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Preliminary Results of a Phase 1A/1B Study of BGB-A317, an Anti-PD-1 Monoclonal Antibody (mAb), in Patients with Advanced Hepatocellular Carcinoma (HCC)

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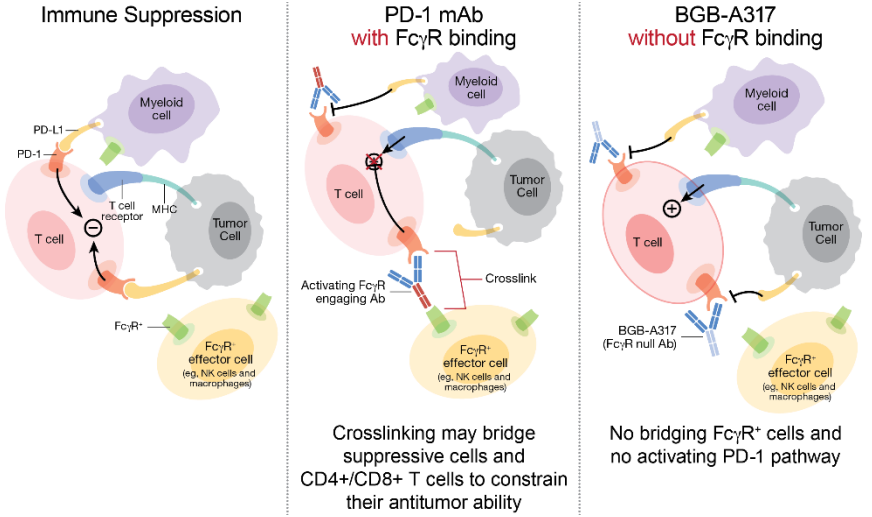
BGB-A317 is a Humanized IgG4 Monoclonal PD-1 Antibody Engineered to Minimize FcγR Binding

- Hepatocellular carcinoma (HCC) is a leading cause of death due to malignancy
  - Sorafenib is the only approved first-line treatment, with modest efficacy and considerable toxicity[1]
- Monoclonal antibodies against the immune checkpoint inhibitory receptor, programmed cell death-1 (PD-1), have demonstrated antitumor activity across multiple malignancies[2], including HCC[3]
- BGB-A317 was specifically engineered to minimize FcγR binding on macrophages to abrogate antibody-dependent phagocytosis, a potential mechanism of T-cell clearance

Figure 1: Lack of FcγR Binging Prevents Macrophage-Mediated T-Cell Clearance



Adapted from Dahan R, et al. *Cancer Cell.* 2015;28:285-295.

1. Samonakis DN, Kouroumalis EA. Systemic treatment for hepatocellular carcinoma: Still unmet expectations. *World J Hepatol.* 2017;9(2):80–90. **2.** Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443–2454. **3.** El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492–2502.

Methods: A Pooled Subset of Patients with Refractory/relapsed HCC Enrolled in a Phase 1A/1B Study

- Previous reports from an ongoing phase 1A/1B study (NCT02407990) of BGB-A317 in patients with advanced solid tumors suggested that BGB-A317 is tolerable; in addition, its toxicity profile demonstrates that adverse events (AEs) are generally of low severity, manageable, and reversible[1]
- Here, we present the preliminary results as of April 28, 2017, of the pooled subset of patients with refractory/relapsed HCC enrolled in this phase 1A/1B study
  - Data presented here are early and immature

