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ORIGINAL RESEARCH

The Impact and Performance of the Molecular Tumor Board: Three-Year Activity in Precision Medicine for Treatment of Patients with Cancer from the Marche Region, in Italy

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ABSTRACT

Introduction: Cancer incidence is rising in Italy, making it harder for researchers to search for innovative and comprehensive treatment strategies. The advancement of precision medicine, the hunt for molecular targets, and the development of drugs that may operate on a specific target have all become increasingly important aspects of the oncological treatment strategy in recent years. The aim of this study is to analyze the activity and performance of the Oncology and Research Center of the Marche Region (CORM) and its Molecular Tumor Board (MTB) in implementing precision medicine to improve cancer treatment.

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***Methods*:** CORM was established to provide multidisciplinary diagnostic and therapeutic services, promoting early diagnosis, innovative treatments, and continuous patients support. The MTB, including various specialists, facilitates the interpretation of genomic profiles to identify targeted therapies.
***Results*:** From June 2021 to May 2024, 118 patients were evaluated at the MTB of the Marche Region, with 77 undergoing molecular profiling. This study highlights the efficacy of the MTB in selecting appropriate molecular tests, interpreting results, and recommending personalized treatment strategies, leading to improved patient outcomes.
***Conclusion*:** Challenges such as the complexity of genomic data interpretation and the need for more computational tools to assist clinicians were also identified. Still, constant multidisciplinary collaboration between experts and the finest possible innovative technological support are required to achieve the best outcomes in cancer treatment.

Keywords: Molecular tumor board; MTB; Clinical oncology; Precision medicine; NGS

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Key Summary Points

Precision medicine is an innovative approach that utilizes an individual's genomic, environmental, and lifestyle information to guide medical management decisions.
Genomic alterations identified as biomarkers are present in approximately 10% of patients with advanced metastatic cancers and are instrumental in selecting precise anticancer treatments.
The aim of the study is to analyze the activity and performance of the Oncology and Research Center of the Marche Region (CORM) Molecular Tumor Board (MTB) and its impact on the health of oncology patients.
The implementation and activity of CORM and MTB have demonstrated significant advancements in the management of patients with cancer through precision medicine.
The multidisciplinary collaboration has proven essential in interpreting complex genetic data and translating it into clinical practice, offering hope for improved survival rates and quality of life for patients with cancer.
The MTB has facilitated more informed therapeutic decisions, thereby enhancing patient outcomes.

INTRODUCTION

Cancer and Cancer Treatment Overview

The incidence of cancer is escalating significantly. According to data provided by the Italian Cancer Registries (*Registro Tumori Italiani*), an estimated 376,600 new cancer cases were reported in Italy in 2020, with 194,700 in men and 181,900 in women. This number was projected to rise to 395,000 by 2023, comprising 208,000 men and 187,000 women. This increase of over 18,000 cases within 3 years underscores

a persistent upward trend. Despite the advancements in targeted and effective treatments, cancer remains a leading cause of mortality, partly due to the aging population. Therefore, it is crucial to prevent late diagnoses by raising awareness about risk factors such as obesity, sedentary lifestyles, alcohol abuse, and tobacco use, and by promoting adherence to screening programs and vaccinations for cancer-causing infections. Moreover, it is essential that all patients be provided with access to innovative treatments.

Clinical conditions that had limited therapeutic options a decade ago now benefit from additional treatment lines through immuno-oncology, targeted therapies, and novel medications. For cases where targeted therapies are available in clinical practice, molecular characterization is now required in addition to traditional histological diagnosis. Immunotherapies and targeted therapies have revolutionized the treatment of advanced tumors, enhancing patient survival and quality of life. The goal of cancer treatment and clinical research is to manage oncological diseases chronically and tailor care approaches to each patient [1].

In this context, the concept of precision medicine has been theorized. Precision medicine is an innovative approach that utilizes an individual's genomic, environmental, and lifestyle information to guide medical management decisions. Genomic and biomarker analysis has laid the foundation for precision oncology, which uses specific information about patients' tumors to assist in diagnosis, treatment planning, treatment efficacy evaluation, and prognosis determination.

Notably, genomic alterations identified as biomarkers are present in approximately 10% of patients with advanced metastatic cancers and are instrumental in selecting precise anticancer treatments according to current care standards. Data suggest that nearly four out of ten patients could benefit from more targeted treatment based on their genetic profiles.

The aim of targeted therapy, which focuses on the genetic changes or proteins that convert healthy cells into cancerous ones, is to be considerably less damaging than conventional cytotoxic treatments by being far more selective towards tumor cells. The innovation in *mutational oncology* lies in treatment based on genomic profiling, irrespective of the tumor's location and histology. This is exemplified by *tissue-agnostic drugs*, which treat cancers based on their mutations rather than their tissue of origin.

