2 STUDY SYNOPSIS

Name of Company: Eisai Inc.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Eribulin mesylate for IV injection/infusion and Pembrolizumab for IV infusion	Referring to Module 5 of the Dossier	
Name of Active Ingredient: Eribulin mesylate (E7389) and Pembrolizumab	Volume: Page:	

Study Title

ENHANCE 1: An Open-Label, Single-Arm, Multicenter Phase 1b/2 Study to Evaluate the Efficacy and Safety of Eribulin Mesylate in Combination With Pembrolizumab in Subjects With Metastatic Triple-Negative Breast Cancer (mTNBC)

Investigators/Sites

Sara Tolaney, MD (lead principal investigator)

Multicenter study conducted at 22 sites (18 sites enrolled subjects) in the United States (refer to Appendix 16.1.4 for the list of investigators and sites).

Publication (Reference)

None

Study Period

28 Aug 2015 (first subject signed informed consent in Phase 1b) to 31 Jul 2019 (data cutoff date for the primary analysis)

Phase of Development

Phase 1b/2

Objectives

Primary Objectives

In subjects with mTNBC previously treated with 0 (Stratum 1) or 1 to 2 (Stratum 2) lines of systemic anticancer therapy in the metastatic setting and currently treated with eribulin mesylate in combination with pembrolizumab:

- For the Phase 1b part – to determine safety and tolerability of eribulin mesylate in combination with pembrolizumab in all subjects (ie, Stratums 1 and 2).
- For the Phase 2 part – to evaluate objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by independent imaging review (IIR) in all subjects.
- For the Phase 2 part – to evaluate ORR per RECIST 1.1 by IIR in Stratum 2 subjects and compare with the historical response rate of pembrolizumab monotherapy of 10%.

Secondary Objectives

- For the Phase 2 part, in all subjects and separately in Stratum 2 subjects, to evaluate progression-free survival (PFS) per RECIST 1.1 by IIR.
- To evaluate overall survival (OS).
- To evaluate duration of response (DOR) per RECIST 1.1 by IIR.
- To evaluate clinical benefit rate (CBR) per RECIST 1.1 by IIR.

- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by investigator review.
- To evaluate efficacy outcomes (ORR, PFS, DOR and CBR) per RECIST 1.1 by IIR and OS outcome by programmed cell death receptor-ligand 1 (PD-L1) expression.
- To evaluate the safety and tolerability of the combination.

Exploratory Objectives

- To evaluate time to response (TTR) per RECIST 1.1 by IIR in all subjects and separately in Stratum 2 subjects.
- To evaluate exposure-response relationship in all subjects.
- To explore potential effects of pembrolizumab co-administration on the pharmacokinetics (PK) of eribulin mesylate in all subjects.
- To explore efficacy outcomes (ORR, PFS, DOR, and CBR) per immune-related RECIST 1.1 (irRECIST) by IIR and investigator review for all subjects and separately in Stratum 2 subjects.

Methodology

This is an ongoing, open-label, single-arm, multicenter, Phase 1b/2 study of eribulin mesylate in combination with pembrolizumab in subjects with mTNBC previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting.

The study consists of 2 phases, Phase 1b and Phase 2. Both phases of the study included a Pretreatment Phase (Screening Period), a Treatment Phase (21-day treatment cycles), and a Posttreatment Phase (End of Treatment and Follow-Up Period).

The Phase 1b part included 1 initial safety run-in cohort in which at least 6 subjects received eribulin mesylate 1.4 mg/m^2 intravenously (IV) on Days 1 and 8 of a 21-day cycle and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (Dose Level 1). Dose-limiting toxicity (DLT) was assessed in the first cycle. Dose Level 1 could be selected as the recommended Phase 2 dose (RP2D) if no more than 1 subject had a DLT. Otherwise, eribulin mesylate dose was to be lowered from 1.4 mg/m^2 to 1.1 mg/m^2 on Days 1 and 8 of a 21-day cycle (Dose Level 0). If no more than 1 out of 6 subjects at Dose Level 0 had a DLT, the Phase 2 part could proceed with Dose Level 0.

