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Phase II trial of GD2-KLH/GD3-KLH vaccine for stage 4 neuroblastoma in ≥2nd remission: Induced anti-GD2 titer strongly correlates with survival

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General Consensus:

High risk patients with refractory/relapsed neuroblastoma have **dismal** survival

- Anti-neuroblastoma VACCINE for potential **life long** protection **without pain** side effects – an attractive option

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Cancer Therapy: Clinical

Clinical Cancer Research

2014

Phase I Trial of a Bivalent Gangliosides Vaccine in Combination with β-Glucan for High-Risk Neuroblastoma in Second or Later Remission

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- **High risk*** patients who had relapsed or progressed were rendered into remission before entering this study
- N=15
- No dose limiting toxicity to vaccine & tolerable to glucan

*** High-risk NB as defined by risk-related treatment guidelines and the International NB Staging System**
- stage 4 with (any age) or without (>18 months old) *MYCN* amplification
- *MYCN*-amplified stage 3 (unresectable; any age)
- *MYCN*-amplified stage 4S or
- disease resistant to standard chemotherapy

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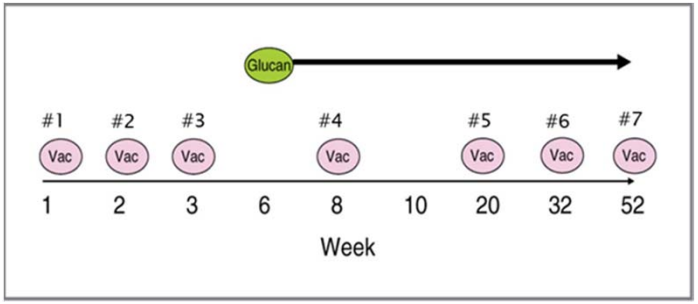
Phase II Vaccine Trial at Memorial Sloan Kettering Cancer Center

(Clinicaltrials.gov NCT00911560)

7 cycles



Vac = GD2-KLH/GD3-KLH + OPT 821 (QS21) → bivalent 30ug each [sc]; 150 ug/m^2 each [sc]

Glucan = yeast beta-glucan (supplied by Biotec Pharmacon, Norway) → 40 mg/kg/day, 2 weeks on and 2 weeks off [oral]

Bivalent vaccine: Abundance of GD2 and GD3 on NB *(Dobrenkov et al. PBC 2016)*

<u>To enhance immunogenicity</u>

- ✓ KLH (keyhole limpet hemocyanin)
- ✓ OPT 821(QS21) (saponin adjuvant)
- ✓ Beta-glucan

<u>To enhance ADCC</u>

- ✓ Beta glucan

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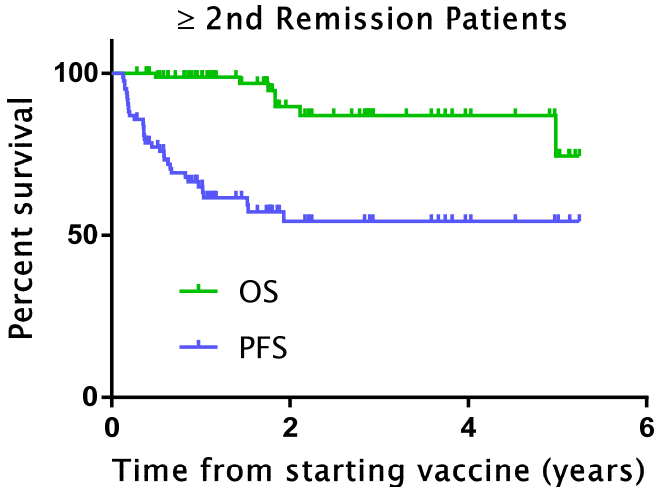
Focus on 2nd and later remission group

2013 to 2017	N
≥ second remission	84
2nd remission	57
3rd remission	18
4th remission	4
5th to 7th remission	5
First remission	56

Very high risk group

Patients with multiple relapses; received vaccine after they got back into remission

- Median followup = 19 m
- At 2 years: OS 90% ± 5%
  PFS 54% ± 6%
- No toxicity ≥ grade 3



