Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study

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Cancer treatments have evolved from indiscriminate cytotoxic agents to selective genome- and immune-targeted drugs that have transformed the outcomes of some malignancies. Tumor complexity and heterogeneity suggest that the ‘precision medicine’ paradigm of cancer therapy requires treatment to be personalized to the individual patient. To date, precision oncology trials have been based on molecular matching with predetermined monotherapies. Several of these trials have been hindered by very low matching rates, often in the 5–10% range, and low response rates. Low matching rates may be due to the use of limited gene panels, restrictive molecular matching algorithms, lack of drug availability, or the deterioration and death of end-stage patients before therapy can be implemented. We hypothesized that personalized treatment with combination therapies would improve outcomes in patients with refractory malignancies. As a first test of this concept, we implemented a cross-institutional prospective study (I-PREDICT, NCT02534675) that used tumor DNA sequencing and timely recommendations for individualized treatment with combination therapies. We found that administration of customized multidrug regimens was feasible, with 49% of consented patients receiving personalized treatment. Targeting of a larger fraction of identified molecular alterations, yielding a higher ‘matching score’, was correlated with significantly improved disease control rates, as well as longer progression-free and overall survival rates, compared to targeting of fewer somatic alterations. Our findings suggest that the current clinical trial paradigm for precision oncology, which pairs one driver mutation with one drug, may be optimized by treating molecularly complex and heterogeneous cancers with combinations of customized agents.

We conducted Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT), a prospective navigation trial, at two centers (University of California, San Diego Moores Cancer Center and Avera Cancer Institute). Tissue genomic profiling using next-generation sequencing (NGS; Foundation Medicine, 236–405 genes), and, if possible, programmed death-ligand 1 (PD-L1) immunohistochemistry (IHC), tumor mutational burden (TMB), microsatellite instability (MSI) status, and the NGS of blood-derived circulating tumor DNA (ctDNA) were performed. Based on this information, a molecular tumor board (MTB) consisting of oncologists, pharmacologists, cancer biologists, geneticists, surgeons, radiologists, pathologists, and bioinformatics experts focused on selecting customized, multidrug combinations to target a majority of the genomic alterations in each patient’s tumor(s) while simultaneously considering potential overlapping drug toxicities. The therapies ultimately administered were based on the treating oncologists’ choice, with physicians crafting the regimen by incorporating MTB discussions, as well as patient preference, attention to comorbidities, consideration of drug toxicities, insurance payor coverage of off-label agent(s), and investigational agent clinical trial availability, hence reflecting actual clinical practice in the United States today.

One hundred and forty-nine patients with previously treated, refractory, lethal metastatic cancers (stage IV disease) were consented to the I-PREDICT trial. Eighty-three patients (56%) were treated and considered evaluable for analysis (Supplementary Table 1 and Supplementary Table 2). These 83 patients had a median of two prior lines of therapy. The other 66 patients could not be evaluated, mainly because they deteriorated or died before treatment could be initiated (Extended Data Fig. 1). The patient demographics of the 83 treated patients are described in Table 1. The most common primary tumor sites were gastrointestinal (including hepatopancreatobiliary) (42.2%), gynecologic (16.9%), breast (14.5%), and central nervous system (7.2%). The median number of characterized genomic alterations per tumor was 5 (range, 1–20; Table 1).

Of the 83 treated patients, 73 (88% of treated patients; 49% of enrolled patients) were administered a personalized, precision therapy consisting of ≥1 molecularly ‘matched’ treatments (≥1 matched treatment), following receipt of molecular profile results. No two molecular profiles were identical; hence, most treatment regimens were not exactly alike. The other 10 patients (12%) were not...
administered matched therapies (no matched treatment), although 9 of them had potential matches for receiving targeted therapies. Instead, they received only ‘unmatched’ standard-of-care drugs for their respective tumor types, most often due to the treating oncologists’ choices (36.4%), patient preference (36.4%), clinical trial availability of other investigational agents (18.2%), and consideration of drug toxicities (9.1%) (Supplementary Table 3). The median time from study consent to treatment initiation was less than one month (0.93 months, 95% confidence interval (CI) 0.73–1.4). Since the protocol permitted use of FoundationOne molecular tests performed as part of physicians’ routine practice (before enrollment), the median time from molecular results until treatment initiation was two months (95% CI 1.3–2.3).

The 73 patients (≥1 matched treatment) had previously been treated with a median of 2 (interquartile range (IQR) 1–3) prior lines of therapy. They received a median of two drugs in their on-study treatment regimens (range, 1–5; Table 1). Figure 1a,b details the percentage of matched genomic alterations in a pathway, complex, or gene that were targeted by the customized therapeutic regimens (median of 2 genomic alterations targeted per patient; range, 1–6). Of the 73 patients, all had matches linked to molecular alterations (see Supplementary Table 2 for molecular results and drug matches with supporting references); in 67 patients (91.8%), the drugs were gene product-targeted drugs, while the others were checkpoint inhibitor immunotherapy, based on the genomic profile (Supplementary Table 4). Specifically, a checkpoint inhibitor was administered (alone or in combination with other drugs) to 14 matched patients (19.1%) based on PD-L1 IHC positivity, high/intermediate TMB, MSI-high status, CD274 (PD-L1) amplification, or when tumors had ≥8 genomic alterations with unknown PD-L1 IHC, TMB, and MSI. Four patients (5.5%) were treated with hormone therapies in combination with other molecularly targeted drugs based on positive hormone status. Only two patients had one genomic alteration and were molecularly matched to one drug. Patients given no matched treatment (N=10) received a median of 2 drugs (range, 1–3).

As described previously, a ‘matching score’ system was then utilized for each patient. Blinded to patient outcomes, the investigators calculated the total number of molecular alterations matched to the drugs administered and divided that number by the total number of characterized genomic aberrations. Further details for scoring are delineated in the Methods (‘Matching score’). We next stratified patients based on matching scores ≥50% (designated as high; N=28 patients) versus ≤50% (designated as low; N=55 patients including 10 patients with no matched treatment administered (matching scores =0%; Supplementary Table 1)). The total number of molecular matches for the high group was 67 (mean, 2.4 matches per patient). Patients with high matching scores received a median of 2 drugs in their regimen (range, 1–5 drugs) as did patients with low matching scores (median, 2 drugs (range: 1–4 drugs); Supplementary Table 2 and Supplementary Table 4).

Patients were followed until progression of disease, treatment intolerance, or death. The overall median follow-up was 10.8 months (95% CI 6.9–14.6; Supplementary Table 5). Overall, 30% of patients evaluable for response achieved disease control (defined as stable disease ≥6 months (N=4); complete response (N=1); or partial response (N=16)). When patients were stratified to high and low groups, a high matching score was an independent predictor of an increased disease control rate (DCR); 50% of patients with a high matching score achieved disease control compared to 22.4% of patients with a low matching score (P=0.028; Table 2). Among the different variables tested, matching score >50% was the only parameter significantly associated with higher DCR (Table 2 and Fig. 1c). The multivariable analysis confirmed that only a high matching score was an independent predictor of higher DCR (odds ratio (OR), 3.6; 95% CI 1.1–11.8; P=0.033).

