NOVARTIS

Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Briefing Document

LEE011

Meeting date	November 5, 2013
Document status:	Final
Release date:	October 1, 2013
Number of pages:	19

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

Table of contents

List of tables

List of figures

List of abbreviations

ADME	Absorption, distribution, metabolism and excretion
AEs	Adverse events
AUC	Area under the curve from time zero to the last measurable concentration sampling time (tlast)
BLRM	Bayesian Logistic Regression Model
BSA	Body surface area
BSEP	Bile salt export pump
CCND1	Cyclin D1
CDK	Cyclin dependent kinase
CL/F	Total body clearance of drug from the plasma
Cmax	Maximum serum concentration after a single dose
CNS	Central nervous system
CSF	Cerebrospinal Fluid
CYP	Cytochrome P450
DLT	Dose limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
EWOC	Escalation With Overdose Control
FIH	First in human
h	Hours
HPV	Human Papilloma virus
HNSCC	Head and neck squamous cell carcinoma
IND	Investigational New Drug
INRC	International Neuroblastoma Response Criteria
i.v.	Intravenous
MCL	Mantle cell lymphomas
MRT	Malignant Rhabdoid Tumors
MTD	Maximum tolerated dose
MXR	Mitoxantrone resistant protein
nM	nanoMolar
NSCLC	Non-small cell lung cancer
PD	Pharmacodynamics
PhI	Phase I
PhII	Phase II
PK	Pharmacokinetic
ORR	Overall Response Rate
PIP	Pediatric Investigational Plan
p.o.	Oral (per os)
pRb	Retinoblastoma protein
RANO	Revised Assessment in Neuro-Oncology
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria for Solid Tumors
PVC	Premature ventricular contraction
QD	Once daily

QTc	QT corrected
QTcF	QT corrected with Fredericia's formula
SAE	Serious Adverse Event
SD	Stable Disease
T1/2	Half-life
TTP	Time to Progression
Vss	Volume of distribution at steady state

1 Introduction

The D-cyclin-CDK4/6-INK4a-pRb pathway is disrupted in cancer to favor cell proliferation. Eighty percent of human neoplasms maintain functional retinoblastoma protein (pRb) but harbor aberrations that effectively inactivate pRb function. These aberrations include genetic or epigenetic changes that directly increase CDK4/6 kinase activity or that deactivate upstream regulators (Ortega 2002, Shapiro 2006). LEE011 is an orally bioavailable, small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/CylinD3 complexes in isolated enzyme assays. It is inactive against the majority of other kinases. LEE011 inhibits the growth of many tumor types *in vitro* and *in vivo*, including mantle cell lymphoma (MCL), liposarcoma, melanoma, rhabdoid cancer, neuroblastoma, and carcinomas of the esophagus, breast, lung and pancreas. The presence of pRb, a target of CDK4/6, is required for LEE011 activity in cells. LEE011 is being evaluated in multiple tumor types as a single agent and in combination.

A pediatric Phase 1 study of LEE011 in Malignant Rhabdoid Tumors (MRT) and neuroblastoma is currently ongoing (CLEE011X2102) and Novartis is seeking advice regarding the development plan of LEE011 in the pediatric population.

2 Regulatory history

LEE011 is currently being explored under multiple INDs in several potential indications, either as a single agent or in combination with other agents. All INDS are under the Division of Oncology Products I or II. The first IND was opened on August 26, 2010.

Novartis requested a pre-IND meeting on March 26, 2010 to discuss the early development program for LEE011 in adults, including the selection of the starting dose and the monitoring plan for key toxicities. Responses provided by the Agency were taken into consideration for the development of the first in human protocol CLEE011X2101.

LEE011 is not approved in any country and a Pediatric Investigational Plan (PIP) has not yet been submitted to the European Medicines Agency (EMA).

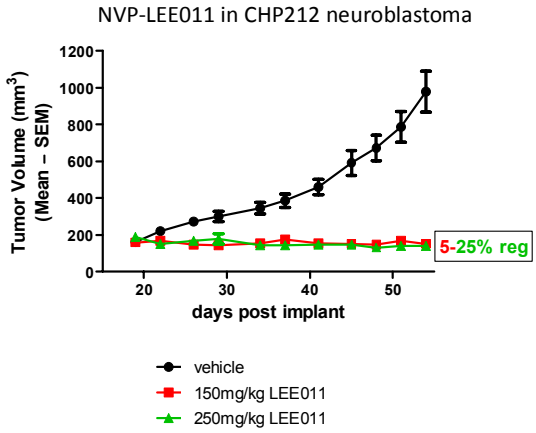
3 Preclinical data supporting clinical studies

