Medical information letter: Switching metastatic colorectal cancer (mCRC) patients to Teysuno® (S-1) after development of cardiotoxicity during treatment with another fluoropyrimidine

Management and treatment of mCRC patients after development of cardiotoxicity on standard fluoropyrimidines such as 5-fluorouracil (5-FU) and capecitabine

Fluoropyrimidines are an essential component in the treatment of colorectal cancer and, in the metastatic setting, comprise the backbone of most treatment combinations (Van Cutsem et al., 2016). Currently approved fluoropyrimidine treatments for mCRC in the EU, 5-FU and capecitabine, are associated with a variety of adverse effects including gastrointestinal events, hand-foot syndrome, bone marrow suppression, fatigue, and potentially serious cardiotoxicity (Cassidy et al., 2002; Van Cutsem et al., 2001; Hoff et al., 2001). Some of these adverse events are general and shared by all fluoropyrimidines while others are drug-specific and the severity of these adverse events varies depending on the drug and the administration method (Polk et al., 2014).

The potentially severe cardiotoxicity has been reported in 4%-6% of mCRC patients receiving 5-FU-/capecitabine-based treatment (Dyhl-Polk et al., 2020; Kwakman et al., 2017a; Leicher et al., 2017). Fluoropyrimidine-induced cardiotoxicity occurs early in treatment, in the first two cycles in more than 80% of patients, and often leads to discontinuation (Dyhl-Polk et al., 2020). The pathophysiological mechanisms underlying these fluoropyrimidine-induced cardiotoxic effects are currently unknown (Polk et al., 2014; Deboever et al., 2013). For instance, some patients who develop cardiotoxicity have underlying cardiac comorbidity, but this has not reliably been shown to be a predisposing factor, and more than 50% have no previous coronary disease. (Polk et al., 2013; Sorrentino et al, 2012; Yeh et al., 2009; Deboever et al., 2013; Jensen et al., 2010). One hypothesis has suggested that 5-FU-induced cardiotoxicity is due to coronary vasospasm induced by 5-FU or its metabolites (Sorrentino et al., 2012; Deboever et al., 2013). Management of cardiotoxicity associated with 5-FU or capecitabine usually includes treatment discontinuation (65% of 5-FU, 73% of capecitabine) (Dhyl-Polk et al., 2020). Symptoms may also be managed with dose reductions and/or antianginal therapy but as many as 75% of patients will experience recurrence of symptoms and this strategy involves significant risk to the patient if they experienced major cardiotoxicity upon initial exposure to a fluoropyrimidine (Dyhl-Polk et al., 2020; Deboever et al., 2013).

Overall, an estimated 3%-4% of mCRC patients are forced to discontinue fluoropyrimidine-based treatment due to cardiotoxicity, leaving them with few options for effective treatment (Dyhl-Polk et al., 2020; Kwakman et al., 2017a; Van Cutsem et al., 2016). Recent evidence from European studies supports the safety of switching these patients to Teysuno® (S-1) (Kwakman et al., 2017b; Österlund et al., 2021, submitted) and a recent meta-analysis of European and Asian studies confirmed the non-inferior efficacy of Teysuno regimens compared to 5-FU-/capecitabine-containing regimens in patients with mCRC (Derksen et al., 2021). These factors have led Nordic Pharma to apply for this indication to make Teysuno available to European mCRC patients who discontinue treatment on another fluoropyrimidine due to cardiotoxicity to enable them to continue recommended fluoropyrimidine treatment (Van Cutsem et al., 2016).

Background on the use of Teysuno® (S-1) in the EU

Teysuno (25 mg/m^2 twice per day [b.i.d.] d1-21 of a 28-day cycle), in combination with cisplatin, has been approved for use in the EU for treatment of advanced gastric cancer (AGC) since 2011 and is associated with improved tolerability with similar efficacy compared to capecitabine and 5-fluorouracil (Teysuno, SmPC; Ter Veer et al., 2017). Teysuno was approved in AGC based on the results of the randomized, phase 3 FLAGS trial that demonstrated that Teysuno in combination with cisplatin was as effective as 5-FU/cisplatin in Caucasian patients with previously untreated AGC (Ajani et al., 2010). Secondary endpoints of the trial indicated that the Teysuno regimen was also better tolerated (Ajani et al., 2010).

