2 SYNOPSIS

Name of Sponsor/Company Sumitomo Dainippon Pharma Oncology, Inc	**Name of Finished Product** Alvocidib (formerly flavopiridol)	**Name of Active Ingredient** 2-(2-Chlorophenyl)-5,7-dihydroxy-8-[(3S, 4R)-3-hydroxy-1-methyl-4-piperidinyl]-4H-chromen-4-one, hydrochloride

Protocol Number: TPI-ALV-201

Title of Study: A Phase 2, Randomized, Biomarker-driven, Clinical Study in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with MCL-1 Dependence ≥30%

Investigators and Study Centers: 40 centers in 4 countries.

Publication (reference): 1. Zeidner JF, Vigil CE, Lin T, Levy MY, Frattini M, Dalovisio A, et al. Phase II study incorporating a novel BH3-profiling biomarker approach of alvocidib followed by cytarabine and mitoxantrone in relapsed/refractory acute myeloid leukemia (AML); PF243 [Internet]. Poster presented at: European Hematology Association 23rd Annual Congress; 2018 Jun 15 [cited 2020 Mar 18]; Stockholm, Sweden.

2. Zeidner JF, Lin T, Vigil CE, Dalovisio A, Wang ES, Levy MY, et al. Zella 201: A biomarker-guided phase II study of alvocidib followed by cytarabine and mitoxantrone in MCL-1 dependent relapsed/refractory acute myeloid leukemia (AML). Presentation presented at: 60th American Society of Hematology (ASH) Annual Meeting and Exposition; 2018 Dec 1; San Diego, CA.

3. Zeidner JF, Lee DJ, Fine G, Wang ES, Bhatt VR, Dalovisio A et al, Zella 201: A biomarker-guided phase ii study of alvocidib followed by cytarabine and mitoxantrone in MCL-1 dependent acute myeloid leukemia (AML): results of newly diagnosed high-risk exploratory arm, (Abstract submitted to ASH 2020)

Study Period (years): 3.9 years **Date of First Enrollment**: 14 March 2016 **Date of Last Completed:** 12 February 2020	**Phase of Development:** Phase 2

Objectives: The primary objectives of this study were:

- To determine the Complete Remission (CR) rate in patients with relapsed or refractory AML with MCL-1 dependence of ≥30%
- To compare CR rates between patients with relapsed or refractory AML with MCL-1 dependence of ≥30% receiving 1 cycle of Alvocidib/Cytarabine/Mitoxantrone (ACM) treatment and those receiving 1 cycle of Cytarabine/Mitoxantrone (CM).

The exploratory study objective was to determine if treatment with ACM would induce CR in patients with relapsed or refractory AML with MCL-1 dependence of ≥30% who failed to achieve CR following 1 cycle of CM.

Methodology:
This was a Phase 2, open-label, randomized, multicenter, two-stage study to determine if MCL-1 dependence demonstrated by mitochondrial profiling in bone marrow samples would increase the CR rate after ACM treatment.

Stage 1
Stage 1 of the study was a single arm (ACM), conducted similarly to the first stage of a Simon 2-stage design. Patients with relapsed or refractory AML with demonstrated MCL-1 dependence of ≥40% by mitochondrial profiling in bone marrow were screened according to study inclusion and exclusion criteria up to 14 days before the initiation of ACM study treatment. Once ≥13 patients enrolled in Stage 1 exhibited a CR, Complete remission with residual neutropenia (CRi), or Complete remission with incomplete platelet recovery (CRp), enrollment into Stage 1 was closed and additional patients were to be enrolled in Stage 2 of the study.

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Enrollment into Stage 1 was limited to no more than 23 evaluable patients, however enrollment into Stage 2 was initiated at any point after confirming CR, CRi or CRp responses in 13 Stage-1 patients.

Stage 2

Patients with relapsed or refractory AML with demonstrated MCL 1 dependence of ≥30% by mitochondrial profiling in bone marrow were randomized 1:1 to receive either ACM or CM. Patients were screened for study inclusion and exclusion criteria up to 14 days before the initiation of study treatment.

Response assessments in Stage 1 were defined by the International Working Group Criteria (Cheson et al., 2003) and the 2010 European LeukemiaNet (ELN) (Dohner et al., 2010). The patient responses during Stage 2 were determined using the 2017 ELN criteria (Dohner et al., 2017).

Please note: The study was initially designed to include patients with relapsed or refractory AML with MCL-1 dependence of ≥40%. The study protocol was modified in August 2019 to lower the limit of MCL-1 dependency for study inclusion from ≥40% to ≥30%.

Response assessments (Section 16.1.1 Protocol TPI-ALV-201, Appendix E) included the following:

- CR rate = Percentage of patients achieving CR
- Combined CR Rate = Percentage of patients achieving:
  - CR = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; hematologic recovery (absolute neutrophil count [ANC] >1 x 10^9/L and platelet count >100 x 10^9/L); independence of red cell transfusions.
  - CRi = Meets all CR criteria except for residual neutropenia (ANC <1 x 10^9/L) or lack of recovery of any other hematopoietic cell.
  - CRp = Meets all CR criteria except for residual thrombocytopenia (platelet count <100 x 10^9/L)
- Combined Response Rate = Percentage of patients achieving:
  - CR
  - CRi
  - CRp
  - Partial remission (PR) = Meets all hematologic values required for CR but with a decrease of at least 50% in the percentage of blasts to ≥5% to ≤25% in bone marrow
- Overall Survival (OS) = Time from randomization (Day 1) until death from any cause
- Event-free Survival (EFS) = Time from randomization (Day 1) until (a) treatment failure, (b) relapse after CR, or (c) death from any cause, whichever occurs first, censored at 2 years
- Rate of Stem Cell Transplantation = Percentage of patients proceeding directly to stem cell transplantation

The CR rate in patients failing 1 cycle of CM and crossing over to receive ACM was determined

Safety assessments were to include:

- Mortality from any cause at 30 and 60 days
- Adverse events graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 in Stage 1 and version 5.0 in Stage 2
  - The multivariate analysis and risk score prediction model by Montesinos and colleagues were used to assess the potential for development of Tumor Lysis Syndrome (TLS) (Montesinos et al., 2008). (Section 16.1.1, Protocol TPI-ALV-201, Appendix F)

Treatment assessments were to include:

- Bone marrow biopsies and/or aspirates performed at hematologic recovery (i.e., absolute neutrophil count (ANC) >1 x 10^9/L and platelet count >100 x 10^9/L) or Day 45, whichever occurred first. Slides from bone marrow samples were collected.

