Precision Medicine for Advanced Pancreas Cancer: The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) Trial

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Abstract

Purpose: Personalized medicine strategies using genomic profiling are particularly pertinent for pancreas cancer. The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial was initially designed to exploit results from genome sequencing of pancreatic cancer under the auspices of the International Cancer Genome Consortium (ICGC) in Australia. Sequencing revealed small subsets of patients with aberrations in their tumor genome that could be targeted with currently available therapies.

Experimental Design: The pilot stage of the IMPaCT trial assessed the feasibility of acquiring suitable tumor specimens for molecular analysis and returning high-quality actionable genomic data within a clinically acceptable timeframe. We screened for three molecular targets: HER2 amplification; KRAS wild-type; and mutations in DNA damage repair pathways (BRCA1, BRCA2, PALB2, ATM).

Results: Tumor biopsy and archived tumor samples were collected from 93 patients and 76 were screened. To date 22 candidate cases have been identified: 14 KRAS wild-type, 5 cases of HER2 amplification, 2 mutations in BRCA2, and 1 ATM mutation. Median time from consent to the return of validated results was 21.5 days. An inability to obtain a biopsy or insufficient tumor content in the available specimen were common reasons for patient exclusion from molecular analysis while deteriorating performance status prohibited a number of patients from proceeding in the study.

Conclusions: Documenting the feasibility of acquiring and screening biospecimens for actionable molecular targets in real time will aid other groups embarking on similar trials. Key elements include the need to better prescreen patients, screen more patients, and offer more attractive clinical trial options. Clin Cancer Res; 21(9); 2029–37. ©2015 AACR.

Introduction

Personalized anticancer therapy in clinical trials

Molecular profiling of tumor specimens has revealed potential targets for personalized anticancer therapy and seen a shift toward an emerging molecular taxonomy of cancer (1). Next-generation sequencing (NGS) is providing unprecedented opportunities to uncover the underlying genetic pathways driving cancer and is accelerating the development of personalized medicine strategies.
Translational Relevance

The Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial aims to improve outcomes by using molecular tumor information to guide treatment decisions for patients with advanced pancreatic cancer. Pancreatic cancer remains one of the most aggressive, lethal solid cancers, with an overall 5-year survival rate of less than 5%, unchanged in almost 50 years. Systemic therapy has been associated with low response rates and has proven only modestly effective in unselected patient populations. The addition of nab-paclitaxel to standard gemcitabine therapy and the FOLFIRINOX (5-fluorouracil, folinic acid, irinotecan, and oxaliplatin) regimen have incrementally improved outcomes of patients with metastatic disease, at the expense of toxicity.

Personalizing treatment according to the presence of molecular targets could improve outcomes for patients with this poor-prognosis disease. This is especially true given that the genetic landscape of pancreatic ductal adenocarcinoma is particularly heterogeneous, with most actionable genetic aberrations exhibiting a frequency of 10% or less.

Acquisition of high-quality biospecimens

Fundamental to the incorporation of tumor genome profiling into routine patient care is the timely and accurate acquisition of high-quality biospecimens. Commonly reported hurdles in obtaining tumor samples suitable for molecular analyses using next-generation sequencing (NGS) technologies encompass issues relating to accessibility of tumors for biopsy; tumor sample size, heterogeneity and cellularity; time elapsed from request to retrieve formalin-fixed paraffin-embedded (FFPE) tumor tissue and receipt at sequencing laboratory; extraction of adequate nucleic acid following formalin fixation of tissue; and returning results of clinical utility in a meaningful timeframe for patients with advanced disease.

Several issues make implementing personalized treatment particularly difficult in pancreas cancer, including the following: relatively inaccessible anatomical position; late presentation and aggressive course with a very poor prognosis of about 6 months when advanced; poor performance status; and medical comorbidity of the demographic usually affected.

Accessing metastatic lesions of pancreatic origin for tissue sampling can be problematic. Difficulties obtaining a suitable percutaneous or endoscopic ultrasound biopsy can be encountered when lesions are small, poorly defined on CT or ultrasound imaging, or inaccessible due to anatomic location. The common use of fine-needle aspiration (FNA) as the initial diagnostic procedure over core biopsy is an additional barrier to obtaining adequate tissue for molecular diagnostics.

