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1. Inventory of Dutch research efforts in this field over the past five years (2008-2013) by ISI web of knowledge

Summary

Top 10 most cited clinical research initiated by Dutch groups 2008-2013 (Table 2).

2. Visibility Dutch research judged by international experts (see also appendix) *To be filled in after completion of international advisors.*

| Areas with good visibility | Areas with less visibility |
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3. Research needs

Facts and Figures (2013)¹

- Each year, 11,000 people will receive the diagnosis lung cancer; It is after prostate cancer the most prevalent cancer in males. In 2010, 6,992 males and 4,443 females have been diagnosed with lung cancer. In the past ten years there has been a strong increased in the number of females diagnosed with lung cancer: from 2479 to 4443 an increase of 79%
- Lung cancer is the most deadly type of cancer. In 2011, there were 10,539 deaths in The Netherlands due to lung cancer: 6585 males, 3954 females. Five years after the diagnosis the survival was 10 to 15%.

Euro costs²

- The costs of lung cancer can be attributed to diagnosis and treatment in the hospital.
- The total costs due to lung cancer was in 2007 a total of 267,2 million Euro, 7.8% of the total costs for healthcare of people with cancer in The Netherlands and 0.35% of the total costs of healthcare in The Netherlands.

Unmet needs (extracted from: LAN verkenning 2010³)

More focus is needed

- There should be more awareness of what other centers are doing
- More nationwide networks on different levels are needed: e.g. networks on biobanking and basic science
- Proper funding for prevention (studies).

References

¹ Feiten en cijfers 2013 Chronische Longziekten, LAN 2013

² Nederlandse Longstichting Longziekten Feiten en Cijfers, Editie 2008

³ Feiten en cijfers Chronische Longziekten, LAN 2010

4. Summary of SWOT analysis

Results of the web-based SWOT

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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><i>Strengths</i></p> <ol style="list-style-type: none"> 1. Phenotyping/PET imaging 2. Diagnosis/monitoring /screening 3. Stereotactic radiotherapy 4. Coordination phase II +III studies | <p><i>Weaknesses</i></p> <ol style="list-style-type: none"> 1. Environment and lifestyle 2. National standardization of management protocols 3. Insight in ongoing basic research 4. Biobanking / datamanagement 5. Non-medical therapy (except radiotherapy) implementation in clinical setting Hardly any research in surgery |
| <p><i>Opportunities</i></p> <ol style="list-style-type: none"> 1. Nationwide cooperation 2. Prevention and screening 3. Research on rare mutations 4. Immunotherapy 5. Radiotherapy (proton therapy) 6. New biologicals 7. Organise Dutch symposia | <p><i>Threats</i></p> <ol style="list-style-type: none"> 1. Uncoordinated research 2. Reduced funding for non-commercial studies 3. Lack of good preclinical model of lung cancer |

*Relevance of research judged by international experts (order of importance):
See Table Relevance of research judged by international experts in appendix*

| | Mean |
|----------------------------------|-------------|
| Phenotyping and Severity | 1.00 |
| Biological mechanisms | 1.33 |
| Environment and lifestyle | 2.00 |
| Development and ageing | 2.00 |
| Prevention | 3.66 |
| Diagnosis monitoring | 3.33 |
| Therapy medical | 4.50 |
| Therapy non-medical | 3.66 |
| Biobanking | 2.66 |
| Data management clinical studies | 4.00 |
| Implementation and care | 4.00 |

5. Description of the interface of lung cancer with other Roadmap areas

Cachexia research has an interface with COPD, as well as participation in population screening for cancer. Exchange of knowledge in basic research on immunotherapy for interstitial diseases may be worthwhile.

6. Priorities for Dutch research in the area for 2014-2019

- Immunotherapy for lung cancer and mesothelioma
- How to best perform screening and prevention of lung cancer
- Ongoing development of radiotherapy
- Prediction of toxicity of radiotherapy
- Treatment of mesothelioma
- Identification of resistance mechanisms
- Approach of oncology in the elderly.
- Retreatment of loco-regional relapses (oa RETHO)
- Oligometastases
- Individualised medicine based on Decision Support Systems
- patient participation based on Decision Aids

7. What is needed to let the research priorities listed be successful?

Nationwide cooperation is important in all fields and focus is required. There is substantial cooperation, but it has to be better coordinated, for instance for the diagnostic work. A decision support system is needed. Also, cooperation between radiotherapy centers is crucial for chemoradiation. There should be more research be performed in surgery.

8. What do patients want?

They want cure and hope. They would like to be involved in management decisions and understand the process, the why and how. Some patients (especially the elderly) give the priority to quality of life. There are connections with relatives of mesothelioma patients.

