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Ph Ib/II study of LEE011 (CDK4/6 inhibitor) and LGX818 (BRAF inhibitor) in *BRAF*-mutant melanoma

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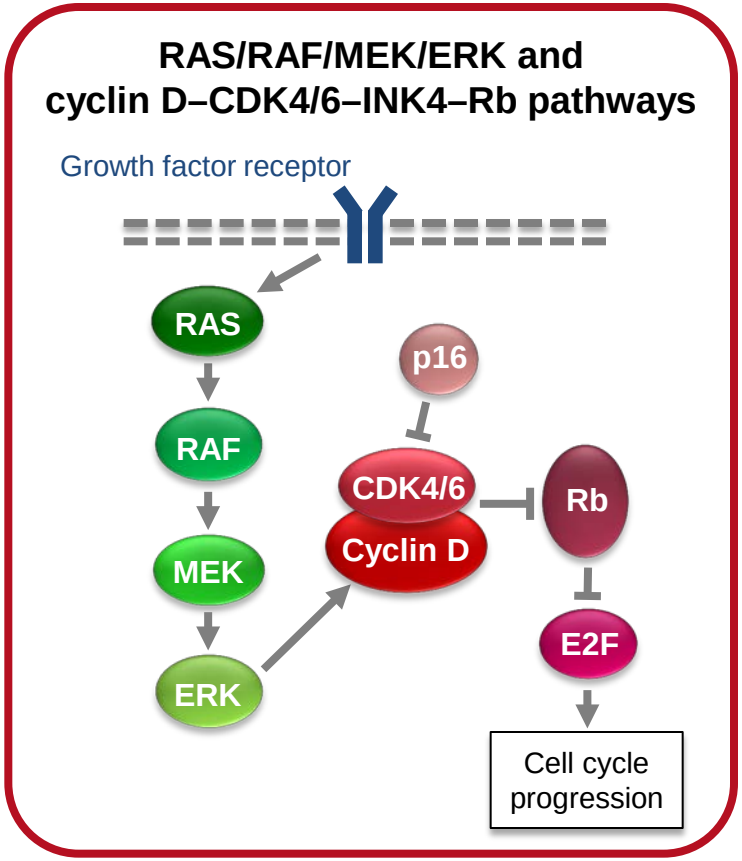
Disclosures

- LEE011 was discovered by NIBR in collaboration with Astex
- This study is sponsored by Novartis Pharmaceuticals Corporation
- Matteo S. Carlino has received honoraria from Novartis

NIBR, Novartis Institutes for BioMedical Research.

