ifosfamide in 2 pts (12%) and other regimens in 3 pts (18%). Pts treated with ibrutinib received 560 mg p.o. daily. Intratechal CT was added in 5 pts (31%) and 7 pts (47%) in standard and ibrutinib cohort. Radiotherapy was delivered to 3 pts, all in the standard cohort, in one case as consolidation and in 2 cases as salvage. With a median follow-up of 10.4 months, the 1-year PFS and OS of the entire study population are 24% and 46%. A statistically significant difference in 1-year PFS was observed in favor of ibrutinib versus standard CT (49% vs 6%, p = 0.044). The difference in 1-year OS in favor of ibrutinib versus standard CT did not reach statistical significance (57% vs 37%, p = 0.097). In the standard cohort only one pt is alive after allogeneic transplantation.

Conclusion: In this study, ibrutinib monotherapy appears to be effective for CNS-MCL; with the usual limitations of a retrospective analysis, our data show a benefit in PFS for CNS-MCL pts treated with ibrutinib in comparison to standard chemoimmunotherapy.

Keywords: ibrutinib; mantle cell lymphoma (MCL); salvage treatment.

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UPDATED SAFETY AND EFFICACY DATA IN THE PHASE 1 TRIAL OF PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) TREATED WITH BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111)

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Introduction: Zanubrutinib, an investigational BTK inhibitor, has demonstrated greater selectivity for BTK vs other TEC- and EGFR-family kinases in biochemical assays and shown favorable PK/PD properties in preclinical studies. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes in patients (pts) treated at 160 mg twice daily (bid; Tam. *Blood* 2016;128:642). Here, we present updated safety and efficacy data from pts with MCL.

Methods: This is a global, phase 1 study investigating zanubrutinib in pts with B-cell malignancies with indication-specific expansion cohorts. In the expansion phase, enrolled pts received zanubrutinib 320 mg daily or 160 mg bid (the RP2D). Treatment emergent adverse events (TEAEs) were summarized according to NCI CTCAE v4.03 and responses were assessed by CT scans as per Lugano Classification (Cheson. *J Clin Oncol* 2014;32:3059).

Results: As of 16 Sep 2018, 48 MCL pts were enrolled: 37 relapsed/refractory (R/R) and 11 treatment-naïve (TN) (**Table**). Of the 48 pts, 45 were evaluable for efficacy; 3 were not efficacy evaluable as they had not yet reached the first 12-week efficacy assessment. Median follow-up for efficacy evaluable pts was 16.0 mo (range, 1.6–38.2). Twenty-six pts discontinued treatment (16 due to progressive disease [PD]; 10 due to TEAEs including peripheral edema, small cell lung cancer, renal hematoma, ANCA-positive vasculitis with acute kidney injury, subdural hematoma, and myelodysplastic syndrome, pneumonia (2 pts), congestive cardiac failure, thalamic infarction). Five pts died due to TEAEs (1 pneumonia, 1 congestive cardiac failure, 1 thalamic infarction, and 2 sepsis/septic shock), none of which were assessed by investigator as related to zanubrutinib. Most common TEAEs of any cause (≥15% of pts) included diarrhea (35%), petechiae/purpura/contusion (31%), upper respiratory tract infection (27%), fatigue (25%), constipation (21%), rash (19%), back pain (17%), headache (17%) and peripheral edema (17%). Overall response rate (ORR) for TN, R/R and overall was 87.5% (7/8), 86.5% (32/37) and 86.7% (39/45) respectively (**Table**). Responses were based on computed tomography scans for most pts, as positron-emission tomography was not required. Median progression-free survival was 15.4 mo (**Table**).

Conclusions: Zanubrutinib monotherapy was shown to be well tolerated and highly active in pts with MCL, with high ORR and rate of CR.

Keywords: BTK inhibitors; mantle cell lymphoma (MCL).

