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泽布替尼（zanubrutinib）在血液系统肿瘤中的研究

以快速实现MRD为导向的治疗策略——泽布替尼联合obinutuzumab/venetoclax治疗CLL的多中心研究初步结果

Initial results of a multicenter, investigator initiated study of MRD driven time limited therapy with zanubrutinib, obinutuzumab, and venetoclax. *First Author: Jacob Drobnyk Soumerai, Massachusetts General Hospital Cancer Center; Harvard Medical School, Boston, MA*

Background: Venetoclax (Ven)-Obinutuzumab (O) is approved for chronic lymphocytic leukemia (CLL) achieving frequent undetectable minimum residual disease (uMRD; Fischer NEJM 2019). Ven-Ibrutinib is synergistic with frequent uMRD but with grade >3 neutropenia in 33-48% patients (pts; Tam ASH 2019; Jain NEJM 2019). Zanubrutinib (B) is a highly specific BTK inhibitor that demonstrated 100% occupancy in lymphoid tissues, so may be preferred to combine with OVen. We hypothesize that treatment (tx) with BOVen using an MRD driven discontinuation strategy will achieve frequent uMRD and durable responses. **Methods:** In this multicenter, investigator initiated phase 2 trial (NCT03824483), eligible pts had previously untreated CLL requiring tx per iwCLL, ECOG PS <2, ANC >1, PLT >75 (ANC >0, PLT >20 if due to CLL). BOVen was administered in 28D cycles: B 160 mg PO BID starting D1; O 1000 mg IV D1 or split D1-2, 8, 15 of C1, D1 of C2-8; Ven ramp up initiated C3D1 (target 400 mg QD). Tx duration was determined by a prespecified uMRD endpoint (min 8 cycles). MRD was assessed in peripheral blood (PB; flow cytometry, sensitivity $>10^{-4}$) starting C7D1 then every 2 cycles. Once PB uMRD was determined and confirmed in bone marrow (BM), tx continued 2 additional cycles. Adverse events (AE) were assessed per CTCAE v5. Median (med) time to uMRD (primary endpoint) was estimated using the Kaplan-Meier method. **Results:** The study accrued 39 pts (3-10/19): med age 59 years (23-73), 3:1 male, CLL IPI >4 26/39 (67%), unmutated IGHV 28/39 (72%), 17p del/*TP53* mutated 4/39 (10%), all pts were evaluable for toxicity with 37 evaluable for efficacy. At a med follow up of 8 months (mo; 3-10), 25/37 (68%) pts achieved PB uMRD. Med time to PB uMRD is 6 mo (4-8+). Another 8/37 (22%) had PB MRD < 0.1%. Of 25 with PB uMRD, 19 had BM uMRD with 10/19 completing 2 additional cycles and discontinued; 3 had BM MRD (all <0.02%); 3 pending. The most common tx emergent AEs were neutropenia (49%), infusion related reaction (41%), bruising (39%), and diarrhea (39%). Grade ≥3 AEs in ≥5% pts were neutropenia (13%), thrombocytopenia (5%), rash (5%), and pneumonia (5%). Of 17 pts at high risk for TLS on C1D1, 2 cycles of BO reduced TLS risk to low/medium at Ven initiation in 15 (88%). No pts had laboratory/clinical TLS (Howard). **Conclusions:** BOVen is well tolerated and achieves rapid uMRD: currently 68% PB uMRD and 51% BM uMRD with limited follow up (to be updated on presentation). Ten (27%) have discontinued treatment thus far. The value of MRD directed treatment duration will be evaluated with continued follow up. Clinical trial information: NCT03824483. Research Sponsor: BeiGene; Genentech/Roche, Other Foundation, Lymphoma Research Fund (Andrew Zelenetz)).

ASPEN：泽布替尼对比依鲁替尼治疗华氏巨球蛋白血症（WM）的III期随机对照试验

ASPEN: Results of a phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenström macroglobulinemia (WM).