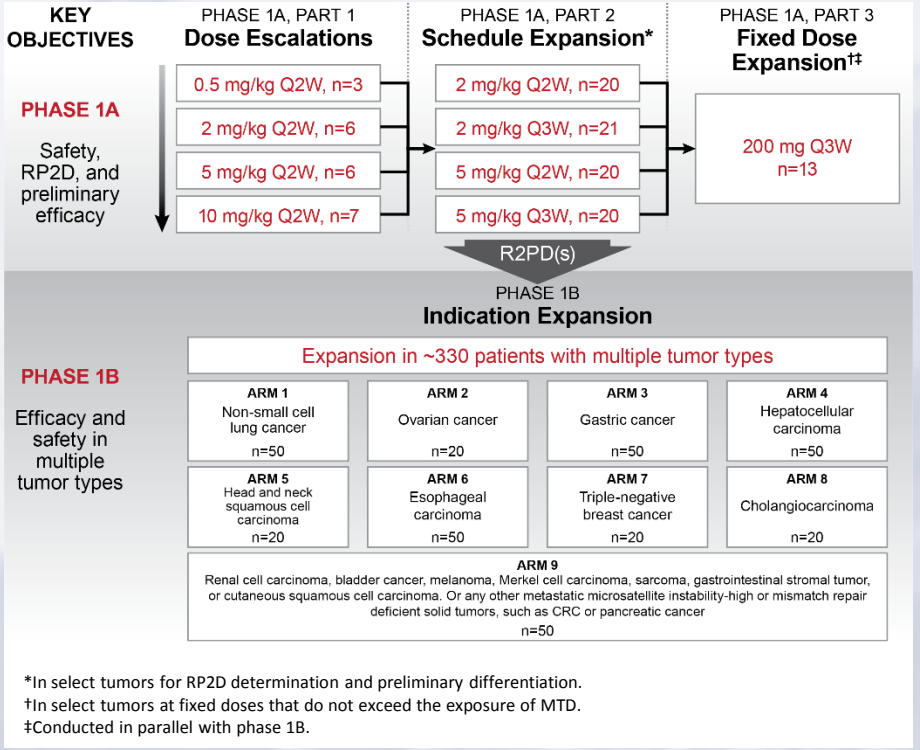
1. Desai J, Markman B, Sandhu SK, et al. Updated safety, efficacy, and pharmacokinetics (PK) results from the phase I study of BGB-A317, an anti-programmed death-1 (PD-1) mAb in patients with advanced solid tumors. *J Immunother Cancer.* 2016;4(Suppl 1):P154.

Study Design

- In phase 1A, 10 mg/kg Q2W was the maximum administered dose; MTD was not reached
- All patients in phase 1B received BGB-A317 as a 5 mg/kg IV infusion Q3W
- Radiographic assessment was every 9 weeks

Key Eligibility of the Pooled HCC Population Subset

- Adult patients (aged ≥18 years) with histologically or cytologically confirmed advanced/metastatic HCC who had not received prior PD-1 or PD-L1 treatment were enrolled
  - Specific inclusion criteria included BCLC stage C or stage B refractory/not amenable to loco-regional therapy, and not amenable to a curative treatment approach, and Child–Pugh A without encephalopathy of any grade
  - Eligible patients must have a HBV viral load <200 IU/mL (~1000 cps/mL) and subjects with active HBV infection need to be on anti-HBV suppression for ≥3 months throughout treatment and for 6 months after
  - Patients with active HCV infection who are untreated are not allowed on study



*In select tumors for RP2D determination and preliminary differentiation.
†In select tumors at fixed doses that do not exceed the exposure of MTD.
‡Conducted in parallel with phase 1B.

BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Results: Patient Demographics and Disease Characteristics

- As of April 28, 2017, 40 patients with advanced HCC, the majority of whom were HBV positive (n=34/40), had enrolled in this study (**Table 1**)
- A total of 24 patients remain on treatment

Table 1. Patient demographics and disease characteristics

		HCC Population (N=40)
Median age, years (min, max)		55.5 (28, 76)
Sex	Male/female	32/8
Race	Asian/White/other	35/3/2
Median treatment duration, days (min, max)		64 (1, 471)
Median number of prior anti-cancer treatment regimens (min, max)		2 (0, 6)
Prior anti-cancer therapy regimens, n*	0	2†
	1	16
	2	12
	≥3	10
Infection status, n	HBV	28
	HCV	2
	HBV/HCV co-infection	6
	No infection	4

