Clinical Cancer Research

Copenhagen Prospective Personalized Oncology (CoPPO)—Clinical Utility of Using Molecular Profiling to Select Patients to Phase I Trials

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Abstract

Purpose: We evaluated the clinical benefit of tumor molecular profiling to select treatment in the phase I setting.

Experimental Design: Patients with advanced solid cancers and exhausted treatment options referred to a phase I unit were included in a prospective, single-center, single-arm open-label study (NCT02290522). Tumor biopsies were obtained for comprehensive genomic analysis including whole-exome sequencing and RNA sequencing. When possible, patients were treated with regimen matched to the genomic profile. Primary endpoint was progression-free survival (PFS).

Results: From May 2013 to January 2017, a total of 591 patients were enrolled, with 500 patients undergoing biopsy. Genomic profiles were obtained in 460 patients and a potential actionable target was identified in 352 (70%) of 500 biopsied patients. A total of 101 patients (20%) received matched treatment based on either gene mutations or RNA expression levels of targets available in early clinical trials or off-label treatment. Objective response according to RECIST1.1 was observed in 15 of 101 patients (0% complete response, 15% partial response), with a median PFS of 12 weeks (95% confidence interval, 9.9–14.4).

Conclusions: Our study supports the feasibility of genomic profiling to select patients in the phase I setting and suggests that genomic matching can be beneficial for a minor subset of patients with no other treatment options. Randomized studies may validate this assumption.

See related commentary by Ratain, p. 1136

Introduction

In recent years, advances in the understanding of specific genetic alterations as fundamental oncogenic driver mechanisms (1, 2) and the development of targeted therapies against abnormally activated molecular targets have changed the concept of clinical cancer care (3). Improved outcomes due to the detection of druggable oncogenic drivers have been reported in several tumor types such as lung cancer, melanoma, colorectal cancer, and gastrointestinal stromal tumor (4–9).

Next-generation sequencing (NGS) allows rapid detection of clinically actionable aberrations. Increasing availability and decreasing cost of NGS have increased pace of the development within individualized cancer treatment guided by genomic profiling. The major goal of precision medicine is to identify the mechanisms of cancer progression at the individual level to apply targeted treatment.

Patients with exhausted treatment options are candidates for early clinical trials. Traditionally, the aims of phase I trials have been to establish dose and assess toxicity in unselected patients regardless of the mechanisms driving tumor growth in the individual patient. As a result, the response rates have remained poor (10, 11). Interestingly, genomic profiling to select patients in the early trial setting seems promising and several studies have reported retrospective clinical benefits from this approach compared with traditional selection (12–15). Furthermore, a meta-analysis from 2016 supported this assumption (16). In addition, enrichment of phase I trials with appropriate patients based on genomic profiling can accelerate drug development (6). However, limited and conflicting outcomes have been reported from prospectively conducted studies (17, 18), and it remains unclear whether using a genomic approach to guide the allocation of patients in early clinical trials may improve the outcome.

Here, we report the results from a single-center, nonrandomized, open-label prospective trial, where we investigated feasibility and efficacy of the comprehensive molecular profiling in selection of treatment for patients with exhausted treatment options in the setting of phase I.

Materials and Methods

Study design and objectives

The Copenhagen Prospective Personalized Oncology study (CoPPO, NCT02290522; ref. 19) is a prospective, single-center,

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Translational Relevance

The clinical potential of precision medicine in cancer care is promising and due to technical advantages and declining cost, it has now become relevant to elaborate the clinical utility in various settings. This study demonstrates the feasibility of extensive molecular profiling to select patients to phase I trials within a clinically relevant timeframe and suggest that genomic matching can be beneficial for a subset of patients with no other treatment options. However, this study could not verify the clinical importance of recommending molecular profiling in the phase I setting. Randomized studies are needed to demonstrate the clinical relevance.

single-arm open-label study conducted in the phase I unit at Rigshospitalet, University of Copenhagen (Copenhagen, Denmark). The primary objective was to evaluate the clinical benefit of using molecular profiling of patient's tumor for selection of treatment in the phase I setting and the primary endpoint for the study was median progression-free survival (PFS). In addition, we investigated the PFS ratio by comparing PFS of the treatment regimen selected by molecular profiling with PFS of the most recent treatment regimen to determine the percentage of patients with PFS ratio >1.3. PFS ratio >1.3 was selected because of the assumption that an improvement in PFS above 30% was clinically meaningful for the patient. Secondary outcomes included the percentage of patients allocated to treatment guided by the genomic profile and response rate according to RECIST1.1 (20) in patients receiving molecular profiling–guided therapy.