Under Protocol Amendment 1, 107 subjects (including subjects in Phase 1b who were on RP2D level) were enrolled in 2 strata and received the same combination treatment at the RP2D level. The strata included no prior systemic anticancer therapy in the metastatic setting (Stratum 1) and previously treated with 1 to 2 lines of systemic anticancer therapy in the metastatic setting (Stratum 2).

Per Protocol Amendment 3, additional subjects were added to Stratum 2 to include a total of 80 evaluable subjects in Stratum 2 for final analysis. As a result, approximately 150 subjects in total (145 evaluable with 80 in Stratum 2) were enrolled. Per Protocol Amendment 4, 20 additional subjects were to be added to Stratum 2 to include a total of at least 100 evaluable subjects in Stratum 2 for final analysis.

Number of Subjects (Planned and Enrolled)

Planned: A total of approximately 170 adult female or male subjects previously treated with 0 to 2 lines of systemic anticancer therapy in the metastatic setting were to be enrolled (including at least 6 subjects from the Phase 1b part).

Enrolled: A total of 167 subjects were enrolled and treated including 7 subjects in Phase 1b at Dose Level 1 (eribulin 1.4 mg/m^2 IV on Days 1 and 8 and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle) that was determined to be the RP2D and 160 subjects in Phase 2 at the RP2D (ie, Phase 1b Dose Level 1).

Diagnosis and Main Criteria for Inclusion

Females or males, aged ≥18 years, with mTNBC (estrogen receptor (ER)-negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2)-negative) that was previously treated with 0 to 2 lines of systemic anticancer therapy (cytotoxic or targeted anticancer agents) in the metastatic setting. Subjects had to have measurable disease meeting protocol specified criteria, life expectancy of ≥3 months, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

Eribulin mesylate was provided as a sterile, ready-to-use, clear, colorless aqueous solution for IV administration. Each vial contained 2 mL of solution at 0.5 mg/mL.

Pembrolizumab was provided as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for reconstitution. Each vial contained 50 mg of pembrolizumab for reconstitution for injection (50 mg/2 mL of solution).

Dose and Mode of Administration

Eribulin mesylate 1.4 mg/m^2 via IV injection over 2 to 5 minutes administered on Day 1 and Day 8 and pembrolizumab 200 mg via IV infusion over 30 minutes administered on Day 1 (21-day cycle). The eribulin mesylate dose could be reduced/ delayed; the pembrolizumab dose could be delayed per protocol in the event of toxicity.

Eribulin mesylate Batch/Lot Nos: N1200923, N1300629, N1401083, N1700655

Pembrolizumab Batch/Lot Nos: 3-SNL-808, 4-SNL-809, 6-SNL-809, 6-SNL-823, 7-SNL-801, 8-SNL-811

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

None

Duration of Treatment

Subjects could remain on study drug as long as there was clinical benefit and continue to receive one or both study drugs until disease progression, intercurrent illness, development of unacceptable toxicity, or withdrawal of consent. Subjects could receive up to 35 treatments (approximately 2 years) with pembrolizumab.

Discontinuation of treatment could be considered for subjects who attained a confirmed complete response (CR) and had been treated for at least 8 cycles (24 weeks) with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

Assessments

Dose-Limiting Toxicity (Phase 1b)

All subjects enrolled in the Phase 1b part of the study were assessed for DLTs during a DLT assessment window of the first cycle of 21 days. A DLT was defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to either of the study drugs:

Hematologic Toxicities

- Any Grade 4 thrombocytopenia or neutropenia lasting >7 days

Nonhematologic Toxicities

- Episcleritis, uveitis, or iritis of Grade 2 or higher
- Any Grade 4 toxicity
- Any Grade 3 toxicity EXCLUDING:
    - Nausea, vomiting, or diarrhea controlled by medical intervention within 72 hours.
    - Grade 3 rash in the absence of desquamation, no mucosal involvement, does not require steroids, and resolves to Grade 1 by the next scheduled dose of pembrolizumab.
    - Transient Grade 3 AST or ALT elevation, defined as no more than 3 days with or without steroid use.
- Discontinuation or delay of more than 2 weeks of either study drug due to treatment-related adverse event (AE) was considered as a DLT.