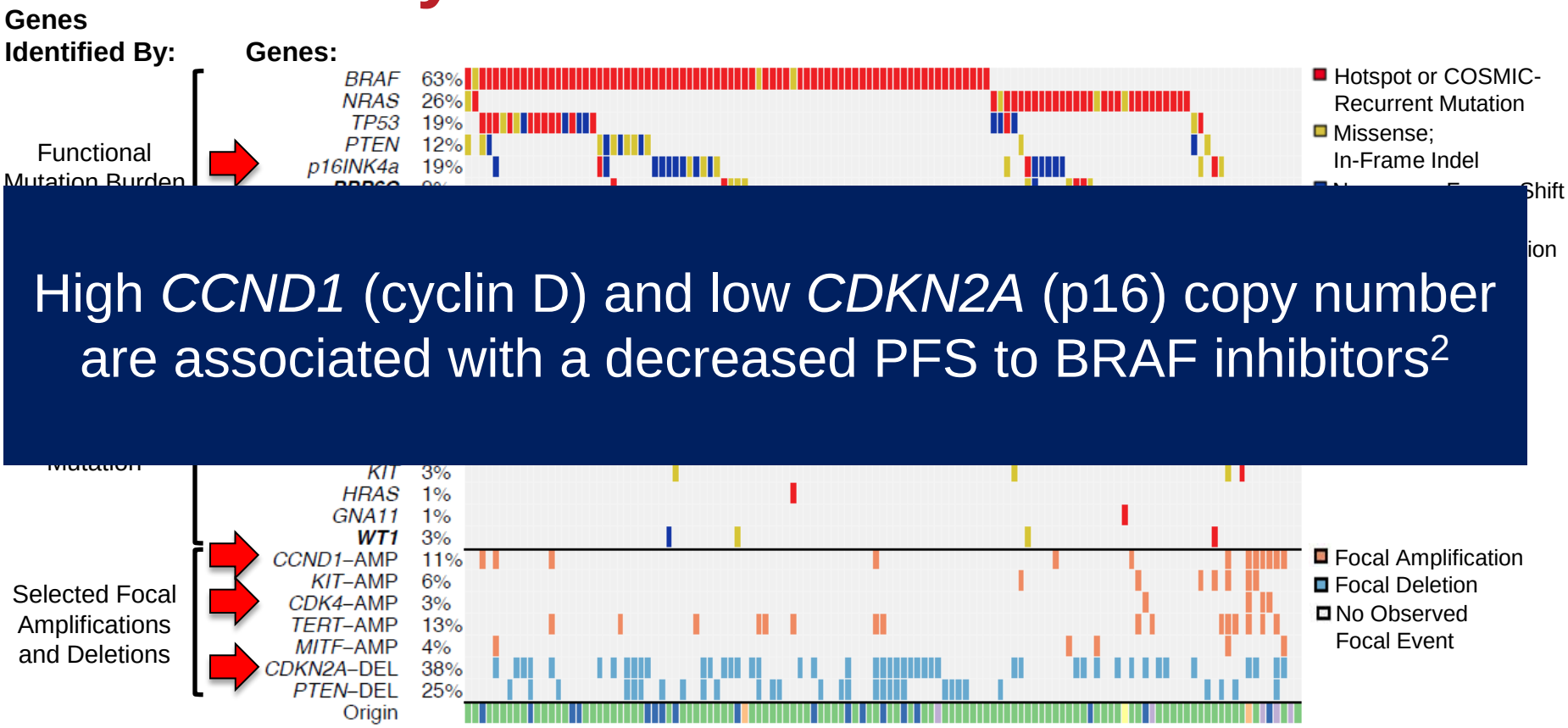
Introduction

- The majority of melanomas exhibit mutations in the RAS/RAF/MEK/ERK pathway; >40% have *BRAF*^{V600} activating mutations
- The cyclin D–CDK4/6–INK4–Rb pathway regulates cell cycle progression



CDK, cyclin-dependent kinase; E2F, E2 transcription factor; ERK, extracellular-signal-regulated kinase; INK4, inhibitor of CDK4; MEK, mitogen-activated protein kinase\ERK kinase; Rb, retinoblastoma protein.

Frequent Cyclin D–CDK4/6–INK4–Rb Pathway Aberrations in Melanoma[1]



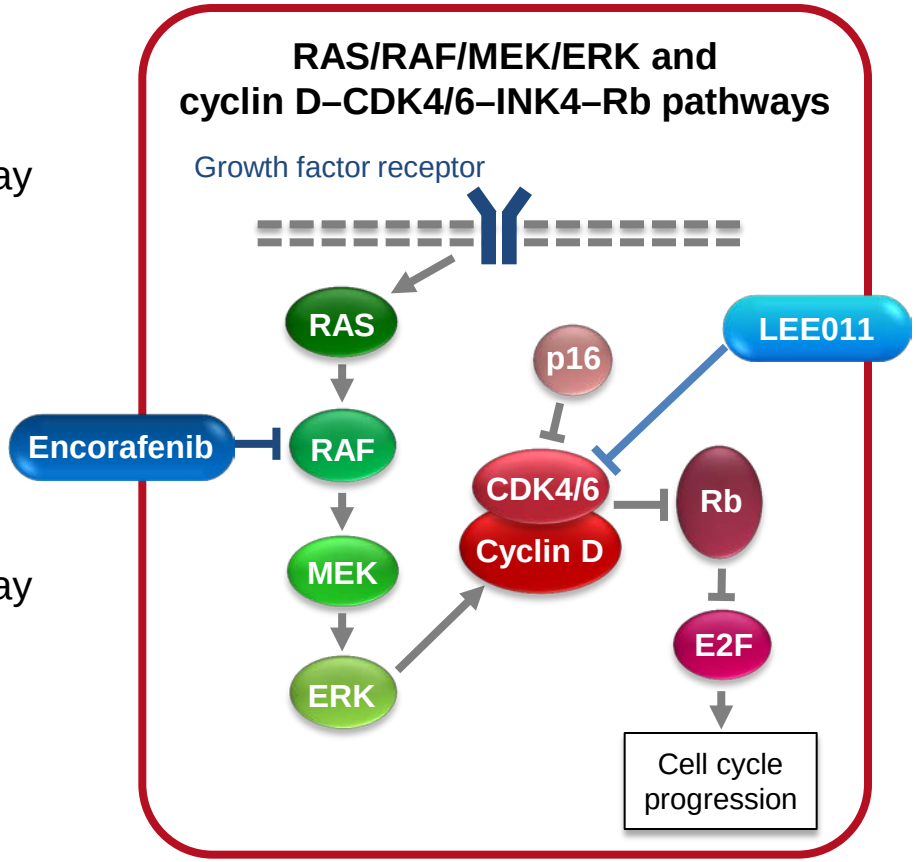
High *CCND1* (cyclin D) and low *CDKN2A* (p16) copy number are associated with a decreased PFS to BRAF inhibitors[2]

COSMIC, Catalog of Somatic Mutations In Cancer; Indel, insertion or deletion; LoF, loss of function; PFS, progression-free survival.

