterations were identified. To ensure maximum diagnostic yield, patients remained eligible for the study provided that at least one profiling modality (either tissue or liquid biopsy) yielded successful results. Conversely, cases in which both characterization methods failed were classified as screening failures. A two-tier selection process was implemented to optimize the MTB resources: initially, the Steering Committee performed a centralized pre-selection to identify cases with potentially actionable alterations. This was followed by a comprehensive MTB review, where the multidisciplinary panel integrated the full NGS report with the patient's clinical context to reach a final consensus. Patients were then randomized in a 1:1 ratio to receive either the tailored treatment (targeted therapy or immunotherapy) based on specific molecular targets as indicated by the MTB or SoC. In the SoC arm, patients received guideline-based standard chemotherapy, targeted therapy, or immunotherapy according to tumor histology and investigator discretion; the MTB could recommend modifications based on molecular profiling when appropriate. Patients with well-established actionable targets for which approved targeted therapies were

already available as standard practice were not intended for randomization in this trial and were excluded per protocol. The study design did not prespecify the direct measurement of MTB decision-making efficacy to prevent interpretative uncertainty and ensure methodological rigor. Crossover was permitted upon progression on initial therapy. Patients who were not randomized were classified as screening failures based on the MTB decision.

Tissue and liquid biopsies

For genomic testing, a tissue sample obtained during the screening phase or within six months before enrolment was required. The biopsy was ideally performed after completion of conventional therapy for recurrent/metastatic cancer. Samples collected within three months prior to the patient's informed consent were accepted, and samples up to six months old were permitted with independent confirmation from the MTB. Archived tissue samples were accepted for patients with glioblastomas and high-grade malignant glioma. Patients with only one available biopsy (liquid or solid), due to failure of one method during screening, remained eligible for MTB evaluation. If both tissue and liquid biopsy characterizations failed, patients were classified as screening failures.

Genomic testing

For tissue biopsies, DNA was isolated from formalin-fixed, paraffin-embedded (FFPE) specimens using the DNAx extraction method. Extracted DNA was analyzed through FoundationOne CDx panel, assessing 324 genes for substitutions, insertions, deletions (indels), copy number alterations (CNAs), and gene rearrangements. Genomic signatures, including MSI and TMB were also evaluated.

For liquid biopsies, circulating cell-free DNA (cfDNA) was isolated from plasma derived from peripheral anti-coagulated whole blood, collected in FoundationOne Liquid CDx cfDNA blood collection tubes. cfDNA was analyzed using FoundationOne Liquid CDx for detection of substitutions, indels in 311 genes, rearrangements in four genes, and copy number alterations in three genes. Tumor fraction, blood-derived TMB (bTMB), and MSI-H status were also determined.

TMB was assessed using a prespecified threshold, with 'TMB-high' defined as ≥10 mutations/Mb. Cases falling slightly below this cutoff (8–9 mutations/Mb) were categorized as 'borderline TMB'. Regarding cases with co-occurring biomarkers, a clear clinical hierarchy was established: MSI-H status prioritized the recommendation for immunotherapy regardless of concurrent alterations. Conversely, (hTMB) was utilized as a primary actionable biomarker specifically within microsatellite stable (MSS) tumors or in instances where it constituted the dominant actionable genomic signal.

MTB Structure and Role

The MTB was composed of members of the Steering Committee, representing various disciplines, and was chaired by a medical oncologist. During the screening phase, patients identified with potentially actionable molecular alterations were discussed in the MTB, which virtually convened weekly to evaluate each eligible patient for a final recommendation. Each case was presented at the MTB meetings by the referring clinician, who provided the patient's medical history, including past and oncological details, and displayed the results of the genomic profiling. The discussion began with an assessment of the presence or absence of a potentially targetable alteration, followed by a clinical evaluation of the case and the possible treatment for each individual patient. The MTB was composed of medical oncologists, pathologists, molecular biologists, geneticists, immunologists, and other figures.

