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Regulatory considerations for clinical development of cancer vaccines

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Abbreviations: AIDS, Acquired Immunodeficiency Syndrome; CAR, T-cell Chimeric Antigen Receptor T-cell; CTL-4, Cytotoxic T-lymphocyte-associated protein 4; DCs, Dendritic cells; EBV, Ebstein Barr Virus; EMA, European Medicines Agency; EU, European Union; FDA, Federal Drug Administration; HHV-8, Human Herpes Virus 8; HTA, Health Technology Assessment; ICH, International Conference on Harmonisation; ICI, Immune Checkpoint Inhibitors; ITF, Innovation Task Force; MDSC, Myeloid-derived suppressor cells; MHRA, Medicines and Healthcare products Regulatory Agency; MUC1, Membrane-bound glycoprotein MUC1 mucin; NICE, National Institute for Heath and Care excellence; OS, Overall survival; PD, Pharmacodynamic; PD-1, Programmed cell death 1; PFS, Progression-free survival; PTLD, Post-transplant lymphoproliferative disease; PMDA, Pharmaceutical and Medical Devices Agency; RECIST, Response Evaluation Criteria in Solid Tumors; Serum Igs, Serum immunoglobulins; siRNA, Small interfering RNA; TAA, Tumor associated antigens; TIMs, Tumor Infiltrating Myeloid Cell; Tregs, Regulatory T cells; US, United States of America

Cancer vaccines are aimed at stimulating an immune response to tumor tissue. There is a high level of clinical activity in this rapidly advancing field with over 1,400 trials registered on Clincaltrials.gov. The recent approval of Sipuleucel-T which is the first cancer vaccine approved in the US and EU has encouraged developers in this field. In contrast to more established approaches for treating cancer such as chemotherapy, regulatory guidelines have been developed relatively recently for cancer vaccines. These guidelines advise on general clinical requirements. As there is an increase in innovative strategies with novel products, a 2-way dialog with regulators is recommended on a case-by-case basis to justify the clinical development plan, taking into account specific quality issues related to the product(s) in development. It is important that the rationale, background and justification for the planned development is convincing when interacting with the regulatory authorities, to enable drug developers and regulators to reach agreement.

Introduction

Cancer is a major public health issue in the aging populations of the EU and US. The idea that a non-toxic treatment for cancer is possible, where the tumor is killed by the patients' own immune system is an active area of research with recent high profile successes. The novelty and range of approaches in this field are broader than ever before with the advent of new technologies and innovative diagnostics. Regulatory considerations for clinical development plans will need to take into account the need for demonstration of a clear proof of concept, evidence to support the mechanism of action as well as efficacy and safety. However the route to achieving this may differ from the standard approach, particularly in the non-clinical program for demonstration of mechanism of action. The drug developer needs to be aware of the regulatory guidelines that are relevant for their clinical development plan and ensure that regulatory input is obtained at a point in the development when a clear plan, rationale and justification have been developed.

The immune system has been shown in certain circumstances to have the capacity to mount a response against tumor tissue.[1] A successful immune response would be expected to lead to specific destruction of the tumor. Furthermore, an effective and specific immune response would not be expected to result in toxicity to normal tissues nor, in contrast to some currently available therapies including radiotherapy, would an increased risk of a second malignancy be of concern. An additional expected benefit from a successful cancer vaccine would be long-lasting immunity. Because of the specificity and memory associated with an immune response, induction of an effective response to an existing tumor (therapeutic vaccination) or priming the immune system to antigens expressed on pre-malignant cells (prophylactic vaccination) would have potential benefits over currently available treatments.

