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# First-in-human phase 1 study of the ICOS agonist feladilimab on patients with advanced solid tumors

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## ABSTRACT

**Background** Inducible costimulator (ICOS) receptor belongs to the CD28/CTLA immunoglobulin super family, whose expression is restricted to T cells and is weakly expressed on resting TH17, follicular helper T cells, and regulatory T cells, but is highly induced on CD4+ and CD8+ T cells on activation by T-cell receptors. ICOS stimulation downstream effects include activation of conventional CD4+cells and cytotoxic CD8+cells, resulting in a durable antitumor response in preclinical models.

**Methods** As part of a larger first-in-human study (GSK Study 204691), this study focused on 2 cohorts of 25 and 67 participants enrolled in a dose escalation and pharmacokinetic/pharmacodynamic (PK/PD) analysis of the ICOS agonist feladilimab (GSK3359609) as monotherapy. For these cohorts, the objectives were to determine the safety, tolerability, maximum tolerated dose (MTD) or maximum administered dose of feladilimab. Additional objectives included determining the recommended dose of feladilimab for further exploration, characterizing the PK properties, and immunogenicity.

**Results** Feladilimab was examined over a range of 4 logs from 0.001 mg/kg to 10 mg/kg, and no MTD was established. Adverse events were manageable and consistent with those observed with other immunomodulatory treatments; fatigue, fever, and anemia were the most common events. PK showed a peak value 1 hour following infusion. Accumulation ratio ranged from 1.4 to 2.5 and was generally consistent with expected patterns of accumulation for a monoclonal antibody, and the drug showed linear dose proportionality. ICOS receptor occupancy was maximal at doses>0.1 mg/kg. Based on the collected data, doses of 0.3 and 1.0 mg/kg were selected for further exploration.

**Conclusions** This study showed the feasibility of a modified Toxicity Proportion Interval design and PK/PD analysis to determine a recommended dose for a compound without a dose-limiting toxicity and a tolerable and manageable safety profile.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Inducible costimulator (ICOS) receptor belongs to the CD28/CTLA immunoglobulin super family, whose expression is restricted to T cells and is weakly expressed on resting TH17, follicular helper T, and regulatory T cells but is highly induced on CD4+ and CD8+ T cells on activation by T-cell receptors. ICOS stimulation downstream effects include activation of conventional CD4+cells and cytotoxic CD8+cells, resulting in a durable antitumor response in preclinical models. Feladilimab (GSK3359609) was developed to be a first-in-class ICOS $IgG_4$ agonist antibody to treat cancers of different histologies.

### WHAT THIS STUDY ADDS

⇒ INDUCE-1 (GSK Study 204691, NCT02723955) was a first time-in-human, open-label, multicenter (28 investigative sites in 9 countries) study enrolling patients with selected advanced solid tumors. Beginning in June 2016 and ending in July 2023, the study investigated the safety, tolerability, pharmacology, pharmacodynamics (PD), and preliminary clinical activity of feladilimab and aimed to establish a recommended dose for further exploration. The results of the study demonstrated that feladilimab as monotherapy in the two cohorts reported here was safe and generally well tolerated. ICOS receptor occupancy was maximal at doses >0.1 mg/kg. Based on the collected data, doses of 0.3 and 1.0 mg/kg were selected for further development.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study showed the feasibility of a Modified Toxicity Proportion interval design and pharmacokinetic/PD analysis to determine a recommended dose for a compound without a dose-limiting toxicity.

## BACKGROUND

Inducible costimulator (ICOS) receptor belongs to the CD28/CTLA immunoglobulin superfamily, whose expression is restricted to T cells.[1] Unlike CD28, another T-cell-specific receptor involved in immune regulation, ICOS is not constitutively expressed; rather, it is weakly expressed on resting T helper (Th)

17, follicular helper T, and regulatory T cells but is highly induced on CD4+ and CD8+ T cells on de novo activation by T-cell receptors.[1] The effect of ICOS agonist activity is to promote activation of cytotoxic CD8+ and conventional CD4+cells, augmenting the expansion, function, and survival of these populations, thereby resulting in an increased antitumor immune response that is durable in preclinical models.[2–5]

ICOS mediates its signal through intracellular recruitment of phosphatidylinositol 3 kinase and downstream activation of the mitogen-activated protein kinases p38, c-JUN N-terminal kinase, and extracellular signal-regulated kinase.[6 7] Upregulation of ICOS leads to both Th1 and Th2 cytokine secretion and sustained effector T cell proliferation and function.[5 8] ICOS signaling is suppressed in the presence of PD-1 engagement[9]; therefore, ICOS activation is considered an important target to overcome acquired or intrinsic resistance that is typically observed with PD-1 inhibitor treatment.[10] A growing body of evidence supports the concept that activating ICOS on CD4+ and CD8+ effector T cells has antitumor potential. The rationale for targeting ICOS in cancer has also been established by multiple lines of nonclinical and clinical evidence,[11] with ICOS agonists demonstrating tumor regression and durable antitumor immunity in a range of preclinical tumor models.[12]

Feladilimab (GSK3359609) was developed to be a first-in-class ICOS IgG4 agonist antibody to treat cancers of different histologies. It is differentiated from the first generation of immunomodulatory antibodies directed against CTLA-4 and PD-1/L1, as it targets a different axis in the antitumor T-cell response cascade by promoting the activation of a costimulatory receptor instead of blocking an inhibitory checkpoint receptor.[13–15]