1. Reprinted from Hodis E, *et al. Cell.* 2012;150:251–263. Copyright 2012, with permission from Elsevier.
2. Nathanson KL, *et al. Clin Cancer Res* 2013;19:4868–4878.

LEE011 and Encorafenib: Single-Agent Data

- Encorafenib (LGX818) is an oral, selective BRAF inhibitor
  - MTD: 450 mg/day and RP2D: 300 mg/day on a continuous schedule[1,2]
  - Preliminary clinical activity observed in BRAFi-naïve patients with *BRAF* V600-mutant melanoma (12 PRs; 50%)[1]
- LEE011 is an oral, selective inhibitor of CDK4/6
  - MTD: 900 mg/day and RP2D: 600 mg/day on a 21-of-28-day schedule[3]
  - Preliminary clinical activity in patients with advanced solid tumours: 3 PRs (3%; 1 in *BRAF/NRAS* wildtype, *CCND1*-amplified melanoma)[3]



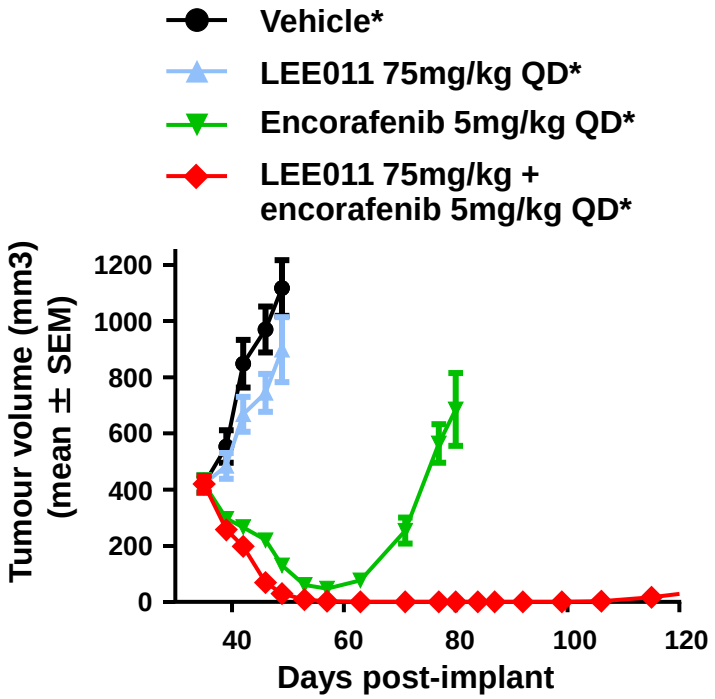
BRAFi, BRAF inhibitor; MTD, maximum tolerated dose; PR, partial response; RP2D, recommended Phase II dose.

1. Dummer R, *et al. Int J Oncol* 2013;31:Abstract 9028;
2. Gomez-Roca C, *et al.* ESMO 2014:Abstract 535P; 3. Infante JR, *et al. J Clin Oncol* 2014;32:Abstract 2528.

Combination of LEE011 and Encorafenib

- Preclinical studies demonstrate enhanced activity for combined LEE011 and encorafenib
  - LEE011 prevents the emergence of resistance to encorafenib
- Simultaneous BRAF and CDK4/6 inhibition may lead to enhanced clinical antitumour activity
- We present the Phase Ib dose escalation data of the LEE011 + encorafenib study in adult patients with *BRAF*-mutant melanoma

