Cancer Research

Cancer Therapy Directed by Comprehensive Genomic Profiling: A Single Center Study

Jennifer J. Wheler[1], Filip Janku[1], Aung Naing[1], Yali Li[2], Bettzy Stephen[1], Ralph Zinner[1], Vivek Subbiah[1], Siqing Fu[1], Daniel Karp[1], Gerald S. Falchook[3], Apostolia M. Tsimberidou[1], Sarina Piha-Paul[1], Roosevelt Anderson[1], Danxia Ke[1], Vincent Miller[2], Roman Yelensky[2], J. Jack Lee[4], David S. Hong[1], and Razelle Kurzrock[5]

Abstract

Innovative molecular diagnostics deployed in the clinic enable new ways to stratify patients into appropriate treatment regimens. These approaches may resolve a major challenge for early-phase clinical trials, which is to recruit patients who, while having failed previous treatments, may nevertheless respond to molecularly targeted drugs. We report the findings of a prospective, single-center study conducted in patients with diverse refractory cancers who underwent comprehensive genomic profiling (CGP; next-generation sequencing, 236 genes). Of the 500 patients enrolled, 188 (37.6%) received either matched (N = 122/188, 65%) or unmatched therapy (N = 66/188, 35%). The most common reasons that patients were not evaluable for treatment included insufficient tissue, death, or hospice transfer. The median number of molecular alterations per patient was five (range, 1–14); median number of prior therapies, four. The most common diagnoses were ovarian cancer (18%), breast cancer (16%), sarcoma (13%), and renal cancer (7%). Of the 339 successfully profiled patients, 317 (93.5%) had at least one potentially actionable alteration. By calculating matching scores, based on the number of drug matches and genomic aberrations per patient, we found that high scores were independently associated with a greater frequency of stable disease $\geq$6 months/partial/complete remission [22% (high scores) vs. 9% (low scores), $P = 0.024$], longer time-to-treatment failure [hazard ratio (HR) = 0.52; 95% confidence interval (CI) = 0.36–0.74; $P = 0.0003$], and survival (HR = 0.65; 95% CI = 0.43–1.0; $P = 0.05$). Collectively, this study offers a clinical proof of concept for the utility of CGP in assigning therapy to patients with refractory malignancies, especially in those patients with multiple genomic aberrations for whom combination therapies could be implemented. *Cancer Res; 76(13); 3690–701. ©2016 AACR.*

Introduction

Comprehensive descriptions of genomic and other molecular alterations that define individual tumors are now possible. Investigations to better determine the role of molecular diagnostics in helping clinical oncologists interrogate and prosecute cancer on a patient-by-patient basis are therefore required. Importantly in this regard, an advancing pipeline of targeted pharmaceuticals is becoming available to patients with cancer, and many of these treatments are effective only in the presence of specific abnormal signals.

Many patients are referred to phase I centers after having failed multiple regimens. In part, because of the advanced nature of the disease, as well as the emergence of resistant clones of tumor cells, the response rates in traditional phase I trials are on the order of 5%–10% (1, 2). Recent advances demonstrate that, by obtaining a genomic "portrait" of the patient's cancer, and matching patients whose tumors harbor specific aberrations with cognate-targeted therapies, higher response rates can be achieved in the heavily pretreated patient with advanced cancer (3–5). Indeed, progression-free survival (PFS) on matched phase I therapy may be better than on prior lines of conventional, approved unmatched therapy (3, 6), and, in some cases, responses may be so significant that the drug is afforded breakthrough status, a designation that is associated with expedited review and approval by the FDA. Remarkably, in 2014, because of high response rates, the FDA-approved ceritinib, an ALK inhibitor, for patients with lung cancer and *ALK* aberrations, after phase I testing (4, 7).

The purpose of the current study was to prospectively investigate the clinical utility of a broad, hybrid capture–based next-generation sequencing (NGS) assay in the phase I oncology ecosystem, including determining the feasibility of performing

[1]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas. [2]Foundation Medicine, Cambridge, Massachusetts. [3]Sarah Cannon Research Institute at HealthONE, Drug Development, Denver, Colorado. [4]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas. [5]Center for Personalized Cancer Therapy, Moores Cancer Center, The University of California San Diego, La Jolla, California.

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

Prior presentation: This study was previously presented at the 2015 ASCO Annual Meeting, Chicago, Illinois.

Clinical trial registration ID: NCT02437617.

Corresponding Author: Razelle Kurzrock, UC San Diego Moores Cancer Center, 3855 Health Sciences Dr, MC #0658, La Jolla, CA 92093-0658. Phone: 858-246-1102; Fax: 858-246-1915; E-mail: rkurzrock@ucsd.edu

doi: 10.1158/0008-5472.CAN-15-3043

AACR

a comprehensive genomic profile (CGP) on the routine biopsy specimens of patients, as well as describing outcome parameters. Outcome variables included rate of stable disease (SD) ≥6 months/partial/complete remission (SD ≥6 months/PR/CR), time-to-treatment failure (TTF), overall survival (OS), as well as TTF on trial compared (TTF2) with the TTF of the immediately prior therapy (TTF1) uninformed by genomics (TTF2 vs. TTF1). In addition, because patients often have multiple genomic alterations and receive combination drug regimens (8), all of which could influence outcome, we also investigated a novel, exploratory Matching Score that incorporated the number of matched agents given to a patient and the number of gene alterations present in the tumor of that individual.

Patients and Methods

Patient population and study design

Patients with advanced malignancies ($N = 500$) were eligible to enroll in this single-arm, nonrandomized study. Tissue analysis could be done on archived tissue or fresh biopsies. Eligibility criteria included Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (9), tissue available for molecular testing, a life expectancy of at least 3 months, and likely suitable to meet the additional enrollment criteria specified in therapy protocols. The study was designed as a navigation trial, where the physician could use the CGP diagnostic, in the context of the patient's other medical conditions and laboratory tests, to choose a therapy, such as a clinical trial within the phase I program. The preplanned study objectives were to determine the effect of CGP-based matching on response rate, as well as other outcome parameters, and to assess the feasibility of CGP in the clinical setting.

The hypothesis was that CGP-based matching would be feasible in a significant subset of patients, and that CGP-matched patients would do better than unmatched patients. The study was planned for 500 patients enrolled. Because of the advanced nature of the disease in the population assessed (associated with frequent, rapid decline in patient health), as well as the fact that diverse cancers were included, it was assumed that only a fraction of the patients would be treated, and there were thus no early stopping rules. The study was not blinded; however, the degree of matching between the aberrations present in the tumor and the treatment chosen was evaluated at the end of the trial by a reviewer blinded at the time of review to patient outcome. Information about the molecular panel, targets, drugs, definition of matching (direct and indirect), prognostic scores, the Matching Score, outcome parameters assessed, and methods of analysis/statistics are described, in detail, below and in Fig. 1 and Supplementary Tables S1–S4; refs. 10–51). This study (NCT02437617) was approved by the MD Anderson Internal Review Board, and all patients gave informed consent.

Prognostic scoring system

Patients were assessed for prognostic features by previously described prognostic classifications [the Royal Marsden Hospital (RMH) and the MD Anderson Cancer Center (MDACC) scoring system] that include the following factors: lactate dehydrogenase (LDH) and albumin levels and number of sites of metastases (RMH score; refs. 46, 49); RMH variables plus ECOG performance status, and whether or not patients had gastrointestinal tumors are part of the MDACC score (42).

CGP using a broad, hybrid capture–based next-generation sequencing assay

Genomic alterations detected include base substitutions, insertions, deletions, copy number alterations, and selected gene fusions (Foundation Medicine; Clinical Laboratory Improvements Amendment laboratory; ref. 48; see details in Supplementary Methods and Supplementary Table S1).

Standard biomarker assessments

Patients were assessed for other biomarkers as per standard of care. For example, patients with breast cancer had assessments for estrogen and progesterone receptors, as well as Her2 by IHC.

Analysis of data

Targets. The CGP panel was evaluated in the context of standard of care. Therefore, a target could be a functionally active protein (e.g., mutated or amplified *BRAF* product detected by CGP, when targeted by a BRAF inhibitor), or a protein preferentially expressed on tumor versus normal cells [estrogen receptor (ER) targeted by a hormone modulator].

Matching. A drug was considered "matched" if the half maximal inhibitory concentration (IC_{50}) impacted the target at low nanomolar range (for small-molecule inhibitors) or if the target was the primary one recognized by an antibody. We also performed exploratory analyses that subdivided "matched" therapy into "matched-direct" and "matched indirect" treatment (see below and Supplementary Table S2). For actual match designations, and additional information about the matching process, see Supplementary Table S3 (10–45).

