Molecular Tumor Board as a Clinical Tool for Converting Molecular Data Into Real-World Patient Care

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ABSTRACT

PURPOSE The investigation of multiple molecular targets with next-generation sequencing (NGS) has entered clinical practice in oncology, yielding to a paradigm shift from the histology-centric approach to the mutational model for personalized treatment. Accordingly, most of the drugs recently approved in oncology are coupled to specific biomarkers. One potential tool for implementing the mutational model of precision oncology in daily practice is represented by the Molecular Tumor Board (MTB), a multidisciplinary team whereby molecular pathologists, biologists, bioinformaticians, geneticists, medical oncologists, and pharmacists cooperate to generate, interpret, and match molecular data with personalized treatments.

PATIENTS AND METHODS Since May 2020, the institutional MTB set at Fondazione IRCCS Istituto Nazionale Tumori of Milan met weekly via teleconference to discuss molecular data and potential therapeutic options for patients with advanced/metastatic solid tumors.

RESULTS Up to October 2021, among 1,996 patients evaluated, we identified >10,000 variants, 43.2% of which were functionally relevant (pathogenic or likely pathogenic). On the basis of functionally relevant variants, 711 patients (35.6%) were potentially eligible to targeted therapy according to European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets tiers, and 9.4% received a personalized treatment. Overall, larger NGS panels (containing >50 genes) significantly outperformed small panels (up to 50 genes) in detecting actionable gene targets across different tumor types.

CONCLUSION Our real-world data provide evidence that MTB is a valuable tool for matching NGS data with targeted treatments, eventually implementing precision oncology in clinical practice.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

In the past 2 decades, the molecular characterization of tumors has become an essential tool to guide patients' treatment. Recent evidence suggests that up to 37% of patients with cancer harbor at least one potentially druggable genetic alteration.[1] Accordingly, in 2021, over a third of new Food and Drug Administration (FDA) drug registrations (6/17) in oncology were represented by compounds targeted to specific DNA-based biomarkers.[2,3] Along this line, European Society for Medical Oncology (ESMO) guidelines recommend routine use of next-generation sequencing (NGS) in patients with advanced nonsquamous non–small-cell lung cancer (NSCLC), colorectal cancer (CRC, if not implying increased costs over single-gene testing), prostate cancer, ovarian cancer (OC), cholangiocarcinoma (CCA),[4] and, more recently, metastatic and/or recurrent thyroid carcinoma (TC) and salivary gland carcinoma.[5,6] In addition, ESMO recommends clinical research centers to extend multigene NGS testing to other cancer types, including breast cancer (BC), pancreatic cancer (PC), and hepatocellular carcinoma,[4] in the context of molecular screening programs to inform clinical researchers and to promote access to innovative drugs. These circumstances, along with a steady decrease in the costs of NGS analyses, led to a widespread diffusion of NGS procedures, which produce

CONTEXT

Key Objective

Molecular Tumor Boards (MTBs) are candidate to represent essential tools for the management of next-generation sequencing (NGS) data for targeted therapies in precision oncology. In 2020, an institutional MTB has been set at the National Cancer Institute of Milan for the weekly discussion of potential therapeutic options for patients with advanced/metastatic solid tumor, on the basis of the mutational model.

Knowledge Generated

The current study reports the composition, workflow, and results of a real-world MTB: in the first 18 months of activity, our MTB indicated the potential eligibility to targeted therapy in 35.6% of almost 2,000 patients, 9.4% of whom ultimately received a personalized treatment. Furthermore, comprehensive genomic profiling was found to outperform the use of small panels in detecting variants potentially actionable in clinical trials.

Relevance

Collectively, these data point toward a central role of MTB in mastering NGS testing and targeted therapy management in clinical practice.

huge volumes of molecular data to be swiftly translated into clinically meaningful information.[7-9] To this aim, several institutions recently set multidisciplinary teams (MDTs) where molecular pathologists, biologists, bioinformaticians, geneticists, clinical oncologists, and pharmacists cooperate to match molecular data with targeted treatments. This multidisciplinary model commonly falls under the definition of Molecular Tumor Board (MTB), as originally described by Kurzrock's group in 2014.[10] Ever since, MTBs have been proposed as valuable tools in dissecting the complex interaction between molecular data and patient management, implementing molecular test application, data interpretation, and access to therapies.[11] Nevertheless, data are still immature relative to the analytical procedures and clinical utility of MTBs in daily clinical practice, with most of the reports focusing on clinical trials or specific cancer settings. Here, we present the structure, composition, procedure, and clinical results of an institutional MTB operating in a cancer center in Italy, focusing on its composition and workflow, type and output of NGS panels used, as well as procedures for variant annotation, definition of actionability, and therapeutic recommendations.

PATIENTS AND METHODS

The prospectively collected mono-institutional cohort described in this study includes consecutive patients with cancer whose tumor specimens were molecularly characterized by NGS at the Pathology Department of the Fondazione IRCCS Istituto Nazionale Tumori (INT) of Milan, and discussed by the institutional MTB, between May 2020 and October 2021. NGS testing was carried out, after informed consent collection, in the following patient settings: (1) meeting the above mentioned ESMO criteria[4]; (2) with metastatic/advanced disease progressing on standard therapeutic options independent of ESMO criteria; (3) potentially eligible in prospective clinical studies requiring NGS characterization; and (4) included in institutional screening programs (NSCLC, melanoma, and gastrointestinal stromal tumors), independent of tumor stage. NGS testing in liquid biopsy was performed at diagnosis whenever tissue analysis was unsafe or in patients relapsing upon therapies with tyrosine kinase inhibitors. NGS was performed in patients with 0-2 performance status.

Baseline demographic, clinical, and molecular data from the institutional electronic health record (EHR) were collected and stored in a dedicated database based on the institutional RedCap platform interface (Data Supplement [Methods]). The study was approved by the INT Institutional Ethics Committee (code INT-277/20) and was carried out in accordance with the Declaration of Helsinki.

