2. SYNOPSIS

Name of Sponsor: Amgen Inc.

Name of Finished Product: To be determined.

Name of Active Ingredients: Blinatumomab and AMG 404.

Title of Study: A Phase 1b Open-label Study Investigating the Safety, Tolerability, Pharmacokinetics, and Efficacy of Administration of Blinatumomab in Combination With AMG 404 for the Treatment of Adults With Relapsed or Refractory B-cell Precursor Acute Lymphoblastic Leukemia (ALL)

Investigators and Study Centers:

This study was conducted at 22 centers in Australia, Austria, France, Germany, Italy, Netherlands, Spain, United Kingdom, and the United States (see Section 16.1.4).

Publication:

Papayannidis C, Borlenghi E, Yeung D, et al. A phase 1b study of blinatumomab with the anti-programmed cell death (PD)-1 antibody AMG 404 in adults with relapsed/refractory (R/R) B-cell precursor acute lymphoblastic leukemia (ALL). *J of Clin Oncol*. 2022;40 (16):e19003-e19003. Abstract Number e19003.

Study Period:

02 October 2020 (first subject enrolled) – 24 January 2023 (last subject completed study).

Development Phase: 1b

Previous Reports for This Study:

None.

Study Rationale:

Blinatumomab is approved for the treatment of patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (R/R B-ALL). AMG 404 is a monoclonal antibody that binds to programmed cell death-1 (PD-1). Programmed cell death-1 has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands. Programmed cell death ligand-1 (PD-L1) is increased in patients with relapsed ALL and in patients with ALL refractory to blinatumomab. The combination of blinatumomab with anti-PD-1/PD-L1 therapy such as AMG 404 may overcome and/or prevent blinatumomab resistance. This phase 1b study was planned to evaluate safety, tolerability, pharmacokinetics (PK), and efficacy of blinatumomab and AMG 404 combination in adult patients with R/R B-ALL.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of blinatumomab in combination with AMG 404 in adults with R/R B-ALL • To estimate the maximum tolerated dose and recommended phase 2	• Dose-limiting toxicities (DLTs) • Treatment-emergent adverse events, serious treatment-emergent adverse events, treatment-related treatment-emergent adverse

Objectives	Endpoints
dose (RP2D) of AMG 404 when combined with continuous intravenous infusion (cIV) blinatumomab	events, and adverse events of interest (EOI)
Secondary	
• To evaluate the efficacy of blinatumomab and AMG 404 combination therapy in the treatment of R/R B-ALL	• Complete remission (CR)/complete remission with partial hematological recovery (CRh) within the first 2 cycles and across all cycles • CR within the first 2 cycles and across all cycles • Duration of CR • Duration of CR/CRh
• To characterize PK following blinatumomab and AMG 404 combination therapy	• Blinatumomab PK parameters • AMG 404 PK parameters
• To evaluate the immunogenicity of blinatumomab and AMG 404 following blinatumomab and AMG 404 combination therapy	• Anti-blinatumomab antibodies • Anti-AMG 404 antibodies

Methodology:

This was a multicenter, nonrandomized, open-label, phase 1b study in adults with R/R B-ALL, that evaluated safety, tolerability, PK, and efficacy of blinatumomab and AMG 404 combination therapy. The study consisted of up to a 3-week screening and prephase period, a treatment period, a safety follow-up (SFU) visit 30 (+ 7) days after the last dose of blinatumomab, and an end of study (EOS) visit 140 (+ 7) days after the last administration of AMG 404. Subjects received at least 2 and up to 5 cycles of combination therapy (blinatumomab + AMG 404).

The study consisted of dose exploration and dose expansion stages. Dose exploration began with cohort 1. For the dose expansion phase, the recommended dose and schedule were determined by the dose level review team (DLRT) using the totality of the clinical and laboratory data from the dose exploration stage.

