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*Review*

# Systematic Review on Infusion Reactions to and Infusion Rate of Monoclonal Antibodies Used in Cancer Treatment

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**Abstract.** *Background: Patients with cancer who are treated with monoclonal antibodies are at risk for developing infusion reactions. However, for some monoclonal antibodies, the incidence of infusion reactions is low or can be lowered by the use of adequate premedication schedules. It is often feasible to increase the infusion rate/lower the post-administration observation time. This review gives an overview of infusion reactions and the possibility of accelerating infusion rates. Materials and Methods: Data on infusion reactions and infusion rates for all monoclonal antibodies that are licensed in the European Union for treatment of solid tumors or hematological malignancies, found by a literature search, were included in this review. Results: For 11 out of the 21 monoclonal antibodies data exceeding the registration text were found and described. Faster infusion schedules are possible for bevacizumab, ipilimumab, nivolumab, panitimumab, and rituximab. Conclusion: We propose optimal infusion schedules for each drug.*

Monoclonal antibodies have gained an important place in systemic anticancer therapy over the past decade. Moreover, combinations of monoclonal antibodies have now reached first-line treatment options for some tumor types. One of the complications of therapy with monoclonal antibodies is the occurrence of infusion-related reactions. Mild to moderate infusion reactions are associated with chills, fever, mild hypotension, dyspnea and rash. Severe reactions are less common and are, amongst other symptoms, associated with severe hypotension, anaphylaxis and cardiac dysfunction (1). An infusion reaction usually starts within 30 to 120 min after the start of administration of the monoclonal antibody, but delayed infusion reactions at up to 24 hours (and even a week for trastuzumab) after infusion have been observed (2, 3).

Both conventional cytotoxic drugs and monoclonal antibodies are known to induce infusion reactions. Although the appearance of the infusion reactions to both types of drugs is very similar, the pathophysiology is not. Infusion reactions to monoclonal antibodies are mostly so-called cytokine-release reactions. By binding of the monoclonal antibody to the target cell, cytokines are released into the circulation and cause symptoms (4). Conventional cytotoxic drugs can induce immunoglobulin E (IgE)-mediated allergic reactions, inducing the release of vasoactive mediators from mast cells and basophil cells. In this respect, rituximab, trastuzumab and cetuximab are exceptions since they are able to induce both types of infusion reactions. In order to clarify the difference between both types of reactions, the National Cancer Institute Common Toxicity Criteria (NCI-CTC) uses separate criteria and grades of severity as is shown in Table I (5). Most articles use the NCI-CTC criteria but different definitions of infusion reactions are used in literature, which sometimes makes it difficult to compare information.

The likelihood of a patient having an infusion reaction is not known prior to treatment. It differs per person, disease and type of monoclonal antibody used (3). Avelumab, rituximab and daratumumab have a high rate of infusion reactions. More than half of the patients develop some type of reaction. Trastuzumab and cetuximab are also known for a relatively high rate of infusion reactions [40% and up to



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Table I. *Common Terminology Criteria for Adverse Events (CTCAE) for infusion-related and allergic reactions (5).*

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Infusion-related reaction* | Mild transient reaction; infusion interruption not indicated; intervention not indicated | Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (*e.g.* antihistamines, NSAIDS, narcotics, *i.v.* fluids); prophylactic medications indicated ≤24 h | Prolonged (*e.g.* not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae | Life threatening consequences; urgent intervention indicated | Death |
| Allergic reaction** | Systemic intervention not indicated | Oral intervention indicated | Bronchospasm; hospitalization indicated for clinical sequelae; *i.v.* intervention indicated | Life-threatening consequences; urgent intervention indicated | Death |

NSAIDS: Non-steroidal anti-inflammatory drugs. *A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances; **A disorder characterized by an adverse local or general response from exposure to an allergen.

22% depending on the investigational area, respectively (6)]. No relationship has been found between the origin of the monoclonal antibody (human, chimeric or mouse) and the incidence of infusion reactions (1, 3). The number of administrations and combination therapy with another drug influences the probability of a reaction (3). Most infusion reactions occur during the first or second infusion. However, 10-30% of infusion reactions happen during subsequent administrations (1). Finally, a higher rate of infusion is associated with a higher likelihood of a reaction (3).

Several options for reducing the risk of infusion-related reactions are available. Firstly, for most monoclonal antibodies, pretreatment with antihistamines, acetaminophen and corticosteroids is mandatory. Secondly, using an incremental escalation of the infusion rate in the first and sometimes second cycle of treatment can prevent infusion reactions. Thirdly, for some monoclonal antibodies, a reduced dose approach in the first cycle is included in the recommended treatment protocols.

Depending on the severity, there are different ways to manage infusion reactions to monoclonal antibodies. Mild to moderate infusion reactions (grade 1 or 2) can be managed by slowing down the infusion rate or by interrupting the infusion until the symptoms disappear, usually this happens within half an hour (6). Afterwards, the infusion can be restarted with half of the infusion rate (4). When the reaction is severe (grade 3 or 4), the infusion should be stopped and adequate medical treatment is needed (6). Restarting administration of the monoclonal antibody after a severe reaction is not recommended in most cases (1). However, successful desensitization schemes have been published as case reports or case series for rituximab, trastuzumab, bevacizumab and cetuximab (7).

All monoclonal antibodies have restrictions on their rate of infusion, mostly determined during registration trials. However, it is known that in some cases, faster infusion is safely possible. This review gives an overview of infusion reactions to monoclonal antibodies used for cancer therapy and the relationship between the rate of infusion and occurrence of these reactions. Knowledge about the maximum tolerated infusion rate and the different ways of reducing infusion reactions while finding the perfect infusion rate will help to make administration of monoclonal antibodies more patient-friendly. Faster infusion of monoclonal antibodies when possible will mean less time in the hospital for the patient and also reduce hospital costs at the same time.

## Materials and Methods

All monoclonal antibodies that were licensed in Europe for one or more indications in the field of oncology (including solid tumors as well as hematological malignancies) until January 1st 2019 were included in the review. Monoclonal antibody–drug conjugates such as brentuximab–vedotin and trastuzumab–emtansin were excluded, since in these cases possible infusion or allergic reactions might originate from either the monoclonal antibody or the cytotoxic part of the drug, and it is impossible to make a distinction between the two.

For each monoclonal antibody, the summary of product characteristics (SmPC) was screened for data on infusion reactions, infusion rate, observation time and supportive measures for reducing the risk of an infusion reaction. When the SmPC had limited data, the phase III trials were also included and screened in the analysis. Furthermore, a literature search using PubMed was performed for each monoclonal antibody including the key words "infusion reaction", "infusion rate" and "infusion time". Articles that were written in English were included in the analysis.

## Results

Twenty-one monoclonal antibodies were identified and included in this review. For 10 of these, no additional information on infusion reactions or infusion rates other than those described by the manufacturer has been published. For the other 11, data exceeding the SmPC were found, either as part of post -marketing surveillance studies, or as independent trials investigating accelerated infusion rates. All of the data are summarized in Table II. The monoclonal antibodies for which post-registration information on infusion reactions was found are outlined in alphabetical order below.

