A Phase I, dose finding study of BI 754111, an anti-LAG-3 antibody, in combination with BI 754091, an anti-PD-1 antibody, in patients with advanced solid tumors: preliminary results from the microsatellite stable metastatic colorectal cancer cohort

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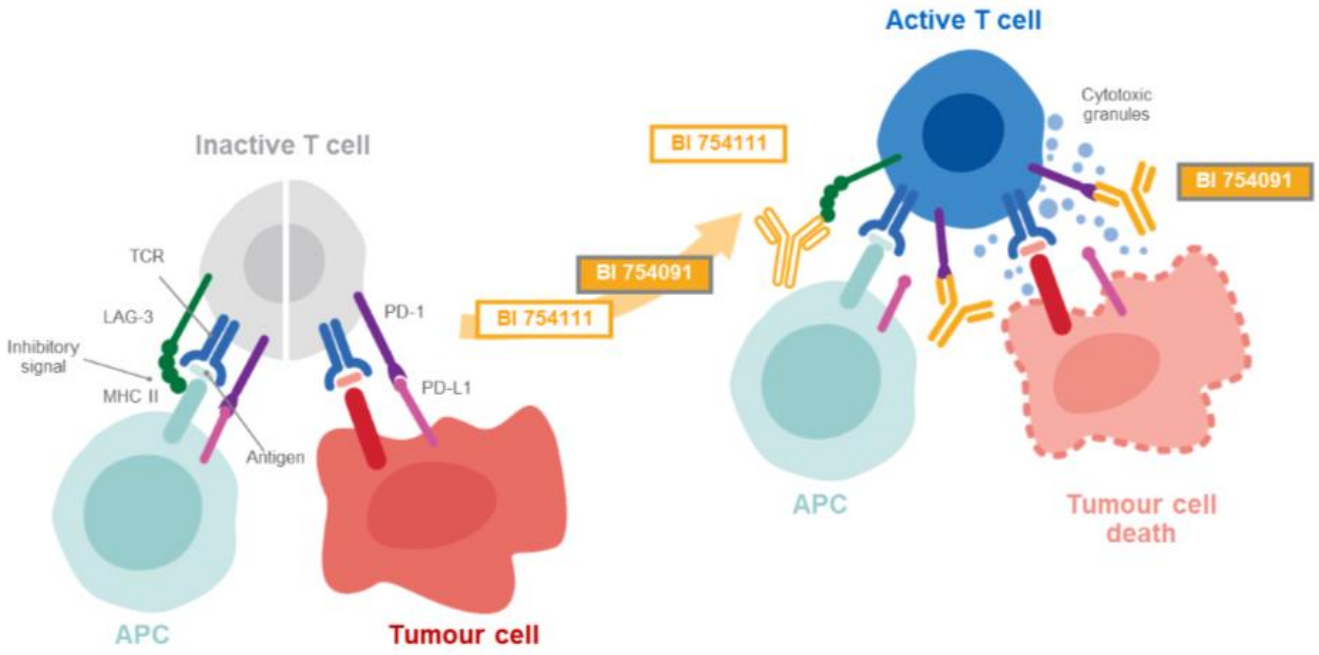
Introduction

- LAG-3, an immune checkpoint inhibitor, is mainly expressed on T cells.[1] Binding of LAG-3 to its ligand, MHC class II, causes a signaling cascade that contributes to immune cell exhaustion[1,2]
- LAG-3 has been found to be co-expressed with PD-1.[3] Dual blockade of PD-1 and LAG-3 has the potential to synergistically restore T-cell functionality and thus enhance anti-tumor immune responses (**Figure 1**)[2,4]
  - BI 754111 is a humanized LAG-3-targeting mAb that inhibits the interaction between LAG-3 and MHC class II[5]
  - BI 754091 is a humanized PD-1-targeting mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2[6]
  - BI 754091 has been shown to be well tolerated, with evidence of anti-tumor activity; the 240 mg q3w dose was selected as RP2D[7]
- This Phase I trial (NCT03156114) is evaluating the combination of BI 754111 and BI 754091 in patients with advanced solid tumors

