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CURRENT TRIALS

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Phase 3 Randomized Placebo-controlled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving Chemotherapy for Treatment of Non-small Cell Lung Cancer (NSCLC), Ovarian Cancer, or Breast Cancer- estimated completion date: 26 February, 2023

NCT03362177

RECITE: A Phase 3 Randomized Placebocontrolled Double-blind Study of Romiplostim for the Treatment of Chemotherapy-induced Thrombocytopenia in Patients Receiving FOLFOX-based Chemotherapy for Treatment of Gastrointestinal or Colorectal Cancer - estimated completion date: 18 December, 2022

Author/year published/ Drug	Type of study	Patient (N)	Indication for use	Chemotherapy	Result
Al-Samkari *et al.* [17] 2020 Romiplostim	Retrospective review	173 (153 solid tumour- most common GI)	Treatment of persistent CIT (>3 weeks since last chemotherapy)	Multiple (most common Platinum, Gemcitabine, Temozolomide, Taxane)	Clinical benefit in 71% of solid tumor patients with achieving platelet count ≥ 75 X 109/L and at least 30X 109/L higher than baseline 98% were able to receive additional chemotherapy (median 4 cycles)
Le Rhun *et al.* [15] 2019 Romiplostim	Phase II single-arm trial	20 patients with Glioblastoma	Treatment of CIT after CCRT (Grade 3/4)	Temozolomide	12/20 (60%) patients were able to continue treatment (6 cycles) without interruption
Fassel H *et al.* [5] 2019 Romiplostim	Case report in paediatric oncology	2 patients with Neuroblastoma	IV Ig and transfusion refractory CIT	Antineuroblastoma chemotherapy (N7 induction, rapid COJEC, ICE)	Allowed safe and timely continuation of chemotherapy without relapse of thrombocytopenia
Frey *et al.* [16] 2019 Eltrombopag	Randomised, double blind, Phase II	148 patients with AML	Prophylactic use (Day 4 of induction, dose escalation if Day 7 platelet count <100x109/L)	Anthracycline-based	Eltrombopag did not improve the time to platelet recovery or incidences of grade 3-4 thrombocytopenia No significant difference in thromboembolic adverse events with eltrombopag
Soff GA *et al.* [8] 2019 Romiplostim	Randomised phase 2 trial compared to observation	23 patients with Solid tumours	Treatment of CIT for at least 4 weeks, despite dose reduction and delay	Multiple regimens	14 out of 15 (93%) patients randomised to Romiplostim, achieved platelet count correction (≥ 100x10 9/L) within 3 weeks, - converted to single arm- 44 of the total 52 (84%) patients also responded. 10.2% developed VTE.
Al-Samkari *et al.* [18] 2018 Romiplostim	Retrospective analysis	22 with CIT or pre-existing thrombocytop-nia	Prophylactic and treatment if Platelet count nadir <100 x10 9/L with or without chemoRx	Multiple (most common FOLFOX)	18/22 (81%) were able to continue treatment without interruption or dose reduction. No thrombotic events
Iuliano *et al.* 2018 [25] and 2016 [7]	Case series	28 patients, 22 with solid tumours, 6 with DLBC	Prophylaxis when platelet count <80 x10 9/L	Platinum-based	1/28 patient required increased dose of Eltrombopag, all other patients achieved endpoints of avoiding Platelet Nadir<50 X 109/L, transfusions, bleeding events, dose reduction or delays.
Newton *et al.* [4] 2018 Eltrombopag	Case report	Patient with GBM	Treatment of prolonged aplastic anaemia (Platelet Nadir-6)	Temozolomide	Benefit noted- hematopoietic recovery at day 131 following first dose of temozolomide AE- stopped Temozolomide due to transaminitis.

