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ASLAN001-009 TreeTopp: Summary of Study Results

Study title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of Varlitinib Plus Capecitabine Versus Placebo Plus Capecitabine in Patients with Advanced or Metastatic Biliary Tract Cancer as Second-Line Systemic Therapy (TreeTopp)
Protocol number:	ASLAN001-009
Phase:	2/3
EudraCT number:	2017-000114-30
Study completion date	11 Dec 2019 (Prematurely ended)

Research Objective:

This study was designed as a multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic biliary tract cancer (BTC) as second-line systemic therapy. The study was planned to be conducted in 3 parts:

Safety Lead-in
To assess the safety and tolerability of varlitinib 300 mg twice daily (BID), in combination with capecitabine 1000 mg/m^2 (BID for 14 days followed by a 7-day rest) as measured by the incidence of adverse events (AEs), and changes from baseline in safety parameters.

Part 1
To assess the efficacy of varlitinib in combination with capecitabine as measured by co-primary endpoints of objective response rate (ORR) and progression-free survival (PFS), both assessed by an Independent Central Review (ICR).

Part 2 (Not Conducted)
To assess the efficacy of varlitinib in combination with capecitabine as measured by overall survival (OS). However, Part 2 of the study was not conducted based upon Part 1 results review.

Background:

Patients with advanced biliary tract cancer who progress on first-line therapy have limited treatment options. The TreeTopp study assessed varlitinib, a reversible small molecule pan- human epidermal growth factor receptor inhibitor, plus capecitabine in previously treated advanced biliary tract cancer.

Patients and Methods:

This global, double-blind, randomized, placebo-controlled study enrolled patients with confirmed unresectable or metastatic biliary tract cancer and disease progression after one prior line of gemcitabine-

containing chemotherapy. Patients received oral varlitinib 300 mg or placebo twice daily (BID) for 21 days, plus oral capecitabine 1000 mg/m^2 BID on Days 1–14, in 21-day treatment cycles. Co-primary endpoints were objective response rate (ORR) and progression-free survival (PFS) according to Response Evaluation Criteria in Solid Tumors v1.1 by Independent Central Review.

Results:

Disposition & Demographics:

Safety Lead-In

During the safety-lead-in period, of the 27 subjects who were screened, 24 subjects were enrolled and treated with varlitinib (V)+ capecitabine (C).

All 24 (100%) subjects treated with varlitinib plus capecitabine were discontinued from the treatment. The most frequent reason for discontinuation from treatment was radiographic disease progression (41.7%, n=10 subjects), followed by adverse events (29.2%, n=7 subjects). Two subjects (8.3%) were discontinued due to being deemed by the investigator as not in their interest to continue in the study. One patient (4.2%) either: voluntarily withdrew from participation, had clinical disease progression, withdrew consent during treatment or other. Two subjects discontinued due to death. One patient discontinued due to death upon clinical disease progression one patient (4.2%) withdrew upon death.

Part 1

Of 188 subjects who were screened, 127 subjects were enrolled and randomized: 64 in the varlitinib plus capecitabine (V+C) group and 63 in the placebo plus capecitabine (P+C) group.

The reasons subjects were discontinued from treatment and from the study were similar in both treatment groups.

Of the 127 randomized subjects, 118 (92.9%) subjects were discontinued from treatment: 59/64 (92.2%) subjects in the V+C group and 59/63 (93.7%). The most frequent reason for discontinuation from treatment was radiographic disease progression (V+C: 65.6%, n = 42 subjects; P+C: 77.8%, n = 49 subjects), followed by clinical disease progression (V+C: 6.3%, n = 4; P+C: 7.9%, n = 5) and AE (V+C: 10.9%, n = 7; P+C: 3.2%, n = 2). Eighty-two (64.6%) subjects were discontinued from the study: 41 subjects in each group. The most frequent reason for discontinuation from the study was death, which occurred in 55.1%: 35 subjects in each group. Eleven (8.7%) subjects withdrew consent: 6 in the V+C group and 5 in the P+C group. One patient (P+C group) was lost to follow-up.