Cohort 1: Each cycle consisted of 42 days and included a 14-day blinatumomab treatment-free interval between days 29 and 42. Blinatumomab cIV was given on days 1 to 28. In cycle 1, blinatumomab was administered at 9 μg/day on days 1 to 7, then at 28 μg/day on days 8 to 28 for subjects ≥ 45 kg, and 5 μg/m^2/day (maximum 9 μg/day), on days 1 to 7, then 15 μg/m^2/day (maximum 28 μg/day) on days 8 to 28 for subjects < 45 kg. In cycles 2 to 5, blinatumomab was administered at a dose of 28 μg/day for subjects ≥ 45 kg and 15 μg/m^2/day (maximum 28 μg/day) for subjects < 45 kg on days 1 to 28. AMG 404 was administered 240 mg intravenously (IV) over approximately 30 minutes starting on day 11 of cycle 1 and dosed every 4 weeks (Q4W) thereafter; however, dosing could be delayed by up to 4 days in the event of any adverse or safety event. AMG 404 was dosed on days 11 and 39 of cycles 1, 3, and 5; and day 25 of cycles 2 and 4.

The DLT-evaluable period (DLT window) began with the first dose of AMG 404 and included 28 days after the second AMG 404 dose was administered. After the DLT evaluation period, the DLRT evaluated all available safety, laboratory, PK, and pharmacodynamics (PD) data as well as rules generated from a modified toxicity probability interval algorithm to guide dose finding decisions.

Cohort 2a: The first treatment cycle in cohort 2a was of 44 days, as dose 1 of AMG 404 was given on day 1 and blinatumomab was started on day 3. For subsequent cycles, blinatumomab was given on days 1 to 28. In cycle 1, blinatumomab was administered as cIV for 28 days at 9 μg/day on days 3 to 9, then at 28 μg/day on days 10 to 30 for subjects ≥ 45 kg and 5 μg/m^2/day (maximum 9 μg/day), on days 3 to 9, then 15 μg/m^2/day (maximum 28 μg/day) on days 10 to 30 for subjects < 45 kg. In cycles 2 to 5, blinatumomab was administered at a dose of 28 μg/day on days 1 to 28 for subjects ≥ 45 kg and 15 μg/m^2/day (maximum 28 μg/day) for subjects < 45 kg. AMG 404 was administered IV over approximately 30 minutes starting on day 1 of cycle 1 and dosed Q4W thereafter. Each cycle included a 14-day blinatumomab treatment-free interval between days 29 and 42 (days 31 to 44 in cycle 1). AMG 404 was dosed on days 1 and 29 of treatment cycle 1, days 13 and 41 of cycles 2 and 4, and day 27 of cycles 3 and 5. The planned dose of AMG 404 in cohort 2a was 480 mg.

Cohorts 1c and 2b: Cohort 1c, de-escalation, if warranted, and cohort 2b was to be considered, if cohort 2a was unsuitable. The treatment cycles of blinatumomab and AMG 404 for cohorts 1c and 2b were same as that mentioned above for cohort 2a. The planned doses for AMG 404 in cohorts 1c and 2b, if de-escalation was warranted, were 120 mg Q4W and 240 mg Q4W, respectively.

Dexamethasone 20 mg IV was given within 6 hours before start of the first dose of blinatumomab and up to 24 mg daily could be used as treatment for any cytokine release syndrome (CRS) and/or neurotoxicity associated with blinatumomab infusion.

Number of Subjects Planned: Up to a total of 15 subjects at RP2D, not exceeding 27 total were planned (including dose exploration and dose expansion).

Diagnosis and Main Criteria for Eligibility:

Adult subjects with B-ALL with any of the following criteria were eligible: refractory to primary induction or refractory to salvage therapy, in untreated first, second or greater relapse or refractory relapse or relapse after salvage therapy, relapse at any time after allogeneic hematopoietic stem cell transplantation (alloHSCT), ≥ 5% blasts in the bone marrow, Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2, relapsed or refractory B-ALL Philadelphia chromosome-positive disease and that were intolerant or refractory to prior tyrosine kinase inhibitors.