The field of cancer immunotherapy includes a very wide range of approaches. These include passive immunisation with monoclonal antibodies to antigens expressed on the tumor cells (e.g. rituximab, trastuzumab), adoptive transfer of tumor specific cells (e.g., tumor infiltrating lymphocytes for melanoma)[2] and removal of the immune-checkpoints which reduce the immune response (CTLA-4 and anti-PD-1).[3] Additional approaches utilize chimeric antigen receptor (CAR) T-cell immunotherapy[4] and bi-specific T cell engager technology.[5] For vaccination a

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variety of strategies and products are in development (peptides, cells, vectors).[6]

This review will focus on approaches which involve vaccination leading to stimulation or amplification of an immune response against tumor associated antigens (TAA).

Increasing knowledge in basic science and technology have led to rapid advances in the fields of tumor pathology and immune response elements, much of which has led to a greater understanding of the balance between the activation status of immune cells and tumor growth and escape mechanisms. This knowledge has been harnessed for therapeutic applications. With the continual increase in understanding of the processes underlying defective or impaired immune responses, a wide array of approaches have been taken to address the clinical need for effective cancer vaccines.

Existing EU and US regulatory clinical guidelines for anticancer medicinal products are based largely on cytotoxic and monoclonal antibody therapy. But more recently guidelines for cancer vaccines have been added.[7,8] In view of the broad heterogeneity of approaches taken in different tumors, navigating the regulatory landscape poses challenges for drug developers and for regulators in terms of ensuring adequate evidence for quality, nonclinical and clinical aspects. These issues will be discussed with a particular focus on the EU, but also with reference to the US.

Background

The evidence for the body's ability to destroy tumor tissue either following a natural infection or following administration of a pro-inflammatory agent dates back to St Peregrine's tumor[9] and Coley's toxins[10] respectively. For Coley's toxin (a mixture of dead bacteria injected directly into the tumor) to demonstrate efficacy, there was a requirement for a systemic inflammatory response. Despite the success of this approach Coley's toxins did not gain widespread use. In a modern-day event reminiscent of Coley's toxin, a case report of spontaneous regression of metastatic melanoma following a febrile response to tetanus–diphtheria–pertussis vaccine immunisation was recently reported.[11]

The underlying explanation for such an effect remains unclear but it seems likely that infections or inflammatory responses can lead to exposure of abnormal self-antigens. An interesting example of this is the membrane-bound glycoprotein MUC1 mucin, which is expressed widely on the epithelial surface of glandular cells.[12] An abnormally glycosylated form of MUC1 is expressed on cells during inflammation, on pre-malignant lesions and on carcinoma cells.[13] Furthermore it has been shown that the presence of antibodies to the abnormal MUC1 following mumps infection is associated with a reduced incidence of ovarian cancer.[14] This implies that development of immunity to abnormal self-antigens expressed during infection could ultimately be protective against pre-cancerous lesions expressing the same abnormally glycosylated MUC1.

Another well-established pointer to the power of the immune system in protecting against malignancy is the evidence that when the immune system is suppressed there is an associated increased incidence of tumors. This has been seen in multiple settings e.g. AIDS (e.g., Kaposi's sarcoma, lymphoma), in some cases of primary immunodeficiency[15] (e.g., lymphoma in common variable immunodeficiency) and in subjects with iatrogenic immunosuppression following organ transplantation (e.g., post-transplant lymphoproliferative disease [PTLD]).[16] In the latter case, it has been shown that reducing the immunosuppression allows emergence of an effective immune response against the PTLD.[17] What is notable for the malignancies that emerge in immunosuppressed patients is that they are often (though not always) associated with viral aetiologies (e.g., Ebstein Barr Virus [EBV], human herpes virus 8 [HHV-8]).

Indeed while the emergence of tumors in immunosuppressed individuals fits with the concept of immune surveillance,[18] it is likely that this surveillance is predominantly against the causative viruses. With the resultant waning of anti-viral immunity, the ability of viruses to survive and induce cellular transformation becomes evident.

How immune surveillance can operate effectively can be seen with prophylactic HPV vaccination, whereby an immune response to the HPV does not allow emergence of virally transformed cells. While delivery of effective HPV vaccination prevents cervical cancer, it is probable that the lack of malignancy is secondary to an anti-viral effect.

