Explore the efficacy of the combination in patients with NSCLC, mCRC, or any anti-PD-1 or anti-PD-L1 pretreated non-small-cell lung cancer (NSCLC) and other solid tumors

The objectives of the dose-expansion portion of the trial are to:
• Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating dose combinations of BI 754111 plus BI 754091 to be used in the expansion phase (Part II).

Inclusion Criteria:
• Advanced, inoperable, and/or metastatic solid tumors
• Dose escalation: any tumor type
• Dose expansion: NSCLC, anti-PD-1/anti-PD-L1 naïve microsatellite stable (MSS) metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated microsatellite stable metastatic colorectal cancer (mCRC), anti-PD-1/anti-PD-L1 pretreated any high TMB (≥10 mutations/Mb) and/or MMRd solid tumors
• Measurable lesions according to RECIST v 1.1
• Exhausted standard treatment options (dose escalation portion)

Exclusion Criteria:
• Active autoimmune disease or a documented history of autoimmune disease
• History of pneumonitis within the last 5 years
• Prolonged QTc/ejection fraction <55%
• Any solid tumor with high TMB and/or MSI-H and/or DNA MMRd solid tumors
• Interstitial lung disease
• Previous treatment with anti-LAG 3 agents
• Prior treatment with anti-LAG-3 agents
• History of pneumonitis within the last 5 years
• Prolonged QTc/ejection fraction <55%
• Any solid tumor with high TMB and/or MSI-H and/or DNA MMRd solid tumors
• Interstitial lung disease
• Previous treatment with anti-LAG-3 agents
• History of pneumonitis within the last 5 years
• Prolonged QTc/ejection fraction <55%
• Any solid tumor with high TMB and/or MSI-H and/or DNA MMRd solid tumors
• Interstitial lung disease
• Previous treatment with anti-LAG-3 agents

STUDY OBJECTIVES
Part I (Dose-Escalation Cohorts):
The objectives of the dose-escalation portion of the trial are to:
• Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating dose combinations of BI 754111 plus BI 754091 in patients with advanced and/or metastatic solid tumors
• Determine the maximum-tolerated dose (MTD) through monitoring dose escalation and investigating the dose-effect relationship
• Investigate the dose-response relationship

Part II (Dose-Escalation Cohorts):
The objectives of the dose-escalation portion of the trial are:
• Further investigate the safety, tolerability, and PK of the selected dose of the combination of BI 754111 plus BI 754091 in patients with non-small-cell lung cancer (NSCLC), microsatellite stable (MSS) metastatic colorectal cancer (mCRC), anti-PD-1/anti-PD-L1 pretreated microsatellite stable solid tumor with high TMB, histologic burden (TMB), and/or mismatch repair deficient (dMMR).
• Explore the efficacy of the combination in patients with NSCLC, mCRC, or any solid tumor with high TMB and/or MSH-H and/or DNA MMRd.

TREATMENT PLAN
- Cycle 1
- 4 inj of BI 754111 plus BI 754091
- DLTs monitored throughout the study

EDUCATIONAL RESOURCES
- ClinicalTrials.gov number NCT03156114
- http://clinicaltrials.gov/ct2/show/NCT03156114

STUDY ENDPOINTS
Primary Endpoint:
• MTD of the BI 754111 plus BI 754091 combination

Secondary Endpoints:
• Objective response per RECIST Version 1.1
• Duration of response

STATISTICAL ANALYSIS
For OR and DC, the frequency and proportion of patients and 95% two-sided confidence interval will be presented. For DFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method.

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REFERENCE
Phase I study of BI 754111 (anti-LAG-3) plus BI 754091 (anti-PD-1) in patients (pts) with advanced solid cancers, followed by expansion in pts with microsatellite stable metastatic colorectal cancer (mCRC), anti-PD-(L)1-pretreated non-small-cell lung cancer (NSCLC) and other solid tumors

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Background

- Tumors may achieve immune evasion by expressing PD ligand-1 (PD-L1) to bind to PD-1 expressed on activated T-cells, initiating immunosuppressive signals within the tumor microenvironment\(^1\)
- Pro-inflammatory anti-tumor activity can be restored when this interaction is blocked by therapeutic PD-1/PD-L1 inhibition\(^2-4\)
- Lymphocyte-activation gene 3 (LAG-3) is a negative regulator of immune response implicated in T-cell exhaustion and tumor immune escape\(^5-8\). Tumor-derived T-cells frequently co-express the PD-1 and LAG-3 co-inhibitory receptors\(^9\)
- Dual blockade of the LAG-3 and PD-1 pathways results in more potent reactivation of T-cell function and anti-tumor immune response than blockade of either individual pathway\(^10-11\)
- BI 754091 and BI 754111 are monoclonal IgG4Pro antibodies (mAbs) against PD-1 and LAG-3, respectively
- In this Phase I study, we investigate the safety, tolerability, PK, and preliminary efficacy of the combination of these 2 mAbs in patients with solid tumors
Background cont’d

Mechanism of BI 754091 and BI 754111 Activity
Study Objectives

**Part I (Dose-Escalation Cohorts):**
The objectives of the dose-escalation portions of the trial are to:

- Investigate the safety, tolerability, and pharmacokinetics (PK) of escalating doses of BI 754111 in combination with BI 754091 in patients with advanced and/or metastatic solid tumors.
- Determine the maximum-tolerated dose (MTD) through monitoring dose-limiting toxicities (DLTs) and/or to determine the dose of the combination of BI 754111 plus BI 754091 to be used in the expansion phase (Part II).
Study Objectives cont’d

