

#### Recommendation Report SCT-7

# A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

### Plerixafor for Autologous Hematopoietic Stem Cell Mobilization and Transplantation for Patients in Ontario

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Recommendation Report SCT-7 is comprised of 3 sections. You can access the summary and full report here:

https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/226

Section 1: Recommendations

Section 2: Recommendation Report Methods Overview

Section 3: Evidence Review

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#### TABLE OF CONTENTS

Section 1: Recommendations	2
Section 2: Recommendation Report Methods Overview	6
Section 3: Evidence Review	8
References	42
Appendix I: Literature Search Strategy	45
Appendix II: Conflict of Interest Declarations	46

#### Recommendation Report SCT-7: Section 1

### Plerixafor for Autologous Hematopoietic Stem Cell Mobilization and Transplantation for Patients in Ontario: Recommendations

#### **RESEARCH QUESTIONS**

- Does the administration of plerixafor in combination with granulocyte-colony stimulating factor (G-CSF) for stem cell mobilization before autologous transplantation improve the outcome of patients who have not been mobilized before, when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- 2. Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients failing mobilization when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- 3. Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients who have failed a prior mobilization regimen when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?

#### TARGET POPULATION

All adult patients considered for autologous stem cell transplantation (SCT) and meeting one of the following criteria:

- Have not been mobilized before (i.e., the case of up front mobilization in naïve patients who may or may not be at risk of being poor mobilizers)
- Are failing initial mobilization (based on peripheral blood CD34<sup>+</sup> cells count before first day of apheresis, or the total number of CD34<sup>+</sup> cells collected on the first day of apheresis)
- Have failed a prior mobilization attempt (i.e., are poor mobilizers)

Of particular interest are outcomes focused on the ability to mobilize and collect an adequate graft to get patients to autologous SCT, such as total number of CD34 $^{+}$  cells collected during apheresis (the minimal required cell number for a graft is  $2.0 \times 10^6$  CD34 $^{+}$  cells/kg), number of apheresis procedures, proportion of patients who proceed to autologous SCT and survival rate post-SCT).

#### **INTENDED PURPOSE**

The purpose of this recommendation report is to summarize the available data regarding the efficacy of plerixafor in enhancing hamatopoietic stem cell mobilization and collection before autologous stem cell transplantation and to provide recommendations on its use. Evidence on the cost-effectiveness of plerixafor was not considered in this report.

#### **INTENDED USERS**

This recommendation report is intended for all healthcare physicians performing SCT in Ontario, as well as for policy makers, program planners and institutions involved in any STC program or team.

#### RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

#### **RECOMMENDATION 1**

Adding plerixafor to G-CSF is an option for initial mobilization for patients with non-Hodgkin lymphoma or multiple myeloma who are eligible for autologous SCT when chemotherapy cannot be used and only G-CSF mobilization is available.

#### Key Evidence for Recommendation 1

The studies described in the evidence involve patients with non-Hodgkin lymphoma, relapsed or refractory Hodgkin lymphoma, and multiple myeloma. All the patients received G-CSF either alone or as part of the initial mobilization therapy.

- Two randomized controlled trials detected that in patients with non-Hodgkin lymphoma or multiple myeloma, the addition of plerixafor to G-CSF resulted in a greater yield of stem cells and fewer days of apheresis, and allowed more patients to proceed to autologous SCT (auto-SCT) (1, 2).
- Likewise, three nonrandomized trials with historical controls (3-5) reported significantly higher response rates in favour of adding plerixafor.

#### Qualifying Statements for Recommendation 1

- The available evidence used patients receiving G-CSF alone as the control group. Therefore, the option of plerixafor as an up front therapy is specific to patients undergoing initial mobilization with G-CSF without chemotherapy.
- There is insufficient evidence to support the addition of plerixafor to G-CSF after chemotherapy as initial mobilization in patients eligible for autologous SCT.
- Adding plerixafor to G-CSF for initial mobilization therapy when chemotherapy cannot be used and only G-CSF mobilization is available is an option irrespective of the underlying malignancy (i.e., plasma cell dyscrasias [myeloma, amyloidosis], non-Hodgkin and Hodgkin lymphoma, germ cell tumours).
- Using plerixafor up front with G-CSF may not be cost-effective, as this strategy was not examined in this review, particularly if compared with the plerixafor "on demand" strategy as per the second recommendation. Therefore the members of the Working Group have determined that up front use may be an option rather than making a strict recommendation for its routine use when compared with G-CSF alone.

#### Interpretation of Evidence for Recommendation 1

The primary outcomes considered to inform the recommendation include the proportion of patients demonstrating successful apheresis harvest (primary end point  $\geq 5 \times 10^6$  CD34<sup>+</sup> cells/kg), the median collection of CD34<sup>+</sup> cells/kg, and the proportion of patients able to proceed to autologous SCT. The certainty of the evidence on the efficacy of G-CSF plus

plerixafor compared with G-CSF alone as up front mobilization therapy in patients with non-Hodgkin lymphoma or myeloma is good. This recommendation is generalizable to all patients with non-Hodgkin lymphoma or myeloma who have not been mobilized before and are eligible for autologous SCT.

The certainty of the evidence for patients with Hodgkin lymphoma is low and therefore this recommendation cannot be easily generalized to patients with hodkin lymphoma. Only two nonrandomized studies with historical controls reported a significantly greater yield of stem cells with plerixafor, but the proportion of patients that were able to proceed to autologous SCT for each individual group was not reported (3, 5).

#### **RECOMMENDATION 2**

For patients with low peripheral blood CD34<sup>+</sup> cells counts (e.g., <10/uL) at the time of anticipated stem cell harvesting, or with an inadequate first-day apheresis collection, it is recommended that plerixafor be added to the mobilization regimen to maximize stem cell collection and to prevent the need for remobilization.

#### Key Evidence for Recommendation 2

- Seven nonrandomized studies reported a variety of outcomes including numbers of stem cells collected and number of days of apheresis (5-11). These studies in general detect that better mobilization response is achieved in patients failing their first mobilization attempt when plerixafor is added to their current mobilization regimens.
- Additionally, three studies demonstrated that a significant proportion of patients were able to proceed to auto-SCT with plerixafor (7, 10, 11).

#### Qualifying Statements for Recommendation 2

- Poor mobilization has been variably defined in these studies, but <10 CD34<sup>+</sup> cells per μL is
  a commonly used criterion. Historical data and consensus opinion have identified that the
  likelihood of successful stem cell harvest is low among patients with <10 CD34<sup>+</sup> cells/μL.
  In these patients, who appear to be at high risk of failing initial mobilization, a strategy of
  on demand use of plerixafor may prevent the need for remobilization and therefore
  minimize further delays in proceeding to auto-SCT.
- Plerixafor is recommended irrespective of the underlying malignancy (i.e., plasma cell dyscrasias [myeloma, amyloidosis], non-Hodgkin and Hodgkin lymphoma, germ cell tumours).

#### Interpretation of Evidence for Recommendation 2

The primary outcomes considered to inform the recommendation include the proportion of patients demonstrating successful apheresis harvest and the median number of apheresis procedures in patients failing their first mobilization attempt.

The certainty of the evidence on the efficacy of adding plerixafor to current mobilization regimens to maximize stem cell collection is moderate. This recommendation is generalizable to patients eligible for autologous SCT and failing their first mobilization attempt irrespective of the underlying malignancy.

#### **RECOMMENDATION 3**

For patients who have failed a previous mobilization attempt, it is recommended that they undergo remobilization with G-CSF and plerixafor, with or without chemotherapy.

#### Key Evidence for Recommendation 3

Several single-arm studies detected that a significant proportion of patients can still collect enough CD34<sup>+</sup> cells to proceed to auto-SCT with plerixafor and G-CSF with or without chemotherapy (1, 2, 7, 12-20).

#### Qualifying Statements for Recommendation 3

- The definition of failed mobilization in this group of studies is variable and includes patients who have not attained at least the minimum number of CD34<sup>+</sup> cells or patients who had low numbers of circulating CD34<sup>+</sup> cells prior to apheresis. It is recognized that every attempt should be made to collect enough CD34<sup>+</sup> cells in such patients to allow them to proceed to definitive therapy with auto-SCT.
- Plerixafor is recommended irrespective of the underlying malignancy (i.e., plasma cell dyscrasias [myeloma, amyloidosis], non-Hodgkin and Hodgkin lymphoma, germ cell tumours).

#### Interpretation of Evidence for Recommendation 3

The primary outcomes considered to inform the recommendation include successful apheresis harvest, the median number of apheresis procedures, and the proportion of patients that are able to proceed to autologous SCT after remobilization with G-CSF and plerixafor with or without chemotherapy.

The certainty of the evidence on the efficacy of G-CSF plus plerixafor, with or without chemotherapy, to remobilize patients who have failed previous mobilization attempts is moderate. This recommendation is generalizable to patients eligible for autologous SCT that have failed previous mobilization attempts, irrespective of the underlying malignancy.

#### **RELATED GUIDELINES**

- Imrie K, Rumble RB, Crump M. Stem cell transplantation in adults. Toronto (ON): Cancer Care Ontario; 2009 January 30. Program in Evidence-Based Care: Recommendation Report.
   Available at: <a href="https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/951">https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/951</a>
- Kouroukis CT, Rumble RB, Kuruvilla J, Crump M, Herst J, Hamm C. Stem cell transplantation in lymphoma. Toronto (ON): Cancer Care Ontario; 2012 December 13.
   Program in Evidence-Based Care: Recommendation Report SCT-4. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/971
- Kouroukis CT, Rumble RB. Stem cell transplantation in multiple myeloma. Toronto (ON):
   Cancer Care Ontario; 2012 March 29. Program in Evidence-Based Care: Recommendation
   Report SCT-1. Available at: <a href="https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/986">https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/986</a>

#### Recommendation Report SCT-7: Section 2

### Plerixafor for Autologous Hematopoietic Stem Cell Mobilization and Transplantation for Patients in Ontario: Recommendation Report Methods Overview

#### THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

#### JUSTIFICATION FOR RECOMMENDATION REPORT

The initiation of this recommendation report was prompted by the following:

- Plerixafor, a novel mobilization agent, has received notice of compliance from Health Canada, but it has not yet received funding approval for patients in Ontario.
- Plerixafor is used by all provincial transplant programmes without consensus guidelines on best practices. There may be inequity to patients in Ontario as access and funding varies between programs.
- The Cancer Care Ontario Stem Cell Transplantation (CCO-SCT) Committee would like to provide an evidence-based opinion on how the drug should be used by the Ontario SCT programmes

#### RECOMMENDATION REPORT DEVELOPERS

This recommendation report was developed by a Working Group consisting of four haematologists/oncologists and a health research methodologist at the request of the Stem Cell Transplant Committee.

The Working Group was responsible for reviewing the evidence base, drafting the recommendations and responding to comments received during the document review process. Conflict of interest declarations for all authors are summarized in Appendix II, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

#### RECOMMENDATION REPORT DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (21, 22). For Recommendation Reports this process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by a methodology experts and final approval by the Sponsoring Committee.