First Author: Constantine S. Tam, Peter MacCallum Cancer Centre, Melbourne, St Vincent's Hospital, Fitzroy, University of Melbourne, Parkville and Royal Melbourne Hospital, Parkville, Victoria, Australia

Background: Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for WM. ASPEN is a randomized phase 3 study comparing zanubrutinib (ZANU), a potent and selective BTK inhibitor, versus ibrutinib (IBR), a first generation BTK inhibitor, in WM patients. **Methods:** Patients with WM and *MYD88* mutation were randomly assigned 1:1 to receive ZANU (160 mg twice daily) or IBR (420 mg once daily). Patients without *MYD88* mutations were assigned to a separate cohort, received ZANU, and are reported separately. Randomization was stratified by CXCR4 mutational status and the number of lines of prior therapy (0 vs 1-3 vs >3). The primary end point was the proportion of patients achieving a complete response or very good partial response (CR+VGPR). Sample size was calculated to provide 81% power to detect a difference in CR+VGPR rate of 35% vs 15% in the subset of patients with relapsed or refractory (R/R) WM. Primary analysis was planned to occur at ~12 months after last patient enrolled. **Results:** In total, 201 patients were randomized from Jan 2017 to Jul 2018. The treatment groups were well balanced for important baseline factors, except in the ZANU arm there were more elderly patients (aged >75 years, 33.3% vs 22.2%) and more anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%). At a median follow-up of 19.4 months, the rate of CR+VGPR was 28.4% vs 19.2% with ZANU vs IBR, respectively (2-sided P=0.09). Rates of atrial fibrillation, contusion, diarrhea, edema peripheral, hemorrhage, muscle spasms, pneumonia, and adverse events (AEs) leading to discontinuation or death were lower with ZANU. The rate of neutropenia was higher with ZANU (Table); however, grade ≥ 3 infection rates were similar (17.8% vs 19.4%). **Conclusions:** ASPEN is the largest phase 3 trial of BTK inhibitors in WM and the first head-to-head comparison of BTK inhibitors in any disease. Although not statistically significant, ZANU was associated with a higher CR+VGPR response rate, and demonstrated clinically meaningful advantages in safety and tolerability compared to IBR. Clinical trial information: NCT03053440. Research Sponsor: BeiGene.

Assessment, %	ZANU (n=102)	IBR (n=99)
CR+VGPR Rate	28.4	19.2
12-mo PFS/OS – overall population	89.7/97.0	87.2/93.9
12-mo PFS/OS – R/R population (n=83 vs 81)	92.4/98.8	85.9/92.5
AEs ≥Grade 3 / Grade 5	58.4 /1.0	63.3/4.1
AEs leading to discontinuation	4.0	9.2
Atrial fibrillation/flutter	2.0	15.3
Hypertension	10.9	17.3
Major bleeding[a]	5.9	9.2
Neutropenia	29.7	13.3

PFS/OS, progression-free survival/overall survival.

[a]Includes grade ≥3 hemorrhage and central nervous system bleeding of any grade.

泽布替尼单药治疗华氏巨球蛋白血症（WM）的3年随访研究。

Three-year follow-up of treatment-naïve and previously treated patients with Waldenström macroglobulinemia (WM) receiving single-agent zanubrutinib.

First Author: Constantine S. Tam, Peter MacCallum Cancer Centre, Melbourne, St Vincent's Hospital, Fitzroy, University of Melbourne, Parkville and Royal Melbourne Hospital, Parkville, Victoria, Australia

