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PANEL 4

Development Paths for New Drugs with Large Treatment Effects Seen Early

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Introduction

Increased understanding of cancer biology, along with advanced technologies in human tumor profiling and drug design, provides promise for significant breakthroughs in treating cancer patients. There is hope that new therapies targeted to individual patients' tumor biology will provide substantial improvements in safety and efficacy.

In settings where large treatment effects on early endpoints (e.g., response rates or PFS) are seen early in development, it can be particularly challenging to balance the tension between wanting to rapidly provide sick patients with better treatments, on the one hand, and ensuring drug safety and efficacy, on the other hand. The hope and optimism that emerges from exciting early results may lead to public pressure to make these new therapies available to patients sooner, and a sense that randomizing patients to not receive a promising therapy would be unethical. Some have called for an expedited process of evaluation in situations in which striking results are seen early (1). The FDA recently released an innovation strategy in which they stated that identifying ways to expedite drug development for exceptional new drugs is a key priority for the Agency (2). Recent and highly prominent examples, discussed later in this document, testify to the timeliness and importance of this topic.

Randomized Phase 2 and Phase 3 trials provide the most reliable evidence about treatment effects. However, randomized trials that are intended to serve as the basis for approval can be extremely time consuming, expensive, and difficult to perform. In contrast, it takes significantly less time to amend a Phase 1 'expansion cohort', or to initiate and complete a single arm Phase 2 trial. For many cancers, because effective therapeutic options are not available, the patient benefits from as expedited a process as possible. When early phase results report response rates and durations that substantially exceed those provided by the current standard of care, continuing down the traditional drug development pathway may be inappropriate. Unfortunately, not every treatment that shows impressive results in early trials ultimately translates into a true therapeutic advance – one that alters the natural course of the disease. Agents may have early promising results in relatively small, uncontrolled trials, in which selection of healthy subjects and treatment in specialized centers may contribute to enhanced outcomes. When these agents are evaluated in larger, multi-center confirmatory trials, efficacy frequently diminishes, and previously unseen adverse events may emerge. Additionally these agents may not provide beneficial

effects on well-defined and reliable measures that directly assess how a patient functions, feels or survives.

In the appendix, we briefly discuss some recent settings in which large treatment effects were found in limited early trials. Specifically, we focus on vemurafenib in melanoma, crizotinib in ALK-positive NSCLC, and iniparib in triple negative breast cancer. These three examples were chosen because they each had very different outcomes. In the first example, FDA granted a full approval and, in the second, accelerated approval was granted by the Agency; different development strategies were used in these instances. In the third example, exciting early results could not be confirmed in subsequent trials. Using these cases as examples, we considered the strengths and weaknesses of specific development strategies for obtaining a reliable evaluation of efficacy and safety of new therapies when large treatment effects are observed early, and identified the alternative approach to full approval described below. It is likely that use of the approach proposed in this paper could have generated the same results in a more expeditious manner.

This panel was convened to identify consensus approaches for new, expedited development pathways for drugs that demonstrate substantial activity early in development. Thus far, single-arm studies with overall response rate (ORR) have been the basis for accelerated approval. While this continues to be a viable tool towards regulatory approval, as discussed in a recent ODAC meeting, and should continue to be an option to address unmet need, it should be used in exception circumstances, ideally while confirmatory trials have already been opened to accrual.

However, this panel has focused on a novel developmental pathway that would support full approval for new drugs that produce dramatic results in early phase trials. Well-conducted, randomized trials are necessary to confirm early results; these trials can be modest in size when treatment effects are very large. In this document, we discuss criteria that would qualify a new drug for an expedited development pathway and describe one potential expedited development pathways and an example of the level of evidence that would be necessary to support full approval. Finally, we explore how use of this particular expedited approach could have been applied to three recent examples of new products that showed high magnitude of benefit early in development. Additionally, two alternate proposals from the FDA are included in an addendum at the end of the document.

