High-dose naxitamab (humanized-3F8) plus stepped-up dosing of granulocyte-macrophage colony-stimulating factor (GM-CSF) for high-risk neuroblastoma resistant to salvage therapy: a Phase II trial

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Background

Advantageous findings with naxitamab 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 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 of 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:
- HR-NB patients with incomplete response to salvage therapy for relapse or progressive disease (PD) (secondary refractory disease).
- 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 then every 1-2 months, through 5 cycles after a major response, but are deferred if human anti-human antibody (HAHA) develops.

Results *(through 1 April 2019)*

At enrollment, the 35 patients (20 males, 15 females) were 2.5-to-32.9 (median 6.4) years old, 0.4-to-10.8 (median 2.5) years post-diagnosis, and status-post 1 (n=23) or ≥2 (n=13) episodes of PD. Thirty-two (89%) patients previously received 1 or more anti-G_{D2} mAbs (dinutuximab, murine-3F8, naxitamab), including at 2 or more time points (n=15). Four (11%) patients became HAHA(+).

Of 30 patients evaluable for response, 11 (37%) achieved major responses (complete or partial response). For the entire cohort, 24-month progression-free survival (PFS) was 36% (95% confidence interval: 17%-to-55%) (Figure 1). 14 patients received an anti-NB vaccine and were not censored at its start.

Treatment was outpatient. Toxicities were as expected with anti-G_{D2} antibodies, including pain, paresthesia, hypertension, hypotension, tachycardia, urticaria, fever and cough. Admissions were limited to 1 patient each with posterior reversible encephalopathy syndrome (PRES), hypertension, and bradycardia. Single cycles in 4 patients were truncated (2 doses) because of intercurrent infections. One adult (32 years old) was electively treated as inpatient and was the sole patient self-removed.

Conclusions

Manageable toxicity, low immunogenicity, and encouraging outcomes of ultra-high-risk patients 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 phase II trial (NCT02502786).

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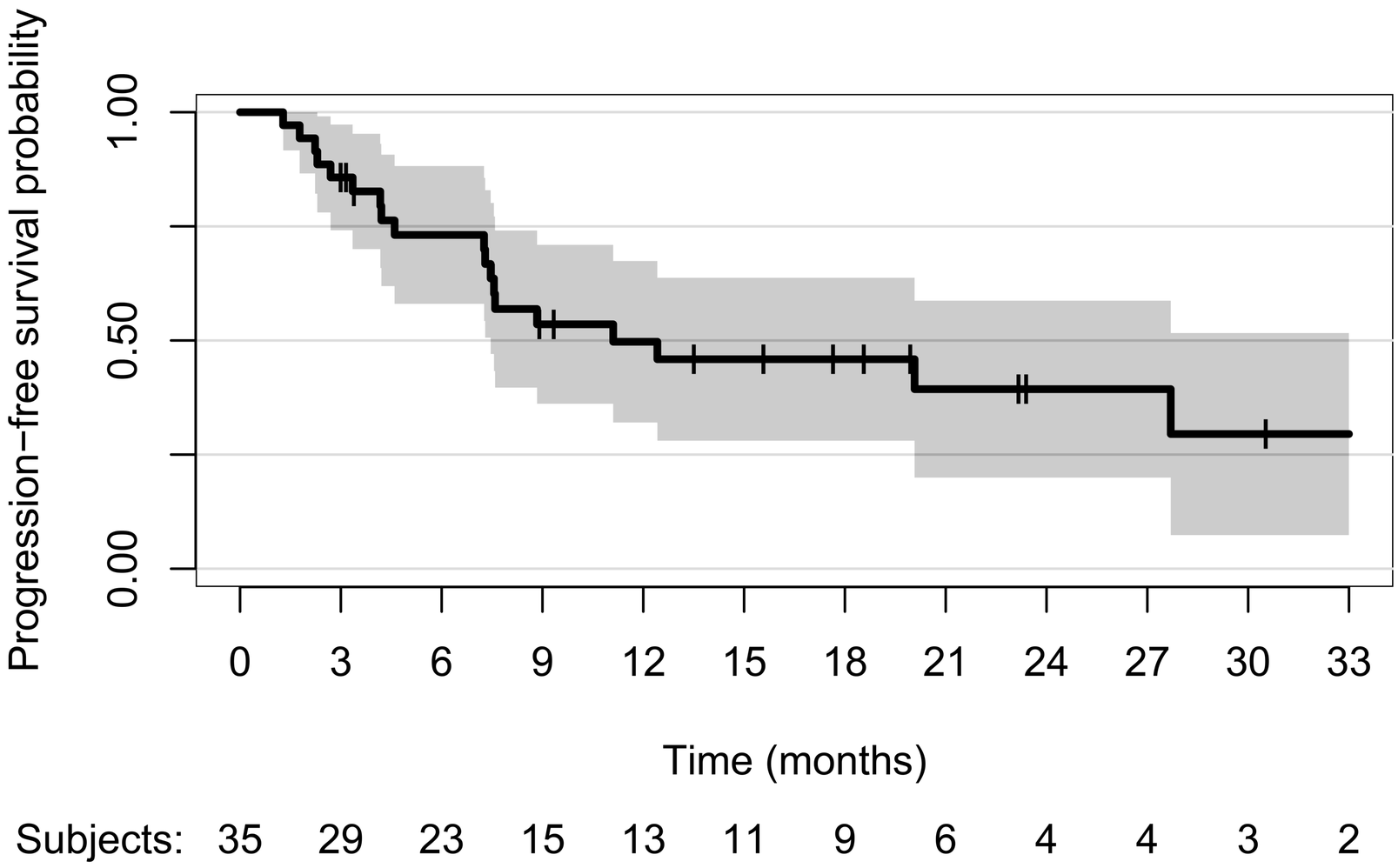

Figure 1. Among the 35 patients with secondary refractory disease, a total of 19 progressions were observed. The median PFS time was 11.1 months. The 12-month PFS was 50% [95% CI: 32 to 67%]. The 24-month PFS was 39% [95% CI: 20 to 59%].