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Implementing precision cancer medicine in the public health services of Norway: the diagnostic infrastructure and a cost estimate

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ABSTRACT

Objective Through the conduct of an individual-based intervention study, the main purpose of this project was to build and evaluate the required infrastructure that may enable routine practice of precision cancer medicine in the public health services of Norway, including modelling of costs.

Methods An eligible patient had end-stage metastatic disease from a solid tumour. Metastatic tissue was analysed by DNA sequencing, using a 50-gene panel and a study-generated pipeline for analysis of sequence data, supplemented with fluorescence in situ hybridisation to cover relevant biomarkers. Cost estimations compared best supportive care, biomarker-agnostic treatment with a molecularly targeted agent and biomarker-based treatment with such a drug. These included costs for medication, outpatient clinic visits, admission from adverse events and the biomarker-based procedures.

Results The diagnostic procedures, which comprised sampling of metastatic tissue, mutation analysis and data interpretation at the Molecular Tumor Board before integration with clinical data at the Clinical Tumor Board, were completed in median 18 (8-39) days for the 22 study patients. The 23 invasive procedures (12 from liver, 6 from lung, 5 from other sites) caused a single adverse event (pneumothorax). Per patient, 0–5 mutations were detected in metastatic tumours; however, no actionable target case was identified for the current single-agent therapy approach. Based on the cost modelling, the biomarker-based approach was 2.5-fold more costly than best supportive care and 2.5-fold less costly than the biomarker-agnostic option.

Conclusions The first project phase established a comprehensive diagnostic infrastructure for precision cancer medicine, which enabled expedite and safe mutation profiling of metastatic tumours and data interpretation at multidisciplinary tumour boards for patients with end-stage cancer. Furthermore, it prepared for protocol amendments, recently approved by the designated authorities for the second study phase, allowing more comprehensive mutation analysis and opportunities to define therapy targets.

Key messages

What is already known about this subject?

- It is assumed that precision cancer medicine may improve patient outcome in routine practice.
- Precision cancer medicine comprises integration of new technologies and molecularly targeted therapies, but also clinical structures and updated education curricula.
- In spite of a national strategy for personalised medicine in healthcare, there has been no attempt so far to establish the required infrastructure which would enable routine practice of precision cancer medicine in the public health services of Norway.

What does this study add?

- The MetAction project established a comprehensive diagnostic infrastructure that enabled expedite and safe mutation profiling of metastatic tumours and data interpretation at multidisciplinary tumour boards for patients with end-stage cancer.
- This was possible following the identification and integration of existing hospital and research facilities and expertise.
- Moreover, the study enabled cost estimation of biomarker-based treatment with molecularly matched medication in routine practice.

How might this impact on clinical practice?

- It is feasible to implement precision cancer medicine in a routine clinical setting, consisting of expedite and safe mutation profiling of metastatic tumours and biomarker-based treatment with molecularly matched medication to patients with end-stage disease.

INTRODUCTION

Programmes within precision cancer medicine are being conducted at an increasing number of cancer centres internationally, in line with recommendations from multiple governmental and independent initiatives.[1] A common objective for such activities is the integration of existing resources and new investments in technologies and therapies that reside in the industrial, regulatory, academic and clinical practice sectors. As such, patient-oriented initiatives in precision cancer medicine bridge multilayer biological data with bioinformatics and biostatistics, and ideally also electronic health records, and may ultimately lead to major changes in clinical practice.[2]

In 2011, the Research Council of Norway launched the 'Programme for Publicly-initiated Clinical Cancer Studies' with the loosely worded objective of strengthening the knowledge basis for effective decision-making in diagnosis, treatment and patient care in cancer.[3] The programme was also anchored at the National Council for Priority Setting in Health Care, which has an advisory role in governmental actions. It was directed to provide funding to research projects that addressed efficacy, safety and cost-effectiveness in clinical practice which by the public health administration sector has been identified to require additional fundamental insights.

