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

Abstract 1243TiP

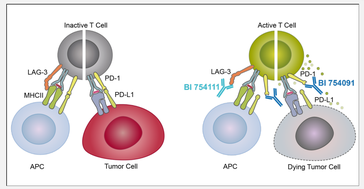
Melissa Johnson, MD[1,2]; Manish R. Patel, MD[1,3]; Susanna V. Ulahannan, MD[1,4]; Aaron Hansen, MD[5]; Ben George, MD[6]; Quincy Chu, MD[7]; Mabrouk Elgadi, MSc, PhD[8]; Miaomiao Ge, PhD[9]; Christine Duffy, MSHS[9]; Ralph Graeser, PhD[10]; Sheetal Khedkar, MD, MSPH[11]; Suzanne F. Jones, PharmD[2]; Howard A. Burris, III, MD[1,2]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Florida Cancer Specialists, Sarasota, FL; [4]Stephenson Cancer Center, Oklahoma University, Oklahoma City, OK; [5]Princess Margaret Hospital, Toronto, ON; [6]Medical College of Wisconsin, Milwaukee, WI; [7]University of Alberta, Edmonton, AB ; [8]Boehringer Ingelheim (Canada) Ltd./Ltee, Burlington, ON; [9]Boehringer Ingelheim Pharmaceuticals, Inc.; [10]Boehringer Ingelheim Pharma GmbH & Co. KG; [11]Sarah Cannon Development Innovations, Nashville, TN

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].

Mechanism of BI 754091 and BI 754111 Activity



- 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.

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).

Part II (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 ELIGIBILTY

Inclusion Criteria

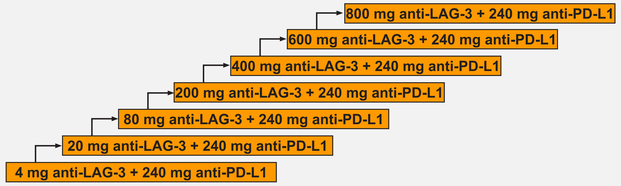
- Advanced, unresectable, and/or metastatic solid tumors
- Dose escalation: any tumor type
- Dose expansion: NSCLC, anti-PD-1/anti-PD-L1 naïve microsatellite stable mCRC, anti-PD-1/anti-PD-L1-pretreated patients with any high TMB (≥10 mutations/Mb) and/or MSI-H and/or DNA MMRd solid tumors
- Measurable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

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

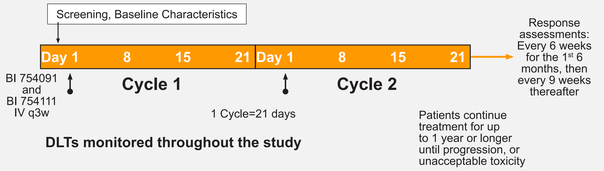
Part I Dose-Escalation Cohorts



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



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

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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Scan the QR code for an electronic copy of the poster †

Presented at ESMO Congress, Munich, Germany 19-23 October, 2018

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Presented at the European Society For Medical Oncology (ESMO) congress, Munich, Germany, October 19–23, 2018

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]
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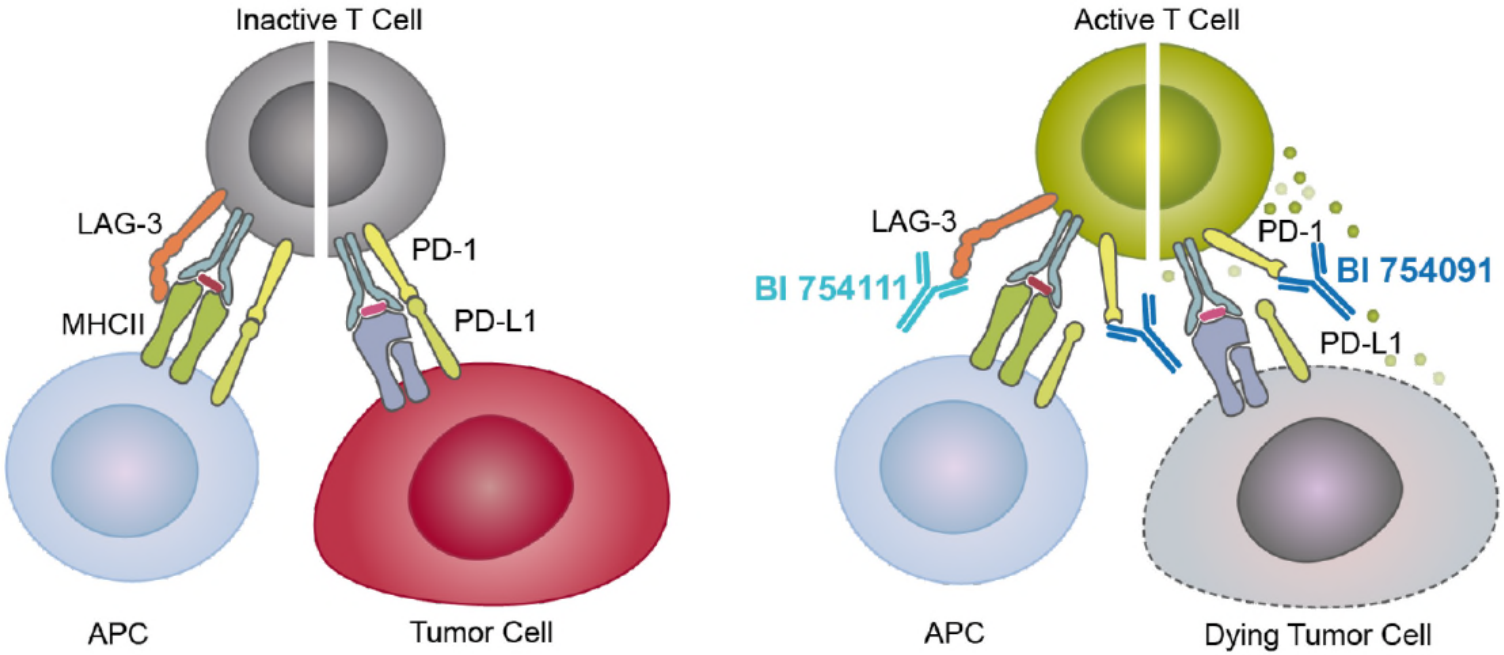

