Phase 1 trial of an anti-PD-1 mAb BI 754091 ± an anti-LAG-3 mAb BI 754111 in Asian patients with advanced solid tumors

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Introduction

Background
- Signaling via the immune checkpoint molecules PD-1 and LAG-3 can lead to T-cell dysfunction and prevent antitumor responses.
- Dual inhibition of PD-1 and LAG-3 may synergistically restore T-cell activation and enhance antitumor immune responses.
- Combined treatment with an anti-PD-1 monoclonal antibody (mAb) and an anti-LAG-3 mAb may achieve greater rates of tumor shrinkage compared with anti-PD-1 mAb monotherapy.
- Anti-PD-1 and anti-LAG-3 mAb combinations have demonstrated encouraging preclinical and clinical antitumor activity.
- Preliminary study results in patients with advanced solid tumors demonstrate that BI 754091 is safe and well-tolerated (up to 450 mg), with evidence of antitumor activity.
- In this Phase I trial (NCT03433898), the anti-PD-1 mAb BI 754091 will be evaluated in Asian patients with advanced, unresectable, and/or metastatic solid tumors (as monotherapy and together with the anti-LAG-3 mAb, BI 754111). Objectives
- Assess the safety, tolerability, and pharmacokinetics (PK) of BI 754091 with and without BI 754111.
- Determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of BI 754091 monotherapy, and BI 754091 plus BI 754111.
- Assess the efficacy of the RP2D of BI 754091 plus BI 754111 in patients with gastric/esophagogastric junction cancer (G/EJC), esophageal cancer (EC) or hepatocellular cancer (HCC).

Eligibility criteria

Key inclusion criteria
- Adult patients
- Measurable lesions, according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1)
- Parts 1 and 2: confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumors (any type)
- Parts 3 (Cohorts 1-3): 18+ of systemic therapy (excluding adjuvant), no prior anti-PD-1/LD-1 mAb therapy
- Part 3 (Cohort 4): disease progression on or after prior anti-PD-1/LD-1 mAb therapy

Key exclusion criteria
- Any prior treatment within 4 weeks or 5 half-life periods (whichever is shorter) of BI 754091 and BI 754111
- Inadequate organ function or bone marrow reserve (based on laboratory values)
- Immunosuppressive corticosteroids (>10 mg/day prednisone, or equivalent) for <4 weeks prior to first dose of treatment
- History of pneumonitis (in last 5 years), HIV or interstitial lung disease
- Active autoimmune disease
- Active infection requiring systemic treatment

Study design

Open-label, single-arm, Phase I trial in patients with advanced solid tumors

| Part 1 | BI 754091 | 240 mg iv q4w; once every three weeks (Q3W) |
| Part 2 | Starting doses: 240 mg from Part 1 and 80 mg iv q4w; Q3W |
| Part 3 | BI 754091 + BI 754111 (at RP2D) |

Endpoints

Primary endpoints
- Parts 1 and 2: MTD of BI 754091 and BI 754111, based on dose-limiting toxicities in Cycle 1
- Part 3: Investigator assessed objective response according to RECIST v1.1

Secondary endpoints
- Parts 1 and 2: BI 754091; BI 754111 plasma C0 and AUC
- Part 1 and 2: Investigator assessed objective response according to RECIST v1.1

Key points

Objectives:
- Parts 1 and 2
  - Determine safety, tolerability, PK, and MTD/RP2D of BI 754091 monotherapy and BI 754091 + BI 754111 combination therapy
- Part 3
  - Explore the efficacy and further investigate safety, tolerability and PK of BI 754091 + BI 754111 in patients with G/EJC, EC or HCC

Study design:
- Open-label, single-arm, Phase I trial in Asian patients with advanced, unresectable, and/or metastatic solid tumors

Current status

Enrollment opened in February, 2018
- Target enrollment is 164 patients from Asian countries including Japan
- Part 1 is complete; no dose limiting toxicities were reported; RP2D of BI 754091 confirmed as 240 mg
- Part 2 opens for recruitment in July 2018

References

Presented at 2018 Japanese Society of Medical Oncology Annual Meeting, July 19–21, 2018, Kobe, Japan

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Phase 1 trial of an anti-PD-1 mAb BI 754091 ± an anti-LAG-3 mAb BI 754111 in Asian patients with advanced solid tumors

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Presented at 2018 Japanese Society of Medical Oncology Annual Meeting (JSMO), July 19–21, 2018, Kobe, Japan
Introduction

Background

• Signaling via the immune checkpoint molecules PD-1 and LAG-3 can lead to T-cell dysfunction and prevent antitumor responses\(^1\)
• Dual inhibition of PD-1 and LAG-3 may synergistically restore T-cell activation and enhance antitumor immune responses\(^{1,2}\)
• Combined treatment with an anti-PD-1 monoclonal antibody (mAb) and an anti-LAG-3 mAb may achieve greater rates and durations of response compared with anti-PD-1 mAb monotherapy
• Anti-PD-1/anti-LAG-3 mAb combinations have demonstrated encouraging preclinical\(^3\) and clinical\(^4\) antitumor activity
• Preliminary study results in patients with advanced solid tumors demonstrate that BI 754091 is safe and well-tolerated up to 400 mg, with evidence of antitumor activity\(^5\)
• In this Phase I trial (NCT03433898), the anti-PD-1 mAb BI 754091 will be evaluated in Asian patients with advanced, unresectable, and/or metastatic solid tumors (as monotherapy and together with the anti-LAG-3 mAb, BI 754111)

mAb, monoclonal antibody
Introduction (cont’d)

