Special Session (Thu, 24 Sep, 09:00−11:00)
Current challenges with the approval and availability of targeted anti-cancer agents

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Approval strategies with new agents: The need to redefine comparator arms

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The regulatory environment in Western countries is influenced by competing needs. On the one hand, most regulatory bodies were established to protect the public from potentially harmful agents and safety remains a paramount concern. On the other hand, effectiveness demonstrated by achieving any of several endpoints (overall survival, progress-free survival, tumor response, surrogate response) can overcome safety concerns. To demonstrate effectiveness, and an acceptable benefit to risk ratio, investigators must select comparator arms in phase 3 clinical trials that reflect the "regulatory reality" but also clinical reality. At times these two realities are not consistent and this can lead to tension between those who regulate drugs and those who develop them. This talk will provide examples of discordant control arms and provide potential solutions which will need to be even more carefully considered as we enter an era of increasing applications for approval of targeted therapies with efficacy limited to newly defined subsets of patients.

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Biosimilars: issues facing clinicians

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Recombinant technology has provided a means of producing a variety of therapeutic proteins, allowing biopharmaceuticals to become important therapeutics. The recent and pending patent expirations for a number of biopharmaceuticals has prompted the development of alternative formulations of biologic products, referred to as biosimilars.
Biosimilars are new biopharmaceuticals that are "similar" but not identical to the reference product. Characteristics of biopharmaceuticals are closely related to the manufacturing process, which cannot be exactly duplicated. Thus, biosimilars are unique molecules and not generic versions of the innovator drug.
When biosimilars are approved, they will be considered comparable to the reference product, but this does not necessary imply therapeutic equivalence. The inherent differences between any two biopharmaceuticals have the potential to produce dissimilarities in pharmacological properties, clinical efficacy, safety and immunogenicity. Switching from one biopharmaceutical to any other should be considered a change in clinical management and must be accompanied by appropriate monitoring.
General regulatory guidelines for biosimilars have been established but the approval process will vary according to the therapeutic product. As there will be limited clinical experience with biosimilars at approval, pharmacovigilance programs will be important to establish a comprehensive safety and efficacy database for these new products. Guidelines also provide a mechanism for extrapolation of clinical indications for biosimilars to indications as for the reference product, ie approval for indications for which the drug has not been studied.
Automatic substitution allows for the dispensing of generic drugs by pharmacists without the knowledge or consent of the treating physician. For a variety of reasons, automatic substitution may not be suitable for biopharmaceutical products. In many European countries automatic substitution of biopharmaceuticals is not allowed/recommended. Automatic substitution would confound the collection of pharmocovigilance data. It may not be possible to properly link adverse events to a specific product if multiple biopharmaceutical products share an INN. It would appear prudent to assign unique international non-proprietary names (INNs) to biopharmaceuticals or use "brand" names.
Production of biopharmaceuticals is very expensive. At introduction, it can not be expected that there is a major difference in price between biosimilars and the reference product. Today, biosimilars are about 20−30% cheaper than the reference products.
The longer a biosimilar is used in clinical practice, the greater the amount of clinical efficacy and safety data will be available. Rigorous pharmacovigilance programs are needed to capture these data and to build a database establishing the clinical use of each product.
Healthcare professionals must be aware of the issues surrounding the introduction of biosimilars and the differences between biosimilars and innovator biopharmaceuticals so that informed decisions can be made and to ensure the appropriate use of biopharmaceuticals.

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Biosimilars: The industry perspective

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Systemic treatment of cancer is rapidly evolving with an increasing number of targeted therapies already approved for cancer and several hundred more in various stages of clinical development. An increasing proportion of these targeted anticancer therapies as well as supportive care drugs are biological agents produced through fermentation processes rather than traditional synthetic chemistry. It is estimated that by 2014, the six biggest selling drugs in the world will be biologicals. Impressively, three of these six drugs will be cancer drugs, i.e., Avastin (estimated to be top selling drug across all therapeutic areas), Rituxan/MabThera and Herceptin. It is also estimated that ~$25 bn dollars worth of biologics will lose patent protection by 2016 and these will include anti-cancer blockbuster drugs such as Herceptin, Rituxan/MabThera. Hence, there is considerable interest in making 'generic' versions of these drugs. For traditional small molecules, it is generally considered sufficient to demonstrate physico-chemical similarity and pharmacokinetics to the respective approved drug in order for a generic equivalent drug to be approved. However, the situation is considerably more complex for biologicals. Not only are these molecules more difficult to manufacture, they often go through post-translational modifications which may significantly change their biological properties. Even minor changes during the manufacturing process can lead to product with altered biological characteristics. The situation is even more complex for biomolecules with multiple mechanisms of action where the contribution of each mechanism to the overall effect may not be known; sometimes, there may be uncertainty even about the primary mechanism of action. For example, it is unknown as to how much of trastuzumab activity is through activation of ADCC and how much of the activity is contributed through inhibition of signaling. Similarly, there is considerable debate as to whether the primary mechanism of efficacy of bevacizumab is through inhibition of angiogenesis or through normalization of tumor vasculature leading to increased delivery of chemotherapeutic drugs.
Given these complexities, it is no surprise that different sectors of the biopharmaceutical enterprise have a different position on the minimum requirements that biosimilars must meet in order to receive regulatory approval. In fact, the use of term 'biosimilar' as opposed to 'biogeneric' is a tacit admission that it is virtually impossible to make an exact copy of a biologic agent. This raises concerns over the safety/efficacy of biosimilars. The industry generally agrees that an approval path needs to be found for biosimilars to avoid an inordinate impact of the soaring costs of new biological agents on the drug budgets of the healthcare system in the not too distant future. However, the 'innovation-driven' industry is striving to achieve a prolonged period of exclusivity for biological while the 'generic/biosimilar' industry is pushing to substantially reduce the barriers to entry of biosimilars into the market. Interestingly, recently, some big pharmaceutical companies that have traditionally focused primarily on innovation have announced major moves into the biosimilars arena. In EU, legislation has already been passed that allows for 10 years of patent protection to biologics. In addition, biosimilar manufacturers must justify the difference between their product and the reference product by conducting appropriate non-clinical and clinical studies. A vigorous debate is currently ongoing in the US Congress as well as among governments and payers in other countries on this issue. At the time of writing this abstract, the US congressional healthcare leadership has proposed an exclusivity period of 5 years, while biotechnology industry has proposed a period of 12−14 years. Even when the debate over the length of exclusivity is settled, industry, regulators and others will still need to come to an agreement on the extent of clinical testing required. It is generally accepted that pharmacokinetic equivalence cannot be the only clinical data required for most anti-cancer biologics. However, there is no consensus yet on the extent of clinical trials required to demonstrate similar efficacy and safety as compared to an approved branded biologic. Similarly, the extent of post-marketing surveillance required for approved biosimilars has also not yet been defined. While the details will likely have to be decided on a case by case basis, it is fairly certain that the cost of development of biosimilars will be substantial and therefore, the price differential between a biosimilar and a branded drug will not be of the same order of magnitude as that between a branded and a generic small molecule drug. Given these complexities and many other emerging uncertainties, it is important for industry, regulators, payers, clinicians and advocacy groups to work together to evolve a viable and pragmatic path for approval and clinical utilization of biosimilars.