

Cancer immunotherapy products

Regulatory aspects in the European Union

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Abbreviations: AEMPS, Agencia Española de Medicamentos y Productos Sanitarios (Spanish Medicines Agency); AJCC, American Joint Committee on Cancer; APCs, antigen-presenting cells; CHMP, for Medicinal Products for Human Use; CT, computed tomography; DFS, disease free survival; ECOG, Eastern Committee Oncology Group; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GM-CSF, granulocyte-macrophage colony-stimulating factor; HR, hazard ratio; HSPPC, heat shock protein-peptide complex; ICH, International Conference on Harmonization; ITT, intention to treat population; MA, marketing authorization; MAA, marketing authorization application; PAP, prostatic acid phosphatase; PBMCs, peripheral-blood mononuclear cells; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetics; RCC, renal cell carcinoma; US, United States

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Active immunotherapy products (widely known as “cancer vaccines”) are products intended to stimulate an immune response to mediate tumor destruction or reduce the progression of disease in patients where cancer has been diagnosed. Some quality attributes of these products are very difficult to characterize or present a high variability (especially if they are for autologous use), further complicating the interpretation of some of the clinical data. Furthermore, questions arise in the evaluation of efficacy and safety data in comparison with current chemical or biological treatments for the same indications. Some of these aspects are discussed in this paper in relationship with the regulatory requirements in the European Union and as applied to two recently assessed medicinal products, Oncophage and Provenge, both considered therapeutic “cancer vaccines” for renal cell carcinoma and prostate cancer, respectively.

Introduction

Today research in cancer involves several approaches; from the classical cytotoxic compounds to biological therapies such as monoclonal antibodies or gene or cell therapy. Biological medicinal products such as ipilimumab¹ or the first vaccine to prevent human papillomavirus infection² have increased interest in cancer immunotherapy and the approval of Provenge[®], the first cell-based immunotherapy or cancer vaccine, by the FDA has raised high expectations for these kinds of products.³

Sipuleucel-T (Provenge[®]) is currently under evaluation in the European Union (EU) and a number of scientific regulatory issues emerge in comparison to other, more conventional cancer treatments. As many other immunotherapy cancer treatments are under development, discussion of those issues is of critical importance in the development of new treatments.

This paper focuses in regulatory issues of active cancer immunotherapy products, also widely referred in the scientific literature as “therapeutic cancer vaccines,” i.e., intended to stimulate an immune response to mediate tumor destruction in patients with an existing diagnosis of cancer. It does not include passive immunotherapeutic products which may mediate their therapeutic effect by targeting the tumor directly, such as monoclonal antibodies (e.g., trastuzumab, bevacizumab) or adoptive T cell therapy. Although the term “cancer vaccine” is widely used, in the EU, from a regulatory perspective, it is preferred to restrict the term “vaccine” to products that stimulate immunity against infectious diseases⁴ and refer to the other treatments as “immunotherapy.”

More than 200 clinical trials are described^{5,6} for indications such as melanoma, glioma, adenoma or prostate, bladder, or esophageal cancer and using a large variety of strategies such as plasmids (Allovectin[®], NY-ESO-1 Plasmid DNA (pPJV7611)), autologous and allogeneic tumor vaccines, liposome-encapsulated peptides (Stimuvax[®]) or peptide antigens conjugated to other agents such as DNP (Ovax[™]), GM-CSF

secreting cancer vaccines (GVAX®), recombinant EGF combined with an adjuvant, mRNA (RNAActive®), dendritic cells loaded with a tumor lysate (Trivax®, DCVax®-L), with a recombinant protein (CVac™) or with RNA (MB-002), viral vectors incorporating particular genes (Trovax®, ALVAC-hB7.1, ProstAtak™), live attenuated bacteria (*Listeria* cancer vaccine ADXS11-001), activated autologous T cells (hTERT primed T cells), and monoclonal antibodies (ipilimumab, farletuzumab).

As mentioned earlier, this paper focuses on active cancer immunotherapy, that is, on those strategies directed at treating and reducing the progression of the disease by stimulating an immune response against the tumor. As a general approach, it would be easier to design a medicinal product for an earlier stage of the disease since, theoretically, the metastatic stage would be harder to treat from a immunological point of view. Unfortunately, the earlier in the course of the disease the intervention takes place, the longer it takes to see efficacy demonstrated in terms of life expectancy. This is the reason why several companies are targeting metastatic disease. The cost of development would be lower and, additionally the preferred variable from a regulatory point of view, i.e., overall survival, would also be tested. Provenge® development and the FDA's approval for metastatic prostate cancer is an example of this kind of approach.

