

Appendix 1: BrECADD 3-day protocol template

For classic Hodgkin Lymphoma (cHL) | 3-day administration schedule

Template use and responsibility

This appendix is intended as a protocol template for local adaptation. It is not a stand-alone chemotherapy prescription. Total drug doses, supportive medication, laboratory thresholds, contraindications, infusion practice, and monitoring requirements must be reviewed and approved according to local institutional policies, national guidance, product information, and the treating physician's judgement before clinical use. **Responsibility for administration remains with the user.**

Table S1: General treatment information

Field	Content
Treatment regimen	Condensed BrECADD regimen, full dose level 4, adapted from GHSG HD21 trial (Borchmann et al., Lancet 2024)
Cycle length	Repeat every 22 days, if clinical and laboratory criteria for treatment are met

Figure S1: Therapy course overview

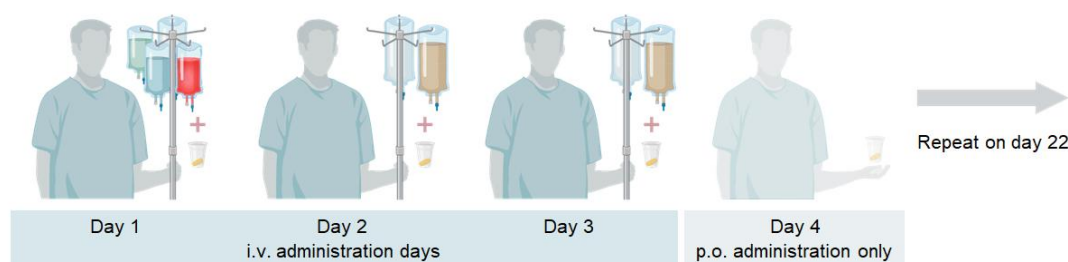


Table S2: Substance doses and dose levels

Substance	Days	Dose level 4, full dose	Dose level 3	Dose level 2	Dose level 1	Baseline dose level
 Brentuximab vedotin (i.v.)	Day 1	1.8 mg/kg (max. 180 mg) ¹⁾	1.8 mg/kg (max. 180 mg) ¹⁾	1.8 mg/kg (max. 180 mg) ¹⁾	1.8 mg/kg (max. 180 mg) ¹⁾	1.8 mg/kg (max. 180 mg) ¹⁾
 Etoposide (i.v.)	Days 1-3	150 mg/m ²	125 mg/m ²	100 mg/m ²	100 mg/m ²	100 mg/m ²
 Cyclophosphamide (i.v.)	Day 1	1250 mg/m ²	1100 mg/m ²	950 mg/m ²	800 mg/m ²	650 mg/m ²
 Doxorubicin (i.v.)	Day 1	40 mg/m ²	40 mg/m ²	40 mg/m ²	40 mg/m ²	35 mg/m ²
 Dacarbazine (i.v.)	Days 2-3	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²	250 mg/m ²
 Dexamethasone (p.o.)	Days 1-4	40 mg	40 mg	40 mg	40 mg	40 mg

1) The dose of Brentuximab vedotin should be reduced to 1.2 mg/kg or permanently discontinued, as signs of neuropathy occur (see SmPC).

