

**Suppl 4.** Details of the dosage regimen and cardiotoxicity outcomes in patients who received capecitabine monotherapy

No.	Author, year	Capecitabine administration	Intervention/control			Cumulative dose capecitabine (mg/m <sup>2</sup> )	Cardiotoxicity outcomes (N)	CTCAE/WHO grading (N)	Type of cardiotoxicity (reported events) <sup>a</sup>
			Arm A	Arm B	Arm C				
1	Granito et al, 2015	Capecitabine oral	Metronomic capecitabine 500 mg every 12 hr	-	-	N/A	2/26	Any grade (1) 3 (1)	Heart failure (1)
2	Harbeck et al, 2017	Capecitabine oral	Capecitabine 1250 mg/m <sup>2</sup> twice daily for 14 days every 21 days	pegylated liposomal doxorubicin 50 mg/m <sup>2</sup> every 28 days	-	N/A	13/102	Any grade (13)	N/A
3	Hoff et al, 2001	Capecitabine oral	5-FU 425 mg/m <sup>2</sup> /LV 20 mg/m <sup>2</sup> daily for 5 days in 4 weeks cycles	Capecitabine monotherapy - orally at a dose of 1,250 mg/m <sup>2</sup> twice daily (total daily dose 2,500 mg/m <sup>2</sup> ) as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by a 1-week rest period)	-	N/A	2/299	3 (2)	Myocarditis (1) Myocardial infarction (1)
4	Jegannathan et al, 2011	Capecitabine oral	Capecitabine dose was between 450 and 550 mg/m <sup>2</sup> twice daily, continuously for 28 days	-	-	10,800-13,200 (1)	1/50	4 (1)	Myocardial infarction (1)
5	Jensen et al, 2006	Capecitabine oral	- Bolus infusion of 5-FU (425 mg/m <sup>2</sup> ) and isovorin (10 mg/m <sup>2</sup> ) for 5 days	- Capecitabine 1,250 mg/m <sup>2</sup> /day bid with oxaliplatin 130	Capecitabine 1,250 mg/m <sup>2</sup> /day	5,000-175,000 (3)	3/214	N/A	N/A

			every 4 weeks for six courses (5-FU Mayo) for adjuvant treatment of colorectal cancer - 5-FU (400 mg/m <sup>2</sup> ) 2-hours bolus infusion followed by (2,400 mg/m <sup>2</sup> ) flat continuous infusion for 46 h (de Gramont) for treatment of colorectal cancer.	mg/m <sup>2</sup> /day i.v. each 3 weeks (XELOX) for palliative treatment of colorectal - Capecitabine (1,000 mg/m <sup>2</sup> bid for 2 weeks), carboplatin (AUC 5) and docetaxel (60 mg/m <sup>2</sup> ) every 4 weeks for treatment of gastric cancer - 5-FU (400 mg/m <sup>2</sup> ) bolus injection followed by (600 mg/m <sup>2</sup> ) flat continuous infusion for 22 h and oxaliplatin (85 mg/m <sup>2</sup> ), for 2 days (FOLFOX4) for treatment of colorectal cancer	bid for 2 weeks for palliative treatment of colorectal cancer				
6	Kosmas et al, 2008	Capecitabine oral	5-FU monotherapy - LV 200 mg/m <sup>2</sup> (i.v. bolus) D1-5, followed by 5-FU 700 mg/m <sup>2</sup> D 1-5 (i.v. 3 h infusion) - LV 200 mg/m <sup>2</sup> (i.v. bolus), followed by 5-FU 700 mg/m <sup>2</sup> (i.v. 2 h infusion) every week - 5-FU 200 mg/m <sup>2</sup> D1-5 (24 h CI)	polychemotherapy - Mitomycin 10 mg/m <sup>2</sup> D1 + LV 500 mg/m <sup>2</sup> D1-D5 + 5-FU 1,000 mg/m <sup>2</sup> D1-D5 - Cisplatin 100 mg/m <sup>2</sup> D1 + 5-FU 1,000 mg/m <sup>2</sup> continuous infusion days 2-6 - Mitomycin 10 mg/m <sup>2</sup> D1+ 5-FU 1,000 mg/m <sup>2</sup> D1-D5	Capecitabine	N/A	3/54	N/A	EKG abnormalities (3)
7	Kwakman et al, 2017	Capecitabine oral	Capecitabine oral	CAPIRI, capecitabine plus irinotecan	CAPOX-B, capecitabine, oxaliplatin and bevacizumab	N/A	19/397	Any Grade (15) 3-4 (4)	Myocardial infarction (15) Arrhythmia (4) Sudden death (1)