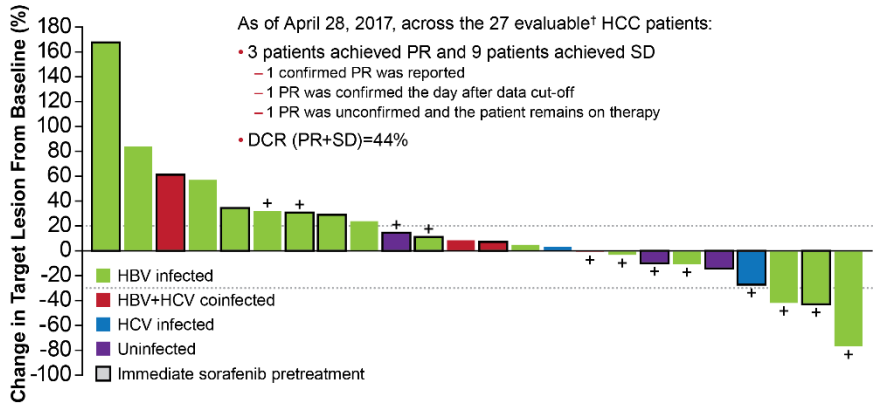
*Only 1 patient was sorafenib naïve;
†Both patients had received sorafenib as adjuvant therapy.

HBV, hepatitis B virus; HCV, hepatitis C virus.

Results: Preliminary Antitumor Activity (1)

- A total of 27 patients were evaluable; 25 had measurable disease and at least 1 evaluable post-baseline tumor assessment; 2 died prior to the 1st scheduled date of tumor assessment

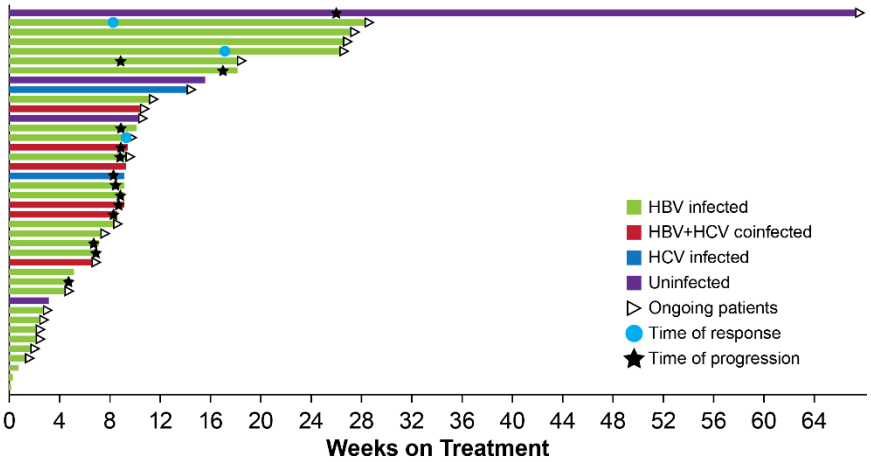
Figure 2: Maximum Tumor Reduction by Hepatitis Infection Status*



+ Indicates patient still on treatment; *Includes 24 of 25 evaluable patients; 1 patient, who progressed due to a new lesion, had no post-baseline target lesion measurement; †Evaluable is defined as a patient who had at least 1 tumor assessment after enrolment on study or had progressed or died prior to the initial tumor assessment after enrollment on study or had progressed or died prior to the initial tumor assessment.

Abbreviations: DCR, disease control rate; PR, partial response; SD, stable disease.

Figure 3: Duration of Treatment and Response

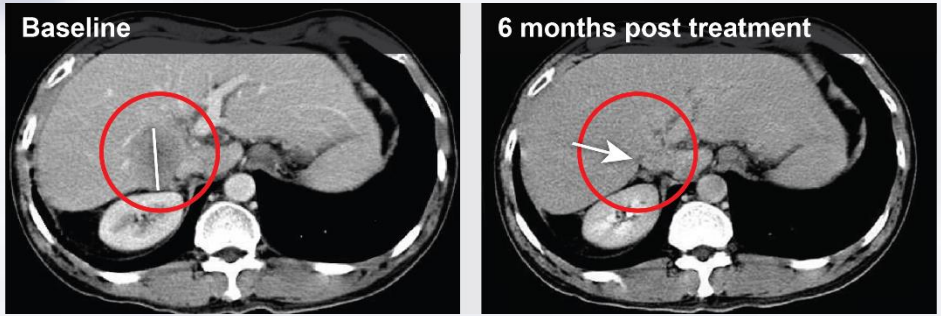


Each line represents an individual patient.

