GALLANT-1: GB1211 Galectin-3 (Gal-3) inhibitor plus atezolizumab (atz) for first line treatment in patients (pts) with advanced/metastatic non-small cell lung cancer (NSCLC)

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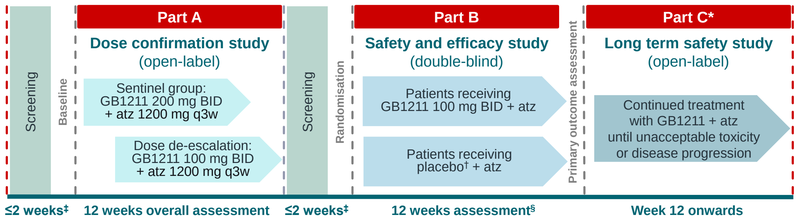
Background

- Galectin-3 (Gal-3) is a lymphocyte activation gene-3 ligand, the expression of which is associated with tumour resistance to checkpoint inhibitors (CPIs).[1]
- In a preclinical study, Gal-3 inhibitor GB1211 restored CPI-binding to their targets in the presence of Gal-3, and enhanced CPI effects in non-small cell lung cancer (NSCLC) mouse models.[2,3]
- Atezolizumab (atz), an anti-programmed death-ligand 1 (PD-L1) monoclonal antibody, is a CPI; response rates of 22–38% have been observed with atz monotherapy in the first-line treatment of advanced NSCLC,[4,5] suggesting there may be a benefit with a GB1211 + atz combination.
- The GALLANT-1 study (NCT05240131) will assess tolerability of the combination GB1211 + atz and whether GB1211 + atz increases anti-tumour effects in patients with advanced or metastatic NSCLC.

Methods

- GALLANT-1 is a Phase IB/IIA study of first line GB1211 + atz in patients with measurable advanced stage 3B/4 or metastatic NSCLC, expressing PD-L1 on at least 50% of tumour cells
  - Concomitant chemotherapy was not permitted
  - The study consists of three parts (**Figure 1**).
- Primary endpoints include safety and tolerability (Parts A, B and C), and tumour shrinkage (Part B only).
- Secondary endpoints include overall response rate (assessed by RECIST 1.1 criteria) and pharmacokinetic measurements.
- Pharmacokinetic serial blood sampling occurred over 12 hours on Days 1 and 21 (6 samples/day) and sparse sampling over 8 hours on Days 42 and 84 (3 samples/day)
  - Plasma concentrations of GB1211 were determined using a high-performance liquid chromatography method with tandem mass spectrometry detection; the lower limit of quantification was 0.500 ng/mL
  - Pharmacokinetic parameters were derived using non-compartmental methods and were compared with data from a first-in-human (FIH) study in healthy volunteers (HV) (NCT03809052) as well as with predictions based on pharmacokinetic data from HV.[6]
- Peripheral immune response was characterised by Chip Cytometry (Canopy Biosciences) at baseline and 12 weeks.
- Here we report data from the ongoing Part A.

Figure 1. GALLANT-1 study design



*Part C includes patients from Parts A and B, who have achieved clinical benefit from the study drug in either Part A or Part B; †Matched to GB1211 dosing; ‡Between Day −14 and Day −1; §Continuation of blinded treatment until the last patient has received 12-weeks of treatment. BID, twice a day; q3w, every three weeks.

Results

Baseline patient demographics

- As of the final data cutoff (30 September 2023), 13 patients have been enrolled: seven patients in the 200 mg cohort and six patients in the 100 mg cohort.
- A total of four patients are currently on treatment and nine patients have discontinued
  - Reasons for discontinuation in the 200 mg cohort include: disease progression (n = 2), adverse events (AEs; n = 3) and withdrawn consent (n = 1)
  - Reasons for discontinuation in the 100 mg cohort include: disease progression (n = 1), AEs (n = 1) and withdrawn consent (n = 1).
- At baseline, the median (range) age was 64 (48–79) years and 10 (76%) patients were male.
- No patients had received treatment for NSCLC stage IIIA or lower.
- Median (range) total weeks on treatment was 14 (6–45) weeks, in evaluable patients only (defined as patients who have had ≥1 post-baseline scan [at Week 6])
  - In the 200 mg cohort, the median (range) total weeks on treatment was 12 (6–45) weeks
  - In the 100 mg cohort, the median (range) total weeks on treatment was 18 (6–36) weeks.

