Personalized Medicine and Imaging

Clinical Cancer Research

Personalized Medicine for Patients with Advanced Cancer in the Phase I Program at MD Anderson: Validation and Landmark Analyses

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Abstract

Purpose: The purpose of this study was to confirm our previous results that targeted agents matched with tumor molecular alterations were associated with improved outcomes compared with nonmatched therapy in patients with advanced cancer.

Experimental Design: Outcomes of patients who were referred for treatment on phase I clinical trials at The University of Texas MD Anderson Cancer Center (Houston, TX) from March 2011 to January 2012 were compared between those who had received targeted therapy and those for whom no targeted therapy was available. Two-month landmark analyses for overall and progression-free survival (PFS) combining previously published and validation cohort patient data were performed.

Results: In patients with one alteration, matched therapy ($n = 143$) compared with treatment without matching ($n = 236$) was associated with a higher objective response rate (12% vs. 5%; $P < 0.0001$), longer PFS (median, 3.9 vs. 2.2 months; $P = 0.001$), and longer survival (median, 11.4 vs. 8.6 months; $P = 0.04$). In multivariate analysis, matched therapy was an independent factor predicting response ($P < 0.015$) and PFS ($P < 0.004$). Two-month landmark analyses in the matched therapy group demonstrated that the median survival of responders was 30.5 months compared with 11.3 months for nonresponders ($P = 0.01$); and the median PFS was 38.7 months compared with 5.9 months, respectively ($P < 0.0001$). The respective values in the nonmatched therapy group were 9.8 and 9.4 months ($P = 0.46$) and 8.5 and 4.2 months ($P = 0.18$).

Conclusion: This validation analysis confirms our previous observations. In the matched therapy group, 2-month landmark analyses demonstrated that responders have longer survival and PFS than nonresponders. *Clin Cancer Res; 20(18); 4827–36. ©2014 AACR.*

Introduction

The sequencing of human DNA for the human genome project has led to the emergence of technologies that identify genomic, transcriptional, proteomic, and epigenetic alterations in patients' tumors. In 2002, the U.S. Food and Drug Administration (FDA) approved the use of the tyrosine kinase inhibitor imatinib for treatment of newly diagnosed Philadelphia chromosome–positive chronic myeloid leukemia (1). In 2007, the preliminary results of the BATTLE program, Biomarker integrated Approaches of Targeted Therapy for Lung cancer Elimination, were encouraging (2). Also in 2007, we initiated a personalized medicine program, IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy), for patients with advanced cancer who were referred to the Phase I Program at The University of Texas MD Anderson Cancer Center (Houston, TX) for experimental treatment. The aim of this project was to use specific targeted therapies to treat patients with targetable tumor molecular alterations on phase I clinical trials.

We have previously shown that targeted agents matched with tumor molecular alterations are associated with improved treatment outcomes in patients with 1 molecular alteration (3). Of 1,144 patients who were treated within a 4-year period in our Phase I Clinical Trials Program, 40.2%

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Translational Relevance

We assessed outcomes of patients who were referred for treatment in the Phase I Clinical Trials Program and were treated with targeted therapy or nonmatched therapy from March 2011 to January 2012 (validation cohort). We also compared these outcomes with those we previously published. Two-month landmark analyses for overall and progression-free survival (PFS) combining previously published and validation cohort patient data were performed.

In the validation cohort in patients with one alteration, matched therapy compared with treatment without matching was associated with higher rates of objective response, PFS, and OS. Two-month landmark analyses in the matched therapy group demonstrated that the median survival and PFS durations were significantly longer in responders compared with nonresponders. In conclusion, this validation analysis confirms our previous observations. Prospective randomized clinical trials to assess whether molecular profiling and targeted therapy are associated with superior outcomes compared with treatment not selected on the basis of molecular targeting were initiated.

had ≥ 1 alteration. In patients with 1 molecular alteration, matched therapy ($n = 175$) compared with treatment without matching ($n = 116$) was associated with a higher overall response rate (27% vs. 5%; $P < 0.0001$), longer time to treatment failure (TTF; median, 5.2 vs. 2.2 months; $P < 0.0001$), and longer survival (median, 13.4 vs. 9.0 months; $P = 0.017$). Matched targeted therapy was also associated with longer TTF compared with their prior systemic therapy in patients with 1 mutation (5.2 vs. 3.1 months, respectively; $P < 0.0001$). In multivariate analysis in patients with 1 molecular alteration, matched therapy was an independent factor predicting response ($P = 0.001$) and TTF ($P = 0.0001$).

To validate our previous results, we analyzed additional patients who were treated in our clinic with the same therapeutic approach from March 2011 to January 2012. To assess the correlation of survival or progression-free survival (PFS) with response by type of therapy (matched therapy vs. nonmatched therapy), we performed 2-month landmark analyses. To increase the statistical power of these analyses, the patient populations analyzed consisted of patients from the current validation analysis and our previously published series.

Patients and Methods

Validation analysis

Patients. Consecutive patients who were referred to our program from March 2011 to January 2012 and who underwent molecular analysis were included in the validation analysis. Briefly, patients with advanced or metastatic cancer who had exhausted the standard of care therapy or had no FDA-approved therapy for the indication were referred to our department for participation in phase I clinical trials. Patients met the eligibility criteria for participation in specific phase I clinical trials and had measurable disease. All patients provided written informed consent, stating that they were aware of the experimental nature of the study. All clinical trials and clinical analyses were conducted with the approval of and in accordance with the guidelines of the MD Anderson Cancer Center Institutional Review Board.

