Interview

Immunotherapy

Interview with Robert Coffin, inventor of T-VEC: the first oncolytic immunotherapy approved for the treatment of cancer

Interviewed by Ellen Clarke, Commissioning Editor, Future Science Group.

Robert Coffin is co-founder and CEO of Replimune. Previously he was Founder and CTO of BioVex Inc, a spin out from his research group at University College London in 1999. He was the inventor of all BioVex products including OncoVEXGM-CSF (talimogene laherparepvec; T-VEC; Imlygic) and oversaw all research and clinical development including bringing T-VEC through to two pivotal Phase 3 studies in melanoma and head and neck cancer. BioVex was acquired by Amgen in 2011 where he was VP Global Development until 2013. T-VEC was approved by the FDA for use in advanced melanoma in October 2015, the first oncolytic therapy or gene therapy to be approved in USA. He was awarded a PhD in virology from Imperial College London prior to his move to University College London in 1991.

First draft submitted: NA; **Accepted for publication:** 30 November 2015; **Published online:** 22 January 2016

Keywords: Imlygic • oncolytic immunotherapy • T-VEC

Robert Coffin
Replimune Ltd, The Oxford Science Park Magdalen Centre, Robinson Avenue, Oxford OX4 4GA.
rob@replimune.com

Q Can you tell us about the current challenges in melanoma treatment?

The field of drug development for melanoma has changed very substantially in recent years. Until less than 5 years ago it was a graveyard of drug development and there was no drug that was proven to improve survival. Prognosis for advanced melanoma patients was dire. However things began to improve with the approval of ipilimumab, which shows long-term benefit in about 10% of treated patients, then with the drugs that target mutations in BRAF and now MEK. However both have also demonstrated the current challenges. Ipilimumab, which targets CTLA-4, clearly gives long-term benefit in patients who respond, but this is a small proportion of patients. In contrast a high proportion of patients with BRAF mutations respond to BRAF targeting drugs, but those responses tend to be relatively transient. The challenge remains to have the benefits of both in one drug, that is a high proportion of long-term responses, which should translate into long-term survival. We are part of the way along with the new checkpoint blockade drugs that target the PD1/PD-L1 axis, which give good levels of long-term responses, much higher than ipilimumab to the extent that now up to half of melanoma patients respond. The challenge now is extending treatment benefits to the other 50% of patients who do not yet benefit from the recently approved drugs.

Q What was the back story behind the Phase 3 T-VEC study?

T-VEC was originally called OncoVEX and was developed in the UK by BioVex. In the early to mid-2000s we first ran a Phase 1 study with T-VEC, which was a traditional all-comers late stage cancer study. We enrolled patients with a number of different tumor types, which happened to be mainly

Future Medicine part of fsg

breast cancer patients due to the particular interest of the lead investigator Charles Coombes of the Hammersmith Hospital (part of Imperial College London, UK). The study also included a few melanoma patients, head and neck cancer patients and a couple of others too. We optimized dose, confirmed good tolerability and showed evidence of biological activity, that being shrinkage of injected tumors and inflammatory effects and some shrinkage in non-injected tumors with just 1–3 doses of the virus. This led us to believe that we had an active drug worthy of further clinical development. We then conducted three studies in different tumor types: head and neck cancer, pancreatic cancer and melanoma. Two of those led to Phase 3 studies, one in head and neck cancer and the other in melanoma, which Amgen took over when recruitment was nearing completion. The study that led up to the Phase 3 study in melanoma was a Phase 2 study in 50 patients with advanced melanoma, stage IIIc to stage IVM1c, showing a very respectable overall response rate of around 30% at the final analysis including 20% of patients with a complete response. This was in an era where there were no approved effective drugs in melanoma other than IL-2 (which while not tested in a controlled survival study appears to have a level of activity similar to ipilimumab). What was also particularly impressive with T-VEC was the durability of the responses seen. Patients tended to respond for many months if not years, which would be anticipated to translate into a survival benefit. What was also promising in that study was that we saw not only responses in tumors that had been injected with T-VEC but also in tumors that had not been injected, including visceral lesions, which showed that we were achieving a truly systemic effect. This led up to the Phase 3 study, which intended to build on what we had found, but in a larger patient population and with a control arm. Ultimately 438 patients with first line and previously treated stage IIIb to stage IVM1c melanoma were enrolled. We looked at durable response rate as the primary end point of the study because this was something we had good data on from the single-arm Phase 2 study, that is, we had a reasonable estimate of the durable response rate we should expect. In actual fact the response rate in the Phase 3 study was nearly identical to Phase 2, which was nice!