The study was conducted in accordance with the Declaration of Helsinki and approved by an institutional review board and the Regional Ethics Committee (Danish Ethical Committee, file number: 1300530). All patients provided signed informed consent.

Patient selection and biopsy procedure

Patients were enrolled from May 2013 to January 2017. Patients with advanced solid malignancies referred to the phase I unit at Rigshospitalet, University of Copenhagen (Copenhagen, Denmark) were offered enrolment. Eligibility criteria were: exhausted treatment options, life expectancy of $\geq$3 months, normal organ function, measurable disease (RECIST1.1), Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, age $\geq$ 18 years, and lesions accessible for biopsy.

A fresh tumor sample primarily from metastatic sites was obtained under local anesthesia. Biopsies were either core-needle biopsies (18-gauge needle) or surgical resection samples. Three samples were obtained from the same lesion. Two samples were stored in RNA*later* (Life Technologies) for RNA expression analyses and DNA gene mutation analyses and one sample was formalin-fixed, paraffin-embedded (FFPE) for histopathologic analyses to confirm the suitability and representativeness of the material. A blood sample (7 mL EDTA) was collected for germline mutation analysis used to identify tumor-specific alterations in the tumor/normal examination.

Molecular analyses

DNA and RNA were extracted from tumor samples in RNA*later* using AllPrep DNA/RNA/protein Extraction Kit (Qiagen) according to manufacturer's instructions. DNA from whole blood samples was isolated using the liquid handling automated station (Tecan). Whole-exome sequencing (WES) was performed from tumor and germline DNA using SureSelect Clinical Research Exome (Agilent) with fragmentation to 300 bp using Covaris S2 (Agilent) and adaptor ligation using KAPA HTP Library Preparation Kit (Roche). RNA sequencing was done using TruSeq Stranded Total RNA Library Prep Kit (Illumina). WES and RNA sequencing libraries were paired-end sequenced on Illumina NextSeq500 or HiSeq2500 platforms. Reads were aligned to the human reference genome (hg19/GRCh37) using CLC Biomedical Genomics Workbench (Qiagen) and variant calling was performed above 10% frequency in the tumor DNA. Identification of somatic mutations was performed using a tumor/normal analysis in which germline variants were subtracted from the tumor variants. The identified somatic mutations were further filtered using Ingenuity Variant Analysis (IVA) from Qiagen to identify cancer-associated variants. Mutational load was assessed in IVA as nonsynonymous variants (missense, nonsense, insertions, deletions, and splice site mutations) after filtering for sequencing quality and excluding common variants (>1% in 1000Genomes, ExAC, and NHLBI ESP databases).

Expression array was performed to molecularly confirm the origin of the primary tumor (21) and to evaluate the expression level of therapeutic targets on the basis of predefined thresholds values. Validation of the expression target was performed by IHC before inclusion in most trials. Copy number alterations were called from SNP Array (CytoScanHD, Affymetrix) by using Nexus Software (BioDiscovery).

Data from the comprehensive molecular profiling was integrated with the clinical profile of each patient to identify potential actionable targets.

Treatment decision and evaluation

Individual genomic reports with results from WES, RNA sequencing, SNP array, and expression array were evaluated every 2 weeks at a multidisciplinary institutional tumor board meeting dedicated to CoPPO attended by experts in clinical oncology, molecular biology, pathology, clinical genetics, and bioinformatics. Actionable targets were defined by the tumor board according to existing level of evidence and a treatment suggestion was proposed when possible. The options were discussed by the tumor board using the following decision strategy (hierarchy) for selecting the therapy: (i) treatment targeting the proposed driver alteration in an early trial; (ii) treatment targeting the proposed driver alteration as compassionate use; (iii) off-label treatment if published clinical data supported the treatment rationale; (iv) if no treatment-relevant driver mechanism was found, studies targeting an observed gene expression were selected; (v) if a patient presented more than one actionable target, the suggested treatment targeting a proposed driver mechanism was chosen. Case examples illustrating the decision procedure is presented in Supplementary Table S1.

The selection of treatment regimens was influenced by the availability of trials at our institution and the emerging evidence for the use of off-label treatment targeting specific genomic alterations, for instance treatment with PARP inhibitor against DNA repair defects in metastatic prostate cancer (22). To describe actionable targets, we introduced two terms (Fig. 1). First, we defined "potentially actionable targets" as findings in the genomic profile that indicated the possibility of an individualized

