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ORIGINAL ARTICLE

Combination treatment of copanlisib and gemcitabine in relapsed/refractory PTCL (COSMOS): an open-label phase I/II trial☆

H.-Y. Yhim[1,2†], T. Kim[3†], S. J. Kim[4], H.-J. Shin[5], Y. Koh[6], J. S. Kim[7], J. Park[8], G. S. Park[9], W. S. Kim[4], J. H. Moon[10*] & D.-H. Yang[11*]

[1]Department of Internal Medicine, Jeonbuk National University Medical School, Jeonju; [2]Research Institute of Clinical Medicine of Jeonbuk National University-Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju; [3]Department of Medical Sciences, Chonnam National University Medical School, Jeollanam-do; [4]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul; [5]Department of Internal Medicine, Pusan National University Hospital, Busan; [6]Department of Internal Medicine, Seoul National University Hospital, Seoul; [7]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul; [8]Department of Internal Medicine, Gachon University Gil Medical Center, Incheon; [9]Department of Pathology, Seoul St. Mary's Hospital, College of Medicine, Catholic University of Korea, Seoul; [10]Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu; [11]Department of Internal Medicine, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Jeollanam-do, Republic of Korea

Available online 25 December 2020

Background: Current treatment options for peripheral T-cell lymphomas (PTCLs) in the relapsed/refractory setting are limited and demonstrate modest response rates with rare achievement of complete response (CR).

Patients and methods: This phase I/II study (NCT03052933) investigated the safety and efficacy of copanlisib, a phosphatidylinositol 3-kinase-α/-δ inhibitor, in combination with gemcitabine in 28 patients with relapsed/refractory PTCL. Patients received escalating doses of intravenous copanlisib on days 1, 8, and 15, administered concomitantly with fixed-dose gemcitabine (1000 mg/m^2 on days 1 and 8) in 28-day cycles.

Results: Dose-limiting toxicity was not observed in the dose-escalation phase and 60 mg copanlisib was selected for phase II evaluation. Twenty-five patients were enrolled in phase II of the study. Frequent grade ≥3 adverse events (AEs) included transient hyperglycemia (57%), neutropenia (45%), thrombocytopenia, (37%), and transient hypertension (19%). However, AEs were manageable, and none were fatal. The overall response rate was 72% with a CR rate of 32%. Median duration of response was 8.2 months, progression-free survival was 6.9 months, and median overall survival was not reached. Combination treatment produced a greater CR rate in patients with angioimmunoblastic T-cell lymphoma than those with PTCL-not otherwise specified (55.6% versus 15.4%, respectively, $P = 0.074$) and progression-free survival was significantly longer (13.0 versus 5.1 months, respectively, $P = 0.024$). In an exploratory gene mutation analysis of 24 tumor samples, *TSC2* mutation was present in 25% of patients and occurred exclusively in responders.

Conclusion: The combination of copanlisib and gemcitabine is a safe and effective treatment option in relapsed/refractory PTCLs and represents an important new option for therapy in this rare group of patients.

Key words: copanlisib, gemcitabine, peripheral T-cell lymphoma, relapsed or refractory, phase I/II trial

INTRODUCTION

Peripheral T-cell lymphomas (PTCLs) are a biologically heterogeneous group of mature T- and natural killer (NK)-cell neoplasms, comprising ∼10%-15% of non-Hodgkin lymphoma.[1] With some exception of anaplastic large-cell lymphoma, anaplastic lymphoma kinase positive, a substantial proportion of patients will experience treatment failure and require salvage treatment.[2] However, treatment outcomes in these patients with relapsed or refractory disease are quite disappointing with a median overall survival (OS) of 5.5 months.[3] Several novel agents, namely, pralatrexate, romidepsin, and belinostat, have shown activity for relapsed/refractory PTCLs,

*Correspondence to: Prof. Deok-Hwan Yang, Department of Internal Medicine, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, 322 Seoyang-ro, Hwasun, Jeollanam-do, 58128, Republic of Korea. Tel: +82-61-379-7636; Fax: +82-61-379-7628
E-mail: drydh1685@hotmail.com (D.-H. Yang).
*Prof. Joon Ho Moon, Department of Hematology/Oncology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, 130 Dongdeok-ro, Jung-gu, Daegu, 41944, Republic of Korea. Tel: +82-53-200-6314; Fax: +82-53-426-2046
E-mail: jhmoon@knu.ac.kr (J. H. Moon).

☆Note: This study was presented in part as an abstract for the 25th European Hematology Association Annual Congress, Virtual edition, 11-21 June 2020.

† These authors contributed equally to this work as co-first authors.

but demonstrate modest overall response rates (ORRs) of ~25% with rare complete response (CR) achievement.[4-6] Such data underscore the need for new treatment options in patients with relapsed/refractory PTCLs, who typically have limited response to salvage therapy and extremely poor OS rates.