MTB therapeutic recommendations were formulated based on a predefined hierarchical framework applied prospectively in real time. This decision-making process systematically integrated: (i) clinical urgency; (ii) the strength of biomarker–drug evidence; (iii) the presence of intrinsic or acquired resistance mechanisms, including prior treatment exposure; (iv) patient-specific safety and comorbidity profiles; and (v) the logistical feasibility of drug procurement and access. From a molecular perspective MTB decisions were primarily guided by the ESCAT framework for gene actionability, classifying molecular alterations according to their clinical relevance and evidence, and drawing on resources such as ClinVAR, OncoKB, and COSMIC. VAF thresholds were set at 1% for tissue biopsies and 2% for liquid biopsies.

During meetings, the MTB determined whether to randomize patients or classify them as screening failures. Recommendations could also include indication for germline testing or modifications of the standard therapy originally proposed by the referring center, considering the detected molecular alterations. All board sessions were systematically recorded, except for two meetings which were unavailable due to technical malfunctions.

All cases discussed at the MTB and classified as eligible or screening failures, underwent retrospective review to document the precise reasons underlying each decision, through analysis of clinical, molecular, and other relevant data. Each case was meticulously examined to identify and document the specific reasons that led to the decision to include or exclude the patient from randomization. At the end of each meeting, a formal vote was taken to confirm the MTB's decision, and a recommendation was issued for the attending physician who had submitted the case. The physician's adherence to the recommendation was documented, and in all cases the attending physician implemented the MTB's proposal in the experimental arm. Multiple reasons for exclusion were recorded where applicable.

For randomized patients, it was assessed whether the inclusion decision was based on a single or multiple alterations. In the subgroup of patients with multiple alterations, the rationale for selecting the therapeutic target was reassessed.

MTB recommendations were formulated prospectively in real-time throughout the study period. The retrospective analysis was limited to the post-hoc structured coding of decision rationales and target selection criteria, which were derived from official MTB documentation and recordings for the purposes of this manuscript.

Ethical Considerations

The trial adhered to the principles of the Declaration of Helsinki regarding research involving human subjects, received institutional review board approval, and obtained written informed consent from all participants.

The study was approved by the institutional ethics committee of the coordinating center (Sapienza no. rif. C.E. 5575; February 2020) and by the ethics committee of each participating center. The investigational sites that approved the study protocol were as follows: AOU Policlinico Umberto I, Rome; European Institute of Oncology (IEO), IRCCS, Milan; Veneto Institute of Oncology IOV-IRCCS, Padua; Division of Medical Oncology, Pisa University Hospital; IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) 'Dino Amadori', Meldola; Istituto Nazionale Tumori IRCCS Fondazione 'G. Pascale', Naples; IRCCS Istituto Nazionale Tumori Regina Elena (IRE), Rome; IRCCS Istituto di Candiolo, Candiolo; Medical Oncology Unit,

ARNAS Garibaldi Catania; Azienda Ospedaliera Santa Maria di Terni, Terni; Pederzoli Hospital, Peschiera del Garda; IRCSS Ospedale Policlinico San Martino, Genoa; Ospedali Galliera, Genoa; Central Hospital of Belcolle, Viterbo; IRCCS Sacro Cuore Don Calabria Hospital, Negrar di Valpolicella; Santa Maria della Misericordia Hospital, Perugia; Nuovo Ospedale di Prato-Santo Stefano, Azienda USL Toscana Centro, Prato; CRO Aviano, National Cancer Institute, IRCCS, Aviano; Santa Maria delle Croci Hospital, AUSL Romagna, Ravenna; Oncology Unit ASST Papa Giovanni XXIII, Bergamo; Ordine Mauriziano Hospital, Turin; AOU Policlinico S. Andrea, Rome; Azienda Ospedaliera Universitaria Federico II, Napoli; Fondazione IRCCS Istituto Tumori di Milano; Fondazione Policlinico Universitario Campus Bio-Medico, Rome; A.O. Papardo-Messina; IRCCS Istituto Tumori 'Giovanni Paolo II', Bari; Policlinico universitario 'Mater Domini', Catanzaro; Centro Oncologico San Leopoldo Mandic, Isola Tiberina Gemelli isola; Rome; University Hospital, Ferrara; Misericordia Hospital, Grosseto; AUSL Piacenza Guglielmo da Saliceto Hospital, Piacenza; Comprehensive Cancer Centre, AUSL-IRCCS di Reggio Emilia, Reggio Emilia; Humanitas Gradenigo, Torino; Foundation IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo; Ramazzini Hospital, Azienda Unità Sanitaria Locale Modena (AUSL), Carpi; AOUP 'Paolo Giaccone', Palermo; and AOU delle Marche, Ancona.