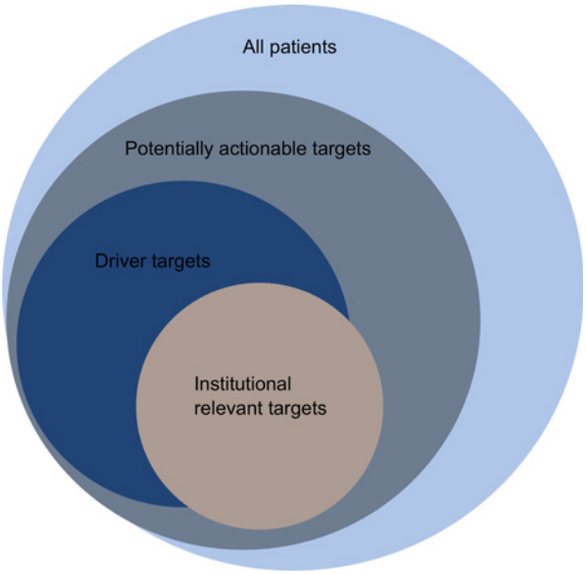

Figure 1.
Illustration of the complexity of reporting actionable targets. First circle (light blue) illustrates that all patients subjected to molecular profiling. Second circle (gray) illustrates that a part of all patients will have a "potentially actionable target," defined as findings in the genomic profile indicating a possibility for individualized treatment. Some of these findings will be commonly accepted "driver targets" (third circle, dark blue). Fourth circle (beige) represents the "institutional relevant targets," defined as targets in trials available at the institution or in a collaborating institution, and includes both driver alterations and nondriver alterations. Institutional relevant targets will differ between settings and in time.

treatment. This could be either a "targetable driver alteration" (a driver target unanimously considered an actionable target in the field of precision medicine; ref. 23) or an "institutional relevant target" defined as targets in trials available at our institution or in a collaborating institution. High expression of targets for antibody–drug conjugates (ADC) available in a clinical trial at our institution is an example of an "institutional relevant target."

Patients offered treatment regimens based on TBM recommendation were treated in the setting of the phase I unit. Response was assessed with predefined evaluations every 6–8 weeks, according to the specific trials and to RECIST1.1 (20) assessed by independent radiologists. Notably, all patients diagnosed with a cancer type for which genomic testing is part of the standard of care (lung cancer, gastrointestinal cancer, breast cancer, etc.) had already been tested and treated according to standard guidelines. These findings were not counted as actionable targets [e.g., *EGFR*-mutations in non–small cell lung cancer (NSCLC)].

Description of most prior treatment was registered at inclusion and sufficient data to support the assessment of PFS1 was secured. PFS1 was calculated as time from treatment initiation on most recent systemic treatment to treatment progression. The assessment of PFS1 was performed retrospectively from electronic medical records.

Statistical considerations

A total of 97 evaluable patients were needed to reject the null hypothesis that PFS ratio >1.3 in less than 15% with a power of 90% and a significance level of 5%. This is with an assumption that the true proportion was 27% based on prior studies (24). According to this study design, sample size was estimated to include 500 biopsied patients, based on our pilot study (25) that we could allocate 21% of included patients to matched treatment. PFS was calculated using Kaplan–Meier method (18). Patients alive at the date of data cutoff (December 1, 2017) were censored. PFS ratio was defined as PFS2/PFS1, where PFS1 was the time from start of the most recent treatment to progression and PFS2 was the time from the start of molecular profiling–matched treatment to progression according to RECIST1.1, clinical progression or death. Statistical analyses were performed using IBM Statistics SPSS (version 22) and R (version 0.99.903).

Results

Study flow

The CONSORT diagram for the study is shown in Fig. 2. A total of 591 patients were included in the CoPPO study between May 2013 and January 2017. Five-hundred patients (85%) were eligible for participation and subjected to biopsy. Reasons for screen failure (15%) are outlined in Fig. 2. A molecular profile was achieved in 460 biopsied patients (92%). WES was achieved in 458 patients and 2 patients were subjected to a targeted panel due to lack of tumor DNA. SNP array was performed in 440 patients. RNA was sufficient for RNA sequencing and expression array in 447 patients. Overall, complete genomic profiles consisting of WES, SNP array, RNA sequencing, and expression array were achieved in 435 biopsied patients (87%). Median turnaround time from biopsy to available genomic profile was 34 days.

Biopsy failure was observed in 67 (13%) of 500 biopsied patients; however, a successful rebiopsy was achieved in 27 patients. The main biopsy sites were liver metastasis ($n = 271$), followed by lymph node metastasis ($n = 68$), subcutaneous metastasis ($n = 36$), and lung metastasis ($n = 25$). Biopsy complications were observed in 15 patients including hematoma ($n = 6$), pneumothorax ($n = 3$), and others ($n = 6$). Short hospitalization was required in 7 patients (median 1 day, range 1–4 days). No biopsy-related deaths occurred.

