Summary of the Trial Report
[Synopsis according to ICH E3]

European Network of Paediatric Hodgkin Lymphoma

Second International Inter-Group Study for Classical Hodgkin Lymphoma in Children and Adolescents

(International, multicentre, randomised controlled trial in children and adolescents)

EuroNet-PHL-C2

Name of Finished Product/Name of Active Substances:

Vincristine, Vinblastine, Etoposide/Etopophos, Prednisone/Prednisolone, Doxorubicine, Cyclophosphamide, Dacarbazine

Indication/Diagnosis: Untreated (newly diagnosed) classical Hodgkin's lymphoma

Phase of Development: IV

EudraCT-Number: 2012-004053-88

Date of report: 2025-10-21
Version: Final 1.0

Trial start: 2015-10-01
End of Trial: 2024-10-31

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Signatures

The signing authors approve the report presented here by their signature. The described clinical trial was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) as well as the applicable statutory provisions.

Legal representative of the sponsor and coordinating investigator	Prof Dr Dieter Koerholz	2025-10-21 Date
Biometry	Dr Dirk Hasenclever	2025-10-21 Date

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1 Name of the Sponsor/Company

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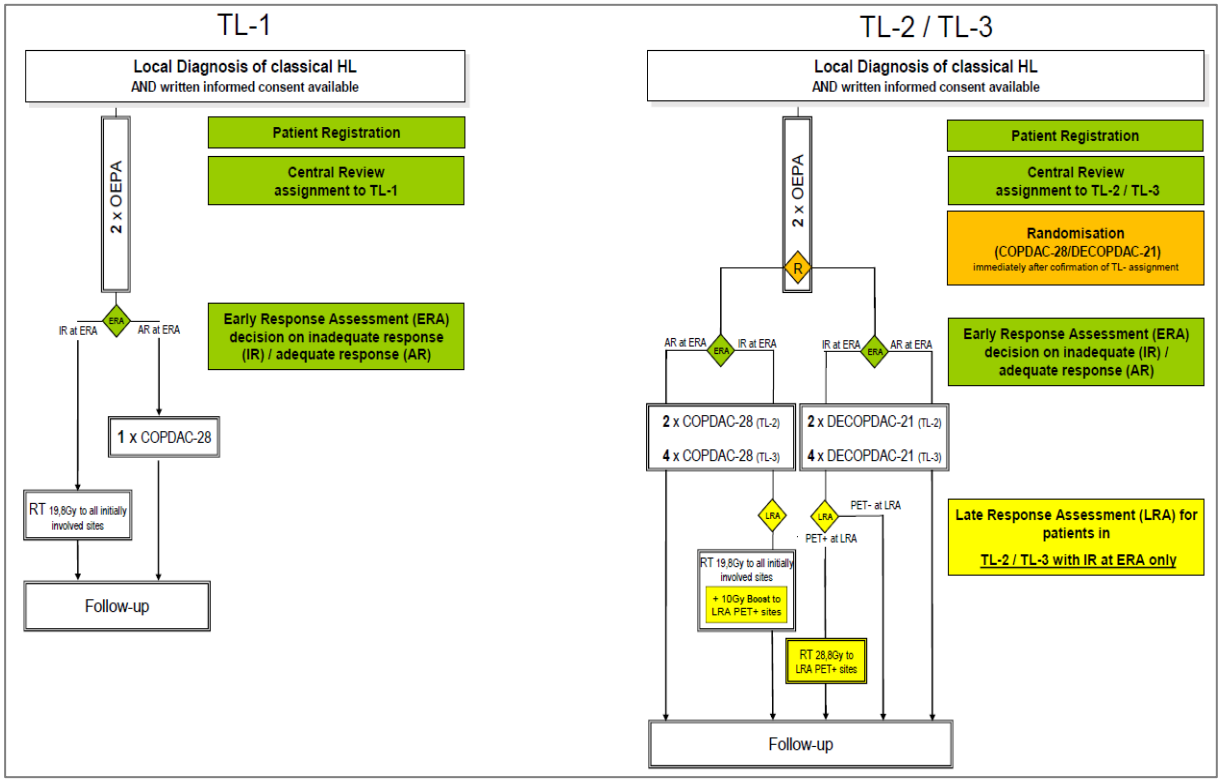
2 Name of Finished Product	3 Name of Active Ingredient
CYCLOPHOSPHAMIDE	The drug products used in this trial are defined by active substances only and have a marketing authorization in the EU. The drugs are sourced from the EU market and are used in the trial without modification. These drugs have been used in paediatric oncology for many years. The packaging and labelling are carried out for local use only as per article 9.2. of the Directive 2005/28/EC (GCP Directive). All Non-EU centres or countries must comply with state federal or national regulations for registration and administration of all chemotherapeutic drugs used in this clinical trial.
DACARBAZINE	
DOXORUBICIN	
ETOPOSIDE/ETOPOPHOS	
VINBLASTINE	
VINCRISTINE	
PREDNISOLONE	
PREDNISONE	

4 Individual study table



5 Title of Study

European Network of Paediatric Hodgkin Lymphoma Second International Inter-Group Study for Classical Hodgkin Lymphoma in Children and Adolescents

Latest version of the trial protocol: final 8.0 as of 2024-07-04.

The following amendments have been implemented after having been approved:

- Amendment 01 2015-07-27
- Amendment 02 2016-06-01
- Amendment 03 2017-05-15
- Amendment 04 2017-07-31
- Amendment 05 2019-08-01
- Amendment 06 2020-09-05
- Amendment 07 2024-07-04

6 Investigator	7 Study Centre(s)
Not applicable	Please see appendix 21.1

Within this clinical trial 2921 patients were recruited in 17 participating countries with 239 active trial sites.

8 Publications

At present: None.

9 Studied period (in years)

Date of first enrolment: 2015-10-01
Date of last completed: 2024-10-31

10 Phase of Development

Phase IV. All Investigational Medicinal Products have market authorization.

11 Objectives

Primary objectives

- To increase event-free survival in ERA PET-negative intermediate and advanced stage patients (TL-2 and TL-3) without radiotherapy by using intensified consolidation chemotherapy (DECOPDAC-21).

- To demonstrate in ERA PET-positive TL-2 and TL-3 patients that the combination of intensified consolidation chemotherapy (DECOPDAC-21) plus restricted field RT to sites that remain FDG-PET positive at the late response assessment (LRA) is comparable to the standard consolidation chemotherapy (COPDAC-28) plus standard involved node radiotherapy.

- To further reduce the radiotherapy indication in early stage patients by increasing the threshold for a positive FDG PET scan at early response assessment (ERA) to Deauville 4+ while still preserving a 5-year EFS estimate at a target of 90% or above.

Secondary objectives

- Evaluation of haematotoxicity by documentation of blood counts during OEPA, COPDAC-28 and DECOPDAC-21 cycles and comparison between COPDAC-28 versus DECOPDAC-21.

- For ERA PET-positive patients to compare the LRA PET-positivity rates after consolidation chemotherapy with COPDAC-28 or DECOPDAC-21.

Tertiary Objective

- Description of treatment delivery and study logistics as quality endpoints.

12 Methodology

The EuroNet-PHL-C2 trial is a multinational, multi-centre trial for all stages of paediatric Hodgkin lymphoma under the age of 18 years (with the exception for specialised units for adolescents and young adults in Australia, France, Italy, New Zealand and the UK, where patients under 25 years of age may also be enrolled.). EuroNet-PHL-C2 is a bundle of three sub-studies.