The competent authority, Agenzia Italiana del Farmaco (AIFA), authorized the trial on 8 July 2020 (AIFA/SC/P/76132). The trial adhered to the principles of the Declaration of Helsinki regarding research involving human subjects. Forty-one centers received ethics approval and participated in the study enrollment. All patients signed the specifically conceived informed consent form (ICF).

The trial is registered on ClinicalTrials.gov with identifier NCT04591431 and in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) with number 2018-002190-21

Data availability

Individual deidentified participant data generated during the current study are available upon reasonable request from academic or qualified clinical researchers affiliated with recognized institutions, strictly for the purpose of conducting non-commercial, ethically approvable research aligned with the original scope of the trial. Applicants are required to submit a detailed research proposal, curriculum vitae and a declaration of non-conflict of interest. Requests must clearly describe the research objectives and methodology and must be reviewed and approved by the steering committee of the ROME trial during dedicated review sessions. Approval is granted based on scientific merit, data availability, intended data use and absence of overlapping research initiatives by the trial investigators. All approved requestors will be required to sign a data access agreement that restricts data use solely to the approved research project and prohibits any further distribution or use. Data will be shared via a secure data-sharing platform within 4–8 weeks of approval, contingent upon data volume and complexity. Data requests will be considered within 12 months of manuscript publication.

The trial registration, study protocol and methodological details are publicly accessible through ClinicalTrials.gov (accession identifier NCT04591431; https://clinicaltrials.gov/ct2/show/NCT04591431).

Additional publicly available datasets used in the analysis include the ClinVar database: freely accessible at https://www.ncbi.nlm.nih.gov/clinvar/; the OncoKB database: accessible at https://www.oncokb.org/; the COSMIC database: accessible at https://cancer.sanger.ac.uk/cosmic; and the ESMO ESCAT scale: accessible at https://www.esmo.org/guidelines/esmo-scale-for-clinical-actionability-of-molecular-targets-escat.

No other public repositories or datasets requiring accession codes were used in this study.

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Generative artificial intelligence (AI-Perplexity) tools were used during the drafting process exclusively to refine language and improve readability. All data collection, analysis, and interpretation were carried out by the Authors. The Authors assume full responsibility for the scientific content, and all text generated with AI support was carefully reviewed, edited, and approved by the Authors prior to submission.

Author contributions

Conceptualization: P.M. and A.B. Patient enrollment and investigation: G.C., M.B., S.L., S.S., L.F., V.G., U.D.G., P.A., M.A., C.C., P.C., S.S. E. Crimini, S.P., S.V., F.D.G., R. Bordonaro, S.B., G. Butturini, L.D.M., A.D.C., A.F., E.F., S.G., G.M., A.P., D.P., F.P., S.T., A.Z., D.M., F.C., F.M., G.T., A.B., A.S., V.A., D.Q., P.T., P.D., B.U., C.B., E.Z., C.P., A.T., L.B., E.M., C.M., A.R. and R. Berardi. MTB: P.M., G.C., M.B., S.S., P.A., G. Blandino., G.D., M.A., C.C., P.C., E. Capoluongo, F.C., B.C., G.G., U.M., F.M., M.N., G.P., L.S. and A.B. Methodology: L.S., M.C., P.M., A.B., S.S., M.B., P.A., G. Blandino, G.D., M.A., C.C., P.C., E. Capoluongo, F.C., B.C., G.G., U.M., F.M., M.N., G.P., N.M. and M.S. Software: M.C. and L.S. Formal analysis and data curation: M.C. and L.S. Validation: P.M., A.B., S.V., L.S. and M.C. Writing—original draft preparation: P.M., G.C., S.S., E. Crimini, S.P., S.V., C.B.W. and A.B. Writing—review and editing: all authors. Visualization: P.M., S.V., S.S., E. Crimini, M.C. and A.B. All authors read and agreed to this version of the manuscript.

