

Challenges in initiating and conducting personalized cancer therapy trials: perspectives from WINTHER, a Worldwide Innovative Network (WIN) Consortium trial

J. Rodon^{1*}, J. C. Soria², R. Berger³, G. Batist^{4,5}, A. Tsimberidou⁶, C. Bresson⁷, J. J. Lee⁶, E. Rubin⁸, A. Onn³, R. L. Schilsky⁹, W. H. Miller^{4,5}, A. M. Eggermont², J. Mendelsohn⁶, V. Lazar² & R. Kurzrock¹⁰

¹Vall D'Hebron Institute of Oncology and Universitat Autònoma de Barcelona, Barcelona, Spain; ²Gustave Roussy Cancer Campus Grand Paris, Villejuif, France;

³Oncology Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel; ⁴Segal Cancer Center, Jewish General Hospital McGill University, Montreal; ⁵Quebec Consortium de Recherche en Oncologie Clinique, Quebec, Canada; ⁶The University of Texas MD Anderson Cancer Center, Houston, USA; ⁷WIN Consortium, Villejuif, France;

⁸The National Institute of Biotechnology in the Negev, Ben Gurion University, Beer-Sheva, Israel; ⁹American Society of Clinical Oncology (ASCO), Alexandria;

¹⁰Center for Personalized Cancer Therapy, UC San Diego–Moore's Cancer Center, La Jolla, USA

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Advances in 'omics' technology and targeted therapeutic molecules are together driving the incorporation of molecular-based diagnostics into the care of patients with cancer. There is an urgent need to assess the efficacy of therapy determined by molecular matching of patients with particular targeted therapies. WINTHER is a clinical trial that uses cutting edge genomic and transcriptomic assays to guide treatment decisions. Through the lens of this ambitious multinational trial (five countries, six sites) coordinated by the Worldwide Innovative Networking Consortium for personalized cancer therapy, we discovered key challenges in initiation and conduct of a prospective, omically driven study. To date, the time from study concept to activation has varied between 19 months at Gustave Roussy Cancer Campus in France to 30 months at the Segal Cancer Center, McGill University (Canada). It took 3+ years to be able to activate US sites due to national regulatory hurdles. Access to medications proposed by the molecular analysis remains a major challenge, since their availability through active clinical trials is highly variable over time within sites and across the network. Rules regarding the off-label use of drugs, or drugs not yet approved at all in some countries, pose a further challenge, and many biopharmaceutical companies lack a simple internal mechanism to supply the drugs even if they wish to do so. These various obstacles should be addressed to test and then implement precision medicine in cancer.

Key words: personalized cancer therapy, biomarker, clinical trials

introduction

Discoveries in molecular biology and the development of targeted therapies for cancer are delineating an important new concept—personalized treatment through matching of a patient's tumor with one or more molecularly targeted agents via the use of biomarkers. High rates of efficacy have been reported in some settings with this approach [1–8].

Most metastatic cancers have a dismal prognosis, and many drugs increase survival by only a few weeks or months [9]. There is an emerging realization that treating unselected patient populations is unlikely to yield more than incremental benefits

because cancers of the same histologic type are comprised of many molecular subgroups [10–12]. The potentially transformative impact of powerful new 'omics' technologies coupled with potent targeted agents [13] mandates that trials of personalized treatment be rapidly implemented and executed in order to validate the concept's utility.

In this context, we planned an ambitious clinical trial, designated WINTHER, with the following features [14]: the use of advanced genomic and transcriptomic platforms to navigate patients to cognate therapy; coordinated by the Worldwide Innovate Networking (WIN) Consortium for personalized cancer therapy [15]; and carried out in six major academic cancer centers in five Western countries by highly experienced investigators (Table 1). Herein, we outline the formidable challenges associated with personalized cancer therapy trials as seen through the lens of this international initiative.