This significant change is enabled by technologies like next-generation sequencing (NGS), a molecular profiling technique that generates vast amounts of data, the analysis of which is particularly complex. The adoption of precision medicine remains low, often due to insufficient support for clinicians in interpreting and acting on NGS results.

In response, many medical centers worldwide have established a molecular tumor board (MTB) to implement precision medicine. The MTB supports clinical decision-making by assessing genomic tests and interpreting molecular profiles in order to identify targeted treatments for oncology patients. The multidisciplinary nature of the MTB ensures accurate and up-to-date diagnoses and the identification of actionable mutations and associated drugs. MTBs are crucial for simplifying the complexity of genomic testing and reporting, increasing access to current treatments and clinical trials, and enhancing the understanding of the clinical utility of precision medicine in oncology [2–4].

CORM

The diagnostic and therapeutic management of patients with cancer requires a multidisciplinary approach and effective interaction among general practitioners, hospital facilities, and the community.

Based on these premises, the Oncology and Research Center of the Marche Region (CORM) was established in April 2021 at the Department of Oncology of "Azienda Ospedaliero Universitaria (AOU [university hospital]) delle Marche," under the patronage of the Ministry of Health. CORM serves as a reference center for the diagnosis and treatment of oncological malignancies, oncology genetics, experimental therapies, and rare tumors. Its activities are conducted in synergy with international cancer centers and

are closely related to several operating units within the institution.

The goal is to offer a comprehensive, interdisciplinary diagnostic and therapeutic approach for patients in the Marche region, encompassing all professional expertise required to ensure an excellence-driven pathway. Additionally, CORM ensures continuity of care and support for family members, even after patient discharge, through home hospitalization and coordination with local facilities [5].

MTB in the Marche Region

Biotechnological advancements have led to the identification of gene expression abnormalities associated with carcinogenesis that may be targeted by specific treatments. Clinicians now face increasing complexity in genetic information, requiring oncologists to navigate molecular findings. Clinical trials are also transitioning from tumor-type-focused research to gene-oriented research, with unique designs tailored to biomarker profiles.

The MTB is a multidisciplinary organization designed to address gaps in cancer treatment, especially when literature data or clear guidelines are lacking. In June 2021, the MTB was established—the first in the Marche region—to enhance cancer patient care through precision medicine. The MTB includes a web-based corporate platform enabling oncologists from different centers to request patient assessments. It serves as a reference for evaluating selected clinical cases treated at other Marche oncology centers or referred by regional and extra-regional healthcare professionals.

The purpose of this study is to analyze the activity and performance of the CORM-MTB and its impact on the health of oncology patients [5].

METHODS

CORM

The major projects of CORM include the following:

- *Website and telemedicine platform*: A website and a telemedicine platform that facilitates connections between our hospital and 13 different oncology hospitals in the Marche region (www.corm-marche.it).
- *MTB*: A multidisciplinary group dedicated to identifying personalized care pathways through advanced molecular analyses and translating complex molecular data into clinically useful information for prognostic purposes and predicting cancer treatment efficacy.
- *Clinical and translational research development*: Initiatives include phase I trials with innovative drugs to provide new therapeutic options for patients with cancer in the Marche area.
- *Oncological genetics research promotion*: This involves close collaboration with the Highly Specialized Regional Center in Oncological Genetics active at the same institution since 2004. The center is equipped with NGS technology to offer genetic counseling in oncology to individuals (and their families) at increased risk of cancer due to hereditary genetic predispositions.
- *Outreach projects*: These are conducted with the full cooperation of voluntary associations [5].

MTB

The MTB consists of a core team and additional specialists. The core team includes a coordinator, secretary, oncologists (including preliminary assessment), pathologists, molecular biologists, geneticists, pharmacists, pharmacologists, data managers, research nurses, case managers, bioethicists, and clinical epidemiologists. Additional specialists such as radiologists, interventional radiologists, radiotherapists, surgeons, gastroenterologists, pulmonologists, or hematologists may be involved in specific consultations. Participation of the core team members is always guaranteed during MTB meetings, characterized by multidisciplinary and multi-professional collaboration, mutual trust, decision-making

convergence, regular meetings, and effective coordination [5, 6].

A registered healthcare physician activates the MTB by submitting a request via the CORM's web-based teleconsultation platform and uploading the patient's health documentation. The case is discussed during semimonthly MTB meetings, where the requesting physician can participate via teleconference. The MTB addresses cases involving the following:

- Patients with advanced/metastatic disease who have undergone genomic profiling and exhibit mutational alterations without unequivocal clinical classification or lack clinically approved molecularly targeted drugs.
- Patients with advanced/metastatic disease and good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0/1) who have exhausted standard therapeutic lines and may benefit from NGS genetic profiling.
- Patients with rare diseases lacking recognized therapeutic approaches or with limited therapeutic alternatives, rapidly progressing after standard therapies, with good performance status for whom NGS profiling is indicated.
- Patients with "oncogene-addicted" malignancies unresponsive to current molecular therapies.
- Patients with a life expectancy of less than 6 months are excluded.