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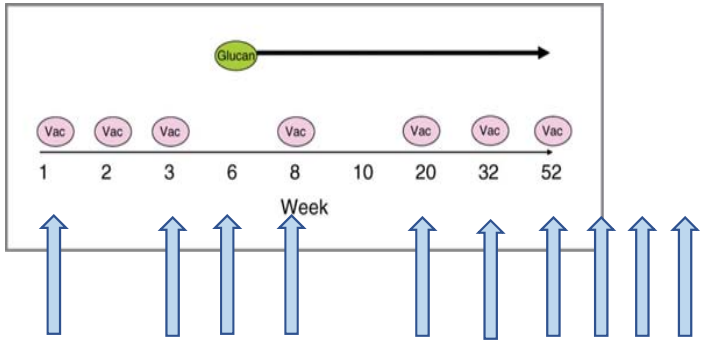
Quantitation of induced anti-GD2 and anti-GD3 response by ELISA



- Patients sera at serial time points
- Serum antibody titers (ng/mL) were integrated over time (i.e. AUC)
- Anti-GD2 and anti-GD3 response expressed as AUC per month

Example

Patient #1: AUC=307 ng/mL/month

Vaccine cycle #	Months from starting vaccine	Anti-GD2 titer (ng/mL)
1	0.0	0
3	0.7	0
4	1.6	84
5	4.4	150
6	7.1	226
post 6	10.1	433
7	11.7	269
post7-1	15.3	483
post7-2	18.4	532
post7-3	21.3	248

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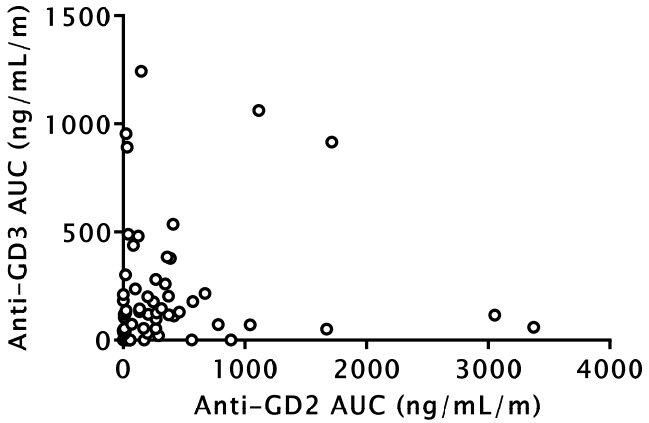
Seroconversion = antibody response

	% patients with positive		
	anti-GD2 titer		anti-GD3 titer
Pre-vaccine	13.3%		29.4%
During vaccine/followup	82.7%		70.4%

No correlation between anti-GD2 and anti-GD3 response



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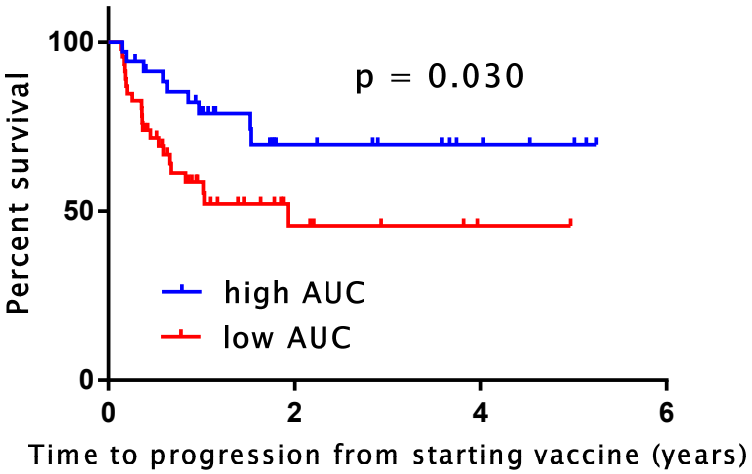
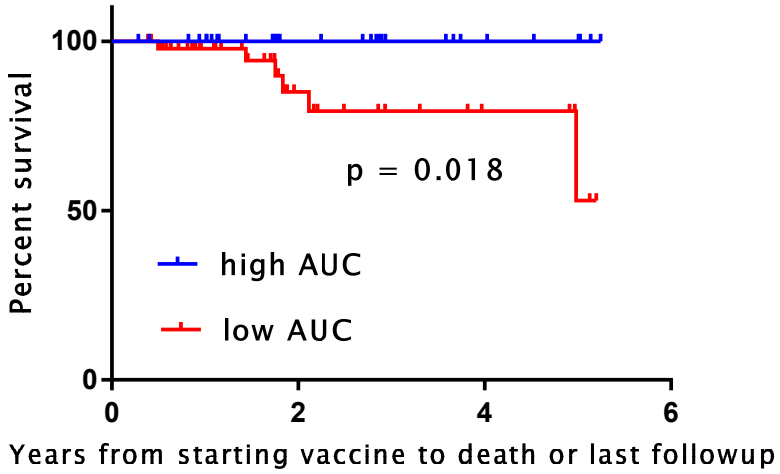
Induction of high anti-GD2 titer correlates with better outcome