Background: Inhibitors of Bruton tyrosine kinase (BTK) have established therapeutic activity in patients with WM. Zanubrutinib, a potent and selective BTK inhibitor was evaluated in a phase 1/2 study in treatment-naïve (TN) and relapsed/refractory (R/R) patients with WM. **Methods:** Patients had TN or R/R WM and required treatment as per International Workshop on WM (IWWM) criteria. Treatment consisted of oral zanubrutinib at 160 mg twice daily (n = 50) or 320 mg once daily (n = 23) until disease progression or unacceptable toxicity. Efficacy endpoints included the proportion of patients achieving a complete response (CR) or very good partial response (VGPR) in accordance with IWWM-6 criteria. Efficacy analyses were conducted on the 73 patients evaluable (24 TN, 49 R/R). **Results:** Between September 2014 and August 2018, 77 patients with WM (24 TN and 53 R/R) began treatment with zanubrutinib (55% aged > 65 years; 21% aged > 75 years). At a median follow up of 32.7 months, 73% remain on treatment. Reasons for treatment discontinuation included adverse events (AE) in 13% (only one related), disease progression (10.4%), and other (3.9%). Results are presented for TN and R/R combined. The overall response rate was 96% and VGPR/CR rate was 45%. The rates of VGPR/CR increased over time; 22% at 6 mos, 33% at 12 months and 45% at 24 months. Three-year progression-free survival (PFS) was 81%, and overall survival (OS) was 85%. The most commonly reported AEs were upper respiratory tract infection (52%), contusion (33%, all grade 1) and cough (22%). AEs of interest include neutropenia (18.2%), major hemorrhage (4%), atrial fibrillation/flutter (5%), and grade 3 diarrhea (3%). **Conclusions:** Long-term follow up with continued zanubrutinib treatment demonstrated deep and durable responses in the majority of WM patients. The rates of VGPR/CR increased with prolonged therapy. Disease progression was uncommon. The safety profile of long-term zanubrutinib therapy in these patients was tolerable. Clinical trial information: NCT02343120. Research Sponsor: BeiGene.

Efficacy and safety outcomes.

Assessment	TN WM (n = 24), %	R/R WM (n = 53), %	Total (n = 77), %
VGPR/CR rate	33.3	51.0	45.2
36-mo PFS	91.5	76.2	80.5
36-mo OS	100.0	80.2	84.8
AEs leading to discontinuation	12.5	13.2	13.0
≥Grade 3 AEs	45.8	64.2	58.4
Grade 5 AEs	0	9.4	6.5
Atrial fibrillation/ flutter	4.2	5.7	5.2
Major hemorrhage	8.3	1.9	3.9
≥Grade 3 infections	8.3	35.9	27.3

泽布替尼(BGB-3111)用于依鲁替尼治疗不耐受的CLL/SLL患者的II期、多中心、单臂研究。

TPS8066 **Poster Session (Board #399), Fri, 8:00 AM-11:00 AM**

Trial in progress: a phase II, multicenter, single-arm study of zanubrutinib (BGB-3111) in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma intolerant of prior treatment with ibrutinib. *First Author: Ian Flinn, Sarah Cannon Research Institute/ Tennessee Oncology, Nashville, TN*

Background: Ibrutinib (ibr), a Bruton tyrosine kinase inhibitor (BTKi), was shown to improve patient outcomes in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); however, adverse events (AEs) were the most common reason for discontinuing ibr (50% and 63% of discontinuations in relapse/refractory (R/R) and frontline patients, respectively; *Haematologica.* 2018:103:874). Zanubrutinib, an approved BTKi for mantle cell lymphoma, was specifically engineered to optimize selectivity. Pooled clinical data from 6 zanubrutinib monotherapy trials in B-cell malignancies (N=682 patients; R/R CLL/SLL [n=91]) suggested that zanubrutinib monotherapy was well tolerated and demonstrated a low rate of treatment discontinuation from AEs (9%; Tam, EHA 2019). Presented here is a trial-in-progress that will evaluate whether zanubrutinib monotherapy may serve as a therapeutic option for patients with CLL/SLL who have become ibr intolerant. **Methods:** The ongoing phase II, multicenter, US, single-arm, open-label study (NCT04116437, BGB-3111-215) will evaluate zanubrutinib monotherapy (160mg twice daily) as a treatment option for patients with CLL/SLL intolerant to prior ibr treatment. Approximately 60 patients will be enrolled from ~30 community medical centers. Key inclusion criteria include CLL/SLL requiring treatment per International Workshop on CLL criteria (*Blood.* 2018;131:2745) before ibr therapy, intolerance to ibr (defined as an unacceptable AE for which, per investigator's opinion, ibr treatment should be discontinued despite optimal supportive therapy), resolution of ibr-related AEs to grade ≤1 or baseline, and an ECOG PS 0-2. Key exclusion criteria include having an intervening cancer therapy between ibr and zanubrutinib, a documented disease progression during ibr treatment up to the time of enrollment, and a history of central nervous system (CNS) hemorrhage. The primary endpoint is frequency and severity of protocol-specified treatment-emergent AEs (diarrhea, myalgia, muscle spasm, arthralgia, hypertension, fatigue, rash, atrial fibrillation, and hemorrhage excluding CNS hemorrhage). The secondary endpoints include overall response rate, progression-free survival, and patient-reported outcomes. An exploratory endpoint was added to evaluate clinical effects (physical activity, treatment-related symptoms, and quality of life) using a smartphone app. Recruitment is ongoing. Clinical trial information: NCT04116437. Research Sponsor: BeiGene.

