DRUG NAME: TRC105

SYNONYM(S): Carotuximab[1]

COMMON TRADE NAME(S):

CLASSIFICATION: molecular targeted agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Carotuximab is a chimeric IgG1 kappa monoclonal antibody which targets human CD105 (endoglin). CD105 expression is required for vascular endothelial cell proliferation. Targeting CD105 is a novel approach to inhibiting angiogenesis in cancer cells.[1]

USES:

Primary uses:

Other uses:
gestational trophoblastic neoplasia[2]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- pregnancy[1]
- history of hypersensitivity reaction to Chinese hamster ovary cell proteins or other recombinant human, chimeric, or humanized antibodies[1,2]

Caution:
- patients with ***Osler-Weber-Rendu syndrome*** are at risk of hemorrhage from abnormal blood vessels that could be exacerbated by treatment with carotuximab[1]

Pregnancy: Developmental toxicity studies have not been conducted; however carotuximab is considered likely to be severely toxic to the developing fetus based on effects of CD105 gene depletion in utero. Two highly effective methods of birth control are recommended for fertile patients and their sexual partners during and for 6 months following treatment.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials. When placebo-controlled trials are available, adverse events will generally be included if the incidence is $\geq$5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (43%); see paragraph following **Side Effects** table
gastrointestinal	*emetogenic potential:* low[3]
	gingival bleeding (22%); see paragraph following **Side Effects** table
	nausea (37%)
	vomiting (28%)
general disorders and administration site conditions	*extravasation hazard:* none[4]
	fatigue (59%)
	pyrexia (19%)
immune system	hypersensitivity (1%)
	infusion related reactions (22.2%); see paragraph following **Side Effects** table
infections and infestations	infection unspecified (2%)
	oral herpes (4%)
	pneumonia (2%)
	sinusitis (3%)
	skin infection (3%)
	tooth abscess (6%)
	upper respiratory tract infection (5%)
	urinary tract infection (10%)
metabolism and nutrition	appetite decrease (29%)
nervous system	***headache*** (60%); see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	***epistaxis*** (54%); see paragraph following **Side Effects** table
	pneumothorax (2%)
skin and subcutaneous tissue	***mucocutaneous telangiectasia*** (12%); see paragraph following **Side Effects** table
vascular	flushing (20%)
	thromboembolic events (3%)

Adapted from standard reference[1] unless specified otherwise.

The most common adverse reactions related to administration can be explained based on known attributes of CD105 inhibition, known phenotypes of Osler-Weber-Rendu syndrome (a syndrome of CD105 heterozygosity), and class effects common to IgG1 antibodies.[1]

Anemia has been observed commonly and is dose limiting. It develops slowly and is a hypoproliferative, non-hemolytic type. It is reversible with dose interruption or reduction, and manageable with standard supportive measures such as erythropoietin, packed red blood cell transfusion, etc. It is believed to result from the suppression of proerythroblasts, but may also be related to blood loss resulting from epistaxis or gingival bleeding associated with mucocutaneous telangiectasia. Adequate hemoglobin levels are necessary for treatment initiation, and should be monitored throughout treatment.[1]

Headaches have been observed with treatment, generally within hours following the completion of the initial infusion. Headaches are a known presentation of Osler-Weber-Rendu syndrome. Headaches are not associated with radiographic abnormalities. They may be throbbing in nature and respond to nonsteroidal anti-inflammatory agents, acetaminophen, triptans, and opioids. Headaches may be particularly prominent in combination with other drugs such as bevacizumab, and may be mitigated by splitting the dose over two days (3 days apart) or by delaying the first dose of carotuximab in relation to the other drug in the combination.[1]

Infusion reactions generally occur with the initial infusion. Common infusion-related reactions have included rigors, nausea, hypertension, flushing, headache, vomiting, and fever. Reactions generally occur with the initial infusion. The severity of the reactions may be reduced by extending the duration of the infusion from 1 to 4 hours and premedicating with glucocorticoids. Depending on the severity of the reaction, carotuximab may require dose interruption or discontinuation.[1]

Mucocutaneous telangiectasia is routinely observed with carotuximab, beginning as early as 2 weeks after starting treatment. Mucocutaneous telangiectasia is a defining characteristic of Osler-Weber-Rendu syndrome and is an expected consequence of treatment with carotuximab. ***Epistaxis*** and ***gingival bleeding*** are known consequences of mucocutaneous telangiectasia. Patients with epistaxis may benefit from saline nasal gel and humidification to prevent drying of mucous membranes. Persistent symptoms may require surgical referral.[1]

INTERACTIONS: no information found

SUPPLY AND STORAGE:

Injection:
Tracon Pharma supplies carotuximab (TRC105) as 200 and 400 mg single-use (preservative free) vials in a concentration of 25 mg/mL. Refrigerate. Protect from light.[1]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found

BCCA administration guideline noted in ***bold***, ***italics***

Intermittent infusion[2]	cycle 1, day 1: over 4 hours cycle 1 day 4: over 2 hours* cycle 1 day 8 (and onwards): over 1 hour* max rate = 25 mg/min; administer with 0.2 micron inline filter * patient must complete the infusion without infusion reactions in order to reduce the duration of next planned infusion (flush line with normal saline following administration)
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	28 days[2]:	**cycle 1**:** **split dose regimen** for cycle 1, days 1 and 4: initial doses: 3 mg/kg IV for one dose on day 1, followed by 7mg/kg on day 4. followed by **full dose regimen**: 10 mg/kg IV for one dose on days 8, 15 and 22 Max weight for dose calculation[2] = 85 kg **cycle 2 onwards****: 10 mg/kg IV for one dose on days 1, 8, 15 and 22 Max weight for dose calculation[2] = 85 kg ****Missed doses**: if dosing is resumed ≥10 days after the previous infusion, the first weekly dose should be split over two days with full premedication as per cycle 1 split dose regimen.[2]
	2 weeks[2]:	15 mg/kg IV for one dose Max weight for dose calculation[2] = 85 kg

REFERENCES:

1. Tracon Pharmaceuticals Inc. TRC105 (carotuximab) investigational brochure. San Diego, California; 14 February 2017 (version 10.0).
2. Tracon Pharmaceuticals Inc. Clincial Protocol: A Phase 2A Study of TRC105 (with Option to Add Bevacizumab) in Patients with Refractory Gestastional Trophoblastic Neoplasia (GTN). San Diego, California; 20 September 2016 Amendment #3.
3. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
4. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.