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Basket Trials and the MD Anderson Precision Medicine Clinical Trials Platform

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Abstract

Precision Medicine incorporates information regarding tumor biology involved in patients' carcinogenesis and individualized treatment of patients using drugs that inhibit the molecular basis of their disease. Implementation of precision medicine accelerated the drug approval process, translating discoveries in basic science and biotechnology into patient care. Clinical trials with innovative or adaptive design including "basket" and "umbrella" trials explore personalized therapies against in selected tumor types and/or across tumor types. In 2007, we started the Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT), the first Precision Medicine program across tumor types. We demonstrated that therapy matched to patients' tumor molecular profiling is associated with improved rates of response, progression-free survival and overall survival compared to non-matched targeted therapy. We have now entered a new era of Precision Medicine that includes comprehensive tumor testing and multiple innovative modalities hoping to overcome the complexity of tumor biology to improve patient outcomes.

Keywords

Basket trials; precision medicine; personalized medicine; targeted therapy; genomic profiling

Introduction

Precision medicine represents a revolutionary step in the management of patients with cancer. This therapeutic strategy takes into consideration patients' tumor genetic abnormalities, immune signatures and other biologic characteristics to select anticancer therapy. In 2007, we initiated IMPACT (Initiative for Molecular Profiling and Advanced Cancer Therapy), the first Personalized Medicine study across tumor types. We demonstrated that in patients with advanced cancer who participated in phase I clinical trials, matched targeted therapy was associated with improved rates of response, progression-free survival and overall survival compared to patients who received non-matched targeted

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Conflict of interest

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therapy. Following our report of encouraging results of IMPACT in 2011, several large trials across tumor types have been initiated worldwide, building on this concept with the goal to accelerate drug development, implementing the personalized medicine approach. To address the genetic variability of tumors and the rarity of tumor alterations, these studies use innovative, adaptive design that enables assessment of drugs that are effective in a small proportion of patients with specific characteristics, leading to expedited drug approval.

The promise of precision oncology has been realized in individual patients treated with matched targeted therapies, and it is exemplified in patients with melanoma using drugs targeting the MEK/RAF pathway^{1,2}, or with lung adenocarcinoma using drugs targeting epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), c-ros oncogene 1 (ROS1)³ or other alterations. The field of precision oncology has been expanded with the advent of immunotherapy. Many tumor types respond to these therapies that unleash the immune system against cancer cells, and elicit prolonged disease control.

Currently, a strikingly high number of clinical trials are assessing novel anticancer agents and biomarkers. Significant ongoing efforts focus on understanding mechanisms of response and resistance to precision oncology strategies which include targeted therapy, immunotherapeutic agents, T-cell therapy, vaccines, and multiple other modalities. Despite these efforts, comprehensive tumor analysis that includes tumor and cell-free DNA analysis, tumor immune markers, transcriptomic, and proteomic analysis, to optimize anticancer therapy is not widely adopted.

In this paper, we describe our Precision Medicine Program and selected clinical trials across tumor types in the Department of Investigational Cancer Therapeutics at MD Anderson Cancer Center.

The IMPACT Program

The hypothesis of IMPACT was that selection of therapy based on patients' tumor molecular analysis would improve clinical outcomes compared to the standard approach. In 2007, it was widely accepted that due to the rarity of specific molecular alterations in solid tumors, it would be inefficient to perform molecular profiling to select therapy, in contrast to the paradigm shift achieved with this approach in selected hematologic malignancies. For instance, imatinib dramatically changed the overall survival of patients with newly—diagnosed chronic myeloid leukemia, targeting bcr-abl, which is expressed in 95% of patients with this disease. Despite this notion, we initiated IMPACT, which was enabled by the development of a specialized department for early phase clinical trials across tumor types at MD Anderson Cancer Center (Department of Investigational Cancer Therapeutics) and the initiation of early phase clinical trials across tumor types. Until the initiation of IMPACT, selection of phase I clinical trials with novel agents was random and therefore not only patients were not enrolled on the most promising trials with investigational agents for their tumor type and alteration, but also the use of these drugs was inefficient. During the first years of IMPACT, a relatively large amount of tumor DNA was required to perform PCR assays to identify specific mutations, such as BRAF, KRAS, or EGFR. This challenge was addressed with rapid advances in technology, leading to availability of multigene assays,

with up to 50 genes in 2012, followed by assays for hundreds of genes using advanced next —generation sequencing methodologies. In parallel, multiple investigational agents gained Food and Drug administration (FDA) approval based on their safety and significant antitumor activity targeting specific molecular alterations for specific tumor types.