All patients start with 2 OEPA chemotherapy and Early Response Assessment (ERA) with PET. If the ERA result is an adequate response (AR) no radiotherapy is given at the end of the consolidation chemotherapy. Patients are streamed into three treatment levels (TL). Patients in early stages TL-1, receive one cycle of consolidation therapy with COPDAC-28, if they responded adequately. Patients in intermediate (TL-2) or advanced stages (TL-3) receive two, respectively four cycles of consolidation chemotherapy and are randomised between COPDAC-28 and the more intense DECOPDAC-21 regimen. In case of an inadequate response (IR), patients in TL-1, and patients in TL2+3 in the COPDAC-28 arm receive a standard radiotherapy to all initially involved sites with 19.8Gy with an additional boost on still PET positive lesions at the end of their allocated chemotherapy. Patients in TL2+3 in the DECOPDAC-21 arm receive a standard radiotherapy of 28.8Gy only to lesions, that are still PET positive (DS4+) at the end of their allocated chemotherapy. Patients in TL-2+3, thus undergo an additional late response assessment (LRA) if they did not respond adequately at ERA.

- **Substudy-1** in early stages (Treatment level TL-1) is a titration trial in a stable patient population addressing consistency of 5-year EFS/PFS rate estimates with a target rate of 90%. Compared to the preceding study generation EuroNet-PHL-C1-trial, indication for radiotherapy has been reduced (Deauville Scores DS1-3 are considered PET negative instead of only DS1-2), but one cycle of consolidation chemotherapy was added in case of adequate response.

Patients in intermediate (TL-2) and advanced stage (TL-3) were randomised between standard COPDAC-28 and intensified DECOPDAC-21 consolidation chemotherapy. To avoid delayed consolidation, randomisation had to be performed before the ERA result was known as soon as the TL-assignment was confirmed by central review. Consequently, depending on the ERA result (adequate or inadequate response), two randomised sub-studies with different objectives resulted:

- **Substudy-2** in TL-2+3 patients with adequate response at ERA and thus not receiving any radiotherapy, we have a randomised controlled trial comparing consolidation chemotherapies COPDAC-28 and DECOPDAC-21.
- **Substudy-3** in TL-2+3 patients with inadequate response at ERA, we have a randomised controlled comparison of combined modality, chemotherapy-radiotherapy treatment strategies. This comparison is confounded since all patients with COPDAC-28 receive involved field irradiated at all initially involved sites, while patients with DECOPDAC-21 receive involved node irradiation only to lesions, that are still PET positive (DS4+) at LRA, if there are any PET-positive residuals at all.

13 Number of patients (planned and analysed)

The original protocol specified: “This is a pragmatic trial. We will recruit as many patients as possible within the study duration of six years. Power calculation will be based on an overall sample size of N = 2200.”

The enrolment was higher than expected. The unexpectedly high accrual was not covered by the original financial plan. Therefore, the enrolment was stopped earlier on 2020-12-31 instead of 2021-09-30. At that time, the minimum sample sizes had been achieved for all three sub-studies, and also for per-protocol analyses.

Overall:

Planned number:	at least 2200 patients
Registered subjects:	2921
Analysed patients (FAS; full analysis set):	2874 (N=47 excluded mainly due to incorrect diagnoses)

Substudy-1:

Planned number:	at least 431 patients
Analysed patients (FAS; full analysis set):	444

Substudy-2:

Planned number:	at least 1345 patients
Analysed patients (FAS; full analysis set):	1442 (randomised and AR at ERA)

Substudy-3:

Planned number:	at least 424 patients
Analysed patients (FAS; full analysis set):	802 (randomised and IR at ERA)

For details see the CONSORT-flow diagrams in Appendix 21.

14 Diagnosis and main criteria for inclusion

Inclusion Criteria

- histologically confirmed primary diagnosis of classical Hodgkin’s lymphoma
- patients under 18 years of age on the date of written informed consent. In specialised Teenage and Young Adult (TYA) units in Australia, France, Italy, New Zealand and UK, patients up to under 25 years of age were able to be enrolled. Lower age limits were country specific according to national laws or formal insurance requirements that may preclude very young patients.
- written informed consent of the patient and/or the patient’s parents or guardian according to national laws
- negative pregnancy test within 2 weeks prior to starting treatment for female patients with childbearing potential

15 Information on the Test Products

Generic Name	**CYCLOPHOSPHAMIDE**
Trade Name	Various (only defined by active substance)

Modes of action	Oxazaphosphorine alkylating agent. Cyclophosphamide is a prodrug which undergoes biotransformation primarily by hepatic P450 mixed function oxidases to 4-hydroxycyclophosphamide. This metabolite decomposes spontaneously to produce the bifunctional alkylating species phosphoramide mustard. Bi-functional alkylating agents are thought to exert their cytotoxicity by forming intra-strand and inter-strand DNA cross-links at the N7 position of guanine residues. The generation of phosphoramide mustard is accompanied by the production of the metabolite acrolein which is thought to be partially responsible for the dose-limiting urotoxic effects of the drug. Co-administration of the uroprotectant agent mesna (Sodium mercaptoethane sulphonate) can help prevent urotoxicity.
Therapeutic class	Cytostatic drug
Manufacturer	Various, e. g. Baxter Oncology GmbH
Dose	500 mg/m^2, per 60 min. infusion day 1 + 8 in COPDAC-28 cycles
Route of administration	Intravenous
Formulation	By slow bolus into established i.v. line or by intravenous infusion over 1 hour. By i.v. infusion in Glucose 5%, Sodium chloride 0.9% or Glucose/saline.
Generic Name	**DACARBAZINE**
Trade Name	Various (only defined by active substance)
Modes of action	– Purine analogue, inhibits purine synthesis – Atypical alkylator – Methylates nucleic acids – Requires metabolic activation
Therapeutic class	Cytostatic drug
Manufacturer	Various, e. g. medac Gesellschaft für klinische Spezialpräparate mbH
Dose	250 mg/m^2 per 15 – 30 min. infusion day 1 – 3 in COPDAC-28 cycles
	250 mg/m^2 per 15 – 30 min. infusion day 1 – 3 in DECOPDAC-21 cycles
	625 mg/m^2, 60 min. infusion day 1 and day 2 in DECOPDAC-21 cycles
Route of administration	Intravenous bolus or infusion intra arterial
Formulation	Powder and solvent for infusion
Generic Name	**DOXORUBICIN**
Trade Name	Various (only defined by active substance)
Modes of action	Doxorubicin is an anthracycline antibiotic active in all phases of the cell cycle with maximal activity in S phase. It has several modes of action including intercalation to DNA double helix, topoisomerase II mediated DNA damage, production of oxygen- free radicals which cause damage to DNA and cell membranes, and complex formation with iron or copper via the hydroquinone moieties. Iron doxorubicin complexes may contribute to cardiotoxicity by toxic free radical generation.
Therapeutic class	Cytostatic drug
Manufacturer	Various, e g. Bendalis GmbH
Dose	40 mg/m^2 per 1-6 hour infusion day 1 + 15 in OEPA cycles

