

ORIGINAL RESEARCH

## PRECISION: the Belgian molecular profiling program of metastatic cancer for clinical decision and treatment assignment

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Available online 12 August 2022

PRECISION is an initiative from the Belgian Society of Medical Oncology (BSMO) in collaboration with several stakeholders, encompassing four programs that aim to boost genomic and clinical knowledge with the ultimate goal to offer patients with metastatic solid tumors molecularly guided treatments. The PRECISION 1 study has led to the creation of a clinico-genomic database. The Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT) and GeNeo studies will increase the number of patients with advanced cancer that have comprehensive genotyping of their cancer. The PRECISION 2 project consists of investigator-initiated phase II studies aiming to provide access to a targeted drug for patients whose tumors harbor actionable mutations in case the matched drug is not available through reimbursement or clinical trials in Belgium.

**Key words:** next-generation sequencing (NGS), metastatic tumors, genomic alterations, genomic-driven therapy, molecular tumor board

### INTRODUCTION

Understanding the genomic mechanisms of sensitivity to targeted anticancer therapies may improve patient selection, response to therapy, and rational treatment designs. In the last years, much progress has been made toward improving the overall prognosis of patients with metastatic cancer. The identification of activated pathways involved in the pathophysiology of carcinogenesis, metastasis, and drug

resistance, as well as the emergence of technologies enabling tumor molecular analysis and the continuous development of targeted therapies have stimulated research focusing on the optimal use of targeted agents.<sup>1-3</sup>

The administration of a therapy specifically targeting an activating genomic alteration may confer more benefit to the patient than a conventional systemic therapy.<sup>4</sup> This approach has been found to be relevant in phase I clinical trials, where patients with refractory, advanced cancer treated with molecularly matched targeted therapy had higher rates of response and longer time to treatment failure and survival than patients treated without matching targeted treatment.<sup>5,6</sup> Most of the genomic alterations are rare<sup>7</sup> and as a consequence escape the pharma-driven validation of matched drug treatments.<sup>8</sup> Given the heterogeneity of cancer-driving events encountered in a given tumor type, comprehensive genomic profiling (CGP) aiming

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to identify single or multiple genomic alterations offers the possibility to capture the variety of genomic alterations the tumor presents with. This strategy ultimately allows the design of genotype-driven clinical trials focusing on different alterations present in a specific cancer type (umbrella trial) or on a specific alteration present in several cancer types (basket trials). Currently, there is an increasing number of studies enrolling patients based on molecular alterations of tumors [e.g. NTRK fusion, microsatellite instability (MSI), tumor mutational burden (TMB), DNA mismatch repair deficiency<sup>9</sup>], and regulatory agencies have approved tumor-agnostic indications (MSI, TMB, NTRK). Furthermore, recent data from a randomized study in the breast cancer field have proven the clinical benefit of molecularly guided therapies against validated targets [ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) levels I and II].<sup>10</sup> The bottleneck of this approach remains the identification of such patients with molecular alterations. Indeed, country-specific reimbursement criteria still frequently lead to the use of small targeted gene panels (Table 1) and hamper the implementation of broad genomic profiling in the routine molecular oncology diagnostics. The lack of tumor-agnostic CGP also threatens the competitiveness of Belgium, currently a leading force in Europe,<sup>11</sup> in the clinical research field with the increase of biomarker-specific clinical trials that could disadvantage countries with smaller populations.

### THE PRECISION INITIATIVE

The Belgian Society of Medical Oncology (BSMO) already acknowledged several years ago three main issues in personalized oncology programs of cancer centers. First, isolated initiatives launched at individual laboratories to sequence tumor DNA from patients with metastatic solid tumors could be significantly more efficient by being part of a large, prospective, collaborative effort that would allow the harmonization of methods and ultimately treatment options. Indeed, they each only generate fragmented results of unknown or small significance in the long term, and collection of data in isolated settings precludes the

