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Preliminary Results From KEYNOTE-A36, a Study of GB1275, a First-in-Class, Oral CD11b Modulator, Alone and With Pembrolizumab or Chemotherapy in Specified Advanced Solid Tumors

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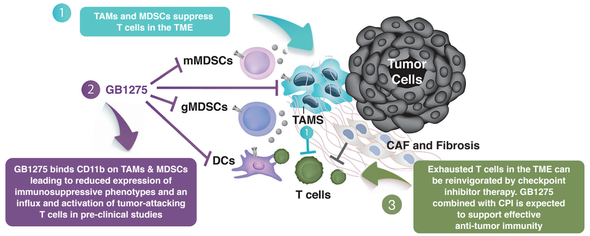
INTRODUCTION

- Tumor influx of CD11b-expressing myeloid-derived suppressor cells (MDSCs) and M2 tumor-associated macrophages (TAMs) creates an immunosuppressive tumor microenvironment (TME) associated with resistance to anti-PD-1 antibody therapy[1-3]
- GB1275 is a first-in-class, CD11b modulator that reduced MDSCs and TAMs at the tumor site, repolarized M2 immunosuppressive TAMs towards an M1 phenotype, and thus increased tumor infiltration of activated CD8+ T cells in preclinical models in vivo[4] (**Figure 1**)
- Preclinical anti-tumor activity was seen with GB1275 as a single agent and synergistically in combination with chemotherapy and immuno-oncology therapies[4]
- GB1275 plus pembrolizumab is hypothesized to address myeloid cell immune suppression and T cell exhaustion in the TME, enhancing anti-tumor response in checkpoint inhibitor-resistant tumors
- We report interim results from Phase 1 dose escalation of a first-in-human study (NCT04060342)

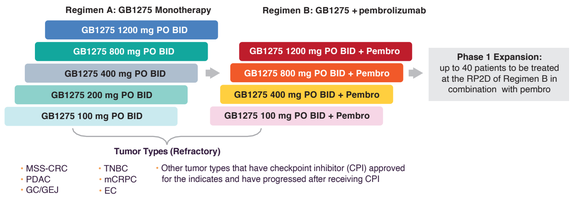
Figure 1. GB1275 mechanism of action: CD11b modulation is a novel MDSC / TAM-targeting approach



METHODS

- Phase 1 dose escalation using a 3+3 design was conducted with Regimen A (GB1275 monotherapy) initiated first; Regimen B (GB1275 + pembrolizumab) commenced after completion of the first two cohorts of Regimen A (**Figure 2**)
- Patients were at least 18 years of age, ECOG PS 0 or 1, and had prespecified refractory tumors
- GB1275 was given orally at escalating dose levels, alone or with pembrolizumab 200 mg IV every 3 weeks
- Once a recommended Phase 2 dose (RP2D) of Regimen B is determined, up to 40 patients will be enrolled into Phase 1 expansion to be treated at the RP2D in combination with pembrolizumab

Figure 2. Phase 1 dose escalation and expansion schema



CPI, checkpoint inhibitor; GC, Gastric cancer; GEJ, gastroesophageal junction; MSS-CRC, microsatellite stable-colorectal cancer; TNBC, triple negative breast cancer; mCRPC, metastatic castrate-resistant prostate cancer; PDAC, adenocarcinoma of the pancreas; EC, esophageal cancer.

- Study endpoints:
  - Safety: Dose-limiting toxicity during the first 21-day cycle, adverse events (AEs)
  - Pharmacokinetic (PK) profile
  - Treatment response: Tumor assessment by RECIST 1.1 every 2 cycles (~every 42 days for Regimens A & B)
  - Pharmacodynamics: Serial blood and tumor samples were collected for PK and biomarker analyses (**please see poster #389**)

RESULTS

Disposition and Baseline Characteristics

- As of September 22, 2020, 40 patients were treated in Regimen A or B in the dose escalation study; baseline characteristics are summarized in **Table 1**

