Safety and Pharmacokinetic Profile from a Phase 1 Trial of BGB-Dinutuximab Beta-101 as Maintenance Therapy in Pediatric Patients with High-Risk Neuroblastoma in China

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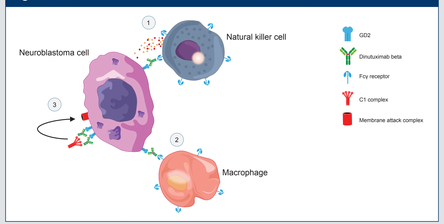
Conclusions

- **Dinutuximab beta in combination with 13-cis-retinoic acid (13-cis-RA) demonstrated an acceptable and manageable safety profile as maintenance therapy in pediatric patients with high-risk neuroblastoma in China**
- **The safety profile of dinutuximab beta in combination with 13-cis-RA was consistent with the known risks of each treatment agent, no new safety signal was identified**
- **The pharmacokinetic data for dinutuximab beta supports the implementation of this regimen in Chinese patients with high-risk neuroblastoma**

Background

- Neuroblastoma is the most common extracranial pediatric solid tumor, representing 8%–10% of childhood tumors and ~15% of pediatric malignancy-related deaths[1-3]
- Disialoganglioside 2 (GD2) has restricted expression in normal tissues; overexpression of GD2 on neuroblastoma cells contributes to tumor development and malignant phenotypes[4]
- Dinutuximab beta is a chimeric anti-GD2 monoclonal antibody approved as maintenance treatment in Europe and China (conditional) for patients ≥12 months with high-risk neuroblastoma who achieved at least partial response after standard-of-care therapy[5-6]
- Binding of dinutuximab beta to GD2 activates immune system effector mechanisms, leading to neuroblastoma cell death (**Figure 1**)
- Isotretinoin, also known as 13-cis-RA, has been shown to promote terminal differentiation of neuroblastoma cells *in vitro* and improve survival of patients with neuroblastoma in clinical trials[7-8]
- This phase 1 trial aimed to evaluate the safety and pharmacokinetics of dinutuximab beta in combination with 13-cis-RA as maintenance therapy in pediatric Chinese patients with high-risk neuroblastoma, to support the regimen implementation in China

Figure 1. Dinutuximab Beta Mechanism of Action



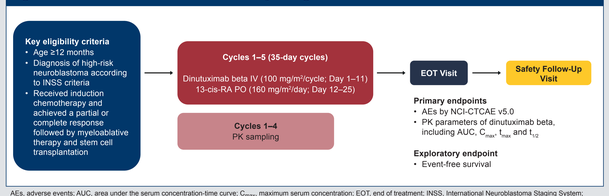
1. Binding of dinutuximab beta to GD2 results in antibody dependent cell-mediated cytotoxicity and neuroblastoma cell lysis by natural killer cells.
2. Dinutuximab beta causes fc-dependent phagocytosis and lysosomal degradation of neuroblastoma cells by macrophages.
3. Antibody-mediated complement fixation results in complement dependent cytotoxicity via formation of the membrane attack complex.

C1, complement component 1; GD2, disialoganglioside 2; Fcγ, Fc-gamma.

Methods

- BGB-dinutuximab beta-101 (NCT05373901) was an open-label, multi-center, single-arm, phase 1 study evaluating the safety and pharmacokinetics of dinutuximab beta in combination with 13-cis-RA as maintenance therapy in pediatric patients with high-risk neuroblastoma in China
- Key eligibility criteria, treatment and endpoints are summarized in **Figure 2**
- Safety was analyzed in patients who received ≥1 dose of the study drug
- Pharmacokinetic analysis of blood samples was performed for all patients included in the safety analyses

Figure 2. BGB-Dinutuximab Beta-101 Study Design



AEs, adverse events; AUC, area under the serum concentration-time curve; C_{max}, maximum serum concentration; EOT, end of treatment; INSS, International Neuroblastoma Staging System; IV, intravenously; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PK, pharmacokinetic; PO, orally; 13-cis-RA, 13-cis-retinoic acid; $t_{1/2}$, half-life; t_{max}, time to maximum serum concentration; v, version.