Objectives

• Assess the safety, tolerability and PK of BI 754091 with and without BI 754111
• Determine the MTD and/or RP2D of BI 754091 monotherapy, and BI 754091 plus BI 754111
• Assess the efficacy of the RP2D of BI 754091 plus BI 754111 in patients with G/EJC, EC or HCC

EC, esophageal cancer; G/EJC, gastric/esophagogastric junction cancer; HCC, hepatocellular cancer; MTD, maximum tolerated dose; PK, pharmacokinetics; RP2D, recommended Phase II dose
### Eligibility criteria

#### Key inclusion criteria

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Adult patients</td>
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<tr>
<td>Measurable lesions, according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1</td>
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<tr>
<td>Parts 1 and 2: confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumors (any type)</td>
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<td>Part 3 (Cohorts 1–3): ≥1 line of systemic therapy (excluding adjuvant), no prior anti-PD-1/PD-L1 mAb therapy</td>
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<tr>
<td>Part 3 (Cohort 4): disease progression on or after prior anti-PD-1/PD-L1 mAb therapy</td>
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mAb, monoclonal antibody; RECIST, Response Evaluation Criteria in Solid Tumors
### Eligibility criteria (cont’d)

<table>
<thead>
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<th>Key exclusion criteria</th>
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<tr>
<td>Antitumor treatment within 4 weeks or 5 half-life periods (whichever is shorter)</td>
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<td>Part 2 and 3 only: prior anti-LAG-3 therapy</td>
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<td>Inadequate organ function or bone marrow reserve (based on laboratory values)</td>
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<td>Immunosuppressive corticosteroids (&gt;10 mg/day prednisone, or equivalent) &lt;4 weeks prior to first dose of treatment</td>
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Study design

Open-label, single-arm, Phase I trial in patients with advanced solid tumors

Part 1
- **BI 754091**
  - 240 mg via iv infusion; Q3W
  - Japanese patients with advanced solid tumors of any type
  - RP2D 6–12

Part 2
- **BI 754091 + BI 754111**
  - Starting doses: 240 mg from Part 1 and 80 mg via iv infusion; Q3W
  - 12–18
  - RP2D

Q3W, once every three weeks
**Study design (cont’d)**

<table>
<thead>
<tr>
<th>Part 3</th>
<th>BI 754091 + BI 754111 (at RP2D)</th>
<th>~140</th>
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</table>
| **Cohort 1** | Gastric/esophagogastric junction cancer |  | • Asian patients (including Japan, Taiwan and Korea)  
| | • No previous anti-PD-1 / PD-L1 mAb therapy  
| | • ≥1 line of systemic therapy |
| **Cohort 2** | Esophageal cancer |  |  |
| **Cohort 3** | Hepatocellular cancer |  |  |
| **Cohort 4** | Gastric/esophagogastric junction, esophageal, or hepatocellular cancer |  | • Asian patients (including Japan, Taiwan and Korea)  
| | • Failure of previous anti-PD-1 / PD-L1 mAb therapy |

mAb, monoclonal antibody; RP2D, recommended Phase II dose
Endpoints

Primary endpoints

Parts 1 and 2
MTD of BI 754091 and BI 754091 + BI 754111, based on dose-limiting toxicities in Cycle 1

Part 3
Investigator assessed objective response according to RECIST v1.1

MTD, maximum tolerated dose; RECIST, Response Evaluation Criteria in Solid Tumors
Endpoints (cont’d)

Secondary endpoints

Parts 1 and 2
BI 754091; BI 754091 + BI 754111
plasma $C_{\text{max}}$ and AUC

Parts 1 and 2
Investigator assessed objective response according to RECIST v1.1

AUC, area under curve; $C_{\text{max}}$, maximum drug concentration; RECIST, Response Evaluation Criteria in Solid Tumors
Endpoints (cont’d)

Secondary endpoints

**Part 3**

**Duration of response**

*From*
Date of first documented investigator-assessed PR or CR according to RECIST v1.1

*To*
Date of progressive disease or death

**Part 3**

**Disease control**
(investigator-assessed PR, CR or stable disease according to RECIST v1.1)

CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors
Key points

Objectives:
- Parts 1 and 2
  - Determine safety, tolerability, PK, and MTD/RP2D of BI 754091 monotherapy and BI 754091 + BI 754111 combination therapy
- Part 3
  - Explore the efficacy, and further investigate safety, tolerability and PK of BI 754091 + BI 754111 in patients with G/EJC, EC or HCC

Study design:
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Current status

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References


Acknowledgments

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