documentation of confident estimates of targeted drug activity to specific variants. Second, broad genomic profiling panels are expensive and not reimbursed, limiting their availability in daily practice. The roadmap to availability includes evidence generation, an increase in reimbursement, and a decrease in the price of the consumables/tests. Finally, even if targetable alterations are detected, providing a recommended drug to the patients remains an issue. Of note, treatment selection in Belgium is strongly dependent on reimbursement and there is no financing for off-label treatments, resulting in the fact that besides clinical trials only medical need programs remain as an option for treatment access in situations where reimbursement is lacking, which is unfortunately the current situation in Belgium for some matched treatments with the highest level of evidence with regard to clinical variant interpretation (e.g. pembrolizumab for TMB/MSI high solid tumors, alpelisib for PIK3CA-altered breast cancer). Medical need programs, however, are dependent on legal restrictions and willingness of the pharmaceutical companies to provide the drug in these settings, and access to matched treatment frequently is often lacking in the absence of reimbursement, clinical trials, or medical need programs. In this context, the BSMO launched four programs in collaboration with several stakeholders (Figure 1 and Table 2) to tackle these issues. The PRECISION 1 protocol provides a setting to collect both genomic and clinical information of patients with metastatic cancer who underwent sequencing of their tumor DNA or circulating tumor DNA and were subsequently treated with a matched drug, standard treatment, or entered existing biomarker-driven clinical trials. The GeNeo and Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT) protocols provide access to broad genomic profiling tests enabling the detection of single-nucleotide variants (SNVs), small indels, copy number variations (CNVs), gene rearrangements/fusions, RNA splice variants, and mutational signatures. PRECISION 2 is a master protocol for basket trials providing biomarker-matching drugs to patients with metastatic cancer in settings where clinical trials are not available.

