Appendix to Provincial Systemic Therapy Policy III-60

Table 1. Duration of physician coverage per parenteral drugs

30 minutes	*60 minutes*	*3 hours*	*During entire administration*	*During entire administration PLUS additional time*
alemtuzumab avelumab bleomycin cabazitaxel CARBOplatin carfilzomib DOCEtaxel etoposide PACLitaxel riTUXimab†	cetuximab‡ siltuximab daratumumab subcut ‖	riTUXimab* oBINutuzumab‖‖‖	atezolizumab bendamustine brentuximab vedotin nivolumab-relatlimab¶¶ oxaliplatin	asparaginase¥ blinatumomab§ daratumumab IV# enfortumab vedotin†† epcoritamab‖‖ glofitamab††† isatuximab‡‡‡ mogamulizumab¶ pegaspargase¥ PERTuzumab¶ polatuzumab vedotin** sacituzumab govitecan‡‡ tebentafusp§§ trastuzumab¶ trastuzumab deruxtecan *** trastuzumab emtansine*** tremelimumab##

† Second and subsequent IV infusions

‡ 60 minutes following end of first and second infusion, may discontinue observation period if no infusion reactions occur for two consecutive doses.

* First IV infusion only; physician does not need to be on site for subcutaneous injection.

¥ 60 minutes following end of infusion

§ Hospitalization recommended for a minimum of the first 9 days of cycle 1 and the first 2 days of cycle 2. Subsequent cycles may be started as an outpatient.

30 minutes following end of IV infusion. Observation not required after 3 treatments with no reaction.

‖ For first dose: 60 minutes following injection if no prior daratumumab. If changing from daratumumab IV to subcutaneous, 30 minutes following the first injection. Observation not required after the first subcutaneous dose with no reaction.

¶ For first dose: additional 60 minutes after end of infusion. For second and third doses: additional 30 minutes after end of infusion. No additional observation period is needed if no reactions after 3 consecutive treatments.

** For first dose: additional 90 minutes after end of infusion. For subsequent doses: additional 30 minutes after end of infusion.

*** For first dose: additional 90 minutes after end of infusion. For subsequent doses if no reactions with first dose: additional 30 minutes after end of infusion. Observation period not required after 3 treatments with no reaction.

†† For first 3 consecutive doses: additional 60 minutes after end of infusion. Observation period not required after 3 treatments with no reaction.

‡‡ 30 minutes following end of infusion.

‡‡‡ 30 minutes following end of first infusion. Observation not required after first treatment with no reaction.

§§ Hospitalization required for minimum of the first 3 doses (Cycle 1 Days 1, 8, and 15). Observation required during infusion and for at least 16 hours following administration. Subsequent doses may be given in ambulatory setting if no Grade 2 or worse hypotension during or after Cycle 1 Day 15 dose. Hospitalization may be required for subsequent administrations after treatment interruption.

tremelimumab infusion is followed by durvalumab infusion. Observation required for 60 minutes following end of durvalumab infusion for first combination treatment. Observation not required for subsequent tremelimumab treatment if no reaction.

‖‖ Patients to be observed for at least 24 hours following the epcoritamab Step-up and first full treatment dose (Cycle 1, Days 1, 8 and 15).

¶¶ For the first 6 cycles. Not required after 6 treatments with no reaction.

‖‖‖ First 1000 mg of oBINutuzumab infused (this may include first, OR first AND second infusions, depending on protocol).

††† Patients to be observed for at least 24 hours following completion of Step-up dose 1 glofitamab infusion (Cycle 1 Day 8), and for at least 24 hours following completion of Step-up dose 2 (Cyle 1 Day 15) or subsequent doses if any grade CRS with previous dose

Appendix to Provincial Systemic Therapy Policy III-60

Table 2. Infusion-related or other toxicity, onset and incidence

The threshold for inclusion was largely based on the emphasis placed by the manufacturer, although in some cases (e.g., oxaliplatin) literature reports may also be pivotal. Any primary literature review would be based on MEDLINE search combining MeSHs of "drug hypersensitivity" or "immediate hypersensitivity" with "antineoplastic agents", limited to humans and English language. Length of physician coverage takes into account of the likely documented onset of reactions and the usual administration time.