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- Complete blood counts and chemistries assessed daily while hospitalized for chemotherapy administration and weekly thereafter.
- Survival monitored monthly during year 1, every 2 months during year 2
- Intensive monitoring of renal function, electrolytes, and uric acid levels

Pharmacodynamic assessments were to include:

- Determination of MCL-1 dependence at prescreening using bone marrow aspirate

Patients who achieved CR, CRi, CRp, or PR after the first cycle (completion of all doses) could receive up to 3 additional optional cycles of treatment

- After completing the first cycle of treatment, continued use of mitoxantrone was optional.
- Mitoxantrone had to be omitted from subsequent cycles if the patient's lifetime daunorubicin equivalent exceeded 460 mg/m2 (Section 16.1.1 Protocol TPI-ALV-201, Appendix G, conversion table) or the left ventricular ejection fraction (LVEF) dropped below 45%.

Patients not demonstrating evidence of CR, CRi, CRp, or PR after the first cycle of treatment were considered for removal from the study, although with permission of the Medical Monitor, induction treatment could continue, if clinically indicated, and provided there was no evidence of toxicity ≥NCI CTCAE grade 4 (v4.03 in Stage 1, v5.0 in Stage 2; Section 16.1.1 Protocol TPI-ALV-201, Appendix C). This study also planned to include a crossover option for those randomized to CM (see below).

- Crossover: Patients randomized to CM with progressive disease or no response after 1 cycle of CM could cross over to receive ACM. In addition, patients randomized to CM with the best response of a PR after 2 cycles of CM could also cross over to receive ACM. Patients who crossed over to ACM could receive up to a combined total (CM + ACM) of 4 cycles. Patients crossing over who met the above criteria (lifetime daunorubicin equivalent exceeds 460 mg/m^2 or the LVEF dropped below 45%) received only AC (alvocidib and cytarabine) for all cycles instead of ACM.

Complete remission rates were to be compared across treatment groups using the Cochran-Mantel-Haenszel general association test stratified by response to most recent induction therapy. The same test was applied to assess the statistical significance of the secondary response rate endpoints.

Incidence rates of treatment-emergent adverse events (TEAEs) were summarized within treatment group at the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and primary system organ class levels. Similar summaries were made for subsets of adverse events (AEs) such as (1) those judged by the Investigator to be related to study treatment, and (2) serious adverse events (SAEs). Other routine safety assessments (e.g., clinical laboratory parameters and vital signs) were summarized by treatment group using mean, standard deviation, median, minimum and maximum changes from baseline values.

An active comparator was used (treatment with cytarabine and mitoxantrone [CM regimen]).

Number of Patients (planned and analyzed):
It was anticipated that up to 137 eligible and evaluable patients (25 patients in Stage 1, 56 patients in the 4 Exploratory Arms (closed after Amendment 8); and 56 patients (28 patients in each of two treatment arms) in Stage 2.) would be enrolled at approximately 40 international investigative sites.
The actual number of patients enrolled were 104 (57 in the 4 Exploratory Arms, 47 in Stage 1 and Stage 2) at 22 investigative sites.

Diagnosis and Main Criteria for Inclusion:

Study Indication: Patients with relapsed or refractory acute myeloid leukemia (AML) with MCL-1 dependence ≥30%

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Inclusion Criteria:

During Prescreening:

1. Was between the ages of ≥18 and ≤65 years
2. Had an established, pathologically confirmed diagnoses of AML by World Health Organization (WHO) criteria excluding acute promyelocytic leukemia (APL-M3) with a bone marrow of >5% blasts based on histology or flow cytometry
3. Was in first relapse (within 24 months of CR) or had failed induction therapy (no CR or CRi after treatment with an intensive regimen [e.g., anthracycline/cytarabine ± etoposide, gemtuzumab ozogamicin, or cladribine])
   Induction therapy could involve 1 or 2 cycles of the same regimen. Efficacy assessment of induction therapy was >21 days from the start of the previous induction cycle.
4. Demonstrated MCL-1 dependence of ≥30% by mitochondrial profiling in bone marrow

During Screening:

1. Had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2
2. Had a serum creatinine level ≤1.8 mg/dL
3. Had an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level ≤5 times upper limit of normal (ULN)
4. Had a total bilirubin level ≤2.0 mg/dL (unless secondary to Gilbert syndrome, hemolysis, or leukemia)
5. Had a LVEF >45% by echocardiogram (ECHO) or multigated acquisition (MUGA) scan
6. Was nonfertile or agreed to use an adequate method of contraception. Sexually active patients and their partners had to use an effective method of contraception associated with a low failure rate during and for at least 6 months after completion of study therapy (see Section 9.4.7.5).
7. Was able to comply with the requirements of the entire study.
8. Provided written informed consent prior to any study related procedure. (In the event that the patient was re-screened for study participation or a protocol amendment altered the care of an ongoing patient, a new informed consent form had to be signed.)

Patient Disposition:

Since the study was terminated early in January 2020, sufficient efficacy results were not available to analyze patients based on the percentage of MCL-1 dependency. Therefore, treatment efficacy was summarized by distributing the safety population into 6 groups based on whether the patients received the ACM vs CM regimen and their disease stages at study entry as follows:

Randomized Stage

- CM relapsed/refractory (n=11) and
- ACM relapsed/refractory (n=11)

All Stages and Cohorts (including Randomized Stage)

- ACM (Stage 1) (n=25)
- ACM relapsed/refractory (n=79)
- ACM newly diagnosed (n-14)
- ACM Total (n=93)

Table 3 summarizes the patient disposition in the Intent-to-Treat (ITT) population.

A total of 104 patients (CM group: n=11; Total ACM group: n=93) were included in the ITT and safety populations (Figure 2). This patient population (n=104) was distributed into 4 groups: CM relapsed/refractory (n=11), ACM relapsed/refractory (n=79), ACM newly diagnosed (n=14), and Total ACM group (n=93) for

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safety and efficacy analyses. Response was evaluated in all except 1 patient from the ACM relapsed/refractory group.

