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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Tislelizumab Plus Zanubrutinib in Patients with Richter Transformation: Primary Endpoint Analysis of the Prospective, Multi-Center, Phase-II RT1 Trial of the German CLL Study Group

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Background

Richter transformation (RT) describes the development of an aggressive lymphoma, in most cases a diffuse large B cell lymphoma (DLBCL) or Hodgkin's lymphoma (HL), in patients (pts) with chronic lymphocytic leukemia (CLL). Pts with RT have a dismal prognosis with chemoimmunotherapy (CIT) like R-CHOP, with overall response rates (ORR) of <40% and median overall survival (OS) of 6-8 months. Targeted therapies have the potential to improve outcomes, but few prospective studies have been run in this entity. Here we present the first data of the international phase-II RT1 trial, in which the PD1 inhibitor tislelizumab is combined with the next-generation BTK inhibitor zanubrutinib to treat pts with RT.

Methods

Pts with histologically confirmed RT (DLBCL or HL [HL only when not eligible for standard therapy]) and up to one prior line of RT-directed therapy were eligible. Each cycle (of 21 days) consisted of one infusion of 200 mg tislelizumab at day 1 and 160 mg zanubrutinib twice daily orally. Six cycles of induction were followed by 6 cycles of consolidation; pts with complete response (CR), partial response (PR) or stable disease (SD) continued maintenance until disease progression/non-tolerance. The primary endpoint was ORR after induction therapy for pts receiving ≥ 3 cycles according to the refined Lugano Classification with the aim to test the null hypothesis of ≤0.40. Secondary endpoints include duration of response (DOR), progression-free survival (PFS), OS and time to next treatment (TTNT).

Results

Of 59 enrolled pts, 48 pts received at least 3 cycles of treatment and comprised the analysis population according to the study protocol. Eleven pts stopped earlier due to withdrawal, death, PD or toxicity. Median observation time was 13.9 months (interquartile range 1.7-35.9).

Median age was 67 years (range 45 - 82). 22 (45.8%) pts had ECOG 1 or higher. Median LDH at enrollment was 335 U/l. Sixteen (34.8%) pts had del(17p)/ *TP53*mut, 29 (70.7%) pts had unmutated IGHV. 25 (64.1%) pts had high or very high-risk CLL according to CLL-IPI, 11 (28.2%) intermediate and 3 (7.7%) low risk. Complex karyotype (≥3 aberrations) was detected in 16 (42.1%) pts. 46 (95.8%) pts had DLBCL-RT and 2 (4.2%) pts had HL-RT. In 26 (54.2%) pts, the RT was reported as clonally related to the CLL (22 [45.8%] unknown). Overall, 36 (75.0%) pts had received prior CLL-directed therapy, including CIT (25 pts) and targeted agents (32 pts) as well as prior allogeneic stem cell transplant (SCT) in 3 pts. 12 (25.0%) pts had treatment-naive CLL. Thirteen pts (27.1%) had received prior RT-directed therapy, including CHOP-like regimens and BTK inhibitors. 35 (72.8%) pts had not received prior RT-directed therapy.

Twenty-eight of 48 pts responded to induction therapy resulting in an ORR of 58.3% (95% CI, 0.43-0.72), including 9 (18.8%) CR and 19 (39.6%) PR, meeting the study's primary endpoint (p=0.008) (Fig A). SD was reported in 6 (12.5%) pts, 11 (22.9%) pts had progressive disease (PD), three had missing assessment due to PD. The median DOR was not reached, the 6-month DOR rate was 70.6%. Median PFS was 10 months (95% CI 3.8 -16.3) with a 12-month rate of 46.9% (Fig B). Median OS was not reached (12-month OS rate 74.7%). Median TTNT was not reached (12-month TTNT rate 56.2%).

Post-protocol treatment included CIT in 21 cases (48.8%), radiation in 1 case (2.3%), BTK/BCL2 inhibition in 7 (16.3%) cases and 8 (18.6%) allogeneic SCT. SCT was conducted as consolidation in two pts with PR, and as salvage treatment for 5 pts with SD/PD (one missing response).

Overall, 606 adverse events (AEs) were reported, of which 173 (28.5%) were ≥ grade 3 and 129 (21.3%) were serious AE. Of the 29 pts who discontinued study treatment, three were due to toxicity, the rest for PD and/or start of next line of therapy. The most frequent AEs were infections and infestations (17.7%), including Covid-19, pneumonia and urinary tract infections, gastrointestinal disorders (12.7%), including diarrhea and nausea, and blood and lymphatic system disorders (11.2%), including anemia, neutropenia and thrombocytopenia.

Conclusions

Combined checkpoint and BTK inhibition by tislelizumab plus zanubrutinib is an effective and well-tolerated treatment strategy for pts with RT. Responses are durable and overall survival in the RT1 study is encouraging given the otherwise poor prognosis of RT. Translational studies are ongoing to identify predictors of response to checkpoint inhibition in RT.