*Avelumab*. The infusion time for avelumab, a fully human IgG1 monoclonal antibody, is 1 hour, unless a grade 1 or 2 infusion reaction occurs (after a grade 3 or 4 reaction, the infusion is stopped). After a grade 1 infusion reaction, the infusion rate should be reduced to 50%. After a grade 2 reaction, the infusion should be temporarily stopped until the severity of the reaction is grade 0 or 1, whereupon the infusion rate should also be resumed at 50%. According to the SmPC, premedication with an antihistaminic and acetaminophen is recommended at least during the first four infusions of avelumab. According to the SmPC, 98.6% of patients have an infusion reaction during one of the first four infusions; 2.7% of these reactions were classified as grade ≥3. After the first four infusions, 1.4% of patients have an infusion reaction, all classified as grade 1 or 2 (8). In the phase III study of Barlesi *et al*., a much lower rate of infusion reaction of 27% was noted, and it was shown that 99% of those happened during the first three infusions (9). The SmPC mentions the fact that infusion reactions can occur during but also after cessation of the infusion. However, it is not stated how long a patient should be observed after treatment.

*Bevacizumab*. By binding to vascular endothelial growth factor, bevacizumab inhibits vascularization of the tumor. It is registered for multiple kinds of cancer, always in combination with other anticancer agents. According to the registration documentation, the first infusion should, independently of the dose, be given intravenously in 90 min. When tolerated, the next infusion can be given in 60 min and all following cycles in 30 min. No systemic premedication is advised. The SmPC classifies the frequency of infusion reactions as 'often' (up to 5%) (10). Reidy *et al*. compared the 90-, 60- and 30-min protocols with an infusion duration of bevacizumab of 30 and 10 min. Retrospectively, more than 8,494 doses of 5 mg/kg bevacizumab were analyzed, given to 765 patients. No infusion reactions occurred in the group that was treated according to the registration protocol (90-, 60- and 30-min infusions; 202 patients), nor in the group that was treated with a standard infusion time of 30 min. In the group of 370 patients that received bevacizumab with the infusion rate of 0.5 mg/kg/min, six patients had some symptoms associated with infusion reactions but all were graded as not clinically relevant. They concluded that an infusion rate of 0.5 mg/kg/min is safe (11).

After Reidy *et al*., Mir *et al*. investigated a faster infusion rate of bevacizumab (7.5 mg/kg) in 10 min compared to 90-60-30 min in 91 patients with non-small cell lung cancer. They stated that 7.5 mg/kg bevacizumab can be safely given in 10 min (12). Gil *et al*. investigated an infusion rate of 0.5 mg/kg/min in 73 patients and saw only one mild infusion-related hypersensitive reaction which did not require any treatment with medication (13). Mahfoud *et al*. compared 5 and 7.5 mg/kg bevacizumab infusions in 10 min *versus* the SmPC-stated regimen in patients with metastatic colorectal cancer. They saw only two grade 2 infusion reactions in the 10-min group (a total of 527 doses given). Since these symptoms were easily treated and comparable to numbers they found in literature, the authors concluded that bevacizumab could be safely infused in 10 min in this group of patients (14). Shah *et al*. stated that besides no hypersensitive reactions, there was also no increase in proteinuria and hypertension seen when a 0.5 mg/kg/min bevacizumab infusion was given (15). Yanmaz *et al*. (16) also showed that infusion in 30 min was safe. They also did not see any infusion reactions in patients treated with 10 mg/kg (four patients) and 15 mg/kg (one patient).

Altogether, there is enough clinical experience with safe administration of bevacizumab in 30 or even 10 min, in contrast to the registration leaflet which indicates 90-, 60- and 30-min infusions.

*Cetuximab*. Cetuximab is registered for colorectal carcinoma in patients with overexpression of epidermal growth factor receptor (EGFR) and 'wild type' *RAS* gene, as well as in squamous cell carcinoma in the head and neck. Cetuximab binds to EGFR and inhibits the signal transduction of this pathway. The SmPC recommends the first dose be infused at 400 mg/m$^2$ in 120 min, with a maximum infusion rate of 5 mg/min. All subsequent infusions of 250 mg/m$^2$ can be infused in 60 min (maximum of 10 mg/min) (17). Infusion-related reactions of grade 1 or 2 happen 'very often' (≥1/10; 15-21%). Slowing down the infusion rate is then advised. Infusion-related reactions with grade 3 or 4 happen 'often' (≥1/100, <1/10; 2-5%) during or after the infusion of cetuximab, despite the use of premedication with a corticosteroid and an antihistaminic. The vast majority of reactions (>90%) occur during the first cycle, but since later reactions have been observed, an observation period of 1 h after infusion is recommended (18). In the SmPC, no distinction is made between infusion-related reactions due to allergic, anaphylactic mechanisms and infusion reaction resulting from cytokine release syndrome (CRS). The time

Table II. *Overview of all data and suggested infusion rates for monoclonal antibodies in clinical use.*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| Atezolizumab | First dose (1,200 mg) in 60 min, subsequent doses in 30 min. | Seen 'often' (≥1/100, <1/10) | Can be considered | Not mentioned | 67 |
| Avelumab | All dose (10 mg/kg) in 60 min | 98.6% During the first four infusions (very often ≥1/10); 2.7% of these were classified as grade ≥3. 1.4% After the first four infusions, all were classified as grade 1 or 2. | Antihistamine and acetaminophen at least during the first four infusions. | Not specified but recommended | 8 |
| | 10 mg/kg in 60 min | 15% Grade 1-2, 1% grade 3, <1% grade 4, 99% during the first three infusions | 25-50 mg Diphenhydramine *p.o.* and 500-600 mg acetaminophen *i.v.* | Not mentioned | 9 |
| Bevacizumab | **Suggested infusion rate: 5-7.5 mg/kg in 10 min, 10-15 mg/kg in 20 min** | | | | |
| | First dose (5-15 mg/kg) during 90 min, second dose during 60 min, all subsequent doses in 30 min. | Often (≥1/100, <1/10), up to 5%. | Not necessary | Not specified | 10 |
| | All doses of 5 mg/kg in 0.5 mg/kg/min | 1.6% (All classified as nonserious) | Mentioned only when the patient had a reaction on previous bevacizumab admissions | Not mentioned | 11 |
| | All doses of 7.5 mg/kg in 0.75 mg/kg/min | No statistical differences in toxicities between 0.75 mg/kg/min and the conventional dosing (90-60-30-min regime) | Antihistamine | Not mentioned | 12 |
| | All doses of 5 mg/kg and 7.5 mg/kg in 10 min in metastatic colorectal cancer | 2 Grade 2 infusion reactions in 527 doses | Not mentioned | Not mentioned | 14 |
| | 0.5 mg/kg/min | Shorter bevacizumab infusions (0.5 mg/kg/min) do not increase the risk of proteinuria and hypertension | Not mentioned | Not mentioned | 15 |
| | 5 mg/kg, 7.5 mg/kg, 10 mg/kg or 15 mg/kg in 30 min | None reported | Ranitidine, 45.5 mg pheniramine maleate and 8 mg dexamethasone | Not mentioned | 16 |
| | 10 mg/kg, First dose in 90 min, following doses in 60 min and 30 min, as tolerated | No HSR were reported | Optional | Not mentioned | 68 |
| | 5 mg/kg or 7.5 mg/kg in 30-90 min | No HSR were reported | Not mentioned | Not mentioned | 69 |
| | 0.5 mg/kg/min From the first infusion | 1 Mild grade 1 HSR/73 infusions (73 patients) | Not mentioned | Not mentioned | 13 |
| Blinatumomab | Philadelphia chromosome-negative relapsed or refractory B-precursor ALL (greater than 45 kg) Day 1-7 (cycle 1): 9 μg/day continuous infusion Day 8-28 (cycle 1): 28 μg/day continuous infusion Day 1-28 (cycle 1+): 28 μg/day continuous infusion MRD-positive precursor-B ALL (greater than 45 kg) Induction cycle 1: Day 1-28: 28 μg/day Consolidation cycle 2-4: Day 1-28: 28 μg/day | Precursor B-ALL: 43.4% | 100 mg Prednisolone intravenously or equivalent should be administered. Antipyretics during the first 48 h are recommended. | Not mentioned | 70 |