*Correspondence to: Dr Jordi Rodon, Early Clinical Drug Development Group, Vall d'Hebron Institute of Oncology (VHIO), Pg Vall d'Hebron 119-129, 08035 Barcelona, Spain. Tel: +34-93-489-4301; E-mail: jrodon@vhio.net

Table 1. Major challenges for implementing the WINTHER trial, per country and site

Site	Principal investigator	Challenge	Solution
Gustave Roussy Cancer Campus (France)	Prof. J. C. Soria, Chair of the Drug Development Department (DITEP) (Study PI)	<ul style="list-style-type: none"> Classified as triage trial. Approved drugs could be used off label after multidisciplinary tumor board discussion, and with permission by the health authorities. 	<ul style="list-style-type: none"> Multiple clinical trials for patients. Charities, pharmaceutical, and institutional funding. Request coverage by health insurance on a case-by-case basis. Encourage pharmaceutical industry to provide free drug if under IRB-approved protocol (perhaps similar to pharmacy assistance program)
UC San Diego Moores Cancer Center (USA)	Prof. Razelle Kurzrock, Senior Deputy Center Director, Clinical Science and Director, Center for Personalized Cancer Therapy Study (co-PI)	<ul style="list-style-type: none"> Classified as triage trial Approved drugs could be used off label. Nongovernment (private) health insurance may cover, albeit unpredictably Diagnostic 'omics' tools need to be CLIA-approved and FDA rules them a 'significant risk' and requests an IDE; initial IDE package rejected by the FDA Relocation of study co-PI (RK) from MD Anderson to UC San Diego Moores led to addition of this site, which was not in original grant. 	<ul style="list-style-type: none"> CLIA laboratory had to be included and results cross-validated with those from GRCC laboratory in France. Need for IDE was an unexpected new requirement and a package had to be prepared for obtaining it. Timeline for package preparation was significant
MD Anderson Cancer Center (USA)	Apostolia Tsimberidou, MD, PhD, Associate Professor, Department of Investigational Cancer Therapeutics	<ul style="list-style-type: none"> The same as UC San Diego Moores Cancer Center (except that site was in the original grant) 	<ul style="list-style-type: none"> The same as UC San Diego Moores Cancer Center
Vall d'Hebron Institute of Oncology (Spain)	Jordi Rodon, MD, Director of the Molecular Therapies Research Unit	<ul style="list-style-type: none"> Classified as a therapeutic clinical trial per Health Authorities that includes the diagnostic and therapeutic part Need to define drugs that will be used in clinical trial Drugs need to be covered by the clinical trial 	<ul style="list-style-type: none"> Need to introduce pharmacovigilance (reporting adverse events). Comprehensive list of drugs available Depends on clinical trial funding for the cost of drugs.
Oncology Institute at the Chaim Sheba Medical Center (Israel)	Raanan Berger, MD, PhD, Director, Division of Medical Oncology	<ul style="list-style-type: none"> Classified as a therapeutic clinical trial per Health Authorities Drug costs need to be covered by the clinical trial Cost of clinical research higher than what is covered 	<ul style="list-style-type: none"> Clinical trial includes the diagnostic and therapeutic part. Depends on clinical trial funding for the cost of drugs. Extra resources need to be allocated to by the site
Segal Cancer Center, McGill University (Canada)	Prof. Wilson Miller, Deputy Director of Segal Cancer Centre and director of the Clinical Research Units, McGill University	<ul style="list-style-type: none"> IRB and Health Authorities had different views regarding the regulatory approach for the study. Classified as a therapeutic trial. Site needs to request Health Authority permission for off-label drug use in each case. Site not included in the initial grant 	<ul style="list-style-type: none"> Coordination between Health Authorities and IRB by the site. Local pharmaceutical affiliates may provide drug for patients. Development of an <i>ad hoc</i> fast-track review system by Health Authorities for this project. Site added in the grant and resources reallocated

^aThis includes time to establish with Health Authorities (FDA) what kind of review will be necessary, time to prepare the documentation (including IDE submission), and the time for actual Health Authorities' review.