In its entirety, precision cancer medicine comprises technological advances in molecular biology, functional imaging and informatics, but also requires implementation of new medical, radiation and surgical remedies as well as updated education curricula, clinical structures and regulatory approval pathways.[2] Recognising this complexity, and also attempting to identify and evaluate distinctive features of such an initiative within the public health services of Norway, the ongoing (estimated duration through 2017) 'Actionable Targets in Cancer Metastasis' (MetAction) project has taken one approach to comply with the purposes of the above-referred programme. The overall aim of the project is to determine gene aberrations in the individual patient's metastatic cancer and target those with systemic agents that are approved for cancer treatment (but for other tumour entities) by The Norwegian Medicines Agency. There have been three specific objectives: first, to establish a workflow for diagnostic procedures with an optimised information pipeline, including expert multidisciplinary teams; second, to conduct a therapy trial with patient accrual from any oncology centre in the country; and third, to generate a cost model that has general applicability.

The MetAction project has two clinical trial phases. This report describes how the conduct of the first phase established an efficient diagnostic infrastructure, implemented existing pipelines for molecular biology and information management, educated the entire project staff within the context of study tumour boards and estimated costs for such an initiative.

METHODS

Patients

Briefly, an eligible patient had metastatic disease from no more than one solid tumour, had failed documented systemic therapies which might provide meaningful benefit but with life expectancy of more than 3 months and was eligible for repeat biopsy sampling of a metastatic lesion. Specifically, the patient had been on the previous line of systemic therapy for6 or more weeks and had radiological evaluation intervals of 6–12 weeks on this therapy with disease progression according to the Response Evaluation Criteria in Solid Tumors. Importantly, the patient showed Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and adequate organ function. The study was approved by the Institutional Review Board at the two study centres, Oslo University Hospital–Norwegian Radium Hospital and Akershus University Hospital, the Regional Committee for Medical and Health Research Ethics of South-East Norway (reference number REK 2013/2099) and the Norwegian Medicines Agency. It was registered at the European Clinical Trials Database (EudraCT number 2013-001363-23) and ClinicalTrials.gov (NCT02142036) and performed in accordance with the Helsinki Declaration. Written informed consent was required for participation.

Design

The study design considered an individual-based intervention, which in the first study phase was a single targeted systemic agent based on actionable target identification (ATI) in a metastatic tumour. ATI was defined as a single driver mutation or the absence of such mutations, and the drugs that were available for possible use as per specific ATIs are listed in table 1. The study population included all patients undergoing biopsy of a metastatic tumour. The study was approved to enrol up to 50 individuals.

Clinical procedures

Figure 1 delineates the study. The baseline diagnostic and clinical work-up was followed by biopsy sampling of a metastatic tumour for analysis of gene mutations. In the end-of-study incident when no ATI was found, the patient was further managed to the discretion of the referring oncologist. Following ATI, the workflow on commencement of therapy would consist of a clinical visit every second week, which also would include the formal recording of on-treatment adverse events (AE), a repeat biopsy sampling after 2 weeks (solely for research purposes) and clinical and radiological evaluation every eighth week until discontinuation following failures such as disease progression, untreatable serious AE or a deterioration of the patient's condition of ECOG ≥3.

Molecular analyses

Following sampling, as described in Results section, DNA was extracted from tumour biopsies and whole blood mononuclear cells. The procedure of targeted DNA sequencing

Table 1 Drugs matched to biomarkers in the first phase of the MetAction study

Biomarker(s)	Assay	Drug	Target(s)
KRAS/BRAF wild-type	Seq.	Cetuximab	EGFR
KRAS/BRAF wild-type	Seq.	Panitumumab	EGFR
EGFR mutation	Seq.	Gefitinib	EGFR
EGFR mutation	Seq.	Erlotinib	EGFR
EGFR mutation	Seq.	Afatinib	EGFR
ALK rearrangement, MET mutation	FISH	Crizotinib	ALK, MET
ERBB2 amplification	FISH	Trastuzumab	ERBB2
ERBB2 amplification	FISH	Lapatinib	ERBB2
BCR-ABL translocation	FISH	Imatinib	KIT, BCR-ABL, PDGFR
BCR-ABL translocation	FISH	Dasatinib	BCR-ABL, SRC
BCR-ABL translocation	FISH	Nilotinib	BCR-ABL
BRAF mutation	Seq.	Vemurafenib	RAF
BRAF mutation	Seq.	Debrafenib	RAF
KIT mutation	Seq.	Sunitinib	PDGFR, VEGFR, KIT
JAK2 mutation	Seq.	Ruxolitinib	JAK2
RET mutation	Seq.	Vandetanib	RET

FISH, fluorescence in situ hybridisation; seq., DNA sequencing.

