2. SYNOPSIS

Title of the Study:	A Phase 1, Open-Label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Antineoplastic Activity of Sym021 (Anti-PD-1) as Monotherapy, in Combination with either Sym022 (Anti-LAG-3) or Sym023 (Anti-TIM-3), and in Combination with Both Sym022 and Sym023 in Patients with Advanced Solid Tumor Malignancies or Lymphomas.		
Investigators/ Study Centers:	Multicenter, 4 sites in North America		
Publication:	Spreafico A, Janku F, Rodon JA et al. A Phase I Study of Sym021, an Anti-PD-1 Antibody (Ab), Alone and in Combination with Sym022 (Anti-LAG-3) or Sym023 (Anti-TIM-3). Abstract presented at: European Society for Medical Oncology (ESMO) Annual Meeting; 2019 Sep 27 – 2019 Oct 01; Barcelona, Spain. Lakhani N, Spreafico A, Tolcher AW, et al. Phase 1 studies of Sym021, an anti-PD-1 antibody (Ab), alone and in combination with Sym022 (anti-LAG-3) or Sym023 (anti-TIM-3). ESMO Congress, September 2020.		
Study Period:	20 Nov 2017 (First patient's informed consent date) to 23 Mar 2022 (Last patient's last visit or contact)	**Clinical Phase:**	Phase 1

Part I: Sym021 Single Agent Dose-Escalation

Objectives:

Primary:

- Evaluation of the safety, tolerability, and dose-limiting toxicities (DLTs) to establish the maximum tolerated dose (MTD) and/or the selected dose of sequential escalating doses of Sym021 (anti-PD-1) when administered once every two weeks (Q2W) by intravenous (IV) infusion to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that were refractory to available therapy or for which no standard therapy was available.

Secondary:

- Evaluation of the immunogenicity of Sym021.
- Characterization of the pharmacokinetic (PK) profile of Sym021 when dosed as a single agent.
- Evaluation of the preliminary antineoplastic effects of Sym021, including:
  - Evidence of objective response (OR) or stable disease (SD)*
  - Duration of OR or SD*
  - Time to progression (TTP) of disease*

  *As assessed throughout the trial by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1), Immune Response Evaluation Criteria in Solid Tumors (iRECIST), and Response Evaluation Criteria in Lymphoma (RECIL 2017).

Exploratory:

- Evaluation of potential pharmacodynamic markers of Sym021, including:
  - In blood: Target engagement by *ex vivo* assay including stimulation with staphylococcal enterotoxin B (SEB) and cytokine analysis
- Evaluation of potential biomarkers of Sym021 effects, including but not limited to assessment of:
  - In blood (plasma): Deoxyribonucleic acid (DNA), proteins, and cytokines

Part II: Doublet Antibody Dose-Escalation

Sym021 + Sym022/Sym023 (anti-PD-1 + anti-LAG-3/anti-TIM-3)

Objectives:

Primary:

- Evaluation of the safety, tolerability, and DLTs to establish the MTD and/or the selected dose of sequential escalating doses of Sym022 or Sym023 when administered Q2W in combination with a fixed dose of 3 mg/kg of Sym021, each by IV infusion to patient cohorts with locally advanced/unresectable or metastatic

solid tumor malignancies or lymphomas that were refractory to available therapy or for which no standard therapy was available.

Secondary:

- Evaluation of the immunogenicity of Sym021 and Sym022 or Sym021 and Sym023 when dosed in combination.
- Characterization of the PK profile of Sym021 and Sym022 or Sym021 and Sym023 when dosed in combination.
- Evaluation of the preliminary antineoplastic effects of Sym021 and Sym022 or Sym021 and Sym023, when dosed in combination, including:
  - Evidence of OR or SD*
  - Duration of OR or SD*
  - TTP of disease*

  *As assessed by RECIST v1.1, iRECIST, and RECIL 2017.

Exploratory:

- Evaluation of potential pharmacodynamic markers of Sym021 and Sym022 or Sym021 and Sym023, including:
  - In blood: Receptor occupancy in peripheral blood mononuclear cells (PBMCs) using Chip Cytometry and target engagement by *ex vivo* stimulation assay and cytokine analysis*
    *Samples may have been used for other biomarker studies, as outlined below, after the receptor occupancy assay was complete.
- Evaluation of potential biomarkers of Sym021 and Sym022 effects or Sym021 and Sym023 effects, including but not limited to assessment of:
  - In blood (plasma): Circulating tumor DNA (ctDNA) and relevant proteins/cytokines.
  - In blood (PBMCs): DNA, ribonucleic acid (RNA), immune cell sub-populations analysis (immune-phenotyping), and relevant proteins/cytokines.
  - In tumor tissue: DNA, RNA, and proteins (biopsies optional).

Part III: Triplet Antibody Dose-Escalation

Sym021 + Sym022 + Sym023 (anti-PD-1 + anti-LAG-3 + anti-TIM-3)

Objectives:

Primary:

- Evaluation of the safety, tolerability, and DLTs to establish the MTD and/or the selected dose of sequential escalating doses of Sym023 when administered Q2W in combination with fixed doses of 3 mg/kg of Sym021 and either 1, 3, or 5 mg/kg of Sym022, each by IV infusion to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that were refractory to available therapy or for which no standard therapy was available.

Secondary:

- Evaluation of the immunogenicity of Sym021, Sym022, and Sym023 when dosed in combination.
- Characterization of the PK profile of Sym021, Sym022, and Sym023 when dosed in combination.
- Evaluation of the preliminary antineoplastic effects of Sym021, Sym022, and Sym023 when dosed in combination, including:
  - Evidence of OR or SD*
  - Duration of OR or SD*
  - TTP of disease*

  *As assessed by RECIST v1.1, iRECIST, and RECIL 2017.

Exploratory:

- Evaluation of potential pharmacodynamic markers of Sym021 + Sym022 + Sym023, including:
  - In blood: receptor occupancy in PBMCs using chip cytometry or equivalent methodology and/or potential target engagement assay and/or cytokine analysis*
    *Samples may have been used for other biomarker studies, as outlined below.
- Evaluation of potential biomarkers of Sym021 + Sym022 + Sym023 effects, including but not limited to assessment of:
  - In blood (plasma): ctDNA and relevant proteins/cytokines

- In blood (PBMCs): DNA, RNA, immune cell sub-populations analysis (immune-phenotyping), and relevant proteins/cytokines
- In tumor tissue: DNA, RNA, and proteins (biopsies optional)

Methodology:

This was a Phase 1, multi-center, open-label, uncontrolled, non-randomized, 3-part study with 3 study drugs. The trial was designed to evaluate safety and DLTs to establish the MTD or maximum administered dose (MAD), and/or the selected dose of sequential escalating doses of Sym021 (anti-programmed cell death protein-1 [PD-1] monoclonal antibody [mAb]) alone (Part I), Sym021 in combination with either Sym022 (anti-lymphocyte-activation gene-3 [LAG-3] mAb) or Sym023 (anti-T-cell immunoglobulin [Ig] and mucin-domain containing-3 [TIM-3] mAb; Part II), and Sym021 in combination with both Sym022 and Sym023 (Part III), when administered Q2W (4 weeks equals 1 cycle) to patients with advanced, refractory solid tumor malignancies or lymphomas.