The MTB's responsibilities include the following:

- Selecting patients eligible for molecular testing.
- Choosing the most suitable and cost-effective molecular test to identify all potential tumor targets.
- Selecting the appropriate sample (liquid biopsy or histological/cytological sample) based on the patient's clinical state, molecular method, and gene panel.
- Verifying the technical and methodological feasibility of molecular investigations based on the quality and quantity of available biological material.
- Interpreting molecular test reports, especially ambiguous cases, to define the biological significance of genetic abnormalities and determine therapeutic actionability. Results are compared with online databases to provide precise treatment recommendations, often off-label.
- Integrating clinical and genomic data to define optimal treatments for individual patients, including evaluation for clinical trial access.
- Issuing detailed reports summarizing relevant results and MTB decisions.
- Collecting data on the clinical outcomes of patients receiving MTB-recommended therapies.

Molecular Tests Proposed by the MTB

During multidisciplinary discussions, the MTB determines which molecular tests are appropriate for each patient according to European (European Society for Medical Oncology [ESMO]) and national (Italian Association of Medical Oncology [AIOM]) guidelines. Italy's compliance with international guidelines was formalized with Law No. 233 of 29 December 2021, establishing the MTB and identifying specialist centers for NGS genomic profiling tests.

Patients must provide written informed consent for personal and genetic data processing. Molecular analyses are typically performed on tumor nucleic acids (DNA or RNA) extracted from formalin-fixed/paraffin-embedded (FFPE) histological samples, or circulating tumor DNA (ctDNA) from liquid biopsies if tumor tissue is unavailable. The MTB chooses between "singleplex" tests able to analyze specific known molecular targets (e.g., real-time polymerase chain reaction [RT-PCR]) and "multiplex" technologies, able to analyze different biomarkers for different patients simultaneously thanks to NGS.

Available tests at thed Department of Pathological Anatomy, of Ancona include the following:

- RT-PCR kits:
  - EasyPGX® ready NTRK fusion.

  - EasyPGX®ready ALK/ROS1/RET/MET.
- Immunohistochemistry (ICH) analyses:
  - ICH DMMR, ICH HER2, ICH PDL1
- NGS technique kits via Illumina® MiSeq:
  - *DNA gene panel with 17 genes*. Myriapod® NGS Cancer Panel DNA cat. no. NG033, Illumina® (CE IVD). The test allows one to identify single-nucleotide variants (SNV) and insertions and deletions (indels) in 17 genes of clinical-diagnostic importance in the main neoplasms (ALK, BRAF, EGFR, ERBB2, FGFR3, HRAS, IDH1, IDH2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET, ROS1, POLE).

    Starting material: DNA extracted from FFPE histological samples or ctDNA.
  - *RNA gene panel with 10 genes*. Myriapod® NGS Cancer Panel RNA, Illumina® (CE IVD). This is the panel dedicated to the study of gene fusions on 10 targets of interest (ALK, ROS1, RET, MET, PPARG, FGFR2, FGFR3, NTRK1, NTRK2, NTRK3) for the prediction of response to oncological drugs, from RNA extracted from tissue FFPE.

    Starting material: RNA extracted from FFPE histological samples.
- *FoundationOne® CDx*, a DNA single-tissue-based test with 324 genes. Test results include microsatellite instability (MSI) and tumor mutational burden (TMB).
- *FoundationOne® Liquid CDx*, which analyzes 324 genes from circulating cell-free DNA.
- *FoundationOne® Heme* combines > 400 DNA-sequenced and > 250 RNA-sequenced genes to detect all four main classes of genomic alterations, including sensitive identification of translocations and fusions.

Mutations that play a fundamental role in cancer development are called "drivers," because they confer a growth advantage on the affected cells. In human tumors, about 350 driver genes implicated in the development of the disease have been identified to date. Tumors strictly dependent on driver mutations are defined as "mutation-addicted."

Genetic alterations are classified as "*actionable*" when they are potentially responsive to a targeted therapy.

In order to offer some guidance, ESMO has published the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), a system that essentially classifies variants according to their clinical impact.

Tier I: Alteration–drug match associated with improved outcomes in clinical trials.

Tier II: Alteration–drug match with known antitumor activity but unknown benefit magnitude.

Tier III: Alteration–drug match suspected to improve outcomes based on clinical trial data from other tumor types or similar alterations.

Tier IV: Preclinical evidence of actionability.

Tier V: Alteration–drug match with objective response but without clinically meaningful benefit.

Tier X: Lack of evidence for actionability.

Based on ESCAT, the ESMO Precision Medicine Working Group recommends using tumor multi-gene NGS in patients presenting with advanced non-squamous non-small cell lung cancer (NSCLC), advanced colorectal cancer, prostate cancer, ovarian cancer, and cholangiocarcinoma, characterized by ESCAT level I mutations.