Patients were enrolled at 22 of the 40 study centers that were opened for accrual and were analyzed in 4 groups based on the treatment administered- Group 1 (CM relapsed/refractory: n=11), Group 2 (Total ACM relapsed/refractory: n=79), Group 3 (ACM newly diagnosed: n=14) and Group 4 (Total ACM: n=93). All patients received at least 1 treatment cycle; several patients from each group underwent 2 treatment cycles (CM relapsed/refractory: n=4, 36.4%; ACM relapsed/refractory: n=14, 17.7%; ACM newly diagnosed: n=3, 21.4%).

Overall, 38 patients from the Total ACM group and 6 patients from the CM group completed the study after achieving CR, CRi or PR. The overall mean study duration was 8.7 (±4.2) weeks in the Total ACM group and 9.0 (±5.5) weeks in the CM group; the study duration was comparable between the 2 groups.

Reasons for withdrawal from the study included lack of efficacy (failure to achieve remission: CM group: n=4, 36.4%; Total ACM group: n=30, 32.3%), progressive disease following response (CM group: n=0; Total ACM group: n=6, 6.5%), physician decision (CM group: n=0; Total ACM group: n=2, 2.2%), death (CM Group: n=0; Total ACM group: n=9, 9.7%), adverse event (CM group: n=0; Total ACM group: n=3, 3.2%), withdrew consent (CM group: n=1, 9.1%; Total ACM group: n=3, 3.2%) and other (CM group: n=0; Total ACM group: n=2, 2.2%).

Post study bone marrow transplant was performed in almost half of the patients in both groups (CM group: n=5, 45.5%; Total ACM group: n=41, 44.1%).

Key Demographics: A summary of demographic and baseline characteristics for the ITT population based on the treatment administered is presented in Table 4.

By patient listings of demographic and baseline data, medical history, and historical diagnostic tests are presented in Section 16.4. The study population comprised a total of 57 male and 47 female patients. The mean age of the study population was 48.0 (±15.2) years for the CM group and 51.6 (±10.6) years for the Total ACM group. The median age of the study population was comparable between all the groups and ranged from 54.8 years to 56.1 years. The majority of the study population was between 46 to 65 years of age.

ECOG performance status (PS) ranged from 0 to 2 for all groups with the exception of 1 patient in the CM relapsed/refractory group that was classified as other. A majority of patients had ECOG PS Grade 0 (CM group: 27.3%; Total ACM group: 45.2%) and Grade 1 (CM group: 54.5%; Total ACM group: 45.2%). The remaining patients from the Total ACM group (n=9, 9.7%) had Grade 2 ECOG PS.

The mean MCL-1 dependence was 47.5 % (±8.8) in the CM group and 39.8% (±23.2) in the Total ACM group.

Mean MCL-1 dependence was higher in the ACM newly diagnosed group at 53.5% (±9.9) compared to the ACM relapsed/refractory group 37.3% (±24.1).

The AML history of the ITT population is presented in Table 5.

As per the 2017 ELN genetic risk criteria, patients were classified as either having adverse, intermediate, or favorable genetic risk. Secondary AML was defined in this study as patients who had prior MDS or were reported to have received prior cytotoxic or radiation therapy or both.

In the CM group (n=11), majority of the patients (n=8, 72.7%) were classified as having an adverse genetic risk, 1 (9.1%) patient had an intermediate risk and the remaining 2 (18.2%) patients had a favorable genetic risk. Patients with prior Myelodysplastic syndrome (MDS) and secondary AML were 2 (18.2%) and 4 (36.4%), respectively. Two (18.2%) patients had prior stem cell transplant and 3 (27.3%) patients had prior cytotoxic/radiation therapy. The mean duration since AML diagnosis was 8.3 (±9.3) months.

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Of the 93 patients in the Total ACM group, ELN risk was available for 49 (52.7%) patients. Of these 49 patients, 29 (31.2%) were classified as having an adverse genetic risk, 13 (14%) patients had an intermediate genetic risk and 7 (7.5%) had a favorable genetic risk. The remaining 44 (47.3%) patient's data was missing. Patients with prior MDS and secondary AML in the total population were 14 (15.1%) and 29 (31.2%), respectively. Eighteen (19.4%) patients had prior stem cell transplant and 24 (25.8%) patients had prior cytotoxic/radiation therapy. The mean duration since AML diagnosis was 7.4 (± 7.9) months.

In the ACM relapsed/refractory group (n=79), 26 (32.9%) patients were classified as having an adverse genetic risk, 13 (16.5%) patients had an intermediate genetic risk and 6 (7.6%) had a favorable genetic risk. ELN data for the remaining 34 (43.0%) patients was missing. Patients with prior MDS and secondary AML were 8 (10.1%) and 20 (25.3%), respectively. Nineteen (24.1%) patients had prior cytotoxic/radiation therapy, while 16 (20.3%) had prior stem cell transplant. Mean duration since AML diagnosis was 8.5 (±8.0) months.

In the ACM newly diagnosed group (n=14), 3 (21.4%) patients were classified as having an adverse genetic risk, and 1 (7.1%) had a favorable genetic risk. ELN data for the remaining 13 (71.4%) patients was missing. Patients with prior MDS and secondary AML were 6 (42.9%) and 9 (64.3%), respectively. Five (35.7%) patients had prior cytotoxic/radiation therapy and 2 (14.3%) patients had prior stem cell transplant. Mean duration since AML diagnosis was 0.6 (±0.6) months.

Test Product, Dose and Mode of Administration, Batch Number:

Test Product (Alvocidib) Batch Numbers:

Lot #	Location (Time period)
IP0003143	US/Canada (2015-2018)
170075	US/Canada and EU (2018+)
180013-1	Us/Canada (2018+)

Stage 1: Treatment with ACM over Days 1-9

- Alvocidib 30 mg/m^2 as a 30-minute (±10 minutes) intravenous (IV) bolus followed by 60 mg/m^2 over 4 hours (±15 minutes) as an IV infusion.
- Cytarabine 2 gm/m^2 by continuous IV infusion over 72 hours (±2.5 hours) (i.e., 667 mg/m^2 daily for total of 2 gm/m^2).
- Mitoxantrone hydrochloride 40 mg/m^2 by IV infusion over 1-2 hours (±10 minutes).