In Part I, approximately 12-24 male and female patients were planned to enter the study. Dose-escalation followed a standard 3+3 design, with a target toxicity level of 33.3% or less as determined by DLTs. Four dose levels up to a maximum dose of 10 mg/kg were planned to be evaluated. The number of patients treated, the number of cohorts evaluated, and the MTD/MAD depended upon the observed tolerability of Sym021 during Cycle 1 (C1); however, the MAD in this trial was not to exceed 10 mg/kg.

In Part II, following the same design schema as above, approximately 39-78 male and female patients were to be sequentially assigned in the order of confirmation of eligibility and next slot availability to receive Sym021 at the selected dose identified in Part I (identified as 3 mg/kg), in combination with escalating doses of either Sym022 (Arm A) or Sym023 (Arm B). It was planned that dose levels of Sym022 up to a MAD of 10 mg/kg and Sym023 up to an MAD of 20 mg/kg were to be evaluated.

The starting doses of Sym022 (Arm A) and Sym023 (Arm B) were at minimum either 2 dose levels below the MTD identified in the corresponding Phase 1 single-agent trials, previously conducted by the Sponsor (Sym022-01 and Sym023-01, respectively), or 2 dose levels below the MAD achieved and tolerated if an MTD had not been identified. The highest dose level of Sym022 or Sym023 when dosed in combination with Sym021 was not to exceed the highest dose level deemed tolerable for each in the respective single-agent trial (i.e., the dose at which during C1 of treatment no more than 1 of 6 evaluable patients had a DLT).

As in Part I, each dose-escalation cohort followed a standard 3+3 design, with a target toxicity level of 33.3% or less as determined by DLTs. The number of patients treated, the number of cohorts evaluated, and the MTD/MAD of each combination depended upon the observed tolerability of Sym021 + Sym022 or Sym021 + Sym023 during C1.

Following C1, in the absence of a DLT or documented progressive disease (PD), patients may have continued to receive additional 4-week cycles of the assigned study drug in Part I, or study drug combination in Part II, at the same dose and infusion duration established for the patient, and on the same Q2W schedule.

In Part III, patients were sequentially assigned in the order of confirmation of eligibility and next slot availability to receive Sym021 (3 mg/kg) and Sym022 (1, 3, or 5 mg/kg) in combination with escalating doses of Sym023. It was planned that dose levels of Sym023 up to an MAD of 20 mg/kg would be evaluated, though escalation was to be stopped before the highest dose level of 20 mg/kg if the doublet dose escalation of Sym021 + Sym023 (Part II, Arm B) provided sufficient evidence that ≤10 mg/kg of Sym023 was an appropriate dose for combination based on tolerability, PK, and/or pharmacodynamic data.

The highest dose level of Sym023 when dosed in combination with Sym021+ Sym022 was not to exceed the highest tolerable dose level when administered alone or in combination with Sym021.

As in Part I and II, each dose-escalation cohort followed a standard 3+3 design, with a target toxicity level of 33.3% or less as determined by DLTs. The number of patients treated, the number of cohorts evaluated, and the MTD/MAD of the mAb combination depended upon observed tolerability during C1.

Following C1, in the absence of a DLT or documented PD, patients may have continued to receive additional 4-week cycles of the assigned study drug combination in Part III. Throughout, patients were followed for clinical as well as laboratory adverse events (AEs), including the occurrence of immune-mediated toxicities.

Patients were assessed for safety and efficacy parameters according to the study schedule. At screening, the following assessments were conducted after obtaining informed consent: eligibility assessment, demographics, medical history, and history of primary malignancy, in addition to baseline safety and disease status assessments.

During the study, patients were monitored closely for signs of toxicity. Safety assessments included DLT assessment (C1 as well as later cycles for evidence of delayed toxicity), AE reporting, concomitant medication/procedure surveys, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) evaluation, vital signs assessment, physical examination, clinical laboratory assessments (hematology, biochemistry, urinalysis, coagulation, and thyroid panels), pregnancy testing, electrocardiogram (ECG), ophthalmology examination, multi-gated acquisition (MUGA) scan or echocardiogram (ECHO; MUGA or ECHO only in patients with a history of congestive heart failure [CHF]), and pulmonary function tests (PFTs).

Efficacy was assessed via tumor marker measurements, diagnostic imaging for assessment of disease (computed tomography [CT]/magnetic resonance imaging [MRI]), and response assessments (per RECIST v1.1, RECIL 2017, and iRECIST). Data on the evidence of and duration of any OR (complete response [CR] or partial response [PR]), SD, and TTP, were also collected.

Serum sampling was used to assess the potential for anti-drug antibody (ADA) formation and the PK profile of the study drug or study drugs in combination. Peripheral blood sampling (pre- and post-dosing) was used to perform a pharmacodynamic evaluation of receptor occupancy/target engagement and to evaluate ctDNA, DNA, RNA, proteins/cytokines, and cellular biomarkers, while tumor tissue sampling (pre- and post-dosing; biopsies optional) was used to evaluate DNA, RNA, protein, and cellular biomarkers.

MTD and DLT Assessments:

Any of the following toxicities, if judged to be related to study drug (i.e., possibly related, probably related, or related) were considered a DLT for the purposes of this trial. During Part II and Part III, occurrence of any of the following during the trial required treatment discontinuation, without exception.

1. ≥Grade 3 evidence of any of the following immune-mediated toxicities:
   - Pneumonitis, myocarditis, adrenal insufficiency, encephalitis, nephritis, renal dysfunction (serum creatinine elevation), episcleritis, uveitis, or iritis, colitis, hypophysitis, hyperglycemia, inflammatory arthritis, myositis, and/or rash
2. ≥Grade 2:
   - Uveitis, eye pain, or blurred vision that did not resolve with topical therapy within 2 weeks
   - AEs that were prolonged excessively based upon the medical judgment of the Investigator, and/or led to permanent discontinuation of the study drug due to poor tolerance
   - Immune-mediated toxicity that required use of glucocorticoids at a dose of ≥1 mg/kg/day of prednisone equivalents for treatment of the toxicity
3. Any confirmed reduction in visual acuity, regardless of grade or duration
4. Hepatic findings:
   - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevation >3 times baseline if elevated at study entry due to hepatic involvement by tumor), with
   - Total bilirubin ≥2 times upper limit of normal (ULN) without initial findings of cholestasis (i.e., serum alkaline phosphatase [ALP] <2 times ULN), and
   - No explanation for the above findings such as viral hepatic injury, preexisting or acute liver disease, or another drug or condition capable of causing the observed liver injury
5. Any other ≥Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of:
   - Grade 3 fatigue
   - Grade 3 nausea, vomiting, or diarrhea lasting ≤2 days with best supportive care
   - Grade 3 asymptomatic electrolyte abnormalities lasting ≤3 days that were not clinically complicated, and resolved spontaneously or responded to conventional medical interventions
   - Other Grade 3 asymptomatic laboratory abnormalities that were clinically nonsignificant in the Investigator's opinion, and that resolved spontaneously or with conventional medical interventions
6. Neutropenia that was:
   - Grade 3 meeting the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 criteria for febrile neutropenia (absolute neutrophil count [ANC] <1000 per mm^3 and a single temperature >38.3ºC [101ºF] or sustained temperature ≥38ºC [100.4ºF] for >1 hour) or Grade 4
7. Thrombocytopenia that was:
   - Grade 3 with clinically significant (CS) hemorrhage or requirement for transfusion or Grade 4 (platelets <25,000 per mm^3)