Recent evidence for immunosurveillance in malignancy which is not virally associated comes from a class of monoclonal antibodies that act as immune checkpoint inhibitors (ICI).[19] Ipilimumab specifically blocks the inhibitory signal of CTLA-4. This blockade results in T-cell activation, proliferation, and lymphocyte infiltration into tumors, leading to tumor cell death. The European Medicines Agency (EMA), and the Food and Drug Administration (FDA) in the US licensed ipilimumab for melanoma in 2011.

Antibodies that target Programmed Cell Death 1 (PD-1), an inhibitory receptor expressed by T cells, have also been approved in 2014 by the Pharmaceutical and Medical Devices Agency (PMDA) in Japan and the FDA for the treatment of melanoma.

Regulatory Considerations

From a regulatory perspective the need to ensure the quality safety and efficacy of medicines remains paramount before marketing authorisation is granted. This regulatory check provides assurance to patients and health care professionals that newly licensed medicines have a positive benefit:risk balance in the indicated population. Continued clinical safety data collection post-authorisation, which also may (depending on the amount of data presented at the time of application) include registry data or additional clinical trial data, is important to ensure that the benefit:risk balance remains positive once licensed. Such information also allows identification of very rare adverse events which were not evident in the initial clinical data. The regulatory requirements for a positive benefit:risk balance, an adequate tailored risk management plan and pharmacovigilance requirements remain

for all products and do not differ for cancer vaccines as a class of product.

The regulatory agencies for Europe, the EMA, and the United States, the FDA, regularly release guidelines for a range of quality, non-clinical and clinical topics. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[20] publishes guidelines that are harmonised between the EU, Japan and the US. These ICH guidelines address quality safety and efficacy as well as multidisciplinary and regulatory issues. As such the ICH guidelines and compliance thereof provide guidance for drug development for more than one region.

Regulatory guidelines relevant for clinical development of cancer vaccines have been recently developed by the FDA and a section on cancer vaccines has been added to the EMA guideline.[7,8] Additional regulatory guidelines relevant for clinical development in oncology are referenced within these documents.

Quality considerations

The complexity, range and rapid increase in the understanding of tumor cell biology and the immune system, combined with the new approaches for therapy, including advanced-therapy medicinal products (ATMPs), means that although guidelines are available for many product types (e.g., gene therapy, cell therapy) on the EMA website, it is not possible for all scenarios to be accommodated in any single guideline. This is because guidelines are written based on regulatory experience. It should be highlighted however that it is not mandatory to follow current guidelines if this is not feasible. In cases where well justified positions are provided by drug developers, particularly when based on new understanding of science and/or disease, it is advisable to interact with regulators to discuss these difference and the specifics of the drug development program. In order to justify deviations successfully the investigators need to have a sound rationale and ideally initial good quality data to support their plan.

Assessment of the quality of cancer vaccines can be more complex particularly in the case of ATMPs compared with e.g. a peptide. So assessing the quality attributes of e.g., a DC-based vaccine as they relate to a pharmacodynamic (PD) marker or an efficacy endpoint can be challenging. Therefore release specifications for some vaccines have to be agreed on a case-by-case basis and ideally these should be related to the mechanism of action of the product.

Non-clinical considerations

The utility of non-clinical models varies depending on the cancer vaccine and tumor targeted. Multiple different products and techniques have been tested including peptides, proteins, cells e.g. DCs, T cells, tumor cells (including cells manipulated *in vitro*, fused, expanded, genetically modified) and combinations of vaccines with cytokines, adjuvants, vectors and ICI therapies.