MTB Composition and Workflow

The core of the MTB was composed of five molecular pathologists, six biologists, two bioinformaticians, two geneticists, five oncologists, one pharmacologist, and one data scientist. The institutional MDTs were involved in MTB activities through formally designed delegates who discussed cases with the MTB core team and reported to the patients. The MTB workflow included (1) selection of patients eligible for molecular testing; (2) identification of suitable and cost-effective gene panels meeting the requirements of the treating oncologist; (3) interpretation of variant biological and clinical significance; (4) identification of the optimal treatment for the individual patient; (5) identification of patients eligible for genetic counseling; (6) creation of a formal report enclosed into the EHR; and (7) prospective annotation of outcome data. The MTB core team and delegates from MDTs met weekly via videoconference

(average meeting duration of 2 hours). Usually, the MTB discussion was carried out within 10 working days from the NGS report.

Further details regarding NGS methodologic procedures, gene variant functional and clinical annotation, and therapeutic recommendations can be found in the Data Supplement (Methods).

RESULTS

Study Population

Between May 2020 and October 2021, tumor samples and/or liquid biopsies from 1996 patients were molecularly characterized through 2,517 NGS tests. Median patient age at the time of NGS analysis was 64.2 years (ranging from 1 month to 91.9 years). Specifically, NGS tests were performed on tumor samples collected during standard diagnostic procedures: tumors from 1,963 patients (98.3%) were characterized on archival formalin-fixed paraffin-embedded blocks, including 1,078 (55%) primary tumors and 885 (45%) metastatic samples, while in 50 patients (2.5%), tumor genomic characterization was performed by liquid biopsy (17 patients were tested on both tumor tissue and plasma). The most common primary site was lung (26%), followed by colon-rectum (14.1%) and female reproductive system (12.3%; Fig 1A; Appendix Table A1).

Most patients (1,533; 76.8%) were characterized by a single molecular test, while multiple panels were applied in 463 patients. In most of these patients (446 of 463), a combination of two panels for the detection of DNA mutations and RNA aberrations was used. Figure 1B shows the gene panels used in NGS analysis and their prevalence.

NGS Results

In the whole study cohort, after polymorphisms and synonymous variant filtering, a total of 10,475 variants (mean, 6.49; median, 2; range, 1-219 mutations per case) were identified in 1,612 patients (80.7%). Three hundred eighty-five patients had no reportable alterations (wild-type, 19.3%). In particular, 43.2% of the variants were classified as functionally relevant (39.9% pathogenic and 3.3% likely pathogenic), while 56.8% were classified as neutral (55.7% variant of unknown significance, 0.4% benign, and 0.7% likely benign), leading to 1,525 (76.4%) patients with at least one pathogenic or likely pathogenic variant (Data Supplement [Fig A1]). The output in Figure 2 depicts the landscape of all the pathogenic variants found in our data set and their specific alteration.

Definition of Clinical Actionability

Pathogenic variants were stratified into European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets (ESCAT) classes. ESCAT I-IV actionable alterations were found in 57.8% (1,154/1,996) of the study population. Table 1 summarizes the prevalence of patients harboring actionable alterations according to ESCAT scale. Of note, 21.7% (433) and 7.1% (141) of patients harbored an ESCAT Tier I or a Tier II mutation, respectively, with a cumulative prevalence of 28.8% (574 patients). As expected, gene variants with strong evidence of clinical actionability

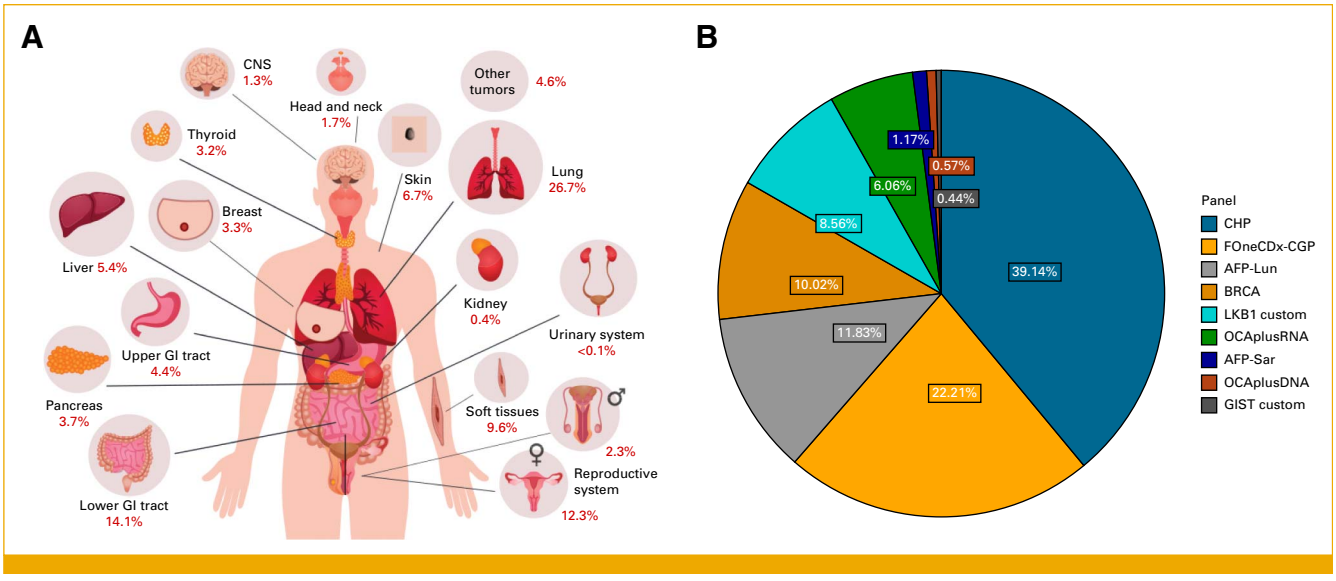

FIG 1. (A) Distribution of patients included in the study cohort by primary tumor localization. (B) Prevalence of the NGS assays used in the study cohort. Most (77.4%) tests were performed in house, and the remaining (22.6%) were outsourced and profiled by FoundationOne CDx (550 cases) or OncotypeMAP (two cases). AFP-Lun, Archer FusionPlex Lung panel; AFP-Sar, Archer FusionPlex Sarcoma panel; BRCA, Oncomine BRCA Research Assay; CHP, Ion AmpliSeq Cancer Hotspot Panel v2; FOneCDX-CGP, FoundationOne CDX; LKB1 custom, custom lung LKB1 v.2 panel; OCAplusDNA, Oncomine Comprehensive Assay Plus, DNA.