Table 1 . Top 10 most cited basic research initiated by a Dutch group:

| Theme | Article | Citations | |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| MicroRNA | Duursma, A. M.; Kedde, M.; Schrier, M; et al. miR-148 targets human DNMT3b protein coding region. Rna-a Publication of the Rna Society. 2008; 14; 872-877 | 202 | 50.5 |
| Chemopreventive diet | de Kok, T.M.; van Breda, S.G.; Manson, M.M. Mechanisms of combined action of different chemopreventive dietary compounds. European Journal of Nutrition. 2008; 47; 51-59 | 86 | 21.5 |
| Air pollution | Beelen, R.; Hoek, G.; Pebesma, Edzer; et al. Mapping of background air pollution at a fine spatial scale across the European Union. Science of the Total Environment. 2009; 407; 1852-1867 | 58 | 19.3 |
| Metastasis Gene expression | Horlings, H.M.; van Laar, R.K.; Kerst, J.M.; et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. Journal of Clinical Oncology . 2008; 26; 4435-4441 | 76 | 19.0 |
| Radiotherapy | Aerts, H. J.W.L.; van Baardwijk, A. A. W.; Petit, S. F.; et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. Radiotherapy and Oncology. 2009; 91: 386-392 | 52 | 17.3 |
| Pathway | Bleeker, F. E.; Felicioni, L.; Buttitta, F.; et al. AKT1(E17K) in human solid tumours. Oncogene. 2008; 27: 5648-5650 | 57 | 14.3 |
| Pathway | Marchetti, S.; de Vries, N.A.; Buckle, T; et al. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1(-/-)/Mdr1a/1b(-/-) (triple-knockout) and wild-type mice. Molecular Cancer Therapeutics. 2008 ; 7 : 2280-2287 | 66 | 13.2 |
| VOCS | Van Berkel, J.J.B.N.; Dalling, J. W.; Moeller, G. M.; et al. Development of accurate classification method based on the analysis of volatile organic compounds from human exhaled air. Journal of Chromatography B-analytical Technologies in the Biomedical and Life Sciences. 2008; 861: 101-107 | 50 | 12.5 |
| Epidemiology | van der Knaap, R.; Siemes, C.; Coebergh, J.W. W.; et al. Renin-angiotensin system inhibitors, angiotensin I-converting enzyme gene insertion/deletion polymorphism, and cancer. Cancer. 2008; 112: 748-757 | 47 | 11.8 |
| | Giovannetti, Elisa; Lemos, Clara; Tekle, Christina; et al. Molecular mechanisms underlying the | 55 | 11.0 |

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|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| | synergistic interaction of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, with the multitargeted antifolate pemetrexed in non-small-cell lung cancer cells. <i>Molecular Pharmacology</i> . 2008; 73: 1290-1300 | | |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|

Table 2. Top 10 most cited clinical research initiated by a Dutch group:

| Theme | Article | Citations | |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Paraneoplastic syndroom | Titulaer, M. J.; Soffiatti, R.; Dalmau, J.; et al. : Screening for tumours in paraneoplastic syndromes: report of an EFNS Task Force. <i>European Journal of Neurology</i> . 2011; 18: 19-E3 | 56 | 56.0 |
| Screening | van Klaveren, R. J.; Oudkerk, M.; Prokop, M.; et al. Management of Lung Nodules Detected by Volume CT Scanning. <i>New England Journal of Medicine</i> . 2009; 361: 2221-2229 | 163 | 54.3 |
| Stereotactic radiotherapy | Lagerwaard, F. J.; Haasbeek, C. J. A.; Smit, E.F.; et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. <i>International Journal of Radiation Oncology Biology Physics</i> . 2008; 70: 685-692 | 178 | 44.5 |
| Air pollution | Beelen, R.; Hoek, G.; van den Brandt, P.A.; et al. Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). <i>Environmental Health Perspectiv</i> . 2008; 116: 196-202 | 127 | 31.8 |
| PET | Oyen, W. J. G.; Hoekstra, C. J.; et al. The Netherlands protocol for standardisation and quantification of FDG whole body PET studies in multi-centre trials. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2008; 35: 2320-2333 | 122 | 30.5 |
| Radiotherapy | Palma, D.; Visser, O.; Lagerwaard, F. J.; et al. Impact of Introducing Stereotactic Lung Radiotherapy for Elderly Patients With Stage I Non-Small-Cell Lung Cancer: A Population-Based Time-Trend Analysis. <i>Journal of Clinical Oncology</i> . 2010; 28: 5153-5159 | 60 | 30.0 |
| E-nose | Dragonieri, S.; Annema, J. T.; Schot, R.; et al. An electronic nose in the discrimination of patients with non-small cell lung cancer and COPD. <i>Lung Cancer</i> . 2009; 64: 166-170 | 84 | 28.0 |
| Radiotherapy | van Baardwijk, A.; Wanders, Stofferinus; Boersma, L.; et al. Mature Results of an Individualized Radiation Dose Prescription Study Based on Normal Tissue Constraints in Stages I to III Non-Small-Cell lung cancer. <i>Journal of Clinical Oncology</i> . 2010; 28: 1380-1386 | 50 | 25.0 |
| Radiotherapy | Hurkmans, C. W.; Cuijpers, J. P.; Lagerwaard, F.J.; et al. Recommendations for implementing stereotactic radiotherapy in peripheral stage IA non-small cell lung cancer: report from the Quality Assurance Working Party of the randomised phase III ROSEL study. <i>Radiation Oncology</i> . 2009; 4: 1186-1748 | 75 | 25.0 |

