

**Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT**

**VI.1. Elements for Summary Tables in the EPAR**

**VI.1.1. Summary Table of Safety Concerns**

**Table 35. Summary of Safety Concerns**

<b>Summary of Safety Concerns</b>	
Important identified risks	1.Acute Cardiotoxicity (arrhythmias) 2.Cardiomyopathy 3. Severe Myelosuppression, Increased Susceptibility to severe infections and Haemorrhages 4. Secondary Leukaemia 5. Gastrointestinal Haemorrhage/Perforation 6. Tumour Lysis Syndrome
Important potential risks	1. Increased toxicity in patients with hepatic impairment 2. Increased toxicity in patients with renal impairment
Missing information	None

**VI.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan**

There are no ongoing or planned studies in the post-authorisation pharmacovigilance development plan.

**VI.1.3. Summary of Post-Authorisation Efficacy Development Plan**

There is no post-authorisation efficacy development plan.

**VI.1.4. Summary Table of Risk Minimisation Measures**

Beyond routine risk minimisation, there are no risk minimisation measures for this RMP.

**VI.2. Elements for a Public Summary**

**VI.2.1. Overview of Disease Epidemiology**

Acute lymphocytic leukaemia (ALL) occurs more commonly in children, and, in Europe, ALL is diagnosed in around 3.59 children (ages 0 to 14 years) per 100,000, and in 1.28 out of every 100,000 adults a year. Deaths per 100,000 among children with ALL ages 0 to 14 years occur up to 4 times more often compared to those without ALL.<sup>115</sup> As a result of toxicity from chemotherapy regimens, patients with ALL have an increased chance of heart complications such as heart attack, congestive heart failure, disease of the lining surrounding the heart and problems with the heart muscle.<sup>116</sup> Other complications from treatment include cerebrovascular (e.g. stroke) and thrombotic events (e.g. blood clots).<sup>117</sup>

In Europe, AML is diagnosed in 3.7 out of every 100,000 adults a year, and in 0.7 among children ages 0 to 14 years, and 0.8 among ages 15 to 24 years.<sup>118</sup> New cases of AML are rising in the population over age 60 years. The diagnosis rate is 9.2 per 100,000 and 10.2 in men and women, aged 65 to 74 years, and even higher among adults aged 75 to 84 years (16.9 and 16.8 in men and women, respectively).<sup>119</sup> Mortality due to AML is higher in adults

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than in children, ranging from 4 to 6 deaths per 100,000 cases in adults compared to 0.2 in children under 20.<sup>120,121</sup> Patients treated for AML are likely to suffer fatal complications such as multi-organ failure from bacterial and fungal infections.<sup>122,123</sup> Elderly patients with AML are at risk for serious central nervous system toxicities that lead to death.<sup>124</sup>

In Europe, breast cancer is diagnosed in 62.8 women out of every 100,000 each year, and among new cases, 20% to 25% have locally advanced breast cancer.<sup>125,126</sup> Among every 100,000 women who are diagnosed with breast cancer in the EU, approximately 22.4 will die each year.<sup>127</sup> Women who are diagnosed with breast cancer at an advanced age may be more likely than younger women to die of breast cancer. Breast cancer patients are more likely to have other medical conditions such as hypertension, heart conditions, stroke, emphysema/asthma/chronic obstructive pulmonary disease, Crohn's Disease, arthritis of the hip, and diabetes.<sup>128</sup>

### **VI.2.2. Summary of Treatment Benefits**

Idarubicin is a cancer drug (chemotherapy drug) belonging to a drug class called anthracyclines. Idarubicin works by killing rapidly dividing cells and interferes with ways in which the cells of the human body grow and increase in number, such as cancer cells. This action can affect normal cells as well.

#### Acute myelogenous (non-lymphocytic) leukaemia in adults:

Three controlled clinical studies were conducted to evaluate the efficacy and safety of a treatment containing idarubicin as compared to a treatment not containing it in untreated adult patients with acute myeloid leukaemia, a type of blood cancer. In these studies, 70% to 80% of the patients receiving treatment with idarubicin obtained a complete response, as compared to 58% to 60% of those who received the comparator treatment. Duration of response and overall survival were (on average) longer in patients receiving the treatment containing idarubicin compared with comparators.<sup>129,130,131</sup>

#### Acute lymphocytic leukaemia in adults and children:

Idarubicin showed significant activity against acute lymphocytic leukaemia in patients who were previously treated for acute leukaemia and did not respond to treatment. Following treatment with idarubicin, all signs of cancer disappeared in 50% to 60% of patients and the duration of response was better than the alternative treatment.<sup>132,133,134</sup>

#### Breast cancer:

Idarubicin was more effective in inducing regression of advanced breast cancer than the comparator treatments. The duration of response in advanced breast cancer patients receiving idarubicin varied from 2 to 6 months. The response rate of idarubicin in patients with breast cancer was comparable to alternative treatment, which consisted of a variety of treatments selected by the treating physician.<sup>135,136,137</sup>

Considering the efficacy and safety reported in various clinical trials of idarubicin for the approved indications, the overall benefit-risk profile of idarubicin remains favourable.

