High-dose naxitamab (humanized-3F8) plus stepped-up dosing of granulocyte-macrophage colony-stimulating factor (GM-CSF) for consolidating ≥2nd complete remission (CR) of high-risk neuroblastoma

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Background

Advantageous findings with naxitamab in preclinical studies include:

- slow k_{off} in antigen-binding kinetics
- enhanced antibody-dependent cellular cytotoxicity (ADCC)
- substantial but less complement activation which efficiently lyses neuroblastoma (NB) yet is associated with 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 other anti-G_{D2} monoclonal antibodies (mAbs) 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 in 2nd or greater CR, i.e., status-post at least 1 prior episode of progressive disease (PD).
- All formally enrolled on 12-230 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.
- 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, but are deferred if human anti-human antibody (HAHA) develops.

Results *(through 1 April 2019)*

At enrollment, the 44 patients (33 males, 11 females) were 2.2-to-24.5 (median 5.5) years old, 0.9-to-17.8 (median 3.1) years post-diagnosis, and status-post 1 (n=29), 2 (n=7), or 3 or more (n=7) relapses or episodes of PD. Prior treatment included anti-GD2 mAb (dinutuximab, murine-3F8, naxitamab) in 38 (88%) patients; 13 (30%) patients were previously treated 2 or more times with anti-GD2 mAb. HAHA developed in 11 (25%) patients after cycle #1 or #2, including 10 prior-treated with anti-GD2 mAb.

24-month progression-free survival (PFS) was 52% (95% confidence interval [CI]: 36%-to-67%) (Figure 1). Post-protocol, 1 patient took DFMO and 20 patients received an anti-NB vaccine (1 also took DFMO). Patients were not censored at start of vaccine or DFMO.

Treatment was outpatient. Toxicities were as expected with anti-G_{D2} mAbs, including pain, paresthesia, hypertension, hypotension, tachycardia, urticaria, fever and cough. Posterior reversible encephalopathy syndrome (PRES) occurred in 1 patient and was suspected in 2 patients. Hypertension prompted admission in 5 patients, including 2 with cycle #1, 1 with relapse in brain noted immediately after cycle #1, and 2 who received multiple cycles without need for admission. An anaphylactic reaction occurred with the 1st infusion of naxitamab in 1 patient.

Conclusions

Manageable toxicity, low immunogenicity, and substantial anti-NB activity support further development of naxitamab which is underway in a pivotal international phase II trial (NCT02502786).

Acknowledgments:
We wish to thank our patients and families as well as the clinical staff of the Memorial Sloan Kettering Cancer Center Department of Pediatrics. We thank Y-mAbs Therapeutics for support of this study.

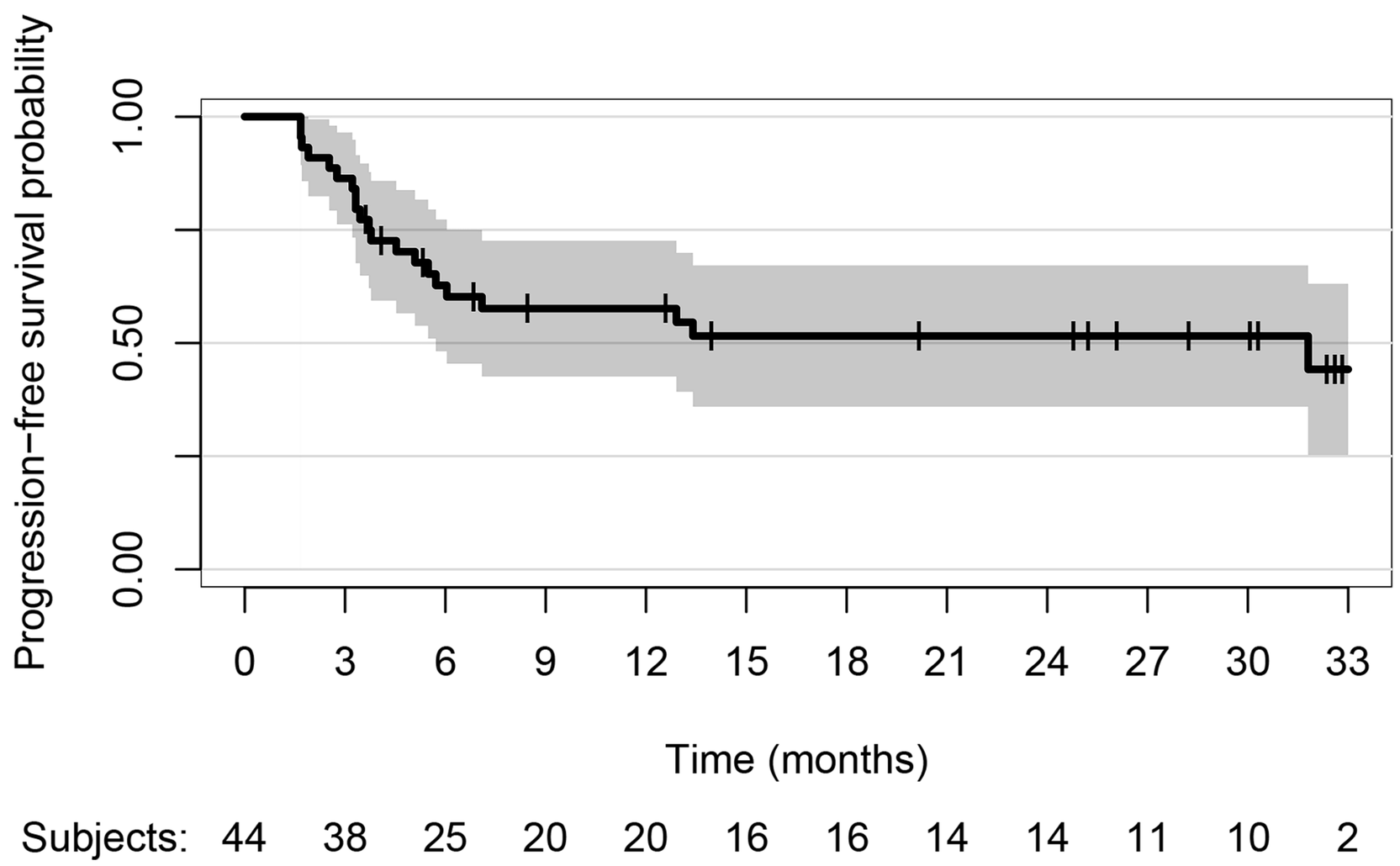

Figure 1. Among the 44 patients in 2nd or greater CR, a total of 21 progressions were observed. The median PFS time was 31.8 months. The 12-month PFS was 58% [95% CI: 43 to 73%]. The 24-month PFS was 52% [95% CI: 36 to 67%].