is detailed in online supplementary methods. Briefly, the Ion Torrent PGM Personal Genome Machine was used with the Ion AmpliSeq Cancer Hotspot Panel v2 and the Torrent Suite Variant Caller (Thermo Fisher Scientific). Gene variant calls were quality-controlled with the Integrative Genomics Viewer[4] and functionally annotated with ANNOVAR, using RefSeq as the underlying gene model[5] and also information from the 1000 Genomes Project[6] and the Catalogue of Somatic Mutations in Cancer.[7] Detection of copy number aberrations and translocations of interest in this first clinical phase was not possible with the Cancer Hotspot Panel. Hence, analysis of such aberrations was performed within designated fluorescence in situ hybridisation (FISH) protocols at the FISH Laboratory at Section for Molecular Diagnostics, Oslo University Hospital. These included ALK Break Apart Probes, probes for centromere 17 and ERBB2 and BCR-ABL fusion gene probes (all by Abbott Molecular Vysis). The hybridisation procedure was performed as described previously.[8]

Endpoints

The primary objective was to compare the progression-free survival using therapy selected by ATI, termed Period B, with progression-free survival for the most recent therapy, termed Period A. If Period B/Period A ≥1.3, the ATI-based therapy would be deemed to be of benefit.[9] Overall survival was a secondary endpoint and ATI rate was an exploratory endpoint.

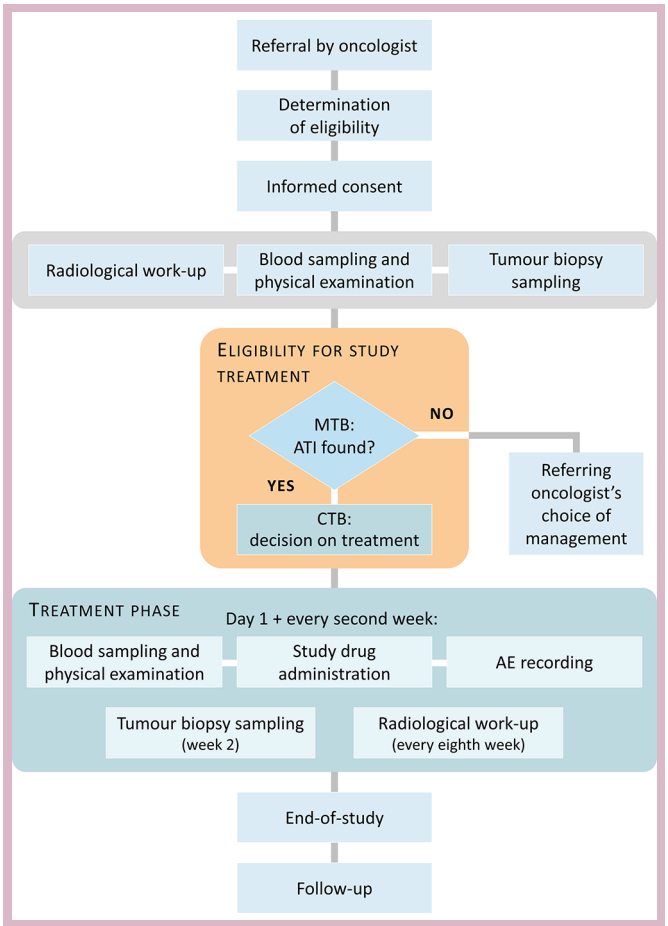

Figure 1 The study mechanics. AE, adverse events; ATI, actionable target identification; CTB, Clinical Tumor Board; MTB, Molecular Tumor Board.

Cost modelling

The estimations of costs were based on modelling where three possible actions following failure of standard-of-care systemic therapies in late-stage metastatic cancer were explored: no further systemic tumour-directed therapy (ie, best supportive care, BSC), biomarker-agnostic treatment with a molecularly targeted agent (ie, therapy without knowledge of tumour biomarker) and biomarker-based treatment with a molecularly targeted agent (ie, the ATI-based approach of the MetAction study). For each of the three pathways, total cost-per-patient (CPP) was estimated for 3 months (90 days) of patient management within the specialist health services. Data were based on information from the MetAction study, literature and expert opinion. The estimations included costs for medication, outpatient clinic visits, admission from AE and biomarker-based procedures, in addition to the basic BSC (see online supplementary tables S1 and S2). As detailed in Results section, the CPP figures comprised three principal groups of input parameters: first, the national diagnosis-related group (DRG) indicators for BSC, outpatient clinic visits for administration of medication and management of patients admitted for AE; second, the mean wholesale price in Norway for five selected index drugs (trastuzumab and panitumumab for