A higher matching score was also an independent predictor of longer progression-free survival (PFS) (Table 2 and Fig. 1e) and overall survival (Table 2 and Fig. 1f) according to the Kaplan–Meier analysis. All treated patients (N=83) were included in the PFS and overall survival analyses of high matching score versus low matching score (median PFS, 6.5 versus 3.1 months, P=0.001; median overall survival, not reached after a median follow-up of 8.5 months versus 10.2 months, P=0.046). In multivariable Cox regression models, adjusting for patient age, sex, matching score, disease site, combination therapy, and therapy line, a high matching score remained the most significant variable associated with a prolonged PFS (hazard ration (HR) for low versus high matching score, 0.34 (95% CI 0.19–0.62, P=0.0004)) and with a prolonged overall survival (HR for low versus high matching score, 0.42 (95% CI 0.18–0.95, P=0.038)).

Generally, PFS becomes shorter with each line of therapy administered. Thus, we compared the PFS in the study (PFS2) with the immediate prior line of unmatched therapy (PFS1), hence, using the patient as their own control. Specifically, we compared the frequency of patients with a PFS ratio (PFS2/PFS1) ≥1.3, based on the work of Von Hoff et al. who reported that 27% (18 of 66) of molecularly matched patients had a PFS ratio of ≥1.3. In the current study, a high

| Table 1 | Patient demographics, molecular pathology, and treatment history |
|---------------------------------------------|
| Consented patients (N) | 149 |
| Treated patients (N (% of consented patients)) | 83 (55.7) |
| Patients with ≥1 matched treatment (N (% of consented patients)) | 73 (49.0) |
| Patients with no matched treatments administered (N (% of consented patients)) | 10 (6.7) |
| Age (median, 95% CI, range) | 62 (59–65, 21–86) |
| Sex (N (%)) | |
| Women | 55 (66.3) |
| Men | 28 (33.7) |
| Ethnicity (N (%)) | |
| White | 67 (80.7) |
| Asian | 4 (4.8) |
| African-American | 1 (1.2) |
| Other or unknown | 11 (13.3) |
| Tumor type (N (%)) | |
| Gastrointestinal and hepatopancreatobiliary | 35 (42.2) |
| Gynecologic | 14 (16.9) |
| Breast | 12 (14.5) |
| Central nervous system | 6 (7.2) |
| Genitourinary | 3 (3.6) |
| Head and neck | 3 (3.6) |
| Lung | 3 (3.6) |
| Other | 7 (8.4) |
| Number of total genomic alterations (median, range; VUS-excluded) | 5 (1–19) |
| Number of administered drugs (median, range) | 2 (1–5) |
| Median number of prior therapies in the metastatic setting (median, IQR) | 2 (1–3) |
Fig. 1 | Molecular alterations targeted by matched therapies and impact of matching score on treatment outcome. a, Pie graph of the percentage of actionable aberrations in the indicated targets or target pathways for the 73 patients who received at least one matched drug. Since some patients had alterations targeted in multiple genes or pathways, the percentages do not add up to 100%. ‘Immune checkpoints’ refers to amplification of the CD274 (PD-L1) and/or PDCD1LG2 (PD-L2) genes, positive PD-L1 expression (IHC), high/intermediate TMB, or high MSI; ‘MAPK pathway’ refers to alterations in the KRAS, BRAF, GNAS, MEK1, NF1, or JAK2 genes; ‘ERBB pathway’ refers to alterations in the ERBB2 or ERBB3 genes; ‘PI3K pathway’ refers to alterations in the AKT1, AKT2, PIK3CA, PIK3R1, or PTEN genes; ‘FGF/FGFR pathway’ refers to alterations/amplifications in the FGFR1/2/3, FGF2, FGF4, FGF6, FGF19, FGF23, and/or FRS2 genes; ‘Beta-catenin pathway’ refers to alterations in the APC, CTNNB1, or FAT1 genes; ‘Cell cycle regulation’ refers to alterations in the CDK2/4/6 genes; ‘HGF/MET pathway’ refers to alterations in the HGF or MET genes; ‘BRCA complex’ refers to alterations in the BRCA1, BRCA2, ATM, BRIPI, or PALB2 genes; ‘Estrogen receptor’ refers to alterations in the ESR1 gene or estrogen receptor positivity as assessed by IHC; ‘Other’ refers to alterations in the MYC, EWSR1, RET, TP53, EGFR, PTCH1, and RET refer to alterations in the genes encoding the proteins. b, Pie graph of the percentage of actionable aberrations in the indicated targets or target pathways for the 28 patients who had a matching score of >50%. In these 28 patients, a total of 67 molecular alterations were matched to treatments. c, Bar graph showing the percentage of patients with stable disease ≥6 months, partial/complete remission, stable disease <6 months, or progression of disease. d, Bar graph showing the percentage of patients with a PFS ratio ≥1.3 or <1.3 among patients with a matching score of ≤50% (N = 49) versus >50% (N = 20). P values were computed using a binary logistic regression test. e, Kaplan–Meier curves displaying overall survival for patients with a matching score ≤50% (N = 55) versus >50% (N = 28). P values are from the two-sided log-rank test. f, Kaplan–Meier curves displaying overall survival for patients with a matching score ≤50% (N = 55) versus >50% (N = 28). P values were calculated by the two-sided log-rank test. The asterisk represents median overall survival not reached after a median follow-up of 8.5 months.
Table 2 | Comparison of DCR, PFS, and overall survival in patients treated on the I-PREDICT trial

| DCR, stable disease ≥ 6 months/partial remission/complete remission* | PFS* | Overall survival* |
|---------------------------------------------------------------|-----------|------------------|
| | Evaluable | Median, months (95% CI) | HR (95% CI) | P | Evaluable | Median, months (95% CI) | HR (95% CI) | P | Evaluable | Median, months (95% CI) | HR (95% CI) | P |
| | N | | | | | | | | | | | |
| Evaluable patients | <62 | ≥62 | | | | | | | | | | |
| Age, years | 36 | 12 (33.3%) | 9 (27.3%) | | 0.75 | 0.27-3.9 | | 0.585 | 0.022-3.2 | | 0.98 | 0.60-17.1 | | 0.046 | | 0.46-17.1 | | 0.003 |
| | | | | | | | | | | | | | | | | |
| Sex | Female | Male | | | | | | | | | | |
| | 45 | 24 | 12 (26.7%) | 9 (37.5%) | | 0.61 | 0.27-2.1 | | 1.34 | 0.71-4.8 | | 0.354 | 0.17-1.8 | | 0.948 | 0.46-2.2 | | 0.730 | 0.34-1.6 |
| | | | | | | | | | | | | | | | | | |
| Matched treatment | >1 matched | Treatment, no matched | | | | | | | | | | |
| | 60 | 9 | 20 (33.3%) | 1 (11.1%) | | 4.00 | 0.47-3.4 | | 0.026 | 0.01-5.1 | | 1.25 | 0.62-2.1 | | 0.253 | 0.13-0.5 | | 0.727 | 0.38-1.6 |
| | | | | | | | | | | | | | | | | | |
| Matching score (%) | >50 | 50 | 20 | 10 (50.0%) | 11 (22.4%) | | 3.46 | 1.15-10.4 | | 0.028 | 0.01-3.9 | | 0.289 | 0.12-1.9 | | 0.001 | 0.01-1.5 | | 0.008 | 0.01-2.3 |
| | | | | | | | | | | | | | | | | | | |
| Gastrointestinal cancer | Yes | No | 32 | 14 (37.8%) | 16 (47.3%) | | 0.46 | 0.16-1.4 | | 0.55 | 0.17-1.8 | | 0.341 | 0.17-1.9 | | 1.21 | 0.74-2.0 | | 0.443 | 0.26-0.7 |
| | | | | | | | | | | | | | | | | | | |
| Gynecologic cancer | Yes | No | 12 | 17 (29.8%) | 18 (32.8%) | | 0.81 | 0.31-2.7 | | 1.14 | 0.60-2.2 | | 0.09 | 0.05-1.9 | | 0.689 | 0.01-0.9 | | 0.881 | 0.01-1.1 |
| | | | | | | | | | | | | | | | | | | |
| Breast cancer | Yes | No | 10 | 16 (27.1%) | 5 (50.0%) | | 2.69 | 0.69-10.3 | | 0.156 | 0.09-2.9 | | 0.663 | 0.29-1.4 | | 0.92 | 0.33-2.9 | | 0.809 | 0.31-2.0 | | 0.657 | 0.29-1.5 |
| | | | | | | | | | | | | | | | | | | |
| Combination therapy | Yes | No | 51 | 18 (27.8%) | 16 (31.8%) | | 1.19 | 0.37-3.9 | | 0.776 | 0.24-2.5 | | 0.62 | 0.22-1.8 | | 0.766 | 0.19-2.9 | | 0.338 | 0.07-1.6 | | 0.338 | 0.07-1.6 |
| | | | | | | | | | | | | | | | | | | |
| Prior lines of therapy | <2 | ≥2 | 21 | 10 (23.8%) | 11 (40.7%) | | 2.05 | 0.77-6.3 | | 0.139 | 0.05-3.4 | | 0.67 | 0.27-2.0 | | 0.49 | 0.19-1.2 | | 0.683 | 0.26-1.8 | | 0.15 | 0.05-0.5 |

