NOVARTIS

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Canakinumab

Trial Indication(s)

Non-small cell lung cancer

Protocol Number

CACZ885V2201C

Protocol Title

A randomized, open-label, phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in subjects with resectable non-small cell lung cancer (CANOPY-N)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: November 05, 2019 (Actual)
Primary Completion Date: April 20, 2022 (Actual)
Study Completion Date: August 15, 2022 (Actual)

Reason for Termination (If applicable)

Study early terminated due to low enrolment compared to the anticipated figures

NOVARTIS

Study Design/Methodology

This was a randomized, phase II, open-label study evaluating canakinumab, an anti-IL-1β monoclonal antibody, or pembrolizumab, a monoclonal antibody designed to block the PD-1 receptor, as monotherapy or in combination as neoadjuvant therapy. The study population included adult subjects with resectable non-small cell lung cancer (NSCLC) planned for surgery in approximately 4-6 weeks. Subjects were treated for a maximum duration of 6 weeks (2 cycles) until surgery, progression, unacceptable toxicity or discontinuation from the study treatment for any other reason.

Subjects were randomized in a 2:2:1 ratio to one of the 3 treatment arms (canakinumab alone or canakinumab in combination with pembrolizumab or pembrolizumab alone). Surgery was performed between 4 to 6 weeks after the first dose of study treatment.

All randomized subjects were followed for safety for up to 130 days following the last dose of study treatment (safety follow-up period).

Centers

29 centers in 12 countries: France(3), Turkey(3), Spain(3), Russia(3), Germany(4), Taiwan(2), Japan(1), United States(4), Greece(1), Netherlands(3), Belgium(1), Canada(1)

Objectives:

Primary objective:

The primary objective was to assess the Major Pathological Rate (MPR) (≤10% of residual viable tumor cells) on resected specimens per central review at the time of surgery in all subjects randomized to canakinumab alone or in combination with pembrolizumab treatment arms.

Secondary objectives

- To assess the prevalence and incidence of immunogenicity (anti-drug antibodies) of canakinumab and pembrolizumab
- To assess overall response rate (ORR) in randomized subjects treated with canakinumab or pembrolizumab as monotherapy and in combination (local review)
- To assess the pharmacokinetics of canakinumab and pembrolizumab as monotherapy and in combination with pembrolizumab
- To assess surgical feasibility rate in each treatment arm based on randomized subjects
- To assess the MPR rate at the time of surgery in (a) all subjects randomized to pembrolizumab monotherapy arm based on central review, (b) all randomized subjects based on local review in each treatment arm, and (c) to estimate the difference in

MPR between subjects randomized to canakinumab + pembrolizumab combination and pembrolizumab alone based on central review
- To evaluate safety and tolerability of canakinumab and pembrolizumab as monotherapy or in combination
- To assess the relationship between key blood or tissue based biomarkers and MPR

Test Product (s), Dose(s), and Mode(s) of Administration

- Canakinumab: 200 mg of canakinumab administered via subcutaneous injections once every 3 weeks for a maximum duration of 6 weeks
- Pembrolizumab: 200 mg of pembrolizumab administered via infusion once every 3 weeks for a maximum duration of 6 weeks

Statistical Methods

Primary endpoint

The primary endpoint was MPR rate as per central review in the canakinumab monotherapy arm and in combination with pembrolizumab arm, defined as the percentage of subjects with ≤10% residual viable cancer cells in the surgical sample. MPR rate was summarized by treatment arm along with the two-sided exact binomial 95% confidence interval.

Secondary endpoints

Efficacy:

- MPR rate (1) based on local review in all 3 treatment arms and (2) based on central review in pembrolizumab monotherapy arm were assessed. MPR rate was summarized by treatment arm along with the two-sided exact binomial 95% confidence interval. Moreover, the difference in MPR rate between canakinumab in combination with pembrolizumab and pembrolizumab single agent arm along with the two-sided exact 95% confidence interval was summarized based on central review
- ORR was defined as the percentage of subjects with a best overall response of complete response (CR) or partial response (PR), as per local assessment. The best overall response was the observed response at the assessment performed on the end of treatment visit prior to surgery. ORR was evaluated according to RECIST 1.1.
- Surgical feasibility rate defined as the percentage of subjects who undergo surgery following study treatment in each treatment based on randomized subjects

Immunogenicity

- Immunogenicity was characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

Pharmacokinetics

- Descriptive statistics for canakinumab concentration and pembrolizumab concentration were presented at each scheduled time point.

