Safety and efficacy of talacotuzumab plus decitabine or decitabine alone in patients with acute myeloid leukemia (AML) not eligible for chemotherapy: Results from a multicenter, randomized, phase2/3 study

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Summary

Talacotuzumab, a humanized anti-CD123 monoclonal antibody, was evaluated in combination with decitabine in elderly patients with acute myeloid leukemia (AML) not eligible for intensive chemotherapy. A multicenter, phase 2/3 study was initiated to determine the recommended phase 2 dose (RP2D) of talacotuzumab (part A) followed by an open-label, randomized comparison of talacotuzumab in combination with decitabine versus decitabine alone to assess achievement of complete response (CR) and overall survival (OS) in part B. Ten patients were enrolled in part A and 316 in part B; the results presented here are based on a database lock on January 25, 2018. Part A confirmed the RP2D of talacotuzumab to be 9 mg/kg. In Part B, CR was achieved in 12/80 (15%) patients receiving combination therapy and in 9/82 (11%) patients receiving decitabine alone (odds ratio: 1.4; 95% CI: 0.6–3.6; p=0.44). Median (95% CI) OS was 5.36 months (4.27–7.95) for talacotuzumab + decitabine versus 7.26 months (6.47–8.64) for decitabine alone (hazard ratio: 1.04; 95% CI: 0.79–1.37; p=0.78). Combination treatment showed no improvement in efficacy versus decitabine alone, resulting in the Independent Data Monitoring Committee's recommendation of early termination of enrollment and discontinuation of talacotuzumab treatment.

Introduction

Treatment options for older patients with acute myeloid leukemia (AML) have been limited; although younger patients with AML can generally tolerate induction chemotherapy, potential risks of standard induction outweigh the benefits in many older AML patients (Kantarjian, *et al* 2010). Treatment alternatives for these patients were limited for many years to either supportive care or low-intensity treatments such as low-dose cytarabine or hypomethylating agents (decitabine or azacitidine). (Dohner, *et al* 2017). Only modest improvements in overall survival (OS) were achieved with both decitabine and azacitidine compared to low-dose cytarabine, with median OS still less than 1 year for patients over 65 years of age.(Dohner, *et al* 2017). Combination strategies based on these agents have been explored to improve outcome while maintaining adequate tolerability for older patients. Venetoclax combined with decitabine or azacitidine has recently gained accelerated approval in the US based on response rates from a non-randomized study.(DiNardo, *et al* 2019)

Leukemic stem and progenitor cells (LSPCs) possess biological properties that render these cells resistant to conventional chemotherapies (Pollyea and Jordan 2017). Thus, targeted approaches to eliminate LSPCs are currently being investigated to improve prognosis and prevent relapses in patients with AML (Hanekamp, *et al* 2017). Human interleukin-3 receptor alpha chain (IL-3Rα or CD123), the major binding protein for IL-3, is overexpressed on AML blast cells and LSPCs (Jordan, *et al* 2000). Upregulated expression of CD123 has been associated with higher blast cells counts at diagnosis and poorer complete response (CR) to standard treatment and survival rates in AML (Graf, *et al* 2004). As a result, increased expression of CD123 on AML-LSPCs provides an opportunity for therapeutic monoclonal antibody (mAb) targeting (Jin, *et al* 2009, Xie, *et al* 2017).

Therapeutic targeting of LSPCs, in addition to leukemic blast cells, could potentially enhance the rate and duration of response in AML patients. The dismal prognosis of patients with advanced age not eligible for intensive chemotherapy suggest this setting may be the best match to demonstrated clinical benefit with Talacotuzumab. Talacotuzumab, a second generation humanized anti-CD123 mAb, binds to CD123 and inhibits the downstream IL-3 signaling cascade. Talacotuzumab has been engineered to have a 100-fold higher affinity to Fc receptor CD16 on natural killer cells, resulting in enhanced ability to induce antibody-dependent cellular cytotoxicity (ADCC) against target cells expressing CD123 (such as AML blasts and LSPCs) (Xie, *et al* 2017). Decitabine promotes re-expression of tumor suppressor genes (Chen et al; 2011, Cancer; 117: 4424–38) and has been used extensively in patients not candidates for intensive chemotherapy (Dohner, et al 2017). However, the median OS following decitabine treatment is less than 8 months for patients ≥65 years of age (Cashen, et al 2010, Kantarjian, et al 2012). The combination of decitabine and talacotuzumab was hypothesized to have complimentary/synergistic effects on leukemic cells due to different underlying mechanisms of action and differences in the leukemic cell populations targeted by these two agents.

The current study was designed to confirm the RP2D of talacotuzumab and to evaluate the CR rate and OS following either talacotuzumab plus decitabine or decitabine alone in patients with previously untreated AML not eligible for intensive induction chemotherapy.

Methods

Patients

In Part A, patients with AML (per WHO 2008 criteria) were eligible if they were treatment naïve or had refractory or relapsed disease. Part B included patients ≥65 years-old with previously untreated AML not eligible for standard intensive induction chemotherapy or allogeneic hematopoietic stem cell transplantation. Inclusion and exclusion criteria are described in detail in the supplementary file.

Study design

This study was a 2-part, open-label (Part A) and randomized (Part B), phase 2/3 study conducted across 96 sites in 15 countries from August 2015 to January 2018. The screening phase was up to 28 days prior to treatment initiation (part A) or randomization (part B). Part A was conducted to assess the safety and confirm the recommended phase 2 dose (RP2D) of talacotuzumab in patients with AML eligible for experimental therapy. Part B was conducted to assess the CR rate and OS in previously untreated patients with AML considered unfit for intense induction chemotherapy.

In Part A, at least 6 patients were to be enrolled and receive 1 dose of talacotuzumab monotherapy at 9 mg/kg on Day 1 of every 28-day cycle as a 180-minute intravenous (IV) infusion. Dose-limiting toxicities (DLTs) were assessed during the subsequent 14-day DLT evaluation period. Pharmacokinetic (PK) and pharmacodynamic (PD) assessments were conducted during the 14-day talacotuzumab evaluation period. RP2D was established by a study evaluation team (SET). Patients in Part A continued the study (in Part A) and started subsequent cycles of combined study therapy with IV decitabine (20 mg/m^2/d) on Days 1-5 followed by 9 mg/kg (or a lower dose if determined by the SET) talacotuzumab on Day 8 and Day 22 of a 28-day cycle.

