

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/28735> holds various files of this Leiden University dissertation

**Author:** Zeestraten, Eliane

**Title:** Clinical application of biomarkers in colon cancer : studies on apoptosis, proliferation and the immune system

**Issue Date:** 2014-09-17



Clinical application of biomarkers in colon cancer  
studies on apoptosis, proliferation and the immune system  
Eliane Zeestraten

## Colophon

Clinical application of biomarkers in colon cancer, studies on apoptosis, proliferation and the immune system

Thesis, Leiden University, The Netherlands, 2014

© Eliane C.M. Zeestraten, 2014, The Netherlands

ISBN/EAN 978-94-6108-727-0

NUR 870

Cover art: Texcetera, Den Haag

Layout: Texcetera, Den Haag

Printed by: Gildeprint, Enschede

The financial support provided by Boehringer Ingelheim, Covidien, Roche, Novartis Oncology, Erbe, Chipsoft, ABN Amro, ISA Pharmaceuticals, Olympus Nederland B.V. and Convatec for the printing of this thesis is gratefully acknowledged.

# Clinical application of biomarkers in colon cancer

*studies on apoptosis, proliferation and the immune system*

PROEFSCHRIFT

Ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden,  
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,  
volgens besluit van het College voor Promoties  
te verdediging op 17 september 2014  
Klokke 15:00

door

**Eliane Cornelia Maria Zeestraten**

geboren te Heerlen in 1983

**Promotiecommissie**

Promotor: Prof. dr. C.J.H. van de Velde

Co-promotoren: Dr. P.J.K. Kuppen

Dr. G.J. Liefers

Overige leden: Prof. dr. R.A.E.M. Tollenaar

Prof. dr. H. Morreau

Prof. dr. G.A. Meijer (Vrije Universiteit Amsterdam)

# Contents

|                   |                                                                                                                                                                                |           |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>Chapter 1</b>  | General introduction and thesis outline                                                                                                                                        | 7         |
| <b>PART ONE</b>   | <b>BIOMARKERS OF APOPTOSIS AND PROLIFERATION</b>                                                                                                                               | <b>14</b> |
| <b>Chapter 2</b>  | The prognostic value of the apoptosis pathway in colorectal cancer: A review of the literature on biomarkers identified by immunohistochemistry                                | 15        |
| <b>Chapter 3</b>  | Combined analysis of biomarkers of proliferation and apoptosis in colon cancer; an immunohistochemistry based study using tissue micro array                                   | 47        |
| <b>Chapter 4</b>  | Specific activity of cyclin-dependent kinase I is a new potential predictor of tumor recurrence in stage II colon cancer                                                       | 65        |
| <b>Chapter 5</b>  | Combined markers of tumor cell proliferation and apoptosis are clinically prognostic in stage II colon cancer patients                                                         | 83        |
| <b>PART TWO</b>   | <b>TUMOR IMMUNE INTERACTIONS</b>                                                                                                                                               | <b>98</b> |
| <b>Chapter 6</b>  | Colorectal cancer vaccines in clinical trials                                                                                                                                  | 99        |
| <b>Chapter 7</b>  | Addition of interferon-alpha to the p53-SLP® vaccine results in increased production of interferon-gamma in vaccinated colorectal cancer patients: A phase I/II clinical trial | 139       |
| <b>Chapter 8</b>  | FoxP3- and CD8-positive infiltrating immune cells together determine clinical outcome in colorectal cancer                                                                     | 163       |
| <b>Chapter 9</b>  | Combined analysis of HLA Class I, HLA-E and HLA-G predicts prognosis in colon cancer patients                                                                                  | 181       |
| <b>Chapter 10</b> | Summary, general discussion, conclusions and future directions                                                                                                                 | 205       |
| <b>Chapter 11</b> | Nederlandse samenvatting                                                                                                                                                       | 217       |
|                   | List of publications                                                                                                                                                           | 231       |
|                   | Acknowledgements                                                                                                                                                               | 234       |
|                   | Curriculum vitae                                                                                                                                                               | 235       |