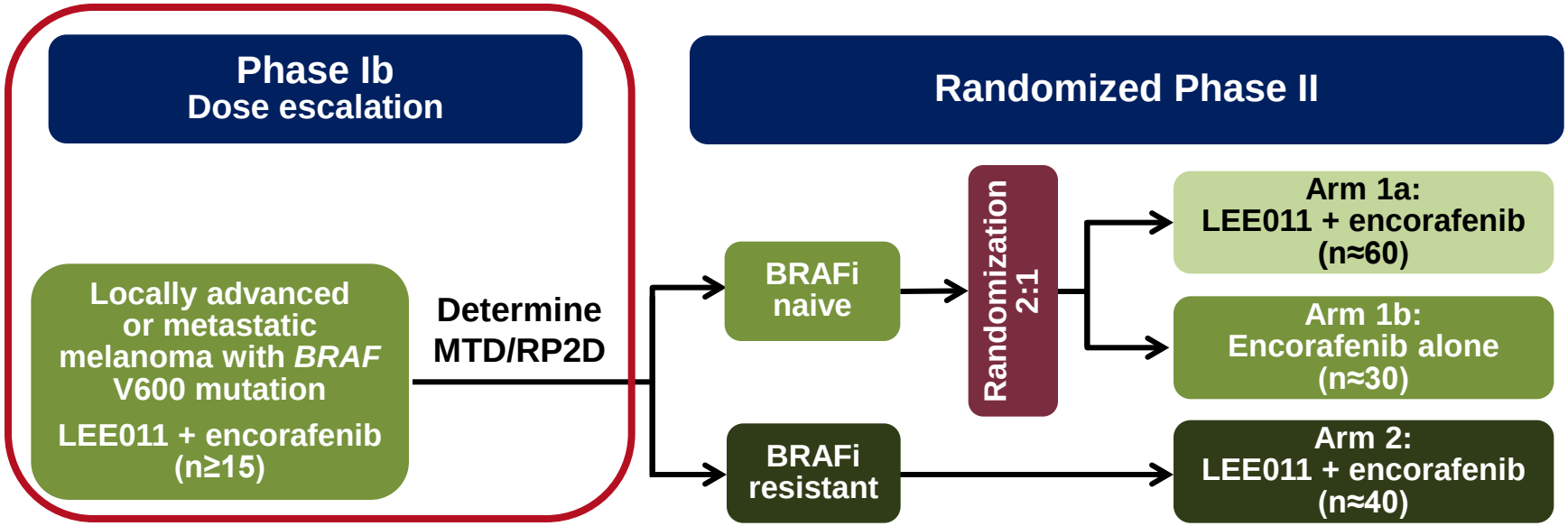
Synergy of LEE011 and encorafenib in a *BRAF*^{V600E}-mutant melanoma model



*Treatment started on Day 35

NCT01777776/CLEE011X2105.
SEM, standard error of the mean; QD, once daily.

CLEE011X2105 Study Design



Phase Ib objectives

- MTD/RP2D
- Safety/tolerability
- PK
- Clinical activity

Starting doses

- LEE011: 200 mg/day, 21-of-28-days
- Encorafenib: 300 mg/day, continuous

PK, pharmacokinetics.

Eligibility Criteria

Key inclusion criteria

- Adults with histologically confirmed locally advanced or metastatic melanoma with *BRAF* V600 mutation
- Evaluable and/or measurable disease as determined by RECIST v1.1
- Representative tumour sample available for molecular testing (unless otherwise agreed)
- ECOG performance status ≤2

Key exclusion criteria

- Symptomatic brain metastases (brain metastases allowed if stable >2 weeks after completion of definitive therapy)
- Symptomatic or untreated leptomeningeal disease
- Impaired cardiac function or clinically significant cardiac disease

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria In Solid Tumours.

Patient Characteristics

Patient characteristic	All N=28
Median age, years (range)	59 (23–81)
Male, n (%)	17 (61)
ECOG PS 0, n (%) 1, n (%) 2, n (%)	8 (29) 19 (68) 1 (4)
Current stage IIIb, n (%) IV, n (%) IVb, n (%) IVc, n (%)	1 (4) 14 (50) 2 (7) 10 (36)
Prior antineoplastic medication, n (%)	26 (93)
# lines 1–2, n (%) 3–4, n (%) >4, n (%)	12 (43) 9 (32) 5 (18)
Prior BRAFi or MEKi	20 (71)
Prior BRAFi only (no MEKi)	8 (29)
Prior MEKi only (no BRAFi)	2 (7)
Prior BRAFi and MEKi	10 (36)

MEKi, MEK inhibitor; PS, performance status.
Data cut-off: 10 July 2014.

