Appendix 8

Characteristics of included studies

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
B2222 Blanke 2008[38,39] Time period: July 2000 to May 2006 Countries involved: 2 (Finland, USA) No. of institutions involved: 4	***n* receiving intervention(s):** 43 ***n* receiving comparator(s):** 0 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** imatinib at 600 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 11/43 (25.6%)
S0033 Blanke 2008[41,68,77] Time period: December 2000 to (CiC information has been removed) Countries involved: 2 (Canada, USA) No. of institutions involved: 148	**n receiving intervention(s):** 118 **n receiving comparator(s):** 0 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 36/117 (30.8%) **Median OS:** 19 months (95% CI 13 to 23 months) ***n* (%) still alive at data cut-off point:** 42/118 (35.6%) **Median PFS:** 5 months (2–10 months) ***n* (%) still progression free at data cut-off point:** 19/118 (16.1%)
Park 2009[79] Time period: June 2001 to June 2006 Countries involved: 1 (Republic of Korea) No. of institutions involved: 1	***n* receiving intervention:** 24 ***n* receiving comparator(s):** 0 **Baseline characteristics:** *Age*: Median, years (range): 52 (31–73) *Sex*: *n* (%) male: 18 (75.0%) *n* (%) female: 6 (25.0%) *ECOG performance status*: 0: 4 (16.7%) 1: 18 (75.0%) 2: 2 (8.3%) *Primary tumour site*: Stomach: 5 (20.8%) Small bowel: 15 (62.5%) Colon or rectum: 3 (12.5%) Omentum: 1 (4.2%) n *receiving previous treatment of*: Surgery: 20 (83.3%) Conventional chemotherapy: 3 (12.5%) Radiofrequency ablation: 1 (4.2%) Transarterial chemoembolization: 1 (4.2%) *Site(s) of metastases at time of dose escalation*: Liver: 20 (83.3%) Peritoneum: 15 (62.5%) Retroperitoneum: 5 (20.8%)	**Escalated dose intervention(s):** imatinib at 600 mg/day; imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** at 600 mg/day – 5/12 (41.6%); at 800 mg/day – 4/12 (33.3%) **Median time to progression:** at 600 mg/day – 1.7 months (range 0.7–24.9 months).