Local rather than systemic therapy and transplant were considered inevaluable for matching. Matching designation was confirmed by one of the investigators (R. Kurzrock), who was blinded at the time of designation to patient outcome.

Definition (matched-direct vs. matched-indirect therapy). Only drugs that directly impacted the target were considered matched-direct (Supplementary Table S2). Matched-direct therapy would include small-molecule inhibitors with an $IC_{50} \leq$ 100 nmol for the target, as well as antibodies whose primary target was the aberrant protein or a differentially expressed protein (see also Supplementary Methods).

Matching Score

It is now well known that advanced tumors have multiple aberrations and that combination therapy is likely to be better than monotherapy (8). Therefore, an exploratory scoring system ("Matching Score") was developed that divided the number of matched drugs by the number of aberrations. Under this system, the higher the Matching Score, the better the match. The score for each match (direct or indirect) was assigned a 1; no match was a zero. If a drug directly impacted two targets present in the patient, a 2 was given (example, a multikinase inhibitor with potent activity against more than one target present in a tumor); if two drugs each impacted a target directly in a patient, a 2 was also given. If two drugs were given that impacted directly (or indirectly) the same target in a patient, the number 2 was still given. If a patient had two mutations in the same gene, it counted as one aberration. The Matching Score was calculated by dividing the number derived from the direct and indirect matches in each patient (numerator) by the number of

aberrations (denominator). For instance, if a patient harboring six genomic aberrations received two drugs, one of which matched an aberration directly and the other matched indirectly, the Matching Score would be 2/6 or 0.33. The Matching Score was also examined, in a subanalysis, wherein "matched direct" was given 1 point and "matched indirect" was given either 0.5 or 0.75 points. In addition, high and low Matching Score was constructed (dichotomized at the median) to examine its effect on treatment outcomes.

Outcome assessment

Patients who were lost to follow up or came off early (before restaging) for insurance reasons were considered inevaluable for SD $\geq$6 months/PR/CR; patients who came off early for toxicity were considered progressors. Patients who had not been restaged at the date of data cutoff [six months after the date of the last enrollment (August 4, 2014)] were considered inevaluable for SD $\geq$6 months/PR/CR. SD, PR, or CR was determined as per the assessment by the treating physician.

TTF and OS were assessed by the method of Kaplan and Meier, and the survival function between groups was compared using a two-sided log-rank test.

TTF was the interval from the initial treatment to documentation of disease progression, death, or removal from study for any reason (mostly toxicity), whichever occurred first. Patients who had not reached any of those endpoints at the date of data cutoff (August 4, 2014) were censored on that date. If they had not reached the endpoints at the time of being lost to follow up, they were censored at the date of last contact.

OS was measured from the time of study enrollment. Patients still alive (for OS) at the date of data cutoff, or the date of last contact for patients lost to follow up, were censored on that date.

TTF2 (that is TTF on therapy after enrollment) was also compared with TTF1 (last prior therapy before enrollment), hence using patients as their own control (TTF2/TTF1; ref. 51).

Matched/unmatched was designated on the basis of the first trial after receiving the CGP result, except when patients were unknowingly placed on a matched therapy at the time of or after consenting, but before getting the CGP result. Local therapy (hepatic arterial infusion, for example) and transplant were considered inevaluable. For local therapy (but not for transplant), the next therapy after the local therapy was the one evaluated for TTF2; the therapy before the local was used for TTF1. Other than this case, TTF2 versus TTF1 referred to the TTF of therapy on study (TTF2) versus the TTF on prior therapy (TTF1). All patients who received transplant as their first therapy after molecular results were known were considered inevaluable for all outcome parameters. If a patient was knowingly matched at the time of consent, the next therapy was evaluated for SD $\geq$6 months/PR/CR, TTF, and OS, but the patient was inevaluable for TTF2 versus TTF1. Patients whose immediate prior therapy met one of the following criteria were considered inevaluable for TTF2 versus TTF1: TTF1 not known; therapy was local therapy (e.g., hepatic arterial infusion), matched therapy, or transplant. However, they were evaluable for SD $\geq$6 months/PR/CR, TTF, and OS. If the therapy immediately before the on-study matched or unmatched therapy was immunotherapy, that patient was inevaluable for all outcome parameters (SD $\geq$6 months/PR/CR, TTF, OS, TTF2 vs. TTF1) because of the potential for delayed responses.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. The χ^2 test or Fisher exact test, as appropriate, was used to evaluate the associations between categorical variables and SD $\geq$6 months/PR/CR. The Mann–Whitney U-test was applied to compare the number of molecular alterations per person between the matched and unmatched groups.

The main endpoints of the study were SD $\geq$6 months/PR/CR as well as TTF, OS, and TTF2/TTF1. These endpoints were prospectively decided. No multiplicity correction was made or felt to be necessary as these are classic endpoints. Multivariable logistic regression was used to identify predictors of SD $\geq$6 months/PR/CR. Kaplan–Meier estimates were computed for the time-to-event data. Log-rank test was applied for comparing the survival curves between groups. The multivariable Cox proportional hazards regression model was used to examine risk factors related to TTF and OS, after adjusting for other factors (47). Covariates included in the stepwise multivariate analysis were those with P value <0.125 in univariate analysis. Only variables with $P \leq 0.10$ in the multivariate analysis (and matched versus unmatched) were included in the final model. Frailty model applying to the Cox regression was used to compare the TTF1 (TTF in the previous treatment) and TTF2 (TTF in the current treatment) by assuming a random effect on each patient to account for within patient correlations. All statistical tests were two-sided, and $P \leq 0.05$ was considered statistically significant. Statistical analyses were carried out using SPSS (version 22.0; SPSS) and R (version 3.1.2; R Foundation for Statistical Computing).

Results

Patient characteristics

Of the 500 patients enrolled, 188 (37.6%) were treated on either matched [N = 122/500 (24.4%); 68% of 188 treated patients] or unmatched therapy [N = 66/500 (13.2%); 32% of 188 treated patients; Fig. 1]. Ninety-seven percent (182/188) of treated patients were evaluable for SD $\geq$6 months/PR/CR; all 188, for TTF and OS (Fig. 1); and 74% (140/188) for TTF2 versus TTF1 [that is TTF on therapy after enrollment (TTF2) as compared with prior TTF (TTF1)]. Of patients who were not evaluable for treatment, the most common reasons were insufficient tissue, death, or transfer to hospice (Fig. 1).

The median age of treated patients was 59 years (range, 19–82 years). Sixty-six (35%) were men. The median number of molecular alterations per patient was 5 (range, 1–14; Table 1); the median number of prior therapies was four. The most common diagnoses were ovarian cancer (18%), breast cancer (16%), sarcoma (13%), and renal cancer (7%). Many patients [123/188 (65%)] received combination regimens. Overall, if matching was not considered, there was no difference in rates of SD $\geq$6 months/PR/CR between those patients who received combination therapy versus those that received monotherapy (17% vs. 13%; $P = 0.5$). Similarly, there was no difference in TTF or OS in these groups.

Of the 339 patients who had CGP (Supplementary Table S1 for gene list) successfully performed, 317 (93.5%) had $\geq$1 potentially actionable alteration.

Matching

Of the 122 patients on matched therapy, 110 were matched on the basis of one or more alterations in their CGP analysis (Materials and Methods and Supplementary Tables S2 and S3;