A potentially actionable target was proposed in 352 patients (70%) and 101 patients (20%) received treatment matched to their molecular profile (Supplementary Table S2). A majority of potential actionable targets were revealed from RNA analysis (59%), in contrast, in the group of patients receiving matched treatment, a preponderance of targets (61%) was revealed from DNA analysis (Fig. 2). Potential actionable targets found in the included cancer subtypes are demonstrated in Supplementary Fig. S3. A total of 100 patients with a potentially actionable target received a nonmatched therapy after molecular profiling, mainly due to lack of an institutional relevant target. The majority of these patients ($n = 70$) were treated in other institutions either in trials or other experimental regimens preferred by the patient. The remaining 30 patients were treated in nonmatched protocols in house. Notably, 151 patients with a potentially actionable target never received further treatment primarily due to rapid decline in performance status.

Patient characteristics

Table 1 reports the patient characteristics of the 460 successfully biopsied patients. The most common tumor types were colorectal

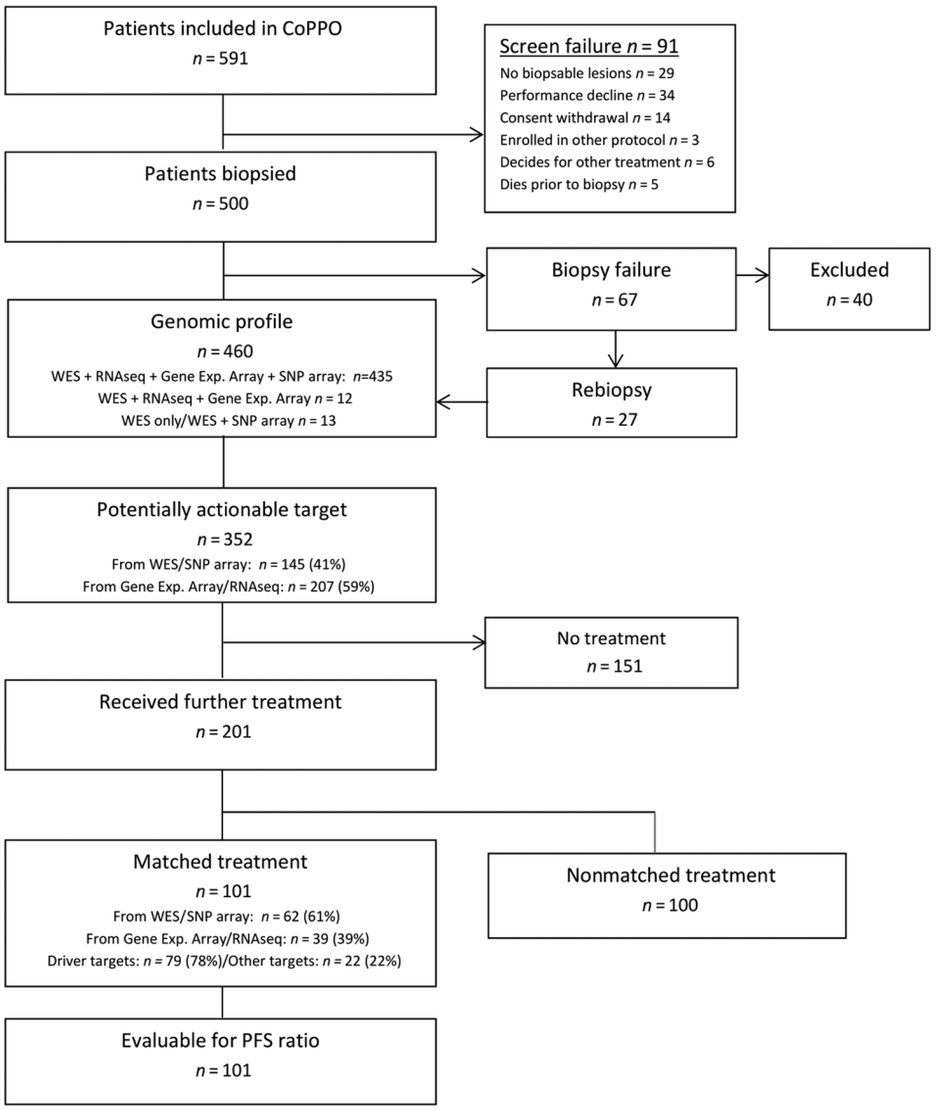

Figure 2.
CONSORT diagram. Gene Exp. Array, gene expression array; RNAseq, RNA sequencing.

cancer ($n = 113$) followed by breast cancer ($n = 47$), pancreatic cancer ($n = 45$), bile duct cancer ($n = 33$), and NSCLC ($n = 20$). Tumor type distribution was similar in the matched treatment population. Median age at inclusion was 59 (range 18–86) and approximately 1 of 3 of patients in both groups presented with ECOG performance of 0. The median Royal Marsden Hospital (RMH) score was 2 (0–3) in both groups. Patients had received a median of three prior treatments (range 1–12) in the metastatic setting. An equal gender distribution was seen in the entire population of biopsied patients with a slight nonsignificant preponderance of women [57%; 95% confidence interval (CI), 47%–67%] over men (43%) in the matched treatment population.