	25 mg/m^2 per 1-6 hour infusion day 1 in DECOPDAC-21 cycles
Route of administration	Intravenous
Formulation	Powder and solvent for infusion
Generic Name	**ETOPOSIDE/ETOPOPHOS**
Trade Name	Various (only defined by active substance)
Mode of action	Acts by inhibition of Topoisomerase II which results in DNA strand breakage.
Therapeutic class	Cytostatic drug
Manufacturer	Various, e. g. Bristol-Myers Squibb GmbH & Co. KGaA
Dose	125 mg/m² Etoposide (NB: 142 mg Etoposide phosphate equals 125 mg etoposide); 2 hrs infusion time day 1 – 5 in OEPA cycles
	100 mg/m^2/day Etoposide infusion over 2 hrs (NB: 113,6 mg Etoposide phosphate equals 100 mg Etoposide) day 1 – 3 in DECOPDAC-21 cycles
Route of administration	Intravenous, oral
Formulation	Powder and solvent for infusion, oral capsules/injection
Generic Name	**VINBLASTINE**
Trade Name	Various (only defined by active substance)
Mode of action	Tubulin binding agent producing mitotic arrest.
Therapeutic class	Cytostatic drug
Manufacturer	TEVA GmbH
Dose	6 mg/m^2 i.v., capping dose 10 mg (single dose); used only as a substitute if acute vincristine toxicity occurs
Route of administration	By bolus injection or into the tubing of a fast-running intravenous infusion.
Formulation	Solution for injection
Generic Name	**VINCRISTINE**
Trade Name	Various (only defined by active substance)
Mode of action	Tubulin binding agent producing mitotic arrest.
Therapeutic class	Cytostatic drug
Manufacturer	TEVA GmbH
Dose	1.5 mg/m^2 i.v. capping dose 2 mg day 1 + 8 + 15 in OEPA cycles
	1.5 mg/m^2 i.v. capping dose 2 mg day 1 + 8 in COPDAC-28 cycles
	1.5 mg/m^2 i.v. capping dose 2 mg day 1 + 8 in DECOPDAC-21 cycles
Route of administration	By bolus injection or into the tubing of a fast-running intravenous infusion.
Formulation	Solution for injection
Generic Name	**PREDNISONE/PREDNISOLONE**
Trade Name	Various (only defined by active substance)

Mode of action	Cytotoxic therapy
Therapeutic class	Cytostatic drug
Manufacturer	Various, e. g. acis Arzneimittel GmbH (tablet) or ROTEXMEDICA GMBH ARZNEIMITTELWERK (injection)
Dose	60 mg/m^2/day p.o. divided into 3 doses day 1 - 15 in OEPA cycles
	40 mg/m^2/day p.o. divided into 3 doses (capping dose 80 mg/day) day 1 – 15 in COPDAC-28 cycles
	40 mg/m^2/day p.o. divided into 3 doses, day 1 - 8, no capping dose prescribed in DECOPDAC-21 cycles
Route of administration	Oral or i.v.
Formulation	Tablet (Prednison), injection (Prednisolone)

16 Duration of Treatment

Treatment Level	Scheduled treatment duration (acc. to response)
TL-1	12 – 14 weeks
TL-2 DECOPDAC-21 arm	14 – 18 weeks
TL-2 COPDAC-28 arm	16 – 20 weeks
TL-3 DECOPDAC-21 arm	20 – 24 weeks
TL-3 COPDAC-28 arm	24 – 28 weeks

17 Reference Therapy

Not applicable.

18 Criteria for Evaluation

18.1 Efficacy

Primary end points:

Event free survival (EFS) defined as time from registration until the first of the following events:

- progression/relapse of disease
- diagnosis of a secondary malignancy
- death of any cause.

Secondary end points:

- Overall survival (OS)
- Progression free survival (PFS)

18.2 Safety

The severity of adverse events will be assessed according to the CTC criteria. Adverse events which are not explicitly listed in the CTC criteria are assessed in analogy to the following 5-point system. Assessment of severity according to *CTCAE V4.0*

19 Statistical Methods/analysis procedures

19.1 Sub-study 1 in TL1

EFS in TL-1 will be illustrated by a Kaplan-Meier curve with confidence band.

Kaplan Meier estimator derived two-sided 95% confidence intervals of the EFS rate at 60 months will be provided with a dual p-value concerning the Null hypothesis EFS = 90%.

Respective rates will be also be provided for EFS in TL-1 patients with or without adequate ERA response.

19.2 Structure of the analysis in sub-study 2 in TL-2+3 with adequate response

The protocol 14.4.2 states the objective of the sub-study in TL-2+3 with adequate ERA response: “In this open randomised parallel group chemotherapy comparison trial we want to show that intense DECOPDAC-21 consolidation therapy improves EFS as compared to standard COPDAC-28 after induction chemotherapy with two OEPA.

A relevant improvement would be an increase in 5 year EFS rates from 88% to 93%, implying a log hazard ratio lhr = 0.566.

We will test the null-hypothesis H0: lhr = 0 using the Wald-test on the coefficient of the treatment indicator in a proportional hazard Cox-regression model including TL as further covariate. A two-sided 95% confidence interval for lhr will be provided.”

EFS in sub-study-2 will be illustrated by Kaplan-Meier curves. Kaplan Meier estimator derived two-sided 95% confidence intervals of the EFS rates at 60 months will be provided.

The treatment effect will be described in subgroups TL-2 versus TL-3 in a pre-planned subgroup analysis. An interaction term in the proportional hazard model will be used to test whether the size of the treatment effect differs by TL.

19.3 Structure of the analysis in sub-study 3 in TL-2+3 with inadequate response

In the TL-2+3 ERA=IR sub-study, the structure of the interim analysis is not fully detailed in the protocol. At the time of protocol writing, we assumed that the sub-study would be seriously underpowered.

The protocol 14.4.3 states the statistical objective of the sub-study in TL-2+3 with inadequate ERA response: “In TL-2 and TL-3 patients with inadequate response at ERA we want to show that more intense consolidation therapy with DECOPDAC-21 combined with radiotherapy restricted to late PET positive sites only has comparable or better EFS as compared to COPDAC-28 plus standard involved field radiotherapy. If this is the case, we would choose the experimental arm as a new standard in order to avoid late toxicity caused by large radiotherapy field volumes.

The power of this sub-study is limited by the number of available patients in Europe. We take pragmatic account of this limitation in our statistical objectives.

As a measure of treatment difference, we estimate the log hazard ratio (lhr) and provide 80% (and 95%) lower confidence limits. Secondarily this difference (and its confidence limit) will be represented as a difference in 5-year EFS rates to facilitate interpretation.

The log hazard ratio (coded such that a positive log hazard ratio favours the experimental arm) will be estimated within a proportional hazard model with TL as a further covariate.

Given our power limitations, we will call outcome of the experimental arm comparable to that to that of the standard arm if the lhr point estimate is less than 0.26 away from equality; i. e. about 4% in EFS rates.”

Note that this is not a standard formal non-inferiority testing design with a clear tolerance limit to be excluded. The idea - given the expected limited power - is to estimate the difference in lhr with a one-sided confidence limit and then use a pragmatic decision rule in a situation with limited evidence.

EFS in sub-study-3 will be illustrated by Kaplan-Meier curves. Kaplan Meier estimator derived two-sided 95% confidence intervals of the EFS rates at 60 months will be provided. In addition, a two-sided 95% confidence interval for the difference in EFS rates at 60 months (with a dual p-value concerning the Null hypothesis Difference EFS = 0%).

The treatment effect will be described in subgroups TL-2 versus TL-3 in a pre-planned subgroup analysis. An interaction term in the proportional hazard model will be used to test whether the size of the treatment effect differs by TL.

20 Summary/Conclusion

20.1 Summary sub-study-1 in early stages (TL-1)

Response-adapted omission of radiotherapy in children and adolescents with early-stage classical Hodgkin lymphoma and no risk factors. Results from the EuroNet-PHL-C2 trial

Background

Children and adolescents with early-stage classical Hodgkin lymphoma without risk factors and an adequate morphologic and metabolic response (AR) to OEPA achieved 5-year Event-Free-Survival (5yrEFS) of 86.5% after treatment with two cycles of OEPA chemotherapy. Here investigated whether additional consolidation with one cycle of COPDAC chemotherapy could improve the results in this patient group.