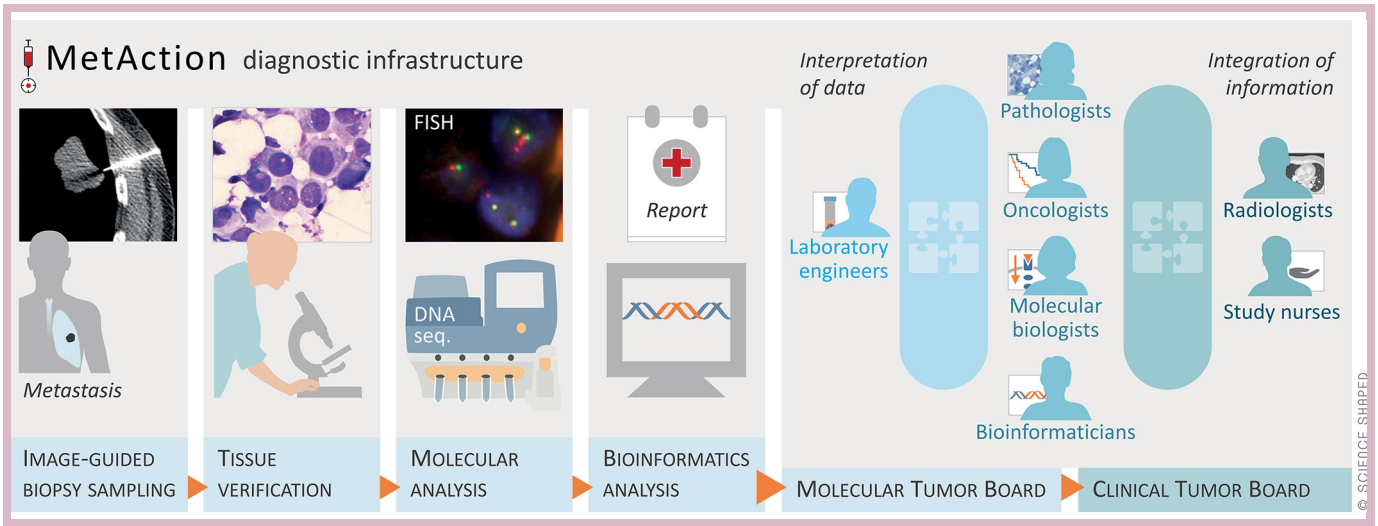

Figure 2 The diagnostic infrastructure. FISH, fluorescence in situ hybridisation; seq., sequencing.

intravenous administration and gefitinib, vemurafenib and everolimus for oral administration), including costs for required oncology nursing to administer the intravenous drugs; and third, personnel costs and factual investments within the study-specific procedures. Possible variability in the costs was addressed by a sensitivity analysis to generate lower and higher limits of the total CPP figures. Costs were converted to EUR using the exchange rate of 9 NOK for 1 EUR.

Statistical considerations

Single-subject trials are appealing for studies such as the current one, which involves evaluation of drugs used for new indications. However, the focus of this study was on the development of a diagnostic framework and an analysis pipeline, making statistical inference less of a priority.

RESULTS

The diagnostic infrastructure

First, the project established a pipeline for diagnostic procedures and information analysis to comprise both study centres and attend the required workflow efficiency for this kind of late-stage patient management. As depicted in figure 2, these comprised expert personnel within a wide range of disciplines: radiology, pathology, laboratory engineering, bioinformatics, molecular biology, oncology and study nursing.

Following enrolment onto the study, which included radiological work-up (for assessment of progression-free survival of Period A), collection of study-specific blood samples and a physical examination, tissue was sampled from a metastatic tumour. The procedure was guided by CT for intrathoracic lesions or ultrasound for intra-abdominal or subcutaneous lesions. First, to verify the diagnosis and ensure that the material from the sampling locus was representative, a regular smear from a fine-needle aspirate was assessed and cellular material from the needle was also preserved for cytospins and FISH analysis. Next, core biopsies were taken and tumour cell content was estimated by tissue imprint prior to freezing in liquid nitrogen. The samples were dispatched to a unit for DNA sequencing which was established at the Institute for Cancer Research, Norwegian Radium Hospital, specifically for the conduct of this study. The sequencing was technically successful for all samples; however, for five cases, cytospins were not of sufficient quality for FISH analysis. The sequence data were stored in the Services for Sensitive Data facility at University of Oslo.[10]