Safety

- Safety assessments included physical examination, ECOG PS, vital signs, body weight, ECG, laboratory assessments, pregnancy tests, as well as collection of adverse events (AEs) at every visit. Safety summaries include only data from on-treatment period (from day of first dose of study medication to 130 days after last dose of study medication)

Biomarkers

- The biomarker analysis investigated the relationship between key IHC markers (PD-L1, CD8), key cytokines (hs-CRP and hs-IL-6) assessed at baseline and post-baseline and MPR was explored. MPR was summarized by treatment arm and subgroup along with the two-sided exact binomial 95% confidence interval

Study Population: Key Inclusion/Exclusion Criteria

Key inclusion criteria:
- Histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors.
- Subject must have been eligible for surgery and with a planned surgical resection in approximately 4-6 weeks (after the first dose of study treatment).
- A mandatory newly obtained tissue biopsy from primary site was required for study enrollment. An archival biopsy was also acceptable if obtained up to 5 months before first day of study treatment and if the subject did not go through antineoplastic systemic therapies between biopsy collection date and beginning of study treatment.
- Eastern Cooperative oncology group (ECOG) performance status of 0 or 1.

Key exclusion criteria:
- Subjects with unresectable or metastatic disease.
- History of severe hypersensitivity reactions to monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction
- Subjects who received prior systemic therapy (including chemotherapy, other anti-cancer therapies and any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) in the past 3 years before screening
-Active autoimmune disease that has required systemic treatment in the past 2 years prior to randomization. Control of the disorder with replacement therapy was permitted

- Subject with suspected or proven immunocompromised state or infections

Participant Flow Table

Treatment Period

	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	Total
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Started	35	35	18	88
Completed	35	35	17	87
Not Completed	0	0	1	1
Adverse Event	0	0	1	1

Safety Follow-up period

	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	Total
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Started	35	35	18	88
Completed	30	32	17	79
Not Completed	5	3	1	9
Death	3	2	1	6

Subject Decision	2	1	0	3

Baseline Characteristics

	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy	Total
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery	
Number of Participants [units: participants]	35	35	18	88
Baseline Analysis Population Description				
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation				
	65.5±9.88	67.1±6.98	66.1±5.61	66.2±7.99
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	13	14	9	36
Male	22	21	9	52
Race/Ethnicity, Customized (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
White	20	25	12	57

Asian	7	3	2	12
Black or African American	1	1	0	2
American Indian or Alaska Native	0	1	0	1
Unknown	7	5	4	16

Primary Outcome Result(s)

Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to canakinumab monotherapy and in combination with pembrolizumab based on central review

Description	MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder. MPR was assessed at the time of surgery in all subjects randomized to canakinumab monotherapy and in combination with pembrolizumab based on central review.
Time Frame	At time of surgery (up to 6 weeks after first dose of study treatment)
Analysis Population Description	All subjects who were randomized to canakinumab monotherapy or canakinumab in combination with pembrolizumab

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35
Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to canakinumab monotherapy and in	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**

combination with pembrolizumab based on central review (units: Percentage of participants)		
	2.9 (0.07 to 14.92)	17.1 (6.56 to 33.65)

Secondary Outcome Result(s)

Canakinumab antidrug antibodies (ADA) prevalence

Description	Canakinumab ADA prevalence at baseline was calculated as the percentage of participants who had a canakinumab ADA positive result at baseline
Time Frame	Predose (0 hour) on Day 1 of Cycle 1 (Cycle=21 days)
Analysis Population Description	All subjects randomized to canakinumab monotherapy or canakinumab in combination with pembrolizumab who received at least one dose of canakinumab.

