ZINNIGE ZORG ROOM FOR IMPROVEMENT REPORT

Appropriate use of expensive medicines in cases of metastatic renal cell carcinoma

Date 7 December 2017
Status Final version

Colophon

Series number	2017015291 2019001481 Engels
Department	Care Sector

Contact	*Zinnige Zorg* Programme Secretary zinnigezorg@zinl.nl www.zorginstituutnederland.nl

Zorginstituut Nederland* and *Zinnige Zorg

Zorginstituut Nederland's motto is "Taking care of good health care: no more and no less than necessary". Every citizen must receive all the care he or she needs, but no more than that.

As a public organisation, the *Zorginstituut* assesses health care systematically. We assess whether diagnostics and (therapeutic) interventions are being deployed in a patient-oriented, effective and cost-effective manner.

We discuss our findings with health care professionals, patients, health care institutions, health care insurers and other governmental agencies. Together with them, we examine what is needed to improve patients' care and avoid unnecessary costs.

Health care organisations are responsible for improving that care. *Zorginstituut Nederland* provides an overview of points for improvement, promotes cooperation and monitors the results.

This is how we contribute to good and affordable health care for everyone.

More information about the activities of *Zorginstituut Nederland* and *Zinnige Zorg* can be found on www.zorginstituutnederland.nl.

Summary

Within the framework of the *Zinnige Zorg Programme, Zorginstituut Nederland* systematically assesses the Dutch minimal and mandatory package of health care that all Dutch health care insurers must provide. There are four phases to this systematic assessment: screening, in-depth assessment, implementation and monitoring. In 2015 we published a screening report: 'Systematic analysis of neoplasms. This Room for Improvement Report is part of the in-depth phase. During the screening phase, one of the topics mentioned by the parties for in-depth assessment was 'appropriate use of expensive oncolytics'. At the time we asked the parties whether they could cite an example of a recommendation by an authoritative organisation that suspected that expensive oncolytics were not being implemented correctly. The Dutch Urological Association stated that an analysis of the guidelines dating from 2011/2012 revealed that more than half of the patients with metastatic renal cell carcinoma received different advice for primary care treatment from that advised in the guidelines. The question was whether this was a case of inappropriate use. Realising appropriate use is essential, not only to realise greater health gains for cancer patients, but also to guarantee accessibility by avoiding unnecessary costs where possible.

Background
Renal cell cancer is a relatively rare disease in which a malignant tumour grows in a kidney. In the case of metastatic renal cell cancer, cure is no longer possible. In this phase, treatment with oncolytics consists of immunotherapy or targeted therapy. The choice of a given therapy depends on patient characteristics, disease characteristics and patient preferences.

Study outcome
For the period 2008-2015, the study confirms the observation from the 2011 analysis of the guidelines, that about half of the patients received different advice on first line treatment from that advised in the guidelines. Based on the available data, it is not really possible to determine whether this is inappropriate use of pharmaceutical products. As a result we are unable to draw any clear conclusions. The contents of the register were inadequate. In other words, we cannot determine whether expensive oncolytics were deployed appropriately.

Room for Improvement Report
Despite the fact that the study did not fully answer the question posed, we were able to formulate three possibilities for improvement based on the study outcome. We regard trying to realise the most appropriate use possible, based in part on the improvements suggested here, as a crucial step in the treatment of not only renal cell cancer, but also other types of tumours where similar developments are taking place.

1. Guideline development

We conclude that the guidelines need to be updated, with special attention to criteria – based on patient characteristics and disease characteristics – for starting and ending treatment, or giving no treatment at all. We feel that the treatment guidelines are not keeping pace with developments, and that this could potentially result in care being deployed less appropriately. This Room for Improvement Report can also apply to other types of tumours where the treatment landscape is continually changing. For example, prostate cancer, melanoma and non-small cell lung carcinoma.

2. Registration at source

We are unable to draw any firm conclusions about the appropriate use of pharmaceutical products in a case of renal cell carcinoma. There are no indications for suspecting that registration was inadequate from the perspective of treatment, but the current analysis makes it clear that registration focussed insufficiently on the systematic collection of feedback information. It is important to actually register the patient characteristics and disease characteristics that in practice may be used to determine what treatment will be given so that these data can subsequently be used to draw relevant conclusions. To date, this has not taken place sufficiently.
Registries are increasingly used for providing feedback information on appropriate use. In general, we can state that if the objective of registers is to provide insight into the appropriate use of pharmaceutical products, then data must be collected prospectively with registration at source.

3. Use of surrogate outcome measures.

In cases of renal cell carcinoma a surrogate outcome measure – progression-free survival – is used to measure the effectiveness of some of the pharmaceutical products used in second line treatment and subsequent care. We feel it is necessary to discuss the clinical relevance of pharmaceutical products whose effectiveness is mainly determined based on a surrogate outcome measure. Carrying out concrete improvement activities in relation to this demands an international investigation, which goes beyond the scope of this report. The *Zorginstituut* does want to discuss the matter within its Dutch context with the parties in the field.

Budget impact

Developments in the costs of pharmaceutical products cannot be explicitly charted for many types of tumour, including those for renal cell carcinoma. This is because treatment possibilities are subject to change, with new pharmaceutical products arriving and the places filled by existing pharmaceutical products changing.
We expect the growing range of treatment possibilities to cause an increase in the costs of treating a certain type of tumour. However, in practice, new treatment options should also lead to increased effectiveness. This raises the question whether this extra effectiveness is worth the extra costs.
This has not actually been demonstrated. As a result it is not clear whether the cost-effectiveness of treatment as a whole has improved. This confirms the need to maximise efforts to promote appropriate use.

Implementation and monitoring

In our opinion, implementing the Room for Improvement Report on this topic is acutely relevant. During consultations, the parties made concrete suggestions and expressed an interest in elaborating upon this jointly. The *Zorginstituut* will remain involved in the further elaboration and monitor developments surrounding the treatment of renal cell carcinoma. Based on this study, and also on our experience with the *Zorginstituut*'s other oncology files, we note that the improvement possibilities can also be relevant to treatment for other types of tumours. Furthermore, we feel that the improvement possibilities are in line with tumour-type-overarching topics that parties in the field have already discussed extensively. For this reason we are emphatically asking for a broad discussion of the applicability of these improvement possibilities to other types of tumour. We want this to take place as part of the implementation phase of this topic.

1 Introduction

Within the framework of the *Zinnige Zorg Programme, Zorginstituut Nederland* systematically assesses the Dutch minimal and mandatory package of health care that Dutch health care insurers must provide. There are four phases to this systematic assessment: screening, in-depth assessment, implementation and monitoring.
This report, which was carried out as part of the in-depth phase, is about the appropriate use of expensive oncolytics. Cancer treatment can also improve when new pharmaceutical products become available. Many new and promising oncolytics are expected to arrive on the market in the next few years. Access to these could be threatened due to the fact that often they are fairly expensive, and in view of the limited budgetary scope. In practice, new treatment options should also lead to increased health gains (effectiveness). This raises the question whether this extra effectiveness is worth the extra costs of these expensive pharmaceutical products. Realising the most appropriate possible use is essential, not only to realise greater health gains for cancer patients, but also to guarantee accessibility by avoiding unnecessary costs where possible. Several parties drew attention to this problem, which was also mentioned in the KWF report dated June 2014, 'Accessibility of expensive cancer medicines, now and in the future'.[1] This is one of the in-depth topics studied by the *Zorginstituut* in response to the screening phase of the systematic analysis of the ICD 10-field Neoplasms.[2]

Aim of this Room for Improvement Report
The aim of this Room for Improvement Report is to provide insight into the potential for improving daily practice with expensive oncolytics with a view to appropriate use.

Case proposed by the parties
We asked the parties whether they could cite an example of a recommendation by an authoritative organisation that suspected that expensive oncolytics were not being implemented correctly. The Dutch Urological Association stated that an analysis of the guidelines dating from 2011/2012 revealed that more than half of the patients with a metastatic renal cell carcinoma received different advice for primary care treatment from that advised in the guidelines.[3] This could suggest under-treatment. The question is whether it is a case of inappropriate use of expensive oncolytics.

Focus
This report focusses on providing insight into the use of expensive oncolytics in cases of metastatic renal cell carcinoma. We expect that certain generic aspects of this study will apply to other types of tumours.

Methods
This in-depth phase, which involved an analysis of care for metastatic renal cell carcinoma, took place based on 'elements of good and appropriate care'. Together, these give an idea of what the *Zorginstituut* regards as good and appropriate care. They are also in line with our quality and package management tasks. In this Room for Improvement Report we focus mainly on the element 'application in practice'. This involves us using various sources (such as claim data, publications, formal and informal consultation) to look at how care takes place in practice and what the experts think of it. We compare this to what is stated in quality standards and treatment guidelines. Adhering to quality standards and treatment guidelines is one

way in which the professional group attempts to use care appropriately.

External research
The *Zorginstituut* commissioned external research into whether, in daily practice, the use of expensive oncolytics in cases of metastatic renal cell carcinoma is in line with the treatments recommended in the guidelines. For the external research, the *Zorginstituut* commissioned the *Institute for Medical Technology Assessment* (iMTA), a research institute of the Erasmus University of Rotterdam. In order to answer the research question, the iMTA made use of data that are available on metastatic renal cell carcinoma (mRCC, both primary and secondary metastases) within the PERCEPTION register (cohort 2008-2010 and cohort 2011-2013) and the EuroTARGET (cohort 2012-2015) register. The PERCEPTION register was primarily set up to study care outcomes for patients with mRCC. The EuroTARGET register focuses on studying the effectiveness of the pharmaceutical products used most frequently to treat mRCC by identifying predictive biomarkers.