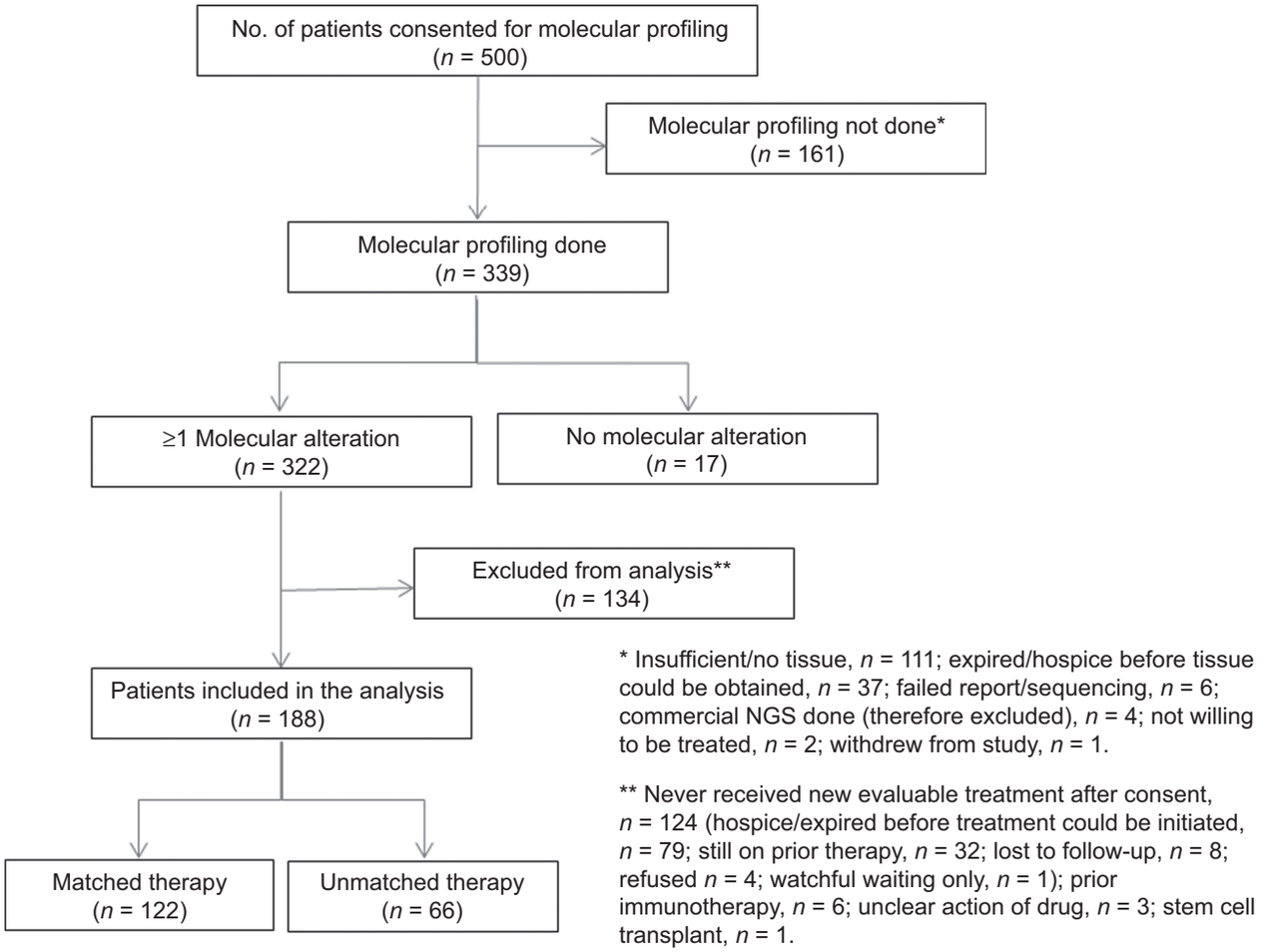

Figure 1.
Consolidated Standards of Reporting Trials (CONSORT) diagram demonstrates the flow of 500 patients who consented for the study.

refs. 10–45) Twelve patients were matched exclusively based on non-CGP biomarkers [ER-positive, $N = 10$; *HER2* amplification, $N = 1$ (*HER2*-amplified by FISH, but not by CGP); and, c-MET positivity by IHC, $N = 1$]. Of the total number of matches that occurred, 34 drugs were directed at a CGP biomarker; six, against a non-CGP biomarker.

Matched versus unmatched patients

Patient characteristics in the matched and unmatched cohorts were generally well balanced as displayed in Table 1. Patients in the unmatched group, however, had a higher incidence of gastrointestinal malignancy and lower serum albumin (both poor prognostic factors) than matched patients. On the other hand, unmatched patients also had a lower incidence of PI3K/Akt/mTOR pathway abnormalities, fewer *TP53* mutations, and fewer molecular alterations than matched patients (all favorable prognostic factors; Tables 1 and 2). Matched versus unmatched patients were balanced for both composite prognostic scores—the RMH score (based on levels of albumin, and LDH, and number of metastatic sites) and the MDACC scoring system (based on RMH with tumor type, and ECOG performance status as additional variables; Table 1; refs. 42, 46, 49).

Direct versus indirect matches

Table 2 shows that patients with direct versus indirect matches (defined in Supplementary Table S2 and Materials and Methods) had numerically better TTF and OS, while SD ≥6 months/PR/CR was numerically higher in the indirectly matched patients (all statistically insignificant).

These results were similar when a second definition of direct versus indirect match was used (direct = impact on product of genomic alteration or one effector removed or aberrantly expressed protein or well-known functional effect such as PARP inhibitors in the presence of *BRCA* mutation; indirect = all other matches).

Univariate analysis (Table 2 and Fig. 2)

Only lower number of prior therapies and high versus low Matching Score (number of molecular matches per patient divided by number of molecular alterations per patient, dichotomized at median; Materials and Methods for complete definition) were significantly associated with higher rates of SD ≥6 months/PR/CR; matched versus unmatched therapy that was dichotomized rather than given a Matching Score showed a trend towards association with higher rates of SD ≥6 months/PR/CR.

Table 1. Patient demographics[a]

Variable	Group	Matched therapy $n = 122$ (%)	Unmatched therapy $n = 66$ (%)	P[b]
Age	≤60 years	67 (55)	36 (55)	1.000
	>60 years	55 (45)	30 (45)	
Sex	Women	80 (66)	42 (64)	0.916
	Men	42 (34)	24 (36)	
Tumor type	Other	106 (87)	48 (73)	**0.027**
	Gastrointestinal	16 (13)	18 (27)	
Metastatic sites	≤2	66 (54)	37 (56)	0.917
	>2	56 (46)	29 (44)	
No. of prior therapies [before TTF2 (therapy on study)]	<3	41 (34)	17 (26)	0.344
	≥3	81 (66)	49 (74)	
ECOG performance status ($n = 170$)	0	24 (21)	10 (19)	0.902
	≥1	92 (79)	44 (81)	
Serum platelets ($n = 183$)	≤440 K/μL	114 (96)	62 (97)	1.000
	>440 K/μL	5 (4)	2 (3)	
Serum LDH ($n = 153$)	≤ 618 U/L	76 (69)	26 (60)	0.408
	>618 U/L	34 (31)	17 (40)	
Serum albumin ($n = 178$)	≥3.5 g/dL	98 (85)	45 (71)	**0.044**
	<3.5 g/dL	17 (15)	18 (29)	
PI3K pathway alteration[c]	No	56 (46)	41 (62)	**0.049**
	Yes	66 (54)	25 (38)	
TP53 alteration	No	46 (38)	36 (55)	**0.039**
	Yes	76 (62)	30 (45)	
RMH score[d] ($N = 153$)	≤1 (low risk)	82 (75)	29 (67)	0.494
	>1 (high risk)	28 (25)	14 (33)	
MDACC score[e] ($N = 150$)	≤2 (low risk)	78 (72)	24 (59)	0.184
	>2 (high risk)	31 (28)	17 (41)	
No. of molecular alterations per person	Median	5	4	**0.006**
	Range	1–14	1–11	
TTF1 (on last prior therapy) ($N = 140$)	Median (range) months	2.6 (0.5 to 19.7)	3.0 (0.4 to 96.0)	0.609

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not available; PS, performance status.

[a]Demographics were at baseline of treatment for TTF2 (protocol treatment is defined in Materials and Methods). Only patients with available data were included.

[b]χ^2 or Fisher exact test as appropriate; Mann–Whitney U test for number of molecular alterations; log-rank test on Kaplan–Meier for TTF and OS. Significant P-values are indicated in bold font.

[c]PI3K pathway alterations include alterations in *PTEN, PIK3CA, PIK3R1, AKT, TSC, NF1, NF2, FBXW7, STK11, CCND1, RPTOR, MTOR*, or *ARID1A* as part of the PI3K/Akt/mTor axis (10, 17, 18, 21–23, 26, 31). RICTOR alterations were not considered sensitizing to PI3K/Akt/mTor inhbitors.

[d]RMH score classified patients according to three variables: LDH normal (0) versus LDH >upper limit of normal (ULN) (+1); albumin ≥3.5 g/dL (0) versus albumin <3.5 g/dL (+1) and number of metastatic sites of disease ≤2 (0) versus metastatic sites of disease ≥3 (+1; refs. 46, 49).

[e]MDACC score included two additional variables to that of RMH score namely, ECOG performance status <1 (0) versus ECOG performance status ≥1 (+1), and, nongastrointestinal tumor type (0) versus gastrointestinal tumor type (+1; ref. 42).