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Dardis, C *et al.* [6] 2017 Eltrombopag Romiplostim	Retrospective Case Series	28 patients with Glioma, who developed CIT	Treatment for CIT (Platelets <100 x10 9/L or physician discretion)	Temozolomide, bevacizumab, lomustine	27/ 28 (96%) patients responded, all patients were able to resume chemotherapy and continue for longer time at higher doses than prior to the treatment (median 32 months). AE- 1 patient had intractable itching, and 1 death (suspected PE)
Winer ES *et al.* [14] 2017 Eltrombopag	Randomised placebo controlled Phase 2	75 (52 received Rx)	Treatment for CIT (pre-treatment platelet count <100 x10 9/L on chemotherapy) Prophylaxis if <150 x10 9/L	Gemcitabine with or without combination with platinum	shortened the time to platelet count recovery and reduced dose delays/reductions Lower rate of (77% vs 100%) grade 3 or more thrombocytopenia Thrombosis (5/52 cf. 2/23 in placebo) Hepatotoxicity (13/52 cf. 4/23 in placebo) Total Serious AEs (16/52 cf. 12/23 in placebo)
Miao, J *et al.* [9] 2016 Romiplostim	Retrospective Case series	32 patients, with CIT (59% GI malignancy)	Treatment for CIT (Mean 68 x10 9/L)	Platinum-based	28 out of 32 (87%) patients responded, and were able to receive 2 or more cycles of chemotherapy without delays or dose reductions for thrombocytopenia, median duration 131.5 days 4 patients developed Venous thromboembolism
Urena LE *et al.* [28] Romiplostim	Case series	15 patients with malignancies (11 non-hematologic)	Treatment for CIT median baseline platelet count- 69 x 109 L (8-90)	Multiple regimens	87% of patients achieved response, in 11 cases with platelet counts of > 100 x 109L. This allowed full-dose of chemotherapy. 2 patients who did not responde were on 9th line of Rx for breast cancer and 4th line for small cell cancer. no treatment-related toxicities observed.
Winer ES *et al.* [10] 2015 Eltrombopag	Randomised placebo controlled phase 1 study	26 patients planned for gemcitabine monotherapy or combination	Prophylaxis if platelet count ≤300 × 109/L	Gemcitabine and platinum-based	14% in Eltrombopag cf. 50% in placebo arm required chemotherapy dose reductions and/or delays Dose not escalated to >100mg/day due to thrombocytosis but no dose limiting toxicity 2 cases of VTE in Eltrombopag arm were considered to be unrelated
Parameswaran, R. *et al.* [12] 2014 Romiplostim	Retrospective review	20 with predominantly solid tumours	Treatment of protracted CIT (<100× 109/L for at least 6 weeks despite dose delay or reduction)	Multiple regimens	clinical benefit in 19/20 (95%) patients (platelet count ≥ 100 × 109/L), 15/20 (75%) patients able to resume chemotherapy without recurrence, 14/20 (70%) patients completed more than 2 subsequent cycles of chemotherapy 3/20 developed DVT
Chawla *et al.* [19] 2013 Eltrombopag	Phase I dose escalation study	12 with CIT in advanced soft tissue sarcoma	Treatment for CIT (<75× 109/L with previous chemotherapy)	doxorubicin and ifosfamide	Clinical benefit in 11/12 (91%) – completed at least 2 cycles of chemotherapy Closed early due to slow recruitment
Hayes, *et al.* [26] 2013	Pooled Pharmacokinetic/ pharmacodynamic data	Combined 3 different studies (Kellum [20], Jenkins, Matthys 2010)	Prophylactic (Studies 1 and 2 were in healthy subjects, study 3-Kellum *et al.*)	Carboplatin/ paclitaxel	Eltrombopag stimulated platelet precursor production, proportional to plasma Eltrombopag concentration

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Winer, E. S. *et al.* [11] 2012 Eltrombopag	Phase 1 placebo controlled	26 with solid tumours	Prophylactic/Treatment (baseline count <300× 109/L, planned for 6 cycles of chemo)	Gemcitabine with or without Cisplatin or Carboplatin	Well-tolerated and improved platelet count compared to placebo especially in combination arm (platelet nadir 53 compared to 113)
Kellum *et al.* [20] 2010 Eltrombopag	Randomized phase 2 study compared to Placebo	183 with advanced solid tumours	Prophylactic (chemo Naïve, planned for at least 2 cycles of carboplatin at 5-6 AUC)	First line Carboplatin/paclitaxel	Post-chemo nadir platelet counts increased during cycles 1 and 2 in all Eltrombopag treatment groups compared with placebo but did not achieve the primary end point of change in platelet count from Day 1 of Cycle 2 to nadir in Cycle 2.
Vadhan-Raj S *et al* [27] 2010 AMG 531	Randomized, placebo-controlled, dose and schedule-finding phase I/II study	50 patients with non-Hodgkin's lymphoma	Prophylactic (patients planned for specific chemo regimen)	RHyper-CVAD alternating with RArac-MTX	The platelet nadir was significantly higher and the duration of thrombocytopenia was shorter, with a reduced need for the platelet transfusions in 4 pts; AE-2 deep vein thrombosis (DVT) and 2 pulmonary embolism (PE)
Fanale M *et al.* (2009)	open-label dose- and schedule-finding study	39 patients with lymphoma	Treatment of CIT (Platelet count <50× 109/L)	Multiple regimens	No dose-dependent effect on the incidence of serious AEs. One patient with stage IV gastric lymphoma died following a serious AE of gastrointestinal hemorrhage
Natale, R *et al.* [13] 2009 Romiplostim	Randomised placebo controlled Phase 2	62 patients with NSCLC (placebo:Romiplostim-12:50)	Treatment of CIT in previous cycle (platelet <100× 109/L)	Gemcitabine and platinum-based	No evidence of beneficial impact on platelet count related efficacy endpoints. Serious AE – 1/12 (placebo) cf. 17/50 (Romiplostim) 3 thrombotic events in Romiplostim group,

