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High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive Non-Hodgkin Lymphoma (NHL) in adults (Review)

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[Intervention Review]

High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive Non-Hodgkin Lymphoma (NHL) in adults

Alexander Greb[1], Julia Bohlius[2], Daniel Schiefer[3], Guido Schwarzer[4], Holger Schulz[5], Andreas Engert[5]

[1]Cologne, Germany. [2]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [3]Department of Internal Medicine II, University Hospital Ulm, Ulm, Germany. [4]German Cochrane Centre, Institute of Medical Biometry and Medical Informatics, University Medical Center Freiburg, Freiburg, Germany. [5]Cochrane Haematological Malignancies Group, Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany

Contact: Alexander Greb, Carl Schurz Strasse 8, Cologne, 50935, Germany. alexandergreb@freenet.de, info@chmg.de.

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ABSTRACT

Background

High-dose chemotherapy with autologous stem cell support (HDT) has been proven effective in relapsed aggressive non-Hodgkin lymphoma (NHL). However, conflicting results of HDT as part of first-line treatment have been reported in randomised controlled trials (RCTs). We undertook a systematic review and meta-analysis to assess the effects of such treatment.

Objectives

To determine whether high-dose chemotherapy with autologous stem cell transplantation as part of first-line treatment improves survival in patients with aggressive non-Hodgkin lymphoma.

Search methods

MEDLINE, EMBASE, Cancer Lit, the Cochrane Library and smaller databases, Internet-databases of ongoing trials, conference proceedings of the American Society of Clinical Oncology and the American Society of Hematology were searched until September 2006. An update search in MEDLINE and CENTRAL was done in June 2010, no more trials fulfilling the inclusion criteria were identified. We included full-text, abstract publications and unpublished data.

Selection criteria

Randomised controlled trials comparing conventional chemotherapy versus high-dose chemotherapy in the first-line treatment of adults with aggressive non-Hodgkin lymphoma were included in this review.

Data collection and analysis

Eligibility and quality assessment, data extraction and analysis were done in duplicate. All authors were contacted to obtain missing data and asked to provide individual patient data.

Main results

Fifteen RCTs including 3079 patients were eligible for this meta-analysis. Overall treatment-related mortality was 6.0% in the HDT group and not significantly different compared to conventional chemotherapy (OR 1.33 [95% CI 0.91 to 1.93], P = 0.14). 13 studies including 2018

patients showed significantly higher CR rates in the group receiving HDT (OR 1.32, [95% CI 1.09 to 1.59], P = 0.004). However, HDT did not have an effect on OS, when compared to conventional chemotherapy. The pooled HR was 1.04 ([95% CI 0.91 to 1.18], P = 0.58). There was no statistical heterogeneity among the trials. Sensitivity analyses underlined the robustness of these results. Subgroup analysis of prognostic groups according to IPI did not show any survival difference between HDT and controls in 12 trials (low and low-intermediate risk IPI: HR 1.41[95% CI 0.95 to 2.10], P = 0.09; high-intermediate and high risk IPI: HR 0.97 [95% CI 0.83 to 1.13], P = 0.71. Event-free survival (EFS) also showed no significant difference between HDT and CT (HR 0.93, [95% CI 0.81 to 1.07], P = 0.31). Other possible risk factors such as the proportion of patient with diffuse large cell lymphoma, protocol adherence, HDT strategy, response status before HDT, conditioning regimens and methodological issues were analysed in sensitivity analyses. However, there was no evidence for an association between these factors and the results of our analyses.

Authors' conclusions

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Despite higher CR rates, there is no benefit for high-dose chemotherapy with stem cell transplantation as a first line treatment in patients with aggressive NHL.

PLAIN LANGUAGE SUMMARY

High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive Non-Hodgkin Lymphoma (NHL) in adults

Aggressive Non-Hodgkin's Lymphomas (NHLs) are fast growing forms of lymphoma. The most common type is a diffuse large B-Cell lymphoma (DLCL) but there are several other subtypes of aggressive lymphoma and variants of DLCL, such as centroblastic, immunoblastic or anaplastic large B-Cell lymphoma. Aggressive NHLs are generally responsive to conventional cancer therapies such as chemotherapy and radiation therapy. In the 1980s, many researchers reported that some patients with diffuse, large-cell lymphoma, who had not responded to conventional chemotherapy, could be cured with high-dose chemotherapy and autologous stem cell or bone marrow transplantation. This techniques may be used to treat the cancer, because the high doses of chemotherapy can destroy the patient's bone marrow. Therefore stem cells or marrow is taken from the patient before treatment. The marrow or the stem cells are then frozen, and the patient is given high-dose chemotherapy with or without radiation therapy to treat the cancer. The marrow or the stem cells that were taken out is then thawed and given back through a needle in a vein to replace the marrow that was destroyed. This type of transplant is called an autologous transplant. If the marrow given is taken from another person, the transplant is called an allogeneic transplant.On the first decade of study into autologous transplantation for the treatment of aggressive lymphoma, the focus was on the use of this approach to rescue patients after relapse or if the disease already progressed under standard chemotherapy. These encouraging results in relapsed or progressive lymphoma led to the testing of the technique as a primary therapy for the disease. However, it was also important to identify factors that could predict outcome of the therapy for patients with aggressive lymphoma. The International Prognostic Index score (IPI) was established in 1993. This score was designed to better predict outcome of aggressive lymphoma. Based on the number of negative prognostic factors present at the time of diagnosis (age >60 years, stage III/IV disease, elevated lactate dehydrogenase [LDH] level, Eastern Cooperative Oncology Group [ECOG] performance status > 2, more than one extranodal site of disease) four outcome groups (low-risk, low-intermediate risk, high-intermediate risk and high-risk) were identified with a 5-year overall survival ranging from 26% to 73%.

In the last few years, several randomised trials of high-dose chemotherapy (HDT) with autologous transplantation in patients with aggressive lymphoma have been reported. These studies have included incorporation of autotransplantation into the initial treatment, use of adjuvant autotransplantation in complete responders, and the use of this treatment approach in patients responding slowly or incompletely to their primary chemotherapy regimen. In this trials conflicting results of high-dose chemotherapy with autologous transplantation as part of first-line treatment have been reported. A few studies indicated a trend towards a better survival for patients with a poor prognosis according to the age-adjusted International Prognostic Index score, whereas others failed to show an advantage for primary high-dose chemotherapy. Therefore we undertook this systematic review and meta-analysis to assess the effects of such treatment on overall survival in patients with aggressive non-Hodgkin lymphoma.

The main results from this analysis are:
(i) In general, there was no evidence that HDT improves overall survival (OS) (HR 1.05; CI 0.92 to 1.19) or event free survival (EFS) (HR 0.92; CI 0.80 to 1.05).
(ii) In patients with good risk aaIPI there was some evidence for worse OS (HR 1.46; CI 1.02 to 2.09) when treated with HDT.
(iii) In contrast, there was suggestive but inconclusive evidence that poor risk patients may benefit from HDT.

Overall, with respect to the large population included in our analyses and the attempts made to minimise bias and confounding, we conclude that there is no evidence for a general benefit of the therapeutic principle of myeloablative chemotherapy followed by autologous stem cell transplantation for patients with aggressive NHL as first-line treatment based on the data presently available.

We have seen improvements for relapse free survival and complete remission rates but this was not translated into a benefit concerning the OS in the respective groups.

Most importantly, IPI low-risk patients appear to be harmed by high-dose chemotherapy in first-line treatment: patients. Furthermore with the availability of the anti-CD20 monoclonal antibody Rituximab good risk patients will have a better overall outcome after a combined

conventional immunochemotherapy. However, if HDT is employed for high risk patients, there may be a benefit, but physicians should not arbitrarily employ HDT during first-line treatment. There is a strong need to treat this group of high-risk patients in large trials with harmonized procedures and definitions, which would facilitate the comparability of results, and improve the assessment of therapeutic intervention. Further research should aim at either reproducing the studies showing positive trends or applying new approaches that do not solely rely on the principle of high-dose chemotherapy with autologous transplantation.

BACKGROUND

Since the standard chemotherapy regimen CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) was established in 1976 (Gottlieb 1973, McKelvey 1976), there has been no substantial improvement in the prognosis of patients with aggressive non-Hodgkin lymphoma (NHL). Complete remission rates and long-term survival rates with CHOP are about 55% and 30% respectively (Agthoven 2003, Project 1993, Fisher 1994). The role of Rituximab, a monoclonal antibody against surface antigen CD20, either combined with conventional chemotherapy or with high-dose chemotherapy is still under investigation.

Several so called third-generation regimens include new agents and different doses and are based on the CHOP backbone. These regimens showed encouraging results in pilot studies. However, three large randomised studies failed to show an improvement in disease-free or overall survival when compared with the CHOP-regimen (Cooper 1994, Gordon 1992, Fisher 1993).

According to the Norton-Simon-hypothesis, relapses are not only caused by resistant tumour cells (genetic resistance), but also by tumour cells with reduced sensitivity to chemotherapeutic agents (kinetic resistance) (Norton 1982). According to this hypothesis, an intensification of chemotherapy with non-cross reacting agents applied after the induction therapy should lead to higher cure rates. With the development of high-dose chemotherapy (HDT) followed by autologous stem-cell transplantation (ASCT) and the increasing feasibility of this approach by improved supportive care, this hypothesis was tested in clinical trials. For patients who relapsed after conventional chemotherapy a significant benefit could be demonstrated when receiving HDT and ASCT as salvage therapy (Philip 1995).

Therefore eradicating the disease at an earlier time point or during first-line therapy might be promising approach sparing a later salvage treatment. Although the initial results of uncontrolled trials using HDT as first-line treatment in aggressive NHL were encouraging (Freedman 1993, Nademanee 1992, Nademanee 1997, Vitolo 1997), several randomised controlled studies showed no significant survival benefit of this approach for the majority of patients (Haioun, Martelli, Kluin-Nelemans, Verdonck).

However, a few studies indicated a trend towards a better survival for patients with a poor prognosis according to the International Prognostic Index score (IPI) that was established in 1993 (Project 1993). This score was designed to further clarify lymphoma staging. Based on the number of negative prognostic factors present at the time of diagnosis (age > 60 years, stage III/IV disease, elevated lactate dehydrogenase [LDH] level, Eastern Cooperative Oncology Group [ECOG] performance status $\geq$ 2, more than one extranodal site of disease, four discrete outcome groups were identified with a 5-year overall survival ranging from 26% to 73%.

The modified age-adjusted IPI score was defined for patients less than 60 years and comprises three factors (performance status, stage and LDH) and also four risk groups. As the feasibility of the HDT approach for older patients was quite unknown, most conducted trials only included younger patients and subsequently applied the age-adjusted score. The randomised LNH87-2 trial demonstrated no difference in terms of overall survival and disease-free survival between patients in complete remission who received conventional therapy or HDT (Haioun). But in a retrospective analysis, the same investigators suggested an improvement for the subgroup of patients with high-intermediate and high risk IPI (Haioun (subgroup)).

The best strategy for the application of HDT is still unclear and subsequently varied among trials. Some trials applied HDT after a reduced number of standard-dose chemotherapy cycles. Others after a full standard-dose regimen or employed a sequence of two or three single drugs in a high but non-myeloablative dose, followed by myeloablative polychemotherapy, named high-dose sequential chemotherapy. Additionally, investigated patient populations differed between trials. Some investigators assumed best efficacy for patients who do respond only slowly to standard chemotherapy, others for patients who achieved a complete remission. Subsequently these investigators randomised patients in complete or partial remission only, respectively.

Single studies are often underpowered. In addition the randomly assigned patients often do not receive the intended therapy, which further diminishes the ability of a single trial to show differences between treatment strategies when using an intention to treat analysis.

By systematically reviewing the literature, identifying randomised controlled trials (RCTs) and pooling individual patient data where possible, this meta-analysis tries to summarize the current evidence for the role of HDT in first-line therapy for patients with aggressive NHL. This also includes the assessment of the impact of different subgroups derived from the IPI score, different HDT strategies, and different remission status of patients receiving HDT. For this individual patient data (IPD) concerning age adjusted outcomes (aaIPI) were requested from the authors of the included trials and a limited IPD analysis was performed next to the conventional meta-analysis.

Two meta-analyses addressing the same question have been published previously (Simnett 2000, Strehl 2003). Neither found clear evidence for the usage of HDT. These analyses did not include all RCTs and neither used hazard ratios or individual patient data to analyse time to event data. The odds ratios used in the previous analyses are based on cumulative death rates at one particular time point and are considered to favour the risk of biased results (Duchateau 2001). We therefore decided to systematically review the literature, to identify randomised controlled trials (RCTs) and to pool the results of individual studies and in case of availability individual patient data to summarize the current evidence for the role of HDT in first-line therapy for patients with aggressive NHL. Therefore we contacted authors to provide us with individual patient data for evaluation of overall survival according to the aaIPI.

OBJECTIVES

To determine the effects of high-dose chemotherapy regimens plus autologous stem cell transplantation for treatment of aggressive non-Hodgkin lymphoma with regard to tumour response and survival and to identify potential modifying effects of poor prognosis features, older age, type of transplant (early vs. late) or type of induction (standard vs. escalated) on this association.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Quasi-randomised studies, e.g. alternate treatment allocation or allocation by date of birth, were excluded as we consider this study design to be of poor quality leading to unreliable study results. Studies with less than 20 adult lymphoma patients in each study group were excluded. Abstracts

and unpublished data were included, if sufficient information on study design, characteristics of participants, interventions and outcomes was available. Otherwise they were excluded or included with reservations following discussion with all the review authors.

Types of participants

Adult patients (aged > 16) diagnosed with an aggressive malignant Non-Hodgkin lymphoma as defined by a clinical classification (Hiddemann 1996) and histological criteria. The following histological classifications were accepted: Working Formulation, Kiel-, REAL- and WHO-classification.

In detail, the following histological entities were included: diffuse large cell lymphoma, large cell anaplastic lymphoma (Ki-1 lymphoma), follicular lymphoma grade III, centroblastic lymphoma, immunoblastic lymphoma, angioimmunoblastic and angiocentric lymphoma, unspecified T-cell lymphoma, pleomorphic lymphoma, mediastinal B-cell lymphoma. These entities are termed "high-grade lymphoma" in the Kiel classification and "high-grade" or "intermediate grade" in the Working Formulation.
Burkitt lymphoma and lymphoblastic lymphoma, which are called "very aggressive" due to the Hiddemann-classification, were excluded as these diseases are often treated within the studies that cover acute leukaemia. After the review of the included studies, it became apparent, that often very aggressive lymphoma patients were also included. As their numbers were small and it was impossible to exclude these patients from our pooled analysis, we ignored this fact.
Plasmocytoma and multiple myeloma were also excluded as this is a separate entity with different biological behaviour and different treatment modalities.

Types of interventions

1. Any high-dose chemotherapy that requires autologous stem cell or autologous bone marrow support in the course of the initial therapy.
2. Standard chemotherapy consisting of the CHOP regimen or any second- or third-generation regimen (as a control).

Types of outcome measures

Primary outcomes

- Overall survival

Justification for primary endpoint: survival is generally considered the primary endpoint relevant for clinical trials in oncology (Schilsky 2002). It is the most clinically relevant endpoint since the population included in this review has a very poor prognosis with all patients eventually dying of the disease if left untreated. In addition, death is an endpoint not susceptible to be biased by the outcome assessor.

Secondary outcomes

- Event-free survival (=Freedom from treatment failure) as defined as the interval from time of randomisation/study entry to the first recurrence of disease (progression or relapse) that is histologically confirmed or requires treatment, to death of any cause, or to lack of complete tumour response (CR)
- Time to progression as defined as the interval between the response to treatment and the time the disease starts to show evidence of growing (or recurring if a CR).
- Disease-free survival The length of time after treatment during which no disease is found. Can be reported for an individual patient or for a study population (includes only patients with complete or partial remission)
- Relapse-free survival (includes patients with prior complete remission)

Further secondary outcome measures:

- Tumour response (CR rate)
- Adverse events (like treatment-related mortality, infection rate)
- Quality of life
- Correlation between time to induction and survival, event-free survival and complete response rate

Search methods for identification of studies

All searches were conducted for the period between 1990 and 2003, as we did not anticipate any published data before that date. No language restriction was used.

Electronic searches

Trials were identified by searching the Cochrane Controlled Trials Register (CCTR) (Issue 3, 2003), MEDLINE, EMBASE, Cancer Lit and smaller databases. Additionally, we searched Internet databases of ongoing trials and unpublished literature.

- Cochrane Controlled Trials Register (CENTRAL/CCTR),
- MEDLINE (1990 to 2006, see Appendix 1 for search strategy),
- Cancer Lit (1990 to 2006),
- EMBASE (1990 to 2006)
- Database of grey literature (SIG LE)

Update search:

- Cochrane Controlled Trials Register (CENTRAL/CCTR) Issue 5, 2010,
- MEDLINE (September 2006 to June 2010 , see Appendix 1 for search strategy),

Databases of ongoing trials:

- www.controlled-trials.com
- http://clinicaltrials.nci.nih.gov
- http://clinicaltrials.gov/ct/gui
- www.eortc.be/
- www.ctc.usyd.edu.au/
- www.trialscentral.org/index.html

Electronic searching of the conference proceedings of

- the American Society of Clinical Oncology (1995 to 2006) and
- the American Society of Hematology (1997 to 2006).

Searching other resources

We hand-searched the conference proceedings of

- the American Society of Hematology (ASH) (1990 to 2003),

- the American Society of Clinical Oncology (ASCO) (1990 to 2003),
- the European Society for Medical Oncology (ESMO),
- the British Society of Haematology,
- the European Haematology Association (EHA) and
- the European Group for Blood and Marrow Transplantation (EBMT).

Citations of all identified trials and of published reviews were checked for additional references.

Hand searching of the following medical journals:

- Annals of Oncology (1990 to 2003),
- Annals of Hematology (1991 to 2003),
- European Journal of Haematology (1990 to 2003),
- Bone Marrow Transplantation (1990 to 2003),
- British Journal of Haematology (1990 to 2003),
- American Journal of Hematology (1990 to 2003)

We also contacted experts in the field for further unpublished data or ongoing trials.

- Groups or individuals who may have done randomised trials in autologous transplantation as first line therapy for lymphoma

Data collection and analysis

Trials Selection

Two reviewers (AG, DHS) independently screened titles and abstracts of identified studies from the above sources for the eligibility criteria stated previously. If this could not be done satisfactorily from the title and abstract, a full text version was obtained for assessment. Studies that seemed to meet the inclusion criteria by this screening were assessed for eligibility with a designed form.

This eligibility form contained the following questions:

1. Is the study described as randomised?
2. Did the participants in the study have aggressive lymphoma?
3. Was the investigated therapy the first therapy the participants received?
4. Were the participants in the experimental arm treated by a high-dose protocol with autologous stem cell support?
5. Were the participants in the control group treated by a polychemotherapy comparable to the standard CHOP protocol or one of the second- and third generation protocols?

After the completion of the protocol in 2002 we modified our eligibility criteria concerning the last aspect, as we also included trials that applied an intensified chemotherapy without stem cell support for the control group.
To be eligible, studies had to meet all of the criteria stated above. If there was insufficient information to judge eligibility, the first author of the report was contacted both by e-mail and by letter for clarification. Any disagreements between the reviewers were solved by discussion. Any duplicate reports were identified. Full text versions of all eligible studies were obtained for quality assessment and data collection.

Inclusion and Exclusion Criteria

Types of participants
To be included trials had to fulfil all criteria described above. The term "aggressive lymphoma" relates to histological entities that are termed high-grade NHL in the Kiel classification and "high-grade" or "intermediate grade" in the Working Formulation. Trials that include Burkitt lymphoma and lymphoblastic lymphoma patients were not excluded. As mentioned above this decision came up after the first review of included studies. If very aggressive NHL were the major subject of a study e.g. the trial by Sweetenham et al. (Sweetenham) we excluded this due to different biological behaviour and treatment strategies. Also excluded were trials investigating plasmacytoma and multiple myeloma as this is a separate entity with different biological behaviour and different treatment modalities. Additionally, age below 16 years was a predefined exclusion criterion, because of different therapy and disease related characteristics in children.

Types of studies
We only considered randomised controlled trials. Quasi-randomised trials were not included. Abstracts and unpublished data were included if sufficient information on study design, characteristics of participants, interventions and outcomes was available. Small studies with less than 20 patients per study arm were also excluded.

Types of intervention
With respect to the control arm we extended our pre-defined criteria for conventional chemotherapy as not all included trials either applied CHOP or a second or third generation regimen. The reason was the frequent use of further regimens such as the so called "intensified conventional chemotherapy". The comparability to CHOP could not be clearly evaluated from the literature. We decided to include these trials in order to include more studies and patients. With respect to the experimental treatment arm, trials had to apply any high-dose protocol such as BEAM or BEAC, which requires stem cell support. There was no restriction for the use of either peripheral or bone marrow harvested stem cells.

Quality Assessment

Two reviewers (DHS, AG) independently judged the quality of the eligible studies by using the full text article. Any disagreements were discussed with the rest of the review authors until consensus was obtained or authors were contacted to clarify. Quality was assessed using an assessment form designed for the topic of this review (sources used: Hollis 1999; Jüni 2001; Moher 1995; Verhagen 1998). The following criteria were considered:

1. Was the method of randomisation satisfactory?
2. Was the treatment allocation concealed?
3. Were numbers and reasons of withdrawals, dropouts and losses to follow-up in each group stated?
4. Were analyses based on the intention-to-treat principle?

In cases we could not answer the mentioned questions from the full text article the authors were contacted to clarify. We explored the influence of individual quality criteria in sensitivity analyses.

Data Collection

Two reviewers (DHS, AG) independently collected data concerning details of study population, interventions and outcomes by using a

standardised data extraction form. This form included at least the following items:

- General information: title, authors, source, contact address, country, language and year of publication, duplicate publications, sponsoring and setting of trial
- Trial characteristics including design, randomisation and concealment of allocation ·Interventions: intervention with dose and timing, co-medications with dose, route and timing, duration of aplasia
- Patients: sampling, exclusion criteria, sample size, baseline characteristics, similarity of groups at baseline, diagnostic criteria, drop-outs
- Outcomes: overall survival, event-free survival, complete response rate, disease-free survival, relapse-free survival, progression-free survival, toxicities (treatment-related mortality, infection rate, myelosuppression), survival after relapse, quality of life, time to induction therapy

The outcome "survival after relapse" was not pre-defined in our protocol.

We contacted the first authors of the included trials and asked for additional data such as trial characteristics e.g. methodological issues and further outcome measures if not adequately published. We further asked for individual patient data according to overall survival, event-free survival and for the outcome of the mentioned subgroups of poor prognosis patients according to the IPI score, if hazard ratios could not be obtained from the publication. Disagreements arising at any stage were resolved by discussion and consensus.

Data Analyses

For statistical analysis we used the Cochrane statistical package MetaView 4.1; the STATA software package was used for additional analyses, which could not be done with MetaView. Both fixed and random effects models were calculated in all meta-analyses. The fixed effect model was given more weight in the analysis; the random effects model was calculated to test the robustness of the results. To estimate treatment effects on time to event data such as OS and EFS, Hazard ratios (HRs) were calculated. If individual patient data (IPD) were not available, data were extracted from published results, e.g. survival curves, using methods described by Parmar et al. (Parmar 1998). For binary data, the relative risk with corresponding 95% confidence intervals was determined. The Mantel-Haenszel Method was used for pooling. Potential causes of heterogeneity were explored with sensitivity analyses. For each endpoint including more than four trials a funnel plot was generated and a linear regression test was performed to test for potential bias (Egger 1998). A P-value of less than 0.05 was considered significant. The correlation between time to induction therapy and OS, EFS and CR was calculated using linear meta-regression analysis.

Sensitivity Analyses and Subgroup Analyses

According to both subgroup and sensitivity analyses tests for interaction have been performed. If no significant difference was present, the result is not shown.

Subgroup analyses:

Prognosis of patients:

Only the age-adjusted IPI score which classifies patients below age 60, was applied to describe the prognosis of patients. In contrast to the IPI the items age as well as extranodal site are not considered. This age-adjusted score separates four different groups according to the number of existing adverse prognostic factors: stage III or IV, LDH above normal value, and performance status. For all subgroup analyses we divided the four possible groups into two: a low risk group with IPI scores of 0 to 1 and a high risk group with IPI scores of 2 to 3. This was done in order to increase the power of the analyses by increasing the number studies in each group. These analyses were done for the outcomes OS, EFS, and complete response rate.

Type of HDT:

Some trials applied a sequential high-dose chemotherapy (HDS); other trials applied HDT after an abbreviated or after a full induction conventional chemotherapy. HDS is a distinctive approach that was defined as employing a sequence of two or three single drugs in a high but non-myeloablative dose, followed by myeloablative polychemotherapy consisting of a different set of drugs.

In some trials the HDT group received a reduced number of induction courses before receiving HDT, as compared to the conventional chemotherapy group. We coined this principle "abbreviated standard treatment" and were initially planning to define this by comparison with six courses of CHOP. However, the induction (conventional) courses differed widely between respective trials and there was not enough published evidence available that allowed us to perform such a comparison for each trial. Thus, we defined "abbreviated" only by comparing the number of induction courses in the HDT and in the control arm, the latter serving as the "standard". The separation of different types of HDT has been similarly described previously (Shipp 1999).

***Patients' status of disease*:**

We created different subgroups according to the response status of patients randomised within the included trials. Some trials randomised patients before the onset of treatment, we called this "irrespectively of their disease status". Others randomised patients after a certain amount of chemotherapy independently of the response to the chemotherapy. These trials were also grouped under "irrespectively of their disease status". Again others applied some amount of chemotherapy and randomised only subgroups of patients such as the group of patients who achieved a partial remission or a patients that achieved a complete remission. Corresponding groups for patients in PR and CR were performed (named "patients in PR" and "CR" respectively). This subgroup analysis was not pre-defined, but a consequence of the observed responses to chemotherapy of different lymphomas and patients. This response can be expected to be of high relevance for the effectiveness of HDT.

***Timing of HDT*:**

In a linear meta-regression analysis we estimated the association between the time point of the application of HDT and OS, EFS as well as CR rate. The time was either the real time extracted from the publication or provided by the investigators, or the allowed time according to the protocol for the respective treatment before HDT.

Age groups:

The previously described analysis of different age groups could not be performed due to the fact that all trials included only patients less than 65 years.

Sensitivity analyses:

Sensitivity analyses were considered for the following outcome criteria:

- overall survival (OS),
- event-free survival (EFS),
- complete response rate (CR),
- and treatment-related mortality (TRM).

Sensitivity analyses included study quality (sufficient versus insufficient/unknown method), study size (threshold 100 patients), proportion of patients with bone marrow involvement (threshold 20%), different HDT regimens (BEAM, BEAC, TBI containing regimens, and others), proportion of patients who actually received HDT (threshold 70%), and source of data (published vs. IPD). Concerning the proportion of patients with diffuse large cell lymphoma (DLCL) two different comparisons were addressed by using a closer and a wider definition (thresholds 70% and 80% of included patients per trial). For the closer definition only group G of the Working Formulation (WF) was counted as diffuse large cell lymphoma (DLCL), whereas groups F, G, and H were defined as DLCL for the wider definition.

Sensitivity analyses were only performed if sufficient number of trial results (N = 4) could be included.

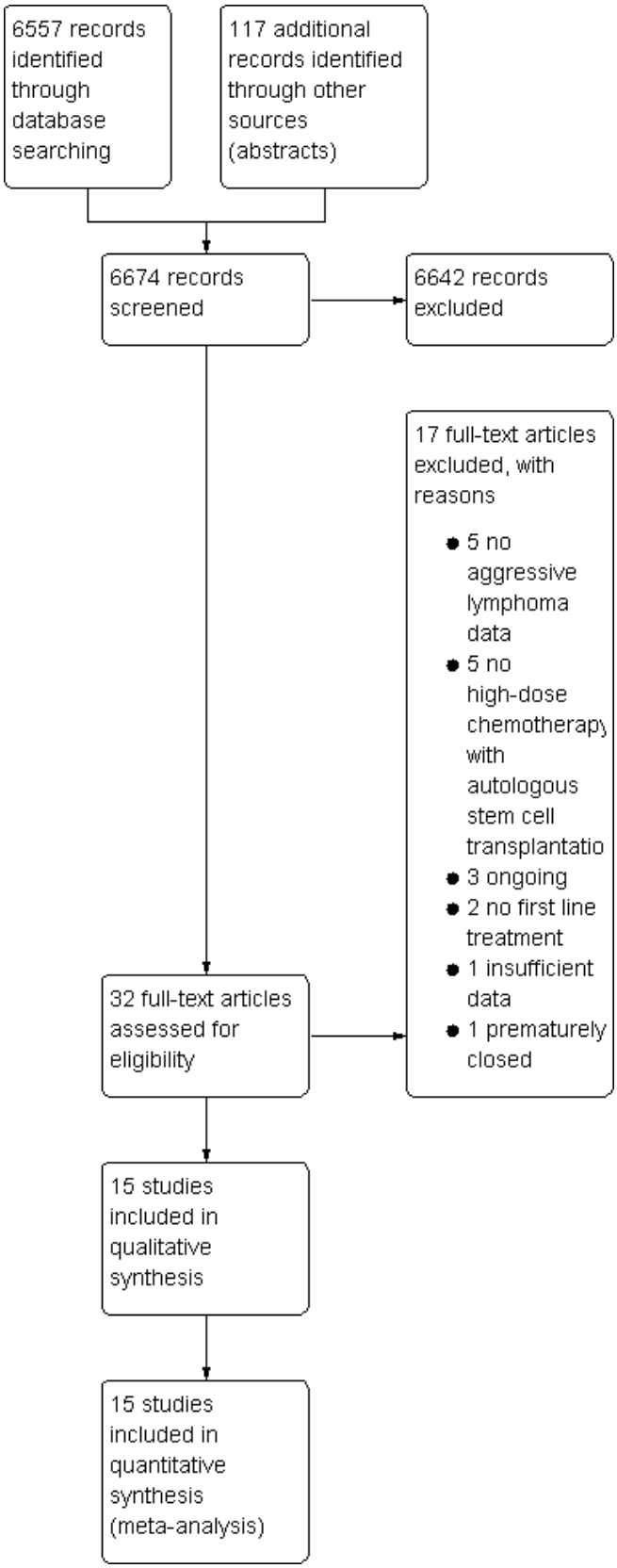
RESULTS

Description of studies

Results of the search

Through electronic literature searches and hand searches we retrieved 5,227 potentially relevant articles and 117 abstracts. This first search, which was done in August and September 2002, was repeated in November 2006. The second search identified one new trial (Rodriguez 2003) that fulfilled the inclusion criteria and some updated publications of already included trials. The studies by Kaiser and Martelli (Kaiser, Martelli 2003) previously published as abstract could be retrieved as paper publication by this search. Figure 1 provides information about the route of identification and integration of the included studies according to the QUORUM statement (Moher 1998).

Figure 1. Study flow diagram.



After a first screening by DHS and AG 75 publications (papers as well as abstracts) remained. Full texts of paper articles had been obtained for further assessment, because we were not able to assess eligibility from the title and abstract. Out of the 75 publications 56 studies were excluded. Out of these the study by Sweetenham et al. (Sweetenham) included only patients with lymphoblastic lymphoma. This study was excluded as only patients with very fast growing NHL were randomised. The biological behaviour as well as the treatment of this histological entity is different from aggressive NHL.

In total 20 randomised controlled trials which fulfilled the inclusion criteria were identified. The ECOG-2493 trial was excluded, because this trial was closed prematurely for poor accrual after enrolment of 14 patients. Results have never been published and no data were available. Furthermore, this trial randomised fewer patients than required for inclusion.

We found additionally 1,280 publications in the update search in June 2010, but no none of the publications fulfilled the inclusion criteria for this review.

Four trials were ongoing at the time of this analysis, of which one (De Souza) could be included in the analysis. One study with 457 patients was excluded for this analysis as the data reported in the abstract did not permit a detailed evaluation (Linch). Thus 15 trials remained.

Included studies

All 15 included studies are randomised controlled trials comparing an experimental group receiving high-dose chemotherapy with autologous stem cell support with a control group on a conventional chemotherapy regimen for the first line therapy of aggressive non-Hodgkin lymphoma.

There were twelve full-text publications and three abstract publications. All main investigators were contacted in writing for additional information and data. Eleven investigators (De Souza, Martelli 2003, Gisselbrecht, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Milpied, Santini, Verdonck, Vitolo) provided additional information and individual patient data on overall survival and the IPI score as well as additional information on study methodology and results. All these data were checked thoroughly to ensure both the accuracy of the statistical analysis and the quality of the trials. Any ambiguities between the published an unpublished data were resolved by discussions with the trial investigators or statisticians. Meta-analyses of survival data were done using both data from published reports and from individual patient data received by the authors. These analyses were compared as a quality control measure.

Twelve trials recruited patients in Europe.

Twelve studies were multicenter trials (De Souza, Martelli 2003,Gisselbrecht, Haioun, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Milpied, Santini, Santini-2, Verdonck). For three studies (Gianni, Rodriguez 2003, Vitolo) it is unknown if they recruited patients in different centres.

Six of the included trials were sponsored by a pharmaceutical company (Gianni, Gisselbrecht, Haioun, Intragumtornchai, Milpied, Vitolo), seven did not have an industrial sponsor (De Souza, Martelli 2003, Kaiser, Kluin-Nelemans, Martelli, Santini, Verdonck), and information on funding is unknown for two trials (Rodriguez 2003, Santini-2).

The dates of patient recruitment lasted from 1987, when the first patient was recruited (Gianni) until the time of performing the present analysis (ongoing study by De Souza).

The distribution of characteristics considered in our subgroup analyses was as follows:

- HDT was applied after a full standard induction therapy in four trials (Haioun, Intragumtornchai, Martelli, Santini),
- after abbreviated standard therapy in nine trials (De Souza, Gisselbrecht, Kaiser, Kluin-Nelemans, Martelli 2003, Milpied, Rodriguez 2003, Verdonck, Santini-2) and
- after sequential high-dose chemotherapy in two trials (Gianni, Vitolo).

For details about the treatment regimens see tables Table 1 and Table 2. Table 3 summarizes the classification of the trials into the different subgroups defined.

Eleven trials randomised patients irrespectively of their response status (De Souza, Gianni, Gisselbrecht, Intragumtornchai, Kaiser, Martelli 2003, Milpied, Rodriguez 2003, Santini, Santini-2, Vitolo).

- In two trials only patients achieving a PR were randomised (Martelli, Verdonck).·
- one trial randomised only patients with CR (Haioun), and
- in another trial only patients with PR or CR were randomised (Kluin-Nelemans)
- the IPI distribution is outlined in Table 4.

For the number of patients randomised and analysed see also Characteristics of included studies. For details of the treatment regimens see Table 1.
At the time of our analysis a Brazilian group (De Souza) was performing a RCT comparing VACOP-B (12 weeks) versus VACOP-B (six weeks) followed by high-dose sequential therapy with stem cell support for patients with aggressive lymphoma (according to the Working Formulation). Sequential high-dose therapy consisted of Cyclophosphamide, Etoposide and BEAM. So far, 54 patients have been randomised and included in our analyses. Patients were randomised before the first cycle of VACOP-B.
Gianni and colleagues (Gianni) compared MACOP-B (12 weeks) with inductive high-dose sequential chemotherapy (HDS) comprising four sequential phases and a fifth phase of myeloablative treatment. Patients without significant response (defined as less than 80% tumour volume reduction) after four phases received MACOP-B as salvage treatment. Patients in the control arm received HDS in case of inadequate response after 12 weeks MACOP-B, thus receiving the same therapy as the study group as salvage treatment. As the trial setting was before 1993 no restriction according to IPI was made but patients with bone marrow involvement were not randomised. The published results are based on data of 98 out of 101 randomised patients.
The LNH93-3 trial (Gisselbrecht) performed a randomised comparison of conventional chemotherapy using the ACVBP regimen for four cycles followed by a non-myeloablative consolidation (outpatient setting) compared with an intensified induction therapy consisting of one cycle CEOP and two cycles ECVBP followed by high-dose therapy (BEAM) and ASCT. Eligible

patients had to present at least two negative prognostic factors according to the age-adjusted IPI. The published results are based on 370 out of 397 randomised patients. 27 patients were excluded from the analysis due to ineligibility. For our IPD analyses, data of all 370 randomised patients were included.

The LNH87-2 trial (Haioun) randomised patients who achieved a complete remission after induction therapy using ACVB or NCVB (ACVB versus NCVB as an independent first randomisation) either to a sequential consolidation therapy according to the LNH84 protocol (Coiffier 1989) or to an intensive consolidation with high-dose methotrexate followed by the CBV regimen and ASCT. Of 916 eligible patients registered onto the study 614 achieved a complete remission and 541 (reasons for exclusion: medical condition, refusal, protocol violation) were randomised and included in our analyses. As patients were recruited before the generation of the IPI score, the inclusion criteria did not specify the IPI score. However, patients had to present with at least one adverse factor (PS > 1, or extranodal disease > 1 lymph node regions, or tumour burden >/= 10 cm, or bone marrow or CNS (central nervous system) involvement, or histological subtype of Burkitt or lymphoblastic lymphoma).

Following the establishment of the IPI score the investigators retrospectively performed a subgroup analysis of 236 patients classified as high-intermediate or high risk (Haioun (subgroup). The results concerning these patients could be included in our analysis, whereas the results of low and low-intermediate IPI risk patients were not available (neither published nor provided) and were therefore not included in our IPI subgroup analyses.

A Thailand group (Intragumtornchai) randomised patients after three cycles of CHOP irrespectively of their treatment response to either five further cycles CHOP or to four cycles of ESHAP followed by high-dose therapy and autologous stem cell support. Only patients with high-intermediate or high risk IPI were included. A total of 48 patients were randomised and included in our analyses.

The German High-Grade NHL Study Group (Kaiser) conducted a trial comparing five cycles of CHOEP with three cycles of CHOEP followed by high-dose therapy (BEAM) and ASCT. Patients were randomised before the first cycle of CHOEP. Only patients with LDH serum level above normal value were included. 312 of 331 randomised patients were included in the final results. 19 patients were excluded due to violation of entry criteria.

Within the EORTC (European Organisation for Research and Treatment of Cancer) 20901 trial (Kluin-Nelemans) patients were treated with three cycles of CHVmP/BV and restaged thereafter. Those patients achieving at least a partial response without bone marrow involvement were randomly assigned to five further cycles of CHVmP/BV or to three further cycles CHVmP/BV followed by high-dose therapy (BEAC) and ASCT. There was no restriction for inclusion of patients according to the IPI. In total this trial randomised and analysed 194 patients. This trial was closed before the planned 200 randomisedN = patients were recruited due to interim results.

Martelli and colleagues (Martelli) randomised 49 patients who achieved a partial response after induction treatment consisting either of eight cycles MACOP-B or of four cycles F-MACHOP (MACOP-B versus F-MACHOP as an independent first randomisation). The control group received an early intensification therapy with the "non-cross resistant" regimen DHAP (6 cycles) and the experimental group was treated with high-dose therapy (BEAC) followed by ASCT. As the trial setting was before 1993 no restriction according to IPI was made. All patients were in included in the final publication and in our analyses.

An Italian study group (Martelli 2003) recently completed a trial comparing MACOP-B (12 weeks) alone with MACOP-B (eight weeks) followed by high-dose therapy (BEAC) and ASCT for poor risk patients (age-adjusted IPI 2 or 3 risk factors). Patients were randomised before the first cycle of MACOP-B. 150 patients were randomised and analysed. All were included in our analyses.

The GOELAMS (Milpied) conducted a RCT comparing eight cycles of CHOP with a high-dose setting consisting of two courses of CEEP, which is an intensified conventional regimen, one course of high-dose Methotrexate plus Cytarabine, and BEAM followed by ASCT. Only non-high risk patients according to the IPI score were included. 197 patients were randomised and analysed. All were included in our analyses?.

Rodriguez and colleagues (Rodriguez 2003) performed a RCT comparing 9 cycles of an alternating regimen (ATT) with brief induction chemotherapy of two cycles followed by two cycles of an intensified dose chemotherapy and BEAM and ASCT. 116 patients were randomised and 108 of them analysed. A subgroup analysis according to different IPI groups was not reported so far.

In a RCT by the Italian NHL Cooperative Study Group (Santini) 124 patients were randomly assigned before treatment to receive either VACOP-B (12 weeks) or the same regimen followed by high-dose therapy (BEAM) and ASCT. Patients in the experimental arm proceeded to HDT and ASCT after VACOP-B independently of their disease status. In the control arm patients without complete response received DHAP as salvage therapy. There was no restriction for inclusion of patients made according to the IPI. All patients were included in the publication and our analyses.

Another RCT conducted by the same group (Santini-2) compared patients receiving VACOP-B (12 weeks) alone with patients receiving abbreviated induction therapy with eight weeks of VACOP-B followed by high-dose sequential therapy (Cyclophosphamide, Etoposide, BEAM) and ASCT. Patients in the control arm underwent HDS and ASCT as salvage therapy in case of persistent disease. There was no restriction for inclusion of patients made according to the IPI. This trial was not included in our analysis for time to event data, because we could not calculate HRs. In total, 223 patients were randomised.

Verdonck and colleagues (Verdonck) randomised patients who achieved a partial response and did not have bone marrow involvement after three cycles of CHOP. The control group received five additional courses of CHOP whereas patients assigned to the experimental group moved on to one further cycle of CHOP and high-dose therapy (Cyclophosphamide and TBI) followed by ASCT. Out of 286 eligible patients receiving three cycles of CHOP 133 achieved a partial response and 106 of them had no bone marrow involvement. Finally 73 of these 106 patients were randomised. There was no restriction for inclusion of patients made according to the IPI.

The Italian Lymphoma Intergroup (Vitolo) performed a RCT comparing patients receiving six to eight courses MegaCHOEP with patients receiving one or two courses APO and high-dose sequential therapy followed by autologous stem cell support. As eligibility criterion patients had to present with at least two risk factors according to the age-adjusted IPI. In total, 126 of 130 randomised patients were analysed.

Characteristics of Participants

Overall 15 trials with a total of 3,079 randomised patients (range within the trials: 48 to 541) fulfilled the inclusion criteria. Five trials included less than 100 patients, five of the trials randomised between 200 and 457 patients.