CLIA, Clinical Laboratory Improvement Amendments; co-PI, Co-Principal Investigator; FDA, Food and Drug Administration; IDE, Investigational Device Exemption; GRCC, Gustave Roussy Cancer Campus; IRB, Institutional Review Board; PI, principal investigator.

companion diagnostics and the emergence of multiplex technologies

First generation trials deploying molecular-based personalization of treatment selection utilized the paradigm of co-development, where a drug and *in vitro* companion diagnostic are developed in parallel and approved together [1, 6, 16]. While salutary effects using this model can be striking, there are significant challenges to companion diagnostics as originally conceived. For instance, with a single companion diagnostic that defines very small subsets of a cancer population (e.g. an ALK diagnostic), hundreds or thousands of patients must be screened to identify the few whose tumors bear the designated molecular marker [6]. Screening in this way entails an enormous workload that benefits very few patients.

Since multiple abnormalities may be present in any one histologic type of cancer (or even in each patient's tumor) [17], interrogation with multiple individual companion diagnostics would be necessary to pinpoint those aberrations that pertain to the patient at hand [18, 19]. Such an effort is incompatible with the urgency with which patients suffering from cancer need to be treated. Fortunately, however, 'omics' technologies have improved at a breathtaking speed, with the price of full sequencing of a human genome falling from about three billion dollars in the year 2000, to <5000 dollars now [20]. Therefore, the potential to exploit multiassay platforms, such as next-generation sequencing (NGS) or transcriptomics [21] instead of single-assay gene diagnostics, is attractive for the following reasons: comparatively less expense per gene assayed, amount of tumor tissue required is minimized, and a more complete portfolio of genomic abnormalities is elucidated.

designing clinical trials for personalized cancer therapy

Omics may represent a disruptive technology in oncology, since classic clinical trial methodologies used for decades are not well suited to personalization. Canonical clinical protocols are drug-centric (or, more recently drug plus companion diagnostic-centric). The effort is to test the efficacy of a drug by identifying commonalities among potential patients, usually based on histology and the organ of origin of the tumor and, more recently, on finding small subsets of patients within a histology that have a similar gene abnormality. However, each patient with metastatic cancer may harbor numerous genetic aberrations, and a multitude of abnormalities may be seen among patients who have the same pathologic diagnosis [22–24]. Furthermore, patients with distinct histologies may share common genomic aberrations [10, 25]. Even so, with new trial constructs, an increasingly significant proportion of patients can be matched with drugs based on molecular data. One of the ways this can be successfully accomplished is to incorporate the omics test into the work-up of patients, and then to navigate them to the best trial or drugs based on their 'genomic diagnosis' [8, 21, 26–28].

the WINTHER trial: overview of design, opportunities, and challenges

The WINTHER trial was designed to use cutting edge genomic and transcriptomic technology to navigate patients with

advanced refractory cancer to a matched targeted drug. Because WIN is a global organization, an international trial was conceived that would leverage expertise across five countries [Canada (McGill/ Segal Cancer Centre), France (Gustave Roussy Cancer Campus (GRCC)), Israel (Sheba Cancer Research Center), Spain (Vall d'Hebron Institute of Oncology, VHIO), and United States (UC San Diego Cancer Center and MD Anderson Cancer Center, MDACC) (Table 1). The trial exploits NGS genomics (in 236 genes) (Foundation One, Cambridge, MA) in arm A and transcriptomics in arm B (including unique features such as comparison of tumor and normal for background subtraction (Figure 1) and a bioinformatics algorithm that prioritizes drugs). The design of the trial was built on the PREDICT/IMPACT genomic trial at MD Anderson Cancer Center and other similar protocols [8, 28]; the transcriptomics was developed at GRCC in France [29].