8. Anaemia that was Grade 4 and not explained by underlying disease
9. Any other Grade 4 hematologic toxicity (other than those specifically excluded) lasting >5 days
10. Any death where a relationship to study drug could not be ruled out
11. Inability to complete C1 at the assigned dose(s) (i.e., receipt of <2 full planned doses of study drug [or study drugs in combination] plus 2 weeks of follow-up [FUP]) due to any toxicity
12. Treatment delays >2 weeks from the scheduled next dose(s) during C1 due to any toxicity

The above criteria were used to make individual patient determinations regarding dose delays or discontinuation throughout the course of the trial; however, only those DLTs that occurred during C1 were used to make decisions regarding cohort dose-escalation and tolerability.

The MTD was defined as the highest dose level of study drug, or study drug combination, at which during C1 of treatment, no more than 1 of 6 evaluable patients had a DLT or, in an expanded cohort, fewer than 33% of patients had a DLT. The MTD was not to be established until all patients in the cohort under evaluation had either completed C1 or discontinued treatment due to the occurrence of a DLT. Previously established tolerability of a dose level was to be reevaluated if DLTs thought to be possibly related, probably related, or related to study drug were observed in later cycles, or, in the event of expansion of a cohort to >6 patients. An MTD may or may not have been identified within the range of dose levels tested for single-agent Sym021, the doublet combinations of Sym021 + Sym022 or Sym021 + Sym023, or the Sym021 + Sym022 + Sym023 triplet combination. All dose levels to be tested may have been tolerated or, alternatively, dose-escalation may have been stopped due to toxicity observations other than DLTs, including events occurring after C1.

Selected Dose Assessment:

For each dose-escalation, including single-agent Sym021 in Part I, combinations of Sym021 + Sym022 or Sym021 + Sym023 in Part II, and combinations of Sym021 + Sym022 + Sym023 in Part III:

- The MAD or MTD (or a dose lower than the MAD or MTD) was to be the selected dose, or dose combination, provided a minimum of 6 evaluable patients had been treated at the MAD or MTD and an acceptable tolerance (i.e., no observed DLT) had been demonstrated in at least 5 of 6 patients treated.
- For Part I and Part II/III dose-escalations, the selected dose, or dose combinations, were to be based on MTD evaluations, safety data, including observations in later cycles of administration of study drug(s), as well as on available PK, pharmacodynamics/biomarkers, and/or other data, including data from the single-agent trials Sym022-01 and Sym023-01, as applicable.

Number of Patients:

One hundred seven (107) patients at 4 study centers were screened with 89 patients being enrolled in the study. All 89 patients were included in the Full Analysis Set (FAS; 17 in Part I, 26 in Part II Arm A, 27 in Part II Arm B, and 19 in Part III) with 88 patients included in the DLT Analysis Set (16 in Part I, 26 in Part II Arm A, 27 in Part II Arm B, and 19 in Part III), 70 patients in the PK Analysis Set (17 in Part I, 26 in Part II Arm A, 27 in Part II Arm B), and 66 patients in the ADA Analysis Set (17 in Part I, 26 in Part II Arm A, 23 in Part II Arm B).

Diagnosis and Criteria for Inclusion:

Patients included in this study were male or female, ≥18 years of age at the time of obtaining informed consent. Patients had a documented (histologically- or cytologically-proven) solid tumor malignancy that was locally advanced or metastatic, or documented lymphoma, that was not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor. Patients refractory to or intolerant of existing therapy(ies) known to provide clinical benefit and those with measurable or non-measurable disease according to RECIST v1.1 or RECIL 2017, as well as those with an ECOG PS of 0 or 1 and anticipated life expectancy of ≥3 months, were included in the study.

Test Products, Doses, Mode of Administrations, Batch Numbers:

Sym021

Sym021 is a recombinant, fully human, effector function-silenced IgG1-L234A, L235A (LALA) antibody that binds human, cynomolgus, and murine PD-1 with sub-nanomolar affinity and blocks binding of the inhibitory ligands programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), thus releasing PD-1-mediated inhibition of the immune response.

Sym021 was administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment, diluted with 0.9% sodium chloride injection, United States Pharmacopeia (USP) or equivalent

solution to a final volume of 100mL for IV infusion, was administered Q2W (4 weeks [28 days] equaled 1 dosing cycle).

- Part I: Study drug was administered over 30 minutes (+10 minutes).
- Part II: Sym021 infusion occurred first (fixed dose of 3 mg/kg); a 30-minute post-dosing interval followed, after which infusion of either Sym022 or Sym023 may have commenced, per cohort assignment. The IV access port should have been flushed with the corresponding diluent, as appropriate, prior to and following each infusion.
- Part III: Sym021 infusion occurred first (fixed dose of 3 mg/kg); a 30-minute post-dosing interval followed, after which infusion of Sym022 commenced, per cohort assignment; another 30-minute post-dosing interval followed, after which infusion of Sym023 commenced, per cohort assignment. The IV access port should have been flushed with the corresponding diluent, as appropriate, prior to and following each infusion.

Batch Numbers: CT3350/1, CT3350/2, CT3350/5, and CT3350/7.

Sym022

Sym022 is a recombinant, fully human, effector function-silenced IgG1- LALA antibody that binds human and cynomolgus LAG-3 with nanomolar affinity but does not cross-react with murine LAG-3.

Sym022 was administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment was administered initially.

- C1: Study drug was administered over 60 minutes (+10 minutes).
- C2 and thereafter: If no Grade 2 infusion-related reaction (IRR) was observed in ≥ two thirds of the patients in a cohort, a decision may have been made to decrease the infusion time to 30 minutes (+10 minutes) as patients within a cohort were treated in C2 and thereafter.

Sym022 was diluted with 5% dextrose injection, USP or equivalent solution for IV infusion such that the final volume infused was equivalent to:

- 100 mL for doses ≤3 mg/kg
- 100 mL for doses of >3 mg/kg to ≤10 mg/kg for patients with body weight ≤80 kg
- 250 mL for doses of >3 mg/kg to ≤10 mg/kg for patients with body weight >80 kg

Batch Numbers: CT3350/3, CT3350/9, and CT3350/12.

Sym023

Sym023 is a recombinant, fully human, immunoglobulin G2 (IgG2) antibody that binds human TIM-3 with nanomolar affinity and cynomolgus TIM-3 with 100-fold reduced affinity.