The median age ranged from 27 to 48 years in 12 trials of the 15 included trials. For three trials the median or mean age of randomised patients was not available but the inclusion criterion age was between 15 and 59 years and therefore comparable to the other trials. In nine of the 12 trials the median age was between 40 and 48 years (Martelli 2003, Gisselbrecht, Kaiser, Kluin-Nelemans, Santini-2, Milpied, Santini, Verdonck, Vitolo). The patients in the study by Martelli had the lowest median age with 27 and 29 years (Martelli) in the respective arms; patients randomised in the trial by Gianni had a median age of 34 and 35 years (Gianni) in the respective arms, and in the trial by De Souza 37.5 years (De Souza).
Due to the substantive changes of the classification of lymphomas over the last three decades the included trials used different classifications both for eligibility of patients and for description of results. In summary the Working Formulation (WF) was used in eight trials, the Kiel classification in two trials, the REAL classification in two trials, the WHO classification in one trial, and three trials did not report which classification was used (one trial applied two classifications). The comparability of the different classifications is limited. Therefore the interpretation and comparison of patient's histological lymphoma subtypes is difficult.
Central pathological review to confirm diagnosis was performed in 10 trials. For two trials (De Souza, Vitolo) this was not done. For two trials there was no information available (Gianni, Santini-2).
Regardless of the different classifications, diffuse large cell lymphoma (DLCL) was the most frequent entity. Detailed information on the histological distribution was available for 13 trials. Using a narrow definition the percentage of patients ranged from 34% (Verdonck) to 100% (Gianni, Intragumtornchai, both used the WF, which may overestimate number of DLCL). When using a wide definition 71% to 100% of the patients had DLCL. Of 13 trials the range of percentage of very fast growing lymphoma, including Burkitt and lymphoblastic lymphoma, was 0% to 8% (Kaiser). Eight trials did not have any patients of this histology. Further common entities were anaplastic large cell lymphoma, peripheral T-cell lymphoma, and diffuse mixed cell lymphoma.
For fourteen trials we had information on the IPI score. The distribution within each trial is shown in Table 4. Five trials randomised high-intermediate or high risk age-adjusted IPI only (De Souza, Martelli 2003, Gisselbrecht, Intragumtornchai, Vitolo). One trial (Milpied) randomised only patients with high-intermediate, low-intermediate or low risk age-adjusted IPI. Patients were retrospectively classified according to the IPI within seven trials (Gianni, Haioun, Kaiser, Kluin-Nelemans, Martelli, Santini, Verdonck).
The proportion of patients who actually received HDT within the HDT arms differed widely between the trials and is outlined in Table 5 (range: 60% to 100%).

Excluded studies

The UK Lymphoma Group initiated the LY02 trial (Linch) in which patients were randomised to six to eight cycles of CHOP or three cycles of CHOP followed by high-dose therapy (BEAM) and ASCT. Only patients with an objective response without progression and bone marrow involvement after three cycles of CHOP proceeded to HDT and ASCT. Patients had to have high-intermediate or high risk IPI. 457 patients have been randomised. So far, this study is only published as abstract and no data were available from the authors. Due to missing information to calculate HRs this trial was not included in our results.

As mentioned before the study by Sweetenham et al. (Sweetenham) included only patients with lymphoblastic lymphoma. This study was excluded as only patients with very fast growing NHL were randomised. The biological behaviour as well as the treatment of this histological entity is different from aggressive NHL.

Risk of bias in included studies

(see Characteristics of included studies and Table 6)

Randomisation

All included studies were described as randomised controlled trials. Ten trials (De Souza, Martelli 2003, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Martelli 2003, Santini, Verdonck, Vitolo) used random number tables for randomisation. In two trials randomisation was assumed to be adequate as it took place centrally (Gisselbrecht, Haioun). In three trials the method of randomisation was not adequately stated (Gianni, Rodriguez 2003, Santini-2) and not available from the study authors.
Stratification was performed in seven trials (Gianni, Gisselbrecht, Haioun, Intragumtornchai, Kaiser, Verdonck, Vitolo). Minimisation technique was used in one trial (Kluin-Nelemans). (Minimisation is designed to reduce any difference in the distribution of known or suspected determinants of outcome. During the randomisation process, patients are assigned using a randomisation weighted towards the group to which assignment minimise the imbalance. After each patient is entered the relevant totals for each determinant are updated. The next patient is subsequently more likely allocated to the treatment group in which his inclusion would improve the balance of the determinants between treatment groups).

Allocation concealment

Concealment of allocation was considered adequate in 12 trials. Of these ten trials deployed an institution separated from the recruitment centres (De Souza, Martelli 2003, Gisselbrecht, Haioun, Kaiser, Kluin-Nelemans, Martelli, Santini, Verdonck, Vitolo). The assignment in two trials was kept in sealed envelopes in the centre where patients were seen (Intragumtornchai, Milpied). The concealment of allocation could not be clarified in three trials, as this information was neither stated in the publication nor provided by the study authors (Gianni, Rodriguez 2003, Santini-2).

Drop-outs and withdrawals

As the number of drop-outs and withdrawals is essential for the calculation of HRs in the main analyses, we included only trials that dealt adequately with drop-outs and withdrawals.

Blinding

None of the trials mentioned blinding, as it appears impossible to apply high-dose therapy with stem cell transplantation in a blinded fashion.

Intention to treat analysis

Table 6 outlines the use of the intention to treat principle in each particular trial. In total, for ten trials data according to this principle could be pooled for our analyses. Data of four trials that did not follow this principle were included. The investigators stated reasons for the exclusion, which can be obtained from Table 6 and reasons were judged adequate by us. In summary, for the present meta-analyses outcomes were in fact recorded for all but 65 patients.

Impact on analyses

In conclusion, 12 of 15 included studies in this review were considered to be of adequate methodological quality, i.e. fulfilling all quality criteria (internal validity). One trial was only considered for the pooled analyses of CR and TRM (Santini-2). This trial was not included in our analysis for time to event data, because we could not calculate HRs due to missing data.

Effects of interventions

Overall survival (OS)

Fourteen studies including 2,444 patients were analysed (De Souza, Martelli 2003, Gianni, Gisselbrecht, Haioun, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Milpied, Rodriguez 2003, Santini, Verdonck, Vitolo). Ten investigators provided us with IPD information according to age-adjusted IPI (aaIPI) and overall survival. For four trials we extracted data from survival curves, because IPD data were not provided through the responsible authors. The pooled hazard ratio (HR) was 1.05 ([95% CI 0.92 to 1.19], P = 0.50). There was no statistical heterogeneity among the trials (P = 0.14). According to the intention-to-treat principle the analysis included all but 61/2,505 (2.5%) patients, who were initially randomised. There was a statistically significant difference (P = 0.033) between studies reporting results by intention-to-treat analysis (HR 0.92; 0.77 to 1.09) compared to no ITT (HR 1.22; 1.00 to 1.49). Excluding those studies where individual patient data were not available the HR as an IPD analysis for overall survival increases (HR 1.14; CI 0.98 to 1.34).

Meta-regression analysis showed no association between the time of HDT application and overall survival (see Figure 2).

The subgroup analysis of prognostic patient groups according to the aaIPI score was based on 12 trials including 2,235 patients. Two trials (Gianni, Rodriguez 2003) had to be excluded from this analysis as aaIPI data were not available. The subgroup of patients with good risk aaIPI showed some evidence for impaired OS with HDT (HR 1.46; CI 1.02 to 2.09). For poor risk patients, there was no difference between the treatment groups (HR 0.95; CI 0.81 to 1.11). The difference between good and poor risk patients was statistically significant (P = 0.032). Within the poor risk group, three studies showed significant effect estimates either favouring HDT (Haioun, Milpied) or in contrast a disadvantage for HDT (Gisselbrecht) and contributed substantially to the heterogeneity observed (P = 0.004). Excluding the detrimental study (Gisselbrecht) heterogeneity was reduced (P = 0.10) and the significant difference between the good and poor risk patients became more apparent (poor risk group HR 0.80; CI 0.67 to 0.96; P-value for difference between groups: 0.004). Excluding the positive studies (Haioun, Milpied) while including the study by Gisselbrecht heterogeneity was also reduced (P = 0.25) and no evidence for an effect of HDT on survival was seen (poor risk: HR 1.10; CI 0.92 to 1.31).

The allocation of trials according to different high-dose protocols can be obtained from Table 3. Two trials (Gianni, Vitolo) with high-dose sequential chemotherapy were analysed. The pooled HR was 1.01 [95% CI 0.65 to 1.56]. However, there was significant statistical heterogeneity (P = 0.04). Eight trials (De Souza, Gisselbrecht, Kaiser, Kluin-Nelemans, Martelli 2003, Milpied, Rodriguez 2003, Verdonck), which applied abbreviated standard induction therapy before HDT, did not show a significant effect but a trend towards better overall survival within the control group (HR 1.15 [95% CI 0.97 to 1.35]). There was no statistical heterogeneity present.

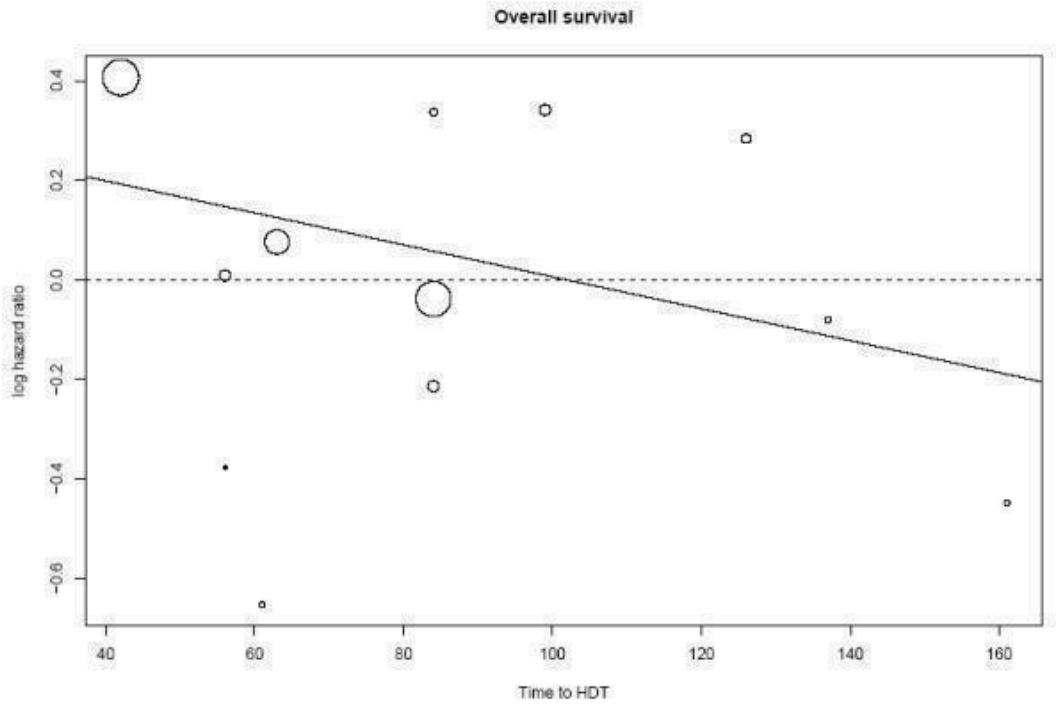
Four trials that applied HDT after full standard induction (Haioun, Intragumtornchai, Martelli, Santini) showed also no difference (HR 0.87 [95% CI 0.69 to 1.10]).

With respect to the different high-dose concepts there were no evidence for statistical heterogeneity or differences between groups.

A subgroup analysis of 11 trials that randomised patients irrespectively of their disease status (De Souza, Gianni, Gisselbrecht, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli 2003, Milpied, Rodriguez 2003, Santini, Vitolo) did not show a significant difference (HR 1.06 [95% CI 0.92 to 1.23], test for heterogeneity 0.09). The exclusion of the EORTC trial (Kluin-Nelemans), which randomised patients in PR and CR, did not change the result (data not shown). Subgroup analysis of two trials (Martelli, Verdonck) that randomised patients with partial response did not reveal a significant difference (HR 1.09 [95% CI 0.65 to 1.83], P = 0.75). One trial (Haioun) that randomised only patients in CR after full standard induction therapy showed no statistical difference between treatment arms (HR 0.96 [95% CI 0.71 to 1.30]).

There was a statistically significant difference (P = 0.033) between studies reporting results by intention-to-treat analysis (HR 0.92; 0.77 to 1.09) compared to no ITT (HR 1.22; 1.00 to 1.49). Excluding those studies where individual patient data were not available the HR for overall survival increases (HR 1.14; CI 0.98 to 1.34). Further sensitivity analyses did not reveal any heterogeneity (see MetaView).

Figure 2. Meta-regression: OS.



Event-free survival (EFS)

This analysis was restricted to studies which randomised patients upfront or in PR. IPD were available from nine trials (De Souza, Gisselbrecht, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Martelli 2003, Santini, Verdonck); for three additional trial HRs were calculated from the published (Gianni, Milpied) or unpublished study data (Vitolo). Thus, twelve trials with 1,795 patients were included. As shown in MetaView, there was no evidence for improved EFS in patients receiving HDT when compared to conventional chemotherapy (HR 0.92; CI 0.80 to 1.05). Strong evidence for statistical heterogeneity among the trials was present (P = 0.002). We observed a significant difference (P = 0.004) between trials including more or less than 70% of patients with diffuse large cell lymphoma favouring studies with higher percentage of patients with DCLC. None of the other subgroups tested demonstrated a statistically significant difference between the subgroups compared. In both good and poor risk patients there was no evidence for an effect of HDT on EFS (good risk: HR 1.02; CI 0.75 to 1.37, poor risk: HR 0.95; CI 0.81 to 1.11). Strong evidence for heterogeneity was present in the poor risk patients group (P = 0.007). After excluding the study published by Gisselbrecht et al. (Gisselbrecht) the heterogeneity observed was reduced (P = 0.10) and a survival benefit became apparent in the poor risk group (HR 0.78, CI 0.65 to 0.94). However, even after excluding Gisselbrecht et al. the difference between good and poor risk patients was not statistically significant (P = 0.145). Excluding the positive studies (Intragumtornchai, Milpied) heterogeneity was reduced (P = 0.18) and no evidence for an effect of HDT on survival was seen (poor risk: HR 1.07; CI 0.90 to 1.26).

Regarding the subgroup of studies with high-dose sequential therapy, the trial by Gianni et al. demonstrated a significant improvement (76% [CI 60 to 89%] for the patients receiving HDT and 49% [CI 32 to 65%] for the control group, log-rank test: P = 0.004); however, the pooled HR was 0.75 ([95% CI 0.51 to 1.12], P = 0.16). There was significant heterogeneity among these trials (P = 0.01). The pooled HR for seven trials that applied HDT after abbreviated induction therapy was 0.97 ([95% CI 0.84 to 1.13], P = 0.7). These subgroup analyses for EFS revealed significant statistical heterogeneity, which was not apparent when excluding the Gisselbrecht trial. There was no significant effect pooling data of trials applying HDT after full standard induction (HR 0.74; CI 0.50 to 1.10).

According to the overall analysis for EFS the performed sensivity analyses revealed further heterogeneity.

Based on the data available, there is no evidence that HDT improves EFS in the first-line treatment of good and poor risk patients with aggressive NHL. The heterogeneity observed was mainly caused by the study published by Gisselbrecht et al. Exclusion of this study eliminates the heterogeneity and results in a significant improvement regarding EFS for patients with poor

prognosis according to the IPI score and for patients who received abbreviated standard induction before HDT.

Complete response rate (CR)

Fourteen studies including 2,126 patients were analysed (De Souza, Gianni, Gisselbrecht, Intragumtornchai, Kaiser, Kluin-Nelemans, Martelli, Martelli 2003, Milpied, Rodriguez 2003, Santini, Santini-2, Verdonck, Vitolo). The relative risk to achieve CR was 1.11 favouring patients treated with HDT (RR 1.11; CI 1.04-1.18). There was no statistical heterogeneity among the trials (P = 0.09).

Subgroup analysis did not reveal significant differences:

The relative risk for patients with low and low-intermediate IPI was RR 0.98 [95% CI 0.80 to 1.21] and for patients with high-intermediate and high risk IPI RR 1.02 [95% CI 0.93 to 1.13] (see MetaView 03-02) with no significant difference between groups. This analysis was based on eight trials and 1,182 patients.

Subgroups analysis according to different high-dose protocols did also not show significant differences between the groups.

Based on the available data there was a significant effect for HDT to improve CR rate in the total study sample size.

Meta-regression analysis

Linear meta-regression analysis of the time when HDT was applied after induction therapy within the trials was performed. The intervals used can be obtained from Table 3. With regard to OS, EFS, and CR rates 12, 9, and 11 trials were included respectively. The results did not show any association between the time of HDT application to these endpoints (see figures: Figure 2, Figure 3, Figure 4).

Based on this analysis, there was no indication that the time point of HDT application influenced the outcome. However, this estimate is based on indirect comparisons only.

Figure 3. Meta-regression: EFS.

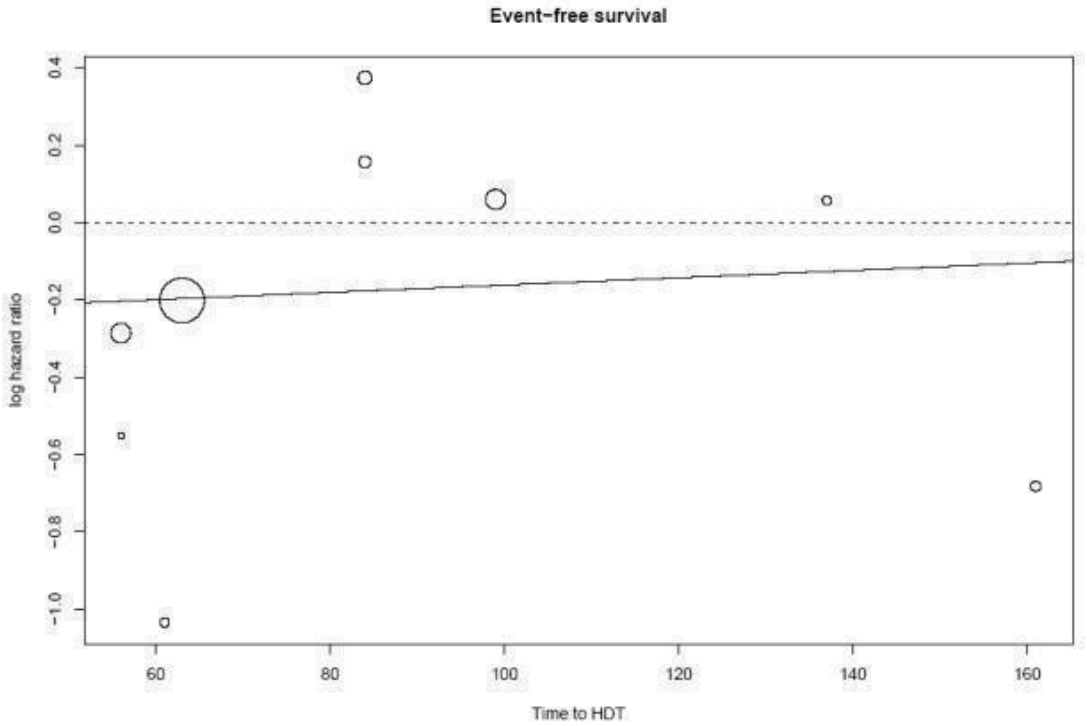
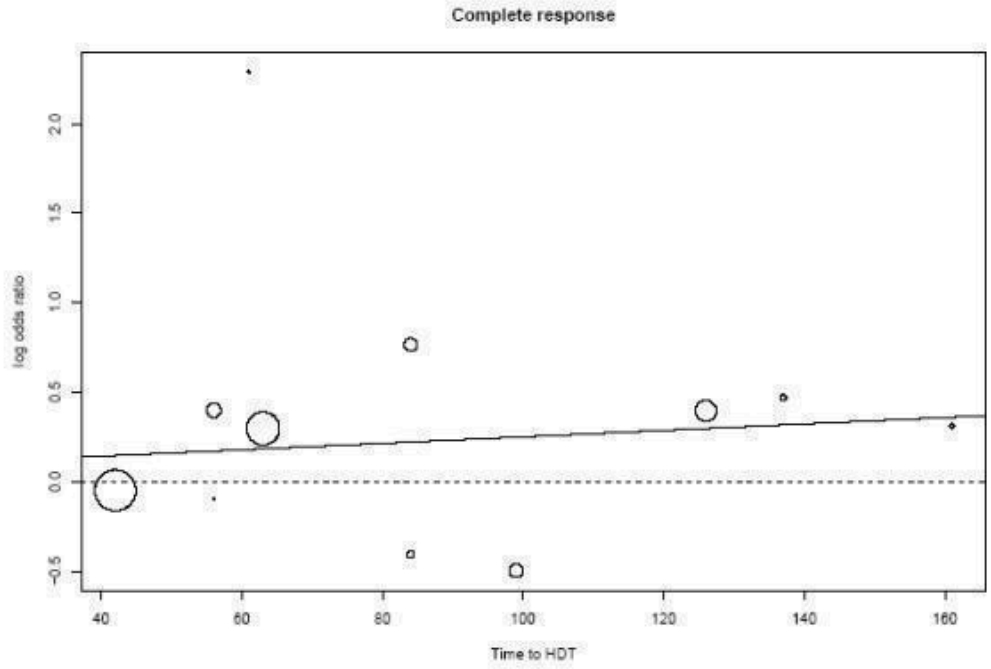


Figure 4. Meta-regression: CR.



Disease-free survival (DFS)/Relapse-free survival (RFS)

DFS was applied only to patients who obtained a CR after induction therapy. The duration was measured from date of achieving CR to the date of relapse, death or last follow-up. RFS was also applied to patients who reached a CR only, and measured to the date of relapse or last follow-up. In contrast to the definition for DFS, patients who died were calculated as censored instead of event.

Five trials with 350 patients were pooled in this analysis (Gianni, Intragumtornchai, Martelli 2003, Santini, Verdonck). The pooled HR was 0.63 in favour of patients receiving HDT using the fixed effect model (HR 0.63 [95% CI 0.42 to 0.96], P = 0.03) (see Meta-View 04). There was no significant heterogeneity among trials (P = 0.10) but the sensitivity analysis addressing the respective end-point used, i.e. DFS or RFS, respectively, revealed a significant between group heterogeneity (P = 0.031). A stronger treatment effect could be seen in three trials in which RFS was assessed (HR 0.37 [95% CI 0.19 to 0.70]) as compared to assessment of DFS in two trials (HR 0.93 [95% CI 0.54 to 1.59]). Therefore, pooling of DFS and RFS was not appropriate.

Based on the available data, there was significantly improved RFS for patients who received a HDT as compared to patients who received conventional chemotherapy.

Survival after relapse

Two trials (Kaiser, Martelli 2003) including 118 patients who relapsed were analysed. The pooled HR was 2.05 [95% CI 1.32 to 3.17] and the test of significance was P = 0.0014, favouring patients who received conventional chemotherapy (see MetaView 05). This effect was similar using both the fixed and the random effects model. There was no statistical heterogeneity between the trials (P = 0.55).

Based on the available data, survival was statistically significantly worse for patients who relapsed after HDT as part of first-line therapy compared to patients who relapse after conventional chemotherapy. No effect was seen for DFS.

Progression-free survival

PFS was reported in four trials. Results could not be pooled, as HR was only estimable in one trial. Reported results are shown in Table 7.

Treatment related mortality (TRM) - Mortality during treatment (MDT)

Thirteen trials including 2,361 patients were analysed (De Souza, Gianni, Gisselbrecht, Haioun, Intragumtornchai, Kaiser, Martelli, Martelli 2003, Milpied, Santini, Santini-2, Verdonck, Vitolo). Higher mortality was seen in patients treated with HDT, but the effect was not statistically significant (OR 1.33 [95% CI 0.91 to 1.93], P = 0.14) (see MetaView 06-01). There was no statistical heterogeneity among the trials (P = 0.59). As definitions for treatment related deaths could not be clarified definitely, a subgroup analysis of "treatment related mortality", "mortality during treatment" and "other similar

terms" as defined in the original publications was performed. In none of these subgroups significant results became apparent and no significant between-groups differences were measured. Sensitivity analyses for quality and size of study, proportion of DLCL, HDT protocol adherence, bone marrow involvement, preparative regimen, type of high-dose protocol did not show significant differences.
The proportion of patients with treatment related deaths ranged widely from 0% to 32%. However, except in the trial by Kaiser et al., none found significant more treatment related deaths in patients treated with HDT. Based on the available data, there was a non-significantly higher risk of treatment related deaths in the HDT group.

Toxicities
Analyses according to the number of patients who had leuko- or neutropenia (four trials with 597 patients) as well as thrombocytopenia (five trials with 967 patients) greater than grade two as defined by the WHO classification did show significantly stronger myelosuppression in the HDT group (RR: 1.59 [1.46; 1.72] and 6.08 [4.74; 7.81]; both analyses P<0.00001) (see MetaView 07). There was significant statistical heterogeneity among trials but all trials demonstrated the same trend.
Six trials were analysed for infection greater than grade two as defined by the WHO classification. The infection rate was significantly higher for patients treated with HDT (RR 4.42 [95% CI 2.75 to 7.08], P<0.00001, test for heterogeneity: P = 0.008) (see MetaView 07).
To assess the incidence of secondary neoplasm six trials including 757 patients could be aggregated. This analysis showed no significant difference between treatment groups (RR 0.94 [95% CI 0.39 to 2.25], P = 0.88, test for heterogeneity: P = 0.48) (see MetaView 07). The median follow-up time was short (range: 39 to 55 months). Based on the available data, there was clear evidence for higher rates of adverse events in the HDT arm. But the median follow-up was too short to draw an accurate conclusion concerning the development of secondary neoplasm. Reported results are shown in Table 8.

Quality of life (QoL)
Two of the included trials assessed QoL. Results could not be pooled as different methods of assessment were applied.
A quality of life-adjusted time without symptom and toxicity (Q-TWIST) method was applied to patients included in the LNH-87 trial (Mounier 2000). This method compares treatments by defining relevant clinical health states and estimating their respective durations without patients self assessment by questionnaires. There was a non-significant trend towards increased median time of Q-TWiST for patients treated with HDT (by analysing areas under the curve). Furthermore, a significant quality-adjusted survival gain in high risk patients treated with HDT was found. In the HOVON study (Verdonck) QoL and cost-utility analyses were done for 51 patients of the 73 randomised. Concerning QoL within the first two years post treatment, complaints and symptoms were more often/severe in the HDT arm than in the CHOP arm. Considering life long consequences in terms of quality-adjusted life years, HDT patients experienced 0.14 life years and 0.22 quality-adjusted life years less than the patients in the CHOP arm (Uyl-de Groot 1995).
The results of these two investigations were contradictory when compared and no definitive conclusion can be drawn.

Results of Methodological Assessment

Selection bias
As described above, in all but two studies (Gianni, Santini-2) the concealment of allocation and method of randomisation was rated as adequate. For the study published by Gianni et al. no information was available. However, inclusion or exclusion of these studies did not change the result for overall survival.

Performance bias
Performance bias can not be excluded since blinding with placebo was not possible for the transplantation procedure used in the included studies.

Attrition bias
Nine trials included for the primary outcome measure followed the intention to treat principle, i.e. including all randomised patients in the final analysis (De Souza, Haioun, Intragumtornchai, Kluin-Nelemans, Milpied, Martelli, Martelli 2003, Santini, Verdonck,). The remaining trials excluded some randomised patients in the final analysis who violated inclusion criteria (Gianni, Gisselbrecht, Kaiser, Rodriguez 2003, Vitolo). For the publication of the HOVON trial (Verdonck) four ineligible patients had been excluded from their analysis. However, due to the availability of IPD, the results of the HOVON trial could be integrated based on the intention-to treat principle. In total, data of 97% randomised patients were evaluable for this analysis. Due to this high number and the fact that adequate reasons for exclusion were given, we assumed the absence of attrition bias.

Publication bias
A funnel plot analysis was performed to investigate for publication bias or other biases. Although graphical asymmetry could be observed for OS and EFS indicating that studies with negative findings might be underrepresented, related linear regression tests did not show significance (data not shown). Consequently there is no evidence for publication bias.

Reporting bias
All included studies have been published. Some data and trial characteristics included in our review were provided and cannot be found in the published reports.
For those trials we were provided with IPD by the investigators we also extracted the results reported in the corresponding articles. This was done as a further component to test the robustness of our results. To achieve this, we compared the results of published data to the results obtained from IPD of the same trials according to OS. It is mentionable that for the analyses of endpoints such as DFS, RFS and survival after relapse in particular, we had to deal with selectiveness, as not all these endpoints were reported for all trials.

Sensitivity analyses
To incorporate the influence of clinical diversity of the included trials to some extent, we performed multiple sensitivity analyses, which are mentioned separately for each outcome measured. In general, we found some imbalance that was related to the largest trial by Gisselbrecht et al.

DISCUSSION

This systematic review was undertaken to evaluate the influence of high dose chemotherapy (HDT) in the first-line treatment of patients with aggressive Non-Hodgkin Lymphoma (NHL). It is based on 15 prospectively randomised trials including a total of 2,728 patients. The following findings emerge from this analysis:

(i) In general, there was no evidence that HDT improves overall survival (OS) (HR 1.05; CI 0.92-1.19) or event free survival (EFS) (HR 0.92; CI 0.80-1.05). (ii) In patients with good risk aaIPI there was some evidence for worse OS (HR 1.46; CI 1.02-2.09) when treated with HDT. (iii) In contrast, there was suggestive but inconclusive evidence that poor risk patients may benefit from HDT. After excluding a clinically unfavourable study (26), the HR was 0.80 for OS (CI 0.67-0.96) and 0.78 for EFS (CI 0.65-0.94).

The fate of patients with aggressive NHL remains unsatisfactory, particularly for those with intermediate and poor risk according to the international prognostic index (Project 1993). In an attempt to improve the prognosis, several clinical trials examined HDT followed by autologous stem cell support. Although retrospective analyses had suggested that HDT might be superior to conventional chemotherapy (Freedman 1993, Nademanee 1997, Fanin 1998, Cortelazzo 1999), the findings of prospectively randomised clinical trials gave conflicting results.

Pooled analyses of the data from published trials may shed some light on the impact of HDT in this setting. Two prior meta-analyses, however, failed to provide definite answers (Simnett 2000, Strehl 2003). This research evaluated a variety of different entities including both solid tumours and haematological malignancies or had fewer patients compared to the present analysis. Most importantly, both studies did not evaluate individual patient data. In contrast, the present systematic review and meta-analysis is primarily based on IPD data for the most important outcome measures OS and EFS. In fact, the odds ratios used in the previous analyses are based on cumulative death rates at one particular time point and are considered to increase the risk of biased results (Duchateau 2001).

Strengths of the present meta-analysis:

The internal validity of 12 out of 15 trials covering more than 90% of included patients was given. Additionally, the performed sensitivity analysis addressing the influence of those two studies with uncertain validity did not indicate any influence. Funnel plot analyses did not show any evidence for publication bias. The presence of attrition bias was unlikely as data of 97% patients randomised were included. Possible bias due to the use of unpublished individual patient data and published data (Buyse 1987, Jeng 1995, Stewart 1993) was ruled out as a comparison of both data types did not show any differences.

By using only hazard ratios for the analysis of time-to-event data, the risk of bias by inaccurate statistical method such as using odds ratios, which base on particular time points only, could be minimised.

Additionally, we incorporated potential confounders such as the response status of patients before receiving HDT, the proportion of protocol adherence and the conditioning regimens used in subgroup and sensitivity analyses. Our analysis suggests that none of these factors have an influence on the results reported here. Further confounders such as different standard chemotherapy could not be addressed on the basis of the data available and are being discussed here. Although CHOP is commonly seen as the gold standard treatment for aggressive lymphoma, there were only four trials which applied CHOP in the control group. Most of the other regimens were not compared in a randomised controlled trial or not compared at all. In addition some trials applied an intensified chemotherapy in the control arm (ACVB, CHOEP, MegaCEOP). With respect to different histologies, the patient characteristics varied considerably across the trials. As certain NHL entities might respond better or worse to HDT (Deconinck 2000, Melnyk 1997, Intragumtornchai 03, Lippman 1988, Coiffier 1990, Gisselbrecht 1998), it is conceivable that these variations might lead to a distortion of our pooled analyses.

With regard to histological classification, it was difficult to assess the proportion of diffuse large cell lymphoma (DLCL) within the trials due to the different classifications used (WF, Kiel, REAL) and the limitations of transferability. However, the proportion of DLCL, which is the largest group of aggressive NHL, was analysed in a sensitivity analysis and thus the influence of this confounder was diminished. Other sub entities such as anaplastic, T-cell, and very fast growing NHL for which different outcome are described in the literature (Deconinck 2000, Intragumtornchai 03, Gisselbrecht 1998, Sweetenham), could not be analysed separately. However, as these sub entities are relatively rare they are unlikely to have distorted the overall analyses.

Taking the results form all clinical studies analysed, there was no evidence for HDT to improve OS or EFS in this group of patients. However, there were some differences between risk groups stratified according to the age-adjusted International Prognostic Index. Good risk patients i.e. those with low or low-intermediate risk according to aaIPI showed some evidence for impaired OS with HDT. In contrast, there was no negative impact of HDT for OS in poor risk patients, i.e. those with high-intermediate and high aaIPI risk score. There was however significant heterogeneity between the trials analysed in the subset of poor risk patients. This heterogeneity can be attributed to three trials which showed either very good (Haioun, Milpied) or very bad results (Gisselbrecht). Excluding the detrimental study published by Gisselbrecht et al resulted in reduction of heterogeneity in the OS and the EFS analysis and improved outcomes for poor risk patients. However, after exclusion of the positive studies (Haioun, Milpied), the positive effects of HDT on OS and EFS in poor patients disappeared. These conflicting results can be accounted for, in part, by different inclusion criteria and chemotherapy regimens used in the trials. The trial by Haioun et al used late consolidation in responders, and the trial by Gisselbrecht et al used early intensification with short therapy.

Obviously, removing the Gisselbrecht et al data on OS and EFS from this analysis poses questions as to the validity of this operation. This trial was stopped at the first interim analysis due to the poor results in the HDT arm (Gisselbrecht). Subsequently, the 5 year OS for patients receiving HDT and standard chemotherapy was 46 +/- 8% and 60 +/- 8%; EFS was 39 +/- 8% and 52 +/- 8% (Gisselbrecht). Even though the rationale of the abbreviated trial design was to introduce HDT early, the dose intensity in the HDT arm was lower in comparison to the conventional arm consisting of a dose-intensified CHOP variant (ACVBP). In the HDT arm, a new CHOP variant (CEOP) was introduced with doxorubicin replaced by the less effective epirubicin. On the other hand, this trial included a substantial number of very high-risk patients such as patients with T-cell lymphoma, bone marrow involvement, bulky disease and elevated LDH. It has been shown that poorly controlled aggressive NHL is associated with a high probability of contaminating malignant cells in the stem cell transplant (Jacquy 2000).

Two studies included in the present meta-analysis had given statistically significant better OS for poor risk patients when treated with HDT (Haioun, Milpied). Interestingly, the LNH87-2 study was the only trial applying HDT for poor risk patients in CR after full standard conventional chemotherapy. The other study randomised 197 patients between standard CHOP and HDT consisting of two cycles of CEEP followed by methotrexate and ARA-C with BEAM (Milpied). In 105 patients with high-intermediate risk according to

aaIPI, OS and EFS were 74% and 56% in the HDT arm and 44% and 28% in the CHOP arm, respectively (P = 0.001). Importantly, although induction treatment before HDT was shorter than in the conventional therapy arm, 86% of these patients achieved CR after two courses of CEEP compared to 84% of patients after four courses of CHOP. Thus, one important aspect in designing clinical trials for patients with poor risk aggressive NHL is the need to adequately control disease activity in these fast growing malignancies as much as possible before HDT is given.

A limitation of our study with regards to OS and EFS is that complete data sets were not available for all the studies included. The analysis was further hampered by the diversity of the various standard and high-dose chemotherapy protocols applied and the lack of standardized definitions for outcome parameters as already mentioned.

Treatment-related mortality (TRM) was not significantly higher with HDT compared to conventional chemotherapy. This finding indicates that the TRM is unlikely responsible for the lack of survival benefit observed in our pooled results. Additionally noteworthy, it was observed or assumed, respectively, that a significant number of patients in the control arm received HDT as second-line therapy, which might have balanced a beneficial effect of first-line HDT for overall survival. This might be exemplified in the trial reported by Santini et al. (Santini-2), which compared first-line HDT with second-line HDT after conventional VACOP-B. In this trial, no survival differences could be detected.

In addition, our analysis of two trials with regard to survival after relapse demonstrated significantly better survival for patients being allocated to the control arm. This may indicate that the outcome of relapsed patients who were previously treated with HDT is poor. This is in accordance to previously published observational studies (Philip 1995, Mills 1995, Kewalramani 2000). Thus, patients who receive HDT as part of their first-line therapy may not be suitable for a second HDT. In contrast, for conventionally treated patients the option of HDT as effective salvage remains. The efficacy of the latter strategy has been previously shown by Philip et al. (Philip 1995). It demonstrated that HDT is more effective than the DHAP regimen as salvage therapy in chemosensitive patients, who relapsed after initial conventional chemotherapy.

Our study indicates that HDT-treated patients showed some evidence for improved CR rates as well as improved RFS but no difference for EFS. Although it is generally expected that patients achieving CR are more likely to survive, the higher rate of patients reaching CR did not translate into better survival. A significant advantage favouring HDT in terms of RFS in three trials suggests at least some influence of HDT as first-line therapy in achieving a better eradication of the disease in the subgroup of patients who reached complete remission. On the other hand, the pooled results for DFS, which by definition also comprises only patients in CR, did not indicate any difference. Our findings concerning EFS have to be interpreted cautiously because statistical heterogeneity was apparent, and we could only consider those eleven trials (1,601 patients) that reported or provided data.

With the availability of the anti-CD20 monoclonal antibody Rituximab for both groups, patients with low grade NHL (Marcus 2005) and patients with aggressive NHL (Coiffier 2002, Coiffier 1998, Vose 2001), nearly all current and future studies will incorporate Rituximab or similar antibodies. This approach is currently being investigated by the Intergroup-trial S9704. Recently published studies have suggested that dose-dense CHOP variants such as CHOP-14 or CHOEP-14 (Pfreundschuh 2004-1, Pfreundschuh 2004-2) or ACVB (Tilly 2003) might also improve the outcome in aggressive NHL. It remains to be seen whether the combination of dose/time intensified CHOP + Rituximab can be improved by HDT.

The principle of dose escalation (i.e. dose-dense chemotherapy) has become steadily more popular in various malignancies in recent years. This view is based on the assumption that the reduction of tumour mass might follow a proportional relation between dose and efficacy. Improved supportive care and the accomplishment of toxicities have decreased the mortality of the HDT approach. In this context the American Society for Blood and Marrow Transplantation (ASBMT) recommends sequential HDT (HDS) as first-line therapy for patients with high-intermediate and high risk IPI (Hahn 2001, Hahn 2003). However, on the basis of our results we cannot confirm this recommendation as we did not find sufficient evidence. This guideline is largely based on a single trial including 98 patients with IPI low to high risk (Gianni) that demonstrated improved EFS without significantly improved OS for the whole trial population. In contrast, when pooling data of three trials applying sequential HDS strategy in our analysis, there was no evidence for a difference between patients receiving HDS and those with standard-dose treatment in terms of OS and EFS. In general, the analysis of different types of HDT including early HDT, late intensification and sequential HDT did not give evidence for a different efficacy or benefit, respectively, for any of these applied strategies.

Our observed results for patients with NHL seems to be in contrast to the improvements achieved for other malignancies, such as those of high-dose therapy in multiple myeloma, or the escalated BEACOPP regimen in patients with Hodgkin's disease. Regarding these entities, the efficacy of treatment might linearly depend on the dose per time or the accumulation of chemotherapy. Concerning aggressive NHL we might have reached the limitation of the biological activity and efficacy, respectively, of the commonly applied drugs, exemplary in shape of the CHOP regimen. This might explain why the present results do not indicate that the sequence or the time point of HDT administration in the treatment setting influences its efficacy.

Another explanation for the missed superiority of HDT might be that the efficacy is less following hypotheses such as of Goldie-Coldman and Norton-Simon (Goldie 1979, Norton 1982, Norton 1986), which assume that the addition of further drugs and shorter therapy intervals, respectively, improve tumour cell kill. In contrast, an other model suggests the hypothesis of reversible resistance, where the interval between chemotherapy cycles should allow sufficient time for the reacquisition of tumour sensitivity. However, this was observed mainly in slow growing tumours (Frei 1999).

AUTHORS' CONCLUSIONS

Implications for practice

Overall, with respect to the large population included in our analyses and the attempts made to minimise bias and confounding, we conclude that there is no evidence for a general benefit of the therapeutic principle of myeloablative chemotherapy followed by autologous stem cell transplantation for patients with aggressive NHL as first-line treatment based on the data presently available. Significant improvements for RFS and CR of all available trials are outweighed by the lack of evidence for a benefit concerning the OS in the respective groups. Most importantly, IPI low-risk patients appear to be harmed by HDT in first-line treatment: patients with good risk had better overall outcome after conventional chemotherapy. However, if HDT is employed for high risk patients,

physicians should not arbitrarily employ HDT during first-line treatment, but adhere to one of the proven beneficial strategies as a whole, or participate in large trials.