After receiving informed consent, each patient is navigated to either an experimental drug (on a clinical trial) or an approved drug (on or off trial, and for off trial, on or off label) or combination. A clinical management committee discusses each patient thoroughly, taking into consideration the omic data as well as comorbidities, health care coverage, and the local availability of a matched drug. The committee's suggestions are advisory, with the ultimate treatment choice being up to the physician and patient, to optimize patient care while being cognizant of logistical constraints.

As the treatment is intended to be 'personalized' in an 'N-of-One' manner, the progression-free survival (PFS) on the matched targeted therapy is compared with the patient's prior PFS on the last regimen [8, 28]. Another committee, blinded to the patient outcomes, rates the degree of matching before final analysis of the results. This design allows testing of the concept of matched therapy in the context of omically informed physician choice, analogous to what might eventually occur in the community.

overview of WINTHER trial timelines and initiation challenges

Multiple new processes were needed for a transnational personalized trial with numerous stakeholders (supplementary Box S1, available at *Annals of Oncology* online). To attenuate the potential challenges, the trial was restricted to highly experienced institutions and/or investigators (Table 1). Even so, initiating WINTHER faced considerable hurdles, which differed by country (Figure 2). The most daunting obstacles to initiation were regulatory, especially in the United States, with the recent mandate for Food and Drug Administration (FDA) oversight of the laboratory-based omics technologies in prospective clinical trials.

The trial concept was developed starting in September 2011 (Figure 2). As of September 2014, all sites had Institutional Review Board (IRB) and other regulatory approvals, though with significant differences in timelines. Timeline from protocol submission to IRB approval was ~1, 1, 4, 6, 9 and 10 months in France, Spain, United States-San Diego, Israel, Canada, and United States-MD Anderson Cancer Center, respectively. Timeline from concept to activation was ~19 months in France, 22 months in Spain and Israel, and 30 months in Canada. It took 3 years to be able to secure all regulatory approvals in the

