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PM01183

PEDIATRIC SUBCOMMITTEE ONCOLOGY DRUG ADVISORY COMMITTEE MEETING

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ADVISORY COMMITTEE BRIEFING MATERIAL: AVAILABLE FOR PUBLIC RELEASE

BRIEFING PACKAGE

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ABBREVIATIONS

AAL	Advanced Acute Leukemia
ADME	Absorption, Distribution, Metabolism and Elimination
AEs	Adverse Events
ALL	Acute Lymphoblastic Leukemia
ALK	Anaplastic Lymphoma Kinase Gene
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
APC	Adenomatous Polyposis Coli Gene
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BEV	Bevacizumab
BSA	Body Surface Area
BRCA	Breast Cancer Gene
CAV	cyclophosphamide, doxorubicin and vincristine
CDDP	Cisplatin
CL	Plasma Clearance
CMLBP	Chronic Myeloid Leukemia in Blastic Phase
CNS	Central Nervous System
CR	Complete Response
CrCL	Creatinine Clearance
CTFI	Chemotherapy-Free Interval
D	Day
DNA	Deoxyribonucleic Acid
DOX	Doxorubicin
DLT	Dose-Limiting Toxicity
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ES	Ewing Sarcoma
EFS	Event Free Survival
EFT	Ewing Family of Tumors
EWS/FLI	Ewing Sarcoma/Friend Leukemia Integration Gene
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
FD	Flat Dose

GCIG	Gynecologic Cancer Intergroup
G-CSF	Granulocyte Colony-Stimulating Factor
GEM	Gemcitabine
GCT	Gamma-Glutamyltransferase
HVA	Homovanillic Acid
ICH	Pagina 24
IND	Investigational New Drug
ISTs	Investigator Sponsored Trials
i.v.	Intravenous
IWG	International Working Group
LDH	Lactate Dehydrogenase
LMO1	LIM Domain Only-1 Gene
MBC	Metastatic Breast Cancer
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic Syndrome
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MYCN	(pagina 23 y 24)
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NET	Neuroendocrine Tumors
NSCLC	Non-small Cell Lung Cancer
OC	Ovarian Cancer
OD	Orphan Drug
ORR	Overall Response Rate
PBPK	Physiologically Based Pharmacokinetic
PD	Progressive Disease
PFS	Progression-Free Survival
PK	Pharmacokinetic
PLD	Pegylated Liposomal Doxorubicin
PR	Partial Response
PRROC	Platinum Resistant/Refractory Ovarian Cancer
PT	Preferred Term

q3wk	Every Three Weeks
q4wk	Every Four Weeks
RD	Recommended Dose
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	Small Cell Lung Cancer
SD	Stable Disease
SDHB	Succinate Dehydrogenase [Ubiquinone] Iron-sulfur Subunit, Mitochondrial Gene
SNPs	Single-Nucleotide Polymorphisms
SOC	System Organ Class
UEC	Unresectable Endometrial Cancer
VMA	Vanillylmandelic Acid
Vss	Volume Steady State
UK	Unknown

1. INTRODUCTION

PM01183 is a new Chemical Entity that binds the DNA leading to the formation of DNA double strand breaks. The binding to DNA is likely occurring in the minor groove region and induces the appearance of double strand breaks, delayed progression trough the phase S/G2 and apoptosis. PM01183 also induces a specific degradation of transcribing RNA Pol II in several human tumor cell lines.

In vitro, PM01183 demonstrated cytotoxic effects against a broad selection of tumor types with values of IC50 in the range of 1-10 nM. Although selectivity was also seen, a clustering of sensitive tumors has not been identified. PM01183 also exhibits an antitumor activity against different murine models of xenografted human-derived tumor types.

The potential hemato- and hepato-toxicities of PM01183 have been explored in vitro with human derived either bone marrow progenitors or primary hepatocytes. Results suggested that PM01183 may target these organs which have been further confirmed in animal toxicology studies.

Finally, safety pharmacology studies did not raise concern related to either neurotoxicity, cardiovascular or respiratory functions.

PM01183 is being investigated in adult patients (single-agent or in combination with other antineoplastic drugs).

A total of 932 patients were included in PharmaMar clinical trials up to the cutoff date of 15 January 2016.

Table 1. Summary of patients included and evaluated in PM01183 clinical program.

Study		Included patients #	Treated patients ##	Evaluated patients ###	Status
Phase I trials					
Solid tumors		**410**	**398**	**379**	
Single-agent		**54**	**52**	**52**	
PM1183-A-001-08	D1 q3wk	33	31	31	Completed
PM1183-A-005-11	D1 and D8 q3wk	21	21	21	Completed
Combination		**356**	**346**	**327**	
PM1183-A-003-10	+ DOX	121	119	101	Ongoing
PM1183-A-004-10	+ GEM	47	45	45	Completed
PM1183-A-006-12	+ Capecitabine	81	79	78	Ongoing *
PM1183-A-007-13	+ Paclitaxel	55	55	55	Ongoing *
	+ Paclitaxel + BEV	14	12	12	
PM1183-A-008-13	+ CDDP	38	36	36	Ongoing
Hematological malignancies		**45**	**42**	**42**	
Single-agent		**45**	**42**	**42**	

Study			Included patients #	Treated patients ##	Evaluated patients ###	Status
PM1183-A-002-10	D1 and D8 q3wk		26	24	24	Ongoing *
	D1-D3 q3wk		19	18	18	
Total phase I trials			**455**	**440**	**421**	
Phase II trials						
Non-randomized trials			**164**	**154**	**154**	
PM1183-B-001-10	Pancreatic cancer		45	44	44	Completed
PM1183-B-003-11	Breast cancer		84	84	84	Ongoing
PM1183-B-005-14	Selected advanced solid tumors		35	26	26	Ongoing
Randomized trials			**150**	**149**	**149**	
PM1183-B-002-11	PRROC	PM01183	52	52	52	Ongoing *
		PM01183 after crossover from topotecan	.	15	15	
		Topotecan	29	29	29	
PM1183-B-004-13	NSCLC	PM01183	22	21	21	Ongoing *
		PM01183 + GEM	25	25	25	
		Docetaxel	22	22	22	
Total phase II trials	**PM01183**		**238**	**242 ****	**242 ****	
	PM01183 + GEM		**25**	**25**	**25**	
	Comparator drugs ***		**51**	**51**	**51**	
	Total		**314**	**303**	**303**	
Phase III trials						
PM1183-C-004-14	PROC	PM01183	**65**	**63**	**63**	Ongoing
		PLD or topotecan	**66**	**65**	**65**	
Total phase III trials			**131**	**128**	**128**	
Investigator-sponsored trials						
IST POLA/ACOG1401	Advanced solid tumors	PM01183 + Olaparib	**5**	**5**	**5**	Ongoing
IST 15-083	STS	PM01183 + DOX	**9**	**9**	**9**	Ongoing
		PM01183 + GEM	**9**	**9**	**9**	
		PM01183	**9**	**9**	**9**	
Total investigator-sponsored trials			**32**	**32**	**32**	
All trials						

Study		Included patients #	Treated patients ##	Evaluated patients ###	Status
Total	PM01183 single-agent	411	393	393	
	PM01183 in combination	404	394	375	
	PM01183 single-agent and in combination, with crossover from topotecan	.	802	783	
	Comparator drugs ***	117	116	116	
Grand total		932	903	884	

Cutoff date: 15 January 2016.

Patients enrolled at cutoff.

A total of 28 patients were included in clinical trials and scheduled to receive PM01183, but were not treated: nine in PM1183-B-005-14, three in PM1183-A-002-10, two each in PM1183-A-001-08, PM1183-A-003-10, PM1183-A-004-10, PM1183-A-006-12, PM1183-A-007-13, PM1183-A-008-13 and PM1183-C-004-14, and one each in PM1183-B-001-10 and PM1183-B-004-13. In addition, one patient was included in study PM1183-C-004-14 and scheduled to receive PLD or topotecan but was not treated.