INDUCE-1 (GSK Study 204691, NCT02723955) was a first-in-human, open-label, multicenter (28 investigative sites in 9 countries) study enrolling patients with selected advanced solid tumors, beginning in June 2016 and ending in July 2023. INDUCE-1 investigated the safety, tolerability, pharmacology, pharmacodynamics (PD), and preliminary clinical activity of feladilimab and aimed to establish a recommended dose for further exploration. The study was divided into 38 cohorts enrolling a total of 827 study participants. One of these cohorts was dedicated to dose escalation of feladilimab monotherapy, and a second cohort was dedicated to monotherapy pharmacokinetic and PD (PK/PD) analysis. This report focuses on these 2 cohorts, which contained 25 and 67 study participants, respectively.

## METHODS

### Study design

The dose-escalation cohort included two rule-based designs. For the first three dose levels, an accelerated titration design was planned with one participant enrolled at each of these dose levels. Each participant must have received at least one dose of feladilimab, completed the 28-day dose-limiting toxicity (DLT) evaluation period, and the available safety data reviewed before a decision to escalate to the next dose level was made (ie, the dose level is cleared). The rationale for the accelerated titration design was to minimize the number of participants enrolled at suboptimal doses based on preclinical data.

Beginning with the fourth dose level, a modified Toxicity Probability Interval (mTPI) design[16] was used, which is a well-validated method to identify the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of a given agent. In the dose levels under evaluation by the mTPI design, a minimum of three participants were accrued to each dose level. In the first dose level under the mTPI design and in all subsequent dose levels, treatment was to be administered at least 1 week apart between the first two participants enrolled; the third and any subsequent participants were to be administered treatment at a minimum of 1 day apart. This staggered approach allowed for an initial assessment of safety in a participant accrued to a dose level before initiating the next participant's treatment. Evaluation of the available safety data over the first 28 days of treatment for each participant enrolled in that dose level was required from at least three participants before a decision was made to enroll participants at the next higher dose level. See online supplemental file 2 for the study protocol.

### Patient and public involvement

The patients and the public were represented by an internal GSK patient advisory program and by the investigators for this dose escalation study. Investigators were selected for their experience and expertise in this type of study. Patients/the public were not directly involved in the design, recruitment, and conduct of this study. Patients/the public were asked to assess the burden of the intervention and time required to participate in the research by proxy through GSK internal patient representative advisors and through the input of experienced and dedicated investigators. GSK has a formal process for results dissemination that has been invoked for this study in the preparation of a Lay Person Summary and through postings to the registry ClinicalTrials.gov.

### Eligibility criteria

The key inclusion criteria were male or female, age ≥18 years (at the time consent is obtained), histological or cytological documentation of an invasive malignancy that was diagnosed as locally advanced or metastatic or relapsed or refractory, and is of one of the following tumor types: bladder/urothelial cancer of the upper and lower urinary tract, cervical, colorectal (includes appendix), esophagus, squamous cell carcinoma of the head and neck, melanoma, malignant pleural mesothelioma, non-small cell lung cancer, or prostate cancer, no more than five prior lines of therapy for advanced disease including both standards of care and investigational therapies, adequate organ function: absolute neutrophil count ≥$1.5\times10^9$/L; hemoglobin >9 g/dL; platelets ≥$100\times10^9$/L;

total bilirubin ≤1.5×upper limit of normal (ULN); total bilirubin for participants with Gilbert's syndrome (only if direct bilirubin <35%) ≤3.0×ULN; alanine transaminase (ALT) <2.5×ULN (or <5×ULN for participants with documented liver metastases); calculated creatinine clearance >30 mL/minute calculated using the Chronic Kidney Disease Epidemiology Collaboration formula; ejection fraction >50% by ECHO or MUGA if ECHO was not available, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and not pregnant or have non-reproductive potential (female participants only).

### Exclusion criteria

The key exclusion criteria were no anticancer therapy or investigational therapy within 30 days or 5 half-lives of the drug, whichever is shorter. At least 14 days must have elapsed between the final dose of prior anticancer agent and the first dose of study drug, prior allogeneic or autologous bone marrow transplantation or other solid organ transplantation, invasive malignancy or history of invasive malignancy other than disease under study within the last 2 years, major surgery <4 weeks before the first dose of study treatment, history or evidence of cardiac abnormalities, current or history of idiopathic pulmonary fibrosis, pneumonitis (for past pneumonitis exclusion only if steroids were required for treatment), interstitial lung disease, or organizing pneumonia or recent history (within 6 months) of uncontrolled symptomatic ascites or pleural effusions.

### Treatment

Study participants received feladilimab at doses ranging from 0.001 mg/kg to 10 mg/kg, given intravenously every 21 days per cohort (ie, over a range of 4 logs) until disease progression, unacceptable toxicity, or withdrawal of consent up to a maximum treatment duration of up to 35 cycles (approximately 2 years). After permanent discontinuation of study treatment, the follow-up period for safety assessments was a minimum of 90 days after the final dose of study treatment or until the start of subsequent anticancer treatment; participants were followed every 12 weeks for up to 2 years to determine survival status and subsequent anticancer therapy.

For participants permanently discontinuing study treatment for reasons other than disease progression, disease assessments were performed every 12 weeks until progression or the start of subsequent anticancer therapy.