In IMPACT, results of patients' tumor molecular profiling were used to select treatment on a clinical trial. The available clinical trials included therapeutic agents against various targets. Patients with targetable alterations were treated with matched targeted therapy, when these trials were available. If clinical trials with matched targeted therapy were unavailable, patients were treated with drugs not matched to their molecular profiling (non-matched targeted therapy). The study was exploratory in nature ().

Our first report on IMPACT included 1,144 sequential patients with advanced cancer who had molecular profiling and were treated with this approach in our Department. Overall, 460 (40.2%) had 1 molecular aberration.⁴ Patients were heavily pretreated with a median of 5 prior therapies. Of patients with 1 alteration, 175 patients were treated with matched targeted therapy and 116 patients with non-matched targeted therapy. Although this was not a randomized study, the baseline characteristics were similar between the two patient groups (matched and non-matched therapy). The overall response rates were higher in patients treated with matched targeted therapy compared to those treated with non-matched therapy (27% vs. 5%; $P < .0001$). The median time to treatment failure (TTF) was 5.2 months in the matched therapy group vs. 2.2 months in the non-matched therapy group ($P < .0001$). The median overall survival was 13.4 months in the matched targeted therapy group compared to 9.0 months in the non-matched therapy group ($P = .017$). Since this was not a randomized study, we compared TTF associated with phase I studies with TTF associated with patients' prior systemic therapy, using a paired time-to-event analysis. TTF is expected to be shorter with subsequent lines of therapy compared to TTF associated with earlier lines of individual patients' therapy. In patients with 1 mutation, matched therapy was associated with longer median TTF compared to TTF in their previous line of therapy (5.2 vs. 3.1 months; $P < .0001$). The median TTF for patients with a molecular aberration treated with matched therapy was 1.68 times longer than that of patients' TTF on previous systemic therapy. In the non-matched therapy group, TTF was not different compared to TTF with their previous systemic therapy (2.2 vs. 2.8 months, respectively, $p = .35$). Taking into consideration that patients were heavily pretreated, the superiority of matched targeted therapy compared to non-matched therapy in overall survival was intriguing. This superiority was statistically significant, regardless of treatment with investigational BRAF inhibitors, that later gained FDA approval, as demonstrated in subset analyses. Multivariate analysis of patients with 1 molecular aberration demonstrated that matched therapy was an independent factor predicting higher rates of overall response ($P = .001$) and TTF ($P = .0001$)⁴.

In 61 evaluable patients with 2 or 3 molecular alterations, there was no statistical difference in clinical outcomes between patients who received matched targeted therapy and those treated with non-matched targeted therapy. The objective response (complete response and partial response) rates were 14% (5 of 36 patients) in the matched targeted therapy vs. 0% in the non-matched targeted therapy groups (0 of 25 patients, $p = .14$). The median TTF in the matched targeted therapy and the non-matched therapy groups were 3.02 and 2.7 months,

respectively ($p=.79$). The median overall survival were 10.6 months and 17.0 months, respectively, ($p=.28$). These results in patients with 2 or 3 molecular alterations may be attributed to the small number of patients and/or the complexity of effectively inhibiting the function of multiple alterations in addition to coexisting mechanisms of carcinogenesis, resulting in measurable clinical benefit and suggest that novel therapeutic modalities are needed to improve the clinical outcomes of these patients.

In 2014, we analyzed an independent set of patients, who were treated with the same approach and we performed a validation analysis combining this patient set with our previously published patients⁵. A 2-month landmark analysis was performed to assess the correlation between overall survival, progression-free survival and treatment response which was dichotomized by matched targeted therapy and non-matched therapy. The landmark method eliminates the negative influence of early death, and it is used to avoid selection bias in the correlation of survival or progression-free survival with response by type of therapy (matched targeted therapy vs. non-matched targeted therapy)^{6,7}. Validation analyses demonstrated that in patients with one alteration, matched targeted therapy ($n=143$) compared to non-matched therapy ($n=236$) was associated with a higher rate of overall response (12% vs. 5%, $P < .0001$), and longer progression-free survival (median, 3.9 vs. 2.2 months, $P=.001$) and overall survival (median, 11.4 vs. 8.6 months, $P=.04$). In the matched targeted therapy group, using 2-month Landmark analysis the median overall survival of responders was 30.5 months compared to 11.3 months of non-responders ($p = 0.01$). The respective median progression-free survival was 38.7 months in responders compared to 5.9 months in non-responders (2-month landmark analysis, $P < .0001$). In the non-matched therapy group, the overall results were dismal and there was no statistical difference between responders and non-responders.⁵ Given the limitations of molecular profiling to understand complete mechanisms of carcinogenesis and the relatively few available targeted therapies, this validation analysis confirmed that matched targeted therapy was associated with higher rates of response, progression-free survival and overall survival compared to non-matched therapy.