Evaluable patients with available data in PharmaMar databases. One patient in study PM1183-A-006-12 was not evaluable because he was found to be ineligible as per protocol (he had mantle cell lymphoma in 2005 that was treated with standard treatment followed by stem cell transplantation).

* Closed recruitment.

** Includes 15 patients who were first enrolled in the topotecan arm in study PM1183-B-002-11 and later crossed over to the PM01183 arm. Thus, 238 patients enrolled in phase II trials and scheduled to receive single-agent PM01183 minus 11 patients who actually were not treated (nine in PM1183-B-005-14 and one each in PM1183-B-001-10 and PM1183-B-004-13), plus 15 patients who crossed over from topotecan in PM1183-B-002-11 gives the total of 242 patients treated with single-agent PM01183 in phase II trials.

*** Topotecan in study PM1183-B-002-11, docetaxel in study PM1183-B-004-13, and PLD or topotecan in study PM1183-C-004-14.

BEV, bevacizumab; CDDP, cisplatin; D, day; DOX, doxorubicin; GEM, gemcitabine; NSCLC, non-small cell lung cancer; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PRROC, platinum resistant/refractory ovarian cancer; q3wk, every three weeks; STS, soft tissue sarcoma.

2. MECHANISM OF ACTION

Transcription is the cellular process through which a segment of the DNA is copied into RNA by an enzyme called RNA polymerase. In eukaryotic cells, protein-coding genes are transcribed into messenger RNAs (mRNAs) by RNA polymerase II (Pol II)[1]. Pol II alone is unable to bind to promoters and initiate transcription, it needs the association of transcription factors to recognize gene promoters and enhancers and start transcription. Therefore transcription factors are essential for differentiation, development and response to the changing requirements of eukaryotic cells through the regulation of gene expression[2].

The majority of cancers start with genetic alterations that create anomalous transcription programs with critical functions in cell differentiation, proliferation, and survival[3]. Differently from non-cancer cells, those altered gene programs in cancer cells have a striking dependence on continuous active transcription, a process called transcription addiction. For example, Ewing sarcoma (ES), an aggressive soft tissue tumor frequently affecting children and adolescents, presents a pathogenic translocation t (11;22) (q24;q12) that generates an EWSR1-FLI1 fusion protein that stands in the origin of the malignancy[4]. EWS-FLI protein is an aberrant transcription factor that initiates an altered transcription program, driving or suppressing the expression of more than 500 genes and, thus promoting oncogenesis[5]. Ewing sarcoma is, therefore, a transcription-addicted tumor that depends on the activity of an aberrant transcription factor for the maintenance of the malignant phenotype.

A similar situation is observed in neuroblastoma, a poor prognosis embryonal tumor affecting the sympathetic nervous system of infants. About 20% of neuroblastomas carry amplifications of MYCN gene, but an additional proportion overexpress MYCN without gene amplification[6,7]. N-MYC is a master regulator of transcription that can activate genes that affect cancer hallmarks, such as sustained growth, and repress genes that drive differentiation[8]. Neuroblastoma cell lines with amplification of MYCN show increased proliferation, downregulation of angiogenesis inhibitors, inhibition of terminal differentiation and increased invasive potential[9]. Since the discovery of the overexpression of MYCN in retinoblastoma, many efforts have been made to target this transcription factor and impair its function. Therefore, cancer cells are addicted to the transcription factors that drive these aberrant transcriptional programs, providing good opportunities for therapeutic intervention[2].

Lurbinectedin, structurally related to trabectedin but differing by the presence of a tetrahydro-B-carboline replacing the third tetrahydroisoquinoline ring of trabectedin, is currently undergoing phase III clinical evaluation in ovarian (clinicaltrials.gov identifier: NCT02421588) and small cell lung cancer (clinicaltrials.gov identifier: NCT02566993). We have recently shown that lurbinectedin inhibits the transcription process by (1) its binding to CG-rich sequences, mainly located around promoters of protein-coding genes; (2) the irreversible stalling of elongating RNA Pol II on the DNA template and its specific degradation by the ubiquitin/proteasome machinery; and (3) the generation of DNA breaks and subsequent apoptosis[10]. Furthermore, lurbinectedin has been shown to functionally inactivate EWS-FLI1 aberrant transcription factor in Ewing sarcoma, by removing the protein from its target sequences and redistributing it into the nucleolus[11]. Therefore, there is a mechanistic rational for the treatment of transcription-addicted tumors, including Ewing sarcoma or neuroblastoma, with the transcription inhibitor lurbinectedin.

3. REGULATORY HISTORY

The initial Investigational New Drug Application for lurbinectedin for the treatment of solid tumors IND 103556, went into effect on December 15, 2008.

Over 19 trials in adults have been initiated in the US, European Union and other countries from which 5 clinical trials have been completed and 14 trials are on-going.

Lurbinectedin received Orphan Drug Designation in the US (Designation number: 12-3765; OD number: 099/12) on August 20, 2012 and in the European Union (EU/3/12/1053) on October 10, 2012.

PREA states, "Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under section 526" FDA has not issued regulations applying PREA to orphan-designated indications. Thus, submission of a pediatric assessment is not required for lurbinectedin in the treatment of ovarian cancer and waivers are not needed at this time.

On October 10, 2016 the FDA agreed on a full waiver for the Initial Pediatric Study Plan (Agreed iPSP) for treatment of patients with extensive stage, small cell lung cancer (SCLC) that has progressed following platinum-containing chemotherapy.

A request to the Paediatric Committee (PDCO) will be made to confirm that the scope of the EMA decision on class waivers in ovarian cancer and small cell lung cancer are applicable to lurbinectedin.

Lurbinectedin is not currently approved for marketing in any country.

4. PRECLINICAL DATA SUPORTING CLINICAL STUDIES

4.1. Nonclinical Pharmacokinetics

In nonclinical species (e.g., mice, rats, dogs and cynomolgus) the plasma concentration-time profile of lurbinectedin displayed multi-compartmental kinetics following single i.v. administration. Plasma levels dropped rapidly, followed by a much more gradual decrease. The terminal elimination half-lives ($t_{1/2}$) were long, with a relatively slow plasma clearance (CL). No gender differences in the volume of distribution at steady state (Vss) were seen. Since Vss was much higher than plasma volume for all animal species tested, an extensive extravascular distribution of lurbinectedin was likely to occur. Toxicokinetic evaluations (in rats and dogs) showed that C_{max}s and AUCs were proportional to dose, up to the MTD, either after single or repeated (up to 4 cycles) administration; however, some degree of compound accumulation (ca. 3-fold) was found on Day 64 compared to Day 1 in rats.

Lurbinectedin was highly protein-bound in vitro. Tissue distribution studies in rats showed that ^{14}C-lurbinectedin related radioactivity was quickly distributed, maximum concentrations recorded in spleen, liver, lymph nodes, thyroid glands, lung, kidney and small intestine; the lowest radioactivity concentrations were detected in the brain and testes. In a ADME rat study, the primary route of excretion was demonstrated to be the feces (mean cumulative excretion ca. 91% up to 168 h post-dose). Urine represented a very minor route of excretion (ca. 3%). Only 3 to 6% of the radioactivity dosed was still present in the carcass at 168 h post-dose.

In vitro, oxidative metabolism of lurbinectedin was very intensive and mainly dominated by CYP3A4.

4.2. Nonclinical Safety, Toxicity and Development Plan

Nonclinical safety pharmacology studies did not raise concern related to either neurotoxicity, cardiovascular o respiratory functions.

In pivotal studies in dog (up to 4 cycles), rat and cynomolgus (both, up to 8 cycles -ongoing-), clinical effects were limited to transient body weight decreases, soft feces and/or diarrhea and/or emesis. Mortality was related to bone marrow suppression, gastrointestinal and hepatic alterations. Lurbinectedin reversibly affected the hematopoietic system, mainly reducing reticulocytes and white blood cells and inducing a slight anemia, as well as bone marrow depletion and atrophy of the lymphoid system. Hepatotoxicity was characterized by markedly increased liver function tests, hepatocellular necrosis and biliary damage. Hepatotoxicity was much less pronounced in nonrodent studies. Other target organs were the gastrointestinal mucosa (atrophy), adrenal gland (cortical hypertrophy) and kidney (cortical tubular vacuolization). In summary the main toxic effects of lurbinectedin –transient bone marrow suppression and hepatotoxicity- are rather commonly seen in compounds that disrupts the cell cycle. Injection site lesions (perivascular hemorrhage, moderate inflammation, edema and chronic phlebitis, necrosis and ulceration) were also seen in studies regardless of the animal species used. On the basis of the in vitro results, lurbinectedin was scored as predictive of a non-phototoxicity inducer.