3.1 Pharmacology

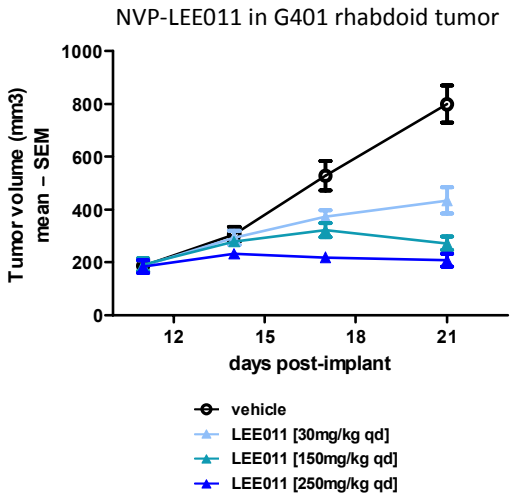
In a screen of > 500 cell lines derived from a variety of different tumor types, MRT and neuroblastoma cell lines were amongst the most sensitive to LEE011. More specifically, LEE011 induced anti-proliferative effects at sub-µM concentrations in both MRT (2/2), and the majority (9/13) of neuroblastoma cell lines examined. In the case of neuroblastoma-derived cell lines, neither activating mutations in the ALK gene, nor amplification of the MYCN gene, two genetic alterations found frequently in neuroblastoma, appeared to be directly associated with LEE011 sensitivity. Consistent with the *in vitro* data, *in vivo* LEE011 demonstrated tumor growth suppression in both MRT and neuroblastoma xenograft models (Figure 3-1).

Figure 3-1 ***In vivo*** **activity of LEE011 in neuroblastoma and rhabdoid xenograft models**

A.



B.



In vivo activities of LEE011 in CHP212 neuroblastoma (panel A) and G401 rhabdoid tumor (panel B) models. At 250 mg/kg dose, complete growth inhibitions was observed in both models.

The high degree of sensitivity to LEE011 demonstrated in MRT and neuroblastoma-derived models in preclinical studies, coupled with the observation that the majority (90-100%) of MRT and neuroblastoma tumors have functional Rb, suggests that LEE011 may be of therapeutic benefit to patients harboring these mutations

3.2 Nonclinical pharmacokinetics and metabolism

The PK of LEE011 has been investigated in four different species: mouse, rat, dog and monkey. After oral administration to rats, LEE011 was moderately absorbed (48 to 84%) with bioavailability ranging from 10 and 65% across animal species. Maximum plasma drug concentration (C_{max}) was observed between 2 and 4 hours (h). The terminal half-life ($T_{1/2}$) of LEE011 was moderate in rodents and monkeys (2 to 7 h), and was comparatively longer (18 h) in dogs. The predicted human PK parameters based on allometric scaling were 1259 mL/min (75.5 L/h for CL/F, 2334 L for Vss/F, and approximately 21 h for T1/2.

The binding of LEE011 to plasma proteins was moderate in humans (unbound fraction: 30 ± 2%). ^{3}H-LEE011 and its metabolites were extensively distributed into the organs and tissues of rats including choroid, ciliary body and meninges with the exception of the brain. The highest radioactivity concentrations were found in tissues such as pituitary gland, pineal gland, spleen, kidney and adrenal medulla with high exposure in the thyroid gland. Distribution of LEE011 and/or its metabolites into melanin-containing structures was seen in pigmented rats.

Oxidative metabolism of LEE011 is dominated by CYP3A4 with a minor contribution (approximately 20%) by flavin-containing monooxygenase 3. LEE011 is a low affinity substrate of P-glycoprotein (P-gp). LEE011 is a time-dependent CYP3A4 inhibitor and a reversible inhibitor of CYP1A2. LEE011 was found to inhibit the mitoxantrone-resistant protein (MXR), and human bile salt export pump (BSEP) but not rat or dog BSEP. LEQ803

(N-demethylation) is a prominent metabolite found in the rat, monkey and human hepatocytes and the only metabolite found in dog hepatocytes.

In rat ADME studies, ^{3}H-related components were predominantly excreted in bile. The elimination of unchanged drug in bile was limited. A minor proportion of the administered dose was excreted in urine. The bulk of the administered dose (87.3%) was excreted *via* urine, feces and bile within 24 hours.

Overall, the elimination of LEE011 may potentially be affected by co-administered drugs that inhibit or induce CYP3A4. LEE011 may inhibit CYP3A4, CYP1A2 and BSEP in a dose dependent manner.

3.3 Safety pharmacology and toxicology

In vitro, LEE011 did not show genotoxic potential.

