

TABLE OF CONTENT

REMERCIEMENTS	1
ABBREVIATIONS	7
SUMMARY	9
RESUME	13
INTRODUCTION	17
1. Lung cancer	18
1.1. Epidemiology and risk factors	18
1.2. Clinical manifestations	20
1.3. Classification and pathology	20
1.4. Non-small cell lung carcinoma	22
1.5. Small cell lung carcinoma	40
1.6. Reasons for treatment failure	43
1.7. Strategies and new perspectives	44
2. Cisplatin, Carboplatin and Paclitaxel	46
2.1. Cisplatin and carboplatin.....	46
2.2. Paclitaxel	52
2.3. Cisplatin, carboplatin and paclitaxel related toxicities	53
3. Inhaled therapy as a loco-regional treatment against lung cancers	66
3.1. The lungs	66
3.2. Drug delivery to the lungs	71
3.3. Pulmonary route for lung cancer treatment.....	81
SCIENTIFIC STRATEGY AND MAIN OBJECTIVES	89
EXPERIMENTAL PART	94
<i>Part I: Optimization of cisplatin-based DPI formulation with controlled-release and lung-retention properties</i>	95
1. Introduction and aims	96
2. Materials and methods	97
2.1. Materials	97
2.2. Safety procedures	98
2.3. Preliminary studies on CIS-DPI-TS.....	98

2.4.	Preparation and <i>in vitro</i> evaluation of new cisplatin DPIs	107
2.5.	Statistical analyses.....	112
3.	Results and discussion	112
3.1.	Preliminary studies on CIS-DPI-TS.....	112
3.2.	Optimization of the cisplatin-based DPI formulation with controlled cisplatin-release and lung-retention properties	122
4.	Conclusion	138

Part II: Selection of the most appropriate CIS-DPI-50 monotherapy regimen..139

1.	Introduction and aims	140
2.	Materials and methods	140
2.1.	Materials.....	140
2.2.	<i>In vivo</i> studies	141
2.3.	Development of Lewis lung carcinoma expressing luciferase model.....	141
2.4.	PK study on LLC1- <i>Luc</i> grafted mice	141
2.5.	Biodistribution of CIS-DPI-50 and immunohistochemistry labelling following the administration of different regimens	142
2.6.	Efficacy study on M109-HiFR- <i>Luc2</i> lung carcinoma model	145
2.7.	Statistical analyses.....	145
3.	Results and discussion	146
3.1.	PK study of CIS-DPI-50 on Lewis lung carcinoma grafted mice	146
3.2.	Selection of the most appropriate CIS-DPI-50 monotherapy regimen	152
3.3.	Efficacy study	166
4.	Conclusion	170

Part III: Evaluation of the combination of CIS-DPI-50 and IV cisplatin-based platinum doublet..... 171

1.	Introduction and aims	172
2.	Material and methods	173
2.1.	Materials.....	173
2.2.	CIS-DPI-50 formulation production and characterization (DPI-0.5 and DPI-1)	173
2.3.	<i>In vivo</i> toxicity studies	173
2.4.	Efficacy study	179
2.5.	Statistical analyses.....	180
3.	Results and discussion	181
3.1.	Overall tolerance	181
3.2.	Pulmonary tolerance assessment of CIS-DPI-50, CIS-IV and their combinations	182
3.3.	Renal tolerance assessment of CIS-DPI-50, CIS-IV and their combinations.....	193
3.4.	Conclusions for pulmonary and renal tolerance	203
3.5.	Efficacy evaluation on the M109-HiFR- <i>Luc2</i> lung carcinoma orthotopic model in mice	203
4.	Conclusion	207

Part IV: Evaluation of the tolerance of the combination of CIS-DPI-50 and IV carboplatin-based platinum doublet..... 209

1. Introduction and aims	210
2. Materials and methods	211
2.1. Materials.....	211
2.2. <i>In vivo</i> toxicity studies	211
2.3. Formulation and administration for <i>in vivo</i> experiments	211
2.4. Regimen administration	212
2.5. Pulmonary tolerance evaluation.....	214
2.6. Renal tolerance evaluation.....	214
2.7. Myelosuppression evaluation.....	214
2.8. Statistical analyses.....	215
3. Results.....	215
3.1. Determination of maximum tolerated dose for CIS-DPI-50 and IV-CARB-PTX	215
3.2. Tolerance of DPI-0.5, IV-CARB-PTX and their combinations	217
3.3. Body weight profiles and general evaluation.....	217
3.4. Evaluation of pulmonary toxicity.....	218
3.5. Evaluation of nephrotoxicity	225
3.6. Evaluation of myelotoxicity.....	226
4. Discussion.....	231
5. Conclusion	239

GENERAL CONCLUSIONS AND PERSPECTIVES 241

BIBLIOGRAPHY..... 248

APPENDIX..... 267

1. Abstract and Poster at Drug Delivery to the Lungs (DDL, 29) Conference, Edinburgh, Scotland, UK. December 12-14, 2018.....	268
2. Abstract and Poster at 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology	270
3. Abstract and Poster at Respiratory Drug Delivery (RDD, 20) Conference, DIGITAL, 2020 ..	272
4. Abstract for an oral presentation at Congrès de la Société Francophone de Néphrologie, Dialyse et Transplantation (SFNDT), DIGITAL, October 7-8 2020.....	274
5. Article 1: Pulmonary and renal tolerance of cisplatin-based regimens combining intravenous and endotracheal routes for lung cancer treatment in mice	277
6. Article 2: The combination of an innovative dry powder for inhalation and a standard cisplatin-based chemotherapy in view of therapeutics intensification against lung tumours	278
7. Article 3: Preclinical tolerance evaluation of the addition of a cisplatin-based dry powder for inhalation to the conventional carboplatin-paclitaxel doublet for the treatment of non-small cell lung cancer.....	279