Efficacy and Safety of Lipegfilgrastim for the Prophylaxis of Chemotherapy-induced Neutropenia in Breast Cancer Patients in Poland

Type
Research paper

Keywords
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This is an exploratory analysis of Polish breast cancer patients participating in a pan-European study of lipegfilgrastim in primary and secondary prophylaxis for patients receiving cytotoxic chemotherapy (Lonquex Observational Cohort Study, LEOS). Patients were followed since the start of neutropenia prophylaxis until 6 to 8 weeks after the last dose of the lipegfilgrastim. The efficacy measures were chemotherapy dose reductions, omissions, delays and the proportion of the planned cumulative dose actually delivered.

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A total of 45 mostly high risk of FN patients were included in the analysis. Overall, 31 of 212 chemotherapy cycles (14.6%) were delayed in 19 patients (42.2%). Cumulative dose of chemotherapy was reduced in 1.4% of the cycles in 4.4% of the patients. The mean percentage of cumulative dose planned actually administrated was 99.95% across all cycles. Only one patient had FN. There were 15 episodes of neutropenia in 3 patients (6.7%). A total of 69 adverse events were reported, which 65% were drug-related. The most common were musculoskeletal pain (17.8%) and myalgia (11.1%) Four adverse events were serious and two of them were related to lipegfilgrastim.

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Introduction

Chemotherapy-induced neutropenia (CIN) is a significant dose-limiting toxicity of chemotherapy. It increases the risk of infectious complications and death. The severity of neutropenia is associated with the development of febrile neutropenia (FN), one of the most serious complications of chemotherapy. Severe neutropenia and/or FN often result in dose reductions or treatment delays, which may compromise the efficacy of cancer therapy [1,2].

Prophylactic use of granulocyte-colony stimulating factors (G-CSFs) was shown to be effective in reducing the severity and duration of severe neutropenia and FN, as well as all-cause mortality [3-6]. US and European guidelines recommend G-CSF therapy in primary prophylaxis in patients receiving high risk FN chemotherapy (>20%). In patients treated with intermediate risk regimens (10-20%) other risk factors should be considered (e.g. age or coexisting diseases). Secondary prophylaxis is also important, i.e. in subsequent cycles in patients after a previous FN episode [1,7].

Lipegfilgrastim (Lonquex®; Teva Pharmaceuticals Industries Ltd, Petach Tikva, Israel) is a glycopegylated, long-acting, fixed dose once per cycle, recombinant G-CSF, approved by the European Medicines Agency for reduction in the duration of neutropenia and the incidence of FN in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) [8].

Phase III randomized trial comparing lipegfilgrastim and pegfilgrastim for prophylaxis of CIN in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy demonstrated comparable efficacy in terms of duration of severe neutropenia and the incidence of FN and duration of FN-related hospitalization and antibiotic use [9,10].

The objective of this exploratory analysis was to assess the efficacy and safety of lipegfilgrastim in real-world clinical practice in breast cancer patients in Poland.

Material and Methods

Trial Design and Oversight

This was a multicentre, prospective, observational cohort study of cancer patients receiving cytotoxic chemotherapy and lipegfilgrastim (Lonquex®) in outpatient and inpatient settings (Lonquex ObsErvational Cohort Study, LEOS). Lipegfilgrastim 6 mg was used in primary or secondary prophylaxis of chemotherapy-induced neutropenia. Patients were followed since the start of neutropenia prophylaxis with lipegfilgrastim until 6 to 8 weeks after the last dose of the drug. The study was conducted in the European Union countries, including Poland. This is an exploratory analysis of Polish breast cancer patients. The trial was conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice (GCP), Polish Pharmaceutical Law, Directive 2010/84/EU, Good Epidemiological Practice (GEP), Good Pharmacoepidemiology Practices and Good Pharmacovigilance Practices (GVP). The protocol was reviewed by local ethic committee in Cracow, Poland. All patients provided written informed consent. The authors wrote the manuscript with the assistance of a medical writer funded by the sponsor.

Patients

Eligible subjects included male and female cancer patients ≥ 18 years of age treated with cytotoxic chemotherapy or biological therapy for solid and haematological malignancies,
excluding chronic myeloid leukaemia and myelodysplastic syndromes, and receiving G-CSF treatment with lipegfilgrastim for primary or secondary prophylaxis of chemotherapy induced neutropenia. Only breast cancer patients were included in the present analysis.