Table II. *Continued*

Table II. *Continued*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| Cetuximab | First infusion (400 mg/m$^2$) in 120 min (maximum 5 mg/min), following infusions (250 mg/m$^2$) in 60 min (maximum 10 mg/min). | Grade 1 and 2: very often (≥1/10), grade 3 and 4: often (≥1/100, <1/10) | Use premedication (antihistamine and corticosteroid) at least 1 h prior infusion. | At least until 1 h after infusion. Infusion reactions can occur until several h after infusion. | 17 |
| | First infusion (400 mg/m$^2$) in 120 min (maximum 5 mg/min), following infusions (250 mg/m$^2$) in 60 min (maximum 10 mg/min) | All grades: 15%, grade 3-4: 3% | *i.v.* Diphenhydramine (50 mg) or an equivalent histamine H1–receptor antagonist, corticosteroid prior to first infusion. | Not mentioned, but before the initial dose was given, a test dose of 20 mg was infused over a 10-min period, which was followed by a 30-min observation period. | 71 |
| | First infusion (400 mg/m$^2$) in 120 min (maximum 5 mg/min), following infusions (250 mg/m$^2$) in 60 min (maximum 10 mg/min). | Grade 3 and 4: 3% | | | 72 |
| | First infusion (400 mg/m$^2$) in 120 min (maximum 5 mg/min), following infusions (250 mg/m$^2$) in 60 min (maximum 10 mg/min). | All grade 1-2: 13%, grade 3: 1%, grade 4: <1%. Dosing resumed with a 50% infusion rate reduction for grade 1-2 reactions but was permanently discontinued for grade 3-4 reactions. | Antihistamine | | 73 |
| Daratumumab | Infusion week 1 (16 mg/kg): 50 ml/h During the first h, then increased by 50 ml/h every h. Maximum: 200 ml/h. OR Infusion week 1 (8 mg/kg on day 1 and 8 mg/kg on day 2): 50 ml/h, increased by 50 ml/h every h. Maximum 200 ml/h. Infusion week 2 (16 mg/kg): 50 ml/h, increased by 50 ml every h. Maximum 200 ml/h. Following infusions (from week 3, 16 mg/kg): 100 ml/h, increased by 50 ml/h, maximum 200 ml/h. | 42% (Very often; ≥1/10) – 57.1% | Before infusion: corticosteroid, antipyretic and antihistamine. Post infusion 1 or 2 days corticosteroids. Patient with COPD: bronchodilators. | Observe until symptoms of infusion reactions disappear. | 22 23 25 26 29 |
| | From the third infusion: a 90 min infusion (20% of the dose in 30 min, remaining 80% in 60 min) | Infusion was tolerated among all 28 patients, no grade 3 or above reaction. | Premedication was used | 30 min after the first infusion | 30 |
| Dinutuximab beta | Continuous infusion during 10 days with 2 ml/h or infusion every day during 8 h with infusion rate 13 ml/h | | Antihistamine 20 min prior to infusion, repeated when needed | | 74 |
| Durvalumab | Dose of 10 mg/kg in 60 min | All grades: 'often' 1.9% (0.3% grade 3) | Consider after an infusion reaction | Not mentioned | 75 |
| Elotuzumab | Dose 10 mg/kg Cycle 1, dose 1: First 30 min 0,5 ml/min, escalated after 30 min to 1 ml/min, after 1 h until end of infusion: 2 ml/min. Cycle 1, dose 2: First 30 min: 3 ml/min, escalate after 30 min to | All grades: 10% or 'often' (≥1/100, <1/10) when premedication was used., 70% during the first infusion. | Premedication with dexamethasone, diphenhydramine, acetaminophen and ranitidine | At least 2 h after infusion | 76, 77 |

Table II. *Continued*

Table II. *Continued*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| | 4 ml/min until end of infusion. Cycle 1, dose 3 and 4: 5 ml/min. | | | | |
| Ipilimumab | **Suggested infusion rate: 1-3 mg/kg in 30 min** | | | | |
| | 3 mg/kg in 90 min or 1 mg/kg in 30 min | 3 mg/kg + 1 mg/kg: Nivolumab 3.8%: all grade 1 or 2. 1 mg/kg + 3 mg/kg nivolumab: 4.0%, all grade 1 or 2 | Use after an infusion reaction | Not mentioned | 31 |
| | 10 mg/kg in 90 min *vs.* 3 mg/kg in 90 min | 10 mg/kg: 2/364 Patients with infusion reaction; 1 grade 1-2, 1 grade 3. 3 mg/kg: 1/362 Patients with infusion reaction; 1 grade 3. | | | 35 |
| | 3 mg/kg in 30 min | 5.8% (6 patients grade 2, 1 patient grade 3.) | Use after an infusion reaction | 1 h after infusion | 36 |
| | 1 mg/kg Nivolumab and 3 mg/kg ipilimumab at 30 min per agent. | One out of 46 patients (total of 100 infusions) had a reaction after infusion of nivolumab | | | 37 |
| Mogmulizumab | 1 mg/kg in at least 60 min | 33%; Most grade 1-2, 4% grade 4; 28.8% during/ after first infusion. | Antipyretic and antihistamine are advised before the first infusion and after an infusion reaction. | Reactions can happen after infusion (all within 24 h). Observation time not specified. | 38 |
| | 1 mg/kg | 32% Grade 1-2, 2% grade 3 | Premedication with an antihistamine and acetaminophen | | 39 |
| | 1 mg/kg | 29.3% Grade 1-2 and 4.8% grade 3. 97% during the first infusion. | Antipyretic, antihistamine and/or a corticosteroid, according to local protocol. | | 40 |
| Nivolumab | **Suggested infusion rate: 240 mg or 3 mg/kg in 30 min, 480 mg in 60 min** | | | | |
| | 240 mg in 30 min or 480 mg in 60 min or in combination with ipilimumab: nivolumab 1-3 mg/kg in 30 min | Nivolumab monotherapy: 4.7% 1 mg/kg + 3 mg/kg ipilimumab: 3.8%, All grade 1 or 2. 3 mg/kg Nivolumab + 1 mg/kg ipilimimab: 4.0%, All grade 1 or 2 | Premedication is advised in case of grade 1-2 infusion reactions according to local protocol | | 41 |
| | 1 mg/kg Nivolumab and 3 mg/kg ipilimumab at 30 min per agent. | One out of 46 patients (total of 100 infusions) had a reaction after infusion of nivolumab. | | | 37 |
| | 3 mg/kg Nivolumab monotherapy in 30 or 60 min | 2% In both groups | Not given | | 42 |
| Obinutuzumab | CLL: Day 1: 100 mg with 25 mg/h, day 2: 900 mg, starting with 50 mg/h and escalated every 30 min up to 400 mg/h. All following doses of 1,000 mg: starting with 100 mg/h, escalated with 100 mg/h every 30 min, maximum 400 mg/h. FL: Day 1: 1,000 mg with 50 mg/h, escalated every 30 min with 50 mg/h, maximum 400 mg/h. All following doses of 1,000 mg: starting with 100 mg/h, escalated with 100 mg/h every 30 min, maximum 400 mg/h. | CLL: 66% at the first infusion of 1,000 mg 20% Grade 3-4, 3% at the second infusion of 1,000 mg and 1% at all following. Using premedication lowered the incidence of infusion reaction (grade 1-2). FL: 12% Of all patients had an IRR of grade 3-4. | Yes, antihistaminic, antipyretic and corticosteroid depending on indication, cycle and earlier reactions, follow the SmPC. | Not mentioned | 78 |