The phosphatidylinositol 3-kinase (PI3K)—serine/threonine-protein kinase B (AKT)—mammalian target of rapamycin (mTOR) pathway plays a crucial role in cellular metabolism, growth, differentiation, and survival.[7] This pathway has been reported to be highly activated in both B-cell and T- or NK-cell lymphoma[8-10] and is identified as a potential therapeutic target of blockage. Copanlisib (Bayer AG, Berlin, Germany), an inhibitor of PI3K-α and -δ isoforms, is under active clinical development for use in treatment against various histologic subtypes of lymphoma. In a phase II trial including relapsed/refractory PTCL patients, copanlisib monotherapy demonstrated preliminary clinical activity with an ORR of 21.4% and two CRs in a cohort of 17 patients.[11] However, as in the case with other novel agents, inhibition of the PI3K—AKT—mTOR pathway by single-agent copanlisib showed only modest ORR and CR rates. This may be a consequence of alternative signaling pathways activated as negative feedback to inhibition of the PI3K—AKT—mTOR pathway, raising the need for combination of copanlisib with other therapeutic agents.[12]

Gemcitabine is a pyrimidine antimetabolite with high tumoricidal activity and moderate toxicity, and is frequently utilized for the treatment of relapsed/refractory B- and T-cell lymphoma patients.[13,14] In a phase II trial of relapsed/refractory PTCL patients, gemcitabine monotherapy (1200 mg/m^2 on days 1, 8, and 15 every 4 weeks) demonstrated an ORR of 51%, including 23% of patients with CR.[13] A preclinical study has shown that the PI3K—AKT pathway inhibition exerts chemosensitivity to gemcitabine in the pancreatic cancer cell line,[15] suggesting potential synergic effects between these agents. Based on such demonstrated activity and proposed mechanisms, the copanlisib and gemcitabine combination therapy may be an effective option for this difficult-to-treat group of patients.

Here we report the results of COSMOS, a phase I/II trial in patients with relapsed/refractory PTCLs, addressing the safety, tolerability, and preliminary activity of the copanlisib and gemcitabine combination.

PATIENTS AND METHODS

Study design and patients

This multicenter, open-label, single-arm phase I/II trial enrolled relapsed/refractory PTCL patients at eight institutions belonging to the Consortium for Improving Survival of Lymphoma (CISL) study group in South Korea. In phase I, dose escalation followed a modified 3 + 3 design to determine the maximum tolerated dose (MTD) of copanlisib in combination with fixed-dose gemcitabine. Phase II evaluated the efficacy and safety of the combination at the dose level determined. An additional maintenance treatment phase was followed in patients with stable disease or better response, but outcomes of the induction combination treatment are the subject of this report. Exploratory analysis of target mutational status was performed for patients with available tumor specimens.

Eligible patients were ≥19 years of age with relapsed/refractory PTCLs or NK/T-cell lymphomas, excluding primary cutaneous T-cell lymphoma or Sezary syndrome. Additional requirements were adequate organ function and the presence of at least one measurable lesion according to the Lugano 2014 classification.[16] Histologic diagnosis was centrally reviewed and confirmed by the CISL Pathology Committee. Exclusion criteria were Eastern Cooperative Oncology Group performance status score >2, central nervous system involvement, prior allogeneic stem cell transplant, diabetes mellitus with HbA1c >8.5%, active infection requiring systemic therapy, other malignancy within the past 3 years, previous exposure to gemcitabine or PI3K inhibitors, pregnancy or lactating, and human immunodeficiency virus or hepatitis B/C seropositivity. Patients positive for anti-HBc antibody were eligible if they were negative for hepatitis B virus DNA quantification. There was no limit to the number of prior treatments.

The study was approved by the institutional review board at each institution and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. An independent data monitoring committee reviewed safety and assessed risk—benefit during the study. All authors had access to primary trial data. This trial was registered at www.clinicaltrials.gov (Registration no. NCT03052933).

Treatment and assessments

Study treatment consisted of induction therapy with a combination of copanlisib and gemcitabine administered every 28 days for six cycles, followed by 12 cycles of maintenance single-agent copanlisib. In phase I, patients were sequentially enrolled in two cohorts to receive escalating doses of intravenous copanlisib at 45 mg (level +0) or 60 mg (level +1) on days 1, 8, and 15, with at least three patients at each dose level, administered concomitantly with fixed-dose gemcitabine at 1000 mg/m^2 on days 1 and 8. A dosing level of 30 mg (level −1) was included for dose de-escalation adopting a modified 3 + 3 design.[17] Prophylactic trimethoprim—sulfamethoxazole once daily was administered throughout treatment but prophylactic use of granulocyte-colony stimulating factor was not allowed. Dose-limiting toxicities (DLTs) were assessed during the 28-day period of cycle one. DLT definitions are described in the Supplementary Materials and Methods, available at https://doi.org/10.1016/j.annonc.2020.12.009. The MTD of copanlisib when combined with gemcitabine was defined as the highest dose level at which less than one-third of the cohort experienced a DLT.

The established MTD of copanlisib was used for phase II evaluation in which patients received combination study treatment for up to six cycles. Patients treated at the MTD in phase I were allowed for entry into phase II. The primary

efficacy endpoint was the ORR defined as the composite of partial response (PR) or CR. For phase I/II, secondary endpoints included duration of response, progression-free survival (PFS), OS, and safety. Tumor response was assessed by each investigator using computed tomography and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging according to the Lugano 2014 classification.[16] Patients underwent computed tomography scan at screening and then at every two cycles during combination therapy, every three cycles during copanlisib maintenance, and every 4 months thereafter. ^{18}F-FDG PET scans were mandated at baseline and the end of combination therapy. Adverse events (AEs) were evaluated using the NCI-CTCAE (version 4.03) from study enrollment to 28 days after the last study treatment.