Although the marketing authorization in the US for Provenge® implies that this cancer vaccine has demonstrated efficacy and safety in the proposed indication, at least from the FDA's point of view, most clinical trials with similar products have failed or have shown a modest effect. Possible reasons include treatment at a late stage of disease progression as, due to the mechanism of action of these immunotherapy products, early disease would be considered more suitable (as described above), previous treatments (e.g., myelosuppressive effect of previous chemotherapy), a limited immune response if only one tumor antigen is targeted, rapid tumor progression (faster than the capacity of the immune system to respond), correlation of the primary

endpoint (survival) with an immune response (normally assessed during the trial) or the validity of the measured immune response.^{7,8} Additionally, some quality attributes of these products are very difficult to characterize or present high variability (e.g., including autologous components) further complicating the interpretation of the clinical data. Some of these aspects are discussed below in relationship with the regulatory requirements in the EU and specifically applied to the products Oncophage and Provenge®.

The European Union Regulatory Framework

In the EU cancer immunotherapy products are considered medicinal products. Due to their general indication (cancer) the assessment of their marketing authorization application (MAA) follows what is called the “centralized procedure.”⁹ Products follow the same evaluation procedure if they include biotechnology-derived products (such as recombinant EGF), gene therapy vectors (such as Trovax®) or cells (such as Trivax®). In the centralized procedure the documentation is assessed by all the National Competent Authorities in the EU and the process is coordinated by the European Medicines Agency (EMA). This results in a single marketing authorization for all the countries in the EU. Pricing and reimbursement are decided nationally. Approval of clinical trials also remains a national decision.

The EMA Committee for Medicinal Products for Human Use (CHMP) has published scientific guidelines to help applicants prepare their MAA dossier for human medicines. The aim of these guidelines is to give recommendations on how to demonstrate quality, efficacy and safety in EU.^{10,11} Guidelines are elaborated taking into account the state of the art and the point of view of different parties, i.e., industry, patients and regulatory authorities. In general, within the framework of the pharmaceutical legislation, guidelines do not have legal force and the definitive legal requirements are those outlined in the relevant Community legislative framework (directives, regulations,

decisions, etc.) as well as appropriate national rules (there are some exceptions with explicit legal basis). However, EU regulators refer to these guidelines as they will facilitate the approval of medicinal products. A deviation from a guideline recommendation is possible if appropriately justified although scientific advice at the EMA and/or by National Authorities is recommended.

In the end, any medicinal product must show quality, efficacy and safety, i.e., a positive benefit/risk ratio, and the same rules apply whether a medicine is a cytotoxic drug or an immunotherapy product. This is sometimes misunderstood for certain innovative therapies (e.g., “cancer vaccines”), and the requirements for approval are not well understood. From a regulatory point of view, the assessment of any drug is performed under the same premises.

Quality issues. A large number of guidelines on quality aspects have been developed and their applicability depends on the nature of the product, i.e., if it is a biological, biotechnology-derived or a gene or cell therapy product.¹¹ Although they include recommendations applicable at the time of MAA it is useful to consider them during the clinical development. If relevant European Pharmacopoeia monographs exist they also apply at the time of MAA.¹²

As for any medicinal product, identity, purity, potency, sterility and stability of the product should be shown. For biotechnology-derived products used as components of a cancer immunotherapy the requirements are identical to other recombinant proteins. There is large experience in the evaluation of these products as many have become the treatment of choice for many diseases. Quality aspects are relatively easy to assess since there is limited heterogeneity within the product (the protein derives from a clonal cell population) and an extensive control testing strategy is possible (batch size and time for control testing are not limiting). Additionally, current test methods allow a thorough characterization of the drug product. However, this is not the case if the product includes a cellular or other autologous component (e.g., Oncophage

or Provenge). The manufacturing process is not so easy to standardize but, at least, it should not contribute to increase the inherent heterogeneity and variability of the resulting product. Drug product characterization could be challenging due to the complexity and/or availability of the product (e.g., if different cell populations exist -Provenge- or autologous tumor derived peptides are included -Oncophage-) and due to time constraints (e.g., short shelflife of cell based products). In any case the components of the active ingredient should be defined and test methods to assess identity on every batch should be described. Cell markers (both positive and negative) are commonly used for cell-based products. The presence of other cell populations in the product, other than the active ingredient, should be controlled and justified. A test for potency is a critical part of the product characterization and is a challenge for the reasons previously described. However, it is a critical parameter to test on every batch and it should be relevant for the expected biological activity of the product. Due to the limited processing of some of these products, microbiological safety testing at several steps during manufacture is recommended. Sterility testing using newer methods using less sample volume and time could be an alternative.