Study Drug-related Adverse Events

(>15% in All Patients)

Adverse events, n (%)	LEE 200 mg + E 300 mg n=6		LEE 300 mg + E 200 mg n=12		LEE 400 mg + E 100 mg n=6		LEE 400 mg + E 200 mg n=4		All N=28	
	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4	All	G 3/4
Hand-foot syndrome*	2 (33)	1 (17)	7 (58)	1 (8)	3 (50)	1 (17)	1 (25)	0	**13 (46)**	**3 (11)**
Nausea	2 (33)	0	5 (42)	0	2 (33)	0	2 (50)	0	**11 (39)**	**0**
Pruritus	2 (33)	0	6 (50)	0	1 (17)	0	2 (50)	0	**11 (39)**	**0**
Rash	4 (67)	1 (17)	3 (25)	0	0	0	2 (50)	0	**9 (32)**	**1 (4)**
Fatigue	2 (33)	0	3 (25)	0	2 (33)	0	1 (25)	0	**8 (29)**	**0**
Alopecia	3 (50)	0	2 (17)	0	1 (17)	0	1 (25)	0	**7 (25)**	**0**
Dry skin	1 (17)	0	4 (33)	0	2 (33)	0	0	0	**7 (25)**	**0**
Myalgia	2 (33)	1 (17)	3 (25)	0	1 (17)	0	0	0	**6 (21)**	**1 (4)**
Vomiting	1 (17)	0	2 (17)	0	2 (33)	0	1 (25)	0	**6 (21)**	**0**
Diarrhea	2 (33)	0	2 (17)	0	0	0	1 (25)	0	**5 (18)**	**0**
Flushing	3 (50)	0	1 (8)	0	0	0	1 (25)	0	**5 (18)**	**0**
Stomatitis	0	0	4 (33)	0	1 (17)	0	0	0	**5 (18)**	**0**

E, encorafenib; G, grade.
*Includes palmar-plantar hyperkeratosis, palmoplantar keratoderma, and palmar-plantar erythrodysaesthesia syndrome.

Dose-limiting Toxicities

Dose	Treated, n	DLTs, n
LEE 200 mg + E 300 mg	6	2 (1 x G3 myalgia, 1 x G3 conjugated hyperbilirubinaemia)
LEE 300 mg + E 200 mg	12	0
LEE 400 mg + E 100 mg	6	1 (1 x G3 neuralgia)
LEE 400 mg + E 200 mg	4	1 (1 x G2 rash requiring dose reduction)

- MTD/RP2D was not established

DLT, dose-limiting toxicity.

Pharmacokinetics

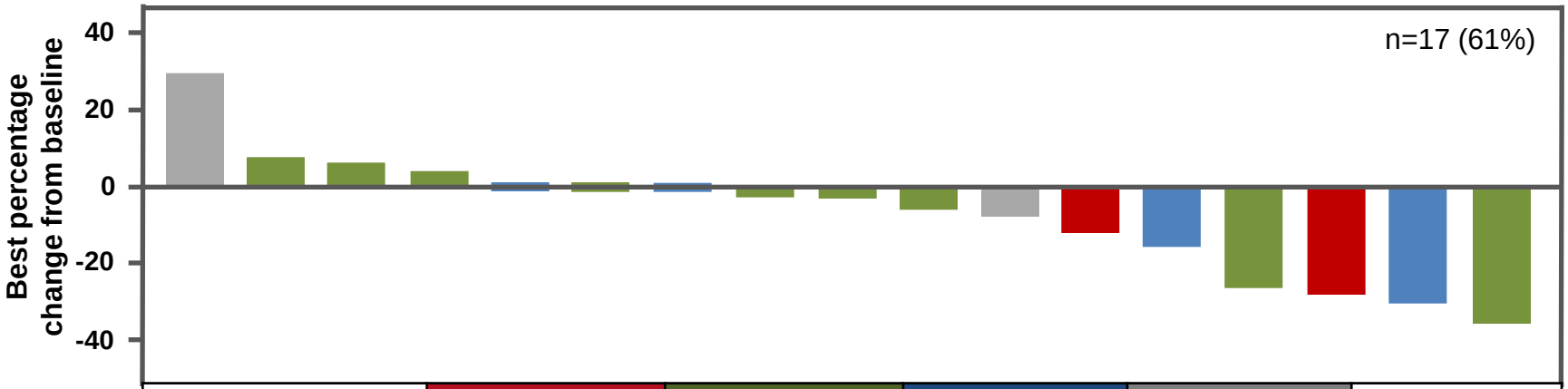
- Both agents were absorbed rapidly (within 1–4 hours)
- LEE011 (CYP3A4 inhibitor) at higher doses increased encorafenib exposure, whereas encorafenib (CYP3A4 inducer) at higher doses decreased LEE011 exposure

