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Genomic Mutation Profiling and Clinical Outcome in Patients Treated With Ribociclib (CDK4/6 inhibitor) in the Signature Program

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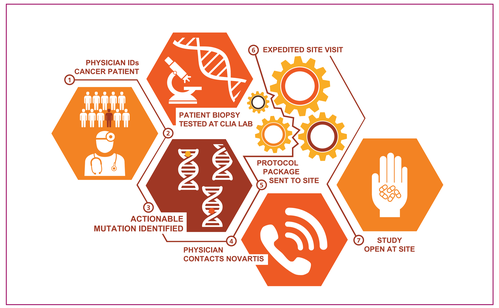
BACKGROUND

What Is the *Signature* Program?

- The Novartis Signature program comprises a series of signal-finding protocols in which 8 different single-agent targeted therapies are being investigated in a tissue-agnostic, mutation-specific manner; a schematic representation of the Signature program is shown in **Figure 1**

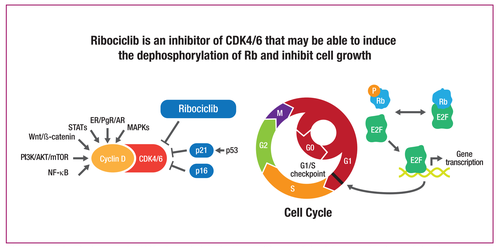
Figure 1. Schematic Representation of the Signature Program Start-Up Process[1]



CLIA, Clinical Laboratory Improvement Amendments.

- One trial (NCT02187783) in the Signature program investigated ribociclib (LEE011), a selective cyclin-dependent kinase-4/6 (CDK4/6) inhibitor
- Alterations in the CDK4/6 pathway (including amplification, mutation, or overexpression) that lead to increased proliferation have been observed in > 80% of human neoplasias[2]
- Ribociclib (LEE011) is a selective inhibitor of CDK4/6 that may be able to induce a dose-dependent dephosphorylation of the retinoblastoma (Rb) protein and inhibit cell growth via G1 arrest (**Figure 2**)

Figure 2. Ribociclib Mechanism of Action



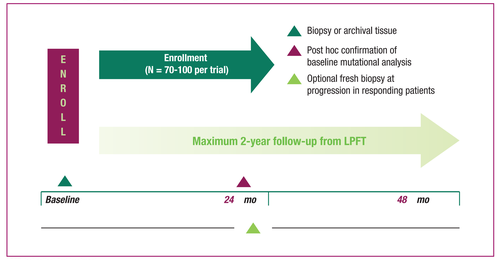
AR, androgen receptor; **ER**, estrogen receptor; **MAPK**, mitogen-activated protein kinase; **mTOR**, mechanistic target of rapamycin; **NF-κB**, nuclear factor–κB; **PgR**, progesterone receptor; **PI3K**, phosphoinositide 3-kinase; **Rb**, retinoblastoma; **STAT**, signal transducer and activator of transcription.

METHODS

- This was a phase 2 signal seeking study that had a target enrollment of 70 to 100 patients and the study design is shown in **Figure 3**
- The primary objective was to assess clinical benefit (complete response, partial response, or stable disease) at 16 weeks based on local investigator assessment using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 or appropriate hematologic criteria
- Tumor cohorts were formed when ≥ 4 patients with a particular tumor type were enrolled
  - A minimum of 10 or 15 patients were required to evaluate early futility or success, respectively, for each tumor type
- Clinical benefit was evaluated using a Bayesian adaptive statistical design that allows dynamic borrowing of information across cohorts based on their degree of similarity[3]

METHODS (CONT)

Figure 3. Study Design[1]



LPFT, last patient first treatment.

[a] Planned enrollment numbers are estimated—final accrual will depend on numbers of cohorts.

- Key eligibility criteria for the ribociclib Signature trial:
  - Confirmed diagnosis of an eligible advanced solid tumor or hematologic malignancy with no available standard therapy options and in need of treatment due to progression or relapse
  - Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 and adequate organ function
- Patients with breast cancer (except triple negative), mantle cell lymphoma, teratoma, liposarcoma, castrate resistant prostate cancer, melanoma, and primary central nervous system cancer were not eligible due to prior demonstration of lack of efficacy with single-agent ribociclib, ongoing investigation of ribociclib in other Novartis-sponsored trials in the same population, or demonstration of early futility or success
- Preidentified as having ≥ 1 of the following genomic alterations: CDK6 mutation or amplification, cyclin D1 (CCND1) amplification, cyclin D3 (CCND3) amplification, p16 (CDKN2A) mutation/loss
- Ribociclib was given orally (600 mg once daily; 3 weeks on, 1 week off)
- Post hoc broad molecular profiling using a next-generation DNA sequencing panel of > 280 cancer-associated genes was performed centrally on pretreatment (archival or fresh) tumor biopsies from all patients

