Interim analysis of a real-world precision medicine platform for molecular profiling of metastatic or advanced cancers: MONDTI

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ABSTRACT

Background High-throughput genomic profiling of tumour specimens facilitates the identification of individual actionable mutations which could be used for individualised targeted therapy. This approach is becoming increasingly more common in the clinic; however, the interpretation of results from molecular profiling tests and efficient guiding of molecular therapies to patients with advanced cancer offer a significant challenge to the oncology community.

Experimental design MONDTI is a precision medicine platform for molecular characterisation of metastatic solid tumours to identify actionable genomic alterations. From 2013 to 2016, comprehensive molecular profiles derived from real-time biopsy specimens and archived tumour tissue samples of 295 patients were performed. Results and treatment suggestions were discussed within multidisciplinary tumour board meetings.

Results The mutational profile was obtained from 293 (99%) patients and a complete immunohistochemical (IHC) and cytogenetic profile was obtained in 181 (61%) and 188 (64%) patients. The most frequent cancer types were colorectal cancer (12%), non-Hodgkin’s lymphomas (9.8%) and head and neck cancers (7.8%). The most commonly detected mutations were TP53 (39%), KRAS (19%) and PIK3CA (9.5%), whereas ≥1 mutation were identified in 217 (74%) samples. Regarding the results for IHC testing, samples were positive for phospho-mammalian target of rapamycin (phospho-mTOR) (71%), epidermal growth factor receptor (EGFR) (68%), mesenchymal epithelial transition (MET) (56%) and/or platelet-derived growth factor alpha (PDGFα)-expression (48%). Of the 288 tumour samples with one or more genetic alteration detected, 160 (55.6%) targeted therapy recommendations through 67 multidisciplinary tumour board meetings were made; in 69 (24%) cases, an individual treatment concept was initiated.

Conclusions The results reveal that the open concept for all solid tumours characterised for molecular profile and immunotherapy could not only match individualised treatment concepts at a high rate but also underscores the challenges encountered when offering molecularly matched therapies to a patient population with an advanced stage cancer.

Key questions

What is already known about this subject?

► Molecular profiling of routine tumour specimens is becoming increasingly more common in the clinic. The ability to offer appropriate treatment recommendations and to efficiently guide molecular therapies to patients is greatly dependent on a multidisciplinary team approach, expertise in molecular oncology and patient selection.

What does this study add?

► This report about our single-institution experience with molecular profiling extends current real-world data and demonstrates the feasibility of such a concept.

How might this impact on clinical practice?

► The experience of the Comprehensive Cancer Center Vienna provides a framework for a successful implementation of a molecular profiling platform in the routine clinic.

INTRODUCTION

Targeted therapy approaches have proven to yield remarkable responses in a wide variety of different tumour entities like melanoma, non-small-cell lung cancer, colorectal cancer, gastrointestinal stroma tumours or chronic myelogenous leukaemia.1-5 Disrupted or superactivated oncogenic molecular pathways, for example, the RAS/RAF/MEK/ERK pathway, are not always limited to a one type of cancer and, therefore, serve as a potential driving force for tumorigenesis and metastasis formation in a wide variety of different malignancies. In the era of molecular medicine, high-throughput genomic profiling has become part of clinical trials and clinical research. Most of these trials unite the concept that molecular profiling of tumour tissue in
an individual patient may lead to effective drug selection, which is thought to target the underlying genomic aberration. Some large series have been published, which evaluated the clinical feasibility of matching an individual molecular profile with targeted agents. Thereby, having its distinct approach for obtaining the molecular profile, although the majority used a specific next-generation sequencing (NGS) panel. For example, in the SHIVA trial, a combination of an NGS panel and a gene copy alteration analysis of the phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and RAF/MEK pathways as well as immunohistochemistry (IHC) for hormone receptor expression were used. Moreover, the National Cancer Institute’s Molecular Analysis for Therapy Choice (NCI-MATCH) is the largest still ongoing trial with over 3000 patients to be screened and enrolled which opened in 2015. In this study, a large NGS panel combined with phosphatase and tensin homolog (PTEN), mutL homolog 1 (MLH1) and mutS homolog 2 (MSH2) IHC are performed.