Subjects with following criteria were excluded from the study: had history or presence of clinically relevant central nervous system (CNS) pathology, presence of ALL in the CNS, isolated extramedullary disease, current autoimmune disease, or history of autoimmune disease with potential CNS involvement, alloHSCT within 12 weeks before the start of protocol-specified therapy, active acute or chronic graft versus host disease cancer chemotherapy within 14 days before study day 1, immunotherapy within 4 weeks before start of protocol-specified therapy, and other medical conditions.

Investigational Products, Dose and Mode of Administration, Manufacturing Batch Number:

Blinatumomab: For subjects ≥ 45 kg: 9/28 μg/day as a cIV per cycle for up to 5 cycles. For subjects < 45 kg: 5 μg/m^2/day to maximum 9 μg/day (from days 1 to 7) and

15 μg/m^2/day (maximum 28 μg/day). One cycle consisted of 6 weeks (4 weeks cIV and 2 weeks infusion-free interval).

AMG 404: AMG 404 240 mg (cohorts 1 and 2b), or 480 mg (cohort 2a), or 120 mg (cohort 1c) Q4W, as an IV infusion over 30 minutes.

Manufacturing batch numbers are provided in Section 16.1.6.

Duration of Treatment:

For subjects who completed the study from the date of first dose through optional cycle 5, the entire duration was approximately 54 weeks.

Statistical Methods:

General Considerations: Descriptive statistics were provided for selected demographics, safety, PK, PD, and efficacy data by dose, dose schedule, and time. Analytical and statistical methods used for exploratory biomarkers are described in the separate Contributing Scientist Report. Descriptive statistics on continuous data included means, medians, standard deviations, and ranges, while categorical data were summarized using frequency counts and percentages. Response rates were presented with 95% exact confidence intervals. Time-to-event endpoints were summarized using the Kaplan-Meier (KM) method. Graphical summaries of the data were presented.

Sample Size Considerations: Up to 15 subjects at RP2D, not exceeding 27 total (including dose exploration and dose expansion) were planned.

Planned Analyses:

Interim Analysis and Early Stopping Guidelines: The DLRT reviewed all accumulating data after each group in dose exploration or all subjects in dose expansion completed the DLT evaluation period. The modified toxicity probability interval method was used as a guide for dose exploration. The DLRT assessed safety after the first 6 subjects treated at the RP2D had completed the DLRT window. All subjects treated at RP2D both from the dose exploration and dose expansion phases were included in interim safety analyses. The stopping rules could use a Bayesian approach to terminate the study if there was posterior probability > 80% that DLT rate was > 30%.

Primary Analysis: The primary analysis occurred when all subjects completed the EOS visit or terminated the study early. The primary analysis was also the final analysis. The purpose of the final analysis was to summarize efficacy and safety after all subjects completed EOS visit.

Summary of Results:

Subject Disposition:

A total of 21 subjects were screened and 17 subjects were enrolled in the study (8 in cohort 1 [blinatumomab + AMG 404 240 mg]; 9 in cohort 2a and dose expansion cohort combined [blinatumomab + AMG 404 480 mg, hereafter, referred to as cohort 2a + dose expansion]). Of the 17 subjects, 16 (94.1%) received blinatumomab and AMG 404 and 1 (5.9%) did not receive blinatumomab and AMG 404. Of the 16 subjects who received blinatumomab and AMG 404, 3 (17.6%) completed treatment and 13 (76.5%) discontinued treatment. The reasons for discontinuation of blinatumomab and AMG 404 were disease progression (7 subjects [41.2%]); and protocol-specified criteria, death, adverse event (2 subjects [11.8%] each). Overall, 7 subjects (41.2%) completed the study. The remaining 10 subjects (58.8%) discontinued the study, 6 (35.3%) died,

2 (11.8%) discontinued because of sponsor's decision, 1 (5.9%) withdrew consent, and 1 (5.9%) was lost to follow-up.

Baseline Demographics:

Sex: 11 subjects (68.8%) men and 5 subjects (31.3%) women.

Age: Mean (SD) age was 46.6 (17.9) years.

Race: 11 subjects (68.8%) White, 2 subjects (12.5%) Black or African American, 2 subjects (12.5%) other, 1 subject (6.3%) Chinese.