Early Considerations for Full Approval

In order to address this complex issue, the panel has agreed on a putative, specific set of circumstances in which an alternative path to FDA approval may be appropriate. Although there will still be gray area surrounding this issue, there is at least a level of benefit/risk improvement at which there is a consensus. For the purposes of this panel that consensus includes:

- The diseases under study will include indications for which the currently accepted standard of care yields poor outcomes (defined as low response rates, poor survival, symptomatic disease or high likelihood of rapidly debilitating symptoms), or for which there is no standard of care.
- The new therapy under consideration has been selected based on both a strong scientific rationale (such as targeting a molecular driver of the disease) and pre-clinical data supporting single agent activity.
- The early clinical data should suggest an extraordinary Overall Response Rate (ORR) and duration of response. The magnitude of treatment would be compared to historical standards in order to determine if the new treatment constitutes substantial benefit.
- The early clinical data would show an acceptable safety profile in a reasonable number of treated patients, Grade 3 and 4 Adverse Event rates would not be higher than those observed with SOC in

similar patient populations. However, acceptable safety data alone would not render a new drug in scope in the absence of a substantial treatment effect.

Evidence for Full Approval

While accelerated approval has been a regulatory pathway used relatively frequently in oncology drug development, it often is not initially based on randomized data, and requires confirmation of treatment effect through randomized study to gain full approval. This section explores one potential scenario that would qualify a new drug for full approval by generating reliable evidence in the phase 2 setting (following significant previous results), thereby expediting the full development process in select situations. An important matter for discussion is the question of determining, if a large effect is seen in the Phase 1 trial, what evidence will be necessary in later phase trials to allow for full FDA approval.

One important concern for determining approval is how to measure clinical benefit in pivotal trials. The options available include overall survival (OS), progression free survival (PFS), High rate of durable response rates (RR) and patient reported outcomes (PRO)/quality of life. The pros and cons of each potential endpoint are given in Table 1. Although the endpoints would need to be individually determined for each trial, the potential pathway, proposed below by part of this panel, is designed with PFS and/or OS as endpoints.

A Randomized Trial Design as an Alternative Pathway to Full Approval

Small Randomized Phase 2b Trial

1. The purpose of the trial is to demonstrate a large treatment effect in a small number of patients, while maintaining the same statistical significance currently used in trials that seek small benefits. This trial design maximizes efficiency in bringing highly active drugs to patients quickly, and in resources used to explore efficacy and safety.
2. Trial size would be approximately 120-150 patients.
    a. This is large enough to support approval if large effects are seen.
    b. The trial is small enough to be a screening trial before Phase 3, if the new therapy is not as efficacious as originally expected.
        i. It can be used as a justification for an expanded Phase 3 randomized trial if moderate effects are seen. This can be part of the agreed-upon study design upon study initiation.
        ii. If results are poor, fewer patients will have been exposed, and the most ineffective treatments will be screened out.
3. Requirements for a Phase 2 trial to be considered as approvable:
    a. Pre-specified benefit observed
    b. High quality study implementation, including adherence to intervention
    c. High quality data collection
    d. Use of Independent Data Monitoring
    e. Study site should be representative of phase 3 sites
4. The use of OS and PFS as endpoints is a topic of discussion and would need to be agreed upon prior to Phase 2.
5. If this well conducted study is positive and was accepted as the pivotal registration trial, what other safety data would be required to support approval?

Conclusions

The paper examines a novel developmental pathway that would support full approval for new drugs that produce dramatic results in early phase trials. In order to further explore how this proposed path of

expedited development might be used, with the above cases as examples, we considered the strengths and weaknesses of specific development strategies for obtaining a reliable evaluation of efficacy and safety of new therapies when large treatment effects are observed early. It is likely that use of the approach proposed in this paper could have generated the same results in a more expeditious manner. Therefore, here we explore how use of this expedited approach might have applied to three recent examples of new products that showed high magnitude of benefit early in development.

Since Phase 1 demonstrated a substantial benefit compared to otherwise available options (ORR=81%), vemurafenib would have qualified for the proposed expedited pathway. Presumably if a randomized phase 2, as described above, resulted in significant benefit, the drug would have been eligible for full approval. This approval would have been at least one month faster than the actual trial, prior to completion of the on-going phase 3, and patients in the control arm of that study could have been transitioned to treatment.

Similarly, since Phase 1 demonstrated a substantial benefit compared to otherwise available options (ORR=57%), crizotinib would have qualified for the proposed expedited pathway as well. Although the time to full approval may have shown little advantage over accelerated approval, this approach may have allowed randomized data to be generated in phase 2 that if significant would have resulted in full approval, as opposed to waiting for randomized data as a post-approval confirmatory commitment, thereby shortening the overall development program.

Iniparib also showed early signs of benefit, but unlike the previous two examples, further studies showed no evidence of benefit. However, based on our conditions specified earlier in our document, the ORR of approximately 44% seen in the Phase 1b trial(3), would not have qualified iniparib for our expedited pathway.