AIOM then implemented the same recommendations.

On May, 2024, the ESMO Precision Medicine Working Group extended these recommendations to other tumor types (advanced breast cancer, gastrointestinal stromal tumors, sarcoma, thyroid cancer, cancer of unknown primary) [5–11].

MTB Outcome

MTB meeting results are summarized and communicated via a specific written report on the CORM platform, indicating the proposed therapeutic options:

- *Standard therapy*: Common treatments include surgery, chemotherapy, and radiation, along with hormonal therapy, locore-

gional treatments, and targeted therapies such as immunotherapy.
- *Enrollment in clinical trials*.
- *Access to drugs through other modes*: Expanded access, off-label treatments, special funds for innovative drugs, etc.

Published real-world experiences indicate that patients treated according to MTB-recommended regimens, based on tumor molecular alterations, exhibit better outcomes in terms of progression-free and overall survival than those treated according to physician choice [2, 6, 7, 12].

The early access to drugs in Italy includes different possibilities:

- Off-label drugs are used in clinical practice for conditions not included in the *summary of product characteristics*, and they are prescribed for different therapeutic indications based on documented scientific evidence and only if better therapeutic alternatives are unavailable.
- Compassionate use means the provision, free of charge, by the pharmaceutical company of medicinal products that have not yet been authorized but have undergone clinical trials (successfully completed phase III or, in particular cases, phase II trials). It includes *nominal use* (individual patient use based on scientific evidence) and *expanded access program* (use in multiple patients under a defined clinical protocol).
- Italian Medicines Agency (AIFA) National Fund Law 326/2003—"Fondo 5%" for orphan drugs treating rare diseases and drugs offering therapeutic hope for serious conditions, pending marketing.

At our Department of Oncology, a dedicated team of professionals coordinates and manages clinical trials of innovative therapies for the treatment of patients with solid tumors, access to which can be allowed through molecular analysis. Most studies involve the use of immunotherapies and biological therapies, either alone or in combination with traditional therapies.

These trials are conducted following Good Clinical Practice guidelines, an international standard of ethics and scientific quality for the design, conduct, and recording of clinical trials involving human subjects.

Within the department, a Phase I Clinical Unit has been activated. It has obtained accreditation from the AIFA for phase I clinical trials. There is a particular interest in early phase I/IIa clinical trials involving a dose-finding and pharmacokinetic analysis design.

The Department of Oncology of the AOU Marche is the only active phase I center in central Italy at the current time.

Data Organization

MTB activity and performance data, demographic data for patients discussed in MTB meetings, and data regarding their therapeutic paths were collected from June 2021 to May 2024 and recorded in a specifically designed database in order to analyze all aspects that will be described in detail in the next paragraph.

The study was conducted in accordance with the precepts of Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Results presented in this article contain no personally identifiable information from the study. Ethical review and approval were waived for this study as per current regulations. Approval by the Chief Medical Officer and by the Quality Manager were required and were obtained (procedure reference: P001.DS).

Informed consent was obtained from all subjects involved in the study through the CORM (Cancer Center) platform.

RESULTS

Patient Characteristics

From June 2021 to May 2024, a total of 118 patients with cancer were discussed by the MTB of AOU Marche. The mean age of these patients was 59 years, with a median age of 61 years; 62

(53%) were female patients, with a median age of 58 years, while 56 (47%) were male patients, with a median age of 63 years.

Forty-one out of 118 patients (35%) were presented by internal oncologists, while the remaining 77 cases were submitted by oncologists from other hospitals within the Marche region. Specifically, 29 requests (24%) came from oncologists in the Province of Pesaro Urbino, 18 requests (15%) from the Province of Macerata, 14 (12%) from the Province of Ancona, 14 (12%) from the Province of Fermo, and two (2%) from the Province of Ascoli Piceno.

For both sexes, requests were highest for the first and second lines, decreasing with subsequent treatment lines. The term "no line" includes patients who had not undergone any chemotherapy and those who received neoadjuvant and/or adjuvant chemotherapy. Table 1 summarizes patient characteristics.

Out of the total cases, 17 (14%) patients had already undergone a molecular analysis identifying a specific mutation.

Among all cases presented to the MTB, 94 (80%) were accepted, while 24 (20%) were rejected; of the 94 accepted cases, 74 (78.72%) had valid biological samples for molecular analysis. In seven cases (7.45%), the biological material was insufficient or unsuitable, and in nine cases (9.57%), no sample was received. In four cases (4.26%), molecular profiling was deemed unnecessary, primarily because these patients had already undergone other molecular analyses but were still considered worthy of discussion.