The PEBC uses the AGREE II framework (23) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the <u>PEBC Document Assessment and Review Protocol</u>. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the <u>PEBC Handbook</u> and the <u>PEBC Methods Handbook</u>.

#### Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation, using the ADAPTE framework (24), or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this document, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), and the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse.
- Electronic Databases: MEDLINE and EMBASE.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument (23). Two guidelines (25, 26) were identified as potentially relevant and considered for full text review and quality assessment using the AGREE II instrument. However, the reporting quality was low, taking into consideration the methods used to search for the evidence, the methods used to formulate the recommendations, and the criteria for selecting the evidence. In addition stakeholder involvement, among other domains needed for undergoing quality assurance, was not reported. For these reasons, the recommendations made in these two guidelines were not considered for endorsement or adaptation and no quality assessment was conducted.

## RECOMMENDATION REPORT REVIEW AND APPROVAL Internal Review

The recommendation report was reviewed by the Director of the PEBC. The Working Group is responsible for ensuring the necessary changes are made. If those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

#### Report Approval by the Stem Cell Transplant Steering Committee

After internal review, the report was presented to the Cancer Care Ontario - Stem Cell Transplant Steering Committee (CCO-SCT). Members of the CCO-SCT reviewed the report, and formally approved the document during a meeting held on Thursday, September 10<sup>th</sup>, 2015.

#### **ACKNOWLEDGEMENTS**

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- Melissa Brouwers, Sheila McNair, and Hans Messersmith for providing feedback on draft versions.
- Kristy Yiu for conducting a data audit.
- Janet Rowe for copy editing.

#### Recommendation Report SCT-7: Section 3

### Plerixafor for Autologous Hematopoietic Stem Cell Mobilization and Transplantation for Patients in Ontario: Evidence Review

#### **INTRODUCTION**

High-dose chemotherapy and autologous stem cell transplantation (SCT) are accepted parts of standard therapy for a variety of hematological malignancies, including non-Hodgkin and Hodgkin lymphoma, multiple myeloma, and germ cell tumours. The benefits of transplant include improvement in disease control and may include an improved overall survival rate. In some situations, autologous transplantation is potentially curative. A necessary step in the process of treating patients with high-dose chemotherapy is the ability to mobilize, collect, and cryopreserve autologous stem cells. Although there are a variety of protocols, stem cell mobilization is usually done using granulocyte-colony stimulating factor (G-CSF) to mobilize peripheral blood CD34<sup>+</sup> stem cells, often with the addition of chemotherapy (e.g., high-dose cyclophosphamide). In some clinical scenarios patients are not able to receive mobilization with chemotherapy and G-CSF and these patients may be at higher risk of failing mobilization. Other risk factors for failing mobilization include previous treatment with multiple lines of chemotherapy or purine analogues, radiation to bone-marrow-containing areas, and patient age - but these factors for the most part remain poorly defined and largely consensus-driven (27).

Plerixafor is a novel mobilization agent and a bicyclam derivative that binds with high affinity to the human C-X-C chemokine receptor type 4 (CXCR4) receptor and disrupts interactions with its cognate ligand stromal cell-derived factor (SDF) 1-alpha. Interruption of the CXCR4/SDF 1-alpha interaction results in mobilization of CD34 $^+$  hematopoietic stem cells to the peripheral blood where they can be collected via apheresis. Plerixafor is absorbed quickly after a subcutaneous injection and, at the recommended dose of 0.24 mg/kg, provides a sustained increase in circulating CD34 $^+$  cells for 10 to 18 hours. Dose adjustments are not needed for patients with hepatic or renal insufficiency and in general the agent is well tolerated. Health Canada approval was granted in December 2011 for use of plerixafor with G-CSF in stem cell mobilization in patients with non-Hodgkin lymphoma or myeloma. In Ontario, plerixafor is currently covered for use with G-CSF in patients with non-Hodgkin lymphoma or myeloma who have suboptimal peripheral blood CD34 $^+$  cells counts after at least four days of G-CSF (CD34 $^+$  count <10/ $\mu$ L), or who have less than half of the required CD34 $^+$  cells after one apheresis procedure, or who have failed a previous apheresis attempt.

In order to make recommendations for clinical practice and to assist Cancer Care Ontario in decision making with respect to this intervention, the Working Group of the Stem Cell Transplant Steering Committee developed this recommendation report. Based on the objectives of the guideline, the members of the Working Group derived the research questions outlined below.

#### **OBJECTIVES AND RESEARCH QUESTIONS**

The main purpose of this report is to evaluate the most current evidence on the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous SCT for patients in Ontario

The members of the Working Group developed the following specific objectives for this report in consultation with the Stem Cell Transplant Expert Panel:

- To assess the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous transplantation for patients who have not been mobilized before (i.e., the case of up front mobilization in naïve patients who may or may not be at risk of being poor mobilizers)
- To assess the efficacy of "just-in-time" salvage plerixafor administration in enhancing hematopoietic stem cell mobilization and collection before autologous transplantation for patients failing mobilization. This is based on data usually collected the day prior or the day of the first planned apheresis procedure (e.g., peripheral blood CD34<sup>+</sup> cells count), or on an inadequate first-day apheresis collection (e.g., <50% of target CD34<sup>+</sup> cells collected)
- To assess the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous transplantation for patients who have failed a prior mobilization regimen (i.e., poor mobilizers)

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives:

- Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients who have not been mobilized before, when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients failing mobilization when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?
- Does the administration of plerixafor in combination with G-CSF for stem cell mobilization before autologous transplantation improve the outcome of patients who have failed a prior mobilization regimen when compared with G-CSF for stem cell mobilization alone or in combination with chemotherapy?

#### **METHODS**

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

#### Search for Existing Systematic Reviews

The Cochrane Database of Systematic Reviews was searched from January 2009 to April 2014 using the word "plerixafor". Systematic reviews older than six years were considered not relevant, because the main goal of a search for systematic reviews is to identify recent secondary sources covering the primary literature that may be helpful in the development of these recommendations.

Systematic reviews were included if:

- 1. The existing systematic review searched for studies evaluating the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection in adult or pediatric patients considered for autologous stem cell transplantation.
- 2. The literature search strategy for the existing review was reproducible and appropriate.

3. The existing systematic review reported the sources searched as well as the dates that were searched.

Identified systematic reviews that met the eligibility criteria would be assessed using the AMSTAR tool (28) to determine whether or not an existing review could be incorporated as part of the evidentiary base. Any identified reviews that did not meet the criteria above, whose AMSTAR assessments indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

#### Search for Primary Literature Literature Search Strategy

The MEDLINE (Ovid) (1996 through April 18, 2014) and EMBASE (Ovid) (1996 through Week 16, 2014) databases were searched for evidence in April 2014 and updated in March 2015. The search strategy included a logical combination of terms for the condition (stem cell transplantation), the intervention (plerixafor), and studies of interest (systematic reviews, clinical trials, nonrandomized studies with an appropriate control group). The full literature strategy used to retrieve potential relevant studies is presented in Appendix 1.

#### Study Selection Criteria and Protocol

Inclusion Criteria

Articles identified in this literature search were eligible for inclusion if they met the following criteria:

- 1. Primary studies evaluating the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation
- 2. Published full-report articles of randomized control trials and nonrandomized studies with an appropriate contemporaneous control group
- 3. Studies reporting the outcomes of interest such as number of CD34<sup>+</sup> cells collected, number of apheresis procedures, proportion of patients who proceed to autologous SCT, and survival rate post-SCT

#### Exclusion Criteria

Studies were excluded if they were:

- 1. Abstracts, letters, case reports, comments, books, notes, or editorial-type publications
- 2. Because resources were not available for translation services, articles published in a language other than English

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (NV), and the reference list from these sources was searched for additional trials. For those items that warranted full text review, one reviewer (NV) assessed each item independently.

#### Data Extraction

Data extraction was conducted by one reviewer (NV). All extracted data and information was assessed by a second reviewer (TK), and audited by an independent auditor (KY) to verify the accuracy of the information obtained from the studies included in this report. For primary studies, key characteristics, including author, year of publication, study design, sample size, treatment arms, plerixafor indication/diagnosis, intervention and mobilization regimen, and years of data collection were extracted. Outcomes of interest

including number of CD34<sup>+</sup> cells collected, number of apheresis procedures, proportion of patients who proceed to autologous SCT, survival rate post SCT, and survival rate in untransplanted patients were extracted when available.

#### Assessment of Study Quality

For systematic reviews that would be used as the sole evidence base for our recommendations, the AMSTAR tool would be used to assess quality. For clinical practice guidelines (CPGs), the AGREE II instrument would be used to assess quality. However, because of the time and effort necessary to properly implement the AGREE II instrument, it would be used only if adaptation of the recommendations was considered feasible by the members of the Working Group given the nature and coverage of the guideline and an informal assessment of the guideline's methods. Where recommendations from CPGs were not adapted, the evidence base in those CPGs would be informally assessed for completeness, and any relevant evidence within would be considered as a basis for recommendations in this report. Any metaanalysis would be assessed for quality using similar criteria as used for randomized controlled trials (RCTs), where appropriate. RCTs would be assessed for quality by examining the following seven criteria: method of randomization, reporting of blinding, power and sample size calculation, length of follow-up, reporting details of the statistical analysis, reporting on withdrawals to treatment and other losses to follow-up, and reporting on the sources of funding for the research. Comparative, nonrandomized, and single-arm evidence would be assessed according to full reporting of the patient selection criteria, the interventions each patient received, all relevant outcomes, and the source of funding. All authors reviewed and discussed a draft of this report with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs, according to the policy of the PEBC.

#### **RESULTS**

#### **Search for Existing Systematic Reviews**

The Cochrane Collaboration released a systematic review protocol in 2013 to evaluate the efficacy and safety of plerixafor for the mobilization of hematopoietic stem cells in people with non-Hodgkin lymphoma, Hodgkin lymphoma, or multiple myeloma and with the indication for autologous transplantation (29), but a full report has not been published yet. No other relevant systematic reviews were identified.

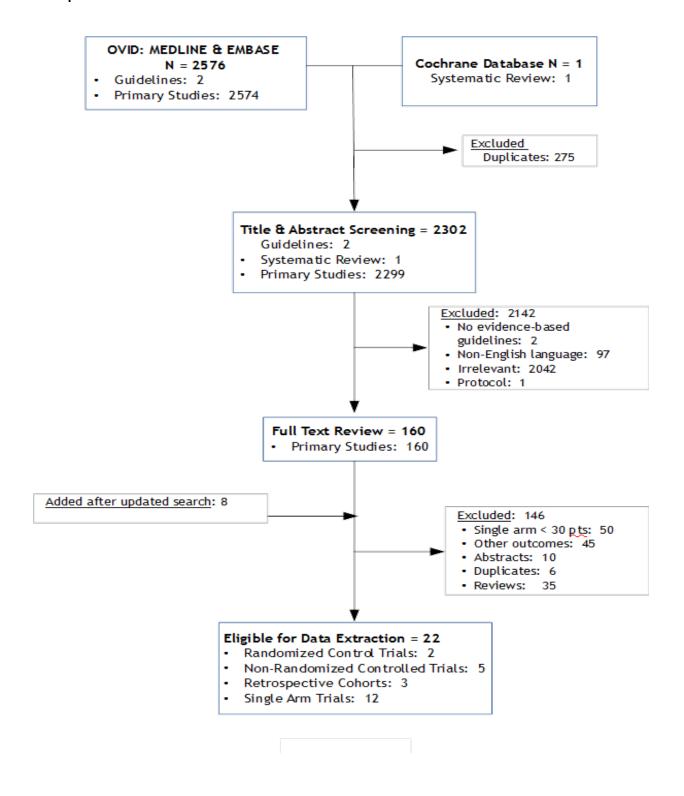
#### Systematic Review of the Primary Literature Literature Search Results

While reviewing the primary literature few studies were identified that met the initial inclusion criteria, and therefore a post hoc subset of nonrandomized studies with historical groups was included, because these types of studies would help to inform the recommendations. Similarly, due to the shortage of comparative studies assessing the efficacy of plerixafor in both patients failing mobilization prior to autologous stem cell transplantation, and patients who have failed a prior mobilization regimen, the inclusion criteria for this population was expanded to include single-arm studies with a sample size of at least 30 participants.