These preclinical findings suggest that the use of lurbinectedin likely will have similar effects in the pediatric population and therefore specific studies in juvenile animals may be not required.

5. CLINICAL TRIALS EXPERIENCE IN ADULTS

5.1. Overview

A total of 1204 adult patients with solid tumors or hematological malignancies were included in 19 clinical trials with lurbinectedin up to 15 January 2017. These 19 trials comprised ten phase 1 trials, five phase 2 trials, two phase 3 trials, and two investigator-sponsored trials (ISTs), and evaluated lurbinectedin alone or in combination with other drugs (e.g., doxorubicin [DOX], gemcitabine [GEM], capecitabine, paclitaxel with or without bevacizumab, cisplatin [CDDP], irinotecan, or olaparib). Clinical indications under investigation include ovarian cancer, small cell lung cancer (SCLC), metastatic breast cancer (MBC), endometrial cancer, non-small cell lung cancer (NSCLC), Ewing family of tumors (EFT), advanced acute leukemia (AAL), myelodysplastic syndrome (MDS), and other tumor types.

Single-agent lurbinectedin has shown antitumor activity in several indications, including ovarian cancer, SCLC, MBC, endometrial cancer, EFT, biliary tract carcinoma and neuroendocrine tumors (NET). Antitumor activity has also been found for combinations of lurbinectedin with other drugs (e.g., DOX, GEM, capecitabine, paclitaxel and cisplatin) in several tumor types.

The first-in-human phase 1 trial (PM1183-A-001-08) evaluated single-agent intravenous (i.v.) lurbinectedin infused over one hour on Day (D) 1 every three weeks (q3wk) in patients with advanced and refractory solid tumors. The single-agent recommended dose (RD) for phase 2 studies was 4.0 mg/m^2 (equivalent to 7.0 mg flat dose [FD]) on D1 q3wk. However, a pooled data logistic regression analysis of phase 2 data suggested that grade 3/4 neutropenia and thrombocytopenia could be related to body surface area (BSA). Following this finding, a BSA-based dosing strategy has been adopted in all ongoing and planned studies to limit severe myelosuppression. In addition, the original RD of 4.0 mg/m^2 on D1 q3wk has been reduced by 20% to 3.2 mg/m^2 on D1 q3wk to further limit myelosuppression. Analysis of preliminary safety data from phase 2 studies has suggested that lurbinectedin given at 3.2 mg/m^2 results in a lower incidence of grade 3/4 hematological and biochemical abnormalities, and of treatment-related gastrointestinal disorders and fatigue, compared to 7.0 mg FD.

Lurbinectedin has a predictable and manageable safety profile. Reversible myelosuppression is the toxicity most frequently related to treatment with lurbinectedin, but is non-cumulative and mostly asymptomatic, and managed with dose adjustment and secondary prophylaxis with growth factors. Other treatment-related adverse events (AEs) are mostly grade 1 or 2, and manageable with dose adjustments or with standard prophylaxis.

5.2. Pharmacokinetics of Lurbinectedin

The pharmacokinetics of lurbinectedin has been characterized in adult patients in multiple clinical trials administered as 1-hour i.v. infusions in two schedules of cycles of three weeks. The dosing days of these schedules were Day (D) 1; and D1 and D8. Lurbinectedin administered at the RD of 4.0 mg/m^2 or 7.0 mg FD on D1 q3wk had a mean total plasma clearance (CL) of 12.5 L/h, a mean terminal half-life ($t_{½}$) of 62.7 h and a mean volume of distribution at steady-state (V_{ss}) of 487 L in Cycle 1. When[12] given at the RD of 5.0 mg FD on D1 and D8 q3wk, mean CL was 19.5 L/h, mean $t_{½}$ was 35.8 h, and mean V_{ss} was 557 L in Cycle 1[13]. These parameters showed linearity over the explored dose range and a high variability among patients.

5.3. Clinical Efficacy of Lurbinectedin

Fifteen ongoing trials are being conducted with lurbinectedin, either alone or combined with other antitumor drugs, in solid tumors and hematological malignancies. The most advanced clinical development is in ovarian cancer, SCLC, MBC and endometrial cancer. Clinical efficacy data from patients with these tumors treated with lurbinectedin alone or in combination with other drugs are presented below.

5.3.1. Ovarian Cancer

The efficacy and safety of lurbinectedin alone or in combination with other drugs in ovarian cancer is being evaluated in five clinical trials: three ongoing phase 1 trials of lurbinectedin in combination with GEM (PM1183-A-004-10)[14], paclitaxel (PM1183-A-007-13)[15] or CDDP (PM1183-A-008-13)[16]; one completed single-agent phase 2 trial (PM1183-B-002-11)[17] and one ongoing single-agent phase 3 trial (PM1183-C-004-14). Key features of these trials are shown in Table 2.

Table 2. Key design features of studies PM1183-A-004-10, PM1183-A-007-13, PM1183-A-008-13, PM1183-B-002-11 and PM1183-C-004-14 in patients with ovarian cancer.

Study	**PM1183-A-004-10**	**PM1183-A-007-13**	**PM1183-A-008-13**	**PM1183-B-002-11**		**PM1183-C-004-14**	
Phase	Phase 1	Phase 1	Phase 1	Phase 2		Phase 3	
Patient population	Advanced solid tumors	Advanced and/or unresectable solid tumors	Advanced solid tumors	Platinum resistant/refractory advanced epithelial ovarian, fallopian tube or primary peritoneal cancer [a]		Platinum-resistant ovarian cancer	
Previous treatment	≤2 lines of chemotherapy for advanced disease	≤3 lines of chemotherapy for advanced disease	≤2 lines of chemotherapy for advanced disease	<3 lines of chemotherapy for advanced disease		≤3 lines of systemic chemotherapy	
No. of planned patients	36	60	50	48 [b]	30	210	210
Treatment dose and schedule	Lurbinectedin 2.5-3.5 mg FD 1-hour i.v. on D1,D8 q3wk + GEM 800-1000 mg/m^2 i.v. on D1,D8 q3wk	Lurbinectedin 3.0-5.0 mg FD or 2.2 mg/m^2 1-hour i.v. on D1 q3wk + Paclitaxel 60-80 mg/m^2 1-hour i.v. on D1,D8 q3wk or Lurbinectedin 2.2 mg/m^2 1-hour i.v. on D1 q3wk + Paclitaxel 60 mg/m^2 1-hour i.v. on D1,D8	Lurbinectedin 0.5-1.7 mg/m^2 1-hour i.v. on D1 q3wk + CDDP 60 mg/m^2 90-min i.v. on D1 q3wk	**Experimental Arm:** Lurbinectedin 7.0 mg FD 1-hour i.v. on D1 q3wk	**Control Arm:** Topotecan 30-min i.v. on D1-5 q3wk or on D1,D8,D15 q4wk [c]	**Experimental Arm:** Lurbinectedin 3.2 mg/m^2 1-hour i.v. on D1 q3wk	**Control Arm:** PLD 50 mg/m^2 i.v. on D1 q4wk or Topotecan 30-min i.v. on D1-5 q3wk [c]

Study	PM1183-A-004-10	PM1183-A-007-13	PM1183-A-008-13	PM1183-B-002-11		PM1183-C-004-14	
		q3wk + BEV 15 mg/kg on D1 q3wk					

[a] Advanced disease was defined as FIGO stages IIC through IV.

[b] Of these 48 patients, 18 in the first stage and 30 in the second stage.

[c] Topotecan dose depended on the patient's ECOG PS score, baseline calculated CrCL value, and number of prior chemotherapy lines for advanced disease.