Introduction (cont'd)

Figure 1. Combination of PD-1 and LAG-3 inhibition[4]



APC, antigen-presenting cell; LAG-3, lymphocyte-activation gene-3 (target of BI 754111); mAb, monoclonal antibody; MHC, major histocompatibility complex; PD-1, programmed cell death-1 (target of BI 754091); PD-L1, programmed cell death-ligand 1; q3w, every 3 weeks; RP2D, recommended phase II dose; TCR, T-cell receptor

Study design

- This open-label study has two parts: Part 1 (dose escalation) and Part 2 (dose expansion)

Part 1: Dose escalation in patients with advanced solid tumors

Part 1 has been completed with no DLTs reported at any of the doses tested

Part 2: Dose expansion

Cohort 1

≥2nd line MSS anti-PD-(L)1 treatment-naïve mCRC

Fully recruited (N=40)
Initial results presented here

Cohort 2

Anti-PD-(L)1 pre-treated TMB ≥10 mutations/Mb and/or MSI-H and/or dMMR solid tumors

Cohort 3

Treatment-naïve *EGFR* and *ALK* wild-type NSCLC

Cohort 4

Anti-PD-(L)1 pre-treated 2nd/3rd line NSCLC that progressed after benefit on previous anti-PD-(L)1 therapy

Open for recruitment; further details via QR code

http://tago.ca/zHe

ALK, anaplastic lymphoma kinase; DLTs, dose-limiting toxicities; EGFR, epidermal growth factor receptor; dMMR, DNA mismatch repair deficient; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability high; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; TMB, tumor mutational burden

Patients

- 40 patients with MSS mCRC received BI 754111 600 mg in combination with BI 754091 240 mg q3w
- At data cut-off (September 2019), five patients remain on treatment, and 35 have discontinued treatment
  - Reasons for discontinuation: progressive disease (n=26), AE (n=5), physician decision (n=2), death (n=1), and lost to follow-up (n=1)
- Baseline characteristics are shown in **Table 1**

Patients (cont'd)

Table 1. Baseline characteristics

	Treated set (N=40)
Gender, n (%)	
Male	27 (67.5)
Race, n (%)	
White	36 (90.0)
Black or African American	2 (5.0)
American Indian or Alaska Native	1 (2.5)
Other	1 (2.5)
Age, years	
Median (range)	56.5 (25–85)
ECOG PS, n (%)	
0	20 (50.0)
1	20 (50.0)
Prior systemic therapies, n	
Median (range)	3.5 (1–10)
Primary cancer diagnosis, n (%)	
Rectal	7 (17.5)
Colon	33 (82.5)

AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status

Efficacy

- Three patients with MSS mCRC had confirmed PR and 11 patients had SD (**Table 2**)
- In some patients, BI 754111 in combination with BI 754091 produced deep and durable responses (**Figure 2**)
- Individual treatment profiles are shown in **Figure 3**