PK parameter at steady state	Encorafenib (Cycle 1 Day 21)			LEE011 (Cycle 1 Day 21)		
	LEE 200 mg + E 300 mg	LEE 300 mg + E 200 mg	LEE 400 mg + E 100 mg	LEE 200 mg + E 300 mg	LEE 300 mg + E 200 mg	LEE 400 mg + E 100 mg
$AUC_{0\text{-}24}$ (hr•ng/mL),* [n]	13600 [1]	7860 (75) [5]	11300 (50) [3]	588 [1]	5030 (47) [5]	17400 (26) [3]
T_{max} (hr),† [n]	1 (0.5–2) [3]	1.6 (1.0–3.6) [6]	2.1 (1–4) [3]	2 (0.5–3.8) [3]	2.8 (0.5–4.2) [6]	4 (2–4.1) [3]
Fold change in $AUC_{0\text{-}24}$	–	~1.6	~2.6	–	0.5–0.7	No change

Historic single-agent data[1,2]	Encorafenib (Cycle 1 Day 15)			LEE011 (Cycle 1 Day 18/21)				
	300 mg	200 mg	100 mg	140 mg	260 mg	280 mg	350 mg	400 mg
$AUC_{0\text{-}24}$ (hr•ng/mL),* [n]	10100 (53) [4]	5060 (36) [3]	4360 (59) [5]	2490 (41) [3]	5990 (34) [4]	6600 (29) [3]	14500 (8) [3]	12400 (68) [3]

*Geo-mean (CV% geo-mean); †median (range).
$AUC_{0\text{-}24}$, area under the curve from time zero to 24 hours post-dose; T_{max}, time of maximum observed concentration.
1. Novartis data on file; 2. Bhansali SG, *et al. ACCP* 2014;Abstract 1-27-1996846.

Activity of LEE011 + Encorafenib

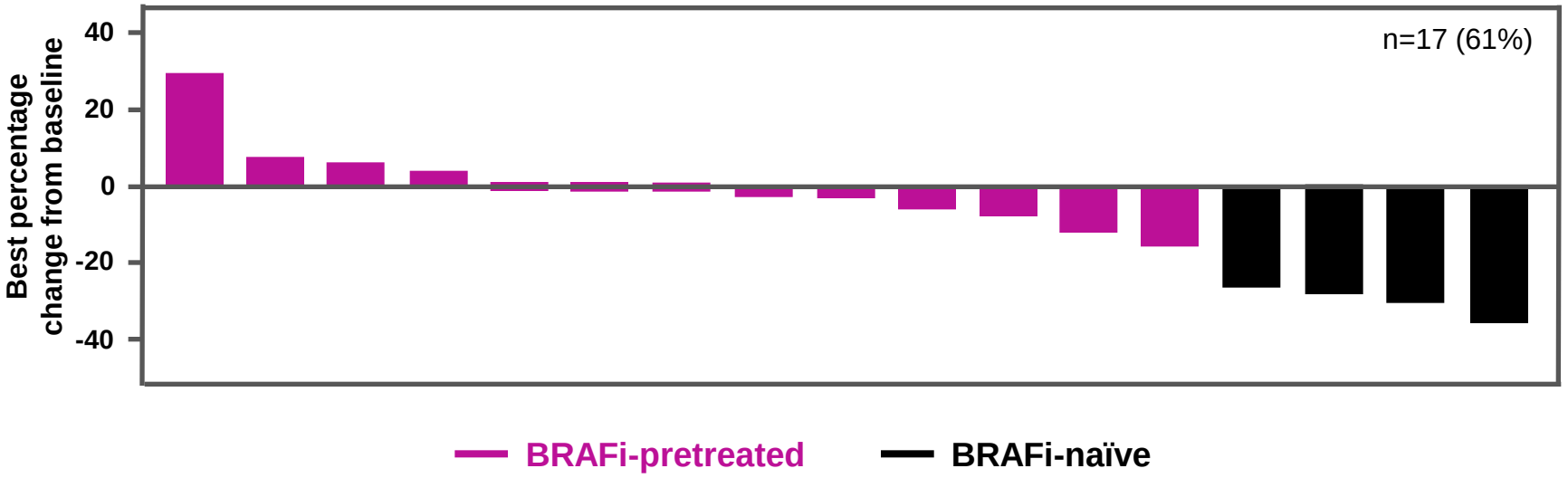


Best overall response, n (%)	LEE 200 mg + E 300 mg n=6	LEE 300 mg + E 200 mg n=12	LEE 400 mg + E 100 mg n=6	LEE 400 mg + E 200 mg n=4	All N=28
PR	1 (17)	1 (8)	0	0	2 (7)
SD*	2 (33)	6 (50)	4 (67)	1 (25)	13 (46)
PD	1 (17)	3 (25)	1 (17)	1 (25)	6 (21)
Unknown	2 (33)	2 (17)	1 (17)	2 (50)	7 (25)

*Includes 3 unconfirmed PRs.