Stage 2: Treatment with ACM or CM

- Randomized to ACM: Treatment with ACM over Days 1-9
  - Alvocidib 30 mg/ m^2 via IV bolus followed by 60 mg/ m^2 via IV infusion.
  - Cytarabine 2 gm/ m^2 by continuous IV infusion.
  - Mitoxantrone hydrochloride 40 mg/ m^2 by IV infusion.
- Randomized to CM: Treatment with CM over Days 1-4
  - Cytarabine 2 gm/m^2 by continuous IV infusion.
  - Mitoxantrone hydrochloride 40 mg/m^2 by IV infusion;

Duration of Treatment:

Stage 1: Treatment with ACM over Days 1-9

Patients enrolled in Stage 1 received treatment with ACM as outlined below:

- Days 1, 2 and 3: alvocidib (A) - Administer Daily 30 mg/m^2 as a 30-minute (±10 minutes) intravenous (IV) bolus followed by 60 mg/m^2 over 4 hours (±15 minutes) as an IV infusion
- Days 4 and 5: Rest (no chemotherapy treatment)
- Days 6, 7, and 8: cytarabine (C) - Continuous over 72 hours 2 gm/m^2 by continuous IV infusion over 72 hours (±2.5 hours) (i.e., 667 mg/m^2 daily for total of 2 gm/m^2)

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- Day 9: mitoxantrone hydrochloride (M) is administered 12 hours after completion of cytarabine treatment 40 mg/m^2 by IV infusion over 1-2 hours (±10 minutes)

Stage 2: Treatment with ACM or CM

Patients enrolled in Stage 2 were randomized to either ACM or CM and received treatment as outlined below:

- Stage 2: Randomized to ACM: Treatment with ACM over Days 1-9
  Follow the Stage 1 treatment schema above
- Stage 2: Randomized to CM: Treatment with CM over Days 1-4
  - Days 1, 2, and 3: cytarabine (C) - Continuous over 72 hours 2 gm/m^2 by continuous IV infusion over 72 hours (±2.5 hours) (i.e., 667 mg/m^2 daily for total of 2 gm/m^2)
  - Day 4: mitoxantrone hydrochloride (M) is administered 12 hours after completion of cytarabine treatment 40 mg/m^2 by IV infusion over 1-2 hours (±10 minutes)

Reference Therapy, Dose and Mode of Administration, Batch Number:

Stage 2: Randomized to CM: Treatment with CM over Days 1-4

- Cytarabine (C) - Continuous over 72 hours 2 gm/m^2 by continuous IV infusion over 72 hours (±2.5 hours) (i.e., 667 mg/m^2 daily for total of 2 gm/m^2)
- Mitoxantrone hydrochloride (M) administered 12 hours after completion of cytarabine treatment 40 mg/m^2 by IV infusion over 1-2 hours (±10 minutes)

Endpoints for Evaluation:

Efficacy:

The primary efficacy endpoint was: Complete remission (CR) rate

The secondary efficacy endpoints were:

- Combined CR rate
- Combined Response Rate
- Overall Survival (OS)
- Event-free Survival (EFS)
- Rate of Stem Cell Transplantation

Safety:

The safety variables evaluated were:

- 30- and 60-day Mortality
- Adverse Events
- Clinical Laboratory Assessments

Statistical Methods:

Details of statistical methods have been included here in this section as these were part of the study protocol. However, only select analyses were completed due to early termination of the study and lack of sufficient data results available for analyses.

Analysis Populations:

The analysis populations were defined as follows:

- Intent-to-treat (ITT) patient population included all patients randomized to receive study drug regardless of whether they actually received study drug and regardless of whether evidence was found indicating they failed to meet study inclusion/exclusion criteria or had other protocol violations. When the ITT patient population was analyzed, patients were grouped according to their randomized treatment regardless of actual treatment received. The ITT patient population was the analysis population for the primary analyses of efficacy endpoints
- Safety patient population: the subset of ITT patients who received at least one dose of study drug. When the safety patient population was analyzed, patients were grouped according to actual treatment received. The safety patient population was the analysis population for all analyses of safety data.

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- Response-available patient population: the subset of safety patients who had at least one response assessment on study. However, patients were to be excluded from the response-available patient population if they had an important protocol deviation, such as when evidence was found indicating they failed to meet any study inclusion/exclusion criterion. When the response-available patient population was analyzed, patients were grouped according to actual treatment received. The response-available population was used for biomarker analyses and sensitivity (secondary, supportive) analyses of efficacy endpoints.
- Per-protocol patient population: the subset of safety patients who either (a) had at least one response assessment on study, or (b) died prior to their first scheduled response assessment. However, patients were excluded from the per-protocol patient population if they had an important protocol deviation, such as when evidence was found indicating they failed to meet any study inclusion/exclusion criterion. When the per-protocol patient population was analyzed, patients were grouped according to actual treatment received. The per-protocol population was used for sensitivity (secondary, supportive) analyses of efficacy endpoints.
- Crossover patient population included all patients randomized to CM who, following 1-2 cycles of CM, received ACM as stipulated in the study protocol.

Each of the patient populations listed above was to be further subdivided for certain analyses. For example, data from ITT patients with relapsed/refractory AML who received ACM (i.e., the ITT population excluding relapsed/refractory patients receiving CM in cycle 1 and patients with newly diagnosed, high-risk AML) was analyzed to quantify the relationship between baseline MCL-1 dependence and the independent binary variable cycle-1 CR.

Interim Analysis:
A single interim analysis was planned in Stage 2 when Cycle-1 response was defined for 28 patients per treatment arm. Cycle-1 response could be available for more than 28 patients in one treatment arm when the alternate treatment arm reaches 28 because the enrollment ratio may not be precisely 1:1 over time. The additional patients in the faster-enrolling treatment arm were to be included in the interim analysis. Therefore, the interim analysis sample size was slightly more than 56 patients.