As presented in Figure 1, out of 2576 titles and abstracts identified in the search of the MEDLINE and EMBASE databases, 2302 appeared potentially eligible on initial review, and 160 of these were verified to be eligible for full text review. Eight additional studies were included for full text review based on the updated search in 2015. From these, 22 full-report studies were identified that evaluated the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation, and

reported the outcome of interest. The remaining 146 studies were excluded because they failed to pass the inclusion criteria.

Figure 1. Selection of studies investigating the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation.



#### **Study and Patient Characteristics**

The systematic review identified 22 studies assessing the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation, and reporting the outcomes of interest (number of CD34<sup>+</sup> cells collected, number of apheresis procedures, proportion of patients who proceed to autologous SCT, and survival rate post-SCT): two randomized controlled trials (1, 2), five nonrandomized controlled trials (3, 5, 8, 30, 31), three retrospective cohort studies with a contemporaneous control arm (4, 7, 10), and 12 single-arm studies (6, 9, 11-20).

Seven trials evaluated the efficacy of plerixafor for up front mobilization in patients who have not been mobilized before. Six of these trials were carried out in the USA (1-3, 30-32) and one was conducted in Italy (5). Fifteen trials assessed the efficacy of plerixafor for "just-in-time" or "salvage" therapy for patients who appear to be failing mobilization or patients who have failed a prior mobilization attempt (1, 2, 5, 9-20).

Overall, the number of patients reported in each paper ranged from a low of 35 patients in the single-arm study reported by Arcaini et al. (12) to a high of 580 in the nonrandomized controlled trial reported by Hübel et al. (17). The included studies involved patients with multiple myeloma, non-Hodgkin lymphoma, or Hodgkin lymphoma. See Table 1 for details.

#### Study Design and Quality

Quality was assessed according to the criteria described in the methods section. See Table 1 below for details on the patient selection criteria, peripheral blood stem cell mobilization regimen, sample size, and outcome reported.

Because the two identified guidelines (25, 26) failed to report the methods used for developing their recommendations, the members of the Working Group decided that adaptation was not feasible, and therefore, a formal assessment of quality using the AGREE II instrument was not performed.

The two RCTs reported by DiPersio et al. (1, 2) were Phase III, multicentre, doubleblind trials with random allocation schemes and involving patients with non-Hodgkin lymphoma or multiple myeloma. In the lymphoma study (1), patients were randomized one to one. but other details are not reported. In the myeloma study (2), patients were stratified by study centre, baseline platelet count, and type of transplantation planned. Both the lymphoma and the myeloma study required a sample size of 93 patients per group to achieve 80% power to measure a difference of 20% in the primary end point of collecting ≥5x10<sup>6</sup> CD34<sup>+</sup> cells/kg in  $\leq 4$  apheresis days; both studies met this sample size requirement. The Pearson  $X^2$ test (unstratified) was used in both studies to compare the proportion of patients meeting the primary (≥5x10<sup>6</sup> CD34<sup>+</sup> cells/kg in ≤4 apheresis days) and secondary (≥2x0<sup>6</sup> CD34<sup>+</sup> cells/kg in ≤4 apheresis days) end points between the groups. The Cochran-Mantel-Haenszel test (stratified by study centre) was used for additional analysis in both studies, and the Kaplan-Meier method was used to estimate the time to achieving the CD34<sup>+</sup> cell target. These RCTs were supported by research funding from Genzyme Corporation (formerly AnorMed Inc) of Cambridge, Massachusetts. Continuous variables were summarized with medians and standard deviation and categorical variables were summarized with total and percentages.

Five nonrandomized controlled trials (3, 5, 10, 30, 31) included in this review had fully described the inclusion and exclusion criteria, mobilization protocol, and outcomes of interest. Four of these studies compared outcomes with matched historical controls mobilized with a therapy not including plerixafor (3, 5, 30, 31). Genzyme Corporation of Cambridge, Massachusetts, provided financial support to the studies reported by Cashen et al. (3), Shaughnessy et al. (31), and Perkins et al. (10). The study reported by Chaudhary et al. (30) was supported by two grants: an American Society for Blood and Marrow Transplantation New

Investigator Award and a Career Development Award from the American Society of Clinical Oncology's Conquer Cancer Foundation (to author Mehdi Hamadani). The study reported by Milone et al. (5) did not report any source of finding. Three additional studies also reported on patients failing mobilization (1, 2, 5).

Twelve single-arm trials (6, 9, 11-20) were also included in this review to inform recommendations for both patients failing mobilization prior to autologous stem cell transplantation and/or patients who have failed a prior mobilization attempt. In all the studies the patients were fully described, and were representative of the population of interest. In all studies the mobilization regimen was consistent with what would be used in Ontario clinical practice. Eight of these studies (12, 13, 15-18, 20, 33) included patients enrolled in a European compassionate-use programmme (CUP), a program for patients who had previously failed conventional mobilization attempts. A full description of the inclusion and exclusion criteria was reported for all of the studies. Malard et al. (20) acknowledged the financial support of Genzyme Corporation for their help in data collection; Arcaini et al. (12) reported no funding; Hubel et al. (17) acknowledged Genzyme Inc. for data acquisition and for taking part in the discussion, and declared that even though the authors have also acted as consultants to Genzyme, their opinions did not necessarily reflect the recommendations of Genzyme; and Basak et al. (13, 33) acknowledged Genzyme Corporation for providing plerixafor free of charge, within the CUP. The studies reported by Duarte et al. (16) and Calandra et al. (15) did not report any source of funding, but some of the authors were reported to have received honoraria from Genzyme. The remaining three trials were independent studies conducted in educational centres in Finland (9) and the USA (11, 19). Selection of patients was based on low peripheral blood CD34<sup>+</sup> cells count or poor yield of the first apheresis procedure. The mobilization regimens were well described, as were the outcomes of median collection, percentage of patients meeting the primary end point of achieving the CD34<sup>+</sup> cell target, and number of apheresis procedures. A Cancer Center Support Grant from the National Institutes of Health supported the study reported by Smith et al. (11). None of the other three studies (6, 9, 19) reported any source of funding.

The reported outcomes included the proportion of patients reaching at least 2x10<sup>6</sup> numbers of CD34<sup>+</sup> cells/kg, median CD34<sup>+</sup> cell collection and range, and number of apheresis procedures. Some studies reported the number and proportion of patients who proceeded to autologous SCT (auto-SCT) and who survived at 12-month follow-up.

Overall, the quality assessment performed found all of the above plerixafor trials to be of acceptable quality given the nature of their study design.

Table 1. Summary of the studies assessing the efficacy of plerixafor in enhancing hematopoietic stem cell mobilization and collection before autologous stem cell transplantation.

Study [study years]	Treatment Allocation	Pts #	Population	PBSC Mobilization Regimen	Outcome Reported
Randomized Cont	rolled Trials				
DiPersio et al., 2009a (1) [Jan 2005 to Aug 2006]	G-CSF + plerixafor	150	Non-Hodgkin lymphoma	Prior to the first day of apheresis (days 1-4)  G-CSF: 10 µg/kg a.m. /4 days Plerixafor: 240 µg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 µg/kg a.m. Apheresis  After first day of apheresis (day 5-) Plerixafor (p.m.), G-CSF (a.m.), and apheresis daily for up to 3 days or until ≥5x106 CD34+ cells/kg collected	Patients not mobilized before: successful apheresis (primary and secondary end point of ≥5x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg, and ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg, respectively), number of apheresis days, CD34 <sup>+</sup> cells collection, auto- SCT, 12-month post-SCT survival
	G-CSF + placebo	148		Prior to the first day of apheresis (days 1-4)  o G-CSF: 10 µg/kg a.m. /4 days  o Placebo on day 4  Apheresis Day (day 5)  o G-CSF: 10 µg/kg a.m.  o Apheresis  After first day of apheresis (day 5-)  o Placebo, G-CSF, and apheresis daily for up to 3 days or until ≥5x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis (primary and secondary end point of ≥5 X 106 CD34 <sup>+</sup> cells/kg, and ≥2 X 106 CD34 <sup>+</sup> cells/kg, respectively), apheresis days, auto-SCT, 12-month post-SCT survival

					rate
DiPersio et al., 2009b (2) [Feb 2005 to July 2006]	G-CSF + plerixafor  G-CSF + placebo	148	Multiple myeloma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis  Postapheresis (day 5- ) Plerixafor (p.m.), G-CSF (a.m.), and Apheresis: daily for up to 3 days or until ≥6x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected  Prior to the first day of apheresis (days 1-4) G-CSF: 10 μg/kg a.m. /4 days Placebo on day 4  Apheresis Day (day 5)	Patients not mobilized before: successful apheresis, apheresis days, CD34* cells collection, auto-SCT, 12-month post-SCT survival rate  Patients who failed prior mobilization regimen: successful apheresis, apheresis days, auto-SCT, 12-month post-SCT survival rate
				Apheresis Day (day 5)  o G-CSF: 10 µg/kg a.m. o Apheresis  After first day of apheresis (day 5- ) o Placebo, G-CSF, and apheresis daily for up to 3 days or until ≥6x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	race
Nonrandomized T	rials - Historical Con	trolled Gr	oup		•
Cashen et al., 2008 (3) [1998 to 2003]	G-CSF + plerixafor +	22	Relapsed or refractory Hodgkin lymphoma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5)	Patients not mobilized before: successful apheresis, apheresis days,