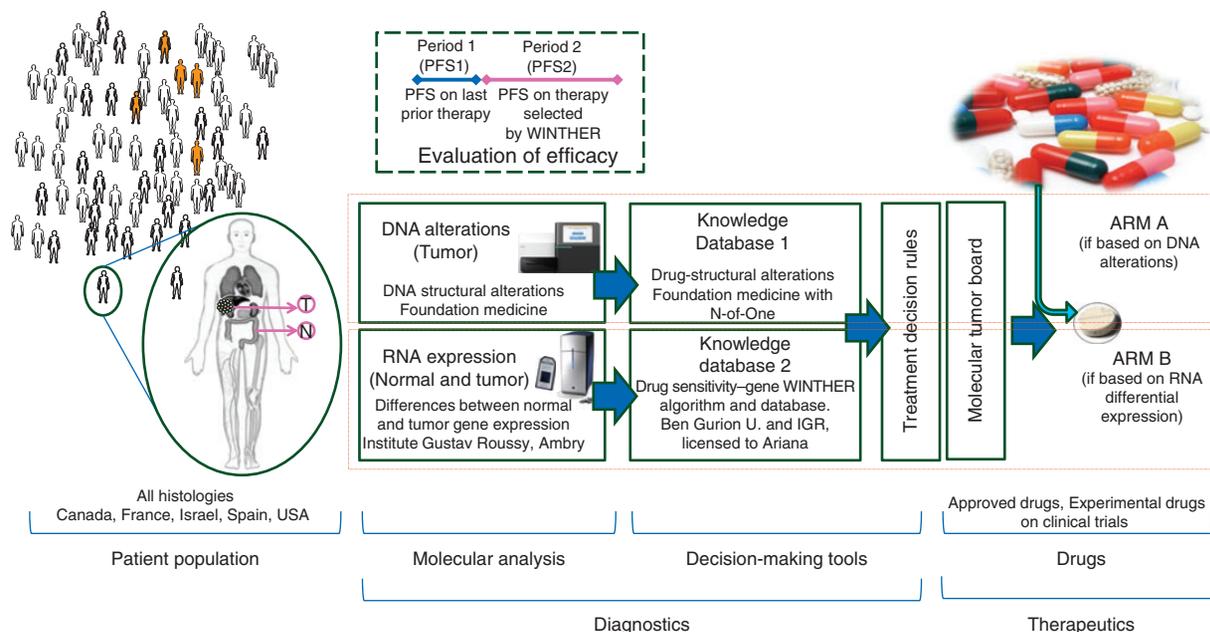


Figure 1. Design of WINTHER trial. In the WINTHER trial [14], each patient undergoes a biopsy of the tumor (or metastasis) and normal tissue from the organ of origin of the tumor. A complete biological profiling of DNA and RNA is undertaken. The choice of therapy is rationally guided either by matching actionable targets (mutations, amplifications, gene rearrangements) found in the tumor (arm A) or the tumor gene expression with the algorithm-predicted sensitivity of the drug based on the WINTHER algorithm (arm B). Launched by the WIN Consortium (Worldwide Innovative Networking Consortium in personalized cancer medicine), it is an international effort with six centers participating in the trial from five different countries, and three laboratories analyzing samples (Foundation Medicine in the United States for NGS; Gustave Roussy Cancer Campus in France and Ambry Genetics in the United States for transcriptomics). It uses two different platforms and knowledge bases as well as a clinical management committee that functions like a molecular tumor board for treatment decisions, and considers both FDA-approved and experimental drugs as potential options for patients. The bioinformatic analysis (WINTHER algorithm) is being carried out jointly by Gustave Roussy Cancer Campus and Ben Gurion University, Israel, and the WINTHER algorithm will be improved and developed together with Ariana Pharma, Paris, France. T, tumor biopsy; N, normal tissue biopsy; PFS, progression-free survival; TTP, time to progression.

United States and, hence, at the time of analysis (September 2014), US sites were not yet activated. The differences in timeline to activation relate almost entirely to national regulatory requirements.

The first patient was enrolled 19 months from concept initiation, at GRCC in France by September 2014, when US sites secured regulatory approval, 134 patients outside of the United States had signed informed consent. We will not discuss in depth the scientific and technical challenges (supplementary Table S1, available at *Annals of Oncology* online) since these have been addressed elsewhere [30, 31]. We found that the two most important impediments were medication acquisition and regulatory hurdles.

concept development and funding

Because the WIN Consortium has an international membership devoted to, and accomplished in, personalized cancer therapy research, the initial steps of conceiving and writing the protocol, selecting the investigators and sites, garnering expert bioinformatics, statistical, and pathology support, outlining standard operating procedures, as well as securing funding, while arduous, were not the most formidable challenges [32].

During its annual summer meeting, WIN brings together high-profile stakeholders from academia, industry and the health care community to discuss cutting edge advances in the field. Consistent e-mail/teleconference communication facilitated the

process of protocol development, as did several trans-Atlantic trips by WIN leadership. The funding effort was also enabled in part by WIN engagement with pharmaceutical companies holding WIN membership providing financial support, in addition to a successful application to the European Union's 7th Framework Programme for Research and Technological Development and a generous donation from *Fondation ARC pour la recherche sur le cancer*. Though this protocol did succeed in garnering grant funding from the European Union, other such studies may not fare as well with other funding agencies. Canonical organizations that evaluate applications in a disease-based approach may be challenged to find histology agnostic, genomically driven proposals attractive or even reviewable.

acquisition of molecularly guided drugs

The whole point of a personalized medicine trial is to individualize the drug(s) chosen for each particular patient. This means that, while the strategy to choose therapy is consistent between patients, the actual drugs administered will differ, based on the complexity of human tumor genomics. Therefore, access to a wide variety of approved or experimental agents is necessary. From the trial standpoint, approaching the drug manufacturers is difficult because patients might require any of a number of drugs from different sponsors. This represented a major rate-limiting step. Careful selection of sites that had many clinical trials with targeted agents available helped secure drugs for