RESULTS

- A total of 106 patients were enrolled in the trial between September 4, 2014, and May 8, 2015
- Patients' baseline characteristics are summarized in **Table 1**

Table 1. Baseline Characteristics of Patients in the LEE011 Protocol[a]

Age, median (range), years	62.5 (19-86)
Race, n (%)	
Caucasian	90 (84.9)
Black	4 (3.8)
Other	12 (11.3)
Sex, n (%)	
Male	56 (52.8)
Female	50 (47.2)
ECOG performance status at baseline, n (%)	
0	36 (34.0)
1	70 (66.0)
Prior lines of antineoplastic medications, median (range), n	3 (0-19)
Prior lines of chemotherapy, median (range), n	2 (0-15)

[a] Data as of 28 August 2015.

- Actionable baseline alterations among patients are summarized in **Table 2**

Table 2. Actionable Baseline Alterations (based on local molecular profiling)

Protocol Predefined Gene Mutation, n (%)	N = 106[a]
CDK4 mutation	1 (0.9)
CDK6 mutation	2 (1.9)
p16 (CDKN2A) mutation	78 (73.6)
CDK4 amplification	10 (9.4)
CDK6 amplification	8 (7.5)
Cyclin D1 (CCND1) amplification	12 (11.3)
Cyclin D3 (CCND3) amplification	5 (4.7)

[a] A patient can be counted in multiple categories and therefore the overall count can be > 106.

RESULTS (CONT)

- Tumor types of patients enrolled are summarized in **Table 3**

Table 3. Primary Tumor Type (N = 106)

Tumor Type	n (%)	Tumor Type	n (%)
Sarcoma	13 (12.3)	Uterus	4 (3.8)
Lung non-small cell adenocarcinoma	9 (8.5)	Esophagus	3 (2.8)
Bladder	7 (6.6)	Ovarian	3 (2.8)
Breast, triple negative	7 (6.6)	Skin nonmelanoma	3 (2.8)
Head and neck squamous cell carcinoma	7 (6.6)	Cholangiocarcinoma	2 (1.9)
Lung non-small cell squamous	6 (5.7)	Colorectal	2 (1.9)
Mesothelioma	5 (4.7)	Kidneys	2 (1.9)
Pancreas	5 (4.7)	Liver	2 (1.9)
Gastroesophageal junction	4 (3.8)	Lung non-small cell nonadenocarcinoma	2 (1.9)
Head and neck nonsquamous cell carcinoma	4 (3.8)	Neuroendocrine	2 (1.9)
Unknown primary	4 (3.8)	Other[a]	10 (9.4)

[a] Includes 1 each (0.9%) of adrenals, cervix, chordoma, gallbladder ducts, gastrointestinal stromal tumor, lymphoma, penile, prostate, salivary gland, and thyroid.

- Patient treatment history:
  - 53 patients (50.0%) had received 2 to 3 lines of prior antineoplastic medications prior to study inclusion
  - 51 patients (48.1%) had received 2 to 3 lines of prior chemotherapy and 21 patients (19.8%) received > 3 lines prior to study inclusion
  - 61 patients (57.5%) received prior antineoplastic radiotherapy and 92 patients (86.8%) had prior surgery for their cancer
- 30 patients (28.3%) had baseline liver metastasis
- At the time of data cutoff (28 August 2015), 96 patients had discontinued treatment (**Table 4**)
  - The majority of patients 67.0% discontinued due to disease progression

Table 4. Treatment Status of Patients

Patients, n (%)	N = 106
Still on treatment	10 (9.4)
Discontinued	
Disease progression	71 (67.0)
Patient/guardian decision	9 (8.5)
Adverse events	8 (7.5)
Death[a]	3 (2.8)
Protocol deviation	3 (2.8)
Physician decision	2 (1.9)

[a] All deaths were unrelated to the study drug.

