Final Clinical Study Synopsis

Protocol: SPRING

Survival Prolongation by Rationale Innovative Genomics (SPRING)

A proof of concept study to explore safety and efficacy of tri-therapy approach in advanced/metastatic non-small cell lung cancer (NSCLC) and retrospectively assess the ability of integrated genomics and transcriptomics to match patients to the combination

Protocol Number: WIN001

Sponsor Information	
Sponsor:	Worldwide Innovative Network (WIN) Association 24 rue Albert Thuret, 94550 Chevilly-Larue, France
Study Coordinating Investigator:	Razelle Kurzrock, MD
Contact Information:	Fanny Wunder, Project Manager, fanny.wunder@winconsortium.org
Sponsor Signatory Name:	Dr Vladimir Lazar
Report Version and Date:	Version 1.0, 29/Aug/2023
Clinical Trial Information	
Study Title	**Survival Prolongation by Rationale Innovative Genomics (SPRING)** A proof of concept study to explore safety and efficacy of tri-therapy approach in advanced/metastatic non-small cell lung cancer and retrospectively assess the ability of integrated genomics and transcriptomics to match patients to the combination
Study Identification	**WIN number:** WIN001 **EudraCT number:** 2017-001455-32 **IND number:** 131601 **NCT number:** NCT03386929

Name of Test Drug / Investigational Product	Avelumab, axitinib and palbociclib in combination
Indication Studied	Non-small cell lung cancer (NSCLC)
Design Description	Open-label non-randomized Phase 1-2 recruiting patients with advanced/metastatic NSCLC with no documented targetable alterations receiving a tri-therapy associating avelumab, axitinib and palbociclib at different doses during the Phase 1.
Study Phase	Phase 1-2 initially planned Only the Phase 1 has been conducted. The trial was early terminated at the end of the Phase 1 due to lack of funding.
Study Initiation Date	30/Apr/2018
Date of Early Study Termination	29/Dec/2022
Study Completion Date	29/Dec/2022
Statement	This Clinical Study was conducted in accordance with the study protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements (including archiving of the Clinical Study essential documents): - International Council for Harmonization (ICH) guidelines on Good Clinical Practices (GCP): ICH-E6(R2) and other applicable ICH guidelines. - EU regulation 2016/679, European Directives (2001/20/EC and 2005/28/EC) and other applicable national regulations. - United States Code of Federal Regulations (CFR) applicable to clinical studies: Title 21 Part 11, Part 50, Part 54, Part 56, Part 201 and Part 312.

LIST OF ABBREVIATIONS

Abbreviations

CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practices
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
MTD	Maximal Tolerated Dose
NSCLC	Non-small Cell Lung Cancer
PD	Progressive Disease
PFS	Progression-Free Survival
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 Dose
SD	Stable Disease
SIMS	Simplified Interventional Mapping System
SPRING	Survival Prolongation by Rationale Innovative Genomics
TMB	Tumor Mutation Burden
WIN	Worldwide Innovative Network Association

SYNOPSIS

Name of Sponsor: Worldwide Innovative Network (WIN) Association
Name of Finished Product: avelumab, Inlyta®, Ibrance®
Name of Active Ingredient: avelumab, axitinib, palbociclib
Title of Study: Survival Prolongation by Rationale Innovative Genomics (SPRING) A proof of concept study to explore safety and efficacy of tri-therapy approach in advanced/metastatic non-small cell lung cancer (NSCLC) and retrospectively assess the ability of integrated genomics and transcriptomics to match patients to the combination
Investigators: Drs Jair Bar, Lyudmila Bazhenova, Guy Berchem, Enriqueta Felip, Razelle Kurzrock, Benjamin Solomon.
Study centre(s): • Institute of Oncology, Sheba Medical Center, Tel Hashomer, Israel • Centre Hospitalier de Luxembourg, Service National d'Hémato-Oncologie, Luxembourg • Vall d'Hebron Institute of Oncology, Barcelona, Spain • UCSD Moores Cancer Center, San Diego, California, USA • Avera Cancer Institute, Sioux Falls, South Dakota, USA
Publication (reference): Solomon B, Callejo A, Bar J, et al. A WIN Consortium phase I study exploring avelumab, palbociclib, and axitinib in advanced non-small cell lung cancer. *Cancer Med.* (2022) ; 00:1–11. doi: 10.1002/cam4.4635.