Competing interests

P.M. had a consultant/advisory role for Bristol Myers Squibb, Roche Genentech, Merck Sharp & Dohme, Novartis, AMGEN, Merck Serono, Pierre Fabre and Incyte. He is a member of the advisory board of Drug-PIN. A.G. is the holder of patent PTC/IB2019/052310. G.C. had a role in advisory board for Roche, AstraZeneca, Daiichi Sankyo, Eli Lilly, Novartis, Pfizer, Gilead, Menarini, Exact Sciences, Bristol Myers Squibb and Merck. C.B.W. served as an advisor for: Astra Zeneca, BMS, Frankfurt Institute of Clinical Cancer Research (IKF), Incyte, Johnson & Johnson, Roche, Taiho. He received honoraria from Amgen, Astra Zeneca, Bayer, BMS, GSK, Johnson & Johnson, Lilly, MSD, Merck, Pierre Fabre, QuIP GmbH, Roche, Servier; received travel support from: Bayer, Johnson & Johnson, Roche, Servier, Taiho and research funding from Roche (institutional). He serves as serves as faculty for European Society of Medical Oncology (ESMO), Deutsche Krebshilfe (DKH) and Arbeitsgemeinschaft internistische Onkologie (AIO), is a member of the EU Commission expert group: Mission Board for cancer and of the BMBF steering committee: Strategiekreis Dekade gegen Krebs. M.B. is employed in the Italian National Institute of Health (Istituto Superiore di Sanità) and is an unpaid member of the Technical and Scientific Committee of the Italian Medicine Agency (AIFA). S.L. was an invited speaker for Amgen, AstraZeneca, Bristol Myers Squibb, Incyte, GlaxoSmithKline, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Pierre Fabre, Roche and Servier and had a role in advisory boards for Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Incyte, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Servier, Takeda, Rottapharm, BeiGene, Fosun Pharma and Nimbus Therapeutics. S.S. was an invited speaker for Pfizer, Eli Lilly, Novartis, Daiichi Sankyo, Gilead, Roche and AstraZeneca. L.F. reports speaking honoraria from Incyte, Bristol Myers Squibb snd Eli Lilly. He also received institutional research funding from Merck Sharp & Dohme, Bristol Myers Squibb, AstraZeneca, Incyte, BeiGene, Astellas, Daiichi Sankyo and Roche. He had a role in advisory boards for Merck Sharp & Dohme, AstraZeneca, Incyte, Taiho, Servier, Daiichi Sankyo, Eli Lilly and Astellas. V.G. has a role in leadership for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, Merck Sharp & Dohme, Novartis, Pfizer, Olema Oncology, Pierre Fabre and Menarini Stemline. She had a role as a speaker for AstraZeneca, Daiichi Sankyo, Eli Lilly, Exact Sciences, Gilead, GlaxoSmithKline, Novartis, Roche, Zentiva and Menarini Stemline and provided expert testimony for Eli Lilly. U.D.G. received consultation fees from Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Esai, Ipsen, Johnson & Johnson Innovative Medicine (formerly Janssen), Merck KGaA, Merck Sharp & Dohme, Novartis and Pfizer and travel expenses for attending symposia from AstraZeneca, Ipsen and Pfizer. P.A., G.B., G.D., M.A., C.C., P.C., E. Crimini and M.C. declare no competing interests. S.P. had a role as consultant/advisor for AstraZeneca, Eli Lilly, Daiichi Sankyo, Novartis, Pfizer, Seagen, Sophos and Gilead and received travel and accommodation fees from Daiichi Sankyo, Pfizer, AstraZeneca, Eli Lilly, Menarini, Novartis and Gilead. S.V. had a role as a speaker for Novartis. R.B. declares no competing interests. S.B. received congress travel support from Merck Sharp & Dohme, Pfizer, Bayer and Ipsen and had a role in advisory boards and steering committees for Pfizer, Bristol Myers Squibb, Merck Sharp & Dohme, Astellas, Roche, Johnson & Johnson, Ipsen, Bayer, Novartis, Merck, AstraZeneca and Gilead. G.B. declares no competing interests. L.D.M. received personal grant for advisory/consultant/speaker activities from Agendia, AstraZeneca, Daiichi Sankyo, Eli Lilly, Eisai, Exact Sciences, Gilead, GlaxoSmithKline, Ipsen, Roche, Seagen, Menarini, Stemline, Merck Sharp & Dohme, Novartis, Olema, Pierre Fabre and Pfizer. A.D.C. declares no competing interests. A.F. received financial fees from Roche, Menarini, Pfizer, Eli Lilly, Novartis, Daiichi Sankyo, AstraZeneca and Gentili. F.DG had consulting fees with Novartis, BMS, MSD, and Pierre-Fabre. E.F., S.G., G.M., A.P. and D.P. declare no competing interests. F.P. received honoraria for advisory boards, activities as a speaker, travel grants and research grants from Amgen, AstraZeneca, Daiichi Sankyo, Celgene, Eisai, Eli Lilly, Exact Sciences, Gilead, Ipsen, Italfarmaco, Menarini, Merck Sharp & Dohme, Novartis, Pierre Fabre, Pfizer, Roche, Seagen, Takeda and Viatris. He received research funding from AstraZeneca, Eisai and Roche. S.T. declares no competing interests. A.Z. received honoraria for consultancy and advisory board from Roche, Novartis, Eli Lilly, AstraZeneca, Pfizer, Exact Sciences, Merck, Daiichi Sankyo, Gilead, Seagen, Menarini and Stemline. D.M. had a role in advisory boards for Roche, Merck Sharp & Dohme, Merck and AstraZeneca and received fees