When lesions are accessible for biopsy, cytololic examinations such as bile duct brushing or FNA biopsy are often the procedure of choice. Unfortunately, these procedures frequently provide insufficient material for molecular testing. Furthermore, even if a tissue biopsy is performed, pancreatic carcinoma may be relatively hypocellular, so that small numbers of neoplastic cells can be greatly outnumbered by nonneoplastic stroma and inflammatory cells. This hindered research efforts to sequence pancreas cancer until the technology advanced.

Formalin fixation of tumor tissue procured for diagnostic purposes is standard practice. Although it is advantageous that such specimens can satisfy the dual requirement for pathologic confirmation and DNA analyses, there can be issues with the quality of DNA obtained. Formalin fixation causes cross-linking of proteins as well as fragmentation and chemical modification of nucleic acids, resulting in poor-quality DNA. FNA specimens consistently yield low amounts of poor-quality DNA that is nonamplifiable and highly fragmented and thus commonly unfit for molecular analysis. Even when cell block preparations are made, FNA may be inadequate and unreliable for the clinical assessment of standard estrogen receptor, progesterone receptor, and HER2 receptor expression in primary breast tumor biopsies. Issues of poor-quality DNA from FFPE material can extend to core biopsies and archival resection specimens.

Timeliness of results

If a suitable tumor sample can be obtained successfully, the timeliness of results arises as the next challenge. Even as the capabilities of biorepositories are shifting toward processing of biospecimens in real time for therapeutic or clinical trial purposes, the logistics and infrastructure required to retrieve, process, and manage suitable biospecimens are often overlooked when budgeting and planning for such projects. The development of an efficient yet precise pathway supported by adequate infrastructure is necessary to process variable samples swiftly with accuracy and deliver clinicians high-quality actionable genomic data. Although the cost of genomic testing is decreasing, clinical costs associated with these approaches are increasing.

The IMPaCT trial

The IMPaCT trial is a molecularly guided clinical trial using NGS technologies for patients with recurrent or metastatic pancreatic ductal adenocarcinoma. The trial is run through the Clinical Trials Centre at The University of Sydney, Australia, and is managed by a multidisciplinary Trial Management Committee and overseen by a data safety management board (DSMB). IMPaCT was originally designed in 2010 as a randomized phase II trial assessing first-line treatment with standard chemotherapy (gemcitabine) versus personalized treatment based on specific tumor characteristics in patients with advanced pancreatic cancer (Fig. 1). Patients with tumors harboring mutations in homologous recombination and DNA damage repair genes (BRCA1, BRCA2, PALB2 or ATM), with amplified HER2 or with an absence of mutations in KRAS are eligible to receive targeted treatment.
The pilot phase of the IMPaCT clinical trial aimed to address key feasibility issues surrounding the collection and analysis of biospecimens, and we detail our experience here to guide others embarking on similar efforts. We discuss challenges including coordinating sample retrieval with clinical departments, optimal biospecimen types, analyte extraction using minimal and heterogeneous samples, and return of results, in order to better inform planning for future studies.

We demonstrate that with a specialized multidisciplinary team working closely with pathology departments and oncology centers, it is feasible to acquire and process tissue specimens, interrogate and report molecular results within a clinically relevant timeframe of ≤28 days.

**Materials and Methods**

**Patient referral and assessment of case suitability**

Patients with recurrent or de novo metastatic pancreas cancer were identified through the established clinical networks of the Australian Pancreatic Cancer Genome Initiative (APGI; Fig. 2). Each case was reviewed according to strict criteria to ensure suitability of the available tissue sample(s): an available FFPE tissue core or incision biopsy sample of adequate size, weight, and tumor composition; and pathologically confirmed metastatic pancreatic ductal adenocarcinoma (PDAC) or an immunohistochemistry (IHC) profile consistent with pancreaticobiliary origin. Associated clinical information was also reviewed to assess eligibility. Written consent was
obtained from patients to enroll in the APGI and to access their tissue specimen(s). The IMPaCT study (Trial registration ID ACTRN12612000777897) was able to take advantage of an International Cancer Genome Consortium (ICGC) research study through the APGI so that there was some prescreening to enrich for actionable phenotypes.