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35
Canakinumab antidrug antibodies (ADA) prevalence (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	0 (%)	0 (%)

Canakinumab ADA incidence

Description	Canakinumab ADA incidence on treatment was calculated as the percentage of participants who were canakinumab treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and canakinumab treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)
Time Frame	From baseline (Predose on Day 1 of Cycle 1) up to 130 days after last dose of study treatment (assessed up to 24.6 weeks). Cycle = 21 days
Analysis Population Description	All subjects randomized to canakinumab monotherapy or canakinumab in combination with pembrolizumab who received at least one dose of canakinumab.

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35
Canakinumab ADA incidence (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	1 (2.86%)	0 (%)

Pembrolizumab ADA prevalence

Description	Pembrolizumab ADA prevalence at baseline was calculated as the percentage of participants who had a pembrolizumab ADA positive result at baseline
Time Frame	Predose (0 hour) on Day 1 of Cycle 1 (Cycle = 21 days)
Analysis Population Description	All subjects randomized to canakinumab in combination with pembrolizumab or pembrolizumab monotherapy who received at least one dose of pembrolizumab.

	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	18
Pembrolizumab ADA prevalence (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
	4 (11.43%)	3 (16.67%)

Pembrolizumab ADA incidence

Description	Pembrolizumab ADA incidence on treatment was calculated as the percentage of participants who were pembrolizumab treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and pembrolizumab treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)
Time Frame	From baseline (Predose on Day 1 of Cycle 1) up to 26 days after last dose of study treatment (assessed up to 10.7 weeks). Cycle = 21 days
Analysis Population Description	All subjects randomized to canakinumab in combination with pembrolizumab or pembrolizumab monotherapy who received at least one dose of pembrolizumab.

	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	18
Pembrolizumab ADA incidence (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**

	3 (8.57%)	4 (22.22%)

Overall response rate (ORR) based on local investigator assessment using RECIST v1.1

Description	ORR is defined as the percentage of subjects with confirmed best overall response of complete response (CR) or partial response (PR), as per local investigator's assessment by RECIST 1.1. CR: Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters
Time Frame	From date of randomization to date of surgery, assessed up to 6 weeks
Analysis Population Description	FAS including all subjects to whom study treatment was assigned by randomization.

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**	**Pembrolizumab monotherapy**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35	18
Overall response rate (ORR) based on local investigator assessment using RECIST v1.1 (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	0 (0.00 to 10.00)	8.6 (1.80 to 23.06)	11.1 (1.38 to 34.71)

Serum canakinumab concentration

Description	Canakinumab serum concentrations were determined at the specified time points.

Time Frame	Predose (0 hour) on Day 1 of Cycles 1 and 2 (Cycle =21 days)
Analysis Population Description	All participants who received at least one dose of canakinumab with at least one evaluable pharmacokinetic (PK) sample. Number analyzed corresponds to the number of participants with an evaluable PK sample at the specified time point

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35
Serum canakinumab concentration (units: microgram/miliLiter (ug/mL))	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1	0 (0%)	0 (0%)
Cycle 2	10.9 (32.9%)	10.3 (41.0%)

Serum pembrolizumab concentration

Description	Pembrolizumab serum concentrations were determined at the specified time points.
Time Frame	Predose (0 hour) and 0.5 hours post dose on Day 1 of Cycle 1 and predose on Cycle 2 (Cycle =21 days)
Analysis Population Description	All participants who received at least one dose of pembrolizumab with at least one evaluable PK sample. Number analyzed corresponds to the number of participants with an evaluable PK sample at the specified time point

	Canakinumab + pembrolizumab	**Pembrolizumab monotherapy**
Arm/Group Description	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for	Participants received 200 mg of pembrolizumab every 3 weeks for a

	a maximum duration of 6 weeks prior to surgery	maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	34	17
Serum pembrolizumab concentration (units: ug/mL)	**Geometric Mean (Geometric Coefficient of Variation)**	**Geometric Mean (Geometric Coefficient of Variation)**
Cycle 1 predose	0 (0%)	0 (0%)
Cyle 1 0.5 hours post dose	65.5 (23.8%)	65.5 (19.9%)
Cycle 2 predose	16.0 (43.4%)	35.5 (13.7%)

Surgical feasibility rate

Description	Surgical feasibility rate was defined as the percentage of subjects who underwent surgery following study treatment.
Time Frame	Up to 6 weeks after first dose
Analysis Population Description	FAS including all subjects to whom study treatment was assigned by randomization.