PFS



OS



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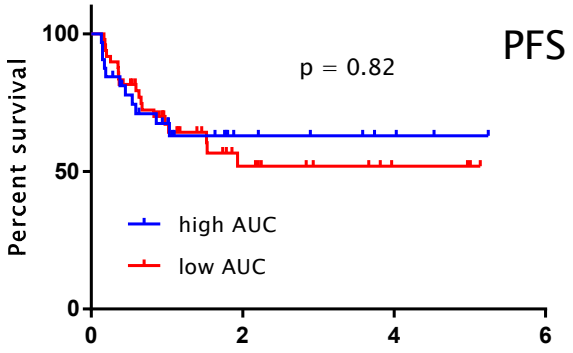
These variables did not correlate with PFS and OS

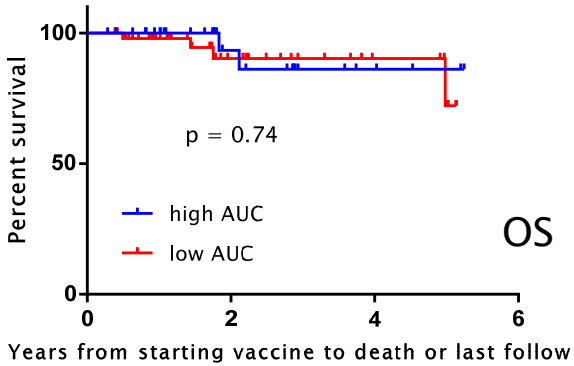
- Age at diagnosis
- Time from diagnosis
- *MYCN* amplification
- Number of prior relapses
- Pre-vaccine antibody titer
- Pre-vaccine anti-GD2 antibody therapy

Prior anti-GD2 antibody	N =84/84
m3F8 only	16
*naxitamab only	5
dinutuximab only	15
m3F8 + naxitamab	24
naxitamab + dinutuximab	16
m3F8 + naxitamab + dinutuximab	8

* Naxitamab = hu3F8



Anti-GD3 response



Eliciting anti-GD3 antibody response did not translate into favorable outcome

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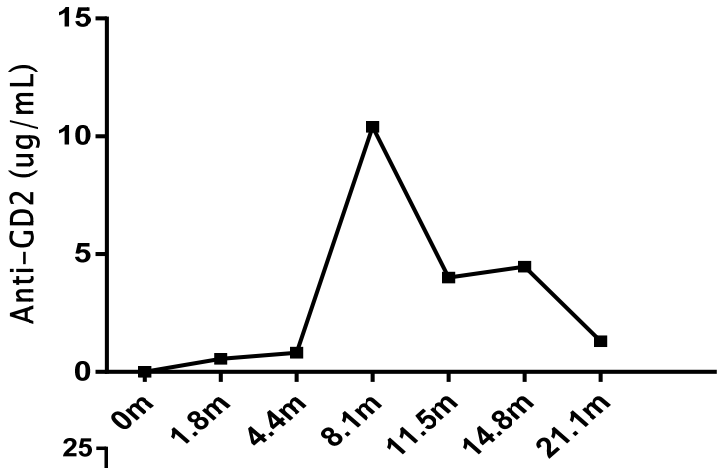
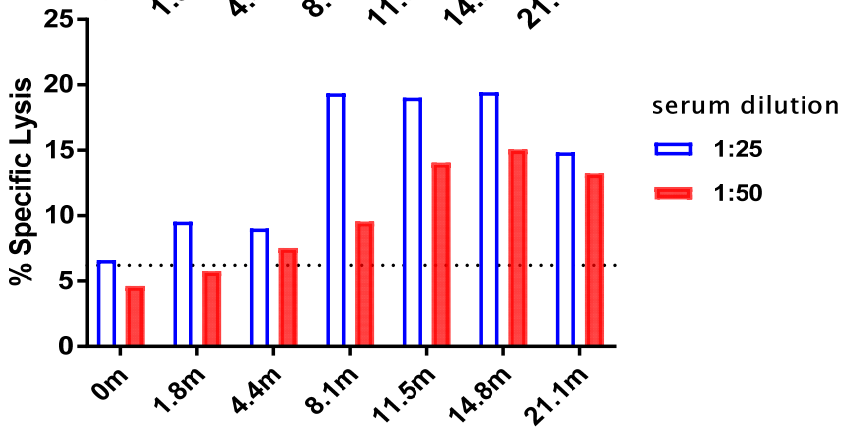
Antibody dependent cell mediated cytotoxicity in sera from a patient with induced anti-GD2 antibody response

