LBA – 004 Efficacy and safety results from IMblaze370, a randomised Phase III study comparing atezolizumab+cobimetinib and atezolizumab monotherapy vs regorafenib in chemotherapy-refractory metastatic colorectal cancer

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Background: Patients with chemotherapy-refractory microsatellite stable (MSS) metastatic colorectal cancer (CRC) are a population with limited treatment options and relatively short survival. Atezolizumab (an anti–PD-L1 mAb) inhibits the binding of PD-L1 to its receptors PD-1 and B7.1, leading to the re-invigoration of tumour-specific T-cell immunity. Cobimetinib inhibits MEK1/MEK2 in the MAPK pathway, and blocking the MAPK pathway has been shown to favourably alter the tumour, tumour microenvironment and T-cell responses to promote anti-tumour immune activity. We hypothesized that combining atezolizumab with cobimetinib may allow better immune recognition and generate greater anti-tumour effects than either agent alone in MSS/microsatellite instability-low (MSI-L) metastatic CRC. Here we report the primary analysis results from IMblaze370 (NCT02788279), a global, multi-centre, open-label, randomised Phase III trial comparing atezolizumab+cobimetinib and atezolizumab monotherapy with standard-of-care regorafenib in patients with previously treated, unresectable locally advanced or metastatic CRC.

Method: Patients were randomised 2:1:1 to receive atezolizumab+cobimetinib, atezolizumab monotherapy or regorafenib, respectively. Atezolizumab was administered intravenously at 840 mg Q2W in the combination arm or at 1200 mg Q3W in the monotherapy arm. Cobimetinib was administered orally at 60 mg on a 21-days-on/7-days-off schedule and regorafenib was administered orally at 160 mg on a 21-days-on/7-days-off schedule. The primary endpoint was OS in intention-to-treat (ITT) patients; secondary endpoints included investigator-assessed PFS, ORR and DOR per RECIST v1.1.

Results: As of March 9, 2018, 363 patients were evaluated for efficacy and safety. The median age was 58 y; 26% of patients had received >3 lines of prior treatment in the metastatic setting. 1.7% of patients enroled were identified as having MSI-High metastatic CRC (91.7% as MSS or MSI-L, 6.6% had missing MSI status); 54.3% had RAS-mutant metastatic CRC. Median OS was 8.9 mo with atezolizumab+cobimetinib vs 8.5 mo with regorafenib (HR, 1.00 [95% CI: 0.73, 1.38] $P = 0.987$) and was 7.1 mo with atezolizumab monotherapy (HR vs regorafenib, 1.19 [95% CI: 0.83, 1.71]). The PFS HR for atezolizumab+cobimetinib vs regorafenib was 1.25 (95% CI: 0.94, 1.65) and for atezolizumab monotherapy vs regorafenib was 1.39 (95% CI: 1.00, 1.94). ORRs were 2.7%, 2.2% and 2.2% with atezolizumab+cobimetinib, atezolizumab monotherapy and regorafenib, respectively. Treatment-related Grade 3-4 AEs were reported in 45% of patients who received atezolizumab+cobimetinib, 10% who received atezolizumab monotherapy and 49% who received regorafenib. Treatment-related AEs of any grade with >30% occurrence were diarrhoea (56%), rash (42%) and nausea (32%) with atezolizumab+cobimetinib, none with atezolizumab monotherapy, and palmar-plantar erythrodyaesthesia (51%), fatigue (43%), diarrhoea (35%) and decreased appetite (34%) with regorafenib. Exploratory analyses, including subgroups defined by MSI and extended RAS mutation status, will be presented.

Conclusions: IMblaze370 did not meet its primary endpoint; atezolizumab+cobimetinib and atezolizumab monotherapy did not demonstrate statistically significant prolonged OS benefit vs regorafenib in the ITT population. PFS and ORR were similar across treatment arms. No new safety signals were observed and the safety profiles of atezolizumab+cobimetinib combination and atezolizumab monotherapy were consistent with previous findings.