	Canakinumab monotherapy	**Canakinumab + pembrolizumab**	**Pembrolizumab monotherapy**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35	18
Surgical feasibility rate (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	91.4 (76.94 to 98.20)	97.1 (85.08 to 99.93)	100 (81.47 to 100.00)

NOVARTIS

Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to pembrolizumab monotherapy based on central review

Description	MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder. MPR was assessed at the time of surgery in all subjects randomized to pembrolizumab monotherapy arm based on central review.
Time Frame	At time of surgery (up to 6 weeks after first dose)
Analysis Population Description	All subjects who were randomized to pembrolizumab monotherapy arm

	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	18
Major Pathological Response (MPR) rate at the time of surgery in subjects randomized to pembrolizumab monotherapy based on central review (units: Percentage of participants)	**Number (95% Confidence Interval)**
	16.7 (3.58 to 41.42)

Difference in Major Pathological Response (MPR) rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review

Description	MPR was defined as the percentage of participants with ≤10% residual viable tumor cells on surgical samples. MPR was assessed at the time of surgery based on central review. The difference in MPR rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review along with the Chang and Zhang confidence interval was assessed.
Time Frame	At tipe of surgery (up to 6 weeks after first dose of study treatment)

Analysis Population Description	All subjects who were randomized to canakinumab in combination with pembrolizumab or pembrolizumab monotherapy arms

	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	18
Difference in Major Pathological Response (MPR) rate between the canakinumab plus pembrolizumab arm and the pembrolizumab arm based on central review (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	17.1 (6.56 to 33.65)	16.7 (3.58 to 41.42)

Statistical Analysis

Groups	Canakinumab + pembrolizumab, Pembrolizumab monotherapy
Type of Statistical Test	Other
Mean Difference (Final Values)	0.5
95 % Confidence Interval 2-Sided	-25.56 to 21.23

Major Pathological Response (MPR) rate at the time of surgery in all subjects based on local review

Description	MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have

	the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder. MPR was assessed at the time of surgery in all subjects based on local review.
Time Frame	At time of surgery (up to 6 weeks after first dose)
Analysis Population Description	FAS including all subjects to whom study treatment was assigned by randomization.

	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35	18
Major Pathological Response (MPR) rate at the time of surgery in all subjects based on local review (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
	0 (0.00 to 10.00)	20.0 (8.44 to 36.94)	22.2 (6.41 to 47.64)

Major Pathological Response (MPR) rate based on the levels of biomarkers

Description	MPR was defined as the percentage of participants with major pathological response (defined as ≤10% residual viable tumor cells on surgical samples). Any participant who had >10% residual viable cancer cells, or started new antineoplastic therapy prior to surgery, or did not have the surgery performed, or had the surgery performed but with unevaluable MPR result, was considered as a non-responder. MPR rate was analyzed by the biomarker subgroups at baseline. Biomarkers included PD-L1, CD8, hs-CRP and hs-IL-6.
Time Frame	From date of randomization up to 6 weeks after first dose
Analysis Population Description	All subjects to whom study treatment was assigned by randomization. Number analyzed is the number of participants with data available for analysis for each category

	Canakinumab monotherapy	Canakinumab + pembrolizumab	Pembrolizumab monotherapy
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Number of Participants Analyzed [units: participants]	35	35	18
Major Pathological Response (MPR) rate based on the levels of biomarkers (units: Percentage of participants)	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**	**Number (95% Confidence Interval)**
PD-L1: <1%	0 (0.00 to 26.46)	7.1 (0.18 to 33.87)	14.3 (0.36 to 57.87)
PD-L1: 1-49%	6.7 (0.17 to 31.95)	15.4 (1.92 to 45.45)	16.7 (0.42 to 64.12)
PD-L1: >=50%	0 (0.00 to 45.93)	42.9 (9.90 to 81.59)	0 (0.00 to 70.76)
hs-CRP: <2mg/L	12.5 (0.32 to 52.65)	7.7 (0.19 to 36.03)	37.5 (8.52 to 75.51)
hs-CRP: >=2mg/L	0 (0.0 to 13.23)	22.7 (7.82 to 45.37)	0 (0.00 to 33.63)
hs-IL-6: <Q1 (2.52 mg/L)	16.7 (0.42 to 64.12)	12.5 (0.32 to 52.65)	14.3 (0.36 to 57.87)
hs-IL-6: >=Q1 (2.52 pg/mL) to <Q2 (5.36 pg/mL)	0 (0.00 to 36.94)	10 (0.25 to 44.50)	33.3 (0.84 to 90.57)
hs-IL-6: >=Q2 (5.36 pg/mL) to <Q3 (12.03 pg/mL)	0 (0.00 to 36.94)	28.6 (3.67 to 70.96)	16.7 (0.42 to 64.12)
hs-IL-6: >=Q3 (12.03 pg/mL)	0 (0.00 to 30.85)	20.0 (2.52 to 55.61)	0 (0.00 to 97.50)

