Results From a Global Phase 2 Study of Tislelizumab, an Investigational PD-1 Antibody, in Patients With Unresectable Hepatocellular Carcinoma

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Introduction: Tislelizumab, an investigational monoclonal antibody with high affinity and binding specificity for PD-1, was engineered to minimize binding of FcγR on macrophages to help abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Two early phase studies (NCT02407990, CTR20160872) demonstrated that single-agent tislelizumab (200 mg) administered intravenously (IV) every 3 weeks (Q3W) was generally well tolerated and showed preliminary antitumor activity in patients with advanced solid tumors, including hepatocellular carcinoma (HCC).

Patients and Methods: This global Phase 2 study (NCT03419897) examined single-agent tislelizumab (200 mg IV Q3W) in patients with unresectable HCC with Child-Pugh A and Barcelona Clinic Liver Cancer (BCLC) stage B/C who had received at least one prior line of systemic therapy. The primary endpoint was overall response rate (ORR) by independent review committee (IRC) (ORR_{IRC}) per RECIST v1.1. Secondary endpoints included progression-free survival by IRC (PFS_{IRC}), ORR per investigator (ORR_{INV}), duration of response (DoR), overall survival (OS), and the safety/tolerability profile of tislelizumab.

Results: As of 27 February 2020, 249 patients (median age 62 years) were enrolled. At study entry, 225 (90%) patients had BCLC stage C and 200 (80%) had extrahepatic spread; 111 (45%) patients had received ≥2 prior systemic therapies. Across the study population, confirmed ORR_{IRC} was 13.3% (95% CI: 9.3, 18.1) with three complete responses (CR) and

30 partial responses (PR); ORR assessed by investigator was similar to IRC. At data cut-off, 22 (66.7%) of the 33 responses were ongoing. With a median study follow-up of 11.7 months, DoR_{IRC} was not reached. Median OS and PFS_{IRC} in the overall population were 13.2 months (95% CI: 10.8, 15.0) and 2.7 months (95% CI: 1.4, 2.8), respectively; the 1-year OS rate was 52.6%. Number of prior lines of therapy did not impact response (one prior line, ORR_{IRC}=13.8% [95% CI: 8.5, 20.7]; ≥2 prior lines, ORR_{IRC}=12.6% [95% CI: 7.1, 20.3]) or survival estimates (one prior line, median OS=13.8 months [95% CI: 10.5, not estimable], median PFS=2.6 months [95% CI: 1.4, 2.8]; ≥2 prior lines, median OS=12.4 months [95% CI: 9.9, 14.9], median PFS=2.7 months [95% CI: 1.4, 2.8]). The most common treatment-related adverse events (TRAEs) were increased aspartate aminotransferase (n=32; 12.9%) and alanine aminotransferase (n=23; 9.2%); increased aspartate aminotransferase (n=7; 2.8%) was the only grade 3-4 TRAE occurring in ≥2% of patients. Two patients had fatal adverse events (infectious pneumonia, hepatic encephalopathy; n=1 each); neither was attributed to treatment by investigator.

Conclusions: Tislelizumab demonstrated durable responses and was well tolerated in patients with previously systemically treated unresectable HCC, a patient population with a continued high unmet medical need. A large, global, randomized Phase 3 study comparing tislelizumab with reference standard of care sorafenib as a first-line treatment in adult patients with unresectable HCC (NCT03412773) is currently ongoing.