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Study Objectives cont'd

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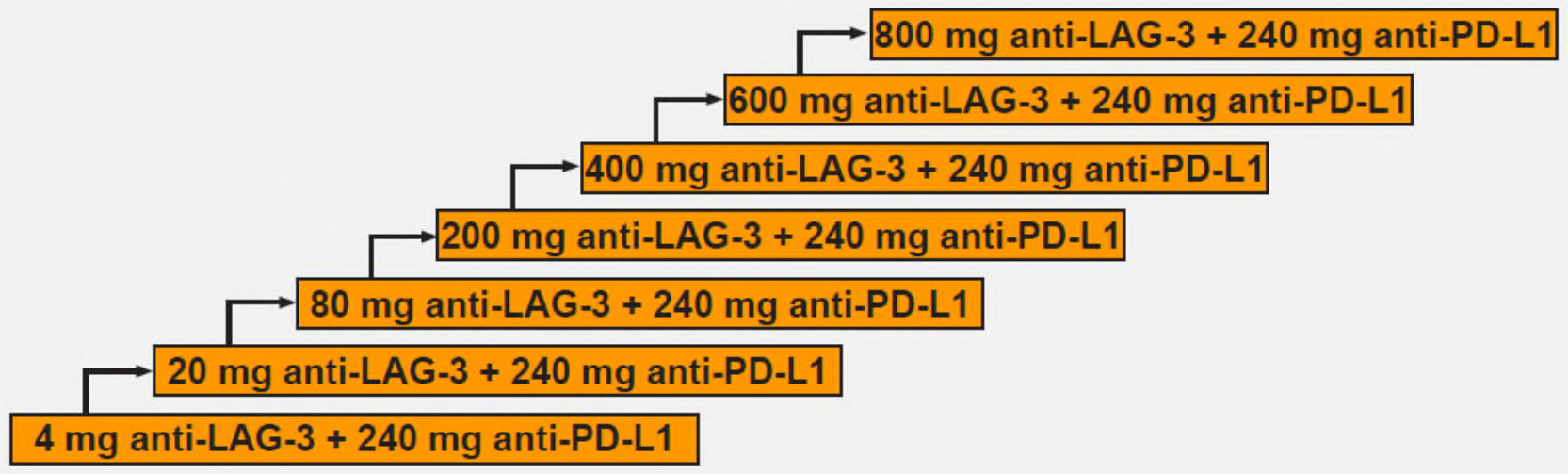
Study Design

Part I Dose-Escalation Cohorts



Study Design (cont'd)

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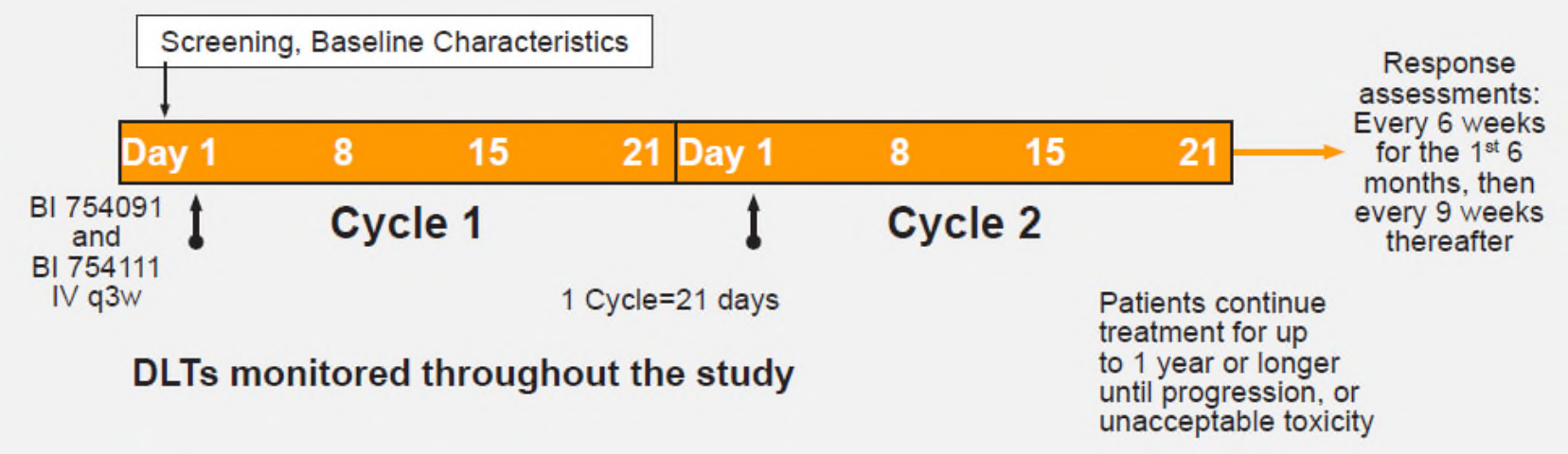

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Study Endpoints (cont'd)

Part II (Dose-Expansion Cohorts)

Primary Endpoint:

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