Sample acquisition and tissue processing for molecular profiling

Once written informed consent was obtained, FFPE tissue biopsy specimens were requested through the routine diagnostic channels of the corresponding pathology department at approved sites. Samples were delivered by standard processes or collected by the tumor bank coordinator if permitted. If we were notified prospectively of a biopsy procedure for which our tumor bank coordinator could be present, a fresh tumor sample (snap-frozen) was also collected in parallel commonly in conjunction with pathologic frozen section examination to confirm malignancy. Following pathologic review of histologic type and adequate tumor content, samples were then processed immediately. Tissue was isolated from FFPE samples for the purpose of DNA extraction (three 1-mm cores from resection specimens; up to seven 10-μm sections were collected from biopsy samples) and homogenized using the TissueLyser II (QIAGEN). DNA was extracted from FFPE tissue using QIAamp DNA FFPE Tissue Kit (QIAGEN) and quantitatively assessed using a Qubit Fluorometer (Life Technologies, Thermo Fisher Scientific, Inc.). Samples were interrogated using a custom Ion Torrent PGM semiconductor sequencing panel, which consists of an AmpliSeq PCR-based targeted library designed to cover all exons and flanking splice sites of four genes involved in DNA damage repair pathways (BRCA1/2, ATM, and PALB2) previously identified in pancreatic cancer, as well as activating mutations in the KRAS gene. The accuracy of the panel was validated against samples that had previously been fully characterized as part of the APGI project on both Illumina and SOLID sequencing platforms.

Sections of FFPE tissue were simultaneously prepared for HER2 in situ hybridization (ISH), performed in a national reference HER2 diagnostic testing laboratory (SydPath, St Vincent's Hospital, Darlinghurst, Australia). If a fresh tissue biopsy sample was collected in parallel, that tissue was snap-frozen in liquid nitrogen, stored at −80°C and, if necessary, DNA was extracted using the AllPrep DNA/RNA Mini Kit (QIAGEN).

Return of molecular profiling results

Any significant molecular findings were discussed at a molecular multidisciplinary team (mMDT) meeting, which...
assembled a team consisting of a genetic pathologist, oncologist, genetic counselor, research coordinator, and project manager. All molecular results indicating eligibility for the IMPaCT trial were verified by Sanger sequencing in a National Association of Testing Authorities, Australia (NATA)-accredited laboratory prior to dissemination: KRAS mutation testing was performed by Healthscope Advanced Pathology (VIC, Australia); BRCA mutation testing was performed by Genetic Technologies Ltd. (VIC, Australia); and ATM mutation testing was performed by The Peter MacCallum Cancer Centre. Results were communicated immediately upon receipt to the clinical care provider or treating medical team for their consideration; a case report summarizing the outcome of molecular screening accompanied a letter explaining the implications of said results. While awaiting the outcome of molecular screening, patients were permitted to start one cycle of standard treatment with gemcitabine (28 days), so there was no delay in treatment. If an eligible genetic signature was confirmed, the candidate could be approached to start personalized treatment on trial.

Specialized personnel

Acquiring and processing biospecimens for the IMPaCT trial is a highly complex operation that depends on specialized personnel. Our team consists of the following: an oncologist who accepts referrals through clinical networks, a tumor bank coordinator (previously qualified as a registered nurse) responsible for approaching patients for their consent to the study and collecting a fresh tissue sample as required; an expert pathologist; a research technician/coordinator responsible for requesting and processing FFPE tissue samples for genomic analysis and distributing samples for external confirmatory testing if required; a genetic pathologist to interpret molecular results; a genetic counselor who serves as a consultant when discussing cases in the mMDT; and a project manager to oversee the entire pathway and facilitate the return of results to the treating clinical team.

Results

Results of preanalytical and sequencing pipeline

From June 2013 to February 2015, 93 patients with recurrent or advanced pancreas cancer were referred to the APGI for screening for the IMPaCT trial and consented to mutation screening for the trial (Fig. 3). Candidate patients either presented with de novo metastatic disease or were identified through APGI at the time of disease recurrence.