Following the report of these two patient sets, we analyzed a subsequent independent patient group of 1,436 patients. Of these patients, 1,179 (82.1%) had 1 alterations, and included 637 who had 1 actionable aberrations⁸. Overall, 390 patients were treated with matched targeted therapy and 247 patients with non-matched targeted therapy. When compared to the unmatched group, the matched targeted therapy group had higher rates of complete and partial response (11% v 5%; $P = .01$), longer failure-free survival (median, 3.4 v 2.9 months; $P = .001$), and longer overall survival (median, 8.4 v 7.3 months; $P = .04$). The median overall survival for the matched targeted therapy group (responders vs. non-responders) was 23.4 vs. 8.5 months ($P < .001$), whereas for the non-matched therapy group, the respective values were 15.2 months vs. 7.5 months ($P = .43$)⁸.

We also performed 2-month landmark analyses for survival and PFS, as previously described.⁵⁻⁷. To increase the statistical power, these analyses included 379 patients from the validation patient group and 291 patients from previously published patient series. Matched targeted therapy ($n = 143$) compared to non-matched targeted therapy ($n = 236$) was associated with a higher overall response rate (12% vs. 5%; $P < .0001$), longer progression-

free survival (median, 3.9 vs. 2.2 months; $P = .001$), and longer overall survival (median, 11.4 vs. 8.6 months; $P = .04$). Multivariate analyses demonstrated that MTT was an independent factor predicting higher rates of response ($P < .015$) and progression-free survival ($P < .004$). The 2-month landmark analyses in the matched therapy group showed that the median survival of responders was 30.5 months compared to 11.3 months for non-responders ($P = .01$); and the median progression-free survival was 38.7 months compared to 5.9 months, respectively ($P < 0.0001$). The respective values in the non-matched therapy group were 9.8 and 9.4 months ($P = .46$) for overall survival and 8.5 and 4.2 months for progression-free survival ($P = .18$)⁵.

To assess the clinical significance of specific genomic characteristics, a separate analysis was performed for patients with TP53 mutations. In this subset analysis, treatments targeting the anti-vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathway were added to matched therapy^{9–11}. The rates of objective response rates were 11% in the matched therapy group compared to 5% in the non-matched therapy group. Similarly, failure-free survival and overall survival was longer in the matched group compared to the non-matched group ($P = .012$ and $P = .07$, respectively). These results indicated that patients with TP53 mutations benefit from anti-VEGF therapy.

To assess the role of targeting PI3K/Akt/mTOR alterations in the presence of RAS/RAF/MEK alterations, we analyzed patients with PI3K/Akt/mTOR alterations with concomitant RAS/RAF/MEK alterations. No statistically significant difference was noted in clinical outcomes between patients treated with PI3K/Akt/mTOR inhibitors and those who did not receive these inhibitors. This observation was in line with prior hypothesis that inhibiting PI3K/Akt/mTOR pathway alone in the presence of RAS/RAF/MEK pathway alterations does not improve clinical outcomes^{12,13}.

The IMPACT2 Program

Following the encouraging results from the first IMPACT study, in 2014 we initiated IMPACT 2 (), a randomized prospective study evaluating molecular profiling and targeted therapy in metastatic cancer. The primary objective of this study is to determine whether patients with advanced cancer treated with matched targeted therapy, selected based on genomic tumor profiling, have longer progression-free survival than those whose treatment is not selected based on their molecular profile. To be eligible, patients must have metastatic disease treated with established standard-of-care therapy, or physicians have determined that such established therapy is not sufficiently efficacious, or patients have declined to receive standard-of-care therapy. Patients must have measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and tumor accessible to biopsy. Comprehensive tumor profiling from fresh biopsies is used to assign therapy. Patients with FDA-approved drugs for the molecular alterations and indications are treated with these approved drugs. Patients with alterations or other information from their profiling which includes genomic profiling, immune markers, mutational tumor burden, or microsatellite instability status and/or transcriptomic analysis are reviewed by the study's tumor board. Treatment options that include clinical trials with investigational drugs or with off-label FDA approved drugs, as single agents or in combination, are discussed in a multidisciplinary

conference for treatment planning. Subsequently, results of tumor molecular profiling and eligibility criteria for clinical trials are discussed with the patients who participate in the study, prior to treatment assignment. Taking into consideration that treatments are experimental and their antitumor activity has not been determined, patients are considered for randomization to matched therapy vs. treatment not taking into consideration patients' tumor profiling. After 391 patients were accrued on the study, the protocol was revised to allow patients to select matched or non-matched therapy or whether they wish to be randomized (Figure 1). The study continues to enroll patients.