Analysis of molecular alterations. Molecular profiling was performed in the Clinical Laboratory Improvement Amendments (CLIA)-certified Molecular Diagnostics Laboratory at MD Anderson as previously described (3).

Treatment. Therapy was considered "matched" if a drug in the clinical trial was known to inhibit the functional activity of at least one of the patient's tumor aberrations. Other therapies were considered "unmatched." Treatment was assigned as previously described (3). Briefly, patients with targetable alterations were preferably treated on clinical trials. The clinical trials varied over time according to protocol availability, eligibility criteria, histologic diagnosis, the patient's prior response to therapy, potential toxicity, insurance coverage, and patient's preference or physician's choice (3).

Endpoints and statistical analysis. All statistical analyses were performed by S. Wen and D. Berry (biostatisticians) using SAS 9.1 (SAS Institute) and S-Plus, version 7.0 (Insightful Corp.) software. Tumor response was assessed by CT "imaging" every two cycles using the Response Evaluation Criteria in Solid Tumors (RECIST; refs. 4, 5). The clinical outcomes of patients with molecular alterations treated with matched therapy were compared with those of consecutive patients seen during the same time period who were not treated with matched therapy. Overall survival (OS) was measured from initiation of participation in the trial until death or last follow-up. PFS was measured from the first day of treatment on a clinical trial until date of disease progression or death, whichever came first. The decision to discontinue treatment on protocol was made by the treating physician and based on the patient's history, clinical presentation, and imaging studies (response assessment using RECIST criteria).

Patients' characteristics were analyzed using descriptive statistics. Survival and hazard functions were estimated using the Kaplan–Meier method, and survival between groups was compared using the two-sided log-rank test. A time-to-event analysis was performed to compare PFS after phase I studies with PFS after the patients' prior systemic therapy (6). The multivariate Cox proportional hazards regression model was used to adjust for other risk factors related to OS and PFS in addressing the role of matched therapy. A backward variable selection procedure was performed to identify the optimal set of independent variables based on the likelihood score statistics. The following factors were included in multivariate analysis: age, sex, number of prior therapies, performance status, number of metastatic sites, platelet count, levels of lactate

dehydrogenase and albumin, type of therapy (matched vs. nonmatched therapy), and inclusion of cytotoxic therapy in the regimen. All *P* values presented are two sided and statistical significance means $P \leq 0.05$.

Landmark analyses

Two-month landmark analyses for survival and PFS were performed for patients in the validation analysis and our previously published series. The landmark method was used to avoid selection bias in the correlation of survival or PFS with response by type of therapy (matched therapy vs. nonmatched therapy; refs. 7, 8). By this method of evaluating outcome, patients who die early do not prejudicially influence the analysis of a postdiagnosis endpoint (7, 8). To increase the statistical power, these analyses included 379 newly enrolled patients from the validation patient group (matched therapy, $n = 143$; nonmatched therapy, $n = 236$) and 291 patients from our previously published patient series (matched therapy, $n = 175$; nonmatched therapy, $n = 116$). The median follow-up of the latter 291 patients was increased by 13 months over that in our previous analyses, to 28 months.