The guideline analysis carried out in 2011 regarding renal cell carcinoma showed that a limited number of the patients were treated with systemic therapy.[2] The purpose of the present study was to carry out an in-depth analysis, based on more recent data collected based on patient files in the PERCEPTION and the EuroTARGET registers, to determine whether systemic therapy is being put to appropriate use.

A summary of the outcomes that resulted in this Room for Improvement Report can be found in appendix 2. For the detailed analyses of the registers, see the iMTA research report.

Structure of this report
The background to renal cell cancer is described in section 2. Further background information about available pharmaceutical products is provided in appendix 1. Section 3 discusses the study results and the resulting Room for Improvement Reports, and section 4 goes into their implementation. The most important outcomes of the Room for Improvement Report are described in appendix 2.

2 Background

This section describes exactly what metastatic clear cell renal cell cancer is, its incidence and its possible consequences for patients.

- Metastatic clear cell renal cell carcinoma is a relatively rare form of cancer that is regarded as incurable.
- Treatment is palliative, focussing on extending life, relieving symptoms and retaining quality of life.
- The choice of treatment is determined by balancing the expected benefits against the burden the treatment places on a patient.

2.1 What is metastatic clear cell renal cell carcinoma and what are the symptoms

Renal cell carcinoma is a relatively rare form of cancer whereby the primary tumour develops in the kidney. Renal cell cancer accounts for about 2% of new cases of cancer. More than 90% of these are renal cell carcinomas. Renal cell carcinomas can be sub-divided into different sub-types, the most frequent of which is the clear cell renal cell carcinoma (about 85% of all renal cell carcinomas). Other sub-types are papillary renal cell carcinoma, multi-ocular cystic clear cell renal cell carcinoma and chromophobe renal cell carcinoma. Other sub-types are rare.[4]

If renal cell carcinoma is diagnosed at an early stage, one treatment option is curative surgery whereby (part of) the kidney is removed. Cure is no longer possible once the disease has spread to other parts of the body. In that case treatment is palliative and focusses on relieving symptoms. Retaining quality of life is the primary objective. Treatment can encompass pharmaceutical products and radiation therapy.[4,5] This report is specifically about the metastatic stage and treatment with pharmaceutical products.

As renal cell carcinoma often has no symptoms, renal cell carcinomas are often diagnosed by accident, e.g. during a CT-scan of the abdominal cavity. The disease is usually more advanced if symptoms such as blood in the urine or a palpable mass are present when a tumour is discovered. Because of this, at the moment of diagnosis, about 20-30% of patients already have metastases. Some patients who had no metastases when first diagnosed, will still develop metastases after local treatment of the tumour (operation). Symptoms such as flank pain or breathlessness may result from metastases in the lung. More general symptoms are tiredness, general fatigue or fever with no apparent cause (possibly accompanied by night sweats).

2.2 Incidence of renal cell carcinoma

In the Netherlands, about 2000 patients are diagnosed with renal cell carcinoma each year. Renal cell carcinoma accounts for about 2-3% of all forms of cancer. Patients are often older than 60 years. About one-third of patients are in an advanced stage of the disease at the moment of diagnosis, i.e., the tumour has spread from the kidney to other organs. Prognosis depends on the stage of the disease. If the tumour is restricted to the kidney, and there are no metastases elsewhere in the body, the five-year survival is about 80-90% (the percentage of patients still alive after five years). If the tumour has spread to the renal capsule, this percentage drops to 40-50%. If the disease has spread from the renal capsule

and metastases are found elsewhere in the body, then the one-year survival is only 38%. The five-year survival is 10 to 15%. Obesity, smoking and hypertension increase the risk of renal cell carcinoma. Genetic factors also play a role in its genesis. Mortality is higher among men than among women.[6]

2.3 Cost developments

In 2015, the costs of pharmaceutical products for renal cell carcinoma amounted to about €23 million. This sum is about the same as the costs claimed in 2014. This is mostly down to TKI's sunitinib and pazopanib, which account for more than €16.5 million. In 2015 the average costs per pharmaceutical product per user were €15,500 per year.[7]

The treatment arsenal was augmented in 2016 and 2017 with nivolumab, cabozantinib and lenvatinib. At the moment it is not clear to what extent the introduction of these products will lead to substitution of existing products or a change in the positioning of existing products. The number of patients has also increased. At the moment it is difficult to estimate how costs will develop over the next few years. For this reason, this Room for Improvement Report does not include a budget impact analysis.

3 Room for Improvement Report

Based on the external research, we answer the question of whether appropriate use is being made of expensive pharmaceutical products for the treatment of metastatic renal cell carcinoma. The Dutch Urological Association stated that an analysis of the guidelines dating from 2011/2012 revealed that more than half of the patients with metastatic renal cell carcinoma received different advice for primary care treatment from that in the guidelines.[3] This could suggest under-treatment. The underlying question is whether this is a case of inappropriate use of expensive oncolytics. The purpose of the present study was to carry out an in-depth analysis, based on more recent data, collected based on patient files in the PERCEPTION and the EuroTARGET registers, to determine whether appropriate use was made of expensive drugs. Our conclusion is as follows:

The study confirms, for the entire period of 2008-2015, the observation from the 2011 analysis of the guidelines involving a limited number of patients treated. Based on the available data, it is difficult to determine whether this is a case of inappropriate use of pharmaceutical products. For this reason, therefore, no conclusions can be drawn. In other words, we cannot determine whether expensive oncolytics were used appropriately.

3.1 Scope of improvement possibilities

Based on the analyses, we see the following three possibilities for improving the treatment of renal cell carcinoma. In our opinion, attempting to realise the best possible use, based in part on the improvements suggested here, is a crucial step in the treatment of not only renal cell carcinoma, but also other types of tumours where similar developments are taking place.

* **Improve the criteria for appropriate care in the guidelines and update the guidelines:** Because of the introduction of new evidence and new pharmaceutical products for the treatment of metastatic renal cell carcinoma, the treatment algorithm in the guidelines needs to be revised, and appropriate use promoted by including improved needs assessment in the guidelines.
* **Registration at source:** Patient characteristics and disease characteristics, which are necessary for determining treatment considerations, and the IMDC-risk score and histological confirmation of the sub-type renal cell carcinoma, must automatically be included in patient files (at source).
* **Determining the value of surrogate outcome measures:** The clinical value of surrogate outcomes on 'progression-free survival' in clinical studies should be studied in greater depth with evidence.

This Room for Improvement Report focusses on the treatment of renal cell carcinoma. Earlier we published a Room for Improvement Report on the use of expensive pharmaceutical products to treat patients with prostate cancer.[15] Improvements in these two topics, and other oncological fields in which the *Zorginstituut* is involved, are in line with matters that are already receiving a lot of attention from the parties in the field. Examples are appropriate use, quality improvement by making use of feedback information based on observational studies (registers) and the clinical value of pharmaceutical products. This can be seen from developments surrounding immunotherapy for lung cancer (nivolumab, pembrolizumab) and the new product palbociclib for breast cancer.

In this sense, we see a broader use for these possibilities for improvement than just renal cell carcinoma. Many new products are becoming available within most fields of oncology. The fact that the BOM committee determined the value of these products has provided important pointers for use in practice. The BOM committee is an expert group from the Dutch association of medical oncologists that develops and timely updates short guidelines for expensive chemotherapy. Nevertheless, in view of possible patient characteristics and disease characteristics, the interplay between various products in the treatment arsenal for a given indication is equally important in promoting appropriate use and avoiding variations in practice. At the moment, the guidelines are the most appropriate tool for this. Unlike the recently updated guidelines for prostate cancer, guidelines in other fields – including those on the treatment of renal cell carcinoma – are outdated in relation to the multitude of new interventions.

When determining the position of pharmaceutical products, many uncertainties still often exist about their clinical value at the moment of market introduction. Clinical research has often been performed on only a limited part of the patient population, so that extrapolation is required. In practice, these data could be collected, e.g. in patient registers (prospectively or, as in the case of the data source used for this study, retrospectively based on patient files). Though the interpretation of this type of data is limited, this limitation is reduced considerably by efficient source registration. This Room for Improvement Report shows that patient files do not automatically collect all patient characteristics and disease characteristics that are important for this feedback information.

The strength of the relationship between PFS and quality of life or survival is not the same for all types of tumours.[16] As a result, this issue concerns oncology trials for all tumour types in which there is a lack of convincing evidence of effects on general survival or quality of life. In view of the significant value that PFS has on interpreting clinical research, evidence of the clinical relevance of PFS (e.g. on OS or quality of life) should preferably take place more structurally. The *Zorginstituut* feels that a critical discussion of the matter among parties in the field remains important in order to be able to provide patients with the best possible care.

3.2 Improved criteria for appropriate care in the guidelines

What does the study show?

The guidelines for the treatment of renal cell carcinoma are outdated, but new therapies are actually deployed in practice. No criteria exist for choosing between various alternatives – nor criteria for cancelling therapy – based on patient characteristics and disease characteristics.

In the opinion of the *Zorginstituut*, the needs assessment in the current treatment guidelines should be updated in view of the introduction of new treatment possibilities. Moreover, improved needs assessment in the guidelines will promote appropriate use.

