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Preliminary Results From a Phase Ib/II, Open-Label, Dose-Escalation Study of the Oral Selective BRAF Inhibitor LGX818 in Combination With the Oral MEK1/2 Inhibitor MEK162 in *BRAF* V600–Dependent Advanced Solid Tumors

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INTRODUCTION

- Combining BRAF and MEK inhibitors in *BRAF* V600 mutant tumors may prevent and/or overcome resistance to monotherapy and potentially improve the safety profile of single-agent therapy[1]
- LGX818 is a potent and highly selective BRAF inhibitor (BRAFi) that has shown signs of efficacy in a phase I study in advanced tumors including melanoma and metastatic colorectal cancer (mCRC)[2]
- MEK162 is a potent, highly selective inhibitor of MEK1/2. Promising data have been reported in trials in advanced solid tumors including *NRAS* or *BRAF* V600 mutant melanoma.[3-6] A phase III study in *NRAS* mutant melanoma is planned[7]
- This phase Ib/II study is evaluating LGX818 + MEK162 in patients with advanced *BRAF* V600 mutant tumors[8]

Figure 1. Mechanism of Action of Study Medications[1,2,6]

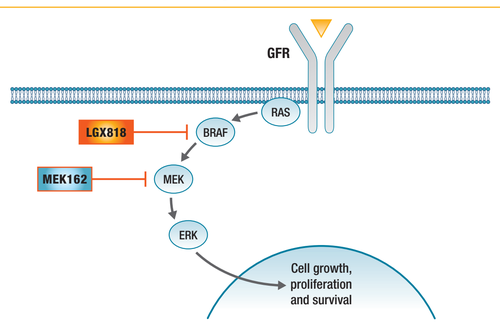
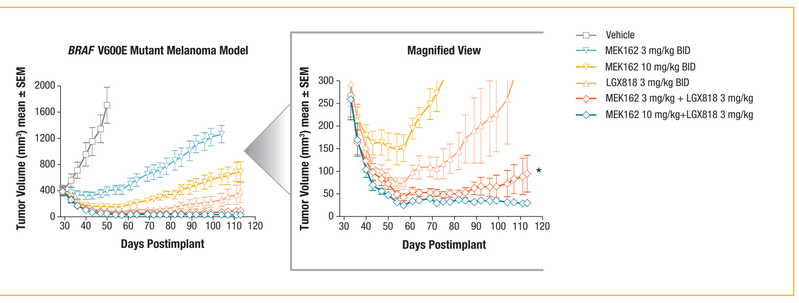


Figure 2. Preclinical Data in a Model of *BRAF* Mutant Melanoma Support the Combination of LGX818 and MEK162



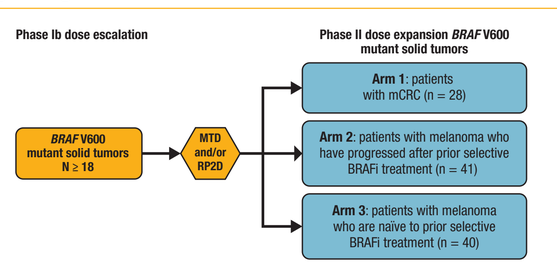
[a] 12.5% of mice had progressive disease.
BID, twice daily; **SEM**, standard error of the mean.

METHODS

Study Design

- An ongoing phase Ib/II study is evaluating once daily (QD) LGX818 + twice daily (BID) MEK162 in BRAFi naïve or pretreated patients with *BRAF* V600 mutant tumors
- The objectives for each part of the study are
  - Phase Ib: to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for LGX818 + MEK162 using a Bayesian logistic regression model.
  - Phase II: to assess the efficacy of the combination in the phase II populations