Notes:
- *Survival analyses included 83 patients. DCR analysis (stable disease ≥ 6 months/partial remission/complete remission) included 69 patients evaluable for response; for the remaining 14 patients, the DCR was too early to assess, since these patients had stable disease but had not yet had the 6-month follow-up scan. Only tumor types with at least 9 patients were tested. 3 P values were computed using binary logistic regression analyses (univariable and multivariable). Variables with P < 0.2 in univariable analyses were included in the multivariable model. 4 P values were computed using the Kaplan-Meier method (two-sided log-rank test for univariable and Cox regression for multivariable analysis); variables with P < 0.2 in univariable analyses were included in the Cox regression model (multivariable). 5 Age cutoffs corresponded to the median age. The cutoff for 50% for the matching score was chosen according to the maximum P value criterion. 6 Gastrointestinal cancer includes hepatocarcinopretrialblary cancer. 7 Combination therapy refers to the administration of molecularly matched multidrug regimens. NR, not reached." The cutoff chosen was the median number of prior lines of therapy administered. P values in bold are those less than 0.05. 8
matching score was the only parameter significantly impacting the PFS ratio ≥1.3 in both the univariable (P = 0.026) and multivariable analyses (P = 0.015; Table 3 and Fig. 1d). Indeed, 75% of patients reached a PFS ratio ≥1.3 if the matching score was >50% compared to 36.6% if the matching score was ≤50% (P = 0.026; Fig. 1d). These findings indicate that PFS can be prolonged by 30% or longer in later lines of therapy when a majority of the molecular alterations are targeted.

We also attempted to understand if other parameters were impacting patient outcomes in a sub-analysis that only included patients who received ≥1 matched treatment (N = 73; Supplementary Table 6). This sub-analysis demonstrated that a time interval between tissue biopsy and molecularly matched treatment initiation of <9 months, as well as the addition of chemotherapy in the regimen, increased the rate of patients achieving disease control (stable disease ≥6 months/complete remission/partial remission) in a multivariable analysis (P = 0.031 and P = 0.033, respectively). However, only the matching score remained a favorable independent predictor in the multivariable analysis for the PFS and overall survival analyses (P = 0.004 and P = 0.050, respectively), further validating earlier studies of this methodology.24

We also evaluated the role of targeting downstream of RAS and TP53, two common mutations in cancers (Fig. 1a,b). To date, no specific drug is known to directly target RAS. Furthermore, the efficacy of dual specificity mitogen-activated protein kinase kinase 1 (MEK) inhibitors has been circumstantial and mixed.25 It is unclear if the weak efficacy of current MEK inhibitors for KRAS targeting is a fundamental property of these inhibitors or if it is related to the fact that KRAS alterations are usually accompanied by other drivers that need to be targeted. Of interest in this regard is a recent report demonstrating that a patient with Rosai–Dorfman disease and a single activating KRAS alteration had a remarkable response to the MEK inhibitor cobimetinib.26 With regard to TP53 aberrations, recent data suggest it may be indirectly/partially target-matched with vascular endothelial growth factor (VEGF)/VEGFR receptor (VEGFR) inhibitors (perhaps because loss of p53 function is associated with upregulation of VEGF-A)27,28. Thus, we evaluated the DCR, PFS, and overall survival in patients with TP53 and/or RAS mutations who were treated with VEGF/VEGFR and/or MEK inhibitors versus patients with TP53 and/or RAS mutations who were not matched to any therapy (Supplementary Table 7). There is no difference between the groups, although the numbers are too small to draw definitive conclusions. However, Wheler et al.29 addressed this question with regard to TP53 alterations matched to VEGF/VEGFR inhibitors. Their report showed that VEGF/VEGFR inhibitor therapy was independently associated with improvement in all outcome parameters for TP53-mutant patients (but not for TP53 wild-type patients, who received no other molecularly matched agents) treated with VEGF/VEGFR inhibitors (versus those not treated with these agents).

Overall, 16 of 83 treated patients (19.3%) experienced ≥1 serious adverse events (SAE) in the study (14 of 73 (19.2%) with ≥1 matched treatment and 2 of 10 (20%) with no matched treatment administered). The number of drugs in the regimen was unrelated to the number of SAEs. The SAEs deemed at least possibly or probably related to drug therapy tended to be less common in patients with a matching score >50% versus ≤50% (1 (3.6%) versus 7 (15.6%); P = 0.14). There were no treatment-related deaths in this study. Taken together, therapy-related SAEs tended to be more common in the patients who received no matched treatment and in patients with a matching score ≤50%. (Supplementary Tables 8–10).

Matching single agents (other than immunotherapies for select individuals) to tumors with multiple genomic alterations is unlikely to result in prolonged or complete remission. In fact, only two patients (2.7%) in our cohort with ≥1 matched treatment had only one genomic alteration identified. Yet, precision medicine trials performed to date concentrate on finding commonalities between patients and then matching them to monotherapy, a design consistent with traditional treatment models, but inconsistent with the reality unveiled by genomics. That is, the vast majority of patients with metastatic tumors have numerous genomic alterations that differ from patient to patient.26

We achieved a matching rate of 49% (73 of 149 patients), a number considerably higher than in many other precision medicine trials of which we are aware. This high matching rate was based on several key factors: (1) molecular interrogation by NGS for a large panel of cancer-related genes, including assessment, when possible, of TMB, MSI status, PD-L1 IHC and ctDNA; (2) timely MTB discussions, which occurred immediately on receipt of molecular results including by ad hoc e-meetings, to inform treatment recommendations without delay; and (3) use of a medication acquisition specialist and clinical trials coordinator to ensure rapid access to drugs. It is important to note that we did not treat canonical tumor types for success. For example, no melanomas were treated and only three lung cancers (3.6%) were included, demonstrating that this approach may be feasible and effective in diseases that are classically not thought of in the setting of molecularly targeted approaches.