Therefore, a brief evaluation of previous studies suggest that use of the expedited pathway to full approval described in this document would be appropriate for use in these contexts. The expedited pathway appears to reach similar conclusions as the methods used by the sponsors; in the case of iniparib, it would not have received full approval using our pathway, although it seems it would still have received accelerated approval, as our pathway is an additional option rather than a replacement for the current pathways. Additionally, in the case of crizotinib and vemurafenib, as full approval would have been granted, speculatively it appears that approval could have been faster or based on studies with less patients, although the potential risk to the sponsor may have been greater.

Table 1. Pros and cons of trial endpoints.

Endpoint	Pros	Cons
Overall Survival (OS)	• Considered the "gold standard" in assessing efficacy- Allows for direct measure of clinical benefit and is the ultimate goal of cancer treatment. • May be required by some reimbursement services.	• Trials require randomization. • Does not allow for treatment crossover. • May be ethical considerations about randomizing patients to placebo or ineffective SOC when treatment is shown to be effective.
Progression Free Survival (PFS)	• May allow crossover.	• Requires randomization. • May require effective blinding of treatment assignment to asses without bias. • May not translate into OS.
High Rate of Durable Objective Response	• Does not require randomized trials.	• May not translate into OS.
Patient Reported Outcomes (PRO)/Quality of Life	• Provides information on full patient experience of undergoing treatment and physical effect of underlying disease.	• Requires randomized trials. • May not be an opportunity to evaluate whether one has proper instruments yielding well-defined, reliable measures.

Appendix- Case Studies

Vemurafenib

Vemurafenib is a targeted therapy which selectively inhibits the kinase activity of $BRAF^{V600E}$. The V600E mutation is present in 50-60% of melanomas and drives proliferation of these malignant cells [reviewed in (4)]. Phase 1 results demonstrated response rates that substantially exceeded responses given by the current standard of care for this deadly disease: twenty-six of 32 patients (81%) positive for the $BRAF^{V600E}$ mutation had an unconfirmed objective response to treatment (5). In contrast, the standard therapies approved for treatment of metastatic melanoma, high-dose interleukin 2 and dacarbazine, have response rates between 10-20% and do not improve overall survival (6, 7). A Phase 2 trial in 132 patients with metastatic melanoma with the $BRAF^{V600E}$ mutation was also conducted and confirmed a confirmed best overall response rate of 52%.

At the time Phase 2 results were obtained, the sponsor was also conducting a randomized, controlled, multicenter Phase 3 trial of vemurafenib vs. darcabazine in patients with previously untreated unresectable or metastatic melanoma with the $BRAFV^{600E}$ mutation. The Phase 3 trial was originally designed with 680 patients (468 events) to detect a difference in median overall survival of 10.7 months in the vemurafenib arm vs. 8 months in the DTIC arm and HR of 0.75 with 80% power and two-sided 2.5% level of significance, accounting for 2 interim analyses with 50% and 75% of information. Overall survival was the primary efficacy endpoint.

Given the impressive Phase 1 and Phase 2 results (response rates of > 50% in the targeted population of patients with metastatic melanoma whose tumors harbored BRAF V600E mutation) the Agency communicated with the applicant to modify the statistical analysis plan of the phase 3 trial (which had accrued approximately 400 patients at that time and about 300 more patients had been screened to enter the study). Specifically the Agency advised the applicant to (1) increase overall study alpha level to two-sided 5% from two-sided 2.5%, (2) set up alpha spending rule with higher probability to cross at interim analysis, (3) less conservative target HR (0.65 instead of 0.75) to be detected, and (4) add progression-free survival as a second primary endpoint. The applicant accordingly revised the statistical analysis plan to conduct final progression-free survival analysis with 187 events at which time an interim survival analysis was to be conducted with 98 deaths (50% information per modified estimates). Although patients were enrolled into the study within a very short period of time at an unexpected high rate of accrual and hence could not reduce the actual number of patients enrolled with the adaptation, the applicant was able to successfully conduct the analysis early in a planned manner with the timely adaptation of the clinical trial. Following the positive analysis any active patients on the control arm, were given the opportunity to cross-over to the experimental arm. Full approval was granted in August, 2011 based on the Phase 3 and Phase 2 trials.