Part B was initiated after the RP2D of talacotuzumab was confirmed; Eligible patients were randomized in a 1:1 ratio using an interactive web response system (IWRS) to receive talacotuzumab + decitabine or decitabine alone. Randomization was stratified by baseline ECOG performance status score (0-1 versus 2), type of AML (*de novo* versus secondary) and cytogenetic risk by European Leukemia Net 2010 (Dohner, *et al* 2010) cytogenetic characterization (adverse versus others).

Treatment

Patients in both treatment arms received decitabine 20 mg/m^2 per day on Days 1 to 5 of each 28-day cycle. Patients in the talacotuzumab + decitabine group were administered 9 mg/kg IV talacotuzumab on Day 8 and Day 22 every 28 days. An Independent Data Monitoring Committee (IDMC) was established to evaluate safety and efficacy data during Part B, including the formal efficacy interim analyses and make recommendations for study conduct.

An Institutional Review Board or Independent Ethics Committee approved the study protocol and amendments. The study was conducted in accordance with ethical principles of the Declaration of Helsinki, Good Clinical Practices (GCP), and applicable regulatory requirements. All patients provided written informed consent before participating in the study. This trial was registered at ClinicalTrials.gov (NCT02472145).

Efficacy assessments

The primary efficacy endpoints were CR rate (proportion of patients achieving CR) and OS (time from randomization to death from any cause). Disease responses were evaluated according to ELN response criteria (Dohner, *et al* 2010) by investigators and a blinded independent data review committee (IRC). Disease status based on independent central review was the primary source for efficacy analyses.

Key secondary efficacy endpoints included: event-free survival (EFS; time from randomization to treatment failure, relapse from CR or CR with incomplete blood count recovery [CRi], or death, whichever occurred first), overall response rate (ORR; CR+CRi), time to response and duration of response for patients who achieved CR or CRi, minimal residual disease (MRD) negativity defined as (less than 1 blast or leukemic stem cell in 10,000 leukocytes [ie, MRD level $<10^{-4}$]). Minimal residual disease (MRD) assessments were performed on bone marrow aspirates and/or whole blood collected at various time points in Part B. Bone marrow aspirate specimens were evaluated for MRD status for patients who achieved a response using flow cytometry at a central laboratory. Additional secondary efficacy endpoints defined in supplementary file.

Pharmacokinetic assessments

In Part A, all patients received a single IV infusion of 9 mg/kg talacotuzumab as monotherapy on Day 1. Serum concentrations of talacotuzumab were measured for PK parameters during the 14-day evaluation period. In Part B, blood samples were collected for decitabine and talacotuzumab PK assessments. The timepoints for sample collection are described in the supplementary file. Serum concentrations of talacotuzumab and plasma concentrations of decitabine were determined using validated and sensitive methods with a lower limit of quantification (LLOQ) of 10 μg/mL for serum talacotuzumab and 1 ng/mL for plasma decitabine concentrations. PK parameters such as C_{max} (maximum observed concentration) and C_{min} (minimum observed concentration) were evaluated in both Part A and Part B. Methods for biomarkers and pharmacodynamic (PD) assessment are included in supplementary file.

Immunogenicity

The immunogenicity of talacotuzumab alone (in Part A) and in combination with decitabine (in Part B) was evaluated based on the development of anti-drug antibodies (ADA) for talacotuzumab. Blood samples were collected for immunogenicity evaluation at predose, end of study and follow-up phase for talacotuzumab.

Safety assessments

Safety evaluations were performed based on treatment-emergent adverse events (TEAEs), laboratory analyte values (clinical hematology and chemistry), vital sign measurements, and periodic electrocardiogram data. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

Statistical Analysis

Sample size determination

Part B of the study was planned to enroll up to 400 patients (approximately 200 for each arm). Both primary endpoints, CR rate and OS, were to be powered for 80% with an overall α allocation of 0.01 and 0.04, respectively. For the CR rate, the effect size to be detected was 40%

for talacotuzumab + decitabine group versus 15% for decitabine alone group, requiring a total of 160 patients (80 per arm). For OS, the targeted effect size in terms of median OS was 11.4 months for talacotuzumab + decitabine group versus 8.0 months for decitabine alone group, or a HR of 0.70, requiring total of 270 deaths.

Interim analysis

For Part B of the study, 3 interim analyses (IA) were planned. The first IA occurred as planned after approximately 80 patients (40 per arm) were randomized and had follow up for at least 4 months. Guided by predefined statistical criteria based on CR and CR + CRi rate, the IDMC were to determine if the study should continue enrolment to the full pre-specified phase 3 sample size of 400 patients. Subsequently, another 2 IAs were planned: (1) after 160 patients were randomized and followed for at least 4 months (final analysis for CR rate and the first IA for OS). (2) when 180 deaths had occurred (second IA of OS); final analysis of OS was planned with a total of 270 deaths. O'Brien-Fleming α spending procedure was utilized for the IA and final analysis for OS.

Analysis sets

Intent-to-Treat (ITT): all patients randomized into the study, grouped per treatment assigned by randomization, regardless of the actual treatment received. Safety: all randomized patients who received at least 1 dose of study medication, grouped according to actual treatment received.

Planned analyses

For PK analysis, descriptive statistics were used to summarize serum talacotuzumab and plasma decitabine concentrations at each sampling timepoint. Number and percent of patients achieving

CR were presented by treatment arm. Odds ratio (talacotuzumab + decitabine vs. decitabine alone) were reported along with the associated 95% CI based on a stratified logistic regression with treatment as the only covariate. The p-value was based on a stratified Cochran-Mantel-Haenszel (CMH) test. Stratification factors are those used in randomization. Kaplan-Meier estimates for OS were presented graphically, and p-value was calculated using the stratified log rank test. Time to response and duration of response were summarized by treatment arm using the Kaplan-Meier method. The safety results were summarized descriptively.