**Efficacy measurements**

Primary efficacy measures included chemotherapy dose reductions, omissions, delays and mean percentages of cumulative doses planned actually administered. Among the secondary efficacy measures were frequencies of febrile neutropenia, neutropenia, hospitalisations, anti-infective treatments and blood transfusions.

**Safety Assessments**

Adverse events were categorized with the use of the Medical Dictionary for Regulatory Activities, version 20.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Typical chemotherapy induced adverse drug reactions were exempt from recording unless they were more severe or more frequent than expected from the treatment or the medical condition itself and included: nausea and vomiting, alopecia, diarrhea and constipation, fatigue, asthenia, neuropathic pain, hand-foot-syndrome, swelling, mouth sores, appetite changes, nervous system effects and cognitive changes or dysfunction only if related to chemotherapy. The adverse event relation to study drug was determined by treating physician.

**Statistical Analysis**

This is an exploratory analysis. No formal statistical hypotheses were tested. Descriptive statistics methods were used. Ninety-five percent confidence intervals were calculated for efficacy and safety measures.

**Results**

**Patients**

From January 2015 through January 2016, a total of 45 breast cancer patients were enrolled and treated with chemotherapy at 6 sites in Poland. Patients demographics and disease characteristics are summarized in Table I. The mean age of the patients was 56.6 years (range, 34.0 to 76.0). Forty percent of the patients were diagnosed with stage II, 33.3% with stage III and 11.1% with stage IV breast cancer. Two or more comorbidities were present in 28.8% of the patients. Over 50% of the patients were fully active (Eastern Cooperative Oncology Group performance status [ECOG-PS] 0) and 40% had ECOG-PS score of 1. The risk of febrile neutropenia was high (>20%) in 62.2% of the patients.

**Treatments**

The majority of patients received adjuvant chemotherapy (68.9%). Most chemotherapy regimens were associated with intermediate or high risk of febrile neutropenia. In 80% of the patients lipegfilgrastim was used in primary prophylaxis. Patients received a total of 212 cycles. Lipegfilgrastim was used in 88.2% of the cycles. Chemotherapy regimens and FN prophylaxis are summarized in Table II.
Efficacy

Overall, 31 of 212 chemotherapy cycles (14.6%; 95% CI, 10.4 to 19.4%) were delayed in 19 patients (42.2%; 95% CI, 28.0 to 57.8). The median delay of following cycle was 7.0 days (95% CI, 6.9 to 7.1). The mean percentage of cumulative dose planned actually administered was 99.95±2.02% across all cycles and 100±0.40% across all cycles and drugs. Cumulative dose of chemotherapy was reduced in 3 of 212 cycles (1.4%; 95% CI, 0.5 to 3.0%) in 2 patients (4.4%). No chemotherapy cycle was omitted. Targeted treatment with trastuzumab was used in six cycles. None of the trastuzumab doses were reduced or omitted.

Frequencies of chemotherapy cycles delays, dose reductions and omissions as well as the percentage of cumulative doses planned actually administered are summarized in Table III.

One patient had febrile neutropenia, which corresponds to an incidence of 2.2%. A total of 15 neutropenia episodes occurred across all cycles (7.1%) in three patients (6.7%), with the exception of two severe (grade 4), the rest were mild (grade 1). Anti-infectives were used 6 times, once intravenously for the treatment of febrile neutropenia and the other 5 orally for other infections (e.g. pharyngitis or wound infection). The median duration of anti-infective therapy was 4 days (range, 2 to 22). Two blood transfusions, one 2 and one 3 units, were used throughout the study.

There were three hospitalizations with a median duration of 8 days (range, 1 to 31). One hospital stay was due to febrile neutropenia and lasted 31 days. One patient had surgery to remove the breast implant due to wound infection, and in the third case it was a planned admission associated with the administration of zoledronic acid in a patient with bone metastasis. No hospital stay required an intensive care unit.

Safety

Overall, 69 adverse events were reported in 42.2% of the patients (95% confidence interval [CI] for the percentage, 28.9 to 57.2). Sixty-five percent of adverse events were drug-related. They occurred in 33.3% of the patients (95% CI, 22.2 to 48.6). None of the patients died during the study. Four adverse events reported in 6.7% of the patients (95% CI, 2.2 to 14.2) were serious (asthenia, hypersensitivity, wound infection, haemothorax), including two drug-related (hypersensitivity and wound infection) reported in 4.4% (95% CI, 0.0 to 9.0). All four severe adverse events reported in 4.4% of the patients were drug-related. They included hypersensitivity, skin toxicity, rash and wound infection. Two adverse events resulted in study drug discontinuation. Frequencies of adverse events are summarized in Table IV.