Implications for research

With respect to the latter, a more reasoned developed concept of trial design building upon previous findings is strongly recommended. This should include the harmonization of procedures and definitions, which would facilitate the comparability of results, and improve the assessment of therapeutic intervention. Further research should aim at either reproducing the studies showing positive trends or applying new approaches that do not solely rely on the principle of myeloablation with non-cross resistant drugs.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

De Souza

Methods	Randomised controlled trial Number of centres: 7 Location: Brazil Years: September 1998, still recruiting Interim results Sponsorship: no industrial Central pathology review: no Definition of Complete Response: ECOG criteria
Participants	Number of patients randomised: 54 (54 analysed) Our analysis: 54 Patients untreated: yes INCLUDED: Histology: Groups F, G, H and K (Working Formulation) IPI score: age-adjusted high-risk only Age: inclusion criterion not clarified (range of randomised patients 17-60 years)

De Souza *(Continued)*

	EXCLUDED: not clarified
Interventions	Control group: VACOP-B 12 weeks Experimental group: VACOP-B 6 weeks followed by sequential high-dose therapy and ABMT Randomization upfront
Outcomes	Overall survival Event-free survival Disease-free survival Response rates
Notes	source: abstract and personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Gianni

Methods	Randomised controlled trial Number of centres: not stated Location: Italy Years: 1987 - not stated Final Analysis Sponsorship: Sandoz and Schering-Plough; Consiglio Nazionale delle Ricerche, Rome; Associazone Italiana per la Ricerca sul Cancro, Milan Central pathology review: not stated Definition of Complete Response: ECOG criteria
Participants	Number of patients randomised: 101 (98 patients analysed) Our analysis: 98 Patients untreated: yes INCLUDED: Histology: groups G and H (Working Formulation) IPI: no restriction Age: 17-60 years EXCLUDED: stage I non-bulky; lymphoma cell infiltration of bone marrow; T-cell immunophenotype; follicular component in biopsy; abnormal cardiac, pulmonary, renal, and hepatic function; HIV, hepatitis B and C
Interventions	Control group: MACOP-B 12 weeks Experimental group: High-dose sequential therapy and PBSC or ABMT, consolidation radiotherapy allowed, cross-over allowed if tumour reduction was 80% or less (patients received respectively MACOP-B and high-dose sequential therapy as salvage) Randomisation upfront
Outcomes	Freedom from disease progression Overall survival Event-free survival Freedom from relapse Response rates
Notes	source: paper

Gianni *(Continued)*

	3 patients excluded from the analysis due to concomitant liver disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Gisselbrecht

Methods	Randomised controlled trial Number of centres: multi-centre Location: France and Belgium Years: March 1993 - September 1995 Preclosure due to significantly lower event-free survival in experimental arm Sponsorship: Ministere de la Sante France, Assistance Publique Hopitaux Paris, Amgen-Roche Neuilly sur Seine, Asta-Mediac Merignac Number of withdrawals: not stated Central pathology review: yes (70% of patients) Definition of Complete Response: disappearance of all clinical evidence of disease and normalization of all laboratory values, radiographs, and biopsies from sites that had initially been abnormal. Pts. with persistent CT abnormalities but >75% regression of the initial tumour were considered to be unconfirmed CR (CRu) if in CR on all other parameters
Participants	Number of patients randomised: 397 (370 patients analysed) Our analysis: 370 Patients untreated: yes INCLUDED: Histology: aggressive lymphoma (Kiel and WHO classification) IPI: age-adjusted: at least 2 factors Age: 15-60 years EXCLUDED: lymphoblastic or Burkitt lymphoma with meningeal or bone marrow involvement, primary cerebral lymphoma; concomitant or previous cancer; congestive heart failure, liver or kidney failure; HIV
Interventions	Control group: ACVBP 4 cycles followed by sequential consolidation Experimental group: shortened induction (CEOP 1 cycle and ECVBP 2 cycles) followed by BEAM and PSCT or ABMT Randomization upfront
Outcomes	Event-free survival Overall survival Disease-free survival Response rates
Notes	source: paper 27 patients excluded from the analysis due to ineligibility (15x incorrect histology, 1x Burkitt with bone marrow involvement, 1x HIV, 10x missing data)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Haioun

Methods	Randomised controlled trial Number of centres: 35 Location: France and Belgium Years: October 1987 - February 1993 Final analysis Sponsorship: Delegation a la Recherche Clinique de l'Assistance Publique-Hopitaux de Paris, Fondation contre la Leucemie Paris, Laboratoires: Roger Bellon Neuilly sur Seine, Wyeth-Lederle Nanterre, Asta Medica Oncology, Merignac Central pathology review: yes (87% of patients) Definition of complete response (evaluated after induction): disappearance of all clinical evidence of disease; normalization of all laboratory values, radiographs, and biopsies; patients with persistent computed tomographic abnormalities but regression greater than 75% of initial tumour
Participants	Number of patients randomised: 541 (subgroup analysis on 236 patients with age-adjusted high-intermediate and high-risk IPI patients) Our analysis: 541 for overall results, 236 for IPI subgroup analysis Patients untreated: yes INCLUDED: Histology: intermediate or high-grade NHL (Working Formulation) IPI: no restriction (setting before 1993) Age: 16-55 years Presentation of at least one of the following adverse factors: ECOG performance status >1, extranodal sites >1, tumour burden 10cm or more, bone marrow or CNS involvement, Burkitt or lymphoblastic subtype (latter two without bone marrow or CNS involvement) EXCLUDED: concomitant or previous cancer; congestive heart failure, recent myocardial infarction or conduction abnormalities, uncontrolled diabetes mellitus, liver or kidney failure; HIV
Interventions	Control group: ACVB or NCVB followed by sequential consolidation regimen Experimental group: ACVB or NCVB followed by intensive consolidation and ABMT Randomization of patients in complete remission after induction therapy with ACVB or NCVB ACVB compared to NCVB as first randomisation (NCVB arm stopped 1991 due to significant advantage of ACVB)
Outcomes	Disease-free survival Overall survival
Notes	source: paper (1994, 1997, 2000) 1043 patients enrolled, 127 of them considered ineligible, so 916 patients received induction chemotherapy, 614 achieved a complete response, of these 541 patients were randomisedN =, 268 patients of these 541 had high-intermediate or high risk IPI

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Haioun (subgroup)

Methods	
Participants	

Haioun (subgroup) *(Continued)*

Interventions	
Outcomes	
Notes	subgroup analysis of Haioun 1997 for IPI high-risk patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	D - Not used

Intragumtornchai

Methods	Randomised controlled trial Number of centres: 2 Location: Thailand Years: May 1995 - April 1998 Target reached Sponsorship: Roche Thailand, International Clinical Epidemiology Network (majority of funding came from industry, reports and database completed and held independently from industry sponsor) Central pathology review: yes Defintion of complete response: disappearance of all measurable or evaluable disease, signs, or symptoms related to the tumour for at least 4 weeks
Participants	Number of patients randomised: 48 Patients Our analysis: 48 untreated: yes INCLUDED: Histology: groups F, G, and H (Working Formulation) IPI: age-adjusted high-intermediate and high risk Age: 15-55 years EXCLUDED: medical history of severe cardiac, renal, and hepatic diseases; HIV
Interventions	Control group: CHOP 8 cycles Experimental group: CHOP 3 cycles followed by ESHAP 2-4 cycles, HDT and PSCT Randomization after 3 cycles of CHOP
Outcomes	Overall survival Disease-free survival Failure-free survival Response rates
Notes	source: paper and personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Kaiser

Methods	Randomised controlled trial Number of centres: 71 Location: Germany, Switzerland, Sweden Years: 1990 - June 1997 Interim results Sponsorship: Deutsche Krebshilfe (no industrial sponsorship) Central pathology review: yes Definition of complete response: disappearance of all tumour detectable (clinical examination, imaging, biochemical analysis, biopsy) Method of randomisation: Computer random-number generator
Participants	Number of patients randomised: 331 (312 patients analysed) Our analysis: 312 Patients untreated: yes INCLUDED: Histology: high-grade (aggressive) lymphoma (Kiel classification) LDH above normal value IPI: no restriction Age: 18-60 years EXCLUDED: stage I
Interventions	Control group: CHOEP 5 cycles Experimental group: CHOEP 3 cycles followed by BEAM and ABMT or PSCT involved field radiotherapy in both arms in case of at least partial remission; staging after 2 cycles CHOEP: treatment continued if patients achieved at least a minor response Randomization upfront
Outcomes	Overall survival Event-free survival Response rates
Notes	source: paper and personal communication 19 patients (13x Control, 6x Experimental group) excluded from the analysis due to violation of entry criteria (9x change of histologic disease by the reference pathologist, 2x secondary lymphoma, 3x bone marrow infiltration greater than 25%, 1x secondary malignancy, 1x age less than 18, 1x immediate withdrawal after randomisation, 1x HIV, 1x extensive bone marrow infiltration)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Kluin-Nelemans

Methods	Randomised controlled trial Number of centres: 22 Location: Netherlands, Belgium, Spain, Italy Years: December 1990 - October 1998 Final analysis Sponsorship: Public Health Service from the National Cancer Institute, National Institutes of Health, Department of Health and Human Servivces Central pathology review: yes

Kluin-Nelemans *(Continued)*

	Definition of complete response: WHO criteria
Participants	Number of patients randomised: 194 (194 patients analysed) Our analysis: 194 Patients untreated: yes INCLUDED: Histology: groups D, E, F, and G (Working Formulation), additionally stages I bulky, II, III, and IV with diffuse large-cell immunoblastic, anaplastic large-cell, large and small cell pleomorphic T-cell, and angio-immunblastic with dysproteinaemia-like T-cell lymphoma IPI: no restriction Age: 15-60 years EXCLUDED: low-grade, lymphoblastic and Burkitt lymphoma, stage I, performance status (WHO) greater than 2, severe cardiac, pulmonary, neurologic, or metabolic disease
Interventions	Control group: CHVmP/BV 8 cycles Experimental group: CHVmP/BV 6 cycles followed by BEAC and ABMT or PSCT Radiotherapy allowed in both arms Randomization: after 3 cycles CHVmP/BV for patients in CR or PR without involvement of bone marrow and without contradictions for bone marrow ablative therapy (WHO performance status 0 or 1, no severe cardiac, pulmonary, neurologic, infectious, or metabolic disease)
Outcomes	Progression-free survival Overall survival
Notes	source: paper and personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Martelli

Methods	Randomised controlled trial Number of centres: 7 Location: Italy Years: August 1988 - August 1991 Precolure due to low recruitment rate Sponsorship: Associazione Italiana per la Ricerca sil Cancro Milano, Associazione Italiana contro le Leucemie Roma (no industrial sponsorship) Central pathology review: yes Definition of complete response: CR, when response exceeds 80% of previous manifestations to the CT scans
Participants	Number of patients randomised: 49 (49 analysed) Our analysis: 49 Patients untreated: yes INCLUDED: Histology: high-grade NHL according to Kiel classification (diffuse large-cell centroblastic and immunoblastic (groups G and H according to Working Formulation), Burkitt lymphoma (group J), anaplastic large-cell and pleomorphic T-cell lymphoma (unclassifiable) IPI: no restriction Age: 15-60 years EXCLUDED:

Martelli *(Continued)*

	stage I without mediastinal presentation; performance status (ECOG) greater than 2; abnormal renal, hepatic, and cardiac function; HIV
Interventions	Control group: F-MACHOP 4 cycles or MACOP-B 8 cycles followed by DHAP 6 cycles Experimental group: F-MACHOP 4 cycles or MACOP-B 8 cycles followed by BEAC and ABMT consolidation radiotherapy allowed Randomization: after 4 cycles F-MACHOP respectively 8 cycles MACOP-B for patients in PR (response between 50-80% of the original manifestation), patients in CR and those with a response of less than 50% were considered out of protocol
Outcomes	Overall survival Progression-free survival
Notes	source: paper and personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Martelli 2003

Methods	Randomised controlled trial Number of centres: 18 Location: Italy Years: September 1994 - September 1999 Target reached Sponsorship: no industrial, Ministero dell' Univerita e Ricerca Scientifica (MURST) 40%, Italy Central pathology review: yes Definition of Complete Response: WHO criteria
Participants	Number of patients randomised: 150 (150 analysed) Our analysis: 150 Patients untreated: yes INCLUDED: Histology: aggressive non-Hodgkin lymphoma (REAL-classification) of diffuse large B-cell, peripheral T-cell, anaplastic lymphoma IPI: age-adjusted high-intermediate and high-risk Age: 15-60 years EXCLUDED: stage I non-bulky; abnormal renal, pulmonary cardiac, and hepatic function; HIV, hepatitis B and C
Interventions	Control group: MACOP-B 12 weeks Experimental group: MACOP-B 8 weeks followed by high-dose therapy and PBSC or ABMT Involved field radiation allowed in both arms on bulky disease and residual mass Randomization upfront
Outcomes	Overall survival Progression-free survival Relapse-free survival Response rates
Notes	source: paper and personal communication

Martelli 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Milpied

Methods	Randomised controlled trial Number of centres: 16 Location: France Years: November 1994 - December 1999 Final analysis Sponsorship: Schering Laboratories of France Central pathology review: yes Definition of Complete Response: disappearance of all documented disease. An unconfirmed complete response was defined by a reduction of at least 70 percent in the largest diameter of all measurable lesions in association with a complete response with respect to all other measures.
Participants	Number of patients randomised: 197 Our analysis: 197 Patients untreated: yes INCLUDED: Histology: intermediate and high-grade NHL IPI: age-adjusted low, low-intermediate, high-intermediate Age: 15-60 years EXCLUDED: IPI high-risk
Interventions	Control group: CHOP 8 cycles Experimental group: CEEP 2 cycles, followed by high-dose MTX and Cytarabine, followed by BEAM and PSCT Randomization: upfront
Outcomes	Overall survival Event-free survival Disease-free survival Freedom from progression
Notes	source: abstract + personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Rodriguez 2003

Methods	Randomised controlled trial Number of centres: number not stated Location: not stated

Rodriguez 2003 *(Continued)*

	Years: September 1995 - April 2002 Sponsorship: not stated Central pathology review: not stated Definition of Complete Response: not stated
Participants	Number of patients randomised: 116 Our analysis: 108 Patients untreated: yes INCLUDED: Histology: large cell lymphoma (diffuse, follicular, anaplastic), peripheral T-cell lymphoma, and high risk clinical presentation tumour score > 2 (bulky mass, high ß2-microglobulin, B-symptoms, stage IV, high LDH, extranodal sites, primary mediastinal presentation) IPI: not stated Age: up to 60 years
Interventions	Control group: 9 cycles of three alternating chemotherapy regimens (ATT), and replacing doxorubicin with idarubicin Experimental group: 2 cycles of ATT, followed by two intensified chemotherapy cycles , followed by BEAM and ASCT
Outcomes	Overall survival, Failure-free survival, Response rates
Notes	source: abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Santini

Methods	Randomised controlled trial Number of centres: 16 Location: Italy Years: October 1991 - June 1995 Target reached Sponsorship: no industrial Central pathology review: yes Definition of Complete Response: complete disappearance of disease for at least 4 weeks, patients with residual mass and no sign of disease for at least 3 months were also judged as CR
Participants	Number of patients randomised: 124 (124 analysed) Our analysis: 124 Patients untreated: yes INCLUDED: Histology: diffuse intermediate and high-grade NHL (including mixed and large-cell according to Working Formulation) IPI: no restriction Age: 15-60 years EXCLUDED: lymphoblastic and Burkitt lymphoma; stage I, stage II non-bulky; bone marrow involvement; abnormal renal, pulmonary, cardiac, and hepatic function; HIV, hepatitis B and C
Interventions	Control group: VACOP-B 12 weeks Experimental group: VACOP-B 12 weeks followed by BEAM and ABMT

Santini *(Continued)*

	consolidation radiotherapy allowed; in both arms DHAP regimen was given for relapsed patients Randomization: upfront
Outcomes	Overall survival Disease-free survival Progression-free survival
Notes	source: paper and personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Santini-2

Methods	Randomised controlled trial Number of centres: 18 Location: Italy Years: August 1995 - March 2001 Final analysis Sponsorship: not stated Central pathology review: not stated Definition of Complete Response: not stated
Participants	Number of patients randomised: 223 Our analysis: 223 Patients untreated: yes INCLUDED: Histology mixed and diffuse large cell NHL IPI: no restriction 15-59 years EXCLUDED: stage I, stage II non-bulky
Interventions	Control group: VACOP-B 12 weeks Experimental group: VACOP-B 8 weeks followed by high-dose sequential therapy and PSCT Patients in control arm received high-dose sequential therapy and PSCT as salvage therapy, patients in experimental arm received DHAP as second line treatment Randomization: upfront
Outcomes	Overall survival Disease-free survival Progression-free survival Response rates
Notes	source: paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Verdonck

Methods	Randomised controlled trial Number of centres: 10 Location: Netherlands and Belgium Years: January 1987 - April 1994 Target reached Sponsorship: no industrial, Commission on Investigative Medicine of the Dutch National Health Insurance Board Central pathology review: yes (88% of patients) Definition of complete response: disappearance of all clinical evidence (physical and radiographic), patients with residual abnormalities decreased in size by 90% and biopsy proven uninvolvement were also considered to be in complete remission
Participants	Number of patients randomised: 73 (73 analysed) Our analysis: 73 Patients untreated: yes INCLUDED: Histology: Working Formulation groups D, E, F, G, and H IPI: no restriction Age: 15-60 years EXCLUDED: low grade lymphoma, group I or J (Working Formulation); stage I; prior cancer (except cervical carcinoma stage I and non-melanoma skin cancer); central nervous system involvement; severe cardiac, pulmonary, neurologic, or metabolic disease; HIV
Interventions	Control group: CHOP 8 cycles Experimental group: CHOP 4 cycles followed by high-dose chemotherapy (including total-body irradiation) and ABMT Randomization: after 3 courses CHOP for patients with partial remission (see notes) and no bone marrow involvement
Outcomes	Event-free survival Overall survival Disease-free survival Response rates
Notes	source: paper and personal communication Definition of partial remission: reduction by at least 25% of the sum of the largest tumour diameters

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Vitolo

Methods	Randomised controlled trial Number of centres: not clarified Location: Italy Years: January 1997 - September 2000 Target reached Sponsorship: Amgen, majority of funding industrial, main reports and database completed and held independently from sponsor Number of withdrawals:

Vitolo *(Continued)*

	Central pathology review: no Definition of complete response: WHO criteria
Participants	Number of patients randomised: 130 (126 analysed) Our analysis: 126 Patients untreated: yes INCLUDED: Histology: diffuse large cell, peripheral T-cell, anaplastic large cell lymphoma (REAL classification) IPI: age-adjusted: intermediate-high or high risk; OR patients with bone marrow involvement regardless of IPI score Age: <60 years EXCLUDED: non-advanced stage; abnormal renal, liver function; cardiac ejection <50%, inadequate bone marrow function (neutrophils < 1,5 x 1000000000/l, platelets < 50 x 1000000000/l); CNS involvement; performance status >2; neoplasia in the last 5 years; life expectancy < 3 months; HbsAg+, hepatitis C, HIV
Interventions	Control group: MegaCEOP 6 to 8 cycles Experimental group: APO 1 to 2 cycles followed by high-dose therapy and ASCT Patients in experimental arm with bone marrow involvement received 2 cycles APO, others 1 course Randomization upfront
Outcomes	Overall survival Disease-free survival Failure-free survival Response rates
Notes	source: abstract and personal communication 4 patients excluded from the analysis due to major violations

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Patients untreated means: no lymphoma related treatment before study entry, according to inclusion and exclusion criteria: only stated criteria are mentioned (especially important for abstract as source, Randomisation upfront=before treatment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Linch	So far, this study is only published as abstract and no data were available from the authors. Due to missing information to calculate HRs this trial was not included in our results.
Sweetenham	This trial included only patients with very fast growing NHL were randomised. The biological behaviour as well as the treatment of this histological entity is different from aggressive NHL.

DATA AND ANALYSES

Comparison 1. Overall Survival

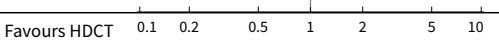
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall Survival - all studies	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
2 Overall Survival - different high-dose settings	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
2.1 High-dose sequential therapy without induction	2		Hazard Ratio (Fixed, 95% CI)	1.01 [0.65, 1.56]
2.2 Abbreviated standard induction	8		Hazard Ratio (Fixed, 95% CI)	1.15 [0.97, 1.35]
2.3 Full standard induction	4		Hazard Ratio (Fixed, 95% CI)	0.87 [0.69, 1.10]
3 Overall Survival - patients' status at randomisation	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
3.1 Patients irrespectively of disease status	11		Hazard Ratio (Fixed, 95% CI)	1.06 [0.92, 1.23]
3.2 Patients in CR	1		Hazard Ratio (Fixed, 95% CI)	0.96 [0.71, 1.30]
3.3 Patients in PR	2		Hazard Ratio (Fixed, 95% CI)	1.09 [0.65, 1.83]
4 Overall Survival - methodological quality	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
4.1 Sufficient method	12		Hazard Ratio (Fixed, 95% CI)	1.06 [0.93, 1.21]
4.2 Insufficient or unknown method	2		Hazard Ratio (Fixed, 95% CI)	0.88 [0.53, 1.45]
5 Overall Survival - intention-to-treat	13		Hazard Ratio (Fixed, 95% CI)	1.04 [0.91, 1.18]
5.1 Intention-to-treat	9		Hazard Ratio (Fixed, 95% CI)	0.92 [0.77, 1.09]
5.2 No intention-to-treat	4		Hazard Ratio (Fixed, 95% CI)	1.22 [1.00, 1.49]
6 Overall Survival - study size	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
6.1 >100 patients	9		Hazard Ratio (Fixed, 95% CI)	1.09 [0.95, 1.25]
6.2 <100 patients	5		Hazard Ratio (Fixed, 95% CI)	0.82 [0.59, 1.15]
7 Overall Survival - protocol adherence to HDT	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
7.1 >70% of patients	9		Hazard Ratio (Fixed, 95% CI)	1.06 [0.90, 1.23]
7.2 < 70% of patients	5		Hazard Ratio (Fixed, 95% CI)	1.02 [0.81, 1.29]
8 Overall Survival - preparative HDT regimen	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 BEAC	3		Hazard Ratio (Fixed, 95% CI)	1.03 [0.73, 1.46]
8.2 BEAM	6		Hazard Ratio (Fixed, 95% CI)	1.09 [0.91, 1.31]
8.3 TBI	3		Hazard Ratio (Fixed, 95% CI)	0.83 [0.55, 1.25]
8.4 Others	2		Hazard Ratio (Fixed, 95% CI)	1.05 [0.81, 1.37]
9 Overall Survival - Bone marrow involvement	12		Hazard Ratio (Fixed, 95% CI)	1.06 [0.91, 1.22]
9.1 > 20 % of patients	5		Hazard Ratio (Fixed, 95% CI)	1.13 [0.93, 1.39]
9.2 < 20% of patients	7		Hazard Ratio (Fixed, 95% CI)	0.98 [0.79, 1.21]
10 Overall Survival - % of patients with DLCL (wide def.)	13		Hazard Ratio (Fixed, 95% CI)	1.04 [0.91, 1.18]
10.1 > 80 % DLCL	7		Hazard Ratio (Fixed, 95% CI)	0.93 [0.75, 1.15]
10.2 < 80 % DLCL	6		Hazard Ratio (Fixed, 95% CI)	1.10 [0.94, 1.30]
11 Overall Survival - % of patients with DLCL (narrow def.)	13		Hazard Ratio (Fixed, 95% CI)	1.04 [0.91, 1.18]
11.1 > 70%	6		Hazard Ratio (Fixed, 95% CI)	0.85 [0.66, 1.08]
11.2 < 70%	7		Hazard Ratio (Fixed, 95% CI)	1.12 [0.96, 1.31]
12 Overall Survival - IPD vs published data	14		Hazard Ratio (Fixed, 95% CI)	1.05 [0.92, 1.19]
12.1 Individual Patient Data	10		Hazard Ratio (Fixed, 95% CI)	1.14 [0.98, 1.34]
12.2 Published Data	4		Hazard Ratio (Fixed, 95% CI)	0.86 [0.69, 1.09]
13 Overall Survival - results from published data vs IPD of the same trials	8		Hazard Ratio (Fixed, 95% CI)	1.17 [1.04, 1.33]
13.1 IPD	8		Hazard Ratio (Fixed, 95% CI)	1.13 [0.96, 1.34]
13.2 Published data	8		Hazard Ratio (Fixed, 95% CI)	1.22 [1.02, 1.46]
14 Overall Survival - IPI groups	12		Hazard Ratio (Fixed, 95% CI)	1.01 [0.88, 1.17]
14.1 IPI - low and low-intermediate risk	6		Hazard Ratio (Fixed, 95% CI)	1.46 [1.02, 2.09]
14.2 IPI - high-intermediate and high risk	12		Hazard Ratio (Fixed, 95% CI)	0.95 [0.81, 1.11]
15 Overall Survival - IPI groups full data set	6		Hazard Ratio (Fixed, 95% CI)	1.13 [0.91, 1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 IPI - low and low-intermediate risk	6		Hazard Ratio (Fixed, 95% CI)	1.46 [1.02, 2.09]
15.2 IPI - high-intermediate and high risk full data set	6		Hazard Ratio (Fixed, 95% CI)	0.99 [0.76, 1.29]

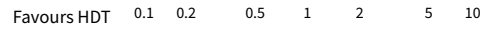
Analysis 1.1. Comparison 1 Overall Survival, Outcome 1 Overall Survival - all studies.

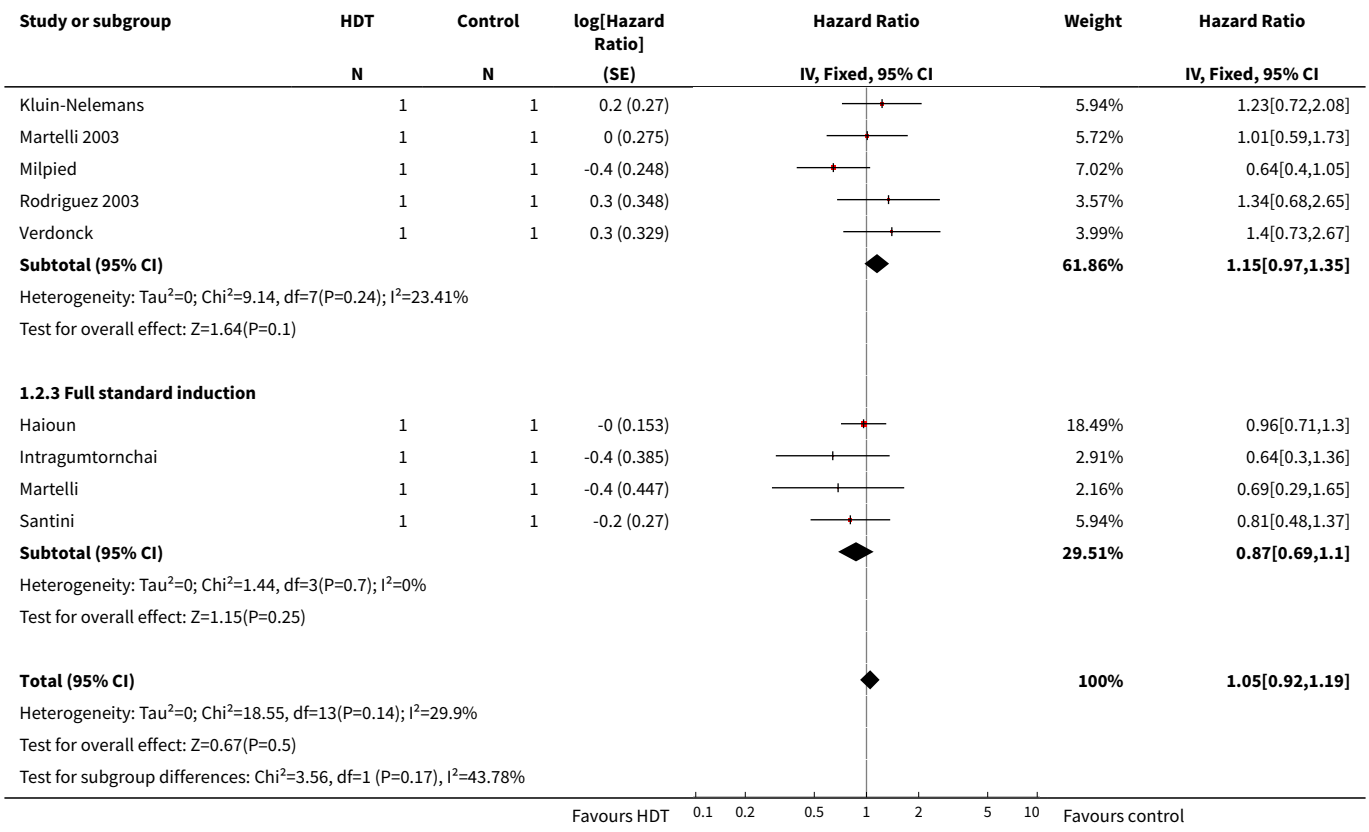
Study or subgroup	HDCT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
De Souza	1	1	-0.1 (0.367)		3.21%	0.92[0.45,1.89]
Gianni	1	1	-0.7 (0.385)		2.92%	0.52[0.24,1.11]
Gisselbrecht	1	1	0.4 (0.149)		19.55%	1.45[1.08,1.93]
Haioun	1	1	-0 (0.153)		18.49%	0.96[0.71,1.3]
Intragumtornchai	1	1	-0.4 (0.385)		2.91%	0.64[0.3,1.36]
Kaiser	1	1	0.1 (0.183)		12.85%	1.08[0.75,1.55]
Kluin-Nelemans	1	1	0.2 (0.27)		5.94%	1.23[0.72,2.08]
Martelli	1	1	-0.4 (0.447)		2.16%	0.69[0.29,1.65]
Martelli 2003	1	1	0 (0.275)		5.72%	1.01[0.59,1.73]
Milpied	1	1	-0.4 (0.248)		7.02%	0.64[0.4,1.05]
Rodriguez 2003	1	1	0.3 (0.348)		3.57%	1.34[0.68,2.65]
Santini	1	1	-0.2 (0.27)		5.94%	0.81[0.48,1.37]
Verdonck	1	1	0.3 (0.329)		3.99%	1.4[0.73,2.67]
Vitolo	1	1	0.3 (0.275)		5.72%	1.41[0.82,2.41]
Total (95% CI)					**100%**	**1.05[0.92,1.19]**
Heterogeneity: Tau^2=0; Chi^2=18.55, df=13(P=0.14); I^2=29.9%						
Test for overall effect: Z=0.67(P=0.5)						



Analysis 1.2. Comparison 1 Overall Survival, Outcome 2 Overall Survival - different high-dose settings.

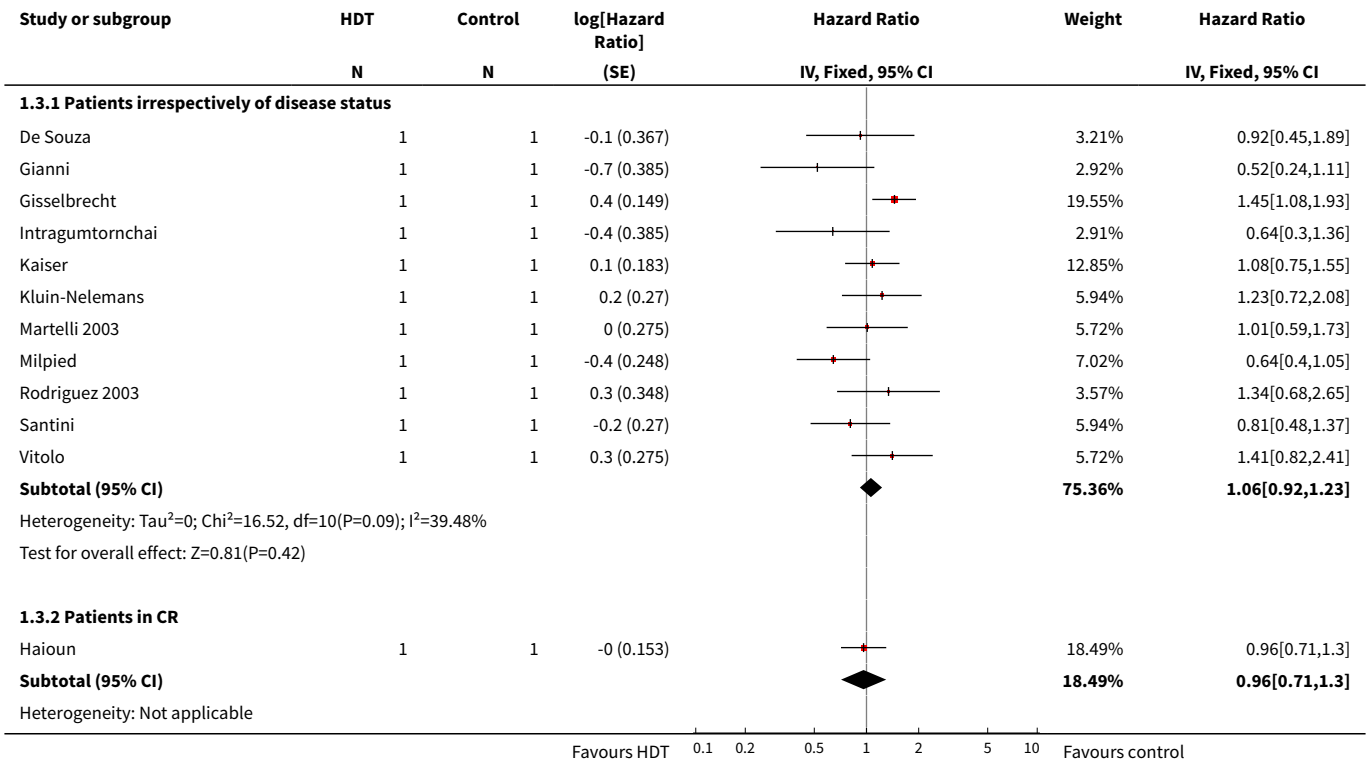
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.2.1 High-dose sequential therapy without induction						
Gianni	1	1	-0.7 (0.385)		2.92%	0.52[0.24,1.11]
Vitolo	1	1	0.3 (0.275)		5.72%	1.41[0.82,2.41]
Subtotal (95% CI)					**8.64%**	**1.01[0.65,1.56]**
Heterogeneity: Tau^2=0; Chi^2=4.41, df=1(P=0.04); I^2=77.34%						
Test for overall effect: Z=0.02(P=0.98)						
1.2.2 Abbreviated standard induction						
De Souza	1	1	-0.1 (0.367)		3.21%	0.92[0.45,1.89]
Gisselbrecht	1	1	0.4 (0.149)		19.55%	1.45[1.08,1.93]
Kaiser	1	1	0.1 (0.183)		12.85%	1.08[0.75,1.55]



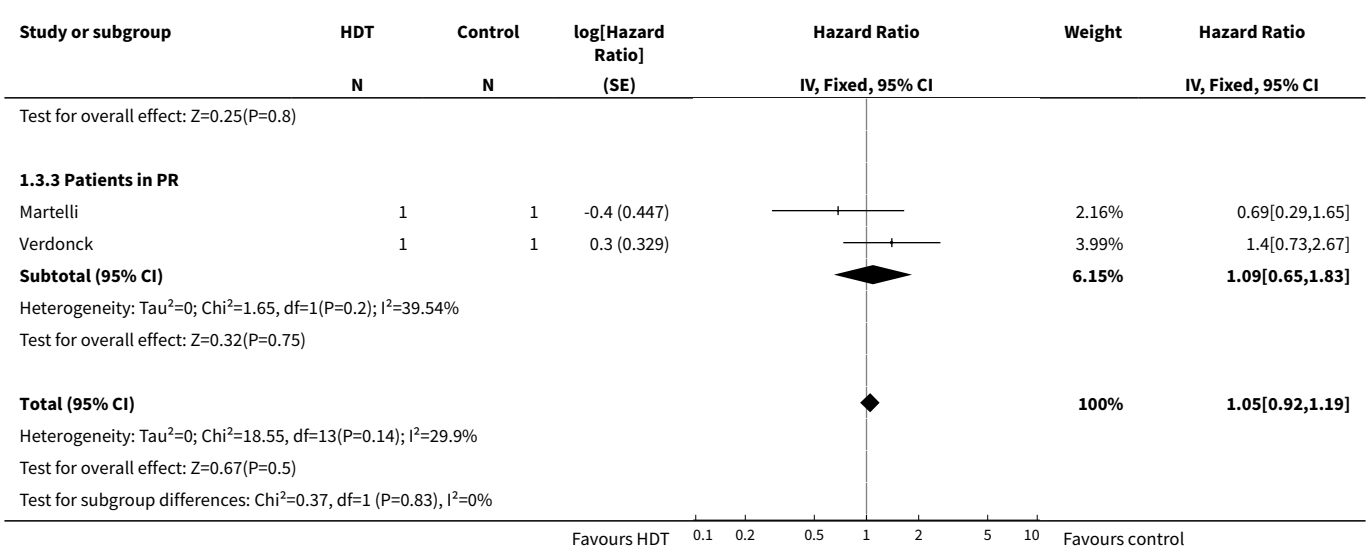


Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
Kluin-Nelemans	1	1	0.2 (0.27)		5.94%	1.23[0.72,2.08]
Martelli 2003	1	1	0 (0.275)		5.72%	1.01[0.59,1.73]
Milpied	1	1	-0.4 (0.248)		7.02%	0.64[0.4,1.05]
Rodriguez 2003	1	1	0.3 (0.348)		3.57%	1.34[0.68,2.65]
Verdonck	1	1	0.3 (0.329)		3.99%	1.4[0.73,2.67]
Subtotal (95% CI)					**61.86%**	**1.15[0.97,1.35]**
Heterogeneity: Tau²=0; Chi²=9.14, df=7(P=0.24); I²=23.41%						
Test for overall effect: Z=1.64(P=0.1)						
1.2.3 Full standard induction						
Haioun	1	1	-0 (0.153)		18.49%	0.96[0.71,1.3]
Intragumtornchai	1	1	-0.4 (0.385)		2.91%	0.64[0.3,1.36]
Martelli	1	1	-0.4 (0.447)		2.16%	0.69[0.29,1.65]
Santini	1	1	-0.2 (0.27)		5.94%	0.81[0.48,1.37]
Subtotal (95% CI)					**29.51%**	**0.87[0.69,1.1]**
Heterogeneity: Tau²=0; Chi²=1.44, df=3(P=0.7); I²=0%						
Test for overall effect: Z=1.15(P=0.25)						
Total (95% CI)					**100%**	**1.05[0.92,1.19]**
Heterogeneity: Tau²=0; Chi²=18.55, df=13(P=0.14); I²=29.9%						
Test for overall effect: Z=0.67(P=0.5)						
Test for subgroup differences: Chi²=3.56, df=1 (P=0.17), I²=43.78%						

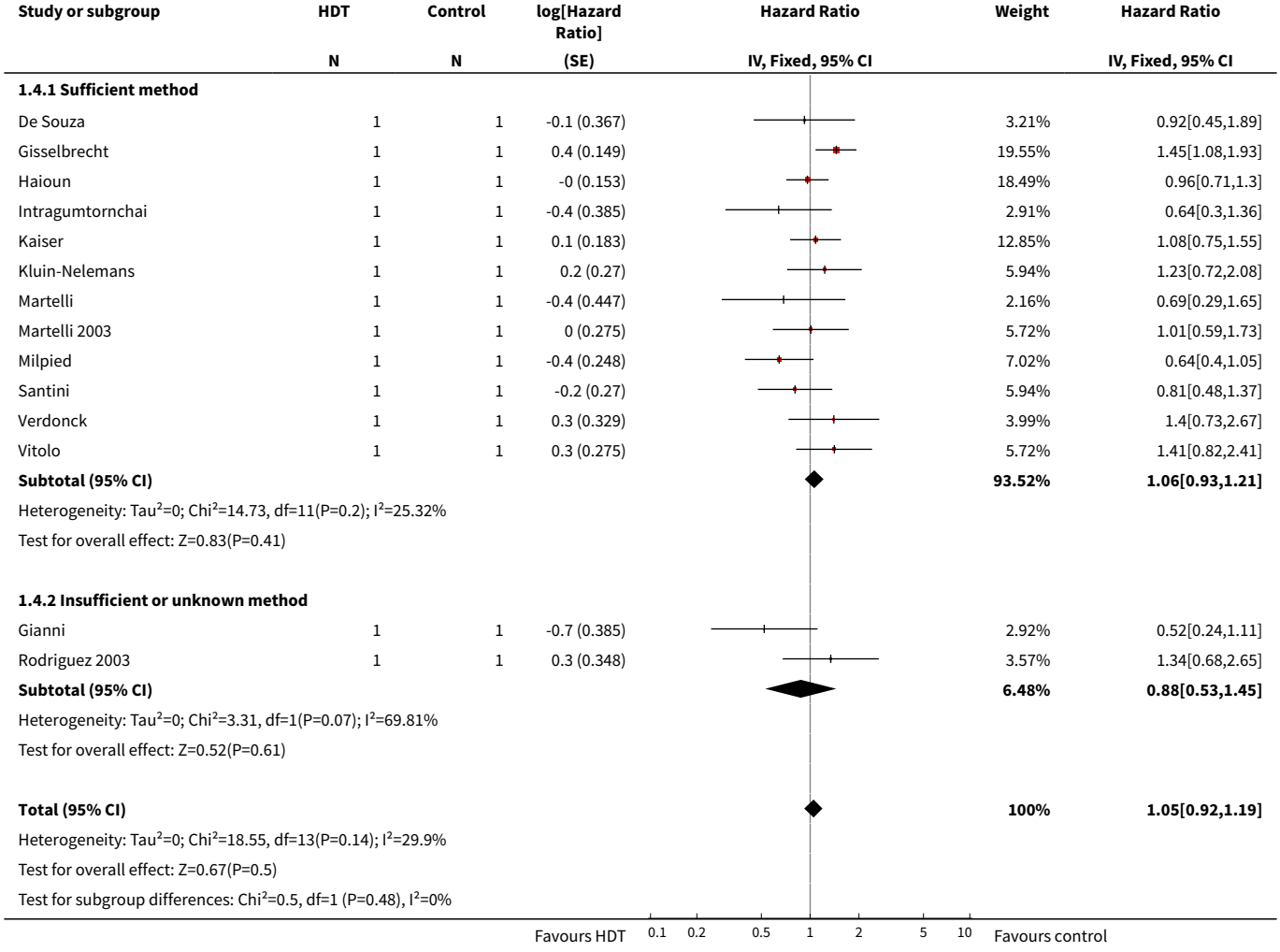
Analysis 1.3. Comparison 1 Overall Survival, Outcome 3 Overall Survival - patients' status at randomisation.