Of the 93 patients considered for the trial, 17 were unable to be screened because tissue was deemed unsuitable for the purpose of molecular testing or we were unable to access the nominated tissue specimen. Of these, we were unable to screen 4 patients for whom an FNA was the only available tissue sample. In addition, pathologic review confirmed no tumor content in the core biopsy for 5 patients. Radiology was unable to obtain a biopsy in one instance (no discrete mass seen on imaging despite malignant cells previously detected in ascitic fluid), and five samples were never received from pathology following our request to access tissue and one sample was exhausted by diagnostic pathology. One patient failed to return a signed copy of the consent form despite expressing verbal agreement.

Of the 76 cases processed for molecular testing, archived FFPE resection specimens of the primary tumor were obtained for 45 patients (59%). Twenty patients who presented with de novo metastatic disease had accessible core biopsies, with incisional (usually laparoscopic) biopsies available for a further 11 patients. The most common biopsy site of metastatic disease was the liver (n = 25; 64.1%), other sites included peritoneum or omentum (n = 7; 17.9%), duodenum (n = 2; 5.1%), lung (n = 2; 5.1%), pancreas (n = 2; 5.1%) and lymph nodes (n = 1; 2.5%). One patient suffered complications from a core biopsy of a metastatic
lungs (pneumothorax). A blood sample for future studies or for subsequent germline analysis was collected concurrently from 13 patients. The retrieval of FFPE specimens from pathology laboratories was often the rate-limiting preanalytical step. The median time for samples to be delivered via regular mail after lodging a request with the relevant pathology department was 11.5 days (range, 4–38 days). Specimen delivery times were significantly improved when our tumor bank coordinator collected samples from local sites, averaging 3 days (range, 1–8 days). In five instances diagnostic staining for routine pathology exhausted all tumor material in the FFPE specimen; 2 of these patients underwent repeat core biopsies.

Archival FFPE resection specimens routinely provided ample DNA for sequencing purposes (DNA yield range, 1.2–10.3 μg). The mean amount of DNA extracted from FFPE excision biopsies (1.16 μg; range, 0.78–1.86 μg) was greater compared to FFPE core biopsies (0.62 μg; range, 0.12–1.5 μg). Where possible, fresh tissue biopsy samples were also collected in parallel (n = 4); fresh tissue core samples (typically weighing 4–5 mg) yielded 1.3–4.2 μg DNA. DNA extracted from 2 FFPE samples failed to pass quality control metrics (insufficient yield) prior to molecular analysis. In two instances DNA extracted from FFPE core biopsy material was extensively fragmented and nonamplifiable, and thus not suitable for sequencing purposes. In these cases we were still able to report HER2 status.

An IMPaCT study-eligible genetic target was identified in 22 patients: 14 KRAS wild-type signatures, 5 cases of HER2 amplification, 2 mutations in BRCA2, and 1 ATM mutation. Enrichment for KRAS relates to our prescreening of eligible candidates from our IGGC project that had occurred. External confirmatory testing in laboratories accredited by the National Association of Testing Authorities of Australia (CATIA equivalent) verified all molecular results (100% concordance) prior to dissemination. The average time to receive external confirmatory results following sample submission was 8 days (range, 1–27 days).

The median time from consent to the return of confirmed results was 21.5 calendar days (range, 7–82 days). We were able to return results in ≤28 calendar days for 75% of patients. The most common reasons for exceeding a 28-day timeframe were delays at external testing facilities (n = 6) and a requirement for a repeat biopsy (n = 1).

**Barriers to enrollment of eligible patients onto the randomized study**

To date no patient has been successfully treated on the IMPaCT study. Of the patients for whom an eligible genetic signature was identified (n = 22), 6 patients died before results were obtained (1 by suicide; 5 from pancreas cancer); 1 had intercurrent prostate cancer rendering him ineligible; 3 individuals could not be offered participation in the trial because of their worsening condition (ECOG ≥2); 1 individual withdrew consent after randomization to the standard treatment arm; 1 declined to consent to the study when randomization was explained further; 2 were found on pathologic review to have cholangiocarcinoma and therefore ineligible; 1 patient had unacceptable derangement of liver function; 4 patients received chemotherapy before results could be returned (before the protocol amendment allowing one cycle of gemcitabine to commence during the testing phase); 3 resected patients are alive without disease recurrence (2 KRAS wild-type; 1 HER2 amplified) and likely to be long-term survivors (Fig. 4).