BEV, bevacizumab; CDDP, cisplatin; CrCL, creatinine clearance; D, Day; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, flat dose; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; GEM, gemcitabine; i.v., intravenous; PLD, pegylated liposomal doxorubicin; q3wk, every three weeks; q4wk, every four weeks.

The three phase 1 trials are multicenter, dose-ranging studies conducted in patients with advanced solid tumors previously treated with up to two (PM1183-A-004-10 or PM1183-A-008-13), or three (PM1183-A-007-13) prior lines of chemotherapy for advanced disease. The maximum tolerated dose (MTD) and the RD of each combination regimen is the primary endpoint of these trials, while their antitumor activity according to the Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 is a secondary endpoint. In these studies, the highest overall response rate (ORR) in advanced ovarian cancer patients was reported for lurbinectedin/paclitaxel with or without BEV. Response was observed in one of three evaluable patients treated with lurbinectedin/paclitaxel and in all three evaluable patients treated with lurbinectedin/paclitaxel/BEV, including one complete response [CR])[15]. Partial responses (PR) were also observed with lurbinectedin/GEM (two of five patients)[14], and with lurbinectedin/CDDP (one of five patients)[16].

The multicenter, phase 2 trial (PM1183-B-002-11) evaluated single-agent lurbinectedin in patients with platinum resistant/refractory ovarian cancer (PRROC) pretreated with less than three chemotherapy-containing lines for advanced disease. The trial was divided into two stages. The first one was an exploratory, single-arm stage to assess the clinical activity of lurbinectedin in this setting. Once efficacy had been observed, the trial proceeded onto a controlled second stage that randomized patients to lurbinectedin or topotecan (standard or weekly regimen, investigator's choice) as control arm. Patients assigned to the topotecan arm were allowed to cross-over to the lurbinectedin arm after disease progression. The primary efficacy endpoint was the ORR according to RECIST v.1.1 or Gynecologic Cancer Intergroup (GCIG) criteria. Twelve responses (one CR and 11 PR) were observed among 52 evaluable patients treated with lurbinectedin (ORR=23%). Ten of these 12 responses occurred among 33 patients with platinum-resistant disease, and the other two among 19 patients with platinum-refractory disease. Median progression-free survival (PFS) was 4.0 months for all patients treated with lurbinectedin, and 5.0 months for those with platinum-resistant disease. In addition, two of 15 topotecan-treated patients who crossed over to the experimental arm also responded to lurbinectedin[17].

Following these findings, an ongoing multicenter, open-label, randomized, controlled phase 3 trial (PM1183-C-004-14) is evaluating the antitumor activity and safety of single-agent lurbinectedin *vs.* pegylated liposomal doxorubicin (PLD) or topotecan in patients with platinum-resistant ovarian cancer previously treated with no more than three prior systemic chemotherapy regimens. The primary efficacy endpoint is the PFS, evaluated by an Independent Review Committee. No efficacy data are available yet.

5.3.2. Small Cell Lung Cancer

The efficacy and safety of lurbinectedin alone or in combination with other antitumor drugs in patients with advanced and/or unresectable SCLC are being evaluated in four studies: two phase 1 trials of lurbinectedin combined with DOX (PM1183-A-003-10)[18] or paclitaxel (PM1183-A-007-13)[15], one phase 2 trial of single-agent lurbinectedin (PM1183-B-005-14), and one phase 3 trial of lurbinectedin combined with DOX (PM1183-C-003-14). All four trials were ongoing. Key features of these trials are shown in Table 3.

Table 3. Key design features of studies PM1183-A-003-10, PM1183-007-13, PM1183-B-005-14 and PM1183-C-003-14 in patients with small cell lung cancer.

Study	**PM1183-A-003-10**	**PM1183-A-007-13**	**PM1183-B-005-14**	**PM1183-C-003-14**	
Phase	Phase 1	Phase 1	Phase 2	Phase 3	
Patient population	Advanced solid tumors	Advanced and/or unresectable solid tumors	Advanced selected solid tumors	Limited or extensive stage SCLC with a CTFI ≥ 30 days	
Previous treatment	≤1 or ≤2 lines of chemotherapy for advanced disease	≤3 lines of chemotherapy for advanced disease	1 line of chemotherapy	1 platinum-containing regimen	
No. of planned patients	100	60	100 [a]	300	300
Treatment dose and schedule	Lurbinectedin 3.0-5.0 mg FD 1-hour i.v. on D1 q3wk + DOX 50 mg/m^2 i.v. on D1 q3wk, or Lurbinectedin 2.0 mg/m^2 1-hour i.v. on D1 q3wk + DOX 40 mg/m^2 i.v. on D1 q3wk	Lurbinectedin 3.0-5.0 mg FD or 2.2 mg/m^2 1-hour i.v. on D1 q3wk + Paclitaxel 60-80 mg/m^2 1-hour i.v. on D1,D8 q3wk	Lurbinectedin 3.2 mg/m^2 1-hour i.v. on D1 q3wk	**Experimental Arm:** Lurbinectedin 2.0 mg/m^2 1-hour i.v. on D1 q3wk + DOX 40 mg/m^2 i.v. on D1 q3wk	**Control Arm:** Investigator's choice between CAV or topotecan

[a] Patients with SCLC to be included in this study.

CAV, cyclophosphamide, doxorubicin and vincristine; CTFI, chemotherapy-free interval; D, day; DOX, doxorubicin; FD, flat dose; i.v., intravenous; q3wk, every three weeks; SCLC, small cell lung cancer.

The PM1183-A-003-10 phase 1 trial is a multicenter, dose-ranging study that enrolled patients with advanced solid tumors pretreated with up to two lines of chemotherapy for advanced disease. The MTD and the RD of the lurbinectedin/DOX combination is the primary endpoint of the study, and its antitumor activity evaluated according to RECIST v.1.1 is a secondary endpoint. The design of the PM1183-A-007-13 phase 1 trial is detailed in Section 5.3.1. Response to lurbinectedin/DOX in the PM1183-A-003-10 study was found in 14 of 21 evaluable SCLC patients treated as second-line (ORR=67%, including one CR)[18]. In the PM1183-A-007-13 study, four of five SCLC patients responded at the RD to lurbinectedin/paclitaxel[15].

The single-agent phase 2 trial (PM1183-B-005-14) is a multicenter study designed to establish or confirm proof of concept of lurbinectedin anticancer activity in several difficult-to-treat tumors. Previously treated patients with advanced SCLC, head and neck carcinoma, neuroendocrine tumors, biliary tract carcinoma, endometrial carcinoma, BRCA1/2-associated MBC, carcinoma of unknown primary site, germ cell tumors, and EFTs are being enrolled in separate cohorts. The primary efficacy endpoint is the ORR, with antitumor activity evaluated

as per RECIST v.1.1. Up to 100 patients with advanced SCLC are expected to participate in this study. No efficacy data are available yet.

Based on the findings of the PM1183-A-003-10 trial, a multicenter, open-label, randomized, controlled phase 3 trial (PM1183-C-003-14) has been started to compare the efficacy and safety of the lurbinectedin/DOX combination *vs.* best Investigator's choice between cyclophosphamide, DOX and vincristine (CAV) or topotecan in SCLC patients previously treated with one prior platinum-containing line but no more than one prior chemotherapy-containing line. The primary efficacy endpoint is the PFS, evaluated by an Independent Review Committee. Approximately 600 patients will be stratified and randomized at a 1:1 ratio in this study. No efficacy data are available yet.

5.3.3. Metastatic Breast Cancer

The efficacy and safety of lurbinectedin alone or in combination with other drugs in patients with advanced MBC are being evaluated in six studies: four phase 1 trials of lurbinectedin combined with DOX (PM1183-A-003-10)[19], GEM (PM1183-A-004-10)[14], capecitabine (PM1183-A-006-12)[20] or paclitaxel (PM1183-A-007-13)[15], and two phase 2 trials of single-agent lurbinectedin (PM1183-B-003-11)[21] and PM1183-B-005-14). One of these studies (PM1183-A-004-10) had been completed prior to January 2017 and the other five were still ongoing. Key features of these trials are shown in Table 4.