MONDTI is a clinical practice precision medicine (PM) platform for molecular characterisation of advanced or metastatic tumours resistant to guideline-based treatment to identify targetable actionable mutations. Patients with solid tumours or lymphomas refractory to standard treatment options were eligible for inclusion in the MONDTI-platform assessment provided that archival tumour material was available or a fresh biopsy was feasible. An NGS panel of 50 different oncogenic genes, IHC of 13 and cytogenic testing of four targetable genomic aberrations were used to obtain the molecular profile. After appropriate workup by molecular pathology, the ensuing results were discussed in a multidisciplinary tumour board to guide potential targeted therapy options. In contrast to the above-mentioned trials, treatment recommendations in MONDTI were not limited to certain pathways or predefined treatment concepts. The feasibility of this concept has been demonstrated in the EXACT (Extended analysis for cancer treatment) trial, which defined the requirements for the multidisciplinary molecular tumour board.

Here, we present an analysis of all patients who have been discussed within 67 MONDTI interdisciplinary tumour board meetings from November 2013 to November 2016. The aim of this study was to assess the feasibility of matching patients to targeted therapy based on the molecular profile of their tumours.

**METHODS**

**Patients**

Patient eligibility criteria included informed consent, any histologic type of metastatic cancer without further standard treatment option, tumour progression by response evaluation criteria in solid tumours (RECIST) criteria, age ≥18 years, Eastern Cooperative Oncology Group performance status 0–1. Fresh tumour biopsy was obtained for pathological analysis. Biopsies were performed by a heterogeneous group of different surgical techniques routinely used at the Department of Interventional Radiology. In case that no fresh tumour biopsy was possible, archival tumour specimens were used.

**Tissue samples**

Tissues from patients with metastatic cancer were formalin fixed and paraffin embedded (FFPE) at the Department of Pathology, Medical University Vienna for histology and molecular diagnostics.

**Cancer gene panel sequencing**

The DNA library was generated by multiplex PCR with the Ion AmpliSeq Cancer Hotspot Panel v2 (Life Technologies/Thermo Fisher, Carlsbad, California, USA). The panel covers mutation hotspots of 50 genes, mostly oncogenes and tumour suppressor genes that are frequently mutated in tumours (ABL, AKT, ALK, APC, ATM, BRAF, CDH, CDKN2A, CSF1R, CTNNB1, EGRF, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAS, GNAQ, HNF1A, HRAS, IDH1, JAK2, JAK3, IDH2, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRα, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL).

Sequencing was performed with an Ion Torrent PGM (Life Technologies). Sequencing data were analysed using Variant Caller and Ion Reporter software (both from Life Technologies/Thermo Fisher). The filter parameters for variant calling were set at a mutant to wild-type allele ratio of 0.05–1.0. Variants with a minor allele frequency >0.01 in normal DNA sequence reference databases, such as Exome Aggregation Consortium and the 1000 Genomes Project, were excluded from further analysis. A minimum nucleotide coverage of ≥100 was required for variant annotation, and only variants with an allele frequency of at least 5% were considered for the final report. For variant interpretation, dbSNP, ClinVar, COSMIC and BRCA Exchange databases were utilised.

**Non-synonymous mutations detected with the Ion Torrent PGM were verified by capillary sequencing. The sequencing of PCR products was carried out with the BigDye Terminator V.1.1 Cycle Sequencing Kit (Applied Biosystems, Waltham, Massachusetts, USA). The resulting DNA fragments were purified with the DyeEx 96 Kit (Qiagen) and sequenced with a 3500 Genetic Analyzer (Life Technologies). Sequencing data were analysed using the SeqScape V.2.7 software (Applied Biosystems).**

**Immunohistochemistry**

IHC was performed with a Ventana Benchmark Ultra stainer (Ventana, Tucson, Arizona, USA). The following antibodies were employed: anaplastic lymphoma kinase (ALK) (clone IA4; ZytoMed, Berlin, Germany), CD30 (clone BerH2; Dako, Vienna, Austria), CD20 (clone L26; Dako), epidermal growth factor receptor (EGFR) (clone 3C6; Ventana), estrogen receptor (clone SP1; Ventana), human epidermal growth factor receptor (HER)2 (clone 4B5; Ventana), HER3 (clone SP71; Abcam), Chit receptor...
diagnostic systems were applied: FISH (PathVysion II; nuclei per tumour were evaluated. To detect HER2, two transfection-receptor (RET) (10q11; Kreatech, Berlin, Abbott, Abbott Park, Illinois, USA), rearranged during death-ligand 1 (PD-L1) (clone E1L3N; Cell Signalling), progesteron receptor (clone 1E2; Ventana), PTEN (clone Y184; Abcam) and ROS1 (clone D4D6; Cell Signalling).