Cycle-1 CR rate (the primary efficacy endpoint) was tested using the statistical procedures described below. As shown in Section 16.1.9, Statistical Analysis Plan, a p-value ≤0.00321 was required to reject the null hypothesis of equal cycle-1 CR rates across treatment arms.

Measures taken to counter the effect of the interim analysis and maintain an overall 2.5% significance level are presented in Section 16.1.9, Statistical Analysis Plan.

Outcomes and Study Continuation
Two outcomes were possible from the interim analysis: statistically significant or nonsignificant. In the event of a nonsignificant difference between ACM and CM Cycle-1 CR rates (p-value >0.00321), the study was to continue to accrue and randomize patients.

If the interim analysis result for the primary analysis of Cycle-1 CR rate was statistically significant (p-value ≤0.00321), then randomization was to be stopped. Additional eligible Stage-2 patients were enrolled into the study to receive open-label ACM until the planned enrollment of 53 ACM patients was complete. No additional patients were enrolled into the CM treatment arm. Terminating randomization after the interim analysis had a negative effect on the power to declare treatment differences in secondary endpoints as statistically significant, however it was understood from polling investigators that they would be unwilling to enroll patients into the study once ACM had been established as superior to CM with respect to Cycle-1 CR rate.

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Efficacy Endpoint Analyses:

Remission Rates

The primary efficacy endpoint was Cycle-1 CR rate (i.e., the percentage of patients who achieve a CR after one cycle of treatment). Cycle 1 did not end until the patient started Cycle 2 or alternative AML therapy other than supportive measures (e.g., blood product transfusions). Therefore, a patient whose first response assessment in Cycle 1 was a CRi or CRp was considered to have achieved CR if neutrophils and platelets recovered prior to initiation of cycle 2 or alternative AML therapy including bone marrow or stem cell transplant. Patients who, for any reason, did not supply bone marrow for response assessment were counted among those not achieving remission. Best response during the study (i.e., best response following one or more cycles of treatment) was not selected as the primary efficacy endpoint due to the anticipated confounding effects of patients who were randomized to CM but crossover after one or two cycles to receive treatment with ACM.

Progression-Free Survival (PFS)

PFS time was defined for all patients and measured from the date of randomization (Day 1) until (a) treatment failure, (b) relapse after combined remission, or (c) death from any cause, whichever occurred first.

Treatment failure was defined as failing to achieve a combined remission following induction therapy. The date of treatment failure was the protocol-specified date for bone marrow collection following the first induction attempt (i.e., at neutrophil and platelet recovery or Day 45 of the treatment cycle, whichever occurred first), regardless of whether the patient received a second induction attempt (unless the second induction resulted in a combined remission in which case "treatment failure" did not apply).

Stem Cell Transplant Rate

Stem cell transplant (SCT) rate was the percentage of patients proceeding to SCT within 90 days after their last dose of study drug regardless of whether the patient remained enrolled in the study. Unless documentation of SCT was provided, patients who were lost to follow-up within the 90 days following their last dose of study drug were counted among those not receiving SCT.

Overall Survival

Overall survival (OS) time was defined for all patients and was to be measured from the date of randomization (Day 1) until death from any cause.

Rules for censoring OS time were:

- A patient with OS continuing as of the date he lost to follow-up had his OS time censored on the date of his last assessment of any type
- A patient with OS continuing as of the database lock had his OS time censored on the date of his last assessment of any type

Relapse-Free Survival (RFS) Following CR

RFS time was defined only for patients who achieved a CR during the study and was to be measured from the date of CR (Day 1) until (a) relapse after CR, or (b) death from any cause, whichever occurs first.

An additional rule for defining RFS time was:

- A patient assessed to have relapsed after missing one or more scheduled response assessments had his RFS time end on the scheduled date for the first missed response assessment following the last confirmation of CR

CR Duration

CR duration was defined only for patients who achieved a CR during the study and was measured from the date of CR (Day 1) until relapse.

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An additional rule for defining CR duration was:

- A patient assessed to have found relapsed after missing one or more scheduled response assessments had his CR duration end on the scheduled date for the first missed response assessment following the last confirmation of CR

ECOG Performance Status

ECOG performance status was summarized within treatment arm using shift tables.

Biomarker Endpoint Analyses:

The biomarker in this study was MCL-1 dependence measured by mitochondrial sensitivity to NOXA BH3 peptides. Relevant data supporting analyses of MCL-1 dependence were listed by patient within treatment arm. Summary of baseline biomarker values included within– and between–treatment-arm descriptive statistics appropriate for continuous variables (Section 16.1.9, Statistical Analysis Plan). An LR model was fit to examine the relationship between baseline MCL-1 dependence and the independent binary variable cycle-1 CR for relapsed and refractory AML patients receiving ACM. In addition, area under the curve (AUC) was calculated (by treatment arm) for the trapezoidal receiver operating characteristic (ROC) curve. This value quantified the ability of MCL-1 dependence to predict cycle-1 CR (Pierceall et al., 2014). Ninety-five percent CIs were calculated by assuming estimated AUC follows a normal distribution.

Safety Analyses:

Summaries of safety endpoints include data collected from the safety patient population. Relevant data supporting safety analyses were listed by patient within treatment arm.

30- and 60-day Mortality

Estimates of 30- and 60-day mortality and their pointwise 95% CIs were derived from Kaplan-Meier (KM) curves for OS by treatment arm (Section 16.1.9, Statistical Analysis Plan, Section 7.9.4).

Adverse Events:

Reported adverse event (AE) terms were mapped to MedDRA preferred terminology. AEs suggestive of TLS were flagged based in the standardized MedDRA query (SMQ) for TLS. All reported events appeared in AE listings; however only treatment-emergent adverse events were summarized. A treatment-emergent adverse event (TEAE) is an AE that started or increased in severity any time after the first administration of any study drug up to 30 days following the last administration of any study drug. AE severity was rated by the investigator according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 criteria. (U.S. Dept of Health and Human Services 2010)

A high-level safety summary was to display the numbers of patients within each treatment arm and overall, who experience one or more AEs in each of the following categories:

- All TEAEs regardless of severity or presumed relationship to study drug
- TEAEs judged related to study drug
- All TLS SMQ TEAEs
- TLS SMQ TEAEs judged related to study drug
- Treatment-emergent serious adverse events (SAEs)
- TEAEs leading to a delay in the administration of study drug
- TEAEs leading to a reduction in the protocol-specified dose of study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from the study
- TEAEs leading to death

The base summary of TEAEs was shown within– and between–treatment-arm incidence rates for each MedDRA primary System Organ Class and/or Preferred Term by highest reported CTCAE severity grade and

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overall. A separate summary was produced each of the AE subsets listed above. Additional AE summaries were to be produced using safety data from subsets of patients and/or characterized using additional SMQs. Partial start and end dates for adverse events were replaced by calendar dates that maximize the duration of the adverse event. The following steps were followed.