Overall, the 127 subjects had a mean age of 62.1 (10.76) years, mostly male (60.6%), most frequently Asian (70.1%) or White (29.1%), had a mean body mass index (BMI) of 24.2 (4.60) kg/m2, and were predominantly located outside of the US (89.8%). Demographic characteristics were similar between the V+C and P+C groups except for sex, in which the proportion of male subjects was greater in the V+C group (68.8%; 44 subjects) than in the P+C group (52.4%; 33 subjects).

Part 2

Part 2 was planned to follow the same design and treatment schedule as Part 1 and to be commenced following review of Part 1 results. However, Part 2 of the study was not conducted upon review of Part 1 results.

Key Efficacy Results:

Objective Response Rate

The overall summary ORR was nearly twice as great in the V+C treatment group, 9.4% (n = 6 subjects) than the P+C group, 4.8% (n = 3 subjects).

Among all 127 subjects, a greater proportion of responders occurred in assessments at the sites (9.4%; n = 12) than for the primary analysis (7.1%; n = 9): 7 subjects vs. 6 subjects in the V+C group and 5 subjects vs. 3 subjects in the P+C group, respectively. The response rate was greater in the V+C group, 10.9%, compared to the P+C group, 7.9%. The OR by site assessment was 1.5777, and as with the primary analysis, neither the 2-sided 95% CI (0.403, 6.713) nor the 2-sided 80% CI (0.608, 4.231) were statistically significant (p = 0.6546 and p = 0.3273, respectively). A post-hoc analysis of confirmed response rates by site assessments had a greater OR, 3.0695, but this was not statistically significant for the 95% CI (p = 0.2933) nor the 80% CI (p = 0.1466).

Progression-free Survival

The progression of disease, in accordance with RECIST criteria, were similar between the groups: 68.8% in the V+C group and 71.4% in the P+C group (Table 22). Five (7.8%) subjects died in the V+C group and 2 (3.2%) in the P+C group. The proportion of patient who were progression-free at their last radiologic assessment was less in the V+C group (15.6%; n = 10 subjects) than the P+C group (22.2%; n = 14).

Overall in the FAS Population as of the data cutoff (DCO) on 15 July 2020, the median PFS was slightly greater in the V+C group, 2.83 months (Q1: 1.48; Q3: 5.62 months), than the P+C group, 2.79 months (Q1: 1.41; Q3: 4.24 months).

The median PFS was greater for the V+C group than the P+C group in GB tumors (2.86 vs. 1.58 months), and other tumors (5.75 vs. 2.83 months). On the other hand, the median PFS was less for the V+C group than the P+C group for extrahepatic bile duct tumors (2.40 vs. 4.24 months). The groups had similar median PFS for intrahepatic bile duct tumors (2.79 vs. 2.76 months), GB tumors: median PFS greater in V+C group than P+C group (2.9 vs. 1.6 months).

Safety:

Safety-Lead-in

Of the 24 subjects, 23/24 (95.8%) subjects reported with at least one TEAE. TEAEs Grade ≥ 3 were reported in 18 (75%) subjects. One patient died due to TEAE. Serious TEAEs were reported in 13 (54.2%) of subjects. Eight (33.3%) subjects discontinued study therapy due to TEAE.

Overall, among the 24 subjects, 75.0% had at least 1 Grade ≥ 3 TEAE. The most frequent Grade ≥ 3 TEAEs were hyponatraemia (16.7%), hypokalaemia (8.3%), blood bilirubin increased (8.3%), aspartate aminotransferase increased (8.3%), asthenia (8.3%), and fatigue (8.3%).

Part 1

Overall, among the 127 subjects, 62.2% had at least 1 Grade ≥ 3 TEAE. The most frequent Grade ≥ 3 TEAEs were blood bilirubin increased (12.6%), anemia (10.2%), abdominal pain (7.9%), cholangitis (6.3%), and vomiting and hyperbilirubinemia (each 5.5%).