Treatment allocation

In total, 101 patients were allocated to treatment based on 29 different targets (Fig. 3A) divided in 8 groups representing the altered pathway (Fig. 3B). The treatment regimens were dominated by treatments targeting *BRAF* (in nonmelanoma tumors) and *BRCA1/2* followed by CEACAM5, a target recognized by an ADC investigated in a trial open for inclusion during the study period.

Clinical ability and outcome

PFS was evaluable in all 101 patients receiving matched treatment and median PFS was 12 weeks (95% CI, 9.9–14.4) as illustrated by Kaplan–Meir plot in Supplementary Fig. S2. Objective responses (RECIST1.1) in the group of 101 patients treated according to their molecular profiles included 15 patients (15%; 95% CI, 9%–24%) with partial response (PR) and no complete responses (CR). Stable disease as best response was achieved in 38 patients (38%) and progressive disease (PD) was observed in 33 patients (33%). The remaining 16 patients (16%) were not evaluated at the predefined evaluation time mainly because of early clinical deterioration (12%). Intention-to-treat analysis revealed a response rate of 2.5% (15 responders of 591 screened patients). Maximum reduction in tumor size according to RECIST1.1 is showed in Fig. 4.

Table 1. Patient characteristics

	Successfully biopsied $n = 460$	Matched treatment $n = 101$
Sex		
Female	227 (49%)	58 (57%)
Male	233 (51%)	43 (43%)
Age		
Median	59	60
Range	18–86	27–86
Number of prior treatment regimens (advanced disease)		
Median	3	3
Range	1–12	1–11
Number of metastatic sites		
Median	3	3
Range	0–8	0–5
ECOG PS		
Median	1	1
0	130 (28%)	39 (39%)
1	323 (70%)	62 (61%)
2	7 (1%)	0 (0%)
RMH prognostic score		
Median	2	2
0	52 (11%)	19 (19%)
1	123 (27%)	27 (27%)
2	165 (36%)	36 (36%)
3	115 (25%)	19 (19%)
Missing	5 (1%)	0
Tumor type		
Colorectal cancer	113 (25%)	25 (25%)
Pancreatic cancer	45 (10%)	6 (6%)
Bile duct cancer	33 (7%)	11 (11%)
Breast cancer	47 (10%)	13 (13%)
Cervical cancer	11 (2%)	2 (2%)
Gastric cancer	14 (3%)	1 (1%)
Head and neck cancer	12 (3%)	1 (1%)
Hepatocellular cancer	10 (2%)	2 (2%)
Melanoma	9 (2%)	2 (2%)
NSCLC	20 (4%)	7 (7%)
SCLC	7 (2%)	0 (0%)
Neuroendocrine cancer	10 (2%)	3 (3%)
Ovarian cancer	15 (3%)	6 (6%)
Adenoid cystic carcinoma (salivary glands)	5 (1%)	4 (4%)
Endometrial cancer	4 (1%)	3 (3%)
Prostate cancer	18 (4%)	7 (7%)
Thymoma	7 (2%)	0 (0%)
Sarcoma[a]	13 (3%)	1 (1%)
Esophageal cancer	11 (2%)	0 (0%)
Urothelial cancer	13 (3%)	1 (1%)
Anogenital cancer	3 (1%)	1 (1%)
Adrenocortical cancer	7 (2%)	1 (1%)
Malignant mesothelioma	7 (2%)	1 (1%)
Renal cell carcinoma	3 (1%)	0 (0%)
Glioblastoma	3 (1%)	1 (1%)
Germ cell tumor	1 (0%)	1 (1%)
Myoepithelial carcinoma (salivary glands)	3 (1%)	1 (1%)
Cancer of unknown primary origin (CUP)	10 (2%)	0 (0%)
Others	6 (1%)	0 (0%)

Abbreviation: SCLC, small cell lung cancer.
[a]Comprises bone (n = 6) and soft tissue (n = 7).

The 15 patients with PR received treatments matched to the following targets: *BRAF* ($n = 7$), *FGFR1/2* ($n = 1$), *NOTCH* ($n = 1$), *BRCA1* ($n = 1$), *ERBB2* ($n = 1$), *ALK* ($n = 1$), *PTEN* ($n = 1$), and *CCND1* ($n = 1$). The *CCND1* target was an amplification and the remaining targets were mutations. Notably, no patients allocated to treatment based on RNA expression obtained response according to RECIST1.1.