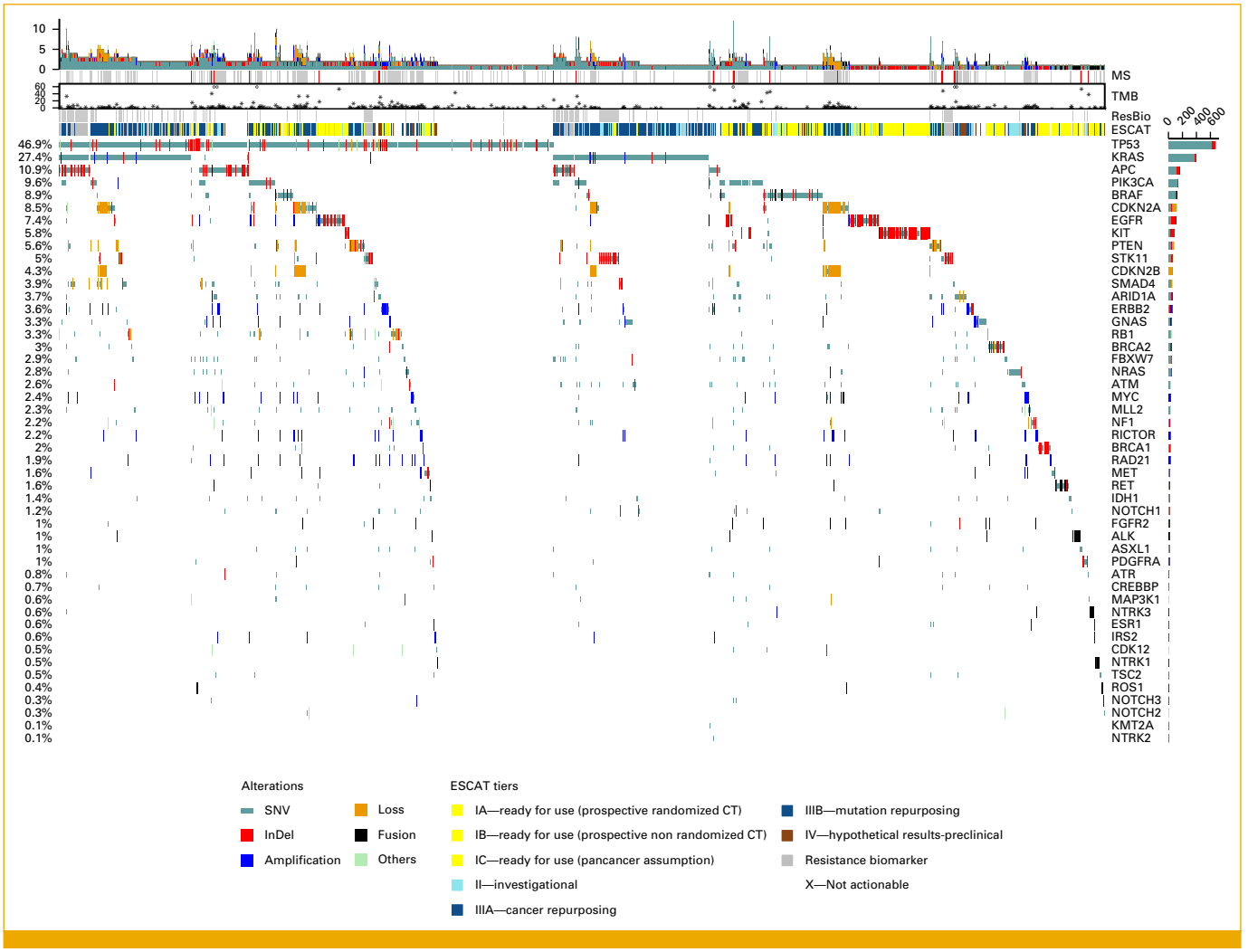

FIG 2. Oncoprint plot visualizing pathogenic genomic alterations in patients of the study cohort (in columns), including SNVs, indels, CNVs, and fusions, ranked according to their prevalence (right bars). MSI status, TMB, whenever available (upper panel), and the level of clinical actionability according to ESCAT classification (right panel) are also provided. As expected, *TP53* and *KRAS* mutations were largely represented, with a prevalence of 47% and 27.1%, respectively. Among 566 (28.4%) patients evaluated with CGP panels (FoundationOne CDx, Oncomine Comprehensive Assay Plus, and OncotypeMap), we were able to obtain TMB and MSI status in 493 and 482 cases, respectively. High MSI was detected in 27 patients (5.6%), with the highest prevalence in patients with gastroesophageal carcinoma (10 of 64 patients, 15.6%) and in patients with CRC (11 of 75 patients, 14.7%). TMB ranged from 0 to 252 mutations/Mbp (median, 3.78). Sixty-three (12.8%) patients had a TMB >10 mutation/Mbp, including a case with a *POLE* mutation and a TMB of 252 mutation/Mbp. Highest percentages of TMB >10 were detected in patients with neuroendocrine carcinoma (5/19; 26.3%), CRC (16/75; 21.3%), gastroesophageal carcinoma (11/61; 18%), and breast carcinoma (5/32; 15.6%). Overall, 149 gene fusions (80) or rearrangements (69) were detected in 135 patients of 1,014 patients (13.3%) tested with Archer lung (29 cases of 296 tests; 9.8%), Archer sarcoma (8/29; 27.5%), FoundationOne CDx (103/550; 18.7%), and Oncomine Comprehensive Assay RNA Plus (9/151; 5.9%) panels, for a total amount of 1,026 tests. Of the 135 patients bearing gene fusions/rearrangements, 56 (41.4%, corresponding to 5.4% of the whole series) had actionable alterations, and targeted treatment was administered to 22 of them (24%, 2.1%), while eight patients were lost at follow-up. CGP, comprehensive genomic profiling; CNVs, copy number variations; CRC, colorectal cancer; ESCAT, European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets; MSI, microsatellite instability; SNVs, single-nucleotide variations; TMB, tumor mutational burden.

were associated with higher rates of treatment recommendation and therapy initiation.

