Formatted for IMJ: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1445-5994/homepage/ForAuthors.html

Version 7 FINAL APPROVED 24th April 2017

Management of patients with previously untreated chronic lymphocytic leukaemia with obinutuzumab and chlorambucil

Constantine Tam[1,2], Bryone Kuss[3], Stephen Opat[4], Joy Boulos[5], Paula Marlton[6,7]

Corresponding author: Constantine Tam
Peter MacCallum Cancer Centre
St Andrew's Place, East Melbourne
Victoria 3002
AUSTRALIA
Ph + 613 9656 1700
Fax + 613 9656 1408
constantine.tam@petermac.org

Acknowledgements: This paper was funded by an unrestricted educational grant from Roche Products Pty Ltd. Medical writing services provided by Dr Belinda Butcher CMPP from WriteSource Medical were funded by Roche Products Ltd in accordance with Good Publication Practice (GPP3) guidelines (http://ismpp.org/gpp3).

[1] St Vincent's Hospital, Melbourne, VIC, Australia

[2] Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

[3] Flinders University and Flinders Medical Centre, Bedford Park, SA, Australia

[4] Monash Medical Centre and Monash University, Clayton, VIC, Australia

[5] Roche Products Limited, Dee Why, NSW, Australia

[6] Princess Alexandra Hospital, Woolloongabba, QLD, Australia

[7] University of Queensland School of Medicine, QLD, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.13493

Conflict of Interest: CT, PM and SO participate in Advisory Boards for Roche and have been the recipients of registration grants to attend the American Society of Hematology meeting from Roche. BK participates in Advisory Boards for Roche and has been the recipient of registration to attend the Lugano CML meeting from Roche. Joy Boulos is an employee of Roche.

Word Count (abstract): 94 (of 250 max)

Word Count (main text): 2,672 (of 3,000 max)

ABSTRACT [250 words MAX]

Patients with chronic lymphocytic leukaemia (CLL) are generally older, with many considered 'unfit' for fludarabine-cyclophosphamide-rituximab therapy. In these patients, the combination of obinutuzumab-chlorambucil may be an appropriate therapeutic choice. Obinutuzumab-chlorambucil has been demonstrated to improve overall survival rates compared to chlorambucil alone, and to improve progression free survival and overall response rates compared to rituximab-chlorambucil. This combination can lead to certain toxicities which need to be addressed through appropriate patient selection, pre-medication and management. In this paper we discuss evidence based and author recommended practical management of first line CLL patients receiving obinutuzumab-chlorambucil.

INTRODUCTION [Limit 3000]

Chronic lymphocytic leukaemia (CLL) is the commonest form of adult leukaemia and primarily affects an older population with a median age at diagnosis of 72 years [1]. The majority of patients are asymptomatic at presentation only requiring treatment with the development of symptoms [1]. Initial treatment of chronic lymphocytic leukaemia (CLL) typically combines a monoclonal antibody with a chemotherapy backbone. The most efficacious combination in a younger cohort was established in the German CLL 8 trial (NCT00281918) where the addition of rituximab to fludarabine and cyclophosphamide (FCR) improved overall survival compared to FC alone and provided outcomes superior to any prior CLL therapy with a subset of patients achieving long term relapse free remissions [2, 3]. However, the FCR regimen is only suitable in younger fitter patients able to tolerate this regimen.

For typical older and less fit patients, alternative options include chlorambucil or bendamustine in combination with a CD20 monoclonal antibody such as rituximab, ofatumumab or obinutuzumab [4].

Obinutuzumab is a glycoengineered humanized type 2 anti CD20 monoclonal antibody with superior antibody-mediated cellular cytotoxicity and direct cell killing in comparison to rituximab [5]. The CLL11 clinical trial (NCT01010061) showed that combining either obinutuzumab or rituximab with chlorambucil was associated with improved overall response rates (ORR) and progression free survival (PFS) compared

to chlorambucil monotherapy [5]. Importantly, the combination of obinutuzumab and chlorambucil also improved overall survival (OS) compared to chlorambucil alone (Table 1) [5].