Ethnicity: 12 subjects (75.0%) not Hispanic or Latino, 4 subjects (25.0%) Hispanic or Latino.

Efficacy Results:

Primary Efficacy Endpoint: The study did not have a primary efficacy endpoint.

Secondary Efficacy Endpoints:

Overall rate of CR/CRh (6 subjects [37.5%] achieved CR and 2 subjects [12.5%] achieved CRh) within the first 2 cycles of treatment initiation was 50.0% (95% CI: 24.7%, 75.3%).

Overall rate of CR/CRh (6 subjects [37.5%] achieved CR and 2 subjects [12.5%] achieved CRh) across all treatment cycles was 50.0% (95% CI: 24.7%, 75.3%). The CR across all treatment cycles was 37.5% (95% CI: 15.2%, 64.6%).

The KM estimate of median duration of CR was not reached. The KM estimate of duration of CR at 6 months was 53.3% (95% CI: 6.8, 86.3).

The KM estimate of median duration of CR/CRh was not reached. The KM estimate of duration of CR/CRh at 6 months was 51.4% (95% CI: 11.8, 81.3).

Other Results:

Pharmacokinetics Results: Blinatumomab was administered by cIV at dose levels of 9 and 28 μg/day to adult subjects with blinatumomab dosing starting on cycle 1 day 1 for cohort 1 and cycle 1 day 3 for cohort 2a and dose expansion cohort. In cycle 1, mean (SD) steady-state concentration (C_{ss}) values were 152 (70.2) and 676 (478) pg/mL, respectively, for subjects from cohort 1 and 210 (177) and 638 (274) pg/mL, respectively, for subjects from cohort 2a and dose expansion cohort combined (hereinafter referred to as cohort 2a + dose expansion). Mean C_{ss} increased in an approximately dose proportional manner (within subjects) in cycle 1 with a 4.4- and 3.0-fold increase in C_{ss} for cohort 1 and cohort 2a + dose expansion, respectively, for a 3.1-fold increase in dose. Blinatumomab C_{ss} values at a dose level of 28 μg/day were consistent between cycles 1 and 2. Mean (SD) clearance (CL) values for cohort 1 of 4.34 (6.13) L/hr were within range of the corresponding values for cohort 2a + dose expansion of 2.08 (0.720) L/hr. Taken together, PK parameters for blinatumomab when given in combination with AMG 404 were similar between subjects from cohort 1 and subjects from cohort 2a + dose expansion. In addition, blinatumomab PK parameters when administered in combination with AMG 404 were consistent with those previously reported in adult subjects with R/R B-ALL administered blinatumomab as a monotherapy from other studies.

AMG 404 was administered as a 30-minute IV infusion at doses of 240 mg Q4W starting on cycle 1 day 11 in cohort 1 and 480 mg Q4W starting on cycle 1 day 1 in cohort 2a

and dose expansion cohort. After first IV Q4W administration of AMG 404, maximum observed serum concentrations (C_{max}) occurred near the end of infusion with median time C_{max} (time to reach maximum concentration [t_{max}]) ranging from 1.5 to 2.5 hours in cycle 1, as expected for a 30-minute IV infusion. AMG 404 exposures increased in an approximately dose-proportional manner over the dose range of 240 to 480 mg. Geometric mean C_{max} and area under the concentration-time curve (AUC) from time 0 to 28 days postdose ($AUC_{0\text{-}28d}$) values increased 2.5- and 2.6-fold, respectively, in cycle 1, for a 2.0-fold increase in dose. AMG 404 PK parameters when administered in combination with blinatumomab in this study were consistent with those previously reported in adult subjects with advanced solid tumors administered AMG 404 as a monotherapy.

Anti-blinatumomab and Anti-AMG 404 Antibodies: Overall, no subjects tested positive for binding or neutralizing antibodies to blinatumomab and to AMG 404.