### Objectives and endpoints

The primary objective of the monotherapy dose-escalation cohort of the study was to determine the safety, tolerability, MTD or maximum administered dose, and RP2D of feladilimab. Endpoints reported here include the frequency and severity of DLTs, adverse events (AEs), AEs of special interest, serious AEs (SAEs) and DLTs/AEs/SAEs leading to dose modifications, delays, or withdrawals. Changes in laboratory parameters (eg, serum analytes including albumin, alkaline phosphatase, ALT, aspartate transaminase, creatinine, and sodium), vital signs, and safety parameters were also assessed.

Secondary endpoints included PK parameters and immunogenicity. Blood and tumor-based biomarkers were assessed as exploratory endpoints.

### Assessments

AEs were coded using Medical Dictionary for Regulatory Activities grouped by system organ class, and graded by the Investigator according to the National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0. Radiographic evaluations of the chest, abdomen, and pelvis were conducted according to RECIST V1.1 at 9 weeks after the first study dose, and then every 6 weeks until week 52, and every 12 weeks thereafter. PK profiles of feladilimab were measured from patient blood samples collected at protocol-defined points, and concentrations calculated using plasma PK parameters were computed via noncompartmental analysis using Phoenix WinNonlin program (V.6.0 or higher; Certara, New Jersey, USA) and descriptively summarized by treatment and cohort using validated bioanalytical methodologies. Blood samples were collected and analyzed by flow cytometry to evaluate the binding of feladilimab to the ICOS receptor and its PD effects on lymphocytes. ICOS receptor occupancy (RO) was determined prior to dosing with feladilimab, after treatment, and at selected time intervals with data presented as the geometric mean of binding between participant samples. Immunogenicity was determined by a validated anti-drug antibody (ADA) assay, and a tiered (screening, confirmation, and titration) analysis was applied. The ADA assay had sufficient drug tolerance (>500 µg/mL feladilimab); therefore, no samples were characterized as false negatives in the screening or confirmation analysis due to high drug levels in the serum sample.

## RESULTS

### Study population

A total of 25 study participants were screened and enrolled into the initial dose-escalation cohort, of which 13 (52%) were female and 12 (48%) were male. Race was 95% white and median age was 59 years (range 36–78). A total of 67 study participants were screened and enrolled into the PK/PD cohort, of which 27 (40%) were female and 40 (60%) were male. Race was predominantly white (91%) and median age was 58 years (range 42–81) (table 1).

For the dose-escalation cohort, the most frequent tumor types were colorectal (40%), cervical, and malignant pleural mesothelioma (12% each) and head and neck squamous cell carcinoma, melanoma, and non-small cell lung cancer (8% each). The median time since diagnosis (for all participants) was 861 days. Previous lines of therapy were 1 (4%), 2 (28%), 3 (28%), and 4 or more (40%).

**Table 1** Patient demographics and baseline characteristics

| Parameter | Dose escalation cohort (N=25) | PK/PD cohort (N=67) |
|---|---|---|
| Age, median (range) | 59 (36–78) | 58 (42–81) |
| Sex, n (%) | | |
| Male | 13 (52) | 40 (60) |
| Female | 12 (48) | 27 (40) |
| Race, n (%) | | |
| White | 24 (95) | 61 (91) |
| Asian | 1 (5) | 1 (2) |
| Black | 0 | 1 (2) |
| Primary tumor, n (%) | | |
| Colon/rectum | 10 (40) | 11 (16) |
| Cervix | 3 (12) | 7 (10) |
| MPM | 3 (12) | 4 (6) |
| Bladder | 1 (4) | 4 (6) |
| Head and neck | 2 (8) | 9 (13) |
| Melanoma | 2 (8) | 13 (19) |
| NSCLC | 2 (8) | 14 (21) |
| Prostate | 1 (4) | 2 (3) |
| Other | 1 (4) | 3 (4) |
| Maximum prior lines of therapy, n (%) | | |
| 1 | 7 (28) | 24 (36) |
| 2 | 2 (8) | 21 (31) |
| ≥3 | 16 (64) | 22 (33) |

MPM, malignant pleural mesothelioma; NSCLC, non-small cell lung cancer; PK/PD, pharmacokinetics/pharmacodynamics.

**Table 2** AEs for Monotherapy and PK/PD cohorts

| Event, n (%) | Monotherapy cohort (N=25) | PK/PD cohort (N=67) |
|---|---|---|
| Any AE | 23 (92) | 64 (96) |
| AEs related to study treatment | 8 (32) | 29 (43) |
| AEs leading to permanent discontinuation of study treatment | 0 | 4 (6) |
| AEs leading to dose interruption/ delay | 4 (16) | 16 (24) |
| Any SAE | 8 (32) | 25 (37) |
| SAEs related to study treatment | 0 | 1 (1) |
| Fatal SAEs | 1 (4) | 0 |
| Fatal SAEs related to study treatment | 0 | 0 |
| Any event* | 23 (92) | 64 (96) |
| Abdominal pain | 5 (20) | 9 (13) |
| Anemia | 5 (20) | 15 (22) |
| Nausea | 5 (20) | 10 (15) |
| Decreased appetite | 4 (16) | 12 (18) |
| Fatigue | 4 (16) | 17 (25) |
| Fever | 4 (16) | 8 (12) |
| Asthenia | 3 (12) | 12 (18) |

*Any AE reported when observed in ≥10% patients in both the monotherapy and PK/PD cohorts. All events are presented in online supplemental tables 1–3.
AE, adverse event; PK/PD, pharmacokinetic/pharmacodynamic; SAE, serious AE.

