

Radiotherapy and immunotherapy

Citation for published version (APA):

Rekers, N. H. (2017). *Radiotherapy and immunotherapy: the perfect partnership*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20170309nr>

Document status and date:

Published: 01/01/2017

DOI:

[10.26481/dis.20170309nr](https://doi.org/10.26481/dis.20170309nr)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Unspecified

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorisation addendum

In this thesis the long-lasting, protective and curative anti-tumour effects of radiotherapy (RT) in combination with the immunocytokine L19-IL2 has been successfully demonstrated in preclinical models. To have societal impact, this knowledge needs to be translated from preclinical (mice) studies to clinical (human) trials to eventually result into new and applicable treatment options. This translational process from findings in the lab towards new patient treatment options is complex and it often takes decades to be successfully achieved. Furthermore, it is mostly a highly disappointing process: despite successful preclinical results, around 85% of early clinical trials investigating novel drugs fail and only half of the successful therapies will eventually be approved. Therefore, it is important to keep the route from ‘preclinical findings’ to ‘a new treatment option’ as short and straightforward as possible. To ensure that the successful preclinical results as described in this dissertation have the potential to create impact as fast as possible, several key elements favouring this translational process are worth to mention. First of all, Maastro clinic has *extended expertise* in treating patients with (stereotactic ablative) RT, a necessary component of the tested novel treatment strategy. Second, both Maastro lab and Maastro clinic have *a long history of conducting translational research* leading to clinical trials. At this moment several phase I clinical studies are recruiting patients [NCT00691548; NCT00777894 and NCT00409994] and three studies are closed with follow-up [NCT00704600; NCT00409994 and NCT00969657]. In addition, L19-IL2 as monotherapy has already *shown to be safe and effective* in several clinical trials. Therefore research does not need to ‘start from scratch’, which can catalyse the translation process from successful preclinical findings towards the patients. The combination of these key elements made it possible that the preclinical results described in this dissertation already lead to the initiation of a phase I clinical study [NCT02086721], the funding of a phase II clinical trial and initiation of a trimodal study, combining RT and L19-IL2 with anti-PD-1. The knowledge described in this dissertation is therefore already being translated into applicable treatment options, though still in study design, and will hopefully result in a new and curative treatment option for patients with (oligo)metastatic disease in the near future.

CLINICAL RELEVANCE

Cancer is one of the leading causes of death worldwide, accounting for 8.2 million deaths in 2012. A major clinical challenge is the management of metastatic cancer, which is responsible for 90% of all cancer deaths. Patients with metastatic cancer mainly rely on palliative treatment and current treatment strategies result in a disappointing median progression-free survival (only 2-12 months for example in metastatic NSCLC). Therefore, there is a high need to develop new effective treatment strategies for these patients. The combinational treatment strategy investigated in this dissertation is of

great clinical relevance. First of all, tumour irradiation will initiate an anti-tumour immune response containing the elements of a patient's own irradiated tumour. Therefore, combination of RT and immunotherapy based treatments has the potential to trigger a personalized (*in situ* generated) 'medicine'. In chapter 3 curative anti-tumour results are described, showing the importance of ED-B presence in the tumour vasculature prior to treatment. Since ED-B expression is restricted predominantly to tumours and it is present in the majority of tumours, most patients with solid tumours may potentially benefit from the treatment combination with little adverse effects as L19-IL2 is a tumour targeted therapy. Furthermore, as described in chapter 5, RT delivered to one tumour can additionally trigger curative anti-tumour effects outside the RT field (OFRI effect). Therefore, this locally triggered combination treatment has the potential to act as an effective systemic therapy. This makes the treatment of great interest for patients with metastatic disease. Last, this combination treatment triggers a long-lasting anti-tumour (memory) immune response. This is of great clinical relevance, since this memory effect enables to target tumour-associated antigens and thus protect patients from recurrences and potentially from development of new tumours.

GAIN FOR SOCIETY

The successful translation of preclinical data described in this dissertation toward society would, firstly and most importantly, benefit a great variety of (metastatic) cancer patients. As described above, treatment options for these patients are limited and therefore new therapeutic approaches are urgently needed. Introducing a new (combination) treatment for these patients will be highly beneficial for this large group of patients, since they will have the potential to be treated with curative intend instead of receiving palliative therapies. Furthermore, the use of L19-IL2 instead of IL2, to specifically target IL2 to tumours, makes this treatment less toxic. Patients may therefore experience a higher quality of life, which is a major gain for society. Additionally, the long-term anti-tumour effects observed in our studies show that the triggered anti-tumour response can prevent tumour formation months after termination of therapy. The combination treatment may therefore 'learn' the patients' immune system what to target, and these long-living pool of memory T cells have the ability to remember their targets months after cure prolonging uncomplicated patients' life. Next, medical doctors will have more opportunities to treat their patients, although proper patient selection is necessary before initiating treatment. Preclinical results described in this dissertation show that the combination treatment is effective in ED-B positive tumour models. Therefore, the development of a biomarker selecting patients based on the intratumoural ED-B expression prior to treatment, would additionally be a major benefit for society. This way, patients with a high chance to benefit from treatment can be selected and patients with a low chance of benefit could receive

alternative therapies. This prevents using ineffective treatments and thus decreases the costs. We additionally showed that CD8⁺ cytotoxic T cells are highly increased inside tumours that can be eliminated due to the combination treatment and that mice able to prevent new tumour formation have a high level of circulating memory T cells as compared with control groups. All of these findings have, once translated into clinical use, the potential to monitor patients during treatment and adapt or extend treatment when necessary. This increases the treatment efficacy and therefore it provides another gain for society. The initiation of the phase I clinical study in our institute [NCT02086721] can be seen as the first step to create impact in society.