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|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|
| Radiotherapy | Sonke, J.J; Lebesque, J.; Van Herk, M. Variability of four-dimensional computed tomography patient models. International Journal of Radiation Oncology Biology Physics. 2008; 70: 590-598 | 96 | 24.0 |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|

Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines):

| Theme | Article | Citations | |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Genomics | Thorgeirsson, TE; Geller, F; Sulem, P; et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008; 452: 638-U9 | 606 | 121.2 |
| Genomics | Hung, RJ; Mckay, JD; Gaborieau, V; et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008; 452: 633-637 | 529 | 105.8 |
| Pathway | Weiss, J; Sos, ML; Seidel, D; et al. Frequent and Focal FGFR1 Amplification Associates with Therapeutically Tractable FGFR1 Dependency in Squamous Cell Lung Cancer. Science Translational Medicine. 2010;2: 62ra93 | 105 | 35.0 |
| Pathway | Jackman, DM; Miller, VA ; Cioffredi, LA ; et al. Impact of Epidermal Growth Factor Receptor and KRAS Mutations on Clinical Outcomes in Previously Untreated Non-Small Cell Lung Cancer Patients: Results of an Online Tumor Registry of Clinical Trials. Clinical Cancer Research. 2009; 15:5267-5273 | 138 | 34.5 |
| Proteomics | Piersma, S.R.; Fiedler, Ulrike; Span, Simone; et al. Workflow Comparison for Label-Free, Quantitative Secretome Proteomics for Cancer Biomarker Discovery: Method Evaluation, Differential Analysis, and Verification in Serum. Journal of Proteome Research. 2010; 9: 1913-1922. | 52 | 26.0 |
| Metastasis Pathways | Smit, M.A.; Geiger, T.R.; Song, Ji-Ying; et al. A Twist-Snail Axis Critical for TrkB-Induced Epithelial-Mesenchymal Transition-Like Transformation, Anoikis Resistance, and Metastasis. Molecular and Cellular Biology . 2009; 29; 3722-3737 | 73 | 24.3 |
| Genomics | Tibaldi, C; Giovannetti, E; Vasile, E; et al. Correlation of CDA, ERCC1, and XPD polymorphisms with response and survival in gemcitabine/cisplatin - Treated advanced non-small cell lung cancer patients. Clinical Cancer Research. 2008; 14: 1797-1803 | 100 | 20.0 |
| Prognostic profiling | Roepman, Paul; Jassem, Jacek; Smit, Egbert F.; et al. An Immune Response Enriched 72-Gene Prognostic Profile for Early-Stage Non-Small-Cell Lung Cancer. Clinical Cancer Research. 2009; 15: 284-290 | 50 | 16.7 |
| Pharmacokinetics | Marchetti, S.; de Vries, N. A.; Buckle, T.; et al. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on | 66 | 16.5 |

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|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|
| | erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1(-/-)/Mdr1a/1b(-/-) (triple-knockout) and wild-type mice. : Molecular Cancer Therapeutics. 2008; 7; 2280-2287 | | |
| Pathway | Giovannetti, Elisa; Lemos, Clara; Tekle, Christina; et al. Molecular mechanisms underlying the synergistic interaction of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, with the multitargeted antifolate pemetrexed in non-small-cell lung cancer cells. Molecular Pharmacology. 2008; 73: 1290-1300 | 55 | 13.8 |

