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PANEL 1

Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics Instead of Histology

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Introduction

The development of new therapies to treat rare conditions has generally encountered different challenges than traditional drug development for diseases with high incidence. For example, rare cancers attract less research funding than more common tumor types, under the rationale that more people are affected by and therefore more patients benefit from clinical developments related to more common tumors. Additionally, clinical trials for rare tumor types often have difficulty accruing the number of patients required for a trial to have adequate statistical power. These challenges may reduce the incentive to explore the potential benefit of a new therapy for cancers with a small patient population. However, advancements in molecular biology, as well as improved understanding of the mechanisms of action of cancerous growth and cell death resistance, have identified numerous new potential drug targets to impede cancer progression. Because these targets are unlikely to be ubiquitously expressed, it has resulted in the further refining of sub-populations of cancer types based on different mutations or molecular markers. This has led to an expansion of research to explore the use of drugs designed toward a specific target in different types of cancer. While further subsetting of cancer patients in some ways increases the challenges faced in developing drugs for diseases, there is hope that common mutations across different histological classifications could indicate potential utility of a new drug in different settings. While this has not always held true (1), it may present opportunity for screening strategies in multiple tumor types to optimize future research or to facilitate research that otherwise may not occur in particularly rare subsets of cancer.

Cancer drugs have traditionally been cytotoxic chemotherapeutic drugs that target and kill rapidly dividing cells. These cytotoxic drugs block the normal cellular function of cell division but lack specificity, meaning that they also kill non-cancerous cells, contributing to their often severe negative side effects. More recently, cancer drugs have been developed that target specific molecules that are key intermediates in pathways that play important roles in tumorigenic processes, such as tumor growth and progression. These drugs, often referred to as targeted therapeutics, function by interacting with mutated proteins and specific molecules, thereby altering a molecular signaling pathway that is dysregulated in cancer cells. Because the molecular target is differentially expressed in the cancer cells compared to normal cells, targeted therapies often show much reduced toxicities compared to traditional cytotoxic drugs. Additionally, the specific interaction between the targeted molecule and the therapy may result in increased effectiveness of the drugs.

Frequently, cancer drugs are prescribed based on the tissue of origin of the cancer and cell histology; if a drug has been shown to have an effect on a specific tumor-type, then other patients with the same cancer and stage of disease are given that drug. Clinical trials are also typically designed based on tumor histology. However, due to the specificity of targeted therapies, traditional prescription and trial procedures may need to be re-examined. The effectiveness of a targeted therapy may be limited to only those patients whose cancers contain the targeted protein that plays an active role in tumorigenesis pathways; in effect, potentially dividing even common tumors into rare clinical subtypes. However, targeted therapies may work across histologies to effectively treat multiple cancers with a common molecular target.

Although multiple oncology drugs are approved for multiple tumor types, many of these studies have been done in separate cancer-specific phase 3 trials. For example, sunitinib was approved for treatment of gastrointestinal stromal tumor (GIST) and advanced renal cell carcinoma (RCC) based on two separate trials (2). It was then later approved against pancreatic neuroendocrine tumor (PNET) after an additional tumor-specific trial (3). This approach towards multiple approvals is very inefficient and time-consuming, and it does not address the inherent problems mentioned above that limit trials for rare cancers. An alternative trial design in which the therapeutic target, rather than tumor histology, is the focus, may improve trial effectiveness in multiple ways.

Because multi-histology trials focus on the therapeutic target and pathway of interest rather than the specific tumor type, they allow multiple cancers to be investigated at once, thereby increasing trial size, and allowing effectiveness to be calculated for rarer cancers. Interestingly, at this stage, it appears that rare cancers may respond more consistently to targeted treatments than more common tumors, which are more likely to have multiple genetic causes (2). However, trials have indicated that targeted therapies can also be histology-specific, with presence of the targeted molecule not ensuring effectiveness of the targeted treatment. For example, the BRAF inhibitor vemurafenib has recently been approved to treat BRAF-mutant melanoma patients, but shows no real benefit in metastatic colorectal cancer, even in BRAF-mutant expressing tumors (1). This must be taken into consideration when designing multi-histology trials; at some point in a phase II study the specific histologies that respond to a target-specific therapy need to be identified.