Efficacy

Tumor assessments were performed by the investigator based on both RECIST 1.1 and irRECIST. Copies of all tumor assessment scans were sent to an imaging core laboratory designated for independent review of efficacy assessment. Tumor assessments were to be performed every 9 weeks ±1 week after the start of study treatment (or sooner if there was evidence of progressive disease) using consistent imaging methodology (ie, CT scan/ MRI or bone scan and consistent use or nonuse of contrast media). In subjects who discontinued study therapy

without documented disease progression, every effort had to be made to continue monitoring their disease status by radiologic imaging every 9 weeks ±1 week during Year 1, and every 12 weeks ±1 week thereafter until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurred first. In addition, OS status (disposition) was to be assessed throughout the study.

Pharmacokinetics and Pharmacodynamics

Blood samples were collected at protocol specified times from all subjects for PK analysis on eribulin mesylate only.

Eribulin mesylate PK/pharmacodynamic analysis is planned to be conducted to evaluate the relationship between exposure and efficacy and exposure and safety when eribulin mesylate is coadministered with pembrolizumab.

Biomarkers

Archived and/or fresh (if possible) tissue samples were collected at screening for assessment of PD-1/PD-L1 expression.

Safety

Safety assessments consisted of monitoring and recording of all AEs, including all CTCAE v4.03 grades for both increasing and decreasing severity, and SAEs; regular monitoring of hematology, clinical chemistry, and urine; periodic measurement of vital signs and ECOG performance status; ECG and the performance of physical examinations.

Bioanalytical Methods

Plasma concentrations of eribulin mesylate were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method.

Statistical Methods

Study Endpoints

Primary Endpoint

Objective Response Rate (ORR) - defined as the proportion of subjects who had best overall response (BOR) of complete response (CR) or partial response (PR).

Secondary Endpoints

- **Progression-Free Survival (PFS)** – defined as the time from date of first dose of study drug to date of first documentation of disease progression or death, whichever occurs first.
- **Overall Survival (OS)** – defined as the time from the date of first dose of study drug until date of death from any cause.
- **Duration of Response (DOR)** – defined as the time from the date that a confirmed objective response is first documented to the date of PD or death due to any cause for those subjects with a confirmed PR or CR.
- **Clinical Benefit Rate (CBR)** – defined as the proportion of subjects who had BOR of CR, PR, or durable SD (≥24 weeks).
- Estimates of ORR, PFS, OS and DOR in the PD-L1 Positive Set, defined as combined positive score (CPS) ≥1 using an investigational version of the PD-L1 assay (IHC 22C3 pharmDx [Agilent, Carpinteria, CA, USA]).

Exploratory Endpoints

- **Time to Response (TTR)** – defined as the time from the first dose date to the date that the confirmed objective response is first documented for subjects who had BOR of CR or PR based on RECIST 1.1.
- Objective response rate, BOR, PFS, DOR, CBR and DCR using irRECIST.

Analysis Sets

The DLT Evaluable Set included subjects in Phase 1b who completed the first treatment cycle (ie, took at least 2 doses of eribulin mesylate with no more than 1 dose reduction and at least 1 dose of pembrolizumab).

Subjects in Phase 2 who had a DLT event were considered evaluable for the dose-limiting toxicity as well. This was the analysis set for DLT evaluation in the Phase 1b part.

The Full Analysis Set (FAS) (Safety Analysis Set) included all subjects who received any amount of either study drug. This was the analysis set for safety analyses and analyses of PFS and OS.

The Evaluable Analysis Set (EAS) (subset of Full Analysis Set) included all subjects treated at RP2D level who had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment, unless discontinued early or death. This was the analysis set for efficacy analyses other than PFS and OS.

The PD-L1 Positive Set (subset of Evaluable Analysis Set) included evaluable subjects whose PD-L1 expression level was above the threshold that specified prior to the final analysis. Key primary and secondary efficacy endpoints (ie, ORR, PFS, OS, and DOR) were summarized in this analysis set.