Only fewer metastatic sites, lower number of prior therapies, better ECOG performance status, higher albumin levels, lower LDH levels, lower platelet counts, matched versus unmatched [Fig. 2A; or high versus low Matching Score (Fig. 2C)] and better RMH (or MDACC score) were significantly associated with longer TTF (keeping in mind, that number of metastatic sites, albumin, and LDH are part of both the RMH and MDACC score, and ECOG performance status is in addition a part of the MDACC score); for TTF, the absence of PI3K pathway aberrations showed a trend towards association with better TTF.

Fewer metastatic sites, lower number of prior therapies, better ECOG performance status, higher albumin and lower LDH levels, absence of PI3K pathway aberrations, and better RMH or MDACC scores were also significantly associated with better OS; lower platelet counts, fewer number of molecular alterations, and matched versus unmatched therapy [Fig. 2B; or high vs. low Matching Score for matching (Fig. 2D)] showed a trend towards association with better OS. The pattern was maintained for TTF and OS when a three-tier stratification based on Matching Score was explored, demonstrating the stepwise improvement in outcomes with increasing Matching Score (Fig. 2E and F).

Comparison of TTF after enrollment to prior TTF (TTF2 vs. TTF1)

Patients normally have a shorter TTF with each subsequent line of systemic therapy. Furthermore, TTF with phase I drugs would be expected to be shorter than TTF with conventional prior therapy or non-phase I regimens. Patients in the various categories showed no significant differences in prior TTF (TTF1) between groups [matched versus unmatched; Matching Score high versus low (or direct versus indirect matches; Supplementary Table S4)], indicating that these patients were well balanced in their outcomes after last prior therapy. Table 3 shows that patients that were unmatched or had a low Matching Score had a TTF2 that was significantly shorter than TTF1, as would be expected. In contrast, there was no shortening of TTF2 vs. TTF1 in patients that were matched or had a high Matching Score.

Multivariate analysis of factors independently associated with rate of SD ≥6 months/PR/CR

Table 4 shows that the factors independently and significantly predictive of higher rate of SD ≥6 months/PR/CR were less number of prior therapies and a higher Matching Score. Matched versus unmatched therapy (without scoring) showed a trend that did not reach statistical significance ($P = 0.06$) for association with a higher rate of SD ≥6 months/PR/CR.

Multivariate analysis of factors independently associated with TTF

Table 4 demonstrates that only matched versus unmatched therapy and MDACC score predicted longer TTF (if instead of MDACC score, its components with $P < 0.125$ in univariate analysis were included in the initial multivariate analysis, lower LDH, lower platelets, fewer prior therapies, and matched versus unmatched predicted longer TTF). When the scoring system was used, a higher Matching Score was also independently and significantly associated with longer TTF (median = 3.4 months vs. 1.9 months; $P = 0.0003$; Tables 2 and 4).

Multivariate analysis of factors independently associated with OS

Table 4 shows that only absence of PI3K aberrations and better MDACC score were associated with longer OS; in contrast, when individual factors were analyzed instead of the MDACC score, better performance status, lower LDH, higher albumin, absence of PI3K pathway aberrations, and lower number of molecular alterations were associated with longer OS. Matched versus unmatched therapy was not associated with OS. When the Matching Score was

Table 2. Univariate analysis of factors affecting SD ≥6 months/PR/CR, TTF, and, OS in 188 patients

Variable	Group	Evaluable for SD ≥6 months/PR/CR ($n = 182$)[b,c]	SD ≥6 months/ PR/CR n (%)[b,c]	P[a]	Evaluable for TTF and OS ($n = 188$)	Median TTF (95% CI; months)	P[a]	Median OS (95% CI; months)	P[a]
Age, y	≤60	100	17 (17)	0.645	103	2.1 (1.6–2.6)	0.81	9.9 (6.8–13.0)	0.213
	>60	82	11 (13)		85	2.7 (2.2–3.2)		7.5 (4.5–10.5)	
Sex	Women	119	17 (14)	0.727	122	2.6 (2.0–3.2)	0.901	8.3 (6.1–10.5)	0.183
	Men	63	11 (17)		66	2.7 (1.9–3.5)		7.1 (3.0–11.2)	
Tumor type	Other	150	21 (14)	0.395	154	2.8 (1.1–4.5)	0.702	8.1 (6.3–9.9)	0.284
	Gastrointestinal	32	7 (22)		34	2.6 (2.1–3.1)		5.1 (0.0–11.0)	
Metastatic sites	≤2	98	19 (19)	0.158	103	2.8 (2.0–3.6)	**0.046**	10.2 (7.4–13.0)	**0.011**
	>2	84	9 (11)		85	2.1 (1.6–2.6)		5.1 (3.2–7.0)	
Prior therapies	<3	55	14 (25)	**0.024**	58	3.3 (2.2–4.4)	**0.04**	11.4 (8.9–13.9)	**0.015**
	≥3	127	14 (11)		130	2.1 (1.6–2.6)		6.9 (4.9–8.9)	
ECOG PS[d]	0	34	9 (26)	0.127	34	3.4 (2.8–4.0)	**0.031**	14.8 (10.2–19.5)	**0.001**
	≥1	131	18 (14)		136	2.5 (2.0–3.0)		6.8 (4.7–8.8)	
Platelets[d]	≤440 K/μL	170	27 (16)	1.000	176	2.7 (2.2–3.2)	**0.011**	8.2 (6.5–9.9)	0.082
	>440 K/μL	7	1 (14)		7	1.8 (0.0–4.6)		5.0 (4.0–6.0)	
Serum LDH[d]	≤618 U/L	99	19 (19)	0.407	102	3.3 (2.8–3.8)	**0.001**	11.1 (8.8–13.4)	<**0.001**
	>618 U/L	49	6 (12)		51	1.7 (1.4–2.0)		4.1 (3.2–5.0)	
Serum albumin[d]	≥3.5 g/dL	138	24 (17)	0.334	143	2.8 (2.1–3.5)	**0.023**	9.8 (7.8–11.8	<**0.001**
	<3.5 g/dL	34	3 (9)		35	1.9 (1.2–2.6)		3.4 (2.6–4.2)	
PI3K pathway alteration	No	94	17 (18)	0.402	97	3.2 (2.4–4.0)	0.056	9.6 (6.6–12.6)	**0.004**
	Yes	88	11 (13)		91	1.9 (1.3–2.5)		5.6 (3.5–7.7)	
TP53 alteration	No	79	11 (14)	0.786	82	2.7 (2.1–3.3)	0.737	9.2 (6.4–12.0)	0.132
	Yes	103	17 (17)		106	2.6 (1.8–3.4)		7.6 (5.6–9.6)	
RMH score[d]	≤1 (low risk)	108	19 (18)	0.899	111	3.1 (2.4–3.8)	**0.048**	10.2 (7.9–12.5)	**0.001**
	>1 (high risk)	40	6 (15)		42	1.9 (1.5–2.3)		4.1 (2.7–5.5)	
MDACC score[d]	≤2 (low risk)	99	18 (18)	0.593	102	3.3 (2.7–3.9)	**0.004**	10.3 (8.3–12.3)	<**0.001**
	>2 (high risk)	46	6 (13)		48	1.8 (1.5–2.1)		4.0 (3.0–5.0)	
Molecular alterations (N)[e]	≤5	119	20 (17)	0.607	123	2.8 (2.1–3.5)	0.234	9.2 (6.8–11.6)	0.064
	>5	63	8 (13)		65	2.1 (1.5–2.7)		6.8 (3.8–9.8)	
Treatment group	Matched	118	23 (19)	0.061	122	2.8 (2.1–3.5)	**0.001**	9.3 (7.3–11.3)	0.087
	Unmatched	64	5 (8)		66	1.9 (1.5–2.3)		7.2 (4.9–9.5)	
Matched therapy	Direct	45	6 (13)	0.277	45	3.1 (2.2–4.0)	0.829	11.1 (9.2–13.0)	0.194
	Indirect	73	17 (23)		77	2.8 (1.6–4.0)		7.3 (4.4–10.2)	
Matching score[e,f]	>0.18	92	20 (22)	**0.028**	94	3.4 (2.6–4.2)	**0.0003**	9.3 (7.3–11.3)	0.121
	≤0.18	90	8 (9)		94	1.9 (1.6–2.2)		7.5 (5.0–10.0)	

Abbreviations: CR, complete remission; ECOG, Eastern Cooperative Oncology Group; PR, partial response; PS, performance status.

[a]Significant P values are indicated in bold font.

[b]Three patients in the matched and three in the unmatched group had SD <6 months as of date of data analysis (August 4, 2014) and were still on the study; they were considered inevaluable for this parameter.

[c]N equals total number of patients available for outcome analysis; the numbers of patients available for assessment of each of SD ≥6 months/PR/CR, TTF, or OS may differ slightly.