Safety pharmacology studies did not reveal any effects on CNS or respiratory functions. In a dog telemetry study, prolongation of the average QT and QTc was observed with the potential to induce premature ventricular contractions (PVCs) at higher exposure levels.

In rats and dogs toxicity studies of up to 4-week daily treatment, LEE011 induced bone marrow hypocellularity, lymphoid depletion, atrophy of the skin and intestinal mucosa, decreased bone formation and testicular atrophy. These are consistent with the mechanism of action of LEE011. In addition, an increased number of ovarian corpora lutea was observed in a single female dog at the highest dose tested. The liver, bile system and gall bladder (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) were identified as additional target organs of toxicity which are not likely related to the primary pharmacology of LEE011. Correlating hematological and/or biochemistry changes were seen for the effects described in the bone marrow, lymphoid system and liver. All the described changes were fully reversible in rats and dogs.

Based on its mechanism of action and preclinical toxicology studies, the major potential toxicities for LEE011 include myelosuppression, hepatobiliary toxicity, and prolongation of the QT interval. The risk of these toxicities may be amplified by concomitant administration of strong inhibitors of CYP3A4.

Embryos defective for CDK4 and CDK6 die during the late stage of embryonic development due to severe anemia. However, these embryos display normal organogenesis and most cell types proliferate normally (Malumbres et.al 2004). These preclinical observations suggest the use of specific CDK4/6 inhibitors may have minimal impact on growth and development of infants and children. Any adverse effects will be carefully monitored.

3.4 Ongoing/planned nonclinical safety studies

As per ICH S9 guideline, in order to support continued clinical development and marketing application in adult and pediatric patients, the nonclinical program will be further complemented by the following studies:

- 13-week rat and dog toxicity studies.
- Embryofetal development studies.

4 Clinical trial experience in adults

4.1 Clinical pharmacology

4.1.1 Clinical pharmacokinetics

Preliminary pharmacokinetic data has been obtained in the first-in human (FIH) phase I study CLEE011X2101, in which LEE011 is administered orally, once daily for 21 days followed by a 1 week rest (28-day cycle) for all dose levels administered up to 1200 mg. Slightly over-proportional increases in exposure across the dose range tested has been shown. Both C_{max} and AUC values consistently increase with increasing dose. Steady state is reached by day 8. Arithmetic mean of accumulation ratio (R_{acc}) calculated from AUC_{tau} on day 21 and AUC_{tau} after a single dose on day 1 across the studied doses of 50 to 1200 mg ranged from 1.55 to 3.13 fold. The dose specific arithmetic mean of effective $T_{1/2}$ based on drug accumulation ranges from 15.9 hours (140 mg QD dose) to 43.1 hours (750 mg QD dose).

4.1.2 Clinical pharmacodynamics

No clinical results of pharmacodynamic studies for LEE011 are available at this time.

4.2 Clinical safety

As of 28 June 2013, 70 patients have been treated with single agent LEE011 in the first-in human (FIH) phase I study CLEE011X2101. Doses ranging from the starting dose of 50 mg to 1200 mg were evaluated on this schedule. In addition, continuous dosing of LEE011 at 600 mg was evaluated (once daily for 28 days of a 28-day cycle).

The most frequently reported AEs regardless of study treatment relationship include anemia (43%), neutropenia (40%), nausea (40%), leukopenia (34%), fatigue (33%), diarrhea (30%), thrombocytopenia (30%), vomiting (29%), asthenia (27%), lymphopenia (27%), decreased appetite (26%), constipation (21%), hyperglycemia (19%), and hypoalbuminemia (17%). The majority are grades 1 or 2 and reversible.

Asymptomatic grade 2 QTcF prolongation was observed with increasing frequency starting at 600 mg; 2 patients (20%) in the 600 mg cohort, 1 patients (13%) in the 750 mg cohort, 4 patients (31%) in the 900 mg cohort, and 2 patients (67%) in the 1200 mg cohort. Two patients at 900 mg had asymptomatic QTcF prolongation that resulted in a QT interval of 500 ms. No new cardiac abnormalities were observed in any patient. QT changes are associated with the maximum drug levels between 1-8 hours post-dose.

4.3 Clinical efficacy

Preliminary antitumor activity of LEE011 was assessed across all dose levels in study CLEE011X2101. Stable disease (SD) for 4 or more cycles was observed in 26% of patients. Stable disease for 6 or more cycles was observed in 14% of all patients with half of them treated at 600 mg. In the 600 mg continuous dose cohort, one patient with ER-positive, HER2-negative breast cancer had a confirmed partial response after 4 cycles of treatment. This patient had received 6 lines of prior treatment including letrozole, fulvestrant, everolimus and exemestane before study entry.