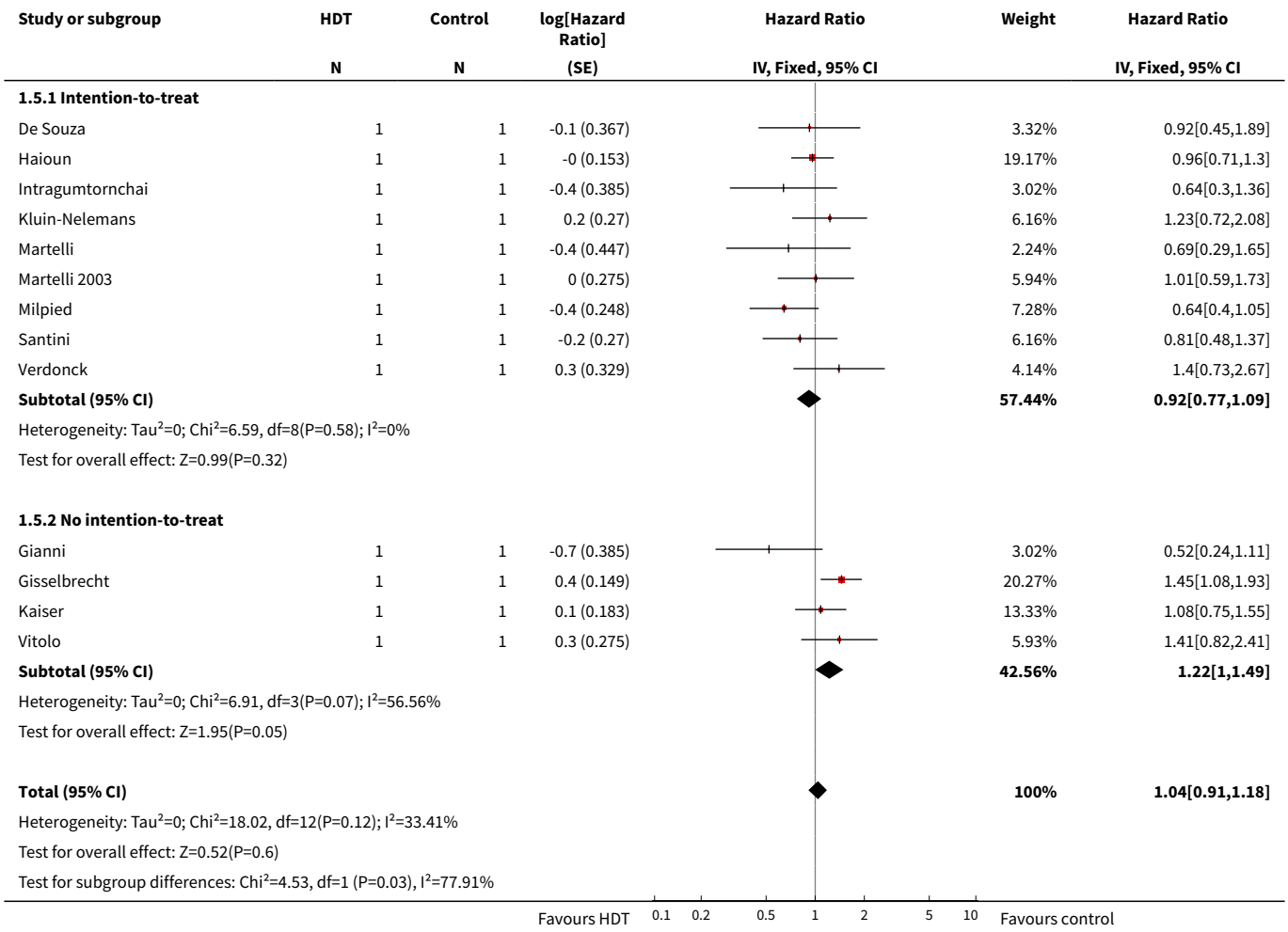
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.3.1 Patients irrespectively of disease status						
De Souza	1	1	-0.1 (0.367)		3.21%	0.92[0.45,1.89]
Gianni	1	1	-0.7 (0.385)		2.92%	0.52[0.24,1.11]
Gisselbrecht	1	1	0.4 (0.149)		19.55%	1.45[1.08,1.93]
Intragumtornchai	1	1	-0.4 (0.385)		2.91%	0.64[0.3,1.36]
Kaiser	1	1	0.1 (0.183)		12.85%	1.08[0.75,1.55]
Kluin-Nelemans	1	1	0.2 (0.27)		5.94%	1.23[0.72,2.08]
Martelli 2003	1	1	0 (0.275)		5.72%	1.01[0.59,1.73]
Milpied	1	1	-0.4 (0.248)		7.02%	0.64[0.4,1.05]
Rodriguez 2003	1	1	0.3 (0.348)		3.57%	1.34[0.68,2.65]
Santini	1	1	-0.2 (0.27)		5.94%	0.81[0.48,1.37]
Vitolo	1	1	0.3 (0.275)		5.72%	1.41[0.82,2.41]
Subtotal (95% CI)					**75.36%**	**1.06[0.92,1.23]**
Heterogeneity: Tau²=0; Chi²=16.52, df=10(P=0.09); I²=39.48%						
Test for overall effect: Z=0.81(P=0.42)						
1.3.2 Patients in CR						
Haioun	1	1	-0 (0.153)		18.49%	0.96[0.71,1.3]
Subtotal (95% CI)					**18.49%**	**0.96[0.71,1.3]**
Heterogeneity: Not applicable						



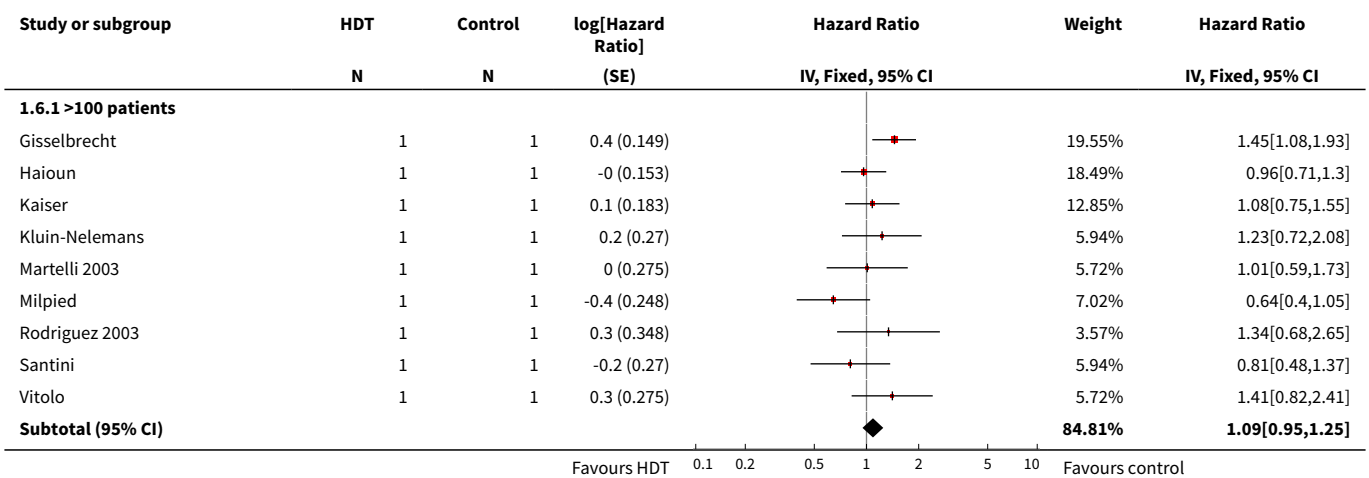
Analysis 1.4. Comparison 1 Overall Survival, Outcome 4 Overall Survival - methodological quality.

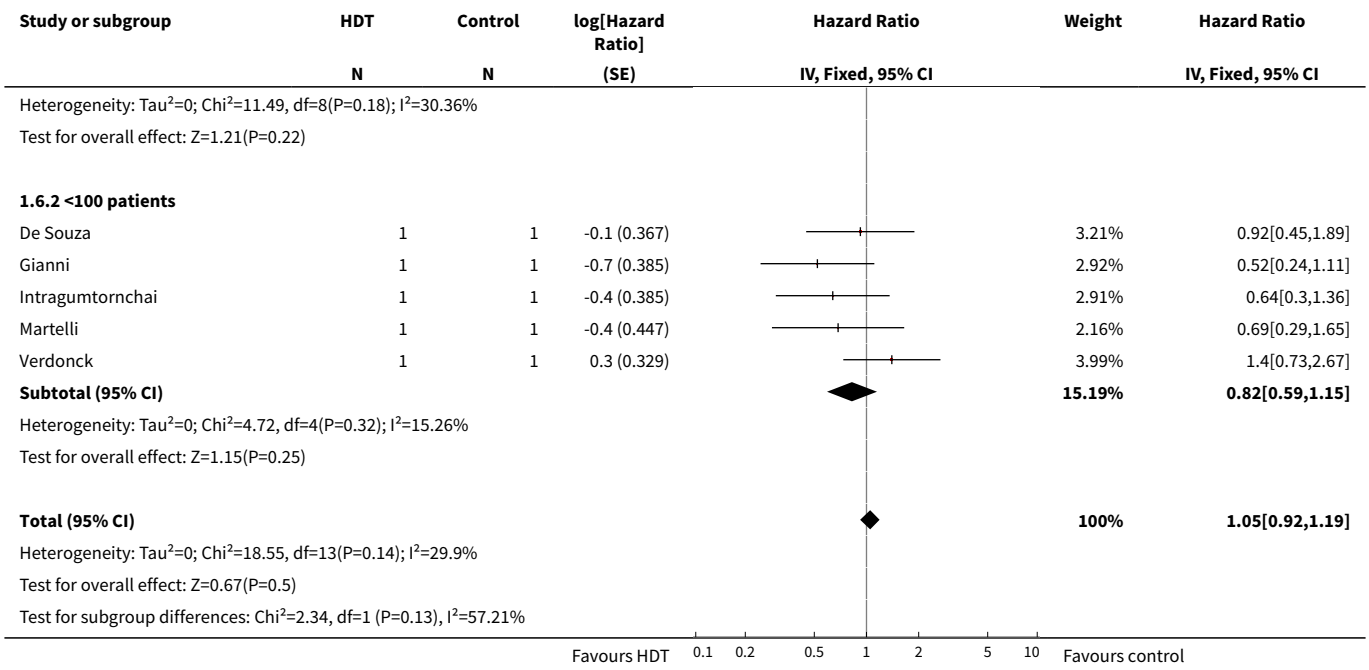


Analysis 1.5. Comparison 1 Overall Survival, Outcome 5 Overall Survival - intention-to-treat.

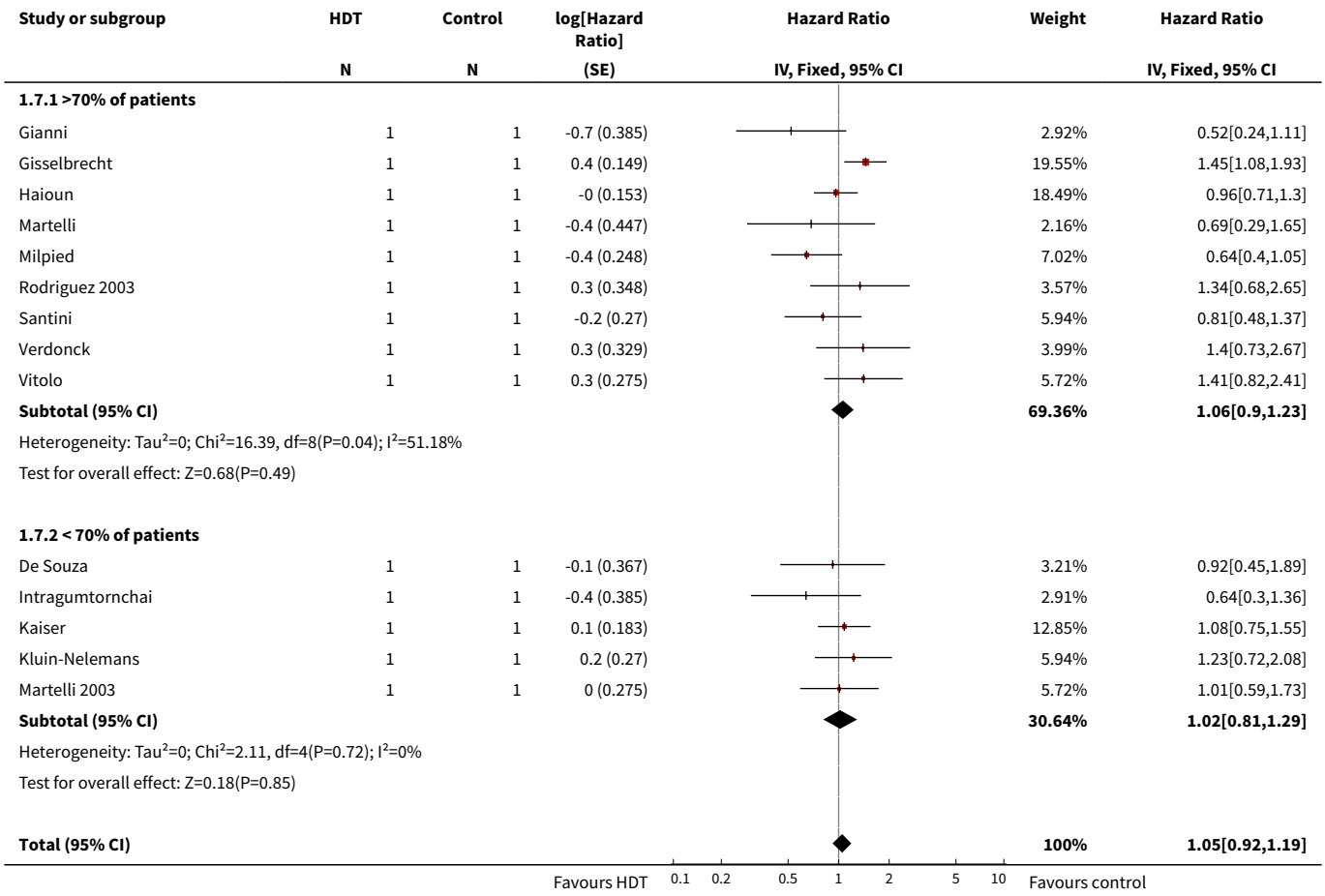


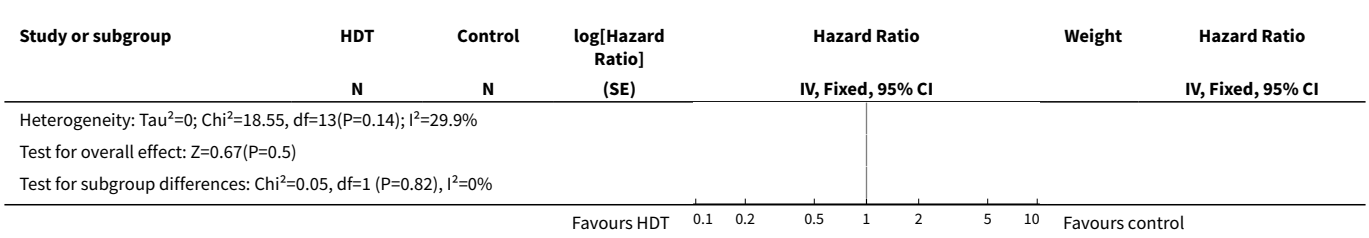
Analysis 1.6. Comparison 1 Overall Survival, Outcome 6 Overall Survival - study size.





Analysis 1.7. Comparison 1 Overall Survival, Outcome 7 Overall Survival - protocol adherence to HDT.





Analysis 1.8. Comparison 1 Overall Survival, Outcome 8 Overall Survival - preparative HDT regimen.

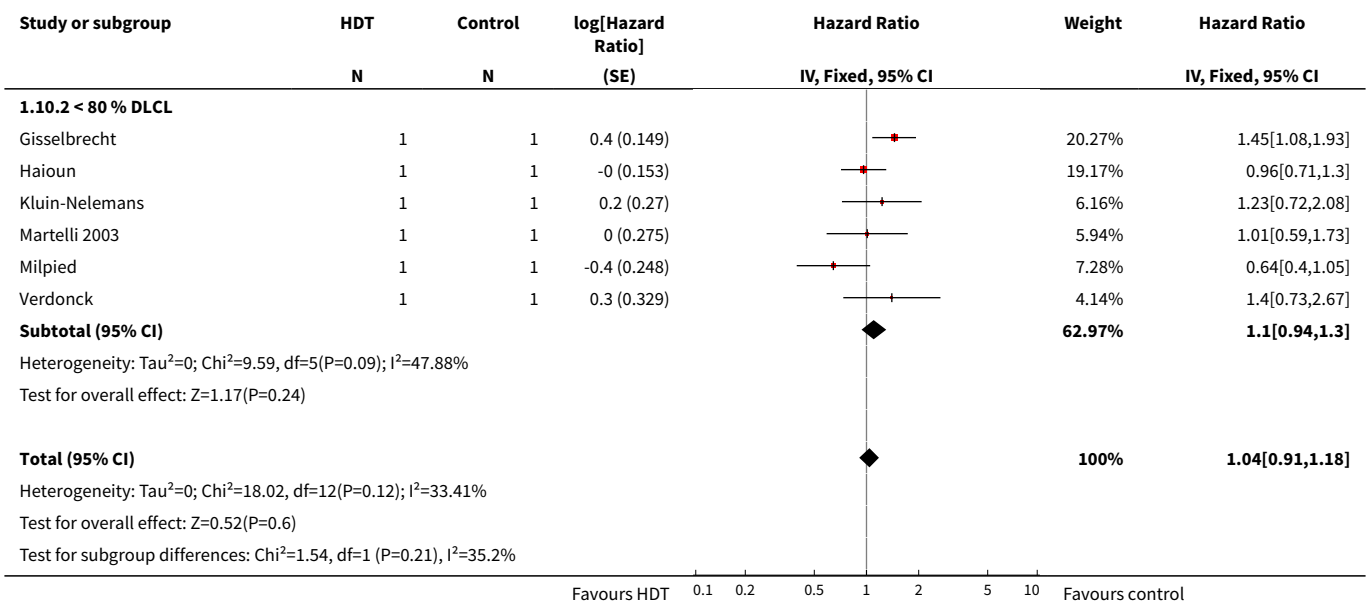
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.8.1 BEAC						
Kluin-Nelemans	1	1	0.2 (0.27)		5.94%	1.23[0.72,2.08]
Martelli	1	1	-0.4 (0.447)		2.16%	0.69[0.29,1.65]
Martelli 2003	1	1	0 (0.275)		5.72%	1.01[0.59,1.73]
Subtotal (95% CI)					**13.83%**	**1.03[0.73,1.46]**
Heterogeneity: Tau²=0; Chi²=1.25, df=2(P=0.54); I²=0%						
Test for overall effect: Z=0.18(P=0.86)						
1.8.2 BEAM						
De Souza	1	1	-0.1 (0.367)		3.21%	0.92[0.45,1.89]
Gisselbrecht	1	1	0.4 (0.149)		19.55%	1.45[1.08,1.93]
Kaiser	1	1	0.1 (0.183)		12.85%	1.08[0.75,1.55]
Milpied	1	1	-0.4 (0.248)		7.02%	0.64[0.4,1.05]
Rodriguez 2003	1	1	0.3 (0.348)		3.57%	1.34[0.68,2.65]
Santini	1	1	-0.2 (0.27)		5.94%	0.81[0.48,1.37]
Subtotal (95% CI)					**52.14%**	**1.09[0.91,1.31]**
Heterogeneity: Tau²=0; Chi²=9.9, df=5(P=0.08); I²=49.49%						
Test for overall effect: Z=0.97(P=0.33)						
1.8.3 TBI						
Gianni	1	1	-0.7 (0.385)		2.92%	0.52[0.24,1.11]
Intragumtornchai	1	1	-0.4 (0.385)		2.91%	0.64[0.3,1.36]
Verdonck	1	1	0.3 (0.329)		3.99%	1.4[0.73,2.67]
Subtotal (95% CI)					**9.82%**	**0.83[0.55,1.25]**
Heterogeneity: Tau²=0; Chi²=4.46, df=2(P=0.11); I²=55.13%						
Test for overall effect: Z=0.9(P=0.37)						
1.8.4 Others						
Haioun	1	1	-0 (0.153)		18.49%	0.96[0.71,1.3]
Vitolo	1	1	0.3 (0.275)		5.72%	1.41[0.82,2.41]
Subtotal (95% CI)					**24.21%**	**1.05[0.81,1.37]**
Heterogeneity: Tau²=0; Chi²=1.46, df=1(P=0.23); I²=31.44%						
Test for overall effect: Z=0.38(P=0.7)						
Total (95% CI)					**100%**	**1.05[0.92,1.19]**
Heterogeneity: Tau²=0; Chi²=18.55, df=13(P=0.14); I²=29.9%						
Test for overall effect: Z=0.67(P=0.5)						
Test for subgroup differences: Chi²=1.48, df=1 (P=0.69), I²=0%						

Analysis 1.9. Comparison 1 Overall Survival, Outcome 9 Overall Survival - Bone marrow involvement.

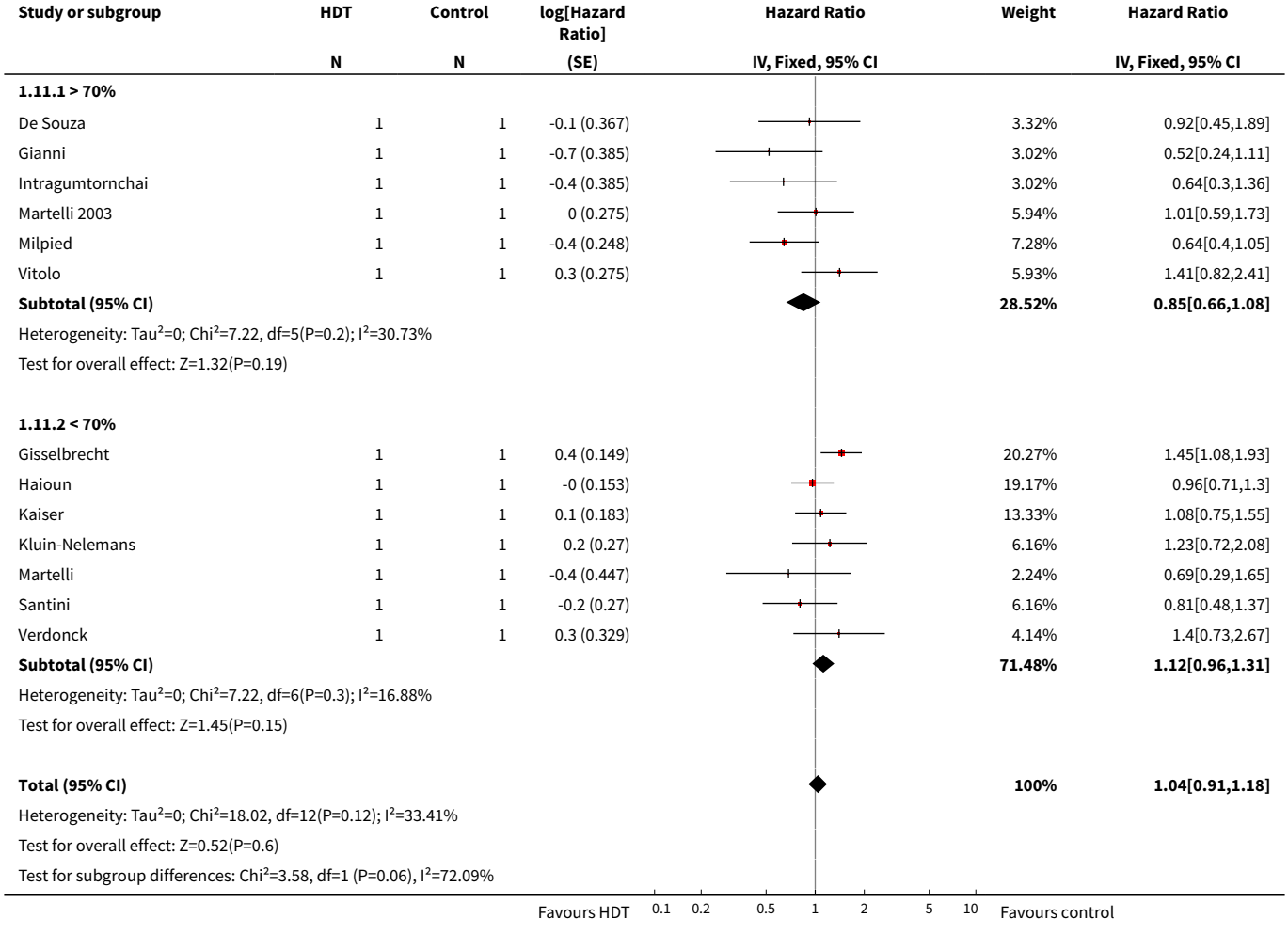
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.9.1 > 20 % of patients						
Gisselbrecht	1	1	0.4 (0.149)		25.08%	1.47[1.1,1.97]
Intragumtornchai	1	1	-0.4 (0.385)		3.74%	0.64[0.3,1.36]
Martelli 2003	1	1	0 (0.275)		7.34%	1.01[0.59,1.73]
Milpied	1	1	-0.4 (0.248)		9.01%	0.64[0.4,1.05]
Vitolo	1	1	0.3 (0.275)		7.34%	1.41[0.82,2.41]
Subtotal (95% CI)					**52.51%**	**1.13[0.93,1.39]**
Heterogeneity: Tau^2=0; Chi^2=11.29, df=4(P=0.02); I^2=64.56%						
Test for overall effect: Z=1.23(P=0.22)						
1.9.2 < 20% of patients						
De Souza	1	1	-0.1 (0.367)		4.11%	0.92[0.45,1.89]
Gianni	1	1	-0.7 (0.385)		3.74%	0.52[0.24,1.11]
Kaiser	1	1	0.1 (0.183)		16.49%	1.08[0.75,1.55]
Kluin-Nelemans	1	1	0.2 (0.27)		7.62%	1.23[0.72,2.08]
Martelli	1	1	-0.4 (0.447)		2.77%	0.69[0.29,1.65]
Santini	1	1	-0.2 (0.27)		7.62%	0.81[0.48,1.37]
Verdonck	1	1	0.3 (0.329)		5.12%	1.4[0.73,2.67]
Subtotal (95% CI)					**47.49%**	**0.98[0.79,1.21]**
Heterogeneity: Tau^2=0; Chi^2=6.02, df=6(P=0.42); I^2=0.32%						
Test for overall effect: Z=0.18(P=0.86)						
Total (95% CI)					**100%**	**1.06[0.91,1.22]**
Heterogeneity: Tau^2=0; Chi^2=18.26, df=11(P=0.08); I^2=39.75%						
Test for overall effect: Z=0.76(P=0.44)						
Test for subgroup differences: Chi^2=0.95, df=1 (P=0.33), I^2=0%						

Analysis 1.10. Comparison 1 Overall Survival, Outcome 10 Overall Survival - % of patients with DLCL (wide def.).

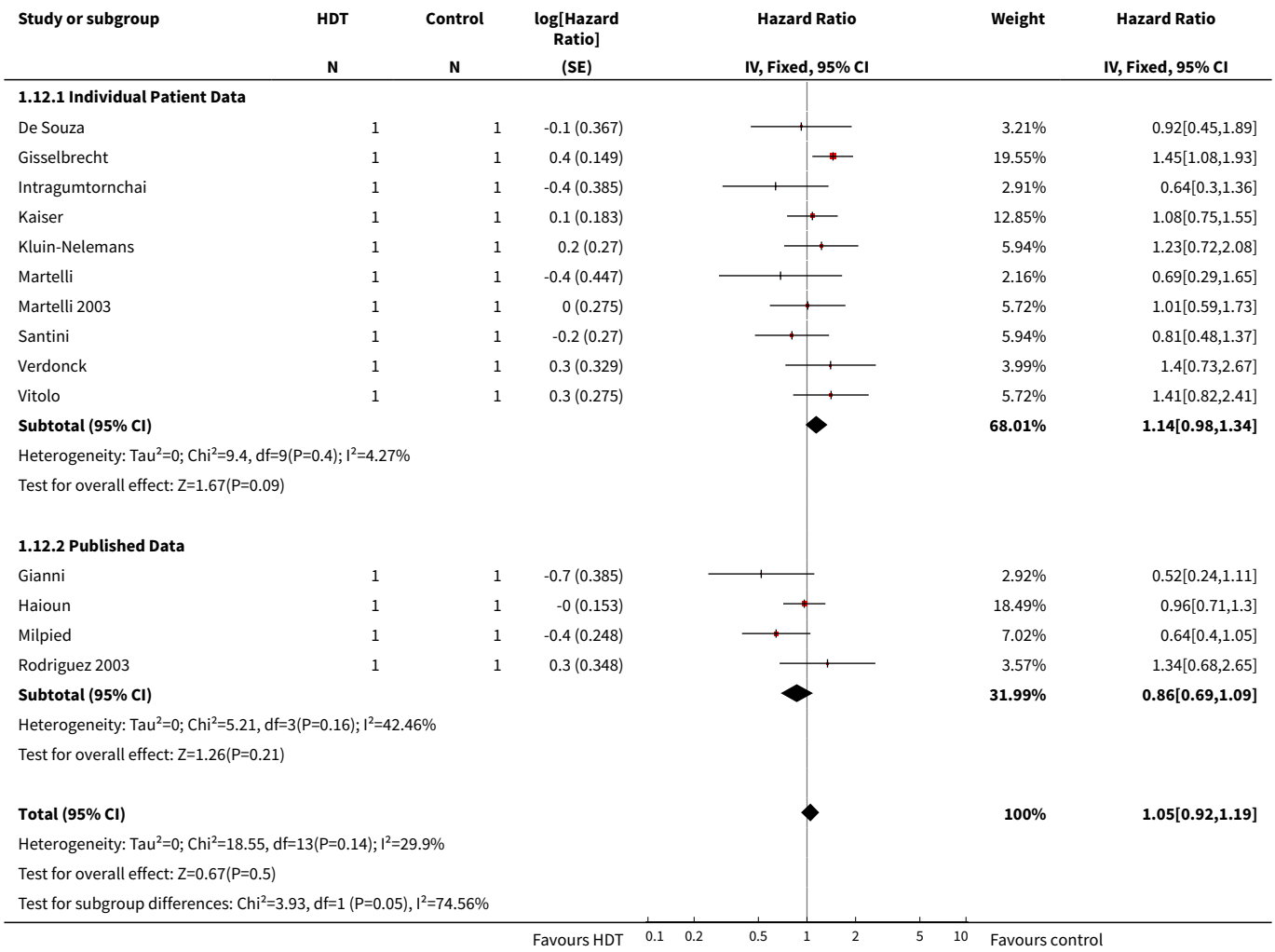
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
1.10.1 > 80 % DLCL						
De Souza	1	1	-0.1 (0.367)		3.32%	0.92[0.45,1.89]
Gianni	1	1	-0.7 (0.385)		3.02%	0.52[0.24,1.11]
Intragumtornchai	1	1	-0.4 (0.385)		3.02%	0.64[0.3,1.36]
Kaiser	1	1	0.1 (0.183)		13.33%	1.08[0.75,1.55]
Martelli	1	1	-0.4 (0.447)		2.24%	0.69[0.29,1.65]
Santini	1	1	-0.2 (0.27)		6.16%	0.81[0.48,1.37]
Vitolo	1	1	0.3 (0.275)		5.93%	1.41[0.82,2.41]
Subtotal (95% CI)					**37.03%**	**0.93[0.75,1.15]**
Heterogeneity: Tau^2=0; Chi^2=6.88, df=6(P=0.33); I^2=12.83%						
Test for overall effect: Z=0.67(P=0.5)						



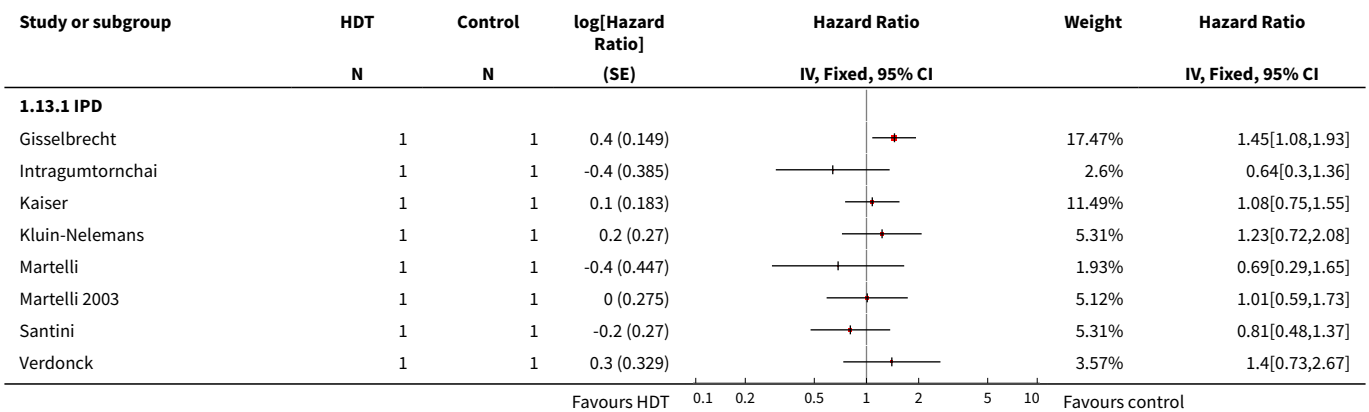
Analysis 1.11. Comparison 1 Overall Survival, Outcome 11 Overall Survival - % of patients with DLCL (narrow def.).

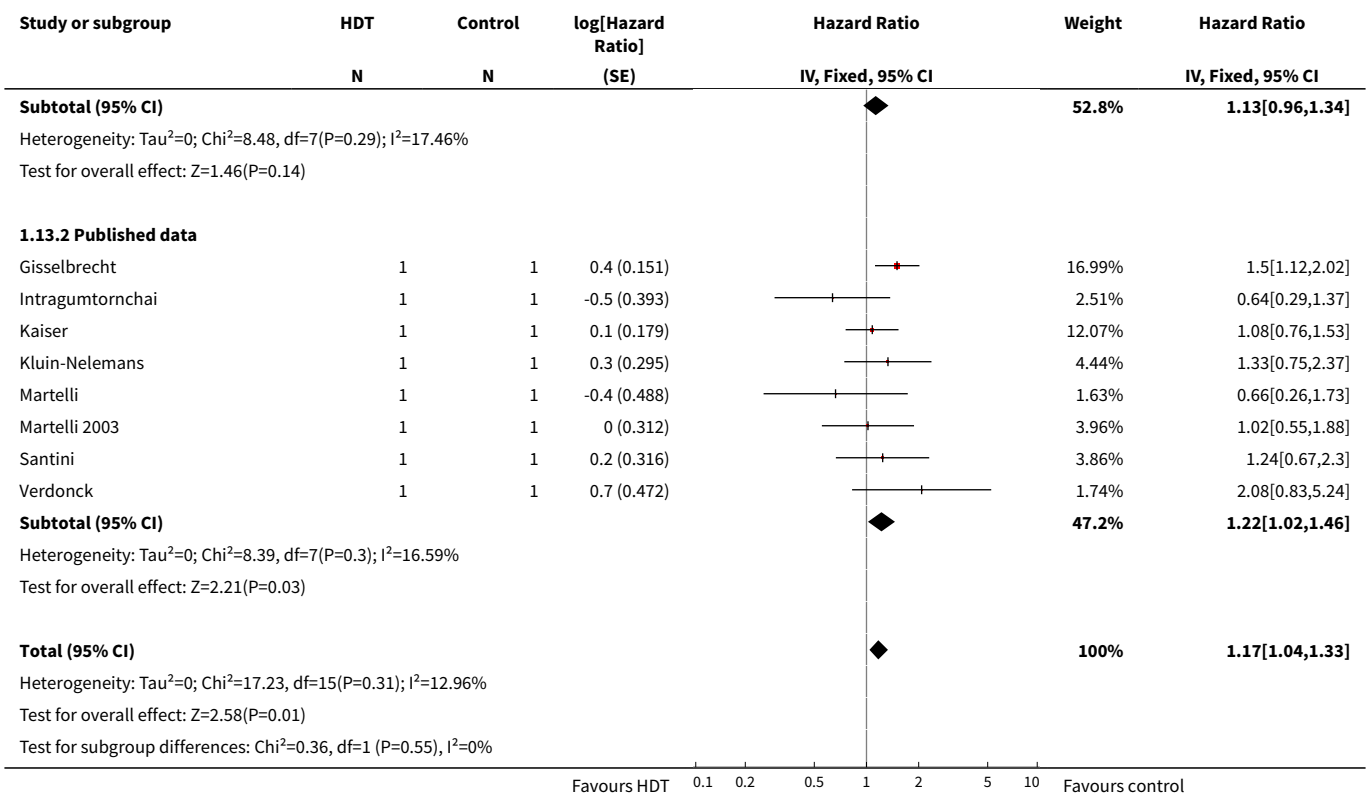


Analysis 1.12. Comparison 1 Overall Survival, Outcome 12 Overall Survival - IPD vs published data.

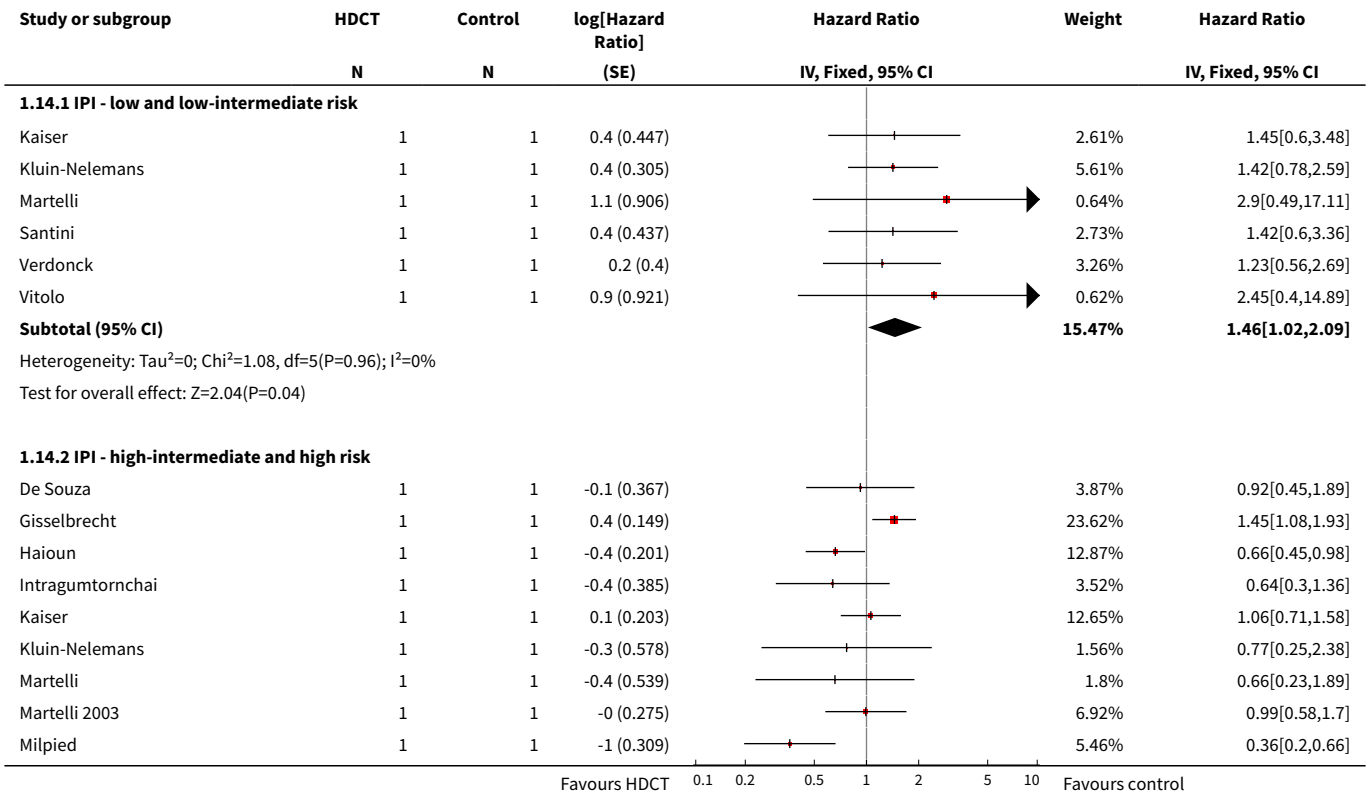


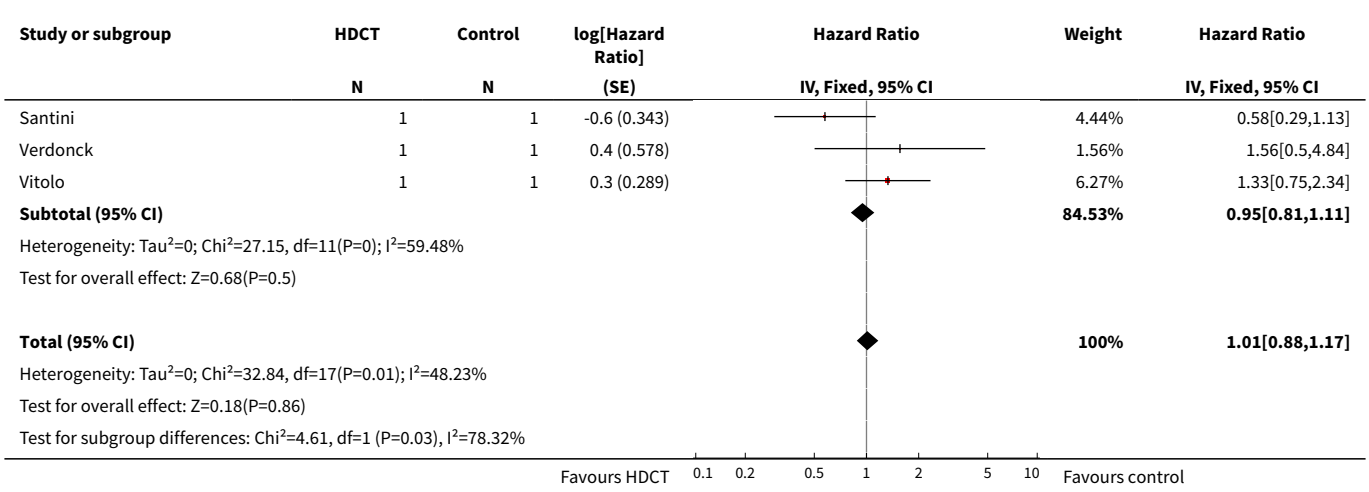
Analysis 1.13. Comparison 1 Overall Survival, Outcome 13 Overall Survival - results from published data vs IPD of the same trials.