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Figures

Figure 1

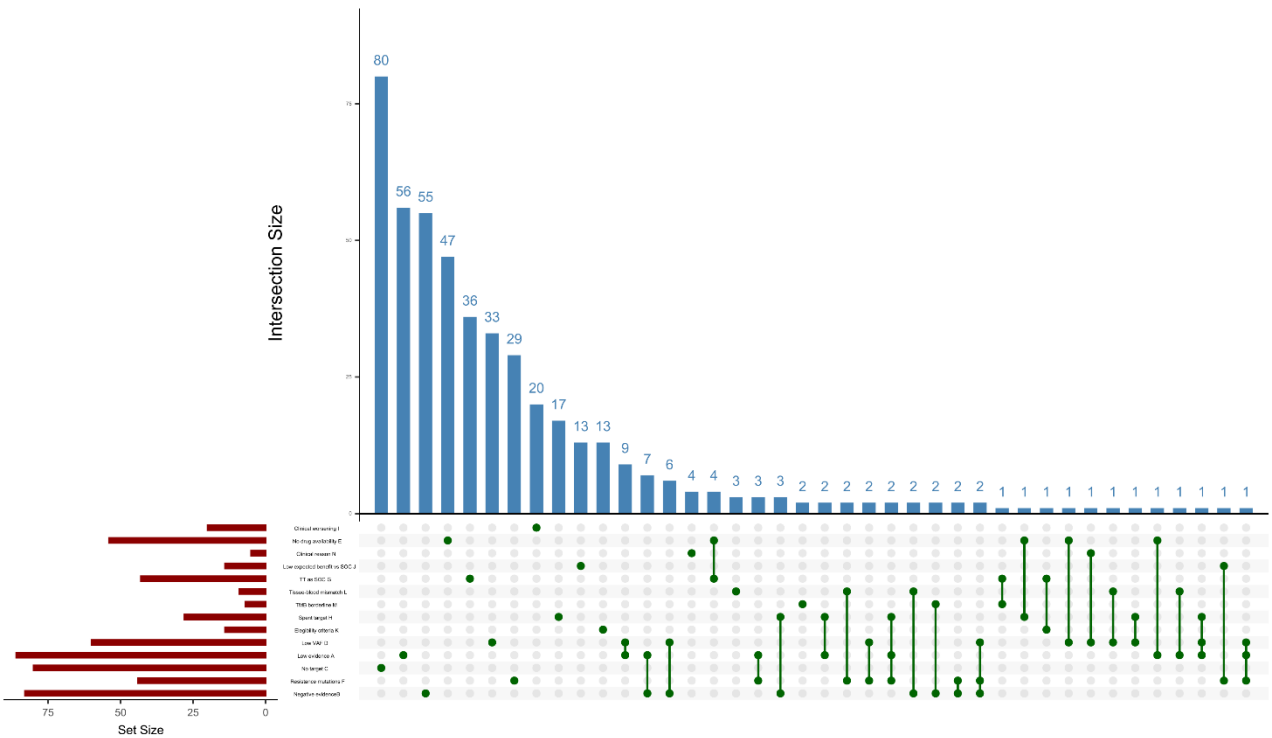


Figure 1. Reasons for patient exclusion from the study

Bar graph showing the distribution of exclusion reasons among patients who were initially considered for enrollment but subsequently excluded from the randomization into the study after MTB discussion. Bars represent the number of patients excluded for each category, stratified by type of decision. The upset plot shows the frequency of co-occurrence in cases where multiple exclusion criteria were identified for a single patient.

