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Introduction: Rituximab maintenance after frontline R+chemo prolongs remissions and is a widely adopted treatment option for patients with follicular lymphoma (FL). Moreover, metabolic and molecular response assessed with FDG-PET and MRD have been confirmed as strong predictors of patients' survival thus suggesting the benefit of a response adapted maintenance strategy as post induction therapy.

Methods: FOLL12 is a multicenter, randomized, phase III, non inferiority study comparing standard vs response adapted maintenance in patients with stage II-IV, previously untreated, intermediate-high risk FL according to FLIPI2, requiring therapeutic intervention. All patients received induction immunochemotherapy (ICT) with 6 cycles of R-CHOP or 6 cycles of R-bendamustine both followed by 2 additional doses of rituximab. After induction ICT, patients in the standard arm were treated with bimonthly rituximab doses for up to two years. Patients in the experimental arm were managed according to centrally reviewed metabolic and molecular response (i.e. Complete metabolic and molecular response: no therapy; Complete metabolic response without molecular response: 4 weekly rituximab doses; Lack of metabolic response (Deauville score 4-5): radiimmunotherapy with ibritumomab tiuxetan followed by standard rituximab maintenance). Primary study endpoint was 3 years progression free survival (PFS) by intention to treat. A sample size of 770 evaluable patients was planned assuming a reference of 3yr PFS at 70% with a non inferiority margin of 7% between arms.

Results: A total of 790 eligible patients were randomized to standard (394 patients) or experimental (396 patients) arm. Groups were well balanced according to patient characteristics and response rates. At the end of induction therapy 88% of cases resulted PET- and 91% MRD-. After a median follow-up of 37 months (range 1-71), the 3-year overall survival (OS) and PFS were 96% and 76%, respectively.

An interim analysis, planned at the occurrence of 70% events, was anticipated at the occurrence of 50% of events and submitted to the external data safety monitoring committee (DSMC). The analysis showed that response oriented experimental arm resulted significantly inferior to the standard maintenance arm in terms of PFS (estimated 3-year PFS, 68% vs. 84%; hazard ratio for PFS, 2.05 [95% CI 1.50-2.81; P < 0.0001]). The DSMC considered unlikely that longer follow-up could modify the results and was favorable in publishing these data.

Conclusions: In patients with intermediate-high risk FL according to FLIPI2 and requiring systemic therapy, omission of R-maintenance resulted in a significantly lower 3-year PFS, despite the attainment of a post-induction complete metabolic response.

Keywords: follicular lymphoma (FL); minimal residual disease (MRD); positron emission tomography (PET).

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105 INTERIM UPDATE FROM A PHASE 2 MULTICENTER STUDY OF TAZEMETOSTAT, AN EZH2 INHIBITOR, IN PATIENTS WITH RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA

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Introduction: Relapsed or refractory (R/R) follicular lymphoma (FL) remains an area of unmet medical need and treatments with novel mechanisms of action are desirable. The histone methyltransferase EZH2 is an important regulator of the germinal center (GC) reaction that is involved in preventing terminal differentiation of GC B-cells. EZH2 activating mutations are present in ~20% of FL patients (pts) and are postulated to be oncogenic drivers. Tazemetostat, a selective, oral EZH2 inhibitor has shown antitumor activity in a phase 1/2 study that included non-Hodgkin lymphoma pts with mutant (MT) or wild-type (WT) EZH2 tumors, providing rationale for further investigation.

Methods: This open-label, multicenter, phase 2 study of tazemetostat enrolled pts with either MT or WT EZH2 R/R diffuse large B-cell lymphoma or FL (Grade 1-3b). Key inclusion criteria included: age ≥ 18 years, ≥ 2 prior treatment regimens, and measurable disease. Tumor tissue was analyzed for EZH2 hot spot activating mutations (Y646X, A682G, A692V) using a cobas[®] EZH2 Mutation Test (Roche Molecular Systems, investigational use only). Tazemetostat 800 mg was administered orally, twice daily. Response was assessed every 8 weeks using 2007 IWG-NHL criteria. The primary endpoint was ORR (CR + PR). Secondary endpoints included PFS and safety/tolerability. Efficacy and safety were analyzed for the EZH2 MT and EZH2 WT groups.

Results: As of February 1, 2019, interim data were summarized from 95 FL pts (41 EZH2 MT and 54 EZH2 WT). The overall median age was 61 years, and median prior lines of therapy was 2 (range: 0-11) in

the EZH2 MT group and 3 (range: 1-8) in the EZH2 WT group. Median follow-up times, ORR, median duration of response for 92 response evaluable patients in both EZH2 MT and WT groups are highlighted in the table. Response duration was greater than 24 weeks in 83% of pts, and 50% of pts had a response duration greater than 1 year. Treatment-emergent adverse events (TEAEs) leading to dose reductions occurred in 8% of pts and study drug discontinuation due to TEAEs occurred in 9% of FL pts. The overall safety profile was similar to what has been previously reported. Grade ≥ 3 treatment-related TEAEs were reported in 18% of pts; no Grade 5 AEs were reported.