Disclosures Al-Sawaf: *Roche:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Janssen:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Gilead:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Eli Lilly:* Speakers Bureau; *BeiGene:* Research Funding, Speakers Bureau; *Adaptive:* Speakers Bureau; *Ascentage:* Membership on an entity's Board of Directors or advisory committees; *AstraZeneca:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Abbvie:* Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau. **Fink:** *Celgene:* Research Funding; *AbbVie:* Other: Travel Support; *Astra Zeneca:* Honoraria, Research Funding. **Tausch:** *BeiGene:* Consultancy, Other: Travel support, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Other: travel support, Speakers Bureau; *Janssen-Cilag:* Consultancy, Honoraria, Other: travel support, Speakers Bureau; *Roche:* Consultancy, Honoraria, Research Funding, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Other: Travel Support, Research Funding, Speakers Bureau. **Schneider:** *Abbvie:* Honoraria, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Speakers Bureau; *BeiGene:* Other: travel support; *Jannsen Cilag:* Consultancy. **Böttcher:** *AstraZeneca:* Honoraria, Speakers Bureau; *Sanofi:* Honoraria, Speakers Bureau; *Abbvie:* Honoraria, Speakers Bureau; *Janssen:* Honoraria, Research Funding, Speakers Bureau; *Roche:* Honoraria, Speakers Bureau. **Ritgen:** *Roche:* Consultancy, Honoraria, Research Funding; *AstraZeneca:* Consultancy, Honoraria, Other: travel support; *Abbvie:* Consultancy, Research Funding; *Janssen:* Consultancy, Honoraria. **Schetelig:** *Novartis:* Honoraria; *Abbvie:* Consultancy, Honoraria; *BeiGene:* Consultancy, Honoraria; *Eurocept:* Honoraria; *BMS:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria. **Von Tresckow:** *Roche:* Consultancy, Honoraria, Other, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Other, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Other: travel grant, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Other, Speakers Bureau. **Wendtner:** *GSK:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *LillyPharma:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau; *Gilead:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau; *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau; *Hoffman-La Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: Travel support, Speakers Bureau; *BeiGene:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Other: travel support, Speakers Bureau. **Fischer:** *Roche:* Honoraria, Other: Travel Support; *AstraZeneca:* Consultancy; *Abbvie:* Honoraria, Other: TRavel support. **Stilgenbauer:** *Novartis:* Consultancy, Honoraria, Other: travel support, Research Funding; *Janssen:* Consultancy, Honoraria, Other: travel support,

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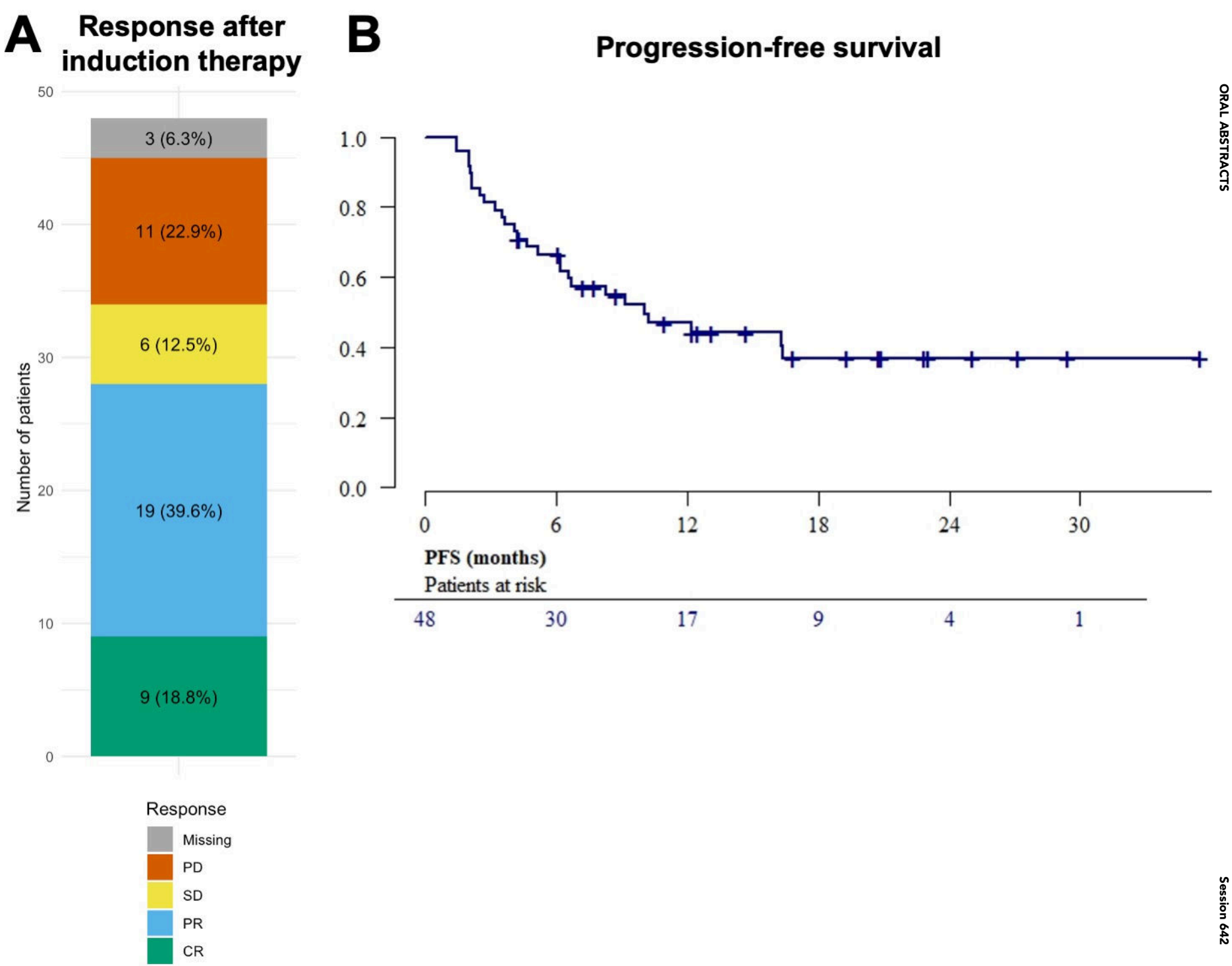

Figure 1