For the PK/PD cohort, the frequent tumor types were non-small cell lung cancer (21%), colorectal (16%), head and neck squamous cell carcinoma (13%), melanoma (12%), and cervical (10%). The median time since diagnosis (for all participants) was 924 days. Previous lines of therapy were 1 (19%), 2 (31%), 3 (19%), and 4 or more (13%). Five participants (7%) had not received any prior systemic therapy.

## Exposure

For the monotherapy dose-escalation cohort, dose allocations were as follows, all in mg/kg: 0.001 (N=1), 0.003 (N=1), 0.01 (N=2), 0.03 (N=3), 0.10 (N=5), 0.30 (N=3), 1.0 (N=4), 3.0 (N=3), 10.0 (N=3). For the PK/PD cohort, dose escalations were as follows, all in mg/kg: 0.03 (N=4), 0.10 (N=19), 0.30 (N=15), 1.0 (N=5), 3.0 (N=20), 10.0 (N=4).

## Safety

In the monotherapy dose-escalation cohort, almost all participants (92%) experienced at least 1 AE. In 32% of participants, the AEs were considered treatment-related by the investigator. The six most common AEs, all occurring in 20% of study participants, were abdominal pain, anemia, back pain, cough, diarrhea, and nausea. Details are presented in table 2 and online supplemental tables 1,2. The most frequent treatment-related AE, none higher than grade 2, was fatigue (16%) (table 3).

There were no permanent treatment discontinuations due to AEs, but treatment was interrupted or delayed due to non-treatment related AEs for 4 (16%) participants. Eight (32%) of the participants experienced at least 1 SAE; none of the SAEs was treatment-related. There was one fatal AE in the cohort.

In the PK/PD cohort, 96% of participants in the cohort experienced at least 1 AE. For 43% of these participants, the AEs were considered treatment-related by the investigator; however, no clear dose dependence was noted with respect to the incidence of AEs. The five most common AEs were fatigue (25%), anemia (22%), asthenia (18%), decreased appetite (18%), and arthralgia (15%). AEs overall are presented in table 2. AEs by dose are listed in online supplemental table 1, with the full listing presented in online supplemental tables 2,3. AEs and treatment-related AEs by grade (NCI-CTCAE V.5.0) are shown in table 3 with the full listing presented in online supplemental tables 4,5

**Table 3** AEs and treatment-related AEs reported by Grade (NCI-CTCAE V.5.0) in ≥10% and ≥3% patients, respectively, in the monotherapy and PK/PD cohorts

| | Monotherapy cohort (N=25) | | | PK/PD cohort (N=67) | | | Overall (N=92) |
|---|---|---|---|---|---|---|---|
| | Grade <3 | Grade ≥3 | Total | Grade <3 | Grade ≥3 | Total | Total |
| Any event | | | 23 (92) | | | 64 (96) | 87 (95) |
| Anemia | 4 (16) | 1 (4) | 5 (20) | 15 (22) | 3 (4) | 18 (27) | 23 (25) |
| Fatigue | 4 (16) | 0 | 4 (16) | 15 (22) | 2 (3) | 17 (25) | 21 (23) |
| Decreased appetite | 4 (16) | 0 | 4 (16) | 13 (19) | 0 | 13 (19) | 17 (18) |
| Asthenia | 3 (12) | 0 | 3 (12) | 12 (18) | 0 | 12 (18) | 15 (16) |
| Nausea | 5 (20) | 0 | 5 (20) | 9 (13) | 1 (1) | 10 (15) | 15 (16) |
| Abdominal pain | 5 (20) | 0 | 5 (20) | 7 (10) | 2 (3) | 9 (13) | 14 (15) |
| Back pain | 3 (12) | 2 (8) | 5 (20) | 5 (7) | 3 (4) | 8 (12) | 13 (14) |
| Arthralgia | 2 (8) | 0 | 2 (8) | 10 (15) | 0 | 10 (15) | 12 (13) |
| Fever | 4 (16) | 0 | 4 (16) | 8 (12) | 0 | 8 (12) | 12 (13) |
| Constipation | 2 (8) | 0 | 2 (8) | 9 (13) | 0 | 9 (13) | 11 (12) |
| Diarrhea | 4 (16) | 1 (4) | 5 (20) | 5 (7) | 1 (1) | 6 (9) | 11 (12) |
| Cough | 5 (20) | 0 | 5 (20) | 5 (7) | 0 | 5 (7) | 10 (11) |
| Dyspnea | 1 (4) | 1 (4) | 2 (8) | 5 (7) | 3 (4) | 8 (12) | 10 (11) |
| Vomiting | 0 | 0 | 0 | 9 (13) | 1 (1) | 10 (15) | 10 (11) |
| Any treatment-related AE | 8 (32) | 0 | 8 (32) | 26 (39) | 3 (4) | 29 (43) | 37 (40) |
| Fatigue | 4 (16) | 0 | 4 (16) | 9 (13) | 0 | 9 (13) | 13 (14) |
| Arthralgia | 0 | 0 | 0 | 6 (9) | 0 | 6 (9) | 6 (7) |
| Asthenia | 1 (4) | 0 | 1 (4) | 4 (6) | 0 | 4 (6) | 5 (5) |
| Aspartate aminotransferase increased | 0 | 0 | 0 | 2 (3) | 2 (3) | 4 (6) | 4 (4) |
| Decreased appetite | 1 (4) | 0 | 1 (4) | 3 (4) | 0 | 3 (4) | 4 (4) |
| Pruritus | 0 | 0 | 0 | 4 (6) | 0 | 4 (6) | 4 (4) |
| Alanine aminotransferase increased | 0 | 0 | 0 | 2 (3) | 1 (1) | 3 (4) | 3 (3) |
| Myalgia | 0 | 0 | 0 | 3 (4) | 0 | 3 (4) | 3 (3) |
| Diarrhea | 1 (4) | 0 | 1 (4) | 2 (3) | 0 | 2 (3) | 3 (3) |
| Nausea | 1 (4) | 0 | 1 (4) | 2 (3) | 0 | 2 (3) | 3 (3) |