The most frequent adverse events overall were fatigue (14.5% of events) and musculoskeletal pain (11.6%) both reported in 6.7% of the patients. The most common drug-related adverse events were musculoskeletal pain (17.8% of drug-related events) and myalgia (11.1%) both in 6.7% of the patients followed by fatigue (11.1%) in 4.4%. Adverse events overall and drug-related are summarized in Table V.

Discussion

This exploratory analysis from an observational study of lipegfilgrastim for the prophylaxis of chemotherapy-induced neutropenia in breast cancer patients in Poland showed that nearly 100% of the planned cumulative doses of various chemotherapy
Regimens across all cycles were administered. None of the patients required omissions of chemotherapy treatment and very few dose reductions were needed. Treatment delays were infrequent and their duration moderate.

In a phase III study of lipogfilgrastim versus pegfilgrastim in breast cancer patients treated with doxorubicin and docetaxel 98.8 to 99.3% of the planned chemotherapy doses were administered in the lipogfilgrastim group [10]. In our study doxorubicin/docetaxel accounted for almost 25% of chemotherapy regimens and the percentage of the planned doses actually administered across all regimens was even higher. The incidence of chemotherapy delays in a cycle was higher than in the phase III study (the highest 22.6% vs. 16.2%) (data not shown), and longer was the average delay across all cycles (median 7.0 [range, 1.0 to 77.0] vs. 0.0 [0.0 to 14.0] days) [10]. In the Protroca study, assessing the effectiveness and safety of lipogfilgrastim in non-selected breast cancer patients the incidence of delay of chemotherapy was similar to our study [11]. Timmer-Bonte et al. reported higher rates of delay, but their study included also the patients with haematological malignancies and solid tumours other than breast cancer [12]. Febrile neutropenia is rare with lipogfilgrastim. It was seen in approx. 1% of patients in another analysis of the already mentioned phase III study [9]. In turn, in the dose-finding phase II study of lipogfilgrastim 3.0, 4.5 or 6 mg in breast cancer patients treated with doxorubicin/docetaxel 3.9% and 6% of the patients experienced FN with 4.5 and 6.0 mg dose of lipogfilgrastim, respectively [13]. The incidence of FN in our analysis was 2.2%. Only two out of 15 episodes of neutropenia were severe, which corresponds to an incidence of 4.4%. In the aforementioned phase II and III studies the incidence of severe neutropenia was substantially higher, i.e. depending on the cycle 8% to 38% (with 6 mg dose of lipogfilgrastim) and 8.5% to 43.6% (50% across all cycles), respectively, with the highest values in cycle 1 [9,13].

In our study typical chemotherapy induced adverse drug reactions were recorded only if they were more severe or more frequent than expected from the treatment or the medical condition. Therefore, the majority of adverse events were drug-related. The incidence of drug-related adverse events (33.3%) was slightly higher than in the phase III study by Bondarenko et al. of breast cancer patients treated with lipogfilgrastim or pegfilgrastim in which drug-related adverse events occurred in 27.7% and 25.7% of the patients, respectively [9]. The incidence of severe drug-related adverse events was low (4.4%), but also slightly higher than in the phase III study (1.0%) [9].

The observed safety profile was typical for G-CSFs with musculoskeletal pain, myalgia and fatigue, as the most commonly observed adverse events. Bone pain-related symptoms are commonly associated with G-CSF therapy [14]. Overall, musculoskeletal pain (17.8% of events), myalgia (11.1%), arthralgia (6.7%), bone pain (4.4%), back pain and pain in extremity (2.2% each) accounted for 44.4% of drug-related adverse events reported in 15.6% of the patients. All bone pain-related symptoms were classified as drug-related. The incidence of bone pain-related symptoms was slightly lower compared to that observed in randomized trials. In an integrated analysis from phase II [13] and III [9] studies in patients with breast cancer treated with lipogfilgrastim or pegfilgrastim, the incidence of bone pain-related adverse events was 25.2% and 21.9%, respectively, and bone pain-related events associated with G-CSF 18.5% and 16.8%, respectively [15]. Nonsteroidal anti-inflammatory drugs and/or acetaminophen were used to manage the symptoms, or they resolved without treatment. In one case, musculoskeletal pain resulted in study drug discontinuation.
The limitation of the presented analysis is the relatively small sample size consisting of 45 patients. Patients were enrolled in various cycles, as some patients had no indication for G-CSF therapy from the first chemotherapy cycle, thus drug exposure may have been lower than in clinical trials.