	G-CSF*	98	Hodgkin lymphoma	<ul> <li>G-CSF: 10 μg/kg a.m.</li> <li>Apheresis after G-CSF</li> <li>Postapheresis (day 5- )</li> <li>Plerixafor (p.m.), G-CSF (a.m.), and apheresis:         <ul> <li>Daily for up to 5 consecutive days or until ≥5 X</li> <li>10<sup>6</sup> CD34<sup>+</sup> cells/kg collected</li> </ul> </li> <li>NR</li> <li>Successful Mobilization Criterion: ≥2 X 10<sup>6</sup> CD34<sup>+</sup> cells/kg</li> </ul>	CD34 <sup>+</sup> cells collection, auto- SCT, 12-month post-SCT survival rate
Milone et al., 2014 (5) [Apr 2012 to May 2013] [Jan 2000 to Jan 2009]	CTX + G-CSF + plerixafor on demand  CTX + G-CSF*	240	Multiple myeloma, lymphoma	<ul> <li>CTX (4 g/m²) or DHAP†</li> <li>G-CSF (5-10 μg/kg) on day 3</li> <li>Plerixafor on demand: 240 μg/kg‡</li> <li>CTX (4 g/m²) or DHAP†</li> <li>G-CSF (5-10 μg/ kg) on day 3</li> </ul>	Patients not mobilized before: successful apheresis, apheresis days, CD34+ cells collection, auto-SCT  Patients who seem to mobilize poorly to current regimens: successful apheresis, apheresis days
Shaughnessy et al., 2011 (31) [July 2008 toJan 2009]	G-CSF + plerixafor	33	Non-Hodgkin lymphoma, multiple myeloma, relapsed Hodgkin disease	Prior to the first day of apheresis (days 1-4)  o G-CSF: 10 μg/kg a.m. /4 days o Plerixafor: 240 μg/kg p.m. on day 4  After first day of apheresis (day 5) o G-CSF: 10 μg/kg a.m. /5 days o Plerixafor: 240 μg/kg p.m. /4 days or until ≥5 X	Patients not mobilized before: successful apheresis, apheresis days, CD34 <sup>+</sup> cells collection, auto-

	CTX + G-CSF*	33		10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected for NHL or HD and ≥6 X 10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected for patients with MM  Prior to the first day of apheresis ○ CTX: 3-5 g/m <sup>2</sup> on day 1 ○ G-CSF: 10 μg/kg on days 2-9  After first day of apheresis (day 10) ○ G-CSF: 10 μg/kg a.m. /6 days	SCT
Chaudhary et al., 2013 (30) [April 2010 to Sept 2012]	G-CSF + plerixafor	33	Multiple myeloma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis after G-CSF  Postapheresis (day 5- ) Plerixafor (p.m.), G-CSF (a.m.), and apheresis: daily for up to 3 additional apheresis sessions	Patients not mobilized before: successful apheresis, apheresis days, CD34+ cells collection
[Jan 2003 to March 2010]	CT + G-CSF	74		<ul> <li>CTX 1.5 gm/m² on day 1</li> <li>G-CSF 10 µg/kg on day 8 until completion of apheresis</li> <li>Successful Mobilization Criterion: ≥2x10<sup>6</sup> CD34<sup>+</sup> cells/kg</li> </ul>	
Hundemer et al., 2014 (8) [2009 to 2010]	CT + G-CSF + plerixafor on demand	60	Multiple myeloma	<ul> <li>CT<sup>S</sup></li> <li>G-CSF: 10 μg/kg a.m. until the end of the stem cell collection</li> <li>Plerixafor after the first apheresis session</li> </ul>	Patients who seem to mobilize poorly to current regimens: CD34* cells collection, apheresis days

	CT + G-CSF	45		<ul> <li>CT<sup>§</sup></li> <li>G-CSF: 10 μg/kg a.m. until the end of the stem cell collection</li> </ul>	
Retrospective Coh	ort Studies - Conten	nporaneou	s Control Group		
Perkins et al., 2012 (10) [Nov 2000 to July 2009]	G-CSF + plerixafor CT + G-CSF	38 15	Non-Hodgkin lymphoma, multiple myeloma, Hodgkin lymphoma	<ul> <li>G-CSF: 10 μg/kg /4 days</li> <li>Plerixafor: 240 μg/kg p.m. on day 4</li> <li>Apheresis, G-CSF, plerixafor on day 5 until completion of apheresis</li> <li>CT** + G-CSF 5 μg/kg/day, starting on the day after the last CT dose and continued until completion of apheresis</li> </ul>	Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34 <sup>+</sup> cells collection, apheresis days, auto-SCT
	G-CSF ± GM-CSF	43		<ul> <li>G-CSF 10-20 μg/kg ± GM-CSF 10μg/kg/4 days</li> <li>Apheresis + G-CSF ± GM-CSF on day 5 until completion of apheresis</li> </ul>	
Kim et al., 2014 (4) [Jan 2008 toApr 2011]	G-CSF + plerixafor G-CSF	25 25	Multiple myeloma	<ul> <li>G-CSF: 10 μg/kg a.m. /5 days</li> <li>Plerixafor: 0.24 mg/kg on day 4 for up to 4 days</li> <li>G-CSF: 10 μg/kg a.m. /5 days</li> </ul>	Patients not mobilized before: apheresis days, CD34+ cells collection
Cheng et al., 2015 (7) [2009 to 2012]	CT +G-CSF + plerixafor	23	Multiple myeloma	<ul> <li>CT</li> <li>G-CSF: 5-10 μg/kg a.m. until the end of the stem cell collection period</li> <li>Plerixafor: about 12 hours before the apheresis procedure</li> </ul>	Patients who seem to mobilize poorly to current regimens and patients who failed prior mobilization: apheresis days,
	CT + G-CSF	23		<ul> <li>CT<sup>††</sup></li> <li>G-CSF: 5-10 µg/kg a.m. until the end of the stem cell collection period</li> </ul>	CD34 <sup>+</sup> cells collection, number of patients

					proceeding to auto- SCT
Single-arm Trials					
Hübel et al., 2011 (18) [May 2008 to Aug. 2009]	G-CSF + plerixafor <sup>#</sup>	60	Non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, Ither diseases <sup>§§</sup>	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis 1 hour after G-CSF  Postapheresis (day 5-) Plerixafor (p.m), G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected, or up to a maximum of 7 days of plerixafor injections  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34 <sup>+</sup> cells collection, apheresis days, auto-SCT
Hübel et al., 2012 (17) [May 2008 to Aug. 2009]	G-CSF + plerixafor <sup>#</sup>	580	Non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis 1 hour after G-CSF Plerixafor (p.m.)  Postapheresis (day 6-) G-CSF (a.m.), apheresis, and plerixafor (p.m.): Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or up to a maximum of 7 days of plerixafor injections  Successful Mobilization Criterion: ≥2 X 10 <sup>6</sup> CD34 <sup>+</sup>	Patients who failed prior mobilization regimen: successful apheresis, CD34+ cells collection, apheresis days

				cells/kg	
Calandra et al., 2008 (15)	G-CSF + plerixafor <sup>‡‡</sup>	115	Non-Hodgkin lymphoma, multiple myeloma, Hodgkin disease	Pre-Apheresis (days 1-4)  □ G-CSF: 10 μg/kg a.m. /4 days □ Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) □ G-CSF: 10 μg/kg a.m. □ Apheresis after G-CSF  Postapheresis (day 5- ) □ Plerixafor (p.m.), G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or mobilization failure as determined by the investigator  □ Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34* cells collection, apheresis days, auto-SCT
Malard et al., 2012 (20) [Jun 2008 to Aug 2010]	G-CSF + plerixafor <sup>#</sup>	83	Non-Hodgkin lymphoma, multiple myeloma	Pre-Apheresis (days 1-4)  ∘ G-CSF: 10 μg/kg a.m. /4 days  ∘ Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5)  ∘ G-CSF: 10 μg/kg a.m.  ∘ Apheresis 1 hour after G-CSF  Postapheresis (day 5- )  ∘ Plerixafor (p.m.), G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or a maximum of 7 plerixafor injections  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34* cells collection, apheresis days
Duarte et al., 2011 (16)	G-CSF + plerixafor <sup>‡‡</sup>	56	Lymphoma, multiple myeloma	Pre-Apheresis (days 1-4)  ο G-CSF: 10 μg/kg a.m. /4 days ο Plerixafor: 240 μg/kg p.m. on day 4	Patients who failed prior mobilization regimen: successful apheresis, CD34*

				Apheresis Day (day 5)  □ G-CSF: 10 μg/kg a.m. □ Apheresis 1 h after G-CSF  Postapheresis (day 5- ) □ Plerixafor (p.m., G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or mobilization failure as determined by the investigator  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	cells collection, apheresis days, auto-SCT
Arcaini et al., 2011 (12) [2008 to 2009]	G-CSF + plerixafor <sup>‡‡</sup>	35	Non-Hodgkin lymphoma, Hodgkin lymphoma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis 1 hour after G-CSF  Postapheresis (day 5- ) Plerixafor (p.m.), G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or mobilization failure as determined by the investigator  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34* cells collection, apheresis days, auto-SCT
Smith et al., 2013 (11) [Jan 2009 to March 2011]	CT + G-CSF + plerixafor	38	Non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma	<ul> <li>G-CSF: 10 μg/kg 24 h after CT</li> <li>Plerixafor: 240 μg/kg 12±2hr before apheresis</li> <li>G-CSF was continued concurrently with plerixafor until apheresis was complete</li> <li>Successful Mobilization Criterion: ≥2x10<sup>6</sup> CD34<sup>+</sup> cells/kg</li> </ul>	Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34 <sup>+</sup> cells collection, apheresis days, auto-SCT

	<u> </u>	<u> </u>			
Jantunen et al., 2011 (9) [Aug 2009 to Oct 2010]	CT + G-CSF + plerixafor	63	Lymphoma, multiple myeloma, Hodgkin lymphoma	<ul> <li>Chemotherapy</li> <li>G-CSF</li> <li>Plerixafor: 12-24 mg / injection</li> <li>Successful Mobilization Criteria: ≥2x10<sup>6</sup> CD34<sup>+</sup> cells/kg and ≥4x10<sup>6</sup> CD34<sup>+</sup> cells for patients with myeloma &lt;65 years old</li> </ul>	Patients who seem to mobilize poorly to current regimens: successful apheresis, CD34* cells collection, apheresis days
Basak et al., 2011 (13)	G-CSF + plerixafor <sup>#</sup>	76	Multiple myeloma	Pre-Apheresis (days 1-4)  □ G-CSF: 10 μg/kg a.m. /4 days  □ Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5)  □ G-CSF: 10 μg/kg a.m.  □ Apheresis 1 hour after G-CSF  Postapheresis (day 5- )  □ Plerixafor (p.m), G-CSF (a.m.), and apheresis: Daily until ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg collected or mobilization failure diagnosed  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34* cells collection, apheresis days
Lor et al., 2012 (19) [Jan 2008 to Dec 2009]	G-CSF + plerixafor	33	Non-Hodgkin lymphoma, multiple myeloma	PreApheresis (days 1-4)  G-CSF (filgrastim): 10 μg/kg a.m. day 1 Plerixafor: 24 μg/kg p.m. on day 4  Apheresis Day (day 5)  Postapheresis (day 5- ) Plerixafor (p.m.), filgrastim (a.m.), and apheresis: until sufficient number of CD34 <sup>+</sup> cells attained or a certain number of days had elapsed Patients who received more than 5 doses of	Patients who failed prior mobilization regimen: successful apheresis, CD34+cells collection, apheresis days