CLL11 Trial

The CLL11 trial (NCT01010061), conducted by the German CLL Study Group, was an international open-label, phase III study that randomised patients with treatment naïve CD20+ CLL who had a cumulative illness rating scale (CIRS) score of more than 6 or a creatinine clearance of 30 to 69 mL/min to receive chlorambucil monotherapy [0.5 mg/kg day 1 and 15 of each cycle (n=116)], or rituximab-chlorambucil [375 mg/m^2 rituximab day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 to 6 plus chlorambucil as per the monotherapy arm (n=321) or obinutuzumab-chlorambucil [1000 mg obinutuzumab on days 1, 8, 15 of cycle 1 and on day 1 of cycles 2 through 6, and chlorambucil as per the monotherapy arm (n=336)]. The chlorambucil dose was chosen on the basis of the median dose used in 'unfit' patients in the earlier German CLL5 trial (NCT00262795), which demonstrated non-inferiority compared to fludarabine in this population, and superior tolerability [6]. The primary endpoint was investigator-assessed PFS [5]. Key results of the trial are shown in .

Obinutuzumab has a wide therapeutic index [7] and is administered as a flat dose of 1000 mg. At this dose, obinutuzumab fully saturates the CD20 target regardless of body surface area or weight. Pharmacokinetic studies have demonstrated that

administering three doses in cycle one on days 1, 8 and 15, rapidly achieves full target saturation and a sustained therapeutic level much more efficiently than traditional once per cycle dosing [8-10]. The first dose is split over two days to attenuate the risk of an infusion related reaction (see below).

Important clinical endpoints in assessing treatments for CLL include OS, PFS and quality of life (QoL) [11]. The time to next treatment (TTNT) is also a relevant endpoint, since it represents the time patients are off therapy, and may have the freedom to work or travel. The longer the TTNT, the greater the positive impact on patients QoL, as well as the greater chance a patient may have to access novel agents that will likely become available in the future. In the CLL11 study, the TTNT on the obinutuzumab-chlorambucil arm was 51 months from the first treatment; 15 months longer than the rituximab-chlorambucil arm, and more than three times longer than that achieved with chlorambucil monotherapy [12].

Another emerging efficacy parameter in assessing CLL treatments is minimal residual disease status which was shown in the CLL8 trial to be perhaps the single best posttreatment predictor of long-term disease control [13]. In the CLL11 study, chlorambucil-obinutuzumab was able to achieve MRD negativity in the bone marrow in 19.5% of patients tested compared to 2.6% of patients receiving chlorambucil-rituximab [5].

This paper provides practical guidance on the management of patients with CLL who are being treated with obinutuzumab. These recommendations were

developed based upon available published clinical evidence, and the authors' experience with this agent.

PATIENT SELECTION

The majority of CLL patients are 70 years or more at diagnosis and usually several years older by the time they commence treatment [14]. Almost 90% of these patients are reported to have comorbidities, with just under half having at least one major comorbidity [15]. This impacts the patient's 'fitness' and ability to tolerate more intensive regimens such as FCR. [14]. Therefore, assessing patient 'fitness' is important; however, there is no consensus on the best method for doing so [14]. In the CLL11 trial, the Cumulative Illness Rating Scale (CIRS) was used [16, 17]. This scale assesses the severity of comorbidities in older patients, with lower scores reflecting fewer or less severe comorbidities.

Organ function, particularly renal function, is also an important factor when considering suitable therapy for patients with CLL [14]. Just over one third of patients over 70 years have glomerular filtration rates (GFR) of less than 60 mL/min/1.73 m^2, indicating impaired renal function [16]. Obinutuzumab is not recommended for patients with severe renal impairment (CrCl < 30 mL/min).

Patients are considered 'fit' for standard FCR therapy if they have a CIRS scores of 6 or under, have a creatinine clearance of more than 70 mL/min, and have no major organ comorbidity [2, 4]. 'Unfit' patients, with a CIRS score over 6, or a creatinine clearance between 30 and 69 mL/min should be considered for treatment with

obinutuzumab-chlorambucil [5]. The Australian Pharmaceutic Benefits Schedule restriction reflects these criteria when reimbursing obinutuzumab.