For 32 of the patients (32%; 95% CI, 23%–42%), a PFS ratio of >1.3 was observed (Fig. 5). Four patients were still on treatment at data cutoff, but had reached PFS ratio >1.3. Among patients with PFS ratio >1.3 we found 8 of 32 patients (25%) with PD as best response. Likewise, among patients with PFS <1.3 we found 5 of 69 patients (7%) PR presented with PFS ratio below 1.3, counting for 33% (5/15) of patients with response according to RECIST1.1.

Discussion

Results from studies evaluating the clinical benefit of precision medicine have been conflicting. In this descriptive study of 500 patients, we demonstrate that genomic profiling is feasible in the

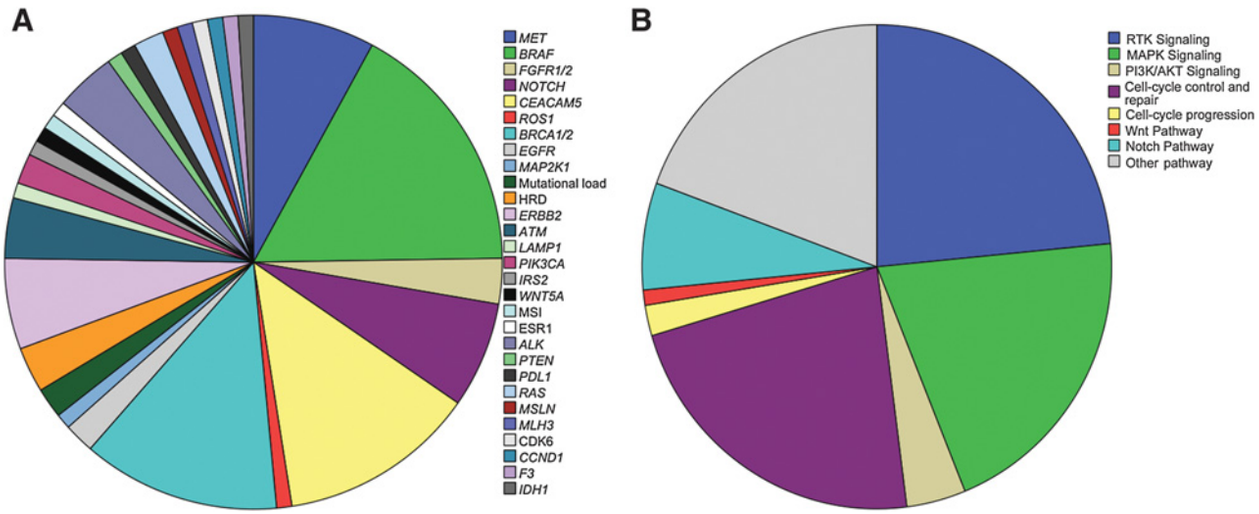

Figure 3.
Distribution of the molecular targets. **A,** Targets used to guide treatment in 101 patients. **B,** Involved pathways in the selected treatment regimens.

phase I setting as indicated by a high proportion of 22% of patients who could be allocated to a matched treatment based on molecular profiling with a clinically meaningful turnaround time of 34 days.

A clear demonstration of an unambiguous clinical benefit for patients that undergo genomic profiling is hampered by the lack of valid endpoints. PFS ratio has been proposed by Von Hoff and colleagues as a useful endpoint (26) for the evaluation of the benefit of matched treatment according to molecular profiling in early clinical trials (24). However, the relevance of PFS ratio has been debated including the proposal that a clinical benefit is related to a PFS ratio above 1.3. One of the premises for the use of PFS ratio is the existence of a strong correlation between PFS1 and PFS2. This assumption has been challenged by Buyse and colleagues when comparing PFS after first- and second-line treatment in colorectal cancer (27). In addition, the most recent PFS have an excessive impact on the outcome of the PFS ratio. In our cohort some patients classified as nonresponders demonstrated a PFS ratio >1.3 mainly due to a very ineffective prior treatment with short PFS demonstrating the reduced clinical value of the estimate. The assumption that clinical benefit could be proven by PFS ratio above 1.3 was furthermore questioned by the large proportion of patients with PD at first evaluation in the group with PFS ratio above 1.3. Overall, our study adds to the shortcomings of using PFS ratio as surrogate for clinical benefit.