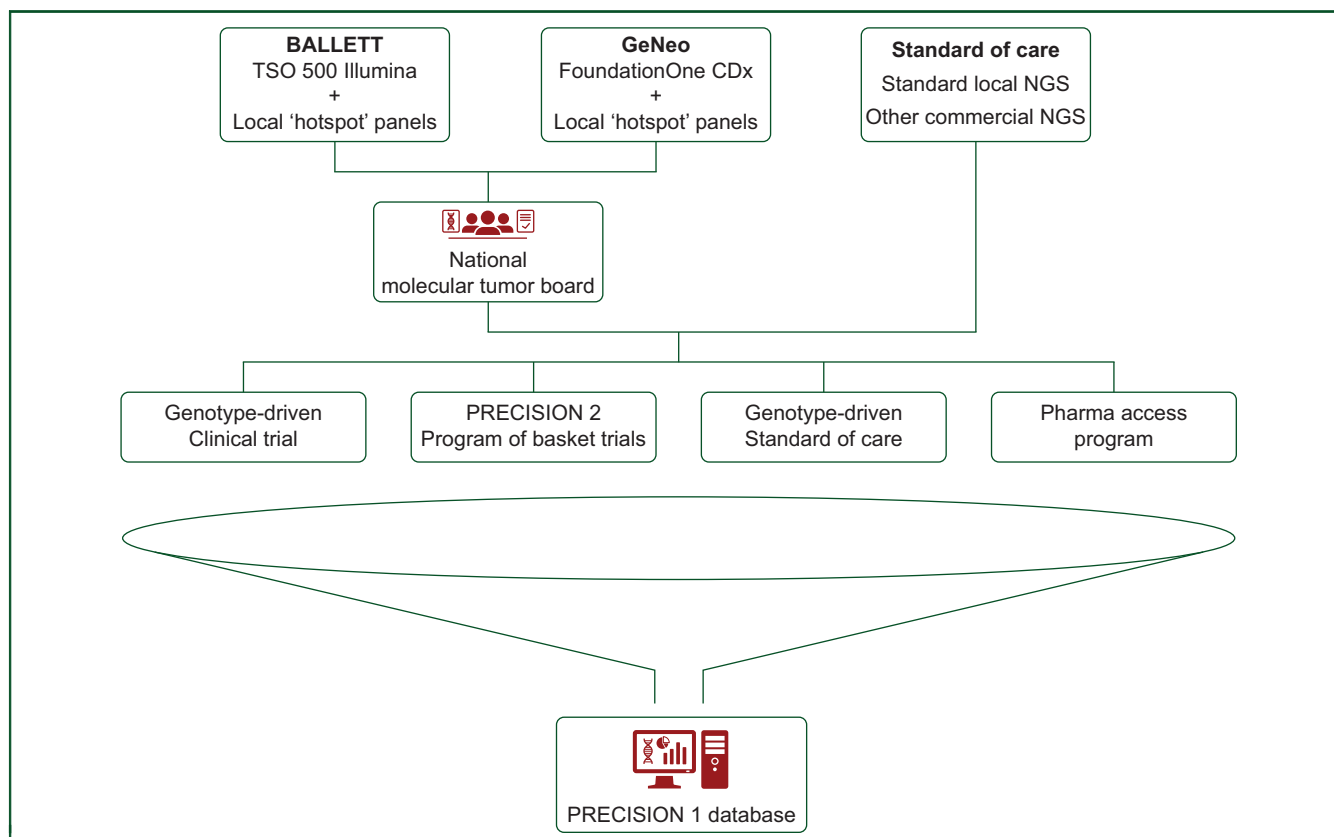
#### The PRECISION 1 study

PRECISION 1 (NCT03873103) is a national multicenter, collaborative molecular profiling program. The aim is to correlate genomic and clinical data of patients with metastatic solid tumors that are eligible for systemic therapy across the participating Belgian oncology centers.

The clinical and molecular data are stored in the Precision Belgium section of the Healthdata database (<https://www.sciensano.be/en/about-sciensano/sciensanos-organogram/healthdatabase>), a national platform developed to collect and store the citizens' health data in a secure and uniform manner. Thus this database has gone through different approval processes including the Belgian government's privacy commission, embedding it in a national legislative context. The anonymized data collected may be shared with physicians and researchers with the aim to directly impact

**Table 1. List of gene panels used in clinical routine in Belgium for solid tumor analysis<sup>31</sup>**

Custom TSCA panel (Illumina, Mechelen, Belgium) with hotspots from 24 genes for a total of 8.1-kb targeted region
Ion AmpliSeq Cancer Hotspot panel v2 (CHP2; ThermoFisher Scientific, Merelbeke, Belgium)
Ion AmpliSeq Colon and Lung Research Panel v2 (CLPv2; ThermoFisher Scientific)
Ion AmpliSeq Panel Gyneco (Custom panel; ThermoFisher Scientific)
Lung-colorectal panel designed with the module AmpliSeq Designer (ThermoFisher Scientific) TruSight Tumor 26 (Illumina)
TruSight tumor 15 (Illumina)
TruSeq Amplicon Cancer Panel (48 genes) (Illumina)
Tumor Hotspot MASTR Plus (Illumina)
Illumina TruSeq Custom Amplicon INCa panel (INCa.bed; Agilent Technologies, Machelen, Belgium) kit 'Human Tumor Actionable Mutations Panel' (Qiagen; Agilent Technologies) Genes: <i>BRaf</i> , <i>cKit</i> , <i>EGFR</i> , <i>IDH1</i> , <i>IDH2</i> , <i>KRas</i> , <i>NRas</i> , and <i>PDGFRA</i>



**Figure 1. The PRECISION initiative design.**

NGS, next-generation sequencing.

the Belgian health care system. Data sharing relies on the Healthdata.be database designed for managing omics projects, allowing the investigators to access a database containing genomic data, clinical data, and anticancer treatments and their efficacy. They will therefore be able to identify how other investigators at different centers treated patients with the same molecular alterations and what the treatment outcome was. The data sharing platform will also provide an overview of the prevalence of different alterations across all cancer types, a helpful information for the design of future clinical trials. Irrespective of treatment choice (chemotherapy, immunotherapy, molecularly guided standard of care, clinical trial), the patient is followed by the collaborating clinician, with follow-up data collected every 6 months with a focus on disease status and survival endpoints (response rate, progression-free survival).

### **GeNeo (NCT04641676) and BALLETT (NCT05058937)**

The current nomenclature used for the reimbursement of next-generation sequencing (NGS) in Belgium with its limited indications and small amount of funding is not supportive of larger panels and a tissue-agnostic approach. Several weaknesses of this 'hotspot' approach can be highlighted.<sup>12,13</sup> First, these panels cover a limited number of potentially actionable genes and focus on hotspot regions. Second, detection of genomic alteration types other than DNA SNVs or small indel (e.g. CNVs, fusions) rearrangements and copy number alterations is not yet

assessed by all NGS laboratories. Third, there are large disparities between the different NGS methodologies. A recent study demonstrated the potential impact of applying a broad agnostic gene panel assessing several types of genetic alterations; by applying the Food and Drug Administration (FDA)-approved NGS panel of 324 genes of Foundation Medicine (Roche FMI) instead of small-panel testing, the detection rate of actionable mutations increased from 28% to 66%.<sup>14</sup> Both GeNeo and BALLETT will investigate the added value of comprehensive and agnostic genomic profiling (centralized FMI testing in GeNeo, decentralized Illumina TSO500 in BALLETT) as compared with reimbursed small-panel hotspot testing in providing patients with advanced/metastatic solid tumors access to a molecular-guided therapy and/or immunotherapy based on genomic results. The use of standardized CE-IVD (CE-IVD mark under the In-Vitro Diagnostics Directive (IVDD 98/79/EC))- and/or FDA-approved commercial panels also facilitates data exchange between centers and creates a leverage for aggregating data in multinational studies with pharma companies.

