# Supplements

Supplementary material to article: Treatment with Tumor-Infiltrating Lymphocytes in advanced melanoma: evaluation of early clinical implementation of an Advanced Therapy Medicinal Product

Submitted to Journal of Immunotherapy

1. Search strategy literature overview ATMP barriers and facilitators
2. Web-based questionnaire aimed at patient to identify factors related to TIL trial participation
3. Results literature overview ATMP barriers and facilitators

## 1. Search strategy literature overview ATMP barriers and facilitators

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| --- |
| **Results literature search** *Searches in July 2017 via Pubmed using filter: Past 5 years*  |
| **Terms** | **Results** |
| advanced-therapy medicinal products AND regulation | 41 |
| advanced therapy medicinal products AND implementation  | 17 (after removing duplicates) |
| advanced therapy medicinal products AND translation | 7 (after removing duplicates) |
| 65 unique articles identified |
| 57 articles were excluded because: * The article was not about ATMPs (10)
* The article was not available in English (9)
* The article described ATMP regulation issues outside of Europe (2)
* The article described matters related to a specific ATMP product but not the implementation barriers/facilitators of this specific product (3)
* The article was related to ATMP issues but did not describe implementation barriers/facilitators (11)
* The article focused on the regulation issues related to ATMPs only (e.g. providing regulatory frameworks) (22)

8 articles were included because of a description of either barriers or facilitators on ATMP implementation in the clinic. |
| Articles included: (Boran et al., 2017) (Faulkner, 2016) (Bubela et al., 2015) (Abou-El-Enein, Elsanhoury, & Reinke, 2016) (de Wilde et al., 2016) (Pearce et al., 2014) (Hartmann-Fritsch, Marino, & Reichmann, 2016) (Galli, 2016) |
| **Snowball** |
| **From** | **Identified and included** |
| Faulkner 2016 (Faulkner, 2016) | (Gardner, Faulkner, Mahalatchimy, & Webster, 2015) |
| Suggestions from journal: Regenerative medicine (future medicine) after reading articles in their journal. *“people who read this article, also read:”* | (Ali, Hollander, Kemp, Webster, & Wilkins, 2014) (Heathman et al., 2015) |
| Regulatory website describing that authors from House of Lords Science and Technology Committee wrote a paper on this issue (Husereau, Henshall, Sampietro-Colom, & Thomas, 2016) | (Corbett, Webster, Hawkins, & Woolacott, 2017) |

## 2. Web-based questionnaire aimed at advanced melanoma patients

**Introduction**

Welcome to this questionnaire evaluating factors related to TIL trial participation. This survey is aimed at stage 3 and 4 melanoma patients.

Tumor-infiltrating lymphocytes therapy is an immunotherapy that aims at strengthening immune response. Recent literature shows approximately 50% chance on response resulting in stable disease or complete remission of tumors. Based on these promising results, TIL-therapy is conditionally included in the insurance package of the Netherlands despite it is still under investigation. TIL treatment is thus only given in a research setting in the Antoni van Leeuwenhoek hospital in which the (cost-)effectiveness of TIL is being evaluated, compared to ipilimumab (another type of immunotherapy).

If you are not familiar with the TIL treatment, below some extra information is listed.

By means of a surgery, a tumor lesion is removed from which immune cells are isolated, the tumor-infiltrating lymphocytes. These are grown in approximately five weeks to a billion of cells. One week before TIL infusion, chemotherapy is given to create space for the big amount of cells that will be infused later on. Then the TILs are infused whereafter treatment with a growth factor will start to create an optimal environment for these cells. This treatment can result in severe side effects that are comparable with high fever.

After approximately three weeks of admission in the hospital (chemotherapy, TIL infusion and recovery) treatment is completed and the patient can recover from this therapy at home. TIL-therapy is thus a one-time, but intensive treatment.