Sym023 was administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment was administered initially over:

- Approximately 30 minutes (+10 minutes) for infusion volumes ≤250 mL
- Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL

Sym023 was diluted with 0.9% sodium chloride injection, USP or equivalent solution for IV infusion such that the final volume infused was equivalent to:

- 50 mL for doses <1 mg/kg
- 100 mL for doses ≥1 mg/kg to ≤3 mg/kg
- 100 mL for doses of >3 mg/kg to ≤10 mg/kg for patients with body weight ≤80 kg
- 250 mL for doses of >3 mg/kg to ≤10 mg/kg for patients with body weight >80 kg
- 250 mL for doses >10 mg/kg for patients with body weight ≤100 kg
- 500 mL for doses >10 mg/kg for patients with body weight >100 kg

Batch Numbers: CT3350/4, CT3350/6, and CT3350/8.

Dose cohorts were numbered sequentially (i.e., Cohort 1, Cohort 2, etc.). The number of cohorts evaluated depended upon toxicities experienced during C1.

Part I: Sym021 Single Agent Dose-Escalation

Sym021 was administered Q2W at up to 3 planned dose levels; potential dose levels included 1, 3, and/or 10 mg/kg.

Intermediate doses may have been explored, if indicated.

Part II: Doublet Antibody Dose-Escalations

- Arm A: Doublet Sym021 + Sym022 patients received:
  - Sym021 Q2W at the dose of 3 mg/kg Q2W, PLUS
  - Sym022 Q2W; beginning at minimum 2 dose levels below either the MTD, if identified, or the MAD achieved and tolerated, if an MTD had not been identified, in the single-agent trial (Sym022-01). Sym022 dose-escalation proceeded from that dose level and may have included up to 4 potential doses of 0.3, 1, 3, and/or 10 mg/kg.
- Arm B: Doublet Sym021 + Sym023 patients received:
  - Sym021 Q2W at the dose of 3 mg/kg Q2W, PLUS
  - Sym023 Q2W; beginning at minimum 2 dose levels below either the MTD, if identified, or the MAD achieved and tolerated, if an MTD had not been identified, in the single-agent trial (Sym023-01). Sym023 dose-escalation proceeded from that dose level and may have included up to 7 potential doses of 0.03, 0.1, 0.3, 1*, 3, 10, and/or 20 mg/kg.
    *Due to the limited clinical experience with combination of anti-PD-1 and anti-TIM-3 antibodies, the starting dose of Sym023 was not to exceed 1 mg/kg.

Intermediate doses of Sym022 (Arm A) or Sym023 (Arm B) may have been explored, if indicated. The highest dose level of Sym022 or Sym023 evaluated in combination did not exceed the highest dose level deemed tolerable in the respective single-agent trial (i.e., the dose at which during C1 of treatment no more than 1 of 6 evaluable patients had a DLT).

Part III: Triplet Antibody Dose Escalation

- Sym021 Q2W at the dose of 3 mg/kg Q2W, PLUS
- Sym022 Q2W for the first dose cohort at the dose of 1 mg/kg and for the following dose cohorts at the dose of 3 mg/kg, PLUS
- Sym023 Q2W; up to 4 dose levels/~6 dose cohorts; potential levels included 1, 3, 10, and 20 mg/kg.
  *Cohort 1: 1 mg/kg of Sym022; next cohorts: 3 mg/kg of Sym022 (all cohorts: 3 mg/kg of Sym021).

Intermediate doses may have been explored, if indicated. Alternative dose level combinations may have been explored using lower doses of Sym022 and/or Sym023, if indicated (e.g., Sym022 at 1 mg/kg, Sym023 at 10 mg/kg). The highest dose level of Sym023 evaluated in combination with Sym021 + Sym022 did not exceed the highest dose level deemed tolerable in the doublet escalation (Part II Arm B) or the single-agent trial (Sym023-01; i.e., the dose at which during C1 of treatment no more than 1 of 6 evaluable patients had a DLT) or the highest dose level tested in case no DLTs were observed.

Once assigned to a dose cohort, patients continued to be treated with study drug(s) at that same dose level(s) throughout the duration of their time on study. There was no intra-patient dose-escalation or reduction.

Reference Treatment, Dose, Mode of Administration, Batch Number(s):

Not applicable. There was no control group in this study.

Duration of Treatment:

Patients received study treatment Q2W (± 2 days) on Day 1 and Day 15 of each 4-week (28 day) dosing cycle.

End of Cycle (EOC) 1 assessments were to be performed on C1/D28 (±2 days). Subsequent cycles with continued Q2W (± 2 days) dosing may have continued, based on tolerability and disease status.

During Part II or Part III, if there was cause for delay of treatment, administration of all mAbs was delayed.

Statistical Methods:

Detailed methodologies for summary and statistical analyses of the data collected in this study were documented in 2 Statistical Analysis Plans (SAPs), dated 10 Dec 2018 (singlet) and 21 May 2020 (doublet) prior to database lock. The 2 SAPs were then combined into a single SAP that included analyses for Part III of the study, dated 22 Apr 2022. In general, continuous variables, including baseline characteristics, were summarized using descriptive statistics by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables were summarized using frequency distributions showing the number and percentage of patients within a category. Time-to-event data were summarized using the Kaplan-Meier method, as appropriate.

Unless indicated otherwise, summary statistics are presented using observed data only. Missing data were maintained as missing unless specified otherwise. For variables where missing data were imputed, the analysis dataset contains one variable with the imputed value and the original variable with missing maintained as missing. If a baseline value was missing, no change from baseline (CFB) was calculated. Baseline was defined as the last available observation prior to the first administration of study drug on C1/D1.

All safety data are summarized by cohort and tumor type. The analysis set for all safety analyses was the FAS. Safety parameters included MTD, DLTs, selected dose, AEs, clinical laboratory measurements, physical examination (including vital signs), ECGs, ECOG PS, and other relevant safety measurements. AEs were classified according to system organ class (SOC) and preferred terms and severity was classified using NCI-CTCAE toxicity criteria. All AEs were listed and only incidences of treatment-emergent AEs (TEAEs) and serious adverse events (SAEs) are summarized by treatment group. Summary tables, CFB, and shift tables are provided for hematology and chemistry parameters for each treatment group.

Efficacy analyses were based on the FAS. The tumor marker measurements were summarized by visit (actual values and CFB), where applicable. The objective response rate (ORR) and clinical benefit rate (CBR) estimates are presented along with the associated Clopper-Pearson 95% confidence intervals (CIs). A waterfall plot for percent CFB of the sum of the target lesion measurements is also presented, at the EOC 2 tumor assessment as well as nadir of sum of all target lesions for each patient, with primary disease site and study treatment dose indicated. Median TTP durations were estimated using the Kaplan-Meier method, along with the corresponding 95% CI. If there were a sufficient number of responses, duration of response (DOR) was analyzed using the same methodology as TTP.

PK analyses were performed for the dose-escalation cohorts on patients who received any amount of their assigned dose of study drug and had an adequate number of concentration determinations to allow for PK calculation. The PK profile of study drug was derived based on the concentration-time curves after the first infusion. Maximum concentration (C_{max}), concentration at the end of infusion (C_{EOI}), trough concentration (C_{trough}), and time to maximum concentration (T_{max}) were derived from observed data while area under the concentration-time curve from start of infusion to infinity (AUC_{inf}), area under the concentration-time curve from start of infusion up to 336 hours (AUC_{τ}), dose-normalized area under the concentration-time curve in a dosing interval ($AUC_{norm, \tau}$), clearance (CL), volume of distribution during the terminal phase after first dose (V_d), and terminal elimination half-life ($T_{½}$) were estimated using non-compartmental methods and actual timepoints. For repeated dosing, C_{EOI} and C_{trough} (equivalent to the concentration at end of infusion [EOI] and start of infusion [SOI], respectively) were assessed.