### VI.2.3. Unknowns Relating to Treatment Benefits

No major differences in treatment benefit with idarubicin were seen across age, gender or ethnicity. Investigators continue to actively study the drug in a controlled clinical setting in different protocols in order to optimize its therapeutic benefit for its approved indications.

### VI.2.4. Summary of Safety Concerns

**Table 36. Important Identified Risks**

<b>Risk</b>	<b>What is Known</b>	<b>Preventability</b>
Heart rhythm changes which may include irregular, slow or rapid heartbeat. (Acute cardiotoxicity)	Common side effects in patients receiving idarubicin (may affect up to 1 in 10 people) may include an increase or decrease in heart rate, or irregular heart beat/pulse. An uncommon side effect (may affect up to 1 in 100 people) may include ECG changes.	Physician supervision and care. Before starting and during treatment you will need regular checks including heart tests.
Heart muscle disease and the heart does not pump properly (Cardiomyopathy)	Congestive heart failure is the most severe form of heart muscle disease and the heart does not pump properly (cardiomyopathy) caused by idarubicin and sometimes limits how many treatments patients can receive. Common side effects in patients receiving idarubicin (may affect up to 1 in 10 people) may include heart failure.	Physician supervision and care. Before starting, during and after treatment you will need regular checks including heart tests.
Abnormally low number of white blood cells, red blood cells or part of the blood that cause clots in the bloodstream (Severe myelosuppression, increased susceptibility to severe infections and haemorrhages)	A decrease in the number of red blood cells, white blood cells or abnormally low amount of the part of the blood that causes clots (platelets) may affect more than 1 in 10 patients receiving idarubicin (very common).  A decrease in the number of white blood cells can make someone more susceptible to infections.	Physician supervision and care. Before starting and during treatment you will need regular checks including blood tests.
Cancer of the blood caused by medication to treat cancer (Secondary leukaemia)	Though used to treat cancer, idarubicin can sometimes cause new cancers, including cancers of blood such as leukaemia.. These may occur many years after treatment and may affect up to 1 in 100 patients (uncommon).	Physician supervision and care.
Abnormal opening in the stomach or intestines (Gastrointestinal perforation/haemorrhage)	Occasionally, episodes of serious gastrointestinal events (perforation or bleeding) have been observed in patients receiving oral idarubicin.	It is not known how to prevent the development of abnormal opening in the stomach or intestines (hole).
A serious condition when cancer treatment causes cancer cells to die quickly (Tumour lysis syndrome)	Tumour lysis syndrome can occur when the dying cancer cells break down and release material into the bloodstream, resulting in damage to the kidneys. Symptoms include nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures (convulsions), clouding of urine and decreased amount of urine and tiredness (frequency cannot be estimated from the available	Physician supervision and care.

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**Table 36. Important Identified Risks**

Risk	What is Known	Preventability
	data). Frequency cannot be estimated from the available data.	

**Table 37. Important Potential Risks**

Risk	What is Known	Preventability
May experience more and/or severe toxic reactions if your liver does not work properly (Increased toxicity in patients with hepatic impairment)	Idarubicin has not been fully evaluated in patients who have liver problems. The dose may need to be decreased in patients with mild liver problems.  Idarubicin should not be used in patients with severe liver disease.  Frequency cannot be estimated from the available data.	Physician supervision and care. Regular medical examinations and periodic blood tests to check liver function.
May experience more and/or severe toxic reactions if your kidneys do not work properly (Increased toxicity in patients with renal impairment)	Idarubicin has not been fully evaluated in patients who have kidney problems. The dose may need to be decreased in patients with mild kidney problems.  Idarubicin should not be used in patients with severe kidney disease.  Frequency cannot be estimated from the available data.	Physician supervision and care. Regular medical examinations and periodic blood tests to check kidney function.

**VI.2.5. Summary of Risk Minimisation Measures by Safety Concern**

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

**VI.2.6. Planned Post-Authorisation Development Plan**

There are no post-authorisation studies planned.

**VI.2.7. Studies that are a Condition of the Marketing Authorisation**

There are no studies that are conditions of the Marketing Authorisation.