Efficacy Analyses

Subjects enrolled in Phase 1b and treated on RP2D level were pooled with subjects in Phase 2 for efficacy analysis.

Response Evaluation Criteria in Solid Tumors version 1.1 was used in the evaluation of tumor status for the primary, secondary and exploratory endpoints and irRECIST was used in the evaluation of tumor status for one of the exploratory endpoints. Tumor response data obtained per RECIST 1.1 by IIR was utilized in the main analysis of ORR, PFS, DOR, CBR, and TTR. In addition, tumor assessment data assessed per RECIST1.1 by investigator review and per irRECIST by IIR and by investigator review were considered as secondary or exploratory.

The primary analysis in the overall population was the comparison of ORR assessed by IIR in the EAS to the historical control rate of 20% using a Bayesian approach. The Bayesian posterior probability P(p>0.2|data) at the final analysis was compared to the prespecified target probability of 0.95. A two-sided 95% credible interval of ORR based on posterior distribution of ORR was constructed. The primary analysis in Stratum 2 [1 to 2 lines of prior systemic anticancer therapies for metastatic disease] was the comparison of ORR assessed by IIR in the EAS to the historical control value of 10% using a binomial exact test. An ORR of 25% in this study was considered a clinically meaningful improvement in Stratum 2 subjects. A 2-sided Clopper-Pearson 95% confidence interval (CI) was constructed for ORR. The PFS and OS in the FAS were analyzed using Kaplan–Meier product limit estimates. Median PFS and OS were presented with 2-sided 95% CIs using generalized Brookmeyer and Crowley method, if estimable. In addition, the cumulative probability of PFS at 6, 9 and 12 months and the cumulative probability of OS at 6, 12 and 18 months were reported along with the 95% CIs using Kaplan-Meier product limit method and Greenwood log-log formula. The CBR was evaluated using the same method as used for ORR. The DOR and TTR were summarized for subjects with BOR of CR or PR. Kaplan-Meier estimated quantiles and their 95% CIs, using the generalized Brookmeyer and Crowley method were provided.

Pharmacokinetic and PK/Pharmacodynamic Analyses

Mean and individual plasma eribulin concentration-time plots for subjects in Phase 1b and scatter plot of sparse plasma eribulin concentration-time plot for subjects in Phase 2 were generated by actual sample collection time. Individual eribulin PK parameters for Phase 1b were calculated based on Cycle 1 Day 1. Plasma eribulin concentration data from Phase 1b and 2 are planned to be pooled with data from other studies to perform population PK or PK/PD modeling. If performed, the results will be detailed in a standalone report.

Safety Analyses

All safety analyses were performed in the Safety Analysis Set (ie, FAS). Safety data were summarized by stratum and combined using descriptive statistics (eg, n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables; and n [%] for categorical variables). Safety variables included treatment-emergent adverse events (TEAEs) and treatment-emergent SAEs, clinical laboratory parameters, vital signs, 12-lead ECG results, ECOG performance status.

The incidence of TEAEs and SAEs was summarized. Laboratory test results, vital signs and their changes from baseline were summarized. Abnormal values were flagged.

Results

Subject Disposition/Analysis Sets

Altogether, 258 subjects signed the informed consent form (ICF), 91 failed screening. Of the total 167 enrolled subjects overall (7 in Phase 1b and 160 in Phase 2) and treated at the RP2D, 9 (5.4%) were ongoing on study treatment at the time of the data cutoff (31 Jul 2019) and 158 (94.6) had discontinued treatment. The most frequent reason for discontinuation of the combination treatment was radiologic disease progression in 101 (63.9%) subjects followed by AEs in 18 (11.4%) subjects and clinical disease progression in 17 (10.8%) subjects.

Overall, all 167 subjects (66 in Stratum 1 [no prior systemic anticancer therapies for metastatic disease] and 101 in Stratum 2 [1 to 2 lines of prior systemic anticancer therapies for metastatic disease] treated at the RP2D) who received any amount of either study drug in Phase 1b or Phase 2 of the study were included in the FAS (primary analysis set used for analysis of PFS and OS and safety analyses). All subjects in the FAS who had both an evaluable baseline tumor assessment and an evaluable postbaseline tumor assessment (unless discontinued early or death) were included in the EAS (analysis set for efficacy analyses). The FAS and EAS were identical. A total of 7 subjects enrolled in Phase 1b and treated at the RP2D were included in the DLT evaluable set.