When stratified by tumor types, patients with gastrointestinal stromal tumors (GIST), BC, TC, lung adenocarcinoma, OC, and melanoma showed the highest prevalence of putatively druggable targets, in line with the high prevalence of *KIT* (GIST), *PIK3CA* (BC), *BRAF* (melanoma and TC) and *RET* (TC), *EGFR*, *ALK* and *ROS1* (lung adenocarcinoma), and *BRCA1* and *BRCA2* (BC and OC) alterations. Figure 3A summarizes the distribution of ESCAT classes across the different tumor types.

Treatment Assignment

After MTB discussion, 711 patients (35.6%) were considered as potentially eligible to a targeted therapy. Of these, the

TABLE 1. Prevalence of ESCAT Classes, Drug Recommendation, and Targeted Treatment in Patients Discussed by the MTB

ESCAT Class	ESCAT Class Prevalence, No. (%)	Personalized Drug Recommendation, No. (%)
I—Ready for use	434 (21.7)	420 (96.7)
II—Investigational	144 (7.2)	109 (75.2)
III—Cancer and mutation repurposing	483 (24.2)	164 (33.9)
IV—Hypothetical target	97 (4.9)	18 (18.5)
X—Not actionable	266 (13.3)	—
Resistance biomarker	103 (5.2)	—
VUS or wild-type	469 (23.5)	—

NOTE. The column ESCAT class prevalence describes the overall prevalence of the highest level of actionability of ESCAT classes across patients.
Abbreviations: ESCAT, European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets; MTB, Molecular Tumor Board; VUS, variant of unknown significance.

MTB gave an indication for a standard-of-care (SOC) treatment (ie, drugs approved by the Italian drug agency Agenzia Italiana del FArmaco (AIFA) and reimbursed by the national/regional health care system [NHS]) in 241 (33.9%) patients, for an off-label drug (not approved or not yet reimbursed by NHS) in 170 patients (23.9%), and for enrollment in a clinical trial in 333 (46.8%) patients; 33 patients with gene alterations classified as ESCAT scale II-IV received more than one indication for potential non-SOC treatments. SOC was more frequently indicated for patients with NSCLC (81; 15.9%), GIST (79; 78.2%), OC (38; 15.7%), and melanoma (33; 13.6%); off-label treatment was more frequently suggested for patients with CRC (24.2%, including combinations with BRAF inhibitors), NSCLC (15.4%, including RET, KRAS G12C, and MET inhibitors), and CCA (7.1%, including IDH1, FGFR inhibitors, and PARP inhibitors in $BRCA^{mut}$ patients). Finally, enrollment into clinical trials was more frequently recommended for patients with NSCLC (27.3%, poziotinib, tepotinib, and RET inhibitors), CRC (13.5%, including immunotherapy for microsatellite instability [MSI]-high and tumor mutational burden [TMB]-high patients, as well as human epidermal growth factor receptor 2 [HER2] inhibitors), melanoma (6.9%, including pan-RAF and MEK inhibitors), BC (6%, including PI3K and PARP inhibitors), and CCA (5.4%, including BRAF, HER2, and MAT2A inhibitors). Median time from MTB discussion to therapy administration, evaluated in 127 of 178 patients (71.3%), was 18 days.

Of the 711 patients eligible for targeted therapies, 118 were lost at follow-up (mainly patients treated in other institutions). Of the remaining 593 patients for whom follow-up data were available, 178 (30%, corresponding to 9.4% of the whole cohort, excluding patients lost at follow-up) received a personalized treatment, including 77 (42.1% of the 178 cases) patients with a SOC recommendation (5.1% of the whole cohort), 63 (35.4%) patients with an off-label therapy recommendation (3.2% of the whole cohort), and 38 (21.3%) patients eligible for enrollment in a clinical trial (1.9% of the whole cohort; Fig 3B).

Of the 415 patients who did not receive personalized treatments after MTB discussion, 21.7% could not be addressed to actively recruiting trials, 15% were patients with early-stage tumors, 40.1% were receiving standard therapy when NGS data were produced and discussed in the MTB, and 3.2% had poor performance status (1.9%) or died before therapy (1.3%; Data Supplement [Figs A2A and A2B]).

Higher rates of druggable alterations and treatment recommendations occurred in patients with GISTs (82.18% and 21.78%, respectively), NSCLC (42.9% and 14.2%, respectively), and melanoma (45.9% and 8.2%, respectively). In rarer tumor types, we found high rates of actionability among medullary TCs (*RET* mutations in 10/11 patients, leading to second-line targeted therapy in two cases) and papillary TC (potentially actionable targets in 10/18 cases, with five patients starting dabrafenib/trametinib combo within a compassionate use program and one patient with an *NTRK3-ETV6* fusion starting entrectinib).

More than 10% of patients with MSI-H, or *EGFR*, *KIT*, *BRAF*, or *RET* gene alterations received personalized treatments. Conversely, despite the high prevalence of cases carrying a *KRAS* mutation, only a minority could have access to targeted therapies (namely, patients with KRAS G12C-mutated NSCLC; Fig 4).

Actionability According to ESCAT Classification

We also analyzed the data set stratified according to ESCAT. In detail, among 434 patients with at least one ESCAT scale I alteration, 77 patients (17.7%) received personalized SOC therapy and eight additional patients were waiting for therapy initiation. The causes of exclusion of the 349 remaining patients are detailed in the Data Supplement [Fig A2B]. It is worth noting that for 181 ESCAT scale I patients who did not receive a SOC personalized therapy (181/349; 51.9%), the matched drug was not approved by the Italian regulatory agency at the time of MTB discussion. For 23 of these patients (12.7%), mainly patients with CRC treated with cetuximab encorafenib combo (19/23; 82.6%), MTB obtained the access to therapy through off-label indications.