IMPROVEMENT IN HEALTH CARE

The successful translation of the described preclinical results will greatly improve the health care for (metastatic) cancer patients. It is expected that this novel bimodal treatment modality will increase cure rates as well as control metastatic disease thereby prolonging patients' life. The efficacy of this treatment approach needs to be proved in clinical trials which have been already initiated in our department. Additionally, several (immunological) parameters (ED-B expression, increase in CD8+ T cells) associated with elimination of irradiated and non-irradiated tumours when combined with L19-IL2 as well as the presence of memory T cells in long-term protected mice, have the potential to be translated into predictive biomarkers. These biomarkers could be implemented and used for the selection and monitoring of patients in the near future. Therefore, health care will be improved directly, because a new treatment option will be provided. Indirectly, the implementation of new predictive biomarkers to select patients, will have a big advantage since only potential responders will receive treatment. Other treatments, more effective in the cohort of non-responders or similarly effective but less expensive, will be offered to non-responders. This will reduce costs of the treatment and will spare these patients from possible therapy induced side-effects.

NOVELTY OF CONCEPT

The conversion of RT as a local treatment into an effective systemic treatment can be seen as the main conceptual novelty. It is known that the effects of RT on the tumour can initiate an anti-tumour immune response, however, this seldom results in the systemic regression of un-irradiated tumours. Using a novel immunotherapeutic approach, the immunocytokine L19-IL2, we are able to further strengthen the RT induced immune response. In our preclinical models, this resulted in the elimination of not only irradiated but also a part of non-irradiated tumours. Additionally, this immune response was able to prevent new tumour formation months after cure. The novelty of

the concept described in this dissertation relies on the interplay between RT and L19-IL2, which may eventually result in a new treatment opportunity for patients with (metastatic) disease.

ROAD TO THE MARKET

The phase I clinical study (NCT02086721, animation available: <https://youtu.be/xHbwQuCTkRc>) is currently ongoing in our institute and will primarily investigate the safety of the combination L19-IL2 with SABR in patients with oligometastatic solid tumours..Progression-free survival, local control rate, quality of life, non-invasive response using PET and overall survival are secondary endpoints. Furthermore, based on our findings a phase II clinical trial has been funded (animation available: <https://youtu.be/6wDE6RkrikA>). This phase II study will investigate the combination of SBRT and L19-IL2 in patients with non-small cell lung cancer (NSCLC). Additionally, the results described in *chapter 5*, showing the presence of immunosuppressive T cells (PD-1⁺) infiltrating tumours outside the RT field, suggest that the RT + L19-IL2 combination treatment might be increased in its therapeutic potential by combining it with an anti-PD-1 checkpoint inhibitor (e.g. nivolumab). Currently, we applied for a KWF grant in which we will establish the safety of this trimodal treatment for stage IV non-small cell lung cancer (NSCLC) patients (animation available: <https://youtu.be/7ckZeWWyhts>). Secondary endpoints in the latter clinical study include overall survival, progression free survival and quality of life. In addition we will include exploratory endpoints to investigate correlations of outcome measures with immunological markers in tumours and blood.

Therefore, the clinical studies as described above, will not only investigate the safety and effectiveness of radiotherapy combined with L19-IL2, the investigated correlations with (immunological) parameters to evaluate therapy response and OFRI effects will be a crucial step on the ‘road to the market’. First of all, the development of a fast and reproducible assay for the detection of ED-B can be marketed. ED-B can be detected in tumours tissues (via ex vivo immunohistochemistry) or using a PET probe. Furthermore, ED-B can also be detected in the blood (serum), though clinical studies should reveal if ED-B expression in the blood correlates with therapeutic efficacy. Second the presence of tumour reactive cytotoxic T cells can form the basis for a marketable product. An assay predicting the adequate (OFRI) anti-tumour response based on effector (memory) T cell reactivity against tumour (neo)antigens in the blood, is an interesting concept. It can become a relevant tool to monitor patients during radiotherapy and L19-IL2 treatment, however, it could be implemented as a novel tool for a panel of different immunotherapeutic approaches. Thus far, there is a lack of reliable biomarkers for the use of immunotherapies, such as checkpoint inhibitors, which is a major limitation of

these therapies. A recent approach to predict treatment outcome based on tumour infiltrating immune cells (Immunoscore) is an interesting development. However, an assay based on tumour reactive T cells in the blood has probably even more potential, because tumour tissue is not always available.

In general, the preclinical results described in this dissertation may open doors to the development of alternative immunocytokines, for example in the absence of low ED-B expression. It may also show that it is possible to repurpose a ‘failed’ immunotherapy by providing a radiotherapy trigger prior to administration. Taken together, the preclinical research results described in this dissertation will have an important clinical relevance and societal impact when successfully translated to the clinic. The preclinical data already resulted in the initiation and approval of phase I and II clinical studies, which will be used to investigate therapeutic efficacy and will form the basis for identifying blood and tissue biomarkers for the selection and/or monitoring of patients in the near future, which can all be marketed.