This Room for Improvement Report came about because we noticed that the guidelines are lagging behind the augmented treatment arsenal of recent years, resulting in a lack of clarity about the place these new products have in the treatment of patients. Nor do the guidelines clearly specify whether existing

products in secondary health care can still be used during later stages of treatment.

To arrive at criteria for appropriate care, the *Zorginstituut* suggests, alongside the established indication criteria, including broader considerations about patient selection when opting for a different pharmaceutical product or opting to cancel therapy. This will provide a basis for opting for systemic therapy as appropriate choice of treatment in a field in which treatment is rapidly changing.

3.3 Registration at source

What does the study show?

Important patient characteristics and disease characteristics that are needed when choosing a therapy were registered insufficiently to be able to draw conclusions on the appropriate use of pharmaceutical products.

Factors that influence treatment choice must be included in patient files so that treatment in practice can reflect the recommendations in the guidelines. Reliable registration requires that this is done 'at source' , i.e. by the doctors themselves. It is important to actually register the patient characteristics and disease characteristics that in practice may be used to determine what treatment will be given so that these data can subsequently be used to draw relevant conclusions. This could include factors based on which the IMDC-risk score is determined and the histological characteristics of the tumour (clear cell versus non-clear cell). There are no indications for suspecting that registration was inadequate from the perspective of treatment, but the current analysis does make clear that registration focussed insufficiently on the systematic collection of feedback information. This is why we feel there is room for improvement here.

3.4 Intermediate outcome measures

What does the study show?

No survival advantage was demonstrated for a number of frequently used pharmaceutical products and evidence of effectiveness was based on an 'intermediate outcome measure': progression-free survival.

Progression-free survival (PFS; time to disease progression or death) is an outcome measure that is frequently used in clinical research in the field of oncology. Outcomes on PFS are expected to correlate with quality of life or survival. Improvements in PFS can actually have clinical relevance, e.g., due to reduced symptoms as a consequence of the tumour. Moreover, from a methodological perspective, measuring PFS has a few advantages over measuring survival. However, the association between PFS and OS has only been demonstrated for a few types of tumour. The *European Society for Medical Oncology* (ESMO) does not regard PFS as a reliable surrogate parameter for survival or quality of life.[12] Thus, in many cases it is not clear whether improved PFS actually leads to a longer survival or a better quality of life.[13,14]

In cases of renal cell carcinoma, there are signs that a longer PFS is correlated with a longer OS.[10] From a methodological perspective, however, no effect on survival was demonstrated, noticeably in the later stages of treatment of renal cell

carcinoma: there are fewer follow-up treatments, so there is less of a chance of the effect being 'watered-down' due to cross-over. Furthermore, an unreasonably long follow-up is not needed at this stage of treatment. As a result, evidence regarding products with demonstrated effects on PFS, but not on overall survival, is less convincing. Moreover, in a number of cases the differences in median PFS were near the lower limit for minimum differences as quoted by the BOM committee.[11] For products available in secondary care in 2015 (among others: sorafenib, pazopanib and everolimus), the ESMO gives a score of 3 to indicate the extent of the clinical advantage (on a scale of 1-5, where 5 reflects the maximum advantage).[12]

The *Zorginstituut* concludes that the clinical value of outcomes on PFS requires more study and evidence. However, obtaining more insight into this would require far-reaching studies that are beyond the scope of the present Room for Improvement Report.

3.5 Budget impact

It is not possible to explicitly chart developments in the costs of pharmaceutical products for renal cell carcinoma. This is because treatment possibilities are subject to change, with new pharmaceutical products arriving and the places filled by existing pharmaceutical products changing. Nor were we able, due to limitations in the source data, to establish whether appropriate use was made of the products available.

We expect the growing range of treatment possibilities to cause an increase in the costs of treating renal cell carcinoma, and thus also in the budget impact. The question then is whether this will be accompanied by an improvement in the cost-effectiveness of treatment as a whole.

Appropriate use is essential to be able to realise the most favourable possible cost-effectiveness. In our opinion, striving to realise the most appropriate use, e.g. by means of the improvements points presented here, is a crucial step in this direction.

4 Implementation and monitoring

Implementing these improvement activities is the task of the parties in health care, based on their respective accountabilities within the health care system. The *Zorginstituut* can, if necessary, play a facilitating role here and seek harmonisation with other parties.

Based on this study, and also on our experience with the *Zorginstituut*'s other oncology files, we note that the improvement possibilities can also be relevant to treatment for other types of tumours. We also feel that that the improvement possibilities are in line with tumour-type-overarching topics that parties in the field have already discussed extensively. For this reason we are emphatically asking for a broad discussion of the applicability of these improvement possibilities to other types of tumour. We want this to take place as part of the implementation phase of this topic.

For this topic, the most important improvements involve activities to promote and increase insight into the appropriate use of existing and new pharmaceutical products for the treatment of renal cell carcinoma. The obvious way to do this is to update the guidelines. Special attention should be given to guideline recommendations on initiating or cancelling treatment based on patient characteristics and disease characteristics. Afterwards, we ask that the professional group pays attention to registering relevant data at source to be able to map out the extent to which appropriate use has taken place. A prospective, indication-wide register would have added value.

The use of surrogate outcome measures within the field of oncology is a very broad topic that still requires a lot of research. In our opinion, implementing the Room for Improvement Report on this topic is acutely relevant. Determining clinical relevance is primarily the responsibility of the professional group, certain aspects of which demand international harmonisation. Concrete points for improvement would not be appropriate within the context of the improvement cycle of the *Zinnige Zorg* programme. Nevertheless, we explicitly ask for a broad discussion of this topic within the Dutch context. We want this to take place as part of the implementation phase of this topic.

In order to implement the improvement points, the *Zorginstituut* wants to organise a meeting to discuss the role each party can play in realising the improvements. We will also facilitate implementation research or give advice. We will also monitor activities and developments.

5 References

1. Signaleringscommissie Kanker van KWF Kankerbestrijding. Toegankelijkheid van dure kankergeneesmiddelen. 2014. via https://www.kwf.nl/sitecollectiondocuments/sck%20rapport%20toegankelijkheid%20van%20dure%20kankergeneesmiddelen.pdf.

2. Zorginstituut Nederland. Systematische analyse Nieuwvormingen (ICD-10: C00-D48). 2015. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/rubrieken/pakket/consultaties/1504-systematische-analyse-nieuwvormingen-icd-10-c00-d48/1504-systematische-analyse-nieuwvormingen-icd-10-c00-d48/Systematische+Analyse+Nieuwvormingen+%28ICD-10+C00-D48%29.pdf.
3. Aben K, Osanto S, Hulsbergen-Van de Kaa C, Soetekouw P, De Groot J, Bex A. Uitkomsten van richtlijnevaluatie van de in 2010 gereviseerde richtlijn niercelcarcinoom. Tijdschrift voor Urologie; 3 (mei), 2013. via https://www.nvu.nl/Portals/_default/Skins/NVU/DocumentHandlerPublic.ashx?id=fdd77f93-adfe-49b8-a095-c446d0d77dd9&filename=Tijdschrift+voor+Urologie+2013-03.pdf.
4. Landelijke Werkgroep Urologische Tumoren. Richtlijn niercelcarcinoom. 2010. via http://www.oncoline.nl/niercelcarcinoom.
5. European Association of Urology. Renal Cell Carcinoma Guideline. 2016. via uroweb.org/guideline/renal-cell-carcinoma/.
6. IKNL. Cijfers over kanker. 2016. via www.cijfersoverkanker.nl.
7. ZPD/Vektis/Zorginstituut Nederland. 2017;
8. Motzer RJ, Hutson TE, McCann L, et al. Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med 2014;370:1769-70.
9. Motzer RJ, McCann L, Deen K. Pazopanib versus sunitinib in renal cancer. N Engl J Med 2013;369:1970.
10. Heng DY, Xie W, Bjarnason GA, et al. Progression-free survival as a predictor of overall survival in metastatic renal cell carcinoma treated with contemporary targeted therapy. Cancer 2011;117:2637-42.
11. NVMO. PASKWIL-criteria aangepast. Medische Oncologie 2016;12.
12. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2016;
13. Booth CM, Eisenhauer EA. Progression-free survival: meaningful or simply measurable? J Clin Oncol 2012;30:1030-3.
14. Fallowfield LJ, Fleissig A. The value of progression-free survival to patients with advanced-stage cancer. Nat Rev Clin Oncol 2011;9:41-7.
15. Zorginstituut Nederland. Verbetersignalement Zinnig gebruik van geneesmiddelen bij patienten met castratierefractair prostaatcarcinoom. 2016. via https://www.zorginstituutnederland.nl/publicaties/rapport/2016/11/21/verbetersignalement-zinnig-gebruik-van-geneesmiddelen-bij-patienten-met-castratie-refractair-prostaatcarcinoom.
16. Prasad V, Kim C, Burotto M, et al. The Strength of Association Between Surrogate End Points and Survival in Oncology: A Systematic Review of Trial-Level Meta-analyses. JAMA Intern Med 2015;175:1389-98.
17. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27:5794-9.
18. Motzer RJ, Bacik J, Murphy BA, et al. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol 2002;20:289-96.
19. NVMO. Sorafenib en sunitinib bij heldercellig niercelcarcinoom (herziene versie). 2007. via http://www.nvmo.org/files/_pdfs_bom/mo2_2007_bom_pag_39-45_rev.pdf.