[d]Numbers of patients with available data for different outcome assessments may differ slightly.

[e]Dichotomized at median.

[f]See Materials and Methods and Supplementary Table S2 for full definition of direct versus indirect matching and Matching Score (for each patient, a match is given a score of 1; no match gets a score of zero. The Matching Score = the number of matches per patient divided by the number of aberrations. The resultant fraction is the Matching Score given).

used, and the MDACC Score included, the Matching Score showed a trend toward association with OS ($P = 0.1$). When the individual factors were analyzed instead of the MDACC Score, a higher Matching Score was independently and significantly associated with OS ($P = 0.05$; Table 4).

Matching Score system for high versus low matching

In multivariate analysis, matched versus unmatched therapy was independently associated with longer TTF, but showed only a trend toward association with higher rates of SD ≥6 months/PR/CR; there was no association with OS. In contrast, when the Matching Score was used, a high Matching Score was independently associated with higher proportion of SD ≥6 months/PR/CR, longer TTF, and OS (Table 4).

Because there was no significant difference in outcomes with direct versus indirect matches (Table 2), the Matching Score system applied one point for either direct or indirect matches. However, other alternative scoring systems were also explored (1 point for direct matches and either 0.5 or 0.75 points for indirect matches). The latter systems produced associations similar to those of matched versus unmatched therapy or to the Matching Score (1 point for direct and 1 point for indirect matches), depending on the outcome parameter examined. Finally, the analysis was run with the patients matched by non-CGP markers removed ($N = 12$, matched by ER or MET IHC or Her2 FISH alone ± four patients matched by CGP as well as a non-CGP marker), and the main significance values were unchanged.

Discussion

We report a prospective investigation of the clinical utility of CGP (Supplementary Table S1) in matching patients with

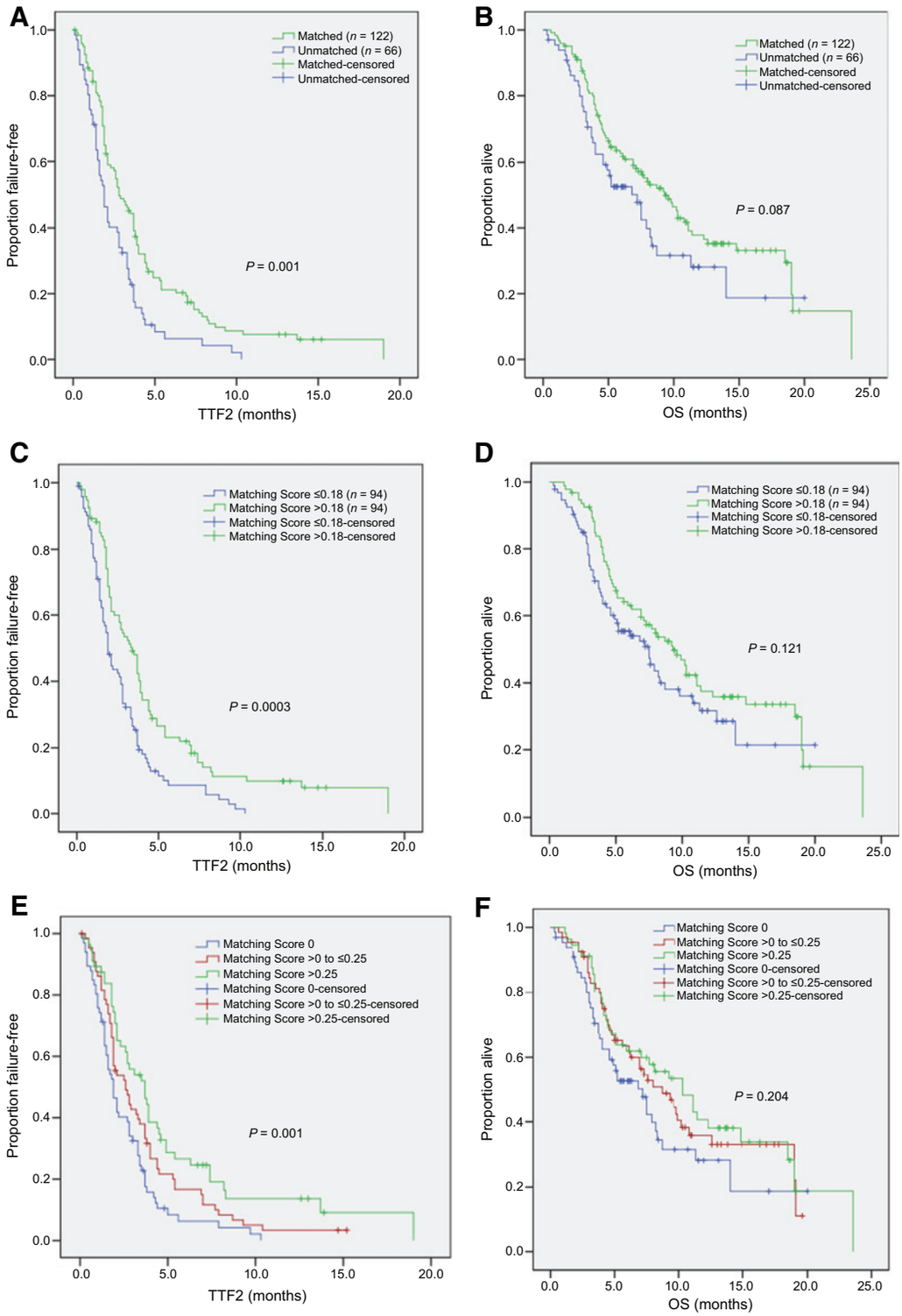

Figure 2.
Kaplan–Meier curves of 188 patients for TTF2 (on treatment) and OS. A, TTF2 (TTF of therapy on study) of patients by type of therapy (matched vs. unmatched). B, OS of patients by type of therapy (matched vs. unmatched). C, TTF2 of patients by scoring system (Matching Score $\leq$0.18 vs. >0.18. D, OS of patients by scoring system (Matching Score $\leq$0.18 vs. >0.18). E, TTF2 of patients by scoring system [Matching Score 0 vs. >0 $\leq$ 0.25 (median of those over 0) vs. >0.25]. F, OS of patients by scoring system (Matching Score 0 vs. >0 $\leq$ 0.25 vs. >0.25). Scoring gave 1 point for direct matches and 1 point for indirect matches. For complete details of scoring, see Materials and Methods and Supplementary Table S2. Data calculated by Kaplan–Meier method (log-rank test).

Table 3. Analysis of TTF2/TTF1[a] ($N = 140$ patients[b])

		Median TTF (months; 95% CI)
Direct match ($n = 31$)	TTF1	2.8 (1.93–3.67)
	TTF2	2.8 (2.15–3.45)
	P	0.75
Indirect match ($n = 50$)		
	TTF1	2.3 (1.90–2.70)
	TTF2	2.8 (1.83–3.77)
	P	0.31
All Matched ($n = 81$)		
	TTF1	2.6 (2.19–3.01)
	TTF2	2.8 (2.29–3.31)
	P	0.64
Unmatched ($n = 59$)		
	TTF1	3.0 (1.82–4.18)
	TTF2	2.1 (1.73–2.47)
	P[c]	**0.047**
Matching Score >0.18 ($n = 58$)[d]		**High match**
(Direct match = 1; indirect match = 1; unmatched = 0)	TTF1	2.3 (1.93–2.67)
	TTF2	3.2 (2.35–4.05)
	P	0.21
Matching Score <0.18 ($n = 82$)		**Low match**
	TTF1	3.0 (1.95–4.05)
	TTF2	2.1 (1.55–2.65)
	P[c]	**0.027**

[a]TTF2/TTF1 = TTF on therapy after enrollment (TTF2) versus TTF on prior therapy (TTF1). See Materials and Methods for full definition of TTF and statistical procedures. (see Supplementary Table S4 for comparison of TTF1 for various groups. There was no significant difference in TTF1 between matched direct versus indirect; matched versus unmatched; or high versus low Matching Score).
[b]140 patients included; excluded $N = 48$ (reasons for exclusion: prior match in TTF1 = 35; no prior therapy that is evaluable = 13).
[c]Significant *P* values are indicated in bold font.
[d]Dichotomized at median.

targeted drugs. The study design was that of a navigational trial, wherein the physician could choose therapy based on the CGP diagnostic, in the context of the patient's comorbidities, mirroring the situation in practice. Five hundred patients were enrolled on the trial; 188 (37.6%) were treated [122/500 (24.4%) on matched, and 66/500 (13.2%) on unmatched therapy; Fig. 1]. All treated patients had advanced cancer (median = four prior therapies in the metastatic setting). Matched and unmatched patients were well balanced for the RMH and MDACC prognostic scores (Table 1; refs. 42, 46, 49). The main reasons for failure to be treated include inadequate tissue for analysis and early death or worsening condition (Fig. 1). These observations indicate that interrogating patients' tumors with CGP, and prosecuting the actionable alterations, is feasible in the refractory setting for a significant subgroup of patients. As a major reason for failure to be treated was death or deterioration due to progressive cancer, increasing the proportion of treated patients will likely require moving CGP assessment to an earlier line of therapy.