Crizotinib

Crizotinib is an inhibitor of anaplastic lymphoma kinase, a gene rearrangement present in approximately 5% of patients with non-small cell lung cancer (NSCLC) (8). Phase 1 results demonstrated a 57% response rate in 82 ALK-positive NSCLC patients, again far exceeding response rates of 10% given by treatment options available at the time (9, 10).

At the End-of-Phase 2 meeting the sponsor asked about accelerated approval based on a single-arm study. The FDA expressed concern about the size of the database and recommended a randomized trial vs. conventional therapy (docetaxel or pemetrexed). Accelerated approval could be considered based on an interim analysis of a surrogate endpoint in the randomized trial. At a following meeting the sponsor asked whether it would be acceptable to submit an NDA for accelerated approval based on two single-arm trials in patients with ALK-positive NSCLC, if the safety profile remained acceptable and the observed ORR results were maintained. FDA agreed and crizotinib went on to receive accelerated approval in August,

2011 based on the results of two single arm trials in which a total of 255 patients with ALK-positive NSCLC demonstrated a median response rate between 50-60% with a median duration of 42 weeks. Randomized confirmatory trials are ongoing.

Iniparib

Iniparib is an inhibitor of the enzyme poly ADP-ribose polymerase (PARP). In an open-label, randomized study of patients with metastatic triple-negative breast cancer iniparib combined with chemotherapy produced an overall response rate of 52% compared to 32% response rates from chemotherapy alone, and prolonged the overall survival from 7.7 months to 12.3 months (hazard ratio = 0.57) (11). A subsequent randomized Phase 3 trial enrolled 519 women who had previously received at least two rounds of chemotherapy. This trial was designed with overall survival and progression-free survival as co-primary endpoints and was unable to demonstrate significant improvements in these endpoints. The sponsor is currently conducting analyses to identify patients who might best respond to iniparib.

Addendum--- Additional proposals for "breakthrough therapies" in cancer
Janet Woodcock

In addition to the development pathway worked out by the Panel 4 group, I would like to add several suggestions. Pathways for breakthrough therapies (and even the definition of a breakthrough therapy) are of course highly indication-specific. A working definition might be "an intervention that, based on information available to date, has the potential to be a very substantial improvement over existing therapies."
Many metastatic solid tumors have very poor options for remission, cure, or even durable stabilization of the disease. In these settings, durable complete response rates, or large overall response rates, can be distinguished from recent historical rates obtainable with currently available therapies.

Durable complete response
If in the initial trial, at a given dose, a substantial number of complete responses are observed, consideration should be given to the possibility that this investigational drug may be a breakthrough therapy. At this point, the sponsor should consider adding a significant number of additional patients at that dose (while also continuing dose finding as appropriate) or rapidly opening a multicenter single arm trial. The purpose of this trial would be to refine the estimate of percentage complete response by adding sufficient numbers of patients, and also following these individuals to assess durability in a fairly large number of people. This would address the criticism that the initial estimate of the treatment effect in Phase 1 trials is usually an overestimate, and also begin to get a handle on the crucial issue of relapse. If the durable CR rate is actually much lower than was initially seen, then a randomized program could be initiated. If the durable CR rate remains well superior to any historical control, then the development program should also focus on evaluating all major toxicities and determining if they outweigh the probable benefit, as well as establishing the length of CR and if possible the reasons for relapse. A full approval could be granted for a drug that provides a substantial number of durable CRs.

Overall response rate
Again, in the setting of metastatic solid tumors with no adequate therapy, an investigational drug that resulted in a very high response rate that was well over that obtained with currently available therapy could turn out to be a breakthrough drug. Here the focus is less on remission and more on stabilization of disease. After recognition of this possibility, the sponsor could focus on rapidly accruing additional patients to establish the response rate with a higher degree of precision. All patients would be followed carefully and monitored for progression. If progression occurs rapidly ("rapidly" being defined in the context of other available therapies) then a randomized program would be initiated. If the very high response rate was maintained that was well over what could be obtained with available therapy, then the sponsor would focus on understanding toxicities as well as accruing a fairly large number of patients to follow until progression occurred. If the new drug is "targeted" i.e., only used in a biomarker-defined subset, then the historical control would need to be the same biomarker-defined subset. Such a control could be established either by previously identified and followed cohorts or patients with the same biomarker results, or by assembly of an concurrent (nonrandomized) control group, perhaps from sites not participating in the trial of the intervention. This approval might be accelerated with the need to follow a large cohort of patients to eventual relapse.

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