Oncology Drug Development: A Regulatory Perspective
Faculty Presenter
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Scholars’ Summaries

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In this session, Dr. Tatiana Prowell started by reviewing regulatory terminology and approval pathways. U.S. Food & Drug Administration (FDA) approval requires demonstrating clinical benefit in how a patient survives, feels, or functions with a favorable benefit/risk ratio. To accelerate the development of drugs treating serious diseases where there is an unmet need, four different somewhat independent expedited development approaches have been developed. Fast track designation is for a specific indication where a minimum of one clinical response has been observed. It is granted early in clinical development prior to submitting a new drug application (NDA) and this designation entitles the sponsor to a rolling NDA or biologics license application (BLA) such that the sponsor can submit completed sections of the application rather than wait to complete the entire application. A priority review designation means that the FDA’s goal is to review and take action on a completed application within 6 months, as opposed to 10 months under a standard review. This may be granted after completing NDA/BLA submissions, if the product represents a significant improvement compared to marketed products or if no satisfactory alternative exists. Accelerated approval permits approval based upon a “surrogate endpoint” that is reasonably likely to predict clinical benefit; however, a confirmatory trial to demonstrate clinical benefit is required. Breakthrough designation is for drugs where early clinical evidence indicates drug may demonstrate substantial improvement over available therapies on clinically significant endpoint(s). This designation provides early and frequent contact with various disciplines at the FDA to provide guidance on an efficient drug development program, including manufacturing requirements.

The next part of the presentation discussed trial endpoints that would meet the regulatory requirements of clinical benefit. In the advanced cancer setting, “clinical benefit” has commonly meant overall survival or progression-free survival of sufficient magnitude. Patient reported outcomes (PROs) may also be an acceptable endpoint as they directly measure clinical benefit. However, the challenge has been to find ways to reliably and appropriately measure clinically meaningful changes using valid instruments. Objective response rate (ORR) can be useful in single arm studies as it can distinguish treatment effect from disease natural history. Traditionally, it could be used to grant accelerated approval as a surrogate endpoint, but did not qualify as a measure of direct clinical benefit for a full approval. However, a case study example of ruxolitinib where ORR in combination with PROs were used to demonstrate clinical benefit highlights how novel drugs may receive regulatory approval using non-traditional trial designs and endpoints to assess clinical benefit.

Lastly, common errors in developing drugs for regulatory approval were discussed. These include a lack of dose optimization, a failure to consider relevance to the U.S. population, or a failure to isolate the effect of the new drug. The need to avoid statistical pitfalls such as distinguishing between statistical versus clinical benefit and non-inferiority versus superiority trials was emphasized.

Authored by Valerie Grignol, MD, The Ohio State University, Columbus, OH, USA

The U.S. Food & Drug Administration (FDA) has several routes for approval and although the naming may imply quicker approval for some knowing the specifics can really affect the time to drug approval. There are two types of early designations for drugs that show a benefit early in testing. Fast track designation for drug development allows for the
investigator to submit a rolling NDA/BLA after just one clinical response to therapy. Breakthrough designation is for therapies that treat a serious or life-threatening condition and early clinical evidence shows a significant improvement over existing therapy at a significant clinical endpoint. This approach to development allows for frequent and regular contact between FDA and investigator through drug development and NDA. Neither fast-track nor breakthrough designation guarantee an approval. In regards to review once the NDA is completed there are also two types: priority and standard review. Priority improves the goal date for regulatory action by 4 months. Priority review is granted for therapies that represent a significant improvement to what is available or no standard therapy exists. Again it has no bearing on approval. Finally, for approval, again there are two options, which are accelerated and standard approval. Accelerated permits approval based on a surrogate endpoint that is likely to have clinical benefit. Accelerated approval requires a confirmatory trial whereas standard does not, as standard approval requires direct clinical benefit to be shown from the outset. Therefore, while accelerated approval may seem enticing, because it requires a confirmatory trial it may actually take longer to obtain full approval. Clinical benefit as described by the FDA is how a patient feels, functions or survives. Direct clinical benefit for cancer therapy has traditionally been overall survival. Recognizing that survival is not the only endpoint in cancer therapy PRO have become an important element in clinical trials when a therapy has a significant impact on symptoms but does not impact survival as strongly. While this is much more subjective, with the correct tool and validation they measure an important endpoint, how a patient feels. These types of therapies are important as they could allow the patient’s symptoms to be managed to the point they could receive other therapies that do impact overall survival.