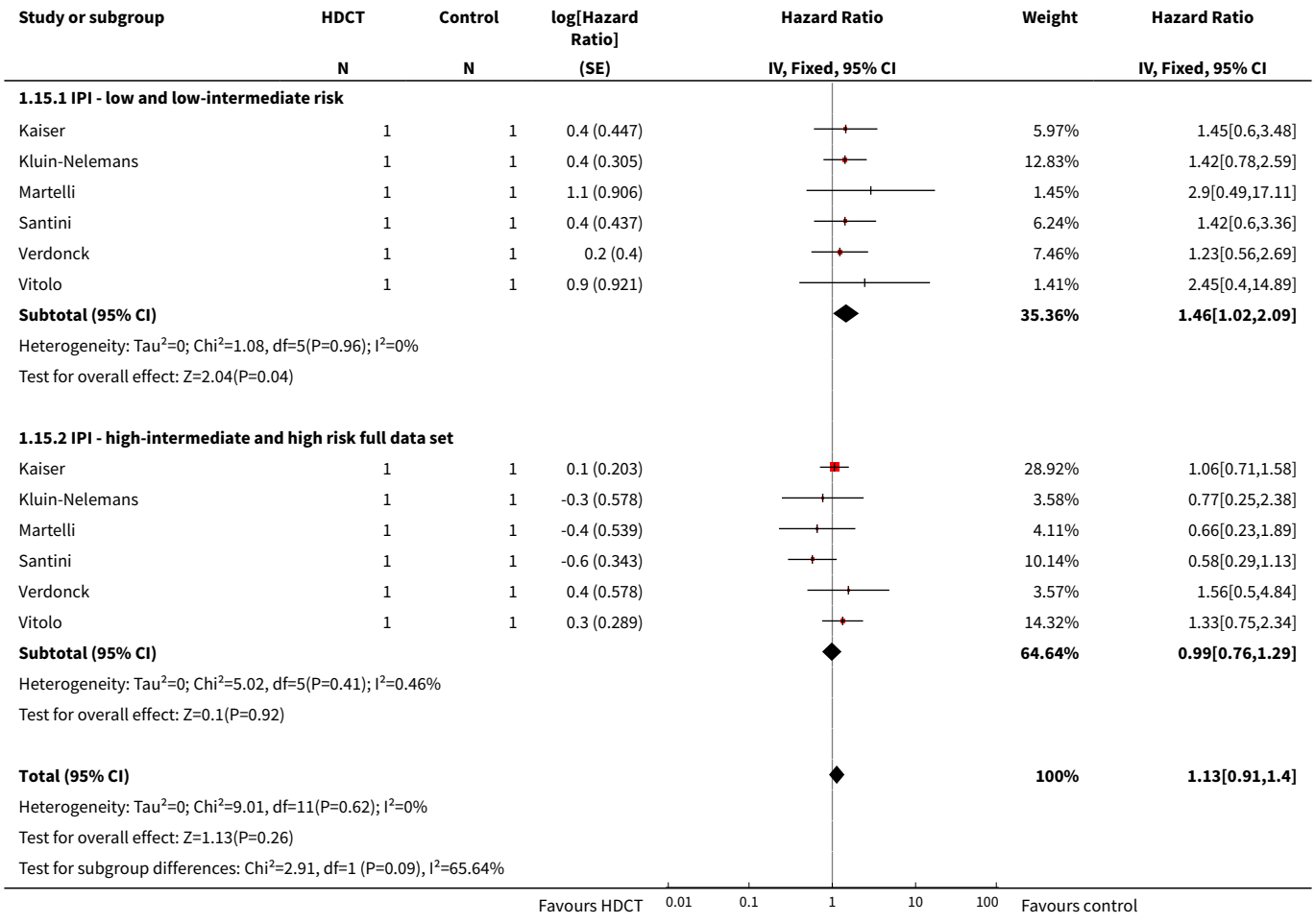


Analysis 1.14. Comparison 1 Overall Survival, Outcome 14 Overall Survival - IPI groups.





Analysis 1.15. Comparison 1 Overall Survival, Outcome 15 Overall Survival - IPI groups full data set.



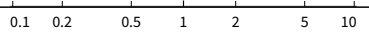
Comparison 2. Event-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Event-free Survival - all studies	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
2 Event-free Survival - different high-dose settings	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
2.1 High-dose sequential therapy without induction	2		Hazard Ratio (Fixed, 95% CI)	0.75 [0.51, 1.12]
2.2 Abbreviated standard induction	7		Hazard Ratio (Fixed, 95% CI)	0.97 [0.84, 1.13]
2.3 Full standard induction	3		Hazard Ratio (Fixed, 95% CI)	0.74 [0.50, 1.10]
3 Event-free Survival - patients' status at randomisation	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
3.1 Patients irrespectively of disease status	10		Hazard Ratio (Fixed, 95% CI)	0.91 [0.79, 1.04]
3.2 Patients in PR	2		Hazard Ratio (Fixed, 95% CI)	1.08 [0.67, 1.73]
4 Event-free Survival - methodological quality	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
4.1 Sufficient method	11		Hazard Ratio (Fixed, 95% CI)	0.95 [0.83, 1.08]
4.2 Insufficient or unknown method	1		Hazard Ratio (Fixed, 95% CI)	0.36 [0.18, 0.72]
5 Event-free Survival - study size	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
5.1 > 100 patients	7		Hazard Ratio (Fixed, 95% CI)	0.96 [0.83, 1.11]
5.2 < 100 patients	5		Hazard Ratio (Fixed, 95% CI)	0.74 [0.55, 1.01]
6 Event-free Survival - protocol adherence to HDT	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
6.1 > 70%	7		Hazard Ratio (Fixed, 95% CI)	1.03 [0.86, 1.22]
6.2 < 70%	5		Hazard Ratio (Fixed, 95% CI)	0.79 [0.65, 0.97]
7 Event-free Survival - bone marrow involvement	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
7.1 >20%	5		Hazard Ratio (Fixed, 95% CI)	0.98 [0.82, 1.18]
7.2 <20%	7		Hazard Ratio (Fixed, 95% CI)	0.85 [0.70, 1.03]
8 Event-free Survival - % of patients with DLCL (wide def.)	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
8.1 > 80%	7		Hazard Ratio (Fixed, 95% CI)	0.80 [0.65, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 < 80%	5		Hazard Ratio (Fixed, 95% CI)	1.02 [0.86, 1.21]
9 Event-free Survival - % of patients with DLCL (narrow def.)	12		Hazard Ratio (Fixed, 95% CI)	0.92 [0.80, 1.05]
9.1 > 70%	6		Hazard Ratio (Fixed, 95% CI)	0.72 [0.58, 0.89]
9.2 < 70%	6		Hazard Ratio (Fixed, 95% CI)	1.06 [0.90, 1.26]
10 Event-free Survival - IPI groups	11		Hazard Ratio (Fixed, 95% CI)	0.96 [0.84, 1.10]
10.1 IPI - low and low-intermediate risk	6		Hazard Ratio (Fixed, 95% CI)	1.02 [0.75, 1.37]
10.2 IPI - high-intermediate and high risk	11		Hazard Ratio (Fixed, 95% CI)	0.95 [0.81, 1.11]

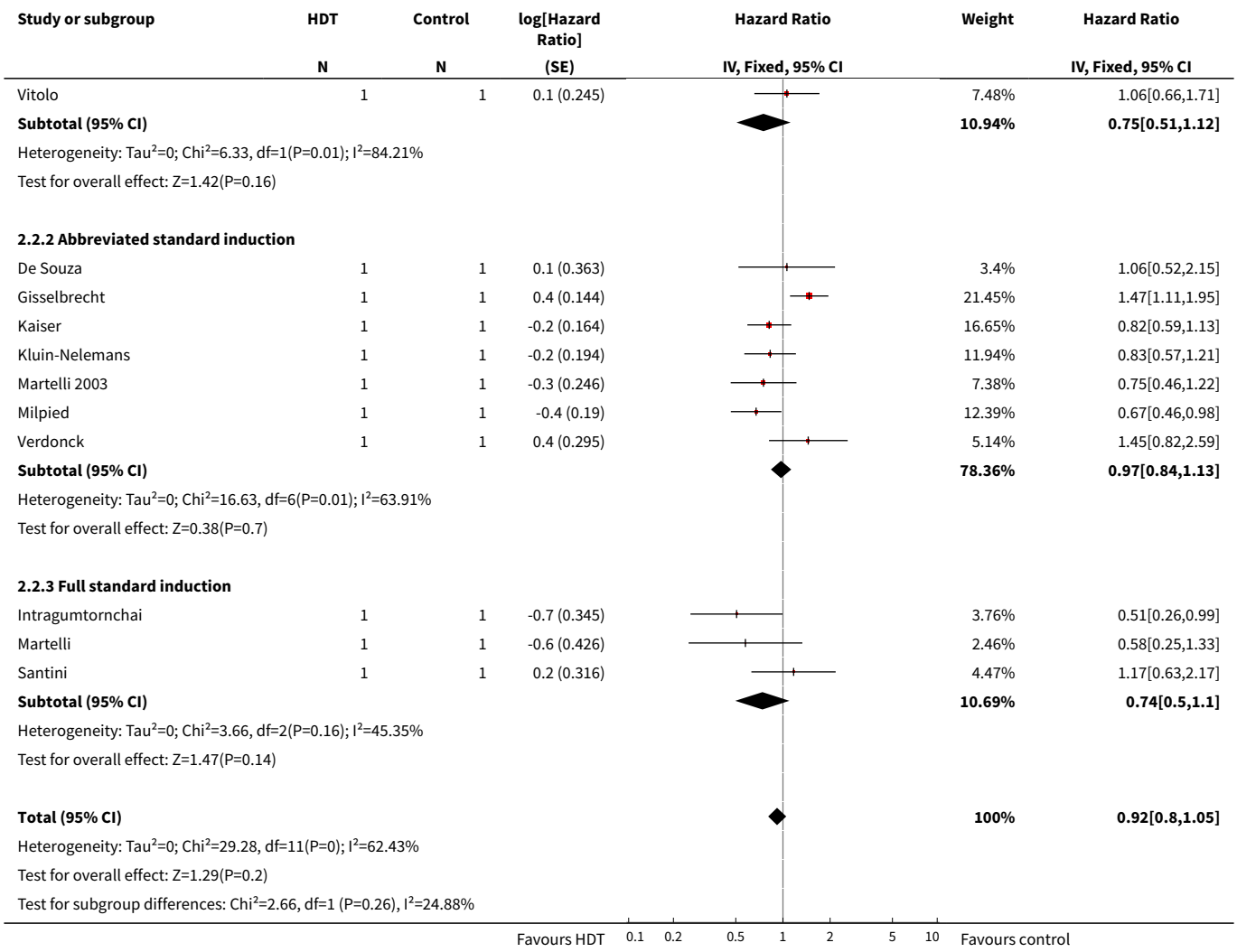
Analysis 2.1. Comparison 2 Event-free survival, Outcome 1 Event-free Survival - all studies.

Study or subgroup	HDCT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
De Souza	1	1	0.1 (0.363)		3.4%	1.06[0.52,2.15]
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]
Gisselbrecht	1	1	0.4 (0.144)		21.45%	1.47[1.11,1.95]
Intragumtornchai	1	1	-0.7 (0.345)		3.76%	0.51[0.26,0.99]
Kaiser	1	1	-0.2 (0.164)		16.65%	0.82[0.59,1.13]
Kluin-Nelemans	1	1	-0.2 (0.194)		11.94%	0.83[0.57,1.21]
Martelli	1	1	-0.6 (0.426)		2.46%	0.58[0.25,1.33]
Martelli 2003	1	1	-0.3 (0.246)		7.38%	0.75[0.46,1.22]
Milpied	1	1	-0.4 (0.19)		12.39%	0.67[0.46,0.98]
Santini	1	1	0.2 (0.316)		4.47%	1.17[0.63,2.17]
Verdonck	1	1	0.4 (0.295)		5.14%	1.45[0.82,2.59]
Vitolo	1	1	0.1 (0.245)		7.48%	1.06[0.66,1.71]
Total (95% CI)					**100%**	**0.92[0.8,1.05]**
Heterogeneity: Tau²=0; Chi²=29.28, df=11(P=0); I²=62.43%						
Test for overall effect: Z=1.29(P=0.2)						

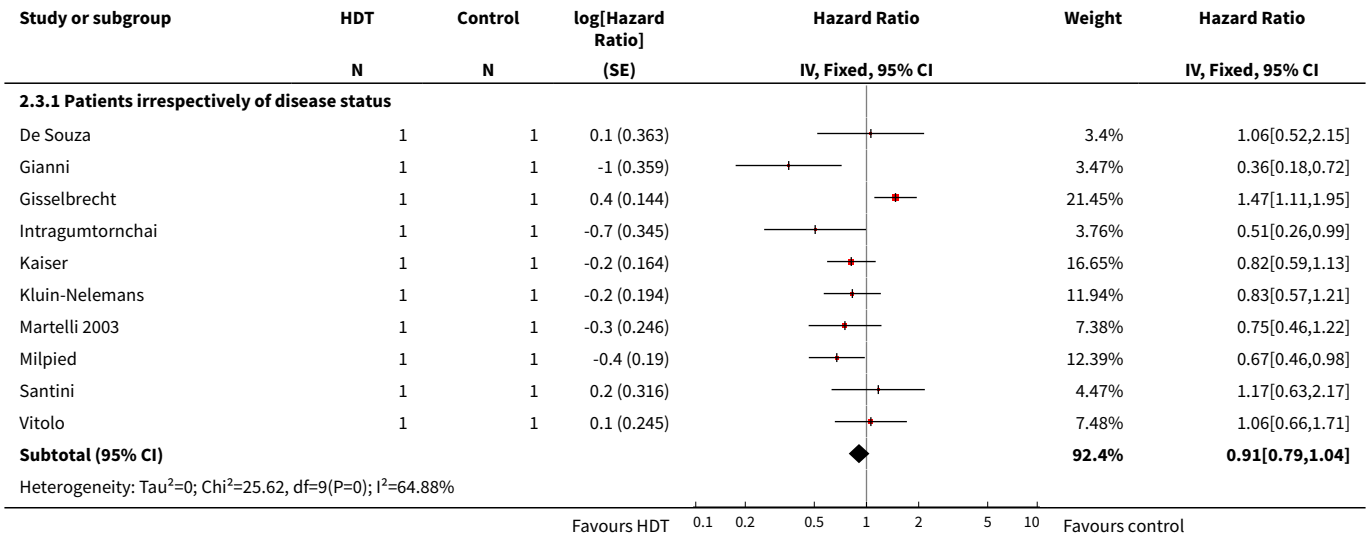


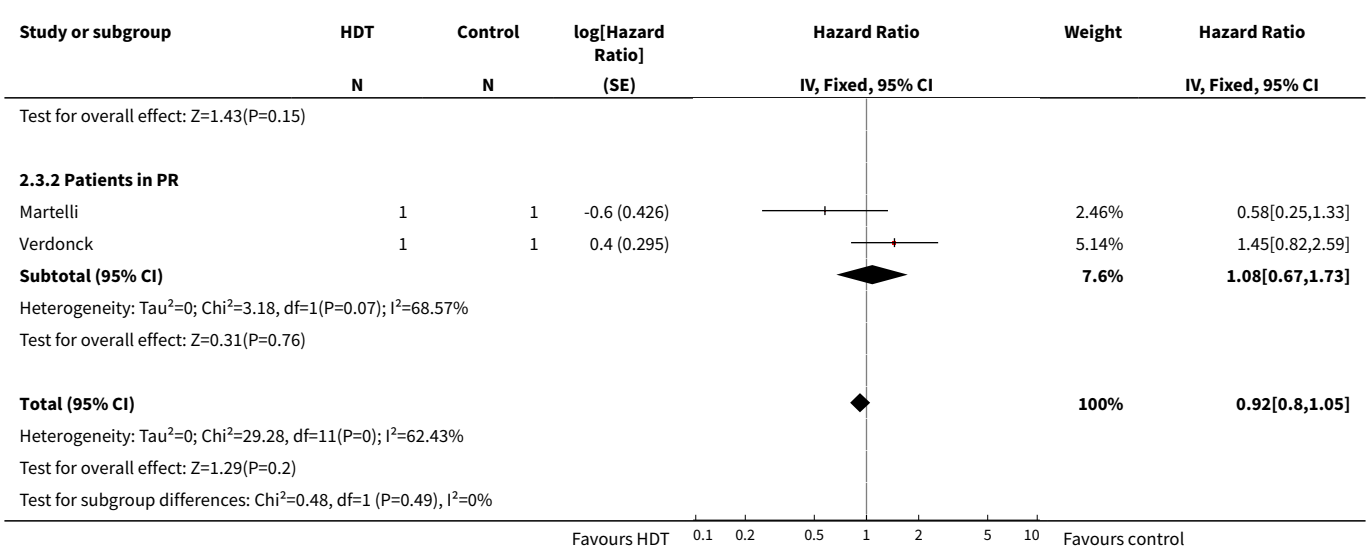
Analysis 2.2. Comparison 2 Event-free survival, Outcome 2 Event-free Survival - different high-dose settings.

Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.2.1 High-dose sequential therapy without induction						
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]

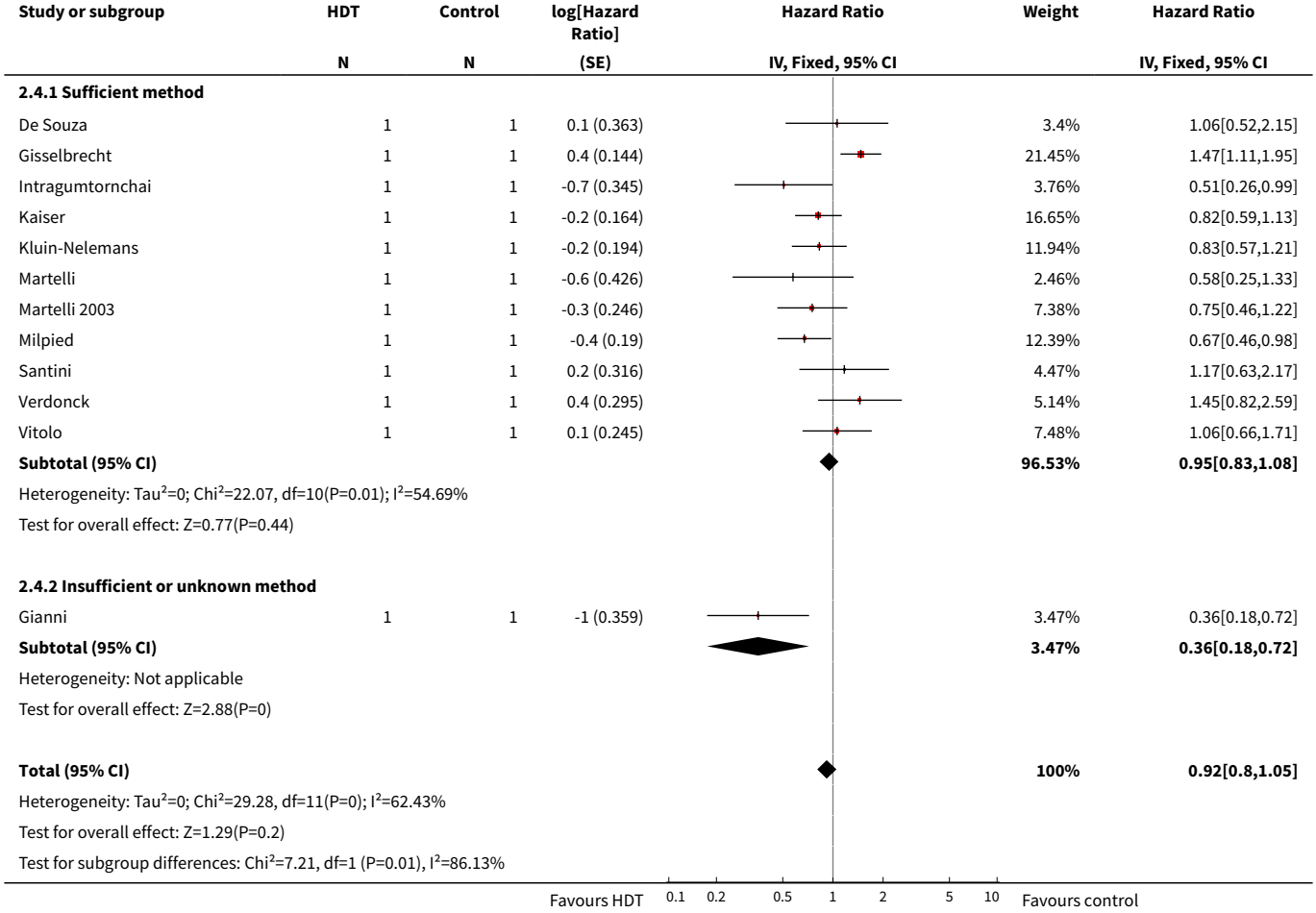


Analysis 2.3. Comparison 2 Event-free survival, Outcome 3 Event-free Survival - patients' status at randomisation.



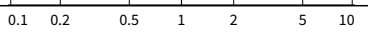


Analysis 2.4. Comparison 2 Event-free survival, Outcome 4 Event-free Survival - methodological quality.



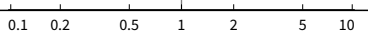
Analysis 2.5. Comparison 2 Event-free survival, Outcome 5 Event-free Survival - study size.

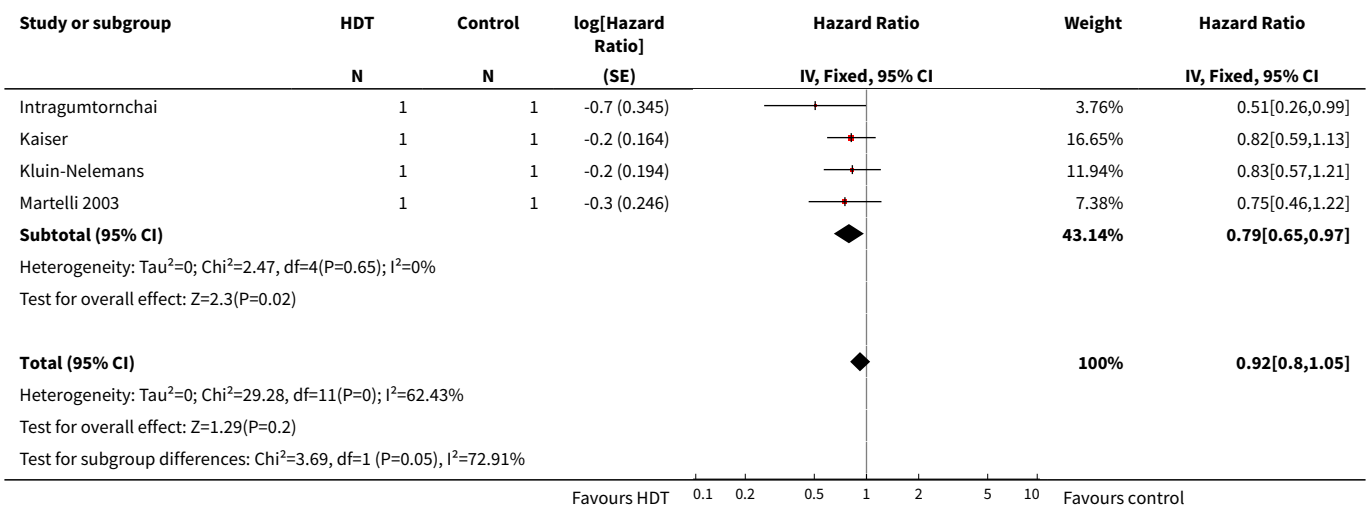
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.5.1 > 100 patients						
Gisselbrecht	1	1	0.4 (0.144)		21.45%	1.47[1.11,1.95]
Kaiser	1	1	-0.2 (0.164)		16.65%	0.82[0.59,1.13]
Kluin-Nelemans	1	1	-0.2 (0.194)		11.94%	0.83[0.57,1.21]
Martelli 2003	1	1	-0.3 (0.246)		7.38%	0.75[0.46,1.22]
Milpied	1	1	-0.4 (0.19)		12.39%	0.67[0.46,0.98]
Santini	1	1	0.2 (0.316)		4.47%	1.17[0.63,2.17]
Vitolo	1	1	0.1 (0.245)		7.48%	1.06[0.66,1.71]
Subtotal (95% CI)					**81.76%**	**0.96[0.83,1.11]**
Heterogeneity: Tau²=0; Chi²=15.16, df=6(P=0.02); I²=60.42%						
Test for overall effect: Z=0.53(P=0.59)						
2.5.2 < 100 patients						
De Souza	1	1	0.1 (0.363)		3.4%	1.06[0.52,2.15]
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]
Intragumtornchai	1	1	-0.7 (0.345)		3.76%	0.51[0.26,0.99]
Martelli	1	1	-0.6 (0.426)		2.46%	0.58[0.25,1.33]
Verdonck	1	1	0.4 (0.295)		5.14%	1.45[0.82,2.59]
Subtotal (95% CI)					**18.24%**	**0.74[0.55,1.01]**
Heterogeneity: Tau²=0; Chi²=11.94, df=4(P=0.02); I²=66.49%						
Test for overall effect: Z=1.89(P=0.06)						
Total (95% CI)					**100%**	**0.92[0.8,1.05]**
Heterogeneity: Tau²=0; Chi²=29.28, df=11(P=0); I²=62.43%						
Test for overall effect: Z=1.29(P=0.2)						
Test for subgroup differences: Chi²=2.18, df=1 (P=0.14), I²=54.2%						



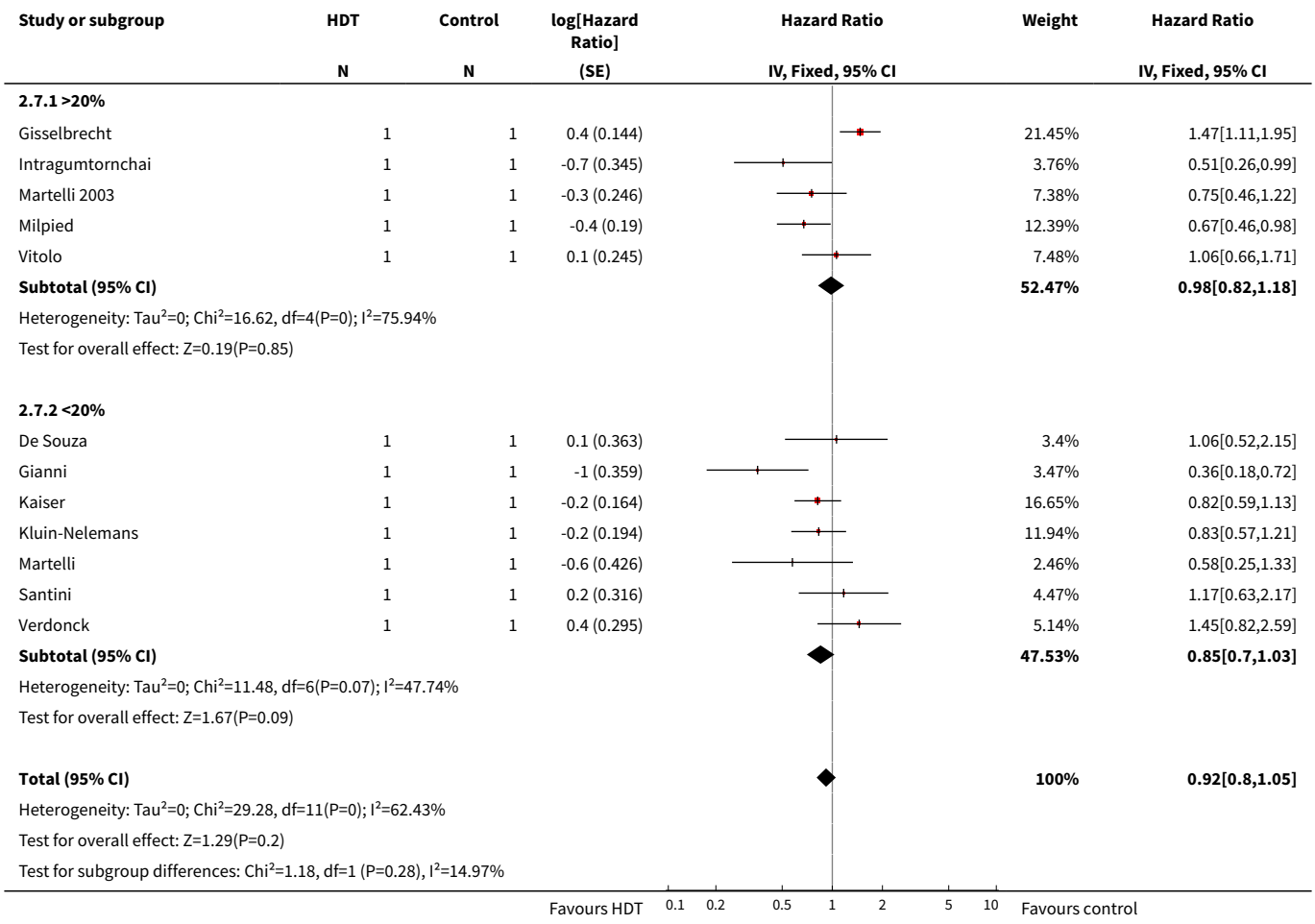
Analysis 2.6. Comparison 2 Event-free survival, Outcome 6 Event-free Survival - protocol adherence to HDT.

Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.6.1 > 70%						
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]
Gisselbrecht	1	1	0.4 (0.144)		21.45%	1.47[1.11,1.95]
Martelli	1	1	-0.6 (0.426)		2.46%	0.58[0.25,1.33]
Milpied	1	1	-0.4 (0.19)		12.39%	0.67[0.46,0.98]
Santini	1	1	0.2 (0.316)		4.47%	1.17[0.63,2.17]
Verdonck	1	1	0.4 (0.295)		5.14%	1.45[0.82,2.59]
Vitolo	1	1	0.1 (0.245)		7.48%	1.06[0.66,1.71]
Subtotal (95% CI)					**56.86%**	**1.03[0.86,1.22]**
Heterogeneity: Tau²=0; Chi²=23.12, df=6(P=0); I²=74.04%						
Test for overall effect: Z=0.29(P=0.77)						
2.6.2 < 70%						
De Souza	1	1	0.1 (0.363)		3.4%	1.06[0.52,2.15]



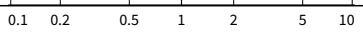


Analysis 2.7. Comparison 2 Event-free survival, Outcome 7 Event-free Survival - bone marrow involvement.



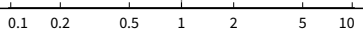
Analysis 2.8. Comparison 2 Event-free survival, Outcome 8 Event-free Survival - % of patients with DLCL (wide def.).

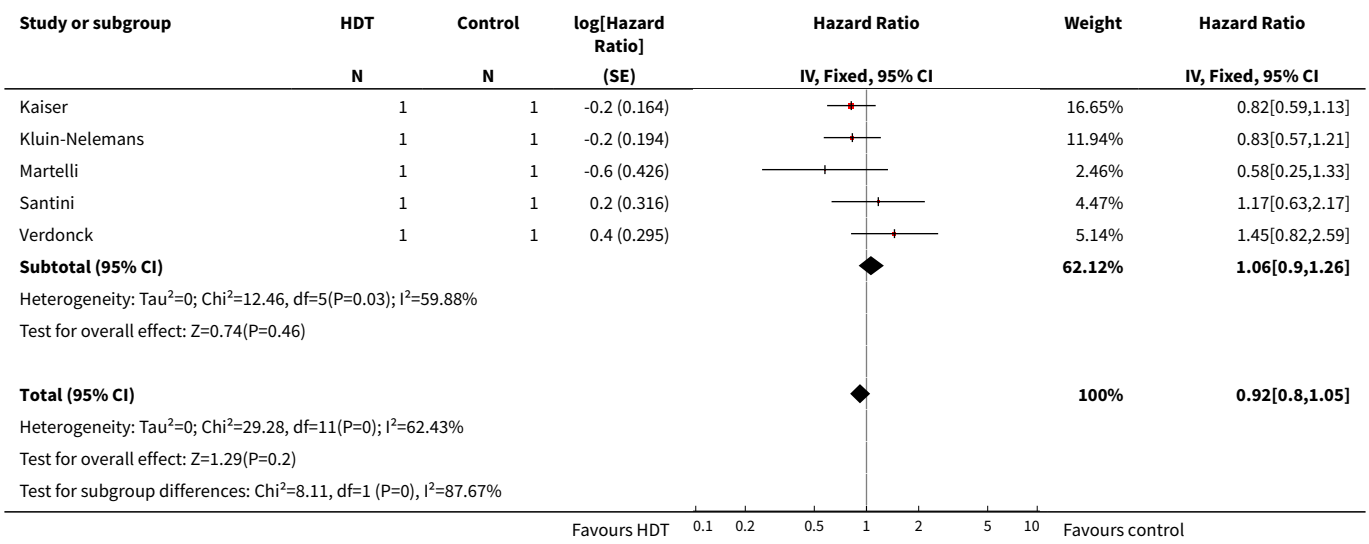
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.8.1 > 80%						
De Souza	1	1	0.1 (0.363)		3.4%	1.06[0.52,2.15]
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]
Intragumtornchai	1	1	-0.7 (0.345)		3.76%	0.51[0.26,0.99]
Kaiser	1	1	-0.2 (0.164)		16.65%	0.82[0.59,1.13]
Martelli	1	1	-0.6 (0.426)		2.46%	0.58[0.25,1.33]
Santini	1	1	0.2 (0.316)		4.47%	1.17[0.63,2.17]
Vitolo	1	1	0.1 (0.245)		7.48%	1.06[0.66,1.71]
Subtotal (95% CI)					**41.69%**	**0.8[0.65,0.97]**
Heterogeneity: Tau²=0; Chi²=10.85, df=6(P=0.09); I²=44.69%						
Test for overall effect: Z=2.2(P=0.03)						
2.8.2 < 80%						
Gisselbrecht	1	1	0.4 (0.144)		21.45%	1.47[1.11,1.95]
Kluin-Nelemans	1	1	-0.2 (0.194)		11.94%	0.83[0.57,1.21]
Martelli 2003	1	1	-0.3 (0.246)		7.38%	0.75[0.46,1.22]
Milpied	1	1	-0.4 (0.19)		12.39%	0.67[0.46,0.98]
Verdonck	1	1	0.4 (0.295)		5.14%	1.45[0.82,2.59]
Subtotal (95% CI)					**58.31%**	**1.02[0.86,1.21]**
Heterogeneity: Tau²=0; Chi²=15.2, df=4(P=0); I²=73.69%						
Test for overall effect: Z=0.18(P=0.86)						
Total (95% CI)					**100%**	**0.92[0.8,1.05]**
Heterogeneity: Tau²=0; Chi²=29.28, df=11(P=0); I²=62.43%						
Test for overall effect: Z=1.29(P=0.2)						
Test for subgroup differences: Chi²=3.23, df=1 (P=0.07), I²=69.03%						



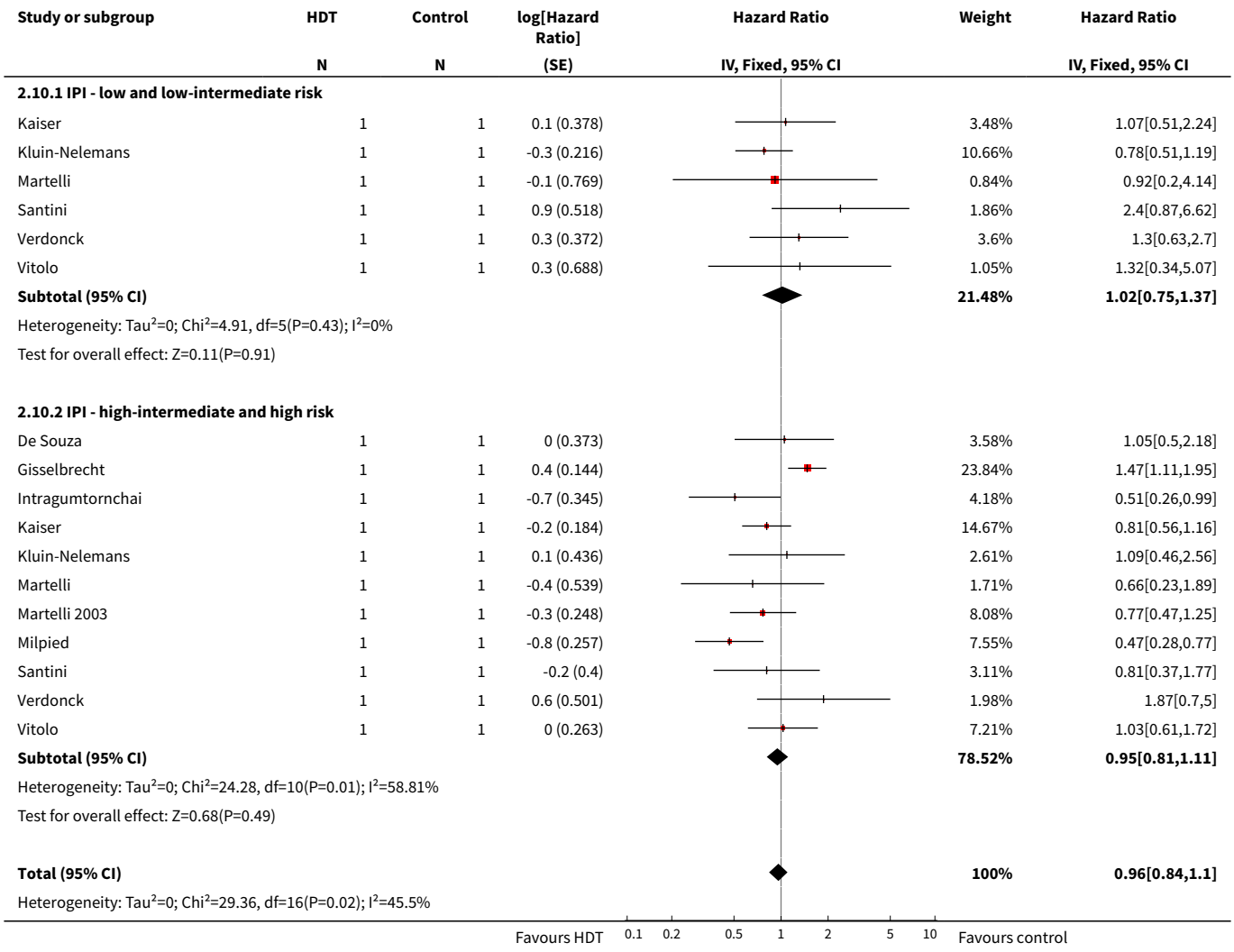
Analysis 2.9. Comparison 2 Event-free survival, Outcome 9 Event-free Survival - % of patients with DLCL (narrow def.).

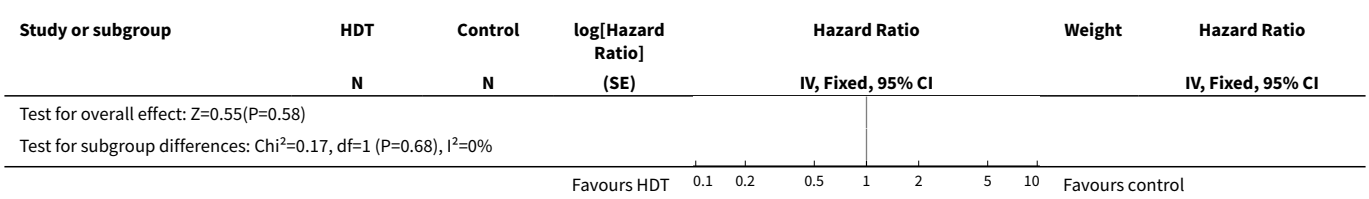
Study or subgroup	HDT N	Control N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Weight	Hazard Ratio IV, Fixed, 95% CI
2.9.1 > 70%						
De Souza	1	1	0.1 (0.363)		3.4%	1.06[0.52,2.15]
Gianni	1	1	-1 (0.359)		3.47%	0.36[0.18,0.72]
Intragumtornchai	1	1	-0.7 (0.345)		3.76%	0.51[0.26,0.99]
Martelli 2003	1	1	-0.3 (0.246)		7.38%	0.75[0.46,1.22]
Milpied	1	1	-0.4 (0.19)		12.39%	0.67[0.46,0.98]
Vitolo	1	1	0.1 (0.245)		7.48%	1.06[0.66,1.71]
Subtotal (95% CI)					**37.88%**	**0.72[0.58,0.89]**
Heterogeneity: Tau²=0; Chi²=8.71, df=5(P=0.12); I²=42.58%						
Test for overall effect: Z=3.04(P=0)						
2.9.2 < 70%						
Gisselbrecht	1	1	0.4 (0.144)		21.45%	1.47[1.11,1.95]





Analysis 2.10. Comparison 2 Event-free survival, Outcome 10 Event-free Survival - IPI groups.





Comparison 3. Complete response rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete Response - all studies	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
2 Complete Response - IPI groups	8	1173	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
2.1 IPI - low and low-intermediate risk	4	171	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.21]
2.2 IPI - high-intermediate and high risk	8	1002	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.13]
3 Complete Response - different high-dose settings	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
3.1 HDS without induction	2	224	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.91, 1.26]
3.2 Abbreviated	9	1681	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.03, 1.18]
3.3 Full course induction	3	221	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.98, 1.63]
4 Complete Response - patients' status at randomisation	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
4.1 only CR or only PR	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.22]
4.2 irrespective of disease status or unclear	12	2004	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.05, 1.19]
5 Complete Response - methodological quality	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
5.1 Sufficient method	11	1697	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.02, 1.18]
5.2 Insufficient or unknown method	3	429	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.02, 1.31]
6 Complete Response - study size	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
6.1 > 100 pts.	9	1804	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.03, 1.17]

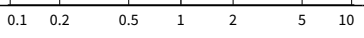
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 < 100 pts.	5	322	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.99, 1.38]
7 Complete Response - protocol adherence to HDT	13	1903	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.05, 1.20]
7.1 >70%	8	1145	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.02, 1.21]
7.2 <70%	5	758	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.02, 1.27]
8 Complete Response - bone marrow involvement	12	1795	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.19]
8.1 >20% of pts.	5	891	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.96, 1.17]
8.2 <20% of pts.	7	904	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.06, 1.28]
9 Complete Response - preparative HDT regimen	14	2126	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.18]
9.1 BEAC	3	393	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.98, 1.32]
9.2 BEAM	7	1388	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [1.03, 1.21]
9.3 TBI	3	219	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.98, 1.38]
9.4 Others	1	126	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.64, 1.09]
10 Complete Response - % of patients with DLCL (wide def.)	12	1795	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.19]
10.1 >80%	8	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.07, 1.29]
10.2 <80%	4	787	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.15]
11 Complete Response - % of patients with DLCL (narrow def.)	12	1795	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.19]
11.1 >70%	6	673	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.05, 1.31]
11.2 <70%	6	1122	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.98, 1.17]

Analysis 3.1. Comparison 3 Complete response rate, Outcome 1 Complete Response - all studies.