GeNeo (Genetic, Neo referring to 'novel techniques') is currently recruiting 1000 consecutive patients with solid metastatic cancer, eligible for a systemic therapy, at 13 Belgian academic and nonacademic hospitals, providing access to a centralized CGP carried out by Foundation Medicine (Roche FMI). Cases meeting Belgian criteria for reimbursement of local targeted NGS testing also undergo CGP. Nonreimbursed indications are only tested using

Table 2. Components of the PRECISION initiative			
	Eligibility criteria	Molecular testing	Treatment
PRECISION 1	<ul style="list-style-type: none"> <li>Patients (age <math>\geq 18</math> years) with metastatic solid tumors that are candidates for systemic therapy that have had tumor genomic profiling</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>
GeNeo and BALLETT	<ul style="list-style-type: none"> <li>Patients (age <math>\geq 18</math> years) with metastatic solid tumors that are candidates for systemic therapy</li> <li>Included in the PRECISION 1 program</li> </ul>	<ul style="list-style-type: none"> <li>FoundationOne CDx, FoundationOne Liquid CDx, FoundationOne Heme (rare tumors)</li> <li>Illumina TruSight Oncology 500</li> <li>Local hotspot panels (when reimbursed)</li> </ul>	Discussed at the MTB with recommendations for genomic standard of care, clinical trials, or PRECISION 2 studies.
PRECISION 2: Olaparib	<ul style="list-style-type: none"> <li>Age <math>\geq 18</math> years</li> <li>Advanced cancer, either locally advanced or metastatic, harboring a specific pathogenic genetic alteration involved in homologous recombination (with the exception of patients with breast or prostate cancer harboring a BRCA1/2 mutation and homologous recombination deficiency ovarian cancer)</li> <li>No approved targeted therapy for the specific genetic alteration in the specific tumor type</li> <li>No other genomic-driven phase I, II, or III trial available for the specific genomic alteration in the specific tumor type</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>	<ul style="list-style-type: none"> <li>Olaparib</li> </ul>
PRECISION 2: Afatinib	<ul style="list-style-type: none"> <li>Age <math>\geq 18</math> years</li> <li>Histologically confirmed advanced cancer, either locally advanced or metastatic, harboring an EGFR, an HER2, or an HER3 mutation.</li> <li>No other genomic-driven phase I, II, or III trial available for the specific tumor type or patient not eligible for such trial</li> <li>Failure of at least one previous line of standard treatment</li> </ul>	<ul style="list-style-type: none"> <li>N/A</li> </ul>	<ul style="list-style-type: none"> <li>Afatinib (+ paclitaxel at disease progression)</li> </ul>

BALLETT, Belgian Approach for Local Laboratory Extensive Tumor Testing; MTB, molecular tumor board.

central CGP. Tissue from a new biopsy is required whenever a patient received therapy known to induce genomic mechanisms of resistance such as with anti-epidermal growth factor receptor (anti-EGFR) therapy in non-small-cell lung cancer. A liquid biopsy cohort capped to 100 patients will recruit patients with no accessible biopsy site. The most frequent tumor types will also be capped and a cohort will be dedicated to rare tumors and tumors with rare histologies.<sup>15</sup>

The Belgian Approach for Local Laboratory Extensive Tumor Testing (BALLETT) initiative aims to examine the clinical value of CGP carried out by a consortium of nine Belgian NGS laboratories. A total of 936 consecutive patients with metastatic solid tumors that are eligible for a systemic therapy are currently recruited at 13 hospitals in Belgium. The patients that consent to enter the BALLETT protocol undergo a local NGS test, in parallel to CGP using the Illumina TSO500 CGP panel. For both studies, the clinical and molecular data are stored in the Precision Belgium section of the Healthdata database through the PRECISION 1 program. The CGP analysis is fully standardized among all NGS laboratories of the BALLETT consortium, with respect to both the wet laboratory CGP execution and the dry laboratory variant analysis. A common BALLETT account on two commercially available, tertiary data analysis software (OncoKDM: OncoDNA and CGW: PierianDx) is being used by all the NGS laboratories.

