Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines

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Introduction:

Improved treatments are needed for relapsed or refractory (R/R) non-Hodgkin lymphoma (NHL) pts. Options are particularly limited for pts with B-cell NHLs who are R/R to CAR-T therapies or for whom a delay in effective therapy precludes this approach. Mosunetuzumab (M; RG7828) is a full-length, fully humanized immunoglobulin G1 (IgG1) bispecific antibody targeting both CD3 (on the surface of T cells) and CD20 (on the surface of B cells). In an ongoing Phase I/Ib study (GO29781; NCT02500407), promising efficacy and favorable tolerability were observed in R/R NHL pts (Budde et al. ASH 2018; Bartlett et al. ASCO 2019). We report complete remissions (CRs) with M in NHL pts who are R/R to CAR-T therapy, as well as activity with M re-treatment.

Methods:

GO29781 is an open-label, multicenter, Phase I/Ib, dose escalation and expansion study of M in R/R B-cell NHL. Data is presented from Group B, in which M is administered with step-up dosing on Days 1, 8, and 15 of Cycle 1, and then as a fixed dose on Day 1 of each subsequent 21-day cycle (maximum 17 cycles). Outcome measures include best objective response rate (ORR) by revised International Working Group criteria, maximum tolerated dose (MTD), and tolerability.

Results:

As of June 4, 2019, 218 pts in Group B had received any amount of M. Indolent NHL (iNHL) pts (n=72) were mainly follicular lymphoma (FL, n=69). Aggressive NHL (aNHL) pts (n=141) were mainly diffuse large B-cell lymphoma (DLBCL, n=87) or transformed FL (trFL, n=29). Median prior systemic therapies was 3 (range: 1-14). Twenty-three pts had prior CAR-T therapy (12 DLBCL, 6 trFL, 5 FL), and 16 were efficacy evaluable (7 DLBCL, 5 trFL, 4 FL). ORR and CR rates were 43.8% (7/16) and 25.0% (4/16, 2 DLBCL and 2 FL), respectively. Expansion of previously administered CAR-Ts after M administration was detected by quantitative PCR, in line with the mechanism of action of M.

Dose escalation is ongoing, supported by a positive exposure-response relationship for efficacy and broad therapeutic window with step-up dosing (Li et al. ASH 2019). Among efficacy-evaluable pts across all dose levels, ORR and CR rates were 64.1% (41/64) and 42.2% (27/64) in iNHL pts and 34.7% (41/119) and 18.6% (22/119) in aNHL pts, respectively.

CRs appeared durable, with 25/27 (92.6%) iNHL pts (median time from first CR: 5.8 months; range: 0.2-28.9) and 15/22 (68.2%) aNHL pts (median time from first CR: 8.8 months; range: 0.0-25.4) who achieved CR remaining in remission. Re-treatment with M was allowed in CR pts who relapsed. Four pts, including 1 in Group A who was initially treated with a fixed, non-step-up dosing schedule, received M re-treatment. One CR and 2 partial responses were observed. All three responses are ongoing, with the CR pt in second remission for 314 days.

The MTD of M has not been reached at doses up to 1/2/60mg (Cycle 1 Day 1, 8, and 15). Adverse events (AEs) leading to treatment withdrawal were uncommon (12/218, 5.5%). Cytokine release syndrome (CRS), graded by Lee criteria (Lee et al. Blood 2014;124:188-95), was observed in 28.4% of pts, and was mostly Grade (Gr) 1 (21.1%) or Gr 2 (6.0%); Gr 3 CRS occurred in 1.4% of pts. Most CRS events occurred in Cycle 1; 5 pts (2.7%) had CRS during or after Cycle 2. Three of 218 pts (1.4%) received tocilizumab for CRS management; all 3 events resolved without sequelae (for 1 pt, CRS resolved after the cutoff date). Neurological AEs (NAEs) were reported in 44% of pts (Gr 1, 28.0%; Gr 2, 12.8%; Gr 3, 3.2%). Common NAEs were headache (14.7%), insomnia (10.1%), and dizziness (9.2%). Potential immune effector cell-associated neurotoxicity syndrome (ICANS)-like NAEs of Gr 1 or Gr 2 confusional state occurred in 3 pts (1.4%) during cycles 1 and 2. The frequency of CRS and NAEs did not correlate with M exposure, likely due to step-up dosing, which effectively mitigates acute toxicities and allows administration of higher doses (Bartlett et

al. ASCO 2019; Li et al. ASH 2019). Among the 4 pts who were re-treated with M, no CRS was observed and NAEs were reported in 1 pt (Gr 1 headache and insomnia). Among the 23 pts who were R/R to CAR-T therapy, CRS occurred in 5 pts (21.7%; Gr 1, 13.0%; Gr 2, 4.3%; Gr 3, 4.3%) and NAEs in 8 pts (34.8%; Gr 1, 17.4%; Gr 2, 13.0%; Gr 3, 4.3%), with no ICANS-like events.