Table 1. Baseline Demographics and Disease Characteristics

	Regimen A: GB1275 Monotherapy	Regimen B: GB1275 + Pembrolizumab	
	All (n = 23)	All (n = 17)	Overall (N = 40)
Age, yr	60 (37,78)	69 (39,79)	63.5 (37,79)
Male	12 (52)	9 (53)	21 (53)
Prior therapy			
< 3	8 (35)	3 (18)	11 (28)
≥ 3	15 (65)	14 (82)	29 (72)
Prior I-O	6 (26)	8 (47)	14 (35)
CPI	4 (17)	7 (41)	11 (28)

I-O, immuno-oncology therapy; CPI, checkpoint inhibitor
Continuous data are presented as median (range); categorical data are presented as n (%).

Safety

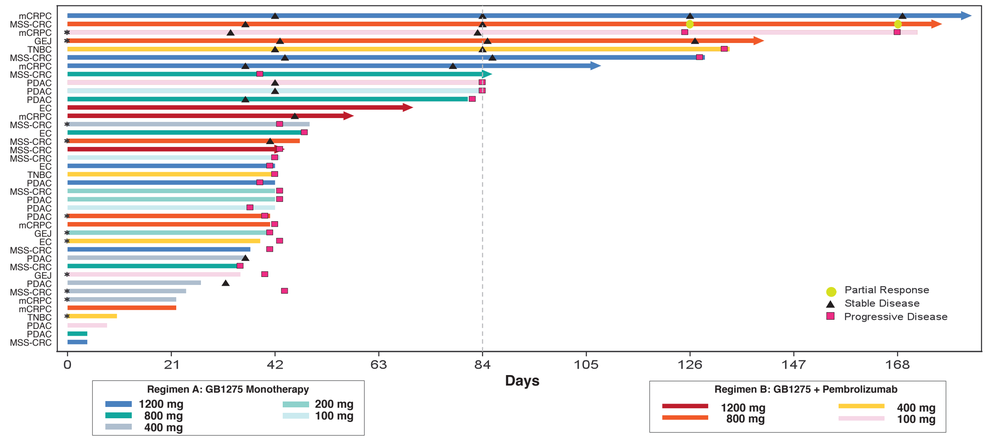
- No dose-limiting toxicity has been reported
- Most frequently reported treatment-emergent AEs (>10%) were grade 1 or 2 and primarily related to underlying disease (**Table 2**)
- GB1275-related AEs were reported in 52.5% of patients; most frequently reported (>10%) were dysaesthesia (15%) and photosensitivity reaction (15%), most were Grade 1 and did not require medical intervention
- AEs considered to be related to pembrolizumab were also considered related to GB1275
- Incidence of immune-related AE was low: one patient in Regimen B required steroid treatment

Table 2. Treatment-Emergent (>10%) Adverse Events Regardless of Causality

n (%)	Overall (N=40)	Grade 1	Grade 2
Diarrhea	8 (20.0)	6 (15.0)	2 (5.0)
Decreased appetite	7 (17.5)	6 (15.0)	1 (2.5)
Dehydration	7 (17.5)	4 (10.0)	3 (7.5)
Dysaesthesia	7 (17.5)	7 (17.5)	0
Photosensitivity reaction	7 (17.5)	6 (15.0)	1 (2.5)
Nausea	6 (15.0)	4 (10.0)	2 (5.0)
Abdominal pain	5 (12.5)	2 (5.0)	3 (7.5)
Creatinine increased	5 (12.5)	5 (12.5)	0
Constipation	5 (12.5)	3 (7.5)	2 (5.0)
Dyspnoea	5 (12.5)	3 (7.5)	2 (5.0)
Oedema peripheral	5 (12.5)	4 (10.0)	1 (2.5)
Weight decreased	5 (12.5)	3 (7.5)	2 (5.0)

Clinical Activity

Figure 3. Exposure and anti-tumor activity by RECIST



GC, Gastric cancer; GEJ, gastroesophageal junction; MSS-CRC, microsatellite stable-colorectal cancer; TNBC, triple negative breast cancer; mCRPC, metastatic castrate-resistant prostate cancer; PDAC, adenocarcinoma of the pancreas; EC: esophageal cancer

*Indicates prior CPI treatment; Data as of 14 October 2020.