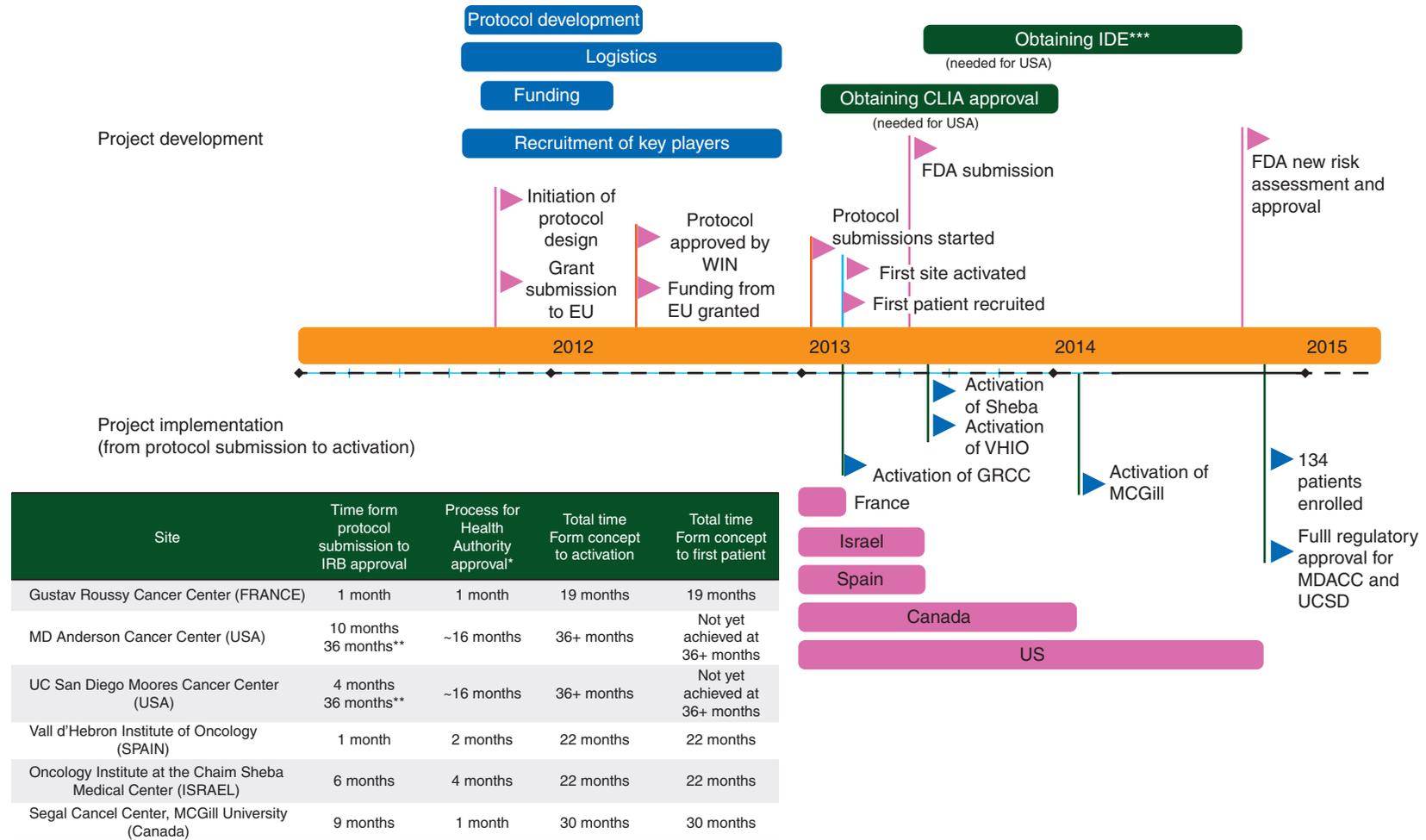


Figure 2. Timeline for WINTHER Activation by Country and Process (analysis as of September 2014). IRB approval times (from submission of the protocol to approval) ranged from 1 month in France to 10 months at MD Anderson in the United States. Delays in regulatory approval in the United States were mainly due to requirement for CLIA and, most importantly, FDA oversight. The dark grey (blue online) bars: timing of the different processes in project development. The black (green online) bars: timing of United States-specific processes in project development. The light grey (pink online) bars: timing of the project implementation in each country (from protocol availability to activation of the site in the site initiation visit). The latter includes the time required for IRB and Health Authority review that are further described in the embedded table. Some processes may occur in parallel and, in some institutes, additional processes beyond IRB and health authority approval were needed before activation could occur. CLIA, Clinical Laboratory Improvement Amendments; IDE, Investigational Device Exemption. Single asterisk: 'Process for Health Authority approval' denotes initial time from investigator decision to ask health authorities what kind of approval was needed to final Health Authority deliberation. The time for Health Authority approval may overlap with time from protocol submission to IRB approval at least in part, as processes were carried out in parallel. Double asterisk: The initial protocol had to be amended following FDA specifications. It therefore took 36 months to have a final regulatory-approved protocol after concept initiation. Triple asterisk: Total time added to study process by need for FDA oversight was 16 months including: 1 month to plan risk assessment request, 12 months for FDA to approve study (includes initial assessment as significant risk necessitating submission of IDE, preparation of IDE, rejection of FDA by IDE, re-evaluation of risk assessment by FDA with new determination of nonsignificant risk, and amendment of protocol per FDA request).

some, but not enough patients. In addition, contributions from a number of pharmaceutical companies defrayed some of the cost of drug acquisition.