Q How did the results of the Phase 3 study lead to the US FDA approval of T-VEC?

Biovex was taken over by Amgen in early 2011 who were then responsible for the management of the latter parts of the study and the filing with the FDA. However, we had previously obtained a special protocol assessment (SPA) from the FDA providing agreement that the design of the Phase 3 clinical trial, if successful, would be expected to generate data that would be suitable for filing for a biologics license application (BLA). The primary objective of the study was easily met that being a substantially better durable response rate for T-VEC compared with the control arm. Secondary endpoints, for which the study was not powered, including overall survival, provided compelling supportive evidence that the primary endpoint of durable response rate was clinically meaningful. Clear systemic benefit was achieved, with, for example, 15% of the visceral tumors in patients in the study responding, none of which had been injected with T-VEC. 32% of patients ultimately achieved an objective response and 17% a complete response. As expected, these responses were also very durable (at the time of the final analysis most were still ongoing). With that background it is not surprising that the committee who reviewed the data for the FDA in April overwhelmingly voted that T-VEC should be approved for the treatment of advanced melanoma, and that the FDA ultimately agreed by granting a label in October 2015. T-VEC was also approved in the EU by the EMA in December 2015. T-VEC (to be marketed as Imlygic) is the first oncolytic immunotherapy to be approved anywhere in the world, and approval is therefore a considerable milestone for the field.

Q What will the approval of T-VEC mean for melanoma patients?

The approval of T-VEC clearly provides an additional option for the treatment of patients with advanced melanoma in addition to the other newly approved drugs. However, if one looks at the data in more detail what one finds is that T-VEC is, in comparison, a very low toxicity option. The side effects are really quite minimal, with predominantly mild-to-moderate fevers and overall substantially less toxic than the other drugs that are available. Parsing down on the data further one finds that patients with earlier disease, particularly patients who do not yet have visceral disease, that is, disease in organs such as the liver, do particularly well. In these patients, which comprised about half of the patients enrolled into the study, there is a much higher response rate (40.5% as compared to 32% for the entire population) and a greatly enhanced survival benefit as compared with patients who had visceral disease at the time of study entry. To put that in context the hazard ratio for those earlier patients was 0.57 with a very clear statistically significant difference between the arms ($p < 0.001$), whereas in the entire study population the overall survival benefit was more modest. For the earlier patients, median survival for T-VEC was 41.1 months as compared to 21.5 months for patients in the control arm. The data therefore demonstrates that these earlier patients in particular can benefit substantially

from treatment with T-VEC, for whom there is every reason to treat with T-VEC as a first-line option, and if this is unsuccessful they can then move on to others of the newly approved treatments that are now available. Alternatively, there are particular opportunities for combining oncolytic immunotherapies such as T-VEC with the checkpoint blockade agents. For these agents to work, a pre-existing anti-tumor immune response is needed, which is only present in some patients, but which oncolytic immunotherapy can provide. Early clinical data with T-VEC in combination with both ipilimumab and pembrolizumab have been very promising, where in both cases response rates of over 50% have been seen. As a result later stage studies are now being run by Amgen to test these combinations in the Phase 2 and Phase 3 setting. This, when T-VEC is used as a single agent, it appears that using it early and upfront is the optimal setting for use, whereas in combination with checkpoint blockade the proportion of patients who benefit who also have visceral disease may be expected to substantially improve. I think that combination of oncolytic immunotherapy with checkpoint blockade will be found to be a very important combination in oncology and may well become the standard first line option for patients with many different tumor types.