Importantly, as multi-gene panels have become available, it is apparent that most patients have numerous alterations (median = five alterations/patient in our study), indicating that customized combination therapy may be necessary (8, 50). For this reason, we developed an exploratory Matching Score that divided the number of matches by the number of molecular anomalies in each participant's malignancy (Materials and Methods). Notably our trial showed an independent and significant association (multivariate analysis) between a high Matching Score and a higher rate of SD $\geq$6 months/PR/CR, as well as better TTF and OS (Table 4). Examining only "matched versus unmatched" as a variable revealed an independent/significant association between matching patients to cognate therapy and TTF, and a trend for higher rates of SD $\geq$6 months/PR/CR, but not OS. Therefore, understanding and optimizing the impact of matching strategies may require taking into account the need for and influence of matched combination treatments (50), as well as the effect of genomic complexity (8, 52).

The current trial is one of the first prospective studies evaluating genomically driven medicine and using an advanced CGP platform ($N = 236$ genes). Several first-generation studies, as well as a randomized trial, have been completed. For example, Von Hoff and colleagues (51) reported 66 patients who were profiled using protein biomarkers; 18 (27%) had a progression-free survival (PFS) ratio of $\geq$1.3 (95% CI, 17%–38%; one-sided, one-sample $P = 0.007$; PFS ratio referring to PFS on biomarker-driven therapy versus prior PFS). Our group previously published the data from the PREDICT/IMPACT (observational, nonrandomized, navigational, non-NGS assay) trial, which showed that of 1,144 patients analyzed, 460 (40.2%) had one or more genomic alterations ($\leq$12 single gene aberrations assessed per patient); in multivariate analysis, matched therapy ($N = 175$ patients treated) was an independent factor predicting response and TTF (compared with the 116 patients treated without matching; ref. 3). In the SHIVA study, patients with heavily pretreated advanced tumors were randomized to physician choice versus an algorithm of matched monotherapy, heavily weighted towards hormone modulators or the mTOR inhibitor everolimus in patients with hormone receptor or PI3K/AKT/mTor signal anomalies, respectively, and outcomes were not improved. (53) Our study differs from one or more of these other trials in several ways, including the participation of patients with diverse cancers, the use of NGS and matched combination drug regimens, taking into consideration the number of alterations per patient, the prospective (albeit nonrandomized) nature of the study, the larger number of patients and higher percentage (24.4%, $N = 122$) who received matched targeted therapy, and the inclusion of results from patients who received either matched or unmatched treatment. The current trial strengthens the findings from the previously published studies above, other than the negative SHIVA study (53), supporting the feasibility of using molecular profiling in the clinic and the improvement in outcomes noted with genomic matching, especially when matched combinations rather than matched monotherapy are used.

Several additional trials that use molecular profiling have been initiated or are planned, including, but not limited to: (i) WINTher (prospective, nonrandomized, navigation trial), an international study to select rational therapeutics based on a CGP platform (NGS, 236 genes; Arm A) and a tumor versus normal transcriptomics comparison (Arm B; NCT01856296); (ii) NCI-MATCH, a prospective, nonrandomized trial in diverse tumors (solid cancers and lymphomas) that will determine if targeted therapies for people whose tumors have specific gene mutations will be effective regardless of their cancer type (NCT02465060); (iii) LUNG-MAP, a prospective, randomized trial for patients with lung cancer (NCT02154490); (iv) IMPACT2, a randomized study in diverse, metastatic malignancies (NCT02152254); and (v) TAPUR, a nonrandomized, prospective trial using commercially available drugs used off-label, sponsored by the American Society of Clinical Oncology.

Table 4. Multivariate analysis of factors affecting SD ≥6 months/PR/CR, TTF, and OS by matched vs. unmatched versus by Matching Score

Factors affecting SD ≥6 months/PR/CR						
	Matching			Matching Score		
Variables[a]	OR[c]	95% CI	*P*[d]	OR[c]	95% CI	*P*[d]
Matched therapy (vs. Unmatched)	2.69	0.96–7.55	0.06			
Prior therapy <3 (vs. ≥3)	2.62	1.14–6.02	**0.024**	2.7	1.17–6.22	**0.02**
Matching Score >0.18 (vs. ≤0.18)[b]				2.79	1.14–6.80	**0.024**

Factors affecting TTF analyzed by (1) Matched vs. Unmatched: individual factors of MDACC score vs. MDACC score						
	Matching: Individual factors			Matching: MDACC Score		
Variables[a]	HR[c]	95% CI	*P*[d]	HR[c]	95% CI	*P*[d]
Unmatched therapy (vs. Matched)	1.6	1.1–2.3	**0.017**	1.6	1.1–2.3	**0.022**
LDH >618 IU/L (vs. ≤618 IU/L)	1.8	1.3–2.6	**0.002**			
Prior therapy ≥3 (vs. <3)	1.7	1.1–2.4	**0.007**			
Platelet >440 K/μL (vs. ≤440 K/μL)	2.5	1.1–5.4	**0.023**	2.2	1.0–4.8	0.054
MDACC score >2 (vs. ≤2)				1.6	1.1–2.3	**0.02**

(2) Matching Score: individual factors of MDACC score vs. MDACC score						
	Matching Score: Individual factors			Matching Score: MDACC Score		
Variables[a]	HR[c]	95% CI	*P*[d]	HR[c]	95% CI	*P*[d]
Matching Score ≤0.18 (vs. >0.18)[b]	1.9	1.35–2.77	**0.0003**	1.8	1.3–2.6	**0.001**
LDH >618 IU/L (vs. ≤618 IU/L)	1.8	1.27–2.66	**0.001**			
PI3K pathway alteration, yes (vs. no)	1.4	1.0–2.03	0.052	1.5	1.1–2.2	**0.023**
Platelet >440 K/μL (vs. ≤440 K/μL)	2.1	0.93–4.56	0.077	2.1	0.9–4.6	**0.076**
MDACC score >2 (vs. ≤2)				1.6	1.1–2.4	**0.012**

Factors affecting OS analyzed by (1) Matched vs. Unmatched: individual factors of MDACC score vs. MDACC score						
	Matching: individual factors			Matching: MDACC Score		
Variables[a]	HR[c]	95% CI	*P*[d]	HR[c]	95% CI	*P*[d]
Unmatched therapy (vs. Matched)	1.29	0.81–2.07	0.285	1.32	0.83–2.10	0.25
ECOG PS ≥1 (vs. <1)	1.88	1.02–3.48	**0.045**			
LDH >618 IU/L (vs. ≤618 IU/L)	2.1	1.31–3.35	**0.002**			
Albumin <3.5 g/dL (vs. ≥3.5 g/dL)	2.02	1.16–3.51	**0.013**			
PI3K pathway alteration, yes (vs. no)	1.56	1.01–2.40	**0.044**	1.85	1.21–2.82	**0.004**
MDACC score >2 (vs. ≤2)				2.35	1.54–3.59	**0.00007**
No. of molecular alterations	1.67	1.06–2.64	**0.027**			

(2) Matching Score: individual factors of MDACC score vs. MDACC score						
	Matching Score: Individual factors			Matching Score: MDACC Score		
Variables[a]	HR[c]	95% CI	*P*[d]	HR[c]	95% CI	*P*[d]
Matching Score ≤0.18 (vs. >0.18)[b]	1.53	1.00–2.35	**0.05**	1.43	0.93–2.19	0.1
LDH >618 IU/L (vs. ≤618 IU/L)	2.62	1.70–4.02	**0.00001**			
PI3K pathway alteration, yes (vs. no)	1.76	1.15–2.68	**0.009**	1.91	1.25–2.92	**0.003**
MDACC score >2 (vs. ≤2)				2.41	1.58–3.67	**0.00005**

Abbreviations: CR, complete remission; ECOG, Eastern Cooperative Oncology Group.

[a]Multivariate included variables with $P < 0.125$ in univariate analysis (Table 2). The variables with $P > 0.10$ in the multivariate analysis were then dropped and the multivariate analysis repeated.

[b]Matching Score dichotomized at median.