AEs, adverse events; NCI-CTCAE, National Cancer Institute–Common Terminology Criteria for Adverse Events; PK/PD, pharmacokinetic/pharmacodynamic.

There were four permanent treatment discontinuations due to AEs with none treatment-related. Treatment was interrupted or delayed due to non-treatment-related AEs for 24% participants. Less than half of the participants (37%) experienced at least 1 SAE; for 1 of these participants, the SAE was treatment-related. There were no fatal AEs in the cohort.

## Efficacy

Though not formally analyzed per protocol, the ORR for these cohorts was <10%, and <10% were alive following study completion. Detailed response data with feladilimab based on tumor type will be available in a separate publication.

## Pharmacokinetics

### Descriptive PK Parameters

The median feladilimab plasma concentration–time data from the participants in the dose-escalation cohort with available PK data (N=22) during the first week of the 21-day cycle for cycle 1 dosing were relatively stable for doses up to 3.0 mg/kg, on both linear and semilogarithmic plots. Feladilimab plasma PK parameters were computed via noncompartmental analysis using Phoenix WinNonlin program (version 6.0 or higher; Certara, New Jersey, USA) and are descriptively summarized by cohort and dose level in table 4.

Following a 30 min intravenous infusion, the median time to maximum plasma concentration ($T_{max}$) occurred around 1 hour. Moderate to high variability was observed in the area under the plasma concentration–time curve $AUC_{(0\text{-}t)}$ at the end of cycle 1 dosing for feladilimab across the dose range of 0.01–3.0 mg/kg, probably due to lower

**Table 4** Feladilimab monotherapy: summary of select plasma PK parameters from cycle 1 of dose-escalation cohort and PK/PD cohort

| Dose (mg/kg) | $C_{max}$ (µg/mL) | $T_{max}$ (hour) | $C_{tau}$ (µg/mL) | $AUC_{(0\text{-}t)}$ (hour×µg/mL) | $AUC_{(0\text{-}t)}$ (hour×µg/mL) | $AUC_{(0\text{-}\infty)}$ (hour×µg/mL) |
|---|---|---|---|---|---|---|
| Dose escalation cohort (n=24) | | | | | | |
| 0.003 (n=1) | 0.09 | 4.50 | ND | 1.71 | ND | ND |
| 0.010 (n=2) | 0.20 (0.07, 0.63) (12.6%) | 1.01 (0.5, 1.5) | ND | 6.21 (0.00, 27 580.14) (118.1%) | ND | ND |
| 0.030 (n=3) | 1.74 (0.25, 11.9) (90.6%) | 1.01 (0.5, 1.5) | 0.24 (ND, ND) (ND) | 135.76 (11.37, 1621.01) (130.7%) | 134.62 (ND, ND) (ND) | 146.43 (ND, ND) (ND) |
| 0.100 (n=5) | 2.30 (1.94, 2.74) (14.1%) | 1.50 (0.6, 2.5) | 0.29 (0.14, 0.58) (62.2%) | 375.49 (281.90, 500.15) (23.4%) | 373.69 (281.20, 496.60) (23.2%) | 431.03 (2.96, 62 835) [60.0% |
| 0.300 (n=3) | 6.46 (3.61, 11.58) (23.8%) | 1.03 (0.5, 2.8) | 1.05 (0.84, 1.33) (9.3%) | 1105.51 (877.24, 1393.02) (9.3%) | 1156.58 (628.10, 2129.72) (6.8%) | 1489.87 (ND, ND) (ND) |
| 1.000 (n=4) | 18.38 (12.5, 26.95) (24.4%) | 1.58 (1.0, 2.70) | 4.31 (2.53, 7.33) (21.6%) | 2802 (853, 9200) (86.5%) | 4839.00 (ND, ND) (ND) | ND |
| 3.000 (n=3) | 74.80 (50.28, 111.28) (16.1%) | 4.50 (1.5, 48.7) | 11.31 (1.80, 71.05) (85.3%) | 13 509 (6352.3, 28 731) (31.1%) | 11 368.10 (ND, ND) (ND) | 12 605.66 (ND, ND) (ND) |
| 10.000 (n=3) | 193.78 (126.81, 296.12) (17.2%) | 4.52 (1.5, 8.0) | 38.08 (22.00, 65.92) (22.4%) | 37 271 (26 033, 53 359) (14.5%) | ND | ND |
| PK/PD cohort (n=67) | | | | | | |
| 0.030 (n=4) | 0.554 (0.235, 1.307) (58%) | 2.51 (1.5, 3.3) | 0.249 (ND, ND) (ND) | 64.3 (14.7, 281.4) (116.8%) | 192.6 (ND, ND) (ND) | ND |
| 0.100 (n=19) | 2.15 (1.85, 2.51) (32.8%) | 1.50 (0.5, 8.4) | 0.399 (0.306, 0.520) (52.9%) | 358.1 (278.4, 460.7) (56.0%) | 392.5 (319.1, 482.7) (31.6%) | 415.4 (238.7, 723.1) (6.17%) |
| 0.300 (n=15) | 8.54 (5.82, 12.5) (78.5%) | 1.5 (0.5, 4.5) | 0.928 (0.681, 1.26) (57.5%) | 1068.4 (906.8, 1258.7) (30.3%) | 1095 (925.1, 1297) (27.0%) | 1097 (738, 1632) (25.3%) |
| 1.000 (n=5) | 22.8 (19.0, 27.4) (11.5%) | 1.03 (0.5, 2.5) | 4.74 (0.762, 29.5) (84.8%) | 2959.4 (592.5, 14 780) (133.3%) | 4701 (2418, 9142) (27.2%) | ND |
| 3.000 (n=20) | 74.2 (66.5, 82.8) (22.9%) | 1.52 (0.5, 8.0) | 13.2 (10.5, 16.6) (50.6%) | 12 670 (11 106, 14 455) (27.9%) | 12 471 (10 328, 15 058) (30.3%) | 10 365 (ND, ND) (ND) |
| 10.000 (n=4) | 195.6 (154.2, 248.1) (15.0%) | 2.03 (1.5, 4.5) | 52.3 (29.9, 91.7) (36.3%) | 33 985 (23 632, 48 872) (23.1%) | 32 656 (14 872, 71 709) (32.5%) | ND |