The study had several limitations, including the lack of a control group. In addition, the number of alterations detected may depend on the number of genes interrogated in a given panel test. Therefore, the specific matching scores and cutoffs could differ between panels. However, the more comprehensive the panel with regard to cancer-related genes, the more accurate the matching score should be. Further, the important finding herein is that higher degrees of matching are associated with better outcomes than lower degrees of matching, and that higher matching scores often require customized combinations, rather than single agents, as are often given in traditional precision oncology trials. Further validation and assay harmonization studies are needed to determine a universal cutoff for matching, although it remains conceivable that degrees of matching and outcome are related in a continuum. Another limitation relates to the fact that some of the matches, especially in the high matching score group, were to immunotherapy and this was often based on high TMB status. Hence, these results may confound our ability to calculate matching of strictly gene-targeted agents. Nonetheless, our findings demonstrate that genomics and other biomarkers are more broadly useful for matching a variety of drugs beyond gene-targeted agents. However, our findings may have a potential self-selection bias for patients that sought out enrollment on the trial or bias based on physician referral. Even so, this study represents real-world practice patterns, and the molecular matching of targets with cognate agents is generally independent of these issues; therefore, it is likely to have low impact on the results. Finally, a limitation of the study is the small number of patients in individual subgroups, such as those with TP53 alterations matched with VEGF/VEGFR inhibitors or RAS mutations matched with MEK inhibitors alone, which precluded determining the efficacy of these matches when not part of a combination regimen. Additional studies with larger sample sizes are needed.

In conclusion, the administration of N-of-1 customized, multi-drug combinations targeting multiple identified molecular alterations (discerned by NGS) based on recommendations from a just-in-time MTB was feasible and safe. Characteristics of this intervention (for example, the matching score) were associated with significant improvements in the DCR and all survival parameters. Although we were able to administer ≥1 matched drug to 49% of our patients, substantial numbers of patients still dropped off, mostly due to disease deterioration with hospice placement or demise. Therefore, personalized precision medicine approaches should be instituted earlier in the course of the disease. At present, there is another study group in the I-PREDICT trial investigating the
administration of customized combination therapies in treatment-naive patients with aggressive unresectable and metastatic disease\(^9\). Enrollment is ongoing. Taken together, our findings underscore the safety, feasibility, and importance of designing precision oncology trials that emphasize personalized, individually tailored combination therapies, rather than scripted monotherapies, for patients with lethal cancers. Follow-up studies with greater numbers of patients are needed to confirm our findings.

**Table 3 | Factors associated with PFS prolongation by 30% or greater in later lines of therapy**

| Parameters | Patients with \(\text{PFS}_2/\text{PFS}_1 \geq 1.3\) (%)\(^a\) | OR (95% CI) Univariable | OR (95% CI) Multivariable |
|------------|-------------------------------------------------|--------------------------|----------------------------|
| Evaluable patients\(^b\) \((N = 53)\) | 24/53 = 45.3 | - | - |
| Age\(^c\) | <62 years old \((N = 24)\) | 9/24 = 37.5 | 0.56 (0.19–1.69) | 0.302 - |
| ≥62 years old \((N = 29)\) | 15/29 = 51.7 | 1.69 | - | - |
| Sex | Women \((N = 36)\) | 15/36 = 41.7 | 0.64 (0.20–2.03) | 0.443 - |
| | Men \((N = 17)\) | 9/17 = 52.9 | - | - |
| Patients with >1 matched therapy administered | Yes \((N = 46)\) | 22/46 = 47.8 | 2.29 (1.04–4.70) | 0.350 - |
| | No \((N = 7)\) | 2/7 = 28.6 | - | - |
| Matching score\(^d\) | >50% \((N = 12)\) | 9/12 = 75.0 | 5.20 (1.22–22.23) | 0.026 8.18 (1.50–44.77) 0.015 |
| | ≤50% \((N = 41)\) | 15/41 = 36.6 | - | - |
| Gastrointestinal cancer (includes hepatopancreaticobiliary cancer) | Yes \((N = 23)\) | 10/23 = 43.5 | 0.88 (0.30–2.62) | 0.817 - |
| | No \((N = 30)\) | 14/30 = 46.7 | - | - |
| Gynecologic cancer | Yes \((N = 10)\) | 3/10 = 30.0 | 0.45 (0.10–1.97) | 0.289 0.20 (0.03–1.42) 0.108 |
| | No \((N = 43)\) | 21/43 = 48.8 | - | - |
| Combination therapy\(^e\) | Yes \((N = 38)\) | 18/38 = 47.4 | 1.35 (0.40–4.54) | 0.628 - |
| | No \((N = 15)\) | 6/15 = 40.0 | - | - |
| Prior lines of therapy\(^f\) | ≤2 \((N = 20)\) | 4/20 = 20.0 | 0.51 (0.16–1.59) | 0.245 0.48 (0.13–1.73) 0.262 |
| | >2 \((N = 33)\) | 17/33 = 51.5 | - | - |

\(^a\)PFS\(_2\) refers to PFS on the I-PREDICT protocol; PFS\(_1\) refers to PFS on the prior unmatched therapy (in a metastatic or an unresectable setting). \(^b\)P-values by Kaplan–Meier method (two-sided log-rank test (univariable analysis); Cox regression model (multivariable analysis)); variables with \(P < 0.3\) in univariable analysis were included in the Cox regression model (multivariable analysis). \(^c\)N = 53 patients were evaluable for this analysis. Patients could not be evaluated mainly because the PFS\(_2\) was in the adjuvant/neoadjuvant setting or was a matched therapy. \(^d\)Age cutoff chosen corresponds to the median age. \(^e\)The cutoff of 50% for the matching score was chosen according to the minimum \(P\) value criteria. \(^f\)Combination therapy refers to the administration of molecularly matched multidrug regimens. The cutoff chosen was the median line of therapy administered.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at [https://doi.org/10.1038/s41591-019-0407-5](https://doi.org/10.1038/s41591-019-0407-5).

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Author contributions
J.K.S. contributed to the conception/design of the work, the acquisition, analysis, and interpretation of the data, and the drafting and substantive revision of the work. S.K. and R.O. contributed to the acquisition, analysis, and interpretation of the data, and the drafting and substantive revision of the work. M.S. contributed to the acquisition, analysis, and interpretation of the data, and the drafting and substantive revision of the work. M.E.H., C.B.W., P.D., and P.T.F. contributed to the acquisition and analysis of data. A.K. and D.E.P. contributed to the acquisition of the data. V.A.M. contributed to the design of the work, the drafting of the work, and the substantive revision of the work. J.J.L. contributed to the conception/design of the work, the analysis, and interpretation of the data, and the drafting of the work. S.M.L. contributed to the conception/design of the work, B.L.-J. contributed to the acquisition, analysis, and interpretation of data, and the drafting of the work. R.K. contributed to the conception/design of the work, the acquisition, analysis, and interpretation of the data, and the drafting and substantive revision of the work. All authors approved the submitted version (and any substantially modified version that involves the authors’ contribution to the study). All authors have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones where the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Competing interests
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Additional information
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Methods

Human research. Ethics committee. The I-PREDICT study was reviewed and approved by the University of California, San Diego Protocol Review and Monitoring Committee and the Human Research Protections Program/Institutional Review Board (protocol no. 15-0538). It was subsequently reviewed and approved by the Avera Cancer Institute Protocol Review and Monitoring Committee and Institutional Review Board (protocol no. 2015.038). The safety of the protocol was also monitored by the University of California, San Diego Moores Cancer Center Data Safety Monitoring Board.

Ethical compliance. During the preparation, submission, conduct, and analysis of this study, we complied with all relevant ethical regulations.