Clinical issues. In the EU, the guidelines applicable for any cancer therapy are the following:

(1) Guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 Rev. 4)

(2) Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man — methodological considerations for using progression-free survival (PFS) as primary endpoints in confirmatory trials for registration (CHMP/EWP/27994/08 Rev. 1)

(3) Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95 rev. 3) on hematological malignancies

(4) Clinical trials with hematopoietic growth factors for the prophylaxis of infection following myelosuppressive or myeloablative therapy (CPMP/EWP/555/95 Rev. 1)

(5) Addendum on pediatric oncology (CPMP/EWP/569/02)

Besides cancer specific guidelines there are general guidelines for efficacy and safety.¹¹ These reflect some important aspects in several areas (e.g., missing data, statistical, choice of a non-inferiority margin, clinical trials in small populations, etc.).

In general, for anticancer medicines, including active cancer immunotherapies, the clinical and methodological outstanding endpoint in confirmatory trials is to increase patient life expectancy. In regulatory jargon this variable is called “Overall Survival” (OS), defined as time from randomization to death from any cause. It is not always feasible to achieve mature data in OS, mainly due to expected survival for some types of cancers. In that case, other variables could be considered [progression free survival (PFS), disease free survival (DFS)], however, the estimated treatment effect on OS should be sufficiently precise to ensure that there are no relevant negative effects on this endpoint. The ideal goal would be to prove an increase in survival or, alternatively, improve the quality of life for the patient. Sometimes the positive effect observed in OS or PFS should balance an increased toxicity. This is part of the benefit risk ratio included in the assessment of any medicinal product.

Case Studies

The regulatory experience with active cancer immunotherapies in the EU is very limited as only two products have applied for MAA through the centralized procedure, Oncophage and Provenge, although a few more under development have applied for scientific advice. The discussion below on regulatory requirements will mainly focus on the information available for those two products, either from the published literature or from the EMA or FDA websites (for Oncophage^{13,14} and Provenge,¹⁵⁻¹⁷ respectively).

Oncophage. Antigenics Therapeutics Ltd. submitted the application for Oncophage in October 2008. It had received an orphan medicinal product designation in 2005 for the treatment of renal cell carcinoma. Oncophage (vitespen or HSPPC-96) in a solution for intradermal

injection contains approximately 25 µg of autologous tumor-derived gp96 heat shock protein-peptide complex (HSPPC-96) in 0.40 mL of a sucrose and potassium phosphate buffer solution. The HSPPC-96 complex is composed of the 96 kDa heat shock protein glycoprotein 96 (gp96) in a non-covalent complex with tumor-derived peptides. The applicant described that it is the peptide component that is tumor- (and patient-) specific and immunogenic. The proposed mechanism of action is the product’s ability to stimulate an immune response against tumor antigens after specific peptides coupled to gp96 have been recognized and a T cell response is triggered. The 25 µg dose is administered once a week for the initial four weeks, then every other week until depletion of supply. The product is approved in Russia for a certain stage of kidney cancer¹⁴.

From a regulatory point of view this product is considered a biological medicinal product as it is obtained after extraction and purification from tumor tissue. The active substance is gp96 coupled with specific peptides derived from the patient’s own renal tumor mass, therefore, the starting material is different for every batch of product (each intended for an individual patient) and this complicates product manufacturing and characterization. Although deficiencies from the quality point of view have been described in detail,¹³ manufacturing and characterization were considered critical limitations. As the variability of the starting material might be high, it is very important to define appropriate specifications (or acceptance criteria) to define an acceptable final product. As for the proposed mechanism of action for Oncophage it would imply the demonstration that both components (gp96 + tumor peptides) necessary for the action are present and in an adequate amount to trigger the desired action *in vivo*. Because of the limited availability of the starting material, alternative approaches could have been acceptable, i.e., data obtained from an appropriate tumor model. In addition, a potency assay (i.e., measure of the biological activity of the product) is necessary to provide assurance that the amount of the active ingredient is sufficient to induce a