Table S3: Day-by-day administration

Day	Time	Purpose	Therapy (dose level 4, full dose)	Notes
Day 1	08:00 – 09:00	Hydration	Balanced crystalloid solution 500 ml i.v. over 1 h	
Day 1	08:00	Anti-infective prophylaxis	Cotrimoxazole 960 mg tablets	From day 1 every Mon, Wed, Fri, throughout the entire treatment course until 1 month after last BrECADD application
Day 1	08:00 and 20:00	Anti-infective prophylaxis	Valaciclovir 500 mg tablets	Non-mandatory but recommended: 1-0-1 from day 1 throughout the entire treatment course until 1 month after last BrECADD application
Day 1	08:00	Tumor lysis prophylaxis	Allopurinol 300 mg tablets	If clinically indicated
Day 1	08:00	Antiemetic prophylaxis	Aprepitant 125 mg tablets	
Day 1	08:00	Antiemetic prophylaxis	Granisetron 1 mg i.v.	Total volume 1 ml Alternatively Ondansetron 8 mg i.v., observe maximum daily dose
Day 1	08:00		Dexamethasone 40 mg tablets	
Day 1	08:00 – 08:30		Brentuximab vedotin 1.8 mg/kg in 250 ml NaCl 0.9% i.v. over 30 min	Maximum 180 mg
Day 1	08:30	Uroprotection	Mesna 400 mg bolus	Total volume 4 ml Administer before cyclophosphamide
Day 1	08:30 – 10:00	Uroprotection	Mesna 800 mg/m ² BSA plus KCl 20 mmol in 1000 ml NaCl 0.9%	Accompanying infusion with cyclophosphamide / doxorubicin
Day 1	08:30 – 9:30		Cyclophosphamide 1250 mg/m² BSA in 500 ml NaCl 0.9% i.v. over 1 h	
Day 1	09:30 – 10:00		Doxorubicin 40 mg/m² BSA in 500 ml NaCl 0.9% i.v. over 30 min	
Day 1	10:00 – 11:00		Etoposide 150 mg/m² BSA in 1000 ml NaCl 0.9% i.v. over 1 h	Alternatively Etoposide phosphate
Day 2	08:00 – 10:00	Hydration	Balanced crystalloid solution 1000 ml i.v. over 2 h	
Day 2	08:00	Antiemetic prophylaxis	Aprepitant 80 mg tablets	
Day 2	08:00	Antiemetic prophylaxis	Granisetron 1 mg i.v.	Total volume 1 ml Alternatively Ondansetron 8 mg i.v., observe maximum daily dose
Day 2	08:00		Dexamethasone 40 mg tablets	
Day 2	08:00 – 10:00		Dacarbazine 250 mg/m² BSA in 250 ml NaCl 0.9% over 2 h	

Day 2	10:00 – 11:00		Etoposide 150 mg/m² BSA in 1000 ml NaCl 0.9% i.v. over 1 h	Alternatively Etoposide phosphate
Day 3	08:00 – 10:00	Hydration	Balanced crystalloid solution 1000 ml i.v. over 2 h	
Day 3	08:00	Antiemetic prophylaxis	Aprepitant 80 mg tablets	
Day 3	08:00	Antiemetic prophylaxis	Granisetron 1 mg i.v.	Total volume 1 ml Alternatively Ondansetron 8 mg i.v., observe maximum daily dose
Day 3	08:00		Dexamethasone 40 mg tablets	
Day 3	08:00 – 10:00		Dacarbazine 250 mg/m² BSA in 250 ml NaCl 0.9% over 2 h	
Day 3	10:00 – 11:00		Etoposide 150 mg/m² BSA in 1000 ml NaCl 0.9% i.v. over 1 h	Alternatively Etoposide phosphate
Day 4	08:00		Dexamethasone 40 mg tablets	
Day 4 onward	08:00	G-CSF support	Pegfilgrastim 6 mg pre-filled syringe s.c. Alternatively G-CSF 150 µg/m ² s.c. daily at 08:00 until leukocyte count is > 1 000/mm ³ on three consecutive days	Mandatory!
Day 8 onward	08:00 and 20:00	Anti-infective prophylaxis	Ciprofloxacin 250 mg tablets	1-0-1 until end of cytopenia (recovery of neutrophil granulocytes (ANC) > 500/mm ³ or leukocytes > 1 000/mm ³)