Figure 2

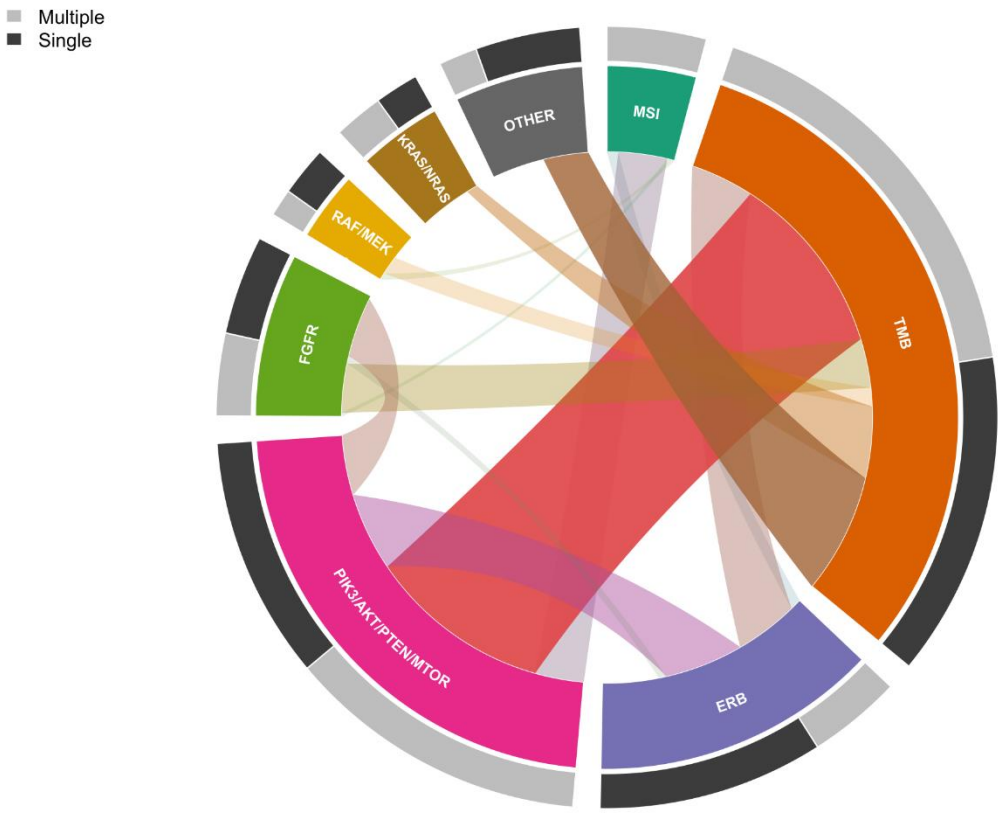


Figure 2. Distribution of molecular biomarkers and co-occurrence patterns in 400 randomized patients.

This pie chart illustrates the prevalence and co-occurrence patterns of molecular biomarkers identified in 400 randomized patients. The inner ring depicts the relative frequency of different biomarker categories: MSI, TMB, ERBB2, PIK3/AKT/PTEN/MTOR pathway alterations, *FGFR* alterations, BRAF/MEK pathway alterations, KRAS/NRAS alterations, and other genomic alterations and co-alteration landscapes. The outer ring indicates single targetable alterations (dark segments, n=198, 49.5%) versus multiple alterations with MTB-selected drivers (grey segments, n=202, 50.5%). The biomarker landscape was heterogeneous: MSI was detected in 4.5% of cases and was consistently concurrent with other mutations. High TMB was observed in 100% of MSI-H samples; however, this association is not displayed in the figure to maintain visual clarity. TMB was the sole driver in 44% of cases, co-occurring in the remaining 56%. *ERBB2* alterations were isolated in 70% of cases; the PIK3/AKT/PTEN/MTOR and BRAF/MEK pathways were single events in 44% and 64% of cases, respectively, and co-occurred with other events in the remainder. *FGFR* and *KRAS/NRAS* alterations were single in 55% and 47% of cases, respectively. The "*other alterations*" category was primarily (70%) single events.