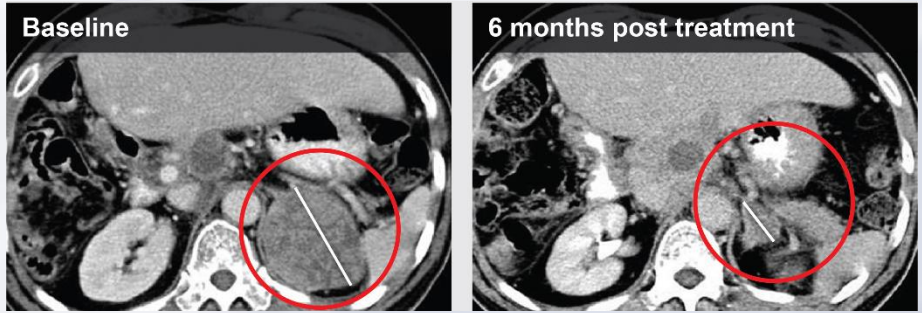
DCR, disease control rate; PR, partial response; SD, stable disease.

Results: Preliminary Antitumor Activity (2)

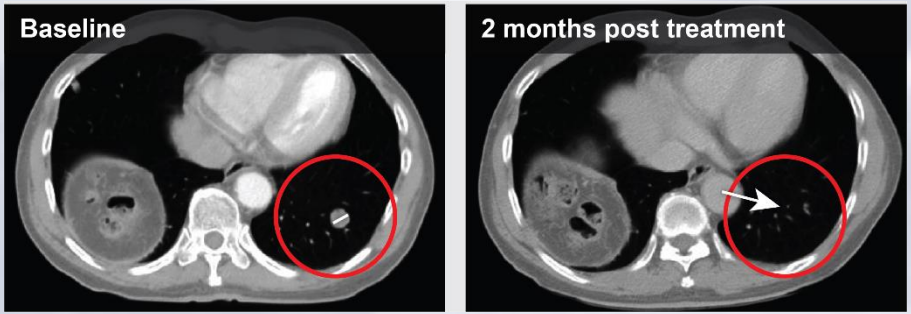
Male patient, 48 years old, lesion site liver
77% overall tumor reduction against baseline, partial response



Male patient, 56 years old, lesion site adrenal metastasis
42% overall tumor reduction against baseline, partial response



Male patient, 71 years old, lesion site lung
45% overall tumor reduction against baseline, partial response



Results: Preliminary Antitumor Activity (3)

- Tumor reductions meeting the definition of “partial response” were observed in 3 patients; all were HBV+ which is associated with poor prognosis (**left panel**)
- Nine patients achieved stable disease, some of whom also had significant reductions in AFP (**right panel**)