Results

Patients and Treatment

- As of July 19, 2023, 8 patients were enrolled; all completed study treatment
- Median study follow-up was 205.0 days
- The median age of patients was 5.0 years; 75% were male (**Table 1**)
- All patients received systemic therapy, radiotherapy, myeloablative therapy, and autologous stem cell transplantation prior to study entry, and did not have metastatic disease at study entry (**Table 1**)

Table 1. Patient Demographics and Disease History

Characteristics	Dinutuximab Beta + 13-cis-RA (N=8)
Male, n (%)	6 (75.0)
Median age, years	5.0
Min, Max	3.0, 7.0
Median BMI, kg/m²	14.5
Min, Max	13.3, 15.9
Median Lansky Play-Performance Scale	100
Min, Max	100, 100
Morphology at study entry, n (%)	
Neuroblastoma poorly differentiated	7 (87.5)
GNB nodular	1 (12.5)
Metastatic disease at study entry, n (%)	
No	8 (100)
Metastatic disease before study entry, n (%)	
Yes	7 (87.5)
No	1 (12.5)
Median time from initial diagnosis of metastatic disease to first dose date, months	14.6
Min, Max	9.2, 21.3
INSS stage at study entry, n (%)	
Phase 3	1 (12.5)
Phase 4	7 (87.5)
Location(s) of metastases before study entry, n (%)[a]	
Bone	6 (75.0)
Liver	1 (12.5)
Lymph node	4 (50.0)
Other	1 (12.5)
Adrenal, renal, inferior vena cava	1 (12.5)
Median number of prior systemic therapy regimens (range)	7 (5–9)
Best overall reponse from last prior systemic therapy, n (%)	
Complete response	7 (87.5)
Partial response	1 (12.5)

[a]A patient could have multiple metastatic sites.
BMI, body mass index; GNB, ganglioneuroblastoma; INSS, International Neuroblastoma Staging System; Max, maximum; Min, minimum; 13-cis-RA, 13-cis-retinoic acid.

Safety of Dinutuximab Beta + 13-cis-RA

- Median duration of exposure to both dinutuximab beta and 13-cis-RA was 180.0 days
- Median relative dose intensity per cycle was 99.7% and 90.9% for dinutuximab beta and 13-cis-RA, respectively
- Safety data are summarized in **Table 2**
- All patients experienced ≥1 treatment-emergent adverse event (TEAE) and ≥1 treatment-related adverse event (TRAE)
- The most common TEAEs were abdominal pain and pyrexia (both 100%), decreased appetite (87.5%), and rash, diarrhea and alanine aminotransferase increased (75.0% each)
- The most common TRAEs were abdominal pain (87.5%), diarrhea, rash, and decreased appetite (75.0% each)
- No AEs led to death or treatment discontinuation
- All patients experienced ≥1 Grade ≥3 TEAE, the most common were pyrexia (50.0%) and neutrophil count decreased (37.5%) (**Table 3**)
- Grade ≥3 TRAEs were recorded for 87.5% of patients, the most common were also pyrexia (50.0%) and neutrophil count decreased (37.5%)
- One patient had serious TEAEs of pneumonia and decreased appetite; however, these were not considered to be treatment-related

Table 2. Safety Overview of Dinutuximab Beta + 13-cis-RA

Patients, n (%)	Dinutuximab Beta + 13-cis-RA (N=8)
With any TEAE	8 (100)
Grade ≥3	8 (100)
Serious	1 (12.5)
Leading to death	0 (0)
Leading to treatment discontinuation	0 (0)
Leading to treatment modification	8 (100)
Dose interruption	6 (75.0)
Dinutuximab beta	6 (75.0)
13-cis-RA	3 (37.5)
Dose reduction	3 (37.5)
Dinutuximab beta	0 (0)
13-cis-RA	3 (37.5)
Dose delay	3 (37.5)
Dinutuximab beta	2 (25.0)
13-cis-RA	1 (12.5)
Infusion rate decrease of dinutuximab beta	6 (75.0)
With any TRAE	8 (100)
Serious	1 (12.5)
Grade ≥3	7 (87.5)
Related to dinutuximab beta	8 (100)
Related to 13-cis-RA	8 (100)
Infusion-related reactions	5 (62.5)
Grade ≥3 infusion-related reactions[a]	3 (37.5)

Adverse events were graded for severity using NCI-CTCAE v5.0.
[a]All Grade ≥3 infusion-related reactions were due to pyrexia.
NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; 13-cis-RA, 13-cis-retinoic acid; TRAE, treatment-related adverse event; v, version.