[c]OR >1, increases odds for SD ≥6 months/PR/CR; HR >1, shorter TTF or OS.

[d]Significant *P* are indicated in bold font.

There were several limitations to this study. Phase I drugs were in the treatment regimens, some of which may not have engaged the target well or had poor pharmacokinetics, and patients at all dose levels were included in our analysis. Limitations such as these might attenuate salutary impact on outcome parameters, even with matching. On the other hand, this was not a randomized study, and there might be unknown biases, unaccounted for despite the multivariate analysis, that positively influence outcome. Some patients were administered part or all their treatment by physicians at home, who designated response, without a centralized review. However, there is a paucity of evidence for the contention that centralized review enhances validity. Another limitation was that this was a navigation trial, and physicians could choose the therapy for their patients. The choices were not locked down and preassigned. Therefore, this approach limited our ability to determine the benefit of matching individual mutations, as more than one drug could be chosen for any one aberration, depending on physician preference, patient health, and agent availability. Even so, the evaluation of the overall strategy of molecular matching was feasible. Furthermore, this design mimicked what would happen in practice, by authorizing physicians to choose the optimal therapy for their patient based on important factors such as comorbidities and patient inclination, rather than just CGP alone. It also permitted taking into account the dynamic nature of the field with rapid new discoveries. Study analysis was also constrained by the number of patients that could not be given therapy on study (most frequently because their condition declined). This was perhaps not unexpected, considering that a refractory population is generally referred to a phase I clinic. Finally, the precise biologic impact of some mutations such as those in the PI3K or MET pathway is still a matter of debate and, in addition, it is possible that NGS

based on archival tissue may not fully reflect the patient's disease after chemotherapy or radiation, all of which may have attenuated benefit rates and merits being addressed in future trials (54).

In conclusion, the current prospective study demonstrated that deploying CGP to assign therapy is feasible for a subset of patients with heavily pretreated, metastatic cancer. Early drop out was mainly due to deterioration or demise from cancer. With the availability of expanded multi-gene NGS tests and an increasing number of targeted drugs in the clinic, it has been reported that a majority of patients (~90%) will harbor genomic alterations that are pharmacologically tractable, often by FDA-approved drugs, albeit off label (55), a result consistent with our current observation that 93.5% of patients who underwent CGP had at least one potentially actionable aberration. Increasing the proportion of patients treated will require moving CGP testing earlier in the disease and addressing the issues of medication access. Importantly, the median number of molecular alterations in our patients was five, and many of our patients received combination therapies. We therefore developed an exploratory Matching Score that divided the number of matched drugs per patient by the number of molecular alterations in their tumor. Notably, in multivariate analysis, a high versus low Matching Score was significantly and independently associated with higher rates of SD $\geq$6 months/PR/CR and longer TTF and OS (Table 4). Patients who were unmatched or had a low Matching Score had a TTF on protocol that was significantly shorter than their last prior TTF (Table 3), as would be expected with progressive lines of therapy and administration of agents in the phase I setting; however, there was no shortening of TTF on trial versus last prior TTF in patients that were matched or had a high Matching Score. Utility of this Matching Score will require further prospective investigations. Taken together, these observations indicate that CGP can provide information that is useful in the selection of treatment for patients with cancer, and that tailored combinations of cognate therapies may be needed to optimize benefit.

Disclosure of Potential Conflicts of Interest

F. Janku reports receiving a commercial research grant from Foundation Medicine, Trovagene, and Biocartis and is a consultant/advisory board member for Trovagene and Foundation Medicine. Y. Li is an associate director, biostatistics, at and has ownership interest (including patents) in Foundation Medicine. A.M. Tsimberidou reports receiving a commercial research grant from Foundation Medicine. V.A. Miller is a chief medical officer at and has ownership interest (including patents) in Foundation Medicine. R. Yelensky is a vice president, biomarkers, at and has ownership interest (including patents) in Foundation Medicine. R. Kurzrock has research funding from Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, and Guardant, as well as consultant/advisory board fees from Sequenom, Actuate Therapeutics, and Xbiotech, and an ownership interest in Novena, Inc. and Curematch, Inc. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: J.J. Wheler, A. Naing, S. Fu, A.M. Tsimberidou, R. Yelensky, J.J. Lee

Development of methodology: J.J. Wheler, A. Naing, V.A. Miller, R. Yelensky, J.J. Lee

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.J. Wheler, F. Janku, A. Naing, Y. Li, V. Subbiah, D.D. Karp, G.S. Falchook, A.M. Tsimberidou, S.A. Piha-Paul, R. Anderson, D. Ke, D. Hong

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.J. Wheler, A. Naing, B. Stephen, V. Subbiah, S. Fu, R. Yelensky, J.J. Lee, D. Hong, R. Kurzrock

Writing, review, and/or revision of the manuscript: J.J. Wheler, F. Janku, A. Naing, B. Stephen, R.G. Zinner, V. Subbiah, S. Fu, D.D. Karp, G.S. Falchook, A.M. Tsimberidou, S.A. Piha-Paul, V.A. Miller, J.J. Lee, R. Kurzrock

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.J. Wheler, V. Subbiah, R. Anderson, V.A. Miller

Study supervision: J.J. Wheler, R. Kurzrock

Other (coordination with outside medical facilities): J.J. Wheler

Acknowledgments

The authors thank the patients and their families. The authors thank Hemwattie Ramnauth, Nilza Marie Biaggie Labiosa, and Thomas Vu in the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center for their role in patient enrollment, regulatory work, and data collection.

Grant Support

This work was supported in part by a research grant from Foundation Medicine.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received November 4, 2015; revised February 16, 2016; accepted April 7, 2016; published OnlineFirst May 18, 2016.

References

1. Horstmann E, McCabe MS, Grochow L, Yamamoto S, Rubinstein L, Budd T, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med 2005;352:895–904.
2. Kurzrock R, Benjamin RS. Risks and benefits of phase 1 oncology trials, revisited. N Engl J Med 2005;352:930–2.
3. Tsimberidou AM, Iskander NG, Hong DS, Wheler JJ, Falchook GS, Fu S, et al. Personalized medicine in a phase I clinical trials program: the MD Anderson Cancer Center initiative. Clin Cancer Res 2012;18:6373–83.
4. Khozin S, Blumenthal GM, Zhang L, Tang S, Brower M, Fox E, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res 2015;21:2436–9.
5. Falchook GS, Millward M, Hong D, Naing A, Piha-Paul S, Waguespack SG, et al. BRAF inhibitor dabrafenib in patients with metastatic *BRAF*-mutant thyroid cancer. Thyroid 2015;25:71–7.
6. Henary H, Hong DS, Falchook GS, Tsimberidou A, George GC, Wen S, et al. Melanoma patients in a phase I clinic: molecular aberrations, targeted therapy and outcomes. Ann Oncol 2013;24:2158–65.
7. Chabner BA. Approval after phase I: ceritinib runs the three-minute mile. Oncologist 2014;19:577–8.
8. Wheler J, Lee JJ, Kurzrock R. Unique molecular landscapes in cancer: implications for individualized, curated drug combinations. Cancer Res 2014;74:7181–4.
9. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–55.
10. Aguirre D, Boya P, Bellet D, Faivre S, Troalen F, Benard J, et al. Bcl-2 and CCND1/CDK4 expression levels predict the cellular effects of mTOR inhibitors in human ovarian carcinoma. Apoptosis 2004;9:797–805.
11. Atipairin A, Canyuk B, Ratanaphan A. The RING heterodimer BRCA1-BARD1 is a ubiquitin ligase inactivated by the platinum-based anticancer drugs. Breast Cancer Res Treat 2011;126:203–9.
12. Awada A, Dirix L, Sanchez LM, Xu B, Luu T, Dieras V, et al. Safety and efficacy of neratinib (HKI-272) plus vinorelbine in the treatment of patients with *ErbB2*-positive metastatic breast cancer pretreated with anti-HER2 therapy. Ann Oncol 2013;24:109–16.