Via the following links more information can be gathered about the study. (Dutch)

<https://www.avl.nl/topmenu/over-avl/nieuws/nieuwe-behandeling-voor-uitgezaaide-melanoom-voorlopig-toegelaten-tot-verzekerde-zorg/>

<https://www.win-o.nl/klinische-studies/melanoom-trials/til>

This questionnaire aims to identify factors related to the decision whether or not to participate with the TIL study. It is a project initiated by the Antoni van Leeuwenhoek hospital in collaboration with Stichting Melanoom. The questionnaire is aimed at stage 3 and 4 melanoma patients and will take approximately 15 minutes. Answers will be confidential and handled anonymously.

Thank you for your time and effort.

**General domain**

1. **Age:** \_\_\_\_\_\_\_\_\_ year
2. **Gender:** M / V
3. **Education**
* Lower or primary school
* Secundary school
* Secondary vocational education
* Upper secondary vocational education
* Higher and academic education
* Other, namely………………………………………………………………………………………………
1. **Diagnosis**
	* Stage 1 melanoma submit form (end questionnaire)
	* Stage 2 melanoma submit form (end questionnaire)
	* Stage 3 / 4 advanced melanoma or non resectable melanoma
	* I don’t know exactly but advanced melanoma
	* I don’t know exactly but metastasized melanoma
	* I don’t know
2. **If you have been previously treated for melanoma, what was this treatment?**

(you can choose mutiple options)

* + Surgical removal
	+ Chemotherapy, namely: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(e.g. dacarbazin)
	+ Immunotherapy, namely:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(e.g. ipilimumab (yervoy), nivolumab (opdivo), pembrolizumab (keytruda), combination therapy, TIL)
	+ Personalized treatment, namely: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_(e.g. trametinib (mekinist), dabrafenib (tafinlar), vemurafenib (zelboraf))
	+ N.A. / I don’t remember
	+ Other, namely………………………………………………………………………………
1. **In which hospital have you been treated?** *(not mandatory)*
2. **Were you informed by your clinician about the TIL study/treatment? Or were you informed in another way?**
* No
* Yes, it was discussed with me
* Yes, I received information
* Yes, it was discussed and I received information
1. **If yes, was the TIL study at that moment a treatment option?**
* No
* Yes
* N.A.
1. **In addition, have you become familiar with the TIL treatment / study via one of the following channels?**
* No, I have not obtained information about the TIL study in another way
* Via media: television and / or (newspapers) articles
* Came to my attention in fora/ Facebook / other online media
* I found information on the internet
* Was brought to my attention during an event (e.g. congress, peers, event from patient association) where I was present
* Other, namely: …………………………………………………………………………………
1. **Did you consider, participation with the TIL trial? (Ipilimumab versus TIL)**
* No, I was not informed about the trial Go to question 12
* No, I was not eligible for this treatment/trial Go to question 10
* Yes, but I chose not to participate Go to question 11
* Yes, and I participated Go to question 12
1. **What was the reason that you were not eligible for the trial? (open)**
2. **What was the main reason for you to not participate with the TIL trial? (open)**

A page with information about TIL trial, explaining both treatments, expected effectiveness and potential side effects. Containing videos and references to scientific articles on both TIL as well as ipilimumab.

1. **Below you will find several factors that may influence the decision to participate with a trial. In the case of TIL, could you please describe whether these aspects have or would have an influence on the decision to participate. If you have any additional factors that influenced the decision there will be room for this later in the questionnaire**.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Factor** | **Strong negative influence** | **Negative influence**  | **Neutral**  | **Positive influence** | **Strong positive influence** |
| Travel distance and / or travel costs*(TIL-therapy is only given in Amsterdam)* | 1 | 2 | 3 | 4 | 5 |
| Expected additional (healthcare) costs for participation  | 1 | 2 | 3 | 4 | 5 |
| Additional meetings and/or investigations in relation to the trial (e.g. biopsies) | 1 | 2 | 3 | 4 | 5 |
| Expected side effects of TIL-therapy  | 1 | 2 | 3 | 4 | 5 |
| Expected promising results (e.g. survival) of TIL-therapy  | 1 | 2 | 3 | 4 | 5 |
| Possibility of receiving the control arm of the trial (ipilimumab) | 1 | 2 | 3 | 4 | 5 |
| It is a randomized trial (chance) | 1 | 2 | 3 | 4 | 5 |
| Clinician recommends me to participate with this trial | 1 | 2 | 3 | 4 | 5 |
| Family and or friends recommend to participate with the trial  | 1 | 2 | 3 | 4 | 5 |
| The need to switch to another hospital | 1 | 2 | 3 | 4 | 5 |