Methods

Children and adolescents with newly diagnosed stage IA, IB and IIA classical Hodgkin Lymphoma (cHL) without bulk ≥ 200 ml and with ESR < 30 mm/h, were treated with two cycles OEPA (vincristine 1.5 mg/m^2 IV capped at 2 mg, days 1, 8, and 15; etoposide 125mg/m^2 IV day 1 through 5; prednisone 60mg/m^2 PO days 1 to 15; and doxorubicin 40mg/m^2 IV days 1 and 15). If no AR had been achieved after 2 OEPA, modified involved field radiotherapy (IFRT) was administered. Patients with AR received one addition cycle of COPDAC (vincristine 1.5 mg/m^2 IV capped at 2 mg, days 1 and 8; prednisone 40mg/m^2 PO days 1 to 15; cyclophosphamide 500 mg/m^2 IV days 1 and 8 and dacarbazine 250 mg/m^2 IV days 1-3). The primary endpoint was EFS. The primary objective was increasing the 5yr EFS rate over 90% in patients with AR to OEPA.

Results

We report on 444 patients treated according to the strategy. Median follow-up was 57.9 (IQR 47.2 to 63.4) months. In 386 of 444 intention-to-treat patients with adequate response 5yrEFS was 95.7% (95%-CI, 93.6% to 97.8%), which is significantly above the prespecified titration target of 90% ($p < 0.0001$). In 56 patients with inadequate response who received additional modified-involved radiotherapy 5yrEFS was 88.9% (95% CI, 80.8 to 97.7%).

The most common (grade 3-4) adverse events with OEPA were neutropenia (91.8% of patients affected) and leukopenia (68.2% of patients affected).

The most common (grade 3-4) adverse events with COPDAC-28 were neutropenia (3.6% of patients affected) and leukopenia (68.2% of patients affected).

There were no treatment related deaths.

Conclusions

In early-stage patients HL without risk factors and an adequate response to OEPA 5yrs EFS was significantly above 90% after introducing a consolidation with one cycle of COPDAC and considering Deauville score 1-3 as PET negative.

20.2 Summary sub-study-2+3 in intermediate and advanced stages (TL-2+3)

Efficacy and Tolerability in DECOPDAC-21 versus COPDAC-28 in paediatric intermediate and advanced stage classical Hodgkin lymphoma: Interim Results of the EURONET-PHL-C2 randomized study

Background

Cure rates in paediatric Hodgkin lymphoma (HL) exceed 95% with risk-adapted treatment, the need for radiotherapy is still 60% in intermediate and advanced stages. The EuroNetPHL-C2 trial aimed at further radiotherapy (RT) reduction randomizing the novel DECOPDAC-21 (doxorubicin, etoposide, cyclophosphamide, vincristine, prednisone, dacarbazine in 21 days) against the standard COPDAC-28 (cyclophosphamide, vincristine, prednisone and dacarbazine in 28 days) and applying RT to residual PET-positive nodes after end of consolidation versus early response assessment (ERA)-guided involved field radiotherapy (IFRT) in PET-positive patients after 2 OEPA (vincristine, etoposide, prednisone, doxorubicin) induction cycles and standard COPDAC-28. We hypothesized non-inferiority in inadequate responding patients (IR) and superiority in adequate responding patients (AR) at ERA in terms of event-free survival (EFS) with low treatment related mortality rates.

Methods

EuroNetPHL-C2 was an international open-label, randomized phase III study including patients with classical HL at first diagnosis up to 25 years. All patients received OEPA induction followed by ERA with PET. Further therapy was guided by PET response, and according to stage and treatment level (TL) allocation according to previously identified risk factors in the EuroNet legacy trials. In intermediate (TL-2) and advanced stages (TL-3) either 2 or 4 COPDAC-28 or DECOPDAC-21 cycles were applied. All AR ERA-PET responding patients received no radiotherapy. All ERA-IR patients received IFRT in the standard COPDAC-28 arm. In DECOPDAC-21 ERA-IR patients the decision on residual node RT was made at LRA. In case of AR, RT was completely omitted. The PET threshold for AR was set at Deauville scores 1-3 and at qPET < 1.3, both at ERA and LRA. The primary endpoint was EFS.

Results

2921 patients were registered. The ITT cohort for TL-2 and TL-3 comprised 2430 patients, 2244 were randomized of which 1442 had AR and 802 had IR after induction.

In the ERA-AR group, 724 patients received DECOPDAC-21 and had 95.3% EFS [95%CI 93.7%-96.9%] and 718 patients received COPDAC-28 and had 89.7% EFS [95%CI 87.4%-92.1%], p<0.001. DECOPDAC-21 is also significantly superior in subgroups T-2 and TL-3 respectively.

In the ERA-IR subgroup, 401 patients received DECOPDAC-21 and had 82.4% EFS [95%CI 78.5%-86.5%] and 401 patients received COPDAC-28 and had 85.6% EFS [95%CI 82.1%-89.1%]. Although slightly worse, DECOPDAC-21 met the protocol criterion for the outcome to be called comparable.

In the DECOPDAC-21 arms 11.4% TL-2 and 14.2% TL-3 patients received RT, whereas in COPDAC-28 TL-2 24.9% and in TL-3 45.9% received IF-RT.

The most common (grade 3-4) adverse events with COPDAC-28 were neutropenia (31.6% of patients affected) and leukopenia (15.1% of patients affected).

The most common (grade 3-4) adverse events with DECOPDAC-21 were neutropenia (94.9% of patients affected) and leukopenia (92.4% of patients affected). 5/1442 AR patients (all with COPDAC-28) and 7/802 IR patients died, 3 in DECOPDAC-21 and 4 in COPDAC-28.

Conclusions

The novel more intense DECOPDAC-21 consolidation chemotherapy showed superior EFS in ERA-AR and a comparable outcome in ERA-IR patients. The aim of RT reduction in paediatric TL-2 and TL-3 patients was fully met. The addition of more intensive chemotherapy in consolidation did not impact treatment related mortality.

21 Appendix

21.1 Study Centres

AUS-001
Monash Medical Centre Clayton
Children's Cancer Centre
246 Clayton Rd
AU 3168 Clayton, Victoria

AUS-002
John Hunter Children's Hospital, New Lambton Heights
Children's Cancer & Haematology Service
Lookout Road
AU 2305 New Lambton Heights, NSW

AUS-004
The Royal Children's Hospital and Murdoch Children's Res. Inst.
Children's Cancer Centre
50 Flemington Road
AU 3052 Parkville (Melbourne), Victoria

AUS-005
Sydney Children's Hospital
Kids Cancer Centre
High Street
AU 2031 Randwick (Sydney), New South Wales

AUS-006
Lady Cilento Children's Hospital South Brisbane
Oncology Services Group
62 Graham Street
AU 4101 South Brisbane

AUS-007
Princess Margaret Hospital for Children
Subiaco
Oncology/Haematology
Robert Road
AU 6008 Subiaco, Perth, Western Australia

AUS-008
Children's Hospital at Westmead
Oncology Department
Cnr Hawkesbury Road and Hainsworth Street
AU 2145 Westmead

AUS-009
Royal Hobart Hospital
Paediatric Oncology
48 Liverpool St
AU 7000 Hobart

A-001
Universitätskinderklinik Graz
Abt. für Hämatologie und Onkologie
Auenbruggerplatz 30
AT 8036 Graz

A-002
Landeskinderklinik Linz
Onkologische Abteilung
Krankenhausstraße 26
AT 4020 Linz

A-003
Steiermärkische Krankenanstalten ges. m.b.H.
Leoben
Kinderklinik
Vordernbergerstraße 42
AT 8700 Leoben

