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

Management and treatment of mCRC patients after development of 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, 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). Consistent with this observation, the mechanism for HFS due to fluoropyrimidine treatment appears to be associated with the accumulation of 5-FU metabolites in the skin (Kwakman, 2020). Grade 1 or 2 HFS, generally associated with with swelling and redness as well as numbness and tingling, not to be confused with neuropathy, may impact activities of daily life for a patient but can generally be managed with supportive care or dose reduction/delay (Kwakman, 2020). Persistent grade 2 or grade 3/4 HFS can be much more painful and debilitating (Kwakman, 2020). In metastatic colorectal cancer (mCRC), 10%-17% of patients are forced to discontinue recommended fluoropyrimidine (iv 5-FU- or capecitabine)-based treatment due to higher grade HFS (Leicher et al., 2017; Kwakman et al., 2017c) and there are few effective alternative treatments for these patients (Van Cutsem, 2016).

Teysuno (S-1) is an oral fluoropyrimidine that was shown in the Phase 3 SALTO trial to cause significantly less HFS compared to capecitabine in European patients treated for mCRC (Kwakman et al. 2017c). Moreover, the efficacy of Teysuno treatment in SALTO was not significantly different from that of capecitabine (Kwakman et al., 2017c). 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) and recent studies support the safety of switching to Teysuno after development of fluoropyrimidine-induced HFS in mCRC patients (Kwakman et al., 2017d; Punt et al., 2021, in preparation). 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 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, 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 in mCRC.

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/m^2 day 1 of a 21-day cycle) was optional in both groups. This trial forms the basis for the dosing recommendations for this frail elderly patient population in mCRC.

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

In addition to the SALTO Phase 3 trial data demonstrating that Teysuno causes less HFS than capecitabine in patients with mCRC, data from a retrospective analysis of data from the Netherlands and Denmark has shown that patients with solid tumours (n=52; 56% mCRC) who develop HFS while on capecitabine can be safely switched to Teysuno and continue treatment (Kwakman et al., 2017c; Kwakman et al., 2017d). Almost all of the patients (94%) had a lower grade of HFS upon switching and most (56%) had complete resolution of HFS. Importantly, 94% started at the full dose of 30 mg/m^2 b.i.d. for monotherapy or 25 mg/m^2 b.i.d. for combination therapy with Teysuno (Kwakman et al., 2017d). The most common combination treatments in this mixed tumour population were gemcitabine, oxaliplatin, and bevacizumab.

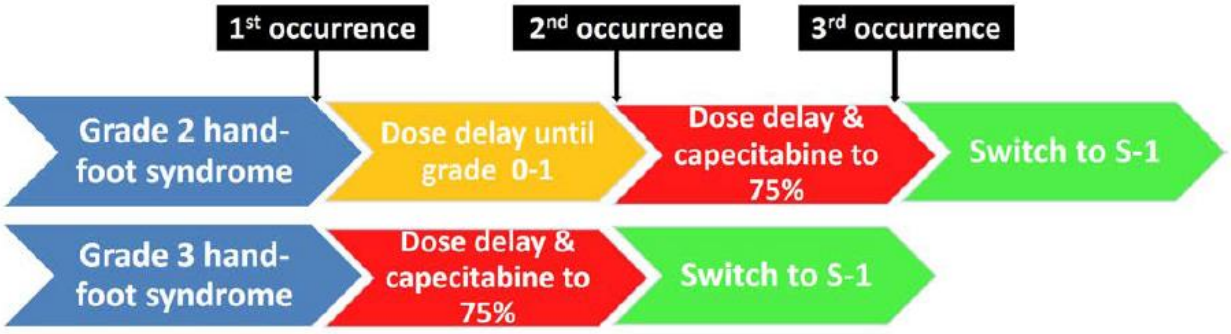
These data are further supported by a Dutch retrospective chart study that included 47 mCRC patients who were switched to Teysuno after developing intolerance to a capecitabine-containing regimen (Punt et al., 2021). (Teysuno has been approved in the Netherlands since 2017 for patients who are intolerant to capecitabine due to hand-foot syndrome or cardiotoxicity). Among the 77% (36/47) of patients who switched from capecitabine-based treatment due to moderate-to-severe (grade 2/3) HFS, 1 patient experienced grade 2 HFS on Teysuno and the remainder experienced grade 1 HFS or complete resolution of HFS. One patient developed new grade 1 HFS on Teysuno (Punt et al., 2021). The starting dose of Teysuno in this study was 30 mg/m^2 for monotherapy and 25 mg/m^2 for combination with oxaliplatin (Punt et al., 2021) (See below for more information on recommended dosing in mCRC)

Management of hand-foot syndrome

Prevention, patient education, symptom amelioration, and dose intensity management are the cornerstones of management of HFS that develops during fluoropyrimidine treatment (Kwakman et al., 2020). Patient education about what to expect and how to reduce stress on skin areas may include advice regarding loose-fitting clothing, avoidance of heat, the use of emollients or creams, and the use of COX-2 inhibitors to avoid COX-2-mediated inflammation associated with 5-FU metabolites (Kwakman et al., 2020).

For higher grade HFS, dose intensity management 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 (Kwakman et al., 2020).



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

How to switch to Teysuno – 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 twice per day 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).

Table 1. Calculating Teysuno dose and dose reductions

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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