The diagnostic sensitivity and specificity of the antibodies has been validated at the Department of Pathology at the Medical University Vienna. For the validation, appropriate positive and negative tissue controls were employed. Furthermore, the omission of primary antibodies and the replacement of primary antibodies by antibodies of the same species, isotype and concentration, having no known reactivity against human tissue, served as negative reagent controls. The antibodies employed in this study have been institutionally approved for the application in routine histopathological diagnostics. The antibodies to ALK, CD30, EGFR, HER2 and MET are additionally licensed in vitro diagnostics, the antibody to CD20 is CE marked.

For the evaluation of staining intensities with antibodies to EGFR, phospho-mTOR, PDGFRα, PDGFRβ and PTEN, an immunohistochemical score was determined by multiplying the percentage of positive cells by their respective staining intensity (0=negative, 1=weak, 2=moderate, 3=strong). IHC score (maximum 300)=(%negative×0)+(%weak×1)+(%moderate×2)+(%strong×3).

ALK, CD30, CD20 and ROS1 staining were categorised as positive or negative with the percentage of reactive neoplastic cells but without scoring of staining intensities. ALK or ROS1 positive cases were consecutively interrogated for the presence of a respective gene translocation by fluorescence in situ hybridisation (FISH). HER2 staining was graduated according to the guidelines of the company Dako for the Dako HercepTestR with possible scores 0 (negative), 1+ (negative), 2+ (positive), 3+ (positive). HER2 2+ cases were further analysed by HER2 in situ hybridisation to verify a HER2 gene amplification. For PD-L1, the percentage of tumour cells with a membranous staining, irrespective of staining intensity, was determined (so-called ‘tumour proportion score’). MET staining was graduated according to a published scoring system that evaluated both staining intensity (negative, weak, moderate or strong) and prevalence of these intensities in tumour cells.\textsuperscript{16}

**Fluorescence in situ hybridisation**

FISH was performed with 4µm thick FFPE tissue sections. The following FISH probes were employed: ALK (2p23.1; Abbott, Abbott Park, Illinois, USA), rearranged during transfection-receptor (RET) (10q11; Kreatech, Berlin, Germany), PTEN (10q23.31/Centromer 10) and ROS1 (Zytovision, Bremerhaven, Germany). Two hundred cell nuclei per tumour were evaluated. To detect HER2, two diagnostic systems were applied: FISH (PathVysion II; Abbott) and chromogenic in situ hybridisation (Ventana Medical Systems by Roche Diagnostics).

**Treatment algorithm**

Patients with refractory metastatic cancer without any standard treatment options according to the National Comprehensive Cancer Network guidelines and/or local guidelines were included. Potential therapeutic targets in individual patient’s tumour sections were individualised by genomic tumour profiling (NGS and FISH) in combination with IHC. The generated data were biostatistically combined with the actual data from clinical trials thus resulting in the identification of druggable targets (drivers) with the highest likelihood of response in each individual patient.

A defined workflow was used to standardise the clinical and decision-making process (figure 1A). Patients were referred to our outpatient clinic to oncologists specialised in the respective field in order to confirm that no standard treatment options were available. If the patient met the eligibility criteria, an appointment for a biopsy was made in case of no appropriate archival tumour tissue was available. After having obtained the patient’s tumour tissue, the molecular profile was performed by a molecular pathologist and the result summary was sent out to all members of the multidisciplinary board in advance to the meeting. Board meetings were organised by the Comprehensive Cancer Centre and held biweekly. The following tasks were performed by board members. The oncologist who has seen the patient in the outpatient clinic introduced the case including the relevant medical history of the patient. The radiologist presented recently performed CT or MRI scans. The pathologist, who performed the molecular tumour profile, reported findings from the molecular profile including information regarding the overall performance of the molecular testing modalities. The translational scientist explained involved pathways and molecular targets. A second medical oncologist, who has experience in and affinity with molecularly targeted cancer treatment, suggested potential treatments, which were then discussed among all members. Treatment decisions were prioritised per level of evidence. Only agents with marketing authorisation and established safety profile for combinations were suggested.

