# High-dose naxitamab plus stepped-up dosing of granulocyte-macrophage colony-stimulating factor for high-risk neuroblastoma: efficacy against histologically-evident primary refractory metastases in bone marrow

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## Background

Advantageous findings with naxitamab (formerly called humanized-3F8) in preclinical studies:

- slow $k_{off}$ in antigen-binding kinetics
- enhanced antibody-dependent cellular cytotoxicity (ADCC)
- substantial but less complement activation which efficiently lyses neuroblastoma (NB) yet causes pain

Promising results in phase I trial of naxitamab+GM-CSF (*JAMA Oncol* 2018; **4**:1729):

- safe dosing >2.5x higher than standard dosages (100mg/m$^2$/cycle) of dinutuximab and murine-3F8
- low immunogenicity
- major anti-NB activity
- pharmacokinetics and manageable toxicity supporting 3 doses/cycle (Mon-Wed-Fri), administered outpatient

Rationale for GM-CSF:

- well-tolerated clinically, without the toxicities associated with IL-2
- exerts a dose-response effect on ADCC *in vitro*, supporting stepped-up dosing in patients
- significantly improves outcome with murine-3F8 (*JCO* 2012; **30**:426)

## Patients and Methods

Subjects:

- High-risk NB patients with histologically-evident chemoresistant disease in bone marrow (BM), but no soft tissue or prior episodes of progressive disease.
- All formally enrolled on 12-230 phase I or phase II (expansion) trial (NCT01757626).

Treatment:

- Naxitamab at 9mg/kg/cycle (~270mg/m$^2$/cycle) divided into 3 doses, infused IV over 30 minutes on Mon-Wed-Fri. Dose-escalated in phase I patients.
- GM-CSF shots begin 5 days pre-naxitamab in priming doses of 250µg/m$^2$/day, then stepped up to 500µg/m$^2$/day with the naxitamab infusions.
- Cycles are repeated monthly x5 then every 1-2 months through 5 cycles after a major response, but are deferred if human anti-human antibody (HAHA) develops.

## Results *(through 7 May 2019)*

The 24 subjects (5 phase I, 19 phase II) enrolled to date were 5m-to-19m (median 7.5m) post-diagnosis and age 2y10m-to-10y1m (median 4y10m). Histology showed primitive NB in 15 and only ganglioneuromatous cells in 9 patients. All (100%) patients achieved complete response (CR) in BM. 22 patients also had NB in bone/BM by $^{123}$I-MIBG scans; Curie scores were $\geq$10 in 14 patients.

The $^{123}$I-MIBG scans showed major response (partial or complete remission) in 19/21 (90%) (Figures 1 and 2). 12 patients remained progression-free 2m+-to-56m+ (median 29m+) from enrollment (Figure 3), including 10 treated with anti-NB vaccine (1 also took DFMO). HAHA developed in 3 patients, all post-cycle 2.

Treatment was outpatient. Toxicities were as expected with anti-$G_{D2}$ antibodies, including pain, paresthesia, hypertension, hypotension, tachycardia, urticaria, fever and cough. A single cycle was truncated in 4 patients for respiratory issues (n=2), bradycardia (n=1), and skin exanthum (n=1). One patient came off study after cycle #1 because of hypotension.

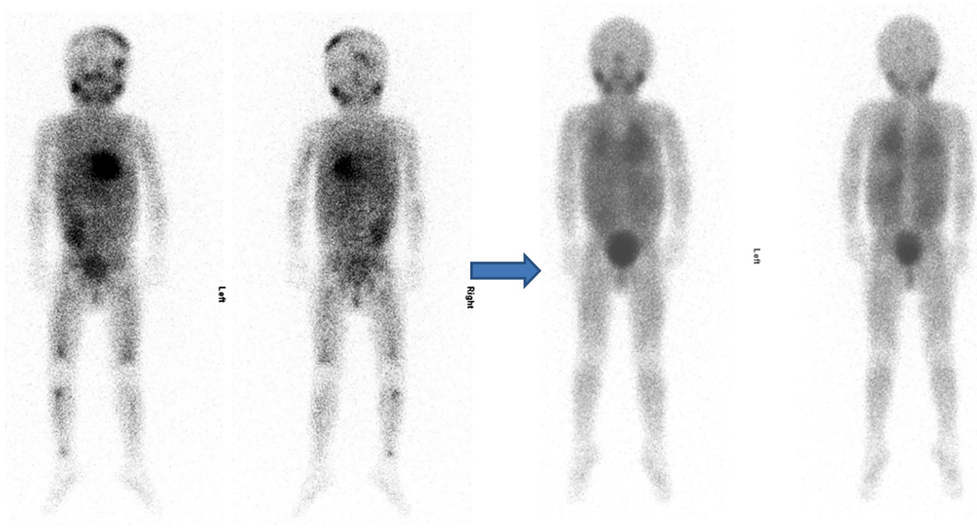


**Figure 1. Three-year old with primary refractory osteo-medullary disease: MIBG scans before and after 2 cycles of naxitamab/GM-CSF showing CR**

