NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Talimogene laherparepvec for treating metastatic melanoma [ID508]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:

Name of your organisation THE INSTITUTE OF CANCER RESEARCH

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? YES
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? YES
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? NO
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: NONE

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

THE EUROPEAN APPROVAL IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. I WILL CONFINE MY COMMENTS TO THAT SUBSET OF PATIENTS.
CURRENT NHS TREATMENT FOR THIS GROUP INCLUDES LOCAL PALLIATIVE SURGERY, ISOLATED LIMB PERFUSION, SYSTEMIC CHEMOTHERAPY (DACARBAZINE SINGLE AGENT, DACARBAZINE PLUS CISPLATIN, OR CARBOPLATIN PLUS PACLITAXEL), IMMUNOTHERAPY (IPILIMUMAB/NIVOLUMAB/PEMBROLIZUMAB) OR TARGETED DRUGS (BRAF INHIBITION +/- MEK INHIBITION).

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

THE EUROPEAN APPROVAL IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. THIS GROUP APPEARED TO DERIVE GREATEST BENEFIT IN THE PHASE III OPTiM STUDY.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

USE OF THIS TECHNOLOGY IS LIKELY TO BE RESTRICTED TO SPECIALIST HOSPITAL UNITS WITH EXPERIENCE OF USING ONCOLYTIC IMMUNOTHERAPIES.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NOT CURRENTLY USED OUTSIDE OF CLINICAL TRIALS.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

THE APPROVED INDICATION IN EUROPE IS FOR PATIENTS WITH STAGE IIIB/IIIC/IVM1A MELANOMA. THIS CAME FROM THE PHASE III OPTiM TRIAL IN WHICH THIS GROUP OF PATIENTS WAS SEEN TO DERIVE THE GREATEST DEGREE OF BENEFIT.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

T-VEC IS ASSOCIATED WITH VERY LITTLE LOCAL AND SYSTEMIC TOXICITY. IN THIS REGARD, IT COMPARES FAVOURABLY WITH OTHER LOCAL (SURGERY/ILP) OR SYSTEMIC TREATMENTS. ADMINISTRATION INVOLVES INTRATUMOURAL INJECTION – SOMETIMES WITH THE NEED FOR ULTRASOUND GUIDANCE. THERE ARE PRACTICAL CONSIDERATIONS REGARDING THE INTRATUMOURAL INJECTIONS – WITH A NEED FOR TRAINING. PATIENT ACCEPTABILITY IS VERY HIGH.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

NO SPECIFIC COMMENTS.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

USE OF THIS AGENT IN CLINICAL TRIALS IS REPRESENTATIVE OF NORMAL CLINICAL PRACTICE. AS SUCH THE AGENT WILL BE APPLICABLE IN NORMAL UK PRACTICE.
THE PRIMARY OUTCOME OF OPTiM WAS DURABLE RESPONSE RATE (DEFINED AS A RESPONSE LASTING AT LEAST 6 MONTHS THAT OCCURRED AT ANY TIME IN THE FIRST 12 MONTHS OF TREATMENT). THIS "SURROGATE MEASURE" HAS BEEN SHOWN TO CORRELATE WITH PROLONGED REMISSION, OVERALL SURVIVAL AND AVOIDANCE OF THE NEED TO START OTHER THERAPIES.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

THE SIDE EFFECT PROFILE IS VERY MILD (THE ONLY GRADE 3 TOXICITY THAT OCCURRED IN MORE THAN 2% OF PATIENTS WAS LOCAL CELLULITIS). ANALYSIS OF THE OPTiM DATA INCLUDED FAVOURABLE NUMBER NEEDED