比较泽布替尼+利妥昔单抗和苯达莫司汀+利妥昔单抗治疗套细胞淋巴瘤(MCL)初治患者的疗效：III期、随机、开放标签研究

TPS8071 **Poster Session (Board #404), Fri, 8:00 AM-11:00 AM**

Trial in progress: A phase III, randomized, open-label study comparing zanubrutinib plus rituximab versus bendamustine plus rituximab in patients with previously untreated mantle cell lymphoma (MCL). *First Author: Martin H. Dreyling, University Hospital Großhadern, Ludwig Maximilians-University, Munich, Germany*

Background: Bruton tyrosine kinase (BTK) mediates B-cell proliferation, migration, and adhesion. BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MCL. Zanubrutinib is a next-generation BTK inhibitor that was designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases, with favorable pharmacokinetic and pharmacodynamic properties. Zanubrutinib monotherapy has been evaluated in 118 patients (pts) with relapsed/refractory MCL in 2 single-arm studies: BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120]. The overall response rate (ORR) by independent review committee (IRC) in both trials was 84% with median durations of response of 19.5 and 18.5 months, respectively. First-line treatment for MCL has failed to cure most pts, particularly elderly or transplant-ineligible groups, and chemotherapy-based approaches result in cumulative, long-term risks. The study described herein is designed to evaluate the safety and efficacy of zanubrutinib plus rituximab versus bendamustine plus rituximab in elderly pts and pts with comorbidities with previously untreated MCL who are ineligible for stem cell transplant. **Methods:** This ongoing phase 3, open-label study will enroll ≈500 pts to be randomized 1:1, stratified by MCL International Prognostic Index score (low vs intermediate/high), age (<70 vs ≥ 70 years), and geographic region (North America/Europe vs Asia-Pacific). In arm A, pts will receive up to six 28-day cycles of oral zanubrutinib 160 mg twice daily in combination with intravenous (IV) rituximab 375 mg/m^2 on day 1 of each cycle. After 6 cycles, zanubrutinib will continue as a monotherapy until progressive disease, unacceptable toxicity, or withdrawal of consent. In arm B, pts will receive up to six 28-day cycles of IV bendamustine 90 mg/m^2 on days 1 and 2 of each cycle and rituximab 375 mg/m^2 on day 1 of each cycle, followed by observation. Eligible pts must have histologically confirmed MCL and be aged ≥ 70 years, or 65-69 years with defined comorbidities. Disease response will be assessed per the 2014 Lugano Classification for non-Hodgkin lymphoma. The primary endpoint is progression-free survival (PFS) determined by IRC. Key secondary end points include PFS by investigator assessment, ORR, time to and duration of response, overall survival, and safety. Recruitment is ongoing. Clinical trial information: NCT04002297. Research Sponsor: BeiGene.