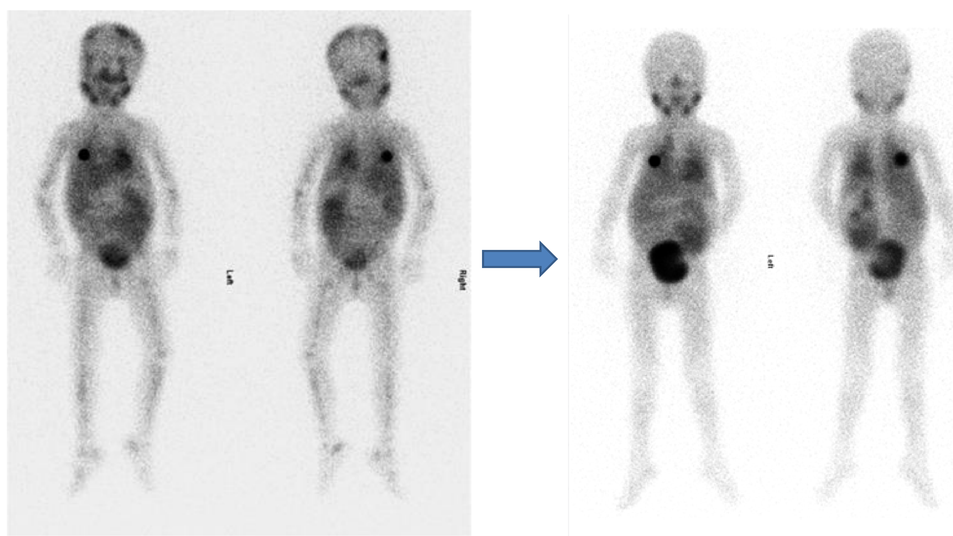

**Figure 2. Another 3-year old with primary refractory osteo-medullary disease: MIBG scans before and after 2 cycles of naxitamab/GM-CSF showing CR**

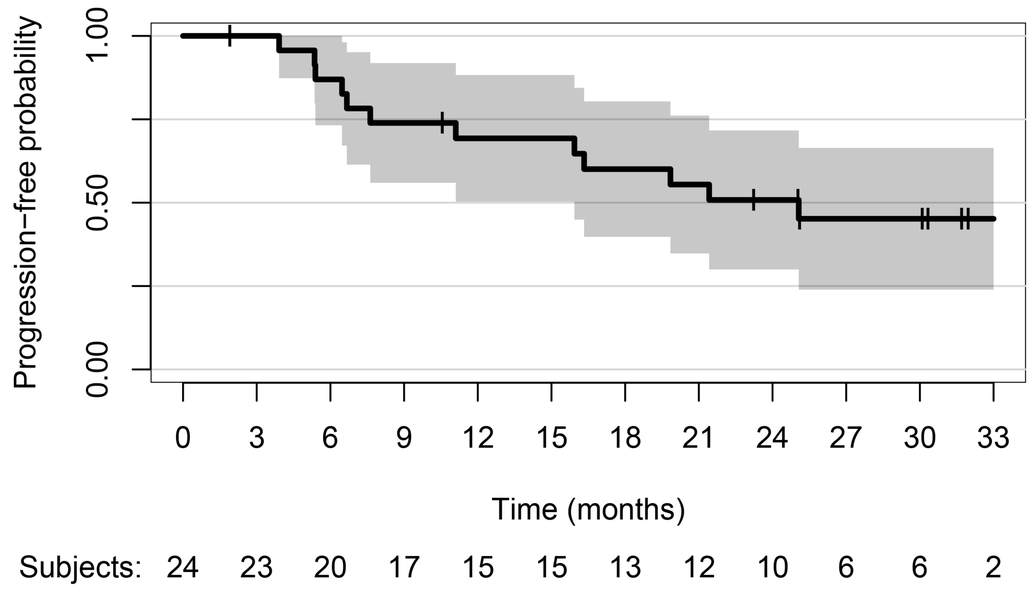


Figure 3. Using Kaplan-Meier method, the median progression-free survival (PFS) time was 25.1 months. The 12-month PFS was 69% [95% confidence interval [CI]: 50 to 88%]. The 24-month PFS was 51% [95% CI: 30 to 72%]. Patients were not censored when they commenced vaccine.

## Conclusions

Manageable toxicity, low immunogenicity, and substantial anti-NB activity have led to Breakthrough Therapy Designation by the Food and Drug Administration. The findings support further development of naxitamab which is proceeding apace and includes a pivotal phase II trial involving US and European institutions.

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