Table 4. Key design features of studies PM1183-A-003-10, PM1183-A-004-10, PM1183-A-006-12, PM1183-007-13, PM1183-B-003-11 and PM1183-B-005-14 in patients with metastatic breast cancer.

Study	**PM1183-A-003-10**	**PM1183-A-004-10**	**PM1183-A-006-12**	**PM1183-A-007-13**	**PM1183-B-003-11**	**PM1183-B-005-14**
Phase	Phase 1	Phase 1	Phase 1	Phase 1	Phase 2	Phase 2
Patient population	Advanced solid tumors	Advanced solid tumors	Advanced solid tumors	Advanced and/or unresectable solid tumors	BRCA1/2-associated or unselected advanced MBC	Advanced selected solid tumors
Previous treatment	≤1 line of chemotherapy for advanced disease	≤2 lines of chemotherapy for advanced disease	≤2 lines of chemotherapy for advanced disease	≤3 lines of chemotherapy for advanced disease	≤3 lines of chemotherapy for advanced disease	1 line of chemotherapy
No. of planned patients	100	36	40	60	110	25 [a]
Treatment dose and schedule	Lurbinectedin 3.0-5.0 mg FD 1-hour i.v. on D1 q3wk + DOX 50 mg/m^2 i.v. on D1 q3wk	Lurbinectedin 2.5-3.5 mg FD 1-hour i.v. on D1,D8 q3wk + GEM 800-1000 mg/m^2 i.v. on D1,D8 q3wk	Lurbinectedin 2.0-3.0 mg FD 1-hour i.v. on D1,D8 q3wk + Capecitabine 1650 mg/m^2 p.o. D1-D14 q3wk or Lurbinectedin 3.0-5.0 mg FD or 2.8 mg/m^2 1-hour i.v. on D1 q3wk + Capecitabine 1650-	Lurbinectedin 3.0-5.0 mg FD or 2.2 mg/m^2 1-hour i.v. on D1 q3wk + Paclitaxel 60-80 mg/m^2 1-hour i.v. on D1,D8 q3wk	Lurbinectedin 7.0 mg FD or 3.5 mg/m^2 1-hour i.v. on D1 q3wk	Lurbinectedin 3.2 mg/m^2 1-hour i.v. on D1 q3wk

Study	PM1183-A-003-10	PM1183-A-004-10	PM1183-A-006-12	PM1183-A-007-13	PM1183-B-003-11	PM1183-B-005-14
			2000 mg/m^2 p.o. on D1-D14 q3wk			

[a] Patients with MBC to be included in this study.

D, day; DOX, doxorubicin; FD, flat dose; GEM, gemcitabine; i.v., intravenous; MBC, metastatic breast cancer; p.o., orally; q3wk, every three weeks.

The PM1183-A-006-12 phase 1 trial is a multicenter, dose-ranging study that enrolled patients with advanced solid tumors pretreated with up to two lines of chemotherapy for advanced disease. The MTD and the RD of the lurbinectedin/capecitabine combination is the primary endpoint of the study, and its antitumor activity as per RECIST v.1.1 is a secondary endpoint. The design of the PM1183-A-003-10, PM1183-A-004-10 and PM1183-A-007-13 phase 1 trials is detailed in Sections 5.3.1 and 5.3.2. Overall response rates were reported in advanced MBC patients enrolled in these studies: for lurbinectedin combined with DOX (one CR and one PR in three evaluable patients)[19], with paclitaxel (four PRs in eight evaluable patients)[15], and with capecitabine (one CR and 13 PR in 25 evaluable patients; ORR=56%)[20]. In addition, lurbinectedin combined with GEM resulted in one PR among six evaluable patients[14].

Response to single-agent lurbinectedin was found in MBC patients enrolled in the phase 2 trial PM1183-B-003-11. In this study, patients with advanced MBC were divided into different cohorts depending on their BRCA1/2 mutation status. The primary endpoint was the ORR as per RECIST v.1.1. A total of one CR and 21 PRs were observed among 54 evaluable patients with BRCA1/2-mutated MBC (ORR=41%), including 61% of patients with BRCA2 mutations[21].

In addition, up to 25 patients with BRCA1/2-associated MBC will be included in the ongoing phase 2 trial PM1183-B-005-14 (see description in Section 5.3.2); no efficacy data are available yet.

5.3.4. Endometrial Cancer

The efficacy and safety of lurbinectedin alone or in combination in patients with advanced endometrial cancer is being evaluated in three ongoing studies: two phase 1 trials of lurbinectedin combined with DOX (PM1183-A-003-10)[19] or paclitaxel (PM1183-A-007-13)[15], and one phase 2 trial of single-agent lurbinectedin (PM1183-B-005-14). Key features of these trials are shown in Table 5.

Table 5. Key design features of studies PM1183-A-003-10, PM1183-007-13 and PM1183-B-005-14 in patients with endometrial cancer.

Study	PM1183-A-003-10	PM1183-A-007-13	PM1183-B-005-14
Phase	**Phase 1**	**Phase 1**	**Phase 2**
Patient population	Advanced solid tumors	Advanced and/or unresectable solid tumors	Advanced selected solid tumors
Previous treatment	≤1 line of chemotherapy for advanced disease	≤3 lines of chemotherapy for advanced disease	1 line of chemotherapy
No. of planned patients	100	60	50 [a]
Treatment dose and schedule	Lurbinectedin 3.0-5.0 mg FD 1-hour i.v. on D1 q3wk + DOX 50 mg/m^2 i.v. on D1 q3wk	Lurbinectedin 3.0-5.0 mg FD or 2.2 mg/m^2 1-hour i.v. on D1 q3wk + Paclitaxel 60-80 mg/m^2 1-hour i.v. on D1,D8 q3wk	Lurbinectedin 3.2 mg/m^2 1-hour i.v. on D1 q3wk

[a] Patients with endometrial cancer to be included in this study.

D, day; DOX, doxorubicin; FD, flat dose; i.v., intravenous; q3wk, every three weeks.

The design and primary endpoints of these three trials have been described in Section 5.3.2.

In the phase 1 trials, response to the combination regimens in endometrial cancer patients comprised one CR and one PR in three evaluable patients treated with lurbinectedin/DOX in trial PM1183-A-003-10[19], and three PRs in 11 evaluable patients treated with lurbinectedin/paclitaxel in trial PM1183-A-007-13[15].

In addition, up to 50 patients with advanced endometrial cancer will be included in the ongoing PM1183-B-005-14 phase 2 trial (see Section 5.3.2); no efficacy data are available yet.

5.4. Clinical Safety of Lurbinectedin

As of 15 January 2017, 1204 patients with various solid tumors or hematological malignancies had been treated with lurbinectedin, alone or in combination, in clinical trials and investigator-sponsored trials. Analysis of clinical data from these studies showed that lurbinectedin has a predictable and manageable safety profile, and that tolerance is acceptable.

Reversible myelosuppression (mostly consisting of neutropenia and thrombocytopenia) was the most consistent and frequent toxicity due to treatment with lurbinectedin, either as a single agent or in combination with other antitumor agents, in adult patients with solid tumors. Myelosuppression was predictable, transient, non-cumulative and mostly asymptomatic, and was managed with dose adjustment and secondary granulocyte colony-stimulating factor (G-CSF) prophylaxis. A pooled data logistic regression analysis suggested that severe neutropenia and thrombocytopenia could be related to BSA. Owing to these findings, a BSA-based dosing strategy is now being used in ongoing and actively recruiting studies, as well as in planned studies, to limit severe myelosuppression. Available data from phase II studies suggested that myelosuppression is less severe with a BSA-based RD of 3.2 mg/m^2 q3wk compared to its equivalent flat dose of 7.0 mg q3wk.

Other treatment-related adverse events (AEs) commonly reported in patients treated with lurbinectedin comprised nausea, fatigue, and vomiting, and less frequently decreased appetite, diarrhea, constipation, alopecia, pyrexia, dysgeusia, abdominal pain, dyspnea, phlebitis and stomatitis. Most of these AEs were grade 1 or 2 in intensity, and were manageable with dose

adjustments or, in the case of nausea and vomiting, with standard antiemetic prophylaxis. Abnormal liver function blood tests were also observed, but were usually asymptomatic.