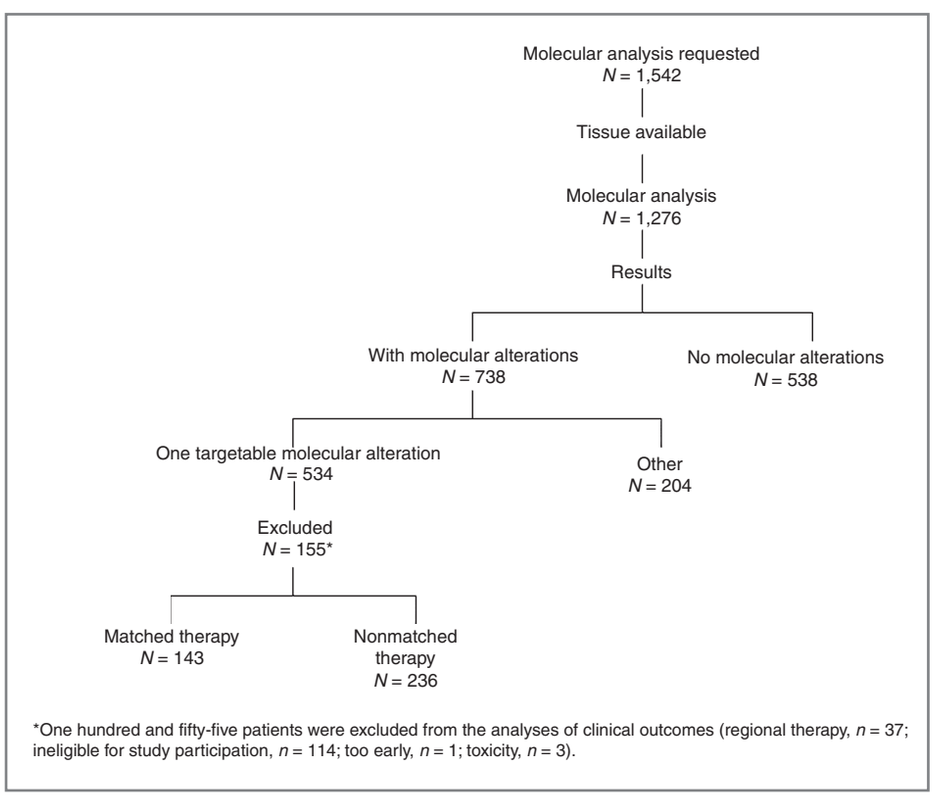
Results

Validation analysis

In the validation patient set, tumor molecular profiling was ordered in 1,542 consecutive patients, and tissue was available for analysis in 1,276 (82.7%) patients (Fig. 1); the remaining patients had inadequate tumor tissue for analysis. Of the 1,276 patients, 738 (57.8%) had $\geq$1 alteration. In the majority of patients, the limited tumor available did not allow testing for all alterations. Of the 738 patients with $\geq$1 alteration, 534 (72.9%) had 1 targetable alteration, and the remaining patients had a nontargetable alteration or $\geq$2 alterations.

The proportions of patients with specific tumor alterations and with alterations by tumor type are shown in Fig. 2A and B. The distribution of the most common alterations was as follows: estrogen receptor (ER) overexpression, 44.8%; progesterone receptor overexpression, 38.0%; *TP53* mutation, 35.6%; *KRAS* mutation, 22.1%; *PTEN* loss or mutation, 14.6%; *PIK3CA* mutation, 9.4%; *HER2* alteration, 8.6%; *BRAF* mutation, 8.1%; *EGFR* alteration, 7.1%; *NRAS* mutation, 6.7%; *MET* alteration, 5.9%; and *CKIT* mutation, 4.5% (Fig. 2A). The distribution of molecular alterations by tumor type is shown in Supplementary Tables S1 and S2. The cancers in which alterations were most commonly found were: endometrial cancer, 71.9%; ovarian cancer, 67.2%; colorectal cancer, 62.7%; breast cancer, 60.8%; melanoma, 55.2%; other gynecological malignancies, 53.4%; lung cancer, 48.3%; pancreatic cancer, 40.5%; head and neck cancer, 39.6%; and thyroid cancer, 36.4% (Fig. 2B).

Patients with one molecular alteration. Of the 534 patients with 1 targetable alteration, 143 patients were treated with matched therapy (42 clinical trials) and 236 patients were treated on clinical trials with nonmatched therapy (68 clinical trials). The types of agents used in



*One hundred and fifty-five patients were excluded from the analyses of clinical outcomes (regional therapy, *n* = 37; ineligible for study participation, *n* = 114; too early, *n* = 1; toxicity, *n* = 3).

Figure 1. Consort diagram.