				plerixafor and did not achieve the minimum CD34 <sup>+</sup> cell yield were allowed to receive another mobilization regimen of filgrastim plus plerixafor after a washout period of at least 11 days  Successful Mobilization Criterion: ≥2x10 <sup>6</sup> CD34 <sup>+</sup> cells/kg	
Basak et al., 2011 (14)	G-CSF + plerixafor <sup>#</sup>	61	Non-Hodgkin lymphoma, multiple myeloma, Hodgkin lymphoma	Pre-Apheresis (days 1-4)  G-CSF: 10 μg/kg a.m. /4 days Plerixafor: 240 μg/kg p.m. on day 4  Apheresis Day (day 5) G-CSF: 10 μg/kg a.m. Apheresis 1 hour after G-CSF  Postapheresis (day 5-) Plerixafor (p.m.), G-CSF (a.m.), and apheresis: Up to 3 days of plerixafor administration or until ≥20 CD34⁺ cells/μL collected  Successful Mobilization Criterion: ≥2x106 CD34⁺ cells/kg	Patients who failed prior mobilization regimen: successful apheresis, CD34* cells collection, apheresis days, auto-SCT
Abhyankar et al., 2012 (6) [April 2009 to Dec 2010]	G-CSF + plerixafor on demand	159	Multiple myeloma (79), lymphoma (76), Germ cell tumours (3), Ewing's sarcoma (1)	<ul> <li>Days 1-4:         <ul> <li>G-CSF: 10 μg/kg a.m.</li> </ul> </li> <li>CD34+ cell count (day 5)         <ul> <li>G-CSF and plerixafor on demand (240 μg/kg) daily until the adequate number of CD34<sup>+</sup> cells was collected</li> </ul> </li> <li>Successful Mobilization Criterion: ≥2.5x10<sup>6</sup> CD34<sup>+</sup> cells/kg</li> </ul>	Patients who seem to mobilize poorly to current regimens: CD34+ cells collection, apheresis days,

CTX (chemotherapy with cyclophosphamide); DHAP (dexamethasone, cytarabine, cisplatin); G-CSF (granulocyte colony-stimulating factor); GM-CSF (granulocyte macrophage colony-stimulating factor); MM (multiple myeloma); NR (not reported); PBSC (peripheral blood stem cells); Pts (patients); SCT (stem cell transplantation).

\*\* Chemotherapy regimens include: (1) cyclophosphamine 50 mg/kg/2 days; (2) cyclophosphamine 50 mg/kg/2 days + etopisode 300 mg/m²/ 2days; or (3) etopisode 100 mg/m² on days 1-3, ifosfamide and mesna 5 g/m² each on day 2 (followed by mesna 10 g on day 3), and carboplatin AUC 5 on day 2

<sup>\*</sup> Historical control population

<sup>†</sup> Dexamethasone 40 mg/4d, cytarabine 2 g/m² on day 2, cisplatin 100 mg/m² or oxaliplatin 130 mg/m² on day 1

<sup>&</sup>lt;sup>‡</sup> A second and third dose of plerixafor was administered only in patients demonstrating a good response (>0.01x10<sup>9</sup> CD34\*cells/L) to plerixafor and needing further apheresis to reach a total of 2x10<sup>6</sup> CD34\*cells/kg

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<sup>&</sup>lt;sup>††</sup> CAD (1000 mg/m²/day cyclophosphamide on day 1; 15 mg/m²/day adriamycin on days 1-4; 40 mg/day dexamethasone on days 1-4);, cyclophosphamide (200 mg/m²/day cyclophosphamide on Days 1 and 2), VCD (q.3 mg/m²/day bortezomib on days 1, 4, 8, and 11; 900 mg/m²/day cyclophosphamide on day 1; 40 mg/day dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12), CD (1000 mg/m²/day cyclophosphamide on day 1, 40 mg/day dexamethasone on days 1-4), and RD (25 mg/day lemalidomide on days 1-21; 20 mg/day dexamethasone on days 1-4, 9-12, and 17-29)

<sup>&</sup>lt;sup>‡‡</sup> Centres participating in the program of compassionate use of plerixafor were also able to combine chemotherapy with G-CSF and plerixafor for mobilization

<sup>§§</sup> Seven children suffering from Wiskott-Aldrich syndrome and neuroblastoma, and six patients with other malignant diseases (1 seminoma, 1 germ cell tumour, 1 thyroid carcinoma, 1 testicular carcinoma, 1 composite lymphoma, and 1 chronic lymphocytic leukemia)

## Outcomes: Patients who have Not Been Mobilized Before (Table 2) Number of CD34\* Cells Collected

The two RCTs reported by DiPersio et al. (2009a,b) detected a statistically significant difference in mobilization rates in favour of regimens using plerixafor over conventional mobilization treatment for both patients with non-Hodgkin lymphoma  $(59.3\% \text{ versus } 19.6\%; p<0.001 \text{ and } 86.7\% \text{ versus } 47.3\%; p<0.001 \text{ for patients collecting } <math>\geq 5 \times 10^6 \text{ and } \geq 2 \times 10^6 \text{ CD34}^+ \text{ cells}$ , respectively) (1) and patients with multiple myeloma  $(71.6\% \text{ versus } 34.4\%; p<0.001 \text{ for patients collecting } \geq 6 \times 10^6 \text{ CD34}^+ \text{ cells/kg})$  (2). Similarly, four nonrandomized trials, using historical controls (3, 5, 30, 31), reported a statistically significant increase in the proportion of patients collecting CD34+ cells in favour of mobilization therapies using plerixafor when compared with conventional therapies (ranging from 68% to 94% versus 15% to 76%, respectively). The two RCTs reported by DiPersio et al. (1, 2) are the current best evidence from research, due to the quality of their study design.

#### Number of Apheresis Procedures

One RCT reported by DiPersio et al. (2) and two trials with historical controls demonstrated the ability of regimens with plerixafor to significantly reduce the time needed to collect the target number of CD34 $^{+}$  cells, when compared with conventional mobilization therapies (1 versus 4; p<0.001) (2), (1.61 versus 1.43; p=0.04) (5), and (3 versus 2;<0.0001)(4). Two trials with historical controls reported no differences in the time of collection between groups (30, 31).

#### Peripheral Blood CD34<sup>+</sup> Cells Counts

Five studies reported a statistically significant increase in the number of CD34 $^{+}$  cells collected after mobilization using plerixafor when compared with conventional mobilization therapies. The reported CD34 $^{+}$  medians were 10.96 versus 6.18; p<0.001 (2), 6.2 versus 3.0; p<0.001 (3), 8.0 versus 6.65; p=0.03 (5), 11.6 versus 7.0; p=0.001 (30), and 7.4 versus 13.2; p=0.0007 (4). Shaughnessy et al. (31) reported a nonsignificant difference between groups (10.7 versus 11.6 for plerixafor and conventional therapy, respectively; p=0.5). DiPersio et al. (1) reported a higher number of CD34 $^{+}$  cells associated with plerixafor mobilization strategy (5.69 versus 1.98) but statistical significance was not reported.

#### Proportion of Patients who Proceed to Auto-SCT

Only the RCT reported by DiPersio et al. (1) detected a statistically significant difference in the proportion of patients undergoing auto-SCT in favour of plerixafor regimens over mobilization therapy using G-CSF only (90% versus 55.4%; p<0.001). None of the other comparative studies reported statistically significant differences between groups (2, 3, 5, 30-32).

#### Survival Rate Post-SCT

Only two studies, the RCTs reported by DiPersio et al. (1, 2) reported on 12-month survival rate after transplantation for both groups (mobilization therapy using G-SCF alone, and with added plerixafor), but the statistical difference between rates was not reported. None of the other studies reported on this outcome (3-5, 30-32).

Table 2: Summary of the outcomes reported by studies assessing the efficacy of plerixafor in patients who have not been mobilized before.

Study	Treatment Arms: Pts	Diagnosis	Successful Aph	nstrating a neresis Harvest (%)	Apheresis [Range]	Median Collection CD34+ x106 Cells/kg /Days of	Proceeded to Auto-SCT	12- month Post-SCT
			≥5x10 <sup>6</sup> CD34 <sup>+</sup> Cells/kg	≥2x10 <sup>6</sup> CD34 <sup>+</sup> Cells/kg		Apheresis [Range]	7.000	Survival Rate
Randomized	Controlled Tria	als						
DiPersio et al., 2009a (1)	G-CSF + plerixafor: 150	Non-Hodgkin lymphoma	89 (59.3%)	130 (86.7%)	Median*: 3 days Median†: 1	5.69 [0.03 - 29.22]	135 (90%)	119 (88.1%)
	6.655		29 (19.6%)	70 (47.3%)	day	1.98 [0.06 - 15.00]	82 (55.4%)	
	G-CSF + placebo: 148		p<0.001	p<0.001	Median <sup>‡</sup> Median <sup>†</sup> : 3 days		p<0.001	71 (86.6%)
DiPersio et al., 2009b (2)	G-CSF + plerixafor: 148	Multiple myeloma	106 (71.6%) <sup>§</sup> 112 (75.7%) <sup>**</sup>	NR	1.0 <sup>§</sup>	10.96 [0.66 - 104.57]	142 (95.9%)	141 (95.3%)
(2)	G-CSF + placebo: 154		53 (34.4%) <sup>§</sup> 79 (51.3%)**		4.0**	6.18 [0.11 - 42.66]	136 (88.3%)	148 (96.1%)
	placebo. 131		p<0.001 <sup>§</sup> p<0.001**		p<0.001	p<0.001	(00.3%)	(70.170)
Nonrandomiz	zed Trials - Hist	torical Control Group	D	1			l	
Cashen et al., 2008 (3)	G-CSF + plerixafor: 22	Relapsed or refractory Hodgkin	15 (68%)	21 (95%)	2.5	6.2 [0.6 - 10.4]/ 1-2 d	21 (95%)	21 (95%)
		lymphoma	15 (15%)	76 (78%);	2.9			
	G-CSF: 98		p<0.001	p=0.071	NS	3.0 / 1-2 d of apheresis	NR	NR
						p<0.001		

Milone et al., 2014 (5)	CTX or DHAP + G-CSF + plerixafor on demand <sup>††</sup> : 102	Multiple myeloma and lymphoma	86% MM 80% L	98 (96%) 70 (97%) MM 28 (93%) L	1.61	8.0 9.43 MM 7.0 L	52 (51%)	NR
	G-CSF + CTX or DHAP:		NR	188 (83%) 153 (85%) MM 35 (73%) L	1.43	6.65	NR	
	228			p=0.0008 p=0.006 MM p=0.02 L	p=0.04	p=0.03		
Shaughnessy et al., 2011 (31)	G-CSF +pPlerixafor: 33	Non-Hodgkin lymphoma, multiple	31 (94%)	33 (100%)	1 [1 - 4]	10.7 [3.5 - 37.9]	33 (100%)	NR
	CTX + G- CSF: 33	myeloma, relapsed Hodgkin	25 (76%)	33 (100%)	1 [1 - 4]	11.6 [2.1 - 69.3]	33 (100%)	
	CSF: 33	lymphoma	p=0.04	NR	p=0.45	p=0.5		
Chaudhary et al., 2013 (30)	G-CSF + plerixafor: 33	Multiple myeloma	31 (93.9%)	31 (93.9%)#	2 [1 - 4]	11.6 [3.0 - 26.8] 6.9 [1.0 - 26.8]#	NR	NR
	CT + G-CSF:		51 (68.9%)	42 (56.7%)#	2 [1 - 5]	7.0 [0 - 18] 2.4 [0 - 15]#		
	74		p=0.01	p=0.001	p=0.17	p=0.001 p=0.001##		
Kim et al., 2014 (4)	G-CSF: 25	Multiple myeloma	NR	NR	3 [1 - 5]	7.4 [2.3 - 21.2]	NR	NR
	G-CSF + lerixafor: 25				2 [1 - 4]	13.2 [4 - 43.4]		
					p=0.0001	p=0.0007		

CT (chemotherapy); CTX (chemotherapy with cyclophosphamide); d (day); DHAP (dexamethasone, cytarabine, cisplatin); G-CSF (granulocyte colony-stimulating factor); L (lymphoma); MM (multiple myeloma); NR (not reported); NS (nonsignificant); Pts (patients).