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
	n *(%) with prior response to standard-dose imatinib of*: PR: 9 (37.5%) SD: 8 (33.3%) PD: 7 (29.2%) n *(%) whose time to progression (TTP) with standard-dose imatinib was*: ≤ 6 months: 8 (33.3%) > 6 months: 16 (66.7%) n *(%) given initial escalated dose of imatinib at*: 600 mg/day: 12 (50.0%) 800 mg/day: 12 (50.0%)		
Seddon 2008[80–86] Time period: not stated to December 2007 Countries involved: 33 (not stated) No. of institutions involved: 96	***n* receiving intervention:** 0 ***n* receiving comparator(s):** 351 **Baseline characteristics:** not stated	**Escalated dose intervention(s):** NA **Comparator(s):** sunitinib at 50 mg/day in a 6-week cycle of 4 weeks on treatment/2 weeks off treatment	**Median OS:** 90 weeks (95% CI 73 to 106 weeks) ***n* (%) still alive at data cut-off point:** 193/351 (55.0%)
Zalcberg 2005[44] Time period: (CiC information has been removed) to April 2004 Countries involved: 13: (Australia, Belgium, Denmark, France, Germany, Italy, the Netherlands, New Zealand, Poland, Singapore, Spain, Switzerland, UK) No. of institutions involved: 56	***n* receiving intervention:** 133 ***n* receiving comparator(s):** 0 **Baseline characteristics:** *Age*: Median, years (range): 59 (20–85) *Sex*: *n* (%) male: 87 (65%) *n* (%) female: 46 (36%) *ECOG performance status*: 0: 63 (47%) 1: 49 (37%) 2: 12 (9%) 3: 9 (7%) n *(%) whose primary tumour site was*: GI: 109 (82%) Gastric: 34 (26%) Small bowel: 35 (26%) Duodenum: 20 (15%) Other GI: 20 (15%) Other abdominal 20 (15%) Retroperitoneal: 4 (3%) n *(%) with time since primary diagnosis of*: < 12 months: 70 (53%) 12–24 months: 29 (22%) > 24 months: 34 (26%)	**Escalated dose intervention(s):** imatinib at 800 mg/day **Comparator(s):** NA	***n* (%) showing response or SD:** 39/133 (29.3%) 'Response to cross-over … occurred significantly more often in wild-type cases (83%) compared with *KIT* exon 11 mutants (7%) ($p = 0.0012$, Fisher's exact test), and in *KIT* exon 9 mutants (57%) compared to *KIT* exon 11 mutants ($p = 0.0017$, Fisher's exact test)' **Median PFS:** 81 days ***n* (%) still progression free at data cut-off point:** 24/133 (18.8%) **Median duration of response:** 153 days (range 37–574 days) ***n* (%) of patients requiring at least one dose reduction:** 12/77 (15.6%) ***n* (%) of patients requiring at least one dose delay:** 18/77 (23.4%) ***n* (%) with adverse events:** Oedema: 99/124 (79.8%) Skin rash: 45/124 (36.3%) Fatigue: 102/124 (82.3%) Dyspnoea: 30/124 (24.2%) Infection: 20/124 (16.1%) Nausea: 82/124 (66.1%) Leucopenia: 56/121 (46.3%) Neutropenia: 49/121 (40.5%) Thrombocytopenia: 7/121 (5.8%) Anaemia: 119/121 (98.3%)

Study ID	Participants	Intervention(s) and comparators	Outcomes summary
	n *(%) with site(s) of active disease at study entry in*:		***n* (%) with adverse event reporting decreased severity after crossover:**
	Site of primary tumour: 50 (38%)		Oedema: 25/99 (25.3%)
	Liver: 96 (72%)		Skin rash: 23/45 (51.1%)
	Lung: 16 (12%)		Fatigue: 21/102 (20.6%)
	Ascites: 12 (9%)		Dyspnoea: 8/30 (26.7%)
	Pleura: 4 (3%)		Infection: 9/20 (45.0%)
	Bone: 3 (2%)		Nausea: 38/82 (46.3%)
	Skin: 3 (2%)		Leucopenia: 25/56 (44.6%)
	n *(%) receiving previous treatment of*:		Neutropenia: 30/49 (61.2%)
	Surgery: 116 (87%)		Thrombocytopenia: 4/7 (57.1%)
	Radiotherapy: 6 (5%)		Anaemia: 15/119 (12.6%)
	Chemotherapy: 51 (38%)		***n* (%) with adverse event reporting increased severity after crossover:**
			Oedema: 33/99 (33.3%)
			Skin rash: 19/45 (42.2%)
			Fatigue: 47/102 (46.1%)
			Dyspnoea: 14/30 (46.7%)
			Infection: 9/20 (45.0%)
			Nausea: 26/82 (31.7%)
			Leucopenia: 16.56 (28.6%)
			Neutropenia: 13/49 (26.5%)
			Thrombocytopenia: 2/7 (28.6%)
			Anaemia: 51/119 (42.9%)
			***n* (%) with adverse event achieving increased severity to grade 3- to grade-4 level:**
			Oedema: 7/99 (7.1%)
			Skin rash: 2/45 (4.4%)
			Fatigue: 10/102 (9.8%)
			Dyspnoea: 1/30 (3.3%)
			Infection: 1/20 (5.0%)
			Nausea: 3/82 (3.7%)
			Leucopenia: 0/56 (0.0%)
			Neutropenia: 0/49 (0.0%)
			Thrombocytopenia: 0/7 (0.0%)
			Anaemia: 17/119 (14.3%)

NA, not available.