BC Cancer Protocol Summary for Treatment of Recurrent/Refractory Ewing Sarcoma using vinCRIStine, Temozolomide and Irinotecan

Protocol Code	*SAAVVIT*
Tumour Group	*Sarcoma*
Contact Physician	*SA Systemic Therapy*

ELIGIBILITY:
Patient must have:
- Recurrent or metastatic Ewing sarcoma with progression on or after at least one prior line of therapy

TESTS:
- Baseline: CBC & Diff, total bilirubin, ALT, creatinine
- Baseline, if clinically indicated: sodium, potassium, alkaline phosphatase, albumin
- Prior to each cycle: CBC & Diff, total bilirubin, ALT, creatinine
- If clinically indicated: alkaline phosphatase, albumin

PREMEDICATIONS:
- Antiemetic protocol for moderate emetogenicity treatment protocols (see protocol SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see Precautions)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia

SUPPORTIVE MEDICATIONS:
- For prophylaxis of late onset diarrhea: cefixime 400 mg PO once daily for 10 days starting 2 days prior to each cycle
- All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with instructions for the management of diarrhea.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
temozolomide	100 mg/m^2* on Days 1 to 5	PO 60 minutes prior to irinotecan
vinCRIStine	1.5 mg/m^2 on Day 1 (maximum 2 mg)	in 25 mL NS over 15 minutes
irinotecan	50 mg/m^2 on Days 1 to 5	IV in 250 to 500 mL D5W over 90 minutes

*select dose per Dose Banding Table (appendix)

Repeat every 21 days until disease progression or intolerable toxicity.

DOSE MODIFICATIONS:

1. **Hematological Toxicity**:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Management
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	or	Less than 100	▪ Delay treatment until recovery to ANC greater than or equal to 1.0 and platelets greater than or equal to 100 ▪ If recovery occurs within 14 days, proceed with treatment at same dose ▪ If recovery takes 14 days or longer, reduce temozolomide dose by 20%, or alternatively shorten temozolomide treatment to Days 1 to 4 of each cycle ▪ Discontinue treatment if toxicity recurs after 2 dose reductions

2. **Neurotoxicity**: vinCRIStine only

Toxicity	Dose Modification
Dysesthesias, areflexia only	100 %
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

3. **Hepatotoxicity**:

For vinCRIStine:

Total bilirubin (micromol/L)	vinCRIStine Dose Modification
Less than or equal to 25	100%
26 to 50	50%
Greater than 50	25%

For temozolomide:

Total bilirubin (micromol/L)		ALT	Temozolomide Dose Modification
Less than 25	and	Less than or equal to 2.5 x ULN	100%
25 to 85	or	2.6 x ULN to 5 x ULN	Reduce by 20%
Greater than 85	or	Greater than 5 x ULN	▪ Delay treatment until recovery of total bilirubin to less than 25 and ALT less than or equal to 2.5 x ULN, then reduce dose by 20% ▪ If toxicity recurs, delay treatment until recovery then reduce dose by an additional 20% ▪ If second recurrence, discontinue temozolomide

ULN = upper limit of normal

4. **Diarrhea:**

Grade	Diarrhea	Irinotecan Dose
1 to 2	Increase of up to 6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output	100%
3 to 4	Increase of 7 or more stools/day or incontinence, malabsorption, severe increase in loose water, colostomy output, grossly bloody diarrhea, may require parenteral support	Delay until Grade 2 or less, then reduce dose to 75%

PRECAUTIONS:

1. **Diarrhea:** may be life threatening and requires prompt, aggressive treatment.
   - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.

- **Late diarrhea** has an onset of 5 to 11 days post-treatment, a duration of 3 to 7 days and must be treated promptly with **loperamide** (e.g., IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
    - **4 mg stat**
    - **then 2 mg every 2 hours until diarrhea-free for 12 hours**
    - may take 4 mg every 4 hours at night
- The use of drinks such as GATORADE® or POWERADE® to replace fluid & body salts is recommended.
- Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.

2. **Other Cholinergic Symptoms:** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
3. **Gilbert's Syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
4. **Hepatic Dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or ALT greater than 3x the upper limit of normal if no liver metastases, or ALT greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17 to 35 micromol/L.
5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Potential Drug Interactions:** Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. carbamazepine, phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.
7. **Extravasation**: vinCRIStine causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
8. **Pneumocystis jiroveci (previously carinii) pneumonia (PJP)**: Occasional reports of PJP in patients receiving concomitant or adjuvant temozolomide have occurred.
9. **Renal Dysfunction:** Renal impairment is not expected to affect temozolomide clearance. Caution should be exercised when treating patients with creatinine clearance less than 36 mL/min.

Contact the SA Systemic Therapy physician at your regional cancer centre or the SA Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Raciborska A, Bilska K, Drabko K et al. Vincristine, Irinotecan, and Temozolomide in Patients With Relapsed and Refractory Ewing Sarcoma. Pediatr Blood Cancer 2013;60:1621–1625.
2. Gupta A, Dietz M, Riedel R et al. Consensus Recommendations for Systemic Therapies in the Management of Relapsed Ewing sarcoma: A Report from the National Ewing Sarcoma Tumor Board. Cancer. 2024;130:4028–4039.
3. Palmerini E, Jones R, Setola E et al. Irinotecan and Temozolomide in Recurrent Ewing Sarcoma: an Analysis in 51 Adult and Pediatric Patients. Acta Oncologica 2018; 57(7): 958–964.

Appendix. Dose Bands

TEMOZOLOMIDE BANDING TABLE

Ordered Dose (mg)		Rounded dose (mg)	Number of Capsules Per Dose				
From:	To:		5 mg	20 mg	100 mg	140 mg	250 mg
38	42	**40**		2			
43	47	**45**	1	2			
48	52	**50**	2	2			
53	56	**55**	3	2			
57	63	**60**		3			
64	68	**65**	1	3			
69	73	**70**	2	3			
74	75	**75**	3	3			
76	84	**80**		4			
85	89	**85**	1	4			
90	94	**90**	2	4			
95	104	**100**			1		
105	109	**105**	1		1		
110	113	**110**	2		1		
114	124	**120**		1	1		
125	129	**125**	1	1	1		
130	132	**130**	2	1	1		
133	144	**140**				1	
145	152	**145**	1			1	
153	164	**160**		1		1	
165	173	**165**	1	1		1	
174	189	**180**		2		1	
190	210	**200**			2		
211	227	**220**		1	2		
228	240	**240**			1	1	
241	262	**250**					1
263	270	**270**		1			1
271	294	**280**				2	
295	315	**300**			3		
316	332	**320**		1	3		
333	367	**350**			1		1
368	370	**370**		1	1		1
371	409	**390**				1	1
410	441	**420**				3	
442	472	**450**			2		1
473	480	**480**			2	2	
481	525	**500**					2
526	569	**550**			3		1
570	630	**600**			1		2