Author by Gaorav Gupta, MD, PhD, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA

Dr. Tatiana Prowell gave a riveting talk on oncology drug development from the perspective of the U.S. Food and Drug Administration (FDA). The topic was one that I had little familiarity with prior to this lecture. Dr. Prowell did a great job of using real-world examples to discuss the different paths to FDA approval. She reviewed the various “designations” that the FDA uses to prioritize new drugs. She also explained the difference between accelerated and regular approval. Significantly, although accelerated approval allows the investigators to use a surrogate clinical endpoint it mandates data on comparative efficacy and a confirmatory trial. Thus, in many ways accelerated approval is more stringent than regular approval. Another interesting topic was a discussion on what constitutes clinical benefit. She described how validated patient-reported outcomes can be useful tools to demonstrate the clinical benefit for a new drug, particularly in palliative settings. Dr. Prowell also used real-world examples of mistakes in study design that led to lack of FDA approval due to an inability to ascertain the clinical benefit of that particular drug. Overall, I left this lecture with a much better understanding of the FDA perspective on oncology drug development—insights that will definitely help me when considering clinical trial design for a new drug.

Author by Richard Lin, MD, PhD, New York University School of Medicine, New York, NY, USA

During the 2015 Annual Society of Translational Oncology Fellow’s Forum, we were given an excellent talk on oncology drug development from a regulatory U.S. Food & Drug Administration (FDA) perspective. The speaker, Dr. Tatiana Prowell, is a director of oncology drug development team at FDA. She took us through considerations of FDA during the drug development process and common mistakes in clinical trial design, drug approval process, and data interpretation. It was a mind boggling session in that research scientists and clinical trialists, even at very high levels in their respective fields, tend to ignore these parameters, which lead to significant amount of wasted labor, energy, and financial resources.

I found the topic extremely interesting for several reasons. First, the FDA perspective represents the interests of public and the government therefore their decision is supposed neutral. Yet the influence of academic researchers and pharmaceutical industry are substantial. It is really a collaborative process. For example, she used the case of ruxolitinib in primary myelofibrosis to illustrate the importance of early discussion with FDA on the use of unconventional end-points, splenic response rate as well as quality of life measures, in the design of pivotal trial for the approval of ruxolitinib. In addition, the increased use of patient reported outcomes (PROs) as validated clinical end points was highlighted.

Interestingly, the FDA has taken several recent steps toward encouraging inclusion of the patient perspective in drug development. It has issued highly influential guidance on the use of patient-reported outcomes (PROs) in drug development, collaborated with the Critical Path Institute and industry to form the PRO Consortium with the aim of developing robust symptom-measurement tools, such as the PRO version of common NCI toxicology criteria CACTE. These FDA efforts are...
evident in the ruxolitinib label and in the label for abiraterone acetate, approved for metastatic prostate cancer, which describes beneficial delays in time to the development of pain and the need for opioid use.

In summary, I believe that an early and ongoing dialogue and collaboration with FDA is essential for oncology drug development. As Dr. Prowell elegantly put it, “We view clinical benefit as regulators in terms of whether the net benefit/risk of a drug is favorable: – Would cancer patients be better off having widespread access to this drug?”

**Authored by Thomas A. Longo, MD, Duke University Medical Center, Durham, NC, USA**

Dr. Tatiana Prowell took us through drug development from the position of the U.S. Food & Drug Administration (FDA), a body largely surrounded by obfuscation. Her explanation illustrated the thoughtfulness of the FDA, and left me with a profound respect for the organization.

Dr. Prowell began with simple definitions that explained the review process. It drew clear distinctions between 4 review processes that sound similar. The advantages pitfalls of each were laid out, and a sound opinion was offered for choosing a review.

The review process flowed nicely into the discussion of a choice of endpoint. As the pressure to receive approval grows, we look for a surrogate endpoint that will meet this need. The defense of overall survival because it captures efficacy and safety is a vindication of medicine throughout history. However, other endpoints were not without hope. Then followed several examples of the appropriate use of surrogates, such as pathologic response rates, patient reported outcomes, their potential hazards, and how they are being improved.

Finally, the discussion of biomarkers was particularly valuable. Once again, the discussion of pitfalls helped my understanding of trial design; if you cannot be a good influence, you can always be a bad example. The importance of a predetermined interim analysis was highlighted, so that a trial could undergo enrichment. There was an explanation to plan futility analysis of control arm to what you want to see, drop one of the control arms. As research resources continue to become scarce, trials designed to get the right drug to the right patient are increasingly important. As custodians of this knowledge, it would be shameful to improperly use these drugs, either because we falsely find an effect or we fail to show efficacy that does exist.