Targeted gene mutational analyses

Details regarding target gene sequencing and mutational analysis of patient tumor specimens are described in the Supplementary Materials and Methods, available at https://doi.org/10.1016/j.annonc.2020.12.009. In brief, genomic DNA was extracted from formalin-fixed paraffin-embedded tissue at relapse. Targeted sequencing was performed for all coding exons of 92 genes covering PTCL- and PI3K-related genes (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.12.009) using the Illumina NextSeq 500 system (San Diego, CA). Captured libraries were sequenced to a median exon coverage depth >500× (DNA). Known confirmed somatic alterations deposited in COSMIC version 62 were called at allele frequencies ≥1%. Then, false-positive variant cells originating from the oxoG artifact were excluded. To obtain a confident variant list, mutations below 2% variant allele frequency and 100× total depth were excluded. Variants were also excluded if they did not change protein sequences or affect splice sites, or if minor allele frequency was ≥1% in the gnomAD, ExAC, and Macrogen Korean Population Database. Frequent germline variants from the 1000 Genomes Project (dbSNP142) were removed. All sequencing data are deposited at the European Nucleotide Archive (Study Accession: PRJEB42182).

Statistical analyses

PI3K inhibition by a single novel agent has been reported to produce an ORR of ∼20% in relapsed/refractory PTCL patients.[11] Sample size for phase II of the study was calculated assuming the target ORR of combination treatment to be 45% with a one-sided type 1 error rate of 5% and at least 80% power. Efficacy of treatment in phase II of the study was assessed according to Simon's optimal two-stage design. In the first stage, 10 patients were to be accrued; if 2 or more patients achieved PR or CR, the study continued until the accrual reached 22 patients. Assuming a dropout rate of 10%, 25 patients were required for enrollment.

The Kaplan–Meier method was used to estimate time-to-event endpoints, and survival curves were compared by the log-rank test. A two-sided $P < 0.05$ was considered significant. Mutational status (mutated versus wild type) was compared using Fisher's exact test according to the treatment response status (responder versus non-responder). For statistical analyses, R statistical software 3.6.3 (the R Foundation for Statistical Computing, Vienna, Austria; available at http://www.r-project.org) was used.

RESULTS

Patient characteristics

Between March 2018 and April 2019, 28 patients were enrolled and received study treatment, all of whom were evaluable for safety and efficacy. Baseline characteristics are listed in Table 1. The median age was 62.5 years (range 22-79), including 23 patients with advanced-stage disease and 6 prior autologous transplant patients. The most common subtype was PTCL-not otherwise specified (PTCL-NOS; $n = 13$) and most patients ($n = 21$) had refractory disease at study entry. At the time of final data analysis (December 2019), 15 patients completed all planned six cycles of the copanlisib/gemcitabine combination. However, 13 patients discontinued combination treatment, primarily due to disease progression ($n = 11$). One patient discontinued combination treatment due to recurrent grade 2 fatigue and another patient discontinued treatment after achieving PR and proceeding to allogeneic stem cell transplant.

MTD and safety

In phase I, six patients were enrolled into the study; three patients each in cohort 1 and cohort 2 were treated with 45 and 60 mg copanlisib, respectively, in combination with gemcitabine. No DLTs were observed and the MTD was not reached at the highest planned dose level. Twenty-two additional patients enrolled into phase II were treated with copanlisib at the determined dose of 60 mg on days 1, 8, and 15, intravenously in combination with 1000 mg/m^2 gemcitabine on days 1 and 8. Thus, a total of 25 patients were treated at the MTD.

AEs were assessed in 132 cycles of treatment (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.12.009). The most common non-hematologic AEs were hyperglycemia (81.1%) and hypertension (44.7%), which included grade 3 (hyperglycemia, 53.0%; hypertension, 18.9%) and grade 4 (hyperglycemia, 3.8%) events. Hyperglycemia and hypertension were copanlisib infusion related, and the majorities were transient and manageable by the temporary use of insulin and antihypertensive drugs. No dose reduction or treatment discontinuation occurred due to recurrent hyperglycemia or hypertension. Other frequently reported grade 3/4 AEs were neutropenia (grade 3, 23.5%; grade 4, 21.2%) and thrombocytopenia (grade 3, 26.5%; grade 4, 10.6%). Febrile neutropenia occurred in five cycles (3.8%; all grade 3) of four patients and resolved with appropriate supportive care. During the combination therapy, seven nonfatal viral infections were observed: five herpes zoster and two unspecified viral pneumonia. The median onset of herpes