Table II. *Continued*

Table II. *Continued*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| Ofatumumab | Dosing depends on indication, see SmPC. First infusion 12 ml/h, increased every 30 min to a maximum of 400 ml/h. First and second infusion for refractory CLL had a maximum of 200 ml. All following: 25 ml/h, increasing every 30 min to a maximum of 400 ml/h | 61% At any time during treatment. The majority of IRRs were grade 1 or grade 2. 7% ≥grade 3. No fatal IRRs. | Acetaminophen, an antihistamine and an *i.v.* glucocorticoid | | 43 |
| | Treatment according to SmPC. | Infusion reactions occurred in 42% of patients in the ofatumumab arm. ≥Grade 3 infusion reaction in 5% (none fatal). | Treatment according to SmPC. | | 44 |
| Panitumumab | **Suggested infusion rate: First infusion in 60 min, second in 30 min, all following in 15 min** | | | | |
| | ≤1,000 mg: First dose in 60 min, all following in 30-60 min. >1,000 mg: All dose in 90 min | All grades: 5%, grade 3-4: 1% | Not mentioned | Not mentioned, but reactions >24 h can occur. | 45 |
| | ≤1,000 mg: First dose in 60 min, all following in 30-60 min. >1,000 mg: All dose in 90 min | All grades: 1.5% Grade 3: 0.2% Grade 4: None. 61.7% During the first infusion, 14.9% at the second, remaining at third or later. After infusion reaction on cetuximab and with premedication: 2.8% Grade 1 | Only given when the patient had an infusion reaction on cetuximab | | 46 |
| | 6 mg/kg Every 2 weeks: First dose in 60 min, all following in 30-60 min or 9 mg/kg every 3 weeks: all dose in 60 min | 1% but none of these were a reason to stop therapy | | | 47 |
| | 6 mg/kg in 60-min for the first infusion, followed by a 30-min infusion, and 15-min infusions thereafter. | No IRRs were noted | | | 48 |
| | 6 mg/kg, Administration according to product label | grade 1-2: 3%, grade 3: <0.5%. | Not given | | 73 |
| Pembrolizumab | 200 mg and 400 mg in 30 min. | Often (≥1/100, <1/10) | If grade 1 or 2 infusion reaction, antipyretic and antihistaminic premedication should be considered. Use of corticosteroids is discouraged. | Not mentioned | 79 |
| Pertuzumab | First dose (840 mg) in 60 min, all following (420 mg) in 30-60 min. | 13.2% During first infusion and 18.6-25.0% during first infusion (when combined with trastuzumab and chemotherapy) | Not mentioned in the SmPC | First dose at least 60 min, all following 30-60 min. | 80 |
| Ramucirumab | Dosing depends on indication, time of infusion not more than 25 mg/min (around 1 h) | Infusion reactions were seen in clinical trials | Antihistamine before infusion. If a infusion reaction grade 1-2 occurs give this before all following infusions. | Observe during infusion | 81 |

Table II. *Continued*

Table II. *Continued*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| | | | When a second infusion reaction grade 1-2 occurs, give dexamethasone and give before the next infusion an intravenous antihistamine, paracetamol and dexamethasone | | |
| Rituximab* | **Suggested infusion rate: First cycle: Incremental scheme from SmPC. Following infusions in 60 min. Use premedication.** | | | | |
| | First infusion: 50 mg/h, increase every 30 min with 50 mg/h, maximum 400 mg/h. All following infusions: 100 mg/h, increase every 30 min with 100 mg/h, maximum 400 mg/h. | 50-77% | Antipyretic and antihistamine, if corticosteroids are not given with chemotherapy then corticosteroids should be considered. CLL-Patients with lymphocytes >25×$10^9$/l should be given 100 mg prednisone/prednisolone | Not mentioned | 49 |
| | NHL: First infusion according to manufacturer's recommendation. Following infusions in 90 min, 20% of the dose during the first 30 min, 80% during remaining time. | No grade 3-4 adverse events. 2.3% Grade 1. | 1,000 mg Paracetamol *p.o.*, hydroxyzine 20 mg, 67% of the infusions were given with the corticosteroid. | 30 min after infusion | 82 |
| | NHL: First infusion according to manufacturer's recommendation. Following infusions in 90 min, 20% of the dose during the first 30 min, 80% during remaining time. | No grade 3-4 adverse events. 4/79 Patients, 269 cycles: 1 grade 1 IRR, 3 nausea/vomiting | 1,000 mg Paracetamol *p.o.*, diphenhydramine 25 mg, corticosteroid when part of the chemotherapy (but after rituximab) | Not mentioned | 53 |
| | First infusion according to manufacturer's recommendation. Following infusions in 90 min, 20% of the dose during the first 30 min, 80% during remaining time. | 0/17 Patients, 73 infusions | 1,000 mg Acetaminophen *p.o.*, 10 mg chlorphenamine *i.v.*, 100 mg hydrocortisone *i.v.* | Not mentioned | 50 |
| | First infusion according to manufacturer's recommendation. Following infusions in 90 min, 20% of the dose during the first 30 min, 80% during remaining time. | No grade 3-4 adverse events. Three grade 1 adverse events/319 infusions (70 patients) (all adverse events) | Acetaminophen, diphenhydramine methylprednisolone (40% of all infusions) | Not mentioned | 52 |
| | NHL: First infusion according to manufacturer's recommendation. Following infusions in 90 min, 20% of the dose during the first 30 min, 80% during remaining time. | No grade 3-4 infusion reactions. | 375 mg Acetaminophen *p.o.*, 50 mg diphenhydramine *p.o.*, corticosteroids according to protocol | Not mentioned | 83 |
| | Second and following infusions in 60 min with a constant rate | 0/105 Infusions (54 patients) | Hydrocortisone *i.v.* 100 mg, 1,000 mg paracetamol *p.o.* and 10 mg chlorphenamine *i.v.* | Not mentioned | 84 |
| | Second and following infusions in 60 min with a constant rate | 5 Grade 1/223 infusions, 0 Grade 3-4/223 infusions (40 patients) | 1,000 mg Paracetamol *p.o.*, 5 mg dexchlorpheniramine *p.o.*, corticosteroids according to protocol | Not mentioned | 85 |
| | First cycle: 10 ml/h (first 1 h) >50 ml/h (second 1 h) >100 ml/h (until end of treatment). Following infusions depending on cohort: range 50-300 ml/h (constant infusion until end of treatment) (<700 mg/h). | No grade 2-4 adverse events.22% grade 1 infusion-related toxicities. | Chlorpheniramine and eveprophene | | 86 |