5 Other clinical trials that are ongoing or completed after approval

LEE011 is not approved in any country.

6 Current drug development plan for other indications in adults

The LEE011 development plan in adults involves studies of single agent LEE011 or in combination with other investigational or approved agents in liposarcoma, MCL, HPV negative squamous cell carcinoma of head and neck (HNSCC), ER+ breast cancer and melanoma. Table 6-1 presents a summary of the active clinical studies with LEE011. A brief rationale supporting the use of LEE011 in those tumor types is provided in the following sections.

6.1 Advanced solid tumors and lymphomas

Patients with MCL, liposarcoma and HPV negative HNSCC have functional pRb and aberrations in the D-cyclin-CDK4/6-INK4a-pRb pathway. Almost all liposarcomas have CDK4 amplification and more than 90% of mantle cell lymphomas have activating D-cyclin translocation. The majority of HPV negative HNSCC tumors have inactivation of p16INK4A and/or cyclin D1 gene amplification and overexpression. Therefore, patients with these tumor types are likely to derive benefit from LEE011 therapy.

6.2 Breast cancer

The Cyclin/CDK/Rb pathway plays an important role in ER+ breast cancer where focal amplifications affecting CCND1 and CDK4 or loss of CDKN2 occur frequently and presumably activate CDK4 function to promote tumor cell proliferation (Beroukhim 2010). CDK4 is required for hormone-independent growth in breast cancer models (Miller 2010). Genomic data indicate that mutations affecting the *Rb* gene, which acts downstream of CDK4 and is required for response to CDK4 inhibition, are uncommon in luminal breast cancer (Beroukhim 2010). Preliminary clinical data suggest that the addition of a CDK4/6 inhibitor to treatment with letrozole in patients with ER+ advanced breast cancer significantly enhances progression-free survival (Finn 2012). LEE011 has demonstrated anti-tumor activity as a single agent in multiple ER+ breast cancer cell lines. In tumor models derived from ER+ breast cancer, LEE011 has demonstrated anti-tumor activity both as single agent and in combinations with a mTOR inhibitor (everolimus) and a PI3K inhibitor.

6.3 Melanoma

Deregulation of cell cycle checkpoints has been well-described in melanoma (Wang 1996). The loss of expression of the p16 tumor suppressor, by mutation, deletion or transcriptional silencing of the CDKN2A locus, is a frequent event in melanoma (Yang 2005). Activating mutations in CDK4 have been described in familial melanoma, as well as in sporadic cases of melanoma, as has CDK4 amplification (Walker 1998). Intact p16 inhibits CDK4 activity, so genetic inactivation of p16 is thought to result in aberrant CDK4 activity. Amplification of cyclin D is observed in a subset of melanoma and provides further genetic evidence that

CDK4 activity is a fundamental element in melanoma transformation (Hodis 2012, Curtin 2005, Smalley 2008). The majority of melanoma tumors (>90%) have functional pRb (Hodis 2012).

LEE011 has demonstrated tumor growth suppression in multiple melanoma xenograft models (including BRAF wild type, BRAF mutant, and NRAS mutant) as a single agent. In addition, LEE011 has also demonstrated anti-tumor activity in combination with a selective inhibitor of MEK1/2). In primary V600E BRAF mutated melanoma models, LEE011 in combination with a selective RAF inhibitor, prevented tumor re-growth associated with the RAF inhibitor single agent treatment, and also produced significant delay in tumor progression. In mouse models resistant to the RAF inhibitor, LEE011 demonstrated tumor growth inhibition as single agent and in combination with the RAF inhibitor, suggesting that either a high dose of LEE011 or a lower dose in combination with the RAF inhibitor may block the resistance mechanism.

Table 6-1 Summary of on-going clinical studies with LEE011 in adults

Study No.	Rationale for study	Indication to be studied	Clinical Design Study design	Number of patients planned	Patient population
CLEE011X2101	A Phase I, multi-center, open-label, dose escalation study of oral LEE011 in patients with advanced solid tumors or lymphomas.	Advanced solid tumor or lymphoma.	Phase I, open label study Dose-escalation and safety expansion part at MTD/RDE	100	Adult patients with advanced solid tumor or lymphoma after failing standard therapy for whom no effective standard therapy exists
CLEE011X1101	A Phase I, multi-center, open-label, dose escalation study of oral LEE011 in Japanese patients with advanced solid tumors	Advanced solid tumors	Phase I, open label study Dose-escalation part followed by safety expansion part at MTD/RDE	~30	Japanese patients with advanced solid tumors after failing standard therapy for whom no effective standard therapy exists
CLEE011X2105	A phase Ib/II multicenter, open-label study of LEE011 in combination with a RAF inhibitor in adult patients with locally advanced or metastatic melanoma	Locally advanced or metastatic melanoma with BRAF mutation	Phase Ib/II open label study. Dose escalation part followed by PhII	~150	Adult patients with locally advanced or metastatic melanoma with BRAF mutation
CMEK162X2114	A Phase1b/II multicenter, open-label study of LEE011 in combination with a MEK 1/2 inhibitor in NRAS mutant Melanoma	Locally advanced or metastatic NRAS mutant melanoma	A Phase Ib/II open label study. Dose escalation part followed by single arm PhII	~60	Adult patients with locally advanced or metastatic NRAS mutant melanoma
CLEE011X2106	A Phase Ib/II multicenter,	Estrogen	A Phase Ib/II	~185	Postmenopausal Women