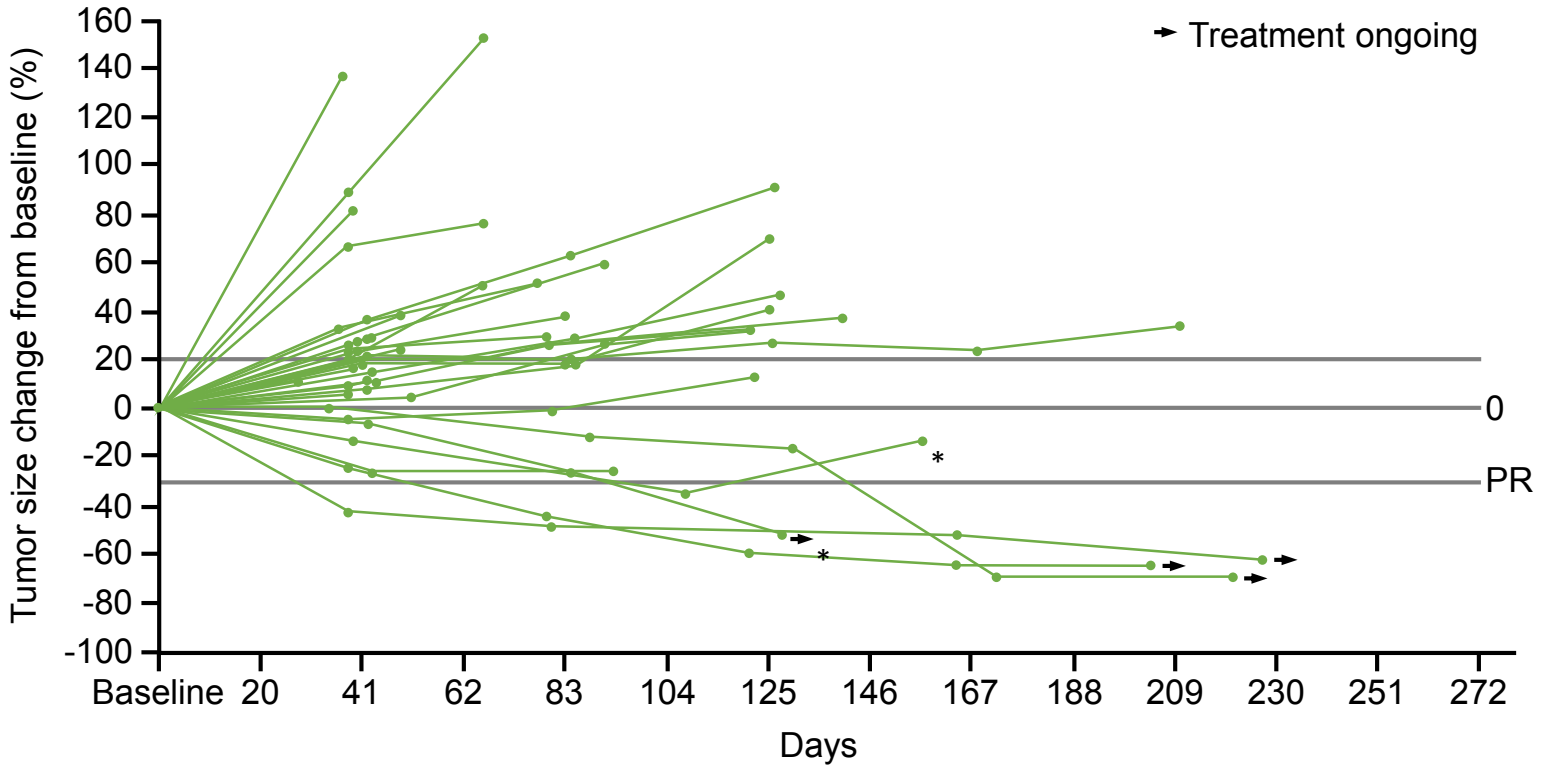
Efficacy (cont'd)

Table 2. Best overall confirmed response

	Treated set (N=40)
Disease control	14 (35.0)
Objective response	3 (7.5)
CR	0
PR	3 (7.5)
SD	11 (27.5)
PD	22 (55.0)
Not available	4 (10.0)

Efficacy (cont'd)