Studied period (years): 2018 - 2022 **Date of first enrolment:** 30/Apr/2018 **Date of last completed:** 29/Dec/2022	**Phase of development:** Phase 1

Primary Objectives: • To determine the safety of the tested 3-drug combination therapy based on CTCAE v4.03 June 14, 2010, • To assess activity parameters, including response rate by RECIST 1.1, duration of response, progression-free survival (PFS), overall survival, • To correlate clinical outcome with the predicted Simplified Interventional Mapping System (SIMS) matching algorithm through a retrospective study. **Secondary Objectives:** • Describe any safety issues related to biopsy acquisition or tri-therapy, • Describe genomic/transcriptomic aberrations seen in NSCLC.
Methodology: Open-label non-randomized study
Number of patients (planned and analysed): Planned: up to 30 treated patients in the Phase 1 and 100 in the Phase 2 Analysed: 15 treated patients in the Phase 1, and none for the Phase 2. The trial was early terminated at the end of the Phase 1 due to lack of funding.

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Name of Finished Product: avelumab, Inlyta®, Ibrance®
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Diagnosis and main criteria for inclusion: Patients with advanced/metastatic NSCLC with no documented targetable alterations (EGFR mutation, ALK translocation, ROS1 mutation if available or MET exon 14 skipping mutation if available) were recruited in the study. Key inclusion criteria: Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, ≤2 prior lines of therapy in the advanced/metastatic setting, adequate hematologic, hepatic, and renal function, and willingness to undergo radiology guided needle biopsy of tumor tissue and biopsy of normal endobronchial mucosa by bronchoscopy. Patients with asymptomatic (treated or untreated) brain metastases were allowed. Key exclusion criteria: *EGFR* mutation, *ALK* fusion, *ROS1* fusion (if tested), and MET alteration (if tested). Patients requiring ongoing anticoagulation or with a bleeding diathesis were also excluded.
Test product, dose and mode of administration, batch number: **Avelumab**: 10 mg/Kg per intra-venous infusion, every two weeks (on day 1 and day 15 of a 28 day cycle) at the hospital (-1/+3 days). Batch numbers: Vial of Avelumab 20 mg/ml: CLI8941, exp 08/12/2018; CLI9029, exp 30/11/2018; CLI9029, exp 30/11/2019; CLI9363, exp 29/02/2020; CLI9363, exp 28/02/2022; CLI 11283, exp 28/02/2023. **Axitinib**: 2 mg to 5 mg, per pills taken orally twice a day, every day of a 28 day cycle. Batch numbers: Bottle of Inlyta 1 mg containing 180 pills: CLI8941 (S86762), exp 29/02/2020; CLI9029 (S86762), exp 29/02/2020; CLI9363 (W27144), exp 31/08/2020; CLI9874 (X43968), exp 31/01/2021; CLI10793 (DN0253), exp 28/02/2022 Box of 4 blisters Inlyta 1 mg containing 56 pills: CLI11280, exp 31/03/2024. Bottle of Inlyta 5 mg containing 60 pills: CLI9029 (S40747), exp 31/10/2019; CLI9363 (W74510), exp 31/10/2020. **Palbociclib**: 75 mg to 125 mg, per capsules taken orally, daily on days 8-28 of a 28 day cycle. Batch numbers: Bottle of Ibrance 100 mg containing 21 caps: CLI9029 (T61690), exp 31/10/2019; CLI9363 (W96782), exp 31/01/2022. Bottle of Ibrance 125 mg containing 21 caps: CLI9029 (T50232), exp 31/01/2020; CLI9363 (W96940), exp 28/02/2022. Bottle of Ibrance 75mg containing 21 caps: CLI8941 (T27567), exp 31/03/2020; CLI9874 (W84578), exp 30/06/2020; CLI9029 (T27567), exp 31/03/2020; CLI9363 (W96788), exp 31/01/2021; CLI10793 (CW4774), exp 30/04/2023.
Duration of treatment: Patients were treated until progression, death or toxicity requiring treatment discontinuation or other discontinuation criteria (consent withdrawal, pregnancy, any intercurrent disease that could affect significantly clinical evaluation and would require resuming treatment, patient unable to comply with protocol requirements, treating physician judged continuation on the study would not be in the patient's best interest).
Reference therapy, dose and mode of administration, batch number: Not Applicable

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Criteria for evaluation

Efficacy:

Efficacy evaluation based on following assessments according to RECIST 1.1 criteria:

- Best Overall Response
- 6-month Response
- Progression-Free Survival (PFS)
- Overall Survival (date of death of the patient collected)

Patients were considered evaluable if they received at least one cycle of treatment and had their baseline scan within 28 days of the start of therapy and follow-up scans about every 8 weeks (+/- 7 days) thereafter.

Safety:

Safety of the tested 3-drug combination therapy evaluated according to NCI CTCAE v4.03 June 14, 2010.