The molecular report was presented at the Molecular Tumor Board (MTB) after annotation of gene variant calls and manual knowledge mining within the context of relevant scientific literature. The MTB secured validation experiments to be performed, if needed, and concluded a consent interpretation of the molecular data. The final determination of actionable targets was taken at the Clinical Tumor Board (CTB) following complete integration of the molecular and clinical information. The CTB was assembled through video-conference between the two study centres. The diagnostic procedures from written informed consent to CTB conclusion were completed in median 18 (8–39) days. For two cases, referred in online supplementary results, deidentified molecular and clinical information was sent for second opinion by international experts in the field.

The clinical study

Between 9 May 2014 and 26 August 2015, 24 patients were enrolled onto the study (see online supplementary table S3). Two patients were found ineligible after enrolment. A fourth of patients were referred from external institutions around the country.

Eligible patient and tumour characteristics are shown in table 2. Median age was 62 (43–70) years. Sixteen patients had the primary tumour site in the gastrointestinal tract and 15 cases had a confirmed adenocarcinoma entity. A total of 23 tissue sampling procedures were performed (one patient had biopsy from two sites), of which 12 were

Table 2 Study cases

Sex	Age	Primary tumour site	Histological diagnosis	Sampling site(s)	Adverse event	Gene mutation(s)
Male	43	Parotid gland	Neuroendocrine carcinoma	Lung	None	None detected
Male	69	Liver	Hepatocellular carcinoma	Liver transplant	None	None detected
Female	59	Pancreas	Adenocarcinoma	Liver	None	KRAS p.G12D
Male	62	Pancreas	Adenocarcinoma	Liver	None	KRAS p.G12D, TP53 p.R306X
Female	66	Pancreas	Not determined	Liver	None	KRAS p.G12D, GNAS p.R201H
Female	46	Right colon	Adenocarcinoma	Liver	None	KRAS p.G12D, SMAD4 p.R361C, TP53 p.C176F
Male	54	Right colon	Adenocarcinoma	Liver	None	KRAS p.G12D, PIK3CA p.E545K, SMAD4 p.G419R
Male	62	Right colon	Adenocarcinoma	Liver	None	KRAS p.G12D, SMAD4 p.Y353C, APC p.Q1444X, TP53 p.T102fs
Male	52	Left colon	Adenocarcinoma	Liver	None	KRAS p.G12V, PIK3CA p.E545Q
Male	59	Left colon	Adenocarcinoma	Liver	None	TP53 p.R273H, TP53 p.L350fs
Male	65	Left colon	Mucinous adenocarcinoma	Lung	None	KRAS p.A146T, PIK3CA p.H1047R
Female	68	Left colon	Adenocarcinoma	Liver transplant	None	KRAS p.G12A, APC p.Q1291fs
Male	70	Left colon	Adenocarcinoma	Liver	None	KRAS p.G13D, APC p.E1306X, APC p.K889fs, TP53 p.R248W
Male	54	Rectum	Adenocarcinoma	Lung	None	KRAS p.G12S, APC p.E1317X, TP53 p.R175G
Male	61	Rectum	Adenocarcinoma	Lung	Pneumo-thorax	KRAS p.G12S, APC p.Q1378X, FBXW7 p.R505C
Male	61	Rectum	Mucinous adenocarcinoma	Lung	None	BRAF p.V600E, SMAD4 p.W524C, TP53 p.R306X
Male	68	Rectum	Adenocarcinoma	Lung	None	KRAS p.G12D, PIK3CA p.E542K
Male	63	Kidney	Clear cell renal cell carcinoma	Thoracic wall	None	VHL p.L158P
Male	65	Kidney	Renal Xp11.2 translocation carcinoma	Liver	None	None detected
Male	61	Urinary bladder	Urothelial carcinoma	Inguinal lymph node and peritoneum	None	None detected
Female	48	Ovary	Small-cell sarcoma*	Peritoneum	None	KRAS p.T58I, PIK3CA p.H1047Y, ERBB2 p.V842I, CTNNB1 p.G34R, TP53 p.R306X*
Male	65	Prostate	Adenocarcinoma	Axillary lymph node	None	TP53 p.D184fs

*The mutation profile of the peritoneal lesion indicated carcinoma.

from liver and 6 from lung. A single case with pneumothorax was recorded as procedure-specific AE. Table 2 also lists all gene mutations that were identified for each patient. In the total population, 36 specific coding somatic mutations (range 0–5 per patient) were detected in metastatic tumours (see online supplementary table S4). Figure 3 summarises the frequency of genes aberrations detected across all cases. Mutations are further described in online supplementary results, including two study cases of note; the first with a metastasis mutation profile that clarified the diagnosis. The second case was treated off-protocol with a combination of panitumumab and vemurafenib.