Table 1. Baseline clinical characteristics

Characteristics	Copanlisib dose		Total ($N = 28$)
	45 mg ($N = 3$)	60 mg ($N = 25$)	
Age, years			
Median	49	63	62.5
Range	39-73	22-79	22-79
Sex			
Male	2 (66.7)	14 (56.0)	16 (57.1)
Female	1 (33.3)	11 (44.0)	12 (42.9)
Histologic subtypes			
PTCL-NOS	1 (33.3)	12 (48.0)	13 (46.4)
AITL	2 (66.7)	7 (28.0)	9 (32.1)
ENKTL	0 (0)	3 (12.0)	3 (10.7)
ALCL, ALK-neg	0 (0)	1 (4.0)	1 (3.6)
EATL	0 (0)	1 (4.0)	1 (3.6)
SPLTL	0 (0)	1 (4.0)	1 (3.6)
Ann Arbor stage at study entry			
1-2	0 (0)	5 (20.0)	5 (17.9)
3-4	3 (100)	20 (80.0)	23 (82.1)
ECOG performance status at study entry			
0 or 1	3 (100)	22 (88.0)	25 (89.3)
2	0 (0)	3 (12.0)	3 (10.7)
B symptoms at study entry			
Absence	2 (66.7)	18 (72.0)	20 (71.4)
Presence	1 (33.3)	7 (28.0)	8 (28.6)
Serum lactate dehydrogenase level at study entry			
Normal	1 (33.3)	12 (48.0)	13 (46.4)
Elevated	2 (66.7)	13 (52.0)	15 (53.6)
BM involvement at study entry			
Absence	3 (100)	19 (76.0)	22 (78.6)
Presence	0 (0)	6 (24.0)	6 (21.4)
Number of prior systemic therapy for PTCL			
1	1 (33.3)	16 (64.0)	17 (60.7)
2	1 (33.3)	9 (36.0)	10 (35.7)
3	1 (33.3)	0 (0)	1 (3.6)
Previous systemic therapy			
CHOP or CHOEP	3 (100)	22 (88.0)	25 (89.3)
ICE	2 (66.7)	5 (20.0)	7 (25.0)
SMILE	1 (33.3)	2 (8.0)	3 (10.7)
VIDL	0 (0)	2 (8.0)	2 (7.1)
VIPD	0 (0)	1 (4.0)	1 (3.6)
GDP	0 (0)	1 (4.0)	1 (3.6)
DHAP	0 (0)	1 (4.0)	1 (3.6)
Prior ASCT	1 (33.3)	5 (20.0)	6 (21.4)
Comorbidities at entry			
Diabetes mellitus	1 (33.3)	8 (32.0)	9 (32.1)
Hypertension	0 (0)	11 (44.0)	11 (39.3)
Disease status at study entry			
Relapsed	1 (33.3)	6 (24.0)	7 (25.0)
Refractory	2 (66.7)	19 (76.0)	21 (75.0)

Values are expressed as number of patients and percentage, unless otherwise indicated.

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK-neg, anaplastic lymphoma kinase-negative; ASCT, autologous stem cell transplantation; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; EATL, enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; ENKTL, extranodal natural killer/T-cell lymphoma; GDP, gemcitabine, dexamethasone, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; SMILE, dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; SPLTL, subcutaneous panniculitis-like T-cell lymphoma; VIDL, etoposide, ifosfamide, dexamethasone, and L-asparaginase; VIPD, etoposide, ifosfamide, cisplatin, and dexamethasone.

zoster from the start of study treatment was 2.9 months (range 0.3-5.7) and all five patients showed localized cutaneous herpes zoster without dissemination.

Four patients required dose reduction of copanlisib to 45 mg due to neutropenia or infection ($n = 3$), and thrombocytopenia ($n = 1$), and one patient received dose reduction to 30 mg due to neutropenia. One patient discontinued combination treatment due to recurrent fatigue. There were no fatal AEs.

Efficacy

Tumor response was evaluable in all 28 patients from phase I/II of the study. For 25 patients included in the phase II analysis, the ORR was 72% (95% CI 54.4-89.6), with 8 achieving CR and 10 achieving PR. Two additional patients, who received copanlisib 45 mg together with gemcitabine in phase I, achieved objective responses (one CR and one PR). A waterfall plot of the best response in target lesions showed that 20 (71.4%) of the 28 patients had at least a 50% reduction in lesions after the combination treatment (Figure 1A). The median time to response was 2.2 months (range 1.6-4.4) in responders. The combination of copanlisib and gemcitabine showed a nonstatistically significant difference in CR rate between patients with angioimmunoblastic T-cell lymphoma (AITL) and those with PTCL-NOS [55.6% (5/9) versus 15.4% (2/13), $P = 0.074$], in which all CR was confirmed by FDG PET scan. The median duration of response was 8.2 months (95% CI 5.0-11.4). Among the seven responders of AITL subtype, four patients continued on study treatment and were in CR after 16.5, 10.3, 8.8, and 7.2 months, respectively (Figure 1B). With a median follow-up of 8.9 months (interquartile range 6.3-12.1), median PFS was 6.9 months (95% CI 3.5-10.3; Figure 2A), and median OS was not reached (Figure 2B). Patients with AITL had significantly longer PFS than those with PTCN-NOS [median, 13.0 months (95% CI 5.4-20.6) versus 5.1 months (95% CI 4.1-6.0), $P = 0.024$; Figure 2C].

Of the 13 patients with PTCL-NOS, one patient was of the T-follicular helper phenotype. This patient achieved CR after four cycles of combination treatment and completed six cycles of therapy as planned.