Figure 4: Change in Tumor Burden over Time

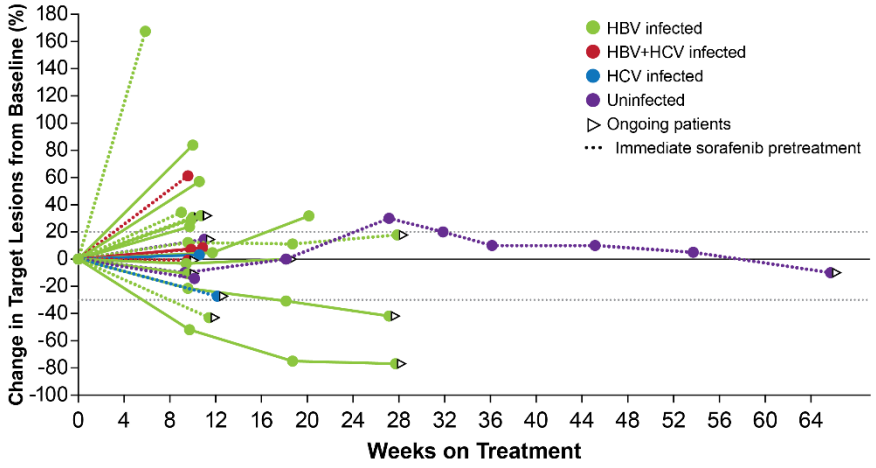
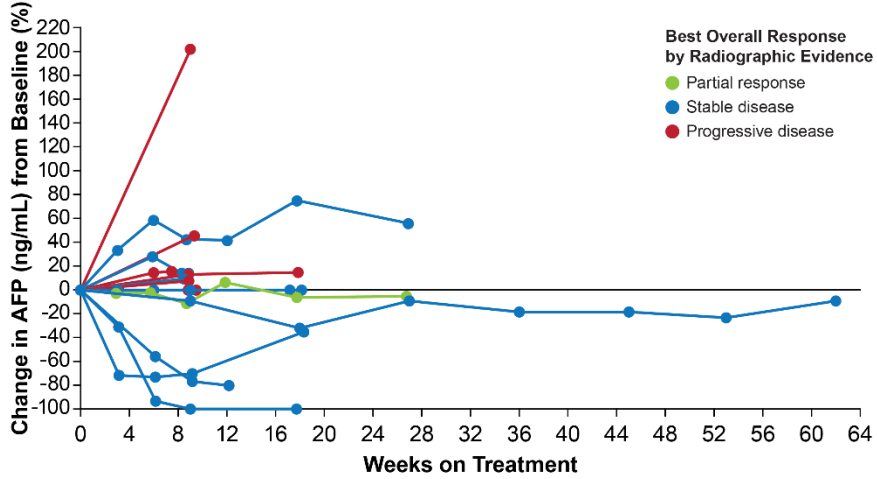


Figure 5: Change in Alpha-Fetoprotein (AFP) from Baseline



AFP, alpha-fetoprotein.

Results: Treatment-related Adverse Events (TRAEs)

- TRAEs occurred in 21 of the 40 patients with HCC (**Table 2**)
  - All but one of these events were grade ≤2
  - The most common events were rash (n=8) and pruritus (n=5)
- Two patients discontinued treatment due to any treatment-emergent AE, one of which was a grade 5 AE considered related to treatment by the investigator:
  - A 49-year-old Asian male with HBV and HCC widely metastatic to brain, liver and lung, developed evidence of progression (disturbed consciousness, abdominal pain, and changes on chest x-ray) shortly following the first and only dose of BGB-A317. The patient died approximately 5 weeks after entering the study, despite treatment with methylprednisolone and entecavir. Viral serology was negative; no autopsy was performed. The cause of death was attributed to acute hepatitis and confounded by rapid disease progression

Table 2. Treatment Related Adverse Events

	HCC Population (N=40)	
AE, n	**All grades**	**Grade ≥3**
Any treatment-related AE	21	1
Rash	8	0
Pruritus	5	0
AST increased	3	0
Fatigue	2	0
Hypothyroidism	2	0
Decreased appetite	2	0
Acute hepatitis*	1	1
ALT increased	1	0
Blood creatine increased	1	0
Blood creatinine increased	1	0
QT prolongation	1	0
Skin reaction	1	0
Chills	1	0
Feeling hot	1	0
Nausea	1	0
Vomiting	1	0
Arthralgia	1	0
Proteinuria	1	0
Cough	1	0
Hypertension	1	0

Bold font indicates events that are possibly immune related.
*Acute hepatitis was fatal (grade 5).

AE, adverse event; HBV, hepatitis B virus; HCV, hepatitis C virus.

Conclusions

- Treatment with BGB-A317 was generally well tolerated in pretreated patients with advanced HCC
  - As of April 28, 2017, in this early report more than half of patients remain on study (n=24/40); median treatment duration is 64 days (range: 1–471 days)
  - Rate of treatment discontinuation due to a treatment-related AE was low (n=1/40)
- Adverse events reported in this cohort were consistent with the overall safety profile observed in the study and were generally of low severity, manageable, and reversible
- Most patients had underlying viral infection (HBV+, n=28; HCV+/HBV+, n=6; HCV+, n=2)
- The preliminary safety profile and antitumor activity support continued development of BGB-A317 in patients with advanced HCC

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