Summary

- This is the first clinical study to show that combining the oral Gal-3 inhibitor GB1211 with atz may enhance the CPI effect
  - Although there is not enough data to determine the exact response rate of atz in this population, there may be a possible benefit with GB1211 + atz, thus further research into the combination is warranted.
- Overall, the safety profile of GB1211 + atz appeared to be manageable, with predominantly Grade 1–2 TEAEs observed
  - The severe skin reactions observed may indicate lymphocyte activation, in line with the GB1211 mode of action; as these skin rashes were not observed in the 100 mg group, there may be a therapeutic window.
- In this initial analysis, four patients achieved a PR (4/10; 40%), three of which were in the 100 mg recommended Phase II dose cohort (3/5; 60%), indicating that there appears to be a potential benefit to the GB1211 + atz combination.
- Pharmacokinetics were predictable and consistent with simulations based on the FIH study in HV and in patients with NSCLC.

Safety

- Treatment-emergent AEs (TEAEs) in the 200 mg and 100 mg cohorts are shown in **Table 1**.
- A total of eight serious AEs (SAEs) were observed: six SAEs in the 200 mg cohort (n = 7) and two SAEs in the 100 mg cohort (n = 6) (**Table 2**).
  - The reason for qualifying as an SAE was hospitalisation in seven cases and prolonged hospitalisation in one case
  - Four SAEs were Grade 2 and four were Grade 3–4; no Grade 3–4 events were seen in the 100 mg cohort
  - No SAEs were deemed related to GB11211 only.
- After two weeks of therapy, two severe (Grade 3–4) immune-related skin rashes were observed: pemphigus deemed related to atz, and perivascular lymphocytic infiltration deemed related to GB1211 + atz
  - Both responded well to steroids
  - Per protocol, based on the two immune-related skin rashes, it was recommended by the safety data monitoring board that the study continue but with a reduced dose (100 mg BID).

Table 1. TEAEs observed during Part A of GALLANT-1

Patients with at least one of the following, n	200 mg cohort (n = 7)	100 mg cohort (n = 6)
TEAE	64	34
Serious	7	2
GB1211-related*	17	12
Serious GB1211-related*	2	0
Grade 1	33	20
Grade 2	24	13
Grade ≥3	7	1
Leading to study drug discontinuation	4	0
Fatal	0	0

*As assessed by the investigator.

Table 2. SAEs observed during Part A of GALLANT-1

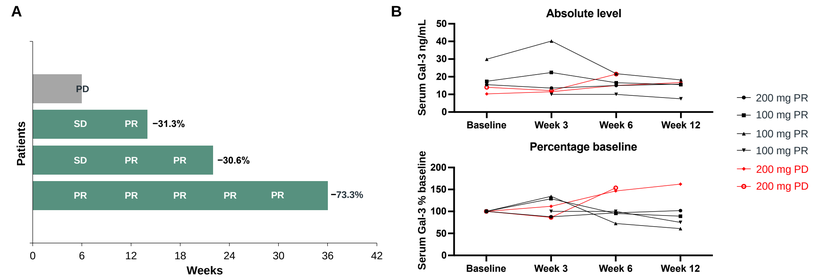
AE TERM (Days since onset after 1st dose)	Grade	Relationship		Action study drug	Outcome (days since onset)
		GB1211	atz		
Major malnutrition (41)	3	No	No	GB1211 interrupted	Recovered (8)
Streptococcus urinary tract infection (13)	2	No	No	GB1211 interrupted	Recovered (10)
Autoimmune pemphigus (13)	3	No	Yes	Discontinued	Recovered (17)
Bone marrow hypocellularity (33)	4	Yes	Yes	NA	Ongoing*
Ischaemic stroke (82)	2	No	No	NA	Not recovered
Skin toxicity (9)	4	Yes	Yes	Discontinued	Recovered (25)
Pulmonary infection (18)†	2	No	No	GB1211 interrupted	Recovered (13)
Weakness (8)†	2	No	No	No action to study drug	Recovered (4)

*Weekly thrombocyte infusion; †100 mg cohort. NA, not applicable.