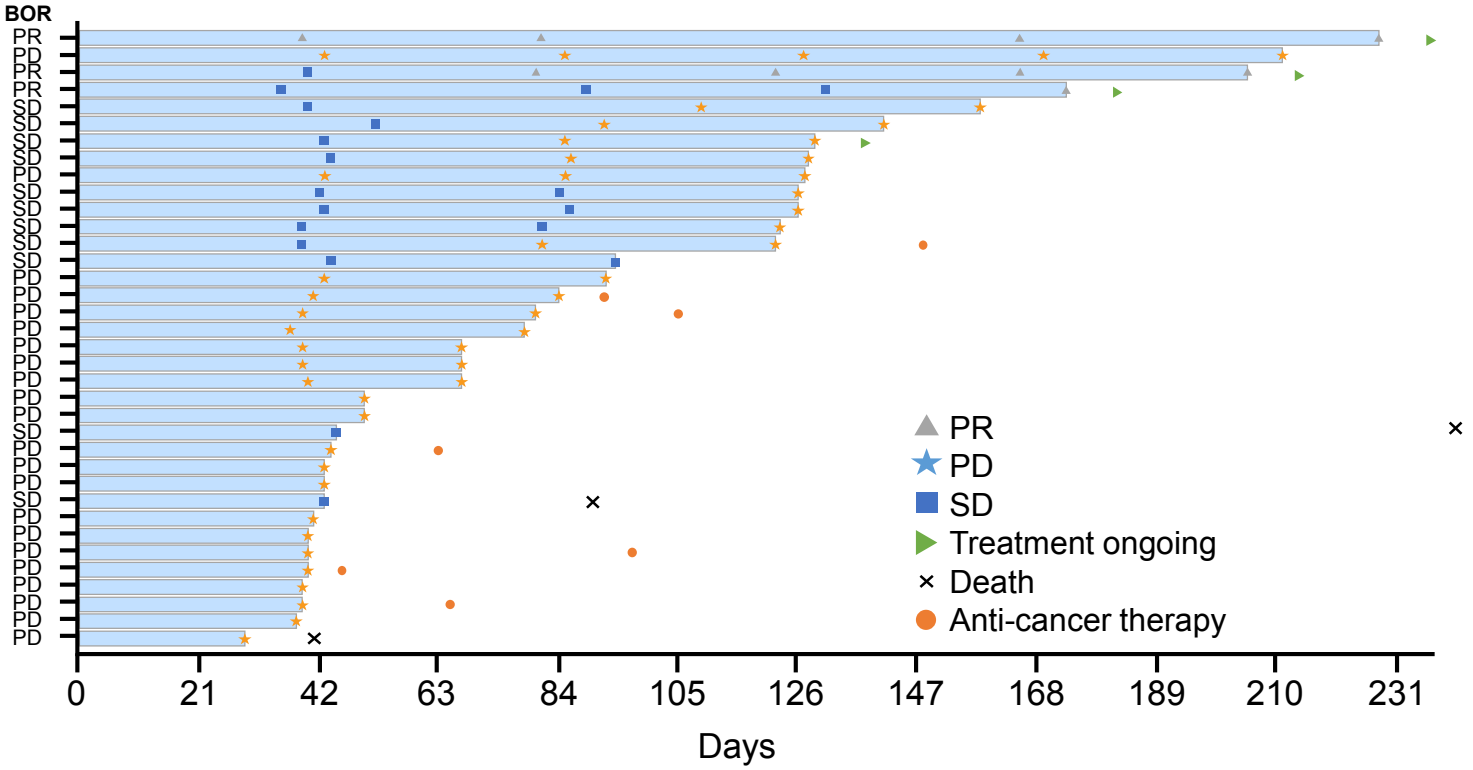
Figure 2. Percentage change from baseline in target lesion size over time (N=36)



*The two patients indicated had PR in their target lesions but developed new tumors

Efficacy (cont'd)

Figure 3. Individual treatment profiles (N=36)