20. NVMO. Beoordeling pazopanib bij RCC en cetuximab bij CRC. 2011. via http://www.nvmo.org/files/_pdfs_bom/MO5%20november%202011%20-%20BOM%20-%20Beoordeling%20pazopanib%20bij%20RCC%20en%20cetuximab%20bij%20CRC.PDF.
21. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013;49:1287-96.
22. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 2010;28:1061-8.
23. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013;369:722-31.
24. NVMO. Temsirolimus bij niercelcarcinoom met ongunstige prognose. 2008. via http://www.nvmo.org/files/_pdfs_bom/MO2_MEI_%202008_BOM.pdf.
25. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
26. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009;27:3584-90.
27. CVZ. Sunitinib: aanpassing nadere voorwaarden. 2007. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2007/0709-sunitinib-sutent/0709-sunitinib-sutent/sunitinib+%28Sutent%29.pdf.
28. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007;370:2103-11.
29. Rini BI, Halabi S, Rosenberg JE, et al. Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clin Oncol 2008;26:5422-8.
30. Escudier B, Bellmunt J, Negrier S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol 2010;28:2144-50.
31. Rini BI, Halabi S, Rosenberg JE, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol 2010;28:2137-43.
32. NVMO. Bevacizumab bij voortgeschreden niercelcarcinoom. 2008. via http://www.nvmo.org/files/_pdfs_bom/MO2_MEI_%202008_BOM.pdf.
33. CVZ. Farmacotherapeutisch rapport bevacizumab bij de indicatie gevorderd en/of gemetastaseerd niercelcarcinoom. 2008. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2008/0805-bevacizumab-avastin/0805-bevacizumab-avastin/bevacizumab+%28Avastin%29.pdf.
34. CVZ. Beoordeling pazopanib. 2011. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2010/1012-pazopanib-votrient/1012-pazopanib-votrient/pazopanib+%28Votrient%29.pdf.
35. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007;356:125-34.
36. Escudier B, Eisen T, Stadler WM, et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. J Clin Oncol 2009;27:3312-8.
37. CVZ. Beoordeling sorafenib. 2006. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2006/0610-sorafenib-nexavar/0610-sorafenib-nexavar/sorafenib+%28Nexavar%29.pdf.
38. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet

2008;372:449-56.
39. Motzer RJ, Escudier B, Oudard S, et al. Phase 3 trial of everolimus for metastatic renal cell carcinoma : final results and analysis of prognostic factors. Cancer 2010;116:4256-65.
40. NVMO. Everolimus bij gemetastaseerd niercelcarcinoom. 2010. via http://www.nvmo.org/files/_pdfs_bom/MO1%20maart%202010%20-%20BOM%20-%20Adviezen%20gefitinib%20en%20everolimus.pdf.
41. CVZ. Beoordeling everolimus. 2010. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2010/1002-everolimus-afinitor/1002-everolimus-afinitor/everolimus+%28Afinitor%29.pdf.
42. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
43. NVMO. Nivolumab als tweedelijns of derdelijns behandeling van het gevorderd of gemetastaseerd heldercellig niercelcarcinoom. 2016.
44. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol 2016;17:917-27.
45. NVMO. Cabozantinib als tweedelijns of laterelijns behandeling van het gevorderd of gemetastaseerd heldercellig niercelcarcinoom. 2016. via http://www.nvmo.org/files/adviezen%20commissie%20BOM/Niercelcarcinoom/_BPM_MO_09-2016_P41-44.pdf.
46. Motzer RJ, Hutson TE, Ren M, et al. Independent assessment of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma. Lancet Oncol 2016;17:e4-e5.
47. NVMO. Lenvatinib in combinatie met everolimus als tweedelijns behandeling van het gevorderd of gemetastaseerd heldercellig niercelcarcinoom. 2017. via https://medischeoncologie.nl/download/32751.pdf.
48. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-81.
49. CVZ. Farmacotherapeutisch rapport temsirolimus. 2008. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/geneesmiddelbeoordelingen/2008/0808-temsirolimus-torisel/0808-temsirolimus-torisel/temsirolimus+%28Torisel%29.pdf.
50. Zorginstituut Nederland. Toetsingskader kwaliteitsstandaarden, informatiestandaarden & meetinstrumenten (versie 2.0). 2015.
51. Zorginstituut Nederland. Begrippenkader gepaste zorg en praktijkvariatie (rapportnr. 1504). 2015.
52. Zorginstituut Nederland. Beoordeling stand van de wetenschap en praktijk (geactualiseerde versie). 2015. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2015/1501-beoordeling-stand-van-de-wetenschap-en-praktijk/Beoordeling+stand+van+de+wetenschap+en+praktijk.pdf.
53. Zorginstituut Nederland. Kosteneffectiviteit in de praktijk. 2015. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2015/1506-kosteneffectiviteit-in-de-praktijk/1506-kosteneffectiviteit-in-de-praktijk/Kosteneffectiviteit+in+de+praktijk.pdf.
54. Zorginstituut Nederland. Pakketbeheer in de praktijk 3. 2013. via https://www.zorginstituutnederland.nl/binaries/content/documents/zinl-www/documenten/publicaties/rapporten-en-standpunten/2013/1310-pakketbeheer-in-de-praktijk-deel-3/1310-pakketbeheer-in-de-praktijk-deel-3/Pakketbeheer+in+de+Praktijk+%28deel+3%29.pdf.

Appendix 1: What form does pharmaceutical care of metastatic renal cell carcinoma take?

In this section we describe the form that pharmaceutical care of metastatic clear cell renal cell carcinoma (mRCC) takes. This is where we describe the context of the research questions.

The guidelines on renal cell carcinoma provide the following recommendations:
- In the event of a *good* or *intermediate* prognosis, **primary care treatment** of mRCC is comprised of sunitinib or interferon-alfa in combination with bevacizumab. An alternative is treatment with pazopanib.

- In the event of a *good* or *intermediate* prognosis, since recently, nivolumab and cabozantinib are the recommended treatments for mRCC in **secondary or tertiary care**. In the past, secondary care treatment for mRCC was in the form of everolimus if prior treatment took the form of a tyrosine kinase-inhibitor. An alternative to everolimus was pazopanib. If primary care treatment was in the form of a cytokine (interferon-alfa), then sorafenib was recommended as secondary care treatment. Lenvatinib also recently became available as secondary care option.

- In the event of an *unfavourable prognosis,* temsirolimus was the **primary care treatment**. No recommendations are given for further treatment of these patients in more specialised care.

Treatment with medicines depends in part on the patient's prognosis. This was based on six clinical characteristics and laboratory tests (WHO performance score, haemoglobin, serum calcium, time since diagnosis to start of first therapy, number of neutrophils and blood platelets). Patients could be categorised, based on cut-off points of values for these factors, as good prognosis (fulfils none of the factors), intermediate prognosis (fulfils one or two of these factors) and poor prognosis (fulfils three or more of these factors).[17] To determine choice of therapy, a sub-division is made into favourable, intermediate or poor prognosis. In the past, the risk score was determined based on the MSKCC-criteria which incorporated five factors.[18]

Chemotherapy in cases of renal cell carcinoma proved ineffective. Treatment with medication is therefore comprised of targeted therapy or immunotherapy.

The treatment of renal cell carcinoma was described in the guidelines dating from 2010.[4] In addition, advice of the Committee for Assessing Oncology Products (BOM committee) of the Dutch Association for Medical Oncology also plays an important and authoritative role in determining the value of pharmaceutical products. Table 1 reflects the treatment logarithm taken from the guidelines. Table 2 provides a summary of the most important pharmaceutical products used for renal cell carcinoma with the most important study results and their place in Dutch practice according to the guidelines and the advice of the BOM committee.

Primary care therapy
Up till 2006 immunotherapy with interferon alfa (IFN-α) was standard treatment for mRCC patients with a favourable prognosis. The most recent Dutch guidelines (2010) cite as primary care treatments for patients with clear cell mRCC and a favourable or intermediate prognosis: sunitinib, or interferon alfa (IFN-α) combined with bevacizumab. Sunitinib improved median progression-free survival from 5 to 11

months, and median total survival from 21.8 to 26.4 months, in comparison with IFN-α monotherapy. Adding bevacizumab to treatment with IFN-α extended median progression-free survival from 5 months to 10 months. In 2007 the BOM committee issued positive advice on sunitinib for patients with a favourable or intermediate prognosis.[19] Based on a placebo-controlled study with pazopanib, the guidelines saw this product as an alternative to sunitinib or IFN-α in primary care. However, the BOM committee concluded that sunitinib remained first choice.[4,20-22] Definitive study results published later showed a survival advantage for pazopanib in comparison with sunitinib. Though this study demonstrated that in primary care pazopanib is not inferior to sunitinib and may be an alternative to sunitinib, it was not included as evidence in the guidelines.[8,23] For patients with cell mRCC and an unfavourable prognosis, temsirolimus is first choice treatment. In 2010 the BOM committee stated that sunitinib may be an alternative for this group of patients.[24]

Table 1: Treatment strategy according to the Dutch guidelines (2010).

Type of RCC	**MSKCC risk group**	**Primary care therapy**	**Secondary care therapy**	**Tertiary care therapy**
Clear cell*	Favourable or intermediate	sunitinib IFN-α+bevacizumab pazopanib	everolimus after previous TKI	everolimus after previous TKI(s)
			sorafenib after previous cytokine therapy pazopanib after previous cytokine therapy	
	Unfavourable	temsirolimus		

* No standard treatment is available for patients with non-clear cell renal cell carcinoma. These patients should be treated within a research context. If no study is available, then in consultation with the patient, the option can be to treat as for clear cell renal cell carcinoma.