In this first phase of the clinical study, no ATI case was identified; hence, the ATI rate was zero and the primary endpoint of the study could not be determined. Since all citizens of Norway have unique personal identification number within the National Registry, we were able to retrieve the date of death of the study participants and thus overall survival, as censored by 9 May 2016. As shown in figure 3, a third of cases (8 patients) did not reach the inclusion-specified criterion of life expectancy of 3 months.

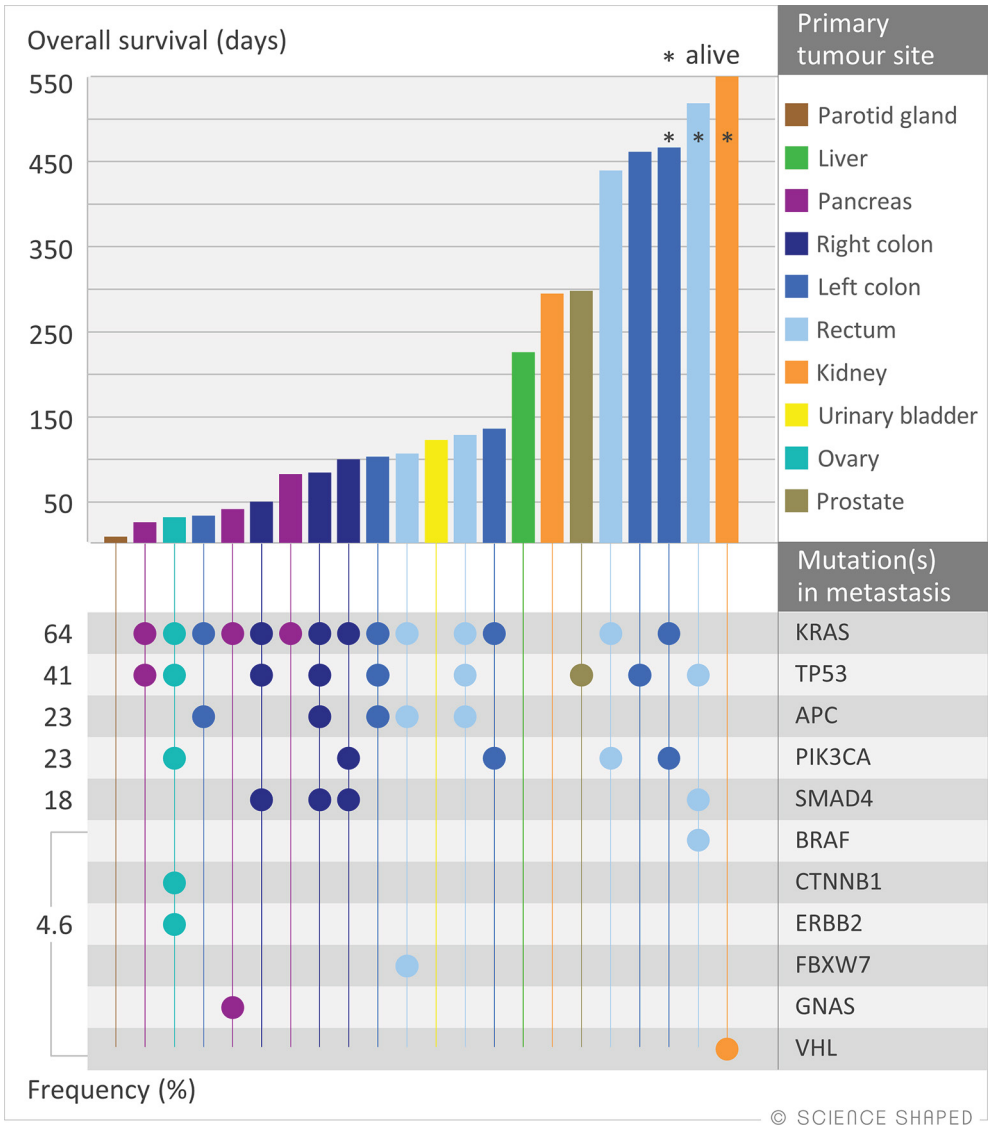

Figure 3 The 22 study patients: overall survival (first patient enrolled 9 May 2014, last patient enrolled 26 August 2015, censoring date 9 May 2016); primary tumour sites; detected mutations in metastatic tumour samples.