SUMMARY OF RESULTS

Safety:

Part I

- There were 17 patients enrolled and treated in Part I of this study.
- Sym021 was well tolerated.
- The MTD was not achieved.
- The MAD of Sym021 10.0 mg/kg was well tolerated.
- At C1, there was 1 DLT of immune-mediated enterocolitis (Grade 3) reported in 1 patient in the Sym021 10.0 mg/kg cohort. There was 1 patient in the Sym021 3.0 mg/kg cohort who experienced a DLT of immune-mediated arthritis (Grade 3) after C1.
- Most patients (94.1%) experienced at least 1 TEAE. The most commonly reported TEAEs were fatigue (47.1%) and back pain, constipation, decreased appetite, nausea, and oedema peripheral (23.5% each). No patients experienced an IRR.
- The majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. There were 9 (52.9%) patients who experienced Grade ≥3 (severe) TEAEs (highest severity), with 8 (47.1%) patients experiencing Grade 3 TEAEs and 1 (5.9%) patient experiencing a Grade 4 TEAE. The Grade 4 TEAE of hypophosphataemia was not assessed as an SAE and was considered not related to study treatment. No patients had a Grade 5 TEAE.
- There were 9 (52.9%) patients who experienced treatment-related TEAEs, with the majority being Grade 1 (mild) or Grade 2 (moderate) in severity. The most commonly reported treatment-related TEAE were fatigue in 3 (17.6%) patients and hypothyroidism in 2 (11.8%) patients, with all other treatment-related TEAEs occurring in 1 (5.9%) patient each.

- Eight (47.1%) patients had SAEs for a total of 20 events overall. Two (11.8%) patients had SAEs related to study treatment, which included immune-mediated arthritis (Grade 3) and immune-mediated enterocolitis (Grade 3).
- There were 2 (11.8%) patients who experienced TEAEs leading to study drug discontinuation, which included immune-mediated arthritis (Sym021 3.0 mg/kg dose cohort) and immune-mediated enterocolitis (Sym021 10.0 mg/kg dose cohort); both were SAEs related to study treatment.
- There were 5 (29.4%) patients who experienced TEAEs leading to study drug delay (1 in Sym021 1.0 mg/kg and 2 each in Sym021 3.0 mg/kg and 10.0 mg/kg dose cohorts). The TEAEs leading to study drug delay in patients in the Sym021 3.0 mg/kg and 10.0 mg/kg dose cohorts were treatment-related.
- There were 2 patients (1 each in the Sym021 3.0 mg/kg and Sym021 10.0 mg/kg dose cohorts) who experienced immune-related AEs and no patients who experienced IRRs.
- Eight deaths were reported in the study with 7 of the deaths occurring more than 30 days after last study drug dose. Seven deaths were related to disease progression and 1 was due to other/unknown reasons.
- With the exception of the reported laboratory-related TEAEs, there were no remarkable or concerning findings noted in any laboratory results or other safety assessments.
- Based on the available safety, exposure, and PK/PD modelling data, the selected Sym021 dose for future dose cohorts in Parts II and III was 3 mg/kg.

<u>Part II Arm A</u>

- There were 26 patients enrolled and treated in Part II Arm A of this study.
- Sym021 + Sym022 was well tolerated.
- The MTD was not achieved.
- The MAD of Sym021 3.0 mg/kg + Sym022 10.0 mg/kg was well tolerated.
- At C1, there was 1 reported DLT of blood creatine phosphokinase increased (Grade 3) in 1 patient in the Sym021 3.0 mg/kg + Sym022 0.3 mg/kg cohort. Additionally, there was 1 patient in the Sym021 3.0 mg/kg + Sym022 3.0 mg/kg cohort who experienced nephrotic syndrome (Grade 3) that was reported as a DLT occurring after C1; however, reported onset was on C1D24 with relevant laboratory assessments collected on C1D22 and the event was considered to be a DLT occurring in C1. There were 2 additional patients who experienced DLTs after C1. One patient in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg cohort experienced hypophysitis (Grade 3) and 1 patient in the Sym021 3.0 mg/kg + Sym022 10.0 mg/kg cohort experienced blood creatine phosphokinase increased twice (Grade 3 and Grade 4). Since these DLTs were reported with onset after C1, they were not considered when determining the MTD per protocol.
- Most patients (96.2%) experienced at least 1 TEAE. The most commonly reported TEAEs were fatigue (34.6%), amylase increased (19.2%), and anaemia, blood creatine phosphokinase increased, decreased appetite, and dyspnoea (15.4% each). There were 2 (7.7%) patients with IRRs (both Grade 1).
- The majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. There were 13 (50.0%) patients who experienced ≥Grade 3 (severe) TEAEs (highest severity), with 10 (38.5%) patients, 2 (7.7%) patients, and 1 (3.8%) patient who experienced Grade 3, Grade 4, and Grade 5 TEAEs, respectively. The Grade 4 TEAEs were confusional state and blood creatine phosphokinase increased that were assessed as SAEs and considered not related and possibly related to study treatment, respectively. The Grade 5 TEAE was urosepsis and was considered not related to study treatment.
- There were 19 (73.1%) patients who experienced treatment-related TEAEs, with the majority being Grade 1 (mild) or Grade 2 (moderate) in severity. The most commonly reported treatment-related TEAEs were fatigue (26.9%), amylase increased and blood creatine phosphokinase increased (15.4%), and decreased appetite (11.5%).
- Ten (38.5%) patients had SAEs for a total of 19 events overall. Six (23.1%) patients had treatment-related SAEs of immune-mediated lung disease (Grade 1), hypophysitis (Grade 3), nephrotic syndrome (Grade 3), blood creatine phosphokinase increased (Grade 3 and Grade 4), and thyroiditis (Grade 2).
- There were 5 (19.2%) patients who experienced TEAEs leading to study drug discontinuation, which included blood creatine phosphokinase increased (Sym021 3.0 mg/kg + Sym022 0.3 mg/kg and Sym021 3.0 mg/kg + Sym022 10.0 mg/kg), hypophysitis (Sym021 3.0 mg/kg + Sym022 1.0 mg/kg), pneumonia (Sym021 3.0 mg/kg + Sym022 1.0 mg/kg), urosepsis (Sym021 3.0 mg/kg + Sym022 3.0 mg/kg), and nephrotic syndrome (Sym021 3.0 mg/kg + Sym022 3.0 mg/kg).
- There were 5 (19.2%) patients who experienced TEAEs leading to study drug delay (2 in Sym021 3.0 mg/kg + Sym022 1.0 mg/kg, and 1 in Sym021 3.0 mg/kg + Sym022 3.0 mg/kg, and 2 in Sym021 3.0 mg/kg +

Sym022 10.0 mg/kg dose cohorts). The TEAEs leading to study drug delay in the patients in the Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohort were treatment-related.