Table II. *Continued*

Table II. *Continued*

| Drug | Infusion rate | Incidence of infusion reactions | Premedication | Observation time after infusion | Ref |
|---|---|---|---|---|---|
| | Depending on cohort, with a maximum of 700 mg/h | No grade 3-4 adverse events were seen. Some grade 1-2 events. | Clemastine and paracetamol | | 87 |
| Siltuximab | 11 mg/kg in 60 min | In clinical trials: 5.1% (0.8% was classified as severe), after long term treatment: 6.3% (1.3% classified as severe) | Can be considered after an infusion reaction | Not mentioned | 88 |
| Trastuzumab | First infusion in 90 min, following in 30 min | 40% | Can be used to prevent an infusion reaction | 6 h after the first infusion, 2 h after the following. | 55 |
| | First infusion in 90 min, following in 30 min | 16.2% Of patients, 1.8% of the doses | Given when recommended with chemotherapy | | 56 |
| | All maintenance doses were given in 30 min | 1.5% Of all infusions, 3.5% of the patients | 66% No premedication, if premedication was used: 100 mg hydrocortisone *i.v.* and 10 mg chlorpheniramine. | | 58 |
| | First dose (8 mg/kg) in 90 min, following infusion (6 mg/kg) in 30 min | 26% | 4 mg Chlorpheniramine and/or 100 mg hydrocortisone or 5 mg dexamethasone *i.v.* | | 60 |
| | 8 mg/kg in 250 ml over 90 min followed by 6 mg/kg in 100 ml over 30 min | 6.5% Grade 2 reaction during the first dose, 0% in following doses. | Not mentioned | Not mentioned | 59 |
| | After run-in chemotherapy and surgery: First infusion of neoadjuvant treatment: ABP 980 or trastuzumab in 90 min. Following infusions: 6 mg/kg ABP 980 or trastuzumab in 30 min. Adjuvant treatment depending on cohort (ABP 980/trastuzumab/ switch to ABP 980 6 mg/kg) in 30 min. | Neoadjuvant treatment: ABP 980: 20% Grade 1-2, 2% grade 3. Trastuzumab: 17% grade 1-2, 2% grade 3. Adjuvant treatment: ABP 98: 8% Grade 1-2, 1% grade 3. Trastuzumab: 7% Grade 1-2, 1% grade 3. Switch from adjuvant trastuzumab to ABP 980: 10% Grade 1-2, 1% grade 3% grade 4. | Not mentioned | 6 h after first infusion, 2 h after the following. | 89 |
| | Loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks given in 30 min. | 45% During first infusion, 29% during second infusion and 20% during the third. Only 3/105 had a serious IRR. | Acetaminophen and diphenhydramine were given to patients at increased risk | | 57 |
| | First dose: 8 mg/kg in 90 min for the first dose. All following doses: 6 mg/kg in 60 min. | Five out of 31 patients | 8 mg Dexamethasone *i.v.* for at least the first three doses | Not mentioned | 90 |

ABP 980: Biosilimar of trastuzumab; HSR: hypersensitivity reaction; ALL: acute lymphoblastic leukemia; MRD: minimal residual disease; CLL: chronic lymphocytic leukemia; FL: follicular lymphoma; *i.v.*: intravenous; *p.o.*: per os; SmPC: summary of product characteristics; NHL: non-Hodgkin's lymphoma, IRR: infusion-related reaction. *For NHL/CLL; for rheumatoid arthritis there is alternative schedule and incidence of infusion reactions, which is outside of the scope of this article, see also the SmPC of rituximab (49). Bold denotes suggested infusion rates.

of onset of the infusion-related reaction depends on the type of reaction. If the reaction happens within the first minute of infusion, it can be an anaphylactic reaction, induced by antibodies to IgE which cross-react with cetuximab. The possibility of restarting therapy after an allergic reaction depends on the grade of the reaction and the chance of the presence of IgE antibodies. If the infusion-related reaction happens after 1 h, it is more likely that the reaction is induced by CRS. Infusion-related reactions can occur during or after the first and subsequent infusions but most and most severe reactions occur during the first infusion (17). Much research has been carried out on infusion-related reactions to

cetuximab. Most research supports the incidence stated by the manufacturer, but interestingly, a higher number of infusion reactions has been found in the southeastern part of the United States (19). Presumably, this is a result of being bitten by specific ticks in this region, after which serum of these persons contained antibodies against the oligosaccharide galactose-alpha-1,3 galactose (20). This is the same oligosaccharide as present on the Fab portion of the cetuximab heavy chain. Panitumumab also targets EGFR but does not contain galactose-alpha-1,3 galactose. This might well explain the lack of cross-reactivity between cetuximab and panitumumab (21).

According to the manufacturer, the first dose of cetuximab must be preceded by an antihistaminic and a corticosteroid. This premedication is optional for subsequent infusions, provided that no reaction occurred during the first cycle. In theory, patients who have received several cycles of cetuximab without any reaction should be able to tolerate a higher infusion reaction, as well as a shorter observation period. As yet, there are no clinical data available, however, that support such an approach.

*Daratumumab*. Although daratumumab is a fully human antibody directed against CD38, it is associated with a relatively high incidence of infusion-related reactions. In the phase III trials leading to its registration, almost half of patients (42-48%) experienced an infusion reaction, of which the majority (>90%) occurred at the first infusion (22, 23). Infusion reaction symptoms of daratumumab typically include nasal congestion, throat irritation, cough, chills and nausea and vomiting (grade 1-2 in 90-95% of cases) or bronchospasms, dyspnea, laryngeal and pulmonary edema, hypoxia and hypertension (grade 3 in 5-10% of cases) (22, 23). Only 7% of patients experienced infusion reactions starting at the second or third dose and only 5% had reactions in more than one cycle (24). Infusion reactions can be managed rather easily by interruption of the infusion, treatment with standard rescue medication such as antihistamines or bronchodilators, and restarting at half of the infusion rate after complete recovery from the symptoms (25). Several approaches to reducing the incidence of infusion-related reactions are mandatory as prescribed by the manufacturer, including i) an incremental infusion rate for the first, second and third infusions; ii) diluting the first dose into 1,000 ml *versus* 500 ml for subsequent doses; iii) pre-treatment with corticosteroids, antipyretics and antihistamines; and iv) post-treatment administration of corticosteroids (25). Following market introduction, a small but significant reduction of infusion reactions was observed when montelukast was added to the premedication (26), or when the first dose was split over 2 consecutive days (27). There is not much data on the occurrence of late-onset infusion reactions, which could be used to establish an evidence-based observation time post infusion. The median time to onset of a reaction is 1.4 h according to the manufacturer (25), which is well within the range of infusion since the first cycle should be given over a minimum of 6.5 hours. An Australian expert panel of myeloma nurses suggested a 2-h observation time after the first cycle (28). In addition, patients with a history of severe chronic obstructive pulmonary disease or asthma should receive extra monitoring and be considered for extra post-infusion inhaled medications (corticosteroids and short- and long-acting bronchodilators) (29). Despite the high rate of infusion reactions, one study group in Ohio performed a small open trial on acceleration of the infusion after patients had received two or more doses in 500 ml at the standard infusion rate without complications. In 28 patients, reducing the administration time to 90 min was found to be safe. Notably in this trial, famotidine was added to the premedication regimen but when doses were tolerated, the premedication was limited to dexamethasone only (30). The results of this study were promising, but ideally should be confirmed in a larger trial before definite recommendations to increase the infusion rate for the overall population can be made.