Cost estimates

Clinical CPP figures for 3 months of patient management are given in supplementary table S1. Omitting study patients who either were referred from external hospitals (n=6), incurred procedure-specific AE (n=1) or received off-protocol treatment (n=1), the 14 remaining internal patients were admitted for an average of 7.2 days out of the 90 index days, which was applied as the input unit for BSC. Applying the median of 18 days for conduct of the diagnostic procedures followed by commencement of treatment the next day, the time course for active therapy was set to 71 of the 90 index days. Further regarding outpatient clinic visits for oncologist consultation, an average of 6 visits was used. Based on published data,[11] it was assumed that AE which typically will lead to admission would be 3.02 times more frequent on active therapy as compared with BSC. This assumption surmised that an event occurred only once.[11] For BSC, outpatient clinic visits and admission, DRG points (low and high rates) were used as valuation. A fixed mean wholesale price for 3 months of treatment with the five index drugs (trastuzumab, panitumumab, gefitinib, vemurafenib and everolimus) was set at €13,890. For the intravenously administered drugs, this included costs for a total of 12 oncology nursing hours.

Furthermore, cost assumptions related to the study-specific diagnostic procedures comprised the total time spent by the involved personnel as well as the acquisition of equipment and disposables (see online supplementary table S2). National wage rates (low and high) including social costs for each group of personnel and a restricted and extended usage (high and low cost estimate, respectively) of the Ion Torrent PGM were employed as valuation. For the latter, the estimates were based on the theoretical minimum of sequencing procedures and the factual number accomplished, which included sequencing of both tumour and whole blood tissues and technical replicates in a few cases. A fixed price for the Ion AmpliSeq Cancer Hotspot Panel with reagents was entered. We

Table 3 Total cost-per-patient (CPP) estimates for 90 days of patient management

Treatment	Input parameter	Low CPP (€)*	High CPP (€)
Best supportive care	Total	4147	6181
Biomarker-agnostic	Medication	13889	13889
	Outpatient clinic visits	3456	5151
	Admission from adverse events	12525	18667
	Total	29870	37707
Biomarker-based	Diagnostic procedures	4492	9374
	Medication	548	548
	Outpatient clinic visits	136	203
	Admission from adverse events	494	736
	Best supportive care	3984	5937
	Total	9654	16798

*Valuation rates in EUR (€) of low and high CPP for the designated parameters are detailed in Result section.

assumed a capacity of 10–20 terabytes might be required to store the sequence data. Importantly, in this cost analysis, we did not consider the possible outsourcing of activities to core facilities but rather the established activities within the conduct of the study.

Total CPP estimates are shown in table 3. For the biomarker-agnostic arm, where all patients would be given tumour-directed therapy, it was assumed that patients would not be in need of BSC during 3 months of treatment. Furthermore, based on the finding that one of the 22 study patients in principle could have been offered ATI-based therapy (the single off-protocol-treated case), it was assumed that 5% of patients undergoing the ATI procedure would be found eligible for biomarker-based therapy; hence, the remaining patients (95%) would have BSC. The modelling of costs for 3 months indicated that the ATI-based approach was 2.5-fold more costly than BSC and approximately 2.5-fold less costly than the biomarker-agnostic option. The main cost drivers for the ATI-based treatment were the diagnostic procedures and BSC, while for the biomarker-agnostic alternative the main drivers were medication and AE management.

DISCUSSION

The first phase of the MetAction project was set up to evaluate feasibility of targeting late-stage disease with a systemic agent used outside marketed indication and based on an actionable molecular aberration in the individual patient's metastatic cancer. Since no patient was identified to be treated as per protocol, and consequently cost estimates had to be partly based on assumptions, the major study achievement was that we succeeded to establish a diagnostic infrastructure with a timeline that worked well in this clinical setting. Importantly, sampling of metastatic lesions was demonstrated to be safe, and we were able to procure adequate tissue material to undertake molecular analysis as per protocol.