A-004
Landeskrankenhaus Klagenfurt
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A-005
Klinik für Kinder- und Jugendheilkunde Innsbruck
Abt. für Hämatologie und Onkologie
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A-006
Landeskliniken Salzburg, St. Johanns-Spital
Kinderonkologie
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A-007
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Zentrum für Kinder- und Jugendheilkunde
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A-008
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BE 4420 Montegnée

B-008
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Wilrijkstraat 10
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CH-001
Universitäts-Kinderspital beider Basel (UKBB)
Abt. für Hämatologie und Onkologie
Spitalstrasse 33
CH 4056 Basel

CH-002
Universitätsklinik für Kinderheilkunde -
Inselspital Bern
Päd. Hämatologie und Onkologie
Freiburgstrasse 4
CH 3010 Bern

CH-003
CHUV-Département de pédiatrie, Lausanne
Unité d'onco-hematologie
Rue du Bugnon 46
CH 1011 Lausanne

CH-004
Luzerner Kantonsspital - Kinderspital Luzern
Pädiatrische Hämatologie und Onkologie
CH 6000 Luzern 16

CH-005
Ostschweizerisches Kinderspital St. Gallen
Hämatologie/Onkologie
Claudiusstr. 6
CH 9006 St. Gallen

CH-006
Universitäts-Kinderspital Zürich
Onkologische Abteilung
Steinwiesstraße 75
CH 8032 Zürich

CH-007
Kantonsspital Aarau
Klinik für Kinder und Jugendliche
Tellstrasse
CH 5001 Aarau

CH-009
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Unité d'Hémato-Oncologie Pédiatrique
Rue Willy Donzé 6
CH 121 Genève

CH-028
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Pediatria, Emato-oncologia pediatrica
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CH 6500 Bellinzona

CZ-00
Faculty Hospital Motol Praha
Department of pediatric hematology and
oncology
V Úvalu 84
CZ
550 06
Praha 5

CZ-004
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I.P. Pavlova 6
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The Child and Youth Clinic, Dept Pediatric
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Blegdamsvej 9
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The Deparment of Pediatric, H2
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DK-007
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The Department of Pediatrics
Palle Juul-Jensens Boulevard 99
DK 8200 N Aarhus

DK-008
University Hospital Aalborg, Nord
The Department of Pediatric
Reberbansgade 15
DK 9000 Aalborg

D-001
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D-002
Universitätskinderklinik Mainz
Onkologische Abteilung
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St.-Jürgen-Str. 1
DE 28177 Bremen

D-005
Angelika-Lautenschläger-Klinik Heidelberg
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Theodor-Stern-Kai 7
DE 60590 Frankfurt/Main

D-011
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Abt. für Hämatologie und Onkologie, Station S24
Moltkestr. 90
DE 76133 Karlsruhe

D-012
Universitätsklinikum Essen
Klinik und Poliklinik für Kinder- und Jugendmedizin, Abt. für Hämatologie und Onkologie
Hufelandstr. 55
DE 45122 Essen

D-013
Helios Kliniken Krefeld
Zentrum für Kinder- und Jugendmedizin
Lutherplatz 40
DE 47805 Krefeld

D-014
Kliniken der Stadt Köln gGmbH
Kinderkrankenhaus Riehl, Station A5
Amsterdamer Str. 59
DE 50735 Köln-Riehl

D-015
Kinderklinik und Kinderpoliklinik im Dr. von Haunerschen Kinderspital München
Abt.für Hämatologie und Onkologie
Lindwurmstr. 4
DE 80337 München

D-016
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Abt. für Hämatologie und Onkologie
Augustenburger Platz 1
DE 13353 Berlin

D-017
Universitätsklinik für Kinder- und Jugendmedizin Homburg
Abt. für Hämatologie und Onkologie
Gebäude 9
DE 66421 Homburg/Saar

D-018
Universitätskinderklinik Würzburg
Pädiatrische Onkologie
Josef-Schneider-Str. 2
DE 97080 Würzburg

D-019
Universitätsklinikum Freiburg - Kinder- und Jugendklinik
Klinik für Pädiatrische Hämatologie und Onkologie
Breisacher Str. 62
DE 79106 Freiburg

D-021
Gemeinschaftsklinikum Mittelrhein - Kemperhof
Pädiatrische Hämatologie und Onkologie
Koblenzer Str. 115-155
DE 56073 Koblenz

D-023
Klinikum Kassel GmbH
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Mönchebergstr. 41-43
DE 34125 Kassel

D-024
Vestische Kinder- und Jugendklinik Datteln
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Dr.-Friedrich-Steiner-Str.5
DE 45711 Datteln

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Universitätskinderklinik Kiel
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DE 24105 Kiel

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Klinik für Kinder- und Jugendmedizin Lübeck
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Ratzeburger Allee 160
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Universitätsklinik für Kinderheilkunde und Jugendmedizin Tübingen
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DE 72076 Tübingen

D-033
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Klinik und Poliklinik für Kinder- und Jugendmedizin Münster
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D-036
Kinderklinik des KH Schwabing der TU München
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Universitätskinderklinik Düsseldorf
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D-055
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D-058
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Universitätsklinik für Kinder und Jugendliche Erlangen
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D-063
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Cnopf'sche Kinderklinik
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Kinder- und Jugendmedizin
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D-132
Klinikum Minden
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Hans-Nolte-Str. 1
DE 32429 Minden

D-149
Klinikum Lippe-Detmold GmbH
Kinder- und Jugendmedizinische Klinik
Röntgenstr. 18 / Hofstr. 11
DE 32756 Detmold

D-152
Klinik und Poliklinik für Kinder- und Jugendmedizin der Universität Regensburg
Päd. Hämatologie, Onkologie und Stammzelltransplantation
Franz-Josef-Strauß-Allee 11
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Paraje Torrecardenas
ES 4009 Almería

E-011
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Plaza de Cruces
ES 48903 Baracaldo-Bilbao

E-012
Hospital Infantil Vall d´Hebron Barcelona
Pediatric Oncology and Hematology
P. Vall d´Hebron
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E-014
Hospital Sant Joan de Deu Barcelona
Pediatric Oncology
Passeig St Joan de Deu
ES 8950 Barcelona (Esplugues-Barcelona)

E-015
Complejo Hospitalario Universitario de Granada
Unidad de Oncohematologia Pediatrica
Avda de las Fuerzas Armadas
ES 18014 Granada

E-018
Comp. Hosp. Univ. Insular-Materno Infantil Las Palmas GC
Hematología
Av/ Marítima del Sur s/n
ES Las Palmas GC

E-019
Hospital Universitario La Paz Madrid
Onco-Hematología Pediátrica
Castellana 261
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Hospital General Universitario Gregorio Marañón Madrid
Onco-Hematología Infantil
C/Maiquez
ES 28007 Madrid

E-021
Hospital Universitario Niño Jesús Madrid
Oncología Pediátrica
Menéndez Pelayo
ES 28009 Madrid

E-022
Hospital Universitario 12 de Octubre Madrid
Hemato-Oncología Pediátrica
Av de Córdoba
ES 28041 Madrid

E-023
Hospital Regional Universitario de Málaga
Oncologia pediatrica
c/ Arroyo de los angeles
ES 29011 Malaga

E-024
Hospital Central Universitario Asturias Oviedo
Oncología Pediátrica
Celestino Villamil
ES 33006 Oviedo

E-025
Hospital Universitario Son Espases Palma de Mallorca
Hemato-Oncología Pediátrica
Valldemossa, 79
ES 7120 Palma de Mallorca

E-026
Complejo Hospitalario de Navarra Pamplona
ONCOLOGÍA INFANTIL
Irunlarrea 4
ES 31008 Pamplona

