INTERNATIONAL, MULTICENTER PHASE II TRIAL WITH HUMANIZED ANTI-GD2 MONOCLONAL ANTIBODY NAXITAMAB FOR TREATMENT OF REFRACTORY/RELAPSED HIGH-RISK NEUROBLASTOMA: EFFICACY AND SAFETY

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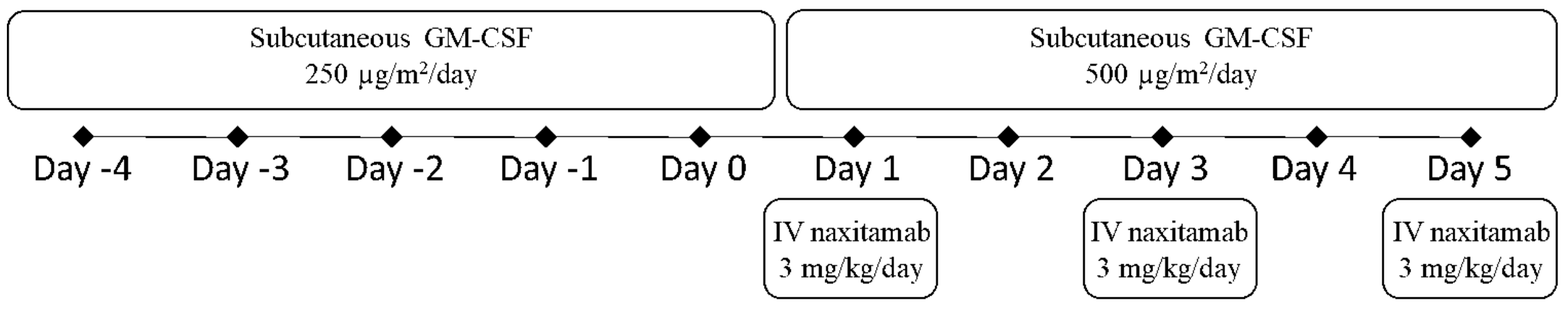
Background/Aim:

- Neuroblastoma (NB) represents the most common extracranial solid tumor of childhood.
- High-risk neuroblastoma (HR-NB) typically includes metastases in bones and/or bone marrow (BM).
- Naxitamab is a humanized monoclonal antibody targeting GD2 abundantly expressed in NB.
- Phase 1 Trial with naxitamab and granulocyte-macrophage colony-stimulating factor (GM-CSF) showed encouraging results (JAMA Oncol 2018; 4:1729).
- We evaluated naxitamab in HR-NB patients who had disease ONLY in bones and/or BM that was refractory to initial treatment(s) or who had insufficient response to therapy for relapsed/progressive disease.

Methods:

In an international multicenter clinical trial (Trial 201), subjects received naxitamab 9 mg/kg/cycle (≈ 270 mg/m^2/cycle) divided into 3 doses administered over 1st week of a pre-planned 4-week treatment cycle. Naxitamab was administered intravenously (IV) over 30-60 minutes in an outpatient setting. Cycles also included subcutaneous injections of GM-CSF.

One dosing cycle for naxitamab + GM-CSF:



Treatment cycles were repeated every 4 weeks (±1 week) until complete response or partial response followed by 5 additional cycles. Subsequent cycles could be repeated every 8 weeks (±2 weeks) through 101 weeks from first infusion at the discretion of the investigator. End of treatment took place around 8 weeks after the last cycle and thereafter long-term follow-up (LTFU) continued.

Subjects were evaluated for safety (CTCAE V4.0) and efficacy was scored using international criteria (JCO 2017;35:2580). We report on the first 25 subjects enrolled hereof 22 subjects evaluated for efficacy (Cohort 1, primary efficacy population).

Statistical Methodology:

Overall response rate (ORR) and complete response (CR) rate: 95% confidence intervals (CIs) were calculated using exact methodology. The duration of response (DoR) was calculated from response either to progression or the time of the last evaluable assessment. The distribution of DoR was estimated with Kaplan-Meier methods.

Results:

Demographics (Safety Population):

Demographics	Category	N=25
Age, years	Mean SD Median Min, Max	5.4 2.10 5.0 1, 10
Sex, n (%)	Female Male	9 (36%) 16 (64%)
Race, n (%)	White Asian Other	12 (48%) 12 (48%) 1 (4%)

Baseline Disease Characteristics (Safety Population):

Baseline disease characteristics	Group	N=25 n (%)
MYCN amplification status	Amplification Gain Neither gain nor amplification Unknown	4 (16%) 1 (4%) 14 (56%) 6 (24%)
INSS stage at diagnosis	Stage 3 Stage 4 Not reported	1 (4%) 21 (84%) 3 (12%)
Prognostic group	Favorable histology Unfavorable histology Not reported	1 (4%) 16 (64%) 8 (32%)
Prior surgery	Yes Not reported	23 (92%) 2 (8%)
Prior chemotherapy	Yes Not reported	24 (96%) 1 (4%)
Prior radiation	Yes Not reported	9 (36%) 16 (64%)
Neuroblastoma location	Bone Bone marrow Both bone and bone marrow	11 (44%) 2 (8%) 12 (48%)
Current neuroblastoma status	Primary refractory Incomplete response to salvage therapy	16 (64%) 9 (36%)

