Medical information letter: Dosing and administration of Teysuno® (S-1) in metastatic colorectal cancer (mCRC) patients who discontinue standard fluoropyrimidine treatment due to cardiotoxicity or hand-foot syndrome (HFS)

Continuation of effective treatment in mCRC patients after development of cardiotoxicity or hand-foot syndrome (HFS) 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, part of almost all first-line 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). Specifically with regards to HFS and cardiotoxicity, there are relevant differences between the fluoropyrimidines.

With regards to HFS, studies of 5-FU or capecitabine-based treatment in European mCRC patients have reported rates of 6.2%-73% with capecitabine generally associated with higher rates of HFS that appear to accumulate over time (Cassidy et al., 2002; Cassidy et al., 2008; Kwakman et al., 2017c; Leicher et al., 2017; Stein et al. 2016). Prevention, patient education, symptom amelioration, and dose intensity management are the cornerstones of management of HFS that develops during fluoropyrimidine treatment but 10%-17% of patients are forced to discontinue recommended fluoropyrimidine-based treatment due to persistent grade 2-3 HFS and these patients have few effective treatment options (Kwakman et al., 2020; Leicher et al., 2017; Kwakman et al., 2017c; Van Cutsem et al., 2016).

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). Fluoropyrimidine-induced cardiotoxicity occurs early in treatment, arising in the first two cycles in more than 80% of patients who experience cardiotoxicity (Dyhl-Polk et al., 2020). Management of cardiotoxicity associated with 5-FU or capecitabine usually includes treatment discontinuation (65% of 5-FU, 73% of capecitabine) (Dyhl-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). Studies in mCRC have reported that 3%-4% of patients must discontinue due to fluoropyrimidine-induced cardiotoxicity, leaving them with few effective treatment options (Dyhl-Polk et al., 2020; Kwakman et al., 2017a; Van Cutsem et al., 2016).

Recent studies support the safety of switching patients, who developed HFS or cardiotoxicity on another fluoropyrimidine, to Teysuno (Kwakman et al., 2017b; Kwakman et al., 2017d; Punt et al., 2021, in preparation; Österlund et al., 2021). In addition, 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 with another fluoropyrimidine due to HFS or 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 (**Figure 1**) (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, a phase 3 randomized multicentre study (SALTO) was conducted in 161 European patients to compare Teysuno monotherapy (30 mg/m^2 b.i.d. d1-14 of a 21-day cycle) to capecitabine (1250 mg/m^2 for <70 years; 1000 mg/m^2 for ≥ 70 years) with optional bevacizumab (7.5 mg/kg IV on day 1) in both groups. The study demonstrated that Teysuno causes significantly lower rates of HFS than capecitabine (45% vs 73% any grade HFS, p=0.0005; 4% vs 21% grade 3 HFS, p=0.003, respectively), with comparable long-term efficacy (Kwakman et al., 2017c, Kwakman et al., 2019). In addition, there were no statistically significant differences between Teysuno and capecitabine in terms of progression-free survival (PFS), overall survival (OS), or response rate (RR) in this Western population of patients with mCRC (Kwakman et al., 2017c). This study forms the basis for the dosing recommendations for Teysuno monotherapy in mCRC (**Figure 1**).

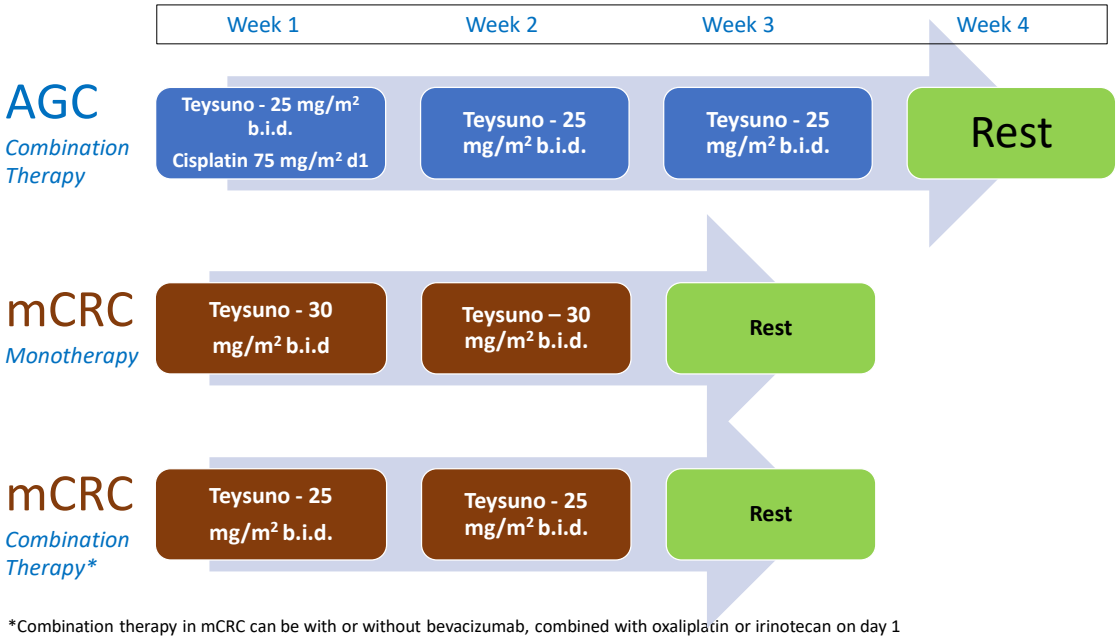

Figure 1. Comparison of dosing schedules for advanced gastric cancer (AGC) and metastatic colorectal cancer in monotherapy and combination therapy (mCRC).