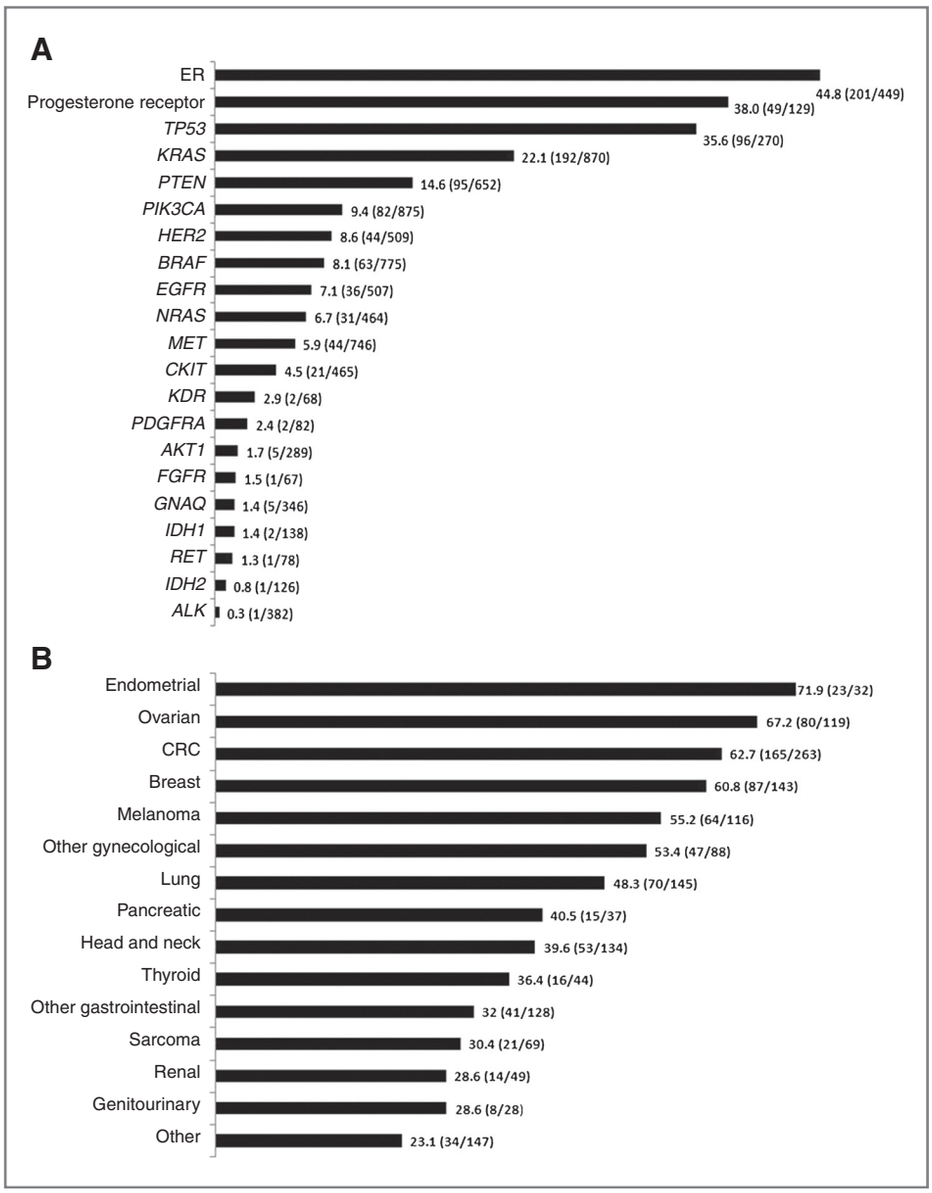


Figure 2. A, proportions of specific molecular alterations ($N = 1,276$). Bars, proportions of patients whose tumors had a molecular alteration (number of patients with alteration/number of patients tested). B, molecular alterations by tumor type ($N = 1,276$). Bars, percentages of patients whose tumors had genetic alterations by type of cancer (number of patients with molecular alterations/number of patients analyzed for the specific alteration). (*Continued on the following page*.)

patients treated with matched or nonmatched therapy are listed in Supplementary Table S3. Overall, 155 patients were excluded from the analyses of clinical outcomes (regional therapy, $n = 37$; ineligible for study participation, $n = 114$; too early, $n = 1$; toxicity, $n = 3$). Twenty (13.9%) of 143 patients in the matched therapy group versus 87 (36.9%) of 236 patients treated with nonmatched therapy had also received a cytotoxic agent in their regimens.

Although this was not a randomized trial, the pretreatment characteristics between the matched and nonmatched therapy groups were similar, with the exception of Eastern Cooperative Oncology Group (ECOG) performance status, which was more favorable in the matched therapy group (Table 1). Tumor types by therapy are listed in Supplementary Table S4.

Response. Of 143 patients treated with matched therapy, 134 were evaluable for response and the objective response (complete + partial response) rate was 12.0% [complete response (CR), 2.2%; partial response (PR), 9.7%). Of 236 patients treated with nonmatched therapy, 219 were evaluable for response and the objective response rate was 5.0% (all PRs; $P < 0.0001$). Disease stabilization for $\geq$6 months was noted in 16.4% and 12.3% of patients treated with matched and nonmatched therapy, respectively (Fig. 2C and D).

PFS and OS. The median PFS duration in patients treated with matched therapy was 3.9 months [95% confidence interval (CI), 3.4–5.0] compared with 2.2 months (95% CI, 2.0–2.8) in patients treated with nonmatched therapy ($P = 0.001$; Fig. 2E). With a median follow-up of