ND: due to insufficient data or missing data. Data are presented as geometric mean (95% CI) (between participant CV) except for $T_{max}$, which is presented as median (min, max). PK parameters for single participant at dose of 0.001 mg/kg are not listed
$AUC_{(0\text{-}t)}$, area under the plasma concentration–time curve; $C_{max}$, maximum plasma concentration; $C_{tau}$, trough concentrations; CV, Coefficient of variation; ; ND, not determinable; PK/PD, pharmacokinetic/pharmacodynamic; $T_{max}$, time to maximum plasma concentration.

sample size. Variability was generally <25% for maximum plasma concentration ($C_{max}$).

The mean feladilimab plasma concentration–time data from the participants with available PK data (N=67) during the first week of the 21-day cycle for cycle 1 dosing were relatively stable for the PK/PD cohort. Feladilimab plasma PK parameters were computed via

**Table 5** Analysis of dose proportionality of feladilimab for cycle 1 using power model and using ANOVA–PK/PD cohort

| Parameter (unit)–power model | Slope | | | 90% CI | | |
|---|---|---|---|---|---|---|
| $AUC_{(0-504)}$ (hour×µg/mL) | 0.98 | | | (0.94 to 1.03) | | |
| $C_{max}$ (µg/mL) | 0.99 | | | (0.95 to 1.05) | | |
| $C_{tau}$ (µg/mL) | 1.04 | | | (0.97 to 1.11) | | |
| | Geometric LS mean | | | | | |
| Parameter (unit)-ANOVA | Feladilimab 0.03 mg/kg (N=4) | Feladilimab 0.1 mg/kg (N=19) | Feladilimab 0.3 mg/kg (N=15) | Feladilimab 1 mg/kg (N=5) | Feladilimab 3 mg/kg (N=20) | Feladilimab 10 mg/kg (N=4) |
| n | 4 | 19 | 15 | 4 | 20 | 4 |
| Dose normalized $AUC_{(0-504)}$ (hour×µg/mL) | 192.58 | 117.75 | 109.53 | 141.04 | 124.71 | 97.97 |
| Dose normalized $C_{max}$ (µg/mL) | 0.55 | 0.65 | 0.85 | 0.69 | 0.74 | 0.59 |
| Dose normalized $C_{tau}$ (µg/mL) | 0.25 | 0.12 | 0.09 | 0.14 | 0.13 | 0.16 |
| Parameter (unit)-ANOVA | Comparison | | | Ratio | 90% CI | %CVw (%) |
| Dose normalized $AUC_{(0-504)}$ (hour×µg/mL) | 0.1 mg/kg vs 0.03 mg/kg | | | 0.61 | (0.37 to 1.02) | 29.7 |
| | 0.3 mg/kg vs 0.03 mg/kg | | | 0.57 | (0.34 to 0.95) | 29.7 |
| | 1 mg/kg vs 0.03 mg/kg | | | 0.73 | (0.42 to 1.29) | 29.7 |
| | 3 mg/kg vs 0.03 mg/kg | | | 0.65 | (0.39 to 1.08) | 29.7 |
| | 10 mg/kg vs 0.03 mg/kg | | | 0.51 | (0.29 to 0.90) | 29.7 |
| Dose normalized $C_{max}$ (µg/mL) | 0.1 mg/kg vs 0.03 mg/kg | | | 1.17 | (0.79 to 1.72) | 44.1 |
| | 0.3 mg/kg vs 0.03 mg/kg | | | 1.54 | (1.04 to 2.29) | 44.1 |
| | 1 mg/kg vs 0.03 mg/kg | | | 1.24 | (0.75 to 2.03) | 44.1 |
| | 3 mg/kg vs 0.03 mg/kg | | | 1.34 | (0.91 to 1.97) | 44.1 |
| | 10 mg/kg vs 0.03 mg/kg | | | 1.06 | (0.64 to 1.74) | 44.1 |
| Dose normalized $C_{tau}$ (µg/mL) | 0.1 mg/kg vs 0.03 mg/kg | | | 0.48 | (0.2 to 1.15) | 53.8 |
| | 0.3 mg/kg vs 0.03 mg/kg | | | 0.37 | (0.16 to 0.89) | 53.8 |
| | 1 mg/kg vs 0.03 mg/kg | | | 0.57 | (0.21 to 1.51) | 53.8 |
| | 3 mg/kg vs 0.03 mg/kg | | | 0.53 | (0.22 to 1.26) | 53.8 |
| | 10 mg/kg vs 0.03 mg/kg | | | 0.63 | (0.24 to 1.62) | 53.8 |

