High-dose naxitamab (humanized-3F8) plus stepped-up dosing of granulocyte-macrophage colony-stimulating factor for neuroblastoma: outpatient treatment low immunogenicity, and major responses in a phase II trial

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Background

In preclinical (*OncoImmunol* 2012;**1**:477) and phase I studies (*OncoImmunol* 2017; **6**:e1358331; *JAMA Oncol* 2018; **4**:1729), naxitamab displayed features promising for improving efficacy and quality of life compared to other anti-G_{D2} antibodies: more prolonged binding to G_{D2}; enhanced antibody-dependent cellular cytotoxicity (ADCC); substantial but less complement activation which efficiently lyses neuroblastoma (NB) yet causes pain; safe dosing >2.5x higher than standard dosages (100mg/m^2/cycle) of dinutuximab and murine-3F8; low immunogenicity; major anti-NB activity; and pharmacokinetics and manageable toxicity supporting 3 doses/cycle administered outpatient. GM-CSF is well-tolerated, exerts a dose-response effect on ADCC (*Blood* 1989; **73**:1936), and significantly improves outcome with murine-3F8 (*JCO* 2012; **30**:426).

Methods

In a phase I/II expansion (NCT01757626, opened 6/2016), patients with primary refractory NB (persistent but no prior progressive disease) in bones/bone marrow received naxitamab 9mg/kg/cycle (~270mg/m2/cycle) divided into 3 doses infused intravenously (30 minutes) Mon-Wed-Fri. Subcutaneously-administered GM-CSF started 5 days pre-naxitamab in priming doses of 250µg/m2/day, then stepped up to 500µg/m2/day with the 1st dose of naxitamab. Response was scored post-cycle #2 and then every 12 weeks. Cycles were monthly through cycle #5. Patients received 5 cycles after a major response (complete or partial response by international criteria). Cycles were deferred if human anti-human antibody (HAHA) developed.

Results *(through 7 May 2019)*

At enrollment, the 23 patients evaluable for response were 2.0-to-10.4 (median 4.6) years old and 4.9-to-19 (median 6.0) months post-diagnosis. Prior therapy included intensive induction chemotherapy (all patients), 2nd-line chemotherapy (n=15), ^{131}I-MIBG (n=5), and combined chemotherapy+anti-G_{D2} antibody (n=5). Fifteen patients had Curie scores >10.

Eighteen patients (78%) achieved a major response (Figures 1 and 2). 24-month progression-free survival was 50% (95% confidence interval [CI]: 27-to-73%) (Figure 3). One patient became HAHA(+) post-cycle #2. Thirteen patients received an anti-NB vaccine (1 also took DFMO).

Treatment was outpatient. Toxicities were as expected with naxitamab (*JAMA Oncol* 2018;**4**:1729) and with other anti-G_{D2} antibodies, including pain, paresthesia, hypertension, hypotension, tachycardia, urticaria, fever and cough. .

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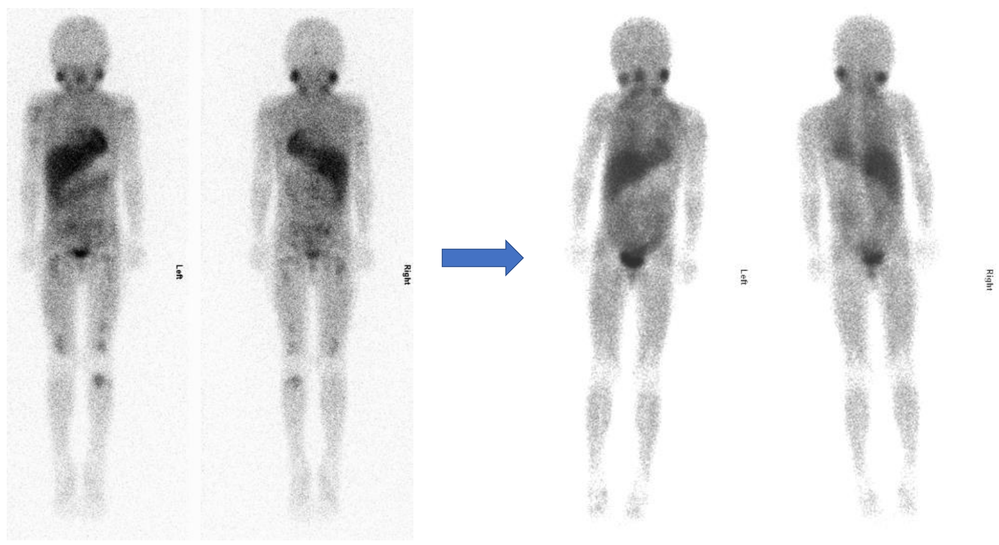

Figure 1. Six-year old with primary refractory osteo-medullary disease: MIBG scans before and after 2 cycles of hu3F8/GM-CSF showing complete response.