Informed consent. All patients enrolled on the I-PREDICT study gave informed consent in their native languages via licensed medical interpreters, as well as signed consent forms in native language. Patients who were navigated to an investigational drug or drug(s) that were part of an investigational study, signed consent for that study also.

Study design. This was a prospective, open-label, navigation investigation to evaluate the feasibility of using molecular profile-based evidence to determine individualized cancer therapy for patients with incurable malignancies. This was a non-randomized, histology-agnostic trial. Although there would be a case mix of histologies, we know that individual histologies are composed of a heterogeneous mix of genomic alterations. It is not clear if one case mix is better or worse than another. Thus, we designed the study to test a strategy of molecular matching that may apply across cancers.

Sample size. This feasibility study has descriptive primary analyses to characterize the study findings. There were three groups, and only results from group 3 (previously treated unresectable/metastatic patients) are described herein; groups 1 and 2 (treatment-naïve unresectable and treatment-naïve metastatic with lethal diseases) are not described and are accruing. An MTB recommended therapy, but treatment decisions were the choice of the physician. The primary study objective was to determine the feasibility of using molecular testing to determine therapy for patients with previously treated cancers with incurable biology (≥50%, 2-year cancer-associated mortality). Primary and secondary end points included: the proportion of patients who receive molecularly targeted matched treatment after recommendations based on genomic analysis (primary end point); and the proportion of patients with actionable genomic alterations and overall response rate, regression rate, PFS and overall survival and incidence of high-grade adverse events (secondary and exploratory end points). Relevant hypotheses included: patients who received targeted therapy based on recommendations from actionable genomic alteration(s) will yield antitumor activity; the PFS on matched therapy will be greater than on their last unmatched therapy. For evaluation of treatment decisions, the study committee assessed the degree of matching that occurred using the best information available at the time of data evaluation. The original plan was to enroll 75 evaluable patients. Since this was a hypothesis-generating, descriptive trial, this number was later expanded to permit enrollment of up to 1,000 patients. Based on the fact that a minority of patients is usually matched to therapy on precision medicine trials, it was expected that we would show feasibility with 40% of the 75 evaluable patients (N=30) being matched and 60% treated with no matched therapy (N=45). With the sample size of 30 matched versus 45 unmatched, we would have 79% power to detect a response rate of 0.25 versus 0.05 in the two arms with a one-sided 10% type I error rate using the continuity-corrected chi-squared test. We calculated that we would have >80% power to detect the difference between the two groups using the log-rank test when the median PFS is 4 months and 2 months for the two arms, respectively. We analyzed group 3 after enrollment of 149 patients; the feasibility to administer matched therapy was confirmed because, of the 83 evaluable treated patients, 73 (88%) of evaluable treated patients and 49% of enrolled patients were matched. The ability to compare matched and unmatched patients was limited by the small number of evaluable unmatched patients (N=10). As part of the descriptive analysis, we evaluated the effect of the degree of matching in patients with low versus high matching scores (N=55 versus 28 patients).

Early safety stopping rule. Simon’s two-stage design was used. The null hypothesis was that the true response rate is 0.05 and this would be tested against a one-sided alternative. In the first stage, 13 patients would be accrued. If there were 0 responses in these 13 patients, the study would be stopped. Other early stopping rules were for >10 drug-related SAEs and >10 drug-related grade 4−5 toxicities. Early stopping was not triggered in the study.

Data exclusion. No data were excluded from the analysis.

Replication. Since this is a clinical trial, no replication was possible or performed.

Patients. We analyzed the clinico-pathologic and outcome data of 149 patients with previously treated advanced or metastatic solid malignancies who consented to the I-PREDICT study (group 3) during the study period. The study was activated on 15 February 2015. Accrual is ongoing in groups 1 and 2 (patients with treatment-naïve unresectable (group 1) or metastatic (group 2) lethal cancers (defined as ≥2-year mortality)) to meet accrual goals for analysis. Genomic profiling (Foundation Medicine; 236−405 genes) and, if possible, PD-L1 IHC, TMB, MSI status, and NGS of blood-derived ctDNA were performed. An MTB discussed the results immediately on receipt and emphasized customized combination therapies. The attending physician made the final treatment decisions. All analyses were based on the drugs administered.

Sites and investigator communication. The protocol was conducted at two sites: the University of California, San Diego Moores Cancer Center for Personalized Cancer Therapy and the Avera Cancer Institute in Sioux Falls, South Dakota. The study was cross-institutional in that all investigators, regardless of disease affiliation, at each of the two group 3 sites were investigators and physician-scientists, as well as study coordinators, reviewed the information by teleconference (and/or face-to-face meetings for University of California, San Diego investigators/coordinators) at least every two weeks. In addition, retreats at the primary site (University of California, San Diego) to review study information occurred at least every two months, with Avera physicians and staff teleconferenced in as needed.

MTB. MTB face-to-face meetings occurred approximately weekly and were attended by oncologists, surgeons, radiologists, pathologists, basic scientists, geneticists, colleagues from the University of California, San Diego Supercomputer Center, biostatisticians, as well as a medical oncology-acquaintance specialist and clinical trial coordinators/navigators. In addition, just-in-time (ad hoc) MTBs occurred electronically for any patients whom the physician felt could not wait for the face-to-face discussion (and for all patients treated at Avera Cancer Institute); in this case, patients were discussed immediately on receipt of results. All MTBs had templated information distribution and complied with HIPAA privacy protection regulations.

NGS, MSI, TMB, and PD-L1 status by IHC. NGS was performed by Foundation Medicine on tissue and blood (FoundationOne, FoundationOne Heme, and FoundationACT; http://www.foundationmedicine.com; Clinical Laboratory Improvement Amendments (CLIA)-certified). The FoundationOne tissue assay utilized during a majority of the study period interrogates 315 genes, as well as all introns of 28 genes involved in rearrangements. The current FoundationOne Heme tissue assay interrogates 406 genes, as well as introns of 31 genes involved in rearrangements, as well as the sequence RNA of 265 genes commonly rearranged in cancer to better identify known and novel gene fusions. Both assays identify all four classes of genomic alterations (that is, base substitutions, insertion and deletions, copy-number alterations, and rearrangements). All specimens were reviewed by a pathologist to ensure specimen viability and tumor content. FoundationACT is a blood-based ctDNA assay for solid tumors that identifies clinically relevant genomic alterations driving the growth of a patient’s cancer1. It interrogates the 62 most clinically relevant cancer genes in solid tumors and is recommended to identify all 4 alteration types (base-pair substitutions, insertions/deletions, copy-number alterations, and rearrangements). Two patients in this study only had ctDNA results available.

Microsatellite status (a measure of MSI) was determined by assessing the indel characteristics at 114 homopolymer repeat loci in, or near, the targeted gene region of FoundationOne assay and was available for N=52 patients. MSI was reported as MSI-high, MSI-stable, MSI-ambiguous, or MSI-unknown when relevant.