Among the 291 patients bearing at least one actionable ESCAT II-IV scale target, the MTB indicated the potential utility of off-label drugs or the enrollment in a clinical trial for 55 and 230, respectively. Figure A3 in the Data Supplement shows the prevalence of drugs suggested according to variant ESCAT classification across different tumor types.

Panel Usage

Then, we analyzed the impact of NGS panels stratified into large or small according to the number of genes evaluated

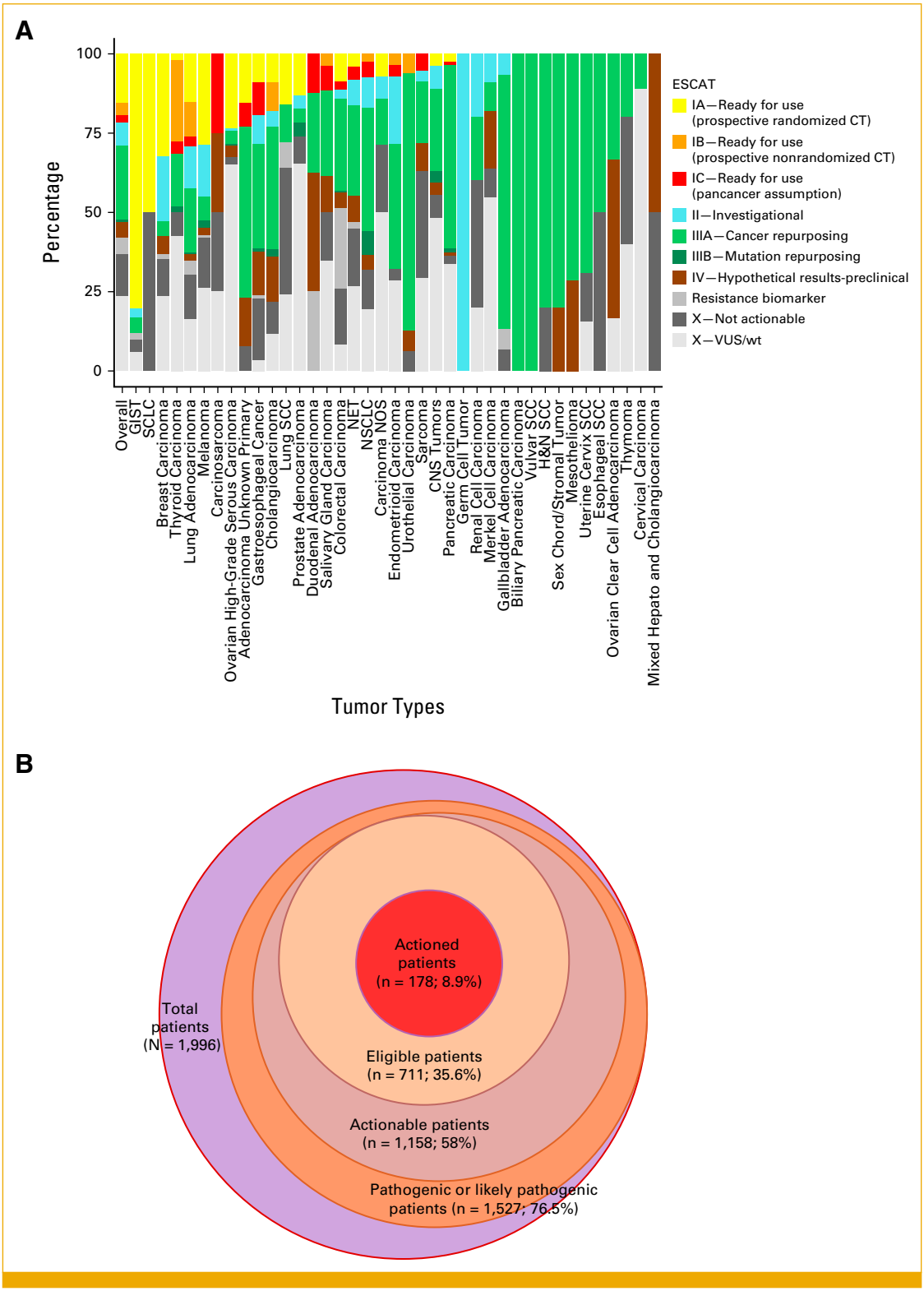

FIG 3. (A) ESCAT classification of pathogenic variants across different tumor types. The high prevalence of targetable genes found in SCLC and carcinosarcoma (ie, malignant mixed mullerian tumors [2/4, including one ALK fusion and one p.L858R EGFR mutation; and 1/4, MSI-high, respectively]) was reasonably due to the small number of patients evaluated. (B) Venn plot describing the prevalences of gene alterations, MTB recommendation, and therapeutic interventions in the whole cohort. Pathogenic or likely pathogenic: patients harboring at least (continued on following page)

FIG 3. (Continued). one functionally significant gene variant; actionable: patients with at least one ESCAT 1-4 alteration; eligible: patients for whom MTB gave a therapeutic recommendation; actioned: patients actually receiving the recommended therapy. CT, computed tomography; ESCAT, European Society of Medical Oncology Scale for Clinical Actionability of Molecular Targets; GIST, gastro-intestinal stromal tumor; MTB, Molecular Tumor Board; NET, neuroendocrine tumor; NOS, not otherwise specified; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; VUS, variant of unknown significance.