**Discussion**

Assessments of the feasibility of acquiring and analyzing biospecimens in real time to guide treatment decisions in a cancer with poor prognosis are multifaceted but can be categorized in four broad areas: (i) screening sufficient numbers of appropriate patients; (ii) the ability to promptly acquire suitable tumor specimens and obtain sufficient DNA for molecular testing; (iii) the capacity to deliver clinicians high-quality actionable genomic data within an acceptable timeframe; and (iv) attractive clinical trial designs and therapeutics. Given the swift progression of pancreas cancer in a metastatic setting, it is challenging to return genomic results in a meaningful timeframe considering the urgency with which patients want to start treatment. Permitting patients to start standard treatment while they are awaiting the outcome of molecular screening has supported an achievable timeframe. We were able to return results in ≤28 calendar days for 75% of patients, with a median time from consent to report of 21.5 days.

Literature is emerging describing other novel attempts to incorporate tumor profiling into the treatment of many cancers. From a preliminary account of a multicenter clinical trial striving to identify actionable mutations in patients with advanced solid cancers, Tran and colleagues (10) report a median time from consent to final report of 20 calendar days (range, 7–63 days). Reasons for exceeding the target timeframe were similar to our experiences reported here and included delays with acquiring archival FFPE specimens from pathology (range, 2–143 days; median time, 22 days), delays in molecular analysis, and the need to repeat biopsies (n = 3). For the first 100 patients enrolled in the SHIVA trial, Le Tourneau and colleagues (11) report a median time between biopsy and therapeutic decision of 26 days (range, 14–42 days). Roychowdhury (12) also report a comparable timeframe (24 days from biopsy) for the MI-ONCSEQ study, which enrolled 2 patients with advanced cancer (colorectal cancer and...
To circumnavigate the pressure of returning results before first-line treatment commences, many studies are designed to enroll patients with any solid advanced refractory cancers, for example the WINThER trial, established by the WIN Consortium (Worldwide Innovative Networking In Personalised Cancer Medicine) in early 2013 (still in progress) and the SHIVA trial. Recruiting a cohort of patients with diverse tumor types also serves to boost study intake. The Personalized Medicine in Phase I Clinical Trials Program at the University of Texas MD Anderson Cancer Center (13) submitted for molecular analysis samples from 1,283 patients with any advanced cancers refractory to standard therapy (median of five prior therapies) or for which no standard therapies were available. Of particular relevance to the IMPaCT trial, 34 pancreatic cancer patients were screened in the program (2.9% of 1,144 with adequate tissue for molecular analysis), with only 1 proceeding to receive matched targeted therapy.

Studies often exclude patients because of an inability to obtain a biopsy, insufficient or no tumor content in the available specimen, deteriorating performance status, or the patient’s withdrawal of consent or choice of an alternate treatment (10, 11, 14–16). For example, Tsimberidou and colleagues (13) report that 10.8% (139/1283) of patients had inadequate tissue for molecular analysis. Similarly, Cooke and colleagues report on 7 patients in whom CT-guided percutaneous biopsies yielded insufficient tissue for the purpose of molecular profiling in non-small cell lung cancer (NSCLC; ref. 17). Of particular relevance to pancreatic cancer, von Hoff and colleagues (14) report on 7 patients in whom CT-guided percutaneous biopsies yielded insufficient tissue for the purpose of molecular profiling in refractory cancers that 17.9% (19/106) of participants were unable to be treated according to molecular analyses due to their worsening condition or further progression of their disease. Similarly, 6.45% (22/341) of NSCLC patients could not be randomized for the BATcLe study because of worsening overall condition (16).

Similar hurdles were encountered in our experience. While FNA cellblocks are a common source of diagnostic material available for patients with metastatic pancreatic cancer, these samples frequently yield low amounts of DNA, which is often of poor quality and unsuitable for sequencing. Patients for whom only an FNA sample was available and who were unwilling or unfit to undergo a repeat core biopsy (n = 4) were unable to be screened for molecular targets. As technology advances, the feasibility of using FNA is likely to improve.