The Foundation Medicine Laboratory is CLIA-certified. The FoundationOne Cdx (F1Cdx) is the first US Food and Drug Administration (FDA)-approved broad companion diagnostic (CDx). The F1Cdx TMB result is pending approval in an expanded CDx claim for nivolumab in the front-line setting for non-small cell lung cancer. The TMB categorization (low, intermediate, high) was assigned as described previously2. TMB was defined as the number of somatic, coding, base substitution, and indel mutations per megabase (Mb) of genome examined. All base substitutions and indels in the coding region of targeted genes, including synonymous codon alterations, are initially counted before filtering as described later. Non-synonymous mutations are counted to reduce sampling noise. While synonymous mutations are not likely to be directly involved in creating immunogenicity, their presence is a signal of mutational processes that will also have resulted in non-synonymous mutations and neantigens elsewhere in the genome. Non-coding alterations were not counted. Alterations listed as known somatic alterations in the Catalogue Of Somatic Mutations In Cancer and truncations in tumor suppressor genes were not counted, since the assay genes are biased toward genes with functional mutations in cancer3. Alterations predicted to be germline by the somatic-germline-zygosity algorithm were not counted. Alterations that were recurrently predicted to be germline in our cohort of clinical specimens were not counted. Known germline alterations in the Single Nucleotide In Situ Human Database were not counted. Germline alterations occurring with two or more counts in the Exome Aggregation Consortium database were not counted. To calculate the TMB per Mb, the total number of mutations counted is divided by the size of the coding region of the targeted territory. The non-parametric
While germline genomic alterations in mismatch repair genes (for example, MLH1 and MSH2) and homology-directed repair genes (pre-diluted by the manufacturer) localize PD-L1 expression in both tumor cells and tumor-infiltrating immune cells within formalin-fixed, paraffin-embedded tissue sections. Detection was performed using the Ventana Optimab Detection System on the Ventana BenchMark ULTRA platform (Roche Diagnostics). If any of these tests had been performed as part of routine physician practice before enrollment, the results could be utilized for recommending therapy.

**Hormone receptor antibodies.** The hormone receptor antibody analyses were performed as part of standard clinical care at each institution. Estrogen receptor status was assessed using the Ventana ER/PR antibody (pre-diluted by the manufacturer) within formalin-fixed, paraffin-embedded tissue sections; detection was performed using the Ventana automated platform at University of California, San Diego. This test was cleared by the FDA and was used according to the manufacturer’s instructions. Estrogen receptor status was assessed by IHC using the Dako I5D estrogen receptor (1:30 dilution; until September 2015) and Dako ER Clone (1:270 dilution; from September 2015 to 2017) at the Avera Cancer Institute. Performance characteristics were verified by either the University of California, San Diego or Avera Cancer Institute Departments of Pathology as per the CLIA (CUL 1988) requirements and in accordance with the College of American Pathologists checklist requirements and guidance. Androgen receptor status was assessed by IHC using the CellMarque androgen receptor (SP107; 1:100 dilution) performed at San Diego Pathology, a College of American Pathologists-accredited and CLIA-certified laboratory. A manual platform with decloaker with EDTA buffer (Biocare Medical, Pacheco, CA) was utilized for antigen retrieval.

**Therapy and matching.** Therapy was recommended by the MTB, but the actual therapy given was the choice of the treating oncologist. Treatment was considered ‘matched’ if at least one agent in the treatment regimen targeted at least one alteration, or pathway component, altered in a patient’s molecular profile or a protein preferentially expressed in the tumor (for example, estrogen or androgen receptor or human epidermal growth factor receptor 2 status as assessed by standard-of-care testing other than NGS, or PD-L1 expression assessed by IHC as stated earlier). For small molecule inhibitors, matching was based on a half maximal inhibitory concentration (IC50) of the drug for the target (generally, <100 nM) or for effectors immediately downstream of the gene product altered. Gene alterations were considered matched if their primary target was the product of the molecular alteration. Matching designation was confirmed by the senior investigators (R.K. and J.K.S.), who were blinded to patient outcomes at the time of designation. Patients were stratified into those having received at least one matched treatment versus no matched treatment administered, with a subsequent stratification into those who received treatment with matching scores ≥50% versus <50%. For patients navigated to a secondary clinical trial, to which they consented, the doses used were as per the clinical trial for that cohort. Otherwise, dosing combinations of drugs were done according to safety rules gleaned from the literature[1,2]. If the combination of drugs had established dosing known from clinical trials in the literature, that dosing was utilized. If the dosing was unknown, we used data from our analyses of almost 75,000 patients treated in the literature[3,4] and further modified this after discussion in our MTB and consultation with our pharmacist (PharmD), as needed. Essentially, for de novo combinations, we started patients at about 50% of the usual dose of each drug for two-drug combinations, and at about one-third of the dose of each drug for three-drug combinations. Patients then received escalation of doses of drugs to tolerance while being monitored closely by their treating physicians. Combinations of drugs with overlapping toxicities were avoided. The safety of the protocol was also monitored by our Data Safety Monitoring Board.

**Medication acquisition specialist and clinical trial coordinators.** To obtain medications in a timely fashion, a medication acquisition specialist and clinical trial coordinators attended the face-to-face MTBs. They were available immediately on physician request at other times. Their purpose was to assist with obtaining on- and/or off-label approved drugs, as well as information about relevant clinical trials utilizing investigational or off-label drugs.

**Matching score.** An exploratory scoring system (matching score) was developed, as described previously[5]. The matching score was calculated post hoc by investigators blinded to the outcomes at the time and it was based on the actual drugs administered. Under this system, the higher the matching score, the better the match. In general, the matching score was calculated by dividing the number of alterations matched in each patient’s tumor (numerator) by the number of characterized aberrations in that patient’s tumor (denominator). For instance, if a patient’s tumor harbored six genomic aberrations and they received two drugs that targeted the patient’s genomic alterations, the matching score would be 3 out of 6 or 50%. This is because certain drugs targeted more than one alteration (for example, many small molecule inhibitors often have activity against multiple kinases) and were counted as matches for each identified genomic alteration that was matched.

Other considerations were as follows: two mutations in the same gene that had the same effect (for example, loss of function) counted as one alteration in the scoring system; the higher the matching score, the better the match. Two different structural alterations in the same gene (for example, amplification and mutation) were counted as two aberrations in the denominator since they have different functional effects (for example, overexpression versus activation); two drugs targeting the same alteration were counted twice in both the numerator and denominator; and all variants of unknown significance were excluded; in the case of cell cycle inhibitors that targeted CDK4/6, we counted any concomitant CDK4/6 and CDK9/2A/B alterations (N = 2 patients) or CCND1/2/3 and CDK9/2A/B alterations (N = 2 patients) as one alteration and one drug target in the numerator and denominator because the CDK9/2A protein, p16[5,6], directly binds to the CDK4/CDK6 cyclin inhibitors, thus regulating cell cycle. If TP53 alterations were matched to antiangiogenic agents, based on data showing that TP53 mutations are associated with upregulation of VEGF-A and that treatment of TP53-mutant tumors with antiangiogenic agents is associated with improved outcomes[7,8]; if the patient was treated with immunotherapy (for example, anti-PD-1 or anti-PD-L1 checkpoint inhibitors), the matching score was 100% for PD-L1 high positive, TP53-high, MSI-high results (or MHL1, MS12, MS16, PMS2 alterations), or if none of the aforementioned were known, but the patient had ≥8 genomic alterations (N = 1 patient) based upon the assumption of a high TMB; if the PD-L1 IHC was low positive, the TMB was intermediate, or there was a C2D4 (PD-L1) antibody; if the matching score was ≥50%; if the patient received a combination of a checkpoint inhibitor and a gene-targeted drug that matched one or more of their genomic alterations, the score was >50%. As an example, if a patient had intermediate TMB and an MET amplification, as well as a TP53 mutation, and was treated with nivolubum and the MET inhibitor, crizotinib, the matching score would be >50%; if more than one NGS report was available, the alterations in each report were counted (since there can be heterogeneity between tissue biopsies); if a patient’s regimen included drugs that did not match any alteration, those drugs received a matching score of 0. The cutoff of 50% for the analyses of low versus high matching scores was chosen according to the minimum P value criteria[9]. See Supplementary Text for selected examples of therapy and matching score methodology.