Results from all patient cases in GeNeo and BALLETT (10 to 25 patients a week) are presented and discussed on a weekly basis at a digital multi-institution national molecular tumor board (MTB) composed of experts from the participating sites. In addition to the complete genomic report, a report summarizing the pathogenic alterations, biological and clinical interpretation, and potential genotype-driven treatment recommendations is sent to the treating physician within 14 days of the receipt of the results. Publicly available resources for variant annotation and treatment matching are used. Recommended treatments can consist of reimbursed treatments, genotype-driven clinical trials with matched drugs, medical need programs, or on/off-label treatment recommendations. The national MTB gives recommendations based on the levels of evidence provided by OncoKB.<sup>8</sup> When the level of evidence is not assessed in OncoKB, we use the same rationale to provide a level of evidence. Every recommendation is given back to investigators with the mention of the level of evidence. In addition, whenever deemed appropriate, referral for genetic counseling can also be recommended in the MTB report. This collaborative effort is leveraging patient referral to centers with clinical trials enrolling rare indications, improving the uptake of precision medicine in the country. Reasons for nonmatching between the MTB recommendation and the final treatment choice are recorded and are an endpoint of the study.

### PRECISION 2 clinical trials

Several genetic alterations identified in the programs are present at very low frequencies in a cancer type, and these are insufficient to develop prospective clinical studies that satisfy the current regulatory context. Many genotype-driven clinical trials are also not available in Belgium.

PRECISION 2 trials were designed to respond to this unmet need. They are explorative open-label phase II basket studies, each assessing a specific drug in the treatment of advanced cancer carrying prespecified genomic alterations. These genomic alterations are considered based on biological evidence supporting the development as a biomarker or previous evidence of their predictive role in drug sensitivity in another cancer type (phase I, II, or III trials). Inclusion requires that the indication is not reimbursed for this cancer type and that a more specific trial for the cancer type in question is absent. Patients may be recruited through PRECISION 1, GeNeo, BALLETT, or through any other genomic test.

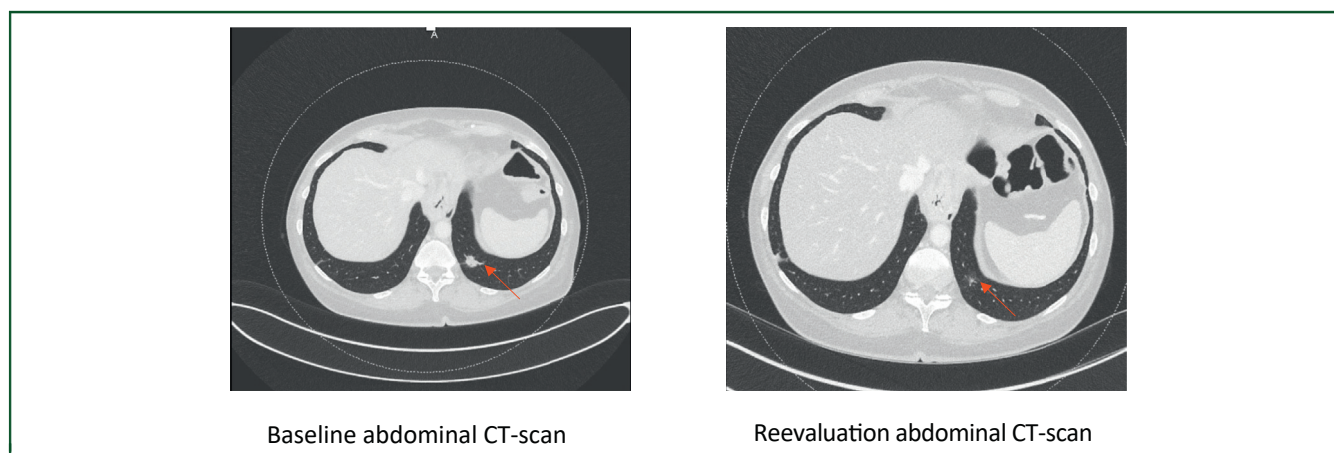
Currently, two PRECISION 2 basket studies are ongoing in Belgium. The first one is testing the efficacy of olaparib in patients with advanced cancer and a germline or somatic mutation in a gene implicated in homologous recombination (NCT03967938), excluding regulatory approved indications. The second one is testing the efficacy of afatinib in the treatment of advanced cancer carrying a somatic *EGFR*, *ERBB2*, or *ERBB3* mutation<sup>16</sup> (NCT03810872), followed by the addition of paclitaxel to afatinib at disease progression. Enrollment in these studies is ongoing.<sup>16</sup>

