Study Design
- An ongoing Phase I/B study is evaluating safety data (q28 days) of LGX818 + MEK162 in BRAF naïve or pretreated patients with BRAF V600E mutant tumors.
- The objectives for each part of the study are:
  - Phase I: to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) for LGX18 + MEK162 using a Bayesian logistic regression model.
  - Phase II: to assess the efficacy of the combination in the phase I populations

RESULTS

Study Status
- As of April 13, 2013, enrolled patients were treated with LGX818 + MEK162: 102 patients treated with BRAF V600E mutant tumors.
- All of the data are from patients treated with LGX818 + MEK162 in BRAF naïve or pretreated patients with BRAF V600E mutant tumors.
- The MTD has not yet been determined in this study and 2 RP2Ds have been declared: 600 mg and 45 mg.
- There were no dose-limiting toxicities (DLTs) in the first 5 DLs. One DLT was reported at the 800 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 DL’s (as of April 16, 2013)

Clinical Pharmacokinetics (PK)
- LGX818 (BID, 100, 200, 400, 450, and 600 mg QD)
  - Maximum and overall exposure was proportional to dose on both days (Figure 6)
  - PK profile of combination with MEK162 was similar to that of monotherapy on both day 1 and day 15

Table 1. Patient Characteristics—Phase II

Table 2. Clinical Efficacy—Phase II

Figure 5. Median PK Profiles at Cycle 1 Day 1 and Day 15 for LGX819 and MEK162

Best Confirmed Response—Dose Escalation
- The disease control rate was 100% for BRAF naïve and 69% for BRAF-pretreated patients with melanoma, 50% for patients with CRC, and 100% for patients with PTC.
- The overall response rate was 65% for BRAF naïve and 21% for BRAF-pretreated patients with melanoma, 47% for patients with CRC, and 0% for patients with PTC.
- No febrile or photosensitivity events have been reported to date.

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

CONCLUSIONS
- The RPDs 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.
- The overall response rate was 100% for BRAF naïve and 69% for BRAF-pretreated patients with melanoma, 50% for patients with CRC, and 100% for patients with PTC.
- There were no febrile or photosensitivity events reported to date in this study and a low incidence of rash (only 1 patient had acrodermatitis).
- Clinical activity was reported for BRAF naïve and pretreated patients with BRAF V600E mutant melanoma and PTC.
- Based on the promising data from this phase II trial, combining LGX818 and MEK162 is due to start on schedule by the end of this year.

Table 3. AEs Suspected to be Treatment Related (≥ 10% of Patients; as per NCI CTCAE V4.03)

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

REFERENCES

DISCLOSURES
- D.T.B. and D.T.T. have received research support from Novartis.
- D.T.B. served on advisory boards for Roche/Genentec and Lilly.
- D.T.B. received research support from Lilly.
- D.T.B. received travel support from Roche/Genentec.

ACKNOWLEDGMENTS
- The authors wish to thank additional Novartis colleagues (Penny Zhu, Nassim Sleiman, Nadege Pfender, and Darrin Stuart) for providing support for this presentation.

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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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Poster Presentation at the 8th World Congress of Melanoma, July 17-20, 2013, Hamburg, Germany.

This study was funded by Novartis Pharmaceuticals Corporation.