Drug	*Toxicity*	*Onset*	*Incidence*
alemtuzumab[1]	infusion reactions (hypotension, rigors, fever, shortness of breath, bronchospasm, chills, rash)	not defined	26-96% (severe 9-16%)
asparaginase[2-4]	hypersensitivity reactions	30-60 min	severe 3-32%
atezolizumab	infusion reactions	not defined	1-2%
avelumab[48]	infusion reactions (flushing, chills, hypotension, dyspnea, wheezing, pyrexia, back pain, abdominal pain, urticaria)	not defined	up to 30% (severe 1%)
bendamustine[5,6]	infusion reactions (fever, chills, pruritus, shortness of breath, hypotension, cyanosis, tachycardia, rash; rarely, severe anaphylactic and anaphylactoid reactions)	during or directly after drug administration	5% (severe 1%)
bleomycin[7,8]	hypersensitivity reactions	30 minutes to 6 hours after first or second dose	1%
blinatumomab[45]	cytokine release syndrome	2 days after start of infusion	11% (severe 1%)

Appendix to Provincial Systemic Therapy Policy III-60

Drug	*Toxicity*	*Onset*	*Incidence*
brentuximab vedotin[9,10]	infusion reactions (chills, nausea, dyspnea, pruritus, pyrexia, cough, wheezing, difficulty breathing, hives, itching, swelling)	immediate or delayed up to 2 days	12%
cabazitaxel[11]	hypersensitivity reactions	not defined	severe <1%
carfilzomib[50]	infusion reactions (fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, angina)	immediate to within 24 hours of infusion	43% (severe 4%)
cetuximab[12,13]	infusion reactions (rapid onset of airway obstruction, urticaria, hypotension)	not defined	13-19% (severe 2-5%)
CARBOplatin[14-17]	hypersensitivity reactions	usually immediately after start of the infusion; may delay for several hours	2-30%

Drug	*Toxicity*	*Onset*	*Incidence*
daratumumab [46-47, 54]	IV: Infusion reactions (cough, wheeze, larynx and throat irritation, bronchospasm, laryngeal and pulmonary edema, hypertension, hypoxia and dyspnea)	generally occur during administration of the infusion or within four hours of its completion.	IV: initial infusion (35-48%, severe 5-7%), subsequent infusions (2-4%, severe <1%)
	Subcutaneous: administration-related systemic reactions. Signs and symptoms as with IV, above	majority occur on day of treatment with a median time to onset of 3.7 hours	subcut: initial injection (8-13%, severe <2%); subsequent injections (<1%, severe <1%)
DOCEtaxel[18,19]	hypersensitivity reactions	a few minutes after start of the infusion	21% (severe 4%)
enfortumab vedotin [55,56]	Infusion-related reactions	not defined	Infusion-related reactions: 9% (severe 1%)
epcoritamab[63,64]	cytokine release syndrome/CRS (pyrexia, hypotension, hypoxia, dyspnea, chills, and tachycardia) and/or immune effector cell-associated neurotoxicity syndrome/ICANS (aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral edema)	CRS: Most events occur during the first cycle, and the majority of those occur after the first full dose on Day 15. Median time to onset after the first full dose is 21 hours. ICANS: Majority of events occur during Cycle 1, with a median time to onset of 17 days	CRS: 50-51%, severe 3% ICANS: 6%, severe <1%

Drug	*Toxicity*	*Onset*	*Incidence*
etoposide[14,20,21]	hypersensitivity reactions	usually during infusion or within minutes after start of infusion; may occur after only a few milligrams have been infused or up to several hours after administration	1-3%
glofitamab	Infusion-related reaction/IRR (fever, nausea, chills, headache, hypotension, hypoxia or organ toxicity); may be clinically indistinguishable from cytokine release syndrome/CRS	Not defined.	4-6%
	CRS (fever, chills, hypoxia, hypotension, dyspnea, tachycardia, and elevated liver enzymes); may be clinically indistinguishable from IRR	Median time to onset: • After Step-up dose 1: 13 h • After Step-up dose 2: 29 h After first 30 mg dose: 29 h	• After Step-up dose 1: 54% • After Step-up dose 2: 33% • After first 30 mg dose: 28% After subsequent doses: 1-2%
	immune effector cell-associated neurotoxicity syndrome/ICANS (headache, confusion, disorientation, speech disturbances, altered levels of consciousness, seizures, muscle weakness, agitation, and tremor)	Median time to onset after Step-up dose 1: 8 days	40%