Study or subgroup	HDCT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
De Souza	14/28	10/26		1.6%	1.3[0.71,2.4]
Gianni	46/48	35/50		5.3%	1.37[1.13,1.66]
Gisselbrecht	119/189	116/181		18.31%	0.98[0.84,1.15]

Favours control — Favours HDCT

Study or subgroup	HDCT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Intragumtornchai	10/23	9/25		1.33%	1.21[0.6,2.43]
Kaiser	110/158	97/154		15.18%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		8.74%	1.17[0.94,1.45]
Martelli	3/22	4/27		0.55%	0.92[0.23,3.68]
Martelli 2003	57/75	51/75		7.88%	1.12[0.91,1.37]
Milpied	74/98	56/99		8.61%	1.33[1.09,1.64]
Rodriguez 2003	39/55	30/53		4.72%	1.25[0.94,1.67]
Santini	46/63	34/61		5.34%	1.31[1,1.71]
Santini-2	80/117	71/106		11.51%	1.02[0.85,1.22]
Verdonck	25/38	26/35		4.18%	0.89[0.66,1.2]
Vitolo	35/60	46/66		6.77%	0.84[0.64,1.09]
Total (95% CI)	**1072**	**1054**		**100%**	**1.11[1.04,1.18]**
Total events: 725 (HDCT), 641 (Control)					
Heterogeneity: Tau²=0; Chi²=20.19, df=13(P=0.09); I²=35.61%					
Test for overall effect: Z=3.2(P=0)					

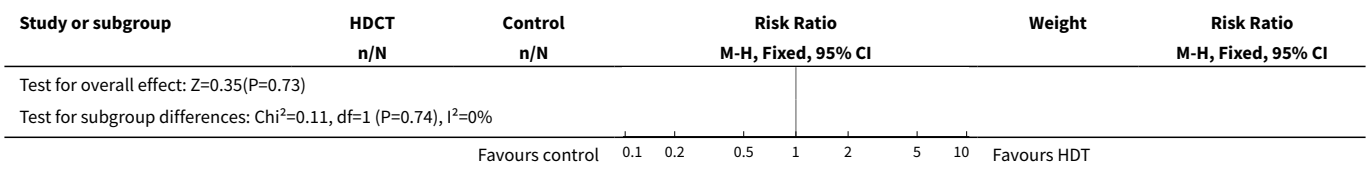


Favours control — Favours HDCT

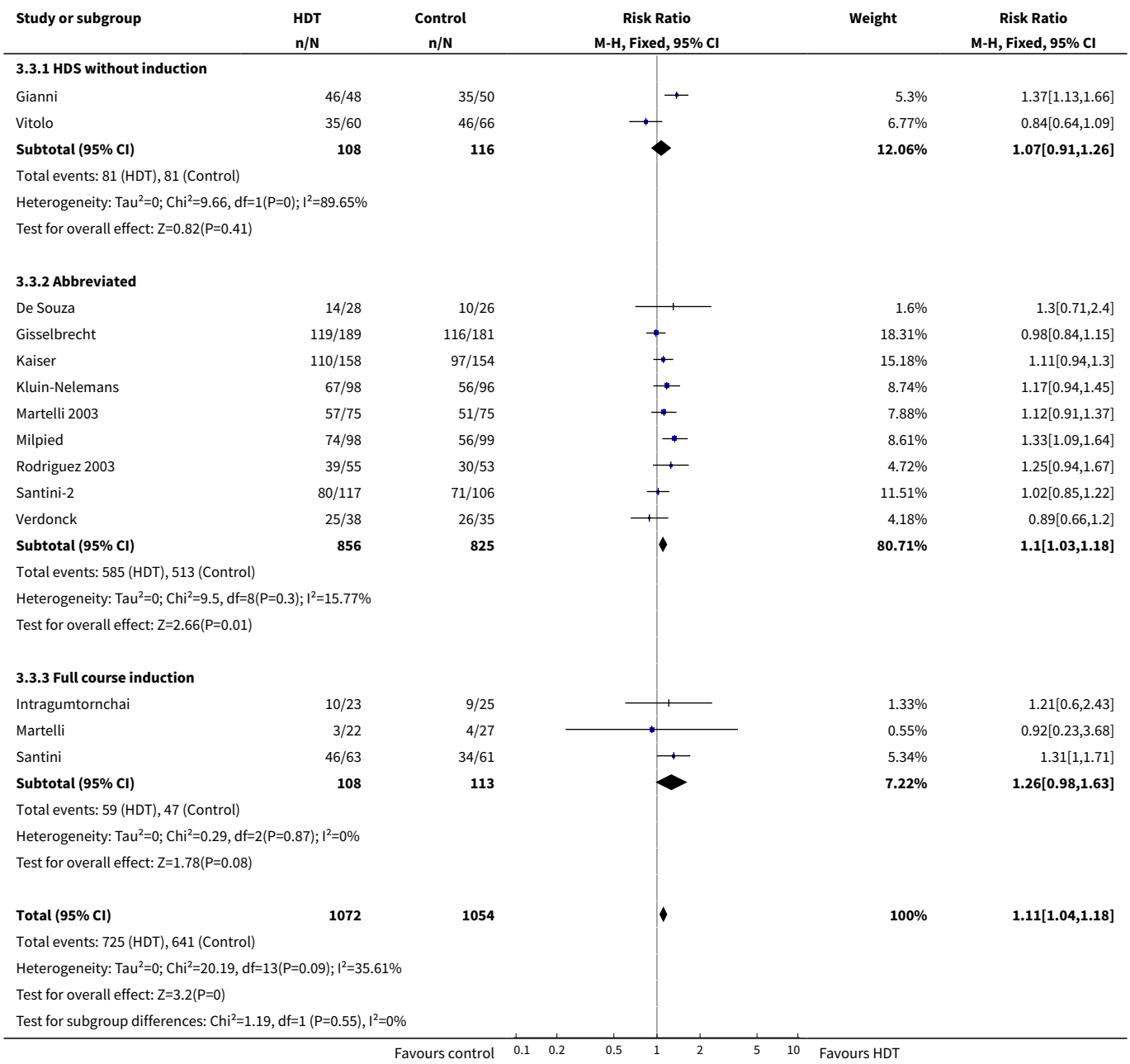
Analysis 3.2. Comparison 3 Complete response rate, Outcome 2 Complete Response - IPI groups.

Study or subgroup	HDCT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 IPI - low and low-intermediate risk					
Kaiser	31/41	26/39		7.52%	1.13[0.86,1.5]
Martelli	1/14	1/9		0.34%	0.64[0.05,9.03]
Verdonck	17/25	16/22		4.8%	0.94[0.65,1.36]
Vitolo	5/8	12/13		2.58%	0.68[0.39,1.18]
Subtotal (95% CI)	**88**	**83**		**15.24%**	**0.98[0.8,1.21]**
Total events: 54 (HDCT), 55 (Control)					
Heterogeneity: Tau²=0; Chi²=2.87, df=3(P=0.41); I²=0%					
Test for overall effect: Z=0.16(P=0.87)					
3.2.2 IPI - high-intermediate and high risk					
De Souza	14/28	10/26		2.93%	1.3[0.71,2.4]
Gisselbrecht	119/189	116/181		33.43%	0.98[0.84,1.15]
Intragumtornchai	10/23	9/25		2.43%	1.21[0.6,2.43]
Kaiser	68/112	66/113		18.54%	1.04[0.84,1.29]
Martelli	2/8	3/18		0.52%	1.5[0.31,7.31]
Martelli 2003	58/75	52/74		14.77%	1.1[0.91,1.33]
Verdonck	8/13	9/12		2.64%	0.82[0.48,1.41]
Vitolo	30/52	34/53		9.5%	0.9[0.66,1.22]
Subtotal (95% CI)	**500**	**502**		**84.76%**	**1.02[0.93,1.13]**
Total events: 309 (HDCT), 299 (Control)					
Heterogeneity: Tau²=0; Chi²=3.18, df=7(P=0.87); I²=0%					
Test for overall effect: Z=0.43(P=0.67)					
Total (95% CI)	**588**	**585**		**100%**	**1.02[0.93,1.11]**
Total events: 363 (HDCT), 354 (Control)					
Heterogeneity: Tau²=0; Chi²=6.1, df=11(P=0.87); I²=0%					

Favours control — Favours HDT



Analysis 3.3. Comparison 3 Complete response rate, Outcome 3 Complete Response - different high-dose settings.

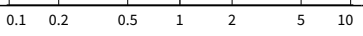


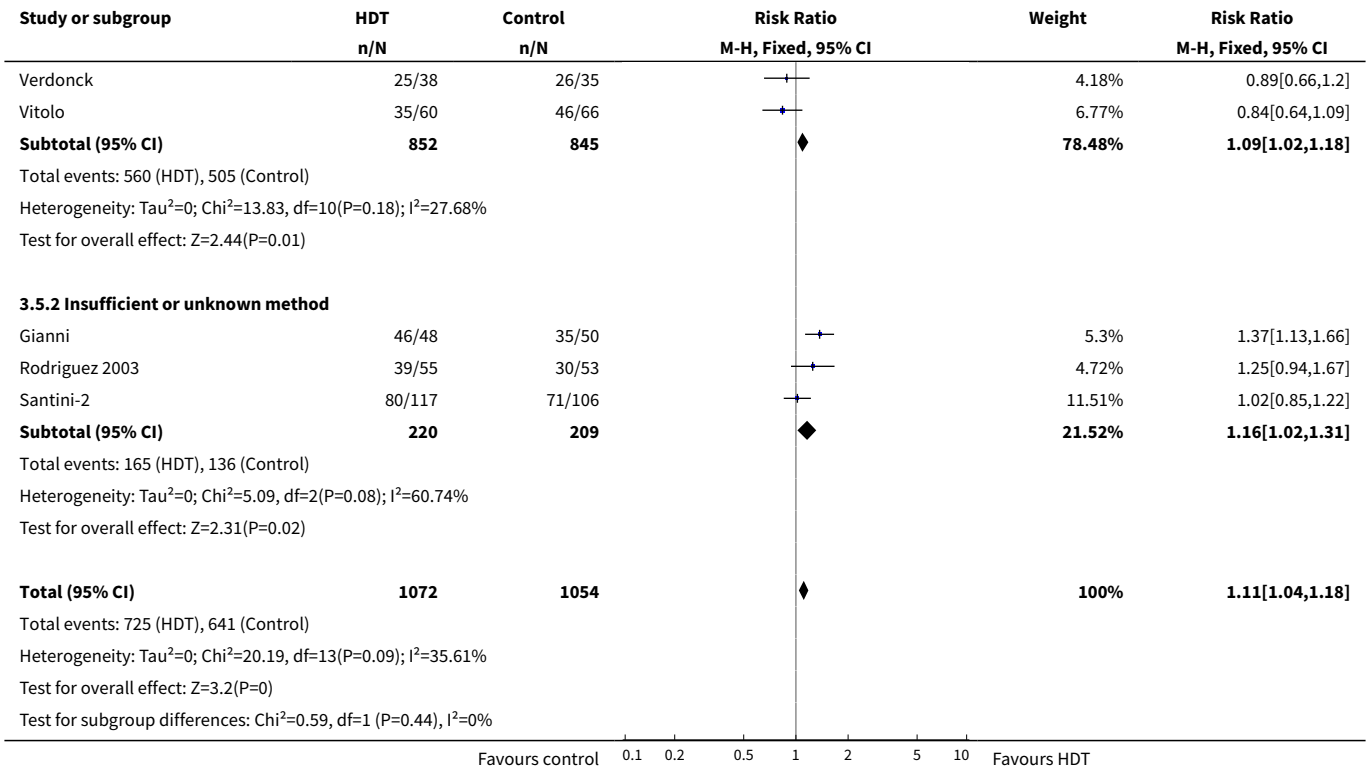
Analysis 3.4. Comparison 3 Complete response rate, Outcome 4 Complete Response - patients' status at randomisation.

Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 only CR or only PR					
Martelli	3/22	4/27		0.55%	0.92[0.23,3.68]
Verdonck	25/38	26/35		4.18%	0.89[0.66,1.2]
Subtotal (95% CI)	**60**	**62**		**4.74%**	**0.89[0.65,1.22]**
Total events: 28 (HDT), 30 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%					
Test for overall effect: Z=0.73(P=0.46)					
3.4.2 irrespective of disease status or unclear					
De Souza	14/28	10/26		1.6%	1.3[0.71,2.4]
Gianni	46/48	35/50		5.3%	1.37[1.13,1.66]
Gisselbrecht	119/189	116/181		18.31%	0.98[0.84,1.15]
Intragumtornchai	10/23	9/25		1.33%	1.21[0.6,2.43]
Kaiser	110/158	97/154		15.18%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		8.74%	1.17[0.94,1.45]
Martelli 2003	57/75	51/75		7.88%	1.12[0.91,1.37]
Milpied	74/98	56/99		8.61%	1.33[1.09,1.64]
Rodriguez 2003	39/55	30/53		4.72%	1.25[0.94,1.67]
Santini	46/63	34/61		5.34%	1.31[1,1.71]
Santini-2	80/117	71/106		11.51%	1.02[0.85,1.22]
Vitolo	35/60	46/66		6.77%	0.84[0.64,1.09]
Subtotal (95% CI)	**1012**	**992**		**95.26%**	**1.12[1.05,1.19]**
Total events: 697 (HDT), 611 (Control)					
Heterogeneity: Tau^2=0; Chi^2=17.75, df=11(P=0.09); I^2=38.04%					
Test for overall effect: Z=3.44(P=0)					
Total (95% CI)	**1072**	**1054**		**100%**	**1.11[1.04,1.18]**
Total events: 725 (HDT), 641 (Control)					
Heterogeneity: Tau^2=0; Chi^2=20.19, df=13(P=0.09); I^2=35.61%					
Test for overall effect: Z=3.2(P=0)					
Test for subgroup differences: Chi^2=1.98, df=1 (P=0.16), I^2=49.45%					

Analysis 3.5. Comparison 3 Complete response rate, Outcome 5 Complete Response - methodological quality.

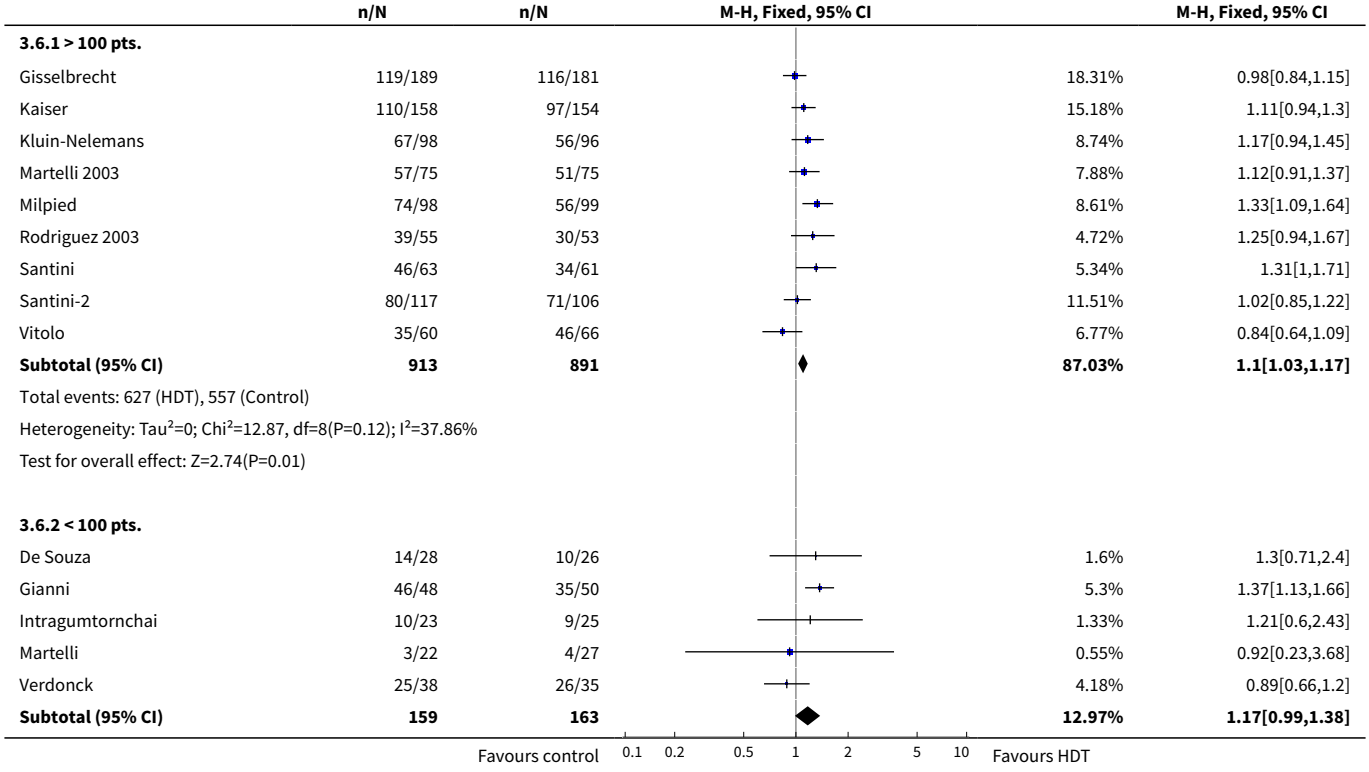
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Sufficient method					
De Souza	14/28	10/26		1.6%	1.3[0.71,2.4]
Gisselbrecht	119/189	116/181		18.31%	0.98[0.84,1.15]
Intragumtornchai	10/23	9/25		1.33%	1.21[0.6,2.43]
Kaiser	110/158	97/154		15.18%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		8.74%	1.17[0.94,1.45]
Martelli	3/22	4/27		0.55%	0.92[0.23,3.68]
Martelli 2003	57/75	51/75		7.88%	1.12[0.91,1.37]
Milpied	74/98	56/99		8.61%	1.33[1.09,1.64]
Santini	46/63	34/61		5.34%	1.31[1,1.71]



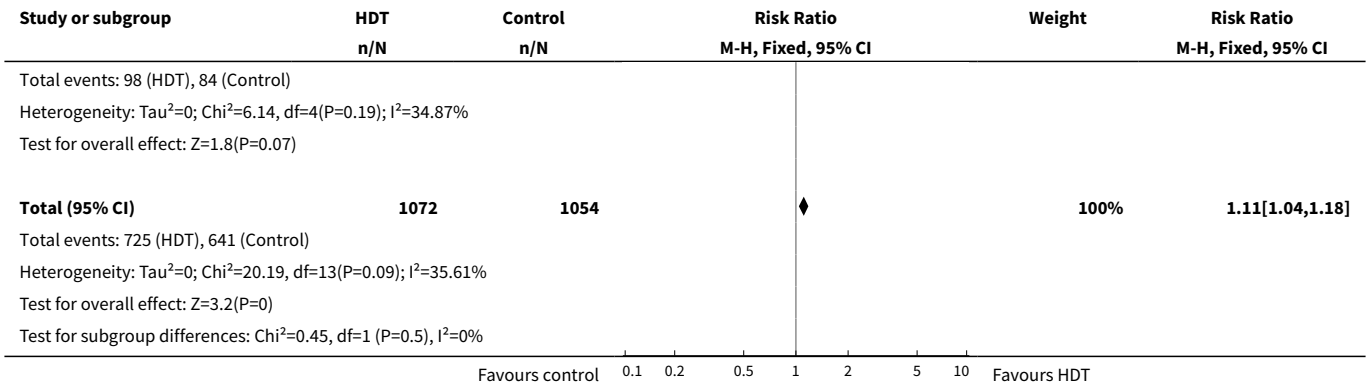


Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Verdonck	25/38	26/35		4.18%	0.89[0.66,1.2]
Vitolo	35/60	46/66		6.77%	0.84[0.64,1.09]
Subtotal (95% CI)	**852**	**845**		**78.48%**	**1.09[1.02,1.18]**
Total events: 560 (HDT), 505 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.83, df=10(P=0.18); I^2=27.68%					
Test for overall effect: Z=2.44(P=0.01)					
3.5.2 Insufficient or unknown method					
Gianni	46/48	35/50		5.3%	1.37[1.13,1.66]
Rodriguez 2003	39/55	30/53		4.72%	1.25[0.94,1.67]
Santini-2	80/117	71/106		11.51%	1.02[0.85,1.22]
Subtotal (95% CI)	**220**	**209**		**21.52%**	**1.16[1.02,1.31]**
Total events: 165 (HDT), 136 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.09, df=2(P=0.08); I^2=60.74%					
Test for overall effect: Z=2.31(P=0.02)					
Total (95% CI)	**1072**	**1054**		**100%**	**1.11[1.04,1.18]**
Total events: 725 (HDT), 641 (Control)					
Heterogeneity: Tau^2=0; Chi^2=20.19, df=13(P=0.09); I^2=35.61%					
Test for overall effect: Z=3.2(P=0)					
Test for subgroup differences: Chi^2=0.59, df=1 (P=0.44), I^2=0%					

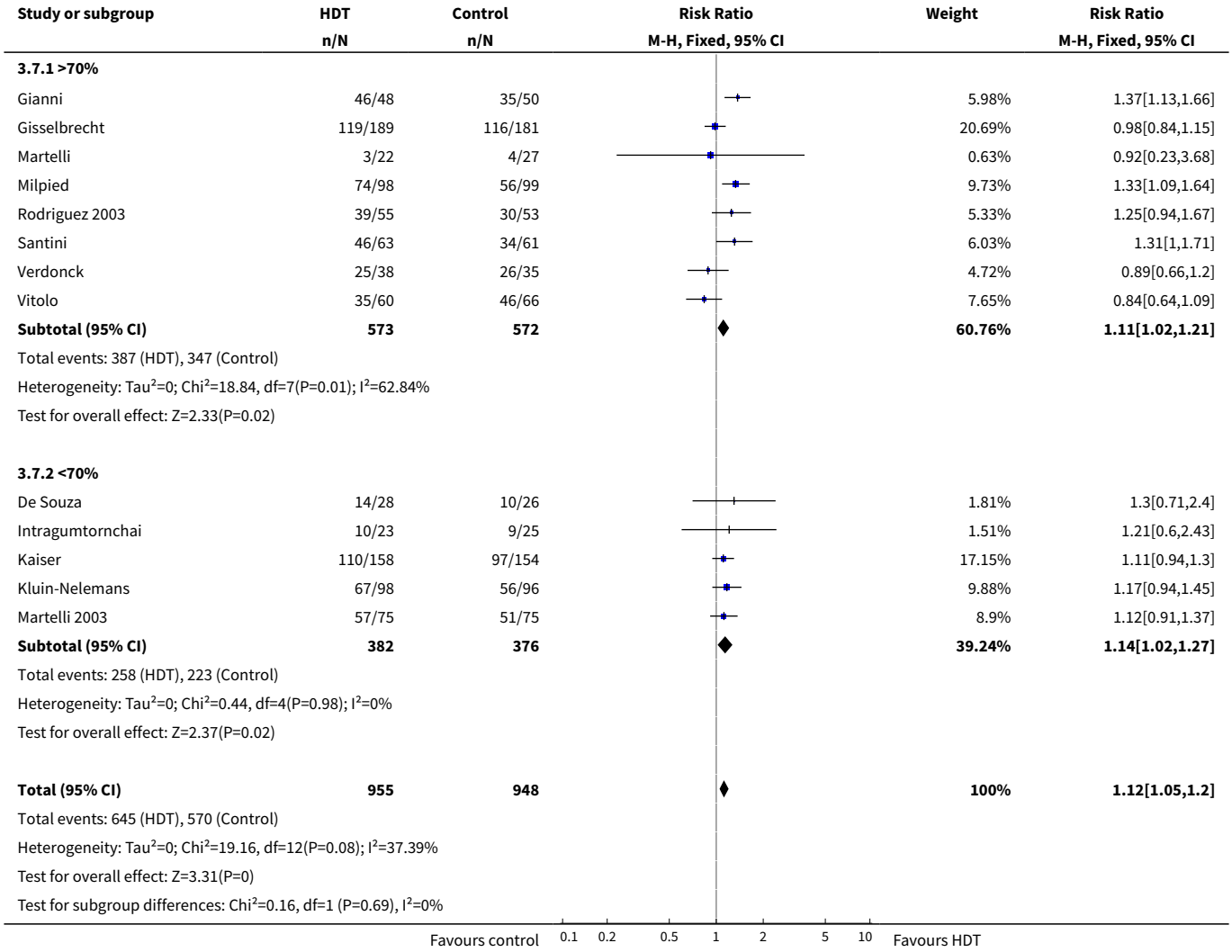
Analysis 3.6. Comparison 3 Complete response rate, Outcome 6 Complete Response - study size.



Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 > 100 pts.					
Gisselbrecht	119/189	116/181		18.31%	0.98[0.84,1.15]
Kaiser	110/158	97/154		15.18%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		8.74%	1.17[0.94,1.45]
Martelli 2003	57/75	51/75		7.88%	1.12[0.91,1.37]
Milpied	74/98	56/99		8.61%	1.33[1.09,1.64]
Rodriguez 2003	39/55	30/53		4.72%	1.25[0.94,1.67]
Santini	46/63	34/61		5.34%	1.31[1,1.71]
Santini-2	80/117	71/106		11.51%	1.02[0.85,1.22]
Vitolo	35/60	46/66		6.77%	0.84[0.64,1.09]
Subtotal (95% CI)	**913**	**891**		**87.03%**	**1.1[1.03,1.17]**
Total events: 627 (HDT), 557 (Control)					
Heterogeneity: Tau^2=0; Chi^2=12.87, df=8(P=0.12); I^2=37.86%					
Test for overall effect: Z=2.74(P=0.01)					
3.6.2 < 100 pts.					
De Souza	14/28	10/26		1.6%	1.3[0.71,2.4]
Gianni	46/48	35/50		5.3%	1.37[1.13,1.66]
Intragumtornchai	10/23	9/25		1.33%	1.21[0.6,2.43]
Martelli	3/22	4/27		0.55%	0.92[0.23,3.68]
Verdonck	25/38	26/35		4.18%	0.89[0.66,1.2]
Subtotal (95% CI)	**159**	**163**		**12.97%**	**1.17[0.99,1.38]**

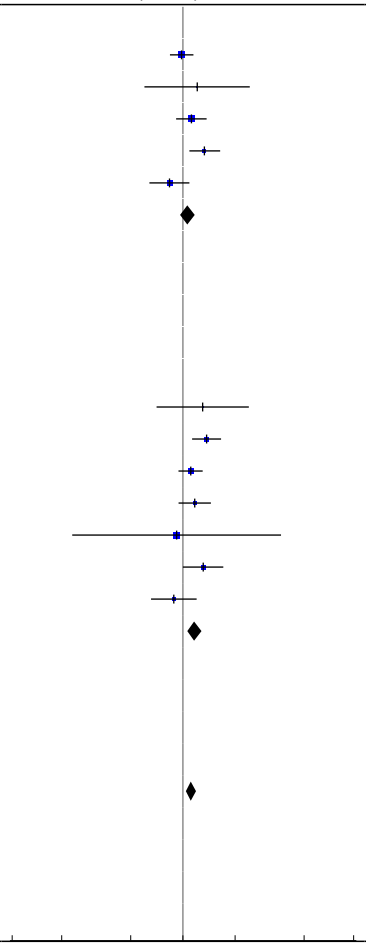


Analysis 3.7. Comparison 3 Complete response rate, Outcome 7 Complete Response - protocol adherence to HDT.



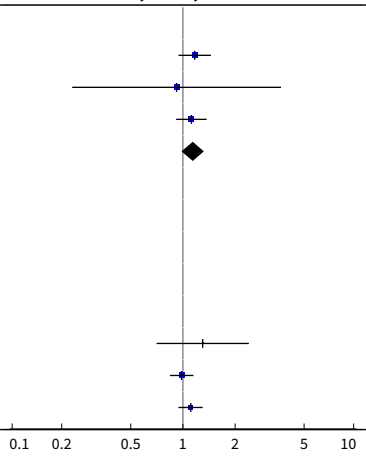
Analysis 3.8. Comparison 3 Complete response rate, Outcome 8 Complete Response - bone marrow involvement.

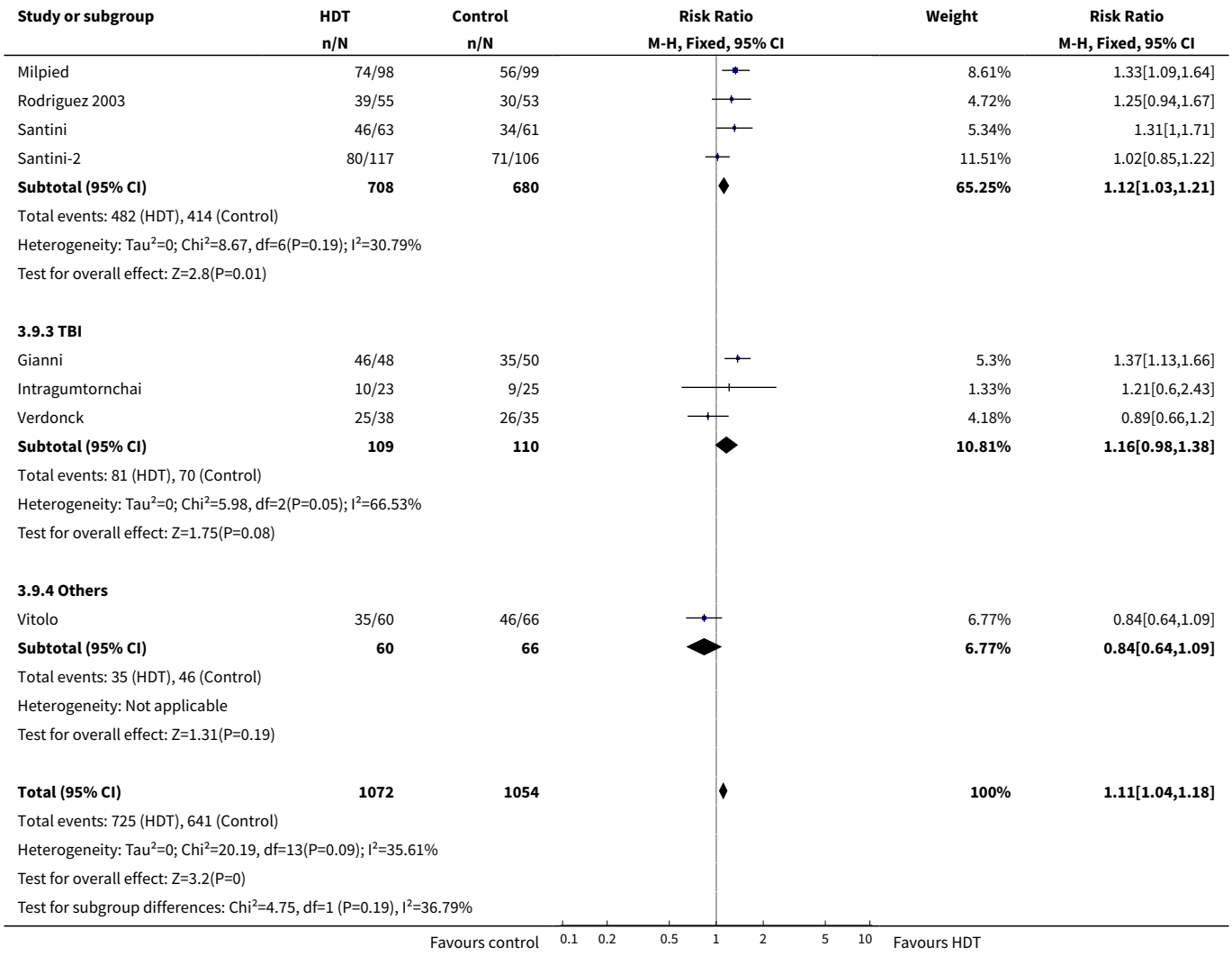
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 >20% of pts.					
Gisselbrecht	119/189	116/181		21.85%	0.98[0.84,1.15]
Intragumtornchai	10/23	9/25		1.59%	1.21[0.6,2.43]
Martelli 2003	57/75	51/75		9.4%	1.12[0.91,1.37]
Milpied	74/98	56/99		10.27%	1.33[1.09,1.64]
Vitolo	35/60	46/66		8.08%	0.84[0.64,1.09]
Subtotal (95% CI)	**445**	**446**		**51.2%**	**1.06[0.96,1.17]**
Total events: 295 (HDT), 278 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.15, df=4(P=0.06); I^2=56.28%					
Test for overall effect: Z=1.21(P=0.23)					
3.8.2 <20% of pts.					
De Souza	14/28	10/26		1.91%	1.3[0.71,2.4]
Gianni	46/48	35/50		6.32%	1.37[1.13,1.66]
Kaiser	110/158	97/154		18.11%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		10.43%	1.17[0.94,1.45]
Martelli	3/22	4/27		0.66%	0.92[0.23,3.68]
Santini	46/63	34/61		6.37%	1.31[1,1.71]
Verdonck	25/38	26/35		4.99%	0.89[0.66,1.2]
Subtotal (95% CI)	**455**	**449**		**48.8%**	**1.16[1.06,1.28]**
Total events: 311 (HDT), 262 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.34, df=6(P=0.29); I^2=18.26%					
Test for overall effect: Z=3.09(P=0)					
Total (95% CI)	**900**	**895**		**100%**	**1.11[1.04,1.19]**
Total events: 606 (HDT), 540 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.66, df=11(P=0.07); I^2=41.04%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=1.69, df=1 (P=0.19), I^2=40.94%					



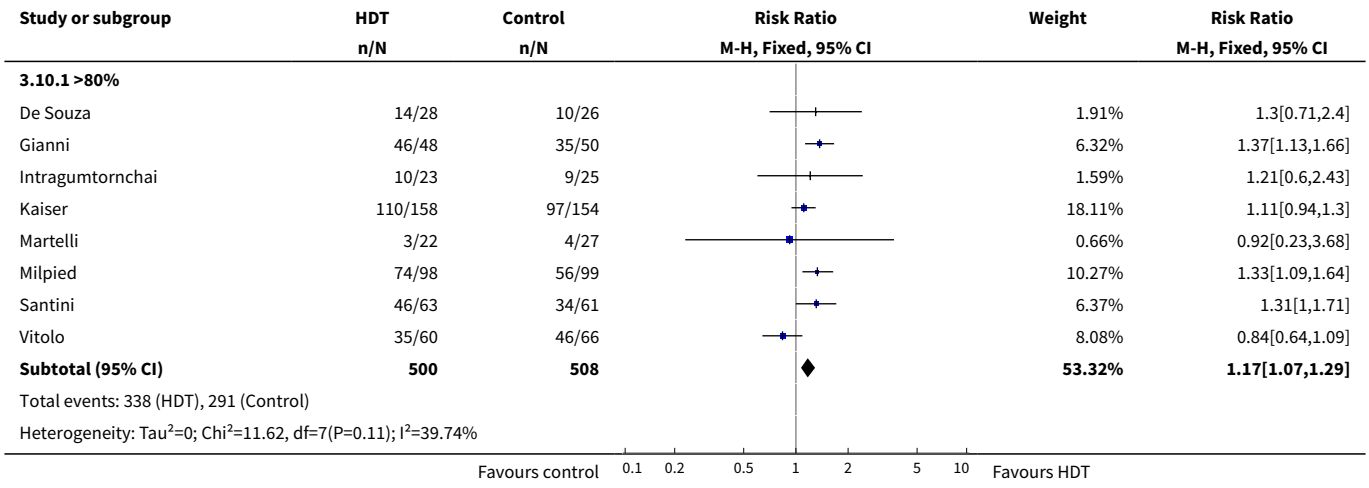
Analysis 3.9. Comparison 3 Complete response rate, Outcome 9 Complete Response - preparative HDT regimen.

Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 BEAC					
Kluin-Nelemans	67/98	56/96		8.74%	1.17[0.94,1.45]
Martelli	3/22	4/27		0.55%	0.92[0.23,3.68]
Martelli 2003	57/75	51/75		7.88%	1.12[0.91,1.37]
Subtotal (95% CI)	**195**	**198**		**17.17%**	**1.14[0.98,1.32]**
Total events: 127 (HDT), 111 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=1.7(P=0.09)					
3.9.2 BEAM					
De Souza	14/28	10/26		1.6%	1.3[0.71,2.4]
Gisselbrecht	119/189	116/181		18.31%	0.98[0.84,1.15]
Kaiser	110/158	97/154		15.18%	1.11[0.94,1.3]





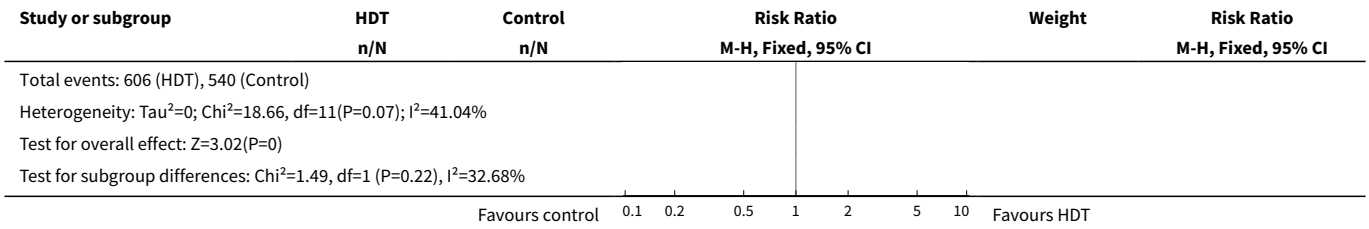
Analysis 3.10. Comparison 3 Complete response rate, Outcome 10 Complete Response - % of patients with DLCL (wide def.).



Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=3.35(P=0)					
3.10.2 <80%					
Gisselbrecht	119/189	116/181		21.85%	0.98[0.84,1.15]
Kluin-Nelemans	67/98	56/96		10.43%	1.17[0.94,1.45]
Martelli 2003	57/75	51/75		9.4%	1.12[0.91,1.37]
Verdonck	25/38	26/35		4.99%	0.89[0.66,1.2]
Subtotal (95% CI)	**400**	**387**		**46.68%**	**1.04[0.94,1.15]**
Total events: 268 (HDT), 249 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.28, df=3(P=0.35); I^2=8.67%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**900**	**895**		**100%**	**1.11[1.04,1.19]**
Total events: 606 (HDT), 540 (Control)					
Heterogeneity: Tau^2=0; Chi^2=18.66, df=11(P=0.07); I^2=41.04%					
Test for overall effect: Z=3.02(P=0)					
Test for subgroup differences: Chi^2=2.84, df=1 (P=0.09), I^2=64.82%					

Analysis 3.11. Comparison 3 Complete response rate, Outcome 11 Complete Response - % of patients with DLCL (narrow def.).

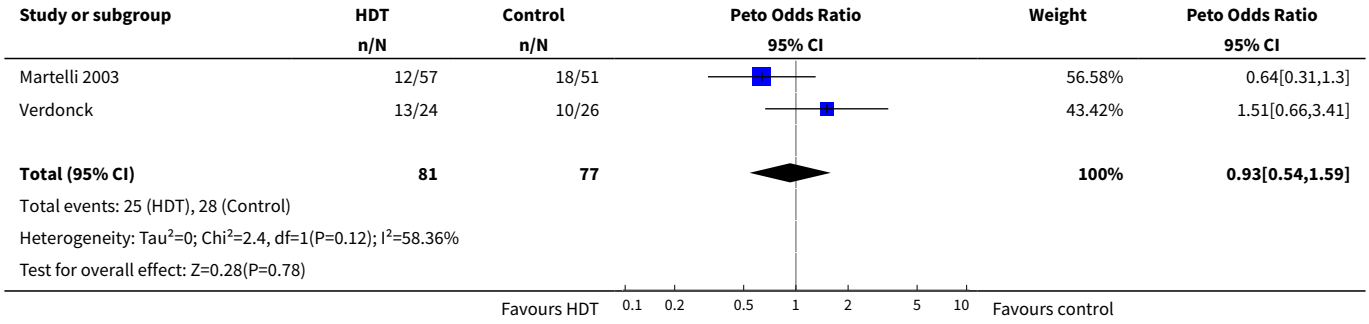
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.11.1 >70%					
De Souza	14/28	10/26		1.91%	1.3[0.71,2.4]
Gianni	46/48	35/50		6.32%	1.37[1.13,1.66]
Intragumtornchai	10/23	9/25		1.59%	1.21[0.6,2.43]
Martelli 2003	57/75	51/75		9.4%	1.12[0.91,1.37]
Milpied	74/98	56/99		10.27%	1.33[1.09,1.64]
Vitolo	35/60	46/66		8.08%	0.84[0.64,1.09]
Subtotal (95% CI)	**332**	**341**		**37.58%**	**1.17[1.05,1.31]**
Total events: 236 (HDT), 207 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.54, df=5(P=0.06); I^2=52.57%					
Test for overall effect: Z=2.9(P=0)					
3.11.2 <70%					
Gisselbrecht	119/189	116/181		21.85%	0.98[0.84,1.15]
Kaiser	110/158	97/154		18.11%	1.11[0.94,1.3]
Kluin-Nelemans	67/98	56/96		10.43%	1.17[0.94,1.45]
Martelli	3/22	4/27		0.66%	0.92[0.23,3.68]
Santini	46/63	34/61		6.37%	1.31[1,1.71]
Verdonck	25/38	26/35		4.99%	0.89[0.66,1.2]
Subtotal (95% CI)	**568**	**554**		**62.42%**	**1.07[0.98,1.17]**
Total events: 370 (HDT), 333 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.75, df=5(P=0.33); I^2=13%					
Test for overall effect: Z=1.59(P=0.11)					
Total (95% CI)	**900**	**895**		**100%**	**1.11[1.04,1.19]**



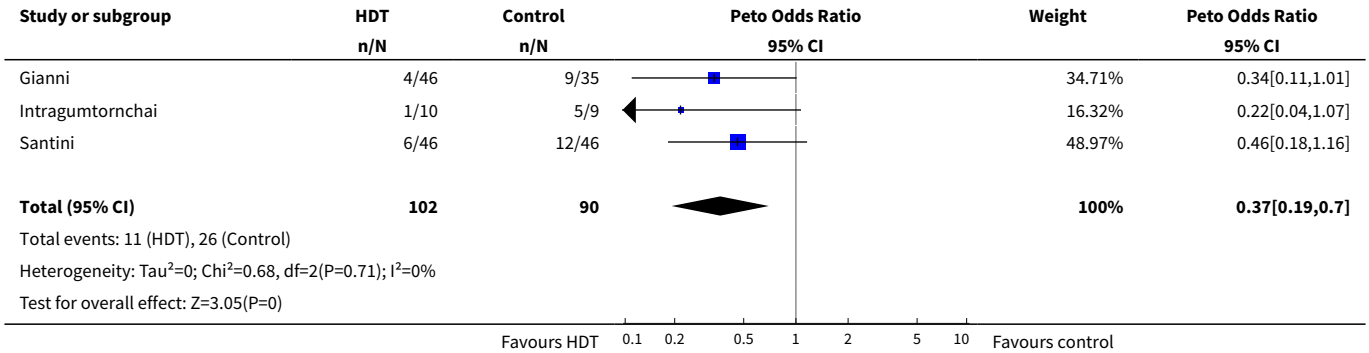
Comparison 4. Disease-free survival/Relapse-free survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease-free Survival (death = event)	2	158	Peto Odds Ratio (95% CI)	0.93 [0.54, 1.59]
2 Relapse-free Survival (death = censored)	3	192	Peto Odds Ratio (95% CI)	0.37 [0.19, 0.70]

Analysis 4.1. Comparison 4 Disease-free survival/Relapse-free survival, Outcome 1 Disease-free Survival (death = event).