### A case illustrating precision medicine delivery

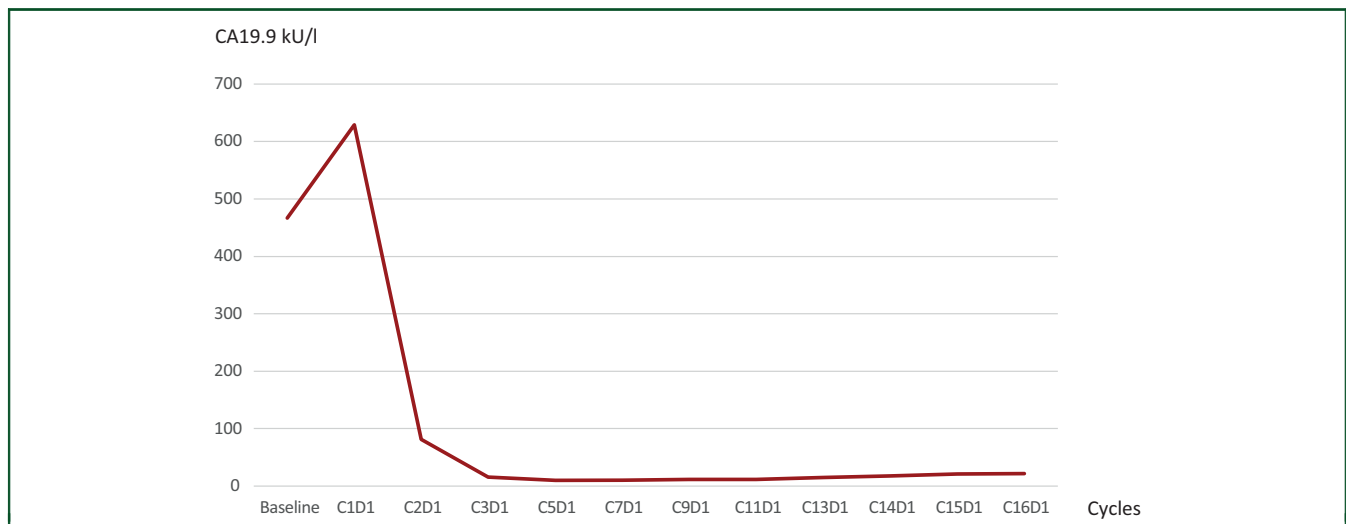
Here we report the case of a 56-year-old female patient treated in a PRECISION 2 basket clinical trial for an advanced pancreatic adenocarcinoma.

The patient underwent duodenopancreatectomy in August 2017 for a pT2N2M0 moderately differentiated pancreatic ductal adenocarcinoma (PDAC), followed by adjuvant chemotherapy with capecitabine and gemcitabine.