In addition, our study demonstrated an urgent need to improve the selection of patients undergoing biopsy for

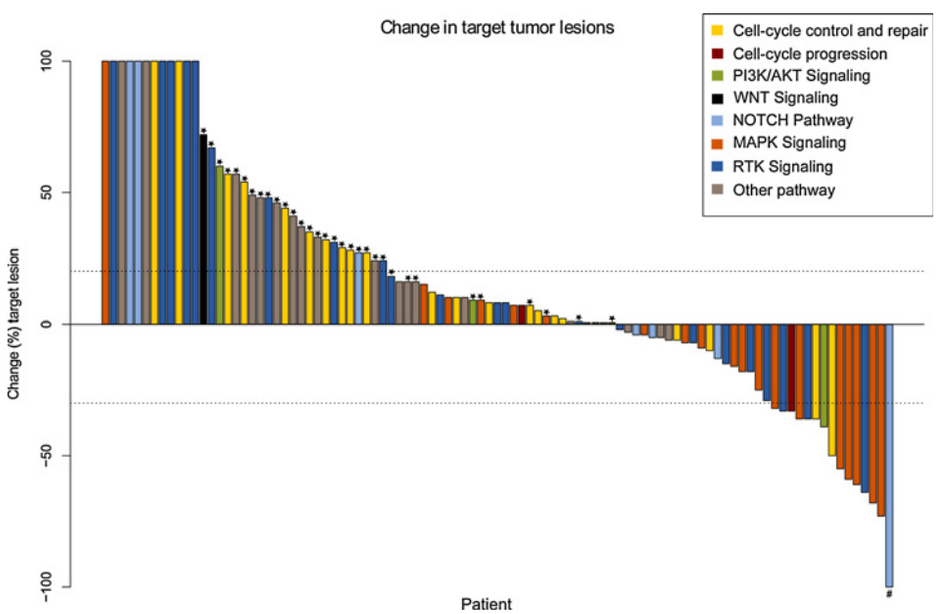

Figure 4.
Waterfall plot. Patients are color-labeled according to the targeted pathway. Patients marked with ★ had PD according to RECIST1.1. One patient marked with **#** had complete regression of target lesions but not a CR due to persistent nontarget lesions. Patients with early deterioration due to clinical progression are placed at the maximum observed increase. Patients with no evaluation and no clinical progression ($n = 4$) are excluded from this figure.

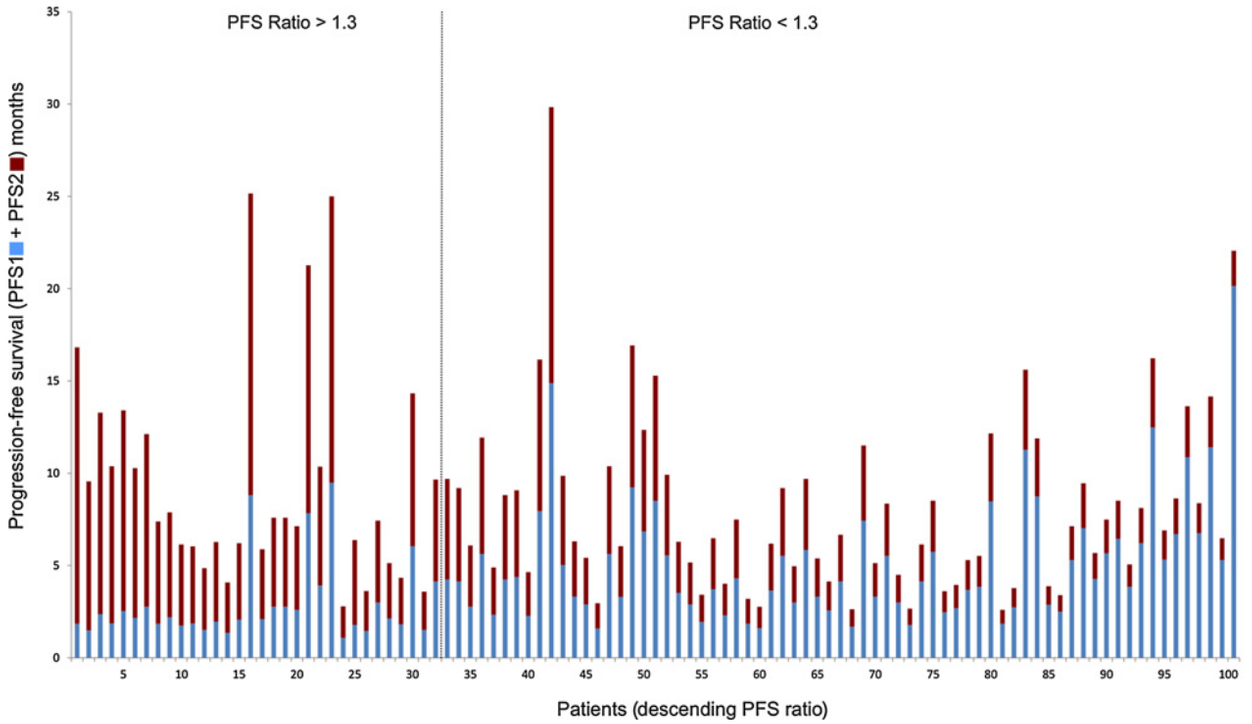

Figure 5.