Drug	*Toxicity*	*Onset*	*Incidence*
isatuximab[58]	infusion-related reactions (dyspnea, cough, chills, nasal congestion, nausea, hypertension, hypotension, bronchospasm, tachycardia)	Majority occur during first infusion. Median time to infusion interruption is 55 minutes.	38-46% (severe 3-5%)
mogamulizumab[62]	infusion-related reactions (chills, nausea, fever, tachycardia, rigors, headache, vomiting)	Most often occur during or shortly after the first infusion	33% (severe 2%)
nivolumab-relatlimab[65, 66]	Infusion-related reactions (chills, shaking, itching, rash, flushing, dyspnea, dizziness, fever)	Median time to onset: 4.1 weeks (range 0.1 to 57.6 weeks)	7%
oBINutuzumab	infusion reactions (nausea, vomiting, chills, hypotension, pyrexia, dyspnea, flushing, hypertension, headache, tachycardia, diarrhea)[22]	not well defined, but probably within 1-2 hours after start of infusion of first dose and more than 5 hours after start of infusion of second dose[23,24]	53% (severe 17%)[25]
oxaliplatin[26-36]	hypersensitivity reactions	usually within 30 min after start of infusion but may occur any time during infusion; rarely shortly after end of infusion	severe 3% (up to 18%)
	pharyngolaryngeal dysesthesia	shortly after end of infusion	1-2%

Drug	*Toxicity*	*Onset*	*Incidence*
PACLitaxel[37]	hypersensitivity reactions	53% within 2-3 min after start of infusion and 78% within 10 min	41% (severe 2%)
pegaspargase[53]	Hypersensitivity reactions	not defined	10% (with no prior asparaginase hypersensitivity), 32% (with prior asparaginase hypersensitivity)
PERTuzumab	infusion reactions (fever, chills, fatigue, headaches, asthenia, hypersensitivity, vomiting)	not defined	11%, (severe 2-5%)
polatuzumab vedotin[52]	Infusion reactions (fever, chills, flushing, dyspnea, hypotension, urticaria)	may be delayed (as late as 24 hours after administration)	7-33% (severe 2-7%)
sacituzumab govitecan[57]	Infusion-related reactions, including hypersensitivity reactions, dyspnea, dizziness, chills, rigors, fever, pruritus, flushing, chest discomfort, allergic rhinitis	Within 24 hours	37%, severe 2%
ritTUXimab[38-40]	infusion-related hypersensitivity (rash, urticaria, fever, chills, bronchospasm, angioedema, flushing, hypotension, rhinitis, nausea, asthenia, headache)[29,30]	< 1–2 h after start of first infusion[31]	up to 80% (severe 7%)

Drug	*Toxicity*	*Onset*	*Incidence*
siltuximab[49]	infusion reactions (back pain, chest pain/discomfort, nausea, vomiting, flushing, erythema, palpitations)	not defined	severe 5-8%
tebentafusp[60]	cytokine release syndrome (fever, chills, hypotension, hypoxia, nausea, vomiting, rash, elevated transaminases, fatigue, dizziness, shortness of breath, myalgia, arthralgia, tachycardia, headache)	Mainly the first 3 infusions. Majority of episodes start the day of infusion.	89%, severe 1%
trastuzumab (HERCEPTIN)[41-43]	infusion reactions (fever, chills)	usually during infusion	36-39%
trastuzumab deruxtecan (ENHERTU)[59]	infusion-related reactions (chills, shaking, shortness of breath, wheezing, itching, rash, hives, flushing, dizziness, fever)	within 24 hours of infusion	1-3%
trastuzumab emtansine (KADCYLA)[44]	infusion reactions (flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, tachycardia)	not defined	1%
tremelimumab[61]	Infusion-related reactions (chills, itching, rash, flushing, shortness of breath, wheezing, dizziness, fever, facial swelling or back/neck pain)	Not defined	2-3% (severe <1%)

References:

1. Berlex Canada. CAMPATH® product monograph. Pointe-Claire, Quebec; November 2005.
2. Asselin BL. The three asparaginases. Comparative pharmacology and optimal use in childhood leukemia. Adv Exp Med Biol 1999;457:621-9.
3. Bryant R. Use of a protocol to minimize hypersensitivity reactions with asparaginase administration. J Intraven Nurs 2001;24(3):169-73.
4. Graham ML. Pegaspargase: a review of clinical studies. Adv Drug Deliv Rev 2003;55(10):1293-302.
5. Lundbeck Canada Inc. TREANDA® product monograph. Montreal, Quebec; 22 August 2012.
6. Cephalon. TREANDA® prescribing information. Frazer, PA; October 2009.
7. McEvoy GK editor. AHFS 2002 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2002.
8. Alcorn BT. Bleomycin hypersensitivity: a case report. Can J Hosp Pharm 1980;33(3):92-93.
9. Seattle Genetics Inc. ADCETRIS® full prescribing information. Bothell, Washington; January 2012.
10. GMD Distribution Inc. for Seattle Genetics Inc. ADCETRIS® product monograph. Oakville, Ontario; 1 February 2013.
11. Lexi-Drugs Online® (database on the Internet). Cabazitaxel. Lexi-Comp Inc., October 2011. Available at: http://online.lexi.com. Accessed 11 October 2011.
12. ImClone LLC (distributed by Bristol-Myers Squibb Canada). ERBITUX® product monograph. Branchburg, New Jersey, USA; 25 May 2010.
13. Thomas M. Cetuximab: adverse event profile and recommendations for toxicity management. Clin J Oncol Nurs 2005;9(3):332-8.
14. Weidmann B, et al. Hypersensitivity reactions to carboplatin. Report of two patients, review of the literature, and discussion of diagnostic procedures and management. Cancer 1994;73(8):2218-22.
15. Markman M, et al. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol 1999;17(4):1141-5.
16. Schiavetti A, et al. Hypersensitivity to carboplatin in children. Med Pediatr Oncol 1999;32(3):183-5.
17. Yu DY, et al. Weekly dosing of carboplatin with vincristine increases risk of allergy in children with brain tumors. Proc Am Soc Clin Oncol 2000;19:abstract 2311.
18. Tankanow RM. Docetaxel: a taxoid for the treatment of metastatic breast cancer. Am J Health-Syst Pharm 1998;55(17):1777-91.
19. Aventis Pharma Inc. Taxotere product monograph. Saint-Laurent, Québec; 26 April 1999.
20. Hoetelmans RM, et al. Hypersensitivity reactions to etoposide. Ann Pharmacother 1996;30(4):367-71.
21. Siderov J, et al. Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. Br J Cancer 2002;86(1):12-3.
22. Hoffmann-La Roche Ltd. GAZYVA® product monograph. Mississauga, Ontario; 21 December 2015.
23. Bosch F, et al. Preliminary safety results from the phase IIIb GREEN study of obinutuzumab (GA101) alone or in combination with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia (CLL). Proc Am Soc Hematol 2014:abstract 3345.
24. Anna Sivojelezova MSc. Personal communication. Drug Information Associate; Hoffmann-La Roche Ltd Drug Information; 26 April 2016.
25. Goede V, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions (Supplementary appendix). N Engl J Med 2014;370:1101-10.
26. Wiseman LR, et al. Oxaliplatin: a review of its use in the management of metastatic colorectal cancer. Drugs Aging 1999;14(6):459-75.
27. Sanofi-Synthelabo Europe. Eloxatin: Summary of product characteristics. 1999.
28. Maindrault-Goebel F, et al. High-dose intensity oxaliplatin added to the simplified bimonthly leucovorin and 5-fluorouracil regimen as second-line therapy for metastatic colorectal cancer (FOLFOX 7). Eur J Cancer 2001;37(8):1000-5.
29. Sanofi-Synthelabo. Eloxatin: Summary of product characteristics. New York, NY, USA; 9 August 2002.
30. Lenz G, et al. Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. Anticancer Drugs 2003;14(9):731-3.
31. Meyer L, et al. Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. J Clin Oncol 2002;20(4):1146-7.
32. Brandi G, et al. Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer 2003;89(3):477-81.
33. Thomas RR, et al. Hypersensitivity and idiosyncratic reactions to oxaliplatin.[see comment]. Cancer 2003;97(9):2301-7.
34. Gowda A, et al. Hypersensitivity Reactions to oxaliplatin: incidence and management. Oncology (Huntingt) 2004;18(13):1671-5; discussion 1676.
35. Bhargava P, et al. Hypersensitivity and idiosyncratic reactions to oxaliplatin.[comment]. Cancer 2004;100(1):211-2.
36. Bonosky K, Miller R. Hypersensitivity reactions to oxaliplatin: what nurses need to know. Clin J Oncol Nurs 2005;9(3):325-30.
37. Bernstein BJ. Docetaxel as an alternative to paclitaxel after acute hypersensitivity reactions. Ann Pharmacother 2000;34(11):1332-5.
38. Hoffmann-LaRoche. Rituxan product monograph. Mississauga, Ontario; 21 June 2000.
39. McLaughlin P, et al. Rituximab in indolent lymphoma: the single-agent pivotal trial. Sem Oncol 1999;26(5 Suppl 14):79-87.
40. Onrust SV, et al. Rituximab. Drugs 1999;58(1):79-88; discussion 89-90.
41. Cobleigh MA, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. J Clin Oncol 1999;17(9):2639-48.
42. Hoffmann-LaRoche. HERCEPTIN® product monograph. Mississauga, Ontario; 26 June 2000.