Figure 3. Study Design

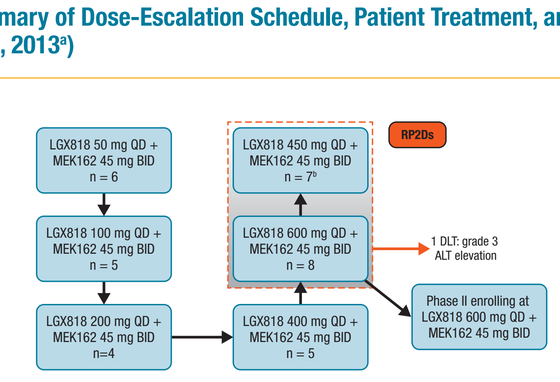


RESULTS

Study Status

- As of March 8, 2013, enrolled patients were treated with LGX818 QD + MEK162 BID at the following dose levels (DLs): 50 mg + 45 mg, 100 mg + 45 mg, 200 mg + 45 mg, 400 mg + 45 mg, 450 mg + 45 mg, and 600 mg + 45 mg
- At the time of data cutoff, 30 patients with *BRAF* V600 mutant tumors have been enrolled across 6 DLs including
  - 9 BRAFi naïve and 14 BRAFi pretreated melanoma
  - 2 BRAFi naïve and 1 BRAFi pretreated papillary thyroid cancer (PTC)
  - 2 BRAFi naïve and 2 BRAFi pretreated mCRC
- There were no dose-limiting toxicities (DLTs) in the first 5 DLs. One DLT was reported at the 600 mg + 45 mg DL (grade 3 alanine aminotransferase [ALT] elevation)
- The MTD has not yet been determined in this study and 2 RP2Ds have been declared: 600 mg + 45 mg and 450 mg + 45 mg
- The phase II part of the study was initiated at 600 mg + 45 mg

Figure 4. Summary of Dose-Escalation Schedule, Patient Treatment, and DLTs (as of April 16, 2013[a])



[a] Additional patients were enrolled after the data cut-off (March 8, 2013) in the phase Ib part at 450 mg + 45 mg and 800 mg + 45 mg to better assess the safety and tolerability of the combination.
[b] Two patients had been enrolled at data cutoff (March 8, 2013), and 5 additional patients have been enrolled since the data cutoff.

Clinical Pharmacokinetics (PK)

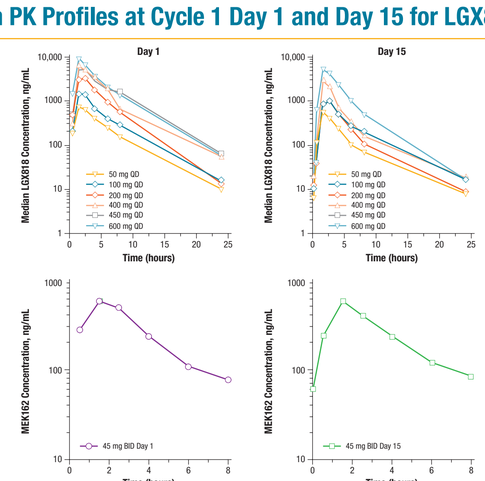
- LGX818 (50, 100, 200, 400, 450, and 600 mg QD)
  - Maximum and overall exposure was proportional to dose on both days (**Figure 5**)
  - PK profile of combination with MEK162 was similar to that of monotherapy on both day 1 and day 15
- MEK162 (45 mg BID)
  - PK profile of combination with any dose of LGX818 was similar to that of monotherapy on both day 1 and day 15
- No drug-drug interaction (DDI) was observed
  - Drug exposures were similar in combination compared with single-agent studies of MEK162 and LGX818

Table 1. Patient Characteristics—Phase Ib

	Melanoma BRAFi Naïve n = 9	Melanoma BRAFi Pretreated n = 14	mCRC n = 4	PTC n = 3
Age, median (range), years	51 (33-68)	51 (25-70)	60 (30-67)	74 (69-75)
Sex, n				
Male	4	8	2	3
Female	5	6	2	0
WHO performance status at baseline, n				
0	6	6	0	2
1	3	8	4	1
Disease stage at baseline, n				
IIIc	0	1	0	0
IV	2	4	4	1
IV M1a	1	0	0	0
IV M1b	0	1	0	0
IV M1c	6	8	0	2
***BRAF* V600 mutation status, n**				
V600E	8	14	4	3
V600K	1	0	0	0
Number of prior antineoplastic therapies				
0	3	0	0	0
1	2	5	0	2
2	2	3	0	0
3	1	3	2	1
> 3	1	3	2	0
For patients previously treated with a selective BRAFi				
Number of patients		14	2	1
Days on prior BRAFi, median (range)		248 (47-1055)	95 (21-168)	223 (NA)
Days since discontinuation of prior BRAFi, median (range)		72 (3-442)	35 (28-42)	107 (NA)

NA, not applicable; **WHO**, World Health Organization.