Multiple possible target antigens have been identified in cancer.[21] The lack of suitable animal models for many of these approaches as well as the specific factors that are involved when, for example autologous therapies are investigated, means that the proof of concept and mechanism of action may be difficult or impossible to demonstrate in the non-clinical models in some instances. This is particularly problematic when autologous personalised vaccines are being developed. As preclinical testing should utilize the product to be taken into man, products such as human cells will not be amenable to pharmacology testing in animals. The utility of animal models (e.g., nude mice, humanised mice,[22] chimeric animals[23]) needs to be considered on a case-by-case basis before planning these experiments.[24]

In cases where a suitable murine model can be used, the advantage of demonstrating proof of concept, if this is possible, provides support for the clinical development. Nonetheless even in these cases there remain limitations. These relate in part to the differences of the murine models compared with patients; typically young mice are used where the treatment results in resistance to an inducible tumor. In the case of therapeutic vaccines patients already have the tumor *in situ* for prolonged periods and also have some immunosuppression and tolerance to the tumor; both as a result of tumor-specific suppression in the tumor microenvironment and also as a result of prior chemotherapy and/or radiotherapy. Furthermore inter-species differences in the immune system can be significant even in cases where non-human primates are utilised. The use of non-human primates is not encouraged,[25] and although closer to the human there are important differences, some of which have only come to light after serious adverse events in a clinical trial.[26]

In vitro testing of human tissues to examine the distribution of a candidate TAA should be performed. Additional *in vitro* testing of human cells to support the expected effects of modulating the candidate antigen should be performed where applicable. Tumor cell lines and tumor tissue can be used to examine antigen expression. Furthermore, as there has been an increased understanding of the effects of the tumor microenvironment on the infiltrating cells, examination of the number and activation status of tumor infiltrating cells (e.g. DCs, TIMs, MDSC, CD4+ T cells, CD8+ T cells, and Tregs) may assist in supporting the proof of concept. In addition if sequential testing of the tumor is possible following vaccination, the findings could further support proof of concept.

The EMA guideline on anticancer products contains a section on therapeutic cancer vaccines.[7] Although the EMA guidelines states that "Non-clinical *in vitro* and *in vivo* proof-of-concept studies should be presented to justify the planned starting dose and schedule in phase I studies" there is a caveat for cases where no relevant animal model is available. In these cases *in vitro* studies with human cells can be acceptable to demonstrate proof-of-concept. This caveat acknowledges the difficulty in providing a standard non-clinical program in support of many types of cancer vaccines.

Clinical considerations

Because of the expected limitations in the non-clinical program for some cancer vaccine products, the need for demonstration of the mechanism of action of the vaccine will rely heavily on human *in vivo* data.

Specific considerations on immune status before and after vaccination

In contrast to murine models of cancer, the baseline immune status of patients with cancer will vary and a reduction in immune function is associated with advancing age and previous therapy.

While immunosurveillance operates, the tumor adapts to escape recognition and destruction by the immune system by a process called immunoediting.[27-31] In addition the tumor microenvironment is immunosuppressive and this can be seen even early in tumourigenesis.[32-34]

These factors may impact on the ability of a patient to respond to a vaccine. Measurement of baseline immune status should be considered in the clinical program (e.g., serum Igs, CD4+, Tregs, CD8+, DC, MDSC, TAA-specific T cells). These parameters may have an impact on prognosis or be predictive of a response to vaccination (e.g. by using a pharmacodynamic (PD) read-out of effect in early clinical trials). If a correlation is found in early phase studies between baseline immune status and response to vaccination, then this information can be used to guide the design of pivotal clinical trials.

Changes following vaccination

Serial in vitro tests (blood/tumor) can enable a read-out of the effect of therapy,[35-38] and if feasible, can provide very useful information in early clinical development. Direct *ex-vivo* analysis on peripheral blood (e.g., number of Tregs, TAA-specific T cells, TAA-specific Ig level) can provide more convincing data than results from *in-vitro* expanded cells taken from peripheral blood. While it is acknowledged that the peripheral blood may not reflect the changes in the immune cells within the tumor, in the absence of serial tumor biopsies this can be a logistically feasible way to search for a PD effect. In cases where examining TAA-specific T cells in peripheral blood is possible then this should be done. Although such measurement will not capture additional effects such as epitope spreading, (which may be part of the proposed effect) it is very relevant for demonstrating a PD effect. Furthermore some readout of a PD effect will strengthen proof of concept, support the mechanism of action and also assist in dose finding. Such information may also potentially inform decisions on what the optimal duration of treatment should be.