**RESULTS**

From November 2013 to November 2016, 297 paraffin-embedded tumour tissue samples from non-resectable advanced or metastatic tumours of patients, in whom standard therapies according to international treatment guidelines failed, were included. Tissue from 142 primary and 155 metastatic lesions was analysed. The most frequent cancer types were colorectal (n=35, 11.8%), malignant lymphomas (n=29, 9.8%), head and neck (n=23, 7.7%), cholangiocellular (n=19, 6.4%), pancreatic (n=19, 6.4%), malignant central nervous system tumours...
(n=17, 5.7%), hepatocellular (n=13, 4.4%) and cancers of unknown primary (n=13, 4.4%) (table 1).

Out of the 297 tumour-tissue samples, 295 were available for molecular profiling (two patients were excluded due to screening failure). The mutational profile was obtained in 293 (99%) samples. In two tumour samples, sequencing failed due to technical issues and could not be repeated because there was only insufficient tumour tissue left. A complete IHC and cytogenetic profile was obtained in 181 (61%) and 188 (64%) cases, respectively, whereas in 92 (31%) and 71 (24%) cases IHC or cytogenetic results were incomplete due to the lack of sufficient tumour material (71 samples with ≥7 valid IHC results and 21 with ≤6 valid IHC results). In 22 (8%) and 36 (12%) samples, the tumour material was not sufficient for performing any IHC or cytogenetic testing. In summary, 150 (51%) complete, 123 (42%) incomplete and 22 (8%) gene cancer panel-only profiles were obtained (figure 1B).

Focusing on the different mutations detected within the 50 gene panel, in 217 (74%) samples, one or more mutations were found (figure 2A). Of these 217
Table 1  Baseline characteristics

| Characteristics                        | Patients (n) (%) |
|----------------------------------------|-----------------|
| **Sex**                                |                 |
| Female                                 | 128 (43)        |
| Male                                   | 169 (57)        |
| **Median age (IQR)**                   |                 |
|                                        | 57 (46–66)      |
| **Tested tissue**                      |                 |
| Primary                                | 142 (48)        |
| Metastatic                             | 155 (52)        |
| **Tumour types**                       |                 |
| Colorectal                             | 35 (11.8)       |
| Lymphoma                               | 29 (9.8)        |
| Head and neck (including salivary)     | 23 (7.7)        |
| Cholangiocellular                      | 19 (6.4)        |
| Pancreatic ductal adenocarcinoma       | 19 (6.4)        |
| Malignant central nervous system tumours | 17 (5.7)    |
| Hepatocellular                         | 13 (4.4)        |
| Cancer of unknown primary              | 13 (4.4)        |
| Ovarian                                | 12 (4.0)        |
| Neuroendocrine                         | 10 (3.4)        |
| Adrenal                                | 10 (3.4)        |
| Cervical                               | 8 (2.7)         |
| Pleural mesothelioma                   | 8 (2.7)         |
| Thyroid                                | 8 (2.7)         |
| Soft tissue (sarcoma)                  | 7 (2.4)         |
| Breast                                 | 7 (2.4)         |
| Gastric                                | 7 (2.4)         |
| Oesophageal                            | 6 (2.0)         |
| Small intestines                       | 5 (1.7)         |
| Urothelial                             | 4 (1.3)         |
| Multiple myeloma                       | 4 (1.3)         |
| Not available                          | 4 (1.3)         |
| Testis                                 | 4 (1.3)         |
| Skin (non-melanoma)                    | 3 (1.0)         |
| Non-small cell lung cancer             | 3 (1.0)         |
| Prostate                               | 2 (0.7)         |
| Gastrointestinal stroma tumours        | 2 (0.7)         |
| Endometrial                            | 2 (0.7)         |
| Urachus                                | 2 (0.7)         |
| Melanoma                               | 2 (0.7)         |
| Hepatoid                               | 1 (0.3)         |
| Primary perivascular epitheloid cell tumour (renal) | 1 (0.3) |
| Haematological                         | 1 (0.3)         |
| Appendix                               | 1 (0.3)         |
| Renal                                  | 1 (0.3)         |
| Haemangioma                            | 1 (0.3)         |
| Adnexial                               | 1 (0.3)         |
| Vulva                                  | 1 (0.3)         |
| Malignant peripheral nerve sheath tumour | 1 (0.3) |

For the complete overview of the IHC and cytogenetic results, we refer to figure 3A, B. Most of the samples were positive for phospho-mTOR (n=210, 71%), EGFR (n=200, 68%), MET (n=166, 56%) and PDGFRA expression (n=143, 49%). Although most of the samples were positive for these frequent alterations, only a minority was highly overexpressing the target proteins (12%, 30%, 12%, 5%). In 64 and 28 samples, loss of PTEN signal was confirmed by either IHC or FISH/silver in situ hybridisation. In 10 samples, concordance between the two testing modalities was observed.