6. CLINICAL TRIALS WITH RELEVANCE TO PEDIATRICS, ADOLESCENTS AND YOUNG ADULTS

Two ongoing clinical trials with single-agent lurbinectedin have provided evidence of antitumor activity in indications potentially relevant to pediatrics, adolescents and young adults. These indications are advanced acute leukemia, relapsed/refractory MDS (in trial PM1183-A-002-10), and cancers belonging to the EFT (in trial PM1183-B-005-14). The key design features of these trials are shown in Table 6, and clinical efficacy data from these trials are presented below.

Table 6. Key design features of studies PM1183-A-002-10 and PM1183-B-005-14 in patients with and Ewing family of tumors.

Study	**PM1183-A-002-10**	**PM1183-B-005-14**
Phase	Phase 1	Phase 2
Patient population	Advanced acute leukemia or relapsed/refractory myelodysplastic syndrome	Advanced selected solid tumors
Previous treatment	Hematopoietic allogeneic stem cell transplantation not within four months before treatment onset, or autologous transplantation not within four weeks before treatment onset	≤2 lines of chemotherapy in the metastatic/recurrent setting
No. of planned patients	50	25 [a]
Treatment dose and schedule	Lurbinectedin 3.5-7.0 mg FD 1-hour i.v. on D1, D8 q3wk, or 1.0-3.0 mg FD 1-hour i.v. on D1-D3 q3wk	Lurbinectedin 3.2 mg/m^2 1-hour i.v. on D1 q3wk

[a] Patients with EFT to be included in this study.

D, day; EFT, Ewing family of tumors; FD, flat dose; i.v., intravenous; q3wk, every three weeks.

6.1. Advanced Acute Leukemia and Relapsed/refractory Myelodysplastic Syndrome

Study PM1183-A-002-10 is a multicenter, open-label, dose-ranging, phase 1 trial designed to determine the MTD and RD of single-agent lurbinectedin administered as 1-hour i.v. infusion on D1 and D8 q3wk or on D1-D3 q3wk in patients with AAL or MDS. Patients first received induction treatment with lurbinectedin according to the schedule allocated. Re-induction was allowed in case of persistent leukemia. Subsequent consolidations were allowed if ≤5% blasts were present in the bone marrow. Patients showing less than partial remission and no evidence of progression could receive further treatment, if considered in their benefit. The antileukemic activity of lurbinectedin was a secondary endpoint of the trial, and was evaluated according to the International Working Group (IWG) criteria for acute myeloid leukemia (AML) and MDS, to standard criteria for acute lymphoblastic leukemia (ALL), or to specific guidelines for chronic myeloid leukemia in blastic phase (CMLBP).

Thirty-five patients were treated with lurbinectedin and were evaluable for efficacy. No objective responses to treatment were observed; only three patients with AML (n=2) or CMLBP (n=1) showed short-lasting decreases in bone marrow blast cell counts.

6.2. Ewing Family of Tumors

The design and endpoints of the PM1183-B-005-14 phase 2 trial have been described in section 5.3.2. Up to March 2017, 20 patients treated with lurbinectedin in this study had EFT. Most of these patients (n=13, 65%) were male. At baseline, 19 of these patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 (n=11, 55%) or 1 (n=8, 40%). Fourteen patients (70%) had two or less sites of disease and six (30%) had three or more sites of disease. Most patients had received one (n=4, 20%) or two (n=12, 60%) prior lines of chemotherapy.

Preliminary efficacy data were available from 14 evaluable patients in March 2017. Three of these patients showed PR to single-agent lurbinectedin (ORR=21%) and seven more had disease stabilization. Of note, six patients (two with PR and four with disease stabilization) were still showing no evidence of disease progression at the time of evaluation.

7. PROPOSED PEDIATRIC DEVELOPMENT PLAN

7.1. Overview of the Diseases Included in the Pediatric Plan

Cancer is the leading medical cause of death beyond infancy in children and young people in developed countries, responsible for some 6,000 deaths every year in Europe.

The National Cancer Institute determined that approximately 10,270 new cases of cancer would present for children under the age of 14 in the United States in 2017, and more than 1,000 children will die from the disease.[22]

The recently published SIOPE Strategic Plan for 2015 to 2020 sets out three main groups of childhood cancers:

- Those with a good prognosis (with a higher than 85 per cent chance of survival after five years) under current standard multi-disciplinary treatments (acute lymphoblastic leukemia, lymphomas, retinoblastoma, renal tumors);
- Those with a poor prognosis (~50% or less five year survival), such as acute myeloid leukemia, several central nervous system (CNS) tumors, neuroblastoma, bone and soft tissue sarcomas. Among these diseases, some have a very poor prognosis, such as diffuse intrinsic pontine glioma, high-risk neuroblastoma and metastatic sarcomas;
- The extremely rare tumors, for which there is insufficient information on their real incidence and survival.

The group of cancers with poor prognosis is the most difficult to treat, and they require innovative new treatments with new mechanisms of action.

Lurbinectedin has antitumor activity against different solid tumor types, and it would provide benefit in some tumors belonging to this group.

The novel mechanism of action of lurbinectedin, plus the preclinical and clinical activity seen thus far, warrant investigation in the pediatric population.

The mechanism of action of lurbinectedin suggests that it inactivates oncoprotein EWS-FLI1 and inhibits MYC; therefore, it might be of great therapeutic utility in pediatric cancer, specifically in Ewing sarcoma (ES) and neuroblastoma.

Tissue distribution studies have shown that lurbinectedin is quickly distributed, with maximum concentrations recorded in spleen, liver, lymph nodes, thyroid glands, lung, kidney and small intestine. The lowest radioactivity concentrations have been detected in the brain

and testes. Hence, it would be not suitable for conducting studies with lurbinectedin to treat CNS tumors.

However, there is still a considerable number of pediatric patients with ES and neuroblastoma who have large non-operable tumors, metastatic disease, or whose disease relapses or is refractory to current therapeutic options. Effective novel therapies are required to address this unmet medical need.

7.1.1. Ewing Sarcoma

Based on the International Classification of Childhood Cancer v.3, extraosseous Ewing tumors, Askin tumors of soft tissue and peripheral primitive neuroectodermal tumors of soft tissue were included in a single category: EFT[23].

Because of their similar histological and immunohistochemical characteristics, and their shared non-random chromosomal translocations, these tumors are considered to be derived from a common cell of origin, although the histogenic origin of this cell is debated.

Epidemiology

ES is the second most common primary malignant bone tumor, after osteosarcoma. It also occurs in soft tissues, with an incidence of 2.9 per million. In America it is responsible for 3.5 percent of cancers in children aged 10 to 14 years old. The peak incidence is between 10 to 15 years of age. However, 30 percent of cases arise in children under the age of 10 years, and another 30 percent occur in adults over the age of 20 years[24].

Pathophysiology

ES can develop in almost any bone or soft tissue, but it is most common in the pelvis, the axial skeleton, and the femur.

ES is characterized by the transcription factor oncoprotein EWS/FLI, which is encoded by the t(11;22)(q24;q12) chromosomal translocation. EWS/FLI isoforms are found in over 85% of ES cases and are required for the cancerous phenotype of ES cells. Some studies suggest that the type 1 isoform of EWS/FLI conferred a survival advantage for patients with ES[25].

Diagnosis

The most common initial symptom of ES is pain (observed in 85% of children) or swelling (observed in 60% of them). Other common symptoms are a palpable mass and pathological fracture. The presence of systemic symptoms, such as weight loss and fever, may initially lead to an erroneous diagnosis (e.g., osteomyelitis). ES involves flat bones and diaphyses of tubular bones, with almost equal frequency, and may occasionally arise in soft tissues. Approximately 20-25% of patients with ES have metastatic disease at the time of diagnosis, with lungs (50%), bone (25%), and bone marrow (25%) being the most common sites of metastases[26].