For a partial start date:

1. Replace a missing month with January
2. Replace a missing calendar day with the first of the month
3. If the replacement date is prior to the first dose of study drug, then set the adverse event start date equal to the date of the first dose

For a partial end date:

1. Replace a missing month with December
2. Replace a missing calendar day with the last day of the month

The replacement date for a missing end date could exceed the end of the adverse event reporting period specified in the study protocol. An end date was not estimated for adverse events that were marked as continuing at the end of the study.

Classification of Tumor Lysis Syndrome

The multivariate analysis and risk score prediction model by Montesinos and colleagues were used to assess the potential for development of TLS (Montesinos et al., 2008) (Section 16.1.1 Protocol TPI-ALV-201, Appendix F). Diagnosis of clinical TLS required the presence of laboratory TLS and elevated serum creatinine levels, cardiac arrhythmia and/or seizures. Criteria for grading the severity of clinical TLS are presented in (Section 16.1.9, Statistical Analysis Plan, Appendix 1). The numbers of patients experiencing laboratory TLS and the various severities of clinical TLS were to be summarized within and between treatment arms.

Clinical Laboratory Tests

Typical comparisons of results summarized by visit had limited interpretability in this study because (1) study drugs from the two treatment arms were administered on different cycle days (Days 1-9 for ACM versus Days 1-4 for CM), (2) the schedule for clinical laboratory evaluations (cycle day and frequency) was different between the treatment arms, and (3) additional cycles of treatment started according to patients' response to treatment rather than based on a predetermined schedule. Therefore, four groups of laboratory data were to be summarized separately:

- Cycle 1 results (from all patients in the safety population) up to the day a patient starts Cycle 2 or 10 weeks after starting Cycle 1, whichever comes first.
- Cycle 2 results (from patients in the safety population who receive at least 2 cycles of study drug) up to the day a patient starts Cycle 3 or 10 weeks after starting Cycle 2, whichever comes first.
- Cycle 3 results (from patients in the safety population who receive at least 3 cycles of study drug) up to the day a patient starts Cycle 4 or 10 weeks after starting Cycle 3, whichever comes first.
- Cycle 4 results (from patients in the safety population who receive 4 cycles of study drug) up to 10 weeks after starting Cycle 4

Laboratory test results measured on a continuous scale and changes from baseline values were to be summarized within treatment arm using mean, standard deviation, median, minimum, and maximum values. Results were to be summarized at baseline, on Days 1-9, and every 7 days starting with Day 15 for patients receiving ACM, and at baseline, on Days 1-4, and every 7 days starting with Day 8 for patients receiving CM. Up to the point of starting a new treatment cycle or withdrawing from the study, a patient's most recent test result was to be carried forward and included in analyses on days when clinical laboratory testing was not performed.

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Ordinal categorical test results were to be summarized within treatment arm using shift tables. Additionally, for tests where CTCAE [version 4.03] severity criteria were specified, CTCAE severity grades were to be summarized in shift tables.

Vital Signs

Vital signs and changes from baseline values were to be summarized by visit and within treatment arm using mean, standard deviation, median, minimum, and maximum values. Results were to be summarized at baseline, on Day 1 of each dosing cycle, and every 7 days thereafter. A patient's most recent test result was to be carried forward and included in analyses on days when vital signs were not assessed. Typical comparisons of results summarized by visit had limited interpretability for the same reasons outlined. Therefore, vital signs were to be analyzed separately for the four groups identified.

Concomitant Medications

Optionally, depending on the perceived relevance, concomitant medications were to be mapped to terminology in the WHO DDE and then summarized within treatment arm by usage rates for each level-1 ATC term and preferred (i.e., standardized) drug name.

Summary of Results:

Efficacy:

The study was terminated early in January 2020 due to a steady and marked decrease in enrollment and therefore could not reach all of its efficacy endpoints. Although the study protocol and the statistical analysis plan (SAP) had planned for a comprehensive analysis of the efficacy data, only select efficacy analyses could be performed due to early termination of the trial. As sufficient efficacy results were not available to analyze patients based on the percentage of MCL-1 dependency, the treatment efficacy was summarized by distributing the safety population into 6 groups based on whether the patients received the ACM or CM regimen and their disease stages at study entry as follows:

Randomized Stage

- CM relapsed/refractory (n=11) and
- ACM relapsed/refractory (n=11)

All Stages and Cohorts (including Randomized Stage)

- ACM Stage 1 (n=25)
- ACM relapsed/refractory (n=79)
- ACM newly diagnosed (n-14)
- ACM Total (N=93)

Table 6 summarizes the response assessment rates in the safety population based on the above 6 groups.

The primary efficacy endpoint was CR rate as assessed by the investigator following treatment with ACM or CM.

In Stage 1, the ACM group (n=25) achieved a CR of 32.0% (n=8). The CRi rate was 20.0% (n=5). One patient (4.0%) had PR and 5 patients (20.0%) had resistant or relapsed disease. The remaining 6 patients were not evaluated. The response rates for complete remission with incomplete recovery (CR or CRi) and any remission (CR, CRi or PR) were 52.0% and 56.0%, respectively. The median duration of response for CR and CR/CRi in Stage 1 was 6.9 months and 8.7 months respectively (Section 16.7). These encouraging results observed in Stage 1 prompted further continuation into the randomized Stage 2 portion of the study.