Results

Patient characteristics and disposition

In Part A of the study, 10 patients were enrolled. All the patients were Caucasian, with a median age of 67.5 (range: 51 to 78) years, and the majority were men (60%) (Table 1). At the time of final clinical cutoff, all patients in Part A had discontinued the study due to death (including 1 death before starting the combination treatment with decitabine) (Figure 1).

In Part B of the study, between October 26, 2015, and July 28, 2017, a total of 316 patients were randomized 1:1 to either talacotuzumab + decitabine (n=157) or decitabine alone (n=159). The patient demographics were similar between the treatment groups. The patients had a median age of 75 (range: 65 to 92) years and were mostly Caucasian (87.0%). The majority of patients presented with *de novo* AML (67.4%) and with a baseline ECOG score of 1 or 2 (81.3%) (Table1). The safety analysis included 312 patients, 147 (93.6%) patients in the talacotuzumab + decitabine group and 165 (103.8%) in decitabine alone group (Figure 1). At the final clinical cutoff (which occurred 6 months after the IDMC recommendation to discontinue treatment with talacotuzumab), 262 (82.9%) patients had discontinued treatment, and treatment with decitabine alone was ongoing for 52 patients (16.5%). Death (n=65; 24.8%) was the most common reason for treatment discontinuation including 25 patients randomized in talacotuzumab + decitabine arm (Figure 1).

The median treatment duration was 3.71 (range: 0.3 to 24) months in the talacotuzumab + decitabine arm, with 67 patients (45.6%) receiving <3 months of treatment and 4 patients (2.7%) receiving at least 18 months of treatment. The median number of cycles received was 2 (range: 1 to 17 cycles). In the decitabine alone arm, the median treatment duration was 3.61 (range: 0.0 to 22.5) months, with 79 patients (47.9%) receiving <3 months of treatment and 3 patients (1.8%) receiving at least 18 months of treatment. The median number of cycles received was 4 (range: 1 to 22 cycles).

Primary Endpoints

As per the IRC assessment based on 162 patients (80 in talacotuzumab + decitabine group and 82 in decitabine alone group) from the second IA, CR was achieved in 12 (15%) patients receiving talacotuzumab + decitabine versus 9 (11%) in patients receiving decitabine alone. The odds ratio for CR rate was 1.4 (95% CI: 0.6, 3.6); p=0.44. In the ITT population of Part B, CR was achieved in 26 (16.6%) patients receiving talacotuzumab + decitabine versus 19 (11.9%) in patients receiving decitabine alone. The odds ratio for CR rate was 1.5 (95% CI: 0.8, 2.8); p=0.47. No clinically meaningful or statistically significant improvement in CR was observed with combined talacotuzumab + decitabine treatment, compared to treatment with decitabine alone in either the IRC assessed group or the overall ITT population. In the talacotuzumab + decitabine arm, 4 (10.3%) patients with low baseline CD123 blasts achieved CR; whereas, higher number of patients (8 [20.5%]) with high baseline CD123 blasts achieved CR. In the decitabine alone arm, 4 (10%) patients with low baseline CD123 blasts and 5 (12.5 %) patients with high baseline CD123 blasts achieved CR.

In the ITT population, deaths occurred in 101 patients (64.3%) in the talacotuzumab + decitabine arm, and 102 patients (64.2%) in the decitabine alone arm. The median OS was 5.36 months (95% CI: 4.27, 7.95) for talacotuzumab + decitabine group and 7.26 months (95% CI: 6.47, 8.64) for decitabine alone, with an estimated HR (talacotuzumab + decitabine versus decitabine alone) of 1.04 (95% CI: 0.79, 1.37; p=0.78) (Table 2 and Figure 2). No improvement in the OS was observed with talacotuzumab + decitabine treatment as compared to treatment with decitabine alone.

Furthermore, the median OS in adverse cytogenetic risk subgroup was 4.90 months in the talacotuzumab + decitabine arm and 3.91 months in decitabine alone arm, with an estimated HR (talacotuzumab + decitabine versus decitabine alone) of 0.78 (95% CI: 0.49, 1.24). The median OS in the non-adverse cytogenetic risk subgroup was 6.90 months in the talacotuzumab + decitabine arm and 8.25 months in decitabine alone arm with an estimated HR (talacotuzumab + decitabine versus decitabine alone) of 1.18 (95% CI: 0.84, 1.66).

Secondary Endpoints

The median EFS was 4.60 months (95% CI: 3.61, 7.20) for talacotuzumab + decitabine versus 4.24 months (95% CI: 3.32, 6.70) for decitabine alone (HR 0.76 (95% CI: 0.53, 1.09; p=0.1286). In the talacotuzumab + decitabine, 9 (11.3%) patients achieved CRi and 8 (9.8%) patients receiving decitabine alone achieved CRi. As per the IRC assessment, the ORR (CR + CRi) was observed in 21 (26.3%) patients following combined treatment with talacotuzumab + decitabine versus 17 (20.7%) patients in the decitabine alone arm, with an odds ratio of 1.4 (95% CI: 0.7, 2.8); p=0.3. Per Investigator assessment, the ORR was observed in 42 (26.8%) patients following combined treatment with talacotuzumab + decitabine versus 32 (20.1%) patients in the decitabine alone arm, with an odds ratio of 1.4 (95% CI: 0.9, 2.4); p=0.41 (Table 2). In the talacotuzumab + decitabine arm, morphologic leukemia-free state (MLFS) was observed in 9 patients (11.3%), partial response (PR) was observed in 1 (1.3%) patient and stable disease (SD) was observed in 30 (37.5%) patients. In the decitabine alone arm, MLFS was reported for 12 patients (14.6%), and SD was reported for 28 patients. (34.1%).

In the talacotuzumab + decitabine arm, 6 (15.4%) patients with low baseline CD123 blasts and 3 (7.7%) patients with high baseline CD123 blasts achieved CRi. In the decitabine alone arm, 4 (10%) patients with low baseline CD123 blasts and 4 (10%) patients with high baseline CD123 blasts achieved CR. Response rates based on baseline CD123 blasts are summarized in supplementary table S1.