The goals of the initial evaluation are to establish the diagnosis, to evaluate local disease extent, and to determine the presence and sites of metastatic spread. Disease extent is determined using bone scan, magnetic resonance imaging (MRI), computed tomography scan of the primary site and the chest, bilateral bone marrow biopsies and aspirates prior to the start of treatment. The site of the primary tumor shows a relationship with the presence of metastatic disease at the time of diagnosis[27].

Currently Available Treatments

Local control in patients with ES may be achieved via surgery, radiation, or both. No prospective randomized studies have evaluated the merits of different local control modalities. Although nearly all prospective studies suggest improved local control and event free survival

(EFS) outcomes for patients receiving surgery, those receiving radiotherapy generally have adverse prognostic factors (e.g., large tumor size) that likely contribute to their poorer outcomes.

Patients with apparently localized disease have only a 10 to 20 percent likelihood of cure if treated with surgery or radiotherapy alone; this is improved dramatically when chemotherapy is added to treatment. Active agents for ES include vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide, and actinomycin.

Despite the fact that fewer than 25 percent of patients have overt metastases at the time of diagnosis, ES is a systemic disease. Because of the high relapse rate (80 to 90 percent) in patients undergoing local therapy alone, it is surmised that the majority of patients have subclinical metastatic disease at the time of diagnosis, even in the absence of overt metastases[28].

Long-term follow-up is needed following therapy because disease relapse, treatment-related complications, and second malignancies all occur beyond five years after treatment is initiated.

Prognosis

Patients with metastatic ES, especially with metastases outside the lung, have a dismal prognosis. The role of mega-therapy (high-dose chemotherapy followed by stem cell rescue) in patients with high-risk and/or metastatic or relapsed ES remains quite controversial, with most studies reporting about a 20% to 30% 2-to-3 year EFS. The poor overall survival in patients with metastatic disease has not changed significantly despite decades of research and intense therapy. Because of the poor survival in this group, radiotherapy is often the treatment of choice for local control because long-term risks for second malignancy and morbidity are less of a concern. In addition, short-term or acute toxicity is often less with radiotherapy than with surgery.

The exception is patients with lung only metastases amenable to surgical resection. Current protocols recommend local therapy for all known sites of metastatic disease if possible. Up to 40 percent of patients with limited pulmonary metastatic disease who undergo intensive chemotherapy and pulmonary resection with or without radiation therapy may be long-term survivors. The prognosis for other subsets of patients with advanced disease is less favorable.

Most patients with advanced or recurrent disease need new approaches to improve outcomes, and participation in clinical trials should be encouraged.

7.1.2. Neuroblastoma

Neuroblastoma is an embryonic malignancy of early childhood originating from neural crest cells. Neuroblastoma is the most common solid malignant neoplasm in the pediatric age group. The term neuroblastoma is commonly used to refer to a spectrum of neuroblastic tumors (including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas) that arise from primitive sympathetic ganglion cells.

Epidemiology

It is the third most common childhood cancer, after leukemia and brain tumors, and is the most common solid extracranial tumor in children. More than 600 cases are diagnosed in the United States each year, and neuroblastoma accounts for approximately 15 percent of all pediatric cancer fatalities.

The median age at diagnosis is 17.3 months, and 40 percent of patients are diagnosed before one year of age. Neuroblastomas are the most common extracranial solid malignant tumor

diagnosed during the first two years of life, and the most common cancer among infants younger than 12 months, in whom the incidence rate is almost twice that of leukemia (58 *vs.* 37 per one million infants). The incidence rate of neuroblastoma in the United States is 7.7 cases per million children and is greater among white than black infants (ratio of 1.7 and 1.9 to 1 for males and females, respectively), but little if any racial difference is apparent among older children. Neuroblastoma is slightly more common among boys compared with girls[29].

Pathophysiology

The majority of neuroblastomas are sporadic and not correlated with any specific constitutional germline chromosomal abnormality, inherited predisposition, or associated congenital anomalies. However, some genetic variations play a causal role in neuroblastoma tumorigenesis. For instance, single-nucleotide polymorphisms (SNPs) at LMO1 have been observed in approximately 12 percent of patients with neuroblastoma, and germline mutations in SDHB, APC, ALK, and BRCA2 in 1 of 100 patients with neuroblastoma[30].

Chromosomal deletions have been found in approximately 50 percent of neuroblastomas, and are consistently located in chromosomes 1p, 11q, and 14q.

Deletions of chromosome 1p are highly associated with amplification (increased copy number) and overexpression of the oncogene MYCN (N-myc), a close relative of the oncogene c-myc that resides on chromosome 2p24-25. Gene overexpression results in persistently high levels of the MYCN protein, a DNA binding transcription factor known to cause malignant transformation in both *in vitro* and *in vivo* tumor models. A 50- to 400-fold amplification of MYCN is found in approximately 25 percent of neuroblastomas and is an indicator of poor prognosis[29].

Diagnosis

Neuroblastomas can arise anywhere throughout the sympathetic nervous system. The adrenal gland is the most common primary site (40 percent), followed by abdominal (25 percent), thoracic (15 percent), cervical (5 percent), and pelvic sympathetic ganglia (5 percent). In approximately 1 percent of cases, a primary tumor cannot be identified[29]. Neuroblastoma metastasizes to lymph nodes, bone marrow, cortical bone, dura, orbits, liver, and skin, and less frequently to pulmonary and intracranial sites.

The presenting symptoms reflect the location of the primary tumor and the extent of metastatic disease, if present.

All patients with suspected neuroblastoma should undergo a complete history and physical examination. Most patients will undergo laboratory evaluations including routine blood counts, serum chemistries, tests of liver and kidney function and radiological studies. Evaluation of urine or serum catecholamine metabolite levels, vanillylmandelic acid (VMA), and homovanillic acid (HVA) should be obtained to assist in diagnosis and monitoring of disease response, since levels are elevated in more than 90 percent of patients with neuroblastoma. In addition, ferritin and lactate dehydrogenase (LDH) concentrations may be helpful; they may be elevated initially and can be expected to return to normal during adequate treatment.

Definitive diagnosis of neuroblastoma must be made by histological confirmation or evidence of metastases to bone marrow with concomitant elevation of catecholamines in urine.

Currently Available Treatments

Treatment outcome for patients with neuroblastoma depends upon both tumor and patient characteristics, including stage, histology, MYCN amplification, DNA ploidy, age at diagnosis, extent and site of metastases.

The correct stratification of neuroblastoma patients within risk groups (low, intermediate, high) is critical for the adequate treatment of the patients.

For children with low-risk disease, surgery is the primary treatment modality when complete resection is feasible. For children with intermediate-risk disease, a combined modality approach that includes chemotherapy with a combination of agents (e.g., platinum agents, cyclophosphamide, DOX, etoposide) and surgical resection is standard.

For children with high-risk neuroblastoma, substantial improvements have been seen with aggressive combined modality approaches. These generally include chemotherapy, surgical resection, high-dose chemotherapy with stem cell rescue, radiation therapy and biological/immunological therapy (e.g., dinutuximab). These approaches have improved EFS, but the majority of patients eventually relapse and die of their disease[29].

Prognosis

Neuroblastoma treatment and outcome depends on pretreatment prognostic factors. Patients with low and very low risk have a very good prognosis with a 5-year overall survival (OS) of 80–90% and receive little to no chemotherapy at all[31].

However, patients older than 18 months with metastases and/or patients of any age with MYCN-amplified tumors are considered of high risk, and their outcome is still poor in spite of intensive multimodal therapy, with a 5-year OS <50%[32].

Approximately 40% of all neuroblastoma patients are classified as high risk, and approximately half of them do not respond to first-line therapy or relapse during the first two years of treatment[33].

Current outcome remains unacceptable, and considerable efforts are being made to use tumor genomics, expression profiling, proteomic studies, and analysis of host factors to better understand this malignancy and to develop more effective therapies.