Illustration of PFS ratio. Comparisons between PFS on molecular profiling–guided treatment (PFS2) and on the most recent treatment (PFS1). Patients are ordered by descending PFS ratio ($n = 101$).

genomic profiling. A considerable proportion of patients biopsied in this study never received further treatment mainly because of rapid decline in performance status. In our study, we only included patients with exhausted treatment options. These patients are heavily pretreated and often present with extensive disease and poor prognosis illustrated by a median RMH prognostic score of 2, which might not be the most appropriate setting to test clinical benefit of molecular profiling.

Selecting the most appropriate design for the decision of actionable targets is challenging. We chose a dynamic approach were our CoPPO-dedicated tumor board discussed each case and defined the targets at an individual level based on the available evidence. This setup resulted in dynamics in the definitions of the targets due to an ongoing evolution in knowledge and the clinical implications with the benefit of being able to continue inclusion of patients over a longer period. However, this approach lacks the clear-cut definition and makes it demanding to report findings. The SHIVA trial (27) had predefined algorithms for treatment allocation with no option to adjust during the trial. These definitions and prioritizations of targets were defined at the study design in 2011 and the algorithm has since been debated particularly as the trial came out negative with respect to its primary endpoint (PFS). For instance, a large proportion (46%) of patients was allocated to single agent mTOR inhibitors based on alterations in the PI3K/AKT/mTOR pathway. However, evidence of limited efficacy of this treatment regimen (28) was available before allocation of the first patients. Nevertheless, the SHIVA trial clearly showed the feasibility of conducting a randomized trial in the field of precision medicine.

Our study was based on a single dedicated phase I unit and we aimed to allocate patients in ongoing trials in-house. During the study we have expanded the number of ongoing trials from 15 to more than 40 trials. We chose to include an extension in actionable targets including ADCs and expression targets. However, some of these targets did not serve as a driver mechanism, which may represent a limitation when including such a broad definition of actionable targets. Furthermore, in some cases the tumor board suggested a combination regimen on the basis of published data, where the response might not be attributable to the molecular testing alone. Our data, however, do support the idea that targeting the suspected driver mechanism is the most clinically relevant approach. These assumptions are clearly demonstrated with the result of targeting BRAF in nonmelanoma patients in our cohort and suggest that focused screening for *BRAF* mutations may be relevant for selected tumor types. The relevance is furthermore supported by the recent FDA approval of combination treatment targeting *BRAF* in thyroid cancer and metastatic NSCLC harboring *BRAF* V600E mutation. However, using tumor-specific mutation analysis, a considerable risk of missing a potential germline driver mutation for instant BRCA mutation is possible. Germline *BRCA* testing may be the most appropriate way to screen for *BRCA* mutations in other populations like newly diagnosed breast cancer and ovarian cancer.

The level of evidence sufficient to select off-label treatment has been debated during the trial and remains contentious. Several knowledge databases initiatives (CIVIC, OnkoKB etc.) are aiming to support the decision part, though we still experience a gap between molecular genomics opportunities and

the clinical interpretation. Furthermore, international collaborations such as The Cancer Genome Atlas, ACCR Project Genomics Evidence Neoplasia Information Exchange, International Cancer Genome Consortium etc. with data sharing initiatives among N-of-1 trials is needed to overcome the challenge of introducing precision medicine in clinical practice. In any case, allocation of patients to early clinical trials driven by molecular profiling may now be an opportunity in a cost-effective way, providing enrichment of early clinical trials and thereby potentially acceleration of drug development, which is beneficial for the society.

In conclusion, genomic profiling is feasible in the setting of a dedicated oncological phase I unit. A total of 22% of patients were allocated to a matched treatment with an overall response rate of 15%. Our study suggests that genomic matching can be beneficial for a minor subset of patients with exhausted treatment options, but the suggested assumption of clinical benefit of using genomic profiling to select patients in the early trial setting remains unclear. Further studies are needed to test this assumption.

Disclosure of Potential Conflicts of Interest

E. Santoni-Rugiu reports receiving commercial research grants from Roche, reports receiving speakers bureau honoraria from Pfizer, and is a consultant/advisory board member for Takeda, Pfizer, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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