For the overall population, the median age of the subjects was 56 years (range: 32 to 88 years) and 70.7% of subjects were ≥50 years of age. All subjects were females. Most of the subjects were White (84.4%) and a small proportion of subjects (11.4%) subjects were Black or African American descent. The proportion of subjects with PD L1 positive (CPS ≥1) and negative tumor status was similar (44.9% and 44.3%, respectively); assessment was not available in remaining 10.8% of subjects. With the exception of 1 subject, all subjects had ECOG PS of 0 or 1.

Efficacy

- Treatment with eribulin + pembrolizumab resulted in an ORR of 23.4% (95% CI: 17.2, 30.5) in the overall population per RECIST 1.1 as assessed by IIR. Complete and partial responses were observed in 8 (4.8%) and 31 (18.6%) subjects, respectively, and 53 (31.7%) subjects had stable disease lasting ≥8 weeks. The Bayesian posterior probability (0.85) that the ORR for the eribulin + pembrolizumab combination treatment was >0.2 (ORR of historical control based on single agents pembrolizumab and eribulin in recent studies) was below the pre-specified target probability of 0.95 to demonstrate the superiority of combination therapy over historical control.
- The ORR per RECIST 1.1 by IIR among Stratum 2 subjects (1 or 2 prior lines of anticancer therapy ie, second or third line) was 21.8% with 22 responders, including 19 subjects with a BOR of confirmed PR and 3 subjects with confirmed CR. The estimated ORR (21.8%) in Stratum 2 was higher than the historical response rate of 10% (one-sided *P* value =0.0004) demonstrating a promising anticancer activity that appears greater than historical report.
- The median PFS for the overall population was 4.1 months (95% CI: 3.5, 4.2) as assessed by IIR with 36.2% subjects progression-free at 6 months, 21.5% at 9 months, and 15.8% at 12 months. The median PFS in Stratum 2 subjects (4.1 months [95% CI: 2.3, 4.4]) was consistent with the median PFS in the overall population.
- The median OS for the overall population was 16.1 months (95% CI: 13.3, 18.5) with a median OS follow-up time of 39.2 months (95% CI: 35.7, 40.0). The OS rate was 83.7% at 6 months, 65.6% at 12 months, and 42.3% at 18 months. The median OS in Stratum 2 subjects (15.5 months [95% CI: 12.5, 18.7]) was consistent with the median OS in the overall population.
- Responses were durable for the responders in the overall population, with the median DOR of 8.3 months (95% CI: 6.5, 22.2) as assessed by IIR per RECIST 1.1. The estimated probability of DOR longer than 6 months was 0.82, and the estimated probability of DOR longer than 12 months was 0.43. The median DOR in Stratum 2 subjects (8.6 months [95% CI: 6.2, 25.1]) was consistent with the median DOR in the overall population.
- The CBR by IIR in the overall population was 32.3% (95% CI: 25.3, 40.0); CBR by investigator assessment was 38.9% (95% CI: 31.5, 46.8). The CBR by IIR in Stratum 2 subjects (29.7% [95% CI: 21.0, 39.6]) was consistent with the overall population.