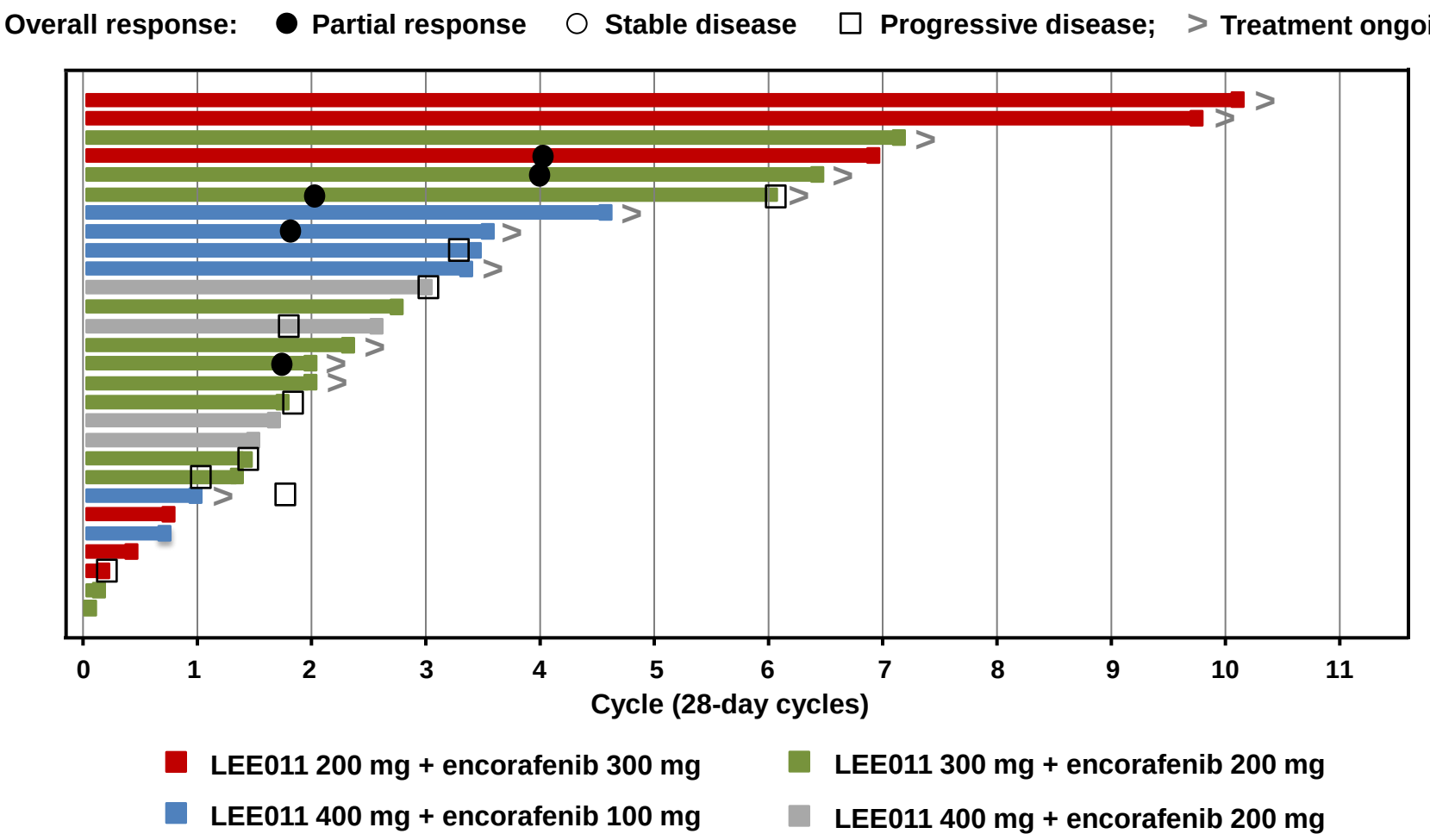
PD, progressive disease; SD, stable disease.