The problems in drug acquisition differed by country (Table 1). In some countries (Spain, Canada, and Israel), the health authorities viewed WINTHER as a therapeutic trial, even though it was designed as a navigation (triage) trial, with the actual therapies being outside the trial. The navigation design avoided the problem of having multiple clinical trials from different pharmaceutical sponsors under one umbrella, since getting a range of companies to cooperate in this way is exceedingly difficult (though it has been accomplished in trials such as I-SPY2 [33]). The Canadian authority (Health Canada) issued a workable plan for the study, in which each individual off-label drug, and even drugs not yet approved, would be expeditiously reviewed within an overall umbrella approach to the protocol. In other countries (France and United States), WINTHER was considered a ‘decision-making’ (triage/navigation) protocol, where the molecular analysis led to suggested options (experimental drugs on trial, approved drugs on or off label). Regulation of off-label use varies between countries. In France, physicians are able to prescribe an off-label drug when published data are available, it is recommended by a tumor board, and health authority permission is obtained. In Canada, health authorities must give permission on a case-by-case basis. In the United States, off-label use is common in oncology [34, 35] and private insurers (though not usually government payors) sometimes (albeit unpredictably) cover the costs [36, 37].

regulatory oversight for a prospective molecular analysis-based trial

In France, Canada, Spain, and Israel, health authorities required only IRB approval and patient consent for use of the genomic diagnostic platform (arm A) and the transcriptomic assays and bioinformatics algorithm (arm B). None of these health authorities considered the omics as a device that required their regulatory oversight, and no additional laboratory certification was required.

In contrast, the complexity of regulatory authorization of clinical diagnostic laboratories and federal oversight of the omics tests was a major obstacle in the United States. The United States requires certification under CLIA and does not accept the clinical use of results from the laboratory at Institute Gustave Roussy (ISO9000-01 certified). We were therefore compelled to find a CLIA-compliant laboratory (Ambry Genetics, Aliso Viejo, CA) that could run a transcriptomic expression array identical to that at Institute Gustave Roussy, and then had to exchange samples to prove that results between the two laboratories were comparable, a process that took ~1 year. Fortunately, we were successful, but the US sites would have been dropped if an identical expression assay had not been identified. The reverse was not a problem—other countries accepted the clinical use of the genomic analysis carried out in the Foundation Medicine CLIA-compliant laboratory in the United States, as well as the non-CLIA Institute Gustave Roussy transcriptomics.