- There were 7 patients (1 in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg and 2 each in the Sym021 3.0 mg/kg + Sym022 0.3 mg/kg, Sym021 3.0 mg/kg + Sym022 3.0 mg/kg, and Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohorts) who experienced immune-related AEs and 2 patients (1 each in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg and Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohorts) who experienced IRRs (Grade 1).
- Twelve deaths were reported in the study with 10 of the deaths occurring more than 30 days after last study drug dose. Ten deaths were due to disease progression, 1 was due to an AE (urosepsis; not treatment-emergent as the event occurred >30 days after last treatment; not related to study drug), and 1 was due to other/unknown.
- With the exception of the reported laboratory-related TEAEs, there were no remarkable or concerning findings noted in any laboratory results or other safety assessments.
- Based on the available safety, exposure, and PK/PD modelling data, the selected Sym022 doses for combination treatment in Part III of the study were 1.0, 3.0, and 5.0 mg/kg and the selected fixed Sym022 dose for future dose expansion studies was 5 mg/kg.

Part II Arm B

- There were 27 patients enrolled and treated in Part II Arm B of this study.
- Sym021 + Sym023 was well tolerated.
- The MTD was not achieved.
- The MAD of Sym021 3.0 mg/kg + Sym023 20.0 mg/kg was well tolerated.
- At C1, there was 1 DLT of fatigue (Grade 3) reported in 1 patient in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg cohort. There was 1 patient in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg cohort who experienced a DLT of rash maculo-papular (Grade 3) after C1.
- Most patients (92.6%) experienced at least 1 TEAE. The most commonly reported TEAEs were fatigue (40.7%), nausea (25.9%), and arthralgia (22.2%). No patients experienced an IRR.
- The majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. There were 13 (48.1%) patients who experienced Grade ≥3 (severe) TEAEs (highest severity), with 12 (44.4%) patients and 1 (3.7%) patient who experienced Grade 3 and Grade 4 TEAEs, respectively. The Grade 4 TEAE was embolism and was assessed as an SAE and considered not related to study treatment. No patients had a Grade 5 TEAE.
- There were 18 (66.7%) patients who experienced treatment-related TEAEs, with the majority being Grade 1 (mild) or Grade 2 (moderate) in severity. The most commonly reported treatment-related TEAEs were fatigue (25.9%), arthralgia (18.5%), and hypothyroidism, immune-mediated lung disease, rash, and rash maculo-papular (11.1% each).
- Twelve (44.4%) patients had SAEs for a total of 30 events overall. Six (22.2%) patients had SAEs related to study treatment, which included rash maculo-papular (2 events), fatigue, immune-mediated lung disease (3 events; 3 patients), immune-mediate hepatitis (3 events), and diarrhoea (3 events).
- There were 3 (11.1%) patients who experienced TEAEs leading to study drug discontinuation, which included fatigue (Sym021 3.0 mg/kg + Sym023 0.3 mg/kg dose cohort), immune-mediated hepatitis (Sym021 3.0 mg/kg + Sym023 1.0 mg/kg dose cohort), and diarrhoea (Sym021 3.0 mg/kg + Sym023 20.0 mg/kg).
- There were 7 (25.9%) patients who experienced TEAEs leading to study drug delay (2 in Sym021 3.0 mg/kg + Sym023 0.3 mg/kg, 2 in Sym021 3.0 mg/kg + Sym023 1.0 mg/kg, and 3 in Sym021 3.0 mg/kg + Sym023 20.0 mg/kg dose cohorts). There was 1 patient in the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg cohort and 1 patient in the 3.0 mg/kg + Sym023 20.0 mg/kg cohort with treatment-related TEAEs that led to study drug delay.
- There were 7 patients (2 in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg dose cohort, 1 in the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg dose cohort, 1 in the Sym021 3.0 mg/kg + Sym023 3.0 mg/kg dose cohort, 2 patients in the Sym021 3.0 mg/kg + Sym023 10.0 mg/kg dose cohort, and 1 patient in the Sym021 3.0 mg/kg + Sym023 20.0 mg/kg dose cohort) who experienced immune-related AEs and no patients who experienced IRRs.
- Five deaths were reported in the study with 4 of the deaths occurring more than 30 days after last study drug dose. All of the deaths were related to disease progression.

- There were 2 patients in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg dose cohort who had abnormal, CS PFT findings in Part II Arm B at the end of treatment (EOT). One patient had a finding for diffusing capacity of carbon monoxide (DL_{CO}; 3.6 mmol/min/kPa), and the other patient had findings for forced vital capacity (FVC; 1.7 L), forced expiratory volume in 1 second (FEV_1; 1.3 L), functional residual capacity (FRC; 2.4 L) residual volume (1.7 L), total lung capacity (3.4 L), and DL_{CO} (2.7 mmol/min/kPa). These findings coincided with the patients experiencing immune-mediated lung disease.
- Based on the available safety, exposure, and PK/PD modelling data, the selected Sym023 doses for combination treatment in Part III of the study were 1.0, 3.0, and 10.0 mg/kg and the selected fixed Sym023 dose for future dose expansion studies was 10 mg/kg.

Part III

- There were 19 patients enrolled and treated in Part III.
- Sym021 + Sym022 + Sym023 was well tolerated.
- The MTD was not achieved.
- The MAD of Sym021 3.0 mg/kg + Sym022 5 mg/kg + Sym023 10.0 mg/kg was well tolerated.
- There were no DLTs reported in any patients.
- All patients experienced at least 1 TEAE. The most commonly reported TEAEs were arthralgia (31.6%) and diarrhoea, fatigue, and hypothyroidism (21.1% each). No patients experienced an IRR.
- The majority of TEAEs were Grade 1 (mild) or Grade 2 (moderate) in severity. There were 6 (31.6%) patients who experienced Grade ≥3 (severe) TEAEs (highest severity), with 4 (21.1%) patients, 1 (5.3%) patient, and 1 (5.3%) patient who experienced Grade 3, Grade 4, and Grade 5 TEAEs, respectively. The Grade 4 TEAE was lymphocyte count decreased and was not considered an SAE and was not related to study treatment. The Grade 5 TEAE was haemorrhagic stroke and was assessed as an SAE and considered not related to study treatment.
- There were 14 (73.7%) patients who experienced treatment-related TEAEs, all being Grade 1 (mild) or Grade 2 (moderate) in severity. The most commonly reported treatment-related TEAEs were hypothyroidism (21.1%) and fatigue and arthralgia (15.8% each).
- Seven (36.8%) patients had SAEs for a total of 9 events overall. Three (15.8%) patients had SAEs related to study treatment, which included thyroiditis, immune-mediated thyroiditis (2 events), and immune-mediated lung disease.
- There were no patients who experienced TEAEs leading to study drug discontinuation.
- There were 2 (10.5%) patients who experienced TEAEs leading to study drug delay (1 each in Sym021 3.0 mg/kg + Sym022 3.0 mg/kg + Sym023 1.0 mg/kg and Sym021 3.0 mg/kg + Sym022 5 mg/kg + Sym023 10.0 mg/kg dose cohorts). Neither of the patients in the two aforementioned dose cohorts experienced treatment-related TEAEs that led to study drug delay.
- There were 7 patients (1 in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg dose cohort, 3 in the Sym021 3.0 mg/kg + Sym022 3.0 mg/kg + Sym023 3.0 mg/kg dose cohort, and 3 in the Sym021 3.0 mg/kg + Sym022 5.0 mg/kg + Sym023 10.0 mg/kg dose cohort) who experienced immune-related AEs and no patients who experienced IRRs.
- Seven deaths were reported in the study with 5 of the deaths occurring more than 30 days after last study drug dose. Six of the deaths were related to disease progression and 1 was due to a TEAE. The TEAE of haemorrhagic stroke resulted in the single patient death and was considered not related to study drug.

