Appendix

Flow Chart saved as separate file

Supplementary Figure 1. Study design. In the main study, patients are randomized to receive chemotherapy with escalated BEACOPP (dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) (standard group) or with BrECADD (brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone) (experimental group). After the first two cycles, a restaging is performed by contrast-enhanced computed tomography (ceCT) and positron-emission tomography (FDG PET/CT) in all patients in order to guide response-adapted continuation of therapy consisting of 4 or only 2 additional cycles of randomized chemotherapy in case of a PET positive or negative staging result, respectively. A second restaging will be performed after completion of chemotherapy; Patients with PET-positive residual disease will receive local irradiation, while patients in complete remission do not receive radiotherapy.

Supplementary List 1. List of predefined MeDDRA codes for SAEs included in the analysis

System Organ Class (SOC)
- Infections and infestations

High Level Group Term (HLGT)
- Infections and infestations congenital
- Ocular infections, irritations and inflammations
- Gastrointestinal infections
- Central nervous system infections and inflammations
- Female reproductive tract infections and inflammations
- Male reproductive tract infections and inflammations
- Respiratory tract infections
- Skin and subcutaneous tissue infections and infestations
- Vascular inflammations
- Microbiology and serology investigations

High Level Term (HLT)
- Cardiac infections and inflammations NEC
- Inner ear infections and inflammations
- Salivary gland infections and inflammations
- Dental and periodontal infections and inflammations
- Gingival infections
- Gastrointestinal inflammatory disorders NEC
- Rectal inflammations NEC
- Oral soft tissue infections, Diverticulum inflammations
- Peritoneal and retroperitoneal disorders
- Bile duct infections and inflammations
- Cholecystitis and cholelithiasis
- Hepatic infections (excl viral), Hepatic viral infections, Hepatocellular damage and hepatitis NEC
- Hepatic and hepatobiliary disorders NEC
- Bursal disorders
- Synovial disorders
- Infectious arthritis
- Musculoskeletal and connective tissue infections and inflammations NEC
- Soft tissue disorders NEC
- Bone and joint infections (excl arthritis)
- Muscle infections and inflammations
- Bladder infections and inflammations
- Genitourinary tract infections and inflammations NEC
- Breast infections and inflammations
- Pleural infections and inflammations

Preferred Term (PT)
- Febrile neutropenia
- Stomatitis