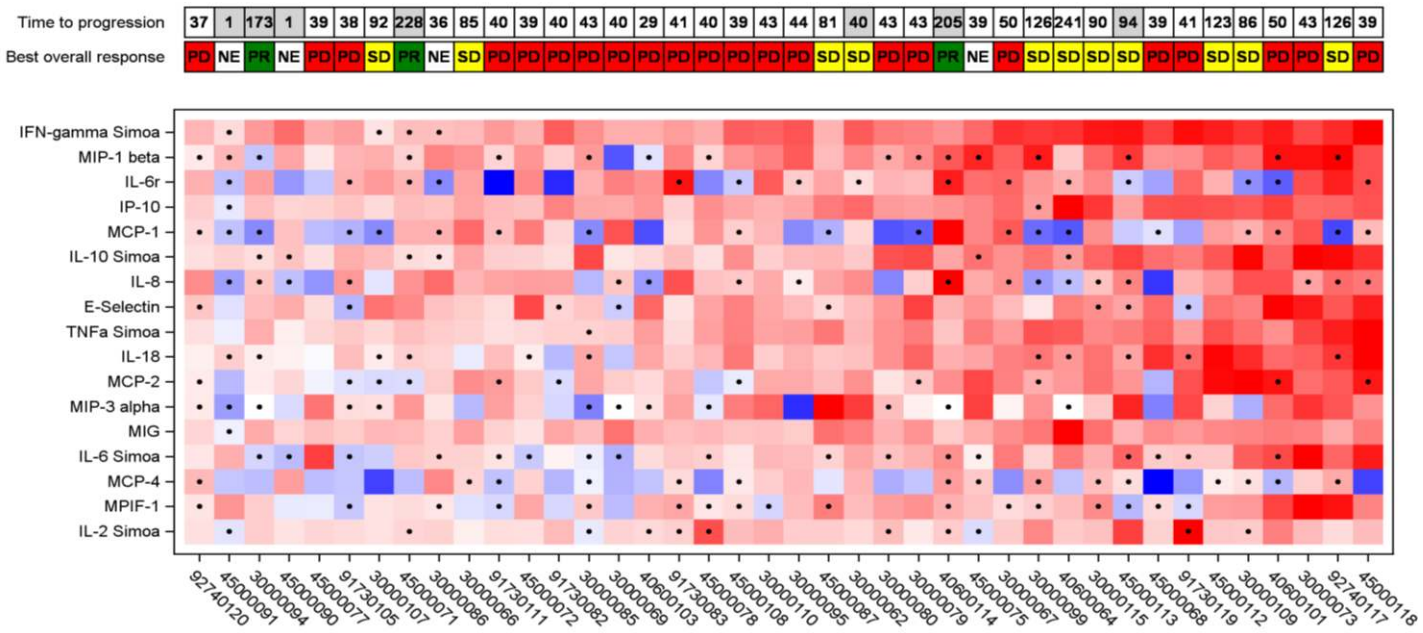
BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

Biomarkers

- Coordinated cytokine increases in blood suggest a treatment-induced systemic immune activation in some patients (**Figure 4**); a trend for more patients with SD was observed in those with greater cytokine induction
- Many patients had CD8 T cells at the tumor periphery at baseline; in some patients, treatment enabled CD8 T cells to infiltrate the tumor (**Figure 5**)

Biomarkers (cont'd)

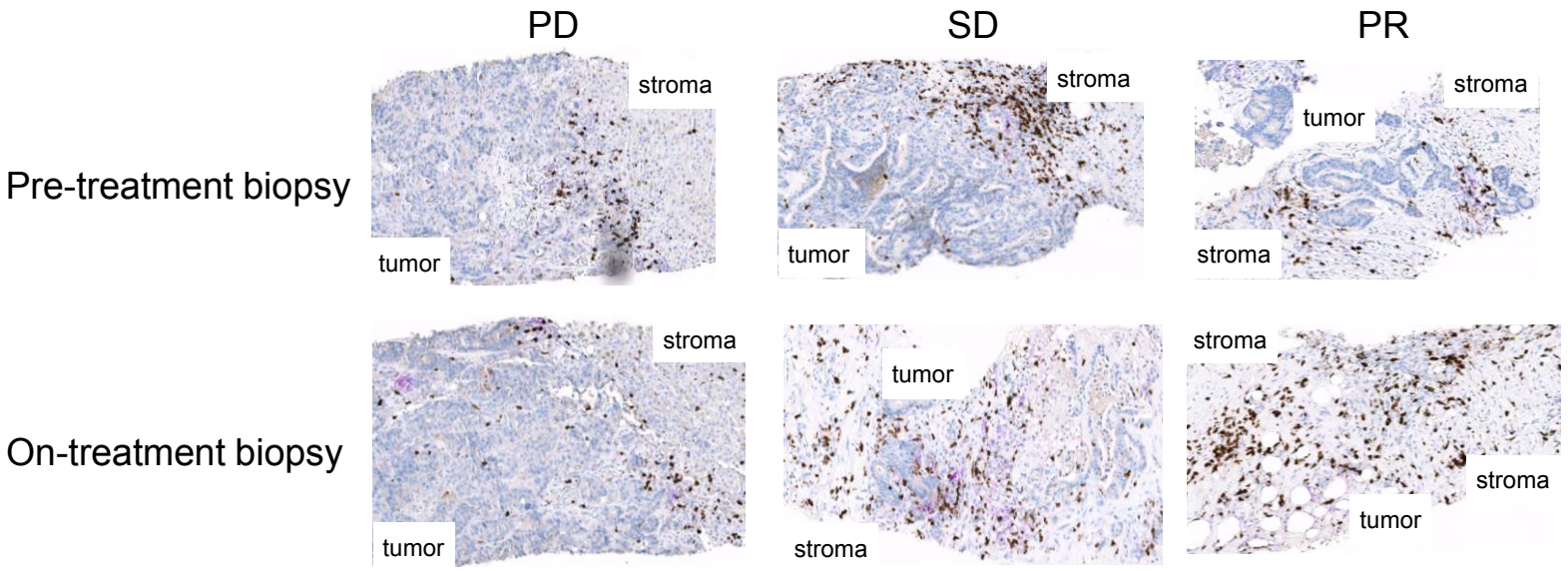
Figure 4. Cytokine measurements in peripheral blood