Conclusions

Lipegfilgrastim proved to be effective and well-tolerated for CIN prophylaxis in patients with breast cancer receiving myelosuppressive chemotherapy in a real-life setting. The average cumulative dose was nearly 100%, although the dose intensity may have been slightly lower compared to previous experience due to longer delays. One FN and very rare severe neutropenia were observed. Safety profile was consistent with that of a G-CSF therapy.

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Conflicts of interest

Streb J and Kucharz J were investigators in LEOS study.
Lipa A, Strzondona M are employees of Teva Pharmaceuticals Polska Sp. z o.o.
Wysocki PJ declares no conflicts of interest

References

1. Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 2011; 47:8-32.
2. Klastersky J, de Naurois J, Rolston K, et al., on behalf of the ESMO Guidelines Committee, Management of febrile neutropaenia: ESMO Clinical Practice Guidelines. 2016 Ann Oncol; 27 (suppl_5): v111–v118.
3. Clark OA, Lyman GH, Castro AA, Clark LGO, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia: a meta-analysis of randomized controlled trials. J Clin Oncol 2005; 23: 4198–4214.
4. Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer 2011; 11: 404.
5. Kuderer NM, Dale DC, Crawford J, Lyman GH. Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 2007; 25: 3158–3167.
6. Lyman GH, Dale DC, Culakova E, et al. The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol 2013; 24: 2475–2484.
7. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006; 24: 3187–3205.
8. Lonquex Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/lonquex-epar-product-information_en.pdf (accessed December 2019).
9. Bondarenko I, Gladkov OA, Elsässer R, Buchner A, Bias P. Efficacy and safety of lipegfilgrastim versus pegfilgrastim: a randomized, multicenter, active-control phase 3 trial in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy. BMC Cancer 2013; 13: 386.
10. Gladkov OA, Buchner A, Bias P, Müller U, Elsässer R. Chemotherapy-associated treatment burden in breast cancer patients receiving lipegfilgrastim or pegfilgrastim: secondary efficacy data from a phase III study. Support Care Cancer 2016; 24: 395-400.
11. Wuerstlein R, Harbeck N, Grischke EM, et al. Protroca: A Noninterventional Study on Prophylactic Lipegfilgrastim against Chemotherapy-Induced Neutropenia in Nonselected Breast Cancer Patients. Breast Care (Basel). 2021;16:50-58.
12. Timmer-Bonte JNH, Ouwerkerk J, Faber LM, et al. Lipegfilgrastim for prophylaxis of chemotherapy-induced neutropenia in Dutch patients. Neth J Med. 2020;78:270-276.
13. Buchner A, Elsässer R, Bias P. A randomized, double-blind, active control, multicenter, dose-finding study of lipegfilgrastim (XM22) in breast cancer patients receiving myelosuppressive therapy. Breast Cancer Res Treat 2014; 148: 107–116.
14. Pfeil AM, Allcott K, Pettengell R, von Minckwitz G, Schwenkglenks M, Szabo Z. Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review. Support Care Cancer 2015; 23: 525-545.
15. Bondarenko IM, Bias P, Buchner A. Incidence of bone pain in patients with breast cancer treated with lipegfilgrastim or pegfilgrastim: an integrated analysis from phase II and III studies. Support Care Cancer 2016; 24: 267-273.
| Characteristic                              | Patients |
|--------------------------------------------|----------|
| Age -years, mean ± standard deviation      | 56.6±10.1|
| Caucasian race no. (%)                     | 45 (100.0) |
| Stage of breast cancer* no. (%)            |          |
| IA                                         | 3 (6.7)  |
| IB                                         | 0        |
| IIA                                        | 12 (26.7)|
| IIB                                        | 6 (13.3) |
| IIIA                                       | 9 (20.0) |
| IIIB                                       | 4 (8.9)  |
| IIIC                                       | 2 (4.4)  |
| IV                                         | 5 (11.1) |
| Unknown                                    | 4 (8.9)  |
| No. of co-morbidities, no. (%)             |          |
| 0                                          | 16 (35.6)|
| 1                                          | 16 (35.6)|
| 2                                          | 5 (11.1) |
| 3                                          | 6 (13.3) |
| 4                                          | 1 (2.2)  |
| 5                                          | 1 (2.2)  |
| ECOG performance status, no. (%)           |          |
| 0                                          | 24 (53.3)|
| 1                                          | 18 (40.0)|
| 2                                          | 3 (6.7)  |
| 3                                          | 0        |
| Febrile neutropenia risk, no. (%)          |          |
| Low (<10%)                                  | 1 (2.2)  |
| Intermediate (10-20%)                       | 16 (35.6)|
| High (>20%)                                 | 28 (62.2)|
| Risk factors for febrile neutropenia, no. (%) |     |
| Advanced disease                            | 13 (28.9%)|
| Age above 65                                | 10 (22.2%)|
| History of prior FN                         | 5 (11.1%)|
| Poor performance status                     | 3 (6.7%)  |
| Poor nutritional status                     | 4 (8.9%)  |
| Female gender                               | 45 (100.0%)|
| Haemoglobin < 12g/dl                        | 6 (13.3%) |
| Liver disease                               | 2 (4.4%)  |
| Renal disease                               | 0 (0.0%)  |
| Cardiovascular disease                      | 17 (37.8%)|
*According to AJCC Cancer Staging Manual, 8th Edition, 2017.