Study No.	Rationale for study	Indication to be studied	Clinical Design Study design	Number of patients planned	Patient population
	open-label study of LEE011 in combination with everolimus and exemestane in ER positive Breast Cancer	Receptor-positive, HER2- breast cancer	open label study. Dose escalation part followed by randomized PhII		With Estrogen Receptor Positive, Her2- Locally Advanced or Metastatic Breast Cancer
CLEE011X2107	A Phase Ib/II, multicenter study of the combination of LEE011 and a PI3K inhibitor with letrozole in adult patients with advanced ER+ breast cancer	ER+ HER2- locally advanced or metastatic breast cancer.	A Phase Ib/II open label study. Dose escalation part followed by single arm PhII	290	Post-menopausal women with ER+ locally advanced or metastatic breast cancer.
CLGX818X2102 (LOGIC)	Phase II, multi-center, open-label study of single-agent RAF inhibitor Followed by a Rational Combination With Agents After Progression on RAF inhibitor, in Adult Patients With Locally Advanced or Metastatic BRAF V600 Melanoma	Adult Patients With Locally Advanced or Metastatic BRAF V600 Melanoma	PhII study of Single-agent RAF inhibitor Followed by a Rational Combination With Agents After Progression on RAF inhibitor	100	Advanced BRAF Melanoma
CLEE011A2201	A randomized pre-surgical pharmacodynamics study to assess the biological activity of LEE011 plus letrozole versus single agent letrozole in primary breast cancer	Estrogen Receptor-positive, HER2- breast cancer Newly diagnosed HR+, HER2-negative, early breast cancer	PhII study of LEE011 in combination with letrozole as compared to single agent letrozole	120	Postmenopausal women with HR+, HER2-negative, newly diagnosed, resectable breast cancer who received no prior antineoplastic therapy

7 EMA PIP

A Pediatric Investigational Plan has not been submitted to the EMA

8 Ongoing clinical trials in pediatrics

Evaluation of LEE011 in pediatric patients at this early stage in development is driven by a strong biological rationale, adequate nonclinical pharmacology and toxicity data, adult clinical data, and a high unmet medical need in the target patient populations.

8.1 Background and rationale for evaluation of LEE011 in malignant rhabdoid tumors and neuroblastoma

Malignant Rhabdoid Tumors are extremely aggressive malignancies that generally occur in infants and young children. The most common locations are in the kidney and central nervous system (CNS), although they can arise in most soft-tissue sites. The incidence rate of MRT is about 1 per million children per year (Woehrer et al 2010). There are no standard or effective therapeutic regimens for these tumors. Most patients receive intensive multimodality treatment including surgery, radiotherapy, chemotherapy, and sometimes high-dose chemotherapy with stem-cell rescue. Despite this aggressive approach, prognosis for children with MRT is poor. Mean survival with surgical intervention alone or with adjuvant chemotherapy and radiotherapy is 3 and 8 months, respectively (Tekautz et al 2005).

Near-uniform biallelic inactivating mutations in SMARCB1 (also known as SNF5, INI1 and BAF47), a gene that encodes a core subunit of the SWI/SNF chromatin remodeling complex, are seen in more than 95% of MRTs (Versteege et al 1998). Studies have revealed that MRTs are exquisitely dependent on cyclin D1 (CCND1) for genesis and survival, and loss of INI1 leads to de-repression of cyclin D1 in primary mouse and human MRTs (Tsikitis 2005, Fujisawa 2005, McKenna 2008). Genetic abrogation of CCND1 eliminates MRT formation in Ini1+/− mice, and siRNA-mediated knockdown of CCND1 is sufficient to induce G0/G1 arrest and apoptosis in MRT cells (Tsikitis et al 2005). These studies suggest that targeting cyclin D1 or the cyclin/CDK axis has the potential to be an effective means of inhibiting MRT growth.