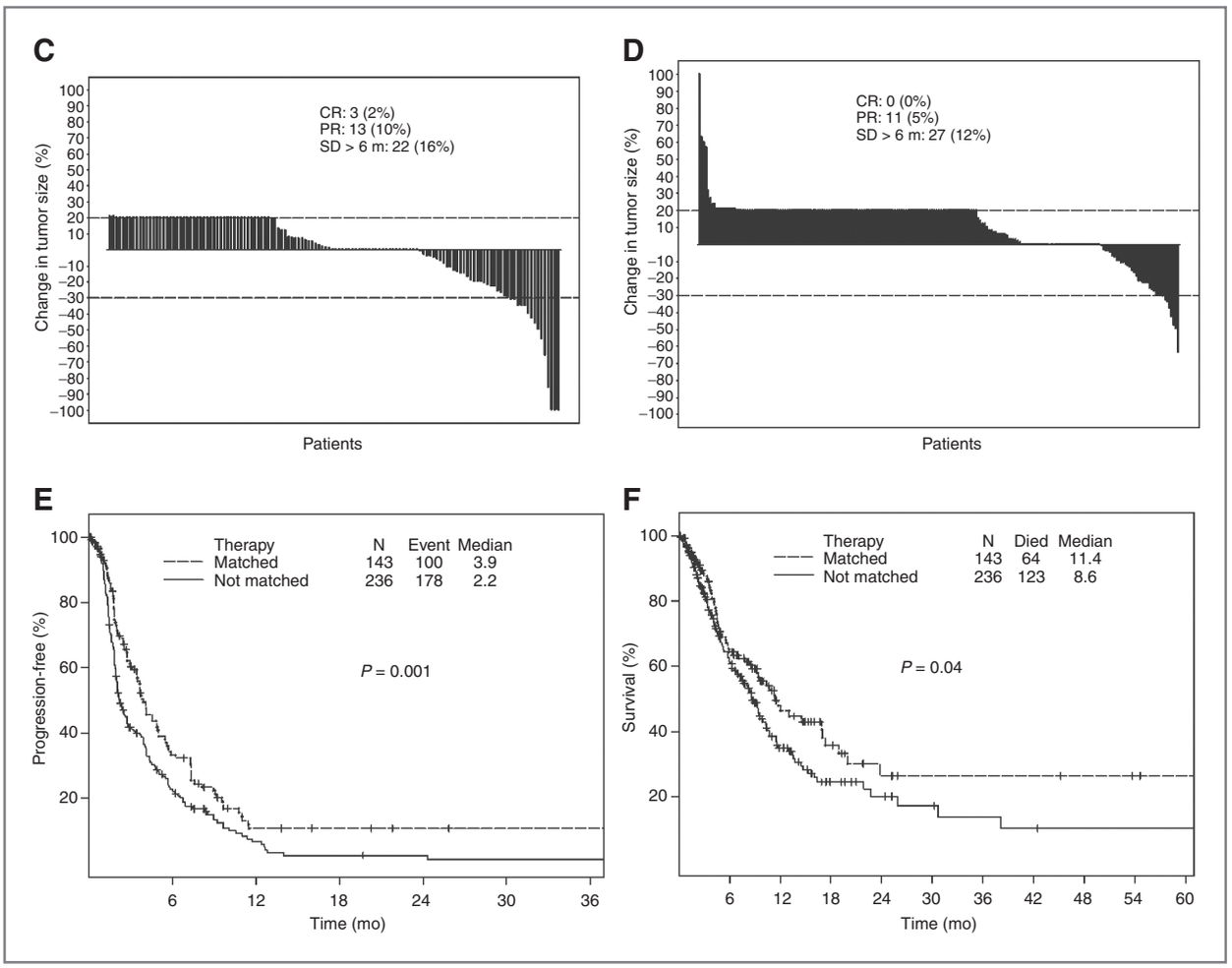


Figure 2. (*Continued*.) C, best response by RECIST of 143 evaluable patients with 1 molecular alteration treated with matched therapy: changes from baseline in tumor measurements (waterfall plot). Patients with new lesions and/or clinical progression are shown as 20% progression (≥20% increase indicates progression; ≥30% decrease indicates partial remission). D, best response by RECIST of 236 evaluable patients with 1 molecular alteration treated without molecular matching: changes from baseline in tumor measurements (waterfall plot; ≥20% increase indicates progression; ≥30% decrease indicates partial response). E, PFS of patients with one molecular alteration by type of therapy (matched vs. not matched). F, survival of patients with one molecular alteration by type of therapy (matched vs. not matched).

10 months, the median OS duration for the 143 patients treated with matched therapy was 11.4 months (95% CI, 9.3–17.3), compared with 8.6 months (95% CI, 7.5–10.4) for the 236 patients treated without matching ($P = 0.04$; Fig. 2F).

Multivariate analyses of response, PFS, and OS. Independent factors predicting response were matched therapy ($P = 0.015$), no liver metastases ($P = 0.046$), and normal albumin levels ($P = 0.047$). Independent factors predicting longer PFS were matched therapy ($P = 0.004$), normal levels of albumin ($P = 0.0005$), no liver metastases ($P = 0.003$), and normal lactate dehydrogenase levels ($P = 0.014$). Number of metastatic sites ≤2 was associated, with marginal significance, with longer PFS ($P = 0.051$; Table 2). Independent factors predicting longer OS were normal albumin levels ($P = 0.0002$), normal lactate dehydrogenase levels ($P = 0.008$), normal platelet counts ($P = 0.019$), and number of metastatic sites ≤2 ($P = 0.047$). Matched therapy was associated, with marginal significance, with longer survival ($P = 0.075$; Table 2). The remaining factors that were included in the model were not significantly associated with response, PFS, or OS.

Landmark analyses

Of 318 patients treated with matched therapy (previously published cohort, $n = 175$; current validation cohort, $n = 143$), a total of 270 patients were alive or had follow-up for at least 2 months and, therefore, were included in the 2-month landmark analysis for survival (Fig. 3A). The median OS of the 26 patients who had an objective response (CR or PR) was 30.5 months (95% CI, 15.2–60+), and the median OS of the 244 patients who did not achieve an objective response was 11.3 months (95% CI, 9.5–14.4; $P = 0.01$).

Of 352 patients treated with nonmatched therapy (previously published cohort, $n = 116$; current validation cohort, $n = 236$), 307 patients were included in the 2-month landmark analysis for survival (Fig. 3B). The median survival of the 10 patients who had an objective response (CR or PR) was 9.8 months (95% CI, 6.7–60+), and the median survival of the 297 patients who did not achieve an objective response was 9.4 months (95% CI, 8.4–10.8; $P = 0.46$).

Of 318 patients treated with matched therapy, 219 patients were alive, had follow-up, or did not have progressive disease for at least 2 months and so were included in the 2-month landmark analysis for PFS (Fig. 4A). The median PFS of the 25 patients who had an objective response (CR or PR) was 38.7 months (95% CI, 9.1–60+), and the median PFS of the 194 patients who did not achieve an objective response was 5.9 months (95% CI, 5.3–7.3; $P < 0.0001$).

Of 352 patients treated with nonmatched therapy, 176 patients were included in the 2-month landmark analysis for PFS (Fig. 4B). The median PFS of the 9 patients who had an objective response (CR or PR) was 8.5 months (95% CI, 6.7–60+), and the median PFS of the 167 patients who did not achieve an objective response was 4.2 months (95% CI, 3.9–5.0; $P = 0.18$).