meaningful response and that the amount is consistent from batch to batch. Ideally, a potency assay should reflect the proposed *in vivo* mechanism of action but the limitations are recognized and alternatives have been accepted for existing products (e.g., measure of antiviral activity for β interferon used in multiple sclerosis). In any case, the potency assay should be able to detect clinically meaningful changes in the amount of active ingredient in a human dose of a product and it is an extremely valuable tool to provide assurance that the product has maintained its desired characteristics throughout the development process or when changes to the manufacturing process are introduced. When clinical results are compelling and robust in terms of efficacy and safety, these aspects become less relevant but when the clinical data are limited, physicochemical and biological characterization is of critical importance to assess the overall benefit/risk of the product.

Antigenics Therapeutics Ltd. applied for the following indication: as adjuvant treatment for localized renal cell carcinoma (RCC) patients at increased risk of recurrence with the following features: Primary tumor stage T1b or T2 with high-grade (3 or 4) histology with no nodal involvement. These characteristics included patients who were considered Stage I or II according to the American Joint Committee on Cancer (AJCC) criteria.

Neither pharmacokinetic (PK) studies nor studies addressing the mechanism of action of Oncophage were submitted. The absence of any PK studies was deemed acceptable considering the route of administration (intradermal), the proposed mechanism of action and the nature of the product (autologous immunotherapy). In contrast, the lack of pharmacodynamic (PD) studies in RCC was raised by the CHMP as a major flaw. The applicant submitted other PD studies with other tumor-derived HSPPC-96, though of limited value, since there was not a proof of concept in RCC.

The efficacy of vitespen treatment was assessed in an open-label single phase 3 study in the adjuvant setting in patients with RCC (protocol C-100-12). Again, no dose-response studies were submitted

in the application. This fact was also considered a major objection.

Regarding the pivotal trial, patients with RCC who were scheduled for or had recently undergone nephrectomy to remove the primary tumor and without metastases, were enrolled in the study. Patients were to receive adjuvant treatment with vitespen or no adjuvant treatment (observation only). The test arm received Oncophage at weekly intervals for 4 weeks (starting about 6 to 8 weeks after surgery), and thereafter at 2-week intervals until the patient's available supply of vitespen was depleted or until recurrence of disease. Randomization was stratified by Fuhrman grade [low (1–2) vs. high (3–4)], regional lymph node status (N0/Nx vs. N+) and ECOG performance status (0 vs. 1).

The primary endpoint of the study was DFS (defined as time from randomization until recurrence of disease or death from any cause). CT scans were conducted in both the experimental and observation arms every 3 months in the first year, every 6 months in the next two years and yearly thereafter. OS was the secondary endpoint. Patients were evenly balanced between groups. 818 patients were randomized and 728 (361 vs 367) patients were included in the ITT population (primary efficacy analysis). No statistically significant difference was seen between the treatment arms in terms of the median or the hazard ratio for recurrence-free survival in the ITT [HR = 0.923; 95% CI (0.729, 1.169)], i.e., the primary endpoint was not met. Additionally, OS was not superior in the experimental group [HR = 0.978; 95% CI (0.702, 1.364)].^{18,19}

Beyond methodological problems and without minimizing their relevance, it is clear that the objective of the study was not achieved. The superiority of Oncophage was not demonstrated. The pivotal study was a failed trial in the most important variables, including the primary endpoint. It should be noted that the company tried to justify a positive effect in one subgroup only (intermediate risk patients). However, from a regulatory and methodological point of view, this strategy is not acceptable. There is always the danger that sponsors will 'cherry-pick' the positive results and present only those. But in this case, the subgroup was

pre-specified. However, with negative results in the primary endpoint and in the key secondary variable for the whole of the study population, the positive outcome seen in a subgroup was not accepted as proof of efficacy.