CD8: <3%	0 (0.00 to 26.46)	13.0 (2.78 to 33.59)	0 (0.00 to 52.18)
CD8: >=3%	0 (0.00 to 18.53)	22.2 (2.81 to 60.01)	33.3 (4.33 to 77.72)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	From day of first dose of study medication to 130 days after last dose of study medication, up to 25.6 weeks
Additional Description	Any sign or symptom that occurs during the study treatment plus the 130 days post treatment
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

NOVARTIS

All-Cause Mortality

	Canakinumab monotherapy N = 35	Canakinumab + pembrolizumab N = 35	Pembrolizumab monotherapy N = 18
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Total Number Affected	3	2	1
Total Number At Risk	35	35	18

Serious Adverse Events

	Canakinumab monotherapy N = 35	Canakinumab + pembrolizumab N = 35	Pembrolizumab monotherapy N = 18
Arm/Group Description	Participants received 200 mg of canakinumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of canakinumab in combination with 200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	Participants received 200 mg of pembrolizumab every 3 weeks for a maximum duration of 6 weeks prior to surgery
Total # Affected by any Serious Adverse Event	10	9	4
Total # at Risk by any Serious Adverse Event	35	35	18
Cardiac disorders			
Arrhythmia	1 (2.86%)	0 (0.00%)	0 (0.00%)
Cardiac failure	1 (2.86%)	0 (0.00%)	0 (0.00%)
Myocardial ischaemia	1 (2.86%)	0 (0.00%)	0 (0.00%)

Endocrine disorders			
Hypothyroidism	0 (0.00%)	0 (0.00%)	1 (5.56%)
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage	0 (0.00%)	0 (0.00%)	1 (5.56%)
Hepatobiliary disorders			
Immune-mediated hepatitis	0 (0.00%)	1 (2.86%)	0 (0.00%)
Infections and infestations			
Bacterial infection	0 (0.00%)	1 (2.86%)	0 (0.00%)
COVID-19	2 (5.71%)	1 (2.86%)	1 (5.56%)
Endocarditis	1 (2.86%)	0 (0.00%)	0 (0.00%)
Infectious pleural effusion	1 (2.86%)	0 (0.00%)	0 (0.00%)
Pneumonia	3 (8.57%)	1 (2.86%)	0 (0.00%)
Pneumonia bacterial	0 (0.00%)	1 (2.86%)	0 (0.00%)
Pneumonia fungal	0 (0.00%)	1 (2.86%)	0 (0.00%)
Pyopneumothorax	1 (2.86%)	0 (0.00%)	0 (0.00%)
Septic shock	1 (2.86%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Postoperative respiratory failure	1 (2.86%)	0 (0.00%)	0 (0.00%)
Procedural pain	1 (2.86%)	0 (0.00%)	0 (0.00%)
Toxicity to various agents	1 (2.86%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Hyperglycaemia	0 (0.00%)	1 (2.86%)	0 (0.00%)

Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema	1 (2.86%)	0 (0.00%)	0 (0.00%)
Dyspnoea	1 (2.86%)	1 (2.86%)	0 (0.00%)
Haemothorax	0 (0.00%)	0 (0.00%)	1 (5.56%)
Pleural effusion	0 (0.00%)	1 (2.86%)	0 (0.00%)
Pneumonitis	1 (2.86%)	0 (0.00%)	0 (0.00%)
Pneumothorax	0 (0.00%)	1 (2.86%)	0 (0.00%)
Pulmonary embolism	0 (0.00%)	1 (2.86%)	0 (0.00%)
Pulmonary oedema	0 (0.00%)	1 (2.86%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Rash	0 (0.00%)	0 (0.00%)	1 (5.56%)
Subcutaneous emphysema	1 (2.86%)	1 (2.86%)	0 (0.00%)
Vascular disorders			
Haematoma	1 (2.86%)	0 (0.00%)	0 (0.00%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	Canakinumab monotherapy N = 35	**Canakinumab + pembrolizumab N = 35**	**Pembrolizumab monotherapy N = 18**
Arm/Group Description	Participants received 200 mg of canakinumab once every 3	Participants received 200 mg of canakinumab in combination with	Participants received 200 mg of pembrolizumab every 3 weeks for

	weeks for a maximum duration of 6 weeks prior to surgery	200 mg of pembrolizumab once every 3 weeks for a maximum duration of 6 weeks prior to surgery	a maximum duration of 6 weeks prior to surgery
Total # Affected by any Other Adverse Event	28	27	14
Total # at Risk by any Other Adverse Event	35	35	18
Blood and lymphatic system disorders			
Anaemia	9 (25.71%)	1 (2.86%)	1 (5.56%)
Cardiac disorders			
Atrial fibrillation	1 (2.86%)	1 (2.86%)	2 (11.11%)
Endocrine disorders			
Hyperthyroidism	0 (0.00%)	5 (14.29%)	1 (5.56%)
Hypothyroidism	0 (0.00%)	3 (8.57%)	1 (5.56%)
Gastrointestinal disorders			
Abdominal discomfort	0 (0.00%)	0 (0.00%)	1 (5.56%)
Constipation	2 (5.71%)	3 (8.57%)	1 (5.56%)
Diarrhoea	1 (2.86%)	6 (17.14%)	0 (0.00%)
Dry mouth	0 (0.00%)	1 (2.86%)	2 (11.11%)
Nausea	4 (11.43%)	3 (8.57%)	3 (16.67%)
Vomiting	2 (5.71%)	0 (0.00%)	1 (5.56%)
General disorders and administration site conditions			
Asthenia	2 (5.71%)	2 (5.71%)	1 (5.56%)
Chest pain	2 (5.71%)	2 (5.71%)	1 (5.56%)
Fatigue	9 (25.71%)	5 (14.29%)	4 (22.22%)

Influenza like illness	0 (0.00%)	0 (0.00%)	1 (5.56%)
Oedema peripheral	1 (2.86%)	0 (0.00%)	1 (5.56%)
Pain	2 (5.71%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (2.86%)	2 (5.71%)	0 (0.00%)
Infections and infestations			
Enterocolitis infectious	0 (0.00%)	0 (0.00%)	1 (5.56%)
Erysipelas	0 (0.00%)	0 (0.00%)	1 (5.56%)
Pneumonia	2 (5.71%)	0 (0.00%)	0 (0.00%)
Post procedural infection	0 (0.00%)	0 (0.00%)	1 (5.56%)
Rash pustular	0 (0.00%)	0 (0.00%)	1 (5.56%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (5.56%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (5.56%)
Vulvovaginal mycotic infection	0 (0.00%)	0 (0.00%)	1 (5.56%)
Wound infection	0 (0.00%)	0 (0.00%)	1 (5.56%)
Injury, poisoning and procedural complications			
Procedural pain	0 (0.00%)	6 (17.14%)	2 (11.11%)
Wound complication	0 (0.00%)	2 (5.71%)	0 (0.00%)
Investigations			
Activated partial thromboplastin time prolonged	0 (0.00%)	0 (0.00%)	1 (5.56%)
Alanine aminotransferase increased	1 (2.86%)	3 (8.57%)	2 (11.11%)
Amylase increased	2 (5.71%)	1 (2.86%)	1 (5.56%)
Aspartate aminotransferase increased	1 (2.86%)	3 (8.57%)	0 (0.00%)
Bilirubin conjugated increased	4 (11.43%)	1 (2.86%)	1 (5.56%)
Blood alkaline phosphatase increased	2 (5.71%)	0 (0.00%)	0 (0.00%)