\* Collecting ≥5x10<sup>6</sup> CD34<sup>+</sup> cells/kg

<sup>&</sup>lt;sup>†</sup> Collecting ≥2x10<sup>6</sup> CD34<sup>+</sup> cells/kg

<sup>&</sup>lt;sup>‡</sup> The median number of apheresis days required to achieve ≥5x10<sup>6</sup> CD34<sup>+</sup> cells/kg was not calculated because less than half of patients reached the target within 4 apheresis days

<sup>§</sup> Collecting ≥6x10<sup>6</sup> CD34<sup>+</sup> cells/kg in 2 or fewer days of apheresis

<sup>\*\*</sup> Collecting ≥6x10<sup>6</sup> CD34<sup>+</sup> cells/kg in 4 or fewer days of apheresis

<sup>&</sup>lt;sup>††</sup> Plerixafor was administrated only to patients with peripheral blood CD34\* <0.01x109/l at day 13 as it was judged to have a high sensitivity for the identification of patients who would subsequently fail to mobilize (peripheral blood CD34\* <0.02x109/l)

<sup>&</sup>lt;sup>‡‡</sup> CD34<sup>+</sup> cells x10<sup>6</sup>/kg collected on day 1

## Outcomes: Patients who Seem to Mobilize Poorly to Current Regimens (Table 3) CD34+ Cells Collected

The "on demand" prospective study, assessing the efficacy of plerixafor in patients who mobilize poorly , was reported by Milone et al. (5). It detected a statistically significant increase in CD34 $^{+}$  harvest rates associated with the use of plerixafor when compared with patients predicted to fail harvest who did not receive plerixafor (60% versus 0%; p=0.01). Similarly, the retrospective study comparing G-CSF (filgrastim) plus plerixafor with other regimens after primary mobilization failure (10) detected a statistically significant increase in favour of plerixafor in the number of CD34 $^{+}$  cells collected in one apheresis procedure after second mobilization (37%, 0%, and 2% for G-CSF plus plerixafor, G-CSF plus chemotherapy [CT], and G-CSF plus granulocyte-macrophage colony-stimulating factor [GM-CSF], respectively; p<0.0001). Two single centres evaluated the efficacy of the pre-emptive use of plerixafor after chemomobilization with G-CSF in patients who seem to mobilize poorly, and reported that the minimum CD34 $^{+}$  collection target was achieved by 80% (9) and 97% (11) of their patients.

#### Peripheral Blood CD34<sup>+</sup> Cells Counts and Number of Apheresis Procedures

Two comparative studies reported a statistically significant increase in the number of CD34 $^{+}$  cells collected as well as in the median number of apheresis procedures in patients who received plerixafor when compared with patients who received other regimens, after primary mobilization failure (8, 10). The retrospective comparative study reported by Perkins et al. (10) reported a median number of CD34 $^{+}$  cells collection of 2.1 cells/1 apheresis procedure, 1.19 cells/2 apheresis procedures, and 1.44 cells/2 apheresis procedures for G-CSF plus plerixafor, G-CSF plus CT, and G-CSF plus GM-CSF, respectively; p=0.01 and p=0.04 for median number of CD34 $^{+}$  cells collected and median number of apheresis procedures, respectively. The study reported by Hundemer et al., in which data were matched to a historical control group on the basis of poor stem cell yield in the first apheresis session (8), reported a median CD34 $^{+}$  collection of 4.9 cells/2 apheresis procedures, and 3.7 cells/4 apheresis procedures for plerixafor and G-CSF, respectively; p=0.01. The comparative study reported by Ceng et al. (7), reported a median CD34 $^{+}$  collection of 8.5 cells for patients with plerixafor versus 4.8 cells for patients without plerixafor; p=0.003, but the median number of apheresis procedures was not reported.

Three single-arm studies reported a median number of CD34 $^{+}$  cells of 2.9, 5.08, and 3.42 with a median number of apheresis procedures of 1 (range: 1 to 3), 5 (range: 1 to 10), and 2 (range: 1 to 4), respectively (6, 9, 11).

#### Proportion of Patients who proceed to Auto-SCT

Only the comparative study reported by Perkins et al. (10) reported a statistically significant difference in the proportion of patients who underwent transplantation in favour of plerixafor when compared with other regimens after primary mobilization failure (84%, 53%, and 84% for G-CSF plus plerixafor, G-CSF plus CT, and G-CSF plus GM-CSF, respectively; p=0.03). Cheng et al. (7) reported that all patients (100%) in the group with plerixafor and 83% of patients in the group without plerixafor underwent transplant, but statistical significance is not reported. The single-arm study reported by Smith et al. (11) reported that among patients who seem to mobilize poorly and who received just-in-time rescue plerixafor plus chemotherapy and G-CSF, 95% proceed to auto-SCT. No other studies reported on this outcome.

#### Survival Rate Post-SCT

None of the studies evaluating the efficacy of plerixafor in mobilization (those who seem to mobilize poorly) reported on this outcome.	patients	failing

Table 3: Summary of the outcomes reported by studies assessing the efficacy of plerixafor in patients who seem to mobilize poorly to current regimens (low peripheral blood CD34<sup>+</sup> collected prior to first apheresis proecdure or inadequate first-day apheresis collection).

	Initial Mobilizati on Therapy: Pts	Criteria for failing mobilization: Peripheral Blood CD34 <sup>+</sup> Cells Count	No. of Patients Failing Mobiliza tion	Efficacy of Plerixafor						
Study				Remobiliza tion Protocol	≥2x10 <sup>6</sup> CD34 <sup>+</sup> x10 <sup>6</sup> cells/kg	Median Collection CD34* x10 <sup>6</sup> cells/kg [Range]	Median Number of Apheresis Days [Range]	Proceed ed to Auto- SCT	12- month Surviva I Rate	
Milone et al., 2014 (5)	CTX or DHAP + G- CSF: 102	PB on day +13 <sup>*</sup> or +15 <sup>†</sup> : <0.02x10 <sup>9</sup> /l	16/102	PLX: 10 No PLX: 6	6/10 (60%) 0/6 (0%) p=0.01		1.44 [1-3]	NR	NR	
Abhyankar et al., 2012 (6)	G-CSF: 159	PB on day 5: <10 <sup>‡</sup> or 20 <sup>§</sup> /µl or  PBSC on day 1: less than one-half of the total CD34 <sup>+</sup> dose needed (≥2.5 <sup>‡</sup> or ≥5 <sup>§</sup> x10 <sup>6</sup> /kg)	55 Total 28 NHL, HL 26 MM 1 Other	PLX		3.42 [0.11-12.49] 2.84 [0.38-6.50] NHL,HL 2.96 [2.78-6.12] MM** 6.46 [0.62-12.49] MM <sup>††</sup> 5.8 other	2 [1 - 4] 2 [1 - 4] 1 [1 - 3] 2 [1 - 3] 2	NR	NR	
Jantunen et al., 2011 (9)	CT + G- CSF: 63	PB: <10x10 <sup>6</sup> /L or PBSC: <1.0x10 <sup>6</sup> /kg	16 Total 12 NHL 1 HL 3 MM	PLX	13 (80%) 10 (77%) NHL 0 (0%) HL 3 (100%) MM	2.9 [1.6 - 6.1]	1 [1-3]	NR	NR	
Smith et al., 2013 (11)	CT + G-CSF	<u>PB</u> : <10x10 <sup>9</sup> /L after CT or <u>PBSC</u> : <0.3x10 <sup>6</sup> /kg/d/2 days	38 Total 27 NHL 3 HL 8 MM	PLX	37 (97%) 26 (96%) NHL 3 (100%) HL 8 (100%)MM	5.08 [1.95-16.55] 4.93 [1.95-10.89] NHL 5.04 [1.95 - 10.89] NHL+HL 8.81 [2.86 - 16.55] MM	5 [1-10] 5 [2-10] NHL 5 [2-10] L 7 [5-9] MM	36 (95%)	NR	

Perkins et al., 2012 (10)	NR	PBSC: <2x10 <sup>6</sup> /kg in first mobilization attempt	96	G-CSF + plerixafor: 38	22 (58%) 14 (37%) <sup>‡‡</sup>	2.10 [0.24 - 14.35]	1 [1-4]	32 (84%)	NR
				CT + G- CSF:15	4 (27%) 0 <sup>#‡</sup>	1.19 [0 - 5.76]	2 [1-3]	8 (53%)	
				G-CSF ± GM-	17 (40%) 1 (2%) <sup>#</sup>	1.44 [0 - 12.01]	2 [1-3]	36 (84%)	
				CSF: 43	=0.08 <0.0001 <sup>‡‡</sup>	=0.01	=0.04	=0.03	
Cheng et al., 2015 (7)	G-CSF + CT	Patients with CD34 <sup>+</sup> levels of 20x10 <sup>6</sup> /L or more in PB and a low	24 MM	PLX: 12	NR	8.5 [5.5 - 16.4]	NR	12 (100%)	NR
		CD34* stem cell yield in the first apheresis session		No PLX: 12		4.8 [2.2 - 10.0] =0.003		10 (83%)	
Hundemer et al., 2014	CT + G-CSF	PBSC: <2x10 <sup>6</sup> cells/kg	15/60 MM	PLX: 15	NR	4.92 [1.6 - 14.1]	2 [2 - 3]	NR	NR
(8)			45 <sup>§§</sup> MM	G-CSF: 45***		3.7 [ 1.08 - 8.0] =0.042	4 [2 - 9] =0.001		

CT (chemotherapy); CTX (chemotherapy with cyclophosphamide); DHAP (dexamethasone, cytarabine, cisplatin); G-CSF (granulocyte colony-stimulating factor); GM-CSF (granulocyte-macrophage colony-stimulating factor); HL (Hodgkin lymphoma); MM (multiple myeloma); NHL (non-Hodgkin lymphoma); NR (not reported); PB (peripheral blood); PBSC (peripheral blood stem cell collection); PLX (plerixafor); Pts (patients).