E-028
Hospital Clinico Universitario de Santiago
Pediatría
Travesía de la Choupana
ES 15706 Santiago de Compostela

E-029
Hospital Universitario Virgen del Rocío
Pediatric Oncology
Manuel Siurot
ES 41005 Sevilla

E-031
Hospital Universitario La Fe
Pediatric Oncology
Campanar
ES 46009 Valencia

E-032
Hospital Universitario Miguel Servet
Oncopediatría
Paseo Isabel la Católica
ES 50008 Zaragoza

E-064
Hospital Virgen de la Arrixaca
Unidad de Oncohematologia Pediatrica
Crtera Madrid Cartagena sn
ES 30120 El Palmar (Murcia)

E-068
Hospital Materno-Infantil de Badajoz
Hematología
c/ La Violet sn
ES 6010 Badajoz

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Unité d'Hématologie Oncologie Pédiatrique
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Place Saint Jacques 2
FR 25030 Besançon

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CHU Caen
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FR 14033 Caen Cedex

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CHU Estaing - Clermont-Ferrand
Onco Hématologie Pédiatrique
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FR 63100 Clermont-Ferrand

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BP1542
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Département de Pédiatrie
BP 217
FR 38043 Grenoble

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Département Pédiatrie Hématologie Oncologie
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FR 87042 Limoges Cedex

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1-3 Place Professeur Jospeh Renaut
FR 69373 Lyon Cedex 08

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Rue Saint-Pierre 264
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CHRU de Montpellier - Hopital Arnaud de Villeneuve
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CHU de Nice - Hopital Archet 2
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Route de St Antoine de Ginestière 151
FR 6202 Nice Cedex 3

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FR 75005 Paris

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FR 75019 Paris

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CHU de Poitiers
Service d'Oncologie Hématologique et de Thérapie Cellulaire
Hopital Jean Bernard
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F-024
CHU de Reims Hopital Américain
Service d'Hémato-oncologie Pédiatrique
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FR 51100 Reims

F-025
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FR 35203 Rennes Cedex 2

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CHU de Rouen
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FR 76031 Rouen Cedex

F-027
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Unité d'Oncologie et Pédiatrique
BP 60008
FR 42055 Saint-Etienne Cedex 2

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CHU de Strasbourg - Hopital de Hautepierre
Pédiatrie 3
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CHU de Toulouse - Hopital des Enfants
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FR 31059 Toulouse Cedex 9

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FR 69373 Lyon Cedex 08

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GB-018
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GB-021
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GB-022
Royal Marsden Hospital Sutton
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GB-105
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Whitchurch
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GB-106
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GB CH634JY Wirral