Neuroblastoma (NB) is the most common extracranial solid cancer in childhood and the most common cancer in infancy, with an annual incidence of about 650 cases per year in the US. The median age at diagnosis is 17 months (London et al 2005). The tumors arise in tissues of the sympathetic nervous system, typically in the adrenal medulla or paraspinal ganglia. These tumors are biologically heterogeneous with a broad spectrum of clinical behavior. Approximately 50% of patients present with metastatic disease. Genetic alterations in ALK have been reported in approximately 15% (Mosse et al 2008) and MYCN amplifications in about 25% of tumors (Brodeur et al 1984). Patients with segmental chromosomal aberrations display wide phenotypic variability and have poor prognosis. Children with localized neuroblastoma and favorable tumor genomic characteristics have an excellent overall survival, with little or no cytotoxic therapy. However, approximately 50% of patients with neuroblastoma have a clinically aggressive form of the disease with overall survival rates of less than 40% at 5 years (Maris 2010; Cohn 2009). Treatment for high risk neuroblastoma

includes high dose, intensive, multi-agent chemotherapy along with targeted immunotherapy. Ten to twenty percent of these patients are refractory to currently available treatment and do not achieve a remission. Moreover, 50% to 60% of patients who respond to and complete treatment will experience a relapse. Currently, no curative salvage regimens for refractory and recurrent high-risk neuroblastoma are available (Maris 2010). Therefore, there is a high unmet medical need and novel approaches for treating these patients are urgently needed.

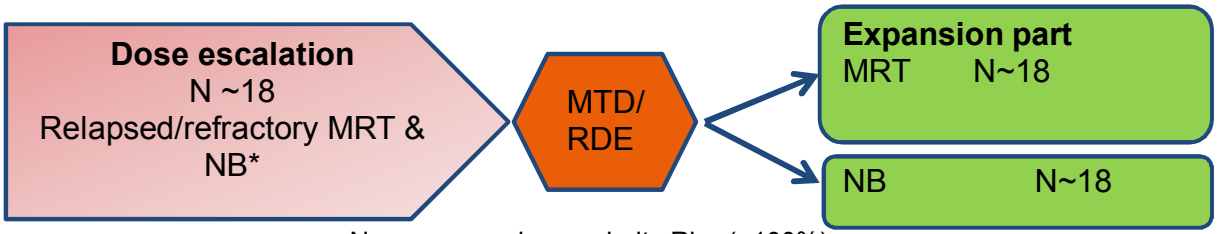
The Rb signaling pathway is important for neuronal differentiation and migration (McClellan 2006). High incidence of Cyclin D1 and CDK4 over-expression has been observed in neuroblastoma cell lines (Molenaar et al 2008). Copy number defects of G1-cell cycle genes (CCND1, CDK4 and CDK6) occur in 30% of patients and correlate with high expression of E2F target genes and a poor prognosis (Molenaar et al 2012). Therefore, targeting the CCND1/CDK4 axis may provide therapeutic benefit to high-risk neuroblastoma patients.

8.2 Study CLEE011X2102

8.2.1 Study design

This is a phase 1, multi-center, open-label study, with a dose escalation part followed by an expansion part (Figure 8-1). The primary purpose of study CLEE011X2102 is to determine the maximum tolerated dose and/or recommended dose for expansion (RDE) in pediatric patients and to delineate a clinical dose to be used in future studies. This study will also assess the safety, tolerability, PK and antitumor activity of LEE011 in patients with MRT, neuroblastoma or other tumors with D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities.

Figure 8-1 CLEE011X2102 Study Schema



Eligible MRT and neuroblastoma patients aged 12 months to 21 years old whose tumor has progressed following standard therapy, or for which no standard, effective therapy exists, will be enrolled in the study. In addition, patients who have documented evidence of D-cyclin-CDK4/6-INK4a-Rb pathway abnormalities will be allowed to enroll in the dose escalation part of the study. Approximately 64 patients will be treated in the entire study. LEE011 will be administered orally, once daily for 21 days followed by a 1 week break on a 28 day cycle.

During the dose escalation part, 3-6 newly enrolled patients in successive cohorts will receive increasing doses of LEE011, with a starting dose of 280 mg/m^2/d following the dosing schedule specified above. A Bayesian Logistic Regression Model (BLRM) along with Escalation With Overdose Control (EWOC) criterion will be used to guide dose escalation. Once the MTD/RDE has been determined, the expansion part will further characterize the safety, tolerability and PK profile of LEE011, as well as assess antitumor activity of LEE011. During the expansion part of the study LEE011 will be dosed at the MTD, or at a lower RDE,

if the available data suggest that the MTD is not appropriate for multiple cycles of therapy. This part will include 2 arms, one restricted to neuroblastoma patients and the second to MRT patients with either CNS or extra-CNS primary. A minimum of 8 patients each will be required for CNS and extra-CNS primary MRT. Enrollment will proceed in parallel. Patients enrolled during the expansion part of the study are required to have measurable disease.