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines):

| Theme | Article | Citations | |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------|
| | | Total | Mean/yr |
| Treatment | Scagliotti, GV; Parikh, P; von Pawel, J; et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. <i>Journal of Clinical Oncology</i> .2008; 26: 3543-3551 | 919 | 183.8 |
| PET | Boellaard, Ronald; O'Doherty, Mike J.; Weber, Wolfgang A.; et al. FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. <i>European Journal of Nuclear Medicine and Molecular Imaging</i> . 2010; 37: 181-200 | 210 | 105.0 |
| EBUS | Annema, Jouke T.; van Meerbeeck, Jan P.; Rintoul, Robert C.; et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer A Randomized Trial. <i>JAMA-Journal of the American Medical Association</i> . 2010; 304: 2245-2252 | 99 | 49.5 |
| Treatment | Herbst, RS; Sun, Y; Eberhardt, WEE; et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. <i>Lancet Oncology</i> . 2010; 11: 619-626 | 138 | 46.0 |
| Survivin | Giaccone, Giuseppe; Zatloukal, Petr; Roubec, Jaromir; et al. Multicenter Phase II Trial of YM155, a Small-Molecule Suppressor of Survivin, in Patients With Advanced, Refractory, Non-Small-Cell Lung Cancer. <i>Journal of Clinical Oncology</i> . 2009; 27: 4481-4486 | 73 | 24.3 |
| Radiotherapy | Sonke, Jan-Jakob; Rossi, Maddalena; Wolthaus, Jochem; et al. Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam ct guidance. <i>International Journal of Radiation Oncology Biology Physics</i> . 2009; 74: 567-574 | 72 | 24.0 |
| Radiotherapy | De Ruysscher, Dirk; Faivre-Finn, Corinne; Nestle, Ursula; et al. European Organisation for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer. <i>Journal of Clinical Oncology</i> . 2010; 28: 5301-5310 | 46 | 23.0 |
| Prophylactic cranial irradiation | Slotman, Berend J.; Mauer, Murielle E.; Bottomley, Andrew; et al. Prophylactic Cranial Irradiation in Extensive Disease Small-Cell Lung Cancer: Short-Term Health-Related Quality of Life and Patient Reported Symptoms-Results of an International | 59 | 19.7 |

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|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|
| | Phase III Randomized Controlled Trial by the EORTC Radiation Oncology and Lung Cancer Groups. Journal of Clinical Oncology. 2009; 27: 78-84 | | |
| EBUS | Herth, FJF; Annema, JT; Eberhardt, R; et al. Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum in lung cancer. Journal of Clinical Oncology. 2008; 26: 3346-3350 | 85 | 17.0 |
| EBUS | Tournoy, Kurt G.; Rintoul, Robert C.; van Meerbeeck, Jan P.; et al. EBUS TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy. Lung Cancer. 2009; 63: 45-49 | 51 | 17.0 |

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators:

| Theme | Article | Citations | |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| miRNA | Duursma, A. M.; Kedde, M.; Schrier, M.; et al. miR-148 targets human DNMT3b protein coding region. RNA-a publication of the RNA Society. 2008: 14; 872-877 | 202 | 50.5 |
| Staging | Postmus, Pieter E.; Brambilla, Elisabeth; Chansky, Kari; et al. The IASLC lung cancer staging project: Proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. Journal of Thoracic Oncology. 2007; 2: 686-693 | 139 | 27.8 |
| Proteomics | Sander R.; Fiedler, U.; Span, S.; et al. Workflow Comparison for Label-Free, Quantitative Secretome Proteomics for Cancer Biomarker Discovery: Method Evaluation, Differential Analysis, and Verification in Serum. Journal of Proteome Research. 2010: 9; 1913-1922 | 52 | 26.0 |
| EMT | Smit, M. A.; Geiger, T. R.; Song, Ji-Ying; et al. A Twist-Snail Axis Critical for TrkB-Induced Epithelial-Mesenchymal Transition-Like Transformation, Anoikis Resistance, and Metastasis. Molecular and Cellular Biology. 2009: 29; 3722-3737 | 73 | 24.3 |
| Chemopreventive nutrition | de Kok, T.M.; van Breda, S. G.; Manson, M.M. Mechanisms of combined action of different chemopreventive dietary compounds. European Journal of Nutrition. 2008: 47; 51-59 | 86 | 21.5 |
| Air pollution | Beelen, R.; Hoek, G.; Pebesma, E.; et al. Mapping of background air pollution at a fine spatial scale across the European Union. Science of the Total Environment. 2009: 407; 1852-1867 | 58 | 19.3 |
| Gene expression profiling | Horlings, H. M.; van Laar, R. K.; Kerst, J.M; et al. Gene expression profiling to identify the histogenetic origin of metastatic adenocarcinomas of unknown primary. Journal of Clinical Oncology. 2008: 26; 4435-4441 | 76 | 19.0 |
| PET | Aerts, H. J. W.L.; van Baardwijk, A. A. W.; Petit, S. F.; et al. Identification of residual metabolic-active areas within individual NSCLC tumours using a pre-radiotherapy (18)Fluorodeoxyglucose-PET-CT scan. Radiotherapy and Oncology. 2009: 91; 386-392 | 52 | 17.3 |
| Prognostic profiling | Roepman, P.; Jassem, J.; Smit, E. F.; et al. An Immune Response Enriched 72-Gene Prognostic Profile for Early-Stage Non-Small-Cell Lung Cancer. Clinical Cancer Research. 2009:15; 284-290 | 50 | 16.7 |