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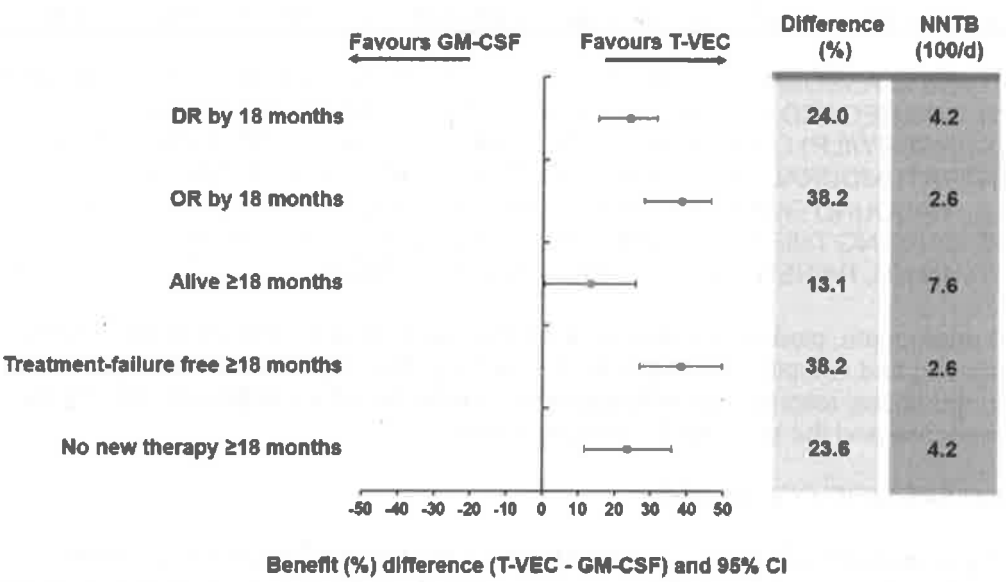
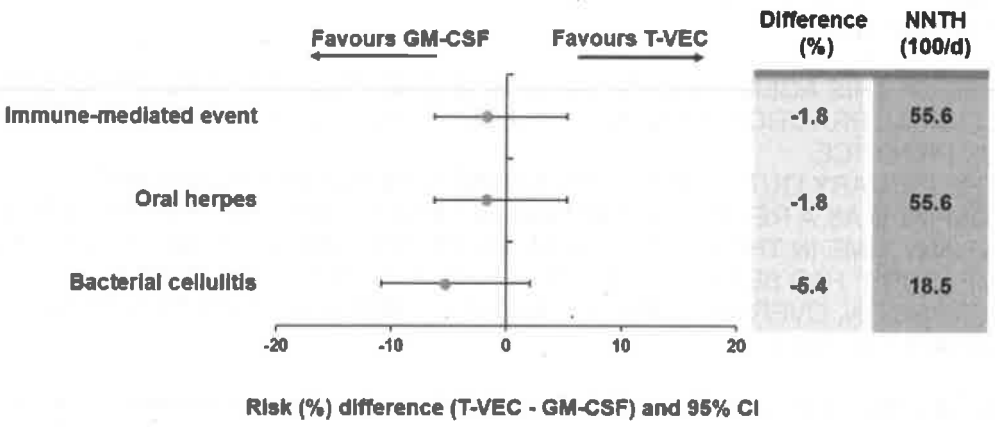
TO TREAT FOR BENEFIT AND NUMBER NEEDED TO TREAT FOR HARM ANALYSES (FIG 1 AND 2).

Figure 1. Benefit-risk analysis. (A) Benefits by 18 months (B) Risks by 18 months for the stage IIIB/C, IVM1a OPTiM subpopulation

A



B



CI, confidence interval; DR, durable response; GM-CSF, granulocyte-macrophage colony-stimulating factor; NNTB, number needed to treat to achieve a benefit; NNTH, number needed to treat to experience a harm; OR, overall response; T-VEC, talimogene laherparepvec.

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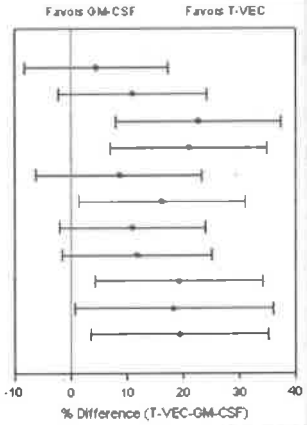
QUALITY OF LIFE ANALYSIS (FIGURE 3) CONFIRMS A FAVOURABLE EFFECT OF T-VEC OVER CONTROL ARM FOR MOST DOMAINS IN FACT-BRM.

Fig 3. Improvement in QoL assessed by FACT-BRM during treatment of T-VEC and GM-CSF in the stage IIIB/C, IVM1a OPTIM subpopulation (ITT)*

Subscale	N	Rate GM-CSF	Rate T-VEC	% Difference (95% CI)
Trial Outcome Index	207	23.4%	28.0%	4.5% (-8.2% - 17.3%)
FACT-BRM Total	215	26.9%	37.8%	11.0% (-2.2% - 24.2%)
Emotional Well-Being	197	31.6%	54.3%	22.7% (8.1% - 37.3%)
Functional Well-Being	193	25.8%	46.6%	20.8% (6.9% - 34.6%)
Physical Well-Being	130	18.2%	26.7%	8.6% (-6.2% - 23.3%)
Social/Family Well-Being	152	21.6%	37.6%	16.1% (1.3% - 30.8%)
Additional Concerns: Physical	166	20.0%	31.0%	11.0% (-2.0% - 23.9%)
Additional Concerns: Mental	189	22.0%	33.8%	11.8% (-1.5% - 25.2%)
QoL	157	22.4%	41.7%	19.2% (4.3% - 34.1%)
Pain	106	20.6%	38.9%	18.3% (0.7% - 36.0%)
Ability to Work	134	20.0%	39.4%	19.4% (3.5% - 35.2%)



CI, confidence interval; FACT-BRM, Functional Assessment of Cancer Therapy-Biologic Response Modifier; GM-CSF, granulocyte-macrophage colony-stimulating factor; QoL, overall quality of life; T-VEC, talimogene laherparepvec.

*Scores from unscheduled visits were not included. A patients is considered evaluable for a domain if baseline score is not the best score and there is at least one post-baseline score. TOI and total improvements are defined as ≥5-point score increase from baseline with a ≥1 cycle duration. QoL, pain and work improvements are defined as ≥1-point score increase from baseline with a ≥1 cycle duration.

THERE HAS BEEN NO "ROUTINE CLINICAL PRACTICE". THEREFORE, NO OTHER ADVERSE EFFECTS HAVE COME TO LIGHT.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

NO CONCERNS

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- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
NO CONCERNS

- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

NO CONCERNS

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

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If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?