ANOVA, analysis of variance; AUC, area under the curve; $C_{max}$, maximum plasma concentration; $C_{tau}$, trough concentrations; CVw, Intrasubject coefficient of variaiton; LS, least square; PK/PD, pharmacokinetic/pharmacodynamic.

non-compartmental analysis and are descriptively summarized (by cohort and dose level) in table 4.

Following a 30 min intravenous infusion, the median $T_{max}$ occurred between 1 and 2.5 hours. Moderate to high variability was observed in $AUC_{(0-t)}$ at the end of cycle 1 dosing for feladilimab across the dose range of 0.03–10.0 mg/kg. Variability was generally low for $C_{max}$ and moderate for geometric mean ratio of trough concentrations ($C_{tau}$).

### Dose proportionality

To calculate proportionality from the PK/PD cohort, the mean slope estimated from the power model and the corresponding 90% CI calculated by restricted maximum likelihood using SAS Proc Mixed are summarized in table 5. The calculated slopes (β~1) for all parameters indicate proportionality, confirming feladilimab PK exposure metrics are linear over this dose range.

Additionally, in the dose proportionality assessment using analysis of variance models, PK parameters were dose-normalized prior to log-transformation by multiplying by reference dose/dose. CIs of ratios for all PK parameter sets and test doses include 1.0, confirming dose proportionality for feladilimab as in the power model test.

### Accumulation ratio

Accumulation of feladilimab following repeat dosing was assessed through $C_{tau}$ in cycle 1 and cycle 6 for the two cohorts combined (table 6). Accumulation ratio ranged from 1.4 to 2.5 across the four doses (data for 0.03 mg/kg were not available) and was generally consistent with expected patterns of accumulation for a monoclonal antibody.

**Table 6** Analysis of accumulation ratio of $C_{tau}$ for feladilimab–PK/PD all-treated population

| | | Geometric LS mean | | | |
|---|---|---|---|---|---|
| Treatment | N | Cycle 1 | Cycle 6 | Ratio | 90% CI |
| Feladilimab 0.1 mg/kg | 6 | 0.4 | 1.5 | 4.0 | (1.9 to 8.6) |
| Feladilimab 0.3 mg/kg | 2 | 0.8 | 1.1 | 1.3 | (0.5 to 3.5) |
| Feladilimab 1 mg/kg | 1 | – | – | – | – |
| Feladilimab 3 mg/kg | 2 | 16.0 | 25.7 | 1.6 | (0.9 to 2.7) |
| Feladilimab 10 mg/kg | 1 | – | – | – | – |

N is the number of subjects with a value available at both cycle 1 and cycle 6. Ratio is based on the value at cycle 6 vs cycle 1. Cycle 6 is considered to be the profile at the sixth received dose.
$C_{tau}$, trough concentrations; LS, least square; PK/PD, pharmacokinetic/pharmacodynamic.

## Pharmacodynamics

Based primarily on the designated monotherapy PK/PD cohort with validation from some other cohorts, the feladilimab RO data from the participants with available PK data (N=67) during the first and second cycle of dosing were summarized descriptively by receptor type, visit, and dose level.

The CD4+baseline RO varied from 15% to 39% with moderate to high variability, possibly due to noise in the assay. CD4+RO at the end of the first cycle dosing (week 3 predose) increased proportionally from 42% to 90% over the dose range of 0.1 to 10 mg/kg. On repeat administration, the CD4+RO at the end of second cycle dosing (week 6 predose) increased from 50% to 93%. Table 7 provides a summary of results.

The CD8+baseline RO appears to have more noise as compared with CD4+which varied from 28% to 46% with moderate to high variability. Similar to CD4+RO, the CD8+RO at week 3 predose increased proportionally from 40% to 96%. However, CD8+RO appeared to decrease from week 3 to week 6 at 10 mg/kg dose level, possibly due to lower sample size of the data.

## Immunogenicity

There was one baseline ADA-positive sample out of 24 detected on day 1 in the monotherapy dose-escalation cohort, likely due to non-specificity of the assay; the ADA was detected as late as the on-study week 33 sample and at 12 weeks post-treatment follow-up in at least one participant. Overall, approximately 16% of the samples in the monotherapy dose-escalation cohort were positive for ADA post-baseline (across week 3 to week 12 post-treatment follow-up). No clinical manifestations of ADA positivity were observed.