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|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|
| Multidrug resistance | Marchetti, S.; de Vries, N. A.; Buckle, T.; et al. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1(-/-)/Mdr1a/1b(-/-) (triple-knockout) and wild-type mice. <i>Molecular Cancer Therapeutics</i> . 2008; 7; 2280-2287 | 66 | 16.5 |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|

Table 1 . Top 10 most cited basic research initiated by a Dutch group Mesothelioma:

| Theme | Article | Citations | |
|------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Cox-2 inhibition | Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Aerts JG, Hegmans JP. COX-2 inhibition improves immunotherapy and is associated with decreased numbers of myeloid-derived suppressor cells in mesothelioma. Celecoxib influences MDSC function. BMC Cancer. 2010; 10;464 | 30 | 15.0 |
| Biomarker | Hollevoet, Kevin; Reitsma, Johannes B.; Creaney, Jenette; et al. Serum Mesothelin for Diagnosing Malignant Pleural Mesothelioma: An Individual Patient Data Meta-Analysis. Journal of Clinical. 2012; 30: 1541-1549 | 29 | 14.5 |
| Immune response | Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Hegmans JP, Aerts JG. Zoledronic acid impairs myeloid differentiation to tumour-associated macrophages in mesothelioma. Br J Cancer. 2010;103; 629-41 | 22 | 11.0 |
| Vandetanib | Giovannetti E, Zucali PA, Assaraf YG, Leon LG, Smid K, Alecci C, Giancola F, Destro A, Gianoncelli L, Lorenzi E, Roncalli M, Santoro A, Peters GJ. Preclinical emergence of vandetanib as a potent antitumour agent in mesothelioma: molecular mechanisms underlying its synergistic interaction with pemetrexed and carboplatin. Br J Cancer. 2011; 105; 1542-53 | 9 | 9.0 |
| Mouse model | Jongsma J, van Montfort E, Vooijs M, Zevenhoven J, Krimpenfort P, van der Valk M, van de Vijver M, Berns A. A conditional mouse model for malignant mesothelioma. Cancer Cell. 2008; 10; 261-71 | 33 | 8.3 |
| Mouse Model | Jongsma, J.; van Montfort, E.; Vooijs, M.; et al. A conditional mouse model for malignant mesothelioma. Cancer Cell. 2008; 13: 261-271 | 33 | 6.6 |
| Radiotherapy | Verbrugge I, Wissink EH, Rooswinkel RW, Jongsma J, Beltraminelli N, Dupuis M, Borst J, Verheij M. Combining radiotherapy with APO010 in cancer treatment. Clin Cancer Res. 2009;15; 15(6): | 18 | 6.0 |
| Dendritic cell-based immunotherapy | Veltman JD, Lambers ME, van Nimwegen M, de Jong S, Hendriks RW, Hoogsteden HC, Aerts JG, Hegmans JP. Low-dose cyclophosphamide synergizes with dendritic cell-based immunotherapy in antitumor activity. J Biomed Biotechnol. 2010 | 7 | 3.5 |
| Proteomics protein | Hegmans JP, Veltman JD, Fung ET, Verch T, Glover C, Zhang F, Allard WJ, T'Jampens D, Hoogsteden HC, Lambrecht BN, Aerts J. Protein | 7 | 2.3 |

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|------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----|
| | profiling of pleural effusions to identify malignant pleural mesothelioma using SELDI-TOF MS. Technol Cancer Res Treat. 2009;8; 323-32 | | |
| Proteomics | Hegmans, Joost P. J. J.; Veltman, Joris D.; Fung, Eric T.; et al. Protein Profiling of Pleural Effusions to Identify Malignant Pleural Mesothelioma Using SELDI-TOF MS. Technology in Cancer Research & Treatment. 2009; 9: 323-332 | 7 | 1.8 |