**VI.2.8. Summary of Changes to the Risk Management Plan Over Time**

Major changes to the Risk Management Plan over time are shown in **Table 38**

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**Table 38. Major Changes to the Risk Management Plan Over Time**

Version	Date	Safety Concerns	Comment
1.0	22 May 2015	Initial RMP	-
1.1	17 March 2016	1) Missing information deleted 2) Important potential risks added 3) Pivotal trial information added to Summary of Treatment Benefits 4) Footnote added for Indications in the Product Overview regarding advanced breast cancer	This update is in response to WS procedure DE/H/xxxx/WS/281 Day 55
1.2	09 June 2016	1) Two important identified risks were revised ( <u>Severe Myelosuppression and Increased Susceptibility to Severe Infections and Haemorrhages; Mucositis/stomatitis/esophagitis (complication including Gastrointestinal haemorrhage/perforation)</u> )  2) Revised language in Section VI.2. Elements for a public summary	This update is in response to WS procedure DE/H/xxxx/WS/281 Day 60.

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## REFERENCES

- 1 Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/), based on November 2013 SEER data submission, posted to the SEER web site, April 2014.
- 2 2015 [last update]/ Online. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. International Agency for Research on Cancer. Available: [http://globocan.iarc.fr/Pages/fact\\_sheets\\_cancer.aspx](http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx). 2 February 2015.
- 3 Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. *Blood*. 2010;116(19):3724-34.
- 4 Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (2000-2011) , National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2013 submission.
- 5 Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)). Prevalence database: "US Estimated Complete Prevalence Counts on 1/1/2011". National Cancer Institute, DCCPS, Surveillance Research Program, Data Modeling Branch, released April 2014, based on the November 2013 SEER data submission.
- 6 Han F, Tan Y, Cui W, Dong L, Li W. Novel insights into etiologies of leukaemia: a HuGE review and meta-analysis of CYP1A1 polymorphisms and leukaemia risk. *Am J Epidemiol* 2013 Aug 15;178(4):493-507.
- 7 Jabbour E, Borthakur G, Bueso-Ramos C, et al. Acute lymphoblastic Leukaemia. In Kantarjian HM, Wolff RA, Koller CA, editors. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2006:p. 3-18.
- 8 Surveillance, Epidemiology, and End Results (SEER) Program ([www.seer.cancer.gov](http://www.seer.cancer.gov)) SEER\*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1990-2011) , National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released July 2014. Underlying mortality data provided by NCHS ([www.cdc.gov/nchs](http://www.cdc.gov/nchs)).

- 9 Cancer Research UK. Acute lymphoblastic leukaemia (ALL) incidence statistics; 2014. Available from: <http://www.cancerresearchuk.org/cancer-info/cancerstats/types/Leukaemia-ALL/Incidence/#source1>, accessed on 11 March 2015.
- 10 De Las Casas C, Bueso-Ramos CE, Estey EH. Acute Myelogenous Leukaemia. In Kantarjian HM, Wolff RA, Koller CA, editors. MD Anderson Manual of Medical Oncology. New York: McGraw-Hill; 2006:p. 19-38.
- 11 Seibel NL, Steinherz PG, et al. Early Post-induction Intensification Therapy Improves Survival for Children and Adolescents with High-risk Acute Lymphoblastic Leukaemia: A Report from the Children's Oncology Group. *Blood* 2008;111(5):2548.
- 12 Schrappe M, Hunger SP, et al. Outcomes After Induction Failure in Childhood Acute Lymphoblastic Leukaemia. *N Engl J Med* 2012 Apr;366(15):1371-81.
- 13 Schrauder A, Reiter A, Gadner H, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukaemia: results from ALL-BFM 90 and 95. *Clin Oncol* 2006;24(36):5742-9.
- 14 Coebergh JW, Pastore G, Gatta G, et al. Variation in survival of European children with acute lymphoblastic leukaemia, diagnosed in 1978--1992: the EURO CARE study. *European journal of cancer (Oxford, England: 1990)* 2001;37(6):687-94.
- 15 Visser O, Trama A, Maynadié M, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. *European Journal of Cancer*. 2012;48(17):3257-66.
- 16 Sandler DP, Collman GW. Cytogenetic and environmental factors in the etiology of the acute leukaemias in adults. *Am J Epidemiol*. 1987;126:1017-1032.
- 17 Deschler B, Lübbert M. Acute myeloid leukaemia: epidemiology and etiology. *Cancer*. 2006 Nov 1;107(9):2099-107.
- 18 Pogoda JM, Preston-Martin S, Nichols PW, Ross RK. Smoking and risk of acute myeloid leukaemia: results from a Los Angeles County case-control study. *Am J Epidemiol*. 2002;155:546-553.
- 19 Bishop JF. The treatment of adult acute myeloid leukaemia. *Semin Oncol* 1997;24(1):57-69.