In mCRC, dosing recommendations for Teysuno in European patients are based on results from two trials, the SALTO phase 3 trial and the NORDIC9 phase 2 trial (Kwakman et al., 2017c; Winther et al., 2019). In the phase 3 randomized multicentre SALTO study, Teysuno monotherapy (30 mg/m^2 b.i.d. d1-14 of a 21-day cycle) was demonstrated to result in lower rates of hand-foot syndrome than capecitabine (1250 mg/m^2 for <70 years; 1000 mg/m^2 for ≥ 70 years), with comparable efficacy (bevacizumab [7.5 mg/kg IV on day 1] was optional in both groups) (Kwakman et al., 2017c, Kwakman et al., 2019). For older (>70 years), more vulnerable patients, the NORDIC9 Phase 2 trial of European mCRC patients demonstrated that a combination of Teysuno (20 mg/m^2 b.i.d. d1-14 of 21-day cycle) and oxaliplatin (100 mg/m^2 on day 1) was more effective than Teysuno monotherapy (30 mg/m^2 b.i.d. d1-14 21-day cycle) and resulted in less toxicity than full dose monotherapy (bevacizumab [7.5 mg/m^2 day 1 of a 21-day cycle] was optional in both groups) (Winther et al., 2019).

Evidence supporting the switch to Teysuno after 5-FU- or capecitabine-induced cardiotoxicity in mCRC

The safety of switching mCRC patients to Teysuno after development of cardiotoxicity on 5-FU- or capecitabine-based treatment was initially suggested by a case series that included patients with solid tumours (n=7; 2 mCRC) who developed coronary artery vasospasm on capecitabine-containing treatment (Kwakman et al., 2017b). All patients were able to safely switch to Teysuno without additional cardiac toxicity (Kwakman et al., 2017b). These initial data were further supported by a Dutch retrospective chart study that included ten mCRC patients who were switched to Teysuno after developing cardiotoxicity on capecitabine-containing regimens (Punt et al., 2021). (Teysuno has been approved in the Netherlands since 2017 for patients who are intolerant to capecitabine due to hand-foot syndrome or cardiotoxicity). Among the ten patients who switched to Teysuno due to cardiotoxicity, none had recurrence of cardiotoxicity and no new cardiotoxicity was observed among the remaining 43 patients who switched to Teysuno for other reasons (Punt et al., 2021, in preparation).

Finally, a recent large multi-centre retrospective cohort study of patients with solid tumours (n=200;78% CRC, 27% mCRC) evaluated the safety of switching to Teysuno-based regimens after developing cardiotoxicity on 5-FU- or capecitabine-containing regimens (Österlund et al., 2021, submitted). Initial cardiotoxicity on a fluoropyrimidine was associated with capecitabine in 85%, infusional 5-FU in 12%, and bolus 5-FU in 4%, and 51% of patients had no cardiovascular comorbidities prior to initiation of fluoropyrimidine treatment. The treatment intent was curative (i.e. adjuvant/neoadjuvant) in 73% of patients and palliative in 28%. Single agent Teysuno was administered to 29% of patients and combination chemotherapy was administered with the same cytotoxic drug as in the initial treatment in 61% of patients and/or with the same biologic in 21%. The most common combination therapies used with Teysuno treatment included oxaliplatin, irinotecan, and bevacizumab.