Blood bilirubin increased	4 (11.43%)	0 (0.00%)	0 (0.00%)
Blood creatinine increased	2 (5.71%)	1 (2.86%)	0 (0.00%)
Blood lactate dehydrogenase increased	2 (5.71%)	0 (0.00%)	1 (5.56%)
Blood thyroid stimulating hormone decreased	2 (5.71%)	0 (0.00%)	1 (5.56%)
Gamma-glutamyltransferase increased	2 (5.71%)	2 (5.71%)	1 (5.56%)
Lipase increased	2 (5.71%)	1 (2.86%)	1 (5.56%)
Lymphocyte count decreased	4 (11.43%)	0 (0.00%)	1 (5.56%)
SARS-CoV-2 test negative	2 (5.71%)	3 (8.57%)	3 (16.67%)
SARS-CoV-2 test positive	2 (5.71%)	1 (2.86%)	1 (5.56%)
Weight decreased	1 (2.86%)	1 (2.86%)	1 (5.56%)
White blood cell count decreased	2 (5.71%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Decreased appetite	6 (17.14%)	1 (2.86%)	0 (0.00%)
Hyperglycaemia	1 (2.86%)	4 (11.43%)	1 (5.56%)
Hypoalbuminaemia	0 (0.00%)	1 (2.86%)	1 (5.56%)
Hypophosphataemia	0 (0.00%)	0 (0.00%)	1 (5.56%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (2.86%)	1 (2.86%)	1 (5.56%)
Musculoskeletal chest pain	1 (2.86%)	1 (2.86%)	1 (5.56%)
Myalgia	0 (0.00%)	3 (8.57%)	0 (0.00%)
Pain in extremity	0 (0.00%)	1 (2.86%)	1 (5.56%)
Polyarthritis	0 (0.00%)	0 (0.00%)	1 (5.56%)
Nervous system disorders			
Dizziness	1 (2.86%)	0 (0.00%)	1 (5.56%)

Dysgeusia	0 (0.00%)	2 (5.71%)	1 (5.56%)
Headache	1 (2.86%)	2 (5.71%)	0 (0.00%)
Psychiatric disorders			
Insomnia	0 (0.00%)	2 (5.71%)	1 (5.56%)
Renal and urinary disorders			
Micturition urgency	0 (0.00%)	1 (2.86%)	1 (5.56%)
Respiratory, thoracic and mediastinal disorders			
Cough	4 (11.43%)	6 (17.14%)	2 (11.11%)
Dysphonia	1 (2.86%)	2 (5.71%)	1 (5.56%)
Dyspnoea	4 (11.43%)	6 (17.14%)	1 (5.56%)
Dyspnoea exertional	1 (2.86%)	0 (0.00%)	1 (5.56%)
Haemoptysis	0 (0.00%)	0 (0.00%)	2 (11.11%)
Productive cough	2 (5.71%)	1 (2.86%)	0 (0.00%)
Skin and subcutaneous tissue disorders			
Ecchymosis	0 (0.00%)	0 (0.00%)	1 (5.56%)
Pruritus	1 (2.86%)	4 (11.43%)	1 (5.56%)
Rash	0 (0.00%)	2 (5.71%)	0 (0.00%)
Vascular disorders			
Hypertension	1 (2.86%)	2 (5.71%)	0 (0.00%)

Other Relevant Findings

None

Conclusion:

This study evaluated canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in participants with resectable NSCLC. Of the total of 88 participants randomized, all participants except for one completed the planned neoadjuvant treatment and 84 participants underwent the planned surgery. The safety data are consistent with the known well-characterized safety profile of canakinumab or pembrolizumab. These data demonstrate that the use of canakinumab either in monotherapy or in combination with immunotherapy in the neoadjuvant setting was safe and did not impact on the surgical feasibility.

The study did not meet its primary endpoint of MPR rate in any of the canakinumab arms (assessed by the percentage of participants with ≤ 10% residual viable cancer cells), thus in this study canakinumab (alone or in combination with pembrolizumab) did not demonstrate efficacy for NSCLC in the neoadjuvant setting.

Date of Clinical Trial Report

09-May-2023