High-dose humanized-3F8 (hu3F8) plus stepped-up dosing of GM-CSF: Outpatient treatment, low immunogenicity, and major responses in a phase II trial

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Background

Advantageous findings with hu3F8 (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 NB yet causes pain

Promising results in phase I trial of hu3F8+GM-CSF:

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

GM-CSF:

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

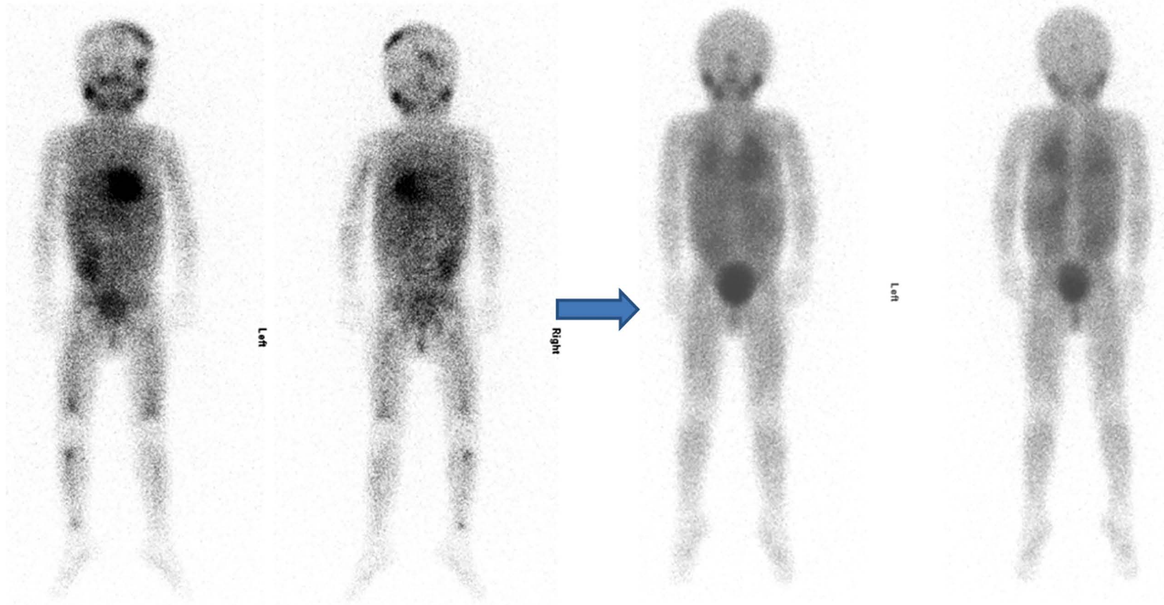

Figure 1. Three-year old with primary refractory disease in bone marrow: MIBG scans before and after 2 cycles of hu3F8/GM-CSF showing complete response

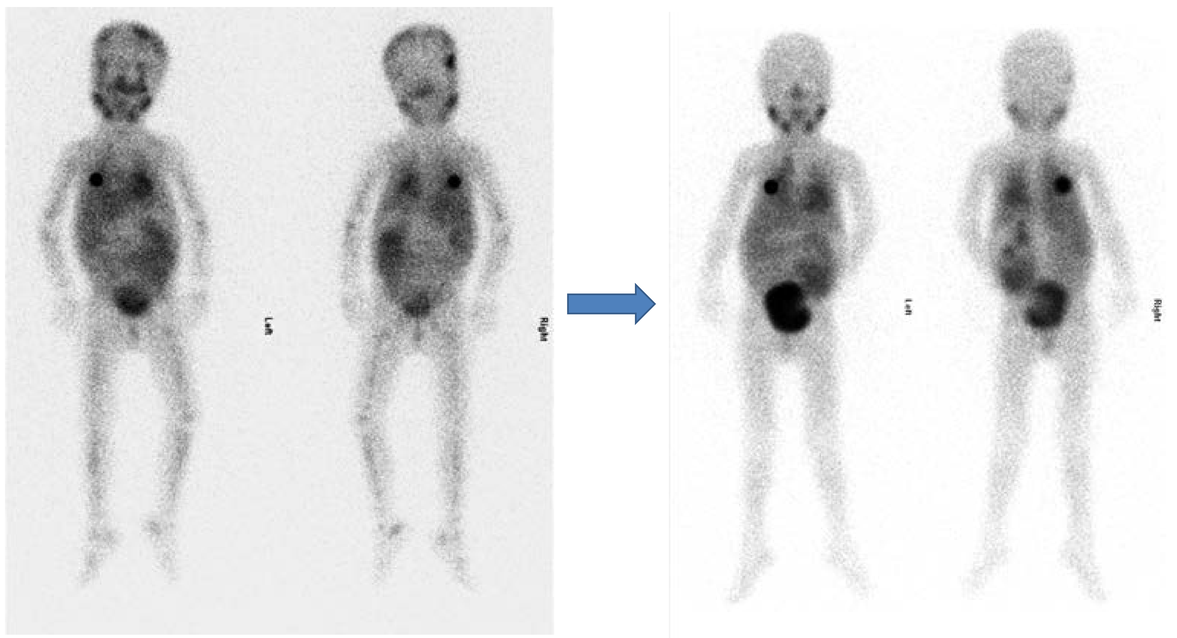

Figure 2. Another 3-year old with primary refractory disease in bone marrow: MIBG scans before and after 2 cycles of hu3F8/GM-CSF showing complete response

Methods

This phase I/II expansion (NCT01757626) is for HR-NB patients:

- Group 1: ≥2nd complete/very good partial remission (CR/VGPR)
- Group 2: primary refractory disease (persistent NB but no prior progression)
- Group 3: secondary refractory disease (persistent NB despite Rx for relapse)

Treatment:

- hu3F8 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-hu3F8 in priming doses of 250µg/m^2/day, then stepped-up to 500µg/m^2/day with the hu3F8 infusions
- cycles are repeated monthly x5 after a major response (1st work-up is post-cycle 2)
- cycles are deferred if human anti-human antibody (HAHA) develops

Results *(through January 2018)*

Group 1 includes 29 patients 0.9-to-17.8 (median 3.3) years post-diagnosis, 2.2-to-24.5 (median 6.3) years old, 25/29 prior-treated with ≥1 anti-G_{D2} antibody, and status-post 1 (n=18) or ≥2 (n=11) relapses; 12-month event-free survival is 74%.

Group 2 includes 17 patients with 15 evaluable for response 5-to-19 (median 6.6) months post-diagnosis, 2.9-to-10.9 (median 5.1) years old, and 9/15 with Curie scores 7-to-23 plus marrow(+); 13/15 (87%) achieved CR/PR (see Figures 1 and 2).

Group 3 includes 25 patients 0.9-to-10.6 (median 3.5) years post-diagnosis, 2.6-to-23.6 (median 6.5) years old, 23/25 prior-treated with ≥1 anti-G_{D2} antibody, and status-post 1 (n=15) or 2-to-6 (n=10) relapses; 12-month progression-free survival is 55%, and 7/23 (30%) patients evaluable for response achieved CR/PR.

HAHA developed in 11/71 (15%) patients; 9/11 HAHA(+) patients were prior-treated with anti-G_{D2} antibody.

Treatment was outpatient, without unexpected toxicities.

Conclusions

Modest toxicity, low immunogenicity, and substantial anti-NB activity support further development of hu3F8 (naxitamab) which is proceeding apace and includes a pivotal phase II trial involving US and European institutions.