In the randomized stage (Stage 2), the CM relapsed/refractory group (n=11) achieved a CR of 54.5% (n=6). The remaining 5 patients in the group had resistant or relapsed disease. No patients had CRi or PR. The ACM

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relapsed/refractory group (n=11) in the randomized portion of the study, achieved a CR of 18.2% (n=2) and a CRi of 27.3% (n-3). The remaining 5 patients in the group had resistant or relapsed disease. Any remission rates (CR, CRi or PR) for the CM group (n=11) and ACM group (n=11) were 54.5% and 45.5 %, respectively. It should be noted that all these patients in the randomized stage (Stage 2) had an MCL-1 score of >30%.

Across all stages (Stage 1 and Stage 2) and exploratory cohorts, a total of 93 patients enrolled received at least 1 cycle of ACM which resulted in a 29.0% CR (n=27) and a CR/CRi of 47.3%. CRi was achieved in 17 (18.3%) patients while 2 (2.2%) patients had PR. A total of 34 (36.6%) patients had resistant /relapsed disease and the remaining 13 (14.0%) were not evaluated.

The ACM relapsed/refractory group (n=79) across all stages and cohorts, 21 (26.6%) patients achieved CR, 15 (19.0%) achieved CRi and 1 (1.3%) achieved PR. A total of 30 (38.0%) patients had resistant /relapsed disease and 12 (15.2%) remained unevaluated. The response rates for complete remission with incomplete recovery (CR or CRi) and any remission (CR, CRi or PR) were 45.6% and 46.8%, respectively.

In the exploratory arm consisting of newly diagnosed ACM patients (n=14), 6 (42.9%) patients achieved CR, 2 (14.3%) achieved CRi and 1 (7.1%) achieved PR. A total of 4 (28.6%) patients had resistant /relapsed disease and 1 (7.1%) was not evaluated. The response rates for complete remission with incomplete recovery (CR or CRi) and any remission (CR, CRi or PR) were 57.1% and 64.3%, respectively.

Safety Results:

A global summary of TEAEs, including patients with at least one AE, treatment-related AEs, SAEs, AEs leading to study withdrawal, and deaths during the study period is presented in Table 9. The incidence of TEAEs by body system and preferred term is summarized in Table 10 for the treatment period. TEAEs that occurred during the treatment period are summarized by their severity and relationship to study medication in Table 11. A summary of possibly or probably related TEAEs by severity that occurred during the treatment period is presented in Table 12 and Table 13 respectively. A summary of SAEs related to study drug is presented in Table 14. A summary of AEs for TLS related to the study medication is presented in Table 15. AEs were reported using MedDRA® (Version 19.1).

Overall TEAE and Non-hematological TEAEs (NH-TEAEs) were observed in all patients of the study population (ACM group: n=93; CM group: n=11).

For the CM group:

- NH-TEAEs with ≥Grade 3 related to the study drug were reported in 27.3% (n=3) of the patients while ≥Grade 4 AEs were 0%.
- TEAEs with ≥Grade 3 included 2 (18.2%) cases of sepsis, and 1 event (9.1%) each of colitis, hypokalemia, and hyperglycemia.
- TEAEs ≥Grade 3 judged Possibly, Probably or Definitely Related to the Study Drug Regimen included: anemia (n=2, 18.2%) and febrile neutropenia (n=2, 18.2%).

In the Total ACM group:

- NH-TEAEs with ≥Grade 3 judged related to study drug regimen were reported in 57 (61.3%) patients while TEAEs with ≥Grade 4 judged related to study drug regimen were observed in 20 (21.5%) patients.
- The most frequent TEAEs ≥Grade 3 were hypokalemia (n=21, 22.6%), hypophosphatemia (n=20, 21.5%), and sepsis (n=16, 17.2%).
- TLS ≥Grade 3 was reported in 21 patients (22.6%).

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- Serious TEAEs reported were cytokine release syndrome in 3 patients (3.2%)

The study reported 12 (12.9%) deaths in the Total ACM group – causes for death included sepsis (n=4), disease progression (n=2) and one event each of acute kidney injury, mitral valve regurgitation, respiratory distress, lung infection, left ventricular systolic dysfunction and suicide.. Of these, 5 deaths were reported in the ACM relapsed/refractory group and causes of death were sepsis, progressive disease, lung infection and general physical health deterioration. Sepsis was thought to be possibly related to the drug regimen. One death was reported in the newly diagnosed ACM group and the cause of death left ventricular dysfunction was probably related to the drug regime. The remaining 6 deaths in the ACM group were caused due to sepsis, acute kidney injury, mitral valve regurgitation, progressive disease, and acute respiratory distress. Sepsis and acute kidney injury were possibly related while mitral valve regurgitation was probably related to the drug regimen. One (9.1%) death was reported in the CM group
In ACM relapsed/refractory group:

- NH-TEAEs with ≥Grade 3 were reported in 48 (60.8%) patients while TEAEs with ≥Grade 4 was observed in 18 (22.8%) patients.
- The most common TEAEs ≥Grade 3 were: TLS (n=18, 22.8%), hypokalemia (n=19, 24.1%), hypophosphatemia (n=17, 21.5%), febrile neutropenia (n=41, 51.9%), anemia (n=23, 29.1%), and sepsis (n=13, 16.5%).
- TEAEs ≥Grade 3 judged possibly, probably, or definitely related to the study drug regimen included: tumor lysis syndrome (n=16, 20.3%) and sepsis (n=7, 8.9%). Other major TEAEs were anemia (n=18, 22.8%) and febrile neutropenia (n=17, 21.5%).
- SAEs included cytokine release syndrome (n=2, 2.5%), tumor lysis syndrome (n=3, 3.8%), and sepsis (n=5, 6.3%).

In ACM newly diagnosed group:

- NH-TEAEs with ≥Grade 3 were reported in 9 (64.3%) patients while TEAEs with ≥Grade 4 was observed in 2 (14.3%) patients.
- The most common TEAEs ≥Grade 3 were: tumor lysis syndrome (n=3, 21.4%), sepsis (n=3, 21.4%), hypokalemia (n=3, 21.4%), hypophosphatemia (n=3, 21.4%), and febrile neutropenia (n=5, 35.7%).
- TEAEs ≥Grade 3 possibly, probably, or definitely related to the study drug regimen included: tumor lysis syndrome (n=3, 21.4%), anemia (n=2, 14.3%), and febrile neutropenia (n=3, 21.4%).
- SAEs included a single case (7.1%) of cytokine release syndrome.