Two studies that have evaluated switch to Teysuno-based regimens after cardiotoxicity or HFS in patients treated with a fluoropyrimidine-based regimen for mCRC have included patients who were treated with Teysuno combination therapy (Österlund et al., 2021; Punt et al., 2021). Patients in these studies safely received Teysuno at a dose of 25 mg/m^2 in combination with oxaliplatin or irinotecan (± 7.5 mg/kg IV d1 bevacizumab) forming the basis for the dosing recommendation in these combinations (Österlund et al., 2021; Punt et al., 2021).

The safety and efficacy of a reduced dose combination for older (>70 years), vulnerable patients were evaluated in the NORDIC9 Phase 2 trial that included 157 European mCRC patients (Winther et al., 2019). The 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 found to be more effective than Teysuno monotherapy (30 mg/m^2 b.i.d. d1-14 21-day cycle) in terms of PFS (6.2 months vs 5.3 months, p=0.047) and resulted in less toxicity than full dose monotherapy. Bevacizumab (7.5 mg/kg IV on day 1) was optional in both groups. This trial forms the basis for the dosing recommendations for this frail elderly patient population in mCRC.

Of note, initial phase 3 studies of Teysuno in Asia led to the standard use of a 40 mg/m^2 dose in studies in Asian mCRC patients (Yamada et al., 2013; Baba et al., 2017; Hong et al., 2012; Kim et al., 2014;

Yamada et al., 2018; Muro et al., 2010; Yasui et al., 2015). However, studies in European patients have identified ethnic differences in tolerability of fluoropyrimidine treatment between Caucasian and Asian patients (Chollet et al., 2003; Van den Brande et al., 2003). At this dose, European patients experience higher rates of gastrointestinal toxicity than Asian patients that are not explained by differences in pharmacokinetic exposure to 5-FU (Chuah et al., 2011). These observations have led to the recommendation that a lower dose of 30 mg/m^2 be used in European patients (25 mg/m^2 for combination therapy) (Teysuno, SmPC). This dosing adjustment has allowed Caucasian AGC patients to be safely treated with Teysuno in Europe and two meta-analyses that compared the efficacy of 5-FU, capecitabine, and Teysuno regimens did not detect any differences in efficacy among these regimens that were attributable to ethnicity (Ter Veer, 2016; Ter Veer, 2017).

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

- 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.
- 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).

Approach for switch after higher grade HFS: Dose intensity management for HFS includes dose delay until the HFS severity returns to grade 1 or 0 for Grade 2 HFS and dose delay along with reduction of dose to 75% of starting dose for grade 3 HFS. These measures may be followed by switch to Teysuno if they are not effective (**Figure 2**) (Kwakman et al., 2020).

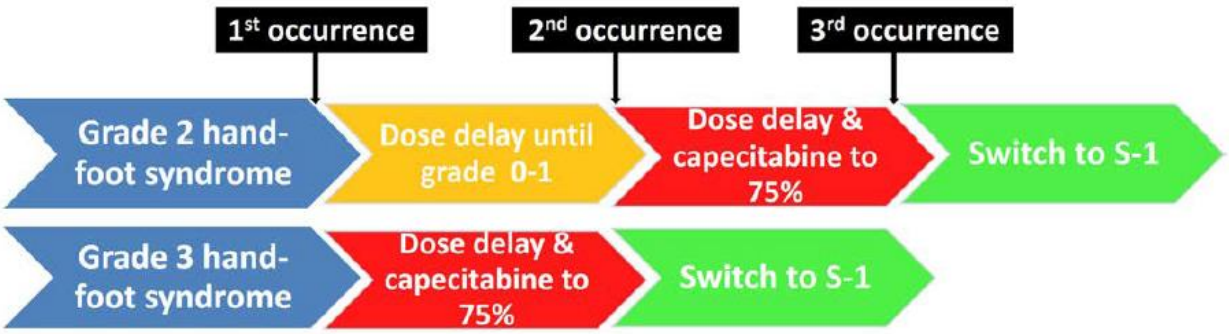

Figure 2. Flowchart for treatment management of capecitabine-induced HFS (from Kwakman et al., 2020, with permission)

Approach for switch after cardiotoxicity:

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).

General dose reduction recommendations:

General recommendation on calculating the dose and dose reductions for an individual patient can be found in Table 1. Dose reduction recommendations for treatment-related toxicities in general (except for hematologic and renal toxicities can be found in Table 2

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®	

Table 2. Teysuno dose reduction schedule for treatment-related toxicities in general, except for hematologic and renal toxicities* (Teysuno, SmPC)

Toxicity grades[a]	Teysuno dose changes within a 21-day treatment cycle	Teysuno dose adjustment for next dose / next cycle
Grade 1		
Any occurrence	Maintain treatment at same dose level	None
Grade 2[b,c]		
Any occurrence	Suspend treatment until Grade 0 or 1	None
Grade 3 or higher[c]		
First occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Second occurrence	Suspend treatment until Grade 0 or 1	Reduce by 1 dose level from previous level
Third occurrence	Discontinue treatment	Discontinue treatment
[a] According to the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. [b] For Grade 2 nausea and/or vomiting, the anti-emetic therapy should be optimized prior to a suspension of Teysuno. [c] At the discretion of the treating physician, patients may continue with treatment without reduction or interruption for adverse reactions (irrespective of grade) considered unlikely to become serious or life-threatening (e.g., alopecia, changes in sexual function, and dry skin).		

*Please see Teysuno SmPC section 4.2 for recommendations regarding dosing modifications in patients with renal or haematological toxicity

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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