Table 2: Summary of the most important outcomes and place of the various pharmaceutical products in the Dutch guidelines on treatment

Treatment	**Marketing authorisation date**	**PFS in months, new treatment versus control (reference treatment)**	**Survival in months, new treatment versus control (reference treatment)**	**BOM committee advice**	**Place in Dutch guidelines (2010)[4]**	***Zorginstituut*'s outcome of assessment**
Favourable/intermediate prognosis: primary care						
Sunitinib	2007	11 vs 5 (IFN-α)[25] HR: 0.54 (95% BI: 0.45-0.64); p<0.001	26.4 vs 21.8 (IFN-α)[26] HR: 0.82 (95% BI: 0.67-1.00); p=0.05*	Positive[19]	Primary care	Added value in comparison with IFN-α[27]
IFN-α + bevacizumab	2008	10.2 vs 5.4 (IFN-α)[28] HR: 0.63 (95% BI: 0.52-0.75); p=0.0001 8.5 vs 5.2 (IFN-α)[29] HR: 0.67 (95% BI: 0.57-0.79); p<0.001	23.3 vs 21.3 (IFN-α)[30] HR: 0.79 (95% BI: 0.62-1.02); p=0.07 18.3 vs 17.4 (IFN-α)[31] HR: 0.86 (95% BI: 0.73-1.01); p=0.07	Positive (sunitinib advantage of oral administration)[32]	Primary care	Added value in comparison with IFN-α[33]
Pazopanib	2010	8.4 vs 9.5 (sunitinib)[23] HR: 1.05 (95% BI: 0.90-1.22)	28.3 vs 29.1 (sunitinib)[8] HR: 0.92 (95% BI: 0.79-1.06)	Positive (sunitinib first choice)[20]	Primary care (as alternative to	Same value as sunitinib (primary care)[34]

		11.1 vs 2.8 (placebo; sub-group therapy-naive patients) HR: 0.40 (95% BI: 0.27-0.60); p<0.001			sunitinib or IFN-α + bevacizumab)	
Favourable/intermediate prognosis: secondary and later care						
Sorafenib	2007	5.5 vs 2.8 (placebo)[35] HR: 0.44 (95% BI: 0.35-0.55); p<0.001	17.8 vs 15.2 (placebo)[36] HR: 0.88 (95% BI: 0.74-1.04)*	Positive (limited added value)[19]	In secondary care after cytokine	Added value in comparison with placebo[37]
Everolimus	2009	4.9 vs 1.9 (placebo)[38,39] HR: 0.33 (95% BI: 0.25-0.43); P<0.001	14.8 vs 14.4 (placebo)[39] HR: 0.87 (95% BI: 0.65-1.15)*	Positive (in secondary care after sunitinib)[40] Positive (in tertiary care after sunitinib and sorafenib)[40]	In secondary care after TKI	Lower value in comparison with sunitinib/sorafenib (secondary care) Added value in comparison with BSC (tertiary care)[41]
Pazopanib	2010	9.2 vs 4.2 (placebo)[22] 7.2 vs 4.2 (placebo; subgroup of patients treated in the past) HR: 0.54 (95% BI: 0.35-0.84); p<0.001	22.9 vs 20.5 (placebo)[21] HR: 0.91 (95% BI: 0.71-1.16); p=0.22*	Positive[20]	In secondary care (after cytokine)	Same value as sunitinib or sorafenib (in secondary care)[34]
Nivolumab	2016	4.6 vs 4.4 (everolimus)[42 #] HR: 0.88 (95% BI: 0.75-1.03); p=0.11	25.0 vs 19.6 (everolimus)[42] HR: 0.73 (98.5% BI: 0.57-0.93); p=0.002	Positive (after one or more levels of treatment with a TKI)[43]	Not included	Not assessed
Cabozantinib	2016	7.4 vs 3.9 (everolimus)[44 #] HR: 0.44 (95% BI: 0.31-0.61)	21.4 vs 16.5 (everolimus)[44] HR: 0.66 (95% BI: 0.53-0.83); p<0.001	Positive (after one or more levels of treatment with a TKI)[45]	Not included	Not assessed
Lenvatinib in combination with everolimus	2016	12.8 vs 5.6 (everolimus)[46] ** HR: 0.45 (95% BI: 0.27-0.79); p=0.0029	25.5 vs 17.5 (everolimus)[46] HR: 0.74 (95% BI: 0.42-1.31); p=0.29	Positive[47]	Not included	Not assessed
Unfavourable prognosis						
Temsirolimus	2007	5.5 vs 3.1 (IFN-α)[48]	10.9 vs 7.3 (IFN-α)[48] HR: 0.73 (95% BI: 0.58-0.92; p=0.008)	Positive[24]	Primary care	Added value in comparison with IFN-α[49]

Abbreviations: PFS: progression-free survival; TKI: tyrosine kinase-inhibitor; IFN: interferon; BSC: best supportive care; cieBOM: committee for the assessment of oncology products; HR:

hazard ratio; BI: reliability interval

* Crossover allowed
# These studies also included patients with an unfavourable prognosis
** Based on independent assessment

Secondary and subsequent care
After previous treatment with a cytokine (interferon) or tyrosine kinase-inhibitors (TKIs, i.e. sunitinib, sorafenib or pazopanib), various follow-up treatments were included in the guidelines. These are everolimus (after TKI) and sorafenib and pazopanib after a cytokine. Nivolumab and cabozantinib (after TKI) after a cytokine recently became available for this line of treatment.

For sorafenib, after failure in response to previous treatment with immunotherapy, a 2.7-month statistically significant difference was found in median PFS in comparison with placebo treatment of patients with clear cell renal cell carcinoma and a favourable or intermediate prognosis; the median progression-free survival was 5.5 months for patients treated with sorafenib and 2.8 months for patients who received a placebo. Total survival increased from 15.2 months to 17.8 months, but this difference was not statistically significant (uncorrected for cross-over).[36] The BOM committee concluded that this was a 'limited added value' in comparison with best supportive care.[19]

In 2010 everolimus was assessed positively by the BOM committee and given a place as secondary or tertiary treatment after previous treatment with a TKI (i.e. after previously trying sunitinib in primary care, or sorafenib in secondary care after previous immunotherapy). The results of the study on which the advice of the BOM committee was based show a statistically significant increase in progression-free survival; median progression-free survival was 1.9 months for patients who received a placebo and 4.0 months for patients who were treated with everolimus.[38] No significant difference was found in total survival; 14.8 in comparison with 14.4 months (not taking cross-over into account).[39] These results were also based on patients with metastatic clear cell renal cell carcinoma, and a favourable or intermediate prognosis (according to the MSKCC criteria).

Pazopanib became available in 2011. Initially the clinical study included only patients with progression after treatment with immunotherapy. Later, patients were also included who had not previously been treated with systemic therapy. Progression-free survival was significantly longer for patients who were treated with pazopanib in comparison with patients who received a placebo (9.2 months vs. 4.2 months).[22] Total survival increased from 20.5 months to 22.9 months, but this difference was not statistically significant (cross-over was not taken into account).[21] These outcomes were confirmed in 2013 by a study in which pazopanib and sunitinib were compared directly with one another and which showed no difference in their effectiveness.[9] However, this study was carried out after the guidelines were published.

A more recent development is the availability of nivolumab and cabozantinib for treatment in secondary and tertiary care, after one or two courses of treatment with TKIs. Lenvatinib also became available as secondary care treatment. Clinical research found a survival advantage of about 5 months for nivolumab and cabozantinib in comparison with everolimus. Moreover, tolerance of treatment with nivolumab was better than treatment with everolimus. However, no statistically significant difference in PFS was found.[42] In July 2016 the BOM committee issued a positive assessment of nivolumab and cabozantinib in the setting studied.[43,45] For

lenvatinib no statistically significant difference was found in overall survival, but the difference in PFS was sufficient for the BOM committee to issue positive advice. The committee did make a marginal comment that the EMA had approved lenvatinib based on a relatively small phase 2 study, while nivolumab and cabozantinib had been the subject of large phase 3 studies. Furthermore, the relative value of the effectiveness of lenvatinib could not be established in relation to that of nivolumab or cabozantinib.[47]

Appendix 2: Study findings

Our study confirms the observation of the analysis of the guidelines in 2011 about the number of patients treated. Of the patients included in the register, 59% received primary care treatment (669/1131) in the period 2008-2015. This means that 41% of patients did not receive systemic therapy. There are signs that over the years the number of people who receive no treatment is dwindling. Of the patients who received primary care treatment, 239 patients (36%) also received secondary care treatment.

Primary care treatment
73% of primary care treatments for patients were in the form of sunitinib and 14% in the form of pazopanib. The third primary care possibility recommended in the guidelines, interferon-alfa in combination with bevacizumab, was only deployed for 1% of patients. Temsirolimus, recommended as primary care treatment for patients with an unfavourable prognosis, was given to 5% of patients. The remaining 8% of patients received a primary care treatment that is not recommended in the guidelines. A noticeable finding is that a large majority of the patients with a confirmed unfavourable prognosis received some other treatment instead of the treatment recommended in the guidelines, temsirolimus.

What does the study show?
In practice, whether treatment is indicated or whether no treatment can be given is determined based on general patient characteristics and tumour characteristics. The analysis shows that patients who did not receive treatment were often older than patients who did receive treatment. Although no firm conclusions on this relationship can be drawn based on the qualitative research results, the guidelines could include more explicit criteria for foregoing treatment.