Figure 5. Median PK Profiles at Cycle 1 Day 1 and Day 15 for LGX818 and MEK162



Safety

- The combination was well tolerated with no substantial increase in adverse events (AEs) for the combination vs single-agent therapy
- The combination may mitigate some on-target AEs common with BRAFi monotherapy including cutaneous toxicities (no events of hyperkeratosis or KA/SCC and only 1 case of grade 1 HFSR), myalgia, and arthralgia
- No febrile or photosensitivity events have been reported to date
- The most common AEs were grade 1/2 gastrointestinal toxicities, visual disturbances, headache, and fatigue
- 5 patients (16.7%) had grade 3 AEs suspected to be treatment related (2 with transaminase increases, 2 with lipase increases, 1 with retinal vein occlusion, and 1 with maculopapular rash)
- 1 patient (3.3%) had a dose reduction of MEK162 and LGX818
- 2 patients (6.7%) discontinued treatment due to an AE (1 due to elevated transaminase levels and 1 due to retinal vein occlusion)

HFSR, hand-foot skin reaction; **KA**, keratoacanthoma; **SCC**, squamous cell carcinoma

Table 3. AEs Suspected to be Treatment Related (≥ 10% of Patients; as per March 8, 2013)

	All Patients N = 30	
	All Grades n (%)	Grade 3[a] n (%)
Total	**26 (86.7)**	**5 (16.7)**
Gastrointestinal disorders		
Nausea	14 (46.7)	—
Diarrhea	10 (33.3)	—
Abdominal pain	5 (16.7)	—
Vomiting	4 (13.3)	—
Ocular effects		
Visual impairment	6 (20.0)	—
Vision blurred	4 (13.3)	—
Laboratory values		
Blood creatine kinase increased	5 (16.7)	—
Transaminases increased	3 (10.0)	2 (6.7)
Nervous system disorders		
Headache	6 (20.0)	—
Dysgeusia	3 (10.0)	—
Other disorders		
Fatigue	7 (23.3)	—
Flushing	4 (13.3)	—
Pain in extremity	3 (10.0)	—
Peripheral edema	3 (10.0)	—

[a] There were no grade 4 AEs. Additional grade 3 AEs not mentioned in this table were increased lipase levels (n = 2), retinal vein occlusion (n = 1), and maculopapular rash (n = 1).

Best Confirmed Response—Dose Escalation

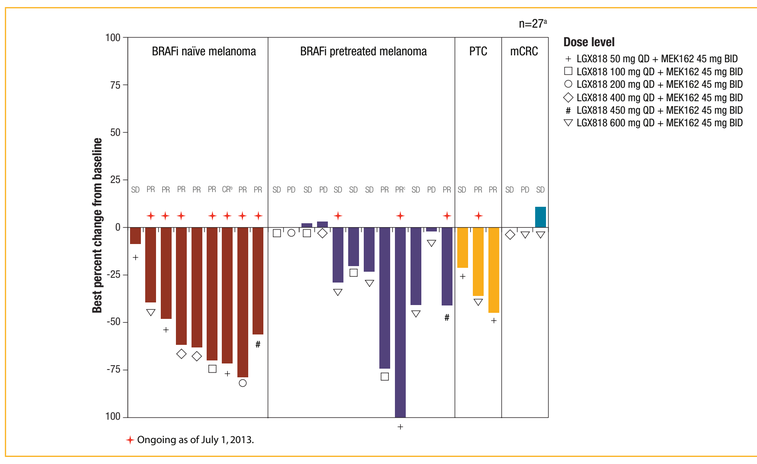
- The disease control rate was 100% for BRAFi naïve and 64% for BRAFi pretreated patients with melanoma, 50% for patients with mCRC, and 100% for patients with PTC
- The overall response rate was 89% for BRAFi naïve and 21% for BRAFi pretreated patients with melanoma and 67% for patients with PTC