Clinical practice recommendations – assessing fitness of patients

1. Assess patients for 'fitness' prior to commencing treatment.
2. Assessments should include a review of comorbidities, and renal function
3. Patients 'fit' for conventional therapy (CIRS ≤ 6; CrCl ≥ 70 mL/min) and with appropriate disease parameters should be treated with fludarabine-cyclophosphamide-rituximab (FCR)[4, 18]. Patients suitability for FCR may also include a consideration of molecular and cytogenetic parameters, as well as the availability of novel therapies.
4. Patients 'unfit' for conventional therapy (CIRS > 6; CrCl 30 to 69 mL/min) should be considered for treatment with chlorambucil and obinutuzumab[4, 5]

INFUSTION RELATED REACTIONS

Monoclonal antibodies including obinutuzumab are commonly associated with infusion related reactions (IRRs) frequently characterized by bronchospasm, dyspnoea, hypotension, fevers, rigors, and tachycardia, among other less common manifestations [19]. Although the exact aetiology of infusion reactions is uncertain, there is an association with release of interleukin 1, interleukin 6, interleukin 8, interleukin 10 tumour necrosis factor alfa, and interferon gamma. Patients with an absolute lymphocyte count of $\geq 50 \times 10^9$ /L are at the higher risk of reactions[20]. In the CLL11 study, infusion related reactions occurred in 66% of patients receiving obinutuzumab-chlorambucil, and 20% had at least moderate (grade 3 or higher) reactions (compared to 38% and 4%, respectively in the rituximab-chlorambucil arm)

[5]. Most infusion related reactions occurred with the first dose of obinutuzumab and most occurred within the first 2 days of treatment, with no Grade 3 or 4 infusion related reactions occurring beyond that time point. [5]. The severity of IRRs can be unpredictable and thus it is appropriate to consider admitting patients for the first cycle of their treatment. To minimise the risk of severe infusion related reactions, the first infusion should be divided over two days, with 100 mg administered on day one, and 900 mg administered on day two[7]. In addition, it is important to ensure patients are well hydrated, have a second intravenous (IV) cannula inserted and resuscitation equipment is readily available. To mitigate the risk of hypotension, antihypertensive therapies should be withheld 12 hours prior to the commencement of the infusion, and it should not be recommenced until at least 1 hour after the infusion has been completed[7]. Patients should be pre-medicated with a potent corticosteroid (methylprednisolone 80 mg IV or dexamethasone 20 mg IV; hydrocortisone is not effective for prevention of infusion related reaction [7]), an oral or IV antihistamine, and paracetamol [5, 7]. Steroids should be completed at least one hour prior to the obinutuzumab infusion (Table 2).

All patients should be alerted to the possibility of an infusion related reaction. Patients should be reassured that in most cases, obinutuzumab can be continued; only 7% of patients on the obinutuzumab-chlorambucil combination in the CLL11 trial discontinued due to this adverse event [5] and no fatal reactions were observed [5].

While rare, grade 4 infusion reactions may occur, and may necessitate transfer to intensive care or coronary care. Symptoms may include severe hypotension that is not responsive to intravenous fluids, hypoxaemia requiring oxygen, and in some cases loss of consciousness. For these patients, retreatment with obinutuzumab is not advised.

If a patient experiences a mild or moderate infusion related reaction, the infusion should be adjusted according to the current guidelines (Table 3). Close monitoring of the patient is required since it is difficult to determine how the reaction will evolve. Patients experiencing severe (Grade 4) reactions should have the infusion stopped permanently. Rechallenge may be hazardous and is not recommended. Patients experiencing moderate reactions should have their infusion ceased, be reclined, and have IV fluids administered through the second IV cannula. Supplemental oxygen may be appropriate. Treat fevers, chills and rigor reaction as required [7]. Further corticosteroids per institutional guidelines, and further antihistamines (oral or IV) should be administered. To assist in a rapid response to infusion related reactions, all orders for additional medications should be pre-charted on admission.