In September 2018, she developed lung and subcutaneous metastases associated with a local recurrence. Until March 2020, she subsequently received three lines of chemotherapy: gemcitabine and nab-paclitaxel, FOLFIRINOX, and cisplatin—5 fluorouracil. Targeted gene sequencing using AmpliSeq (Life Technologies, Merelbeke, Belgium), a panel of 19 genes, reported an in-frame deletion in exon 19 of the *EGFR* gene (c.2237\_2255delinsT, p.Glu746\_Ser752delinsVal) as the only identified genomic alteration. Previous data, generated in the non-small-cell lung cancer field, demonstrate the clinical sensitivity to EGFR tyrosine kinase inhibitors (TKIs) conferred by these rare alterations located in this genomic region.<sup>17</sup> MSI testing by PCR was negative. After informed consent, she was included in the PRECISION 2 afatinib trial, an open-label phase II study of afatinib for advanced cancers with a pathogenic variant in *EGFR*, *ERBB2*, or *ERBB3*. Afatinib is a second-generation EGFR TKI, which irreversibly binds to the EGFR tyrosine kinase domain and more potently inhibits its activation than first-generation EGFR-TKI. The patient has been treated with afatinib at the dose of 40 mg daily without dose interruptions to date. Adverse events were grade 2 acneiform rash treated with topic antibiotics and grade 1 intermittent diarrhea. Partial response (decrease of ~40% of the lung and hepatic target lesions according to RECIST version 1.1) and CA 19-9 normalization were noted after two cycles and were still ongoing at the latest follow-up after >12 months (Figures 2 and 3). Here we reported the case of a patient with a chemorefractory PDAC harboring an *EGFR* mutation who experienced a durable and deep partial response on afatinib. Indeed, metastatic PDACs represent a very aggressive disease and the prognosis remain poor.<sup>18</sup> In PDAC, EGFR mutations are found in <1% of the cases.<sup>19</sup> In the literature, only few cases reported the use of EGFR-targeted therapy, mainly erlotinib, in the treatment of metastatic PDAC.<sup>20</sup> For instance, erlotinib, an EGFR TKI, in combination with gemcitabine is an FDA-approved treatment of metastatic PDAC despite the low difference in median overall survival of only 10 days.<sup>21</sup> Of note, this trial was not conducted in biomarker-selected patients.



**Figure 2.** Serial computed tomography (CT) scan images illustrating the partial response on afatinib in a patient with metastatic EGFR-mutated pancreatic cancer. EGFR, epidermal growth factor receptor.



**Figure 3.** Evolution of CA 19-9 on afatinib for a patient with metastatic EGFR-mutated pancreatic cancer. EGFR, epidermal growth factor receptor.

## DISCUSSION

The four components of the PRECISION initiative aim to tackle the main challenges hindering the routine implementation of precision oncology in the clinic: to identify as many actionable mutations as possible using one comprehensive genomic assay, to establish benefits of genotype-driven treatment, to enlarge the range of therapeutic actionability for patients, and to scale-up the logistics through the establishment of a centralized clinico-genomic database to support optimal treatment decisions. This could ultimately allow to generate data and demonstrate the impact of CGP versus standard of care, to generate discussion regarding the securing of reimbursement of CGP, and to create a clinico-genomic database enabling data sharing and eventually better treatment decisions in routine care.

CGP allowing the detection of the four classes of molecular alterations (SNVs, indels, CNVs, and genomic rearrangements) in addition to MSI and signatures such as loss of heterozygosity, and TMB, could dramatically increase the enrollment of patients in genotype-driven clinical trials.<sup>22</sup> DNA damage response genes beyond *BRCA1* and *BRCA2* are one example, and most of the Belgian cancer centers would not be able to enroll patients in the PRECISION 2 olaparib trial through their local NGS panel. Genomic rearrangements resulting in aberrant gene fusions are also genomic events driving oncogenesis across the spectrum of cancer types.<sup>23</sup> Inhibitors of specific rearrangement events have obtained regulatory approvals following impressive clinical activity while being agnostic of the tumor type in indications such as *NTRK*<sup>10</sup> and *RET* fusions.<sup>24</sup> These events are typically detected by FISH, which is rather unspecific<sup>23</sup> as a screening method and requires specific gene probes implicated in the rearrangement. Gene rearrangements can also be detected by NGS, preferably of RNA molecules as this allows to directly identify the resulting fusion gene product at the expression level. Moreover, hybridization-based NGS of RNA molecules

does not require prior knowledge of the involved fusion partner. The participation of national regulatory bodies as stakeholders should allow more adequate and wider reimbursement of molecular diagnostics if this initiative demonstrates that a larger proportion of patients were able to access molecularly guided therapies.

The continuously evolving complexity in the area of personalized cancer care is a growing challenge for all oncology professionals. The rapid expansion of genomic testing in daily practice leads to an increasing quantity of generated data and also highlights an educational gap.<sup>24</sup> Indeed, recent studies emphasized the lack of confidence in the use of tumor genomic profiling, mostly due to lack of appropriate genomic training.<sup>24</sup> The ESMO-American Society of Clinical Oncology (ASCO) global oncology training curriculum points out this need and describes the specific skills and knowledge required in this field.<sup>25</sup> Furthermore, results from molecular profiling are differently reported by each laboratory, making their interpretation difficult for clinicians.<sup>26</sup> The MTB allows the synchronization and homogenization of data generated by tumor genomic profiling and helps physicians to choose a biomarker-driven treatment according to the latest evidence available. Furthermore, the MTB can help to improve the prognosis of patients, through the joint analysis of medical history as well as clinical and genomic data of patients.<sup>27</sup> Therefore this could lead to an improvement in the enrollment rate into molecularly guided clinical trials.<sup>28</sup> The national MTB is the cornerstone of discussions with the industry regarding off-label access (currently not available in Belgium) to molecularly guided therapies.