- At the time of the data cutoff (28 August 2015), the median exposure of study drug was 1.61 months (range, 0-7.8 months) for all patients treated
- Clinical benefit was achieved for 19 patients (**Table 5**)
  - 3 partial responses were achieved: 1 patient with sarcoma (soft tissue) with CDK4 amplification, 1 patient with bladder cancer with CCND1 amplification, and 1 patient with an unknown primary cancer with CDK6 amplification

Table 5. Patient Responses to Ribociclib (solid tumors)[a]

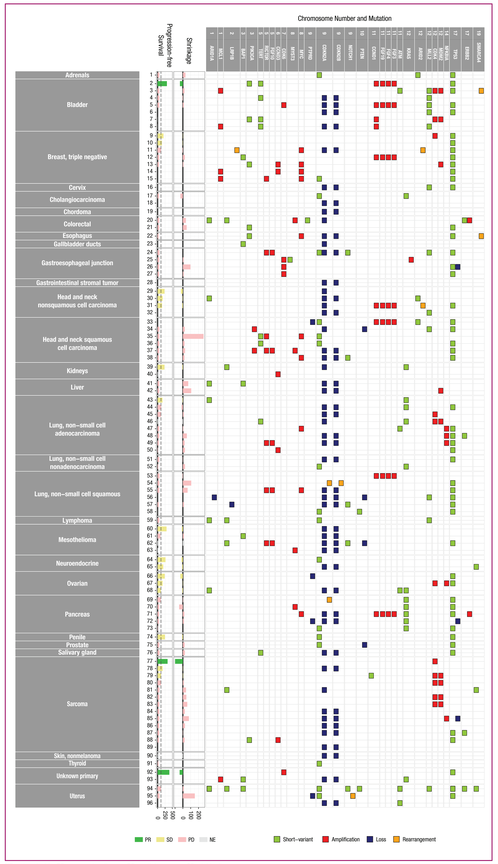
Patients, n (%)	N = 105
Response	
Complete response	0 (0)
Partial response	3 (2.9)
Stable disease	16 (15.2)
Progressive disease	71 (67.6)
Nonevaluable	15 (14.3)
Clinical benefit rate[b]	19 (18.1)

Note, the patient with stage III DLBCL did not meet clinical benefit criteria.

[a] Data as of 28 April 2016.

[b] Clinical benefit rate is defined as complete response + partial response + stable disease.

Figure 4. Mutation Profiles Across Patients With Clinical Variables[a]



NE, not evaluable; **PD**, progressive disease; **PR**, partial response; **SD**, stable disease.

Note, central genomic analysis results were not available for 10 patients.

[a] Genes altered in ≥ 5% of patients are shown.

- No clear correlation between specific mutational profile based on central analysis and clinical benefit was observed (**Figure 4**); preliminary observations suggest that:
  - Patients with clinical benefit showed a single hit in the CDK4/6 pathways
  - The *p16* deletion existed mutually exclusive of the *tp53* mutation in patients with a clinical benefit; conversely, patients without clinical benefit often displayed multiple mutational events affecting both pathways
  - Neutropenia, nausea, fatigue, and vomiting were the most commonly reported adverse events, irrespective of study treatment relationship (**Table 6**)

Table 6. Adverse Events With ≥ 15% Incidence, Irrespective of Study Treatment Relationship, by Preferred Term and Maximum CTCAE Grade

Preferred Term	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)
Total	105 (99.1)	53 (50.0)	19 (17.9)
Neutropenia/neutrophil count decreased[a]	48 (45.3)	23 (21.7)	5 (4.7)
Nausea	46 (43.4)	3 (2.8)	0
Fatigue	43 (40.6)	6 (5.7)	0
Vomiting	32 (30.2)	3 (2.8)	0
Anemia	27 (25.5)	10 (9.4)	0
Diarrhea	27 (25.5)	3 (2.8)	0
Dyspnea	25 (23.6)	5 (4.7)	2 (1.9)
Constipation	20 (18.9)	0	0
Decreased appetite	20 (18.9)	1 (0.9)	0
White blood cell count decreased	18 (17.0)	5 (4.7)	0

[a] Data for preferred term "Neutropenia" and "Neutrophil count decreased" were pooled.

- Overall there were 42 deaths (39.6%) reported throughout the study
  - 28 of the deaths (66.7%) occurred > 30 days after the last dose of study drug
  - 14 on-treatment deaths (including 30 days after last dose) occurred; per investigator's assessment, none were suspected to be related to study drug

CONCLUSIONS

- **This study enrolled 106 patients across multiple malignancies**
- **Both safety and efficacy profiles align with data from other ribociclib single-agent study/studies**
- **Reflective of a patient population with extensive disease, clinical benefit was achieved for 19 patients (16 patients with stable disease and 3 patients with partial responses)**
- **Overall, the drug was well tolerated; neutropenia, nausea, fatigue, and vomiting were the most commonly reported adverse events**
- **Preliminary observations suggested that the *p16* deletion existed mutually exclusive of the *tp53* mutation in patients with a clinical benefit; conversely, patients without clinical benefit often displayed multiple mutational events affecting both pathways**
- **The correlation of clinical benefit and genomic mutation profiling is ongoing and will help to determine the significance of these mutations and potential for combination of ribociclib with other agents**

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