Conclusion: Tazemetostat 800 mg BID appears to be generally well tolerated with observed meaningful clinical activity and durability of response in pts with R/R FL. ORR was pronounced in pts with EZH2 activating mutations. Late onset responses have been reported on tazemetostat. Given the consistently favorable safety and low rates of discontinuation due to TEAEs, these encouraging phase 2 data demonstrate that EZH2 inhibition may be an important and effective therapeutic target in FL.

Keywords: follicular lymphoma (FL); germinal center B cell-like (GCB).

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	EZH2 MT group (n= 39 evaluable)	EZH2 WT group (n= 53 evaluable)
Objective response rate, % (95% CI)	74 (57.9, 87.0)	34 (21.5, 48.3)
Complete response, %	10	6
Partial response, %	64	28
Stable disease, %	26	30
Progressive disease, %	0	28
Progression-free survival, weeks (95% CI)	60.0 (46.7, 83.9)	24.6 (15.1, 47.9)
Median duration of response, weeks (95% CI)	40 (22.3, NE)	56 (31.7, NE)
Median follow-up, weeks (min, max)	64 (5-161 weeks)	107 (1-178 weeks)

CI, confidence interval; MT, mutant; NE, not estimable; WT, wild type

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SESSION 9 – EXTRANODAL LYMPHOMAS

106 INTEGRATIVE GENOMIC ANALYSIS IDENTIFIES KEY PATHOGENIC CONCEPTS IN PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA

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Introduction: Primary mediastinal large B-cell lymphoma (PMBCL) is recognized as a distinct entity in the current WHO classification, accounting for 2-3% of non-Hodgkin lymphomas. Molecular studies have provided evidence that PMBCL can be distinguished from diffuse large B-cell lymphoma (DLBCL) and highlighted a strong relationship between PMBCL and classical Hodgkin lymphoma (cHL). There is cumulative evidence to support that correct classification is important for patient risk stratification and therapeutic decision making. We aimed to comprehensively describe genetic alterations and perturbed pathways in molecularly defined PMBCL, as targeted sequencing studies in the past have focused on a limited number of genetic lesions involved in disease pathogenesis.

Methods: We performed whole-exome sequencing of 95 centrally reviewed PMBCL cases, using the SureSelect Human All Exon V6 +UTR baits (Agilent) followed by massively parallel sequencing. For 21 cases paired germline DNA was available. Somatic SNV/indel variants were identified using the intersection of predictions by VarScan, Strelka and MuTect, and annotated with SnpEff. We inform on oncogenic driver genes as identified by MutSigCV and recurrent copy number alterations utilizing CNVkit and GISTIC. For 69 patients global gene expression profiling performed on the DASL platform (Illumina) was available and 90 cases have been molecularly classified using the Lymph3Cx assay. The impact of somatic mutations on gene expression was assessed using xseq.

Results: Tumor and normal samples were sequenced to an average coverage of 115X. Analysis of somatic alterations in tumor-normal pairs yielded 50 putative driver genes recurrently mutated in PMBCL. Besides mutations in the JAK-STAT (*SOCS1, STAT6, IL4R, PTPN1*) and NFκB-pathway (*TNFAIP3, NFKBIE, TRAF3*), we provide additional evidence of the importance of immune evasion in this disease (*CIITA, CD58, B2M*) and identified the IRF-pathway as a putative novel hallmark. As expected, the most significant regions of copy number gain predicted by GISTIC were located on 9p (72%). The most frequent regions of loss were mapped to 10q, 8p, 1p, and 7p. PMBCL driver genes, with the exception of *EZH2*, were significantly more frequently mutated in comparison to DLBCL, whereas only three genes were significantly different between PMBCL and cHL.

Conclusions: Here we identified candidate driver genes with clear evidence of somatic mutations in PMBCL, the majority being distinct from DLBCL. We observed an enrichment of somatic mutations affecting genes involved in the JAK-STAT- and NFκB-pathway, and propose that the IRF-pathway is critically involved in PMBCL pathogenesis.

Keywords: molecular genetics; primary mediastinal large B-cell lymphoma (PMLBCL).

107 OUTCOME OF PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA: IMPACT OF A PET-GUIDED APPROACH

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Background: Primary mediastinal large B-cell lymphoma (PMBCL) is a rare subtype of lymphoma which typically presents in females with a bulky anterior mediastinal mass. Patients (pts) are treated with chemotherapy ± consolidative radiotherapy (CRT). Herein, we reviewed outcomes of PMBCL pts treated at BC Cancer in the rituximab era and the impact of a PET-adapted approach.

Methods: The BC Cancer Lymphoid Cancer Database was used to identify pts >16 years (y) of age with newly diagnosed PMBCL based on the WHO classification who were treated with chemotherapy + rituximab. Prior to the availability of FDG-PET scan at end of treatment (EOT) in July 2005, all pts were recommended to receive R-