Part 2 (Dose-Expansion Cohorts):
The objectives of the dose-expansion portion of the trial are to:

• Further investigate the safety, tolerability, and PK of the selected expansion dose of the combination of BI 754111 plus BI 754091 in patients with non-small-cell lung cancer (NSCLC), microsatellite stable (MSS) metastatic colorectal cancer (mCRC), or any anti-PD-1 or anti-PD-L1 pretreated solid tumor with high tumor mutational burden (TMB) and/or microsatellite instability high (MSI-H) and/or DNA mismatch repair deficient (MMRd)

• Explore the efficacy of the combination in patients with NSCLC, mCRC, or any solid tumor with high TMB and/or MSI-H and/or DNA MMRd
Key Eligibility

**Inclusion Criteria**

- Advanced, unresectable, and/or metastatic solid tumors
- Dose escalation: any tumor type
- Dose expansion: NSCLC, anti-PD-1/anti-PD-L1 naïve microsatellite stable mCRC, anti-PD-1/anti-PD-L1-pretreated patients with any high TMB (>10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumors
- Measurable lesions according to RECIST v 1.1
- Exhausted standard treatment options (dose escalation portion)
Key Eligibility cont’d

Exclusion Criteria

• Active autoimmune disease or a documented history of autoimmune disease
• Interstitial lung disease
• History of pneumonitis within the last 5 years
• Prolonged QTc/ejection fraction <55%
• History of hypersensitivity reactions to other mAbs
• Prior treatment with anti-LAG 3 agents
• Any investigational or antitumor treatment within 4 weeks or 5 half-life period (whichever is shorter) prior to the initial administration of study drug treatment
• Inadequate organ function
• Untreated brain metastasis considered to be active
Study Design

Part I Dose-Escalation Cohorts

- 4 mg anti-LAG-3 + 240 mg anti-PD-L1
- 20 mg anti-LAG-3 + 240 mg anti-PD-L1
- 80 mg anti-LAG-3 + 240 mg anti-PD-L1
- 200 mg anti-LAG-3 + 240 mg anti-PD-L1
- 400 mg anti-LAG-3 + 240 mg anti-PD-L1
- 600 mg anti-LAG-3 + 240 mg anti-PD-L1
- 800 mg anti-LAG-3 + 240 mg anti-PD-L1
Study Design (cont’d)

Part II Dose-Expansion Cohorts

- Second and third line NSCLC who progressed on anti-PD-1 or anti-PD-L1 treatment after achieving benefit of 8 months for non-squamous NSCLC or 6 months for all other patients, and a minimum duration of prior anti-PD-1 or anti-PD-L1 of 2 months
- Second line or greater microsatellite stable anti-PD-1 and anti-PD-L1 treatment-naïve mCRC
- Any solid tumor with high TMB and/or MSI-H and/or DNA MMRd solid tumors who have received 1 prior anti-PD-1 or anti-PD-L1 treatment regimen
- First line epidermal growth factor receptor (EGFR) wildtype and anaplastic lymphoma kinase (ALK) WT NSCLC. Patients may have any level of PD-L1 expression, but only a maximum of 10 patients with PD-L1 high expression (≥50% PD-L1) can be enrolled
Treatment Plan

Screening, Baseline Characteristics

Day 1 8 15 21

Cycle 1

BI 754091 and BI 754111
IV q3w

1 Cycle=21 days

Day 1 8 15 21

Cycle 2

Response assessments: Every 6 weeks for the 1st 6 months, then every 9 weeks thereafter

DLTs monitored throughout the study

Patients continue treatment for up to 1 year or longer until progression, or unacceptable toxicity
Study Endpoints

Part I (Dose-Escalation)

Primary Endpoint:
• MTD of the BI 754111 plus BI 754091 combination
• Number of patients experiencing DLTs during Cycle 1

Secondary Endpoints:
• PK parameters will be calculated for BI 754111 and for BI 754091
• Number of patients experiencing DLTs from start until end of treatment
• Objective response per RECIST Version 1.1
Study Endpoints (cont’d)

Part II (Dose-Expansion Cohorts)

Primary Endpoint:
- Objective response per RECIST Version 1.1

Secondary Endpoints:
- Duration of response
- Disease control per RECIST Version 1.1
- Progression-free survival
- PK parameters will be calculated for BI 754111 and BI 754091
Statistical Analysis

Part I:

- Dose escalation will be guided by Bayesian Logistic Regression Models (BLRMs) with overdose control that will be fitted to binary toxicity outcomes. The estimate of parameters will be updated as data are accumulated using BLRMs.
- At the end of dose escalation, the toxicity probability at each dose combination level will be calculated to determine an estimate of the selected expansion dose of the combination of BI 754111 plus BI 754091.
- If there are too few or no DLTs for BLRM guided dose selection, PK and/or biomarker data will be taken into consideration for dose determination.

Part II:

- Efficacy response endpoints will be summarized descriptively.
- For OR and DC, the frequency and proportion of patients and 95% two-sided confidence interval will be presented.
- For PFS and duration of response, the median and 95% two-sided confidence interval will be presented using the Kaplan-Meier method.
- No hypothesis testing is planned in this trial.
Trial Status

- This study is currently open to accrual
- The dose escalation portion has been completed
- An expansion dose of 600 mg BI 754111/240 mg BI 754091 has been selected
- The expansion cohorts have opened
- ClinicalTrials.gov number NCT03156114
- EudraCT number 2017-005042-29
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