The median time to initial response was 15.6 weeks in the talacotuzumab + decitabine group versus 9.43 weeks for decitabine alone; while the median time to best response was 16.71 weeks in the talacotuzumab + decitabine group and 15.43 weeks for those receiving decitabine alone. The median duration of best response for talacotuzumab + decitabine was longer compared to decitabine alone; 56.43 (95% CI :16.00, 56.43) weeks and 23.43 (95% CI: 8.71, 33.71), respectively.

Analysis of MRD was based on 160 patients included in the second IA, and assessed at the time of response (CR, CRi, or MLFS), as confirmed by investigators. MRD negativity occurred in 16.3% receiving talacotuzumab + decitabine versus 10.0% for those treated with decitabine alone (p=0.34). Overall, there were no clinically meaningful or statistically significant improvements in EFS, ORR, or MRD negativity for the talacotuzumab + decitabine group compared with decitabine alone.

Pharmacokinetics

In Part A, patients who received a single IV infusion of talacotuzumab as monotherapy at 9 mg/kg on day 1 and who were evaluable for PK analysis had observed mean C_{max} (C1D1 30 min) of 135.7 µg/mL and observed mean C_{min} (C2D1 predose) of 9.8 µg/mL (Figure 3A). Since the mean C_{min} concentration of talacotuzumab following the first IV dose was above the desired target of 9 µg/mL,the pre-defined criteria for Part B initiation at the RP2D of 9 mg/kg every 14 days was met. In Part B, the observed mean plasma decitabine C_{max} in cycle 1 was higher in the talacotuzumab + decitabine group (215.9 ng/mL) than that in decitabine alone group (164.1 ng/mL). Mean serum talacotuzumab C_{max} after cycle 1 (179.6 µg/mL) and cycle 4 (187.6 µg/mL) were comparable (Figure 3B). The observed mean trough concentration at cycle 2 (14.7 µg/mL) was lower than that at cycle 4 (30.1 µg/mL). In both parts of the study, inter-individual variability in talacotuzumab PK was observed.

Immunogenicity

Immunogenicity samples were available from 10 patients in Part A and 136 patients in Part B (talacotuzumab + decitabine group only) treated with talacotuzumab. Among these patients, 1 (10%) patient in Part A and 35 (26%) patients in Part B developed ADA. Neutralizing antibody (Nab) was evaluated in 33 of 35 ADA positive patients and 21 (63.6%) patients were found to be Nab positive.

Biomarkers and pharmacodynamics

In Part A, treatment with talacotuzumab demonstrated a reduction of basophils, pDCs, NK cells, and blasts in the peripheral blood, indicative of a PD response to a single IV infusion, which supported the RP2D of 9 mg/kg. In Part B, rapid reduction of basophils and pDCs were noted equally for both treatment arms. Other efficacy biomarkers (blasts and NK cells) were also reduced similarly between both treatment arms. The frequency of peripheral blood target positive (CD123+) blasts as a percentage of total blasts was reduced in patients treated with talacotuzumab + decitabine compared with decitabine alone.

Safety

In Part A, all 10 patients reported at least 1 TEAE; 7 patients (70%) reported drug-related TEAEs and 7 (70%) with Grade ≥3 TEAEs. Serious TEAEs were reported for 4 (40%) of 10 patients. One patient died due to a TEAE of a pre-existing condition aggravated with the combination of talacotuzumab + decitabine. Nine patients from Part A were subsequently treated with combination treatment, and all were reported with at least 1 TEAE. Eight (88.9%) patients reported with drug-related TEAEs, which were attributed to decitabine and talacotuzumab. Two (22.2%) patients reported TEAEs leading to treatment discontinuation and 5 (55.6%) patients died due to TEAEs (Table 3).

In Part B, all 147 (100%) patients in talacotuzumab + decitabine group and 164 (99.4%) patients in decitabine alone group reported at least 1 TEAE. The most common TEAEs leading to death (talacotuzumab + decitabine group vs decitabine alone group) included sepsis 4.8% vs 0.6%), multiple organ dysfunction syndrome (5.4% vs 5.5%), pneumonia (3.4% vs 5.5%), septic shock (3.4% vs 0.6%), and sudden death (0.7% vs 3%). In the talacotuzumab + decitabine group, 55 (37.4%) patients reported IRR-associated TEAEs, of whom 22 (15.0%) patients had Grade ≥3 TEAEs and 1 (0.7%) patient had Grade 5 TEAEs. The commonly reported IRR-associated TEAEs included chills (16.3%), pyrexia (5.4%), and hypoxia (4.8%). In the decitabine alone group, none of the patients reported an infusion-related TEAE. Blood and lymphatic systems disorders were observed in 82.3% patients in the combination arm and 80% in decitabine alone arm of which most common (talacotuzumab + decitabine group vs decitabine alone group) were anemia (51% vs 43%), thrombocytopenia (49.7% vs 50.3%), neutropenia (44.2% vs 36.4%), and febrile neutropenia (40.1% vs 30.3).

Discussion

Results from part A, confirmed the RP2D for talacotuzumab as 9 mg/kg. The results of part B suggest that addition of talacotuzumab to decitabine monotherapy regimen was not superior to decitabine monotherapy in older patients with AML. No clinically meaningful or statistically significant difference in CR, OS, and other secondary efficacy endpoints were observed in the combination arm as compared with the decitabine alone arm. Higher incidence of infusion-related reactions in the decitabine + talacotuzumab arm as compared with decitabine alone arm were reported. The lack of efficacy and a concerning safety profile, resulted in an unfavorable risk/benefit profile that did not support the continuation of treatment with talacotuzumab.