GB-108
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GB-109
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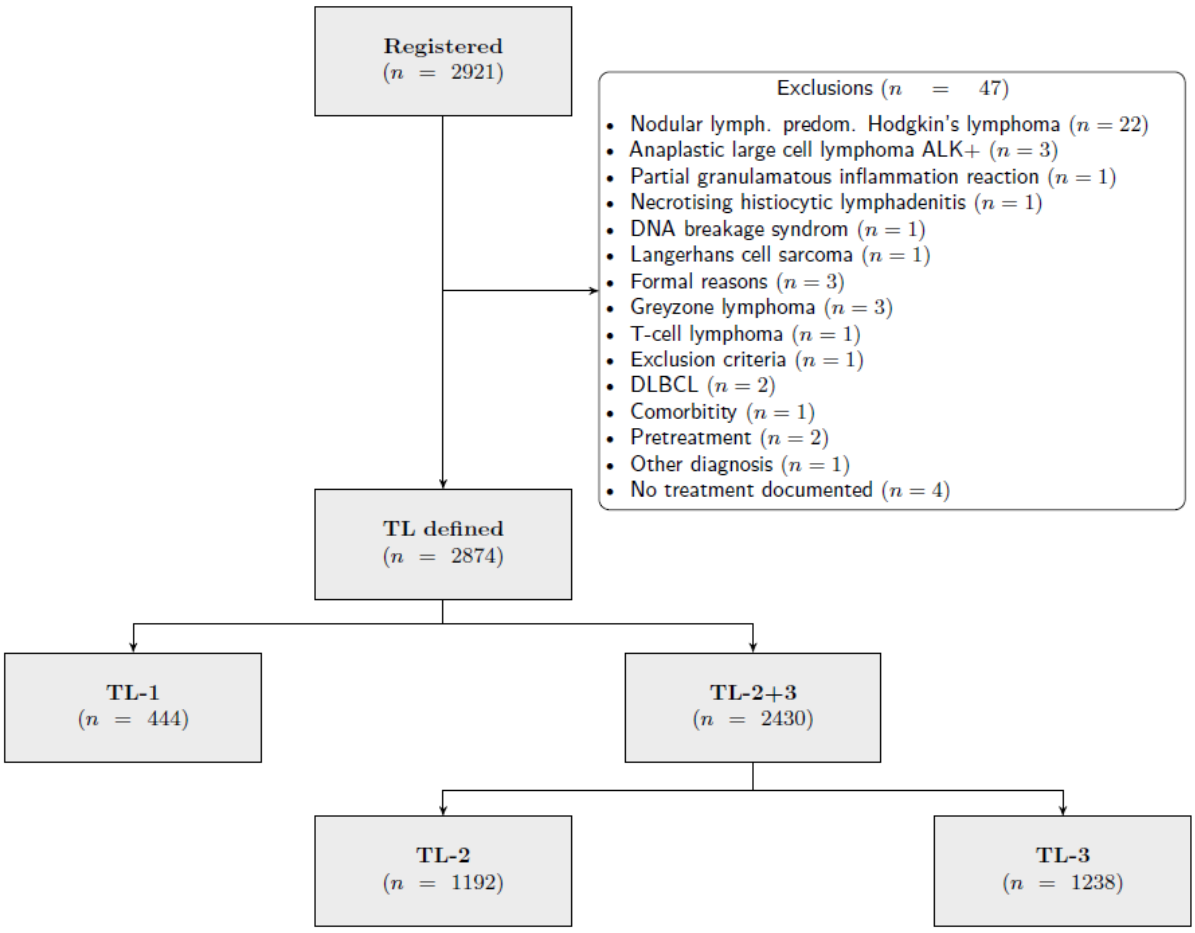
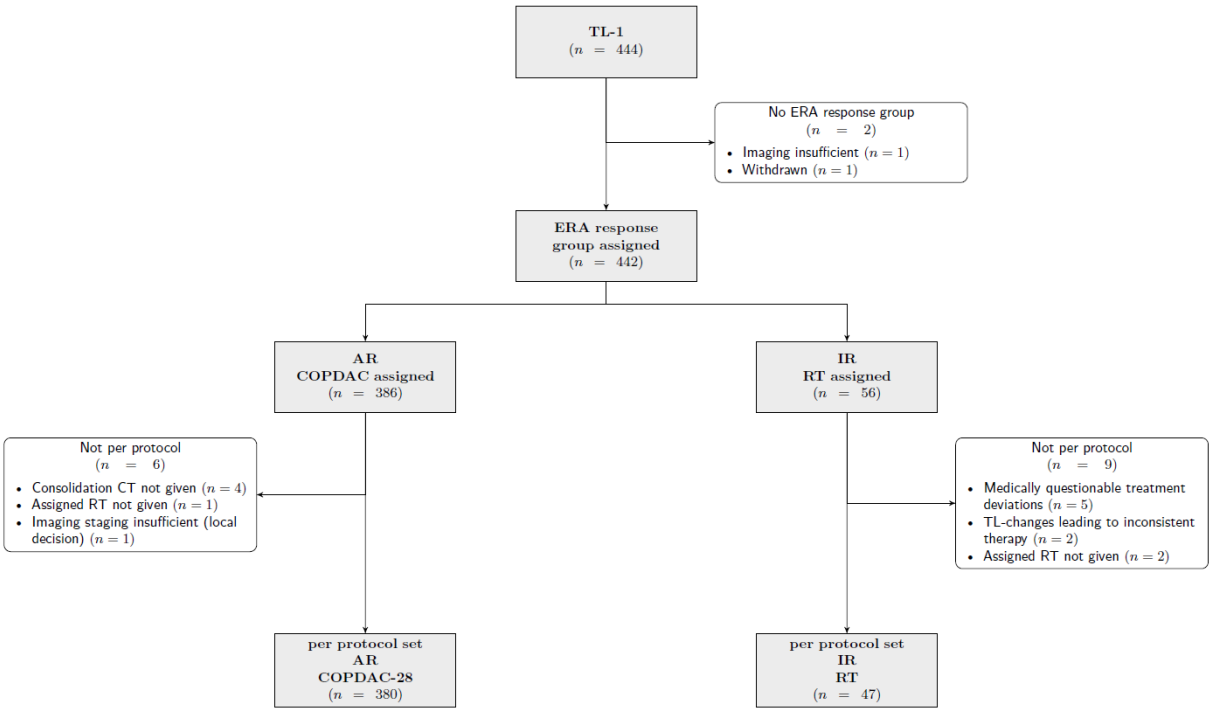
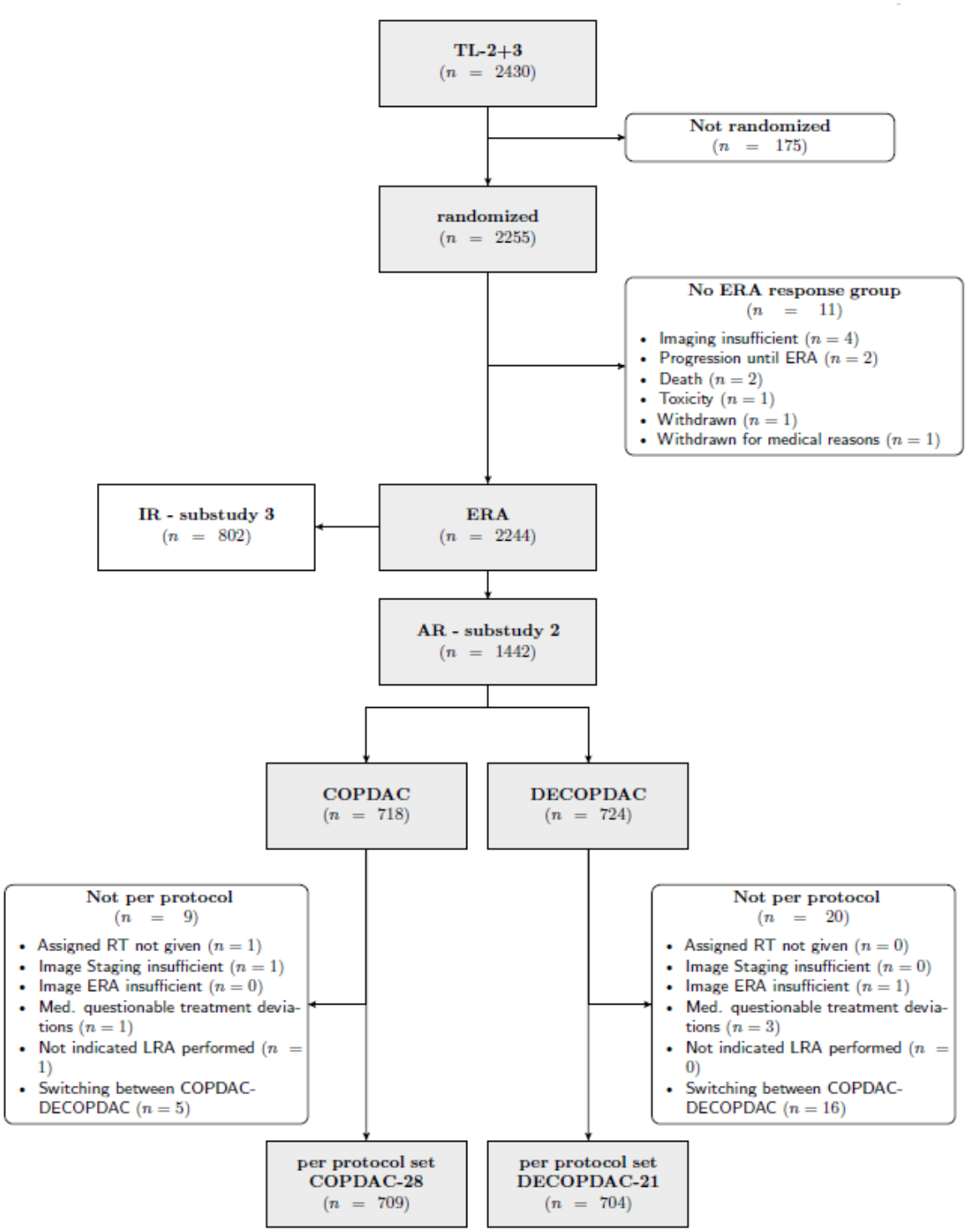
21.2 General inclusion