Efficacy

- The best response for the evaluable patients in the 100 mg cohort are shown in **Figure 2A**
  - In the 200 mg cohort, 4/7 patients were not evaluable due to withdrawn consent (n = 2), skin toxicity and urinary tract infection/skin toxicity (n = 1 each)
  - In the 100 mg cohort, 2/6 patients were not evaluable due to withdrawn consent and being withdrawn due to AEs (n = 1 each).
- Excluding three patients who withdrew their consent, 4/10 (40%) patients achieved a response across both cohorts; in the 100 mg recommended Phase II dose cohort, five patients had measurable disease at baseline and ≥1 subsequent scan, and three of these five patients (60%) achieved a response
  - Four patients achieved a partial response (PR): one in the 200 mg cohort (at Week 18), and three in the 100 mg cohort (one at Week 6, two at Week 12; **Figure 2A**); all responses are ongoing, with a median (range) duration of response of 29 (14–45) weeks
  - Three patients had progressive disease (PD): two in the 200 mg cohort (one at Week 6 and one at Week 12, after achieving stable disease [SD] at Week 6), and one in the 100 mg cohort (Week 6).
- Despite some variability at baseline, where trends for increased serum Gal-3 at baseline were observed for responders (n = 4), the percentage change indicates that patients with PR had stable or declining serum Gal-3, while those who progressed had increased serum Gal-3 (**Figure 2B**).

Figure 2. Best response at each timepoint in evaluable patients in the 100 mg cohort (A) and serum Gal-3 levels recorded at baseline and Weeks 3, 6 and 12 (B)



Percentages after the bars represent changes in tumour size from baseline to the most recent scan.

Pharmacokinetics

- The pharmacokinetics of GB1211 in combination with atz in patients with NSCLC was not altered when comparing with HV from the FIH study (**Table 3**).
- Steady-state plasma exposure and accumulation at 100 mg BID were similar between patients with NSCLC and HV at the same dose from the FIH study.
- Steady-state plasma exposure at 200 mg BID in patients with NSCLC was as expected and was consistent with pharmacokinetic simulations based on the FIH study at 100 mg BID in HV and in patients with NSCLC.

Table 3. Comparison between geometric mean (geometric mean CV%) plasma exposure pharmacokinetic parameters of GB1211 in GALLANT-1 Part A (patients with NSCLC) and in the FIH study (HV)

	FIH study[3]			GALLANT-1 Part A		FIH study[3]	GALLANT-1 Part A	
	HV			NSCLC		HV	NSCLC	
	100 mg single dose	100 mg BID Day 1	100 mg BID Day 21	100 mg BID Day 1	100 mg BID Day 21	200 mg single dose	200 mg BID Day 1	200 mg BID Day 21
AUC_{last}* (h.ng/mL)	5910 (18.8)	-	-	3640 (113)	6820 (95.0)	11500 (36.5)	7380 (33.2)	14900 (26.2)
AUC_{tau}† (h.ng/mL)	-	3560 (42.9)	7530 (21.1)	5360 (63.7)	6820 (95.0)	-	8050 (33.5)	14900 (26.2)
C_{max} (ng/mL)	525 (23.6)	546 (53.5)	975 (21.9)	620 (54.9)	905 (72.5)	1010 (54.1)	1290 (42.7)	2080 (14.5)
RA_{AUCtau}‡	-	-	2.11 (31.4)	-	1.79 (17.1)	-	-	1.69 (14.1)
RA_{Cmax}‡	-	-	1.79 (39.6)	-	1.67 (13.2)	-	-	1.38 (29.7)

*Up to 48 hours for SD, up to 12 hours for BID; †Up to 12 hours; ‡RAtio between Day 1 and Day 10 (FIH study) or between Day 1 and Day 21 (GALLANT-1). AUC_{last}, area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; AUC_{tau}, area under the plasma concentration-time curve over a dosing interval (12 hours); C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; RA_{AUCtau}, accumulation ratio based on AUC_{tau}; RA_{Cmax}, accumulation ratio based on C_{max}.

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