Efficacy, Pharmacokinetics, Immunogenicity, and Pharmacodynamics:

To be assigned a status of PR or CR, changes in disease status must have been confirmed by repeat assessments performed 4 weeks (+7 days) after the criteria for response were first met.

Part I

- There were 17 patients enrolled and treated in Part I of this study.
- There was 1 patient in the Sym021 10.0 mg/kg dose cohort with a confirmed CR, 1 patient in the Sym021 3.0 mg/kg dose cohort with a confirmed PR, and 1 patient in the Sym021 10.0 mg/kg dose cohort with SD >16 weeks.
- The ORR per RECIST v1.1 overall was 11.8% (95% CI: 1.5% to 36.4%) and for the Sym021 3.0 mg/kg and Sym021 10.0 mg/kg dose cohorts were 16.7% (95% CI: 0.4% to 64.1%), and 12.5% (95% CI: 0.3% to 52.7%), respectively. Results were similar per iRECIST.

- Per RECIST v1.1, the median duration of OR overall in the 2 patients with a response was 8.57 months (95% CI: 5.8, NA; range 5.82 to 11.33 months). The median duration of OR was longest for the patient in the Sym021 3.0 mg/kg (11.33 months) dose cohort (lacrimal gland carcinoma), and shortest for the patient in the Sym021 10.0 mg/kg (5.82 months) dose cohort (gastric carcinoma).
- The CBR per RECIST v1.1 overall was 17.6% (95% CI: 3.8% to 43.4%). The CBR for the Sym021 3.0 mg/kg and 10.0 mg/kg dose cohorts was 16.7% (95% CI: 0.4% to 64.1%) and 25.0% (95% CI: 3.2%, 65.1%), respectively. Results were similar per iRECIST.
- Per RECIST v1.1, the median TTP overall was 1.64 months (95% CI: 1.4, 1.9; range 0.03 to 13.14 months). Median TTP was longest for the Sym021 10.0 mg/kg (1.86 months) dose cohort, and shortest for the Sym021 1.0 mg/kg (1.54 months) dose cohort.
- There was one patient in the Sym021 3.0 mg/kg cohort with a positive anti-Sym021 ADA serum titer (titer of 100; 4-fold above baseline).
- The PK parameters for Sym021 showed a linear correlation between dose levels and exposure with a half-life ranging from 9 to 12 days. Sym021 appeared to exhibit linear PK in the dose range of 1 to 10 mg/kg.
- Exploratory PD analysis of Sym021 target engagement following an *ex vivo* SEB stimulation assay on PBMCs indicated there was full target engagement at all dose levels from one day after first dosing (i.e., C1D2) in 11/13 patients.

Part II Arm A

- There were 26 patients enrolled and treated in Part II Arm A of this study.
- There were no patients with a confirmed CR, 1 patient in the Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohort with a confirmed PR, and 1 patient each in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg and Sym021 3.0 mg/kg + Sym022 3.0 mg/kg dose cohorts with SD >16 weeks.
- The ORR per RECIST v1.1 overall was 3.8% (95% CI: 0.1% to 19.6%). The ORR for the Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohort was 14.3% (95% CI: 0.4% to 57.9%). Results were similar per iRECIST.
- One patient in the Sym021 3.0 mg/kg + Sym022 10 mg/kg dose cohort with alveolar soft part sarcoma had a PR, and they did not have documented radiological PD and initiation of non-study anti-cancer treatment, hence the DOR was censored at 20.3 months. The estimated median DOR was not calculable.
- The CBR per RECIST v1.1 overall was 11.5% (95% CI: 2.4% to 30.2%). The CBR for the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg, Sym021 3.0 mg/kg + Sym022 3.0 mg/kg, and Sym021 3.0 mg/kg + Sym022 10.0 mg/kg dose cohorts was 25.0% (95% CI: 0.6% to 80.6%), 16.7% (95% CI: 0.4% to 64.1%), and 14.3% (95% CI: 0.4% to 57.9%), respectively. Results were similar per iRECIST.
- Per RECIST v1.1, the median TTP overall was 1.87 months (95% CI: 1.6, 3.5; range 0.62 to 23.98 months). Median TTP was longest for the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg (3.52 months) dose cohort, and shortest for the Sym021 3.0 mg/kg + Sym022 0.3 mg/kg (1.64 months) dose cohort.
- There were no patients with a positive anti-Sym021 or anti-Sym022 ADA serum titer.
- The PK parameters for Sym021 at 3 mg/kg were not impacted by the co-administration of Sym022 at any dose level. The PK parameters for Sym022 showed a dose-proportional increase in exposure ($AUC_{0\text{-}336h}$) at dose levels >0.3 mg/kg with a half-life ranging from 5 to 7 days.
- Exploratory PD analysis of Sym021 + Sym022 target engagement following an *ex vivo* phytohaemagglutinin (PHA) stimulation assay on PBMCs indicated there was full target engagement at C1D2 in 17/21 patients, regardless of Sym022 dose level. In addition, most patients showed a decrease in Sym022-free LAG3+ T-cells during the treatment phase compared with C1D1, indicative of LAG3 receptor occupancy by Sym022.

Part II Arm B

- There were 27 patients enrolled and treated in Part II Arm B of this study.
- There was 1 patient in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg dose cohort with a confirmed CR, 1 patient each in the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg and Sym021 3.0 mg/kg + Sym023 10.0 mg/kg dose cohort with a confirmed PR, and 5 patients, 2 in the Sym021 3.0 mg/kg + Sym023 20.0 mg/kg dose cohort and 1 patient each in the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg, Sym021 3.0 mg/kg + Sym023 3.0 mg/kg and Sym021 3.0 mg/kg + Sym023 10.0 mg/kg dose cohorts, with SD >16 weeks.
- The ORR per RECIST v1.1 overall was 11.1% (95% CI: 2.4% to 29.2%). The ORR for the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg, Sym021 3.0 mg/kg + Sym023 1.0 mg/kg, and Sym021 3.0 mg/kg + Sym023 10.0 mg/kg dose cohorts was 14.3% (95% CI: 0.4% to 57.9%), 25.0% (95% CI: 0.6% to 80.6%), and 16.7% (95% CI: 0.4% to 64.1%), respectively. Results were similar per iRECIST.