*Ipilimumab*. Ipilimumab is a fully human monoclonal antibody directed against the cytotoxic T-lymphocyte antigen-4. Its first registration was for monotherapy at 3 mg/kg in patients with metastatic melanoma, followed by combination therapy of 3 mg/kg with nivolumab (1 mg/kg) for melanoma, and combination at 1 mg/kg with nivolumab (3 mg/kg) for renal cell carcinoma. The licensed infusion duration is 90 min for 3 mg/kg, and 30 min for 1 mg/kg (31). The landmark clinical trials with ipilimumab in melanoma (3 mg/kg) include the Checkmate as well as the Keynote studies, which showed infusion-related reactions in 0.6-4.1% of patients (32-34). A higher dose as well as combination with nivolumab appears to have an association with a slightly higher incidence of infusion reactions. In the NCT01515189 trial on advanced melanoma, 10 mg/kg ipilimumab infused over 90 min was compared to 3 mg/kg, also infused over 90 min. In the 10 mg/kg arm, 2/364 patients experienced an infusion reaction, one being of grade 1-2, and the other of grade 3. In the 3 mg/kg arm, 1/362 patients experienced a grade 3 infusion reaction (35). From these data, where 10 mg/kg was safely be infused over the same time as 3 mg/kg, the idea came that 3 mg/kg might also be safely infused at the rate of 1 mg/kg. This concept was prospectively studied in 120 patients receiving ipilimumab at 3 mg/kg in 30 min; 5.8% experienced infusion-related reactions (seven patients, of whom six had a grade 2 and one experienced a grade 3 reaction). All reactions occurred at the second dose, which implicates the first dose as a sensitizing cycle. Although the incidence of infusion reactions was slightly higher than seen in the large phase III trials, it was not significantly different from that in patients who were

given 3 mg/kg over 90 min at the same institution (36). Substantiation for safe administration of 3 mg/kg over 30 min comes from a German study which combined ipilimumab and nivolumab at 30 min per agent. Forty-six patients received 100 of these rapid cycles and none had a *bona fide* infusion-related reaction (37). Arguably, if this concept were to be extrapolated to the lowest licensed dose of 1 mg/kg, that might safely be infused in only 10 min. However, as yet, no data for this effect have been presented. Late-onset infusion-related reaction has not been described in the landmark trials, but was observed post marketing in one of the rapid-infusion studies in a single patient at 30-min post infusion. The manufacturer does not prescribe an observation time after infusion (31).

*Mogamulizumab*. Mogamulizumab is a humanized IgG1κ specifically targeting CC-chemokine receptor 4. This receptor is usually overexpressed on malignant T-cells. It is licensed in Europe and the USA for the treatment of *mycosis fungoides* (cutaneous T-cell lymphoma) and Sezary syndrome that is either refractory to or has manifested as a relapse following at least one prior line of treatment (38). In Japan, an additional licensing was launched in 2012 for refractory adult T-cell leukemia-lymphoma, under the condition that a post marketing all-case surveillance study would be conducted. The landmark phase III trial upon which the European registration was granted compared mogamulizumab with vorinostat in cutaneous T-cell lymphoma. In this trial, 58/184 (32%) patients in the mogamulizumab arm experienced a grade 1 or 2 infusion reaction, and 3/184 (2%) had a grade 3 reaction, despite premedication with an antihistamine and acetaminophen. Symptoms consisted of chills, fever, headache, nausea, rigors, tachycardia and vomiting (39). Earlier data, before the introduction of the pre-medication schedule, showed infusion reactions in 42% of cases. Hence, premedication is able to reduce but not eliminate the occurrence of infusion reactions. The Japanese post-marketing surveillance included 484 patients, and observed infusion-related reactions in 29.3% (grade 1 or 2) and 4.8% (grade 3) of patients, respectively. All but one patient received premedication with an antipyretic, antihistaminic/corticosteroid, according to local protocol. When comparing the group which received a corticosteroid with the group which did not, reactions in 27.5% and 35%, respectively, were reported, indicating that adding a corticosteroid to the premedication regime has an additional effect but still does not eliminate the incidence of infusion-related reactions; 97% of the patients who experienced an infusion reaction, did so in the first course of their mogamulizumab treatment (40).

*Nivolumab*. Nivolumab, a human immunoglobulin G4 monoclonal antibody to the programmed death-1 receptor, is registered as monotherapy for melanoma (also as adjuvant therapy), non-small cell lung cancer, renal cell carcinoma, classical Hodgkin lymphoma, squamous cell cancer of the head and neck and urothelial carcinoma, and in combination with ipilimumab in the treatment of melanoma and renal cell carcinoma. According to the SmPC, nivolumab is given at an infusion rate of 240 mg in 30 min or 480 mg in 60 min. Nivolumab combined with ipilimumab is given in 1-3 mg/kg in 30 min (41). The SmPC states that in <1% of the patients, a grade 3 or 4 treatment-related hypersensitivity or infusion reaction was found to lead to treatment discontinuation (41). To read more about the infusion reaction in dual monoclonal antibody therapy, please also see the section on 'ipilimumab'. In 2018, Waterhouse *et al*. investigated monotherapy nivolumab 3 mg/kg for advanced non-small cell lung cancer to see whether this dose could be safely given in 30 min instead of 60 min. In both groups, an incidence of 2% hypersensitivity or infusion-related reactions was seen, leading to the conclusion that an infusion time of 30 min is safe (42). As yet, no data on faster infusion of the high dose of 480 mg have been published.