For patients experiencing mild to moderate (grade 1 to 3) reactions, once stabilised, the infusion can be reinstated at half the rate at which the infusion reaction occurred.

Clinical practice recommendations – infusion related reactions

1. Consider admitting patients for their first cycle of treatment (particularly if

ALC >50 x 10^9/L).

2. Insert a second intravenous cannula and have resuscitation equipment close at hand.
3. Cease antihypertensive drugs 12 hours prior to the infusion, and do not recommence until at least 1 hour after infusion has been completed [7]
4. Pre-medicate patients with a potent corticosteroid (methylprednisolone 80 mg IV or dexamethasone 20 mg IV) [5, 7], an antihistamine, and paracetamol. Steroids should be administered at least 1 hour before the obinutuzumab infusion.
5. Split the first dose of obinutuzumab over two days, 100 mg administered on day 1 and 900 mg administered on day 2 [7]. Repeat steroid premedication is required for day 2.
6. Pre-chart all medications required in the case of an infusion related reaction.

NEUTROPENIA

An increase in neutropenia was observed in the CLL11 study in the obinutuzumab-chlorambucil arm, with 35% of patients experiencing grade 3 or 4 neutropenia [5]. , Severe and life-threatening neutropenia, including febrile neutropenia and late-onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting >28 days after treatment has been ceased) have been reported. Serious bacterial, fungal, and new or reactivated viral infections, including fatal infections [7] have also been reported. In elderly patients (aged 80 years or over), neutropenia is more common occurring in up to 50% of patients [5].

Patients should be monitored weekly for neutropenia in the first cycle of treatment, and then at least just prior to each further cycle. If grade 3 or 4 neutropenia is observed (<1.0 x 10^9/L), obinutuzumab-chlorambucil should be withheld until the

neutropenia resolves to less than grade 2 (≥1.0 x 10^9/L). Granulocyte-colony stimulating factor (GCSF) may be used as required. If there are repeated dose delays, reduce the chlorambucil dose by 25% increments, and cease if chlorambucil dose is already reduced to 50% [5].

Late onset neutropenia was first recognized with rituximab therapy and has also been reported with obinutuzumab. It usually responds well to G-CSF and is self-limiting however, prolonged GCSF may be required in some patients [7].

Despite relatively high rates of neutropenia with obinutuzumab-chlorambucil, this did not translate into an increased rate of infection in the CLL11 trial, with rates of grade 3 or 4 neutropenia between 11 and 14% being reported [5]. In patients where repeated doses of corticosteroids cannot be avoided, prophylaxis against *Pneumotcystis jirovecii* pneumonia with Bactrim (trimethoprim and sulfamethoxazole) or equivalent should be instituted [5]. Anti-viral prophylaxis should be considered according to institutional guidelines. Patients should be encouraged to be appropriately vaccinated, including with the pneumococcal vaccination. Vaccination with live viruses during treatment is contraindicated. [7].

Reactivation of hepatitis B is a serious recognised complication of therapy with CD20 monoclonal antibodies. All patients should be screened for hepatitis B and for those at risk should be referred for suppressive therapy with lamivudine or entecavir and hepatitis B viral DNA titres monitored. Infection with the John Cunningham (JC) virus has also been observed in patients treated with obinutuzumab, thus any patient with

neurological symptoms should be investigated, and where required, appropriately treated [7].

Clinical practice recommendations – neutropenia

1. Neutropenia occurs relatively frequently, but does not appear to be associated with increased infections
2. Monitor patients weekly for neutropenia in the first cycle, and then prior to each subsequent cycle and as indicated.
3. Prophylaxis with antibacterial and antiviral therapy should be considered on a case-by-case basis and according to institutional guidelines.
4. Reactivation of hepatitis B may occur. Testing and appropriate suppressive therapy is required.
5. Consider JC virus infection in patients with neurological symptoms

TUMOUR LYSIS SYNDROME

Patients at highest risk of tumour lysis syndrome (TLS) are those with bulky disease, or those with a very high circulating tumour burden, for example those with white cell counts of more than 50 x 10^9 /L, [7, 21]. TLS was observed in 14 patients (4%) treated with obinutuzumab-chlorambucil in the CLL11 study, compared to none in the rituximab-chlorambucil arm and < 1% in the chlorambucil monotherapy arm. Of these in the obinutuzumab-chlorambucil arm, 6 patients (2%) had grade 3 or 4 events, 4 were hospitalised, and 2 required treatment modification [5]. TLS may occur in conjunction with an infusion related reaction.