The guidelines and the BOM committee advise sunitinib as product of first choice. Seen in this light, it is noticeable that pazopanib is given relatively often (14%) as primary care treatment. The use of pazopanib seems to have increased particularly since 2013. This may relate to research published after the guidelines were published, in which pazopanib and sunitinib were directly compared with one another in a randomised study and which showed that pazopanib was not inferior to sunitinib.[20,48] Clearly the guidelines are no longer entirely up to date, but changes have taken place in practice.

However, there is a lack of overarching indications for making an appropriate choice that takes patient characteristics and disease characteristics into account. In practice these characteristics probably are used for foregoing treatment, e.g. in the event of a poor state of health or a good state of health/low volume disease, as is apparent from the qualitative analysis. This could explain the number of untreated patients. However, variations in practice are inevitable in view of the lack of updated guidelines with unequivocal needs assessment.

A qualitative study using a questionnaire was sent to 38 clinical experts, 12 of whom responded (34%), in order to provide more insight into this. It revealed that most of the doctors who responded regard a patient's poor state of health, a good state of

health with 'low-volume disease', the presence of a severe co-morbidity and a short life expectancy on the patient's part as important, stand-alone reasons for not prescribing systemic therapy. However, firm conclusions cannot be drawn as the results are probably distorted due to lack of data.

What does the study show?
The data source used contained insufficient patient characteristics and disease characteristics to be able to determine whether the use of pharmaceutical products, or foregoing their use, was justified or not. In particular it was impossible to determine a prognosis based on the IMDC risk score from insufficient patients (unknown for 51% of the patients). According to the guidelines, the IMDC-risk score helps to determine the therapy choice.

The number of patients with a confirmed unfavourable prognosis who were treated with temsirolimus as recommended in the guidelines was low (9%). Instead, 72% of the patients with a confirmed unfavourable prognosis were treated with sunitinib. The qualitative analysis based on 12 respondents shows that most of the respondents cited their preference for sunitinib's oral delivery formulation above the intravenous delivery formulation of temsirolimus as the reason for prescribing sunitinib instead of temsirolimus. A small minority of the respondents cited the patient's preference for the oral delivery formulation as a reason. Also mentioned as a reason was that there is insufficient scientific evidence for temsirolimus in relation to these patients. In view of the choices made in practice, diagnosis needs to improve for these patients, whereby opting for either an oral or an intravenous delivery formulation is also a possibility. At the moment the guidelines strongly recommend temsirolimus, implying that most patients should receive this treatment. A weak recommendation, indicating that it applies only to some patients, would probably do more justice to the uncertainties about the effectiveness of temsirolimus in relation to that of sunitinib for patients with an unfavourable prognosis, and to the preferences of doctors and patients for a given delivery formulation. This should be weighed up by a guideline committee responsible for updating the guidelines.

Secondary and subsequent care
36% of patients in the registers who received primary care treatment also received secondary care treatment: everolimus for 44% of the patients, sorafenib for 18%, sunitinib for 13% and pazopanib for 10% (15% others). Just as we were unable to draw any firm conclusions regarding the use of pharmaceutical products in primary care, the same applies to the appropriate use of products in secondary care due to lack of data. Based on the qualitative analysis, for which doctors provided input via questionnaires, it seems that almost all doctors (90-100%) regard a patient's poor state of health, for whom best supportive care is a better option, and a patient's short life expectancy, as important individual reasons for not prescribing secondary care therapy. Most respondents cited the patient's refusal to undergo follow-up treatment and the presence of co-morbidities as important reasons for foregoing follow-up treatment. None of the respondents mentioned advanced age, insufficient scientific evidence, lack of experience or hurdles in respect of access to the available products as reasons for not offering follow-up treatment.

Various noteworthy observations can be made regarding the field of treatment for the products available in secondary and subsequent care. Two new treatments recently arrived on the market, nivolumab and cabozantinib. Unlike the products available to date, both of them have a demonstrated survival advantage. In view of this added value, both products are expected to have a massive impact on the

treatment of renal cell carcinoma. Moreover, the field of treatment may continue to change. For instance, nivolumab is currently already the subject of a phase 3 study as primary care treatment, and in combination with other products in secondary care. Based on feedback information, though no relevant improvement proposals can be made that could improve current treatment practice, they may well lead to general insights. We propose that the introduction of new products and the resulting new treatment algorithms requires that the guidelines are updated.

It is impossible to estimate correctly whether products were used appropriately in secondary care, or in primary care, due to the lack of data. For this reason, therefore, no conclusions can be drawn.

The two recent studies that examined treatment with nivolumab and cabozantinib as secondary care treatment also included patients with an unfavourable prognosis. This may extend the treatment arsenal for these patients. However, in these studies, primary care treatment comprised of TKI and not temsirolimus, so lack of clarity could still exist on the optimum treatment for patients with an unfavourable prognosis.

Clear cell and non-clear cell renal cell carcinoma
66% of the patients in the study had a confirmed clear cell renal cell carcinoma, 68% of whom received systemic therapy. 11% of the patients had another confirmed sub-type (58% of whom received systemic therapy). For 8% of the patients, the sub-type was not described in detail (52% of whom received systemic therapy) and for 14% there was no question of histologically confirmed, but only clinically confirmed, renal cell carcinoma (25% received systemic therapy).

As little evidence is available on the effectiveness of systemic therapy on patients with non-clear cell renal cell carcinoma, the guidelines state that no standard treatment can be stipulated for these patients. Preferably these patients should be treated within a research context, or possibly as indicated for clear cell renal cell carcinoma. The guidelines do suggest that in the case of metastatic disease, histological needle biopts should be taken to determine the histological sub-type of tumour to prove the usefulness of systemic therapy. In this sense, noticeable is that systemic therapy was given to a quarter or the patients with renal cell carcinoma that had not been histologically confirmed.

The study does not clearly state the reasons for not carrying out histological research. The guidelines state that the histological characteristics of the tumour should be determined before starting systemic therapy. The factors to be considered before starting or foregoing treatment for non-clear cell renal cell carcinoma are less explicit. For this reason it is impossible to determine whether systemic therapy was used appropriately for these patients, so no clear pointers for improvement can be given.

Use of surrogate outcome measures in clinical trials

What does the study show?
No survival advantage was demonstrated in randomized studies for any of the products used in secondary care before nivolumab and cabozantinib came onto the market. This may (in part) be because the studies permitted crossover. Positive treatment advice was therefore based on progression-free survival (PFS) outcomes.

PFS is defined as time to progression, or to death should it occur earlier, irrespective of the cause. Often cited advantages of PFS above overall survival (OS) as endpoint in clinical trials are that fewer trials are needed, a shorter follow-up is needed and that these outcome measures are not 'watered down' by different therapies that may be given in later treatment, sometimes as a consequence of crossover, which could result in ascribing any difference, or lack of a difference, to one or more follow-up treatments.

In cases of renal cell carcinoma, there are signs that a longer PFS is correlated with a longer OS.[10] From a methodological perspective, however, no effect on survival was demonstrated, noticeably in the later stages of treatment of renal cell carcinoma: there are fewer follow-up treatments, so there is less of a chance of the effect being 'watered-down' due to cross-over. Furthermore, an unreasonably long follow-up is not needed at this stage of treatment. As a result, evidence regarding products with demonstrated effects on PFS, but not on overall survival, is less convincing. Moreover, in a number of cases the differences in median PFS were near the lower limit for minimum differences as quoted by the BOM committee.[11] Generic cut-off measures are currently used for PFS outcomes in order to weigh up whether there is any clinically relevant effect for the patient. The question is whether PFS effects are equally clinically relevant for all types of tumour.

In view of the significant value that PFS has on interpreting clinical research, evidence of the clinical relevance of PFS (e.g. on OS or quality of life) should preferably be obtained more structurally. However, obtaining more insight into this would require far-reaching studies that are beyond the scope of the present Room for Improvement Report.

Appendix 3: Accountability

Points of departure

The *Zorginstituut* designed a systematic working method for the *Zinnige Zorg* Programme for examining the use that is made of care in the insured package. The key is to identify and reduce ineffective and/or unnecessary care, in order to improve the quality of care for patients, increase health gains and avoid unnecessary costs. We carry out a systematic assessment for a field of disorders as defined in the ICD-10 classification system. A systematic assessment is carried out based on a number of points of departure:

Central role for patients
When assessing care, we give a central role to patients and the care pathway they follow. The underlying question is always how much does a patient benefit from the care given? Is he receiving care that is appropriate to his situation, or is he perhaps receiving too little care (under-treatment) or too much care (over-treatment)?

Shared decision-making
Care must be in keeping with patients' personal circumstances. In addition to the diagnosis, patient-related matters play a role in the choice of treatment, such as a patient's expectations, his professional situation, impact on social functioning, pain perception, motivation, etc. For some diagnoses it is clear which treatment options should be deployed. Often, however, various treatment options exist, each with their pros and cons, and opting for a given treatment will depend more on the preferences of the patient and his carer. Shared decision-making is a way of arriving at an optimum treatment pathway together with a patient. Various instruments exist that can support the shared decision-making of doctors and patients effectively – such as decision aids, option grids and patients' versions of guidelines – and which increase the quality of the decision-making process.

Stepped care
We assume that courses of treatment start based on the stepped care principle. According to this principle, care is offered based on a step-by-step plan: the least burdensome effective treatment is used first, and only when this gives insufficient results are more complex or more invasive interventions offered. Stepped care is a general point of departure, not a mandatory requirement. The 'start moment' is not necessarily step 1, as steps may be skipped, according to the symptoms with which a patient presents.

