Improved survival with TAS-102 in mets colorectal cancer refractory to standard therapies

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The new combination agent TAS-102 is able to improve overall survival compared to placebo in patients whose metastatic colorectal cancer is refractory to standard therapies, researchers said at the ESMO 16th World Congress on Gastrointestinal Cancer in Barcelona.

"Around 50% of patients with colorectal cancer develop metastases but eventually many of them do not respond to standard therapies," said Takayuki Yoshino of the National Cancer Centre Hospital East in Chiba, Japan, lead author of the phase III RECOURSE trial. "The RECOURSE study shows that TAS-102 improves overall survival in these patients compared to placebo. I believe that this agent will become one of the standards of care in the refractory setting of metastatic colorectal cancer in Japan and worldwide."

TAS-102 is a novel nucleoside anti-tumour agent consisting of trifluridine (FTD) and tipiracil hydrochloride (TPI). FTD is the active component of TAS-102 and is directly incorporated into cancer DNA, leading to DNA dysfunction. However, when FTD is taken orally it is largely degraded to an inactive form. TPI prevents the degradation of FTD. This mechanism of action is different to that of fluoropyrimidine, oxaliplatin and irinotecan.

The phase II trial of TAS-102 had found an overall survival benefit in Japanese patients with metastatic colorectal cancer refractory to

fluoropyrimidine 5-fluorouracil (5-FU), irinotecan and oxaliplatin.[1]

The current RECOURSE study was a global phase III trial conducted in 13 countries at 114 centres. Patients had metastatic colorectal cancer refractory to all standard therapies including fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and cetuximab or panitumumab for patients with wild-type KRAS tumours. Patients were randomised 2:1 to TAS-102 (534 patients) or placebo (266 patients). The primary endpoint was overall survival.

The researchers found that TAS-102 prolonged overall survival compared to placebo (hazard ratio 0.68): median overall survival was 7.1 months for TAS-102 and 5.3 months for placebo. TAS-102 also improved progression-free survival compared to placebo (hazard ratio 0.48), which was a secondary endpoint. Yoshino said: "We found a statistically significant difference in overall and progression-free survival, and a clinically meaningful improvement."

"TAS-102 has a mild safety profile and the most common side-effect is hematologic toxicity including neutropenia. Patients with metastatic colorectal cancer refractory to standard therapies now have a strong treatment option."

Commenting on the data, ESMO spokesperson Jean Yves Douillard, professor of medical oncology, Institut de Cancérologie de l'Ouest (ICO) René Gauducheau, Saint-Herblain, France, said: "The phase III trial of TAS-102 is a global study and confirms the results of the phase II study in Japanese patients, whose response to fluoropyrimidine is slightly different to patients in Europe and the US. It is good to know that the magnitude of benefit shown in the smaller phase II trial is confirmed in the larger phase III trial and that the results apply to Asians and Caucasians alike."

TAS-102 is a combination of two components. The tipiracil hydrochloride (TPI) prevents degradation of trifluridine (FTD) and also has angiogenic activity. "This is probably why TAS-102 is effective in classical fluoropyrimidine 5-fluorouracil (5-FU) resistant patients. The drug is very promising, tolerance is good and it is manageable with supportive care."

Douillard concluded: "In RECOURSE, TAS-102 was tested in patients who had received all types of chemotherapy available for colorectal cancer. I would probably move this drug into an earlier line of treatment and I would also combine it with either irinotecan or oxaliplatin."

More information: References

[1] Yoshino T, Mizunuma N, Yamazaki K, Nishina T, Komatsu Y, Baba H, Tsuji A, Yamaguchi K, Muro K, Sugimoto N, Tsuji Y, Moriwaki T, Esaki T, Hamada C, Tanase T, Ohtsu A. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. Lancet Oncol. 2012;13(10):993-1001.

[2] Abstracts from the 16th ESMO World Congress on Gastrointestinal Cancer are published in Annals of Oncology, Volume 25 suppl 2 June 2014 (Ann Oncol 2014 Jun; 25(Suppl 2): 1-117) annonc.oxfordjournals.org/content/25/suppl_2.toc

[3] Abstract presentation: Saturday, 28 June 2014, 12:00 hrs, Session XIX: Metastatic colorectal cancer

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