Discussion

This analysis of 1,276 patients, leading to a validation analysis of 379 patients with one alteration, demonstrates that matched targeted therapy was associated with a higher objective response rate than nonmatched therapy (12% vs. 5%, respectively; $P = <0.0001$). This improved disease control was associated with improved PFS; the respective median PFS durations were 3.9 and 2.2 months ($P < 0.0001$). The OS duration was also longer in the matched therapy group compared with the nonmatched therapy group (median OS, 11.4 months vs. 8.6 months, respectively; $P = 0.04$). Matched therapy (vs. nonmatched therapy) was an independent factor predicting response and PFS but not OS, perhaps because patients received subsequent therapy after failure of a phase I clinical trial or because the number of patients was relatively small.

In our previous series, 40.2% of 1,144 patients had a molecular alteration (3). The increased proportion of molecular alterations in the current study (57.8%) is attributed to the availability of next-generation sequencing technology to identify molecular alterations. Although the outcomes results were similar in the two studies, in the previous series the difference in the objective response rates was greater (27% vs. 4% in the matched and nonmatched therapy groups, respectively; $P < 0.0001$). This difference in response rates may be attributed to the different targeted agents that were used in the two patient groups or to unknown factors. Overall, in the updated series, the differences in response, PFS, and OS between the matched and nonmatched therapy groups were still significant.

Our 2-month landmark analyses of patients in the current validation analysis and our previously published series who had 1 molecular alteration and were treated with matched therapy demonstrated a significantly longer OS duration in patients who achieved an objective response (CR or PR) than in those who did not respond to therapy (median OS, 30.5 vs. 11.3 months; $P = 0.01$). Two-month landmark analyses also demonstrated a statistically longer PFS in responders compared with nonresponders (median PFS, 38.7 vs. 5.9 months; $P < 0.0001$).

In contrast, no significant difference in OS or PFS was noted by 2-month landmark analysis in patients treated with nonmatched therapy ($P = 0.46$ and $P = 0.18$, respectively).

These results are intriguing in that in patients who achieved a CR or PR with matched targeted therapy, PFS and survival were significantly longer than in patients who did not have a response. An interesting finding is that no plateau in survival or PFS was noted, suggesting that the agents used in the matched therapy group in this heavily pretreated patient group with various tumor types could not cure cancer.

Several other investigators have reported that targeted therapy with BRAF or ALK inhibitors is associated with superior clinical outcomes in patients with BRAF mutations or ALK rearrangements, respectively (9–11). Both agents were approved by the FDA in 2011. Von Hoff and colleagues reported that 98% of patients had a defined tumor alteration, including overexpression of genes in the tumor compared with the control organ tissue (12).

In 2013, the FDA approved additional targeted agents showing higher rates of response and PFS than standard treatment: dabrafenib and trametinib were both approved for patients with melanoma and V600E (dabrafenib) or V600E/V600K (trametinib) BRAF mutations.

Recent clinical trials provide additional evidence of improved outcomes with the use of novel targeted therapies. Data from a study targeting the PI3K/PTEN/Akt pathway are encouraging. In HER2-positive metastatic breast cancer, the use of the antibody–drug conjugate T-DM1 was associated with longer PFS and OS than capecitabine plus lapatinib (13). The investigators concluded that patients with PIK3CA mutations treated with T-DM1 had treatment benefits similar to those of patients without these mutations and proposed that TDM1 may overcome the resistance associated with PIK3CA mutations (13). We previously reported results in patients with breast and gynecologic malignancies harboring *PI3KCA* mutations (14, 15). Of 23 patients with PI3KCA mutations treated with PI3K/AKT/mTOR inhibitors, 9 (39%) had stable disease or partial responses, as compared with only 7 of 70 (10%) patients with wild-type PI3KCA treated on the same protocols ($P = 0.04$; ref. 14). In another study of 1,656 patients with advanced, refractory cancers tested for *PI3KCA* or *PTEN* abnormalities, we observed that treatment with a PI3K/AKT/mTOR inhibitor was the only independent factor predicting response to treatment in patients with a *PIK3CA* or

Table 1. Baseline characteristics of 379 patients with one mutation by type of therapy

Characteristic		Matched (%) ($n = 143$)	Nonmatched (%) ($n = 236$)	*P*
Age, y	<60	86 (60)	133 (56)	0.54
	≥60	57 (40)	103 (44)	
Sex	Male	64 (45)	93 (39)	0.36
	Female	79 (55)	143 (61)	
Number of prior therapies	≤3	80 (57)	116 (49)	0.19
	>3	61 (43)	120 (51)	
ECOG performance status	0	48 (34)	52 (22)	0.02
	1–2	95 (66)	184 (78)	
Platelet count, $\times 10^9$/L	≤440	136 (95)	222 (94)	0.84
	>440	7 (5)	14 (6)	
Number of metastatic sites	0–2	99 (69)	160 (68)	0.86
	>2	44 (31)	76 (32)	
Liver metastases	Yes	54 (38)	89 (38)	0.92
	No	89 (62)	147 (62)	
Lactate dehydrogenase ≥618 IU/L	Yes	54 (38)	93 (39)	0.83
	No	89 (62)	143 (61)	
Albumin <3.5 g/dL	Yes	14 (10)	25 (11)	0.94
	No	129 (90)	211 (89)	
Royal Marsden Hospital score	0 or 1	116 (81)	185 (78)	0.61
	2 or 3	27 (19)	51 (22)	

PTEN aberration (15). Other investigators demonstrated that the AKT1, 2, and 3 inhibitor AZD5363 was associated with PRs in patients with driver mutations in the PI3K pathway (16). Other phase I trials also support the clinical benefit of a β isoform–sparing PI3K inhibitor, GDC-0032, and a PI3Kα-specific inhibitor, BYL719, in patients with mutations in the PI3K pathway (17, 18).