Of the 288 tumour samples with one or more genetic alteration detected, 160 (55.6%) targeted therapy recommendations were made by 67 multidisciplinary tumour board sessions (figure 4A); in 69 (24%) cases, an individual treatment concept was initiated (figure 4B, online supplementary figure 1). In 81 (50.6%) cases, treatment recommendations were considering one, in 58 (36.3%) cases two, in 20 cases (12.5%) three and in one (0.6%) case four molecular alterations. In 64 and 26 samples, loss of PTEN signal was confirmed by either IHC or FISH/silver in situ hybridisation. In 10 samples, concordance between the two testing modalities was observed.

A series of clinical trials have tried to assess the impact and the efficacy of PM in patients with cancer. PM defines the molecular or immunohistochemical detection of a druggable target in malignant tissue and the subsequent application of a certain pharmacological compound which, based on its mode of action, could be expected to modify the course of the underlying disorder by interfering with a decisive signal the cell
Figure 2  Profile of tumour mutations. (A) Relative distribution of tumour mutations as assessed by the cancer gene panel. From 295 tumour samples, 293 next-generation sequencing results are available. (B) Results for absolute numbers of tumour mutations as assessed by the cancer gene panel.

uses for sustained growth, proliferation and spread. The development of the concept and the ability to diagnose certain molecular aberrations has been accompanied by an avalanche of registrations of drugs targeting these molecular detections and/or protein overexpression. Regularly and despite of the common share of identical molecular findings or protein overexpression at various sites, drug registrations are being done according to the anatomic location of a certain malignancy until today with the necessity to prove the validity of the identical concept. Thus, many questions have been asked on the efficacy of the use of molecularly targeted drugs within the context of malignancies sharing a certain molecular characteristic resulting in quite disappointing outcomes. This is not entirely surprising, as it is not quite self-evident that organs at various sites should be dictated in their biology by identical molecular mechanisms, although exceptions to the rule are well known.

Tumour biology varies widely by its origin, acquired somatic mutations, variably altered transcriptional networks and influences of the tumour microenvironment. However, the proof of an efficacy of particularly molecularly targeted treatment very much depends on trial design, patient selection, disease stage, pretreatment and, finally, the choice of the particular pathway to be studied.

Currently, we are confronted with a series of trial setups which intend to test for the efficacy of the application of concepts of PM into the clinic.

First, the ‘classical’ trials test for the efficacy of a targeted compound added to ‘conventional’ treatment. Examples are, among others, the PALOMA (PALbociclib:Ongoing trials in the MAnagement of breast cancer) trials, the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis) trials or the PROFILE 1014 trial indicating that the
concept is applicable to various malignancies if only the target is biologically valid and important.

Second, the detection of various druggable mutations within a very certain molecular and disease context (eg, in non-small cell lung cancer) testing for the efficacy of a certain targeted treatment and the possibility of its amelioration by another targeted drug usually overcoming or delaying treatment resistance (eg, within the context of some of the LUX LUNG trials or the J-ALEX trial).\textsuperscript{25} These trials were largely successful and often led to a practice changing outcome regarding the replacement of one drug by another one.

Third, ‘basket trials’ assume that a certain molecular mutation would be similarly amenable to identical targeted treatment which has been shown to be efficacious within a clearly defined context. One typical example is the BRAF V600E mutation targeting basket trial which could only partly confirm the validity of the concept until the results of new and ongoing trials will be available.\textsuperscript{26} Finally, PM has been offered to patients in treatment-refractory cancers after having had a real-time biopsy.\textsuperscript{12,27-29}