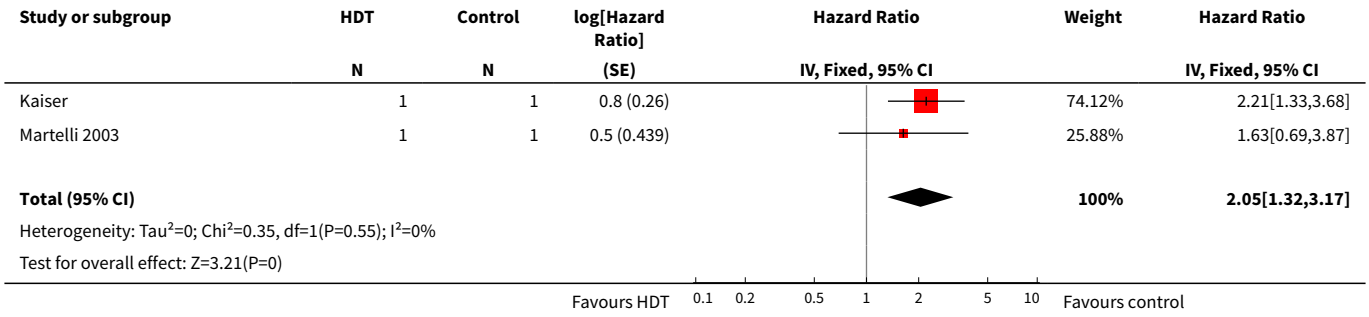
Analysis 4.2. Comparison 4 Disease-free survival/Relapse-free survival, Outcome 2 Relapse-free Survival (death = censored).



Comparison 5. Survival after relapse

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival after relapse	2		Hazard Ratio (Fixed, 95% CI)	2.05 [1.32, 3.17]

Analysis 5.1. Comparison 5 Survival after relapse, Outcome 1 Survival after relapse.



Comparison 6. Treatment related mortality / Mortality during treatment (TRM/MDT)

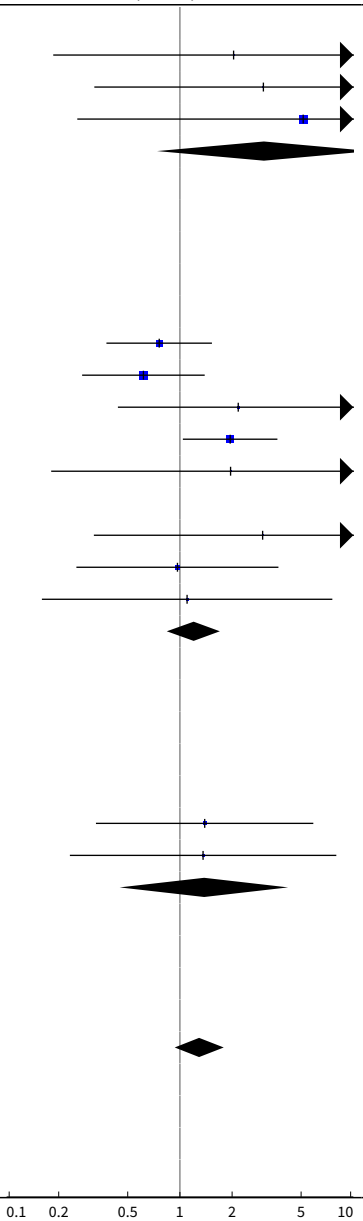
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TRM/MDT - all studies	14	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
1.1 TRM	3	807	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [0.74, 12.64]
1.2 MDT	9	1427	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.84, 1.70]
1.3 Others	2	321	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.45, 4.21]
2 TRM/MDT - different high-dose settings	14	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
2.1 High-dose sequential therapy without induction	2	224	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.40, 4.04]
2.2 Abbreviated standard induction therapy	8	1569	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.88, 1.83]
2.3 Full standard induction therapy	4	762	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.57, 3.67]
3 TRM/MDT - patients' status at randomisation	14	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
3.1 Patients irrespectively of disease status	11	1896	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.89, 1.74]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Patients in CR or PR	3	659	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.49, 19.20]
4 TRM/MDT - methodological quality	14	2555	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
4.1 Sufficient method	12	2234	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.91, 1.81]
4.2 Insufficient or unknown method	2	321	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.45, 4.21]
5 TRM/MDT - study size	13	2014	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.92, 1.78]
5.1 >100 pts.	8	1696	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.89, 1.99]
5.2 <100 pts.	5	318	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.66, 2.05]
6 TRM/MDT - protocol adherence to HDT	12	1791	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.91, 1.79]
6.1 >70%	7	1033	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.58, 1.70]
6.2 <70%	5	758	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.99, 2.34]
7 TRM/MDT - preparative HDT regimen	13	2014	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.92, 1.78]
7.1 BEAC	3	393	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.49, 12.58]
7.2 BEAM	6	1280	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.80, 1.66]
7.3 TBI	3	215	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.75, 5.43]
7.4 Others	1	126	Risk Ratio (M-H, Fixed, 95% CI)	1.1 [0.16, 7.57]
8 TRM/MDT - bone marrow involvement	12	1791	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.91, 1.79]
8.1 >20% of pts.	5	891	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.58, 1.89]
8.2 <20% of pts.	7	900	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.94, 2.13]
9 TRM/MDT - % of patients with DLCL (wide def.)	12	1791	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.91, 1.79]
9.1 >80%	8	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.96, 2.10]
9.2 <80%	4	783	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.50, 1.89]
10 TRM/MDT - % of patients with DLCL (narrow def.)	12	1791	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.91, 1.79]
10.1 >70%	6	673	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.73, 2.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 <70%	6	1118	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.84, 2.01]

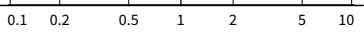
Analysis 6.1. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 1 TRM/MDT - all studies.

Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 TRM					
Haioun	2/268	1/273		1.76%	2.04[0.19,22.34]
Milpied	3/98	1/99		1.77%	3.03[0.32,28.64]
Verdonck	2/34	0/35		0.88%	5.14[0.26,103.35]
Subtotal (95% CI)	**400**	**407**		**4.4%**	**3.05[0.74,12.64]**
Total events: 7 (HDT), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=2(P=0.89); I^2=0%					
Test for overall effect: Z=1.54(P=0.12)					
6.1.2 MDT					
De Souza	9/28	11/26		20.27%	0.76[0.38,1.53]
Gisselbrecht	9/189	14/181		25.41%	0.62[0.27,1.39]
Intragumtornchai	4/23	2/25		3.41%	2.17[0.44,10.77]
Kaiser	26/158	13/154		23.39%	1.95[1.04,3.65]
Kluin-Nelemans	2/98	1/96		1.79%	1.96[0.18,21.25]
Martelli	0/22	0/27			Not estimable
Martelli 2003	3/75	1/75		1.78%	3[0.32,28.19]
Santini	4/63	4/61		7.22%	0.97[0.25,3.7]
Vitolo	2/60	2/66		3.38%	1.1[0.16,7.57]
Subtotal (95% CI)	**716**	**711**		**86.65%**	**1.2[0.84,1.7]**
Total events: 59 (HDT), 48 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.95, df=7(P=0.34); I^2=12%					
Test for overall effect: Z=0.99(P=0.32)					
6.1.3 Others					
Gianni	4/48	3/50		5.22%	1.39[0.33,5.88]
Santini-2	3/117	2/106		3.73%	1.36[0.23,7.98]
Subtotal (95% CI)	**165**	**156**		**8.95%**	**1.38[0.45,4.21]**
Total events: 7 (HDT), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.56(P=0.58)					
Total (95% CI)	**1281**	**1274**		**100%**	**1.29[0.93,1.79]**
Total events: 73 (HDT), 55 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.85, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=1.55(P=0.12)					
Test for subgroup differences: Chi^2=1.6, df=1 (P=0.45), I^2=0%					



Analysis 6.2. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 2 TRM/MDT - different high-dose settings.

Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.2.1 High-dose sequential therapy without induction					
Gianni	4/48	3/50		5.22%	1.39[0.33,5.88]
Vitolo	2/60	2/66		3.38%	1.1[0.16,7.57]
Subtotal (95% CI)	**108**	**116**		**8.6%**	**1.28[0.4,4.04]**
Total events: 6 (HDT), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=0.41(P=0.68)					
6.2.2 Abbreviated standard induction therapy					
De Souza	9/28	11/26		20.27%	0.76[0.38,1.53]
Gisselbrecht	9/189	14/181		25.41%	0.62[0.27,1.39]
Kaiser	26/158	13/154		23.39%	1.95[1.04,3.65]
Kluin-Nelemans	2/98	1/96		1.79%	1.96[0.18,21.25]
Martelli 2003	3/75	1/75		1.78%	3[0.32,28.19]
Milpied	3/98	1/99		1.77%	3.03[0.32,28.64]
Santini-2	3/117	2/106		3.73%	1.36[0.23,7.98]
Verdonck	2/34	0/35		0.88%	5.14[0.26,103.35]
Subtotal (95% CI)	**797**	**772**		**79.01%**	**1.27[0.88,1.83]**
Total events: 57 (HDT), 43 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.02, df=7(P=0.25); I^2=22.39%					
Test for overall effect: Z=1.28(P=0.2)					
6.2.3 Full standard induction therapy					
Haioun	2/268	1/273		1.76%	2.04[0.19,22.34]
Intragumtornchai	4/23	2/25		3.41%	2.17[0.44,10.77]
Martelli	0/22	0/27			Not estimable
Santini	4/63	4/61		7.22%	0.97[0.25,3.7]
Subtotal (95% CI)	**376**	**386**		**12.39%**	**1.45[0.57,3.67]**
Total events: 10 (HDT), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					
Total (95% CI)	**1281**	**1274**		**100%**	**1.29[0.93,1.79]**
Total events: 73 (HDT), 55 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.85, df=12(P=0.63); I^2=0%					
Test for overall effect: Z=1.55(P=0.12)					
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.97), I^2=0%					

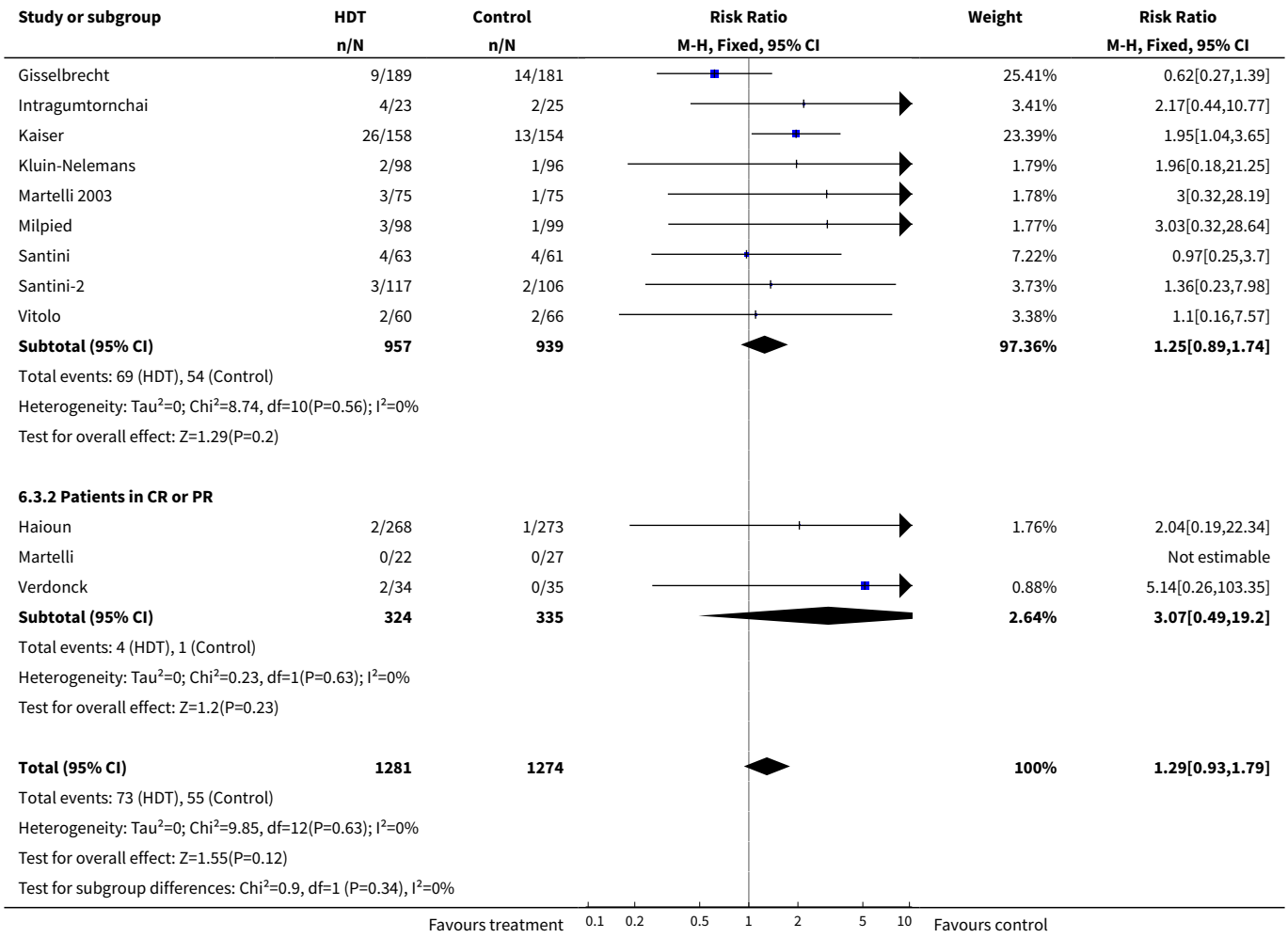


Favours treatment — Favours control

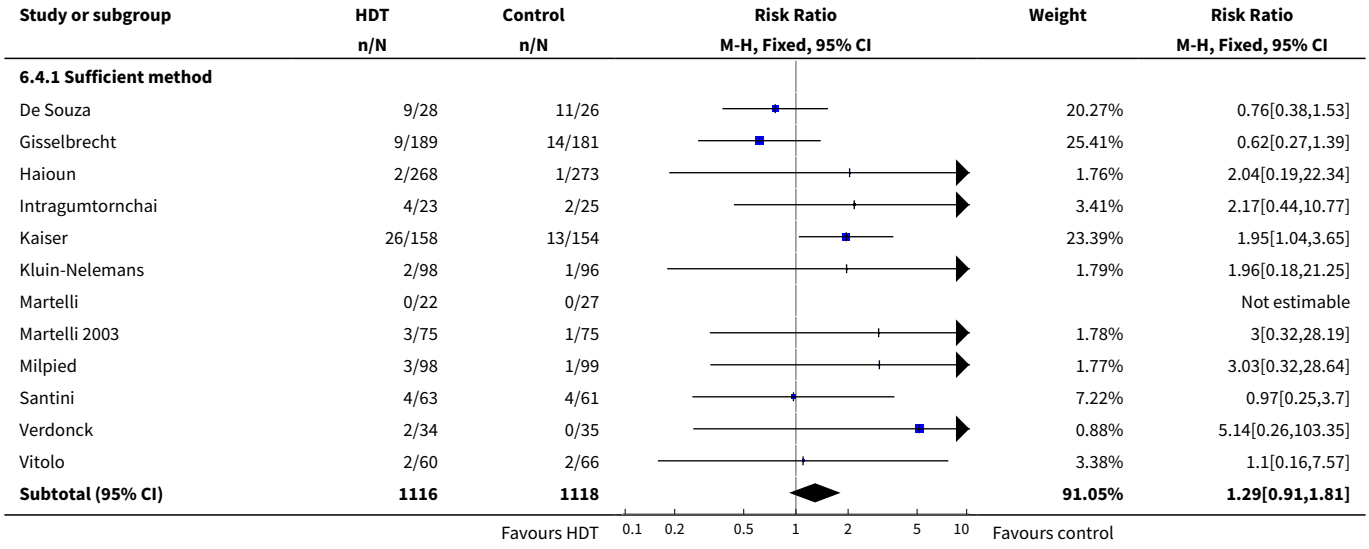
Analysis 6.3. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 3 TRM/MDT - patients' status at randomisation.

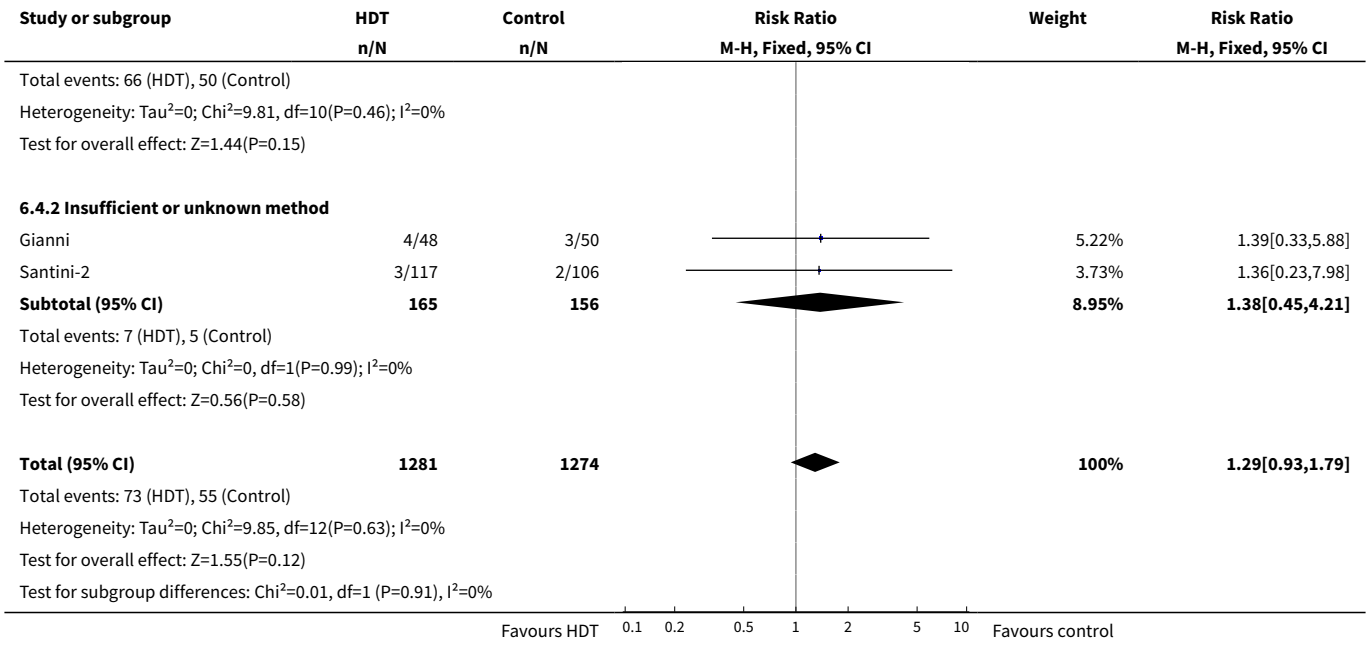
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 Patients irrespectively of disease status					
De Souza	9/28	11/26		20.27%	0.76[0.38,1.53]
Gianni	4/48	3/50		5.22%	1.39[0.33,5.88]

Favours treatment — Favours control

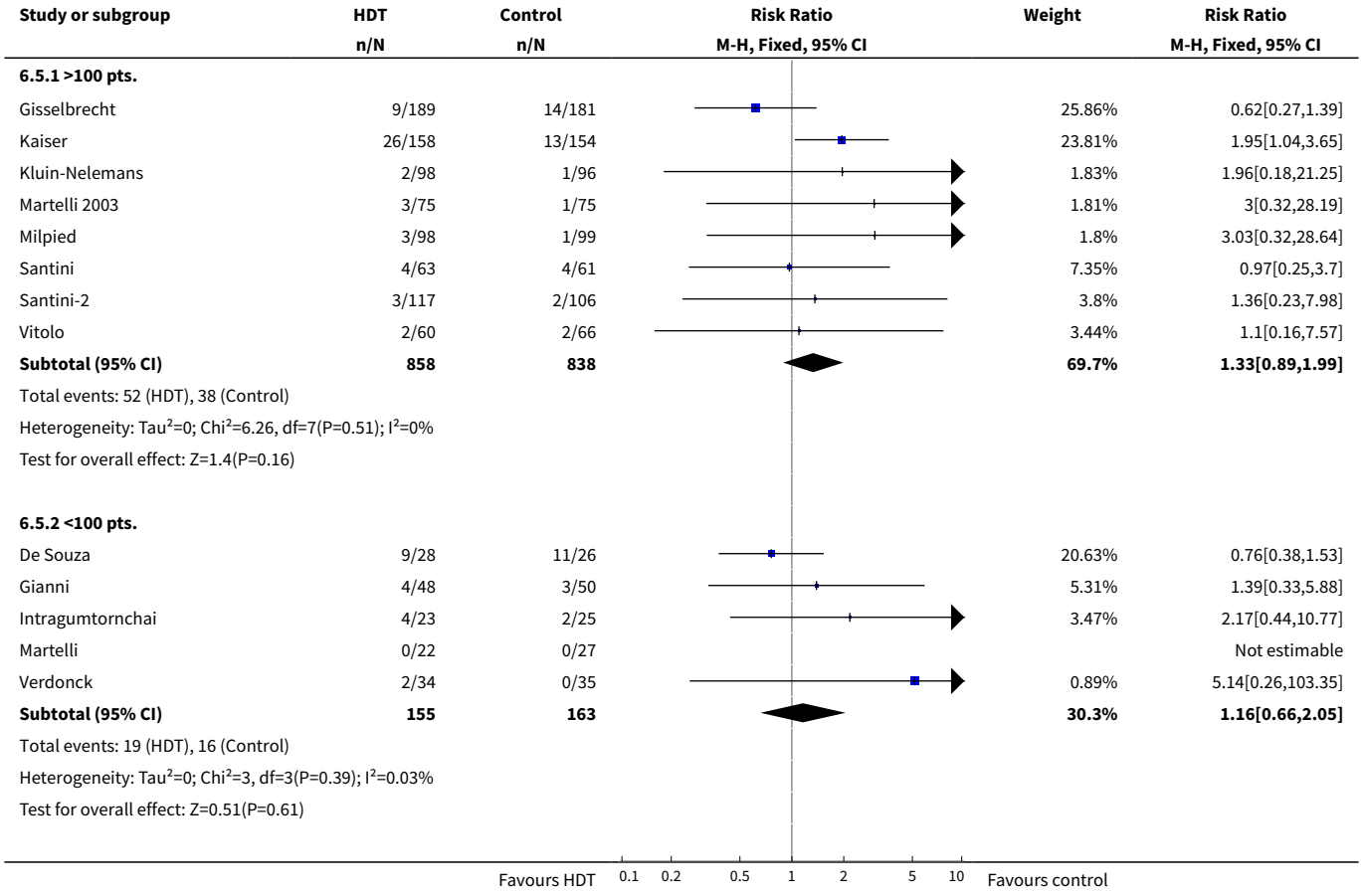


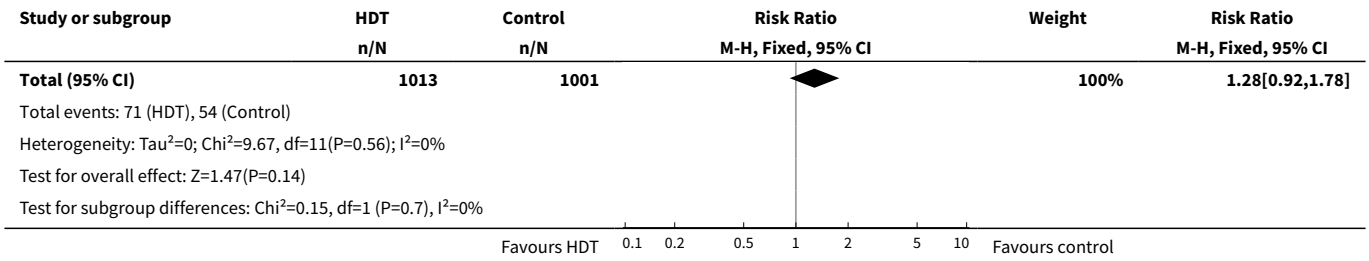
Analysis 6.4. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 4 TRM/MDT - methodological quality.



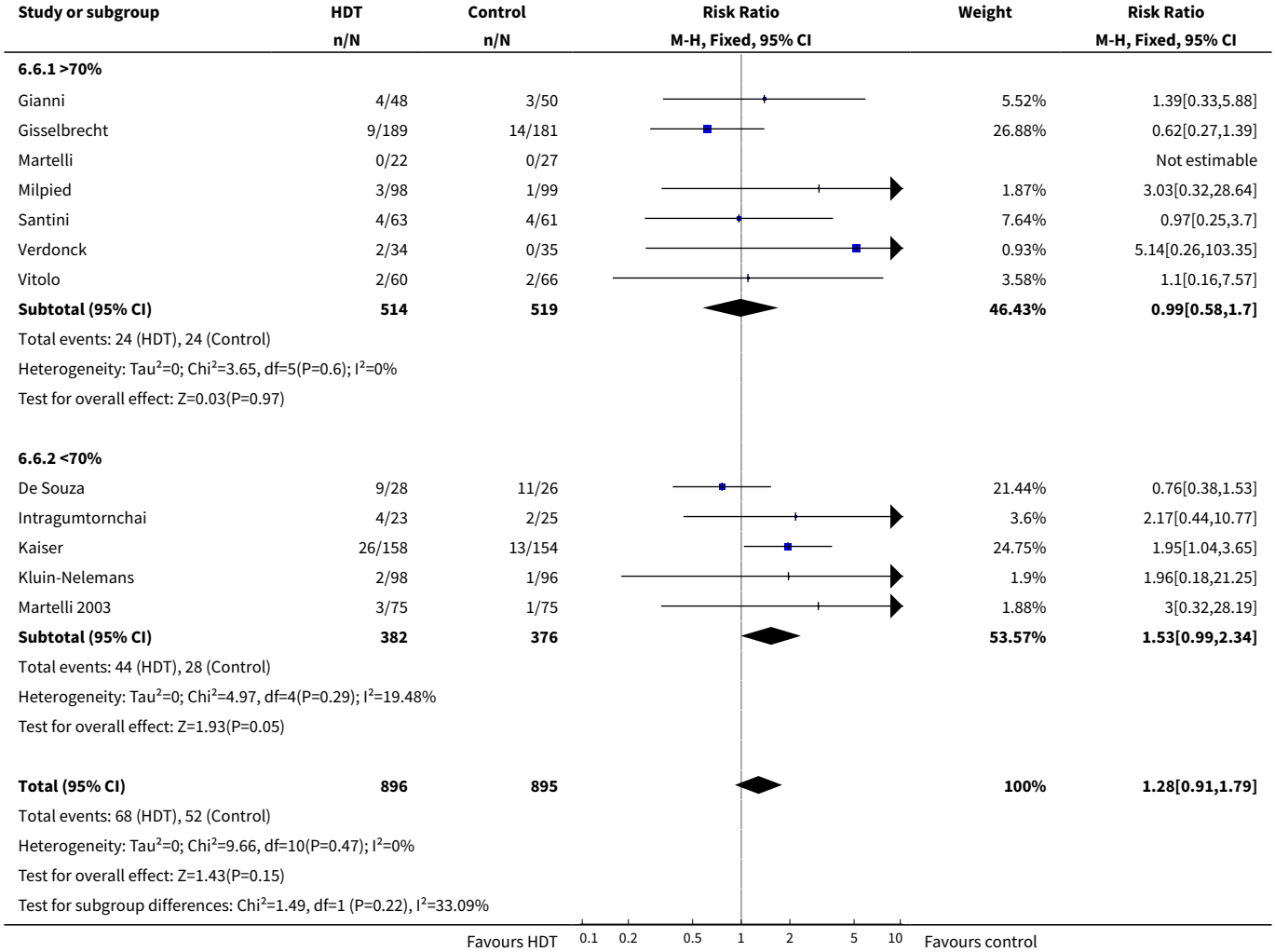


Analysis 6.5. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 5 TRM/MDT - study size.



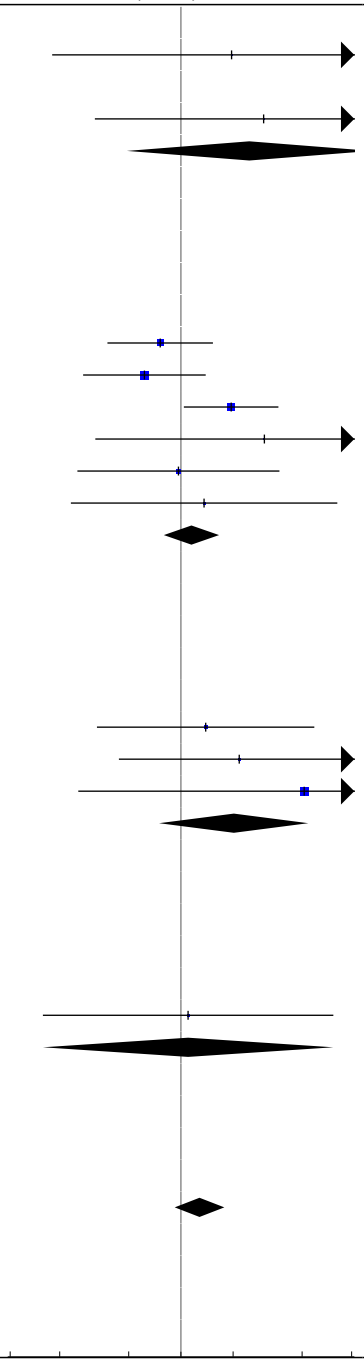


Analysis 6.6. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 6 TRM/MDT - protocol adherence to HDT.



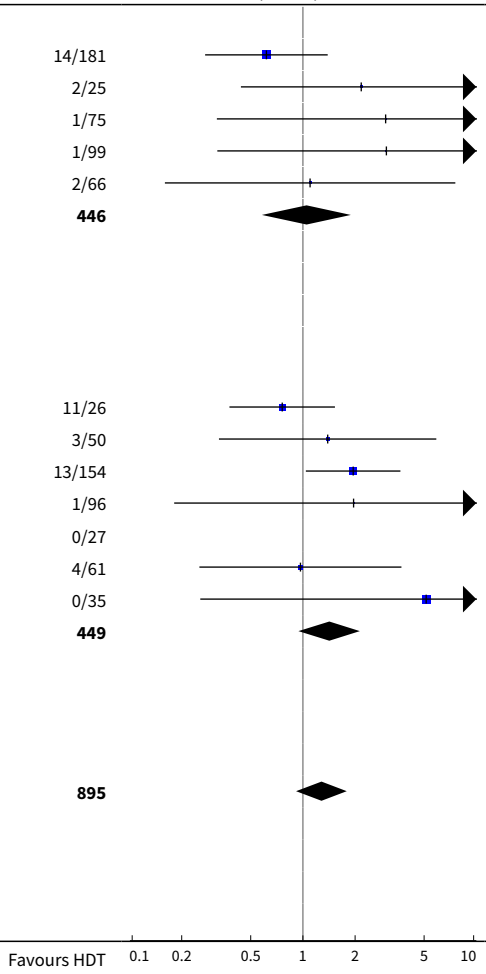
Analysis 6.7. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 7 TRM/MDT - preparative HDT regimen.

Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.7.1 BEAC					
Kluin-Nelemans	2/98	1/96		1.83%	1.96[0.18,21.25]
Martelli	0/22	0/27			Not estimable
Martelli 2003	3/75	1/75		1.81%	3[0.32,28.19]
Subtotal (95% CI)	**195**	**198**		**3.64%**	**2.48[0.49,12.58]**
Total events: 5 (HDT), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=1.09(P=0.27)					
6.7.2 BEAM					
De Souza	9/28	11/26		20.63%	0.76[0.38,1.53]
Gisselbrecht	9/189	14/181		25.86%	0.62[0.27,1.39]
Kaiser	26/158	13/154		23.81%	1.95[1.04,3.65]
Milpied	3/98	1/99		1.8%	3.03[0.32,28.64]
Santini	4/63	4/61		7.35%	0.97[0.25,3.7]
Santini-2	3/117	2/106		3.8%	1.36[0.23,7.98]
Subtotal (95% CI)	**653**	**627**		**83.25%**	**1.15[0.8,1.66]**
Total events: 54 (HDT), 45 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.15, df=5(P=0.21); I^2=30.03%					
Test for overall effect: Z=0.75(P=0.45)					
6.7.3 TBI					
Gianni	4/48	3/50		5.31%	1.39[0.33,5.88]
Intragumtornchai	4/23	2/25		3.47%	2.17[0.44,10.77]
Verdonck	2/34	0/35		0.89%	5.14[0.26,103.35]
Subtotal (95% CI)	**105**	**110**		**9.67%**	**2.02[0.75,5.43]**
Total events: 10 (HDT), 5 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=1.39(P=0.17)					
6.7.4 Others					
Vitolo	2/60	2/66		3.44%	1.1[0.16,7.57]
Subtotal (95% CI)	**60**	**66**		**3.44%**	**1.1[0.16,7.57]**
Total events: 2 (HDT), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.1(P=0.92)					
Total (95% CI)	**1013**	**1001**		**100%**	**1.28[0.92,1.78]**
Total events: 71 (HDT), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.67, df=11(P=0.56); I^2=0%					
Test for overall effect: Z=1.47(P=0.14)					
Test for subgroup differences: Chi^2=1.79, df=1 (P=0.62), I^2=0%					



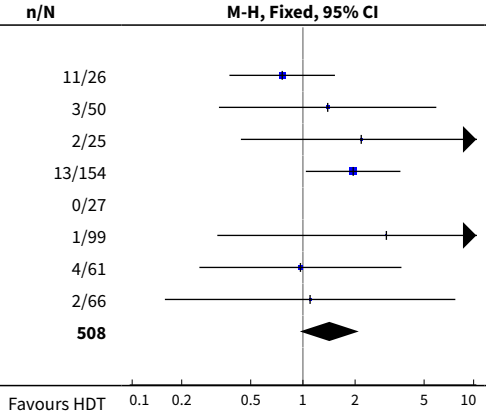
Analysis 6.8. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 8 TRM/MDT - bone marrow involvement.

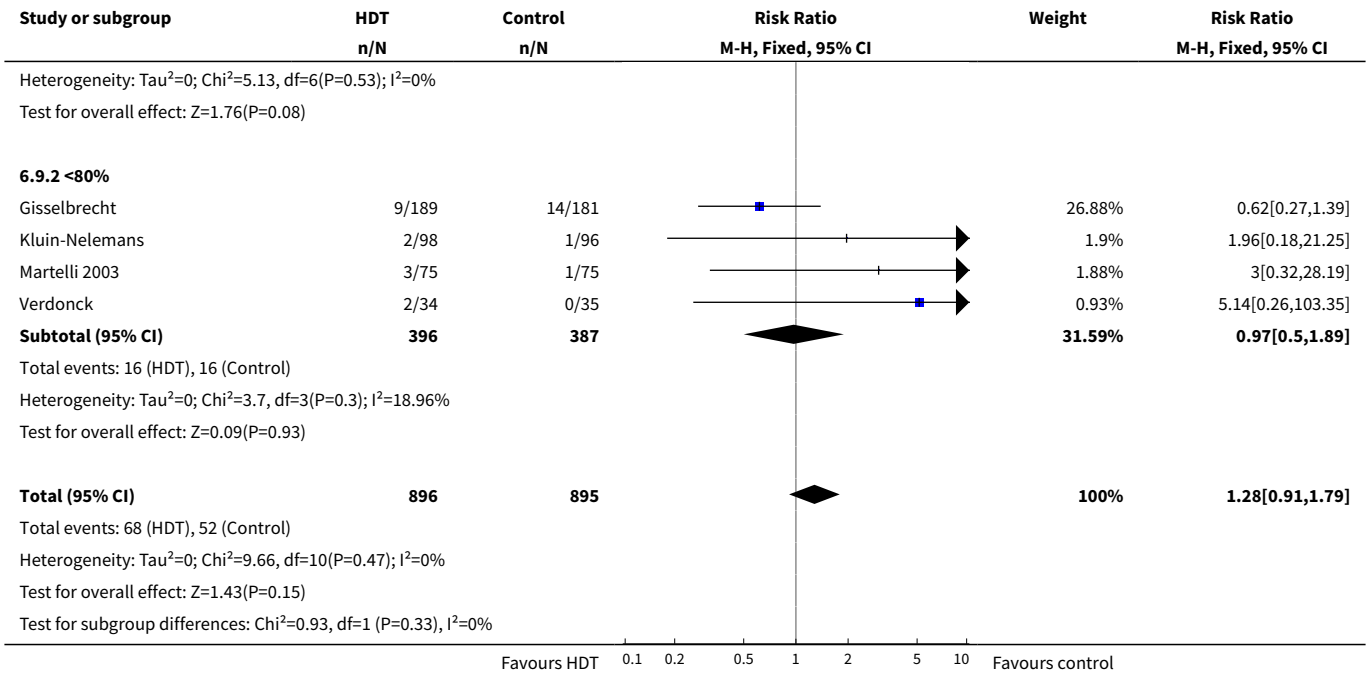
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.8.1 >20% of pts.					
Gisselbrecht	9/189	14/181		26.88%	0.62[0.27,1.39]
Intragumtornchai	4/23	2/25		3.6%	2.17[0.44,10.77]
Martelli 2003	3/75	1/75		1.88%	3[0.32,28.19]
Milpied	3/98	1/99		1.87%	3.03[0.32,28.64]
Vitolo	2/60	2/66		3.58%	1.1[0.16,7.57]
Subtotal (95% CI)	**445**	**446**		**37.82%**	**1.05[0.58,1.89]**
Total events: 21 (HDT), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.15, df=4(P=0.39); I^2=3.71%					
Test for overall effect: Z=0.15(P=0.88)					
6.8.2 <20% of pts.					
De Souza	9/28	11/26		21.44%	0.76[0.38,1.53]
Gianni	4/48	3/50		5.52%	1.39[0.33,5.88]
Kaiser	26/158	13/154		24.75%	1.95[1.04,3.65]
Kluin-Nelemans	2/98	1/96		1.9%	1.96[0.18,21.25]
Martelli	0/22	0/27			Not estimable
Santini	4/63	4/61		7.64%	0.97[0.25,3.7]
Verdonck	2/34	0/35		0.93%	5.14[0.26,103.35]
Subtotal (95% CI)	**451**	**449**		**62.18%**	**1.42[0.94,2.13]**
Total events: 47 (HDT), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.12, df=5(P=0.4); I^2=2.36%					
Test for overall effect: Z=1.67(P=0.09)					
Total (95% CI)	**896**	**895**		**100%**	**1.28[0.91,1.79]**
Total events: 68 (HDT), 52 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.66, df=10(P=0.47); I^2=0%					
Test for overall effect: Z=1.43(P=0.15)					
Test for subgroup differences: Chi^2=0.68, df=1 (P=0.41), I^2=0%					



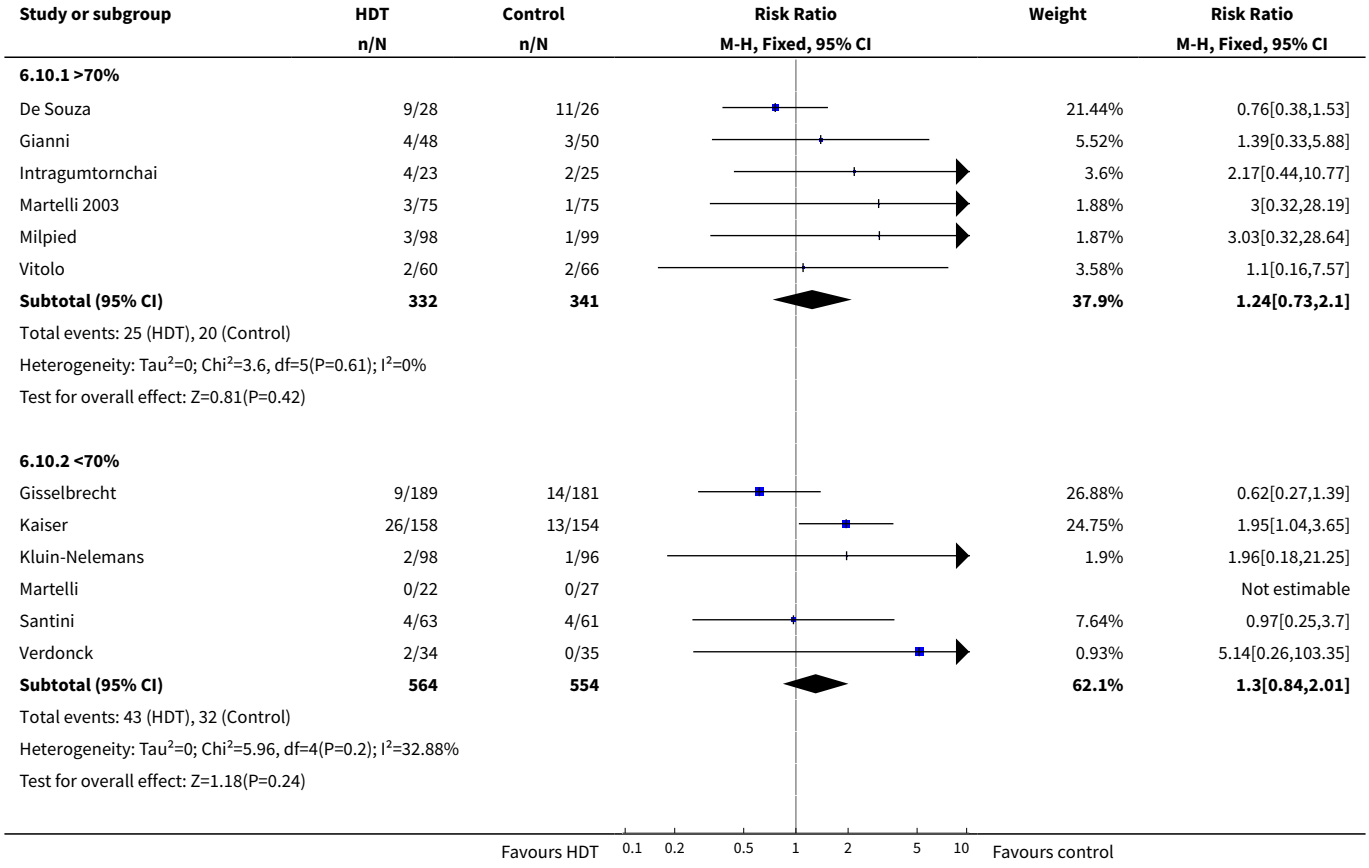
Analysis 6.9. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 9 TRM/MDT - % of patients with DLCL (wide def.).