**Table 2. Top 10 most cited clinical research initiated by a Dutch group
Mesothelioma:**

| Theme | Article | Citations | |
|------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Dendritic cell-based immunotherapy | Hegmans JP, Veltman JD, Lambers ME, de Vries IJ, Figdor CG, Hendriks RW, Hoogsteden HC, Lambrecht BN, Aerts JG. Consolidative dendritic cell-based immunotherapy elicits cytotoxicity against malignant mesothelioma. <i>Am J Respir Crit Care Med.</i> 2010;181; 1383-90. | 26 | 13.0 |
| Pathogenesis | De Bruin ML, Burgers JA, Baas P, van 't Veer MB, Noordijk EM, Louwman MW, Zijlstra JM, van den Berg H, Aleman BM, van Leeuwen FE. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. <i>Blood.</i> 2009;113; 3679-81 | 15 | 5.0 |
| Tumour markers | van den Heuvel MM, Korse CM, Bonfrer JM, Baas P. Non-invasive diagnosis of pleural malignancies: the role of tumour markers. <i>Lung Cancer.</i> 2008;59; 350-4. | 18 | 4.5 |
| Exposure assessment | Lenters V, Vermeulen R, Dogger S, Stayner L, Portengen L, Burdorf A, Heederik D. A meta-analysis of asbestos and lung cancer: is better quality exposure assessment associated with steeper slopes of the exposure-response relationships? <i>Environ Health Perspect.</i> 2011;119; 1547-55 | 4 | 4.0 |
| Novel chemotherapy | Damhuis RA, Schroten C, Burgers JA. Population-based survival for malignant mesothelioma after introduction of novel chemotherapy. <i>Eur Respir J.</i> 2012;40; 185-9. | 3 | 3.0 |
| Surgical treatment | van Sandick JW, Kappers I, Baas P, Haas RL, Klomp HM. Surgical treatment in the management of malignant pleural mesothelioma: a single institution's experience. <i>Ann Surg Oncol.</i> 2008;6; 1757-64. | 10 | 2.5 |
| Surgical treatment | van Sandick, J. W.; Kappers, I.; Baas, P.; et al. Surgical treatment in the management of malignant pleural mesothelioma: A single institution's experience. <i>Annals of Surgical Oncology.</i> 2008; 15: 1757-1764 | 10 | 2.0 |
| Ultrasound guided biopsies | Stigt JA, Boers JE, Groen HJ. Analysis of "dry" mesothelioma with ultrasound guided biopsies. <i>Lung Cancer.</i> 2012;78; 229-33. | 2 | 2.0 |
| Maintenance treatment | Buikhuisen WA, Burgers JA, Vincent AD, Korse CM, van Klaveren RJ, Schramel FM, Pavlakis N, Nowak AK, Custers FL, Schouwink JH, Gans SJ, Groen HJ, Strankinga WF, Baas P. Thalidomide versus active supportive care for maintenance in patients with malignant mesothelioma after first-line chemotherapy (NVALT 5): an open-label, | 1 | 0.5 |

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|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----|
| | multicentre, randomised phase 3 study. Lancet Oncol. 2013;14; 543-51. | | |
| Pleural catheters | Boshuizen RC, Onderwater S, Burgers SJ, van den Heuvel MM. The use of indwelling pleural catheters for the management of malignant pleural effusion - direct costs in a Dutch hospital. Respiration. 2013;86; 224-8. | 1 | 0.5 |

Table 3. Top 10 most cited collaborative international basic research (excl. reviews, guidelines) Mesothelioma:

| Theme | Article | Citations | |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Targeted therapy | Miselis, N.R.; Wu, Z.J.; Van Rooijen, N.; et al. Targeting tumor-associated macrophages in an orthotopic murine model of diffuse malignant mesothelioma. <i>Molecular Cancer Therapeutics</i> . 2008; 7: 788-799 | 42 | 8.4 |
| Biomarker | Hollevoet, K.; Reitsma, J.B.; Creaney, J.; et al. Serum Mesothelin for Diagnosing Malignant Pleural Mesothelioma: An Individual Patient Data Meta-Analysis. <i>Journal of Clinical Oncology</i> . 2012; 30: 1541-1549 | 29 | 14.5 |
| Predictors | Zucali, P. A.; Giovannetti, E.; Destro, A.; et al. Thymidylate Synthase and Excision Repair Cross-Complementing Group-1 as Predictors of Responsiveness in Mesothelioma Patients Treated with Pemetrexed/Carboplatin. <i>Clinical Cancer Research</i> . 2011; 17: 2581-2590 | 28 | 14.0 |
| Molecular mechanisms | Giovannetti, E.; Zucali, P. A.; Assaraf, Y. G.; et al. Preclinical emergence of vandetanib as a potent antitumour agent in mesothelioma: molecular mechanisms underlying its synergistic interaction with pemetrexed and carboplatin. <i>British Journal of Cancer</i> . 2011; 105: 1542-1553 | 10 | 5.0 |