Patients will continue to receive treatment with LEE011 until disease progression, occurrence of unacceptable toxicity, or if treatment is discontinued at the discretion of the investigator or by patient's withdrawal of consent. All patients will have an EOT visit within 14 days of permanently discontinuing LEE011 and will be followed for 30 days after last dose of study treatment.

8.2.2 Rationale for dose selection and dosage form

The initial dose at which the first cohort of children in this trial will be treated is 280 mg/m^2/d. This dose is equivalent to 80% of the recommended dose for future development (600 mg/d) in the ongoing adult study CLEE011X2101, divided by the average adult body surface area (BSA) of 1.72 m^2. LEE011 will be dosed once a day for 21 consecutive days followed by a 7-day planned break as part of each 28-day cycle of treatment consistent with the regimen used in CLEE011X2101. During the dose escalation part, 3-6 newly enrolled patients in successive cohorts will receive increasing doses of LEE011 with the dosing schedule specified above.

An age appropriate ready to use water or Orasweet (or equivalent) based formulation of LEE011 is being developed and will be available for the expansion part of the study. The dosage form will be delivered in an amber bottle with a child resistant screw-cap closure for single or multiple uses. The concentration of the active drug in the solution is planned to be 30 mg/mL and the dose volume will likely be between 4-20 mL depending on the prescribed dose.

8.2.3 Objectives and endpoints

Objectives and related endpoints of the trial are described in Table 8-2.

Table 8-2 Objectives and related endpoints

Objective	Endpoint
Primary	
Determine the MTD and/or RDE of LEE011 in the pediatric population	Incidence rate of DLTs in Cycle 1
Secondary	
(1) Characterize the safety and tolerability of LEE011	(1) AEs and serious adverse events (SAEs), changes in laboratory values and electrocardiograms (ECGs).
(2) Characterize the PK of LEE011 and any clinically significant metabolites that may be identified	(2) Plasma concentration time profiles of LEE011, PK parameters, including but not limited to AUC_{tau}, C_{max}, T_{max}, CL/F, accumulation ratio (R_{acc}), and $T_{1/2,acc}$
(3) Assess the anti-tumor activity of LEE011	(3) Overall response rate (ORR), duration of response (DOR), and time to progression (TTP) per RECIST 1.1. In addition, for neuroblastoma, response by INRC and, for primary CNS tumors, response by RANO Criteria.
Exploratory	
(1) Evaluate the relationship between anti-tumor activity and molecular aberrations in the D-cyclin-CDK4/6-INK4a-Rb pathway and other cancer-related genes	(1) Correlate ORR and gene mutations, rearrangements and amplification using archival tumor samples.
(2) Evaluate PD effects in patients with neuroblastoma	(2) Changes in biomarkers associated with the pharmacologic activity of LEE01 by comparing pre-treatment and post-treatment samples when available.
(3) To characterize the relationship between QTc prolongation and exposure to LEE011 and/or any of its relevant metabolites.	(3) ECG interval parameters (e.g. QTcF, QTcB, QT, QRS, RR, PR, HR), plasma concentration time profiles of LEE011and PK parameters such as C_{min}, C_{max}, AUC_{tau}

8.2.4 Pharmacokinetics

At the specified time points, 1 mL of blood will be collected for pharmacokinetic assessment. Also, if cerebrospinal fluid (CSF) is collected as a part of efficacy assessment or routine/standard care at any time after patient has received first dose of LEE011, a sample will be requested for assaying LEE011 concentration levels (maximum 2 mL volume). When CSF is obtained, a PK blood sample (1 mL) is required at the same time point for plasma concentration analysis. T_{max} for LEE011 is around 2-4 hours and steady state is reached in about 8 days. Recommended timing for CSF and PK sampling is after 8 days of continuous treatment and within 2-5 hours after dosing with LEE011.

The PK parameters (including but not limited AUC_{tau}, C_{max}, T_{max}, CL/F, R_{acc}, $T_{1/2}$) for LEE011 will be estimated and reported as appropriate from the individual plasma concentration versus time profiles using a non-compartmental method. Exploratory PK analysis will be conducted using compartmental modeling as required.

PK information along with safety data from pediatric patients will be used to guide dose-escalation and refine dosing in this study.

9 Potential challenges for clinical development of LEE011 in pediatric indications

The main challenge for the clinical development of LEE011 in MRT and neuroblastoma is the low incidence of these diseases (MRT has an annual incident rate of about 1 per million and neuroblastoma about 10 per million children) as well as the lack of established surrogate endpoints predictive of clinical benefit.