- 20 Weick JK, Kopecky KJ, Appelbaum FR, et al. A randomised investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukaemia: a Southwest Oncology Group study. *Blood* October 1996;88 (8):2841–51.
- 21 Bishop JF, Matthews JP, Young GA, et al. A randomised study of high-dose cytarabine in induction in acute myeloid leukaemia. *Blood* 1996;87 (5):710–7.
- 22 Van Der Jagt R, Robinson KS, Belch A, et al. Canadian Leukaemia Studies Group. Sequential response-adapted induction and consolidation regimens idarubicin/cytarabine and mitoxantrone/etoposide in adult acute myelogenous leukaemia: 10 year follow-up of a study by the Canadian Leukaemia Studies Group. *Leuk Lymphoma* 2006;47:697–706.
- 23 Brune M, Castaigne S, Catalano J, et al. Improved leukaemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukaemia results of a randomized phase 3 trial. *Blood* 2006;108(1):88-96.
- 24 Adult Acute Myeloid Leukaemia Treatment (PDQ®) National Cancer Institute. 06/24/2013.
- 25 NCCN clinical practice guidelines in oncology. Acute myeloid leukaemia. 2013.
- 26 Fey M, Dreyling M, Group Obot EGW. Acute myeloblastic leukaemia in adult patients: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Annals of Oncology* 2009;20(suppl 4):iv100-iv1.
- 27 Kaatsch P. Epidemiology of childhood cancer. *Cancer treatment reviews*. 2010;36(4):277-85.
- 28 Fong CT, Brodeur GM. Down's syndrome and leukaemia: epidemiology, genetics, cytogenetics and mechanisms of leukemogenesis. *Cancer Genet Cytogenet* 1987;28:55–76.
- 29 Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukaemia in young children. *Am J Epidemiol*. 2002;155:603–613.
- 30 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013 Apr;49(6):1374-403.
- 31 Fanale MA, Buzdar AU. Early-stage, locally advanced, and inflammatory breast cancer. In Kantarjian HM, Wolff RA, Koller CA, editors. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2006: p. 464-502.

090177e18861ec9fApproved\Approved On: 10-Jun-2016 11:39

- 32 Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 21 February 2015.
- 33 A de Glas N, de Craen AJM, Bastiaannet E, Land EG. Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands: population based study. *BMJ*. 2014;349:g5410.
- 34 Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *New England Journal of Medicine*. 2012;367(21):1998-2005.
- 35 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013 Apr;49(6):1374-403. doi: 10.1016/j.ejca.2012.12.027.
- 36 DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin*. 2014;64(1):52-62(Abstract).
- 37 Iqbal J, Ginsburg O, Rochon PA, Sun P, Narod SA. Differences in breast cancer stage at diagnosis and cancer-specific survival by race and ethnicity in the United States. *Jama*. 2015;313(2):165-73.
- 38 Forbes, J.F. The incidence of breast cancer: the global burden, public health considerations. *Seminars in Oncology* 1997;24(1, suppl 1):S1-20–S1-35.
- 39 Althius MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev* 2004;13(10):1558-68.
- 40 Kols A. Breast Cancer: Increasing Incidence, Limited Options. *PATH* 2002;19:4.
- 41 Phipps AI, Malone KE, Porter PL, et al. Body size and risk of luminal, HER2-overexpressing, and triple-negative breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prevent* 2008;17(8):2078-86.
- 42 Mohan A, et al. Newer therapies for the treatment of metastatic breast cancer: a Clinical Update. *Indian J Pharm Sci* 2013;75(3):251-61.
- 43 F. Cardoso, et al. First international consensus guidelines for advanced breast cancer (ABC 1). *The Breast* 2012;1-11.

