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MAYA trial: Temozolomide (TMZ) priming followed by combination with low-dose ipilimumab and nivolumab in patients with microsatellite stable (MSS), MGMT silenced metastatic colorectal cancer (mCRC)

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Background

The activity of TMZ in patients with mCRC is modest, but restricted to those with MSS status and MGMT silencing (negative IHC + *MGMT* methylation). In this hyperselected population, acquired resistance to TMZ is linked to emergence of mutations in mismatch repair genes and hypermutation. Thus, TMZ may be used as priming agent for immune-sensitization of MSS CRCs.

Methods

MAYA was a multicenter, single-arm phase II trial enrolling patients with pretreated MSS mCRC and MGMT silencing as centrally assessed by IHC + pyrosequencing (NCT03832621). The trial was designed to evaluate the safety and efficacy of 2 priming cycles of TMZ 150 mg/sqm d1-5q4w followed in absence of disease progression by its combination with ipilimumab 1 mg/kg q8w/nivolumab 480 mg q4w. Primary endpoint: 8-month progression-free survival rate (8m PFS). Secondary endpoints: overall survival (OS), overall response rate (ORR), safety, patient-reported outcomes. According to a single-stage design, 27 patients were required to increase 8m PFS from 5% to 20% with α- and β-error of 5% and 20%.

Results

Among 703 patients prescreened from March 2019 to November 2020, 204 (29%) were molecularly eligible and 135 started the priming phase, of whom 33 (24%) reached the second treatment phase. For these, median age: 58 years, M/F 52/48%, *RAS* mutated/wild-type 76/24% (no BRAF mutated); 1/2/≥3 previous lines 6/45/49%. Overall, 10 were alive and progression free after 8 months, 21 had PFS <8 months (2 too early). The primary endpoint was met: 8m PFS was 32%; median PFS and OS: 7.1 and 18.5 months; ORR 39%, with delayed/gradual responses consistent with efficacy of immunotherapy. The rate of any grade/grade ≥3 immune-related adverse events was 48/6%, all easily manageable with protocol guidelines. On/post-therapy re-biopsies were analyzed in 9 cases with emergence of either TMB>10 mut/mb or MGMT expression, which predicted 8m PFS status.

Conclusions

MAYA study proved the immune-sensitizing role of TMZ in MSS/MGMT silenced mCRC. The safety and efficacy of TMZ priming followed by ipilimumab/nivolumab combo strategy is worthy of further development and extensive biomarker analyses are ongoing.

Clinical trial identification

NCT03832621.

Legal entity responsible for the study

Istituto Nazionale dei Tumori di Milano - Fondazione IRCCS, Milan, Italy.

Funding

Bristol-Myers Squibb.

Disclosure

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