**Alternative approach to matching score for immune checkpoint blockade.** There may be alternative approaches to scoring matches, especially in the case of immunotherapy, since one drug may be used in some circumstances to theoretically target multiple genomic alterations. It is becoming increasingly evident that immune checkpoint blockade and genomics are not separate silo-established synergy (for example, the FDA-approved combinations of dabrafenib and trametinib for BRAF mutations, or pertuzumab and trastuzumab for ERBB2 alterations); only if the patient was matched (in part) based on hormone (estrogen receptor) positivity in the tissue biopsied for genomic analysis, the hormone receptor component would then be nominated. The numerator was the number of alterations matched and the denominator, all variants of unknown significance were excluded; in the case of cell cycle inhibitors that targeted CDK4/6, we counted any concomitant CDK4/6 and CDK9/2A/B alterations (N = 2 patients) or CCND1/2/3 and CDK9/2A/B alterations (N = 2 patients) as one alteration and one drug target in the numerator and denominator because the CDK9/2A protein, p16[5,6], directly binds to the CDK4/CDK6 cyclin inhibitors, thus regulating cell cycle. If TP53 alterations were matched to antiangiogenic agents, based on data showing that TP53 mutations are associated with upregulation of VEGF-A and that treatment of TP53-mutant tumors with antiangiogenic agents is associated with improved outcomes[7,8]; if the patient was treated with immunotherapy (for example, anti-PD-1 or anti-PD-L1 checkpoint inhibitors), the matching score was 100% for PD-L1 high positive, TP53-high, MSI-high results (or MHL1, MS12, MS16, PMS2 alterations), or if none of the aforementioned were known, but the patient had ≥8 genomic alterations (N = 1 patient) based upon the assumption of a high TMB; if the PD-L1 IHC was low positive, the TMB was intermediate, or there was a C2D4 (PD-L1) antibody; if the matching score was ≥50%; if the patient received a combination of a checkpoint inhibitor and a gene-targeted drug that matched one or more of their genomic alterations, the score was >50%. As an example, if a patient had intermediate TMB and an MET amplification, and as well as a TP53 mutation, and was treated with nivolubum and the MET inhibitor, crizotinib, the matching score would be >50%; if more than one NGS report was available, the alterations in each report were counted (since there can be heterogeneity between tissue biopsies); if a patient’s regimen included drugs that did not match any alteration, those drugs received a matching score of 0. The cutoff of 50% for the analyses of low versus high matching scores was chosen according to the minimum P value criteria[9]. See Supplementary Text for selected examples of therapy and matching score methodology.
Four patients (47, 121, 155, A011) had high TMB and received immunotherapy, while four more patients (102, 115, A035, A037) had intermediate TMB and received immunotherapy. Following evaluation with this alternative matching score approach, all eight patients remained in their same assigned group with matching scores >50%. Thus, none of the results changed. Furthermore, if we assessed CD274 amplification targeted with immunotherapy as one alteration targeted by one drug, the two patients (141, A016) with CD274 amplification and 11 or 12 other alterations who received immunotherapy remained in the matching score ≤50% group. Again, the group assignments of the two patients did not change with the alternative scoring. See Supplementary Text for selected examples of immunotherapy and alternative matching score methodology.

Response/outcome end points. All patients were assessed using RECIST v.1.1 by board-certified radiologists at both University of California, San Diego and Avera Cancer Institute. Selected Avera cases were secondarily reviewed at University of California, San Diego. The following radiological end points were considered: (1) DCR = rate of stable disease ≥6 months + partial response + complete response according to RECIST v.1.1 (ref. 1); (2) PFS of therapy given under the I-PREDICT protocol (PPS2); (3) PFS2 versus PFS1 (immediate prior line of therapy using patients as their own controls) (refs. 1, 11); and (4) percentage of patients with a PPS2/PPS1 ratio ≥1.3 (ref. 1). Stable disease, partial response, or complete response were initially determined per the assessment of the treating physician. Patients with ongoing stable disease for less than six months at the date of data cutoff could not be evaluated for the DCR. However, they were evaluable for PFS and overall survival. PFS was defined as the time from the beginning of therapy to disease progression, or the time to last follow-up for patients that were progression-free. Patients who were progression-free on the date of last follow-up were censored on that date. Overall survival was defined as the time from the beginning of therapy to death, or last follow-up date for patients who were alive (the latter were censored on that date). The cutoff date of the analysis was 15 August 2017 and cutoff date for patients included was consent by the end of June 2017.

Patients could not be evaluated for comparison of PFS on study to prior PFS if prior PFS was for therapy given in the adjuvant or neoadjuvant setting, or if prior therapy included a matched drug. Patients could not be evaluated for therapy outcome if: (1) they did not receive treatment by 6 months after consent; (2) had not received at least 10 d of therapy (if the drug was taken orally); (3) had not received two doses of an intravenous drug given once every two weeks or more often; or (4) had received only one dose of drug in case of an intravenous drug given every three weeks or less frequently.

Data collection and analysis. All data was collected in a Microsoft Access 2013 (v.13.0) database. Logistic regressions were performed for binary end points. HRs for PFS and overall survival were analyzed by the Kaplan–Meier method and the log-rank test was used to compare the survival end points by groups. Cox regression models were used as multivariable analysis when appropriate for survival end points. The importance of a prognostic factor was assessed by the OR, using the log-rank test and logistic regression/Cox regression models. Statistical analysis was performed by M.S. and R.O. and verified by J.J.L. using SPSS v24.0 (IBM Corporation).

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability
Supporting source data for all figures and tables are made available in Supplementary Table 1 and Supplementary Table 2.

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Extended Data Fig. 1 | Consolidated Standards of Reporting Trials (CONSORT) diagram, which includes the 149 patients that consented to I-PREDICT.

*Treated evaluable patients includes patients who received >10 d of treatment for drugs given on a daily basis (generally drugs given by mouth) or at least two doses of a drug normally given every two weeks or more frequently (the latter generally being intravenous drugs). Only patients whose treatment was reviewed and validated by data analysis lockdown are included. **One patient had inadequate tissue for NGS and declined biopsy; he was later reenrolled after he agreed to undergo biopsy. One treated patient who initially was believed to have prior therapy was found, after data lockdown analysis, to have not received the prior regimen.
Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- n/a
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☐ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
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☐ For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted
  - Give P values as exact values whenever suitable.
☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐ Estimates of effect sizes (e.g. Cohen's d, Pearson's r), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

| Data collection | Microsoft Access 2013 (version 15.0) |
| Data analysis   | SPSS version 24.0                   |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Supporting raw data for all figures and tables are be made available in Supplemental Tables 1-2.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences  ☐ Behavioural & social sciences  ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf
Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size

