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Biweekly versus conventional trifluridine/tipiracil plus bevacizumab for refractory metastatic colorectal cancer: The pragmatic phase 3 PRABITAS trial

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Background

In later-line metastatic colorectal cancer (mCRC), survival gains are modest, so toxicity largely determines net clinical benefit. Trifluridine/tipiracil (FTD/TPI) plus bevacizumab is a standard of care, but its conventional 28-day schedule causes frequent neutropenia and gastrointestinal toxicity. A biweekly schedule may reduce this burden, but randomized evidence is lacking. Such a question is well suited to a pragmatic design.

Methods

PRABITAS was a pragmatic, investigator-initiated, open-label, randomized, phase 3 noninferiority trial. Patients with refractory mCRC were assigned 1:1 to FTD/TPI plus bevacizumab on a conventional 28-day schedule (days 1–5 and 8–12) or a biweekly schedule (days 1–5). Eligibility criteria were broad, treatment decisions followed everyday practice, and sites received no per-patient payment. The primary endpoint was overall survival (OS) in the intention-to-treat (ITT) population, with a noninferiority margin of 1.25 for the hazard ratio (HR).

Results

Altogether, 972 patients were randomized at 178 of 252 activated sites in Japan within 17 months; 970 comprised the ITT population, 15% of whom would have been ineligible for conventional trials because of organ dysfunction, comorbidity, or ECOG PS 2. At a median follow-up of 17.9 months, the biweekly schedule was noninferior for OS (median, 11.3 vs 10.3 months; stratified HR, 0.93; 95% CI, 0.80–1.08) and had similar PFS (median, 3.9 vs 3.9 months; HR, 0.93; 95% CI, 0.81–1.06); OS remained consistent in the 825 patients (85%) meeting standard eligibility criteria (HR 0.90; 95% CI, 0.76–1.05). Biweekly treatment reduced grade ≥ 3 neutropenia (13% vs 39%), febrile neutropenia (1% vs 5%), G-CSF use (3% vs 13%), grade ≥ 2 anorexia (15% vs 26%) and diarrhea (4% vs 10%). Dose reductions (31% vs 48%) and cycle delays (58% vs 68%) were also less frequent, with higher relative dose intensity (83% vs 77%).

Conclusions

Changing the schedule alone preserved survival while reducing toxicity, supporting biweekly FTD/TPI plus bevacizumab as the new standard schedule in later-line mCRC. PRABITAS demonstrates how pragmatic investigator-initiated trials can rapidly and affordably address common clinical questions.

Clinical trial identification

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Legal entity responsible for the study

Aichi Cancer Center Hospital.

Funding

Aichi Cancer Center Hospital.

Disclosure

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