As the entirety of the data supporting proof of concept may be limited in terms of the evidence available from the non-clinical data, use of all available clinical information is recommended.

A potential concern for cancer vaccines is that there is also evidence that vaccination itself can lead to a paradoxical effect on the tumor infiltrating cells with an increase in tumor-specific immunosuppression.[39] This raises the possibility that vaccination may not always be a safe approach. This finding further underlies the need for and benefits of demonstrating proof of concept in humans and / or identifying a PD readout following vaccination. Such evidence in humans should be available before designing pivotal studies.

A newer approach which may involve fewer complexities in terms of overcoming immune suppression is that of prophylactic cancer vaccines. Here the aim is to target subjects without cancer but who have a high risk of developing a malignancy, such as those with pre-cancerous lesions.[40,41] So a prophylactic cancer vaccine approach will require a different strategy compared with a therapeutic cancer vaccine in terms of selection of patients and choice of feasible endpoints for the pivotal clinical trials. This is an area where surrogate efficacy endpoints will require development and validation. In view of the limited experience in this area and the lack of regulatory guidelines, a 2-way dialog with regulators is recommended. This should be done once good quality initial data and a justified rationale for further development is ready.

For therapeutic cancer vaccines clinical dose finding studies are generally required as are serial monitoring of the immune response. As assays form an integral part of a cancer vaccine development, the guidelines also specify the need for the analytical assays to be fully described. Serial tumor biopsies are considered important (although this cannot be done in all cases) but the results could provide a marker of anti-tumor activity. In that case data from early clinical trials, using a limited number of patients who undergo serial tumor biopsies, could provide proof of concept. Although not stated in the guideline it is probable that imaging results on tumors inaccessible to safe biopsies could also provide evidence for such a response.

The appropriate choice of patient groups for the pivotal trials is difficult to decide in view of the immune suppression in patients with late stage disease and large tumors, who will have a limited life expectancy. Therefore the EMA guideline suggests that those with low or minimal burden of disease could be studied.

Although the likelihood of success from an immune stimulation perspective may higher in patients who have early disease (e.g. newly diagnosed cases) and so have not been heavily pretreated, choosing such a population where alternative therapies exist will need to be justified. For such a scenario, where there is a sound rationale which supports such an approach, and a good proof of concept, then discussion with regulators to seek agreement on the clinical development plan is advised. For read-out of efficacy the guidelines allow a delayed response for cancer vaccines and state that "revised criteria defining progression is accepted if properly justified." This is in line with the revised Response Evaluation Criteria in Solid Tumors (RECIST) criteria, which highlight that there can be a time-lag in mounting an effective immune response, resulting in a slower tumor response as compared with cytotoxic agents.[42] However the main efficacy endpoint recommended by the EMA is overall survival (OS).

While OS is a clear endpoint, if a cancer vaccine has shown strong proof of concept and results in a clinically and statistically relevant increase in progression-free survival (PFS) against an appropriate comparator then this could be acceptable. This will be relevant for cancers where the long duration of trials required to provide sufficient data on OS would not be practical prelicensing. However additional data on OS post-licensing will be of particular importance in these instances to ensure that there is no evidence for any detrimental effect on OS.

For assessment of PFS a double-blind trial is recommended. If double-blinding is not possible then blinded efficacy evaluation

should be used in the trial. If radiological evaluations are the main read-out of efficacy it is advisable to have these read centrally by blinded evaluators.