Table S4: Treatment management

Field	Content
Pre-treatment phase	A pre-treatment phase with 40 mg dexamethasone over 4 days may be administered if clinically indicated.
Continuation of subsequent cycle	Prerequisite on day 22 (first day of subsequent cycle): leukocytes > 2 500/mm³ or neutrophil granulocytes (ANC) > 1 500/mm³ and thrombocytes >80 000/mm³ , no active infection or severe toxicity. Otherwise, therapy postponement or dose reduction according to respective criteria. Also with leukocytes > 15 000/mm ³ with G-CSF therapy, postpone until values are lower again.
Dose reduction	Dose reduction follows a predefined de-escalation strategy, which is based upon the occurrence of toxic events in previous cycles. The following are regarded as toxic events: - Leukopenia for more than 4 days (leukocytes < 1 000/mm³) - Thrombocytopenia on one or more days (thrombocytes < 25 000/mm³) - Infection CTCAE grade 4 - Other CTCAE grade 4 toxicities, e.g. mucositis - Treatment delay of more than 2 weeks due to inadequate recovery of blood values If one or more toxic events occur in a given cycle, the dose in all following cycles has to be reduced by one dose level. If toxic events occur in two successive cycles, the doses are reduced to baseline level. (For dose levels, see page 1)

Additional checks	Blood count twice a week , check differential blood counts 2-3 times on the expected nadir on days 8-15 , also check creatinine, urea, uric acid, GOT, GPT, gamma-GT, AP, bilirubin, potassium, sodium and urine status.
PET-guided treatment for advanced stage cHL	
Number of cycles	Response-adapted treatment with 4 or 6 cycles, with interim PET assessment after 2 cycles
Interim PET/CT timepoint and evaluation	PET-2 including diagnostic CT on days 17-21 of the second cycle. Patients with negative PET-2 receive 4 cycles in total, patients with positive PET-2 receive 6 cycles in total.
Final PET/CT timepoint and evaluation	PET-4 / PET-6 within 4 weeks after last therapy cycle. Only if this PET-4 or -6 is positive, residual tumors are irradiated with 30 Gy.
Response assessment	A Deauville score of 1-3 is defined as PET-negative, a Deauville score of 4-5 as PET-positive

Drug-specific notes

Brentuximab vedotin

Side effects: peripheral polyneuropathy (common), haematotoxicity (dose adjustment may be necessary), tumor lysis syndrome, anaphylaxis (rare).

Infusion rate at start 30 ml/h. Increase rapidly, if well tolerated.

Cyclophosphamide

Caution: Adjust dose according to renal function (for GFR < 60 ml/min, 75% of the dose). Ensure adequate fluid intake (drinking, irrigation, urine output should be at least 200 ml/h).

Side effects: Hemorrhagic cystitis. Mesna prophylaxis at 500 – 1 000 mg/m². Premedication 800 mg absolute as bolus without obligatory Mesna administration in irrigation, for cyclophosphamide > 1,000 mg/m² 20% of the dose equivalent should be administered as bolus and 80% in irrigation before therapy. Possible cardiotoxicity at high doses, pneumonitis, neurotoxicity.

Doxorubicin (Adriamycin)

Caution: Threshold dose for cardiotoxicity 550 mg/m² (cardiac and individual risk assessment at least by means of cardiac echo). Dose reduction for bilirubin levels > 1.5 mg/dl. Administer in light protection.

Caution: Must be administered with irrigation!

Etoposide

Side effects: Blood pressure drop (rare), arrhythmias (infusion duration at least 1 hour). Reduce dose to 75% if GFR < 60 ml/min; for bilirubin > 1.5 mg/dl.

Caution: Calcium antagonists may increase toxicity, do not administer etoposide and sodium bicarbonate via the same access.

Alternatively Etoposide phosphate: Etoposide phosphate as etoposide-equivalent dose: 113 mg etoposide phosphate is equivalent to 100 mg etoposide. This difference is due to different molecular weights.

Dacarbazine

Caution: highly emetogenic! Reduce dose to 75% if GFR <60 ml/min or bilirubin >1.5 mg/dl. Avoid sun exposure due to photosensitivity.

Dexamethasone

Caution: Diabetics (no glucose infusions, blood sugar measurement on treatment days daily at 17:00)

Literature

Borchmann et al., Lancet 2024. [https://doi.org/10.1016/S0140-6736\(24\)01315-1](https://doi.org/10.1016/S0140-6736(24)01315-1)