Prophylactic treatment includes adequate pre-hydration and a uricostatic agent (e.g. allopurinol or rasburicase). Patients at high risk of TLS should be admitted for

their first infusion, (see also **Infusion Related Reactions**). During the admission, TLS biochemical markers should be monitored pre-dose, 8 hours post dose, and 24 hours post dose prior to the second part of the first split dose. (Day 2, 900 mg).

Clinical practice recommendations – tumour lysis syndrome

1. Assess the risk of TLS and admit for the first cycle if high risk.
2. Pre- hydration and prophylactic treatment with a uricostatic agent should be administered.
3. Monitor for biochemical parameters of TLS (potassium, phosphate, uric acid and renal function) during first cycle admission.

THROMBOCYTOPENIA

Severe thrombocytopenia was observed following chlorambucil-obinutuzumab in the CLL11 trial, including fatal haemorrhagic events (although a clear relationship between thrombocytopenia and haemorrhagic events was not established) [5]. Thrombocytopenia of any grade (< 75 x 10^9/L platelets) affected14% of patients receiving administered obinutuzumab-chlorambucil, and 10% of patients experienced grade 3 or higher events (< 50 x 10^9/L platelets) [5]. Severe thrombocytopenia is largely restricted to the first cycle, and resolves spontaneously. Platelet counts should be monitored during the first cycle, particularly in patients with pre-existing thrombocytopenia. In patients that develop severe thrombocytopenia, obinutuzumab and chlorambucil should be withheld until the platelet count has recovered and platelet transfusions provided as required. Consider withholding anti-

platelet agents and anticoagulants prior to administration of the first cycle where feasible.

Clinical practice recommendations - thrombocytopenia

1. Thrombocytopenia may worsen with the first cycle infusion. Consider withholding anti-platelet agents and anticoagulants prior to administration of the first cycle.
2. Monitor the platelet count weekly during the first cycle.
3. Treat patients with platelet transfusions as required.

KEY POINTS

1. Chlorambucil and obinutuzumab is a highly active regimen in patients not fit for FCR.
2. The major risks are infusion related reactions, tumour lysis syndrome, neutropenia, and thrombocytopenia.
3. With appropriate care, the majority of patients are able to successfully complete this therapy.

REFERENCES

1. Kipps, T.J., et al., *Chronic lymphocytic leukaemia.* Nat Rev Dis Primers, 2017. **3**: p. 16096.

2. Hallek, M., et al., *Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial.* Lancet, 2010. **376**(9747): p. 1164-74.

3. Tam, C.S., et al., *Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia.* Blood, 2008. **112**(4): p. 975-80.

4. National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphotic Leukemia / Small Lymphocytic Leukaemia*. 2017.

5. Goede, V., et al., *Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.* N Engl J Med, 2014. **370**(12): p. 1101-10.

6. Eichhorst, B.F., et al., *First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia.* Blood, 2009. **114**(16): p. 3382-91.

7. Roche Products Pty Limited, *Gazyva Approved Product Information*. 2015.

8. Cartron, G., et al., *Rationale for optimal obinutuzumab/GA101 dosing regimen in B-cell non-Hodgkin lymphoma.* Haematologica, 2016. **101**(2): p. 226-34.

9. Byrd, J.C., et al., *Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia.* Blood, 2016. **127**(1): p. 79-86.

10. Sehn, L.H., et al., *Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-*

Hodgkin Lymphoma: Final Analysis of the GAUSS Study. J Clin Oncol, 2015. **33**(30): p. 3467-74.