Table 3. Grade ≥3 TEAEs by Preferred Term

Patients, n (%)	Dinutuximab Beta + 13-cis-RA (N=8)
Patients With Any Grade ≥3 TEAE	8 (100)
Pyrexia	4 (50.0)
Neutrophil count decreased	3 (37.5)
C-reactive protein increased	1 (12.5)
Gamma-glutamyltransferase increased	1 (12.5)
Platelet count decreased	1 (12.5)
Anemia	1 (12.5)
Neutropenia	1 (12.5)
Thrombocytopenia	1 (12.5)
Catheter site infection	1 (12.5)
Myringitis	1 (12.5)
Diarrhea	1 (12.5)
Hypokalemia	1 (12.5)
Urticaria	1 (12.5)

Adverse events were classified based on MedDRA v25.0 and graded for severity using NCI-CTCAE v5.0.
MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event; 13-cis-RA, 13-cis-retinoic acid; v, version.

Pharmacokinetics of Dinutuximab Beta in Cycle 1

- The pharmacokinetic parameters of dinutuximab beta following 10-day consecutive infusion at 10 mg/m²/day are summarized in **Table 4**
- The geometric mean (geometric coefficient of variation %) area under the curve and maximum serum concentration for dinutuximab beta were 3956.3 h*μg/mL (33.11) and 13.49 μg/mL (32.69), respectively
- The geometric mean (minimum, maximum) half-life for dinutuximab beta was 253.9 hours (200, 332)

Table 4. Summary of Dinutuximab Beta Pharmacokinetic Parameters

Parameter	AUC_{0-t} (h*μg mL)	$AUC_{0-\infty}$ (h*μg/mL)	C_{max} (μg/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL (mL/h)	V_z (mL)	V_{ss} (mL)
n	8	8	8	8	8	8	8	8
Mean	4155.9	4426.9	14.15	NA	NA	18.00	6838.2	3790.3
SD	1502.36	1542.21	4.971	NA	NA	5.454	2627.13	1250.82
CV (%)	36.15	34.84	35.134	NA	NA	30.301	38.42	33.00
Median	3532.5	3807.0	12.57	240.4	NA	18.85	7322.2	4019.0
Min	2932	3044	10.1	168	200	9.8	2999	1980
Max	6884	7264	23.4	252	332	25.6	9836	5654
Geometric mean	3956.3	4228.6	13.49	NA	253.9	17.19	6295.9	3594.0
Geometric CV (%)	33.11	31.94	32.682	NA	NA	34.627	48.87	37.12

Geometric mean was calculated as the exponential of the arithmetic mean for parameters of study drug in the logarithmic scale.
Geometric CV (%) = sqrt(exp(S2) - 1) x 100, where S2 was the sample variance for parameters of study drug in the logarithmic scale.
AUC_{0-t}, area under the serum concentration-time curve from zero to the last measurable concentration; $AUC_{0-\infty}$, area under the serum concentration-time curve from zero to infinity; C_{max}, maximum serum concentration; CL, clearance; CV, coefficient of variation; exp, exponential; NA, not applicable; SD, standard deviation; sqrt, square root; $t_{1/2}$, half-life; t_{max}, time to maximum serum concentration; V_{ss}, volume of distribution at steady state; V_z, volume of distribution during terminal phase.

Event-Free Survival

- There were no events of disease progression, deaths, relapses, or secondary malignancy observed during the study

References

1. Papaioannou G and McHugh K. *Cancer Imaging*. 2005;5(1):116-127.
2. Colon NC and Chung DH. *Adv Pediatr*. 2011;58(1):297-311.
3. Whittle SB et al. *Expert Rev Anticancer Ther*. 2017;17(4):369-386.
4. Nazha B et al. *Front Oncol*. 2020;10:1000.
5. BeiGene. BeiGene and EUSA Pharma Announce China NMPA Approval of QARZIBA® (Dinutuximab Beta) for Patients with High-Risk Neuroblastoma. Available at https://hkexir.beigene.com/news/beigene-and-eusa-pharma-announce-china-nmpa-approval-of-qarziba-dinutuximab-beta-for-patients-with/6caa8fc9-986d-4ff3-9fc9-bf9f6072d571/. Accessed July 2024.
6. European Medicines Agency. Qarziba (previously Dinutuximab beta EUSA and Dinutuximab beta APEIRON Biologics). Available at https://www.ema.europa.eu/en/medicines/human/EPAR/qarziba#authorisation-details-section. Accessed July 2024.
7. Bayeva N et al. *J Pers Med*. 2021;11(3):211.
8. Matthay KK et al. *N Engl J Med*. 1999;341(16):1165-1173.

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Presenter Disclosures

Qiang Zhao has no conflicts of interest to report.

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