Here we present an analysis of tumours derived from 295 patients with late-stage malignancies resistant to guideline-based treatment, which have been
molecularly characterised by the MONDTI platform between November 2013 and November 2016. The molecular tests used for this projects consider predictive markers obtained by an NGS panel, IHC and cytogenetic analysis. With a very high analysis rate of 98% by the 50 gene NGS-panel comparable to the rate reported by the NEXT-1 trial (95%),30 the NCI-MATCH (87%),13 the SHIVA trial (71%)12 or the SAFIR 01 trial (70%),8 treatment decisions were possible in 24% of all included patients. Compared with previous trials, the success rate for treatment recommendation is higher than described in previous trials such as SAFIR or SHIVA. This can partially be explained by the following facts. First, MONDTI is an open panel for all solid tumours, which are considered as non-resectable and failed standard treatment options, while other trials were limited to the certain tumour types such as breast cancer (SAFIR-1) or lung cancer (BATTLE-1). Second, beside an NGS panel, MONDTI included also protein-level analysis via IHC staining as well as a cytogenetic analysis. In fact, treatment recommendation were mainly driven by these analysis: Of the 160 therapy recommendations, 144 were based solely or partly on the results of the IHC or FISH tests, while only in 16 recommendations the results of the NGS panel were the determining factor. Third, we have learnt that involvement of a multidisciplinary team in treatment decisions is crucial. Beside molecular pathologists, radiologists and medical oncologists, the tumour boards considered the experience of basic and translational researchers for a comprehensive understanding of the complex mechanism interfering signalling pathways in the context of an individual disease. In this respect, we would like to reference two exceptional case studies to better demonstrate how the multidisciplinary team helped to identify molecular targets and guide the treatment within the context of the MONDTI profiling platform.31 32  Notably, treatment recommendations were not limited to certain pathways, which is different to previous trials, such as SAFIR-1. Furthermore, and most importantly, the fact that the panel also considered potential predictive biomarkers for immunotherapies such as PD-L1 staining or mismatch repair deficiency testing led to the treatment recommendations of experimental immunotherapeutic agents such as pembrolizumab or nivolumab in 34 patients of whom 20 patients actually were treated with these agents. Gaining faster access to molecular drugs and accelerating the clinical and pathological workflow will be important for the future to increase the ratio of patients which can start a recommended molecularly guided therapy. If invasive biopsies can be entirely replaced by liquid biopsies is a controversial topic. Sequencing of circulating tumour DNA to detect targetable mutations has been shown to be feasible and hopefully soon will expand our possibilities to offer molecularly tailored therapies to patients which are not fit enough...
to undergo invasive biopsies or where tumour tissue is not accessible.\textsuperscript{33–35} In that respect, it is now more and more understood that the tumour microenvironment (TME) acts a critical component of malignant diseases.\textsuperscript{36} Although novel approaches to assess serum biomarkers from non-malignant cells within the TME seem promising, profiling of the TME by liquid biopsies still remains in its infancy.\textsuperscript{37–40}

To explore the role of new biomarkers, molecular profiling platforms should also provide the opportunity for patients to participate in molecular trials. In this respect, a commonly reported challenge is the lack of standardised tumour profiling tests and data sharing practice. This fact is underscored by a recent survey article which found wide varying sequencing procedures and bioinformatics pipelines using different mutation calling and variant annotation.\textsuperscript{41} More efforts towards a global harmonisation of molecular pathology workflow and guidelines on how to report the results of the respective testing modalities should be undertaken which has also been recently addressed, for example, by the The Global Alliance for Genomics and Health.\textsuperscript{42}

In summary, we have successfully established a platform for molecular profiling at our institution, but aim for an integrated registry to exchange meaningful experience in targeted treatment. In this context, the American Society of Clinical Oncology (ASCO) already runs the Targeted Agent and Profiling Utilisation Registry (TAPUR) study that aims to evaluate potential effectiveness of marketed, targeted anticancer drugs when applied outside of their approved indications. ASCO aims thereby to facilitate patient access to marketed agents that are predicted to be beneficial based on analysis of patients’ tumour’s genomic profile. Furthermore and most importantly, by capturing their outcomes in a prospective database this approach will improve the understanding which treatment concepts might lead to patient benefit. TAPUR is thereby conceptually similar to both the ongoing major initiative of the US NCI, the MATCH trial as well as the AcSé programme being conducted by the French National Cancer Institute. These approaches might overcome the limitation of single-centre experiences. In this context, we emphasise to include potential predictive markers for immunotherapy to improve treatment efficacy.

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