43. Hoffmann-LaRoche. HERCEPTIN® product monograph - important drug warning. Mississauga, Ontario; 4 May 2000.
44. Hoffmann-LaRoche. KADCYLA® product monograph. Mississauga, Ontario; 3 July 2020.
45. Amgen Canada Inc. BLINCYTO® product monograph. Mississauga, Ontario; 28 April 2017.
46. Janssen Inc. DARZALEX® product monograph. Toronto, Ontario; 13 April 2017
47. Janssen Biotech Inc. DARZALEX® full prescribing information. Horsham, PA, USA; June 2017.
48. EMD Serono. BAVENCIO® product monograph. Mississauga, Ontario; 4 May 2018.
49. Janssen Inc. SYLVANT® product monograph. Toronto, Ontario; 6 January 2016.
50. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 15 January 2016.
51. Genentech Inc. TECENTRIQ® full prescribing information. South San Francisco, CA, USA; October 2016
52. Hoffman-La Roche Limited. POLIVY® product monograph. Mississauga, Ontario; April 27, 2021
53. Servier Canada Inc. Oncaspar® product monograph. Laval, Quebec; March 5, 2019
54. Janssen Inc. DARZALEX® SC product monograph. Toronto, Ontario; 29 July 2020.
55. Powles T, Rosenberg JE, Sonpavde GP, et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. N Engl J Med 2021;384(12):1125-1135
56.Seagen Inc. Enfortumab vedotin-ejfv: Adverse Event Management Resource (Powerpoint presentation). Bothell, Washington, USA; February 28 2022
57. Gilead Sciences Canada Inc. TRODELVY® product monograph. Mississauga, ON; August 2, 2022.
58. Sanofi-aventis Canada Inc. SARCLISA ® product monograph. Laval, QC; October 12, 2022
59. AstraZeneca Canada Inc. ENHERTU® product monograph. Mississauga, ON; January 6, 2023
60. Immunocore Ireland Limited (distributed by Medison Pharma Canada Inc.) KIMMTRAK® product monograph. Toronto, Ontario; 7 June 2022
61. AstraZeneca Canada Inc.IMJUDO ® product monograph. Mississauga, ON; 26 Jan 2024
62. Kyowa Kirin, Inc. (distributed by *Innomar Strategies*). POTELIGEO® product monograph. Oakville, ON; June 20, 2022
63. AbbVie Corporation. EPKINLY® product monograph. St-Laurent, Quebec; October 13, 2023
64. Genmab US Inc and AbbVie Inc. EPKINLY® full prescribing information. Plainsboro, New Jersey, USA; May 2023
65. Bristol-Myers Squibb Canada. OPDUALAG® product monograph. Montreal, Quebec; 13 September 2023
66. Bristol-Myers Squibb Canada_9Sep2024_nivolumab-relatlimab_timing of infusion-related reactions
67. Hoffmann-La Roche Limited. COLUMVI® product monograph. Mississauga, Ontario; 13 Dec 2024