- Investigator findings corroborated IIR findings per RECIST 1.1 and irRECIST. There was a high level of concordance (74.9%) in tumor response between IIR and investigator assessments by RECIST 1.1 for the overall population. This was supported by Cohen's Kappa Statistic value of 0.6597, showing substantial agreement between IIR and investigator assessments.
- Overall, the PFS results were consistent between IIR and investigator assessments. The median DOR was longer (9.8 months vs 8.3 months) and CBR was higher (38.9% vs 32.3%) by investigator vs IIR assessment for the overall population.
- Results for the primary and secondary efficacy endpoints (ORR, DOR, CBR, and PFS) per IIR by irRECIST supported the IIR findings by RECIST 1.1 for the overall population.
- Efficacy analysis by PD-L1 tumor expression status indicated higher efficacy outcomes in subjects with PD-L1 positive tumors (ie, CPS ≥1) versus those with PD-L1 negative tumors in Stratum 1 subjects with no prior systemic therapy: ORR, 34.5% (95% CI: 17.9, 54.3) vs 16.1% (95% CI: 5.5, 33.7); PFS, 6.1 months (95% CI: 4.1, 10.2) vs 3.5 months (95% CI: 2.0, 4.2); OS, 21.0 months (95% CI: 8.3, 29.0) vs 15.2 months (95% CI: 12.8, 19.4).
- Subgroup analysis by prior lines of therapy indicated a numerically higher ORR among Stratum 1 subjects with no prior systemic therapy compared to Stratum 2 subjects who had 1 to 2 prior lines of systemic therapies (25.8% [95% CI: 15.8, 38.0] vs 21.8% [95% CI: 14.2, 31.1], respectively). The median PFS was similar across strata (Stratum 1: 4.2 months [95% CI: 3.5, 5.5]; Stratum 2: 4.1 months [95% CI: 2.3, 4.4]). The median OS was numerically higher for Stratum 1 versus Stratum 2 (17.4 months [95% CI: 13.2, 21.0] vs 15.5 months [95% CI: 12.5, 18.7]).
- Coadministration of pembrolizumab did not impact PK of eribulin in Phase 1b as the PK of eribulin on Day 1 following 1.4 mg/m^2 IV infusion was similar to previously reported values when administered alone.

Safety

- At the time of the data cutoff date for this report (31 Jul 2019), the median overall duration of eribulin plus pembrolizumab was 3.9 months (range: 0.03 to 41.7 months), for eribulin 3.7 months (0.03, 41.7) and for pembrolizumab 3.5 months (0.03, 28.1). The relative dose intensity for eribulin (ie, total dose received as a percentage of the planned total dose) was 94.5%.
- Of the 7 subjects enrolled in the DLT evaluation part (Phase 1b), all subjects received eribulin mesylate 1.4 mg/m^2 IV on Days 1 and 8 and pembrolizumab 200 mg IV on Day 1 of a 21-day cycle (Dose Level 1) and were assessed for DLTs in the first cycle. None of the 7 subjects experienced any DLTs and eribulin mesylate 1.4 mg/m^2 and pembrolizumab 200 mg was selected as the RP2D to be administered in the Phase 2 part of the study.
- All subjects in the overall population reported at least 1 TEAE. The most frequent TEAEs reported in ≥20% of subjects in the overall population were fatigue (65.9%), nausea (57.5%), peripheral sensory neuropathy (41.3%), alopecia (39.5%), constipation (36.5%), neutropenia (35.9%), cough (32.3%), pyrexia (31.7%), decreased appetite (31.1%), diarrhea (30.5%), anemia (28.1%), arthralgia (27.5%), vomiting (26.9%), weight decreased, headache, and dyspnea (24.6%, each).
- CTCAE Grade 3 or higher TEAEs were reported in 74.9% of subjects overall, worst CTCAE Grade 3 TEAEs in 49.1% and Grade 4 in 16.8% of subjects. The most frequently reported TEAE with worst CTCAE Grade 3 in the overall population was neutropenia (16.8%), followed by decreased neutrophil count (7.8%), fatigue and peripheral sensory neuropathy (7.2% each), anemia (6.0%), and hyponatremia (5.4%). Worst CTCAE Grade 4 TEAEs reported were neutropenia (9.6%), decreased neutrophil count (2.4%), hypokalemia (0.8%), and decreased white blood cell count (0.8%).
- Treatment-related TEAEs were reported in 96.4% of subjects overall.
  - The most frequent TEAEs assessed as related to eribulin by the investigator were peripheral sensory neuropathy (35.9%), alopecia (35.3%), neutropenia (28.7%), nausea (25.7%), anemia (19.8%), stomatitis and fatigue (16.8%), decreased appetite (13.8%), neutrophil count decreased (11.4%), and vomiting (10.2%).
  - The most frequent TEAEs assessed as related to pembrolizumab by the investigator were hypothyroidism (15.6%), pyrexia (9.0%), pneumonitis (9.6%), arthralgia (8.4%), diarrhea and rash (7.2% each), hyperthyroidism (6.6%), cough (6.0%), and fatigue and pruritus (5.4% each).