Among the 24 rejected cases, in 12 instances (50%) the MTB recommended molecular profiling only in the event of disease progression, while the remaining 12 cases (50%) were referred to Oncological Genetics or another ward. Of these 12 cases, two patients exhibited disease progression and were subsequently rediscussed, providing valid samples for molecular investigations. Only one of the seven cases with initially insufficient material later provided a valid sample. Consequently, analyses were performed on 77 valid samples.

Besides strictly male and female cancers, almost all types affect both sexes, with notable differences in gastrointestinal (GI) and lung cancers. Specifically, 14 female patients (11.86%) had GI cancers, compared to eight male patients (6.78%). For lung cancer, there were six male patients (5.08%) and only one female patient (0.85%). Figure 1 summarizes

Table 1 Patient characteristics

Total patients	***N*** **= 118**
Age at diagnosis (years), median	61
Sex, *n* (%)	
Male	56 (47%)
Female	62 (53%)
Oncology site, *n* (%)	
AOU delle Marche	41 (35%)
Province of Pesaro-Urbino	29 (24%)
Pesaro	17 (59%)
Fano	3 (10%)
Urbino	9 (31%)
Province of Ancona	14 (12%)
Senigallia	6 (43%)
Jesi	4 (28.5%)
Fabriano	4 (28.5%)
Province of Macerata	18 (15%)
Macerata	10 (56%)
Civitanova Marche	8 (44%)
Province of Fermo	14 (12%)
Province of Ascoli Piceno	2 (2%)
Line of therapy, *n* (%)	
No line	9 (8%)
First	39 (33%)
Second	27 (23%)
Third	19 (16%)
Fourth	7 (6%)
> Fourth	10 (8%)
Unknown	7 (6%)