Conclusions:

M has favorable tolerability and durable efficacy in pts with heavily pre-treated R/R B-cell NHL, including CRs in pts with disease progression after CAR-T therapies. Preliminary data support the possibility for re-treatment with M.

KTE-X19, an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, in Patients (Pts) With Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL): Results of the Phase 2 ZUMA-2 Study

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Background:

Outcomes with salvage regimens in pts with MCL who progress after Bruton tyrosine kinase inhibitor (BTKi) therapy are poor, with a median overall survival (OS) of 5.8 months (Martin, et al. *Blood*. 2016) and few pts proceeding to allogeneic stem cell transplant. ZUMA-2 is a Phase 2,

registrational, multicenter, global study evaluating KTE-X19, an autologous anti-CD19 CAR T cell therapy, in pts with R/R MCL who received 1-5 prior therapies, including a BTKi. Here, we present interim efficacy and safety results from ZUMA-2.

Methods:

Eligible adults (aged ≥ 18 years) with R/R MCL had an ECOG score of 0 – 1 and ≤ 5 prior therapies, including chemotherapy, an anti-CD20 antibody, and a BTKi. Pts underwent leukapheresis and conditioning chemotherapy (cyclophosphamide 300 mg/m^2/d and fludarabine 30 mg/m^2/d for 3 days) followed by a single infusion of KTE-X19 at a target dose of 2×10^6 CAR T cells/kg. Pts could have received bridging therapy with dexamethasone, ibrutinib, or acalabrutinib after leukapheresis and before conditioning chemotherapy at the investigator's discretion. The primary endpoint was objective response rate (ORR [complete response (CR) + partial response]) assessed by an Independent Review Committee according to the Lugano Classification (Cheson, et al. *J Clin Oncol*. 2014). Interim efficacy endpoints were investigator-assessed using the revised IWG Response Criteria for Malignant Lymphoma (Cheson, et al. *J Clin Oncol*. 2007). Key secondary endpoints were duration of response (DOR), progression-free survival (PFS), OS, frequency of adverse events (AEs), levels of CAR T cells in blood, and levels of cytokines in serum. Efficacy and safety analyses included all pts who received KTE-X19. A total of 60 pts received KTE-X19; here, we present results in pts who had ≥ 1 year of follow-up. Updated safety and efficacy results in the full 60 pts, including pts who received revised AE management with the aim of decreasing toxicity, will be reported in the presentation.

Results:

As of May 30, 2018, 28 pts received KTE-X19 with ≥ 1 year of follow-up (median 13.2 months [range, 11.5 – 18.5]). The median age was 65 years (range, 50 – 75) and 86% of pts were male. Forty-three percent of pts had ECOG score of 1, 21% had blastoid morphology, 82% had stage IV disease, 50% had intermediate/high-risk MIPI, 86% received a median of 4 (range, 1 – 5) prior therapies, and 57% were refractory to last prior therapy. In 20/28 pts with available data, the median Ki-67 index was 38% (range, 5% – 80%). Eight pts received bridging therapy; all had disease present post-bridging.

Investigator-assessed ORR was 86% (95% CI, 67% – 96%) with a CR rate of 57% (95% CI, 37% – 76%). As of May 30, 2018, 75% of responders remained in response and 64% of treated pts had ongoing responses. The 12-month estimates of DOR, PFS and OS were 83% (95% CI, 60% – 93%), 71% (95% CI, 50% – 84%), and 86% (95% CI, 66% – 94%), respectively and the medians were not reached. The most common Grade ≥ 3 AEs (≥ 20% of pts) were anemia (54%), platelet count decreased (39%), neutropenia (36%), neutrophil count decreased (32%), white blood cell count decreased (29%), encephalopathy (25%), and hypertension (21%). Grade 3/4 cytokine release syndrome (CRS) assessed by Lee et al. (*Blood.* 2014) was reported in 18% of pts, most commonly manifesting as hypotension (14%), hypoxia (14%), and pyrexia (11%). Grade 3/4 neurologic events

(NE) were reported in 46% of pts and included encephalopathy (25%), confusional state (14%), and aphasia (11%). No Grade 5 CRS or NE occurred. All CRS events and most NE (15/17 pts) were reversible. Median time to onset and resolution of CRS was 2 days (range, 1 – 7) and 13 days (range, 4 – 60), respectively. Median time to onset of NE was 6 days (range, 1 – 15) and median time to resolution was 20 days (range, 9 – 99). There was 1 Grade 5 AE of organizing pneumonia that was considered related to conditioning chemotherapy. Median CAR T cell levels as measured by peak and area under the curve were 99 cells/μL (range, 0.4 – 2589) and 1542 cells/μL (range, 5.5 – 27239), respectively. Peak CAR T cell expansion was observed between Days 8 and 15 and declined over time.

Conclusions:

ZUMA-2 is the first multicenter Phase 2 study of CAR T cell therapy in pts with R/R MCL. With ≥ 1 year of follow-up, KTE-X19 demonstrated significant and durable clinical benefit, including a majority of pts achieving CR, and a manageable safety profile in pts with R/R MCL for whom there are no curative treatment options.