

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/22281> holds various files of this Leiden University dissertation.

Author: Oosterwijk, Jolieke Gerdy van

Title: Chondrosarcoma models : understanding chemoresistance mechanisms for use in targeted treatment

Issue Date: 2013-11-19

CHONDROSARCOMA MODELS: UNDERSTANDING
CHEMORESISTANCE MECHANISMS FOR USE IN TARGETED
TREATMENT

The work presented in this thesis was financially supported by EuroBoNet, a European Commission granted network of Excellence for studying the pathology and genetics of bone tumors (917-67-315), EuroSARC, a European Commission granted FP7 clinical trials network (278742), and the Dutch Cancer Society (UL2010-4873).

Cover art: Photograph taken by J.G. van Oosterwijk of the "Hernando de Soto", or "M", bridge from Memphis, TN, to Arkansas. Editing by Thijs van Himbergen.

Printed by: Drukkerij Mostert en van Onderen, Leiden, the Netherlands.

**CHONDROSARCOMA MODELS: UNDERSTANDING
CHEMARESISTANCE MECHANISMS FOR USE IN TARGETED
TREATMENT**

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 dinsdag 19 november 2013
klokke 13.45 uur

door

Jolieke Gerdy van Oosterwijk
geboren te Leiden
in 1984

Promotiecommissie

Promotor: Prof. dr. J.V.M.G. Bovée

Overige leden: Prof. dr. P.C.W. Hogendoorn

Prof. dr. A.J. Gelderblom

Prof. B. van de Water

Prof. dr. J.-Y. Blay (Université Claude Bernard Lyon I, Centre Léon Bérard,
France)

Voor Opa

CONTENTS

Chapter 1	General Introduction	7
Chapter 2	Update on targets and novel treatment options for high grade chondrosarcoma	29
Chapter 3	Three new chondrosarcoma cell lines: one grade III conventional central chondrosarcoma and two dedifferentiated chondrosarcomas of bone	53
Chapter 4	Orthotopic mouse model for chondrosarcoma of bone: an <i>in vivo</i> tool for drug testing	71
Chapter 5	Restoration of chemosensitivity for doxorubicin and cisplatin in chondrosarcoma <i>in vitro</i> : Bcl-2 family members cause chemoresistance	87
Chapter 6	Screening for potential targets for therapy in mesenchymal, clear cell, and dedifferentiated chondrosarcoma reveals Bcl-2 family members and TGFbeta as potential targets	107
Chapter 7	Src kinases in chondrosarcoma chemoresistance and migration: dasatinib sensitizes to doxorubicin in TP53 mutant cells	127
Chapter 8	Functional profiling of receptor tyrosine kinases and downstream signaling in human chondrosarcomas identifies pathways for rational targeted therapy	149
Chapter 9	Summary and concluding remarks	181
Chapter 10	Nederlandse Samenvatting Curriculum vitae List of publications Acknowledgements	191 199 201 203