Table 4. Top 10 Most cited collaborative international clinical research (excl, reviews, guidelines) Mesothelioma:

| Theme | Article | Citations | |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|---------|
| | | Total | Mean/yr |
| Electronic nose | Dragonieri S, van der Schee MP, Massaro T, Schiavulli N, Brinkman P, Pinca A, Carratú P, Spanevello A, Resta O, Musti M, Sterk PJ. An electronic nose distinguishes exhaled breath of patients with Malignant Pleural Mesothelioma from controls. <i>Lung Cancer</i> . 2012;75; 326-31 | 9 | 9.0 |
| Environmental exposure | Driee HA, Siesling S, Swuste PH, Burdorf A. Assessment of cancer risks due to environmental exposure to asbestos. <i>J Expo Sci Environ Epidemiol</i> . 2010;20; 478-85. | 12 | 6.0 |
| Second-line treatment | Fennell DA, McDowell C, Busacca S, Webb G, Moulton B, Cakana A, O'Byrne KJ, Meerbeeck JV, Donnellan P, McCaffrey J, Baas P. Phase II clinical trial of first or second-line treatment with bortezomib in patients with malignant pleural mesothelioma. <i>J Thorac Oncol</i> . 2012;9; 1466-70. | 5 | 5.0 |
| Biomarkers | Grefte JM, de Wilde PC, Salet-van de Pol MR, Tomassen M, Raaymakers-van Geloof WL, Bulten J. Improved identification of malignant cells in serous effusions using a small, robust panel of antibodies on paraffin-embedded cell suspensions. <i>Acta Cytol</i> . 2008;52; 35-44. | 10 | 2.5 |
| Transesophageal endoscopic ultrasound | Tournoy KG, Burgers SA, Annema JT, Vermassen F, Praet M, Smits M, Klomp HM, van Meerbeeck JP, Baas P. Transesophageal endoscopic ultrasound with fine needle aspiration in the preoperative staging of malignant pleural mesothelioma. <i>Clin Cancer Res</i> . 2008;19; 6259-63 | 7 | 1.8 |
| EORTC trial | O'Brien ME, Gaafar RM, Popat S, Grossi F, Price A, Talbot DC, Cufer T, Ottensmeier C, Danson S, Pallis A, Hasan B, Van Meerbeeck JP, Baas P. Phase II study of first-line bortezomib and cisplatin in malignant pleural mesothelioma and prospective validation of progression free survival rate as a primary end-point for mesothelioma clinical trials (European Organisation for Research and Treatment of Cancer 08052). <i>Eur J Cancer</i> . 2013;49; 2815-22. | 1 | 0.5 |
| Surgery | Treasure, T.; Lang-Lazdunski, L.; Waller, D.; et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. <i>Lancet Oncology</i> . 2011; 12: 763-772 | 75 | 37.5 |
| Chemo therapy | Santoro, Armando; O'Brien, Mary E.; Stahel, Rolf | 51 | 10.2 |

| | | | |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|------|
| | A.; et al. Pemetrexed plus cisplatin or pemetrexed plus carboplatin for chemo-naïve patients with malignant pleural mesothelioma: Results of the International Expanded Access Program. <i>Journal of Thoracic Oncology</i> . 2008; 3: 756-763 | | |
| EORTC | Van Schil, P. E.; Baas, P.; Gaafar, R.; et al. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. <i>European Respiratory Journal</i> . 2010; 36: 1362-1369 | 46 | 15.3 |
| Chemo therapy | Taylor, P.; Castagneto, B.; Dark, G.; et al. Single-agent pemetrexed for chemo-naïve and pretreated patients with malignant pleural mesothelioma - Results of an International Expanded Access Program. <i>Journal of Thoracic Oncology</i> . 2008; 3: 764-771 | 17 | 3.4 |