Parties in health care are involved throughout the entire process
The *Zorginstituut* wants to realise active agreement with the parties in health care. This will benefit the quality of the analyses and the basis of support for improvement measures. We involve the parties who bear responsibility in all phases of the systematic assessment.
The parties are invited to attend various consultations via umbrella arrangements. They are also given an opportunity to participate in supervising the research of external research bureaus. Lastly, we ask parties for comments on draft versions of reports.

Phases of systematic assessment

In order to promote good care, we carry out a systematic assessment according to a

quality circle, or improvement circle, as illustrated in the following figure. This circle is comprised of four sequential phases:

1. Screening phase
2. In-Depth Analysis Phase
3. Implementation phase
4. Evaluation phase

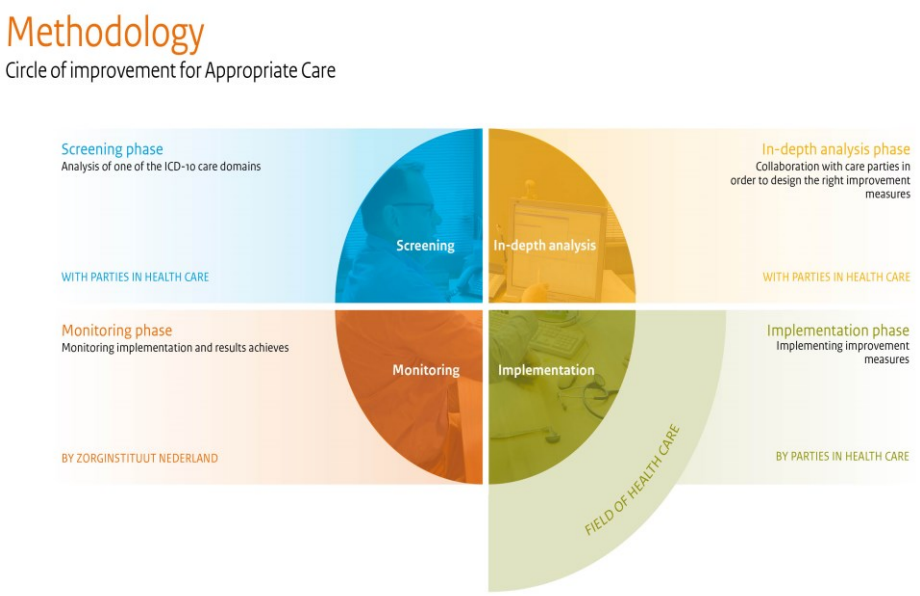

Figure 1: Zinnige Zorg's circle of improvement

Zinnige Zorg's circle of improvement starts with a screening phase, in which we analyse how care is currently being given. Based on this, a number of topics are chosen for in-depth analysis. In the second phase, the in-depth phase, we determine the potential for improvement, per topic. In the third phase (implementation) it is mainly up to the parties in health care to implement the agreed improvement measures. Lastly, in the evaluation phase we examine the extent to which the goals set have been achieved and whether a new circle of improvement should start, possibly using different instruments for improvement. Where necessary, if insufficient results are realised, the *Zorginstituut* can make use of its statutory instruments (e.g., clarification, advising on inclusion in – or exclusion from – the package, power to overrule within the framework of the Multi-Year Agenda). The Multi-Year Agenda offers an overview of top-priority fields of care for which quality standards, measuring instruments and information standards (hereafter: quality products) are being developed. If the *Zorginstituut* sees that the parties involved are in default, after the periods specified in the Multi-Year Agenda have lapsed, the *Zorginstituut* will take over the initiative or the coordination of developing a quality product. This is referred to as the power to overrule. Below we describe the four phases of the circle of improvement in more detail.

<u>Screening phase</u>

The objective of the screening phase is to select a number of topics for in-depth analysis with a possible potential for improving the quality and effectiveness of care by using care more appropriately. These topics are recorded in a report that is sent,

together with the underlying analysis, to the parties in health care and to the Minister of Health Welfare and Sport.

Figure 2 shows how we establish in-depth topics by consulting various sources in a systematic analysis. Sources include the quality standards (guidelines, care standards and care modules), scientific literature, claim data and other data, and the parties in health care. This involves not only collecting and analysing all the detailed information, but also searching for signals from daily practice in order to obtain a succinct picture of the care provided in the current situation. We look at the care pathway that a patient follows from the perspective of the *Zorginstituut*, with the elements that the *Zorginstituut* defines as good and appropriate care (see explanation below).

Figure 2: From sources to in-depth topics in the screening phase

The choice of in-depth topics is based on the systematic analysis (based on the elements of good and appropriate care), the size of the topic (number of patients, burden of disease, budget impact), possible improvements and what the parties in health care feel is important.

<u>In-Depth Analysis Phase</u>
The screening phase is followed by the in-depth phase. The objective of this phase is to make the method for achieving potential improvements in the selected topics as concrete as possible.

Per topic, based once again on the elements of good and appropriate care, we carry out an in-depth study and we supply any missing knowledge in the form of extra data-analyses, scientific reviews, studies of daily practice and/or literature studies.

The final results are recorded in a so-called Room for Improvement Report. This states which improvements in care and in health the *Zorginstituut* feels are possible, in respect of both content and amount, and provides an estimate of the total sum of

costs involved (budget impact). We try to ensure that agreements with the parties on improvement measures are as concrete as possible. The Room for Improvement Report is also sent to the parties in health care and to the Minister of VWS.

Implementation phase
The implementation phase is primarily a task for the parties in health care: patients, care professionals, institutions and health insurers. It takes place based on agreements made in the in-depth phase. In the implementation phase the *Zorginstituut* can play a supportive and facilitative role, for instance, by organising meetings, providing data and feedback, and by carrying out additional research. In order to guarantee compliance with agreements, both in respect of content and time, the *Zorginstituut* can place action points from the Room for Improvement Report that relate to quality standards and measuring instruments on the Multi-Year Agenda.
Periodically, the *Zorginstituut* reports on progress booked to the accountable parties and to the Minister of VWS.

Evaluation phase
During the evaluation phase, the *Zorginstituut* examines, together with the parties involved, whether the results mentioned in the Improvement Report have been achieved. Based on this, we determine whether a new circle of improvement should start, possibly using different instruments for improvement. During this phase we also examine whether all necessary information is structurally available.

Elements of good and appropriate care

We carry out an analysis of care in both the screening phase and the in-depth phase. To do this, we use the "elements of good and appropriate care". Together, these give an idea of what the *Zorginstituut* regards as good and appropriate care. They are also in keeping with our quality and package management tasks. The following analysis scheme is used:

1. Knowledge about good care
A description of what we know about the availability of national and international quality standards (such as guidelines), measuring instruments (questionnaires and indicators) and information standards. We see whether these can be found in, e.g., the *Zorginstituut*'s Register. Their entry in the Register shows that they fulfil the procedural criteria of the Assessment Framework[50]. We try to ensure that everything that can be found is included in *Zorginzicht.nl*. Does patients' information exist, such as a patients' version of guidelines, or information about diagnosis and treatment on the website of a patients' association or on *KiesBeter* or *thuisarts.nl*? Are there decision aids, option grids or outcome indicators which are relevant to patients, such as measures of quality of life, PROMs[51] and PREMs? On which websites (public database and public information) can they be found?

In addition to procedural matters, we also look at the content of standards and guidelines: what recommendations are made that are relevant to our topic and is there sufficient scientific evidence for (recommendations in the) guidelines? Lastly, we look at concordance between guidelines for primary and secondary care.

2. Application in practice
We use various sources (such as claim data, publications, formal and informal consultations) to look at how care takes place in practice (including concordance between primary and secondary care) and what the experts think about it.
We compare this to what we found in practice on recommendations in quality

standards.

3. Care outcomes
Do patients benefit from the treatment? Is information available about quality of care and care outcomes, and can it be found by care providers, patients and citizens? For instance, is there a complication register, statistics on post-surgery mortality, experiences of patients with outcomes or experiences (measured with PROMs and PREMs)? And where can we find this information, e.g. on websites such as ZorginZicht.nl (public database), Kiesbeter.nl or Zorgkaartnederland.nl?

4. Effectiveness
Is the care effective? If we feel that the scientific evidence in the guidelines (as assessed under element 1, Knowledge about good care) is of sufficient quality, we use the recommendations from the guidelines as point of departure for good care. If the guidelines are of insufficient quality, or are dated, then we can let the parties know that the guidelines need to be updated. A formal assessment based on the criteria established by the *Zorginstituut*, including a systematic review based on the GRADE system[52], only takes place if this is dictated by bottlenecks and there are no recommendations in the guidelines or there seems to be insufficient scientific evidence.

An important part of an assessment of effectiveness are the primary questions, as described in the so-called *PICOT*: Patient – Intervention – Comparator - Outcome - Time. For which group of patients is the care intended and is that the group for which research is available? Which treatment or care is being offered and has this care been studied? With which control treatment (regular care, standard therapy) was that care compared and what is the added value of the recommended care? And which outcomes relevant to patients were examined in order to determine whether the care was effective and for how long?

5. Cost-effectiveness[53]
Cost-effectiveness shows whether the (added) costs of treatment are reasonably in proportion with the added effectiveness. We look at whether the guidelines have anything to say about cost-effectiveness, we look at the (scientific) literature, and, if necessary, we carry out our own cost-effectiveness study.

