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Clinical development of 2NME-based oncology treatment regimens

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ABSTRACT

Over the past decade many signaling pathways have been identified and implicated in cancer development. This has lead to rational drug development of many new molecules that target specific nodes on one or more signaling pathways. It is now believed that targeting key parallel or compensatory pathways may require combining two or more new molecular entities (2NMEs). This approach to drug development differs from the classic case where a single component of a new combination regimen has yet to receive FDA approval. The approach presents numerous challenges to both regulatory authorities and industry sponsors. Of course, the key challenge is the usual demonstration of both safety and efficacy of the proposed combination. In addition, however, superiority of the 2NME-based regimen over both of the individual NME-based regimens and the standard of care (SOC) must be demonstrated. If the individual NME-based regimens are not very effective, then it is desirable to demonstrate the superiority of the 2NME-based regimen as early as possible in the clinical development program so that the number of patients exposed to an ineffective regimen is minimized. In this manuscript we present several strategies for clinical development programs for a 2NME-based oncology regimen. We make recommendations regarding settings where the proposed development strategies are most well suited.

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1. Introduction

An increased understanding in the role played by various signaling cascades in the pathogenesis of cancer has resulted in attempts at rational drug development involving combination strategies that simultaneously target multiple pathways. For example activation of various homo and heterodimers of the family of epidermal growth factor receptors (EGFRs) leads to protein phosphorylation and subsequent activation of different signaling pathways including the Ras-Raf-MAPK, PI3K/Akt, Crk/c-Abl, and the PKC pathways. These pathways play a key role in cell survival, protein synthesis, cell proliferation and cell migration. All members of the EGFR family have been implicated in breast, cervical, lung, colorectal, ovarian, glioma, non-small cell lung cancer (NSCLC), prostate, esophageal, bladder, endometrial and head and neck cancer. In spite of this, minimal single agent activity has been observed for EGFR inhibitors. The greatest benefit of the EGFR inhibitors has been observed in combination with chemotherapy or as part of a cancer prevention strategy. One possibility for this observation is the need for a diagnostic strategy to enable patient selection. Another possibility may be the need to target multiple nodes on one or more cancer signaling pathways. There are numerous ongoing clinical trials combining EGFR inhibitors with other targeted agents. (www.clinicaltrials.gov) [6,7,9].

It is likely that combination targeted therapeutic strategies are needed because of the biologic intelligence inherent to multiple signaling pathways. There are cross-talk, redundancy, and feedback mechanisms that allow for compensation and continued tumor proliferation when a single pathway is targeted. Therefore, a paradigm shift must occur in drug development wherein multiple pathways, targets, and networks are evaluated, and combination strategies involving two or more new molecular entities (NMEs) are interrogated. Such an approach may hold great promise in addressing unmet medical

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needs if "game changing" therapeutic regimens are enabled by the 2NME strategy.

There are many practical challenges however. For example, if a 2NME-based regimen results in truly "game changing" efficacy this will necessitate minimizing the number of patients treated with ineffective single NME-based regimens during clinical development. In addition, if overwhelming signs of efficacy are observed very early on, for example in an expansion cohort during Phase 1b, or during the conduct of a Phase 2 study in a highly refractory population, there may be fairly limited safety data for the combination regimen at the point when it is desired to do a larger confirmatory study. Thus any decisions made related to the efficacy of the individual NMEs will be made with limited data and therefore the required bar for efficacy may seem lower than is typically required. In this setting demonstration of superiority of the 2NME regimen may not always be based solely upon statistical significance, but rather a combination of a very strong scientific rationale, consistency of greater benefit across multiple endpoints, and information from previously conducted studies of the individual NMEs.

In this paper we propose clinical development strategies for 2NME-based oncology treatment regimens. By "2NME-based" we mean a regimen consisting solely of the 2NMEs, or a regimen combining the 2NMEs with standard of care (SOC). Likewise an individual NME (1NME) based regimen would consist of the single-agent entity or the NME added to SOC. We discuss statistical, operational, and regulatory challenges likely to be encountered during clinical development along with the potential impact on registration of the 2NME-based regimen. In Section 2 we discuss study options for establishing proof of concept (PoC) and subsequent clinical development paths. In Section 3 we outline simulation studies used to address the problem at hand, and in Section 4 we present results of these simulations. Finally, in Section 5 we end with a discussion of the results and additional issues for consideration.