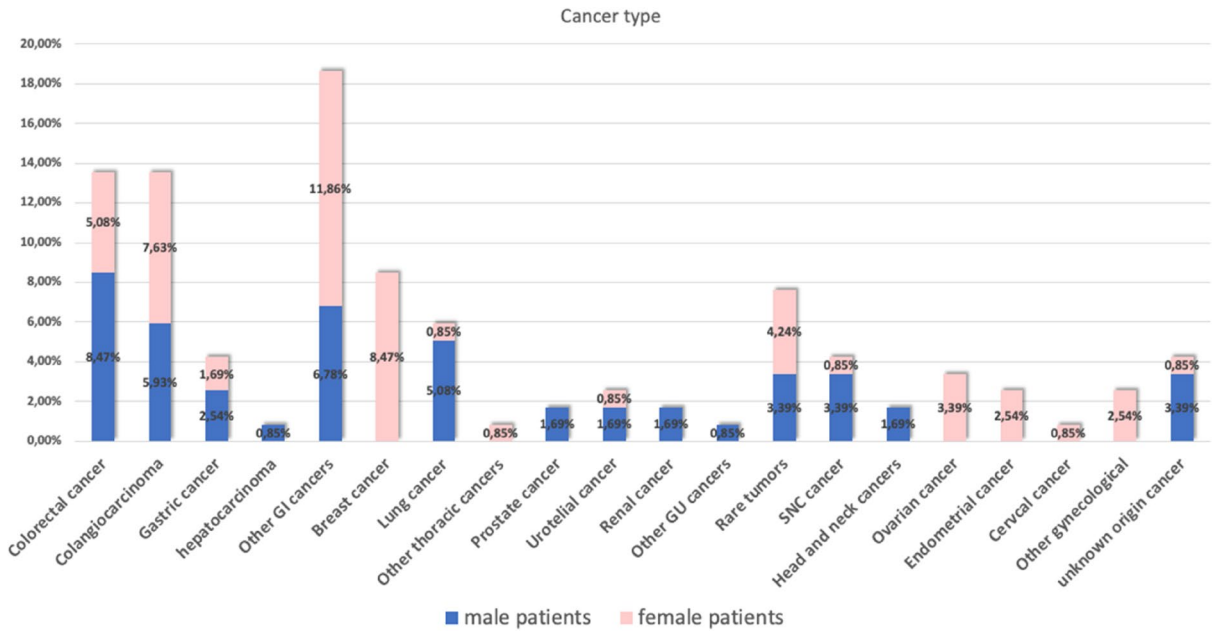

Fig. 1 Treatment lines at the time of MTB assessment requests

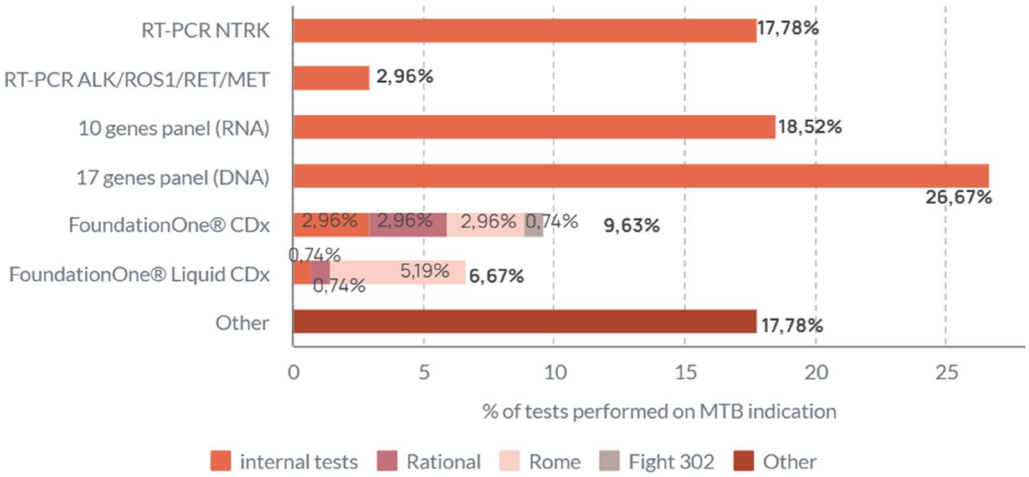

Fig. 2 Percentages of various tests performed as indicated by the MTB. "Other" includes tests such as immunohistochemistry, PIK3CA, IDH1/2 kits, and trial-specific tests like FoundationOne Heme

the percentages of patients, categorized by sex and cancer type, discussed by the MTB.

Genomic Profiling and Therapeutic Decisions

Several techniques were used in the analyses performed on the samples: RT-PCR, NGS with a small panel of DNA and/or RNA, or NGS with

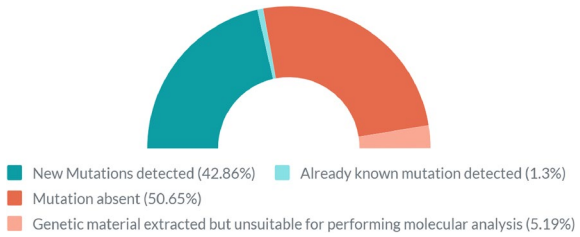

Fig. 3 Outcomes of genomic profiling for 77 patients

a larger panel such as FoundationOne or FoundationOne Liquid.

Figure 2 shows the percentages of various tests performed as indicated by the MTB.

Percentages for tests within clinical trial protocols (e.g., Rational, Rome, FIGHT-302) are also included. Specifically, 3.7% represents FoundationOne and/or Liquid performed in the Rational trial, 8.15% in the Rome trial, and 0.74% in the FIGHT-302 trial; the other 3.7% of FoundationOne and/or Liquid tests were provided free of charge by Roche. All the analysis based on RT-PCR, 10-gene RNA and 17-gene DNA panels, immunohistochemistry, and PIK3CA or IDH kits were reimbursed by Sistema Sanitario Nazionale (SSN).

Notably, all patients profiled within the Rome protocol were screen failures. Multiple tests and panels were used for several patients, so percentages refer to the total number of tests performed (135).

Among the 77 profiled patients, four (5.19%) had unsuitable genetic material for molecular analysis. No mutations were found in 39 patients (50.65%), while one patient (1.37%) had only a known mutation. New mutations were detected in 33 patients (42.86%), with four of these 33 also having known mutations. Figure 3 summarizes these results.

For patients who underwent molecular profiling, no differences were observed in the likelihood of discovering new mutations based on age, treatment line, gender, or type of neoplasm. This indicates that it is not possible to identify a specific "type" of patient who is more likely to have a druggable mutation; in other words, it becomes evident that the demographic and clinical characteristics of patients do not influence the likelihood of finding actionable mutations.

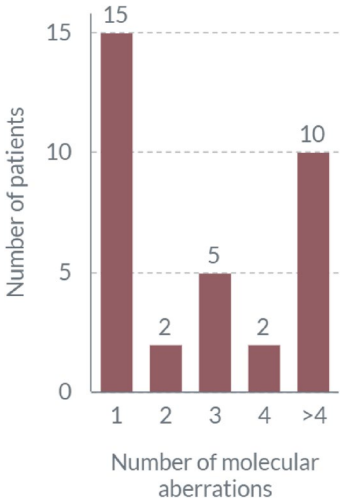

Fig. 4 Distribution of molecular aberrations among patients

As depicted in Fig. 4, 15 patients had one molecular aberration, two patients had two aberrations, five had three aberrations, two had four aberrations, and 10 had more than four aberrations. The most frequent mutation was in the KRAS gene, identified in 32.35% of mutated patients (11/34; 32.35%). (The number of molecular aberrations includes known mutations.)

The MTB issued therapeutic decisions for 80 patients, as shown in Fig. 5.

It is interesting to note that after MTB discussion and subsequent molecular profiling, the probability of receiving a recommendation for a new therapy is independent of treatment line, gender, or age. The only factor correlated with receiving a new therapy is the identification of a druggable mutation ($p = 0.008$). This underscores the importance of molecular profiling, as the discovery of actionable mutations remains the critical factor in increasing the likelihood of new treatment options.