(>50 genes and ≤50 genes, respectively). Notably, in the whole patient cohort, large panels were able to identify actionable targets at significantly higher frequencies than small panels. Specifically, large and small panels detected actionable variants in 270/566 (47.7%) and 545/1,951 (27.9%) of patients evaluated ($P < 10^{-6}$), respectively. Large panels were able to identify a significantly higher prevalence of actionable alterations in almost all the tumor types, including CRC ($P < 1 \times 10^{-7}$), PC ($P < 1 \times 10^{-6}$), gastric ($P = 2.5 \times 10^{-3}$), and ovarian ($P = .023$) carcinomas. As shown in Figure 5, we found a statistically significant benefit deriving from large panel usage. Likewise, large panels identified a significantly higher prevalence of actionable alterations in most of the tumor types analyzed, with an overall absolute increase of detection of 12.5% (37.1% *v* 24.6%; $P = 1.38 \times 10^{-8}$; Fig 5, left chart).

Overall, the prevalence of patients starting a targeted therapy was not significantly different using large or small panels, with 50 (8.8%) and 142 (7.3%) actioned molecular alterations identified, respectively ($P = .46$). Nonetheless, in patients with CRC, there was a significant increase in the prescription of immune checkpoint inhibitors when using large panels ($P < 1 \times 10^{-4}$), mostly because of their capability to capture MSI status. A clear trend, although not statistically significant, was also observed in gastric cancers (mainly because of immunotherapy administration in MSI-H and high TMB patients).

Of interest, large panels led patients to treatment with non-SOC therapies more frequently: among 566 cases profiled with large panels, 15 and 35 patients were treated within clinical trials or with off-label therapies (2.6% and 6.2% of patients profiled, respectively), in comparison with 27 and 29 patients, respectively, among the 1,951 cases profiled with small panels (1.4% and 1.5%, respectively; $P < 10^{-6}$). Appendix Table A2 summarizes the distribution of the actioned targets stratified according to the NGS panel.

DISCUSSION

Herein, we report procedures and results of the first 18 months of activity of the MTB operating at INT. To the best of our knowledge, this study represents the largest mono-institutional case series reporting the activity of an MTB platform in Italy.

It has been proposed that MTB should be activated only in specific circumstances, including the finding of unusual mutational landscapes, the exhaustion of standard therapeutic

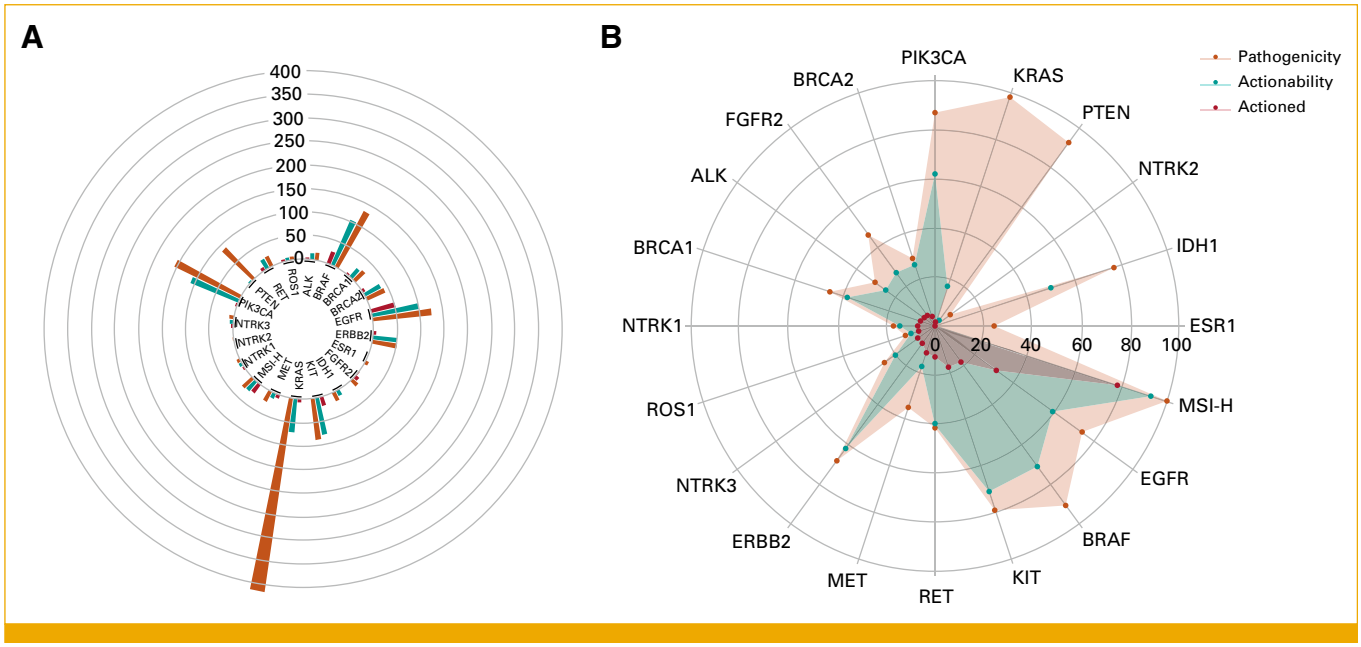

FIG 4. The top-20 actioned genes in our data set. For any gene, (A) absolute and (B) relative values of pathogenic, actionable (eligibility to targeted therapy), and actioned (patients actually receiving a targeted therapy) variants are shown.