As an aside, several speakers alluded to the fact that drugs are intended for a global market and not just the U.S. The discussion that followed was fascinating, and Dr. Prowell was able to shed the most light on the topic. It was heartening to hear that if a drug was so effective at an interim analysis, the FDA would encourage crossover, so that all patients enrolled in the trial could benefit from the new therapy. It was also interesting to hear that a drug company would consider the global population and understand the need to prove their drugs value (financial savings for a national healthcare system) to markets outside the U.S. Therefore, they may continue their phase 3 as originally designed so they could prove its superiority not only in efficacy, but in cost savings against gold standard, and thereby make the drug available throughout the world. Perhaps it is naïve, but I believe that most involved in medicine have helping humanity as their ultimate goal.

**Authored by Tracy L. Rose, MD, MPH, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA**

There are several pathways through the U.S. Food & Drug Administration (FDA) that can expedite the drug development and approval process. A drug is put on the “fast track” early in drug development. This entitles a company to a rolling new drug application submission and this designation is given if there is any indication the drug may have clinical responders. A drug is given “priority review” after a new drug application is submitted and only if the drug could represent a significant improvement compared with marketed products, or if no satisfactory alternative exists. With priority review, the goal date for regulatory action is 6 months. “Accelerated approval” means that approval is based on a surrogate endpoint that is reasonably expected to predict clinical benefit. Therefore, a confirmatory trial is required to demonstrate clinical benefit. “Breakthrough” therapy designation is given if a drug shows early clinical evidence that it may demonstrate substantial improvement over existing therapies. This designation provides early and frequent contact with all disciplines at the FDA. “Clinical benefit” includes overall survival (OS), but can also include progression-free survival (PFS) (if of sufficient magnitude) and other symptom-oriented endpoints like pain. For example, ruxolitinib was approved based on a clinical
benefit of an improvement in symptoms.

There are other potential pitfalls in the drug development pathway from the regulatory perspective. Dose optimization can be an issue, as the historically-used maximum tolerated dose may not be the best choice for targeted therapies. The population included in trials being used for approval should be reflective of the U.S. population. For example, supportive care used in the trial should be comparable to that used in the U.S. Biomarker design needs to be thoughtful. Statistical considerations should include making sure endpoints are clinically significant, subgroup analyses are defined a priori, and interim analyses are well-planned.

Authored by W. Iris Zhi, MD, PhD, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Dr. Tatiana Prowell’s lecture explained in great detail about the U.S. Food & Drug Administration (FDA) oncology drug approval pathway, endpoint selection and trial design problems and errors.

There are four expedited drug development pathway: fast track designation, priority review, accelerated approval and breakthrough therapy designation. Those four tracks have different roles in drug development. Fast track is usually granted early during the drug development based on clinical response, in a specific clinical contest and a reasonable development plan. Fast track designation will allow the drug company to a NDA/BLA submission. In contrast, priority review is determined after the completion of NDA/BLA submission and usually is given to a product with significant of improvement of current guideline and no other satisfactory alternative therapy exists. Priority review means an expedited 6-month timeframe for regulatory action rather than 10-months for standard review. Accelerated approval permits the surrogate endpoint that is reasonably likely to predict a clinical benefit. It is neither not based on marginal evidence in an established endpoint or salvage a failed trial. In comparison with regular approval, accelerated approval is required to have a confirmatory trial with direct clinical benefit and usually is considered in a disease of serious or life threatening condition.

The breakthrough therapy designation is indicated for any product to treat specific serious disease with evidences of possible substantial improvement. This path provides early and frequent contact with FDA, however, does not guarantee a approval. Clinical benefit is the key element from regulatory standpoint. It needs to be a direct measure of patient symptoms, life quality, and survival. Traditionally, clinical benefit means a better overall survival or a better progression free survival. Those endpoints can be measured precisely without any gray zone for interpretation; can capture both safety and efficacy; and rarely missing data or difficulty to verify. In the lieu of immunotherapy, overall survival is superior to median PFS in terms of correctly evaluation of therapeutic efficacy. Clinical benefit is the net of benefit and risks of any drug would provide to our cancer patients. FDA plays a vital role of appropriate trials designs and endpoints to assess clinical benefit.