Conclusions:
The TPI-ALV-201 study was a Phase 2, randomized, biomarker-driven, clinical study in patients with relapsed or refractory acute AML with MCL-1 dependence ≥30%. This abbreviated report aims to elaborate on the safety profile of the ACM regimen versus the CM regimen in the above study population.

The study protocol underwent a few major amendments during the course of the trial from 2016 to 2020. The treatment arms were expanded to include an additional exploratory arm for newly diagnosed high-risk AML patients and one separate exploratory arm for patients with a NOXA BH3 priming range of 30-39%. The study protocol was further amended and changed scope in May 2019 (Amendment 9) to remove the exploratory arms and closed arms to further enrollment. Stage 2 enrollment was limited to 56 patients with relapsed/primary refractory AML to shorten the time to study completion and to allow for expeditious analysis and reporting of outcomes. A final amendment in August 2019 (Amendment 11) modified the lower limit of MCL-1

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dependency for study inclusion from ≥40% to ≥30%.

The study was terminated early in January 2020 due to marked decreased in enrollment and therefore could not reach all of its efficacy endpoints. Although the study protocol and the SAP had planned for a comprehensive analysis of the efficacy data, only select efficacy analyses could be performed due to early termination of the trial. As sufficient efficacy results were not available to analyze patients based on the percentage of MCL-1 dependency, the treatment efficacy was summarized by distributing the safety population into 6 groups based on whether the patients received the ACM or CM regimen and their disease stages at study entry, detailed in Section 11.4.

Treatment with ACM in Stage 1 (n=25) showed a 32.0% CR and a CR/CRi rate of 52.0%. Any remission (CR, CRi and PR) rate for this group was 56.0%. The median duration of response for CR and CR/CRi in Stage 1 was 6.9 months and 8.7 months, respectively (Section 16.7). These encouraging results observed in Stage 1 prompted further continuation into the randomized Stage 2 portion of the study.

Overall, treatment with ACM in the Total ACM group (n=93) across both Stage 1 and Stage 2 including the exploratory cohorts was found to show a 29.0% CR with a CR/CRi rate of 47.3%. A total of 36.6% (n=34) in this group had resistant or relapsed disease. A total of 18.3% (n=17) patients in the Total ACM group had CRi. The CM group (n=11) from the randomized stage had a 54.5% CR and the remaining 45.5% patients had resistant or relapsed disease The CR rates in the ACM relapsed/refractory group (n=79) and the ACM newly diagnosed group (n=14) across both the stages were 26.6% and 42.9% respectively.

CR/CRi rates across all the 6 groups ranged from 45.5% to 57.1%. Remission rates (CR, CRi or PR) for the Total ACM and CM group were at 49.5% and 54.5% respectively.

Overall survival for the Total ACM group and the CM group was 9.7 months (95% CI: 6.6,16.8) and 7.6 months (95% CI: 2.7, NA). Median RFS was 11.8 months in Total ACM group, but was not reached for the CM group as of the data cutoff date 08 July 2020. 30-and 60- day survival rates did not vary substantially across the Total ACM group and the CM group. The Total ACM group achieved a 1-year survival of 44.7%. while it was not reached for the CM group as of the data cutoff date of 08 July 2020.

This report provides a detailed safety evaluation of patients receiving the ACM vs CM regimen (Section 12.2.

Overall, TEAE and NH-TEAE were observed in all patients of the study population (Total ACM group: n=93; CM group: n=11).

NH-TEAE Grades 3, 4 or 5 judged related to study drug regimen were reported in the Total ACM group (n=57, 61.3%), and CM group (n=3, 27.3%). In the Total ACM group (n=93), commonly reported TEAEs ≥Grade 3 in the Total ACM group included hypokalemia (n=21, 22.6%), TLS (n=21, 22.6%), hypophosphatemia (n=20, 21.5%), and sepsis (n=16, 17.2%). Cytokine release syndrome was the most commonly reported SAE in 3 patients (3.2%).

In the CM group (n=11), commonly reported TEAEs with ≥Grade 3 included 2 (18.2%) cases of sepsis, and 1 event (9.1%) each of colitis, hypokalemia, and hyperglycemia.

NH-TEAE Grades 4 or 5 judged related to study drug regimen occurred in 20 (21.5%) patients in the Total ACM group; there were no reports in the CM group.

There were 34 (36.6%) serious NH-TEAEs in the Total ACM group, and 3 (27.3%) in the CM group. Commonly reported SAEs in the Total ACM group included cytokine release syndrome (n=3, 3.2%) and tumor lysis syndrome (n=3, 3.2%), and sepsis (n=5, 5.4%). NH-TEAE judged related to the study drug regimen occurred in 87 (93.5%) and 8 (72.7%) patients in Total ACM group and CM group, respectively.

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Any serious NH-TEAE related to study drug regimen occurred more frequently in the Total ACM group (n=16, 17.2%) compared to CM group (n=0). Fatal NH-TEAEs in Total ACM group and CM group were reported to be 12.9% and 9.1%, respectively.

The study reported 12 (12.9%) deaths in the Total ACM group. Of these, 5 deaths were reported in the ACM relapsed/refractory group and causes of death were sepsis, progressive disease, lung infection and general physical health deterioration. Sepsis was thought to be possibly related to the drug regimen. One death was reported in the newly diagnosed ACM group and the cause of death left ventricular dysfunction was probably related to the drug regime. The remaining 6 deaths in the ACM group were caused due to sepsis, acute kidney injury, mitral valve regurgitation, progressive disease, and acute respiratory distress. Sepsis and acute kidney injury were possibly related while mitral valve regurgitation was probably related to the drug regimen. One (9.1%) death was reported in the CM group.

Overall, higher rates of AEs and SAEs related to the study drug regimen were reported in the ACM groups compared to the CM group. However, the adverse event profile of the ACM regimen did not detect any unexpected safety signals in the safety population. It is also important to note that the sample size of the CM group was much lower compared to the total ACM group.

In conclusion, the safety results indicate that the ACM regimen has an acceptable safety profile and can be well tolerated in patients with relapsed/refractory AML patients with MCL-1 dependence ≥30% when compared with the CM regimen.

Date of the Report:

04 November 2020