*Ofatumumab*. Ofatumumab is a fully human monoclonal antibody specifically targeting CD20. It is used in combination with fludarabine and cyclophosphamide for relapsed chronic lymphocyte leukemia (CLL) or in combination with bendamustin and chlorambucil for newly diagnosed CLL. Ofatumumab binds to a specific epitope comprising both the small and the large loops of CD20. It has activity, among others, in rituximab-resistant B-cell lymphocytes. Although fully human, ofatumumab administration results in a very high incidence of infusion-related reactions which are potentially fatal (43). These reactions occur in 42-44% of patients during the first cycle (which consists of a low dose of 300 mg, preceded by acetaminophen, an antihistamine and intravenous glucocorticoid) and in 29% during the second cycle (43, 44). The symptoms of infusion reaction with ofatumumab are transient rigors, pyrexia, fatigue, rash, and increased sweating (mild), but can also be more severe, including bronchospasms, dyspnea, laryngeal and pulmonary edema, hypertension and hypotension, syncope, back pain, urticaria and angioedema (43). Because of this high incidence of infusion reactions, all measures to avoid these should be used in ofatumumab treatment (43). Firstly, all patients should be treated with adequate premedication consisting of acetaminophen, an antihistamine and intravenous glucocorticoid. Secondly, the first infusion must always be a reduced dose. Thirdly, slow increment of the infusion rate is prescribed, starting at 12 ml/h; if no reaction occurs, the rate of infusion can be increased stepwise to a maximum of 200 ml/h every 30 min. In addition, the second infusion, at full dose, should again start at the low rate of 12 ml/h. Subsequent cycles still require stepwise infusion rate titration but can start at 25 ml/h if no complication has been observed previously. From the

published study data, there appear to be no delayed infusion reactions with ofatumumab, therefore a clinical observation time after the end of a cycle when no events were noted during the administration appears unnecessary.

*Panitumumab*. Panitumumab is an EGFR-directed fully human IgG2 monoclonal antibody, derived using a different cell culture technique from that for cetuximab. In contrast to cetuximab, the panitumumab molecule does not hold galactose 1,3-alpha galactose on the Fab fragment. The licensed infusion instructions state that the first infusion should be given in 60 min, and subsequent infusions can be administered in 30 min if the first cycle was well tolerated. However, doses of over 1,000 mg should always be administered in 90 min. The SmPC also combined all phase II and III studies (total of 2,224 patients) to evaluate the rate of infusion reactions. These totaled to 5%, and 1% were grade 3-4 (45). This low rate of reactions was later confirmed in a Japanese post-marketing surveillance study of 3,085 patients, where treatment was administered according to the directions by the manufacturer: 47 patients (1.5%) showed an infusion reaction. Grade 3 or serious cases occurred in six out of the 3,085 patients (0.2%). No grade 4 reactions were observed. In 61.7% of cases, the reaction occurred at the first infusion and 14.9% at the second. The remaining patients had a reaction at the third or later infusion, with the latest reaction occurring at the 21st administration. In this analysis, 70 patients with a history of infusion reaction to cetuximab received panitumumab. These were treated with premedication and a reduced infusion speed. Two of these 70 patients had a mild infusion reaction (grade 1), while none had a severe reaction (46). Two trials investigating accelerated infusion schemes have been published to date. The first was an open label study investigating two dosing schedules of panitumumab: 6 mg/kg every 2 weeks, and 9 mg/kg every 3 weeks. The patients who received the two-weekly schedule, were given the first dose in 60 min, followed by subsequent doses in 30 min if the first infusion was well tolerated. The patients receiving the higher dose of 9 mg/kg, received all doses in 60-min. In this trial, 68 patients were enrolled, and no infusion reactions were reported. A *post-hoc* analysis, however, identified five potential infusion reactions, resulting in a 1% rate of infusion reactions overall, but none of these infusions were stopped nor was therapy withheld because of it. The study concluded that both the 60-min 9 mg/kg as well as the 60-min followed by 30-min 6 mg/kg regimens were safe (47). The second trial included 43 patients who received 6 mg/kg panitumumab in 60-min for the first infusion, followed by a 30-min infusion, and 15-min infusions thereafter. Nine patients did not reach the 15-min infusion, mainly due to disease progression. The remaining 34 patients received a total of 187 doses in 15 min. No infusion-related reactions were noted in the entire study, resulting in the investigators' conclusion that the short-infusion regimen was well tolerated and did not compromise safety or efficacy (48).

In conclusion, the differentiation between higher and lower doses (>1,000 and ≤1,000 mg, respectively), as well as the minimum infusion duration of 30-min, might both be unnecessarily strict. However, the data published on faster infusions are based on relatively small numbers of patients and a larger cohort of rapid infusion data would be of great value.

*Rituximab*. Rituximab binds to CD20-positive B-lymphocytes, inducing their death and activating an anti-CD-20 immunoreaction. Infusion reactions, including CRS, are seen often [77% of patients with non-Hodgkin lymphoma (NHL) or CLL], mostly during the first infusion in the first 2 h. During subsequent infusions, the likelihood of an infusion reaction is lower. Around 12% of these reactions are severe and fatal cases have been reported (49). Symptoms of tumor lysis syndrome and CRS can be seen. Symptoms of a tumor lysis syndrome are hyperuricemia, hyperkaliemia, hypocalcemia, hyperphosphatemia, acute kidney failure and respiratory depression. CRS following rituximab is known for dyspnea, bronchospasm, hypoxia, fever, chills, rigors and angioedema. Patients with bulky disease or $>25\times10^9$/l lymphocytes, mostly patients with CLL, have a higher probability of CRS and should be monitored carefully (49, 50). A lower infusion rate or dividing the dose over 2 days should be considered for these patients.

Rituximab is registered for several different diseases. According to the product information, the infusion rate during the first infusion is the same for all indications (49). However, the infusion rate during the following infusion depends on the indication, since the infusions for rheumatoid arthritis can be faster for most patients because the incidence of infusion reactions in rheumatoid arthritis is lower. The first infusion should always be given with an infusion rate of 50 mg/h and can be accelerated up to a maximum of 400 mg/h, increasing by 50 mg/h every 30 min. According to the manufacturer, all further infusions should be given at the same maximum infusion rate of 400 mg/h but one can start with an infusion rate of 100 mg/h, accelerating with 100 mg/h every 30 min. Post-marketing research showed that faster infusion is possible. A meta-analysis of Lang *et al*. compared 90- and 60-min regimens of rituximab in the treatment of NHL and CLL. During the 90-min infusion, 20% of the dose was given in the first 30 min and the remaining dose in the next hour. In the 60-min infusion regimes for NHL studies all doses were given at the same constant infusion rate. All studies that were included in the meta-analysis followed the advice of using premedication (studies that were available in full text are included in Table II). They concluded that the faster regimen is safe for patients with NHL since they saw a low incidence of reactions, which could be due to the high percentage of corticosteroid use and the absence of 'bulky disease' and leukocytosis. Lang *et al*. warned against rapid

infusion for patients with CLL since the evidence of their analysis was weak (only a limited number of patients included) (51). The results in CLL looked promising, with a low incidence of adverse reactions. However, more research on fast infusion in this patient group is required.

Premedication with antipyretics and antihistamine are recommended in the SmPC, as well as the use of corticosteroids if they are not already given as part of the chemotherapy. Although several studies did not give corticosteroids as premedication, it is still unclear if this influences the number of infusion reactions (52, 53). More research is important since rituximab is also given as monotherapy. When patients with CLL have lymphocytes $>25\times10^9$/l, 100 mg of prednisone/prednisolone should always be given to reduce the chance of a severe infusion reaction or CRS (49). Premedication and a slow first infusion are then common practice. Laudati *et al*. also suggested priming of the intravenous line, since this gives a lower chance of developing hypersensitivity reaction during the first infusion (35% in diluent-primed arm *versus* 19% in the drug-primed arm) (54).