Although multi-histology trials have been completed, and new trials are in the recruiting stage, they are still quite rare overall, and the number of successful trials has been limited to those drugs with significant effects that were approved following a phase II trial. However, use of this trial approach may enable research in particularly rare cancers that otherwise may not feasibly be involved in new drug trials because the patient population is too small to accrue a sufficient number of patients.

Comprehensive path forward

In an effort to improve treatments of rare cancers, the panel has posited a trial design to function as proof of principle and demonstrate that a multi-histology trial is a feasible approach for treating disease and receiving drug approval. In addition to giving other investigators a potential blueprint to follow for future histology-independent trials, this potential developmental plan will aid in making the drug testing and approval process faster, more efficient, and therefore more effective.

Multi-histology phase II trials have already been run to investigate the response of multiple malignancies to topotecan (4), lapatinib (5), or imatinib (6), with varying results. While multiple FDA approvals based on phase II results were issued for imatinib (7-11), the lapatinib study was closed early due to both low response rate and low enrollment (5). These studies confirmed, as mentioned above, that even with identical mutations, specific tumor types show varying response to the same therapy, reaffirming the

continued importance of histology in determining therapeutic care. An optimal phase 2 approach would allow for identifying which histologies within a given mutation or molecular profile are predictive for response to a targeted therapy. The trial proposed here will be based on the parameters of these initial studies, with a focus on the imatinib trial, a phase 2, open-label, single arm study, described in Heinrich, et al (6).

Proposal for registration pathway

We propose here a potential development plan based on a clinical trial design in which a therapy against a molecular target will be tested in multiple histologies. Specifically, a histology-agnostic trial is proposed in BRAF V600E mutated tumors, using the combination of the BRAF inhibitor GSK2118436 and the MEK inhibitor GSK1120212, in order to demonstrate that a multi-histology trial is a feasible approach and can lead to registration with a label for “BRAF-mutated tumors”. In melanoma the BRAF V600E mutation has been identified as a key driver mutation of tumorigenesis, and BRAF inhibitors such as vemurafenib and GSK2118436 have demonstrated dramatic efficacy in this setting. Because BRAF V600E mutated tumors have been shown to develop resistance to BRAF inhibitors, the novel-novel combination of a BRAF and MEK inhibitor provides a rational approach intended to hit multiple targets within one pathway and avoid drug resistance. The combination of GSK2118436 and GSK1120212 has been dosed successfully in BRAF mutant melanoma with substantial safety data already available at full combined monotherapy doses. Given the low prevalence of V600E mutations within any given histology to be included in a given trial, this trial will act as a representative example for therapies for rare cancers.

Proposed Design for an adequate and well controlled trial

A multi-histology trial is proposed using the combination of GSK’s BRAF inhibitor GSK2118436 and MEK inhibitor GSK1120212. The rationale for this trial is based on the current understanding of BRAF as a driver mutation within the RAF/RAS/MEK/ERK pathway and the need to hit multiple targets in order to block alternative activation of the pathway and drug resistance when a BRAF inhibitor is used as monotherapy.

Population

The trial will enroll subjects with the BRAF V600E mutation across multiple solid tumor and hematologic malignancies. It is intended to enroll a population with a high unmet need; therefore, to be eligible, patients must have exhausted all available standard treatment options. With the exception of melanoma, all solid tumor and hematologic malignancies will be considered for enrollment in this trial. However, if there is strong pre-clinical evidence suggesting no activity in a particular histology, that histology may be excluded from the trial.