With the backdrop of extensive international actions, one may question the necessity of a more limited initiative in precision cancer medicine in Norway. In spite of the recent report on a national strategy for personalised medicine in healthcare,[12] there has been no attempt so far to establish the required infrastructure which would enable routine practice of precision cancer medicine in the public health services of Norway, to which the citizens hold general access through universal healthcare coverage. Although individual elements of precision cancer medicine, such as DNA sequencing and bioinformatics analysis, in principle could be performed anywhere in the world, issues regarding data security and expedite performance of the required procedures would be unsolved. The MetAction project took on the responsibility of building a diagnostic pipeline by identifying, integrating and sharing existing hospital and research facilities and expertise at the two study sites. Importantly, the project established and supported, through project funding, components that were identified as missing in the existing practice in order to achieve a satisfactory workflow. Within this, education of multidisciplinary teams to provide decision support for the treating oncologists, which is essential to a precision cancer medicine programme, was a main purpose.

The choice of molecular diagnostics strategy was debated within the project group. With regard to sequencing platform, we decided on the only equipment that was certified by the Clinical Laboratory Improvement Amendments at the time. The 50-gene panel supplemented with designated FISH analyses of three actionable gene aberrations covered the biomarkers that were relevant for the current study phase, obviating the need for exome sequencing. Also, outsourcing to a research core facility was considered impractical in the context of a clinical study.

In order to realise the aims of the MetAction project inside the required timeline, a standalone analytical pipeline for sequence data was built. A summary report was generated for each study case and distributed to project participants using security-approved mechanisms. Archiving functions were maintained for research purposes using the Services for Sensitive Data facility at University of Oslo,[10] which provides a research-based secure storage of person-sensitive sequence data. It was deemed outside the scope of the project to develop solutions for integration of clinical and molecular data. However, in precision cancer medicine, this is a requirement for efficient practice and also to enable future systematic use of the compiled data.

No ATI case was identified among the 22 patients of the first study phase, probably as a direct result of our conservative approach. This was dictated by caution with regard to interpretation of mutation data at the inexperienced

MTB and CTB and possible toxicity from resulting interventions for patients with end-stage cancer. Thus, a chosen intervention was to be based on a single targeted systemic agent strictly matched to a single driver mutation (or its absence). The experiences gained have resulted in three specific study amendments that have been applied in the second study phase, as summarised below.

One particular challenge that remains also in the second study phase is drug availability. Costs related to the medication are perhaps the major obstacle in the conduct of studies of this kind. Our initiative has not been successful in setting up collaboration with the pharmaceutical industry. We believe that initiatives like MetAction, regrettably, are hampered by the fact that drug development often focuses on demonstrating efficacy in major patient populations. It might also be that the risk of unexpected toxicity may restrict collaboration from the pharmaceutical industry with academic investigators. The unfortunate consequence may be that the clinical potential of a novel drug is not fully realised.

For development of cost estimates, approximations included that biomarker-based therapy would be offered to 5% of patients undergoing biomarker screening, which may be an underestimation. In addition, the literature on admission from treatment toxicity is scarce and data therefore uncertain. The real data in the present cost estimations were related to personnel wage rates applicable to a high-cost country, acquisition of equipment and disposables, price for medication and DRG indicators within specialist healthcare. The input units for costs related to BSC and time spent to undertake the diagnostic procedures were also real data. The second study phase will probably enable real data for each single component of a repeat cost estimation.

In summary, the first phase of the MetAction project established a comprehensive diagnostic infrastructure, characterised gene mutations in metastatic tumours from 22 end-stage patients and estimated costs for the initiative. However, as no patient was identified for treatment as per protocol, three principal amendments have been undertaken and approved by the designated authorities for the second study phase, which is ongoing. First, the diagnostic gene mutation panel has been changed to the Ion Oncomine Comprehensive Panel.[13] Importantly, the MTB has been permitted extended liberty to interpret the mutation data, specifically in regard to describing signalling pathways. Finally, the CTB has been provided the opportunity to conclude on combination regimens (given that safety data of the combination is established). To this end, the first study phase was successful in enabling expedite and safe mutation profiling of metastatic tumours in order to offer biomarker-based treatment with molecularly matched medication to patients with end-stage cancer.

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