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TABLE 1 Patient Characteristics, Safety, and Efficacy

Patient characteristics	**N = 48**		
Median (range) age, y	71 (42–90)		
ECOG PS, n (%)			
0	20 (41.7)		
1	22 (45.8)		
2	6 (12.5)		
Stage at study entry, n (%)			
Stage I	3 (6.3)		
Stage II	1 (2.1)		
Stage III	4 (8.3)		
Stage IV	40 (83.3)		
MIPI, n (%)			
Low risk	12 (25.0)		
Intermediate risk	18 (37.5)		
High risk	18 (37.5)		
Disease status, n (%)			
Treatment-naïve	11 (22.9)		
Relapsed/refractory	37 (77.1)		
Median (range) no. of prior therapies	1 (1–4)		
Median (range) follow-up, mo	15.1 (0.6–38.2)		
Bulky disease >10 cm, n (%)	3 (6.3)		
Safety, n (%)	**N = 48**		
Any AE	47 (97.9)		
Grade ≥3 AEs	28 (58.3)		
Serious AEs	19 (39.6)		
AEs leading to zanubrutinib discontinuation	11 (22.9)		
AEs leading to death	5 (10.4)		
Efficacy			
Best response per investigator (n)	**TN (n=8)**	**R/R (n=37)**	**Overall (n=45)**
Overall response rate, n (%); 95% CI	7 (87.5); 47.3, 99.7	32 (86.5); 71.2, 95.5	39 (86.7); 73.2, 94.9
Complete response, n (%)	3 (37.5)	11 (29.7)	14 (31.1)
Partial response, n (%)	4 (50.0)	21 (56.8)	25 (55.6)
Stable disease, n (%)	0 (0.0)	2 (5.4)	2 (4.4)
Progressive disease, n (%)	1 (12.5)	3 (8.1)	4 (8.9)
Median follow up (min, max)	8.6 (1.6, 25.0)	17.1 (1.9, 38.2)	16.0 (1.6, 38.2)
Duration of response (mo)	**R/R (n=32)**		**Overall (n=39)**
Follow up, median (min, max)[a]	14.7 (0.0, 28.2)	14.3 (0.0, 28.2)	
Median (95% CI)[b]	14.7 (10.6, 18.5)	14.7 (10.6, 18.5)	

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; CI, confidence interval.
[a]Follow-up time is estimated by the reverse Kaplan-Meier method.
[b]Median is estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

Abbvie, *Takeda*, *Merck*, *Gilead*, *Epizyme*. **Cull, G:** Research Funding: *Beigene*, *Glycomimetics*, *Abbvie*; Other Remuneration: *Travel*, *Accommodations*, *Expenses: Amgen*, *Roche*. **Munoz, J:** Consultant Advisory Role: *Pharmacyclics LLC*, *Bayer*, *Gilead/Kite Pharma*, *Bristol-Myers Squibb*, *Janssen*, *Juno/Celgene*; Other Remuneration: *Speaker's Bureau: Kite Pharma*, *Gilead*, *Bayer*, *Pharmacyclics/Janssen*, *AstraZeneca*. **Phillips, T:** Consultant Advisory Role: *Bayer*, *Gilead*, *Seattle Genetics*, *Genentech*, *Incyte*, *Pharmacyclics*; Research Funding: *Pharmacyclics*, *Abbvie*. **Kim, W:** Research Funding: *Roche*, *Takeda*, *Mundipharma*, *J&J*, *Celltrion*, *Kyowa kirin*, *Donga*. **Atwal, S:** Employment Leadership Position: *BeiGene*; Stock Ownership: *BeiGene*; Research Funding: *BeiGene*; Other Remuneration: *Leadership: BeiGene*. **Wei, R:** Employment Leadership Position: *BeiGene*;

Stock Ownership: *BeiGene*. **Huang, J:** Employment Leadership Position: *BeiGene*; Stock Ownership: *BeiGene*. **Elstrom, R:** Employment Leadership Position: *BeiGene*; Stock Ownership: *BeiGene*. **Trotman, J:** Research Funding: *PCYC, Roche, Janssen, Celgene, BeiGene*.