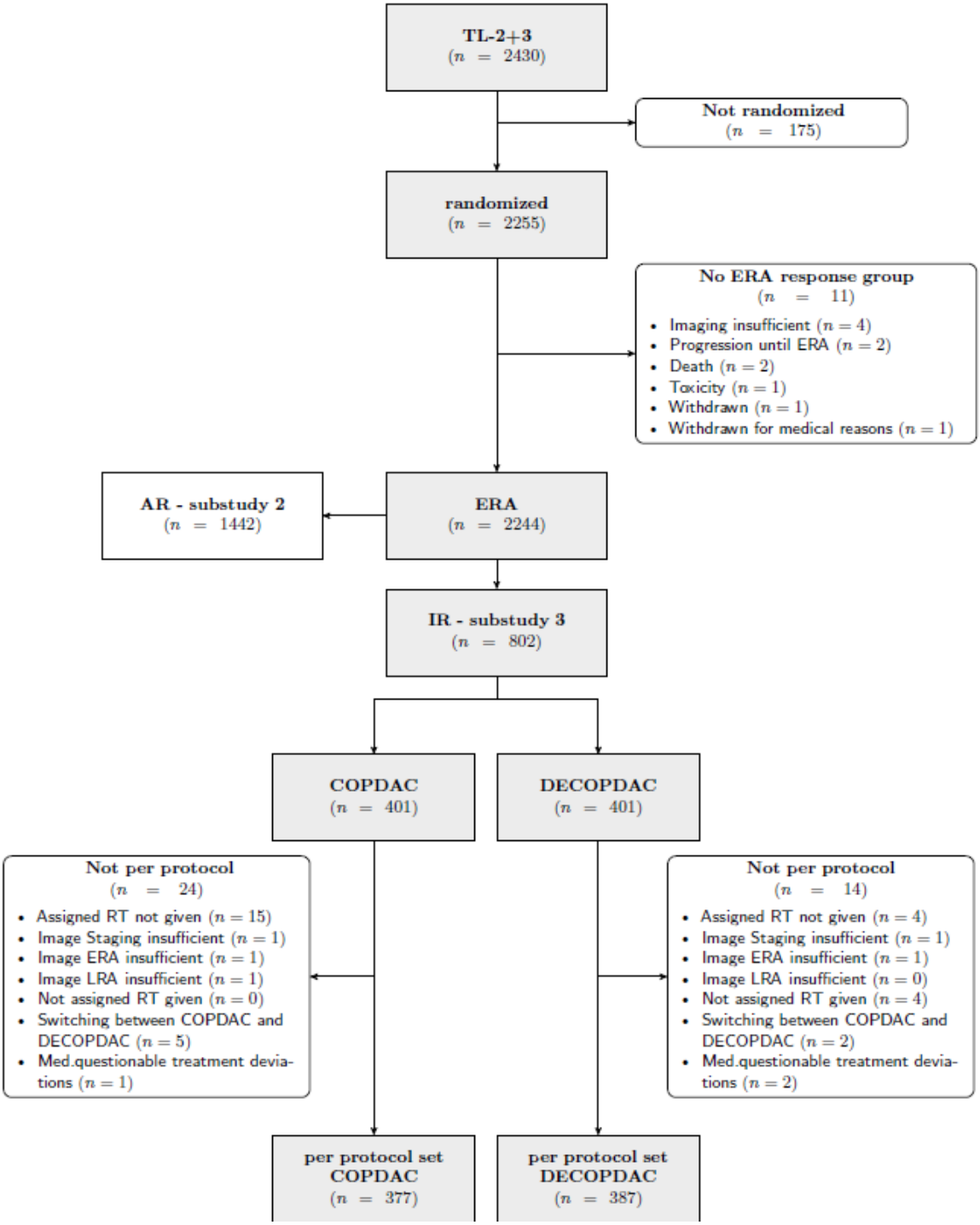
21.3 Flowchart sub-study 1 in TL-1



21.4 Flowchart sub-study 2 in TL-2+3 AR



21.5 Flowchart sub-study 3 in TL-2+3 IR



22 Safety of chemotherapy regimens

22.1 OEPA

	CTC-0		CTC-1		CTC-2		CTC-3		CTC-4		CTC-5		ALL	
Toxicity	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Haemoglobin	397	13.8	640	22.3	1376	47.9	415	14.5	43	1.5	0	0.0	2871	100.0
White Blood Count	118	4.1	212	7.4	574	20.0	1080	37.6	887	30.9	0	0.0	2871	100.0
Neutrophils	86	3.0	48	1.7	89	3.1	378	13.2	2255	78.9	1	0.0	2857	99.5
Platelets	2387	83.1	240	8.4	139	4.8	86	3.0	19	0.7	0	0.0	2871	100.0
Creatinine	2631	91.8	216	7.5	14	0.5	4	0.1	0	0.0	0	0.0	2865	99.8
Bilirubin	2545	93.0	154	5.6	30	1.1	4	0.1	4	0.1	0	0.0	2737	95.3
Liver enzymes	952	33.5	1160	40.8	483	17.0	233	8.2	12	0.4	0	0.0	2840	98.9
Fever	2120	73.8	586	20.4	141	4.9	19	0.7	5	0.2	0	0.0	2871	100.0
Infection	2016	70.2	390	13.6	297	10.3	141	4.9	25	0.9	2	0.1	2871	100.0
Stomatitis / pharyngitis	1984	69.2	536	18.7	255	8.9	77	2.7	17	0.6	0	0.0	2869	99.9
Vomiting	2033	70.9	470	16.4	324	11.3	40	1.4	2	0.1	0	0.0	2869	99.9
Diarrhoea	2398	83.6	291	10.1	133	4.6	39	1.4	8	0.3	0	0.0	2869	99.9
Constipation	1835	64.0	730	25.4	259	9.0	38	1.3	7	0.2	0	0.0	2869	99.9
Sensory	2195	76.5	501	17.5	135	4.7	37	1.3	0	0.0	0	0.0	2868	99.9
Motor activity	2481	86.5	233	8.1	120	4.2	33	1.2	2	0.1	0	0.0	2869	99.9

22.2 COPDAC-28

	CTC-0		CTC-1		CTC-2		CTC-3		CTC-4		CTC-5		ALL	
Toxicity	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Haemoglobin	583	34.8	568	33.9	474	28.3	47	2.8	5	0.3	0	0	1677	99.9
White Blood Count	520	31.0	447	26.7	502	29.9	174	10.4	34	2.0	0	0	1677	99.9
Neutrophils	541	32.4	306	18.3	366	21.9	352	21.1	107	6.4	0	0	1672	99.6
Platelets	1527	91.1	83	5.0	30	1.8	31	1.8	5	0.3	0	0	1676	99.8
Creatinine	1538	92.5	115	6.9	7	0.4	1	0.1	1	0.1	0	0	1662	99.0
Bilirubin	1486	94.5	70	4.5	14	0.9	2	0.1	0	0.0	0	0	1572	93.6
Liver enzymes	606	37.0	736	44.9	217	13.2	78	4.8	3	0.2	0	0	1640	97.7
Fever	1469	87.6	151	9.0	46	2.7	11	0.7	0	0.0	0	0	1677	99.9
Infection	1427	85.1	157	9.4	68	4.1	22	1.3	2	0.1	0	0	1676	99.8
Stomatitis / pharyngitis	1558	93.0	90	5.4	26	1.6	1	0.1	0	0.0	0	0	1675	99.8
Vomiting	1521	90.8	100	6.0	52	3.1	3	0.2	0	0.0	0	0	1676	99.8
Diarrhoea	1600	95.5	59	3.5	16	1.0	1	0.1	0	0.0	0	0	1676	99.8
Constipation	1419	84.7	209	12.5	46	2.7	2	0.1	0	0.0	0	0	1676	99.8
Sensory	1372	82.0	215	12.8	68	4.1	19	1.1	0	0.0	0	0	1674	99.7
Motor activity	1471	88.0	111	6.6	61	3.7	28	1.7	0	0.0	0	0	1671	99.5

22.3 DECOPDAC-21

	CTC-0		CTC-1		CTC-2		CTC-3		CTC-4		CTC-5		ALL	
Toxicity	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Haemoglobin	63	5.6	140	12.4	538	47.5	333	29.4	58	5.1	0	0	1132	100.0
White Blood Count	8	0.7	14	1.2	64	5.7	214	18.9	832	73.5	0	0	1132	100.0
Neutrophils	18	1.6	18	1.6	22	2.0	74	6.6	996	88.3	0	0	1128	99.6
Platelets	821	72.5	126	11.1	87	7.7	86	7.6	12	1.1	0	0	1132	100.0
Creatinine	1043	92.3	81	7.2	4	0.4	2	0.2	0	0.0	0	0	1130	99.8
Bilirubin	1028	94.9	50	4.6	5	0.5	0	0.0	0	0.0	0	0	1083	95.7
Liver enzymes	424	37.7	504	44.8	154	13.7	39	3.5	3	0.3	0	0	1124	99.3
Fever	655	57.9	339	30.0	127	11.2	9	0.8	1	0.1	0	0	1131	99.9
Infection	739	65.3	184	16.3	150	13.3	49	4.3	9	0.8	0	0	1131	99.9
Stomatitis / pharyngitis	844	74.7	190	16.8	80	7.1	14	1.2	2	0.2	0	0	1130	99.8
Vomiting	909	80.4	130	11.5	84	7.4	6	0.5	1	0.1	0	0	1130	99.8
Diarrhoea	999	88.4	87	7.7	31	2.7	9	0.8	4	0.4	0	0	1130	99.8
Constipation	892	78.9	183	16.2	52	4.6	3	0.3	0	0.0	0	0	1130	99.8
Sensory	875	77.8	189	16.8	50	4.4	10	0.9	0	0.0	0	0	1124	99.3
Motor activity	959	85.1	94	8.3	56	5.0	18	1.6	0	0.0	0	0	1127	99.6