Figure 3

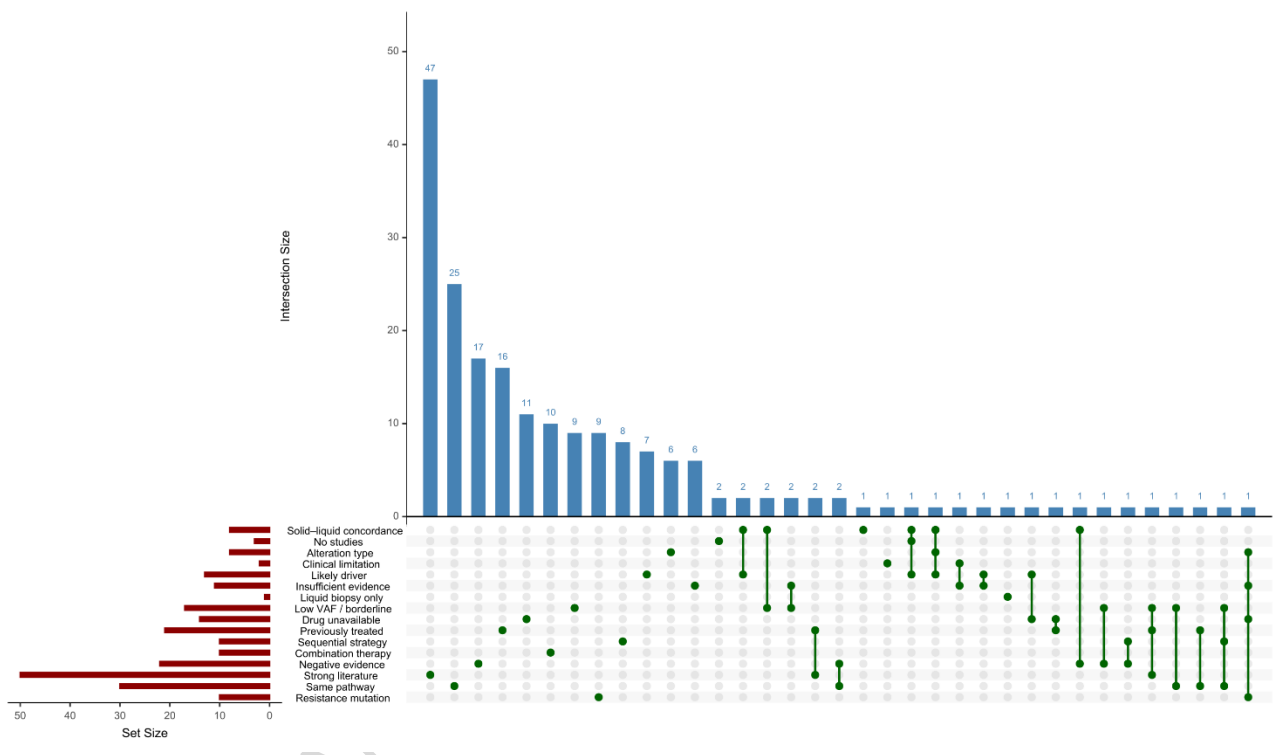
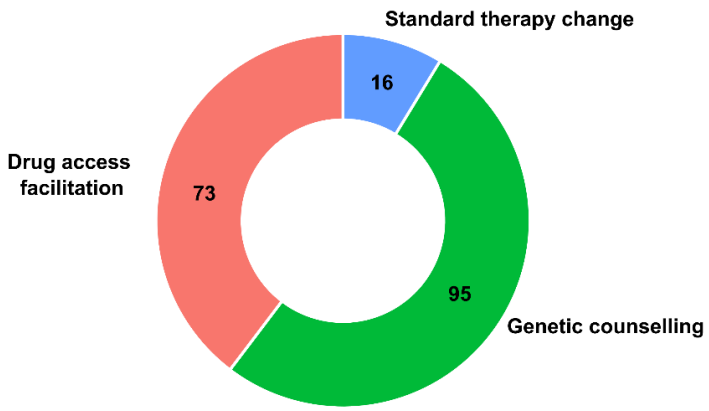


Figure 3. Rationale for target selection in patients with multiple targetable alterations.

