Table of contents

General introduction

1. BRCA1-deficient breast cancer 11
2. Physiology of DNA topoisomerases and inhibitors of these enzymes as anticancer agents 12
3. Other therapeutic options to treat BRCA1-deficient breast cancers 13
4. Synergism between TOP1 and PARP inhibition 15
5. Mechanisms of resistance to topoisomerase inhibitors 15
   5.1. ABC efflux transporters 16
   5.2. Drug target-related resistance mechanisms 16
   5.3. Drug target-independent resistance mechanisms 17
6. Therapeutic strategies to prevent or overcome resistance to topoisomerase inhibitors 18
7. The K14cre;Brca1F/F;p53F/F mouse model of BRCA1-deficient breast cancer as a tool to study resistance mechanisms to topoisomerase inhibitors 19
8. Objectives and outline of this thesis 20
   References 21

Chapter 1


Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6
General discussion

1. Comparison of genetically engineered mouse models (GEMM) and xenograft models as in vivo tools to investigate clinically relevant resistance mechanisms

2. Resistance to topoisomerase inhibitors through ABC transporters

3. Resistance to topoisomerase inhibitors through drug target-related mechanisms

4. Alternative mechanisms to overcome cell killing by topoisomerase inhibitors
   4.1. Drug resistance
   4.2. Drug tolerance

5. Phytoestrogens and chemoprevention of breast cancer

6. Conclusions

References

General summary

Algemene samenvatting

List of abbreviations

List of publications

Curriculum vitae

Dankwoord