The incidence of AML increases progressively with age; advanced age, comorbidities, compromised organ functions contribute to poor prognosis in older patients with AML (Klepin and Balducci 2009). Intensive and aggressive chemotherapy may improve the efficacy outcomes in these patients, but toxicity and adverse events limit their use in elderly patients unfit for intensive therapy (He, *et al* 2017). Until recently, the recommended standard of care for these patients is low-intensity therapies such as decitabine, azacitidine, and low-dose cytarabine, but the prognosis is suboptimal (Burnett, *et al* 2007, Dombret, *et al* 2015, Kantarjian, *et al* 2012). Studies evaluating new treatments or combinations for older patients with AML are underway, including the emerging data of venetoclax in combination with decitabine or azacitidine that potentially can become standard care for these patients. In the current study, patient population comprised of elderly patients (median age: 75 years [range: 65 to 92 years]), with more than 50%

patients having de novo AML, nearly 40% patients with ECOG score of 2, about one-third with adverse-risk cytogenetics and 42% median baseline blasts in bone marrow. Baseline disease characteristics of patient enrolled in this current study were similar to those who participated in the multicenter phase 3 decitabine study. Furthermore, for the decitabine monotherapy arm, the median OS (7.26 months [95% CI: 6.47; 8.64]) was consistent with median OS for decitabine in reported in the decitabine phase 2 study (7.7 months [95% CI: 5.7 ;11.6 months])(Cashen, *et al* 2010) and decitabine phase 3 study (7.7 months [95% CI: 6.2; 9.2]) (Kantarjian, *et al* 2012).

In the current study, nearly all patients in both treatment arms experienced at least one TEAE. The percentage of patient with serious TEAEs, TEAEs leading to treatment discontinuation, serious TEAEs leading to hospitalization were higher in the talacotuzumab + decitabine arm as compared with decitabine alone arm. All patients in either arm experienced myelosuppression, however, the proportion was higher in the talacotuzumab + decitabine arm. Infusion-related reactions (pyrexia, peripheral edema, and chills) were substantially higher in the talacotuzumab + decitabine arm as compared with decitabine alone arm. The number of deaths in the talacotuzumab + decitabine arm was lower as compared with decitabine alone arm. Insignificant improvement in efficacy outcomes, high risk of myelosuppression, infusion related reactions leading to treatment discontinuations and deaths resulted in an unfavorable risk/benefit profile and contributed to the early discontinuation of talacotuzumab treatment.

A comparison of complete and overall response between the two treatment arms showed that numerically higher values for CR, ORR (CR+CRi) and MRD negativity were observed for the talacotuzumab + decitabine arm versus decitabine alone. Further, reductions of basophils, pDCs, NK cells, blasts/leucocytes and CD123+ blasts in the peripheral blood were observed suggesting a pharmacodynamic response to talacotuzumab. Rapid reduction of basophils and pDCs for both treatment arms suggest that decitabine may have a cytotoxic effect on talacotuzumab cellular pharmacodynamic biomarkers. Treatment with talcotuzumab reduced the CD123 targets based on post-dose changes in NK cells, and reduced the CD123+ blasts as a percentage of total blasts in patients treated combination treatment as compared with decitabine alone. Taken together, these observations suggest that talacotuzumab could demonstrate improved antileukemic efficacy but lacked optimal safety requirement leading to unacceptable benefit/ risk profile.

Monoclonal antibodies (mAbs) are known to elicit their responses either via induction of cellular apoptosis or via ADCC. Targeted Fc engineering either by glycosylation or by mutagenesis is known to increase the molecular affinity towards the target cells such as CD16 on the NK cells which further accentuate the NK-mediated ADCC (Romain, *et al* 2014). Talacotuzumab, has been engineered towards human IgG (humanized) and is known to have increased affinity to the Fc receptor CD16 on NK cells through which it has effectively induced ADCC of AML blasts in a phase 1 study (Smith, *et al* 2014). In the current study, more patients with high baseline CD123+ blasts responded to the combination treatment versus the low CD123+ blasts. Whereas the response rate in the low and high CD123 blast groups were comparable in the decitabine alone arm. This finding suggests that talacotuzumab exerts its ADCC effects via the CD123. However, in spite of demonstrated ADCC activity of talacotuzumab, the combination treatment could not achieve significant improvement in the current study. One possible explanation to the suboptimal response of the talacotuzumab + decitabine group would be the antagonistic effect of decitabine on ADCC effectors such as NK cells. However, further studies to evaluate this effect are warranted.

Conclusion

In summary, the results of the current study demonstrated an unfavorable risk/benefit ratio for the talacotuzumab and decitabine combination for the treatment of AML in the older population not eligible for intensive chemotherapy. However, the results may indicate that CD123 expression is elevated in AML and can serve as a viable target for the AML treatment paradigm, since targeting of LSPCs is being considered to be a potential strategy to improve the long-term survival of AML patients.

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Disclosures

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Figure Legends:

Figure 1: Study design and patient disposition

[a]Patients randomized in the decitabine + talacotuzumab arm who received only decitabine and not talacotuzumab were grouped in the decitabine alone arm; [b]Patients still being treated with decitabine as they continued to derive benefit from the treatment. RP2D: recommended phase 2 dose