The WINTHER Trial

Building on the results of our first IMPACT trial and on evolving data from collaborating institutions assessing tumor RNA profiling, in 2012 we contributed to the initiation of the WINTHER trial (). This study was conducted in 5 countries, through the Worldwide Innovative Network (WIN) Consortium for personalized cancer therapy. The rationale for treatment selection was based on the analysis of fresh biopsy-derived DNA sequencing (arm A; 236-gene panel) or RNA expression (arm B, comparing tumor to normal tissue)¹⁴. The priority was targeted therapy towards DNA genomic alterations, while RNA-guided therapy was considered as exploratory. The primary endpoint of the study was the ratio of progression-free survival PFS1 (in WINTHER) compared to patient's progression-free survival on the most recent regimen on which the patient had experienced progression (PFS2). A clinical management committee comprised of investigators from five participating countries recommended therapies and prioritized genomic matches. The patients' treating physicians made the final decision and determined the therapy given. Afterwards, a matching score was calculated for each patient based on the drug(s) that the patients received using the number of matched alterations from DNA analysis divided by the total alteration number (arm A) or drugs matched to RNA expression profiling (arm B). Between April 2013 and December 2015, 303 patients consented to participate in the trial and 107 (35%) patients received treatment. Of patients available for response, 69 patients were treated in arm A and 38 patients in arm B. In these 107 evaluable patients, the overall rate of complete response, partial response, and stable disease lasting ≥ 6 months was 26.2% (23.2% and 31.6% in arms A and B respectively; $P = .37$). The ratio of PFS2/PFS1 was 1.5 in 22.4% of patients but the study pre-specified primary endpoint was not met. In this study, a higher matching score was associated with longer progression-free survival ($P < .05$). The study demonstrated that in addition to genomic testing, transcriptomic profiling provides valuable information to offer more matched therapies to patients, leading to favorable progression – free survival.

Collaborative trials across tumor types

Patients treated with the Precision Medicine approach can be enrolled on industry-sponsored trials or on the following large trials across tumor types that are available in many institutions in the United States, including MD Anderson Cancer Center. These large trials provide personalized matched therapy (targeted therapy or immunotherapy) at no cost to selected patients with available tumor molecular profiling who meet eligibility criteria for treatment.

NCI Programs

In December 2013, the United States National Cancer Institute (NCI) launched the NCI-MPACT (Molecular Profiling-Based Assignment of Cancer Therapy) and in August 2015 the NCI-MATCH (Molecular Analysis for Therapy Choice) study. Through these trials the NCI-designated institutions can offer to patients with advanced metastatic cancer or rare tumors access to tumor molecular profiling and/or targeted agents, if patients meet specific eligibility criteria for molecular testing and/or treatment.

The NCI-MPACT () is a phase II trial that enrolls patients with advanced refractory cancers to one of the four pre-identified treatment arms based on patients' molecular profiling aberrations. The treatment arms are: Arm 1, veliparib (ABT-888, a PARP inhibitor) and temozolomide; Arm 2, adavosertib (WEE1 inhibitor) and carboplatin; Arm 3, everolimus and Arm 4, trametinib. The primary objective of the study is to evaluate the proportion of patients with objective response and the secondary objective is the progression-free survival. The target number of enrolled patients in NCI-MPACT is 700.

The NCI-MATCH (), also known as the MATCH study was initiated as a collaboration with the ECOG-ACRIN Cancer Research Group. This is a phase 2 clinical trial to treat patients with advanced refractory cancer, lymphoma, or multiple myeloma based on the precision medicine concept. Enrolled patients are to receive preassigned treatment at no cost based on their molecular profiling. The study drugs used in the MATCH trials are either FDA—approved drugs or investigational agents with evidence of antitumor activity. Several treatment arms were available with the plan to enroll 35 patients per arm; however, arms with common genetic alterations were to enroll up to 70 patients per arm. Overall, at least 1 therapeutic agent is to be evaluated in each arm across various tumors. The primary objective of this study is to assess the proportion of patients with objective response to the predetermined treatment arms. Initially, 3,000 patients were to be screened and to be treated in 10 arms. After an interim analysis in 2016, the screening goal was increased to 6,000 patients and the treatment arms increased to 24 and were expanded to 30 arms in 2017. As of May 2019, > 6,400 patients were enrolled. The estimated completion date is June 30, 2022.