Given the strong biological rationale for the combination, consideration was also given to studying patients with less advanced disease in earlier lines of therapy with the aim of making the combination more broadly available. However, it was recognized that expanding the population would significantly increase the complexity in design and interpretation of the trial.

Treatment

The majority of patients will receive treatment with the combination of GSK2118436 and GSK1120212 until progression or unacceptable toxicity. As described in the statistical considerations, emerging data from within the trial will also be used to decide whether to continue enrollment of certain histologies.

Endpoints

The primary endpoint of this trial will be tumor response rates (RR) using response criteria appropriate to each particular histology. It is anticipated that RECIST will be used in all of the solid tumor histologies

enrolled. While overall survival (OS) and progression-free survival (PFS) will also be documented, both may vary substantially from histology to histology. Therefore, RR represents the most uniform way by which to evaluate the activity of the combination in this trial. This is further reinforced by the fact that the population enrolled into this trial is expected to have a very low RR to existing therapies. The trial target of a 40% RR should therefore provide reasonable evidence for the activity of the combination.

Additional survival data on the combination therapy may be collected via a patient registry in order to augment data collected in the trial. The data collected via the registry will be combined with the trial data and be used to increase the precision in estimation of OS across multiple histologies and to further substantiate the benefit observed with response rate. When possible, patient samples will be collected initially before treatment, as well as 6 weeks following therapy initiation, for genotyping and to look at other potential molecular profiles that may be predictive.

Hypothesis and statistical considerations

The trial will target a RR of approximately 40%, which will be considered as clinically meaningful. Bayesian methods that allow borrowing of information between histologies will be used to continuously analyze accruing data from the trial. If there is evidence suggesting no activity in a certain histology based on prospectively defined criteria, then that histology will no longer be considered for enrollment in the trial. A minimum of approximately 5-10 patients will need to be evaluated prior to dropping a histology from the trial.

A maximum sample size will be defined for the study with an accompanying statistical rationale. The sample size will be sufficiently large to allow for suitable operating characteristics and specifically to allow for reasonable precision to evaluate the consistency of effect across histologies.

Companion Diagnostic

Targeted therapies depend on the accuracy and reliability of the molecular diagnostic used to determine the presence or overexpression of the drug's molecular target, depending on the mechanism of the target. In order to effectively treat patients with targeted drugs, the diagnostic must allow for measurement and reproducibility in clinical samples, and must correlate clearly and consistently with clinical outcome. The combination of GSK2118436 and GSK1120212 has been successfully evaluated in BRAF mutant melanoma. In this setting the companion diagnostic is a simple genetic test for which a significant amount of validation has already been performed. This trial will incorporate the cDx (IUO) co-developed with both drugs to screen patients for study eligibility. Full analytical validation has been performed on the assay and clinical validation is ongoing towards a PMA submission. Because the assay detects the presence of a mutation in DNA from tumor samples, it is anticipated this will be easily transferred to other tumor types with minimal additional analytical validation required. The application and validation of the diagnostic for additional histologies should therefore be relatively straightforward. Clinical validation of the companion diagnostic in these additional histologies will be based on the data generated from within this trial.

Key Outcomes from the Trial

The proposed trial design and statistical plan should provide robust evidence of activity across all histologies enrolled. If sufficient evidence of activity is observed, it is intended that this trial could provide the basis for a registration with a label for "BRAF mutated tumors." Additionally, it would demonstrate that a multi-histology trial is a feasible approach and similarly designed trials could also lead to targeted approval.

Conclusions

Histology agnostic trials may be the most comprehensive mode by which to investigate the effectiveness of therapeutics on rare cancers. Here we propose a trial protocol that may be generalized and used to simplify the strategy required to identify therapeutic effectiveness. This design is intended for use as a tool by both the FDA and investigators to allow for a more formalized trial design with a molecular, stratified approach. This proposal systematically addresses potential issues, and proposes the best way to conduct multi-histology trials moving forward.

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