

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/33832> holds various files of this Leiden University dissertation

Author: Krens, Lisanne

Title: Refining EGFR-monoclonal antibody treatment in colorectal cancer

Issue Date: 2015-07-02

Refining

EGFR-MONOCLONAL
ANTIBODY TREATMENT

***in colorectal
cancer***

Lisanne Krens

The research presented at this thesis was performed at the department of Clinical Pharmacy and Toxicology and Clinical Oncology of Leiden University Medical Center, Leiden, The Netherlands.

Financial support for the publication of this thesis was provided by AZL Onderzoeks- en Ontwikkelingskrediet Apotheek and Raad van bestuur Ziekenhuisgroep Twente.

Cover design Esther Ris, Proefschriftomslag.nl
Layout Esther Ris, Proefschriftomslag.nl
Printed by Gildeprint, Enschede
ISBN/EAN 978-94-92026-05-7

© 2015 Lisanne Krens. Except: Chapter 2: Reproduced with permission from Drug Discovery Today: Krens et al. 15 June 2010 – volume 15 – Issue 13-14 - p502-516. Elsevier LTD. Chapter 7: Reproduced with permission from Cancer Chemotherapy and Pharmacology: Krens et al. February 2014 - volume 73 - issue 2 - p429-433. Springer-Verlag Berlin Heidelberg. Chapter 8: Reproduced with permission from Cancer Chemotherapy and Pharmacology: Krens et al. June 2014 - volume 73 – issue 6 - p1303- 1306. Springer-Verlag Berlin Heidelberg

All rights reserved. No part of this thesis may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage or retrieval, without permission in writing from the author.

***Refining EGFR-monoclonal
antibody treatment in colorectal
cancer***

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 verdedigen op donderdag 2 juli 2015
klokke 16.15 uur

door

Lisanne Laura Krens
geboren te Pijnacker
in 1984

Promotiecommissie

Promotores	Prof. dr. H.-J. Guchelaar Prof. dr. A.J. Gelderblom
Copromotor	Dr. R.J.H.M. van der Straaten
Overige Leden	Prof. dr. ir. J.J.M. van der Hoeven Prof. dr. J.G.W. Kosterink, Rijksuniversiteit Groningen Prof. dr. C.J.H. van de Velde

Table of Contents

Chapter 1: General introduction	7
PART I: Colorectal cancer, KRAS, FCGR3A and statins	
Chapter 2: Therapeutic modulation of KRAS signaling in colorectal cancer	17
Chapter 3: Simvastatin in G13D <i>KRAS</i> mutated colorectal cancer cells render cells susceptible for cetuximab	47
Chapter 4: Statin use is not associated with improved progression free survival in cetuximab treated <i>KRAS</i> mutant metastatic colorectal cancer patients: results from the CAIRO2 study	61
Chapter 5: Safety and efficacy of the addition of simvastatin to cetuximab in previously treated <i>KRAS</i> mutant metastatic colorectal cancer patients	73
Chapter 6: Safety and efficacy of the addition of simvastatin to panitumumab in previously treated <i>KRAS</i> mutant metastatic colorectal cancer patients	87
Chapter 7: Effect of the Fc gamma receptor polymorphism V158F status on the survival of metastatic colorectal cancer patients treated with cetuximab: a meta-analysis	99
PART II: EGFR antibodies in special populations	
Chapter 8: Pharmacokinetics of panitumumab in a patient with liver dysfunction: a case report	119
Chapter 9: Pharmacokinetics and safety of cetuximab in a patient with renal dysfunction	129
Chapter 10: General discussion	137
Chapter 11: Summary	147
Chapter 12: Nederlandse samenvatting	151
Dankwoord	157
Curriculum Vitae	161
List of publications	165