Mutational profiles

Targeted gene mutational analysis was performed in 25 of 28 patients with available formalin-fixed paraffin-embedded samples at relapse. All patients provided written informed consent and evaluable data meeting quality standards were available for 24 of 25 patients. Data were most frequently available in PTCL-NOS ($n = 10$) and AITL ($n = 9$) tumor samples with some information in extranodal NK/T-cell lymphoma ($n = 3$), anaplastic large cell lymphoma ($n = 1$), and enteropathy-associated T-cell lymphoma ($n = 1$). The most common mutations across all subtypes were *TYK2* ($n = 20$) followed by *RPTOR* ($n = 17$) and *TET2* ($n = 13$; Figure 3). *TET2* ($n = 8/9$), *IDH2* ($n = 4/9$), and *RHOA* ($n = 5/9$) mutations were frequently observed in patients with AITL. In addition, *TSC2* ($n = 6$), *IDH2* ($n = 4$), *PIK3C2B* ($n = 3$), and *YTHDF2* ($n = 3$) mutations occurred exclusively in the responders, whereas *VAV1* ($n = 3$) mutation was observed only in non-responders. Patients with *TSC2*

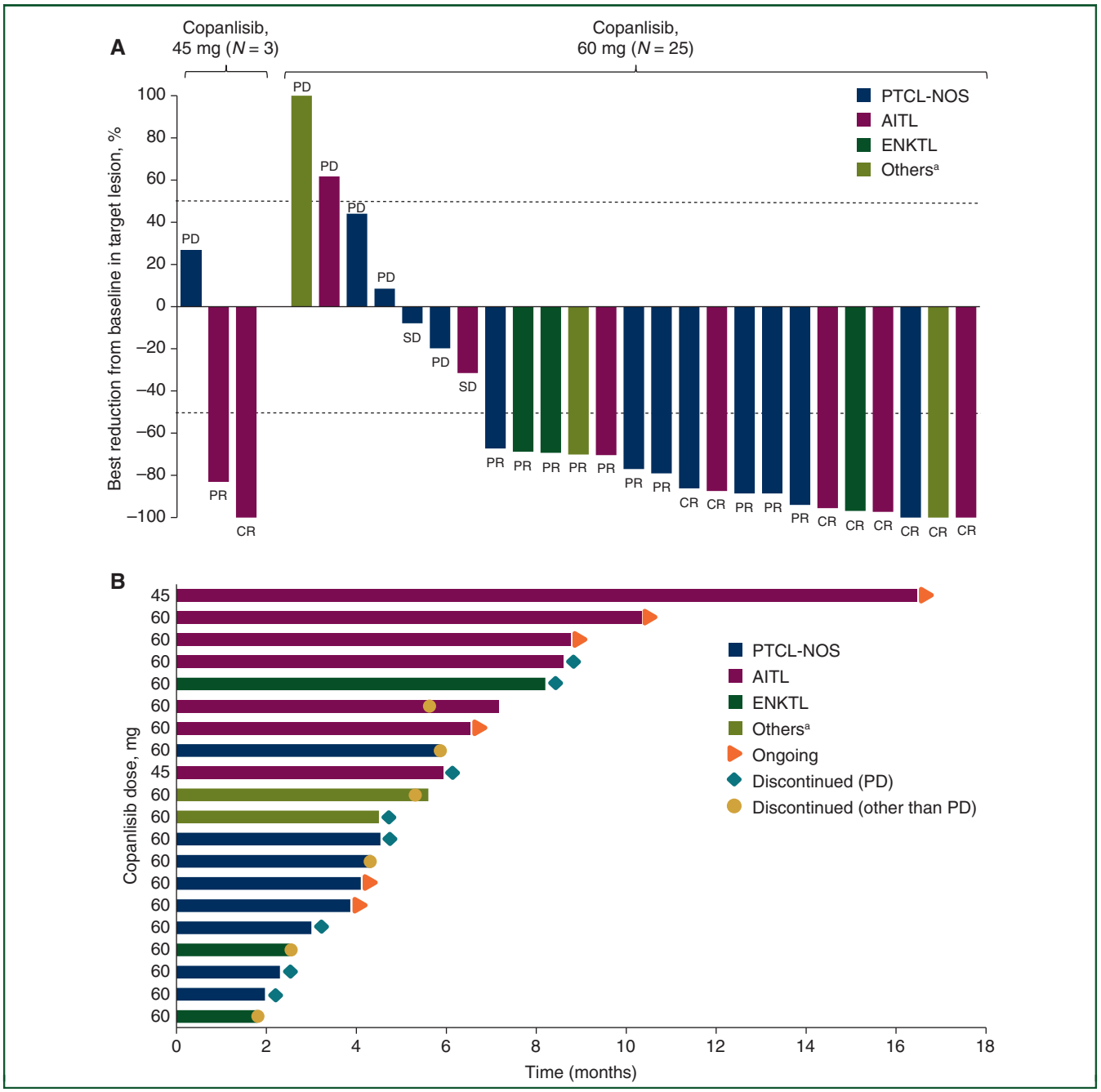

Figure 1. Waterfall and swimmer plots.
(A) Best percentage change in tumor burden and (B) duration of disease response. Reasons for treatment discontinuation other than disease progression included recurrent low-grade nonhematologic adverse event ($n = 4$), consent withdrawal ($n = 1$), and proceeding to allogeneic transplant ($n = 1$). For patients who underwent allogeneic stem cell transplantation, the duration of response was censored at the time of procedure.
AITL, angioimmunoblastic T-cell lymphoma; CR, complete response; ENKTL, extranodal natural killer/T-cell lymphoma; PD, progressive disease; PR, partial response; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; SD, stable disease.
[a] Others include anaplastic large cell lymphoma, anaplastic lymphoma kinase-negative ($N = 1$), subcutaneous panniculitis-like T-cell lymphoma ($N = 1$), and enteropathy-associated T-cell lymphoma ($N = 1$).

mutation showed higher ORR [37.5% (6/16) versus 0% (0/8), $P = 0.066$] and longer PFS [13.0 months (95% CI 6.9-NA) versus 5.1 months (95% CI 3.4-10.2), $P = 0.089$; Figure 2D].