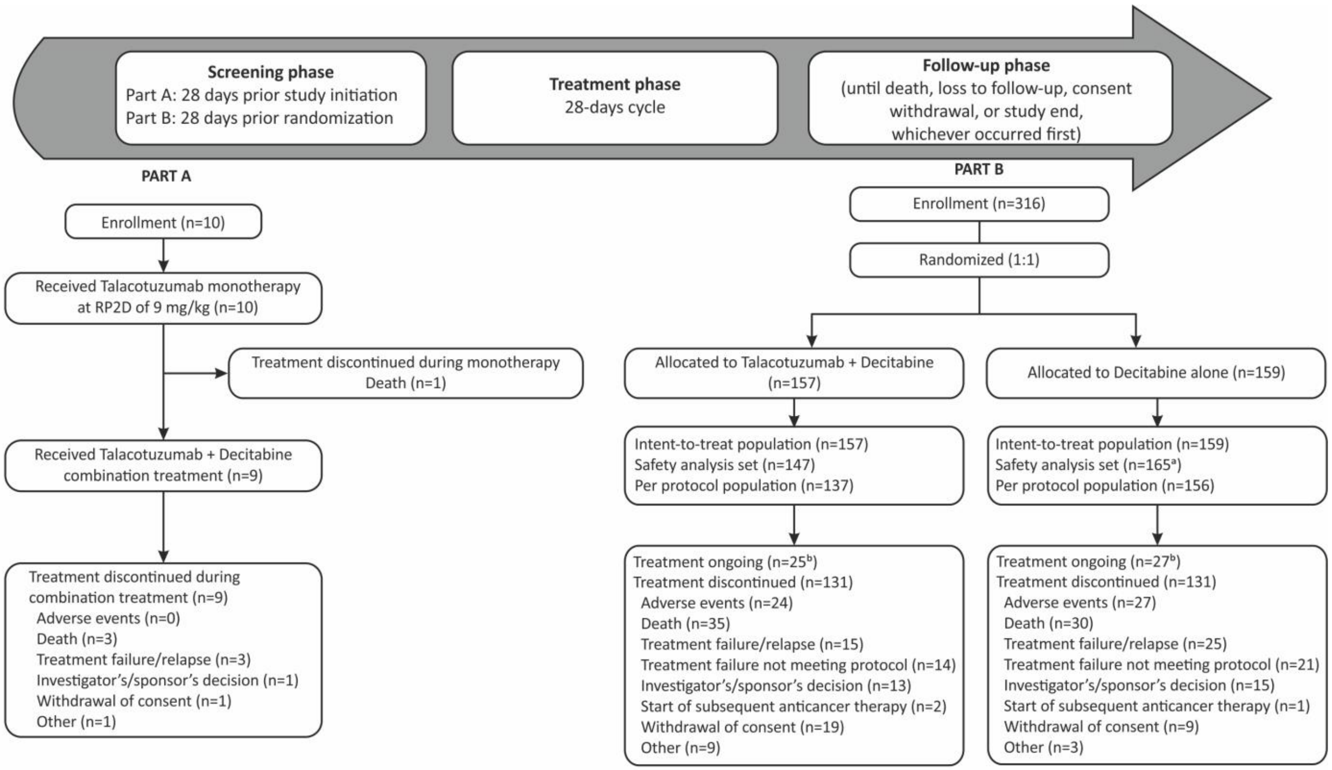
Figure 2: Kaplan-Meier Curves for Overall Survival; ITT Analysis Set

Figure 3: (A) Serum concentration of talacotuzumab in part A

Figure 3: (B) Serum concentration of decitabine+talacotuzumab in part B

Figures

Figure 1: Study design and patient disposition



[a]Patient randomized in the Talacotuzumab + Decitabine arm who received only Decitabine and not Talcotuzumab were grouped in the Decitabine alone arm; [b]Patients still being treated with decitabine as they continued to derive benefit from the treatment.
RP2D: recommended phase 2 dose