2. PoC and clinical development path options

2.1. Establishing PoC

The development of a 2NME-based oncology regimen typically begins with the conduct of Phase 1a studies for each individual NME. This approach allows for marginal examination of the single-agent pharmacokinetic (PK) and safety profiles of each agent. Given the operating hypothesis of the need for a combination, little or no single-agent activity is expected. Once maximum tolerated doses (MTDs) are identified for each of the component NMEs, a Phase 1b study is initiated. Numerous approaches may be taken to define the dose combination levels to be explored during dose escalation. We assume however that there is some fixed number, K, of escalation cohorts such that if we are combining NME A and NME B we explore $A_1B_1, \ldots, A_KB_K$ as the fixed-dose combinations. In this setting escalation rules are used to define a bivariate dose-escalation path; thus it is possible that two MTDs are identified. At present we assume that 3–6 subjects will be treated in each of the dose-escalation cohorts until a *single* MTD is reached. Typically 15–20 additional patients will be treated at the MTD during the expansion phase. In this setting early indicators of PoC can take on a variety of forms. For example, specialized assays or imaging modalities such as FDG-PET or DCE-MRI may be used to evaluate pathway knockdown, target inhibition, glucose uptake, or anti-angiogenic activity. In addition, RECIST-based [10] tumor responses maybe observed during the expansion phase. If enough responses are observed at the MTD for the 2NME combination relative to historical data for a specific indication then it is arguable that PoC has been established.

For the remainder of the manuscript we assume that an MTD and recommended Phase 2 dose (RP2D) have been established in a Phase 1b study. Following Phase 1b we consider three different types of randomized studies to establish PoC for the 2NME regimen.

We refer to the first PoC study as the "Quick-Kill" randomized Phase 2 study (rPh2) where the 2NME-based regimen is compared to SOC. The assumption here is that there is a desire to rapidly establish the "game-changing" impact of the 2NME-based regimen and therefore the study is designed to target hazard ratios (HRs) between 0.45 and 0.55 using an intermediate endpoint that is likely to be predictive of overall survival (OS). One such potential endpoint is progression-free survival (PFS). We would likely conduct such a study in a highly pretreated population (2nd Line or later) with a fairly short median duration of PFS. The "Quick-Kill rPh2" may prove useful in gating spend in a clinical development program as well as aid in indication selection. With "game-changing" assumptions, reasonable operating characteristics (Type I error, Power, Study Duration) can be achieved with just 40–70 events in 80–100 patients.

We refer to the second PoC study as the "Large 4-Arm rPh2." This study has additional goals as compared with the "Quick-Kill rPh2." First, there is a desire to obtain safety and efficacy data on the 2NME-based regimen relative to each individual NME-based regimen and a SOC. Second, there is a desire to distinguish the 2NME-based regimen by achieving "game-changing" efficacy. And finally, there is a desire to generate data that might support a standard two-arm confirmatory study comparing the 2NME-based regimen to a SOC regimen, thereby minimizing the number of patients treated with a likely ineffective single NME-based regimen. These two PoC options are displayed below in Figs. 1 and 2.

We refer to the third and final PoC study as the "Integrated 4-Arm rPh2/3." This study has additional goals as compared with the "Large 4-Arm rPh2." First, it incorporates an interim futility analysis of the 2NME-based regimen versus SOC, and also enables dropping individual NME-based arms based upon establishing superiority of the 2NME-based regimen using an intermediate endpoint such as PFS. Second, the final analysis is based upon the primary endpoint of overall survival (OS). Use of interim efficacy and futility analyses to

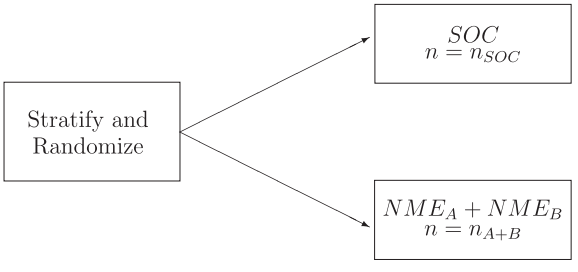

Fig. 1. Study 1: "Quick-Kill rPh2" study.

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