Safety Results:

Extent of Exposure: Overall, mean (SD) number of cycles completed were 1.8 (1.9). The mean (SD) duration of blinatumomab treatment was 57.35 (48.41) days and mean (SD) cumulative dose for blinatumomab was 1436.85 (1290.27) μg. The mean (SD) number of AMG 404 doses was 3.5 (2.8) doses and mean (SD) cumulative dose for AMG 404 was 1275.0 (1083.0) mg. Blinatumomab dose interruptions in subjects overall occurred for the reasons of adverse event for 9 subjects (56.3%) and 'other' for 3 subjects (18.8%). No dose interruptions were reported for AMG 404.

Dose-limiting Toxicity: Of the 10 subjects that were DLT-evaluable; 3 were in cohort 1 and 7 were in cohort 2a + dose expansion; no subject reported DLT-events across the cohorts.

Adverse Events: All 16 subjects (100%) had treatment-emergent adverse events; hereafter referred to as adverse events. Adverse events by preferred term reported for > 25% of subjects overall were pyrexia (11 [68.8%]), CRS (8 [50.0%]), hypokalemia (6 [37.5%]), and neutropenia and sinus tachycardia (5 [31.3%] each).

Grade ≥ 3 Adverse Events: Overall, 15 subjects (93.8%) had grade ≥ 3 adverse events; that reported for > 1 subject were neutropenia (5 [31.3%]) and encephalopathy (2 [12.5%]).

Treatment-related Adverse Events: Overall, 14 subjects (87.5%) had blinatumomab-related and 7 subjects (43.8%) had AMG 404-related adverse events. Blinatumomab-related adverse events by preferred term reported for ≥ 10% of subjects overall were CRS (8 [50.0%]); pyrexia (6 [37.5%]); neutropenia (3 [18.8%]); and thrombocytopenia, encephalopathy, and headache (2 [12.5%] each]). No subject had AMG 404-related adverse event by preferred term reported for > 1 subject.

Withdrawal From Investigational Product Due to Adverse Events: Overall, adverse events leading to discontinuation of blinatumomab and AMG 404 were reported for 4 subjects (25.0%) each, the adverse events by preferred term were pain, ALL, encephalopathy, and seizure (1 subject [6.3%] each]). Overall, 9 subjects (56.3%) had adverse events leading to interruption of blinatumomab. No subject had adverse event leading to interruption of AMG 404

Serious Adverse Events: Overall, serious adverse events were reported for 13 subjects (81.3%). Serious adverse events by preferred term reported for > 1 subject were CRS and encephalopathy (2 subjects [12.5%] each]). Blinatumomab-related serious adverse events were reported for 6 subjects (37.5%) overall; that reported for

> 1 subject was CRS (2 [12.5%]). AMG 404-related serious adverse events were reported for 2 subjects (12.5%) overall; events by preferred term were cognitive disorder and encephalopathy in 1 subject (6.3%) each.

Fatal Adverse Events: Overall, 3 subjects (18.8%) had fatal adverse events; pneumonia and ALL (1 subject [12.5%] each in cohort 1) and cardiac arrest (1 subject [12.5%]) in cohort 2a + dose expansion. All 3 fatal adverse events were considered by the investigator as not related to investigational products. Fatal adverse events including the extended period were reported for 6 subjects (37.5%) overall. The fatal adverse events reported in extended period were ALL (2 subjects [25.0%]) and pneumonia (1 subject [12.5%]) in cohort 1 and cardiac arrest, condition aggravated, and ALL (1 subject [12.5%] each) in cohort 2a + dose expansion.