Figure 2: Kaplan-Meier Curves for Overall Survival; ITT Analysis Set

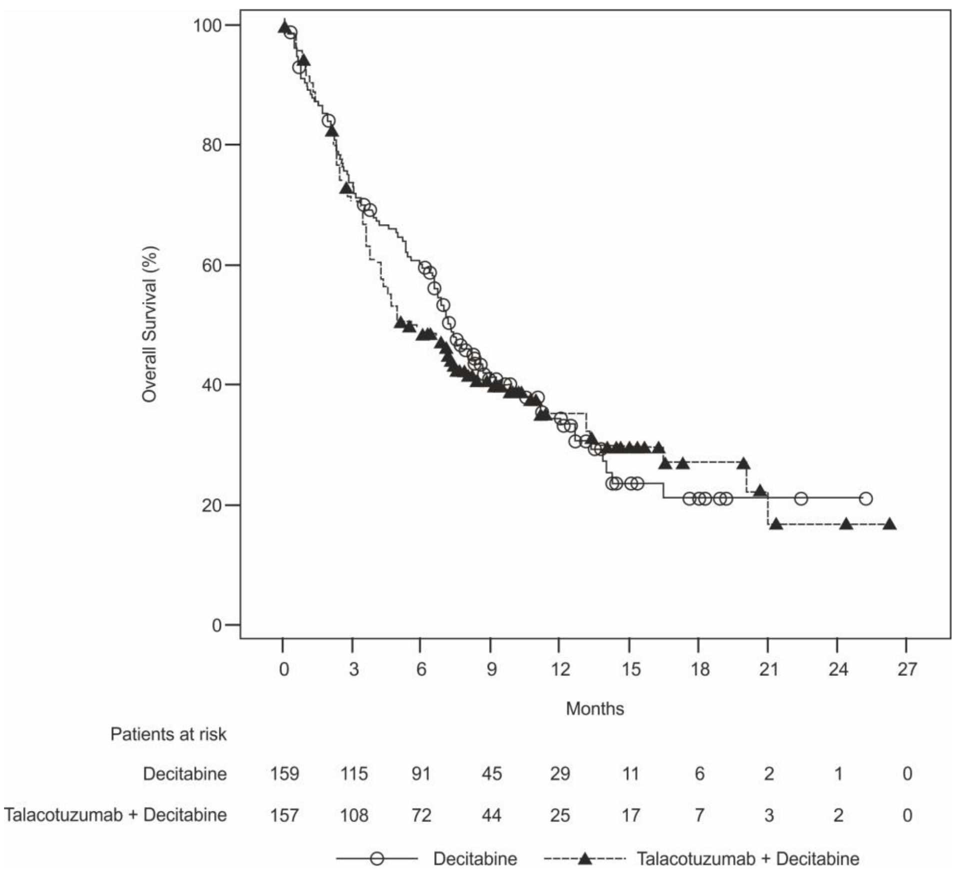


Figure 3: (A) Serum concentration of talacotuzumab in part A

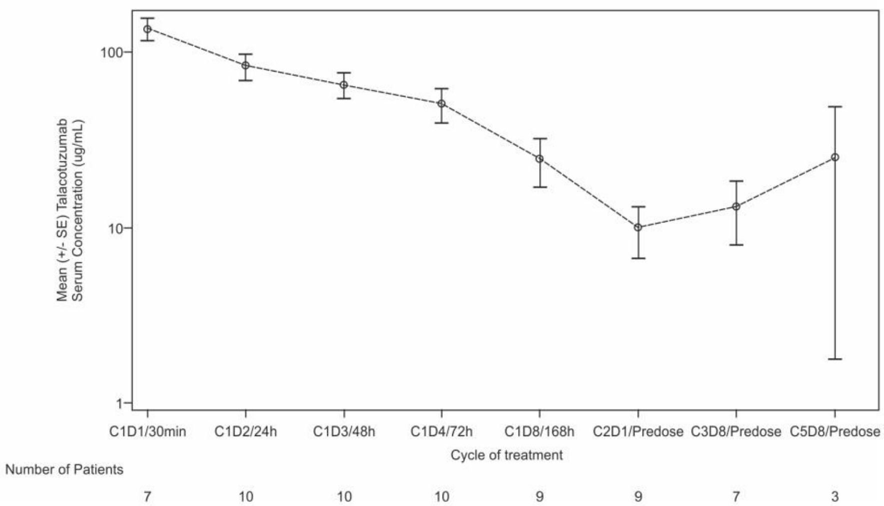
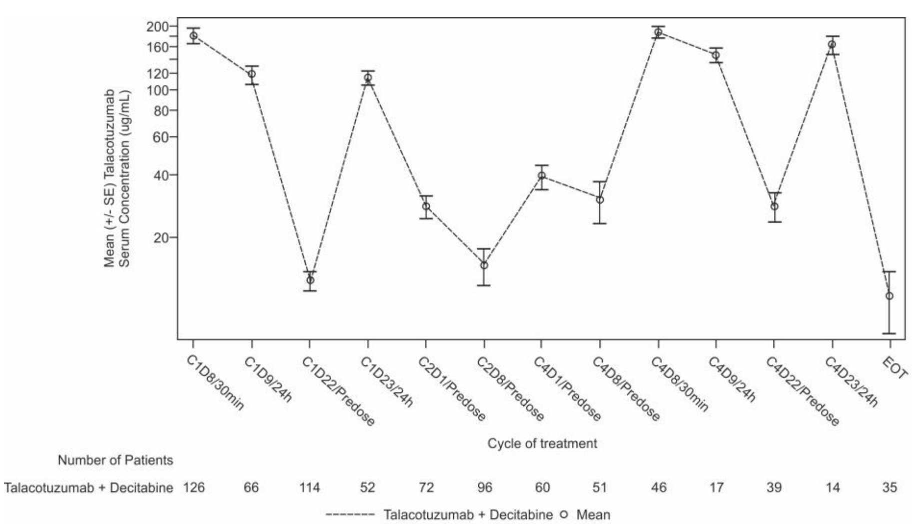


Figure 3: (B) Serum concentration of talacotuzumab + decitabine in part B



Tables

Table 1: Patient demographics and baseline characteristics

Characteristics	**Part A (All enrolled set)**	**Part B (ITT analysis set)**		
	Talacotuzumab alone (n=10)	Decitabine alone (n=159)	talacotuzumab + decitabine (n=157)	Total (n=316)
Age (years), median (range)	67.5 (51-78)	75.0 (65-89)	75.0 (65-92)	75.0 (65-92)
Gender, n (%)				
Men	6 (60)	91 (57.2)	80 (51.0)	171 (54.1)
Race, n (%)				
White	10 (100)	133 (84.2)	141 (89.8)	274 (87.0)
Type of AML, n (%)				
De novo		106 (66.7)	107 (68.2)	213 (67.4)
Secondary		53 (33.3)	50 (31.8)	103 (32.6)
History of MDS		24 (45.3)	21 (42.0)	45 (43.7)
History of myeloproliferative disorder		19 (35.8)	23 (46.0)	42 (40.8)
Previous leukemogenic exposure		10 (18.9)	6 (12.0)	16 (15.5)
ECOG performance status, n (%)				
0		29 (18.2)	30 (19.1)	59 (18.7)
1		69 (43.4)	65 (41.4)	134 (42.4)
2		61 (38.4)	62 (39.5)	123 (38.9)
Bone marrow blast – Aspiration, median (range)		39.50 (15.0; 100.0)	45.00 (14.0; 100.0)	42.00 (14.0; 100.0)
Bone marrow blast – Biopsy, median (range)		38.00 (4.0; 90.0)	40.00 (0.0; 92.0)	40.00 (0.0; 92.0)
Classification of risk, n (%)				
Favorable		8 (5.0)	10 (6.4)	18 (5.7)
Intermediate-I		61 (38.4)	51 (32.5)	112 (35.4)
Intermediate-II		33 (20.8)	32 (20.4)	65 (20.6)
Adverse		47 (29.6)	57 (36.3)	104 (32.9)
Patients with previous cancer-related therapy, n (%)				
Systemic therapy		33 (20.8)	24 (15.3)	57 (18.0)
Radiotherapy		1 (0.6)	5 (3.2)	6 (1.9)
Cancer-related surgery/procedure		10 (6.3)	10 (6.4)	20 (6.3)

Abbreviations: AML: acute myeloid leukemia; ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; MDS: myelodysplastic syndrome; SD: standard deviation

Table 2: Primary and secondary efficacy endpoints (Intent-to-treat population)

	Intent-to-treat population* (Per investigators assessment)		Per the IRC assessment	
Parameter	**Decitabine + Talacotuzumab**	**Decitabine**	**Decitabine + Talacotuzumab**	**Decitabine**
Primary endpoint				
N[a]	**157**	**159**	**80**	**82**
Complete response (CR), n (%)	26 (16.6%)	19 (11.9)	12 (15)	9 (11)
Odds ratio (95% CI)[b]	1.5 (0.8; 2.8)		1.4 (0.6; 3.6)	
p-value[c]	0.4145		0.4403	
N	**157**	**159**		
Overall Survival, months, median (95% CI)	5.36 (4.27; 7.95)	7.26 (6.47; 8.64)		
Hazard ratio (95% CI)[d]	1.04 (0.79; 1.37)			
p-value[e]	0.7817			
Secondary endpoints				
N[a]	**157**	**159**	**80**	**82**
CR with incomplete blood counts recovery (CRi), n (%)	16 (10.2)	13 (8.2)	9 (11.3)	8 (9.8)
Overall response (CR+CRi), n (%)	42 (26.8)	32 (20.1)	21 (26.3)	17 (20.7)
Odds ratio (95% CI)[b]	1.4 (0.92; 2.4)		1.4 (0.7; 2.8)	
p-value[c]	0.4145		0.2805	
MLFS, n (%)	14 (8.9)	24 (15.1)	9 (11.3)	12 (14.6%)
Time to initial response (weeks)[f], median (range)			15.57 (7.1-60.0)	9.43 (6.4-46.1)
Time to best response (weeks)[g], median (range)			16.71 (7.4-60.0)	15.43 (7.1-46.1)
Duration of best response (weeks)[h], median (95% CI)			56.43 (16.00; 56.43)	23.43 (8.71; 33.71)
Event free survival (months), median (95% CI)			4.60 (3.61; 7.20)	4.24 (3.32; 6.70)
Hazard ratio (95% CI)[d]			0.76 (0.53; 1.09)	
p-value[e]			0.1286	
N[a]			**80**	**80**
MRD-Negative (CR+CRi+MLFS), n (%)			13 (16.3)	8 (10.0)
p-value[i]			0.3493	