090177e18861ec9fApproved\Approved On: 10-Jun-2016 11:39

- 44 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013 Apr;49(6):1374-403. doi: 10.1016/j.ejca.2012.12.027.
- 45 Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukaemia: general overview and implications for long-term cardiac health. *Expert review of hematology*. 2011;4(2):185-197. doi:10.1586/ehm.11.8.
- 46 Vagace JM, de la Maya MD, Caceres-Marzal C, et al. Central nervous system chemotoxicity during treatment of paediatric acute lymphoblastic leukaemia/lymphoma. *Critical reviews in oncology/hematology*. 2012;84(2):274-86.
- 47 Creutzig U, Zimmermann M, Reinhardt D, et al. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukaemia: analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2004;22(21):4384-93.
- 48 Burnett AK, Milligan D, Prentice AG, et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukaemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive chemotherapy. *Cancer*. 2007;109:1114–1124.
- 49 Mayer RJ, Davis RB, Schiffer CA, et al for the Cancer and Leukaemia Group B. Intensive postremission chemotherapy in adults with acute myeloid leukaemia. *N Engl J Med*. 1994;331:896–903
- 50 Smith AW, Reeve BB, Bellizzi KM, et al. Cancer, comorbidities, and health-related quality of life in older adults. *Health Care Financ Rev* 2008;29(4): 41-56.
- 51 Gunnarsson K. Idarubicin Injection: Abbreviated Expert Report on the Toxicopharmacological (Pre-Clinical) Documentation. October 2002: 1-24.
- 52 Idarubicin Core Data Sheet, Pfizer Inc. March 2014
- 53 Hurteloup P, Armand JP, et al. Phase II trial of idarubicin (4-demethoxydaunorubicin) in advanced breast cancer. *Eur J Cancer Clin Oncol* 1989; 25(3):423-28.
- 54 Kolaric K, Mechl Z, et al. Phase II study of oral 4-demethoxydaunorubicin in previously treated (except anthracyclines) metastatic breast cancer patients. *Oncology* 1987;44(2):82-6.

- 55 Bertelli G, Amoroso D, et al. Idarubicin: An evaluation of cardiac toxicity in 77 patients with solid tumours. *Anticancer Research* 1988;8(4):645-6.
- 56 Shaikh AS, Saleem AF, Mohsin SS, et al. Anthracycline-induced cardiotoxicity: prospective cohort study from Pakistan. *BMJ Open*. 2013 Nov 20;3(11).
- 57 Chen C, Housch, A. et al. Present Risk of Anthracycline or Radiation-induced Cardiac Sequelae Following Therapy of Malignancies in Children and Adolescents. *Klin Padiatr* 2009;221:162-166.
- 58 Pai V, Nahata M. Cardiotoxicity of chemotherapeutic agents. *Drug Safety* 2000;22(4):263-302.
- 59 Lopez M, Contegiacomo A, et al. A Prospective Randomized Trial of Doxorubicin Versus Idarubicin in the Treatment of Advanced Breast Cancer 1989;64(12):2431-6.
- 60 Floyd J, Nguyen D, et al. Cardiotoxicity of Cancer Therapy. *Journal of Clinical Oncology*. 2005;23(30):7685-7696.
- 61 Nysom K, Holm K, Lipsitz SR, et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukaemia. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 1998;16(2):545-50.
- 62 Kremer L, Van Dalen E, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *Journal of Clinical Oncology*. 2001;19(1):191-6.
- 63 Temming P, Qureshi A, Hardt J, et al. Prevalence and predictors of anthracycline cardiotoxicity in children treated for acute myeloid leukaemia: retrospective cohort study in a single centre in the United Kingdom. *Paediatric blood & cancer*. 2011;56(4):625-30.
- 64 Creutzig U, Diekamp S, Zimmermann M, Reinhardt D. Longitudinal evaluation of early and late anthracycline cardiotoxicity in children with AML. *Paediatric blood & cancer*. 2007;48(7):651-62.
- 65 Ryberg M, Nielsen D, Cortese G, et al. New insight into epirubicin cardiac toxicity: Competing risks analysis of 1097 breast cancer patients. *Journal of the National Cancer Institute*. 2008;100(15):1058-67.
- 66 Bowles EJA, Wellman R, Feigelson HS, et al. Risk of Heart Failure in Breast Cancer Patients After Anthracycline and Trastuzumab Treatment:

- A Retrospective Cohort Study. *Journal of the National Cancer Institute*. 2012;104(17):1293-305.
- 67 Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. *Annals of oncology : official journal of the European Society for Medical Oncology/ESMO*. 2002;13(5):699-709.
- 68 Garcia JB, Lei X, Wierda W, et al. Pneumonia during remission induction chemotherapy in patients with acute leukaemia. *Annals of the American Thoracic Society*. 2013;10(5):432-40.
- 69 Patel S, Liedtke M, Ngo D, Medeiros BC. A single-center experience of the nationwide daunorubicin shortage: substitution with doxorubicin in adult acute lymphoblastic leukaemia. *Leukaemia & lymphoma*. 2013;54(10):2231-5.
- 70 Jackson N, Reddy SC, Harun MH, Quah SH, Low HC. Macular haemorrhage in adult acute leukaemia patients at presentation and the risk of subsequent intracranial haemorrhage. *Br J Haematol*. 1997 Jul;98(1):204-9.
- 71 Reaman GH, Sposto R, Sensel MG, et al. Treatment outcome and prognostic factors for infants with acute lymphoblastic leukaemia treated on two consecutive trials of the Children's Cancer Group. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 1999;17(2):445-55.
- 72 Katsimpardi K, Papadakis V, Pangalis A, et al. Infections in a paediatric patient cohort with acute lymphoblastic leukaemia during the entire course of treatment. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*. 2006;14(3):277-84.
- 73 Slats AM, Egeler RM, van der Does-van den Berg A, Korbijn C, Hählen K, Kamps WA, Veerman AJ, Zwaan CM. Causes of death--other than progressive leukemia—in childhood acute lymphoblastic (ALL) and myeloid leukemia (AML): the Dutch Childhood Oncology Group experience. *Leukemia*. 2005 Apr;19(4):537-44.
- 74 Cannas G, Pautas C, Raffoux E, Quesnel B, et al. Infectious complications in adult acute myeloid leukaemia: analysis of the Acute Leukaemia French Association-9802 prospective multicenter clinical trial. *Leukaemia and Lymphoma*. 2012;53(6):1068-1076.