Titer



ADCC

NK92MI-CD16 as effector
LAN-1 as target
(E:T ratio of 20:1)



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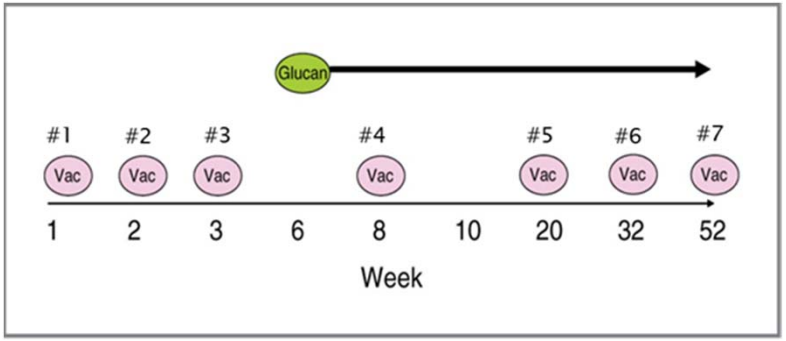
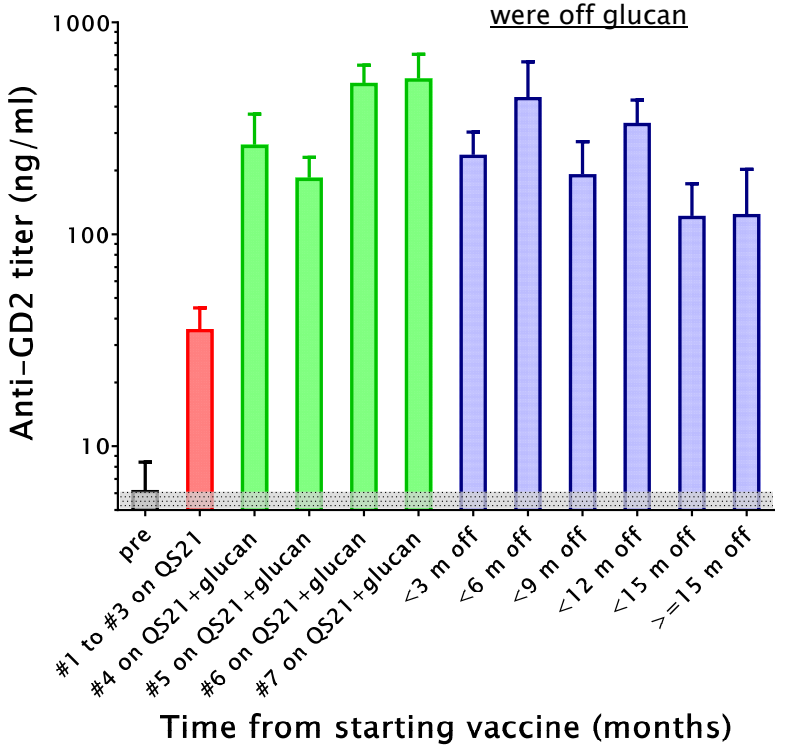
Beta-glucan markedly enhanced anti-GD2 titers when compared with standard adjuvant QS21 by >10 folds