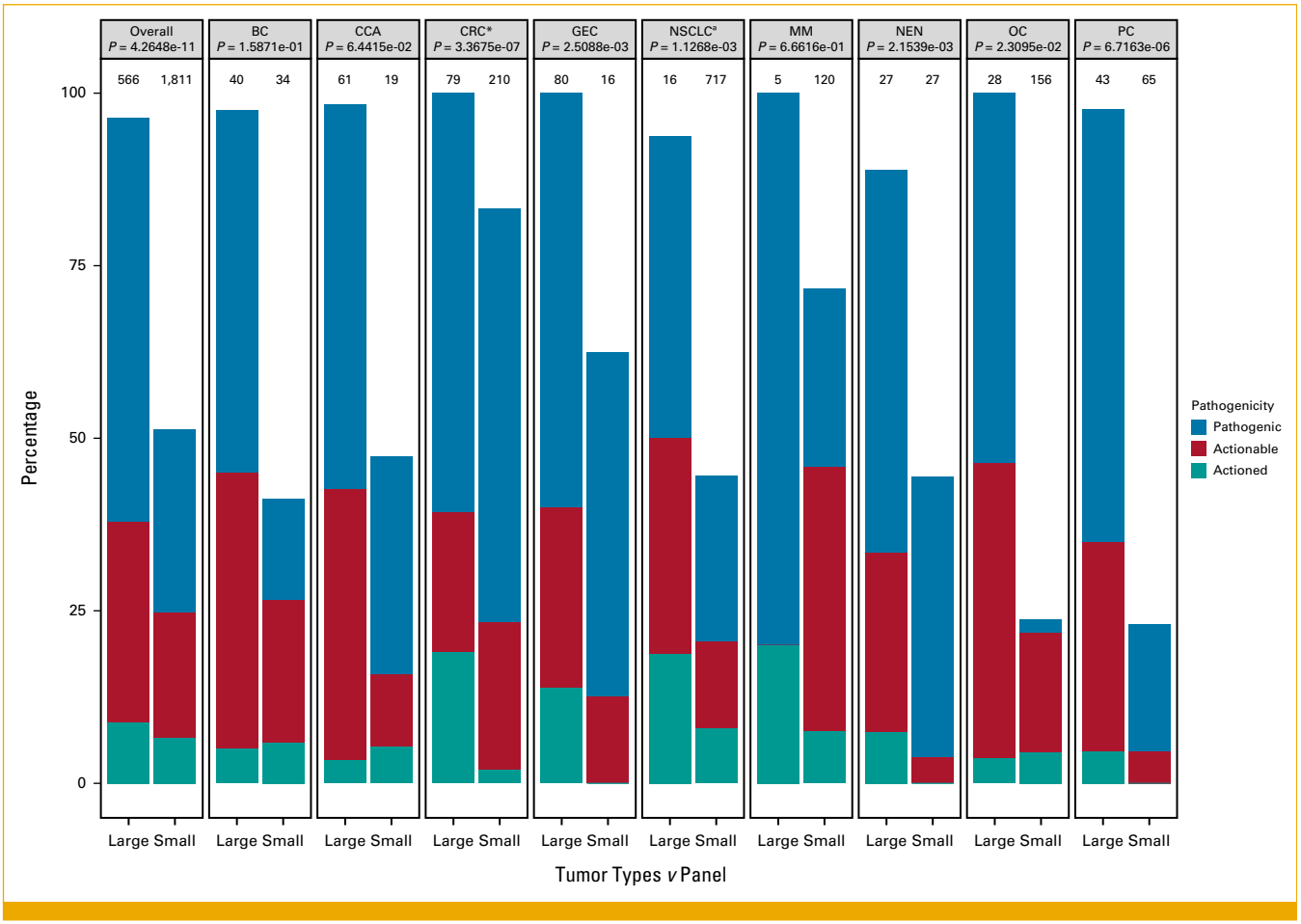

FIG 5. Prevalence of pathogenic (blue), actionable (eligibility to targeted therapy; red), and actioned (patients actually receiving a targeted therapy; teal) variants in the commonest tumor types included in our cohort according to the extent of the NGS panel used. Specifically, FoundationOne CDx (324 genes), Oncomine Comprehensive Plus Assays (501 genes investigated for DNA alterations, and 49 for RNA fusions), and OncotypeMAP panel (290 genes), which are able to detect gene mutations, CNVs, gene fusions, MSI, and TMB, were defined as large panels; however, the Ion AmpliSeq Cancer Hotspot Panel v2 (50 genes), the Oncomine BRCA Research Assay (two BRCA genes), the LKB1 v.2 panel (seven genes), the GIST panel (14 genes), the FusionPlex Sarcoma panel (26 genes), and the FusionPlex Lung panel (14 genes) were classified as small panels. In patients with lung adenocarcinoma, for an unbiased evaluation of the putative added value of large panels over standard diagnostic procedures, the output of large panels was compared with that of small DNA panels (Hotspot and LKB1.v2 panels) plus RNA panels (Archer FusionPlex Lung and Oncomine Comprehensive Assay RNA Plus, which assess *ALK*, *ROS1*, and *RET* fusions). *P* values refer to the prevalence of actionable targets in large panels compared with small panels. **P* < .05 in actioned targets in large versus small panel. [a]For an unbiased evaluation, in NSCLC only cases with available paired DNA and RNA tests in small panels have been included in the chart. BC, breast cancer; CCA, cholangiocarcinoma; CNVs, copy number variations; CRC, colorectal carcinoma; GEC, gastroesophageal adenocarcinoma; GIST, gastro-intestinal stromal tumor; MM, malignant melanoma; MSI, microsatellite instability; NEN, neuroendocrine neoplasm (including 21 gastroenteropancreatic tumors, 14 lung tumors, and 10 rarer tumors from different districts); NGS, next-generation sequencing; NSCLC, non–small-cell lung cancer; OC, ovarian carcinoma; PC, pancreatic carcinoma; TMB, tumor mutational burden.

regimens, or for clinical trial enrollment.[12] Consistently, several studies reported the outcome of monothematic MTBs, which limited data analysis and discussion to patients affected by specific tumor types.[13] Our MTB routinely discusses all NGS-profiled consecutive patients, with a real-world approach that leads to unique and realistic portrait of targeted therapy accessibility in an unselected population.

In our series, MTB gave an indication for personalized treatments for 35.6% of the patients evaluated, with 9.4% receiving target therapy. This is in line with data from the Profiler trial, which found actionable genomic aberrations in 27% of the 2,579 patients enrolled, with 6% receiving a targeted therapy.[14] In the experience of the Institute Curie, 10% of the patients discussed within the MTB were enrolled in clinical trials with matched therapy.[15] The Johns Hopkins' MTB recommended genomically matched therapy in 43% of 155 selected patients, resulting in treatment administration in 15% (11 off-label and 13 clinical trials).[16]

The application of ESCAT classification to all pathogenic and likely pathogenic variants in our series allows us analyzing its robustness and enforceability in the workflow of a real-world MTB. In the Aurora trial, at least one ESCAT I-II

alteration was identified for 51% of patients with BC. These data are in line with the results from our cohort of patients with BC, that includes 22/68 (32.4%) and 36/68 (52.9%) patients with ESCAT I or ESCAT I-II alterations, respectively, mainly represented by *PIK3CA*, *BRCA1*, *BRCA2*, and *ERBB2* alterations.