With regard to treatment, 60 patients (75%) received *standard therapy*:

- Twenty-nine patients (36.25%) received standard therapy as no mutation was detected.
- Twenty-seven patients (33.75%) received standard therapy due to a lack of suitable clinical trials for detected or known muta-

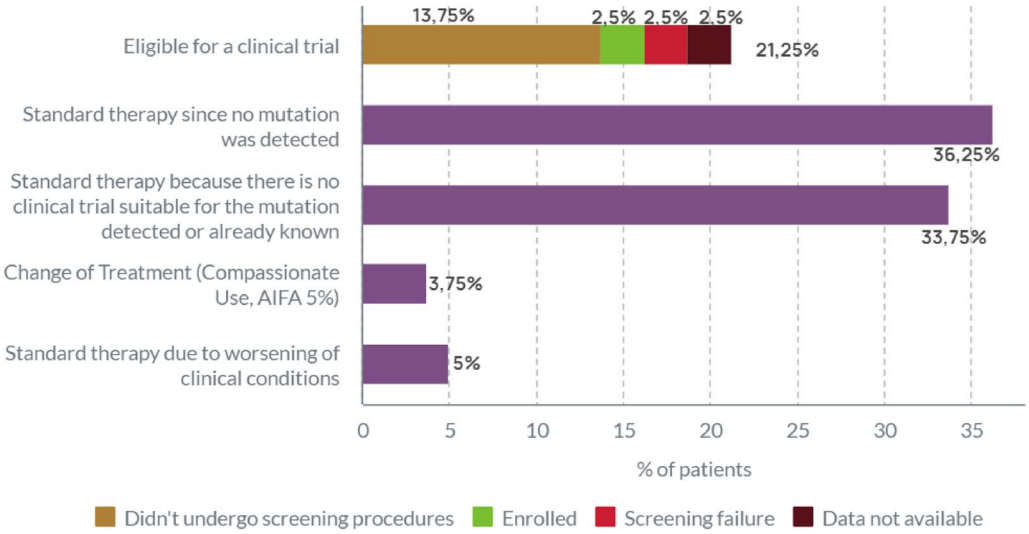

Fig. 5 Therapeutic decisions issued by the MTB for 80 patients

tions, meaning that no actionable mutation was found.
- Four patients (5%) received standard care due to worsening of their clinical conditions.

Additionally, 17 patients (21.25%) were deemed *eligible for clinical trials*. This group includes patients for whom molecular profiling was not indicated due to known actionable mutations or eligibility based on diagnosis and tumor staging.

- Eleven patients (13.75%) did not undergo trial screening, mainly due to declining clinical conditions or due to the distance to trial sites.
- Two patients (2.5%) were screen failures, one for the FIGHT-302 trial (NCT03656536) and another one for the THOR trial (NCT03390504).
- Two patients (2.5%) were enrolled in the COSTAR Lung trial (NCT04655976).
- No data were available for the other two eligible patients.

The MTB recommended *treatment changes* for three patients (3.75%):

- *Larotrectinib* for a patient with NTRK-fusion-positive infiltrating ductal carcinoma
- *Ivosidenib* for a patient with IDH1-mutated cholangiocarcinoma.
- *Carboplatin and pemetrexed* for a patient with pulmonary adenocarcinoma, previously treated with osimertinib, found positive for the EGFR exon 20 mutation (C797S), which confers resistance to osimertinib.

Analysis of Timing

The response times of the MTB were calculated to evaluate its performance:

- Average time from request to case discussion: 12 days.
- Average time from case discussion to MTB report: 28 days.
- Average time from sample reception to MTB report: 25 days.
- Average time from request date to final MTB report: 35 days for NTRK gene fusion.

DISCUSSION

The implementation and activity of the CORM and MTB have demonstrated significant advancements in the management of patients with cancer through precision medicine. The

data collected from June 2021 to May 2024 illustrate the effectiveness of a multidisciplinary approach in delivering personalized care pathways and optimizing treatment plans based on genomic profiling. Despite the challenges associated with the complexity of molecular data and the limited availability of targeted therapies, the CORM-MTB has facilitated more informed therapeutic decisions, thereby enhancing patient outcomes.

The integration of technologies such as NGS has been pivotal in identifying actionable mutations and tailoring treatments accordingly. The establishment of the MTB has not only streamlined the molecular testing process but also ensured that oncologists have access to the latest advancements and clinical trials. This multidisciplinary collaboration has proven essential in interpreting complex genetic data and translating it into clinical practice, offering hope for improved survival rates and quality of life for patients with cancer in the Marche region.