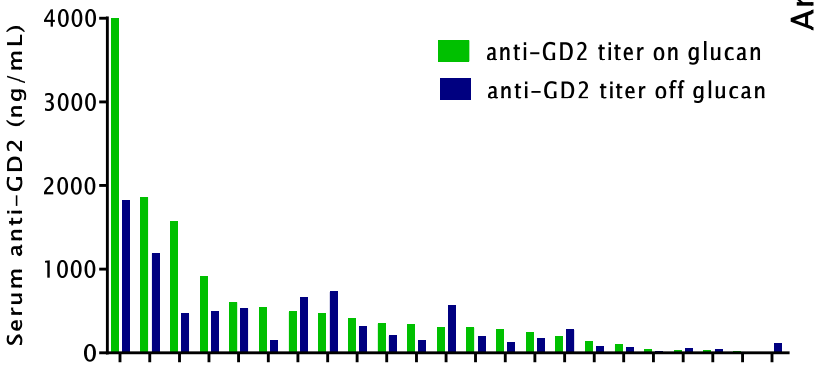
≥2nd remission cohort (N=84)



Glucan adjuvant effect persisted when patients were off glucan



Antibody titers persisted even when individual patients were off glucan



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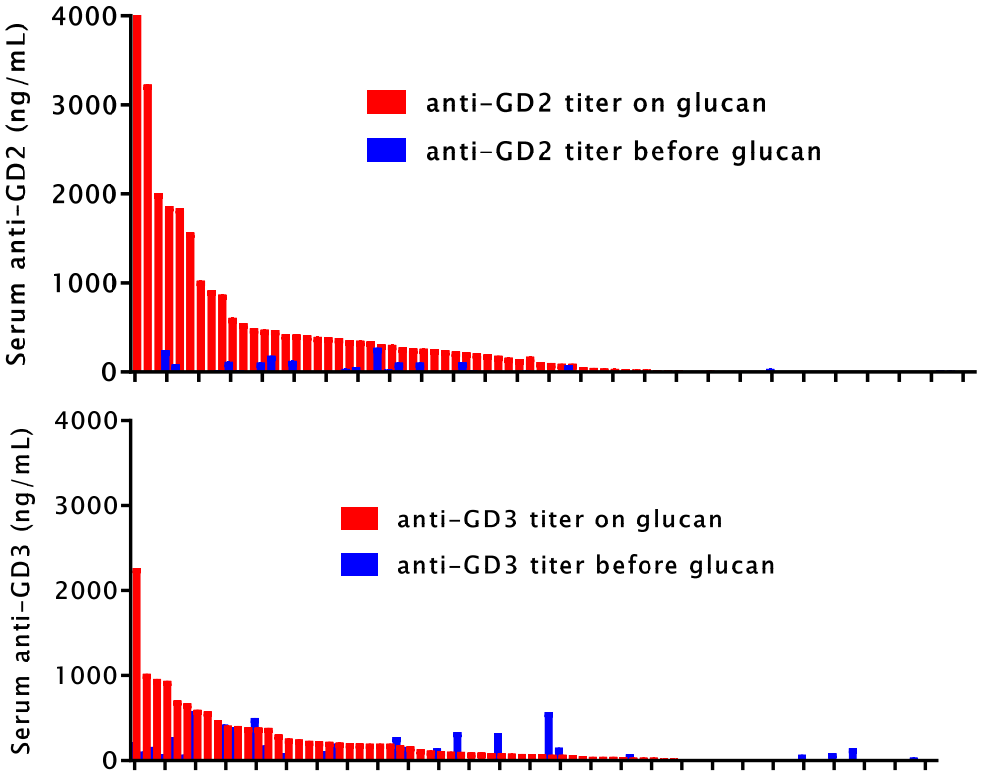
Glucan markedly enhanced induced anti-GD2 and anti-GD3 titers among individual patients



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Conclusions

- ✓ Oral glucan was a potent adjuvant on vaccination. Initiating glucan was associated with a substantial increase in anti-ganglioside antibody response
- ✓ Induced anti-GD2 antibody had cytotoxic function, and its response (AUC) may serve as a surrogate marker of survival benefit
- ✓ But anti-GD3 response did not correlate with PFS or OS
- ✓ Patients experienced no pain side effects nor neuropathy
- ✓ GD2 vaccine plus oral glucan could provide a viable option to improve the outlook for patients with relapsed high risk neuroblastoma