10 References available upon request

Beroukhim R, Mermel CH, Porter D, et al (2010). The landscape of somatic copy-number alteration across human cancers: Nature. Feb 18;463 (7283):899-905. doi:10.1038/nature08822

Brodeur GM, Seeger RC, Schwab M, et al (1984). Amplification of N-*myc* in untreated human neuroblastomas correlates with advanced disease stage. Science; 224:1121-4.

Cohn SL, Pearson AD, London WB, et al (2009). The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report. J Clin Oncol; 27:289-97.

Curtin JA, Fridlyand J, Kageshita T, et al (2005). Distinct sets of genetic alterations in melanoma. N Engl J Med; 353: 2135-2147.

Finn RS, Crown JP, Lang I, et al (2012). Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HER2- advanced breast cancer (BC). Abstract S1-6, SABCS.

Fujisawa H (2005) Cyclin D1 is overexpressed in atypical teratoid/rhabdoid tumor with hSNF5/INI1 gene activation. J Neurooncol; 73(2): 117-24.

Hodis E, Watson IR, Kryukov GV, et al (2012). A landscape of driver mutations in melanoma. Cell; 150(2): 251-63.

London WB, Castleberry RP, Matthay KK, et al (2005). Evidence for an age cutoff greater than 365 days for neuroblastoma risk group stratification in the Children's Oncology Group. J Clin Oncol; 23:6459-65.

Malumbres M, Sotillo R, Santamaría D, Galán J, Cerezo A, Ortega S, Dubus P, Barbacid M. (2004). Cell; 118(4):493-504

Maris JM (2010) Recent Advances in Neuroblastoma. NEJM; 362(23):2202-2211.

McClellan KA, Slack RS (2006). Novel functions for cell cycle genes in nervous system development. Cell Cycle; 5:1506–13.

McKenna ES, Sansam CG, Cho YJ, et al (2008). Loss of the epigenetic tumor suppressor SNF5 leads to cancer without genomic instability. Mol Cell Biol; 28:6223–6233.

Miller WR (2010). Aromatase inhibitors: prediction of response and nature of resistance. Expert Opin Pharmacother. 11(11):1873-87.

Molenaar JJ, Ebus ME, Koster J, et al (2008). Cyclin D1 and CDK4 Activity Contribute to the Undifferentiated Phenotype in Neuroblastoma. Cancer Research; 68(8): 2599-2609.

Molenaar JJ, Koster J, Ebus ME, et al (2012). Copy Number Defects of G1-Cell Cycle Genes in Neuroblastoma are Frequent and Correlate with High Expression of E2F Target Genes and a Poor Prognosis. Genes, Chromosomes & Cancer; 51:10–19.

Mosse YP, Laudenslager M, Longo L, et al (2008). Identification of ALK as a major familial neuroblastoma predisposition gene. Nature; 455:930-5.

Ortega S, Malumbres M, Barbacid M (2002). Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochimica et Biophysica Acta-Reviews on Cancer; 1602 (1):73-87.

Shapiro GI (2006). Cyclin-dependent kinase pathways as targets for cancer treatment. Journal of Clinical Oncology; 24 (11):1770-1783.

Smalley KS, Contractor R, Nguyen T, et al (2008). Identification of a novel subgroup of melanomas with KIT/Cyclin-dependant kinase-4 overexpression. Cancer Res; 68(14): 5743-52.

Tekautz TM, Fuller CE, Blaney S, et al (2005). Atypical teratoid/rhabdoid tumors (AT/RT): Improved survival in children 3 years of age and older with radiation therapy and high-dose alkylator-based chemotherapy. J Clin Oncol; 23:1491–1499.

Tsikitis M, Zhang Z, Edelman, et al (2005). PNAS; 102(34);12129-12134.

Versteege I, Sevenet N, Lange J, et al (1998). Nature; 394:203–206.

Walker GJ, Flores JF, Glendening JM, et al (1998). Virtually 100% of melanoma cells lines harbor alterations at the DNA level within CDKN2A, CDKN2B, or one of their downstream targets. Genes Chromosomes Cancer; 22(2): 157-63.

Wang Y, Becker D (1996). Differential expression of the cyclin-dependent kinase inhibitors p16 and p21 in human melanocytic system. Oncogene;12(5):1069-75.

Yang G, Rajadurai A, Tsao H (2005). Recurrent patterns of dual RB and p53 pathway inactivation in melanoma. J Invest Dermatol; 125: 1242-1251.

Woehrer A, Slavc I, Waldhoer T, et al (2010). Cancer; OO:1-8.