Statistical Methods: Statistical analysis as planned in the protocol has not been performed since the trial has been early terminated after completion of the Phase 1 portion of the trial.

SUMMARY – CONCLUSIONS

Efficacy Results:

Among the 15 patients treated, one patient was considered inevaluable for response because that patient did not receive a complete course of therapy (infusion reaction to avelumab on day 1) (refer to Table 3 in publication). 4 patients (27%) achieved a partial response (PR), including two PRs in patients who had previously experienced progression on pembrolizumab. 2 of the PRs occurred in patients on dose level 1, indicating that this dose level (the recommended Phase 2 dose) shows clinical activity. The PFS in the 4 patients with PRs was 14, 24, 25, and 221+ weeks. 4 patients had stable disease (SD) that lasted ≥ 24 weeks: 24, 27, 29, and 64 weeks. Therefore, a total of 8 of 15 patients (53%) achieved clinical benefit (SD ≥ 24 weeks and/or PR). The patient with the longest response is a 64-year- old woman with no prior therapies in the metastatic setting, who had PD-L1 positivity of 60% on Immunohistochemistry (IHC) screening and an ERBB2 exon 20 insertion alteration (refer to Table S1 in publication); her tumors have shown >80% regression on imaging. After closure of the SPRING study, the patient was transferred to a rollover protocol (SPRING Rollover, EU CT #2022-500041-24-00**)** to enable her to continue being treated. She progressed very recently with a PFS of 5 years (261 weeks). The other 3 PRs were attained in patients with 0%, 0%, and 70% PD-L1 positivity by IHC. Among the 4 patients achieving PR, 2 had available tumor mutation burden (TMB) and both were below 10 mutations/Mb.

Safety Results:

The most common Grade 3 or higher adverse events that were at least possibly treatment related were neutrophil count decreased, lymphocyte count decreased, white blood cell count decreased and hypertension. Other Grade 3 or higher adverse events included respiratory failure, diarrhea, infusion related reaction, fatigue, electrocardiogram QT prolonged, alanine aminotransferase increased, weight decreased, hypertriglyceridemia, hyponatremia, and thrombosis. A single occurrence of Grade 5 respiratory failure was documented as possibly drug related. This event occurred in a patient with underlying cardiopulmonary comorbidities.

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6 patients were treated at dose level 1, 6 patients at dose level 2, and 3 patients at dose level 3. There were no dose-limiting toxicities (DLTs) at dose level 1. 1 patient had a DLT on dose level 2, which was an infusion reaction to avelumab. Hence the dose level was expanded to 6 patients without further DLTs. There were 2 patients with DLTs at dose level 3 (respiratory failure in one patient and palmar-plantar erythrodysesthesia as well as fatigue in the second patient). Per protocol, the MTD was dose level 2: avelumab 10 mg/kg every 2 weeks, axitinib 5 mg by mouth twice per day, and palbociclib 75 mg by mouth daily on days 8–28 of a 28-day cycle. However, due to multiple treatment interruptions and dose reductions occurring beyond the DLT window in dose level 2 (first 4 weeks of treatment), dose level 1 was expanded to 6 patients; based on the tolerable side effect profile of dose level 1 compared to dose level 2 (5 of 6 patients at dose level 2 versus 1 of 6 patients at dose level 1 had ≥ 1 drug held during the first 60 days of treatment), the MTD (dose level 2) was declared by the Clinical Monitoring Committee to be above the recommended Phase 2 dose (RP2D). Thus, dose level 1– avelumab 10 mg/kg every 2 weeks, axitinib 3 mg by mouth twice per day, and palbociclib 75 mg by mouth daily on days 8–28 of a 28-day cycle – is the RP2D. **Conclusion:** A total of 15 patients were enrolled and treated with the combination; 5 were women and 10 were men. Median age was 67 years (range 51–80 years). 1 patient was treated in first line, 9 patients in second line, and 5 patients in third line in the metastatic setting. The most common histology was adenocarcinoma. 10 patients had been previously treated with regimens containing immune checkpoint inhibitors. In conclusion, the combination is generally well tolerated at dose level 1 and exhibits encouraging evidence of activity in patients with advanced NSCLC at that dose level, with 4 of 6 patients (66%) attaining SD ≥ 6 months/PR. The RP2D for the combination is avelumab 10 mg/kg IV every 2 weeks, axitinib 3 mg by mouth twice per day, and palbociclib 75 mg by mouth daily on days 8–28 of each 28-day cycle. Responding patients included those with low TMB and no PD-L1 expression on immunohistochemistry. Future study is warranted to further explore antitumor activity of this triplet combination of immunotherapy and targeted therapy to better identify biomarkers predictive of response.
Date of the report: 29/August/2023