Targeted Agent and Profiling Utilization Registry (TAPUR)

In March 2016, the American Society of Clinical Oncology (ASCO) initiated TAPUR (), a non-randomized clinical trial to assess the safety and efficacy of targeted anticancer therapies that are commercially available. The goal of TAPUR is to describe the anti-tumor activity and toxicity of commercially available, targeted therapy of patients with advanced cancer whose tumor harbors a genomic variant known to be a drug target; to learn from the real- world practice of prescribing targeted therapies; and to educate oncologists regarding implementation of precision medicine in clinical practice. Enrolled patients with advanced, refractory cancer with potentially actionable genomic alterations are to receive FDA-approved matched targeted therapies that are offered at no cost to patients. Patients must meet the eligibility criteria for treatment, based on TAPUR's matching rules of drugs targeting specific alterations. The target number of enrolled participants is currently estimated to be 2,980 patients and multiple treatment arms are available. TAPUR's primary

endpoint is to evaluate the objective response rate, defined by the percentage of enrolled patients with a specific alteration and tumor type who have complete or partial response or stable disease according to standard response criteria at 16 weeks of treatment. The secondary endpoint is to assess the overall survival, which is measured from enrollment on study until death from any cause assessed throughout the study, with a follow-up up to 3 years.

Discussion

In the era of precision oncology, clinical trials with innovative or adaptive design including “basket” and “umbrella” trials are used to accelerate the drug approval process. Basket trials (also referred as pan-tumor or tissue-agnostic trials) are designed to evaluate the effect of a drug that targets a single mutation or a specific pathway in various tumor types (Figure 2)¹⁵. These trials are simple, including specific treatment arms for various tumors of origin and location “baskets”; or complex, evaluating multiple drugs across selected genetic alterations in various tumor types¹⁶. Typically, basket trials are designed to assess the safety, tolerability, and antitumor activity of candidate drugs, and if results appear promising, they are evaluated in larger trials with specific targets and/or tumor types. Based on significant antitumor activity demonstrated in basket trials, the FDA recently approved drugs irrespective of tumor origin. Examples are pembrolizumab for “microsatellite instability”-high tumors (May 2017) and larotrectinib for patients with neurotrophic receptor tyrosine kinase (NTRK) fusion without an acquired resistance mutation (November 2018)^{17–19}. Tissue-agnostic FDA approval prompted routine testing for microsatellite instability and NTRK fusion in patients with metastatic cancer and emphasize the clinical significance of comprehensive tumor analysis to select therapy.

Similar to our IMPACT studies, the NCI-MATCH and TAPUR studies are enrolling patients with advanced metastatic cancer who have exhausted standard treatments and/or with rare tumors and genetic alterations, for whom curative treatments do not exist. Although these studies have the potential to accelerate the implementation of precision oncology, they are still offered to patients with very advanced disease. To implement precision oncology, tumor profiling should be performed earlier at the stage of the disease. Clinical trials should explore tumor testing at the time of diagnosis and in frequent time intervals, as well as adjustment of treatment based on evolving tumor alterations to prevent disease progression and resistance to treatment.

After 12 years since we initiated IMPACT, we have now entered a new era of effective modern anticancer therapies. Following the FDA approval of multiple agents, patients with selected tumor types such as melanoma and lung adenocarcinoma have several treatment options that lead to improved clinical outcomes and prolonged overall survival. However, patients with other tumors, such as non-“microsatellite instability”-high colorectal cancer and pancreatic cancer have limited treatment options because these diseases are typically unresponsive to immunotherapy and their tumor alterations are infrequent or they cannot be targeted with the available drugs. Further translational research is warranted to build on the unprecedented progress we have witnessed with precision medicine.

In conclusion, a new landscape for advanced metastatic cancer has emerged with the advancement of the above large trials. The currently limited access to tumor testing and new drugs should expand to all patients. Future clinical advances might involve comprehensive tumor testing that includes whole genome sequencing, immune markers, transcriptomic, proteomic and metabolomics analyses; as well as cell-free DNA analyses. The current model of clinical trials should be modified to include multiple modalities investigating combinations of drugs, sequential regimens or promising innovative therapeutic approaches hoping to tackle the complexity of tumor biology to improve patient outcomes.

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Figure 1.
IMPACT 2 Trial algorithm

Figure 2.
Example of Basket Trial Design