Events of Interest for Blinatumomab: Adverse EOI identified for blinatumomab at start of this study were capillary leak syndrome, CRS, decreased immunoglobulins, elevated liver enzyme, embolic and thrombotic events, immunogenicity, infections, infusion reactions, leukoencephalopathy, medication errors, neurologic events, neutropenia and febrile neutropenia, pancreatitis, and tumor lysis syndrome and are summarized below

- Capillary Leak Syndrome: No subjects had EOI of capillary leak syndrome.
- Cytokine Release Syndrome: Overall, 8 subjects (50.0%) had EOI of CRS, the preferred term was CRS for all subjects. The median time to first onset of EOI of CRS was 4.0 days (range: 1 to 50 days). Two subjects (12.5%) had serious CRS, 1 subject (6.3%) had grade ≥ 3 CRS, and 4 subjects (25.0%) had CRS event that led to interruption of blinatumomab. The median time to first grade ≥ 3 EOI of CRS event was 2.0 days. No EOI of CRS had the outcome reported as resolved; hence the duration of CRS was not reported.
- Decreased Immunoglobulins: Overall, 1 subject (6.3%) had EOI of decreased immunoglobulins; the events by preferred term were hypogammaglobulinemia and immunoglobulins decreased. None of these events were deemed serious or grade ≥ 3 in severity, or led to interruption or discontinuation of blinatumomab or AMG 404.
- Elevated Liver Enzyme: Overall, 7 subjects (43.8%) had EOI of elevated liver enzyme; by preferred term, events reported (≥ 2 subjects) were alanine aminotransferase (ALT increased 4 [25.0%]), aspartate aminotransferase (AST increased, 3 [18.8%]), and gamma-glutamyl transferase (GGT increased, 2 [12.5%]). One subject (6.3%) had serious EOI of elevated liver enzyme; by preferred term, event was hepatic enzyme increased. Two subjects (12.5%) had grade ≥ 3 EOI of elevated liver enzyme; by preferred term events reported in 1 subject (6.3%) each were ALT increased, AST increased, GGT increased, and hepatic enzyme increased. Two subjects (12.5%) had EOI of elevated liver enzyme that led to interruption of blinatumomab; by preferred term events reported in 1 subject (6.3%) each were ALT increased, AST increased, GGT increased, and hepatic enzyme increased.
- Embolic and Thrombotic Events: Overall, 1 subject (6.3%) had EOI of embolic and thrombotic events; by preferred term, event was deep vein thrombosis. This event was not deemed serious or of grade ≥ 3 in severity, or led to interruption or discontinuation of blinatumomab or AMG 404.
- Immunogenicity: No subjects had EOI of immunogenicity.

- Infections: Overall, 9 subjects (56.3%) had EOI of infections, by preferred term events reported in ≥ 2 subjects were coronavirus disease 2019 (COVID-19), cellulitis, and vascular device infection (2 [12.5%] each); median time to first EOI of infection was 15.0 days (range: 1 to 258 days). Five subjects (31.3%) had serious EOI of infections; by preferred term, events reported in 1 subject (6.3%) each were COVID-19, COVID-19 pneumonia, pneumonia, sepsis, sialoadenitis, and urosepsis. Six subjects (37.5%) had grade ≥ 3 EOI of infections; events by preferred term, reported in 1 subject (6.3%) each were COVID-19 pneumonia, cellulitis, conjunctivitis, perineal abscess, pneumonia, puncture site cellulitis, sepsis, sialoadenitis, urosepsis, and vascular device infection. The median time to first grade ≥ 3 EOI of infection was 57.5 days (range: 11 to 258 days). No EOI of infection had the outcome reported as resolved; hence the duration of infection was not reported. Two subjects (12.5%) had EOI of infections that led to interruption of blinatumomab; events by preferred term were COVID-19 pneumonia, sepsis, and vascular device infection (1 subject [6.3%] each). One subject (12.5%) had fatal EOI of infection in cohort 1 (preferred term: pneumonia). No fatal EOI of infection was reported in cohort 2a + dose expansion.
- Infusion Reactions: Overall, 14 subjects (87.5%) had EOI of infusion reactions, by preferred term (≥ 2 subjects) were pyrexia (11 [68.8%]), CRS (8 [50.0%]), myalgia (4 [25.0%]), hypotension (3 [18.8%]), and rash (2 [12.5%]). Three subjects (18.8%) had serious EOI infusion reactions, events were CRS (2 [12.5%]) and acute kidney injury (1 [6.3%]). Four subjects (25.0%) had grade ≥ 3 EOI of infusion reactions, events reported in 1 subject (6.3%) each were acute kidney injury, CRS, hypertension, and pyrexia. Five subjects (31.3%) had EOI of infusion reactions that led to interruption of blinatumomab; events were CRS (4 [25.0%]), hypotension and pyrexia (1 [6.3%] each).
- Leukoencephalopathy: No subjects had EOI of leukoencephalopathy.
- Medication Errors: No subjects had EOI of medication errors.
- Neurologic Events: Overall, 11 subjects (68.8%) had EOI of neurologic events, by preferred terms, events reported (≥ 2 subjects) were headache (4 [25.0%]); and encephalopathy, insomnia, and tremor (2 [12.5%] each); median time to first onset was 11.0 days (range: 2 to 148 days). Three subjects (18.8%) had serious EOI of neurologic events; encephalopathy (2 [12.5%]), cognitive disorder and seizure (1 [6.3%] each). Three subjects (18.8%) had grade ≥ 3 EOI of neurologic events; encephalopathy (2 [12.5%]) and headache (1 [6.3%]); median time to first grade ≥ 3 EOI was 16.0 days (range: 11 to 40 days). No neurologic event had the outcome reported as resolved; hence the duration of neurologic event was not reported. Two subjects (12.5%) had EOI of neurologic events that led to interruption of blinatumomab; events were cognitive disorder, encephalopathy, and seizure (1 subject [6.3%] each). Two subjects (12.5%) had EOI of neurologic events that led to discontinuation of blinatumomab; events were encephalopathy and seizure (1 subject [6.3%] each). Two subjects (12.5%) had EOI of neurologic events that led to discontinuation of AMG 404; events were encephalopathy and seizure (1 subject [6.3%] each).
- Neutropenia and Febrile Neutropenia: Overall, 7 subjects (43.8%) had EOI of neutropenia and febrile neutropenia, by preferred term, event reported (≥ 2 subjects) was neutropenia (5 [31.3%]). Two subjects (12.5%) had serious EOI of neutropenia