13. Byrski T, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, et al. Pathologic complete response rates in young women with *BRCA1*-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol 2010;28:375–9.
14. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with *BRAF* V600E mutation. N Engl J Med 2011;364:2507–16.
15. Demetri GD, von Mehren M, Blanke CD, Van den Abbeele AD, Eisenberg B, Roberts PJ, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472–80.
16. Harris PA, Boloor A, Cheung M, Kumar R, Crosby RM, Davis-Ward RG, et al. Discovery of 5-[[4-[(2,3-dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methyl-b enzenesulfonamide (Pazopanib), a novel and potent vascular endothelial growth factor receptor inhibitor. J Med Chem 2008;51:4632–40.
17. Janku F, Hong DS, Fu S, Piha-Paul SA, Naing A, Falchook GS, et al. Assessing *PIK3CA* and *PTEN* in early-phase trials with PI3K/AKT/mTOR inhibitors. Cell Rep 2014;6:377–87.
18. Janku F, Tsimberidou AM, Garrido-Laguna I, Wang X, Luthra R, Hong DS, et al. *PIK3CA* mutations in patients with advanced cancers treated with PI3K/AKT/mTOR axis inhibitors. Mol Cancer Ther 2011;10:558–65.
19. Kelly K, Mazieres J, Leighl N, Barlesi F, Zalcman G, Gordon M, et al. Oral MEK1/MEK2 inhibitor trametinib (GSK1120212) in combination with pemetrexed for *KRAS*-mutant and wild-type (WT) advanced non-small cell lung cancer (NSCLC): a phase I/Ib trial. J Clin Oncol 31, 2013(suppl; abstr 8027).
20. Kumar R, Knick VB, Rudolph SK, Johnson JH, Crosby RM, Crouthamel MC, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. Mol Cancer Ther 2007; 6:2012–21.
21. Lai LP, Lilley BN, Sanes JR, McMahon AP. Lkb1/Stk11 regulation of mTOR signaling controls the transition of chondrocyte fates and suppresses skeletal tumor formation. Proc Natl Acad Sci U S A 2013;110:19450–5.
22. Mao JH, Kim IJ, Wu D, Climent J, Kang HC, DelRosario R, et al. *FBXW7* targets mTOR for degradation and cooperates with PTEN in tumor suppression. Science 2008;321:1499–502.
23. Martini M, De Santis MC, Braccini L, Gulluni F, Hirsch E. PI3K/AKT signaling pathway and cancer: an updated review. Ann Med 2014;46: 372–83.
24. Natsume H, Shinmura K, Tao H, Igarashi H, Suzuki M, Nagura K, et al. The *CRKL* gene encoding an adaptor protein is amplified, overexpressed, and a possible therapeutic target in gastric cancer. J Transl Med 2012;10:97.
25. Nissan MH, Pratilas CA, Jones AM, Ramirez R, Won HL, Liu CL, et al. Loss of *NF1* in cutaneous melanoma is associated with *RAS* activation and MEK dependence. Cancer Res 2014;74:2340–50.
26. Piha-Paul SA, Hong DS, Kurzrock R. Response of lymphangioleiomyomatosis to a mammalian target of rapamycin inhibitor (temsirolimus) -based treatment. J Clin Oncol 2011;29:e333–5.
27. Rini BI, Jaeger E, Weinberg V, Sein N, Chew K, Fong K, et al. Clinical response to therapy targeted at vascular endothelial growth factor in metastatic renal cell carcinoma: impact of patient characteristics and Von Hippel-Lindau gene status. BJU Int 2006;98:756–62.
28. Romer MU, Jensen NF, Nielsen SL, Muller S, Nielsen KV, Nielsen HJ, et al. *TOP1* gene copy numbers in colorectal cancer samples and cell lines and their association to in vitro drug sensitivity. Scand J Gastroenterol 2012;47: 68–79.
29. Said R, Hong DS, Warneke CL, Lee JJ, Wheler JJ, Janku F, et al. *P53* mutations in advanced cancers: clinical characteristics, outcomes, and correlation between progression-free survival and bevacizumab-containing therapy. Oncotarget 2013;4:705–14.
30. Sak MM, Szymanska M, Bertelsen V, Hasmann M, Madshus IH, Stang E. Pertuzumab counteracts the inhibitory effect of *ErbB2* on degradation of *ErbB3*. Carcinogenesis 2013;34:2031–8.
31. Samartzis EP, Gutsche K, Dedes KJ, Fink D, Stucki M, Imesch P. Loss of ARID1A expression sensitizes cancer cells to PI3K- and AKT-inhibition. Oncotarget 2014;5:5295–303.
32. Schittenhelm MM, Shiraga S, Schroeder A, Corbin AS, Griffith D, Lee FY, et al. Dasatinib (BMS-354825), a dual SRC/ABL kinase inhibitor, inhibits the kinase activity of wild-type, juxtamembrane, and activation loop mutant *KIT* isoforms associated with human malignancies. Cancer Res 2006;66:473–81.
33. Schwaederle M, Lazar V, Validire P, Hansson J, Lacroix L, Soria JC, et al. VEGF-A expression correlates with *TP53* mutations in non-small cell lung cancer: implications for antiangiogenesis therapy. Cancer Res 2015;75: 1187–90.
34. Sheppard KE, McArthur GA. The cell-cycle regulator CDK4: an emerging therapeutic target in melanoma. Clin Cancer Res 2013;19: 5320–28.
35. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med 2003;348:2431–42.
36. Sonpavde G, Willey CD, Sudarshan S. Fibroblast growth factor receptors as therapeutic targets in clear-cell renal cell carcinoma. Expert Opin Investig Drugs 2014;23:305–15.
37. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235–44.
38. Vandyke K, Fitter S, Zannettino AC. The tyrosine kinase inhibitor dasatinib (SPRYCEL) inhibits chondrocyte activity and proliferation. Blood Cancer J 2011;1:e2.
39. Verstovsek S, Kantarjian HM, Estrov Z, Cortes JE, Thomas DA, Kadia T, et al. Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: survival advantage in comparison to matched historical controls. Blood 2012;120: 1202–9.
40. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719–26.
41. Ward JE, Stadler WM. Pazopanib in renal cell carcinoma. Clin Cancer Res 2010;16:5923–7.
42. Wheler J, Tsimberidou AM, Hong D, Naing A, Falchook G, Piha-Paul S, et al. Survival of 1,181 patients in a phase I clinic: the MD Anderson Clinical Center for targeted therapy experience. Clin Cancer Res 2012; 18:2922–9.
43. Wheler JJ, Tsimberidou AM, Falchook GS, Zinner RG, Hong DS, Fok JY, et al. Combining erlotinib and cetuximab is associated with activity in patients with non small cell lung cancer (including squamous cell carcinomas) and wild-type *EGFR* or resistant mutations. Mol Cancer Ther 2013;12:2167–75.
44. Williams JA, Guicherit CM, Zaharian B, Xu Y, Chai L, Wichterle H, et al. Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions (vol 100, pg 4616, 2003). Proc Natl Acad Sci U S A 2003;100:8607–07.
45. Zhou CC, Wu YL, Chen GY, Feng JF, Liu XQ, Wang CL, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735–42.
46. Arkenau HT, Barriuso J, Olmos D, Ang JE, de Bono J, Judson I, et al. Prospective validation of a prognostic score to improve patient selection for oncology phase I trials. J Clin Oncol 2009;27:2692–96.
47. Cox DR. Regression models and life-tables. J Roy Stat Soc Series B Stat Methodol 1972;34:187–220.
48. Frampton GM, Fichtenholtz A, Otto GA, Wang K, Downing SR, He J, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31: 1023–31.
49. Garrido-Laguna I, Janku F, Vaklavas C, Falchook GS, Fu SQ, Hong DS, et al. Validation of the royal marsden hospital prognostic score in patients treated in the phase I clinical trials program at the MD Anderson Cancer Center. Cancer 2012;118:1422–28.
50. Lazar V, Rubin E, Depil S, Pawitan Y, Martini JF, Gomez-Navarro J, et al. A simplified interventional mapping system (SIMS) for the selection of combinations of targeted treatments in non-small cell lung cancer. Oncotarget 2015;6:14139–52.
51. Von Hoff DD, Stephenson JJ, Rosen P, Loesch DM, Borad MJ, Anthony S, et al. Pilot study using molecular profiling of patients' tumors to find potential targets and select treatments for their refractory cancers. J Clin Oncol 2010;28:4877–82.

52. Wheler JJ, Parker BA, Lee JJ, Atkins JT, Janku F, Tsimberidou AM, et al. Unique molecular signatures as a hallmark of patients with metastatic breast cancer: Implications for current treatment paradigms. Oncotarget 2014;5:2349–54.
53. Le Tourneau C, Delord JP, Goncalves A, Gavoille C, Dubot C, Isambert N, et al. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. Lancet Oncol 2015;16:1324–34.
54. Myers AP, Cantley LC. Targeting a common collaborator in cancer development. Sci Transl Med 2010:2:48ps45.
55. Schwaederle M, Daniels GA, Piccioni DE, Fanta PT, Schwab RB, Shimabukuro KA, et al. On the road to precision cancer medicine: analysis of genomic biomarker actionability in 439 patients. Mol Cancer Ther 2015;14:1488–94.