Activity of LEE011 + Encorafenib by Prior BRAF Inhibitor Treatment



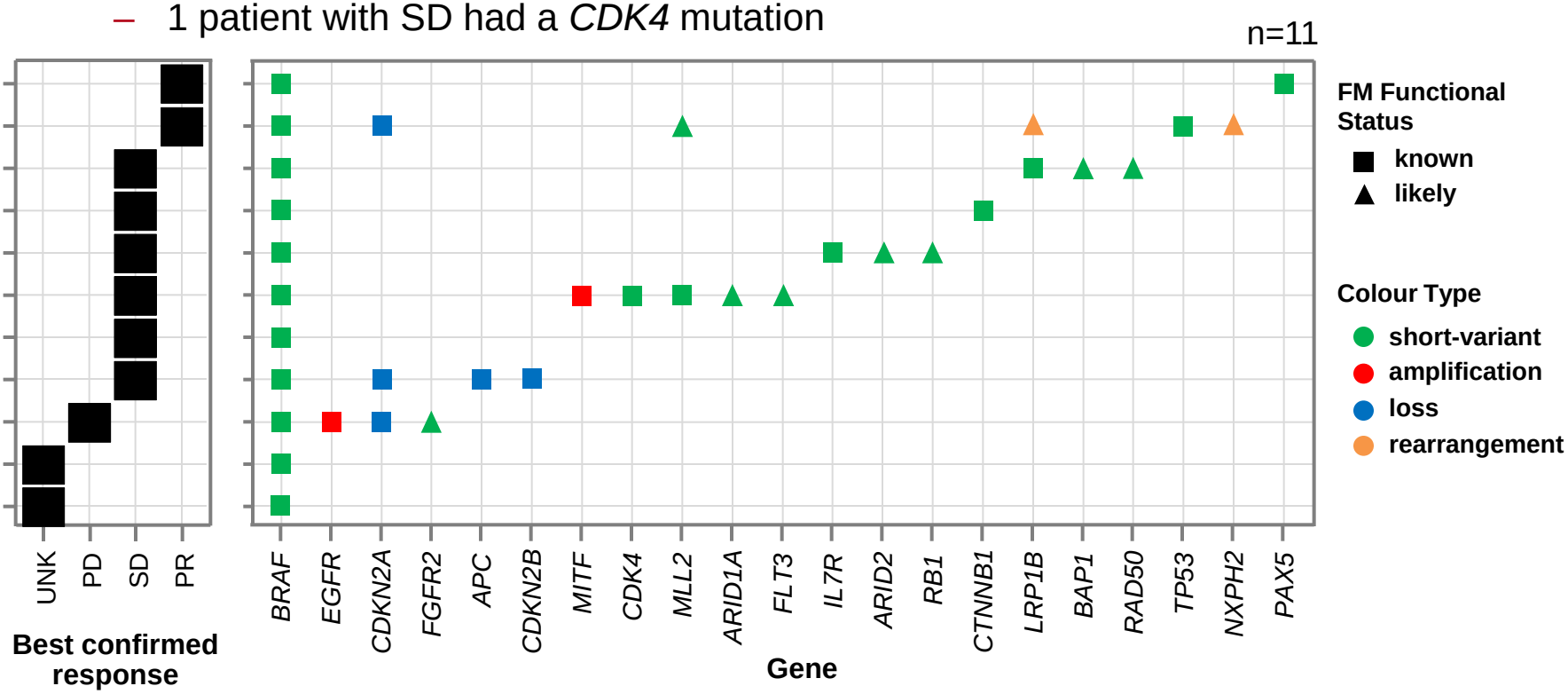
- One patient with a PR was BRAFi-naïve, the other was previously treated with a BRAFi

Duration of Exposure and RECIST Evaluation



Genomic Aberrations Identified by NGS

- An NGS panel of 327 genes was used
  - 3 patients had *CDKN2A* (p16) loss (1 PR, 1 SD, 1 PD)
  - 1 patient with SD had a *CDK4* mutation



FM, foundation medicine; NGS, next-generation sequencing.

Summary

- Combination of LEE011 and encorafenib had an acceptable safety profile
  - Grade 3/4 adverse events were rare; hand-foot syndrome (n=3; 11%) and anaemia (n=2; 7%) were most common
- SD was best response in 46% of patients, one SD lasted >9 cycles
- Evidence of clinical activity was observed: 2 confirmed PRs and 3 unconfirmed PRs
- Little evidence of response was documented in patients resistant to BRAF inhibition
- A study with the triple combination of LEE011 + encorafenib + MEK162 (binimetinib; MEK inhibitor) in *BRAF*-mutant melanoma (NCT01543698) is ongoing

Acknowledgements

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