and febrile neutropenia; events were febrile neutropenia and neutropenic colitis (1 [6.3%] each). Grade ≥ 3 EOI of neutropenia and febrile neutropenia reported in 7 subjects (43.8%), by preferred term, event (≥ 2 subjects) was neutropenia (5 [31.3%]). None of these events led to interruption or discontinuation of blinatumomab or of AMG 404.

- Pancreatitis: No subject had EOI of pancreatitis.
- Tumor Lysis Syndrome: Overall, 1 subject (6.3%) had grade ≥ 3 EOI, by preferred term, event was tumor lysis syndrome.

Events of Interest for AMG 404: The adverse events of interest identified for AMG 404 were noninfectious diarrhea and immune-mediated events associated with oncologic immunotherapies.

- Noninfectious Diarrhea: Overall, 1 subject (6.3%) had serious and grade ≥ 3 EOI; by preferred term, events were colitis and neutropenic colitis. The EOI of neutropenic colitis was of grade ≥ 3 severity.
- Immune-mediated Events Associated With Oncologic Immunotherapies: No subjects had EOI of immune-mediated events associated with oncologic immunotherapies.

No notable trends in clinical laboratory results or vital signs were observed during the study.

Conclusions:

The combination dose of blinatumomab as cIV (9 μg/day on days 1 to 7, then at 28 μg/day on days 8 to 28 in cycle 1, and then at 28 μg/day on days 1 to 28 in cycles 2 to 5) with AMG 404 at 240 mg (cycle 1 day 11 and then Q4W) was determined as safe and tolerable. The RP2D of AMG 404 was determined at 480 mg Q4W (starting on cycle 1 day 1) when combined with blinatumomab cIV (9/28 μg/day for 28 days); the demonstrated efficacy of blinatumomab at this dose was not considered superior to blinatumomab monotherapy. Amgen determined that the combination of blinatumomab and AMG 404 is without clear clinical benefit for patients and thus this study was closed for further patient enrollment. The premature study closure was not related to safety concerns of blinatumomab or AMG 404.

Report Date:

Document Version	Date
Final Analysis	18 August 2023