Efficacy:

We report efficacy from 22 subjects recruited from April 2018 with a data cut-off in July 2020. ORR and CR rate (independent review [IR] assessments):

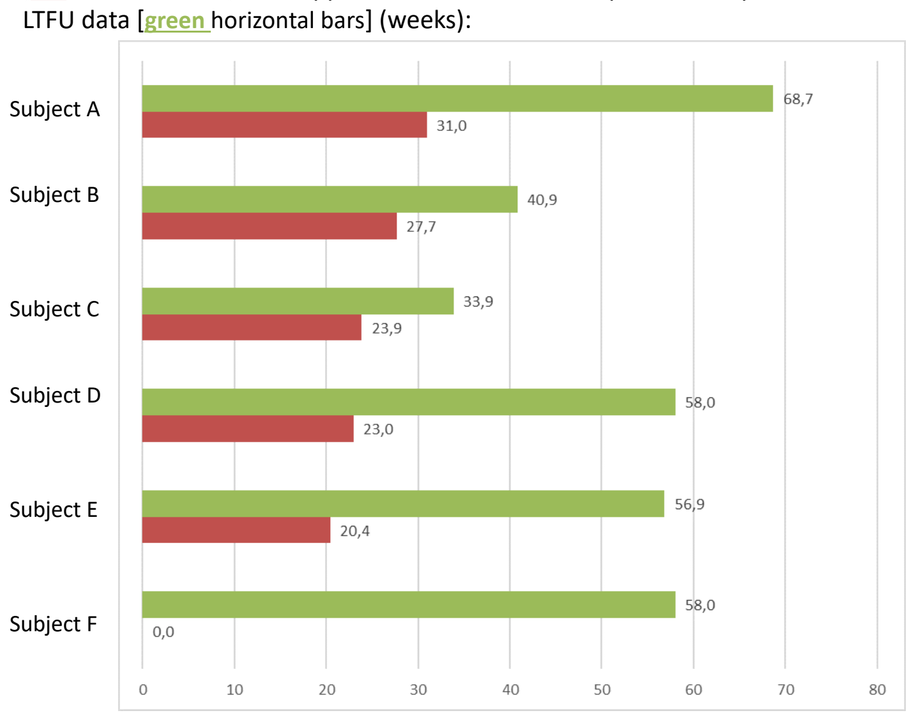
Group	Endpoint	n (%)	95% CI Lower limit	95% CI Upper limit
Overall (N=22)	ORR	15 (68%)	45%	86%
	CR rate	13 (59%)	36%	79%
Refractory (N=14)	ORR	10 (71%)	42%	92%
	CR rate	9 (64%)	35%	87%
Relapse (N=8)	ORR	5 (63%)	24%	91%
	CR rate	4 (50%)	16%	84%

BM clearance in subjects with positive BM at trial start (IR): CR in BM was observed in 7 of 9 subjects.

The median DoR (IR) was 25 weeks (95% CI [19, not estimable]).

For the 15 responders identified in the IR, the DoR assessment has been supplemented with available long-term follow-up (LTFU) data for 6 out of the 8 subjects in remission. The median DoR (IR+LTFU) was 27 weeks (95% CI [19, not estimable]).

DoR for subjects with an ongoing response at the end of the IR assessments only [red horizontal bars] and supplemented with non-independent response assessed LTFU data [green horizontal bars] (weeks):



Green: IR supplemented with LTFU as per 23Jul2020; Red: IR as per 23Jul2020

All 6 subjects with available LTFU information were still in remission at the last LTFU assessment.

Safety:

Summary of naxitamab related treatment-emergent adverse events with a CTCAE Grade of 3 or 4 reported by at least 10% of subjects (no CTCAE Grade 5 was reported):

System Organ Class/ Preferred Term	N=25 n (%)
Subjects with at least one related treatment-emergent adverse event Grade 3 or 4	22 (88%)§
General disorders and administration site conditions	18 (72%)*
Pain	18 (72%)*
Vascular disorders	15 (60%)*
Hypotension	15 (60%)*
Respiratory, thoracic and mediastinal disorders	11 (44%)#
Bronchospasm	7 (28%)*
Skin and subcutaneous tissue disorders	10 (40%)*
Urticaria	10 (40%)*
Gastrointestinal disorders	3 (12%)*
Abdominal pain	3 (12%)*
Immune system disorders	3 (12%)¤
Anaphylactic reaction	3 (12%)¤

§ Three Grade 4; * All Grade 3; # One Grade 4; ¤ Two Grade 4

Six related treatment-emergent serious adverse events (anaphylactic reaction 4 events, pyrexia 1 event and respiratory depression 1 event) were reported in 5 subjects.

Anti-drug antibody formation was observed in 2/25 (8%) subjects.

Conclusions:

- In relapsed/refractory HR-NB in the B/BM compartment, naxitamab + GM-CSF can achieve **major clinical responses**
- **CR was achieved in 13 of 22 evaluable subjects** as per independent review assessments
- In the updated analysis the **ORR was 68%**
- Naxitamab offers a **unique option** for treatment of patients in the **outpatient setting**

Future Directions for Research:

The efficacy results and convenience to subjects in Trial 201 strongly support further development of naxitamab for HR-NB.

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Clinical Trial Information: Trial 201/NCT03363373

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