Despite the proliferation of effective targeted agents, several challenges in the field of personalized medicine exist. Cumulative evidence suggests that molecular analyses of a single metastatic site may provide limited information because of intra-patient heterogeneity, and this heterogeneity may explain tumor adaptation and therapeutic failure (19). This limited ability to validate oncologic biomarkers,

Table 2. Multivariate analyses of treated patients with one molecular alteration ($N = 379$)

Response	OR[a]	HR[b]	95% CI	*P*
Matched therapy (vs. nonmatched)	1.91		1.14–3.22	0.015
Albumin ≥ 3.5 g/dL (vs. < 3.5)	3.43		1.02–11.52	0.047
No hepatic metastases (vs. hepatic metastases)	1.78		1.01–3.13	0.046
PFS				
Matched therapy (vs. nonmatched)		0.69	0.54–0.89	0.004
Albumin ≥ 3.5 g/dL (vs. < 3.5)		0.51	0.35–0.74	0.0005
No hepatic metastases (vs. hepatic metastases)		0.69	0.54–0.89	0.003
Lactate dehydrogenase ≤ 618 IU/L (vs. > 618 IU/L)		0.73	0.57–0.94	0.014
No. of metastatic sites ≤ 2		0.78	0.61–1.00	0.051
Overall survival				
Lactate dehydrogenase ≤ 618 IU/L (vs. > 618 IU/L)		0.67	0.50–0.90	0.008
Albumin ≥ 3.5 g/dL (vs. < 3.5)		0.44	0.29–0.67	0.0002
Number of metastatic sites ≤ 2		0.73	0.54–0.90	0.047
Platelet count ≤ 440 $\times 10^9$/L (vs. > 440 $\times 10^9$/L)		0.55	0.33–0.91	0.019
Matched therapy (vs. non-matched)		0.76	0.56–1.03	0.075

[a]OR (>1 is associated with higher response).
[b]HR (<1 is associated with longer PFS or OS).

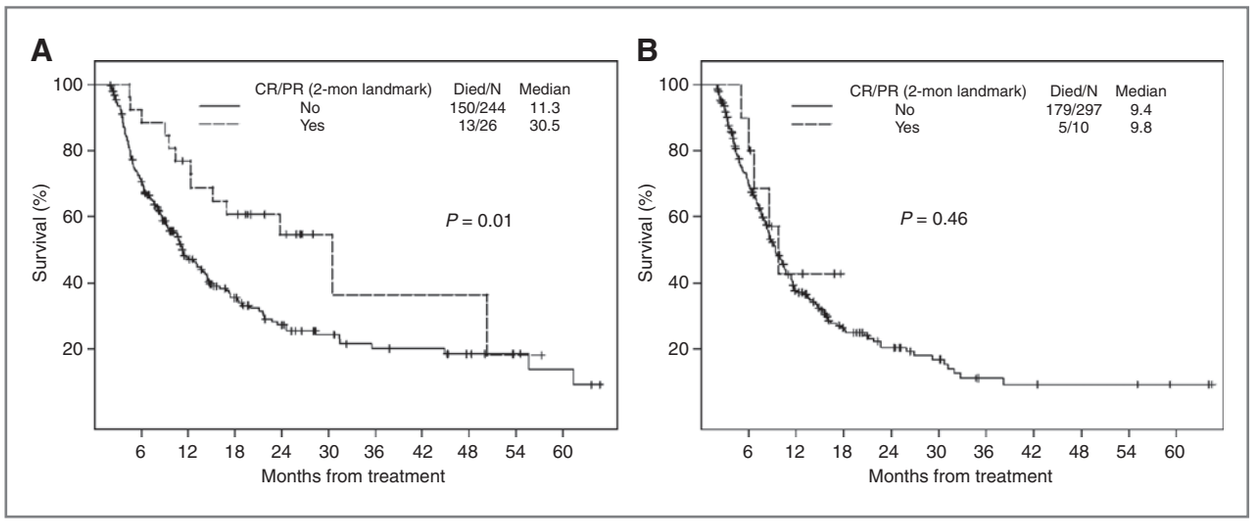


Figure 3. A, two-month landmark analysis of survival for the matched therapy group. B, two-month landmark analysis of survival for the nonmatched group.

which is attributed in part to sampling bias, may be overcome by the identification of alterations associated with the trunk of the phylogenetic tree, which is expected to lead to clinically significant biomarkers (19). Extensive research in breast cancer has confirmed plasticity and heterogeneity within biologic subtypes of breast tumors (20) and the need to determine individual tumor clonal genotypes in triple-negative breast cancer to understand the biology and to select therapy (21). Genomic instability-driven carcinogenesis is more common in triple-negative breast cancers than in other breast tumors, even though the majority of all breast tumors demonstrate many DNA copy number alterations. It is thought that the genes that contribute to this instability presentation may prove useful as clinical predictors of response to treatment (22). A better understanding of cancer subgroups and their molecular drivers that integrate genome and transcriptome information such as analysis of copy number and gene expression, like the one reported in breast tumors, will lead to the clinically useful molecular stratification of patients with cancer (23). The clinical significance of these dynamic changes in the genome was shown in patients with lung cancer bearing EGFR mutations (24). Histologic evolution in addition to genotypic plasticity was documented after treatment with EGFR inhibitors, providing strong evidence that biopsies are needed at the time of progression to understand the mechanisms of resistance and to optimize treatment (24).