[a]Include patients whose data were reviewed by IRC; [b]Odds ratio >1 favors Talacotuzumab + decitabine; Odds Ratio is from a logistic regression with treatment as the only covariate; [c]p-value is from a CMH Chi-square test adjusted for stratification factors; [d]Hazard ratio is from a stratified proportional hazards model. A hazard ratio < 1 favors talacotuzumab + decitabine; [e]p-value is from a log-rank test stratified by two randomisation stratification factors: baseline ECOG performance status (0-1 versus 2) and type of AML (*de novo* versus secondary); [f]Time to initial response is calculated as the time from the randomisation date to first documented response for patients who achieved CR or Cri; [g]Time to best response is calculated as the time from the randomisation date to the first documented date for the best response for patients who achieved CR or Cri; [h]Duration of best response is calculated as the number of weeks from documented best response (CR or CRi) for patients who achieved CR or CRi to relapse, death due to relapse, or date of censoring; [i]p-values are based on Fisher's Exact test.
Abbreviations: AML: acute myeloid leukemia; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; IRC: Independent Review committee; MLFS: morphologic leukemia-free state

Table 3: Summary of treatment-emergent adverse events (Safety Population)

TEAEs	**Part A (all enrolled set)**	**Part B (safety analysis set)**	
	Talacotuzumab* (n=10)	**Decitabine + Talacotuzumab (n=147)**	**Decitabine alone (n=165)**
TEAEs	10 (100)	147 (100)	164 (99.4)
Drug-related adverse events	7 (70)	128 (87.1)	124 (75.2)
Grade ≥3 TEAEs	7 (70)	145 (98.6)	157 (95.2)
Serious TEAEs	4 (40)	126 (85.7)	120 (72.7)
Grade ≥3 serious TEAEs	4 (40)	124 (84.4)	115 (69.7)
TEAEs leading to treatment discontinuation	0	40 (27.2)	26 (15.8)
Decitabine	-	33 (22.4)	26 (15.8)
Talacotuzumab	0	32 (21.8)	2 (1.2)
TEAEs leading to death	1 (10)	49 (33.3)	46 (27.9)
Serious TEAEs leading to hospitalization	3 (30)	112 (76.2)	99 (60.0)
Most common TEAEs (>20% of patients)			
Dyspnoea	5 (50)	25 (17.0)	24 (14.5)
Pyrexia	4 (40)	60 (40.8)	48 (29.1)
Anaemia	3 (30)	80 (54.4)	80 (48.5)
Asthenia	2 (20)	27 (18.4)	25 (15.2)
Chills	2 (20)	31 (21.1)	7 (4.2)
Peripheral oedema	2 (20)	46 (31.3)	25 (15.2)
Nausea	2 (20)	38 (25.9)	33 (20.0)
Thrombocytopenia	-	81 (55.1)	87 (52.7)
Neutropenia	1 (10)	66 (44.9)	61 (37.0)
Febrile neutropenia	1 (10)	59 (40.1)	50 (30.3)
Hypokalaemia	-	53 (36.1)	41 (24.8)
Diarrhoea	1 (10)	50 (34.0)	44 (26.7)
Constipation	1 (10)	47 (32.0)	51 (30.9)
Pneumonia	1 (10)	39 (26.5)	37 (22.4)
Fatigue	-	31 (21.1)	31 (18.8)
Most common Grade ≥3 TEAEs (>20% of patients)			
Anaemia	3 (30)	75 (51.0)	71 (43.0)
Dyspnoea	2 (20)	9 (6.1)	5 (3.0)
Thrombocytopenia	-	73 (49.7)	83 (50.3)
Neutropenia	1 (10)	65 (44.2)	60 (36.4)
Febrile neutropenia	1 (10)	59 (40.1)	50 (30.3)
Pneumonia	1 (10)	36 (24.5)	33 (20.0)
Infusion-related TEAEs	-	55 (37.4)	0

Grade 3	-	20 (13.6)	0
Grade 4	-	2 (1.4)	0
Grade 5	-	1 (0.7)	0

*Patients on talacotuzumab alone, prior to initiating combination treatment. TEAE: treatment-emergent adverse event

Supplementary Table S1: Response rates based on baseline CD123 blasts

	Low baseline CD123 blasts		High baseline CD123 blasts	
Response, n (%)	**Talacotuzumab + decitabine (N=39)**	**Decitabine (N=40)**	**Talacotuzumab + decitabine (N=39)**	**Decitabine (N=40)**
CR	4 (10.3)	4 (10.0)	8 (20.5)	5 (12.5)
CRi	6 (15.4)	4 (10.0)	3 (7.7)	4 (10.0)
MLFS	3 (7.7)	5 (12.5)	6 (15.4)	7 (17.5)
PR	1 (2.6)	0	0	0
CR + CRi	10 (25.6)	8 (20.0)	11 (28.2)	9 (22.5)
CR + CRi + MLFS	13 (33.3)	13 (32.5)	17 (43.6)	16 (40.0)

The CD123 expression subgroups were determined by the median baseline CD123 value of total 158 patients (Low: CD123 expression ≤91.5% & High: CD123 expression >91.5%). Four patients did not have baseline CD123 measures.