**Table 7** Summary of feladilimab receptor occupancy at select visits, PK/PD cohort

| Dose, mg/kg | Receptor | Baseline | Week 3 predose | Week 6 predose |
|---|---|---|---|---|
| 0.030 (N=4) | CD4+ | 39.1 (82.2%) | ND | ND |
| | CD8+ | 27.9 (276%) | ND | ND |
| 0.100 (N=19) | CD4+ | 27.9 (110%) | 41.7 (47.9%) | 50.3 (28.4%) |
| | CD8+ | 40.7 (58.1%) | 40.1 (43.3%) | 40.6 (43.9%) |
| 0.300 (N=15) | CD4+ | 33.1 (113%) | 57.9 (70.4%) | 66.6 (22.1%) |
| | CD8+ | 45.9 (75.4%) | 61.9 (42.7%) | 54.7 (34.3%) |
| 1.000 (N=5) | CD4+ | 27.7 (53.6%) | 70.0 (ND) | 79.4 (0.8%) |
| | CD8+ | 42.9 (37.6%) | 57.9 (ND) | 77.4 (3.5%) |
| 3.000 (N=20) | CD4+ | 35.9 (83.4%) | 84.4 (11.9%) | 80.9 (15.7%) |
| | CD8+ | 43.4 (78.7%) | 74.3 (37.4%) | 78.6 (16.9%) |
| 10.000 (N=4) | CD4+ | 15.7 (186%) | 89.8 (5.7%) | 92.8 (7.5%) |
| | CD8+ | 32.1 (25.4%) | 95.9 (53.7%) | 73.7 (22.0%) |

ND: due to insufficient data or missing data. Data are presented as geometric mean (between participant CV).
CV, Coefficient of variation; ND, not determinable; PK/PD, pharmacokinetic/pharmacodynamic.

## Recommended phase 2 dose

On the basis of the absence of DLT, the PK, and the RO data, both 0.3 mg/kg and 1.0 mg/kg were selected as doses for further development. The results of feladilimab dose-expansion studies as monotherapy and in various combinations, along with the further evolution of the dosing paradigm, are presented in a separate publication.

## DISCUSSION

The INDUCE-1 study monotherapy dose-escalation and PK/PD cohorts aimed to evaluate the safety, tolerability, PK/PD, and identify a RP2D for feladilimab in a population of patients with advanced solid tumors. The demographic characteristics of the study participants were consistent with those expected from patients in this disease setting. Most participants had received multiple lines of prior anticancer therapy and represent heavily pretreated populations.

Treatment with feladilimab monotherapy in the two cohorts reported here was safe and generally well tolerated. The AEs were consistent with known toxicities associated with other immunotherapies such as fever, fatigue, and anemia. Based on the results of the monotherapy

dose escalation and the PK/PD cohorts, peak feladilimab concentrations occurred about 1 hour following a 30 min intravenous infusion. On repeat dose administration, no DLT was reached.

RO PD data showed that RO for both CD4+ and CD8+ cells increased from baseline after one cycle of dosing in a dose-proportional manner. After a second cycle, the RO levels were maintained. Receptor saturation as a criterion for dose selection is a relatively new approach in oncology, although it has been used in other disease settings. The target level of saturation is dependent on the intended mode of action. It was opted for maximal saturation as a target in anticipation of converting 'cold' tumors to immunologically active tumors and modulating tumor microenvironments. Based on preliminary data reported for other agonist molecules, alternate dosing approaches to achieve either partial RO or complete occupancy for a short duration of time may also need to be explored to identify the optimal way to target agonist immunomodulatory agents. The impact of the various dosing approaches on the downstream PD changes and on efficacy has to be evaluated in a methodical way and in a less heterogeneous patient population.

As no DLTs were identified and proportional PK was demonstrated, the feladilimab RP2D of 0.3 mg/kg and 1.0 mg/kg was based on doses that consistently provided maximal receptor saturation.

The efficacy of feladilimab was not formally evaluated in these two cohorts, but ORR was below 10% and less than 10% of participants completed the study. Clinical benefit, including response parameters, was evaluated in subsequent dose-expansion cohorts comprizing approximately 735 participants with 9 broad categories of solid tumors exposed to feladilimab as monotherapy and in combination with other immunotherapies and cytotoxic chemotherapy. Results of the dose-expansion phase will be described in a separate publication.

Replacing the conventional 3+3 dose escalation schema with the mTPI methodology accelerated the selection of candidate dosing regimens to carry forward, by arriving at the dose range that yielded maximum RO and the highest proportion of study participants with >grade 3 toxicity within seven participants. The 3+3 design would have taken up to 15 participants. Using toxicity and receptor binding as guiding parameters, 15 (60%) of the total of 25 participants were exposed to doses that were within 1–2 dose levels of the RP2D. Because feladilimab was well tolerated (no DLTs and no treatment-related deaths or study withdrawals) at all dose levels across 4 orders of magnitude, the mTPI methodology approach was not tested to the same extent as an agent with greater toxicity and lower tolerance. Nevertheless, the efficiency of the approach combined with the hybrid PK/PD readouts for dose selection permitted a transition to more extensive efficacy and combination testing with a high degree of confidence.

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