Understanding "driver" versus "passenger" alterations through adaptation of the most synchronous technology,

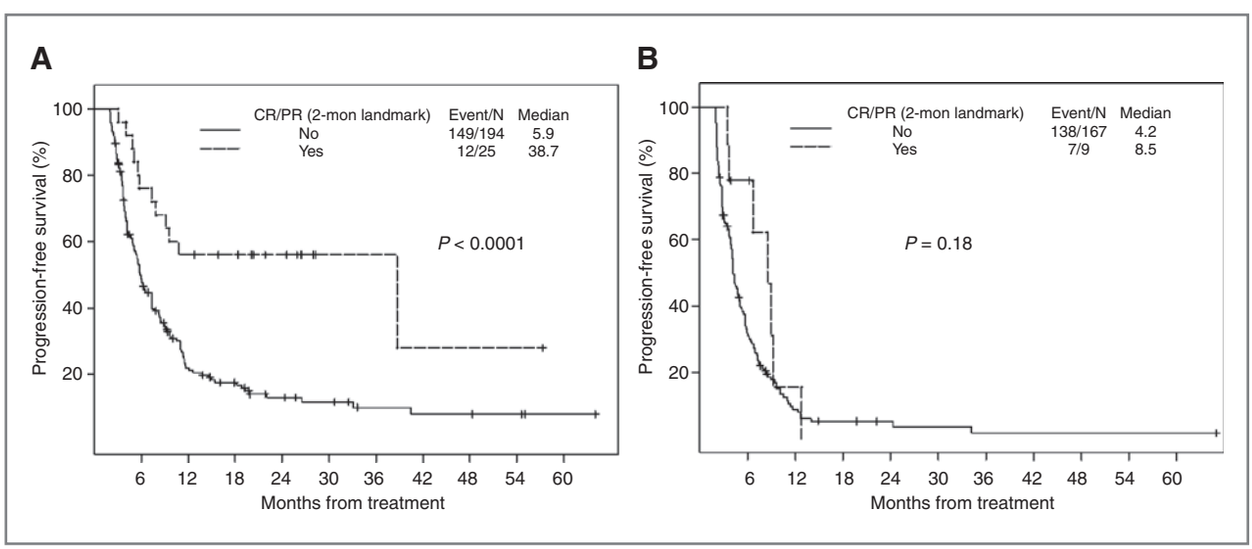


Figure 4. A, two-month landmark analysis of PFS for the matched therapy group. B, two-month landmark analysis of PFS for the nonmatched therapy group.

optimization of bioinformatics, discovery of new targeted agents, and carefully designed clinical trials is needed to improve the use of targeted therapy and patient care. The selection of "driver" alterations is particularly relevant, as next-generation sequencing can identify multiple molecular alterations, including many nontargetable alterations. In the current analysis, we included patients with one targetable molecular alteration. Keeping in mind that currently using next-generation sequencing multiple alterations are identified in many patients, patients in our analysis were tested for the limited number of alterations that were CLIA certified during the time of patient assessment for participation in clinical trials and that tumor tissue was not adequate for testing multiple alterations. Additional limitations are the inclusion of several genetic alterations, different types of alterations for a certain gene, and various clinical trials, which may influence clinical outcomes.

Robust preclinical models that reflect the genomic diversity of human cancers, such as those generated by the Cancer Cell Line Encyclopedia (gene expression, chromosomal copy number, and sequencing data from 947 human cancer cell lines) may provide information about genetic predictors of drug response (25). Use of this information in clinical trial design may expedite the development of "personalized" therapeutic regimens (25). Other investigators have screened several hundred cancer cell lines with 130 drugs, and they demonstrated that such pharmacogenomic profiling in cancer cell lines linking drug activity to the functional complexity of cancer genomes may provide a discovery platform to guide personalized medicine (26).

In summary, given the limited available knowledge regarding the functional, mechanistic, and pathologic features of molecular alterations, and the relatively few available targeted therapies, our validation analysis confirms the results of our previously published cohort showing that patients with 1 tumor molecular alteration treated with targeted therapy matched to that alteration had overall higher rates of response, PFS, and OS compared with patients who were unable to receive matched therapy.

To eliminate bias in reporting the results of molecular profiling and personalized medicine studies, several prospective randomized clinical trials to assess whether molecular profiling and targeted therapy is associated with superior outcomes compared with treatment not selected on the basis of molecular targeting are being developed and will enroll patients in 2014.

Disclosure of Potential Conflicts of Interest

F. Janku reports receiving commercial research grants from Biocartis, Biomed Valley Discoveries, Novartis, and Trovagene. D. Berry is an employee of, holds ownership interest (including patents) in, and is a consultant/advisory board member for Berry Consultants, LLC. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A.-M. Tsimberidou, R. Kurzrock, D.Berry
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