					CAPOX-BC, capecitabine, oxaliplatin and bevacizumab plus cetuximab				
8	Mayer et al, 2021	Capecitabine oral	Capecitabine 1,000 mg/m <sup>2</sup> twice daily, days 1-14, every 3 weeks, for a total of six cycles	Platinum agent (treating physician choice of cisplatin 75 mg/m <sup>2</sup> or carboplatin AUC 6 on day 1), once every 3 weeks, for a total of four cycles	-	N/A	2/198	4 (1) 3 (1)	DVT/VTE (1)
9	Primrose et al, 2019	Capecitabine oral	Oral capecitabine (1250 mg/m <sup>2</sup> ) was given postoperatively twice a day on days 1 to 14 of a 3-weekly cycle for 24 weeks (eight cycles)	observation commenced within 16 weeks of surgery	-	N/A	2/213	3	Chest pain (1) DVT/VTE (1)
10	Smorenburg et al, 2014	Capecitabine oral	Eight cycles of capecitabine 1000 mg/m <sup>2</sup> twice daily, taken orally on day 1–14 every 3 weeks	six cycles of PLD 45 mg/m <sup>2</sup> given i.v. on day 1 every 4 weeks	-	N/A	0/38	-	N/A
11	Stockler et al, 2011	Capecitabine oral	Intermittent capecitabine was started at 1,000 mg/m <sup>2</sup> twice daily on days 1 through 14 and repeated every 3 weeks - The dose was increased to 1,250 mg/m <sup>2</sup> twice daily in the absence of adverse events after two cycles Continuous capecitabine was started at 650 mg/m <sup>2</sup>	CMF consisted of oral cyclophosphamide 100 mg/m <sup>2</sup> on days 1 through 14, with methotrexate 40 mg/m <sup>2</sup> and fluorouracil 600 mg/m <sup>2</sup> administered intravenously on days 1 and 8 and repeated every 4 weeks	-	N/A	16/107	Serious Adverse Events	DVT/VTE (4)

			twice daily on days 1 through 21 and repeated every 3 weeks with no dose escalation						
12	Van Cutsem et al, 2001	Capecitabine oral	Capecitabine 1,250 mg/m <sup>2</sup> administered twice daily days 1 to 14 every 3 weeks	5-FU/LV; LV 20 mg/m <sup>2</sup> as a rapid IV injection followed by an IV bolus injection of 5-FU 425 mg/m <sup>2</sup> , administered daily for 5 days in 4-week cycles	-	175,000 (7)	7/301	3 (4) 4 (1)	Myocarditis (1) Tachycardia (1) DVT/VTE (5)
13	Van Erning et al, 2016	Capecitabine oral	Capecitabine monotherapy	CAPOX, capecitabine and oxaliplatin	FOLFOX	189,195 (7)	7/164	3 (7)	N/A
14	Wenzel et al, 2002	Capecitabine oral	Capecitabine dose of 2,500 mg/m <sup>2</sup> /d divided into two doses for 14 days, followed by 7 days of rest. This schedule was repeated in 3-week cycles	-	-	N/A	0/26	-	N/A

<sup>a</sup>Some included studies may not completely report the number of cardiotoxicity subtypes. 5-FU: 5-fluorouracil, AUC: Area under the curve, CTCAE: Common Terminology Criteria for Adverse Events, d: day, DVT: Deep Vein Thrombosis, EKG: Electrocardiogram, hr/h: hour, IV: Intravenous, LV: Leucovorin, N/A: Not applicable, PLD: Pegylated liposomal doxorubicin, VTE: Venous Thromboembolism, WHO: World Health Organization.