Overall, 96% of patients had no recurrent cardiotoxicity upon switch to Teysuno-based regimens and 99% were able to successfully complete planned fluoropyrimidine treatment (Österlund et al., 2021). Of 8 patients who had recurrent cardiotoxicity, five had cardiovascular comorbidities at baseline. The only demographic/disease-related factor that was found to be different between those with recurrent cardiotoxicity and those without was the presence of ischemic heart disease (OR 6.18: 95% CI 1.36-28.11). Non-cardiac adverse events during Teysuno treatment included grade 3-4 haematologic toxicity in 6% and grade 2-4 non-haematologic adverse events occurred in 22%, including neuropathy, nausea, diarrhoea, infection, and hand-foot syndrome. Higher rates of non-cardiac adverse events were reported during Teysuno treatment compared to initial fluoropyrimidine treatment but this difference is

likely attributable to the much longer duration of Teysuno chemotherapy (147 days versus 5 days). Furthermore, although survival was not an endpoint of this study, the efficacy of Teysuno after switch was in line with previous reports for 5-FU and capecitabine in this population with a 5-year survival rate of 83% in colorectal cancer and a median overall survival for the subgroup of patients with mCRC of 26 months (95% CI 22-31) (Österlund et al., 2021).

How to switch to Teysuno – dosing, administration, dose reductions, combinations in mCRC

- Teysuno is administered orally, 30 mg/m^2, b.i.d. on days 1-14 of a 21-day cycle (Optional: bevacizumab 7.5 mg/kg on day 1) (Kwakman et al., 2017c)
- For combination therapy with oxaliplatin or irinotecan, the recommended Teysuno dose is 25 mg/m^2 b.i.d. on days 1-14 of a 21-day cycle. (Optional: bevacizumab 7.5 mg/kg on day 1)
- For frail elderly patients (>70 years), the recommended dose is 20 mg/m^2, b.i.d., on days 1-14 of a 21-day cycle in combination with a reduced dose of oxaliplatin (100 mg/m^2 on day 1 of a 21-day cycle) (Optional: bevacizumab 7.5 mg/kg on day 1) (Winther et al., 2019).
- Please note that there are no specific recommendations for the switch to Teysuno after cardiotoxicity occurred on other fluoropyrimidines. There are cases described in the publications of Kwakman and Österlund (Kwakman 2017b and Österlund 2021) where patients were successfully switched without any delay and those who interrupted their treatment (for a short or prolonged time).
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Table 1. Calculating Teysuno dose and dose reductions in mCRC

Teysuno dose	Each dose in mg (each dose)[a]	Total daily dose in mg[a]	Number of capsules for each dose (2 doses/day)	
Standard dose[a]: 30 mg/m^2			Capsule 15 mg[a] (brown/white)	Capsule 20 mg[a] (white)
BSA ≥ 2.30 m^2	70	140	2	2
BSA = 2.10 – 2.29 m^2	65	130	3	1
BSA = 1.90 – 2.09 m^2	60	120	0	3
BSA = 1.70 – 1.89 m^2	55	110	1	2
BSA = 1.50 – 1.69 m^2	50	100	2	1
BSA = 1.30 – 1.49 m^2	40	80	0	2
BSA ≤ 1.29 m^2	35	70	1	1
First dose reduction[a]: to 25 mg/m^2				
BSA ≥ 2.30 m^2	60	120	0	3

BSA = 2.10 – 2.29 m^2	55	110	1	2
BSA = 1.90 – 2.09 m^2	50	100	2	1
BSA = 1.70 – 1.89 m^2	45	90	3	0
BSA = 1.50 – 1.69 m^2	40	80	0	2
BSA = 1.30 – 1.49 m^2	35	70	1	1
BSA ≤ 1.29 m^2	30	60	2	0
Second dose reduction [a]: to 20 mg/m^2				
BSA ≥ 2.13 m^2	45	90	3	0
BSA = 1.88 – 2.12 m^2	40	80	0	2
BSA = 1.63 – 1.87 m^2	35	70	1	1
BSA = 1.30 – 1.62 m^2	30	60	2	0
BSA ≤ 1.29 m^2	20	40	0	1
Calculate the BSA to the second decimal [a] expressed as tegafur content				Source: SmPC Teysuno®

Teysuno is indicated in adults: (Teysuno SmPC)

- for the treatment of advanced gastric cancer when given in combination with cisplatin
- as monotherapy or in combination with oxaliplatin or irinotecan, with or without bevacizumab, for the treatment of patients with metastatic colorectal cancer for whom it is not possible to continue treatment with another fluoropyrimidine due to hand-foot syndrome or cardiovascular toxicity that developed in the adjuvant or metastatic setting

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