A Phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable or metastatic microsatellite instability-high/mismatch repair deficient solid tumors.

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Background:

Tislelizumab is an anti-programmed cell death protein 1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis. In early phase clinical studies, tislelizumab monotherapy was generally well tolerated and had antitumor activity in patients (pts) with solid tumors, including microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors such as colorectal cancer (CRC).

Methods:

This single-arm, multicenter, open-label, Phase 2 study evaluated the efficacy and safety of tislelizumab monotherapy in adult Chinese pts with previously treated, locally advanced, unresectable or metastatic histologically confirmed MSI-H/dMMR solid tumors by central lab. Pts received tislelizumab 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. Radiological imaging was performed at 9 weeks then every 6 weeks for the first year of therapy and every 12 weeks thereafter. The primary efficacy analysis set was all pts who received any dose of tislelizumab with measurable disease per independent review committee (IRC) at baseline. The primary endpoint was IRC-assessed overall response rate (ORR; RECIST v1.1). Secondary endpoints included duration of response (DoR) and disease control rate. Using a binomial exact test, the null hypothesis of ORR = 10% (historical rate) was rejected if 1-sided p≤0.025.

Results:

Between Sep 2018-Aug 2020, 80 pts were enrolled (median age 53 years; range 19-81 years) and 74 were included in the primary efficacy analysis set. At median study follow-up of 11.78 months, ORR by IRC was 45.9% (n = 34/74; 95% CI 34.3, 57.9) in all tumor types (1-sided p < 0.0001), including 4 complete responses (CR) and 30 partial responses (PR). Observed ORR by IRC was 39.1% (n = 18/46; 95% CI 25.1, 54.6) in CRC pts and 57.1% (n = 16/28; 95% CI 37.2, 75.5) in non-CRC pts. Of 74 pts, 53 (71.6%) had disease control and 39 (52.7%) achieved CR, PR or durable stable disease by IRC ≥24 weeks. Median DoR by IRC has not been reached; no disease progression was reported in the 34 responders (CR+PR), with 33 responders still on treatment (12-month DoR rate = 100%). Treatment-emergent adverse events (TEAEs) ≥Grade 3 occurred in 47.5% (n = 38/80) pts, of which 21.3% (n = 17/80) were lab abnormalities. Immune-mediated TEAEs ≥Grade 3 were 5% (n = 4/80).

Conclusions:

Tislelizumab achieved statistical significance and demonstrated clinically meaningful improvement in ORR in pts with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors. Treatment effect was consistent and durable across tumor types and endpoints. Tislelizumab was generally well tolerated and no new safety signals were identified. The data support tislelizumab as a new treatment option in this population.