Finally, data sharing in oncology between cancer centers, academia, and industry is suboptimal but holds multiple opportunities, allowing to improve the statistical planning of biomarker-driven trials and to increase the likelihood to reach the predefined inclusion numbers in basket and umbrella trials. Furthermore, this could

decrease the number of duplicated monocentric trials, a factor to prevent selective reporting of treatment effects in small populations and could allow corroboration of real-world and trial data. A notable example is the American Association of Cancer Research (AACR) project GENIE, an international data-sharing consortium focused on generating a database for generating evidence in precision cancer medicine by integrating clinical-grade cancer genomic data with clinical outcome data for tens of thousands of patients with cancer treated at multiple institutions worldwide. This project already publicly released data from 19 000 samples, and is expected to grow to 100 000 samples in the next 5 years.<sup>29</sup> Furthermore, there are now more initiatives aiming to define clinical evidence-based criteria to select patients carrying genomic abnormalities for targeted therapies. They provide a common terminology regarding the interpretation of the genomic abnormalities detected, representing a useful tool for oncologists.<sup>8,30</sup> In the current PRECISION program, the interplatform cooperation and harmonization of sequencing approaches across the cancer centers of the country, and the optimization of the interpretation of genomic data are valuable elements to direct patients to existing genotype-based clinical trials, reinforcing the Belgian position on the world map of clinical research. If the results of the ongoing GeNeo and BALLETT trials show an added value of CGP over the currently reimbursed NGS indications, the efforts within the PRECISION program can hopefully lead to extended reimbursement of molecular profiling and access to molecular-guided treatments.

## FUNDING

This work was supported by grants from the 1 study and grants from the Belgian Foundation against Cancer and Kom op Tegen Kanker to the PRECISION 1 and 2 studies and the Biltema Foundation (no grant number). GeNeo is funded by a grant from Roche (no grant number). BALLETT is funded by grants from Illumina and OncoDNA (no grant number).

## DISCLOSURE

GR, MV, EVV, and AH are employees of Sciensano. JM and MH are employees of BSMO. DVS is an employee of Belgian Foundation against Cancer. FPD reports receiving consulting fees from Roche, Pfizer, AstraZeneca, Lilly, Novartis, Amgen, Daiichi Sankyo, Pierre Fabre, and Seagen outside the submitted work. PP reports grants and personal fees from AstraZeneca, Roche, Biocartis, MSD; personal fees from Pfizer, BMS, Takeda, Novartis, and Amgen, all outside the submitted work. KP reports grants and other from MSD; grants from Sanofi; other from Astra Zeneca, Gilead Sciences, Eli Lilly, Mundi Pharma, Novartis, Pfizer, Roche, Vifor Pharma, Medscape, Seattle Genetics, Teva, Pierre Fabre, Roche, AstraZeneca, PharmaMar, outside the submitted work; and is also the board member of the Belgian Society for Medical Oncology. KBMC reports other from Astra Zeneca, outside the submitted work. SR is the President of the BSMO. BM reports nonfinancial support and other from

Illumina, during the conduct of the study; personal fees from AstraZeneca, Novartis, and Pfizer, outside the submitted work. LD reports grants from Roche, Boehringer Ingelheim, AstraZeneca, Kom op tegen Kanker, during the conduct of the study; and also grants from MSD, Roche, Astra Zeneca, BMS, outside the submitted work. CVM reports grants from BSMO, during the conduct of the study; grants from Amgen, AstraZeneca, Eli Lilly, Mundipharma, Novartis, Pfizer, Roche, Seagen, Teva, outside the submitted work. PA reports personal fees from Boehringer Ingelheim, MacroGenics, amcure, Synthron, Servier, G1 Therapeutics, Roche, Novartis, Amgen, Radius, Deloitte, Menarini, and Gilead, outside the submitted work; nonfinancial support from MSD, Roche, Pfizer, Amgen. All other authors have declared no conflicts of interest.

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