Table 5: Top 10 best cited review and guideline papers with Dutch collaborators Mesothelioma:

| Theme | Article | Citations | |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|
| | | Total | Mean/ yr |
| Guidelines | Scherpereel, A.; Astoul, P.; Baas, P.; et al. Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. European Respiratory Journal. 2010; 35: 479-495 | 101 | 33.7 |
| Serum Mesothelin | Hollevoet, Kevin; Reitsma, Johannes B.; Creaney, Jenette; et al. Serum Mesothelin for Diagnosing Malignant Pleural Mesothelioma: An Individual Patient Data Meta-Analysis. Journal of Clinical Oncology. 2012;30; 1541-1549 | 25 | 25.0 |
| Standard of care | van Meerbeeck, Jan P.; Scherpereel, Arnaud; Surmont, Veerle F.; et al. Malignant pleural mesothelioma: The standard of care and challenges for future management. Critical Reviews in Oncology Hematology. 2011;78; 92-111 | 17 | 17.0 |
| Markers | van der Bij, S.; Schaake, E.; Koffijberg, H.; et al. Markers for the non-invasive diagnosis of mesothelioma: a systematic review. British Journal of Cancer. 2011;104; 1325-1333 | 17 | 17.0 |
| Biomarkers | Greillier, Laurent; Baas, Paul; Welch, John J.; et al. Biomarkers for Malignant Pleural Mesothelioma Current Status. Molecular Diagnosis & Therapy. 2008;12; 375-390 | 24 | 6.0 |
| Biomarkers | Greillier, Laurent; Baas, Paul; Welch, John J.; et al. Biomarkers for Malignant Pleural Mesothelioma Current Status. Molecular Diagnosis & Therapy. 2008; 12: 375-390 | 24 | 4.8 |
| Biomarkers | van den Heuvel, Michel M.; Korse, Catharina M.; Bonfrer, Johannes M. G.; et al. Non-invasive diagnosis of pleural malignancies: The role of tumour markers. Lung Cancer. 2008; 59: 350-354 | 19 | 3.8 |
| Implementing Immunotherapy | Cornelissen, R.; Heuvers, M. E.; Maat, A. P.; et al. New Roads Open Up for Implementing Immunotherapy in Mesothelioma. Clinical & Developmental Immunology. 2012: 10.1155/2012/927240 | 3 | 3.0 |
| Dendritic cell-based immunotherapy | Cornelissen, Robin; Lievens, Lysanne A.; Heuvers, Marlies E.; et al. Dendritic cell-based immunotherapy in mesothelioma. : Immunotherapy. 2012;4; 1011-1022 | 1 | 1.0 |
| Pemetrexed | Boons, Christel C. L. M.; Van Tulder, Maurits W.; Burgers, Jacobus A.; et al. The Value of Pemetrexed for the Treatment of Malignant Pleural | 0 | 0 |

| | | | |
|--|----------------------------------------------------------------------------------|--|--|
| | Mesothelioma: A Comprehensive Review. Anticancer Research. 2013;33; 3553-3561 | | |
|--|----------------------------------------------------------------------------------|--|--|

APPENDIX

Opinions of international key opinion leaders

Questions were sent to international experts in the field about the visibility of Dutch Lung Cancer research.

Question 1

Which research topics and groups in Lung cancer research are visible and have impact on pulmonary physicians and researchers outside the Netherland?

Expert 1

Topic SBRT, groups in Amsterdam (all centers)

Topic imaging guided RT, groups in Maastricht/Leuven and NKI

Expert 2

- Screening (NELSON trial)
- RT (SABRT)
- PET staging
- EBUS implementation

Expert 3

- Epidemiology
- Pathology
- PET imaging
- Cooperative studies
- NVALT

Question 2

Which research topics in Lung Cancer research are less visible to physicians and researchers outside the Netherland?

Expert 1

Expert 2

1: genomic research

2: large scale international phase 3 RCT (international collaboration)

Expert 3

I believe the Dutch do a great job to promote themselves outside of the country. This is reflected by the high ranking of most Dutch universities.

Relevance of research judged by international experts (order of importance)

Research performed in the Netherlands in the field of **Lung Cancer**

0= no relevant research

5= excellent research, international top level

| | 1 | 2 | 3 | 4 | Mean |
|-----------------------------------------|----------|----------|----------|----------|-------------|
| Phenotyping and Severity | NE | 0 | 2 | 1 | 1.00 |
| Biological mechanisms | NE | 0 | 3 | 1 | 1.33 |
| Environment and lifestyle | NE | 0 | 4 | 2 | 2.00 |
| Development and ageing | NE | 2 | 3 | 1 | 2.00 |
| Prevention | NE | 5 | 4 | 2 | 3.66 |
| Diagnosis monitoring | NE | 4 | 3 | 3 | 3.33 |
| Therapy medical | 5 | 3 | 5 | 5 | 4.50 |
| Therapy non-medical | NE | 2 | 5 | 4 | 3.66 |
| Biobanking | NE | 1 | 4 | 3 | 2.66 |
| Data management clinical studies | NE | 5 | 4 | 3 | 4.00 |
| Implementation and care | NE | 4 | 4 | 4 | 4.00 |

NE= No expertise