- Overall, 120 (71.9%) deaths were reported in the study. Deaths due to TEAEs were reported in 15 (9.0%) subjects. None of the fatal TEAEs was assessed as related to study treatment; all were assessed as related to PD.
- The incidence of non-fatal SAEs was 49.7%. The most frequent SAEs (≥3%) reported in the overall population were pneumonia (4.8%), pyrexia and pneumonitis (3.6% each), and neutropenia (3.0%).
- Study drug dose adjustments due to TEAEs were required in 70.7% of subjects.
  - Overall, 25.1% of subjects required study drug withdrawal (eribulin, pembrolizumab, or both) due to TEAEs. The most frequent TEAEs leading to discontinuation of study drugs were increased AST (2.4%), pneumonitis (2.4%), and peripheral sensory neuropathy (1.8%).
  - Overall, dose interruption of eribulin, pembrolizumab or both were required in 53.3% of subjects. The most frequently reported TEAEs leading to interruption of eribulin, pembrolizumab, or both were neutropenia (13.2%), peripheral sensory neuropathy (7.2%), and neutrophil count decreased (6.0%).
  - A total of 32.9% subjects required dose reduction of eribulin. The most frequent TEAEs leading to eribulin dose reduction were neutropenia (10.2%) and peripheral sensory neuropathy (7.2%).
- In the overall population, ECIs for eribulin were reported in 94.6% of subjects. The most frequent ECIs (≥20%) for eribulin were asthenia fatigue (68.9%), peripheral neuropathy (53.3%), neutropenia (47.3%), alopecia (39.5%), arthralgia myalgia (31.1%), and hepatotoxicity (26.9%).
- In the overall population, ECIs for pembrolizumab were reported in 42.5% of subjects and the most frequent ECIs (≥5%) were hypothyroidism (18.0%), pneumonitis (10.8%), hyperthyroidism (7.8%), and severe skin reactions (5.4%).
- Only 1 subject reported ECI for both eribulin and pembrolizumab (hepatitis, 0.6%).
- One subject was identified as fulfilling laboratory criteria for potential Hy's Law case. After thorough medical review of both laboratory and clinical information, the sponsor determined that this was not a case of drug-induced liver injury.
- Clinical laboratory data, vital signs, ECG, and other observations related to safety did not reveal any new safety signals.
- The safety profile of eribulin plus pembrolizumab was generally consistent with the known safety profiles of each drug when used as monotherapy, and no new safety signals were identified with the combination.

Conclusions

In this study population of subjects with mTNBC who had received 0 to 2 lines of prior systemic anticancer therapy, eribulin in combination with pembrolizumab showed promising antitumor activity as demonstrated by the results for primary and secondary efficacy endpoints; however, the primary endpoint of ORR did not reach statistical significance in the overall population when compared with historical control, albeit, a statistically significant difference in ORR in favor of study subjects who received 1 or 2 prior lines of systemic anticancer therapies (Stratum 2) was observed when compared to historical control. Furthermore, numerical differences in efficacy results were observed between PD-L1 positive as measured by CPS ≥1 versus those with PD-L1 negative tumors in Stratum 1 subjects with no prior systemic therapy, indicating PD-L1 status (as measured by CPS ≥1) may be predictive of antitumor activity for the study drug combination in this mTNBC population.

Overall, the combination of eribulin plus pembrolizumab was generally well tolerated with a predictable safety profile in subjects with mTNBC. Treatment-emergent AEs were manageable with standard medical care/supportive medication, protocol specified dose interruption or reduction of eribulin, and dose interruption of pembrolizumab. The safety profile of the combination treatment is consistent with the known profiles of eribulin and pembrolizumab, and no new safety signal or risk was identified for either eribulin or pembrolizumab in this study.

These results support further clinical development of eribulin plus pembrolizumab as a potential antitumor treatment strategy for subjects with mTNBC.

Date of Report

04 Aug 2020