Mutations in \textit{BRAF} and \textit{NRAS} account for 40\%-50\% and 15\%-25\% of mutations in cutaneous melanoma, respectively, and treatment is rapidly evolving with the recent approval of therapies targeting the MAPK-signaling pathway. Encorafenib (LGX818), a potent, highly selective RAF inhibitor, has demonstrated phase 1 single-agent clinical activity in \textit{BRAF} \textit{IgG1} naive (overall response rate [ORR], 65\% [17/26]) and \textit{BRAF} \textit{IgG2} pretreated (ORR, 11\% [3/28]) patients with \textit{BRAF} V600–mutant metastatic melanoma (Dummer et al. ASCO, 2013;[abstract 9028]). Similar to other \textit{BRAF}is, common adverse events (AEs) associated with encorafenib included cutaneous toxicities (palmar-plantar erythrodysesthesia syndrome, hyperkeratosis, keratosis pilaris, alopecia, dry skin), arthralgia, and fatigue.

Currently, there are no approved specific therapies for patients with \textit{NRAS}-mutant melanoma. In a phase 2 study, the MEK inhibitor binimetinib (MEK162) was the first targeted agent to show clinical activity in the \textit{NRAS}-mutant subset, with 20\% of melanoma patients with \textit{NRAS} mutations (6/30) achieving partial response (Ascierto et al. \textit{Lancet Oncol}, 2013). Binimetinib-associated AEs included dermatitis acneiform, peripheral or facial edema, diarrhea, increased creatine phosphokinase, and retinal events. A phase 3 trial evaluating binimetinib vs dacarbazine in \textit{NRAS}-mutant melanoma (NEMO) is currently recruiting worldwide.

To increase response duration to encorafenib monotherapy and potentially improve single-agent safety, combined encorafenib and binimetinib in \textit{BRAF} V600–mutant melanoma was investigated in a phase 1b/2 study. Clinical response was achieved in both \textit{BRAF} naive (ORR, 89\% [8/9]) and \textit{BRAF} pretreated (ORR, 21\% [3/14]) patients (Keeford et al. World Congress of Melanoma, 2013;[abstract P-320]). The combination also mitigated some on-target \textit{BRAF}-associated AEs, including cutaneous toxicities, myalgia, and arthralgia. No febrile events or photosensitivity were observed. A phase 3 trial assessing encorafenib plus binimetinib or encorafenib alone vs vemurafenib in \textit{BRAF} V600–mutant melanoma (COLUMBUS) is currently enrolling globally.

A summary of the data supporting clinical development of encorafenib and binimetinib will be presented.
Binimetinib (MEK162) is a potent, highly-selective inhibitor of MEK1/2 that has shown promising clinical activity in NRAS-mutant and BRAF V600–mutant metastatic melanoma\textsuperscript{1,2}.

Single-agent binimetinib in NRAS-mutant and BRAF V600–mutant melanoma (Phase 2, NCT01320085; N = 71)\textsuperscript{1,2}

- An ORR of 20% was observed for both groups
- Disease control rate (DCR):
  - NRAS-mutant group: 63%; BRAF-mutant group: 51%
- Median progression-free survival (PFS):
  - NRAS-mutant group: 3.7 months (95% CI, 2.5-5.4 months); BRAF-mutant group: 3.3 months (95% CI, 2.0-3.8 months)

Maximum Tumor Reduction from Baseline with Binimetinib in Patients with NRAS-Mutant Melanoma

NEMO: Phase 3 Trial of Binimetinib in NRAS-Mutant Melanoma

Patients with advanced unresectable or metastatic cutaneous melanoma
- Cutaneous melanoma or melanoma of unknown primary origin
- Any number of prior immunotherapy regimens allowed (N = 393)

Prescreening to centrally confirm NRAS Q61 mutation

RANDOMIZATION 2:1
Stratification by stage (IIIC, IVM1a, and IVM1b vs IVM1c), Eastern Cooperative Oncology Group performance status (0 vs 1), and prior immunotherapy (yes vs no)

Binimetinib
45 mg BID
n = 262

Dacarbazine
1000 mg/m² q3w
n = 131

Primary endpoint: PFS; Secondary endpoints: OS, ORR, TTR, DOR, DCR, safety, quality of life (QoL).

Encorafenib (LGX818), a highly-selective BRAF inhibitor (BRAFi), has demonstrated:

- An extended dissociation half-life, longer-lasting target inhibition, and more potent antiproliferative activity in BRAF V600E–mutant melanoma models than approved BRAF inhibitors vemurafenib and dabrafenib\(^1\)
- Clinical activity alone or in combination with binimetinib in BRAF V600–mutant metastatic melanoma\(^2,3\)

### Combined encorafenib and binimetinib in BRAFi-naive or –pretreated BRAF V600–mutant melanoma (Phase 1/2, NCT01543698; N = 54)\(^2,4\)

- The DCR was 100.0% for BRAFi-naive patients and 64.3% for BRAFi-pretreated patients with melanoma
- The ORR was 88.9% for BRAFi-naive patients and 21.4% for BRAFi-pretreated patients with melanoma
- The combination was well tolerated with no substantial increase in AEs for the combination vs single-agent therapy
- The combination may mitigate some on-target AEs common with BRAFi monotherapy including
  - No events of hyperkeratosis, KA, or SCC
  - Only 1 case of grade 1 hand-foot skin reaction
  - Reduced myalgia and arthralgia
  - Only a low occurrence of febrile or photosensitivity events have been reported to date

### Maximum Tumor Reduction from Baseline with Encorafenib Plus Binimetinib—Dose Escalation

Patients with unresectable or metastatic melanoma (N = 900)

Prescreening to centrally confirm *BRAF* V600E or V600K mutation

RANDOMIZATION 1:1:1
Stratification by stage (IIIB + IIIC + IVM1a + IVM1b vs IVM1c), ECOG performance status (0 vs 1), and prior first-line immunotherapy (yes vs no)

- Encorafenib + Binimetinib
  450 mg QD  45 mg BID
  n = 300

- Encorafenib
  300 mg QD
  n = 300

- Vemurafenib
  960 mg BID
  n = 300

**Primary endpoint:** PFS; **Secondary endpoints:** OS, ORR, TTR, DCR, DOR, safety, performance status, QoL.

Conclusions

- Overall, binimetinib and encorafenib have demonstrated promising efficacy and acceptable safety profiles alone or in combination in NRAS-mutant or BRAF V600–mutant metastatic cutaneous melanoma, warranting further clinical investigation.
- Binimetinib is the first targeted therapy to show activity in patients with NRAS-mutant melanoma.
- Encorafenib was associated with low rates of pyrexia, squamous cell carcinoma, keratoacanthoma, and photosensitivity, which have been described in the safety profile of other BRAF inhibitors\(^1,2\).
- Encorafenib demonstrated a further improved safety profile when administered in combination with binimetinib.
- Pivotal randomized phase 3 trials of binimetinib and/or encorafenib in NRAS-mutant (NEMO) and BRAF V600–mutant (COLUMBUS) melanoma are ongoing.