Table II. Chemotherapy and FN Prophylaxis

| Treatment                                                                 | Patients |
|---------------------------------------------------------------------------|---------|
| Chemotherapy setting, no. (%)                                             |         |
| Adjuvant                                                                  | 31 (68.9) |
| Neoadjuvant                                                               | 9 (20.0)  |
| Metastatic Disease                                                        | 5 (11.1)  |
| Chemotherapy regimen, no. (%)                                             |         |
| Doxorubicin and docetaxel                                                 | 11 (24.4) |
| Docetaxel and cyclophosphamide                                            | 6 (13.3)  |
| Doxorubicin and cyclophosphamide                                          | 6 (13.3)  |
| Doxorubicin, cyclophosphamide followed by docetaxel                       | 4 (8.9)   |
| Fluorouracil, epirubicin and cyclophosphamide (FEC)                       | 4 (8.9)   |
| Fluorouracil, epirubicin and cyclophosphamide followed by docetaxel (FEC-D) | 3 (6.7) |
| Fluorouracil, doxorubicin and cyclophosphamide (FAC 50)                   | 3 (7.7)   |
| Doxorubicin, cyclophosphamide followed by paclitaxel (AC-T)               | 2 (4.4)   |
| Docorubicin and paclitaxel                                                | 1 (2.2)   |
| Docetaxel, doxorubicin, and cyclophosphamide (TAC)                        | 1 (2.2)   |
| Docetaxel                                                                  | 1 (2.2)   |
| Docetaxel followed by epirubicin                                          | 1 (2.2)   |
| Paclitaxel                                                                 | 1 (2.2)   |
| Docetaxel, carboplatin, trastuzumab (TCH)                                 | 1 (2.2)   |
| No. of chemotherapy cycles (mean ± standard deviation)                    | 212 (6.2 ± 1.8) |
| No. of lipogfilgrastim doses (%)                                          | 187 (88.2) |
| Type of febrile neutropenia prophylaxis, no. (%)                          |         |
| Primary                                                                   | 36 (80.0) |
| Secondary                                                                 | 9 (20.0)  |
| No. of patients with delayed chemotherapy cycles (%)                       | 19 (42.2%) |
| No. of delayed chemotherapy cycles (%)                                     | 31 (14.6) |
| Duration of chemotherapy delays across all cycles, days                   |         |
Mean (±standard deviation) 10.3 (14.9) 
Median (range) 7.0 (1.0, 77.0) 6.9, 7.1  

Percentage of cumulative chemotherapy dose planned actually administered across all cycles*
Mean (±standard deviation) 99.9 (2.0) 
Median (range) 100 (78.1, 118.7) 100.0, 100.0 

Percentage of cumulative chemotherapy dose planned actually administered across all cycles and drugs**
Mean (±standard deviation) 100 (0.40) 
Median (range) 100 (98.6, 102.1) 100.0, 100.0 

No. of patients with chemotherapy cumulative dose reductions (%) 2 (4.4) 0.0, 9.0 
No. of cycles with chemotherapy cumulative dose reductions (%) 3 (1.4) 0.5, 3.0 
No. of patients with omitted cycles (%) 0  
No. of omitted cycles (%) 0  

* In each cycle for each patient the average percentage of dose planned actually administered across drugs was calculated.  
** For each patient the average of dose planned actually administered across drugs and cycles was calculated.  