The proportion of the 64 subjects in the V+C group who had at least 1 Grade ≥ 3 TEAE (65.6%) was similar to the proportion of the 63 subjects in the P+C group (58.7%). As well, the proportion were similar for blood bilirubin increased (V+C: 14.1%; P+C: 11.1%), abdominal pain (V+C: 7.8%; P+C: 7.9%), cholangitis (V+C and P+C each 6.3%), and anemia (V+C: 10.9%; P+C: 9.5%). The incidence of hyperbilirubinemia was higher in the V+C group than the P+C group (9.4% vs. 1.6%) as was vomiting (7.8% vs. 3.2%).

Eight subjects died due to an AE in the study: 5 in the V+C group (Subjects #S1092, #S1099, #S1153, #S1197, and #S1201) and 3 in the P+C group (Subjects #S1113, #S1208, and #S1211). Only one death was considered possibly related to study medication (Patient S1197 in the V+C group had cholangiolitis).

The most frequent cause of death was disease progression: 2 subjects (S1099 and S1201) in the V+C group and 2 subjects (S1208 and S1211) in the P+C group. None were considered related to study medication.

In the V+C group, Patient S1092 died due to liver abscess and Patient S1153 died due to general physical health deterioration and hyperbilirubinemia. Neither was considered related to study medication. Patient S1197 died from worsening cholangiolitis. The event was considered possibly related to varlitinib and possibly related to capecitabine.

In the P+C group, in addition to the 2 subjects who died from disease progression, Patient S1113 died due to acute respiratory failure. The TEAE was not considered related to study medication.

Overall, 40.9% (n = 52) of the 127 subjects had at least 1 SAE. The incidence of SAEs were similar for the 64 subjects in the V+C group (39.1%) and the 63 subjects in the P+C group (42.9%). The most frequent SAEs overall by SOC were hepatobiliary disorders (15.0%; n = 19 subjects), general disorders and administration site conditions (11.0%; n = 14 subjects), investigations (9.4%; n = 12 subjects), GI disorders (8.7%; n = 11 subjects), and infections and infestations (7.1%; n = 9 subjects). The incidence of SAEs by SOC were in the V+C group and P+C group were similar.

Overall, the most frequent SAE by PT was blood bilirubin increased (7.9%), followed by cholangitis (6.3%); vomiting (4.7%); and disease progression and hyperbilirubinemia (each 3.1%). The frequency of most SAEs in the V+C group was similar to the P+C group: blood bilirubin increased (7.8% vs. 7.9%), cholangitis (each 6.3%), and disease progression (3.1% vs. 3.2%). Only hyperbilirubinemia occurred more frequently in the V+C group (6.3% vs. 0%).

Twenty subjects had a SAE possibly, probably, or definitely related to study medication. Related SAEs occurred more often in the V+C group (n = 12 subjects) than the P+C group (n = 8 subjects).

The most frequent SAE considered related to study medication was blood bilirubin increased (4 subjects: 2 in each treatment group), followed by vomiting (3 subjects: 2 in the V+C group and 1 in the P+C group) and decreased appetite (2 subjects: 1 in each treatment group).

Conclusions:

This was a Phase 2, multicenter, double-blind, randomized, placebo-controlled study of varlitinib plus capecitabine versus placebo plus capecitabine in patients with advanced or metastatic biliary tract cancer (BTC) as second-line systemic therapy. The study was planned to be conducted in three parts: safety lead-in, Part 1 and Part 2.

The primary objectives of the study were to assess the safety and tolerability of varlitinib 300 mg BID (every day), in combination with capecitabine 1000 mg/m2 (BID for 14 days followed by a 7-day rest) as measured by incidence of AEs and changes from baseline in safety parameters. The other objective was to assess the efficacy of varlitinib in combination with capecitabine as measured by co-primary endpoints of ORR and PFS.