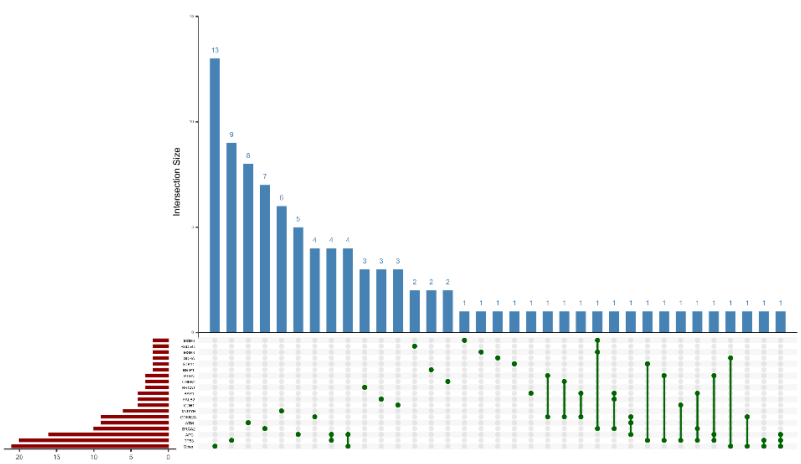
Stacked bar chart illustrating the decision-making factors used by the MTB to select the primary therapeutic target among randomized patients presenting multiple potentially targetable genomic alterations. The height of each segment reflects the frequency of that rationale in the decision-making process. The upset plot illustrates the distribution of overlapping decision criteria among patients who met multiple conditions.

Figure 4

A


Standard therapy change
16
Drug access facilitation
73
95
Genetic counselling

B


Intersection Size
Set Size

C

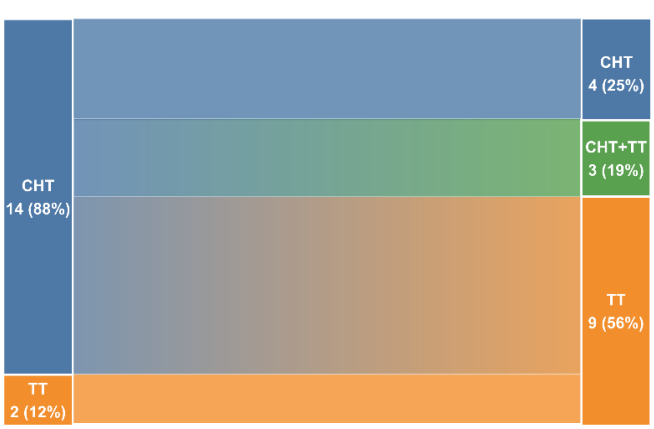

CHT
14 (88%)
TT
2 (12%)
CHT
4 (25%)
CHT+TT
3 (19%)
TT
9 (56%)

Figure 4. Additional clinical impact derived from molecular tumor board discussion for screening-failed patients.

(A) Distribution of MTB recommendations different from targeted therapy indication. The donut plot shows the number of cases in which the MTB facilitated drug access, suggested genetic counselling, or proposed a change in standard therapy.
(B) UpSet plot summarizing the spectrum of suspected germline alterations identified in the cohort for which genetic counselling was indicated by MTB. Each bar represents the number of patients carrying specific combinations of potentially germline variants, while the side bars indicate the total frequency of each altered gene. All detected alterations are shown, highlighting the co-occurrence patterns.
(C) Sankey diagram illustrating changes between site-proposed therapy classes and MTB-recommended therapy classes. The width of each flow is proportional to the number of patients whose treatment was modified. Colors represent therapy classes (chemotherapy, targeted therapy, or combined approaches). Percentages indicate the fraction of patients within each therapy class before and after MTB discussion.