In our case series, as expected, patients with alteration(s) classified in ESCAT I frequently received therapeutic recommendation and a matched treatment more frequently (96.7% and 36%, respectively) than patients with II-IV alterations. Consistently, a recent study on simulated data indicated high concordance rates in treatment recommendations across 10 different Japanese MTBs mainly in tumor types where SOC therapies offer consolidate solutions.[17] Other groups already demonstrated the predictive role of ESCAT classification in tumor type–specific case series. In a large cohort of 327 patients with CCA, 184 patients (56%) had an actionable mutation (ESCAT I-IV), 50 of whom received a matched therapy with significant benefit in terms of OS. Interestingly, patients with ESCAT I-II alterations showed longer progression-free survival (PFS) than patients with ESCAT III-IV.[18] Results from the SAFIR02-BREAST showed that NGS-driven targeted therapies improved PFS in patients with ESCAT I/II variants (hazard ratio [HR], 0.41; $P < .001$), while no improvements were observed in the targeted therapies arm (unadjusted HR, 1.15) for ESCAT III-IV.[19]

The main limitation of our study is the lack, to date, of data regarding outcome and, specifically, survival of our patients: for the time being, survival data are still immature and incomplete, and we are prospectively collecting the clinical outcome of an expanded cohort including roughly 4,000 patients in our institutional database, planning to address this topic in a subsequent publication.

Large NGS panels captured a significantly higher number of actionable variants than small panels across most of the tumor types analyzed, leading to increased treatment recommendations. Unfortunately, this finding did not translate into a significant increase in personalized treatments (8.8% *v* 7.3%, for large *v* small panels, respectively), with the exception of patients with CRC in which large panels provided data on MSI and *ERBB2* amplifications (Appendix Table A2). Different from small panels, designed for capturing the variants most frequently actioned using personalized SOC therapy, large panels usually identify higher prevalence of ESCAT III-IV alterations targetable only in clinical trials or using off-label drugs. It has also to be underlined that several drugs validated by FDA are still under consideration in Italy (ie, immunotherapy for TMB^{high}), further hampering the treatment of patients with actionable variants. These data highlight the urgent need to speed and harmonize the drug validation process across European countries, as well as ease off-label treatments and recruitment within national clinical trials. Furthermore, establishing the cost-effectiveness of comprehensive genomic profiling is pivotal, since its implementation has a number of nontrivial infrastructural, organizational, and scientific implications for pathology laboratories. The access to active off-label drugs and clinical trials represents the bottleneck for personalized treatment and would strongly benefit from a closer relationship between institutions, regulatory agencies, and stakeholders. Our experience significantly sustains a structured governance, in the perspective of strengthening a robust platform capable of implementing existing clinical and diagnostic data collections; improving the process of integration, updating, and interdisciplinary sharing; and optimizing the quality of existing prospective data sources and their availability for secondary analysis, innovating sharing of anonymous data and information among institutions, private companies, and the academia.

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The data analyzed during the current study are available from the corresponding author on reasonable request. The underlying code for this study is not publicly available but may be made available to qualified researchers on reasonable request to the corresponding author.

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APPENDIX

TABLE A1. Number and Prevalence of Tumor Types in the Study Cohort

Tumor Type	Patients, No.	Frequency, %
Breast	68	3.39
CNS	27	1.35
Colorectal cancer	283	14.11
Female reproductive system	247	12.32
Gastroesophageal cancer	90	4.49
Head and neck cancer	34	1.70
Liver and biliary tract	98	4.89
Lung and pleura	538	26.83
Male reproductive system	46	2.29
Pancreatic cancer	83	4.14
Renal and adrenal gland cancer	8	0.40
Skin	135	6.73
Soft tissues	193	9.63
Thyroid	65	3.24
Urinary tract	1	0.05
Others	89	4.43

TABLE A2. Actioned Targets in Different Tumor Types

Tumor Type	Molecular Tests	Patients, No.	Actioned Targets	AIFA	Trial	Off-Label	Genes
Breast	74	72	4	0	4	0	Two PIK3CA, one BRCA1, one BRCA2
Cholangiocarcinoma	80	78	3	0	2	1	Two FGFR2, one BRAF
Colon	289	285	20	0	2	18	Five BRAF, **four ERBB2 ampl**, **10 MSI-H, one SMARCB1**
Gastric	96	93	11	0	5	6	**One ARID1A**, **one ERBB2 ampl**, **eight MSI-H, one TMB high**
NSCLC	873	503	83	49	18	16	Three ALK fusions, two BRAF, 52 EGFR, seven KRAS, seven MET, seven RET fusions, four ROS1 fusions, **one MSI-H**
Melanoma	125	125	10	9	1	0	Nine BRAF, one NRAS
Neuroendocrine	54	48	2	0	2	0	**One NTRK3 fusion**, one TMB high
Ovarian	184	178	8	6	0	1	Four BRCA1, three BRCA2, one BRAF
Pancreas	108	100	2	0	1	1	One EGFR, **one TMB high**
Salivary gland carcinoma	10	10	1	0	0	1	**One ERBB2 ampl**
Thyroid carcinoma	47	28	12	0	2	10	Seven BRAF, one HRAS, **one NTRK3 fusion, one RET fusion**

NOTE. The numbers of corresponding therapies administered under SOC, off-label, or trial regimen are indicated, together with the number of patients tested for each histotype and the number of molecular tests performed. Bold indicates alterations peculiarly detected by large panels. Abbreviations: AIFA, Agenzia Italiana del FArmaco; ampl, amplification; MSI, microsatellite instability; NSCLC, non–small-cell lung cancer; SOC, standard-of-care; TMB, tumor mutational burden.