Even more importantly, FDA initially considered the genomics and transcriptomics as a ‘device’ of ‘significant risk’ for patients, and required FDA oversight of the trial and an investigational device exemption (IDE) [38]. An IDE allows a ‘device’

to be used in a clinical study; the word ‘exemption’ can be confusing because, in this case, it only means exemption from certain commercial regulations. Obtaining an IDE requires FDA approval of a comprehensive test validation package; this bar is far higher than that for CLIA authorization of laboratory tests, which is adequate without FDA approval for the vast majority of tests used in clinical trials or practice in the United States [39]. While the IDE qualification was meant to fortify omic assay reliability in clinical trials, and is reasonable when seeking FDA commercialization approval, the industry-level validation requires considerable resources. Furthermore, the FDA requirement to lock down the test is incompatible with exploratory trials where learning takes place during the course of the clinical investigation. Paradoxically, the same molecular diagnostic tests carried out under CLIA can be used in clinical practice in the United States without FDA oversight or approval.

In July 2014, a new assessment by the FDA after protocol amendment determined that IDE was no longer required. The IDE process added over 16 months to the regulatory approval process in the United States. These timelines are crucial because of the urgency of the cancer problem. In addition, the chance of protocol failure increases precipitously if the timeline to activation is over 2 years [40], perhaps because the science evolves, stakeholders such as pharmaceutical industries or commercial vendors and/or laboratories responsible for molecular diagnostic tests modify priorities and personnel, and personal circumstances of the principal investigators change. Furthermore, when the activation energy of a protocol exceeds a certain threshold, it may become more difficult or impossible for investigators to pursue the implementation of the study.

perspectives and future directions for clinical research in personalized cancer therapy: lessons learned

Clinical research has been grounded in the developmental model of cytotoxics, where patients are grouped together based on histologic diagnosis. Although improvements have been achieved, most patients with metastatic cancer succumb. Omic technology has revealed a complex and potentially transformative new reality about cancer: (i) tumors have complicated genomic landscapes; (ii) malignancies that originate in the same organ can have vastly different genomic drivers; and (iii) many molecular aberrations do not segregate by histology. Furthermore, any one drug or combination may benefit only a small subset of patients. These factors drive the need to develop and validate a personalized cancer therapy paradigm. However, the traditional drug-centric clinical research model does not fit well with individualized, patient-centric clinical trials

WINTHER, a multinational personalized cancer clinical trial that exploits advanced genomic and transcriptomic technology and international clinical trials expertise, encountered significant challenges in initiation and implementation. The WINTHER experience provides an important perspective on these obstacles and their solutions. The following key observations were made:

Medication acquisition and regulatory complexity appear to be the most significant logistical obstacles for personalized cancer therapy trials:

- (i) The regulatory environment differs across Western countries and, as the regulatory burden increases, the timeline to activation lengthens. Harmonization of regulations for diagnostic tests is needed for international collaborative trials. France, Spain, Israel, and Canada accepted molecular diagnostic tests carried out under an ISO9000-01-certified laboratory in France, while the United States did not. The need for FDA oversight of the omics and the initial FDA assessment requiring an IDE in the United States has been the most formidable hurdle.
- (ii) A large number of drugs must be available through clinical trials with a variety of experimental agents, as well as approved drugs, which may need to be used on or off label.
- (iii) The cost of approved but off-label drugs for responders, who may be on therapy for long periods of time, can be prohibitive.

In conclusion, investigators pursuing research in personalized cancer care will need to craft innovative designs for their clinical trials. One such design is the navigation trial, which uses the study technology to produce a molecular signature that then directs patients to matched therapy. As the technology is advancing at a startling pace, enabling rapid activation by reducing regulatory burdens is essential, and permitting early exploratory clinical studies to benefit from learning through the study life cycle, rather than being locked down, will be critical.

funding

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disclosure

The authors have declared no conflicts of interest.

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