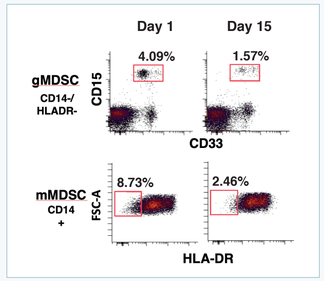
- 12 patients had an initial RECIST assessment of SD; median duration of treatment: 102.5 days
  - Prolonged SD (> 84 days) was noted in 7 patients with MSS CRC, mCRPC, TNBC, or GC (3 in Regimen A, 4 in Regimen B); 5 of 7 involved GB1275 doses ≥ 800 mg BID
- Disease control was observed in Regimen B patients who had received prior checkpoint inhibitor therapy (**see patient case report #2 and #3**)
- One MSS CRC patient had a partial response, starting on Study Day 126

Case Reports

1 Patient with MSS CRC achieved partial response starting on Study Day 126, continuing study treatment

- 62-year-old female with stage IV rectal cancer at initial diagnosis, received 5 prior lines of therapy. MSS status was confirmed by next generation sequencing prior to initiating the last regimen
- Patient received Regimen B: GB1275 800 mg PO BID + pembrolizumab
- A partial response was noted starting on Study Day 126 and confirmed on Study Day 168
- Patient continues to receive study treatment
- Peripheral MDSC reduction noted on study Day 15 (**Figure 4**)

Figure 4. Change in peripheral MDSC in MSS-CRC patient who achieved a partial response



2 Patient with mCRPC who progressed on prior atezolizumab was on study treatment for 172 days

- 79-year-old male with mCRPC, Gleason score 5 at initial diagnosis, prostate specific antigen (PSA) 3730 ng/mL at study entry, received > 10 prior lines of treatment, progressive disease to atezolizumab (was on treatment for ~2 months)
- Initiated Regimen B: GB1275 100 mg PO BID + pembrolizumab
- Best response was stable disease, maximum reduction of PSA 52% on Study Day 41
- Patient discontinued study treatment after 8 cycles due to radiographic progression

3 Patient with gastric cancer who progressed on prior pembrolizumab in combination with bavituximab has stable disease for >126 days, continuing study treatment

- 75-year-old female with stage IV gastric cancer (fundus) at initial diagnosis, received 2 prior treatment lines, with progressive disease to the last regimen of pembrolizumab and bavituximab (on treatment < 3 months)
- Initiated Regimen B: GB1275 800 mg PO BID + pembrolizumab
- Best response was stable disease with last tumor assessment prior to the data cut performed at Study Day 127
- Patient continues to receive study treatment

CONCLUSIONS

- Clinical safety data to date suggest that GB1275 alone and combined with pembrolizumab (up to 1200 mg PO BID) is well tolerated; the maximum tolerated dose of GB1275 has not been reached
- No significant overlapping toxicities between GB1275 and pembrolizumab were observed, suggesting that GB1275 can be safely combined with pembrolizumab
- Encouraging anti-tumor activity, particularly at GB1275 doses ≥ 800 mg BID, was seen in tumor types that are known to be less responsive to CPI, i.e.,TNBC, CRPC, MSS CRC or GC
- Biological activity (peripheral MDSC, gene and protein modulation in the blood and TILs, and CD8+ T cell changes in tumor tissue) was observed with GB1275 alone and in combination with pembrolizumab, supporting the mechanism of action of GB1275 in modulating myeloid cell biology in the TME, potentially to enhance anti-tumor response when it is combined with a checkpoint inhibitor (**please see poster #389**)
- These findings will be further verified during the phase 1 expansion study once the RP2D of GB1275 in combination with pembrolizumab is determined

REFERENCES

1. Fleming V, et al. *Front Immunol.* 2018; 9:398.
2. Kumar V, et al. *Trends Immunol.* 2016; 37(3):208-220.
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4. Panni R, et al. *Sci Transl Med.* 2019; 11: eaau9240.

DISCLOSURES

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