Sample size: This feasibility study has descriptive primary analyses to characterize the study findings. There were three groups and only results from Group 3 (previously treated unresectable/metastatic patients) are described herein; groups 1 and 2 (treatment-naive unresectable and treatment-naive metastatic with lethal diseases) are not described and are accruing. A Molecular Tumor Board recommended therapy, but treatment decisions were the choice of the physician. The primary study objective was to determine the feasibility of using molecular testing to determine therapy for patients with previously treated cancers with incurable biology (≥50% 2-year cancer-associated mortality). Primary and secondary endpoints included: the proportion of patients who receive molecularly targeted matched treatment after recommendations based on genomic analysis (primary endpoint); proportion of patients with actionable genomic alterations and overall response rate, regression rate, progression-free and overall survival and incidence of high-grade adverse events (secondary and exploratory endpoints). Relevant hypotheses included: patients who receive targeted therapy based upon recommendations from actionable genomic alteration(s) will yield anti-tumor activity; the PFS on matched therapy will be greater than on their last unmatched therapy. For evaluation of treatment decisions, the Study Committee assessed the degree of matching that occurred using the best information available at the time of the data evaluation. The original plan was to enroll 75 evaluable patients. Since this was a hypothesis-generating, descriptive trial, this number was later expanded to permit enrollment of up to 1,000 patients. Based on the fact that a minority of patients is usually matched to therapy on precision medicine trials, it was expected that we would show feasibility with 40% of the 75 evaluable patients (N=30) being matched and 60% treated with no matched therapy (N=45). With the sample size of 30 matched versus 45 unmatched, we would have 79% power to detect a response rate of 0.25 versus 0.05 in the two arms with one-sided 10% type I error rate using the continuity corrected chi-square test. We calculated we would have more than 80% power to detect the difference between the two groups using the log-rank test when the median PFS is 4 months and 2 months for the two arms, respectively. We analyzed group 3 after enrollment of 149 patients; feasibility to administer matched therapy was confirmed because, of the 83 evaluable treated patients, 73 (88% of evaluable treated patients and 49% of enrolled patients) were matched. The ability to compare matched and unmatched patient was limited by the small number of evaluable unmatched patients (N=10). As part of the descriptive analysis, we evaluated the effect of degree of matching in patients with low versus high matching scores (N=55 versus 28 patients).

Data exclusions

No data were excluded from analysis.

Replication

As this is a clinical trial, no replication was possible or performed.

Randomization

This is a non-randomized clinical trial.

Blinding

Matching designation was confirmed by the senior investigators (RK and JS), who were blinded at the time of designation to the outcomes.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

| n/a | Involved in the study |
|-----|-----------------------|
| ☐   | Antibodies           |
| ☒   | Eukaryotic cell lines |
| ☒   | Palaeontology        |
| ☐   | Animals and other organisms |
| ☒   | Human research participants |
| ☒   | Clinical data        |

Methods

| n/a | Involved in the study |
|-----|-----------------------|
| ☒   | ChIP-seq              |
| ☒   | Flow cytometry        |
| ☒   | MRI-based neuroimaging |

Antibodies

Antibodies used

PD-L1 Antibodies:
PD-L1 status (performed by Foundation Medicine) was assessed by immunohistochemistry using the U.S. Food and Drug Administration (FDA)-approved Dako 22C3 PD-L1 pharmDx qualitative immunohistochemical assay (pre-diluted by manufacturer), which localizes PD-L1 expression in both tumor cells and tumor-infiltrating immunocytes within formalin-fixed, paraffin-embedded (FFPE) tissue sections. Detection was performed using the Ventana Optiview DAB detection system on the Ventana Benchmark ULTRA platform. If any of these tests had been performed as part of routine physician practice before enrollment, the results could be utilized for recommending therapy.

Hormone Receptor Antibodies:
The hormone receptor antibody analyses were performed as part of standard clinic care at each institution. Estrogen receptor (ER) status was assessed by immunohistochemistry using the Ventana ER (SP1) antibody (pre-diluted by manufacturer) within FFPE tissue sections and detection was performed using the Ventana automated platform at UC San Diego. This test was cleared by the FDA and was used per manufacturer's instructions. ER status was assessed by immunohistochemistry using the Dako DS ER (1:30 dilution; until 9/2015) and Dako EP1 Ready-To-Use Clone (dilution: 1:270; 9/2015-2017) at Avera Cancer Institute.
Validation

This test has been cleared or approved by the U.S. Food and Drug Administration and is used per manufacturer’s instructions. Performance characteristics were verified by Foundation Medicine, Inc. per Clinical Laboratory Improvement Amendments (CLIA ’88) requirements in accordance with College of American Pathologists (CAP) checklist requirements and guidance.

Human research participants

Population characteristics

Characteristics of human research subjects included patient demographics (age, gender, ethnicity), tumor type, tumor molecular analyses, prior and current therapies, lines of therapy, matching score, objective radiologic responses, and progression-free and overall survival outcomes.

Recruitment

Patients seen at UC San Diego Moores Cancer Center and Avera Cancer Institute were enrolled. Enrolled patients were offered genomic/molecular testing and the potential for personalized, precision oncology therapy. Not all medical oncologists in each cancer center enrolled patients. This was not a randomized trial.

Ethics oversight

The Investigation of Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT) was reviewed and approved by the UC San Diego Protocol Review and Monitoring Committee (PRMC) and the Human Research Protections Program (HRPP)/Institutional Review Board (IRB) (Protocol 141758). It was subsequently reviewed and approved by the Avera Cancer Institute PRMC and IRB (Protocol 2015.058). The safety of the protocol was also monitored by the UC San Diego Moores Cancer Center Data Safety Monitoring Board (DSMB).

Early safety stopping rule: Simon’s two-stage design was used. The null hypothesis was that the true response rate is 0.05 and this would be tested against a one-sided alternative. In the first stage, 13 patients would be accrued. If there were 0 responses in these 13 patients, the study would be stopped. Other early stopping rules were for >10 drug related severe adverse events and >10 drug-related Grade 4-5 toxicities. Early stopping was not triggered in the study.

Clinical data

Clinical trial registration

NCT02534675

Study protocol

Study protocol available in Supplemental Files.

Data collection

UC San Diego Health and Avera Cancer Institute from 02/13/2015-06/30/2017

Outcomes

All patients were assessed using RECIST version 1.1 by board-certified radiologists at both UC San Diego and Avera Cancer Institute. Selected Avera cases were secondarily reviewed at UC San Diego. The following radiological endpoints were considered: (i) disease control rate (DCR) = rate of [stable disease (SD) ≥6 months + partial response (PR) + complete response (CR)] according to RECIST 1.1; (ii) progression-free survival (PFS) of therapy given under the I-PREDICT protocol (PFS2); (iii) PFS2 versus PFS1 (immediate prior line of therapy using patients as their own control); (iv) percent of patients with a PFS2/PFS1 ratio ≥1.3; and (v) overall survival (OS). SD, PR, or CR was initially determined per the assessment of the treating physician. Patients with ongoing SD for less than six months at the date of data cut off were considered inevaluable for the DCR. However, they were evaluable for PFS and OS. PFS was defined as the time from the beginning of therapy to disease progression, or the time to last follow up for patients that were progression-free (patients that were progression-free on the date of last follow up were censored on that date). OS was defined as the time from the beginning of therapy to death, or last follow-up date for patients who were alive (the latter were censored on that date). The cut-off date of the analysis was August 15, 2017 and cut-off date for patients included was consent by end of June 2017.

Patients were inevaluable for comparison of PFS on study to prior PFS if prior PFS was for therapy given in the adjuvant or neo-adjuvant setting or if prior therapy included a matched drug. Patients were considered inevaluable for therapy outcome if: (i) they did not receive treatment by 6 months after consent; (ii) patients had not received at least 10 days of therapy (if the drug was taken orally); (iii) patients had not received two doses of an intravenous drug given once every two weeks or more often; or (iv) patients had received only one dose of drug in case of an intravenous drug given every three weeks or less frequently.