During the SLI part, of the 27 subjects who were screened, 24 subjects were enrolled and treated with varlitinib plus capecitabine. For SLI, among non-responders, the SD rate was 20.8%, while the PD rate was 37.5%. Two subjects died (8.3%) and the RECIST Progression rate was 29.2%. As per the OS analysis, 17 of 24 subjects were alive, 2 subjects withdrew consent, 4 subjects died, and one patient withdrew due to an adverse event.

The following safety findings for SLI were observed during the study: All (100%) subjects reported with at least one AE. Of these, 75% of subjects had an AE of Grade $\geqslant$ 3. Two subjects died, one due to AE and one due to disease progression. All subjects had at least 1 TEAE. Twenty-three (95.5%) subjects had TEAE related to V+C. Eighteen (75%) subjects reported with at least one TEAE CTCAE of $\geqslant$ grade 3. One (4.2%) subject had a TEAE with an outcome of death. Thirteen (54.2%) subjects had a serious TEAE. Eight (33.3%) subjects had a TEAE leading to discontinuation of study therapy. Six (25%) subjects had a TEAE leading to discontinuation due to V+C.

All (100%) subjects had at least one AE. 75% of subjects had an AE of Grade $\geqslant$ 3. Two subjects died, one due to AE and one due to an AE related to the disease. All subjects had at least 1 TEAE. 23 (95.5%) subjects had TEAE related to V+C. 18 (75%) subjects had at least a single TEAE CTCAE of grade 3 or higher. One (4.2%) subject had a TEAE with an outcome of death. 13 (54.2%) subjects had a serious TEAE. Eight (33.3%) subjects had a TEAE leading to discontinuation of study therapy. Six (25%) subjects had a TEAE leading to discontinuation due to V+C.

For Part 1, overall, 127 subjects were randomized (V+C, n = 64; P+C, n = 63) and the demographics/baseline characteristics were generally well balanced, although the V+C arm had a lower proportion of females vs. P+C (31% vs. 48%). The odds ratio for ORR was numerically higher with V+C vs. P+C was 2.278 (9.4% vs. 4.8%, p = 0.42), the HR for PFS for V+C vs. P+C was 0.90 (median PFS, 2.8 vs. 2.8 months; p = 0.63), and the HR for OS for P+C vs. V+C was 1.11 (median OS, 7.8 vs. 7.5 months; p = 0.66). However, for Part 1, neither co-primary endpoints were met. Although ORR was noted to be higher numerically in the Varlitinib arm compared to placebo, it was not statistically significant, 6 (9.4%) vs 3 (4.8%). For this reason, Part 2 of the study was cancelled.

Although not powered to evaluate sub-group interactions, in sub-group analysis, V+C showed PFS benefit versus P+C in two sub-groups; gallbladder cancer (GBC, HR = 0.55, 95% CI: 0.25, 1.22; median PFS, 2.9 vs. 1.6 months) and females (HR = 0.59, 95% CI: 0.28, 1.23; median PFS, 4.1 vs. 2.8 months). There was no PFS benefit for V+C vs. P+C among males and non-GBC.

Toxicities were generally balanced between arms apart from a slightly higher incidence of hyperbilirubinemia, diarrhoea and fatigue in the V+C vs. P+C arm. Grade 3/4 toxicities were reported in 66% and 59% of subjects in the V+C and P+C arms, respectively.

For Part 1, V+C was well tolerated but did not improve ORR, PFS or OS vs. P+C in second-line advanced BTC. Exploratory analyses suggested that subjects with GBC and female subjects achieved comparatively higher median PFS with V+C vs. P+C. The median PFS was 2.83 months for varlitinib in combination with capecitabine arm of the study versus median PFS of 2.79 in the control arm. ORR was 9.4% in the varlitinib arm versus 4.8% in the control arm. These were not significant at the pre-specified level. Varlitinib was generally well tolerated and had an acceptable safety profile which was consistent with previous studies.

Dissemination of findings:

1. Clinical Study Report submitted to all CEC/IEC/IRB and regulatory authorities in participating countries
2. Original research manuscript published in ESMO Open, Volume 7, Issue 1, 2022 https://doi.org/10.1016/j.esmoop.2021.100314