Table IV. Frequencies of Adverse Events

|                           | Adverse Events Overall | Drug-related Adverse Events |
|---------------------------|------------------------|-----------------------------|
| No. of patients with adverse event (%) | 19 (42.2)              | 15 (33.3)                   |
| No. of adverse events (%)  | 69 (100.0)             | 45 (65.2)                   |
| No. of patients with serious adverse event* (%) | 3 (6.7)              | 2 (4.4)                     |
| No. of serious adverse events (%) | 4 (5.8)              | 2 (2.9)                     |
| No. of patients with severe adverse event** (%) | 2 (4.4)              | 2 (4.4)                     |
| No. of severe adverse events (%) | 4 (5.8)              | 4 (5.8)                     |
| No. of patients discontinued study drug due to adverse events (%)*** | 2 (4.4)              | 2 (4.4)                     |

*Serious adverse event was an adverse event resulted in death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was congenital anomaly/birth defect or was life-threatening or required medical intervention to prevent the above outcomes.
According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ‘severe’ refers to grade 3 severity of adverse events, which includes severe or medically significant but not immediately life-threatening events; indication for hospitalization or prolongation of hospitalization; disabling; limiting self-care activities of daily living, e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

***One observation was missing.

Table V. Adverse Events Overall and Drug-related

| Adverse event* | Number of patients (%)** | Number of events (%) | Number of patients (%)** | Number of events (%) |
|----------------|--------------------------|----------------------|--------------------------|----------------------|
|                | Overall                  | Drug-related         |                          |                      |
| Fatigue        | 3 (6.7)                  | 10 (14.5)            | 2 (4.4)                  | 5 (11.1)             |
| Musculoskeletal pain*** | 3 (6.7)                  | 8 (11.6)            | 3 (6.7)                  | 8 (17.8)             |
| Pyrexia        | 2 (4.4)                  | 6 (8.7)              | 1 (2.2)                  | 1 (2.2)              |
| Myalgia***     | 3 (6.7)                  | 5 (7.2)              | 3 (6.7)                  | 5 (11.1)             |
| Headache       | 2 (4.4)                  | 4 (5.8)              | 1 (2.2)                  | 1 (2.2)              |
| Arthralgia***  | 1 (2.2)                  | 3 (4.3)              | 1 (2.2)                  | 3 (6.7)              |
| Spinal pain    | 1 (2.2)                  | 3 (4.3)              | 0                        | 0                    |
| Hyperaesthesia | 1 (2.2)                  | 3 (4.3)              | 1 (2.2)                  | 3 (6.7)              |
| Bone pain***   | 2 (4.4)                  | 2 (2.9)              | 2 (4.4)                  | 2 (4.4)              |
| Asthenia       | 2 (4.4)                  | 2 (2.9)              | 1 (2.2)                  | 1 (2.2)              |
| Chest pain     | 1 (2.2)                  | 2 (2.9)              | 0                        | 0                    |
| Immune thrombocytopenic purpura | 1 (1.4)                  | 0                        | 0                        |
| Vomiting       | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Influenza like illness | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Malaise        | 1 (2.2)                  | 1 (1.4)              | 0                        | 0                    |
| Hypersensitivity | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Face oedema    | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Infection      | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Periodontitis  | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Pharyngitis    | 1 (2.2)                  | 1 (1.4)              | 0                        | 0                    |
| Rhinitis       | 1 (2.2)                  | 1 (1.4)              | 0                        | 0                    |
| Wound infection | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Body temperature increased | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Back pain***   | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Pain in extremity*** | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Insomnia       | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Haemothorax    | 1 (2.2)                  | 1 (1.4)              | 0                        | 0                    |
| Rash           | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Rash papular   | 1 (2.2)                  | 1 (1.4)              | 1 (2.2)                  | 1 (2.2)              |
| Adverse event* | Number of patients (%)** | Number of events (%) | Number of patients (%)** | Number of events (%) |
|----------------|--------------------------|----------------------|--------------------------|----------------------|
| Skin exfoliation | 1 (2.2) | 1 (1.4) | 1 (2.2) | 1 (2.2) |
| Skin toxicity    | 1 (2.2) | 1 (1.4) | 1 (2.2) | 1 (2.2) |
| Exfoliative rash | 1 (2.2) | 1 (1.4) | 1 (2.2) | 1 (2.2) |

*Typical chemotherapy induced adverse drug reactions were exempt from recording unless they were more severe or more frequent than expected from the treatment, summary of product characteristics, or the medical condition.

**Patients could have more than one adverse event.

***Bone pain-related symptoms occurred in a total of 7 patients (15.6%) with drug-related adverse events. All bone pain-related symptoms were classified as drug-related.