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THE CLINICAL COURSE OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) OVER TIME: A MULTISTATE SURVIVAL ANALYSIS USING META-DATA FROM 13 FIRST-LINE RANDOMIZED TRIALS

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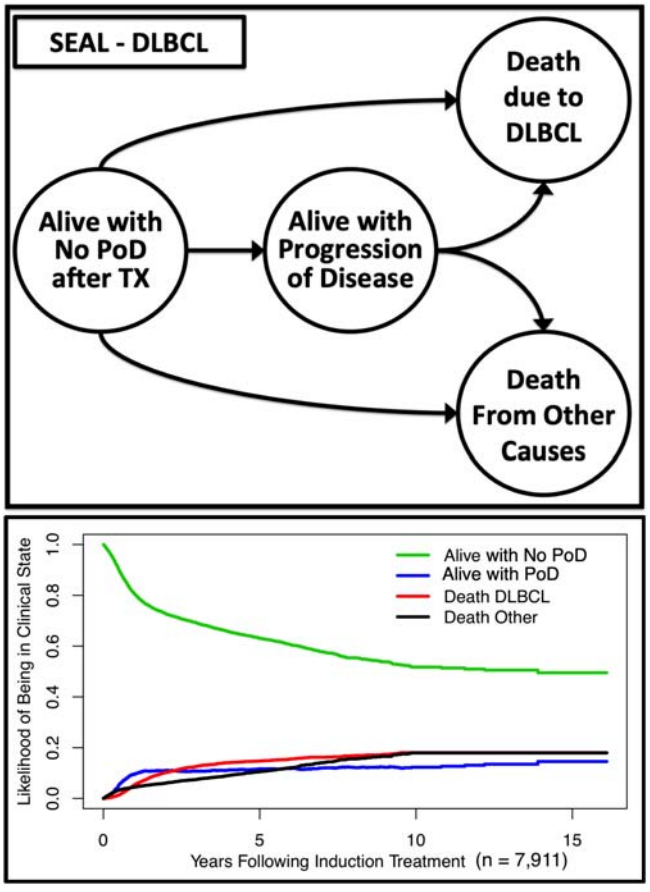

Introduction: The Surrogate Endpoints for Aggressive Lymphoma (SEAL) collaboration established a meta-database integrating individual patient data from 13 first-line randomized clinical trials on previously untreated diffuse large B-cell lymphoma (DLBCL). This meta-database provides an opportunity to investigate the impact of clinical factors and treatment response on DLBCL-specific and other causes of death following initial therapy to define new opportunities for trials and improve survivorship.

Methods: Using the SEAL database, we studied DLBCL outcomes for patients receiving anthracycline-based chemotherapy with/without added rituximab (R-Chemo) in a multistate survival analysis model having the model states "Alive with No Progression of Disease (PoD) after Treatment (TX)", "Alive after PoD", "Death from DLBCL", and "Death from Other Causes" (top Figure). The Aalen-Johansen estimator was used to calculate the likelihood of being in each model state and project the course of DLBCL over time (bottom Figure).

Results: We identified 7,911 DLBCL patients (Figure) with median age 62 (range 18-92) years, 62.1% stage III/IV, 64.7% IPI ≥ 2, including 5,108 treated with R-Chemo. Following initial TX for all patients (or with R- Chemo), 2- and 5-year DLBCL-specific death rate were 7.5% (5.9%) and 8.8% (7.0%) for patients age < 40 at initial TX, 8.9% (7.2%) and 12.8% (10.6%) for age 40-60, 10.4% (9.8%) and 15.2% (14.6%) for age 60-70, and 12.8% (12.5%) and 18.3% (17.6%) for age ≥ 70. Death rates at 2- and 5-year from all other causes were 2.3% (2.1%) and 3.5% (3.8%) for age < 40, 4% (3.1%) and 6.5% (5.1%) for age 40-60, 5.1% (4.8%) and 9.4% (7.9%) for age 60-70, and 11.3% (12.3%) and 18.3% (20.0%) for age ≥ 70. Following R- Chemo (n = 5,108), 2-year PoD rates were 12.3% for patients achieving CR, 24.1% for PR, and 28.4% for SD; 2- and 5- year DLBCL-specific mortality rates were 4.6% and 8.7% for CR, 11.8% and 18.6% for PR, 20.3% and 25.6% for SD, and 69.1% and 71.2% for PD. These rates were similar for "non R-Chemo" regimens. International Prognostic Index (IPI) affected the 2- and 5-year DLBCL-specific mortality rates, which were 4.8% and 8% for IPI = 0 or 1, 7.8% and 11.9% for IPI = 2, 13.3% and 18.6% for IPI = 3, and 24.4% and 29.7% for IPI = 4 or 5 in the whole SEAL population (n = 7,911).