In accordance with the MTB protocol, patients were either candidates for off-label treatments if a drug against the driver mutations was available for a different indication, or they were enrolled in targeted therapy in a clinical trial setting after discovering a biomarker-based study that was underway at our department or at other locations. Whether the patients were enrolled in the trial or received the targeted therapy determined their eligibility and the likelihood of off-label or compassionate use of the specific drug.

Concerning clinical trials, eligibility criteria ensure participant safety in clinical studies but can be overly restrictive, unjustifiably excluding patients from trials [13]. A review of randomized controlled trials found that 47.2% of criteria were not scientifically justified, leading to failed recruitment and exclusion of real-world populations from potential treatments [14]. In actuality, our research showed that only 2.5% of individuals with a mutation were included in a clinical trial, even though 21% of them would have been eligible.

Additionally, due to the initial inexperience, hospital facilities that refer patients to our MTB tended to refer patients who were highly pretreated and had a poor prognosis, making them ineligible. As a result, individuals were unable to gain from being treated with targeted medicines or included in research trials. Therefore, our study's low actionability seems to be consistent with that of other Italian and European centers.

Flexible, data-driven eligibility criteria are needed, with artificial intelligence (AI) and machine learning playing a crucial role in evaluating suitable patients for studies beyond restrictive exclusion/inclusion approaches [15]. Identifying suitable treatments or trial options is challenging due to the vast number of recruiting studies, actionable mutations, and growing literature. Trial-matching software can assist clinicians in reviewing available studies based on patient profiling results, beyond clinicians' local and clinical trial knowledge [13, 16].

Looking ahead, several key areas warrant further development to sustain and enhance the impact of precision oncology in cancer treatment.

First, increasing the adoption and integration of advanced computational tools and artificial intelligence can aid in the interpretation of complex genomic data, enabling more precise and individualized treatment plans. These technologies can also facilitate the identification of suitable clinical trials, thus expanding treatment options for patients with rare or difficult-to-treat cancers.

However, according to Frost et al., treatment rates do not increase significantly with more complex testing, potentially due to a lack of drugs for these genomic alterations or due to the difficulty clinicians face in discerning actionable mutations from excessive data. Developing computational methods to aid in integrating and interpreting multi-test data linked to current literature and treatment options could alleviate this burden. Drug availability remains a limiting factor that may improve over time [13].

Second, fostering international collaborations can also enhance the sharing of knowledge and resources, thereby accelerating the development and implementation of new therapies. Ongoing education and training for healthcare professionals in the field of genomic medicine are essential to keep pace with the rapid advancements in this area. This includes not only oncologists but also geneticists, molecular biologists,

and other specialists involved in the multidisciplinary care of patients with cancer.

By addressing these areas, the CORM-MTB can continue to lead the way in precision oncology, ultimately contributing to advancement towards a future where cancer is not only treatable but also manageable as a chronic disease.

There are two major limitations of our study. The first is the small sample size (118 patients), which did not allow for certain statistically significant analyses such as gender-based oncology. Indeed, no substantial differences were observed between male and female patients, and no statistically significant differences were observed regarding the correlation between treatment line and gender ($p=0.051$ for the overall trend and $p=0.672$ for the specific trend). In addition, in the patient population evaluated within the MTB, there were no apparent differences in terms of tumor type, line of treatment, or age.

The second limitation is the extremely small panel that is utilized for the great majority of evaluations. Because of the low number of genes evaluated by our local panels, our patients were only able to benefit from a restricted set of targets. This is precisely why expanding the quantity of knowledge currently available on innovative specific synergies that may develop into therapeutic techniques is crucial. However, in order to obtain more data, we will soon be conducting a study with a larger panel (50 genes).

CONCLUSION

The opportunity to learn more about the use of precision medicine and better patient outcomes has been made possible by the MTB. A well-thought-out MTB system will advance with technology to guarantee that patients receive the greatest care possible without incurring needless expense or risk. As this will assist clinicians in making judgments, it might also enhance clinical expertise.

The commitment to personalized care, continuous research, and patient-centric approaches will be the cornerstone of this progress.

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Declarations

Conflict of Interest. Rossana Berardi has been involved as a consultant and expert witness for AstraZeneca, Bayer, Boehringher Ingelheim, EISAI, Gilead, Incyte, Lilly, Menarini, Merck, and MSD. Veronica Agostinelli has been involved as a consultant and expert witness for Amgen,

Regeneron, and GSK. All other named authors confirm that they have nothing to disclose. Rossana Berardi is an Editorial Board member of *Oncology and Therapy*. Rossana Berardi was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

Ethical Approval. The study was conducted in accordance with the precepts of Good Clinical Practice and the ethical principles of the Declaration of Helsinki. Results presented in this article contain no personally identifiable information from the study. Ethical review and approval were waived for this study as per current regulations. The approval by the Chief Medical Officer and by the Quality Manager was required and obtained (procedure reference: P001.DS). Informed consent was obtained from all subjects involved in the study through the CORM (Cancer Center) platform.

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