primary mediastinal B-cell lymphoma (PMBCL) at many institutions despite limited data in the multi-center setting. We report a large, multi-center retrospective analysis of children and adults with PMBCL treated with DA-EPOCH-R to characterize outcomes, specifically assess both pediatric and adult patients, and to evaluate potential prognostic factors.

**Methods:** 156 patients with PMBCL treated with DA-EPOCH-R across 24 academic medical centers were assessed, including 38 children and 118 adults. All patients received at least one cycle of DA-EPOCH-R. Radiation therapy was administered at the completion of DA-EPOCH-R in 14.7% of patients.

**Results:** With median follow-up of 22.6 months (range 2.7–101.0 months), the estimated 3-year EFS is 85.9% (95% CI 80.3–91.5) and OS is 95.4% (95% CI 91.8–99.0). Outcomes were similar in pediatric and adult patients. Pediatric patients were more likely to present with bulky mediastinal disease and were more likely to be escalated to at least dose level 4. Thrombotic complications were reported in 28.2% of patients and were more common in pediatric patients (45.9% vs. 22.9%, p < 0.011). The sites of thromboses included: upper extremity (n = 22), internal jugular vein or superior vena cava (n = 10), intracardiac (n = 5), pulmonary embolism (n = 5), and lower extremity (n = 2). Seventy-five percent of patients had a negative FDG-PET scan at the completion of DA-EPOCH-R, defined as Deauville score 1–3. Negative FDG-PET at end-of-therapy was associated with improved EFS (95.4% vs. 54.9%, p < 0.001).

**Conclusions:** Our multicenter data support the use of DA-EPOCH-R for the treatment of PMBCL in children, adolescents, and adults with PMBCL. The high rate of thrombosis suggests that prophylactic anticoagulation should be considered in this setting. Patients with a positive end-of-therapy FDG-PET scan have an inferior outcome and may benefit from augmented or novel therapy.

**Keywords:** DA-R-EPOCH; primary mediastinal large B-cell lymphoma (PMLBCL).

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**ABSTRACT**

**Introduction:** PMBCL frequently harbors genetic abnormalities at the 9p24 locus, resulting in overexpression of the PD-1 ligands PD-L1 and PD-L2. This may serve as an immune evasion mechanism for this tumor type that could be targeted with PD-1 blockade. In a phase 1 clinical trial, the anti–PD-1 antibody pembrolizumab showed promising antitumor activity against rrPMBCL. Here we present interim results from the rrPMBCL cohort of the two-cohort, multicenter, Phase 2 KEYNOTE-170 study (NCT02576990), evaluating safety and efficacy of pembrolizumab in this population.

**Methods:** This cohort enrolls adult patients with rrPMBCL, who failed or are ineligible for autologous stem cell transplant (auto SCT); patients ineligible for auto SCT must have failed ≥2 lines of prior therapy. Patients receive pembrolizumab 200 mg IV every 3 weeks until disease progression, unacceptable toxicity, or completion of 35 treatment cycles. Response is assessed every 12 weeks. Primary end point was objective response rate (ORR) by blinded independent central review (BICR) according to 2007 response criteria. Key secondary end points were ORR by investigator assessment and adverse events (AE).

**Results:** Patients were enrolled at 14 sites in 9 countries. At the analysis cutoff date (7 December 2016), 33 patients were treated in the rrPMBCL cohort: median age 32 years (range: 20–58), 58% female, median 3 lines of prior therapy (range: 1–5), 24% with prior radiation, and 70% auto SCT ineligible due to chemorefractory disease. Median follow-up duration was 2.5 mos (range: 0.1–9.4); 15 patients discontinued treatment due to progressive disease (n = 10), death (n = 2), physician decision (n = 2), or AE (n = 1). At the time of data cutoff, 10 treated patients had not yet reached the first response assessment (none had discontinued). Among the remaining 23 patients, ORR was 35% by BICR and by investigator assessment. By BICR, responses were: 3 complete responses (13%), 5 partial responses (22%), 4 stable disease (17%), 5 progressive disease (22%), and 6 non-evaluable (26%). Median time to response was 2.8 mos (range: 2.4–5.5), and all responses were ongoing (range: 0.0 to 5.4 mos) at data cut-off. Among evaluable patients, 81% had target lesion reductions (Figure). Overall, 6/33 patients (18%) experienced serious AEs and 19/33 (58%) experienced drug-related adverse events (DRAEs). Grade 3 DRAEs were neutropenia (n = 5 patients), increased hepatic enzymes (n = 2), asthenia (n = 1), and pneumonia (n = 1). One patient had a grade 4 DRAE (neutropenia). There were no drug-related deaths.

**Conclusions:** In this ongoing global trial, pembrolizumab showed promising antitumor activity and a manageable safety profile in patients...
with rrPMBCl (including heavily pretreated patients), similar to results of the Phase 1b KEYNOTE-013 trial. Enrollment is ongoing.

**Keywords:** diffuse large B-cell lymphoma (DLBCL); non-Hodgkin lymphoma (NHL); salvage treatment.

**SESSION 3: HODGKIN LYMPHOMA**

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**RESTORE & TARGET: A CONCEPTUALLY NOVEL TREATMENT APPROACH TO CLASSICAL HODGKIN’S LYMPHOMA**

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**Introduction:** Irrespective of its genomic B-cell origin, classical Hodgkin’s lymphoma (cHL) is characterized by the virtual lack of gene products whose expression constitutes the B-cell phenotype. Epigenetic repression of B-cell-specific genes was previously postulated to contribute to the lost B-cell phenotype in cHL. Restoration of the B-cell phenotype may not only revert a hallmark of cHL but provide a new Achilles’ heel by sensitizing cHL to clinically established antibody therapies targeting B-cell surface receptors as well as small compounds interfering with B-cell receptor (BCR) signaling.

**Methods:** We engineered cHL cell lines to carry a CD19 reporter, and conducted a high-throughput pharmacological screening with more than 28,000 compounds to identify drugs that promote re-expression of the B-cell phenotype.

**Results:** We found three chemicals to robustly enhance CD19 transcription. Since two of them reportedly interfere with epigenetic regulators, we performed chromatin immunoprecipitation assays, showing that these compounds lowered transcriptionally repressive lysine 9-trimethylated histone H3 (H3K9me3) levels at the CD19 promoter. Inhibition of the H3K9-methyltransferase EHMT2, a possible target structure of these two compounds, by BIX-01294 or shRNA-mediated knockdown resulted in increased CD19 transcript levels, suggesting that EHMT2 might be involved in repression of the B-cell phenotype in cHL. Furthermore, the anti-leukemic and differentiation-promoting agents arsenic trioxide (ATO) and all-trans retinoic acid (ATRA), both not part of the screened library, were found to reconstitute the silenced B-cell transcriptional program and impair viability of cHL cell lines. In combination with a screening-identified chemical, ATO evoked re-expression of the CD20 surface receptor, which could be therapeutically exploited by enabling CD20 antibody-mediated direct apoptosis and antibody-dependent cellular cytotoxicity of Hodgkin cells. Even more strikingly, restoration of the B-cell phenotype profoundly