*Trastuzumab*. Trastuzumab is a humanized monoclonal antibody used in the treatment of human epidermal growth factor receptor-2 (HER2)-overexpressing cancer. The product specifications recommend the first infusion of trastuzumab be given over 90 min and, when tolerated, all following infusions in half an hour. Trastuzumab is associated with infusion reactions not only during but also after infusion. The product information reports an incidence of 40% (55), but numbers vary in literature (see also Table II). Thompson *et al*. retrospectively investigated the incidence of infusion reactions in clinical practice in patients with breast cancer. They used the same infusion rates as recommended in the product information and gave premedication when this was part of the chemotherapy protocol. Total incidence of infusion reactions was 16.2% and 91% of the reactions were seen during the first dose. No grade 3 or 4 reactions were documented (56). Baselga *et al*. saw an incidence which was almost three-fold higher during the first infusion, although they used an infusion rate of 90 min for all infusions. The incidence they reported was 45% during the first infusion, 29% during the second infusion and 20% during the third infusion. Baselga *et al*. explained the higher incidence compared to other trials by the broad definition of infusion-related reactions that was used (57). Ring *et al*. reported an infusion reaction incidence of 3.5% for all patients with 30-min infusion for all maintenance doses (58). Abe *et al*. investigated whether 30-min infusion of trastuzumab with 100 ml saline from the second dose differed from trastuzumab with 250 ml saline, as is recommended by the product specification. No differences were seen in the incidence of infusion reactions (6.5% grade 2 reactions) (59).

Trastuzumab is not only used in the treatment of breast cancer but less research has been performed on infusion reactions in other indications. Oh *et al*. investigated infusion reactions due to trastuzumab infusion combined with chemotherapy in the treatment of HER2-positive gastric cancer. They saw an incidence of 26% when trastuzumab was infused over 30 min. There were no infusion reactions seen when trastuzumab was given as monotherapy, so it is uncertain if the reactions reported were only due to trastuzumab. Nevertheless, Oh *et al*. concluded that infusion of trastuzumab in 30 min together with chemotherapy was safe in the treatment of gastric cancer (60).

Most infusion reactions to trastuzumab were classified as grade 1-2 but there are reports of fatal cases (55). Cook *et al*. reported an incidence of 0.04% fatal cases according to post-marketing surveillance data (61). Patients have the highest chance of developing an infusion reaction during the first infusion. Moreover, patients who have a reaction during the first hour have the highest chance of having a subsequent serious infusion reaction (61). Analyses of 74 patients experiencing symptoms of a serious infusion-related reaction showed that these patients were suffering from respiratory symptoms (65%) and chills/rigors (32%) (61). Patients should be warned of the late signs of an infusion reaction since there are cases which had a delayed infusion reaction up to a week after infusion. Therefore the SmPC recommends that patients should be observed for 6 h after the first infusion and at least 2 h after all subsequent ones (55). However, in our practice this is often reduced if a patient shows no hypersensitivity reaction during the first two cycles. Patients with dyspnea due to their malignancy seem to have a higher probability of a fatal infusion reaction and these patients should therefore not receive trastuzumab (55). Thomson *et al*. also saw a higher incidence of infusion reaction in patients with obesity, probably due to a higher dose of trastuzumab but the underlying reason is not known. A higher maintenance dose was not associated with a higher likelihood of an infusion reaction. The stage of disease, however, was found to be associated with the risk of developing an infusion reaction: Patients with metastatic disease had a significantly higher likelihood of developing an infusion reaction (56).

According to the SmPC, premedication is not recommended but can be used to reduce the chance of an infusion reaction (55). Thomson *et al*. saw a lower incidence of infusion reactions in patients who used premedication with their chemotherapy. Although this result was not statistically significant ($p$=0.065), the relevance of using premedication should be investigated more extensively (56). Tanz *et al*. described two cases of patients with a severe infusion reaction after the first and sixth infusion, who were successfully rechallenged with premedication consisting of antihistamine and corticosteroids and a very low infusion rate (3 and 5 h instead of 90 min) (62).

## Discussion

Infusion reactions can occur with all monoclonal antibodies. The incidence does not appear to correlate with the origin (human, chimeric or mouse) of the drug, which might be explained by the fact that cytokine release is more often the causative factor than pure IgE-mediated allergy. The data on rituximab, where infusion reactions occur at double the rate in oncology patients when compared to patients with rheumatoid arthritis, supports this hypothesis. For several monoclonal antibodies, different approaches to reduce the incidence of these reactions have been attempted. These include the use of preventative drugs prior to infusion, as well as starting with a lower dose or infusion rate. However, none of these measures can fully eliminate the occurrence of infusion reactions, not even when they are all used in combination. Hence, adequate protocols to manage reactions remain pivotal.

Recently, several monoclonal antibodies in oncology have become available as subcutaneous infusion or injection (trastuzumab and rituximab), while others are currently being evaluated in clinical tests (daratumumab). Pharmacokinetics of subcutaneous administration differ from those of intravenous administration, resulting in a slower increase in serum level of the monoclonal antibody and, as a consequence, in a later and lower maximum concentration (Cmax). If rapid cytokine release is enhanced by a fast and high Cmax, which is to be expected from a pharmacological viewpoint, subcutaneous administration may reduce the incidence as well as the severity of reactions. This has in fact been demonstrated for trastuzumab (63, 64) and rituximab (65, 66), but appears to come at the cost of a substantial number of patients experiencing injection site reactions (63-66).

In order to improve patient satisfaction in combination with reducing hospital drug-delivery related healthcare costs, shortening infusion duration or shortening post-administration observation time is an attractive option. With the ever-increasing number of monoclonal antibodies reaching the market in the field of oncology, this approach is gaining more and more attention. From our review, we conclude that administration of the following monoclonal antibodies in an increased infusion rate as compared to the one stated by the manufacturer is safe: Bevacizumab, ipilimumab, nivolumab (low dose), panitumumab and rituximab. In addition, a shorter observation time for trastuzumab post infusion also seems feasible. For monoclonal antibodies associated with a low incidence of infusion reactions, such as durvalumab and pembrolizumab, a similar approach might be achievable but no data are currently available.

Most monoclonal antibodies are given with premedication (antihistamine, antipyretics and corticosteroids) when they are used in a protocol with chemotherapy in order to reduce the likelihood of side-effects of the treatment such as infusion-related reactions. Moreover, when monoclonal antibodies are given as monotherapy, premedication is used but not always. In order to reduce the risk of an infusion reaction and time in hospital, the relevance of premedication should be investigated to decide which patients benefit from it. In this way, one can make a decision between treating with premedication when needed, or not giving premedication with the benefit of preventing their side-effects.

There are limited post-marketing studies available on infusion reactions and the infusion rate used for administration of monoclonal antibodies. Most studies are relatively small, and since these studies sometimes use different definitions of infusion-related reactions, the apparent incidence can vary. Even fewer studies on post administration observation time have been performed. This makes it challenging to define recommendations. More research is needed on this subject to improve patient satisfaction and to reduce hospital drug delivery-related healthcare costs.

## Conflicts of Interest

No conflicts of interest to be declared.

## Authors' Contributions

MR executed the study, analyzed the findings and prepared the article. ES interpreted and analyzed the results and was involved in the writing of the manuscript. AvdE interpreted and analyzed the results and was involved in the writing of the manuscript. MC designed the study and prepared the article.

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