DISCUSSION

COSMOS is to our knowledge the first study to investigate the combination of conventional gemcitabine with the PI3K-α and -δ inhibitor copanlisib in patients with relapsed/refractory PTCL. In phase I of the trial, we found that copanlisib and gemcitabine could be safely administered in combination with favorable toxicity profiles compared with those of either agent alone,[11,13,18] with no DLTs. Copanlisib doses beyond 60 mg were not planned because copanlisib at the dose of 60 mg was previously evaluated in a phase II trial for single-agent activity in relapsed/refractory lymphoma patients and concerns for infectious complications of the oral agent PI3K-δ inhibitor idelalisib were raised at the time

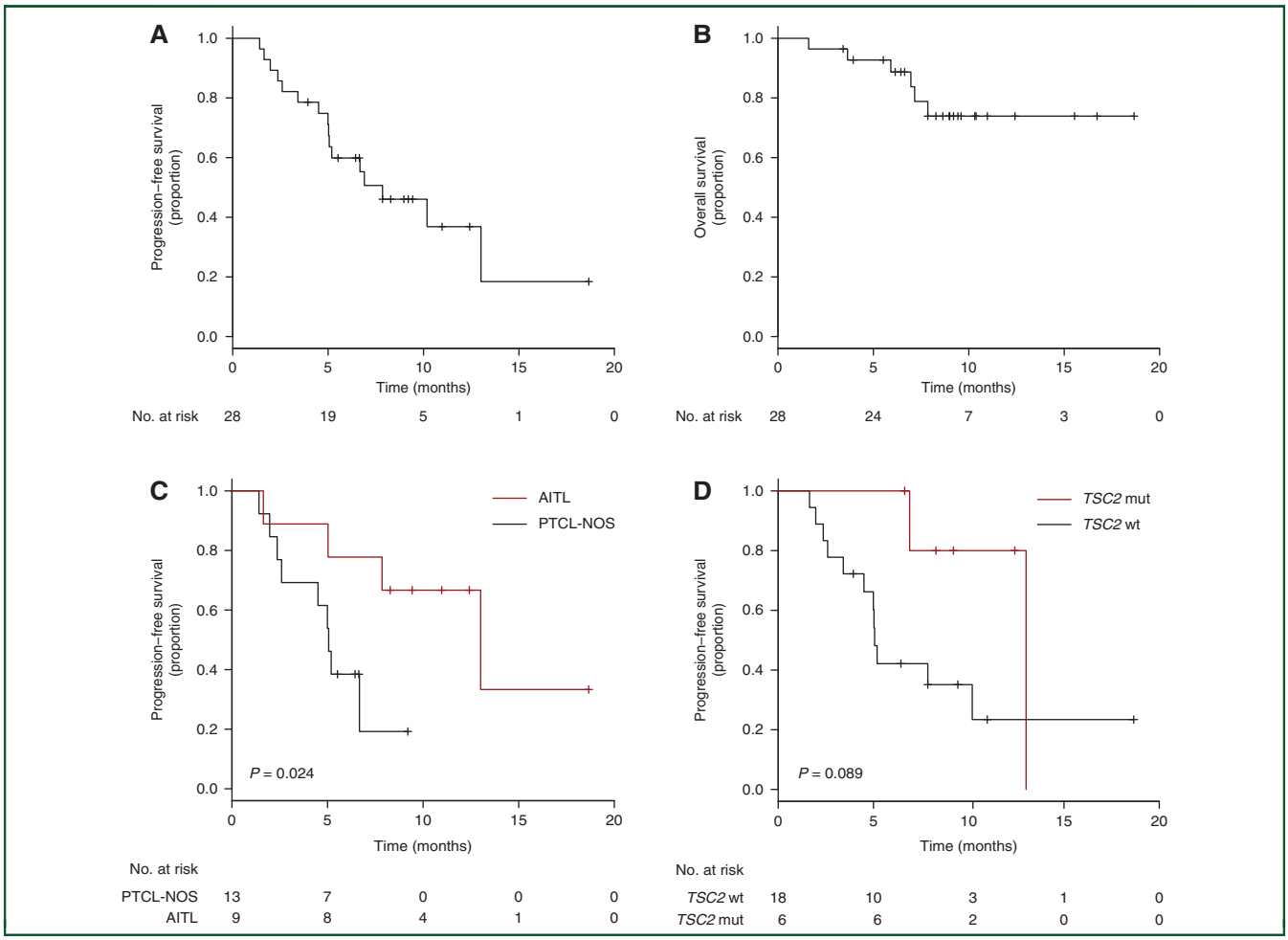

Figure 2. Progression-free survival and overall survival.
(A) Progression-free survival and (B) overall survival in full study cohort. (C) Progression-free survival in angioimmunoblastic T-cell lymphoma ($N = 9$) and peripheral T-cell lymphoma-not otherwise specified ($N = 13$). (D) Progression-free survival according to *TSC2* mutational status.
AITL, angioimmunoblastic T-cell lymphoma; mut, mutant; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; wt, wild type.