With respect to adequate tumor content in the samples acquired for our study, pathologic review confirmed no tumor content or insufficient tumor content in 4% of core biopsy specimens. Likewise, von Hoff and colleagues (14) and Tran and colleagues (10) report insufficient tumor content in 3 (2.8%) and 5 (10.2%) biopsy samples, respectively. No international standard of optimal tumor cellularity for downstream molecular analyses has been set. The Cancer Genome Atlas (TCGA) has a strict threshold for cellularity (>60%) across their multiple high profile genomic projects. Other studies have reported thresholds of ≥200 malignant cells on each FFPE section (16) and a tumor content of ≥60% (12) for core biopsy samples for molecular profiling. High thresholds of tumor cellularity can exclude a large proportion of patients, as described by Le Tourneau and colleagues (11), in whose study genomic analyses could not be performed in 32% of patients because of tumor cellularity less than 50%. Thresholds of tumor content are less critical for targeted sequencing approaches, as opposed to whole-genome or exome sequencing.

Typically, FFPE core biopsy samples acquired for this study consisted of 2 to 3 tissue cores, measuring 3 to 20 mm in length and 1 mm in diameter; this is consistent with core biopsy samples collected by Kim and colleagues for the BATcLe trial (16). The mean amount of DNA extracted from core biopsy samples was 0.62 µg (range, 0.12–1.5 µg). Although yields were lower than those reported for biopsy samples from solid tumors (biopsy sites included soft tissue, liver, abdominal mass, superficial lymph node, and lung) processed by Tran and colleagues (3.9 µg; range, 0.09–88.2 µg), sufficient DNA of adequate concentration for molecular analysis was yielded in all but 2 cases in our study.

As technology advances, it may be possible to perform targeted molecular analysis using “liquid biopsies” using circulating tumor cells or cell-free DNA. This approach could solve many of the problems that we have encountered in obtaining tumor tissue. Significant efforts are under way to explore these approaches for clinical applicability.
From 93 referrals, 76 patients were successfully screened for molecular targets for the IMPaCT trial. A total of 22 patients were found to have eligible genetic signatures. Although front-end sample issues were overcome, the next phase of trial recruitment introduces a new level of complexity. Of the 22 eligible patients, none have started treatment on trial. Most were unable to be enrolled because of declining performance status or death. This highlights the challenge of patient selection for molecularly targeted trials involving a lag time to treatment, particularly in cancers in which disease trajectory can be fast and sometimes difficult to predict, as is true of pancreas cancer. Allowing treatment to commence during analysis has not overcome this barrier; perhaps determining second-line therapy may be more realistic. Randomization also proved to be unappealing to patients and a barrier to recruitment; therefore we amended the study protocol to a single-arm feasibility study (Fig. 5).

The pilot phase of the IMPaCT study demonstrates the feasibility of procuring and processing biopsies for molecular profiling in a clinical trial setting in pancreas cancer specifically, while highlighting a variety of issues. Having a dedicated multidisciplinary team is necessary to combat these hurdles on a case-by-case basis. It is proposed that to advance molecularly selected therapy trials, a new organizational structure is needed that would include specific clinical disciplines such as interventional radiology and molecular pathology responsible for the skilled procurement of these specimens in centers of excellence that can generate rapid turnaround times. Establishing these "biopsy teams" is critical, as is developing an efficient yet precise pipeline to generate high-quality genomic data, and will be especially challenging for multisite trials.

For pancreatic cancer, we can deliver appropriate assays in a clinically relevant timeframe, but we need to focus on pancreatic cancer-specific challenges, including the following: (i) better prescreening of patients; (ii) screening a larger number of patients; and (iii) providing more attractive trial options for patients and their treating clinicians. (See Box 1 for key learning points.) These challenges are surmountable, particularly because we have made significant advances in the molecular phenotyping of cancer. We now need to adjust the health care ecosystem to align with these new and potentially transformative approaches. Barriers to enrollment in a molecularly guided treatment trial in a poor-prognosis cancer such as pancreas cancer are significant and have taught us that early adaptations in response to these issues can enable the study to evolve into a clinically appropriate trial.

Box 1. Practical recommendations for precision medicine trials

- Formation of a cohesive, collaborative tissue acquisition team focused at key sites
- Consent for tissue acquisition and screening undertaken at time of biopsy
- Personal transport and processing by team members
- Consideration of incorporating newer "liquid biopsy" techniques instead of tissue analysis
- Effective channels of communicating results to clinicians in real time
- Design of studies that appeal to patients: nonrandomized studies of novel agents allowing standard treatment to start while analysis is undertaken

References
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