1. **Please describe your level of agreement with the following statements**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Statement** | **Strongly agree** | **Agree** | **Nor agree nor disagree** | **Disagree** | **Strongly disagree** | **I don’t know** |
| 1 | TIL treatment is the best possible option in my situation | 1 | 2 | 3 | 4 | 5 | 0 |
| 2 | The advantages of TIL-therapy (expected response rate) outweighs expected side effects | 1 | 2 | 3 | 4 | 5 | 0 |
| 3 | Both treatments in the TIL-trial would be a good option for me | 1 | 2 | 3 | 4 | 5 | 0 |
| 4 | I strongly prefer to receive TIL-therapy in this trial | 1 | 2 | 3 | 4 | 5 | 0 |
| 5 | I was afraid for progression if I wouldn’t start with the trial.  | 1 | 2 | 3 | 4 | 5 | 0 |
| 6 | The idea of randomization worried me.  | 1 | 2 | 3 | 4 | 5 | 0 |
| 7 | I received sufficient information about the trial and treatment | 1 | 2 | 3 | 4 | 5 | 0 |
| 8 | I could not say no to participation  | 1 | 2 | 3 | 4 | 5 | 0 |
| 9 | I wanted to stay in my own hospital or with the same clinician for my treatment.  | 1 | 2 | 3 | 4 | 5 | 0 |
| 10 | I wanted to help clinicians with their research | 1 | 2 | 3 | 4 | 5 | 0 |
| 11 | I think my participation will be beneficial for other patients | 1 | 2 | 3 | 4 | 5 | 0 |
| 12 | The clinician wanted for me to participate | 1 | 2 | 3 | 4 | 5 | 0 |
| 13 | Family and friends wanted me to participate | 1 | 2 | 3 | 4 | 5 | 0 |

1. **Which of the above statements would be the most important one for when deciding to participate in a trial (1-13)**
2. **Which additional factors (would have) played a role in deciding to participate with the TIL trial?**
* N.A.
* \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (open)
1. **After this questionnaire, do you consider to participate with the TIL trial?**
* No
* Yes
1. **Can you shortly comment on this?**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **If 17 answered with yes,** do you want to receive more information from one of our clinicians? Please leave your email address or telephone number and we will contact you.
* Yes, I want to receive more information via: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
* Yes I would like to be called on: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
1. **Regarding information provision, what would you recommend us?**
* Nothing, I had sufficient information
* More information via internet
* More information via specialists
* Information flyer for patients
* Designing a website for the study
* Possibility to ask questions to one of the clinicians involved in the trial.
* Other, namely \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
1. Do you have any final remarks? You can describe them here. (open)

On behalf of Stichting Melanoom and Antoni van Leeuwenhoek hospital, we want to thank you for your time and participation to this survey!

## 3. Results literature overview ATMP barriers and facilitators

Identified barriers and facilitators from the literature overview on clinical implementation of ATMPs structured according the six CTA domains.

|  |  |  |
| --- | --- | --- |
| CTA domain | Barrier (general ATMPs) | (Potential) Facilitators (general ATMPs) |
| 1. Clinical | Therapeutic risks because of using live tissue 1* Dosing and administration different from usual drugs 3
* Dosing based on pre-clinical data should be handled carefully 2
* Need for training of clinicians 9
 | Use clinical implementation model in which trained personnel takes responsibility to integrate new therapy into routine clinical practice 1 |
| 2. Patient-related | Therapeutic risks because of using live tissue 1Patient enrollment 7 |  |
| 3. Organizational  | MA 3,10* Study designs and feasibility of monitoring efficacy 1,2,3,4,5,6,9 :
* Complex regulatory environment 6,9
* Heterogeneity in regulations and HEC implementation across Europe 2,5,12