of trial design.[18,19] Furthermore, gemcitabine was administered at a lower dose than previously used in monotherapy (1000 mg/m^2 versus 1200 mg/m^2) and omitted on day 15 because of the high rate (48%) of grade $\geq$3 neutropenia observed in a dose-escalation trial of advanced solid cancer patients, in which the combination of copanlisib (0.8 mg/kg) and gemcitabine (1000 mg/m^2) was administered on days 1, 8, and 15.[13,20] Nonetheless, this investigation revealed that the combination of fixed-dose copanlisib and gemcitabine was highly active and well-tolerated overall, even at the highest examined copanlisib dose.

Given previous observations of increased risk of *Pneumocystis jirovecii* infection with idelalisib and chemoimmunotherapy,[19] all patients received prophylactic trimethoprim–sulfamethoxazole during the study period and no incidents of *P. jirovecii* pneumonia occurred. Five febrile neutropenic episodes occurred during induction combination therapy, but none were fatal. Myelosuppressive effects of copanlisib and gemcitabine were manageable with supportive measures and dose reduction despite prohibited routine use of prophylactic colony-stimulating factors in this study. However, we observed seven viral infectious complications (five herpes zoster and two unspecified viral pneumonia). This observation raises the need for further investigation of infection risk and viral prophylaxis during combination therapy. Although all events were nonfatal and resolved with appropriate care, these viral infections led to dosing delay and dose reduction. Furthermore, recent data have demonstrated that effective antiviral prophylaxis reduces the risk of varicella-zoster virus reactivation in patients with lymphoid malignancies.[21] Future assessment of infectious complication risk and benefits of viral prophylaxis when treating with combination regimens involving PI3K inhibitors and chemotherapeutic agents is warranted in order to establish effective prophylactic strategies.

Another common AE observed in our trial was PI3K-α inhibition-related hyperglycemia.[22] Hyperglycemia occurred in 81.1% of the total cycles administered, 56.8% grade 3 or 4, where observed rates are higher than previous reports.[11,18] This is probably attributed to the fact that approximately one-third of the patients in our cohort had diabetes mellitus at trial entry as a comorbidity. However, consistent with previous reports of copanlisib,[11,18]