11. Beauchemin, C., et al., *Relationship between progression-free survival and overall survival in chronic lymphocytic leukemia: a literature-based analysis.* Curr Oncol, 2015. **22**(3): p. e148-56.

12. Goede, V., et al., *Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study.* Leukemia, 2015. **29**(7): p. 1602-4.

13. Thompson, P.A. and W.G. Wierda, *Eliminating minimal residual disease as a therapeutic end point: working toward cure for patients with CLL.* Blood, 2016. **127**(3): p. 279-86.

14. Shanafelt, T., *Treatment of older patients with chronic lymphocytic leukemia: key questions and current answers.* Hematology Am Soc Hematol Educ Program, 2013. **2013**: p. 158-67.

15. Thurmes, P., et al., *Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia.* Leuk Lymphoma, 2008. **49**(1): p. 49-56.

16. Miller, M.D., et al., *Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale.* Psychiatry Res, 1992. **41**(3): p. 237-48.

17. Salvi, F., et al., *A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients.* J Am Geriatr Soc, 2008. **56**(10): p. 1926-31.

18. Molica, S., *Progress in the treatment of chronic lymphocytic leukemia: results of the German CLL8 trial.* Expert Rev Anticancer Ther, 2011. **11**(9): p. 1333-40.

19. Doessegger, L. and M.L. Banholzer, *Clinical development methodology for infusion-related reactions with monoclonal antibodies.* Clin Transl Immunology, 2015. **4**(7): p. e39.

20. Freeman, C.L., et al., *Cytokine release in patients with CLL treated with obinutuzumab and possible relationship with infusion-related reactions.* Blood, 2015. **126**(24): p. 2646-9.

21. Howard, S.C., et al., *Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review.* Ann Hematol, 2016. **95**(4): p. 563-73.

TABLES

Table 1: Overall response rate, progression free survival, and overall survival observed in CLL11 study of chlorambucil vs rituximab-chlorambucil vs obinutuzumab-chlorambucil[5].

	Chlorambucil	Rituximab-chlorambucil	Obinutuzumab-chlorambucil
Overall response rate (%)	31.4%	65.7%	77.3%
Progression free survival, months, median HR compared to chlorambucil (95% confidence interval)	11.1	16.3 0.44 (0.34, 0.57) p<0.001	26.7 0.18 (0.13, 0.24) p<0.001
Overall survival, HR compared to chlorambucil (95% confidence interval)		0.66 (0.39, 1.11) p=0.11	0.41 (0.23, 0.74) p=0.002

Table 2: Management of potential infusion related reactions

	Cycle 1: Days 1 and 2	Subsequent infusions		
	All patients	Patients without any IRR symptoms	Patients with Grades 1–2 (mild to moderate) IRR with the previous infusion	Patients with a Grade 3 (severe) IRR with the previous infusion OR with a lymphocyte count >25 x 10^9/L prior to next treatment
COMPLETE AT LEAST 60 MINUTES PRIOR TO INFUSION **Intravenous corticosteroid** (20 mg dexamethasone or 80 mg methylprednisolone)	X			
30 MINUTES PRIOR TO INFUSION **Antihistamine medicine** (e.g. H1 histamine receptor blockade)	X		X	X
30 MINUTES PRIOR TO INFUSION **Oral analgesic /anti pyretic** (e.g. 1000 mg paracetamol)	X	X	X	X

Table 3: Adjusting the obinutuzumab dose if an infusion related reaction occurs.

If the patient experiences an IRR during infusion, adjust the infusion as outlined below [7]	
Grade 4 (life threatening)	• Stop infusion and permanently discontinue therapy
Grade 3 (severe)	• Temporarily interrupt infusion and treat symptoms as appropriate • Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) • If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. The Day 1 infusion rate may be increased back to 25 mg/h after 60 minutes, but not increased further • Stop infusion and permanently discontinue therapy if patients experience a second occurrence of a Grade 3 IRR
Grade 1-2 (mild to moderate)	• Reduce infusion rate and treat symptoms as appropriate • Upon resolution of symptoms, continue infusion • If patient does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. The Day 1 infusion rate may be increased back to 25 mg/h after 60 minutes, but not increased further