Table 2. Clinical Efficacy—Phase Ib

Endpoint, n (%)[a] *All dose levels pooled*	Melanoma BRAFi Naïve (n = 9)	Melanoma BRAFi Pretreated (n = 14)	mCRC (n = 4)	PTC (n = 3)
Patients evaluable for response	9	14	4	3
Best overall response (confirmed)				
Complete response (CR)	1 (11.1)	0	0	0
Partial response (PR)	7 (77.8)	3 (21.4)	0	2 (66.7)
Stable disease (SD)	1 (11.1)	6 (42.9)[b]	2 (50.0)	1 (33.3)
Progressive disease (PD)	0	4 (28.6)	1 (25.0)	0
Unknown	0	1 (7.1)[c]	1 (25.0)[c]	0
Overall response rate (CR + PR)	8 (88.9)	3 (21.4)	0	2 (66.7)
Disease control rate (CR + PR + SD)	9 (100.0)	9 (64.3)	2 (50.0)	3 (100.0)

[a] Study ongoing at data cutoff (March 8, 2013); patients updated as of June 25, 2013.
[b] Includes 1 unconfirmed PR.
[c] Patient discontinued due to death from underlying disease.

Figure 6. Best Confirmed Response by Disease State and BRAFi Status



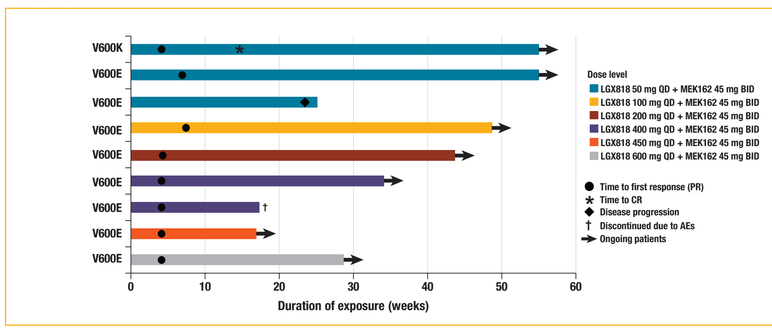
[a] Patients with missing best percent change from baseline and unknown overall response are not included.
[b] Only nodular lesions assessed.
[c] PR with 100% tumor reduction; however, non-target lesions were still present.

Duration of Exposure

As of July 1, 2013, 11 of 30 patients were ongoing, including

- 7 of 9 patients with BRAFi naïve melanoma
  - Range duration of exposure was 3.9-12.6 months
- 3 of 14 patients with BRAFi pretreated melanoma
  - Range duration of exposure was 0.2-12.6 months
- 1 of 7 patients with mCRC or PTC
  - Range duration of exposure was 0.2-8.4 months

Figure 7. Days on Treatment for Patients With BRAFi Naïve Melanoma as of July 1, 2013



CONCLUSIONS

- **The RP2Ds were declared for the combination of LGX818 and MEK162 at 450 mg + 45 mg and 600 mg + 45 mg DLs (LGX818 QD + MEK162 BID, respectively)**
- **The phase II part of the study is enrolling patients at the 600 mg + 45 mg DL**
- **LGX818 exposure increased in a dose proportional manner and no DDI between LGX818 and MEK162 exposure was observed**
- **Preliminary data from this study indicate that LGX818 + MEK162 can be safely combined**
  - **The combination may mitigate some on-target AEs common with single BRAFi therapy**
  - **There were no febrile or photosensitivity events reported to date in this study and a low incidence of rash (only 1 patient had acneiform dermatitis)**
- **Clinical activity was reported in BRAFi naïve and pretreated patients with *BRAF* V600 mutant melanoma and PTC**
- **Based on the promising data from this study, a phase III trial combining LGX818 and MEK162 is due to start accrual by the end of this year**

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DISCLOSURES

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