https://doi.org/10.1016/j.annonc.2020.12.009

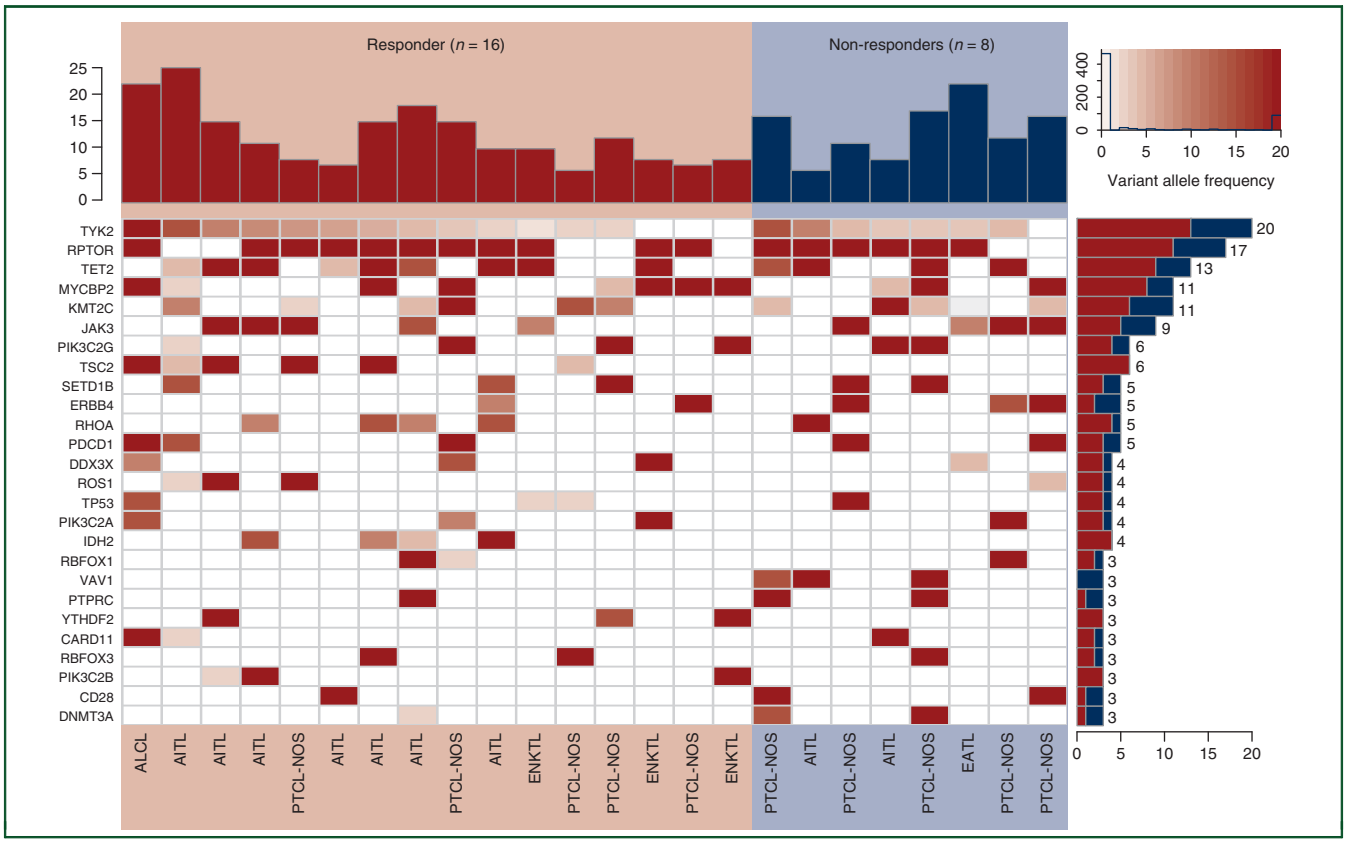

Figure 3. Heatmap of genetic alteration occurring in >10% of cases.
Each column represents one case. Red, present; White, absent.
AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; EATL, enteropathy-associated T-cell lymphoma; ENKTL, extranodal natural killer/T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified.

hyperglycemia was infusion-related and transient. It did not lead to significant treatment modification or discontinuation, although most patients with grade 3 or 4 hyperglycemia required temporary use of short-acting insulin.

Combination therapy with copanlisib and gemcitabine achieved promising response rates. In 25 patients, we observed ORR rates of 72%, which exceeded the prespecified target ORR of 45% in phase II of the trial. Considerable histologic subtype selectivity for CR achievement with copanlisib/gemcitabine therapy was present, where the CR rate in AITL patients was 55.6%, in comparison to 15.4% for PTCL-NOS. Response in the AITL subtype was durable, with four patients still in CR after 16.5, 10.3, 8.8, and 7.2 months, respectively. This is noteworthy considering 75% of the patients included in our study had refractory disease, the majority of whom seldom achieve CR with conventional chemotherapy alone.

A recent study investigating the genetic etiology of PTCL molecular subtypes reported that *IDH2* wild-type cases of AITL possess focal deletion of genes associated with the PI3K—AKT—mTOR pathway, including negative regulators such as *STK11, PPP2R2D, PHLPP1,* and *TSC2*.[23] Significant enrichment of nuclear factor-kappa B (NF-κB) and PI3K—AKT pathway signatures was observed in DAVID analysis of AITL without chromosome 5 gain with similar associations apparent in *IDH2* wild-type cases. Such constitutive activation of the PI3K—AKT pathway would provide basis of increased vulnerability to PI3K—AKT—mTOR inhibitors in AITL patients. The high CR rate and response durability observed in our AITL cohort coincide with these proposed mechanisms.

Mutations in genes regulating the epigenome including *TET2*, *IDH2*, and *RHOA* were common in the cohort of AITL and consistent with previous reports.[24,25] Notably, *TSC2* mutations were detected in 6 of 24 patients, 3 of these patients were of the AITL subtype, with all 6 patients achieving objective response to combination therapy, mutational status exclusive to responders. *TSC2* is a critical negative regulator of mTOR.[7,26] Phosphorylation of *TSC2* by AKT or other kinases inactivates *TSC2*, leading to activation of mTOR. Therefore, loss-of-function mutation of the *TSC2* gene results in unrestrained activation of the PI3K—AKT—mTOR pathway, providing rationale for targeting the PI3K—AKT—mTOR pathway in *TSC2* mutant tumors.[7,26] Preclinical data have also reported that *TSC2* mutation may confer sensitivity to mTOR inhibition.[26,27] Higher expression levels of PI3K in gene expression profiling have also been associated with a higher response to copanlisib treatment in patients with indolent lymphoma.[11,18] Thus, although our results are not definitive due to small sample size, the exclusive nature of mutations in responders and longer PFS observed in these patients suggest that *TSC2* mutational status may have some value as a response biomarker to copanlisib/gemcitabine therapy in PTCLs.

In summary, COSMOS established a safe and effective dosing regimen for relapsed/refractory PTCL patients treated with the combination of copanlisib and gemcitabine. We observed a high CR rate and durable response in the AITL subtype. AEs, particularly infectious complications, were manageable. This regimen represents an important new option for therapy in this rare and challenging patient group, and further studies elucidating the role of potential clinical biomarkers in a larger population are needed to guide patient selection.

ACKNOWLEDGEMENTS

We express our appreciation to the patients and their families, all study staff, and nurses for their effort in enrolling and managing patients. We thank Borum Sagong and Macrogen Incorporation for their support in gene mutational analyses.

FUNDING

This work was supported by Bayer HealthCare Pharmaceuticals, Inc. (no grant number) and by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR20C0021).

DISCLOSURE

D-HY reports receipt of institutional research funding from Bayer HealthCare Pharmaceuticals, Inc. All remaining authors have declared no conflicts of interest.

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