The FDA Guidance for Industry on clinical considerations for therapeutic cancer vaccines[8] provides a more detailed discussion including the development of companion diagnostics. However, and similar to the EU guidelines, the issues of which patient population to use and how to choose a feasible endpoint remain. If the patient population chosen has low (or no) residual disease, the efficacy endpoint of disease recurrence will entail prolonged follow-up. Monitoring of the immunes response is considered exploratory by the FDA and the utility of such measurements are seen as useful in proof of concept, dose finding and possible correlation with clinical efficacy. The FDA supports the use of exploratory biomarkers for proof of concept, and also provides some guidance on adjuvants and multi-antigen therapy. In view of the wide range of approaches for therapeutic vaccines the guideline recommends that the main clinical endpoints should be clinically relevant and discussed with the FDA.

On review of the EMA and FDA guidelines it is clear that the basic requirements for quality safety and efficacy remain as for any product and the route to gain marketing approval will be on a case-by-case basis.

Where the guidelines that are available do not encompass the approach taken in a new drug development, as is expected for many therapeutic cancer vaccines and for all prophylactic cancer vaccines, then discussion with regulators to seek agreement on the basis of a well justified rationale and planned clinical development program is advised.

For prophylactic cancer vaccines there are no regulatory guidelines available at present. It is important to view this type of prophylactic vaccine differently as the patients enrolled into trials will be healthy, unlike those receiving therapeutic cancer vaccines. As such safety will be more of a concern in this setting, requiring a larger patient safety population than for a therapeutic vaccine used in late stage cancer patients. Another consideration would be that for safety, the uncertainty will be higher for a gene therapy product as compared with e.g., a peptide vaccine. The absence of guidance for prophylactic cancer vaccines should be seen by drug developers more as an opportunity to influence regulatory thinking than as a barrier. Such early dialogue is welcomed by regulators and these meetings can take the form of meeting with the innovation task force (ITF) at the EMA.

While regulatory approval is a prerequisite it is not a guarantee of success in terms of the final outcomes of patient access and reimbursement. For this early commercialisation considerations are important. Interaction with Health Technology Assessment (HTA) Bodies is also advisable to ensure that endpoints recommended by regulators will be acceptable to HTAs and payers. The EMA held a workshop on EMA/ HTA-body parallel scientific advice in drug development in November 2011. The documents and presentations are available at the EMA website.[43] While not indication-specific the overall message from this workshop is clear; whatever the program it is optimal to have regulatory and HTA/payer input early on. Such an approach is expected to reduce the likelihood of failure at the reimbursement stage post-licensing. Such joint advice procedures are also available at a national level and parallel scientific advice meetings with NICE and the MHRA are available in the UK.

Conclusions

Development of cancer vaccines is a very active area of research. The approval for Sipuleucel-T in both the US and EU is the first example of a successful outcome for a cell based autologous cancer vaccine.[44]

In view of range of product types in development, cancer vaccines consist of a very heterogeneous range of products where no single quality or non-clinical guideline can apply to all.

The parallel success of ICI therapies and advances in science, (including genetics, biomarker development and immunology) is expected to result in the development of additional new products and combinations of therapies. Combination of ICI therapy with specific cancer vaccines in order to circumvent the immunosuppression present in cancer patients is a very promising newer approach.[45,46]

A likely future advance in this area will be the identification of mechanism based predictive biomarkers for response to the vaccine. For future cancer vaccines, particularly prophylactic vaccines, development and validation of surrogate endpoints are foreseen as necessary. This will need regulatory agreement as clinically relevant endpoints are expected for product approval.

It is expected that regulatory guidelines will be updated to accommodate new developments in the field, although due to the fast moving and broad range of approaches being developed it is not foreseen that guidelines will be specific to each product or combination of products that are likely to be investigated.

Because of the high level of activity in this area sponsors should actively engage with regulators, both on a case-by-case basis and also by providing input into draft clinical guidelines relevant to their product.

At the EMA the option for informal interaction with the Innovation Task Force (ITF) allows an open dialog on the regulatory challenges specific to the product or product class in development. The Association of Cancer Immunotherapy met with the ITF to discuss actively personalised vaccines in 2012.[47] Such interactions will assist in alignment of scientific advances and regulation to enable safe effective novel therapies to be approved.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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