<sup>\*</sup> For patients received mobilizing chemotherapy based on CTX

<sup>&</sup>lt;sup>†</sup> For patients receiving the DHAP schedule

<sup>&</sup>lt;sup>‡</sup> For one transplant

<sup>§</sup> For more than one transplant

<sup>\*\*</sup> Target of 2.5x10<sup>6</sup> CD34<sup>+</sup> cells/kg

<sup>&</sup>lt;sup>††</sup> Target of 5.0x10<sup>6</sup> CD34<sup>+</sup> cells/kg

<sup>&</sup>lt;sup>‡‡</sup> Collecting >2x10<sup>6</sup> CD34<sup>+</sup> cells/kg in one apheresis procedure only

<sup>§§</sup> Matched historical control group who also had a poor stem cell yield in the first apheresis session, but continued mobilization with G-CSF alone

<sup>\*\*\*</sup> Historical control group

## Outcomes: Patients who have Failed Prior Mobilization Regimen (Table 4) CD34\* Cells Collected

Eleven studies reported on the efficacy of plerixafor in patients who mobilize poorly . One comparative study reported by DiPersio et al. (1) reported that among patients with non-Hodgkin lymphoma who failed prior mobilization regimens with G-CSF plus plerixafor and G-CSF plus placebo, 40% and 64% were able to achieve at least the minimum collection target. These authors also reported that all patients with multiple myeloma who failed previous mobilization attempts (7/7) were able to achieve the minimum collection target of 2x106 CD34 $^{+}$  x106 cells/kg (2). An additional single-arm study reported by Lor et al. (19) assessed the efficacy of plerixafor plus G-CSF (filgrastim) as a second-line therapy for patients who failed to respond to G-CSF (filgrastim) plus chemotherapy (cyclophosphamide) as the initial mobilization strategy. Plerixafor plus G-CSF successfully mobilized at least the minimum CD34 $^{+}$  collection target in 84% of the patients (100% of patients with multiple myeloma and 67% of patients with non-Hodgkin lymphoma). The study reported by Calandra et al. (15) reported that the success of patients collecting  $\geq 2x10^6$  CD34 $^{+}$  cells/kg was >66% overall, and was higher for patients with Hodgkin disease (77%) and multiple myeloma (71%), but not for patients with non-Hodgkin disease (60%).

The remaining seven studies reported results from 13 European countries (Austria, Belgium, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Portugal, Slovakia, Spain, and the United Kingdom) that enrolled patients in a compassionate use program that provided plerixafor to patients who had prior failed mobilization attempts (12-14, 16-18, 20). Hubel et al. (2012), in a subgroup analysis of the European Consortium of Stem Cell Mobilization, reported the results of 580 patients all enrolled in European CUPs (17). In a second report, the same authors (18) present the results from a subgroup of 60 patients from 23 centres in Germany that participated in a CUP. Basak et al. reported the results from a cohort of 61 patients from 11 Polish centres (14), and from a subgroup of 76 patients from Poland with multiple myeloma who also participated in a CUP (13). Duarte et al. (16) reported the outcomes from a subgroup of 56 patients from 15 participating centres in Spain and the United Kingdom. The study reported by Arcaini et al. (12) involves 35 patients from seven Italian centres participating in a CUP. Malard et al. (20) reported the outcomes from 83 patients enrolled in a CUP who were previously treated with fludarabine or lenalidomide. Overall, the success of collecting 2x10<sup>6</sup> CD34<sup>+</sup> cells/kg among patients who participate in European CUPs was significantly higher in patients with multiple myeloma (MM) than in patients with non-Hodgkin lymphoma (NHL) (82% versus 65%; p<0.0001), and also significantly higher in patients with Hodgkin lymphoma (HL) than in patients with NHL (82% vs. 65%; p=0.017) (17). For the remaining studies, the rates of adequate CD34<sup>+</sup> cell collection ranged from a low of 37% in patients with non-Hodgkin lymphoma and patients with Hodgkin lymphoma combined (12) to a high of 100% in patients with Hodgkin disease (18).

#### Peripheral Blood CD34<sup>+</sup> Cells Counts and Number of Apheresis Procedures

Results from a subgroup analysis of the European Consortium of Stem Cell Mobilization, including 580 patients, found that overall, the CD34 $^{+}$  collection yield was significantly higher in patients with MM than in patients with NHL (3.60 versus 2.56; p<0.0001), and also significantly higher in patients with HL than in patients with NHL (3.14 versus 2.56; p=0.013). No differences in the time of collection between groups were detected (17). Similarly, Lor et al. (19) and Calandra et al. (15) reported higher CD34 $^{+}$  cell collection yield in patients with MM than in patients with NHL, but statistical significance was not reported. No significant differences in the time of collection between groups were reported by these authors.

## Proportion of Patients who Proceed to Auto-SCT

Dipersio et al. (2009) found that 84% (52/62) of patients with NHL (1) and 100% (7/7) of patients with MM (2) who had failed a prior mobilization regimen underwent auto-SCT after remobilization with plerixafor. Calandra et al. (15) reported that more than 70% of patients who failed prior mobilization regimens proceed to auto-SCT after having been remobilized with plerixafor. Five additional studies reported auto-SCT rates ranging from a low of 17% (12) to a high of 88% (18).

### Survival Rate Post-SCT

Only DiPersio et al. (2009) reported a 12-month survival rate after remobilization with plerixafor of 86% and 100% in patients with NHL and MM, respectively (1, 2). None of the other studies reported on this outcome (7, 12-20).

Table 4: Summary of the outcomes reported by studies assessing the efficacy of plerixafor in patients who have failed a prior mobilization regimen (poor mobilizers).

Study	Initial Mobilization Therapy: Pts	Criteria for Poor Mobilizers CD34* x106 cells/kg	No. of Patients Identified as Poor Mobilizers	Efficacy of Plerixafor						
				Remobilizati on Protocol	≥2x10 <sup>6</sup> CD34 <sup>+</sup> x10 <sup>6</sup> cells/kg	Median Collection CD34 <sup>+</sup> x10 <sup>6</sup> cells/kg [Range]	Median Number of Apheresis Days [Range]	Proceeded to Auto-SCT	12-month Survival Rate	
Single-	arm Studies									
DiPersio et al., 2009a (1)	G-CSF + PLX: 150	PBSC: <0.8 or <2.0 within 2 and 4 apheresis days, respectively.	10/150 NHL	G-CSF + plerixafor w/wo CT	4/10 (40%)	NR	≤4	52/62 (84%)	53/62 (85.5%)	
	G-CSF + placebo: 148		52/148 NHL		33/52 (64%)					
DiPersio et al., 2009b (2)	G-CSF + PLX: 148 G-CSF + placebo: 154	PBSC: <0.8 or <2.0 within 2 and 4 apheresis days, respectively,  or  Patients planned for tandem transplantation with	0/145 MM 7/154 MM	G-CSF + plerixafor w/wo CT	7/7	NR	4	7/7 (100%)*	7/7 (100%)	
		<4 within 3 apheresis days								
Lor et al., 2012 (19)	G-CSF + CTX: 33	PBSC: <2.0 in a median number of three apheresis sessions	19 Total 10 MM 9 NHL)	G-CSF + plerixafor	16 (84%) 10 (100%) MM 6 (67%) NHL	4.32 7.84 [2 - 10.16] MM 2.45 [0.39- 6.45]NHL	3 3 [1-11] MM 3 [1-10] NHL	NR	NR	
Basak et al., 2011 (14) <sup>†</sup>	G-CSF w/wo CT	Previously failed to proceed to apheresis due to low PB cell count: <10 CD34*/µl before apheresis	61 <sup>‡</sup> Total 23 MM 20 NHL 18 HL	G-CSF +pPlerixafor	40 <sup>§</sup> (66%) 18 (78%) MM 8 (40%) NHL 14 (78%) HL	2.8 [0.94 - 5.4] 2.8 [0.6 - 5.5] MM 0.89 [0 - 6.5] NHL 2.8 [0 - 8.0] HL	2 [0-4]	34 (56%)	NR	

Section 3: Evidence Review Page 36

	1				p<0.05	p<0.05		1	
		or PBSC: <2.0 / 7 apheresis procedures max.			p 6.65	<i>p</i> 0.00			
Basak et al., 2011 (13)†	G-CSF w/wo CT	Previously failed to proceed to apheresis due to low PB cell count: <10 CD34*/µl before apheresis or PBSC: <2.0 / 7 apheresis procedures max.	76** Total MM 30 <sup>††</sup> MM 46 <sup>‡†</sup> MM	G-CSF + plerixafor	59 (78%) 21 (70%) <sup>††</sup> 38 (83%) <sup>‡‡</sup> p=NS	3.6 [0.6 - 14.2] 2.8 [0.6 - 8.3] <sup>††</sup> 4.2 [0.6 - 14.2] <sup>‡‡</sup> p<0.05	2 [1-3] 2 [1-3] <sup>††</sup> 2 [1-3] <sup>‡‡</sup> p=NS	NR	NR
Calandra et al., 2008 (15) <sup>†</sup>	Conventional regimen	Previously failed to proceed to apheresis due to low PB cell count: <10 CD34*/µl before apheresis or PBSC: <2.0 / 7 apheresis procedures max.	115 Total	G-CSF + plerixafor	76 (66%) 38 (60%) NHL 25 (71%) MM 13 (77%) HD	3.51 [SD: 2.90] 2.97 [SD: 2.51] NHL 4.44 [SD: 3.68] MM 4.54 [SD: 4.22] HD	3 [0-7] 3 [0-7] NHL 4 [1-7] MM 3 [1-5] HD	87 (76%) 45 (71%) NHL 27 (77%) MM 15 (88%) HD	NR
Hübel et al., 2011 (18) <sup>†</sup>	Conventional regimen (G- CSF w/wo CT)	Previously failed to proceed to apheresis due to low PB cell count: <10 CD34*/µl before apheresis or PBSC: <2.0 / 7 apheresis procedures max.	60 Total  28 NHL 17 MM 2 HD 13 Others <sup>§§</sup>	G-CSF + plerixafor w/wo CT	45 (75%) 18 (64%) NHL 15 (88%) MM 2 (100%) HD 10 (77%)others	3.35 [0 - 29.53]  2.21 [0 - 8.77] NHL 5.38 [0 - 10.98] MM 2.41 [2.01 - 2.8] HD 3.3 [0.89-29.5] others	2 [0-5] 2 [0-3] NHL 2 [0-5] MM 2 [2-2] HD 2 [1-4] others	40 (67%) 16 (57%) NHL 15 (88%) MM 1 (50%) HD 8 (62%)other	NR
Hübel et al., 2012 (17) <sup>†</sup>	Conventional regimen	Previously failed to proceed to apheresis due to low PB cell count: <10 CD34*/µl before apheresis or	580 Total 270 NHL 54 HL 256 MM	G-CSF + plerixafor w/wo CT	428 (74%)  175 (65%) NHL  44 (82%) HL  209 (82%) MM  NHL vs MM  p<0.0001	3.06 [0 - 32.6] 2.56 [0 - 17.4] NHL 3.14 [0 - 32.6] HL 3.60 [0 - 15.27] MM NHL vs MM	2 [1-5] 2 [1-4] NHL 2 [1-4] HL 2 [1-5] MM	NR	NR