- 75 Buckley SA, Othus M, Vainstein V, et al. Prediction of adverse events during intensive induction chemotherapy for acute myeloid leukaemia or high-grade myelodysplastic syndromes. *Am J Hematol*. 2014;89(4):423-8.
- 76 Lehrnbecher T, Varwig D, Kaiser J, et al. Infectious complications in paediatric acute myeloid leukaemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukaemia*. 2004;18(1):72-7.
- 77 Stemmler HJ, Harbeck N, Gröll de Rivera I, et al. Prospective multicenter randomized phase iii study of weekly versus standard docetaxel plus Doxorubicin (D4) for first-line treatment of metastatic breast cancer. *Oncology*. 2010;79(3-4):204-10.
- 78 Bontenbal M, Andersson M, Wildiers J, Cocconi G, Jassem J, Paridaens R, Rotmensz N, Sylvester R, Mouridsen HT, Klijn JG, van Oosterom AT. Doxorubicin vs epirubicin, report of a second-line randomized phase II/III study in advanced breast cancer. EORTC Breast Cancer Cooperative Group. *Br J Cancer*. 1998 Jun;77(12):2257-63.
- 79 Verma D, O'Brien S, Thomas D, et al. Therapy-related acute myelogenous leukaemia and myelodysplastic syndrome in patients with acute lymphoblastic leukaemia treated with the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimens. *Cancer*. 2009 Jan 1;115(1):101-6.
- 80 Winick NJ, McKenna RW, Shuster JJ, et al. Secondary acute myeloid leukaemia in children with acute lymphoblastic leukaemia treated with etoposide. *Journal of Clinical Oncology*. 1993;11(2):209-17.
- 81 Hulegårdh E, Nilsson C, Lazarevic V, et al. Characterization and prognostic features of secondary acute myeloid leukaemia in a population-based setting: A report from the Swedish Acute Leukaemia Registry. *American Journal of Hematology*. 2015;90(3):208-14.
- 82 Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukaemia: the University of Chicago series. 2003;10(1):43-52.
- 83 Campone M, Roche H, Kerbrat P, et al. Secondary leukaemia after epirubicin-based adjuvant chemotherapy in operable breast cancer patients: 16 years experience of the French Adjuvant Study Group. *Ann Oncol*. 2005;16(8):1343-51.
- 84 Blasiak J, Gloc E, et al. Genotoxicity of idarubicin and its modulation of vitamins C and E and amifostine. *Chemico-Biological Interactions*, 2002;140(1):1-118.

