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ORAL ABSTRACTS

627.AGGRESSIVE LYMPHOMAS: CLINICAL AND EPIDEMIOLOGICAL

A Simplified IPI Including BCL2 Identifies IPI 3 Patients with Poor Prognosis - a GLA/ Dshnhl and Lysa Collaboration

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Introduction: The original IPI remains valid to identify prognostic groups of DLBCL patients (pts) treated with R-CHOP (Ruppert et al. Blood 2020) and has been used to define eligibility for more than 20 studies randomizing pts between R-CHOP and R-CHOP + X, none of which except the Polarix study met its endpoint. One reason why some studies failed was the inclusion of IPI 2/3 pts equalizing the difference between standard and experimental arm although significant survival differences in pts with higher IPI were detected. Following the WHO-HAEM5 classification, determination of *BCL2* and *MYC* rearrangements is mandatory to diagnose DLBCL, NOS and HGBL- *MYC/ BCL2*. As surrogate markers, we included immunohistochemistry (IHC) for MYC and BCL2 into the IPI model hoping for a wider spread of survival curves and better selection of pts suitable for future clinical trials.
Methods: We analyzed 2765 pts treated on DSHNHL (German high-grade lymphoma study group) phase 2/3 studies, calculated the IPI, and added results for BCL2 and MYC expressionto individual IPI factors using published thresholds (50%; 70%) (Ziepert et al. Haematologica 2020). **I**n univariate analyses, log-rank tests were used. Proportional hazard models for each of the biologic markers were separately adjusted for IPI factors. Using a variable selection algorithm the final model was built. Hazard ratios (HR) with p-values are presented.
Results: 2765 DLBCL pts by reference pathology treated on 12 DSHNHL phase 2/ 3 studies were eligible. Median age at diagnosis was 57 years (range: 18-80 years), 43% of pts were female. Median observation time was 5 years. All pts had been treated with R-CHOP or variations. At diagnosis, 610 pts (22%) scored an IPI of 0, IPI was 1, 2, 3, 4, or 5 in 895 (32%), 546 (20%), 436 (16%), 212 (8%) and 64 (2%) pts with 3-year PFS- and OS-rates of 95%,87%,77%,66%,66%,47% and 98%,92%,83%,71%,73% and 54%, respectively. Multivariate analyses confirmed the significance of IPI factors (age, stage, performance status, and LDH) except the number of extranodal sites (EN) which did not significantly contribute to the model in this cohort (HR

$_{EFS,PFS,OS}$=1.0). Accordingly, EN>1 was deleted also resulting in better distinction of IPI groups (3-year PFS- and OS-rates: 95%,87%,74%,63%,51% and 98%,92%,80%,70%,57%%). In the final model, adjusted for all IPI factors except EN>1, BCL2 and MYC expression remained significant (HR $_{PFS}$=2.3 and 2.0, p<0.001 and p=0.003).
These results were validated and confirmed in 1176 DLBCL patients from 5 French (LYSA) studies. EN>1 but also MYC expression did not significantly contribute the final model in the validation set. Thus, MYC expression was deleted from the final model.
Using the IPI deleting EN>1 but including BCL2 expression we observed 3-year PFS-rates of 74% vs. 83% in BCL2-positive vs. BCL2-negative patients with IPI 2 (p=0.136). In pts with IPI 3 the 3-year PFS rates were 53% vs. 80% (p=0.011) (see figure 1); in pts with IPI 4 the respective 3-year PFS rates were 49%% vs. 71%. This latter difference was not significant due to small pt numbers (p=0.381).
Conclusions: Deletingthe number of extranodal sites and adding BCL2expression tothe original IPI factors as the only readily available biologic marker allows building an IPI model which effectively separates IPI 3 pts in 2 groups with significantly different prognosis. Restricting eligibility for future clinical trials to DLBCL pts with IPI 3 (and IPI 4) who are BCL2-pos. may help to avoid overtreatment of pts well treated with R-CHOP and at the same time better select pts representing a group with truly unmet medical need who are most likely to benefit from experimental therapies.

Disclosures Poeschel: *Swedish Orphan Biovitrum GmbH:* Membership on an entity's Board of Directors or advisory committees; *Janssen-Cilag:* Consultancy; *Genmab:* Consultancy; *Roche:* Other: travel expenses, congress support; *AstraZeneca:* Honoraria; *EUSA Pharma:* Consultancy; *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *PentixaPharm GmbH:* Membership on an entity's Board of Directors or advisory committees; *Amgen:* Other: travel expenses, congress support; *Lilly:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Other: travel expenses, congress support; *Bristol-Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: travel expenses, congress support; *Gilead:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Other: travel expenses, congress support. **Recher:** *Servier:* Other: Personal fees; *Jazz Pharmaceuticals:* Other: Personal fees, Research Funding; *Novartis:* Other: Personal fees; *Astellas:* Other: Personal fees; *BMS:* Other: Personal fees, Research Funding; *Amgen:* Research Funding; *Abbvie:* Honoraria; *MaatPharma:* Research Funding; *IQVIA:* Research Funding; *Takeda:* Other: Personal fees. **Molina:** *Janssen:* Other: Travel and congress fees. **Lenz:** *BeiGene:* Membership on an entity's Board of Directors or advisory committees; *NanoString:* Membership on an entity's Board of Directors or advisory committees; *Celgene:* Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *University Hospital Munster:* Current Employment; *Lilly:* Consultancy; *Hexal/Sandoz:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Genase:* Consultancy; *Immagene:* Consultancy; *Sobi:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *PentixPharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Miltenyi:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *ADC Therapeutics:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Constellation:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Karyopharm:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Genmab:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Morphosys:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Incyte:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AbbVie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Takeda:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AstraZeneca:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Bayer:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Janssen:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *Gilead:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding, Speakers Bureau; *F. 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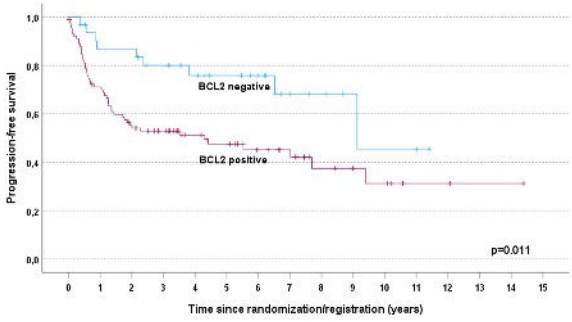

Figure 1

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