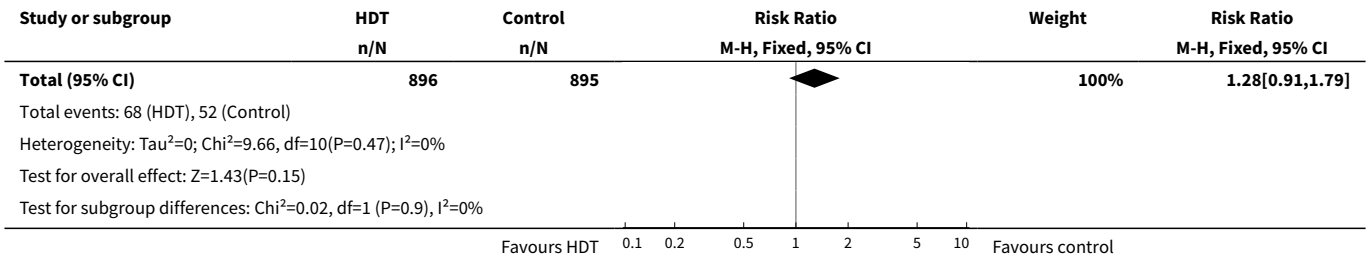
Study or subgroup	HDT n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
6.9.1 >80%					
De Souza	9/28	11/26		21.44%	0.76[0.38,1.53]
Gianni	4/48	3/50		5.52%	1.39[0.33,5.88]
Intragumtornchai	4/23	2/25		3.6%	2.17[0.44,10.77]
Kaiser	26/158	13/154		24.75%	1.95[1.04,3.65]
Martelli	0/22	0/27			Not estimable
Milpied	3/98	1/99		1.87%	3.03[0.32,28.64]
Santini	4/63	4/61		7.64%	0.97[0.25,3.7]
Vitolo	2/60	2/66		3.58%	1.1[0.16,7.57]
Subtotal (95% CI)	**500**	**508**		**68.41%**	**1.42[0.96,2.1]**
Total events: 52 (HDT), 36 (Control)					





Analysis 6.10. Comparison 6 Treatment related mortality / Mortality during treatment (TRM/MDT), Outcome 10 TRM/MDT - % of patients with DLCL (narrow def.).

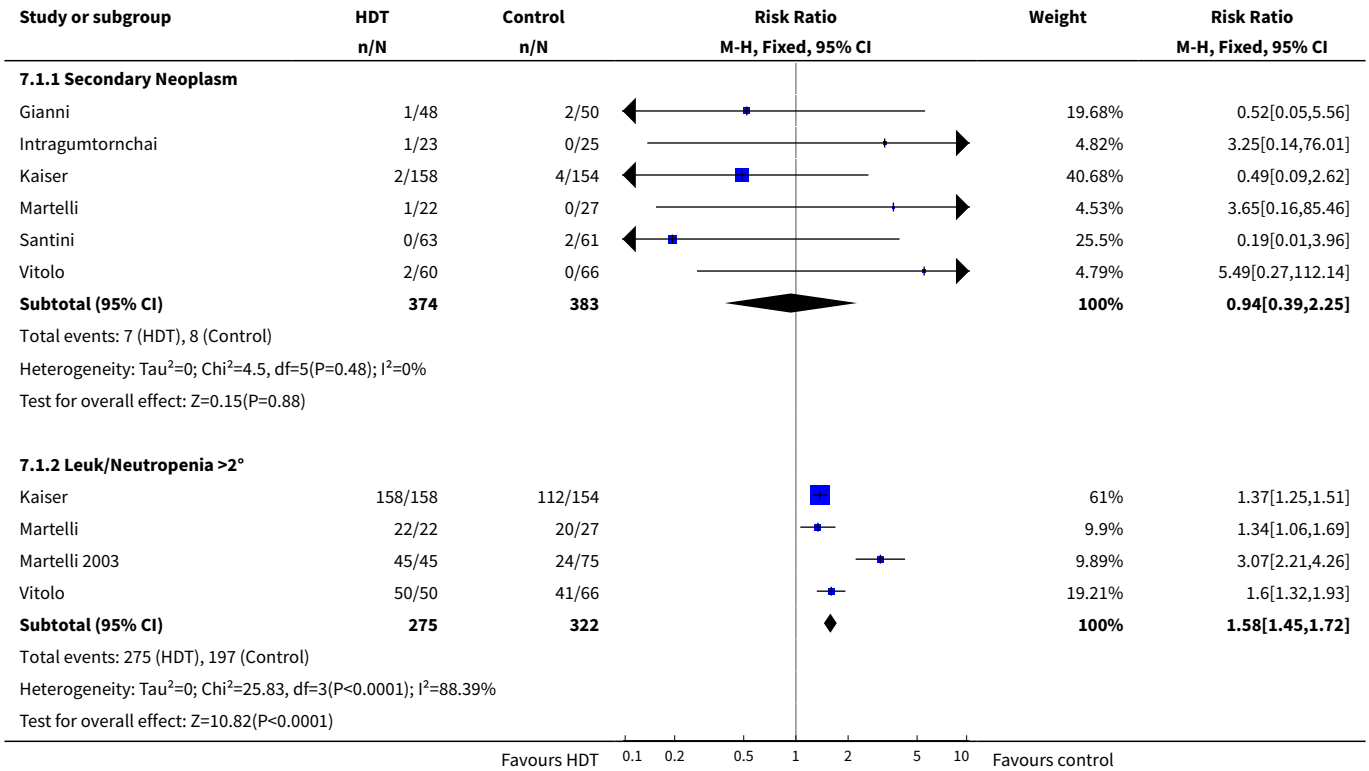


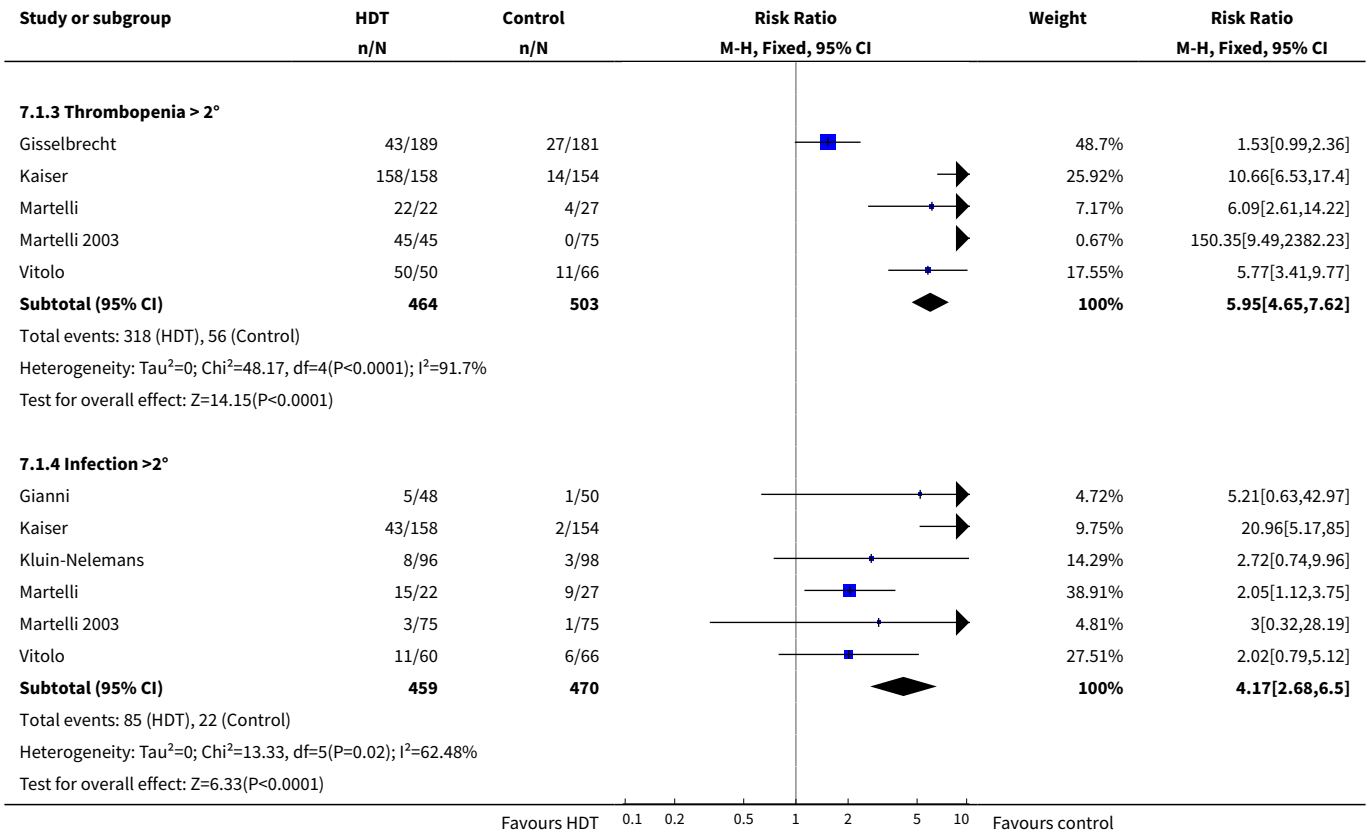


Comparison 7. Further Toxicities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Toxicities	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Secondary Neoplasm	6	757	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.39, 2.25]
1.2 Leuk/Neutropenia >2°	4	597	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.45, 1.72]
1.3 Thrombopenia > 2°	5	967	Risk Ratio (M-H, Fixed, 95% CI)	5.95 [4.65, 7.62]
1.4 Infection >2°	6	929	Risk Ratio (M-H, Fixed, 95% CI)	4.17 [2.68, 6.50]

Analysis 7.1. Comparison 7 Further Toxicities, Outcome 1 Toxicities.





ADDITIONAL TABLES

Table 1. Treatment regimens

Study	Control arm	Experimental arm
De Souza	VACOP-B 12 weeks: ETO 250 mg/m2; DOX 50 mg/m2; CY 350 mg/m2; VCR 1.2 mg/m2; BLEO 10 U/m2; PDN 45mg/m2	VACOP-B 6 weeks followed by HDS: CY 4 g/m2 - ETO 2 g/m2 - BEAM
Martelli 2003	MACOP-B 12 weeks	MACOP-B 8 weeks followed by BEAC
Gianni	MACOP-B 12 weeks (followed by restaging, if reduction in tumour volume >80%: +/- radiotherapy; if reduction in tumour volume <80%: HDS)	HDS consisting of 5 phases: DOX 50 mg/m² i.v. d1, PDN 40 mg/m² oral d1 to d21, VCR 1.4 mg/m² d1,8,15 - (2) CY 7 g/m² i.v. d1, stem cell harvesting d16 - (3) VCR 1.4 mg/m² i.v. d1, MTX 8 g/m² i.v. d1, Folinacid 9 mg/m² 12 doses i.v. d2 to d4 - (4) ETO 2 g/m² i.v. d1 - Restaging: if reduction in tumour <80%: MACOP-B, if reduction in tumour >80%: phase (5) TBI 2.5 Gy a 5 doses every 12 hrs starting d1, MEL 120-140 mg/m² i.v. d4, autografting d5 - due to substantial toxic effects of TBI phase (5) regimen changed for last 18 pts: MITOX 60 mg/m² i.v. d1, MEL 180 mg/m² i.v. d4, autografting d5 - +/- radiotherapy
Gisselbrecht	4 cycles ACVB (DOX 75 mg/m² d1, CY 1200 mg/m² d1, VIN 2 mg/m² d1+d5, BLEO 10 mg d1+d5, PDN 60 mg/m² d1-d5, i.t. MTX 15 mg	1 cycle CEOP (CY 750 mg/m² d1, EPI 70 mg/m² d1, VCR 1 mg/m² d1, PDN 40 mg/m² days 1-5, i.t. MTX 15 mg d1) and 2x ECVBP d15+d36 (EPI 120 mg/m² d1, CY 2000 mg/

Table 1. Treatment regimens *(Continued)*

	d2), 2 week-interval outpatient consolidation (4 months) with 2x MTX 3g/m² + Leukovorin, 4x ETO 300 mg/m², IFO 1500 mg/m² und 2x CYTA 100 mg/m², 2 week-interval	m² d1, VIN 2 mg/m² d1+d5, BLEO 10 mg d1+d5, PDN 40 mg/m² d1-5, intrathekal MTX 15 mg); on day 60: BEAM followed by ASCT
Haioun	Induction: 4x ACVB-14 (DOX 75 mg/m² d1, CY 1200 mg/m² d1, VIN 2 mg/m² d1+d5, BLEO 10 mg d1+d5, PDN 60 mg/m² d1-d5) or 4x NCVB-14 (MITOX 12 mg/m² instead of DOX) - Consolidation: 2x MTX 3g/m² (2 weeks), IFO 1500 mg/m², ETO 300 mg/m² (2 weeks), ASP 50000 IU/m² (week), CYTA 4x 100mg/m² (2 weeks) [note: NCVB versus AVCB as first randomisation, NCVB arm stopped due to superiority of ACVB]	Induction: 4x ACVB-14 - Consolidation: 2x MTX 3g/m², followed by CBV (CY 1500mg/m² d-7 to d-4, CARM 300mg/m² d-4, ETO 250mg/m² d-7 to -4), and ABMT [note: NCVB versus AVCB as first randomisation, NCVB arm stopped due to superiority of ACVB]
Intragumtornchai	CHOP-21 8 cycles: VCR 1.4mg/m² i.v. d1, CY 750mg/m² i.v. d1, DOX 50mg/m² i.v. d1, PDN 75mg p.o. d1 to5 (i.t. prophylaxis MTX 12,5mg e.g. BM+)	CHOP-21 3 cycles followed by ESHAP (2-4 cycles): ETO 40mg/m² i.v. d1 to 4, M-PDN 500mg i.v. d1 to 5, CYTA 2g/m² i.v. d5, CIS 25mg/m² d1 to 4; HD: TBI (1200cGy - 200cGy p fraction d-8 to -6 OR CARM 450mg/m² d-6, ETO 60mg/kg, d-4 , CY 60mg/kg d-2 to -1, stem cells d0
Kaiser	5x CHOEP (CY 750 mg/m² d1, DOX 50 mg/m² d1, VCR 2 mg d1, ETO 100 mg/m² d1-d3, PDN 100mg d1-d5, repeated d22), IF RT	3x CHOEP (CY 750 mg/m² d1, DOX 50mg/m² d1, VCR 2mg d1, ETO 100mg/m² d1-d3, PDN 100mg d1-d5, repeated d22), BEAM (CARM 300mg/m² d-5, ETO 100mg/m² d-5 bis -2 (2x daily), CYTA 200mg/m² d-5 bis -2 (2x daily), MEL 140mg/m² d-5) + ASCT (within 28d), IF RT
Kluin-Nelemans	8 cycles CHVmP/BV (CY 600 mg/m², DOX 50 mg/m², TEN 60 mg/m², i.v. d1; PDN 40 mg/m² oral d1 bis d5; BLEO 10 mg/m² (total) d15 i.v., VCR 1.4 mg/m² d15 i.v.)	6 cycles CHVmP/BV (CY 600 mg/m², DOX 50 mg/m², TEN 60 mg/m², i.v. d1; PDN 40 mg/m² oral d1 bis d5; BLEO 10 mg/m² (total) d15 i.v., VCR 1.4 mg/m² d15 i.v.) followed by BEAC and ABMT
Martelli 1996	MACOP-B (8 courses) or F-MACHOP (4 courses) [equals 2/3 of therapy], thereafter restaging (atypic CR-definition, if response >80%: CR); patients in CR proceed to MACOP-B or F-MACHOP; if response < 50%: patients ex protocol; patients in PR were randomised, DHAP 6 cycles (DEXA 40mg/d d1-d4, CIS 100mg/m² cont. infusion for 24h d1, CYTA 2g/m² 3h infusion repeated after 12h d2), therapy repeated every 3-4 weeks and continued in responding patients	MACOP-B (8 courses) or F-MACHOP (4 courses) [equals 2/3 of therapy], thereafter restaging (if response >80%: CR); patients in CR proceed to MACOP-B or F-MACHOP, if response < 50% patients ex protocol, patients in PR were randomised; > BEAC and ABMT
Milpied	8x CHOP-21 (CY 750 mg/m², DOX 50 mg/m², VCR 1.4 mg/m², PDN 100 mg), evaluation after 4 cycles: patients in PR or CR received 4 further cycles CHOP, others received salvage therapy	2x CEEP (CY 1.2g/m², EPI 100mg/m², VIN 3mg/m², PDN 80mg/m² d1 to d5) every 15d, patients in PR or CR continued to HD-MTX 3g/m² d1, CYTA 100mg d1 to d5, and BEAM + ASCT, others received salvage therapy
Rodriguez 2003	9 cycles of 3 alternating chemotherapy regimens (ATT), and replacing doxorubicin with idarubicin	2 cycles of ATT, 2 intensified dose chemotherapy cycles (IFO 10gm/m², ETO 800mg/m²; IFO 10gm/m², Mitoxantrone 20mg/m²), followed by stem cell collection if response, then BEAM/ASCT
Santini 1998	VACOP-B 12 weeks, DHAP for patients in PR or NR after induction), IF RT	VACOP-B 12 weeks followed by BEAM and ASCT (irrespectively of disease status)

Table 1. Treatment regimens *(Continued)*

Santini 2003	VACOP-B 12 weeks - Salvage: in case of persisting disease: CY-ETO-BEAM (like experimental arm)	VACOP-B 8 weeks followed by HD-CY 7g/m^2, HD-ETO 2g/m^2, BEAM and ASCT
Verdonck	CHOP-21 (CY 750 mg/m^2, DOX 50 mg/m^2, VCR 1.4 mg/m^2, PDN 100 mg) patients with PR and BM+ and patients with CR 5x CHOP, patients with NR or progression were not studied further	4x CHOP followed by HDT (CY 60 mg/kg d-4 and d-3, TBI 800cGy d-1) and ABMT
Vitolo	6x MegaCEOP (8x if bone marrow involvement), CY 1.2g/m^2, EPI 110mg/m^2, VCR 1.4 mg/m^2, repeated after 14d	APO (Doxo 50 mg/m^2 d1 +d22, Vincristin 2 mg (total dose) d1 + d8, Pred 40 mg/m^2 d1 to d22) one course if bone marrow negative, 2 courses if bone marrow involvement, followed by CY 7 g/m^2, MTX 8 g/m^2, ETO 2 g/m^2, VCR 1.4 mg/m^2 (+ 2x DHAP in BM+)

Table 2. Preparative regimens and mobilization technique

Study	Preparative regimen	Mobilization tech.
De Souza	BEAM (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/m^2 MEL)	not clarified
Martelli 2003	BEAC (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/kg CY)	G-CSF 24h after MACOP-B week 8 OR G-CSF alone 2 weeks after MACOP-B
Gianni	30 pts: TBI (12.5 Gy total) + 120-140 mg/m^2 MEL, then (due to tox.) 18 pts: MITOX 60 mg/m^2 + MEL 180 mg/m^2	Phase II: HD-CY (7 g/m^2) + G-CSF or GM-CSF
Gisselbrecht	BEAM (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/m^2 MEL)	after 1st or 2nd ECVBP cycle + G-CSF
Haioun	CBV (6000 mg/m^2 CY, 300 mg/m^2 CARM, 1000 mg/m^2 ETO)	after 1st or 2nd HD-MTX course (G-CSF not mentioned)
Intragumtonchai	TBI (12 Gy total) OR 450 mg/m^2 CARM, 60 mg/kg ETO, 120 mg/kg CY	7 days after last ESHAP: G-CSF
Kaiser	BEAM (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/m^2 MEL)	after 2. or 3. CHOEP with G-CSF
Kluin-Nelemans	BEAC (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/kg CY)	between 4th and 6th CHVmP/BV cycle + G-CSF or GM-CSF
Martelli 1996	BEAC (300 mg/m^2 CARM, 800 mg/m^2 ETO, 800 mg/m^2 CYTA, 140 mg/kg CY)	bone marrow collection at a median of 10 days after response evaluation
Milpied	BEAM (300 mg/m^2 CARM, 1600 mg/m^2 ETO, 1600 mg/m^2 CYTA, 140 mg/m^2 MEL)	after 1st or 2nd CEEP
Rodriguez 2003	BEAM	stem cell collection after 3x ATT and 2 intensified dose chemotherapy
Santini 1998	BEAM (according to Mills)	bone marrow collection after last VACOP-B cycle

Table 2. Preparative regimens and mobilization technique *(Continued)*

Santini 2003	BEAM	peripheral blood progenitor cells were collected after HD-CY plus G-CSF
Verdonck	120 mg/kg CY + TBI (8 Gy total [1 fraction only])	bone marrow collection after 3x CHOP
Vitolo	60 mg/m^2 MITOX + 180 mg/m^2 MEL	not clarified

Table 3. Further study characteristics

Trial	Included in analyses	HDT strategy	Time to HDT (days)
De Souza	OS, EFS, CR, TRM	Abbreviated standard induction	137
Martelli 2003	OS, EFS, DFS, survival after relapse, CR, TRM	Abbreviated standard induction	56
Gianni	OS, EFS, RFS, CR, TRM	Sequential high-dose	61
Gisselbrecht	OS, EFS, CR, TRM	Abbreviated standard induction	63
Haioun	OS, TRM	Full standard induction	84
Intragumtornchai	OS, EFS, RFS, CR, TRM	Full standard induction	161
Kaiser	OS, EFS, survival after relapse, CR, TRM	Abbreviated standard induction	63
Kluin-Nelemans	OS, CR	Abbreviated standard induction	126
Martelli 1996	OS, EFS, CR, TRM	Full standard induction	56
Milpied	OS, EFS, CR, TRM	Abbreviated standard induction	66
Rodriguez 2003	OS, CR, PR	Abbreviated standard induction	-
Santini 1998	OS, EFS, RFS, CR, TRM	Full standard induction	84
Santini 2003	CR, TRM	Abbreviated standard induction	87
Verdonck	OS, EFS, DFS, CR, TRM	Abbreviated standard induction	84
Vitolo	OS, EFS, CR, TRM	Sequential high-dose	99

Table 4. Prognostic factors/Baseline characteristics

Study	Histology	IPI	Age	Gender	Stage
De Souza	WF (n): F (2), G (42), H (8), others (2)	high risk (54/54)	median: 37.5y, mean: 37.4	female: 27.8%, male: 72.2%	I (0%), II (6%), III (24%), IV (70%)

Table 4. Prognostic factors/Baseline characteristics *(Continued)*

Martelli 2003	REAL (n): diffuse large B-cell (114), peripheral T-cell (14), anaplastic large cell (14), large cell not specified (8)	high-intermediate (99/150), high (50/150), unknown (1/150)	median: CON: 45y, EXP: 41y	female: 37%, male: 63%	I (1%), II (9%), III (25%), IV (65%)
Gianni	WF: G (89%), H (11%)	low (N = 1), low-intermediate (N = 15), high-intermediate (N = 41), high (N = 41)	median (range): CON: 35y (17-60), EXP: 34y (18-59)	female: 57%, male: 43%	I (7%), II (22%), III or IV (70%)
Gisselbrecht	Kiel and WHO (n): diffuse large cell (227), non-anaplastic peripheral T-cell (55), anaplastic peripheral T-cell (29), lymphoblastic (12), Burkitt (7), unclassifiable diffuse aggressive (40); T-cell: 76/370 (21%)	low (N = 0), low-intermediate (N = 7), high-intermediate (N = 231), high (N = 127)	median: CON: 46y, EXP: 46y	female: 41%, male: 59%	I (1%), II (5%), III (14%), IV (81%)
Haioun	WF at study entry for 916 eligible patients (of whom 541 were randomised later): diffuse large cell 54%, immunoblastic 11%, diffuse mixed cell 6%, small cell noncleaved 5%, lymphoblastic 4%, follicular large cell 3%, diffuse small cleaved cell 3%, anaplastic (Ki-1) 7%, unclassified 6%, unclassifiable 1%; T-cell 16%	low 15%, low-intermediate 40%, high-intermediate 35%, high 10%; high-intermediate or high (N = 268)	median and mean not stated, inclusion criterion: 16-55y; median age of 916 eligible patients: 40y	female: 42%; male: 58% (N = 541)	I or II (39%), III or IV (61%)
Intragumtornchai	WF (n): F (8/48), G (40/48)	high-intermediate (N = 20), high (N = 28)	>45 years: CON: 7/25, EXP: 4/23; inclusion criterion: 15-55y	female: 42%, male: 58%	I or II (17%), III or IV (83%)
Kaiser	Kiel (n): centroblastic (157), immunoblastic (27), large cell mediastinal (39), anaplastic large cell (29), lymphoblastic (13), Burkitt (12), T-cell (11), others (22), unknown (2)	low (N = 0), low-intermediate (N = 80), high-intermediate (N = 152), high (N = 73)	median (range): CON: 46y (19-60), EXP: 45y (19-60)	female: 45%, male: 55%	I (0%), II (35%), III (28%), IV (37%)
Kluin-Nelemans	For inclusion: WF; for pathological review and results: REAL (n): diffuse large B-cell (105), anaplastic large-cell (29), marginal zone B-cell (5), mantle cell (4), unclassifiable (30), follicular (6), Burkitt (3), others (12)	48/194 low, 87/194 low-intermediate, 46/194 high-intermediate, 12/194 high (1 unknown)	median (range): CON: 44y (16-63), EXP: 41y (16-65)	female: 39%, male: 61%	CON: I (10%), II (38%), III (24%), IV (28%); EXP I (6%), II (37%), III (24%), IV (33%)
Martelli 1996	Kiel (n): centroblastic (13), immunoblastic (13), anaplastic large cell (17), Burkitt (3), pleomorphic T-Cell (3)	low (N = 8), low-intermediate (15), high-intermediate (22), high (4)	median: CON: 29y, EXP 27y	female: 53%, male: 47%	I (2%), II (43%), III (27%), IV (29%)
Milpied	WF: DLCL (75%), anaplastic (8%), T-cell (5%), diffuse aggressive unclassifiable (12%)	low (6%), low-intermediate (41%), high-intermediate (53%	median: CON: 50y, EXP: 45y	female: 38%, males: 62%	II with abdominal bulk (19%), III (21%), IV (60%)

Table 4. Prognostic factors/Baseline characteristics *(Continued)*

Rodriguez 2003	distribution not reported	low or low-intermediate (24%), high-intermediate or high (76%)	not reported	not reported	not reported
Santini 1998	WF (n): DLCL (67/124), large-cell immunoblastic (25/124), diffuse mixed (11/124), anaplastic/Ki-1 (12/124), unclassifiable (9/124); T-cell (14/124)	low (N = 14), low-intermediate (N = 40), high-intermediate (N = 54), high (N = 16)	median (range): CON: 45y (18-59), EXP: 40y (16-60)	female: 50%, male: 50%	I (0%), II bulky (32%), III (20%), IV (48%)
Santini 2003	WF (n): DLCL (129/223), diffuse mixed (16/223), large-cell immunoblastic (30/223), anaplastic (31/223), unclassifiable (12/223), others (4/223)	good risk N = 67, poor risk N = 156	median age: CON: 42y, EXP 46y	female: 50%, male 50%	II (N = 39), III (N = 47), IV (N = 137)
Verdonck	WF (n): DLCL (22/69), diffuse-mixed (13/69), diffuse small cleaved cell (2/69), immunoblastic, 7/69 follicular-large, 7/69 unclassifiable high-grade, 4/69 unclassifiable intermediate-grade (14/69); T-cell (4/69)	low (N = 13), low-intermediate (N = 34), high-intermediate (N = 23), high (N = 2), unknown (N = 1)	median: 45y, mean: 42,8y	female: 41%, male: 59%	I (0%), II (44%), III (22%), IV (34%)
Vitolo	diffuse large cell (119/126), peripheral T-cell (6/126), large cell anaplastic lymphoma (1/126)	low (N = 0), low-intermediate (N = 21), high-intermediate (N = 59), high (N = 46)	median (range): CON: 43y (18-60), EXP: 41y (18-59)	female: 43%, male: 57%	I (0%), II (22%), III (21%), IV (56%)
Haioun (subgroup)	WF: diffuse large-cell 58%, follicular large-cell 3%, diffuse small cleaved cell 1%, diffuse mixed 3%, immunoblastic 12%, lymphoblastic 2%, small non-cleaved 6%, anaplastic (Ki-1) 9%, unclassified 4%, unclassifiable 2%; T-cell 14%	high-intermediate (N = 185), high (N = 51)	median and median not stated, inclusion criterion: 16-55y; median age of 916 eligible patients: 40 years	not reported	I or II 8%, III or IV 92%

Table 5. Patients in experimental arm who underwent HD and SCT (%)

Study	% HD and SCT	Reasons for not
De Souza	18/28 (64%)	3x refusal, 7x death
Martelli 2003	45/75 (60%)	7x refusal, 2x inadequate collection , 12x early progression, 1x death, 3x low performance status, 1x thrombosis/embolic event, 1x BM involvement, 1x ulcer perforation, 1x hyperglycaemic coma, 1x acute occlusion femoral artery
Gianni	48/48 (100%)	all patients received HDT
Gisselbrecht	139/189 (74%)	24x progression, 3x refusal, 9x severe toxicity during induction, 8x death, 6x miscellaneous
Haioun	198/268 (74%)	"most commonly refusal or early relapse"

Table 5. Patients in experimental arm who underwent HD and SCT (%) *(Continued)*

Intragumtornchai	14/23 (61%)	5x death, 2x refusal, 2x "protocol violation"
Kaiser	103/158 (65%)	19x lack of response/progression, 14x refusal, 4x concomitant disease, 5x toxicity of induction, 2x collection failure, 7x others, 3x death
Kluin-Nelemans	60/98 (61%)	12x relapse/progression, 6x toxicity, 15x refusal, 5x lost to FU/no data
Martelli 1996	22/29 (76%)	3x progression, 1x refusal, 2x medical decision, 1x protocol violation
Milpied	83/98 (85%)	13x: progression or no PR and CR
Rodriguez 2003	44/59 (75%)	not reported
Santini 1998	45/63 (71%)	1x ineligible, 2x death, 5x refusal, 10x progression
Santini 2003	79/117 (68%)	10x refusal, 7x toxicity, 14x progressive disease or death, 5x ineligible, 1x lost to follow-up, 1x protocol violation
Verdonck	26/34 (76%)	5x progression, 3x refusal
Vitolo	50/60 (83%)	-
Haioun (subgroup)	86/125 (69%)	-

Table 6. Quality of included studies

Study	Randomisation	Method randomisation	Concealed allocation	Intention-to-treat
De Souza	Yes	Computer random-number tables, balanced blocks	Yes (centrally)	Yes (54/54)
Martelli 2003	Yes	Random number tables, restriction to randomisation: none	Yes (centrally)	Yes (150/150)
Gianni	Yes	Stratification according to presence or absence of bulky disease and the number of sites of extranodal disease, nothing else stated	not reported	101 patients randomised, 98 patients analysed (exclusion due to concomitant liver disease)
Gisselbrecht	Yes	Random number tables, balanced blocks, stratification according to centres	Yes (centrally)	397 patients randomised, 370 patients analysed; 27 patients excluded from the analysis due to ineligibility (15x incorrect histology, 1x Burkitt with bone marrow involvement, 1x HIV, 10x missing data)
Haioun	Yes	Generation by the GELA Coordinating Center, stratification according to centres	Assignement by the GELA Coordinating Center, allocation by telephone	Yes (541/541)

Table 6. Quality of included studies *(Continued)*

Intragumtornchai	Yes	Computer random number generator, stratification according to age and tumour response, blocks (size 3 and 4)	Yes (sealed envelopes in each center)	Yes (48/48)
Kaiser	Yes	Computer random number generator, stratification according age, LDH and stage	Yes (centrally)	331 patients randomised, 312 patients analysed (19 patients excluded from the analysis due to violation of entry criteria)
Kluin-Nelemans	Yes	Computer random number generator, minimization with stratification	Yes (centrally)	Yes (194/194)
Martelli 1996	Yes	Computer random-number generator, restriction to randomisation: none	Yes (centrally)	Yes (49/49)
Milpied	Yes	Random number tables, no restriction	Sealed envelopes	Yes (197/197)
Rodriguez 2003	Yes	not reported	not reported	116 patients randomised, 108 patients analysed
Santini 1998	Yes	Random number tables, balanced blocks (size 4 and 6)	Yes (centrally)	Yes (124/124)
Santini 2003	Yes	Randomisation was carried out by telephone	unclear	Yes
Verdonck	Yes	Random number tables, stratification for institution, balanced blocks (size 4)	Yes (centrally)	in paper: 69/73 patients analysed, in provided data 73/73 patients
Vitolo	Yes	Computer random-number tables, stratification	Yes (centrally)	130 patients randomised, 126 analysed (4 patients excluded due to major violations)

Table 7. Further results (not pooled)

Study	OS	EFS	DFS/RFS	PFS	FFS
De Souza	included	included	CON: 88% - EXP 80% (NS) (total N = 20), median FU 329 days	-	-
Martelli 2003	included	included	included	-	-
Gianni	included	included	included	CON: 49% - EXP: 84% (P < 0.001), median FU 55 months	-
Gisselbrecht	included	included	CON: 76% - EXP: 58% (P = 0.004) at 5 years, median FU 5 years	-	-
Haioun	included	-	CON: 54% - EXP: 62% (P = 0.20) at 5 years	-	-

Table 7. Further results (not pooled) *(Continued)*

Intragumtornchai	included	included	included	-	CON: 15% - EXP: 38% (P = 0.04), at 4 years, median FU 39 months
Kaiser	included	included	-	-	-
Kluin-Nelemans	included	-	-	CON: 56% - EXP: 61% (P = 0.71) at 5 years, median FU 53 months	-
Martelli 1996	included	included	-	-	-
Milpied	included	subgroup: IPI high-intermediate included, subgroup: IPI low and low-intermediate: CON:45%; EXP: 54% (P = 0.4)	DFS of patients with at least PR after 4x CHOP and 2x CEEP respectively: CON: 65%, EXP: 45% (P = 0.05)	CON: 37% - EXP: 58% (P = 0.018) at 5 years, median FU 46 months	-
Rodriguez 2003	included	-	-	-	P = 0.09
Santini 1998	included	included	included	-	-
Santini 2003	CON: 60% - EXP: 58% (P = 0.5) at 7 years, median FU 62 months	-	CON: 62% - EXP: 71% (P = 0.2) at 7 years	CON: 45% - EXP: 41% (P = 0.7) at 7 years	-
Verdonck	included	included	included	-	-
Vitolo	included	included	CON: 69% - EXP: 77% (NS) at 4 years, median FU 43 months	-	CON: 44% - EXP: 46% (NS) at 4 years, median FU 43 months

Table 8. Toxicities

Study	Leuko-/ neutropenia > Grade 2	Thrombopenia > Grade 2	Median duration leuko-/ neutropenia	Median duration thrombopenia	Infection >2	other toxicities	TRM and MDT	Notes
De Souza	-	-	-	-	-	-	MDT: CON: 9/28, EXP: 11/26	
Martelli 2003	CON: 24/75, EXP 45/45	CON: 0/75, EXP: 45/45	CON: 3, EXP 12	CON:0, EXP: 13	EXP: 3/75 (1x pneumonia, 2x herpes simplex), CON: 1/75 (hepatitis) [EXP: 45/45 FUO, CON: 4/75 FUO]	CON: 1/75 EXP: 6/75	MDT: CON: 11/26, EXP: 9/28	
Gianni	-	-	reported for EXP only	reported for EXP only	CON: 2%, EXP: 10%	secondary neoplasms: CON: N = 2, EXP: N = 1; 3° and 4° toxicities (%): thrombosis: CON: 0, EXP: 10; FUO: CON: 0, EXP: 19; genitourinary abnormality: CON: 0, EXP: 2, vomiting: CON: 0, EXP: 10; diarrhea: CON: 0, EXP: 0; mucositis: CON: 26, EXP: 33; liver-enzyme abnormalities: CON: 12, EXP: 10; VOD: CON: 0, EXP: 0; pulmonary abnormalities: CON: 0, EXP: 4; cardiac abnormalities: CON: 6, EXP: 0; hypertension: CON: 0, EXP: 0; conjunctivitis: CON: 0, EXP: 0; dermatitis: CON: 0, EXP: 0; bone necrosis: CON: 7, EXP: 0; neurologic abnormalities: CON: 21, EXP: 4; psychiatric impairment: CON: 2, EXP: 0; hyperglycaemia: CON: 0, EXP: 0	Fatal toxic reactions: CON: 6% (all infection), EXP: 8% (50% infection, 50% VOD)	
Gisselbrecht	-	CON: 27/181, EXP: 43/189	EXP: recovery of neutrophil count >0.5 x 1000000000/ l after a mean of 12.4 days (range 7-41)	-	1. cycle: CON: 26%, EXP: 19%; other cycles: CONTROL: 18%, EXP:18%; HDT: 10%	mucositis 3° or 4°: CON: not reported, EXP: 14%	MDT: CON: 8%, EXP: 6%	according to 370 patients analysed

Table 8. Toxicities *(Continued)*

Haioun	see note	see note	see note	see note	see note	see note	TRM: CON: N = 1, EXP N = 2	no data according to randomised patient population, toxicities of subgroup high-intermediate and high risk IPI are listed in the publication
Intragumtornchai	-	-	-	-	CON: 5/25, EXP: not reported	febrile neutropenia: CON: 5/25, EXP: 23/23; 3° mucositis: CONTROL: 0/25, EXP: 1/23; 3° skin inflammation: CONTROL: 0/25, EXP: 1/23; diarrhea: CONTROL: 0/25, EXP: 1/23; secondary neoplasms: CONTROL: 0/25, EXP: 1/23	MDT: CON: 2/25, EXP: 4/23	
Kaiser	CON: 73%, EXP: 100%	CON: 9%, EXP: 100%	-	-	Comparison: 4th and 5th cycle chemotherapy versus HDT: CON: 1% (N = 2), EXP: 27% (N = 43)	Comparison: 4th and 5th cycle chemotherapy versus HDT: 3° or 4° stomatitis: CONTROL: 0%, EXP: 39%; 3° or 4° diarrhea: CONTROL: 0%, EXP: 17%; secondary neoplasms: CON: N = 4, EXP: N = 2	MDT: CON: 13/154, EXP: 26/158	according to 312 patients
Kluin-Nelemans	of 1634 CHVmP/BV cycles (both arms): 74%-85% granulocytopenia 3° or 4°	of 1634 CHVmP/BV cycles (both arms): 24-28% thrombocytopenia 3° or 4°	EXP: median duration granulocyte count less than 0.5 x 1000000 cells/ml: 10 days (range: 1-25), for a count less than 0,1 x 1000000 cells/ml: 8 days (range 2-19)		CON: 3/98, EXP: 8/96	of 1634 CHVmP/BV cycles (both arms): 27-34% anaemia 3° or 4°; EXP: Median number of days with fever greater than 38°C: 4 days (range 0-20), median number of platelet transfusions: 3 (range 0-29), N = 1 x 4° septicaemia, N = 6 infection 3°, N = 4x diarrhea 3°, N = 4 x mucositis, N = 1 pulmonary complications	3 toxicity-related deaths (N = 2 arm unknown, N = 1 EXP arm)	

Table 8. Toxicities *(Continued)*

Martelli 1996	CON: 20/27, EXP: 22/22	CON: 4/27, EXP: 22/22	CON: 3, EXP: 14 (range 2-20)	CON: 5, EXP: 16 (range 12-35)	CON: 9/27, EXP: 15/22	secondary neoplasms: CON: 0/27, EXP: 1/22; neurotoxicity >2°: CONTROL: 3/27; liver toxicity >2°: EXP: 4/27; cardiovascular >2°: EXP: 3/27	MDT: 0 in both arms	
Milpied	-	-	-	-	-	-	TRM: CON: N = 1/99, EXP: 3/98	
Rodriguez 2003	-	-	-	-	-	-	-	
Santini-1	CON: < 21%, EXP: not reported	CON: 1/61, EXP: -	CON: -, EXP: median time to reach self-sustaining granulocyte recovery greater than 0.5 x 1000000000/l was 12 days (range 9-16)	CON: -, EXP: median time for platelet recovery greater than 20 x 1000000000/l was 16 days (range 11-15)	CON: 3/61, EXP: -	secondary neoplasms: CON: 2/61, EXP: 0/63; other toxicities: CONTROL: 6/61, EXP: -; anaemia 3° or 4°: CONTROL: 10%, EXP: -; all patients in EXP had pancytopenia (grade unknown) and most patients had infections (grade unknown)	TRM: CON: N = 4/61, EXP: 6/63	TRM: calculated from paper
Santini-2	-	-	-	-	-	bone marrow toxicity: CONTROL: 19%, EXP: 48%	Procedure-related: CON: N = 2, EXP: N = 3	
Verdonck	-	-	-	-	-	-	TRM: CON: 0/35, EXP: 2/34	TRM according 69 patients
Vitolo	Neutropenia >2°: CON: 41/66, EXP: 50/50	CON: 11/66, EXP: 50/50	CON: not reported, EXP: 10 days (standard error 0.289)	Thrombopenia 3° and 4°: CON: -, EXP: 12 days (standard error 0.866)	CON: 6/66, EXP: 11/60	secondary neoplasms: CON: 0/66, EXP: 2/60	MDT: CON: 2/66, EXP: 2/60	Toxicities according to 50 patients who actually received HDT

APPENDICES

Appendix 1. MEDLINE search strategy

#1 highly sensitive randomisation filter (Dickersin 1994; Robinson 2002)
#2 LYMPHOMA*:ME
#3 HEMATOLOGIC-NEOPLASMS*:ME
#4 LYMPHOM*
#5 NON-HODGKIN*
#6 NONHODGKIN*
#7 (NON near HODGKIN*)
#8 NHL
#9 (HEMATO* near MALIGN*)
#10 (HAEMATO* near MALIGN*)
#11 (HEMATO* near NEOPLAS*)
#12 (HAEMATO* near NEOPLAS*)
#13 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#14 AUTOLOG*
#15 AUTOGRAFT*
#16 AUTO-TRANSPLANT*
#17 AUTOTRANSPLANT*
#18 (AUTO* NEAR TRANSPLANT*)
#19 BONE-MARROW
#20 (BONE near MARROW)
#21 STEMCELL*
#22 STEM-CELL*
#23 STEM near CELL
#24 PBSCT
#25 PSCT
#26 BSCT
#27 ASCT
#28 ABMT
#29 HIGHDOSE
#30 HIGH-DOSE
#31 (HIGH near DOSE)
#32 TOTAL-BODY
#33 (TOTAL near BODY)
#34 TBI
#35 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
#36(#1 AND #13 AND #33)
This search strategy was adapted for the databases as outlined.

WHAT'S NEW

Date	Event	Description
3 April 2011	New search has been performed	New search, no new trials included

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 1, 2008

Date	Event	Description
15 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

DS: protocol development, searching, selection of studies, eligibility and quality assessment, data extraction and analysis, drafting of final review
AG: searching for trials, eligibility and quality assessment, data extraction and analysis
JB: data analysis, searching for trials, eligibility and quality assessment, data extraction and analysis, statistical and methodological advice
HS: clinical advice for final publication
AE: clinical and scientific advice, data analysis, content input
GS: Statistical and methodological advice, data analysis, content input

DECLARATIONS OF INTEREST

None known

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INDEX TERMS

Medical Subject Headings (MeSH)

*Stem Cell Transplantation [mortality]; Antineoplastic Combined Chemotherapy Protocols [*administration & dosage]; Combined Modality Therapy [methods]; Lymphoma, Non-Hodgkin [*drug therapy] [mortality] [*surgery]; Randomized Controlled Trials as Topic; Transplantation, Autologous

MeSH check words

Adult; Humans