- 85 Pagano L, Pulsoni A, et al. Clinical and Biological Features of Acute Myloid Leukaemia occurring as Secondary Malignancy: GIMEMA archive in Adult Acute Leukaemia. *British Journal of Haematology*. 2001;112:109-117.
- 86 Mitchell E. Gastrointestinal toxicity of chemotherapeutic agents. *seminars in Oncology* 2006;33:106-120.
- 87 Ikeda AK, Tumor lysis syndrome, Medscape (last updated Dec 03, 2014). <http://emedicine.medscape.com/article/282171-overview>.
- 88 Wossmann W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumour lysis syndrome in children with advanced stage Burkitt's lymphoma/leukaemia before and after introduction of prophylactic use of urate oxidase. *Annals of hematology* 2003;82(3):160-5.
- 89 Truong TH, Beyene J, Hitzler J, Abla O, Maloney AM, Weitzman S, et al. Features at presentation predict children with acute lymphoblastic leukaemia at low risk for tumour lysis syndrome. *Cancer* 2007;110(8):1832-9.
- 90 Montesinos P, Lorenzo I, Martín G, et al. Tumour lysis syndrome in patients with acute myeloid leukaemia: identification of risk factors and development of a predictive model. *Haematologica* 2008;93(1):67.
- 91 Seftel MD, Bruyere H, Copland M, et al. Fulminant tumour lysis syndrome in acute myelogenous leukaemia with inv(16)(p13;q22). *European journal of haematology*. Available from: <http://onlinelibrary.wiley.com.proxy1.athensams.net/doi/10.1034/j.1600-0609.2002.02802.x/abstract>, accessed on 11 March 2014.
- 92 Lu K, et al. Clinical Pharmacology of 4-demethoxydaunorubicin (DMDR). *Cancer Chemotherapy and Pharmacology*. 1986;17:143-148.
- 93 Rowe J, Patel S, Mazo-Canola M, et al. An evaluation of elderly patients (>=70 years old) enrolled in Phase I clinical trials at University of Texas Health Science Center at San Antonio-Cancer Therapy Research Center from 2009 to 2011. *J Geriatr Oncol* 2014;5:65-70.
- 94 Lotan E, Leader A, Lishner M, et al. Unrecognized renal insufficiency and chemotherapy-associated adverse effects among breast cancer patients. *Anticancer Drugs* 2012;23:991-5.
- 95 Camaggi, CM, Strocchi, E, et al. Idarubicin Metabolism and Pharmacokinetics After Intravenous and Oral Administration in Cancer

- Patients: A Crossover Study. *Cancer Chemotherapy and Pharmacology* 1992;30:307-316.
- 96 Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet* 1997;32(3):210-258.
- 97 Sridhar R, Dwivedi C, Anderson J, et al. Effects of verapamil on the acute toxicity of doxorubicin in vivo. *J Natl Cancer Inst* 1992;84(21):1653-1660.
- 98 M, Ross K, Hamm K, Hossfeld DK. Effects of verapamil on the pharmacokinetics of epirubicin. *Cancer Chemother Pharmacol* 1993;31(5):369-375.
- 99 Gelmon KA, Mackey J, Verma S, et al. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. *Clin Breast Cancer*. 2004 Apr;5(1):52-8
- 100 Jones AL, Leyland-Jones B. Optimizing treatment of HER2-positive metastatic breast cancer. *Semin Oncol*. 2004 Oct; 31(5 Suppl 10):29-34.
- 101 Boekhout AH, Beijnen JH, Schellens JHM. Trastuzumab. *Oncologist*. 2011 June;16(6):800-810.
- 102 Bruno R, Washington CB, Lu JF, et al. Population pharmacokinetics of trastuzumab in patients with HER2+ metastatic breast cancer. *Cancer Chemother Pharmacol*. 2005 Oct; 56(4):361-9.
- 103 Leveque D, Gigou L, Bergerat JP. Clinical pharmacology of trastuzumab. *Curr Clin Pharmacol*. 2008 Jan;3(1):51-5.
- 104 Wynne C, Harvey V, Schwabe C, et al. Comparison of subcutaneous and intravenous administration of Trastuzumab: A Phase I/Ib trial in healthy male volunteers and patients with HER2-positive breast cancer. *J Clin Pharmacol*. 2012 Feb 22.
- 105 Sanford M. Trastuzumab: a review of its use in HER2-positive advanced gastric cancer. *Drugs*. 2013 Sep; 73(14):1605-15.
- 106 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/000278/WC500074922.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000278/WC500074922.pdf)
- 107 Doroshow JH. Anthracycline and Anthracenediones. In: *Cancer Chemotherapy and Biotherapy*, 2nd Edition, ed. by Chabner BA and Longo DL. Lippincott-Raven, Philadelphia, Pa. pp.409-434, 1996.