- Per RECIST v1.1, the median duration of OR overall in the 2 patients with a response followed by PD was 9.07 months (95% CI: 3.6, NA). The median duration of OR was longest for the patient in the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg (9.07 months; neuroendocrine carcinoma of the breast) dose cohort, and shortest for the patient in the Sym021 3.0 mg/kg + Sym023 10.0 mg/kg (3.61 months; uterine carcinosarcoma) dose cohort.
  - One patient in the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg dose cohort with gallbladder carcinoma had a PR on Study Day 74 that was maintained until a CR was noted on Study Day 472. The CR was maintained as of Study Day 1053 (the final study day on this trial) with no PD noted.
- The CBR per RECIST v1.1 overall was 29.6% (95% CI: 13.8, 50.2%). The CBR for the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg, Sym021 3.0 mg/kg + Sym023 1.0 mg/kg, Sym021 3.0 mg/kg + Sym023 3.0 mg/kg, Sym021 3.0 mg/kg + Sym023 10.0 mg/kg, and Sym021 3.0 mg/kg + Sym023 20.0 mg/kg dose cohorts was 14.3% (95% CI: 0.4% to 57.9%), 50.0% (95% CI: 6.8% to 93.2%), 33.3% (95% CI: 0.8% to 90.6%), 33.3% (95% CI: 4.3% to 77.7%), and 28.6% (95% CI: 3.7% to 71.0%), respectively. Results were similar per iRECIST.
- Per RECIST v1.1, the median TTP overall was 1.82 months (95% CI: 1.7, 5.3; range 0.76 to 34.60 months). Median TTP was longest for the Sym021 3.0 mg/kg + Sym023 1.0 mg/kg (5.45 months) dose cohort, and shortest for the Sym021 3.0 mg/kg + Sym023 0.3 mg/kg (1.64 months) dose cohort.
- There was 1 patient in the Sym021 3 mg/kg + Sym023 20 mg/kg cohort with a positive anti-Sym021 ADA serum titer (titer of 100; 4-fold above baseline). There were no patients with a positive anti-Sym023 ADA serum titer.
- The PK parameters for Sym021 at 3 mg/kg were not impacted by the co-administration of Sym023 at any dose level. The PK parameters for Sym023 showed an increase in exposure with increasing dose and increased in a greater than dose-proportional way at the dose levels >0.3 mg/kg, with half-lives ranging from 9 to 14 days.
- Exploratory PD analysis of Sym021 + Sym023 target engagement following an *ex vivo* SEB stimulation assay on PBMCs indicated there was full target engagement at C1D2 in 20/22 patients, regardless of Sym023 dose level.

<u>Part III</u>

- There were 19 patients enrolled and treated in Part III of this study.
- There were no patients with a confirmed CR, 1 patient in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg dose cohort with a confirmed PR, and 3 patients, 1 in the Sym021 3.0 mg/kg + Sym022 5.0 mg/kg + Sym023 3.0 mg/kg dose cohort and 2 in the Sym021 3.0 mg/kg + Sym022 5.0 mg/kg + Sym023 10.0 mg/kg dose cohort, with SD >16 weeks.
- The ORR per RECIST v1.1 overall was 5.3% (95% CI: 0.1% to 26.0%). The ORR for the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg dose cohort was 25.0% (95% CI: 0.6% to 80.6%). Results were similar as per iRECIST.
- One patient in the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg dose cohort with small cell lung carcinoma had a PR, and they did not have documented radiological PD and initiation of non-study anti-cancer treatment (as the patient died due to haemorrhagic stroke considered not related to study treatment), hence the DOR was censored at 10.7 months. The estimated median DOR was not calculable.
- The CBR per RECIST v1.1 overall was 21.1% (95% CI: 6.1% to 45.6%). The CBR for the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg, Sym021 3.0 mg/kg + Sym022 5 mg/kg + Sym023 3.0 mg/kg, and Sym021 3.0 mg/kg + Sym022 5.0 mg/kg + Sym023 10.0 mg/kg dose cohorts was 25.0% (95% CI: 0.6% to 80.6%), 33.3% (95% CI: 0.8% to 90.6%), 33.3% (95% CI: 4.3% to 77.7%), respectively. Results were similar per iRECIST.
- Per RECIST v1.1, the median TTP overall was 2.04 months (95% CI: 1.6, 3.5; range 0.03 to 12.29 months). Median TTP was longest for the Sym021 3.0 mg/kg + Sym022 5.0 mg/kg + Sym023 10.0 mg/kg (3.52 months) dose cohort, and shortest for the Sym021 3.0 mg/kg + Sym022 1.0 mg/kg + Sym023 1.0 mg/kg and Sym021 3.0 mg/kg + Sym022 3.0 mg/kg + Sym023 1.0 mg/kg (1.64 months) dose cohorts.
- There were 3 out 19 patients with positive ADA titers, one (1/19) patient with Sym021 ADA, one (1/19) patient with Sym022 ADA, and one (1/19) patient with Sym023 ADA.
- The PK parameters for Sym021 at 3 mg/kg were not impacted by the co-administration of Sym022 + Sym023 at any dose level combination. In addition, when compared with historical derived PK parameters from Sym022 monotherapy (Study Sym022-01; ClinicalTrials.gov identifier: NCT03489369) and Sym023

monotherapy (Study Sym023-01; ClinicalTrials.gov identifier: NCT03489343), the co-administration of Sym021 + Sym022 + Sym023 did not impact the PK parameters of either Sym022 or Sym023, which both showed an increase in exposure with increasing dose when combined with Sym021.

CONCLUSIONS:

- All Sym021, Sym022, and Sym023 combinations were well tolerated.
- An MTD was not reached for any Sym021, Sym022, and Sym023 combinations. The selected doses of Sym021 3.0 mg/kg, Sym022 5.0 mg/kg, and Sym023 10.0 mg/kg were considered well tolerated.
- During C1, there was 1 DLT in 1 patient each in Part I (Sym021 alone) and Part II Arm B of the study (Sym021 + Sym023 combination), and 2 DLTs in 2 patients in Part II Arm A (Sym021 + Sym022 combination). No DLTs occurred in patients in Part III (Sym021 + Sym022 + Sym023 combination) of the study.
- The overall ORRs (RECIST v1.1) for Part I, Part II Arm A, Part II Arm B, and Part III were 11.8%, 3.8%, 11.1%, and 5.3%, respectively.
- The overall CBRs (RECIST v1.1) for Part I, Part II Arm A, Part II Arm B, and Part III were 17.6%, 11.5%, 29.6%, and 21.1%, respectively.
- The PK parameters of Sym021, Sym022 and Sym023 were consistent in Part I, Part II, and Part III and in the monotherapy studies (Study Sym022-01; ClinicalTrials.gov identifier: NCT03489369 and Study Sym023-01; ClinicalTrials.gov identifier: NCT03489343), indicating that the 3 compounds do not interfere with each other. The PK parameters of Sym022 and Sym023 were not impacted by the co-administration schedules in Part II and Part III.
- Immunogenicity (ADA) incidences during Part I, Part II, and Part III were of low frequency and of low magnitude. Due to the limited number of ADA positive patients, a correlation analysis of ADA with exposure was not possible.

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