Lack of GMP compliant facilities (adoption) 12Institutional:* Gain management support 9
* Hard to change existing workflows 7,9
 | Improve MA* Contact regulatory authorities early in product development stage to anticipate on challenges faced per specific product 3
* Drafting legislation and guidelines that provide streamlined reimbursement of EU countries 1
* Engagement of HTA organization alongside development process to support value assessment 2,4
* Greater coordination between EMA and national agencies 9
* Develop process with a realistic reimbursable price point at all stages of scale (low costs of goods) 11
* Innovative study design: accept surrogate endpoints and non-straight forward comparator 2,5
* Advice from EMA on clinical trial design and MA 2
* Abou-El-Enein (2016) developed a stepwise model for MA describing facilitators 1

Establish a cell therapy center of excellence to provide guidance and knowledge (adoption) 9Introduce cryopreservation steps to control for the process 11 |
| 4. Technological | Lack of regulatory knowledge (GMP, ATMP) 1,6Comply with GMP regulation to anticipate on risks with using live tissue and assure quality: 2,8,9* In process controls 8,10
* Risk analysis 8,10
* Documentation (e.g. IMPD) 9,10,12
* Consumables, raw and starting material 6,8,10
* Assigning / hiring QP 9,10
* Training of staff 2,10

In clinical trials: establishment of safety monitoring board (IDSMB) 10Upscaling production 2* Unclear responsibilities when exported 6
* In exporting: local QP needed for release 9,12
* Under developed infrastructure 9
* Transport 10

Rapidly evolving field: selected ATMP overtaken by other innovative medicinal product 6Clinicians reluctant because of potential risks: 1* Patient enrollment 6
* Lack of motivation for implementation 9
 | To improve GMP implementation:* Documents on GMP guidelines: 3,6,8
	+ (European Commission, 2017)
	+ (EudraLex, 2016)
	+ (Scientific Committees of the European Commission, n.d.)
	+ (Flory & Reinhardt, 2013)
	+ (Salmikangas et al., 2015)
* Use a standard method for risk analysis: e.g. FMEA 10
* Guidance on IMPD in (Committee for Medicinal Products for Human Use, 2006) 10
* Set up a knowledge platform to support development route of ATMPs 6,9
* Education or training organized by government or academic institutions 6

Quality: Use semi-closed followed by a closed process 11Improve scaling-up:* Collaboration of Production Facilities? (in and over countries) 10
* Include cryopreservation steps in the production process for minimalizing failures in the process when scaling up 11
* Consider scaling out instead of scaling up 5
 |
| 5. Economical | Inadequate financial support for:* Required investments for GMP 3,9,10,11,12
* High manufacturing costs (small target population) 1
* Clinical trial costs 4,6,10 (hard to receive research funding)

Limited flexibilities by funding agencies (e.g. extended time lines) 6 | Adaptive licensing approaches e.g. accelerated assessment, exceptional circumstances licensing, conditional approval mechanisms and other risk sharing principles 2,4,5,7,9More automative process and more productions per year could reduce costs 11 |
| 6. Future | n.a.  |  n.a. |
| 1 Abou-El-Enein et al., 2016; 2 Ali et al 2014; 3 Boran et al 2017; 4 Bubela et al 2015; 5 Corbett et al., 2017; 6 de Wilde et al., 2016; 7 Faulkner, 2016; 8 Galli, 2016; 9 Gardner et al., 2015; 10 Hartmann-Frisch et al., 2016; 11 Heathman et al., 2015; 12 Pearce et al., 2014Abbreviations: MA: Market Approval ; GMP: Good Manufacturing Products ; ATMP: Advanced Therapeutic Medicinal Product; IMPD: Investigational Medicinal Product Dossier; QP: Qualified person; QC: Quality controller; IDSMB: Independent Data and Safety Monitoring Board |