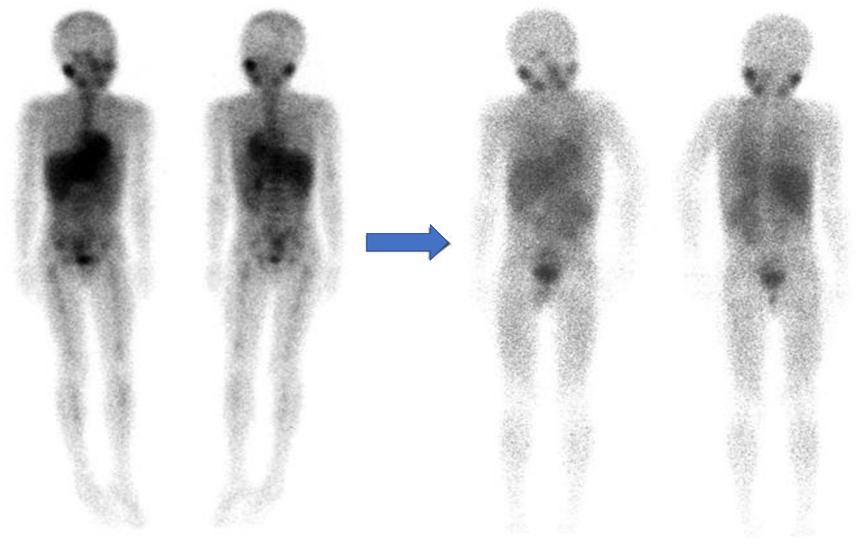

Figure 2. Another 6-year old with primary refractory osteo-medullary disease: MIBG scans before and after 2 cycles of hu3F8/GM-CSF showing complete response.

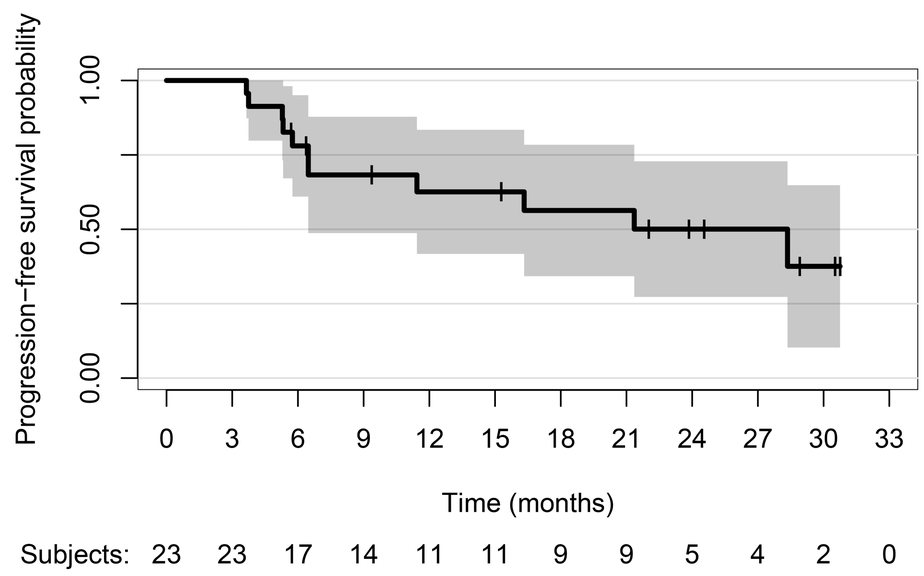

Figure 3. Using Kaplan-Meier method, the median progression-free survival (PFS) time was 28.4 months. The 12-month PFS was 63% [95% CI: 42-to-83%]. The 24-month PFS was 50% [95% CI: 27-to-73%]. Patients were not censored at start of anti-NB vaccine.

Conclusions

Manageable toxicity, low immunogenicity, and substantial anti-neuroblastoma activity have led to Breakthrough Therapy Designation by the Food and Drug Administration and support further development of naxitamab which is underway in a pivotal international trial (NCT02502786).

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