Short-term toxicity, for most agents currently administered to children with ES, is mainly hematological and comprises neutropenia, febrile neutropenia (complicated with bacterial or viral infections), thrombocytopenia (which may lead to bleeding and need for platelet transfusions), mucositis and acute renal failure. All of these events may affect treatment compliance and may also increase both the number and the duration of hospitalization(s). In addition, these patients may also experience several long-term sequelae of chemotherapy, including cardiomyopathy (with DOX, cyclophosphamide), renal impairment and gonadal hormonal failure/infertility (with ifosfamide, cyclophosphamide) and secondary tumors (with DOX and ifosfamide, etoposide, cyclophosphamide).

The relatively tolerable safety profile of lurbinectedin offers an additional benefit over current standard approaches due to most (adverse) events being transient and reversible, as well as generally well-controlled with no cumulative toxicity.

7.2. Planned Pediatric Clinical Studies

7.2.1. Pediatric Pharmacokinetic Studies

Study Design

The first-in-children trials should be initiated upon careful assessment of risk and benefit to maximize therapeutic intent in this vulnerable population.

An initial non-controlled, open-label, phase 1 trial of lurbinectedin will be performed on a small sample of patients. The classical 3+3 trial design with the modified Fibonacci mathematical series will be used because it is an optimal method to determine the RD,

focusing on safety considerations and reducing the risk of exposure to unnecessary toxicities. Results of this trial will provide information on the MTD, the RD and the toxicity of lurbinectedin, as well as on its pharmacokinetic (PK) characteristics in toddlers, children and adolescents with relapsed or refractory solid tumors.

Objectives

The primary objectives are to assess the safety, tolerability and PK, and to determine the MTD and dose-limiting toxicity (DLT) of lurbinectedin and establish a RD to be used in phase 2 trials.

Population

According to the age classification suggested in the ICH Topic E 11 "Clinical Investigation of Medicinal Products in the Paediatric Population−January 2001 CPMP/ICH/2711/99",, the following classification will be used: preterm newborn infants, term newborn infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years), and adolescents (12 to 17 years).

The age group selected to participate in these trials will consist of children and adolescents. Pediatric populations from birth to 23 months of age will be excluded due to safety reasons. The immature liver of patients up to 27 days of age would not be able to fully metabolize lurbinectedin to the same extent as older children and adults. Thus, the systemic presence of the drug substance in this subgroup of patients would be longer and its toxic effects increased. In addition, the mode of administration of lurbinectedin (i.e., a volume of at least 100 mL infused over one hour) may result in safety issues in infants and toddlers due to the latter's low body weight.

Pediatric Formulation and Dose

The starting dose in pediatric patients will be selected on the basis of PK predictions derived from an adult PK, assuming allometric scaling. Additionally, modelling and simulation studies could be optimally used to support dose selection (i.e., physiologically based pharmacokinetic [PBPK] methods are of special relevance in pediatric bridging studies for establishing a first-in-children dose).

Lurbinectedin will be administered as a solution diluted in either 100 mL (for administration via a central catheter) of glucose 50 mg/mL (5%) or sodium chloride 9 mg/mL (0.9%) solution for infusion.

Patients will receive lurbinectedin as a one-hour i.v. infusion on D1 q3wk.

Endpoints

In the PK asset, innovative techniques will be used to reduce the number and volume of samples required. Variables such as the area under the curve (AUC), the peak plasma concentration (C_{max}), the CL, the $t_{½}$ and the V_{ss} will be calculated.

The evaluation of safety will include the reporting of AEs and the assessing of routine laboratory values (blood counts and differential, serum chemistries, urinalysis), physical examination, and recording of vital signs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.4.03.

This study will obtain preliminary information on the clinical antitumor activity of lurbinectedin in this study population. Activity will be assessed according to RECIST v.1.1 every three cycles after treatment onset in all patients with measurable disease.

7.2.2. Clinical Effectiveness and Safety Studies

If preliminary evidence for the efficacy of lurbinectedin is observed in some, or all, assessed pediatric tumor cohorts, and if the overall safety profile of the drug is acceptable, the Sponsor proposes to perform phase 2 and 3 studies to confirm efficacy in the different diseases included in the pediatric plan.

The endpoints will be selected on the basis of the tumor type to be studied. The safety profile will be evaluated in all phases as a single agent and in combination with other anticancer drugs.

The RECIST have become widely accepted as the preferred method to assess tumor changes in adults. The pediatric oncology community has also implemented its use, although RECIST guidelines have not yet been thoroughly validated in children.

Potential limitations for the use of RECIST might exist in children due to the fundamental differences between adult and childhood cancers. Nonetheless, in the absence of a clearly superior alternative, RECIST guidelines are widely applied in pediatric oncology clinical trials and constitute our main criteria for tumor response assessment.

Another limitation is the low number of patients that are available for participation in clinical studies, which would complicate the conduct of early phase clinical trials.

Table 7. Summary of planned clinical trials.

Clinical trials	Phase 1	Phase 2	Phase 3
Objective(s)	Single-agent dose-finding (MTD), the RD and tolerability.	Safety and dose-refinement, as single agent or in combination	Activity, efficacy and safety (benefit/risk).
Design	Single-agent dose escalation, successive cohorts, classical 3+3. In combination (i.e., with DOX).	Single-arm or randomized, according to efficacy observed in phase 1 trials	• Randomized add-on to multi-agent chemotherapy, futility interim analysis. • Randomized, in combination with a front-line treatment regimen.
Population	Solid malignant tumors potentially susceptible to mechanism of action and for which no effective therapy is known. Second or subsequent relapse. Possibly after at least two (failed) treatment attempt using active anti-cancer medicines. Children and adolescents.	• Refractory ES/neuroblastoma with no therapy option. • First relapse of localized ES with unfavorable prognostic factors. • Metastatic ES/neuroblastoma. Possibly restricted to presence or function of marker (biomarker, pharmacogenomic marker, EWS/FLI isoforms).	• First, untreated relapse of ES, and refractory ES with no local treatment option. • Newly diagnosed untreated ES. • First, untreated relapse of neuroblastoma, and refractory neuroblastoma with no treatment option. • Newly diagnosed untreated neuroblastoma.
Dose	Dose escalation. Duration as long as clinical benefit.	• Starting from study 1 (RD). •.Different administration schedule(s).	Based on preceding study(ies).
Endpoints	• Acute toxicities. • Cumulating toxicity.	• Antitumor activity (RECIST) by ORR.	Time to event (failure-free, progression-free, event-free

Clinical trials	Phase 1	Phase 2	Phase 3
	• Pharmacokinetics. • Activity (ORR).	• Pharmacodynamic activity on targets and related pathways.	survival) with supportive overall survival.
Analyses	• Pharmacokinetics. • Modelling of dose including adult data.	Pharmacodynamics and any interaction.	Interim analysis (blinded) on response rates (futility).

DOX, doxorubicin; ES, Ewing sarcoma; MTD, maximum tolerated dose; ORR, overall response rate; RD, recommended dose; RECIST, Response Evaluation Criteria In Solid Tumors.

8. POTENTIAL CHALLENGES FOR CLINICAL DEVELOPMENT OF PM1183 IN PEDIATRIC INDICATIONS

Lurbinectedin is currently provided as a lyophilized drug product with strength of 4 mg/vial. Before use, the vial is reconstituted with water for injection and further diluted with 5% glucose or 0.9% sodium chloride solution for infusion for i.v. administration. A short i.v. infusion (one hour) is the preferred administration schedule.

The design and development of age-appropriate pediatric formulations present a number of challenges in terms of balancing the acceptability and preference for different potential pediatric dosage forms. Oral administration forms such as oral solutions, dispersible granulates and capsules are the preferred presentations. Unfortunately, oral administration of lurbinectedin is precluded due to its very low permeability through oral mucosa, resulting in an oral bioavailability below 5%. Therefore, i.v. administration must be used for pediatric patients.

Based on the lower doses required for the pediatric population, optimization of the lurbinectedin strength per vial and the infusion volumes is desirable to ensure accurate dose measurement, to reduce the risk of dosing errors and to allow an appropriate lurbinectedin concentration during infusion that will prevent subcutaneous lesions in case of extravasation. Small syringe pumps or small volume reservoirs are recommended, as well as any portable i.v. administration system that could contribute to increase patient mobility and comfort during infusion.

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