Maximum absolute change within the 1st treatment cycle (red: increase; blue: decrease). A dot indicates that not all post-baseline values were consistent with the direction of the maximum change. Time to progression: time patients stayed on treatment, grey highlighted values indicate censoring

Biomarkers (cont'd)

Figure 5. Immunohistochemical analysis



For illustration purposes only. One example each of a patient with PD, SD, or PR, respectively, as best response.
On-treatment biopsy taken at Cycle 3, Day 1. Brown: CD8; Purple: PD-L1

Safety

- 24 (60.0%) patients had a TRAE (**Table 3**)
  - Five (12.5%) patients had a G3/4 TRAE; there were no G5 AEs

Table 3. TRAEs (in ≥10% of patients)

	Treated set (N=40)	
N (%)	**All**	**G3/4**
Any drug-related AE	24 (60.0)	5 (12.5)
Fatigue	5 (12.5)	0
Infusion-related reaction	5 (12.5)	0
Hypothyroidism	4 (10.0)	0
Myalgia	4 (10.0)	0
Pruritus	4 (10.0)	0

G, grade; TRAE, treatment-related AE

Safety (cont'd)

- Five (12.5%) patients had AEs leading to discontinuation (all-cause; infusion-related reaction [n=3]; diabetic ketoacidosis [n=1]; and immune-mediated enterocolitis [n=1]
- SAEs (all-cause) occurred in 14 (35.0%) patients; 11 (27.5%) had G3/4 SAEs
  - SAEs occurring in more than one patient were: diabetic ketoacidosis (n=2; both G4) and pleural effusion (n=2; one G2 and one G3)
- Treatment-emergent immune-related AEs are shown in **Table 4**

Safety (cont'd)

Table 4. Treatment-emergent immune-related AEs (in ≥5% of patients)

	Treated set (N=40)	
N (%)	**All**	**G3/4**
Any treatment-emergent immune-related AE	11 (27.5)	5 (12.5)
Infusion-related reaction	5 (12.5)	0
Diabetic ketoacidosis	2 (5.0)	2 (5.0)
Maculo-papular rash	2 (5.0)	2 (5.0)
Myalgia	2 (5.0)	0

SAE, serious AE

Key findings and conclusions

- BI 754111 + BI 754091 combination was well tolerated and showed preliminary activity in patients with previously treated MSS mCRC
  - BI 754111 + BI 754091 resulted in deep and durable responses in some of these patients
- **The trial is open for recruitment in three further cohorts**
  - **Anti-PD-(L)1 pre-treated solid tumors with TMB ≥10 mutations/Mb and/or MSI-H and/or dMMR**
  - **Treatment-naïve *EGFR* and *ALK* wild-type NSCLC**
  - **Anti-PD-(L)1 pre-treated 2nd and 3rd line NSCLC that progressed after having achieved benefit on previous anti-PD-(L)1 therapy**

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