Table 1: Literature search for the use of thrombopoietin agonists in the setting of chemotherapy-induced thrombocytopenia

Date	WCC	Neutrophil	Platelet	Hb	Remark
4 January 2019	5.7	3.2	253	127	
7 January 2019	Commenced Concurrent ChemoRadiotherapy				
14 January 2019	5.6	3.5	275	130	Developed grade 1 diarrhoea
29 January 2019	5.5	3.3	199	120	
1 February 2019	6.4	5.8	117	121	
2 February 2019					Stopped dexamethasone due to severe esophagitis
4 February 2019	4.4	3.5	53	121	Temozolomide stopped, asymptomatic
06 February 2019	2.5	1.8	22	118	
07 February 2019	2.6	2.1	13	120	Admission and First Platelet Transfusion
11 February 2019	1.2	0.8	5	108	Tx- when Platelet <10 (almost Second daily platelet transfusion)
13 February 2019	0.9	0.4	14	104	Developed bruising, rashes but no bleeding
15 February 2019	0.8	0.1	4	102	Started Prednisone 1 mg/kg/day , daily platelet transfusion, GCSF, with plan to arrange HLA matched platelets,
18 February 2019	0.6	0.1	3	89	
19 February 2019	0.8	0.1	4	81	No change in Platelet/ Neutrophil count despite stopping temozolomide for 2 weeks
20 February 2019	0.5	0.2	5	76	Received last dose of RT (29/30 #) prior to transfer to tertiary centre for ongoing haematology input
23 February 2019	1.0	0.3	2	87	Platelet Transfusion
27 February 2019	1.9	0.7	4	82	

Date	WCC	Neutrophil	Platelet	Hb	Remark
02 March 2019	2.2	0.9	4	89	
07 March 2019	2.0	0.8	9	80	Post Bone marrow aspiration
15 March 2019	8.3	6.4	9	82	Platelet Transfusion
21 March 2019	3.1	1.7	13	90	Platelet Transfusion
27 March 2019	7.1	5.0	15	92	
03 April 2019	5.9	4.2	21	88	
11 April 2019	Application for Eltrombopag				
14 April 2019	2.7	1.5	39	93	
Post platelet Tx	3	1.8	78	88	First significant increase in count post HLA matched Platelet Tx
16 May 2019	7	5.3	30	88	Platelet Tx
	6	4.4	76	88	Post Platelet Tx
21 May 2019	Commenced on Eltrombopag 50 mg daily, Platelet transfusion decreased to weekly, Continued GCSF twice weekly				
23 May 2019	8.5	6.4	54	107	
28 May 2019	3.3	1.9	74	109	
04 June 2019	3.	2.4	66	116	
11 June 2019	3.8	2.3	73	114	
17 June 2019	5	3	87	123	
24 June 2019	5.6	3.9	100	120	
08 July 2019	5.1	3.5	108	128	
15 July 2019	6.1	4.4	121	126	
22 July 2019	GCSF reduced to weekly dose				
1 August 2019	10	3.6	125	129	
27 August 2019	5.6	3.9	151	122	
19 September 2019	3.8	2.2	171	127	

Table 2: WCC (10^9/L), neutrophil (10^9/L), platelet (10^9/L) and Hb (g/L) levels from 04 January to 19 September 2019