86 Necessity[54]
This is where we examine whether a form of care should be part of the basic health insurance or whether it involves costs that people could pay for themselves. Weighing this up involves two different aspects: severity of the disease (burden of disease) and the societal necessity of actually insuring the treatment concerned. With burden of disease the emphasis is on medical necessity, while with 'necessity to insure' the emphasis is on whether insurance is actually necessary.

6. Feasibility[54]
Care that is not feasible cannot be supplied. The feasibility element indicates whether the preconditions have been fulfilled and how sustainable including an intervention in the basic package is. Relevant to this are, e.g., basis (of support, how care is organised, indications and administration), funding, jurisdiction and ethics. This also involves, for instance, whether a funding formula (intervention description) exists for an intervention that should be included in the basic package.

7. Consistency in quality circles
This is where we look at whether quality circles are used that focus on improving care, who uses them, and the interdependence that exists between quality circles.

Difference in the screening phase and the in-depth phase

The spectacles with which we examine care are, in principle, the same for all phases of the assessment, based on the eight elements mentioned above. Sometimes the nature and intensity of the systematic analysis differs in the screening phase and in the in-depth phase. The terminology itself shows that the first involves a global inventory, at the level of a disorder (ICD-10), and that the selected topics are examined in more detail during the in-depth phase. This phase often also combines various data sources.

Parties involved

The following parties are involved in the in-depth phase:

- Dutch Patients' Federation
- Dutch Federation of Cancer Patients Organisations (NFK)
- Netherlands Association of Internal Medicine (NIV)
- Netherlands Association for Medical Oncology (NVMO)
- Netherlands Association for Urology (NVU)
- Federation of Medical Specialists (FMS)
- Dutch Nurses & Care Givers (V&VN) Oncology
- Association of Dutch Healthcare Insurers (ZN)
- Dutch Association of Hospitals (NVZ)
- Top Clinical Hospitals Association (STZ)
- Dutch Federation of University Medical Centres (NFU)

Use of data in the analysis

The *Zinnige Zorg* programme makes regular use of quantitative data. Using these data meticulously is particularly important for the quality of the analysis, acceptance of the findings and to protect privacy. The *Zorginstituut* explicitly recognises the importance of this and takes all necessary measures for processing the available data meticulously. The following is an explanation of key elements of how we process quantitative data.

Based on care-related questions, the *Zorginstituut* carries out data research into how care from the basic package is used in daily practice. This may involve related fields, such as prevention, self-care and other forms of care not included in the basic package, based on the point of departure that we examine the care path integrally. To do this we collect information from many sources: from discussions with interested parties to scientific publications, from RIVM statistics to claim data.

These are in part quantitative data, often claim data such as those of the Declaration Information System (DIS), Care Interventions and Claims (ZPD), and the Medicines and Medical Device Information Project (GIP). When using data, the *Zorginstituut* has various measures for ensuring that security and privacy are guaranteed optimally. For example, the *Zorginstituut* uses pseudonymised personal data over several years and from various sources, which can be combined to answer a specific problem.

We use claim data to get an idea of daily practice in health care. Claim data reflect registration practices and not necessarily the care actually provided. Nevertheless, these data do form an important source of information, sometimes the only one, and can provide valuable signals relating to care quality. An in-depth exploration of the possibility of using other data sources is currently taking place, in collaboration

with VWS and other parties in health care.

Safeguarding privacy is of paramount importance. Personal data used are therefore pseudonymised and cannot be traced back to individuals. Nevertheless, they are regarded as sensitive personal data, so we are very meticulous in carrying out analyses and always comply with current legislation. The data are only used for research goals/analyses defined in advance, they are not made available/used for other objectives and they are not disseminated. The results of the analyses are published at a level that precludes any tracing back to the level of individual persons, patients, insurers or care providers.

Appendix 4: Parties' responses

Dutch Federation of Cancer Patients' Organisations and Living with cancer of the bladder or kidney

The Dutch Federation of Cancer Patients' Organisations and Living with Cancer of the Bladder or Kidney largely agree with the improvement points. The organisations propose setting up centres of expertise for the treatment of patients with renal cell cancer as a fourth improvement point in order to minimise variations in practice, maximise harmonisation of the diagnostics and treatment with recent developments and guarantee compliance with the SONCOS-norms. They refer to the vision document of those organisations. Lastly, they drew up a number of substantive explanatory questions about the report.

Zorginstituut Nederland's response
We are pleased that the NFK confirms the importance of the improvement points in improving care for patients with renal cell cancer. We have included your suggestion regarding an additional improvement point in the report. In general, the analysis carried out does not supply us with unequivocal answers to substantive questions. For instance, using the available data it is not possible to determine all possible reasons for not giving systemic therapy, such as forgoing treatment at the request of a patient. This is due to the retrospective nature of the study, whereby the data depend on the quality of the patient files that served as source. Therefore we can neither preclude nor confirm whether care or under-treatment was appropriate and according to guidelines. We do feel that improved diagnosis in the guidelines, and improved registration (at source), based on our improvement points, can contribute to shedding light on the degree of appropriateness in practice. We can agree to your suggestion to include in the guidelines criteria for foregoing treatment and appreciate your proposed efforts in implementing this.

We understand your desire for centres of expertise for this care and appreciate the potential for quality of care as a result of concentration. However, the relationship between the concentration of care and appropriate care was not part of our analysis. For this reason at the moment we cannot conclude that inappropriate care was supplied as a result of dilution of the supply of care. The *Zorginstituut* sees an added value in also deploying implementation to organise the care of renal cancer appropriately. The parties have already started several good initiatives in this respect. We will as far as possible ensure that implementation is in line with the initiatives in the field of care and with the respective accountability of all parties.

Dutch Association for Medical Oncology (NVMO)/Dutch Association of Internists (NIV)

The NVMO and the NIV support the three improvement suggestions. The parties do comment that registration at source must not involve an unnecessary administrative burden and should preferably be incorporated into current initiatives. The parties would like to continue the dialogue with the *Zorginstituut* regarding implementation. Lastly, attention is requested for a number of substantive matters relating to the survival gains with the products sunitinib, nivolumab and cabozantinib.

Zorginstituut Nederland's response
We appreciate the support of the NIV and the NVMO for the improvement suggestions and the proposed efforts in implementing them. Harmonisation with the

relevant parties, including the NIV and the NVMO, with regard to implementation is very important and we will continue the dialogue.

We hope that registering at source will promote the quality and efficiency of the registration process. We understand the viewpoint that this must not involve an increased administrative burden for the professionals and will consider this during the implementation phase.

Lastly, we agree that recent additions have indeed appeared on the market for which survival gains have been demonstrated. An alternative statistical analysis also demonstrated a survival advantage for sunitinib. It was never our intention to argue that there are no products with demonstrated survival advantages. Nevertheless, we do see that the demonstrated PFS gains of some of the treatments cannot unequivocally be translated into clinical relevance. We hope that evidence on PFS can improve to promote positioning of the various products.

Dutch Association for Urology (NVU)

The NVU supports the arguments and the improvement suggestions regarding the need to update the guidelines and to create a national multidisciplinary registry of renal tumours. The NVU will start updating the guidelines in the near future.

Zorginstituut Nederland's response
Revising the guidelines is a good development. In this respect we also want to draw attention to specific patient characteristics and disease characteristics as a basis for choosing a treatment or deciding to forego treatment. We will follow the guideline development closely during the course of implementing out improvement suggestions.

Dutch Association of Hospitals (NVZ)

The NVZ is aware of the importance of collecting relevant patient data at source to the potential for improvement and feels that this improvement can be put to broad use, but wonders how this improvement will be revealed in the analyses. For the other improvement suggestions, the NVZ advises seeking sufficient support from the scientific association.

Zorginstituut Nederland's response
We want to thank the NVZ for their analysis of our Room for Improvement Report and we are pleased with their response which we interpret as support for our improvement suggestions. First and foremost during implementation we will seek harmonisation with the relevant parties, including the scientific associations and the NVZ.

Regarding registration at source: our analysis provides strong evidence that many fields that are relevant to the choice of treatment are not completed in the patient registry. Due to the retrospective nature of the study, its completion depended on the quality of the patient files, which served as source. It follows that in some cases the care provider felt no need to register data that are, however, important for feedback information. With registration at source, a care provider collects data prospectively, whereby use is made of a minimum dataset so that data can be used for several purposes. Registration has to take place only once, which will limit the administrative burden imposed.

Federation of University Medical Centres in the Netherlands (NFU)

The NFU suggests that the updated guidelines could be made more dynamic than a conventional revision, which would facilitate a quicker response in future to changes in the treatment landscape. The NFU suggests seeking to work together with an organisation such as the IKNL for effective registration at source. The NFU would like to see studies into treatment sequences. This potential for improvement can also apply to other types of tumour. The NFU suggests updating the report to reflect the most recent developments.

Zorginstituut Nederland's response
We would like to thank the NFU for their constructive suggestions for implementing the improvement suggestions effectively. We would like to include these in our implementation and want to ask the NFU to remain involved in that process. Our report did not discuss surgical treatments because its scope was restricted to pharmaceutical products. It is true that pharmaceutical developments surrounding the treatment of renal cell carcinoma are constantly changing. We feel that our improvement suggestions are relevant despite recent developments. At the moment we feel that the time is not ripe to update our report with the combination treatment ipilimumab with nivolumab, because these treatment results are only available in the form of an abstract and have not been published in peer-reviewed journals. This treatment has not yet been granted marketing authorisation.