Q Are there any limitations associated with T-VEC?

The side effects are particularly mild for a cancer therapy, so that is a great advantage. There is a limitation with regard to the degree of efficacy seen in the more advanced patients with extensive visceral disease. As a result, in most circumstances single agent T-VEC is not likely to be the best option for patients with advanced visceral disease, but I believe that will be addressed through combination with checkpoint blockade, as I said above. It could be argued that the fact that T-VEC is injected into lesions rather than given orally or by intravenous dosing is to some extent a limitation. For single agent T-VEC you probably need to inject multiple tumors quite a few times for optimal activity, which may not be truly feasible for anything other than cutaneous, subcutaneous or lymph node tumors. In combination with other drugs, however, particularly checkpoint blockade agents, it may be the case that two or three injections are all you need, which is entirely feasible for really any tumor using essentially the same approaches that are currently used to for example to take a biopsy.

Q Are there any ongoing T-VEC trials that you can tell us about?

Amgen have a number of ongoing and planned studies with T-VEC. They have a neoadjuvant study in melanoma where T-VEC is injected into lymph node tumors prior to surgery, and then looking to see if prior injection with T-VEC vaccinates the patient to reduce the numbers of patients who relapse. They have an ongoing 200 patient Phase 2 study with T-VEC in combination with ipilimumab compared with ipilimumab alone, the results of which I would expect might be available sometime next year. They have just finished a Phase 1b study with T-VEC in combination with pembrolizumab in melanoma, which also gave a very high response rate of close to 60%, and are about to start a Phase 3 study with that combination in collaboration with Merck in 660 patients. Amgen have also announced a partnership with Roche to test T-VEC in combination with atezolimumab, that being their anti PD-L1 drug, in a number of different tumor types.

Q Does melanoma respond particularly well to immunotherapy compared with other types of cancer?

It certainly appears to be in the top group of immune responsive cancer types, particularly with regards to checkpoint blockade. Other tumor types also seem to respond in some cases remarkably well, including tumor types that were not expected to do so well historically. For example lung cancer patients can also respond well to checkpoint blockade. The degree of efficacy all seems to hinge on the burden of *de novo* mutations in the cancer, that is the number of neoepitopes there are for the immune system to respond to. Certainly melanoma has led the way but I am sure immunotherapy as a single agent or in combinations of these newer agents, including oncolytic immunotherapies such as T-VEC, will expand the range of tumor types that respond well. This already includes glioma, triple negative breast cancer, renal cancer too.

Q Why is there currently so much excitement about cancer immunotherapy?

I think cancer immunotherapy is taking us into a new era of cancer therapy after a period of relative stasis, where survival was not really increased in many tumor types for 20 years or more. Immunotherapy is taking us into an era where we can imagine that many tumor types may become diseases that are treated chronically, even if they are not cured, and for which patients experience long term survival such that ultimate death is by another cause. Previously diseases such as advanced lung cancer or melanoma were truly a death sentence for which there was no effective therapy. Immuno-oncology is transforming the treatment of cancer in those initial indications, but I am sure in the future in a much broader range of indications too.

Immuno-oncology is truly transforming cancer treatment and would in many cases be expected to supersede other historical options such as chemotherapy, and be far more effective and of lower toxicity than these too.

Disclaimer

The opinions expressed in this interview are those of the interviewee and do not necessarily reflect the views of Future Medicine Ltd.

Financial & competing interests disclosure

R Coffin is a shareholder and employee of Replimune Ltd, a company developing next generation oncolytic immunotherapies. R Coffin has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.