Section 3: Evidence Review Page 37

		PBSC: <2.0 / 7			T	p<0.0001	1	1	
		apheresis			NHL vs HL	p 0.0001			
		procedures max.			p=0.017	NHL vs HL			
						p=0.013			
Malard	Flu: 48 NHL	Previously failed to	83 Total	G-CSF +	28 (58%) NHL	2.3 [0.3 - 13.4] NHL	2 [1-3] NHL	NR	NR
et al., 2012	25 444***	proceed to apheresis due to low	40 \\	plerixafor	24 (69%) MM	3.4 [1.1 - 14.8] MM	2 [1-4] MM		
(20) <sup>†</sup>	Len: 35 MM	PB cell count: <10	48 NHL 35 MM		21 (07/0) //#	3.1[1.1 11.0] //#/	2[]		
		CD34+/µl before apheresis							
		or							
		<u>PBSC</u> : <2.0 / 7							
		apheresis procedures max.							
Duarte	G-CSF w/wo	Previously failed to	56 Total	G-CSF +	42 (75%)	2.6 [0.4 - 10.6]	2 [0-4]	35 (63%)	NR
et al., 2011	СТ	proceed to apheresis due to low	24 L	plerixafor	15 (63%) L	2.3 [1.1 - 4.6] L	2 [0-4]		
(16) <sup>†</sup>		PB cell count: <10	32 MM		27 (84%) MM	2.8 [0.4 - 10.6] MM	2 [1-4]		
		CD34+/µl before apheresis			p=0.06				
		or			p-0.00				
		<u>PBSC</u> : <2.0 / 7							
		apheresis procedures max.							
Arcaini	CT + G-CSF	Previously failed to proceed to	35 Total	G-CSF + plerixafor	13 (37%)	2.6 [0.7 - 5.7]	1 [1-4]	6 (17%)	NR
et al., 2011		apheresis due to low	29 HL	pterixator					
(12) <sup>†</sup>		PB cell count: <10 CD34+/µl before	6 NHL						
		apheresis							
		or							
		PBSC: <2.0 / 7 apheresis							
		procedures max.							
Chora at	G-CSF + CT	DD: 200	22 MM	Plerixafor	NR	5.6 [2.3 - 9.4]	NR	9 (81.8%)	NR
Cheng et et al.,	U-C3F + C1	<u>PB</u> : <20	∠∠ /YUY\	riciixalui	INE		INIZ		INK
2015 (7)						3.5 [2.1 - 9.2]		9 (81.8%)	
						p=0.282			

Section 3: Evidence Review Page 38

CT (chemotherapy); Flu (fludarabine); G-CSF (granulocyte colony-stimulating factor); HD (Hodgkin disease); HL (Hodgkin lymphoma); Len (lenalidomide); max. (maximum); MM (multiple myeloma); NHL (non-Hodgkin lymphoma); NR (not reported); PB (peripheral blood); PBSC (peripheral blood stem cell collection); PLX (plerixafor); Pts (patients); w/wo (with or without).

Section 3: Evidence Review Page 39

<sup>\*</sup> Four of seven underwent tandem transplantation

<sup>†</sup> Plerixafor Compassionate Use Programmes (CUP) or named patient programs for patients who had prior failed mobilization attempts (previous conventional therapies for hematopoietic stem cell collection had failed, or on the basis of a low peripheral blood CD34<sup>+</sup> cells count following conventional mobilization therapy, the physician did not think there was a reasonable chance of collecting enough cells)

<sup>&</sup>lt;sup>‡</sup> This number includes 10 patients who were predicted to be poor mobilizers

<sup>§</sup> Thirty patients had already undergone stem cell transplantation

<sup>\*\*</sup> This number includes 24 patients who were predicted to be poor mobilizers, and 52 patients who had failed a previous mobilization attempt (30 of 52 poor mobilizers had already undergone auto-SCT in the past, and about 16 of them were mobilized with plerixafor)

<sup>&</sup>lt;sup>††</sup> Transplanted previously

<sup>&</sup>lt;sup>‡‡</sup> Not transplanted previously

<sup>§§</sup> Seven children suffering from Wiskott-Aldrich syndrome and neuroblastoma, and six patients with other malignant diseases (one seminoma, one germ cell tumour, one thyroid carcinoma, one testicular carcinoma, one composite lymphoma, and one chronic lymphocytic leukemia)

<sup>\*\*\*</sup> Seven patients (20%) had received a prior autologous hematopoietic stem cell transplant before salvage mobilization with plerixafor

#### DISCUSSION

Autologous stem cell transplantation is an important treatment for patients with hematological malignancies, providing improvement in disease control and survival rate, and in some situations may be potentially curative. A necessary step for this treatment is the successful collection of peripheral blood stem cells to facilitate engraftment and to reduce treatment-related toxicities. Mobilization of stem cells needs to be done in the most efficient manner that allows patients to proceed to transplant in a timely fashion, at the same time being aware of resource utilization and costs required from a pharmacy, nursing, apheresis, and lab perspective.

Plerixafor is a novel mobilization agent that has been approved for use in Canada with G-CSF in the mobilization of stem cells in patients with non-Hodgkin lymphoma or multiple myeloma who require high-dose chemotherapy and autologous stem cell transplantation. This recommendation report was created to help better define the optimal use of plerixafor in patients undergoing their initial mobilization, in patients who appear to be failing mobilization, and in patients who have failed a previous mobilization and who require remobilization. We did not specifically seek out studies evaluating the cost-effectiveness of any specific approach to mobilization.

The available studies on using plerixafor for initial mobilization (Table 2) could not answer the question of how a plerixafor plus G-CSF mobilization may compare with one using chemotherapy plus G-CSF. A mobilization of plerixafor plus G-CSF appeared superior to a mobilization of G-CSF alone in patients with lymphoma, but not necessarily superior in patients with myeloma. Administering chemotherapy for mobilization may introduce additional adverse effects that could contribute to morbidity and may delay patients getting to transplant, but the available studies were not designed to answer that type of question one focused on healthcare utilization or trade-offs. We therefore felt that the standard mobilization of chemotherapy plus GCSF was a reasonable practice to continue, but that in patients with lymphoma who could not receive chemotherapy plus G-CSF (because, e.g., of renal insufficiency), a plerixafor plus G-CSF initial mobilization appears to be preferred and is therefore recommended.

The use of plerixafor plus G-CSF "on demand" for those patients who appear to be mobilizing poorly was felt to be a useful strategy to maximize the benefits of plerixafor, minimize the risk of requiring remobilization, and therefore allow patients to proceed to transplant in a timely fashion. It is accepted that there may not be a uniform definition of what constitutes a poor mobilizer but commonly used measurements of peripheral blood CD34<sup>+</sup> cells count or stem cell yields on the first day of apheresis were felt to be quite reasonable.

The use of plerixafor plus G-CSF for remobilization is completely endorsed despite the nature of the available literature. Patients who are candidates for autologous stem cell transplantation have no other option than to try to get to transplant and therefore the use of plerixafor plus G-CSF is strongly recommended. With many health-care centres opting to use plerixafor plus G-CSF "on demand" in poor mobilizers, the number of patients requiring remobilization is expected to decrease over time.

The current Health Canada recommendation is to use plerixafor plus G-CSF in patients with non-Hodgkin lymphoma or myeloma. The biological activity of the drug and the similarities of the stem cell mobilization process in Hodgkin lymphoma and germ cell tumours are expected to be similar to the drug activity and the mobilization process in non-Hodgkin lymphoma and myeloma. Some studies did include some patients with Hodgkin lymphoma and other indications. We felt therefore that we could generalize the benefits of plerixafor to patients with Hodgkin lymphoma or germ cell tumours and that plerixafor should be used for

these patients in a similar fashion to the way it is used for patients with non-Hodgkin lymphoma or myeloma.	

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References Page 44

# **APPENDIX I. SCT-7 - LITERATURE SEARCH STRATEGY**

Database: Ovid MEDLINE and EMBASE n=2577

	1	D 11 T 1 1 1 1 1 2 1 5 1 1
Section A: Disease and/or population		exp Bone Marrow Transplantation/ or exp Stem Cell Transplantation or (bone marrow transplantation or stem cell transplantation or peripheral stem cell transplantation).mp.
Section B: Intervention or diagnostic test		exp Plerixafor/ or exp Hematopoietic stem cell mobilization/
	3	Receptors, CXCR4/tu, ad, de [Therapeutic Use, Administration & Dosage, Drug Effects]
	4	2 or 3
Section C: Study design (this example only focuses on RCTs and phase II, III, IV trials)	5	exp Clinical Trial/ or exp Clinical Study/ or exp Controlled Clinical Trial/ or exp Multicenter Study/ or exp Phase 1 Clinical Trial/ or exp Phase 2 Clinical Trial/ or exp Phase 3 Clinical Trial/ or exp Phase 4 Clinical Trial/ or exp Clinical trial, controlled/ or exp Clinical trial, Phase 1/ or Clinical trial, Phase 2/ or exp Clinical trial, Phase 3/ or exp Clinical trial, Phase I/ or Clinical trial, Phase I/ or Clinical trial, Phase II/ or exp Clinical trial, Phase II/ or exp Clinical trial, Phase IV/ or exp Comparative studies/ or exp Prospective Studies/
	6	(((Clinical Trial\$ or random\$) adj3 trial\$) or Comparative Study).mp.
	7	(Systematic Review or Pooled Analysis or Meta-analysis or systematic overview or Health Technology Assessment or Practice Guideline).mp
	8	exp Evidence Based Medicine/ or exp Practice Guideline/
	9	or/5-8
Section D: Exclusion strategy	10	(Case Report\$ or Editorial\$ or Comment\$ or Letter\$).pt.
	11	Animal/ not Human/
	12	or/10-11
Combining Section A, B, C, D	13	(1 and 4 and 9) not 12

Resources: ©Embase 1996 to 2014 Week 16, ©Ovid MEDLINE(R) without Revisions 1996 to April Week 2 2014, ©Ovid MEDLINE(R) Daily Update April 18, 2014, ©Ovid MEDLINE(R) In-Process & Other Nonindexed Citations April 18, 2014. Literature Search was updated in March 2015.

Appendices Page 45

# APPENDIX II. MEMBERS OF THE PLERIXAFOR WORKING GROUP and their CONFLICT OF INTEREST DECLARATION

In accordance with the PEBC Conflict of Interest (COI) Policy, the authors of this recommendation report and internal reviewers were asked to disclose potential conflicts of interest. One author declared no conflicts of interest, and four (TK, CB, JK, AX) declared conflicts. TK reported receiving honoraria for work regarding plerixafor as a clinical reviewer for the Canadian Agency for Drugs and Technologies in Health. CB reported being the president-elect of the Canadian Blood and Marrow Transplant Group, which had received \$5000 or more in a single year from Sanofi, the clinical developer of plerixafor. CB, JK, and AX declared that they had received research grant support from Sanofi. JK also declared that he had been a principal investigator for a clinical trial involving plerixafor.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by e-mail at <a href="mailto:ccopgi@mcmaster.ca">ccopgi@mcmaster.ca</a>.

Appendices Page 46