Provenge. Sipuleucel-T (Provenge, APC8015) is a patient-specific autologous cellular therapy for the treatment of hormone refractory prostate cancer. The active ingredient of the product is autologous peripheral-blood mononuclear cells (PBMCs), including antigen-presenting cells (APCs), that have been activated *ex vivo* with a recombinant fusion protein [PA2024, prostatic acid phosphatase (PAP) fused to GM-CSF (granulocyte–macrophage colony-stimulating factor)]. The proposed mechanism of action is through APCs in the product that will become activated and present the PAP antigen to T cells in the patient which then target and kill cancer cells. Potency is measured as the number of cells expressing and the upregulation of the costimulatory molecule CD54.¹⁵

From a regulatory point of view, in the EU this product is considered a cell-based immunotherapy and falls within the definition of an "advanced therapy medicinal product"²⁰ and, therefore, in addition to the cancer indication, it makes it subject to the evaluation through the centralized procedure coordinated by the EMA. Provenge received marketing approval by the FDA in April 2010 (April 29, 2010 Approval Letter — Provenge) and it is currently under evaluation in the EU. After a controversial approval in the US²¹ followed by a lot of hype,³ some critical voices have been raised.^{22,23}

From a quality perspective, a thorough characterization of the cellular component is expected in terms of identity, purity, potency, viability and suitability for the intended use.²⁴ As described Provenge contains different cell populations and only a very small fraction of APCs, key players in the claimed mechanism of action. The potential impact, either positive or negative of the other cell types in the product should, at least, be discussed but preferably also controlled routinely for quality monitoring purposes. Also, as an autologous product, high inherent variability is expected from

patient to patient but the manufacturer should demonstrate product consistency in accordance with the selected relevant parameters. It remains a challenging aspect for cell-based products in general to show that the specifications set are truly meaningful. Requirements for the fusion protein, a critical component, should not differ from any other biotechnological product. The manufacturing process is quite straightforward but any change introduced, either during development or after approval (such as alternative manufacturing sites), would require a comparability assessment in order to show the product maintains the relevant characteristics that showed clinical benefit.

Regarding efficacy data, three double-blind, placebo-controlled, multi-center phase 3 studies (D9901, D9902A and D9902B) have been submitted in order to demonstrate the efficacy and safety of the product. The phase III-studies have similar inclusion/exclusion criteria (patients with asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer), control arms, and investigational products. The endpoints were initially time to disease/tumor progression, though in the Study D9902B the primary endpoint was changed to OS after the assessment of the results from the study 9901. Results from the main study, 9902B are widely known, an improvement in overall survival of 4.1 months was observed (HR = 0.775, 95%-CI 0.614, 0.979). This gain in survival is statistically significant and clinically meaningful. With these data, the FDA deemed the application approvable and as a consequence, taking in consideration the safety profile and that the benefits outweigh the risks, Provenge was commercialized in the US. The same data are currently being assessed in the EU. This product is considered the turning point in the development of “cancer vaccines” since it has been the first in obtaining an MA in one of the ICH’s regions. Nevertheless, some uncertainties have been cast. The most relevant flaws of the dossier could be the possible deleterious effect of the “placebo” group, the lack of consistency between the primary endpoint and the outcomes from

the secondary variables and the effect of the subsequent chemotherapy on the gain in life expectancy.^{22,23} Additionally one could also wonder what would have happened if the control group had been docetaxel, given that symptomatic patients would be susceptible to being treated with chemotherapy.^{25,26} Taken together, the FDA’s approval does not warrant a positive opinion in the EU. In the end, the possible uncertainties of any product must be clarified to allow the drawing of firm conclusions on efficacy and safety.

Conclusion

Even though the efficacy results from currently available active cancer immunotherapies do not seem very encouraging there are lessons to be learned that can benefit the development of future treatments. From a quality point of view the components of the product should be characterized and justified as far as possible and manufacturing processes should be designed to reduce the potential inherent variability of the starting material. From a clinical perspective, after review of two case studies, first, it is absolutely necessary to obtain positive results from the pivotal trial(s), especially for the primary endpoint. The design of the study should be adequate in order to exclude any doubts of bias in the study. The scientific advice from EU National Authorities and/or EMA is strongly encouraged, given the apparent association between the compliance with scientific advice and the success of the application.²⁷ Indeed, a relevant result in one subgroup will not be accepted as proof of efficacy in the absence of positive outcomes in the whole study population. Moreover, the possible uncertainties raised about the study should be ruled out, allowing the benefit to outweigh the risk. Finally, statistical significance is not enough to obtain a marketing authorization; the clinical relevance of the results should be clearly shown, in other words results must be clinically meaningful.

In conclusion, active cancer immunotherapies are going to be assessed as all medicinal products, that is, demonstrating quality, efficacy and safety.

Disclaimer

The views expressed in this article are those from the authors and do not necessarily represent the view of the Spanish Agency on Medicines and Healthcare Products (AEMPS) or the EMA Committees.

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