- 108 Turowski RC, Durthaler JM. Visual compatibility of idarubicin hydrochloride with selected drugs during simulated Y-site injection. *Am J Hosp Pharm* 1991e; 48:2181-2184.
- 109 Zavedos 5 mg Hard Capsules. Summary of Product Characteristics (Pfizer). July 2014.
- 110 Epirubicin 2 mg/mL Injection. Summary of Product Characteristics (Hospira). 17 Mar 2014.
- 111 Daunorubicin 20 mg Powder for Injection. Summary of Product Characteristics (Galen). 10 Jun 2014.
- 112 Adriblastina Local Product Document (Pfizer). Sep 2009.
- 113 Mitoxantrone 2 mg/mL Sterile Concentrate. Summary of Product Characteristics (Accord). 12 Feb 2015.
- 114 Zentiva Daunorubicin SmPC (18-Nov-2013), <http://www.medicines.org.uk/emc/medicine/26175>. Retrieved on 04 March 2016.
- 115 Coebergh JW, Pastore G, Gatta G, Corazziari I, Kamps W. Variation in survival of European children with acute lymphoblastic leukaemia, diagnosed in 1978--1992: the EURO CARE study. *European journal of cancer (Oxford, England: 1990)*. 2001;37(6):687-94.
- 116 Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukaemia: general overview and implications for long-term cardiac health. *Expert review of hematology* 2011;4(2):185-197. doi:10.1586/ehm.11.8.
- 117 Vagace JM, de la Maya MD, Caceres-Marzal C, et al. Central nervous system chemotoxicity during treatment of paediatric acute lymphoblastic leukaemia/lymphoma. *Critical reviews in oncology/hematology*. 2012;84(2):274-86.
- 118 Visser O, Trama A, Maynadié M, et al. Incidence, survival and prevalence of myeloid malignancies in Europe. *European Journal of Cancer*. 2012;48(17):3257-66.
- 119 Ness KK, Armenian SH, Kadan-Lottick N, Gurney JG. Adverse effects of treatment in childhood acute lymphoblastic leukaemia: general overview and implications for long-term cardiac health. *Expert review of hematology* 2011;4(2):185-197. doi:10.1586/ehm.11.8.

- 120 Fey M, Dreyling M, Group Obot EGW. Acute myeloblastic leukaemia in adult patients: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. *Annals of Oncology*. 2009;20(suppl 4):iv100-iv1.
- 121 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER\*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. (1990-2011) , National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released July 2014. Underlying mortality data provided by NCHS (www.cdc.gov/nchs).
- 122 De Las Casas C, Bueso-Ramos CE, Estey EH. Acute Myelogenous Leukaemia. In Kantarjian HM, Wolff RA, Koller CA, editors. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2006: p. 19-38.
- 123 Creutzig U, Zimmermann M, Reinhardt D, et al. Early deaths and treatment-related mortality in children undergoing therapy for acute myeloid leukaemia: analysis of the multicenter clinical trials AML-BFM 93 and AML-BFM 98. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*. 2004;22(21):4384-93.
- 124 Mayer RJ, Davis RB, Schiffer CA, et al., for the Cancer and Leukaemia Group B. Intensive postremission chemotherapy in adults with acute myeloid leukaemia. *N Engl J Med*. 1994;331:896-903.
- 125 Cardoso F, Harbeck N, Fallowfield L, Kyriakides S, Senkus E, Group obotEGW. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2012;23(suppl 7):vii11-vii9.
- 126 Fanale MA, Buzdar AU. Early-stage, locally advanced, and inflammatory breast cancer. In Kantarjian HM, Wolff RA, Koller CA, editors. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2006: p. 464-502.
- 127 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013 Apr;49(6):1374-403. doi: 10.1016/j.ejca.2012.12.027.
- 128 Smith AW, Reeve BB, Bellizzi KM, et al. Cancer, comorbidities, and health-related quality of life in older adults. *Health Care Financ Rev* 2008;29(4):41-56.
- 129 Berman E, Heller G, Santorsa J, et al. Results of a randomized trial comparing idarubicin and cytosine arabinoside with daunorubicin and cytosine arabinoside in adult patients with newly diagnosed acute myelogenous leukaemia. *Blood* 1991;77(8):1666-74.

- 130 Vogler WR, Velez-Garcia E, Weiner RS, et al. A phase III trial comparing idarubicin and daunorubicin in combination with cytarabine in acute myelogenous leukaemia: A Southeastern Cancer Study Group study. *J Clin Oncol* 1992;10(7):1103-11.
- 131 Wiernik PH, Banks PLC, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukaemia. *Blood* 1992;79(2):313-9.
- 132 Carella AM et al. 4-Demethoxydaunorubicin (Idarubicin) in refractory or relapsed acute leukemias. A pilot study. *Cancer*. 1985 Apr 1;55(7):1452-4.
- 133 Mandelli F et al. Phase II trial of high dose Idarubicin (IMI 30) + ARA-C combination in acute lymphoblastic leukemias with recurrence. 1987;19(4):1051-1063.
- 134 Giona F et al. Idarubicin in the treatment of adults with recurring Acute Lymphocytic Leukemia (ALL). 30th National Congress of the Italian Haematology Society. 1985;19(4):1064-1065.
- 135 Phase II clinical evaluation of 4-demethoxy daunorubicin (Idarubicin, IMI 30) administered by intravenous or oral route in the treatment of advanced breast cancer.
- 136 Lopez M et al. Phase II trial with oral idarubicin in advanced breast cancer. *Invest New Drugs*. 1986;4(1):39-42.
- 137 Lionetto R et al. Idarubicin in advanced breast cancer: a phase II study. *Cancer Treat Rep*. 1986 Dec;70(12):1439-40.